

**SYNTHESES AND REACTIONS OF AMINOXYCARBENES FROM  
THERMOLYSIS OF  $\Delta^3$ -1,3,4-OXADIAZOLINES**

By

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## **AMINOXYCARBENES**

*À Linda, avec qui...*  
*À mes parents, sans qui...*

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## Abstract

$\Delta^3$ -1,3,4-Oxadiazolines, spiro-fused at C2 to C2 to oxazolidines (**33a,b**) or to C2 of tetrahydro-1,3-oxazines (**106a-c**), were synthesized by oxidation of semicarbazones **103** with  $\text{PhI}(\text{OAc})_2$ . Oxadiazoline **33a** was reacted with acylating agents and with benzenesulfonyl chloride to give **33c-j** and **33k**, respectively. Oxadiazolines **106d** and **106e** were prepared by reacting **106a** and **106b**, respectively, with benzoyl chloride.

Thermolysis of oxadiazolines **33** and **106** in benzene at 90 °C ( $k^{90} \sim 1\text{-}50 \times 10^{-5} \text{ s}^{-1}$ ) generated oxazolidin-2-ylidenes **28** and tetrahydro-1,3-oxazin-2-ylidenes **113**, respectively, as major fragmentation intermediates. Specifically, **33c-j** and **106d,e** (N-carbonyl) gave essentially quantitative yields of the corresponding aminooxycarbenes, while thermolysis of **33b** (N-methyl) produced *ca.* 70% of **28b**; for **106c** (N-methyl), an upper limit of *ca.* 20% was determined for the formation of **113c**.

Experiments on the thermolysis of 2,2-dioxy oxadiazolines **86** at 110 °C in benzene led to the detection (and isolation, in one case) of ketene acetals **87** as minor products; compounds tentatively identified as oxiranes **94** were also observed. Formation of these and other products was rationalized in terms of a thermolytic scheme involving the intermediacy of carbonyl ylides **91** which predominantly fragment to dioxycarbenes **92** and acetone.

Aminooxycarbenes **28b-g,j** and **113d,e** were intercepted with phenols to give OH insertion products **119/124**; an activation energy of 20.4 kcal/mol was measured for nitrogen inversion in oxazolidines **119**. Carbenes **28b,d-f** and **113d** reacted with two equivalents of methyl or phenyl isocyanate to give hydantoins **120**; in contrast, 4(5*H*)-oxazolones **125** formed when **28d,f** or dimethoxycarbene (**3**) were generated in the presence of benzoyl isocyanate. The major products in the reaction of **28d-f** with dimethyl acetylenedicarboxylate or with methyl propiolate, oxazoles **157**, resulted from apparent acyl transfers from N to C in the proposed dipolar intermediates. Carbene **28f** inserted into the activated CH bond of 1,3-diones to produce **170**; the minor products of these reactions (*e.g.* **173**) provided evidence for the involvement of ion pairs.

$\beta$ -Lactam-4-ylidene **194**, generated from thermolysis of  $\beta$ -lactam oxadiazoline **193**, underwent intramolecular OH insertion to give 2,3-benzooxapenam **195** in 53% yield.

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## Table of Contents

<b>Abstract.....</b>	<b>iii</b>
<b>Acknowledgements.....</b>	<b>v</b>
<b>List of Figures.....</b>	<b>x</b>
<b>List of Tables.....</b>	<b>xi</b>
<b>Glossary of Abbreviations .....</b>	<b>xii</b>
 <b>Chapter 1    Introduction .....</b>	 <b>1</b>
<b>1.1    Electronic Structure of Carbenes.....</b>	<b>2</b>
<b>1.2    Detection of Carbenes.....</b>	<b>5</b>
<b>1.3    Singlet vs Triplet Carbene Reactivity.....</b>	<b>5</b>
<b>1.4    Electrophilic vs Nucleophilic Carbene Reactivity .....</b>	<b>7</b>
<b>1.5    Synthesis of Nucleophilic Carbenes .....</b>	<b>12</b>
<b>1.5.1    Dioxycarbenes .....</b>	<b>13</b>
<b>1.5.1.1    Classical Methods of Generation .....</b>	<b>13</b>
<b>1.5.1.2    Thermolysis of Oxadiazolines.....</b>	<b>17</b>
<b>1.5.2    Diaminocarbenes .....</b>	<b>20</b>
<b>1.5.3    Aminooxycarbenes.....</b>	<b>24</b>
<b>1.6    Chemistry of Nucleophilic Carbenes.....</b>	<b>26</b>
<b>1.6.1    Intramolecular Reactions .....</b>	<b>26</b>
<b>1.6.1.1    Fragmentations to Radicals .....</b>	<b>28</b>
<b>1.6.1.2    1,2 Migrations .....</b>	<b>28</b>
<b>1.6.1.3    Fragmentation of Cyclic Carbenes.....</b>	<b>31</b>
<b>1.6.1.4    [2,3]-Sigmatropic Rearrangements.....</b>	<b>32</b>
<b>1.6.2    Intermolecular Reactions .....</b>	<b>33</b>
<b>1.6.2.1    Miscellaneous Reactions .....</b>	<b>33</b>

1.6.2.2	Insertions into X-H Bonds .....	35
1.6.2.3	Reactions with Double Bonds .....	39
1.6.2.3.1	Alkenes.....	39
1.6.2.3.2	C=X Bonds.....	44
1.6.2.3.3	Heterocumulenes .....	47
1.6.2.4	Reactions with Alkynes.....	50
1.7	Objectives.....	53
Chapter 2 Results and Discussion.....		55
2.1	Thermolysis of 2-Aryloxy-2-methoxy- $\Delta^3$ -1,3,4-oxadiazolines.....	55
2.2	Synthesis of 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines .....	65
2.3	Thermolysis of 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines.....	79
2.3.1	Thermolysis Rate Constants.....	79
2.3.2	General Thermolytic Scheme .....	83
2.3.3	Thermolysis of 33b.....	85
2.3.4	Thermolysis of 106c .....	89
2.3.5	Thermolysis of 33f.....	92
2.3.6	Thermolysis of Other N-Carbonyl Oxadiazolines 33 .....	99
2.3.7	Thermolysis of 106d and 106e .....	100
2.3.8	Thermolysis of 33k.....	102
2.3.9	Thermolysis of 33a .....	103
2.4	Intermolecular Reactions of Aminooxycarbenes .....	108
2.4.1	Insertions into O-H bonds.....	108
2.4.1.1	Reactions with Alcohols .....	108
2.4.1.2	Reactions with Phenols .....	109
2.4.1.2.1	3-Methyloxazolidin-2-ylidene (28b) .....	109
2.4.1.2.2	3-Carbonyloxazolidin-2-ylidenes (28c-f,j and 113d).....	121
2.4.1.2.3	3-(Phenylsulfonyl)oxazolidin-2-ylidene (28k) .....	125

2.4.2	Reactions with Methyl or Phenyl Isocyanate .....	127
2.4.3	Reactions with Alkynes.....	130
2.4.4	Reactions with 1,3-Diones .....	137
2.5	1,3-Benzoxazol-2-ylidenes.....	146
2.6	Intramolecular Trapping of a Novel $\beta$ -Lactam-4-Ylidene .....	152
 Chapter 3 Summary and Conclusions.....		157
3.1	Thermolysis Mechanisms .....	157
3.2	Chemistry of Aminooxycarbenes.....	159
3.3	$\beta$ -Lactam-4-ylidene 194.....	162
 Chapter 4 Experimental .....		163
4.1	Thermolysis of 2-Aryloxy-2-methoxy- $\Delta^3$ -1,3,4-oxadiazolines.....	164
4.2	Synthesis of 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines .....	171
4.3	Thermolysis of 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines.....	193
4.3.1	Thermolysis Rate Constants.....	193
4.3.2	General Thermolytic Scheme .....	194
4.3.3	Thermolysis of 33b.....	195
4.3.4	Thermolysis of 106c .....	197
4.3.5	Thermolysis of 33f.....	198
4.3.6	Thermolysis of Other N-Carbonyl Oxadiazolines 33.....	204
4.3.7	Thermolysis of 106d and 106e .....	205
4.3.8	Thermolysis of 33k.....	205
4.3.9	Thermolysis of 33a .....	205
4.4	Intermolecular Reactions of Aminooxycarbenes .....	207
4.4.1	Insertions into O-H bonds.....	207
4.4.1.1	Reactions with Alcohols .....	207
4.4.1.2	Reactions with Phenols .....	209

4.4.1.2.1	3-Methyloxazolidin-2-ylidene ( <b>28b</b> ) .....	210
4.4.1.2.2	3-Carbonyloxazolidin-2-ylidenes ( <b>28c-f,j</b> and <b>113d</b> ).....	211
4.4.1.2.3	3-(Phenylsulfonyl)oxazolidin-2-ylidene ( <b>28k</b> ) .....	217
4.4.2	Reactions with Methyl or Phenyl Isocyanate .....	219
4.4.3	Reactions with Alkynes.....	224
4.4.4	Reactions with 1,3-Diones .....	233
4.5	1,3-Benzoxazol-2-ylidenes .....	238
4.6	Intramolecular Trapping of a Novel $\beta$ -Lactam-4-Ylidene .....	243
References .....		248
Appendix I. Thermolysis Rate Constants .....		261
Appendix II. Inversion Barriers in 2-Aryloxy-3-methyloxazolidines <b>119a,b</b> .....		274
Appendix III. X-Ray Crystallography Data for Oxadiazoline <b>33f</b> .....		275

## List of Figures

1. Electronic structures of low-valent carbon species .....	1
2. Electronic structures of singlet and triplet carbenes .....	2
3. Stabilization of a singlet carbene by $\pi$ donation .....	4
4. Mechanisms of carbene insertion into C-H bonds.....	6
5. Mechanisms of additions of carbenes to alkenes.....	6
6. FMO interactions in carbene + alkene cycloadditions .....	9
7. Dipolar character of nucleophilic carbenes .....	9
8. Modes of approach in carbene + alkene cycloadditions .....	11
9. Resonance structures in imidazol-2-ylidenes .....	23
10. Aminooxycarbenes generated in solution.....	26
11. 1,2-H Migration in a singlet carbene.....	29
12. Yields of <b>87c</b> and <b>94c</b> as a function of oxadiazoline <b>86c</b> concentration .....	64
13. Crystal structure of oxadiazoline <b>33f</b> .....	71
14. Experimental and simulated $^1\text{H}$ -NMR spectrum of oxadiazoline <b>33b</b> .....	73-74
15. Ring flexing in the oxazolidine ring of <b>33b</b> .....	75
16. $^1\text{H}$ -NMR spectrum of <b>33f</b> as a function of temperature.....	77-78
17. Numbering system for spiro oxadiazolines <b>33</b> and <b>106</b> .....	79
18. $^{13}\text{C}$ -NMR spectrum of <b>119b</b> .....	111
19. NMR data from compounds related to <b>119</b> .....	112
20. NMR data for oxazolidine <b>141</b> and its corresponding cation .....	113
21. $^1\text{H}$ -NMR spectrum of <b>119b</b> as a function of temperature.....	115-116
22. Depiction of the process of pyramidal inversion in amines .....	117
23. Effect of ring size on nitrogen inversion barriers .....	117
24. Effect of substituent size on nitrogen inversion barriers.....	118
25. Conjugative effects on nitrogen inversion barriers .....	118
I.1-I.13 Plots of $\ln(I/I_0)$ vs time for thermolyses of <b>33/106</b> .....	261-273



## List of Tables

I.	Absolute rate constants for reactions of methoxycarbenes with methanol .....	38
II.	Absolute rate constants for carbene + alkene cycloadditions .....	40
III.	<sup>1</sup> H-NMR data for ketene acetals <b>87</b> .....	57
IV.	Yields of thermolysis products from <b>86c</b> .....	63
V.	2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines synthesized .....	68
VI.	<sup>1</sup> H-NMR data for the ABMX spin system in <b>33b</b> .....	75
VII.	Rate constants for the thermolysis of oxadiazolines <b>33</b> and <b>106</b> .....	80
VIII.	Selected NMR data for 2-aryloxy-3-methyloxazolidines <b>119</b> .....	111
IX.	N-Carbonyl carbene - phenol adducts isolated.....	122
X.	Selected NMR data for products from the reaction of N-carbonyl carbenes with phenol .....	124
XI.	Hydantoins <b>120</b> isolated from reactions of aminooxycarbenes with isocyanates.....	128
XII.	Selected NMR data for compound <b>170b</b> .....	140
XIII.	Selected NMR data for compound <b>174</b> .....	143
III-1 to III-6 X-Ray crystallography data for oxadiazoline <b>33f</b> .....		275-280

## **Glossary of Abbreviations**

<b>CA</b>	<b>Collisional activation</b>
<b>CI</b>	<b>Chemical ionization</b>
<b>DMAD</b>	<b>Dimethyl acetylenedicarboxylate</b>
<b>EI</b>	<b>Electron impact ionization</b>
<b>ESR</b>	<b>Electron spin resonance</b>
<b>FMO</b>	<b>Frontier molecular orbital</b>
<b>GC</b>	<b>Gas chromatography</b>
<b>KIE</b>	<b>Kinetic isotope effect</b>
<b>IR</b>	<b>Infrared (spectroscopy)</b>
<b>LFP</b>	<b>Laser flash photolysis</b>
<b>MS</b>	<b>Mass spectrometry</b>
<b>N.A.</b>	<b>Not available</b>
<b>NMR</b>	<b>Nuclear magnetic resonance</b>
<b>NRMS</b>	<b>Neutralization-reionization mass spectrometry</b>
<b>SCF</b>	<b>Self-consistent field</b>
<b>VLVP</b>	<b>Very low vapour pressure</b>
<b>VT</b>	<b>Variable-temperature</b>

## Chapter 1

### Introduction

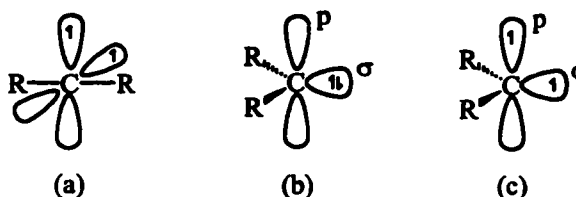
Over the last two centuries, organic chemistry has evolved from a science initially concerned strictly with substances derived from natural sources to one which now encompasses the study of carbon-containing compounds in general. In the vast majority of organic compounds, each carbon atom is tetravalent: four electron pairs are covalently shared between the carbon and the atoms directly bonded to it. Di- or trivalent carbon atoms, however, also exist in four distinct types of organic species: (1) carbenium ions, (2) free radicals, (3) carbanions, and (4) carbenes (Figure 1). Although some examples of stable, even isolable low-valent carbon compounds are known, they are usually highly reactive, short-lived species formed as *reactive intermediates* in the course of chemical reactions. The study of their structures and properties is therefore of central importance for the advancement of contemporary chemistry.<sup>1-3</sup>



**Figure 1.** Comparison of the electronic structures of low-valent carbon species.

## 1.1 Electronic Structure of Carbenes

Carbenes are neutral species in which the divalent carbon possesses a total of four valence electrons: two bonding and two non-bonding. The electronic configuration and geometry of the simplest carbene, methylene ( $\text{CH}_2$ ), have attracted considerable attention since the 1930s.<sup>4</sup> One can imagine a linear geometry for methylene, corresponding to  $sp$  hybridization at carbon, with each of the two degenerate non-bonding  $p$  orbitals occupied by a single electron (Figure 2(a)). This proposed geometry, however, does not reflect reality: triplet state methylene has a H-C-H bond angle of about  $130^\circ$ .<sup>5,6</sup>



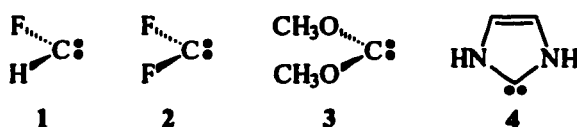
**Figure 2.** Electronic structures of (a) hypothetical linear triplet carbene, (b) typical singlet carbene, and (c) typical triplet carbene.

Carbenes can generally be thought of as being  $sp^2$  hybridized, with two non-degenerate non-bonding orbitals: an in-plane  $sp^2$  orbital generally labelled  $\sigma$ , and a perpendicular  $p$  orbital. For a given carbene, the distribution of the two non-bonding electrons in the non-bonding molecular orbitals, and hence the multiplicity of the ground state, is determined by both the relative orbital energies and electron-electron repulsion. In a ground state singlet carbene, the energy required to promote one of the two non-bonding electrons to the vacant  $p$  orbital exceeds that due to the mutual repulsion of the two paired electrons in the  $sp^2$  ( $\sigma$ ) orbital. Thus, in the lowest energy singlet state, the

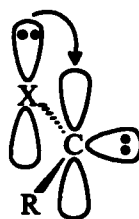
two non-bonding electrons occupy an in-plane orbital, leaving a vacant non-bonding orbital perpendicular to the plane of the molecule (Figure 2(b)). In contrast, in a ground state triplet carbene, the energy requirement for the promotion of one electron from the in-plane  $sp^2$  to the perpendicular p orbital is less costly than that for pairing the electrons in the same orbital. In addition, according to Hund's rule, an energy minimum is reached when the two unpaired electrons in the triplet carbene have parallel spins (Figure 2(c)).

For methylene, experimental and theoretical estimates of the singlet-triplet energy gap ( $\Delta_{ST}$ ) place the singlet state at 9-12 kcal/mol above the triplet state.<sup>7,8</sup> Simple aryl and vinyl derivatives of methylene also have triplet ground states, as do carbenes with electron-withdrawing substituents ( $CF_3$ , CN,  $C(O)R$ , etc.) directly attached to the divalent carbon.<sup>9</sup> The typically small  $\Delta_{ST}$  values, however, particularly for alkyl carbenes, sometimes leave some uncertainty regarding the nature of the ground state. The case of dimethylcarbene, for instance, is not yet settled.<sup>10</sup>

Heteroatoms such as the halogens, oxygen, and nitrogen substantially stabilize the singlet state. Substituting one F atom for H in methylene brings the singlet state in fluorocarbene (1) 15 kcal/mol lower than the triplet state; substitution of a second F increases  $\Delta_{ST}$  to about 56 kcal/mol in difluorocarbene, 2.<sup>8</sup> *Ab initio* calculations have also yielded  $\Delta_{ST}$  values as high as 76 kcal/mol for dimethoxycarbene<sup>11</sup>(3) and 79 kcal/mol for imidazol-2-ylidene<sup>12</sup> (4).



It is generally recognized that the major factor contributing to this stabilization of the singlet state by heteroatoms is the conjugative donation of non-bonding electrons from the heteroatom(s) to the formally vacant carbene p orbital (Figure 3).<sup>8,13,14</sup> In addition, inductive withdrawal by electronegative substituents lowers the energy of the singlet state by increasing the s character of the non-bonding in-plane  $\sigma$  orbital of the carbene.<sup>15</sup>



**Figure 3.** Stabilization of a singlet carbene by  $\pi$  donation from a heteroatom.

The geometry of carbenes is, to a large extent, determined by their multiplicity, which in turn depends on substituents. In general, singlet carbenes have smaller R-C-R bond angles ( $\sim 100^\circ$ ) than triplet carbenes ( $\sim 120$ - $135^\circ$ ).<sup>14</sup> This can be attributed to the electronic repulsion between the filled  $\sigma$  orbital and the bonding orbitals in the singlet state. In methylene, for instance, the triplet (ground state) is bent with an angle of about  $130^\circ$ , as mentioned above, compared to *ca.*  $102^\circ$  in the lowest energy singlet state.<sup>6,14-17</sup>

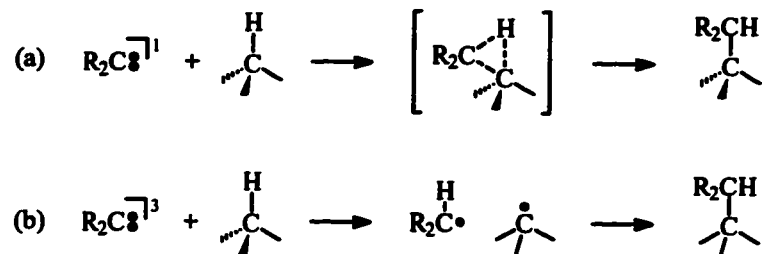
## 1.2 Detection of Carbenes

Despite the inherently short lifetime of most carbenes, direct observation of these reactive intermediates can sometimes be achieved with ultrafast spectroscopic methods. For example, laser flash photolysis (LFP) of appropriate precursors, coupled with UV detection, allows the study of the energetics, dynamics, and reactivities of carbenes.<sup>3,18,19</sup> In some cases, the lifetimes of carbenes generated in inert rigid matrices at low temperature may be sufficiently long to allow the utilization of conventional detection techniques such as IR and UV-vis spectroscopy.<sup>3</sup> The paramagnetic nature of triplet carbenes permits their detection by electron spin resonance (ESR) spectroscopy; this technique may yield information on ground-state multiplicities and structures of carbenes isolated in frozen matrices.<sup>1,3,20</sup> As will be discussed throughout this thesis, however, the intermediacy of carbenes in chemical reactions is most often studied with chemical trapping methods, from which knowledge of carbene structure and reactivity can often be deduced.

## 1.3 Singlet vs Triplet Carbene Reactivity

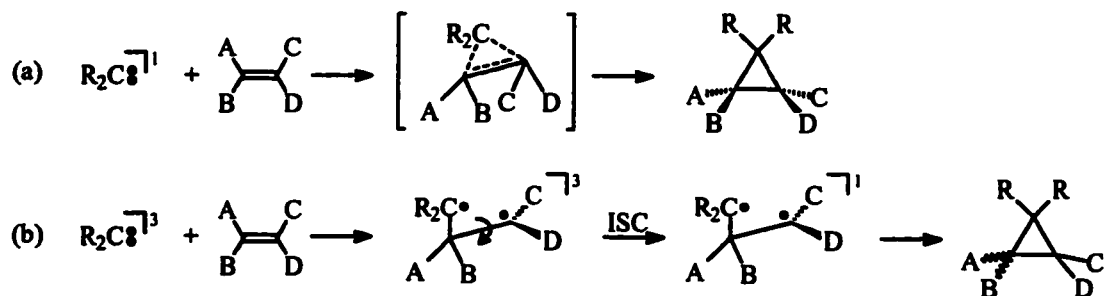
The chemistry of carbenes is strongly influenced by their multiplicity.<sup>2</sup> Triplet carbenes generally behave as free radicals, participating in stepwise reactions involving biradicals or radical pairs. In contrast, reactions of singlet carbenes are usually concerted. This is exemplified in Figure 4 with a comparison of the mechanisms of insertion into C-H bonds for singlet vs triplet carbenes. Retention of configuration is observed for concerted

insertions involving singlet carbenes, whereas stereochemical integrity of the substrate may be lost in reactions with triplet carbenes.



**Figure 4.** Typical mechanisms of insertion into a C-H bond: (a) concerted mechanism for a singlet carbene; (b) “hydrogen abstraction, recombination” mechanism for a triplet carbene.

Addition of a singlet carbene to an olefinic double bond also proceeds in a single step, so that the geometry of the reacting alkene is preserved in the resulting cyclopropane (Figure 5).<sup>i</sup> In contrast, concerted additions are not possible for triplet carbenes due to spin conservation requirements. *Cis-trans* isomerization can thus occur by bond rotations in the intermediate biradical, depending on the rate of spin inversion. This formed the basis for the generalization known as the Skell hypothesis (or Skell’s rule), which has been used for four decades as a chemical diagnosis of carbene state multiplicity.<sup>4,21,22</sup>



**Figure 5.** Typical mechanisms of addition of carbenes to alkenes: (a) concerted mechanism for a singlet carbene; (b) stepwise mechanism for a triplet carbene.

<sup>i</sup> Some additions involving nucleophilic carbenes may not be concerted, as discussed further.



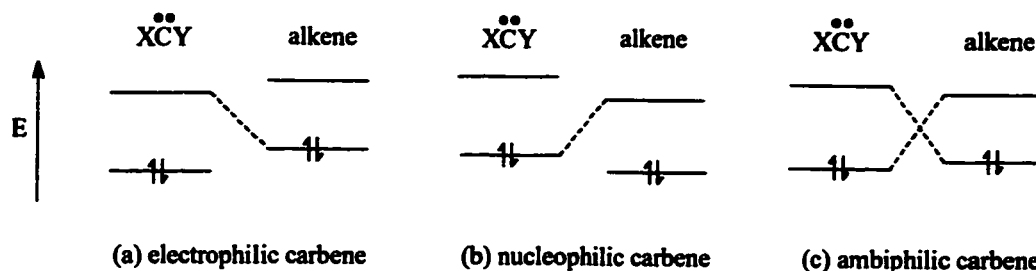
## 1.4 Electrophilic vs Nucleophilic Carbene Reactivity

The driving force behind carbene reactions in general is to seek electrons to complete the octet around the electron-deficient carbon. It is therefore expected that carbenes should behave as electrophiles, and react faster with electron-rich alkenes than with electron-deficient ones. Indeed, relative reactivity measurements carried out by Skell<sup>23</sup> and Doering<sup>24</sup> in the late 1950s demonstrated such electrophilic natures for both  $\text{CBr}_2$  and  $\text{CCl}_2$ . Since then, however, the selection of carbenes available has grown tremendously, and “philicity” in singlet carbenes now extends from the traditional electrophiles to the more unconventional ambiphiles and nucleophiles.

Moss and his co-workers have established a scale, the “carbene selectivity spectrum”, in which the position of a particular carbene reflects its philicity.<sup>25-27</sup> Carbenes are classified according to their selectivity index,  $m_{\text{CXY}}$ , which is a measure of their relative reactivities towards a standard set of alkenes (all of them electron-rich, to varying degrees). By definition,  $m_{\text{CXY}}$  for  $\text{CCl}_2$  is 1.00.  $\text{CF}_2$ , which is more selective (less electrophilic) than  $\text{CCl}_2$ , has an experimental  $m_{\text{CXY}}$  value of 1.48. Correlations of the dependence of  $m_{\text{CXY}}$  on  $\sigma_{\text{R}}^+$  and  $\sigma_{\text{I}}$  of carbene substituents allow estimates of  $m_{\text{CXY}}$  to be calculated for unknown carbenes or for those that are unreactive with the chosen set of alkenes. For instance, the calculated  $m_{\text{CXY}}$  values for  $(\text{MeO})_2\text{C}$  (**3**) and  $\text{MeOCN}(\text{Me})_2$  are 2.22 and 2.91, respectively. These values correspond to the nucleophilic end of the selectivity spectrum, and carbenes such as those react only with alkenes bearing electron-

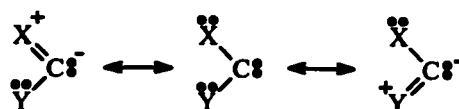
withdrawing groups,<sup>28</sup> and with other electrophilic substrates (Section 1.6).<sup>28-31</sup> In the middle of this spectrum come ambiphilic carbenes, such as MeOCCl ( $m_{\text{CXY}} = 1.59$ ), which react faster with both electron-rich and electron-deficient alkenes than with *trans*-2-butene.<sup>26</sup>

A basic understanding of Moss' selectivity spectrum can be acquired using a simple frontier molecular orbital (FMO) approach. With this model, in the addition of a singlet carbene to an alkene, one examines two simultaneous interactions: (1) that between the vacant carbenic p orbital (LUMO) and the filled  $\pi$  orbital (HOMO) of the alkene; and (2) that of the filled carbenic  $\sigma$  orbital (HOMO) and the empty  $\pi^*$  orbital (LUMO) of the alkene (Figure 6). Of these two interactions, the dominant one is the one for which the differential HOMO/LUMO energy is the smallest. For instance, in the reaction between an electrophilic carbene (*e.g.*  $\text{CCl}_2$ ) and an electron-rich alkene (*e.g.* tetramethylethylene), the  $\text{LUMO}_{\text{carbene}}/\text{HOMO}_{\text{alkene}}$  dominates (Figure 6(a)), so that the net electron transfer, in the transition state, is from the alkene to the carbene. In contrast, the  $\text{HOMO}_{\text{carbene}}/\text{LUMO}_{\text{alkene}}$  interaction prevails in the addition of the nucleophilic  $(\text{MeO})_2\text{C}$  (3) to an electron-deficient alkene such as dimethyl fumarate (Figure 6(b)); the carbene carbon therefore has a reduced charge density in the transition state. The reactivity of a given nucleophilic carbene will increase as the  $\pi^*$  orbital of the alkene is lowered, *i.e.* as the alkene becomes more electron-deficient. Finally, with comparable HOMO/LUMO differential energies (Figure 6(c)), ambiphilic reactivity is observed.



**Figure 6.** Schematic representation of FMO interactions in carbene + alkene cycloadditions.

It follows, from this FMO picture, that any factor which contributes to raise a carbene LUMO, such as  $\pi$ -donation by heteroatom substituents, will increase carbene stability, and concurrently augment nucleophilic character. The intrinsic need to acquire a complete valence is not as strong in nucleophilic carbenes, as expected from their dipolar character depicted in Figure 7. In the extreme, this stabilization results in stable, “bottle-able” carbenes (see Section 1.5.2).

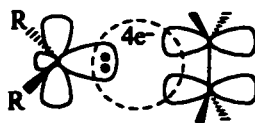


**Figure 7.** Representation of the dipolar character of nucleophilic carbenes.

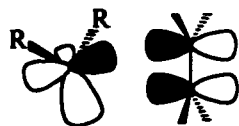
The simplified FMO approach presented above is supported by theoretical investigations. *Ab initio* calculations (4-31G // STO-3G) by Houk *et al.* on cycloadditions of carbenes to ethylene<sup>32</sup> have shown that these reactions follow the usual reactivity-selectivity principle.<sup>33</sup> Unselective, highly electrophilic carbenes have “early” transition states of low energy, whereas more stabilized nucleophilic carbenes have “late”, higher energy transition states and are more selective. Accordingly, the exothermicity of the

reactions decreases with increasing carbene nucleophilicity. A subsequent study (3-21G // STO-3G) by Moreno and co-workers, however, has shown that this trend may be reversed for highly nucleophilic carbenes.<sup>34</sup> This reinvestigation of carbene + ethylene cycloadditions has found a slightly lower barrier for diaminocarbene than for the less nucleophilic dihydroxycarbene, attributed to an important charge transfer from carbene to ethylene in the transition state.

The above-mentioned calculations<sup>32,34</sup> on those [1 + 2] cycloadditions also support the side-on mode of approach of the two reactants that was first proposed 40 years ago by Skell and Garner.<sup>23</sup> Direct synchronous approach, as shown in Figure 8(a), is forbidden by orbital symmetry, since an antiaromatic transition state with 4 electrons would result. Bonding interactions do occur, however, when the two substrates come together as shown in Figure 8(b,c). Both  $\text{HOMO}_{\text{alkene}}/\text{LUMO}_{\text{carbene}}$  and  $\text{HOMO}_{\text{carbene}}/\text{LUMO}_{\text{alkene}}$  interactions are favourable, in this case. Of these two, the dominant interaction (and therefore the geometry of the transition state) depends on the respective philicity in the carbene/alkene pair.



(a) forbidden direct approach

(b) HOMO<sub>alkene</sub>/LUMO<sub>carbene</sub>(c) HOMO<sub>carbene</sub>/LUMO<sub>alkene</sub>**Figure 8.** Modes of approach in carbene + alkene cycloadditions.

It has been recognized for decades that carbene reactivity spans an enormous range. The now famous description of methylene as “the most indiscriminate reagent known in organic chemistry” by W. von E. Doering<sup>35</sup> in 1956 contrasts with the unreactivity of dimethoxycarbene (3) with non-electrophilic alkenes.<sup>36</sup> What does this mean, however, in terms of absolute rates in bimolecular carbene reactions? The addition of singlet methylene to ethylene has no energy barrier,<sup>32,37</sup> and the rate should therefore be diffusion-controlled in solution. Time-resolved LFP has afforded the first absolute rate constants measured for bimolecular reactions of carbenes in solution. The accessible optical absorption of aryl carbenes makes them ideally suited for this technique. Rate data are now particularly abundant for the electrophilic arylhalocarbenes.<sup>19</sup> For example, the bimolecular rate constants for the additions of PhCCl to tetramethylethylene and to 1-hexene were measured as  $3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$  and  $2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ , respectively. In 1995, Moss *et al.* reported rate constants for additions of several ambiphilic carbenes to a series of

alkenes.<sup>38</sup> Combination of LFP measurements, to determine rate constants of addition to the electron-deficient chloroacrylonitrile, with relative rate data obtained by classical competitive methods, allowed them to derive rate constants for the relatively unreactive electron-rich alkenes. For example, the measured rate constant for addition of MeOCCl to chloroacrylonitrile,  $5.6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ , allowed a value to be derived for addition of the same carbene to *trans*-2-butene:  $330 \text{ M}^{-1} \text{ s}^{-1}$ . This rate constant represents the lowest value reported yet for any carbene + alkene addition in solution. The low yields associated with such reactions, where competitive carbene reactions such as dimerization become predominant, impose a practical limit to these rate constant determinations.

## 1.5 Synthesis of Nucleophilic Carbenes

The pioneering work of H.-W. Wanzlick, in the 1960s, marked the beginnings of the chemistry of nucleophilic carbenes.<sup>39</sup> The importance of these reactive intermediates is exemplified, for instance, in the mechanism of action of thiamine (vitamin B<sub>1</sub>, an aminothiocarbene in its deprotonated form) first described by Breslow.<sup>40</sup> Since those early days, nucleophilic carbenes have attracted the interest of an ever-growing number of scientists. The following sections briefly summarize some of the progress achieved in this field over the past 35 years. Because of the prominence of dioxycarbenes, and of the general applicability of their reaction mechanisms to other nucleophilic carbenes, they are discussed first. This brief review is restricted mostly to precursors that generate nucleophilic carbenes in solution with useful yields.

### 1.5.1 Dioxycarbenes

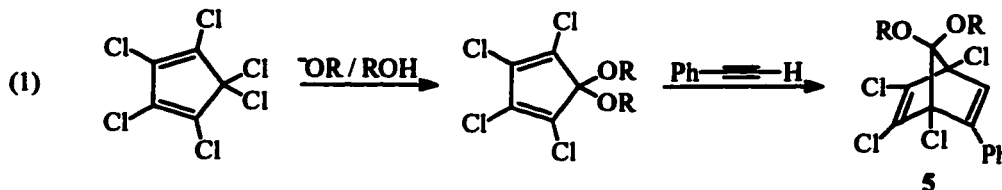
#### 1.5.1.1 *Classical Methods of Generation*

Classically, the most useful methods of generation of dioxycarbenes are based on the formal extrusion of the carbene by cycloreversion from rings made of an odd number of atoms. These processes are generally driven by the formation of thermodynamically stable products such as N<sub>2</sub> or aromatic compounds, and usually only work for the relatively stable nucleophilic carbenes. In 1964, Lemal and co-workers<sup>41</sup> and Hoffmann and Häuser<sup>42</sup> independently established norbornadienone ketals (see 5) as the first convenient sources of dialkoxycarbenes. This method, which involves thermolysis of these cyclic ketals at temperatures of 85-200 °C, has permitted the synthesis of a number of dioxycarbenes (RO)<sub>2</sub>C (R is an alkyl, benzyl, or aryl group), as well as other nucleophilic carbenes which will be discussed in the following sections.

A synthesis for the most common norbornadienone ketals 5 is illustrated in eq. 1. A serious limitation results as a consequence of the initial synthetic step: only symmetrical carbenes can be generated since the two R substituents in the ketal must be the same. In addition, the instability of cyclopentadienone and of its ketal derivatives towards dimerization dictates the use of the tetrachloro derivative<sup>i</sup> in the Diels-Alder reaction with the alkyne (most often phenylacetylene, as shown). Direct ketalization of norbornadienones, as an alternative synthetic route, is not viable due to the instability of those ketones.

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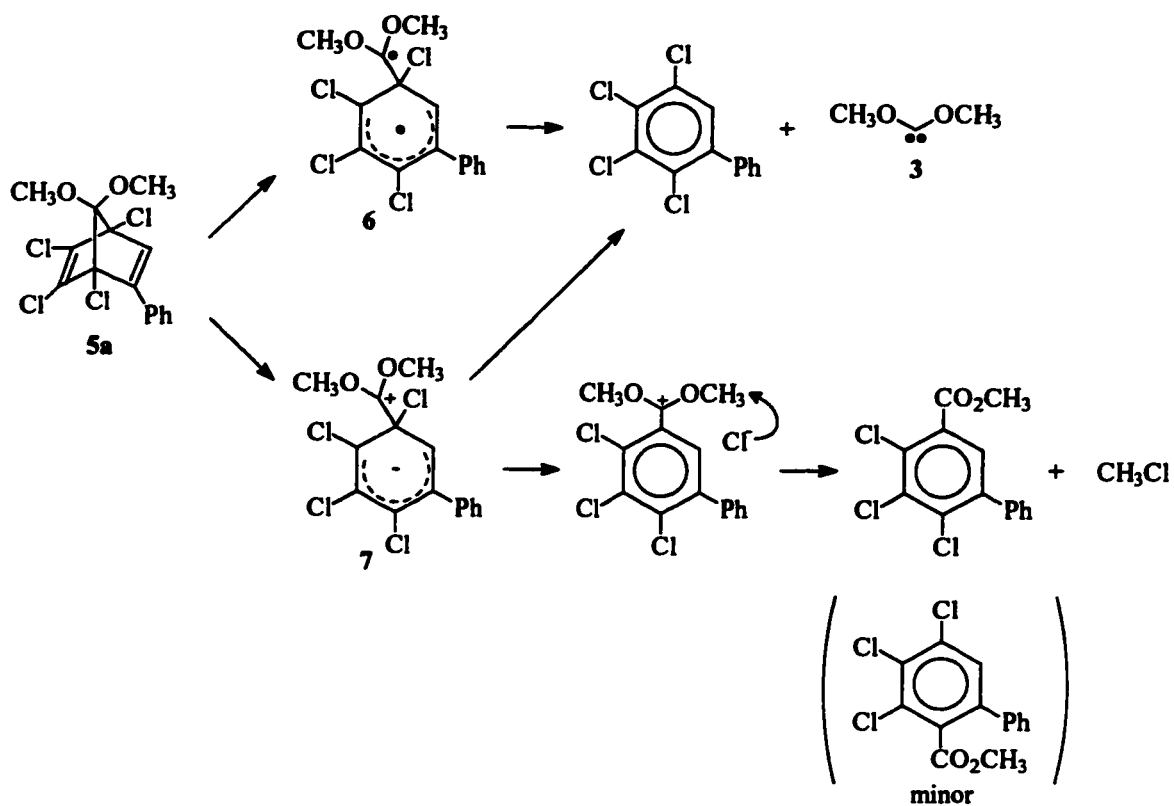
<sup>i</sup> Tetrachlorinated 5a has been the most common choice for routine generation of dimethoxycarbene (3), for instance, but non-chlorinated analogues have also been used.



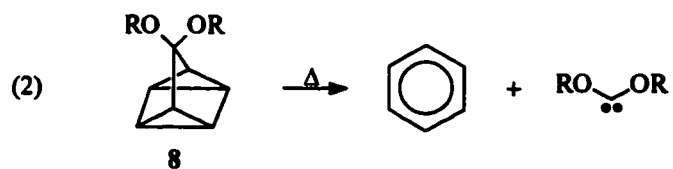
Mechanistic aspects of the thermal decomposition of compounds **5** have been investigated.<sup>36,43,44</sup> As shown in Scheme I for the 7,7-dimethoxy derivative **5a**, products from two competing pathways generally result. Although a symmetry-allowed chelotropic reaction is conceivable for the extrusion of dimethoxycarbene, **3**, stepwise processes are believed to take place, involving either diradical (**6**) or ionic (**7**) intermediates, the latter being favoured at least in the case of non-chlorinated 7,7-dioxynorbornadienes. The purification of carbene-derived products is obviously complicated by the co-formation of the biphenyl, as well as by the occurrence of the thermolysis pathway leading to the esters.



Scheme I

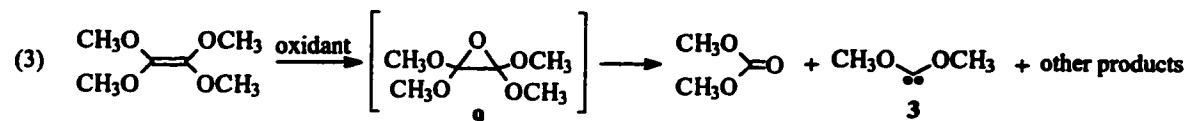


The related quadricyclanone ketals **8** have also been utilized to generate dialkoxycarbenes and other nucleophilic carbenes (eq. 2).<sup>45</sup>

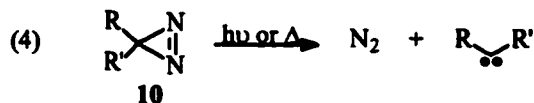


Some three-membered heterocycles are also sources of dioxycarbenes. Tetramethoxyoxirane (**9**), for instance, a possible intermediate in the oxidation of tetramethoxyethylene, was postulated to decompose to dimethoxycarbene (**3**) and

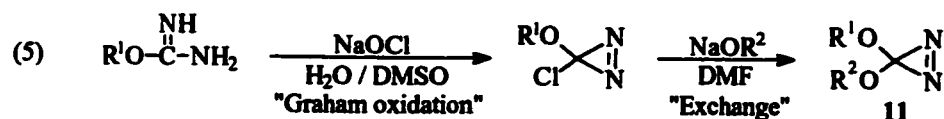
dimethyl carbonate (eq. 3; see also Section 2.1).<sup>43,46</sup> Electrocyclic ring opening of oxiranes lead to carbonyl ylides<sup>47,48</sup> and the latter are potential precursors of carbenes (Section 1.5.1.2); however, oxiranes have not found widespread use in the generation of dioxycarbenes.



Diazirines **10** are well-established sources of carbenes.<sup>2,9</sup> They have the advantage of yielding carbenes not only thermally, but also photochemically, with innocuous molecular nitrogen as the only by-product (eq. 4). In 1987, Moss *et al.* reported the synthesis of the first diazirine precursor to a dioxycarbene, namely 3-methoxy-3-phenoxydiazirine (**11**, R<sup>1</sup> = Me, R<sup>2</sup> = Ph), via the "diazirine exchange reaction" shown in eq. 5.<sup>49</sup> The few other dioxycarbenes so far generated from diazirines include dimethoxycarbene (**3**),<sup>11</sup> as well as methoxy(trifluoroethoxy)carbene and bis-(trifluoroethoxy)carbene.<sup>50</sup> Despite their relative rareness due in part to their thermal instability,<sup>i</sup> 3,3-dioxydiazirines have assumed an important role in providing the first opportunities for direct observation of dioxycarbenes.

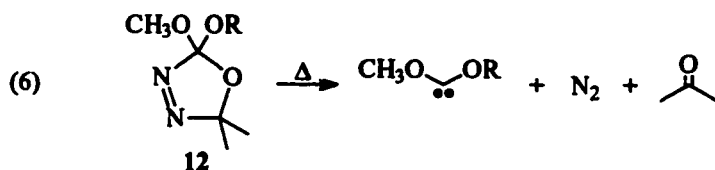


<sup>i</sup> Typical lifetimes for 3,3-dioxydiazirines in pentane are on the order of 20-60 min, at 25 °C.<sup>27</sup>



### 1.5.1.2 Thermolysis of Oxadiazolines

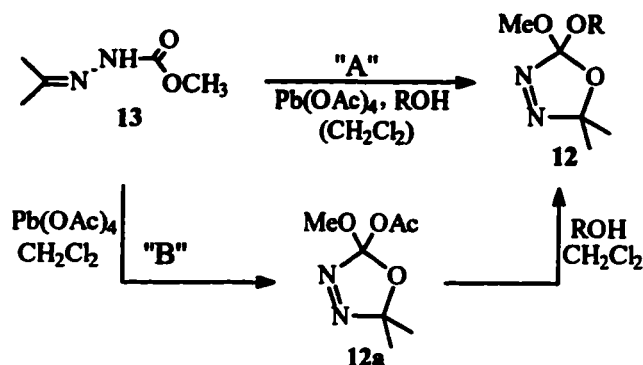
In 1992, J. Warkentin *et al.* introduced a novel and promising method of generation of dioxycarbenes from thermolysis (*ca.* 100 °C) of 2,2-dioxy- $\Delta^3$ -1,3,4-oxadiazolines **12** (eq. 6);<sup>51</sup> this discovery stemmed from previous studies on related systems.<sup>i</sup>



Oxadiazolines **12** were prepared by the oxidative cyclization of the (methoxycarbonyl)hydrazone of acetone, **13**, with  $\text{Pb}(\text{OAc})_4$  in alcohol ROH or in dichloromethane containing the alcohol (route A in Scheme II). This method suffered the disadvantage of not allowing the use of easily-oxidized hydroxyl compounds such as phenols. Thus, an alternative and more widely applicable preparation, involving exchange of the acetoxy substituent of **12a** with alcohols or phenols, was developed (route B, Scheme II).<sup>52</sup>

<sup>i</sup> Closely related were the studies of Békhazi and Warkentin on monoalkoxy oxadiazolines<sup>54-58,211</sup> and of Zoghbi and Warkentin on spiro-fused  $\beta$ -lactam oxadiazolines,<sup>144,189,191,212-214</sup> for instance.

Scheme II

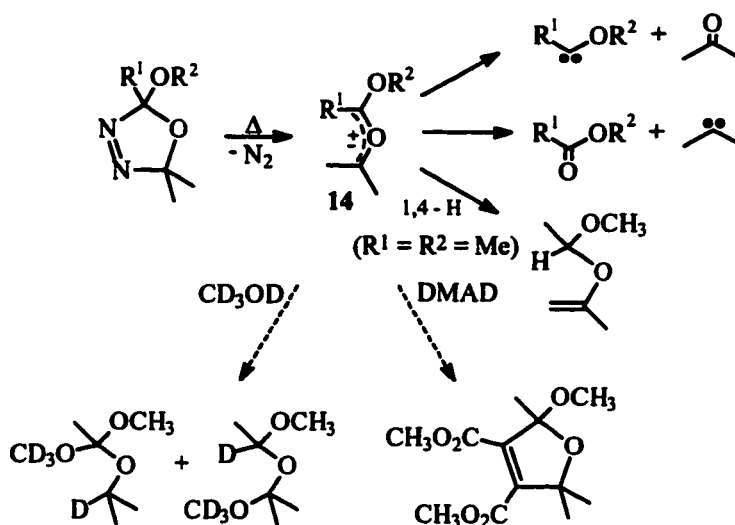


The advantages of 2,2-dioxy- $\Delta^3$ -1,3,4-oxadiazolines **12**, over the few other established thermal precursors of dioxycarbenes, are considerable. In contrast to 3,3-dioxydiazirines **11**, they are shelf-stable and can be conveniently handled and stored as neat compounds. In addition, appropriate substitution of the oxadiazoline ring results in thermolysates containing only volatile by-products that are easily separated from the desired carbene-derived products. As will become obvious in the following sections, the versatility of the "oxadiazoline method" has already greatly contributed to the field of carbene chemistry, by giving access to a wide range of diheteroatom-substituted carbenes in synthetically useful quantities.

The mechanism of thermolysis of oxadiazolines, resulting in the extrusion of carbenes, has been described in terms of successive fragmentations, rather than as a single-step process.<sup>51,53-60</sup> As shown in Scheme III, an initial orbital-symmetry-allowed 1,3-dipolar cycloreversion liberates  $\text{N}_2$  and produces a carbonyl ylide (**14**) as an intermediate. In the case of 2-alkyl-2-alkoxy oxadiazolines, products clearly derived from carbonyl

ylides have been identified, thus proving the intermediacy of such species; for example, carbonyl ylide **14** ( $R^1 = R^2 = \text{Me}$ ) from thermolysis of 2-methoxy-2,5,5-trimethyl- $\Delta^3$ -1,3,4-oxadiazoline, has been trapped with methanol and with dipolarophiles such as dimethyl acetylenedicarboxylate (DMAD), in competition with an intramolecular 1,4-H migration and with fragmentation to carbonyl compounds and carbenes (Scheme III).<sup>54,56</sup>

Scheme III



The thermolysis mechanism is more ambiguous, however, for 2,2-dioxy oxadiazolines. The postulate of a stepwise mechanism, in this case, has rested mostly on the analogy to the monoalkoxy system, since trapping of dialkoxy carbonyl ylides has not been observed,<sup>i</sup> presumably due to the comparatively short lifetimes of these ylides for which fragmentation to the stabilized dioxycarbenes is energetically more favourable.<sup>48</sup>

<sup>i</sup>An apparent carbonyl ylide-derived product was isolated from the thermolysis of 2-(2-hydroxyphenoxy)-2-methoxy-5,5-dimethyl- $\Delta^3$ -1,3,4-oxadiazoline (**86g**, see Section 2.1).<sup>133</sup>

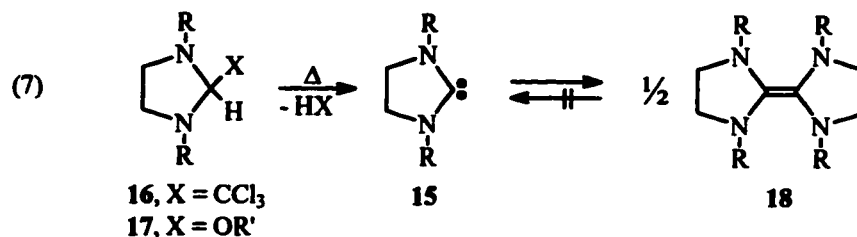
Recently, the proposed stepwise decomposition mechanism has been challenged. W. B. Smith performed *ab initio* calculations<sup>61</sup> which indicated that extrusion of N<sub>2</sub> and dialkoxycarbene from a 2-(3-butyn-1-oxy)-2-methoxy oxadiazoline<sup>62</sup> may be a concerted process, avoiding a carbonyl ylide intermediate altogether. While those computational results pertain to only one oxadiazoline, they imply that concerted decomposition may generally apply to 2,2-dioxy oxadiazolines. New experimental evidence for the stepwise decomposition of 2-aryloxy-2-methoxy oxadiazolines has recently been obtained;<sup>63</sup> it is presented in Chapter 2.

According to *ab initio* calculations performed by Houk *et al.*,<sup>48</sup> thermal fragmentation of a carbonyl ylide from a coplanar ground state is a disallowed process; however, donor substituents on the carbonyl ylide lower the barrier to rotation so that a nonplanar state is probably accessible, in the case of monooxy- and dioxy-substituted carbonyl ylides.

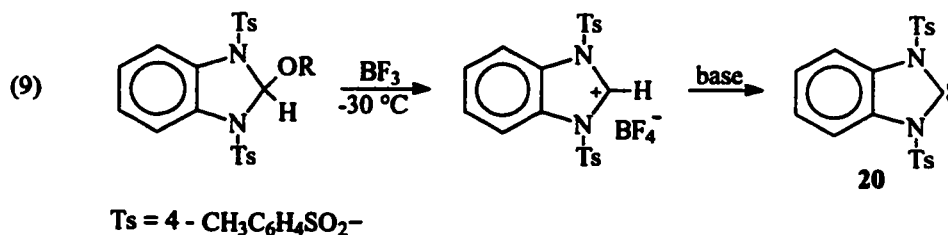
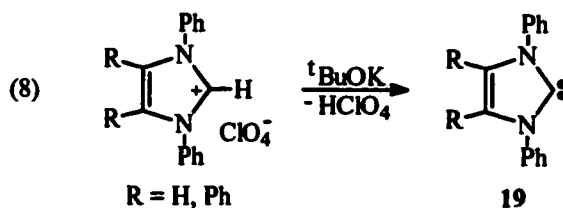
### 1.5.2 Diaminocarbenes

In the 1960s, H.-W. Wanzlick and his co-workers showed that imidazolin-2-ylidenes **15** could be produced by thermal elimination of CHCl<sub>3</sub> from **16** or of R'OH from **17** (eq. 7).<sup>39</sup> At the time, diaminocarbenes **15** were thought to exist in equilibrium with tetraaminoalkenes **18** at high temperature (*ca.* 150 °C), but this hypothetical dissociation of **18** was refuted by Lemal *et al.*, who found no crossover products when a mixture of

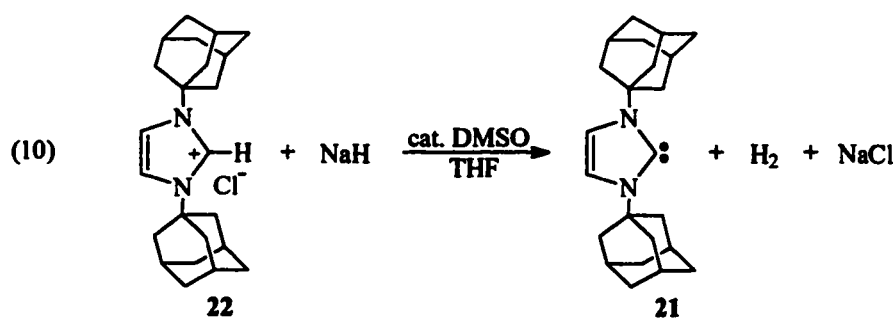
two carbene dimers **18** bearing different N-substituents were heated under reflux in xylene for 2 h.<sup>64</sup>



A few years later, continuing his investigation of the chemistry of nucleophilic carbenes, Wanzlick's group reported the synthesis of imidazol-2-ylidenes **19**, the unsaturated analogues of **15**, by deprotonation of the corresponding salts with strong bases such as *tert*-butoxide (eq. 8).<sup>65,66</sup> Around the same period, a similar method was used by G. Scherowski for the generation of 1,3-benzimidazol-2-ylidene **20**, as shown in eq. 9.<sup>67</sup>



In a 1962 article, Wanzlick wrote:<sup>39</sup> “How can stability be improved beyond the degree achieved in carbene [19]? [...] The aromatic system has a great potential for enhancing resonance stability. Inclusion of the carbene carbon atom into a quasi-aromatic system was expected to result in a very efficient stabilization.” Despite this explicit recognition of the potentially high stability of imidazol-2-ylidenes, almost 30 years had passed when, in 1991, A. J. Arduengo, III, and his co-workers had the honour of reporting the isolation of the first stable (“bottle-able”) carbene.<sup>68</sup> Thus, **21** was obtained as colourless crystals (Mp 240-241 °C) from the deprotonation of 1,3-di-1-adamantylimidazolium chloride (**22**) with sodium hydride and a catalytic amount of dimethyl sulfoxide (DMSO) in THF (eq. 10). Carbene **21** was found to be stable in the absence of oxygen and moisture.

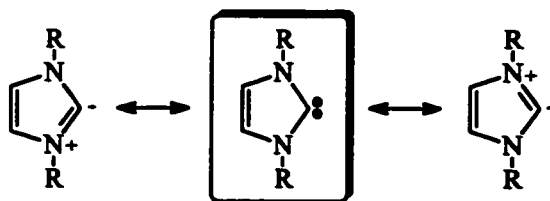


Since Arduengo's original report, several new stable diaminocarbenes have been prepared.<sup>i</sup> At the same time, researchers have attempted, through both experimental and theoretical studies, to determine the origin of their stability. Of fundamental importance is the question of the real nature of these species: are they true carbenes, or are they more

<sup>i</sup> See Arduengo *et al.*,<sup>71</sup> and references cited therein.

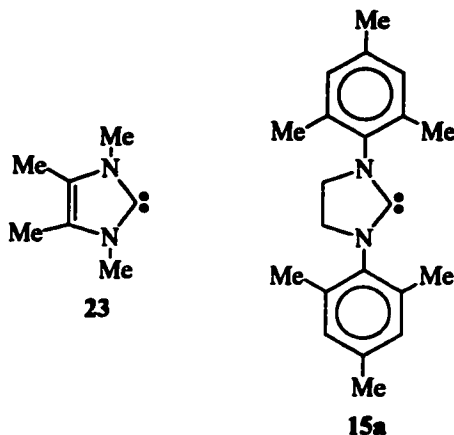


adequately represented as ylides (Figure 9)? The answer to this question was obtained from extended basis set *ab initio* SCF calculations, carried out by Dixon and Arduengo, which showed only a small negative charge at C2 for the non-substituted imidazol-2-ylidene (4), a result consistent with a carbene structure.<sup>12</sup> Electron-density measurements obtained from neutron and X-ray diffraction experiments on a related imidazol-2-ylidene confirmed this verdict.<sup>69</sup>



**Figure 9.** The carbenic resonance structure is dominant, in imidazol-2-ylidenes.

Originally, two structural features of **21** were regarded as essential to its exceptional stability: the unsaturation at C4-C5 (thermodynamic effect), and the bulky N-substituents (kinetic effect). Those ideas, however, were soon proven wrong, with the isolation of the tetramethyl compound **23** in 1992,<sup>70</sup> and of the first stable saturated analogue, **15a**, in 1995.<sup>71</sup>



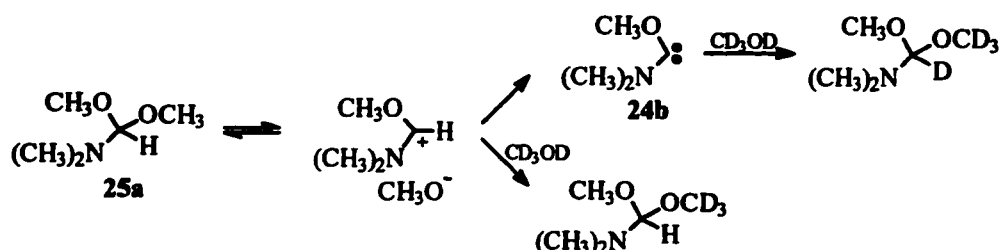
The concept of aromaticity in imidazol-2-ylidenes has been investigated by theoretical methods. Both Schwarz *et al.*<sup>72</sup> (1996) and Boehme and Frenking<sup>73</sup> (1996) came to the conclusion, using high-level *ab initio* methods as well as the theory of “atoms-in-molecules”,<sup>74</sup> that some cyclic electron delocalization occurs, although it is less pronounced than in benzene or in the imidazolium cation, for example. In contrast, Arduengo *et al.* had found, in a study published in 1994, no significant role for  $\pi$  delocalization in these carbenes;<sup>69</sup> this, combined with the fact that the estimated  $\Delta H_{298}$  for dimerization of these carbenes is close to zero,<sup>69,75</sup> had led those authors to attribute this stability to kinetic, rather than thermodynamic, factors.

### 1.5.3 Aminooxycarbenes

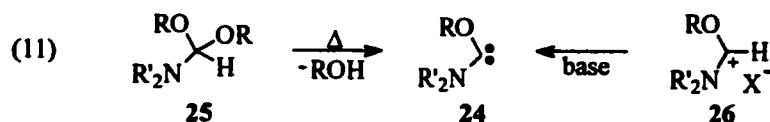
Relatively little has been published about free carbenes with one oxygen and one nitrogen alpha to the carbene centre.<sup>31,32,76-88</sup> In a 1971 communication, Brown and Place postulated the intermediacy of dimethylamino(methoxy)carbene, **24b**, to account for the

methine hydrogen exchange reaction of dimethylformamide dimethyl acetal (**25a**) with  $\text{CD}_3\text{OD}$ , as illustrated in Scheme IV.<sup>87</sup>

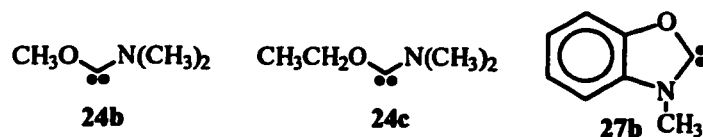
Scheme IV



Before this thesis work was undertaken, aminooxycarbenes (**24**) had been generated, in solution, either from the thermal decomposition of amide acetals (**25**) or by deprotonation of oxazolium ions (**26**, eq. 11). The former method has found a synthetic application in the conversion of allylic alcohols to  $\beta,\gamma$ -unsaturated amides,<sup>81-83</sup> a reaction discussed in Section 1.6.1.4. To our knowledge, only three other aminooxycarbenes have been unambiguously generated in solution and trapped by intermolecular reactions;<sup>i</sup> they are shown in Figure 10.

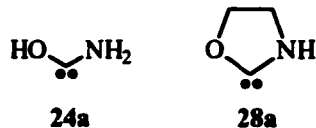


<sup>i</sup> An amino(lithioxy)carbene,  $\text{LiO}-\text{C}-\text{NH}^t\text{Bu}$ , has been postulated in the reaction of carbon monoxide with lithium *tert*-butylamide.<sup>88</sup>



**Figure 10.** Aminooxycarbenes generated in solution; **24b**: Reiffen and Hoffmann, 1977;<sup>31</sup> **24c**: Seitz *et al.*, 1991,<sup>84</sup> 1992;<sup>85</sup> **27b**: Wanzlick and Steinmaus, 1968.<sup>86</sup>

The parent carbene, aminohydroxycarbene (**24a**),<sup>77</sup> and oxazolidin-2-ylidene (**28a**)<sup>76</sup> have both been generated in the gas phase and studied by mass spectrometry (Section 1.6.1). Although our current interests lie mainly in the field of metal-free carbenes, it should be mentioned that several aminooxycarbenoids have been reported. Carbene **28a**, for instance, which is the prototype of a series of carbenes studied in the present work has been complexed<sup>i</sup> with Pd,<sup>89</sup> Pt,<sup>89-92</sup> Fe,<sup>93</sup> and Mg.<sup>93</sup>



## 1.6 Chemistry of Nucleophilic Carbenes

### 1.6.1 Intramolecular Reactions

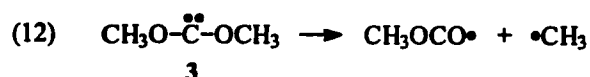
Although we wish to place greater emphasis on the solution chemistry of nucleophilic carbenes, some important unimolecular reactions that occur in the gas phase are also discussed.

<sup>i</sup> This list of references is not exhaustive.

Terlouw and co-workers have generated a variety of carbenes, such as diaminocarbene (29),<sup>94</sup> oxazolidin-2-ylidene (28a),<sup>76</sup> and some dialkoxycarbenes,<sup>76,95</sup> in the dilute gas phase of a mass spectrometer, which is ideally suited for the study of such reactive species because of the low probability of intermolecular processes. These investigations often involve two different techniques: neutralization-reionization mass spectrometry (NRMS), and very low vapour pressure (VLVP) pyrolysis experiments. In NR experiments, a radical cation produced by the dissociative electron impact ionization (EI) of an appropriate carbene precursor is neutralized by a single electron transfer; this reduction occurs by collision of the ion with a reducing agent such as N,N-dimethylaniline. The carbenes thus produced are then reionized with O<sub>2</sub> in a second collision chamber, and the mass spectrum of these “survivor ions” and their charged dissociation products is observed. Alternatively, collisional activation (CA) spectra of the survivor ions can be obtained by colliding them with He in a third chamber of the spectrometer. One requirement of the NR method is carbene stability with respect to dissociation and isomerization, on the time scale of the experiment ( $\mu$ s). Even in the case of unstable carbenes, however, useful information concerning the decomposition pathways can sometimes be inferred from the observed products. The second approach used in these studies consists of generating the carbene by pyrolysis of the precursor molecule inside the mass spectrometer. MS data from the ionized carbene and other charged species provide valuable information, which is complementary to that obtained from NR experiments, concerning carbene stability and isomerization processes.

### 1.6.1.1 Fragmentations to Radicals

Dioxycarbenes generated by NRMS experiments are sometimes unstable with respect to dissociation. Dimethoxycarbene (3) was found by Terlouw *et al.* to be stable under their experimental conditions, although some dissociation, as shown in eq. 12, was observed.<sup>76</sup> This reaction, estimated from enthalpies of formation to be endothermic by *ca.* 56 kcal/mol, was suggested to occur for some energy-rich carbenes produced by the neutralization process. Under similar conditions, methoxy-(2,2,2-trifluoroethoxy)carbene undergoes complete dissociation.<sup>95</sup>



### 1.6.1.2 1,2 Migrations

1,2 Migrations undoubtedly constitute the most common type of carbenic rearrangements. The usual order of migratory ability holds, *i.e.* H > aryl > alkyl.<sup>96</sup> The low activation barrier to isomerisation of alkylcarbenes by 1,2-H shifts usually prevents bimolecular reactions for the free carbenes; for example, Evanseck and Houk predicted, from theoretical calculations, a barrier of only 0.6 kcal/mol for the rearrangement of methylcarbene to ethylene.<sup>97</sup>

1,2 Shifts, at least those involving hydrogen, are generally thought to involve movement of the migrating group with its pair of electrons to the formally vacant carbenic

p orbital; this requires coplanarity of the orbitals implicated on the way to the transition state, as shown in Figure 11 for a hydride shift. We also note that the p orbital of dioxycarbenes and related species is not really vacant, due to  $\pi$ -donation by the heteroatoms (see Figure 3), and this explains in part the higher barriers to 1,2 shifts in these nucleophilic carbenes, as discussed below. In addition, the energy cost to twist the molecule from the planar ground state to the required geometry may be significant.<sup>i</sup>

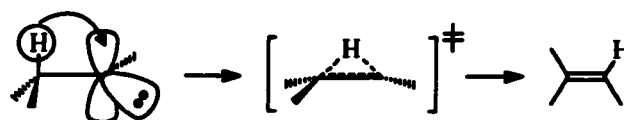


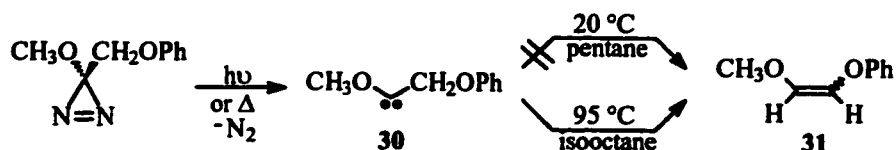
Figure 11. 1,2-H Migration in a generalized singlet carbene.

Intuitively, based on the nucleophilic nature of the rearrangement, one would expect that the presence of either an electron-donating group at the migration origin, or of an electron-withdrawing substituent at the migrating terminus, should cause a decrease in the activation barrier. This substituent effect is in fact observed, both in theoretical and experimental studies. For instance, the calculated activation energy for 1,2-H shift in  $\text{CH}_3\text{-C-X}$  was found to correlate with the  $\pi$ -electron-donating ability of X (kcal/mol):  $\text{H} (0.6) < \text{Cl} (11.5) < \text{F} (19) < \text{trans-OMe} (27)$ .<sup>97</sup> Thus the presence of a heteroatom at the carbene centre can considerably retard the rate of 1,2 migration and, in the extreme, the 1,2-H shift can be effectively stopped. Moss and co-workers, for instance, have found that methoxy(phenoxymethyl)carbene (**30**), generated at 20 °C by photolysis or

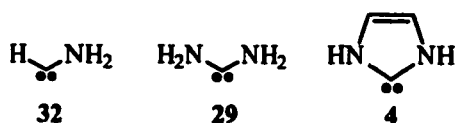
<sup>i</sup> The related barrier for isomerization of the all-*trans* to the *cis-trans* conformation of dimethoxycarbene (**3**) has been calculated from *ab initio* methods to be 15.8 kcal/mol.<sup>11</sup>

thermolysis of the diazirine precursor, does not produce detectable amounts of alkene **31**; thermal activation, however, is possible and 1,2-H shift is observed when the same carbene is generated at 95 °C (Scheme V).<sup>98</sup>

Scheme V



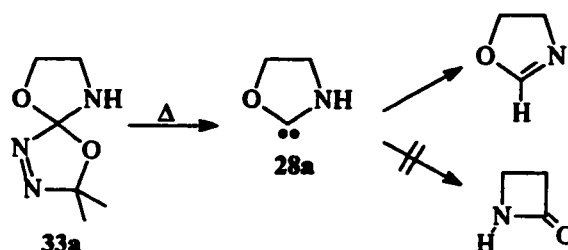
1,2 Migrations in nucleophilic carbenes are seldom observed because of their apparently high activation energies. Aminocarbene (**32**), diaminocarbene (**29**), and imidazol-2-ylidene (**4**) all have  $\Delta E_{\text{act}}$  values of more than 45 kcal/mol, according to *ab initio* calculations (TZ2P basis set) performed by Heinemann and Thiel.<sup>75</sup>



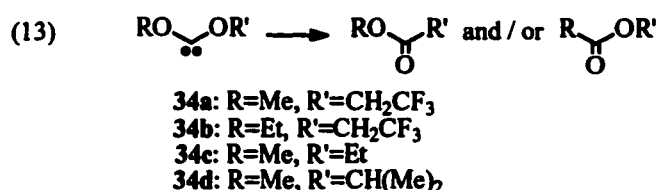
Hydrogen migration from N to C has been observed for oxazolidin-2-ylidene (**28a**) generated in VLVP pyrolysis MS experiments from oxadiazoline **33a** at temperatures between 280-530 °C; the alternative 1,2-alkyl migration to 2-azetidinone was not observed (Scheme VI).<sup>76</sup> Carbene **28a**, however, was a viable species when generated at lower temperature in NRMS experiments, indicating a substantial activation energy for the hydrogen shift.



## Scheme VI



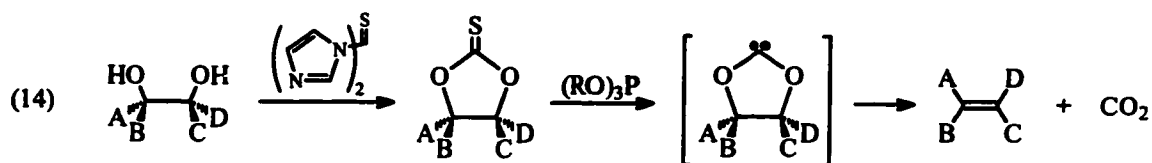
1,2-Alkyl migrations in dialkoxycarbenes **34** were also studied by VLVP pyrolysis mass spectrometry.<sup>95</sup> Carbenes **34a** and **34b** rearranged exclusively by migration of the  $\text{CH}_2\text{CF}_3$  group, while **34c** and **34d** showed a slight preference for ethyl or isopropyl (vs methyl) transfer (eq. 13). The relatively facile  $\text{CH}_2\text{CF}_3$  migration is consistent with the above model in which the migrating group keeps the electron pair, the transition state being stabilized by the electron-withdrawing  $\text{CF}_3$  group. The slightly greater migratory aptitude of ethyl and isopropyl relative to methyl was rationalized in terms of the greater polarizability of the former two substituents.



### 1.6.1.3 Fragmentation of Cyclic Carbenes

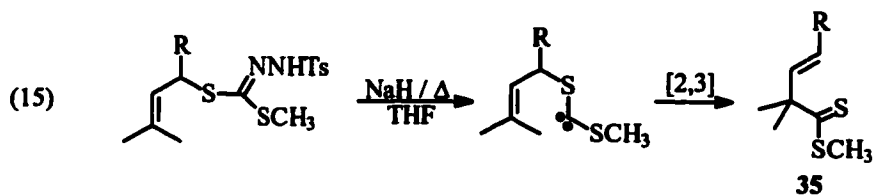
A synthetically important reaction involving dioxycarbenes is the famous Corey-Winter stereospecific conversion of diols to alkenes.<sup>99,100</sup> The key step of this reaction is

the thermal fragmentation of an intermediate cyclic dioxycarbene,<sup>101</sup> formed by desulfurization of a thionocarbonate, to CO<sub>2</sub> and the alkene (eq. 14). Several variations of this reaction, where dioxycarbenes are probably also involved, have been developed, such as eliminations from orthoesters<sup>102,103</sup> and amide acetals.<sup>104,105</sup> The fragmentation of cyclic carbenes is not restricted to dioxycarbenes: 5-membered rings with heteroatoms such as S and N may also fragment thermally. This reaction is discussed in more detail in Section 2.3.2.

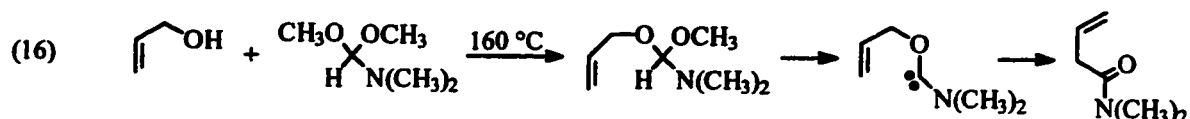


#### 1.6.1.4 [2,3]-Sigmatropic Rearrangements

In 1972, Baldwin and Walker reported a new intramolecular reaction for dithiocarbenes possessing an allylic substituent, namely the [2,3]-sigmatropic rearrangement, as shown in eq. 15.<sup>106</sup> A few years later, Nakai and Mikami reported a high degree of stereoselectivity in those rearrangements, favouring the *trans* geometry of the newly formed double bond in **35** (R = Me or Si(Me)<sub>3</sub>).<sup>81</sup>

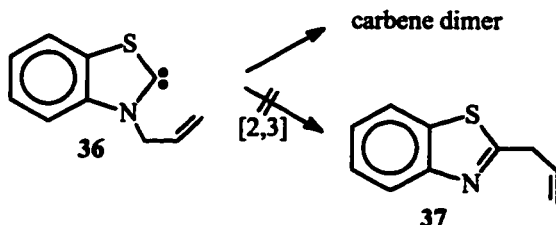


[2,3]-Sigmatropic rearrangements of aminooxycarbenes have also been used for the conversion of allylic alcohols to  $\beta,\gamma$ -unsaturated amides.<sup>81-83</sup> This sequence involves exchange of a methoxy group from the acetal of N,N-dimethylformamide with the alcohol, followed by *in situ* generation of the carbene, as shown in eq. 16 for allyl alcohol.



Interestingly, generation of N-allylbenzothiazol-2-ylidene **36** gave exclusively a carbene dimer (of unknown geometry), with no apparent formation of **37** (Scheme VII).<sup>107</sup>

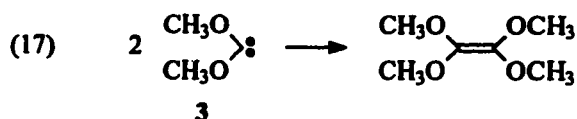
Scheme VII



## 1.6.2 Intermolecular Reactions

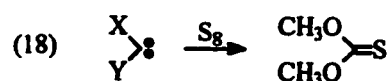
### 1.6.2.1 Miscellaneous Reactions

A reaction common to most nucleophilic carbenes is dimerization. For instance, the dimerization of dimethoxycarbene (**3**) to tetramethoxyethylene, eq. 17, was reported by Lemal *et al.* in 1964.<sup>41</sup>

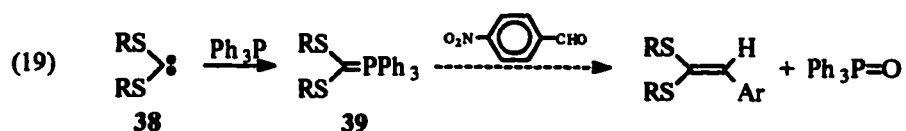


The stability of some diaminocarbenes was discussed earlier (Section 1.5.2). Their reluctance to dimerize constitutes an exception, probably attributable to a combination of kinetic and thermodynamic factors.

Reactions between  $S_8$  and dithio-,<sup>108</sup> aminothio-,<sup>109</sup> and aminooxycarbenes<sup>31</sup> have been observed to yield thioxo compounds, as shown in generalized form in eq. 18. An analogous reaction between a dithiocarbene and elemental Se, producing a selenoxo derivative, has also been reported.<sup>108</sup>

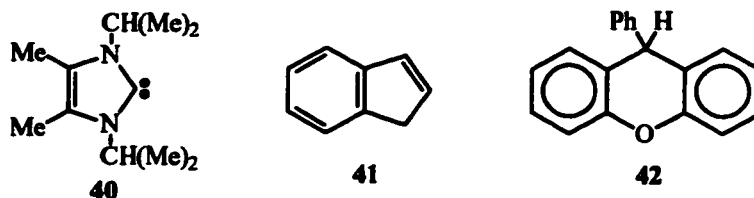


Dithiocarbenes **38** have been intercepted by triphenylphosphine (eq. 19).<sup>110</sup> Ylides **39** were not isolated but were converted, in a Wittig-type reaction with 4-nitrobenzaldehyde, to the dithioalkenes, with overall yields of 64% (R = Me) and 71% (R = Et).

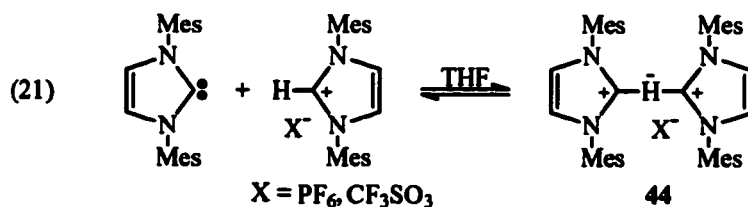
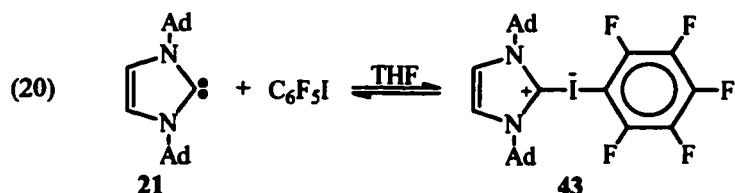


The basicity of imidazol-2-ylidene **40** has recently been examined by Alder *et al.*, who reported a  $pK_a$  (conjugate acid) of 24 in  $(CD_3)_2SO$ .<sup>111</sup> In the same solvent, **40** was found to deprotonate indene completely (**41**,  $pK_a$  20.1), while 9-phenylxanthene (**42**,  $pK_a$  27.7) was not converted to its anion to a measurable extent. In order to evaluate the

potential of diaminocarbenes for use as strong bases in synthetic applications, reactions of **40** with primary and secondary haloalkanes were carried out, with the result that substitution was favoured over elimination, indicating a relatively high nucleophilicity.



The nucleophilicity and basicity of related diaminocarbenes is also apparent from their ylide-forming reactions with pentafluoriodobenzene<sup>112</sup> (eq. 20) and with their precursor imidazolium ions<sup>113</sup> (eq. 21). Ylides **43** and **44** are both isolable, stable solids.



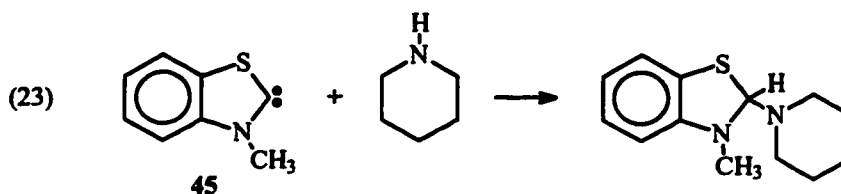
#### 1.6.2.2 Insertions into X-H Bonds

Nucleophilic carbenes do not generally insert into C-H bonds, although reactions have been observed with activated methylene compounds such as 1,3-diones, as discussed

further (Section 2.4.4). In contrast, insertions into O-H bonds are common, and alcohols and phenols are often used as chemical traps to provide evidence for the intermediacy of carbenes in a given reaction (eq. 22). A variety of nucleophilic carbenes have been reported to undergo such insertions into hydroxyl compounds, including dioxy-,<sup>11,51,114,115</sup> diamino-,<sup>116</sup> and aminothiocarbenes.<sup>109</sup>



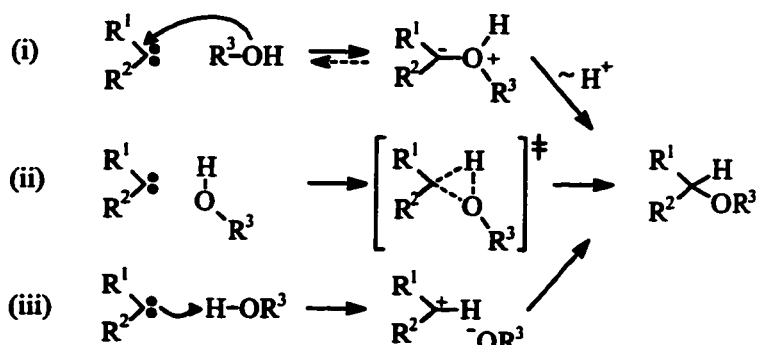
Analogous insertions into NH bonds have also been reported, for example in the reaction of a benzothiazol-2-ylidene **45** with piperidine (eq. 23).<sup>117</sup>



Three mechanisms are usually considered for the formal insertions of singlet carbenes into O-H bonds:<sup>7</sup> (i) attack of the divalent carbon at oxygen, involving interaction of the carbene LUMO with the alcohol HOMO (the non-bonding electrons on oxygen), resulting in the formation of an intermediate ylide, followed by proton transfer; (ii) concerted insertion *via* a three-membered transition state; and (iii) proton abstraction by the carbene followed by collapse of the resulting ion pair (Scheme VIII). The nature of the carbene appears to be the determining factor in dictating the path followed, with

electrophilic carbenes reacting by mechanisms (i) or (ii), and nucleophilic carbenes *via* (ii) or (iii).

**Scheme VIII**



LFP methods have been used to measure rate constants for reactions of a variety of carbenes with methanol and other hydroxyl compounds. In these experiments, a carbene is generated in an inert solvent such as pentane, usually by photolysis of a diazirine precursor, and its decay is monitored by UV spectroscopy.<sup>i</sup> The absolute bimolecular rate constant ( $k_{\text{abs}}$ ) for reaction of the carbene with a given hydroxyl compound is obtained from the plot of the observed pseudo first-order rate constants for decay of the carbene as a function of ROH concentration. Some  $k_{\text{abs}}$  values for reactions of a few related carbenes with oligomeric methanol are listed in Table I.

<sup>i</sup> Dimethoxycarbene (3), for instance, has  $\lambda_{\text{max}}$  at 255 nm.<sup>215</sup>

**Table I.** Absolute rate constants for reactions of methoxycarbenes with oligomeric methanol.

Carbene	$k_{\text{abs}}$ ( $\text{M}^{-1} \text{s}^{-1}$ )	Reference
MeOCPh	$\sim 10^{10}$ (25 °C)	Moss <i>et al.</i> , 1987 <sup>118</sup>
MeOCMe	$5.26 \times 10^9$ (20 °C)	Moss <i>et al.</i> , 1988 <sup>119</sup>
MeOCCl <sup>a</sup>	$\sim 6.8 \times 10^4$ (25 °C)	LaVilla and Goodman, 1989 <sup>120</sup>
(MeO) <sub>2</sub> C	$2.5 \times 10^6$ (25 °C)	Moss <i>et al.</i> , 1988 <sup>11</sup>

<sup>a</sup>Measured by photoacoustic calorimetry.

A primary kinetic isotope effect (KIE) of  $3.3 \pm 0.5$  was observed for the reaction of dimethoxycarbene (3) with MeOH(D) in solution.<sup>119</sup> This result, which suggests a significant degree of O-H bond stretching in the transition state, is consistent with either mechanism (ii) or (iii) in Scheme VIII. This relatively large KIE contrasts with the analogous values measured for the less nucleophilic methoxymethylcarbene and the electrophilic phenylchlorocarbene, neither of which is significantly different from unity.<sup>119</sup>

The relative reactivities of dimethoxycarbene (3) and methoxyfluorocarbene with a series of hydroxyl substrates have been reported.<sup>115</sup> For 3, a linear correlation was found between the rate of reaction and  $\text{pK}_{\text{a}}$  of the substrate, with pseudo first-order rate constants for reactions with 1 M alcohols in acetonitrile (20 °C) ranging from  $3.2 \pm 0.9 \times 10^4 \text{ s}^{-1}$ , for EtOH (aqueous  $\text{pK}_{\text{a}}$  15.90), to  $6.7 \pm 0.7 \times 10^8 \text{ s}^{-1}$  in the case of the more acidic  $(\text{F}_3\text{C})_2\text{CHOH}$  (aqueous  $\text{pK}_{\text{a}}$  9.30). These data clearly support the acid-base mechanism (eq. iii, Scheme VIII). Interestingly, 3 was found to be much more reactive, in this study, than methoxyfluorocarbene; in fact, quenching of the latter with most of the alcohols used



was too slow to be observed by LFP. This may seem surprising since the more stable **3** might be expected to be the least reactive, on the basis of the usual reactivity-selectivity principle.<sup>33</sup> However, this apparent divergence may indicate that different mechanisms are operative, with the less nucleophilic methoxyfluorocarbene possibly following a reaction path closer to the concerted insertion of (ii) in Scheme VIII.

### **1.6.2.3 Reactions with Double Bonds**

#### **1.6.2.3.1 Alkenes**

Whereas electrophilic and ambiphilic carbenes undergo [1 + 2] cycloadditions with electron-rich alkenes, as discussed in Section 1.4, strongly nucleophilic carbenes such as dioxycarbenes are generally unreactive with those substrates. Those carbene, however, react readily with electron-deficient alkenes. Selected absolute rate constants for additions of dimethoxycarbene (**3**) and some related carbenes to various alkenes are shown in Table II. The trends observed for all carbenes, *i.e.* higher reactivity with more electrophilic substrates, clearly reflect their nucleophilic (or ambiphilic) nature. The relative stability of **3** is also perceivable from its generally lower reactivity.

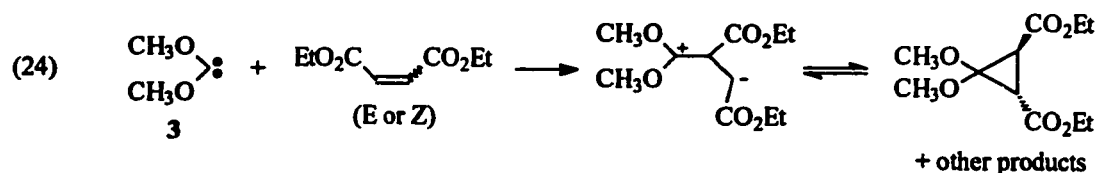
**Table II.** Absolute rate constants<sup>a</sup> (25 °C) for carbene + alkene cyclo-additions determined by LFP methods.

Alkene	(MeO) <sub>2</sub> C	$k_{\text{abs}}$ (M <sup>-1</sup> s <sup>-1</sup> )		
		MeOCCl	MeOCPh	MeOCMe
Me <sub>2</sub> C=CH <sub>2</sub>	N.A. <sup>b</sup>	1.8 x 10 <sup>3</sup>	4.0 x 10 <sup>4</sup>	4.8 x 10 <sup>3</sup>
CH <sub>2</sub> =CHCN	~ 10 <sup>3</sup>	1.8 x 10 <sup>4</sup>	1.7 x 10 <sup>6</sup>	1.5 x 10 <sup>6</sup>
CH <sub>2</sub> =CClCN	5.0 x 10 <sup>5</sup>	5.6 x 10 <sup>5</sup>	3.4 x 10 <sup>7</sup>	4.9 x 10 <sup>7</sup>

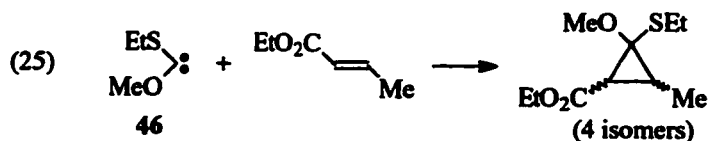
<sup>a</sup>Taken from Moss *et al.*, 1995,<sup>38</sup> except for dimethoxycarbene: Moss *et al.*, 1988;<sup>11</sup>

<sup>b</sup>Quenching not observed with tetramethylethylene ( $k_{\text{abs}} < 10^3 \text{ M}^{-1} \text{ s}^{-1}$ ).

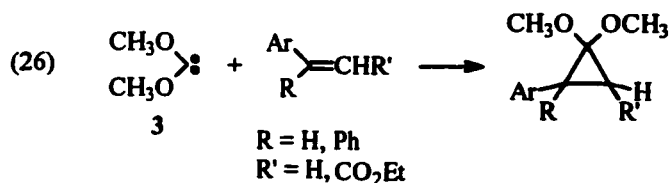
Although a concerted nucleophilic carbene + alkene cycloaddition seems likely in some cases (*vide infra*), stepwise processes involving dipolar intermediates have more frequently been postulated in the case of highly electron-deficient alkenes. In 1974, Hoffmann *et al.*<sup>28</sup> reported that the reaction of dimethoxycarbene (3) with either diethyl fumarate or diethyl maleate results exclusively in the formation of the *trans* cyclopropane derivative (eq. 24); although this suggests a stepwise mechanism, the alternative concerted addition, followed by isomerization of the initially-formed product, cannot be ruled out. Nevertheless, such cycloadducts are generally formed non-stereospecifically.



Another more recent example involving a different carbene is the reaction of (ethylthio)methoxycarbene (46) with ethyl crotonate, reported by Warkentin *et al.*,<sup>60</sup> which yielded all four possible geometric isomers (eq. 25).



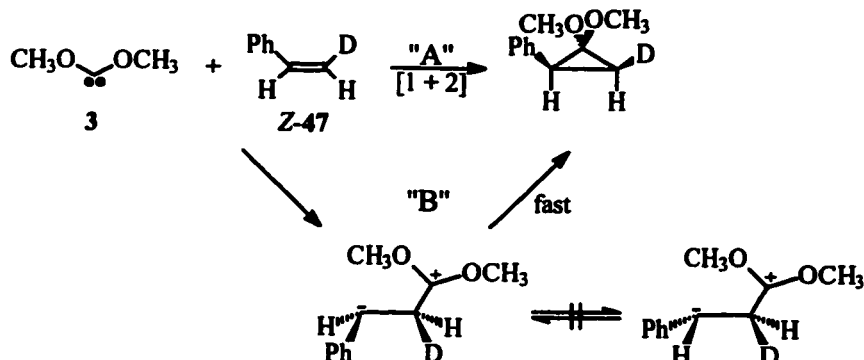
Some reactions of nucleophilic carbenes with less electron-deficient alkenes have also been reported. For example, dimethoxycarbene (3) has been trapped by Hoffmann *et al.* with various styrene derivatives, but the yields of 1,1-dimethoxycyclopropanes were 35% or less (eq. 26).<sup>28</sup>



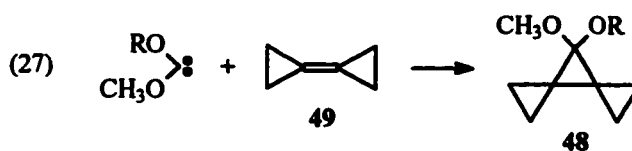
Moss and Huselton have reinvestigated this reaction of dimethoxycarbene (3) with styrene in an effort to distinguish between concerted and stepwise mechanisms.<sup>121</sup> When generated at 125 °C from a norbornadienone ketal (Section 1.5.1.1), 3 was found to add stereospecifically to *E*- and *Z*-β-deuteriostyrene (47), as shown in Scheme IX for the *Z*-isomer. This result suggests the occurrence of a concerted [1 + 2] cycloaddition, path A, between the carbene and the weakly electrophilic alkene. There is an alternative route, however, which cannot be ruled out: stepwise addition where the zwitterionic intermediate cyclizes before bond rotation occurs, thus retaining the stereochemical integrity of the substrate (path B). Rapid closure to the cyclopropane is possible because there is no spin-

inversion barrier in this case, in contrast to the additions involving triplet carbenes (see Section 1.3).

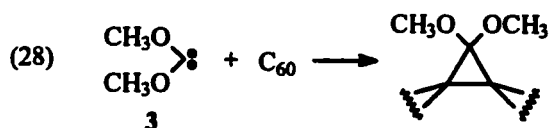
**Scheme IX**



Recently, de Meijere *et al.* reported the formation of 7,7-dioxy[3]triangulanes **48** from the reaction of bicyclopropylidene, **49**, with dioxycarbenes thermally generated from  $\Delta^3$ -1,3,4-oxadiazolines (eq. 27).<sup>122</sup> The isolated yields ranged from 37% (R = *tert*-Bu, partially decomposed during purification) to 91% (R = CH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>).

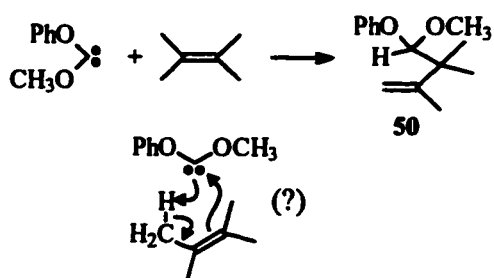


Dimethoxycarbene (**3**) also reacts with the electrophilic double bonds of buckminsterfullerene (C<sub>60</sub>) in a formal [1 + 2] cycloaddition, as shown in eq. 28.<sup>123,124</sup>



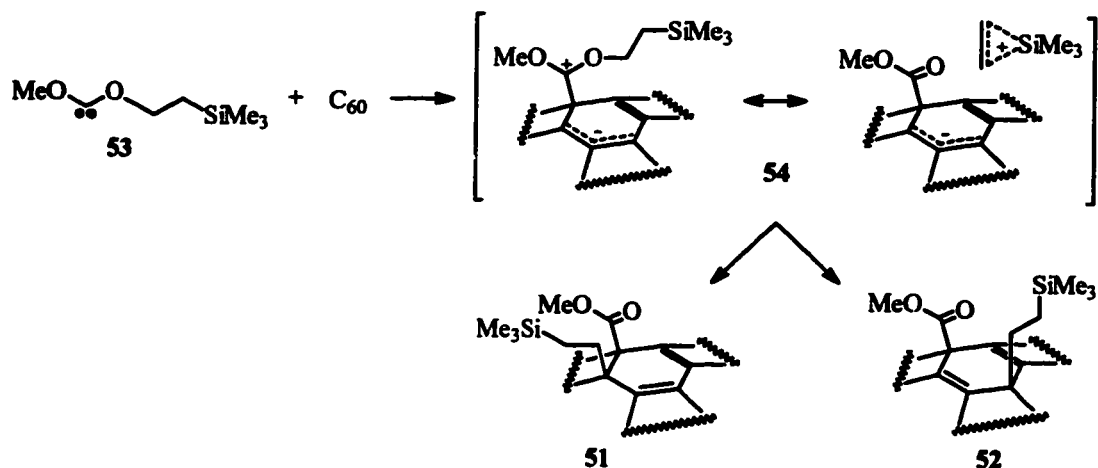
Some nucleophilic carbenes react with olefins to give non [1 + 2] adducts. Compound **50**, for instance, was the observed product of the reaction of methoxy(phenoxy)carbene with tetramethylethylene (yield was not reported); it may have formed from an “ene-type” reaction, as shown in Scheme X, or from rearrangement of the expected cyclopropane derivative.<sup>49</sup>

Scheme X



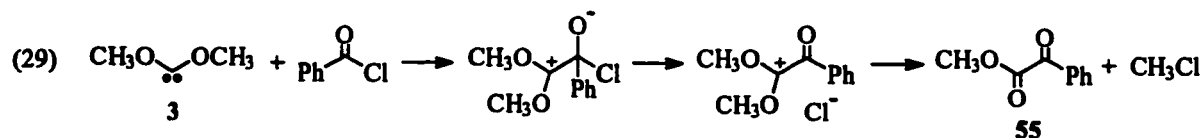
Wudl *et al.* recently reported the formation of two 1: 1 adducts, **51** and **52**, as the sole products obtained from the reaction of dioxycarbene **53** with  $\text{C}_{60}$ .<sup>125</sup> A mechanism involving dipolar intermediate **54** was proposed (Scheme XI), although the authors explicitly recognized the possibility of a concerted mechanism.

Scheme XI



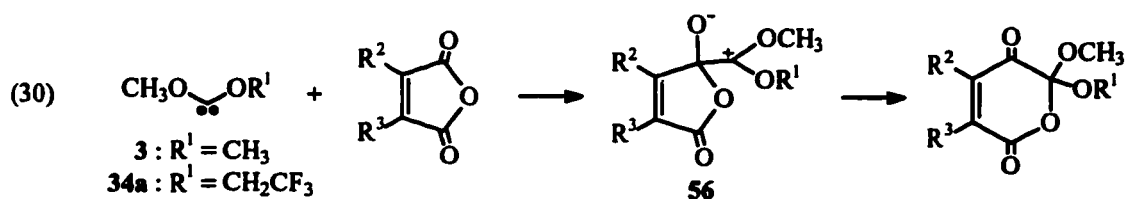
#### 1.6.2.3.2 C=X Bonds

Carbonyl groups are known to react with a wide variety of nucleophiles. It is therefore not surprising that they also participate in reactions with some nucleophilic carbenes. The formal insertion of dimethoxycarbene (**3**) into the C-Cl bond of benzoyl chloride to give glyoxylate derivative **55** was reported by Hoffmann *et al.* in 1974.<sup>28</sup> Again, the typical ionic (dipolar) chemistry of those carbenes is exemplified in the proposed mechanism shown in eq. 29.



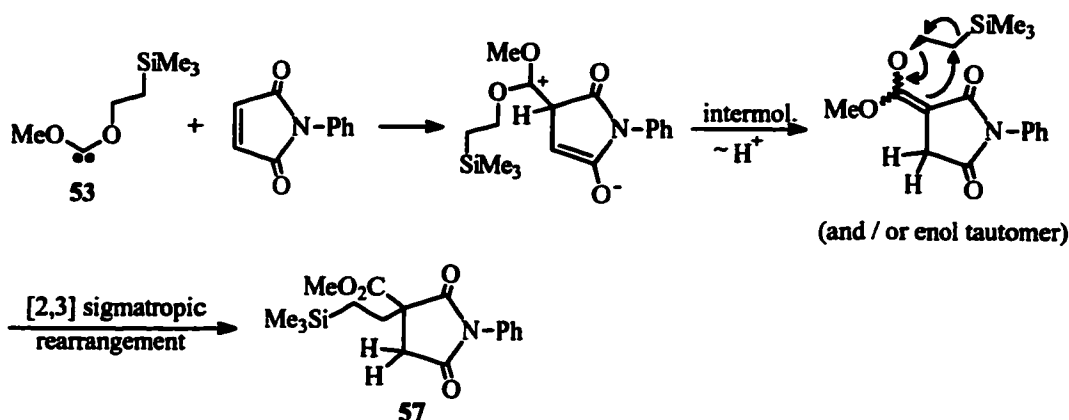
More recently, Pole and Warkentin studied the reactions of some dioxycarbenes with unsaturated cyclic anhydrides.<sup>126</sup> The general reaction is shown in eq. 30, along with

the proposed dipolar intermediate, **56**. Their results may be summarized as follows: (1) with both dimethoxycarbene, **3**, and methoxy-(2,2,2-trifluoroethoxy)carbene, **34a**, reaction occurred exclusively at carbonyl, with no observable products derived from attack at the olefinic bond; (2) for non-symmetric anhydrides, preferential attack at the most electron-deficient carbonyl group was observed, overriding opposing steric effects; (3) in accordance with the reactivity-selectivity principle,<sup>33</sup> the most reactive carbene, **34a**, was also the least selective one in its choice of non-equivalent carbonyl centres in a given substrate; and (4) competition experiments involving **3** showed the following reactivity order: 3,4-dimethylmaleic anhydride < maleic anhydride < 3,4-dichloromaleic anhydride, in accordance with the nucleophilicity of the carbene.



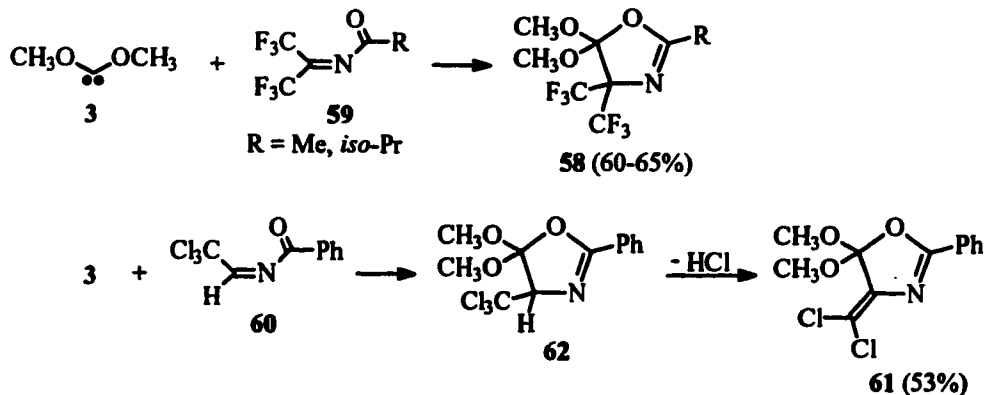
The reactions of some (alkylthio)methoxycarbenes with dichloromaleic anhydride took the same course as shown above in eq. 30, affording the analogous products with yields of 75-89%.<sup>60</sup> In contrast, the reaction between carbene **53** and N-phenylmaleimide involved attack at the C=C bond to give **57** in 69% yield; a plausible mechanism is proposed in Scheme XII.<sup>114</sup>

## Scheme XII



Dimethoxycarbene (**3**) undergoes formal [1 + 4] cycloadditions with electron-deficient conjugated imines. For example, Hoffmann *et al.* found that 2-oxazolines **58** are produced from the reaction of **3** with N-acylimines of hexafluoroacetone, **59** (Scheme XIII). With imine **60**, product **61**, formed by the elimination of HCl from **62**, was obtained.<sup>127</sup>

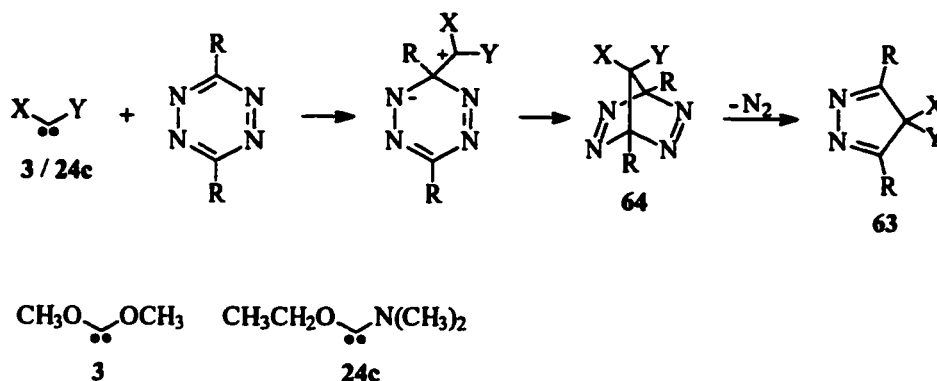
## Scheme XIII





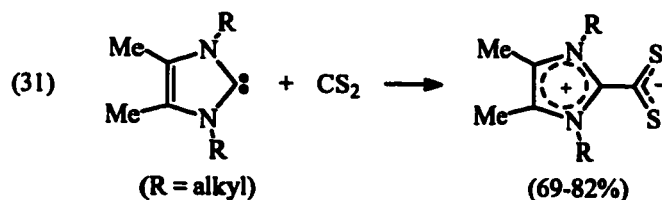
Seitz and co-workers have investigated the related reactions of nucleophilic carbenes with 1,2,4,5-tetrazines. With both dimethoxycarbene (**3**)<sup>85</sup> and (dimethylamino)-ethoxycarbene (**24c**),<sup>84,85</sup> isopyrazoles **63** are produced *via* an initial formal [4 + 1] cycloaddition, followed by loss of N<sub>2</sub> from cycloreversion of **64** (Scheme XIV).

Scheme XIV

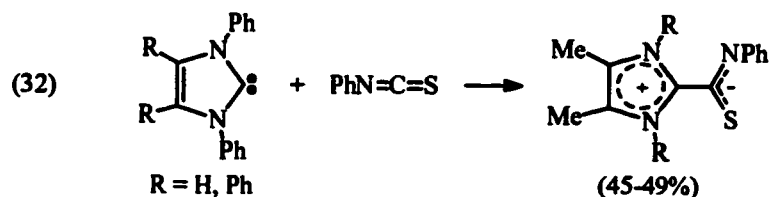


#### 1.6.2.3.3 Heterocumulenes

The reactions of nucleophilic carbenes with heterocumulenes may follow different courses, depending on both the nature of the carbene and the substrate. However, the initial step is invariably nucleophilic addition of the carbene to the sp-hybridized carbon. In some cases, the dipole thus produced is stable and constitutes the final product. This is seen, for instance, in the reaction of some imidazol-2-ylidenes with carbon disulfide, as depicted in eq. 31.<sup>128</sup>

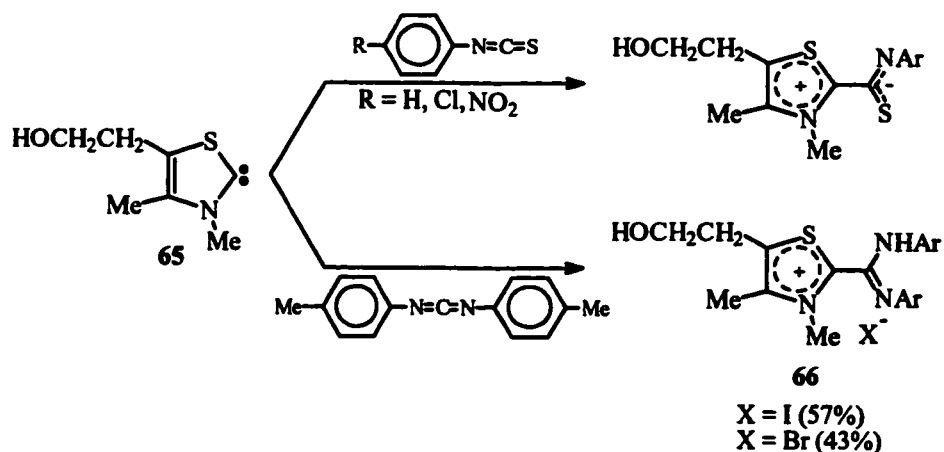


Those carbenes also yield analogous 1,3-dipoles in their reaction with phenyl isothiocyanate (eq. 32).<sup>65,66</sup>

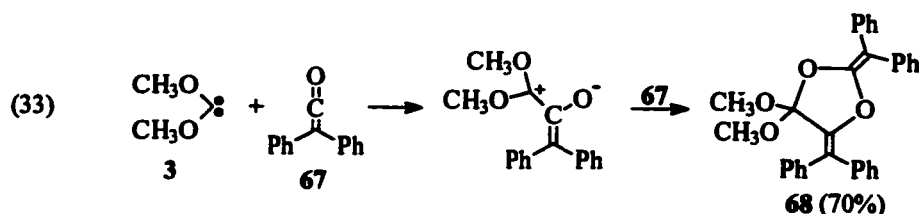


Nucleophilic carbenes other than diaminocarbenes also produce stable 1: 1 adducts, as shown in Scheme XV for the reaction of aminothiocabene **65** with some substituted phenyl isothiocyanates.<sup>129</sup> Generation of **65** from thiazolium halide precursors in the presence of di-*p*-tolylcarbodiimide yields salts **66**.<sup>129</sup>

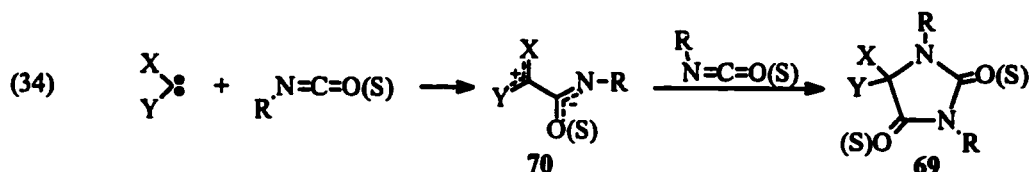
**Scheme XV**



In contrast to the examples cited above, the dipole formed in the reaction of dimethoxycarbene (**3**) with diphenylketene (**67**) adds across the carbonyl group of a second molecule of the ketene to give compound **68** in moderate yield (eq. 33).<sup>28</sup>

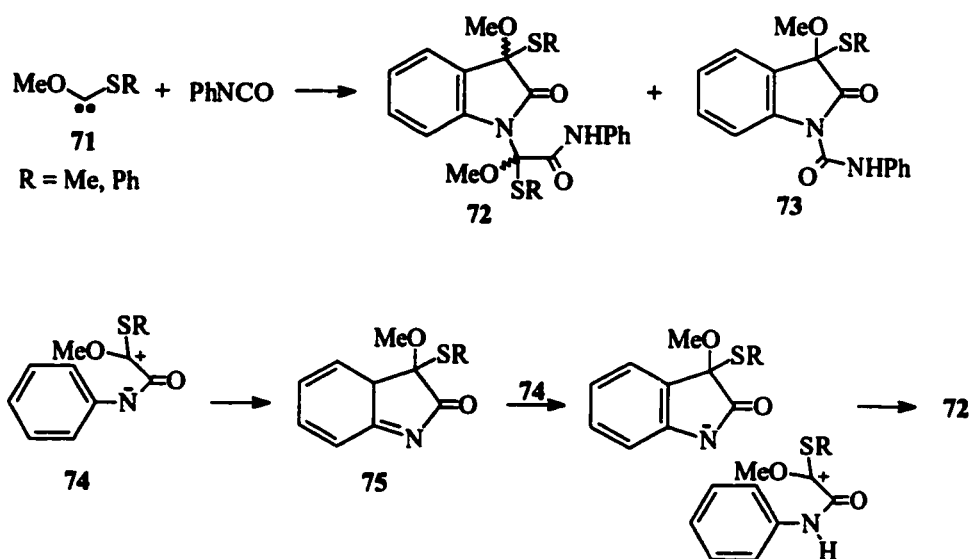


With most nucleophilic carbenes, hydantoin derivatives (**69**) result from reactions with alkyl or aryl isocyanates and isothiocyanates. This is believed to occur *via* the 1,3-dipolar cycloaddition of intermediate **70** across C=N, and not C=O, of the iso(thio)cyanate, as depicted in generalized form in eq. 34. This type of reaction has been observed for a variety of carbenes, including dimethoxycarbene (**3**),<sup>29,30,51</sup> diamino-,<sup>130,131</sup> aminoxy-,<sup>31</sup> and aminothiocarbenes.<sup>132</sup> Hoffmann and Reiffen determined a  $\rho$  value of 2.0 for the reaction of **3** with aryl isocyanates, as determined by competition experiments involving its addition to phenyl isothiocyanate vs substituted aryl isocyanates.<sup>30</sup> The positive sign of the measured value of  $\rho$  supports a transition state where negative charge accumulates at N from nucleophilic attack of the carbene, as shown above in eq. 34.



The recently reported reactions of oxythiocarbenes **71** with phenyl isocyanate did not yield the anticipated adduct.<sup>60</sup> In each case, the major products were a pair of diastereomeric 2:2 adducts, **72**, formed along with **73** (Scheme XVI). The proposed mechanism involves an unprecedented intramolecular cyclization of dipolar intermediate **74** to **75**. Disproportionation between **74** and **75** produces an ion pair which then collapses to oxindoles **72**. It was suggested that the differences in behaviour between dipole **74** and dioxy analogues, for instance, may be attributed to the lower stability of the former.

Scheme XVI

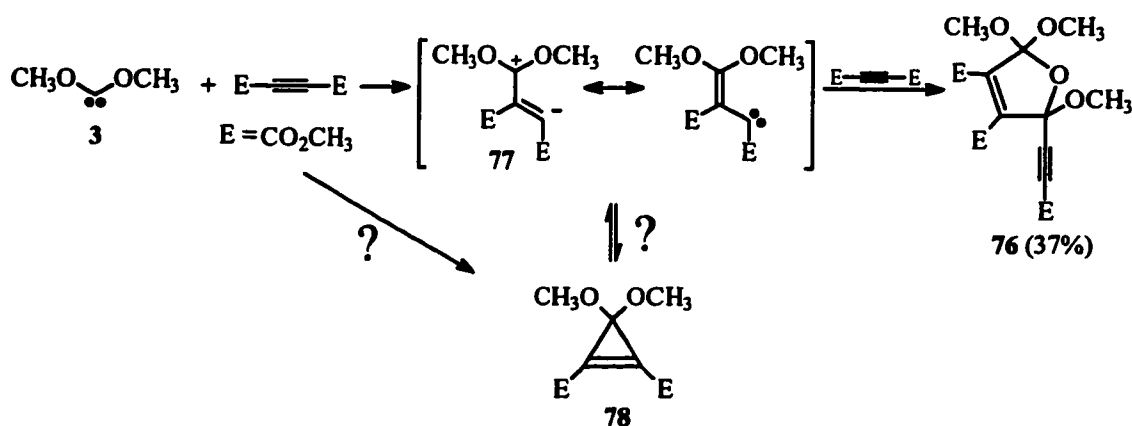


#### 1.6.2.4 Reactions with Alkynes

Nucleophilic carbenes, in general, react readily with alkynes bearing one or more electron-withdrawing substituents. In 1974, Hoffmann *et al.* obtained dihydrofuran

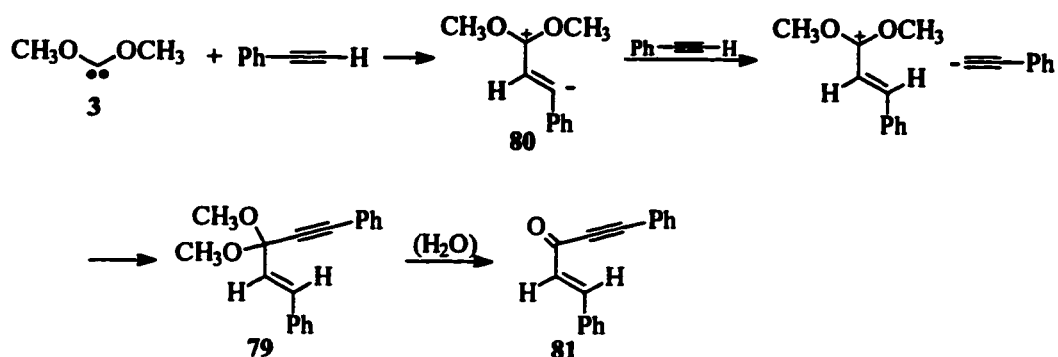
derivative **76** when dimethoxycarbene (**3**) was generated in the presence of an excess of DMAD (Scheme XVII).<sup>28</sup> A mechanism was proposed in which dipolar intermediate **77** (which can also be written as a vinyl carbene), produced by attack of the carbene at a triple-bonded carbon, adds across the carbonyl group of a second molecule of the alkyne. It is noteworthy that the alternative cycloaddition of **77** across the triple bond of DMAD (not shown) was not observed. The involvement of labile cyclopropene derivatives such as **78**, in those reactions, is uncertain. Analogues of **76** have also been reported for the reaction of DMAD with other dioxycarbenes<sup>114</sup> and with oxythiocarbenes.<sup>60</sup>

Scheme XVII

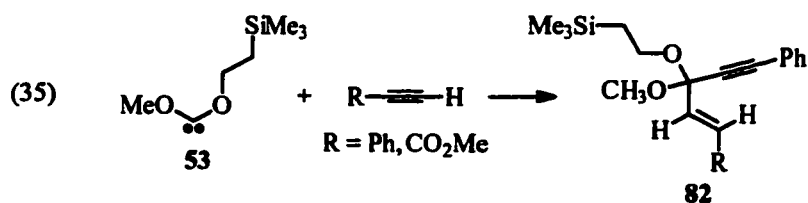


The acidity of alkynyl hydrogens in terminal alkynes alters the outcome of those reactions. Thus the reaction of **3** with phenyl acetylene, for instance, led to the formation of acetal **79**, probably formed by proton transfer between dipole **80** and the alkyne, followed by collapse of the ion pair; the hydrolysed product, **81**, was isolated (Scheme XVIII).<sup>28</sup>

## Scheme XVIII

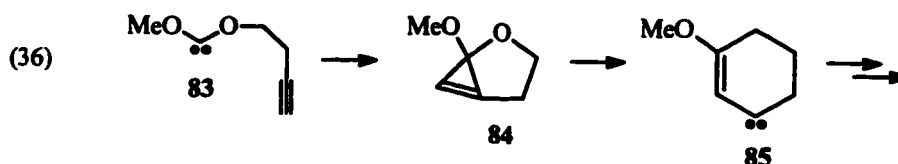


As shown in eq. 35, a similar reaction was observed between carbene **53** and phenyl acetylene or methyl propiolate but, in this case, the acetals (**82**) were isolated (62% yield with  $\text{R} = \text{CO}_2\text{Me}$ ).<sup>114</sup> The *E* geometry in compounds **82** was established from the magnitude of the coupling constants between the vinylic protons.



Reactions of unactivated triple bonds with nucleophilic carbenes are not common. The intrinsic advantage of intramolecular reactions, however, was sufficient to drive the addition of carbene **83** to its tethered alkyne (eq. 36), in the reaction reported by Kassam and Warkentin.<sup>62</sup> This initial step is followed by a most remarkable cascade of successive reactions, involving trapping of some by-products formed in the thermolysis of the carbene precursor (not shown in eq. 36). The authors suggested the formation of a cyclopropene

intermediate (**84**) in the initial step leading to vinyl carbene **85**. This postulate, however, was not supported by a computational study presented by W. B. Smith, who favoured the direct conversion of **83** to **85**.<sup>61</sup>



## 1.7 Objectives

The brief overview of the chemistry of nucleophilic carbenes presented above demonstrated the dearth of experimental data on aminooxycarbenes.  $\Delta^3$ -1,3,4-Oxadiazolines are now established thermolytic sources of nucleophilic carbenes and, therefore, they represent potential precursors of aminooxycarbenes. The original research work presented in the following sections was conducted with two broad objectives: first, to determine the feasibility of generating aminooxycarbenes in solution from the thermolysis of  $\Delta^3$ -1,3,4-oxadiazolines; and second, to study the chemistry of aminooxycarbenes in relation to that of other nucleophilic carbenes. Of particular interest is the question regarding the viability of intermolecular trapping of oxazolidin-2-ylidenes (Section 2.3.2).

The initial step of this project was the synthesis of  $\Delta^3$ -1,3,4-oxadiazolines bearing one O and one N at C2. An investigation of the mechanisms involved in the thermolysis of those 2-alkoxy-2-amino oxadiazolines, based mainly on product studies, was then

conducted to confirm that aminooxycarbenes are in fact produced. Finally, the reactivity of aminooxycarbenes was probed by means of chemical trapping experiments involving the generation of the carbenes in the presence of a variety of substrates.



## Chapter 2

### Results and Discussion

In the following pages, evidence for the intermediacy of carbonyl ylides in the thermal decomposition of 2-aryloxy-2-methoxy- $\Delta^3$ -1,3,4-oxadiazolines is presented first. In the next section, the syntheses of oxadiazoline precursors to cyclic aminooxycarbenes are described. An investigation of the thermolysis of these oxadiazolines follows, first with the introduction of a general decomposition scheme, and then with the details specific to each type of 2-amino-2-oxy- $\Delta^3$ -1,3,4-oxadiazoline. Our study of intermolecular reactions of aminooxycarbenes is then presented. The generation of unsaturated cyclic aminooxycarbenes from oxadiazolines, and some related work on the generation and intramolecular trapping of a novel  $\beta$ -lactam-4-ylidene, are the subjects of the last two sections of this chapter.

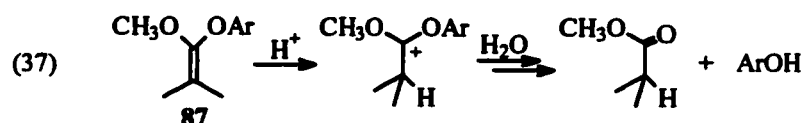
#### 2.1 Thermolysis of 2-Aryloxy-2-methoxy- $\Delta^3$ -1,3,4-oxadiazolines

In the course of experiments involving thermolyses of 2-methoxy-5,5-dimethyl-2-(4-nitrophenoxy)- $\Delta^3$ -1,3,4-oxadiazoline,<sup>i</sup> **86a**, an interesting compound was unexpectedly isolated in low yield (*ca.* 7%), following radial chromatography of the product mixture. Its <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>) showed the presence of two non-equivalent methyl

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<sup>i</sup> Oxadiazolines **86a-f** were prepared by M. El-Saidi.<sup>133</sup>

singlets at 1.56 ppm and 1.75 ppm, presumably derived from the two methyl groups at C5 in the original oxadiazoline, in addition to another methyl singlet at 3.52 ppm, as well as two sets of aromatic multiplets, each integrating for two protons. These data suggested structure **87a** (Ar = 4-C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>) and this was confirmed by additional data from <sup>13</sup>C-NMR, IR spectroscopy, and MS. In addition, an attempt to repeat the isolation of this ketene acetal resulted in its partial hydrolysis, during chromatography, to methyl isobutyrate and 4-nitrophenol, a result consistent with the proposed structure (eq. 37).



In order to probe for the generality of the ketene acetal-forming pathway, thermolyses of the related 2-aryloxy-2-methoxy oxadiazolines **86b-f** were carried out. The corresponding ketene acetals (**87b-f**) were observed but, in contrast to **87a**, they could not be isolated without at least partial decomposition. The higher stability of **87a** is undoubtedly due to the destabilizing effect of the nitro group on the intermediate cation formed by protonation of the ketene acetal (see eq. 37). Partial <sup>1</sup>H-NMR assignments for those less stable ketene acetals were obtained from the crude thermolysates, by analogy to the NMR spectrum of **87a**; the available methoxy and methyl chemical shifts are listed Table III.

**Table III.**  $^1\text{H}$ -NMR data for ketene acetals **87**.

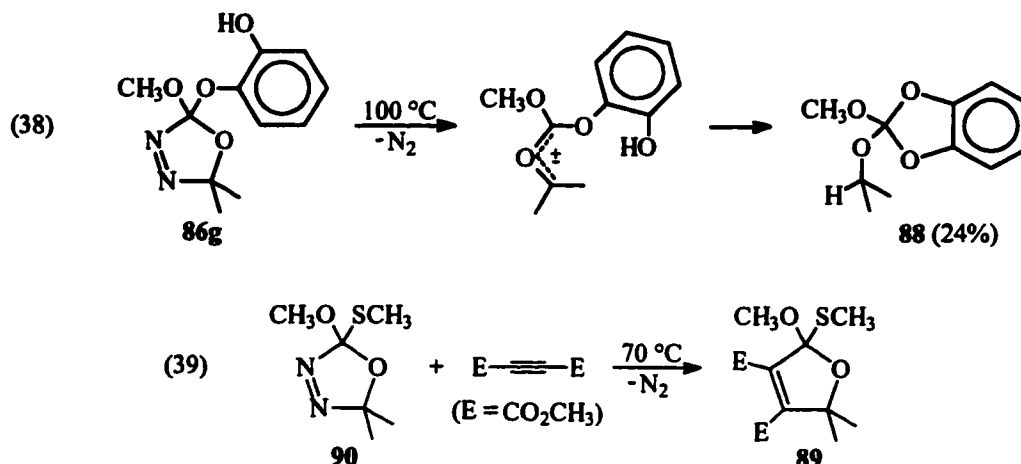
<b>87, X</b> (Ar = 4-C <sub>6</sub> H <sub>4</sub> X)	$^1\text{H}$ -NMR $\delta$ (ppm, CDCl <sub>3</sub> )	
	OCH <sub>3</sub>	C(CH <sub>3</sub> ) <sub>2</sub>
<b>87a</b> , NO <sub>2</sub>	3.52	1.56, 1.75
<b>87b</b> , CF <sub>3</sub>	3.51	1.57, 1.74
<b>87c</b> , Cl	3.45	1.58, 1.72
<b>87d</b> , H	3.48	1.56, 1.75
<b>87e</b> , CH <sub>3</sub> <sup>a</sup>	N.A.	N.A.
<b>87f</b> , OCH <sub>3</sub>	3.47	1.56, 1.74

<sup>a</sup>Observed only by GC-MS.

Gas chromatography did separate the ketene acetals (**87**) from other products, allowing mass spectra to be acquired by GC-MS. In each case, a species with the mass of the molecular ion was observed as a relatively intense signal, comprising 18-36% of the intensity of the base peak. The latter corresponded, in each case, to M-59. This pattern is in keeping with a common connectivity, although the identity of the fragment giving rise to this signal is not known. One possibility is that M-59 is the cation  $[\text{ArCMe}_2]^+$ , resulting from loss of MeO and CO from the molecular ion.

The exact origin of ketene acetals **87**, formed during the thermolysis of **86**, is of particular interest. The fact that they retained the *gem* dimethyl portion of **86** suggests the intermediacy of carbonyl ylides in these thermolyses. The thermal extrusion of dioxycarbenes from 2,2-dioxy oxadiazolines has long been thought to be initiated by an orbital symmetry-allowed  $[4\pi + 2\pi]$  cycloreversion to N<sub>2</sub> and a carbonyl ylide, as discussed in Section 1.5.1.2. However, only two examples of *apparent* carbonyl ylide-derived products, from thermolysis of oxadiazolines with two heteroatom substituents at

C2, have so far been observed. In one case, **88** was formed in the thermolysis of **86g**, as shown in eq. 38, probably *via* an intermolecular proton transfer.<sup>133</sup> Similarly, dihydrofuran **89** was isolated from the thermolysis of 2-methoxy-2-methylthio- $\Delta^3$ -1,3,4-oxadiazoline **90** with DMAD (eq. 39).<sup>60</sup> At least in this latter example, the intermediacy of a carbonyl ylide remains uncertain, as an alternative mechanism involving cycloaddition of a methoxy(methylthio)carbene-DMAD adduct to acetone could be postulated.

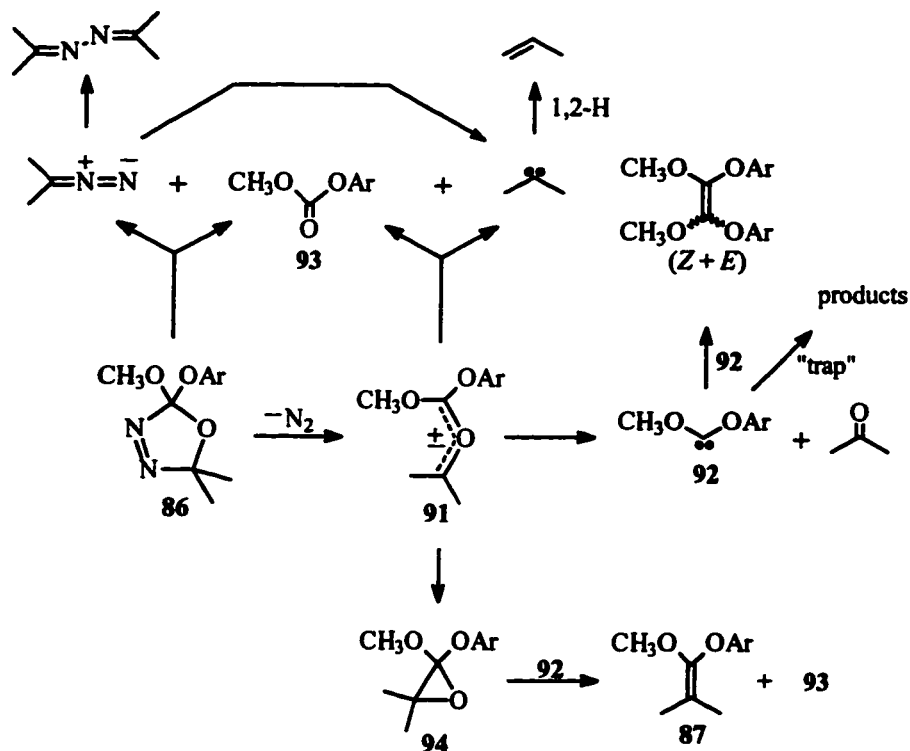


Scheme XIX illustrates the numerous recognized decomposition pathways<sup>i</sup> for thermolysis (benzene, 110 °C) of oxadiazolines of type **86**, including the proposed pathway leading to **87**. Again, the major route is presumably initiated with the loss of molecular nitrogen to give carbonyl ylide **91**. Once formed, **91** preferentially fragments to acetone and a dioxycarbene **92**, although breaking of the other ylidic C-O bond possibly occurs, as a minor pathway, to form carbonate **93** and 2-propylidene, the latter undergoing a fast 1,2-H shift to propene. The generation of dioxycarbenes **92** has been

<sup>i</sup> This Scheme is based, in part, on the results of M. El-Saidi.<sup>133</sup>

unambiguously demonstrated by trapping experiments.<sup>133</sup> Carbonate **93** is also produced from a direct cycloreversion of **86** which yields 2-diazopropane as a coproduct.

Scheme XIX

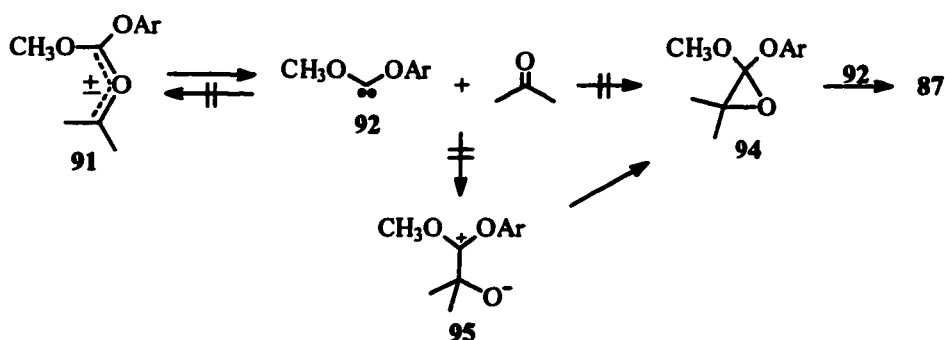


An alternative fate for carbonyl ylide **91**, which had not been previously observed in thermolyses of 2,2-dioxy oxadiazolines, is closure to oxirane **94**; this results in the formation of the new C-C bond required for **87**. The proposed transformation of oxirane **94** into ketene acetal **87** involves attack on **94** by a dioxycarbene **92**. There are precedents for deoxygenation of oxiranes by carbenes, although the carbenes known to do so are electrophilic or ambiphilic species that attack at oxygen to afford ylide intermediates.<sup>134</sup> The carbenes in this study should range from nucleophilic to ambiphilic,<sup>27,49</sup> and they

might be expected to attack oxiranes at carbon. Unfortunately, the low yields of **87** prevented any inference about the effects of the substituents on the efficiency of their formation. The exact mechanism of conversion of **94** into **87** therefore remains unknown.

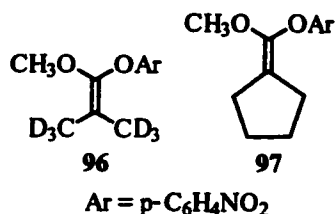
So far, we have assumed that carbonyl ylide **91** is the source of oxirane **94**, and that **91** is generated from the loss of N<sub>2</sub> by oxadiazoline **86**. The alternatives shown in Scheme XX, however, must also be considered. For instance, fragmentation of **91** to carbene **92** and acetone could be reversible, although this is unlikely in the case of nucleophilic carbenes; also, oxirane **94** could be produced by the reaction of **92** with acetone, either by a direct [1 + 2] cycloaddition, or *via* dipolar intermediate **95**.

Scheme XX



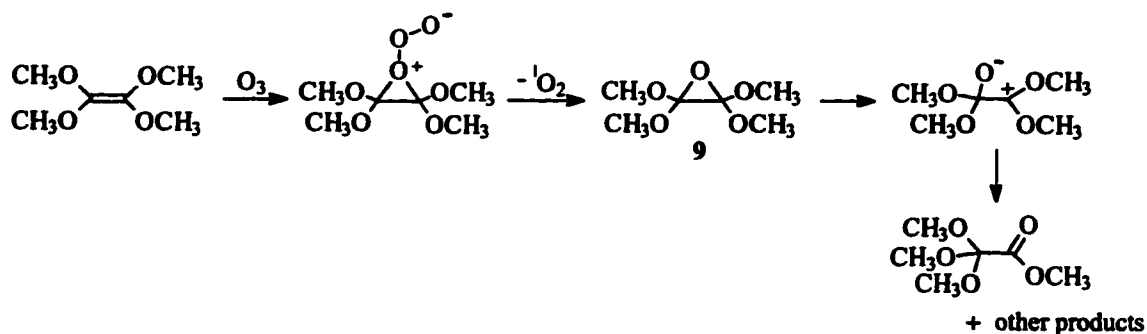
In order to investigate those possibilities, two probes were applied with oxadiazoline **86a**, one involving addition of acetone-d<sub>6</sub>, and the other of cyclopentanone, to the solvent prior to thermolysis. The cross products (**96** and **97**) expected if ketone from solution had been incorporated were not detectable (<sup>1</sup>H-NMR, GC-MS). These results rule out all mechanisms involving reaction of a free carbene with acetone to form

oxirane **94**, leaving the contentious carbonyl ylide mechanism as the most obvious alternative.



Oxiranes **94** are formally carbonyl-protected  $\alpha$ -lactones which are unknown as a class. Tetramethoxyoxirane (**9**) was proposed by Hoffmann and Schneider<sup>43,46</sup> as a reactive intermediate formed in the oxidation of tetramethoxyethylene under various conditions (oxidation with air,  $^3\text{O}_2$ ,  $\text{O}_3$ , ...). Similarly, Kopecky *et al.* have also considered **9** as an intermediate from the ozonolysis of tetramethoxyethylene (Scheme XXI), but they were also unable to detect it and concluded that, even at  $-90^\circ\text{C}$ , it must be very short-lived ( $< 2$  s) if it is formed at all.<sup>135</sup> In the present study, it was possible, in 5 cases out of 6, to detect a compound by GC to which we have tentatively assigned structure **94**. Each oxadiazoline **86** afforded a species that eluted just ahead of the ketene acetal **87**. The mass spectra (GC-MS) of **94b-f** gave highest  $m/z$  signals corresponding to dioxycarbene + H (aryloxymethoxymethyl cation) or to an isomeric structure.

Scheme XXI



Experiments to support the assignment of the oxirane structure to **94** were based on the expectation that the yield ratio **94**: **87** should be sensitive to the initial concentration of oxadiazoline **86**. According to our proposed scheme, the yield of a **87** should increase, relative to that of **94**, as the initial concentration of **86** in the thermolysis solution is increased, since a larger amount of carbene **92** produced should result in a higher conversion of **94** into **87**.<sup>i</sup> Oxadiazoline **86c** was chosen, and a set of thermolyses was carried out in which the initial oxadiazoline concentration was varied from 36.5 to 194 mM (Table IV). After completion of the thermolyses, a known amount of ethyl benzoate was added as an integration standard, and the thermolysates were analysed by GC. As shown in Figure 12, the percent yield of oxirane **94c** was found to decrease, and that of the ketene acetal (**87c**) to increase, as the oxadiazoline concentration was augmented.

<sup>i</sup> The kinetic scheme is complicated, but ketene acetal formation is of higher order in oxadiazoline than oxirane formation.



**Table IV.** Yields of thermolysis products from **86c**.

[ <b>86</b> ]i (mM)	Average % Yields <sup>a</sup>			<b>87c</b> / <b>94c</b>
	carbonate <b>93c</b>	oxirane <b>94c</b>	ket.acetal <b>87c</b>	
36.5	16.7 ± 0.7	0.95 ± 0.07	2.89 ± 0.33	3.06
61.8	16.2 ± 0.5	0.63 ± 0.10	3.35 ± 0.24	5.41
83.9	15.9 ± 0.8	0.44 ± 0.19	3.42 ± 0.23	8.70
120	16.3 ± 0.6	0.39 ± 0.02	4.12 ± 0.20	10.5
154	16.8 ± 1.0	0.41 ± 0.03	4.54 ± 0.29	11.1
194	15.9 ± 0.4	0.40 ± 0.03	4.54 ± 0.15	11.3

<sup>a</sup>Results are expressed as average ± standard deviation for five GC measurements on the same thermolysates.

The absolute yields in Table IV were calculated by assuming equivalent responses on the FID detector, on a molar basis, by all compounds; although this may lead to a systematic error in absolute terms, the trends should not be affected by this assumption. As a comparison, a thermolysis carried out in a sealed NMR tube, with an initial concentration in **86c** of 250 mM, gave a yield for **87c** of 5.4% by NMR, in excellent agreement with the yields determined by GC. Also, the percent yield of carbonate **93c** was constant, within experimental error, at *ca.* 16%, in concordance with M. El-Saidi's results.<sup>i</sup>

<sup>i</sup> NMR yields of carbonates **93**, from thermolysis of **86a-f**, were found to be in the range 16-19%.<sup>133</sup>

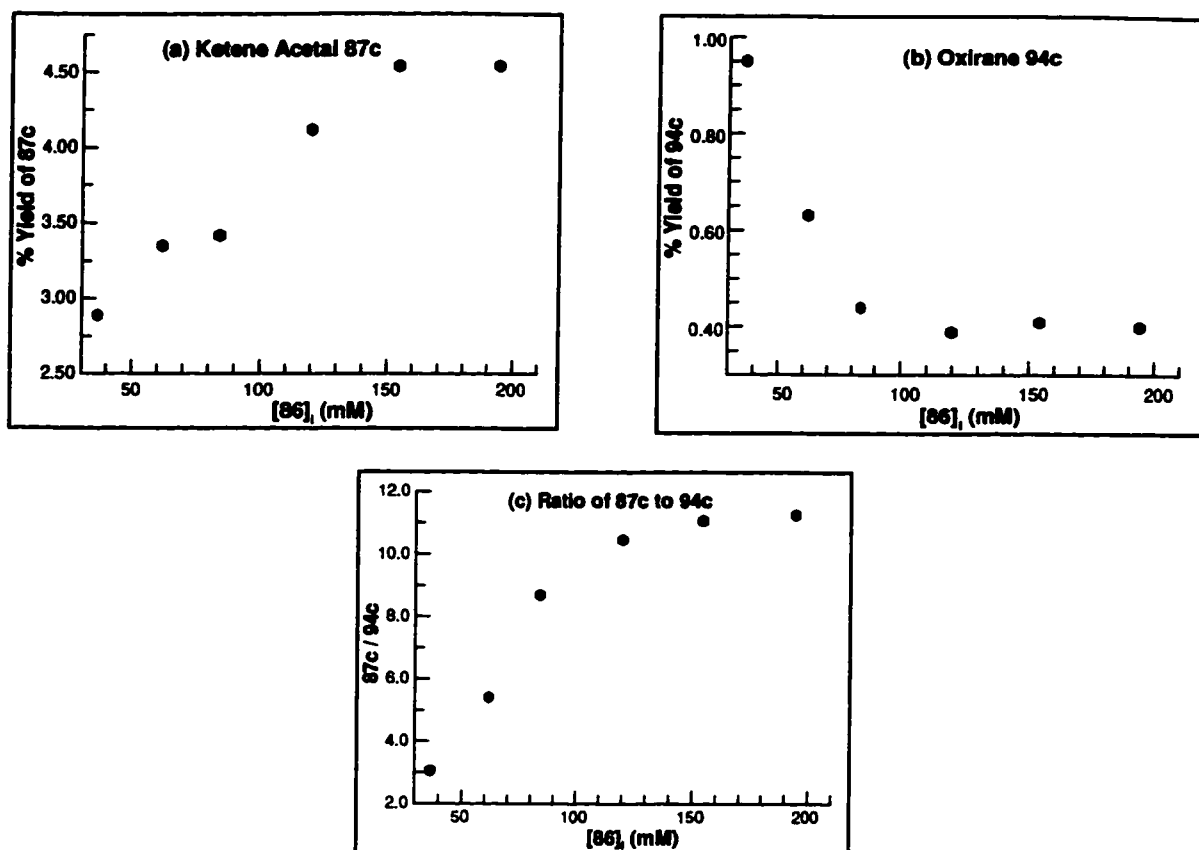
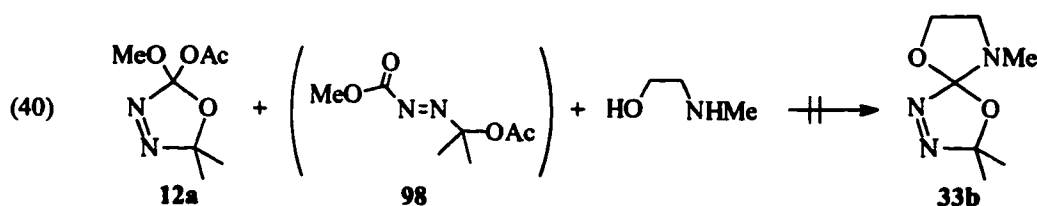


Figure 12. Percent yields of 87c and 94c as a function of the initial oxadiazoline (86c) concentration.

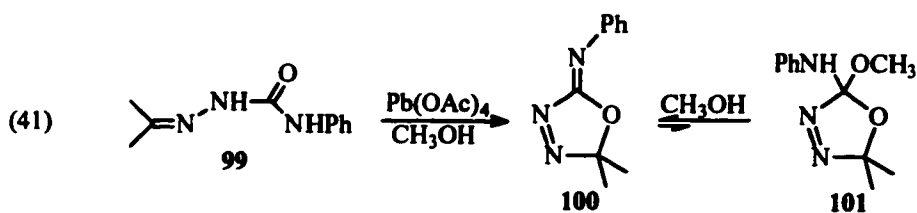
In summary, the results presented above provide evidence for the intermediacy of carbonyl ylides in the thermolysis of 2-aryloxy-2-methoxy oxadiazolines **86**. Although this sequential process does not necessarily apply to 2,2-dialkoxy oxadiazolines, their chemistry can be rationalized in the same way, simply by recognizing that their corresponding ylides probably fragment more rapidly, to afford more stabilized carbenes, and therefore yield oxiranes in undetectable (or zero) yields.

## 2.2 Synthesis of 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines

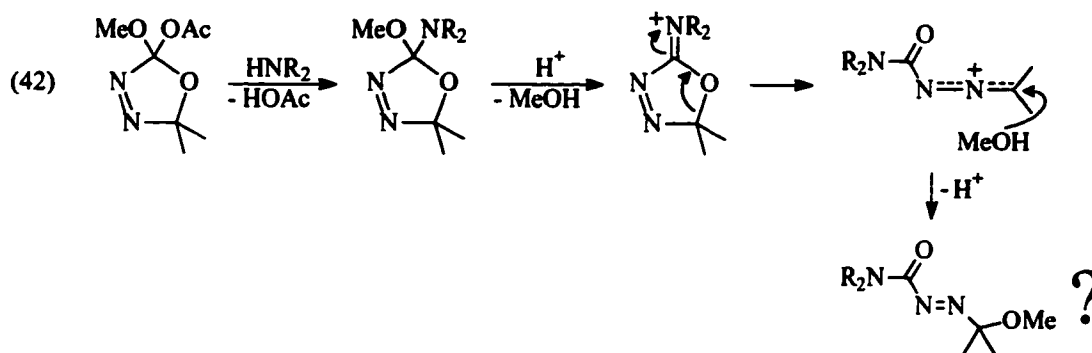
A general method for the preparation of 2,2-dioxy- and 2-oxy-2-thio- $\Delta^3$ -1,3,4-oxadiazolines involves the acetoxy exchange method, using 2-acetoxy-2-methoxy- $\Delta^3$ -1,3,4-oxadiazoline (**12a**), discussed in Chapter 1. However, this approach fails in the case of exchanges with amines. In an attempt to prepare **33b**, a mixture of **12a** and its acyclic isomer, **98**, was treated with 2-(methylamino)ethanol: immediate reaction between the amine and base-sensitive azo compound **98** was obvious from spontaneous gas evolution (eq. 40). The reaction was therefore repeated after purification of **12a** by slow distillation under vacuum. Unfortunately, this resulted in an intractable mixture, without formation of any **33b** (or the related 2-alkoxy-2-methoxy oxadiazoline). Similar exchange reactions were also attempted, without success, with other amines such as dimethylamine, diphenylamine (for which there was no apparent reaction by TLC), and aniline.



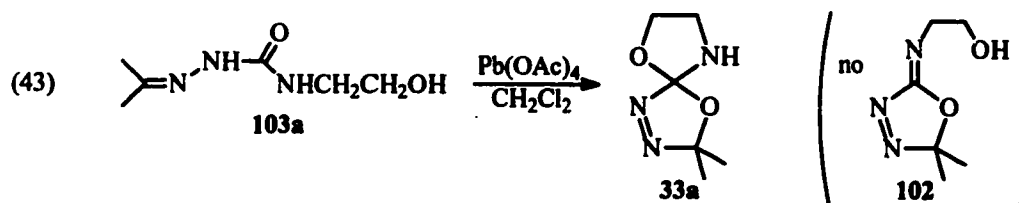
It was previously reported that oxidative cyclization of semicarbazone **99** with  $\text{Pb}(\text{OAc})_4$  in methanol produces a mixture of imino oxadiazoline **100** and 2-methoxy-2-phenylamino oxadiazoline **101**; however, **101** could not be obtained free of **100**, and loss of methanol from it was complete within a week, in  $\text{CDCl}_3$  at room temperature (eq. 41).<sup>136</sup>



In our attempted exchange reaction involving aniline and acetoxy oxadiazoline **12a**, however, neither **100** nor **101** were among the observed products. In the case of reactions involving secondary amines such as dimethylamine, it is possible that some 2-amino-2-oxy oxadiazolines initially form, but subsequently decompose as proposed in eq. 42.

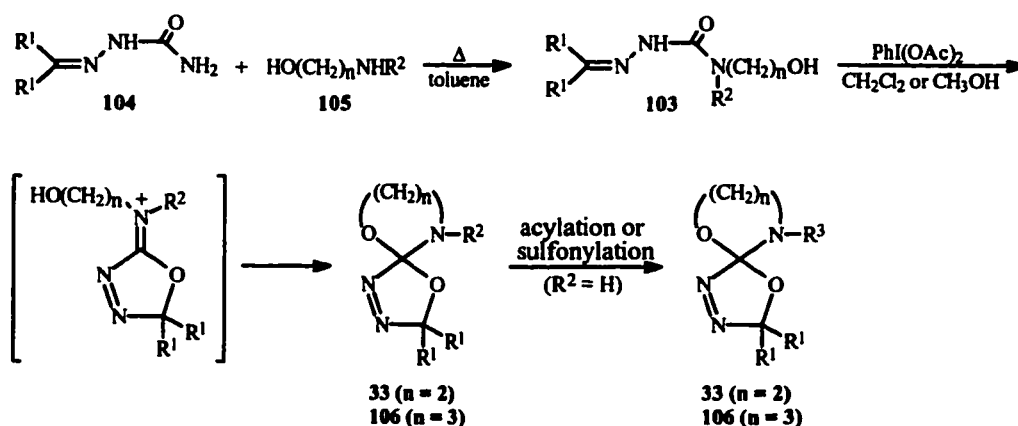


An alternative approach for the preparation of 2-amino-2-oxy oxadiazolines was suggested from the reported synthesis of **33a** by Zoghbi, who unexpectedly obtained this compound, instead of the desired **102**, from  $\text{Pb(OAc)}_4$  oxidation of semicarbazone **103a** (eq. 43).<sup>136</sup>



A series of substituted semicarbazones **103** was therefore prepared, in 59% to 81% yields, by refluxing the semicarbazone of acetone (**104**,  $R^1 = \text{Me}$ ) or of cyclohexanone (**104**,  $R^1R^1 = (\text{CH}_2)_5$ ) with an appropriate amino alcohol **105** in toluene<sup>137</sup> for 7 to 15 hours.<sup>i</sup> Although  $\text{Pb}(\text{OAc})_4$  oxidation of **103** ( $n = 2$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) produces **33a** in reasonable yield, it repeatedly failed in the case of oxidation of **103** ( $n = 2$ ,  $R^1 = R^2 = \text{Me}$ ) to **33b**. Instead,  $\text{PhI}(\text{OAc})_2$ , which has previously been utilized in the synthesis of 2-alkoxy- $\Delta^3$ -1,3,4-oxadiazolines,<sup>138</sup> was found to be the reagent of choice. Thus, the appropriate semicarbazones **103** were reacted with  $\text{PhI}(\text{OAc})_2$  in dichloromethane or, in one case, in methanol, to afford oxadiazolines **33a,b** and **106a-c** in 35-66% yields (Scheme XXII, Table V). It must be noted, however, that both  $\text{Pb}(\text{OAc})_4$  and  $\text{PhI}(\text{OAc})_2$  oxidations of acetone 4-(2-hydroxyethyl)-4-phenylsemicarbazone (**103**,  $n = 2$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{Ph}$ ) failed to produce the expected N-phenyl oxadiazoline (**33**,  $R^1 = \text{Me}$ ,  $R^2 = \text{Ph}$ ).

Scheme XXII



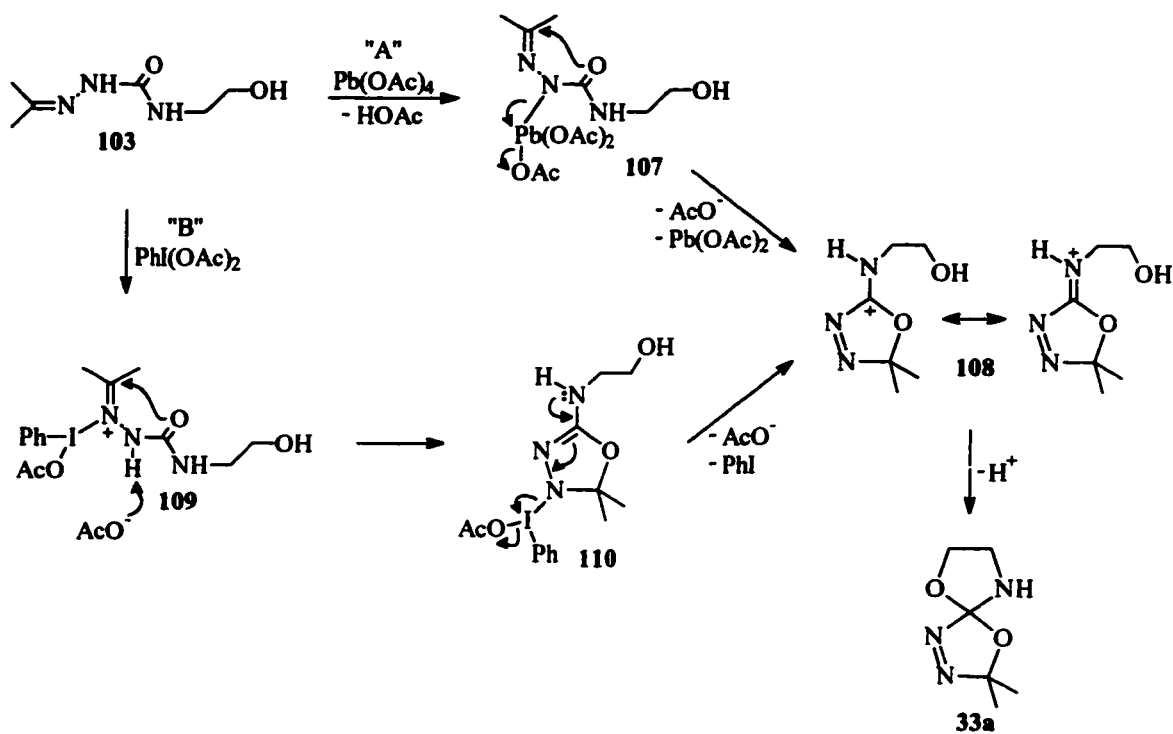
<sup>i</sup> An attempt to prepare acetone 4,4-diphenylsemicarbazone by this procedure failed (see Experimental Section).

**Table V.** 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines synthesized.

	n	R <sup>1</sup>	R <sup>2</sup> / R <sup>3</sup>
<b>33a</b>	2	Me	H
<b>33b</b>	2	Me	Me
<b>33b<sup>*</sup></b>	2	Me	CD <sub>3</sub>
<b>33b<sup>*</sup></b>	2	Me	<sup>13</sup> CH <sub>3</sub>
<b>33c</b>	2	Me	C(O)H
<b>33d</b>	2	Me	C(O)Me
<b>33e</b>	2	Me	C(O)C(Me)=CH <sub>2</sub>
<b>33f</b>	2	Me	C(O)Ph
<b>33g</b>	2	Me	C(O)C <sub>6</sub> H <sub>4</sub> (2-OMe)
<b>33h</b>	2	Me	C(O)C <sub>6</sub> H <sub>4</sub> (4-OMe)
<b>33i</b>	2	Me	C(O)C <sub>6</sub> H <sub>4</sub> (4-NO <sub>2</sub> )
<b>33j</b>	2	Me	C(O)OMe
<b>33k</b>	2	Me	SO <sub>2</sub> Ph
<b>106a</b>	3	Me	H
<b>106b</b>	3	R <sup>1</sup> R <sup>1</sup> = (CH <sub>2</sub> ) <sub>5</sub>	H
<b>106c</b>	3	R <sup>1</sup> R <sup>1</sup> = (CH <sub>2</sub> ) <sub>5</sub>	Me
<b>106d</b>	3	Me	C(O)Ph
<b>106e</b>	3	R <sup>1</sup> R <sup>1</sup> = (CH <sub>2</sub> ) <sub>5</sub>	C(O)Ph

The mechanism of oxidation of semicarbazones **103** with Pb(OAc)<sub>4</sub> is uncertain. A mechanism analogous to that shown in Scheme XXIII (route A) for **103** (n = 2, R<sup>1</sup> = Me, R<sup>2</sup> = H) has been proposed for related hydrazones and semicarbazones.<sup>139</sup> Formation of organolead compound **107** is followed by cyclization to **108**, in which the  $\Delta^3$ -1,3,4-oxadiazoline skeleton is constructed; this is accompanied by elimination of the lead as Pb(OAc)<sub>2</sub>. Attack of the tethered hydroxyl group on iminium ion **108**, followed by proton loss, then yields the spiro oxadiazoline **33a**.

## Scheme XXIII

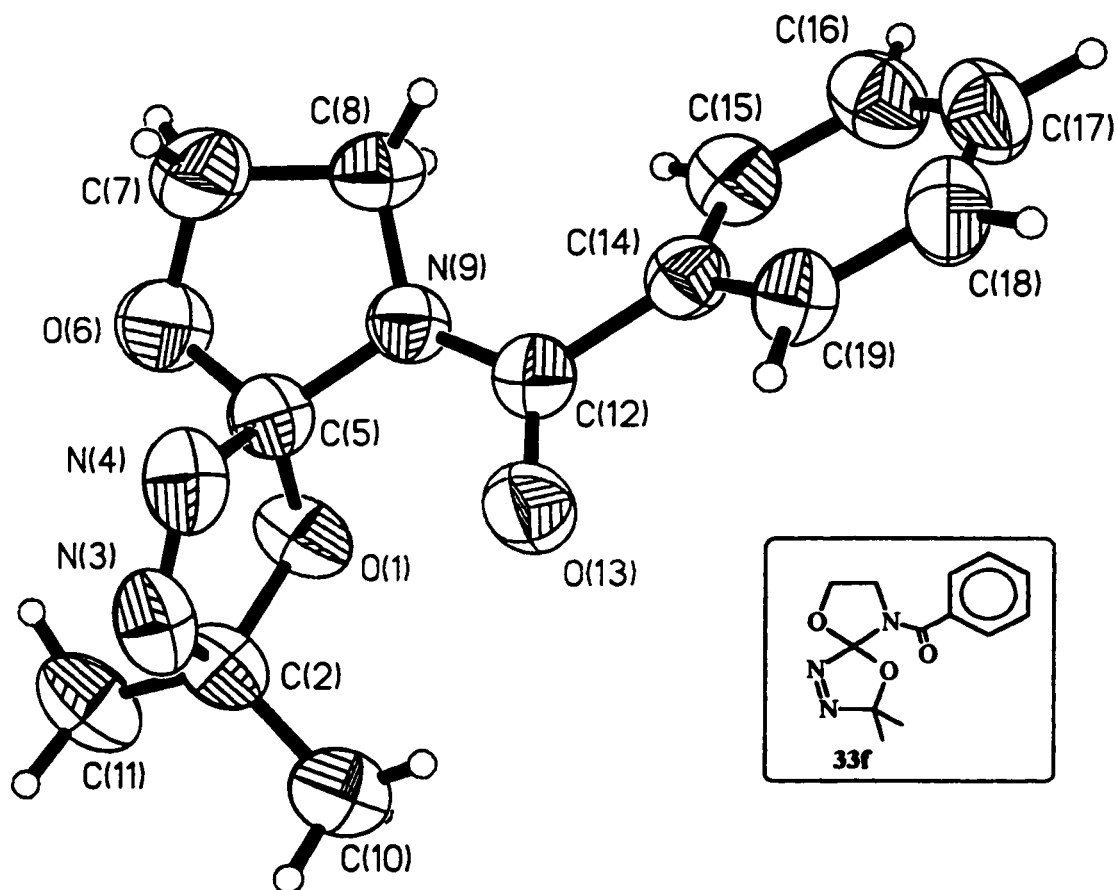


This mechanism contrasts with that recently proposed by Yang and Dai for oxidative cyclization of N-phenylsemicarbazone with  $\text{PhI}(\text{OAc})_2$ ,<sup>138</sup> as illustrated in Scheme XXIII (route B) for the same semicarbazone. In this case, displacement of the acetoxy ligand of the oxidant is thought to involve attack by the imino nitrogen of **103**, resulting in hypervalent iodine intermediate **109**, which can then cyclize to **110** via attack by the carbonyl oxygen. Iminium ion **108** is then produced by an intramolecular reductive elimination of  $\text{PhI}$  from intermediate **110**. This latter mechanism may in fact be operative with both  $\text{PhI}(\text{OAc})_2$  and  $\text{Pb}(\text{OAc})_4$ , based on the presumably greater nucleophilicity of the imino nitrogen, relative to the "amide" nitrogen, in **103**.

N-carbonyl oxadiazolines **33d-i** and **106d,e** were prepared by acylation of the appropriate NH oxadiazolines, using standard methods, in yields ranging from *ca.* 10% to 33% from the semicarbazones. N-Methylation of **33a** with CD<sub>3</sub>I or <sup>13</sup>CH<sub>3</sub>I produced labelled **33b**; these labelled compounds were required for a mass spectral study of **33b** (*vide infra*). Sulfonamide derivative **33k** was prepared by reaction of **33a** with benzenesulfonyl chloride. Preparation of **33c** proved to be more difficult. Only negligible amounts could be obtained by reacting **33a** with ethyl formate under various conditions. Similarly, attempts to react the lithium salt of **33a**, generated using n-butyl lithium, with ethyl formate, yielded essentially no **33c**. This oxadiazoline was finally prepared in satisfactory yield by increasing the reactivity of the formate.<sup>140</sup> Thus the reaction between **33a** and 4-nitrophenyl formate in dichloromethane at room temperature was complete in less than 72 h. Several conditions were also examined for the synthesis of carbamate derivative **33j** from **33a** and methyl chloroformate. The initial attempted reactions using dichloromethane as solvent, in the presence of triethylamine, were not successful. A method adapted from that of Maclean *et al.*,<sup>141</sup> which consisted of reacting the two substrates in 1,2-dichloroethane while keeping alkaline conditions by addition of aqueous NaOH, yielded a mixture of carbamate **33j** and unreacted **33a** after about 12 h. The most convenient procedure, however, was that of Corey *et al.*:<sup>142</sup> reaction of **33a** with 4 equivalents of methyl chloroformate and 6 equivalents of K<sub>2</sub>CO<sub>3</sub> in acetone gave, after two days at room temperature, the desired **33j** in about 50% yield.



The crystal structure of **33f**, crystallized as a single enantiomer, was elucidated by X-ray crystallography<sup>i</sup> (Figure 13). Complete crystallographic data are presented in Appendix III.



**Figure 13.** Crystal structure of oxadiazoline **33f**.

<sup>i</sup> Performed by Dr. J. Britten.

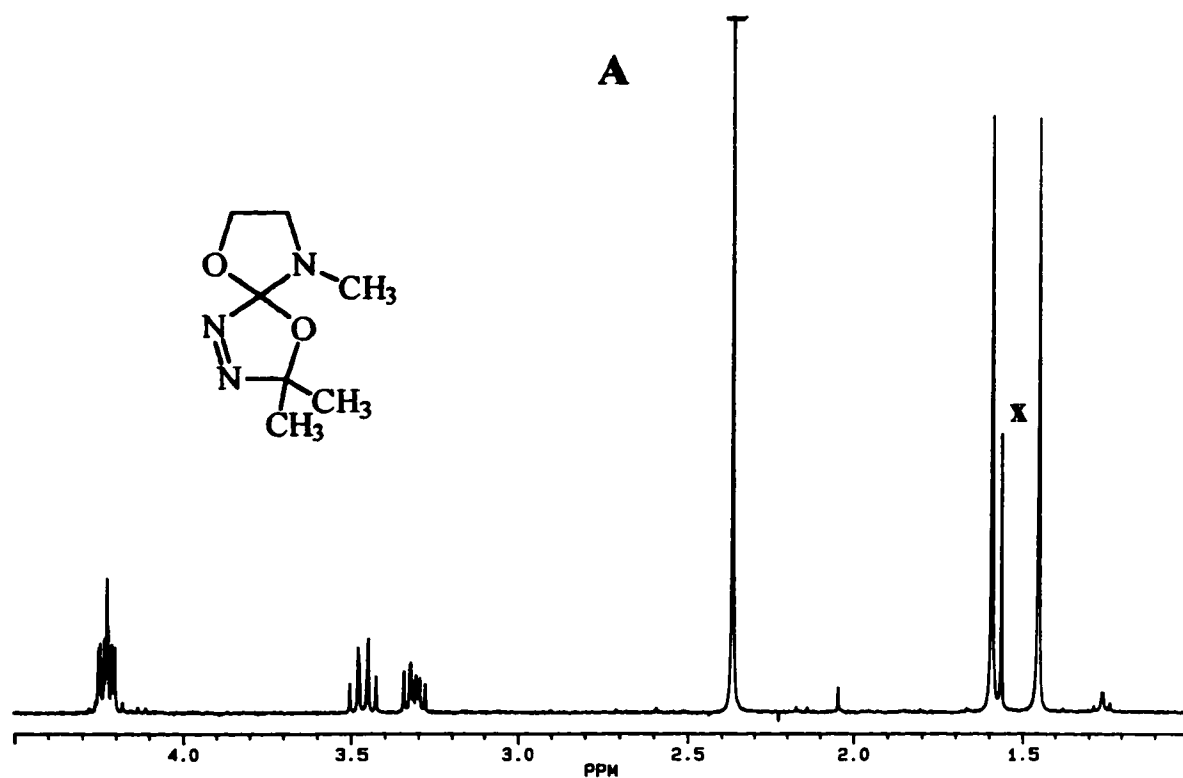
Various functional groups (NH, C=O, Ph, etc.) on the spiro oxadiazolines synthesized in this work give rise to recognizable infrared bands. One common feature, however, is the characteristic low-intensity N=N band at 1572-1581  $\text{cm}^{-1}$ .

The fragility of these oxadiazolines dictated the application of special techniques for the acquisition of mass spectra (see Section 4.2c). A detailed mass spectral study involving **33b** is currently in progress, in collaboration with D. Lavorato and Prof. J. K. Terlouw.

The  $^1\text{H}$ -NMR spectra of **33a-k**, in which the oxadiazoline ring is fused at C2 to C2 of an oxazolidine, exhibit complex splitting of the four methylene protons. For example, the 300 MHz  $^1\text{H}$  spectrum of **33b** is shown in Figure 14. The multiplets centered at about 3.38 ppm and 4.23 ppm are due to  $\text{NCH}_2$  and  $\text{OCH}_2$ , respectively. In order to explain this apparent complexity, a computer simulation<sup>i</sup> was performed, using PANIC (Bruker). The simulated spectrum, also presented in Figure 14, accurately reproduces the experimental spectrum. This analysis allowed extraction of the coupling constants from this ABMX spin system (Table VI). The geminal coupling constants ( $J_{\text{AB}} = -7.500$  Hz and  $J_{\text{MX}} = -8.130$  Hz) are comparable to those of 1,3-dioxolane, for which  $J = -8.3$  Hz.<sup>143</sup> Although the *cis/trans* relationship between  $\text{H}_\text{A}/\text{H}_\text{B}$  and  $\text{H}_\text{M}/\text{H}_\text{X}$  is not known, the similar magnitudes of the vicinal coupling constants suggest some averaging due to fast ring flexing (Figure 15). Again, these values are comparable to those of 1,3-dioxolane for which  $J_{\text{cis}} = 7.3$  Hz and  $J_{\text{trans}} = 6.0$  Hz.<sup>143</sup>

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<sup>i</sup> This simulation was performed by Christopher Barr, Agriculture Canada (St-Hyacinthe, Québec).



**Figure 14.** <sup>1</sup>H-NMR spectrum of oxadiazoline 33b. (A) Full experimental spectrum (200 MHz, CDCl<sub>3</sub>); X = dissolved H<sub>2</sub>O; (B) expansion of the experimental spectrum (processed with LB = -1, GB = 0.3); (C) simulated spectrum.

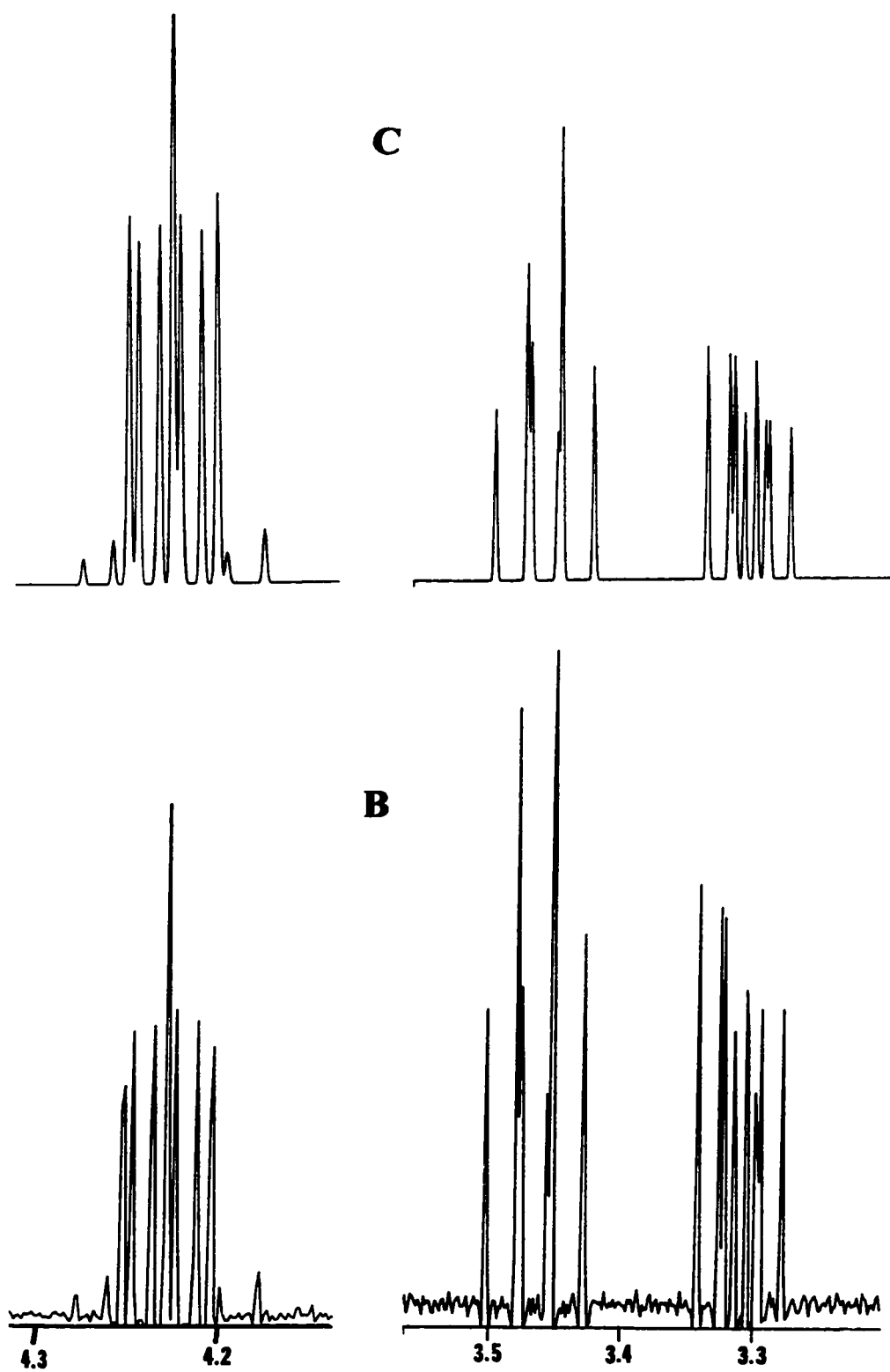
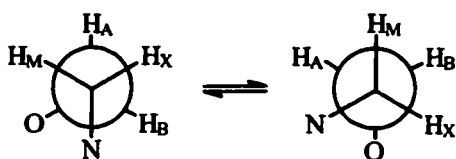


Figure 14 (continued).

**Table VI.**  $^1\text{H}$ -NMR data for the ABMX spin system in **33b**.

Chemical shifts, ppm		Calculated coupling constants, Hz <sup>a</sup>	
$\text{H}_\text{A}$	4.24	$J_\text{AB}$	-7.500
$\text{H}_\text{B}$	4.22	$J_\text{MX}$	-8.130
$\text{H}_\text{M}$	3.46	$J_\text{AM}$	7.029
$\text{H}_\text{X}$	3.31	$J_\text{AX}$	4.460
		$J_\text{BM}$	7.347
		$J_\text{BX}$	6.299

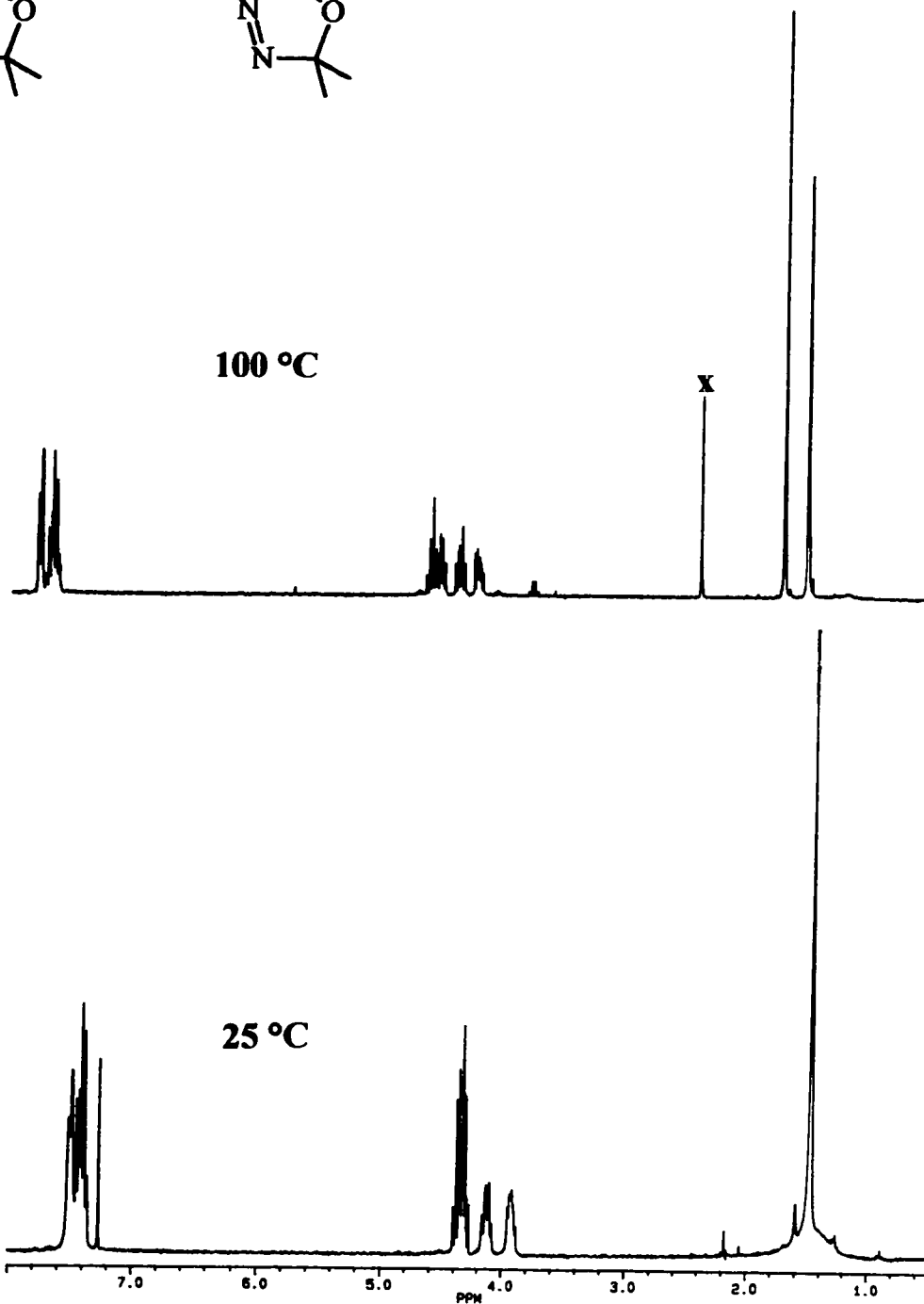
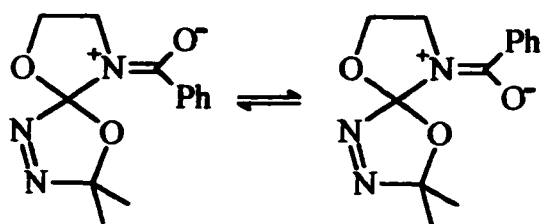
<sup>a</sup>Values accurate to  $\pm 0.05$  Hz (RMS error of analysis).**Figure 15.** Ring flexing in the oxazolidine ring of **33b**. The actual *cis/trans* relationship between  $\text{H}_\text{A}/\text{H}_\text{B}$  and  $\text{H}_\text{M}/\text{H}_\text{X}$  is not known.

The NMR spectra of N-carbonyl oxadiazolines **33c-j** were complicated by slow *cis-trans* isomerism, on the NMR time scale, of the amide bond. This generally resulted in broad resonances for spectra recorded at room temperature. Figure 16 shows the experimental  $^1\text{H}$  spectrum of **33f** as a function of temperature. Separate spectra for the two geometric isomers are observed as the temperature is lowered to *ca.*  $-60\text{ }^\circ\text{C}$  ( $\text{CDCl}_3$ , 300 MHz); complete coalescence does not occur until about  $100\text{ }^\circ\text{C}$ . Interestingly, one of the methyl groups at C2 resonates at 0.35 ppm; this somewhat unusual chemical shift is likely attributable to a conformation where the methyl group lies above the phenyl ring, subject to shielding caused by ring current effects. The enthalpy of activation for rotation of the amide C-N bond in **33f**, measured by dynamic NMR methods, is  $50.85 \pm 0.78$

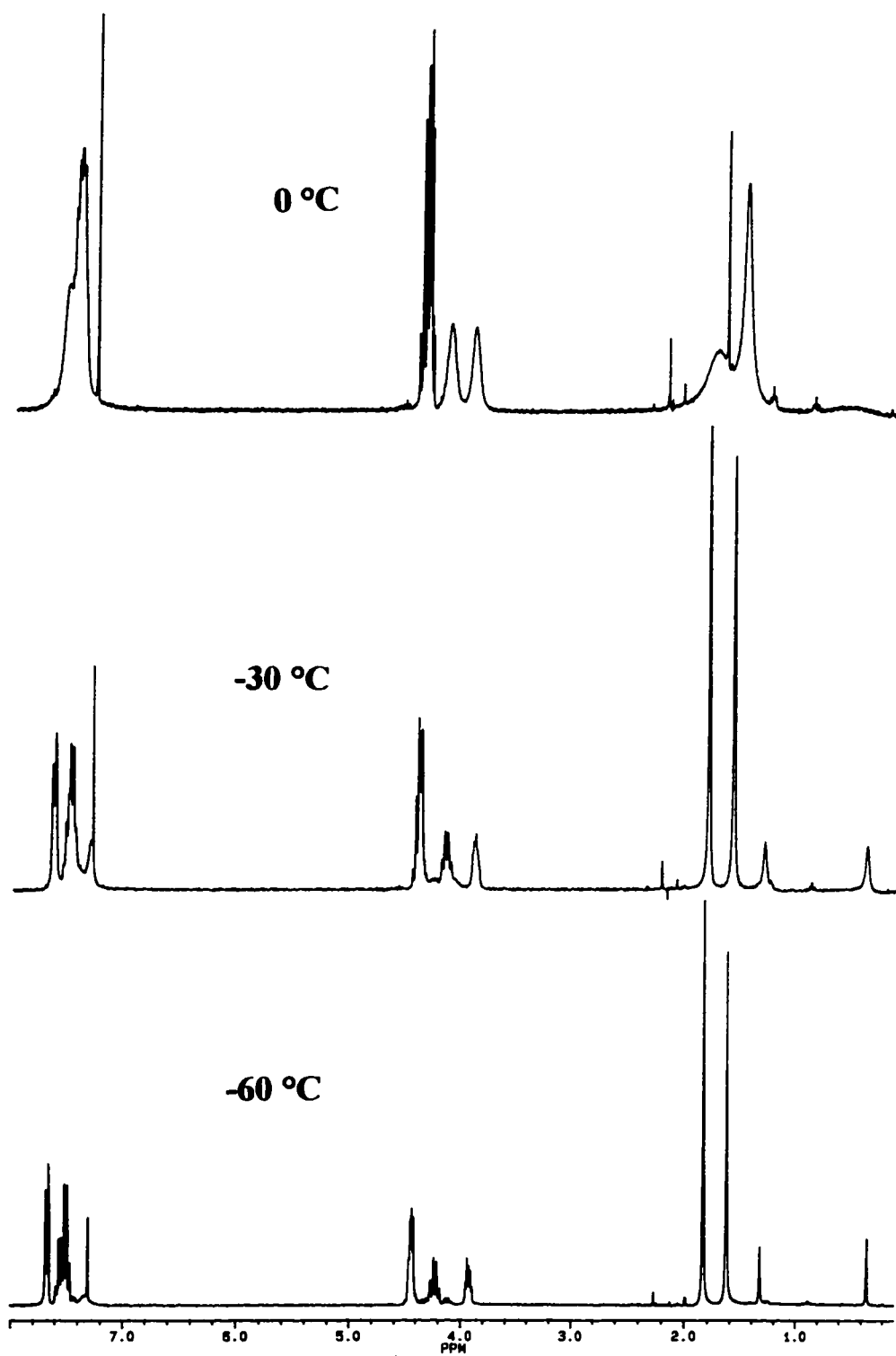
kcal/mol.<sup>i</sup> A study involving a series of N-carbonyl oxadiazolines described in this work and aimed at determining the relationship between structure and the activation parameters is currently in progress, in collaboration with P. Hazendonk and Prof. A. D. Bain.

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<sup>i</sup> Determined by P. Hazendonk.



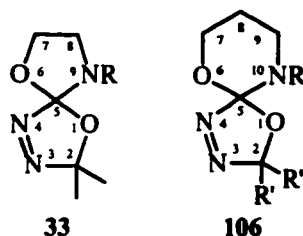
**Figure 16.** 300 MHz  $^1\text{H}$ -NMR spectrum of 33f as a function of temperature; in  $\text{CDCl}_3$  ( $-60^\circ$  to  $25^\circ\text{C}$ ) or in hexachlorobutadiene ( $100^\circ\text{C}$ ); X = acetone, from thermolysis of 33f.



**Figure 16 (continued).**



$^{13}\text{C}$ -NMR spectroscopy was the most useful tool in the identification of these spiro oxadiazolines, with two characteristic carbons generally resonating in the regions 116-123 ppm (C2) and 128-139 ppm (C5) (see Figure 17). Complete data for these compounds are listed in the Experimental Section.



**Figure 17.** Numbering system used throughout this thesis for spiro oxadiazolines **33** and **106**.

## 2.3 Thermolysis of 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines

### 2.3.1 Thermolysis Rate Constants

Oxadiazolines **33a-k** and **106c-e** were thermolyzed in benzene- $d_6$ , at 90 °C, in sealed NMR tubes. Disappearance of starting material was monitored by means of integration of appropriate resonances in the 300 MHz  $^1\text{H}$ -NMR spectra. The choice of the  $^1\text{H}$  resonance(s) for integration was sometimes limited by the complexity of the spectrum and, in several cases, resonances were broad due to restricted rotation about the C-N amide bond (see Section 2.2). Nevertheless, good fits to the first-order rate equation were obtained for five to ten experimental points generally covering the range 0-60% (or more) of completion. Experimental details are given in Section 4.3.1, and complete thermolysis data are shown in Appendix I.

The rate data, collected in Table VII, show a relatively low sensitivity to structure. There is some risk of overinterpretation of the data because the observed values span only a 30-fold rate change. Moreover, as will be seen in the following sections, there is not a unique decomposition pathway for all oxadiazolines and, in some cases, at least two competing initial steps may be involved in a thermolysis. Nonetheless, some trends in the rate constants are evident.

**Table VII.** First-order rate constants for the thermolysis of oxadiazolines **33** and **106** at 90 °C in benzene- $d_6$ .

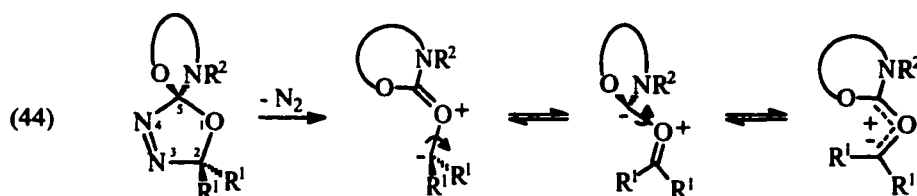
Oxadiazoline	First-order rate constant, $s^{-1}$ ( $\times 10^5$ ) <sup>a</sup> (half-life, h)		$k_{rel}$
<b>33a</b>	$1.61 \pm 0.16$	(11.95)	1.00
<b>33b</b>	$4.78 \pm 0.21$	(4.03)	2.97
<b>33c</b>	$4.66 \pm 0.14$	(4.13)	2.89
<b>33d</b>	$14.0 \pm 0.3$	(1.38)	8.70
<b>33e</b>	$5.62 \pm 0.23$	(3.43)	3.49
<b>33f</b>	$7.14 \pm 0.50$	(2.70)	4.43
<b>33g</b>	$5.76 \pm 0.36$	(3.34)	3.58
<b>33h</b>	$5.60 \pm 0.32$	(3.44)	3.48
<b>33i</b>	$8.74 \pm 0.29$	(2.20)	5.43
<b>33j</b> <sup>b</sup>	(estimated $t_{1/2} > 12$ h)		< 1
<b>33k</b>	$3.28 \pm 0.02$	(5.87)	2.04
<b>106c</b>	$9.02 \pm 0.29$	(2.13)	5.60
<b>106d</b>	$48.2 \pm 5.5$	(0.40)	29.9
<b>106e</b>	$16.2 \pm 0.6$	(1.19)	10.1

<sup>a</sup> Based on error limits of slope at 95% confidence level (see Appendix I).

<sup>b</sup> Could not be determined due to wide, unresolved resonances.

Both steric and electronic factors are expected to influence the rate of decomposition of these oxadiazolines. The first thermolytic step is generally a cycloreversion affording molecular nitrogen and a carbonyl ylide. At the transition state,

the 1,3-interactions between groups  $R^1$  at C2 and substituents at C5 will be relieved because of bond rotations, as shown in eq. 44. Thus, relief of strain from non-bonded interactions should be a factor. Bulky substituents therefore place the ground state closer in energy to the transition state. In addition, as ylide character develops, negative charge accumulates at C2 and C5 of the oxadiazoline, and electron withdrawing groups in proximity to the sites of charge development should cause some rate enhancement from inductive effects. For example, a  $\rho$  value of 0.21 was found from a Hammett plot of thermolysis rate constants (100 °C) vs  $\sigma$  values of *para* substituents on the aryl group of 2-aryloxy-2-methoxy- $\Delta^3$ -1,3,4-oxadiazolines.<sup>133</sup> A similar thermolysis rate enhancement caused by inductive effects of electron-withdrawing groups was observed in spiro-fused  $\beta$ -lactam oxadiazolines.<sup>144</sup>



Experimentally, we find that compounds where the oxadiazoline moiety is fused to a six-membered ring have larger rate constants than analogous compounds in which the oxadiazoline ring is fused to a five-membered ring:  $k_{106d}, k_{106e} > k_{33f}$ , and  $k_{106c} > k_{33b}$ . This effect may be due in part to a small increase in 1,3-interactions in going from a five-membered to a six-membered ring fused at C5 (the internal bond angles<sup>145</sup> in cyclopentane, *ca.* 105°, are slightly smaller than those in cyclohexane, *ca.* 111.5°), and to easier increase,

in the larger ring system, of the OCN bond angle as the relevant carbons rehybridize from  $sp^3$  in the oxadiazoline to roughly  $sp^2$  in the ylide. The origin of the 3-fold increase in rate constant from **106e** to **106d** could be ascribed to the same feature, **106e** having bond angle constraints at both C2 and C5.

The nature of the substituent on the nitrogen also affects the rate of thermolysis. For instance, in the series of analogous compounds **33a**, **33b**, **33f**, and **33k**, there is an observable effect on the rate constant in changing  $R^2$  from hydrogen ( $k_{rel} = 1.00$ ) to methyl (2.97), carbonyl (4.43), or sulfonyl (2.04), consistent with the expected stabilization of the transition state by electron-withdrawing groups. Within the N-carbonyl series, we find the following trend in relative rate constants ( $k_{rel}$ ):  $k_{33j}$  ( $OCH_3$ ,  $< 1$ )  $< k_{33c}$  (H, 2.89)  $< k_{33e}$  (vinyl, 3.49)  $< k_{33f}$  (Ph, 4.43)  $< k_{33d}$  ( $CH_3$ , 8.70); thus, substituents that reduce the electron-withdrawing effect of the N-carbonyl group (*e.g.* methoxy in **33j**) tend to decrease the rate of decomposition of the oxadiazoline (the reason for the relatively large rate constant for thermolysis of **33d** is not understood). Comparison of the analogous N-benzoyl derivatives also shows a rise in the rate constants<sup>i</sup> caused by increasingly electron-withdrawing substituents, although the spread of  $k$  values is small:  $k_{33g}$  (2-OMe, 3.58)  $\approx k_{33h}$  (4-OMe, 3.48)  $< k_{33f}$  (unsubstituted, 4.43)  $< k_{33i}$  (4- $NO_2$ , 5.43).

The above trends in thermolysis rate constants support the intermediacy of carbonyl ylides in the thermolysis of these spiro oxadiazolines: if carbenes were the initial species formed, then electron-donating groups, which stabilize the carbenes, would be

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<sup>i</sup> For consistency, rate constants for **33f**, **33h**, and **33i** were all measured from an analogous  $OCH_2$  multiplet, but the same resonance could not be used in the case of **33g**.

expected to also stabilize the corresponding transition states, and therefore to increase the rate of thermolysis. Clearly, the opposite effect is observed.

### 2.3.2 General Thermolytic Scheme

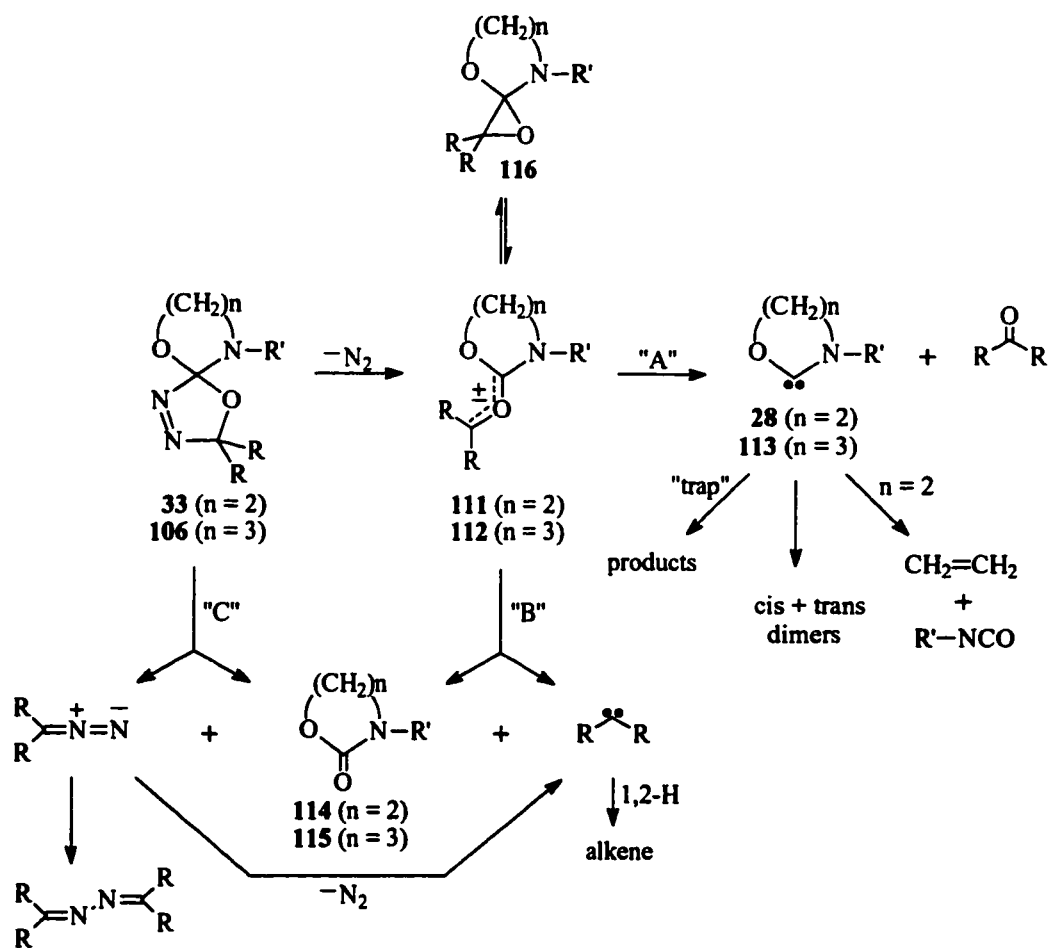
In this section, a generalized scheme for thermal decomposition of the spiro 2-alkoxy-2-amino oxadiazolines is first presented. Experimental evidence, based on product studies, for the mechanisms specifically involved in the thermolysis of each oxadiazoline will then be discussed in detail in the following pages.

Experimentally, oxadiazolines **33** and **106** were thermolysed as degassed benzene (or benzene- $d_6$ ) solutions at 90 °C. Decomposition was usually complete within 24 h, although longer reaction times were necessary with a few oxadiazolines (see Table VII). For small scale experiments carried out in sealed NMR tubes, initial substrate concentrations were on the order of 0.25 M. Larger scale thermolyses were performed in sealable tubes, usually at initial concentrations of approximately 0.05 M.

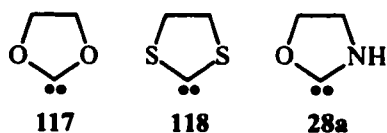
Invariably, the major route in the thermolysis of these compounds is initiated by extrusion of molecular nitrogen, which produces carbonyl ylide **111/112** (Scheme XXIV). Fragmentation of this transient species may then occur through pathway A to generate aminooxycarbene **28/113** and a ketone. An alternative reaction for ylide **111/112** is rupture of the other C-O bond, pathway B, yielding in this case a dialkyl carbene, which undergoes fast 1,2-H migration to the alkene, and carbonyl compound **114/115**. Another possible fate for **111/112** is reversible electrocyclic ring closure to spiro-fused oxirane

**116.** Decomposition of **33/106** may also take place through a different 1,3-dipolar cycloreversion to form a diazoalkane and, again, carbonyl compound **114/115** (pathway C). Under our thermolytic conditions, most of the diazoalkane reacts further to generate an azine, by a mechanism that is yet unknown, while a small fraction of it may generate a dialkyl carbene from loss of nitrogen.

**Scheme XXIV**



Five-membered aminooxycarbenes **28** produced at elevated temperatures sometimes fragment to ethylene and an isocyanate, a lifetime-limiting reaction known to occur in dioxo<sup>45,79,99,100,146</sup> and dithio<sup>79,110,147</sup> analogues where CO<sub>2</sub> and CS<sub>2</sub>, respectively, are the coproducts of ethylene (see also Section 1.6.1.3). Sauers has calculated (MP2 / 6-31G\*\*) the activation energy for fragmentation of the dioxy<sup>146</sup> (**117**), dithio<sup>148</sup> (**118**), and aminooxy<sup>148</sup> (**28a**) carbenes as 8.8, 6.4, and 17.6 kcal/mol, respectively. This suggests that the facile fragmentation, particularly for **117** and **118**, may effectively prevent any useful bimolecular reactions of these carbenes. In fact, to the best of our knowledge, no intermolecular reactions have been reported for carbenes **117** and **118**, although the product from an apparent intramolecular insertion into an OH bond has been isolated (1% yield) for a derivative of **117**.<sup>101</sup> In the following sections, our experimental results will unambiguously demonstrate that derivatives of **28a** participate in bimolecular reactions with a wide variety of substrates.

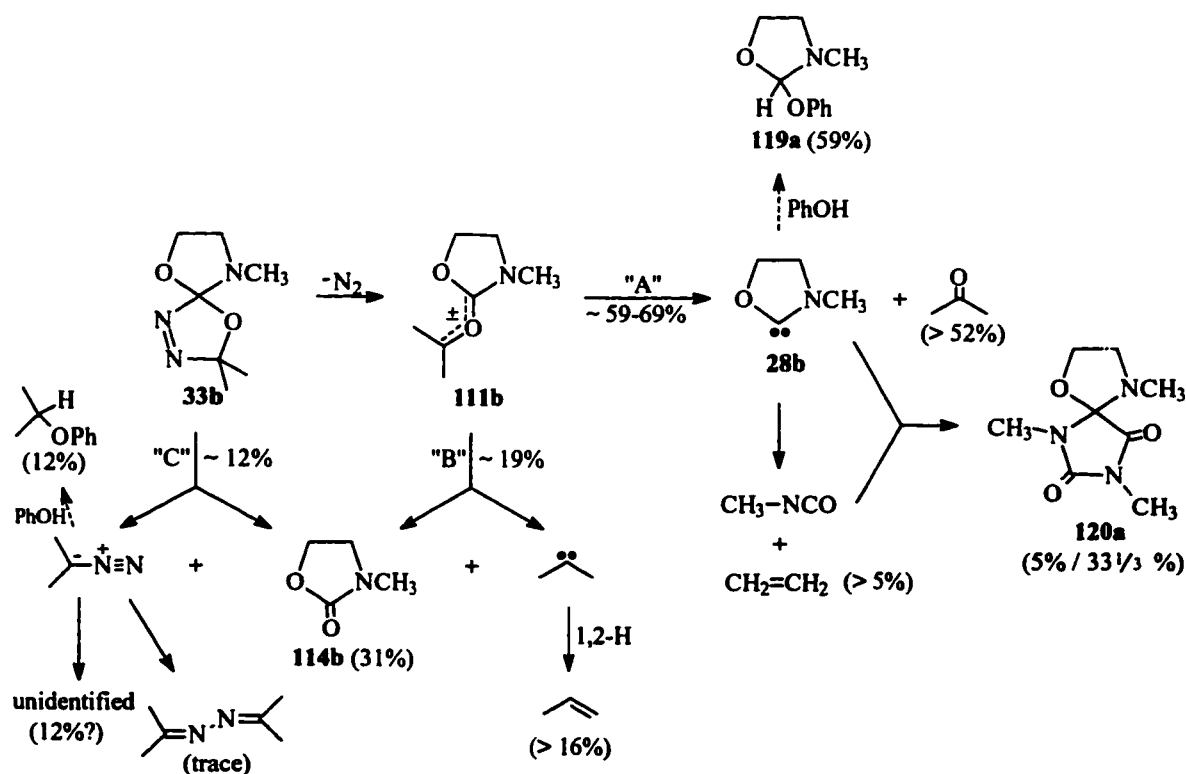


### 2.3.3 Thermolysis of **33b**

Oxadiazoline **33b** was the first compound of this type for which a detailed thermolytic scheme was completed (Scheme XXV). The intermediate carbonyl ylide **111b**, formed by initial extrusion of N<sub>2</sub>, fragments predominantly *via* pathway A to form

3-methyloxazolidin-2-ylidene, **28b**, and acetone. Trapping of **28b** with phenol, in an NMR tube, gave carbene adduct **119a** in 59% yield. In the absence of an efficient trap, this carbene does not dimerize; it fragments to ethylene and methyl isocyanate. The latter then acts as a trap for newly-formed carbene **28b**, and a 1: 2 (carbene: trap) adduct, spiro hydantoin **120a**, is found as a final product in about 15% yield. Formation of **120a** was confirmed by comparison of the NMR and GC-MS data of the product mixture with an authentic sample prepared by thermolysing **33b** in the presence of an excess of methyl isocyanate (refer to Section 2.4.2 for a discussion of this reaction and related ones).

Scheme XXV





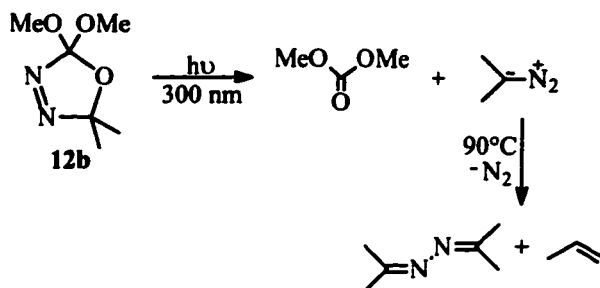
Other products resulting from the thermal decomposition of this oxadiazoline include 3-methyl-2-oxazolidinone (114b) and propene, as well as traces of acetone azine. Their formation suggests that both pathways B and C compete with pathway A. Although diazo compounds are known thermal sources of carbenes, under our experimental conditions 2-diazopropane produces almost exclusively acetone azine, and very little 2-propylidene. This was confirmed by two independent experiments, described in the next paragraphs.

In the first experiment, 2-methoxy-5,5-dimethyl-2-phenoxy- $\Delta^3$ -1,3,4-oxadiazoline (86d), which is known to decompose partially *via* a pathway analogous to C (Section 2.1), was thermolysed under our experimental conditions and found to produce mostly azine, with only traces of propene, a result which is opposite to that of 33b.

The second experiment involved thermolysis of 2-diazopropane at 90 °C in order to determine the relative yields of acetone azine and propene. Two identical benzene- $d_6$  solutions of 2,2-dimethoxy-5,5-dimethyl- $\Delta^3$ -1,3,4-oxadiazoline (12b), a clean photolytic source of 2-diazopropane,<sup>149</sup> were photolysed to completion at 300 nm. Following irradiation, one sample was immersed in an oil bath at 90 °C, while the other was left at room temperature in the dark. According to Scheme XXVI, the amount of 2-diazopropane produced in the photolysis should equal that of dimethylcarbonate. Integration of the acetone azine resonances at 1.86 ppm and 1.89 ppm, relative to that of dimethylcarbonate (3.38 ppm), indicated that in both samples 86% of the 2-diazopropane had produced acetone azine. An unidentified product giving rise to two singlets at 1.64

and 1.68 ppm accounted for most of the difference, while propene was barely detectable. Within experimental error, the final product ratios in the two samples were identical. Although the initial concentration of 2-diazopropane during thermolysis in this experiment was higher than it would be at any time during the thermolysis of oxadiazolines, these experiments support the idea that under our conditions, very little propene is derived from 2-diazopropane.

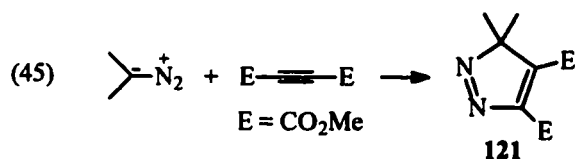
Scheme XXVI



As mentioned above, 3-methyl-2-oxazolidinone (114b), a product common to pathways B and C, is produced in 31% yield in the thermolysis of 33b, while only trace amounts of acetone azine are detected. However, an unidentified compound shows up in the  $^1\text{H}$ -NMR spectrum of the crude thermolysate with equal intensity singlets at 1.09 ppm (C-CH<sub>3</sub>), 1.26 ppm (C-CH<sub>3</sub>), 2.43 ppm (N-CH<sub>3</sub>), and 2.44 ppm (N-CH<sub>3</sub>) (in benzene-d<sub>6</sub>); this product seems to be derived from 2-diazopropane, although its exact nature could not be determined. All attempts to isolate it failed, and it could not be associated with certainty to any peak in the GC-MS trace of the thermolysed mixture. Assuming the above  $^1\text{H}$ -NMR assignments are correct, it is formed in 12% yield. Interestingly,

formation of this product was quenched by addition of phenol to the solution of **33b** prior to thermolysis; with this trap, 2-phenoxypropane is formed, also in 12% yield. This undoubtedly results from reaction of 2-diazopropane with phenol. In the light of these results, it appears that pathway C in Scheme XXV contributes to approximately 12% of the decomposition of **33b**, while pathway B must account for the remaining 19% of **114b** produced. This therefore provides an upper limit of about 69% for the yield of carbene **28b**.

The formation of both ethylene and propene from **33b**, observed by  $^1\text{H-NMR}$ , was confirmed by their conversion to 1,2-dibromoethane and 1,2-dibromopropane, respectively, followed by GC-MS detection (see Experimental Section). Formation of 2-diazopropane was also confirmed by the identification of pyrazole **121**, when **33b** was thermolysed in the presence of DMAD (eq. 45).<sup>150</sup>

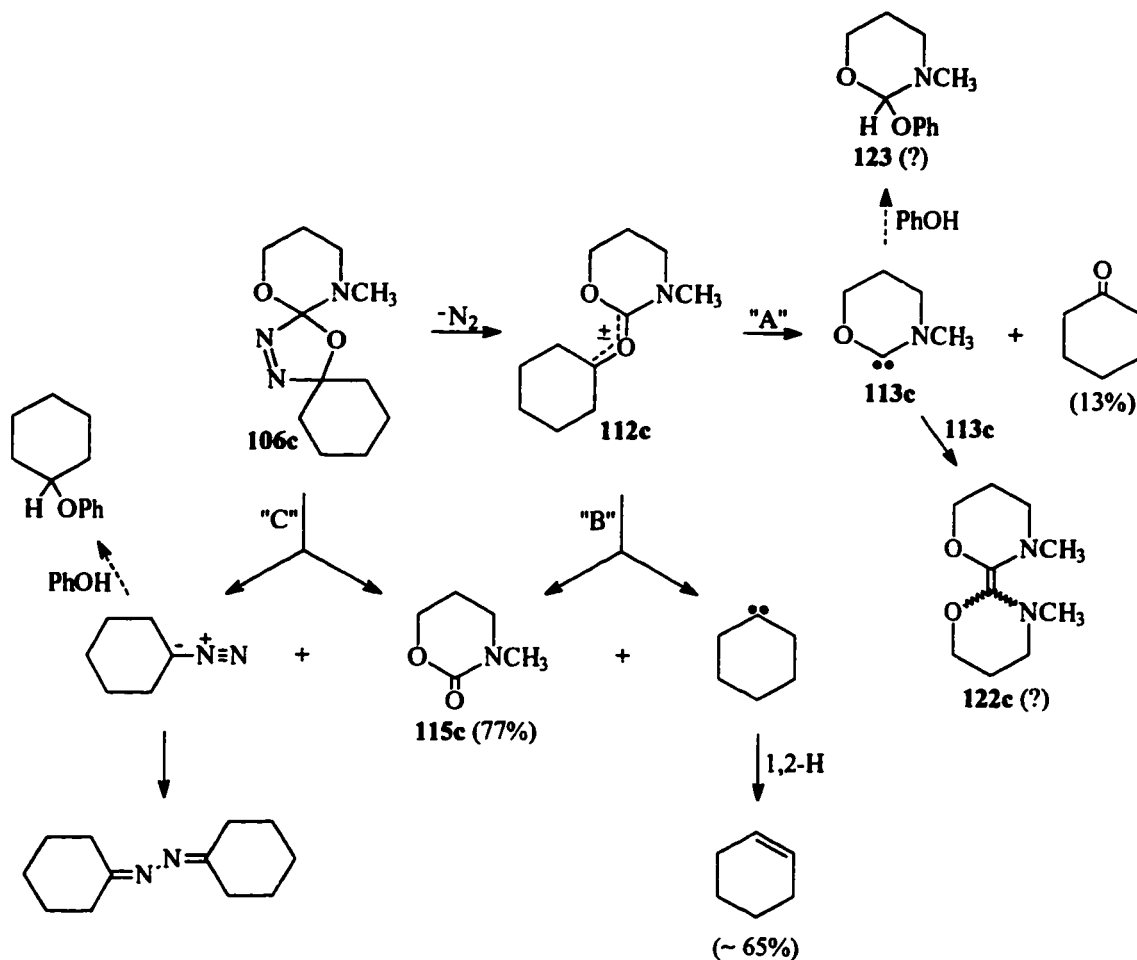


#### 2.3.4 Thermolysis of **106c**

Oxadiazoline **106c** was synthesized as a possible precursor to the six-membered alkoxyaminocarbene **113c**. In contrast to the five-membered analogue, **28b**, fragmentation of **113c** should not occur to limit its lifetime. Results from the product studies on the thermolysis of **106c**, however, were disappointing. With this oxadiazoline,

competition between pathways A and B for the decomposition of carbonyl ylide **112c** was found to favor pathway B (Scheme XXVII). Thus, observed NMR yields were 77% for carbonyl compound **115c** and *ca.* 65% for cyclohexene, compared to only 13% for cyclohexanone, the coproduct in the formation of carbene **113c**. A small amount of the azine of cyclohexanone was also detected by GC-MS analysis; it indicates that a small fraction of the oxadiazoline decomposes *via* pathway C. This accounts, at least in part, for the discrepancy between the yields found for **115c** (77%) and cyclohexene (*ca.* 65%). It must be noted that no carbene dimer (**122c**) could be unambiguously identified in the thermolysates.

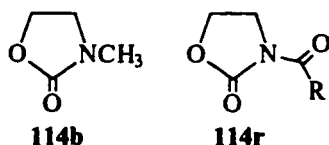
## Scheme XXVII



A sample of **106c** was also thermolysed in a sealed NMR tube in the presence of excess phenol. Although the yield of carbene **113c** should be on the order of 13%, based on the amount of cyclohexanone produced, no conclusive evidence ( $^1\text{H}$ -NMR, GC-MS) could be found for O-H insertion product **123**. However, in addition to the products mentioned above, phenoxy-cyclohexane was detected by GC-MS. This compound results from the reaction of diazocyclohexane, produced *via* pathway C, with phenol.

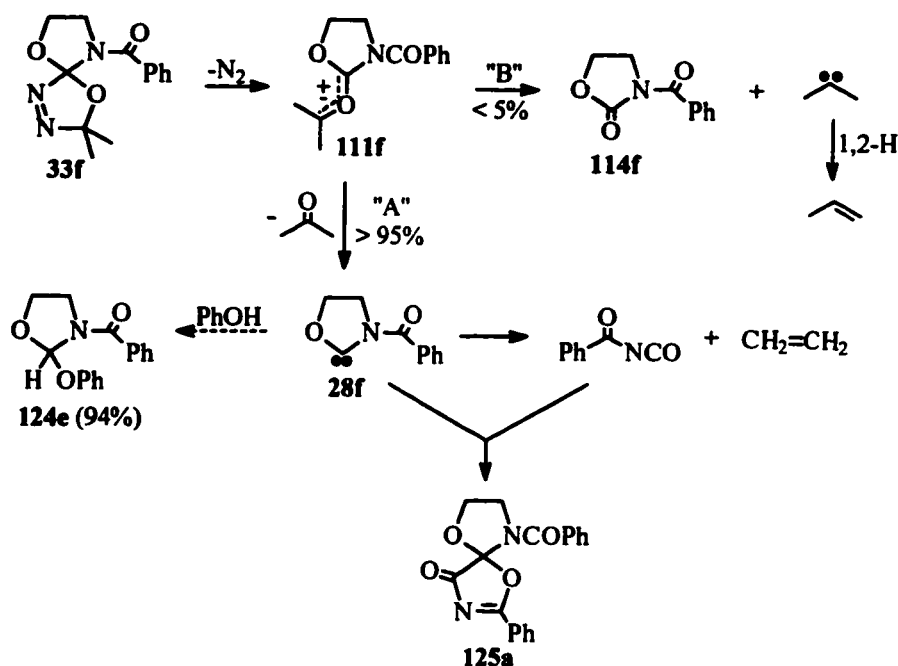
### 2.3.5 Thermolysis of 33f

The above results showed that oxadiazolines **33b** and **106c** (N-methyl) generate aminooxycarbenes upon thermolysis, although the yields of these reactive intermediates are not quantitative because of competing decomposition reactions. It was thought that fragmentation of the carbonyl ylide in the desired sense (pathway A in Scheme XXIV) might be optimized by destabilizing the unwanted fragmentation product. For instance, this could perhaps be accomplished by changing the N-substituent in **114b** to an electron-withdrawing carbonyl group, as in **114r**:



In contrast to the N-methyl oxadiazolines, N-carbonyl oxadiazolines such as **33f** proved to be very efficient sources of cyclic aminooxycarbenes. Extrusion of N<sub>2</sub> from **33f** results in carbonyl ylide **111f** which fragments essentially unidirectionally *via* pathway A to the oxazolidin-2-ylidene **28f** and acetone (Scheme XXVIII). Thermolysis of the oxadiazoline in the presence of phenol in an NMR tube revealed a 94% yield for the phenol insertion product **124e**. In comparison, the yield of 3-benzoyl-2-oxazolidinone (**114f**), formed by either routes B or C, was too low to be measured by integration of its <sup>1</sup>H-NMR signals; however, **114f** has been isolated from a larger scale thermolysis in *ca.* 2% yield (Section 4.4.3).

## Scheme XXVIII



Extensive studies on the thermal decomposition of **33f** at 90 °C in benzene also demonstrated the formation of ethylene but, in this case, neither propene nor acetone azine were detectable by  $^1\text{H-NMR}$ , in accordance with the proposed scheme. NMR spectroscopy suggested the formation of a unique non-volatile product in high yield. However, GC-MS analyses of the thermolysates showed the presence of at least three apparently related compounds, in addition to two or three other minor products formed in very low yield ( $< 5\%$  each, *vide infra*). It latter became obvious that the major product does not survive GC-MS, and therefore only the low-yield compounds were being observed by GC-MS. Identification of the apparently most important component (as

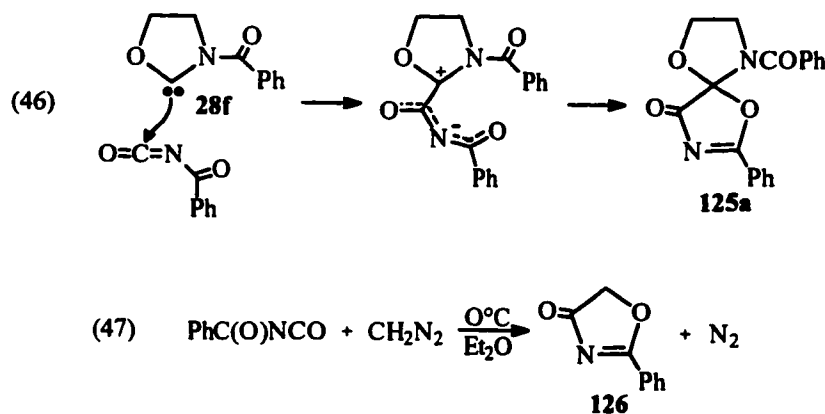
observed by GC-MS) as benzoyl isocyanate suggested that the actual major product might be derived from reaction of carbene **28f** with benzoyl isocyanate.

Several experiments were necessary to determine the exact identity of this major product, which was eventually found to be spiro 4(5*H*)-oxazolone **125a**. Attempts to isolate it by chromatography resulted in its complete decomposition. Similarly, crystallization of **125a** from the crude oily product mixture, by addition of 40% ethyl acetate in hexane, for instance, was not successful. However, a white solid was obtained after dissolving the crude in diethyl ether followed by evaporation of the solvent on a rotary evaporator. The  $^1\text{H}$ -NMR spectrum of these crystals was very similar to that of the crude thermolysate, thus demonstrating that its yield is nearly quantitative. An oxazolidine ring in **125a** was suggested by multiplets ( $\text{CDCl}_3$ ) at 4.00-4.12 ppm ( $\text{NCH}_2$ ) and 4.47-4.59 ppm ( $\text{OCH}_2$ ), and the aromatic region showed a complex multiplet at 7.25-7.80 ppm, integrating for about 8 Hs, as well as a poorly resolved doublet at 8.26 ppm (2 Hs), corresponding to the *ortho* protons of a  $\text{PhC(O)}$  group. In spite of its instability towards hydrolysis, its  $^{13}\text{C}$  spectrum could also be inferred, with a high degree of certainty, by comparing spectra from samples of varying purity and subtracting peaks due to impurities which were eventually identified. Characteristic  $^{13}\text{C}$  resonances ( $\text{CDCl}_3$ , in ppm) include: 47.14 ( $\text{NCH}_2$ ), 68.43 ( $\text{OCH}_2$ ), 108.38 (spiro C), 167.73 ( $\text{PhC(O)}$ ), as well as 181.80 and 184.13 which were assigned to carbons 2 and 4 of the oxazolone ring. The crude product turned out to be pure enough to allow MS experiments: the EI spectrum showed a low-intensity molecular ion ( $m/z$  322, too small to obtain high-resolution data), while CI-MS



using  $\text{NH}_3$  gave the expected  $(\text{M}+\text{H})^+$ . IR spectra of 4(5*H*)-oxazolones typically show characteristic bands in the ranges  $1786\text{--}1754\text{ cm}^{-1}$  for  $\text{C}=\text{O}$  and  $1575\text{--}1499\text{ cm}^{-1}$  for  $\text{C}=\text{N}$  stretchings;<sup>151</sup> accordingly, two intense bands appeared at  $1783\text{ cm}^{-1}$  and  $1558\text{ cm}^{-1}$  in the IR spectrum of **125a**.

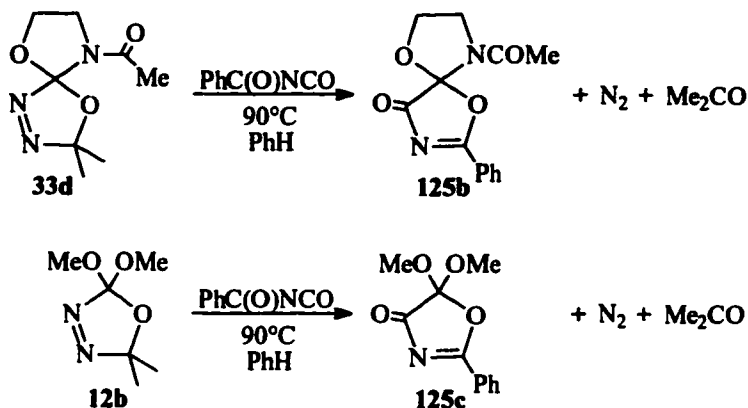
The novel spiro oxazolone **125a** with two heteroatom substituents at C5 presumably forms by the initial nucleophilic attack of carbene **28f** on benzoyl isocyanate, followed by cyclization of the dipolar intermediate (eq. 46). This reaction is analogous to that between diazomethane and benzoyl isocyanate which was reported to yield 68-70% of **126**, a 4(5*H*)-oxazolone unsubstituted at C5 (eq. 47).<sup>152</sup>



In order to obtain independent support for the structure of **125a**, as well as to probe for the generality of this reaction between benzoyl isocyanate and nucleophilic carbenes, aminooxycarbene **28d** and dimethoxycarbene (**3**), generated from oxadiazoline precursors, were separately reacted with benzoyl isocyanate. In both cases, spectroscopic data obtained from crude product mixtures paralleled those from **125a**, indicating

formation of oxazolones **125b** and **125c** (Scheme XXIX). This new reaction contrasts that between nucleophilic carbenes and alkyl or aryl isocyanates which usually produces 1:2 adducts (Section 1.6.2.3.3).

Scheme XXIX



As mentioned above, compound **125a** hydrolyses relatively rapidly when exposed to the atmosphere, and this results in a single product. Its deliberate hydrolysis, by exposing the crude thermolysed mixture to water for several days, resulted in slightly impure samples from which preliminary spectroscopic data could be obtained. These data are consistent with structure **127a** (see Scheme XXX). As with its precursor oxazolone, attempted purification by chromatography resulted in its complete decomposition. However, a sample of **127a** of reasonable purity was obtained by precipitation from a benzene solution, over the course of a few weeks; the results of an elemental analysis of this sample (Section 4.3.5) support the proposed structure, despite the discrepancies between calculated and observed values due to impurities. All attempts to obtain crystals suitable for X-ray analysis failed. The  $^{13}\text{C}$ -NMR spectrum of **127a** recorded in  $\text{CDCl}_3$  was

puzzling because only three of the expected four resonances were observed in the carbonyl region, at 160.19, 165.64, and 167.84 ppm. This is due to overlap of two peaks at 160.19 ppm, as was revealed by obtaining the spectrum in CD<sub>3</sub>OD, in which two distinct peaks were observed at 158.81 and 159.48 ppm, in addition to the other two at 170.61 and 172.41 ppm. The latter two resonances were tentatively assigned to the two non-equivalent PhC(=O)N groups, while the former likely correspond to the two carbonyl groups of the oxalyl moiety, by comparison with published data for oxalic acid derivatives.<sup>i</sup> Another noteworthy feature of the <sup>13</sup>C spectrum is the possible slow rotation about one of the amide C-N bonds, as implied by a barely-resolved small resonance appearing next to the main OCH<sub>2</sub> peak, suggestive of a minor conformational isomer. Other spectroscopic data, presented in Section 4.3.5, support the proposed structure. Hydrolysis of **125b** also gave the analogous product (not shown).

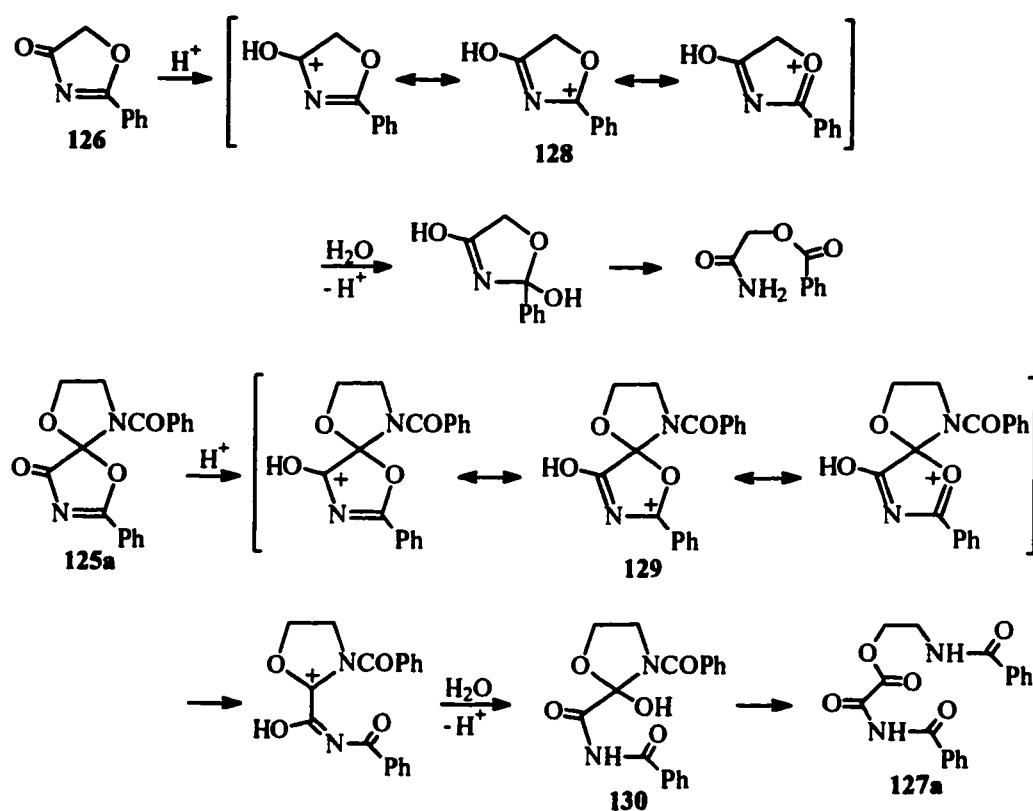
Hydrolysis of a 4(5*H*)-oxazolone fused at C5 to C2 of an oxazolidine thus results in cleavage of the C(5)-O bond of the oxazolone; this contrasts with hydrolyses reported for other 4(5*H*)-oxazolones, in which cleavage occurs at the carbon-nitrogen double bond.<sup>152,153</sup> A possible mechanism for the acid-catalysed hydrolysis of **125a** is proposed in Scheme XXX and compared to that of the unsubstituted compound. Initial protonation of the carbonyl group in **126** and **125a** would result in stabilized cations **128** and **129**, respectively. For the unsubstituted compound, nucleophilic attack by water presumably occurs on **128**, and is followed by ring opening through C-N bond cleavage. In contrast,

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<sup>i</sup> For example, dimethyl oxalate:  $\delta$  C=O (CDCl<sub>3</sub>) 157.63 ppm; and the diamide of oxalic acid:  $\delta$  C=O (DMSO-*d*<sub>6</sub>) 162.49 ppm.<sup>216</sup>

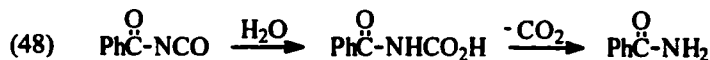
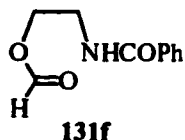
in the case of **129**, ring opening may occur *via* breakage of the C-O bond to form another cation, stabilized in part by the C2 heteroatoms. This could eventually result in an unstable oxazolidine, **130**, substituted with a hydroxyl group at C2; further hydrolysis of this intermediate would yield the final product, **127a**. 2-Hydroxyoxazolidines have been postulated as intermediates in the hydrolysis of oxazolines.<sup>154</sup>

Scheme XXX



3-Benzoyl-2-oxazolidinone, **114f**, was mentioned above as one of the minor products formed in the thermolysis of **33f**. Two others were benzamide and N-[2-(formyloxy)ethyl]benzamide (**131f**). The former is attributed to decarboxylation of N-benzoylcarbamic acid formed from hydrolysis of benzoyl isocyanate by traces of water

present during or after thermolysis (eq. 48).<sup>i</sup> Compound **131f** is most likely a hydrolysis product derived from the aminooxycarbene, **28f**. Thermolysis of **33f** in the presence of a few drops of water yielded **131f** as the main product (*ca.* 56%), along with benzamide (*ca.* 20%).



### 2.3.6 Thermolysis of Other N-Carbonyl Oxadiazolines **33**

During the course of this work, a number of N-carbonyl oxadiazolines analogous to **33f** were synthesized. A number of them were prepared mainly for the purpose of investigating the rotational barriers of their amide bonds (see Section 2.2), and their thermal chemistry was therefore not investigated in detail. However, **33d** (N-acetyl) and **33e** (N-methacryloyl) were used extensively as thermal sources of aminooxycarbenes which they produce, like **33f** (N-benzoyl), in essentially quantitative yields. These experiments are described below.

Available spectroscopic data for compounds derived from N-carbonyl oxadiazolines **33** are presented in Section 4.3.6.

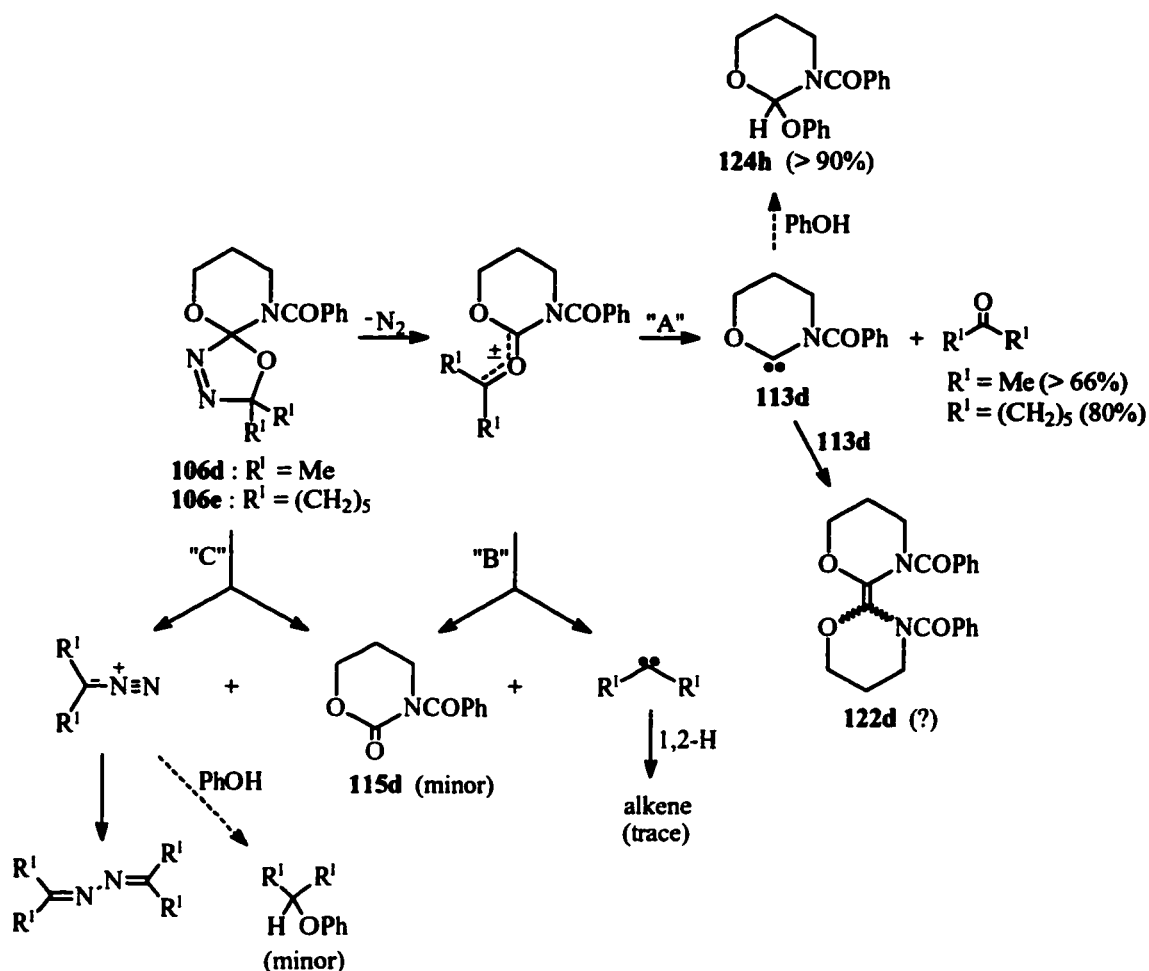
<sup>i</sup> A sample of benzoyl isocyanate stored on the shelves was gradually converted to benzamide and N,N'-dibenzoylurea, the latter presumably arising from the reaction of benzamide with benzoyl isocyanate.

### 2.3.7 Thermolysis of 106d and 106e

As for **106c**, the precursor to the six-membered N-methyl aminooxycarbene (**113c**), oxadiazolines **106d** and **106e** were synthesized as six-membered N-carbonyl carbene precursors in which fragmentation would not limit the carbene lifetime, in contrast to the five-membered analogues. The preparation and purification of both of these compounds were problematic, and they could only be obtained in low yields.

Initial attempts to generate carbene **113d** involved dispiro oxadiazoline **106e**. Thermolyses of this compound in NMR tubes resulted in the production of cyclohexanone, the coproduct of **113d**, in about 80% yield (Scheme XXXI). In addition to traces of cyclohexene, detected by  $^1\text{H}$ -NMR, a small amount of carbonyl compound **115d** was found by GC-MS analyses. Thermolysis of **106e** in the presence of phenol resulted in the formation of the expected O-H insertion product **124h** in almost quantitative yield, in addition to a minor amount of phenoxy cyclohexane presumably produced from the reaction of diazocyclohexane with phenol. The formation of these products implies that both pathways B and C are involved in the decomposition of this oxadiazoline, although pathway A, leading to the desired tetrahydro-1,3-oxazin-2-ylidene **113d** is, by far, the most important route. Similarly, thermolysis of the related oxadiazoline **106d** resulted in the production of acetone (> 66%) and carbene **113d**, which was quantitatively trapped by phenol to give adduct **124h**.

## Scheme XXXI



The fate of carbene **113d**, generated in solution in the absence of a trap, is questionable. It is likely that this carbene dimerizes to *E* and *Z* alkenes (**122d**). However, these products could not be clearly identified, probably due to their lability towards hydrolysis. In addition, complex NMR spectra are expected for the two geometric isomers due to the probable slow rotation about the amide C-N bond. Interestingly, ions with *m/z* 378, corresponding to the molecular ions of carbene dimers, were found in MS

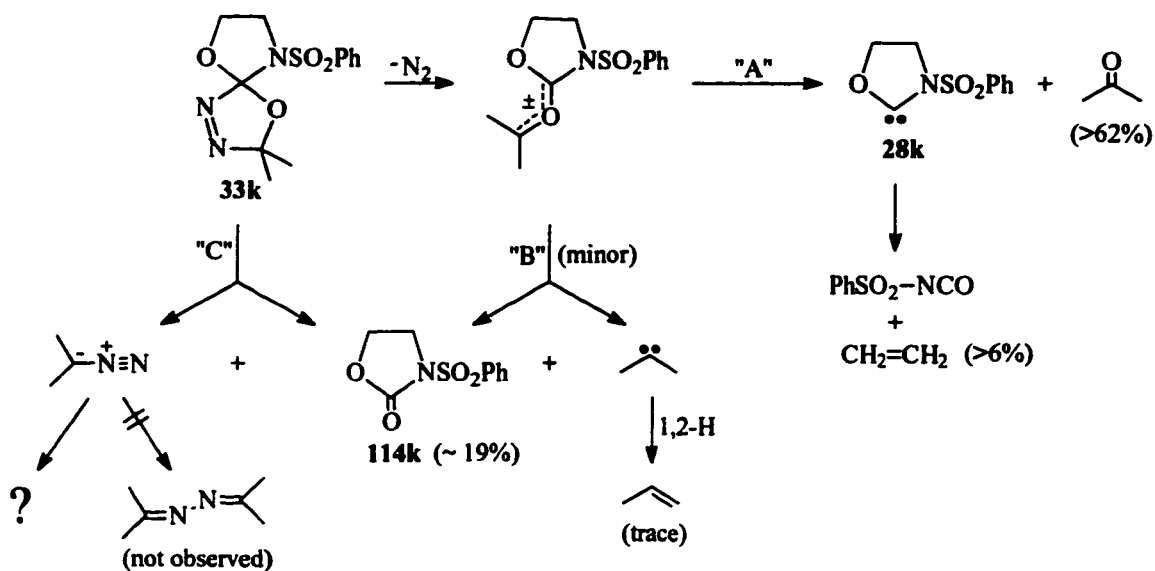
experiments carried out with the aim to confirm the identity of oxadiazoline **106e** (Section 4.2c). These species were generated in the gas phase, inside the spectrometer, by the unavoidable partial thermolysis of the fragile oxadiazoline.

### 2.3.8 Thermolysis of **33k**

Oxadiazoline **33k** was prepared in order to study the chemistry of a new aminooxycarbene, as well as to extend our investigation of the effects N-substituents on the thermal decomposition of our spiro oxadiazolines. As for oxadiazoline **33b** (N-methyl), this compound does not generate the aminooxycarbene quantitatively, although a yield > 62% was found for acetone (by <sup>1</sup>H-NMR spectroscopy), the coproduct of carbene **28k** (Scheme XXXII). Formation of **28k** was supported by the detection of ethylene presumably formed in its thermal fragmentation. 3-(Phenylsulfonyl)-2-oxazolidinone, **114k**, was produced in *ca.* 19% yield. The fact that only traces of propene could be detected by <sup>1</sup>H-NMR suggests that **114k** is generated mostly *via* pathway C rather than through pathway B. However, acetone azine, which usually results from the self-reaction of 2-diazopropane, was not observed; any 2-diazopropane formed may possibly react with another species present in the thermolysis solution to form unidentified products, as it seems to happen in the case of **33b** (Section 2.3.3).



## Scheme XXXII



## 2.3.9 Thermolysis of 33a

Experiments conducted to investigate the thermal chemistry of the parent oxadiazoline 33a were frustrated with problems concerning product stability, which in most cases prevented their separation and further characterization. Nevertheless, the apparently distinct behaviour of 33a justifies the following brief account.

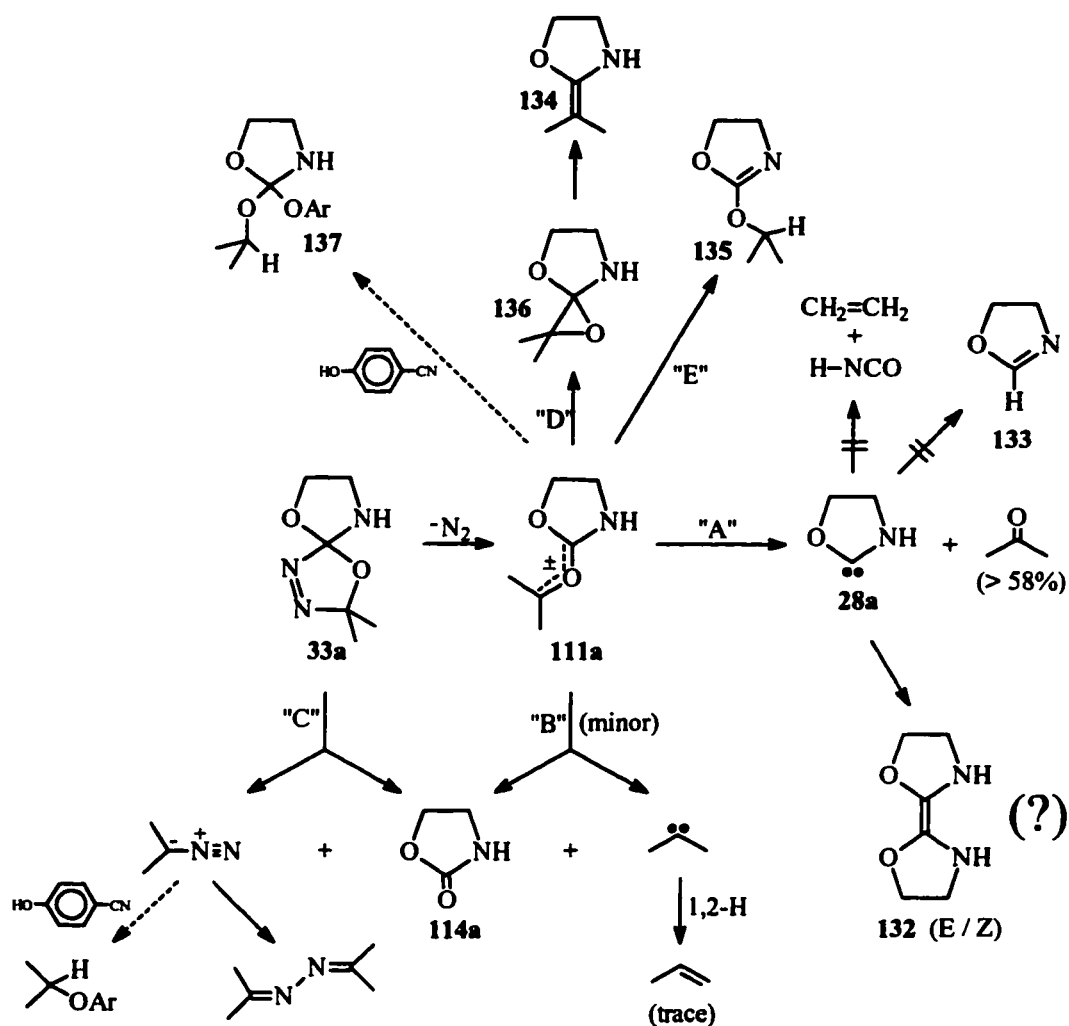
Scheme XXXIII shows the proposed thermolytic pathways for 33a. The initial thermolysis of this compound was carried out in a sealed NMR tube (0.33 M in  $C_6D_6$ ) to determine its rate of decomposition (Section 2.3.1). From this experiment, acetone (> 58% by NMR) and small amounts of propene and acetone azine were found in the thermolysate. The moderate yield of acetone suggested the co-formation of oxazolidin-2-ylidene (28a) but, in contrast to the other oxadiazolines 33, no ethylene was detected.

Under these conditions, the major product(s) in the crude thermolysate gave rise to a complex multiplet at 3.30-3.60 ppm (in  $C_6D_6$ ), which may be consistent with the previously unreported (*E/Z*) carbene dimer **132**. No evidence was found for the product of 1,2-H migration in carbene **28a**, namely 4,5-dihydrooxazole (**133**);<sup>i</sup> this is not surprising considering the relatively high energy barrier expected for this rearrangement, as discussed in Section 1.6.1.2. The absence of ethylene was confirmed by treatment of a larger scale thermolysate with bromine, as described in Section 4.3.3: 1,2-dibromopropane was observed, but not 1,2-dibromoethane.

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<sup>i</sup> The  $^1H$ -NMR spectrum of **133** (neat sample,  $\delta$ : 3.73, 4.15, 6.92) was reported by Abraham *et al.*<sup>217</sup>

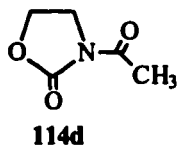
Scheme XXXIII



Thermolysis of 33a was repeated several times on larger scales, under the usual conditions (50-100 mM in benzene), and the product mixture appeared to be more complex than anticipated from the small scale experiment. The major product observed by  $^1H$ -NMR ( $CDCl_3$ ) analysis of the thermolysate was possibly 132, as it showed only two equal-intensity triplets ( $J = 7.9$  Hz) at 3.62 and 4.45 ppm. In addition, several resonances

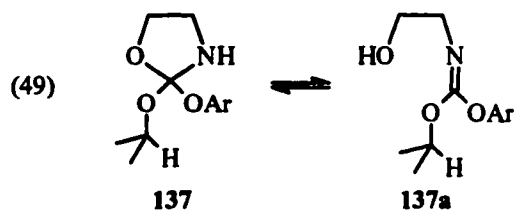
in the methyl region suggested that three different products were derived from carbonyl ylide **111a**. The most intense pair of signals, at 1.48 and 1.53 ppm, was attributed to **134**, an analogue of the ketene acetals **87** discussed in Section 2.1. This assignment is based on the  $^1\text{H}$  and  $^{13}\text{C}$  spectra of isolated samples of **134** of varying purity; complete NMR data are shown in Section 4.3.9. Also present in the product mixture was a compound, tentatively assigned to 2-isopropoxy-2-oxazoline (**135**), showing a doublet ( $J = 6.2$  Hz) at 1.39 ppm and a septet at 4.92 ppm (the presumed methylene multiplets overlapped with those of other products). This product apparently comes from 1,4-H migration in **111a** (pathway E), a reaction previously observed in related oxadiazolines (see Section 1.5.1.2). Finally, a pair of low-intensity singlets at 1.20 and 1.23 ppm, possibly from oxirane **136**, was also observed.

As noted above, attempts to separate those thermolysis products resulted in their decomposition, although **134** could be partially purified. Unexpectedly, 3-acetyl-2-oxazolidinone (**114d**) was isolated in *ca.* 5% yield; its spectral data were identical to those of **114d** obtained from **33d**. Examination of the spectra of the crude thermolysates unequivocally demonstrated that it was formed during thermolysis, and not in the work-up. Its origin remains unknown.



In an effort to circumvent the problematic product lability, a crude thermolysate was treated with acetyl chloride / pyridine to acylate the product oxazolidines at nitrogen. Unfortunately, no recognizable products could be isolated by chromatography following this procedure.

In the thermolysis of **33a** with an excess of 4-cyanophenol, no solid evidence for trapping of carbene **28a** was obtained. A possible complication is the acid-base reaction between **33a** and the phenol, which may result in a significant concentration of the N-protonated **33a**, and thus affect the thermolytic scheme. Nevertheless, a reaction between carbonyl ylide **111a** and the phenol apparently occurred to give a compound tentatively assigned as oxazolidine **137**. This product was repeatedly obtained, following chromatography of the product mixture, as impure samples (< 5% yields). The apparent NMR equivalence of the two methyl groups of **137** (see Experimental Section) may indicate the predominance of the open-chain tautomer **137a** in solution (eq. 49), although the multiplicity of the  $\text{NCH}_2$   $^1\text{H}$  resonance suggests the presence of the hydrogen on N, by comparison to the spectra of other products described in this work. 2-(4-Cyanophenoxy)propane, resulting from the reaction of 2-diazopropane with the phenol, was also isolated in 6% yield.



In summary, these results suggest the occurrence of two new pathways in the thermal decomposition of **33a**, D and E in Scheme XXXIII, which have not been observed for related oxadiazolines **33**.

## 2.4 Intermolecular Reactions of Aminooxycarbenes

### 2.4.1 Insertions into O-H bonds

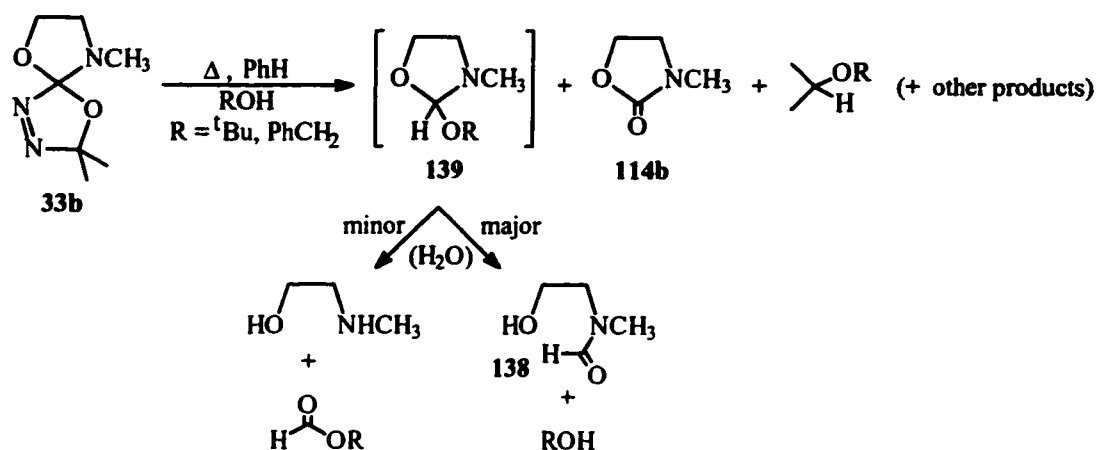
#### 2.4.1.1 *Reactions with Alcohols*

Trapping of carbene **28b** was first attempted by thermolysing the precursor oxadiazoline, **33b**, in the presence of *tert*-butyl alcohol. However, the expected O-H insertion product could not be detected in the product mixture. Instead, <sup>1</sup>H-NMR and GC-MS analyses revealed that N-(2-hydroxyethyl)-N-methylformamide, **138**, was the major product, in addition to 3-methyl-2-oxazolidinone (**114b**) formed in lower yield. The identity of **138** was confirmed by comparing the data with those obtained from an authentic sample, prepared from the reaction of 2-(methylamino)-1-ethanol with ethyl formate.<sup>155</sup> A similar result was obtained in the thermolysis of **33b** with benzyl alcohol. Again, formamide **138** was the major product, in addition to 2-benzyloxypropane, formed from the reaction of 2-diazopropane with benzyl alcohol. In addition, a small amount of benzyl formate was observed by GC-MS.

These results suggest that O-H insertion products, **139**, do form when carbene **28b** is generated in the presence of alcohols, but that they rapidly hydrolyse upon exposure to the atmosphere (Scheme XXXIV). It is also clear, from the observed products, that under

these conditions at least two mechanisms are operative in the hydrolysis of compounds **139**. Although proton resonances due to 2-(methylamino)ethanol, the expected coproduct of benzyl formate, could not be unambiguously assigned, due to overlap in the complex mixture, its presence was probable.

Scheme XXXIV



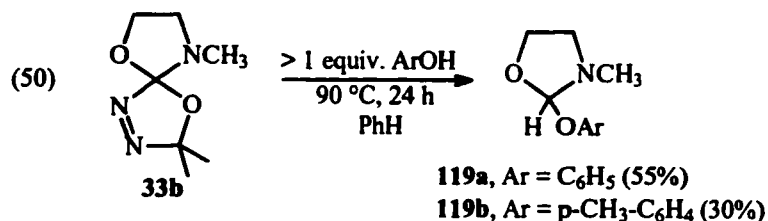
#### 2.4.1.2 Reactions with Phenols

##### 2.4.1.2.1 3-Methyloxazolidin-2-ylidene (**28b**)

In contrast to the products of insertion of 3-methyloxazolidin-2-ylidene (**28b**) into the O-H bond of alcohols, those resulting from insertion into phenolic O-H bonds were stable enough towards hydrolysis to be purified by chromatography. The 2-aryloxy-3-methyloxazolidines **119a** and **119b**, prepared by thermolysis of **33b** with phenol or with p-cresol, were isolated in 55% and 30% yields, respectively<sup>i</sup> (eq. 50). The EI-MS of these

<sup>i</sup> The significantly lower yield of the p-cresol product may be attributed to some loss of material, possibly through partial hydrolysis, during purification.

compounds showed low-intensity molecular ions (too small to allow acquisition of high-resolution spectra), while the base peak, in both cases, was at  $m/z$  86, representing the cation resulting from loss of the aryloxy group from the molecular ion.



These novel oxazolidines were found to have interesting NMR spectra due to the slow pyramidal inversion about the nitrogen, on the NMR time scale. Thus, at room temperature, two sets of well-resolved resonances of almost equal intensity, each one corresponding to one conformer (or “invertomer”), are observed in both the <sup>1</sup>H (see Figure 21) and <sup>13</sup>C (Figure 18) spectra, as shown for compounds **119b**. Peak assignments for both **119a** and **119b** are presented in Table VIII. These assignments were confirmed by means of double-irradiation experiments: for instance, the OCH<sub>2</sub> triplet at 4.07 ppm, in **119a**, is coupled to the NCH<sub>2</sub> triplet at 3.62 ppm.



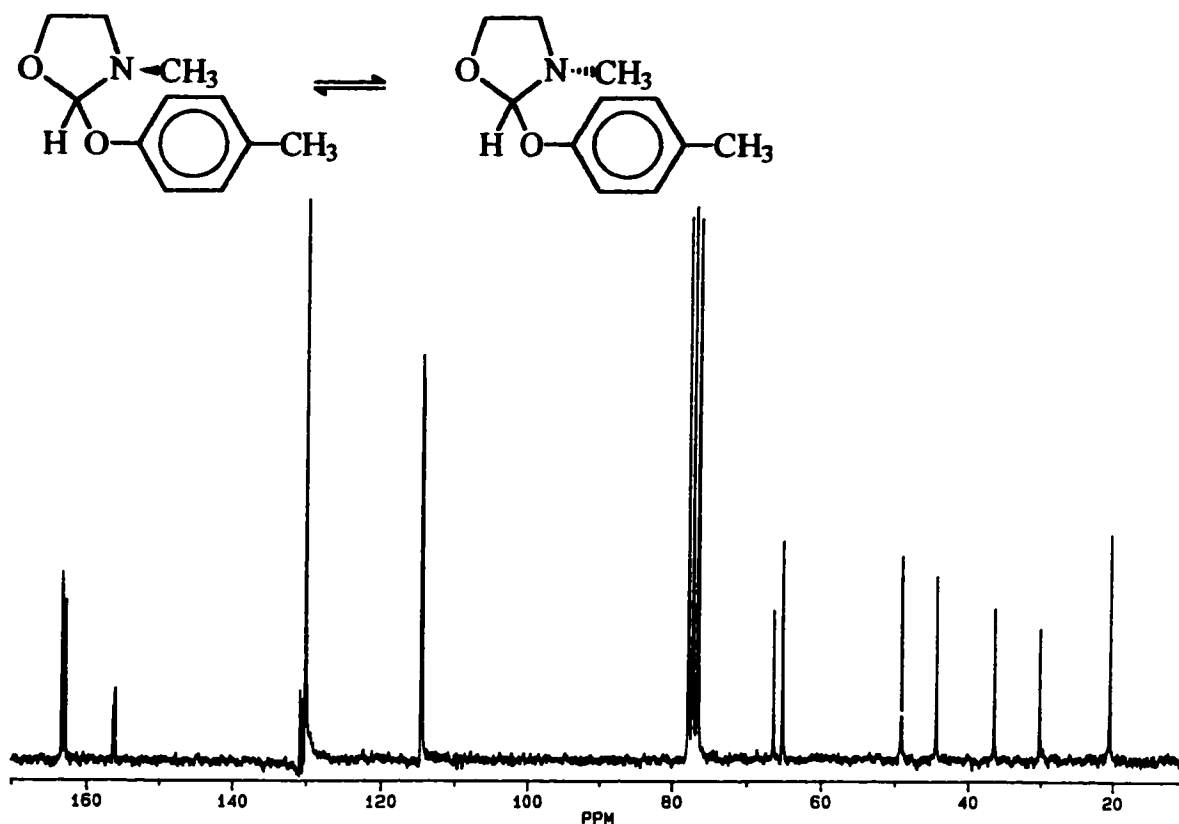


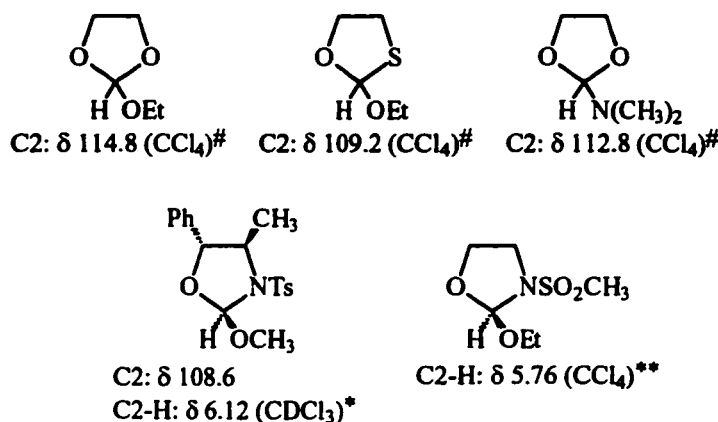
Figure 18. Room temperature  $^{13}\text{C}$ -NMR spectrum of **119b** (50 MHz,  $\text{CDCl}_3$ ).

**Table VIII.** Selected NMR data<sup>a</sup> for 2-aryloxy-3-methyloxazolidines **119**.

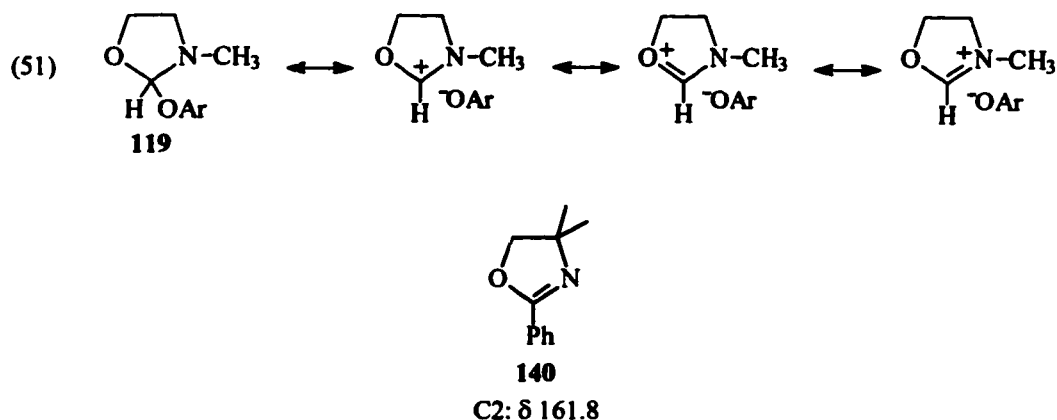
		<b>119a</b> (~ 53: 47)	<b>119b</b> (~ 54: 46)
$^1\text{H}$ -NMR	NCH <sub>3</sub>	<b>2.96</b> (s), 3.12 (s)	<b>2.95</b> (s), 3.10 (s)
	NCH <sub>2</sub>	<b>3.62</b> (t), 3.73 (t)	<b>3.60</b> (t), 3.71 (t)
	OCH <sub>2</sub>	<b>4.07</b> (t), 4.14 (t)	<b>4.03</b> (t), 4.10 (t)
	C2-H	8.08 (s), <b>8.14</b> (s)	8.07 (s), <b>8.13</b> (s)
$^{13}\text{C}$ -NMR	NCH <sub>3</sub>	30.24, <b>36.42</b>	30.18, <b>36.35</b>
	NCH <sub>2</sub>	44.29, <b>49.04</b>	44.28, <b>49.04</b>
	OCH <sub>2</sub>	<b>64.90</b> , 66.17	<b>65.11</b> , 66.34
	C2	<b>162.86</b> , <b>163.25</b>	<b>162.82</b> , <b>163.23</b>

<sup>a</sup>Reported in ppm (in  $\text{CDCl}_3$ ); resonances from major conformers are in bold, with the relative populations indicated in parentheses.

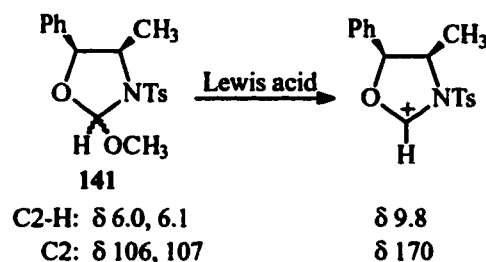
Another noteworthy feature in the NMR spectra of **119a** and **119b** is the unusual chemical shift of C2, at *ca.* 163 ppm, and of the proton attached to it (*ca.* 8.1 ppm). Most of the related NMR data in the literature are from oxazolidines with an electron-withdrawing group on N. The few related examples shown in Figure 19 suggest that the C2 resonance of amide acetals **119** might be expected around 112 ppm. Similarly, C2 of 2-aryloxyoxazolidines bearing a carbonyl group on N typically resonates around 105 ppm, while C2-H is observed at 6.0-6.7 ppm (see Table X).



**Figure 19.** NMR data from compounds related to 119. Ts = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>-. References: #Dostovalova *et al.*,<sup>156</sup> \*Conde-Frieboes and Hoppe,<sup>157</sup> and \*\*Crank and Eastwood.<sup>158</sup>



The best support for this model, however, comes from NMR experiments conducted by Bernardi *et al.*<sup>160</sup> on 2-methoxyoxazolidines, such as **141**, and their cations generated with Lewis acids. As shown in Figure 20, the proton at C2 in **141** moves from 6.0, 6.1 ppm (*trans* and *cis* isomers, respectively) to 9.8 ppm in the corresponding cation, while the chemical shift of C2 changes from 106, 107 ppm in **141** to 170 ppm in the cation. An analogous contribution from ionic species, in our oxazolidines **119**, would also explain the multiplicity of the methylene protons at C4 and C5, which appear as triplets instead of the complex multiplets of an ABMX system expected for each of the non-ionic contributors to **119**; a relevant discussion of the appearance of the -CH<sub>2</sub>CH<sub>2</sub>- resonances in oxazolidines vs those in 2-oxazolines follows in Section 2.4.3.



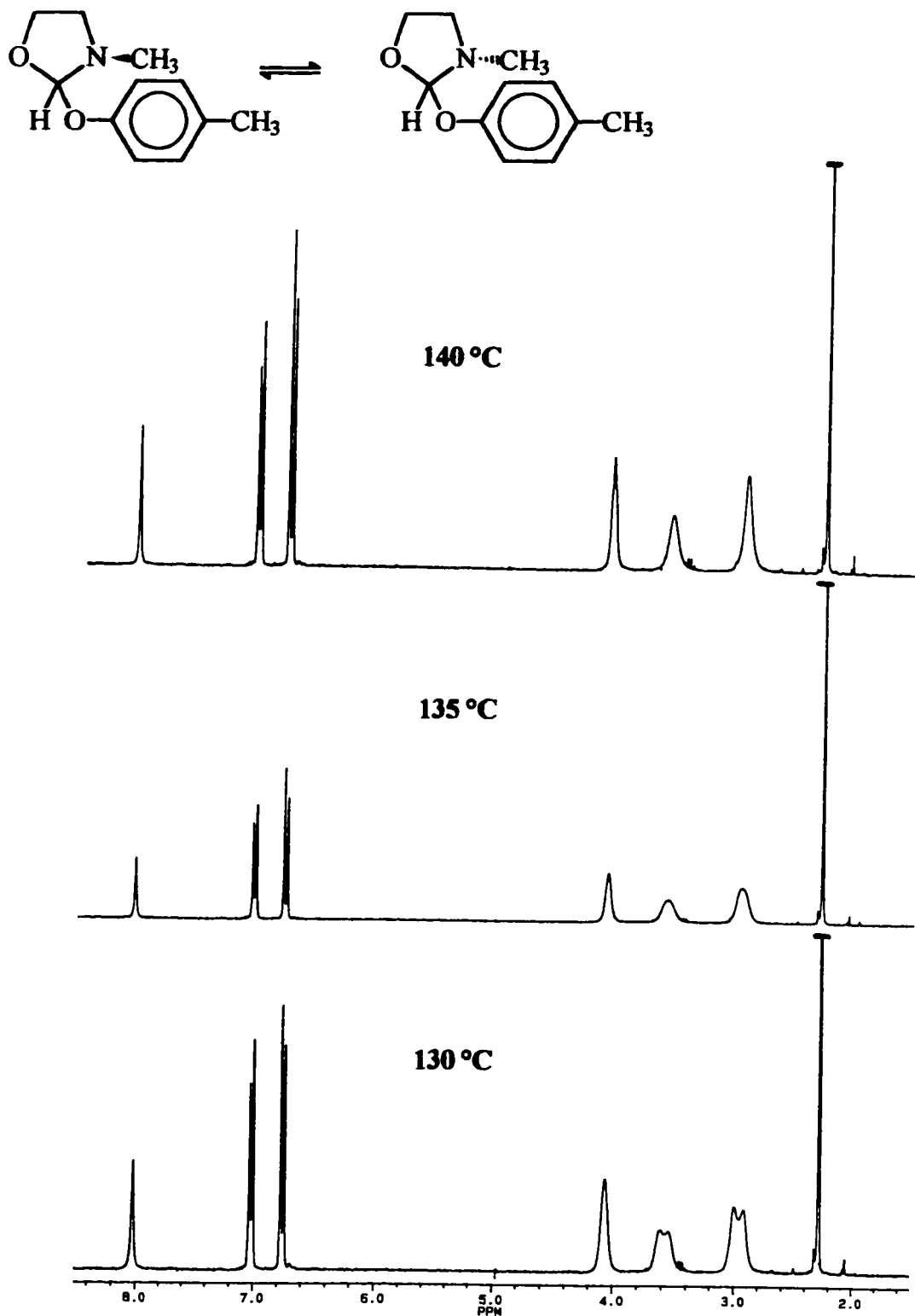
**Figure 20.** NMR data for oxazolidine **141** and its corresponding cation (in CD<sub>2</sub>Cl<sub>2</sub>); taken from Scolastico *et al.*<sup>160</sup>

In order to determine the magnitude of the barrier separating the two conformers (from N-inversion) in oxazolidines **119**, variable-temperature (VT)  $^1\text{H}$ -NMR experiments were conducted in the range 40 °C - 140 °C, at 300 MHz. Figure 21 shows selected spectra for compound **119b**. The almost equal conformer populations allowed us to estimate  $\Delta G^\ddagger$  for their interconversion by the coalescence method,<sup>143</sup> using eq. 52, where  $\Delta G^\ddagger$  is the free energy of activation (kcal/mol),  $R$  is the gas constant ( $1.987 \times 10^{-3}$  kcal K $^{-1}$  mol $^{-1}$ ),  $T_c$  is the coalescence temperature (K) of a given pair of resonances, and  $\delta_0$  is the chemical shift difference, in Hz, between the two peaks in the absence of exchange. Within experimental error, the barriers in oxazolidines **119a** and **119b** were identical: 20.4 kcal/mol.<sup>i</sup> Experimental details and calculations are given in Appendix 2.

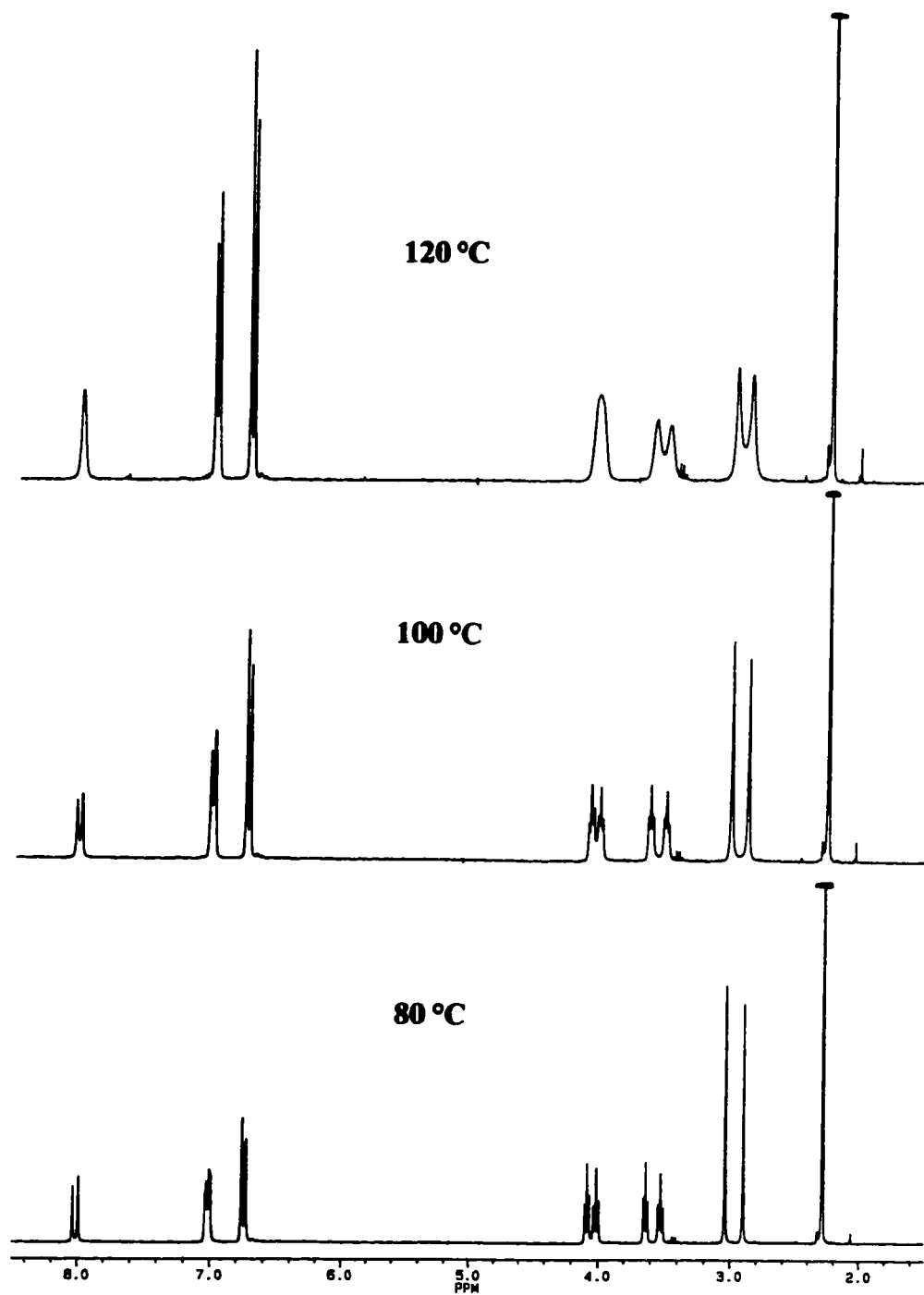
$$(52) \quad \frac{\Delta G^\ddagger}{RT_c} = 22.96 + \ln\left(\frac{T_c}{\delta_0}\right)$$

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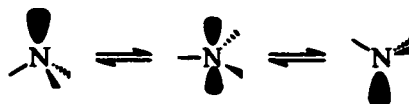
<sup>i</sup> With both compounds, identical numbers were obtained from calculations involving the N-CH<sub>3</sub> and C2-H singlets.



**Figure 21.**  $^1\text{H}$ -NMR spectrum of 119b as a function of temperature (300 MHz, in hexachloro-1,3-butadiene).

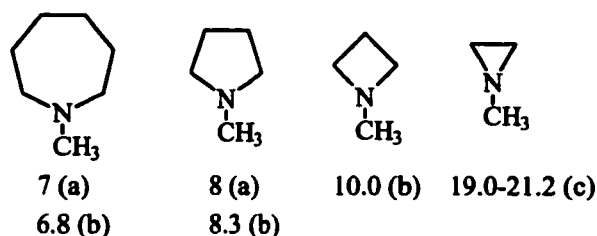
**Figure 21 (continued).**

Pyramidal inversion in amines takes place through a planar transition state by a change in hybridization:  $sp^3 \rightarrow sp^2 \rightarrow sp^3$  (Figure 22).



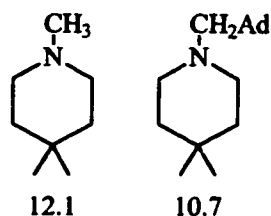
**Figure 22.** Depiction of the process of pyramidal inversion in amines.

The inversion barrier in the parent compound, ammonia, has an experimental value of 5.8 kcal/mol;<sup>161</sup> theoretical results are generally in the range 4.7-6.1 kcal/mol.<sup>162-165</sup> Most acyclic amines also have low barriers, typically less than 9 kcal/mol.<sup>162,165,166</sup> This inversion process, however, is affected by several factors including electronic and steric effects caused by substituents on nitrogen, and the degree of angular constraint (*e.g.* in cyclic systems).<sup>167,168</sup> Contribution of the latter is obvious when cyclic amines of varying ring sizes are compared. Thus  $\Delta G^\ddagger$  for the interconversion of invertomers generally augments in the order: homopiperidines < pyrrolidines < azetidines < aziridines (Figure 23). This can be interpreted in terms of the higher strain imposed on a 3-membered ring in order to reach a transition state with an ideal internal C-N-C bond angle of  $120^\circ$ .



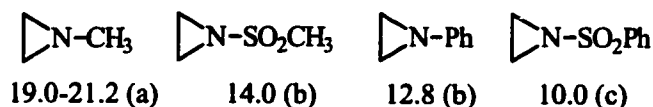
**Figure 23.** Effect of ring size on nitrogen inversion barriers ( $\Delta G^\ddagger$ , in kcal/mol). References: (a) Lambert and Oliver;<sup>169</sup> (b) Lambert *et al.*;<sup>170</sup> (c) Drakenberg and Lehn.<sup>171</sup>

Sterically bulkier groups on nitrogen tend to decrease inversion barriers (Figure 24) since steric repulsion is more important in the pyramidal ground state than in the planar transition state.<sup>167,172</sup>



**Figure 24.** Effect of substituent size on nitrogen inversion barriers ( $\Delta G^\ddagger$ , in kcal/mol); Ad = 1-adamantyl. From Lambert and Wharry.<sup>172</sup>

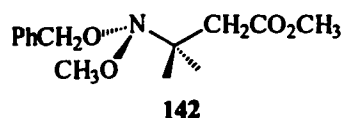
Electronic factors affecting inversion barriers originate through stabilization or destabilization of the nitrogen orbitals, particularly of the lone pair orbital which changes from  $sp^3$  in the ground state to pure p in the transition state. Any factor which favours this rehybridization, through conjugation for instance, flattens the ring, making the pyramidal structures closer to the planar transition state and thus decreasing the barrier; this is exemplified by the near planarity of the amide bond. This effect of delocalization of the nitrogen lone pair in related aziridines is also clearly seen in Figure 25.



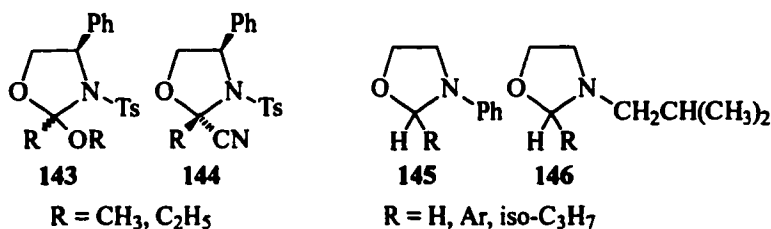
**Figure 25.** Conjugative effects on nitrogen inversion barriers ( $\Delta G^\ddagger$ , in kcal/mol). References: (a) Drakenberg and Lehn;<sup>171</sup> (b) Anet and Osyany;<sup>173</sup> (c) Anet *et al.*<sup>174</sup>

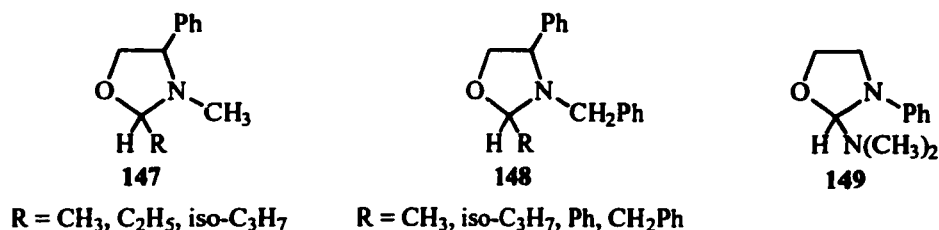


In contrast, compounds in which the nitrogen bears a heteroatom X possessing an unshared pair of electrons often show high inversion barriers. This is, at least in part, due to the mutual electronic repulsion of the N and X lone pairs which particularly disfavours the planar transition state. Even acyclic systems of this type may have high barriers. Compound **142**, for instance, has been resolved into (+) and (-) enantiomers; racemization at 20 °C occurs with a half-life of 5.18 h ( $\Delta G^\ddagger = 23.47$  kcal/mol).<sup>175</sup>

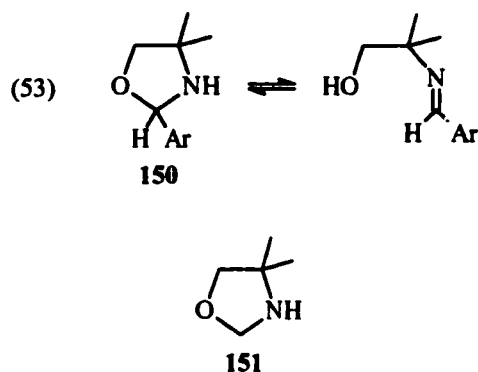


Despite the relative commonness of oxazolidines, little is known about pyramidal inversion in these systems. Compounds closely related to the 2-aryloxyoxazolidines **119**, such as **143** and **144** for instance,<sup>176</sup> have been reported to exhibit “normal” NMR spectra, *i.e.* showing no sign of slow inversion under usual conditions, although the presence of an electron-withdrawing group on nitrogen is expected to reduce the inversion barrier significantly. Other oxazolidines such as **145** and **146**,<sup>177</sup> **147**,<sup>178</sup> **148**,<sup>179</sup> and **149**<sup>156</sup> also have apparently low barriers.





To our knowledge, only one report of high inversion barriers in oxazolidines appears in the literature. These 2-aryloxazolidines, **150**, studied by Yang and co-workers,<sup>180</sup> are unsubstituted at N and thus exist in solution in equilibrium with the acyclic tautomer (eq. 53), thereby giving rise to complex <sup>1</sup>H spectra. Nevertheless, activation parameters for oxazolidines **150** could be determined by line shape analyses, and barriers of 20.7-22.3 kcal/mol were found, of the same order of magnitude as those of our oxazolidines (**119**). The authors of this study believed that the presence of an aryl substituent at C2 was a requirement for high inversion barriers as 4,4-dimethyloxazolidine, **151**, showed only an “averaged [methyl] singlet in the <sup>1</sup>H-NMR spectrum until -90 °C”.<sup>180</sup>

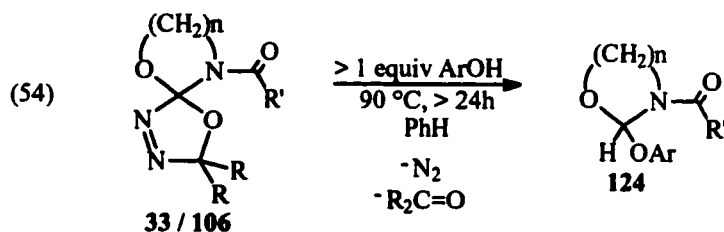


The exceptional character of such high barriers in **119** and **150**, compared to the ostensibly low ones in most other known oxazolidines, is puzzling. Common

characteristics of **119** and **150** include the combination of a small substituent on the nitrogen (H or CH<sub>3</sub>) and, at C2, one hydrogen along with one large group (Ar or OAr). The real impact of the suggested ionic contributors for **119** (see eq. 51) on the magnitude of the barriers is unknown, but such contributors would be expected to stabilize the transition state (and therefore lower  $\Delta G^\ddagger$ ), based on electronic arguments presented above.

#### 2.4.1.2.2 3-Carbonyloxazolidin-2-ylidenes (**28c-f,j** and **113d**)

Small scale thermolyses of some of the N-carbonyl oxadiazolines in the presence of phenol, carried out in sealed NMR tubes, were mentioned in Sections 2.3.5-2.3.7 to give yields of O-H insertion products on the order of 95%. These thermolyses were repeated on larger scales in order to isolate the products (eq. 54, Table IX).



**Table IX.** N-Carbonyl carbene - phenol adducts isolated.

	n	R'	Ar	Yield (%)
<b>124a</b>	2	H	Ph	75
<b>124b</b>	2	Me	Ph	89
<b>124c</b>	2	C(Me)=CH <sub>2</sub>	Ph	97
<b>124d</b>	2	C(Me)=CH <sub>2</sub>	4-C <sub>6</sub> H <sub>4</sub> CN	84
<b>124e</b>	2	Ph	Ph	76
<b>124f</b>	2	Ph	4-C <sub>6</sub> H <sub>4</sub> CN	90
<b>124g</b>	2	OMe	Ph	> 95
<b>124h</b>	3	Ph	Ph	97

The 2-aryloxy-3-carbonyloxazolidines were found to be much more sensitive to hydrolysis than the N-methyl analogues discussed in the previous section. As a result, they could not be purified by chromatography without total decomposition. Compound **124e**, resulting from the thermolysis of **33f** with phenol, could be crystallized by addition of a mixture of ethyl acetate / hexane to the crude oil. Unfortunately, this procedure failed to produce crystals with most other products **124**. It was found, however, that essentially pure products could be obtained in high yields by simply base-washing the thermolysates in order to remove the excess phenol; the benzene solutions were then dried over MgSO<sub>4</sub>, and the solvent and volatile products were evaporated *in vacuo*.

In the thermal decomposition of **106e** ( $n = 3$ ,  $RR = (CH_2)_5$ ,  $R' = Ph$ , in eq. 54) with phenol, a high yield of the tetrahydro-1,3-oxazine **124h** was also obtained although it could not be separated from the non-volatile cyclohexanone, the coproduct of carbene **113d**. Trapping of the same carbene was therefore repeated by generating it from **106d**

( $n = 3$ ,  $R = \text{Me}$ ,  $R' = \text{Ph}$ ), which produces acetone instead of cyclohexanone as a by-product. This resulted in the isolation of **124h** in about 97% yield. The only observable impurity in its  $^{13}\text{C}$  spectrum was a comparatively minor amount of its hydrolysis product, **152** (*vide infra*). Isolation of **124h** allowed its positive identification from the above-mentioned thermolysis of **106e** with phenol, by comparison of the  $^1\text{H}$  and  $^{13}\text{C}$  spectral data.

The  $^1\text{H}$ - as well as  $^{13}\text{C}$ -NMR spectra of compounds **124** usually showed broad resonances and/or more than one set of peaks due to restricted rotation about the amide C-N bond. Selected NMR data for these compounds are presented in Table X; they can be compared to those of the N-methyl analogues shown above in Table VIII. In particular, whereas the chemical shifts in the oxazolidine and tetrahydro-1,3-oxazine rings for the N-carbonyl series are relatively invariable, changing the N-substituent to methyl is seen to have a dramatic effect on the chemical shifts of C2 and the proton attached to it, as discussed in Section 2.4.1.2.1. Molecular ions in the mass spectra were generally observed, although their low intensity prevented high-resolution spectra to be acquired. In addition, characteristic  $(\text{M-OAr})^+$  peaks of high intensity were observed in all cases.

**Table X.** Selected NMR data<sup>a</sup> for products from the reaction of N-carbonyl carbenes with phenol.

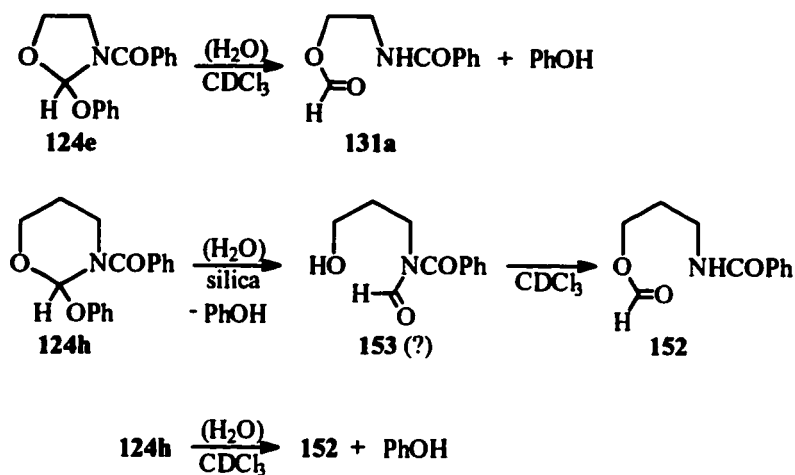
	C2-H	NCH <sub>2</sub>	OCH <sub>2</sub>	C2	C=O
<b>124a</b>	6.03, 6.07	41.42, 42.09	64.61	102.91, 104.34	158.87, 159.27
<b>124b</b>	6.39, 6.66	43.27, 44.65	64.83, 65.31	103.84, 104.34	168.12, 168.43
<b>124c</b>	6.51 (br.)	43.31	64.52	105.23	169.09
<b>124e</b>	6.21 (br.)	43.48	64.60	105.19	169.00
<b>124g</b>	6.46, 6.74	43.83	64.73, 65.14	104.52, 105.52	153.38/156.35 <sup>c</sup>
<b>124h</b>	ca. 6.80-7.25 <sup>b</sup>	37.97	59.49	99.66	169.36

<sup>a</sup>Reported in ppm; in CDCl<sub>3</sub> for **124b,c,e** and C<sub>6</sub>D<sub>6</sub> for **124a,g,h**.<sup>b</sup>Hidden under the multiplets from aromatic protons.<sup>c</sup>Exact assignments for C=O and phenyl C1 are uncertain.

The lability of compounds **124** towards hydrolysis was mentioned above. A sample of **124e**, dissolved in CDCl<sub>3</sub> and kept in the refrigerator, hydrolysed cleanly and completely to N-[2-(formyloxy)ethyl]benzamide (**131a**) and phenol (Scheme XXXV), in less than two months.<sup>i</sup> Tetrahydro-1,3-oxazine **124h** was even more unstable and partial hydrolysis was noticeable immediately after dissolving it in CDCl<sub>3</sub>. Again, in this solvent, hydrolysis produced exclusively phenol and benzamide **152**. In contrast, the major fraction collected during an attempt to purify **124h** by chromatography on silica was shown to consist of a mixture of two hydrolysis products, **152** and possibly **153**; periodic recording of the <sup>1</sup>H spectrum of this mixture, kept in CDCl<sub>3</sub> at or below room temperature, showed the gradual conversion of **153** into **152**, which was complete within one month.

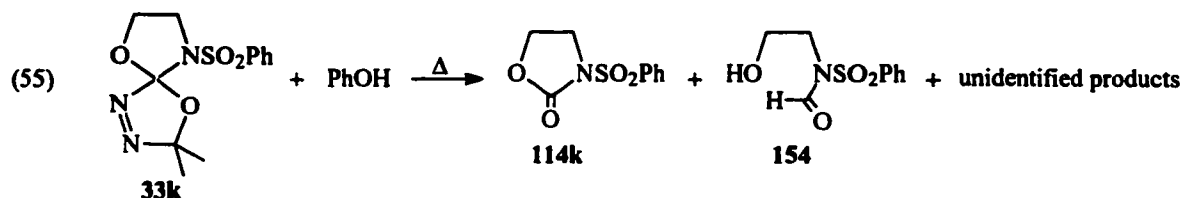
<sup>i</sup> It is likely that hydrolysis was complete earlier, as the sample was not examined regularly.

## Scheme XXXV

2.4.1.2.3 3-(Phenylsulfonyl)oxazolidin-2-ylidene (**28k**)

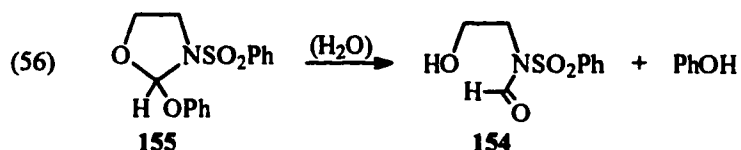
In order to try to confirm the generation of aminooxycarbene **28k**, oxadiazoline **33k** was thermolysed in the presence of phenol. Analysis of the product mixture using  $^1\text{H}$ -NMR and GC-MS, before any separation was attempted, revealed the presence of at least four important products (eq. 55). Among them were oxazolidinone **114k** and formamide **154**, but the anticipated carbene insertion product (**155**) could not be unambiguously identified. Another compound, showing a doublet at 0.97 ppm and a multiplet at 4.62 ppm (in  $\text{C}_6\text{D}_6$ ), was observed in the thermolysate. Although this partial spectrum is reminiscent of 2-phenoxypropane, which could result from the reaction of 2-diazopropane with phenol, it did not match the  $^1\text{H}$  spectrum of 2-phenoxypropane obtained from other thermolyses; in addition, 2-phenoxypropane was not observed by GC-MS under conditions in which it is normally detected. The fact that 2-phenoxypropane was not found supports the idea stated in Section 2.3.8 that 2-diazopropane, which is likely the

coproduct of oxazolidinone **114k**, is efficiently trapped with some species present during the thermolysis.



The second intriguing thermolysis product (identified as **U1** in Section 4.4.1.2.3), which was also observed in the thermolysis of **33k** with methyl isocyanate (see Section 2.4.2), showed two triplets at 3.76 and 4.12 ppm for  $R_2NCH_2$  ( $R \neq H$ ) and  $OCH_2$ , respectively, as well as a singlet at 9.01 ppm probably from  $C(=O)-H$ , while the aromatic region integrated for 10 protons. Its identity remains unknown.

It is likely that product **154** was formed from hydrolysis of **155** (eq. 56); the latter may have hydrolysed completely during work-up.



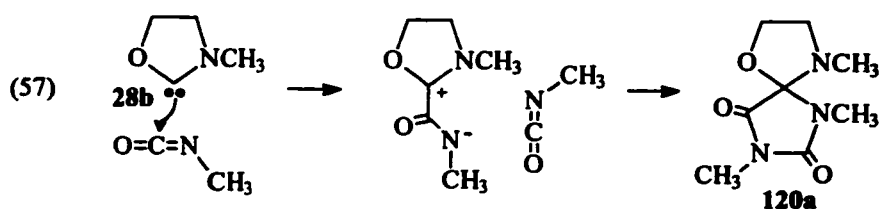
Oxadiazoline **33k** was also thermolysed in  $C_6D_6$  with an excess of 4-cyanophenol, in a sealed NMR tube. The  $^1H$ -NMR spectrum of the thermolysate, recorded before opening the tube to the atmosphere, showed two relatively well-resolved multiplets at 3.29-3.41 ppm (1H) and 3.43-3.61 ppm (1H), as well as a singlet at 7.60 ppm (1H). Peak overlap among the products prevented further analysis. The former two resonances were



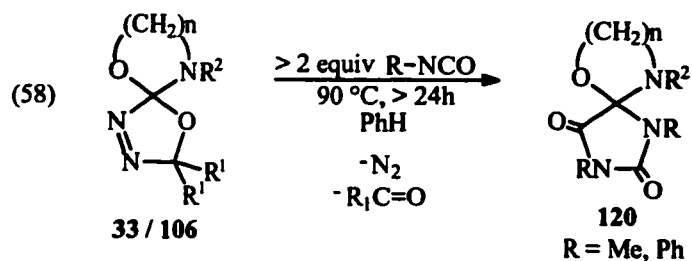
tentatively assigned to the non-equivalent  $\text{OCH}_2$  protons of the 4-cyanophenoxy analogue of **155**, while the latter is possibly attributable to the hydrogen at C2 of the oxazolidine ring. The identity of this O-H insertion product could not be confirmed by GC-MS analysis of the product mixture, probably because of its complete hydrolysis upon exposure to the atmosphere or in the GC column. In this thermolysis, a small amount of 2-(4-cyanophenoxy)propane was observed ( $^1\text{H-NMR}$ , GC-MS).

#### **2.4.2 Reactions with Methyl or Phenyl Isocyanate**

In Section 2.3.3, one of the final products in the thermolysis of **33b** (without added trap) was described as a spiro hydantoin (**120a**) resulting from the reaction of the aminooxycarbene (**28b**) with two equivalents of methyl isocyanate, the latter being generated from **33b** during the thermolysis. Formation of this product is rationalized in terms of a mechanism analogous to that proposed by Hoffmann and co-workers for the reactions of dimethoxycarbene<sup>29</sup> (**3**) and of (dimethylamino)methoxycarbene<sup>31</sup> (**24b**) with aryl isocyanates: initial attack of the nucleophilic carbene on the carbonyl group of the isocyanate results in a 1,3-dipolar intermediate which then adds across the  $\text{C}=\text{N}$  bond of a second molecule of  $\text{MeNCO}$  (eq. 57; see also Section 1.6.2.3.3). Because of the low yield of **120a** obtained, no attempt was made to isolate it from the product mixture. However, thermolysis of **33b** as a benzene solution to which excess methyl isocyanate had been previously added gave the same product, isolated in 44% yield by chromatography.



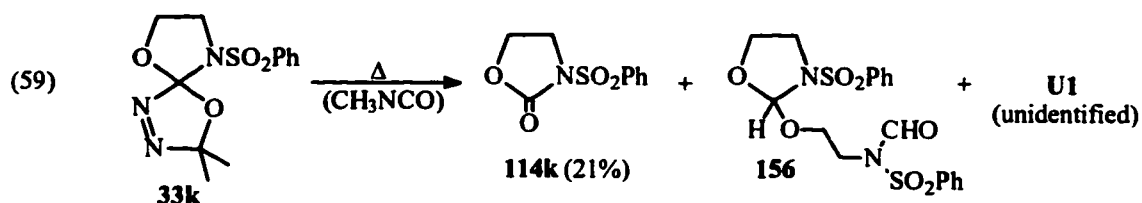
The reactions of several other aminooxycarbenes with methyl or phenyl isocyanate were investigated, and 2-amino-2-oxyhydantoin were invariably obtained (eq. 58, Table XI). These compounds, in general, had low solubility in most common solvents, although the N-methyl hydantoin, obtained with methyl isocyanate, were more soluble than their N-phenyl counterparts. Purification was commonly achieved by crystallization of the product from the crude by addition of a mixture of ethyl acetate / hexane, sometimes followed by recrystallization from the same solvent system.



**Table XI.** 2-Amino-2-oxyhydantoin **120** isolated from reactions of aminooxycarbenes with methyl or phenyl isocyanate.

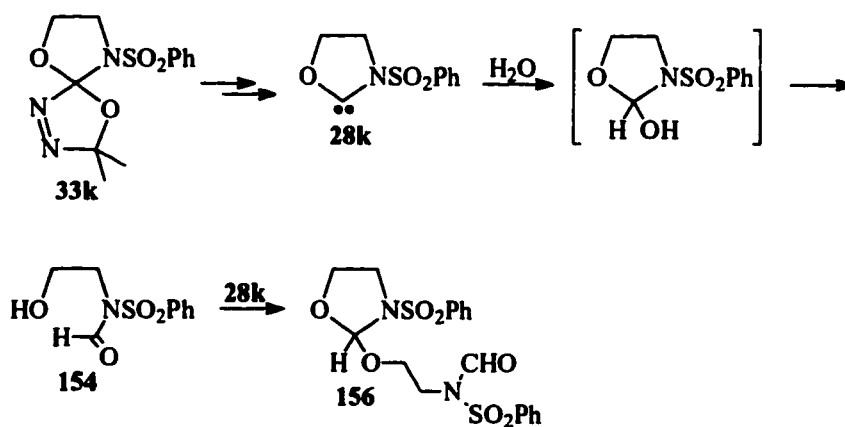
	n	R	R <sup>2</sup>	Yield (%)
<b>120a</b>	2	Me	Me	44
<b>120b</b>	2	Ph	Me	27
<b>120c</b>	2	Ph	C(O)Me	ca. 87
<b>120d</b>	2	Ph	C(O)C(Me)=CH <sub>2</sub>	72
<b>120e</b>	2	Ph	C(O)Ph	76
<b>120f</b>	3	Me	C(O)Ph	78

Attempts to isolate a similar hydantoin by trapping of the presumed aminooxycarbene **28k** with methyl isocyanate repeatedly failed. Three other products, however, were obtained from this reaction: oxazolidinone **114k**, isolated in 21% yield, an unidentified compound (**U1**) described above in Section 2.4.1.2.3, and a product also formed in low yield which was assigned structure **156** on the basis of the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR, IR, and MS spectral data (eq. 59).



Compound **156** was obtained only once, from a thermolysis solution which visibly contained some water. One possible route for its formation is shown in Scheme XXXVI. The isolation of **156** thus provides additional, though indirect, evidence for the generation of carbene **28k** from oxadiazoline **33k**.

**Scheme XXXVI**



### 2.4.3 Reactions with Alkynes

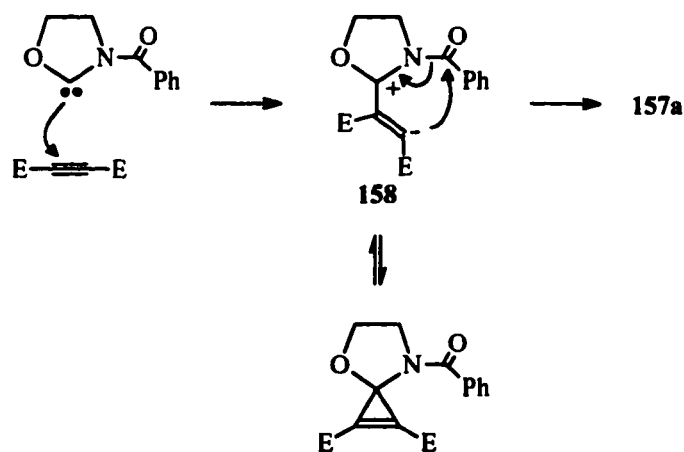
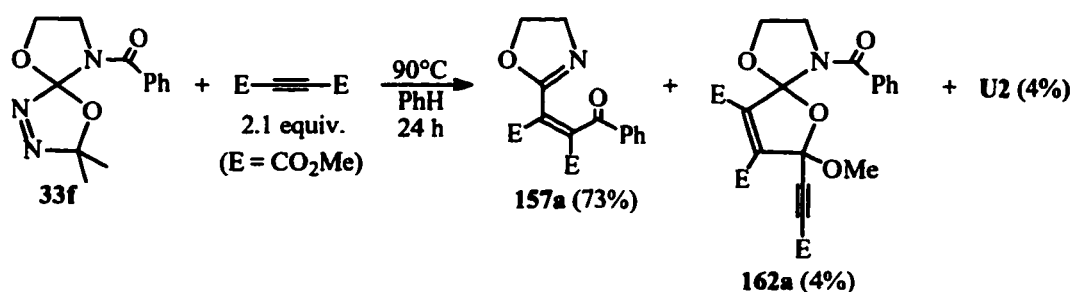
In order to probe for the reactivity of our aminooxycarbenes with activated triple bonds, oxadiazoline **33f** was thermolysed in benzene with 2.1 equiv. of DMAD. In addition to 3-benzoyl-2-oxazolidinone (**114f**) and N-[2-(formyloxy)ethyl]benzamide (**131f**), both isolated in about 2% yield (see Section 2.3.5), three products derived from reactions of carbene **28f** with DMAD were separated by chromatography (Scheme XXXVII). The major product, 2-oxazoline **157a**, obtained in 73% yield, was apparently formed *via* an interesting benzoyl group transfer from N to C in the 1,3-dipolar intermediate **158**. Formal oxidation of the oxazolidine ring in the reactant to the product 2-oxazoline was evident from several spectral characteristics, the most evident being the general appearance of the two methylene resonances in the  $^1\text{H}$  spectrum. Whereas oxazolidines unsubstituted at C4 and C5 typically show complex multiplets in the methylene region, as discussed earlier for the simulation of the ABMX spin system of **33b** (Section 2.2), the  $\text{CH}_2\text{CH}_2$  unit of oxazoline **157a**, in contrast, appears as a pair of doublets of triplets ( $J = 6.5$  Hz, and  $\sim 1$  Hz). This change in appearance, of great diagnostic value, can probably be attributed to the flatter geometry of the unsaturated oxazolines.<sup>181</sup> The  $^{13}\text{C}$  spectrum was also helpful in the identification of **157a**, showing C2 of the oxazoline at about 160 ppm,<sup>i</sup> in addition to the new ketonic carbon resonance at 190.02 ppm. The IR spectrum of **157a** was consistent with an oxazoline structure,<sup>182</sup>

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<sup>i</sup> C2 of **157a** is one of three resonances in that region, with the two ester carbonyl peaks.

showing a medium intensity band at  $1645\text{ cm}^{-1}$  assigned to  $\text{C}=\text{N}$ . Finally, its EI and CI mass spectra gave the expected  $\text{M}^+$  and  $(\text{M}+\text{H})^+$  signals.

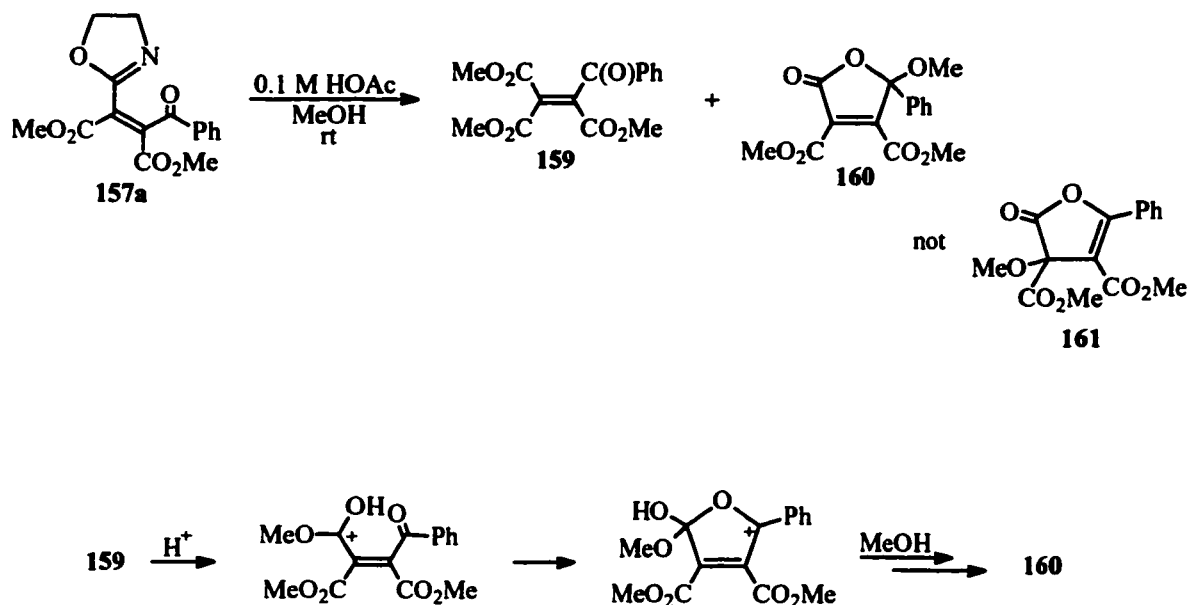
### Scheme XXXVII



2-Oxazolines bearing a substituent at C2 can be cleaved by hydrolysis or alcoholysis to the corresponding carboxylic acids or esters, respectively.<sup>154,183</sup> As a further test for the proposed structure, **157a** was treated with 0.1 M acetic acid in methanol. A mixture of two inseparable compounds was obtained (Scheme XXXVIII), consisting of the known<sup>184</sup> expected product, **159**, and an isomer tentatively assigned structure **160**;

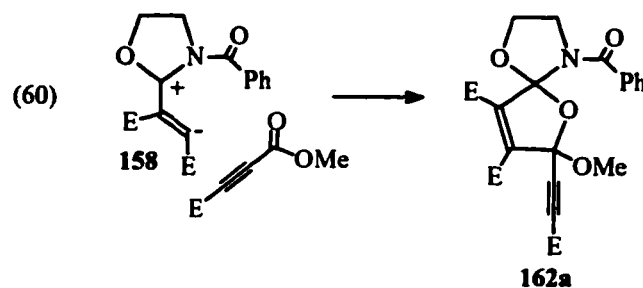
isomer **161** was ruled out on the basis of its dissimilar reported spectral properties.<sup>184</sup> A possible mechanism for the formation of **160** from the acid-catalysed rearrangement of **159** in methanol is included in Scheme XXXVIII.

Scheme XXXVIII



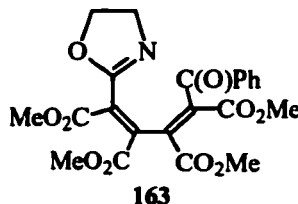
One of the minor products obtained from the thermolysis of **33f** with DMAD was assigned structure **162a** (one of two possible diastereomers), by comparison of its spectral data with those of analogous dihydrofurans formed in the reaction of DMAD with other nucleophilic carbenes.<sup>28,60,114</sup> In contrast to **157a**, it was clear from the appearance of the -CH<sub>2</sub>CH<sub>2</sub>- unit in its <sup>1</sup>H spectrum that the oxazolidine ring of the starting oxadiazoline had remained intact. Its formation is rationalized in terms of the mechanism proposed by Hoffmann *et al.* for the reaction of dimethoxycarbene with DMAD<sup>28</sup> (see Section 1.6.2.4).

As shown in eq. 60, it is believed to result from 1,3-dipolar addition of **158** across one of the carbonyl groups of a molecule of DMAD.

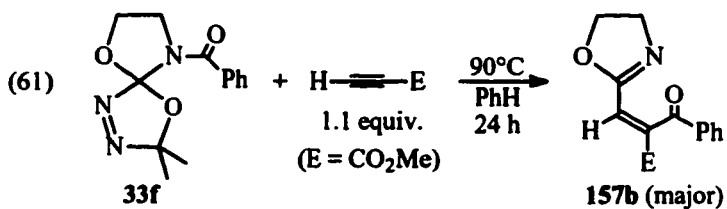


The identity of the third component (U2) purified from the product mixture remains a mystery. All spectral data was consistent with a 1: 2 stoichiometry (carbene: DMAD), but it clearly was not the geometric isomer of **162a**. Its unique  $^1\text{H}$  spectrum showed two triplets for the  $-\text{CH}_2\text{CH}_2-$  unit, reminiscent of those of **157a**, although in this case they both appeared at a much lower field (the  $\text{NCH}_2$  and  $\text{OCH}_2$  groups in **157a** resonate at 3.86 and 4.04 ppm, respectively, compared to 4.49 and 4.98 ppm, in U2). Similarly,  $^{13}\text{C}$  peaks at 75.06 and 92.26 ppm were tentatively assigned to the carbons of the original  $\text{NCH}_2$  and  $\text{OCH}_2$  groups, respectively. Structure **163**, which could conceivably result from attack of the dipolar intermediate **158** on the triple bond of a second molecule of DMAD, followed by benzoyl group migration as above, was considered. The highly conjugated system could perhaps be responsible for the unusual NMR shifts of the ring methylene groups. However, such a pronounced effect seems unlikely; moreover, the absence of a  $^{13}\text{C}$  peak near 190 ppm for the ketone (as in **157a**) is discordant. In summary, these unusual chemical shifts are not consistent with the presence

of an oxazolidine ring and, by comparison with compound **157a**, an oxazoline ring also seems improbable.

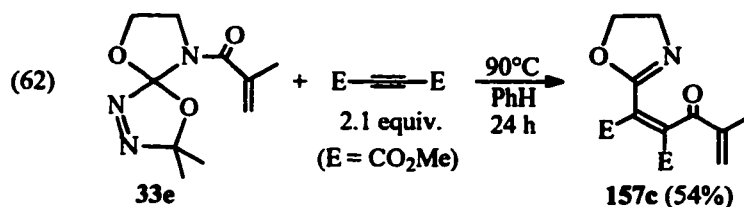


It was of interest to investigate whether carbene **28f** would react with a less electrophilic alkyne. Oxadiazoline **33f** was therefore thermolysed in the presence of methyl propiolate. From  $^1\text{H}$ -NMR analysis of the product mixture, oxazoline **157b** was clearly the major product although some spiro 4(5*H*)-oxazolone **125a**, derived from **33f** alone (see Section 2.3.5), was also present, probably due in part to the lower excess of alkyne (1.1 equiv.) used in this case (eq. 61). Substantial decomposition of **157b** during two successive separations by chromatography was responsible for the low isolated yield (4%).



The reactions with DMAD of aminooxycarbenes **28d** and **28e** were also investigated. Carbonyl group transfers were observed in both cases. The reaction of oxadiazoline **33e** was very clean, affording oxazoline **157c**, isolated in 54% yield, as the only product formed in significant amount (eq. 62).

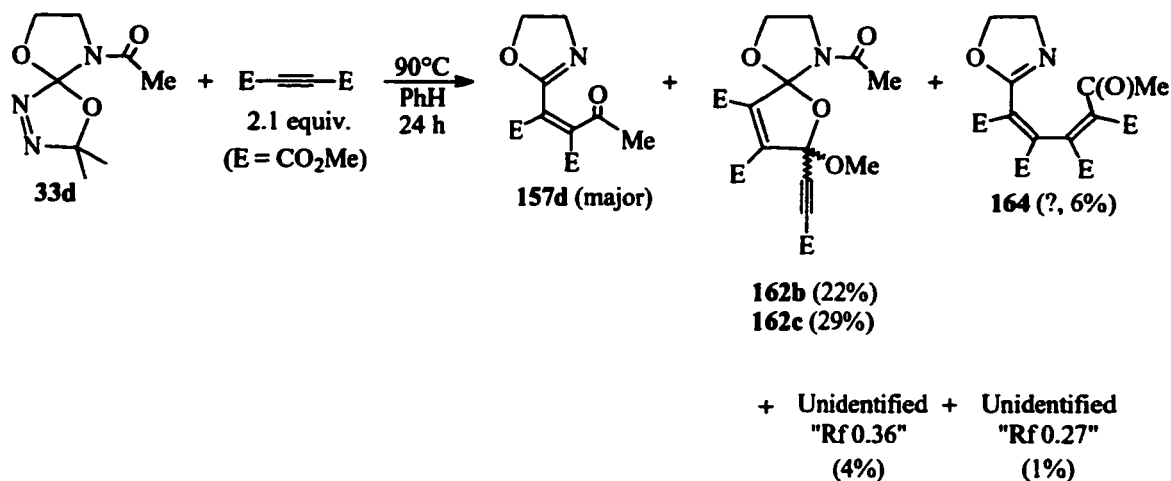




In contrast, thermolysis of **33d** under similar conditions produced at least five different 1: 2 adducts (carbene: DMAD), in addition to the oxazoline **157d** (Scheme XXXIX). The latter, which appeared to be the major product from analysis of the crude thermolysate, decomposed completely during separation by centrifugal chromatography. This procedure, however, was successful in separating the 1: 2 adducts from one another. The first two adducts to elute from the silica plate, using ethyl acetate / hexane as solvent, were identified as the pair of diastereomers **162b** (Rf 0.45, 22% yield) and **162c** (Rf 0.39, 29% yield);<sup>i</sup> the latter is the analogue of **162a** (see Scheme XXXVII above). Of the remaining three adducts, one (Rf 0.27, ~ 1% yield) was the analogue of the unidentified product U2 in the reaction of DMAD with **33f**. Another component with an Rf value of 0.36 (4% yield) could not be identified. Finally, the last component to elute (Rf 0.11, 6% yield) could have structure **164** as a <sup>13</sup>C peak, which apparently comes from a ketonic C=O, was observed at 203.94 ppm. The match of the carbon spectrum with this structure, however, is highly questionable, although the poor signal-to-noise ratio (due to the small amount of product isolated) coupled with the possible presence of peaks arising from impurities, do not allow us to rule out this possibility.

<sup>i</sup> Rf values in 70% ethyl acetate in hexane (silica plates).

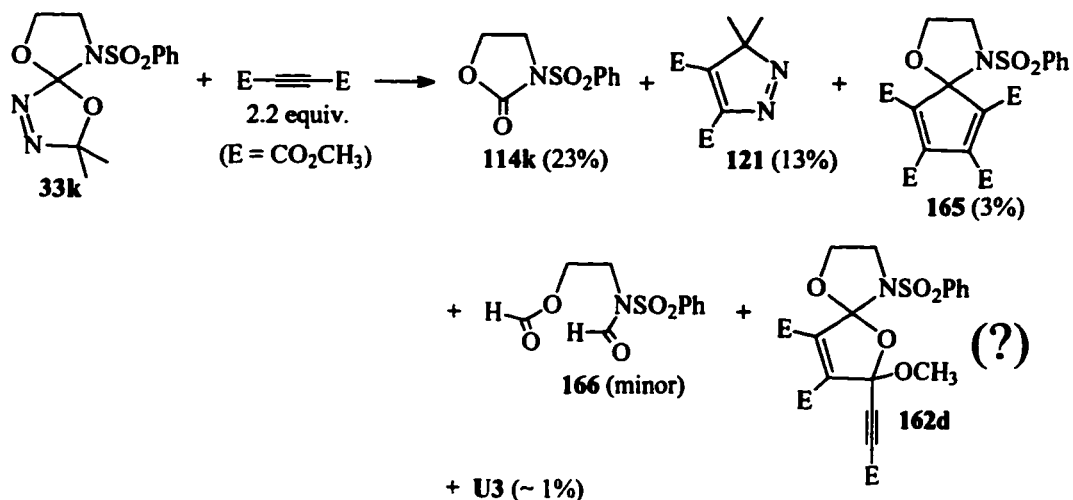
## Scheme XXXIX



Thermolysis of oxadiazoline **33k** in the presence of DMAD led to the formation of several products, as shown in Scheme XL. Among them was oxazolidinone **114k** which was isolated in 23% yield, in agreement with the results from thermolysis of **33k** (no trap, *ca.* 19% **114k** by NMR, Section 2.3.8) and of **33k** + methyl isocyanate (21%, Section 2.4.1.2.3). 2-Diazopropane, the coproduct of **114b**, reacted with DMAD to give pyrazole **121** (see eq. 45, Section 2.3.3). The only carbene + DMAD adduct which could be unambiguously identified was spiro-fused cyclopentadiene **165**, which apparently results from the unusual addition of the dipolar intermediate (see **158**, eq. 60) across the triple bond of a second molecule of DMAD. The more common 1 carbene: 2 DMAD adducts, diastereomers **162d**, were probably among the products but they could not be identified with certainty, due to difficulties in the separation. A 1 carbene: 3 DMAD adduct (**U3**), as determined by  $^1H$ - and  $^{13}C$ -NMR, as well as from MS data, was also isolated, but its low yield (*ca.* 1%) prevented a definite structural assignment to be made.

Finally, compound **166** was also isolated in low yield from the thermolysate; its origin is not known at present.

**Scheme XL**



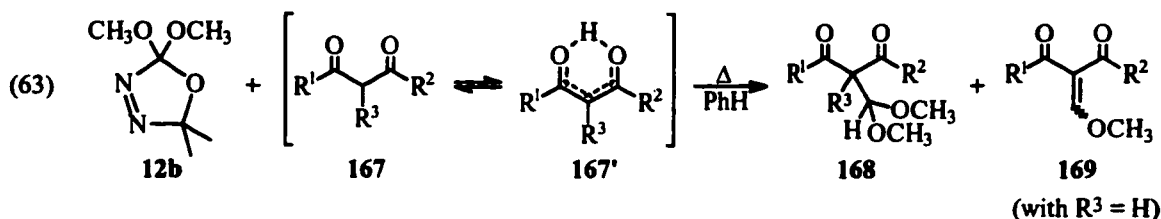
#### 2.4.4 Reactions with 1,3-Diones

In the course of a study on the reactions of dialkoxycarbenes with carbonyl compounds, D.L. Pole examined the mechanism of insertion of dimethoxycarbene (**3**), generated by thermolysis of 2,2-dimethoxy-5,5-dimethyl- $\Delta^3$ -1,3,4-oxadiazoline (**12b**), into C-H bonds of activated methylene compounds.<sup>185</sup> His results are briefly summarized here.

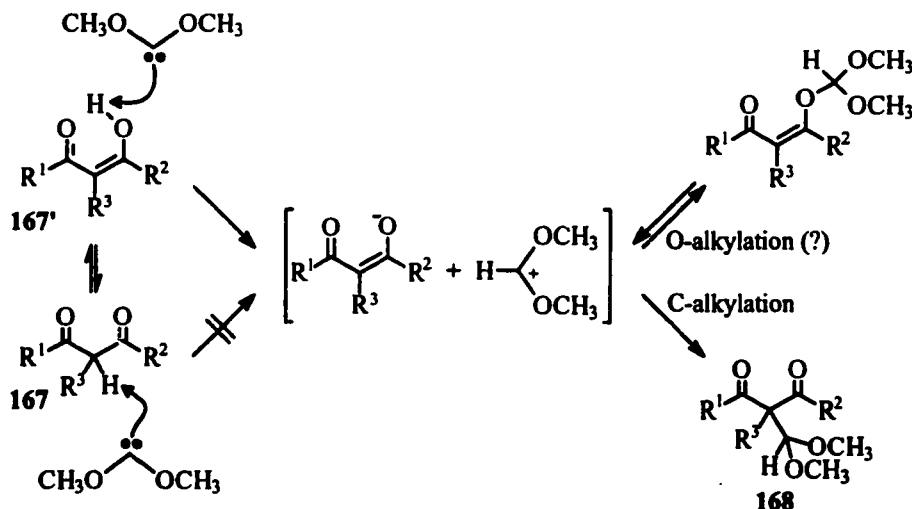
$\beta$ -Dicarbonyl compounds of type **167** are carbon acids and exist, in solution, in equilibrium with their enol tautomers, **167'**. As discussed in Chapter 1, the insertion of dialkoxycarbenes into O-H bonds appears to proceed in a stepwise manner and to involve ion-pair intermediates. Deprotonation of the enol (**167'**) by the nucleophilic carbene should therefore yield an ion pair which could then, in principle, recombine either at the

oxygen or at the carbon of the enolate; alternatively, deprotonation could also occur at the acidic carbon in **167**, with a similar result. Experimentally, the reaction of dimethoxycarbene (**3**) with a series of 1,3-diones **167** yielded exclusively the more thermodynamically stable C-alkylation products (**168** and **169**, in eq. 63), although the possible occurrence of a kinetically preferred, but reversible, O-alkylation reaction was pointed out. In addition, based on an apparent correlation between product yield and the enol content of the system, as opposed to the pKa of the carbon acid, deprotonation of the enol was favoured, as the probable mechanism, over proton abstraction at carbon in **167**.

These mechanistic aspects are summarized in Scheme XLI.

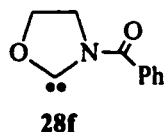


Scheme XLI

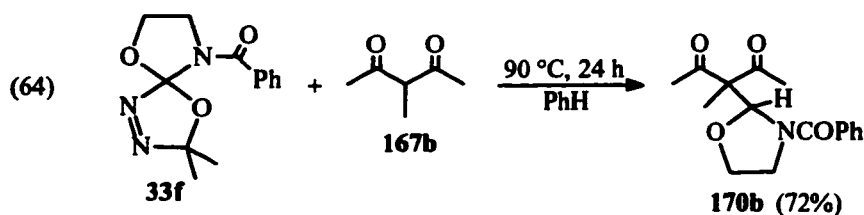


Elimination of methanol from **168** to **169** was explained in terms of rapid proton transfers between ion-pair intermediates and other species present in solution, such as **167** and **168**. These results clearly demonstrate the stepwise nature of these insertion reactions and the intermediacy of ion pairs.

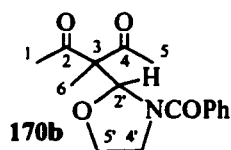
Pole's results constitute the first study of the reaction of a nucleophilic carbene with 1,3-diones. It was therefore of interest to extend this investigation to other nucleophilic carbenes, such as aminooxycarbenes, to establish the generality of these mechanisms. To this end, the reactions of 3-benzoyloxazolidin-2-ylidene (**28f**) with 2,4-pentanedione and with 3-methyl-2,4-pentanedione were probed. This particular carbene was chosen because of its quantitative formation from the oxadiazoline precursor; in addition, the thermal decomposition of its precursor has been studied in detail (Section 2.3.5), and this facilitates product identification.



The reaction of carbene **28f** with 3-methyl-2,4-pentanedione, **167b**, was found to be essentially unidirectional. Thus, when oxadiazoline **33f** was thermolysed as a 49 mM benzene solution in the presence of 1.2 equiv. of **167b**, the C-alkylation product, **170b**, was obtained as a colourless oil in 72% yield, after purification by centrifugal chromatography (eq. 64).



The identification of **170b** was unequivocal. Mass spectral data was consistent with a 1: 1 adduct. The NMR data for **170b**, presented in Table XII, shows the expected non-equivalence of the two acetyl groups caused by the asymmetric centre at C(2') of the oxazolidine.

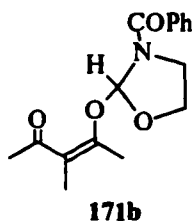


**Table XII.** Selected NMR data for compound **170b** (ppm, in CDCl<sub>3</sub>).

	<sup>1</sup> H-NMR	<sup>13</sup> C-NMR
CH <sub>3</sub> (1), CH <sub>3</sub> (5)	2.24 (s), 2.29 (s)	27.72, 28.12
C(2), C(4)		203.25, 204.26
C(3)		71.19
CH <sub>3</sub> (6)	1.44 (s)	13.22
CH(2')	6.28 (s)	90.75
CH <sub>2</sub> (4')	3.58-3.66 (m)	48.90
CH <sub>2</sub> (5')	3.67-3.81 (m), 4.04-4.19 (m)	66.55

The possibility that this compound was the O-alkylation product (**171b**) was ruled out for several reasons, including: (1) C(2') of **170b** resonates at 90.75 ppm, in agreement with other 2-alkyloxazolidines,<sup>186</sup> while C(2) in 2-oxyoazolidines typically resonates around 105 ppm (see Table X, Section 2.4.1.2.2); (2) two distinct peaks are observed for

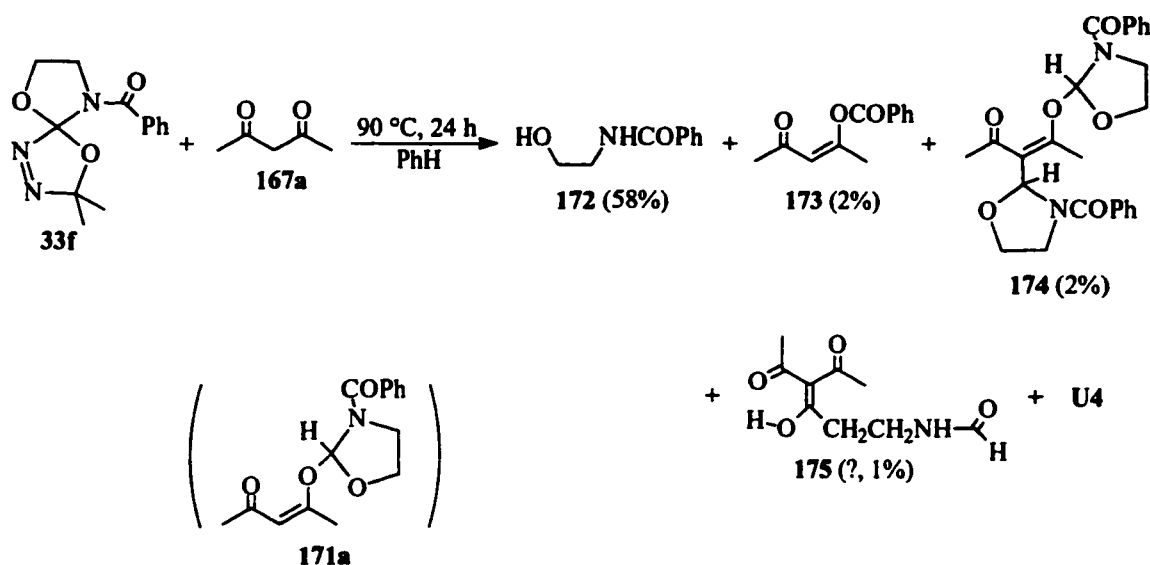
carbonyl carbons C(2) and C(4) around 204 ppm, but compound **171b** would show one peak at *ca.* 195 ppm for C=O and one around 165 ppm for =C-O, as observed in related compounds described below.



Some of the other fractions collected during the separation contained minor products, but only in negligible amounts, and these compounds were therefore not characterized. Comparison of the  $^1\text{H}$  spectrum of **170b** with that of the crude mixture recorded prior to chromatography confirmed that it was the only significant product, the other resonances belonging to the excess dione.

Thermolysis of **33f** with 2,4-pentanedione, **167a**, under similar conditions led to the isolation of five products, although only one was obtained in high yield (Scheme XLII).

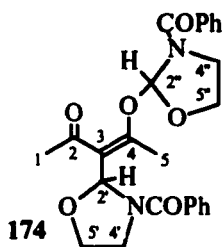
## Scheme XLII



N-(2-Hydroxyethyl)benzamide (**172**) was isolated by chromatography in 58% yield. Of the other four isolated compounds, (Z)-4-(benzoyloxy)-3-penten-2-one, **173**, and the double insertion product, **174**, were both obtained in 2% yield, while the structures of the remaining two compounds are not firmly established. The CI ( $\text{NH}_3$ ) mass spectrum of **174** had peaks at  $m/z$  468 and 451 for  $(\text{M}+\text{NH}_4)^+$  and  $(\text{M}+\text{H})^+$ , respectively, thereby confirming the 2: 1 (carbene: dione) stoichiometry. Its NMR spectra (Table XIII) are also consistent with the proposed structure. The identity of **173** was confirmed by comparison of its  $^1\text{H}$  and  $^{13}\text{C}$  spectra with those of an authentic sample, prepared by reacting **167a** with benzoyl chloride in the presence of pyridine. One of the unidentified products (**U4**), isolated in 5% yield, is a 1: 1 adduct, based on mass spectral and NMR data. The determining factor in the rejection of structure **171a** was the presence of two



relatively intense peaks at 194.26 and 200.66 ppm, suggestive of two distinct ketonic carbonyl groups, in addition to a signal at 160.27 ppm which could correspond to C4 in an analogue of 171a. Spectral data for the last product are most consistent with structure 175.



**Table XIII.** Selected NMR data for compound 174 (ppm, in CDCl<sub>3</sub>).

	<sup>1</sup> H-NMR	<sup>13</sup> C-NMR
CH <sub>3</sub> (1)	2.31 (s) <sup>a</sup>	29.18
C(2)		193.78
C(3)		116.84
C(4)		<i>ca.</i> 168 <sup>b</sup>
CH <sub>3</sub> (5)	2.25 (s) <sup>a</sup>	15.14
CH(2')	5.25 (br.s)	82.46
CH(2'')	~ 7.20-7.65	113.75
CH <sub>2</sub> (4'), CH(4'')	~ 3.60-4.30 (m)	40.11, 47.40
CH <sub>2</sub> (5'), CH(5'')	~ 3.60-4.30 (m)	65.60, 69.81

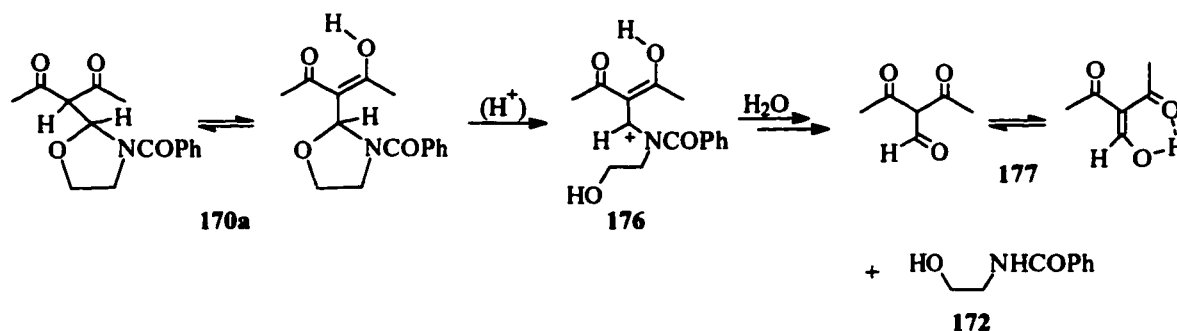
<sup>a</sup>Interchangeable.

<sup>b</sup>One of three peaks around 168 ppm.

The formation of 172, which had not been previously observed in thermolyses involving 33f, deserves some attention. It must first be mentioned that, in contrast to the thermolysis with 3-methyl-2,4-pentanedione (167b), the major isolated product, in this case, was present in the initial crude thermolysate only as a relatively minor component

(by  $^1\text{H}$ -NMR). It is believed to result from hydrolysis of the C-alkylation product, **170a**, during work-up. This facile hydrolysis contrasts with that of the analogous **170b**, which remained intact under similar conditions. Hydrolysis of **170a**, possibly catalysed by traces of acid, is expected to involve the enol tautomer, and to proceed *via* stabilized ionic intermediate **176** (Scheme XLIII); in contrast, keto-enol tautomerization of **170b** is blocked by a methyl group, and hydrolysis of the keto form is undoubtedly much slower. Although the coproduct resulting from hydrolysis of **170a**, compound **177**, was not isolated, it was identified in the  $^1\text{H}$  spectrum of the crude with its two characteristic singlets<sup>i</sup> at 10.01 ppm and 18.33 ppm.

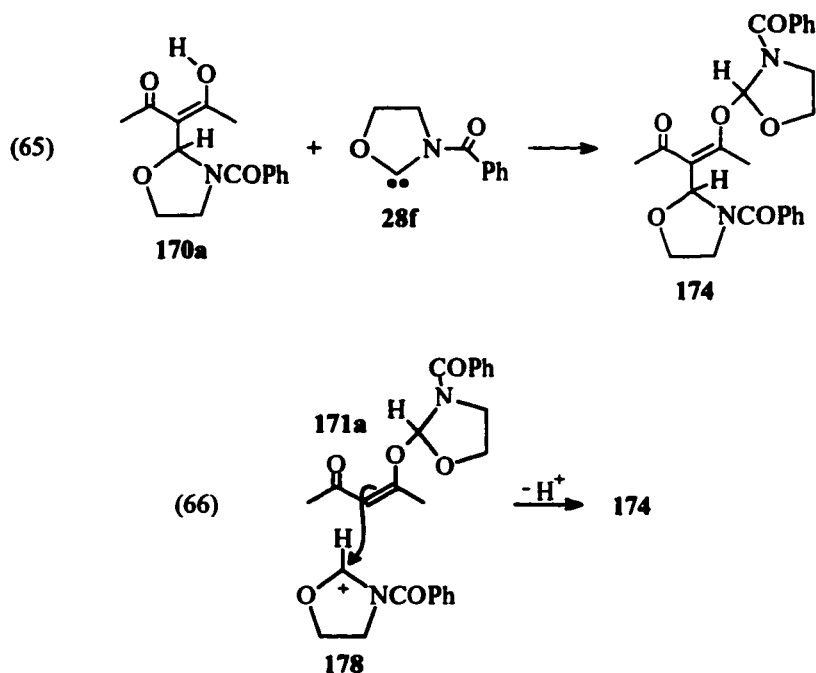
Scheme XLIII



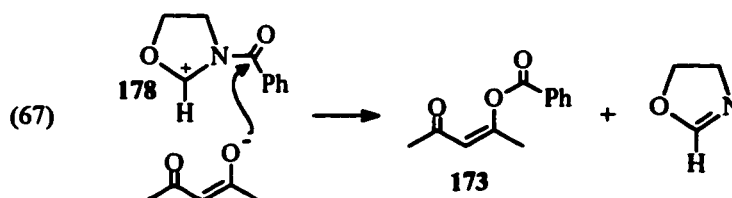
These experimental results on the reaction of aminoxycarbene **28f** with 1,3-diones **167** are in line with those involving dimethoxycarbene (**3**).<sup>185</sup> The intermediate ion pair, presumably formed by deprotonation of the enol tautomer, eventually yields the more thermodynamically stable C-alkylation product. Formation of the double insertion product **174**, in the thermolysis of **33f** with 2,4-dione **167a**, likely results from insertion of carbene

<sup>i</sup> D. L. Pole, personal communication.

**28f** into the OH bond of **170a** (eq. 65); however, the alternative C-alkylation of **171a**, by its nucleophilic attack on oxazolidinium ion **178**, for instance, is possible (eq. 66).

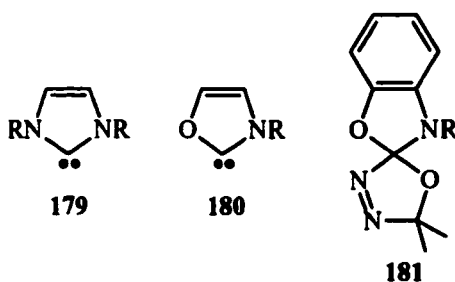


Most astonishing is the fact that **174** could be purified without complete hydrolysis of the 2-alkoxyoxazolidine moiety, in view of their usual fragility (see Section 2.4.1.2.2); this may be due to the steric hindrance provided by the large C2 substituent. The isolation of **173** is also revealing. It can most adequately be explained by postulating the attack of the enolate, in the ion pair, on the carbonyl carbon of the oxazolidinium ion (**178**), as shown in eq. 67. That the coproduct of **173**, 2-oxazoline, was not observed is not surprising considering the low yield of **173**. This, again, demonstrates the involvement of ionic species in these overall insertion reactions.



## 2.5 1,3-Benzoxazol-2-ylidenes

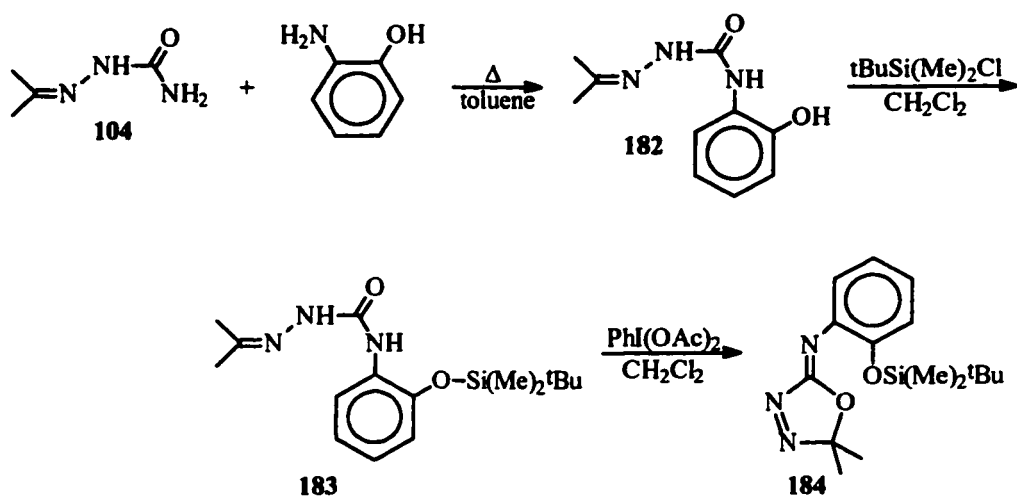
Based on the recent reports<sup>71</sup> of stable diaminocarbenes of type **179**, it was of interest to try generating analogous unsaturated five-membered aminooxycarbenes **180**. Oxadiazolines of type **181** were chosen as potential precursors of such unsaturated carbenes. In addition to providing a comparison of the reactivity of these species both with known diaminocarbenes and with our saturated aminooxycarbenes, this would allow us to verify if unimolecular fragmentation, a reaction that limits the lifetime of some 5-membered cyclic carbenes, would be prevented by the addition of the fused benzene ring. If fragmentation still occurred, another reactive intermediate, benzyne, would be generated in the process.



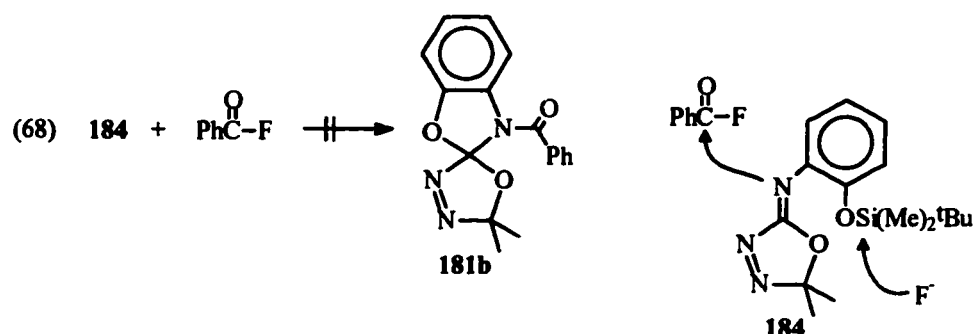
The first step towards the synthesis of compounds of type **181** was the preparation of semicarbazone **182**, which was accomplished by transamination of acetone

semicarbazone (**104**) with 2-aminophenol under the usual conditions (Scheme XLIV). As expected, reaction of substituted semicarbazone **182** with  $\text{PhI}(\text{OAc})_2$  did not lead to the corresponding oxadiazoline; instead, the immediate colour change produced by addition of the oxidant to the semicarbazone solution suggested that oxidation of the phenol was occurring. The phenol was therefore protected with a *tert*-butyldimethylsilyl group, and oxidation of **183** with  $\text{PhI}(\text{OAc})_2$  produced imino oxadiazoline **184**.

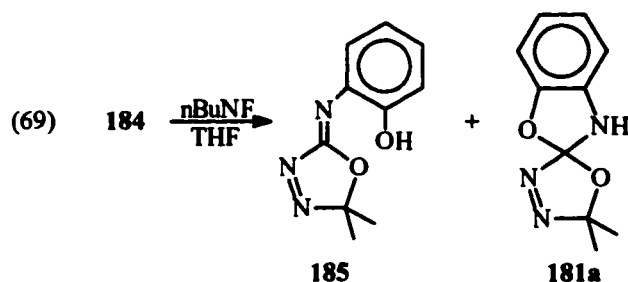
Scheme XLIV



Deprotection of **184** was initially attempted using benzoyl fluoride in order to make **181b** directly as shown in eq. 68. Although some reaction occurred slowly, at room temperature, over the course of three weeks (as observed from changes in the  $^1\text{H}$ -NMR spectrum of the reaction mixture), no evidence for the formation of **181b** could be found. In any case, the expected thermal instability of **181b** (*vide infra*) would undoubtedly obviate the synthetic utility of this method.



Successful deprotection of the imino oxadiazoline (**184**) was carried out with tetrabutylammonium fluoride and resulted in a mixture of **185** and **181a**, which could not be separated by chromatography, possibly due to their fast interconversion (eq. 69). Their identification was based primarily on the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra of mixtures of these two compounds in various proportions which allowed spectral assignments to be inferred. For instance,  $^1\text{H}$  spectra ( $\text{CDCl}_3$ ) showed two related methyl singlets at 1.60 and 1.64 ppm, assigned to **181a**, and one singlet at 1.74 ppm for **185**. In addition, resonances at 119.45 and 133.72 in the  $^{13}\text{C}$  spectrum were tentatively assigned to C2 ( $\text{CMe}_2$ ) and C5 (spiro C), respectively, of **181a**.

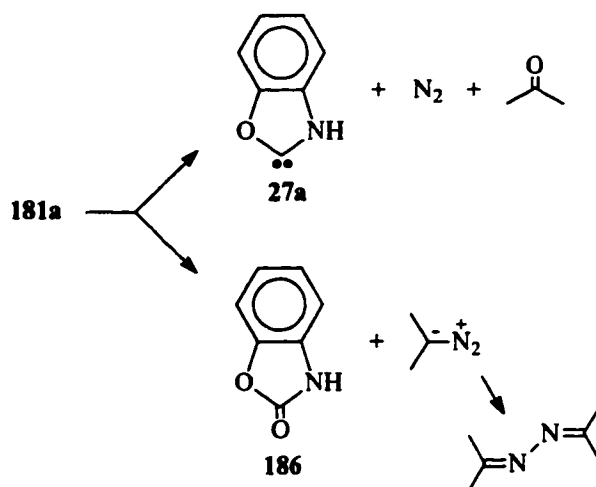


Various attempts to try to force cyclization of **185**, which was always the major isomer obtained, through the use of different acids (acetic acid in benzene, aqueous hydrochloric acid, ...) or by stirring in these acidic media for longer periods, in the work-up of the deprotection reaction, did not provide the desired results. In addition, this cyclization did not occur at any useful rate, if at all, in  $\text{CDCl}_3$ , as observed in mixtures of the two compounds kept either at room temperature or at *ca.*  $-10^\circ\text{C}$ ; in fact, decomposition of **181a** was found to be much faster than its formation from **185**.

In contrast to the saturated oxadiazolines **33** and **106**, **181a** is thermally unstable at room temperature, with an estimated half-life on the order of 6-12 h. Some of its decomposition products could be identified. Both acetone and acetone azine were found, by  $^1\text{H}$ -NMR, to increase in concentration with time, in isolated mixtures of **185** and **181a**. 2(3*H*)-Benzoxazolone (**186**) was also isolated during the separation of the oxadiazoline mixture. These products can be accounted for by the occurrence of two simultaneous thermolytic pathways, as proposed in Scheme XLV. Without an added trap, however, no product could be unambiguously identified as being derived from 1,3-benzoxazol-2-ylidene (**27a**), although the formation of acetone supports its generation from **181a**. It should be noted that although the fast decomposition of this oxadiazoline might be a photochemical, rather than thermal, process, this has been ruled out by the observation that acetone was being formed during the acquisition of a  $^{13}\text{C}$  spectrum, over about one hour, while the sample was at room temperature, in the dark, inside the NMR probe (decomposition also clearly occurred in samples kept inside the refrigerator or freezer).

Similarly, the possibility that some of the decomposition products may come from **185**, rather than from **181a**, was ruled out for the following reasons: (1) under similar conditions, imino oxadiazoline **184** is thermally stable; (2) related 5,5-diaryl-2-phenylimino oxadiazolines thermolyse at significant rates only at higher temperatures.<sup>187</sup>

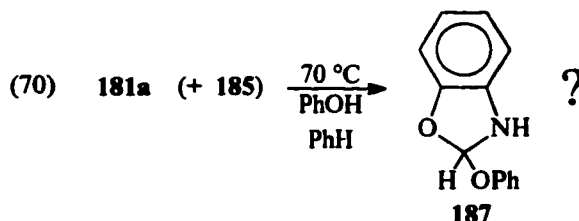
#### Scheme XLV



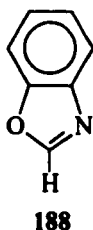
In order to try to demonstrate the intermediacy of carbene **27a** in the decomposition of **181a**, a sample (*ca.* 45 mg) containing some of this oxadiazoline was thermolysed in benzene, at 70 °C, in the presence of a large excess of phenol. The complexity of the resulting product mixture, due in large part to a highly impure starting oxadiazoline, prevented an unambiguous confirmation of the generation of **27a**. However,  $^1H$ -NMR analysis of the crude thermolysate showed singlets at 6.43 and 6.49 ppm, either of which could be due to the amide acetal proton of the expected phenol insertion product, **187** (eq. 70). In principle, carbene insertion into the phenolic OH of **185**, or into



the NH bond of **181a** or some decomposition product, could also have occurred, although those pathways should be relatively unimportant because the concentration of added phenol was at least ten times higher than that of any other potential trap.

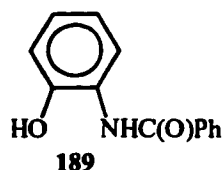


From this thermolysis at 70 °C, the presence of benzoxazole (**188**), a potential product resulting from 1,2-H migration in carbene **27a**, could not be ruled out since a small singlet which could be attributed to its vinyl proton appeared near 8.13 ppm.<sup>188</sup> Thermal decomposition of **181a** at or below room temperature, however, clearly did not produce this compound in detectable amount (by <sup>1</sup>H-NMR). This is not surprising in view of the apparently high activation energy for the analogous rearrangement of the related oxazolidin-2-ylidene (**28a**, see Section 1.6.1.2).



Benzoylation of **181a** was attempted by reaction with benzoyl chloride. Unfortunately, separation of the resulting product mixture only led to the isolation of

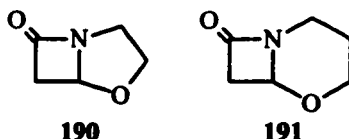
2(3*H*)-benzoxazolone (**186**) and of *N*-(2-hydroxyphenyl)benzamide, **189**. The exact origin of the latter is, at present, unknown.



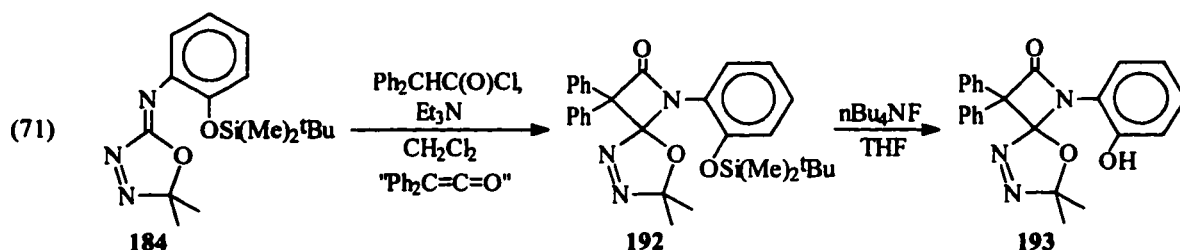
In summary, the low thermal stability of oxadiazolines of type **181**, combined with the impossibility of obtaining pure samples, precluded a detailed study of their thermal chemistry. This instability may be related to an increased stability of their corresponding carbenes, as compared to the saturated analogues, although the above results demonstrate the occurrence of at least two competing decomposition pathways in the case of **181a**, one of which does not lead to carbene **27a**.

## 2.6 Intramolecular Trapping of a Novel $\beta$ -Lactam-4-Ylidene

Recently, Zoghbi and Warkentin demonstrated the synthetic utility of intramolecular insertion reactions of  $\beta$ -lactam-4-ylidenes in the construction of oxapenam (**190**) and oxacepham (**191**) nuclei.<sup>136,189</sup> The considerable potential of this methodology is evident in view of the importance of  $\beta$ -lactams as therapeutic agents.<sup>190</sup> The availability of imino oxadiazoline **184**, initially synthesized as a precursor to the unsaturated carbenes **27** (Section 2.5), prompted us investigate the possibility of constructing a benzo-fused oxapenam nucleus using the  $\beta$ -lactam-4-ylidene method.

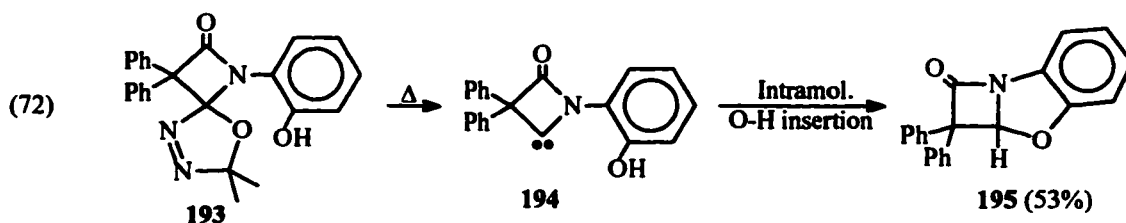


From **184**, only two steps were required to get to the desired carbene precursor, as shown in eq. 71. Following Zoghbi's method,<sup>136</sup> **184** was converted to spiro-fused  $\beta$ -lactam oxadiazoline **192** in 85% yield by treatment with diphenylacetyl chloride and triethylamine (a diphenylketene equivalent). Deprotection of the phenoxy group of **192** with  $n\text{Bu}_4\text{NF}$  gave **193** in up to 77% yield.



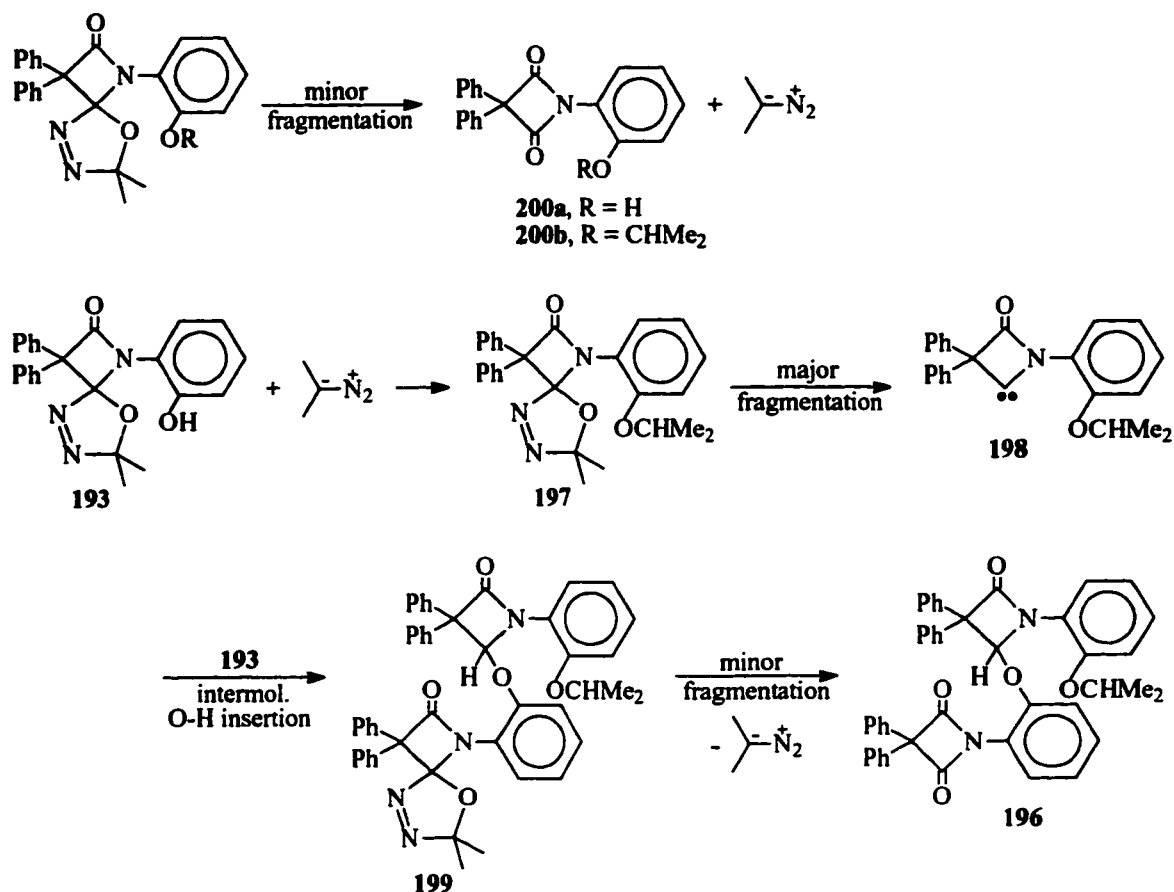
Thermal decomposition of  $\beta$ -lactam oxadiazoline **193** was expected to generate  $\beta$ -lactam-4-ylidene **194**, which is perfectly set up to undergo an intramolecular O-H insertion and thus yield benzo-fused oxapenam **195** (eq. 72). Experimentally, thermolysis (100 °C, 24 h) of **193**, as a 14 mM solution in benzene, gave **195** in 53% yield along with several other products formed in low yield. Of these minor products, only **196**, isolated in 7% yield, could be unambiguously identified.<sup>i</sup>

<sup>i</sup> Its connectivity was unambiguously determined by X-ray crystallography but a high-quality set of data could not be obtained.



A multi-step mechanism accounting for formation of **196** is proposed in Scheme XLVI. It involves two 1,3-dipolar cycloreversions of an oxadiazoline ring to 2-diazopropane and a 2,4-azetidinedione; no evidence for the occurrence of these minor pathways from thermolysis of spiro  $\beta$ -lactam oxadiazolines had previously been found,<sup>136,191</sup> although they are common in oxadiazolines in general, as shown for example in previous sections of this thesis. The 2-diazopropane thus generated reacts with the starting material, phenol **193**, to give ether **197**. The predominant fragmentation pathway of **197** generates carbene **198**, which undergoes an intermolecular O-H insertion reaction, with the starting material in this case, to give **199**. Finally, fragmentation of the oxadiazoline moiety of **199** by the minor pathway (loss of 2-diazopropane) yields **196**.

## Scheme XLVI



Scheme XLVI hints to the multiplicity of intermolecular reactions that may occur, leading to a complex mixture of minor products. Interestingly, Zoghbi found that reducing the initial concentration of his analogue of **193** from 150 mM to 8 mM actually resulted in a somewhat lower yield of the apparent intramolecular insertion product.<sup>136</sup> According to Scheme XLVI, we would expect to find compounds **200a** and **200b** among the thermolysis products. As pointed out, it was not possible to identify with certainty most of the minor products, because of the impossibility, in several cases, of obtaining

sufficient amounts of high purity compounds. Partial spectral data are listed, in Section 4.6, for two of those products. The  $^1\text{H}$  spectrum of one of them demonstrated the presence of an isopropoxy group;<sup>i</sup> its  $^{13}\text{C}$  spectrum may be consistent with structure **200b**, although some signals appear to be missing, possibly due to the low intensity of these signals and to spectral overlap.

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<sup>i</sup> Other unidentified products that are not described in Section 4.6 also had at least one such isopropoxy group.

## Chapter 3

### Summary and Conclusions

The first contribution of this work was to provide a series of  $\Delta^3$ -1,3,4-oxadiazolines, substituted at C2 with one O and one N, as novel precursors of aminooxycarbenes. This has led us to study both the mechanisms involved in the thermolysis of oxadiazolines and the chemistry of the aminooxycarbenes generated. In addition, some unexpected avenues were explored. The results presented in Chapter 2 are summarized below.

#### 3.1 Thermolysis Mechanisms

The specific mechanisms involved in a thermolysis depend on the substituents present on the  $\Delta^3$ -1,3,4-oxadiazoline skeleton. In general, the major fragmentation pathway starts with a cycloreversion releasing N<sub>2</sub>, and leads to the desired nucleophilic carbenes. Competing reactions, however, sometimes lower the effective yield of carbenes. For example, 2-aryloxy-2-methoxy oxadiazolines **86** undergo a relatively minor (< 20%) fragmentation to 2-diazopropane and a carbonate (**93**); this pathway is also minor in the case of 2-amino-2-oxy oxadiazolines **33** and **106** in general, and it is insignificant for the N-carbonyl compounds (**33c-j** and **106d,e**). A second unwanted pathway is fragmentation of the carbonyl ylide in the “reverse sense”, *i.e.* yielding a dialkyl carbene and a carbonyl

compound; this occurs to a significant extent for **33b** and **106b**, both N-methyl compounds, but not for other oxadiazolines **33/106** and **86**.

It was possible to optimize the yield of aminooxycarbenes **28/113** with an appropriate choice of substituent on N of the spiro-fused oxazolidine ring. Thus, all N-carbonyl oxadiazolines which were studied in some detail (**33c-g,j** and **106d,e**) conveniently gave essentially quantitative yields of aminooxycarbenes.

The involvement of carbonyl ylides (*e.g.* **91**) in the thermolysis of oxadiazolines possessing two heteroatoms at C2 has been a subject of controversy, as discussed above. For the first time, their intermediacy was clearly demonstrated with the identification of ketene acetals **87** from the thermolysis of 2,2-dioxy oxadiazolines **86**; compounds **87** are derived from carbonyl ylides **91** by a minor pathway which competes with carbene formation. In the case of N-substituted **33b-k** and **106b-e**, no definite evidence was found for the intermediacy of carbonyl ylides. However, experiments on **33a** (NH) led to the observation of several products apparently derived from carbonyl ylide **111a**, including ketene acetal **134**; evidence was also found for trapping of **111a**, both intramolecularly *via* a 1,4-H migration to oxazoline **135**, and intermolecularly with 4-cyanophenol to give oxazolidine **137**. These results can be interpreted in terms of different stabilities (or lifetimes) for carbonyl ylides bearing different substituents.

Substituent effects are also manifested in the first-order thermolysis rate constants of oxadiazolines **33/106**. As described in Section 2.3.1, within a series of analogous 2-amino-2-oxy oxadiazolines, the rates of decomposition tend to augment with increasingly



electron-withdrawing groups on the amino substituent, covering a slightly greater than 30-fold rate change. This trend is consistent with the intermediacy of carbonyl ylides which, bearing a partial negative charge at C2,<sup>i</sup> are expected to be stabilized by electron withdrawal. A much more dramatic substituent effect on the thermal stability of 2-amino-2-oxy oxadiazolines is observed by comparing benzo-fused oxadiazoline **181a** ( $t_{1/2} \approx 6$ -12 h at room temperature) to the related oxadiazolines **33/106** ( $t_{1/2} \approx 1$ -12 h at 90 °C). The lability of **181a** is understood in terms of the relative stability of its decomposition products, one of them being the “aromatic” 1,3-benzoxazol-2-ylidene (**27a**).

### 3.2 Chemistry of Aminooxycarbenes

One of the most important aspects of this work is the demonstration that 5-membered aminooxycarbenes generated in solution at moderate temperatures (90 °C, in this work) participate in a wide variety of bimolecular reactions; fragmentation to ethylene and R-NCO was only observed when carbenes were generated in the absence of a trap. In the case of the parent carbene, oxazolidin-2-ylidene (**28a**), fragmentation was not observed at all, although the generation of this carbene from thermolysis of **33a** was not as firmly established as for other carbenes **28**. These relatively high barriers to fragmentation contrast with those of oxygen (**117**) and sulfur (**118**) analogues which fragment too rapidly to be trapped intermolecularly.

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<sup>i</sup> The carbon attached to O and N.

Carbenes **28b-g,j** and **113d,e** were trapped efficiently by insertion into the O-H bond of phenols. The 2-aryloxy-3-methyloxazolidines (**119**) obtained by the reactions of **28b** with phenols proved to be hydrolytically more stable than their 3-carbonyl counterparts **124**. The barrier to inversion about nitrogen, in oxazolidines **119**, was measured as 20.4 kcal/mol. The reasons for this unusually high activation energy is not fully understood.

The reactions of aminooxycarbenes with isocyanates paralleled those of dioxycarbenes (Section 1.6.2.3.3). With both methyl isocyanate and phenyl isocyanate, spiro-fused hydantoins (**120**) were isolated. Their formation was rationalized in terms of the nucleophilic attack of the carbene on the carbonyl carbon of the isocyanate, followed by cycloaddition of the resulting 1,3-dipole across the C=N bond of a second molecule of the isocyanate. In contrast, the dipolar intermediates produced in the reaction of acyl isocyanates with nucleophilic carbenes are ideally suited for intramolecular cyclization. Thus, both aminooxycarbenes **28d,f** and dimethoxycarbene (**3**) reacted with benzoyl isocyanate to form 4(*5H*)-oxazolones. Those novel oxazolones with two heteroatoms at C5 are also the final products formed in high yields when oxadiazolines such as **33f** are thermolysed in the absence of an added trap, the aroyl isocyanate being formed in the fragmentation of some of the 5-membered carbenes.

The nucleophilicity of aminooxycarbenes proved sufficient to allow their addition to triple bonds, both with DMAD and with the less electrophilic methyl propiolate. The major products formed in the reaction of DMAD with dioxycarbenes (Section 1.6.2.4),

dihydrofurans of type **76/162**, were also found in the reaction with aminooxycarbenes, but only as minor products. The unexpected major products (**157**), isolated in up to 73% yield, resulted from apparent acyl group transfers from N to C in the 1,3-dipolar intermediates **158**. Such acyl transfers were observed for acetyl, vinyl, and benzoyl groups. The large number of minor products with 1: 2 stoichiometry obtained in the case of **33d** can probably be attributed to the lower steric hindrance, as compared to **33e** and **33f**, to attack by the dipolar intermediate on a second molecule of the alkyne. A previously unreported reaction also occurred in the case of **33k** (N-sulfonyl): cycloaddition of the 1,3-dipole across the triple bond of a second molecule of DMAD to produce cyclopentadiene **165** in low yield.

The reactions between aminooxycarbene **28f** and 1,3-diones (**167**) yielded predominantly the formal C-H insertion products (**170**), as previously reported in the case of dimethoxycarbene (**3**, Section 2.4.4). In addition, the minor products provided valuable support for the proposed mechanism. For instance, the isolation of **173** constitutes strong evidence for the involvement of ion pairs. Similarly, insertion into the enolic OH bond was shown, from the formation of the double insertion product **174**, to occur as a minor pathway.

In conclusion, our investigation demonstrated the similarities between the chemistry of aminooxycarbenes and that of other, better-known nucleophilic carbenes, where stepwise mechanisms involving dipolar intermediates or ion pairs best account for the observed products.

### 3.3 $\beta$ -Lactam-4-ylidene **194**

The availability of a close precursor to  $\beta$ -lactam oxadiazoline **193** allowed us to generate  $\beta$ -lactam-4-ylidene **194** which, as expected, underwent intramolecular OH insertion to produce the novel 2,3-benzooxapenam **195** in 53% yield. This relatively low yield, identical to that previously obtained by Zoghbi and Warkentin in an analogous reaction,<sup>189</sup> can now be explained by the occurrence of a competing thermolytic pathway for **193** and analogues which yields 4-oxo- $\beta$ -lactam derivatives (*e.g.* **200**). This was confirmed by the isolation of **196** as a minor product.

## Chapter 4

### Experimental

This chapter is subdivided in the same manner as Chapter 2 (Results and Discussion), so that experimental details for the work described in Section 2.2, for instance, can be found in Section 4.2.

#### General

NMR spectra were recorded on a Bruker AC-200 or AC-300 NMR spectrometer, as specified for each compound. Chemical shifts for  $^1\text{H}$  spectra are referenced with respect to TMS at 0.00 ppm, or with respect to residual solvent resonances ( $\text{CHCl}_3$ , 7.27 ppm;  $\text{C}_6\text{HD}_5$ , 7.23 ppm; acetone- $\text{d}_5$ , 2.04 ppm). Some compounds show complex NMR spectra due to the slow interconversion, on the NMR time scale, between two or more isomers; in some cases, this results in two distinct sets of resonances, while some spectra show broad, unresolved multiplets labelled below as "um". For  $^{13}\text{C}$  spectra, solvent peaks were used as chemical shift references ( $\text{CDCl}_3$ , 77.00 ppm;  $\text{C}_6\text{D}_6$ , 128.00 ppm, acetone- $\text{d}_6$ , 29.80 ppm). Infrared spectra were recorded either as  $\text{CCl}_4$  solutions, in a cell of 0.5 mm path length, or as KBr pellets, using a Biorad FTS-40 spectrophotometer. The IR bands are labelled qualitatively with the symbols *br* for broad, and *s*, *m*, and *w* for strong, medium, and weak intensities, respectively; bands from C-H

stretching vibrations between 2850-3100  $\text{cm}^{-1}$  are omitted, as are very weak bands. Melting points were recorded on a Thomas Hoover capillary melting point apparatus, and are reported uncorrected. Mass spectra were obtained on a ZAB-E double-focusing mass spectrometer or on a Hewlett Packard MSD GC-MS, model 5971A. Benzene used as a thermolysis solvent was distilled from sodium benzophenone, and stored over molecular sieves. Hexane used for chromatography was distilled. Radial chromatography was performed using a Chromatotron, model 7924T (Harrison Research Inc.), with silica-coated plates of 1 mm, 2 mm, or 4 mm thickness. Elemental analyses were performed by Guelph Chemical Laboratories, Ltd (Guelph, ON).

Appropriate references are given for known compounds, except in the case of common ones. Compounds which are not referenced have not been previously reported, to the best of our knowledge.

#### 4.1 Thermolysis of 2-Aryloxy-2-methoxy- $\Delta^3$ -1,3,4-oxadiazolines

**Synthesis of 2-aryloxy-2-methoxy- $\Delta^3$ -1,3,4-oxadiazolines (86a-f).** These compounds were prepared by M. El-Saidi.<sup>133</sup> Most of them were further purified by radial chromatography on a silica plate, using ethyl acetate/hexane in various proportions as elution solvent.

**Thermolysis of 2-methoxy-5,5-dimethyl-2-(4-nitrophenoxy)- $\Delta^3$ -1,3,4-oxadiazoline (86a).** A benzene solution (10 mL) of 86a (139 mg, 0.52 mmol) in a sealable thermolysis tube was evacuated. Thermolysis was carried out by immersing the tube in a constant

temperature oil bath, at  $110.0 \pm 0.2$  °C, for 24 h. After completion of the thermolysis, the tube was opened and volatile products and the solvent were evaporated *in vacuo*.  $^1\text{H}$ -NMR and GC-MS spectra of the residue were recorded. The thermolysis products were then separated by radial chromatography, on a 1 mm-thick silica plate, using mixtures of ethyl acetate and hexane as elution solvent (starting at 5% ethyl acetate and gradually increasing to 20%). Some spectral data for the thermolysis products of this and other oxadiazolines are given below; additional spectral data (on carbonates **93** and carbene dimers, but not on ketene acetals **87** and oxiranes **94**) and yields may be found in M. El-Saidi's thesis.<sup>133</sup>

**Thermolysis of 86a in the presence of cyclopentanone.** The thermolysis was carried out as described above using 135 mg (0.51 mmol) of **86a** and 92 mg (1.1 mmol) of cyclopentanone in enough benzene to make 9 mL of solution. Analysis of the product mixture by  $^1\text{H}$ -NMR and GC-MS revealed the presence of **87a**, but not the analogous ketene acetal (**97**) from incorporation of cyclopentanone.

**Thermolysis of 86a in the presence of acetone- $\text{d}_6$ .** The thermolysis was carried out as described above using 50 mg (0.19 mmol) of **86a** and 0.44 g (6.9 mmol) of acetone- $\text{d}_6$  in enough benzene to make 6 mL of solution.  $^1\text{H}$ -NMR of the crude product showed **87a** for which, within experimental error, the integrated area of each of the two  $\text{C-CH}_3$  singlets was equal to that of the  $\text{OCH}_3$  singlet. In addition, the GC-MS spectrum of the ketene acetal corresponded to that of the non-deuterated species.

**Determination of product yields from thermolysis of 86c.** Oxadiazoline 86c was thermolysed (at concentrations specified in Table IV) in 5.0 mL of benzene, at 110 °C, for 24 h. Following thermolysis, 5.0 µl of ethyl benzoate was added to the thermolysate. Product yields were determined using a Varian Vista 6000 GC, equipped with a FID and a DB-5, 30 m column. Yields of 87c, 93c, and 94c were normalized with respect to ethyl benzoate, and were not corrected for differential responses from the detector. Each data point represents the average of five measurements.

» *1-Methoxy-2,2-dimethyl-1-(4-nitrophenoxy)ethylene*, **87a**. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.56 (s, 3H, CCH<sub>3</sub>), 1.75 (s, 3H, CCH<sub>3</sub>), 3.52 (s, 3H, OCH<sub>3</sub>), 7.02-7.16 (m, 2H, Ar-o, p), 8.14-8.29 (m, 2H, Ar-m); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 16.17 (2 x CCH<sub>3</sub>, coincident), 57.08 (OCH<sub>3</sub>), 100.67 (=C(Me)<sub>2</sub>), 115.88 (Ar C2, C6), 125.87 (Ar C3, C5), 142.67 (Ar C4), 147.94 (=C(OR)<sub>2</sub>), 161.23 (Ar C1); IR (CCl<sub>4</sub>): 1715m, 1594m, 1530s (NO<sub>2</sub>), 1492m, 1456w, 1438w, 1344s (NO<sub>2</sub>), 1263m, 1225s, 1160m, 1124s, 1017m, 927w, 863m, 851m; MS (EI) m/z: 223 (M<sup>+</sup>, 30), 208 (M-CH<sub>3</sub>, 1), 180 (4), 164 (100), 148 (7), 136 (16), 118 (16), 106 (15), 91 (12), 85 (12), 76 (23), 70 (67), 63 (27), 55 (28), 50 (23), 41 (63), 30 (24), 27 (7); MS (CI, NH<sub>3</sub>) m/z: 241 (M+NH<sub>4</sub>)<sup>+</sup>, 224 (M+H)<sup>+</sup>; HRMS calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub> (M<sup>+</sup>) m/z 223.0845, obsd 223.0845.

Note: ketene acetals **87b-f** were not isolated, and the MS data listed below were obtained by GC-MS analyses of the thermolysates; partial <sup>1</sup>H-NMR data are presented in Table III.



» *1-Methoxy-2,2-dimethyl-1-(4-trifluoromethylphenoxy)ethylene*, **87b**. MS (EI)  $m/z$ : 246 ( $M^+$ , 36), 227 (M-F, 14), 187 (100), 159 (83), 145 (42), 133 (14), 125 (18), 113 (17), 95 (19), 70 (50), 55 (25), 41 (67), 27 (8).

» *1-(4-Chlorophenoxy)-1-methoxy-2,2-dimethylethylene*, **87c**. MS (EI)  $m/z$ : 214 ( $^{37}\text{Cl } M^+$ , 7), 212 ( $^{35}\text{Cl } M^+$ , 21), 197 ( $^{35}\text{Cl } M-\text{CH}_3$ , 2), 181 (1), 171 (2), 169 (9), 155 (36), 153 (100), 142 (6), 127 (23), 125 (37), 111 (18), 99 (33), 85 (21), 75 (43), 70 (73), 63 (20), 55 (39), 50 (20), 41 (83), 39 (55), 27 (11).

» *1-Methoxy-2,2-dimethyl-1-phenoxyethylene*, **87d**. MS (EI)  $m/z$ : 178 ( $M^+$ , 29), 135 (10), 119 (100), 107 (12), 91 (74), 77 (56), 70 (56), 65 (41), 55 (32), 51 (41), 41 (65), 39 (68), 27 (13).

» *1-Methoxy-2,2-dimethyl-1-(4-methylphenoxy)ethylene*, **87e**. MS (EI)  $m/z$ : 192 ( $M^+$ , 26), 149 (9), 133 (100), 121 (8), 105 (55), 91 (23), 77 (31), 70 (28), 65 (19), 55 (16), 41 (31), 39 (25), 27 (7).

» *1-Methoxy-1-(4-methoxyphenoxy)-2,2-dimethylethylene*, **87f**. MS (EI)  $m/z$ : 208 ( $M^+$ , 18), 149 (100), 138 (6), 123 (41), 109 (16), 95 (21), 77 (19), 70 (25), 63 (14), 55 (15), 41 (27), 27 (3).

» *Methyl 4-nitrophenyl carbonate*, **93a**.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.96 (s, 3H,  $\text{CH}_3$ ), 7.39 (d,  $^3J = 9.2$  Hz, 2H, Ar), 8.30 (d,  $^3J = 9.2$  Hz, 2H, Ar); MS (EI)  $m/z$ : 197 ( $M^+$ , 4), 153 (M- $\text{CO}_2$ , 4), 123 (100), 107 (4), 95 (19), 92 (24), 77 (20), 63 (42), 59 (21), 50 (12), 38 (12), 30 (26).

» *Methyl 4-trifluoromethylphenyl carbonate, 93b.*  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.94 (s, 3H,  $\text{CH}_3$ ), 7.33 (d,  $^3J = 8.5$  Hz, 2H, Ar), 7.68 (d,  $^3J = 8.5$  Hz, 2H, Ar); MS (EI)  $m/z$ : 220 ( $\text{M}^+$ , 32), 201 (M-F, 14), 189 (1), 176 (M- $\text{CO}_2$ , 100), 161 ( $\text{ArO}^+$ , 9), 157 (49), 145 (80), 133 (95), 127 (30), 113 (80), 107 (12), 96 (25), 90 (18), 83 (51), 79 (24), 75 (22), 71 (13), 63 (41), 59 (37), 57 (20), 50 (12), 38 (10), 29 (16).

» *4-Chlorophenyl methyl carbonate, 93c.*  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.92 (s, 3H,  $\text{CH}_3$ ), 7.12 (d,  $^3J = 9.0$  Hz, 2H, Ar), 7.36 (d,  $^3J = 9.0$  Hz, 2H, Ar); MS (EI)  $m/z$ : 188 ( $^{37}\text{Cl}$   $\text{M}^+$ , 9), 186 ( $^{35}\text{Cl}$   $\text{M}^+$ , 24), 144 ( $^{37}\text{Cl}$  M- $\text{CO}_2$ , 13), 142 ( $^{35}\text{Cl}$  M- $\text{CO}_2$ , 40), 129 ( $^{37}\text{Cl}$   $\text{ArO}^+$ , 20), 127 ( $^{35}\text{Cl}$   $\text{ArO}^+$ , 66), 113 (6), 111 (15), 101 (33), 99 (100), 75 (25), 73 (33), 63 (31), 59 (13), 50 (8), 38 (7), 29 (9).

» *Methyl phenyl carbonate, 93d.*  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.92 (s, 3H,  $\text{CH}_3$ ), *ca.* 7.1-7.5 (Ar); MS (EI)  $m/z$ : 152 ( $\text{M}^+$ , 30), 108 (M- $\text{CO}_2$ , 25), 93 ( $\text{ArO}^+$ , 16), 78 (66), 65 (100), 59 (13), 51 (19), 39 (50), 29 (12).

» *Methyl 4-methylphenyl carbonate, 93e.*  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.36 (s, 3H,  $\text{ArCH}_3$ ), 3.91 (s, 3H,  $\text{OCH}_3$ ), *ca.* 6.75-7.20 (Ar); MS (EI)  $m/z$ : 166 ( $\text{M}^+$ , 36), 121 (51), 107 ( $\text{ArO}^+$ , 55), 91 (30), 77 ( $\text{Ph}^+$ , 100), 63 (16), 59 (15), 51 (27), 39 (16), 29 (14).

» *4-Methoxyphenyl methyl carbonate, 93f.*  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : *ca.* 3.82 (s, 3H,  $\text{ArOCH}_3$ ), 3.91 (s, 3H), *ca.* 6.8-7.2 (Ar); MS (EI)  $m/z$ : 182 ( $\text{M}^+$ , 20), 138 (M- $\text{CO}_2$ , 6), 123 ( $\text{ArO}^+$ , 100), 107 (3), 95 (55), 80 (7), 77 (6), 63 (12), 59 (8), 52 (11), 41 (10), 29 (6).

» *2-Methoxy-3,3-dimethyl-2-(4-nitrophenoxy)oxirane, 94a.* Not observed.

» *2-Methoxy-3,3-dimethyl-2-(4-trifluoromethylphenoxy)oxirane, 94b*. MS (EI)  $m/z$ : 205 (44), 162 (8), 145 (28), 113 (14), 75 (100), 31 (36), 28 (7).

» *2-(4-Chlorophenoxy)-2-methoxy-3,3-dimethyloxirane, 94c*. MS (EI)  $m/z$ : 173 (11), 171 (30), 154 (2), 143 (3), 130 (6), 128 (18), 113 (5), 111 (13), 101 (5), 99 (16), 75 (100), 65 (8), 63 (14), 50 (6), 47 (28), 39 (6), 31 (22), 29 (15).

» *2-Methoxy-3,3-dimethyl-2-phenoxyoxirane, 94d*. MS (EI)  $m/z$ : 137 (79), 109 (12), 94 (36), 77 (58), 75 (100), 65 (46), 51 (19), 47 (50), 39 (42), 31 (34), 29 (32).

» *2-Methoxy-3,3-dimethyl-2-(4-methylphenoxy)oxirane, 94e*. MS (EI)  $m/z$ : 182 (2), 151 (54), 123 (15), 107 (27), 91 (27), 75 (100), 65 (13), 51 (12), 47 (30), 31 (20), 29 (17).

» *2-Methoxy-2-(4-methoxyphenoxy)-3,3-dimethyloxirane, 94f*. MS (EI)  $m/z$ : 167 (42), 152 (2), 139 (14), 124 (36), 109 (30), 95 (17), 92 (16), 81 (18), 75 (100), 63 (18), 53 (16), 47 (32), 41 (8), 39 (14), 31 (26), 29 (24).

» *Methyl isobutyrate*.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.18 (d,  $^3J = 7.0$  Hz, 6H,  $\text{C}(\text{CH}_3)_2$ ), 2.58 (septet,  $^3J = 7.0$  Hz, 1H, CH), 3.69 (s, 3H,  $\text{OCH}_3$ ).

» *1,2-Dimethoxy-1,2-di(4-nitrophenoxy)ethylene*.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ) *Z*-isomer  $\delta$ : 3.61 (s, 6H,  $\text{CH}_3$ ), 7.22 (d,  $^3J = 9.2$  Hz, 2H, Ar), 8.29 (d,  $^3J = 9.2$  Hz, 2H, Ar); *E*-isomer  $\delta$ : 3.77 (s, 6H,  $\text{CH}_3$ ), 7.11 (d,  $^3J = 9.2$  Hz, 2H, Ar), 8.21 (d,  $^3J = 9.2$  Hz, 2H, Ar); MS (EI)  $m/z$ : 182 (18), 136 (2), 123 (1), 108 (4), 103 (19), 92 (3), 75 (100), 63 (10), 50 (7), 47 (15), 29 (11).

» *1,2-Dimethoxy-1,2-di(4-trifluoromethylphenoxy)ethylene*.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ) *Z*-isomer  $\delta$ : 3.59 (s, 3H,  $\text{CH}_3$ ), 7.21 (d,  $^3J = 8.4$  Hz, 2H, Ar), 7.64 (d,  $^3J = 8.4$  Hz, 2H,

Ar); *E*-isomer  $\delta$ : 3.74 (s, 3H, CH<sub>3</sub>), 7.10 (d,  $^3J = 8.5$  Hz, 2H, Ar), 7.56 (d,  $^3J = 8.5$  Hz, 2H, Ar); MS (EI)  $m/z$ : 393 (M-CH<sub>3</sub>, 21), 365 (35), 327 (1), 306 (1), 281 (5), 263 (6), 235 (3), 201 (3), 185 (6), 173 (10), 157 (13), 145 (100), 133 (11), 125 (10), 113 (6), 95 (16), 83 (5), 75 (10), 59 (34).

» *1,2-di(4-Chlorophenoxy)-1,2-dimethoxyethylene*.  $^1\text{H-NMR}$  (200 MHz, CDCl<sub>3</sub>) *Z*-isomer  $\delta$ : 3.57 (s, 3H, CH<sub>3</sub>), 7.06 (d,  $^3J = 9.1$  Hz, 2H, Ar), 7.31 (d,  $^3J = 9.1$  Hz, 2H, Ar); *E*-isomer  $\delta$ : 3.71 (s, 3H, CH<sub>3</sub>), 6.97 (d,  $^3J = 9.1$  Hz, 2H, Ar), 7.24 (d,  $^3J = 9.1$  Hz, 2H, Ar); MS (EI)  $m/z$ : 344 ( $^{37}\text{Cl } ^{37}\text{Cl M}^+$ , 4), 342 ( $^{37}\text{Cl } ^{35}\text{Cl M}^+$ , 18), 340 ( $^{35}\text{Cl } ^{35}\text{Cl M}^+$ , 25), 329 ( $^{37}\text{Cl } ^{37}\text{Cl M-CH}_3$ , 5), 327 ( $^{37}\text{Cl } ^{35}\text{Cl M-CH}_3$ , 22), 325 ( $^{35}\text{Cl } ^{35}\text{Cl M-CH}_3$ , 34), 301 (10), 299 (45), 297 (67), 236 (9), 238 (13), 231 (4), 229 (11), 220 (3), 218 (8), 203 (6), 197 (7), 175 (9), 168 (6), 155 (6), 144 (7), 142 (22), 129 (14), 127 (42), 113 (34), 111 (100), 101 (15), 99 (46), 75 (56), 63 (15), 59 (34), 50 (13).

» *1,2-Dimethoxy-1,2-diphenoxyethylene*.  $^1\text{H-NMR}$  (200 MHz, CDCl<sub>3</sub>) *Z*-isomer  $\delta$ : 3.59 (s, 3H, CH<sub>3</sub>), 7.02-7.43 (m, 5H, Ar); *E*-isomer  $\delta$ : 3.73 (s, 3H, Ar), 6.98-7.35 (m, 5H, Ar); MS (EI)  $m/z$ : 272 ( $\text{M}^+$ , 17), 257 (M-CH<sub>3</sub>, 30), 229 (53), 195 (6), 170 (16), 152 (17), 141 (7), 108 (11), 93(10), 77 ( $\text{Ph}^+$ , 100), 65 (26), 59 (19), 51 (32), 39 (14).

» *1,2-Dimethoxy-1,2-di(4-methoxyphenoxy)ethylene*.  $^1\text{H-NMR}$  (200 MHz, CDCl<sub>3</sub>) *Z*-isomer  $\delta$ : 3.60 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.80 (s, 3H, ArOCH<sub>3</sub>), *ca.* 6.78-7.18 (Ar); *E*-isomer  $\delta$ : 3.71 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.78 (s, 3H, ArOCH<sub>3</sub>), *ca.* 6.78-7.18 (Ar); MS (EI)  $m/z$ : 332 ( $\text{M}^+$ , 34), 317 (M-CH<sub>3</sub>, 27), 289 (72), 257 (6), 230 (19), 225 (8), 215 (8), 198 (7), 193 (21),

187 (5), 165 (11), 151 (9), 138 (18), 135 (22), 123 (100), 107 (16), 95 (26), 92 (47), 77 (48), 64 (21), 59 (9), 50 (8), 41 (8).

» *1,2-Dimethoxy-1,2-di(4-methylphenoxy)ethylene*.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ) *Z*-isomer  $\delta$ : 2.33 (s, 3H,  $\text{ArCH}_3$ ), 3.58 (s, 3H,  $\text{OCH}_3$ ), *ca.* 6.90-7.30 (Ar); *E*-isomer  $\delta$ : 2.30 (s, 3H,  $\text{ArCH}_3$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), *ca.* 6.90-7.30 (Ar); MS (EI)  $m/z$ : 300 ( $\text{M}^+$ , 32), 285 ( $\text{M-CH}_3$ , 33), 257 (100), 225 (9), 209 (13), 198 (31), 177 (18), 166 (16), 149 (8), 135 (6), 122 (22), 107 (40), 91 (99), 77 (36), 65 (50), 59 (15), 49 (10), 39 (12).

## 4.2 Synthesis of 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines

### *Attempted exchange reactions with amines and hydroxy amines.*

» *2-Acetoxy-2-methoxy-5,5-dimethyl- $\Delta^3$ -1,3,4-oxadiazoline, 12a*.<sup>52</sup> Typically, a solution of the (methoxycarbonyl)hydrazone of acetone (42.1 g, 0.32 mol) in  $\text{CH}_2\text{Cl}_2$  (90 mL) was added dropwise (over *ca.* 20 min), under a dry nitrogen atmosphere, to a well-stirred, ice-cold mixture of  $\text{Pb}(\text{OAc})_4$  (145.7 g, 0.33 mol) partially dissolved in  $\text{CH}_2\text{Cl}_2$  (150 mL). After completion of addition, the reaction mixture was kept at 0 °C for another 30 min, and was then allowed to warm to room temperature over 1.5 h. The mixture was filtered by suction filtration through a thin pad of Celite to remove the precipitate. The resulting solution was washed with 3 portions of aq.  $\text{NaHCO}_3$  (5%), and with one portion of water. Drying over  $\text{MgSO}_4$ , followed by removal of the solvent afforded 45.8 g (75%) of a mixture of **12a** and its acyclic isomer **98**, in a ratio of *ca.* 70 (**12a**): 30 (**98**), as determined by  $^1\text{H-NMR}$ . Although **12a** was generally used in subsequent acetoxy exchange reactions

without separation from **98**, it could be purified by slow distillation using a short Vigreux column ( $T = 30\text{ }^{\circ}\text{C}$ ;  $P = 0.6\text{ Torr}$ ).  $^1\text{H-NMR}$  of **12a** (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.54 (s, 3H,  $\text{C}(\text{CH}_3)_2$ ), 1.65 (s, 3H,  $\text{C}(\text{CH}_3)_2$ ), 2.12 (s, 3H,  $\text{C}(\text{O})\text{CH}_3$ ), 3.61 (s, 3H,  $\text{OCH}_3$ ).  $^1\text{H-NMR}$  of **98** (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.65 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 2.09 (s, 3H,  $\text{C}(\text{O})\text{CH}_3$ ), 4.00 (s, 3H,  $\text{OCH}_3$ ).

**Attempted exchange reaction with 2-(methylamino)-1-ethanol.** In the initial attempt to synthesize **33b** by the exchange method, a sample (29 mg, *ca.* 0.10 mmol) of **12a** (as a mixture containing **98**) was allowed to react, at room temperature, with 3 equiv. of 2-(methylamino)-1-ethanol in about 1 mL of  $\text{CDCl}_3$ . Immediate reaction was evident from the evolution of gas bubbles as the reagents were mixed.  $^1\text{H-NMR}$  analysis of the reaction solution, 15 min after mixing, revealed the total disappearance of **98**. A second  $^1\text{H}$  spectrum showed the complete disappearance of **12a**, after the sample was left at room temperature for 3 days, but no **33b** was observed. In a second attempt, purified **12a** was reacted with the aminoalcohol under similar conditions but the results were similar. In a larger scale experiment, pure **12a** (0.57 g, *ca.* 2 mmol) was stirred with an excess of the aminoalcohol in  $\text{CH}_2\text{Cl}_2$  (25 mL) for 3 days at room temperature. The solution was then washed with 3 portions of aq.  $\text{NaHCO}_3$  (5%), and with water, and dried ( $\text{MgSO}_4$ ). The pale yellow oil obtained after removal of the solvent did not contain any **33b** ( $^1\text{H-NMR}$ ); no attempt was made to identify the products.

**Attempted exchange reaction with dimethylamine.** This exchange reaction was attempted on a small scale in an NMR tube, essentially as described for the aminoalcohol

above; none of the expected 2-dimethylamino-2-methoxy oxadiazoline could be identified, by  $^1\text{H}$ -NMR, in the reaction mixture.

**Attempted exchange reactions with diphenylamine and aniline.** Crude **12a** (65%, 1.00 g, *ca.* 3.5 mmol) was stirred at room temperature in  $\text{CH}_2\text{Cl}_2$  (25 mL) with diphenylamine (0.64 g, 3.8 mmol) and a catalytic amount of acetic acid (glacial, 0.5 mL). No apparent reaction (by TLC) had occurred after 25 h. Aniline (0.35 g, 3.8 mmol) was therefore added directly to this solution. After a further 24 h, the solvent was evaporated *in vacuo* and the resulting oil was stirred vigorously with aq. KOH (2.5 g in 20 mL of water) for 2 h. Extraction with 3 portions of  $\text{CH}_2\text{Cl}_2$  (total of 50 mL) was followed by washing of the organic layer with 5% bicarbonate (10 mL) and water (10 mL), and drying over  $\text{MgSO}_4$ .  $^1\text{H}$ -NMR analysis of the resulting oil showed no evidence for formation of the expected 2-methoxy-2-phenylamino oxadiazoline **101** or the related phenylimino oxadiazoline **100**.

### ***Synthesis of oxadiazolines 33 and 106.***

**(a) Synthesis of ketone semicarbazones.** Ketone semicarbazones were prepared by the method described by Vogel,<sup>192</sup> and were recrystallized from 50% aq. ethanol.

» *Acetone semicarbazone (104,  $\text{R}^1 = \text{Me}$ ).* White solid obtained in 78% yield, Mp 185-186 °C (lit.<sup>193</sup> 190-191 °C);  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.83 (s, 3H,  $\text{CH}_3$ ), 1.99 (s, 3H,  $\text{CH}_3$ ), 7.4 (br.s, 1H, NH) ( $\text{NH}_2$  was invisible under these conditions).

» *Cyclohexanone semicarbazone (104, R<sup>1</sup>R<sup>1</sup> = (CH<sub>2</sub>)<sub>5</sub>)*. White solid obtained in 75% yield, Mp 165-166 °C (lit.<sup>193</sup> 166-167 °C); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.50-1.90 (m, 6H, C-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-C), 2.15-2.45 (m, 4H, =CCH<sub>2</sub>), 5.6 (br.s, 2H, NH<sub>2</sub>), 8.53 (s, 1H, NH).

**(b) Synthesis of 4-substituted ketone semicarbazones.** The procedure for the preparation of compounds **103** is based on that of Iwao.<sup>137</sup> Typically, a solution of the appropriate ketone semicarbazone (0.30 mol) and aminoalcohol (0.32 mol) was refluxed in toluene (100 mL), under a dry nitrogen atmosphere, for 7-15 h, after which evolution of ammonia had subsided. The solution was allowed to cool to room temperature, and precipitation of the product usually occurred within a few hours (in some cases, crystallisation was induced by addition of diethyl ether). The product was then collected by filtration and triturated with diethyl ether. When appropriate recrystallization solvents could not be found, the semicarbazones were used without further purification; recrystallization solvents for the others are listed below. Several semicarbazones did not give useful mass spectra, under routine conditions.

» *2-Aminoethanol*. Commercial, distilled under a dry nitrogen atmosphere at 166-169 °C.

» *2-(Methylamino)-1-ethanol*. Commercial, distilled under N<sub>2</sub> at 156-158.5 °C.

» *2-(Phenylamino)-1-ethanol*. Commercial, used as received.

» *3-Amino-1-propanol*. Commercial, distilled under N<sub>2</sub> at 186-187 °C.

» *2-Aminophenol*. Commercial, recrystallized from ethanol/toluene, Mp 174 °C (lit.<sup>193</sup> 174 °C).



» *N*-(3-Hydroxypropyl)formamide.<sup>194</sup> Ethyl formate (43.1 g, 0.58 mol) was added dropwise, over 20 min, through a pressure-equalizing addition funnel under a gentle flow of dry nitrogen, to the neat 3-aminopropanol (40.0 g, 0.53 mol) at 0 °C. The solution was stirred in ice for another 6 h, before removing excess ethyl formate *in vacuo*. Distillation of the residue at 117-118 °C (2 Torr), using a fractionating column, yielded 51.1 g (93%) of the formamide as a colourless liquid. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.60-2.00 (m, 2H, CCH<sub>2</sub>C), 3.06 (br.s, 1H, OH), 3.34-3.55 (m, 2H, NCH<sub>2</sub>), 3.60-3.88 (m, 2H, OCH<sub>2</sub>), 6.25 (br.s, 1H, NH), 8.20 (s, 1H, CHO).

» 3-(Methylamino)-1-propanol.<sup>194</sup> *N*-(3-Hydroxypropyl)formamide (21.4 g, 0.208 mol), dissolved in dry THF (20 mL), was added dropwise over 1.5 h, under nitrogen, to a suspension of LiAlH<sub>4</sub> (8.9 g, 0.23 mol) in dry THF (68 mL) at 0 °C. After stirring the solution in the ice bath for a further 15 min, a condenser was attached and the solution was allowed to warm to room temperature over 30 min, and was refluxed for 3 h, then left at room temperature overnight. Hydrolysis was carried out by stirring the mixture with a total of 45 mL of 5% aq. NaOH at 0 °C for 2 h. The solid was removed by filtration and washed with several portions of fresh THF which were added to the filtrate. Separation of the organic layer, followed by evaporation of the solvent *in vacuo*, afforded a crude oil which was distilled at 35 °C (0.2 Torr) to give more than 10.4 g (59%) of the aminoalcohol as a colourless liquid. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 1.62-1.77 (m, 2H, CCH<sub>2</sub>C), 2.42 (s, 3H, CH<sub>3</sub>), *ca.* 2.6-3.0 (OH, appears as a distortion in baseline), 2.84 (t, <sup>3</sup>J = 5.8 Hz, 2H, NCH<sub>2</sub>), 3.30 (t, <sup>3</sup>J = 5.4 Hz, 2H, OCH<sub>2</sub>).

» *Acetone 4-(2-hydroxyethyl)semicarbazone (103, n = 2, R<sup>1</sup> = Me, R<sup>2</sup> = H).* Pale yellow solid obtained in 81% yield, Mp 89-94 °C (lit.<sup>137</sup> 94-96 °C); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.84 (s, 3H, CH<sub>3</sub>), 1.97 (s, 3H, CH<sub>3</sub>), 3.39-3.53 (m, 2H, NCH<sub>2</sub>), 3.69-3.82 (m, 2H, OCH<sub>2</sub>), 6.56 (br.s, 1H, C(O)NHC), 8.02 (br.s, 1H, C(O)NHN) (OH caused a slight distortion in the baseline between 3-4 ppm); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 16.36 (CH<sub>3</sub>), 25.20 (CH<sub>3</sub>), 42.85 (NCH<sub>2</sub>), 63.35 (OCH<sub>2</sub>), 147.85 (C=N), 157.88 (C=O); IR (KBr) cm<sup>-1</sup>: 3379br, 3317br, 3210br, 3070br, 1652s (C=O), 1554s (C=N), 1458w, 1427m, 1365m, 1337m, 1281w, 1254m, 1212m, 1157w, 1132m, 1088w, 1068m, 980w, 884w, 836w, 773m, 722m.

» *Acetone 4-(2-hydroxyethyl)-4-methylsemicarbazone (103, n = 2, R<sup>1</sup> = R<sup>2</sup> = Me).* White solid obtained in 60% yield, after recrystallization from ethanol/diethyl ether, Mp 132-134 °C; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.83 (s, 3H, =C-CH<sub>3</sub>), 2.00 (s, 3H, =C-CH<sub>3</sub>), 2.95 (s, 3H, NCH<sub>3</sub>), 3.39 (t, <sup>3</sup>J = 4.6 Hz, 2H, NCH<sub>2</sub>), 3.84 (t, <sup>3</sup>J = 4.6 Hz, 2H, OCH<sub>2</sub>), 4.92 (br.s, 1H, OH), 8.79 (br.s, 1H, NH); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 16.89 (=C-CH<sub>3</sub>), 25.19 (=C-CH<sub>3</sub>), 35.02 (NCH<sub>3</sub>), 52.45 (NCH<sub>2</sub>), 61.05 (OCH<sub>2</sub>), 150.33 (C=N), 157.83 (C=O); IR (KBr) cm<sup>-1</sup>: 3223br, 1644s (C=O), 1557s (C=N), 1471m, 1424w, 1394m, 1359w, 1276m, 1223m, 1187m, 1115w, 1080w, 1041m, 965w, 871w, 757w; anal. calcd. for C<sub>7</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 48.54; H, 8.73; measured: C, 48.83; H, 8.79.

» *Acetone 4-(2-hydroxyethyl)-4-phenylsemicarbazone (103, n = 2, R<sup>1</sup> = Me, R<sup>2</sup> = Ph).* Recrystallized first from ethanol/diethyl ether, then from benzene (yield N.A.). White solid, Mp 125-126 °C; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.84 (s, 3H, =C-CH<sub>3</sub>), 2.06 (s, 3H,

=C-CH<sub>3</sub>), 3.45 (t, <sup>3</sup>J = 5.4 Hz, 2H, CH<sub>2</sub>N), 4.45 (t, <sup>3</sup>J = 5.4 Hz, 2H, CH<sub>2</sub>O), 6.61-6.78 (m, 3H, Ar-o, p), 7.13-7.25 (m, 2H, Ar-m), 7.57 (br.s, 1H, NH), (OH does not appear); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 16.06 (=C-CH<sub>3</sub>), 25.26 (=C-CH<sub>3</sub>), 43.22 (NCH<sub>2</sub>), 64.21 (OCH<sub>2</sub>), 112.79 (Ar C2, C6), 117.65 (Ar C4), 129.19 (Ar C3, C5), 147.63 (Ar C1), 151.39 (C=N), 154.00 (C=O); IR (KBr) cm<sup>-1</sup>: 3414br, 3385br, 3233br, 1726s (C=O), 1652w, 1603m, 1509s, 1457w, 1434w, 1374w, 1315w, 1278m, 1242m, 1221s, 1133w, 1061w, 1036m, 935w, 886w, 755m; MS (EI) m/z: 235 (M<sup>+</sup>, 6), 119 (75), 106 (100), 91 (17), 77 (63), 65 (22), 56 (13), 51 (16); MS (CI, NH<sub>3</sub>) m/z: 236 (M+H)<sup>+</sup>; HRMS calcd for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> (M<sup>+</sup>) m/z 235.1321, obsd m/z 235.1337.

» *Acetone 4-(3-hydroxypropyl)semicarbazone (103, n = 3, R<sup>1</sup> = Me, R<sup>2</sup> = H)*. White solid obtained in 60% yield, Mp 107-109 °C; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.62-1.78 (m, 2H, CCH<sub>2</sub>C), 1.84 (s, 3H, CH<sub>3</sub>), 1.97 (s, 3H, CH<sub>3</sub>), 3.40-3.53 (m, 2H, NCH<sub>2</sub>), 3.60-3.80 (m, 3H, OCH<sub>2</sub> and OH), 6.36 (m, 1H, C(O)NHC), 8.01 (br.s, 1H, C(O)NHN); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 16.33 (CH<sub>3</sub>), 25.19 (CH<sub>3</sub>), 33.14 (NCH<sub>2</sub>), 35.43 (CCH<sub>2</sub>C), 58.47 (OCH<sub>2</sub>), 147.68 (C=N), 157.85 (C=O); IR (KBr) cm<sup>-1</sup>: 3396br, 3303br, 3206br, 1643s (C=O), 1552s (C=N), 1439w, 1423w, 1380w, 1330w, 1254w, 1223w, 1116w, 1071w, 986w.

» *Cyclohexanone 4-(3-hydroxypropyl)semicarbazone (103, n = 3, R<sup>1</sup>R<sup>1</sup> = (CH<sub>2</sub>)<sub>5</sub>, R<sup>2</sup> = H)*. White solid, obtained in 79% yield after recrystallization from ethanol/diethyl ether. Mp 124-126 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.56-1.75 (m), 1.93 (br.s), 2.22-2.35 (m) (12H, CCH<sub>2</sub>C), 3.46 (app q, <sup>3</sup>J = 6.3 Hz, 2H, NCH<sub>2</sub>), 3.65 (app q, <sup>3</sup>J = 6.0 Hz, 2H,

OCH<sub>2</sub>), 3.85 (app t, <sup>3</sup>J = 6.8 Hz, 1H, OH), 6.38 (ut, 1H, C(O)NHC), 8.46 (br.s, 1H, C(O)NHN); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 25.54 (CH<sub>2</sub>), 25.72 (CH<sub>2</sub>), 26.40 (CH<sub>2</sub>), 27.00 (CH<sub>2</sub>), 33.22 (NCH<sub>2</sub>), 35.41 (CCH<sub>2</sub>C of propyl chain and another CH<sub>2</sub> signal overlapped), 58.43 (OCH<sub>2</sub>), 154.04 (C=N), 158.43 (C=O); IR (KBr) cm<sup>-1</sup>: 3363br, 3299br, 3200br, 1639s (C=O), 1558s (C=N), 1470w, 1440m, 1378w, 1350w, 1318m, 1273w, 1254w, 1225w, 1197w, 1138w, 1111w, 1071m, 1019w, 988m, 907w, 831w, 810w, 702m.

» *Cyclohexanone 4-(3-hydroxypropyl)-4-methylsemicarbazone (103, n = 3, R<sup>1</sup>R<sup>1</sup> = (CH<sub>2</sub>)<sub>5</sub>, R<sup>2</sup> = Me).* Pale yellow solid obtained in 60% yield after recrystallization from ethyl acetate. Mp 94-96 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.52-1.77 (m, 8H, CH<sub>2</sub>), 2.17-2.40 (m, 4H, CH<sub>2</sub>), 2.90 (s, 3H, CH<sub>3</sub>), 3.43 (t, <sup>3</sup>J = 5.7 Hz, 2H, NCH<sub>2</sub>) 3.58 (t, <sup>3</sup>J = 5.7 Hz, 2H, OCH<sub>2</sub>), 4.27 (br.s, 1H, OH), 8.20 (br.s, 1H, NH); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 25.50 (CH<sub>2</sub>), 25.64 (CH<sub>2</sub>), 26.61 (CH<sub>2</sub>), 26.72 (CH<sub>2</sub>), 29.31 (CH<sub>2</sub>), 33.87 (CH<sub>2</sub>), 35.18 (CH<sub>3</sub>), 44.72 (NCH<sub>2</sub>), 57.39 (OCH<sub>2</sub>), 157.36 (C=N or C=O), 157.70 (C=N or C=O); IR (KBr) cm<sup>-1</sup>: 3222br, 1661s (C=O), 1547s (C=N), 1473m, 1446w, 1416w, 1389m, 1343w, 1289w, 1216m, 1196m, 1139m, 1077m, 1018w, 989w, 952w, 910w, 756w.

**Attempted preparation of acetone 4,4-diphenylsemicarbazone.** Evolution of NH<sub>3</sub> was observed when a toluene solution of acetone semicarbazone was heated to reflux with diphenylamine in the usual manner. However, the heterogeneous dark solid that was obtained after work-up did not appear to be the expected product.

**(c) Synthesis of oxadiazolines.** As most of these compounds were prepared several times, typical procedures for the preparations of **33a-k** and **106a-e** are given below. Under routine conditions, these compounds do not give useful mass spectra. For most solid oxadiazolines, melting points are approximate because these compounds generally start to decompose on heating above *ca.* 80 °C. Unless otherwise indicated, the chemical shift of peaks in <sup>1</sup>H- and <sup>13</sup>C-NMR spectra are those from room temperature spectra. In order to confirm their identity, MS experiments involving LRP and HRP electron impact (EI), collisional activation (CA) spectrometry<sup>i</sup> and chemical ionization (CI) using ammonia were performed on **33b,d,f** and **106c,d**. In agreement with earlier work on **33a** and related compounds<sup>i,ii</sup>, the EI spectra do not show molecular ions (CI yields [M+H]<sup>+</sup> and [M+H+NH<sub>3</sub>]<sup>+</sup> ions) but rather [M-N<sub>2</sub>]<sup>++</sup> ions which (as established by CA spectrometry) form the precursor of most of the fragment ions. Principal peaks (m/z; elemental compositions in parentheses were experimentally determined; rel. I) in the 70 eV EI mass spectra are as indicated below. A thorough mass spectrometric study involving **33b** is currently in progress, in collaboration with D. Lavorato and Prof. J. K. Terlouw.

» *Iodobenzene diacetate*.<sup>195</sup> To a large beaker containing 150 g (0.74 mol) of iodobenzene at 30 °C was added aq. peracetic acid (32% by wt, 330 g) over 70 min. While keeping the temperature constant, stirring was continued for another 1 h, after which the beaker was chilled in ice for 1 h. The precipitated product was collected by on

<sup>i</sup> See Terlouw *et al.*<sup>76</sup> The experiments were performed on a VG Analytical ZAB-R mass spectrometer of BEE geometry. Compounds were introduced using a direct insertion probe kept at room temperature at a source temperature of 100-120°C. Under these conditions the degree of thermolysis is negligible.

<sup>ii</sup> Terlouw *et al.*<sup>95</sup>

a Buchner funnel, washed with several portions of ice-cold water, and dried in a dessicator for several days to afford 219 g (92%) of  $\text{PhI}(\text{OAc})_2$  as a white solid, Mp 159-160 °C (lit.<sup>195</sup> 158-159 °C).

» *3,4,9-Triaza-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33a**.<sup>136</sup> Typically,  $\text{PhI}(\text{OAc})_2$  (7.47 g, 0.023 mol), dissolved in  $\text{CH}_2\text{Cl}_2$  (150 mL), was added dropwise, over 1-2 h, to a stirred solution of semicarbazone **103** ( $n = 2$ ,  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ) (3.50 g, 0.022 mol) in  $\text{CH}_2\text{Cl}_2$  (200 mL) at 0 °C, under nitrogen. After addition was complete, the solution was kept in the ice bath for another 2 h, and was then allowed to warm to room temperature overnight. After evaporating approximately one half of the solvent *in vacuo*, the solution was washed with 4 x 30 mL of aqueous  $\text{NaHCO}_3$  (5%), followed by 30 mL of brine. The combined aqueous layers were extracted with one portion of  $\text{CH}_2\text{Cl}_2$ . Drying ( $\text{MgSO}_4$ ), filtration by gravity, and evaporation of the solvent afforded an oil (*ca.* 6 g) containing a mixture of **33a** and  $\text{PhI}$ , which was sometimes used in subsequent acylation reactions without purification. Purification of **33a** was performed, when necessary, by radial chromatography on silica, starting with 10% ethyl acetate in hexane and gradually increasing solvent polarity to 60% ethyl acetate in hexane. This typically gave a 47% yield of slightly impure **33a**, which could be further purified by bulb-to-bulb distillation (*ca.* 30-40 °C, 2 Torr) to obtain pure **33a** as a clear, colourless oil.  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.48 (s, 3H,  $\text{CH}_3$ ), 1.53 (s, 3H,  $\text{CH}_3$ ), 2.87 (br.s, 1H, NH), 3.44-3.54 (m, 2H,  $\text{NCH}_2$ ), 4.14-4.33 (m, 2H,  $\text{OCH}_2$ );  $^{13}\text{C}$ -NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 24.45 ( $\text{CH}_3$ ), 24.64 ( $\text{CH}_3$ ), 44.71 ( $\text{NCH}_2$ ), 67.87 ( $\text{OCH}_2$ ), 117.68 (C2), 139.18 (C5); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 3397br (NH), 1794s,

1711s, 1574w (N=N), 1481w, 1459w, 1417w, 1384m, 1362w, 1309m, 1229m, 1207m, 1138w, 1105w, 1057w, 1038w, 987w, 957w, 915w; MS (EI)  $m/z$ : 129 (M-N<sub>2</sub>, 10), 101 (18), 88 (22), 71 (8), 59 (18), 49 (29), 43 (100); MS (CI, NH<sub>3</sub>)  $m/z$ : 158 (M+H)<sup>+</sup>.

» *3,4,9-Triaza-2,2,9-trimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33b**. PhI(OAc)<sub>2</sub> (5.86 g, 0.018 mol), dissolved in 200 mL of CH<sub>2</sub>Cl<sub>2</sub>, was added dropwise, under a nitrogen atmosphere, to an ice-cold solution of the semicarbazone **103** (n = 2, R<sup>1</sup> = R<sup>2</sup> = Me) (3.00 g, 0.017 mol) in 200 mL of CH<sub>2</sub>Cl<sub>2</sub>. After addition was complete (*ca.* 2 h), the solution was allowed to warm to room temperature, and stirring was continued overnight. Approximately two thirds of the solvent was evaporated, and the solution was washed first with 4 x 25 mL of aq. NaHCO<sub>3</sub> (5%), then with 25 mL of brine. The combined aqueous layers were extracted with one portion of CH<sub>2</sub>Cl<sub>2</sub>. After drying over MgSO<sub>4</sub> and evaporating the solvent, an oil was obtained, consisting mainly of **33b** and PhI. Purification of **33b** was accomplished by radial chromatography, starting with 5% ethyl acetate in hexane and gradually increasing the concentration of ethyl acetate to 40%. Typically, 1.95 g (66%) of a pale yellow oil was obtained. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>)<sup>i</sup> δ: 1.45 (s, 3H, CCH<sub>3</sub>), 1.59 (s, 3H, CCH<sub>3</sub>), 2.37 (s, 3H, NCH<sub>3</sub>), 3.26-3.36 (m, 1H, NCH<sub>2</sub>), 3.41-3.52 (m, 1H, NCH<sub>2</sub>), 4.19-4.27 (m, 2H, OCH<sub>2</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 24.07 (CCH<sub>3</sub>), 24.93 (CCH<sub>3</sub>), 32.36 (NCH<sub>3</sub>), 51.38 (NCH<sub>2</sub>), 65.66 (OCH<sub>2</sub>), 116.46 (C2), 139.17 (C5); IR (neat) cm<sup>-1</sup>: 1757m, 1576w (N=N), 1459s, 1363s, 1295s, 1238s, 1209s, 1132s, 1079s, 1041m, 988m, 953w, 902s, 846m, 762w, 714w; MS: 143

<sup>i</sup> See data from spectral simulation (Figure 14).

([M-N<sub>2</sub>]<sup>++</sup> (C<sub>7</sub>H<sub>13</sub>NO<sub>2</sub>), 15), 102 ([M-N<sub>2</sub>-C<sub>3</sub>H<sub>5</sub>]<sup>+</sup>, 90), 101 ([M-N<sub>2</sub>-C<sub>3</sub>H<sub>6</sub>]<sup>++</sup>, 95), 86 (23), 85 ([M-N<sub>2</sub>-C<sub>3</sub>H<sub>6</sub>O]<sup>++</sup>, 68), 58 (81), 57 (68), 56 (39), 43 (100), 42 (75), 28 (90).

**N-CD<sub>3</sub> and N-<sup>13</sup>CH<sub>3</sub> labelled 33b.** These oxadiazolines were prepared by N-methylation of **33a** with the appropriately labelled methyl iodide. For each one, the following procedure was repeated three times in order to obtain about 100 mg of labelled compound. Typically, **33a** (425 mg, 2.70 mmol) and 2.0 mmol of labelled MeI were heated to reflux, for 3.5 h, in 4.0 mL of dry THF under a gentle stream of N<sub>2</sub>. Aq. NaOH (10%, 5 mL) was then added, and the mixture was stirred for a few minutes. The solvent from the organic phase was evaporated, and the residue, re-dissolved in CH<sub>2</sub>Cl<sub>2</sub>, was combined with the original aqueous layer. The mixture was extracted with several portions of CH<sub>2</sub>Cl<sub>2</sub> and the combined organic phases dried over MgSO<sub>4</sub> before evaporation of the solvent. Labelled **33b** was separated from unreacted **33a** by chromatography (2 mm plate, 10%-60% ethyl acetate in hexane).

» *3,4,9-Triaza-9-formyl-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33c**. Oxadiazoline **33a** (0.85 g, 5.4 mmol), prepared and purified by chromatography as indicated above, was stirred at room temperature in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) with 4-nitrophenyl formate<sup>140</sup> (0.99 g, 5.9 mmol). After 3 days (the reaction may have been over in as little as 12 h), the yellow solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and washed successively with aq. NaHCO<sub>3</sub> (5%) and brine. After drying over MgSO<sub>4</sub>, the solvent was evaporated. <sup>1</sup>H-NMR of the resulting yellow oil showed mostly **33c**, along with some impurities; no unreacted **33a** was present. Separation of **33c** by chromatography, using either 10%-40% ethyl acetate in



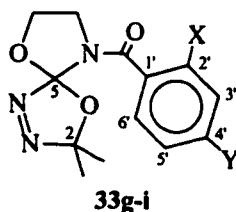
hexane or 1% methanol in chloroform, was repeated several times to obtain a sample of **33c** of high purity as a pale orange oil (41% yield, one trial).  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.50 (s, 3H,  $\text{CH}_3$ ), 1.64 (s, 3H,  $\text{CH}_3$ ), 3.80-4.05 (m, 2H,  $\text{NCH}_2$ ), 4.22-4.45 (m, 2H,  $\text{OCH}_2$ ), 7.90 (s, 1H,  $\text{C(O)H}$ );  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 23.96 ( $\text{CH}_3$ ), 24.70 ( $\text{CH}_3$ ), 42.00 ( $\text{NCH}_2$ ), 65.67 ( $\text{OCH}_2$ ), 120.26 (C2), 133.13 (C5), 158.65 ( $\text{C=O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1702s ( $\text{C=O}$ ), 1573w ( $\text{N=N}$ ), 1474w, 1459w, 1412w, 1377m, 1340w, 1271m, 1234m, 1208w, 1179m, 1115m, 1060w, 1031w, 1008w, 980w, 911w.

» *3,4,9-Triaza-9-acetyl-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33d**. The synthesis of **33d** was accomplished by the same method as for **33f** (see below) using acetic anhydride for the acetylation. This oxadiazoline was recrystallized from methanol/diethyl ether, to give white crystals (33% yield from **103**) with a Mp of 87-88 °C;  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ; slow exchange)  $\delta$ : 1.49 (s, 3H,  $\text{C(2)CH}_3$ ), 1.73 (s, 3H,  $\text{C(2)CH}_3$ ), 1.77 (s) & 2.14 (s) (3H,  $\text{C(O)CH}_3$ ), 3.85-4.08 (m, 2H,  $\text{NCH}_2$ ), 4.13-4.45 (m, 2H,  $\text{OCH}_2$ );  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ; slow exchange, resonance due to major isomer is underlined, when obvious)  $\delta$ : 21.64 ( $\text{CH}_3$ ), 22.02 ( $\text{CH}_3$ ), 22.20 ( $\text{CH}_3$ ), 23.94 ( $\text{CH}_3$ ), 25.20 ( $\text{CH}_3$ ), 25.45 ( $\text{CH}_3$ ), 45.36 & 46.15 ( $\text{NCH}_2$ ), 64.65 & 65.22 ( $\text{OCH}_2$ ), 118.77 & 120.72 (C2), 131.86 & 133.15 (C5), 167.96 ( $\text{C=O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1690s ( $\text{C=O}$ ), 1580w ( $\text{N=N}$ ), 1392s, 1350m, 1277m, 1234m, 1208m, 1138w, 1109s, 1046w, 1019w, 982w, 908w; MS: 171 ( $[\text{M-N}_2]^{++}$  ( $\text{C}_8\text{H}_{13}\text{NO}_3$ ), 0.7%), 130 ( $[\text{M-N}_2-\text{C}_3\text{H}_5]^+$ , 6), 129 ( $[\text{M-N}_2-\text{C}_3\text{H}_6]^{++}$ , 6), 113 ( $[\text{M-N}_2-\text{C}_3\text{H}_6\text{O}]^{++}$ , 23), 88 (50), 85 (4), 72 (6), 69 (24), 59 (14), 43 ( $[\text{CH}_3\text{CO}^+]$ , 100); anal. calcd. for  $\text{C}_8\text{H}_{13}\text{N}_3\text{O}_3$ : C, 48.23; H, 6.58; measured: C, 48.50; H, 6.70.

» *3,4,9-Triaza-9-methacryloyl-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33e**. This oxadiazoline was prepared as described for **33f** (see below) using methacryloyl chloride in the acylation step. Repeated recrystallizations of the product from ethyl acetate/hexane yielded a white solid (19% from **103**), Mp *ca.* 45-47 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.48 (s, 3H, C(2)CH<sub>3</sub>), 1.69 (s, 3H, C(2)CH<sub>3</sub>), 1.93 (s, 3H, =C-CH<sub>3</sub>), 3.90-4.08 (m, 2H, NCH<sub>2</sub>), 4.22-4.40 (m, 2H, OCH<sub>2</sub>), 5.21 & 5.23 (overlapped s, 2H, =CH<sub>2</sub>); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 19.67 (=C-CH<sub>3</sub>), 21.44 C(2)CH<sub>3</sub>, 25.24 (C(2)CH<sub>3</sub>), 46.48 (NCH<sub>2</sub>), 65.15 (OCH<sub>2</sub>), 118.16 (=CH<sub>2</sub>), 120.14 (C2), 132.95 (C5), 140.11 (=CR<sub>2</sub>), 169.80 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1676s (C=O), 1636m, 1578w (N=N), 1454w, 1415w, 1386s, 1366s, 1344w, 1277m, 1233s, 1180s, 1120m, 1096m, 1048w, 1018w, 982w, 920m, 861w, 834w; MS (EI) m/z: 156 (4), 139 (9), 124 (7), 110 (50), 100 (15), 95 (22), 84 (46), 69 (90), 49 (34), 41 (100).

» *3,4,9-Triaza-9-benzoyl-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33f**. The crude mixture containing **33a** (starting with 22 mmol of **103**) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL), and pyridine (1.10 g, 13.9 mmol) was added. Benzoyl chloride (1.86 g, 13.2 mmol) was added dropwise to this stirred solution over *ca.* 10 min. After stirring at room temperature for another 30 min, the solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed successively with water, aq. NaHCO<sub>3</sub> (5%), and brine. The organic phase was dried over MgSO<sub>4</sub>, the solvent was evaporated, and hexane was added to the crude product to induce crystallization. Recrystallization from methanol/diethyl ether yielded 1.41 g (25%, from the semicarbazone **103**) of **33f** as a white solid, Mp 108-110 °C (dec.); see crystal

structure in Figure 13, Section 2.2;  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ , slow exchange)  $\delta$ : 1.47 (s) & 1.62 (s) & 1.20-1.80 (br.) (6H,  $\text{CH}_3$ ), 3.85-4.00 (um, 1H,  $\text{NCH}_2$ ), 4.05-4.20 (um, 1H,  $\text{NCH}_2$ ), 4.25-4.45 (m, 2H,  $\text{OCH}_2$ ), 7.35-7.60 (m, 5H, Ar);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 21.40 ( $\text{CH}_3$ ), 25.19 ( $\text{CH}_3$ ), 47.35 ( $\text{NCH}_2$ ), 65.40 ( $\text{OCH}_2$ ), 120.41 (C2), 127.26 (Ar C2, C6), 128.36 (Ar C3, C5), 130.94 (Ar C4), 133.22 (C5), 135.40 (Ar C1), 169.00 ( $\text{C=O}$ ); IR (KBr)  $\text{cm}^{-1}$ : 1655s ( $\text{C=O}$ ), 1578w ( $\text{N=N}$ ), 1453w, 1389s, 1272m, 1222m, 1162m, 1115m, 1081w, 1046w, 1011w, 973w, 921m, 856w, 817w, 798w, 722m; MS: 233 ( $[\text{M-N}_2]^+$ , 0.9), 192 ( $[\text{M-N}_2-\text{C}_3\text{H}_5]^+$ , 5), 175 ( $[\text{M-N}_2-\text{C}_3\text{H}_6\text{O}]^+$  ( $\text{C}_{10}\text{H}_9\text{NO}_2$ ), 27), 174 (30), 147 (15), 146 (10), 145 (12), 131 (43), 117 (20), 105 ( $[\text{C}_6\text{H}_5\text{CO}^+]$ , 100), 103 (21), 88 (25), 77 ( $[\text{C}_6\text{H}_5^+]$ , 35), 51 (21).



» *3,4,9-Triaza-9-(2-methoxybenzoyl)-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33g**.

The preparation of **33g** was effected by the same procedure as for **33f**, using *o*-anisoyl chloride as the acylating agent. Recrystallization from ethyl acetate/hexane gave a white solid, Mp 143-144 °C, in 26% yield (from **103**).  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ , slow exchange)  $\delta$ : 0.50 (br.s) & 1.30 (br.s) & 1.54 (br.s) & 1.81 (br.s) (6H,  $\text{C}(\text{CH}_3)_2$ ), 3.60-4.45 (br. m's, 7H,  $\text{NCH}_2$ ,  $\text{OCH}_2$ ,  $\text{OCH}_3$ ), 6.75-7.50 (br. m's, 4H, Ar);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ , slow exchange, resonance due to major isomer is underlined)  $\delta$ : 20.93 & 21.66 ( $\text{CCH}_3$ ), 24.79 & 25.38 ( $\text{CCH}_3$ ), 45.55 & 46.01 ( $\text{NCH}_2$ ), 55.72 ( $\text{OCH}_3$ ), 64.24 &

65.57 (OCH<sub>2</sub>), 111.23 (probably C3'), 118.45 (C2), 119.69 & 120.91 (probably C5'), 124.80 & 125.70 (probably C1'), 127.55 & 128.26 (probably C6'), 130.93 & 131.45 (probably C4'), 133.31 (C5), 155.34 & 156.49 (C2'), 166.63 (C=O); IR (KBr) cm<sup>-1</sup>: 1656s (C=O), 1603m, 1581w (N=N), 1493m, 1462m, 1438m, 1399s, 1364m, 1272m, 1250m, 1224m, 1162m, 1123s, 1079m, 1037w, 1017m, 973w, 922m, 899w, 858w, 830w, 763m, 725w; MS (EI) m/z: 248 (3), 204 (4), 174 (6), 148 (4), 135 (100), 118 (28), 92 (11), 77 (22); MS (CI, NH<sub>3</sub>) m/z: 309 (M+NH<sub>4</sub>)<sup>+</sup>, 292 (M+H)<sup>+</sup>.

» *3,4,9-Triaza-9-(4-methoxybenzoyl)-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33h**.

This compound was prepared in essentially the same way as **33f**, using purified **33a** for the acylation with *p*-anisoyl chloride. Recrystallization from ethyl acetate/hexane and methanol/diethyl ether yielded a white solid in 63% yield, Mp *ca.* 110 °C (melts with decomposition); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, slow exchange) δ: 1.48 (br.s., 6H, C(CH<sub>3</sub>)<sub>2</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), *ca.* 3.80-3.98 (overlapped m, 1H, NCH<sub>2</sub>), 4.03-4.21 (m, 1H, NCH<sub>2</sub>), 4.22-4.44 (m, 2H, OCH<sub>2</sub>), 6.88 (d, <sup>3</sup>J = 8.8 Hz, 2H, CH(3', 5')), 7.50 (d, <sup>3</sup>J = 8.8 Hz, 2H, CH(2', 6')); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>, slow exchange) δ: 21.32 & 21.62 (CCH<sub>3</sub>), 24.98 & 25.28 (CCH<sub>3</sub>), 47.54 (NCH<sub>2</sub>), 55.20 & 55.47 (OCH<sub>3</sub>), 65.46 (OCH<sub>2</sub>), 113.42 & 113.57 (C3', C5'), 120.25 (C2), 127.48 (C1'), 129.26 & 129.58 (C2', C6'), 133.45 (C5), 161.72 (Ar C4'), 168.56 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1671s (C=O), 1609m, 1579w (N=N), 1513m, 1462w, 1418w, 1374s, 1306w, 1255s, 1228s, 1173s, 1119m, 1037m, 982w, 921m, 861w, 841w; MS (EI) m/z: 205 (M-N<sub>2</sub>-acetone, 11), 177 (7), 135 (ArCO<sup>+</sup>, 100), 92 (10), 77 (12); MS (CI, NH<sub>3</sub>) m/z: 309 (M+NH<sub>4</sub>)<sup>+</sup>, 292 (M+H)<sup>+</sup>.

» *3,4,9-Triaza-9-(4-nitrobenzoyl)-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33i**. This compound was prepared in essentially the same way as **33f**, using purified **33a** for the acylation with 4-nitrobenzoyl chloride. Recrystallization from ethyl acetate/hexane yielded a pale yellow solid in 50% yield (one crop), Mp *ca.* 135 °C (dec.); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, slow exchange) δ: 1.47 (s, on top of a broad resonance, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 3.81-4.18 (um, 2H, NCH<sub>2</sub>), 4.26-4.46 (m, 2H, OCH<sub>2</sub>), 7.67 (br. d, app. <sup>3</sup>J = 7.7 Hz, 2H, (CH(2', 6')), 8.26 (d, <sup>3</sup>J = 8.5 Hz, CH(3', 5')); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>, slow exchange) δ: 21.40 (CH<sub>3</sub>), 25.07 (CH<sub>3</sub>), 47.07 (NCH<sub>2</sub>), 65.27 (OCH<sub>2</sub>), 120.73 (br., C2), 123.65 (C2', C6'), 128.33 (C3', C5'), *ca.* 133 (br., C5), 141.00 (C1'), 148.98 (C4'), 166.51 (C=O); IR (KBr) cm<sup>-1</sup>: 1665s (C=O), 1604w, 1524s (NO<sub>2</sub>), 1415m, 1392m, 1346s (NO<sub>2</sub>), 1266w, 1224m, 1158m, 1119m, 1081w, 1040w, 1012w, 980w, 922m, 870w, 849m, 817w, 725m; MS (EI) m/z: 237 (8), 219 (20), 176 (46), 150 (ArCO<sup>+</sup>, 100), 104 (38), 76 (26); MS (CI, NH<sub>3</sub>) m/z: 324 (M+NH<sub>4</sub>)<sup>+</sup>, 307 (M+H)<sup>+</sup>.

» *3,4,9-Triaza-9-methoxycarbonyl-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene*, **33j**. This carbamate was prepared most conveniently from **33a** according to the method of Corey *et al.*<sup>142</sup> To a vigorously stirred mixture of **33a** (2.41 g, 15.3 mmol) and K<sub>2</sub>CO<sub>3</sub> (12.72 g, 92.0 mmol) in acetone (35 mL) was added methyl chloroformate (5.80 g, 61.4 mmol); slight warming of the solution was observed. After two days at room temperature, the solution was filtered and the solvent evaporated. Radial chromatography, using 10-60% ethyl acetate in hexane, followed by drying over MgSO<sub>4</sub>, afforded **33j** as a colourless oil in *ca.* 50 % yield. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, slow exchange) δ: 1.47 (s, 3H, CCH<sub>3</sub>), 1.70

(br.s., 3H, CCH<sub>3</sub>), 3.67 (br.s., 3H, OCH<sub>3</sub>), 3.75-4.05 (um, 2H, NCH<sub>2</sub>), 4.18-4.42 (m, 2H, OCH<sub>2</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>, some peaks are broad due to slow exchange) δ: 22.15 (CCH<sub>3</sub>), 25.24 (CCH<sub>3</sub>), 45.14 (NCH<sub>2</sub>), 52.62 (OCH<sub>3</sub>), 65.34 (OCH<sub>2</sub>), 120.16 (C2), 132.86 (C5), 152.27 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1742s (C=O), 1578w (N=N), 1448m, 1380s, 1280m, 1232m, 1211s, 1159w, 1117m, 1063m, 1040m, 985w, 935w, 911w, 845w.

» *3,4,9-Triaza-2,2-dimethyl-1,6-dioxo-9-phenylsulfonylspiro[4.4]non-3-ene*, **33k**.

Purified oxadiazoline **33a** (1.50 g, 9.54 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was stirred at room temperature for 13 days with benzenesulfonyl chloride (2.00 g, 11.3 mmol) in the presence of pyridine (0.94 g, 12 mmol). Aq. NaHCO<sub>3</sub> (5%, ca. 25 mL) was then added, and the mixture was stirred vigorously for 20 min. The organic layer was separated, and the aqueous layer was extracted with 4 portions of CH<sub>2</sub>Cl<sub>2</sub>. After drying the combined organic layers (MgSO<sub>4</sub>) and evaporating the solvent, the crude product was dissolved in diethyl ether/methanol and decanted to leave most of the undissolved pyridine behind. Nice white crystals precipitated from the ether/methanol solution; after leaving for several days in the refrigerator, **33k** was collected and washed well with ether and cold methanol, and kept in a dessicator. Yield: 1.29 g (46%). <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.46 (s, 3H, CH<sub>3</sub>), 1.81 (s, 3H, CH<sub>3</sub>), 3.60-3.87 (m, 2H, NCH<sub>2</sub>), 4.14-4.35 (m, 2H, OCH<sub>2</sub>), 7.50-7.64 (m, 3H, Ar-m,p), 7.89-7.96 (m, 2H, Ar-o); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 22.36 (CH<sub>3</sub>), 25.14 (CH<sub>3</sub>), 46.47 (NCH<sub>2</sub>), 65.23 (OCH<sub>2</sub>), 120.46 (C2), 127.96 (Ar C2, C6), 129.02 (Ar C3, C5), 133.30 (Ar C4 & oxadiazoline C5, overlapped), 138.57 (Ar C1); IR (KBr) cm<sup>-1</sup>: 1576w (N=N), 1481w, 1448m, 1359s (NSO<sub>2</sub>), 1270m, 1227m, 1211m, 1169s

(NSO<sub>2</sub>), 1125s, 1053m, 1022m, 976w, 914m, 836m, 760w, 728m, 687m, 614m, 573m; MS (EI) m/z: 281 (2), 228 (15), 210 (31), 183 (4), 141 (PhSO<sub>2</sub><sup>+</sup>, 37), 117 (26), 88 (50), 77 (100), 51 (26); MS (CI, NH<sub>3</sub>) m/z: 315 (M+NH<sub>4</sub>)<sup>+</sup>.

» *5,14,15-Triaza-1,7-dioxadispiro[5.1.5.2]pentadec-14-ene*, **106b**. The method used for the synthesis of this oxadiazoline was similar to that for **33a**, using **103** (n = 3, R<sup>1</sup>R<sup>1</sup> = (CH<sub>2</sub>)<sub>5</sub>, R<sup>2</sup> = H) as the semicarbazone. Again, separation by chromatography, followed by slow bulb-to-bulb distillation (75-100 °C, 2 Torr) gave a pale yellow oil (yield not available). <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.40-2.10 (m), 2.10-2.45 (m) (12H, CCH<sub>2</sub>C), 3.15-4.50 (m, 4H, NCH<sub>2</sub>, OCH<sub>2</sub>) (NH did not appear or is hidden under intense multiplets); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 22.77 (CH<sub>2</sub>), 22.89 (CH<sub>2</sub>), 24.23 (CH<sub>2</sub>), 24.76 (CH<sub>2</sub>), 34.43 (2 x CH<sub>2</sub>), 41.38 (NCH<sub>2</sub>), 65.40 (OCH<sub>2</sub>), 120.64 (C2), 130.20 (C5).

» *5,14,15-Triaza-5-methyl-1,7-dioxadispiro[5.1.5.2]pentadec-14-ene*, **106c**. Preparation of **106c** was carried out essentially as for **33b**, using 2.36 g (10.4 mmol) of **103** (n = 3, R<sup>1</sup>R<sup>1</sup> = (CH<sub>2</sub>)<sub>5</sub>, R<sup>2</sup> = Me) and 3.51 g (10.9 mmol) of PhI(OAc)<sub>2</sub>, in a total of 300 mL of CH<sub>2</sub>Cl<sub>2</sub>. Purification of the resulting oil by column chromatography on silica (20% ethyl acetate in hexane) resulted in a slightly impure oxadiazoline, which was further purified by radial chromatography, using the same solvent mixture, to give 0.82 g (35%) of pure **106c** as a pale yellow oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.40-2.10 (m), 2.30-2.36 (m) (12H, CCH<sub>2</sub>C), 2.14 (s, 3H, CH<sub>3</sub>), 2.90-3.05 (m, 1H, NCH<sub>2</sub>), 3.23-3.34 (m, 1H, NCH<sub>2</sub>), 3.93-4.05 (m, 1H, OCH<sub>2</sub>), 4.14-4.27 (m, 1H, OCH<sub>2</sub>); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 22.53, 22.93, 24.48, 24.75, 32.69, 34.54, 37.11 (CH<sub>2</sub>'s and CH<sub>3</sub>), 49.61 (NCH<sub>2</sub>), 64.22 (OCH<sub>2</sub>),

120.27 (C2), 132.94 (C5); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1715w, 1572w (N=N), 1478m, 1450m, 1377m, 1346w, 1306m, 1282m, 1241s, 1218m, 1157m, 1142m, 1103s, 1061m, 1023w, 997m, 953w, 908m, 880m, 842w; MS: 197 ([M-N<sub>2</sub>]<sup>++</sup> (C<sub>11</sub>H<sub>19</sub>NO<sub>2</sub>), 8), 116 ([M-N<sub>2</sub>-C<sub>6</sub>H<sub>9</sub>]<sup>+</sup>, 25), 115 ([M-N<sub>2</sub>-C<sub>6</sub>H<sub>10</sub>]<sup>++</sup>, 40), 114 (17), 99 ([M-N<sub>2</sub>-C<sub>6</sub>H<sub>10</sub>O]<sup>++</sup> (C<sub>5</sub>H<sub>9</sub>NO), 48), 98 ((C<sub>5</sub>H<sub>8</sub>NO), 100), 88 (25), 44 ((C<sub>2</sub>H<sub>6</sub>N), 57), 42 (59), 28 (25).

» *3,4,10-Triaza-10-benzoyl-2,2-dimethyl-1,6-dioxaspiro[4.5]dec-3-ene*, **106d**.

PhI(OAc)<sub>2</sub> (6.14 g, 19.1 mmol), dissolved in 75 mL of methanol, was added dropwise to an ice-cold solution of **103** (n = 3, R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = H) (3.00 g, 17.3 mmol) in 75 mL of methanol, under nitrogen. After completion of the addition (1.5 h), the solution was stirred at room temperature for 24 h. Evaporation of the solvent gave an oil which was redissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed successively with aq. NaHCO<sub>3</sub> (5%) and water. The crude product, recovered after drying (MgSO<sub>4</sub>) the solution and evaporating the solvent, was redissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, together with pyridine (1.44 g, 18.2 mmol), and benzoyl chloride (2.46 g, 17.5 mmol) was added dropwise. After 1.5 h at room temperature, the usual workup was performed (see under 33f). Separation of the crude mixture by column chromatography, using first 5% and then 10% ethyl acetate in hexane, gave a 15% yield of an oil which proved to be a mixture of **106d** and, possibly, an isomer, which could not be identified. Pure **106d** crystallized out of a methanol/diethyl ether solution kept at ca. -10 °C. White solid, Mp 94 °C (dec.); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.53 (s, 3H, CH<sub>3</sub>), 1.70 (s, 3H, CH<sub>3</sub>), 1.95-2.31 (m, 2H, CCH<sub>2</sub>C), 3.59-3.93 (m, 2H, NCH<sub>2</sub>), 3.98-4.30 (m, 2H, OCH<sub>2</sub>), 7.30-7.64 (m, 5H, Ar); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ:



21.87 (CH<sub>3</sub>), 23.59 (CCH<sub>2</sub>C), 25.20 (CH<sub>3</sub>), 43.02 (NCH<sub>2</sub>), 60.79 (OCH<sub>2</sub>), 121.22 (C2), 127.40 (Ar C2, C6), 128.38 (Ar C3, C5), 129.01 (C5), 130.64 (Ar C4), 135.29 (Ar C1), 170.92 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1678s (C=O), 1601w, 1581w (N=N), 1492w, 1448w, 1380s, 1279m, 1213s, 1156m, 1096s, 984w, 949w, 912m, 849w, 700m; MS: 247 ([M-N<sub>2</sub>]<sup>+</sup>, 0.4), 206 ([M-N<sub>2</sub>-C<sub>3</sub>H<sub>5</sub>]<sup>+</sup>, 1), 189 ([M-N<sub>2</sub>-C<sub>3</sub>H<sub>6</sub>O]<sup>+</sup> (C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>), 17), 188 ((C<sub>11</sub>H<sub>10</sub>NO<sub>2</sub>), 50), 161 (10), 160 (29), 145 (40), 119 (10), 117 (17), 105 ([C<sub>6</sub>H<sub>5</sub>CO<sup>+</sup>], 100), 102 (15), 77 ([C<sub>6</sub>H<sub>5</sub><sup>+</sup>], 35).

» *Unidentified product formed with 106d.* <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, probable assignments, slightly impure sample) δ: 1.57 (s, 6H, CH<sub>3</sub>), 2.08-2.26 (m, 2H, CCH<sub>2</sub>C), 3.61 (t, <sup>3</sup>J = 6.7 Hz, 2H, NCH<sub>2</sub>), 4.45 (t, <sup>3</sup>J = 6.3 Hz, 2H, OCH<sub>2</sub>), 7.36-7.64 (m, 3H, Ar-m,p), 7.99-8.10 (m, 2H, Ar-o); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 23.51 (CH<sub>3</sub>), 29.47 (CCH<sub>2</sub>C), 45.05 (NCH<sub>2</sub>), 62.74 (OCH<sub>2</sub>), 101.17, 120.61, 128.30 (Ar C2, C6), 129.51 (Ar C3, C5), (130.31?), 132.85, (133.04?), (162.85?), 166.49; IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 3461br, 3423br, 1719s (probably C=O), 1604w, 1582w, 1505m, 1453m, 1386m, 1315w, 1273s, 1207m, 1179m, 1117s, 1071w, 1028w, 983w, 937w, 874w; MS (EI) m/z: 206 (36), 188 (9), 160 (6), 105 (PhCO<sup>+</sup>, 100), 77 (41); MS (CI, NH<sub>3</sub>) m/z: 276 (M+H)<sup>+</sup>(?).

» *5,14,15-Triaza-5-benzoyl-1,7-dioxadispiro[5.1.5.2]pentadec-14-ene, 106e.* After oxidation of **103** (n = 3, R<sup>1</sup>R<sup>1</sup> = (CH<sub>2</sub>)<sub>5</sub>, R<sup>2</sup> = H) (2.50 g, 11.7 mmol) with PhI(OAc)<sub>2</sub> (4.09 g, 12.7 mmol), carried out essentially as for **33a**, the resulting crude NH oxadiazoline was reacted with benzoyl chloride (1.58 g, 11.2 mmol) in 22 mL of benzene, in the presence of pyridine (1.16 g, 14.7 mmol), as described for **33f**. As crystallization of

**106e** could not be induced from the crude, it was purified by repeated chromatography, and obtained in *ca.* 8% yield (from the semicarbazone). The resulting product was a thick, sticky, colourless oil, which only partially crystallized in the refrigerator over several weeks.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.40-1.75 (m, 5H,  $\text{CCH}_2\text{C}$ ), 1.75-2.00 (m, 4H,  $\text{CCH}_2\text{C}$ ), 2.00-2.27 (m, 3H,  $\text{CCH}_2\text{C}$ ), 3.70-3.80 (m, 1H,  $\text{NCH}_2$ ), 3.80-3.90 (m, 1H,  $\text{NCH}_2$ ), 4.00-4.14 (m, 1H,  $\text{OCH}_2$ ), 4.14-4.28 (m, 1H,  $\text{OCH}_2$ ), 7.36-7.60 (m, 5H, Ar);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 22.73 ( $\text{CH}_2$ ), 23.22 ( $\text{CH}_2$ ), 23.65 ( $\text{CH}_2$ ), 24.86 ( $\text{CH}_2$ ), 30.93 ( $\text{CH}_2$ ), 34.72 ( $\text{CH}_2$ ), 43.06 ( $\text{NCH}_2$ ), 60.85 ( $\text{OCH}_2$ ), 123.16 ( $\text{C}_2$ ), 127.49 (Ar  $\text{C}_2$ ,  $\text{C}_6$ ), 128.00 ( $\text{C}_5$ ), 128.35 (Ar  $\text{C}_3$ ,  $\text{C}_5$ ), 130.61 (Ar  $\text{C}_4$ ), 135.46 (Ar  $\text{C}_1$ ), 170.96 ( $\text{C}=\text{O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1678s ( $\text{C}=\text{O}$ ), 1602w, 1580w ( $\text{N}=\text{N}$ ), 1493w, 1448m, 1378s, 1263m, 1218m, 1157m, 1087s, 976w, 948w, 895m, 847w, 700m; MS (EI)  $m/z$ : 206 (3), 188 (30), 160 (13), 145 (15), 105 ( $\text{PhCO}^+$ , 100), 84 (18), 77 (32), 67 (38); MS (CI,  $\text{NH}_3$ )  $m/z$ : 316 ( $\text{M}+\text{H}$ ) $^+$ .

**Attempted synthesis of 3,4,9-triaza-2,2-dimethyl-9-phenyl-1,6-dioxaspiro[4.4]non-3-ene, 33 ( $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Ph}$ ).** In an initial attempt, acetone 4-(2-hydroxyethyl)-4-phenylsemicarbazone (**103**,  $n = 2$ ,  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Ph}$ ) was reacted with  $\text{PhI}(\text{OAc})_2$  in  $\text{CH}_2\text{Cl}_2$  by the usual procedure. After completion of addition of the oxidant to the semicarbazone, the solution was dark brown, instead of the usual pale yellow (or colourless). The thick brown oil recovered, after work-up, contained some unreacted semicarbazone in addition to other unidentified products (by  $^1\text{H-NMR}$ ); however, none of the desired product seemed present. In a second attempt, oxidation of the semicarbazone

with  $\text{Pb}(\text{OAc})_4$  in  $\text{CH}_2\text{Cl}_2$  was also found to be incomplete after the usual reaction time (*ca.* 4.5 h); the small amount of desired oxadiazoline produced, if any, did not justify further efforts.

### 4.3 Thermolysis of 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines

#### 4.3.1 Thermolysis Rate Constants

The rate of decomposition of the oxadiazolines was monitored by  $^1\text{H}$ -NMR spectroscopy at 300 MHz. Typically,  $1.25 \times 10^{-4}$  mol of oxadiazoline and 7 mg of *p*-xylene (used as an internal standard for integration) were dissolved in *ca.* 0.5 mL  $\text{C}_6\text{D}_6$ . This solution was transferred to a medium-walled NMR tube which was sealed after three freeze-pump-thaw cycles. After recording an initial  $^1\text{H}$ -NMR spectrum, the tube was immersed in a constant-temperature oil bath at  $90.0 \pm 0.2$  °C. At appropriate time intervals, the tube was removed from the oil bath and quickly chilled to room temperature, and  $^1\text{H}$ -NMR spectra were recorded. No corrections were made to account for the time periods when the sample was outside the oil bath.

Linear regression analyses were performed for the plots of  $\ln(I/I_0)$  vs time, where  $I$  and  $I_0$  are the normalized integrals of a given resonance at time  $t$  and at time zero, respectively. The first-order decomposition rate constants were obtained from the slopes of the calculated best lines forced to pass through the origin. The thermolysis data, regression analysis results, and plots are shown in Appendix I.

NMR yields of thermolysis products were determined by comparison of the integrals of appropriate resonances, after completion of thermolysis, to the integrals of the oxadiazoline peaks at  $t = 0$ , using internal p-xylene for normalization.

In a few cases (as specified in text), NMR yields from thermolyses of oxadiazolines with phenols were also determined from thermolyses carried out in sealed NMR tubes. Samples for thermolysis were prepared as described above, using  $1.0 \times 10^{-4}$  mol of oxadiazoline with 1.25 equivalent of phenol, and p-xylene as an integration standard. Peak assignments for carbene + phenol adducts were known from isolated samples.

#### 4.3.2 General Thermolytic Scheme

##### *Large scale thermolyses*

A general thermolysis experiment is described here. Important details are described below in the appropriate sections. A benzene solution (10 mL) of the oxadiazoline (0.5 mmol, 50 mM) and an appropriate amount of compound used as a carbene trap were transferred to a sealable thermolysis tube. In some cases, this was preceded by distilling, under a dry nitrogen atmosphere, approximately 20 mL of the solution to be thermolysed down to 10 mL, in order to azeotrope out any water. The tube was then evacuated, and immersed in a constant temperature oil bath at  $90\text{ }^{\circ}\text{C} \pm 0.2\text{ }^{\circ}\text{C}$  for 24 h or until complete decomposition of the oxadiazoline.

### 4.3.3 Thermolysis of 33b

» *Acetone*.  $^1\text{H-NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 1.65 (s).

» *Acetone azine* (or *2-propanone (1-methylethylidene)hydrazone*).  $^1\text{H-NMR}$  (200 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 1.86 (s, 6H), 1.89 (s, 6H);  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.82 (s, 6H), 1.99 (s, 6H); MS (EI)  $m/z$ : 112 ( $\text{M}^+$ , 25), 97 (79), 70 (17), 56 (100), 39 (58), 28 (17).

» *Ethylene*.  $^1\text{H-NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 5.31 (s).

» *Propene*.  $^1\text{H-NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 1.57-1.64 (m, 3H,  $\text{CH}_3$ ), 4.95-5.15 (m, 2H,  $=\text{CH}_2$ ), 5.65-5.90 (m, 1H,  $=\text{CH}$ ).

» *3-Methyl-2-oxazolidinone*, **114b**.<sup>196</sup>  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.89 (s, 3H,  $\text{CH}_3$ ), 3.51-3.63 (m, 2H,  $\text{NCH}_2$ ), 4.26-4.38 (m, 2H,  $\text{OCH}_2$ );  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 31.14 ( $\text{CH}_3$ ), 46.85 ( $\text{NCH}_2$ ), 61.45 ( $\text{OCH}_2$ ), 158.76 ( $\text{C=O}$ ); MS (EI)  $m/z$ : 101 ( $\text{M}^+$ , 17), 72 (2), 56 (25), 42 (100), 28 (33).

» *Unidentified product*, Scheme XXV.  $^1\text{H-NMR}$  (200 MHz,  $\text{C}_6\text{D}_6$ , partial spectrum deduced from crude mixture with probable assignments)  $\delta$ : 1.06 ppm ( $\text{CCH}_3$ ), 1.26 ppm ( $\text{CCH}_3$ ), 2.41 ppm ( $\text{NCH}_3$ ), 2.44 ppm ( $\text{NCH}_3$ ).

**Bromination of ethylene and propene.** After complete thermolysis of 98 mg (0.57 mmol) of **33b**, the thermolysis tube was immersed in liquid nitrogen for several minutes. About 1 mL of bromine solution (0.5 M, in  $\text{CCl}_4$ ) was then added, the tube was sealed again and the contents were allowed to thaw. After mixing the solution at room temperature, the tube was re-opened and the solution was washed with 2 x 10 mL of aq.  $\text{NaHCO}_3$  (5%), followed by 10 mL of water. An aliquot of the resulting colourless

solution was analysed by GC-MS. Both 1,2-dibromoethane and 1,2-dibromopropane were detected and their spectra matched those from authentic samples.

» *1,2-Dibromoethane*. MS (EI)  $m/z$ : 190 ( $^{81}\text{Br } ^{81}\text{Br M}^+$ , 3), 188 ( $^{81}\text{Br } ^{79}\text{Br M}^+$ , 5), 186 ( $^{79}\text{Br } ^{79}\text{Br M}^+$ , 3), 162 (2) & 160 (4) & 158 (2) ( $\text{Br}_2^+$ ), 109 (95) & 107 (100) ( $\text{M-Br}^+$ ), 95 (9) & 93 (13) ( $\text{CH}_2\text{Br}^+$ ), 81 (31) & 79 (31) ( $\text{Br}^+$ ), 27 (41).

» *1,2-Dibromopropane*. MS (EI)  $m/z$ : 204 ( $^{81}\text{Br } ^{81}\text{Br M}^+$ , 1), 202 ( $^{81}\text{Br } ^{79}\text{Br M}^+$ , 2), 200 ( $^{79}\text{Br } ^{79}\text{Br M}^+$ , 1), 189 (< 1) & 187 (1) & 185 (< 1) ( $\text{M-CH}_3^+$ ), 162 (1) & 160 (2) & 158 (1) ( $\text{Br}_2^+$ ), 123 (100) & 121 (100) ( $\text{M-Br}^+$ ), 107 (7) & 105 (5) ( $\text{M-CH}_2\text{Br}^+$ ), 95 (13) & 93 (15) ( $\text{CH}_2\text{Br}^+$ ), 81 (18) & 79 (17) ( $\text{Br}^+$ ), 41 (95), 27 (11).

**Photolysis of 2,2-dimethoxy-5,5-dimethyl- $\Delta^3$ -1,3,4-oxadiazoline (12b); thermolysis of 2-diazopropane.** Two medium-walled NMR tubes, each containing *ca.* 22 mg (0.14 mmol) of **12b**<sup>i</sup> and *ca.* 0.5 mL benzene- $\text{d}_6$ , were sealed after three freeze-pump-thaw cycles. Both tubes were irradiated with 300 nm light in a Rayonet apparatus for 50 min. One of the tube was then immersed in a constant temperature oil bath at 90 °C for 20 h, while the other tube was kept at room temperature in the dark. The resulting product distribution was determined using  $^1\text{H-NMR}$ . Results are described in Section 2.3.3.

**Thermolysis of 33b with DMAD.** Oxadiazoline **33b** (98 mg, 0.58 mmol) was thermolysed with DMAD (254 mg, 1.79 mmol) in 10 mL of benzene. A complex of mixture of products was obtained, including **121**.

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<sup>i</sup> Oxadiazoline **12b** was kindly provided by D. L. Pole.

» *Dimethyl 3,3-dimethyl-3H-pyrazole-4,5-dicarboxylate*, **121**.<sup>150</sup> <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.58 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 20.86 (C(CH<sub>3</sub>)<sub>2</sub>), 52.98 (2 x OCH<sub>3</sub>, coincident), 97.46 (C3), 144.68 (C4), 153.56 (C5), 160.81 (C=O), 162.97 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1732s (C=O), 1647w, 1438w, 1334w, 1264s, 1198w, 1167w, 1114w, 1033w, 909m; MS (EI) m/z: 183 (3), 169 (3), 152 (33), 141 (50), 125 (36), 109 (34), 93 (55), 79 (65), 67 (100), 59 (43), 53 (31), 39 (50), 29 (18).

#### 4.3.4 Thermolysis of 106c

» *Cyclohexene*. <sup>1</sup>H-NMR (200 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 1.46-1.71 (m, 4H, CH<sub>2</sub>(4,5)), 1.86-2.11 (m, 4H, CH<sub>2</sub>(3,6)), 5.68-5.84 (m, 2H, CH(1,2)).

» *Cyclohexanone*. <sup>1</sup>H-NMR (200 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 1.12-1.31 (m, 2H, CH<sub>2</sub>(4)), 1.32-1.52 (m, 4H, CH<sub>2</sub>(3,5)), 1.95-2.15 (m, 4H, CH<sub>2</sub>(2,6)).

» *Cyclohexanone azine (or cyclohexanone cyclohexylidenehydrazone)*. MS (EI) m/z: 192 (M<sup>+</sup>, 60), 163 (57), 149 (100), 136 (59), 124 (26), 110 (69), 96 (43), 81 (24), 67 (45), 55 (57), 41 (93), 27 (27).

» *3-Methyltetrahydro-2H-1,3-oxazin-2-one*, **115c**.<sup>197</sup> <sup>1</sup>H-NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 1.10-1.20 (m, 2H, CCH<sub>2</sub>C), 2.40 (t, <sup>3</sup>J = 6.3 Hz, 2H, NCH<sub>2</sub>), 2.68 (s, 3H, CH<sub>3</sub>), 3.58 (t, <sup>3</sup>J = 5.3 Hz, 2H, OCH<sub>2</sub>); MS (EI) m/z: 115 (M<sup>+</sup>, 21), 87 (13), 70 (13), 56 (27), 42 (100), 28 (27).

#### 4.3.5 Thermolysis of 33f

**Preparation of benzoyl isocyanate.** This compound was prepared by the method of Speziale and Smith.<sup>198</sup> Benzamide (3.0 g, 25 mmol) and oxalyl chloride (4.0 g, 32 mmol) were refluxed in 100 mL of 1,2-dichloroethane (distilled and kept over 4 Å molecular sieves), under dry nitrogen, for 16 h. After removal of the solvent on a rotary evaporator, the crude product was distilled at *ca.* 40 °C, 0.2 Torr, to yield about 1.7 g (47%) of benzoyl isocyanate. White solid, lit.<sup>193</sup> Mp 26 °C; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 7.42-7.58 (m, 2H, Ar-m), 7.59-7.73 (m, 1H, Ar-p), 8.02-8.13 (m, 2H, Ar-o); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 128.92 (Ar C2, C6), 130.54 (Ar C3, C5), 131.34 (N=C=O), 131.99 (Ar C1), 134.78 (Ar C4), 165.12 (PhC=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 2336s, 2243s (NCO), 2177w, 1696s (PhC=O), 1580w, 1399w, 1359w, 1232w, 971m, 703m; MS (EI) m/z: 147 (M<sup>+</sup>, 34), 105 (PhCO<sup>+</sup>, 100), 91 (2), 77 (88), 70 (6), 63 (4), 51 (28), 38 (4), 26 (2).

**Thermolyses of 33f.** As discussed in Section 2.3.5, oxadiazoline 33f was thermolysed several times, in the usual way, in order to obtain the data that follow. The major product, **125a**, was formed in almost quantitative yield. Attempted purification by chromatography resulted in its complete decomposition. Small amounts of essentially pure crystals could be obtained by dissolving the crude product mixture in diethyl ether, followed by removal of the solvent on a rotary evaporator. Similarly, its sole hydrolysis product, **127a**, which could be obtained by leaving the crude product in contact with a few drops of water over several days, did not survive chromatography. However, pure **127a** precipitated from a benzene solution left at or below room temperature over a few weeks. Of the minor non-



volatile products resulting from thermolysis of **33f**, benzoyl isocyanate was detected by GC-MS (and matched an authentic sample); **114f** was repeatedly isolated by radial chromatography from various samples of thermolysed **33f**; benzamide and **131f**, detected by GC-MS when **33f** was thermolysed without added trap, were both isolated by chromatography in the thermolysis of **33f** in the presence of water (see below).

**Thermolysis of 33f in the presence of water.** Oxadiazoline **33f** (224 mg, 0.86 mmol) was thermolysed in 100 mL benzene, with about 15 drops of water. Repeated separation by radial chromatography, using ethyl acetate/hexane in various proportions, afforded about 21 mg (20%) of benzamide and 92 mg (56%) of **131f**.

**Thermolysis of 33f with benzoyl isocyanate.** Oxadiazoline **33f** (118 mg, 0.45 mmol) was thermolysed with benzoyl isocyanate (110 mg, 0.75 mmol) in 10 mL of benzene. Spectroscopic data (GC-MS,  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR in both  $\text{C}_6\text{D}_6$  and  $\text{CDCl}_3$ ) for the crude thermolysate were similar to those obtained from thermolyses of **33f** without added trap, *i.e.* formation of **125a** as the major product.

**Thermolysis of 33d with benzoyl isocyanate.** Oxadiazoline **33d** (90 mg, 0.45 mmol) was thermolysed with benzoyl isocyanate (124 mg, 0.84 mmol) in 10 mL of benzene. GC-MS, as well as  $^1\text{H}$  and  $^{13}\text{C}$  spectra of the crude product mixture indicated that **125b** was the major product. Slightly impure **127b** was obtained by exposing **125b** to  $\text{H}_2\text{O}$  during several days.

**Thermolysis of 2,2-dimethoxy oxadiazoline 12b with benzoyl isocyanate.** Oxadiazoline **12b** (85 mg, 0.53 mmol) was thermolysed at 110 °C for 24 h with benzoyl

isocyanate (143 mg, 0.97 mmol) in 10 mL of benzene. GC-MS, as well as  $^1\text{H}$  and  $^{13}\text{C}$  spectra of the crude product mixture, indicated that **125c** was the major product.

**Control “thermolysis” of benzoyl isocyanate.** Slightly impure benzoyl isocyanate (110 mg, 0.75 mmol) was dissolved in 10 mL of dry benzene and subjected to the usual thermolysis conditions. GC-MS, as well as  $^1\text{H}$  and  $^{13}\text{C}$  spectra of the crude, sparingly-solubility product mixture indicated that very little benzoyl isocyanate remained (detected only by GC-MS, not by  $^{13}\text{C}$ -NMR). Inspection of the  $^{13}\text{C}$  spectrum demonstrated the presence of benzamide and of N,N'-dibenzoylurea. The latter was identified by comparison with a pure sample obtained by recrystallization (ethyl acetate) of a completely decomposed sample of benzoyl isocyanate.

» *3-Benzoyl-2-oxazolidinone*, **114f**. Lit.<sup>199</sup> Mp 166-168 °C;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.19 (t,  $^3J = 7.8$  Hz, 2H,  $\text{NCH}_2$ ), 4.51 (t,  $^3J = 7.8$  Hz, 2H,  $\text{OCH}_2$ ), 7.40-7.50 (m, 2H, Ar-m), 7.51-7.60 (m, 1H, Ar-p), 7.62-7.70 (m, 2H, Ar-o);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 43.71 ( $\text{NCH}_2$ ), 62.22 ( $\text{OCH}_2$ ), 127.87 (Ar C2, C6), 129.10 (Ar C3, C5), 132.43 (Ar C4) (Ar C1 and C=O peaks not observed due to low S/N); MS (EI)  $m/z$ : 191 ( $\text{M}^+$ , 15), 163 (3), 147 (3), 121 (1), 105 ( $\text{PhCO}^+$ , 100), 91 (1), 77 (82), 63 (2), 51 (35), 42 (5), 28 (6).

» *Spiro-fused 4(5H)-oxazolone* **125a**. Solid, Mp N.A.;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.00-4.12 (m, 2H,  $\text{NCH}_2$ ), 4.47-4.59 (m, 2H,  $\text{OCH}_2$ ), 7.25-7.80 (m, 8H, Ar), 8.21-8.31 (m, 2H,  $\text{PhCO-o}$ );  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 47.14 ( $\text{NCH}_2$ ), 68.43 ( $\text{OCH}_2$ ), 108.38 (spiro C), 125.35 (Ar), 127.18 (Ar), (127.59?, Ar), 128.32 (Ar), 128.70 (Ar), 130.21 (Ar), 131.25 (Ar), 135.60 (Ar), 167.73 ( $\text{PhC=O}$ ), 181.80 and 184.13 (oxazolone C2 and

C4);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 46.94 ( $\text{NCH}_2$ ), 68.48 ( $\text{OCH}_2$ ), 108.95 (spiro C), 125.89 (Ar), 127.36 (Ar), (127.56?, Ar), 128.23 (Ar), 128.68 (Ar), 130.02 (Ar), 130.97 (Ar), 135.16 (Ar), 167.58 ( $\text{C}=\text{O}$ ), 181.81 and 184.04 (oxazolone C2 and C4); IR (crude product,  $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1783s (oxazolone  $\text{C}=\text{O}$ ), 1736w, 1677s ( $\text{PhC}=\text{O}$ ), 1605m, 1558s ( $\text{C}=\text{N}$ ), 1492w, 1451m, 1384s, 1274w, 1196m, 1170m, 1141m, 1100w, 1055w, 854w; MS (EI)  $m/z$ : 322 ( $\text{M}^+$ , 1), 175 (20), 147 (9), 131 (12), 105 ( $\text{PhCO}^+$ , 100), 83 (53), 78 (57), 49 (100); MS (CI,  $\text{NH}_3$ )  $m/z$ : 323 ( $\text{M}+\text{H}^+$ ).

» *Spiro-fused 4(5H)-oxazolone 125b*.  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ , possible slow exchange)  $\delta$ : 2.13 (s, ~3H,  $\text{CH}_3$ ), 3.90-4.07 (m, 2H,  $\text{NCH}_2$ ), 4.40-4.64 (m, 2H,  $\text{OCH}_2$ ), *ca.* 7.34-7.76 (m, 3H, Ar-m,p), 8.13-8.27 (m, 2H, Ar-o);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 22.42 ( $\text{CH}_3$ ), 45.76 ( $\text{NCH}_2$ ), 68.30 ( $\text{OCH}_2$ ), 108.02 (spiro C), 125.51 (Ar C2, C6), 128.77 (Ar C3, C5), 130.31 (Ar C4), 135.63 (Ar C1), 168.18 ( $\text{PhC}=\text{O}$ ), 181.67 and 184.11 (oxazolone C2 and C4); IR (partial spectrum,  $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1782 (oxazolone  $\text{C}=\text{O}$ ), 1603, 1557 ( $\text{C}=\text{N}$ ).

» *5,5-Dimethoxy-2-phenyl-4(5H)-oxazolone, 125c*.  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.60 (s, 6H,  $\text{OCH}_3$ ), *ca.* 7.33-7.80 (m, 3H, Ar-m,p), 8.21-8.35 (m, 2H, Ar-o);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 52.22 ( $\text{OCH}_3$ ), 114.02 (C5 oxazolone), 125.15 (Ar), 128.96 (Ar), 130.27 (Ar), 136.02 (Ar), 181.45 and 184.62 (oxazolone C2 and C4); IR (partial spectrum,  $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1778 ( $\text{C}=\text{O}$ ), 1734, 1600, 1553 ( $\text{C}=\text{N}$ ); MS (EI)  $m/z$ : 221 ( $\text{M}^+$ , 2), 193 (1), 190 (1), 162 (5), 147 (2), 131 (8), 118 (9), 103 (100), 91 (3), 77 (37), 59 (35), 51 (13), 39 (2), 29 (4).

» *Oxalic acid derivative 127a*. White solid, Mp *ca.* 170 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 3.87-3.97 (m, 2H, NCH<sub>2</sub>), 4.59 (t, <sup>3</sup>J = 4.9 Hz, 2H, OCH<sub>2</sub>), 7.05 (br.s., 1H, NH), 7.30-7.60 (m, 5H, Ar), 7.63-7.73 (m, 1H, Ar), 7.75-7.83 (m, 2H, PhCO-o), 7.86-7.94 (m, 2H, PhCO-o), 9.64 (br.s., 1H, NH); <sup>13</sup>C-NMR (50 MHz, CD<sub>3</sub>OD, slow exchange) δ: 39.68 (NCH<sub>2</sub>), 65.95 & 66.20 (OCH<sub>2</sub>), 128.31 (Ar C2, C6), 128.64 (Ar C2, C6), 129.51 (2 x Ar C3, C5), 132.76 (Ar C4), 132.91 (2 x Ar C4), 134.96 (Ar C1), 135.43 (Ar C1), 158.81 (oxalyl C=O), 159.48 (oxalyl C=O), 170.61 (PhC=O), 172.41 (PhC=O); IR (KBr) cm<sup>-1</sup>: 3453m (NH), 3306br (NH), 1753s, 1721m, 1682m, 1641s, 1602w, 1578w, 1536s, 1464m, 1427w, 1399m, 1365m, 1318m, 1250m, 1208m, 1182s, 1121w, 1021m, 972w, 909w, 799w, 773w, 741w, 700s; MS (EI) m/z: 164 (17), 147 (42), 117 (32), 105 (PhCO<sup>+</sup>, 100), 77 (43), 51 (22), 44 (11); MS (CI, NH<sub>3</sub>) m/z: 341 (M+H)<sup>+</sup>; anal. calcd. for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>: C, 63.52; H, 4.74; N, 8.23; measured: C, 59.89; H, 4.98; N, 7.86.

» *Oxalic acid derivative 127b*. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.97 (s, 3H, CH<sub>3</sub>), 3.58-3.70 (m, 2H, NCH<sub>2</sub>), 4.46 (t, <sup>3</sup>J = 4.9 Hz, 2H, OCH<sub>2</sub>), 6.79 (um, 1H, NH), *ca.* 7.30-7.70 (overlapped m, probably 3H, Ar-m,p), 7.97-8.06 (m, 2H, Ar-o), 10.94 (br.s., 1H, NH); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 22.98 (CH<sub>3</sub>), 38.19 (NCH<sub>2</sub>), 65.83 (OCH<sub>2</sub>), 126-135 (Ar), 160.37 (overlapped, 2 x oxalyl C=O), 166.31 and 170.97 (CH<sub>3</sub>C=O and PhC=O); IR (partial spectrum, CCl<sub>4</sub>) cm<sup>-1</sup>: 1762, 1718, 1604.

» *N-[2-(Formyloxy)ethyl]benzamide, 131f*.<sup>200</sup> White solid, Mp 59-60 °C (slightly impure sample); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 3.77 (q, <sup>3</sup>J = 5.4 Hz, 2H, NCH<sub>2</sub>), 4.39 (t, <sup>3</sup>J = 5.2 Hz, 2H, OCH<sub>2</sub>), 6.55 (br.s., 1H, NH), 7.35-7.60 (m, 3H, Ar-m,p), 7.72-7.84 (m, 2H, Ar-

o), 8.11 (s, 1H, C(O)H);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 38.94 ( $\text{NCH}_2$ ), 62.58 ( $\text{OCH}_2$ ), 126.88 (Ar C2, C6), 128.41 (Ar C3, C5), 131.50 (Ar C4), 133.98 (Ar C1), 160.89 (O-C=O), 167.79 (N-C=O); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 3465br (NH), 1735s (OC=O), 1677s (NC=O), 1517m, 1486w, 1302m, 1174s, 909w; MS (EI)  $m/z$ : 193 ( $\text{M}^+$ , 5), 164 (3), 147 (19), 134 (5), 105 ( $\text{PhCO}^+$ , 100), 77 (58), 51 (22), 31 (8); MS (CI,  $\text{NH}_3$ )  $m/z$ : 211 ( $\text{M}+\text{NH}_3$ ) $^+$ , 194 ( $\text{M}+\text{H}$ ) $^+$ .

» *Benzamide*. White solid, lit.<sup>193</sup> Mp 130 °C;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.50-6.40 (two overlapping br.s, NH's), 7.41-7.59 (m, 3H, Ar-m,p), 7.78-7.85 (m, 2H, Ar-o);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 127.31 (Ar C2, C6), 128.49 (Ar C3, C5), 131.94 (Ar C4), 133.34 (Ar C1), 169.66 (C=O); IR (KBr)  $\text{cm}^{-1}$ : 3370s (NH), 3174s (NH), 1659s (C=O), 1624m, 1577m, 1450w, 1403m, 1297w, 1143w, 1122w, 791w, 705w; MS (EI)  $m/z$ : 121 ( $\text{M}^+$ , 57), 105 ( $\text{PhCO}^+$ , 76), 77 (100), 51 (58), 44 (19), 39 (8); MS (CI,  $\text{NH}_3$ )  $m/z$ : 139 ( $\text{M}+\text{NH}_4$ ) $^+$ , 122 ( $\text{M}+\text{H}$ ) $^+$ .

» *N,N'*-Dibenzoylurea. White solid, Mp 213-217 °C (lit.<sup>218</sup> 212-216 °C);  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.50-7.75 (m, 6H, Ar-m,p), 7.97-8.12 (m, 4H, Ar-o) (the NH signals were not visible);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 128.09 (Ar C2, C6), 128.93 (Ar C3, C5), 131.90 (Ar C4), 133.53 (Ar C1), 150.42 (NC(O)N), 167.16 (PhCO); IR (KBr)  $\text{cm}^{-1}$ : 3431br (NH), 1757s (C=O), 1670m (C=O), 1475s, 1262m, 1197m, 775w.

### 4.3.6 Thermolysis of Other N-Carbonyl Oxadiazolines 33

- » *3-Acetyl-2-oxazolidinone*, **114d**. Lit.<sup>199</sup> Mp 85 °C; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.54 (s, 3H, CH<sub>3</sub>), 4.02 (t, <sup>3</sup>J = 8.1 Hz, 2H, NCH<sub>2</sub>), 4.42 (t, <sup>3</sup>J = 8.1 Hz, 2H, OCH<sub>2</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 23.19 (CH<sub>3</sub>), 42.34 (NCH<sub>2</sub>), 61.93 (OCH<sub>2</sub>), 153.68 (OC=O), 170.44 (CH<sub>3</sub>C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1794s (OC=O), 1711s (CH<sub>3</sub>C=O), 1482w, 1384m, 1309m, 1224m, 1138w, 1057w, 1037w, 956w; MS (EI) m/z: 129 (M<sup>+</sup>, 16), 101 (74), 88 (14), 70 (6), 56 (10), 43 (100), 28 (20); MS (CI, NH<sub>3</sub>) m/z: 147 (M+NH<sub>4</sub>)<sup>+</sup>, 130 (M+H)<sup>+</sup>.
- » *N-[2-(Formyloxy)ethyl]acetamide*, **131d**.<sup>200</sup> Not isolated; MS (EI) m/z: 131 (M<sup>+</sup>, 2), 102 (7), 85 (54), 72 (25), 60 (14), 43 (100), 29 (40).
- » *3-Methacryloyl-2-oxazolidinone*, **114e**. Not isolated; MS (EI) m/z: 155 (M<sup>+</sup>, 18), 140 (1), 127 (13), 112 (7), 96 (6), 83 (25), 69 (86), 56 (11), 41 (100), 28 (18).
- » *N-[2-(Formyloxy)ethyl]methacrylamide*, **131e**. Not isolated; MS (EI) m/z: 157 (M<sup>+</sup>, 5), 128 (9), 111 (25), 98 (19), 83 (38), 69 (100), 41 (66), 29 (25).
- » *3-(2-Methoxybenzoyl)-2-oxazolidinone*, **114g**. Not isolated; MS (EI) m/z: 221 (M<sup>+</sup>, 16), 190 (3), 135 (ArCO<sup>+</sup>, 100), 120 (6), 105 (5), 92 (22), 77 (24), 64 (7), 51 (5).
- » *Spiro-fused 4(5H)-oxazolone 125* from thermolysis of **33g**. Not isolated, data from thermolysate resulting from the thermolysis of **33g** without added trap. Spectrum complicated by slow exchange, and only resonances from the major isomer are given (2 aromatic resonances could not be identified due to complexity of spectrum); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 45.59 (NCH<sub>2</sub>), 55.95 (OCH<sub>3</sub>), 56.10 (OCH<sub>3</sub>), 68.17 (OCH<sub>2</sub>), 106.89 (spiro C), 111.32 (Ar), 112.32 (Ar), 120.25 (Ar), 120.81 (Ar), 128.47 (Ar), 131.71 (Ar),

133.08 (Ar), 136.75 (Ar), 155.36 (Ar), 161.31 (Ar), 166.51 (ArC=O), 182.09 and 183.91 (oxazolone C2 and C4).

#### 4.3.7 Thermolysis of 106d and 106e

» *3-Benzoyltetrahydro-2H-1,3-oxazin-2-one*, **115d**. Not isolated, lit.<sup>199</sup> Mp 87 °C; MS (EI) m/z: 205 (M<sup>+</sup>, 15), 177 (28), 105 (PhCO<sup>+</sup>, 100), 77 (60), 51 (22), 28 (8).

#### 4.3.8 Thermolysis of 33k

» *3-(Phenylsulfonyl)-2-oxazolidinone*, **114k**. Lit.<sup>199</sup> Mp 136-138 °C; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 4.00-4.15 (m, 2H, NCH<sub>2</sub>), 4.32-4.46 (m, 2H, OCH<sub>2</sub>), 7.50-7.80 (m, 3H, Ar-m,p), 8.02-8.13 (m, 2H, Ar-o); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 44.61 (NCH<sub>2</sub>), 62.28 (OCH<sub>2</sub>), 128.26 (Ar C2, C6), 129.30 (Ar C3, C5), 134.55 (Ar C4), 136.81 (Ar C1), 151.91 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1801s, 1480w, 1450w, 1382m (NSO<sub>2</sub>), 1264w, 1180s (NSO<sub>2</sub>), 1147s, 1094w, 1050w, 909w; MS (EI) m/z: 163 (30), 141 (PhSO<sub>2</sub><sup>+</sup>, 12), 118 (8), 104 (53), 91 (6), 77 (100), 56 (6), 51 (28), 28 (2); MS (CI, NH<sub>3</sub>) m/z: 245 (M+NH<sub>4</sub>)<sup>+</sup>.

#### 4.3.9 Thermolysis of 33a

Thermolysis of **33a** in the usual way led to the isolation of **114d** (see under **33d** in 4.3.6) in ca. 5% yield by radial chromatography (ethyl acetate/hexane). The lability of the other products prevented their purification. The following spectroscopic data were extracted from the crude thermolysates or from partially purified samples.

» *Carbene dimer 132*. Identity is uncertain;  $^1\text{H-NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : *ca.* 3.30-3.60 (m,  $\text{NCH}_2\text{CH}_2\text{O}$ );  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.62 (t,  $^3J = 7.9$  Hz, 2H,  $\text{NCH}_2$ ), 4.45 (t,  $^3J = 7.9$  Hz, 2H,  $\text{OCH}_2$ ).

» *2-(2-Propylidene)oxazolidine, 134*.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.48 (s, 3H,  $\text{CH}_3$ ), 1.53 (s, 3H,  $\text{CH}_3$ ), 3.42-3.57 (m, 2H,  $\text{NCH}_2$ ), 4.14-4.34 (m, 2H,  $\text{OCH}_2$ ) (NH not observed);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 24.43 ( $\text{CH}_3$ ), 24.63 ( $\text{CH}_3$ ), 44.68 ( $\text{NCH}_2$ ), 67.83 ( $\text{OCH}_2$ ), 117.69 ( $=\text{C}(\text{CH}_3)_2$ ), 139.22 (oxazolidine C2).

» *2-Isopropoxy-2-oxazoline, 135*.  $^1\text{H-NMR}$  (200 MHz,  $\text{C}_6\text{D}_6$ , partial spectrum)  $\delta$ : 1.23 (d,  $^3J = 6.2$  Hz, 6H,  $\text{C}(\text{CH}_3)_2$ ), 5.05 (septet,  $^3J = 6.2$  Hz, 1H,  $\text{CH}(\text{Me})_2$ );  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ , partial spectrum)  $\delta$ : 1.39 (d,  $^3J = 6.2$  Hz, 6H,  $\text{C}(\text{CH}_3)_2$ ), 4.92 (septet,  $^3J = 6.2$  Hz, 1H,  $\text{CH}(\text{Me})_2$ ).

» *Spiro-fused oxirane 136*. Identity is uncertain;  $^1\text{H-NMR}$  (200 MHz,  $\text{C}_6\text{D}_6$ , partial spectrum)  $\delta$ : 0.80 (s, 3H,  $\text{CH}_3$ ), 0.83 (s, 3H,  $\text{CH}_3$ );  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ , partial spectrum)  $\delta$ : 1.20 (s, 3H,  $\text{CH}_3$ ), 1.23 (s, 3H,  $\text{CH}_3$ ).

**Thermolysis of 33a followed by acylation of the thermolysate.** Oxadiazoline 33a (133 mg, 0.85 mmol) was thermolysed in 10 mL of benzene at 90 °C for 72 h. The cooled thermolysate was transferred to a flask containing pyridine (*ca.* 100 mg, 1.3 mmol), and acetyl chloride (*ca.* 80 mg, 1.0 mmol) was then added dropwise. Stirring was continued for a further 10 min. The solution was diluted with 10 mL of benzene, washed with water (3 x 5 mL) and brine (5 mL), and dried over  $\text{MgSO}_4$ . Attempted separation of the product



mixture by radial chromatography on silica (ethyl acetate/hexane) failed to yield any recognizable products.

**Thermolysis of 33a with 4-cyanophenol.** Typically, 33a (98 mg, 0.62 mmol) was thermolysed with 4-cyanophenol (115 mg, 0.97 mmol) in 11 mL of benzene. The crude thermolysate was base-washed as described in Section 4.4.1.2.2. Separation by radial chromatography, using mixtures of ethyl acetate/hexane as eluent, gave 2-(4-cyanophenoxy)propane (see Section 4.4.1.2) in 6% yield and a few mgs of impure 137.

» *2-(4-Cyanophenoxy)-2-isopropoxyoxazolidine, 137.* Identity is uncertain;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.25 (d,  $^3J = 6.3$  Hz, 6H,  $\text{CH}(\underline{\text{CH}_3})_2$ ), 3.53-3.70 (m, 2H,  $\text{NCH}_2$ ), 4.09 (t,  $^3J = 5.2$  Hz, 2H,  $\text{OCH}_2$ ), 4.93 (septet,  $^3J = 6.3$  Hz, 1H,  $\underline{\text{CH}}(\text{CH}_3)_2$ ), 6.89-7.01 (m, 2H, Ar C2, C6), 7.54-7.66 (m, 2H, Ar C3, C5);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 22.12 ( $\text{CH}(\underline{\text{CH}_3})_2$ ), 40.16 ( $\text{NCH}_2$ ), 67.38 ( $\text{OCH}_2$ ), 68.55 ( $\underline{\text{CH}}(\text{CH}_3)_2$ ), 115.14 (Ar C2, C6), 134.05 (Ar C3, C5), 161.78 (Ar C1), 104.45 (Ar C4), 119.04 ( $\text{C}\equiv\text{N}$ ), 156.18 (oxazolidine C2); MS (EI)  $m/z$ : 161 (11, M-isopropoxy-CO), 146 (3), 119 (100), 102 (6), 91 (19), 75 (5), 64 (17).

## 4.4 Intermolecular Reactions of Aminooxycarbenes

### 4.4.1 Insertions into O-H bonds

#### 4.4.1.1 Reactions with Alcohols

**Thermolysis of 33b with *tert*-butyl alcohol.** Performed on a small scale: 33b (15 mg, 0.085 mmol) was thermolysed with *tert*-butyl alcohol (40  $\mu\text{L}$ , 0.42 mmol, dried by

refluxing over calcium hydride followed by distillation) in a sealed NMR tube in *ca.* 0.5 mL benzene- $d_6$ . Analysis of the crude thermolysate was performed by  $^1\text{H}$ -NMR and GC-MS.

**Thermolysis of 33b with benzyl alcohol.** Oxadiazoline 33b (103 mg, 0.60 mmol) was thermolysed with benzyl alcohol (99 mg, 0.91 mmol) in 10 mL of benzene. Results are described in Section 2.4.1.1.

» *N*-(2-Hydroxyethyl)-*N*-methylformamide, **138**. An authentic sample was prepared in 62% yield from the reaction of 2-(methylamino)-1-ethanol with ethyl formate, as described by Shibamura *et al.*<sup>155</sup> Colourless oil;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ , slow exchange, resonances due to major isomer are underlined, A:B  $\approx$  60:40)  $\delta$ : 2.87 (s) & 3.02 (s) (3H,  $\text{NCH}_3$ ), 3.24-3.85 (m) and 4.25-4.35 (m) (5H,  $\text{CH}_2\text{CH}_2$ , OH), 8.00 (s) & 8.05 (s) (1H, C(O)H);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 29.78 & 35.81 ( $\text{NCH}_3$ ), 47.54 & 52.13 ( $\text{NCH}_2$ ), 58.62 & 60.11 ( $\text{OCH}_2$ ), 163.56 & 163.78 (C=O); MS (EI)  $m/z$ : 103 ( $\text{M}^+$ , 2), 85 (5), 72 (19), 60 (11), 56 (8), 44 (100), 29 (45).

» *Phenylmethyl formate*.<sup>201</sup> MS (EI)  $m/z$ : 136 ( $\text{M}^+$ , 27), 108 (37), 91 (100), 77 (75), 65 (37), 51 (43), 39 (26), 29 (49).

» *2-Benzyloxypropane*.<sup>202</sup> MS (EI)  $m/z$ : 150 ( $\text{M}^+$ , 1), 135 (1), 107 (6), 91 (100), 77 (26), 65 (27), 51 (16), 43 (19), 39 (16), 29 (13).

#### 4.4.1.2 Reactions with Phenols

» *2-Phenoxypropane*.<sup>203</sup> <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, partial spectrum, data from crude thermolysate)  $\delta$ : 1.34 (d, <sup>3</sup>J = 6.1 Hz, 6H, CH<sub>3</sub>), 4.47 (septet, <sup>3</sup>J = 6.1 Hz, 1H, methine CH); MS (EI) m/z: 136 (M<sup>+</sup>, 15), 121 (4), 107 (2), 94 (100), 77 (15), 66 (62), 51 (16), 39 (59), 27 (17).

» *2-(4-Methylphenoxy)propane*.<sup>204</sup> <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.33 (d, <sup>3</sup>J = 6.0 Hz, 6H, CH<sub>3</sub>), 2.29 (s, 3H, Ar CH<sub>3</sub>), 4.50 (septet, <sup>3</sup>J = N.A., 1H, methine CH), 6.80 (app. d, <sup>3</sup>J = 8.6 Hz, 2H, Ar-o), 7.08 (app. d, <sup>3</sup>J = 8.2 Hz, 2H, Ar-m); MS (EI) m/z: 150 (M<sup>+</sup>, 19), 135 (2), 121 (2), 108 (100), 91 (11), 77 (70), 65 (12), 51 (19), 39 (22), 27 (16).

» *2-(4-Cyanophenoxy)propane*.<sup>205</sup> <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.37 (d, <sup>3</sup>J = 6.1 Hz, 6H, CH<sub>3</sub>), 4.62 (septet, <sup>3</sup>J = 6.1 Hz, 1H, methine CH), 6.85-6.97 (m, 2H, Ar C(2,6)H), 7.51-7.63 (m, 2H, Ar C(3,5)H); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 21.77 (CH<sub>3</sub>), 70.37 (CMe<sub>2</sub>), 103.36 (Ar C4), 116.02 (Ar C2, C6), 119.31 (C $\equiv$ N), 133.98 (Ar C3, C5), 161.34 (Ar C1); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 2228m (C $\equiv$ N), 1607s, 1507s, 1386w, 1297m, 1257s, 1175m, 1119m, 953m, 835m; MS (EI) m/z: 161 (M<sup>+</sup>, 10), 146 (2), 119 (100), 102 (5), 91 (14), 75 (4), 64 (12), 39 (8), 27 (5); MS (CI, NH<sub>3</sub>) m/z: 179 (M+18), 162 (M+1).

» *Phenoxycyclohexane*.<sup>206</sup> MS (EI) m/z: 176 (M<sup>+</sup>, 10), 94 (100), 77 (10), 65 (15), 55 (14), 51 (7), 41 (14), 39 (22), 27 (5).

#### 4.4.1.2.1 3-Methyloxazolidin-2-ylidene (28b)

» *3-Methyl-2-phenoxyoxazolidine*, **119a**. Oxadiazoline **33b** (84 mg, 0.49 mmol) was thermolysed with phenol (58 mg, 0.62 mmol) in 10 mL of benzene. The product, **119a**, was purified by radial chromatography, using 10%-60% ethyl acetate in hexane (55% yield). Colourless oil;  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ , slow inversion, resonance due to major isomer is underlined, A: B  $\approx$  53 : 47)  $\delta$ : 2.96 (s) & 3.12 (s) (3H,  $\text{NCH}_3$ ), 3.62 (t,  $^3J = 5.2$  Hz) & 3.73 (t,  $^3J = 5.2$  Hz) (2H,  $\text{NCH}_2$ ), 4.07 (t,  $^3J = 5.2$  Hz) & 4.14 (t,  $^3J = 5.2$  Hz) (2H,  $\text{OCH}_2$ ), 6.84-7.02 (m, 3H, Ar-o,p), 7.23-7.33 (m, 2H, Ar-m), 8.08 (s) & 8.14 (s) (1H, C(2)H);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 30.24 & 36.42 ( $\text{NCH}_3$ ), 44.29 & 49.04 ( $\text{NCH}_2$ ), 64.90 & 66.17 ( $\text{OCH}_2$ ), 114.42 & 114.56 (OPh C2, C6), 121.14 & 121.46 (OPh C4), 129.59 (OPh C3, C5), 158.13 & 158.41 (OPh C1), 162.86 & 163.25 (C2); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1771m, 1684s, 1600m, 1497s, 1382m, 1301w, 1242s, 1173w, 1081m, 1056m, 908w; MS (EI)  $m/z$ : 179 ( $\text{M}^+$ , 1), 149 (1), 120 (14), 107 (6), 91 (19), 86 (M-OPh, 100), 77 (81), 72 (21), 65 (42), 58 (84), 51 (45), 44 (81), 39 (47), 28 (36); MS (CI,  $\text{NH}_3$ )  $m/z$ : 197 ( $\text{M}+\text{NH}_4$ ) $^+$ , 180 ( $\text{M}+\text{H}$ ) $^+$ .

» *3-Methyl-2-(4-methylphenoxy)oxazolidine*, **119b**. Oxadiazoline **33b** (90 mg, 0.52 mmol) was thermolysed with p-cresol (93 mg, 0.86 mmol) in 10 mL of benzene. The product, **119b**, was purified by radial chromatography, using 20%-40% ethyl acetate in hexane (30% yield). Colourless oil;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ , slow inversion, resonance due to major isomer is underlined, A: B  $\approx$  54 : 46)  $\delta$ : 2.28 (s, 3H, Ar- $\text{CH}_3$ ), 2.95 (s) & 3.10 (s) (3H,  $\text{NCH}_3$ ), 3.60 (t,  $^3J = 5.2$  Hz) & 3.71 (t,  $^3J = 5.2$  Hz) (2H,  $\text{NCH}_2$ ),

4.03 (t,  $^3J = 5.2$  Hz) & 4.10 (t,  $^3J = 5.2$  Hz) (2H, OCH<sub>2</sub>), 6.77 (app. d,  $^3J = 8.6$  Hz, 2H, Ar C(2,6)H), 7.08 (app. d,  $^3J = 8.6$  Hz, 2H, Ar C(3,5)), 8.07 (s) & 8.13 (s) (1H, C(2)H); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 20.46 (Ar CH<sub>3</sub>), 30.18 & 36.35 (NCH<sub>3</sub>), 44.28 & 49.04 (NCH<sub>2</sub>), 65.11 & 66.34 (OCH<sub>2</sub>), 114.29 & 114.45 (OAr C2, C6), 130.00 (OAr C3, C5), 130.34 & 130.72 (OAr C4), 156.06 & 156.31 (OAr C1), 162.82 & 163.23 (C2); MS (EI)  $m/z$ : 193 (M<sup>+</sup>, 1), 149 (1), 134 (5), 119 (7), 107 (15), 91 (40), 86 (M-OPh, 100), 77 (37), 65 (28), 58 (73), 51 (16), 44 (42), 28 (19).

#### 4.4.1.2.2 3-Carbonyloxazolidin-2-ylidenes (**28c-f,j** and **113d**)

The OH insertion products of N-carbonyl oxadiazolines were hydrolytically unstable, and could therefore not be purified by chromatography. However, because of the essentially quantitative yields of carbenes produced by these oxadiazolines, products of high purity were generally obtained after the following work-up: the excess phenol was removed by washing the thermolysate, diluted to 25 mL with fresh benzene, with 4 x 5 mL of aq. NaOH (5%), followed by 5 mL of water or brine; this was followed by extraction of the combined aqueous layers with one portion of benzene, and drying over MgSO<sub>4</sub>. In a few instances, as indicated in the appropriate sub-sections below, a different work-up procedure was followed.

» *3-Formyl-2-phenoxyoxazolidine*, **124a**. Oxadiazoline **33c** (49 mg, 0.26 mmol) was thermolysed with phenol (39 mg, 0.41 mmol) in 10 mL of benzene. The usual work-up gave a colourless oil, **124a**, in 75% yield; <sup>1</sup>H-NMR (200 MHz, C<sub>6</sub>D<sub>6</sub>, slow exchange)  $\delta$ :

*ca.* 2.4-3.9 (um's, 4H, OCH<sub>2</sub>CH<sub>2</sub>N), 6.03 (s) & 6.07 (s) (1H, C(2)H), 6.85-7.40 (m, 5H, Ar), 7.90 (br.s) & 8.27 (br.s) (1H, C(O)H); <sup>13</sup>C-NMR (50 MHz, C<sub>6</sub>D<sub>6</sub>, slow exchange, resonance due to major isomer is underlined) δ: 41.12 & 42.09 (NCH<sub>2</sub>), 64.61 (OCH<sub>2</sub>), 102.91 & 104.34 (C2), 117.96 & 118.52 (OPh C2, C6), 123.18 (OPh C4), 129.79 (OPh C3, C5), 155.47 (OPh C1), 158.87 & 159.27 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1699s (C=O), 1591m, 1494m, 1415m, 1385m, 1356m, 1297w, 1205s, 1117w, 1083m, 1030w, 1010m, 991m, 953w, 876w; MS (EI) m/z: 193 (M<sup>+</sup>, 1), 134 (2), 107 (1), 100 (M-OPh, 100), 94 (27), 78 (8), 72 (68), 65 (28), 51 (7), 44 (72), 39 (31), 29 (15); MS (CI, NH<sub>3</sub>) did not give useful information.

» *3-Acetyl-2-phenoxyoxazolidine*, **124b**. Oxadiazoline **33d** (96 mg, 0.48 mmol) was thermolysed with phenol (59 mg, 0.63 mmol) in 10 mL of benzene. The usual work-up yielded the product in 89% yield. All attempts to crystallize the resulting oil, which was essentially pure **124b**, failed; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, slow exchange) δ: 1.85 (s) & 2.15 (s) (3H, CH<sub>3</sub>), 3.58-3.92 (m, 2H, NCH<sub>2</sub>), 4.20-4.52 (m, 2H, OCH<sub>2</sub>), 6.39 (s) & 6.66 (s) (1H, C(2)H), 7.06-7.17 (m, 3H, Ar-o,p), 7.25-7.40 (m, 2H, Ar-m); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>, slow exchange, resonance due to major isomer is underlined) δ: 22.41 & 22.79 (CH<sub>3</sub>), 43.27 & 44.65 (NCH<sub>2</sub>), 64.83 & 65.31 (OCH<sub>2</sub>), 103.84 & 104.34 (C2), 117.52 & 118.21 (OPh C2, C6), 122.96 & 123.24 (OPh C4), 129.41 & 129.68 (OPh C3, C5), 154.93 & 155.45 (OPh C1), 168.12 & 168.43 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1735w, 1683s (C=O), 1594m, 1494m, 1406m, 1357m, 1210s, 1099w, 1061w, 1007m, 980m, 946m; MS

(EI)  $m/z$ : 207 ( $M^+$ , 2), 135 (3), 114 (M-OPh, 65), 94 (29), 84 (13), 72 (100), 65 (18), 49 (20), 44 (39); MS (CI,  $NH_3$ )  $m/z$ : 208 ( $M+H$ ) $^+$ .

» **3-Methacryloyl-2-phenoxyoxazolidine, 124c.** Oxadiazoline 33e (71 mg, 0.32 mmol) was thermolysed with phenol (44 mg, 0.68 mmol) in 10 mL of benzene. The usual work-up gave a viscous, colourless oil, **124c**, in 97% yield;  $^1H$ -NMR (200 MHz,  $CDCl_3$ , slow exchange, some peaks are broad)  $\delta$ : 2.00 (app t,  $^4J = 1.3$  Hz, 3H,  $CH_3$ ), 3.75-3.87 (m, 2H,  $NCH_2$ ), 4.20-4.44 (m, 2H,  $OCH_2$ ), 5.31 (br.s, 1H,  $=CH_2$ ), 5.42 (app t,  $^4J = 0.9$  Hz, 1H,  $=CH_2$ ), 6.51 (br.s, 1H, C(2)H), 7.00-7.13 (m, 3H, Ar-o,p), 7.25-7.39 (m, 2H, Ar-m);  $^{13}C$ -NMR (50 MHz,  $CDCl_3$ )  $\delta$ : 19.98 ( $CH_3$ ), 43.31 ( $NCH_2$ ), 64.52 ( $OCH_2$ ), 105.23 (C2), 117.62 and 117.82 (OPh C2, C6 and  $=CH_2$ ), 123.02 (OPh C4), 129.85 (OPh C3, C5), 141.66 ( $=CR_2$ ), 155.69 (OPh C1), 169.09 (C=O); IR ( $CCl_4$ )  $cm^{-1}$ : 1734w, 1667s (C=O), 1632m, 1591w, 1496m, 1454w, 1396m, 1370m, 1200s, 1118w, 1084w, 1007m, 982s, 948m, 891; MS (EI) did not give useful information; MS (CI,  $NH_3$ )  $m/z$ : 234 ( $M+H$ ) $^+$ .

» **2-(4-Cyanophenoxy)-3-methacryloyloxazolidine, 124d.** Oxadiazoline 33e (100 mg, 0.44 mmol) was thermolysed with 4-cyanophenol (62 mg, 0.52 mmol) in 10 mL of benzene. A partially crystalline oil (84% yield) resulted from the usual work-up;  $^1H$ -NMR (200 MHz,  $C_6D_6$ , slow exchange)  $\delta$ : 1.81 (s, 3H,  $CH_3$ ), *ca.* 3.0-4.0 (um, 4H,  $NCH_2$ ,  $OCH_2$ ), 4.89 (br.s, 1H,  $=CH_2$ ), 5.11 (br.s, 1H,  $CH_2$ ), 6.14 (br.s) & 6.38 (br.s) (1H, C(2)H), 6.55-7.20 (um, 4H, Ar);  $^{13}C$ -NMR (50 MHz,  $C_6D_6$ )  $\delta$ : 19.84 ( $CH_3$ ), 43.47 (br.,  $NCH_2$ ), 65.11 ( $OCH_2$ ), 104.69 (OAr C4), 106.62 (C2), 117.53 (OAr C2, C6), 118.12 ( $=CH_2$ ), 122.66 ( $C\equiv N$ ), 134.00 (OAr C3, C5), 141.31 ( $=CR_2$ ), 158.35 (OAr C1), 169.06

(C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: N.A.; MS (EI) m/z: 140 (M-OAr, 35), 119 (6), 84 (5), 69 (acylation, 100), 64 (4), 49 (10), 41 (72); MS (CI, NH<sub>3</sub>) m/z: 276 (M+NH<sub>4</sub>)<sup>+</sup>, 259 (M+H)<sup>+</sup>.

» *3-Benzoyl-2-phenoxyoxazolidine, 124e*. Oxadiazoline 33f (105 mg, 0.40 mmol) was thermolysed with phenol (72 mg, 0.77 mmol) in 10 mL of benzene. After removal of the solvent and volatile products on the rotary evaporator, **124e** solidified upon addition of 20% ethyl acetate in hexane. Recrystallization from the same solvent mixture yielded a white solid, Mp 89-91 °C (76%); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, slow exchange) δ: 3.70-4.10 (um, 2H, NCH<sub>2</sub>), 4.10-4.45 (um, 2H, OCH<sub>2</sub>), 6.21 (br.s, 1H, C(2)H), 6.70-7.10 (um, 3H, Ar), 7.10-7.45 (um, 5H, Ar), 7.55-7.65 (m, 2H, Ar); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 43.48 (NCH<sub>2</sub>), 64.60 (OCH<sub>2</sub>), 105.19 (C2), 117.79 (OPh C2, C6), 123.12 (OPh C4), 127.58 (benzoyl C2, C6), 128.42 (benzoyl C3, C5), 129.52 (OPh C3, C5), 130.92 (benzoyl C4), 135.45 (benzoyl C1), 154.67 (OPh C1), 169.00 (C=O); IR (KBr) cm<sup>-1</sup>: 1660s (C=O), 1591s, 1493w, 1448w, 1399s, 1201m, 1168w, 1115w, 1084m, 951m, 933m, 887m, 791w, 770w, 725w; MS (EI) m/z: 269 (M<sup>+</sup>, 2), 198 (2), 176 (M-OPh, 14), 147 (18), 117 (20), 105 (PhCO<sup>+</sup>, 100), 94 (21), 84 (42), 77 (42), 49 (54); MS (CI, NH<sub>3</sub>) m/z: 270 (M+H)<sup>+</sup>.

» *2-(4-Cyanophenoxy)-3-benzoyloxazolidine, 124f*. Oxadiazoline 33f (107 mg, 0.41 mmol) was thermolysed with 4-cyanophenol (59 mg, 0.49 mmol) in 10 mL of benzene. The usual work-up gave **124f** as a white solid (90% yield), Mp N.A.; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, slow exchange) δ: *ca.* 3-4 (um, 4H, NCH<sub>2</sub>, OCH<sub>2</sub>), *ca.* 5.8-8.3 (um, 10H, C(2)H, Ar); <sup>13</sup>C-NMR (50 MHz, C<sub>6</sub>D<sub>6</sub>, slightly impure sample, tentative assignments) δ: 44.06



(br., NCH<sub>2</sub>), 65.10 (OCH<sub>2</sub>), 104.96 (OAr C4), 106.74 (C2), 117.57 (OAr C2, C6), 122.74 (C≡N), *ca.* 128 (overlapped with solvent triplet, aroyl C2, C6 and C3, C5), 131.04 (aroyl C4), 135.83 (aroyl C1), 133.88 (OAr C3, C5), 158.19 (OAr C1), 168.6 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 2230m (C≡N), 1751s, 1672s (C=O), 1605s, 1507m, 1451w, 1384s, 1257m, 1210s, 1172m, 1080m, 1056m, 1022w, 962s, 889w, 836w; MS (EI) *m/z*: 176 (M-OAr, 38), 105 (PhCO<sup>+</sup>, 100), 90 (6), 77 (32), 51 (10); MS (CI, NH<sub>3</sub>) *m/z*: 295 (M+H)<sup>+</sup>.

» *3-Methoxycarbonyl-2-phenoxyoxazolidine*, **124g**. Oxadiazoline **33j** (55 mg, 0.26 mmol) was thermolysed with phenol (30 mg, 0.32 mmol) in 10 mL of benzene. The usual work-up gave a colourless oil, **124g**, in quantitative yield; <sup>1</sup>H-NMR (200 MHz, C<sub>6</sub>D<sub>6</sub>, slow exchange) δ: *ca.* 2.9-4.1 (um's, 7H, NCH<sub>2</sub>, OCH<sub>2</sub>, CH<sub>3</sub>), 6.46 (br.s) & 6.74 (br.s) (1H, C(2)H), *ca.* 6.8-7.4 (um, 5H, Ar); <sup>13</sup>C-NMR (50 MHz, C<sub>6</sub>D<sub>6</sub>, slow exchange) δ: 43.83 (NCH<sub>2</sub>), 52.42 (CH<sub>3</sub>), 64.73 & 65.14 (OCH<sub>2</sub>), 104.52 & 105.52 (C2), 118.18 (OPh C2, C6), 122.97 (OPh C4), 129.79 (OPh C3, C5), 153.38 and 156.35 (OPh C1 and C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1728s (C=O), 1593m, 1494m, 1451s, 1391s, 1301w, 1212s, 1137w, 1076m, 987s, 692; MS (EI) *m/z*: 223 (M<sup>+</sup>, < 1), 192 (2), 130 (M-OPh, 100), 94 (8), 78 (5), 70 (5), 65 (17), 58 (35), 39 (16), 30 (8); MS (CI, NH<sub>3</sub>) *m/z*: did not show (M+H)<sup>+</sup> or (M+NH<sub>4</sub>)<sup>+</sup>.

**Thermolysis of 106d with phenol.** Oxadiazoline **106d** (100 mg, 0.36 mmol) was thermolysed with phenol (52 mg, 0.55 mmol) in 10 mL of benzene. The product obtained after the usual work-up was almost pure **124h** (100 mg, 97%). Crystals were obtained from 10% ethyl acetate in hexane. An attempt was made to purify another sample of

**124h**, obtained in a similar way, using radial chromatography (20-60% ethyl acetate in hexane); the major band collected was found to consist initially of a mixture of **152** and **153**. The latter was completely converted to **152** when the mixture was left in  $\text{CDCl}_3$  over one month, at or below room temperature.

**Thermolysis of 106e with phenol.** Oxadiazoline **106e** (70 mg, 0.22 mmol) was thermolysed with phenol (47 mg, 0.50 mmol) in 10 mL of benzene. The usual work-up gave a thick oil which was found ( $^1\text{H}$ - and  $^{13}\text{C}$ -NMR) to consist of a mixture of **124h** and cyclohexanone.

» *3-Benzoyl-2-phenoxytetrahydro-2H-1,3-oxazine*, **124h**. White solid, Mp ~83-92 °C;  $^1\text{H}$ -NMR (300 MHz,  $\text{C}_6\text{D}_6$ , slow exchange)  $\delta$ : 0.86-1.12 (um, 1H,  $\text{CCH}_2\text{C}$ ), 1.63-1.85 (um, 1H,  $\text{CCH}_2\text{C}$ ), 3.34-3.53 (um, 2H,  $\text{NCH}_2$ ), 3.81-4.00 (um, 1H,  $\text{OCH}_2$ ), 4.16-4.35 (um, 1H,  $\text{OCH}_2$ )<sup>i</sup>, 6.80-7.25 (um, 9H) and 7.40-7.65 (um, 2H) (Ar and C(2)H);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{C}_6\text{D}_6$ , slow exchange)  $\delta$ : 24.28 ( $\text{CCH}_2\text{C}$ ), 37.97<sup>ii</sup> ( $\text{NCH}_2$ ), 59.49 ( $\text{OCH}_2$ ), 99.66<sup>iii</sup> (C2), 117.26 (OPh C2, C6), 122.74 (OPh C4), *ca.* 127.5 (benzoyl C2, C6, under solvent triplet), 128.57 (benzoyl C3, C5), 129.85 (OPh C3, C5), 130.21 (benzoyl C4), 135.68 (benzoyl C1), 155.58 (OPh C1), 169.36 ( $\text{C}=\text{O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1732w, 1663s ( $\text{C}=\text{O}$ ), 1597m, 1496m, 1448w, 1416m, 1381m, 1356w, 1333w, 1287m, 1218m, 1196m, 1173m, 1090m, 1017m, 977s, 930m, 903w, 853w; MS (EI)  $m/z$  266 (2), 190 (M-OPh, 66), 172

<sup>i</sup> One of the  $\text{OCH}_2$  proton signals disappears at room temperature; at 90°C, it appears at 4.16-4.35 (um).

<sup>ii</sup> At room temperature,  $\text{NCH}_2$  signal appears as a very wide resonance in the range 35-40 ppm; at 77°C, it is a slightly broadened singlet at 37.97 ppm.

<sup>iii</sup> Taken at 77°C; at room temperature, the signal is broad, in the range 97-102 ppm.

(4), 105 ( $\text{PhCO}^+$ , 100), 94 (6), 84 (8), 77 (23), 65 (5), 49 (12); MS (CI,  $\text{NH}_3$ )  $m/z$ : 284 ( $\text{M}+\text{H}$ )<sup>+</sup>.

» *N*-[3-(Formyloxy)propyl]-benzamide, **152**.<sup>200</sup> Colourless oil;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.90-2.08 (m, 2H,  $\text{CCH}_2\text{C}$ ), 3.53 (app.q,  $^3J = 6.4$  Hz, 2H,  $\text{NCH}_2$ ), 4.30 (t,  $^3J = 6.1$  Hz, 2H,  $\text{OCH}_2$ ), 6.66 (br.s., 1H, NH), 7.30-7.65 (m, 3H, Ar-m,p), 7.70-7.85 (m, 2H, Ar-o), 8.10 (s, 1H,  $\text{C}(\text{O})\text{H}$ );  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 28.61 ( $\text{CCH}_2\text{C}$ ), 36.58 ( $\text{NCH}_2$ ), 61.48 ( $\text{OCH}_2$ ), 126.82 (Ar C2, C6), 128.55 (Ar C3, C5), 131.47 (Ar C4), 134.36 (Ar C1), 161.21 ( $\text{HC}=\text{O}$ ), 167.61 ( $\text{PhC}=\text{O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 3454m (NH), 1728s ( $\text{OC}=\text{O}$ ), 1674s ( $\text{NC}=\text{O}$ ), 1605w, 1580w, 1519s, 1487m, 1304w, 1278m, 1176s, 913w, 711m; MS (EI)  $m/z$ : 207 ( $\text{M}^+$ , 3), 162 (14), 134 (8), 105 ( $\text{PhCO}^+$ , 100), 77 (53), 51 (18); MS (CI,  $\text{NH}_3$ )  $m/z$ : 225 ( $\text{M}+\text{NH}_4$ )<sup>+</sup>, 208( $\text{M}+\text{H}$ )<sup>+</sup>.

» *N*-[3-(Hydroxy)propyl]-*N*-formylbenzamide, **153**. Identity is uncertain; not obtained pure, as mixture with **152**.  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.85-*ca.*2.0 (m, 2H,  $\text{CCH}_2\text{C}$ ), 3.64 (t,  $^3J = 5.7$  Hz, 2H,  $\text{NCH}_2$ ), 4.04 (t,  $^3J = 6.4$  Hz, 2H,  $\text{OCH}_2$ ), *ca.* 7.30-7.85 (Ar), 8.96 (s, 1H,  $\text{C}(\text{O})\text{H}$ );  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ , partial spectrum)  $\delta$ : 30.70 ( $\text{CCH}_2\text{C}$ ), 37.36 ( $\text{NCH}_2$ ), 59.22 ( $\text{OCH}_2$ ), 128.85 (Ar), 129.00 (Ar), 132.35 (Ar), 164.75 ( $\text{HC}=\text{O}$ ), 172.90 ( $\text{PhC}=\text{O}$ ).

#### 4.4.1.2.3 3-(Phenylsulfonyl)oxazolidin-2-ylidene (28k)

**Thermolysis of 33k with phenol.** Oxadiazoline **33k** (143 mg, 0.48 mmol) was thermolysed at 90 °C for 48 h in the presence of phenol (69 mg, 0.74 mmol) in 10 mL of

benzene. This was followed by base-washing of the crude product mixture as described in Section 4.4.1.2.2. Separation of the thermolysate by radial chromatography (10-30% ethyl acetate in hexane) gave compounds **114k**, **154**, unidentified compound **U1**, and another unidentified product briefly described in Section 2.4.1.2.3.

» *N-Formyl-N-(2-hydroxyethyl)benzenesulfonamide*, **154**.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ , slow exchange)  $\delta$ : 3.20-3.36 (m, 2H,  $\text{NCH}_2$ ), 4.04-4.26 (m, 2H,  $\text{OCH}_2$ ), 5.03 (br.s., 1H, OH), 7.44-7.93 (m, *ca.* 6H, Ar and  $\text{C(O)H}$ );  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ , only peaks from major conformer are given)  $\delta$ : 41.99 ( $\text{NCH}_2$ ), 62.41 ( $\text{OCH}_2$ ), 126.99 (Ar C2, C6), 129.24 (Ar C3, C5), 132.91 (Ar C4), 139.83 (Ar C1), 160.42 ( $\text{C=O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 3425-3000 (OH), 1736s ( $\text{C=O}$ ), 1449w, 1417w, 1345m ( $\text{NSO}_2$ ), 1264m, 1165s ( $\text{NSO}_2$ ), 1097m, 1027w, 950w, 909w, 858w; MS (EI)  $m/z$ : 183 (16), 170 (43), 141 ( $\text{PhSO}_2^+$ , 57), 119 (6), 92 (4), 77 (100), 51 (22), 31 (5); MS (CI,  $\text{NH}_3$ )  $m/z$ : 247 ( $\text{M}+\text{NH}_4$ ) $^+$ , 230 ( $\text{M}+\text{H}$ ) $^+$ .

» *Unidentified product U1*. Obtained as a partially crystalline compound;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.76 (t,  $^3J = 6.2$  Hz, 2H,  $\text{NCH}_2$ ), 4.12 (t,  $^3J = 6.2$  Hz, 2H,  $\text{OCH}_2$ ), 7.49-7.93 (m, 10H, Ar), 9.01 (s, 1H,  $\text{C(O)H}$ );  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 40.94 ( $\text{NCH}_2$ ), 65.76 ( $\text{OCH}_2$ ), 127.49 (Ar C2, C6), 127.97 (Ar C2, C6), 129.33 (Ar C3, C5), 129.89 (Ar C3, C5), 134.04 (Ar C4), 134.63 (Ar C4), 135.37 (Ar C1), 137.32 (Ar C1), 160.95 ( $\text{C=O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1709s, 1449w, 1375s ( $\text{NSO}_2$ ), 1318w, 1264m, 1230w, 1181s ( $\text{NSO}_2$ ), 1095w, 997m, 970m, 907m; MS (EI)  $m/z$ : (305?, 5), 228 (7), 212 (18), 170 (18), 141 ( $\text{PhSO}_2^+$ , 70), 94 (49), 84 (18), 77 (100), 51 (26), 45 (41); MS (CI,  $\text{NH}_3$ )  $m/z$ : (387?), 247, 229.

#### 4.4.2 Reactions with Methyl or Phenyl Isocyanate

» *Spiro-fused hydantoin 120a*. Oxadiazoline **33b** (102 mg, 0.60 mmol) was thermolysed with MeNCO (85 mg, 1.5 mmol) in 10 mL of benzene. The product, **120a**, was purified by radial chromatography, using 30%-40% ethyl acetate in hexane, and obtained in 44% yield. White solid, Mp 71-73 °C; <sup>1</sup>H-NMR (200 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 1.97 (s, 3H, oxazolidine NCH<sub>3</sub>), 2.65 (s, 3H, CH<sub>3</sub>), 2.73 (s, 3H, CH<sub>3</sub>), *ca.* 2.52-2.77 (overlapped m, 1H, NCH<sub>2</sub>), 3.10-3.27 (m, 1H, NCH<sub>2</sub>), 3.57-3.72 (m, 1H, OCH<sub>2</sub>), 3.77-3.90 (m, 1H, OCH<sub>2</sub>); <sup>13</sup>C-NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 23.06 (CH<sub>3</sub>), 23.43 (CH<sub>3</sub>), 32.69 (CH<sub>3</sub>), 51.18 (NCH<sub>2</sub>), 65.17 (OCH<sub>2</sub>), 101.67 (spiro C), 155.33 (NC(O)N), 170.24 (NC(O)C); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1785m (C=O), 1729s (C=O), 1461s, 1419m, 1392m, 1299m, 1267w, 1231w, 1184w, 1144w, 1079s, 1015w, 993w, 973w, 949w; MS (EI) m/z: 199 (M<sup>+</sup>, 1), 171 (M-CO, 4), 154 (16), 141 (4), 127 (9), 113 (92), 99 (2), 86 (21), 70 (36), 57 (100), 42 (71), 28 (36); MS (CI, NH<sub>3</sub>) m/z: 200 (M+H)<sup>+</sup>; anal. calcd. for C<sub>8</sub>H<sub>13</sub>N<sub>3</sub>O: C, 48.23; H, 6.58; N, 21.09; measured: C, 48.03; H, 6.81; N, 21.00.

» *Spiro-fused hydantoin 120b*. Oxadiazoline **33b** (101 mg, 0.59 mmol) was thermolysed with PhNCO (168 mg, 1.4 mmol) in 10 mL of benzene. The product, **120b**, precipitated from crude thermolysate by addition of 30% ethyl acetate in hexane and, after various unsuccessful attempts to recrystallize it, was washed using the same solvent mixture (27% yield). White solid, Mp 156-158 °C; <sup>1</sup>H-NMR (200 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 2.20 (s, 3H, CH<sub>3</sub>), 2.47-2.58 (m, 1H, NCH<sub>2</sub>), 3.10-3.28 (m, 1H, NCH<sub>2</sub>), 3.50-3.68 (m, 1H, OCH<sub>2</sub>), 3.71-3.86 (m, 1H, OCH<sub>2</sub>), 6.93-*ca.*7.35 (m, 6H, Ar-m,p, overlapped with solvent), 7.46-7.58 (m,

2H, Ar-o), 7.58-7.70 (m, 2H, Ar-o);  $^{13}\text{C}$ -NMR (50 MHz, acetone- $d_6$ )  $\delta$ : 33.28 ( $\text{CH}_3$ ), 52.02 ( $\text{NCH}_2$ ), 66.09 ( $\text{OCH}_2$ ), 103.42 (spiro C), 119.37 (Ar), 122.80 (Ar), 127.54 (Ar), 129.55 (Ar), 129.67 (Ar), 132.53 (Ar), 135.11 (Ar), 153.72 ( $\text{NC}(\text{O})\text{N}$ ), 172.14 ( $\text{NC}(\text{O})\text{C}$ ) (two Ar peaks overlap); IR (KBr)  $\text{cm}^{-1}$ : 1786w ( $\text{C}=\text{O}$ ), 1730s ( $\text{C}=\text{O}$ ), 1647w, 1596w, 1494m, 1405m, 1372w, 1278w, 1188w, 1163w, 1069w, 941w, 760w; MS (EI)  $m/z$ : 323 ( $\text{M}^+$ , 3), 292 (1), 212 (3), 203 (6), 176 (30), 162 (7), 127 (100), 119 ( $\text{PhNCO}^+$ , 18), 105 (6), 93 (22), 85 (18), 77 (11), 57 (16); MS (CI,  $\text{NH}_3$ )  $m/z$ : 324 ( $\text{M}+\text{H}$ ) $^+$ ; HRMS calcd. for  $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_3$  ( $\text{M}^+$ ):  $m/z$  323.1270, obsd  $m/z$  323.1262.

» *Spiro-fused hydantoin 120c*. Oxadiazoline **33d** (101 mg, 0.51 mmol) was thermolysed with  $\text{PhNCO}$  (137 mg, 1.2 mmol) in 10 mL of benzene. The product could not be purified by chromatography due to its low solubility in most common solvents. The crude oil crystallized in 20% ethyl acetate in hexane to give **120c**, as a slightly impure solid, in 87% yield. Mp (good crystals) 132-133  $^{\circ}\text{C}$ ;  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.62 (s, 3H,  $\text{CH}_3$ ), 3.52-3.70 (m, 1H,  $\text{NCH}_2$ ), 4.03-4.18 (m, 1H,  $\text{NCH}_2$ ), 4.23-4.54 (m, 2H,  $\text{OCH}_2$ ), 7.08-7.55 (m, 10H, Ar);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 24.00 ( $\text{CH}_3$ ), 43.76 ( $\text{NCH}_2$ ), 68.69 ( $\text{OCH}_2$ ), 109.88 (spiro C), 119-139 (Ar, overlapped with solvent), 157.14 ( $\text{NC}(\text{O})\text{N}$ ), 164.80 ( $\text{NC}(\text{O})\text{C}$ ), 167.64 ( $\text{NC}(\text{O})\text{CH}_3$ ); IR (KBr)  $\text{cm}^{-1}$ : 1735s ( $\text{C}=\text{O}$ ), 1664m, 1598m, 1557m, 1500m, 1440m, 1411m, 1322m, 1266w, 1201w, 1169w, 1138w, 1111m, 1018w, 980w, 845w, 755m; MS (EI)  $m/z$ : 248 (2), 220 (52), 217 (3), 178 (1), 146 (2), 133 (1), 119 ( $\text{PhNCO}^+$ , 100), 101 (24), 91 (22), 77 (3), 71 (18), 64 (11), 56 (23), 51 (4), 42 (13), 28 (4); MS (CI,  $\text{NH}_3$ ) did not give useful information.

» *Spiro-fused hydantoin 120d*. Oxadiazoline 33e (115 mg, 0.51 mmol) was thermolysed with PhNCO (136 mg, 1.1 mmol) in 10 mL of benzene. Washing of the resulting product with ethyl acetate/hexane resulted in a pale yellow solid (**120d**, 72% yield). A few crystals obtained from recrystallization in the same solvent mixture had a Mp of 240-241 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.63 (s, 3H, CH<sub>3</sub>), 3.48-3.63 (m, 1H, NCH<sub>2</sub>), 4.02-4.13 (m, 1H, NCH<sub>2</sub>), 4.25-4.38 (m, 1H, OCH<sub>2</sub>), 4.43-4.54 (m, 1H, OCH<sub>2</sub>), 5.22 (s, 1H, =CH<sub>2</sub>), 5.29 (s, 1H, =CH<sub>2</sub>), 6.64 (d, <sup>3</sup>J = 7.5 Hz, 2H, Ar), 6.85-7.60 (m, 8H, Ar); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 20.20 (CH<sub>3</sub>), 43.82 (NCH<sub>2</sub>), 69.75 (OCH<sub>2</sub>), 109.00 (spiro C), 119-130 (overlapping signals) and 131.05 and 134.08 (=CH<sub>2</sub> and Ar), 145.83 (=CR<sub>2</sub>), 156.17 (NC(O)N), 157.32 (methacryloyl C=O), 163.57 (NC(O)C); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1805w (hydantoin C=O), 1747s (hydantoin C=O), 1679m (methacryloyl C=O), 1624w, 1598w, 1502w, 1438w, 1400m, 1322m, 1246w, 1167m, 1138w, 1107w, 1080m, 1050m, 911w, 853w; MS (EI) m/z: 377 (M<sup>+</sup>, 3), 258 (5), 230 (32), 217 (26), 202 (6), 173 (22), 146 (10), 139 (12), 119 (PhNCO<sup>+</sup>, 100), 112 (15), 98 (11), 91 (40), 77 (12), 69 (86), 64 (16), 42 (62); MS (CI, NH<sub>3</sub>) m/z: 378 (M+H)<sup>+</sup>.

» *Spiro-fused hydantoin 120e*. Oxadiazoline 33f (90 mg, 0.35 mmol) was thermolysed with PhNCO (132 mg, 1.1 mmol) in 10 mL of benzene. The sparingly-soluble **120e** crystallized from the crude thermolysate, over time, after addition of ethyl acetate, and was recrystallized from the same solvent (76% yield). White solid, Mp 151-152 °C; <sup>1</sup>H-NMR (300 MHz, acetone-d<sub>6</sub>) δ: 3.72-3.86 (m, 1H, NCH<sub>2</sub>), 4.13-4.28 (m, 1H, NCH<sub>2</sub>), 4.47-4.60 (m, 1H, OCH<sub>2</sub>), 4.60-4.73 (m, 1H, OCH<sub>2</sub>), 6.62-6.74 (m, 2H, Ar), 6.95-7.06

(m, 1H, Ar), 7.13-7.50 (m, 12H, Ar);  $^{13}\text{C}$ -NMR (75 MHz, acetone- $d_6$ )  $\delta$ : 44.73 (NCH<sub>2</sub>), 70.88 (OCH<sub>2</sub>), 110.53 (spiro C), 121.80 (Ar), 124.45 (Ar), 127.43 (Ar), 128.79 (Ar), 129.13 (Ar), 129.18 (Ar), 129.63 (Ar), 129.94 (Ar), 130.23 (Ar), 131.85 (Ar), 132.74 (Ar), 147.28 (Ar), 156.31 (NC(O)N), 157.79 (PhC(O)N), 164.41 (NC(O)C); IR (KBr)  $\text{cm}^{-1}$ : 1796w (hydantoin C=O), 1741s (hydantoin C=O), 1667m (PhC=O), 1594w, 1501w, 1451w, 1398m, 1326w, 1292w, 1240w, 1168w, 1141w, 1111w, 1079m, 1043m, 911w, 852w, 768w, 748w; MS (EI)  $m/z$ : 216 (34), 189 (8), 146 (8), 119 (PhNCO<sup>+</sup>, 100), 105 (PhCO<sup>+</sup>, 57), 98 (13), 91 (28), 86 (37), 84 (56), 77 (38), 70 (37); anal. calcd. for C<sub>24</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>: C, 69.72; H, 4.63; measured: C, 69.33; H, 4.86.

» *Spiro-fused hydantoin 120f*. Oxadiazoline 106d (100 mg, 0.36 mmol) was thermolysed with MeNCO (54 mg, 0.95 mmol) in 10 mL of benzene. The product, 120f, crystallized from the crude upon addition of ethyl acetate/hexane. The crystals were collected and washed with 10% ethyl acetate in hexane. White solid (78% yield); Mp 87-89 °C;  $^1\text{H}$ -NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.57-1.72 (m, 1H, CCH<sub>2</sub>C), 1.90-2.13 (m, 1H, CCH<sub>2</sub>C), 3.12 (s, 3H, CH<sub>3</sub>), 3.25 (s, 3H, CH<sub>3</sub>), *ca.* 2.98-3.32 (overlapped m, 1H, NCH<sub>2</sub>), 4.02-4.22 (m, 3H, NCH<sub>2</sub>, OCH<sub>2</sub>), 7.37-7.62 (m, 5H, Ar);  $^{13}\text{C}$ -NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 23.89 (CH<sub>3</sub>), 24.74 (CH<sub>3</sub>), 35.22 and 35.36 (CCH<sub>2</sub>C and NCH<sub>2</sub>), 63.62 (OCH<sub>2</sub>), 126.80 (Ar), 128.16 (Ar), 128.52 (Ar), 131.48 (Ar), 135.23 (Ar), 154.90 (NC(O)N), 169.05 (PhC(O)N), 174.48 (NC(O)C) (some aromatic Cs overlap); IR (CCl<sub>4</sub>)  $\text{cm}^{-1}$ : 1794w (hydantoin C=O), 1734s (hydantoin C=O), 1673m (PhC=O), 1465m, 1396w, 1334w, 1298w, 1273w, 1231w, 1169w, 1140w, 1081w, 1056m, 962w, 924w; MS (EI)  $m/z$ : 303 (M<sup>+</sup>, 1), 198 (2),



190 (4), 169 (100), 141 (9), 118 (6), 113 (5), 105 ( $\text{PhCO}^+$ , 13), 84 (14), 77 (15), 56 (15); MS (CI,  $\text{NH}_3$ )  $m/z$ : 304 ( $\text{M}+\text{H}^+$ ); anal. calcd. for  $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4$ : C, 59.40; H, 5.65; measured: C, 59.20; H, 6.00.

**Thermolysis of 33k with methyl isocyanate.** In one case, **33k** was thermolysed at 90 °C for 48 h in the presence of excess MeNCO in 10 mL of benzene. Since the solution was cloudy, water was azeotroped out before thermolysis although some water remained after this procedure (a second portion of MeNCO was added afterwards since the initial portion may have been distilled off). Separation of the products by radial chromatography, using 10-40% ethyl acetate in hexane, gave compounds **156** and **U1** (see Section 4.4.1.2.3) in addition to **114k**. This thermolysis was later repeated using carefully dried **33k** and, in this case, the only recognizable product was **114k**.

» *Oxazolidine 156.*  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.29-3.39 (m, 2H,  $\text{NCH}_2$ ), 3.40-3.54 (m, 1H,  $\text{OCH}_2$ ), 3.55-3.75 (m, 2H,  $\text{NCH}_2$ ), 4.01-4.12 (m, 1H,  $\text{OCH}_2$ ), 4.21-4.40 (m, 2H,  $\text{OCH}_2$ ), 6.60 (s, 1H, oxazolidine C(2)H), 7.48-7.78 (m, *ca.* 6H, Ar-m,p), 7.90-8.02 (m, *ca.* 5H, Ar-o, C(O)H);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 40.47 ( $\text{NCH}_2$ ), 46.61 ( $\text{NCH}_2$ ), 62.08 ( $\text{OCH}_2$ ), 65.72 ( $\text{OCH}_2$ ), 96.33 (oxazolidine C2), 127.83 (Ar C2, C6), 127.97 (Ar C2, C6), 129.00 (Ar C3, C5), 129.57 (Ar C3, C5), 133.16 (Ar C4), 133.80 (Ar C4), 136.61 (Ar C1), 139.19 (Ar C1), 160.61 (C=O); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1730s, 1476w, 1449w, 1412w, 1366s ( $\text{NSO}_2$ ), 1270w, 1175s ( $\text{NSO}_2$ ), 1092w, 999w, 937w, 909w; MS (EI)  $m/z$ : 212 (34), 141 ( $\text{PhSO}_2^+$ , 30), 77 (100); MS (CI,  $\text{NH}_3$ )  $m/z$ : 459 ( $\text{M}+\text{NH}_4^+$ ), 442 ( $\text{M}+\text{H}^+$ ).

#### 4.4.3 Reactions with Alkynes

**Thermolysis of 33d with DMAD.** Oxadiazoline 33d (99 mg, 0.50 mmol) was thermolysed with DMAD (158 mg, 1.1 mmol) in 12 mL of benzene. <sup>1</sup>H-NMR analysis of the crude revealed 157d to be the major product. Repeated separations by radial chromatography, using mixtures of ethyl acetate and hexane as elution solvent, gave the five 1: 2 (carbene : DMAD) adducts described below, but the major product could not be recovered, presumably due to its decomposition on the silica plate.

» *Oxazoline 157d.* Not isolated, data from crude thermolysate; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.45 (s, 3H, C(O)CH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 4.03 (app. dt, J ~ 1 Hz, <sup>3</sup>J = 9.4 Hz, 2H, NCH<sub>2</sub>), 4.37 (app. dt, J ~ 1 Hz, <sup>3</sup>J = 9.4 Hz, 2H, OCH<sub>2</sub>); MS (EI) m/z: 255 (M<sup>+</sup>, 7), 240 (M-CH<sub>3</sub>, 100), 224 (M-OCH<sub>3</sub>, 27), 208 (55), 196 (19), 182 (20), 168 (20), 154 (32), 140 (8), 125 (37), 111 (62), 97 (34), 80 (17), 66 (26), 59 (28), 53 (18), 43 (64), 39 (20), 29 (11).

» *Spiro-fused dihydrofuran 162b.* Pale yellow oil, 22% yield; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.83 (s, 3H, C(O)CH<sub>3</sub>), 3.68 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), *ca.* 3.60-3.90 (overlapped m, 2H, NCH<sub>2</sub>), 4.27-4.57 (m, 2H, OCH<sub>2</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 19.07 (C(O)CH<sub>3</sub>), 45.34 (NCH<sub>2</sub>), 51.60 (OCH<sub>3</sub>), 52.32 (OCH<sub>3</sub>), 52.57 (OCH<sub>3</sub>), 53.01 (OCH<sub>3</sub>), 67.65 (OCH<sub>2</sub>), 81.97 (alkyne), 104.08 (alkyne), 114.03 (C(C)(C)(O)(O)), 125.22 (alkene), 140.89 and 144.04 (alkene and spiro C), 161.49 (C=O), 162.43 (C=O), 163.73 (C=O), 164.47 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1740s (C=O's), 1643m, 1559m, 1437m, 1386w, 1322m, 1288s, 1254s, 1223s, 1164m, 1126w,

1082m, 1045m; MS (EI)  $m/z$ : 366 (M-OCH<sub>3</sub>, 6), 354 (M-C(O)CH<sub>3</sub>, 100), 338 (M-CO<sub>2</sub>CH<sub>3</sub>, 7), 237 (6), 179 (10), 84 (35), 59 (12), 49 (21); MS (CI, NH<sub>3</sub>)  $m/z$ : 415 (M+NH<sub>4</sub>)<sup>+</sup>, 398 (M+H)<sup>+</sup>.

» *Spiro-fused dihydrofuran 162c*. Isolated as a partially solidified oil in 29% yield; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.28 (s, 3H, C(O)CH<sub>3</sub>), 3.23-3.38 (m, 1H, NCH<sub>2</sub>), *ca.* 3.56-3.70 (overlapped m, 1H, NCH<sub>2</sub>), 3.64 (s, 3H, OCH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 4.14-4.37 (m, 2H, OCH<sub>2</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.18 (C(O)CH<sub>3</sub>), 48.37 (NCH<sub>2</sub>), 51.03 (OCH<sub>3</sub>), 52.15 (OCH<sub>3</sub>), 52.75 (OCH<sub>3</sub>), 53.01 (OCH<sub>3</sub>), 68.10 (alkyne), 69.52 (OCH<sub>2</sub>), 104.48 (alkyne), 121.35 (C(C)(C)(O)(O)), 130.60 (alkene C), 142.26 (alkene C), 160.90 and 163.76 and 164.13 and 166.67 and 168.77 (4 x C=O, spiro C); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1740s (C=O's), 1655m, 1624w, 1438m, 1382w, 1358w, 1332w, 1253s, 1204m, 1139m, 1111w, 1053w, 995m, 934w, 906w, 882w; MS (EI)  $m/z$ : 397 (M<sup>+</sup>, 2), 366 (M-OCH<sub>3</sub>, 4), 354 (M-C(O)CH<sub>3</sub>, 100), 338 (M-CO<sub>2</sub>CH<sub>3</sub>, 7), 322 (3), 310 (6), 278 (3), 264 (3), 250 (14), 236 (3), 218 (14), 204 (2), 192 (3), 176 (3), 165 (2), 150 (2), 135 (3), 118 (2), 106 (2), 91 (2), 77 (2), 59 (12), 43 (9); MS (CI, NH<sub>3</sub>)  $m/z$ : 398 (M+H)<sup>+</sup>.

» *Unidentified compound (Rf 0.36)*. Isolated as a solid in 4% yield; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.31 (s, 3H, C(O)CH<sub>3</sub>), *ca.* 3.6-4.0 (overlapped m, 1H?, NCH<sub>2</sub>),<sup>i</sup> 4.05-4.25 (m, 1H, NCH<sub>2</sub>), 4.50-4.65 (m, 2H, OCH<sub>2</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 3.79 (s,

<sup>i</sup> The following resonances were also observed, which could account for one of the NCH<sub>2</sub> protons:  $\delta$  3.56 (app. t,  $J = 2.3$  Hz,  $\sim 0.5H$ ) & 3.62 (app. t,  $J = 2.3$  Hz,  $\sim 0.5H$ ) (slow exchange is expected in these compounds); alternatively, these could be due to impurities.

3H, OCH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 17.51 (C(O)CH<sub>3</sub>), 44.11 (NCH<sub>2</sub>), 51.77 (OCH<sub>3</sub>), 52.09 (OCH<sub>3</sub>), 53.57 (OCH<sub>3</sub>), 54.10 (OCH<sub>3</sub>), 67.23 (OCH<sub>2</sub>), 68.04 (spiro C?), 107.67 (alkene?), 111.61 (alkene?), 139.51 (alkene?), 145.05 (alkene?), 163.30 and 163.73 and 165.35 and 166.19 and 168.62 (4 x OC=O, NC=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1743s (C=O's), 1601w, 1521w, 1436m, 1397w, 1332m, 1293m, 1244m, 1209s, 1133m, 1072w, 910w; MS (EI) m/z: 397 (M<sup>+</sup>, 1), 366 (M-OCH<sub>3</sub>, 10), 353 (1), 338 (M-CO<sub>2</sub>CH<sub>3</sub>, 100), 306 (5), 235 (6), 221 (6), 163 (10), 84 (9), 61 (4), 49 (7); MS (CI, NH<sub>3</sub>) m/z: 415 (M+NH<sub>4</sub>)<sup>+</sup>, 398 (M+H)<sup>+</sup>.

» *Unidentified compound (Rf 0.27)*. Isolated as a solid in *ca.* 1% yield; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.49 (s, 3H, C(O)CH<sub>3</sub>), 3.69 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 4.47 (app. t, <sup>3</sup>J = 8.0 Hz, 2H, NCH<sub>2</sub>), 4.95 (app. t, <sup>3</sup>J = 8.0 Hz, 2H, OCH<sub>2</sub>); <sup>13</sup>C-NMR: N.A.; IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1769s (C=O), 1730s (C=O), 1695s (NC=O), 1651w, 1592w, 1505m, 1445m, 1378w, 1335m, 1246s, 1211m, 1158m, 1123m, 1065w, 1007w; MS (EI) did not give useful information; MS (CI, NH<sub>3</sub>) m/z: 415 (M+NH<sub>4</sub>)<sup>+</sup>, 398 (M+H)<sup>+</sup>.

» *Unidentified compound (Rf 0.11)*. Isolated as an oil in 6% yield; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.42 (s, 3H, C(O)CH<sub>3</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), *ca.* 3.55-3.90 (overlapped m, ~2H, NCH<sub>2</sub>), 4.62 (app. t, <sup>3</sup>J = 7.8 Hz, 2H, OCH<sub>2</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 27.71 (C(O)CH<sub>3</sub>), 44.82 (NCH<sub>2</sub>), 51.49 (OCH<sub>3</sub>), 52.30 (OCH<sub>3</sub>), 52.81 (OCH<sub>3</sub>), 53.39 (OCH<sub>3</sub>), 62.39, 68.34 (OCH<sub>2</sub>), 80.97, 102.44, 107.49, 110.04, 137.52, 156.35 and 163.21 and 165.44 and 166.22 and 171.60 (4

x OC=O and oxazoline C2), 203.94 ( $\text{CH}_3\text{C}=\text{O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1748s (C=O), 1719s (C=O), 1597m, 1477w, 1437m, 1421m, 1353w, 1298m, 1236s, 1196m, 1144m, 1057w; MS (EI) m/z: 366 (M-OCH<sub>3</sub>, 6), 354 (M-C(O)CH<sub>3</sub>, 100), 338 (M-CO<sub>2</sub>CH<sub>3</sub>, 6), 237 (6), 179 (8), 121 (6), 84 (6), 59 (5), 49 (4); MS (CI, NH<sub>3</sub>) m/z: 415 (M+NH<sub>4</sub>)<sup>+</sup>, 398 (M+H)<sup>+</sup>.

**Thermolysis of 33e with DMAD.** Oxadiazoline 33e (112 mg, 0.50 mmol) was thermolysed with DMAD (146 mg, 1.0 mmol) in 10 mL of benzene. The crude product mixture was found (<sup>1</sup>H-NMR) to contain almost only 157c, along with the excess DMAD. However, repeated separations by radial chromatography (ethyl acetate/hexane) were necessary to separate 157c completely from two minor products. The latter were not characterized.

» *Oxazoline 157c.* Isolated as a solid in 54% yield, Mp: N.A.; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.95 (s, 3H, CCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 3.95 (app. dt, J ~ 1 Hz, <sup>3</sup>J = 9.4 Hz, NCH<sub>2</sub>), 4.25 (app. dt, J ~ 1 Hz, <sup>3</sup>J = 9.4 Hz, OCH<sub>2</sub>), 5.82 (app. d, <sup>4</sup>J = 0.7 Hz, 1H, =CH<sub>2</sub>), 5.92 (app. d, <sup>4</sup>J = 1.4 Hz, 1H, =CH<sub>2</sub>); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 16.66 (CCH<sub>3</sub>), 53.23 (2 x OCH<sub>3</sub>, coincident signals), 55.22 (NCH<sub>2</sub>), 68.50 (OCH<sub>2</sub>), 128.30 (=CH<sub>2</sub>), 132.20 and 137.44 (tetrasubstituted alkene C's), 144.36 (H<sub>2</sub>C=C<sub>2</sub>), 160.00 (oxazoline C2), 163.09 (OC=O), 164.57 (OC=O), 191.69 (ketone C=O); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1745s (OC=O's), 1682s (NC=O's), 1644m, 1611m, 1435m, 1379m, 1321m, 1285m, 1251s, 1152m, 1055m, 1026m, 976w, 909m, 877w, 845w; MS (EI) m/z: 282 (M+H<sup>+</sup>, 8), 266 (M-CH<sub>3</sub>, 8), 252 (100), 241 (19), 239 (18), 222 (30), 208 (23), 194 (30), 190 (18), 181 (6), 163 (25), 154 (7), 135 (31), 124 (9), 111 (22), 96 (8), 84 (36), 71 (34),

59 (26), 49 (28), 45 (37), 41 (70); MS (CI, NH<sub>3</sub>) m/z: 282 (M+H)<sup>+</sup>; HRMS calcd for C<sub>13</sub>H<sub>16</sub>NO<sub>6</sub> (M+H<sup>+</sup>) m/z 282.0978, obsd 282.0966.

**Thermolysis of 33f with DMAD.** Oxadiazoline 33f (187 mg, 0.72 mmol) was thermolysed with 2.1 equiv. of DMAD (217 mg, 1.5 mmol) in 14 mL of benzene. The products were separated by chromatography, using ethyl acetate/hexane as elution solvent. Among the products were 114f, isolated in 2% yield, and a few mgs of 131f (see Section 4.3.5). The other three purified products are described below.

» *Oxazoline 157a.* White solid (73% yield), Mp 109-111 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 3.73 (s, 3H, OCH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 3.86 (app. dt, J ~ 1 Hz, <sup>3</sup>J = 6.5 Hz, 2H, NCH<sub>2</sub>), 4.04 (app. dt, J ~ 1 Hz, <sup>3</sup>J = 6.5 Hz, 2H, OCH<sub>2</sub>), 7.44-7.56 (m, 2H, Ar-m), 7.57-7.65 (m, 1H, Ar p), 7.86-7.94 (m, 2H, Ar-o); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 53.26 (2 x OCH<sub>3</sub>, coincident signals), 55.13 (NCH<sub>2</sub>), 68.42 (OCH<sub>2</sub>), 128.71 and 128.76 (Ar C2, C6 and Ar C3, C5), 132.60 (Ar C4), 133.76 and 135.73 and 137.02 (Ar C1 and C=C), 159.87 and 163.02 and 164.55 (2 x OC=O and oxazoline C2), 190.02 (PhC=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1745s (OC=O's), 1688s (PhC=O), 1645m (C=N), 1611m (C=C), 1507w, 1443m, 1381w, 1242s, 1115m, 1028s, 976w, 910m, 879w, 843w; MS (EI) m/z: 317 (M<sup>+</sup>, 20), 302 (M-CH<sub>3</sub>, 10), 288 (63), 257 (16), 230 (38), 199 (17), 171 (24), 105 (PhCO<sup>+</sup>, 100), 77 (87); MS (CI, NH<sub>3</sub>) m/z: 318 (M+H)<sup>+</sup>; HRMS calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>6</sub> (M<sup>+</sup>) m/z 317.0899, obsd 317.0901.

» *Spiro-fused dihydrofuran 162a.* Isolated in 4% yield; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 3.35-3.45 (m, 1H, NCH<sub>2</sub>), ca. 3.60-3.75 (overlapped m, 1H, NCH<sub>2</sub>), 3.62 (s, 3H, OCH<sub>3</sub>),

3.77 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 4.22-4.42 (m, 2H, OCH<sub>2</sub>), 7.35-7.50 (m, 3H, Ar-m,p), 7.76-7.84 (m, 2H, Ar-o); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 48.34 (NCH<sub>2</sub>), 51.21 (OCH<sub>3</sub>), 52.21 (OCH<sub>3</sub>), 52.83 (OCH<sub>3</sub>), 53.11 (OCH<sub>3</sub>), 69.42 (≡C), 69.64 (OCH<sub>2</sub>), 104.09 (≡C), 120.76 (C(C)(C)(O)(O)), 127-131 (overlapping peaks, Ar and =C), 142.86 (=C), 161.02 and 163.69 and 163.80 and 165.32 and 166.81 (3 x OC=O, PhC=O, and spiro C); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 2257w (C≡C), 1741s (OC=O's), 1637m (NC=O), 1577w, 1494w, 1437m, 1361m, 1254s, 1210m, 1119m, 1067w, 1020m, 995m, 909m; MS (EI) m/z: 400 (M-CO<sub>2</sub>Me, 16), 354 (M-C(O)Ph, 100), 344 (8), 105 (PhCO<sup>+</sup>, 54), 77 (20); MS (CI, NH<sub>3</sub>) m/z: 460 (M+H)<sup>+</sup>.

» *Unidentified adduct U2*. Isolated in 4% yield; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 3.53 (s, 3H, OCH<sub>3</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 4.49 (t, <sup>3</sup>J = 8.1 Hz, 2H, NCH<sub>2</sub>), 4.98 (t, <sup>3</sup>J = 8.1 Hz, 2H, OCH<sub>2</sub>), 7.32-7.47 (m, 5H, Ar); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 45.90 (OCH<sub>3</sub>), 51.67 (OCH<sub>3</sub>), 51.86 (OCH<sub>3</sub>), 55.28 (OCH<sub>3</sub>), 75.06 (NCH<sub>2</sub>), 92.26 (OCH<sub>2</sub>), 111.43, 114.58, 124.23, 127.98, 128.07, 129.00, 129.53, 131.18, 134.81, 151.61, (152.48), 152.65, 160.20, 164.12, 167.23; IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1776m (C=O), 1737s (C=O), 1697m (C=O), 1582w, 1506m, 1441m, 1338w, 1232s, 1122m, 1012w, 949w, 910w; MS (EI) m/z: 459 (M<sup>+</sup>, 35), 428 (M-OCH<sub>3</sub>, 6), 415 (6), 400 (M-CO<sub>2</sub>CH<sub>3</sub>, 12), 384 (23), 372 (20), 369 (6), 356 (4), 344 (30), 340 (3), 326 (6), 310 (5), 298 (6), 282 (7), 268 (6), 252 (11), 236 (6), 151 (12), 105 (PhCO<sup>+</sup>, 100), 84 (39), 77 (56), 61 (18), 49 (39); MS (CI, NH<sub>3</sub>) m/z: N.A.

**Alcoholysis of 157a.** Compound **157a** (1.12 g, 3.5 mmol) was stirred in 10 mL of 0.1 M acetic acid in methanol for 13 days at room temperature. After evaporation of the solvent, the oil was redissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, and washed successively with NaHCO<sub>3</sub> (5%, 4 x 10 mL), and water; after extraction of the aqueous layer with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layers were dried over MgSO<sub>4</sub>. Separation by radial chromatography, using 10-50% ethyl acetate in hexane, gave a mixture of two inseparable products, **159** and **160**, in a ratio of *ca.* 70: 30 (total yield not measured). The spectral data shown below was recorded using the mixture.

» *(Z)*-3-Oxo-3-phenyl-1-propene-1,1,2-tricarboxylic acid, trimethyl ester (**159**). Lit.<sup>184</sup> Mp 66-68 °C; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 3.65 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), *ca.* 7.35-7.70 (m, 3H, Ar-m,p), *ca.* 7.84-7.98 (m, 2H, Ar-o); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 52.4-53.6 (overlapped OCH<sub>3</sub>'s), 128.67 and 128.91 (Ar C2, C6 and Ar C3, C5), 134.09 (Ar C4), 135.19 (Ar C1), 142.44 and *ca.* 151.7 (below noise level, C=C), 161.94 (OC=O), 162.63 (OC=O), 163.94 (OC=O), 190.00 (PhC=O); MS (EI) *m/z*: 306 (M<sup>+</sup>, 16), 275 (M-OCH<sub>3</sub>, 12), 247 (M-CO<sub>2</sub>CH<sub>3</sub>, 3), 229 (1), 215 (1), 198 (1), 157 (1), 129 (3), 105 (PhCO<sup>+</sup>, 100), 77 (41), 59 (5), 51 (8), 44 (3), 29 (1).

» 4,5-Dihydro-4-methoxy-5-oxo-2-phenyl-3,4-furandicarboxylic acid, dimethyl ester (**160**). Identity is uncertain; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 3.50 (s, 3H, OCH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), *ca.* 7.35-7.70 (m, 5H, Ar); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 52.4-53.6 (overlapped OCH<sub>3</sub>'s), 107.50, 126.22, 126.93, 129.28, 130.21, 133.16, 135.06, (157.05?), 159.71 (OC=O), 160.44 (OC=O), 164.17 (OC=O); MS (EI) *m/z*: 306



( $M^+$ , 8), 275 (M-OCH<sub>3</sub>, 39), 247 (M-CO<sub>2</sub>CH<sub>3</sub>, 38), 230 (91), 215 (70), 203 (34), 187 (15), 175 (8), 157 (13), 151 (5), 144 (10), 140 (10), 129 (15), 111 (19), 105 (PhCO<sup>+</sup>, 100), 102 (11), 91 (5), 82 (5), 77 (62), 59 (19), 51 (15), 39 (12), 29 (4).

**Thermolysis of 33f with methyl propiolate.** Oxadiazoline 33f (187 mg, 0.72 mmol) was thermolysed with 1.1 equiv. of methyl propiolate (67 mg, 0.80 mmol) in 14 mL of benzene. The product mixture was found to consist mainly of 157b, with some 125a present. In order to obtain pure 157b, two successive separations (radial chromatography, ethyl acetate/hexane) had to be performed; this resulted in substantial decomposition of the major product, which was finally obtained in only 4% yield.

» *Oxazoline 157b.* <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 3.76 (s, 3H, OCH<sub>3</sub>), 3.87 (app. t, <sup>3</sup>J = 8.9 Hz, 2H, NCH<sub>2</sub>), 4.06 (app. t, <sup>3</sup>J = 8.9 Hz, 2H, OCH<sub>2</sub>), 7.37 (s, 1H, =C-H), *ca.* 7.35-7.65 (overlapped m, 3H, Ar-m,p), 7.81-7.95 (m, 2H, Ar-o); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 53.05 (OCH<sub>3</sub>), 55.17 (NCH<sub>2</sub>), 68.21 (OCH<sub>2</sub>), 127.66 (=C-H), 128.66 and 128.89 (Ar C2, C6 and Ar C3, C5), 133.63 (Ar C4), 136.07 and 139.90 (Ar C1 and =CR<sub>2</sub>), 162.20 (oxazoline C2), 164.18 (OC=O), 192.27 (PhC=O); IR: N.A.; MS (EI) m/z: 259 ( $M^+$ , 22), 230 (100), 216 (45), 172 (27), 128 (9), 105 (PhCO<sup>+</sup>, 63), 84 (24), 77 (55), 49 (16); MS (CI, NH<sub>3</sub>) m/z: 260 (M+H)<sup>+</sup>; HRMS calcd for C<sub>14</sub>H<sub>13</sub>NO<sub>4</sub> ( $M^+$ ) m/z 259.0845, obsd 259.0857.

**Thermolysis of 33k with DMAD.** Typically, 33k (297 mg, 1.00 mmol) was thermolysed with DMAD (310 mg, 2.18 mmol) in 16 mL of benzene. Repeated separations by radial chromatography (ethyl acetate/hexane) led to the isolation of oxazolidinone 114k (23%),

pyrazole **121** (13%, see under **33b** in Section 4.3.3), spiro-fused cyclopentadiene **165** (3%), compound **166**, and 1: 3 adduct (carbene: DMAD) **U3** (*ca.* 1%). Other products were also present (including one or more 1: 2 adducts) but they could not be obtained sufficiently pure to allow unambiguous identification.

» *Spiro-fused cyclopentadiene 165*. Obtained as a pale yellow oil;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.58 (s, 6H,  $\text{OCH}_3$ ), 3.89 (s, 6H,  $\text{OCH}_3$ ), 3.97 (t,  $^3J = 6.5$  Hz, 2H,  $\text{NCH}_2$ ), 4.39 (t,  $^3J = 6.5$  Hz, 2H,  $\text{OCH}_2$ ), 7.42-7.65 (m, 3H, Ar-m,p), 7.80-7.88 (m, 2H, Ar-o);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 47.66 ( $\text{NCH}_2$ ), 52.08 ( $\text{OCH}_3$ ), 52.85 ( $\text{OCH}_3$ ), 67.44 ( $\text{OCH}_2$ ), 101.18 (spiro C), 127.78 (Ar C2, C6), 128.97 (Ar C3, C5), 132.80 (Ar C4), 138.29 (probably Ar C1), 139.00 (probably  $=\underline{\text{C}}-\text{C}-\underline{\text{C}}=$ ), 140.32 (probably  $=\text{C}-\text{C}=$ ), 160.45 ( $\text{C}=\text{O}$ ), 162.60 ( $\text{C}=\text{O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1730s ( $\text{C}=\text{O}$ ), 1649w, 1437m, 1368m ( $\text{NSO}_2$ ), 1342m, 1262s, 1203m, 1169m ( $\text{NSO}_2$ ), 1096w, 1015w, 995w, 909s; MS (EI)  $m/z$ : 495 ( $\text{M}^+$ , 2), 464 ( $\text{M}-\text{OCH}_3$ , 5), 431 (3), 354 ( $\text{M}-\text{SO}_2\text{Ph}$ , 30), 322 (28), 310 (49), 290 (14), 264 (30), 182 (12), 141 ( $\text{PhSO}_2^+$ , 15), 84 (26), 77 (100), 59 (27); MS (CI,  $\text{NH}_3$ )  $m/z$ : 513 ( $\text{M}+\text{NH}_4$ ) $^+$ ; HRMS calcd. for  $\text{C}_{21}\text{H}_{21}\text{NO}_{11}\text{S}$  ( $\text{M}^+$ ):  $m/z$  495.0835, obsd  $m/z$  495.0835.

» *N-Formyl-N-(2-(formyloxy)ethyl)benzenesulfonamide, 166*.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.79 (t,  $^3J = 5.7$  Hz, 2H,  $\text{NCH}_2$ ), 4.28 (t,  $^3J = 5.7$  Hz, 2H,  $\text{OCH}_2$ ), 7.50-7.80 (m, 3H, Ar-m,p), 7.81-8.00 (m, 3H, Ar-o and  $\text{NC}(\text{O})\text{H}$ ), 9.15 (s, 1H,  $\text{OC}(\text{O})\text{H}$ );  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 41.00 ( $\text{NCH}_2$ ), 60.21 ( $\text{OCH}_2$ ), 127.45 (Ar C2, C6), 129.80 (Ar C3, C5), 134.47 (Ar C4), 137.80 (Ar C1), 160.26 ( $\text{C}=\text{O}$ ), 161.28 ( $\text{C}=\text{O}$ ); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1737s ( $\text{C}=\text{O}$ ), 1710s ( $\text{C}=\text{O}$ ), 1449w, 1401w, 1371m ( $\text{NSO}_2$ ), 1311w, 1286w, 1232w,

1172s (NSO<sub>2</sub>), 1091w, 1013w, 975w, 944w; MS (EI) m/z: 230 (2), 186 (4), 170 (10), 141 (PhSO<sub>2</sub><sup>+</sup>, 36), 94 (58), 84 (42), 77 (100), 49 (37); MS (CI, NH<sub>3</sub>) m/z: 275 (M+NH<sub>4</sub>)<sup>+</sup>.  
 » *Unidentified 1: 3 adduct (U3)*. Pale yellow solid, Mp N.A.; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 3.31 (s, 3H, OCH<sub>3</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), (NCH<sub>2</sub> overlapped with OCH<sub>3</sub>'s), 4.72-4.84 (m, 2H, OCH<sub>2</sub>), 7.52-7.72 (m, 3H, Ar-m,p), 7.99-8.05 (m, 2H, Ar-o); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>, partial spectrum) δ: 46.21 (NCH<sub>2</sub>), 51.38 (OCH<sub>3</sub>), 51.56 (OCH<sub>3</sub>), 52.46 (OCH<sub>3</sub>), 53.49 (OCH<sub>3</sub>), 54.06 (OCH<sub>3</sub>), 54.25 (OCH<sub>3</sub>), 69.43 (NCH<sub>2</sub>), 128.82 and 128.88 (Ar C2, C6 and Ar C3, C5), 134.40 (probably Ar C4), 139.56, 145.33, 161-168 (several overlapping peaks); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1748s (C=O), 1607m, 1500m, 1469w, 1435m, 1362w (NSO<sub>2</sub>), 1343w, 1259s, 1164m (NSO<sub>2</sub>), 1108w, 1025m; MS (EI) m/z: 606 (M-OCH<sub>3</sub>, 5), 578 (M-CO<sub>2</sub>CH<sub>3</sub>, 100), 438 (5), 394 (6), 378 (11), 364 (6), 354 (18), 320 (7), 141 (PhSO<sub>2</sub><sup>+</sup>, 8), 77 (35), 59 (18); MS (CI, NH<sub>3</sub>) m/z: 638 (M+H)<sup>+</sup>.

#### 4.4.4 Reactions with 1,3-Diones

**Thermolysis of 33f with 2,4-pentanedione (167a).** Oxadiazoline 33f (260 mg, 0.99 mmol) was thermolysed with 2,4-pentanedione (167a, 112 mg, 1.1 mmol) in 20 mL of benzene. The thermolysis products were separated by chromatography, using ethyl acetate/hexane mixtures or 8% MeOH in CHCl<sub>3</sub>; this had to be repeated several times, on various fractions, in order to obtain a good separation. Spectral data and isolated yields are given below.

» *N*-(2-Hydroxyethyl)benzamide, **172**. White solid (58% yield), Mp 60.5-61.5 °C (lit.<sup>207</sup> Mp 60 °C); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 3.09 (br.s, 1H, OH), 3.56-3.66 (m, 2H, NCH<sub>2</sub>), 3.75-3.84 (um, 2H, OCH<sub>2</sub>), 6.84 (br.s, 1H, NH), 7.30-7.57 (m, 3H, Ar-m,p), 7.73-7.81 (m, 2H, Ar-o); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 42.74 (NCH<sub>2</sub>), 61.83 (OCH<sub>2</sub>), 126.93 (Ar C2, C6), 128.47 (Ar C3, C5), 131.57 (Ar C4), 134.00 (Ar C1), 168.68 (C=O); IR (KBr) cm<sup>-1</sup>: 3100-3600 (NH, OH), 1637s (C=O), 1542s, 1491w, 1310m, 1067m, 712m; MS (EI) m/z: 165 (M<sup>+</sup>, 2), 147 (M-H<sub>2</sub>O, 12), 134 (10), 122 (19), 105 (PhCO<sup>+</sup>, 100), 84 (16), 77 (61), 51 (28); MS (CI, NH<sub>3</sub>) m/z: 166 (M+H)<sup>+</sup>.

» (*Z*)-4-(Benzoyloxy)-3-penten-2-one, **173**.<sup>208</sup> Colourless oil isolated in 2% yield; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.18 (s, 3H, CH<sub>3</sub>), 2.22 (s, 3H, CH<sub>3</sub>), 5.92 (s, 1H, =C-H), 7.45-7.70 (m, 3H, Ar-m,p), 8.08-8.16 (m, 2H, Ar-o); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ: 21.51 (C5), 31.03 (C1), 117.40 (C3), 128.67 (Ar C2, C6), 129.02 (Ar C4), 130.20 (Ar C3, C5), 133.81 (Ar C1), 158.14 and 163.50 (OC=O, C4), 195.56 (C2); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1741s (OC=O), 1706w (s-*cis* C=C-C=O), 1673m (s-*trans* C=C-C=O), 1637w (C=C), 1451w, 1426w, 1378w, 1359w, 1262s, 1195m, 1177w, 1153m, 1082m, 1065m, 1024w; MS (EI) m/z: 204 (M<sup>+</sup>, < 1), 161 (1), 105 (PhCO<sup>+</sup>, 100), 77 (48), 51 (18), 43 (17); MS (CI, NH<sub>3</sub>) m/z: 222 (M+NH<sub>3</sub>)<sup>+</sup>, 205 (M+H)<sup>+</sup>.

» *Compound 174*. Isolated in 2% yield, after up to six separations by chromatography (see numbering system, Section 2.4.4); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 2.25 (s, 3H) and 2.31 (s, 3H) (CH<sub>3</sub>(1,5)), 3.60-4.30 (m, 8H, NCH<sub>2</sub>(4', 4''), OCH<sub>2</sub>(5', 5''), 5.25 (br.s, 1H, CH(2')), 7.20-7.65 (m, 9H, CH(2''), Ar), 7.85-7.94 (m, 2H, Ar); <sup>13</sup>C-NMR (75 MHz,

CDCl<sub>3</sub>)  $\delta$ : 15.14 (C5), 29.18 (C1), 40.11 and 47.40 (NCH<sub>2</sub>(4', 4'')), 65.60 and 69.81 (OCH<sub>2</sub>(5', 5'')), 82.46 (C2'), 113.75 (C2''), 116.84 (C3), 127.05 (Ar C2, C6 - two coincident signals from analogous C's), 128.12 (Ar C3, C5), 128.48 (Ar C3, C5), 131.13 (Ar C4), 131.39 (Ar C4), 134.39 (Ar C1), 135.31 (Ar C1), 167.35 and 167.68 and 168.76 (C4 and 2 x NC=O), 193.78 (C2); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1669s (C=O), 1636m (C=O), 1617m, 1523w, 1486w, 1385m, 1288w, 1262w, 1149w, 1094w, 1024w, 965w, 909s, 849w; MS (EI) m/z: 303 (3), 286 (5), 260 (3), 244 (4), 214 (2), 198 (3), 180 (5), 148 (66), 105 (PhCO<sup>+</sup>, 100), 77 (43); MS (CI, NH<sub>3</sub>) m/z: 468 (M+NH<sub>4</sub>)<sup>+</sup>, 451 (M+H)<sup>+</sup>.

» *Compound 175*. Isolated in *ca.* 1% yield as a white solid; <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>, note solvent effect on chemical shifts)  $\delta$ : 2.29 (s, 3H, CH<sub>3</sub>), 2.50 (s, 3H, CH<sub>3</sub>), 3.65 (app q, <sup>3</sup>J = 5.6 Hz, 2H, probably NHCH<sub>2</sub>CH<sub>2</sub>O), 4.34 (t, <sup>3</sup>J = 5.0 Hz, 2H, probably NHCH<sub>2</sub>CH<sub>2</sub>O), 7.72 (s, 0.5H) & 7.78 (s, 0.5H) (probably NC(O)H), 8.10 (s, 1H), 11.15 (br.s., OH?); <sup>1</sup>H-NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$ : 2.01 (s, 3H, CH<sub>3</sub>), 2.31 (app.q, <sup>3</sup>J = 5.6 Hz, 2H, NHCH<sub>2</sub>CH<sub>2</sub>O), 2.79 (s, 3H, CH<sub>3</sub>), 3.43 (t, <sup>3</sup>J = 5.3 Hz, NHCH<sub>2</sub>CH<sub>2</sub>O), 7.04 (s, 0.5H), 7.09 (s, 0.5H), 7.33 (s, 1H); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 27.30, 31.88, 48.50, 62.45, (109.57?), 112.20, 160.13, 160.27, 194.31, 200.71; IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1737m (C=O), 1635s (NC=O), 1589m, 1390m, 1357w, 1309m, 1240m, 1164m, 1027w, 977w, 909w; MS (EI) m/z: 199 (M<sup>+</sup>, 28), 184 (M-CH<sub>3</sub>, 64), 154 (15), 142 (39), 126 (85), 122 (40), 114 (32), 96 (57), 80 (15), 73 (31), 69 (26), 53 (20), 43 (100), 29 (22); MS (CI, NH<sub>3</sub>) m/z: 200 (M+H)<sup>+</sup>.

» *Unidentified product (U4)*. Isolated as a solid in 5% yield;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.20 (s, 3H,  $\text{CH}_3$ ), 2.49 (s, 3H,  $\text{CH}_3$ ), *ca.* 3.50-3.90 (br.m., ~3H,  $\text{NCH}_2$ , OH?), 4.49 (t,  $^3J = 5.3$  Hz, 2H,  $\text{OCH}_2$ ), 7.15-8.15 (m, ~6H), 11.21 (s, H-bonded OH?);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ , slow exchange, the most intense resonance of a pair is underlined)  $\delta$ : 27.12 ( $=\text{C}-\underline{\text{CH}_3}$ ), 31.86 ( $\text{C}(\text{O})\underline{\text{CH}_3}$ ), 48.73 ( $\text{NCH}_2$ ), 63.46 ( $\text{OCH}_2$ ), 105.84, 112.05, 127.00 & 127.20 (Ar C2, C6), 128.40 & 128.58 (Ar C3, C5), 129.24 & 129.58 (Ar C4), 130.88, 133.51 (Ar C1), 160.27, 166.07, 194.26, 200.66; IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1730m, 1665m, 1635s, 1586m, 1519w, 1486w, 1450w, 1389m, 1357w, 1309w, 1266m, 1177w, 1107w, 1069w, 1029w, 909m; MS (EI)  $m/z$ : 275 ( $\text{M}^+$ , 4), 260 ( $\text{M}-\text{CH}_3$ , 3), 192 (2), 167 (1), 153 (22), 149 (6), 138 (12), 126 (14), 122 (18), 105 ( $\text{PhCO}^+$ , 100), 96 (6), 84 (22), 77 (51), 68 (6), 51 (18), 43 (37); MS (CI,  $\text{NH}_3$ )  $m/z$ : 276 ( $\text{M}+\text{H}^+$ ); HRMS calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_4$  ( $\text{M}^+$ )  $m/z$  275.1158, obsd 275.1156.

**Preparation of (*Z*)-4-(benzoyloxy)-3-penten-2-one, 173.** Benzoyl chloride (0.74 g, 5.3 mmol) was added to a solution of 2,4-pentanedione (**167a**, 0.50 g, 5.0 mmol) and pyridine (0.42 g, 5.3 mmol) in 10 mL of  $\text{CH}_2\text{Cl}_2$ . After stirring at room temperature overnight, the solution was diluted with 10 mL of  $\text{CH}_2\text{Cl}_2$  and washed with water (2 x 10 mL), aq.  $\text{NaHCO}_3$  (5%, 2 x 10 mL), and water (10 mL) again, before drying over  $\text{MgSO}_4$ .  $^1\text{H-NMR}$  analysis of the crude, after evaporation of the solvent, showed, in addition to the desired product, some unreacted **167a** and other unidentified products. Purification of **173** was done by chromatography (10-20% ethyl acetate in hexane); its  $^1\text{H}$  and  $^{13}\text{C}$  spectra were identical to those of **173** isolated from thermolysis of **33f** with **167a**.

**Thermolysis of 33f with 3-methyl-2,4-pentanedione (167b).** Oxadiazoline 33f (129 mg, 0.49 mmol) was thermolysed with 3-methyl-2,4-pentanedione (167b, 69 mg, 0.61 mmol) in 10 mL of benzene. The major product, 170b, was obtained as a colourless oil in 72% yield after purification by chromatography using 10-30% ethyl acetate in hexane as elution solvent.

» *3-(2-(3-Benzoyl)oxazolidinyl)-3-methyl-2,4-pentanedione (170b).* See numbering system, Section 2.4.4;  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.44 (s, 3H,  $\text{CH}_3(6)$ ), 2.24 (s, 3H) and 2.29 (s, 3H) ( $\text{CH}_3(1,5)$ ), 3.58-3.66 (m, 2H,  $\text{NCH}_2(4')$ ), 3.67-3.81 (m, 1H,  $\text{OCH}_2(5')$ ), 4.04-4.19 (m, 1H,  $\text{OCH}_2(5')$ ), 6.28 (s, 1H,  $\text{CH}(2')$ ), 7.35-7.57 (m, 5H, Ar);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.22 (C6), 27.72 and 28.12 (C1 and C5), 48.90 ( $\text{NCH}_2(4')$ ), 66.55 ( $\text{OCH}_2(5')$ ), 71.19 (C3), 90.75 (C2'), 127.43 (Ar C2, C6), 128.41 (Ar C3, C5), 131.08 (Ar C4), 135.18 (Ar C1), 169.78 ( $\text{NC=O}$ ), 203.25 and 204.26 (C2 and C4); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1800w, 1705s ( $\text{CH}_3\text{C=O's}$ ), 1650s ( $\text{NC=O}$ ), 1581w, 1497w, 1449w, 1416m, 1377m, 1356m, 1296w, 1203m, 1157w, 1081m, 1029w, 958w, 909w; MS (EI)  $m/z$ : 246 (7), 176 (oxazolidinium cation, 16), 148 (7), 105 ( $\text{PhCO}^+$ , 100), 77 (41), 51 (10), 47 (27); MS (CI,  $\text{NH}_3$ )  $m/z$ : 290 ( $\text{M+H}^+$ ); anal. calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}_4$ : C, 66.42; H, 6.62; N, 4.84; measured: C, 64.97;<sup>i</sup> H, 6.84; N, 4.78.

<sup>i</sup> The reason for the poor correlation for C is not known.

#### 4.5 1,3-Benzoxazol-2-ylidenes

» *Acetone 4-(2-hydroxyphenyl)semicarbazone, 182.* Prepared as described in Section 4.2b in 59% yield. Compound **182** could be recrystallized, with some decomposition, from ethanol/diethyl ether; white solid, Mp 165-166 °C (starts to turn orange at *ca.* 140 °C); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.91 (s, 3H, CH<sub>3</sub>), 2.05 (s, 3H, CH<sub>3</sub>), 6.60-7.20 (m, 4H, Ar), 8.27 (br.s, 1H, NH/OH), 8.61 (br.s, 1H, NH/OH), 9.57 (br.s, 1H, NH/OH); <sup>13</sup>C-NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 16.14 (CH<sub>3</sub>), 24.66 (CH<sub>3</sub>), 120.18 (Ar), 120.22 (Ar), 122.40 (Ar), 126.03 (Ar), 126.39 (Ar), *ca.* 128 (overlapped with solvent, Ar), 149.72 (C=N), 156.06 (C=O); IR (KBr) cm<sup>-1</sup>: 3500-2500s, 1654s (C=O), 1597m, 1558s, 1457m, 1376w, 1340m, 1308w, 1276m, 1239m, 1196w, 1131w, 1042w, 925w, 838w, 756m; MS (EI) m/z: 207 (M<sup>+</sup>, 21), 135 (6), 109 (100), 99 (23), 79 (23), 72 (35); MS (CI, NH<sub>3</sub>) m/z: 208 (M+H)<sup>+</sup>; HRMS calcd for C<sub>10</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> (M<sup>+</sup>) m/z 207.1008, obsd m/z 207.1008.

» *Acetone 4-(2-(tert-butyldimethylsilyloxy)phenyl)semicarbazone, 183.* Semicarbazone **182** (3.40 g, 16 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) to which triethylamine (3.00 g, 30 mmol) was added. A *tert*-BuSiMe<sub>2</sub>Cl solution (3.71 g, 25 mmol, in 35 mL of CH<sub>2</sub>Cl<sub>2</sub>) was then added dropwise, from an addition funnel, to the semicarbazone solution stirred under N<sub>2</sub> in an ice bath. After completion of addition, the solution was kept at 0 °C for another 5 h, and was then allowed to warm to room temperature overnight. The solid recovered after evaporation of the solvent was washed with water (to remove Et<sub>3</sub>NH<sup>+</sup>Cl<sup>-</sup>) and recrystallized from toluene (43% yield); beige solid, Mp 170-171 °C; <sup>1</sup>H-NMR (200



MHz, CDCl<sub>3</sub>)  $\delta$ : 0.29 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 1.05 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.92 (s, 3H, =CCH<sub>3</sub>), 2.03 (s, 3H, =CCH<sub>3</sub>), 6.80-7.00 (m, 3H, Ar), 8.10 (br.s, 1H, C(O)NHC), 8.28 (dd, <sup>4</sup>J = 1.8 Hz, <sup>3</sup>J = 7.8 Hz, Ar, probably *ortho* to OTBDMS), 8.69 (br.s, 1H, C(O)NHN); <sup>13</sup>C-NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$ : -4.28 (Si(CH<sub>3</sub>)<sub>2</sub>), 16.54 (=C(CH<sub>3</sub>)<sub>2</sub>), 24.98 (=C(CH<sub>3</sub>)<sub>2</sub>), 18.22 (Si-C(CH<sub>3</sub>)<sub>3</sub>), 25.85 (C(CH<sub>3</sub>)<sub>3</sub>), 117.52 (Ar), 119.35 (Ar), 121.47 (Ar), 122.17 (Ar), 130.09 (Ar C-N), 144.14 (Ar C-O), 147.31 (C=N), 153.54 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 3387br (NH), 3207br (NH), 1688s (C=O), 1596m, 1534s, 1484w, 1455m, 1370w, 1332, 1264m, 1200w, 1137w, 1111w, 916m, 841w; MS (EI) m/z: 321 (M<sup>+</sup>, 8), 264 (M-<sup>t</sup>Bu, 100), 208 (10), 166 (57), 150 (46), 135 (26), 99 (22), 73 (61), 56 (29); MS (CI, NH<sub>3</sub>) m/z: 322 (M+H)<sup>+</sup>; HRMS calcd for C<sub>16</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>Si (M<sup>+</sup>) m/z 321.1873, obsd m/z 321.1868.

» *5,5-Dimethyl-2-(2-(tert-butyldimethylsilyloxy)phenyl)imino- $\Delta^3$ -1,3,4-oxadiazoline*, **184**.

Semicarbazone **183** (3.00 g, 9.3 mmol), dissolved in CH<sub>2</sub>Cl<sub>2</sub> (75 mL), was oxidized with PhI(OAc)<sub>2</sub> (3.75 g, 12 mmol, in 75 mL CH<sub>2</sub>Cl<sub>2</sub>) in the usual fashion (see Section 4.2b). Separation of the product mixture by column chromatography on silica, eluting first with hexane, then with 5% ethyl acetate in hexane, gave 1.55 g (52%) of **184** as a dark yellow solid, Mp N.A. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.21 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.99 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.63 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 6.88-7.02 (m, 2H, Ar), 7.02-7.14 (m, 1H, Ar), 7.23-7.33 (m, 1H, Ar); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : -4.35 (Si(CH<sub>3</sub>)<sub>2</sub>), 18.34 (C(CH<sub>3</sub>)<sub>3</sub>), 23.54 (C(CH<sub>3</sub>)<sub>2</sub>), 25.70 (C(CH<sub>3</sub>)<sub>3</sub>), 121.11 (Ar), 121.32 (Ar), 121.72 (C2), 122.86 (Ar), 126.76 (Ar), 135.21 (Ar C-N), 149.04 (Ar C-O), 159.63 (C=N); IR (KBr) cm<sup>-1</sup>: 1709s (C=N), 1592w (N=N), 1481s, 1451w, 1370w, 1265s, 1226m, 1107s, 1042w, 982w, 927s,

890m, 842s; MS (EI)  $m/z$ : 262 (M-<sup>t</sup>Bu, 14), 206 (16), 192 (81), 176 (68), 164 (23), 150 (6), 135 (6), 100 (14), 84 (39), 74 (18), 47 (100); MS (CI, NH<sub>3</sub>)  $m/z$ : 320 (M+H)<sup>+</sup>.

**Attempted deprotection of 184 with benzoyl fluoride.** Imino oxadiazoline 184 (94 mg, 0.29 mmol) was dissolved in 1.0 mL of CH<sub>2</sub>Cl<sub>2</sub>, to which *ca.* 40 mg (0.32 mmol) of benzoyl fluoride, in 0.25 mL of CH<sub>2</sub>Cl<sub>2</sub>, was added. The slow reaction (room temperature) was followed by <sup>1</sup>H-NMR over 3 weeks. From the slow disappearance of the methyl resonances, the starting material was clearly being consumed. However, the emerging methyl resonance at 1.68 ppm could not be assigned to the expected new oxadiazoline, since two distinct singlets were expected.

**Deprotection of 184.** Typically, 98 mg (0.3 mmol) of the protected oxadiazoline, dissolved in THF (1.0 mL), was reacted with 0.40 mL of *n*-Bu<sub>4</sub>NF solution (1.0 M in THF, 0.4 mmol) under a nitrogen atmosphere at 0 °C. Addition of the first drop of *n*-Bu<sub>4</sub>NF solution turned the solution dark, probably indicating immediate formation of the phenoxide anion. After completion of addition of the deprotecting agent (*ca.* 10 min), the solution was stirred to a further 15 min in the ice bath. The reaction was quenched by addition of acetic acid (20 mL, 0.10 M in benzene) (in one case, aq. 0.1 N HCl was used, but this did not give more favourable results), which turned the solution from very dark to pale yellow, and stirring at 0 °C was continued for a further 30 min. The benzene solution was then washed with aq. NaHCO<sub>3</sub> (5%, 4 x 5 mL), followed by 5 mL of water (all ice-cold, to minimize thermal decomposition of products). After drying (MgSO<sub>4</sub>) and evaporation of the solvent *in vacuo*, the crude product mixture was quickly separated by

radial chromatography, with 10%-40% ethyl acetate in hexane. The first band eluted was shown by  $^1\text{H-NMR}$  to consist of a mixture of **185** and **181a** (the ratio varied with every attempt to prepared **181a**, but it could not be optimized). Periodic recording of  $^1\text{H-NMR}$  spectra showed the relatively fast decomposition of the **181a** (estimated half-life on the order of 6-12 h at room temperature), while cyclization of the acyclic isomer, in  $\text{CDCl}_3$ , did not seem to occur to any appreciable extent. Another product collected during chromatography was shown to be **186**, a probable decomposition product from **181a**.

» *5,5-Dimethyl-2-(2-hydroxyphenyl)imino- $\Delta^3$ -1,3,4-oxadiazoline*, **185**. Not obtained pure;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.74 (s, 6H,  $\text{CH}_3$ ), 4.90 (br.s., 1H, OH), 6.75-7.30 (m, Ar, overlapped with **181a**), 7.70 (dd,  $^4J = 1.5$  Hz,  $^3J = 8.1$  Hz, 1H, Ar C(3)H);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ , partial spectrum)  $\delta$ : 23.69 (2 x  $\text{CH}_3$ ), 114.79 (Ar), 119.70 (Ar), 123.27 (Ar), 129.46 (Ar C-N), 153.53 (Ar C-O), 159.50 (C=N).

» *Spiro-fused oxadiazoline 181a*. Not obtained pure;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.60 (s, 3H,  $\text{CH}_3$ ), 1.64 (s, 3H,  $\text{CH}_3$ ), 6.75-7.30 (m, Ar C(4,5,6)H, overlapped with **185**), 7.70 (dd,  $^4J = 1.5$  Hz,  $^3J = 8.1$  Hz, Ar C(3)H);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ , partial and uncertain)  $\delta$ : 20.71 ( $\text{CH}_3$ ), 24.38 ( $\text{CH}_3$ ), 108.32 and 109.36 (Ar C3 and C6), 119.45 (oxadiazoline C2), 121.09/122.22/123.89 (Ar C4 and C5), 133.72 (oxadiazoline C5); IR of **181a** + **185** mixture ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 3432br (NH, OH), 1774m, 1698s (C=N of **185**), 1585 (N=N), 1487s.

» *2(3H)-Benzoxazolone*, **186**.<sup>209</sup>  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.07-7.28 (m, Ar and NH);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 110.11 (C5 and C8, coincident), 122.66 (C7), 124.14

(C6), 129.42 (C4), 143.86 (C9), 156.20 (C2); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 3500-2800 (NH), 1772s (C=O), 1624w, 1482m, 1406w, 1306w, 1257w, 1147w, 949w; MS (EI) m/z: 135 (M<sup>+</sup>, 100), 106 (3), 91 (M-CO<sub>2</sub>, 15), 79 (94), 63 (19), 52 (65), 38 (14), 28 (11); MS (CI, NH<sub>3</sub>) m/z: 153 (M+NH<sub>4</sub>)<sup>+</sup>.

**Attempted benzoylation of 181a.** To the crude product mixture, obtained as indicated above (starting with 96 mg, 0.30 mmol of 184), was added pyridine (32 mg, 0.40 mmol), followed by benzoyl chloride (57 mg, 0.40 mmol), while keeping the solution at 0 °C. After washing the reaction mixture with aq. NaHCO<sub>3</sub> (5%) and water, and drying over MgSO<sub>4</sub>, radial chromatography was performed, but none of the isolated components could be identified as the desired product; 186 and 189 were isolated.

» *N*-(2-Hydroxyphenyl)benzamide, 189. Lit.<sup>210</sup> Mp 168-168.5 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.88-6.98 (m, 1H, Ar), 7.04-7.12 (m, 1H, Ar), 7.13-7.26 (m, 2H, Ar), 7.48-7.66 (m, 3H, Ar), 7.87-7.96 (m, 2H, Ar), 8.14 (br.s., 1H, OH), 8.61 (s, 1H, NH); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 119.86 and 120.67 and 122.33 (Ar C3, C4, C5, C6; two signals overlap), 125.62 (Ar C-N), 127.31 (Ph C2, C6), 128.97 (Ph C3, C5), 132.54 (Ph C4), 133.18 (Ph C1), 148.80 (Ar C-O), 167.12 (C=O); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 3410m (NH), 3500-2500 (OH), 1645s (C=O), 1614m, 1592m, 1577m, 1544s, 1453s, 1368m, 1287m, 1239w, 1203w, 1096w, 905w, 856w, 748s, 703s; MS (EI) m/z: 213 (M<sup>+</sup>, 21), 195 (3), 105 (PhCO<sup>+</sup>, 100), 84 (8), 77 (37); MS (CI, NH<sub>3</sub>) m/z: 214 (M+H)<sup>+</sup>.

**Thermolysis of 181a + 185 mixture with phenol.** A mixture of 181a and 185 (ca. 45 mg, 0.3: 1 favouring 185), prepared as described above, was thermolysed at 70 °C, in

8 mL of 0.45 M phenol in benzene, for 14 h.  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ ) and GC-MS spectra of the complex product mixture were recorded, after base washing the thermolysed solution. One of two singlets in the  $^1\text{H}$  spectrum, at 6.43 and 6.49 ppm, could possibly be assigned to C(2)H of the expected amide acetal, **187**. The GC-MS spectrum demonstrated the presence of **186**, as well as several other products which could not be unambiguously identified as the expected phenol carbene + phenol adduct.

#### 4.6 Intramolecular Trapping of a Novel $\beta$ -Lactam-4-Ylidene

**Preparation of diphenylacetyl chloride.** A mixture of diphenylacetic acid (10.6 g, 50.0 mmol) and  $\text{SOCl}_2$  (12.0 g, 101 mmol) was heated to reflux, under  $\text{N}_2$ , for 1 h. The excess thionyl chloride was evaporated *in vacuo*. Recrystallization from petroleum ether (35–60 °C) gave 10.1 g (88%) of the desired product, Mp 52–54 °C (lit.<sup>193</sup> 56–57 °C).

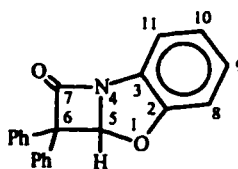
» *1,7,8-Triaza-1-(2-(tert-butyl dimethylsilyloxy)phenyl)-6,6-dimethyl-5-oxa-2-oxo-3,3-diphenylspiro[3.4]oct-7-ene*, **192**. This reaction was carried out essentially as described by Zoghbi<sup>136</sup> in his preparation of related compounds. A solution of imino oxadiazoline **184** (0.82 g, 2.6 mmol) and triethylamine (0.66 g, 6.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 mL) was cooled in a  $\text{CCl}_4$ /dry ice bath (–23 °C) under a nitrogen atmosphere. From an addition funnel, diphenylacetyl chloride (0.74 g, 3.2 mmol, in 13 mL of  $\text{CH}_2\text{Cl}_2$ ) was added dropwise over about 30 min. The solution was kept in the cold bath for an additional 1 h, and was then allowed to warm up to room temperature overnight. It was then washed with 3 portions of aq.  $\text{NaHCO}_3$  (5%) and one portion of brine, and the combined aqueous layers were re-

extracted once with  $\text{CH}_2\text{Cl}_2$ . After drying ( $\text{MgSO}_4$ ), the solvent was evaporated. 1.12 g (85%) of pure **192** was obtained as a white solid following purification by radial chromatography (5-10% ethyl acetate in hexane); Mp *ca.* 118-120 °C (dec.);  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.16 (s, 3H,  $\text{SiCH}_3$ ), 0.17 (s, 3H,  $\text{SiCH}_3$ ), 0.83 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.14 (s, 3H,  $\text{C}(\text{CH}_3)_2$ ), 1.58 (s, 3H,  $\text{C}(\text{CH}_3)_2$ ), 6.79-6.93 (m, 2H, Ar), 7.08-7.60 (m, 12H, Ar);  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : -4.16 ( $\text{Si}(\text{CH}_3)_2$ ), 18.21 ( $\text{C}(\text{CH}_3)_3$ ), 24.26 ( $\text{C}(\text{CH}_3)_2$ ), 24.73 ( $\text{C}(\text{CH}_3)_2$ ), 25.57 ( $\text{C}(\text{CH}_3)_3$ ), 74.42 ( $\text{C}(\text{Ph})_2$ ), 119.49, 120.69, 122.20, 122.64 (probably  $\text{C}(\text{CH}_3)_2$ ), 125.43 (probably spiro C), 127.44, 127.90, 128.17, 128.29, 128.38, 130.19, 135.99, 137.21, 153.01 (Ar C-O), 166.87 (C=O); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1786s (C=O), 1597w (N=N), 1501s, 1457m, 1377m, 1291m, 1257m, 1207m, 1164m, 918m, 839m, 701m; MS (EI)  $m/z$ : 514 ( $\text{M}^+$ , 3%), 457 ( $\text{M}-^i\text{Bu}$ , 10), 444 ( $\text{M}-(2\text{-diazopropane})$ , 9), 428 ( $\text{M}-\text{N}_2\text{-Me}_2\text{CO}$ , 34), 400 (100), 387 (14), 358 (26), 342 (96), 265 (16), 249 (43), 234 (23), 194 ( $[\text{Ph}_2\text{C}=\text{C}=\text{O}]^+$ , 70), 165 (69), 117 (13), 73 (47); MS (CI,  $\text{NH}_3$ )  $m/z$ : 514 ( $\text{M}+\text{H}$ ) $^+$ .

» *1,7,8-Triaza-1-(2-hydroxyphenyl)-6,6-dimethyl-5-oxa-2-oxo-3,3-diphenylspiro[3.4]oct-7-ene*, **193**. Typically, a solution of **192** (0.66 g, 1.3 mmol) in dry THF (3.0 mL) was placed in a flask fitted with a septum. After flushing with dry  $\text{N}_2$ , the flask was immersed in an ice bath for several minutes, before adding 1.75 mL of  $n\text{Bu}_4\text{NF}$  (1.0 M in THF, 1.75 mmol) by syringe, over about 15 min. The sample was kept in ice for an additional 20-30 min., and was then left at room temperature for 2 h. After evaporation of the solvent, a mixture of 15 mL of  $\text{CH}_2\text{Cl}_2$  + 6 mL of 0.1 N HCl was added to the crude product

mixture. After separation of the two layers, the aqueous phase was extracted with 3 portions of  $\text{CH}_2\text{Cl}_2$ , and the combined organic fractions were washed with aq.  $\text{NaHCO}_3$  (5%) and water. Slightly impure **193**, obtained after chromatography on silica using 10-40% ethyl acetate in hexane as elution solvent, was recrystallized from ethyl acetate/hexane. White solid (72-77% yield), Mp *ca.* 120-150 °C (melts with decomposition);  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.43 (s, 3H,  $\text{CH}_3$ ), 1.49 (s, 3H,  $\text{CH}_3$ ), 6.79-6.93 (m, 2H, Ar), 7.01-7.12 (m, 2H, Ar), 7.17-7.26 (m, 1H, Ar), 7.28-7.50 (m, 10H, Ar);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ , some peaks overlap)  $\delta$ : 24.17 ( $\text{CH}_3$ ), 24.22 ( $\text{CH}_3$ ), 74.77 ( $\text{C}(\text{Ph})_2$ ), 119.07, 120.72, 120.95, 123.36, 124.52, 128.07, 128.39, 128.44, 128.67, 129.98, 133.97, 135.74, 151.29 (Ar C-O), 163.53 (C=O); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 3600-3000br (OH), 1792m, 1745s (C=O), 1590 (N=N), 1497s, 1451w, 1388m, 1255m, 1206s, 1163m, 1117w, 933w, 840w, 700m; MS (EI)  $m/z$ : 285 (13), 254 (4), 208 (5), 194 ( $[\text{Ph}_2\text{C}=\text{C}=\text{O}]^+$ , 89), 177 (9), 165 (100), 152 (7), 135 (23), 115 (7), 84 (10), 77 (7), 63 (10), 45 (46); MS (CI,  $\text{NH}_3$ )  $m/z$ : 417 ( $\text{M}+\text{NH}_4$ ) $^+$ , 400 ( $\text{M}+\text{H}$ ) $^+$ ; anal. calcd. for  $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_3$ : C, 72.17; H, 5.30; N, 10.52; measured: C, 72.45; H, 5.00; N, 10.55.

**Thermolysis of spiro-fused  $\beta$ -lactam oxadiazoline 193.** A sample of oxadiazoline **193** (285 mg, 0.71 mmol), dissolved in 50 mL of benzene, was thermolysed at 100 °C for 24 h. The thermolysis products, described below, were separated by radial chromatography (silica plate, with solutions of ethyl acetate and hexane in various proportions).

**195**

» *2,3-Benzo-6,6-diphenyloxapenam*, **195**. Recrystallized from ethyl acetate/hexane.

White solid (53% yield), Mp 157-158 °C;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.46 (s, 1H, C(5)H), 6.77-7.12 (m, 3H, Ar), 7.20-7.50 (m, 11H, Ar);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 76.59 (C6), 97.08 (C5), 109.73 (C8), 117.49 (C11), 121.76 (C9), 126.49, 126.87, 127.68, 128.00, 128.06, 128.41, 129.11, 130.31, 135.06, 138.20, 155.71 (C2), 177.19 (C7); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1801s (C=O), 1602w, 1473s, 1334w, 1274m, 1224w, 1107w, 1075w, 1037w, 1010, 921w, 895w; MS (EI)  $m/z$ : 194 (32,  $[\text{Ph}_2\text{C}=\text{C}=\text{O}]^+$ ), 165 (100), 139 (11), 115 (4), 86 (6), 74 (4), 63 (6), 51 (6); MS (CI,  $\text{NH}_3$ )  $m/z$ : 331 ( $\text{M}+\text{NH}_4$ ) $^+$ , 314 ( $\text{M}+\text{H}$ ) $^+$ ; anal. calcd. for  $\text{C}_{21}\text{H}_{15}\text{NO}_2$ : C, 80.49; H, 4.82; N, 4.47; measured: C, 80.59; H, 4.87; 4.39.

» *Compound 196*. White solid obtained in 7% yield after recrystallization from ethyl acetate/hexane (structure determined by X-ray crystallography); Mp 176-177 °C;  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.01 (d,  $^3J = 6.0$  Hz, 3H,  $\text{CH}_3$ ), 1.24 (d,  $^3J = 6.0$  Hz, 3H,  $\text{CH}_3$ ), 4.54 (septet,  $^3J = 6.0$  Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 6.7-7.7 (m, 29H, Ar and  $\beta$ -lactam CH);  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 21.63 ( $\text{CH}_3$ ), 22.01 ( $\text{CH}_3$ ), 70.00 ( $\text{CH}(\text{CH}_3)_2$ ), 73.25 and 74.51 ( $\text{C}(\text{Ph})_2$ ,  $\beta$ -lactam and dione), 89.80 ( $\beta$ -lactam  $\text{CHOAr}$ ), 112.93, 114.21, 119.63, 120.30, 121.85, 123.46, 125.26, 126.78, 127.28, 127.51, 127.66, 127.79, 127.91, 128.24, 128.78, 128.92, 130.09, 134.84, 135.19, 138.10, 150.07 (Ar C-O), 150.87 (Ar C-O), 167.02 ( $\beta$ -lactam C=O), 168.08 (dione C=O's); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : 1771m (C=O), 1754s



(C=O), 1598w, 1501m, 1459w, 1382m, 1287w, 1245m, 1153w, 1119w, 1059w, 953w; MS (EI) m/z: 684 ( $M^+$ , 2), 507 (12), 490 (6), 356 (41), 328 (100), 314 (20), 286 (91), 194 (65,  $[\text{Ph}_2\text{C}=\text{C}=\text{O}]^+$ ), 180 (15), 165 (65), 120 (21).

» *Unidentified Compound (tt 2-3)*. Selected data only, impure sample;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ , partial spectrum)  $\delta$ : 1.25 (d,  $^3J = 6.1$  Hz, 6H,  $\text{CH}(\underline{\text{CH}_3})_2$ ), 4.60 (septet,  $^3J = 6.1$  Hz, 1H,  $\underline{\text{CH}}(\text{CH}_3)_2$ );  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ , partial spectrum, some peaks may be due to impurities)  $\delta$ : 21.70 ( $\text{CH}(\underline{\text{CH}_3})_2$ ), 70.86 ( $\underline{\text{CH}}(\text{CH}_3)_2$ ), (85.69?), (88.77?), 113.89, 120.27, 126.99, 128.90, 130.47, 135.26, (137.51?), 152.73 (Ar C-O), 169.20 (C=O).

» *Unidentified Compound (tt 4-5)*.  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.06 (s, 1H, OH?), 7.20-7.65 (m, > 20H);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : (74.86?), 123.49, 123.68, 125.26, 126.25, 126.68, 127.40, 128.53, 128.64, 128.70, 129.14, 129.34, 134.88, 137.65, 143.95, 168.04 (C=O), 170.27 (C=O); IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ : (no obvious OH) 1753s (C=O), 1600w, 1497s, 1452m, 1378m, 1215m, 1155w, 1115s, 1064w, 1033w, 952w, 908w; MS (EI) m/z: 328 (3), 286 (6), 194 (78,  $[\text{Ph}_2\text{C}=\text{C}=\text{O}]^+$ ), 167 (100); MS (CI,  $\text{NH}_3$ ) m/z: 541.

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# Appendix I - Thermolysis Rate Constants

## First-order thermal decomposition of 33a at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	10
58	-0.15	$R^2$	0.9507
120	-0.29	Slope	9.67E-04
180	-0.25	$k^{90} (s^{-1})$	1.61E-5
300	-0.39		( $\pm 10.2\%$ ) <sup>ii</sup>
480	-0.62	$t_{1/2}^{90} (h)$	12
651	-0.73		
891	-0.81		
1251	-1.20		
1648	-1.50		

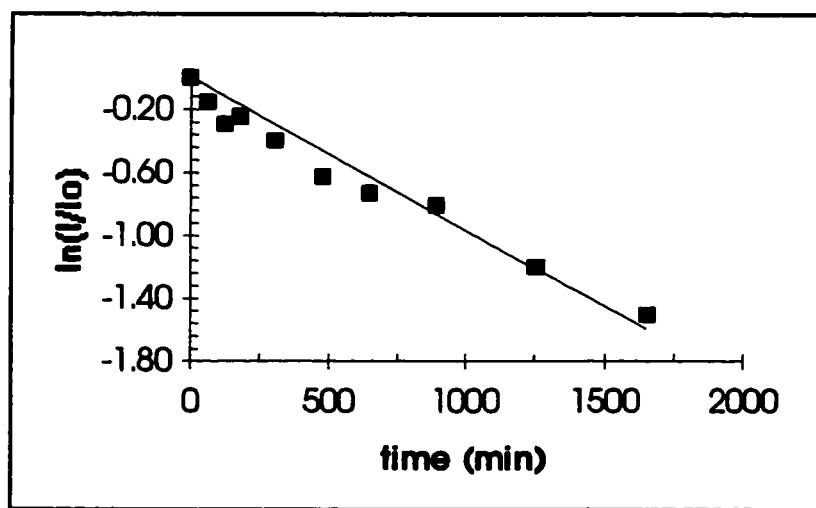


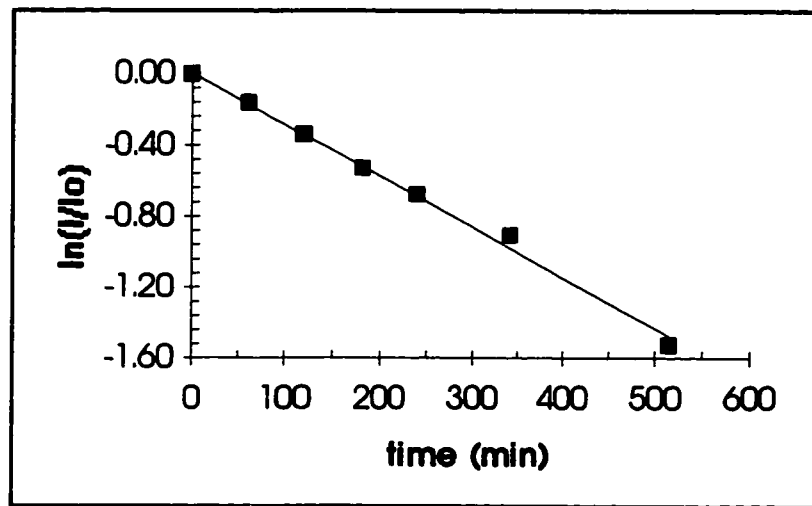
Figure I-1. Plot of  $\ln(I/I_0)$  vs time for 33a.

<sup>i</sup> Resonance followed:  $NCH_2$  multiplet (1H) centred at 2.72 ppm.

<sup>ii</sup> Based on error limits of slope at 95% confidence level.

First-order thermal decomposition **33b** at 90 °C

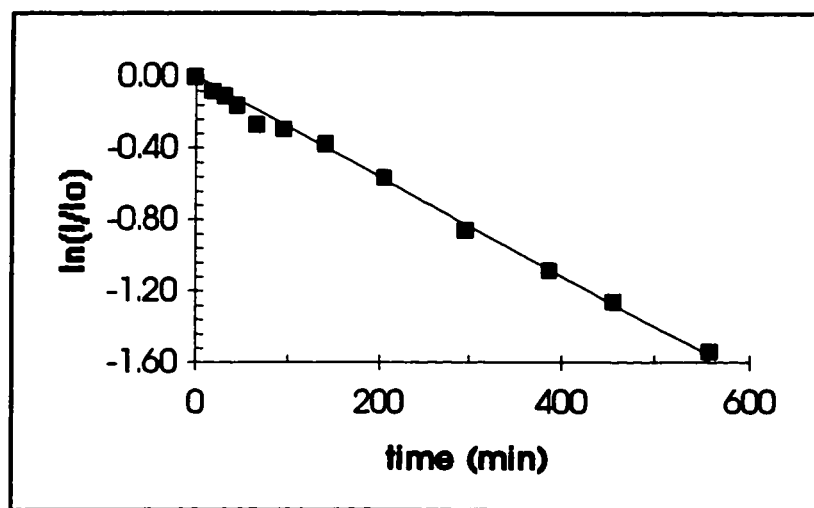
time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	7
60	-0.16	$R^2$	0.9952
120	-0.34	Slope	-2.87E-03
180	-0.53	$k^{90}$ (s <sup>-1</sup> )	4.78E-05
240	-0.68		(± 4.35%)
340	-0.91	$t_{1/2}^{90}$ (h)	4.0
515	-1.52		

Figure I-2. Plot of  $\ln(I/I_0)$  vs time for **33b**.<sup>i</sup> Resonances followed: two overlapped methyl singlets at 1.38 ppm.



## First-order thermal decomposition of 33c at 90 °C

time (min)	$\ln(I/I_0)^1$	Regression Analysis	
0	0.00	Observations	12
17	-0.08	$R^2$	0.9956
31	-0.11	Slope	-2.79E-03
45	-0.16	$k^{90} (s^{-1})$	4.66E-05
65	-0.27		( $\pm 2.95\%$ )
95	-0.29	$t_{1/2}^{90} (h)$	4.1
140	-0.38		
205	-0.56		
295	-0.89		
387	-1.09		
455	-1.26		
558	-1.54		

Figure I-3. Plot of  $\ln(I/I_0)$  vs time for 33c.<sup>1</sup> Resonances followed: average of the two methyl singlets at 1.16 ppm and 1.23 ppm.

### First-order thermal decomposition of **33d** at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	8
25	-0.21	$R^2$	0.9977
50	-0.44	Slope	-8.39E-03
75	-0.62	$k^{90}$ (s <sup>-1</sup> )	1.40E-04
108	-0.97		(± 2.43%)
138	-1.17	$t_{1/2}^{90}$ (h)	1.4
171	-1.43		
202	-1.66		

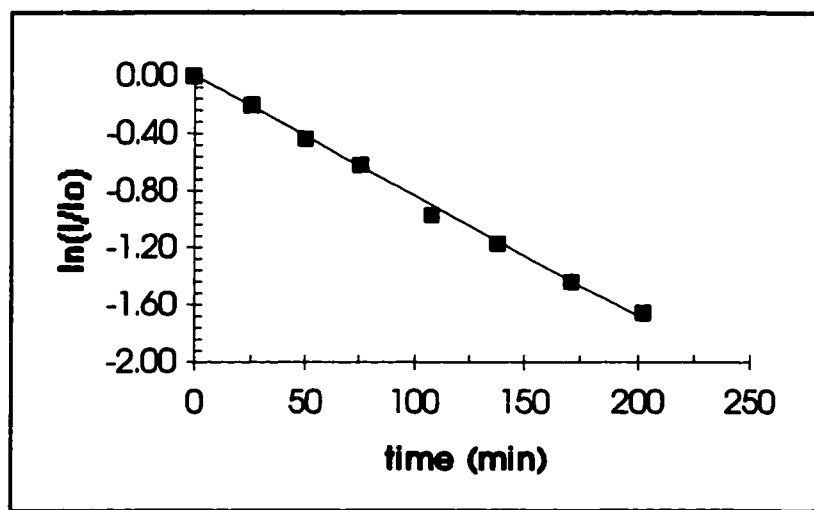
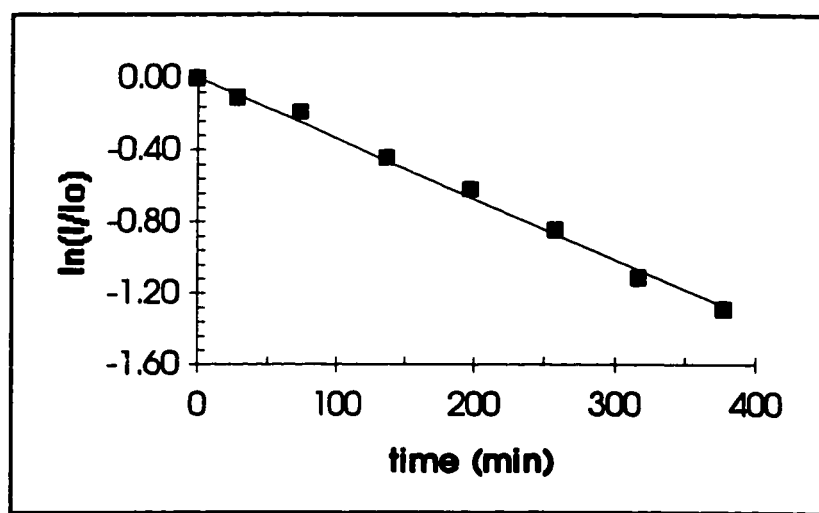


Figure I-4. Plot of  $\ln(I/I_0)$  vs time for **33d**.

<sup>i</sup> Resonance followed: C(O)CH<sub>3</sub> singlet at 1.85 ppm.

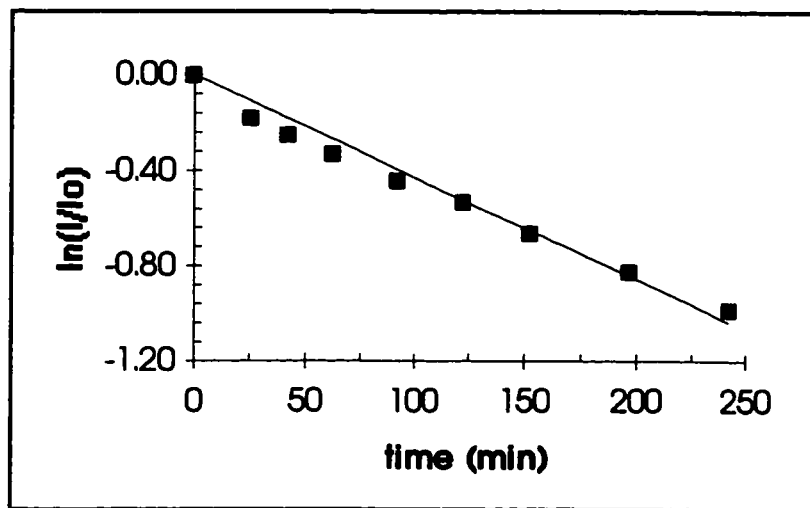
## First-order thermal decomposition of 33e at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	8
28	-0.11	$R^2$	0.9946
73	-0.19	Slope	-3.37E-03
136	-0.44	$k^{90}$ (s <sup>-1</sup> )	5.62E-05
197	-0.62		(± 4.05%)
257	-0.85	$t_{1/2}^{90}$ (h)	3.4
317	-1.11		
377	-1.29		

Figure I-5. Plot of  $\ln(I/I_0)$  vs time for 33e.<sup>i</sup> Resonance followed: one methyl singlet (oxadiazoline moiety) at 1.39 ppm.

First-order thermal decomposition of **33f** at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	9
25	-0.18	$R^2$	0.9752
42	-0.25	Slope	-4.28E-03
62	-0.33	$k^{90} (s^{-1})$	7.14E-05
92	-0.44		( $\pm 6.95\%$ )
122	-0.53	$t_{1/2}^{90} (h)$	2.7
152	-0.66		
197	-0.83		
242	-0.99		

Figure I-6. Plot of  $\ln(I/I_0)$  vs time for **33f**.<sup>i</sup> Resonance followed: OCH<sub>2</sub> multiplet (1H) centred at 3.62 ppm.

### First-order thermal decomposition of 33g at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
5	0.00	Observations	9
29	-0.04	$R^2$	0.9846
59	-0.12	Slope	-3.46E-03
92	-0.29	$k^{90} (s^{-1})$	5.76E-05
122	-0.41		( $\pm 6.25\%$ )
152	-0.50	$t_{1/2}^{90} (h)$	3.3
187	-0.67		
234	-0.80		
282	-1.02		

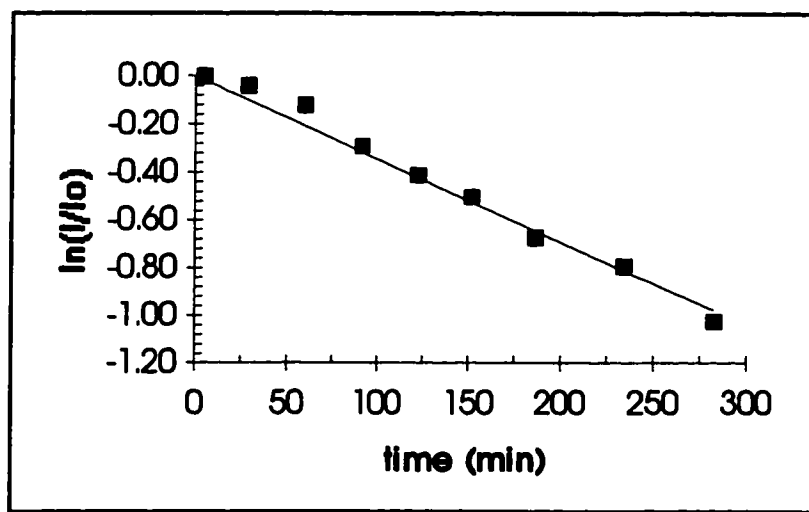
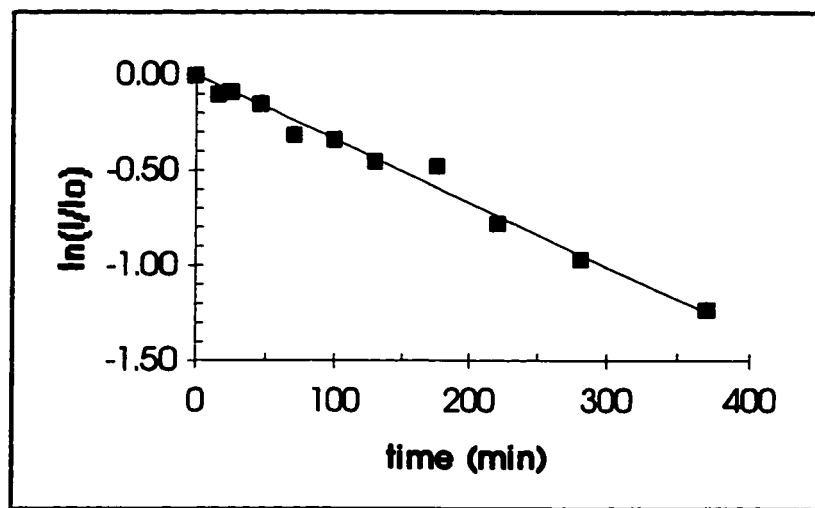


Figure I-7. Plot of  $\ln(I/I_0)$  vs time for 33g.

<sup>i</sup> Resonance followed: one methyl singlet at 1.47 ppm.

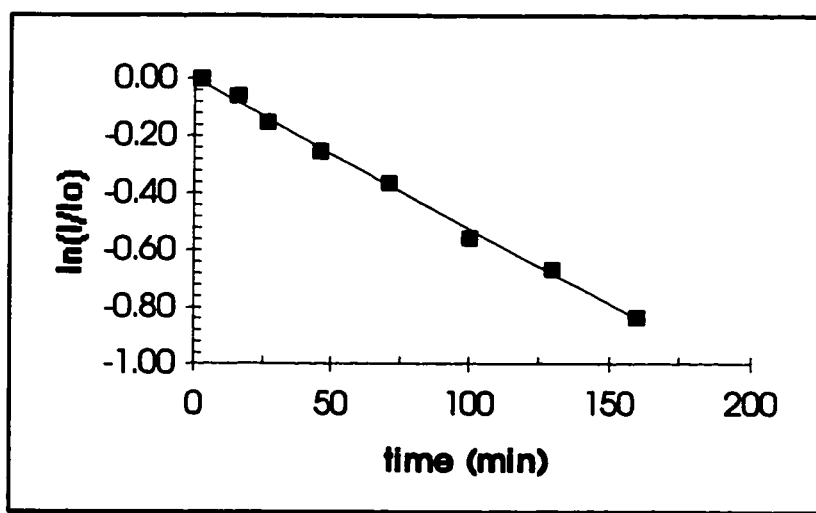
First-order thermal decomposition of **33h** at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	11
15	-0.10	$R^2$	0.9839
25	-0.09	Slope	-3.36E-03
45	-0.45	$k^{90} (s^{-1})$	<b>5.60E-05</b>
70	-0.31		( $\pm 5.79\%$ )
99	-0.34	$t_{1/2}^{90} (h)$	<b>3.4</b>
130	-0.45		
175	-0.47		
220	-0.78		
280	-0.97		
370	-1.23		

Figure I-8. Plot of  $\ln(I/I_0)$  vs time for **33h**.<sup>i</sup> Resonance followed: OCH<sub>2</sub> multiplet (1H) centred at 3.65 ppm.

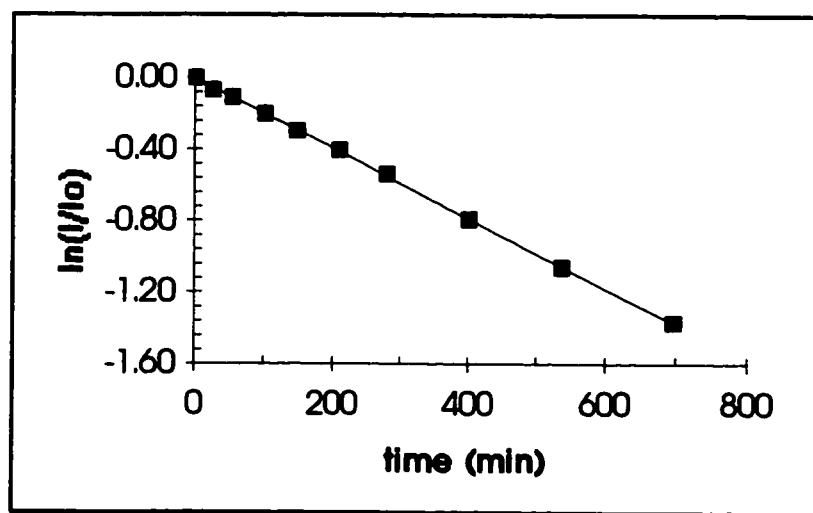
## First-order thermal decomposition of 33i at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
2	0.00	Observations	8
16	-0.06	$R^2$	0.9963
26	-0.15	Slope	-5.25E-03
46	-0.25	$k^{90}$ (s <sup>-1</sup> )	8.74E-05
71	-0.37		(± 3.35%)
100	-0.56	$t_{1/2}^{90}$ (h)	2.2
130	-0.66		
160	-0.83		

Figure I-9. Plot of  $\ln(I/I_0)$  vs time for 33i.<sup>i</sup> Resonance followed: OCH<sub>2</sub> multiplet (1H) centred at 3.61 ppm.

## First-order thermal decomposition of 33k at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
3	0.00	Observations	10
26	-0.06	$R^2$	0.9998
57	-0.10	Slope	-1.97E-03
102	-0.20	$k^{90} (s^{-1})$	3.28E-05
147	-0.29		( $\pm 0.80\%$ )
207	-0.40	$t_{1/2}^{90} (h)$	5.9
279	-0.54		
400	-0.79		
536	-1.05		
695	-1.37		

Figure I-10. Plot of  $\ln(I/I_0)$  vs time for 33k.

<sup>i</sup> Resonances followed: average of the two methyl singlets at 1.32 ppm and 1.78 ppm.



# First-order thermal decomposition of 106c at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	7
47	-0.28	$R^2$	0.9970
99	-0.55	Slope	-5.41E-03
141	-0.81	$k^{90}$ (s <sup>-1</sup> )	9.02E-05
231	-1.24		(± 3.24%)
291	-1.50	$t_{1/2}^{90}$ (h)	2.1
383	-2.11		

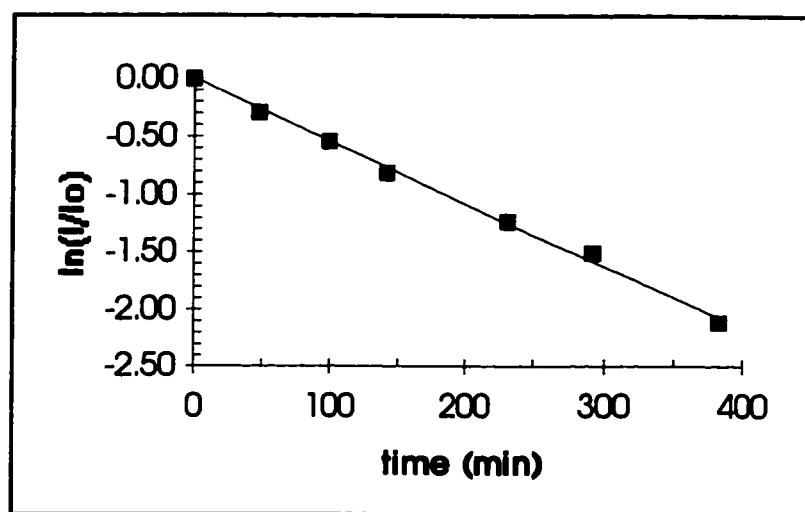


Figure I-11. Plot of  $\ln(I/I_0)$  vs time for 106c.

<sup>i</sup> Resonance followed: OCH<sub>2</sub> multiplet (1H) centred at 4.04 ppm.

### First-order thermal decomposition of **106d** at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	5
25	-0.85	$R^2$	0.9849
50	-1.70	Slope	-2.89E-02
75	-2.23	$k^{90}$ (s <sup>-1</sup> )	<b>4.82E-04</b>
110	-3.00	(± 11.5%)	
		$t_{1/2}^{90}$ (h)	<b>0.40</b>

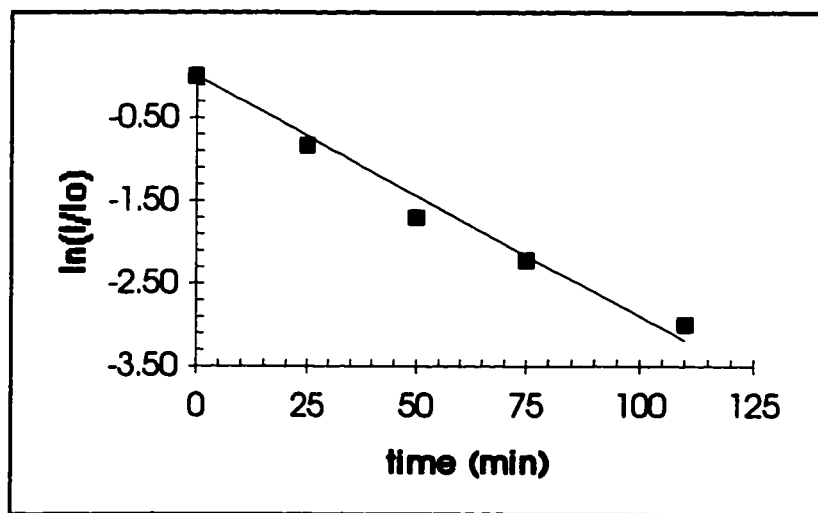
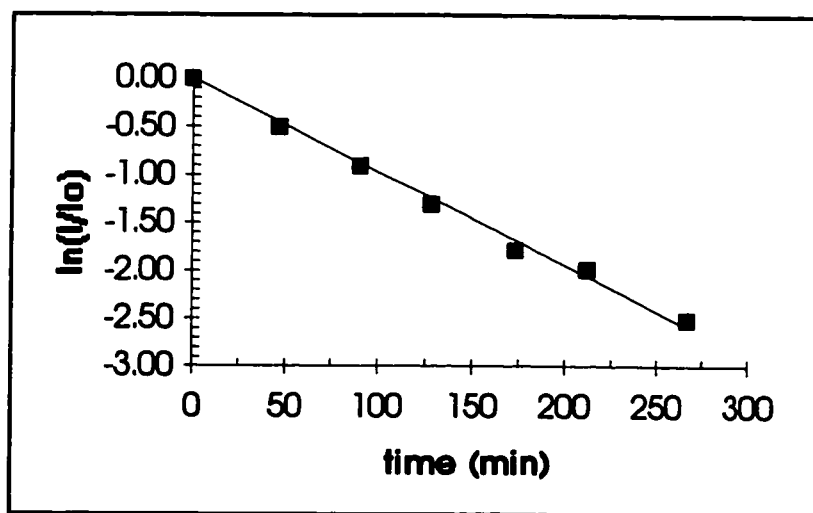


Figure I-12. Plot of  $\ln(I/I_0)$  vs time for **106d**.

<sup>i</sup> Resonance followed: one methyl singlet at 1.82 ppm.

# First-order thermal decomposition of **106e** at 90 °C

time (min)	$\ln(I/I_0)^i$	Regression Analysis	
0	0.00	Observations	7
46	-0.51	$R^2$	0.9782
90	-0.90	Slope	-9.69E-03
127	-1.30	$k^{90}$ (s <sup>-1</sup> )	1.62E-04
173	-1.77		(± 4.07%)
212	-2.00	$t_{1/2}^{90}$ (h)	1.2
266	-2.51		



**Figure I-13.** Plot of  $\ln(I/I_0)$  vs time for **106e**.

<sup>i</sup> Resonance followed: multiplet from two *ortho* protons centred at 7.38 ppm.

## Appendix II - Inversion Barriers in 2-Aryloxy-3-methyloxazolidines **119a,b**

### *Experimental*

Compounds **119a** (11 mg) and **119b** (31 mg) were each dissolved in approximately 1 ml of hexachloro-1,3-butadiene.  $^1\text{H}$  spectra were recorded at temperatures up to 140 °C on a Bruker AC-300 NMR spectrometer equipped with a variable-temperature control unit. Temperatures were measured, after allowing sufficient equilibration time, by means of a thermocouple inserted in an NMR tube and lowered inside the probe. Careful shimming was accomplished, using the FID, before each acquisition. Sixteen scans were collected for each spectrum, with the magnetic field "unlocked". A final spectrum acquired at room temperature after the conclusion of the high-temperature experiments was identical to the initial spectrum, and thus confirmed the "reversibility" of this dynamic process.

### *NMR data and calculations*

As explained in Section 2.4.1.2.1,  $\Delta G^\ddagger$  was calculated from eq. 52. For both compounds, a barrier of 20.4 kcal/mol is obtained using both the C2-H and NCH<sub>3</sub> singlets.

$$(52) \quad \frac{\Delta G^\ddagger}{RT_c} = 22.96 + \ln\left(\frac{T_c}{f_{\text{obs}}}\right)$$

#### Oxazolidine 119a

##### **C2-H**

$T_c = 120\text{ }^\circ\text{C}$

$\delta\nu = 16.1\text{ Hz}$

Calc'd  $\Delta G^\ddagger = 20.4\text{ kcal/mol}$   
(85.4 kJ/mol)

##### **NCH<sub>3</sub>**

$T_c = 135\text{ }^\circ\text{C}$

$\delta\nu = 47.3\text{ Hz}$

Calc'd  $\Delta G^\ddagger = 20.4\text{ kcal/mol}$   
(85.1 kJ/mol)

#### Oxazolidine 119b

##### **C2-H**

$T_c = 120\text{ }^\circ\text{C}$

$\delta\nu = 15.8\text{ Hz}$

Calc'd  $\Delta G^\ddagger = 20.4\text{ kcal/mol}$   
(85.4 kJ/mol)

##### **NCH<sub>3</sub>**

$T_c = 135\text{ }^\circ\text{C}$

$\delta\nu = 45.9\text{ Hz}$

Calc'd  $\Delta G^\ddagger = 20.4\text{ kcal/mol}$   
(85.2 kJ/mol)

### Appendix III - X-Ray Crystallography Data for Oxadiazoline 33f

**Table III-1.** Crystal data and structure refinement for 33f.

Identification code	phil2
Empirical formula	$C_{13}H_{15}N_3O_3$
Formula weight	261.28
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	$a = 8.9717(3)$ Å, $\alpha = 90^\circ$ $b = 11.2543(4)$ Å, $\beta = 90^\circ$ $c = 13.0149(5)$ Å, $\gamma = 90^\circ$
Volume, Z	1314.12(8) Å <sup>3</sup> , 4
Density (calculated)	1.321 Mg/m <sup>3</sup>
Absorption coefficient	0.096 mm <sup>-1</sup>
F(000)	552
Crystal size	.45 x .50 x .50 mm
Theta range for data collection	2.39° to 23.26°
Limiting indices	-9 ≤ h ≤ 9, -11 ≤ k ≤ 12, -14 ≤ l ≤ 8
Reflections collected	5225
Independent reflections	1885 (R(int) = 0.0139)
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	1885 / 0 / 233
Goodness-of-fit on F <sup>2</sup>	0.984
Final R indices (I > 2σ(I))	R1 = 0.0214, wR2 = 0.0622
R indices (all data)	R1 = 0.0222, wR2 = 0.0638
Absolute structure parameter	0.6(9)
Extinction coefficient	0.049(4)
Largest diff. peak and hole	0.075 and -0.074 e.Å <sup>-3</sup>

**Table III-2.** Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for **33f**.  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

	x	y	z	$U(\text{eq})$
O(1)	742(1)	8443(1)	1251(1)	60(1)
C(2)	1169(2)	9379(1)	1939(1)	59(1)
N(3)	2755(1)	9587(1)	1702(1)	61(1)
N(4)	3175(1)	8956(1)	980(1)	62(1)
C(5)	1885(1)	8257(1)	567(1)	52(1)
O(6)	1545(1)	8725(1)	-390(1)	76(1)
C(7)	2219(3)	7980(2)	-1150(1)	81(1)
C(8)	2085(2)	6758(1)	-714(1)	59(1)
N(9)	2206(1)	7016(1)	390(1)	51(1)
C(10)	1017(3)	8951(2)	3025(2)	87(1)
C(11)	308(2)	10505(2)	1695(2)	79(1)
C(12)	2771(1)	6333(1)	1162(1)	50(1)
O(13)	3040(1)	6770(1)	2001(1)	68(1)
C(14)	3035(1)	5037(1)	984(1)	49(1)
C(15)	2179(2)	4335(1)	332(1)	60(1)
C(16)	2463(2)	3125(1)	260(1)	72(1)
C(17)	3584(2)	2618(1)	823(1)	73(1)
C(18)	4432(2)	3301(1)	1471(1)	67(1)
C(19)	4157(2)	4507(1)	1559(1)	55(1)

**Table III-3.** Bond lengths (r, Å) and angles (∠, °) for 33f.

r		∠	
O(1)-C(5)	1.375(2)	C(5)-O(1)-C(2)	108.48(10)
O(1)-C(2)	1.434(2)	O(1)-C(2)-N(3)	104.10(11)
C(2)-N(3)	1.475(2)	O(1)-C(2)-C(10)	109.17(13)
C(2)-C(10)	1.500(3)	N(3)-C(2)-C(10)	109.6(2)
C(2)-C(11)	1.518(2)	O(1)-C(2)-C(11)	110.27(12)
N(3)-N(4)	1.237(2)	N(3)-C(2)-C(11)	108.32(13)
N(4)-C(5)	1.499(2)	C(10)-C(2)-C(11)	114.8(2)
C(5)-O(6)	1.386(2)	N(4)-N(3)-C(2)	111.21(11)
C(5)-N(9)	1.444(2)	N(3)-N(4)-C(5)	109.79(11)
O(6)-C(7)	1.430(2)	O(1)-C(5)-O(6)	111.10(10)
C(7)-C(8)	1.493(2)	O(1)-C(5)-N(9)	113.56(10)
C(8)-N(9)	1.469(2)	O(6)-C(5)-N(9)	105.54(10)
N(9)-C(12)	1.363(2)	O(1)-C(5)-N(4)	105.30(10)
C(12)-O(13)	1.222(2)	O(6)-C(5)-N(4)	107.03(11)
C(12)-C(14)	1.496(2)	N(9)-C(5)-N(4)	114.21(10)
C(14)-C(19)	1.389(2)	C(5)-O(6)-C(7)	107.77(11)
C(14)-C(15)	1.391(2)	O(6)-C(7)-C(8)	104.07(13)
C(15)-C(16)	1.389(2)	N(9)-C(8)-C(7)	100.56(12)
C(16)-C(17)	1.369(3)	C(12)-N(9)-C(5)	120.14(10)
C(17)-C(18)	1.371(2)	C(12)-N(9)-C(8)	129.54(11)
C(18)-C(19)	1.384(2)	C(5)-N(9)-C(8)	109.42(10)
		O(13)-C(12)-N(9)	120.36(11)
		O(13)-C(12)-C(14)	119.96(11)
		N(9)-C(12)-C(14)	119.67(11)
		C(19)-C(14)-C(15)	119.05(12)
		C(19)-C(14)-C(12)	116.74(11)
		C(15)-C(14)-C(12)	124.10(12)
		C(16)-C(15)-C(14)	119.77(14)
		C(17)-C(16)-C(15)	120.5(2)
		C(16)-C(17)-C(18)	120.2(2)
		C(17)-C(18)-C(19)	120.2(2)
		C(18)-C(19)-C(14)	120.31(14)

**Table III-4.** Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 33f. The anisotropic displacement factor exponent takes the form:  $-\pi^2(h^2a^{*2}U11 + \dots + 2hka^*b^*U12)$ .

	U11	U22	U33	U23	U13	U12
O(1)	42(1)	59(1)	78(1)	-20(1)	2(1)	-3(1)
C(2)	55(1)	51(1)	69(1)	-11(1)	-5(1)	-2(1)
N(3)	56(1)	47(1)	81(1)	5(1)	-16(1)	-4(1)
N(4)	48(1)	53(1)	83(1)	12(1)	-2(1)	0(1)
C(5)	46(1)	52(1)	58(1)	2(1)	-4(1)	8(1)
O(6)	95(1)	69(1)	65(1)	7(1)	-14(1)	28(1)
C(7)	109(1)	78(1)	57(1)	11(1)	-1(1)	19(1)
C(8)	55(1)	70(1)	51(1)	-4(1)	0(1)	9(1)
N(9)	50(1)	52(1)	51(1)	-1(1)	-4(1)	8(1)
C(10)	112(2)	72(1)	75(1)	-14(1)	14(1)	-5(1)
C(11)	71(1)	65(1)	102(1)	-22(1)	-19(1)	13(1)
C(12)	47(1)	50(1)	54(1)	2(1)	-4(1)	-3(1)
O(13)	91(1)	55(1)	59(1)	-4(1)	-21(1)	4(1)
C(14)	46(1)	48(1)	52(1)	3(1)	4(1)	-5(1)
C(15)	50(1)	60(1)	69(1)	-3(1)	0(1)	-7(1)
C(16)	68(1)	59(1)	89(1)	-16(1)	6(1)	-14(1)
C(17)	76(1)	47(1)	98(1)	1(1)	19(1)	-3(1)
C(18)	66(1)	55(1)	80(1)	16(1)	6(1)	4(1)
C(19)	55(1)	51(1)	59(1)	8(1)	-3(1)	-5(1)



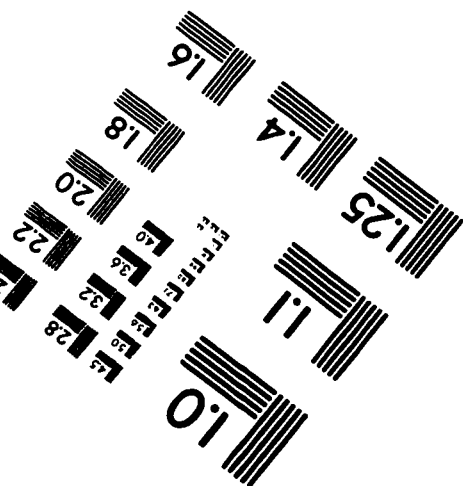
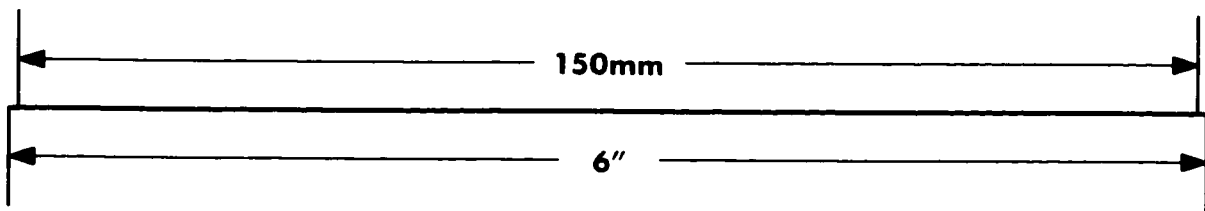
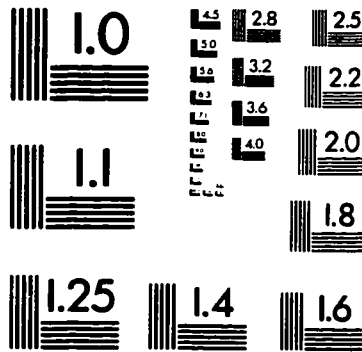
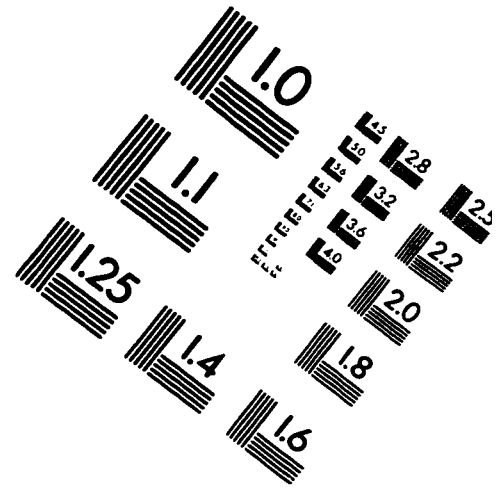
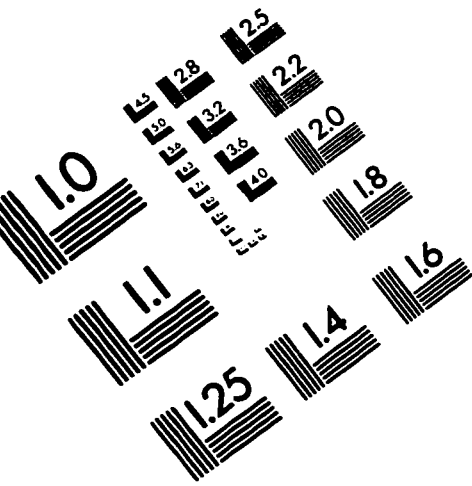
**Table III-5.** Hydrogen coordinates (  $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 33f.

	x	y	z	U(eq)
H(7A)	3425(27)	8216(20)	-1201(17)	110(7)
H(7B)	1718(21)	8116(16)	-1755(16)	86(5)
H(8A)	2848(17)	6217(13)	-927(11)	58(4)
H(8B)	1099(19)	6369(13)	-870(11)	61(4)
H(10A)	1374(24)	9534(21)	3458(17)	95(6)
H(10B)	-40(33)	8783(25)	3160(20)	127(9)
H(10C)	1589(26)	8267(22)	3122(16)	103(7)
H(11A)	639(23)	11173(20)	2095(15)	91(5)
H(11B)	-729(27)	10427(19)	1846(17)	103(7)
H(11C)	393(23)	10653(20)	953(18)	100(7)
H(15)	1388(20)	4683(14)	-91(13)	69(4)
H(16)	1872(22)	2679(18)	-193(15)	92(6)
H(17)	3764(20)	1773(18)	776(13)	85(5)
H(18)	5227(20)	2951(17)	1863(14)	74(5)
H(19)	4708(20)	4955(14)	2047(13)	67(4)

**Table III-6. Selected torsion angles for 33f.**

C5-O1-C2-N3	-8.93	(0.13)
C5-O1-C2-C10	-125.92	(0.15)
C5-O1-C2-C11	107.06	(0.15)
O1-C2-N3-N4	3.23	(0.14)
C10-C2-N3-N4	119.91	(0.14)
C11-C2-N3-N4	-114.12	(0.14)
C2-N3-N4-C5	3.34	(0.14)
C2-O1-C5-O6	-104.83	(0.12)
C2-O1-C5-N9	136.38	(0.11)
C2-O1-C5-N4	10.71	(0.13)
N3-N4-C5-O1	-8.96	(0.14)
N3-N4-C5-O6	109.34	(0.12)
N3-N4-C5-N9	-134.23	(0.11)
O1-C5-O6-C7	-146.74	(0.13)
N9-C5-O6-C7	-23.24	(0.16)
N4-C5-O6-C7	98.80	(0.15)
C5-O6-C7-C8	35.92	(0.18)
O6-C7-C8-N9	-32.46	(0.17)
O1-C5-N9-C12	-66.57	(0.14)
O6-C5-N9-C12	171.49	(0.11)
N4-C5-N9-C12	54.20	(0.16)
O1-C5-N9-C8	123.34	(0.12)
O6-C5-N9-C8	1.41	(0.14)
N4-C5-N9-C8	-115.88	(0.12)
C7-C8-N9-C12	-149.54	(0.14)
C7-C8-N9-C5	19.32	(0.15)
C5-N9-C12-O13	-1.61	(0.18)
C8-N9-C12-O13	166.22	(0.14)
C5-N9-C12-C14	177.24	(0.11)
C8-N9-C12-C14	-14.93	(0.20)
O13-C12-C14-C19	-28.98	(0.18)
N9-C12-C14-C19	152.16	(0.12)
O13-C12-C14-C15	147.19	(0.13)
N9-C12-C14-C15	-31.67	(0.18)
C19-C14-C15-C16	-0.54	(0.20)
C12-C14-C15-C16	-176.62	(0.13)
C14-C15-C16-C17	-0.21	(0.23)
C15-C16-C17-C18	0.46	(0.24)
C16-C17-C18-C19	0.04	(0.24)
C17-C18-C19-C14	-0.79	(0.22)
C15-C14-C19-C18	1.03	(0.20)
C12-C14-C19-C18	177.41	(0.13)

# IMAGE EVALUATION TEST TARGET (QA-3)



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