A MICHAEL ADDITION APPROACH TOWARDS A THIENAMYCIN SYNTHESIS

by

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A MICHAEL ADDITION APPROACH TOWARDS A THIENAMYCIN SYNTHESIS

To my wife and friend

Shahin

DOCTOR OF PHILOSOPHY (1983)
(Chemistry)

McMASTER UNIVERSITY
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TITLE: A Michael Addition Approach Towards a Thienamycin Synthesis

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ABSTRACT

A number of 2-aryl, 2-alkyl-4-[(E and Z)-1-alkoxyethylidene]-5-oxazolones, 2-alkylthio-4-[(E and Z)-1-alkoxyethylidene]-5-thiazolones and 2-ethoxy-4-[(E and Z)-1-ethoxyethylidene]-5-thiazolone were prepared. The configurations of the E and Z isomers of these compounds were assigned on the basis of the X-ray crystal structure of 4-[(Z)-1-ethoxyethylidene]-2-phenyl-5-oxazolone and by ^{1}H and ^{13}C chemical shift data. These compounds were studied for reactivity to nucleophiles and electrophiles. Substitution reactions on the alkoxyethylidene portion of these compounds were effected with nitrogen, oxygen and sulfur nucleophiles and reaction with ring positions of 4-[(Z)-1-ethoxyethylidene]-2-phenyl-5-oxazolone and 2-ethoxy-4-[(Z)-1-ethoxyethylidene]-5-thiazolone gave ethyl 2-benzamido-3-ethoxy-2-butenoate and 4-[(Z)-1-ethoxyethylidene]-2,5-thiazolidinedione. The later product was ring opened to give ethyl 3-ethoxy-2-[N-methyl(methylthioamido)]-2-butenoate.

Dienolate anions of many of the 4-(1-alkoxyethylidene)-5-oxazolones and corresponding thiazolones were prepared by removal of an allylic proton. These anions reacted with methyl 2-(chloromethylene)-3-oxobutanoate in a Michael reaction. The resulting 4-(1-alkoxy-4-carbomethoxy-5-hydroxy-2,4-hexadienylidene)-5-oxazolones and thiazolones were found to be susceptible

tible to cyclization to the corresponding 4-(5-carbomethoxy-6-methyl-2-pyranylidene)-5-oxazolones and thiazolones.

The dienolate anion of 4-[(Z)-1-ethoxyethylidene]-2-phenyl-5-oxazolone, was found to undergo Michael addition reactions with methyl 2-(chloromethylene)-3-oxobutanoate, methyl 2-(methoxymethylene)-3-oxobutanoate and ethyl 2-(phenylthio)-propenoate but not with ethyl 2-(phenylsulfinyl)propenoate, methyl (Z)-3-bromopropenoate and methyl (E)-3-chloropropoenoate.

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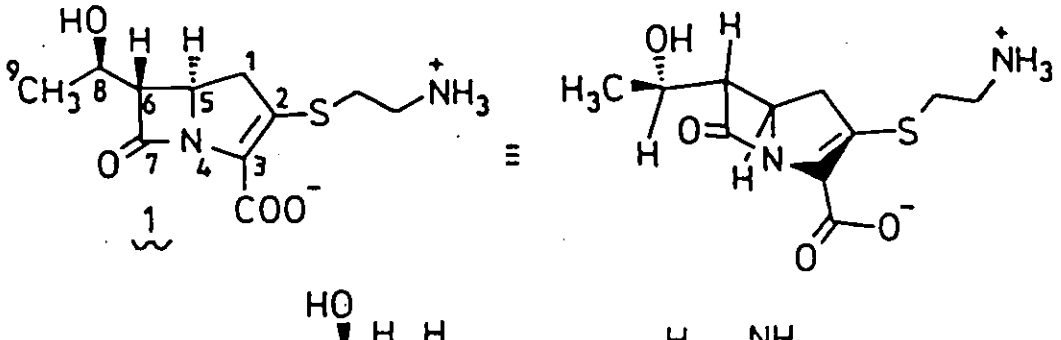
INTRODUCTION

CHAPTER 1

REVIEW OF THIENAMYCIN

1.1 Thienamycin: Isolation, Structure and Biological Activity

Thienamycin, 1, is an antibiotic of exceptional potency and breadth of antibacterial activity. It was isolated by researchers in the Merck, Sharp and Dohme Research Laboratories (Rahway N.J.) from fermentation broths of the soil microorganism *Steptomyces cattleya* (1-3). This β-lactam antibiotic shows high potency against gram-positive and the full range of gram-negative bacteria. Of particular interest is its activity against *Pseudomonas* species and its resistance to bacterial β-lactamases (1). Recently, several other related antibiotics,



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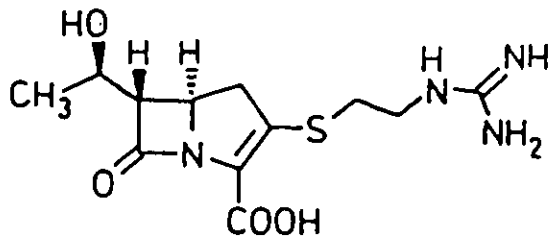


2

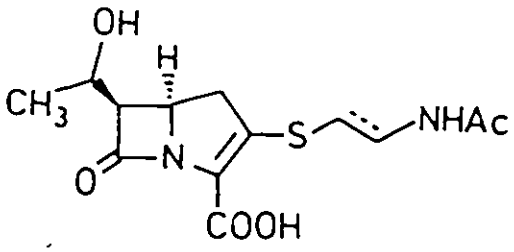
3 - 9 (see Figure 1.1), have been isolated (4,5), but thienamycin remains unique in its breadth of antibiotic potency (6).

Thienamycin's pharmaceutical potential and the failure of a viable commercial preparation by fermentation processes (6) have catalyzed experimental efforts towards its total synthesis (see Section 1.2). Merck, Sharp and Dohme is already preparing the synthetic antibiotic in bulk quantities for clinical testing. The drug is to be marketed soon as the formamidine derivative, 2 (6).

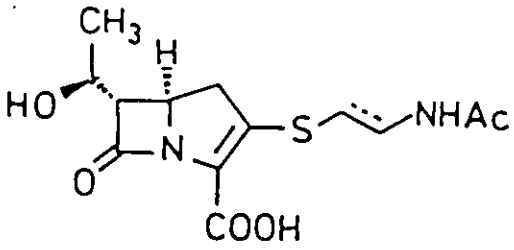
Thienamycin has three structural features not found in the 'classical' β-lactam antibiotics, the penicillins, 10, and cephalosporins, 11 (see Figure 1.2). Firstly, the unusual hydroxyethyl side chain is present on the α-face (trans to the pyrrolidine ring junction) rather than the 'classical' amido functionality on the β-face. Secondly, the cysteamine (2-aminoethanethiol) side chain is unique to thienamycin and its analogues. Finally, the nucleus contains an unsaturated 5-membered ring with a methylene replacing the sulfur in position 1 of the classical antibiotics (7).

It is interesting to note that 1-carbapen-2-em-3-carboxylic acid, 12, is, in itself, an antibiotic (7). However, most of the other structural features of thienamycin have proved important to its activity against bacterial strains resistant to other β-lactam antibiotics (4,7,8).

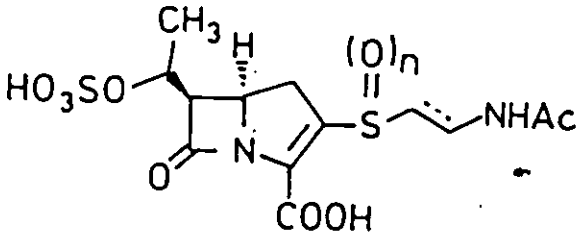
Figure 1.1: Thienamycin Analogues



saturated - 3
unsaturated - 4

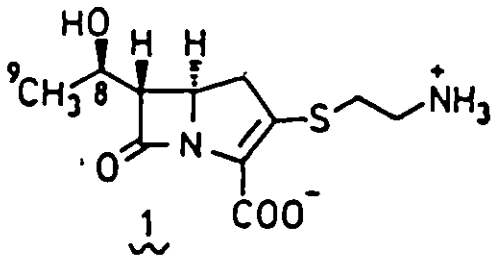


saturated - 5
unsaturated - 6

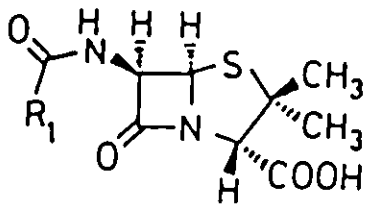


n = 0, unsaturated - 7
n = 1, unsaturated - 8
n = 0, saturated - 9

Figure 1.2: Structural Features of β-Lactam Antibiotics



1



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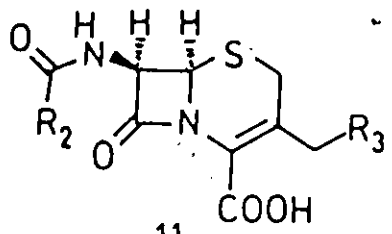

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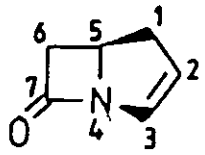
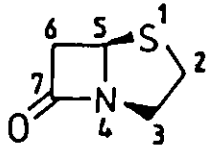
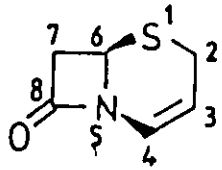


1-carbapen-2-em



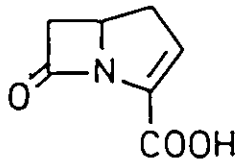
penam



ceph-3-em

α-face - below the plane of the paper
β-face - above the plane of the paper

The numbering system of the thienamycin skeleton is chosen to be consistent with other β-lactam antibiotics.



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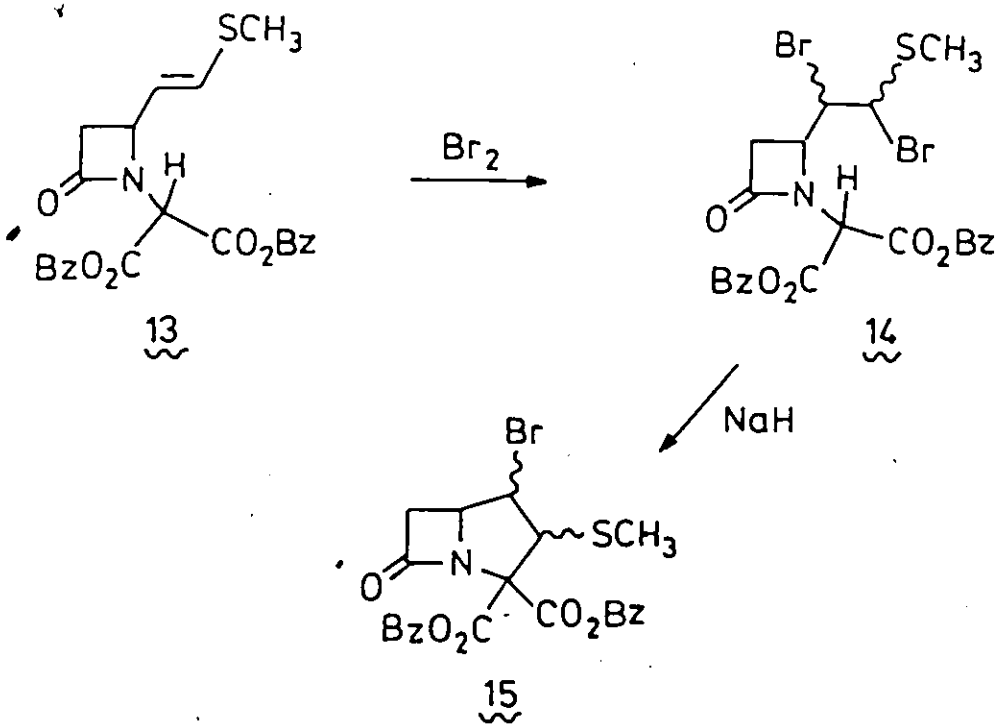
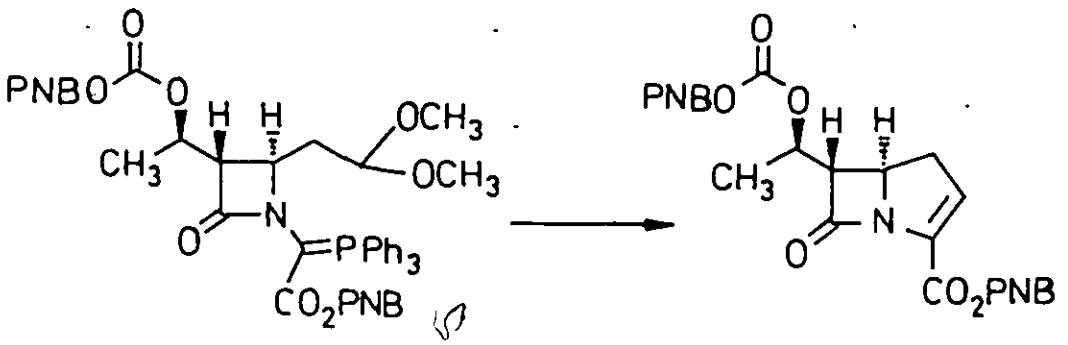
1.2: Thienamycin: A Review of Previous Synthetic Studies

The report by the Merck research team to the Sixteenth Interscience Conference on Antimicrobial Agents and Chemotherapy in October of 1976 (1) (and subsequent publications (2,3)) on the isolation, structure and antibacterial potency of thienamycin, 1, sparked much activity towards its chemical synthesis. Efforts, mainly by the Merck and Kametani (Pharmaceutical Institute, Tohoku University, Japan) groups have already led to the total syntheses of the racemic (9-22) and optically active (23-25) antibiotic.

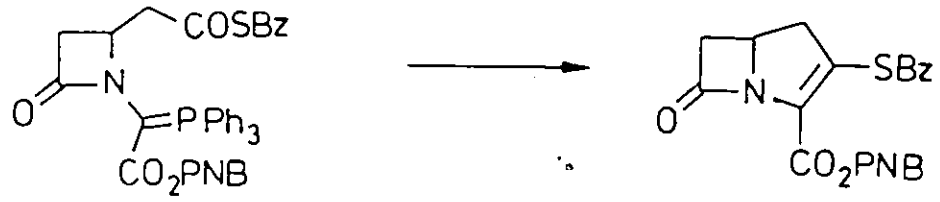
There are two major challenges in the thienamycin synthetic stratagem, the bicyclic carbapenem (or carbapenam) preparation and the stereocontrol of the three chiral centres. Four approaches have been successfully applied to the preparation of the carbapenam skeleton. The first, developed in model studies by a Merck group (11) involved the bromination of 13 to give 14 which, on treatment with sodium hydride, formed the carbapenam 15. The procedure has been used in the total syn-



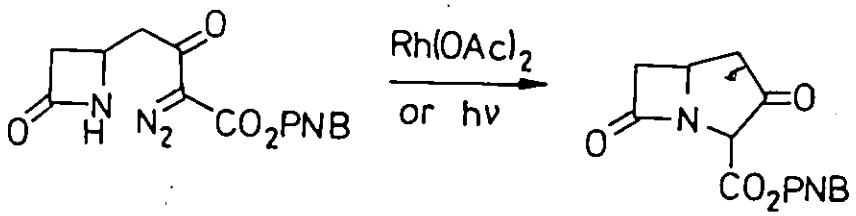
thesis of thienamycin (9,12) and some of its derivatives (7). The second method, involves a Wittig cyclization as illustrated in the following examples (19,26).



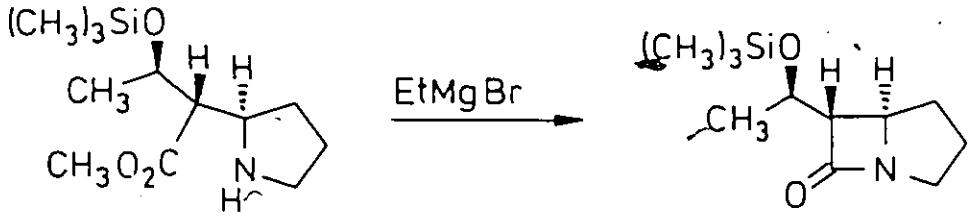
PNB = O_2N—⟨benzene⟩—CH_2—



Although this method has been applied satisfactorily in model studies and in the preparation of some thienamycin derivatives, its use in the preparation of thienamycin itself has had poor success (21). The third route, also pioneered by the Merck group (27) and used in thienamycin total syntheses (14,15, 21-25,28) involves a carbene insertion into a N-H bond (see below). The final method, which has not been used in a thiena-

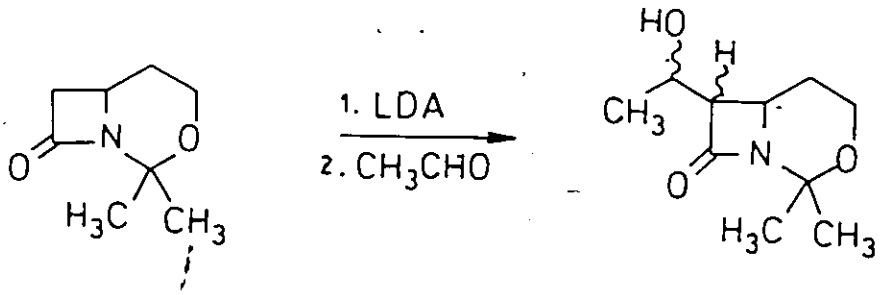


mycin synthesis, is the lactam ring closure of the α-amino acid derivative as illustrated by the work of Tufariello and co-workers (29).



16 17

One useful route to the desired stereochemistry of thienamycin has been in the controlled introduction of the hydroxyethyl side chain. In the penicillin and cephalosporin series, the substituents at C-6 and C-7 respectively (see Figure 1.2) are cis to the ring junction (on the β-face). In thienamycin the hydroxyethyl group is in the thermodynamically more stable trans geometry. This has been used to advantage in the stereocontrol of the C-6 (and C-8) sites. The first published total synthesis (9-12) included an addition of acetaldehyde to the β-lactam giving stereoselectivity at sites C-6 and C-8 via chiral induction from C-5. A 98% yield was obtained in this transformation, 89% of which was in the trans

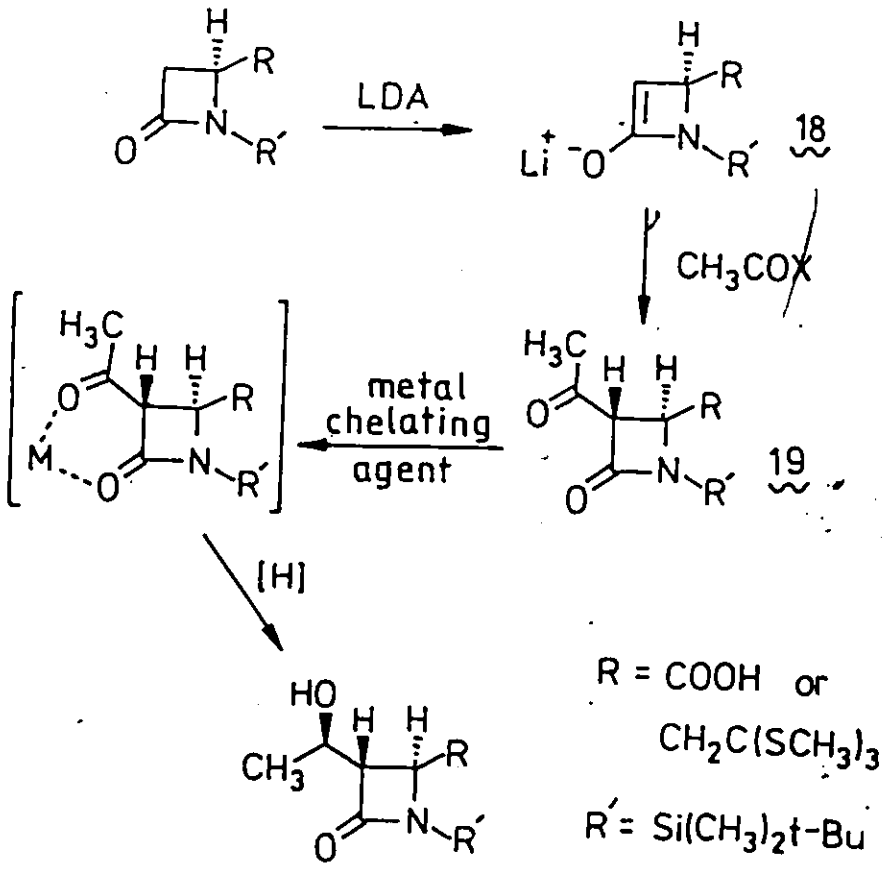


LDA = $LiN(CH(CH_3)_2)_2$

geometry with an epimeric mixture at C-8 in a 2:3 (R:S) ratio. More encouraging results (39% isolated yield of the desired 6S, 8R isomer) have been achieved by Miyashita et al. (30) and also by Salzman et al. (> 50%) (24) in similar experiments.

A modification of the stereocontrolled introduction of the two carbon unit (shown above) is via a two step sequence. Addition of acetylimidazole (CH_3COX) to the lactam anion 18 gives the trans-acetyl-lactam 19 (see Scheme 1.1). Reduction with the appropriate reagents, provides the desired stereochemistry. Two reducing agents (potassium tri(sec-butyl)boron hydride-potassium iodide and diisopropylamine-borane-magnesium trifluoroacetate) have been employed for the second step. It has been suggested that both methods involve metal cation coordination of the two carbonyls forcing hydride attack from the less hindered face. The tributylboron hydride reagent provided an

Scheme 1.1



88:12 (R:S) ratio in 81% yield (13,24) while the amine-borane reagent gave a 96:4 ratio in 79% yield (25,28).

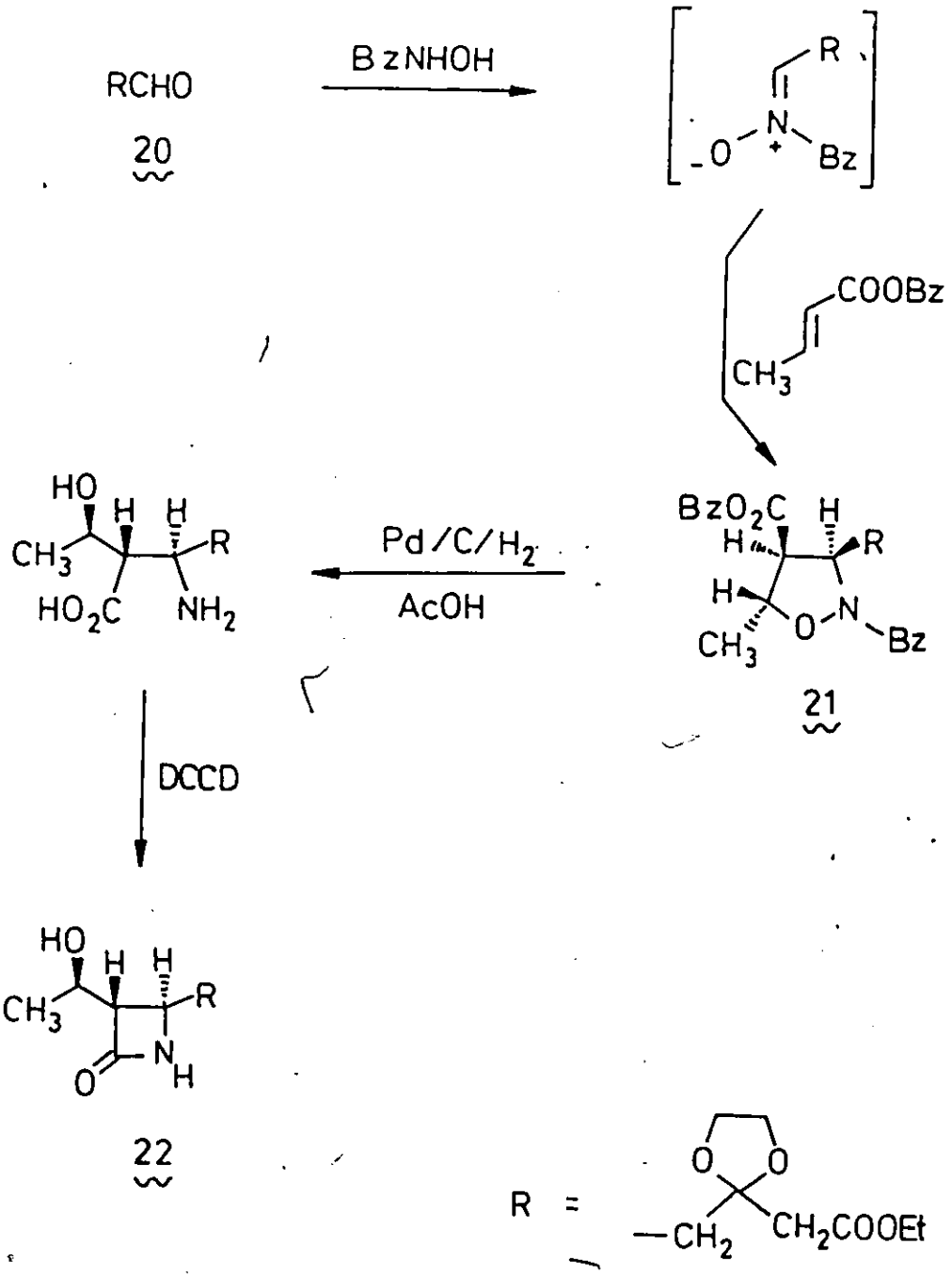
Syntheses using these hydroxyethyl side chain addition methodologies have been accomplished with materials optically active and inactive at C-5 giving both (+) and (±)-thienamycin. Thus, L-aspartic acid, when used as an optically active precursor, gives (+)-thienamycin (23-25) whereas chlorosulfonyl isocyanate and acetoxybutadiene leads to (±)-thienamycin (9-12).

Another method of stereoselection at the C-5, C-6 and C-8 sites has been via cycloadditions of nitrile oxides (16-19) and nitrones to crotonates (22,29). The nitrone method, developed by Tufariello (29) and used by the Kametani group in an imaginative synthesis of a thienamycin derivative (22), is the more successful in obtaining the desired relative stereochemical control of the two dipolar routes. After preparation of the oxazolidine, 21 (Scheme 1.2), from the aldehyde, 20, in 84% yield, catalytic hydrogenation followed by treatment of dicyclohexylcarbodiimide (DCCD) gave 22 as the sole cyclized product in 40% yield from 21 (22).

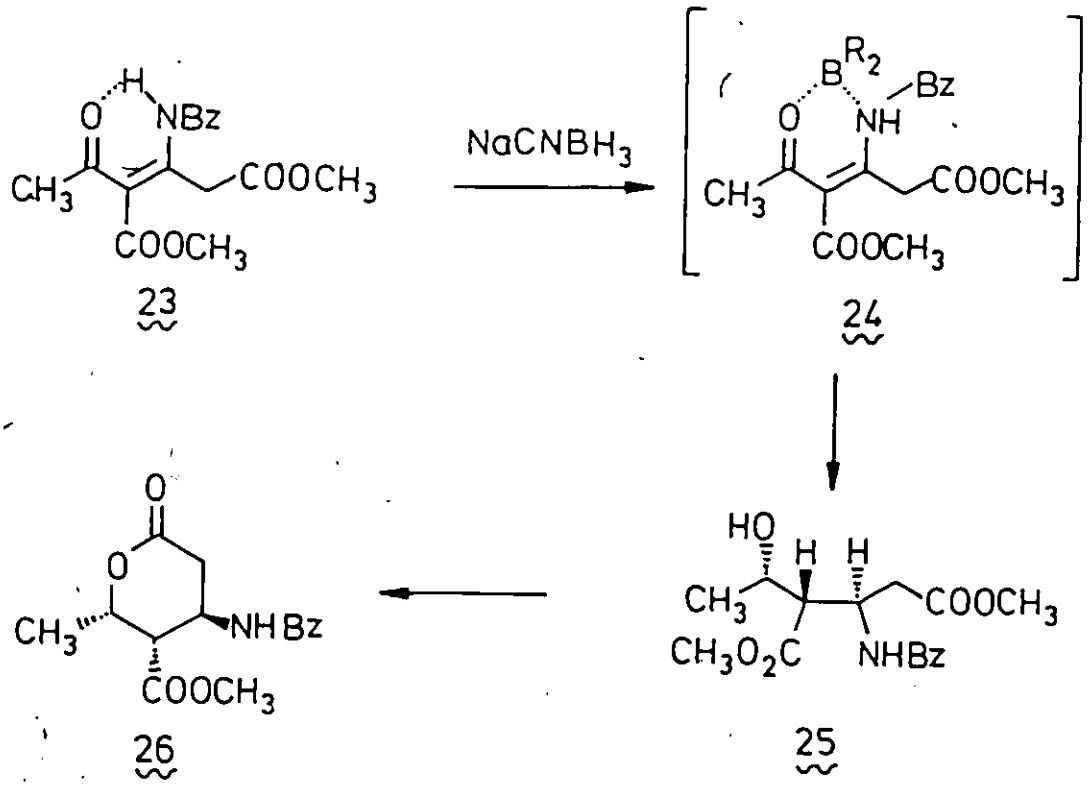
Similar stereochemical control for a key thienamycin intermediate has been achieved by reduction of the ketoenamine, 23, with a borohydride providing the diester, 25, which was isolated as the crystalline lactone 26 (14,15) (Scheme 1.3). The Merck synthetic group suggested that the high degree of stereoselectivity is a result of the rigid cyclic structure caused by boron coordination as shown in structure 24.

In addition to the work described above, there are two laborious syntheses of thienamycin intermediate with the chirality of all three pertinent carbons derived from D-glucose (31,32). Further studies in thienamycin syntheses are reported in references 33 through 38.

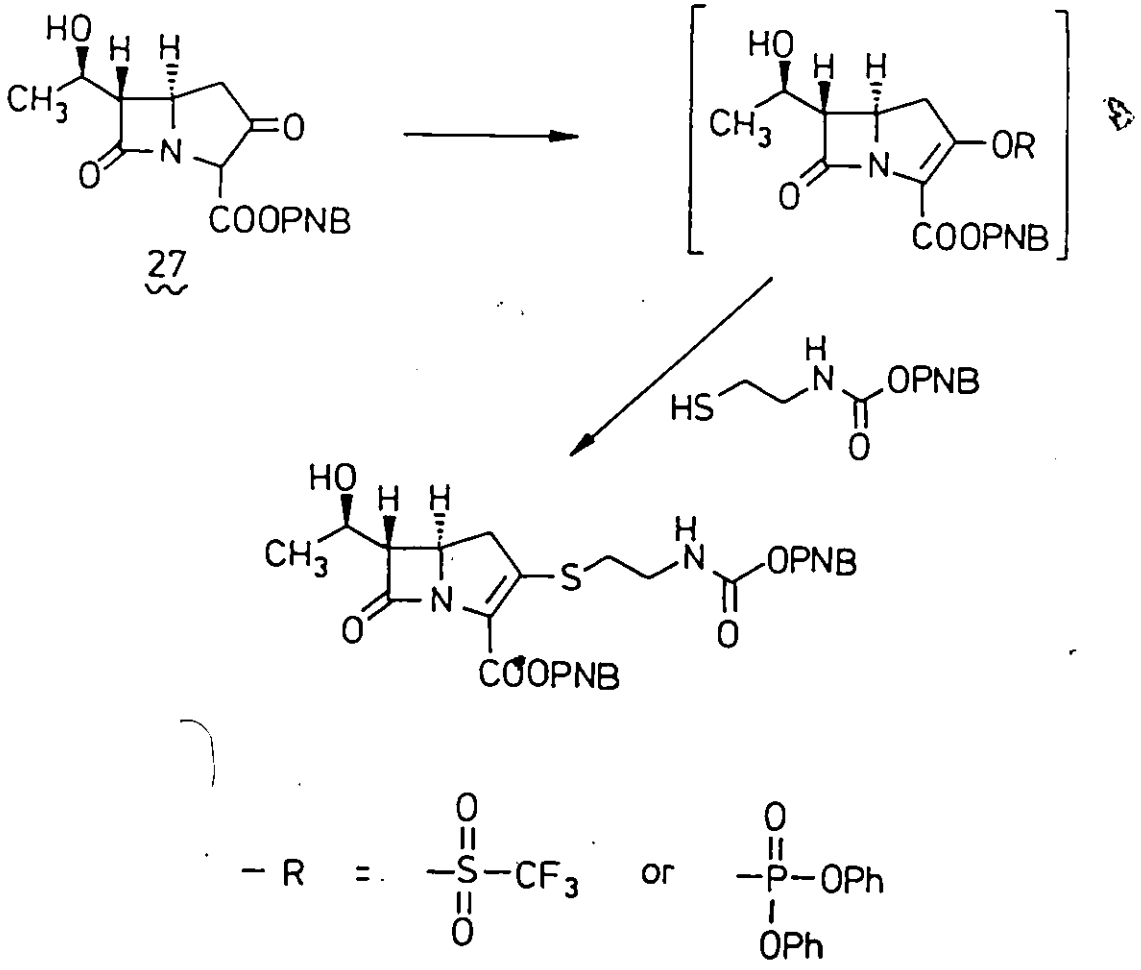
Scheme 1.2


RCHO
20
BzNHOH
R
N
O
Bz
COOBz
CH3
BzO2C
H
R
CH3
O
N
Bz
21
Pd/C/H2
AcOH
HO
H
H
CH3
R
HO2C
NH2
DCCD
HO
H
H
CH3
R
O
N
H
22
R =
O
O
CH2
CH2COOEt

Scheme 1.3



One final synthetic transformation investigated by the Merck group deserves comment. Two "one-pot" methods have been developed for the transformation of 2-oxo-3-carbalkoxycarbapenams to the N-protected 3-cysteamine moiety thus establishing the ketocarbapenam of structural type 27 as a useful target intermediate (39).



$$-R = -\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-CF_3 \quad \text{or} \quad -\overset{\overset{O}{\|}}{\underset{\underset{OPh}{|}}{P}}-OPh$$

CHAPTER 2

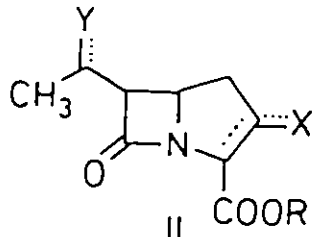
SYNTHETIC PLANNING

2.1: Overall Synthetic Plan

Outlines of the synthetic strategies for thienamycin syntheses in this project are presented in Schemes 2.1 through 2.3. The uppermost structure in each Scheme represents an immediate thienamycin precursor. The functionalities or protecting groups, X through Z, are not necessarily intented to be constant throughout the synthesis. Examples of possible protecting groups and functionalities representing various stages in the synthesis are given in Table 2.1. Precedents for transformations A, B,C, E, Q and R have already been presented in Section 1.2. Precedents are also in the literature for the intramolecular Michael addition and pyrrolidine formation represented in transformation S (40,41). Schemes 2.1 and 2.2 present two parallel routes to thienamycin. As shown in Scheme 2.3, both routes, via synthons A and B, provide alternatives in strategy late in the synthesis.

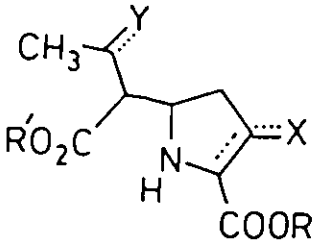
The general structure of the materials studied as potential synthons, A, B and C, in this work, are listed in Figure 2.1. The first portion of this work (Chapts. 3 and 4), deals with the synthesis, structure and properties of these materials.

Scheme 2.1 : Synthetic Strategy : Synthon 'A'

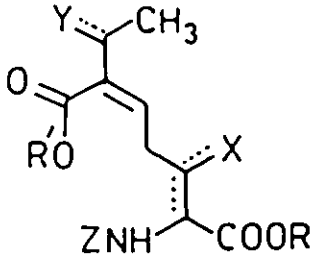


Transformation :

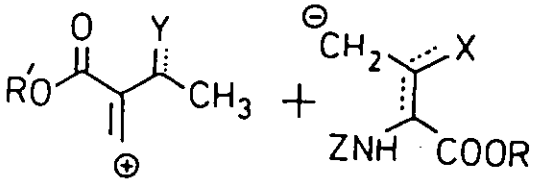
⇓ ---·-·-·-·-·- R ---·-·- β-Lactam Formation



⇓ ---·-·-·-·-·- S ---·-·- Pyrrolidine Formation

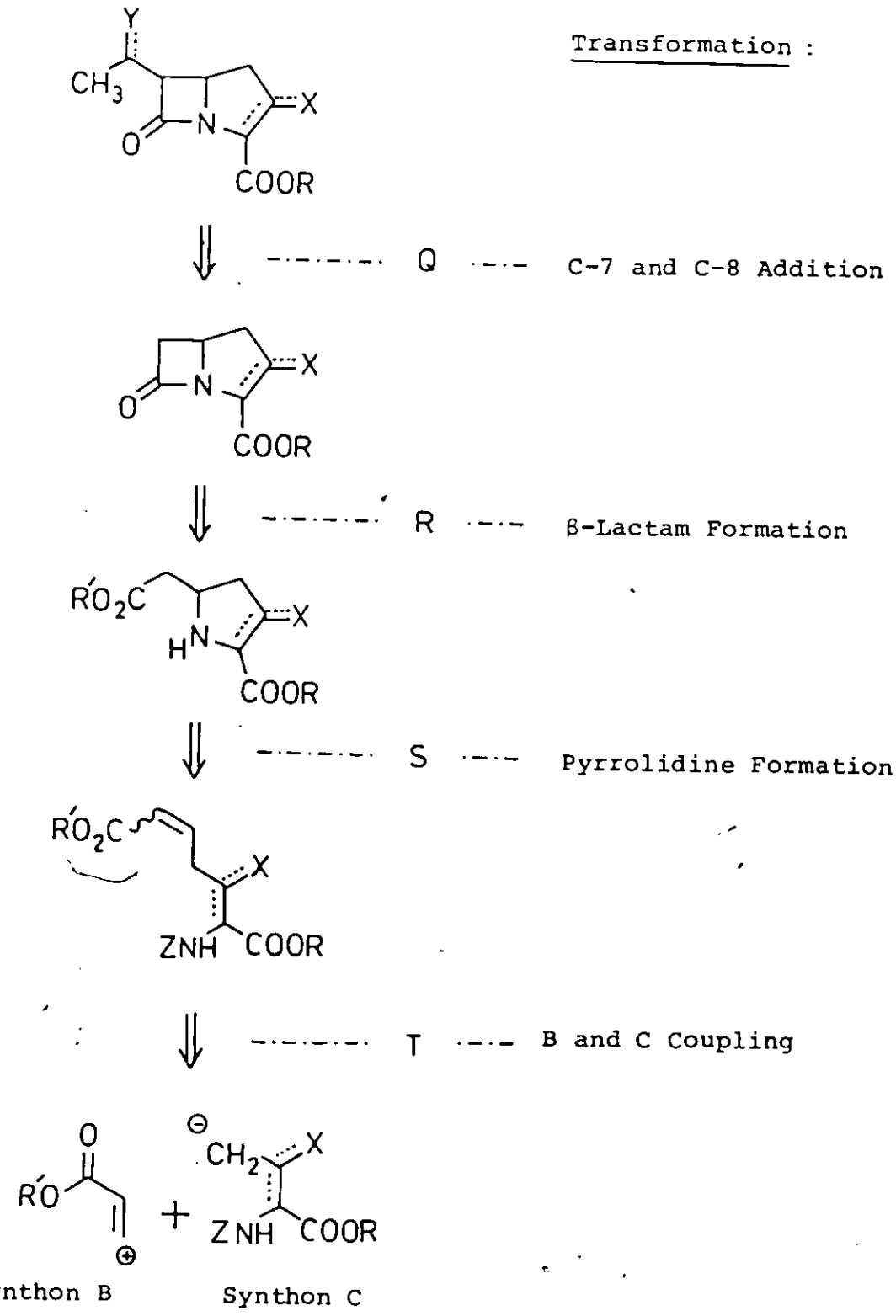


⇓ ---·-·-·-·-·- T ---·-·- A and C Coupling

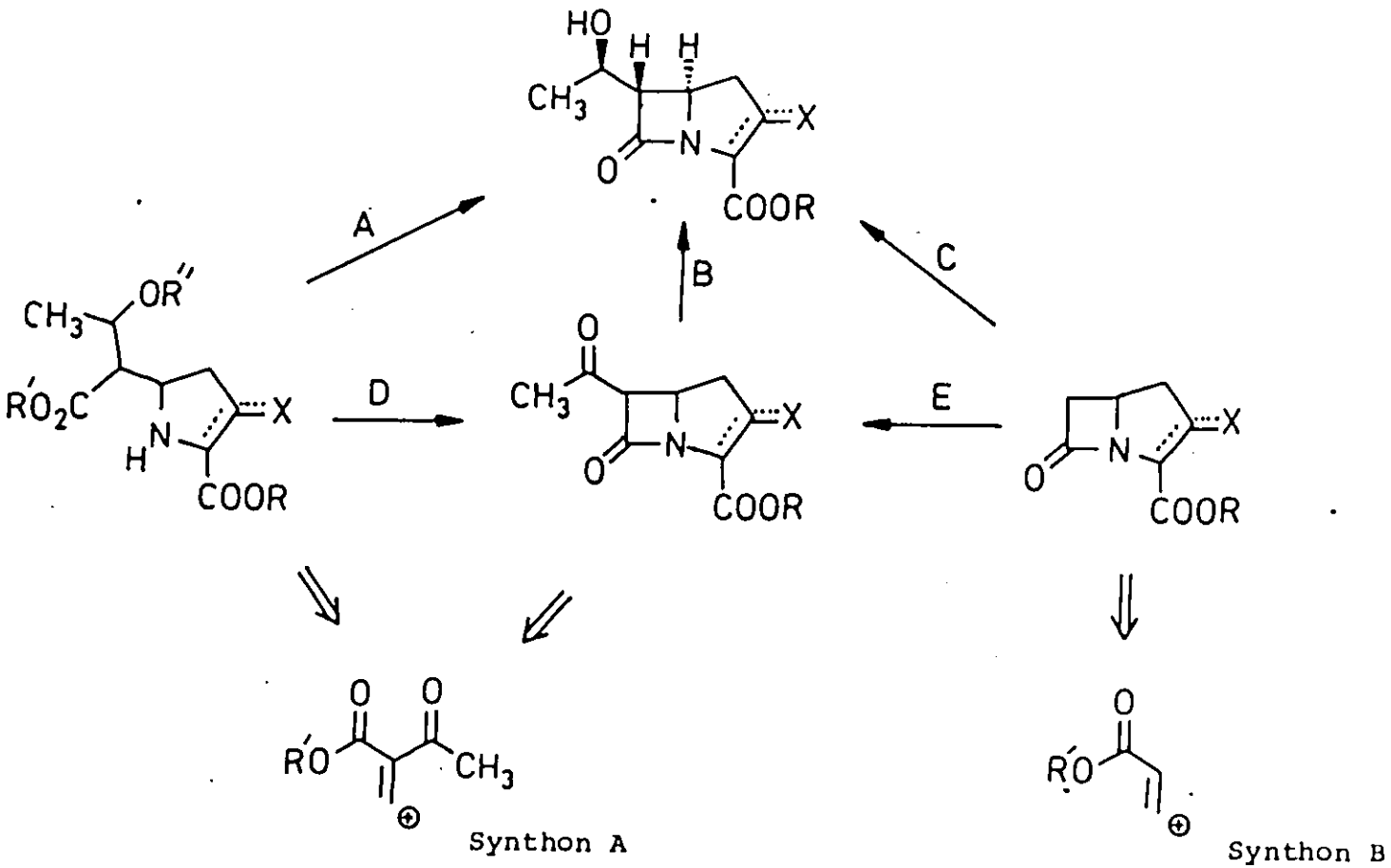


Synthon A Synthon C

Scheme 2.2 : Synthetic Strategy : Synthon 'B'

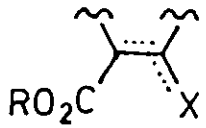
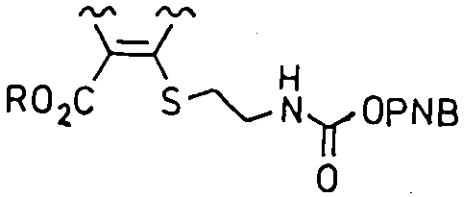
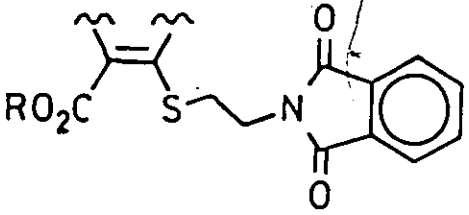
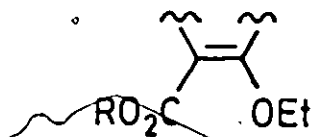
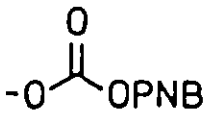
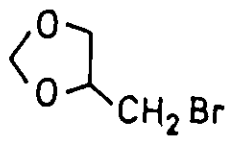


Scheme 2.3



Transformations: (A) β-Lactam Formation, (B) Acetyl Reduction, (C) Aldol addition, (D) β-Lactam formation followed by oxidation and (E) Acetyl addition.

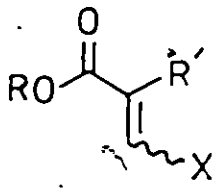
Table 2.1: Possible Protecting Groups in Thienamycin Synthesis[a]

	=Y	-R	-R´
	=O	-Et	$-CH_3$
	$-OSi(CH_3)_3$	-Bz	-Et
	$-OSi(CH_3)_2t\text{-}Bu$	-PNB	-H
		-H	
			
	-OH		

[a] these protection groups relate to Schemes 2.1-2.3

Figure 2.1: Potential Thienamycin Synthons

Substituted Acrylates

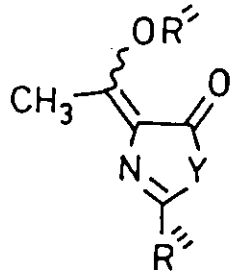


$R' = H, COCH_3, SPh, SOPh$

$X = Cl, Br, H, OCH_3$

Potential Synthons A and B

4-(1-Alkoxyethylidene)-5-oxazolones and thiazolones



$Y = S, O$

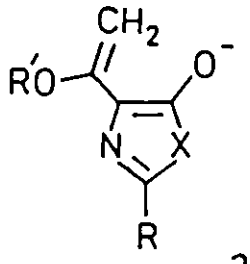
Potential Synthon C

R, R" and R'" = alkyl or aryl

The remainder of the thesis (discussed in Chapter 5) examines the coupling of these materials and also, the properties of the coupled products.

The objective of this thesis is to identify and obtain substituted acrylates, oxazolones and thiazolones with the required properties for use as synthons in the total synthesis of thienamycin. The following synthon properties are required:

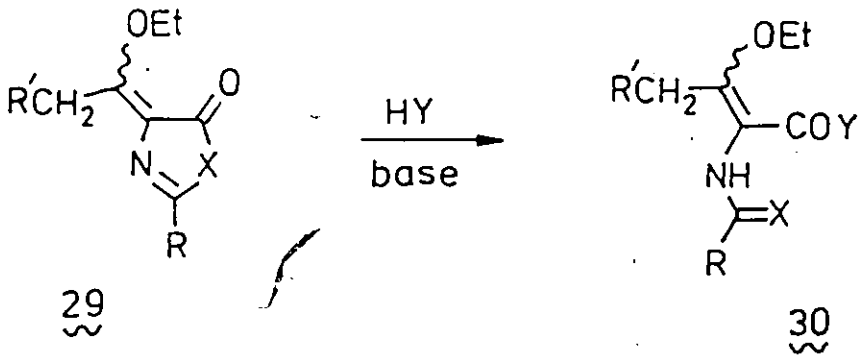
(a) The anion of the thiazolone or oxazolone (28) must be preparable and stable at temperatures required for coupling reactions.



28

(b) The donor (the anion above) must couple with the desired acrylate (the acceptor) in a Michael addition reaction.

(c) The oxazolone or thiazolone ring must be readily opened to facilitate pyrrolidine formation (see Schemes 2.1 and 2.2). Thus the type of transformation illustrated by the conversion of 29 to 30 must be possible.



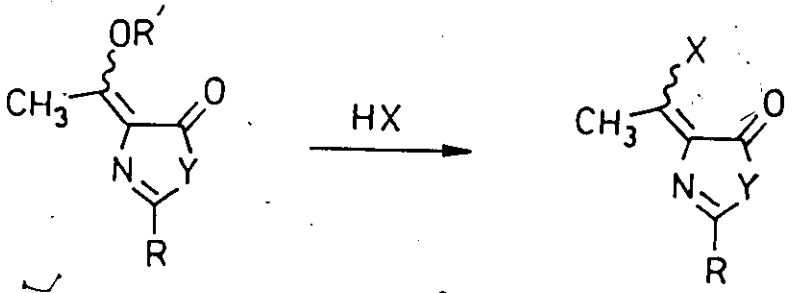
29 30

(d) The amide (or thioamide) of the resulting ring opened material (30) must be removable by hydrolysis to facilitate β-lactam formation.

In addition to the above required properties, the following properties are desirable:

(e) That the carbon-carbon double bond (in structure 30) be obtainable in the E geometry, thus facilitating pyrrolidine formation without further protecting group manipulations.

(f) That substitution be possible on the exocyclic enol ether, thus allowing more flexibility in protecting groups



and functionalities at this site.

2.2: Michael Reactions: A General Introduction

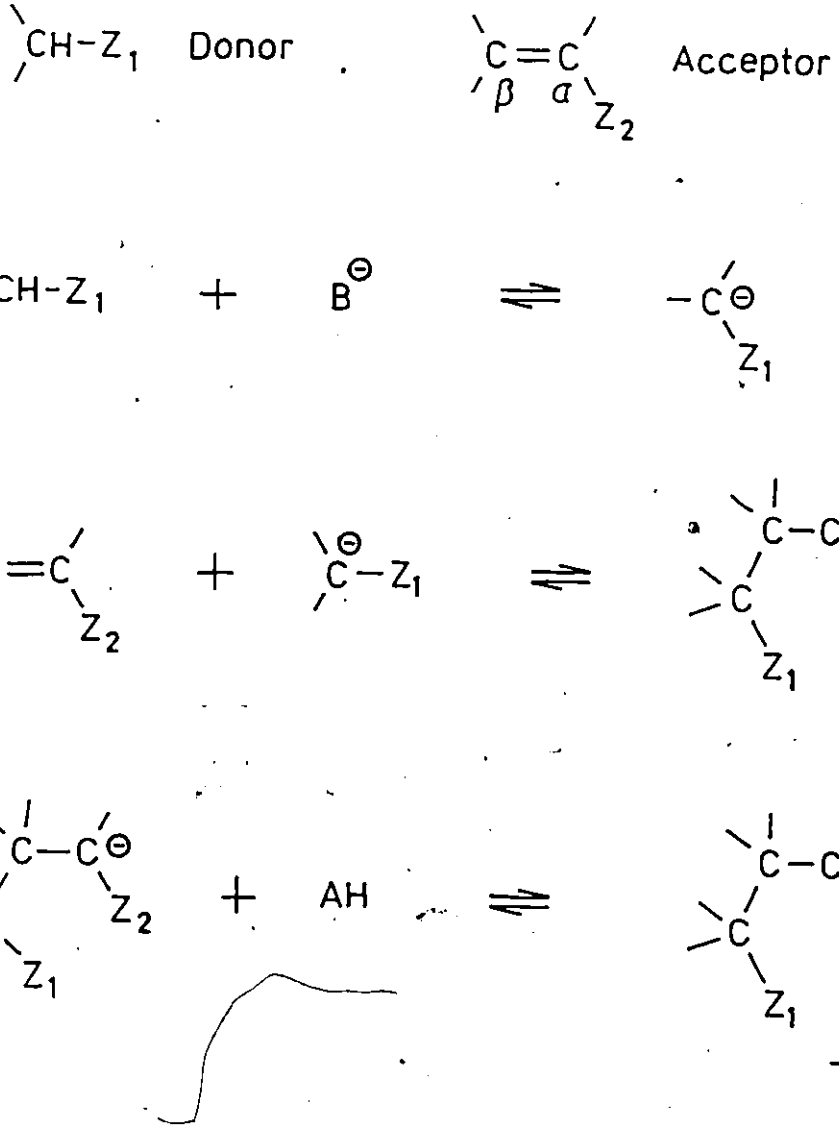
The synthetic strategy requires a Michael condensation of synthons A or B, with C. This section provides a general description of the Michael reaction as well as some of the factors influencing it.

The terms Michael addition, Michael condensation, Michael reaction and 1,4-addition will be used synonymously throughout the thesis.

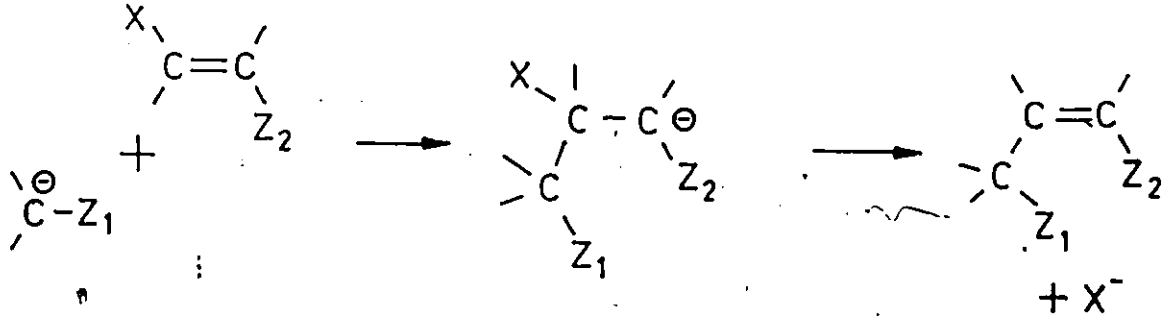
The Michael addition (42 - 45) with a carbon nucleophile can be generalized by the sequence in Scheme 2.4. Groups Z_1 and Z_2 are electron accepting groups (e.g. - CN, - $COOCH_3$, $COCH_3$). Under the reaction conditions described in this thesis, reactions [1] and [3] are irreversible. After carbanion formation is achieved, the acceptor is added for the condensation step. Acidification quenches the net reaction. The major competing reaction is polymerization of the acceptor by nucleophile promoted self-condensation. This polymerization is, in itself, a Michael addition.

The balance of the equilibrium of equation [2] is dependent on the relative energies of products versus reactants. If a good leaving group, X, is present on the β-position, then the reaction sequence in Scheme 2.4 is altered and the possibility of equilibrium is no longer present (Scheme 2.5). The net sequence is more than a simple Michael addition; the addition is succeeded by a rapid elimination. The result is a

Scheme 2.4



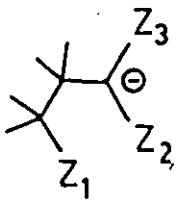
Scheme 2.5



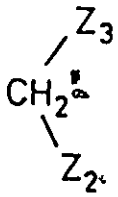
substitution of the β-carbon and will be denoted subsequently as a Michael substitution.

In a Michael reaction with any one donor, an estimate of the order of the activation energies, and thus the order of reactivity of acceptors, can often be predicted successfully (43). Estimates of activation energies can be approached from either side of the position of the transition state on the reaction coordinate. Relative product stabilities indicate the relative energies late in the reaction coordinate while an indication of relative energies early in the reaction coordinate is available from frontier orbital theory (46 - 49). Both methods are used frequently for estimating relative transition state energies and thus relative reactivities (43,49).

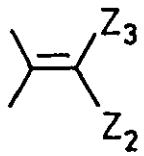
The relative stabilities of the product anions, 31, are related to the abilities of the Z_2 and Z_3 groups to stabilize a negative charge. Thus, in general, pK_a values of the carbon



31



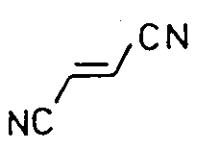
32



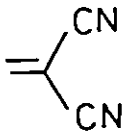
33

acids 32 successfully predict the order of reactivity of acceptors 33 (43).

Frontier orbital considerations have proved useful for understanding of some experimental results contrary to pK_a arguments. For example, by frontier orbital theory, 34 is predicted correctly to be the more active acceptor, not 35 as is predicted by pK_a data (43). Nevertheless, reactivity orders



34



35

predicted from pK_a data and frontier orbital theory are often complementary because most electron accepting groups are also electron withdrawing groups. Electron withdrawing groups lower the energy of the lowest unoccupied molecular orbital (LUMO) and thus activate by frontier orbital effects.

The order of acceptor reactivities is not entirely donor independent. The energies of early stages in the reaction coordinate are affected by electronic factors not accounted for in frontier orbital theory (50). Soft nucleophiles are affected by steric factors more than hard nucleophiles. Hard nucleophiles are attracted more by bond dipoles than soft nucleophiles. Since the β-site is the position of donor attack, these effects

are most pronounced for acceptors differing in β-substituents. In summary, one must be cautious in assigning an absolute reactivity order of acceptors with differing β-substituents without consideration of the nucleophile involved.

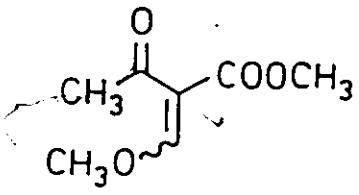
Since fragments A and B are to be coupled with C (see Schemes 2.1 and 2.2) by a Michael reaction, potential synthons A and B are the acceptors and potential synthons C the donors. An introduction to these substituted acrylate acceptors and oxazolone and thiazolone donors is the subject of the remainder of this chapter.

2.3 Choice of Michael Acceptors

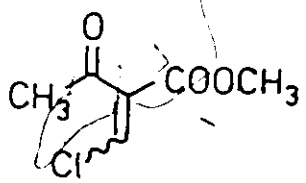
A list of all Michael acceptors used in this work is given in Figure 2.2. The acceptors 37, 38, 39 and 40 have excellent leaving groups in the β-position and are expected to react in a substitution manner. The materials 41 and 42, having no β-substituent, are expected to give normal 1,4-addition products. The β-methoxy material 36, with a poorer β-leaving group than the halides on 37 through 40, can react either by substitution or simple addition depending on the conditions (see Section 2.5).

With the exception of compound 38, all of the acceptors in Figure 2.2 are of interest because of their possible utility in thienamycin synthesis. Acceptors 36 and 37 are potential type 'A' synthons (see Section 2.1) while 39 and 40 are

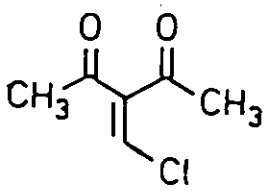
Figure 2.2: Michael Acceptors



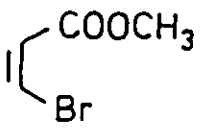
36



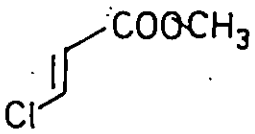
37



38



39



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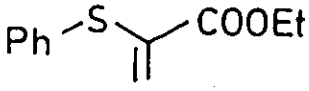

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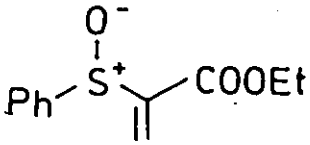
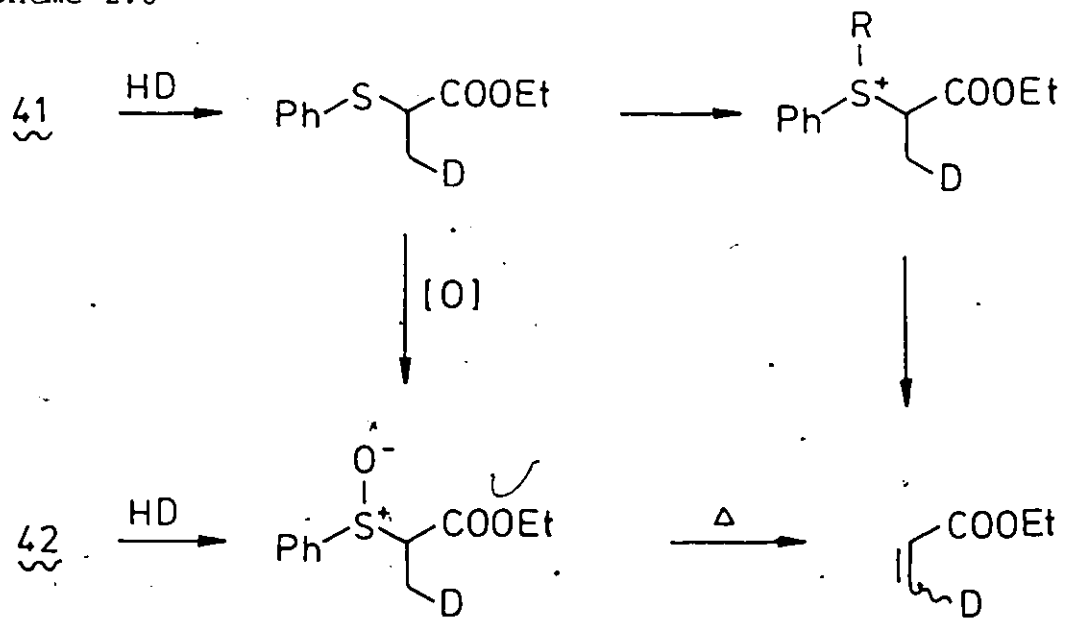


42

potential type 'B' synthons. The α-substituted acrylates 41 and 42 are also potential type 'B' synthons since, after addition, elimination of the α-sulfinyl or α-sulfenyl groups generates the desired double bond (as illustrated in Scheme 2.6). Precedence for each of these steps is given in referen-

Scheme 2.6



ces 51 through 53.

Acceptor 38 has no direct use in thienamycin synthesis. Its addition behaviour was examined only to demonstrate an extension of general synthetic uses of acceptors similar to 37.

By both product anion stability and frontier orbital arguments outlined in Section 2.2, the relative reactivities

of the acceptors with similar β-substituents can be ordered as shown in Figures 2.3a and b. In Figure 2.3c, a reactivity order is presented based primarily on product stability influence on the transition state and without regard for differing β-substituents. The major differences in anion product stabilities represented in the three categories in Figure 2.3c should override any nucleophile dependent influence on the Michael addition transition state energies. Any further classification of the acceptors in Figure 2.2 - other than what is presented in Figures 2.3a, b and c - is not justifiable without considering the nucleophile involved.

2.4 Choice of Michael Donors

Interest in the substituted oxazolones and thiazolones arises from their potential as aminoacetoacetate synthons (see Figure 2.4). The heterocycles studied in this work as possible synthons of type C are listed in Table 2.2. Since compound 44 is crystalline and readily available (54 - 56), it was used for many of the Michael addition model studies. The 2-alkyl substituted oxazolones 46 and 47 were prepared and examined in Michael reactions because they were expected to ring open under milder conditions than the 2-aryl analogues (see Section 3.4). Thiazolones 48 and 49 were studied with the intention of providing alternatives in nitrogen protecting groups.

Figure 2.3: Relative Reactivities of Michael Acceptors

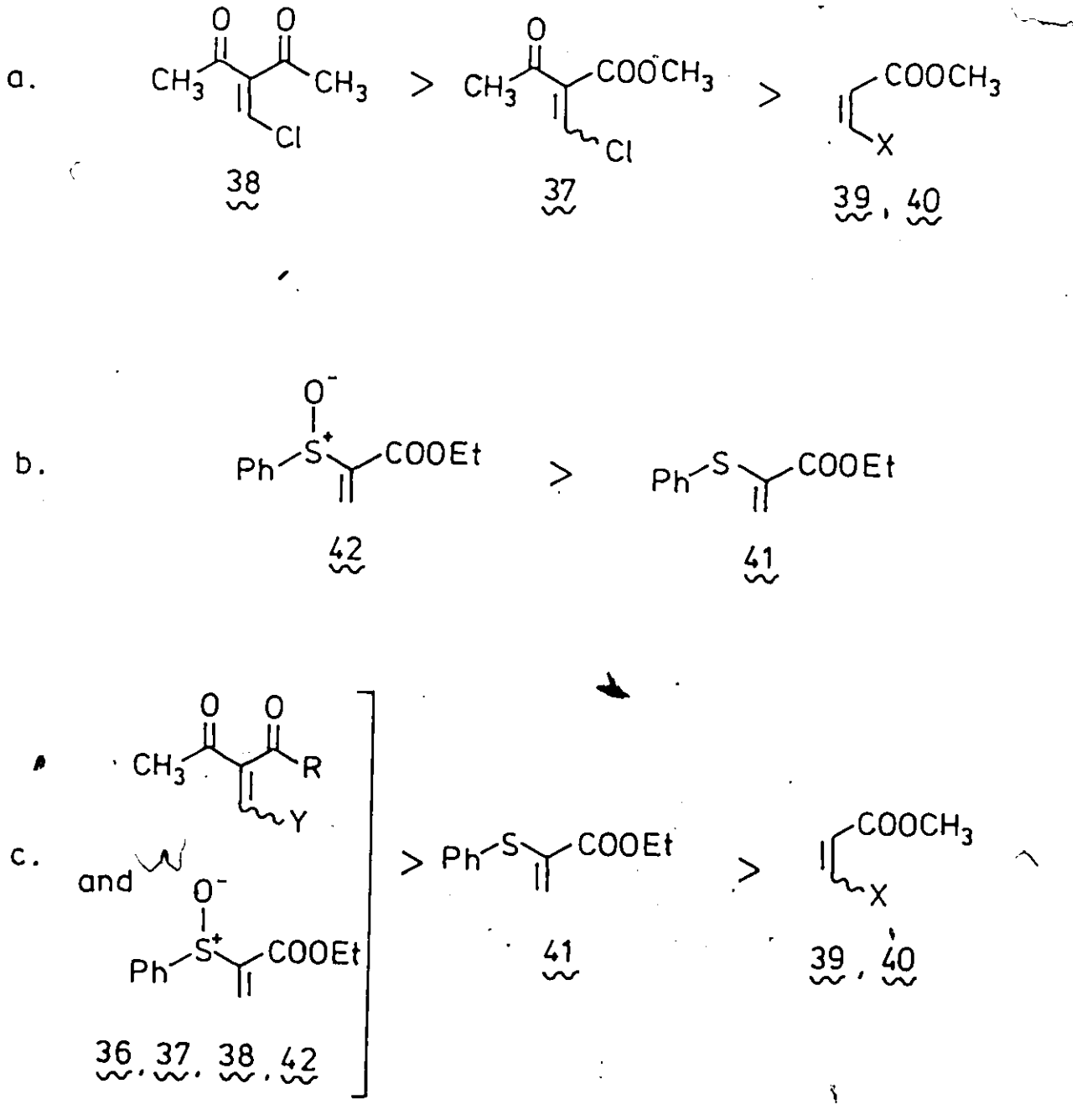


Figure 2.4: Synthon C

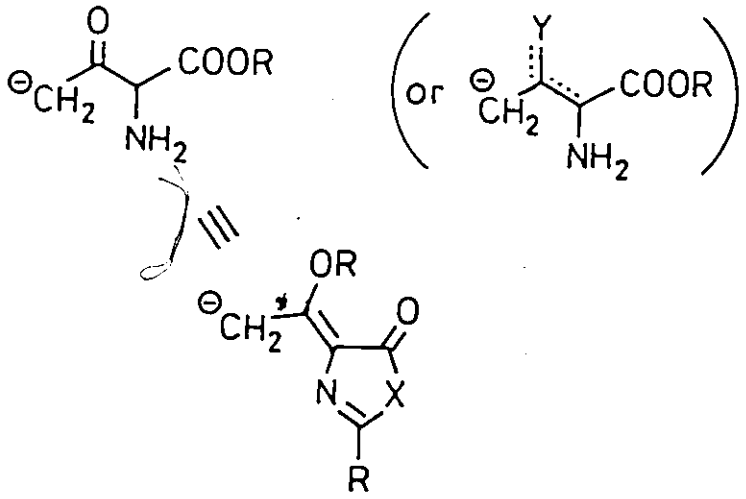
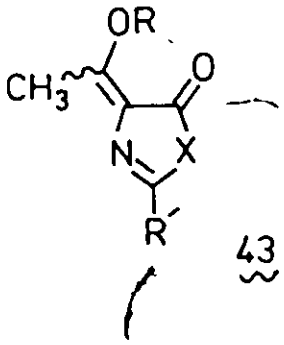


Table 2.2: Michael Donors



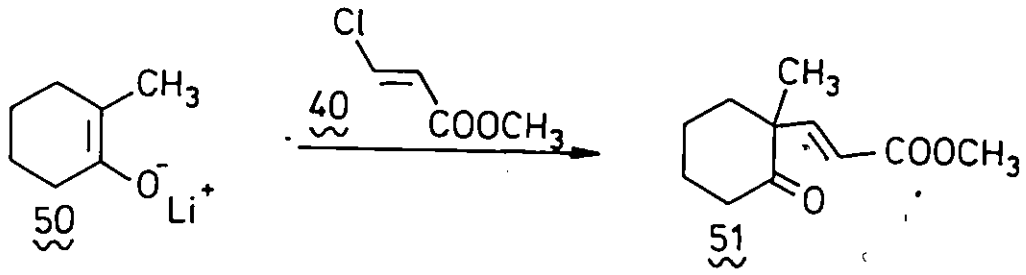
43

R'	R	X	Compound #
Ph	Et	0	44
Ph	CH_3	0	45
Bz	Et	0	46
t-Bu	Et	0	47
SBz	Et	S	48
OEt	Et	S	49

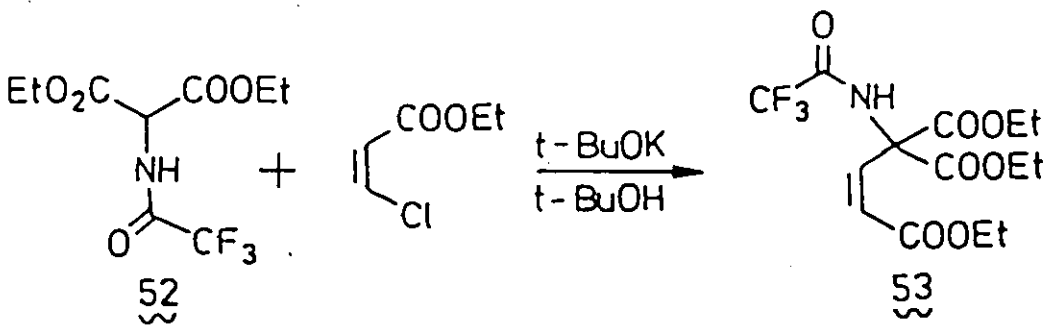
2.5 A Literature Review of the Michael Acceptors

Many of the compounds listed in Figure 2.2 have been used previously as acceptors for enolates in 1,4-addition reactions. The following is a review of these additions.

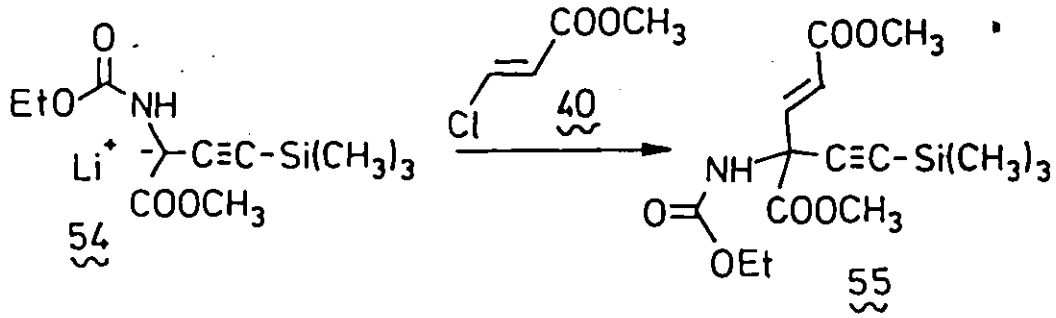
In the work of Dionne and Engel (57), the lithium enolate 50, when treated with methyl trans-β-chloroacrylate (40) at 0° provided the coupled product 51 in 25% yield. The product was found to be exclusively in the E configuration showing retention of geometry about the double bond. The same reaction with the cis-acrylate also gave retention of configuration.

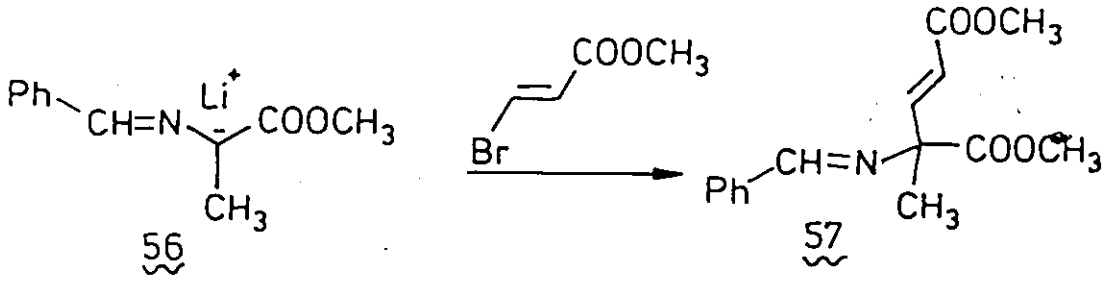


Addition of acylamidomalonic esters to chloroacrylates has been reported by two groups (58,59). For example, the malonate 52 gave the coupled material 53 in 70% yield on treatment with the corresponding acrylate and one equivalent of potassium t-butoxide.

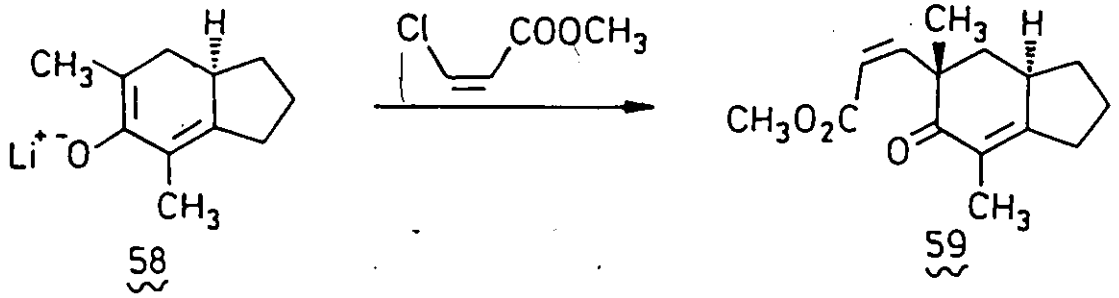


Casara and coworkers (60) prepared the product 55 by addition of the enolate 54 to methyl (E)-3-chloropropenoate, 40, while Bey and Vevert (61) prepared 57 from the enolate 56, and the corresponding bromopropenoate.





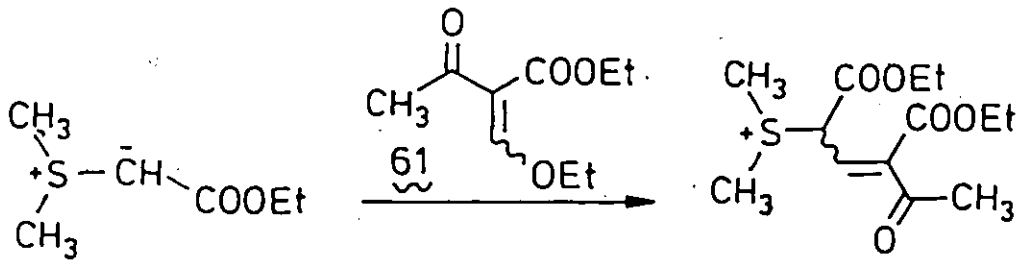
Two similar examples of cross-conjugated enolate additions appear in the literature (62,63). Boeckman and Bershas (62) prepared 59 in 78% yield on addition of cis-chloroacrylate to the enolate 58 at -28°C.



Retention of geometry on nucleophilic substitution has been observed for β-halocrotonates (64) as well as β-haloacrylates. It occurs because rotation of the α-β carbon-carbon

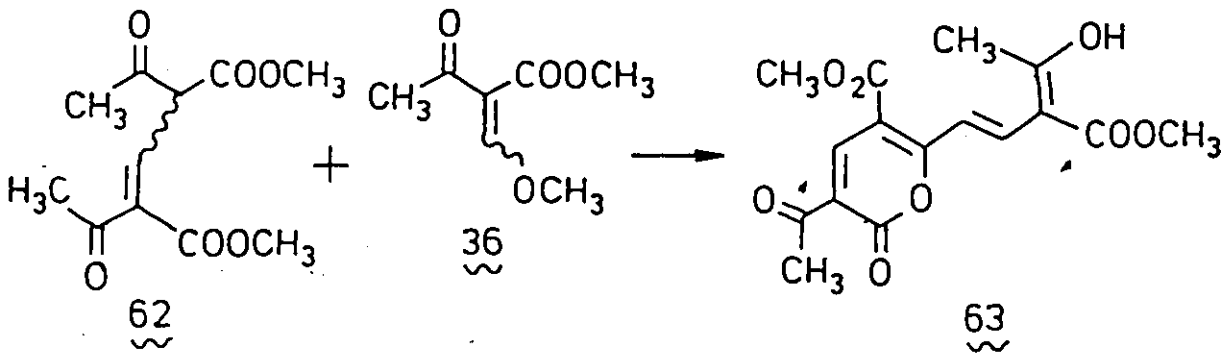
bond must occur before the leaving group, X, is in position for elimination that is periplanar to the p-orbital of the carbanion (see Scheme 2.7), and because eclipsed interactions are minimized on rotation in the direction providing retention of geometry (64).

Watanabe and coworkers (65) reported the addition of the sulfur ylide 60, to 61, as well as to other closely related acceptors.



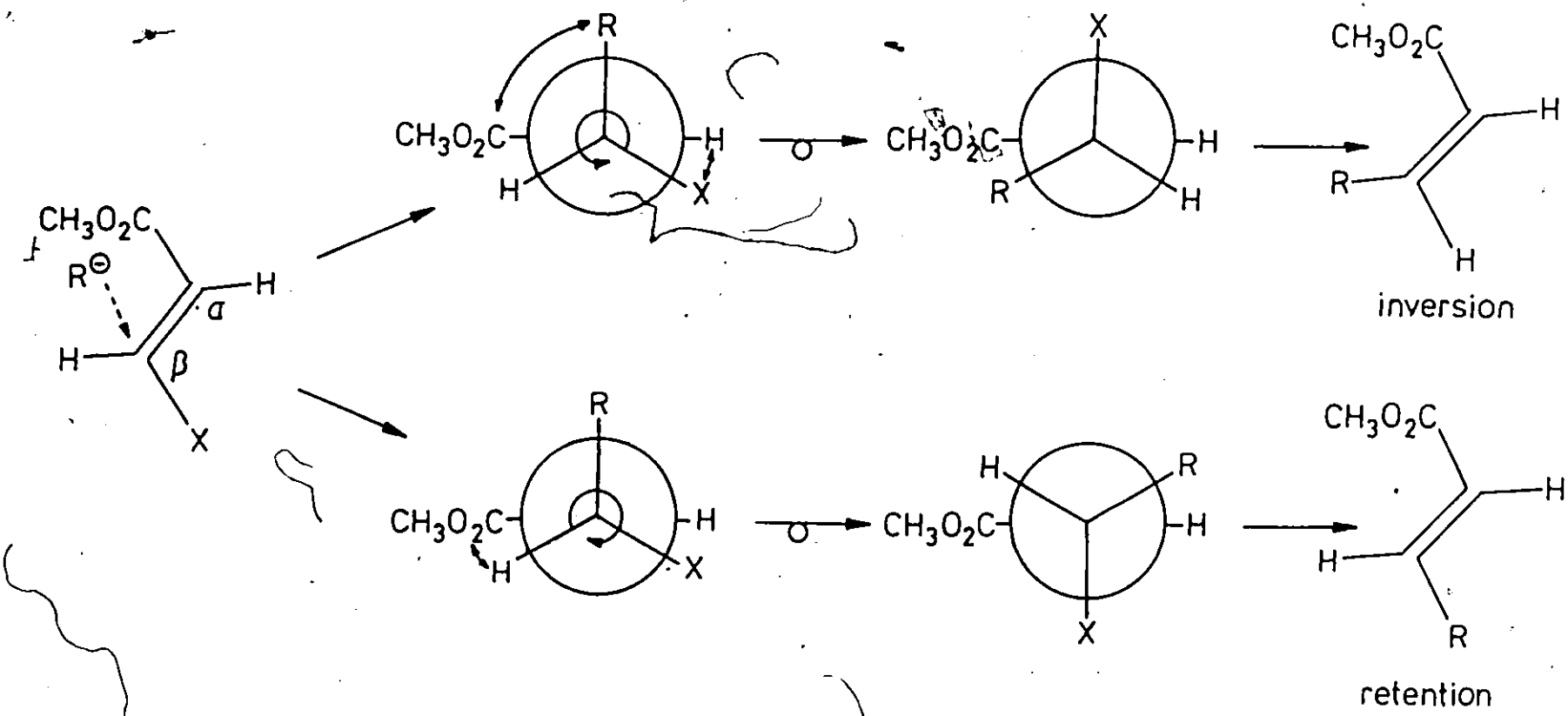
60 61

A reaction of the diacetylglutaconate 62 and 36 with methoxide catalysis was reported (66) to give the xanthyrone 63.



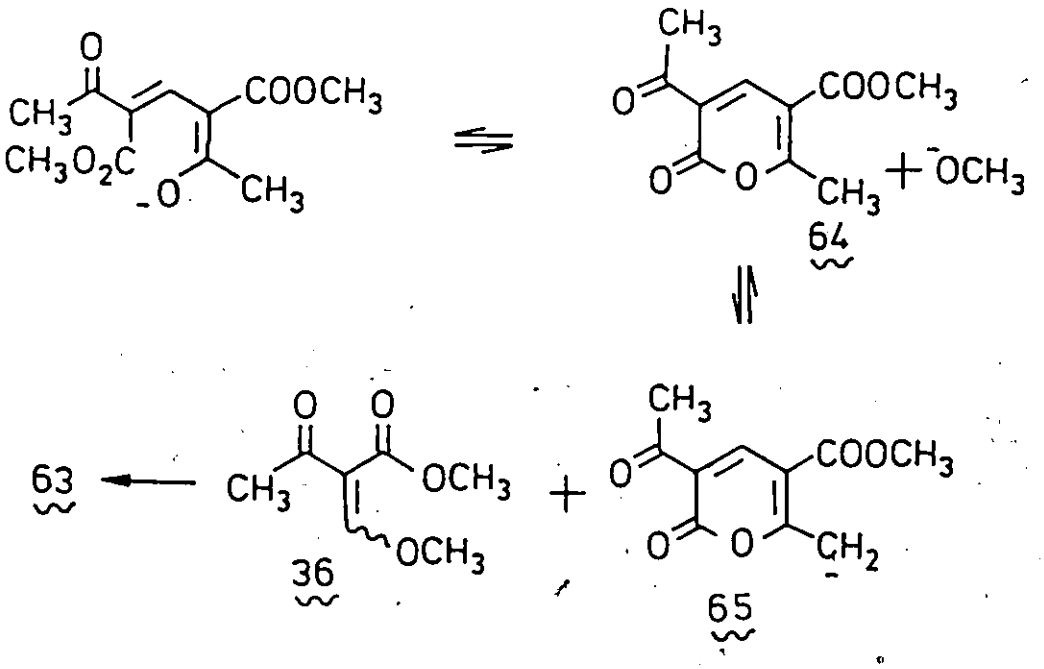
62 36 63

Scheme 2.7



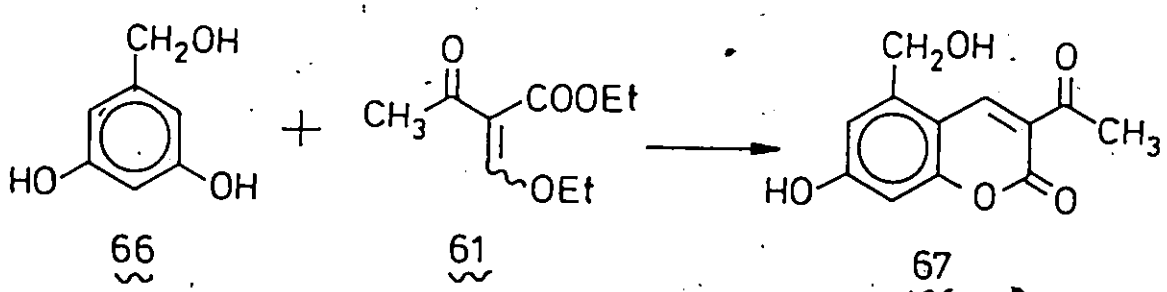
The authors provided evidence that this reaction proceeds via a rapid equilibrium of the glutaconate with the pyrone 64 (Scheme 2.8).

Scheme 2.8



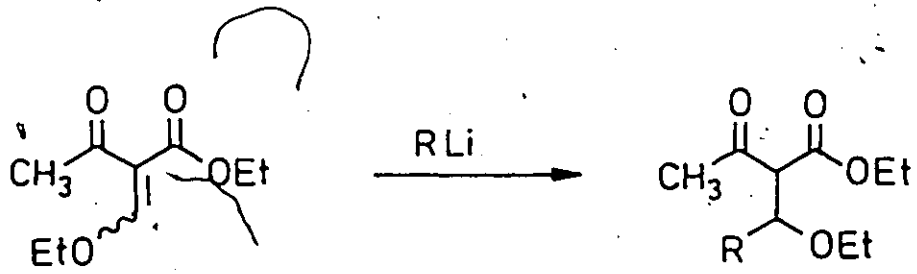
The anion of this pyrone (65) was considered to be the attacking nucleophile.

The propenoate acceptors 36 and 61 are potentiallly useful in benzopyrone syntheses. A reaction demonstrating this potential is the preparation of the Armillarin A, 67 by the condensation of the phenol 66 with 61 (67).



66 61 67

In addition to the Michael substitution reactions of 36 and 61 (as shown above), Krauss and Pezzanite (68) reported the 1,4-additions of methyllithium and n-butyllithium to 61.

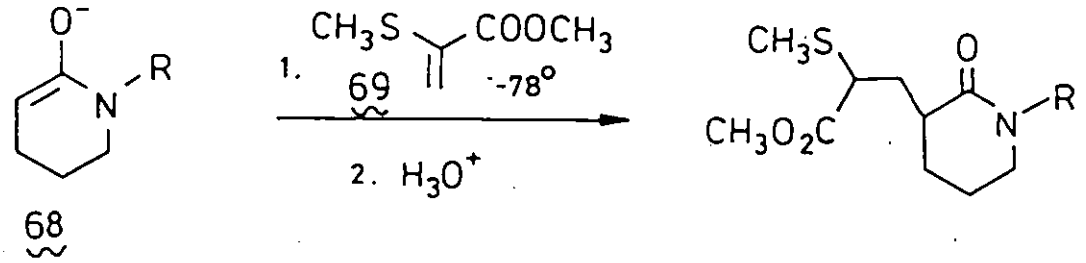


61

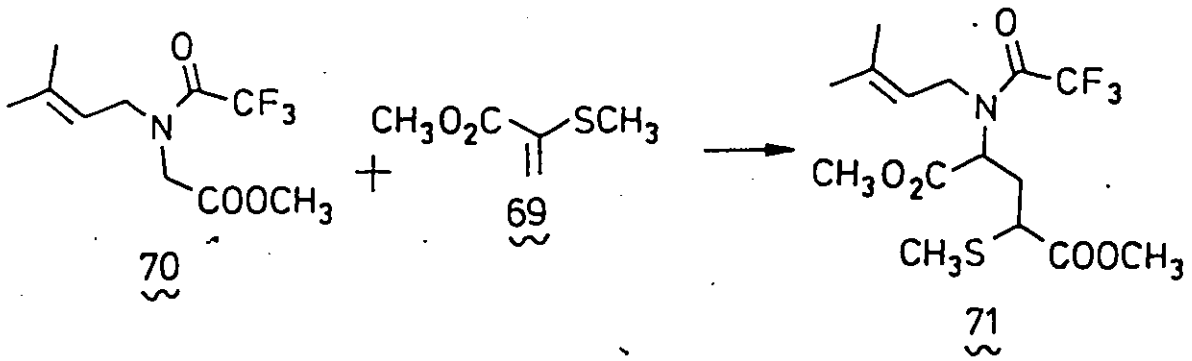
-R = -CH_3 , -$(CH_2)_3CH_3$

Although the preparation of the α-sulfenyl and α-sulfinyl acrylates 41 and 42 were recently reported for use as Michael acceptors (69), no Michael reactions have appeared in the literature with these acceptors. The following 1,4-additions with closely related acceptors have been reported.

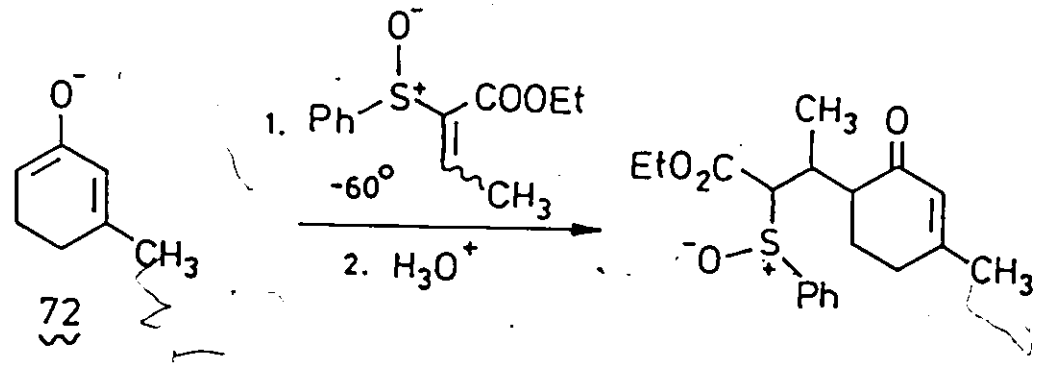
Herrmann and coworkers (70) coupled the anion 68 to methyl 2-(methylthio)acrylate, 69, in high yield (98%).



Similarly, Oppolzer and Andres (71) prepared the diester 71 by adding lithium isopropyclcyclohexylamide to a mixture of 69 and 70 at -78°C followed by an acid quench.

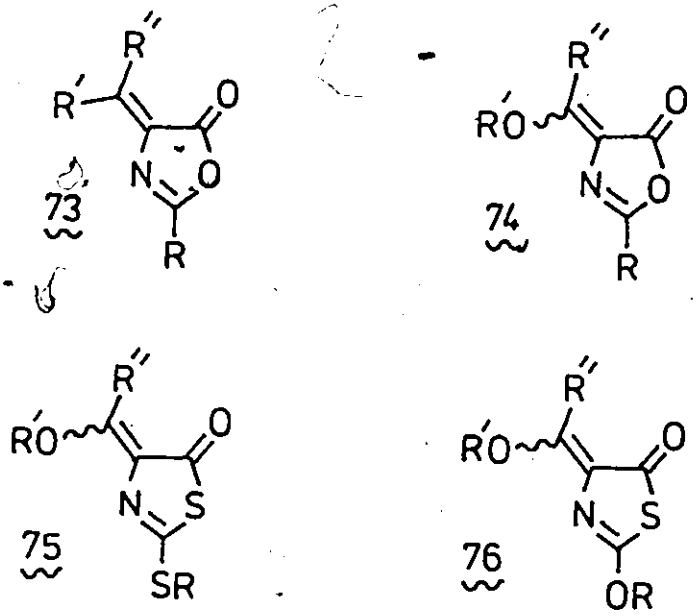


Finally, ethyl 2-(phenylsulfenyl)crotonate has been coupled with the crossconjugated enolate 72 in 48% yield by Hagiwara et al. (51).



2.6 Review of Oxazolones and Thiazolones Related to the Michael Donors

The synthesis, geometric isomerism and reactions of materials with general structures 73 through 76 is reviewed below.

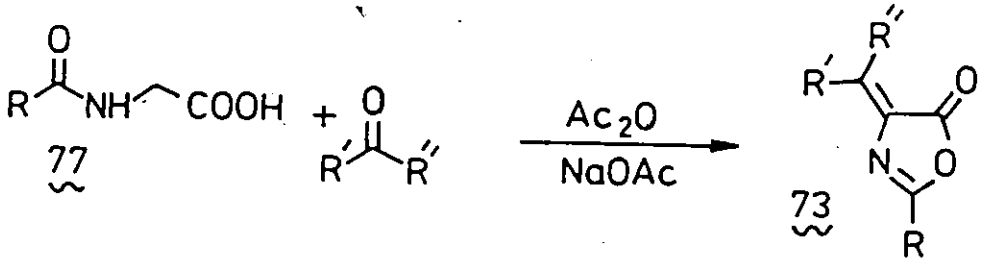


R, R', R'' = alkyl, aryl or H

2.6.1 Synthesis

Azlactones of structure 73 are prepared readily by the Plöchl-Erlenmeyer route (72 - 74). Normally, when aldehydes are used, only one geometric isomer is isolated. In some cases, the other isomer has been obtained but as a minor product which

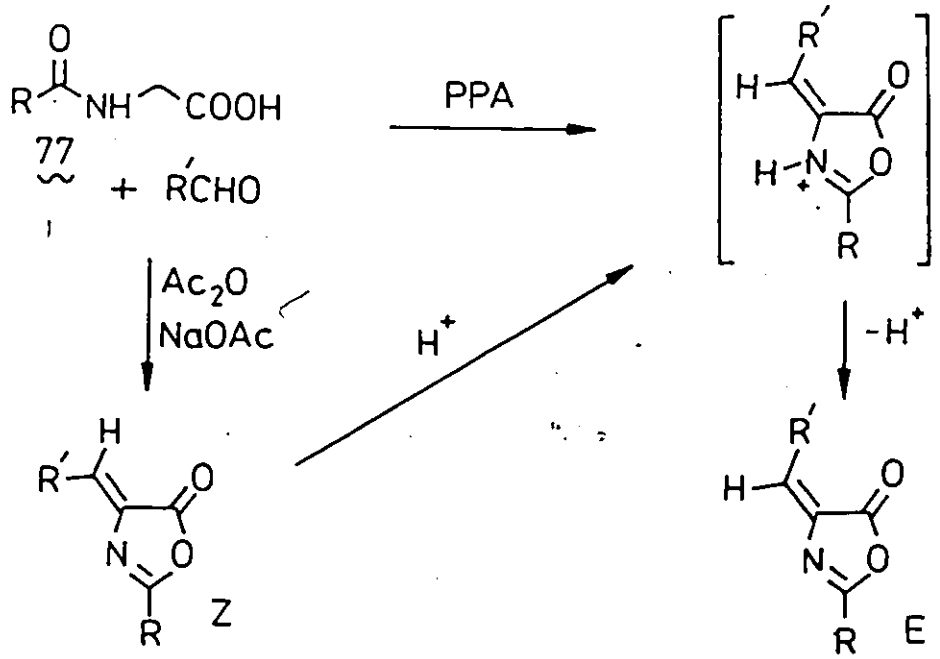
Plöchl-Erlenmeyer Synthesis



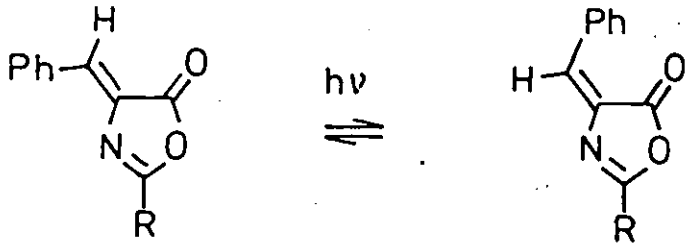
R, R', R'' = alkyl, aryl or H

on dissolution in pyridine interconverted to the major isomer (74,75). The thermodynamically stable isomer is known to have the Z geometry (74,76,77). In general, the E isomer may be prepared by rapid quenching of the protonated oxazolone. Thus, the less stable azlactone can be obtained by isomerizing the thermodynamic adduct with strong acid or by direct synthesis from the N-acylglycine in polyphosphoric acid (74) (see Scheme 2.9). Apparently, the protonation of the oxazolone forces the substituent (R') into the E geometry by steric interactions.

Scheme 2.9



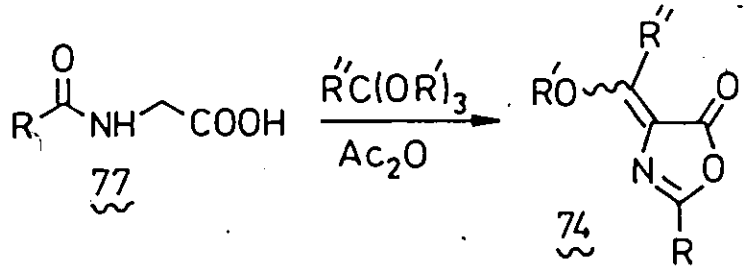
Photoisomerization of 4-alkylidene-5-oxazolones has been reported in a few cases (74,78). For example, in acetonitrile the photostationary state of (E)-78 to (Z)-78 was 2:3 (74).

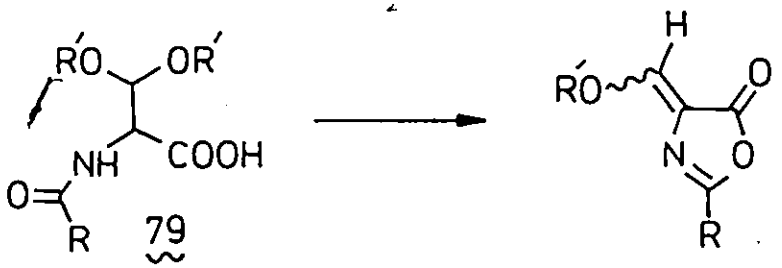


(Z)-78 (E)-78

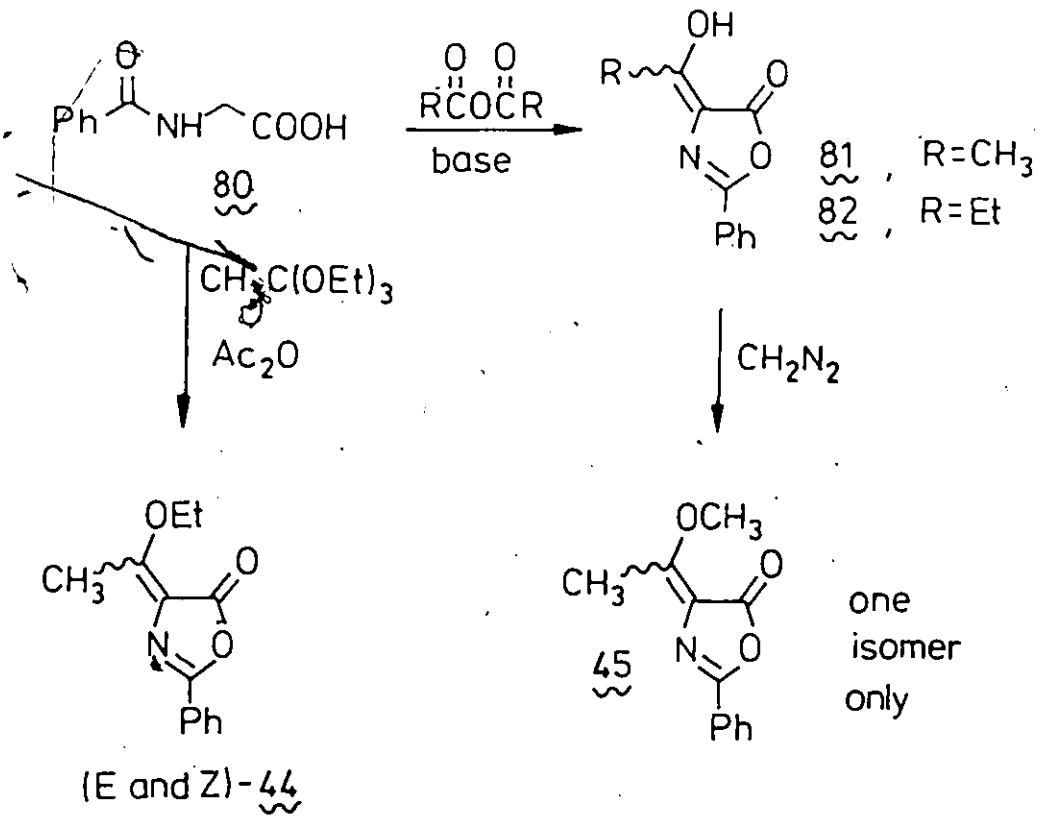
For the Plöchl-Elenmeyer synthesis, where R' and R" ≠ H (and R' ≠ R"), mixtures of E and Z isomers were often obtained (79 - 82). Geometric assignments have been attempted but were contradictory (79 - 82).

During World War II, the chemistry of oxazolones advanced greatly because oxazolones were linked to the structure and chemistry of penicillin (83 - 85). It is the penicillin research effort which is the foundation of the work on oxazolones of structure 74. These materials are preparable by the treatment of N-aroyl and N-acylglycines, 77, with orthoester and acetic anhydride. 4-(Alkoxymethylene)-5-oxazolones (74, R" = H) have been prepared from the penaldic acid acetals, 79 (83 - 85).



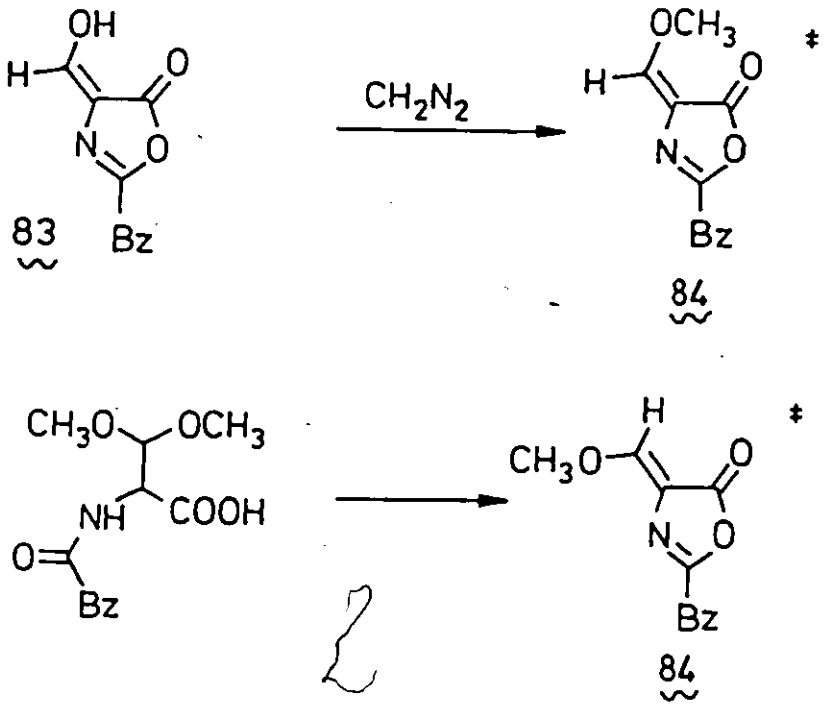


In a reaction similar to the orthoester reactions, hippuric acid, 80, reacted directly with acetic or propanoic anhydride to give the hydroxyalkylideneoxazolones 81 and 82. Product 81 was methylated with diazomethane to give 45 (86).



In most cases, only one isomer of oxazolones 74 has been prepared. An exception is the orthoacetate synthesis of 44 (above), where a small amount of minor isomer was isolated (55,56). Another possible example of geometric isomerism is the reported syntheses of the same oxazolone (84) but with differing melting points (87). The two products were prepared by

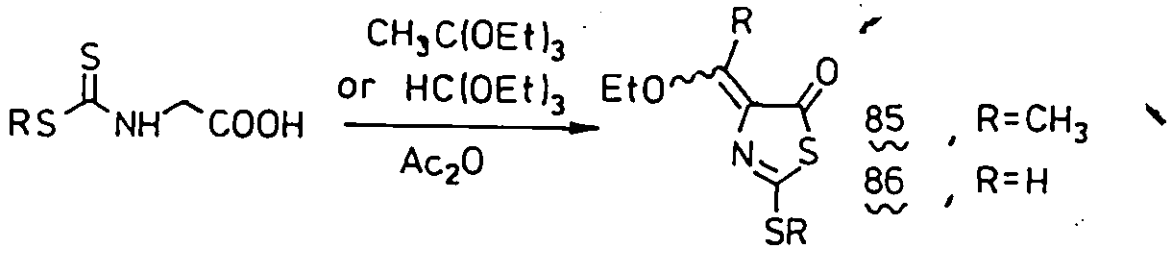
separate research groups and by different procedures, one by diazomethane addition to the hydroxymethylene material, 83, and the other, by the penaldate method.

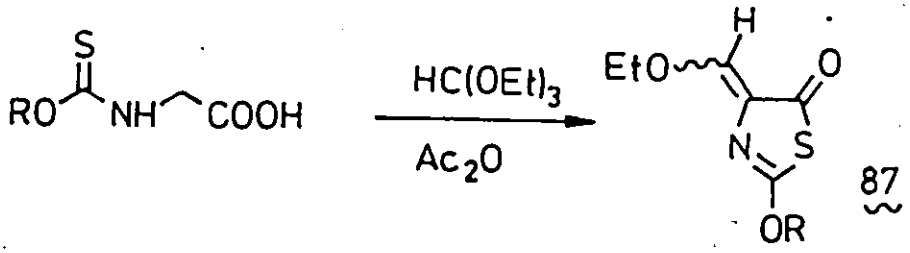


* these assignments may be reversed

Geometric assignments have never been attempted for 4-(alkoxy-alkylidene)-5-oxazolones (74)

N-(Dithiocarbalkoxy)glycines were reacted with triethyl orthoformate and orthoacetate in acetic anhydride to give the respective 4-(1-ethoxyalkylidene)-5-thiazolones, 85 and 86 (88,89). Similarly N-(thiocarbalkoxy)glycines were reported to give the corresponding thiazolones, 87, with orthoformate and acetic





anhydride (90). These 2-alkoxy derivatives (87) were reported to be crystalline solids but those with short alkyl chains rapidly decomposed. Only those with alkyl chains of ten carbons or more were fully characterized (90). In thiazolones

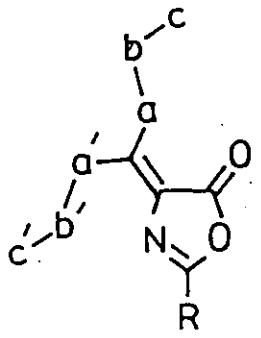
85 through 87, geometric isomerism has not been reported.

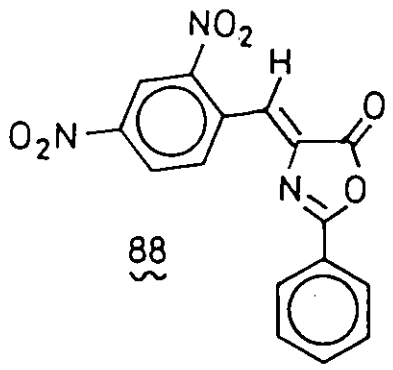
2.6.2 Geometric Assignments

Potentially, the E and Z isomers can be differentiated by comparison of the nuclear magnetic resonance (NMR) chemical shifts of the protons or carbon atoms at positions a vs a', b vs b' or c vs c' (Figure 2.5).

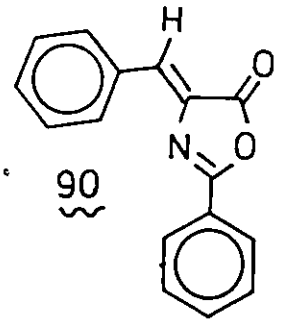
As previously mentioned, the geometry of the Erlenmeyer azlactones, 73, where R' or R" = H has been established. X-ray analysis of the oxazolone 88 (76), as well as α-benzamido-cinnamic acid 89 (77), the hydrolysis product of 90, has shown that the thermodynamic isomer possessed the Z geometry. The

Figure 2.5: Labelling of the Alkylidene Substituents

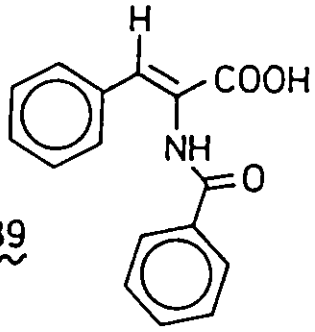




88



90

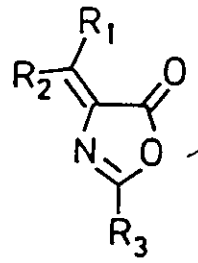


89

olefinic protons of the E isomers were 0.2 to 0.3 ppm downfield from those of the Z isomers (74). Therefore, in this series, geometry could be determined by comparison of ^{1}H NMR data.

The chemical shifts of the allylic protons (protons on carbon atoms at positions a or a' in Figure 2.5) showed small but consistent differences between E and Z isomers for the 4-(1-alkylethylidene)-5-oxazolones listed in Table 2.3 (79) The E and Z assignments in Table 2.3 were based on the assignments of the ring hydrolysis products. Thus, the assignments of the oxazolone 91 can be related to the amides 92 and 93.

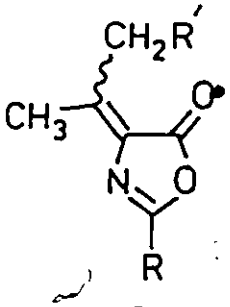
Table 2.3: Allylic Chemical Shifts of 4-(1-Alkylethylidene)-5-oxazolones (79)



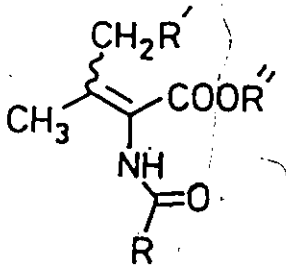
Isomer	R_1	δ*	R_2	δ*	R_3
E	$\underline{CH_2}CH_3$	2.65	CH_3	2.32	$C(CH_3)=CHPh$
Z	CH_3	2.24	$\underline{CH_2}CH_3$	2.79	$C(CH_3)=CHPh$
	CH_3	2.20	CH_3	2.30	$C(CH_3)=CHPh$
	CH_3	2.24	CH_3	2.32	$CH=CHPh$

*Chemical shifts are in ppm relative to tetramethylsilane (TMS).

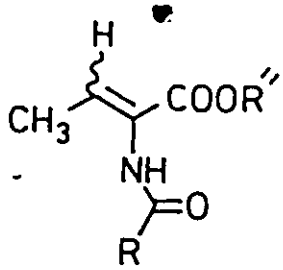
The olefinic protons (and thus the allylic protons) of E and Z 93 can be assigned from the X-ray structure of 89.



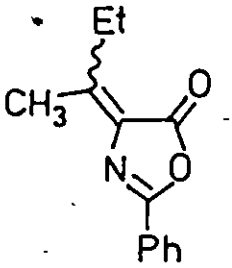
91



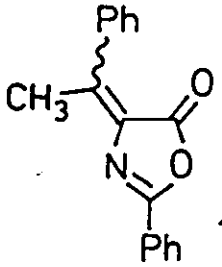
92



93



94



95

Two research groups, apparently unaware of these previous allylic assignments, have published assignments for 94 (80) and 95 (81,82) contrary to those above. The first group based their assignments on ^{1}H NMR solvent shifts and the second group, on relative chemical shifts with the assumption that the methyl group closer to the carbonyl to be the more

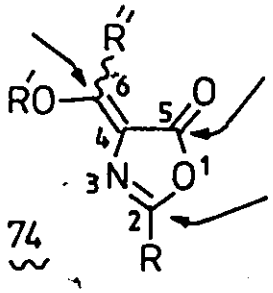
deshielded.

For 4-alkylidene-5-oxazolones, there is only one example of chemical shift data of protons on carbons b and b' being reported in the literature (80). The observed difference in chemical shifts (δ 1.20 versus 1.22 ppm) is too small for use in geometric assignments.

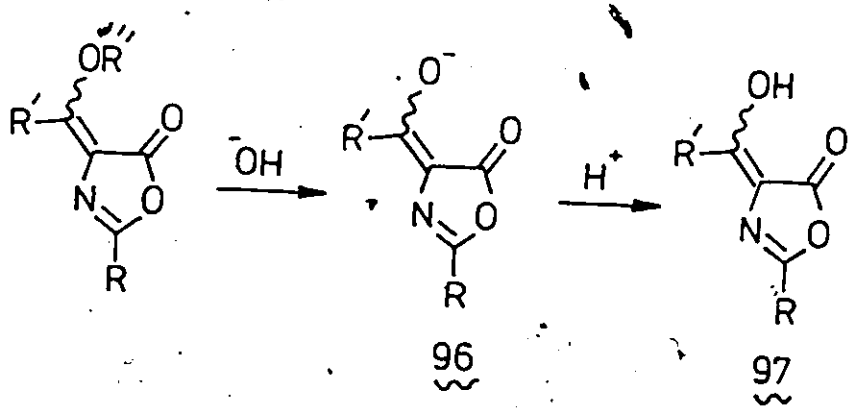
2.6.3 Reactions

The three electron defidient centres C-2, C-5 and C-6 of the oxazolones, 74, compete in attraction for nucleophiles (Figure 2.6). The substitution reaction at C-6 often predominates. Direct substitution with amines, acid catalyzed alcohol exchange and pyridine catalyzed thiol substitutions are all typical reactions (91). In general, treatment with hydroxide gives the stable anion 96 which on acidification gives the hydroxyalkylidene oxazolone 97 (91).

Figure 2.6: Possible Sites of Nucleophilic Attack on 4-(1-Alkoxyalkylidene)-5-oxazolones



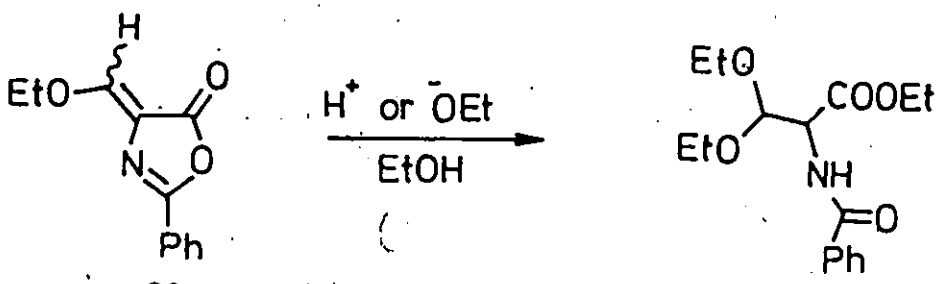
74



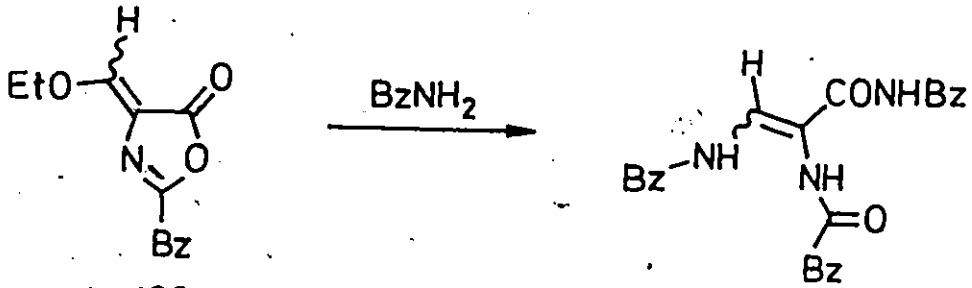
96 97

Ring opening results from attack at C-5 as illustrated by the reactions in Scheme 2.10 (92). In both of these cases

Scheme 2.10



98 99

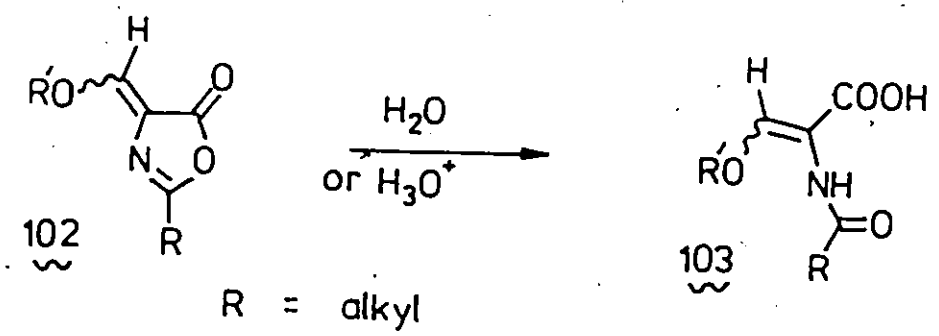


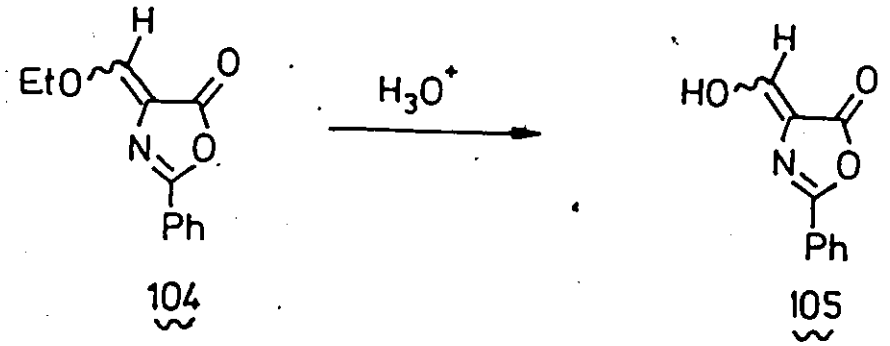
100 101

it is possible that C-6 is the initial site of nucleophilic attack.

2-Alkyl substituted alkoxymethylene oxazolones 102 ring open with warm water, moist air or aqueous acid to the corresponding acrylates 103. The 2-phenyl analogues are much more

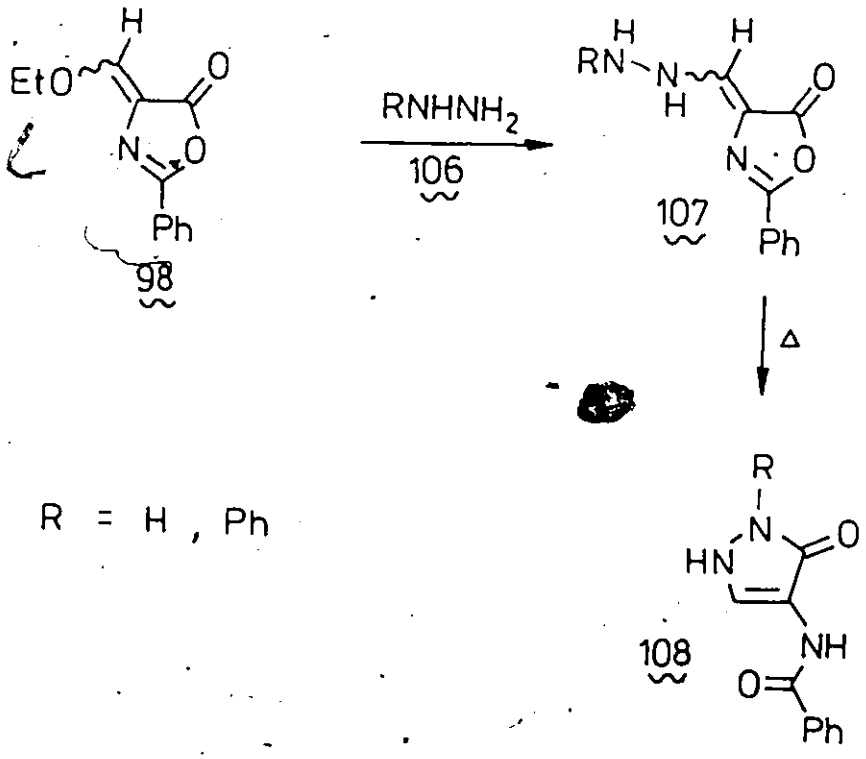
stable to acid conditions (92,93). Oxazolone 104 was not





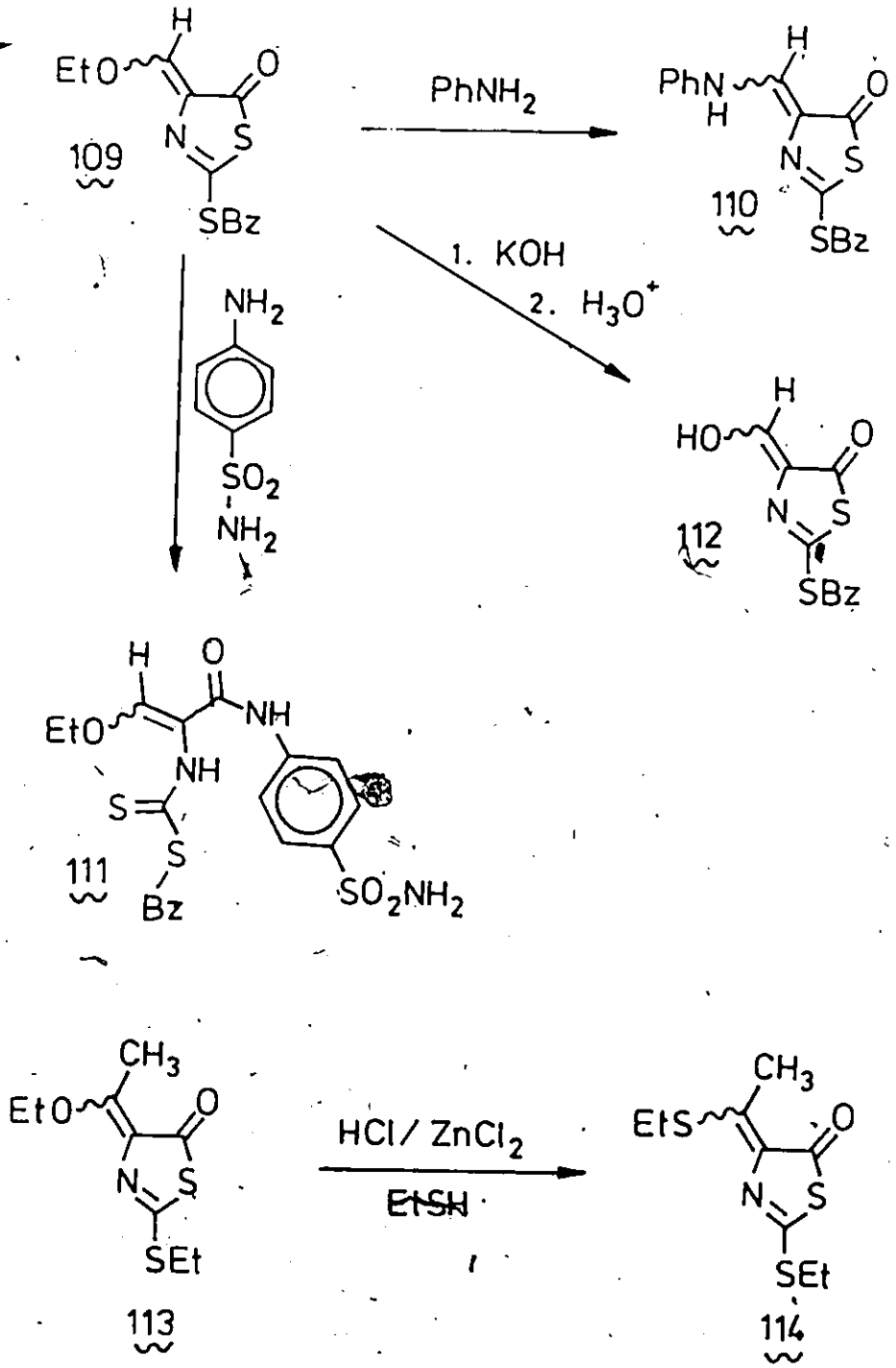
ring opened with aqueous acid but hydrolysed to the hydroxymethylene derivative, 105 (93).

Hydrazines, 106, reacted at C-6 of 98 yielding substitution products, 107, which on heating, underwent opening of the oxazoline ring and formed a new ring system, the pyrazolinones 108 (94).



Published reactions of 4-(1-alkoxyethylidene)-2-alkylthio-5-thiazolones are similar to the 2-alkyl and 2-aryloxazolone analogues. Both substitution at C-6 and ring opening have been reported (88,89) (Scheme 2.11). A surprising control in the site of nucleophilic attack on 109 with aniline and sulfanilamide was observed by Cook et al. (88). Apparently aniline provided the C-6 substitution product while sulfanilamide, the ring opened product from attack at C-5. For 113 to 114, C-6 attack is observed.

Scheme 2.11

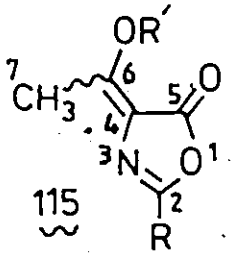

EtO
H
O
N
S
SBz
109
PhNH2
PhN
H
110
1. KOH
2. H3O+
HO
112
NH2
SO2
NH2
NH
S
Bz
111
SO2NH2
CH3
113
HCl/ ZnCl2
EtSH
EtS
114

RESULTS AND DISCUSSION

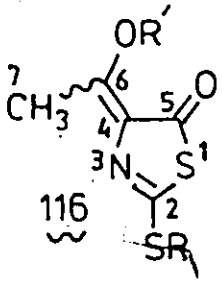
CHAPTER 3

PREPARATION AND PROPERTIES OF THE MICHAEL DONORS

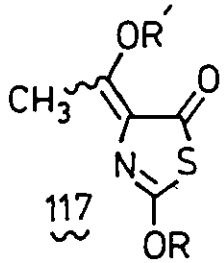
The 4-(1-alkoxyethylidene)-5-oxazolones and thiazolones (115 - 117) were of general interest as potential type 'C' synthons (see Sections 2.1 and 2.4). The preparation of these



115



116



117

R, R' = alkyl , aryl

compounds is examined in Section 3.1. Investigations in substitution reactions of C-6 and ring opening reactions of 115, 116 and 117 are examined in Sections 3.3 and 3.4. The configuration of the geometric isomers about the C-6, C-4 exocyclic double bond were assigned on the basis of the X-ray crystal structure of 4-[(Z)-1-ethoxyethylidene]-2-phenyl-5-oxazolone, (Z)-44, and by NMR chemical shift data as discussed in Section 3.2.

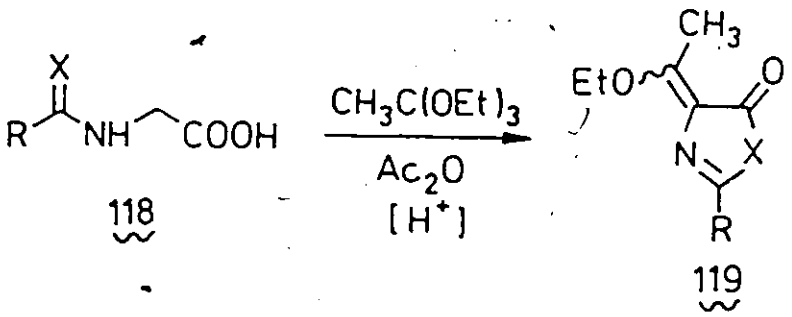
3.1 Synthesis of 4-(1-Alkoxyethylidene)-5-oxazolones and 4-(1-Alkoxyethylidene)-5-thiazolones

3.1.1 Orthoacetate-Acetic Anhydride Synthesis

The majority of the 4-(1-ethoxyethylidene)-5-oxazolones and thiazolones, 119, were prepared by the action of triethyl orthoacetate and acetic anhydride on N-acyl or N-aroylglycines, N-dithiocarbobenzyloxyglycine, 124, and N-thiocarbethoxyglycine, 125 as summarized in Table 3.1. Equilibrium mixtures of E and Z isomers were obtained, the equilibrium always favoring the Z isomer. The NMR spectrum of a typical equilibrium mixture of isomers is shown in Figure 3.1. For the oxazolones 46 and 47, this equilibrium was so unbalanced that the E isomers were not observed in the crude reaction mixtures. In the preparation of thiazolones 48 and 49, yields were improved by the addition of toluenesulfonic acid as catalyst. In all cases, the isomers were readily separated by chromatographic techniques.

The probable reaction sequence for the orthoacetate-acetic anhydride synthesis is summarized in Scheme 3.1. An intermediate in this reaction is the 4H-oxazolone or 4H-thiazolone 128 (85). A competing reaction in the orthoacetate condensation, 118 to 119, appears to be the esterification of 118 via ring opening of 128 with ethanol released during the condensation. The esters were not fully characterized from this reaction but were identified by ^1H NMR spectra of the crude reaction mixtures and of the filtrates after crystallization of some of the desired products, 119. The CH_2 of the glycinate esters (at approximately

Table 3.1: Products of the Orthoacetate Synthesis

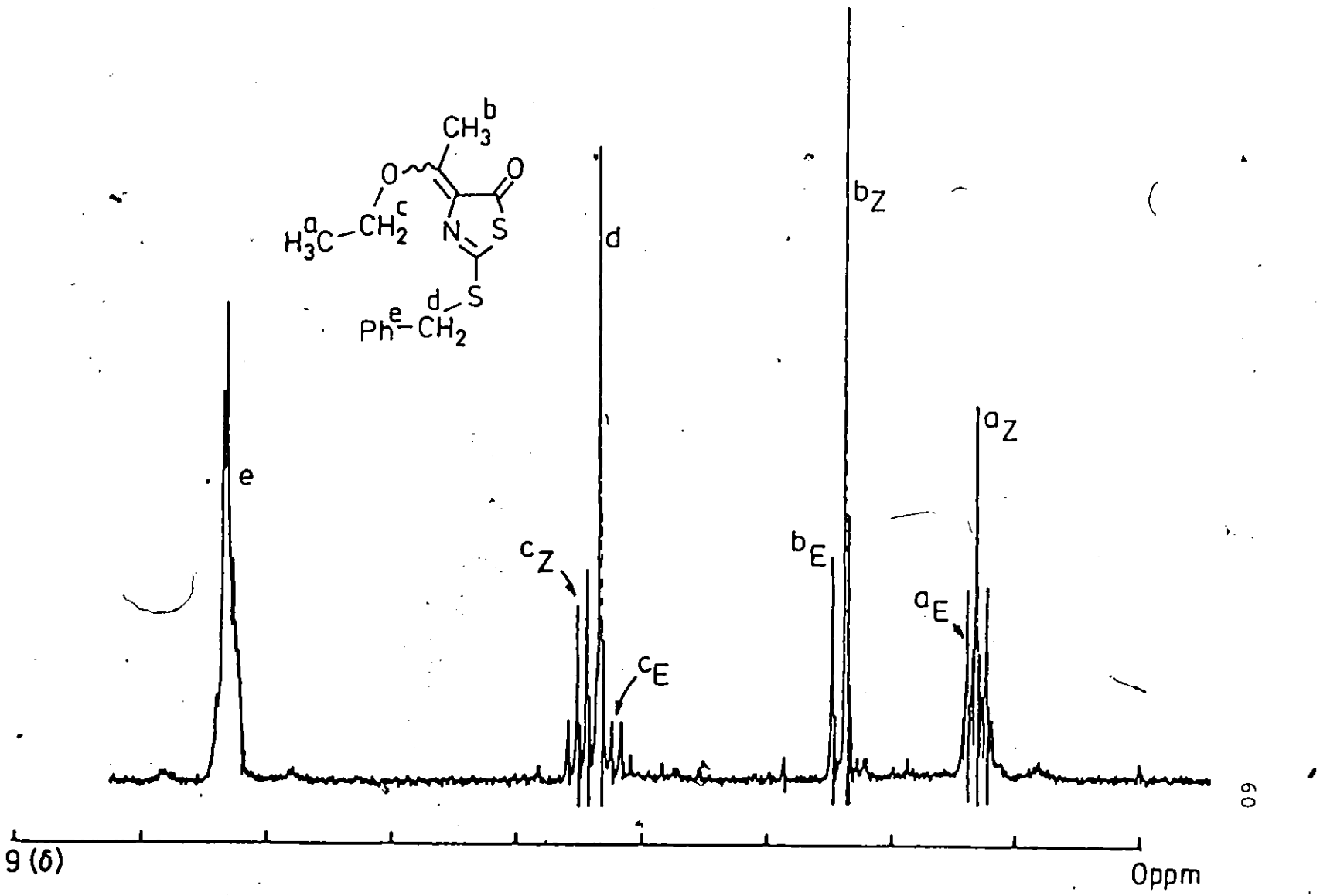


118	R	X	Crude E/Z[a]	Isolated Yield E(%)	Isolated Yield Z(%)	119
80	Ph	O	1:5	-	52	44
120	p-ClPh	O	1:4	14	60	126
121	p-BrPh	O	1:4	12	45	127
122	Bz	O	small	-	44	46
123	t-Bu	O	small	-	64	47
124	SBz	S	1:4	-	67	48
125	OEt	S	-[b]	-	25	49

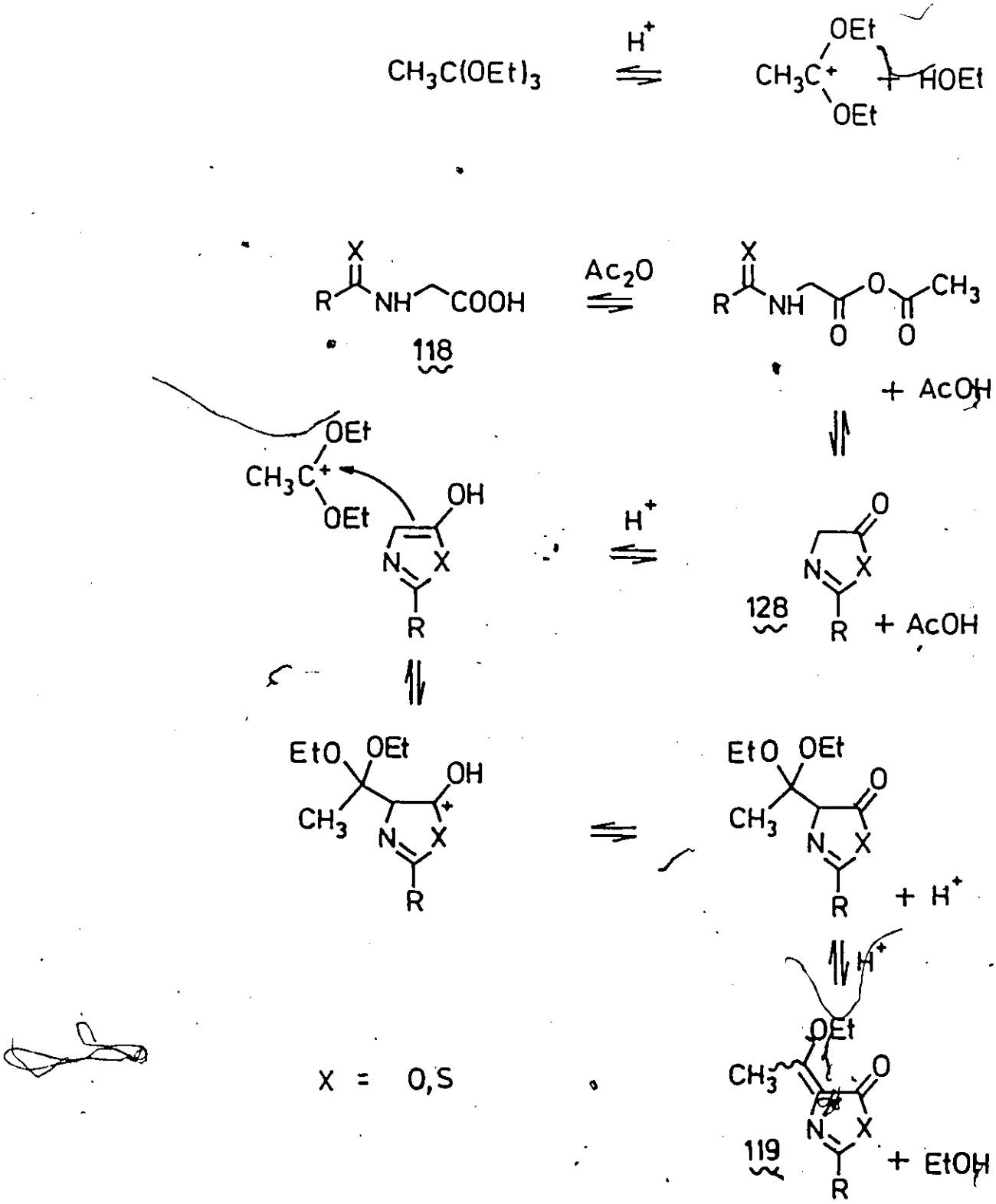
[a] as determined by ^{1}H NMR spectroscopy.

[b] ratio not determined because of ^{1}H NMR signal overlap.

Figure 3.1: ^{1}H NMR Spectrum of an Equilibrium Mixture of 2-Benzylthio-4-[(E and Z)-ethoxyethylidene]-5-thiazolone, (Z and E)-48

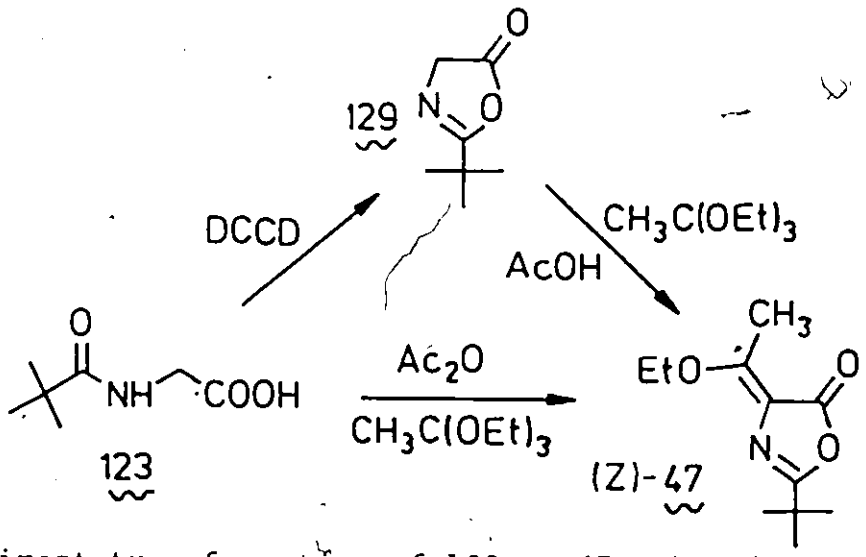


Scheme 3.1


CH3C(OEt)3
H+
OEt
CH3C+
HOEt
OEt
X
R
NH
COOH
118
Ac2O
O
CH3
+ AcOH
OH
N
X
128
+ AcOH
EtO
OEt
CH3
+ H+
H+
OEt
CH3
119
+ EtOH
X = O,S

4.2 ppm) showed a 5 - 6 Hz coupling with the NH proton, a coupling which was also characteristic of the free acids 118.

For one of the oxazolones (R = t-Bu), the intermediate of general structure 128 was prepared in quantitative yield by dehydration of the corresponding glycinate, 123, with dicyclohexylcarbodiimide (DCCD). The resulting 4H-oxazolone, 129, was treated with triethyl orthoacetate and acetic acid to give the 4-(1-ethoxyethylidene)-5-oxazolone, 47, in 30% yield. In

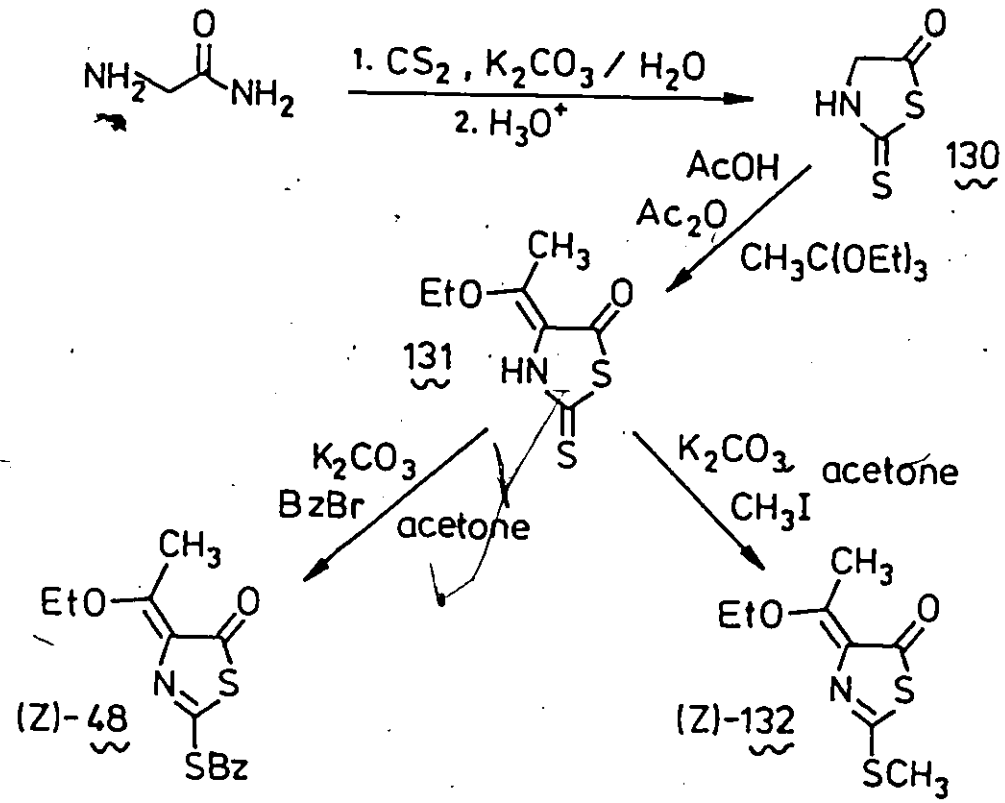


the direct transformation of 123 to 47, the kinetic concentration of free ethanol was limited by reaction of ethanol with acetic anhydride. For the reaction of 129 with triethyl orthoacetate, in the absence of acetic anhydride, the competitive formation of ethyl N-pivaloylglycinate was favored over the desired product (as indicated by ^1H NMR spectroscopy) and accounts for the modest yield of 47.

3.1.2 S-Alkylation

Another route to the thiazolone 48 was by S-benzylation of 4-(1-ethoxyethylidene)-2-thioxo-5-thiazolidinone, 131 (see Scheme 3.2). Similarly prepared was the methylthio analogue 132. By this S-alkylation route, the thiazolones 48 and 132 were obtained as pure Z isomers. If the product was not isolated promptly from the reaction mixture, a small amount of the E isomer also appeared, presumably by base catalyzed isomerization of the Z product.

Scheme 3.2

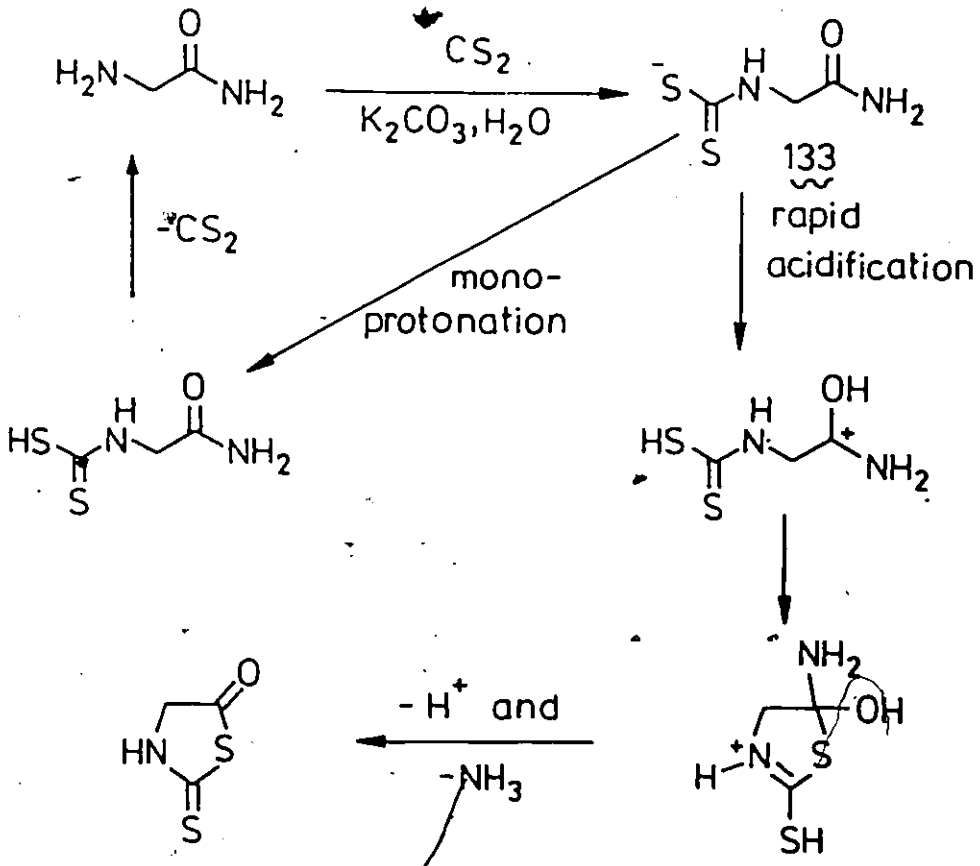


Cook et al. had described previously the preparation of the ethoxymethylene analogue of compound 131 (95), but had not reported S-alkylation. According to their procedure, treatment of aqueous glycinamide and carbon disulfide with base followed by strong acidification, yielded the thione 130. In repeating this experiment, it was found that the thione was obtained only when the acidification was carried out rapidly. A proposed course of this reaction is given in Scheme 3.3 which is consistent with the observations. As is shown in Scheme 3.3, rapid double-protonation of 133 is probably required to force the cyclization to take place.

In a reaction similar to the preparation of the oxazolones and thiazolones 119, the thiazolidinone, 130, when heated with triethyl orthoacetate, acetic anhydride and a[illegible]ic acid, provided 131 in 57% yield. The structure was co[illegible]d by the presence of ^{1}H NMR and infrared (IR) signals in the respective spectra for the thioamide NH (9.30 ppm and 3110 cm^{-1} respectively) and by the structure of the S-alkylation products 48 and 132.

Since kinetic S-alkylation of 131 gave (Z)-48 and (Z)-132, 131 must possess the Z geometry.

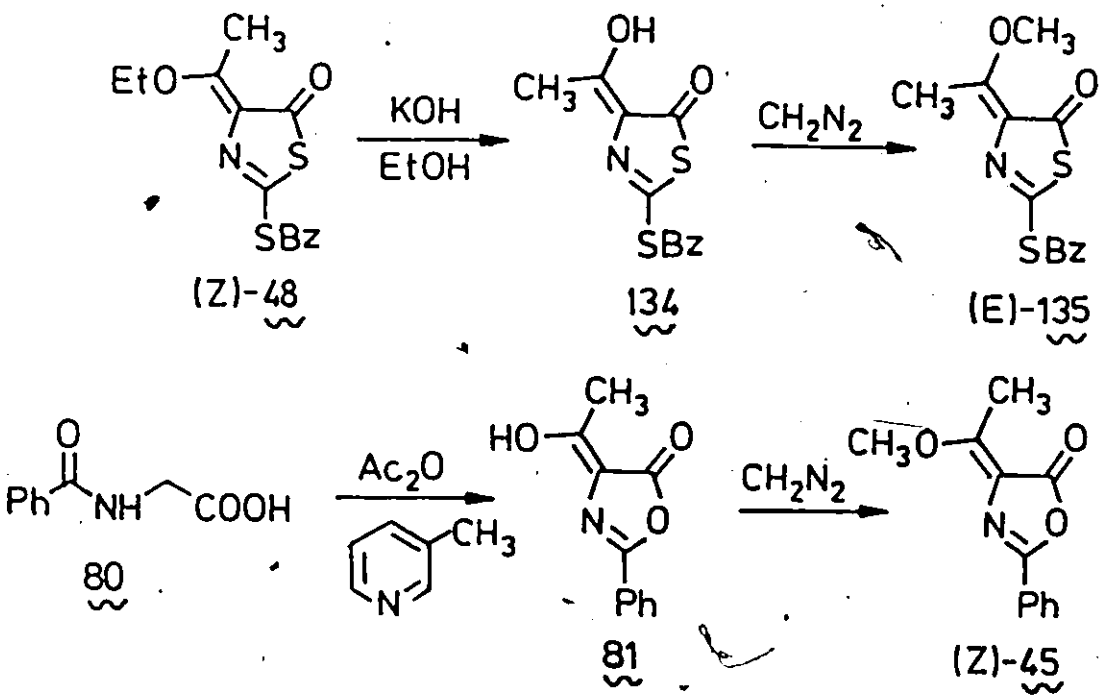
Scheme 3.3



3.1.3 Diazomethane O-Methylation

There is precedent in the literature to suggest that diazomethane methylation would provide a route to the less stable E isomer (see Section 2.6.1). Indeed, the E isomer of 2-benzylthio-4-(1-methoxyethylidene)-5-thiazolone, (E)-135 was prepared in this manner, but 4-[(Z)-1-methoxyethylidene]-2-phenyl-5-oxazolone, (Z)-45, was the product of diazomethane addition to 81 (see Section 3.2 for isomer identification). In analogy with structures assigned to (E)-135 and (Z)-45, the hydroxyethylidenethiazolone, 134, and oxazolone 81 were assigned the E and Z geometries respectively. Apparently, the

Scheme 3.4

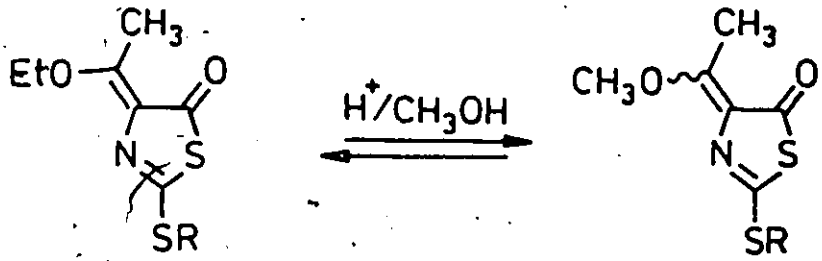


hydroxyl is hydrogen bonded with the ring carbonyl of 134 and to the ring nitrogen of 81.

Compound 81 was prepared from hippuric acid, 80, by the procedure of Attenburrow et al. (96) while potassium hydroxide hydrolysis of (Z)-48 gave compound 134 (see Section 3.3).

3.1.4 Alcohol Exchange

A number of 4-(1-alkoxyethylidene)-5-thiazolones were prepared to examine the NMR spectroscopic differences between E and Z isomers (see Section 3.2). The methoxyethylidene materials 135 and 136 were made by acid catalyzed alcohol exchange from 48 and 132. Equilibrium mixtures of the E and Z isomers in a ratio of 1:3 (as determined by ^{1}H NMR spectroscopy) were isolated but isomer separation was not attempted.



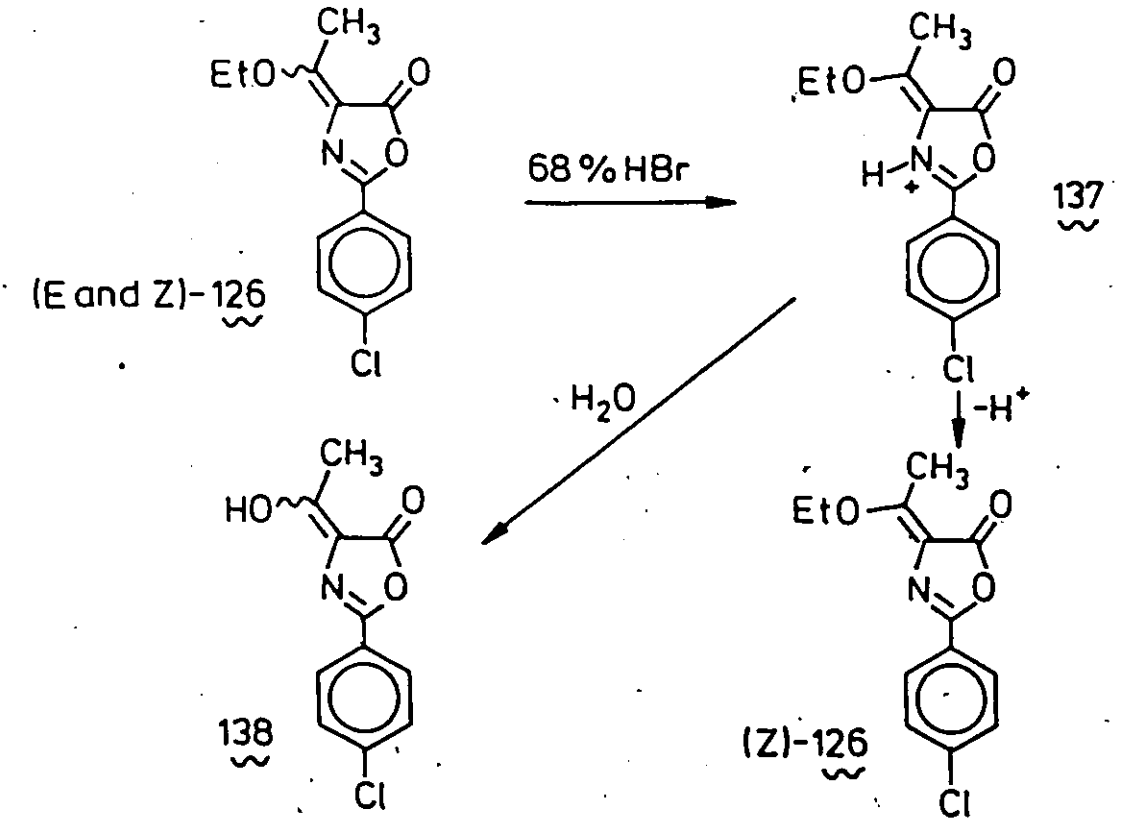
48, R = Bz
132, R = CH_3

135, R = Bz
136, R = CH_3

3.1.5 Double Bond Isomerization

The trapping of the E isomer by treatment with strong acids reported for the Erlenmeyer azlactones 73 (R" = H) (see Section 2.6) proved unsuccessful for the oxazolone 126. A 1:4 mixture of (E and Z)-126 dissolved in saturated aqueous hydrogen bromide solution and since this oxazolone is insoluble in water, its dissolution indicated substantial protonation. On rapid quenching, only the Z isomer precipitated (along with some hydrolysis product 138) but no E isomer was present (see Scheme 3.5). Therefore, in contrast to the Erlenmeyer azlactones, 73

Scheme 3.5



(R" = H), the Z isomer is preferred on protonation of 126.

The isomers of the 4-(1-alkoxyethylidene)-5-oxazolones and corresponding thiazolones were readily equilibrated in alcoholic hydrogen chloride, acetic acid or pyridine solutions. Solutions of pure isomers in chloroform were observed to equilibrate over a period of days to weeks (depending on the sample) without the addition of catalyst.

The procedures described above did not provide a route to the E isomers of the 2-t-butyl and 2-benzyloxazolones 47 and 46. Assignment of geometry to the available isomer was tentative because the second isomer was not at hand for comparison. Fortunately, photoirradiation proved to be of general use in

equilibration of the isomers about the exocyclic double bond.

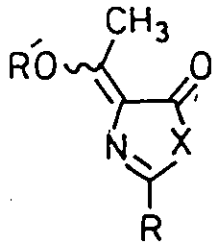
Photoisomerization was achieved by irradiation of the Z isomers of 44, 45, 46, 47 and 49 with 300 nm light. A listing of the acid catalyzed equilibrium ratios and photostationary ratios is given in Table 3.2. Photoirradiations of (Z)-44, (Z)-46 and (Z)-49 on preparative scales (100 to 350 mg) provided mixtures which were readily separated by flash column chromatography. In all of these cases there were no significant material losses from the photoirradiation and chromatographic processes.

3.2 Structure of 4-(1-Alkoxyethylidene)-5-oxazolones and 4-(1-Alkoxyethylidene)-5-thiazolones

3.2.1 Structure and Conformation

For reasons of synthetic design, it was necessary to assign the geometry of the isomers of the 4-(1-alkoxyethylidene)-5-oxazolone and thiazolone donors. The thermodynamically more stable isomers were found to be consistently less polar in chromatographic behavior, and in their ^{1}H NMR spectra, the chemical shifts of the protons on C-8 were 0.1 to 0.4 ppm downfield from the less stable isomer (see Table 3.3). Similarly, in the ^{13}C NMR, the C-8 signals of less polar isomers were 2 to 3 ppm downfield from the other isomer (see Table 3.3). It became evident that the thermodynamic product always had the same configuration and could be distinguished easily from the other isomer by comparison of physical properties, notably by

Table 3.2: Acid and Light Catalyzed Equilibrium Ratios of 4-(1-Alkoxyethylidene)-5-oxazolones and 4-(1-Alkoxyethylidene)-5-thiazolones



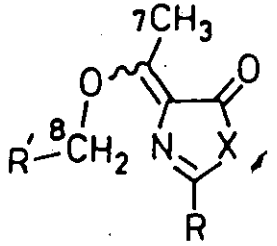
Compound #	R	R'	X	Acid Catalyzed E/Z Ratio[a]	Photostationary E/Z Ratio[a]
44	Ph	Et	O	1:5	2:3
45	Ph	CH_3	O	1:20	2:3
46	Bz	Et	O	small	2:3
47	t-Bu	Et	O	small	1:2
48	SBz	Et	S	1:5	-
49	OEt	Et	S	- [b]	1:2
126	p-ClPh	Et	O	1:4	-
127	p-BrPh	Et	O	1:4	-
132	SCH_3	Et	S	2:7[c]	-
135	SBz	CH_3	S	1:3	-
136	SCH_3	CH_3	S	1:3	-

[a] as determined by ^1H NMR spectroscopy

[b] ratio not determined because of ^1H NMR signal overlap

[c] base catalyzed ratio

Table 3.3: Selected ^{1}H and ^{13}C NMR Chemical Shifts of 4-(1-Alkoxyethylidene)-5-oxazolones and 4-(1-Alkoxyethylidene)-5-thiazolones[a]



Compound #	R	R'	X	C-7 CH_3[b,c] ^{1}H NMR E	C-7 CH_3[b,c] ^{1}H NMR Z	C-7 CH_3[b,c] ^{13}C NMR E	C-7 CH_3[b,c] ^{13}C NMR Z	C-8 CH_2[b] ^{1}H NMR E	C-8 CH_2[b] ^{1}H NMR Z	C-8 CH_2[b] ^{13}C NMR E	C-8 CH_2[b] ^{13}C NMR Z
44	Ph	CH_3	O	2.51	2.49	15.8	17.6	4.30	4.73	66.4	69.0
126	p-ClPh	CH_3	O	2.55	2.52	15.9	17.5	4.37	4.74	66.5	69.1
127	p-BrPh	CH_3	O	2.53	2.51	15.9	17.6	4.35	4.72	66.5	69.1
46	Bz	CH_3	O	2.41	2.44	15.9	16.5	4.29	4.57	66.3	68.1
47	t-Bu	CH_3	O	2.43	2.42	-	16.8[d]	4.30	4.64	-	68.8[d]
48	SBz	CH_3	S	2.54	2.44	16.5[d]	16.5[d]	4.27	4.55	65.8[d]	68.2[d]
132	SCH_3	CH_3	S	2.56	2.45	16.8[d]	17.1[d]	4.26	4.53	65.9[d]	68.8[d]
49	OEt	CH_3	O	2.40	2.40	16.0[d]	17.5[d]	4.20	4.50	65.4[d,e]	67.9[d]
45	Ph	H	O	2.53	2.53	-	16.3	4.04	4.29	-	59.6
135	SBz	H	S	2.58	2.48	15.4[d]	16.1[d]	4.00	4.15	56.9[d]	59.0[d]
136	SCH_3	H	S	2.58[f]	2.50[f]	-	-	3.98[f]	4.09[f]	-	-

Table 3.3 (continued)

[a]Detailed shifts and assignments for each compound are to be found in the experimental section and in Section 3.2.2.

[b]Chemical shifts are listed in ppm relative to TMS as internal standard and the samples were dissolved in deuteriochloroform unless otherwise indicated.

[c]The C-7 methyl data is included for comparison purposes. The chemical shifts of the C-7 protons showed little differences between E and Z isomers, whereas in ^{13}C NMR, the C-7 resonance of the Z isomers was consistently downfield (48 was the only exception, C-7 of both isomers was at 16.5 ppm in acetone-d_6).

[d]Acetone-d_6 as solvent.

[e]May be assigned to a 65.0 resonance.

[f]DMSO-d_6 as solvent.

NMR spectroscopy. Therefore the determination of the absolute structure of one isomer, that of 4-[(Z)-1-ethoxyethylidene]-2-phenyl-5-oxazolone, (Z)-44, by X-ray diffraction, was sufficient to assign the structure of all of the compounds in Table 3.3.

The X-ray structural determination of (Z)-44 was performed by C.J.L. Lock and R. Faggiani of the Department of Chemistry, McMaster University (97). Crystals suitable for X-ray diffraction studies were prepared by crystallization from absolute ethanol in 1-2 h. A stereo-view of the molecular structure is presented in Figure 3.2 and selected interatomic distances and angles are given in Table 3.4.

Although there are minor deviations, the structure (except for the hydrogen atoms), (Z)-44, is essentially planar. The largest distances out of the plane are at C-6 (0.055(4)Å), C-7 (0.136(6)Å), O-3 (0.065(3)Å) and C-9 (0.087(9)Å).

There are very strong repulsive interactions, especially around the C-4,C-6 double bond. These repulsions are caused primarily by steric compression between the C-7 methyl group and the carbonyl oxygen (O-2) as well as compression between the C-8 protons and the ring nitrogen (N-3). The methyl group at C-7 is oriented such that one of the methyl protons is pointed directly at O-2, giving a short $H\text{-}7_C$,O-2 distance of 2.26 Å. The nitrogen is flanked by the C-8 protons with N-3 to $H\text{-}8_A$ and $H\text{-}8_B$ distances of 2.45 and 2.63 Å respectively. As expected,

Figure 3.2 X-ray Determined Stereoview of 4-[(Z)-1-Ethoxyethylidene]-2-phenyl-5-oxazolone, (Z)-44

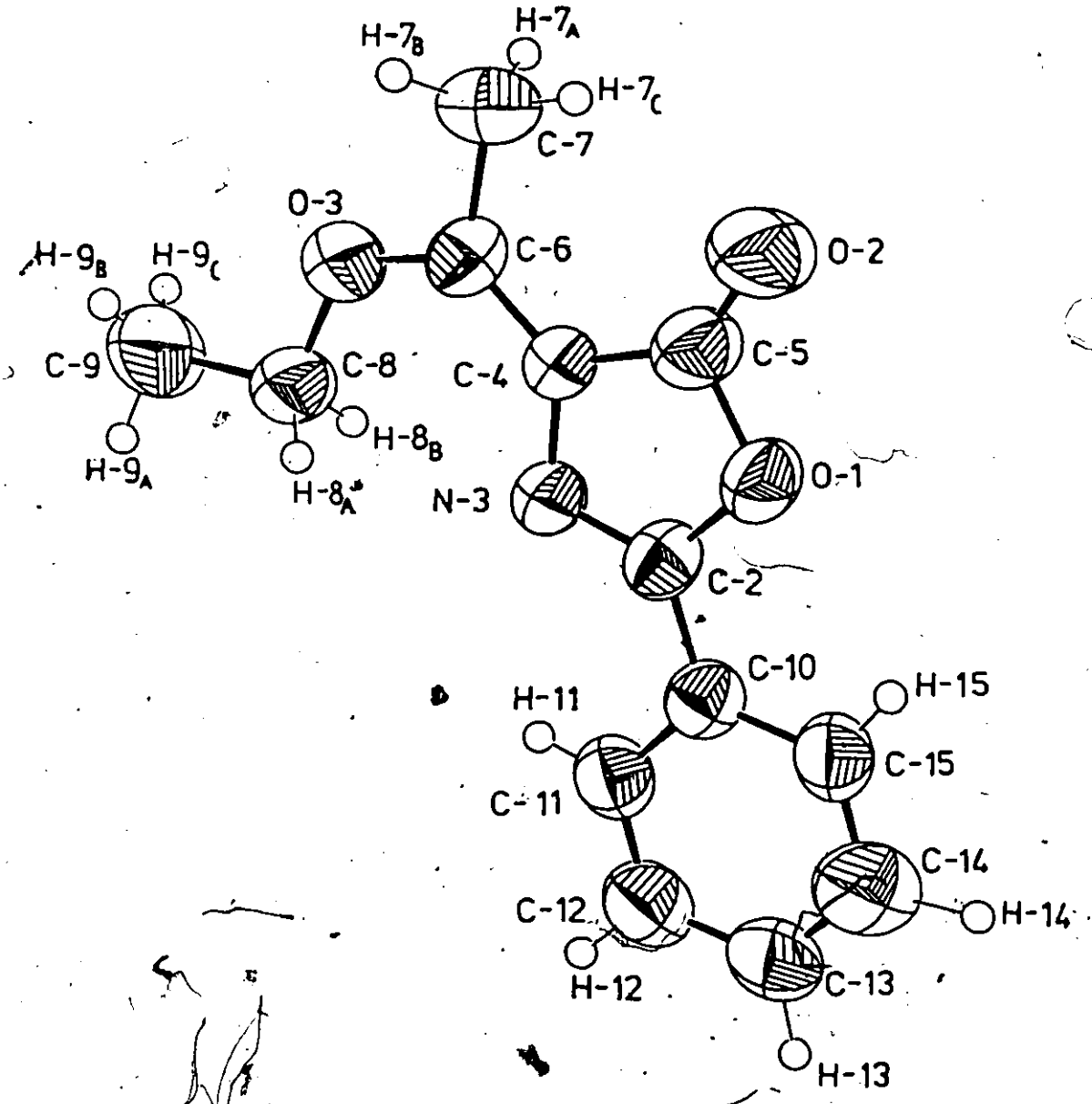
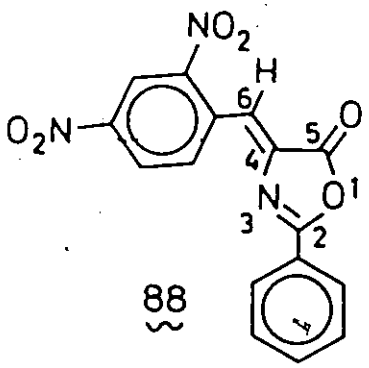


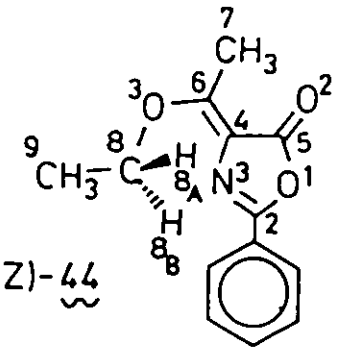
Table 3.4: Selected Interatomic Distances (Å) and Angles (deg):

O-1,C-2	1.393(4)	C-2,N-3	1.272(4)	N-3,C-4	1.405(4)
C-4,C-5	1.444(5)	C-5,O-1	1.397(4)	C-5,O-2	1.206(4)
C-4,C-6	1.358(4)	C-6,C-7	1.511(5)	C-6,O-3	1.339(4)
O-3,C-8	1.427(4)	C-8,C-9	1.519(6)	C-2,C-10	1.457(5)
C-10,C-11	1.387(5)	C-11,C-12	1.374(5)	C-12,C-13	1.396(6)
C-13,C-14	1.364(6)	C-14,C-15	1.377(6)	C-15,C-10	1.383(5)
C-5,O-1,C-2	105.6(3)	O-1,C-2,N-3	114.9(3)	C-2,N-3,C-4	106.1(3)
N-3,C-4,C-5	108.6(3)	C-4,C-5,O-1	104.8(3)	O-1,C-5,O-2	119.3(4)
C-4,C-5,O-2	135.9(4)	N-3,C-4,C-6	127.9(3)	C-5,C-4,C-6	123.4(3)
C-4,C-6,C-7	124.6(4)	C-4,C-6,O-3	127.3(3)	C-7,C-6,O-3	108.1(4)
C-6,O-3,C-8	122.1(3)	O-3,C-8,C-9	106.4(4)	O-1,C-2,C-10	116.5(3)
N-3,C-2,C-10	128.5(3)	C-2,C-10,C-11	118.9(3)	C-2,C-10,C-15	122.6(3)
C-15,C-10,C-11	118.5(4)	C-10,C-11,C-12	121.0(4)	C-11,C-12,C-13	119.3(5)
C-12,C-13,C-14	120.1(4)	C-13,C-14,C-15	120.1(4)	C-14,C-15,C-10	120.9(4)

the bond angles are affected by the double bond steric compressions. In comparison to the X-ray structure of 88 (76), the C-5,C-4,C-6 and C-4,C-6,C-7 angles are larger in (Z)-44



88



(Z)-44

(123.4(3)°, 124.6(4)° versus 120.8°, 119°) while the N-3,C-4, C-6 and C-4,C-6,O-3 angles are smaller (127.9(3)°, 127.3(3)° versus 131.2°, 128.9°). The C-7,C-6,O-3 angle of 108.1(4)° is very small for olefins (97) and there is a small but observable twist of 2.9(2)° in this exocyclic double bond.

In the comparison of bond lengths of (Z)-44 to 88, it is evident that (Z)-44 has less delocalization in the C-4,N-3, C-2,O-1 system and more delocalization in the C-6,C-4,C-5,O-2 system. Strong double bond character of the C-6,O-3 bond is indicated by its very short length (1.339(4)Å) and the large C-6,O-3,C-8 angle of 122.1(3)°. Apparently it is to maximize the p-π conjugation of O-3 to the C-6,C-4 double bond (and accompanying conjugated double bonds) that forces C-8 to be approximately coplanar with the ring system despite the crowding of the H-8 atoms with N-2.

Figure 3.3 shows other possible conformations of the two geometries of 44 using the bond lengths and angles of the basic ethylidene structure and assuming O-3 to be p-π conjugated to the ring system. From the severe steric interactions shown in Figures 3.3 b-e, it is understandable why compound 44 prefers the conformation and geometry in Figure 3.3a. Furthermore, Figure 3.3b demonstrates severe restraints to free rotation of the C-6,O-3 bond. For this reason, and because of the strong multiple bond character in the O-3,C-6 bond, (Z)-44 must be essentially fixed in the same conformation in solution as is observed in the crystal structure.

The preference for the conformation shown in Figure 3.3a rationalizes many of the physical property differences observed between the E and Z isomers of the 4-(1-alkoxyethylidene)-5-oxazolone and thiazolone compounds. Since in the Z isomer, the nitrogen is buried by two alkoxide hydrogens, this site is less available for coordination and explains the large difference in chromatographic polarity between isomers. The positioning of these same hydrogens in the deshielding regions of the carbon-nitrogen double bond explains the large downfield shift in the ^{1}H NMR of these atoms (see Table 3.3).

It is worth noting that the large difference in chemical shifts of the C-8 alkoxy protons of the E versus the Z isomers of 45 (see Figure 3.4 and for more examples Table 3.3) is in contrast to the small difference observed for the homo-

Figure 3.3: Possible Conformations of 44

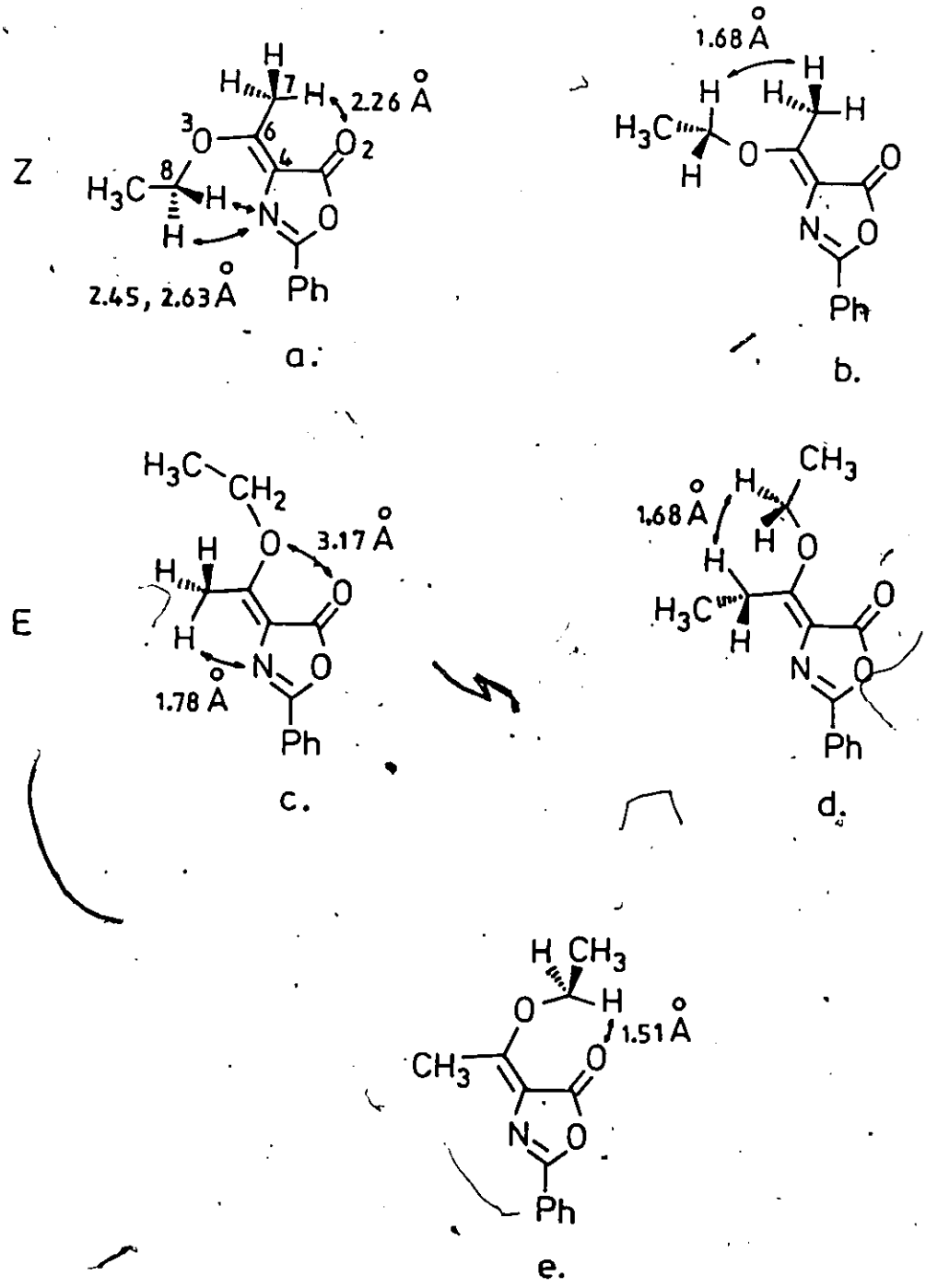
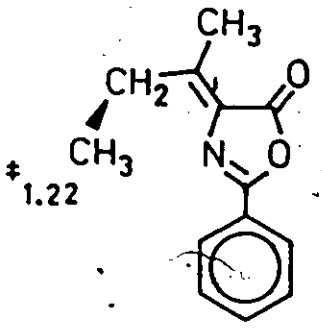
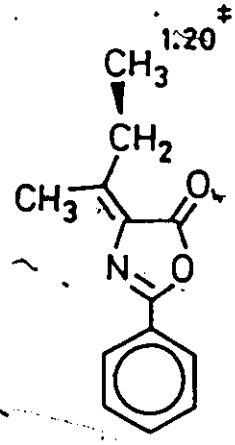


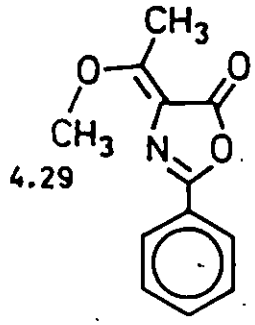
Figure 3.4: Comparison of the ^1H NMR Chemical Shifts of the Homoallylic Protons of 4-(Methylpropylidene)-2-phenyl-5-oxazolone, 139 with those of the Methoxy Protons of 4-(1-Methoxyethylidene)-2-phenyl-5-oxazolone, 45.



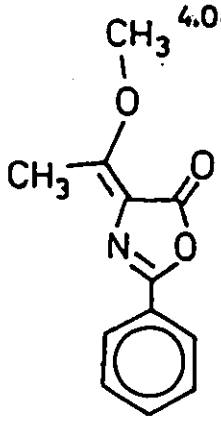
(Z)-139



(E)-139



(Z)-45



(E)-45

‡ These assignments may be reversed.

allylic protons in (E and Z)-139 (also shown in Figure 3.4) (80). However, the alkoxyethylidene series has an additional conformational restraint that is lacking in the alkylidene materials. The O-3,C-6 p-π conjugation forces the planarity of C-8, a requirement not present for the alkylidene substituents. Because of steric constraints around the exocyclic double bond similar to those in structure 44, the alkylidene allylic methyls are expected to be out of the plane (as illustrated in Figure 3.4) and therefore in magnetic environments which are not comparable to the alkoxyethylidene materials.

The ^{13}C NMR data of the alkoxide carbons in Table 3.3 provide further evidence for the general conformational preference of the alkoxy group to be as represented in the crystal structure of (Z)-44. The 2 to 3 ppm downfield shift of the Z isomers relative to the E isomers is consistent with the expected downfield "δ-effect" (98) (C-8 being δ to the nitrogen) whereas if the conformation with the C-8 CH_2 adjacent to the C-7 methyl were significantly populated, then an upfield shift would be anticipated (98) ("γ-effect", C-8 being γ to C-7).

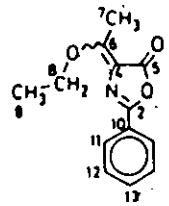
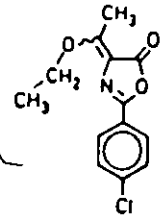
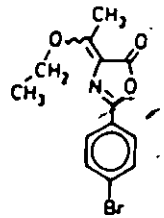
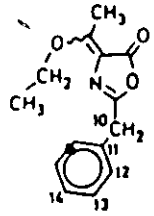
The X-ray study was initiated in order to establish the geometries of the isomers of the heterocycles listed in Table 3.3 as well as the geometries of synthetically related materials. The structural information obtained in the X-ray process was also of use in the understanding of the behavior of these compounds. Explanations for some of the physical properties and the isomer stabilities have already been mentioned,

but in many cases, the chemical reactivity of these compounds can be related to the structural information obtained from the X-ray diffraction studies. Their relative inactivity to electrophiles is discussed later in this chapter and is related to the nitrogen being "buried" and inaccessible to attack. In general, these compounds are poor Michael donors because of steric constraints about the anion, a subject discussed in Chapter 5.

3.2.2 ^{13}C NMR Assignments

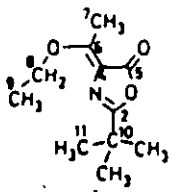
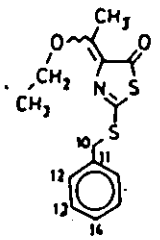
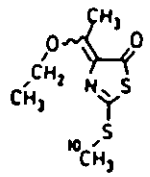
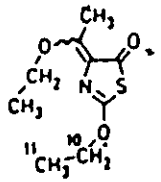
The main difficulties in assigning the ^{13}C NMR signals of the oxazolones and thiazolones listed in Table 3.5 were in the differentiation of the C-2, C-4 , C-5 and C-6 quaternary signals and of the C-7 and C-9 methyl signals. For both the oxazolones and thiazolones, the C-4 position was assigned to the quaternary signal at highest field because of electron donation to this centre from the alkoxy oxygen. In the oxazolones, the C-2 carbon was assigned to the resonance which was most affected by changes in substituent on C-2. Note especially the C-2 chemical shifts of the 2-t-butyl versus the 2-phenyl materials ((Z)-47 at 165.2 ppm versus (Z)-44 at 155.4 ppm) where the C-2 substituent effect is comparable with that shown for compounds 140 and 141 in Figure 3.5. The C-2 and C-5 positions, which are outside of the exocyclic double bond, were assigned to the signals that were only slightly affected by the change in geometry about the C-4,C-6 double bond (an observed chemical

Table 3.5 ^{13}C Chemical Shifts and Assignments of 4-(1-Alkoxyethylidene)-5-oxazolones and 4-(1-Alkoxyethylidene)-5-thiazolones.[a]

Structure	Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14
	(Z)-44	155.4	116.4	168.6	166.9	17.6	69.0	15.3	127.0(?)	127.0	128.7	131.3	
	(E)-44	155.8	118.5	168.7	163.9	15.8	66.4	15.2	126.7	127.2	128.7	131.6	
	(Z)-126	154.5	115.0	168.3	167.4	17.5	69.1	15.3	125.2	128.4	129.1	137.8	
	(E)-126	154.9	118.4	169.2	163.6	15.9	66.5	15.2	125.5	128.2	129.1	137.6	
	(Z)-127	154.5	114.9	168.2	167.4	17.6	69.1	15.2	125.5	128.5	132.0	126.3	
	(E)-127	154.9	118.4	169.4	163.5	15.9	66.5	15.2	125.9[b]	128.4	132.0	126.1[b]	
	(Z)-46	158.2	114.3	168.7	166.6	16.5	68.1	15.2	35.6	134.2	128.8	129.1	127.3
	(E)-46	158.4	117.4	168.2	164.1	15.9	66.3	15.2	35.8	134.2	128.8	129.1	127.3

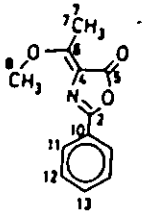
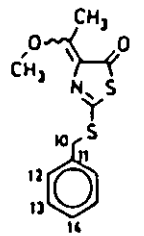
cont...

Table 3.5 (continued)

Structure	Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14
	(Z)-47[c]	165.2[b]	113.8	168.6	165.5[b]	16.8	68.8	14.9	33.6	26.9			
	(Z)-48	154.0	~129(?)	193.3	165.2	17.4	68.3	15.4	35.2	136.5	129.0	128.7	127.6
	(Z)-48[c]	152.6	128.2	192.3	165.9	16.5	68.2	14.9	34.8	137.0	129.1	128.5	127.4
	(E)-48[c]	-[d]	-[d]	-[d]	169.7	16.5[e]	65.8	14.9[e]	34.8[e]	137.0[e]	129.1[e]	128.5[e]	127.4[e]
	(Z)-132	155.2	128.9	193.6	165.0	17.6	68.5	15.5	13.7				
	(Z)-132[c]	153.9	128.5	-[d]	165.9	17.1	68.8	15.1	13.0				
	(E)-132[c]	-[d]	132.0	-[d]	166.8	16.8	65.9	15.2	13.5				
	(Z)-49[c]	157.7	126.7	191.4	162.7	17.5	67.9	15.2	65.5	14.0			
	(E)-49[c]	158.0	129.1	194.2	164.5	16.0	65.0[b]	14.8	65.4[b]	14.0			

cont...

Table 3.5 (continued)

Structure	Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14
	(Z)-45	155.4	115.8	168.4	167.2	16.3	59.6		126.6	127.3	128.8	131.8	
	(Z)-135[c]	- [d]	- [d]	- [d]	- [d]	16.1	59.0		34.8	- [d]	129.3	128.8	127.7
	(E)-135[c]	- [d]	- [d]	- [d]	- [d]	15.4	56.9		34.8[e]	- [d]	129.3[e]	128.8[e]	127.7[e]

[a] Chemical shifts are listed in ppm relative to TMS as internal standard and the samples were dissolved in deuteriochloroform unless otherwise indicated.

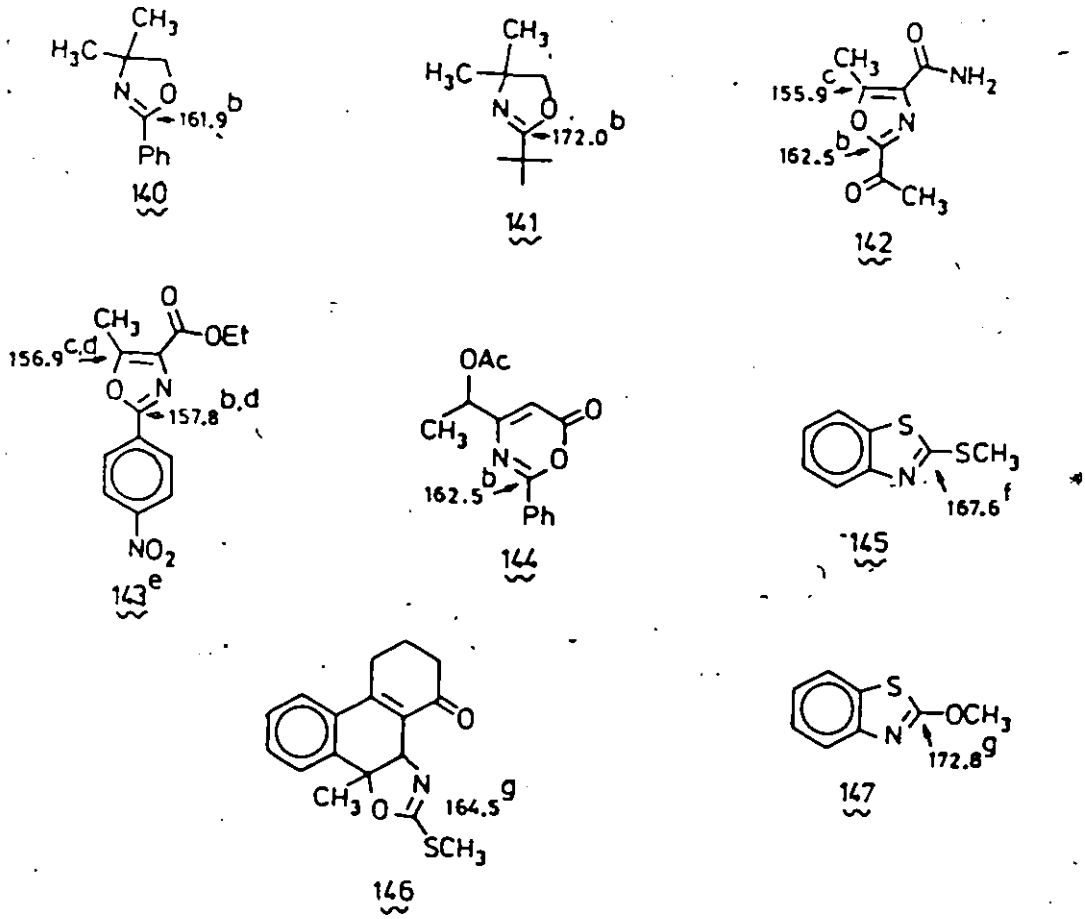
[b] These assignments may be reversed.

[c] Acetone-d_6 as solvent.

[d] These signals were too weak (within the spectrum noise level) for assignment.

[e] Data obtained as a mixture of isomers, the chemical shifts of these carbons are assumed to be the same as those of the major component.

Figure 3.5 ^{13}C Chemical Shifts of Model Compounds for the Assignment of C-2 and C-6 ^{13}C Signals in Table 3.5[a]



[a]Source; reference 99, unless otherwise indicated
[b]Compare with the C-2 signals of the oxazolones in Table 3.5
[c]Compare with the C-6 signals in Table 3.5
[d]These assignments may be reversed
[e]Source; this thesis, Section 3.5
[f]Compare with the C-2 signals of the 2-alkylthio substituted thiazolones in Table 3.5
[g]Compare with the C-2 signals of 49 in Table 3.5. See also Figure 3.6.

shift difference of 0.2 - 0.4 ppm at C-2 and 0.1 - 0.9 ppm at C-5), whereas, the actual C-4,C-6 double bond carbons were assigned to the signals that were most affected by the change in geometry (a difference of 3.1 - 3.9 ppm at C-4 and 2.4 - 3.9 ppm at C-6).

For the thiazolones in Table 3.5, the C-6 carbon was assigned to the signal in the same region as in the oxazolone analogues and C-5 was assigned to the downfield signal at 191.4 to 194.2 ppm (this is within the accepted region of similarly substituted carbons; 185 - 195 ppm (100)). The remaining quaternary signal was assigned to the C-2 carbon.

The comparison of the chemical shifts of the 2-(alkylthio)thiazolones 132 and 48 with those of the 2-ethoxythiazolone 49 provides confirmation of these assignments. The C-2 carbon is shifted downfield on substitution of sulfur with the more electronegative oxygen (compare the shifts shown for compounds 145 and 147 in Figure 3.5). Signals for C-4, C-5 and C-6 are all shifted upfield, as is expected from the stronger electron donating properties of oxygen versus sulfur.

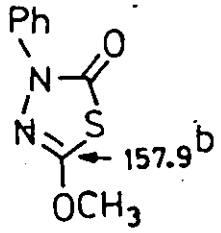
Although the assignments in Table 3.5 are consistent with the given data, the assignments at C-2 and C-6 are reversed to those predicted from the position of the signals for similarly substituted carbons. Some such typical chemical shifts are shown in Figure 3.5.

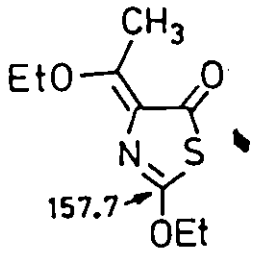
Apparently, the C-6 signals are downfield and the C-2

signals are, in general, upfield from the signals of the model compounds in Figure 3.5 because of the strong multiple bond character of the O-3,C-6 bond (see Section 3.2.1) and the resulting electron donation of O-3 to the ring. A similar chemical shift to that observed for C-2 of (Z)-49 is observed on replacement of C-4 in the ring with an electron donating nitrogen as is shown in Figure 3.6.

To define the assignments more precisely, the ^{1}H-^{13}C couplings present in the oxazolone (Z)-126 were examined.

Figure 3.6 Comparison of the C-2 ^{13}C Chemical Shift of 2-Ethoxy-4-[(Z)-1-ethoxyethylidene]-5-thiazolone), (Z)-49, with the Analogous Chemical Shift of 3-Phenyl-5-methoxy-1,3,4-thiadiazolin-2-one.[a]





(Z)-49

[a]Compare with the chemical shifts shown for compounds 146 and 147 in Figure 3.5.

[b]Source; Reference 99.

By selective ^{1}H decoupling experiments, summarized in Figure 3.7, it was demonstrated that, in the absence of decoupling power, the carbons assigned in the ^{13}C NMR spectra as C-4 and C-6 experienced long range coupling to the C-7 protons (at 2.52 ppm in the ^{1}H NMR) and C-2 experienced long range coupling to the downfield p-chlorophenyl protons (at 8.96 ppm). The C-5 signal was a sharp singlet in the absence of any ^{1}H decoupling. This ^{1}H-^{13}C coupling information is consistent with the assignments given in Table 3.5.

As was achieved for the quaternary carbons, the assignments of the C-7 and C-9 methyls were confirmed by the observation of long range ^{1}H-^{13}C coupling of the C-8 protons with the C-9 carbons in both the oxazolone (Z)-126 and the thiazolone (Z)-132.

3.3 Substitution Reactions

Substitution reactions at C-6 of the 4-(1-ethoxyethylidene)-5-oxazolones and 4-(1-ethoxyethylidene)-5-thiazolones were readily accomplished in good yields with oxygen, nitrogen and sulfur nucleophiles. An example of oxygen substitution is the hydrolysis of the ethoxyethylidene materials 48, 49 and 126 to the hydroxyethylidene analogues 134, 148 and 138 as summarized in Table 3.6. In place of the ethoxy signals present in the ^{1}H NMR of the precursors, these hydroxy compounds showed a downfield proton (at 9.85, 11.52 and 11.02 ppm respectively)

Figure 3.7: Determination of the Assignments of the Quaternary Oxazolone Carbons of 2-(4-Chlorophenyl)-4-[(Z)-1-ethoxyethylidene]-5-oxazolone, (Z)-126, via ^{1}H-^{13}C Decoupling Experiments

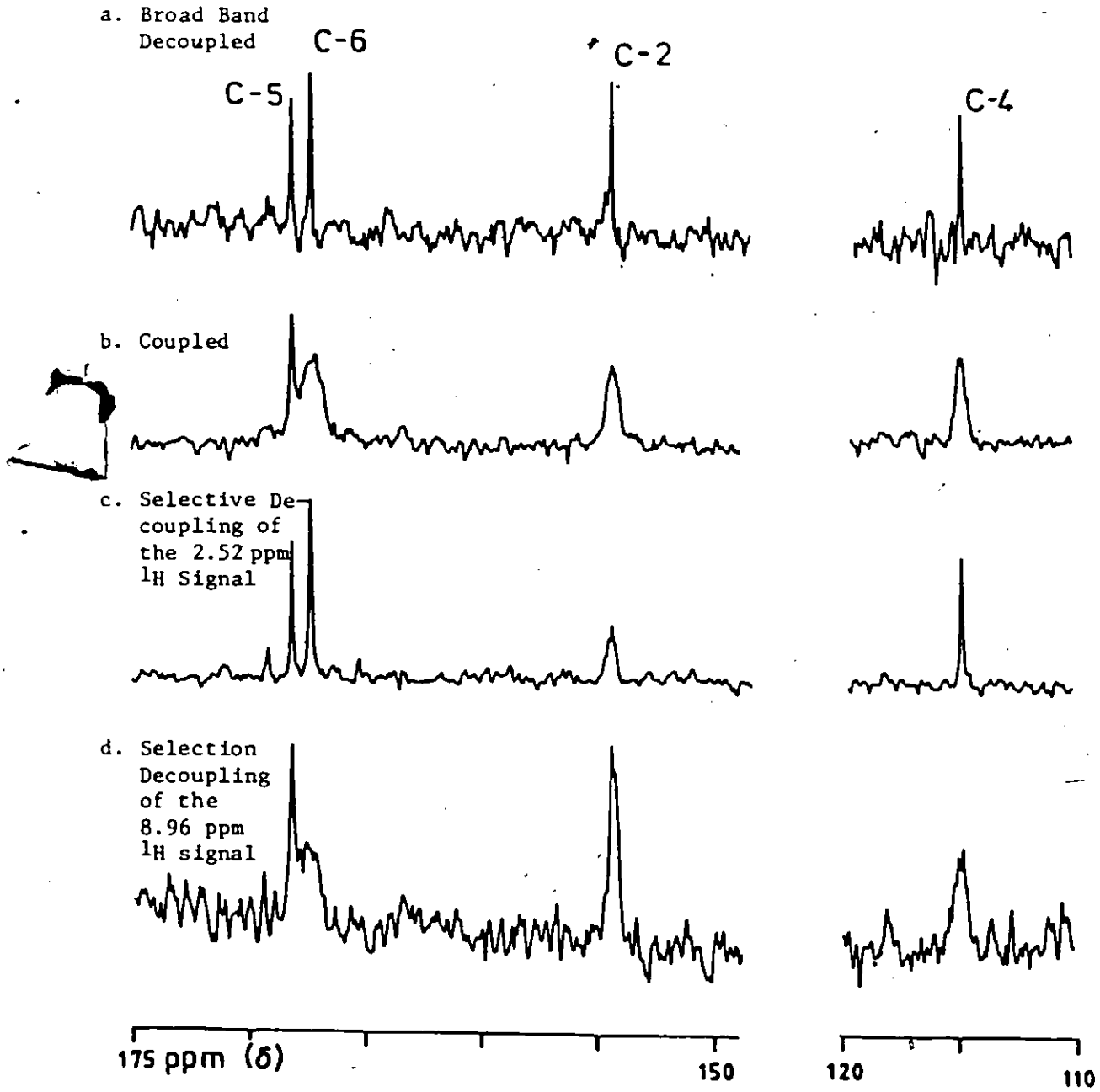
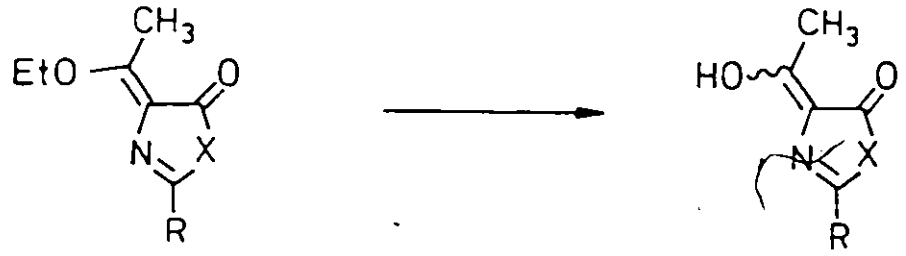


Table 3.6: 4-(1-Hydroxyethylidene)-5-oxazolone and 4-(1-Hydroxyethylidene)-5-thiazolone Preparation by Hydrolysis of the Ethoxyethylidene Analogues

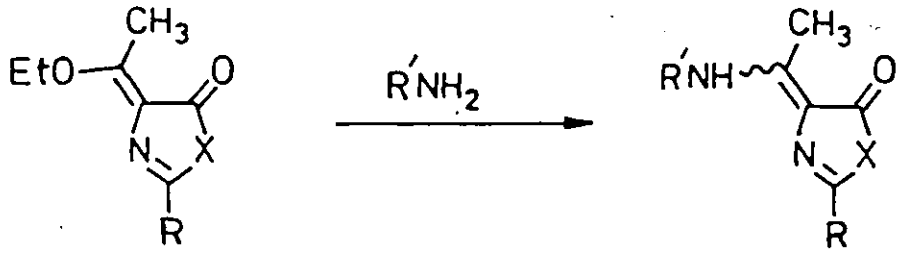


Starting Material	R	X	Catalyst	Product Yield (%)	Hydroxy Product
(Z)-48	SBz	S	KOH	60	134
(Z)-49	OEt	S	conc H_2SO_4	81	148
(Z)-126	p-ClPh	O	conc HBr	55	138

characteristic of enols. For 134 methylation of the enol with diazomethane provided the methoxyethylidene material, (E)-135, a product also obtained by alcohol exchange from 48 (see Section 3.1). The alcohol exchange reactions of the thiazolones 48 and 132 to 135 and 136 (Section 3.1) are other examples of substitution at C-6 by oxygen nucleophiles.

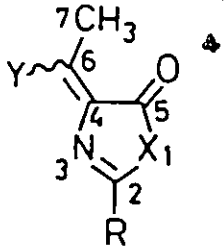
Substitutions by nitrogen nucleophiles are summarized in Table 3.7 The ^{1}H NMR spectra of these compounds showed the vinylic N-H resonance at 8.2 to 11.1 ppm. The IR spectra showed the expected N-H stretching mode at 3198 to 3255 cm^{-1} and the ^{13}C NMR spectra (obtained only for compounds 151 and 154) resembled the alkoxyethylidene materials. A comparison of ^{13}C NMR data between the (phenylhydrazino)ethylidene and ethoxyethylidene analogues is shown in Figure 3.8. As expected, the C-2,4,5,6 and 7 signals of the nitrogen substituted materials are all shifted upfield relative to the oxygen analogues because of the difference in electronegativity and electron donating properties of nitrogen versus oxygen. There is a surprising change in the magnitude of the upfield shift at C-2 and C-4 in the oxazolone versus the thiazolones when comparing the hydrazinoethylidene and alkoxyethylidene materials (see Figure 3.8). The oxazolones experience a large upfield shift at C-4 (a change of 7.8 and 8.0 ppm) and a moderate upfield shift at C-2 (a change of 2.9 and 2.8 ppm) while the C-4 and C-2 signals of the thiazolone (Z)-151 are 7.2 and $\sim$ 4.5 ppm respectively upfield from the same carbons of (Z)-48. Apparently,

Table 3.7: C-6 Substitution Reactions with Nitrogen Nucleophiles



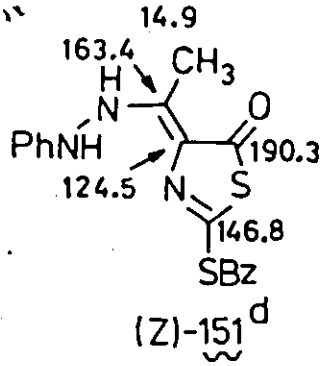
Starting Material	R	X	R'	Product Yield (%)	Substitution Product
(Z)-48	SBz	S	-Ph	>95	149
(Z)-48	SBz	S	-p-$PhSO_2NH_2$	>95	150
(Z)-48	SBz	S	-NHPh	>95	151
(Z)-132	SCH_3	S	$-CH_2CH_2SH$	62	152
(Z)-49	OEt	S	-Ph	>95	153
(Z)-44	Ph	O	-NHPh	>95	154

Figure 3.8 Comparison of ^{13}C NMR Chemical Shifts of 2-Benzylthio-4-[(Z)-1(phenylhydrazino)ethylidene]-5-thiazolone (Z)-151, with 2-Phenyl-4-[(E and Z)-1-(phenylhydrazino)ethylidene]-5-oxazolone, (E and Z)-154 and their Ethoxyethylidene Analogues[a,b].

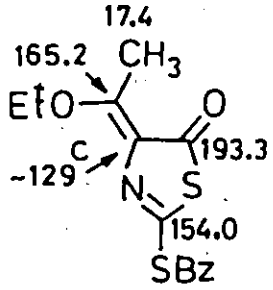


X = O,S

Y = PhNHNH , EtO



(Z)-151[d]



(Z)-48

Position	$\delta_{48} - \delta_{143}$
7	2.5
6	1.8
5	3.0
4	~4.5
2	7.2

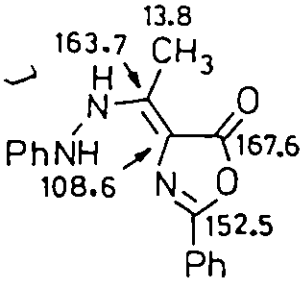
[a] Further shifts and assignments for each compound are to be found in the experimental section and in Table 3.5.

[b] Chemical shifts are listed in ppm relative to TMS as internal standard and the samples are dissolved in deuteriochloroform unless otherwise indicated.

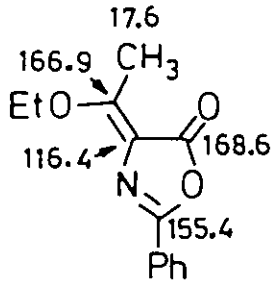
[c] This C-4 signal is obscured by a benzyl aromatic signal, the C-4 signal of the 2-methylthio analogue is at 128.9 ppm

cont...

Figure 3.8 cont.

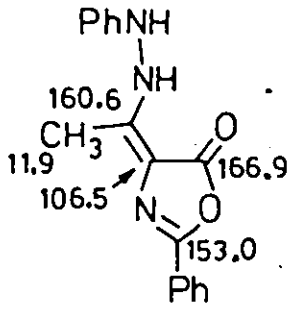


(Z)-154[e]

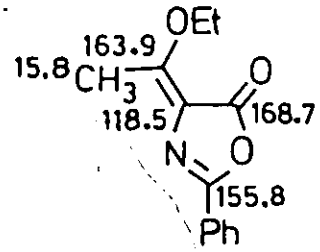


(Z)-44

Position	$\delta_{44}-\delta_{146}$
7	4.9
6	3.2
5	1.0
4	7.8
2	2.0



(E)-154[e]



(E)-44

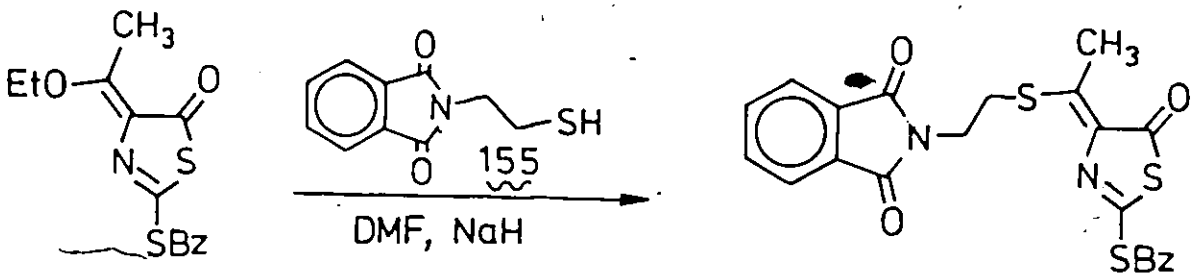
7	3.9
6	3.3
5	1.8
4	8.0
2	2.8

[d]assigned tentatively to the Z-geometry

[e]in acetone-d_6 as solvent

nitrogen lone pair electron donation is directed more towards C-2 in the thiazolone than in the oxazolones, perhaps because of charge stabilization from the d-orbitals of the sulfurs.

An example of substitution with sulfur is the condensation of 2-phthalimidoethanethiol, 155, with the thiazolone (Z)-48. Alkoxymethyleneoxazolones are known to undergo C-6 substitutions with thiols in pyridine solution (91), however, no reaction occurred on dissolving 155 and 48 in pyridine.

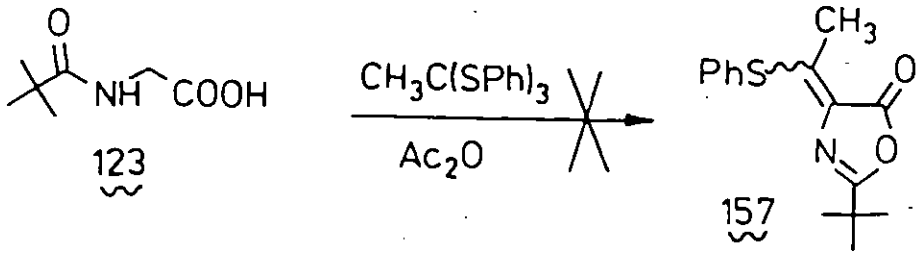


(Z)-48 156

With the use of a stronger base, these materials were successfully coupled to give the desired product 156. One isomer only was obtained assigned tentatively the Z geometry in analogy to the alkoxyethylidene materials where the Z geometry is preferred because of steric constraints (see Section 3.2.1). In the ^{1}H NMR spectrum, the product showed the phthalimdoethyl methylenes as triplets (3.33 and 4.02 ppm; J = 7 Hz), the vinyl methyl signal in the same region as the nitrogen and oxygen substituted

materials (2.64 ppm) and the expected benzyl and phthalimido signals (4.43, 7.25-7.53 and 7.67-8.00 ppm).

On attempted direct preparation of the S-substituted material 157, with triphenyl trithioorthoacetate (101,102) none of the desired 4-[(1-phenylthio)ethylidene]-5-oxazolone was observed in the crude reaction mixture. Knott (89) previously



reported a similar failure with triethyl trithioorthoformate.

In addition to the demonstration of the generality of substitution at C-6, most of the C-6 substitution reactions were intended for more specific interests. Compound 134 was prepared for diazomethane methylation and to determine the geometry of the resulting methoxy product (Section 3.1). The other hydroxyethylidene materials were prepared incidentally. Compound 148 was obtained on attempted C-2 hydrolysis of compound 49 (see Section 3.4) and 138 was isolated on attempted acid catalyzed isomerization of (Z)-126 (Section 3.1.5).

Reactions in which adducts 152 and 156 were prepared were intended to demonstrate the possibility of early cysteamine introduction for thienamycin synthesis.

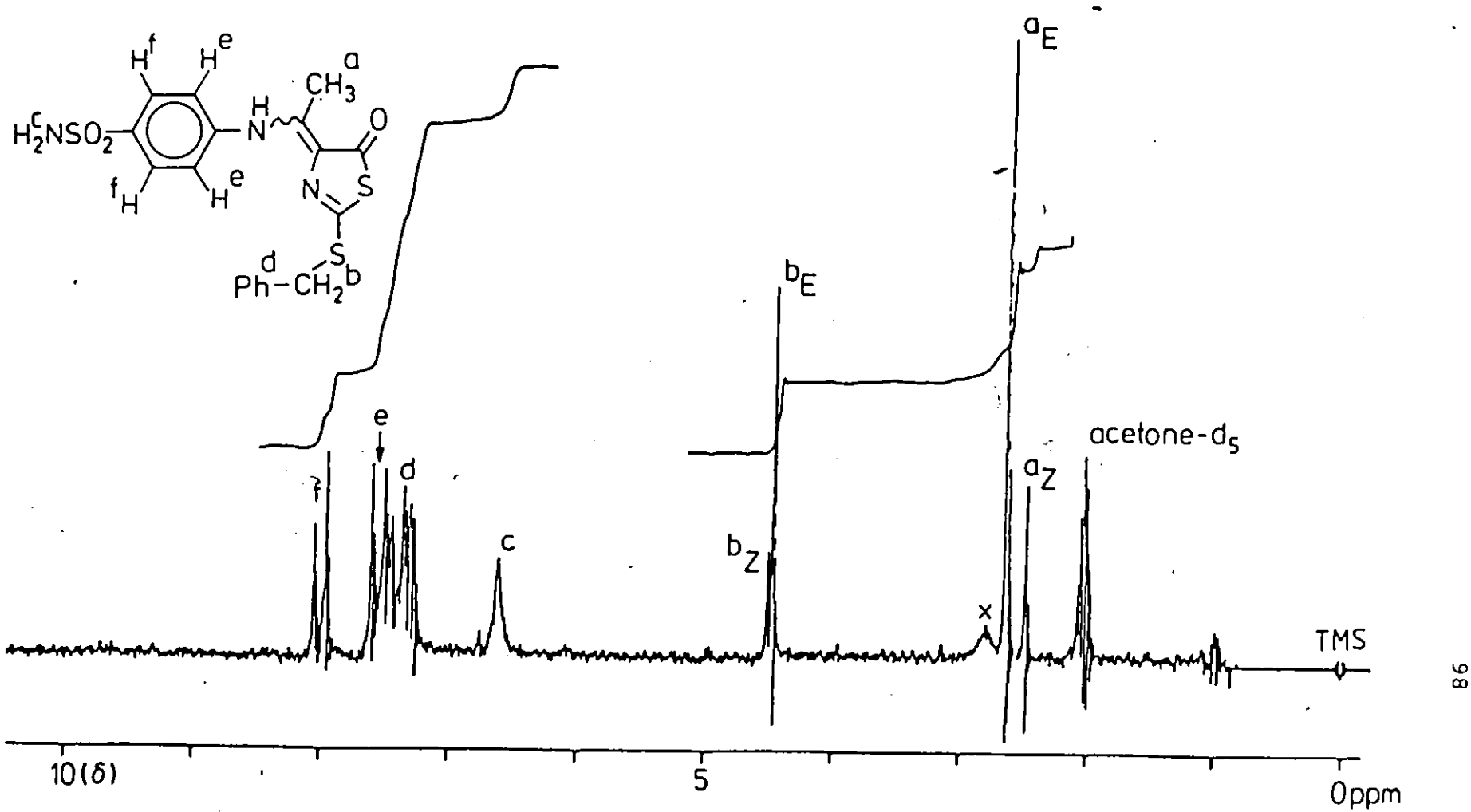
Since aniline and sulfanilamide were reported to attack different sites on the ethoxymethylenethiazolone, 109 (Scheme 2.11), these nucleophiles were added to 48. In this case, both amines attacked the C-6 position giving the substitution adducts.

Products 151 and 154 were prepared for studies in oxazolone and thiazolone ring opening by pyrazolinone formation (see Sections 2.6 and 3.4.3).

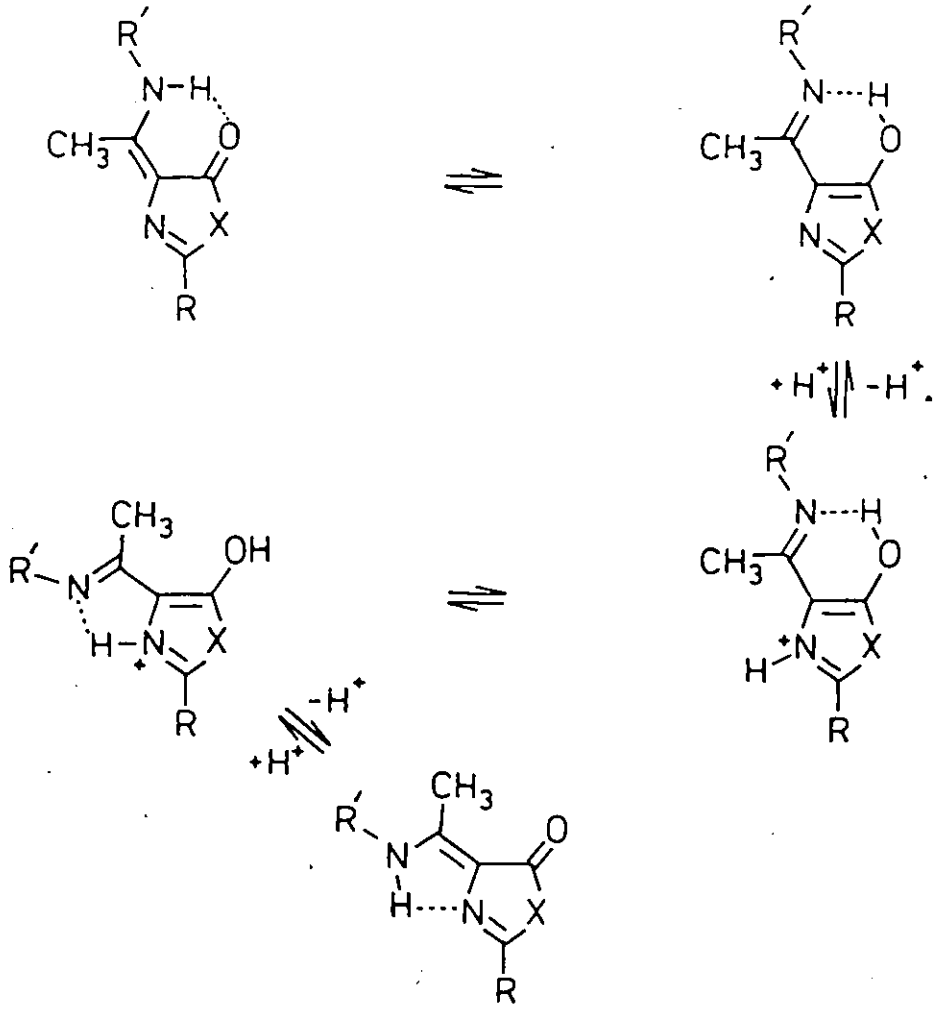
Three of the nitrogen substituted materials, 150, 154 and 153, in solution, showed the presence of both E and Z isomers (the ^{1}H NMR spectrum of the isomers of 150 is shown in Figure 3.9) yet compounds 150 and 154 had sharp, well-defined melting points. These seemingly contradictory properties can be explained by equilibration as shown in Scheme 3.6. In this way, conversion into one preferred structure occurs during crystallization.

Assignment of the geometry of the nitrogen substituted compounds 150 through 154 was made on the basis of NMR spectroscopy. Selected chemical shifts are listed in Table 3.8. The E and Z isomers of compound 154 were assigned by a comparison of ^{13}C NMR data with the ethoxyethylidene analogues as shown in Figure 3.8. Compound 151 was assigned the Z geometry by comparison of its ^{13}C NMR data with that of (Z)-48 and (E and Z)-154 (see Figure 3.8). In this case, since data are available

Figure 3.9: ^{1}H NMR Spectrum of 2-Benzylthio-4-[(E and Z)-1-(4-sulfonamidoanolino)-ethylidene]-5-thiazolone, (E and Z)-150

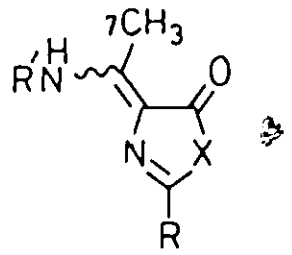


Scheme 3.6



on one isomer only, this assignment is tentative. The geometries of the two isomers of 150 and 153 were tentatively assigned on the premise that the downfield C-7 methyl in the ^{1}H NMR spectra, is the E isomer (in analogy to the general trend in the alkoxyethylidene materials; see Table 3.3). The geometries of 149 and 152 were tentatively assigned by comparison with other ^{1}H NMR shifts listed in Table 3.8.

Table 3.8 Geometric Assignments of 4-(1-Aminoethylidene)-5-oxazolones and 4-(1-Aminoethylidene)-5-thiazolones



Compound #	R	X	R'	^{1}H NMR of Protons on C-7 (δ)[a,b]		^{13}C NMR of C-7 (δ)[b,c]		E/Z
				E	Z	E	Z	
149	SBz	S	Ph	-	2.51	-	-	-
150	SBz	S	p-$PhSO_2NH_2$	2.66	2.50	-	-	4:1
151	SBz	S	NHPh	-	2.53	-	14.9	
152	SCH_3	S	CH_2CH_2SH	-	2.53	-	-	-
153	OEt	S	Ph	2.48	2.43	-	-	4:5
154	Ph	O	NHPh	2.53	2.51	11.0[d]	13.8[d]	2:3

[a]Detailed shifts and assignments are to be found in the experimental section.

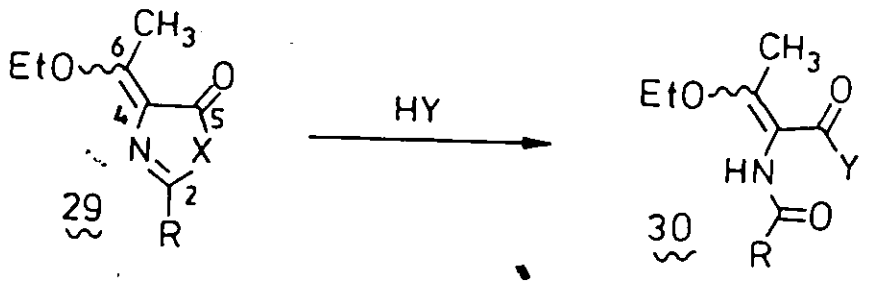
[b]Chemical shifts are listed in ppm relative to TMS as internal standard and the samples are dissolved in deuteriochloroform.

[c]Detailed shifts and assignments are to be found in Figure 3.8 and in the experimental section.

[d]In acetone-d_6 as solvent.

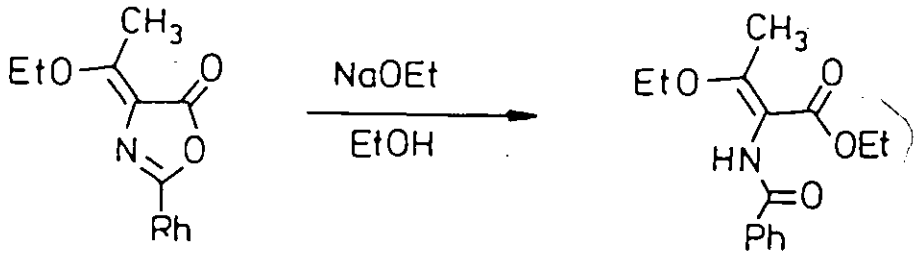
3.4 Ring modification and Ring Opening Reactions

The experiments discussed in this section were directed at two objectives: (i) to discover the conditions feasible for ring opening of type 29 to 30, and (ii) to obtain the ring opening product, 30, in the E geometry (the synthetic objectives are discussed in detail in Section 2.1).



3.4.1 Nucleophilic ring opening

Ring opening by nucleophilic attack at C-5 was achieved on the ethoxyethylideneoxazolones but not on the corresponding thiazolones. By treatment of the oxazolone (Z)-44 with sodium ethoxide in absolute ethanol, the desired ring opening was accomplished giving the crotonate (Z)-158 in 65% isolated yield. One pure isomer only was obtained, tentatively assigned the Z geometry (see Section 3.4.5). The 2-phenyl and 2-t-butyl analogues (Z)-46 and (Z)-47 were similarly ring opened, but these products were not fully characterized. Attempted ethoxide ring opening of 2-benzylthio-4-[(Z)-1-ethoxyethylidene]-5-thiazolone, (Z)-48 led only to unidentified decomposition products.



(Z)-44 (Z)-158

The addition of ethanol in the ring opening of (Z)-44 was confirmed by the presence of signals for the ethyl ester in the ^{1}H and ^{13}C NMR spectra of (Z)-158 (the ^{1}H spectrum of (Z)-158 is shown in Figure 3.10, the ^{13}C assignments are shown in Figure 3.11). The two carbonyls of the product are observed in the ^{13}C NMR spectrum at 165.7 and 165.9 ppm and in the IR spectrum at 1714 cm^{-1} (ester) and 1641 cm^{-1} (amide). The amide N-H is observed in the ^{1}H NMR spectrum at 7.21 ppm and in the IR spectrum at 3243 cm^{-1}. The chemical shifts of the signals in the ^{13}C NMR for the carbon-carbon double bond are upfield from those of the precursor, (Z)-44 (159.9 and 108.9 ppm for (Z)-158, 166.9 and 116.4 ppm for (Z)-44). Electron donation by the amide nitrogen and the absence of ring current explain the relative upfield positions of the 159.9 and 108.9 ppm signals.

Figure 3.10: ^{1}H NMR Spectrum of Ethyl (Z)-2-Benzamido-3-ethoxy-2-butenoate, (Z)-158

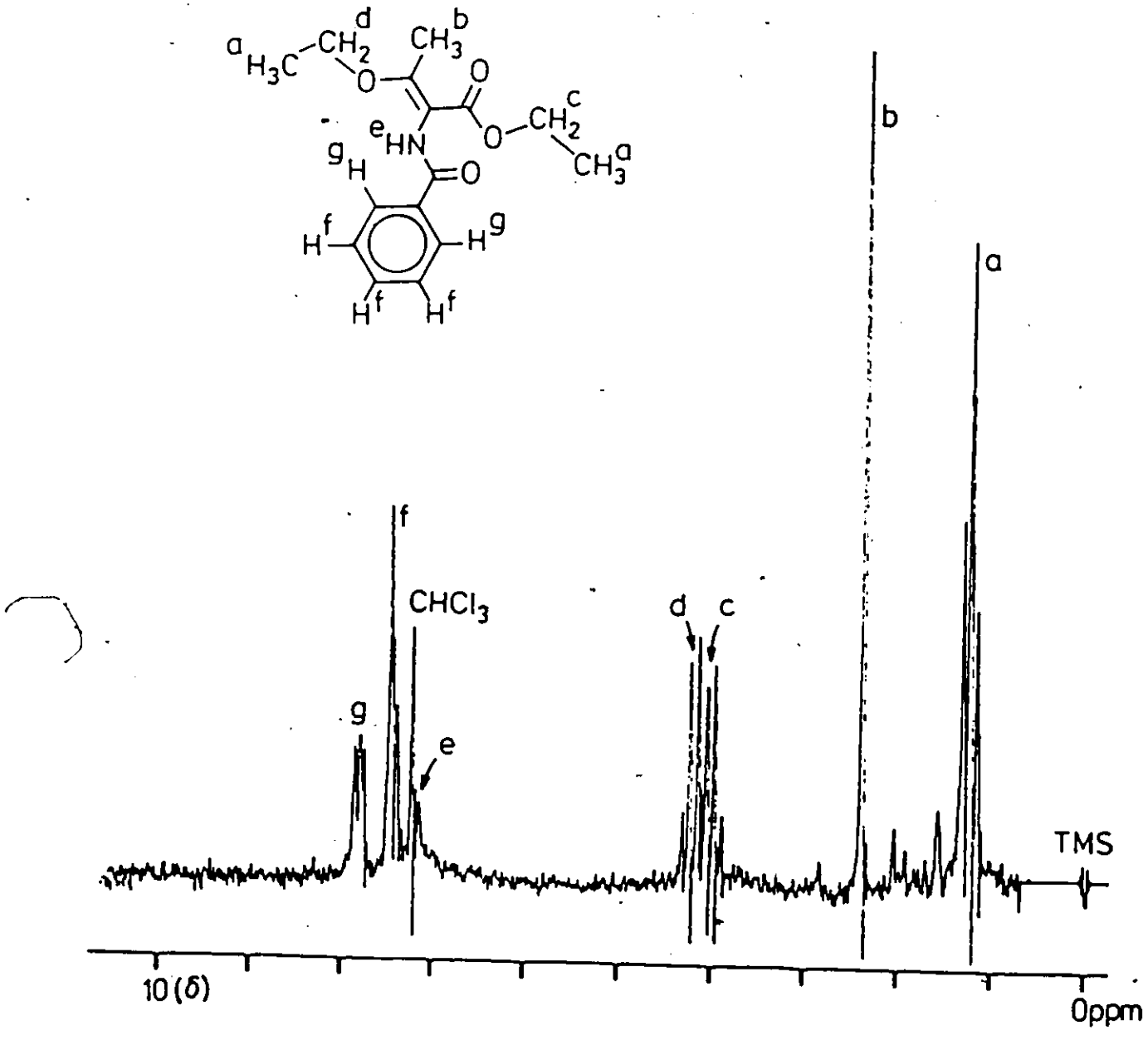
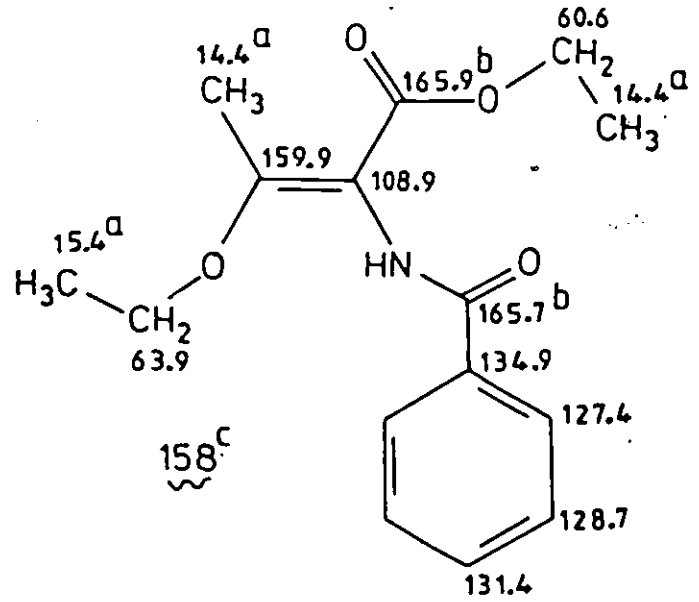
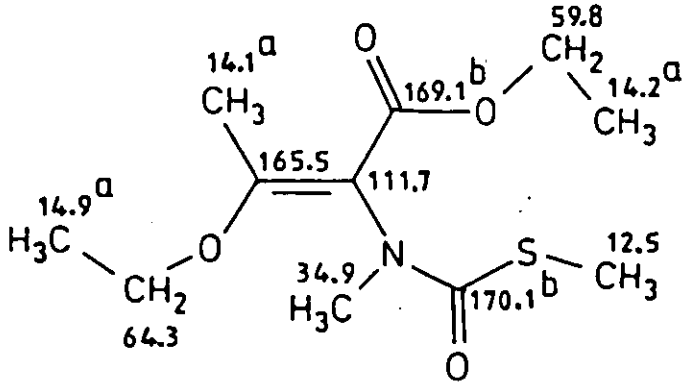


Figure 3.11 Summary of ^{13}C Chemical Shift Assignments for Related Ring Opened and Ring Modification Products



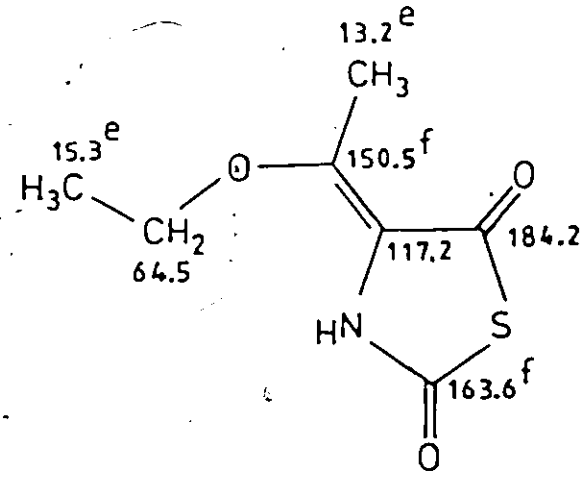
158[c]



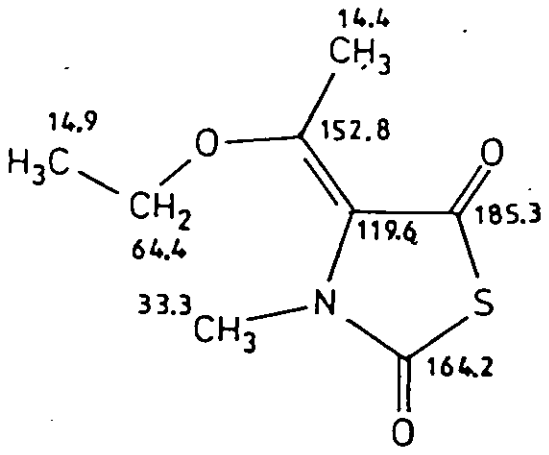
(Z)-159[d]

cont...

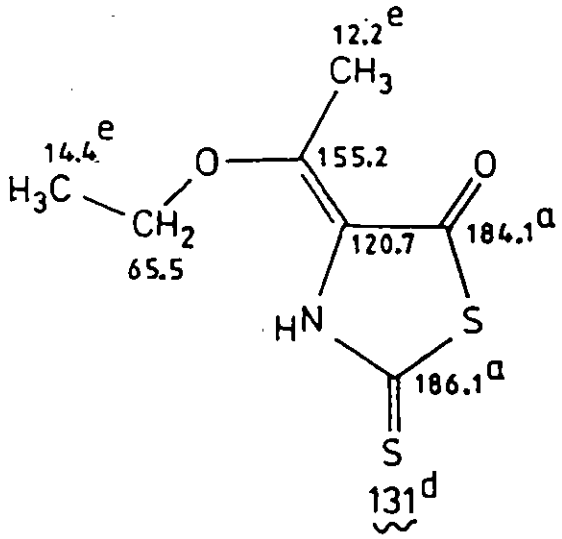
Figure 3.11 (cont.)



(Z)-160[c]



(Z)-161



131[d]

[a,b] Assignments may be reversed

[c] $CDCl_3$ as solvent, reference TMS

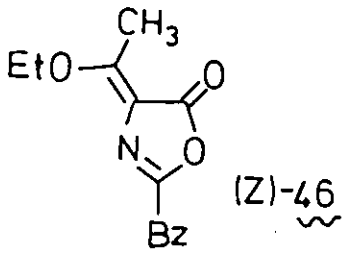
[d] Acetone-d_6 as solvent, reference acetone-d_6 at 29.2 ppm

[e,f] Assignments confirmed by ^{1}H-^{13}C coupling studies.

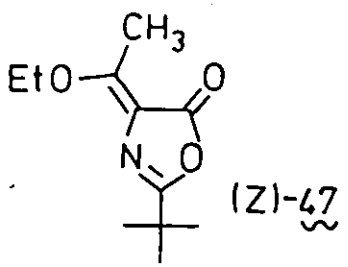
3.4.2 Reactivity to electrophiles

The 4-(1-ethoxyethylidene)-5-oxazolones and corresponding thiazolones were remarkably resistant to electrophilic attack. Apparently, the ring nitrogen is inaccessible to electrophiles because of the inherent crowding around this centre (see Section 3.2.1). Protonation occurred only under severe conditions and, in general, under these conditions, either decomposition or hydrolysis of the C-6 enol ether occurred before simple ring opening.

Attempts to prepare the hydrochloride salt, reported for some alkoxymethyleneoxazolones (103) were not successful on the 2-benzyloxazolone (Z)-46 and the treatment of the 2-t-butyloxazolone (Z)-47 with ethanolic hydrogen chloride



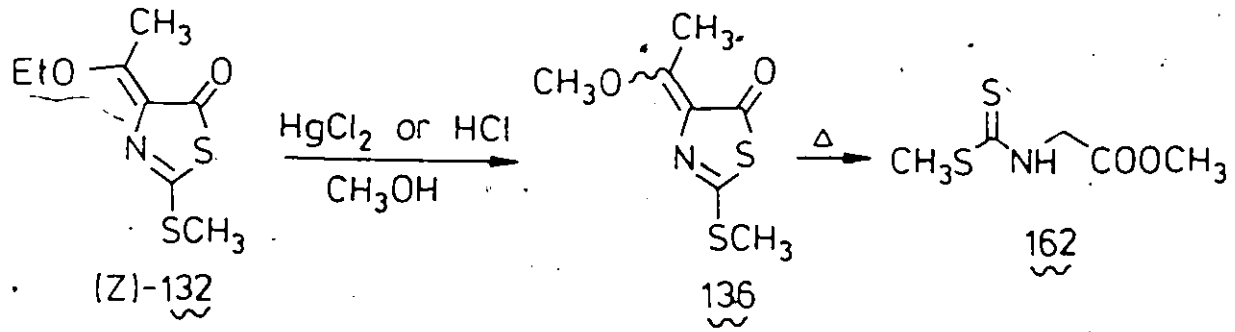
(Z)-46



(Z)-47

resulted in decomposition (apparently polymerization) rather than the desired ring opening.

The thiazolone (Z)-132 was not alkylated at nitrogen or sulfur with triethyloxonium fluoroborate ($Et_3O^+.BF_4^-$), nor with methyl iodide. Treatment of (Z)-132 with mercuric chloride in methanol or methanolic hydrogen chloride, under severe conditions, gave only the methyl ester 162. Under milder tem-



(Z)-132 136 162

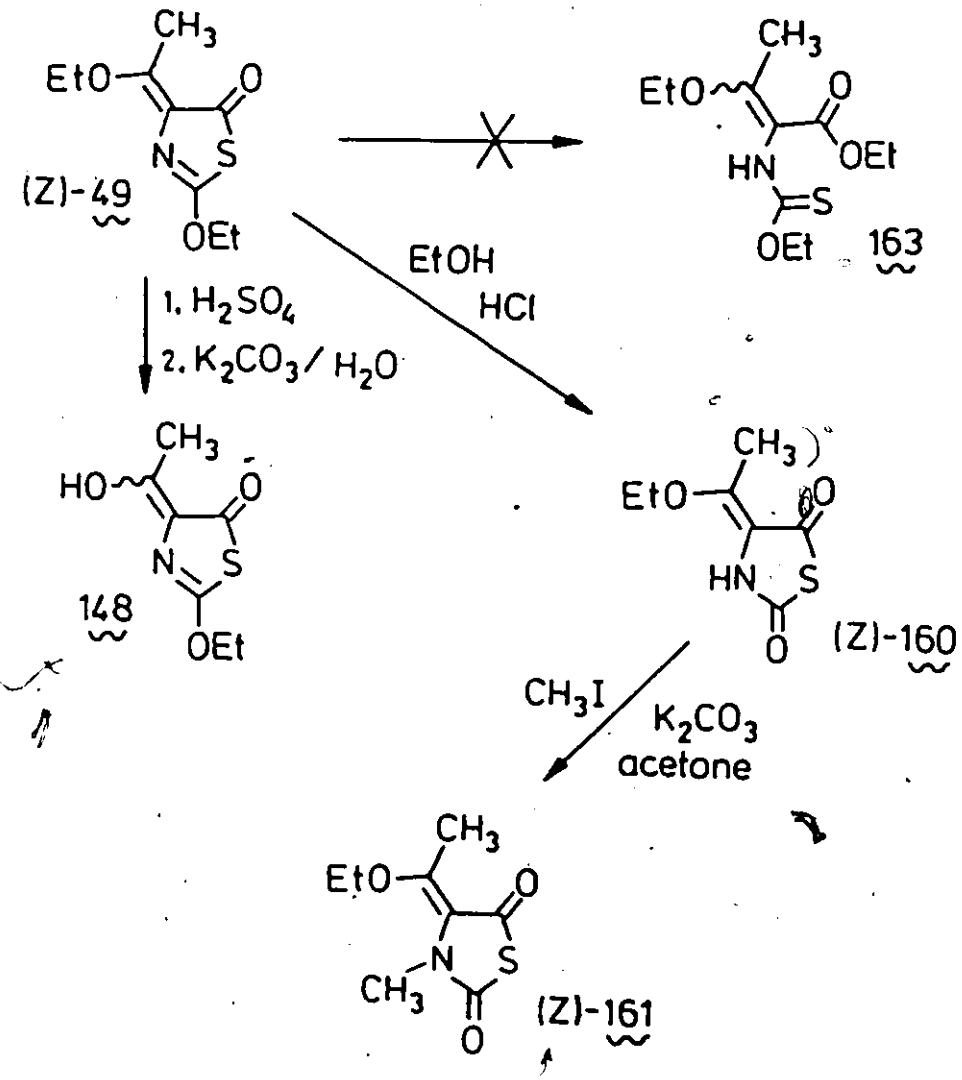
perature conditions, these reagents catalyzed alcohol exchange.

The unsuccessful electrophilic and nucleophilic ring openings of the 2-(alkylthio)thiazolones 48 and 132 forced a modification in strategy. It was reasoned that a 2-alkoxy substituted 4-(1-alkoxyethylidene)-5-thiazolone should have a more basic ring nitrogen arising from electron donation from the oxygen and, because of this enhanced basicity, be more susceptible to acid catalyzed ring opening. The 2-ethoxythiazolone (Z)-49 was prepared to investigate this possibility.

Precedence for the difference in stability of 2-alkoxy versus 2-alkylthio substituted materials appears in the work of Aubert et al. (90) where the 2-alkoxy-4-(ethoxymethylene)-5-thiazones were found to be less stable than the alkylthio analogues prepared by Cook et al. (88). Their stability was found to be related to the size of the alkoxy substituent (see Section 2.6.1). The relationship between the substituent size and the compound stability can be rationalized by the accessibility of the ring nitrogen to electrophilic attack, the larger substituents hindering approach of the electrophile.

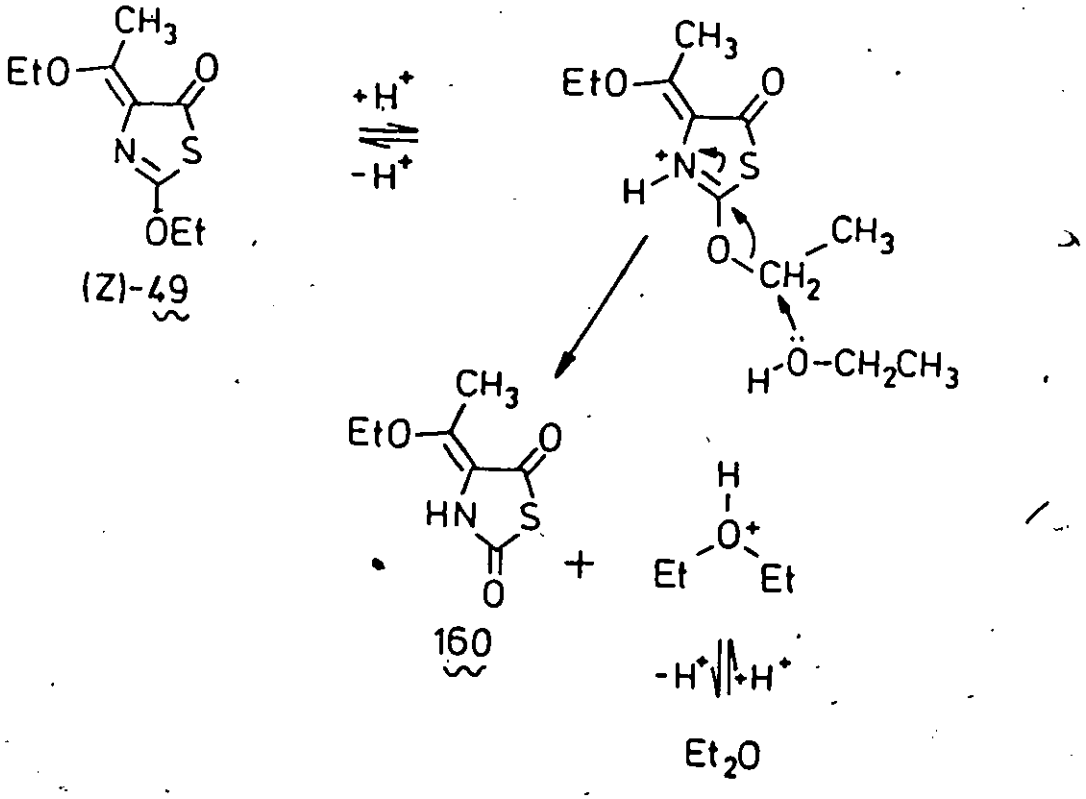
Treatment of (Z)-49 with hydrogen chloride in absolute ethanol gave the dione (Z)-160, in 87% isolated yield, not the expected ring opened ester 163 (see Scheme 3.7). One isomer only was isolated. The assignment of the geometry of 160 (and of related products) will be discussed in Section 3.4.5).

Scheme 3.7



A change in reaction conditions gave surprising results. The presence of water in the reaction solution or on work-up was disadvantageous to dione production. On replacing the solvent, absolute ethanol, with 95% ethanol, a mixture of the dione (Z)-160 and the C-6 hydrolysis product 148 was obtained. The hydroxyethylidene material, 148 (described previously in Section 3.3), was the only product observed on quenching of a solution of the thiazolone (Z)-49 in concentrated sulfuric acid with aqueous base. It was concluded that attack of water at C-2 of 49 was not the mechanism of formation of the dione (Z)-160. A possible alternative O-alkyl cleavage process is presented in Scheme 3.8.

Scheme 3.8



The presence of an amide function in (Z)-160 demonstrated that ethoxide had been lost at C-2 in the transformation of (Z)-49. The evidence for the amide was the presence of an NH signal at 7.55 ppm in the ^{1}H NMR spectrum and at 3180 cm^{-1} in the IR spectrum and the absence of these signals in the N-methylation product (Z)-161 (Scheme 3.7). The ethoxyethylidene substituent was present in (Z)-160 as evidenced by the vinyl methyl signal (at 2.45 ppm) and the ethoxy signals (at 4.14 and 1.35 ppm) in the ^{1}H NMR spectrum. The ^{13}C NMR assignments of both (Z)-160 and the N-methyl analogue (Z)-161 are shown in Figure 3.11 and are based on a correlation with other compounds found in Figure 3.11 and Table 3.5. Long range coupling observed between the methyl protons at C-7 and C-6, , and between the methylene protons at C-8 and C-9 enabled the signals for C-6 and C-9 in (Z)-160 to be assigned definitively.

Note that the sites of alkylation of 131 and (Z)-160 followed the normal order of nucleophilic strengths of sulfur, nitrogen and oxygen. The thioamide of 131 was S-alkylated with methyl iodide (see Section 3.1.2) while the amide, (Z)-160, was N-alkylated despite the severe crowding around the nitrogen.

3.4.3 Indirect ring opening

A multistep sequence was developed for the ring opening of the thiazolone (Z)-49 via the ring modified products (Z)-160 and (Z)-161. Thus, ring opening of the dione (Z)-161 was achieved by treatment with sodium ethoxide, giving the anionic intermediate 164 (see Scheme 3.9). Treatment of a solution of the anion 164 with methyl iodide provided the crotonate (Z)-159 in 47% yield from (Z)-161. Only one isomer of 159 was isolated, tentatively assigned the Z geometry (see Section 3.4.5).

In the ring opening of the dione (Z)-161, there are two possible sites of attack, yielding the products 159 and 165 (Scheme 3.9). Both products would be expected to have similar spectroscopic properties. The absence of a downfield carbonyl resonance in the ^{13}C NMR spectrum of the ring opened product was the evidence that eliminated 165 as the structure. The farthest downfield signal in the ^{13}C spectrum of (Z)-159 was at 170.1 ppm, a position far upfield of the expected region (185-195 ppm (100)) of the thioester signal of 165. The ^{1}H NMR spectrum of (Z)-159 is shown in Figure 3.12 and the ^{13}C NMR assignments are shown in Figure 3.11 along with the assignments of related products. The assigned resonance for the (methylthio)amido carbonyl carbon of 170.1 (or 169.1) ppm is within the region of similarly substituted carbons as illustrated in Figure 3.13.

Scheme 3.9

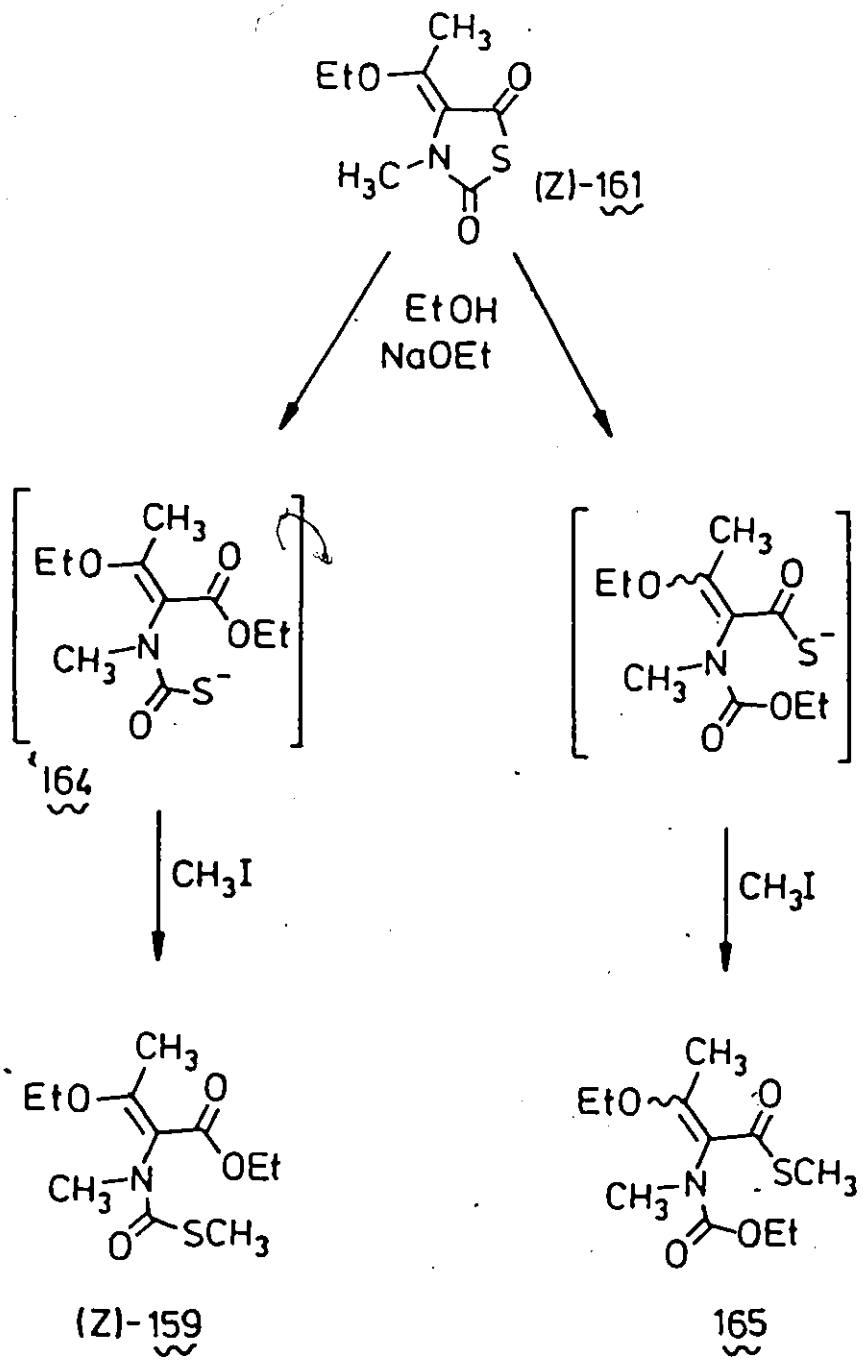

CH3
EtO
O
H3C
N
S
O
(Z)-161
EtOH
NaOEt
CH3
EtO
O
OEt
CH3
N
S-
O
164
CH3I
CH3
EtO
O
S-
CH3
N
OEt
O
CH3I
CH3
EtO
O
OEt
CH3
N
SCH3
O
(Z)-159
CH3
EtO
O
SCH3
CH3
N
O
OEt
165

Figure 3.12: ^{1}H NMR Spectrum of Ethyl (Z)-3-Ethoxy-2-[N-methyl(methylthio)amido]-2-butenoate, (Z)-159

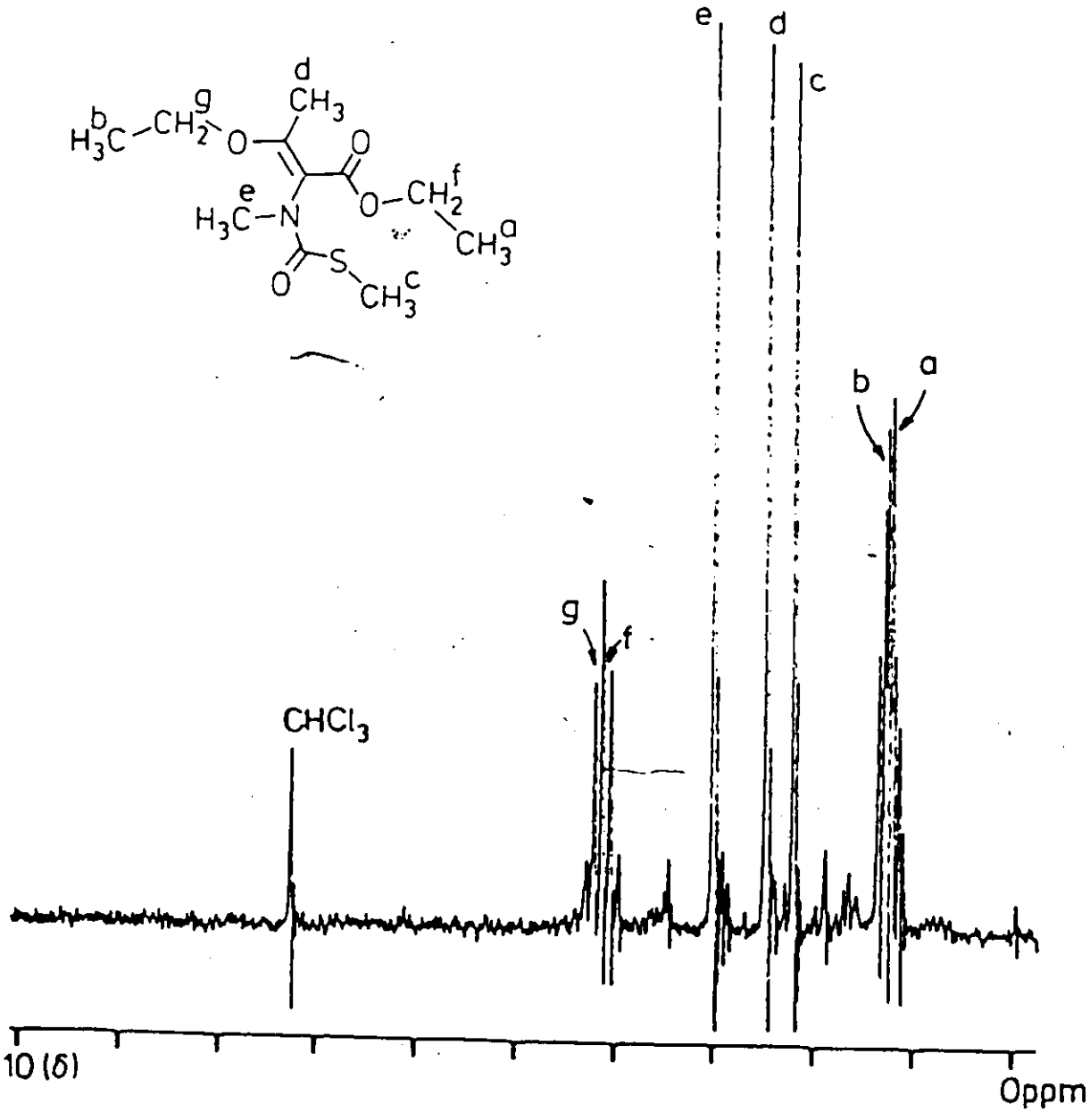
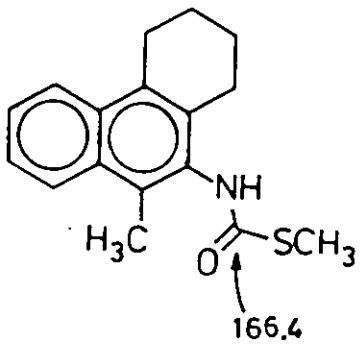
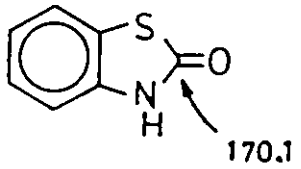


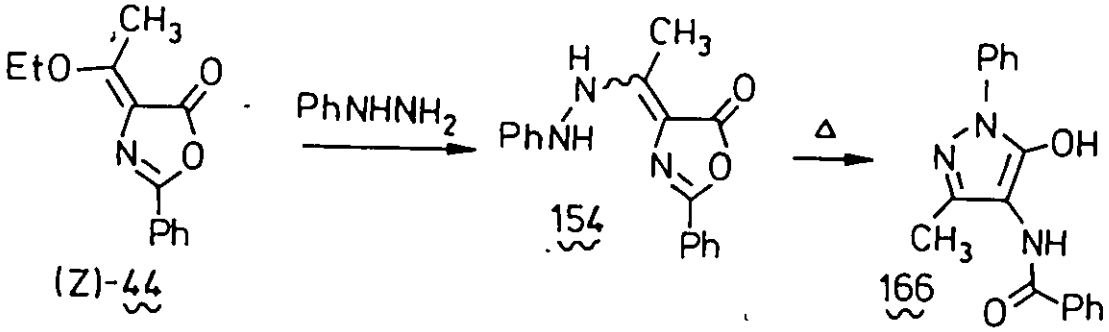
Figure 3.13: ^{13}C Chemical Shifts of Model Compounds[a] for the Assigning of the (Methylthio)amido Carbonyl Signal of Ethyl (Z)-3-Ethoxy-2-[N-methyl(methylthio)amido]-2-butenoate, (Z)-159.





[a]Source, reference 99.

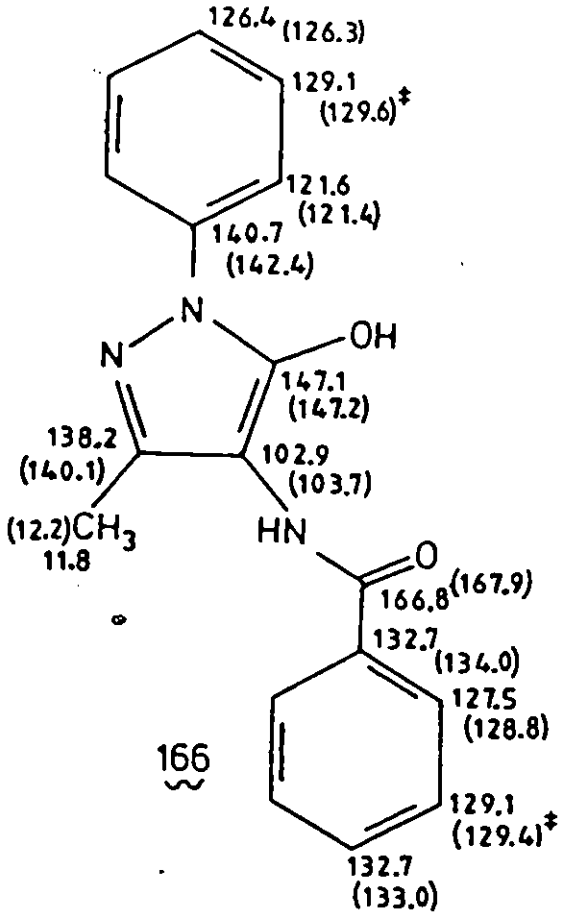
An indirect method of ring opening of (Z)-44, was achieved in two steps. Reaction of (Z)-44 with phenylhydrazine (see Section 3.3) gave 154 which yielded the pyrazole 166 on



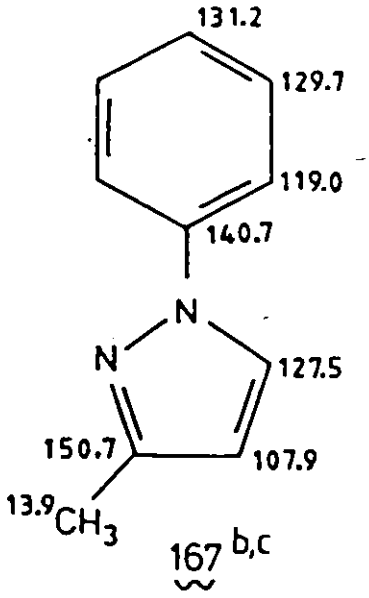
heating. This type of transformation has been reported previously for the hydrazinomethylene analogues (94) (see Section 2.6). The ^{13}C assignments made for 166 (Figure 3.14) were based on literature assignments of the substituted pyrazoles

Figure 3.14: ^{13}C NMR Assignments of 4-Benzamido-5-hydroxy-3-methyl-1-phenylpyrazole, 166

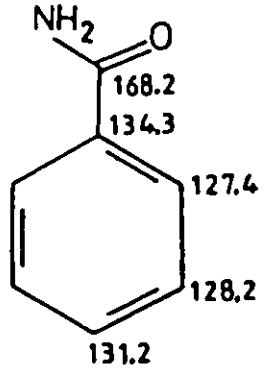
Observed Chemical Shifts[a]



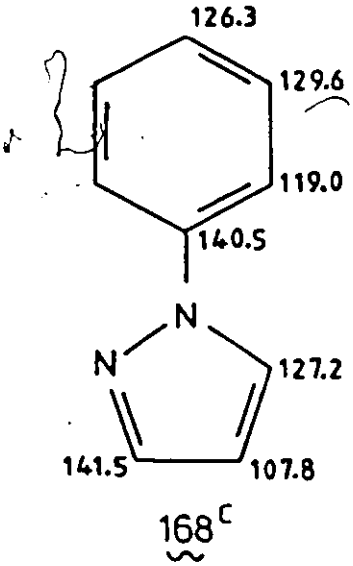
166



167 b,c



169 d



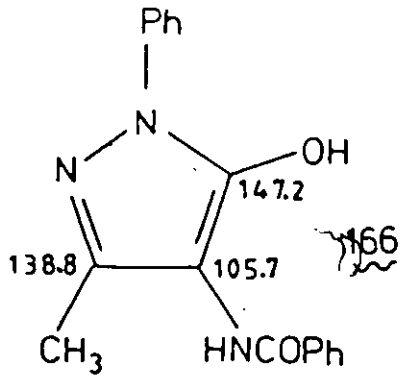
168 c

Figure 3.14 (cont.)

Benzene Substituent Effects[d,e]

Substituent	Substituted Carbon	o	m
- CH_3	+ 8.9	+10.7	-0.1
- OH	+26.9	-12.7	+1.4
- $HNCOCH_3$	+10.5	- 7.2	+0.9

Calculated Chemical Shifts[f]



‡These assignments may be reversed

[a]Chemical shifts in parentheses were obtained from 166 dissolved in acetone-d_6; the other shifts were obtained with $CDCl_3$ as solvent.

[b]$CHCl_3$ as solvent

[c]Source; reference 104

[d]Source; reference 99

[e]Source; reference 105

[f]Obtained by summing the OH and $NHCOCH_3$ substituent affects onto the chemical shifts of 167

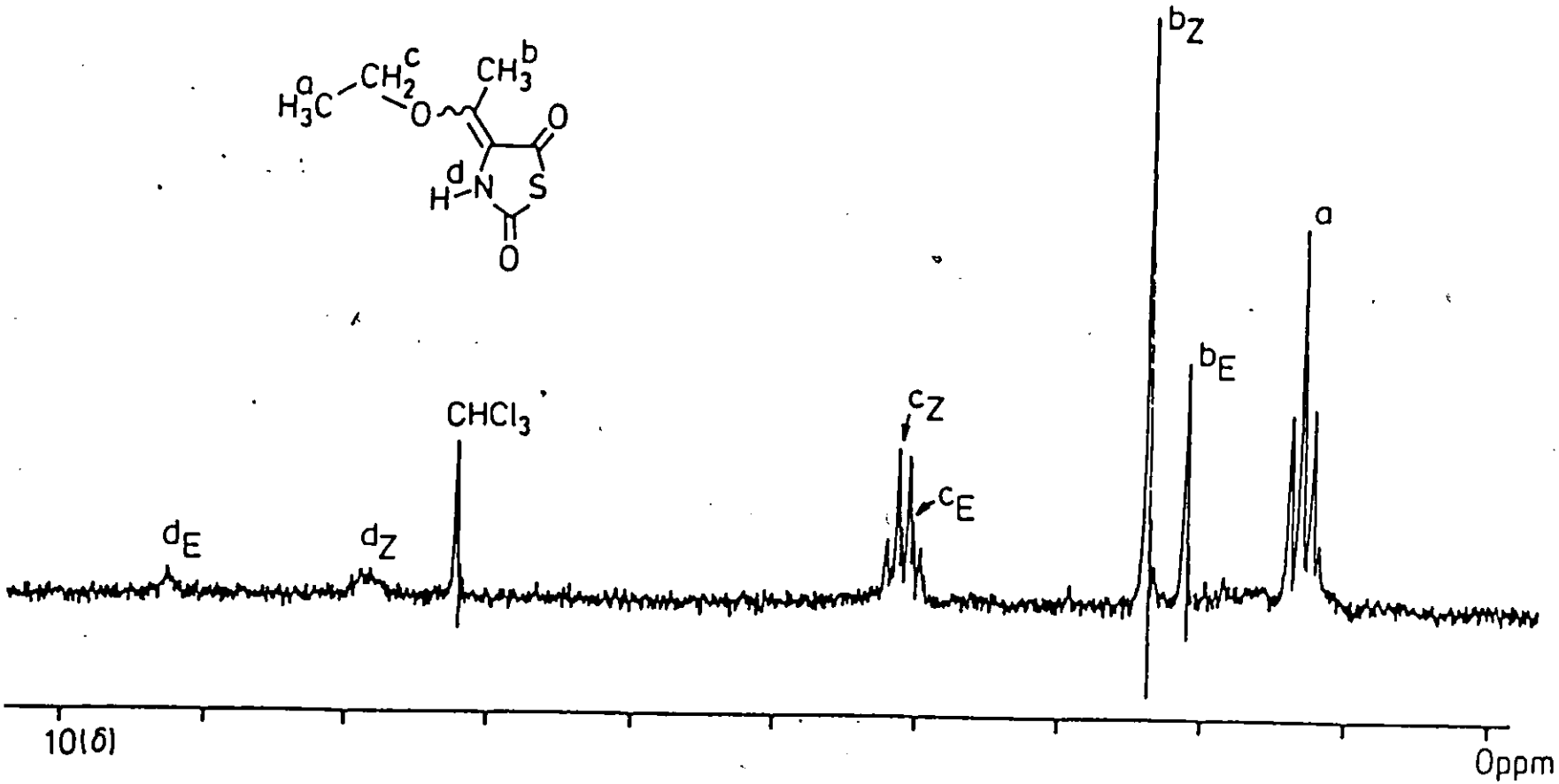
167 and 168 (104) and benzamide 169 (99). The chemical shifts of the pyrazole carbons were calculated by adding substituent effects from substituted benzenes onto the chemical shifts of 167 as summarized in Figure 3.14. These approximate values assisted in the identification of the signals from these carbons.

3.4.4 Photoisomerization

The ring opened and ring modified products (Z)-158, (Z)-159, (Z)-160 and (Z)-161, photoisomerized on irradiation with 300 nm light (as indicated by ^{1}H NMR spectroscopy). Compounds 159, 160 and 161 were stable to long exposure to light (48 h) but 160 and 161 reverted to the original isomer in 6 to 24 hours while in the dark, most probably by catalysis with traces of acid. Therefore, the photostationary E to Z ratios of 1:3 and 1:4 for 160 and 161 respectively do not necessarily reflect the photoequilibria alone. The ^{1}H NMR spectra of the photostationary mixture of isomers of 160 is shown in Figure 3.15.

The crotonate 159 gave a photostationary ratio of E to Z isomers of 2:3. The mixture, when dissolved in deuteriochloroform showed only slow reconversion to the original isomer over a period of days to weeks. The amide 158 apparently photoisomerizes but decomposes to unidentified products on long term irradiation.

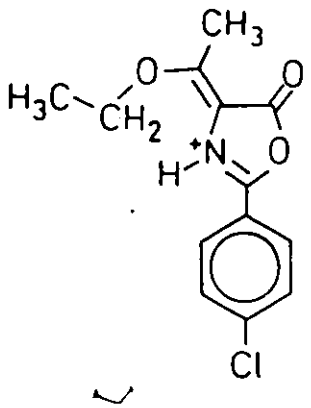
Figure 3.15: ^{1}H NMR Spectrum of 4-[(E and Z)-1-Ethoxyethylidene]-2,5-thiazolidinedione, (E and Z)-160



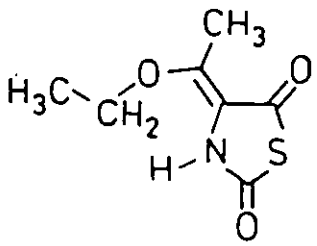
3.4.5 Geometry assignments

The thermodynamically more stable isomers of the diones 160 and 161 were assigned to the Z geometry by correlation of ^{1}H NMR chemical shifts of allylic protons with the previously assigned (see Section 3.1.2) thioxo analogue 131 ((E)-160 and (E)-161, 2.15 and 2.23 ppm respectively, compared with (Z)-160, (Z)-161 and 131, 2.45, 2.50 and 2.46, respectively).

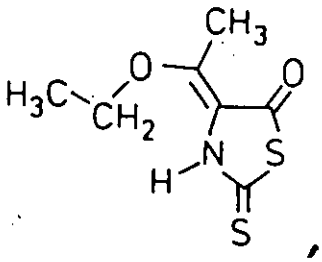
By analogy to the ethoxyethylidenethiazolones and corresponding oxazolones, in which the isomer ratio is controlled predominantly by steric factors, the thermodynamically more stable isomers of 131 and 160 were expected to be of the same geometry because of the similarity in structure around the double bond. Further corroborating evidence for the preference of 160 to be in the Z geometry is the apparent preferred geometry of the protonated species 137 (see Section 3.1.5). As illustrated below, the structures have similar steric constraints about the exocyclic double bond.



137



(Z)-160



131

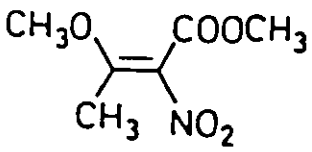
The assignments of the ring opened materials 158 and 159 are on more tenuous grounds. Although the chemical shifts of the allylic protons of 159 follow those of the diones above (E 2.22 ppm and Z 2.51 ppm), the correlation is not present for 158 (E 2.43 and Z 2.39 ppm). The average environments of the allylic protons may not be comparable from the ring opened to the cyclic systems because of the added possible conformations in the ring opened materials. Therefore, the assignment of the Z geometry for the thermodynamically more stable isomers of 158 and 159 are tentative and based on steric arguments analogous to the cyclic systems.

Even though the ring opened products, as isolated, have the wrong geometry for synthetic purposes, the experiments described in Section 3.4.4 have demonstrated that equilibria between isomers can be established readily.

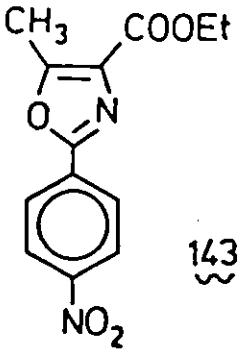
3.5 Synthesis of Other Michael Donors

In the development of the synthetic strategy, other Michael donor structures were considered. Two such structures are 170 and 143, in which carbanion formation would be affected by removal of an allylic proton.

The oxazole 143 was prepared in two steps from p-nitrobenzaldehyde (Scheme 3.10). The second step was effectively achieved with tributylphosphine at room temperature. Phosphorous trichloride was also effective but required much more rigorous conditions. This order of reactivity of $P(n\text{-}Bu)_3$ and PCl_3 is

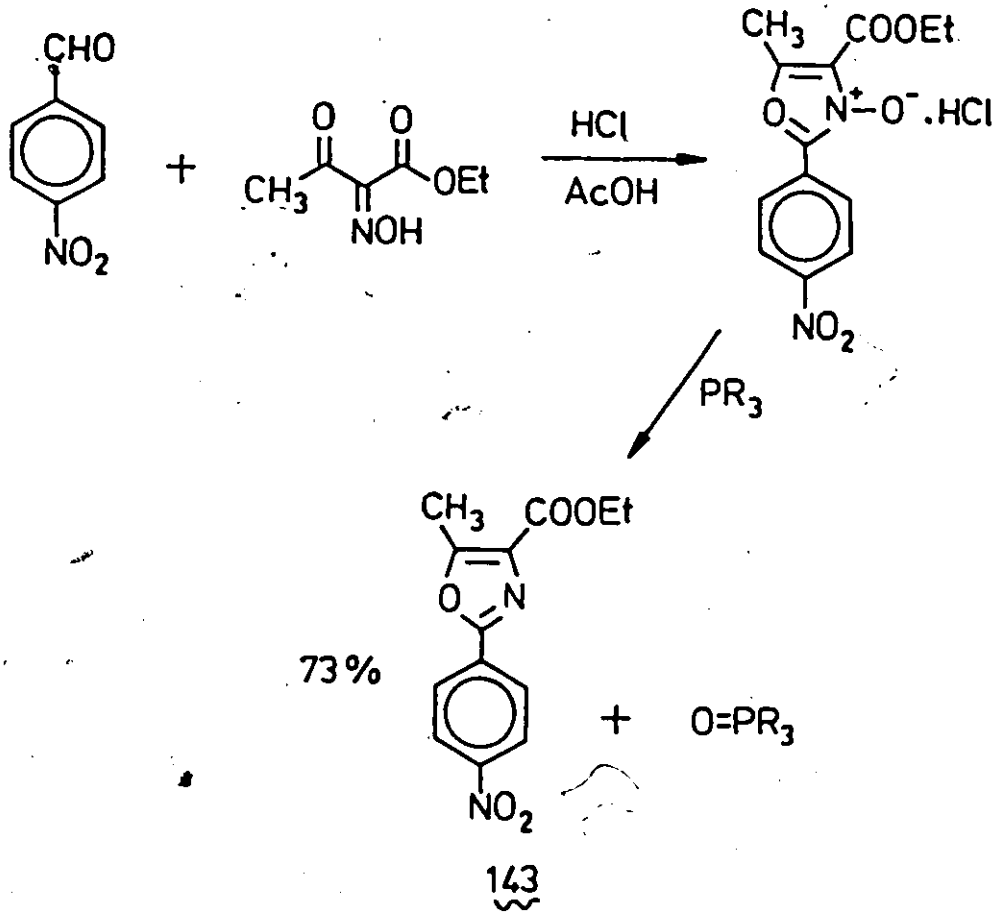


170



143

Scheme 3.10



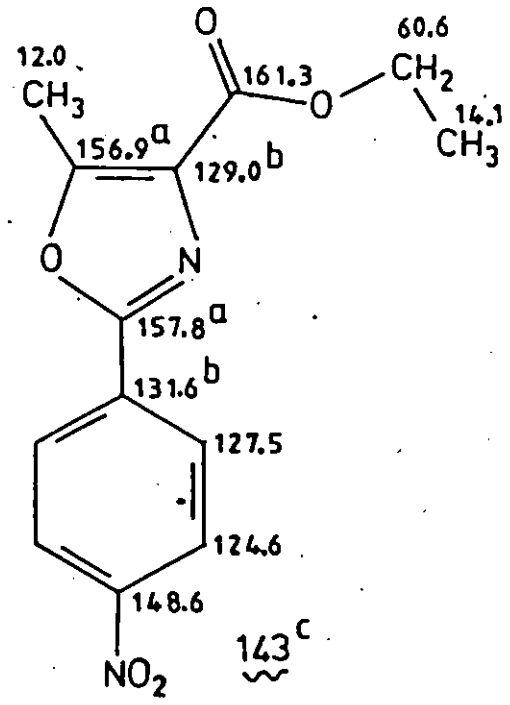
opposite to that reported previously for the reduction of N-oxides (106). The reason for this rate behaviour in phosphine reductions is unclear.

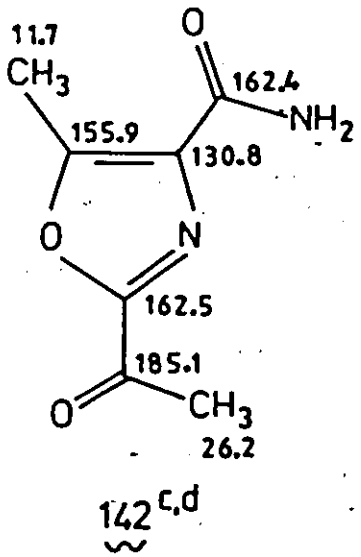
The ethyl ester 143 had similar IR spectroscopic properties to the previously known carboxylic acid analogue (the ester 143 showed; 1711(s), 1608(s), 1567(m) and 1525(s) cm^{-1}, and the corresponding carboxylic acid showed; 1684(s), 1603(s), 1564(m) and 1524(s) cm^{-1} (107)). The ^{13}C NMR assignments of 143 are shown in Figure 3.16 along with the reported assignments of the oxazole analogue 142 (99).

The oxazole 143 decomposed on attempted anion formation at -78°C and therefore was unsuitable for use as a potential Michael donor.

An attempt to synthesize 170 by diazomethane addition to methyl 2-nitroacetoacetate (171), was unsuccessful. Instead, diazomethane methylation gave the nitronic ester 172 (Scheme 3.11). The nitronic ester thermally decomposed at room temperature over a period of one week or on attempted distillation. It yielded the oxime 173 and formaldehyde which was observed as the trimer, trioxane (presence ascertained by its 5.15 ppm signal in the ^{1}H NMR spectrum of the decomposition mixture). This facile redox reaction is an example of a general reaction of nitronic esters (108). The oxime 173, a previously known compound (109), reacted with diazomethane to give 174.

Figure 3.16 ^{13}C NMR Assignments of 4-Carbethoxy-5-methyl-2-(4-nitrophenyl)oxazole, 143 and an Oxazole Analogue, 142



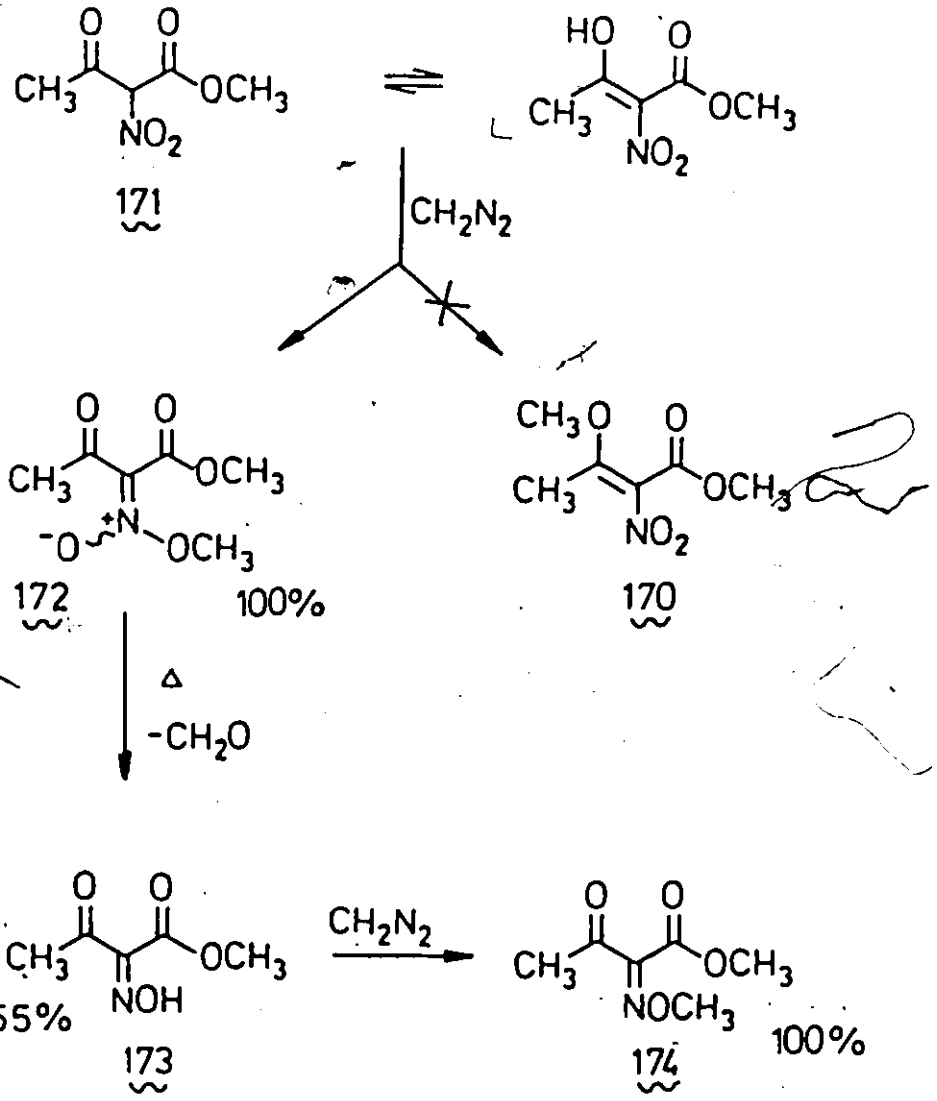


a,b These assignments may be reversed

c Dimethylsulfoxide-d_6 as solvent, reference TMS

d Source, Reference 99

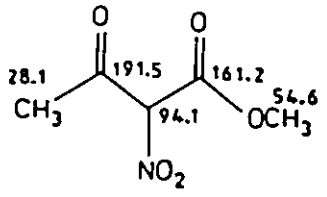
Scheme 3.11



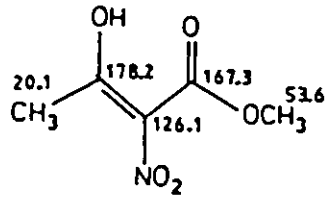
The acetoacetate 171, dissolved in deuteriochloroform, was found by ^{1}H and ^{13}C NMR to be a 3:2 mixture of the nitroketone and nitroenol. Nevertheless, it was the nitronic ester that formed on diazomethane methylation as indicated by the 1675 cm^{-1} signal in the IR spectrum (C=N stretch) and on the formation of the oxime, 172 on thermal decomposition. The ^{13}C NMR assignments for the tautomers of 171 and of compounds 172, 173 and 174 are given in Figure 3.17.

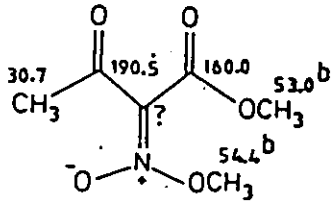
This general synthetic route was abandoned on the development of the oxazolone and thiazolone strategies.

Figure 3.17: ^{13}C Assignments of Some Substituted Methyl Acetoacetates[a].

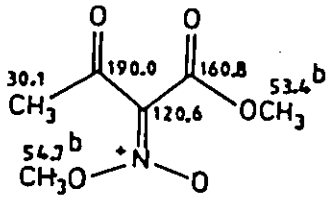


171

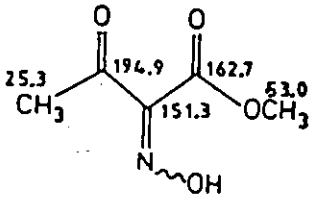




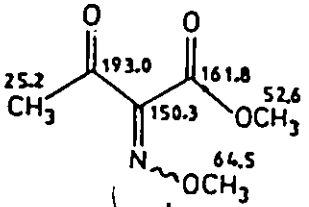
(Z)-172[c]



(E)-172[c]



173[d]



174[d]

[a]Deuteriochloroform as solvent, TMS internal reference

[b]Assignments may be reversed

[c]Assigned the geometries as shown because of analogous shift behaviour of the E and Z isomers to that of compound 36 (Figure 4.1)

[d]One isomer only, of undetermined geometry.

CHAPTER 4

MICHAEL ACCEPTORS: SYNTHESIS AND STRUCTURE

Michael acceptors 36, 39, and 40 were prepared by standard methods as outlined in Scheme 4.1 (57,66,110-112). For the butanoate 36 a mixture of E and Z isomers (E:Z = 2:1) was obtained. Assignment of the geometries was on the basis of ^{13}C NMR chemical shift data which was consistent with published data on substituted acrylates (113-115). Carbon-13 chemical shift data on all the acceptors prepared for this work as well as other pertinent substituted acrylates and butenones are summarized in Figures 4.1 and 4.2.

The chloromethylene acceptors 37 and 38 were prepared in two steps from the methoxymethylene analogues (Scheme 4.2). The reaction of 36 or 175 with aqueous cupric acetate gave the cupric salts presumed to have structure 176 (66,110). These cuprates with thionyl chloride gave 37 and 38. Overall yield in both cases was approximately 40% with most of the losses caused by polymerization on distillation. The procedure provided a mixture of approximately equal quantities of E and Z isomers of the butanoate 37. This product was stable to storage at -10°C with only slight discoloration gradually appearing over a period of months. The dione 38 darkened rapidly

Scheme 4.1

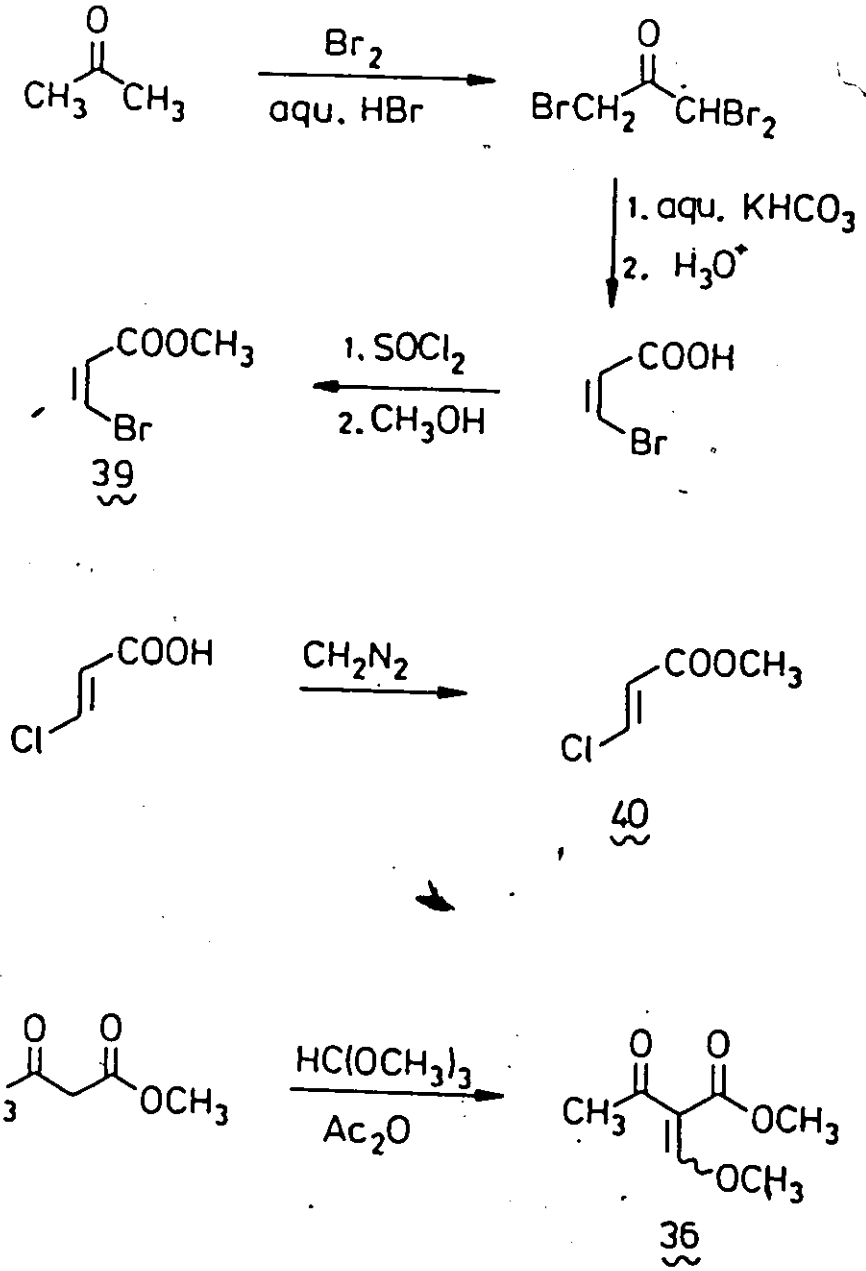
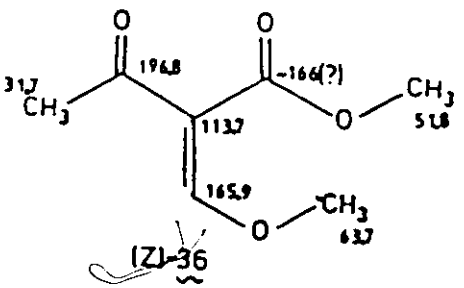
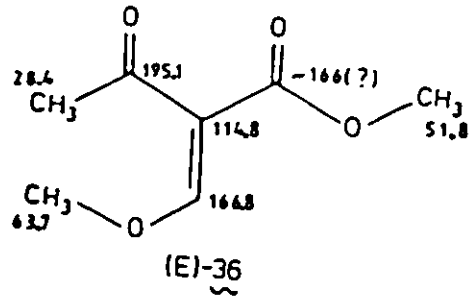

O
CH3 CH3
Br2
aqu. HBr
BrCH2 CHBr2
1. aqu. KHCO3
2. H3O+
COOCH3
Br
39
1. SOCl2
2. CH3OH
COOH
Br
COOH
Cl
CH2N2
COOCH3
Cl
40
O O
CH3 OCH3
HC(OCH3)3
Ac2O
O O
CH3 OCH3
OCH3
36

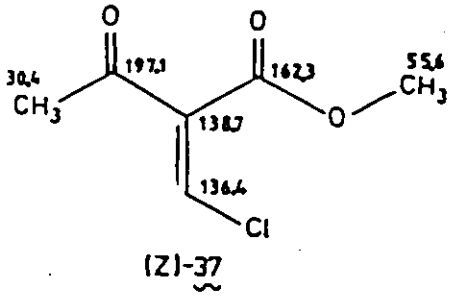
Figure 4.1: ^{13}C NMR Assignments of the Michael Acceptors



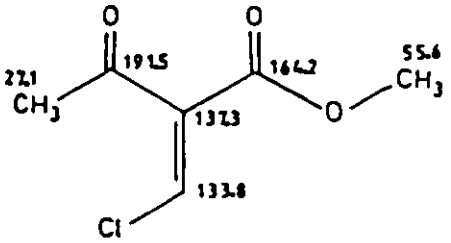
(Z)-36



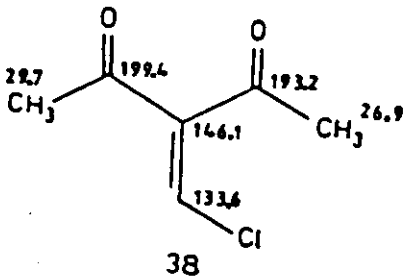
(E)-36



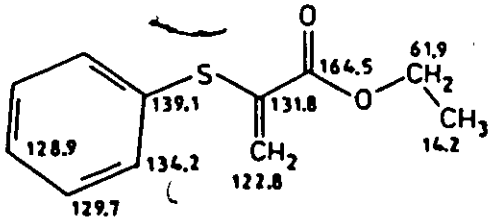
(Z)-37



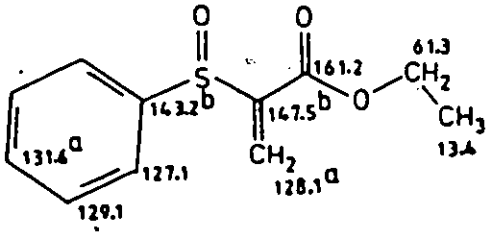
(E)-37



38



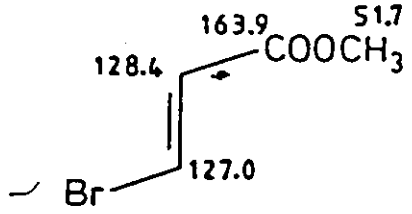
41

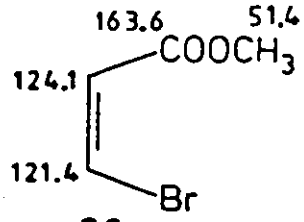


42

a,b These assignments may be reversed.

Figure 4.2: ^{13}C NMR Assignments of Substituted Acrylates

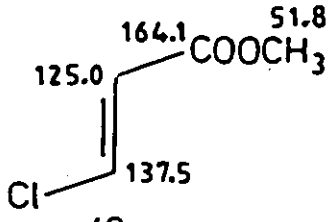




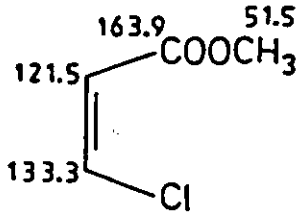
39

Reference source

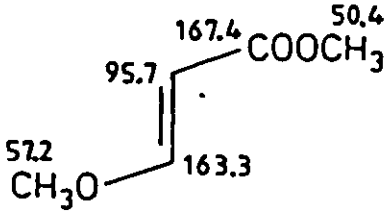
113

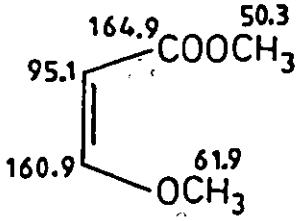


40

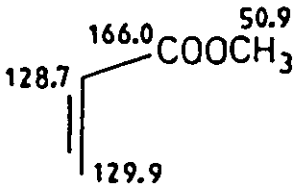


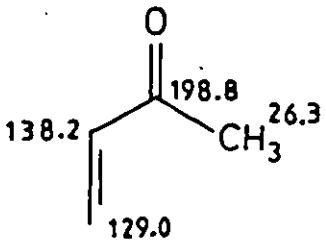
113



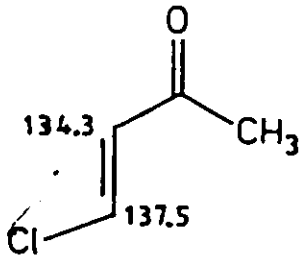


113



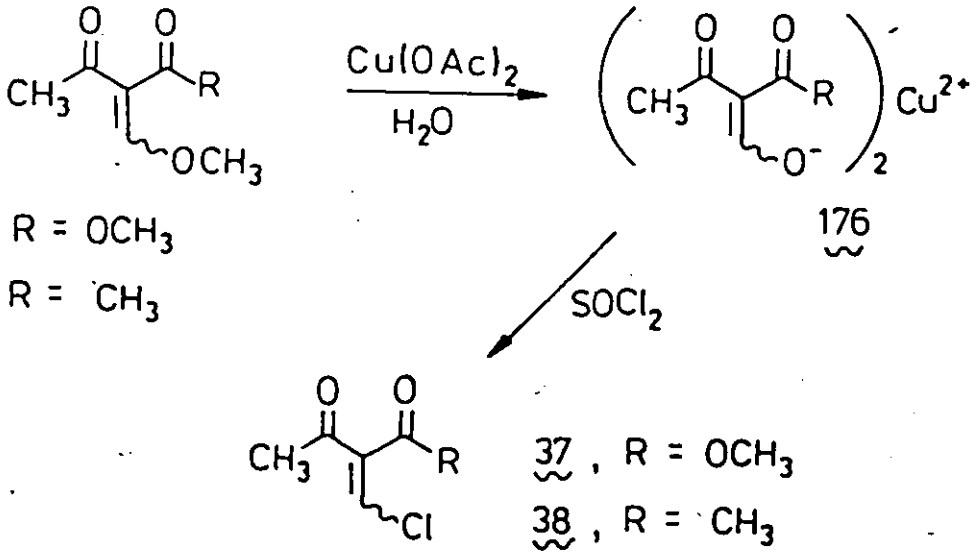


113,114



115

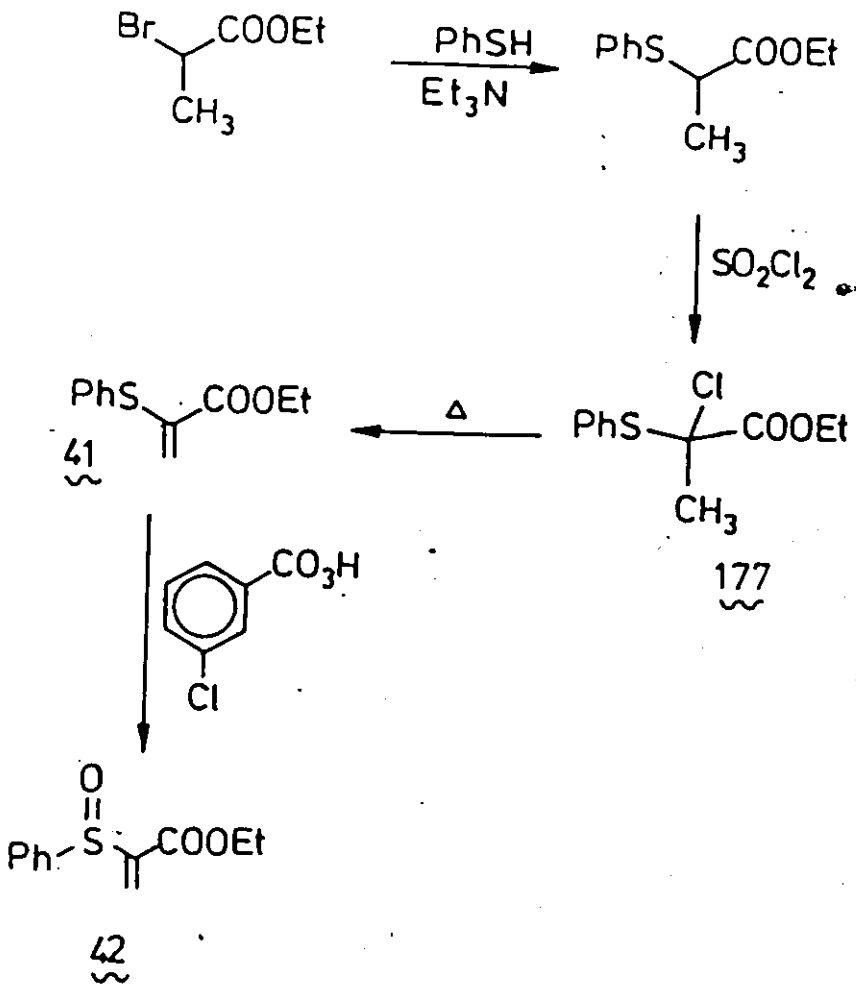
Scheme 4.2



within one hour of distillation, presumably via polymerization.

The synthetic route used for the preparation of acceptors 41 and 42 (Scheme 4.3) followed that outlined in a recent communication by Leyendecker and Comte (69). The only difficulty in repeating this synthesis was in the pyrolysis/distillation of 177 to the acrylate 41. The pyrolysis proceeded in good yield (81%) but required exacting conditions of temperature and pressure (see Experimental section).

Scheme 4.3

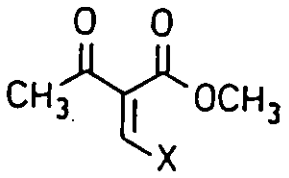

Br
COOEt
CH3
PhSH
Et3N
PhS
COOEt
CH3
SO2Cl2
Cl
PhS
COOEt
CH3
177
Δ
PhS
COOEt
41
CO3H
Cl
O
Ph
S
COOEt
42

CHAPTER 5

MICHAEL ADDITION REACTIONS AND PRODUCTS

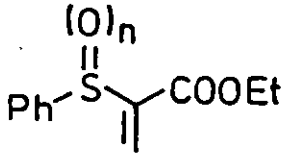
A critical property required of the alkoxyethylidene-oxazolones and corresponding thiazolones in Figure 5.1 and the substituted acrylates in Figure 2.2 for use in thienamycin synthesis is their ability to couple in a Michael addition reaction. The objective of the work examined in this chapter was to find materials that qualify by this criteria as type 'A, B and C' synthons.

Potential Type 'A' Synthons

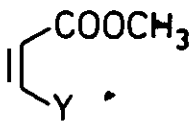


X = Cl, OCH_3

Potential Type 'B' Synthons

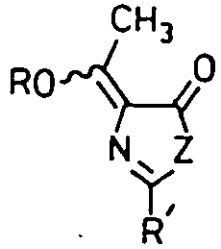


n = 0,1



Y = Cl, Br

Potential Type 'C' Synthons

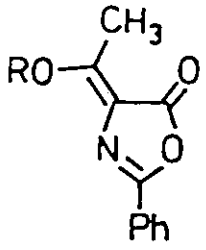


Z = O, S

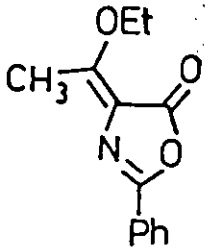
R = Et, CH_3

R' = Ph, Bz, t-Bu, SBz, OEt

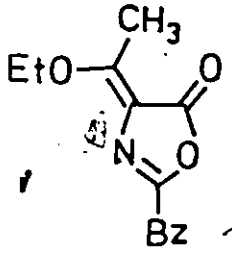
Figure 5.1: Michael Donors



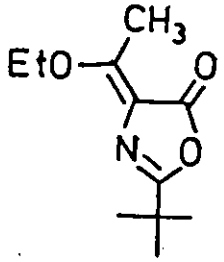
R = CH_3, (Z)-45
R = Et , (Z)-44



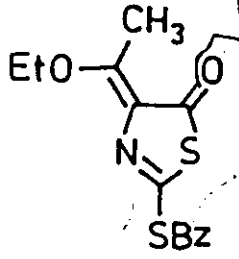
(E)-44



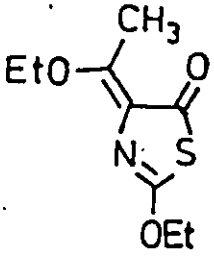
(Z)-46



(Z)-47



(Z)-48



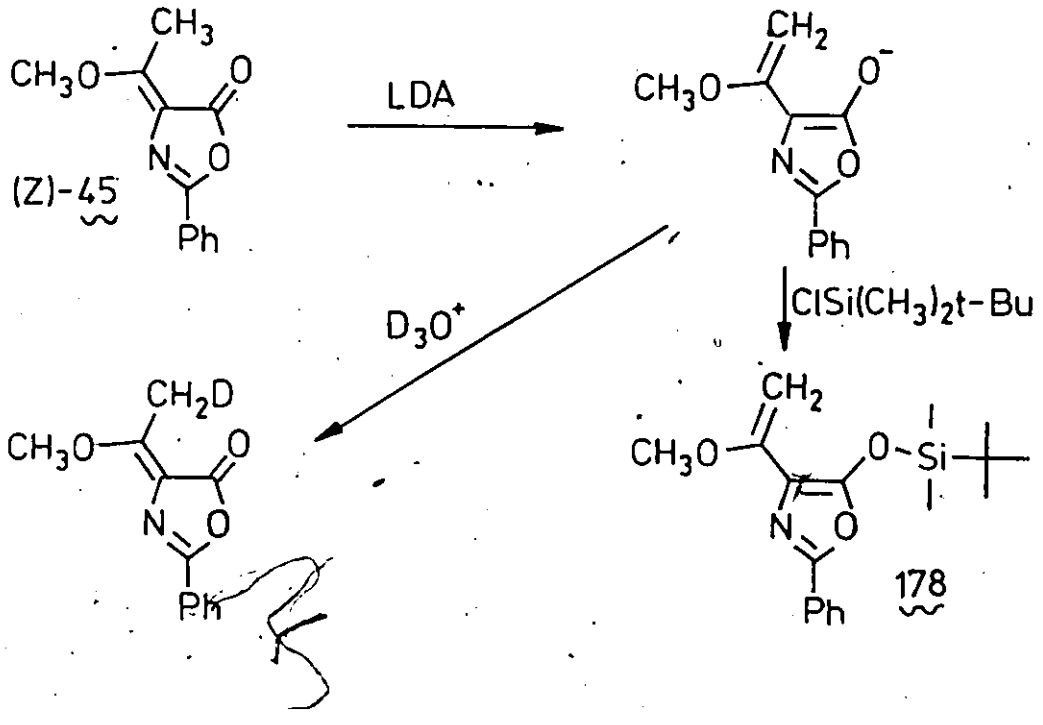
(Z)-49

5.1 Anion Preparation and Properties

The donors studied are listed in Figure 5.1.

In general, anions were prepared by addition of the oxazolone or thiazolone to 1.1 to 1.2 equivalents of lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C. Quenching of the anion of (Z)-45 with acidic deuterium oxide solution (D_3O^+) and trapping with t-butyldimethylchlorosilane demonstrated essentially quantitative preparation of the anion (Scheme 5.1). In the case of the thiazolone 48, this anion preparation procedure gave substantial decomposition presumbaly via self-condensation. Addition of 48 to a large excess of LDA (3 equivalents) and subsequent neutralization of the excess base with acetic acid provided this anion without decomposition.

Scheme 5.1



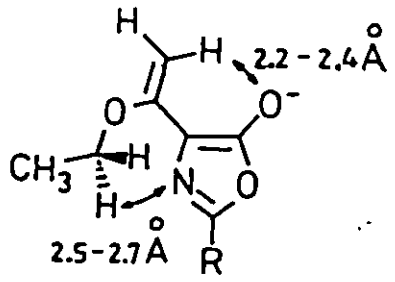
The 2-benzyloxazolone, 46, was unstable to anion formation. On addition of this material to LDA solution at -78°C, the solution immediately turned brown and quenching with acid gave only uncharacterized polymeric materials. Fortunately, the t-butyl analogue, 47, proved to be stable to the anion preparation procedure. This difference in behaviour suggests that deprotonation is occurring at the benzylic position of 46 either in competition with or preferentially over the vinyl methyl position.

It is reasonable to expect that similar steric constraints exist on the anions as in their conjugate acids (see Section 3.2). Indeed, molecular model studies (Dreiding stick models manufactured by Büchi, Switzerland) of the anion indicate strong repulsive interactions when C-7, C-6, C-4 and C-5 are planar for either the E or Z anions (see Figure 5.2). Thus it is likely that because of repulsive interactions, the anion of E or Z 44 is not strictly planar along C-7, C-6, C-4, C-5 with a twist similar to that observed for the exocyclic double bond of (Z)-44. In any event, only a small distortion (less than 10°) is required to relieve any significant repulsive interactions and strong double bond character may remain between C-4 and C-6.

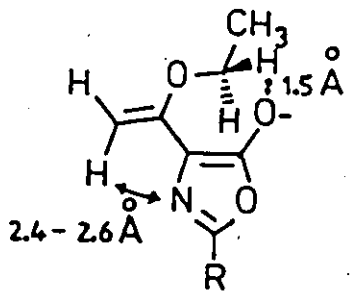
The conformations drawn in Figure 5.2 present C-8 as planar to the ring system. A rotation of the C-8,O-3 bond to place C-8 out of the plane would relieve some of the com-

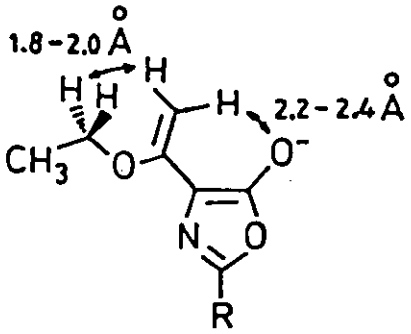
Figure 5.2: Estimated Non-Bonding Distances of Conformations of the Anion of 4-(1-Ethoxyethylidene)-5-oxazolones

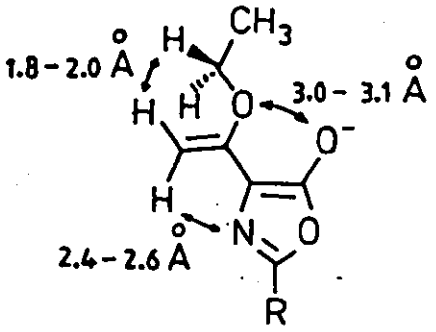
Z anion (cisoid)



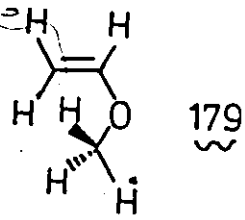
E anion (transoid)







pression, however this would also reduce the O-3 p-orbital overlap with the double bond. Methyl vinyl ether, 179, is known to prefer the planar geometry shown below with a barrier of rotation of 16 KJ/mole (as determined by microwave spectroscopy (116) and confirmed by ab initio calculations (117)). Therefore, using methyl vinyl ether as a model, C-8 is predicted to be approximately planar with the ring as shown in Figure 5.2.

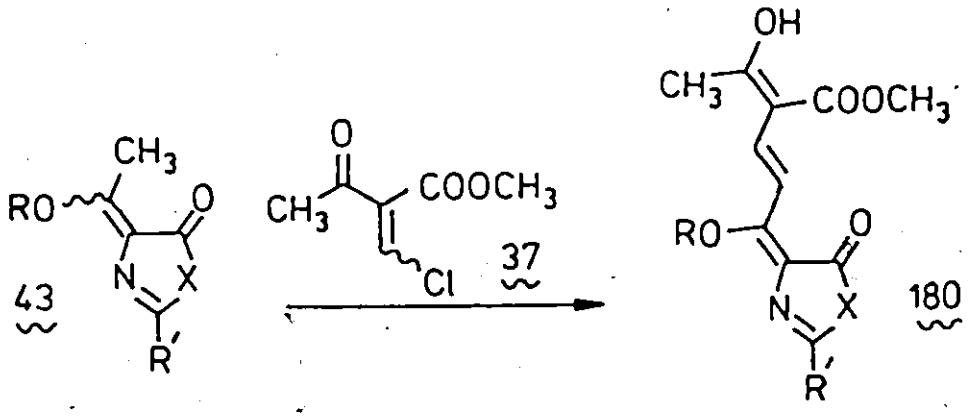


179

5.2 Donor Coupling with Methyl 2-(Chloromethylene)-3-oxobutanoate (37)

The coupling of anions of 4-(1-alkoxyethylidene)-5-oxazolones and corresponding thiazolones to the acceptor 37 was successful for all donors tried, giving yellow to orange-red crystalline products after purification. Products were isolated even when the reactions were quenched at low temperatures (approximately -78°C), indicating that these Michael additions had proceeded at low temperatures. The reactions attempted and the products prepared are summarized in Table 5.1. All of these products were in the geometry and tautomeric form shown, as

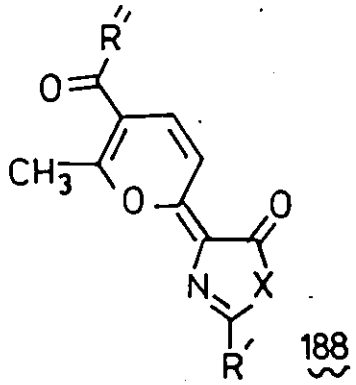
Table 5.1: Michael Donor Additions to Methyl 2-(Chloromethylene)-3-oxobutanoate (37)



Starting Material	R	R'	X	Product (180)	Isolated Yield (%)
(Z)-45	CH_3	Ph	O	181	Not isolated
(Z)-44	Et	Ph	O	182	40
(E)-44	Et	Ph	O	182	23
(Z)-47	Et	t-Bu	O	183	55
(Z)-48	Et	SBz	S	184	30
(Z)-49	Et	OEt	S	185	28

indicated by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of 183 (Figure 5.3) is an illustrative example; the relative downfield position of the vinyl OCH_2 signal at 4.78 ppm indicated the Z geometry of the exocyclic double bond (see Section 3.2.1), the coupling constant (of H_g and H_f) of 16 Hz indicated the trans double bond and the signal at 13.95 ppm indicated a strongly hydrogen bonded hydroxyl characteristic of a β-ketoester in the enolic tautomeric form. This tautomer was consistent with that observed by Crombie et al. for the related coupled product 63 (66). The ^{13}C NMR assignments of 183 are shown in Figure 5.4 beside the assignments of model compounds from which the assignments were derived.

The compounds of general structure 180, readily cyclized by mild acid catalysis to the intensely red pyranylidene compounds 188 (discussed further in Section 5.5). Catalysis of



188

this reaction by silica gel caused substantial losses of coupled product during chromatographic purification of materials 180. These losses were a major factor explaining the relatively modest yields for the products listed in Table 5.1.

Figure 5.3 ^{1}H NMR Spectrum of 4-(4-Carbomethoxy-1-ethoxy-5-hydroxy-2,4-hexadienylidene)-2-(1,1 dimethylethyl)-5-oxazolone, 183

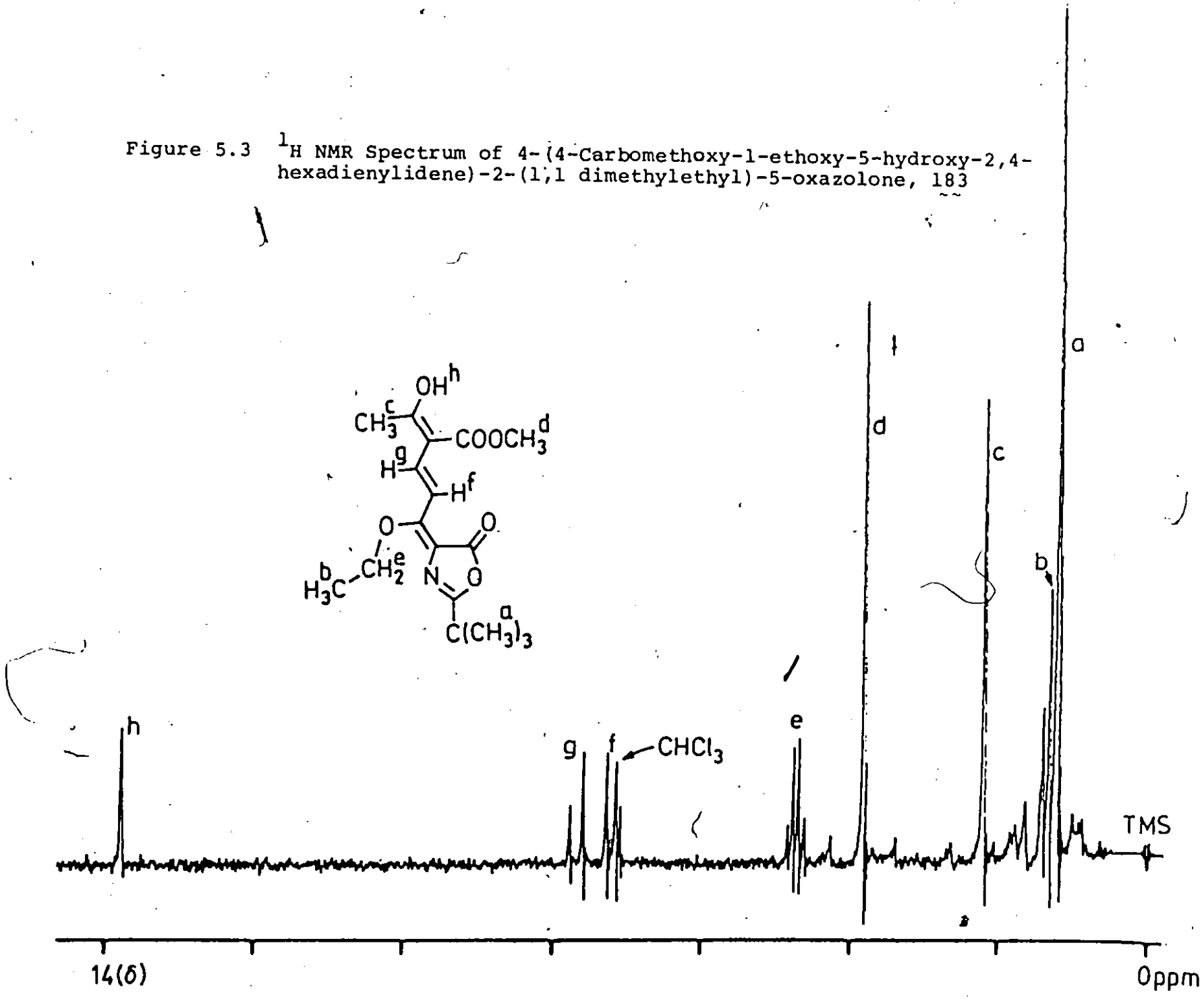
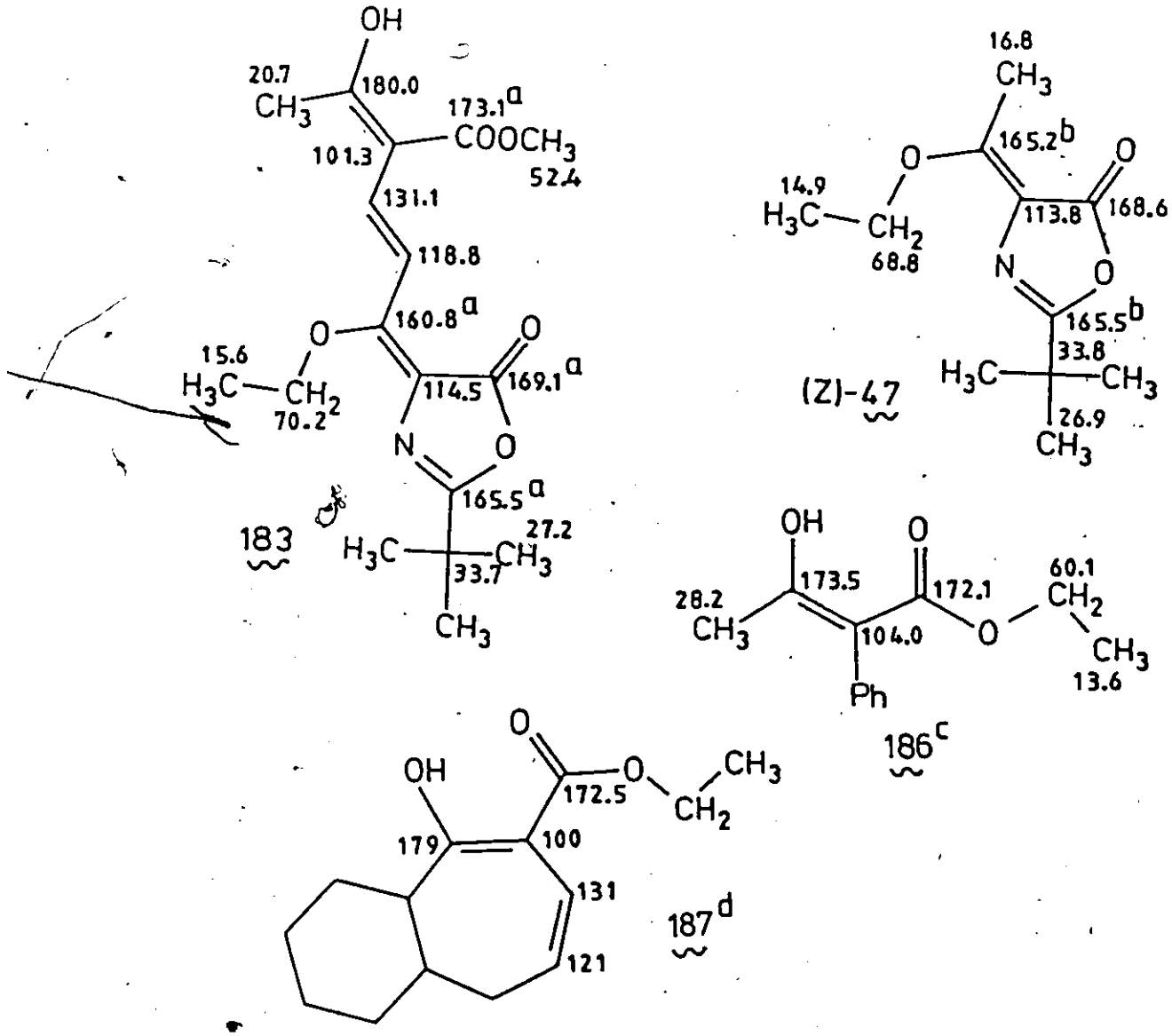


Figure 5.4: ^{13}C NMR Assignments of 4-(4-Carbomethoxy-1-ethoxy-5-hydroxy-2,4-hexadienylidene)-2-(1,1-dimethyl-ethyl)-5-oxazolone, 183



[a] Tentatively assigned from the given model systems.

[b] Assignments may be reversed.

[c] Source: reference 99

[d] Source: reference 118. The chemical shifts were not assigned by the original authors, however multiplicities were reported. Assignments were made on the reported multiplicites and from a correlation with the assignments of 186.

The anion prepared from (E)-44, when coupled with 37 gave the same product as that prepared from (Z)-44 for which there are two plausible explanations. Either the anions rearranged from the transoid to the cisoid geometries before coupling occurred (i.e. rotation about the 4,6-bond), or, the initially formed product in the E geometry rearranged to the Z geometry after coupling. It was not determined which of these pathways was followed.

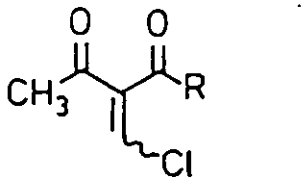
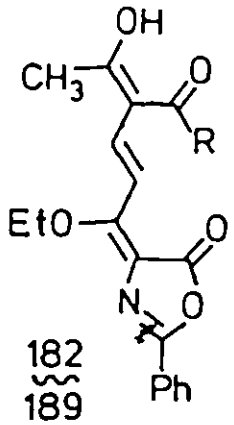
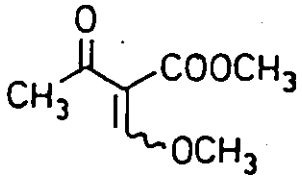
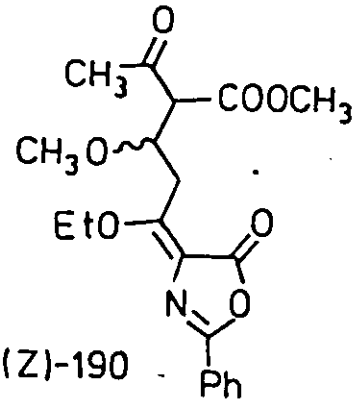
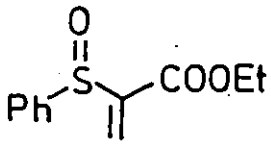
5.3 Acceptor Coupling with 4-[(Z)-1-Ethoxyethylidene]-2-phenyl-5-oxazolone, (Z)-44

Michael addition reactions were attempted between the anion of (Z)-44 and all of the acceptors in Figure 2.2. The resulting products and yields are listed in Table 5.2.

Acceptor 37 and oxazolone (Z)-44 gave a modest yield of the coupled product 182 as described in the previous section. Similarly, acceptor 38 gave product 189. Compound 189 was not easily separated from the starting material, (Z)-44, by the chromatographic conditions attempted, so it was converted directly to 192 by acid catalysis and 192 isolated in 15% overall yield (see Section 5.5).

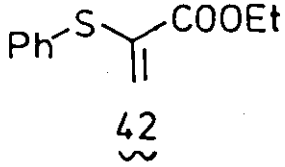
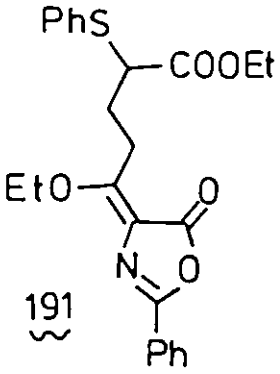
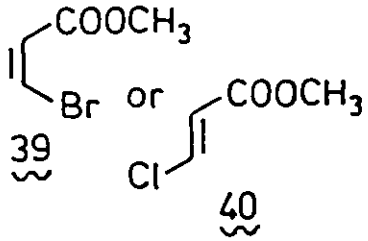
Coupling of 36 and (Z)-44 was achieved in good yield (78%). The product obtained was the simple addition adduct, (Z)-190, not the substitution product 182 (there is precedence for both substitution and addition reactions with 36 and similar acceptors; see Section 2.5). The purified product, as an oil, was red in colour, indicating traces of the highly conjugated

Table 5.2: Acceptor Coupling with 4-[(Z)-1-Ethoxymethylidene]-2-phenyl-5-oxazolone, (Z)-44

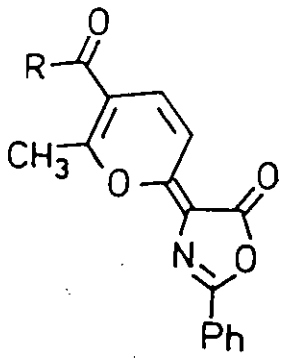
Acceptor	Product	Isolated Yie (%)
 R = OCH_3 , 37 R = CH_3 , 38	 182 189	40 15[a]
 36	 (Z)-190	78
 41	polymer	0

cont....

Table 5.2 (cont.)

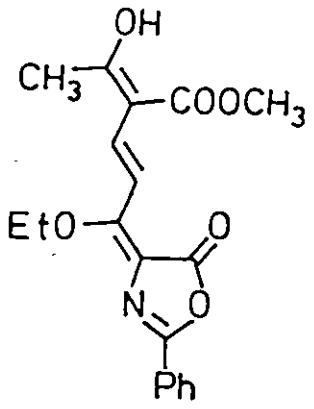
Acceptor	Product	Isolated Yield (%)
 42	 191	0-35[b]
 39 or 40	no reaction	0

[a] Isolated as product 192 (see Section 5,5)
[b] Crude yield



R = CH_3 , 192

R = OCH_3 , 193



182

elimination products 182 or 193. The addition product (Z)-190 was isolated as a mixture of two disastereomers in a 9 to 7 ratio as indicated by the ^1H NMR spectrum shown in Figure 5.5. Assignment of the erythro and threo forms was not attempted. The ^{13}C NMR assignments are shown in Figure 5.6 along with the assignments of the model compounds from which they were derived.

The successful couplings described above demonstrated the availability of useful type 'A' acceptors, however, defining useful type 'B' acceptors was a more difficult task.

The β-haloacrylates 39 and 40 were inactive to Michael substitution reactions with the anion of (Z)-44. At elevated temperatures (refluxing tetrahydrofuran), the acrylates were untouched but the anion decomposed. In contrast, when 42 was added to the anion of (Z)-44 it was the acceptor that disappeared

Figure 5.5: ^{1}H NMR of 4-[(Z)-4-carbomethoxy-1-ethoxy-3-methoxy-5-oxohexylidene]-2-phenyl-5-oxazolone, 190

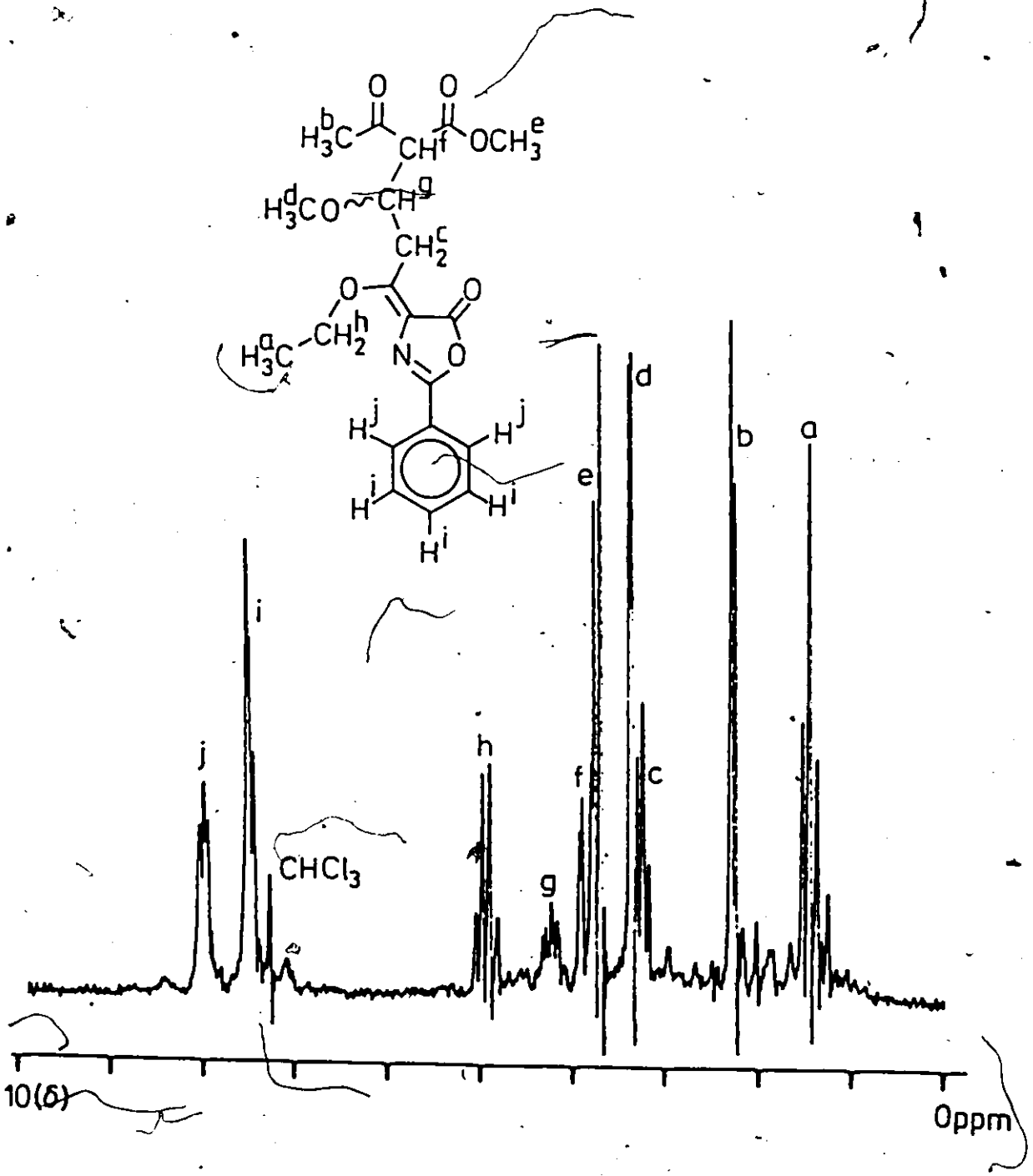
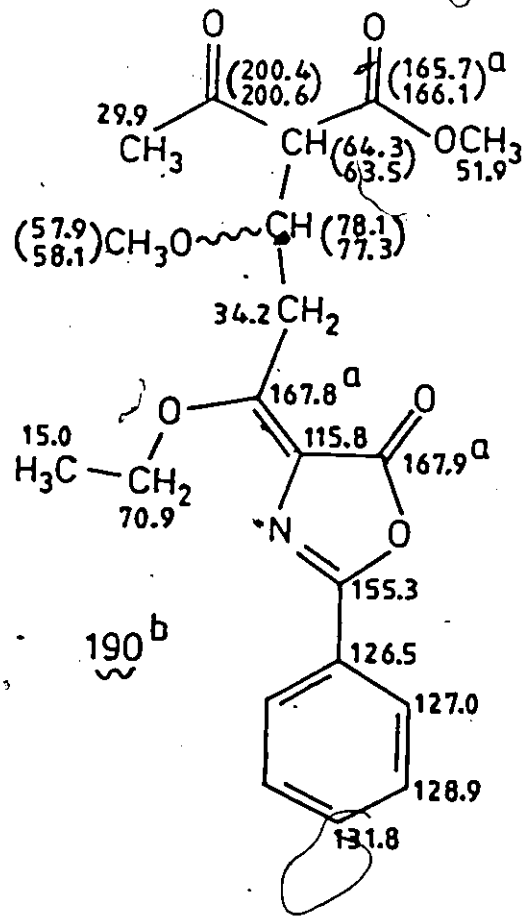
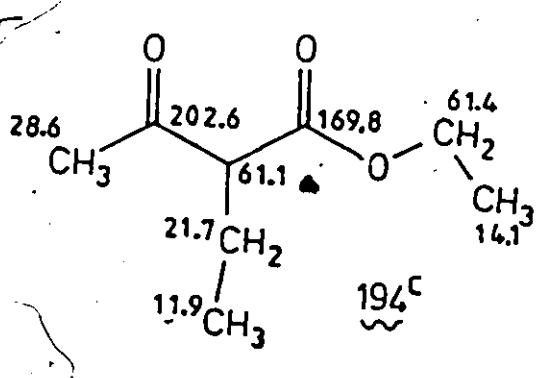


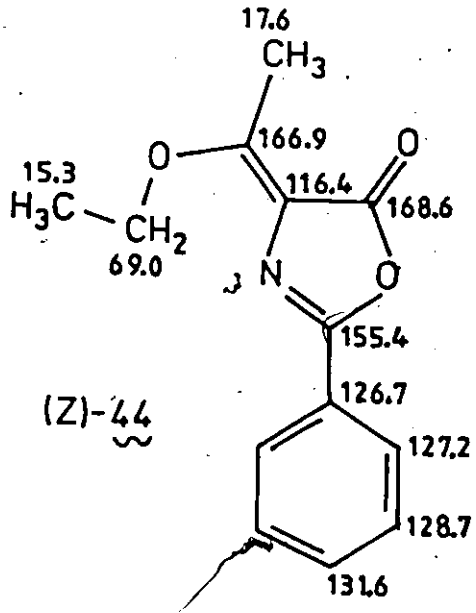
Figure 5.6: ^{13}C NMR Assignments of 4-[(Z)-4-Carbomethoxy-1-ethoxy-3-methoxy-5-oxohexylidene]-2-phenyl-5-oxazolone, 190



190[b]



194[c]



(Z)-44

[a]Assignments may be reversed.

[b]Numbers in brackets indicate the two diastereomers of 190.

[c]Source; reference 99.

(even at -95°C, presumably by self-condensation) and the donor was recovered.

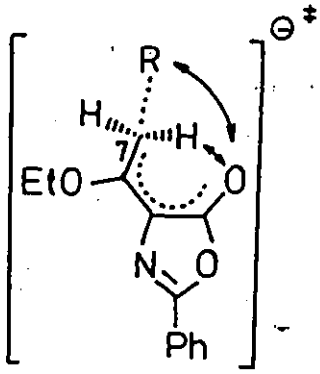
Acceptor 41 (a type 'B' synthon) was successfully coupled with the anion of (Z)-44 to give 191. Unfortunately, self-condensation of 41 competed with coupling and yields were low and inconsistent. Addition of cuprous iodide, zinc chloride and/or hexamethylphosphoric triamide to the anionic solution did not alleviate these problems. In all cases, the coupling reaction did not begin until the reaction temperature was above 0°C (as monitored by thin layer chromatography).

All of the coupled products 182, 189, 190 and 191 retained the Z geometry of the exocyclic double bond as indicated by the downfield position observed for the ^{1}H NMR signals of the $-OCH_2-$ protons of the products (4.95, 4.98, 4.92, and 4.86 ppm respectively; compare 4.73 and 4.30 ppm for Z and E 44).

Several comments on experiments summarized in Table 5.2 follow. Firstly, with acceptors 38, 41 and 42, polymerization was competitive with addition. Since self condensation involves a softer anion, and since softer anions are more influenced by steric factors than harder anions (see Section 2.2), the acceptors most seriously affected were the softer acceptors and/or the acceptors without β-substituents. Secondly, the order of acceptor reactivity followed expected behaviour (see Sections 2.2 and 2.3). Acceptor 37 reacted with the anion of (Z)-44 at low temperature (∿ 78°C), 42 reacted only above 0° while

39 and 40 did not react at all. Finally, the anion of (Z)-44 was a poor enolate donor as compared to the literature examples (see Section 2.5). The lack of reactivity with 39 and 40 are illustrations of this point.

The relatively poor nucleophilicity of the anion is explained by the steric compression of the anion (see Figure 5.2) and the steric interactions developed in rehybridization of C-7 during Michael addition. Attack of an electrophile on the anion of (Z)-44 requires the attacking group to approach O-2 during rehybridization. The resulting steric interactions cause an unusually high energy barrier to reaction.

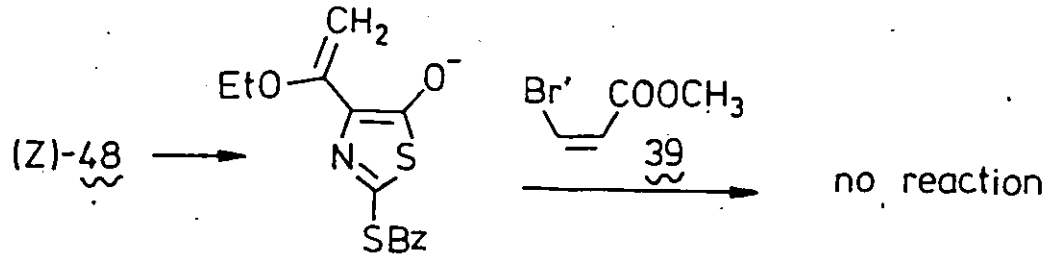


5.4 Miscellaneous Michael Additions

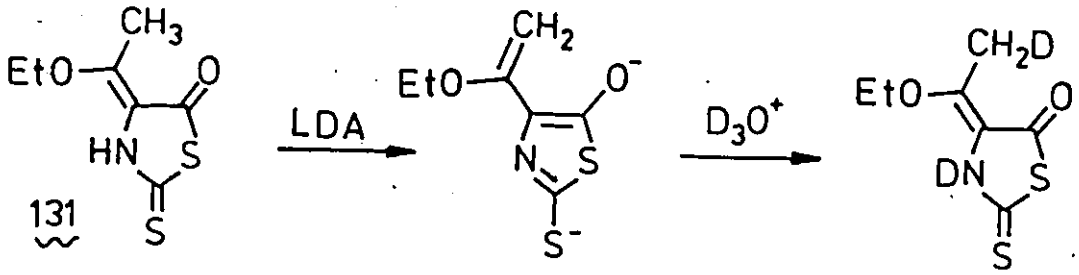
In order to investigate further the utility of β-haloacrylates as type 'B' synthons, two other Michael reactions were attempted.

As with the anion of (Z)-44, the anion of (Z)-48 was found to be inactive to Michael substitution reactions on com-

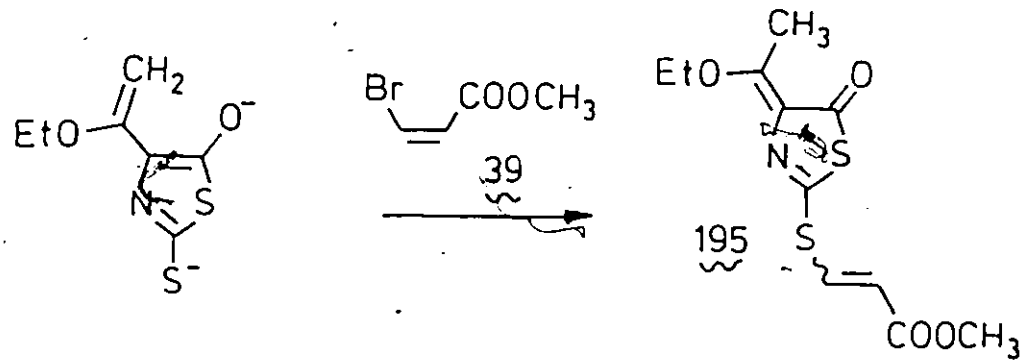
pound 39. In this case, the anion decomposed above 0°C. Again, the acceptor was untouched.



The dianion of 131 was prepared and quenched with acidic deuterium oxide (D_3O^+). The mass and ^1H NMR spectra of the deuterium quenched material showed approximately 80% deuterium incorporation in the vinyl methyl group demonstrating approximately 80% dianion formation.



When 39 was added to a solution of the dianion of 131, Michael substitution occurred at the sulfur atom rather than the carbon atom giving the product 195. Not surprisingly, the softer nucleophilic site was the preferred position of attack.

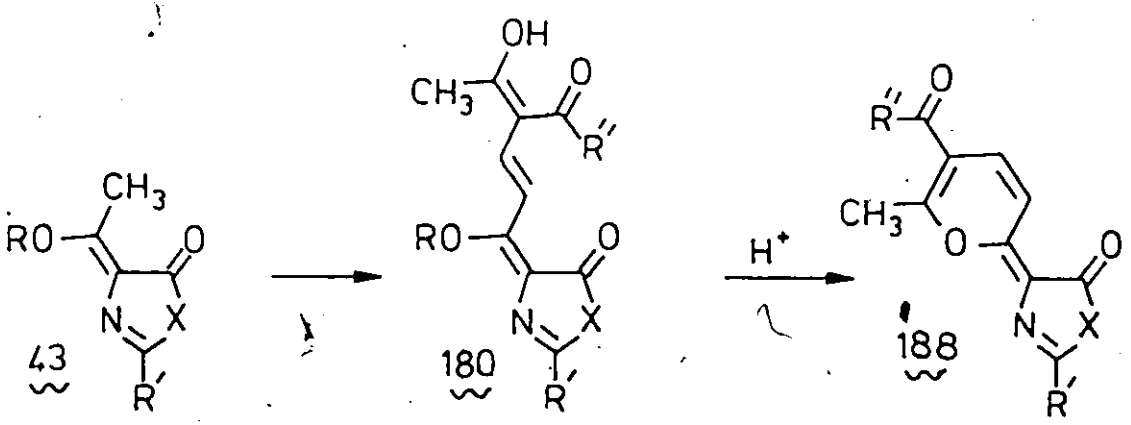


5.5 Reactions of the Michael Addition Products

The dominant property of the coupled products 180 was their facile cyclization to the pyranylidenes 188. The pyranylidenes that were isolated are listed in Table 5.3. The fact that ~ 50% of 184 was converted to 196 during recrystallization of 184 in ethanol illustrates the facile nature of this ring cyclization. The formation of compounds 188 was confirmed by the observed loss of ethanol from the precursors 180 (as indicated by their ^{1}H NMR and mass spectra and from the presence of a cis double bond (as evidenced by the 9-10 Hz ^{1}H-^{1}H coupling constants). The mechanism for the formation of compounds 188 was apparently by acid catalyzed substitution at C-6 by one of the enolic tautomers of the β-ketoester. Both isomers about the exocyclic double bond of the thiazolone 196 were isolated in a 1 to 5 ratio. The oxazolones 192 and 193 were isolated as one isomer only. The geometries of these products were not assigned.

All of the uncyclized compounds 180 had similar thin layer chromatographic behaviour characterized by a clean orange

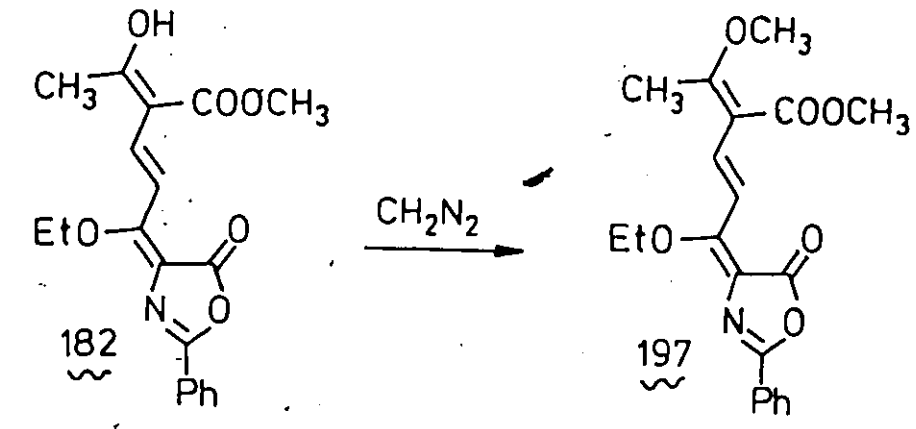
Table 5.3: Preparation of Pyranylideneoxazolones, 188



Starting Materials 43	180	R	R'	R"	X	Product (188)	Isolated Yield (%) from 43	from 180
(Z)-45	181	CH_3	Ph	OCH_3	O	193	25	-
(Z)-44	182	Et	Ph	OCH_3	O	193	29	60
(Z)-44	189	Et	Ph	CH_3	O	192	15	-
(Z)-48	184	Et	SBz	OCH_3	S	196	30	25

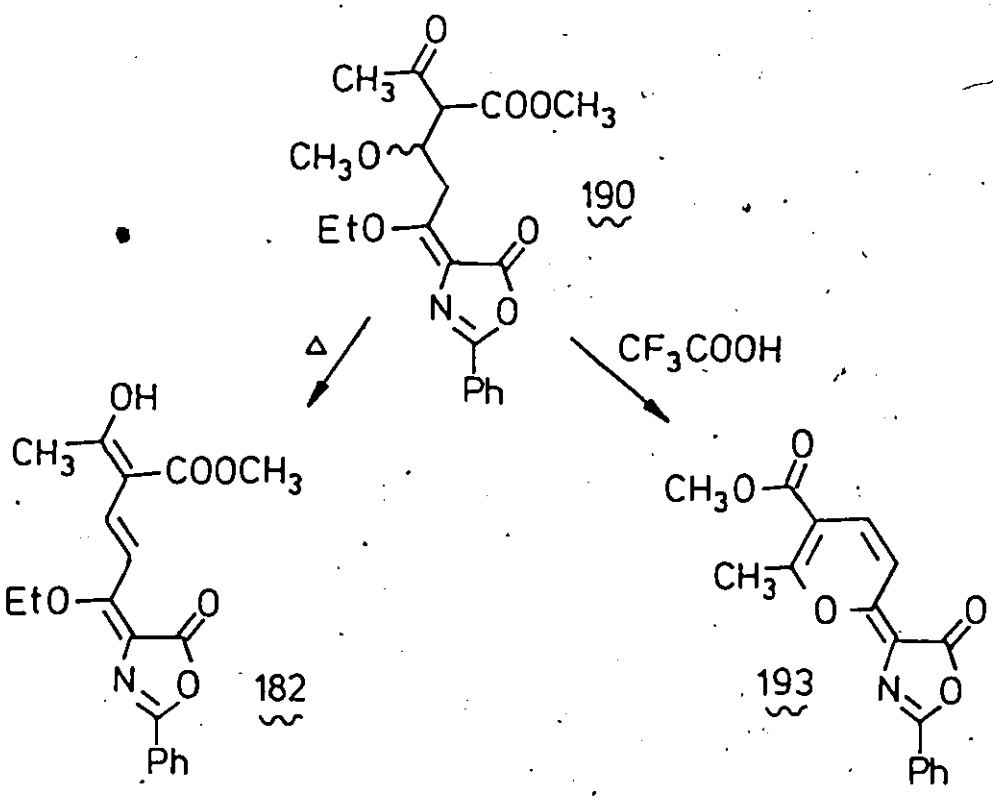
spot followed by red to orange tailing. If the plate was developed for too long a time, the spot disappeared and left only the tailing of colour behind. In one case, after attempted preparative thin layer chromatography of 181, the remaining "tail" of material was isolated and found to be identical with samples of 193 prepared by other cyclizations procedures. It was concluded that cyclization occurred readily for all coupled products of structure 180.

The uncyclized material 182 was O-methylated when treated with diazomethane to give 197 as indicated by the disappearance of the OH signal for the precursor 182 and the appearance of an additional OCH_3 signal at 3.87 ppm in the ^1H NMR spectrum.



182 197

The addition adduct (Z)-190 eliminated methanol to give 182 only after persistent heating. Direct transformation of (Z)-190 to 193 was accomplished by acid catalysis. On monitoring this reaction by ^{1}H NMR spectroscopy, disappearance of (Z)-190 and appearance of 193 was observed. Compound 182 was not observed as an intermediate.



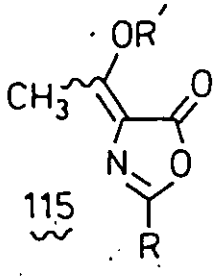
Small samples of 193, 182 and 190 were photoirradiated in order to observe isomerism about the exocyclic double bonds. Photoisomerization was observed for 193 and 190 giving respectively 3 to 1 and 3 to 2 ratios (as indicated by ^{1}H NMR spectroscopy) the major component corresponding to the original isomer.

These photoproduced isomers were not isolated. Photoisomerization was not observed for 182. Compound 193 decomposed on prolonged exposure to 300 nm light as evidenced by the gradual disappearance of the ^{1}H signals in the NMR samples irradiated over a 24 h period.

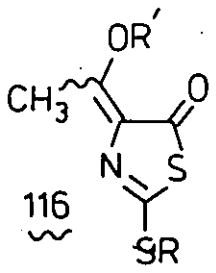
CONCLUSIONS

Throughout this thesis, the preparation and chemistry of oxazolones, 115, and thiazolones 116 and 49 were studied. The orthoacetate synthesis gave a mixture of E and Z isomers (about the C-4, C-6 double bond) with the Z isomer being the major product. Equilibration of these isomers was catalyzed by acid, base or light. The conformation of the Z isomer of these compounds while in solution was the same as that in the X-ray structure of (Z)-44 where the ring nitrogen (N-3) is buried by the protons on C-8. Identification of the geometry of the isomers of 115, 116 and 49 was obtained by ^{1}H and ^{13}C NMR spectroscopy. The NMR data will be of general use in determining the geometries of new and related oxazolones and thiazolones.

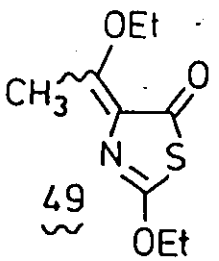
During investigation of the reactivity of the oxazolones and thiazolones, compounds 115, 116 and 49 were observed to sub-



115

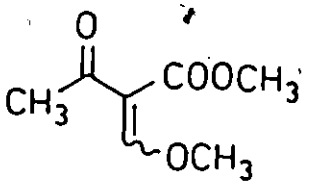


116

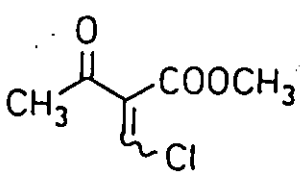


49

R,R = alkyl , aryl



36



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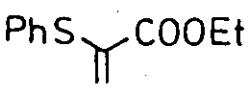

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stitute at C-6 with oxygen, nitrogen and sulfur nucleophiles. The ring nitrogens were surprisingly inactive to attack by electrophiles. The oxazolones 115 were ring opened by nucleophilic attack at C-5. The thiazolones did not undergo this simple transformation. The understanding of the reactions of these heterocyclic compounds has been expanded, advancing the knowledge in this neglected area of chemistry.

In general, an allylic proton from the heterocycles 115, 116 and 49 was removed by strong base to form stable dienolate anions. These anions were used in Michael addition reactions, but were less active than common enolate donors and acceptor polymerization often competed with addition. Anions of 4-alkylidene-5-oxazolones and thiazolones have now been prepared. The Michael addition reactions of these anions represent new transformations for oxazolones and thiazolones.

This thesis provides the groundwork from which a total synthesis of thienamycin can be attempted. Michael acceptors and donors have been prepared which fulfill all of the properties required for synthons A, B and C outlined in Section 2.1. Compounds 36 and 37, and 42 have been shown to be successful Michael acceptors and these compounds can be applied as synthons A and B respectively. Compounds 115 and 49 were (i) successful Michael donors, (ii) ring opened with sodium ethoxide (either by direct or multistep tranformations), (iii) substituted at C-6 with nitrogen, oxygen or sulfur nucleophiles and (iv) the ring opened products were available in the E configuration by equilibration mechanisms. Therefore, these compounds can be used as synthons C.

EXPERIMENTAL METHODS

General Introduction

Melting points were recorded on a Kofler micro hot stage apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian EM-390, Bruker WP80 and Bruker WM250 spectrometers in deuteriochloroform using tetramethylsilane (TMS) as internal standard except where noted otherwise. The abbreviations s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet are used in the description of the spin-spin splitting pattern present in the spectra. The natural abundance carbon-13 magnetic resonances (^{13}C NMR) were recorded on Bruker WP80 (at 20.115 MHz) and Bruker WM250 (at 62.896 MHz) instruments in deuteriochloroform with TMS as the internal standard except where noted. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were run at 70 eV on a VG Micromass 7070F double focusing mass spectrometer, the samples being introduced through a direct inlet system. Infrared spectra (IR) were recorded on a Perkin Elmer 283 spectrometer. Liquid IR samples were run neat, while solids were prepared in potassium bromide discs unless indicated otherwise. The symbols (s) = strong (m) = medium and (w) = weak are used in recording of IR data to indicate the intensity of the recorded bands.

When dry solvents were required, standard drying procedures were used. Triethylamine, hexamethylphosphoric triamide and diisopropylamine were dried over and distilled from calcium hydride. Dimethylformamide was dried and distilled from barium oxide. All of these solvents were stored over 4Å molecular sieves until needed. Tetrahydrofuran was dried by refluxing and distilling from sodium and benzophenone under dry nitrogen and was collected from the still just prior to use.

Diazomethane was prepared by the method of de Boer and Backer (119) using etheral N-methyl-N-nitroso-p-toluenesulfonamide (Diazald) in alcoholic sodium hydroxide.

n-Butyllithium was routinely standardized using the procedure of Kofron (120) (diphenylacetic acid in tetrahydrofuran).

The general procedure for the formation of lithium diisopropylamide (LDA) was as follows: 1.0 equiv. of an approximately 1.5 M n-butyllithium solution in hexane (Aldrich Chem. Co.) was placed under argon into a meticulously dry flask. To this stirred solution at 0°C, was added 1.0 equiv of dry diisopropylamine. After 5 min , the solution was diluted to approximately three times original volume with dry tetrahydrofuran and the solution was ready to use.

When column chromatography was required, silica gel 60 (E. Merck Co. suppliers) of 0.063 to 0.200 mm particle size

(70-230 mesh ASTM) was employed. Whenever the sample to be chromatographed was found to be insoluble in a small amount of the eluting solvent, the sample was dissolved in a minimum amount of chloroform in order to be introduced onto the column.

Silica gel 60 F_{254} (E. Merck Co. suppliers) plates of 0.2 mm thickness were used for analytical thin layer chromatography (TLC). For preparative TLC, Machery-Nagel Co. Sil G200 UV_{254} 2.0 mm silica gel plates were used.

A Rayonet Photochemical Reactor (Southern New England UV Co. manufacturers) was used for photoirradiations using the 300 nm fluorescent lamps supplied.

Orthoacetate-Acetic Anhydride Synthesis of 2-Alkyl and 2-Aryl-4-(1-ethoxyethylidene)-5-oxazolones (Z)-44, (Z)-46, (Z)-47, (E and Z)-126 and (E and Z)-127.

The preparation of 4-(1-ethoxyethylid[illegible])-5-oxazolones (or, in general, 4-(1-alkoxyalkylidene)-5-ox[illegible]nes) by action of triethyl orthoacetate (or other orthoesters) and acetic anhydride on N-acylglycines is documented (54-56,83).

To a hot solution of N-(phenylacetyl)glycine 122 (121) (1.04 g, 5.39 mmoles) in 12 mL acetic anhydride was added 3.0 mL triethyl orthoacetate (2.6 g, 16 mmoles) and the solution heated on a steam bath for 20 min. After this, the solvent was removed with strong heating (forced-air heater) at reduced pressure (25 mm). The crude product, after eluting through a 20 mm × 0.18 m silica gel column with 10% ethyl acetate in petroleum ether, provided 0.580 g of pure 46 (44% yield) as a pale yellow oil which solidified on standing overnight (mp 37-41°C).

Compound (Z)-46 showed:

HRMS: for $C_{14}H_{15}NO_3$; calcd. 245.1052; obs. 245.1023.

MS: m/z(RI%); 245(10), 118(35), 91(100) and 65(25).

IR: ν_{max}; 2990(m), 2932(m), 1795(m), 1762(s)[C=O], 1653(s)[C=N], 1604(s) and 1595(s)[exocyclic C=C] cm^{-1}.

^1H NMR: 1.39(t, J=7 Hz, 3H, ethoxy CH_3), 2.44(s, 3H, vinyl CH_3), 3.83(s, 2H, benzyl CH_2), 4.57(q, J=7 Hz, 2H, ethoxy CH_2) and 7.33(broad s, 5H, aromatic).

^{13}C NMR: as summarized in Table 3.5.

Similarly, (Z)-47, (Z)-44, (E and Z)-127 and (E and Z)-126 were obtained from N-pivaloylglycine 123 (prepared as in ref. 122 and recrystallized from acetone-petroleum ether), N-benzoylglycine (80)(Eastman suppliers), N-(4-bromobenzoyl)glycine (121) (123, 124) and N-(4-chlorobenzoyl)glycine (120) (123, 124) respectively using the procedure described above (for the 2-benzyl analogue) with the following changes:

(a) In the preparation of (Z)-47, the N-pivaloylglycine in acetic anhydride was heated on a steam bath for 5 min before triethyl orthoacetate addition. Column chromatographic purification utilized 9% ethyl acetate in petroleum ether. Yield of (Z)-47 from 222 mg (1.40 mmoles) 123 was 188 mg (64%) of a light yellow oil which solidified in the refrigerator on storage (mp 35-8°C).

(b) In the preparation of 44, both E and Z isomers were present in the crude mixture in a ratio of 1:5 (E:Z as indicated by ^1H NMR spectroscopy). The pure Z isomer was obtained by recrystallization from absolute ethanol or ethanol-water

(mp 111-112°C; lit. mp 112-113°C (55,56), 113°C (54)). A yield of 1.34 g (52%) was obtained from 2.0 g (11 mmoles) N-benzoylglycine.

(c) In the preparation of 127, both E and Z isomeric products co-crystallized on recrystallization of the crude mixture from absolute ethanol giving a 1:4 ratio of E to Z (as determined by ^{1}H NMR spectroscopy; yellow-orange plates mp 116-124°C). A yield of 0.341 g (65%) was obtained from 0.441 g (1.7 moles) of 121. Flash chromatography of 0.278 g of this mixture of isomers (10% ethyl acetate in petroleum ether as the eluant) gave 0.215 g (45% from 121) of pure Z isomer (yellow-orange plates from absolute ethanol mp 128.5-129.5°C) and 55 mg (12% from 121) of the pure E isomer (cream coloured needles from absolute ethanol mp 142.0-143.0°C). TLC of (E and Z)-127 (developed with 10% ethyl acetate in petroleum ether) gave R_f 0.08(E) and 0.36(Z).

(d) In the preparation of 126, 1.39 g (6.53 mmoles) of 120 gave 1.32 g (76%) of a co-crystalline mixture of E and Z isomers of 126 (1:4 ratio as determined by ^{1}H NMR spectroscopy). Flash chromatography of 0.503 g of this mixture (20% ethyl acetate in petroleum ether as eluant) gave 0.398 g Z isomer (orange plates from absolute ethanol mp 122.5-123.0°C, a 60% yield from 120) and 90.8 mg E isomer (colourless needles from absolute ethanol mp 130-132°C, a 14% yield from 120). TLC of (E and Z)-126 developed with 30% ethyl acetate in

in petroleum ether gave R_f 0.18 (E) and 0.52 (Z).

Compound (Z)-47 showed:

HRMS: for $C_{11}H_{17}NO_3$; calcd. 211.1208; obs. 211.1217.

MS: m/z(RI%); 211(15), 183(10), 168(15), 167(15) and 57(100).

IR: ν_{max}; 1788(s)[C=O], 1764(s)[C=O], 1643(s)[C=N] and 1598(s) cm^{-1}.

^1H NMR: 1.28(s, 9H, t-butyl), 1.38(t, J=7 Hz, 3H, ethoxy CH_3), 2.42(s, 3H, vinyl CH_3) and 4.64(q, J=7 Hz, 2H, ethoxy CH_2).

^{13}C NMR: as summarized in Table 3.5.

Compound (Z)-44 showed:

IR: ν_{max}; 1768(m), 1758(s)[C=O], 1640(s)[C=N], 1602(m) and 1587(s)[exocyclic C=C] cm^{-1}.

^1H NMR: 1.43(t, J=7 Hz, 3H, ethoxy CH_3), 2.49(s, 3H, vinyl CH_3), 4.73 (q, J=7 Hz, 2H, ethoxy CH_2), 7.36-7.53(m, 3H, aromatic) and 7.92-8.07(m, 2H, aromatic).

^{13}C NMR: as summarized in Table 3.5.

Compound (E)-127 showed:

HRMS: for $C_{13}H_{12}NOBr_3$; calcd, 309.0000; obs. 309.0046.

MS: m/z(RI%); 311(25), 309(25), 283(20), 281(20), 265(20), 263(20), 185(100), 183(100), 157(30), 155(30), 104(10), 76(30) and 75(20).

IR: ν_{max}; 1793(s), 1770(m), 1645(s), 1597(s) and 1584(s) cm^{-1}.

^1H NMR: 1.45(t, J=7 Hz, 3H, ethoxy CH_3), 2.53(s, 3H, vinyl CH_3), 4.35(q, J=7 Hz, 2H, ethoxy CH_2), 7.58 and 7.84(AA'BB', J_{ortho} = 9 Hz, J_{para} = 0 Hz, 2H and 2H, aromatic).

^{13}C NMR: as summarized in Table 3.5.

Compound (Z)-127 showed:

HRMS: for $C_{13}H_{12}NO_3Br$; calcd. 309.0000; obs 309.0059.

MS: indistinguishable from the E isomer.

IR: ν_{max}; 1792(s), 1762(m), 1637(s), 1592(s) and 1581(s) cm^{-1}.

^1H NMR: 1.45(t, J=7, 3H ethoxy CH_3), 2.51(s, 3H, vinyl CH_3), 4.72(q, J=7 Hz, 2H, ethoxy CH_2), 7.58 and 7.85 (AA'BB', J_{ortho} = 9 Hz, J_{para} = 0 Hz, 2H and 2H, aromati

^{13}C NMR: as summarized in Table 3.5.

Compound (E)-126 showed:

HRMS: for $C_{13}H_{12}NO_3Cl$; calcd. 265.0506; obs 265.0502.

MS: m/z(RI%), 267(5) and 265(15)[M^+], 239(3), 237(10), 221(3), 219(10), 141(30), 139(100), 113(10), 111(30) and 75(15).

IR: ν_{max}; 1792(s)[C=0], 1769(m)[C=0], 1644(s)[C=N], 1599(m) and 1583(s) cm^{-1}.

^1H NMR: 1.47(t, J=7 Hz, 3H, ethyl CH_3), 2.55(s, 3H, vinyl CH_3), 4.37(q, J=7 Hz, 2H, ethyl CH_2), 7.43 and 8.94 (AA'BB', J_{ortho} = 9 Hz, J_{para} = 0 Hz, 2H and 2H, aromatic).

^{13}C NMR: as summarized in Table 3.5.

Compound (Z)-126 showed:

HRMS: for $C_{13}H_{12}NO_3Cl$; calcd. 265.0506; obs. 265.0554.

MS: indistinguishable from the E isomer.

IR: ν_{max}; 1791(s)[C=0], 1762(m)[C=0], 1637(s)[C=N], 1596(m), 1580(s) cm^{-1}.

^1H NMR: 1.44(t, J=7 Hz, 3H, ethyl CH_3), 2.52(s, 3H, vinyl CH_3), 4.74(q, J=7 Hz, 2H, ethyl CH_2), 7.43 and 8.95 (AA'BB', J_{ortho} = 9 Hz, J_{para} = 0 Hz, 2H and 2H, aromatic)

^{13}C NMR: as summarized in Table 3.5.

Preparation of 2-Benzylthio-4-[(E and Z)-1-ethoxyethylidene]-5-thiazolone, (E and Z)-48 from 124

The method of Knott (89) for the preparation of 48 was used with some modification.

To a 0.75 mL of acetic anhydride were added 50.5 mg (0.27 mmoles) of N-dithiocarbobenzyloxyglycine (124) (88). This mixture was swirled and warmed on a steam bath until dissolution of the solid. The mixture was removed from the heat source and 1 crystal of toluenesulfonic acid (approximately 1 mg) was added. Immediately following this, 42 μL (37 mg, 0.27 mmoles) triethyl orthoacetate were added, the mixture swirled to ensure homogeneity and replaced on the steam bath for 10 min. Upon removal from the heat, the mixture was diluted with 1 mL saturated sodium bicarbonate and 5 mL water and extracted twice with chloroform. The chloroform layer was dried with anhydrous sodium sulfate, filtered and the volatiles removed initially by rotoevaporator distillation and finally by evacuation at 0.5

mm overnight. This left 61 mg of a yellow oil (48) (quantitative yield) with a 4:1 ratio of Z:E isomers as indicated by ^{1}H NMR spectroscopy. This mixture was sufficiently pure for further synthetic experiments.

Small quantities of 48 were purified by Kugelrohr distillation at 190-200°C and 0.3 mm (lit. bp 208°C at 1 mm (88)) without substantial losses due to polymerization. Otherwise, purification and isomer separation were effected by column chromatography with silica gel (7% ethyl acetate in 30-60 ° petroleum ether). An experiment using 233 mg of 124 after chromatography through a 2 mm × 0.15 m column of silica gel, gave 192 mg of pure Z isomer (67% yield).

Compound 48 showed:

HRMS: for $C_{14}H_{15}NO_2S_2$; calcd. 293.0477; obs. 293.0521.

MS: m/z(RI%); 293(25) and 91(100).

TLC: R_f(25% ethyl acetate in petroleum ether); Z 0.65, E 0.33.

IR: ν_{max}; 2986(m), 1694(s)[C=O], 1640(m)[C=N], 1602(m, shoulder) and 1574(s)[exocyclic C=C] cm^{-1}.

^{1}H NMR: Z; δ 1.39(t, J=7 Hz, 3H, ethyl CH_3), 2.44(s, 3H, vinyl CH_3), 4.40(s, 2H, benzyl CH_2), 4.55(q, J=7 Hz, 2H, ethyl CH_2), 7.22-7.44(m, 5H, aromatic).

E: δ 1.43(t, J=7 Hz, 3H, ethyl CH_3), 2.54(s, 3H, vinyl CH_3), 4.27(q, J=7 Hz, 2H, ethyl CH_2), 4.40(s, 2H, benzyl CH_2) and 7.22-7.44(m, 5H, aromatic).

^{13}C NMR: $CDCl_3$ (ref. $CDCl_3$) and acetone-d_6 (ref. acetone-d_6 29.2 ppm) as summarized in Table 3.5.

Preparation of 2-Ethoxy-4-[(Z)-1-ethoxyethylidene]-5-thiazolone (Z)-49

The method of Knott (88) for the preparation of 48 was used with some modification.

To 14 mL of acetic anhydride were added 0.870 g (5.34 mmoles) of N-thiocarbethoxyglycine 125 (90). This mixture was swirled and warmed on a steam bath until dissolution of the solid. The mixture was removed from the heat source after which 8 mg (0.05 mmoles) of toluenesulfonic acid and 1.5 mL (1.3 g, 8.0 mmoles) of triethyl orthoacetate were added in rapid succession. The solution was swirled to ensure homogeneity and replaced on a steam bath for 5 min. After removal from the steam bath, the volatiles were removed by rotoevaporator distillation with strong heating (forced air heater) and then by evacuation for 30 min. Flash column chromatography of the residue on silica gel (7.5% ethyl acetate in petroleum ether) gave 0.288 g (25%) of pure (Z)-49 as a pale yellow oil. Some E isomer was also present in the crude reaction mixture as evidenced by TLC. Separation of this isomer was not possible from other side products by the chromatography method employed. The E:Z ratio in the crude mixture was not determined because of signal overlap in the ^1H NMR spectrum.

Compound (Z)-49 showed:

HRMS: for $C_9H_{13}NO_3S$; calcd. 215.0616 obs. 215.0613.

MS: m/z(RI%); 215(95)[M^+], 187(40), 172(15), 159(100)[$M^+-C_3H_4O$], 141(60), 71(75), 70(35) and 56(30).

IR: ν_{max}; 1699(s)[C=O], 1606(s)[C=N] and 1570(s)[C=C] cm

^{1}H NMR: 1.38(t, J=7 HZ, 6H, both ethyl CH_3's), 2.40(s, 3H, vinyl CH_3), 4.43(q, J=7 Hz, 2H, 2-ethoxy CH_2) an 4.50(q, J=7 Hz, 2H, vinyl ethoxy CH_2).

^{13}C NMR: as summarized in Table 3.5.

Synthesis of 2-(1,1-Dimethylethyl)-4H-5-oxazolone, 129

Into a solution of 0.202 g (1.0 mmoles) N,N'-dicyclohexylcarbodiimide in 3 mL ether were added 0.155 g (1.0 mmoles) or N-pivaloylglycine (123). The solution was stirred for 30 min, then filtered and the ether removed leaving 0.14 g of 129, a quantitative yield (> 95% pure by ^{1}H NMR spectroscopy).

Compound 129 showed:

^{1}H NMR: δ 1.32(s, 9H, t-butyl), 4.17(s, 2H, methylene).

On heating 129 with triethyl orthoacetate and acetic acid the corresponding 4-(1-ethoxyethylidene)oxazolone (Z)-47 was prepared in 30% yield.

Preparation of 2-Thioxo-5-thiazolidinone, 130

The desired compound (130) was prepared by the method of Cook et al. (95) from glycinamide and also directly from the commerically available glycinamide hydrochloride (Sigma) as described below.

Glycinamide hydrochloride (1.00 g, 9.05 mmoles), potassium carbonate (1.25 g, 9.06 mmoles) and potassium hydroxide (0.51 g, 9.1 mmoles) were dissolved in 5 mL water. Into this solution was added 0.60 mL (0.76 g, 10 mmoles) carbon disulfide. The mixture was stirred vigorously for 5.5 hours at room temperature after which 2.0 mL 50% sulfuric acid was added rapidly (caution: effervescence!) with continued stirring. After about 30 sec, as a yellow precipitate of 130 was formed, the solution was diluted with 5 mL water. Stirring continued a further 30 min after which the precipitate was filtered, washed with water and dried in vacuo giving 0.509 g 130 (42%). This sample was sufficiently pure for subsequent preparations; mp decomp. > 300°C (lit. mp decomp. > 300°C (95)).

Compound 130 showed:

^{1}H NMR: (acetone-d_6); 4.70(s, 2H, methylene) and 9.83(broad s, 1H, NH).

Preparation of 4-[(Z)-1-Ethoxyethylidene]-2-thioxo-5-thiazolidinone, 131

Cook's work (95) on the preparation of an ethoxymethylene derivative of 2-thioxo-5-thiazolidinone, 130, formed the basis for the preparation of 131.

After dissolution of 92.2 mg (0.69 mmoles) of 130 in 2 mL warm acetic anhydride, 79 µL (83 mg, 1.38 mmoles) acetic acid and 0.25 mL triethyl orthoacetate (0.221 g, 1.36 mmoles) were added in rapid succession. Immediately, the reaction flask was swirled (to ensure homogeneity) and placed on a steam bath for 10 min. On removal from the steam bath, the volatiles were removed by rotoevaporator distillation (25 mm) with strong heating (forced air heater). The solid residue was recrystallized from absolute ethanol (decolourizing charcoal) to give 80.2 g (57%) 131, the pure Z isomer, as tan crystals mp 185-6°C.

Compound 131 showed:

HRMS: for $C_7H_9NO_2S_2$; calcd 203.0075; ~~obs~~ 203.0082.

MS: m/z(RI%); 203(100), 175(45), 141(50), 113(20) and 71(35).

IR: ν_{max}; 3110(m)[N-H], 1703(s)[C=0] and 1607(s)[C=C] cm^{-1}.

^1H NMR: δ 1.42(t, J=7 Hz, 3H, ethyl CH_3), 2.46(s, 3H, vinyl CH_3), 4.24(q, J=7 Hz, 2H, ethyl CH_2) and 9.30(broad s, ~~1H, NH~~).

^{13}C NMR: acetone-d_6 (ref. acetone-d_6 29.2 ppm); as summarized in Figure 3.11.

Preparation of 4-[(Z)-1-Ethoxyethylidene]-2-methylthio-5-thiazolone, (E and Z)-132

Potassium carbonate (304 mg, 2.2 mmoles), the 2-thioxo-5-thiazolidinone, 131 (149 mg, 0.734 mmoles) and methyl iodide (0.14 mL, 312 mg, 2.2 mmoles) were stirred in 2 mL of acetone for 30 min. Following this, the mixture was diluted with 10 mL of water, extracted twice with chloroform, the chloroform layer dried over anhydrous sodium sulfate and the solvent removed by rotoevaporator and then vacuum (0.5 mm, 60 min) to give 145 mg (91%) of 132 as oil which solidified to tan coloured needles, mp 35.0-37.5°C, on standing. This product was one isomer only, assigned the Z geometry from its ^{1}H NMR spectrum. When the reaction time was longer (approximately 14 h), an equilibrium mixture of the E and Z isomers was obtained (7.2 = Z:E as determined by ^{1}H NMR spectroscopy) as an oil.

Compound 132 showed:

HRMS: for $C_8H_{11}NO_2S_2$; calcd. 217.0231; obs. 217.0251.

MS: m/z(RI%); 217(50), 189(45), 142(35) and 91(100).

IR: (E and Z), ν_{max}; 3024(s), 3000(m), 2936(m), 1695(s) [C=O], 1672(s)[C=N] and 1570[exocyclic C=C]cm^{-1}.

^{1}H NMR: Z; δ 1.40(t, J=7 Hz, 3H, ethyl CH_3), 2.45(s, 3H, vinyl CH_3), 2.59(s, 3H, SCH_3) and 4.53(q, J=7 Hz, 2H, ethyl CH_2).

E; δ 1.40(t, J=7 Hz, 3H, ethyl CH_3), 2.56(s, 3H, vinyl CH_3), 2.59(s, 3H, SCH_3) and 4.26(q, J=7 Hz, 2H, ethyl CH_2).

^{13}C NMR: in $CDCl_3$ (ref. TMS) and acetone-d_6 (ref. acetone 29.2 ppm); as summarized in Table 3.5.

Preparation of 2-Benzylthio-4-[(Z)-1-ethoxyethylidene)-5-thiazolone, 48 from 131.

With the same procedure as that given above, 48 was prepared from potassium carbonate (44 mg, 0.37 mmoles), 131 (25 mg, 0.123 mmoles) and benzyl bromide (38 µL, 55 mg, 0.32 mmoles) in 92% yield (23 mg). The product so prepared was identical by TLC and ^1H NMR spectroscopy with the Z isomer obtained previously by the action of triethyl orthoacetate on 124.

Preparation of 4-[(Z)-1-Methoxyethylidene]-2-phenyl-4-oxazolone, (Z)-45

The oxazole (Z)-45 (mp. 101-102°C from 95% ethanol; lit. 101-102° from petroleum ether (86)) was prepared by the action of diazomethane on the hydroxymethylene analogue (86) which, in turn, was prepared by the method of Attenburrow et al. (96) from acetic anhydride and sodium hippurate.

Compound (Z)-45 showed:

^1H NMR: δ 2.53(s, 3H, vinyl CH_3), 4.29(s, 3H, OCH_3), 7.45-7.55(m, 2H aromatic) and 7.98-8.15(m, 3H, aromatic).

^{13}C NMR: as summarized in Table 3.5.

2-Benzylthio-4-[(E)-1-hydroxyethylidene]-5-thiazolone, 134

Hydrolysis of the 4-(1-alkoxyalkylidene) side chain of 5-thiazolones is analogous to those in the literature for the oxazolone series (83,85). To thiazolone, (Z)-48 (35 mg, 0.12 mmoles), was added, with stirring, 2 mL of 2M potassium hydroxide in 95% ethanol. The mixture was heated on a hot plate until most of the solid had dissolved. The solution was cooled and decanted from the remaining residue and acidified (to litmus) with 1M hydrochloric acid. The solution was diluted with 5 mL of water, extracted twice with chloroform and the chloroform layer dried over anhydrous sodium sulfate. After removal of solvent (rotoevaporator and then vacuum; 0.5 mm, 30 min), a light pinkish solid of the hydroxyethylidenethiazolone 134 remained. After recrystallization from acetone-water a yield of 19 mg (60%) was obtained (mp 102-104°C). Compound 134 showed:

HRMS: for $C_{12}H_{11}NO_2S_2$; calcd. 265.0231; obs. 265.0217.

MS: m/z(RI%): 265(25) and 91(100).

IR: ν_{max}; 1680(s)[C=O], 1655(m)[C=N], 1578(s) and 1570(s) cm^{-1}.

^1H NMR: 2.44(s, 3H, CH_3), 4.35(s, 2H, benzyl CH_2), 7.27-7.41(m, 5H, aromatic) and 9.85(broad s, 1H, OH).

2-Benzylthio-4-[(E)-1-methoxyethylidene]-5-thiazolone, (E)-135

Thiazolone 134 (10.2 mg, 38.5 μmoles) was dissolved in excess etheral diazomethane. After 10 min, the excess diazomethane was removed by passing a stream of nitrogen through the solution. Removal of solvent (by vacuum distillation) and purification by silica gel column chromatography (10% ethyl acetate in petroleum ether eluant) gave 4.4 mg (41%) of (E)-135 as in oil. This was assigned the E stereochemistry from its ^{1}H NMR spectrum. Compound (E)-135 showed:

MS: m/z(RI%); 279(25) and 91(100).

^{1}H NMR: 2.58(s, 3H, vinyl CH_3), 4.00(s, 3H, OCH_3), 4.40(s, 2H, benzyl CH_2) and 7.26-7.40(m, 5H, aromatic).

2-Benzylthio-4-[(E and Z)-1-methoxyethylidene]-5-thiazolone (E and Z)-135 and 4-[(E and Z)-1-ethoxyethylidene]-2-methylthio-5-thiazolone (E and Z)-136 by Alcohol Exchange

Precedence for acidic exchange reactions of the alkoxy substituent of 4-(1-alkoxyethylidene)-5-thiazolones is given in the work of E.B. Knott (89).

The oxazolone (Z)-132 (11.2 mg, 52 μmoles) was dissolved in 1 mL of methanol and a stream of hydrogen chloride gas was passed through the solution for approximately 30 seconds (the resulting acid concentration was not determined). After 1 h at room temperature, the reaction was quenched with 5 mL saturated sodium bicarbonate and the resulting mixture extracted twice with chloroform, the chloroform layer dried over anhydrous

sodium sulfate and the solvent removed by rotoevaporation and evacuation at 0.5 mm. The residue (10.1 mg, 96%) contained a 1:3 ratio (as determined by ^{1}H NMR spectroscopy) of E to Z isomers of 136 (mp 83-90°C). These were the only products observed by TLC and ^{1}H NMR spectroscopy..

Compound 136 showed:

MS: m/z(RI%); 203(50)[M^+], 174(10), 156(16)[M^+-SCH_3], 91(100)[CH_3SCS^+].

IR: ν_{max}; 1678(s)[C=0], 1655(m)[C=N], 1595(s), 1572(s) cm^{-1}.

TLC: (20% ethyl acetate in pet: ether) R_f 0.15(E), 0.34(Z).

^{1}H NMR: (DMSO-d_6)E; 2.58(s, 3H, vinyl CH_3), 2.58(s, 3H, SCH_3) and 3.98(s, 3H, OCH_3).

Z; 2.50(s, 3H, vinyl CH_3), 2.58(s, 3H, SCH_3) and 4.09(s, 3H, OCH_3).

Similarly, a 1:3 ratio of E to Z isomers of 135 was prepared using the procedure above.

Compound 135 showed:

HRMS: for $C_{13}H_{13}NS_2O_2$; calcd. 279.0342; obs, 279.0341.

MS: m/z(RI%); 279(25)[M^+] and 91(100).

IR: ν_{max}; 1682(s)[C=0], 1638(s)[C=N], 1600(m, shoulder), 1582(s) cm^{-1}.

TLC: (25% ethyl acetate-pet. ether) R_f 0.16(E), 0.49(Z).

^{1}H NMR: E - given above.

Z; 2.48(s, 3H, vinyl CH_3), 4.15(s, 3H, OCH_3), 4.42(s, 2H, benzyl CH_2) and 7.26-7.40(m, 5H, aromatic).

^{13}C NMR: as summarized in Table 3.5.

Attempted Oxazolone Isomerization with Concentrated Hydrogen Bromide Solution; Preparation of 2-(4-Chlorophenyl)-4-(1-hydroxyethylidene)-5-oxazolone, 138

4-Phenylmethylene-5-oxazolone isomerization of Z to E geometry has been accomplished by the action of concentrated aqueous hydrobromic acid solution (74).

A mixture of the two isomers of the ethoxyethylidene-oxazolone, 126 (33 mg, 0.12 mmoles), as prepared directly from the N-acylglycine 120, was suspended in 48% hydrobromic acid solution at 0°C. Anhydrous hydrogen bromide was bubbled into the solution. After 10 min, the compound completely dissolved and after hydrogen bromide saturation (another 10 min.), the flask was stoppered and left in the refrigerator (-2°C) for 7 h. The resulting precipitate was filtered and washed with water and dried in vacuo, yielding 16.2 mg (55%) of a light yellow powdery solid (mp 204-5°, melts and immediately evaporates) assigned structure 138.

In a similar experiment, 5 min following dissolution of the azlactone, the solution was quenched by the addition of ice-water and 10% aqueous potassium carbonate. A precipitate was formed which was extracted with dichloromethane, the dichloromethane layer dried over anhydrous sodium sulfate and removed by rotoevaporation. The product on analysis by both TLC and ^{1}H NMR spectroscopy showed no (E)-126. ^{1}H NMR showed (Z)-126 (approximately 90%) and 138 (approximately 10%).

Compound 138 showed:

HRMS: for $C_{11}H_8NO_3Cl$; calcd. 237.0192; obs. 237.0161.

MS: m/z(RI%); 239(10) and 237(30)(M^+), 221(2) and 219(5)[M^+-H_2O], 141(30), 139(100), 113(10), 111(30) and 75(15).

IR: ν_{max}; 1784(s), 1607(m) and 1560(s) cm^{-1}.

^1H NMR: (DMSO-d_6); 2.39(s, 3H, CH_3), 7.58 and 7.93 (AA'BB', J_{ortho} = 9 Hz, J_{para} = 0 Hz, 2H and 2H, aromatic) and 11.02(broad s, 1H, OH).

Photoisomerization of 44, 45, 46, 47 and 49; Isolation of (E)-44, (E)-46 and (E)-49

Photoisomerizations of phenylmethyleneoxazolones have been reported (74,78).

Irradiations were carried out in a Rayonet Photochemical reactor with 300 nm fluorescent lighting.

On approximately 30 μmole scale, 4-(1-alkoxyethylidene)-5-oxazolones and thiazolones 44, 45, 46, 47 and 49 were irradiated in 5 mm NMR tubes (4 mm ID) and in 0.5 mL $CDCl_3$. The isomerizations were monitored by ^1H NMR spectroscopy. Photostationary states were obtained after 2 days of irradiation giving a 2:3 ratio of E to Z isomers of 44, 45 and 46 and a 1:2 ratio for 47 and 49. In all of the irradiations, the two isomeric products were the only products observed as indicated by TLC and ^1H NMR spectroscopy.

On a preparative scale, pure (Z)-46 (0.220 g, 0.898 mmoles) was dissolved in 8 mL of chloroform and placed in a 10 mm OD tube (9 mm ID) and irradiated for 26 h. Solvent was

removed and flash chromatography (initially with 20% ethyl acetate in petroleum ether until elution of the Z isomer, then 30% ethyl acetate to elute the E isomer) giving 142 mg of recovered (Z)-46 (65%) and 68 mg (E)-46 (31%) both as pale yellow oils.

Similarly, when (Z)-44 (0.148 g, 0.642 mmoles) was irradiated for 18 h, 58.0 mg (39%) of pure (E)-44 was obtained (mp 132.0-134.5°C from absolute ethanol; lit. 136-8°C (55)) with 84.8 mg (57%) (Z)-44 recovered after flash chromatography (eluting with 15% ethyl acetate-petroleum ether).

Similarly when (Z)-49 (150.1 mg, 0.698 mmoles) was irradiated for 6 h, 44.9 mg (30%) of pure (E)-49 was obtained (as a pale yellow oil) with 98.0 mg (65%) of (Z)-49 recovered after flash chromatography (eluting with 7.5% ethyl acetate-petroleum ether).

For these compounds, the following TLC data were obtained with ethyl acetate (shown as per cent) in petroleum ether:

46 (30%) R_f - 0.15 (E), 0.47 (Z)

45 (30%) R_f - 0.15 (E), 0.35 (Z)

47 (20%) R_f - 0.26 (E), 0.62 (Z)

49 (15%) R_f - 0.28 (E), 0.51 (Z)

Compound (E)-44 showed:

^{1}H NMR: 1.43(t, J = 7Hz, 3H, ethoxy CH_3), 2.51(s, 3H, vinyl CH_3), 4.30(q, J = 7 HZ, 2H, ethoxy CH_2).
7.36 - 7.53(m, 2H, aromatic) and 7.92 - 8.07(m, 2H, aromatic).

^{13}C NMR: as summarized in Table 3.5.

Compound (E)-46 showed:

HRMS: for $C_{14}H_{15}NO_3$; calcd. 245.1052; obs. 245.1057.

MS: indistinguishable from that of (Z)-46.

IR: ν_{max}; 1805(s)[C=O], 1770(s)[C=O], 1665(s)[C=N] 1606(m), 1588(m) cm^{-1}.

^1H NMR 1.37(t, J = 7 Hz, 3H, ethyl CH_3), 2.41(s, 3H, vinyl CH_3), 3.80(s, 2H, benzyl CH_2), 4.29(q, J = 7 Hz, 2H, ethyl CH_2), 7.33(broad s, 5H, aromatic).

^{13}C NMR: as summarized in Table 3.5.

Compound (E)-47 showed:

^1H NMR: 1.27(s, 9H, t-butyl), 1.40(t, J = 7 HZ, 3H, ethyl CH_3), 2.43(s, 3H, vinyl CH_3), 4.30(q, J = 7 Hz, 2H, ethyl CH_2).

Compound (E)-45 showed:

^1H NMR: 2.53(s, 3H, vinyl CH_3), 4.04(s, 3H, OCH_3), 7.45 - 7.55(m, 3H, aromatic) and 7.98 - 8.15(m, 3H, aromatic).

Compound (E)-49 showed

MS: indistinguishable from that of (Z)-49.

IR: ν_{max}; 1704(s)[C=O], 1608(s)[C=N] and 1573(s)[C=C] cm^{-1}.

^1H NMR: 1.38(t, J = 7 Hz, 6H, both ethyl CH_3's), 2.40(s, 3H, vinyl CH_3), 4.20(q, J = 7 HZ, 2H, vinyl ethoxy CH_2) and 4.40(q, J = 7 Hz, 2H, 2-ethoxy CH_2).

^{13}C NMR: as summarized in Table 3.5.

Preparation of 2-Ethoxy-4-(1-hydroxyethylidene)-5-thiazolone, 148

Base catalyzed enol ether hydrolysis of 2-Benzylthio-4-ethoxymethylene-5-thiazolone, 109 (88), and acid catalyzed enol ether hydrolysis of 4-(1-alkoxyalkylidene)-2-aryl-5-oxazolones (92, 93), have been reported.

The thiazolone (Z)-49 (28.2 mg, 0.131 mmoles) was dissolved in 0.5 mL of concentrated sulfuric acid. To this stirred solution was added dropwise 5% aqueous potassium carbonate until pH 4 was obtained. The solution was extracted with chloroform, the chloroform layer dried over anhydrous sodium sulfate, filtered and the solvent removed by vacuum distillation giving an oil which solidified on standing. This material, on sublimation (at 1 mm, heating rapidly with a forced air heater), gave 21 mg (81%) of 148, mp 49 - 51°C.

Compound 148 showed:

MS: m/z(RI%); 187(85)[M^+], 159(100)[$M^+-C_2H_4$], 141(45)[M^+ - EtOH], 113(25), 71(100)[$C_3H_5NO^+$] and 70(35)[$C_2H_4NO^+$].

HRMS: for $C_7H_9NO_3S$; calcd. 187.0303; obs. 187.0300.

IR: ν_{max}; 1656(s)[C=O], 1615(s)[C=N] and 1588(s)[C=C] cm^{-1}.

^1H NMR: δ 1.38(t, J = 7 Hz, 3H, ethyl CH_3), 2.31(s, 3H, vinyl CH_3), 4.45(q, J = 7 Hz, 2H, ethyl CH_2) and 11.52 (broad s, 1H, OH).

Preparation of 2-Benzylthio-4-[(Z)-1-anilinoethylidene]-5-thiazolone, 149

Substitution reactions of nitrogen and sulfur nucleophiles on the exocyclic portion of 4-(1-alkoxyalkylidene)-5-thiazolones have been reported previously (88).

Aniline (4.1 µL, 4.2 mg, 45 µmoles) and the 4-(1-ethoxyethylidene)thiazolone (Z)-48 (13.2 mg, 45.1 µmoles) were dissolved in 2 mL of absolute ethanol and refluxed for 15 min. Removal of solvent by rotoevaporator and then by vacuum (0.5 mm, 1 h) gave a quantitative yield (15 mg) of the Z isomer of 149 as yellow-green crystals from 95% ethanol, mp 82.0 - 82.5°C. Compound 149 showed:

HRMS: for $C_{18}H_{16}N_2OS_2$; calcd. 340.0704; obs. 340.0678.

MS: m/z(RI%); 340(100), 307(35), 249(50), 118(60) and 91(70).

^{1}H NMR: 2.51(s, 3H, CH_3), 4.39(s, 2H, benzyl CH_2) and 7.12 - 7.52(m, 10H, aromatic) and 11.31(broad s, 1H, NH).

Preparation of 2-Benzylthio-4-[(E and Z)-1-(4-sulfonamidoanilino)-ethylidene-5-thiazolone, 150

Sulfanilamide (30.6 mg, 0.180 mmoles) and the thiazolone (Z)-48 (52 mg, 0.18 mmoles) were dissolved in 5 mL absolute ethanol and refluxed for 3 h. Removal of solvent by rotoevaporator and then by vacuum (0.5 mm, 2h) gave a quantitative yield (76 mg) of 150 as a 4:1 ratio (as determined by ^{1}H NMR spectroscopy) of E and Z isomers. The major isomer was assigned the E geometry. Crystallization from 95% ethanol gave 150 as

green crystals, mp 159.5 - 160.0°C.

Compound 150 showed:

MS: m/z(RI%); 419(3), 386(2), 172(11), 156(10), 124(20) and 91(100).

IR: ν_{max}: 3370(m)[N-H], 3240(m)[N-H], 1623(s), 1594(s) and 1570(s) cm^{-1}.

^1H NMR: E; δ 2.66(s, 3H, CH_3), 4.48(s, 2H, benzyl CH_2), 6.61(broad s, 2H, NH_2), 7.27 - 7.50(m, 5H, benzyl aromatic), 7.52 and 7.98(AA'BB' system, J = 8 Hz, 4H, sulfanilino aromatic) and 11.40(broad s, 1H, NH).
Z; δ 2.50(s, 3H, CH_3), 4.51(s, 2H, benzyl CH_2), 6.61(broad s, 2H, NH_2), 7.27 - 7.50(m, 5H, benzyl aromatic), 7.52 and 7.98(AA'BB' system, J = 8 Hz, 4H, sulfanilino aromatic) and 11.40(broad s, 1H, NH).

Preparation of 2-Benzylthio-4-[(Z)-1-phenylhydrazoethylidene]-5-thiazolone, 151

Phenylhydrazine (23 mg, 0.21 mmoles) and the thiazolone (Z)-48 (62 mg, 0.21 mmoles) were dissolved in 0.5 mL of absolute ethanol. After 10 min at room temperature the solvent was removed (also at room temperature) by evacuation (0.5 mm, 30 min). This produced a quantitative yield (76 mg) of the Z isomer of 151 as red-brown crystals from absolute ethanol, mp 126.0 - 127.5°C.

Compound 151 showed:

MS: m/z(RI%); 355(5), 231(50), 124(25), 91(100) and 77(25).

HRMS: for $C_{18}H_{17}N_3S_2O$; calcd. 355.0813; obs. 355.0808.

IR: ν_{max}; 3303(m)[N-H], 3212(m)[N-H], 1615(s, shoulder) [C=O], 1610(s)[C=N], 1593(s) and 1580(s)[exocyclic C=C] cm^{-1}.

^1H NMR: δ 2.53(s, 3H, CH_3), 4.37(s, 2H, benzyl CH_2), 5.93(broad s, 1H, aromatic NH), 6.73 - 7.08(m, 3H, aromatic), 7.13 - 7.50(m, 7H, aromatic) and 10.87 (broad s, 1H, vinyl NH).

^{13}C NMR: as summarized in Figure 3.8. Also 36.3(benzyl CH_2), 137.2, 128.7[a], 129.7[a], 127.6(benzyl aromatic C-1, C-2, C-3 and C-4 respectively), 148.2, 113.2, 129.2[a] and 122.0(phenylhydrazino C-1, C-2, C-3 and C-4 respectively).

[a]these assignments may be reversed.

Preparation of 4-[1-(2-Mercaptoethylamino)ethylidene]-2-methylthio-5-thiazolone (152)

Aminoethanethiol (8 mg, 0.1 mmoles) and the thiazolone (Z)-132 (12.0 mg, 55 µmoles) were dissolved in 2 mL of absolute ethanol. After 18 h at 20°C the solvent was removed by vacuum distillation and the residue chromatographed on silica gel (6 mm× 0.19 m; eluting with 1% acetic acid, 24% ethyl acetate and 75% petroleum ether) gave, after evacuation overnight, 8.4 mg (62%) of a tan-coloured solid residue, mp 95 - 7°C. One isomer only was obtained, tentatively assigned the Z geometry.

Compound 152 showed:

MS: m/z(RI%); 248(100)[M^+], 215(20)[M^+-SH], 201(55) [M^+-SCH_3], 167(15)[M^+-CH_5S_2], 153(25), 141(30), 91(70)[CH_3SCS^+], 69(50) and 61(80).

HRMS: for $C_8H_{12}N_2OS_3$; calcd. 248.0112; obs. 248.0094.

IR: ν_{max}; 3220(m)[NH] and 1607(s)[C=O and C=N] cm^{-1}.

^1H NMR: δ 1.53(t, J = 8 Hz, 1H, SH), 2.52(s, 5H, vinyl CH_3), 2.55(s, 3H, SCH_3), 2.75(dt, J = 8 and 6 Hz, 2H, CH_2S), 3.60(dt, J = 6 and 6 Hz, 2H, CH_2N) and 10.08(broad s, 1H, NH).

Selective proton-proton decoupling experiments provided the following information. On irradiation of the 10.08 ppm resonance, the 3.60 ppm resonance collapsed to a triplet (J = 6 Hz). On irradiation of the 2.75 ppm resonance, the 3.60 ppm resonance collapsed to a triplet (J = 6 Hz) and the 1.53 ppm resonance collapsed to a singlet.

TLC: (1% acetic acid, 24% ethyl acetate, 75% petroleum ether) R_f - 0.32.

Preparation of 4-[(E and Z)-1-Anilinoethylidene]-2-ethoxy-5-thiazolone, (E and Z)-153

In 2 mL of absolute ethanol were dissolved (Z)-49 (39.5 mg, 0.184 mmoles) and aniline (42 mL, 43 mg, 0.44 mmoles) and refluxed for 1.5 h. The solvent was removed by vacuum distillation and the residue dissolved in dichloromethane and extracted with saturated aqueous ammonium chloride solution. The dichloromethane layer was dried over anhydrous sodium sulfate and the solvent removed by vacuum distillation and evacuation. The resulting 47.7 mg of 153 (99%) solidifed on storage overnight, mp 70-85°C. Apparently both E and Z isomers co-crystallized.

Nevertheless one spot only was observed by TLC. The isomers were in a 4:5 ratio (E:Z) as determined by ^{1}H NMR spectroscopy. Recrystallization from petroleum ether did not give sharp melting material. Compound 153 showed:

HRMS: for $C_{13}H_{14}N_2SO_2$; calcd. 262.0776; obs. 262.0745.

MS: m/z (RI%); 262(40), 173(10), 146(15), 145(45), 118(100), 93(20), 91(15), 65(20) and 51(40).

IR: (10% ethyl acetate in petroleum ether) R_f - 0.52.

^{1}H NMR: Z; δ 1.40(t,J=7 Hz, 3H, ethyl CH_3), 2.43(s, 3H, vinyl CH_3), 4.40(q, J=7 Hz, 2H, CH_2), 7.08-7.53(m, 5H, aromatic) and 11.01(broad s, 1H, OH).

E; δ 1.38(t, J=7 Hz, 3H, ethyl CH_3), 2.48(s, 3H, vinyl CH_3), 4.38(q, J=7 Hz, 2H, CH_2), 7.08-7.53(m, 5H, aromatic) and 8.17(broad s, 1H, OH).

Aniline substitution occurs at C-6 since the C-2 product would have shown the C-6 ethoxy signal for the Z isomer ∿ 0.3 ppm downfield of the E isomer (compare with E and Z 48 and 49).

Preparation of 2-Phenyl-4-(1-phenylhydrazoethylidene)-5-oxazolone, 154

Substitution on the exocyclic portion of 4-(alkoxyalkylidene)-5-oxazolones by nitrogen nucleophiles is established in the literature (83,85).

Phenylhydrazine (107 mg, 0.99 moles) and the oxazolone (Z)-44 (229 mg, 0.99 mmoles) were dissolved in 0.5 mL of absolute ethanol. After 60 min at room temperature, the solvent was removed (at room temperature) by evacuation (0.55 mm, 30 min). This produced a quantitative yield (291 mg) of 154

as cream crystals from absolute ethanol, mp 126.0 - 128.0°C. Both isomers were present in approximately 3:2 ratio as determined by ^{1}H NMR spectroscopy. The major isomer was assigned the Z geometry.

Compound 154 showed:

MS: m/z(RI%); 293(25), 105(100) and 77(55).

IR: ν_{max}; 3320(m)[N-H], 3255(m)[N-H], 1729(s)[C=O], 1635(s)[C=N], 1607(m) and 1585(s)[exocyclic C=C] cm^{-1}.

^{1}H NMR: Z; δ 2.51(s, 3H, CH_3), 5.85(broad s, 1H, aromatic NH) 6.73-7.07(m, 3H, hydrazo aromatic), 7.18-7.34(m, 2H, hydrazo aromatic), 7.37-7.49(m, 3H, 2-phenyl aromatic), 7.93-8.03(m, 2H, 2-phenyl aromatic) and 9.57(broad s, 1H, vinyl NH).

E; δ 2.53(s, 3H, CH_3), 5.85(broad s, 1H, aromatic NH), 6.73-7.07(m, 3H, hydrazo aromatic), 7.18-7.34(m, 2H, hydrazo aromatic), 7.37-7.49(m, 3H, 2-phenyl aromatic), 7.93-8.03(m, 2H, 2-phenyl aromatic) and 9.57(broad s, 1H, vinyl NH).

^{13}C NMR: (in acetone-d_6) as summarized in Figure 3.8. Also, δ 128.4, 129.7[a], 126.9, 131.2, ((Z)-2-phenyl C-1, C-2, C-3 and C-4 respectively), 127.3, 129.7[a], 126.6, 131.5 ((E)-2-phenyl C-1, C-2, C-3 and C-4 respectively), 149.3, 113.5, 130.2[a], 121.6 and 121.3 (hydrazo C-1, C-2, C-3, (Z)-C-4 and (E)-C-4 respectively).

[a]these assignments may be reversed.

Preparation of 2-Benzylthio-4-[1-(2-phthalimidoethylthio)ethylidene]-5-thiazolone, 156

The 2-phthalimidoethanethiol (155) used in the following reaction was prepared by the method of Baddiley (125) from 1-bromo-2-phthalimidoethane which in turn was prepared by the method of Gabriel (126, 127) from 1,2-dibromoethane.

At room temperature and under dry nitrogen, 4 mg (0.08 mmoles) of 50% sodium hydride in oil were suspended in 1 mL of dry dimethylformamide. To this suspension was added 155 (61 mg, 0.29 mmoles). After the solution became homogeneous (10 min), 48 (43 mg, 0.15 mmoles) was added with stirring. After 3h, 5 mL of pH7 phosphate buffer solution was added and the mixture extracted three times with chloroform. After drying the chloroform layer over anhydrous sodium sulfate and removal of solvent at reduced pressure the crude residue was purified by silica gel chromatography (13% ethyl acetate in petroleum ether eluant) giving 28 mg (42%) of 156 as a pale yellow oil.

Compound 156 showed:

MS: m/z(RI%); 454(3), 207(20), 174(40), 160(100), 130(20), and 76(30).

^{1}H NMR: δ 2.64(s, 3H, CH_3), 3.33(t, J = 7 Hz, 2H, SCH_2), 4.02(t, J = 7 Hz, 2H, NCH_2), 4.43(s, 2H, benzyl CH_2), 7.25-7.53(m, 5H, benzyl aromatic) and 7.61-8.00(m, AA'BB', 4H, phthalimido aromatic).

Base Catalyzed Ring Opening of (Z)-44. Preparation of Ethyl (Z)-2-Benzamido-3-ethoxy-2-butenoate, (Z)-158

Sodium ethoxide catalyzed ring opening of 4-alkoxymethylene-5-oxazolones has been reported (92).

Sodium (4 mg, 0.17 mmoles) was dissolved in 1 mL of absolute ethanol and added to 172 mg (0.744 mmoles) of the oxazolone (Z)-44 in 10 mL of absolute ethanol. The solution was warmed on a steam bath for 2 min and then the solvent removed by vacuum distillation. Saturated aqueous sodium bicarbonate and dichloromethane were added to the residue. The dichloromethane layer was dried over anhydrous sodium sulfate, filtered and the dichloromethane removed by vacuum distillation. The white crystalline mass was recrystallized from tetrachloromethane giving 135 mg (65%) of 158 (fine needles mp 142-5°C, the product appeared to decompose near the mp). Only one isomer was observed, tentatively assigned the Z geometry. Compound (Z)-158 showed:

MS: m/z(RI%); 277(5)[M^+], 232(10)[M^+-OEt], 172(10), 117(25), 105(100)[$C_6H_5CO^+$], 89(10), 77(35)[$C_6H_5^+$] and 61(20).

HRMS: for $C_{15}H_{19}NO_4$; calcd. 277.1314; obs. 277.1289.

IR; ν_{max}; 3243(broad m)[NH], 1714(s)[ester C=0], 1641(s)[amide C=0], 1603(m) and 1580(m) cm^{-1}.

^1H NMR: (see Figure 3.10) δ 1.23 and 1.25(t, J = 7 Hz, 3H and 3H, ethyl CH_3's), 2.39(s, 3H, vinyl CH_3), 4.04(q, J = 7 Hz, 2H, ester CH_2), 4.22(q, J = 7 Hz, 2H, vinyl ether CH_2), 7.21(broad s, 1H, amide NH),

7.43-7.60(m, 3H, aromatic) and 8.80-8.94(m, 2H, aromatic).

^{13}C NMR: as summarized in Figure 3.11.

Attempted Acid Catalyzed Ring Opening of (Z)-47

Alcoholic hydrogen chloride catalyzed ring opening of 4-alkoxymethylene-5-oxazolones has been reported (92).

No reaction was observed on refluxing the 2-t-butyl-oxazolone (Z)-47 in ethanol and trifluoroacetic acid for 0.5 h. An increase of acid strength by the use of hydrogen chloride in ethanol or sulfuric acid in ethanol gave only decomposition and/or polymerization with none of the desired ring opened products observed.

Ring Opening of (Z)-132. Preparation of Methyl Dithiocarbomethoxyglycinate 162

The thiazolone (Z)-132 (19 mg, 0.089 mmoles) and mercuric chloride (24.3 mg, 0.089 mmoles) were dissolved in 2 mL of methanol. This solution was heated to 70°C for 14 h in a sealed glass tube. Filtration of the resulting precipitate, vacuum distillation of the solvent and flash column chromatography of the residue (40% ethyl acetate-petroleum ether as eluant) yielded 8.0 mg (50%) of 162 as a pale yellow oil which solidified on standing overnight, mp 43-5°C; lit. mp 44-6°; IR, NMR and MS data were consistent with those observed for 162 (137).

This same product (as indicated by ^{1}H NMR spectroscopy and TLC) was obtained by heating 132 in methanolic hydrogen chloride in a sealed tube at 70°C for 21 h. The crude product obtained as an oil was approximately 95% pure (as ascertained by ^{1}H NMR spectroscopy) but was not further purified. TLC (40% ethyl acetate - petroleum ether) R_f - 0.58.

Preparation of 4-[(Z)-1-Ethoxyethylidene]-2,5-thiazolidinedione (Z)-160)

The thiazolone (Z)-49 (186.3 mg, 0.867 mmoles) was dissolved in 6 mL of absolute ethanol. To this stirred solution was bubbled hydrogen chloride gas initially at room temperature and after approximately 5 min, as the solution warmed, with ice bath cooling. Hydrogen chloride addition was continued a further 15 min by which time formation of a white precipitate had ceased. The volatiles were removed by vacuum distillation and the solid residue dissolved in chloroform and extracted with saturated aqueous sodium bicarbonate solution. The chloroform layer was dried over anhydrous sodium sulfate, filtered and the solvent removed by vacuum distillation leaving 151 mg of colourless solid. Recrystallization from tetrachloromethane gave 141 mg (87%) colourless needles, mp 178-179°C. Only one isomer was obtained which was assigned the Z geometry. Compound (Z)-160 showed:

MS: m/z(RI%); 187(100)[M^+], 159(70)[$M^+-C_2H_4$], 126(15), 99(95), 71(85) and 70(40).

HRMS: for $C_7H_9NO_3S$; calcd. 187.0303; obs. 187.0283.

IR: ν_{max}; 3180(m)[NH], 1674(s)[both C=O's] and 1617(s)[C=C] cm^{-1}.

TLC: (50% ethyl acetate - petroleum ether) R_f - 0.64

^1H NMR: δ 1.35(t, J = 7 Hz, 3H, ethyl CH_3), 2.45(s, 3H, vinyl CH_3), 4.14(q, J = 7 Hz, 2H, ethyl CH_2) and 7.55(broad s, 1H, NH).

^{13}C NMR: as summarized in Figure 3.11.

Preparation of 4-[(Z)-1-Ethoxyethylidene]-3-methyl-2,5-thiazolidinedione ((Z)-161)

The dione (Z)-160 (106.1 mg, 0.567 mmoles) was dissolved in 3 mL of acetone. Potassium carbonate (303 mg, 2.09 mmoles) was suspended in this solution and methyl iodide (0.68 g, 0.3 mL, 4.8 mmoles) was added. After 4 h, the reaction was quenched by the addition of saturated aqueous bicarbonate and extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate and the solvent removed by vacuum distillation. Recrystallization from petroleum ether gave 101.0 mg (89%) colourless crystals (mp 81-2°C). Compound (Z)-161 showed:

MS: m/z(RI%); 201(100)[M^+], 173(50)[$M^+-C_2H_4$], 113(45)[$M^+-C_2O_2S$], 85(70)[$C_4H_7NO^+$] and 84(45)[$C_4H_6NO^+$].

HRMS: for $C_8H_{11}NO_3S$; calcd. 201.0459; obs. 201.0472.

IR: ν_{max}; 1675(s, shoulder)[C=O], 1665(s)[C=O] and 1585(s)[C=C] cm^{-1}.

TLC: (50% ethyl acetate in pet. ether) R_f - 0.71.

^{1}H NMR δ 1.39(t, J = 7 Hz, 3H, ethyl CH_3), 2.50(s, 3H vinyl CH_3), 3.47(s, 3H, amide CH_3) and 4.14(q, J = 7 Hz, 2H, ethyl CH_2).

^{13}C NMR: as summarized in Figure 3.11.

Preparation of Ethyl (Z)-3-Ethoxy-2-[N-methyl(methylthio)amido]-2-butenoate, (Z)-159

To a stirred solution of the dione 161 (21.8 mg, 0.108 mmoles) in 1 mL of absolute ethanol was added, all at once, a solution of sodium (2.7 mg, 0.117 mmoles) in 0.55 mL of absolute ethanol. Methyl iodide (0.10 mL, 0.23 g, 1.6 mmoles) was added to the stirred solution, and after 5 min, saturated aqueous sodium bicarbonate was added and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, filtered and the solvent removed by vacuum distillation. The crude product was purified by flash column chromatography (25% ethyl acetate in petroleum ether as eluant) giving 13.2 mg (47%) of 159 as a colourless oil Compound (Z)-159 showed:

MS: m/z(RI%); 261(40)[M^+], 216(35)[M^+-OEt], 214(30)[M^+-SCH_3], 186(80), 158(55), 144(35), 114(50), 84(50) and 75(100)[CH_3SCO^+].

HRMS: for $C_{11}H_{19}NO_4S$; calcd. 261.1035; obs. 261.1073.

IR: ν_{max}; 1704(s)[ester C=0], 1668(s)[thioamido C=0] and 1603(s)[C=C] cm^{-1}.

TLC: (30% ethyl acetate in petroleum ether) R_f - 0.57.

^{1}H NMR: (see Figure 3.12) δ 1.23 and 1.29(t, J = 7 Hz, 3H and 3H, ethyl CH_3's), 2.22(s, 3H, SCH_3), 2.51(s, 3H, vinyl CH_3), 3.02(s, 3H, NCH_3), 4.10(q, J=7 Hz, 2H, ester CH_2) and 4.17(q, J = 7 Hz, 2H, vinyl OCH_2).

^{13}C NMR: (acetone-d_6, ref. acetone-d_6 29.2 ppm) as summarized in Figure 3.11.

Preparation of 4-Benzamido-5-hydroxy-3-methyl-1-phenylpyrazole, 166

4-Hydrazomethylene-5-oxazolones form pyrzaolone rings on heating (94). Use of a 4-hydrazoethylidene-5-oxazolone was a simple extension of this reaction.

After dissolving the (phenylhydrazo)ethylideneoxazolone 154 (115 mg, 0.392 mmoles) in 3 mL of chloroform the sample was sealed in a glass tube and heated to 60°C for 45 min. After cooling to room temperature, the seal was broken and the solution exposed to the atmosphere for 2 h. Removal of solvent (rotoevaporator and then vacuum (0.3 mm overnight)) gave 121 mg of 166 (quantitative yield), a white crystalline hydrate (melts and recrystallizes at 110-120°C, remelts at 188.0-189.0°C: lit; melts and recrystallizes at 110-115°C with loss of water, remelts at 183°C (128); 181°C (129)).

Compound 30 showed:

MS: m/z(RI%); 293(30)[M^+], 275(20), 105(100) and 77(60)

HRMS: for $C_{17}H_{15}N_3O_2$; calcd. 293.1164; obs. 293.1146.

IR: ν_{max}: 3072(m), 1650(s), 1627(s), 1604(s), 1583(s) and 1501(s) cm^{-1}.

^{1}H NMR: δ 2.16(s, 3H, CH_3), 6.80(broad s, 1H, NH) and 7.13-7.95(m, 11H, aromatic and OH).

^{13}C NMR: (in $CDCl_3$ and acetone-d_6) as summarized in Figure 3.14.

Photoisomerization of 158, 159, 160 and 161

Photoirradiations were carried out with 300 nm fluorescent lighting on approximately 30 μmole scale. Samples were dissolved in 0.5 mL of $CDCl_3$ and placed in 5 mm NMR tubes and monitored by ^{1}H NMR spectroscopy. Photostationary states of 159, 160 and 161 were obtained after 20 h of irradiation and showed E to Z ratios of 2:3, 1:3 and 1:4 respectively. Compound 158 decomposed on long term irradiation the ^{1}H NMR signals disappearing over a 12-24 h irradiation period. In all cases, the photoinduced E isomer was not isolated.

Compound (E)-158 showed:

^{1}H NMR: δ 2.43(s, 3H, vinyl CH_3). Other signals were at approximately the same position as for the Z isomer.

Compound (E)-159 showed:

^{1}H NMR: δ 2.02(s, 3H, SCH_3), 2.22(s, 3H, vinyl CH_3) and 3.04(s, 3H, NCH_3).

Other signals were at approximately the same position as for the Z isomer.

Compound (E)-160 showed:

^{1}H NMR: δ 1.35(t, J = 7 Hz, 3H, ethyl CH_3), 2.15(s, 3H, vinyl CH_3), 4.12(q, J = 7 Hz, 2H, ethyl CH_2) and 9.28(broad s, 1H, NH).

Compound (E)-161 showed:

^{1}H NMR: δ 1.39(t, J = 7 Hz, 3H, ethyl CH_3), 2.23(s, 3H, vinyl CH_3), 3.33(s, 3H, NCH_3) and 4.12(q, J = 7 Hz, 2H, ethyl CH_2).

Preparation of 4-Carbethoxy-5-methyl-2-(4-nitrophenyl)oxazole, 143

The N-oxide hydrochloride precursor used for this reduction was prepared in 63% yield by the method of Weintraub (130) from p-nitrobenzaldehyde, ethyl 2-hydroximino-3-oxo-butanoate (131) and hydrogen chloride in acetic acid. Precedence for the use of phosphines in the reduction of N-oxides has been reported (106,107).

The N-oxide hydrochloride of 143 (0.388 g, 1.18 mmoles) and tributylphosphine (0.39 g, 1.0 mmoles) were dissolved in 2 mL of chloroform and left to stand at room temperature. After 15 min, the chloroform was removed by distillation at reduced pressure (∿ 25 mm) in a water bath at approximately 50°C. The solid residue on recrystallization from carbon tetrachloride gave 0.238 g (73%) of 143 (mp 136.5-138.5°C).

This same reaction was achieved by heating the N-oxide to 145°C for 16 h in a sealed tube and dissolved in a large excess of phosphorus trichloride.

Compound 143 showed:

HRMS: for $C_{13}H_{12}N_2O_5$; calcd. 276.0746; obs. 276.0726.

MS: m/z(RI%); 276(100), 230(15)[M^+-EtOH] and 150(25).

IR: ν_{max}; 1711(s)[C=0], 1608(s), 1567(m) and 1525(s) cm^{-1}.

^1H NMR: δ 1.41(t, 7 Hz, 3H, ester CH_3), 2.77(s, 3H, ring CH_3), 4.45(q, J = 7 Hz, 2H, ester CH_2) and 8.27-8.45(m, AA'BB', 4H, aromatic).

^{13}C NMR: (in dimethyl sulfoxide-d_6) as summarized in Figure 3.16.

Preparation of Methyl 2-Nitro-3-oxobutanoate, 171

Compound 171 was prepared by the method of Sifniades (132). The product was an oil, and found to co-exist in both ketonic and enolic forms, their ratio being approximately 3:2 as determined by ^1H NMR spectroscopy.

Compound 171 showed:

IR: ν_{max}; 3480(w), 2465(m), 1765(s), 1756(s), 1745(s), 1740(s), 1575(s), and 1565(s) cm^{-1}.

^1H NMR: (Ref. $CHCl_3$ - 7.26 ppm) Ketonic form; δ 2.40(s, 3H, CH_3CO), 3.91(s, 3H, ester CH_3) and 5.79(s, 1H, CH) Enolic form; δ 2.39(s, 3H, vinyl CH_3), 3.88(s, 3H, ester CH_3) and 12.15(broad s, 1H, OH).

^{13}C NMR as summarized in Figure 3.17.

Preparation of Methyl 2-(O-Methylacinitro)-3-oxobutanoate, 172

The action of diazomethane on nitro compounds was used as a method of nitronic ester preparation (133)

After 171 (2.3 g, 14 mmoles) was treated with excess etheral diazomethane for 30 min, the excess diazomethane and the ether were removed at room temperature and under reduced pressure (approximately 20 mm). This gave a quantitative yield (2.5 g) of 172 as an oil with both E and Z isomers present in a ratio of approximately 9:1 as determined by ^{13}C NMR spectroscopy. The major isomer was tentatively assigned the E geometry. On standing at room temperature for 1 week or on distillation, the product 172 decomposed to methyl 2-hydroxyimino-3-oxobutanoate 173.

Compound 172 showed:

IR: ν_{max}; 2964(m), 1755(s)[ester C=0], 1730(s, shoulder) [ketone C=0], 1675(m)[C=N], 1605 cm^{-1}.

^1H NMR: (reference $CHCl_3$ - 7.26 ppm) δ 2.52(s, 3H, CH_3CO), 3.85(s, 3H, carboxylic ester*) and 3.89(s, 3H, nitronic ester*).

*these assignments may be reversed.

^{13}C NMR: as summarized in Figure 3.17.

Preparation of Methyl 2-Hydroxyimino-3-oxobutanoate, 173

Thermal decomposition of nitronic esters to the corresponding oxime and aldehyde is established in the literature (108).

Compound 172 (above) (172 mg, 0.98 mmoles) was left standing at room temperature for 1 week. The resulting mixture 173 and formaldehyde (presence ascertained by ^1H NMR spectroscopy) was distilled in a Kugelrohr apparatus at 0.5 mm and 80°C

giving 78 mg (55%) of pure 173 as an oil (lit. bp at 0.15 mm, 82-6°C (109)).

Compound 173 showed:

MS: m/z(RI%); 145(15), 54(10), 43(100) and 28(20).

IR: ν_{max}; 3030(s), 1748(s)[ester C=0], 1703(s)[ketone C=0], 1697(s)[C=N], 1630(m).

^{1}H NMR: (ref $CHCL_3$ - 7.26 ppm) δ 2.40(s, 3H, CH_3CO) and 3.88(s, 3H, ester CH_3).

^{13}C NMR: as summarized in Figure 3.17.

Preparation of Methyl 2-Methoxyimino-3-oxobutanoate, 174

Treatment of the oxime 173 (105 mg, 0.80 mmoles) with excess etheral diazomethane gave a quantitative yield (130 mg) of 174 after removal of ether and excess diazomethane by flushing with nitrogen.

Compound 174 showed:

IR; ν_{max}; 2960(m), 1755(s)[ester C=0], 1700(s, shoulder) [ketone C=0] and 1696(s)[C=N] cm^{-1}.

^{1}H NMR: δ 2.39(s, 3H, CH_3CO), 3.85(s, 3H, ester OCH_3) and 4.08(s, 3H, $NOCH_3$).

^{13}C NMR: as summarized in Figure 3.17.

Preparation of Methyl 2-[(E and Z)-Methoxymethylene]-3-oxobutanoate, 36

The procedure used was that of L. Claisen (110). Into a flask was placed 5.8 g (5.4 mL, 50 mmoles) methyl acetoacetate, 5.3 g (5.5 mL, 50 mmoles) trimethyl orthoformate and 10.2 g (9.4 mL, 100 mmoles) of acetic anhydride. The mixture was refluxed for 24 h, and the bulk of the lower boiling components

was removed by rotoevaporator and the remainder distilled. The fraction boiling at 124-6°C and 20 mm Hg was collected (lit. 80-4° at 0.15 mm (66), 150° at 16 mm (110)). The resulting 3.5 g of 36 (44% yield) solidified after a few days in a refrigerator (mp 51-55°C). Both E and Z isomers were observed and the approximate ratio of these isomers as 2:1 was determined by ^{1}H NMR spectroscopy. The major isomer was assigned the E isomer.

MS: m/z(RI%); 158(15), 143(75), 85(70), 75(100) and 43(95).

IR: ν_{max}; 2980, 1715, 1685, 1657, 1634, 1620 and 1595 cm^{-1}.

^{1}H NMR: E (ref. $CHCl_3$); δ 2.28(s, 3H, CH_3CO), 3.75(s, 3H, ester CH_3), 3.96(s, 3H, vinyl OCH_3) and 7.53(s, 1H, vinyl). Z(ref. $CHCl_3$); δ 2.36(s, 3H, CH_3CO), 3.69(s, 3H, ester CH_3), 3.96(s, 3H, vinyl OCH_3) and 7.52(s, 1H, vinyl).

^{13}C NMR: as summarized in Figure 4.1.

Synthesis of Methyl 2-[(E and Z)-Chloromethylene]-3-oxobutanoate, 37

The preparation of the copper salt 176 (R = OCH_3) was based on that of L. Claisen (110) with some modification.

To a stirred hot solution (∿ 90°C) of 7.50 g (37 mmoles) of cupric acetate monohydrate in 50 mL water was added dropwise 11.5 g (73 mmoles) of 36. After addition, the solution was allowed to cool to room temperature and then cooled to 0°C. The resultant blue precipitate of 176 (R = OCH_3) was collected by filtration, rinsed with cold water, then a small amount of

acetone and dried under vacuum (yield; 12.2 g, 96%).

Without further purification, 12.2 g (36 mmoles) of compound 176 were added to 30 mL thionyl chloride. After 30 min of stirring the solution was filtered and the precipitate washed with ether. Thionyl chloride and ether were removed from the combined filtrates (rotoevaporator) leaving 8.97 g crude 37 (75% from 36). Although this crude product was > 95% pure by ^{1}H NMR spectroscopy, it was distilled before further use to give 4.79 g 37 (bp 115°C, 40 mm), 40% from 36 (loss due to polymerization - a lower distilling pressure is recommended). Both E and Z isomers were observed by ^{1}H and ^{13}C NMR spectroscopies and the ratio was approximately 1:1 as ascertained by ^{1}H NMR.

Compound 37 showed:

Density: 1.24 g/ml.

HRMS: for $C_6H_7O_3Cl$; calcd. 162.0084; obs. 162.0099.

MS: m/z(RI%); 164(15), 162(65), 149(35), 147(100)[M^+-CH_3], 133(10), 132(5), 131(40)[M^+-OCH_3], 130(20), 91(10), 89(45), 79(15), 59(40), 53(50).

IR: ν_{max}; 2960(w), 1743(s), [ester C=0] 1728(s)[ketone C=0] and 1688(s) cm^{-1}.

^{1}H NMR: E; δ 2.35(s, 3H, CH_3CO), 3.91(s, 3H, ester CH_3), 7.45(s, 1H, vinyl).

Z; δ 2.45(s, 3H, CH_3CO), 3.82(s, 3H, ester CH_3) and 7.42(s, 1H, vinyl).

^{13}C NMR: as summarized in Figure 4.1.

Synthesis of 3-(Chloromethylene)-2,4-pentanedione, 38

The synthesis of 38 from 3-(methoxymethylene)-2,4-pentanedione, 175 (66,110), via the known cupric salt 176 (R = CH_3) (110,134) followed the same procedure as given above for the preparation of 37 from 36.

From 1.51 g (10.6 mmoles), 175, 1.42 g (4.47 mmoles) of copper salt was obtained (84% yield). From 139 mg (0.438 mmoles) cupric salt, 104 mg crude 38 was obtained. This, upon Kugelrohr distillation at 70°C (4 mm) provided 63 mg pure 38 (41% yield from 175). The product polymerized rapidly on standing (even at -4°C) and was prepared immediately prior to use. Compound 38 showed:

Density: 1.23 g/ml.

IR: ν_{max}; 3085(m), 2930(w), 1725(s)[C=0], 1679(s) and 1600(s) cm^{-1}.

^1H NMR: δ 2.28(s, 3H, CH_3CO), 2.38(s, 3H, CH_3CO) and 7.30(s, 1H, vinyl).

^{13}C NMR: as summarized in Figure 4.1.

Preparation of Ethyl 2-(Phenylthio)propenoate (41)

This preparation was based on the procedure outlined by Leyendecker and Comte (69). Compound 41 has also been prepared by Pummerer rearrangement (135).

A solution of triethylamine (3.40 g, 4.67 mL, 33.6 mmoles), freshly distilled ethyl 2-bromopropanoate (3.71 g, 33.6 mmoles) and thiophenol (6.09 g, 33.6 mmoles) in 50 mL of diethyl ether was refluxed for 7 h. The voluminous precipitate was filtered and the ether removed from the filtrate by vacuum

distillation. The residue was purified by bulb-to-bulb distillation at 120°C and 0.1 mm giving 6.08 g (86%) of ethyl 2-(phenylthio)propanoate.

To ethyl 2-(phenylthio)propanoate (0.584 g, 2.78 mmoles) in 10 mL of dichloromethane at 0°C was added dropwise freshly distilled sulfuryl chloride (0.375 g, 0.225 mL, 2.78 mmoles). After the volatiles were removed by vacuum distillation, the only product observed by ^{1}H NMR spectroscopy was ethyl 2-chloro-2-(phenylthio)propanoate which was used directly without further purification for pyrolysis.

Pyrolysis was achieved by rapid bulb-to-bulb distillation at 290°C and 40 mm giving 0.470 g (81% from ethyl 2-(phenylthio)propanoate) of 41 as a colourless oil. The distillation rate and pressure were found to be crucial for successful pyrolysis. Higher pressures and slower distillation rates were found to give decomposition products while lower pressures gave incomplete pyrolysis.

Compound 41 showed:

^{1}H NMR: 1.27(t, J = 7 Hz, 3H, CH_3), 4.25(q, J = 7 Hz, 2H, ethyl CH_2), 5.28(s, 1H, vinyl), 6.33(s, 1H, vinyl) and 7.26-7.63(m, 5H, aromatic).

^{13}C NMR: as summarized in Figure 4.1.

Preparation of Ethyl 2-(Phenylsulfinyl)propenoate (42)

This preparation is based on the procedure outlined by Leyendecker and Comte (69).

In 10 mL of dichloromethane was dissolved 0.413 g (1.99 mmoles) of 41. The solution was stirred and cooled in an ice bath while 99% m-chloroperbenzoic acid (0.343 g, 1.99 mmoles) (136) in 20 mL of dichloromethane was added dropwise. The solution was left in a refrigerator (-2°C) overnight and then extracted twice with saturated aqueous sodium bicarbonate solution. The dichloromethane solution was dried over anhydrous sodium sulfate, the solvent removed by vacuum distillation and the residue purified by bulb-to-bulb distillation (170-180°C, 0.2 mm) giving 0.354 g (77%) as a colourless oil.

Compound 42 showed:

IR: ν_{max}; 1718(s)[C=O] and 1618(m)[C=C] cm^{-1}

^1H NMR: δ 1.18(t, J = 7 Hz, 3H, CH_3), 4.17(q, J = 7 Hz, 2H, ethyl CH_2), 6.80(s, 1H, vinyl), 6.88(s, 1H, vinyl), 7.40-7.60(m, 3H, aromatic) and 7.68-7.88(m, 2H, aromatic).

^{13}C NMR: (DMSO-d_6, ref. DMSO-d_6 39.5 ppm) as summarized in Figure 4.1.

Anion Formation of the Alkoxyethylideneoxazolones 44, 45 and 47 and the thiazolone 49

Anions of 44, 45, 47 and 49 were prepared by the addition of these compounds (dissolved in tetrahydrofuran) to a stirred LDA (1.0 to 1.5 equiv) solution at -78°C, under argon.

Evidence of complete anion formation of (Z)-45 was provided by quenching experiments with both 5% sodium dideuterium phosphate in deuterium oxide (deuterium incorporation observed by a reduction in the integral of the methyl signal in the ^{1}H NMR spectrum), and t-butyldimethylsilyl chloride (giving the corresponding ketene acetal 178, see below).

Compound (Z)-46 was not stable to anion formation. On additions of (Z)-46 to the LDA solution, a dark brown colour was immediately observed and no starting material was observed after standard anion quenching and work-up.

Preparation of 5-(t-Butyldimethylsiloxy)-4-(1-methoxyethenyl)-2-phenyloxazole, 178

To a stirred solution of 1.0 equiv (52 μmoles) LDA at -78°C and under argon, was added dropwise 12 mg (52 μmoles) of (Z)-45 in 0.5 mL of dry tetrahydrofuran. Twenty minutes following the addition, 16 mg (0.10 mmoles) of t-butyldimethylsilyl chloride was added in 0.5 mL of tetrahydrofuran. This mixture was allowed to warm to 0°C and the solvent removed by evaquation at 0.2 mm, initially at 0°C, then at room temperature for 15 min. The crude residue was dissolved in dry deuteriochloroform and its ^{1}H NMR spectrum recorded. Yield of 178, 95%, as judged from its ^{1}H NMR spectrum (with approximately 5% starting material present).

Compound 178 showed:

^{1}H NMR: δ 0.10(s, 6H, gem dimethyl), 1.02(s, 9H, t-butyl), 3.71(s, 3H, OCH_3), 4.23(d, J = 2.5 Hz, 1H, vinyl), 4.72(d, J = 2.5 Hz, 1H, vinyl), 7.38-7.53(m, 3H, aromatic), and 7.88-8.05(m, 3H, aromatic).

Preparation of 4-[(Z-2E-4Z)-4-Carbomethoxy-5-hydroxy-1-methoxy-2,4-hexadienylidene]-2-phenyl-5-oxazolone, 181

The anion of 37.2 mg (0.161 mmoles) of (Z)-45 was prepared with 1.0 equiv of LDA as described above. To this stirred solution, at -78°C under argon, was added, 22 μL (28 mg, 0.17 mmoles) of 37 all at once. The solution was left to stir for 20 min and then allowed to warm to room temperature and solvent removed under vacuum (0.5 mm) giving a residue of 75 mg of crude oil (181). An attempt to purify 181 by preparative TLC, led to the cyclized material 196.

Crude compound 181 showed:

^{1}H NMR: δ 2.35(s, 3H, vinyl CH_3), 3.95(s, 3H, ester), 4.52(s, 3H, vinyl OCH_3), 7.39-7.64(m, 4H, aromatic and one vinyl H), 7.83(d, J = 15 Hz, 1H, vinyl) and 7.92-8.18 (m, 2H, aromatic).

Preparation of 4-[(Z-2E-4Z)-4-Carbomethoxy-1-ethoxy-5-hydroxy-2,4-hexadienylidene]-2-phenyl-5-oxazolone, 182

Method A: From 4-[(Z)-1-ethoxyethylidene]-2-phenyl-5-oxazolone, (Z)-44

The anion of (Z)-44 (28 mg, 0.119 mmoles) was prepared in the same manner as the anions in the previous experiments, with 1.1 equiv of LDA solution. To this stirred solution at -78°C under argon was added 18 μL (22.2 mg 0.13 mmoles) of 37

all at once. The solution was left to stir for 20 min after which the reaction flask was allowed to warm to room temperature. Solvent was removed under vacuum (at room temperature) and the residue dissolved in chloroform and extracted with pH 7 phosphate buffer solution. The chloroform layer was dried with anhydrous sodium sulfate and the chloroform removed by roto-evaporator distillation. This residue (41 mg) was purified by column chromatography (silica gel; 15% ethyl acetate in petroleum ether eluant), yielding 17 mg (40%) of pure 182 as yellow crystals from ethyl acetate-petroleum ether, mp 153.0-154.0°C. Compound 182 showed:

MS: m/z(RI%); 357(5), 325(5)[M^+-CH_3OH], 311(5), 105(100) and 77(15).

HRMS: for $C_{19}H_{19}NO_6$; calcd. 357.1212; obs. 357.1180.

IR: ν_{max}; 1759(s)[C=O], 1631(s)[C=N], 1607(s), 1594(S), 1579(s) and 1542(s) cm^{-1}.

^1H NMR: (250 MHz) δ 1.48(t, J = 7 Hz, 3H, ethyl CH_3), 2.34(s, 3H, vinyl CH_3), 3.95(s, 3H, ester), 4.95(q, J = 7 Hz, 2H, ethyl CH_2), 7.37(d, J = 15 Hz, 1H, vinyl), 7.40-7.54 (m, 3H, aromatic), 7.86(d, J = 15 Hz, 1H, vinyl), 7.95-8.03(m, 2H, aromatic) and 14.06(broad s, 1H, OH).

Method B: From 4-[(E)-1-ethoxyethylidene]-2-phenyl-5-oxazolone, (E)-44

To a solution of the anion of (E)-44 (prepared in the usual manner from 126 mg, 0.545 mmoles of (E)-44 and 1.1 equivalents of LDA solution) cooled in a dry ice/acetone slush bath and under argon, was added 0.141 mL (178 mg, 1.1 mmoles) of

acceptor 37 all at once. The mixture was allowed to warm to 0°C, quenched with 5% aqueous sodium dihydrogen phosphate solution and extracted with methylene chloride. The methylene chloride layer was dried over anhydrous sodium sulfate and removed by vacuum distillation. The semisolid was purified by flash column chromatography with 15% ethyl acetate in petroleum ether as eluant yielding 45 mg (23%) of 182 (mp undepressed from the product prepared by the (Z)-44 route).

Preparation of 4-[(Z-2E-4Z)-4-Carbomethoxy-1-ethoxy-5-hydroxy-2,4-hexadienylidene]-2-(1,1-dimethylethyl)-5-oxazolone (183)

To a solution of the anion of (Z)-47 (prepared in the usual manner from 0.132 g, 0.629 mmoles of (Z)-47 and 1.1 equiv of LDA solution) cooled in a dry ice/acetone slush bath, was added rapidly acceptor 37 (0.165 mL, 204 mg, 1.26 mmoles). The reaction mixture was allowed to warm to 0°C and quenched with 5% aqueous sodium dihydrogen phosphate and extracted with dichloromethane. The dichloromethane layer was dried over anhydrous sodium sulfate, filtered and the solvent removed by vacuum distillation and evacuation. The crude was purified by flash column chromatography (10% ethyl acetate in petroleum ether as eluant) giving 101.2 mg (55%) of 183 as a yellow crystalline mass, mp 90-2°C (after evacuation overnight).

Compound 183 showed:

MS: m/z(RI%); 337(3)[M^+], 305(5)[M^+-CH_3OH], 295(4)[$M^+-C_2H_2O$], 291(4)[M^+-EtOH], 277(5), 235(8), 179(5), 165(6), 95(4), 85(6), 56(4) and 57(100)[$t\text{-}Bu^+$].

HRMS: for $C_{17}H_{23}NO_6$; calcd. 337.1525; obs. 337.1533

IR: ν_{max}; 1750(s)[both CO's], 1635(s)[C=N], 1618(m), 1586(s) and 1560(s) cm^{-1}.

^1H NMR: (see Figure 5.3) δ 1.25(s, 9H, t-butyl), 1.37(t, J = 7 Hz, 3H, ethyl CH_3), 2.26(s, 3H, vinyl CH_3), 3.88(s, 3H, ester CH_3), 4.78(q, J = 7 Hz, 2H, ethyl CH_2), 7.30(d, J = 16 Hz, 1H, vinyl), 7.78(d, J = 16 Hz, 1H, vinyl H) and 13.95(s, 1H, OH).

^{13}C NMR: as summarized in Figure 5.4.

Preparation of 2-Benzylthio-4-[(Z-2E-4Z)-4-carbomethoxy-1-ethoxy-5-hydroxy-2,4-hexadienylidene]-5-thiazolone (184)

To 3.0 equiv (0.378 mmoles) of a stirred solution of LDA (at -78°C under argon) was added dropwise 36.9 mg (0.126 mmoles) of (Z)-48 in 0.8 mL of tetrahydrofuran. Ten min after this addition, excess LDA was back titrated by the addition of 13 μL (13.6 mg, 0.23 mmoles) of acetic acid. Vigorous stirring was continued while 25 μL (31 mg, 0.19 mmoles) of 37 was added all at once. The solution was left to stir for 1 h at -78°C. The reaction mixture was quenched with 5% aqueous sodium dihydrogen phosphate solution, extracted twice with chloroform, the chloroform layer dried over anhydrous sodium sulfate and the chloroform removed by distillation at reduced pressure. The residual oil, when triturated with n-pentane, gave 16 mg (30%) of 184 as a red solid. This solid, although > 95% pure by ^1H NMR spectroscopy could not be recrystallized without substantial decomposition to 196.

Compound 184 showed:

MS: m/z(RI%); 419(2), 373(80)[M^+-EtOH], 340(25), 282(50), 254(60), 178(30) and 91(100).

^{1}H NMR: δ 1.35(t, J=7 Hz, 3H, ethyl ether CH_3), 2.30(s, 3H, vinyl CH_3), 3.92(s, 3H, methyl ester), 4.45(s, 2H, benzyl CH_2), 4.61(q, J=7 Hz, 2H, ethyl ether CH_2), 7.24-7.46(m, 5H, aromatic), 7.43(d, J=16 Hz, 1H, vinyl) and 7.78(d, J=16 Hz, 1H, vinyl).

Preparation of 4-[(Z-2E-4Z)-4-Carbomethoxy-1-ethoxy-5-hydroxy-2,4-hexadienylidene]-2-ethoxy-5-thiazolone (185)

The thiazolone (Z)-49 (37.4 g, 0.174 mmoles) in 0.5 mL of tetrahydrofuran was added dropwise to a stirred and cooled (dry ice/acetone slush bath) LDA solution (1.3 equiv prepared in the usual way). Ten minutes following this addition, 55 μL (69 mg, 0.422 mmoles) of 37 were added dropwise. The mixture was allowed to warm to room temperature when the reaction was quenched with 5% aqueous sodium dihydrogen phosphate solution and extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate and the solvent removed by vacuum distillation. The crude product was purified by flash column chromatography (eluting with 12% ethyl acetate in petroleum ether) to give 21.9 mg of 185 (approximately 95% pure, containing ∿ 5% (Z)-49 as determined by ^{1}H NMR spectroscopy). This, after recrystallization from petroleum ether, gave 16.6 mg (28%) of pure 185 as yellow needles (mp 101-3°C).

Compound 185 showed:

MS: m/Z(RI%); 341(25)[M^+], 295(100)[M^+-EtOH], 266(35), 238(40), 226(35), 206(35); 178(90)[$C_9H_8NO_3^+$], 164(20), 137(40), 122(30), 95(50) and 59(20).

HRMS: for $C_{15}H_{19}NO_6S$; calcd. 341.0933; obs. 341.0985.

IR: ν_{max}; 1660(s)[C=O], 1612(s)[C=N], 1595(s)[C=C] and 1573(s)[C=C] cm^{-1}.

TLC: (15% ethyl acetate in pet. ether) R_f - 0.79.

^1H NMR: 1.38 and 1.40(t, J=7 Hz, 3H and 3H, ethyl CH_3's), 2.28(s, 3H, vinyl CH_3), 3.90(s, 3H, ester CH_3), 4.45(q, J=7 Hz, 2H, 2-ethoxy CH_2), 4.57(q, J=7 Hz, 2H, vinyl ethoxy CH_2), 7.32(d, J=16 Hz, 1H, vinyl H), 7.70(d, J=16 Hz, 1H, vinyl H) and 12.94(s, 1H, OH).

Preparation of 4-(5-Acetyl-6-methyl-2-pyranylidene)-2-phenyl-5-oxazolone (192) via 4-[(Z-2E-4Z)-4-Acetyl-1-ethoxy-5-hydroxy-2,4-hexadienylidene]-2-phenyl-5-oxazolone (189)

A solution of the anion of (Z)-44 was prepared in the usual way from 99 mg (0.428 mmoles) of (Z)-44 and 1.1 equiv of LDA solution. To this stirred and cooled (dry ice/acetone slush bath) solution was added dropwise 0.1 mL (0.12 g, 0.82 mmoles) of 38 (prepared and distilled immediately before use). Ten minutes following addition, the solution was allowed to warm to room temperature and was quenched with 5% aqueous sodium dihydrogen phosphate. The mixture was extracted with chloroform, the chloroform layer dried over anhydrous sodium sulfate, filtered and the solvent removed by vacuum distillation. Flash column chromatography gave a 2:1 mixture of starting material 44

to product 189 (as indicated by TLC and ^{1}H NMR spectroscopy). This mixture without separation, was dissolved in 5 mL chloroform with 100 mg of silica gel (chromatography grade, 0.063 to 0.200 mm particle size) and 0.1 mL of trifluoroacetic acid. After 2 days, the solution was filtered, the solid washed with acetone and the solvent removed by vacuum distillation from the combined filtrates. Recrystallization of the residue from absolute ethanol gave 19.4 mg (15%) of 192 (red crystals, mp 212-5°C on rapid heating, decomposes ∿ 210°C on slower heating). One isomer only was observed of unassigned geometry.

Compound 192 showed:

MS: m/Z(RI%); 295(25)[M^+], 105(100)[$C_6H_5CO^+$] and 77(35)[$C_6H_5^+$].

HRMS: for $C_{17}H_{23}NO_6$; calcd. 295.0844; obs. 295.0487.

IR: ν_{max}; 1774(m), 1764(m), 1746(s)[ring C=0], 1693(s)[ketone C=0], 1633(s)[C=N], 1598(s)[C=C], 1590(m) and 1582(m) cm^{-1}.

^{1}H NMR: (CD_2Cl_2, ref. TMS) δ 2.45(s, 3H, $COCH_3$), 2.69(s, 3H, pyranyl CH_3), 7.35(d, J=10 Hz, 1H, pyranyl H), 7.47-7.60(m, 3H, aromatic), 7.75(d, J=10 Hz, 1H, pyranyl H) and 7.98-8.13(m, 2H, aromatic).

Compound 189 showed:

^{1}H NMR: 1.50(t, J=7 Hz, 3H, ethyl CH_3), 2.36(s, 6H, β-diketonic CH_3's) 4.98(q, J=7 Hz, 2H, ethyl CH_2) and 17.6(s, 1H, OH).

For compound 189, the vinyl protons were obscured in the aromatic region. Thus the Z assigned geometry of the 2-hexadienylidene double bond is based on analogy to other prepared compounds rather than by the magnitude of observed coupling constants.

Preparation of 4-[(Z)-4-Carbomethoxy-1-ethoxy-3-methoxy-5-oxohexylidene]-2-phenyl-5-oxazolone, (Z)-190

The oxazolone (Z)-44 (52 mg, 0.225 mmoles) dissolved in 0.8 mL tetrahydrofuran was added dropwise to a stirred solution of 1.2 equiv of LDA in tetrahydrofuran at -78°C under argon. Ten minutes following this addition, 71.0 mg (0.50 mmoles) of 36 in 0.5 mL of tetrahydrofuran was added to the stirred solution all at once. After 5 min, this solution was allowed to warm to room temperature and was quenched with pH 7 aqueous phosphate buffer and extracted with dichloromethane. The dichloromethane layer was dried over anhydrous sodium sulfate, filtered and the solvent removed at reduced pressure. This crude product was purified by flash column chromatography on silica gel (20% ethyl acetate-petroleum ether as eluant) giving 68.2 mg (78%) of (Z)-190 as an orange-red oil. Both diastereomers were prepared as indicated by ^{1}H and ^{13}C NMR spectroscopies in a 9:7 ratio (as indicated by ^{1}H NMR spectroscopy).
Compound (Z)-190 showed:

MS: m/z(RI%); 389(0.2)[M^+], 357(2)[M^+-CH_3OH], 311(10)[M^+-EtOH], 273(15), 117(30), 105(100)[$C_6H_5CO^+$] and 77(35)[$C_6H_5^+$].

TLC: (20% ethyl acetate-petroleum ether) R_f - 0.18 (one spot only).

IR: ν_{max}; 1787(s)[ring C=O], 1752(s)[ester C=O], 1720(s)[ketone CO], 1641(s)[C=N], 1602(m)[aromatic C=C] and 1587[exocyclic C=C] cm^{-1}.

^1H NMR: (see Figure 5.5) δ 1.43(t, J=7 Hz, 3H, ethyl CH_3), 2.25(s, 3H, minor $COCH_3$), 2.28(s, 3H, major $COCH_3$), 3.25(m, 2H, vinylic CH_2), 3.36(s, 3H, major ethereal CH_3), 3.39(s, 3H, minor ethereal CH_3), 3.68(s, 3H, major ester CH_3), 3.74(s, 3H, minor ester CH_3), 3.85(d, J=7.5 Hz, 1H, minor acetoacetyl CH), 3.87(d, J=7 Hz, 1H, major acetoacetyl CH), 4.27(m, 1H, ethereal CH), 4.92(q, J=7 Hz, ethyl CH_2), 7.47(m, 3H, aromatic) and 7.98(m, 2H, aromatic).

^{13}C NMR: (acetone-d_6 - reference acetone-d_6 29.2 ppm) as summarized in Figure 5.6.

Attempted Coupling of (Z)-44 and 42

The anion of (Z)-44 was prepared in the usual manner, with 1.1 equiv of LDA solution. Dropwise addition of excess 42 dissolved in tetrahydrofuran and cooled by a dry ice jacketed syringe, to a solution of the anion of (Z)-44 cooled with a slush bath at -95°C gave only recovered (Z)-44 after standard work-up. Neither coupled product nor acceptor 42 were obtained. Other reaction attempts with bath temperatures of -78°C and room temperature gave the same results.

Preparation of 4-[(Z)-4-Carbethoxy-1-ethoxy-4-phenylthio-butylidene]-2-phenyl-5-oxazolone (191).

Yields of the following reaction varied from 0 to 35% (as estimated by the ratio of product 191 to starting material (Z)-44 observed by ^{1}H NMR spectroscopy in the crude reaction mixtures). The coupling reaction, as monitored by TLC did not initiate until the reaction temperature was above approximately 0°C. Neither careful purification of 41 by redistillation and/or flash column chromatography (4% ethyl acetate - petroleum ether as eluant) nor the use of cuprous iodide, zinc chloride and/or hexamethylphosphoric triamide in the anion solution alleviated the inconsistenty in yields. A typical reaction is as follows:

The anion was prepared in the usual manner with 87.5 mg (0.379 mmmoles) of (Z)-44 and 1.1 equiv of LDA solution. To this solution, cooled in a dry ice - acetone slush bath, was added, all at once, 118 mg (0.568 mmoles) of 41 in 0.8 mL tetrahydrofuran. The solution was allowed to warm to room temperature and remained at this temperature for 5 min before quenching with saturated aqueous ammonium chloride solution. The mixture was extracted twice with dichloromethane, the dichloromethane layer dried over anhydrous sodium sulfate and solvent removed at reduced pressure. Flash column chromatography (with 5% methanol in petroleum ether as eluant) gave 25 mg (15%) of 191 as a yellow oil contaminated with approximately 5% starting material 44 (as indicated by TLC and quan-

tified by ^{1}H NMR spectroscopy). Compound 191 showed:

MS: m/z(RI%); 439(1)[M^+], 356(4), 293(4), 244(30) [$M^+-C_6H_5SCHCOOEt$], 231(20), 135(10), 105(100) [$C_6H_5CO^+$] and 77(35)[$C_6H_5^+$].

HRMS: for $C_{24}H_{25}NO_5S$; calcd. 439.1453; obs. 439.1449.

IR: ν_{max}; 1787(s) and 1758(s)[ring C=O], 1732(s) ester [C=O], 1641(s)[C=N], 1601(m)[aromatic] and 1587(s) [exocyclic C=C] cm^{-1}.

TLC: (20% ethyl acetate - petroleum ether) R_f - .60, (10% acetone - petroleum ether) R_f - .33, (5% methanol - petroleum ether) R_f - .23.

^{1}H NMR: δ 1.15(t, J=7 Hz, 3H, ester CH_3), 1.28(t, J=7 Hz, 3H, vinyl ethoxy CH_3), 2.13(m, 2H, alkyl CH_2), 3.05(broadened t, J=7 Hz, 2H, allylic), 3.69(t, J=7.5 Hz, 1H, CH), 4.08(q, J=7 Hz, 2H, ester CH_2), 4.86(q, J=7 Hz, 2H, vinyl ethoxy CH_2), 7.23-7.62(m, 8H, aromatic) and 7.90-8.10(m, 2H, aromatic).

Attempted Coupling of (Z)-44 with Methyl (Z)-3-Bromopropenoate, 39, and Methyl (E)-3-Chloropropenoate, 40

The lithio anion of (Z)-44 was prepared in the usual manner. When excess 39 (111,112) or 40 (57) was added and the temperature raised from -78°C to refluxing tetrahydrofuran, no identifiable coupling product was observed. At higher temperatures 39 or 40 was recovered, while at room temperature and below, (Z)-44 was also recovered.

Attempted Coupling of (Z)-48 with Methyl(Z)-3-Bromopropenoate, 39

The lithio anion of (Z)-48 was prepared in the usual manner. When excess 39 (111,112) was added and the temperature raised from -78°C to room temperature, no identifiable coupling product was observed. Above approximately 0°C, 39 and only small amounts of 48 could be recovered while at lower temperatures both starting materials were recovered.

Dianion Formation of 131

To a stirred solution of LDA (0.15 mmoles, 4 mole equiv), at -78°C and under argon, were added dropwise 7.8 mg (38 μmoles) of 131 in 0.1 mL dry tetrahydrofuran. The solution was warmed to -35°C for 100 min (at higher temperatures, competition arose between dianion formation and decomposition).

To quantify the yield of the dilithio dianion, the solution prepared above was quenched by the addition of 3 mL of 5% sodium dideuterium phosphate in deuterium oxide. This solution was extracted twice with dichloromethane, the dichloromethane layer dried over anhydrous sodium sulfate and filtered. Acetic acid (3 mL) was added to the dichloromethane solution and the solvents were removed by rotoevaporator and then evacuated (0.5 mm, 1h). The resultant sample of 131-d_1 was examined by mass spectrometry. The dianion formation of 131 was approximately 80% as evidenced by the intensity of the M+1 peak observed in the MS.

Preparation of 2-(2-Carbomethoxyvinylthio)-4-(1-ethoxyethylidene)-5-thiazolone, 195

A solution of the dianion (from 20.5 mg, 0.101 mmoles of 131), prepared as above, was cooled to -78° and 20.6 µL (33.3 mg, 0.202 mmoles) of methyl (Z)-3-bromopropenoate (39) (111, 112) were added dropwise with stirring. This solution was warmed to -35°C for 30 min and then quenched with 5% sodium dihydrogen phosphate solution, extracted with dichloromethane, the dichloromethane layer dried over anhydrous sodium sulfate and the solvent removed by rotoevaporator and finally under vacuum (0.5 mm) overnight. This provided a semi-solid residue of 25 mg of 195 (78%, approximately 90% pure by ^{1}H NMR spectroscopy). the product was not further purified. A mixture of E and Z isomers was observed by ^{1}H NMR spectroscopy and their ratios were approximately 2:2:1 for [exo-Z-thio-Z]: [exo-Z-thio-E]: [exo-E-thio-Z] (where 'exo' refers to the exocyclic double bond and thio refers to the vinylthio side chain).

Compound 195 showed:

MS: m/z(RI%); 287(45), 228(75), 200(100), 142(40), 114(55) and 59(65).

HRMS: for $C_{11}H_{13}NO_4S_2$; calcd. 287.0245; obs. 287.0294.

^{1}H NMR: exo-Z-thio-Z; δ 1.44(t, J=7 Hz, 3H, ethyl CH_3), 2.47(s, 3H, vinyl CH_3), 3.78(s, 3H, ester), 4.66(q, J=7 Hz, 2H, ethyl CH_2), 6.09(d, J=11 Hz, 1H, vinyl) and 8.10(d, J=11 Hz, 1H, vinyl).

exo-Z-thio-E; δ 1.44(t, J=7 Hz, 3H, ethyl CH_3), 2.49(s, 3H, vinyl CH_3), 3.80(s, 3H, ester), 4.58(q, J=7 Hz, 2H, ethyl CH_2), 6.18(d, J=15 Hz, 1H, vinyl

and 8.27(d, J=15 Hz, 1H, vinyl).

exo-E-thio-Z; δ 1.44(t, J=7 Hz, 3H, ethyl CH_3), 2.59(s, 3H, vinyl CH_3), 3.78(s, 3H, ester), 4.31 (q, J=7 Hz, 2H, ethyl CH_2), 6.09(d, J=10 Hz, 1H, vinyl) and 8.13(d, J=10 Hz, 1H, vinyl).

Preparation of 4-(5-Carbomethoxy-6-methyl-2-pyranylidene)-2-phenyl-5-oxazolone, 193, from 181

Compound 181 (40.1 mg of crude, as prepared above) was dissolved in a small quantity of tetrahydrofuran and placed on a preparative TLC plate (silica gel) and developed with chloroform. The resulting broad orange band of silica gel was removed from the glass plate and extracted with acetone until colourless. The acetone was distilled under reduced pressure (rotoevaporator) and the solid residue recrystallized from 95% ethanol yielding 6.7 mg (25% from 45) of 193 (mp=222-4°C) as bright red needles. Compound 193 showed:

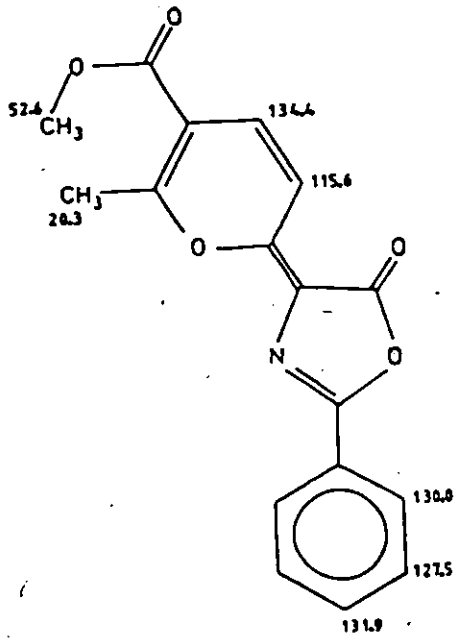
MS: m/z(RI%); 311(10), 266(25), 254(50) and 151(100).

HRMS: for $C_{17}H_{13}NO_5$; calcd. 311.0793; obs. 311.0773.

IR: ν_{max}; 1769(s) and 1739(s)[ring C=0], 1724(s)[ester C=0], 1640(s)[C=N], 1598(m), 1582(s) and 1540(s) cm^{-1}.

^1H NMR: (ref. $CHCl_3$); δ 2.78(s, 3H, pyranyl CH_3), 3.83(s, 3H, ester), 7.37(d, J=9 Hz, 1H, pyranyl C-3 H), 7.37-7.64 (m, 3H, aromatic), 7.71(d, J=9 Hz, 1H, pyranyl C-4H) and 7.96-8.15(m, 3H, aromatic).

^{13}C NMR: (ref. $CDCl_3$ 77.2 ppm) as summarized below (the quaternary resonances recorded from this sample were within the noise level and too weak for definitive assignment):



Cyclization of 182 to 4-(5-Carbomethoxy-6-methyl-2-pyranylidene)-2-phenyl-5-oxazolone, 193

Compound 182 (7.0 mg, 20 mmoles) and toluenesulfonic acid (3 mg, 16 mmoles) were dissolved in benzene and refluxed in a Dean-Stark apparatus. Following this, the benzene solution was extracted with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and the solvent removed by vacuum

distillation. The residue, after recrystallization from 95% ethanol, gave 3.7 mg (60%) of 193 identical with the product obtained from 45 (mixture melting point undepressed).

Preparation of 2-Benzylthio-4-[(E and Z)-5-carbomethoxy-6-methyl-2-pyranylidene]-5-thiazolone, 196

After refluxing 184 (16 mg, 38 mmoles) in absolute ethanol for 30 min, the solvent was removed under reduced pressure giving a quantitative yield of 196 (14 mg). Both isomers were present in a ratio of approximately 5:1 as determined by ^{1}H NMR spectroscopy. Recrystallization from acetone gave 10 mg (71%) of the major isomer (red needles mp 152-4°C). Compound 196 showed:

HRMS: for $C_{18}H_{15}NO_4S_2$; calcd. 373.0442; obs. 373.0443.

MS: m/z(RI%); 373(80), 340(25), 282(50), 254(60) and 91(100).

IR: ν_{max}; 1723(s)[ester C=0], 1662(s)[ring C=0], 1620(s), 1561(s), and 1549(s) cm^{-1}.

^{1}H NMR: major; δ 2.75(s, 3H, pyranyl CH_3), 3.87(s, 3H, ester), 4.48(s, 2H, benzyl CH_2), 7.30-7.55(m, 6H, benzyl aromatic, pyranyl C-3 H) and 7.80(d, J=10 Hz, 1H, pyranyl C-4 H).

minor: δ 2.69(s, 3H, pyranyl CH_3), 3.87(s, 3H, ester), 4.41(s, 2H, benzyl CH_2), 7.30-7.55(m, 6H, benzyl aromatic and pyranyl C-3 H) and 7.80(d, J=10 Hz, 1H, pyranyl C-4 H).

Preparation of 4-[(Z-2E-4Z)-4-Carbomethoxy-1-ethoxy-5-methoxy-2,4-hexadienylidene]-2-phenyl-5-oxazolone, 197

To 41 mg of crude 182, as prepared above, was added excess etheral diazomethane at room temperature. After 20 min, unreacted diazomethane was removed by passing a stream of nitrogen through the solution for 10 min. The remaining solvent was removed by rotoevaporator distillation. The resulting crude residue was purified by column chromatography (silica gel; 10% ethyl acetate in petroleum) to give 19 mg (42% yield from 44) of 197 as orange needles from absolute ethanol, mp 140.5-142.0°C .

MS: m/z(RI%); 371(60), 238(30), 178(10), 105(100) and 77(35).

HRMS: for $C_{20}H_{21}NO_6$; calcd. 371.1369; obs. 371.1362.

^1H NMR: δ 1.47(t, J=7 Hz, 3H, ester CH_3), 2.39(s, 3H, vinyl CH_3), 3.87(s, 3H, OCH_3), 3.91(s, 3H, OCH_3), 4.93(q, J=7 Hz, 2H, ester CH_2), 7.40-7.60(m, 3H, aromatic), 7.70(d, J=17 Hz, 1H, vinyl), 7.90(d, J=17 Hz, 1H, vinyl) and 7.93-8.20(m, 2H, aromatic).

Conversion of (Z)-190 to 182.

In 5 mL of toluene were dissolved 22 mg (57 μmoles) of (Z)-190. After refluxing this solution for 7 h, the solvent was removed by vacuum distillation and the solid residue recrystallized (from ethyl acetate - petroleum ether) giving 16 mg (80%)

of 182 (mixture mp undepressed from the sample of 182 obtained by the previous route).

Conversion of (Z)-190 to 193

One drop of trifluoroacetic acid and 9 mg (23 μmoles) of (Z)-190 were dissolved in 0.8 mL of deuteriochloroform. After one month, 6.2 mg (86%) of 193 was collected which crystallized from the slowly evaporating solvent. The mixture mp was undepressed from the sample of 193 obtained by the previous route.

Photoirradiation of 182, 190 and 193

Photoirradiations were carried out, as before, with 300 nm fluorescent lighting on approximately 30 μmole scale. Samples were dissolved in 0.5 mL of $CDCl_3$ and placed in 5 mm NMR tubes and monitored by ^1H NMR spectroscopy. Photoisomerization was observed for 190 and 193 but not 182. The photostationary state of 190 was obtained after 20 h of irradiation and showed an E to Z ratio of 2 to 3. Compound 193 decomposed on long term irradiation, the ^1H NMR signals disappearing over a 12-24 h irradiation period.

Compound (E)-190 showed:

^1H NMR: δ 4.44(q, 2H, ethyl CH_2). Other signals were at approximately the same position as for the Z isomer.

The photoproduced isomer of 193 showed:

^1H NMR: δ 2.70(s, 3H, pyranyl CH_3). Other signals were at approximately the same position as for the other isomer.

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