THERMAL REARRANGEMENTS OF 3*H*-PYRAZOLES, 4*H*-PYRAZOLES, AND CYCLOPENTADIENES

By

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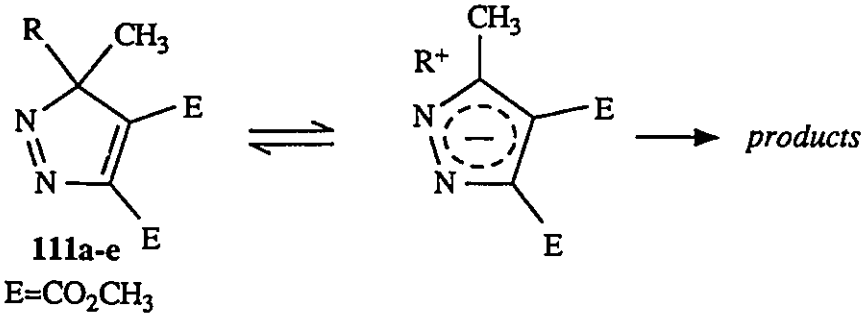
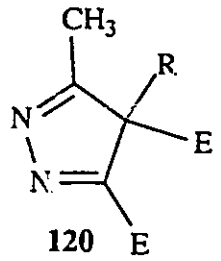
Abstract

3*H*-Pyrazoles generally undergo thermal rearrangement by concerted [1,5]-sigmatropic migrations. It has been discovered that 3*H*-pyrazoles **111a-e** undergo thermal rearrangement by an alternative mechanism. A stepwise, ion-pair, mechanism operates in these rearrangements in benzene/toluene, chloroform, and methanol solvents. This mechanism operates because the R substituents can form relatively stable cations. Large rate enhancements for these rearrangements combined with ion-pair trapping by methanol support this mechanism.



(**a**: R=$CHPh_2$; **b**: R=CH_2OMe; **c**: R=CMe_3; **d**: R=1-adamantyl; **e**: R=p-$CH_2C_6H_4OMe$)

Since 3*H*-pyrazoles **111b** and **111e** rearrange to afford 4*H*-pyrazoles **120b** and **120e**, respectively, the thermal rearrangements of these more stable isomers were investigated. Ion-pair trapping experiments with methanol suggest that these 4*H*-pyrazoles also rearrange by a stepwise mechanism and that different ion-pair intermediates are formed from these 4*H*-pyrazoles compared to the isomeric 3*H*-pyrazoles.



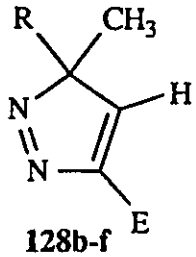
120 E

(**b**: R=CH_2OMe; **e**: R=p-$CH_2C_6H_4OMe$)

The sensitivity of the stepwise mechanism to the stabilization of the pyrazole nucleus was explored in the study of the thermal rearrangements of **128b-e**. Based on cation trapping experiments with methanol it appears that 3*H*-pyrazoles **128b-e** rearrange by a stepwise mechanism in methanol, but with "tighter" ion pair intermediates. A concerted mechanism, with some charge separation, seems to operate in the thermal rearrangement of **128f**.

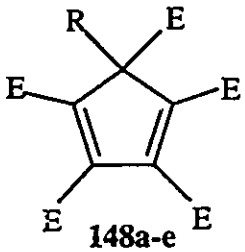
The generality of rearrangement by a stepwise mechanism was explored by studying the thermal rearrangements of cyclopentadienes **148a-e**. Cyclopentadienes **148a-d** undergo stepwise rearrangement in methanol solvent, based on ion-pair trapping experiments, while cyclopentadiene **148e** rearranges by concerted [1,5]-sigmatropic migrations of carbomethoxy.

This work has shown that thermal rearrangements, where a concerted sigmatropic mechanism can in theory operate, do not necessarily proceed by this mechanism. Furthermore, transition states for such rearrangements seem to run from those with little or no charge separation, through transition states with increasing charge separation, to the two-step, ion-pair extreme.



128b-f

b: R=CH_2OMe
c: R=CMe_3
d: R=1-adamantyl
e: R=p-$CH_2C_6H_4OMe$
f: R=$CH_2C_6H_5$



148a-e

a: R=$CHPh_2$
b: R=CH_2OMe
c: R=1-adamantyl
d: R=p-$CH_2C_6H_4OMe$
e: R=$CH_2C_6H_5$

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CHAPTER 1

Introduction

1.1 [1,5]-Sigmatropic Rearrangements in Cyclopentadienes

1.1.1 Sigmatropic rearrangements (general)

Reactions in which more than one bond is broken or formed can be divided into two classes. The first is one in which all the bond forming and breaking processes occur simultaneously so that a one-step transformation of reactants to products occurs without the intervention of an intermediate. Such reactions are called concerted since the bond changes occur in concert, at the same time, at more than one centre. The second broad class of reactions is one in which the bond forming and breaking processes occur consecutively so that one or more intermediates is involved. These intermediates may be stable molecules capable of isolation, or they may be reactive species of only transient existence (ie. ion pairs or radical pairs). When the intermediates are unstable the process is normally considered one reaction which proceeds in a stepwise manner.

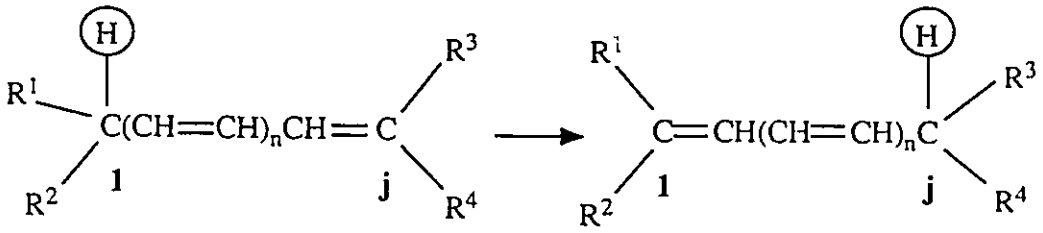
Sigmatropic rearrangements belong to a category of concerted reactions called pericyclic reactions. Other reactions falling in the pericyclic category include cycloaddition, electrocyclic, cheletropic, and group transfer processes. Pericyclic reactions are characterized by bonding changes which take place through the reorganization of

electron pairs within a closed loop of interacting orbitals. In order for a reaction to be classified as pericyclic, the bonds breaking and forming must do so simultaneously rather than in two or more steps. Not all bonding changes necessarily have to take place to the same extent at all stages along the reaction coordinate. It is possible for bond formation or cleavage at one site to run substantially ahead of bond formation or cleavage at another. Bond formation and breakage in a pericyclic reaction is therefore simultaneous, but not necessarily synchronous. The application of the fundamental principles of orbital symmetry theory, introduced by Woodward and Hoffmann[1] and since developed considerably by them[2-4] and others,[5-15] has provided much insight into these reactions.

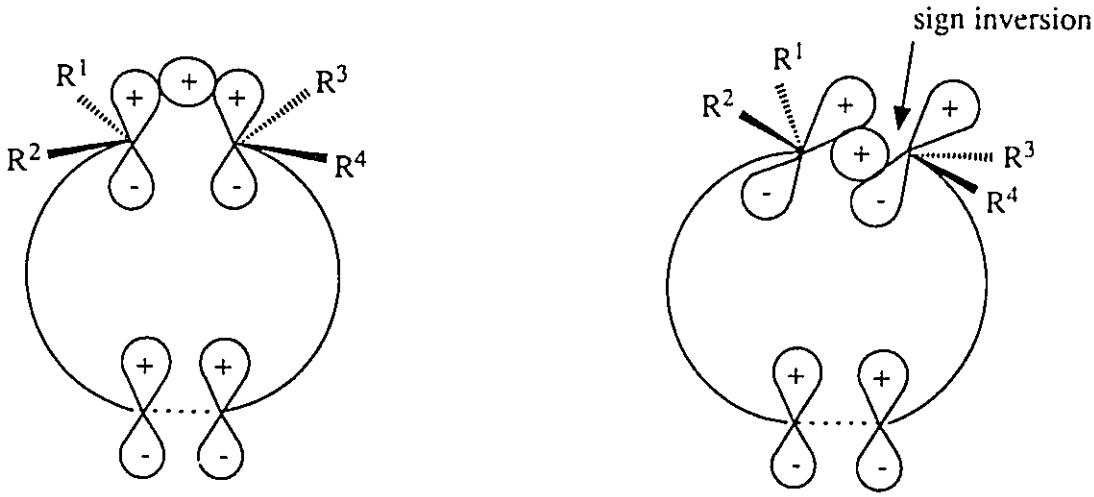
Sigmatropic reactions are concerted, uncatalysed bond migrations involving a transition state in which an atom or group is simultaneously joined to both termini of a π-electron system. Woodward and Hoffmann have given the name *sigmatropic rearrangements* to such reactions; the adjective "*sigmatropic*" indicating movement of a sigma bond. Several reviews have been published on sigmatropic reactions.[16-21]

A formal system of nomenclature is widely used for classifying sigmatropic rearrangements. This is characterized by square brackets containing two numbers; the first number is the position of the migration origin, the second number is the position of the migration terminus. For example, in a [1,j]-sigmatropic shift of hydrogen between the ends of a polyene, one end of the migrating σ bond remains fixed while the other end moves to the next atom or to a more remote position at the end of an adjacent π system (Scheme 1). The orbital on C-1 eventually becomes an sp^2-hybridized bonding orbital of the polyene while that on C-j becomes an sp^3-hybridized bonding orbital.

There are two stereochemically distinct ways in which overlap can take place in the transition state for a migrating hydrogen (atomic orbital representation, Figure 1). The spherically symmetrical hydrogen orbital can maintain contact at all times with the same face of the π system (*suprafacial* overlap) or move from one face of the π system to the other as the reaction takes place (*antarafacial* overlap). This requirement makes antarafacial [1,3]-hydrogen migration very difficult because transfer of hydrogen to the opposite face of the π system is required.



Scheme 1



suprafacial overlap *antarafacial overlap*

Figure 1

If the migrating group is capable of undergoing stereochemical inversion, then four distinct possibilities exist; both suprafacial or antarafacial routes exist, each of which occur with retention or inversion of configuration at the migrating centre. As an illustrative example of the former, Figure 2 demonstrates possible routes for suprafacial [1,3]-alkyl migration.[19] The use of the front face of the alkyl bonding orbital gives a transition state with no sign inversion while the use of the back face of the alkyl bonding orbital gives a transition state with a sign inversion. The stereochemical consequences of the two processes are distinct because the former process leads to retention of configuration of the migrating group while the latter process leads to inversion of configuration of the migrating group.

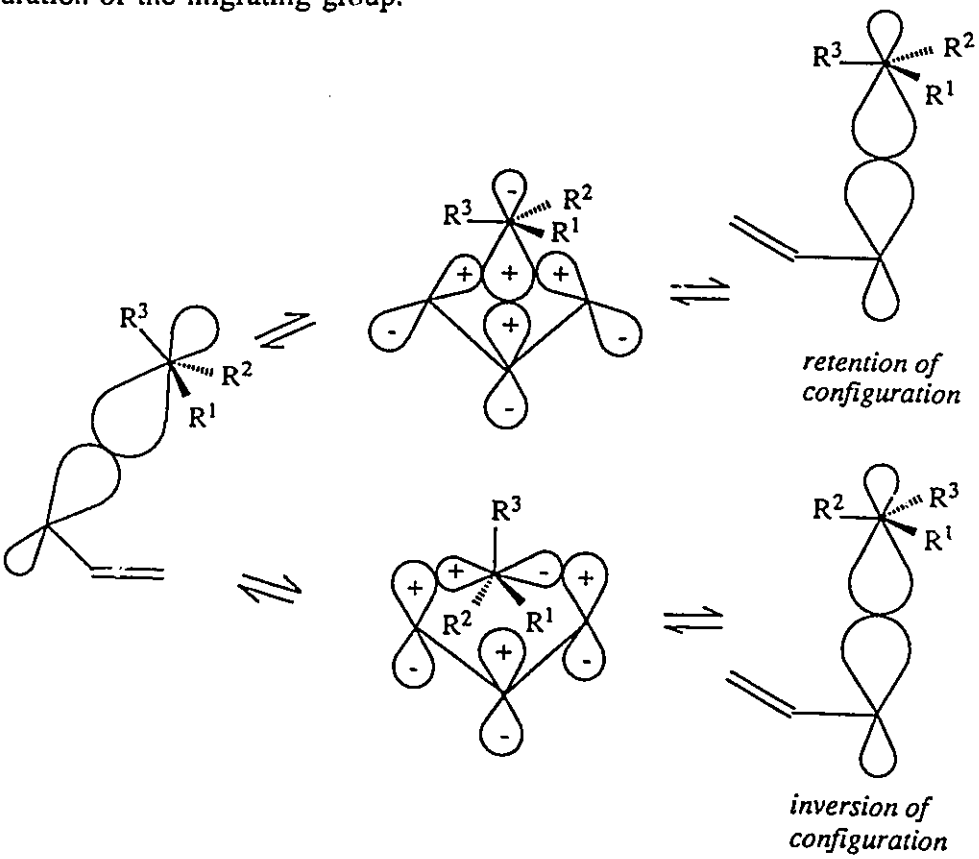


Figure 2

Selection rules for thermally allowed sigmatropic rearrangements can be derived by application of the Hückel-Möbius approach (Table 1).[6b,7b] This approach considers that sigmatropic migration must occur via aromatic transition states. Möbius transition states are aromatic for $4n$ π electrons, with one sign inversion in the cycle, while Hückel transition states are aromatic for $(4n+2)$ π electrons, with no sign inversions. A [1,3]-alkyl migration involving 4 π electrons can occur antarafacially via a Möbius transition state, while a [1,5]-sigmatropic hydrogen migration involving 6 π electrons can occur suprafacially via a Hückel transition state.

[1,5]-Sigmatropic rearrangement is also possible in cyclic systems as well as acyclic systems. In the following sections (1.1.2-1.1.6), [1,5]-sigmatropic rearrangements of some cyclopentadienes are discussed.

Table 1. Selection rules for thermal [1,j] sigmatropic migrations.

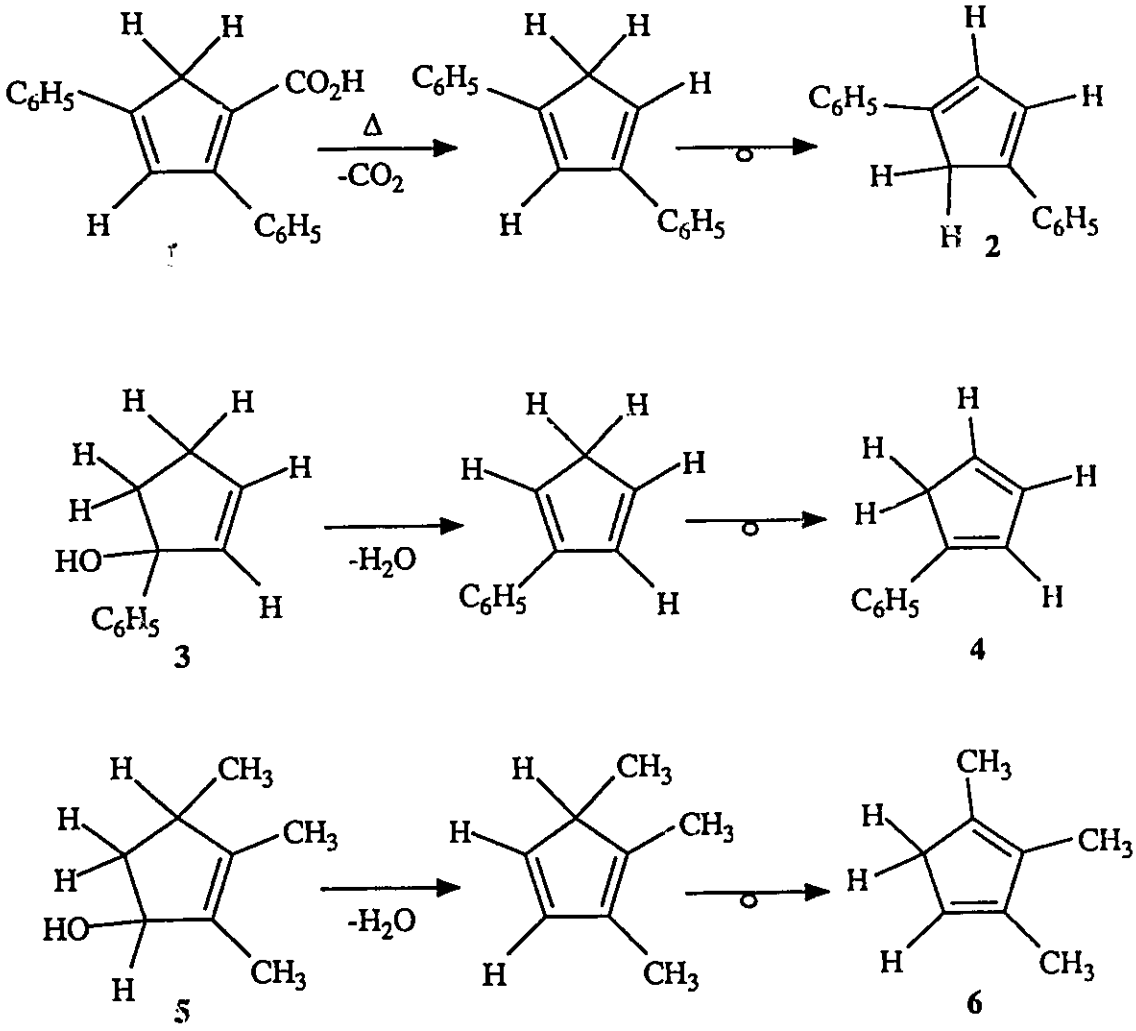
Number of electrons	System Type	j	Allowed Migration
4	Möbius	3	antarafacial-retention suprafacial-inversion
6	Hückel	5	antarafacial-inversion suprafacial-retention
$4n$	Möbius	$(4n-1)$	antarafacial-retention suprafacial-inversion
$4n+2$	Hückel	$(4n+1)$	antarafacial-inversion suprafacial-retention

1.1.2 Migration of hydrogen/deuterium in cyclopentadienes

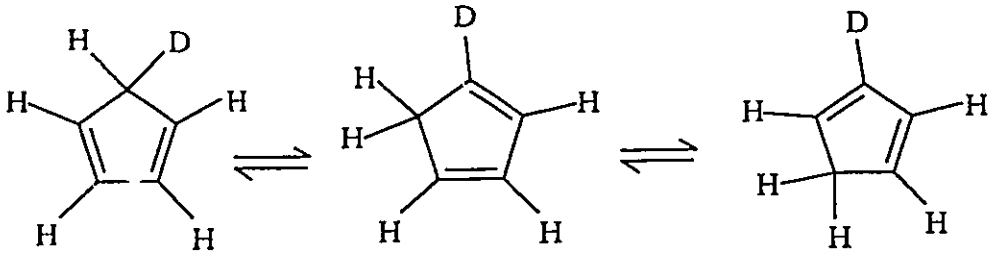
In the early chemical literature, a number of anomalies were reported during the synthesis of substituted cyclopentadienes where the distribution of double bonds in the product cyclopentadiene was inconsistent with what was expected, based on a synthetic plan (Scheme 2). Decarboxylation of 2,4-diphenylcyclopentadiene-1-carboxylic acid (**1**) gave 1,4-diphenylcyclopentadiene (**2**), instead of the expected 1,3-compound.[22] The dehydration of 1-phenylcyclopent-2-en-1-ol (**3**) yielded 1-phenylcyclopentadiene (**4**), instead of 2-phenylcyclopentadiene.[23] Furthermore, the dehydration of 2,3,4-trimethylcyclopent-2-ene-1-ol (**5**) led to 1,2,3-trimethylcyclopentadiene (**6**) instead of the 1,2,5-substituted compound.[24] The authors either did not attempt to explain these anomalies or explained them by the irreversible isomerization of the initial substituted cyclopentadiene to the energetically more favourable isomer. The majority of these authors were convinced that the endocyclic double bonds in the cyclopentadiene ring were fixed.

The [1,5]-hydrogen shift was discovered in 1961 by Mironov and coworkers.[25] Direct interconversions of isomeric cyclopentadienes by [1,5]-hydrogen migrations were observed in 5-deuterocyclopentadiene (**7**), synthesized by treating cyclopentadienylmagnesium bromide with deuterium oxide at -5 °C.[26,27] In the course of 1 hour at 60 °C, cyclopentadiene **7** was converted into a mixture of equal amounts of **7**, **8**, and **9**. The measurement of the infrared spectra at successive time intervals during the attainment of this equilibrium showed that the deuterocyclopentadienes isomerize in the following sequence **7** ⇌ **8** ⇌ **9**.[28] A [1,5]-deuterium migration in cyclopentadiene **7** is

degenerate. It was suggested that bridged proton-cyclopentadienyl anions were probably transition states in the transformation of isomers (Figure 3).



Scheme 2



7 8 9

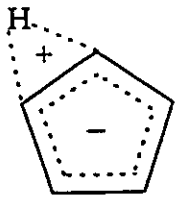
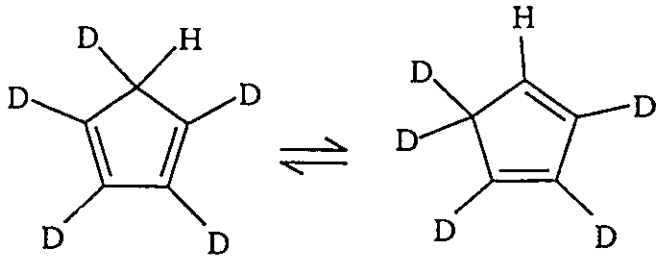


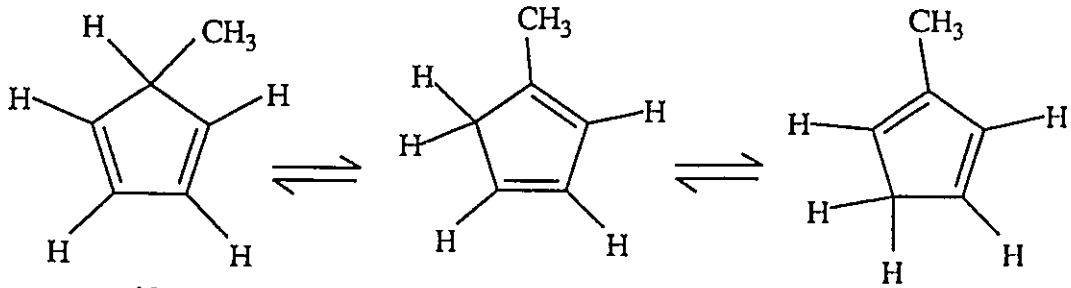
Figure 3

In 1964 Roth synthesized 1,2,3,4,5-pentadeuterocyclopentadiene (**10**) and established that when the cyclopentadiene was heated to 45-65 °C it underwent rearrangement by [1,5]-deuterium migration.[29] The hydrogen atoms were distributed uniformly among the 1-, 2-, and 5-positions of the cyclopentadiene ring. A [1,5]-hydrogen migration in **10** is degenerate. The kinetic parameters for the isomerization of (**10**)→(**11**) were determined to be log A = 12.11, $\Delta H^{\ddagger}$ = 23.6 kcal/mol, and $\Delta S^{\ddagger}$ = -3.3 eu.[29,30]



10 **11**

Mironov and coworkers were the first to study the rearrangement of 5-methylcyclopentadiene (**12**).[27,31,32] They established that at 25 °C in the liquid and gas phases 5-methylcyclopentadiene (**12**) isomerizes to 1-substituted cyclopentadiene **13**. The reaction is virtually complete after 3 hours in the liquid phase and after 4 hours in the gas phase; 2-methylcyclopentadiene (**14**) is then formed only in insignificant amounts (< 5%). It was noted that the concentration of isomer **12** decreases by a factor of two after equal time intervals (reaction half-life is constant). Cyclopentadiene **13** rearranges more slowly and after 2-3 days at 25 °C it is transformed into a mixture of approximately equal amounts of **13** and **14** containing < 3% of isomer **12**. Distillation of cyclopentadienes **12**, **13**, or **14** at atmospheric pressure led to the formation of the same mixture of cyclopentadienes **13** and **14**. It was concluded that the interconversions of the isomeric cyclopentadienes take place by a [1,5]-sigmatropic migration of hydrogen from the C-5 position in the cyclopentadiene ring to a neighbouring carbon atom.

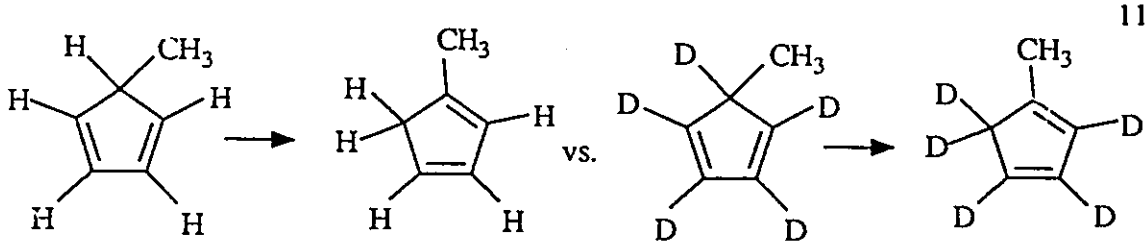


12 **13** **14**

McLean and Haynes also studied the thermal rearrangement of methylcyclopentadiene **12** by using ^{1}H NMR techniques.[33] The first order rate constant for hydrogen migration in **12** was $k^{30\,°C} = 62.0 \times 10^{-5}\ s^{-1}$. Kinetic parameters were also determined ($\Delta H^{\ddagger}$ = 20.4 kcal/mol and $\Delta S^{\ddagger}$ = -10 eu) for the rearrangement of **12** to **13**.

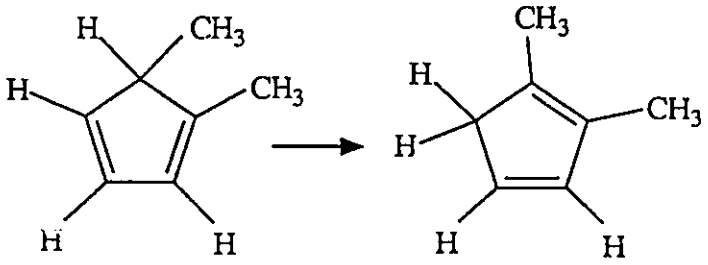
McLean and Haynes also suggested the presence of a polar transition state involving a bridged proton-cyclopentadienyl anion for this concerted reaction. The failure of the authors to observe deuterium incorporation during rearrangements carried out in the presence of D_2O was taken as evidence that separated ions were not formed during rearrangement. In 5-substituted cyclopentadienes, the [1,5]-hydrogen shift takes place at a rate much higher than in their isomers with a free methylene group.[31,32]

Insight into the structure of the transition state for the concerted [1,5]-hydrogen migration in cyclopentadienes was provided by a study on deuterium isotope effects by McLean and coworkers.[34] They compared the kinetic parameters for the conversion of 5-methylpentadeuterocyclopentadiene (Scheme 3) into the 1-isomer ($\Delta H^{\ddagger}$ = 21.7 kcal/mol, $\Delta S^{\ddagger}$ = -6.2 eu) with the corresponding values for 5-methylcyclopentadiene ($\Delta H^{\ddagger}$ = 19.3 kcal/mol, $\Delta S^{\ddagger}$ = -10.8 eu) and calculated the kinetic isotope effect (k_H/k_D = 6 at 27 °C). The measured k_H/k_D represents the product of the primary kinetic isotope effect and the secondary effect generated by the four D atoms attached to the double bonds, although it was suggested that the latter hardly constituted 10% of the quoted value. Therefore, it was suggested that the primary kinetic isotope effect of the [1,5]-hydrogen shift exceeded the value which might have been expected from the difference between the dissociation energies of the C-D and C-H bonds. It was concluded that, in the transition state, the migrating hydrogen (deuterium) atom is equidistant from the initial (C-5) and final (C-1) migration centres. Furthermore, the high negative entropy of activation for the reaction is suggestive of a rigorously ordered transition state.



Scheme 3

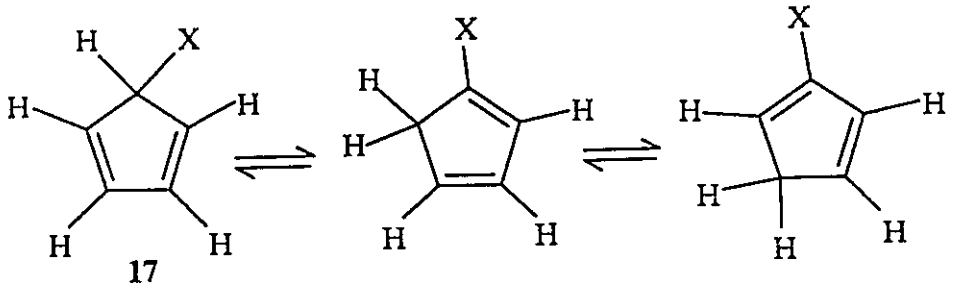
The accumulation of alkyl groups in the cyclopentadiene ring lowers the rate of reaction.[27,33] McLean and Haynes studied the rearrangement of **15** and found k_{obsd} = 5.5 x 10^{-5} s^{-1} (30 °C) for the rate of hydrogen migration from C-5 to C-4 in neat **15**. Its activation parameters are $\Delta H^{\ddagger}$ = 22.5 kcal/mol and $\Delta S^{\ddagger}$ = -4 eu.[33]



15 **16**

Breslow and coworkers studied the effect of C-5 halogen substitution on [1,5]-hydrogen migration in cyclopentadiene **17** (X = Cl, Br, I).[35] Halogen substitution slows down the rate of hydrogen migration compared to the parent hydrocarbon (ie. X = D) even though it stabilizes the reaction product. 5-Deuterocyclopentadiene was reported to equilibrate to an equal mixture of the three isomers in 1 hour at 60 °C,[27] however, Breslow found that **17** (X = Cl) required 2 hours at 75 °C to reach equilibrium containing only the 1- and 2- isomers. Furthermore, cyclopentadiene **17** (X = Br) required 2 hours at 100 °C to reach equilibrium, while **17** (X = I) was not completely equilibrated after 6 hours at 100 °C. Breslow rationalized this rate retardation by stating that a local

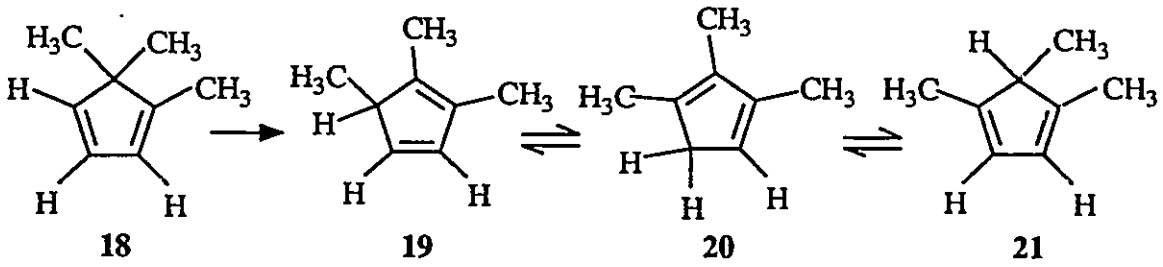
positive charge on carbon must be involved in the transition state for [1,5]-sigmatropic rearrangement. This suggestion is contrary to both Mironov and McLean who proposed a bridged proton-cyclopentadienyl anion transition state was involved.[27,33] The mechanism of this rate retardation for [1,5]-hydrogen migration from the C-5 position carrying a halogen substituent is obscure and still open to reinterpretation.



17

1.1.3 Migration of alkyl substituents in cyclopentadienes

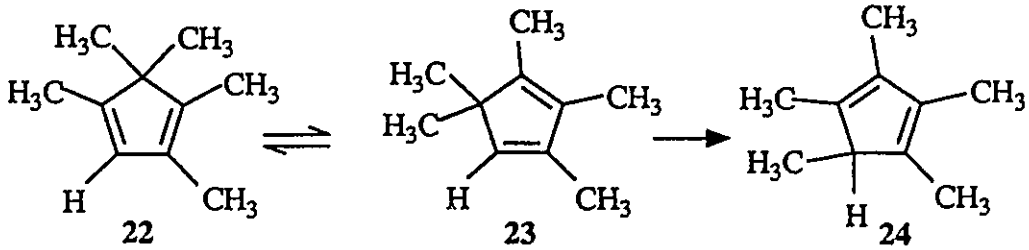
[1,5]-Sigmatropic migrations in cyclopentadienes are not limited to having hydrogen as the migrating group. Cyclopentadienes can also undergo [1,5]-alkyl migrations. For example, irreversible thermal isomerization of 1,5,5-trimethylcyclopentadiene (**18**) to 1,2,3-trimethylcyclopentadiene (**19**) leads to an equilibrium mixture of substituted trimethylcyclopentadienes (**19**, **20**, and **21**) in which isomer **20** predominates. The following kinetic parameters were obtained for the isomerization of **18** to **20**: $\Delta H^{\ddagger}$ = 40.3 kcal/mol and $\Delta S^{\ddagger}$ = -1 eu (350-400 °C), according to the data of de Haan and Kloosterziel[36,37] and $\Delta H^{\ddagger}$ = 43.8 kcal/mol and $\Delta S^{\ddagger}$ = 0.7 eu (328-430 °C), according to the data of Herndon and Manion.[38,39]



18 **19** **20** **21**

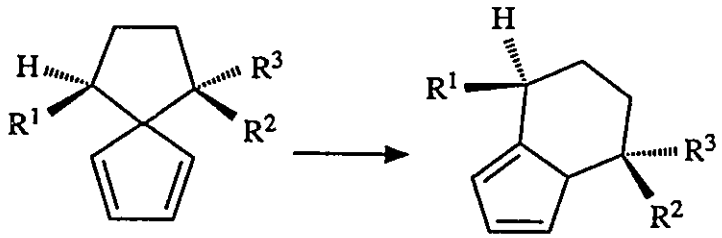
The mechanism of rearrangement involves an initial slow [1,5]-methyl migration followed by rapid [1,5]-hydrogen migrations which eventually leads to a preponderance of the more stable trimethylcyclopentadiene **20**. The enthalpy of activation is approximately 20 kcal/mol higher than that for a similar [1,5]-hydrogen migration.[33] McLean and Findlay found similar activation parameters for [1,5]-methyl migration in 5,5-dimethylcyclopentadiene[40] and Mironov and coworkers established that [1,5]-methyl migration was indeed reversible in a series of studies of di-, tri-, and tetramethylcyclopentadienes.[41-44]

The thermal rearrangement of a 5,5-disubstituted cyclopentadiene in which the [1,5]-alkyl shift does not lead to the elimination of geminal substitution was also investigated. 1,2,4,5,5-Pentamethylcyclopentadiene (**22**) is converted at 400-500 °C (contact time approximately 8 seconds) into 1,2,3,4,5-pentamethylcyclopentadiene (**24**) via intermediate **23**.[45] The first and rate-determining stage is the reversible isomerization of **22** ⇌ **23** by [1,5]-methyl shifts. The second irreversible stage (**23** → **24**) leads to a cyclopentadiene in which [1,5]-hydrogen migration is degenerate.



22 **23** **24**

Kloosterziel and coworkers established the stereospecificity of alkyl migration in the rearrangements of *cis*- and *trans*-6,9-dimethylspiro[4.4]nona-1,3-diene (**25a** and **25b**). Compound **26a** was obtained from the rearrangement of **25a** while compound **26b** was obtained from the rearrangement of **25b**. The migration of alkyl occurred via a suprafacial pathway with retention of configuration at the migrating carbon.[46,47]

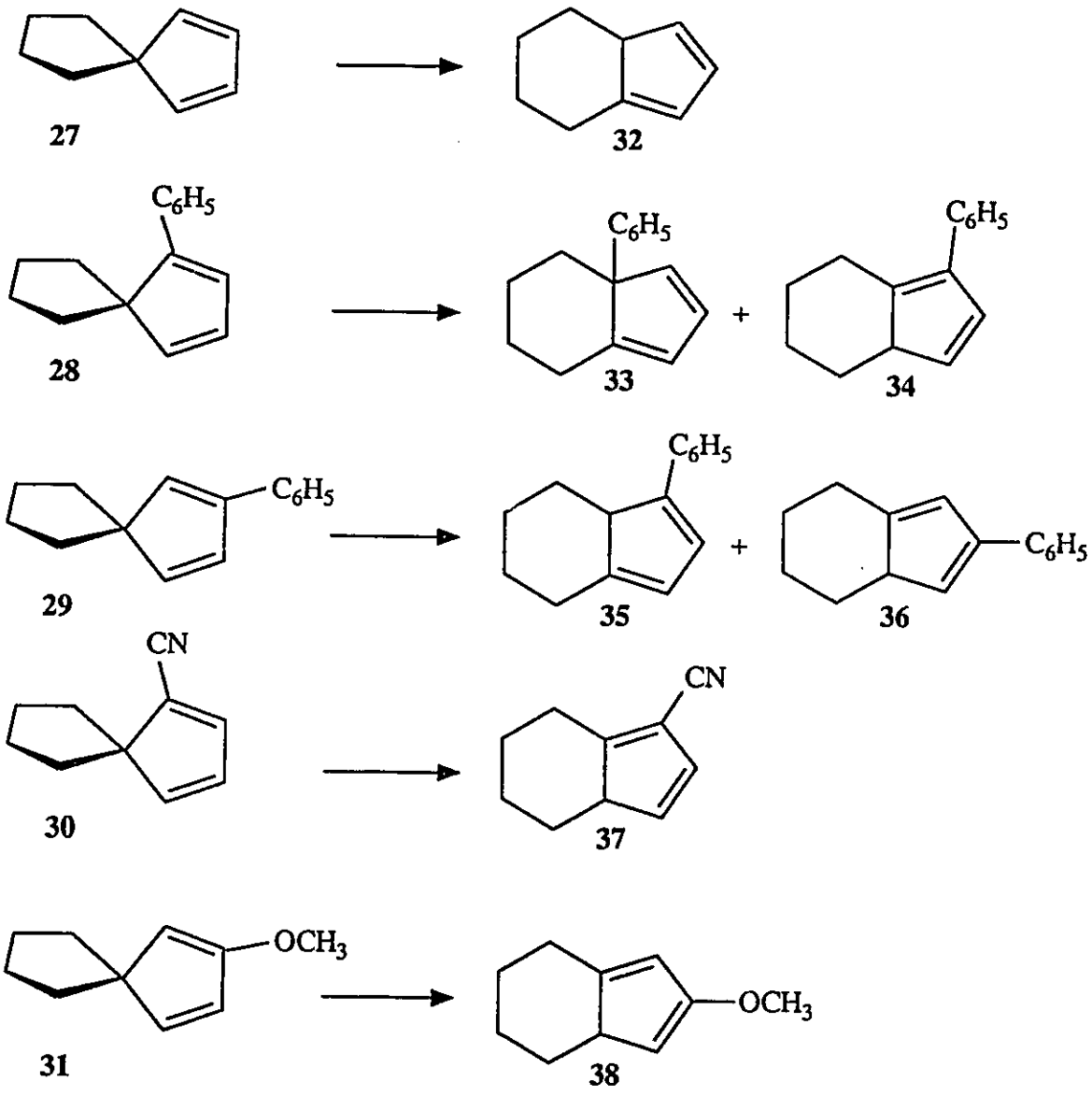


25 **26**

(**a**: R^1=R^2=CH_3, R^3=H; **b**: R^1=R^3=CH_3, R^2=H)

Evidence in support of a polar transition state in cyclopentadiene [1,5]-alkyl shifts comes from a study of the thermolysis of phenyl-, cyano-, and methoxy-substituted spiro[4.4]nona-1,3-dienes.[48] Carpenter and Replogle studied the kinetics of rearrangement of compounds **27-31** (Scheme 4) and some of their results are summarized in Table 2.

The suggestion of partial charge development in the transition state for alkyl migration was made because both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were reduced when the solvent was changed from isooctane to isopropyl alcohol (entries 1, 2, 7, and 8). The cyano group reduces $\Delta H^{\ddagger}$ by 2.4 kcal/mol in isooctane and 4.3 kcal/mol in isopropyl alcohol. This substituent effect was not attributed to steric, conjugating, or radical stabilizing properties of a cyano group since a phenyl substituent at the same location had virtually no effect on $\Delta H^{\ddagger}$ (entry 4). The effect of the cyano group was attributed to its electron-withdrawing properties.



Scheme 4

Table 2. Kinetic data for compounds **27-31.**

Entry	Compound	Temp. Range (°C)	Solvent	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	k_{rel} (150 °C)
1	**27→32**	141-196	isooctane	32.0 ± 0.2	-5.1 ± 0.5	1.0
2	**27→32**	136-175	isopropyl alcohol	30.9 ± 0.6	-6.7 ± 1.3	1.7
3	**28→33**	146-185	isooctane	35.4 ± 1.1	-0.4 ± 2.6	0.2
4	**28→34**	146-185	isooctane	32.6 ± 0.6	-4.3 ± 1.3	0.7
5	**29→35**	146-185	isooctane	32.4 ± 0.5	-4.8 ± 1.0	0.7
6	**29→36**	146-185	isooctane	34.4 ± 0.6	-0.3 ± 1.2	0.6
7	**30→37**	120-160	isooctane	29.6 ± 0.2	-5.7 ± 0.5	13
8	**30→37**	106-146	isopropyl alcohol	26.6 ± 0.2	-9.9 ± 0.4	55
9	**31→38**	160-200	isooctane	32.8 ± 0.4	-4.8 ± 0.5	0.4

Compounds **28** and **29**, containing phenyl on the cyclopentadiene ring, exhibited both regiochemistries for [1,5]-shifts, while compounds **30** and **31** gave only one product. The suggestion was that the regioselectivities observed with compounds **30** and **31** are of electronic origin rather than steric. The charge distribution in bicyclo[3.1.0]hexatriene was calculated by the Hückel molecular orbital model and was like that of an allyl anion fused to a cyclopropenium ion (Figure 4). Therefore, C-2 and C-4 carry the largest negative charges, C-3 the smallest negative charge, and C-1, C-5, and C-6 carry positive charges. Figure 5 shows possible transition states for the thermal rearrangements of **30** and **31.**

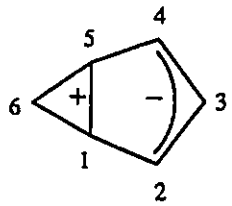


Figure 4

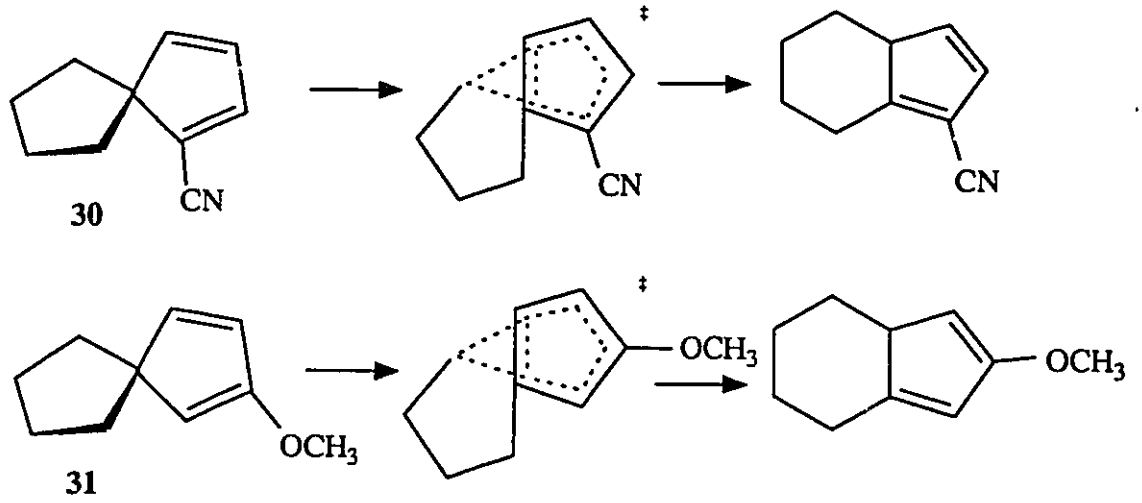


Figure 5

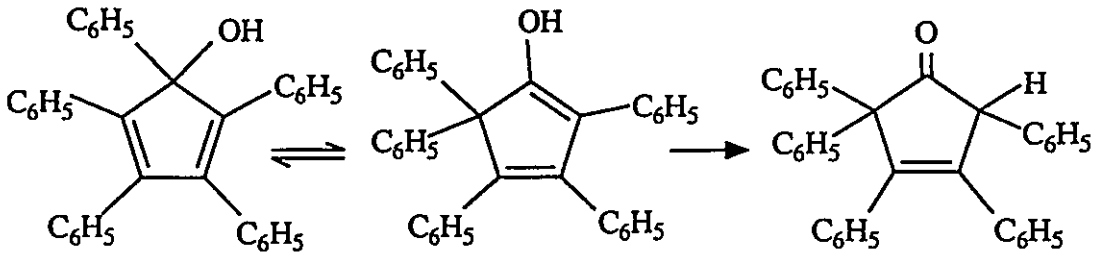
In the rearrangement of **30**, the two possible regiochemistries correspond to placing the acceptor substituent at C-1 or C-2 of the transition state model, Figure 4. One would expect C-2 to be preferred as was observed. For compound **31** the choice is between C-2 and C-3 and since **31** bears a π-donor substituent, one would expect the site of smaller negative charge, i.e., C-3, to be preferred and this regioselectivity was observed.

1.1.4 Migration of carbon-based functional groups in cyclopentadienes

Carbon-based functional groups are also capable of [1,5]-sigmatropic migration in cyclopentadienes. The migration of the following substituents from C-5 of a cyclopentadiene are considered: Ph, CHO, and COOMe.

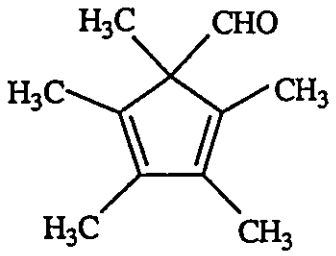
An example of a [1,5]-phenyl migration in a cyclopentadiene ring was described by Youssef and Ogliaruso.[49,50] Refluxing a solution of 1,2,3,4,5-pentaphenylcyclopentadienol (**39**) in diphenyl ether produced **40** from a slow [1,5]-phenyl

migration which was followed by tautomerization to the keto form (**41**). Activation parameters were determined (173-200 °C) to be $\Delta H^{\ddagger}$ = 35.3 kcal/mol and $\Delta S^{\ddagger}$ = -7.5 eu.



39 **40** **41**

[1,5]-Sigmatropic formyl migration in 5-formyl-1,2,3,4,5-pentamethylcyclopenta-1,3-diene (**42**) is rapid at 25 °C (k_{isom} = 90 s^{-1}).[51] Line shape analysis of ^1H NMR spectra obtained between -20 and +70 °C revealed that migration is associated with an activation enthalpy of 13.2 ± 0.3 kcal/mol and an activation entropy of -5.1 ± -0.2 eu.



42

1,5-Alkyl shifts in cyclopentadienes commonly require temperatures above 330 °C and proceed with $\Delta H^{\ddagger}$ > 43 kcal/mol.[16] The easy migration of the formyl group compared to alkyl groups was attributed to secondary orbital interactions between the vacant π^*-orbital of the formyl group and the HOMO of the diene (Figure 6).[51]

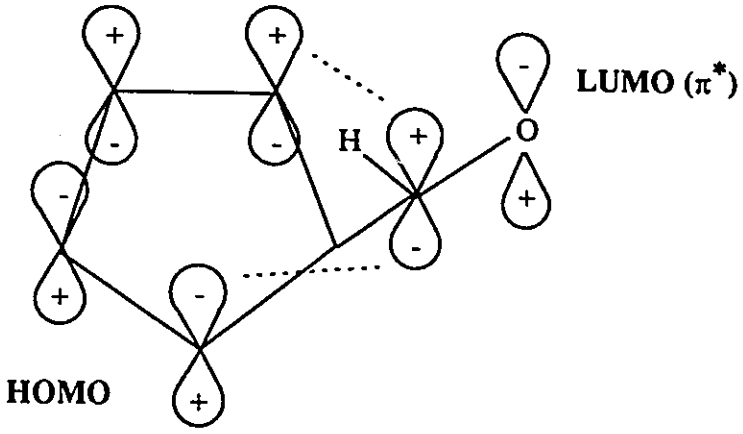
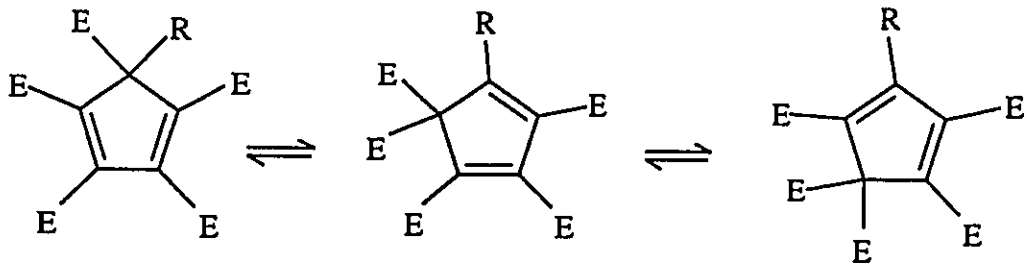


Figure 6

Carbomethoxy is also a very good migrating group. Hoffmann and coworkers studied the [1,5]-carbomethoxy shift in some 5-R-pentakis(methoxycarbonyl) cyclopentadienes.[52-55] At 100-150 °C, the transformation **43** → **44** takes place, while at higher temperatures, (> 160 °C), transformation **44** → **45** occurs as well. Activation parameters for the isomerization of **43a-d** to **44a-d** in dichlorobenzene are presented in Table 3.



43a-d **44a-d** **45a-d**

E=CO_2CH_3

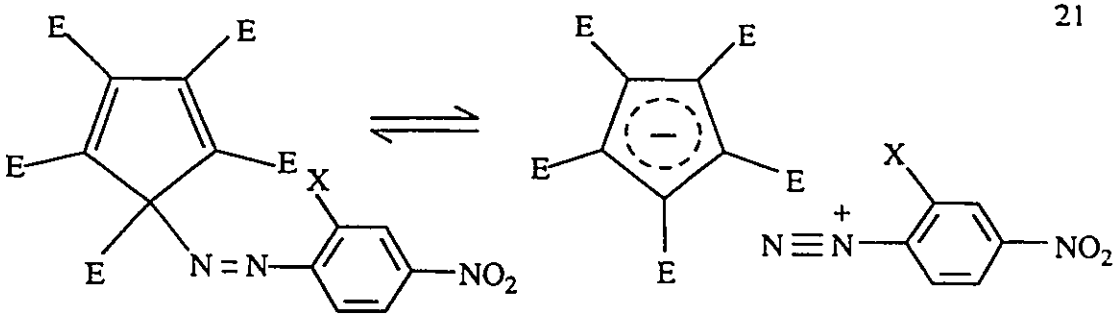
(**a**: R=Me; **b**: R=CH_2CH_3; **c**: R=$CH(Me)_2$; **d**: R=Cl)

Table 3. Activation parameters for the rearrangement **43a-d** → **44a-d.**

43	**Temp. Range** (°C)	$\Delta G^{\ddagger}$ (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)
43a, R=Me	104.4-144.8	30.2 ± 0.2	26.9 ± 1.0	-8.6 ± 3.5
43b, R=CH_2CH_3	99.1-128.9	30.4 ± 0.2	29.3 ± 0.5	-3.4 ± 3.0
43c, R=$CH(Me)_2$	99.1-128.9	30.0 ± 0.2	30.6 ± 0.7	+1.2 ± 2.1
43d, R=Cl	150.2-190.2	31.7 ± 0.2	27.3 ± 1.8	-10.3 ± 4.6

1.1.5 Migration of arylazo in cyclopentadienes

Mikhailov and coworkers investigated the rearrangement of cyclopentadienes **46a-f.**[56] In the ^1H NMR spectra of **46c-f** in benzonitrile solution, the signal for the protons of the carbomethoxy groups at 30 °C appear in the form of a singlet. With a decrease in the temperature of the solution, this peak is broadened and at -35 °C (for compounds **46c-f**) it splits into a triplet with intensity ratios of 2 : 2 : 1. Such spectral behaviour was attributed to the exchange of the positions of the arylazo group in the cyclopentadiene ring, which takes place through the reversible formation of ion pair **47** from covalent substrate **46.**



46a-f **47a-f**

(**a**: X=OMe; **b**: X=Me; **c**: X=H; **d**: X=I; **e**: X=Cl; **f**: X=Br)

For compounds **46a** and **46b**, the migration of arylazo around the cyclopentadiene ring takes place very rapidly on the ^{1}H NMR time scale. Even in solutions at -50 to -70 °C the signal for the protons of the carbomethoxy groups is in the form of a narrow singlet. Table 4 gives the rate constants and activation parameters for the migration of the arylazo groups in **46c-f**. Electron-withdrawing substituents at the ortho position of the aryl group retard the exchange process because they destabilize the intermediate diazonium cation.

Table 4. Activation parameters for the rearrangement of arylazo groups in compounds **46c-f**.

Compound	X	k_{298} (x 10^2 s^{-1})	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	$\Delta G^{\ddagger}$ (kcal/mol)
46c	H	8.9	11.1 ± 0.4	-7.7 ± 0.6	13.4
46d	I	6.3	14.2 ± 0.2	+2.1 ± 0.3	13.6
46e	Cl	5.4	11.3 ± 0.2	-8.2 ± 0.3	13.7
46f	Br	4.6	11.7 ± 0.4	-7.0 ± 0.7	13.8

1.1.6 Summary of [1,5]-sigmatropic migrations in cyclopentadienes

Generally, the migration of a C-5 substituent in a cyclopentadiene ring occurs by a suprafacial [1,5]-sigmatropic migration. This process has been shown by means of numerous experimental[16-21] and theoretical studies[33,48,57,58,59] to occur in a concerted manner.

The nature of the transition state is an interesting feature of these rearrangements. The idea of a proton-cyclopentadienyl anion transition state for [1,5]-hydrogen migration in cyclopentadiene, originally suggested by Mironov and coworkers in 1963,[27] was also suggested by both Houk[57] and Carpenter[48] in independent theoretical studies. The nature of the transition state, however, is dependent on both the structure of the cyclopentadiene and the migrating group. The transition state for concerted migrations seems to vary from one highly ordered, with no charge separation, to one with some degree of charge separation. However, the mechanism for rearrangement of some arylazo 1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadienes is stepwise, involving a cyclopentadienyl anion and a diazonium cation[56]. Therefore, it seems that when both the potential cation portion (migrating group) and anion portion of a cyclopentadiene are well stabilized then rearrangement occurs via a stepwise process.

The factors governing the migratory aptitude of substituents in [1,5]-sigmatropic shifts is not well understood. It is clear from various studies that the migratory aptitude of some substituents at C-5 of a cyclopentadiene are the following, in decreasing order: CHO > H > D > COOMe > C_6H_5 > Me. Ground state strain or bond strength of the shifting σ-bond are factors contributing to some migration tendencies. Furthermore, it appears that secondary orbital interactions between an empty π^*-orbital of some migrating

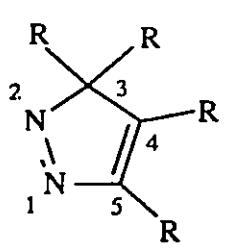
groups and an occupied molecular orbital of the array of atoms in the cyclopentadiene ring is another contributing factor.

Heterocyclic cyclopentadiene-like systems such as 3*H*-pyrazoles are also prone to [1,5]-sigmatropic rearrangement. The next portion of this introduction (1.2) is a discussion of several aspects of 3*H*-pyrazole chemistry.

1.2 3*H*-Pyrazoles

1.2.1 General

A 3*H*-pyrazole (**48**) is a cyclopentadiene-like ring system containing two nitrogen atoms in a 1,2-relationship. The 3*H*, 4*H*, and *1*H prefixes denote the position of the tetrahedral carbon atom in the ring. Isomeric with 3*H*-pyrazoles are 4*H*-pyrazoles (**49**) and 1*H*-pyrazoles (**50**). A 4*H*-pyrazole has the tetrahedral carbon centre at the fourth atom in the ring while a 1*H*-pyrazole carries a substituent on a nitrogen atom. The 4*H*-pyrazole is more stable than the 3*H*-pyrazole because of the two relatively strong carbon-nitrogen double bonds, while the most stable pyrazole isomer is the 1*H*-pyrazole because of its aromatic sextet of π electrons. The 1-nitrogen atom of **50** contributes its electron pair to the formation of the aromatic sextet.



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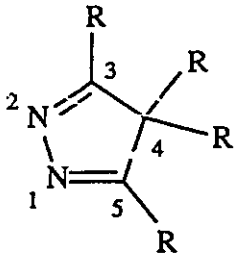

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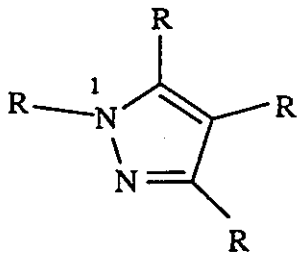

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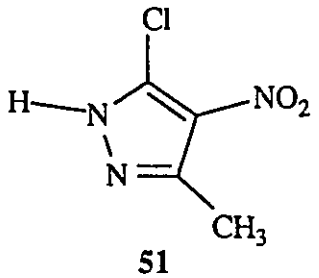
An excellent review of 3*H*-pyrazole chemistry was published in 1983 by Sammes and Katritzky.[60] Some discussion of the chemistry of 3*H*-pyrazoles is also included in other reviews[61-64] and books on heterocyclic chemistry.[65-68]

3*H*-Pyrazoles, like their cyclopentadiene analogues, are also prone to thermal rearrangement. The study of these thermal rearrangements has been of interest to many physical organic chemists. 3*H*-Pyrazoles undergo thermal rearrangement and frequently afford 1*H*-pyrazole isomers. Therefore, 3*H*-pyrazoles can provide a synthetic route to 1*H*-pyrazoles. The synthesis of 1*H*-pyrazoles has been of interest because the aromatic pyrazole nucleus was found to be associated with various biological activities; numerous pyrazole patents have been assigned. As examples of useful 1*H*-pyrazoles, 1*H*-pyrazole **51** was found useful for fruit abscission[69] while 1*H*-pyrazole **52** provides excellent herbicidal activity in corn.[70,71] Other uses of 1*H*-pyrazoles are as fungicides, pesticides, antibacterials, hypnotics, and textile dyes.[64]



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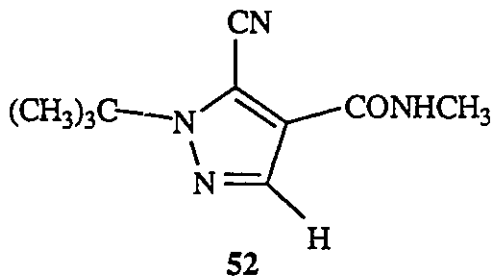

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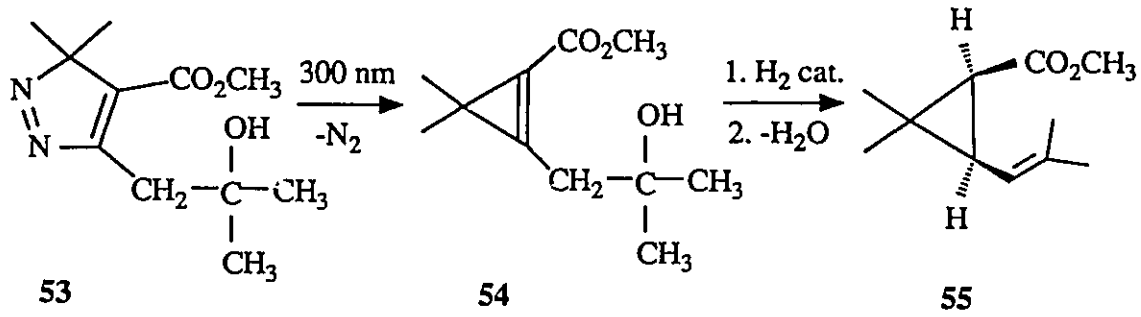
Further interest in 3*H*-pyrazoles arises from their photolysis, which leads to cyclopropenes via nitrogen elimination. Therefore, 3*H*-pyrazoles can provide a convenient synthetic route to cyclopropenes. For example, Franck-Neumann and coworkers synthesized 3*H*-pyrazole **53** which provided a route, via cyclopropene **54**, to the cis-disubstituted gem-dimethyl cyclopropanic ester **55**, a direct precursor of a class of insecticides called pyrethroids (Scheme 5).[72]



53 **54** **55**

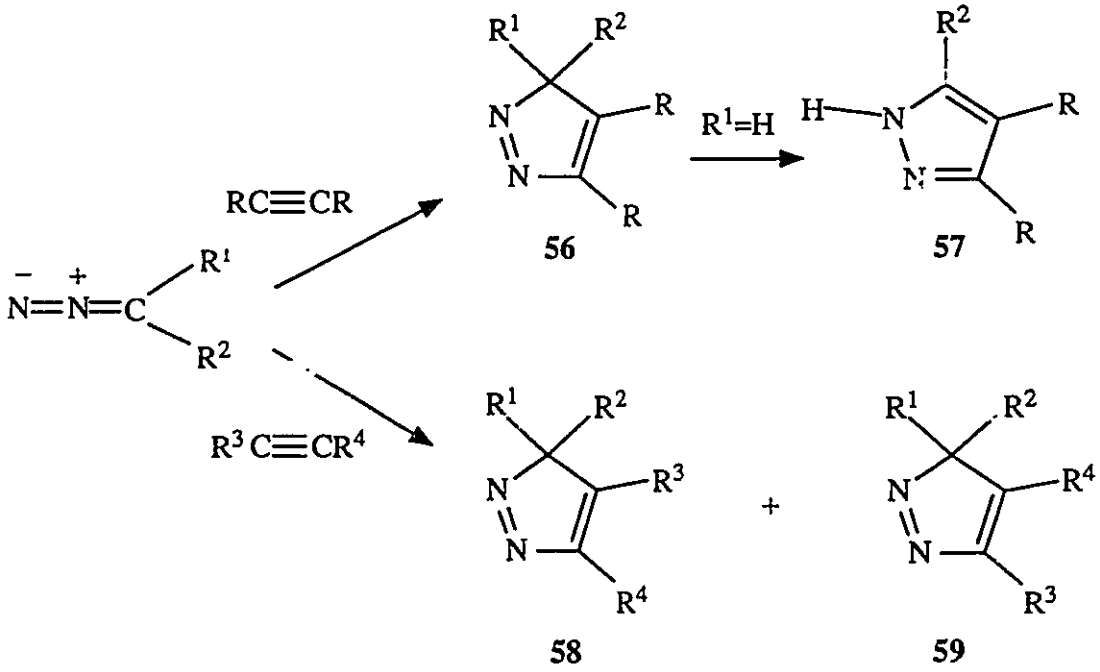
Scheme 5

2.2.2 Synthesis of 3*H*-pyrazoles from alkynes and diazo compounds

The most popular method for the synthesis of 3*H*-pyrazoles involves a 1,3-dipolar cycloaddition between a diazo compound and an alkyne. This is a convenient, one-step synthesis for a variety of 3*H*-pyrazoles.

For over a century, the reaction between alkynes and diazomethane or monosubstituted diazomethanes has been known to yield 1*H*-pyrazoles.[73] According to Scheme 6, a 1,3-dipolar cycloaddition between a monosubstituted diazo compound (R^1 = H) yields an unstable 3*H*-pyrazole (**56**) which undergoes a hydrogen migration to give the 1*H*-pyrazole (**57**). When a disubstituted diazomethane is used (R^1, $R^2 \neq$ H), **56** can be

isolated, although it could still rearrange under the reaction conditions. When an unsymmetric disubstituted alkyne is used 2 regioisomers (**58** and **59**) may be isolated.



Scheme 6

The most common diazoalkanes used in the synthesis of 3*H*-pyrazoles have been diphenyldiazomethane and 2-diazopropane. Some other examples include the following: 1-phenyldiazoethane,[74,75] methyl 4-diazo-4-phenylbutanoate,[76] hexafluoro-2-diazopropane,[77] diaryldiazomethanes,[74] diazocyclopentadienes and -indenes,[78-81] α-diazo ketones (acyclic[82-85] and cyclic[83,86-88]), and α-diazoesters.[76,82,84,89,90]

The most common alkyne used in cycloaddition reactions with diazo compounds for the synthesis of 3*H*-pyrazoles is dimethyl acetylenedicarboxylate. Some examples of other alkynes that have been used successfully include the following: ethyne,[91,92]

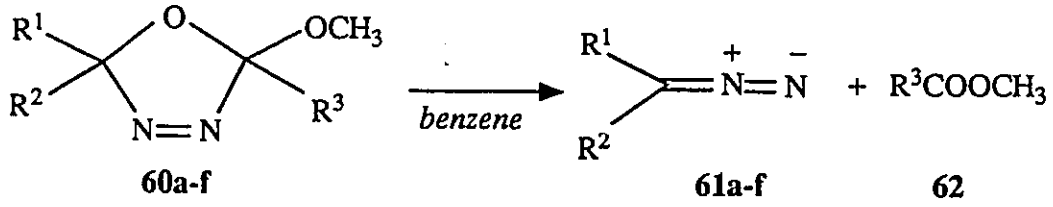
mono-[93-95] and dialkylethynes,[96] trifluoromethylethynes,[77,78] phenylethyne,[74,76,78,79,86,87,97-99] diphenylethyne,[76,100] 1-diethylaminopropyne,[80,85,90] propynal,[74,101] phenylpropynal,[74] mono-[84,95,99,102-104] and diacyl alkynes,[80,84,104,105] propynoic esters,[74,78,81,84,91,98,103,106-110] 3-alkyl-[105,110] and 3-phenylpropynoic esters,[98,105,106,109,111-113] propynonitrile,[84,105,114] and dicyanoethyne.[78,79,105,114]

The mechanism of the reaction between an alkyne and a diazo compound is a thermally allowed, concerted, 1,3-dipolar cycloaddition process. It is generally controlled by the interaction between the highest occupied molecular orbital (HOMO) of the dipole (diazoalkane) and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile (alkyne).[18] The smaller the energy difference between the HOMO of the dipole and the LUMO of the dipolarophile, the faster the rate of the reaction.[115] Electron-withdrawing substituents R^1,R^2 and R^3,R^4 decrease the energy of the HOMO and LUMO, respectively, while electron-donating substituents R^1,R^2 and R^3,R^4 increase the energy of the HOMO and LUMO, respectively. For example, the relative rates for the cycloaddition of phenylethyne, methyl propynoate, and dimethyl acetylenedicarboxylate to diphenyldiazomethane at 40 °C are, respectively, 1 : 900 : 8200.[98] Increasing the electron-withdrawing power of substituents R^3 and R^4 decreases the alkyne LUMO energy leading to a smaller energy separation between the HOMO and LUMO.

In extreme cases of strong electron-withdrawing R^1 and R^2, and electron-donating R^3 and R^4, the cycloaddition occurs via overlap of the diazoalkane LUMO with the alkyne HOMO. An example of this type of cycloaddition is the reaction of dimethyl diazomalonate with 1-diethylaminopropyne.[85]

Diazo compounds, which are important precursors of 3*H*-pyrazoles, have been prepared, for example, by the oxidation of the appropriate hydrazones or base-promoted cleavage of tosylhydrazones.[116,117] Although a number of diazo compounds have been synthesized by these or other methods, very few dialkyl diazomethanes ($R^1R^2CN_2$) have been utilized. 2-Diazopropane, for example, is purified by codistillation with ether and used as a solution in ether.[118] Higher molecular weight diazoalkanes presumably are difficult to obtain because of the problem of purifying them safely.

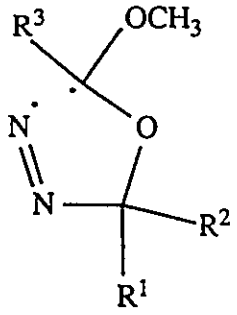
Recently, Warkentin and coworkers reported that 2-alkoxy-2,5,5-trialkyl-Δ^3-1,3,4-oxadiazolines can serve as convenient sources of diazoalkanes.[119] They reported that the photolysis of 2-alkoxy-2,5,5-trialkyl-Δ^3-1,3,4-oxadiazolines (**60a-f**) at 300 nm in a Rayonet apparatus led to fragmentation to diazoalkanes **61a-f** and ester **62** in high yield (Scheme 7). It was proposed that the oxadiazolines **60a-f** decompose via diazenyl diradicals **63a-f**.



60a-f **61a-f** **62**

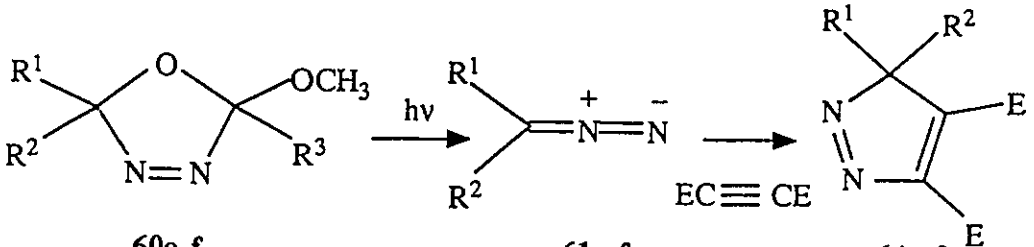
a: $R^1=R^2=R^3=CH_3$
b: $R^1=R^3=CH_3$, $R^2=C_2H_5$
c: $R^1=R^2=C_2H_5$, $R^3=CH_3$
d: $R^1=CH(CH_3)_2$, $R^2=R^3=CH_3$
e: R^1 $R^2=(CH_2)_4$, $R^3=CH_3$
f: R^1 $R^2=(CH_2)_5$, $R^3=CH_3$

Scheme 7



63a-f

These oxadiazolines were particularly useful for the *in situ* 1,3-dipolar cycloaddition reactions of diazoalkanes with dimethyl acetylenedicarboxylate, which afforded 3*H*-pyrazoles. Photolysis of **60a-f** at 300 nm in benzene containing dimethyl acetylenedicarboxylate for a 5 hour period gave 3*H*-pyrazoles **64a-f** (56-67% yields). Since the diazoalkanes were trapped as they were being generated, bimolecular conversion of diazoalkanes to azine was minimized. Therefore, this method can provide access to a variety of 3*H*-pyrazoles of general structure **64**, bearing different alkyl substituents at C-3.



60a-f (E=CO_2CH_3) **61a-f** **64a-f**

a: $R^1=R^2=R^3=CH_3$

b: $R^1=R^3=CH_3$, $R^2=C_2H_5$

c: $R^1=R^2=C_2H_5$, $R^3=CH_3$

d: $R^1=CH(CH_3)_2$, $R^2=R^3=CH_3$

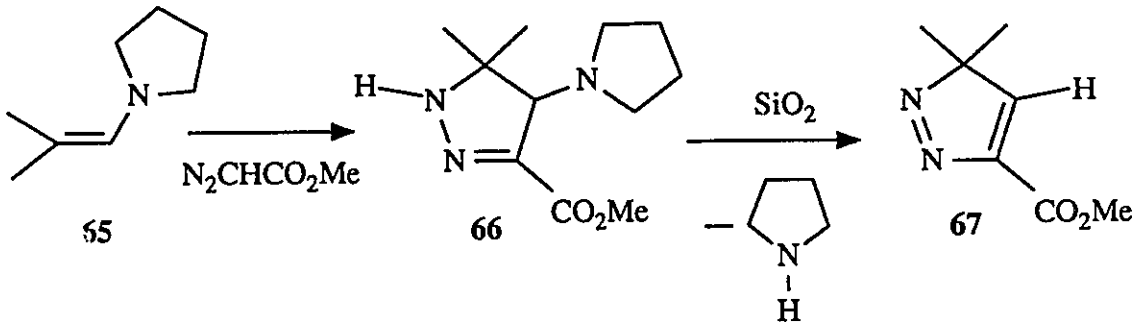
e: R^1 $R^2=(CH_2)_4$, $R^3=CH_3$

f: R^1 $R^2=(CH_2)_5$, $R^3=CH_3$

1.2.3 Synthesis of 3*H*-pyrazoles from alkenes and diazo compounds

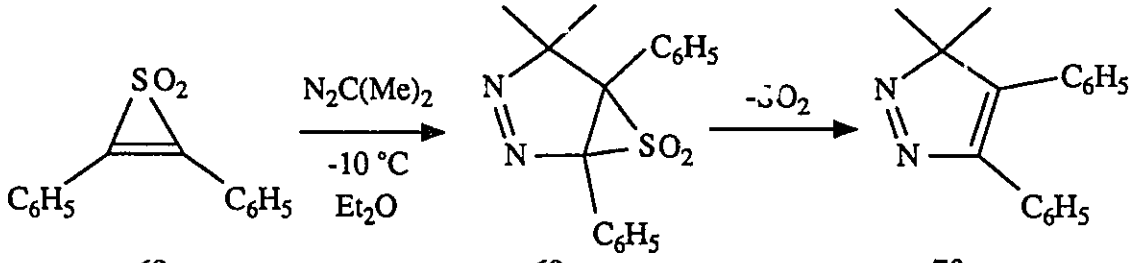
3*H*-Pyrazoles can also be synthesized indirectly by a 1,3-dipolar cycloaddition between an alkene and a diazo compound to afford a cycloadduct, which in some cases can be transformed into a 3*H*-pyrazole by a subsequent reaction. A few examples illustrating this methodology are discussed below.

α-Diazocarbonyl compounds can undergo 1,3-dipolar cycloadditions with enamines. This provides a synthetic route to some 3*H*-pyrazoles. Cycloaddition between enamine **65** and methyl diazoacetate in boiling chloroform gave a high yield of **66** which was almost quantitatively converted to **67** by chromatography on silica.[120]



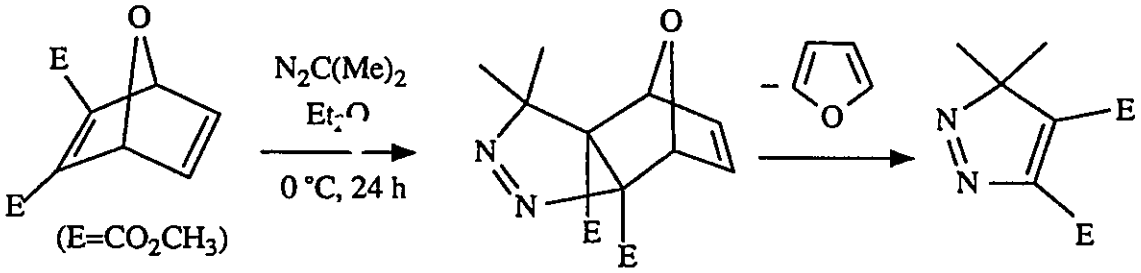
65 66 67

Diazoalkanes can also undergo 1,3-dipolar cycloadditions with cyclopropenes. Cycloaddition of thiirene dioxide **68** to 2-diazopropane gives bicyclic adduct **69** which spontaneously extrudes sulfur dioxide to afford 3*H*-pyrazole **70** in a 72% yield.[121]



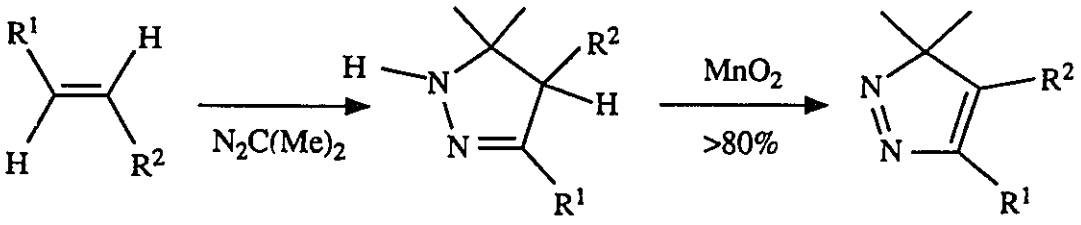
68 69 70

Adduct **71**, from furan and dimethyl acetylenedicarboxylate forms a transient intermediate (**72**) from reaction with 2-diazopropane. This intermediate spontaneously extrudes furan yielding, quantitatively, 3*H*-pyrazole **73**.[122]



71 **72** **73**

3*H*-Pyrazoles can also be synthesized by the oxidation of some Δ^2-pyrazolines. The cycloaddition of 2-diazopropane to disubstituted alkenes affords the Δ^2-pyrazolines (**74a-f**), which can be oxidized with manganese dioxide to yield 3*H*-pyrazoles **75a-f**. The ease of oxidation, however, is strongly dependent on substituents R^1 and R^2 of **74**.[123]

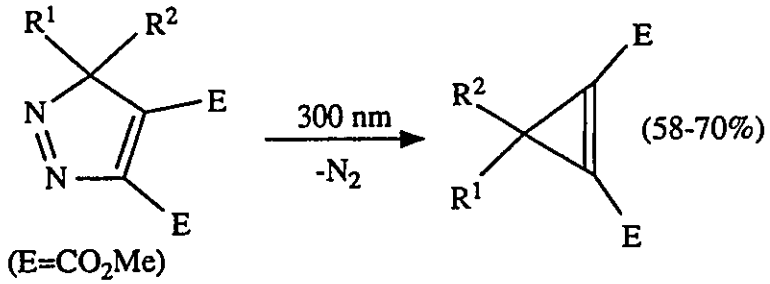


a: R^1=R^2=CN
b: R^1=NO_2, R^2=C_6H_5
c: R^1=NO_2, R^2=CN
d: R^1=CO_2CH_3, R^2=CN
e: R^1=CN, R^2=CO_2CH_3
f: R^1=$COCH_3$, R^2=CN

74a-f **75a-f**

1.2.4 Photochemical loss of nitrogen from 3*H*-pyrazoles

The photolysis of 3*H*-pyrazoles at the wavelength of the ring n→π* transition, results in loss of nitrogen and the formation of a cyclopropene. This is a well known preparative method for the synthesis of cyclopropenes.[100,109-111,124-131] For example, Warkentin and coworkers synthesized cyclopropenes **77a-e** from the photolysis of 3*H*-pyrazoles **76a-e**.[119]

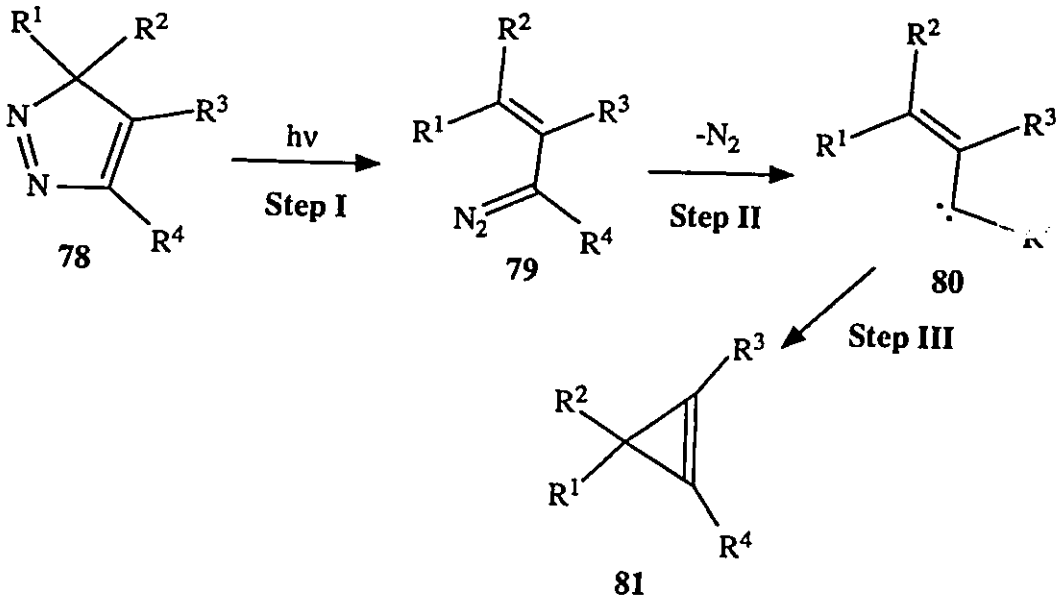


(E=CO_2Me)

76a-e **77a-e**

a: R^1=R^2=CH_3
b: R^1=CH_3, R^2=C_2H_5
c: R^1=R^2=C_2H_5
d: R^1=$CH(CH_3)_2$, R^2=CH_3
e: R^1=cyclopropyl, R^2=CH_3

A general mechanism for cyclopropene formation is shown in Scheme 8. The first step involves ring opening of 3*H*-pyrazole **78** to vinyldiazo compound **79**. The vinyldiazo compound **79** is formed from absorption of UV light at the wavelength of the pyrazole ring n→π* transition.



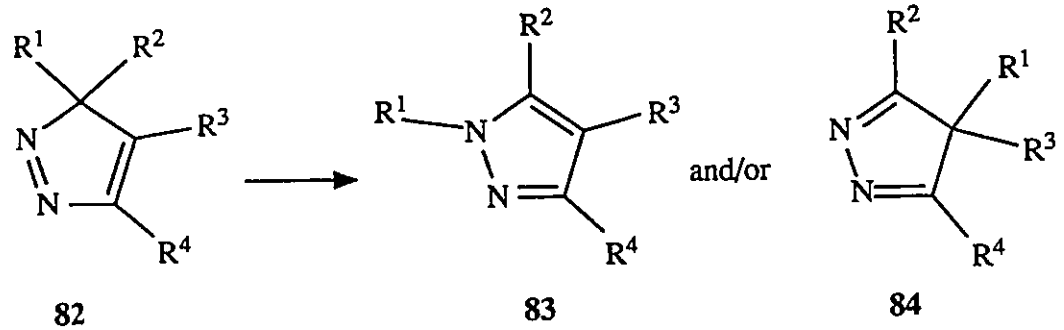
Scheme 8

The confirmation that the diazo compound was a true intermediate was verified by a number of observations. First, a red colour was formed during an induction period prior to nitrogen evolution.[132] Second, in one reaction only 10% of the cyclopropene had been formed when all of the 3*H*-pyrazole had disappeared.[100] Third, the use of filters to give a narrow band of UV light (320-380 nm) resulted in formation of the diazo compound but suppression of the cyclopropene.[112,129,133,134] Finally, in some cases the vinyldiazo compound has been isolated.[100,105,112,120]

The second step in the mechanism is the formation of vinylcarbene **80** from the vinyldiazo compound by the absorption of light at longer wavelength (>380 nm). The existence of the carbene intermediate was demonstrated by the formation of dimers[76,135] and by trapping with active alkenes.[136-138] The intermediate carbene (**80**) can also react intramolecularly by insertion into the double bond to give a cyclopropene (**81**, Step III).

1.2.5 Thermal rearrangement of 3*H*-pyrazoles

The thermal migration of a substituent from the tetrahedral carbon atom (C-3) of a 3*H*-pyrazole to another ring carbon or nitrogen atom is referred to as a van Alphen-Hüttle rearrangement because of the early work of both van Alphen[106,139] in 1943 and Hüttle in 1960.[74] A general representation of these rearrangements is Scheme 9. The formation of the product pyrazoles has been accommodated in terms of competitive, suprafacial [1,5]-shifts by a substituent at C-3.[140] A [1,5] anti-clockwise migration of R^1 in **82** affords the 1*H*-pyrazole (**83**) while a [1,5] clockwise migration of R^1 in **82** affords the 4*H*-pyrazole (**84**).

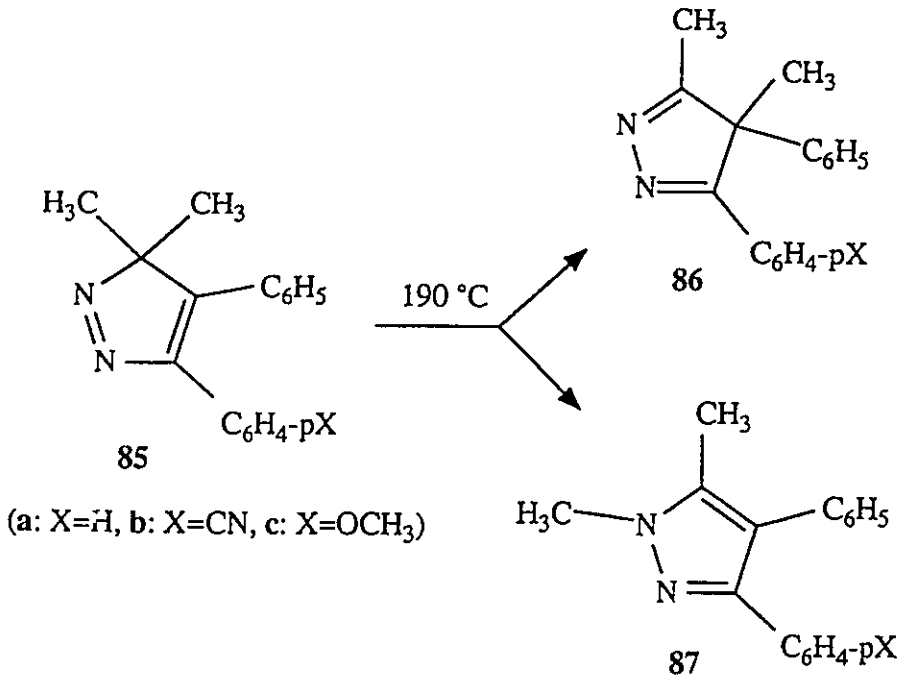


Scheme 9

1.2.6 Studies on the mechanism of 3*H*-pyrazole rearrangement

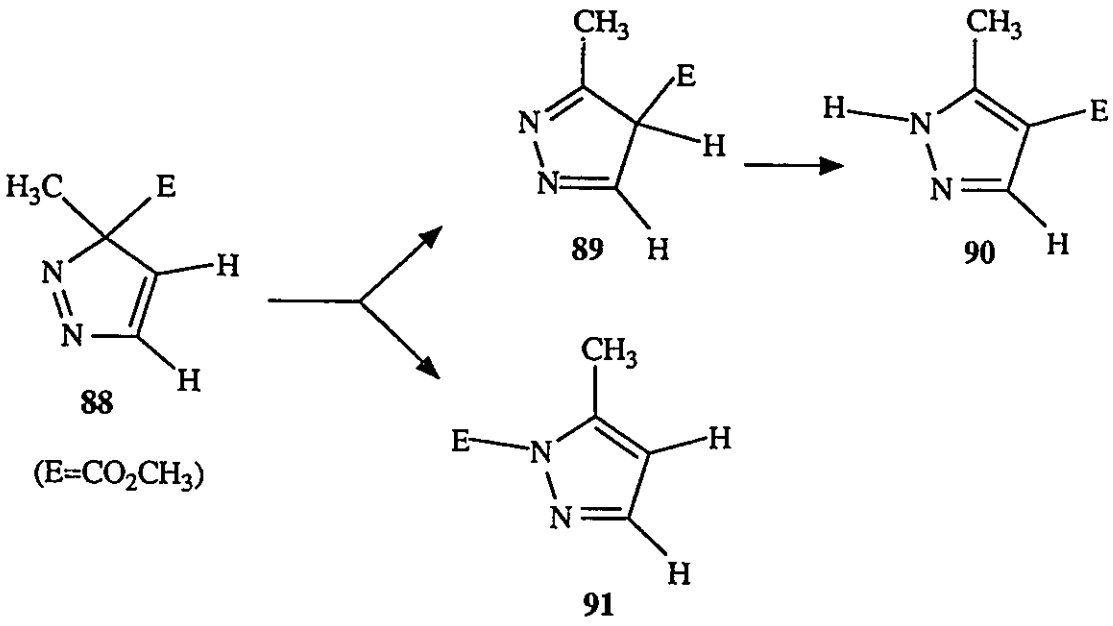
Leigh and Arnold carried out a kinetic study on the rearrangement of 3*H*-pyrazoles **85a-c** in diphenyl ether solution at 190 °C (Scheme 10).[141] They concluded that these 3*H*-pyrazole rearrangements were concerted in nature. The products of rearrangement, **86** and **87**, were formed in a 10 : 1 ratio. Arrhenius parameters were $E_a = 34.2 \pm 0.7$ kcal

mol^{-1} and $\Delta S^{\ddagger} = -5.6 \pm 1.6$ eu for **85a** → **86a** and $E_a = 35.6 \pm 1.1$ kcal mol^{-1} and $\Delta S^{\ddagger} = -7.0 \pm 2.3$ eu for **85a** → **87a**. The thermodynamically more stable product was the aromatic 1*H*-pyrazole **87**. The 4*H*-pyrazole **86** was stable at 190 °C so the product ratio reflects the relative rates of the two competitive [1,5]-methyl migrations. Therefore, product formation is controlled by kinetic factors. The fact that the 4*H*-pyrazole isomer (**86**) is favoured was rationalized in the following manner. Suprafacial migration of methyl from C-3 to N-2 makes N-2 tetrahedral, therefore, conformational and electronic reorganization must occur before aromatic stabilization can develop. Thus, it was suggested that, in the absence of aromatic stabilization, the bonding arrangement in the 4*H*-pyrazole, with two relatively strong carbon-nitrogen double bonds, is more stable than that in the 1*H*-pyrazole. The observation of only one of the two possible isomeric N-substituted pyrazole products is consistent with a concerted [1,5]-sigmatropic rearrangement. A Hammet plot [$\log(k_X/k_H)$ vs. σ_p] gave a straight line with a slope of + 0.33 for ρ. Leigh and Arnold suggested that this small positive ρ value is consistent with a concerted reaction. However, it may also suggest a small amount of negative charge development in the pyrazole ring at the transition state for rearrangement.



Scheme 10

Schiess and Stalder studied the thermal rearrangement of 3*H*-pyrazole **88** at 65 °C (Scheme 11).[142] The carbomethoxy substituent migrates to both C-4 and N-2. Migration to carbon generates intermediate 4*H*-pyrazole **89** which undergoes further rearrangement to 1*H*-pyrazole **90**. Migration of the carbomethoxy substituent to nitrogen yields 1*H*-pyrazole **91**. Activation parameters for the conversion of **88** to **90** and **91** were determined as the following: $E_a = 24.0 \pm 0.4$ kcal/mol and log A = 11.8 ± 0.4. A kinetic study revealed the influence of solvent polarity on the rate and direction of this rearrangement (Table 5). The overall first order rate constants for the formation of **90** and **91** from **88** showed a small but significant solvent effect. Zwitterionic structures such as **92** or **93** were excluded as distinct reaction intermediates.

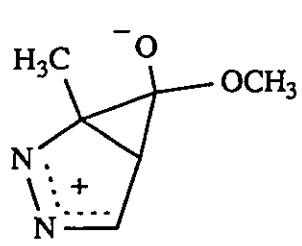


Scheme 11

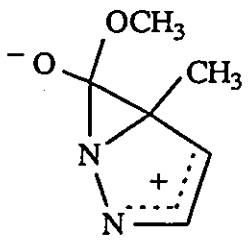
Table 5. Isomerization of **88** to **90** and **91** at 65 °C.

Solvent	E_T[a]	k_{obs} ($x10^{-4}$ s^{-1})	Products **90:91**
CCl_4	32.5	1.09	20:80
dioxane	36.0	1.36	22:78
C_6H_5Cl	37.5	1.70	28:72
C_6H_5CN	42.0	2.57	39:61
t-butyl alcohol	43.9	3.19	44:56
DMSO	45.0	3.09	46:54

[a]Solvent Polarity Parameter.



92



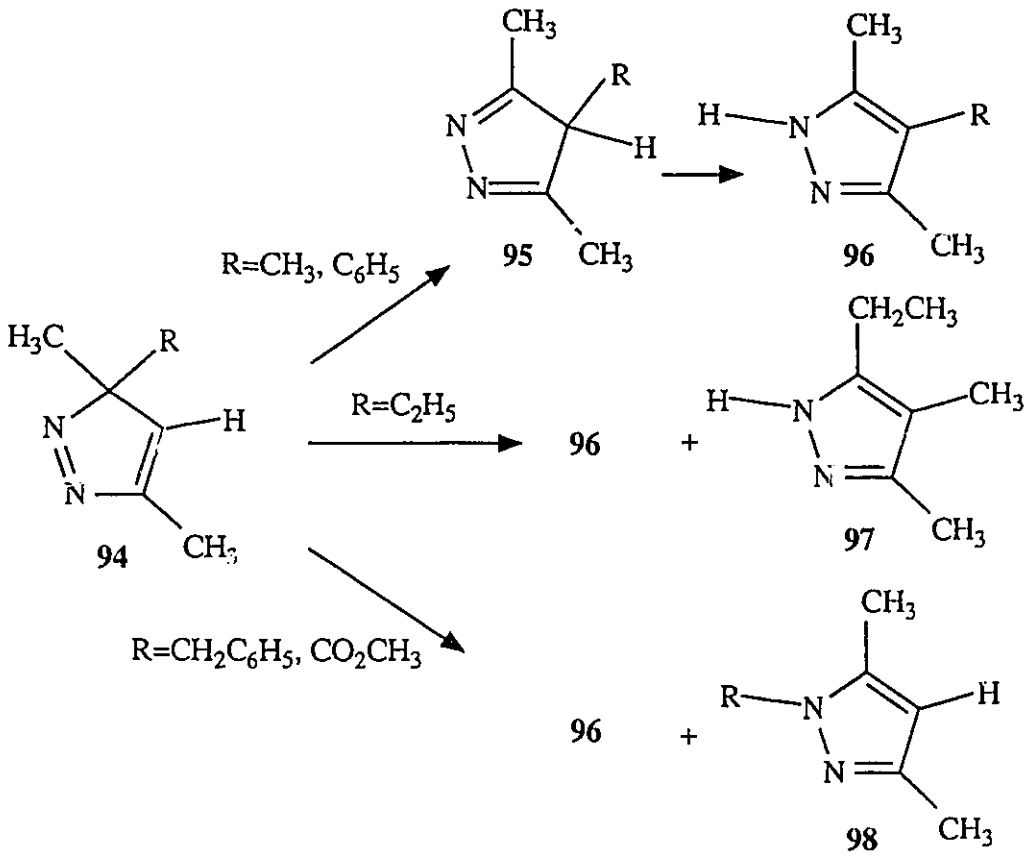
93

1.2.7 Migratory aptitude of substituents in 3*H*-pyrazole rearrangements

Schiess and Stalder studied the migration tendencies of some substituents toward sigmatropic rearrangement in 3*H*-pyrazoles **94a-e** (Scheme 12).[143] Migration of methyl and phenyl in **94a** and **94c**, respectively, occur exclusively to the adjacent carbon atom giving 1*H*-pyrazoles **96a** and **96c**, respectively. 4*H*-Pyrazoles **95a** and **95c** are intermediates in these rearrangements. 3*H*-Pyrazole **94b** rearranges to give **97** as well as **96b** since the migration of methyl is competitive with the migration of ethyl. The benzyl group in **94d** and the carbomethoxy group in **94e** migrate to both C-4 and N-2. Table 6 summarizes the results of the kinetic study.

The migration tendency of the R substituents is the following, in increasing order: methyl < ethyl < benzyl < phenyl < carbomethoxy. The second order interaction of the empty π^*-orbital of a migrating group with an occupied molecular orbital of the array of atoms in the heterocyclic ring contributes to the higher migratory aptitude of some substituents.[144,145] Presumably, the importance of this interaction decreases the higher the energy of the π^*-level in the migrating group. Alkyl groups which lack a π^*-orbital have low migratory aptitudes. Furthermore, the differences in the migration tendencies between methyl, ethyl, and benzyl show that there must be additional factors such as

ground state strain or bond strength of the shifting σ-bond which contribute to the migration tendency of a substituent in [1,5]-sigmatropic migrations.[143]



(a: $R=CH_3$; b: $R=C_2H_5$; c: $R=C_6H_5$; d: $R=CH_2C_6H_5$; e: CO_2CH_3)

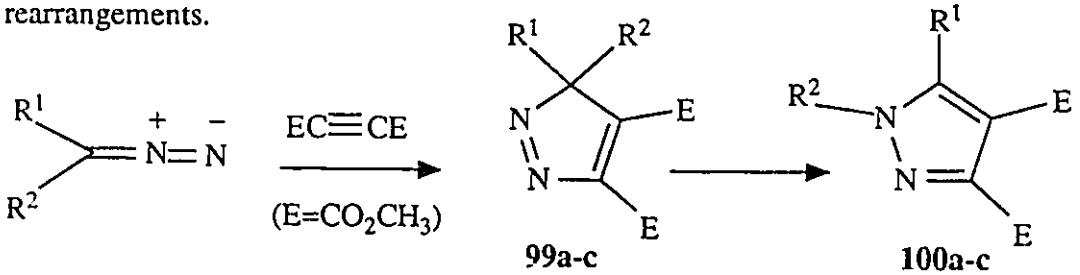
Scheme 12

Table 6. Rearrangement of **94a-e** at 120 °C.

94	Products (%)			Ea (kcal/mol)	k_{obs}[a] (s^{-1})	k_{rel}[b]
	96	97	98			
94a,[c] R=CH_3	100	-	-	30.8 ± 0.7	1.15 ± 10^{-6}	1[e]
94b,[c] R=C_2H_5	94	6	-	28.4 ± 0.4	1.42 ± 10^{-5}	23
94c,[d] R=C_6H_5	100	-	-	27.0 ± 0.4	3.05 ± 10^{-4}	530
94d,[d] R=$CH_2C_6H_5$	67	-	33	28.4 ± 0.4	1.35 ± 10^{-4}	157
94e,[c] R=CO_2CH_3	31	-	69	23.4 ± 0.4	3.53 ± 10^{-2}	19000

[a]Overall first order rate constants for the disappearance of **94**.
[b]Relative rates for the migration of R to carbon (**94**→**96**).
[c]In *tert*-butyl alcohol.
[d]In DMSO.
[e]Corrected for by a statistical factor of 2.

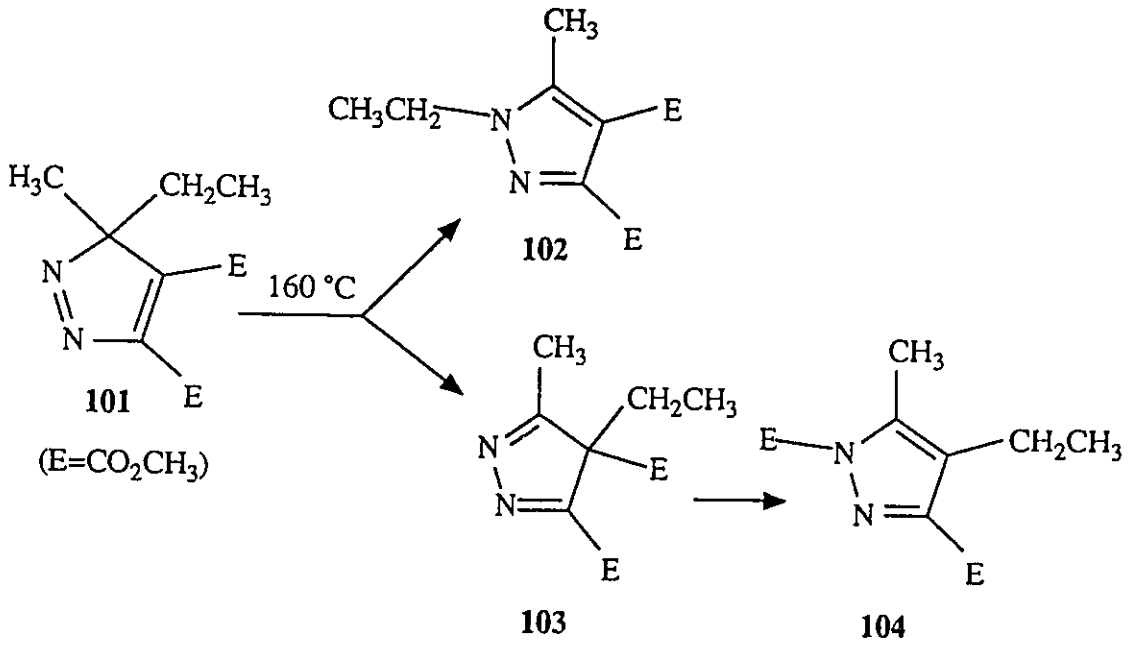
Franck-Neumann and coworkers discovered that 3*H*-pyrazoles **99a-c** undergo spontaneous rearrangement at ambient temperature, under the conditions of their formation, to yield 1*H*-pyrazoles **100a-c** (Scheme 13).[82,84] Therefore, the following substituents have high migratory aptitudes: acetyl, carbomethoxy, and cyano. The rearrangements were mechanistically described as concerted [1,5]-sigmatropic rearrangements.



(**a**: R^1=CH_3, R^2=$COCH_3$, **b**: R^1=CH_3, R^2=CO_2CH_3, **c**: R^1=$CH(CH_3)_2$, R^2=CN)

Scheme 13

Warkentin and coworkers recently investigated the thermal rearrangement of 3*H*-pyrazole **101** in benzene-d_6 at 160 °C (Scheme 14).[146] 3*H*-Pyrazole **101** underwent rearrangement by sequential [1,5]-sigmatropic shifts. 1*H*-Pyrazoles **102** and **104** were formed in a 1 : 2 ratio, respectively. 1*H*-Pyrazole **102** was formed from a [1,5]-anti-clockwise migration of ethyl to nitrogen (ethyl has a higher migratory aptitude than methyl). An initial [1,5]-shift of ethyl to carbon afforded the intermediate 4*H*-pyrazole **103** which was unstable at 160 °C. A [1,5]-anti-clockwise migration of carbomethoxy to the carbon bearing the methyl substituent, followed by another [1,5]-anticlockwise migration of carbomethoxy to nitrogen gave 1*H*-pyrazole **104**. This study demonstrates how the migratory aptitude of each substituent on the tetrahedral carbon of a pyrazole dictates the type of products formed from thermal rearrangement.



Scheme 14

1.3 Nucleophilic Aliphatic Substitution Reactions involving Ion-Pair Intermediates

1.3.1 Nucleophilic aliphatic substitution reactions (general)

A nucleophilic substitution reaction converts a nucleophile and a substrate into a product and a leaving group (Equation 1). These reactions are classically treated in terms of S_N2 (Equation 2) and S_N1 (Equation 3) mechanisms which were developed by Hughes and Ingold.[147,148]

$$\text{Nucleophile} + \text{R-X} \longrightarrow \text{Nucleophile-R} + \text{X} \qquad (1)$$

$$\text{Y} + \text{R-X} \longrightarrow [\text{Y}\cdots\text{R}\cdots\text{X}]^{\ddagger} \longrightarrow \text{R-Y} + \text{X} \qquad (2)$$

$$\text{R-X} \xrightarrow{\text{slow}} \text{R}^+ + \text{X}, \text{ followed by } \text{R}^+ + \text{Y} \xrightarrow{\text{fast}} \text{R-Y} \qquad (3)$$

An S_N2 reaction is bimolecular and the rate is first order both in the nucleophile and in the substrate concentration, while an S_N1 reaction is unimolecular and the rate depends on the concentration of the substrate and is independent of the concentration of the nucleophile. The first, effectively reversible, step is followed by fast reaction of the resulting carbocation with a nucleophile. An S_N2 reaction is a direct, one-step displacement with no intermediate while an S_N1 reaction is stepwise. There are several reviews on nucleophilic aliphatic substitution reactions.[149-158]

In the 1950's, Winstein showed convincingly that the S_N1 mechanism was more complex than had been first postulated by Hughes and Ingold.[159,160] Winstein obtained evidence that ionization takes place in several stages and he distinguished between "intimate ion pairs" (II) and "solvent-separated ion pairs" (III) as two distinct types of discrete intermediates before the stage of a free carbocation is reached (Scheme 15).

$$\underset{\mathbf{I}}{R\text{-}X} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathbf{II}}{R^+X^-} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{\mathbf{III}}{R^+ \| X^-} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \underset{\mathbf{IV}}{R^+ + X^-}$$

Scheme 15

The Winstein Ion-Pair Model provides the simplest treatment of nucleophilic aliphatic substitution reactions consistent with the available experimental evidence. An S_N1 reaction can be seen as one in which the rate-limiting step is unimolecular formation of II, III, or IV (ie. k_1, k_2, or k_3) followed by fast reaction with a nucleophile. Several factors influence whether I, II, III, or IV will be involved in a particular reaction. An increase in carbocation or leaving group stability promotes reaction through a more dissociated intermediate. An increase in solvent ionizing power also promotes dissociation, but an increase in nucleophilicity has the opposite effect, promoting reaction at an earlier, less dissociated, stage. Classical S_N1 reactions are even more complex than the Winstein ion pair model suggests. For example, there is a continuum between S_N1 and S_N2 reaction mechanisms. Furthermore, the solvent may provide nucleophilic assistance to ionization.

A new system of nomenclature for describing nucleophilic substitution reactions has been recently recommended by IUPAC[161,162] and is useful since the Ingold nomenclature has become "overburdened with non-systematic modification for 30 years."[153]

The formation of a new bond during the transformation of one molecular structure to another is symbolized by "A" (association or attachment), while the bond breaking components are symbolized by "D" (dissociation or detachment). When the changes take place in separate reaction steps, they are separated by a "+". A symbol "*" is used instead of a "+" to designate an intermediate which is of such a short lifetime that it reacts in a step faster than diffusion but slower than a molecular vibration. A subscript "N" is used to designate bond formation to a nucleophile or bond cleavage with loss of a nucleofuge (leaving group). A concerted nucleophilic substitution can then be described as "D_NA_N". A stepwise nucleophilic substitution reaction where an intermediate can diffuse through the solvent can be described as "D_N+A_N" ("classical S_N1"). "D_N*A_N" describes a stepwise nucleophilic substitution reaction involving an ion-pair intermediate which is not diffusionally equilibrated with the bulk of the solvent (contact or solvent-separated ion pair).

The following discussion focuses on some rates of S_N1 solvolyses (D_N+A_N and/or D_N*A_N). Two factors which affect the rate of ionization include substrate stability and leaving group ability.

1.3.2 Substrate stability

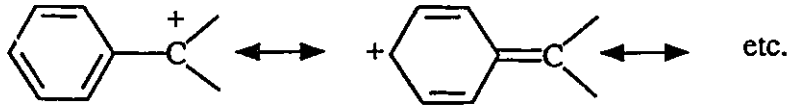
Reaction by an S_N1 (D_N+A_N and/or D_N*A_N) mechanism commonly occurs for tertiary alkyl halides and resonance stabilized secondary alkyl halides, in polar solvents. Changes in substrate structure effect the rate of ionization in such a reaction. The rates of ionization of alkyl halides depend on the stabilities of the corresponding cations.[163] The effect of an alkyl group, compared to hydrogen, when bonded to an sp^2 cationic centre is inductively electron-donating and stabilization by hyperconjugation is very important. The effects of α-methyl substitution on the rates of solvolysis of some simple alkyl compounds are shown in Table 7.[164,165] *tert*-Butyl bromide solvolyzes approximately 320 times faster than methyl bromide in marked contrast to its relative unreactivity in S_N2 (A_ND_N) reactions. Schleyer and coworkers estimated that for S_N1 reactions (D_N+A_N or D_N*A_N) with no assistance to ionization by nucleophiles, the substitution of H by CH_3 on the reacting carbon in 2-adamantyl solvolysis accelerates the rate by a factor of 10^8.[166]

Table 7. Solvolysis rates of alkyl bromides, $R^1R^2R^3CBr$, in EtOH at 55 °C.

R^1	R^2	R^3	Relative Rates
H	H	H	1.00
CH_3	H	H	0.38
CH_3	CH_3	H	0.28
CH_3	CH_3	CH_3	320

An aryl group attached to the α-carbon atom assists a reaction occurring by the S_N1 (D_N+A_N and/or D_N*A_N) mechanism by allowing the developing positive charge to be distributed over the conjugated system **105**. In Table 8 the effects of α-substitution on

the reacting carbon are compared.[167-170] *tert*-Butyl chloride solvolyzes approximately 83 times faster than benzyl chloride, while *tert*-butyl chloride and α-phenylethyl chloride are alike in reactivities. A rough approximation is that a phenyl group is as effective in stabilizing a carbocation as are two methyl groups.

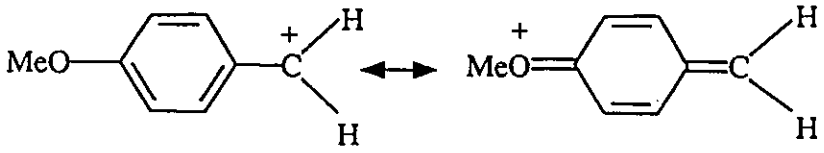


105

Table 8. Solvolysis rates of arylmethyl chlorides, $R^1R^2R^3CCl$, and *t*-butyl chloride, $R^1R^2R^3CCl$, in 80% EtOH at 50 °C.

R^1	R^2	R^3	Relative Rates
CH_3	CH_3	CH_3	1.00
C_6H_5	H	H	0.01
C_6H_5	CH_3	H	0.90
C_6H_5	C_6H_5	H	1300

The effect of a methoxy group in the para position of a benzyl halide is striking. In 67% aqueous acetone solvent, para-methoxybenzyl chloride solvolyzes approximately 10^3 times faster than benzyl chloride.[171] The para-methoxybenzyl cation is resonance stabilized because the oxygen atom can accept a considerable fraction of the positive charge via resonance, as illustrated with **106**. Furthermore, a Hammet plot [log (k_X/k_H) vs. σ^+] for the solvoiysis of cumyl chlorides **107** in 90% aqueous acetone at 25 °C gave a ρ value of -4.54.[172]



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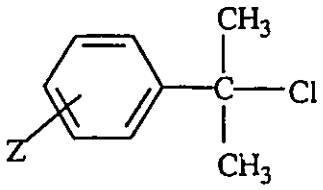

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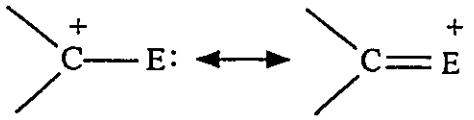
When atoms with unshared electron pairs are bonded to the reaction centre in an S_N1 (D_N+A_N and/or D_N*A_N) reaction, two effects must be considered: the inductive effect which is usually electron-withdrawing, and the electron-donating conjugative effect (**108**).



108

For more basic atoms, O,N,S, conjugation is dominant as the following relative solvolysis rate shows. For example, in ethanol, methyl chloromethyl ether solvolyzes approximately 10^{13} times faster than *n*-propyl chloride.[173] The intermediate in the solvolysis of methyl chloromethyl ether should be regarded more as oxonium ion **109** rather than a carbonium ion.

109

The first order rate constant for the solvolysis of *tert*-butyl bromide ($k^{25\,°C}$ = 3.58 x 10^{-4} s^{-1}) is approximately 10^3 times greater than the first order rate constant for the solvolysis of 1-adamantyl bromide ($k^{25\,°C}$ = 5.10 x 10^{-7} s^{-1}) in 80% aqueous ethanol solution but only 3 times faster in the nonnucleophilic solvent mixture of 97% hexafluoroisopropyl alcohol/water.[174-176] It was suggested by Bentley and coworkers that *tert*-butyl chloride most likely undergoes assisted ionization in nucleophilic solvents (ie. the nucleophile attacks a carbocation-leaving group ion-pair). Bentley and coworkers found that the equilibrium for anion exchange between 1-adamantyl and *tert*-butyl cations favours the 1-adamantyl cation in both the gas phase and in solution.[174] They suggested that the extra β-and γ-carbons provide sufficient stabilization (ie. C-C hyperconjugation) to overcome angle strain effects as an sp^2-hybridized positively charged carbon in the comparatively rigid 1-adamantyl framework is formed. Since S_N1 solvolysis rates parallel carbocation stabilities, the rates of solvolysis of *tert*-butyl halides should be lower than those for 1-adamantyl halides. It was predicted that in less nucleophilic solvents, 1-adamantyl halides should solvolyze faster than *tert*-butyl halides.[174] It has been suggested, however, that the solvent effect in *tert*-butyl halide solvolysis is not due to nucleophilic assistance to substitution but to electrophilic assistance to ionization.[172]

1.3.3 Leaving group ability

The leaving group can determine reactivity in nucleophilic substitution. Leaving groups which depart with the bonding electron pair are termed "nucleofuges".[178] Nucleofugality, the tendency of an atom or group to depart with the bonding electron pair

has been little studied as available data on most reactions cover only restricted ranges of leaving groups and in many systems the leaving groups are conjugate bases of strong acids. The rate of the reaction will reflect nucleofugality only if the leaving group is involved in the rate determining step as in S_N1 reactions (D_N+A_N and/or D_N*A_N). It is a misconception that nucleofugality depends simply upon the pK_a (H_2O) of the conjugate acid of the leaving group.[178] The analogy of basicity toward proton and basicity toward carbon fails for leaving groups of different types (ie. sulfonates vs. halides). For a reaction in solution, cleavage of a bond to a leaving group must involve the C-X bond strength [D(C-X)], the ability of X to accept the electron pair of the C-X bond as reflected in the electron affinity of X, and the solvation energy of the leaving group.[179] Transfer of charge to the leaving group is also assisted by resonance delocalization in the leaving group.

Some relative reaction rates for some common leaving groups are given in Table 9.[159,180-182] As the electron-withdrawing ability of X increases the rate increases and the sulfonates are much better leaving groups than the halogens.

Table 9. Relative reaction rates for some common leaving groups in S_N1 reactions.[a]

Entry	Leaving Group	Relative Rates
1	OSO_2CF_3[b]	2.5×10^{14}
2	$OSO_2C_6H_4$-p-Br[c]	7.5×10^{9}
3	$OSO_2C_6H_4$-p-Me[b]	2.5×10^{9}
4	Br[b]	5.0×10^{5}
5	Cl[b,e]	1.3×10^{4}
6	$OCOC_6H_4$-p-NO_2[d]	1.0

[a]Relative rates are approximate because they are not independent of substrate structure.
[b]Comparisons are for bridgehead solvolysis.
[c]Entry 2 is compared with entry 3 for 3-anisyl-2-butyl.
[d]Entry 6 is compared with entry 5 for benzhydryl.
[e]Data obtained by extrapolation.

CHAPTER 2

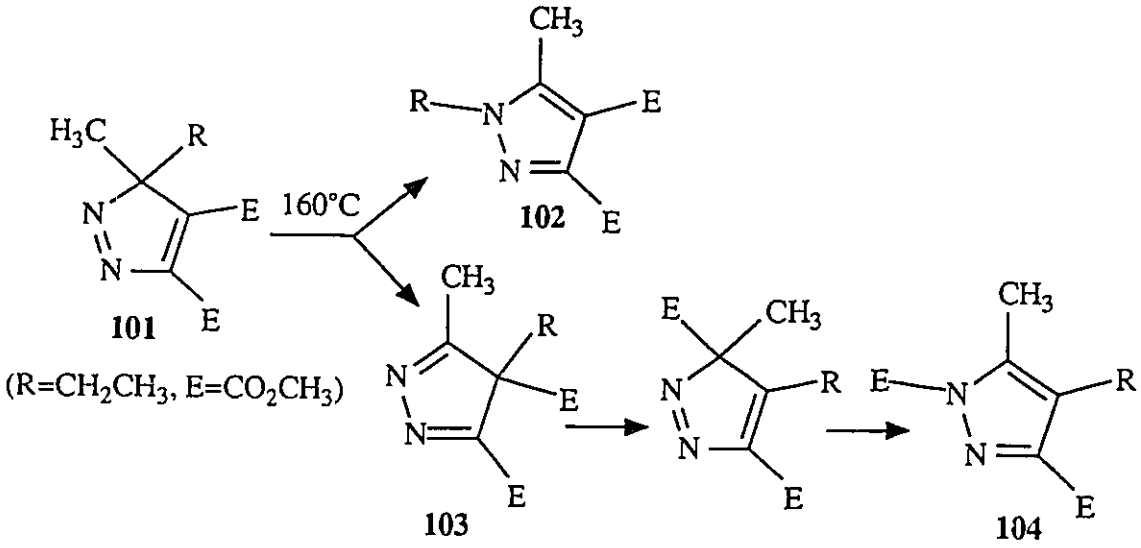
Studies of the Thermal Rearrangements of Dimethyl 3-Alkyl-3-methyl-3*H*-pyrazole-4,5-dicarboxylates

2.0 Objective

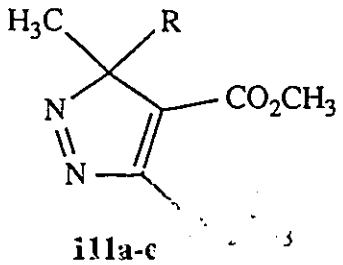
3*H*-Pyrazoles generally undergo thermal rearrangement by competitive [1,5]-sigmatropic shifts of a substituent from the tetrahedral carbon centre.[78, 82-85, 90, 107, 108, 141, 143] An example of a 3*H*-pyrazole which undergoes "typical" [1,5]-sigmatropic rearrangement is given in Scheme 16. 3-Ethyl-3-methyl-3*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester (**101**) rearranges at 160 °C to give **102** (33%) and **104** (67%). A [1,5]-ethyl migration to nitrogen forms **102** while a [1,5]-ethyl migration to carbon forms intermediate **103**, which undergoes two consecutive anti-clockwise [1,5]-carbomethoxy migrations to give **104**.[146]

It became of interest to investigate the thermal rearrangement of a series of similar 3*H*-pyrazoles, but ones which may undergo thermal rearrangement by an alternative mechanism. The objective was to study the thermal rearrangement of dimethyl 3-alkyl-3-methyl-3*H*-pyrazole-4,5-dicarboxylates (**111a-e**) bearing alkyl substituents at C-3 which are relatively stable in cationic form. The R substituents (benzhydryl, methoxymethyl, *tert*-butyl, 1-adamantyl, and para-methoxybenzyl) were chosen because they form cations

in nucleophilic aliphatic substitution reactions of R-X (X = halide).[150,153] One could determine whether the rearrangement of 3*H*-pyrazoles **111a-e** takes place by a concerted or a stepwise, ion-pair mechanism. Non-concerted [1,5]-sigmatropic rearrangements of 3*H*-pyrazoles are unknown. A preliminary report of the research in this chapter was communicated in 1990,[183] and subsequently a full paper has been published in the *Journal of the American Chemical Society* in 1992.[184]



Scheme 16



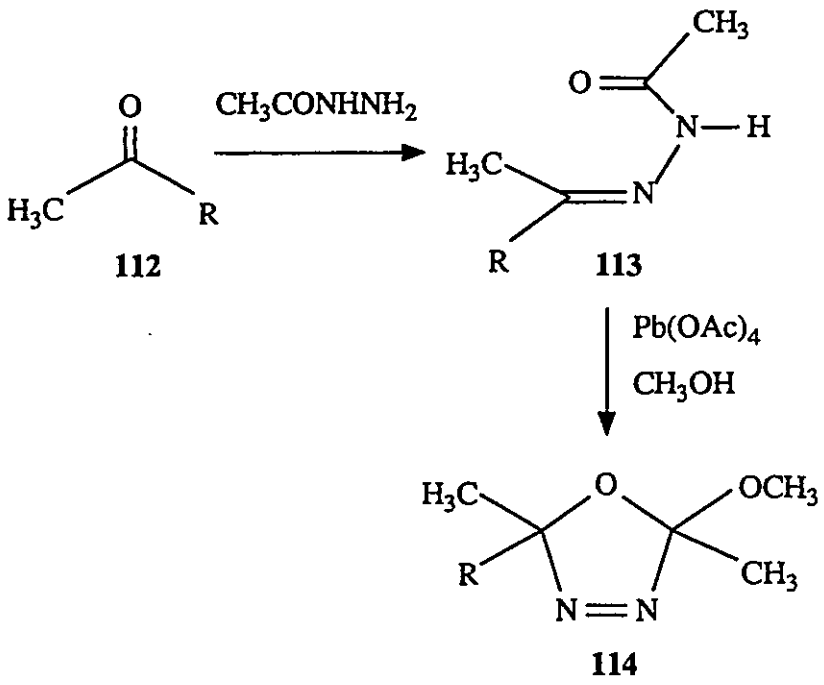
111a-e

(**a**: R=CHPh$_2$; **b**: R=CH$_2$OMe; **c**: R=C(Me)$_3$; **d**: R=1-adamantyl; **e**: R=p-CH$_2$C$_6$H$_4$OMe)

The methodology utilized for the synthesis of 3*H*-pyrazoles **111a-e** was developed by Warkentin and coworkers in 1989.[119] Photochemical reaction of Δ^3-1,3,4-oxadiazolines generates diazoalkanes which can readily react with dimethyl acetylenedicarboxylate via 1,3-dipolar cycloadditions to afford the target 3*H*-pyrazoles. The synthesis of the appropriate oxadiazolines was required.

2.1 Synthesis of 5-alkyl-2-methoxy-2,5-dimethyl-Δ^3-1,3,4-oxadiazolines

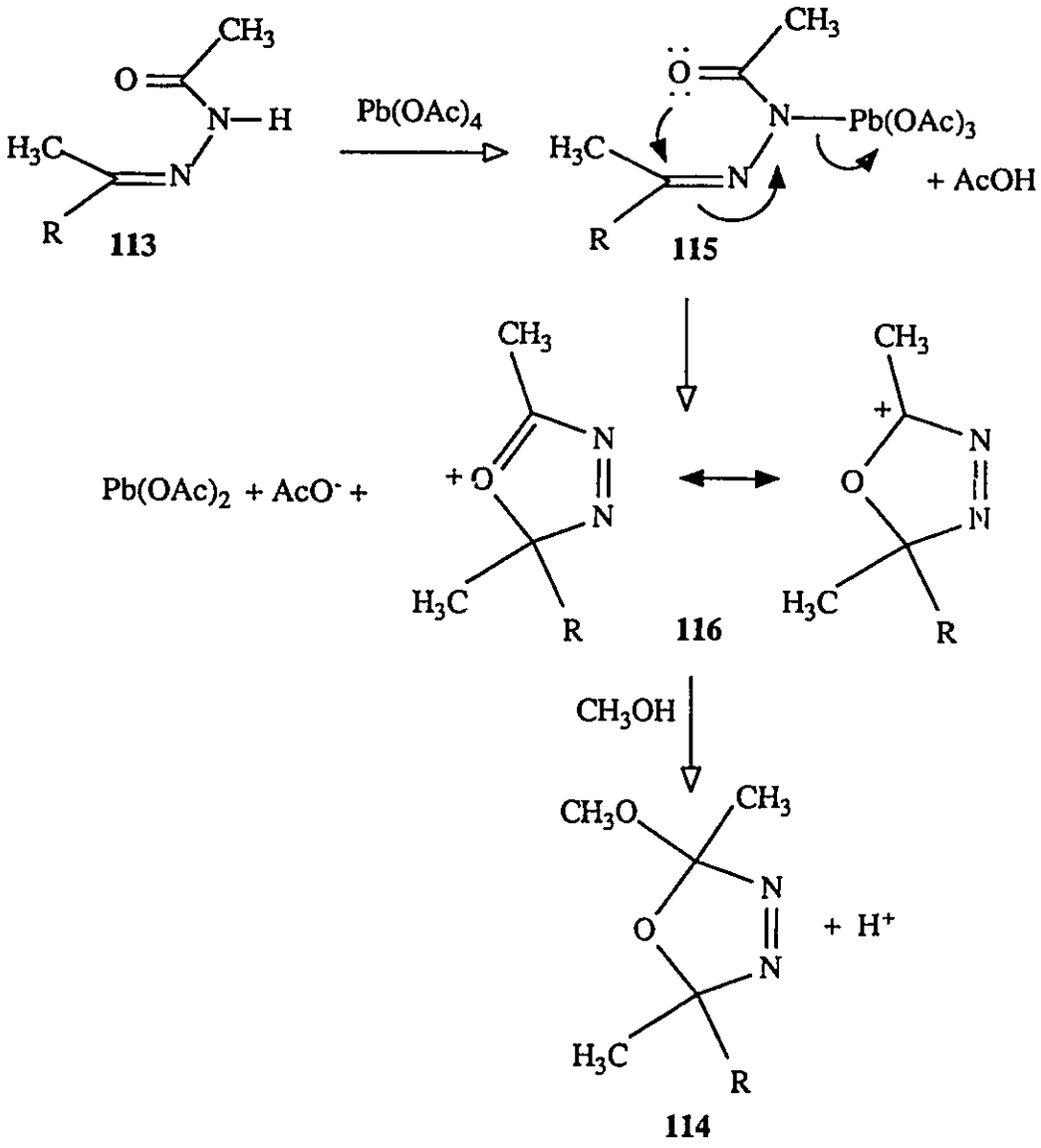
The first step in the synthesis of oxadiazolines **114a-e** involved the condensation of ketones **112a-e** with acetic hydrazide to afford acetyl hydrazones **113a-e** (Scheme 17). The acetyl hydrazones were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as high resolution mass spectroscopy. Although the synthesis of acetyl hydrazone **113c** was previously reported,[119] the preparative procedure was modified in this work. The second step in the synthesis of the oxadiazolines involved the oxidative cyclization of **113a-e** with lead tetraacetate in methanol solvent to afford oxadiazolines **114a-e**. The synthesis of other oxadiazolines by this preparative method has been reported,[119,146, 185-188] and the synthesis of oxadiazoline **114c** was previously reported.[119] The oxadiazolines **114a**, **114b**, **114d**, and **114e** are new compounds, which were characterized by both ^{1}H and ^{13}C NMR spectroscopy as well as high resolution mass spectrometry. A mixture of cis and trans isomers was obtained for oxadiazolines **114** and those percentages are reported in Chapter 5 (Experimental).



(**a**: R=$CHPh_2$; **b**: R=CH_2OMe; **c**: R=$C(Me)_3$; **d**: R=1-adamantyl; **e**: R=p-$CH_2C_6H_4OMe$)

Scheme 17

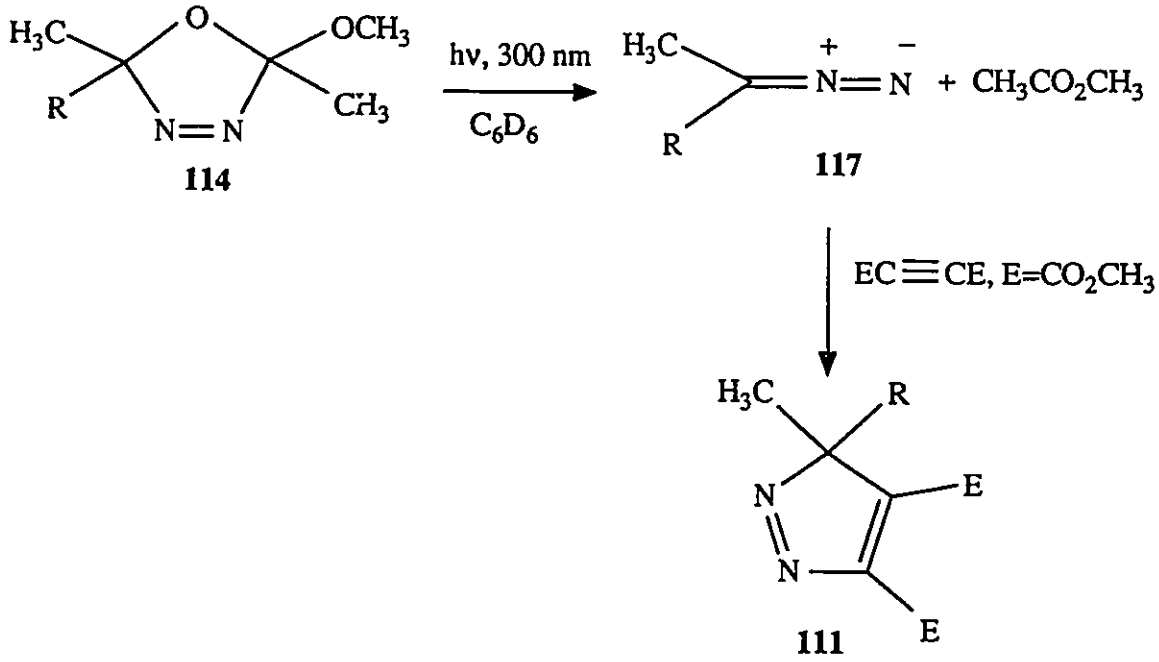
The proposed mechanism of oxidation of **113** with lead tetraacetate (Scheme 18) is not firmly established,[185] but it provides a qualitative understanding of the cyclization process. An intermediate organolead species (**115**) is formed having a nitrogen-lead bond.[189] This intermediate then cyclizes by an internal nucleophilic substitution. The lone pair of electrons on the carbonyl oxygen attack the carbon-nitrogen double bond to form intermediate carbocation **116**, which subsequently undergoes nucleophilic attack by methanol solvent to give oxadiazoline **114**.


CH3
O
N—H
H3C
N
R
113
Pb(OAc)4
CH3
O
N—Pb(OAc)3
H3C
N
R
115
+ AcOH
Pb(OAc)2 + AcO- +
CH3
+O
N
N
H3C
R
116
CH3
+
N
O
N
H3C
R
CH3OH
CH3O
CH3
N
O
N
H3C
R
+ H+
114

Scheme 18

2.2 Synthesis of 3*H*-pyrazoles

Solutions of 5-alkyl-2-methoxy-2,5-dimethyl-Δ^3-1,3,4-oxadiazolines **114a-e** in benzene containing dimethyl acetylenedicarboxylate were each photolyzed at 300 nm for 6 hours in a Rayonet apparatus. The oxadiazolines **114a-e** underwent C-N bond cleavage and subsequent fragmentation to afford diazoalkanes **117a-e** and methyl acetate. The intermediate diazoalkanes (**117a-e**) rapidly underwent 1,3-dipolar cycloadditions to dimethyl acetylenedicarboxylate to give solutions of unstable 3*H*-pyrazoles **111a-e** (Scheme 19). It was surprising that these 3*H*-pyrazoles rearranged in the media in which they were generated considering that 3*H*-pyrazole **101** requires a temperature of 160 °C for thermal rearrangement.[146]



(**a**: R=$CHPh_2$; **b**: R=CH_2OMe; **c**: R=$C(Me)_3$; **d**: R=1-adamantyl; **e**: R=p-$CH_2C_6H_4OMe$)

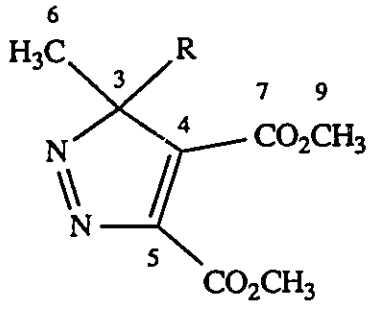
Scheme 19

By working quickly at low temperatures, it was possible to observe 3*H*-pyrazoles **111c** and **111d** by both ^{1}H and ^{13}C NMR spectroscopy while 3*H*-pyrazole **111e** could only be observed by ^{1}H NMR spectroscopy in a solution with its rearrangement products. The diazoalkanes (**117c-e**) were generated at -73 °C in toluene and dimethyl acetylenedicarboxylate was added with the Rayonet bulbs switched off. The mixtures were warmed quickly to room temperature to allow the cycloaddition reactions to proceed, and the toluene and volatiles were evaporated with a stream of dry N_2. Each residue was dissolved in benzene-d_6 and its NMR spectrum was acquired immediately. In Table 10, the ^{1}H NMR data and selected ^{13}C NMR chemical shifts have been tabulated for these 3*H*-pyrazoles. Some of the ^{13}C NMR chemical shifts were assigned by comparison to chemical shift assignments made by others for other 3*H*-pyrazoles.[190]

3*H*-Pyrazoles **111a** and **111b** rearranged too rapidly to be observed by ^{1}H NMR spectroscopy. Even when they were generated by the photolysis of **114a** and **114b**, respectively, in solutions of toluene-d_8 at -73 °C followed by the addition of dimethyl acetylenedicarboxylate with the Rayonet bulbs switched off, quick warming to room temperature for ^{1}H NMR spectroscopy showed only products resulting from the rearrangements of **111a** and **111b**.

Table 10.

^{1}H NMR and selected ^{13}C NMR chemical shifts (ppm) for 3*H*-pyrazoles in C_6D_6.



111

3*H*-Pyrazole, **111**	^{1}H NMR (200 MHz)	^{13}C NMR[a] (50 MHz)
111c, R=C(Me)$_3$	3.40 (s, 3 H, CO_2Me), 3.38 (s, 3 H, CO_2Me), 1.32 (s, 3 H, Me), 0.87 (s, 9 H, C(Me)$_3$).	107.63 (C-3), 156.37 (C-4), 145.19 (C-5), 16.32 (C-6), 165.52 (C-7), 160.67 (C-8), 52.40 (C-9), 52.06 (C-10).
111d, R=1-adamantyl	3.45 (s, 3 H, CO_2Me), 3.43 (s, 3 H CO_2Me), 1.87-1.45 (m, 15 H), 1.37 (s, 3 H, Me).	108.20 (C-3), 156.30 (C-4), 145.25 (C-5), 15.04 (C-6), 165.68 (C-7), 160.75 (C-8), 52.36 (C-9), 52.04 (C-10).
111e[b], R=p-$CH_2C_6H_4OMe$	6.99 (d, 2 H, J = 8.5 Hz), 6.57 (d, 2 H, J = 8.5 Hz), 3.44 (d, 1 H, J = -13.6 Hz), 3.35 (s, 3 H, CO_2Me), 3.26 (s, 3 H, CO_2Me), 3.15 (s, 3 H, OMe), 3.04 (d, 1 H, J= - 13.6 Hz), 1.30 (s, 3 H, Me).	

[a] C-7 and C-8 may be reversed. C-9 and C-10 may be reversed.

[b] The ^{1}H NMR spectrum was obtained from solutions containing **118e** (25%), **120e** (10%), and **111e** (65%). The ^{13}C NMR spectrum of **111e** could not be determined from this solution.

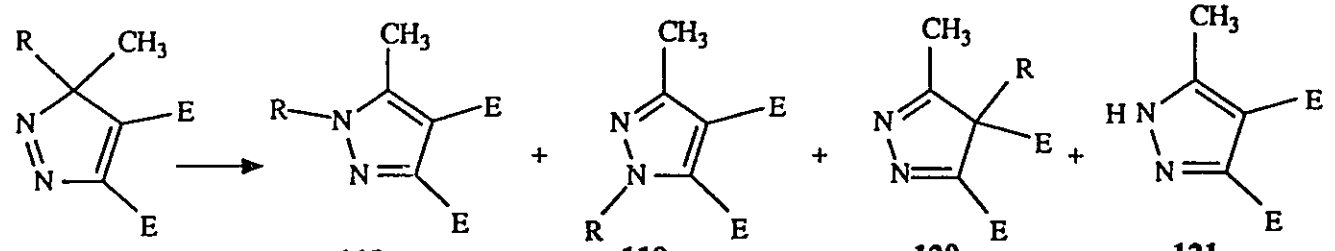
2.3 Rearrangement of 3*H*-pyrazoles 111a-e in benzene-d_6/toluene solvent

Table 11 reveals the products from rearrangement of 3*H*-pyrazoles **111a-e** in benzene-d_6 solvent. Rearrangement of 3*H*-pyrazole **111a** gave two 1*H*-pyrazoles, **118a** (91%) and **119a** (9%). 3*H*-Pyrazole **111b** rearranged to give **118b** (77%) and **120b** (23%), a 4*H*-pyrazole. The 4*H*-pyrazole could not be isolated as it was unstable under the conditions of centrifugal chromatography (silica gel) but its ^{1}H NMR spectrum could be obtained from the ^{1}H NMR spectrum of the mixture following photolysis. Centrifugal chromatography (silica gel) of the photolysis residue gave **118b** (66%) and **121** (19%). The identification of **121**, a known 1*H*-pyrazole, was confirmed by comparing both its ^{1}H NMR spectrum and its melting point with those reported in the literature.[83]

Unlike 3*H*-pyrazoles **111a** and **111b**, 3*H*-pyrazoles **111c-e** could be observed by ^{1}H NMR spectroscopy. Therefore, the observed rate constants for rearrangement of these 3*H*-pyrazoles could be determined by integration of their respective ^{1}H NMR spectra over time.

Observation of both the ^{1}H and ^{13}C NMR spectra of the photolysis mixture revealed that **111c** was formed in a quantitative yield. The rearrangement of 3*H*-pyrazole **111c** in benzene-d_6 was not cleanly first-order, but a good fit to first order kinetics resulted from the addition of 2.5 equivalents of triethylenediamine. Successive integration of the ^{1}H NMR spectrum over time gave an observed rate constant of $(6.2 \pm 0.2) \times 10^{-5}$ s^{-1} at 35 °C. 3*H*-Pyrazole **111c** rearranged in benzene-d_6 to give **118c** (39%), **121** (61%), and isobutene (60%). The ratio of products formed in the presence of triethylenediamine were very similar. The presence of isobutene was confirmed by a ^{1}H

Table 11. Products and product yields[a] from the thermal rearrangements of **111a-e** at ambient temperature in benzene-d_6.



111	**118**	**119**	**120**	**121**	+ other
111a, R=$CHPh_2$	91	9	nil	nil	
111b, R=CH_2OMe	77	nil	23	nil	
111c,[b] R=$C(Me)_3$	39	nil	nil	61	60 isobutene
111d,[c] R=1-adamantyl	63[d]	nil	nil	nil	
111e,[e] R=p-$CH_2C_6H_4OMe$	64	nil	36	nil	

[a] At the level of detection afforded by ^1H NMR spectroscopy, the products listed were the only products from rearrangement and yield numbers (%) reflect complete materials balance prior to opening of a tube, unless otherwise indicated.

[b] $k = (6.2 \pm 0.2) \times 10^{-5}\ s^{-1}$ at 35 °C.

[c] $k = (5.6 \pm 0.2) \times 10^{-5}\ s^{-1}$ at 35 °C.

[d] Yield of isolated product. The rearrangement appeared to go in quantitative yield.

[e] $k = (9.8 \pm 0.4) \times 10^{-5}\ s^{-1}$ at 20 °C.

NMR spectroscopy decoupling experiment on the reaction mixture after the rearrangement of **111c** (sealed nmr tube). Irradiation of the multiplet at 4.74 ppm (CH_2) caused the collapse of the triplet at 1.60 ppm (2 CH_3).

3*H*-Pyrazole **111d** was prepared as a solution in benzene-d_6 and observation of the ^1H and ^{13}C NMR spectra of the photolysis mixture revealed that **111d** was formed in a quantitative yield. The observed rate constant for the increase in concentration of rearrangement product **118d** at 35 °C was (5.6 ± 0.2) x 10^{-5} s^{-1}. 3*H*-Pyrazole **111d** rearranged to afford only **118d**.

The ^1H NMR spectrum of **111e** was obtained from a solution containing **118e** (10%), **120e** (10%), and **111e** (65%) in benzene-d_6. It was not possible to assign the ^{13}C NMR signals of **111e** from the spectrum in that solution. The observed rate constant for the disappearance of **111e** at 20 °C was (9.80 ± 0.4) x 10^{-5} s^{-1}. 3*H*-Pyrazole **111e** rearranged in benzene-d_6 to give **118e** (64%) and **120e** (36%). 4*H*-Pyrazole **120e** could be isolated by centrifugal chromatography (silica gel) and it was relatively stable.

2.4 Mechanism of rearrangement of 3*H*-pyrazoles 111a-e in benzene

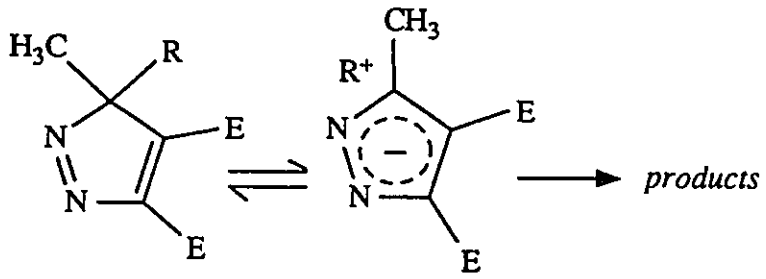
From observed rate constants for the rearrangement of 3*H*-pyrazoles in benzene-d_6, the order of rate constants was established as **111a** and **111b** > **111e** > **111c** ≈ **111d**. Rate constants for the fast rearrangements of 3*H*-pyrazoles **111a** and **111b** were not determined. The relative rates of rearrangement of 3*H*-pyrazoles **111e**, **111c**, and **111d** were approximately 4.9, 1.1, and 1.0, respectively. A 2.8-fold increase in the rate of rearrangement of **111e** compared to **111c** was assumed for the 15 °C temperature

difference between which these observed rate constants were determined. The five 3*H*-pyrazoles rearrange with large rate enhancements (approximately 10^4 for the slowest) compared to 3*H*-pyrazole **101** (R = CH_2CH_3) which is known to rearrange at 160 °C, presumably by consecutive [1,5]-sigmatropic migrations.[146] The presence of isobutene as a product in the rearrangement of 3*H*-pyrazole **111c** suggests the presence of a *tert*-butyl cation intermediate, which subsequently undergoes proton loss. The large rate enhancements for rearrangement of **111a-e**, in addition to the fact that **111c** gave isobutene and **121** as fragmentation products, suggest that these 3*H*-pyrazoles undergo thermal rearrangement by an alternative mechanism.

The major rearrangement product of the 3*H*-pyrazoles (except **111c**) in benzene-d_6 was 1*H*-pyrazole **118**. It is interesting that the rearrangement of 3*H*-pyrazoles **111b** and **111e** gave the 4*H*-pyrazole as the minor product. This observation is contrary to the reported rearrangements of other 3*H*-pyrazoles which rearrange by concerted alkyl migrations from C-3 of the 3*H*-pyrazoles. These include the rearrangement of 4,5-diaryl-3,3-dimethyl-3*H*-pyrazoles,[141] 3-alkyl-3,5-dimethyl-3*H*-pyrazoles (where alkyl = methyl, ethyl, or benzyl),[143] and dimethyl 3-alkyl-3-methyl-3*H*-pyrazole-4,5-dicarboxylates (where alkyl = methyl, ethyl).[146] Those rearrangements primarily give the kinetic product initially, the corresponding 4*H*-pyrazole, rather than the thermodynamically more stable aromatic counterpart, by what are believed to be concerted [1,5]-sigmatropic rearrangements. Since 3*H*-pyrazoles **111b** and **111e** do not afford the 4*H*-pyrazole as the major rearrangement product, this suggests that a different mechanism may be operating

in the thermal rearrangement of the 3*H*-pyrazoles.

A stepwise mechanism involving a discrete ion-pair intermediate (an alkyl cation and a pyrazole anion) is proposed for the rearrangement of 3*H*-pyrazoles **111a-e** in benzene solvent (Scheme 20). The first step is reversible covalent bond cleavage to an ion pair. The second step is collapse of the ion pair to afford more stable pyrazole isomers.



Scheme 20

A radical-pair mechanism seems less likely since the rate determining homolysis of para-substituted dibenzylmercury (**122**) into a radical pair is enhanced only 1.1-fold for X = CH_3 and 3.4-fold for X = OCH_3 compared to **122**, where X = H.[191] Therefore, if radical pairs were intermediates in the thermal rearrangement of **111a-e**, large rate enhancements for rearrangement would not be observed.

$$p\text{-}XC_6H_4CH_2HgCH_2C_6H_4p\text{-}X \longrightarrow p\text{-}XC_6H_4CH_2\cdot + \cdot HgCH_2C_6H_4p\text{-}X$$

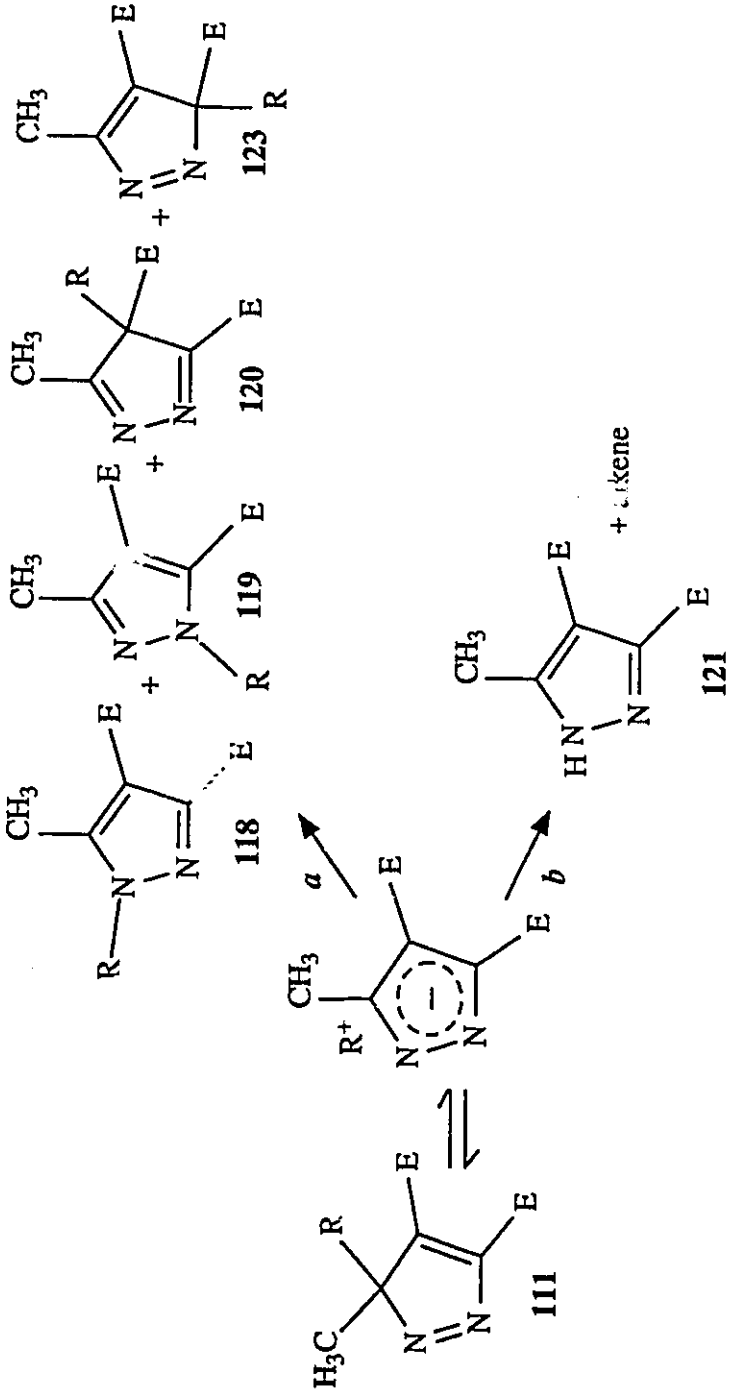
122

Furthermore, the rearrangement of 3*H*-pyrazoles **111c-e** were observed by ^1H NMR spectroscopy and CIDNP (Chemically Induced Dynamic Nuclear Polarization) was not observed. Although the absence of a CIDNP spectrum is not compelling evidence for the absence of radical pair chemistry, a free radical mechanism is incompatible with the overall evidence.

Scheme 21 shows, in mechanistic terms, the potential products that can be expected from rearrangement of 3*H*-pyrazole **111** by a stepwise mechanism involving ion-pair formation. An ion-pair intermediate could return to starting material or suffer collapse in four alternative ways (path **a**). Collapse on either nitrogen atom of the pyrazole anion gives two stable aromatic 1*H*-pyrazoles (**118** and **119**). Collapse of the cation to the carbon nearest to the migration origin yields a 4*H*-pyrazole (**120**). This is a more stable pyrazole isomer compared to **111** because of its two relatively strong carbon-nitrogen double bonds. Collapse of the cation to the carbon furthest from the migration origin gives another 3*H*-pyrazole (**123**). If the cation has a β-hydrogen, proton transfer could generate **121** plus alkene (path **b**).

The products obtained from the rearrangement of 3*H*-pyrazoles **111a-e** in benzene-d_6, can be rationalized in terms of an ion-pair mechanism for rearrangement. In these rearrangements, the major product from collapse of an intermediate ion pair is 1*H*-pyrazole **118**. For the rearrangement of 3*H*-pyrazole **111c**, loss of a proton from the *tert*-butyl cation of the ion pair competes with collapse of the ion pair. One would expect collapse of a free carbocation and free pyrazole anion to give the two most stable pyrazoles (**118** and **119**) in roughly equal amounts. Therefore, it appears that relatively tight ion pairs are formed because only the 1*H*-pyrazole, with one exception, resulting from collapse of the cation to the nitrogen nearest to its migration origin is observed.

Only in the rearrangement of 3*H*-pyrazoles **111b** and **111e** were 4*H*-pyrazoles (**120**) detected as minor products. These were formed from migration of the cation to the nearest carbon centre. Since the other 3*H*-pyrazoles (**111a**, **111c**, and **111d**) have larger



Scheme 21

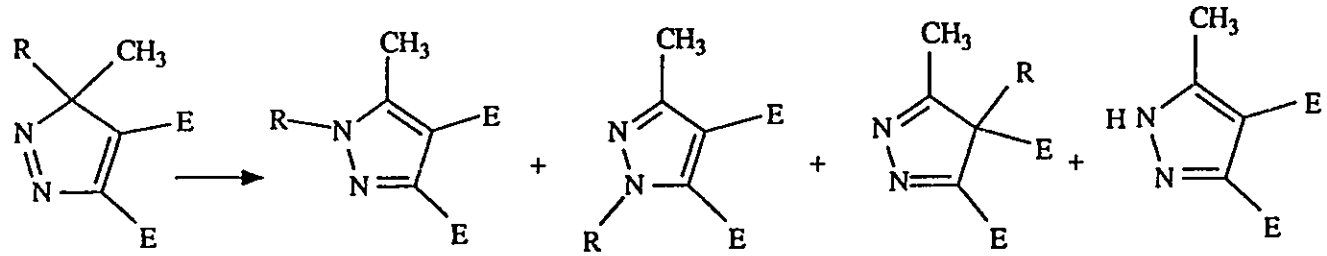
migrating groups, steric hindrance with the carbomethoxy group appears to be an important product determining factor. Either the 4*H*-pyrazoles are not formed during these rearrangements or they undergo further rearrangement to a 1*H*-pyrazole. In addition, only the rearrangement of **111a** led to a mixture of two 1*H*-pyrazoles. This observation is compatible with an ion-pair mechanism involving rather "tight" ion pairs. The benzhydryl substituent of **111a** forms the most stable cation and therefore is likely to become more separated from the anion during its longer lifetime and therefore, collapse of the cation to the distal nitrogen atom occurs to give **119a**.

Therefore, by analysis of product distributions, it seems that the rearrangement of 3*H*-pyrazoles **111a-e** led to rather tight ion-pair intermediates in benzene-d_6. The polarity of the rearrangement solvent was increased in an attempt to promote ion-pair separations. This could give rise to a mixture of two stable, aromatic 1*H*-pyrazoles from the rearrangements of **111a-e**.

2.5 Rearrangement of 3*H*-pyrazoles 111a-e in chloroform or chloroform-*d*

Table 12 shows the products from the rearrangement of 3*H*-pyrazoles **111a-e** in chloroform solvent. 3*H*-Pyrazole **111a** rearranged in chloroform solvent to give isomeric 1*H*-pyrazoles, **118a** (73%) and **119a** (27%). Since the percentage of **119a** increased from 9% to 27% as a result of moving from benzene-d_6 to chloroform solvent this suggests an increase in ion-pair separations.

Table 12. Products and product yields[a] from the thermal rearrangements of **111a-e** at ambient temperature in chloroform.



111	**118**	**119**	**120**	**121**	+ other
111a, R=$CHPh_2$	73	27	nil	nil	
111b, R=CH_2OMe	72	28	nil	nil	
111c,[b] R=$C(Me)_3$	28	5	nil	67	55 isobutene
111d, R=1-adamantyl	69	31	nil	nil	
111e, R=p-$CH_2C_6H_4OMe$	56	11	32	nil	

[a] At the level of detection afforded by ^1H NMR spectroscopy, the products listed were the only products from rearrangement and yield numbers (%) reflect complete materials balance prior to opening of a tube.

[b] Reaction solvent was $CDCl_3$.

An increase in ion-pair separation causes an increased probability of ion-pair collapse at a site far from the migration origin. The rearrangement of 3*H*-pyrazoles **111b-e** in chloroform led to a higher percentage of 1*H*-pyrazole **119**, suggesting that ion pairs from the rearrangement of **111b-e** are more separated in chloroform than in benzene. However, since the two 1*H*-pyrazoles are not formed in roughly equal amounts in all cases, this suggests that the ion pairs are still rather tight and probably not solvent-separated.

The clean chemistry of **111a-e** in chloroform is easily rationalized in terms of the ion-pair mechanism, whereas radical pair chemistry in $CHCl_3$ would be expected to lead to some RH and to the formation of RD from reactions run in $CDCl_3$. There was no evidence for these products.

2.6 Rearrangement of 3*H*-pyrazoles 111a-e in methanol or methanol-d_4

The 3*H*-pyrazoles **111a-e** were generated in a nucleophilic solvent, in an effort to trap the ion-pair intermediates. If successful, this would provide strong evidence in support of an ion-pair mechanism for the rearrangement of 3*H*-pyrazoles **111a-e**.

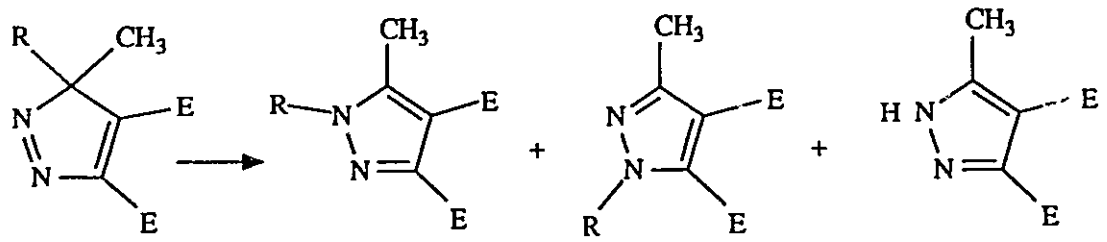
Table 13 lists the products from the rearrangement of 3*H*-pyrazoles **111a-e** in methanol or methanol-d_4. Interception of the cationic migrating group with methanol competed with ion-pair collapse to 1*H*-pyrazole (**118** and/or **119**). 3*H*-Pyrazoles **111b** and **111c**, both of which afforded a volatile methyl ether, were generated in deuterated solvent in order to determine the percentage of the methyl ether product conveniently by ^{1}H NMR spectroscopy.

Rearrangement of 3*H*-pyrazole **111a** in methanol gave **118a** (26%), **119a** (22%), **121** (52%), and **124a** (52%). Similarly, 3*H*-pyrazole **111b** rearranged in methanol-d_4 to give **118b** (25%), **121** (as the D analogue, 75%), and **124b** (dimethoxymethane-d_3, 61%). Rearrangement of 3*H*-pyrazole **111c** in methanol-d_4, gave **118c** (20%), **121** (a mixture of H and D analogues, 80%), **124c** (*tert*-butyl methyl ether-d_3, 72%), and isobutene (5%). 3*H*-Pyrazole **111d** gave **118d** (54%), **119d** (17%), **121**(29%), and **124d** (23%) from rearrangement in methanol. Likewise, 3*H*-pyrazole **111e** gave **118e** (45%), **119e** (4%), **121** (51%), and **124e** (47%) from rearrangement in methanol.

The presence of dimethoxymethane-d_3 and *tert*-butyl methyl ether-d_3 from reaction of **111b** and **111c** in methanol-d_4 was confirmed by gas chromatography and ^{1}H NMR spectroscopy in spiking experiments with authentic samples of the non-deuterated analogues. The deuterated ethers, **124b** and **124c**, had ^{1}H NMR chemical shifts and gas chromatography retention times identical to those of non-deuterated analogues. The presence of benzhydryl methyl ether was confirmed by comparing spectroscopic data with those in the literature[192] while 1-adamantyl methyl ether and p-methoxybenzyl methyl ether were confirmed by comparing spectroscopic data with those of samples prepared by another route.[193,194]

The chemistry of 3*H*-pyrazoles **111a-e** in methanol provides powerful evidence that rearrangement occurs by an ion-pair mechanism. For 3*H*-pyrazoles **111a-e**, interception of R^+ with methanol competed with ion-pair collapse to give 1*H*-pyrazoles.

Table 13. Products and product yields[a] from the thermal rearrangements of **111a-e** in methanol or methanol-d_4 at ambient temperature.



111	**118**	**119**	**121**	**+ $ROCH_3$ (124)**	**+ other**
111a, R=$CHPh_2$	26	22	52	52	
111b, R=CH_2OMe	25	nil	75[b]	61[d]	
111c, R=$C(Me)_3$	20	nil	80[c]	72[d]	5 isobutene
111d, R=1-adamantyl	54	17	29	23	
111e, R=p-$CH_2C_6H_4OMe$	45	4	51	47	

[a] At the level of detection afforded by ^1H NMR spectroscopy, the products listed were the only products from rearrangement and yield numbers (%) reflect complete materials balance prior to opening of a tube.

[b] D analogue.

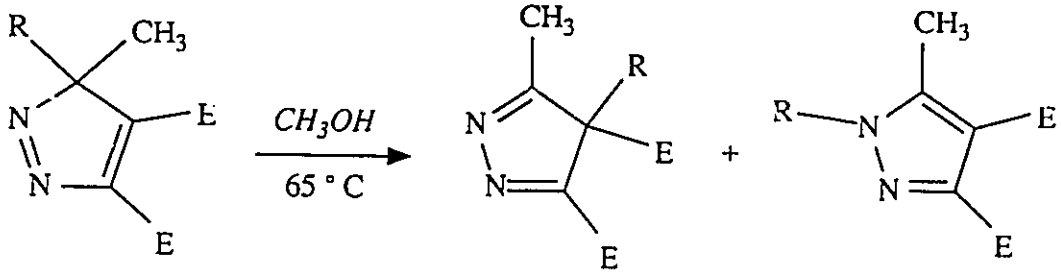
[c] Mixture of H and D analogues.

[d] $ROCD_3$ from reaction in CD_3OD.

2.7 Rearrangement of 3-benzyl-3-methyl-3*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester

Since 3*H*-pyrazole **111e** presumably rearranges by a stepwise mechanism it was of interest to study the rearrangement of 3*H*-pyrazole **111f** (R = benzyl) to determine if the para-methoxy substituent of **111e** is necessary for stepwise rearrangement. The para-methoxy substituent enhances the stabilization of the cation portion of the ion-pair intermediate formed from the rearrangement of **111e**.

3*H*-Pyrazole **111f** was synthesized by a modification of the preparative procedure used for the synthesis of 3*H*-pyrazoles **111a-e** (see Experimental). Unlike **111a-e**, this 3*H*-pyrazole was stable to the conditions of its purification by centrifugal chromatography (silica gel). 3*H*-Pyrazole **111f** was refluxed in neat methanol and after 0.5 hours, had rearranged to afford 4*H*-pyrazole **120f** (58%) and 1*H*-pyrazole **118f** (42%) (Scheme 22). Benzyl methyl ether was not detected.



111f ($R=CH_2C_6H_5$) **120f** (58%) **118f** (42%)

Scheme 22

Like other concerted 3*H*-pyrazole rearrangements,[141,143,146] **111f** afforded the 4*H*-pyrazole as the major product. Therefore, it appears that **111f** rearranges by a concerted mechanism rather than a stepwise mechanism, involving an ion-pair intermediate since a potential benzyl cation intermediate was not intercepted in methanol. This observation

was not too surprising considering that in 67% aqueous acetone, para-methoxybenzyl chloride solvolyzes approximately 10^3 times faster than benzyl chloride.[171]

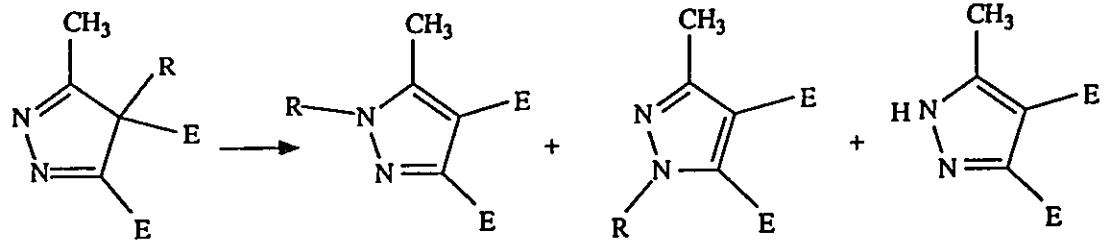
2.8 Rearrangement of 4*H*-pyrazoles 120b and 120e

The rearrangement of 3*H*-pyrazoles **111b** and **111e** afforded 4*H*-pyrazoles as rearrangement products, providing one with the opportunity to study the rearrangements of these more stable pyrazole isomers. Thermal rearrangements of 4*H*-pyrazoles have received considerably less attention than the thermal rearrangements of 3*H*-pyrazoles, in general.[195] The temperatures necessary for 3*H*-pyrazole rearrangement sometimes provokes rearrangement of a 4*H*-pyrazole product.[143,146]

Inspection of Table 14 reveals the products formed from the rearrangement of 4*H*-pyrazoles, **120b** and **120e**, in benzene-d_6 and methanol or methanol-d_4 solvents. As mentioned above, 4*H*-pyrazole **120b** could not be isolated. It was obtained as a solution, after the rearrangement of **111b** in benzene-d_6 solvent, which gave **118b** (77%) and **120b** (23%). The observed rate constant for the disappearance of **120b** at 90 °C from this reaction mixture was (1.10 ± 0.05) x 10^{-4} s^{-1}. After the thermal rearrangement of **120b**, the mixture consisted of **118b** (90%) and **119b** (10%). Therefore, **120b** rearranges to give compounds **118b** and **119b** in the ratio 1.3 : 1.0.

4*H*-Pyrazole **120e** could be isolated and its rearrangement in benzene-d_6 was followed by ^{1}H NMR spectroscopy. The increase in the concentrations of the rearrangement products **118e** and **119e** gave an observed rate constant of (1.45 ± 0.08) x 10^{-4} s^{-1} at 130 °C. The products **118e** and **119e** were in the ratio 1.4 : 1.0.

Table 14. Product and product yields[a] from thermal rearrangements of **120b** and **120e**.

Solvent	 **120**	**118**	**119**	**121**	+ other
Benzene-d_6	R=CH_2OMe[b,c]	57	43		
	R=p-$CH_2C_6H_4OMe_2$[d]	58	42		
Methanol	R=CH_2OMe[c,e,f]	nil	nil	100	100 $ROCD_3$
	R=p-$CH_2C_6H_4OMe$[e]	nil	nil	100	100 $ROCH_3$

[a] At the level of detection afforded by ^1H NMR spectroscopy, the products listed were the only products and the yield numbers (%) were determined by ^1H NMR spectroscopy.

[b] Rearrangement at 90 °C with $k = (1.10 \pm 0.05) \times 10^{-4}\ s^{-1}$.

[c] Rearrangement of **120b** from solutions containing **120b** (23%) and **118b** (77%).

[d] Rearrangement at 130 °C with $k = (1.45 \pm 0.08) \times 10^{-4}\ s^{-1}$.

[e] Rearrangement at ambient temperature.

[f] Rearrangement in CD_3OD.

4*H*-Pyrazoles are more stable than their 3*H*-pyrazole counterparts due to the presence of two relatively strong C=N double bonds, and consequently they have a higher barrier to ion-pair formation. 4*H*-Pyrazole **120b** could not be isolated without decomposition while **120e** could be isolated by centrifugal chromatography. The faster observed rate of rearrangement of **120b** (R = CH_2OMe) compared to **120e** (R = p-$CH_2C_6H_4OMe$) is a reflection of the relative stabilities of the different intermediate cations.

Both **120b** and **120e** rearrange to give the isomeric 1*H*-pyrazoles (**118** and **119**) in about the same ratio (**118** : **119** = 1.3-1.4 : 1.0). It would be expected that ion-pair formation from a 4*H*-pyrazole would lead to two isomeric 1*H*-pyrazoles in approximately the same ratio because the cation would have a similar probability of collapsing on each nitrogen site, given that the migration origin is equidistant from those nitrogen atoms and that ion-pair collapse in benzene can not have a substantial activation energy.

Further evidence that rearrangement takes place by a mechanism other than a concerted one arises from the fact that carbomethoxy migration does not occur from C-4 of the 4*H*-pyrazoles. It is known that a carbomethoxy substituent has a higher migratory aptitude than both benzyl and ethyl substituents in [1,5]-sigmatropic migrations from C-3 in 3*H*-pyrazoles.[143,146]

The rearrangement of 4*H*-pyrazoles **120b** and **120e** in methanol solvent could provide evidence for a stepwise mechanism if the intermediate cations of the ion pairs could be trapped. The 4*H*-pyrazoles, **120b** and **120e**, were dissolved in methanol-d_4, and methanol, respectively, to determine if the migrating groups could be trapped as cations.

The photolysis mixture from the generation of 3*H*-pyrazole **111b** in benzene-d_6 and its subsequent rearrangement to **118b** (79%) and **120b** (21%), was freed from volatiles and the residue was dissolved in methanol-d_4. The ^{1}H NMR spectrum, taken immediately revealed **118b** (79%), **121** (21%), and dimethoxymethane-d_3 (21%) indicating that 4*H*-pyrazole **120b** had dissociated to give exclusively methanolysis products. Similarly, 4*H*-pyrazole **120e** was dissolved in methanol solvent and after ten minutes, the solvent was removed in vacuo and the residue was dissolved in $CDCl_3$. The ^{1}H NMR spectrum, taken immediately, revealed that p-methoxybenzyl methyl ether (100%) and **121** (100%) had been formed (Table 14). Therefore, it appears these 4*H*-pyrazoles rearrange by a stepwise mechanism, in both benzene and methanol solvents.

2.9 Different ion pairs from isomeric 3*H*-pyrazoles and 4*H*-pyrazoles

It was found that both 4*H*-pyrazole **120b** and **120e** undergo methanolysis at room temperature and that virtually all the migrating cation is intercepted by methanol solvent in each case (Table 14). The rearrangement of 3*H*-pyrazoles **111b** and **111e** gave 61% and 47% of the appropriate methyl ethers, respectively (Table 13).

The fact that, in methanol, a larger percentage of the migrating group is trapped by solvent if it originates from a 4*H*-pyrazole than if it originates from the isomeric 3*H*-pyrazole suggests that these isomeric pyrazoles lead to different ion pairs! Since those ion pairs must be identical once they have become well separated, the suggestion is that the ones from the 4*H*-pyrazoles are more solvent-separated than the ones from the 3*H*-pyrazoles or that the former become solvent-separated but the latter do not.

The different fates of isomeric 3*H*-pyrazoles and 4*H*-pyrazoles in methanol could also be explained in terms of competing stepwise and concerted mechanisms for the former. A common ion-pair mechanism seems more likely, with differentiation arising out of small differences between the ion-pair geometries (memory effects or different degrees of separation) rather than an accidental matching of the activation free energies for concerted and stepwise mechanisms.

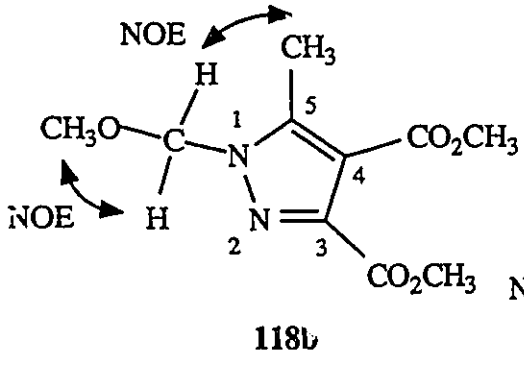
2.10 Structural determination of 1*H*-pyrazoles and 4*H*-pyrazoles

The ^{1}H NMR and ^{13}C NMR spectra were taken for all pyrazole rearrangement products from 3*H*-pyrazoles **111a-f** and their mass spectrometric molecular masses were determined. The key spectral features which were important in distinguishing between the isomeric pyrazoles are discussed below.

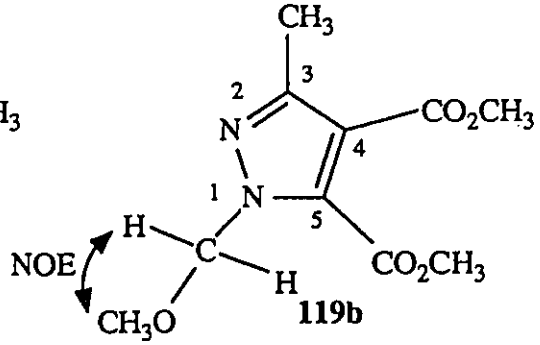
The 1*H*-pyrazoles **118** and **119** can be easily differentiated from the isomeric 3*H*-pyrazoles **111** by ^{1}H NMR spectroscopy. The methyl singlet of a 1-R-5-methyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester or a 1-R-3-methyl-1*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester is shifted approximately 1 ppm downfield compared to the methyl singlet of an isomeric 3-R-3-methyl-3*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester. The carbomethoxy singlets for both 1*H*-pyrazole **118** and **119** are also shifted downfield in their ^{1}H NMR spectra by approximately 0.4 to 0.6 ppm compared to the isomeric 3*H*-pyrazole **111**. Furthermore, the signal from the proton/s attached to the nitrogen bearing carbon of the R group of 1*H*-pyrazoles **118** and **119** is also downfield compared to the corresponding signal for the 3*H*-pyrazole isomer. In particular, when R

contains a methylene group, the methylene protons are diastereotopic (AB spin system, doublet of doublets) in the ^{1}H NMR spectrum of the 3*H*-pyrazole (ie. **111e**) while the methylene protons appear in the form of a singlet in the spectra of the isomeric 1*H*-pyrazoles. For example, the methylene protons of **118b**, **118e**, **119b**, and **119e** appear in the form of a singlet in their respective ^{1}H NMR spectra.

Differentiating between a pair of isomeric 1*H*-pyrazoles by ^{1}H NMR spectroscopy is difficult. W. Holzer showed recently that the ^{1}H NOE (Nuclear Overhauser Effect) is a versatile tool for spectral and structural assignment in various N-substituted pyrazoles.[196] Indeed, it was found that a ^{1}H NOE experiment was useful in distinguishing between 1*H*-pyrazoles **118b** and **119b**. Irradiation of the N-methylene resonance (5.43 ppm) in compound **118b** led to an enhancement of both the singlet at 3.33 ppm (OCH_3) and the singlet at 2.57 ppm (CH_3). Since an NOE is observed on the C-methyl signal this is consistent with adjacent methoxymethyl and methyl groups in the 1- and 5- positions of the pyrazole moiety. Irradiation of the N-methylene resonance (5.47 ppm) in compound **119b** leads to an enhancement of only the singlet at 3.29 ppm (OCH_3). This is consistent with the methoxymethyl and methyl groups in the 1- and 3- positions of the pyrazole moiety. The results of this experiment distinguish **118b** from **119b** and therefore the ^{13}C NMR spectra could be assigned to the appropriate 1*H*-pyrazoles.



118b



119b

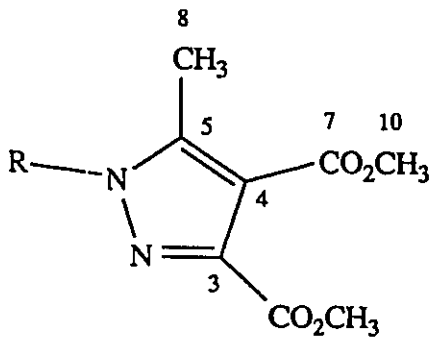
1*H*-Pyrazoles **118** can also be differentiated from isomeric 1*H*-pyrazoles **119** by ^{13}C NMR. Table 15 contains selected ^{13}C NMR chemical shifts for **118a-f** while Table 16 contains selected ^{13}C NMR chemical shifts for **119a-e.** The C-3 and C-5 chemical shifts were useful for distinguishing between the isomeric 1*H*-pyrazoles. The C-3 chemical shifts of **118a-f** appear in the region of 142.47-144.55 ppm while the C-5 chemical shifts arise at higher field, from 140.82-143.50 ppm. The C-3 chemical shifts of **119a-e** appear in the region of 135.59-137.17 ppm while the C-5 chemical shifts of **119a-e** arise in the region of 148.39-149.98 ppm. The ^{13}C chemical shifts were assigned by comparison with the chemical shift assignments made by others, for other 1*H*-pyrazoles.[197]

The isomeric 1*H*-pyrazoles can also be set apart based on their different polarities. For example, when separating a product solution containing both isomeric 1*H*-pyrazoles by centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate), 1*H*-pyrazole **119** elutes before 1*H*-pyrazole **118.**

The ^{1}H NMR and selected ^{13}C NMR chemical shifts of 4*H*-pyrazoles **120e** and **120f** are located in Table 17. The sp^3-hybridized carbon (C-4) resonates at 76.31 ppm for **120e** while it resonates at 76.16 ppm for **120f.** This particular high field chemical shift is useful for distinguishing 4*H*-pyrazoles from their 1*H*-pyrazole isomers. The ^{13}C chemical shifts were assigned by comparison to the chemical shift assignments made by others for other 4*H*-pyrazoles.[190] The 4*H*-pyrazoles **120b** and **120e** contain methylene protons which are diastereotopic and appear in the form of a doublet of doublets in their

Table 15.

Selected ^{13}C NMR (50 MHz) chemical shifts (ppm) for 1*H*-pyrazoles **118a-i** in $CDCl_3$.



118

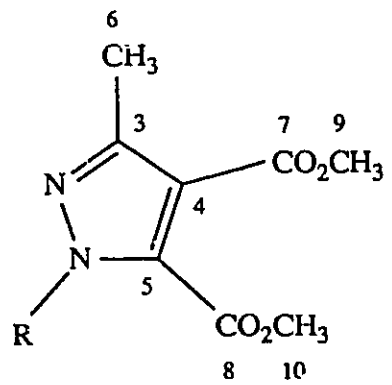
118	C-3	C-4	C-5	C-8	C-6, C-7 [a]	C-9, C-10 [b]
118a	144.00	112.31	143.50	11.00	163.21, 163.53	51.67, 52.35
118b	144.55	113.50	143.36	10.33	163.23, 163.66	51.74, 52.83
118c	142.47	113.91	140.82	13.15	163.43, 164.04	51.65, 52.31
118d	142.53	113.99	141.06	13.48	163.46, 164.20	51.66, 52.30
118e	143.46	112.83	142.77	10.76	162.66, 163.34	51.61, 52.36
118f	143.79	113.01	142.97	10.85	162.68, 163.43	51.76, 52.52

[a] C-6 and C-7 may be reversed.

[b] C-9 and C-10 may be reversed.

Table 16.

Selected ^{13}C NMR (50 MHz) chemical shifts (ppm) of 1*H*-pyrazoles **119a-e** in $CDCl_3$.



119

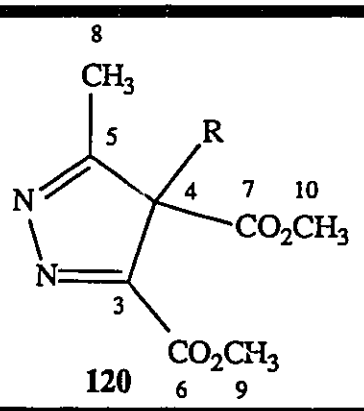
119	C-3	C-4	C-5	C-6	C-7, C-8 [a]	C-9, C-10 [b]
119a	137.15	112.93	149.98	13.50	161.46, 163.50	51.61, 52.92
119b	135.96	114.27	149.70	12.99	160.48, 163.05	51.56, 52.83
119c	137.17	111.37	148.40	13.55	163.34, 164.19	51.39, 53.22
119d	136.90	111.12	148.39	13.60	164.33, 164.39	51.34, 53.24
119e	135.59	113.38	149.70	13.25	161.12, 163.40	51.63, 52.85

[a] C-7 and C-8 may be reversed.

[b] C-9 and C-10 may be reversed.

Table 17.

^{1}H NMR and selected ^{13}C NMR chemical shifts (ppm) for some 4*H*-pyrazoles.



120

4*H*-Pyrazole, **120**	^{1}H NMR (200 MHz)	^{13}C NMR[d,e] (50 MHz)
120b,[a,b] R=CH_2OMe	4.28 (d, 1 H, J= - 9.3 Hz), 3.92 (d, 1 H, J= - 9.3 Hz), 3.38 (s, 3 H, CO_2Me), 3.09 (s, 3 H, CO_2Me), 2.76 (s, 3 H, Me).	
120e,[c] R=p-$CH_2C_6H_4OMe$	6.69 (d, 2 H, J = 8.7 Hz), 6.81 (d, 2 H, J = 8.7 Hz), 3.97 (s, 3 H, CO_2Me), 3.71 (s, 6 H, OMe + CO_2Me), 3.80 (d, 1 H, J = -14 Hz), 3.45 (d, 1 H, J = -14 Hz), 2.38 (s, 3 H, Me).	176.52 (C-3), 76.31 (C-4), 166.69 (C-5), 165.27 (C-6), 160.61 (C-7), 13.76 (C-8), 53.65 (C-9), 53.09 (C-10).
120f,[c] R=$CH_2C_6H_5$	6.88-7.27 (m, 5 H, C_6H_5), 3.97 (s, 3 H, CO_2Me), 3.85 (d, 1 H, J= - 14 Hz), 3.72 (s, 3 H, CO_2Me), 3.50 (d, 1 H, J= - 14 Hz), 2.39 (s, 3 H, Me).	176.32 (C-3), 76.16 (C-4), 166.63 (C-5), 165.36 (C-6), 160.71 (C-7), 13.80 (C-8), 53.72 (C-9), 53.10 (C-10)

[a] Solvent is C_6D_6.
[b] The ^{1}H NMR spectrum was obtained from solutions containing **118b** (77%) and **120b** (23%). The ^{13}C NMR spectrum of **120b** could not be determined from this solution.
[c] Solvent is $CDCl_3$.
[d] C-6 and C-7 may be reversed.
[e] C-9 and C-10 may be reversed.

^{1}H NMR spectra while their isomeric 1*H*-pyrazoles have ^{1}H NMR spectra in which those methylene protons appear in the form of a singlet.

2.11 Conclusion

The 3*H*-pyrazoles **111a-e** undergo rearrangement by a stepwise mechanism in benzene, chloroform, and methanol solvents. A summary of the evidence which supports this statement follows. First, in benzene-d_6 solvent, the 3*H*-pyrazoles **111a-e** rearrange with large rate enhancements (approximately 10^4 for the slowest) compared to the rearrangement of 3*H*-pyrazole **101** (R = CH_2CH_3). Second, the 4*H*-pyrazole is not the major product from the rearrangement of **111b** and **111e** in benzene-d_6 solvent, contrary to the products of those 3*H*-pyrazoles which rearrange by a concerted mechanism. Third, isobutene is formed, presumably from a *tert*-butyl cation intermediate, in the rearrangement of 3*H*-pyrazole **111c** in all three solvents. In addition, the clean chemistry for the rearrangement of the 3*H*-pyrazoles in chloroform solvent disputes a radical-pair mechanism. Finally, methanol solvent intercepts the migrating groups during the rearrangement of the 3*H*-pyrazoles, diverting them to **121** and the appropriate methyl ethers.

The 4*H*-pyrazoles **120b** and **120e** also rearrange by a stepwise, ion-pair mechanism, at least in methanol solvent because the migrating groups were completely intercepted. It appears that these 4*H*-pyrazoles also rearrange by the two-step mechanism

in benzene-d_6, at the higher temperatures required, because roughly equal amounts of isomeric 1*H*-pyrazoles (**118** and **119**) were formed.

These rearrangements can be described mechanistically as "formal" [1,5]-sigmatropic rearrangements because some of the products of rearrangement are those that could have arisen by [1,5]-sigmatropic migrations. Reports of such "formal" [1,5]-sigmatropic rearrangements are very rare in the literature.[56] These rearrangements represent part of a mechanistic continuum which runs from concerted, with very little charge separation, through transition structures with increasing separation of charge, to the two-step, ion-pair extreme.

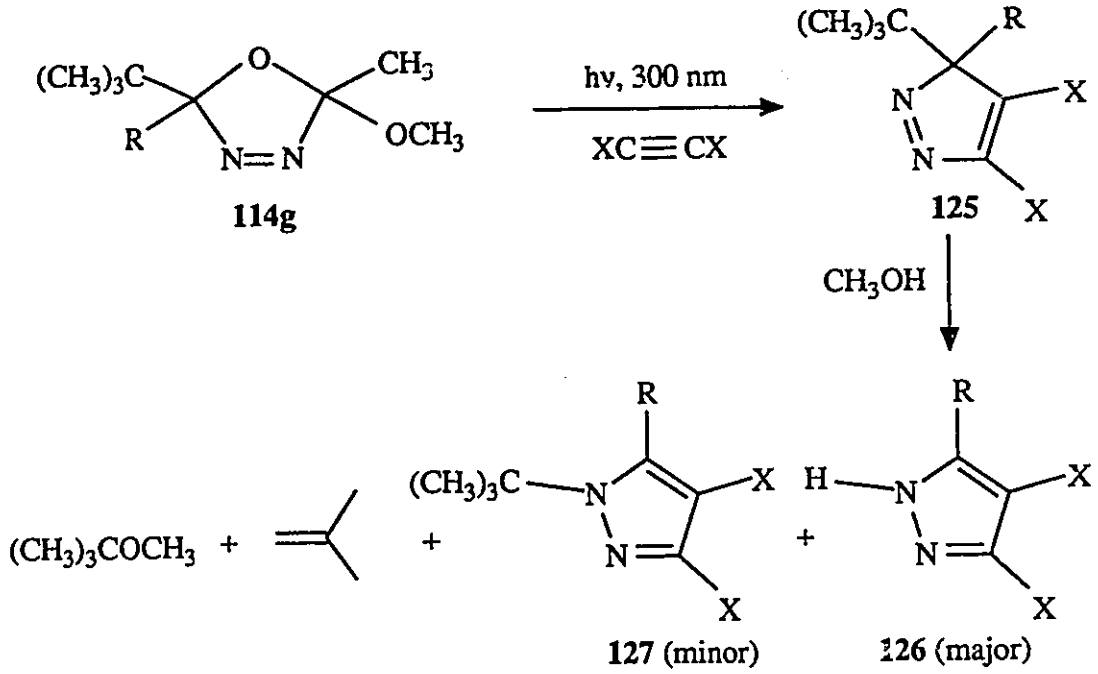
Cycloaddition reactions, like sigmatropic reactions, belong to the pericyclic category of reactions. There are several examples of cycloaddition reactions which are known to occur by a stepwise mechanism rather than by a concerted process, either synchronous or asynchronous.[198] One type of cycloaddition reaction which has received much attention in the literature is the Diels Alder reaction, a $2\pi + 4\pi$ cycloaddition process; stepwise Diels Alder reactions have recently been discovered.[199-202] The work in this chapter is unique because "formal" [1,5]-sigmatropic rearrangements of both 3*H*-pyrazoles and 4*H*-pyrazoles have never been reported and "formal" [1,5]-sigmatropic rearrangements of cyclopentadienes are rare.[56]

2.12 Synthetic applications

3*H*-Pyrazoles **111a-e** are all new compounds, as are the pyrazole rearrangement products, except for 1*H*-pyrazole **121**. The 1*H*-pyrazoles **118a**, **118b**, **118d**, and **118e** can

be made in good yields from the rearrangement of the appropriate 3*H*-pyrazoles at room temperature (Table 11). The one-pot synthesis of these 1*H*-pyrazoles from the appropriate oxadiazolines and dimethyl acetylenedicarboxylate is both convenient and mild. These new 1*H*-pyrazoles might have some use as pesticides or herbicides since the 1*H*-pyrazole nucleus has been found to be biologically active.[61,64]

The rearrangement of 3*H*-pyrazole **111c** in methanol gave a high yield of 1*H*-pyrazole **121**. This rearrangement could be useful for the mild synthesis of other NH-pyrazoles by simply modifying the substituents at C-3, C-4, and C-5 (Scheme 23). Other alkyl substituents could be located at C-3 (ie. R = CH_2CH_3, $CH(CH_3)_2$) of 3*H*-pyrazole **125** by the synthesis of the appropriate oxadiazoline **114g**. Use of a different alkyne in the 1,3-dipolar cycloaddition reaction with the diazo compound would give other substituents at C-4 and C-5 (ie. X = CN, $COCH_3$, COPh, and CF_3) of the 3*H*-pyrazole. Rearrangement of 3*H*-pyrazole **125** should give NH-pyrazole **126** as the major product. The minor pyrazole product would be 1*H*-pyrazole **127**. Isobutene and *tert*-butyl methyl ether would also be reaction products, but they could easily be removed during the rotary evaporation of the reaction solvent. Centrifugal chromatography would only be necessary for the separation of NH-pyrazole **126** from 1*H*-pyrazole **127**. Therefore, the stepwise rearrangement of 3*H*-pyrazole **111c** could provide a convenient route to other NH-pyrazoles (**126**) which may be useful as precursors of both pesticides and herbicides.


(CH3)3C
O
CH3
R
N=N
OCH3
114g
hv, 300 nm
XC≡CX
(CH3)3C
R
N
X
N
125
X
CH3OH
(CH3)3COCH3
+
R
(CH3)3C
X
N
N
X
127 (minor)
+
R
H
X
N
N
X
126 (major)

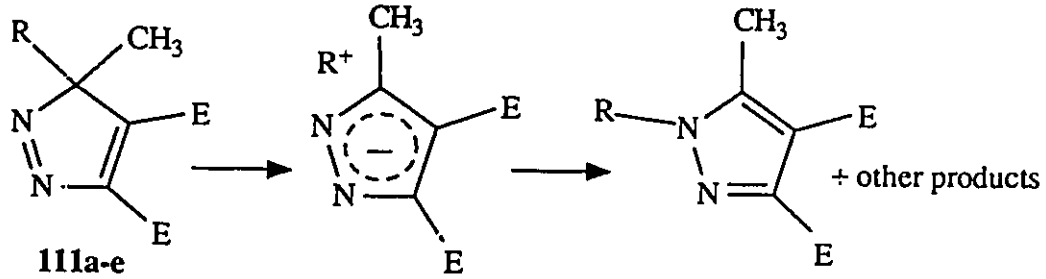
Scheme 23

CHAPTER 3

Studies of the Thermal Rearrangements of Methyl 3-alkyl-3-methyl-3*H*-pyrazole-5-carboxylates

3.0 Objective

It was discovered that 3*H*-pyrazoles **111a-e** undergo thermal rearrangement by a stepwise mechanism involving ion-pair intermediates (Scheme 24). This mechanism for rearrangement appears to operate because the migrating group is relatively stable as a cation and the counterion is a stabilized, aromatic, pyrazole anion derivative. These "formal" [1,5]-sigmatropic rearrangements were discussed in detail in Chapter 2.

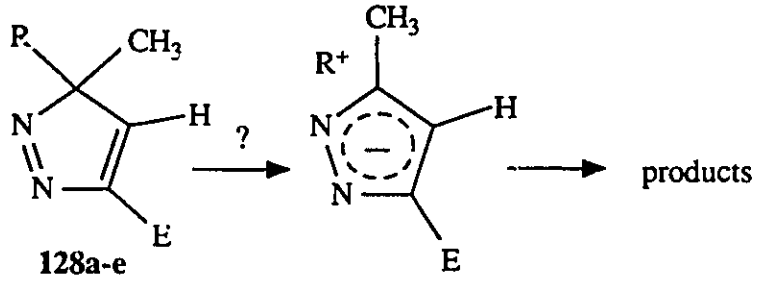


(**a**: R=$CHPh_2$; **b**: R=CH_2OMe; **c**: R=$C(Me)_3$; **d**: R=1-adamantyl; **e**: R=p-$CH_2C_6H_4OMe$)

Scheme 24

It was of interest to investigate the thermal rearrangement of another series of 3*H*-pyrazoles (**128a-e**) and determine whether thermal rearrangement takes place by a

concerted or a stepwise mechanism (Scheme 25). The potential pyrazole anion intermediate bears only one carbomethoxy substituent, which renders it less stable than the pyrazole anion formed in the rearrangement of 3*H*-pyrazoles **111a-e**. The R substituents were again chosen as $CHPh_2$, CH_2OMe, $C(Me)_3$, 1-adamantyl, and p-$CH_2C_6H_4OMe$ because they readily dissociate as cations in solvolysis reactions of R-X (X = halogen).[150,153] It is known that R^+ must be a relatively stable cation for stepwise rearrangement, but the sensitivity of the stepwise mechanism to the stabilization of the pyrazole nucleus has not been explored.



128a-e

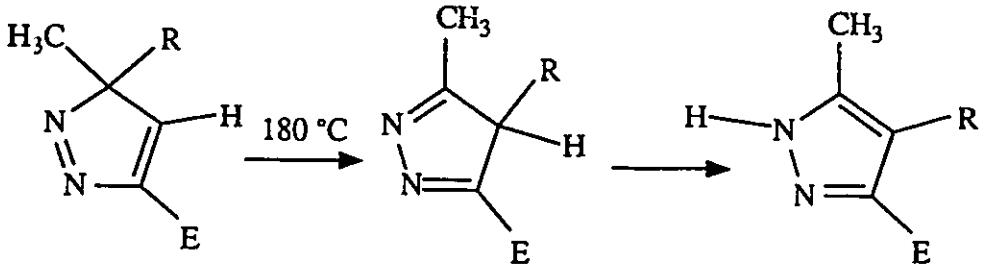
(E=CO_2Me)

(**a**: R=$CHPh_2$; **b**: R=CH_2OMe; **c**: R=$C(Me)_3$; **d**: R=1-adamantyl; **e**: R=p-$CH_2C_6H_4OMe$)

Scheme 25

The thermal rearrangement of 3*H*-pyrazole **128f** (where R = $CH_2C_6H_5$) would also be investigated in order to compare it to the thermal rearrangements of 3*H*-pyrazoles **128a-e**. Presumably, 3*H*-pyrazole **128f** would rearrange by a concerted mechanism, involving [1,5]-sigmatropic benzyl shifts, since 3*H*-pyrazole **111f** (where R = $CH_2C_6H_5$) appears to rearrange by this mechanism. Methanol did not get involved in the chemistry of the rearrangement of **111f**, which implies that ion pairs are not formed.

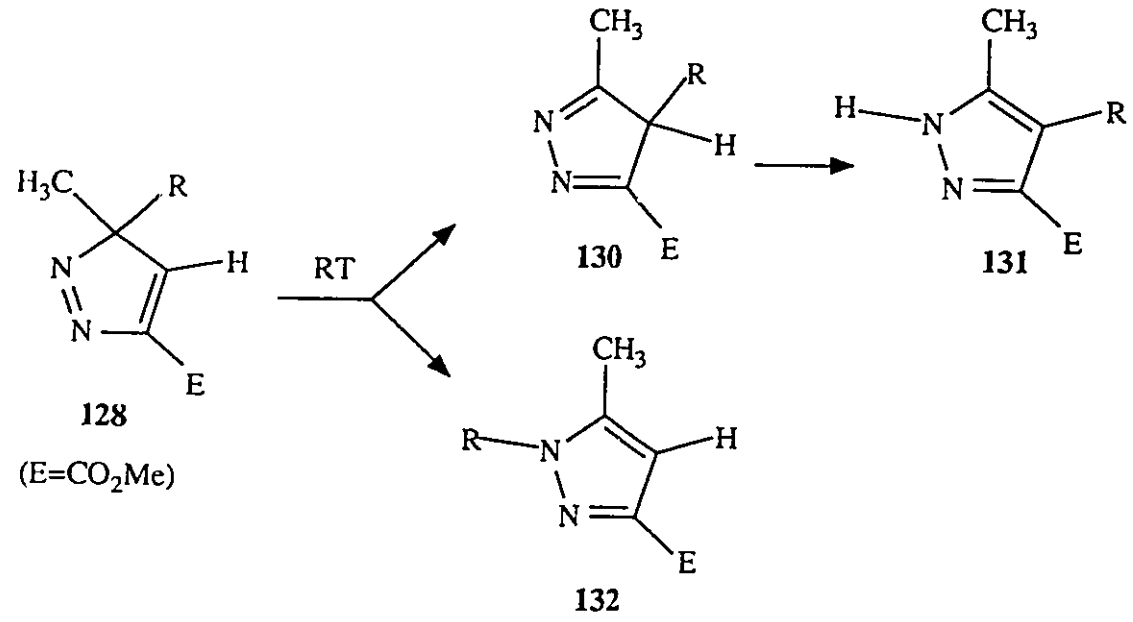
The thermal rearrangements of some 3*H*-pyrazoles, similar in structure to 3*H*-pyrazoles **128a-f**, were previously investigated. It is important to review this work briefly because of its relationship to the work described in this chapter. Franck-Neumann and Dietrich-Buchecker studied the thermal rearrangement of 3*H*-pyrazole **128g** (R = Me, a substituent which cannot form a relatively stable cation) and found that during 3 hours at 180 °C rearrangement afforded only 1*H*-pyrazole **131g** (Scheme 26).[84] The product **131g** was accounted for in terms of an initial [1,5]-sigmatropic migration of methyl to C-4, generating intermediate 4*H*-pyrazole **130g**, which underwent further rearrangement by a hydrogen migration to nitrogen.



128g (R=Me, E=CO_2Me) **130g** **131g**

Scheme 26

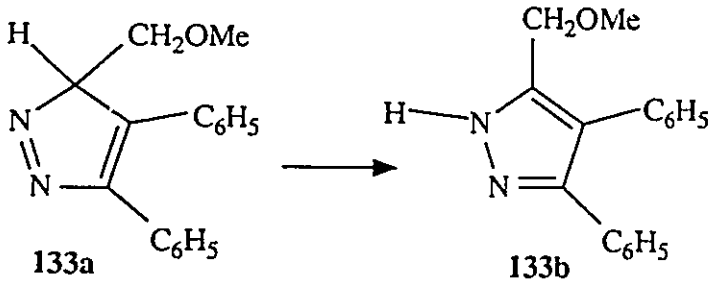
Franck-Neumann and Dietrich-Buchecker also studied the thermal rearrangement of 3*H*-pyrazoles **128h** (R = CO_2Me) and **128i** (R = COMe) and found that, at room temperature, the acyl group migrated competitively to both carbon and nitrogen by [1,5]-sigmatropic shifts (Scheme 27).[84] Carbomethoxy and acyl groups are known to have high migratory aptitudes in [1,5]-sigmatropic rearrangements.[51-55] Rearrangement of 3*H*-pyrazole **128h** gave **131h** (58%) and **132h** (42%) while 3*H*-pyrazole **128i** gave **131i** (95%) and **132i** (5%).



(**h**: R=CO_2Me; **i**: R=COMe)

Scheme 27

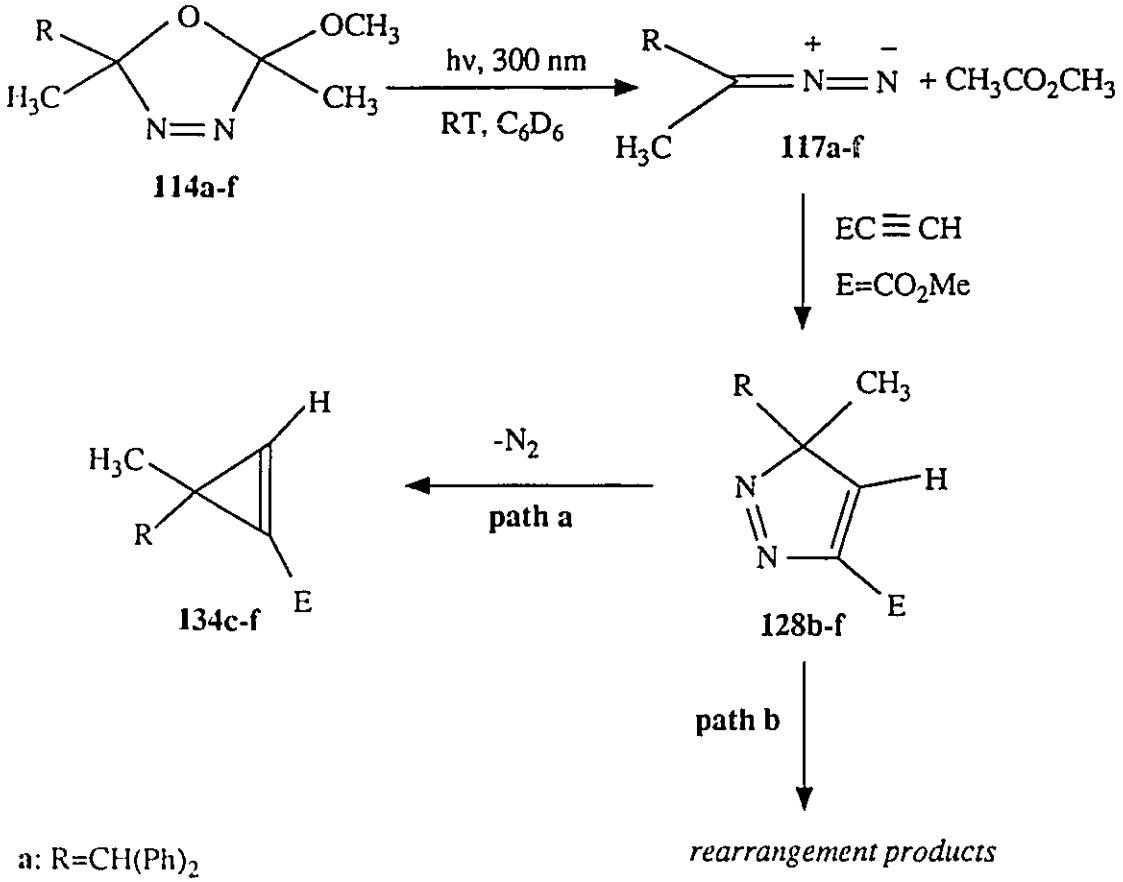
The sense of rearrangement of 3*H*-pyrazoles **128a-f** could be determined by the ratio of pyrazole rearrangement products. Clearly, the percentage of 1*H*-pyrazole **132** would reflect the percentage of migration of R to nitrogen. Similarly, the percentage of 1*H*-pyrazole **131** should reflect the percentage of migration of R to C-4, since the 4*H*-pyrazole **130** should undergo further rearrangement by hydrogen migration to nitrogen. Even substituents with high migratory aptitudes in sigmatropic rearrangements (ie. COOMe, COMe) cannot compete with the fast hydrogen migration in 4*H*-pyrazole **130**. It is known that the rearrangement of 3*H*-pyrazole **133a** gives 1*H*-pyrazole **133b**.[203] By analogy, if 4*H*-pyrazole **130b** (R = CH_2OMe) were formed, rearrangement should afford 1*H*-pyrazole **131b**.



3.1 Photolysis of oxadiazolines 114a-f in the presence of methyl propiolate

The method chosen for the synthesis of 3*H*-pyrazoles **128a-f** was similar to that utilized for the synthesis of 3*H*-pyrazoles **111a-e**. It involves diazoalkane generation from the photolysis of oxadiazolines, followed by *in situ* trapping of these diazoalkanes with methyl propiolate. The 1,3-dipolar cycloaddition was found to be regiospecific with several other diazo compounds.[84,109] The synthesis of oxadiazolines **114a-f**, which are precursors of diazoalkanes **117a-f**, was described in Chapter 2. The oxadiazolines (**114a-f**) were irradiated at 300 nm at ambient temperature in benzene-d_6 solution in the presence of methyl propiolate (Scheme 28). Only 3*H*-pyrazoles **128c-f** could be detected by this method. However, 3*H*-pyrazoles **128c-f** could not be isolated in very good yields because nitrogen extrusion from the 3*H*-pyrazoles occurred, giving cyclopropenes **134c-f**, even when oxadiazolines **114c-f** were still present in solution (path a). For example, after 1 hour of photolysis, 54% of oxadiazoline **114c** was depleted and the solution consisted of cyclopropene **134c** (28%) and 3*H*-pyrazole **128c** (72%). Furthermore, after 4 hours of photolysis, when 87% of oxadiazoline **114c** was depleted, the photolysis solution consisted of **134c** (43%) and **128c** (57%). Likewise, after 1 hour of photolysis, when 87% of oxadiazoline **114d** was depleted, the photolysis solution consisted of **134d** (41%)

and **128d** (59%). The preparative procedure for the synthesis of *3H*-pyrazoles **128c-f** had to be modified in order to obtain improved yields.



a: R=$CH(Ph)_2$
b: R=CH_2OMe
c: R=$C(Me)_3$
d: R=1-adamantyl
e: R=p-$CH_2C_6H_4OMe$
f: R=$CH_2C_6H_5$

Scheme 28

3*H*-Pyrazoles **128** are generally more photolabile than 3*H*-pyrazoles **111** when exposed to 300 nm irradiation because the wavelength of their n-π^* absorption is blue-shifted closer to 300 nm. For example, the n→π^* transition for methyl 3,3-dimethyl-3*H*-pyrazole-5-carboxylate is at 349 nm (MeOH) while the n→π^* transition for dimethyl 3,3-dimethyl-3*H*-pyrazole-4,5-dicarboxylate is at 358 nm (MeOH).[109]

Neither 3*H*-pyrazole **128b** nor cyclopropene **134b** was observed, following the photolysis of **114b**, and only rearrangement products could be detected (Scheme 28, path **b**). The rearrangement products of this 3*H*-pyrazole are discussed in Section 3.4.

There were no products resulting from the cycloaddition of diazoalkane **117a** to methyl propiolate, according to ^{1}H NMR spectroscopy. Even when the photolysis of oxadiazoline **114a** was carried out in neat methyl propiolate, no products resulting from the cycloaddition of diazoalkane **117a** to methyl propiolate could be detected. Presumably this cycloaddition reaction is too slow at room temperature.

3.2 Synthesis of cyclopropenes 134c-f

If the solutions from the irradiation of oxadiazolines **114c-f** in the presence of methyl propiolate were photolyzed until the extrusion of nitrogen from 3*H*-pyrazoles **128c-f** was complete, good yields (52-63%) of cyclopropenes **134c-f** could be obtained. This one-pot synthesis provides a convenient route to cyclopropenes of general structure **134**.

Cyclopropenes **134c-f** were identified on the basis of their ^{1}H and ^{13}C NMR spectra as well as their mass spectrometric masses. The ^{1}H NMR data and selected ^{13}C

NMR chemical shifts for these cyclopropenes are tabulated in Table 18. In the ^{1}H NMR spectra of cyclopropenes **134c-f**, the vinyl proton signal arises in the region of 7.83-7.92 ppm while the methyl signal arises in the region of 1.14-1.30 ppm. In the ^{13}C NMR spectra of these cyclopropenes, the C-1 signal is located in the region of 124.76-125.97 ppm, the C-2 signal is located in the region of 131.21-131.69 ppm, and the C-3 signal is located in the region of 29.43-36.22 ppm. The C-1 signal was differentiated from the C-2 signal on the basis of a ^{13}C NMR spin sort experiment with compound **134c**.

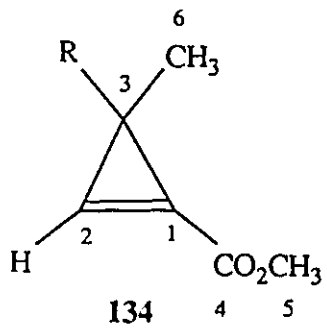
3.3 Synthesis of 3*H*-pyrazoles 128c-f: Modified preparative procedure

3*H*-Pyrazoles **128c-f** were synthesized by a modified preparative procedure in an effort to obtain these compounds in good yields. The photolysis of the 3*H*-pyrazoles, to cyclopropenes, had to be avoided.

The oxadiazolines **114c-f** were photolyzed at 300 nm in toluene solvent for 6 hours at -73 °C (Scheme 29). This generated pink solutions of **117c-f** at -73 °C. Methyl propiolate was added to those photolysis solutions with the Rayonet bulbs switched off, and then the solutions were allowed to warm to room temperature. This procedure prevented exposure of the 3*H*-pyrazoles to the 300 nm irradiation and because of the low temperature, suppressed the formation of azines. The 3*H*-pyrazoles **128c-f** were isolated in good yields (43-65%) and were found to be stable compounds at room temperature.

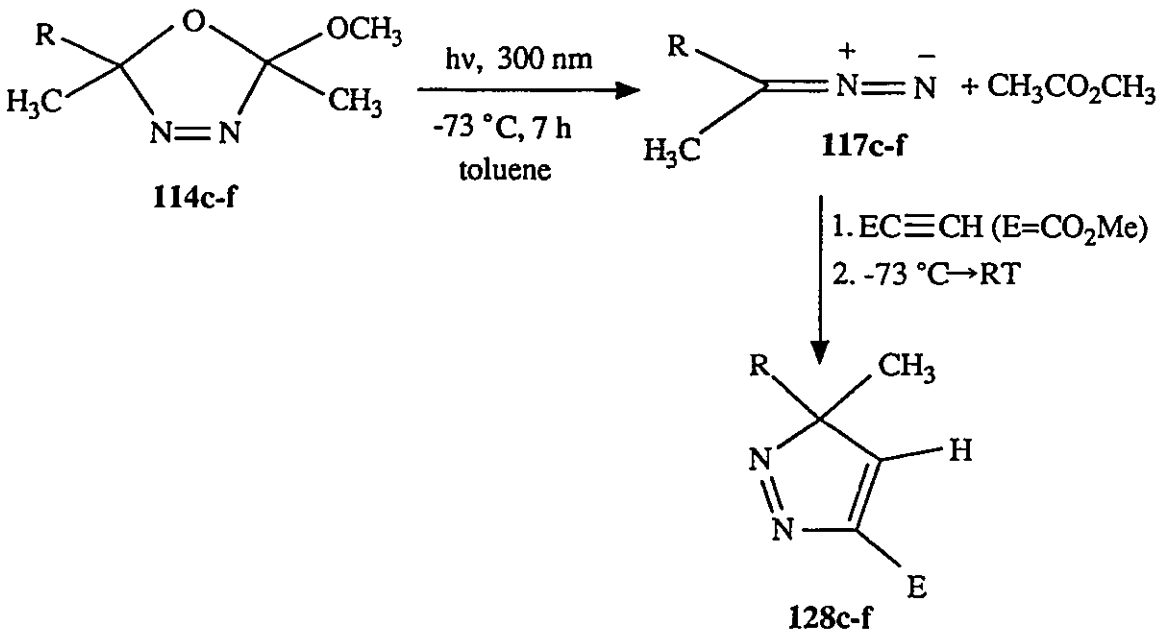
Table 18.

^{1}H NMR and selected ^{13}C NMR chemical shifts (ppm) for cyclopropenes **134c-f** in $CDCl_3$



134

Cyclopropene **134**	^{1}H NMR (200 MHz)	^{13}C NMR (50 Mhz)
134c, R=C(Me)$_3$	7.88 (s, 1 H, CH), 3.77 (s, 3 H, CO_2Me), 1.18 (s, 3 H, Me), 0.82 (s, 9 H, CMe_3).	125.49 (C-1), 131.65 (C-2), 35.08 (C-3), 162.27 (C-4), 52.05 (C-5), 21.23 (C-6).
134d, R=1-adamantyl	7.92 (s, 1 H, CH), 3.80 (s, 3 H, CO_2Me), 1.93 (bs, 3 H, CH), 1.52-1.72 (m, 6 H, CH_2), 1.39-1.41 (m, 6 H, CH_2), 1.14 (s, 3 H, Me).	125.49 (C-1), 131.21 (C-2), 36.22 (C-3), 162.46(C-4), 52.04 (C-5), 20.03 (C-6).
134e, R=p-$CH_2C_6H_4OMe$	7.83 (s, 1 H, CH), 7.01 (d, 2 H, CH, J = 8.5 Hz), 6.80 (d, 2 H, CH, J = 8.5 Hz), 3.80 (s, 3 H, CO_2Me), 3.78 (s, 3 H, OMe), 2.86 (s, 2H, CH_2), 1.29 (s, 3 H, Me).	125.72 (C-1), 131.69 (C-2), 29.65 (C-3), 161.82 (C-4), 52.05 (C-5), 25.19 (C-6).
134f, R=$CH_2C_6H_5$	7.84 (s, 3 H, CH), 7.26-7.08 (m, 5 H, Ph), 3.80 (s, 3 H, CO_2Me), 2.92 (s, 2 H, CH_2), 1.30 (s, 3 H, Me).	125.97 (C-1), 131.65 (C-2), 29.43 (C-3), 161.76(C-4), 52.04 (C-5), 25.23 (C-6)



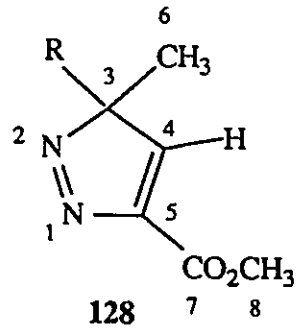
(**c**: R=C(Me)$_3$; **d**: R=1-adamantyl; **e**: R=p-$CH_2C_6H_4OMe$; **f**: R=$CH_2C_6H_5$)

Scheme 29

3*H*-Pyrazoles **128c-f** were identified on the basis of their ^{1}H and ^{13}C NMR spectra as well as their mass spectrometric masses. The ^{1}H NMR data and selected ^{13}C NMR chemical shifts of these 3*H*-pyrazoles are tabulated in Table 19. In the ^{1}H NMR spectra of 3*H*-pyrazoles **128c-f**, the vinyl proton signal arises in the region of 7.66-7.77 ppm, while the methyl signal arises in the region of 1.33-1.47 ppm. In the ^{13}C NMR spectra of these 3*H*-pyrazoles, the C-3 signal is located in the region of 98.96-105.60, the C-4 signal is located in the region of 152.86-154.47 ppm, and the C-5 signal is located in the region of 147.01-147.66 ppm. The C-4 signal was differentiated from the C-5 signal on the basis of ^{13}C NMR spin sort experiments with compounds **128c** and **128d**.

Table 19.

^{1}H NMR and selected ^{13}C NMR chemical shifts (ppm) for 3*H*-pyrazoles **128c-f** in $CDCl_3$



128

3*H*-Pyrazole, **128**	^{1}H NMR (200 MHz)	^{13}C NMR (50 MHz)
128c, R=C(*Me*)$_3$	7.77 (s, 1 H, CH), 3.99 (s, 3 H, CO_2Me), 1.38 (s, 3 H, Me), 1.06 (s, 9 H, CMe_3).	105.08 (C-3), 153.37 (C-4), 147.02 (C-5), 15.06 (C-6), 161.38 (C-7), 52.38 (C-8).
128d, R=1-adamantyl	7.77 (s, 1 H, CH), 3.98 (s, 3 H, CO_2Me), 1.99 (bs, 3 H, CH), 1.68 (bs, 12 H, CH_2), 1.33 (s, 3 H, Me).	105.60 (C-3), 154.47 (C-4), 147.01 (C-5), 13.73 (C-6), 161.39 (C-7), 52.33 (C-8).
128e, R=p-$CH_2C_6H_4OMe$	7.66 (s, 1 H, CH), 7.00 (d, 2 H, CH, J = 8.2 Hz), 6.78 (d, 2 H, CH, J = 8.2 Hz), 3.94 (s, 3 H, CO_2Me), 3.77 (s, 3 H, OMe), 3.29 (d, 1 H, J= - 14 Hz), 3.07 (d, 1 H, J= - 14 Hz), 1.46 (s, 3 H, Me).	99.30 (C-3), 153.11 (C-4), 147.66 (C-5), 18.01 (C-6), 161.09 (C-7), 52.40 (C-8).
128f, R=$CH_2C_6H_5$	7.66 (s, 3 H, CH), 7.26-7.07 (m, 5 H, Ph), 3.93 (s, 3 H, CO_2Me), 3.34 (d, 1 H, J= -13 Hz), 3.10 (d, 1 H, J= -13 Hz), 1.47 (s, 3 H, Me).	98.96 (C-3), 152.86 (C-4), 147.60 (C-5), 18.03 (C-6), 161.00 (C-7), 52.34 (C-8)

3.4 Rearrangements of 3*H*-pyrazoles 128b-f in benzene-d_6 solvent

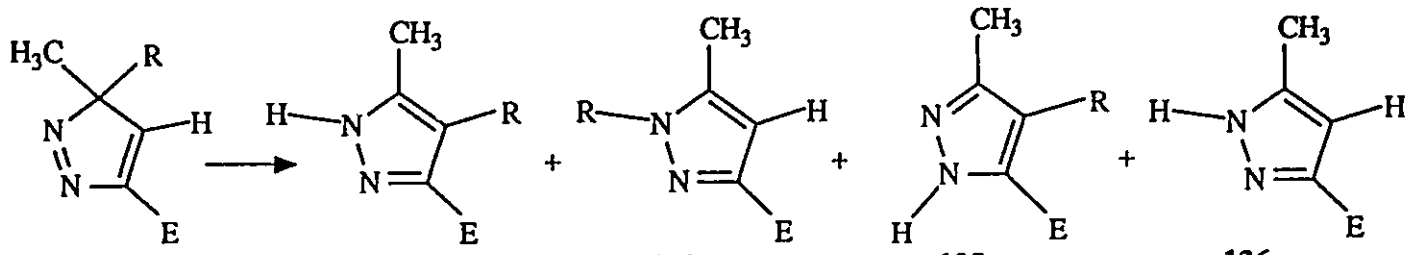
The thermal rearrangements of 3*H*-pyrazoles **128c-f** were investigated in benzene-d_6 solvent. As mentioned above, 3*H*-pyrazole **128b** rearranged in benzene-d_6 solvent in the medium in which it was generated.

Table 20 reveals the products of the rearrangements of 3*H*-pyrazoles **128b-f** in benzene-d_6 solvent. The rearrangements led to very clean product solutions and the numbers reported are percentages determined by ^{1}H NMR spectroscopy.

3*H*-Pyrazole **128b** rearranged in the medium in which it was generated to give **131b** (52%) and **132b** (48%). Presumably, 1*H*-pyrazole **131b** was formed by a hydrogen migration in unstable 4*H*-pyrazole **130b** (where R = CH_2OMe). Migration of the methoxymethyl substituent to both N-2 and C-4 had occurred in roughly equal amounts. Since the rearrangement of 3*H*-pyrazole **128b** is fast at room temperature, it is reasonable to assume an ion-pair mechanism is operating in this rearrangement, especially since 3*H*-pyrazole **128g** (R = CH_3) requires a temperature of 180 °C for thermal rearrangement. Furthermore, **128g** affords only **131g** from thermal rearrangement.

Unlike 3*H*-pyrazole **128b**, 3*H*-pyrazole **128c** was stable at room temperature. The overall rate constant for the decrease in concentration of 3*H*-pyrazole **128c** in benzene-d_6 solvent at 90 °C is (1.06 ± .03) x 10^{-4} s^{-1}. A fragmentation reaction of **128c** gave **136** (55%) and isobutene (55%). The presence of **136** and isobutene suggests that a pyrazole anion and a *tert*-butyl cation are reaction intermediates. The presence of isobutene was confirmed by a ^{1}H NMR spectroscopy decoupling experiment on the thermolysis mixture

Table 20. Products and product yields[a] from the thermal rearrangements of **128b-f** in benzene-d_6



128	**131**	**132**	**135**	**136**	**+ others**
128b,[b] R=CH_2OMe	52	48	nil	nil	
128c,[c] R=$C(Me)_3$	28	15	2	55	isobutene, 55
128d,[d] R=1-adamantyl	72	28	nil	nil	
128e,[e] R=p-$CH_2C_6H_4OMe$	78	22	nil	nil	
128f,[f] R=$CH_2C_6H_5$	100	nil	nil	nil	

[a] At the level of detection afforded by ^1H NMR spectroscopy, the products listed were the only products from rearrangement and the yield numbers (%) reflect materials balance prior to opening of a tube.

[b] Rearrangement at ambient temperature.

[c] Rearrangement at 90 °C with $k = (1.06 \pm .03) \times 10^{-4}\ s^{-1}$.

[d] Rearrangement at 90 °C with $k = (1.10 \pm .09) \times 10^{-4}\ s^{-1}$.

[e] Rearrangement at 60 °C with $k = (3.6 \pm 0.2) \times 10^{-4}\ s^{-1}$.

[f] Rearrangement at 90 °C with $k = (2.8 \pm 0.1) \times 10^{-4}\ s^{-1}$.

(sealed nmr tube). Irradiation of the multiplet at 4.74 ppm (CH_2) caused the collapse of the triplet at 1.60 ppm (2 CH_3). 1*H*-Pyrazole **132c** (15%), from migration of *tert*-butyl to nitrogen and 1*H*-pyrazoles **131c** (28%) and **135c** (2%) from migration of *tert*-butyl to carbon were also products in the rearrangement of **128c**.

3*H*-Pyrazole **128d** underwent thermal rearrangement at 90 °C with an observed rate constant of $(1.10 \pm .09) \times 10^{-4}$ s^{-1}, which is similar to the observed rate constant for the rearrangement of 3*H*-pyrazole **128c**. Rearrangement of **128d** afforded **131d** (72%) and **132d** (28%).

3*H*-Pyrazole **128e** rearranged faster than both **128c** and **128d** with an observed rate constant of $(3.6 \pm 0.2) \times 10^{-4}$ s^{-1} (average of 2 runs) at 60 °C. The products of rearrangement of **128e** were **131e** (78%) and **132e** (22%).

The thermal rearrangement of **128f** afforded only **131f**; the benzyl substituent had migrated only to C-4 in 3*H*-pyrazole **128f**. In contrast, the rearrangements of **128b-e** gave a mixture of 1*H*-pyrazoles **131** and **132**; the result of R substituent migration to both C-4 and N-2. The observed rate constant for rearrangement of **128f** at 90 °C is $(2.8 \pm 0.1) \times 10^{-4}$ s^{-1}.

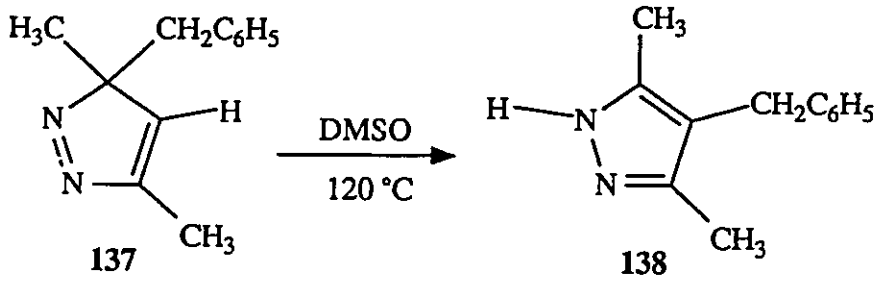
It appears that 3*H*-pyrazoles **128b** and **128c** rearrange in benzene-d_6 solvent by a stepwise mechanism, involving the formation of ion pairs. 3*H*-Pyrazole **128b** (R = CH_2OMe) rearranges with a rate enhancement of at least 10^5, while 3*H*-pyrazole **128c** rearranges with a rate enhancement of approximately 10^3, compared to the rearrangement of **128g** (R = Me). Furthermore, 3*H*-pyrazole **128c** affords both **136** and isobutene as products of thermal reaction which is suggestive of an ion-pair intermediate.

Whether or not 3*H*-pyrazoles **128d-f** undergo rearrangement by a stepwise or a concerted mechanism is ambiguous. The approximate relative order of rates of rearrangement of 3*H*-pyrazoles **128c-f** are the following: **128c** (1.0), **128d** (1.0), **128f** (2.6), and **128e** (27). All these 3*H*-pyrazoles rearrange with large rate enhancements compared to the thermal rearrangement of **128g**, where a concerted mechanism for rearrangement is assumed. Furthermore, with the exception of **128f**, these thermal rearrangements afford rearrangement products from migration of R to both C-4 and N-2. In contrast, the thermal rearrangement of **128g** affords only **131g** from migration of methyl to C-4.

It is informative that 3*H*-pyrazole **128e** (R = p-$CH_2C_6H_4OMe$) rearranges approximately 10 times faster than 3*H*-pyrazole **128f** (R = $CH_2C_6H_5$), assuming a 2-fold increase in the observed rate for every 10 °C increase in temperature. The rate enhancement for **128e**, compared to **128f** suggests development of some positive charge in the migrating group at the transition state for thermal rearrangement. 3*H*-Pyrazole **128f** may rearrange either by a stepwise or a concerted mechanism involving some degree of charge separation.

The thermal rearrangement of a 3*H*-pyrazole analogue of **128f**, was previously investigated. Schiess and Stalder studied the thermal rearrangement of 3*H*-pyrazole **137**, similar in structure to 3*H*-pyrazole **128f** except that a methyl substituent replaces the carbomethoxy substituent at C-5.[143] Rearrangement of **137** occurred at 120 °C in DMSO solvent, with an overall first order rate constant of $3.05 \times 10^{-4}\ s^{-1}$. Thermal rearrangement

afforded only **138** from initial migration of benzyl to C-4 followed by hydrogen migration to nitrogen.



137 **138**

3*H*-Pyrazole **128f** rearranges at least 9 times faster than 3*H*-pyrazole **137**, assuming a factor of 2 per 10 °C for the temperature difference and an additional rate factor for the solvents (C_6D_6 for **128f**, DMSO for **137**). The carbomethoxy substituent at C-5 of **128f** is rate enhancing compared to the methyl group at C-5 of 3*H*-pyrazole **137**. This suggests that there is some negative charge developed within the pyrazole nucleus at the transition state for the rearrangement of **128f**. The carbomethoxy substituent is stabilizing toward negative charge development in the pyrazole nucleus compared to the methyl substituent. It seems that 3*H*-pyrazole **128f** rearranges by a concerted mechanism with some charge separation at the transition state for rearrangement. 3*H*-Pyrazole **128f**, like 3*H*-pyrazole **137**, afforded only the rearrangement product from initial migration of benzyl to C-4.

It is unclear clear whether 3*H*-pyrazoles **128d** and **128e** rearrange by a concerted or a stepwise mechanism in spite of their large rate enhancements for rearrangement

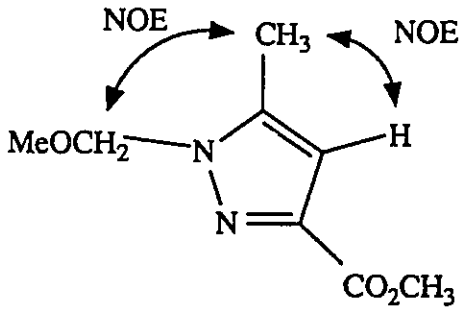
compared to **128g**. However, because they afford two rearrangement products (**131** and **132**), unlike the thermal rearrangement of **128g**, this may suggest that they rearrange by a non-concerted mechanism.

3.5 Structural determination of pyrazole rearrangement products

The pyrazole products from the thermal rearrangements of **128b-f** were all new compounds, except for 1*H*-pyrazole **136**. 1*H*-Pyrazoles **132b-e** and 1*H*-pyrazoles **131b-f** were identified on the basis of their ^{1}H and ^{13}C NMR spectra as well as their mass spectrometric masses.

In the ^{1}H NMR spectra of 1*H*-pyrazoles **132b-e**, the vinyl proton appears in the region of 6.54-6.63 ppm, the carbomethoxy singlet appears in the region of 3.86-3.92 ppm, and the methyl singlet appears in the region of 2.12-2.51 ppm.

A ^{1}H NOE experiment on compound **132b** confirmed that the methoxymethyl substituent was located on N-1 in a 1,5-relationship with the methyl substituent. Irradiation of the methyl singlet at 2.38 ppm caused enhancement of both the CH_2 singlet at 5.45 ppm and the vinyl proton singlet at 6.63 ppm.



132b

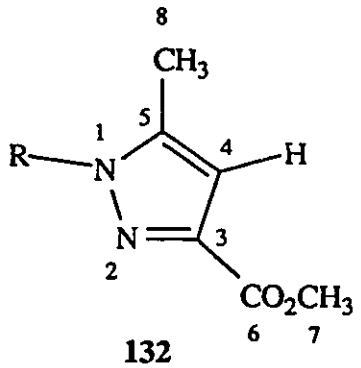
The similarities of the ^{13}C NMR spectra of **132c-e** to the ^{13}C NMR spectrum of **132b** confirm that the R substituents of **132b-e** are also in a 1,5-relationship with the methyl substituent. Selected ^{13}C NMR chemical shifts for compounds **132b-e** are tabulated in Table 21. Some of the ^{13}C NMR chemical shifts were assigned by comparison with ^{13}C NMR chemical shift assignments made by others for similar 1*H*-pyrazoles.[197] The C-3 chemical shifts appear in the region of 139.42-140.88 ppm, the C-4 chemical shifts appear in the region of 108.94-111.27 ppm, and the C-5 chemical shifts appear in the region of 139.99-142.66 ppm.

1*H*-Pyrazoles **131b-f** are solids, unlike 1*H*-pyrazoles **132b-e** which are oils. In the ^1H NMR spectra of these compounds, the carbomethoxy singlet appears in the region of 3.85-3.92 ppm and the methyl singlet appears in the region of 2.21-2.47 ppm. Only for compounds **131d** and **131f**, was a broad NH singlet observed in their ^1H NMR spectra (4.5-5.1 ppm). Selected ^{13}C NMR chemical shifts for 1*H*-pyrazoles **131b-f** are located in Table 22. Some of the ^{13}C NMR chemical shifts were assigned by comparison with chemical shift assignments made by others, for similar 1*H*-pyrazoles.[197] The C-3 chemical shifts appear in the region of 130.03-139.91 ppm, the C-4 chemical shifts appear in the region of 114.50-129.12 ppm, and the C-5 chemical shifts arise in the region of 137.23-144.31 ppm.

The structure of compound **135c** was assigned because of the close similarity of its ^1H NMR spectrum to the ^1H NMR spectrum of **131c**. Furthermore, **135c** eluted just before **131c** in centrifugal chromatography (silica gel). As mentioned in Chapter 2, compound **119** is less polar than compound **118**.

Table 21.

Selected ^{13}C NMR chemical shifts of **132b-e** in $CDCl_3$.

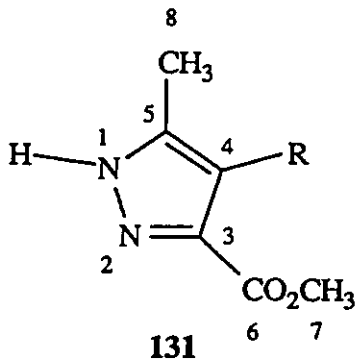


132

132	C-3	C-4	C-5	C-6	C-7	C-8
132b	140.88	109.23	142.56	162.85	51.97	10.69
132c	139.42	111.27	139.99	163.24	51.76	14.65
132d	139.50	111.26	140.16	163.30	51.80	15.00
132e	139.95	108.94	142.03	163.03	51.91	11.29

Table 22.

Selected ^{13}C NMR chemical shifts of **131b-f** in $CDCl_3$.



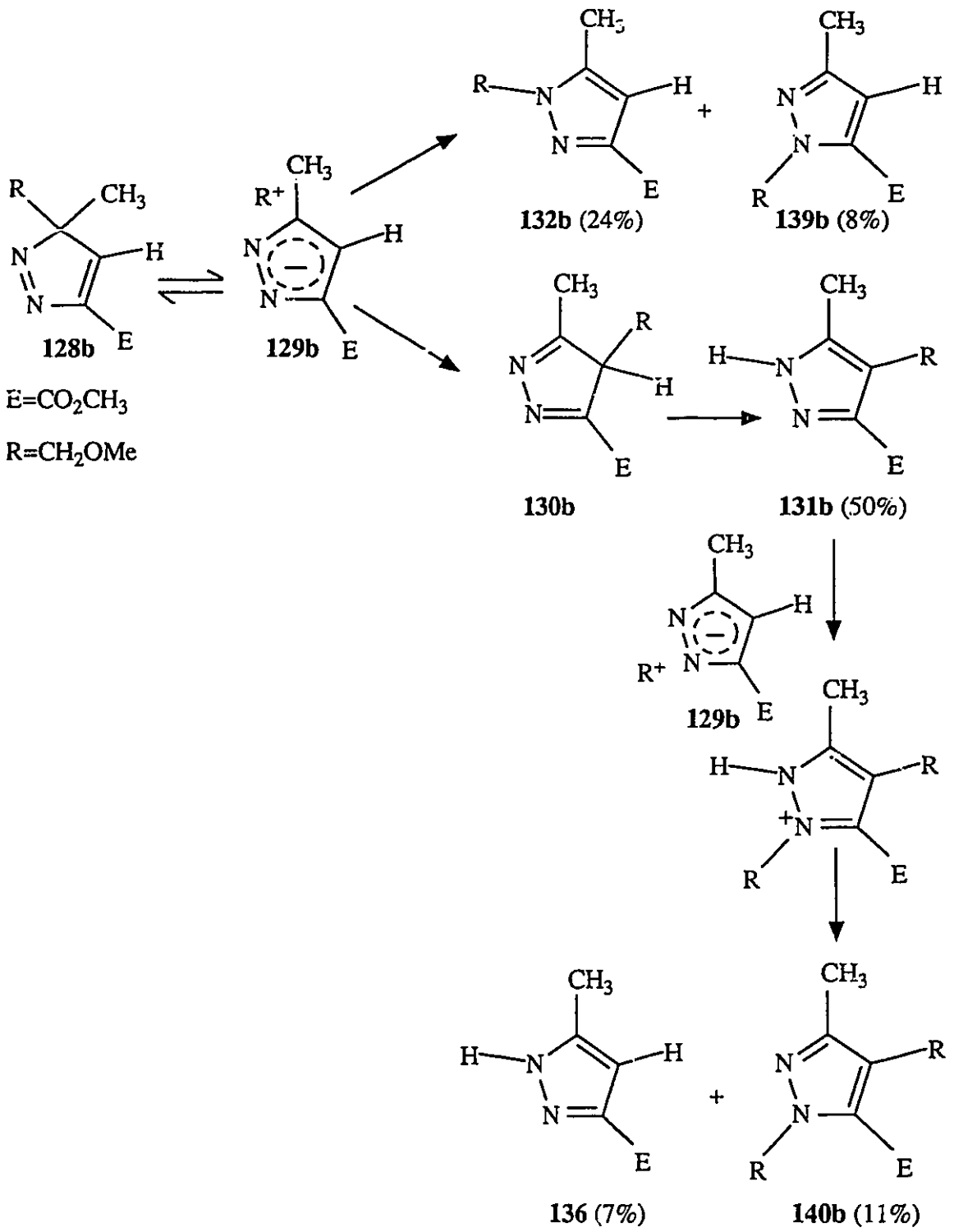
131

131	C-3	C-4	C-5	C-6	C-7	C-8
131b	137.95	117.88	144.31	161.93	10.39	51.92
131c	139.91	129.12	142.49	163.01	14.16	51.92
131d	130.03	114.50	137.23	162.71	15.37	52.05
131e	136.75	120.91	143.21	162.21	10.50	51.63
131f	136.91	120.45	143.31	162.22	10.48	51.61

3.6 Rearrangement of 128b in dichloromethane

The rearrangement of 3*H*-pyrazole **128b** in dichloromethane was investigated. This solvent should increase ion-pair separations and give pyrazole products resulting from collapse of a more separated ion-pair intermediate.

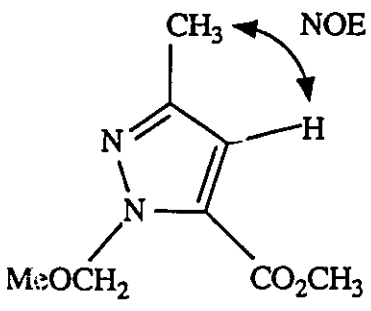
Oxadiazoline **114b** and methyl propiolate were dissolved in dichloromethane (base washed and distilled) and irradiated at 300 nm for 6 hours. 3*H*-Pyrazole **128b** rearranged in the medium in which it was generated to give several interesting rearrangement products. Scheme 30 gives the percentages of those products (by ^{1}H NMR spectroscopy) as well as a proposed mechanistic outline for their formation. 3*H*-Pyrazole **128b** dissociates to ion-pair **129b** in dichloromethane. The methoxymethyl cation then collapses on both nitrogen atoms of the pyrazole anion to give **132b** (24%) and **139b** (8%). The methoxymethyl cation also collapses on carbon, adjacent to the migration origin, to afford unstable 4*H*-pyrazole **130b**. Fast migration of hydrogen to nitrogen in this pyrazole to nitrogen affords 1*H*-pyrazole **131b** (50%). The other products are **140b** and **136**. Alkylation of **131b** with the cation of ion-pair intermediate **129b** results in proton loss and the formation of **140b** (11%). Protonation of the anion of ion-pair **129b** gives rise to compound **136**. The formation of **139b**, **136**, and **140b** supports a stepwise mechanism involving an ion-pair intermediate in the rearrangement of 3*H*-pyrazole **128b**.


128b
129b
E=CO2CH3
R=CH2OMe
132b (24%)
139b (8%)
130b
131b (50%)
129b
136 (7%)
140b (11%)

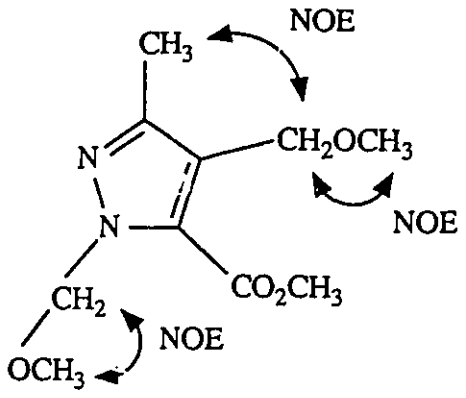
Scheme 30

The structures of compounds **139b** and **140b** were assigned on the basis of ^{1}H and ^{13}C NMR spectroscopy as well as their mass spectrometric molecular masses. ^{1}H NMR NOE experiments were very useful in determining the structures of compounds **139b** and **140b**. Irradiation of the methyl singlet at 2.30 ppm of **139b** gave enhancement only at 6.70 ppm (vinyl proton). This experiment confirms that the methoxymethyl substituent is not in a 1,5-relationship with the methyl substituent. As mentioned above, for compound **132b**, irradiation of the methyl singlet at 2.38 ppm caused enhancement of both the CH_2 singlet of methoxymethyl at 5.45 ppm and the CH singlet at 6.63 ppm (methoxymethyl and methyl substituents are in a 1,5-relationship).

^{1}H NOE experiments were crucial in determining the structure of compound **140b**. Irradiation of the N-methylene singlet of **140b** showed enhancement only at 3.32 ppm (N-$CH_2O\underline{CH_3}$). This experiment confirms that the methoxymethyl substituent is not in a 1,5-relationship with the methyl substituent. Furthermore, irradiation of the C-methylene singlet at 4.55 ppm showed enhancement of both the singlet at 3.35 ppm (C-$CH_2O\underline{CH_3}$) and the singlet at 2.34 ppm (CH_3). This experiment demonstrates that the methoxymethyl substituent on carbon is in a 3,4-relationship with the methyl substituent.



139b



140b

3.7 Rearrangement of 3*H*-pyrazoles 128c-f in acetone-d_6

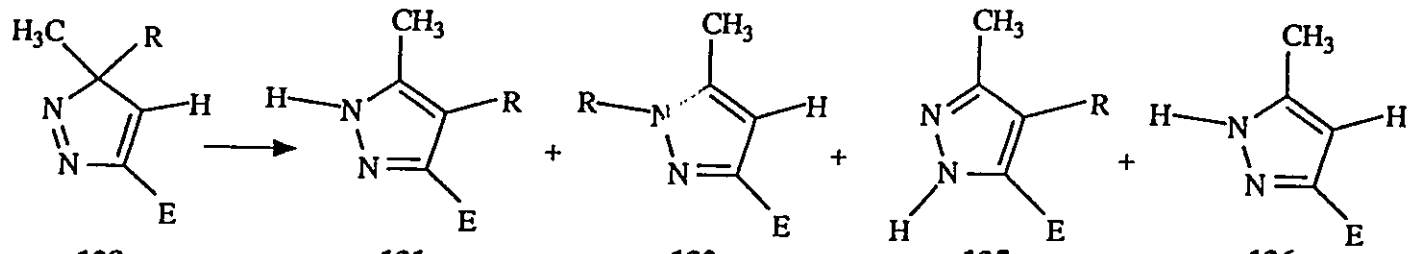
The rearrangements of 3*H*-pyrazoles **128c-f** in acetone-d_6 were also investigated. Since the observed rate constants for the rearrangement of these 3*H*-pyrazoles could be determined, it was possible to quantitate the effect of a change of solvent polarity (benzene-d_6 to acetone-d_6) on the observed rates of rearrangement.

Table 23 gives the products from the rearrangement of 3*H*-pyrazoles **128c-f** in acetone-d_6 solvent. The percentage yields were determined by ^{1}H NMR spectroscopy after the rearrangement of these 3*H*-pyrazoles was complete.

3*H*-Pyrazole **128c** rearranged in acetone-d_6 at 90 °C with an observed rate constant of $9.7 \pm 0.3 \times 10^{-5}$ s^{-1}, which is similar to its observed rate constant of $(1.06 \pm 0.03) \times 10^{-4}$ s^{-1} in benzene-d_6. This is very unusual for a rearrangement which presumably proceeds via an ion-pair intermediate. The move to a more polar solvent should increase the rate of rearrangement. The products of rearrangement in acetone-d_6 were **131c** (38%), **135c** (7%), **132c** (15%), **136** (41%), and isobutene (34%). The ratio of rates of migration of *tert*-butyl to C-4 and N-2 was 3 : 1. The reaction products **136** and isobutene suggest the presence of a *tert*-butyl cation and pyrazole anion intermediate.

The rearrangement of **128d** also proceeded with similar rate constants in both acetone-d_6 [$k = (8.9 \pm 0.4) \times 10^{-5}$ s^{-1}] and benzene-d_6 [$k = (1.1 \pm 0.1) \times 10^{-4}$ s^{-1}] solvents. The products of rearrangement in acetone-d_6 were **131d** (72%) and **132d** (28%). The ratio of migration rates of 1-adamantyl to C-4 and N-2 was approximately 3 : 1.

Table 23. Products and product yields[a] from the thermal rearrangements of **128b-f** in acetone-d_6



128	**131**	**132**	**135**	**136**	**+ others**
128c,[b] $R=C(Me)_3$	38	15	7	41	isobutene, 34
128d,[c] R=1-adamantyl	72	28	nil	nil	
128e,[d] $R=p\text{-}CH_2C_6H_4OMe$	91	9	nil	nil	
128f,[e] $R=CH_2C_6H_5$	100	nil	nil	nil	

[a] At the level of detection afforded by ^1H NMR spectroscopy, the products listed were the only products from rearrangement and the yield numbers (%) reflect materials balance prior to opening of a tube.

[b] Rearrangement at 90 °C with $k = (9.7 \pm 0.3) \times 10^{-5}\ s^{-1}$.

[c] Rearrangement at 90 °C with $k = (8.9 \pm 0.4) \times 10^{-5}\ s^{-1}$.

[d] Rearrangement at 60 °C with $k = (2.1 \pm 0.1) \times 10^{-4}\ s^{-1}$.

[e] Rearrangement at 90 °C with $k = (2.80 \pm .05) \times 10^{-4}\ s^{-1}$.

The observed rate of rearrangement of **128e** in acetone-d_6 [k = (2.1 ± 0.1) x 10^{-4} s^{-1}] was less than its observed rate of rearrangement in benzene-d_6 [k = (3.6 ± 0.2) x 10^{-4} s^{-1}]. The products of rearrangement in acetone-d_6 were **131e** (91%) and **132e** (9%) from which the ratio of rates of migration of p-methoxybenzyl to C-4 and N-2 was approximately 10 : 1.0.

3*H*-Pyrazole **128f** rearranged in acetone-d_6 [k = (2.80 ± 0.05) x $10^{-4}$$s^{-1}$] with essentially the same rate constant as it did in benzene-d_6 solvent. Once again, the only rearrangement product was **131f**. If the rearrangement of 3*H*-pyrazole **128f** was concerted in nature, a change in solvent polarity should not effect the rate of rearrangement; this was observed.

The similar rates of rearrangement of 3*H*-pyrazoles **128c-e** in benzene-d_6 and acetone-d_6 solvents seems to conflict with an ion-pair mechanism for rearrangement. First, 3*H*-pyrazole **128c** fragments to give isobutene and **136** as products in both solvents, which suggests the presence of an ion-pair intermediate. However, moving to a more polar solvent does not increase the rate of rearrangement of **128c** as would be expected. Second, 3*H*-pyrazole **128e** (R = p-$CH_2C_6H_4OMe$) rearranges approximately 10 times faster than 3*H*-pyrazole **128f** (R = $CH_2C_6H_5$); this substituent effect on the rate of rearrangement suggests some degree of positive charge development on R in the transition state for migration of the p-methoxybenzyl substituent. Therefore, moving to a more polar solvent should increase the rate of rearrangement of **128e**. Unfortunately, a comparison of the rates of solvolysis of RX (X = halide) in benzene and acetone solvents is not available.

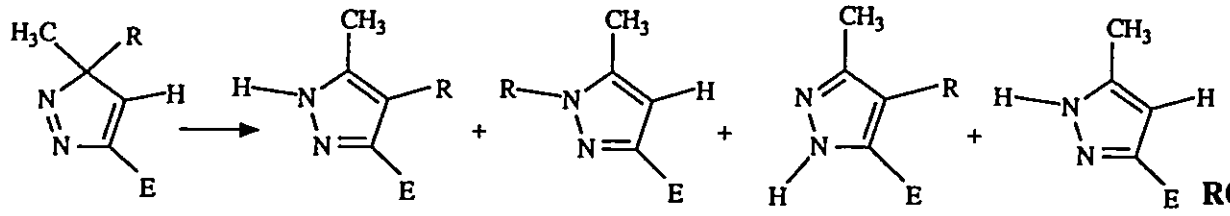
3.8 Rearrangement of 3*H*-pyrazoles 128b-f in methanol or methanol-d_4

In an effort to trap any intermediate ion pairs in the rearrangements of **128b-f**, the rearrangements were carried out in methanol solvent. Perhaps this hydrogen-bonding solvent would give rise to rate enhancements for the rearrangement of 3*H*-pyrazoles **128c-f**.

Table 24 reveals the products from the rearrangement of 3*H*-pyrazoles **128b-f** in methanol or methanol-d_4 solvents. The percentages reported were determined by ^{1}H NMR spectroscopy, following the complete rearrangement of **128b-f**.

3*H*-Pyrazole **128b** rearranged at ambient temperature in methanol-d_4 solvent in the medium in which it was generated. Rearrangement gave **131b** (53%), from migration of the methoxymethyl cation to carbon and **132b** (21%), from migration of the methoxymethyl cation to nitrogen. 1*H*-Pyrazole **136** (D analogue, 26%) and **141** (dimethoxymethane-d_3, 26%) are also products. Dimethoxymethane-d_3 was confirmed by ^{1}H NMR spectroscopy and gas chromatography spiking experiments with an authentic sample of the non-deuterated analogue. Trapping of an ion-pair intermediate provides strong evidence that 3*H*-pyrazole **128b** rearranges by a stepwise mechanism. A smaller portion of the cation intermediate was intercepted from **128b** (26%) compared to **111b** (75%), which suggests that the ion-pair intermediate from **128b** is "tighter" than the ion-pair intermediate from **111b**.

Table 24. Products and product yields[a] from the thermal rearrangements of **128b-f** in methanol.



128	**131**	**132**	**135**	**136**	**ROCH$_3$ (141)**	**+ other**
128b,[b] R=CH_2OMe	53	21	nil	26[c]	26[d]	
128c,[e] R=$C(Me)_3$	18	16	6	60[f]	31[d]	isobutene, 27
128d,[g] R=1-adamantyl	81	19	nil	trace amount	trace amount	
128e,[g] R=p-$CH_2C_6H_4OMe$	75	25	nil	trace amount	trace amount	
128f,[g] R=$CH_2C_6H_5$	100	nil	nil	nil	nil	

[a] At the level of detection afforded by ^{1}H NMR spectroscopy, the products listed were the only products from rearrangement and the yield numbers (%) reflect materials balance prior to opening of a tube.
[b] Rearrangement at ambient temperature.
[c] D anaologue.
[d] CD_3OR, from rearrangement in CD_3OD at ambient temperature.
[e] Rearrangement at 90 °C.
[f] Mixture of H and D analogues.
[g] Rearrangement in methanol at 65 °C.

Likewise, an ion-pair intermediate from 3*H*-pyrazole **128c** was intercepted by methanol-d_4. After 3*H*-pyrazole **128c** was heated at 90 °C for 20 minutes, ^{1}H NMR spectroscopy revealed that thermal rearrangement was complete. *tert*-Butyl methyl ether-d_3 (**141c**) was present in a 31% yield. The presence of this compound was confirmed by ^{1}H NMR spectroscopy and gas chromatography spiking experiments with an authentic sample of the non-deuterated analogue. Other products included **136** (a mixture of H and D analogues, 60%), **131c** (18%), **132c** (16%), **135c** (6%), and isobutene (27%). The products force the conclusion that an intermediate ion pair was generated during the rearrangement of **128c** in methanol-d_4.

In another experiment, the observed rate constant [$(4.7 \pm 0.1) \times 10^{-4}$ s^{-1}] was determined for the rearrangement of **128c** in methanol-d_4 at 50 °C. The observed rate constant for rearrangement of **128c** is approximately 80 times greater in methanol-d_4, compared to acetone-d_6. This rate enhancement was estimated by assuming a factor of 2 per 10 °C for the temperature difference.

Thermal rearrangement of both **128d** and **128e** afforded only trace amounts of **136** and **141**, after refluxing in methanol solvent for 0.5 hours. The presence of these compounds was confirmed by ^{1}H NMR and gas chromatography spiking experiments with compounds prepared by another route.[193,194] 3*H*-Pyrazole **128d** afforded **131d** (81%) and **132** (19%) from rearrangement in methanol solvent while **128e** afforded **131e** (75%) and **132e** (25%). Since rearrangement is complete after 0.5 hours at 65 °C there is a rearrangement rate enhancement for both these 3*H*-pyrazoles compared to their rearrangements in benzene-d_6 or acetone-d_6. Presumably, an ion-pair mechanism operates

in these rearrangements, but the ion-pairs in these cases are very "tight" and do not become solvent-separated.

3*H*-Pyrazole **128f** rearranged completely, after refluxing in methanol for 0.5 hours, to afford only **131f**. Benzyl methyl ether and **136** could not be detected. Since rearrangement was complete after only 0.5 hours at 65 °C, there is also a rate enhancement (at least 41-fold) in this solvent of higher polarity. Presumably, 3*H*-pyrazole **128f** rearranges by a concerted mechanism with some charge separation.

3.9 Conclusion.

It appears that 3*H*-pyrazoles **128b-e** rearrange by a stepwise mechanism in methanol solvent since a portion of an ion-pair intermediate was intercepted. However, it seems that the ion pairs from these 3*H*-pyrazoles are very "tight" since a smaller portion of the ion-pair intermediate was intercepted than from the analogous 3*H*-pyrazoles (**111b-e**). This is reasonable because the intermediate pyrazole anion derived from 3*H*-pyrazoles **128b-e** is less stable than the anion derived from 3*H*-pyrazoles **111b-e** (Scheme 24). The large rate enhancements for the rearrangements of 3*H*-pyrazoles **128b-e** in methanol compared to benzene also provides support for a stepwise mechanism for rearrangement in methanol solvent.

3*H*-Pyrazole **128b** rearranges by a stepwise mechanism in both benzene and dichloromethane because of the large rate enhancements for these rearrangements compared to 3*H*-pyrazole **128f** (R = CH_3). Furthermore, in dichloromethane solvent **128b** affords some products (**136**, **139b**, and **140b**) which could not have arisen from a

concerted mechanism for rearrangement. 3*H*-Pyrazole **128c** appears to rearrange by a stepwise mechanism in both benzene-d_6 and acetone-d_6 because isobutene and **136** were reaction products. For 3*H*-pyrazoles **128d** and **128e** it is unclear whether their rearrangements in benzene-d_6 and acetone-d_6 solvents are concerted, with some charge separation, or stepwise. It seems that 3*H*-pyrazole **128f** rearranges by "normal" [1,5]-sigmatropic shifts of benzyl in benzene-d_6, acetone-d_6, and methanol solvents. Its rearrangement in methanol seems to involve some charge separation because of the rate enhancement observed in this solvent of higher polarity even though there was no evidence, from trapping, that an ion-pair intermediate is involved.

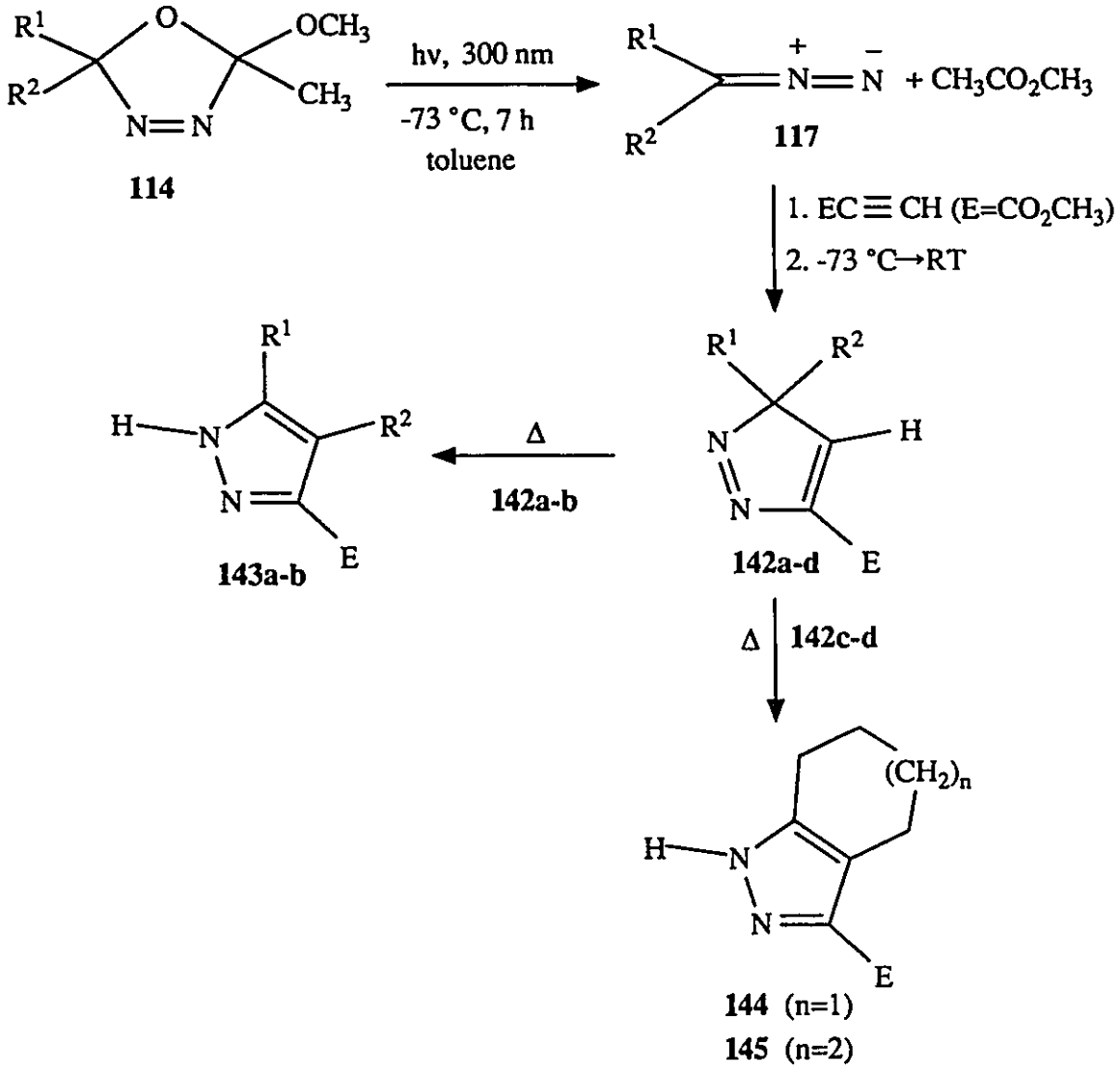
The observed rate constants for the thermal rearrangements of **128c-e** can be compared to the observed rate constants for the thermal rearrangements of **111c-e** (Chapter 2) in benzene-d_6. The following rate enhancements were estimated by assuming a 2-fold increase in the rate constant for every 10 °C increase in temperature. There is a 27-fold increase in the rate of rearrangement of **111c** ($k = 6.2 \times 10^{-5}$ s^{-1}, 35 °C) compared to **128c** ($k = 1.06 \times 10^{-4}$ s^{-1}, 90 °C), a 23-fold increase in the rate of rearrangement of **111d** ($k = 5.6 \times 10^{-5}$ s^{-1}, 35 °C) compared to **128d** ($k = 1.1 \times 10^{-4}$ s^{-1}, 90 °C), and a 4-fold increase in the rate of rearrangement of **111e** ($k = 9.80 \times 10^{-5}$ s^{-1}, 20 °C) compared to **128e** ($k = 3.6 \times 10^{-4}$ s^{-1}, 60 °C). Therefore, replacing a carbomethoxy group by a hydrogen atom at C-4 of 3*H*-pyrazole **111** reduces the overall rate of rearrangement. However, the rate reduction is more pronounced for migrating groups which are less stable in cationic form (ie. R = $C(Me)_3$ and R = 1-adamantyl).

A continuum exists in [1,5]-sigmatropic rearrangements which runs from concerted

with very little charge separation, through transition structures with increasing charge separation, to the two-step, ion-pair extreme. This is reflected in the results in this chapter. The rearrangement of 3*H*-pyrazole **128f** seems to fall in the concerted category with some degree of charge separation. 3*H*-Pyrazoles **128d** and **128e** seem to be "borderline" between concerted with considerable charge separation and ion pair. At the other extreme, the rearrangement of 3*H*-pyrazoles **128b** and **128c** appear to proceed by a stepwise, ion-pair mechanism.

3.10 Synthetic applications

This work has shown that good yields of 1*H*-pyrazoles **131d, 131e,** and **131f,** can be obtained by a convenient synthetic route. This synthetic methodology could provide access to other 1*H*-pyrazoles of general structure **143** with a variety of alkyl substituents at C-4 and C-5 (Scheme 31). New oxadiazolines **114** would provide diazoalkanes with different R^1 and R^2 substituents. A 1,3-dipolar cycloaddition of **117** to methyl propiolate generates 3*H*-pyrazole **142** with different substituents at the tetrahedral carbon centre (ie. $R^1 = R^2 = CH_2CH_3$ or $CH(CH_3)_2$). Thermal rearrangement of this 3*H*-pyrazole gives a 1*H*-pyrazole with new substituents at C-4 and C-5 of **143.** If 3*H*-pyrazole **142** contained substituents where $R^1R^2 = (CH_2)_4$ or $R^1R^2 = (CH_2)_5$ bicyclic compounds such as **144** and **145** could be synthesized. The synthesis of these new compounds could be useful, since the pyrazole nucleus has been found to be biologically active.[61,64]



114 **117** **143a-b** **142a-d** **144** (n=1) **145** (n=2)

(**a**: $R^1=R^2=CH_2CH_3$; **b**: $R^1=R^2=CH(CH_3)_2$; **c**: $R^1R^2=(CH_2)_4$; **d**: $R^1R^2=(CH_2)_5$)

Scheme 31

CHAPTER 4

Thermal Rearrangements of 5-Alkyl-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadienes

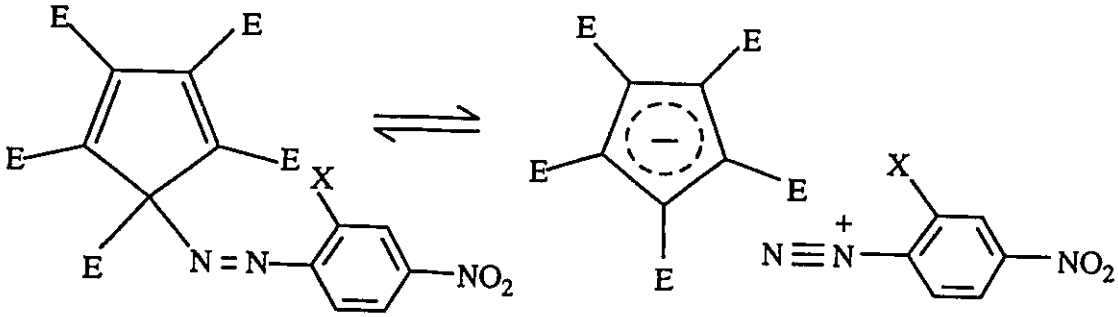
4.0. Objective

The discovery that some 3*H*-pyrazoles, as well as some 4*H*-pyrazoles, undergo thermal rearrangement by a stepwise mechanism involving the formation of intermediate ion pairs (Chapters 2 and 3) raised a question about the generality of rearrangement by such a mechanism. It became of interest to determine if any non-heterocyclic analogues of 3*H*-pyrazoles, some cyclopentadiene derivatives, were also capable of thermal rearrangement via a stepwise mechanism.

Cyclopentadienes generally undergo thermal rearrangement by [1,5]-sigmatropic migrations of a substituent from the tetrahedral carbon centre of the cyclopentadiene ring, but in 1984 Mikhailov and coworkers discovered that 5-arylazo-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadienes **146a-f** undergo thermal rearrangements via ion-pair intermediates (Scheme 32).[56]

In the ^{1}H NMR spectra of **146a-d** in benzonitrile solution, the signals for the protons of the methoxycarbonyl groups appear in the form of a singlet at 30 °C. With a decrease in temperature of the solution this peak broadens, and at -35 °C splits into

a triplet with intensity ratios of 2 : 2 : 1. Such spectral behaviour was attributed to the exchange of the positions of the arylazo groups in the cyclopentadiene rings, which takes place by reversible formation of ion-pair intermediates **147a-d** from covalent substrates **146a-d**. For compounds **146e** and **146f** the migration of arylazo around the cyclopentadiene ring takes place very rapidly on the ^{1}H NMR time scale, and even in solutions at -50 to -70 °C, the signal for the protons of the methoxycarbonyl groups is in the form of a narrow singlet. The degenerate rearrangement of these cyclopentadienes can be viewed as "formal" [1,5]-sigmatropic rearrangements because the products of rearrangement are the same as those from concerted [1,5]-sigmatropic migrations of the arylazo groups.



146a-f (E=CO_2CH_3) **147a-f**

(**a**: X=H; **b**: X=I; **c**: X=Cl; **d**: X=Br; **e**: X=OMe; **f**: X=Me)

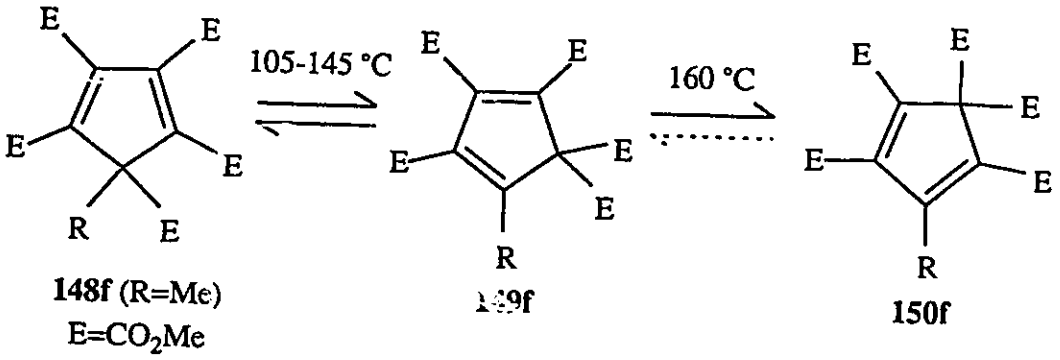
Scheme 32

Presumably, stepwise rearrangements of **146a-f** take place because the arylazo groups form relatively stable cations and the cyclopentadiene anions are stabilized by electron-withdrawing carbomethoxy substituents. Electron-donating substituents in the ortho position of the arylazo ring were found to enhance the rate of rearrangement; a result of increased stabilization of the cation intermediate.

The thermal rearrangements of several 5-alkyl-1,2,3,4,5-pentakis (methoxycarbonyl)cyclopentadienes were investigated by Hoffmann and coworkers.[52,54,55] An example of a "typical" rearrangement of a 5-alkyl-1,2,3,4,5-pentakis (methoxycarbonyl)cyclopentadiene (Scheme 33) comes from their studies of **148f** (R=Me).[54] Between 105 and 145 °C in 1,2-dichlorobenzene, an equilibrium is set up between **148f** and **149f** by [1,5]-sigmatropic carbomethoxy shifts. The cyclopentadienes **148f** and **149f** were obtained in an equimolar ratio and could not be individually isolated by chromatography techniques. At a higher temperature (160 °C), **148f** (34%), **149f** (29%), and **150f** (37%) were obtained in solution. Therefore, at the higher temperature, another [1,5]-sigmatropic carbomethoxy migration in **149f** generates **150f**.

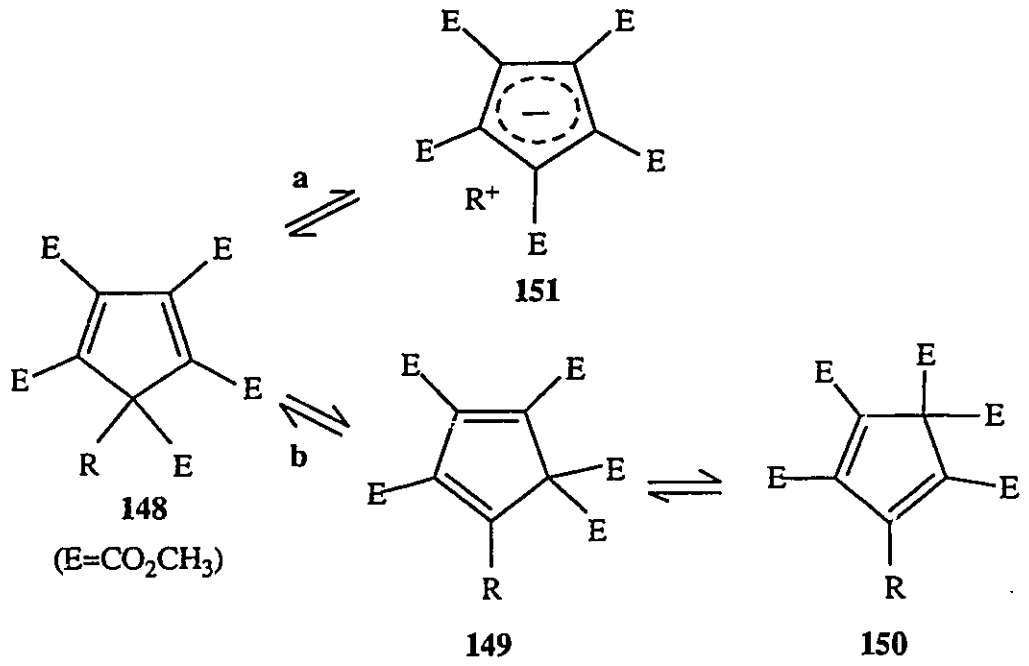
It follows from Hoffmann's investigations that 5-alkyl-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadienes generally rearrange by [1,5]-sigmatropic carbomethoxy migrations. The carbomethoxy substituent is known to have a high migratory aptitude in [1,5]-sigmatropic rearrangements,[51-56] but a low migratory aptitude in carbocation rearrangements.[183,184] Hoffmann and coworkers did not investigate the thermal rearrangements of any 5-alkyl-1,2,3,4,5-pentakis(methoxycarbonyl)

cyclopentadienes bearing alkyl substituents at C-5 that are relatively stable in cationic form.



Scheme 33

It became of interest to investigate the thermal rearrangements of **148a-e** (Scheme 34) to determine if dissociation to ion-pairs **151a-e** occurs during rearrangement (path **a**) or if rearrangement occurs by concerted [1,5]-sigmatropic migrations of the carbomethoxy substituents (path **b**). The alkyl substituents chosen were $CHPh_2$, CH_2OMe, 1-adamantyl, p-$CH_2C_6H_4OMe$, and $CH_2C_6H_5$ because they readily form cations in solvolysis reactions of R-X (X = halogen).[150,153] If **148a-e** undergo thermal rearrangement by successive migrations of R (path **a**), then the 5 carbomethoxy substituents of **148a-e** would appear in the form of a singlet in the ^1H NMR spectra. Rate constants and activation parameters for these degenerate rearrangements could be determined by ^1H NMR spectroscopy, based on line shape analysis at various temperatures.



(**a**: R=$CHPh_2$; **b**: R=CH_2OMe; **c**: R=1-adamantyl; **d**: R=p-$CH_2C_6H_4OMe$; **e**: R=$CH_2C_6H_5$)

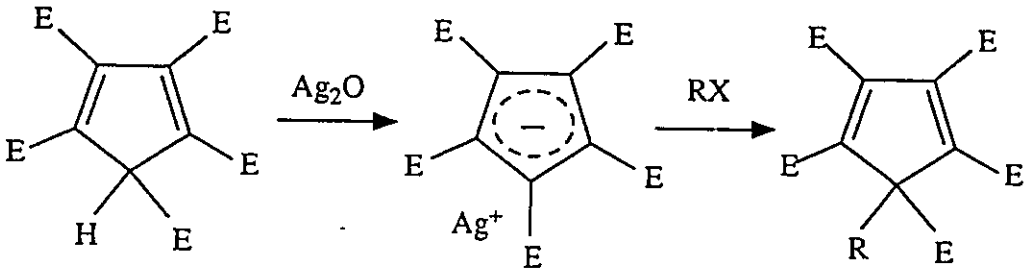
Scheme 34

4.1 Synthesis of 5-alkyl-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadienes 148a-f

Compounds **148a-e** were prepared by a modification of a procedure used for the synthesis of 5-ethyl-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadiene.[54] Compound **148f** was also synthesized so that spectral data could be obtained for its rearrangement products **149f** and **150f**. If cyclopentadienes **148a-e** rearrange by [1,5]-carbomethoxy migrations, the rearrangement products could be identified by comparing their spectral data to those of **149f** and **150f**.

Cyclopentadienes **148a-f** were synthesized (Scheme 35) by first mixing pentakis(methoxycarbonyl)cyclopentadiene with Ag_2O in benzene solution to generate ion-pair **153**. Second, the anion of **153** was alkylated with the appropriate alkyl halide. The

percentage yields of **148a-f** were not optimized. Cyclopentadiene **148f** had been previously prepared by others.[54,55,205]



152 (E=CO_2Me) **153** **148**

a: R=$CH(Ph)_2$
b: R=CH_2OMe
c: R=1-adamantyl
d: R=p-$CH_2C_6H_4OMe$
e: R=$CH_2C_6H_5$
f: R=Me

Scheme 35

Cyclopentadienes **148a-f** are stable compounds at ambient temperature in $CDCl_3$ solution and do not undergo rearrangement according to their ^1H NMR spectra. Furthermore, compounds **148a-d** do not undergo rearrangement in benzonitrile solvent according to their ^1H NMR spectra. The compounds were identified on the basis of their ^1H and ^{13}C NMR spectra as well as their mass spectrometric masses. The ^1H NMR spectra of cyclopentadienes **148a-f** are reported in Table 25. A total of 3 carbomethoxy singlets, in a 2 : 2 : 1 integrated intensity ratio, are observed in the ^1H NMR spectra of compounds **148a-d** and compound **148f**. For cyclopentadiene **148e**, the CH_2 singlet appears at the same chemical shift as one of the carbomethoxy proton singlets.

Selected ^{13}C NMR chemical shifts for compounds **148a-f** are reported in Table 26. The C-1 and C-4 chemical shifts appear in the range of 141.78-144.86 ppm while the C-2 and C-3 chemical shifts appear in the range of 139.65-142.67 ppm. Furthermore, the C-5 chemical shift of cyclopentadienes **148a-f** appears in the range of 63.60-71.84 ppm. Some of the ^{13}C NMR chemical shifts were assigned on the basis of the ^{13}C NMR chemical shift assignments made for 1,3-cyclopentadiene.[206]

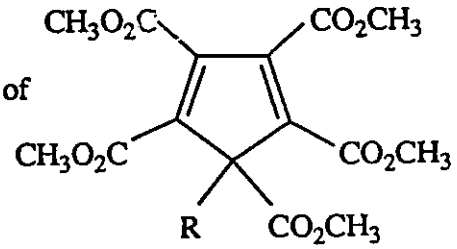
4.2 Heating cyclopentadienes 148a and 148b in the NMR probe

If cyclopentadienes **148a-e** undergo thermal rearrangement by migration of their respective R groups, these degenerate rearrangements could be observed by ^1H NMR spectroscopy. Cyclopentadienes **148a** and **148b** were heated in the NMR probe in an effort to observe any potential rearrangement. These cyclopentadienes contain R substituents which, in cationic form, are the most stable ones in the series of cyclopentadienes **148a-e.**

Compounds **148a** and **148b** were warmed in the NMR probe to 80 °C in toluene-d_8 solvent. At this temperature, 3 carbomethoxy singlets were observed in the ^1H NMR spectra of both **148a** and **148b.** Furthermore, there was no broadening of the carbomethoxy singlets in these ^1H NMR spectra at 80 °C. Therefore, rearrangement was not observable by ^1H NMR spectroscopy at this temperature.

Table 25.

^{1}H NMR chemical shifts (ppm) of cyclopentadienes **148a-f** in $CDCl_3$.

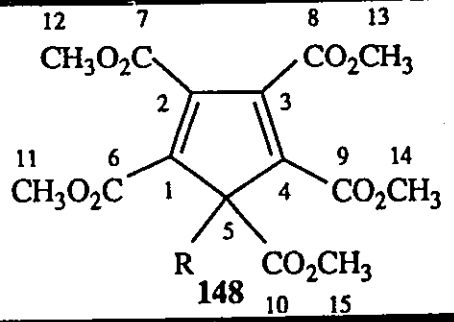


148

148	**^{1}H NMR (200 MHz)**
148a, R=$CHPh_2$	7.35-7.17 (m, 10 H, 2 Ph), 5.60 (s, 1 H, CH), 3.81 (s, 6 H, 2 COOMe), 3.63 (s, 3 H, COOMe), 3.36 (s, 6 H, COOMe).
148b, R=CH_2OMe	4.23 (s, 2 H, CH_2), 3.88 (s, 6 H, COOMe), 3.83 (s, 6 H, 2 COOMe), 3.68 (s, 3 H, COOMe), 3.26 (s, 3 H, OMe).
148c, R=1-adamantyl	3.86 (s, 6 H, 2 COOMe), 3.81 (s, 6 H, 2 COOMe), 3.64 (s, 3 H, COOMe), 1.95 (bs, 3 H, CH), 1.88 (bs, 6 H, 3 CH_2), 1.65 (bs, 6 H, 3 CH_2).
148d, R=p-$CH_2C_6H_4OMe$	6.92 (d, J= 8.7 Hz, 2 H, CH_{ortho}), 6.69 (d, J = 8.7 Hz, 2 H, CH_{meta}), 3.87 (s, 6 H, 2 COOMe), 3.77 (s, 6 H, 2 COOMe), 3.74 (s, 3 H, COOMe), 3.71 (s, 2 H, CH_2), 3.69 (s, 3 H, OMe).
148e, R=$CH_2C_6H_5$	7.19-7.00 (m, 5 H, Ph), 3.87 (s, 6 H, 2 COOMe), 3.76 (s, 8 H, 2 COOMe + CH_2), 3.70 (s, 3 H, COOMe).
148f, R=Me	3.88 (s, 6 H, 2 COOMe), 3.83 (s, 6 H, 2 COOMe), 3.66 (s, 3 H, COOMe), 1.69 (s, 3 H, Me).

Table 26.

Selected ^{13}C NMR chemical shifts for **148a-f** in $CDCl_3$ (50 MHz).



148

148	C_1, $C_{1'}$	C_2, C_3	C_5	C_6, C_9[a]	C_7, C_8[a]	C_{10}	C_{11}, C_{14}[b]	C_{12}, C_{13}[b]	C_{15}
148a, R=$CHPh_2$	143.76	142.67	71.45	162.66	161.48	166.70	52.65	52.80	52.80
148b, R=CH_2OMe	141.78	141.67	71.84	162.55	161.92	165.76	52.72	52.56	53.21
148c, R=1-adamantyl	144.51	140.70	74.77	165.31	162.61	165.65	52.60	52.46	52.21
148d, R=p-$CH_2C_6H_4OMe$	142.87	141.70	68.48	162.34	162.11	167.33	52.66	52.66	53.30
148e, R=$CH_2C_6H_5$	142.70	141.82	68.13	162.30	162.06	176.29	52.69	52.67	53.35
148f, R=Me	144.86	139.65	63.60	162.62	161.82	167.40	52.75	52.59	53.24

[a] C_6,C_9 and C_7,C_8 may be reversed.
[b] C_{11},C_{14} and C_{12},C_{13} may be reversed.

The polarity of the solvent was increased to see if this would give observable rearrangement of **148b** at an elevated temperature in the NMR probe. Cyclopentadiene **148b** was heated to 75 °C in nitromethane-d_3 solvent and at this temperature, three sharp carbomethoxy singlets were once again observed. Rearrangement in this solvent of higher polarity was still unobservable by ^{1}H NMR spectroscopy.

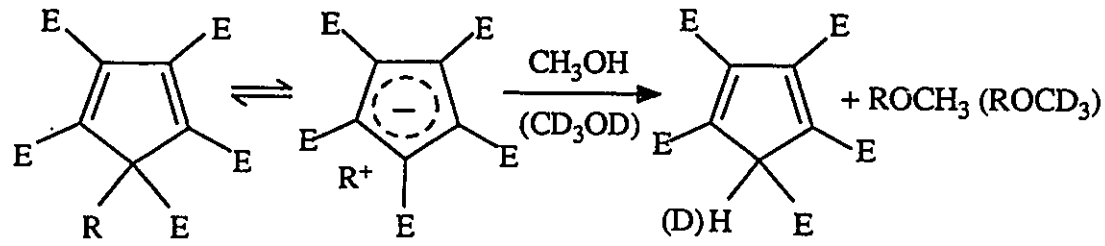
The maximum value for the observed constant for rearrangement that would not result in detectible line broadening is in the range of 3.1 - 4.7 s^{-1} (Appendix II contains the calculation of this value).[207] Therefore, it seems that the rates of rearrangement of both **148a** and **148b** are too slow on the NMR time scale for detection.

4.3 Rearrangement of 148a-d in methanol

It was then decided to look at the reactions of cyclopentadienes **148a-e** in methanol since this solvent could intercept any ion pairs that are formed during the migrations of R in cyclopentadienes **148a-e**.

Cyclopentadiene **148a** (R = $CHPh_2$) was dissolved in methanol-d_4 and after 3 minutes at room temperature, ^{1}H NMR spectroscopy revealed **148a** (49%), **152** (51%), and **154f** (D analogue, 51%) according to Scheme 36. The rate constant for the overall disappearance of **148a** was estimated as 4 x 10^{-3} s^{-1}, assuming first order kinetics. In another experiment, cyclopentadiene **148a** was dissolved in methanol and after 20 minutes at room temperature, it had been converted to benzhydryl methyl ether and **152** in

quantitative yield. The identity of the methyl ether was confirmed by comparison of its spectroscopic data with those reported in the literature.[192] This cyclopentadiene must have dissociated to an ion-pair intermediate, a cyclopentadiene anion derivative and a benzhydryl cation, which was subsequently trapped by methanol. It could not be determined if ion-pair collapse occurred in competition with ion-pair capture by methanol. Ion-pair collapse of **151a** is actually overall degenerate rearrangement of **148a** by a stepwise mechanism rather than by a concerted mechanism.



148a-d **151a-d** **152a-d** **154a-d**

(a: R=$CH(Ph)_2$; **b**: R=CH_2OMe; **c**: R=1-adamantyl; **d**: R=p-$CH_2C_6H_4OMe$)

Scheme 36

Cyclopentadiene **148b** (R = CH_2OMe) dissociates in methanol-d_4 at 40 °C with an observed rate constant of (6.2 ± 0.3) x 10^{-4} s^{-1}. After 2 hours at 40 °C, ^1H NMR spectroscopy revealed dimethoxymethane-d_3 (100%) and **152** (D-analogue, 100%). Dimethoxymethane-d_3 was confirmed by ^1H NMR and gas chromatography spiking experiments with an authentic sample of dimethoxymethane. As in **148a**, an ion-pair intermediate must have been formed and intercepted. The fact that **148a** dissociates faster than **148b** is a reflection of the stability of the intermediate cations of the ion-pairs;

benzhydryl cation being more stable than methoxymethyl cation. Cyclopentadiene **148a** dissociates approximately 18 times faster than cyclopentadiene **148b**, assuming a 2.8-fold increase in the observed rate constant for the 15 °C temperature difference.

Cyclopentadiene **148c** (R = 1-adamantyl) also dissociates to an ion-pair intermediate in methanol solvent. The observed rate constant for the decrease in concentration of **148c** in methanol-d_4 at 50 °C was $(5.2 \pm 0.2) \times 10^{-4}$ s^{-1}. After 2 hours at 65 °C in methanol, **148c** was quantitatively converted to **152** and 1-adamantyl methyl ether. The 1-adamantyl methyl ether was confirmed by comparison of its spectroscopic data to those of a sample prepared by another route.[193] Cyclopentadiene **148b** dissociates in methanol-d_4 approximately twice as fast as cyclopentadiene **148c**, assuming a 2-fold increase in the observed rate constant for the 10 °C temperature difference.

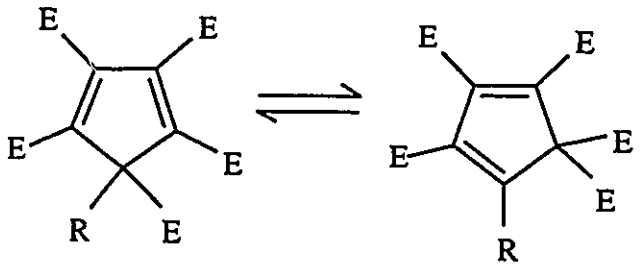
Cyclopentadiene **148d** dissociates at 100 °C in methanol-d_4 with an observed rate constant of $(3.14 \pm 0.08) \times 10^{-4}$. After 4 hours in methanol at 100 °C, it was converted to **154d** (100%) and **152** (100%). The identity of the methyl ether was confirmed by comparison of its spectroscopic data to those of a sample prepared by another route.[194] Cyclopentadiene **148c** dissociates in methanol-d_4 approximately 19 times faster than **148d**, assuming a 2-fold increase in the observed rate constant for every 10 °C increase in temperature.

It is clear that cyclopentadienes **148a-d** form ion pairs in methanol solvent which are subsequently intercepted by that solvent to give the appropriate methyl ethers (**154**) and cyclopentadiene **152** (Scheme 36). It is very unlikely that methanol reacts with cyclopentadienes **148a-d** by a bimolecular nucleophilic substitution reaction at C-5

because for **148c** especially, backside attack of a nucleophile is not possible due to the "bulkiness" of the 1-adamantyl substituent. The approximate relative rates for dissociation of these cyclopentadienes in methanol solvent are as follows: **148a** (76), **148b** (38), **148c** (19), and **148d** (1.0).

4.4 Rearrangement of 144e and 144f in methanol-d_4

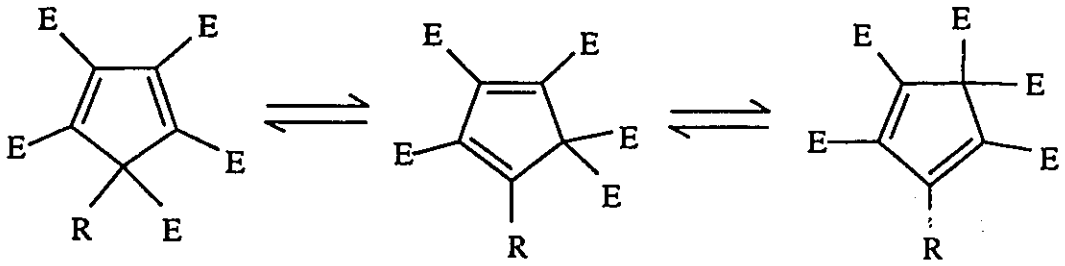
The rearrangement of cyclopentadiene **148f** (R = Me) had been studied previously,[52,54,55] however, it was decided to reexamine the rearrangement of **148f** in order to obtain spectral data on its rearrangement products to aid in the identification of the rearrangement products from **148e**. Cyclopentadiene **148f** was dissolved in methanol-d_4 and heated in a sealed nmr tube at 140 °C for 35 minutes. ^{1}H NMR spectroscopy revealed **148f** (62%) and **149f** (38%) according to Scheme 37. This cyclopentadiene rearranges by [1,5]-sigmatropic carbomethoxy shifts at this temperature. Cyclopentadienes **148f** and **149f** could not be separated, but their ^{1}H and ^{13}C NMR spectra could be obtained from this solution.



148f (R=Me) **149f**

Scheme 37

Cyclopentadiene **148e** (R = $CH_2C_6H_5$) was dissolved in methanol-d_4 and heated in a sealed nmr tube at 140 °C for 3 hours. ^{1}H NMR spectroscopy of the solution revealed **148e** (63%), **149e** (29%), and **150e** (8%) according to Scheme 38. This mixture of cyclopentadiene isomers could not be separated by centrifugal chromatography and compounds **149e** and **150e** were identified on the basis of ^{1}H NMR spectroscopy. It follows from the structures of the products that cyclopentadiene **148e** undergoes thermal rearrangement by [1,5]-sigmatropic carbomethoxy migrations. Presumably, the benzyl substituent is not stable enough as a cation to dissociate heterolytically from covalent **148e** in methanol solvent. Therefore, the para-methoxy substituent of **148d** (R = p-$CH_2C_6H_4OMe$) is essential for ion-pair formation.



148e (R=$CH_2C_6H_5$) **149e** **150e**

Scheme 38

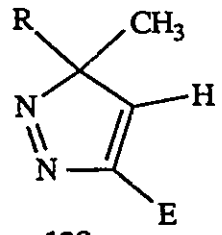
4.5 Conclusion

From the evidence presented above, it is clear that cyclopentadienes **148a-d** dissociate in methanol solvent to give ion pairs. Presumably, collapse of the ion pairs to covalent **148a-d** competes with solvent interception of these ion pairs. It has thus been

shown that cyclopentadienes with carbon-based alkyl groups can undergo stepwise rearrangement.

Unfortunately, these degenerate rearrangements could not be observed by ^{1}H NMR spectroscopy. Cyclopentadienes **146a-f** undergo faster stepwise rearrangement than **148a-d** since rearrangements of the former in benzonitrile solution could be observed by ^{1}H NMR spectroscopy while rearrangements of the latter could not. Therefore, the arylazo cations of **146a-f** must be more stable than the alkyl-based cations formed from **148a-d.**

The order of ease of dissociation of cyclopentadienes **148a-d** in methanol-d_4 was established as **148a** (R = $CHPh_2$) > **148b** (R = CH_2OMe) > **148c** (R = 1-adamantyl) > **148d** (R = p-$CH_2C_6H_4OMe$). For 3*H*-pyrazoles **128**, the order of rearrangement (methanol-d_4) was established as **128b** (R = CH_2OMe) > **128e** (R = p-$CH_2C_6H_4OMe$) > **128d** (R = 1-adamantyl). The reactivity order (1-adamantyl < p-$CH_2C_6H_4OMe$) in the pyrazole series is reversed in the cyclopentadiene series. Steric hindrance in the ground state as well as cation stability presumably govern the rate of rearrangement of both the cyclopentadienes and the 3*H*-pyrazoles. It appears, however, that rate acceleration due to steric hindrance in the ground state of **148c** may be the critical factor leading to a faster rate of dissociation of **148c** compared to **148d.** Steric acceleration is probably less important in the rates of rearrangement of 3*H*-pyrazoles **128d** and **128e** because of reduced steric crowding at C-3 in **128.** A more frequent collapse of the ion pair from **148d** (ion-pair return) compared to collapse of the ion pair from **148c** (a factor where steric crowding could also play a role) could also lead to the overall faster rate of dissociation of **148c.**



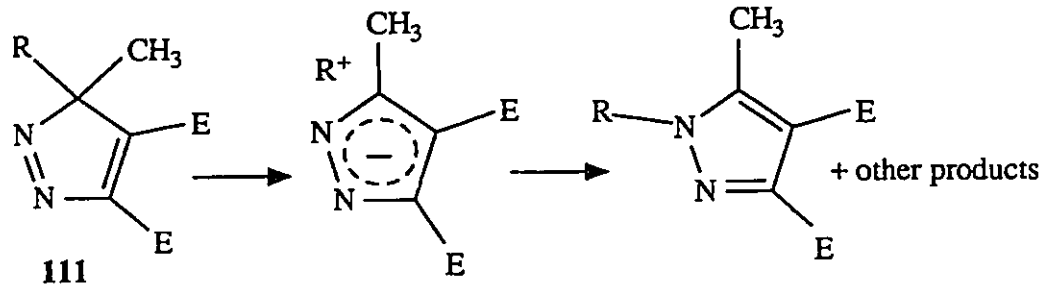
128

(E=CO_2Me)

(**b**: R=CH_2OMe; **d**: R=1-adamantyl; **e**: R=p-$CH_2C_6H_4OMe$)

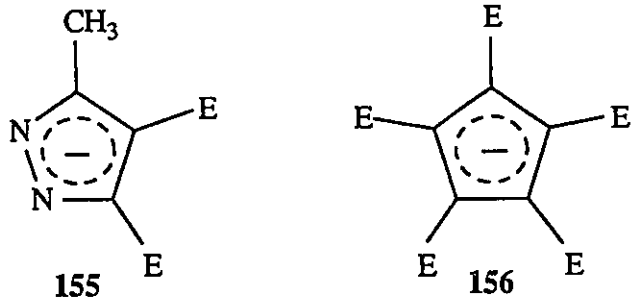
Cyclopentadienes **148a-d** are stable compounds in $CDCl_3$ according to ^1H NMR spectroscopy at ambient temperature while the 3*H*-pyrazoles **111a**, **111b**, **111d**, and **111e** are not stable compounds in $CDCl_3$ at ambient temperature. 3*H*-Pyrazoles **111** undergo thermal rearrangements via ion-pair intermediates (Scheme 39). Therefore, this suggests that anion **155** is more stable than anion **156**. The 5 carbomethoxy substituents must be less stabilizing towards a cyclopentadiene anion than the combination of two ring nitrogen atoms, 2 carbomethoxy substituents, and a destabilizing methyl substituent. Perhaps, the intermediate anion formed from the dissociation of **148a-d** is less planar than the pyrazole anion formed from the thermal rearrangement of **111** since the carbomethoxy substituents are presumably twisted out of plane in **156** to avoid steric congestion.

The rearrangement of cyclopentadiene **148e** (R = $CH_2C_6H_5$) does not belong in the same mechanistic category as the rearrangements of cyclopentadienes **148a-d**, which presumably rearrange by a stepwise mechanism. Cyclopentadiene **148e** appears to rearrange by a concerted mechanism involving [1,5]-sigmatropic carbomethoxy migrations. The benzyl substituent must not be sufficiently stable in cationic form for heterolytic cleavage in **148e**.



(**a**: R=$CHPh_2$; **b**: R=CH_2OMe; **d**: R=1-adamantyl; **e**: R=p-$CH_2C_6H_4OMe$)

Scheme 39



CHAPTER 5

Experimental

5.0 General

Melting points were determined on a Thomas Hoover capillary melting point apparatus. Centrifugal chromatography was performed with silica gel (Merck Kieselgel 60 PF_{254}) coated plates (2-mm or 4-mm thick) spinning in a Chromatotron Model 7924T apparatus. Analytical thin-layer chromatography was performed with silica gel plates (E. Merck, D-Plastikfolien, Kieselgel 60 F_{254}). Proton nuclear magnetic resonance (^{1}H NMR) data were obtained on Varian EM-390, Bruker AC-200, Bruker WM-250, or Bruker AM-500 spectrometers. Chemical shifts are reported in delta (δ) units [parts per million (ppm)] downfield from tetramethylsilane, relative to the singlet at 7.24 ppm for chloroform in chloroform-d_1 or relative to the singlet at 7.15 ppm for benzene-d_5 in benzene-d_6. Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad singlet. Coupling constants are reported in hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained at 50 MHz on a Bruker AC-200 or at 125 MHz on a Bruker AM-500 spectrometer and are reported in ppm relative to the centre line of a triplet at 77.0 ppm for samples run in chloroform-d_1 or a triplet at 128.0 for samples run in benzene-d_6. High resolution EI spectra were recorded

on a VG ZAB-E double focussing mass spectrometer. Samples were run at 70 eV, source temperature 200 °C, resolution 5000. Samples were introduced by direct insertion probe. Photolyses employed a Rayonet photochemical reactor fitted with 300 nm lamps. The infrared spectra of a selected group of compounds are reported in Appendix III.

5.1 Preparation of 2-acetylhydrazones of ketones, (113).

The following ketones were purchased from Aldrich Chemical Co. and were used as supplied: 1,1-diphenylacetone, methoxyacetone, pinacolone, 1-adamantyl methyl ketone, 4-methoxyphenylacetone and phenylacetone. Compounds **113a**, **113c**, and **113d** were prepared by refluxing equimolar amounts of acetyl hydrazine and the appropriate ketone in ethanol for 24 hours with 5 mol % of acetic acid. After the mixture was cooled to room temperature, crystals formed. For the preparation of **113b** and **113e**, solutions of equimolar amounts of acetyl hydrazine and the appropriate ketone in benzene were refluxed until all the water was removed (Dean-Stark trap, 1 h for **113b** and 4 h for **113e**). The preparation of **111f** was previously reported.[188]

1-Acetyl-2-(1,1-diphenyl-2-propylidene)hydrazine, (113a): 73% yield; mp 158-159° C (EtOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.82 (bs, 1 H, NH), 7.45-7.18 (m, 10 H, 2 Ph), 5.02 (s, 1 H), 2.08 (s, 3 H, Ac), 1.87 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.02, 151.73, 140.33 (2), 129.04 (4), 128.33 (4), 126.77 (2), 59.92, 20.34, 15.41; MS *m/z* (M^+) for $C_{17}H_{18}N_2O$ calcd 266.1419, found 266.1403.

1-Acetyl-2-(1-methoxy-2-propylidene)hydrazine, (113b): 74% yield; mp 82-84 °C (EtOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.62 (bs, 1 H, NH), 4.00 (s, 2 H), 3.37 (s, 3 H, OMe), 2.28 (s, 3 H, Ac), 1.88 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.15, 149.25, 75.97, 57.99, 20.28, 12.56; MS (CI, CH_4) *m/z* $(M+H)^+$ for $C_6H_{12}N_2O_2$+H calcd 145.0977, found 145.0979.

1-Acetyl-2-(3,3-dimethyl-2-butylidene)hydrazine, (113c): 75% yield; mp 82-83 °C (EtOH); (lit.[119] mp 80-82 °C); The ^{1}H NMR spectrum was reported.[119] ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.01, 157.47, 38.52, 27.45 (3), 20.42, 11.12.

1-Acetyl-2-[1-(1-adamantyl)-1-ethylidene]hydrazine, (113d): 75% yield; mp 169-170 °C (EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.50 (bs, 1 H, NH), 2.27 (s, 3 H, Ac), 2.05 (bs, 3 H, CH), 1.74 (bs, 15 H, Me + 6 CH_2) ^{13}C NMR (50 MHz,$CDCl_3$) δ 173.84, 157.38, 40.35, 39.77, 39.45 (2), 36.88, 36.75 (2), 28.36, 28.19 (2), 20.43, 10.05; MS *m/z* (M^+) for $C_{14}H_{22}N_2O$ calcd 234.1732, found 234.1736.

1-Acetyl-2-[1-(4-methoxyphenyl)-2-propylidene]hydrazine, (113e): 90% yield; mp 122-124°C (EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.76 (bs, 1 H, NH), 7.19 (d, 2 H, J = 7.9 Hz), 6.85 (d, 2 H, J = 7.9 Hz), 3.79 (s, 3 H, OMe), 3.48 (s, 2 H), 2.28 (s, 3 H, Ac), 1.75 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.79, 158.29, 151.45, 129.71 (2), 128.73, 113.78 (2), 54.96, 44.29, 20.27, 14.53; MS *m/z* (M^+) for $C_{12}H_{16}N_2O_2$ calcd 220.1212, found 220.1207.

5.2 Preparation of 5-alkyl-2-methoxy-2,5-dimethyl-Δ^3-1,3,4-oxadiazolines, (114).

These compounds were obtained by a procedure similar to those described previously.[119,188] However, a few modifications were made and therefore the complete procedure for their synthesis is reported here. To a yellow solution of lead tetraacetate (16.5 mmol) in absolute methanol (65 mL) at -10 °C was added the acetyl hydrazone **113** (15.0 mmol). The solution was stirred during the addition and thereafter. After 1 h, if the yellow colour had not been discharged, the cold bath was removed. After the yellow colour was eventually discharged, the reaction flask was once again cooled to -10 °C and potassium hydroxide (pellets, 16.5 mmol, dissolved in 10 mL of absolute methanol) was added to the reaction flask to destroy the acetoxy-oxadiazoline coproduct. The solution was allowed to warm to room temperature slowly and the reaction mixture was left stirring overnight. Most of the solvent was removed in vacuo, water was added to the residue, and the aqueous solution was extracted with CH_2Cl_2. The organic layer was washed once with water before it was dried over magnesium sulfate. The solution was filtered and the solvent was removed in vacuo. The residue was purified by centrifugal chromatography (silica gel, 19:1 hexane/ethyl acetate). The synthesis and spectral data of oxadiazoline **114f** were previously reported.[188]

2-Methoxy-2,5-dimethyl-5-(1,1-diphenylmethyl)-Δ^3-1,3,4-oxadiazoline, (114a): 63% yield; > 98% trans (by ^{1}H NMR); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47-7.14 (m, 10 H, 2 Ph) 4.74 (s, 1 H, CH), 3.21 (s, 3 H, OMe), 1.53 (s, 3 H, Me), 0.80 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.63, 138.53, 133.83, 130.07 (4), 128.32 (2), 127.98 (2),

126.97, 126.91, 124.57, 59.46, 50.89, 23.78, 19.78; MS *m/z* (M^+-N_2) for $C_{18}H_{20}O_2$ calcd 268.1463, found 268.1452.

2-Methoxy-5-methoxymethyl-2,5-dimethyl-Δ^3-1,3,4-oxadiazoline, (114b): 45% yield; cis : trans ratio = 1.0 : 5.0; ^{1}H NMR of trans isomer (500 MHz, $CDCl_3$) δ 3.78 (d, 1 H, *J* = -10.8 Hz), 3.55 (d, 1 H, *J* = -10.8 Hz), 3.33 (s, 3 H, CH_2OMe), 3.12 (s, 3 H, OMe), 1.72 (s, 3 H, Me), 1.56 (s, 3 H, Me); ^{1}H NMR of cis isomer (500 MHz, $CDCl_3$) δ 3.72 (d, 1 H, *J* = -10.8 Hz), 3.69 (d, 1 H, *J* = -10.8 Hz), 3.41 (s, 3 H, CH_2OMe), 3.23 (s, 3 H, OMe), 1.63 (s, 3 H, Me), 1.45 (s, 3 H, Me); ^{13}C NMR of trans isomer (50 MHz, $CDCl_3$) δ 134.82, 121.28, 74.80, 59.39, 50.26, 22.38, 19.38; ^{13}C NMR of cis isomer (50 MHz, $CDCl_3$) δ 133.72, 120.42, 74.92, 59.52, 50.61, 23.52, 20.32; MS *m/z* (M^+-OMe) for $C_6H_{11}N_2O_2$ calcd 143.0821, found 143.0804.

2-Methoxy-2,5-dimethyl-5-(2,2-dimethylethyl)-Δ^3-1,3,4-oxadiazoline, (114c): 70% yield; The ^{1}H NMR spectrum was reported previously.[119] ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.05, 127.77, 50.80, 37.35, 25.31 (3), 19.17, 19.09.

5-(1-Adamantyl)-2-methoxy-2,5-dimethyl-Δ^3-1,3,4-oxadiazoline, (114d): 81% yield; mp 54-57 °C; > 94% trans (by ^{1}H NMR, 90 MHz);^{1}H NMR (200 MHz, $CDCl_3$) δ 3.37 (s, 3 H, OMe), 2.09-1.48 (m, 15 H), 1.77 (s, 3 H, Me), 1.37 (s, 3 H, Me). ^{13}C NMR (50 MHz, $CDCl_3$) δ 130.76, 127.62, 50.86, 39.11, 36.74 (3), 36.65 (3), 28.16 (3), 19.15, 18.03; MS *m/z* (M^+-OMe) for $C_{14}H_{21}N_2O$ calcd 233.1654, found 233.1645.

2-Methoxy-5-(4-methoxybenzyl)-2,5-dimethyl-Δ^3-1,3,4-oxadiazoline, (114e): 73% yield; cis : trans ratio = 1.0 : 2.7; ^{1}H NMR of trans isomer (500 MHz, $CDCl_3$) δ 7.07 (d, 2 H, J = 8.7 Hz), 6.80 (d, 2 H, J = 8.7 Hz), 3.77 (s, 3 H, C_6H_4OMe), 3.12 (s, 3 H, OMe), 3.18 (d, 1 H, J = -14.2 Hz), 3.04 (d, 1 H, J = -14.2 Hz), 1.56 (s, 3 H, Me), 1.21 (s, 3 H, Me); ^{1}H NMR of cis isomer (500 MHz, $CDCl_3$) δ 7.22 (d, 2 H, J = 8.7 Hz), 6.85 (d, 2 H, J = 8.7 Hz), 3.79 (s, 3 H, C_6H_4-OMe), 3.23 (s, 1 H, J = -14.2 Hz), 3.13 (s, 3 H, OMe), 2.98 (d, 1 H, J = -14.2 Hz), 1.62 (s, 3 H, Me), 1.33 (s, 3 H, Me). Composite integrals for overlapping peaks were satisfactory. ^{13}C NMR of trans isomer (50 MHz, $CDCl_3$) δ 158.54, 133.85, 131.51 (2), 126.28, 122.10, 113.30 (2), 54.87, 50.28, 43.28, 22.48, 21.79; ^{13}C NMR of cis isomer (50 MHz, $CDCl_3$) δ 158.54 (overlaps with trans isomer), 133.35, 131.23 (2), 126.62, 121.38, 113.52 (2), 54.87 (overlaps with trans isomer), 50.40, 42.57, 23.16, 22.12; MS m/z (M^+-N_2) for $C_{13}H_{18}O_3$ calcd 222.1256, found 222.1269.

5.3 Rearrangement of 3*H*-pyrazoles 111a-e in benzene-d_6

General method. Oxadiazoline **114** (0.25 mmol) and dimethyl acetylenedicarboxylate (DMAD) (0.30 mmol) in C_6D_6 (0.5 mL) were irradiated at room temperature with 300 nm light (Rayonet apparatus) for 6 h. A ^{1}H NMR spectrum was taken of the photolysis solution to determine the percentages of reaction products.

Rearrangement of 111a. The percentages of **118a** and **119a** determined by ^{1}H NMR spectroscopy (200 MHz) after photolysis of **114a** were 91 and 9, respectively. The

volatiles were removed in vacuo and centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate) gave **118a** (51%) and **119a** (8%).

5-Methyl-(1,1-diphenylmethyl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester, (118a): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.17 (m, 10 H, 2 Ph), 6.71 (s, 1 H), 3.87 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 2.45 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.53, 163.21, 144.00, 143.50, 137.81 (2), 128.61 (4), 128.39 (4), 128.17 (2), 112.31, 67.00, 52.35, 51.67, 11.00; MS *m/z* (M^+) for $C_{21}H_{20}N_2O_4$ calcd 364.1423, found 364.1438.

3-Methyl-(1,1-diphenylmethyl)-1*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (119a): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.16 (m, 10 H, 2 Ph) 6.95 (s, 1H), 3.79 (s, 3H, COOMe), 3.78 (s, 3H, COOMe), 2.38 (s, 3H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.50, 161.46, 149.98, 138.46 (2), 137.15, 128.66 (4), 128.42 (4), 128.06 (2), 112.93, 67.53, 52.92, 51.61, 13.50; MS *m/z* (M^+) for $C_{21}H_{20}N_2O_4$ calcd 364.1423, found 364.1413.

Rearrangement of 111b. The percentages of **118b** and **120b** determined by ^{1}H NMR spectroscopy (200 MHz) after the photolysis of **114b** were 77 and 23, respectively. The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **118b** (66%) and **121** (19%). The spectroscopic data for **121** were identical to those previously reported.[192] 4*H*-Pyrazole **120b** could not be isolated without decomposition.

1-Methoxymethyl-5-methyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester, (118b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (s, 2 H), 3.93 (s, 3 H, COOMe), 3.85 (s, 3 H, COOMe), 3.33 (s, 3 H, OMe), 2.57 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.23, 162.66, 144.55, 143.36, 113.50, 80.53, 56.80, 52.83, 51.74, 10.33; MS *m/z* (M^+) for $C_{10}H_{14}N_2O_5$ calcd 242.0903, found 242.0888.

In a ^{1}H NOE experiment, irradiation of the N-methylene resonance (5.43 ppm) led to an enhancement of both the singlet at 3.33 ppm (OMe) and the singlet at 2.57 ppm (Me).

4-Methoxymethyl-5-methyl-4*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester, (120b): ^{1}H NMR (200 MHz, C_6D_6) δ 4.28 (d, 1 H, J = -9.3 Hz), 3.92 (d, 1 H, J = -9.3 Hz), 3.38 (s, 3 H, COOMe), 3.09 (s, 3 H, COOMe), 2.76 (s, 3 H, OMe), 1.97 (s, 3 H, Me).

Rearrangement of 111c. The percentages of **118c**, **121**, and isobutene determined by ^{1}H NMR spectroscopy (90 MHz, sealed tube) were 39, 61, and 60, respectively. The solvent was removed in vacuo and the residue was separated by centrifugal chromatography (silica gel, 2:1 hexane/ethyl acetate) to give **118c** (24%) and **121** (38%).

1-(*tert*-Butyl)-5-methyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester, (118c): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.91 (s, 3 H, COOMe), 3.83 (s, 3 H, COOMe), 2.65 (s, 3 H, Me), 1.67 (s, 9 H, $C(Me)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.04, 163.43, 142.47, 140.82,

113.91, 61.87, 52.31, 51.65, 29.75, 13.15; MS *m/z* (M^+) for $C_{12}H_{18}N_2O_4$ calcd 254.1267, found 254.1266.

Rearrangement of 111d. The rearrangement of **111d** appeared to go in quantitative yield by observation of the ^1H NMR (200 MHz) spectrum. Centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate) gave **118d** (63%).

1-(1-Adamantyl)-5-methyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester, (118d): mp 141-143 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.90 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 2.69 (s, 3 H, Me), 2.31 (bs, 6 H, 3 CH_2), 2.24 (bs, 3 H, 3 CH), 1.75 (bs, 6 H, 3 CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.20, 163.46, 142.53, 141.06, 113.99, 63.24, 52.30, 51.66, 41.66 (3), 35.89 (3), 29.79 (3), 13.48; MS *m/z* (M^+) for $C_{18}H_{24}N_2O_4$ calcd 332.1736, found 332.1739.

Rearrangement of 111e. The percentages of **118e** and **120e** determined by ^1H NMR spectroscopy (200 MHz) were 64 and 36, respectively. The volatiles were removed in vacuo and centrifugal chromatography (silica gel, 3:2 hexane/ethyl acetate) gave **118e** (37%) and **120e** (17%).

1-(4-Methoxybenzyl)-5-methyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester, (118e): ^1H NMR (200 MHz, $CDCl_3$) δ 7.09 (d, 2 H, CH, J = 8.4 Hz) 6.84 (d, 2 H, CH, J = 8.4 Hz), 5.29 (s, 2 H, CH_2), 3.94 (s, 3 H, COOMe), 3.83 (s, 3 H, COOMe), 3.78 (s,

3 H, OMe), 2.40 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.34, 162.66, 159.40, 143.46, 142.77, 128.32 (2), 126.88, 114.22 (2), 112.83, 55.18, 53.52, 52.36, 51.61, 10.76; MS *m/z* (M^+) for $C_{16}H_{18}N_2O_5$ calcd 318.1216, found 318.1217.

4-(4-Methoxybenzyl)-5-methyl-4*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester, (120e): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.81 (d, 2 H, CH, *J* = 8.7 Hz), 6.69 (d, 2 H, CH, *J* = 8.7 Hz), 3.97 (s, 3 H, COOMe), 3.80 (d, 1 H, CH, *J* = -14 Hz), 3.71 (s, 3 H, COOMe), 3.71 (s, 3 H, OMe), 3.45 (d, 1 H, CH, *J* = -14 Hz), 2.38 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.52, 166.69, 165.27, 160.61, 159.08, 129.39 (2), 124.29, 114.86, 113.93 (2), 55.07, 53.65, 53.09, 36.77, 13.76; MS *m/z* (M^+) for $C_{16}H_{18}N_2O_5$ calcd 318.1216, found 318.1233.

5.4 Modified preparative procedure for the observation of 3*H*-pyrazoles 111c-e.

Oxadiazoline **114** (0.25 mmol) in toluene (0.5 mL) was irradiated at approximately -73 °C with 300 nm light (Rayonet apparatus) for 7 h. At -73 °C with the Rayonet bulbs switched off, DMAD (0.30 mmol) in 0.1 mL of toluene was added to the photolysis mixture. The mixture was warmed to room temperature and the toluene and volatiles were evaporated at low temperature, with a stream of dry nitrogen gas. NMR spectral data were recorded immediately in benzene-d_6. 3*H*-Pyrazoles **111a** and **111b** could not be observed by ^{1}H NMR spectroscopy, as the rearrangement of these 3*H*-pyrazoles had already taken place.

3-(*tert*-Butyl)-3-methyl-3*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (111c): quantitative yield; ^{1}H NMR (200 MHz, C_6D_6) δ 3.40 (s, 3 H, COOMe), 3.38 (s, 3 H, COOMe), 1.32 (s, 3 H, Me), 0.87 (s, 9 H, $C(Me)_3$); ^{13}C NMR (50 MHz, C_6D_6) δ 165.52, 160.67, 156.37, 145.19, 107.63, 52.40, 52.06, 37.94, 26.20, 16.32.

3-(1-Adamantyl)-3-methyl-3*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (111d): quantitative yield; ^{1}H NMR (200 MHz, C_6D_6) δ 3.45 (s, 3 H, COOMe), 3.43 (s, 3 H, COOMe), 1.87-1.45 (m, 15 H), 1.37 (s, 3 H, Me); ^{13}C NMR (50 MHz, C_6D_6) δ 165.68, 160.75, 156.30, 145.25, 108.20, 52.36, 52.04, 41.38, 37.98 (3), 36.73 (3), 29.06 (3), 15.04.

3-(4-Methoxybenzyl)-3-methyl-3*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (111e): ^{1}H NMR (200 MHz, C_6D_6) δ 6.99 (d, 2 H, J = 8.5 Hz), 6.57 (d, 2 H, J = 8.5 Hz), 3.44 (d, 1 H, J = -13.6 Hz) 3.35 (s, 3 H, COOMe), 3.26 (s, 3 H, COOMe), 3.15 (s, 3 H, OMe), 3.04 (d, 1 H, J = -13.6 Hz), 1.30 (s, 3 H, Me). Since 3*H*-pyrazole **111e** is unstable at room temperature, the ^{1}H NMR spectrum was obtained from solutions containing **118e** (25%), **120e** (10%), and **111e** (65%).

5.5 Determination of k_{obs} for the rearrangement of 3*H*-pyrazoles 111c-e.

3*H*-Pyrazole **111c, 111d**, and **111e** in benzene-d_6 solvent were generated by the method outlined above. To the solution containing **111c**, triethylenediamine (2.5 equivalents) was added. Progress of the rearrangements of the 3*H*-pyrazoles was monitored by ^{1}H NMR spectroscopy at 250 MHz. Concentration vs. time data (14 or

more points) were obtained for the rearrangements of **111c** and **111e** to at least two half lifes by normalizing the integrated intensity of the methyl singlet of toluene (internal standard) against the integrated intensity of the methyl singlet for each of the 3*H*-pyrazoles. Concentration vs. time data (8 points) were obtained for the rearrangement of **111d** to two half lifes by normalizing the integrated intensity of the methyl singlet of residual DMAD against the increasing integrated intensity of the methyl singlet of 1*H*-pyrazole **118d** at 2.42 ppm. The resultant plots of ln{(A-x)/A} vs *t* gave the following observed rate constants: $k^{35\,^{\circ}C}$(**111c**) = (6.2 ± 0.2) x 10^{-5} s^{-1} (correlation coefficient = 0.9941), $k^{35\,^{\circ}C}$(**111d**) = (5.6 ± 0.2) x 10^{-5} s^{-1} (correlation coefficient = 0.9912), $k^{20\,^{\circ}C}$(**111e**) = (9.8 ± 0.4) x 10^{-5} s^{-1} (correlation coefficient = 0.9953). The data for these plots are tabulated in Appendix I.

5.6 Synthesis of 3*H*-pyrazole 111f.

Oxadiazoline **114e** (0.25 mmol) in toluene (0.5 mL) was irradiated at approximately -73 °C with 300 nm light (Rayonet apparatus) for 7 hours. At -73 °C with the Rayonet bulbs switched off, dimethyl acetylenedicarboxylate (0.30 mmol) in 0.1 mL of toluene was added to the photolysis mixture. The mixture was warmed to room temperature and the toluene and volatiles were evaporated with a stream of dry nitrogen. The residue was purified by centrifugal chromatography (silica gel, 7:3 hexanes/ethyl acetate) to give **111f** (51%).

3-Benzyl-3-methyl-3*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (111f): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18-7.05 (m, 5 H, Ph), 3.90 (s, 6 H, 2 COOMe), 3.67 (d, 1 H, J = -14 Hz), 3.28 (d, 1 H, J = -14 Hz), 1.64 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.62, 160.50, 151.06, 146.48, 133.67, 129.62 (2), 127.94 (2), 127.24, 101.02, 52.82, 52.78, 41.57, 19.17; MS *m/z* (M^+) for $C_{15}H_{16}N_2O_4$ calcd 288.1110, found 288.1121.

5.7 Rearrangement of 3*H*-pyrazoles 111a-e in chloroform

General method. Oxadiazoline **114** (0.25 mmol) and DMAD (0.30 mmol) in 0.5 mL of $CHCl_3$ (**114c** was irradiated in $CDCl_3$) were irradiated at room temperature with 300 nm light (Rayonet apparatus) for 6 h. The volatiles from the photolysis mixture were removed in vacuo (except photolysis solution containing the rearrangement products from **111c**) and the residues were each dissolved in $CDCl_3$.

Rearrangement of 111a. The percentages of **118a** and **119a** by ^{1}H NMR spectroscopy (90 MHz) were 73 and 27, respectively. The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate) to give **118a** (50%) and **119a** (19%).

Rearrangement of 111b. The percentages of **118b** and **119b** by ^{1}H NMR spectroscopy (200 MHz) were 72 and 28 respectively. The volatiles were removed in vacuo and the residue was separated by centrifugal chromatography (silica gel, 3:2 hexane/ethyl acetate)

to give **118b** (56%) and **119b** (27%).

1-Methoxymethyl-3-methyl-1*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (119b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (s, 2 H), 3.92 (s, 3 H, COOMe), 3.81 (s, 3 H, COOMe), 3.29 (s, 3 H, OMe), 2.40 (s, 3 H, Me) ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.05, 160.48, 149.70, 135.96, 114.27, 80.84, 56.82, 52.83, 51.56, 12.99; MS *m/z* (M^+) for $C_{10}H_{14}N_2O_5$ calcd 242.0903, found 242.0898.

In a ^{1}H NOE experiment, irradiation of the N-methylene singlet at 5.47 ppm led to an enhancement of the singlet at 3.29 ppm (OMe).

Rearrangement of 111c. The percentages determined by ^{1}H NMR spectroscopy (200 MHz, sealed nmr tube) of **118c**, **121**, **119c**, and isobutene were 28, 67, 5, and 55, respectively. The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 2:1 hexane/ethyl acetate) to give **118c** (20%), **121** (47%), and **119c** (4%).

1-(*tert*-Butyl)-3-methyl-1*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (119c): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.95 (s, 3 H, COOMe), 3.79 (s, 3 H, COOMe), 2.42(s, 3 H, Me), 1.59 (s, 9 H, $C(Me)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.19, 163.34, 148.40, 137.17, 111.37, 62.11, 53.22, 51.39, 29.57 (3), 13.55; MS *m/z* (M^+) for $C_{12}H_{18}N_2O_4$ calcd 254.1267, found 254.1269.

Rearrangement of 111d. The percentages of **118d** and **119d** determined by ^{1}H NMR spectroscopy (200 MHz) were 69 and 31, respectively. The volatiles were removed in vacuo and the residue was separated by centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate) to give **118d** (40%) and **119d** (19%).

1-(1-Adamantyl)-3-methyl-1*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (119d): ^{1}H NMR (200 MHz, $CDCl_3$) ō 3.95 (s, 3 H, COOMe), 3.79 (s, 3 H, COOMe), 2.41 (s, 3 H, Me), 2.21 (bs, 9 H), 1.72 (bs, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.33, 163.39, 148.39, 136.90, 111.12, 63.01, 53.24, 51.34, 41.93 (3), 35.85 (3), 29.74 (3), 13.60; MS *m/z* (M^+) for $C_{18}H_{24}N_2O_4$ calcd 332.1736, found 332.1739.

Rearrangement of 111e. The percentages of **118e**, **120e**, and **119e** determined by ^{1}H NMR spectroscopy (200 MHz) were 56, 32, and 11, respectively. The volatiles were removed in vacuo and the residue was separated by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **118e** (37%), **120e** (7%), and **119e** (7%).

1-(4-Methoxybenzyl)-3-methyl-1*H*-pyrazole-4,5-dicarboxylic acid dimethyl ester, (119e): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17 (d, 2 H, J = 8.7 Hz), 6.83 (d, 2 H, J = 8.7 Hz), 2.34 (s, 2 H, CH_2), 3.85 (s, 3 H, COOMe), 3.81 (s, 3 H, COOMe), 3.78 (s, 3 H, OMe), 2.41 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.40, 161.12, 159.40, 149.70, 135.59, 130.31, 129.16 (2), 127.79, 114.00 (2), 55.22, 54.29, 52.85, 51.63, 13.25; MS *m/z* (M^+) for $C_{16}H_{18}N_2O_5$ calcd 318.1216, found 318.1225.

5.8 Rearrangement of 3*H*-pyrazoles 111a-e in methanol.

General method. Oxadiazoline **114** (0.25 mmol) and DMAD (0.30 mmol) in CD_3OD or CH_3OH (0.5 mL) were irradiated at ambient temperature with 300 nm light (Rayonet apparatus) for 6 hours.

Rearrangement of 111a in CH_3OH. The volatiles were removed in vacuo and the residue was dissolved in $CDCl_3$. The percentages of **118a**, **119a**, **121**, and benzhydryl methyl ether by ^1H NMR spectroscopy (200 MHz, $CDCl_3$) were 26, 22, 52, and 52, respectively. The solvent was removed in vacuo and the residue was separated by centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate) to give **118a** (19%), **119a** (17%), **121** (38%), and benzhydryl methyl ether (40%). The spectroscopic data for benzhydryl methyl ether were identical to those previously reported.[192]

Rearrangement of 111b in CD_3OD. The percentages of **118b**, **121** (the D analogue), and dimethoxymethane-d_3 were 25, 75, and 61, respectively by ^1H NMR spectroscopy (200 MHz). Bulb to bulb distillation (0.01 mm Hg) separated the volatiles from the pyrazoles. The presence of dimethoxymethane-d_3 in the volatiles was confirmed by gas chromatography and ^1H NMR spectroscopy spiking experiments with a sample of dimethoxymethane. The residue from bulb to bulb distillation was separated by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **118b** (18%) and **121** (D analogue) (58%).

Rearrangement of 111c in CD_3OD. The percentages of **118c**, **121** (a mixture of H and D analogues), isobutene, and *tert*-butyl methyl ether were 20, 80, 5, and 72, respectively by ^1H NMR spectroscopy (90 MHz). Bulb to bulb distillation (0.01 mm Hg) separated the volatiles from the pyrazoles. The presence of *tert*-butyl methyl ether-d_3 in the volatiles was confirmed by gas chromatography and ^1H NMR spiking experiments with a sample of *tert*-butyl methyl ether. The residue was separated by centrifugal chromatography (silica gel, 2:1 hexane/ethyl acetate) to give **118c** (14%) and **121** (56%).

Rearrangement of 111d in CH_3OH. The volatiles were removed in vacuo and the residue was dissolved in $CDCl_3$. The percentages of **118d**, **119d**, **121**, and 1-adamantyl methyl ether determined by ^1H NMR spectroscopy (200 MHz) were 54, 17, 29, and 23, respectively. The volatiles were removed in vacuo and the residue was separated by centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate) to give **118d** (34%), **119d** (17%), **121** (27%), and 1-adamantyl methyl ether (16%). The spectral data for 1-adamantyl methyl ether were identical to those of a sample prepared by another route.[193]

Rearrangement of 111e in CH_3OH. The volatiles were removed in vacuo and the residue dissolved in $CDCl_3$. The percentages of **118e**, **119e**, **121**, and p-methoxybenzyl methyl ether were determined to be 45, 4, 51, and 47 by ^1H NMR spectroscopy (200 MHz). The solvent was removed in vacuo and the residue separated by centrifugal chromatography (silica gel, 3:2 hexane/ethyl acetate) to give **118e** (38%), **119e** (2%), **121** (51%), and p-methoxybenzyl methyl ether (45%). The spectral data for p-methoxybenzyl

methyl ether were identical to those of a sample prepared by another route.[194]

3*H*-Pyrazole **111e** was also generated in CH_3OH in the absence of 300 nm irradiation. Oxadiazoline **114e** (0.25 mmol) in CH_3OH (0.5 mL) was irradiated at -73 °C with 300 nm light for 7 h. The Rayonet bulbs were switched off and DMAD (0.6 mmol) in 0.1 mL of CH_3OH was added to the photolysis mixture at -73 °C. The solution was then warmed quickly to ambient temperature and the volatiles were removed in vacuo. The residue was dissolved in $CDCl_3$ and the percentages of **118e**, **119e**, **121**, and p-methoxybenzyl methyl ether, by ^1H NMR spectroscopy (200 MHz) were 56, 12, 32, and 28, respectively.

5.9 Rearrangement of 111f in methanol.

3*H*-pyrazole **111f** (0.123 g, 0.428 mmol) was dissolved in 8 mL of methanol and refluxed for 15 minutes. Thin layer chromatography revealed that 3*H*-pyrazole **111f** was no longer present. The solvent was removed in vacuo and the residue was dissolved in $CDCl_3$. The ^1H NMR spectrum (200 MHz, $CDCl_3$) revealed **118f** (42%) and **120f** (58%). The $CDCl_3$ was removed in vacuo and the residue was separated by centrifugal chromatography (silica gel, 3:2 hexane/ethyl acetate) to give **120f** (45%) and **118f** (32%).

4-Benzyl-5-methyl-4*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (120f): mp 136-138 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20-6.88 (m, 5 H, Ph), 3.97 (s, 3 H, COOMe), 3.85 (d, 1 H, J = -14 Hz), 3.72 (s, 3 H, COOMe), 3.50 (d, 1 H, J = -14 Hz), 2.39 (s, 3 H, Me); ^{13}C (50 MHz, $CDCl_3$) δ 176.32, 166.63, 165.36, 160.71, 132.57, 128.65 (2),

128.38 (2), 127.96, 76.16, 53.72, 53.10, 37.41, 13.80; MS *m/z* (M^+) for $C_{15}H_{16}N_2O_4$ calcd 288.1110, found 288.1110.

1-Benzyl-5-methyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester, (118f): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.10 (m, 5 H, Ph), 5.36 (s, 2 H, CH_2), 3.95 (s, 3 H, COOMe), 3.84 (s, 3 H, COOMe), 2.39 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.43, 162.68, 143.79, 142.97, 134.90, 128.97 (2), 128.22, 126.86 (2), 1[illegible]1, 54.04, 52.52, 51.76, 10.85; MS *m/z* (M^+) for $C_{15}H_{16}N_2O_4$ calcd 288.1110, found 288.1119.

5.10 Thermal rearrangements of 4*H*-pyrazoles 120b and 120e in benzene-d_6.

Rearrangement of 120b. Oxadiazoline **114b** (0.25 mmol) and DMAD (0.30 mmol) were dissolved in C_6D_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in an nmr tube. Irradiation at room temperature with 300 nm light (Rayonet apparatus) for 6 h gave rearrangement products **118b** (77%) and **120b** (23%). The tube was then heated at 90 °C and progress of the rearrangement of **120b** was monitored by ^{1}H NMR spectroscopy at 200 MHz. Concentration vs. time data (10 points) were obtained by normalizing the integrated intensity of the methyl singlet of methyl acetate (generated as a by-product in the photolysis of **114b**) against the integrated intensity of the methyl singlet of **120b** for two half lifes. The resultant plot of ln {(A-x)/A} vs. *t* yielded an observed rate constant ($1.10 \pm 0.05 \times 10^{-4}$ s^{-1}, correlation coefficient = 0.9905) for the decrease in concentration of **111b**. After the rearrangement of **111b** was complete, the

solution consisted of **118b** (90%) and **119b** (10%). The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 3:2 hexane/ethyl acetate) to give **118b** (75%) and **119b** (6%).

Rearrangement of 120e. Compound **120e** (0.072 g, 0.226 mmol) and methyl acetate (0.113 mmol, internal standard) were dissolved in C_6D_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a nmr tube. The tube was then heated at 130 °C and progress of the rearrangement of **120e** was monitored by ^{1}H NMR spectroscopy (200 MHz). Concentration vs. time data were obtained by normalizing the integrated intensity of the methyl singlet of methyl acetate against the sum of the integrated intensity of the CH_2 singlets of the two 1*H*-pyrazole rearrangement products (**118e** and **119e**) for two half lifes. The resultant plot of ln {(A-x)/A} vs. *t* yielded an observed rate constant ($1.45 \pm 0.08 \times 10^{-4}$ s^{-1}, correlation coefficient = 0.9939) for the increase in concentration of the two 1*H*-pyrazoles. After the thermal rearrangement of **120e** was complete, the mixture consisted of **118e** (58%) and **119e** (42%). The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **118e** (50%) and **119e** (35%).

5.11 Thermal rearrangements of 4*H*-pyrazoles 120b and 120e in methanol/methanol-d_4.

Rearrangement of 120b. The volatiles from the photolysis mixture, after generation of 3*H*-pyrazole **111b** in C_6D_6 (79% of **118b** and 21% of **120b**), were removed and the residue was dissolved in CD_3OD. A ^1H NMR spectrum was taken immediately and it revealed **118b** (79%), **121** (21%), and dimethoxymethane-d_3 (21%). Bulb to bulb distillation (0.01 mm Hg) separated the volatiles from the pyrazoles. The presence of dimethoxymethane-d_3 in the volatiles was confirmed by gas chromatography and ^1H NMR spectroscopy spiking experiments with an authentic sample of dimethoxymethane. The residue from bulb to bulb distillation was separated by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **118b** (65%) and **121** (D analogue) (16%).

Rearrangement of 120e. Compound **120e** (0.06 g, 0.189 mmol) was dissolved in methanol for ten minutes. The methanol was then removed in vacuo and the residue was dissolved in $CDCl_3$ and a ^1H NMR spectrum was taken. ^1H NMR spectroscopy revealed a quantitative yield of **121** and p-methoxybenzyl methyl ether. The $CDCl_3$ was removed and the residue was separated by centrifugal chromatography (silica gel, 3:2 hexane/ethyl acetate) to give **121** (76%) and p-methoxybenzyl methyl ether (80%).

5.12 Preparation of 3-alkyl-3-methyl-3*H*-pyrazole-5-carboxylic acid methyl esters (128c-f).

General. The oxadiazolines **114b-f** (0.25 mmol) were dissolved in toluene (0.5 mL) and irradiated at -73 °C with 300 nm light (Rayonet apparatus) for 7 hours. At -73 °C, with the Rayonet bulbs switched off, methyl propiolate (0.50 mmol in 0.1 mL of toluene) was added to the photolysis mixtures. The mixtures were warmed to room temperature and the volatiles were removed in vacuo and the residues dissolved in hexane. The solid 3*H*-pyrazoles were filtered and washed with hexane.

3-Methyl-3-(*tert*)-butyl-3*H*-pyrazole-5-carboxylic acid methyl ester, (128c): 43% yield, mp 55-58 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (s, 1 H, CH), 3.99 (s, 3 H, COOMe), 1.38 (s, 3 H, Me), 1.06 (s, 9 H, $C(Me)_3$); ^{13}C NMR spin sort (50 MHz, $CDCl_3$) δ 161.38 (+ve), 154.37(-ve), 147.02 (+ve), 105.08 (+ve), 52.38 (-ve), 37.45 (+ve), 26.77 (3, -ve), 15.06 (-ve); MS *m/z* (M^+) for $C_{10}H_{16}N_2O_2$ calcd 196.1212, found 196.1211.

3-(1-Adamantyl)-3-methyl-3*H*-pyrazole-5-carboxylic acid methyl ester, (128d): 52% yield, mp 120-121 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (s, 1 H, CH), 3.98 (s, 3 H, COOMe), 1.99 (bs, 3 H, CH), 1.68 (bs, 12 H, CH_2), 1.33 (s, 3 H, Me); ^{13}C NMR spin sort (50 MHz, $CDCl_3$) δ 161.39 (+ve), 154.47 (-ve), 147.01 (+ve), 105.60 (+ve), 52.33 (-ve), 40.60 (+ve), 38.59 (3, +ve), 36.68 (3, +ve), 28.72 (3, -ve), 13.73 (-ve). MS *m/z* (M^+) for $C_{16}H_{22}N_2O_2$ calcd 274.1681, found 274.1690.

3-(4-Methoxybenzyl)-3-methyl-3*H*-pyrazole-5-carboxylic acid methyl ester, (128e): 45% yield, mp 127-130 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (s, 1 H, CH), 7.00 (d, 2 H, J = 8.2 Hz), 6.78 (d, 2 H, J = 8.2 Hz), 3.94 (s, 3 H, COOMe), 3.77 (s, 3 H, OMe), 3.29 (d, 1H, CH, J = -13.7 Hz), 3.07 (d, 1 H, CH, J = -13.7 Hz), 1.46 (s, 3 H, Me); ^{13}C NMR (200 MHz, $CDCl_3$) δ 161.09, 158.65, 153.11, 147.66, 130.70 (2), 129.07, 113.66, 99.30, 55.14, 52.40, 40.45, 28.09, 18.01; MS *m/z* (M^+) for $C_{14}H_{16}N_2O_3$ calcd 260.1161, found 260.1155.

3-Benzyl-3-methyl-3*H*-pyrazole-5-carboxylic acid methyl ester, (128f): 65% yield, mp 114-116 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (s, 1 H, CH), 7.26-7.07 (m, 5 H, Ph), 3.93 (s, 3 H, COOMe), 3.34 (d, 1 H, J = -13.4 Hz), 3.10 (d, 1 H, J = -13.4 Hz), 1.47 (s, 3 H, Me); ^{13}C NMR (200 MHz, $CDCl_3$) δ 161.00, 152.86, 147.60, 134.72, 129.60 (2), 128.25 (2), 127.17, 98.96, 52.34, 41.12, 18.03; MS *m/z* (M^+) for $C_{13}H_{14}N_2O_2$ calcd 230.1055, found 230.1065.

5.13 Synthesis of 3-alkyl-1-methoxycarbonyl-3-methylcyclopropenes (134c-f):

General. Oxadiazolines **114** (0.25 mmol) in 0.5 mL of benzene-d_6 containing methyl propiolate (0.30 mmol) were photolyzed (t = 16 hours for **114c**, t = 7 hours for **114d**, t = 12 hours for **114e** and **114f**) until loss of nitrogen from 3*H*-pyrazoles **128c-f** was complete and only cyclopropenes **134c-f** could be observed by ^{1}H NMR spectroscopy.

These ^{1}H NMR spectra revealed quantitative yields of cylopropenes. The cyclopropenes were isolated by centrifugal chromatography (silica gel, 98:2 hexane/ethyl acetate).

3-(*tert*-Butyl)-1-methoxycarbonyl-3-methylcyclopropene, (134c): 60% yield, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (s, 1 H, CH), 3.77 (s, 3 H, COOMe), 1.18 (s, 3 H, Me), 0.82 (s, 9 H, Me_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.27, 131.65, 125.49, 52.02, 36.54, 35.08, 28.68 (3), 21.23; MS *m/z* (M^+) for $C_{10}H_{16}O_2$ calcd 168.1150, found 168.1152.

3-(1-Adamantyl)-1-methoxycarbonyl-3-methylcyclopropene, (134d): 55% yield, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.92 (s, 1 H, CH), 3.80 (s, 3 H, COOMe), 1.93 (bs, 3 H, CH), 1.52-1.72 (m, 6 H, CH_2), 1.39-1.41 (m, 6 H, CH_2), 1.14 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.46, 131.21, 124.76, 52.04, 41.07 (3), 36.96 (3), 36.69, 36.22, 28.77 (3), 20.03; MS *m/z* (M^+) for $C_{16}H_{22}O_2$ calcd 246.1620, found 246.1617.

3-(4-Methoxybenzyl)-1-methoxycarbonyl-3-methylcyclopropene, (134e): 52% yield, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (s, 1 H, CH), 7.01 (d, 2 H, J = 8.5 Hz), 6.80 (d, 2 H, J = 8.5 Hz), 3.80 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 2.86 (s, 2 H, CH_2), 1.29 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.82, 157.88, 131.76, 131.69, 130.23 (2), 125.72, 113.64 (2), 55.18, 52.05, 44.92, 29.65, 25.19; MS *m/z* (M^+) for $C_{14}H_{16}O_3$ calcd 232.1099, found 232.1096.

3-Benzyl-1-methoxycarbonyl-3-methylcylopropene, (134f): 63% yield, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (s, 1 H, CH), 7.08-7.26 (m, 5 H, Ph), 3.80 (s, 3 H, COOMe), 2.92 (s, 2 H, CH_2), 1.30 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.74, 139.56, 131.64, 129.30 (2), 128.22 (2), 125.96, 52.03, 45.86, 29.41, 25.22; MS *m/z* (M^+) for $C_{13}H_{14}O_2$ calcd 202.0994, found 202.0984.

5.14 Rearrangement of 3*H*-pyrazoles 128b-f in benzene-d_6.

Rearrangement of 128b. Oxadiazoline **114b** (0.25 mmol) and methyl propiolate (0.50 mmol) in C_6D_6 (0.5 mL) were irradiated at room temperature with 300 nm light (Rayonet apparatus) for 6 hours. A 1.1:1.0 ratio of **131b**:**132b** was indicated by ^{1}H NMR spectroscopy (200 MHz, C_6D_6). The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **131b** (28%) and **132b** (31%).

1-Methoxymethyl-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (132b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1 H, CH), 5.45 (s, 2 H, CH_2), 3.92 (s, 3 H, COOMe), 3.32 (s, 3 H, OMe), 2.38 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.85, 142.66, 140.88, 109.23, 80.33, 56.40, 51.97, 10.69; MS *m/z* (M^+) for $C_8H_{12}N_2O_3$ calcd 184.0848, found 184.0843.

In a ^{1}H NOE experiment, irradiation of the methyl singlet at 2.38 ppm caused enhancement at both 5.45 ppm (CH_2) and 6.63 ppm (vinyl proton).

4-Methoxymethyl-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (131b): mp 85-88 °C ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.62 (s, 2 H, CH_2), 3.92 (s, 3 H, COOMe), 3.37 (s, 3 H, OMe), 2.36 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.93, 144.31, 137.95, 117.88, 63.41, 57.88, 51.92, 10.39; MS *m/z* (M^+) for $C_8H_{12}N_2O_3$ calcd 184.0848, found 184.0841.

Rearrangement of 128c. 3*H*-Pyrazole **128c** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in C_6D_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a nmr tube. The tube was heated at 90 °C for 15 hours. The percentages of **131c**, **132c**, **135c**, **136**, and isobutene by ^{1}H NMR spectroscopy (200 MHz) were 28, 15, 2, 55, and 25, respectively. The presence of isobutene was confirmed by a ^{1}H NMR decoupling experiment on the reaction mixture following the rearrangement of **128c**. Irradiation of the multiplet at 4.74 ppm (CH_2) caused collapse of the triplet at 1.60 ppm (2 Me). The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **131c** (19%), **132c** (7%), **135c** (1%), and **136** (42%).

4-(*tert*-Butyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (131c): mp 145-148 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 3 H, OMe), 2.42 (s, 3 H, Me), 1.42 (s, 9 H, $C(Me)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.01, 142.49, 139.91, 129.12, 51.92, 31.49, 31.12 (3), 14.16; MS *m/z* (M^+) for $C_{10}H_{16}N_2O_3$ calcd 196.1211, found 196.1197.

1-(*tert*-Butyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (132c): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.58 (s, 1 H, CH), 3.89 (s, 3 H, COOMe), 2.47 (s, 3 H, Me), 1.67 (s, 9 H, $C(Me)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.24, 139.99, 139.42, 111.27, 61.12, 51.76, 29.82 (3), 14.65; MS *m/z* (M^+) for $C_{10}H_{16}N_2O_3$ calcd 196.1211, found 196.1212.

4-(*tert*-Butyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid methyl ester, (135c): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90 (s, 3 H, COOMe), 2.41 (s, 3 H, Me), 1.39 (s, 9 H, $C(Me)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.12, 154.00, 137.11, 116.81, 51.66, 31.08, 29.16, 10.13; MS *m/z* (M^+) for $C_{10}H_{16}N_2O_3$ calcd 196.1211, found 196.1204.

5-Methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (136):[204] mp 74-76 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.57 (s, 1 H, CH), 3.89 (s, 3 H, OMe), 2.38 (s, 3 H, Me); ^{13}C NMR (50.32, $CDCl_3$) δ 162.51, 142.61, 141.77, 107.19, 51.78, 11.22; MS *m/z* (M^+) for $C_6H_8N_2O_2$ calcd 140.0586, found 140.0570.

Rearrangement of 128d. 3*H*-Pyrazole **128d** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in C_6D_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a NMR tube. The tube was heated at 90 °C for 14 hours. The percentages of **131d** and **132d** by ^{1}H NMR spectroscopy (200 MHz) were 72 and 28. The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **131d** (55%) and **132d** (18%).

4-(1-Adamantyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (131d): mp 239-241 °C (sublimes) ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.50 (s, 1 H, NH), 3.90 (s, 3 H, COOMe), 2.46 (s, 3 H, Me), 2.14 (bs, 6 H, CH_2), 2.03 (bs, 3H, CH), 1.76 (bs, 6 H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.71, 137.23, 130.03, 114.50, 52.05, 41.76 (3), 36.67 (3), 34.14, 28.87 (3), 15.37; MS *m/z* (M^+) for $C_{16}H_{22}N_2O_2$ calcd 274.1681, found 274.1688.

1-(1-Adamantyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (132d): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.57 (s, 1 H, CH), 3.89 (s, 3 H, COOMe), 2.51 (s, 3 H, Me), 2.32 (bs, 6 H, CH_2), 2.23 (bs, 3 H, CH), 1.75 (bs, 6 H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.30, 140.16, 139.50, 111.26, 62.28, 51.80, 41.64 (3), 36.08 (3), 29.71 (3), 15.00; MS *m/z* (M^+) for $C_{16}H_{22}N_2O_2$ calcd 274.1681, found 274.1685.

Rearrangement of 128e. 3*H*-pyrazole **128e** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in C_6D_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a NMR tube. The tube was heated at 60 °C for 5 hours. The percentages of **131e** and **132e** by ^{1}H NMR spectroscopy (200 MHz) were 78 and 22. The volatiles were removed in vacuo and the residue was subjected to centrifugal chromatography (silica gel, 70:30 hexane/ethyl acetate) to give **131e** (60%) and **132e** (15%).

4-(4-Methoxybenzyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (131e): mp 129-131 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.07 (d, 2 H, CH, J = 8.6 Hz, 6.78 (d, 2 H,

CH, J = 8.6 Hz), 4.03 (s, 2 H, CH_2), 3.85 (s, 3 H, COOMe), 3.76 (s, 3 H, OMe), 2.21 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.21, 157.68, 143.21, 136.75, 132.46, 129.05 (2), 120.91, 113.62 (2), 55.16, 51.63, 28.12, 10.50; MS *m/z* (M^+) for $C_{14}H_{16}N_2O_3$ calcd 260.1161, found 260.1164.

1-(4-Methoxybenzyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (132e): ^1H NMR (200 MHz, $CDCl_3$) δ 7.01 (d, 2 H, CH, J = 8.8 Hz), 6.77 (d, 2 H, CH, J = 8.8 Hz), 6.54 (s, 1 H, CH), 5.24 (s, 2 H, CH_2), 3.86 (s, 3 H, COOMe), 3.71 (s, 3 H, OMe), 2.12 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.01, 159.24, 142.03, 128.26 (2), 127.78, 114.14 (2), 108.94, 55.23, 53.63, 51.91, 11.29; MS *m/z* (M^+) for $C_{14}H_{16}N_2O_3$ calcd 260.1161, found 260.1149.

Rearrangement of 128f. 3*H*-Pyrazole **128f** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in C_6D_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a nmr tube. The tube was heated at 90 °C for 6 hours. 1*H*-Pyrazole **131f** appeared to be formed in quantitative yield by ^1H NMR spectroscopy (200 MHz). The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 60:40 hexane/ethyl acetate) to give **131f** (81%).

4-Benzyl-5-methyl-1*H*-pyrazole-3-carboxylic acid methyl ester, (131f): mp 102-104 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.17-7.36 (m, 5 H, Ph), 5.10 (s, 1 H, NH), 4.11 (s, 2 H, CH_2), 3.88 (s, 3 H, COOMe), 2.21 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.22,

143.31, 140.34, 136.91, 128.24, 128.15 (2), 125.84 (2), 120.45, 51.61, 29.05, 10.48; MS *m/z* (M^+) for $C_{13}H_{14}N_2O_2$ calcd 230.1055, found 230.1062.

5.15 Determination of k_{obs} for the rearrangement of 3*H*-pyrazoles 128c-f in benzene-d_6.

3*H*-Pyrazole **128** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in C_6D_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a nmr tube. The tube was heated at 90 °C for **128c**, **128d**, and **128f** and at 60 °C for **128e**, and progress of the rearrangement of **128** was monitored by ^{1}H NMR spectroscopy (200 MHz). Concentration vs. time data were obtained by normalizing the integrated intensity of the CH_2 singlet of phenoxy-2-propanone against the integrated intensity of the methyl singlet of 3*H*-pyrazole **128**. The decrease in concentration of **128** was monitored to at least 2 half lifes. The resultant plots of ln {(A-x)/A} vs *t* gave the following observed rate constants :

$k^{90\,°C}$(**128c**) = (1.06 ± .03) x 10^{-4} s^{-1} (correlation coefficient = 0.9975)

$k^{90\,°C}$(**128d**) = (1.10 ± .09) x 10^{-4} s^{-1} (correlation coefficient = 0.9850)

$k^{60\,°C}$(**128e**) = (3.8 ± 0.1) x 10^{-4} s^{-1} (correlation coefficent = 0.9952)

$k^{60\,°C}$(**128e**) = (3.3 ± 0.2) x 10^{-4} s^{-1} (correlation coefficent = 0.9898)

$k^{90\,°C}$(**128f**) = (2.8 ± 0.1) x 10^{-4} s^{-1} (correlation coefficient = 0.9955)

5.16 Rearrangement of 128b in dichloromethane.

Oxadiazoline **114b** (0.92 mmol) and methyl propiolate (1.21 mmol) were dissolved in CH_2Cl_2 (0.5 mL, base washed with $NaHCO_3$ and distilled) and irradiated at room temperature with 300 nm light (Rayonet apparatus) for 6 hours. The volatiles were removed in vacuo and the residue was dissolved in $CDCl_3$ and the percentages of products determined by ^1H NMR spectroscopy were **131b** (50), **132b** (24), **136** (7), **139b** (8), and **140b** (11). The residue was purified by centrifugal chromatography (silica gel, 2:1 diethyl ether/hexanes) to give **131b** (32%), **132b** (18%), **136** (4%), **139b** (5%), and **140b** (7%).

1-Methoxymethyl-3-methyl-1*H*-pyrazole-5-carboxylic acid methyl ester, (139b): ^1H NMR (500 MHz, $CDCl_3$) δ 6.69 (s, 1 H, CH), 5.75 (s, 2 H, CH_2), 3.88 (s, 3 H, COOMe), 3.35 (s, 3 H, OMe), 2.30 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.95, 148.30, 133.09, 112.20, 80.52, 56.75, 51.99, 13.34; MS (CI, CH_4) *m/z* (M^+) for $C_8H_{12}N_2O_3$-H calcd 183.0770, found 183.0759.

In a ^1H NOE experiment, irradiation of the methyl singlet at 2.30 ppm caused enhancement at 6.69 ppm (vinyl proton).

1,4-bis(Methoxymethyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid methyl ester, (140b): ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (s, 2 H, N-CH_2), 4.55 (s, 2 H, C-CH_2), 3.95 (s, 3 H, COOMe), 3.35 (s, 3 H, C-CH_2OMe), 3.32 (s, 3 H, N-CH_2OMe), 2.32 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.22, 148.96, 130.98, 121.78, 81.23, 64.06, 57.94, 56.77,

52.08, 11.77; MS (CI, CH_4) *m/z* (M^+) for $C_{10}H_{16}N_2O_4$ calcd 228.1110, found 228.1096.

In a ^1H NOE experiment, irradiation of the methyl singlet at 2.32 ppm caused enhancement of the singlet at 4.55 ppm (C-$\underline{CH_2}$), while irradiation of the methylene singlet at 5.72 caused enhancement of the singlet at 3.32 (N-$CH_2\underline{OCH_3}$). Furthermore, irradiation of the methylene singlet at 4.55 caused enhancement of the singlet at 3.35 ppm (C-$CH_2\underline{OCH_3}$)

5.17 Rearrangement of 3*H*-pyrazoles 128c-f in acetone-d_6.

Rearrangement of 128c. 3*H*-Pyrazole **128c** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in acetone-d_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a NMR tube. The tube was heated at 90 °C for 16 hours. The percentages of **131c**, **132c**, **135c**, **136**, and isobutene by ^1H NMR spectroscopy (200 MHz) were 38, 15, 7, 41, and 34, respectively. The presence of isobutene was confirmed by a ^1H NMR decoupling experiment on the reaction mixture following the rearrangement of **128c**. Irradiation of the multiplet at 4.74 ppm (CH_2) caused collapse of the triplet at 1.60 ppm (2 Me). The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **131c** (24%), **132c** (8%), **135c** (3%), and **136** (32%).

Rearrangement of 128d. 3*H*-Pyrazole **128d** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in acetone-d_6 (0.5 mL), degassed (three

freeze-pump-thaw cycles), and sealed in a nmr tube. The tube was heated at 90 °C for 16 hours. The percentages of **131d** and **132d** by ^{1}H NMR spectroscopy (200 MHz) were 72 and 28, respectively. The volatiles were removed in vacuo and the residue was subjected to centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **131d** (58%) and **132d** (21%).

Rearrangement of 128e. 3*H*-Pyrazole **128e** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in acetone-d_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a nmr tube. The tube was heated at 60 °C for 6 hours. The percentages of **131e** and **132e** by ^{1}H NMR spectroscopy (200 MHz) were 90 and 9, respectively. The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 70:30 hexane/ethyl acetate) to give **131e** (80%) and **132e** (5%).

Rearrangement of 128f. 3*H*-Pyrazole **128f** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in acetone-d_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a nmr tube. The tube was heated at 90 °C for 6 hours. 1*H*-pyrazole **131f** appeared to be formed in quantitative yield by ^{1}H NMR spectroscopy (200 MHz). The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 60:40 hexane/ethyl acetate) to give **131f** (84%).

5.18 Determination of k_{obs} for the rearrangement of 3*H*-pyrazoles 128c-f in acetone-d_6.

3*H*-pyrazole **128** (0.200 mmol) and phenoxy-2-propanone (0.100 mmol, internal standard) were dissolved in acetone-d_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a nmr tube. The tube was heated at 90 °C for **128c**, **128d**, and **128f** and at 60 °C for **128e**, and progress of the rearrangement of **128** was monitored by ^{1}H NMR spectroscopy (200 MHz). Concentration vs. time data were obtained by normalizing the integrated intensity of the CH_2 singlet of phenoxy-2-propanone against the integrated intensity of the methyl singlet of 3*H*-pyrazole **128**. The decrease in concentration of **128** was monitored to at least 2 half lifes. The resultant plots of ln {(A-x)/A} vs *t* gave the following observed rate constants :

$k^{90\,°C}$(**128c**) = (9.7 ± 0.3) x 10^{-5} s^{-1} (correlation coefficient = 0.9954)

$k^{90\,°C}$(**128d**) = (8.9 ± 0.4) x 10^{-5} s^{-1} (correlation coefficient = 0.9924)

$k^{60\,°C}$(**128e**) = (2.1 ± 0.1) x 10^{-4} s^{-1} (correlation coefficent = 0.9990)

$k^{90\,°C}$(**128f**) = (2.80 ± .05) x 10^{-4} s^{-1} (correlation coefficient = 0.9988)

5.19 Rearrangement of 3*H*-pyrazoles 128b-f in methanol.

Rearrangement of 128b. Oxadiazoline **114b** (0.25 mmol) and methyl propiolate (0.50 mmol) were dissolved in methanol-d_4 (0.5 mL) and irradiated at room temperature with 300 nm light (Rayonet apparatus) for 6 hours. The percentages by ^{1}H NMR (200 MHz,

CD_3OD) of **131b**, **132b**, **136**, and dimethoxymethane-d_3 were 53%, 21%, 26% and 26%, respectively. Bulb to bulb distillation at 0.01 mm Hg separated the volatiles from the pyrazoles. Dimethoxymethane-d_3 was confirmed by ^{1}H NMR and gas chromatography spiking experiments with an authentic sample of dimethoxymethane. The residue was separated by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **131b** (48%), **132** (16%), and **136** (24%).

Rearrangement of 128c. 3*H*-Pyrazole **128c** (0.200 mmol) was dissolved in C_6D_6 (0.5 mL), degassed (three freeze-pump-thaw cycles), and sealed in a NMR tube. The tube was heated at 90 °C for 20 minutes. The percentages of **131c**, **132c**, **135c**, **136**, *tert*-butyl methyl ether-d_3, and isobutene by ^{1}H NMR spectroscopy (200 MHz) were 18, 16, 6, 60, 31, and 27, respectively. The presence of isobutene was confirmed by a ^{1}H NMR decoupling experiment on the reaction mixture following the rearrangement of **128c**. Irradiation of the multiplet at 4.74 ppm (CH_2) caused collapse of the triplet at 1.60 ppm (2 Me). Bulb to bulb distillation at 0.01 mm Hg separated the volatiles from the pyrazoles. *tert*-Butyl methyl ether-d_3 was confirmed by ^{1}H NMR and gas chromatography spiking experiments. The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **131c** (11%), **132c** (12%), **135c** (4%), and **136** (55%).

In another experiment 3*H*-pyrazole **128c** (20 mg, 0.102 mmol) and 2-phenoxy-2-propanone (7.7 mg, 0.05 mg, internal standard) were dissolved in methanol-d_4. The tube was heated at 50 °C for 1 hour and the progress of the rearrangement of **128c** was

monitored by ^{1}H NMR spectroscopy. Concentration vs. time data were obtained by normalizing the integrated intensity of the CH_2 singlet of phenoxy-2-propanone against the integrated intensity of the methyl singlet of 3*H*-pyrazole **128c**. The decrease in concentration of **128c** was monitored for 2.4 half lifes. The resultant plot of ln {(A-x)/A} vs *t* with 5 data points gave a rate constant of $4.7 \pm 0.1 \times 10^{-4}$ s^{-1} (correlation coefficient = 0.9993).

Rearrangement of 128d. 3*H*-Pyrazole **128d** (0.200 mmol) was dissolved in methanol (5 mL) and refluxed for 0.5 hours. The percentages of **131d** and **132d** by ^{1}H NMR spectroscopy (200 MHz) were 81 and 19. Only trace amounts of **136** and 1-adamantyl methyl ether were detected by gas chromatography and ^{1}H NMR spectroscopy. The volatiles were removed in vacuo and the residue was subjected to centrifugal chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **131d** (70%) and **132d** (13%).

In another experiment **128d** (0.100 mmol) and phenoxy-2-propanone (0.05 mmol, internal standard) were dissolved in methanol-d_4 and heated at 50 °C for 30 minutes. ^{1}H NMR spectroscopy revealed **128d** (7%), **131d** (76%), and **132d** (17%).

Rearrangement of 128e. 3*H*-Pyrazole **128e** (0.200 mmol) was dissolved in methanol (5 mL) and the solution was refluxed for 0.5 hours. The percentages of **131e** and **132e** by ^{1}H NMR spectroscopy (200 MHz) were 75 and 25, respectively. Only trace amounts of **136** and p-methoxybenzyl methyl ether were detected by gas chromatography and ^{1}H NMR spectroscopy. The volatiles were removed in vacuo and the residue was purified

by centrifugal chromatography (silica gel, 70:30 hexane/ethyl acetate) to give **131e** (63%) and **132e** (16%).

In another experiment, **128e** (0.100 mmol) and phenoxy-2-propanone (0.05 mmol, internal standard) were dissolved in 0.5 mL of methanol-d_4. After 9 minutes at ambient temperature, ^{1}H NMR spectroscopy (200 MHz) revealed **128e** (8%), **131e** (65%), and **132e** (27%). After 15 minutes at ambient temperature the solution consisted of **131e** (81%) and **132e** (19%).

Rearrangement of 128f. 3*H*-Pyrazole **128f** (0.200 mmol) was dissolved in methanol (5 mL) and refluxed for 0.5 hours. The solution was not homogeneous. 1*H*-Pyrazole **131f** appeared to be formed in quantitative yield by ^{1}H NMR spectroscopy (200 MHz). The volatiles were removed in vacuo and the residue was purified by centrifugal chromatography (silica gel, 60:40 hexane/ethyl acetate) to give **131f** (86%).

In another experiment, **128f** (0.100 mmol) and phenoxy-2-propanone (0.05 mmol, internal standard) in 0.5 mL of methanol-d_4 were placed in an nmr tube. Initially the solution was not homogeneous. However, the solution was homogeneous after 1.6 hours at 40 °C and it contained **128f** (42%) and **131f** (58%). The solution was then heated at 50 °C for 30 minutes after which it contained **128f** (21%) and **131f** (79%).

5.20 Synthesis of 5-Alkyl-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadienes (148a-f):

General. The syntheses of 5-alkyl-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadienes were adapted from a procedure for the synthesis of 5-ethyl-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadiene.[54] Pentakis(methoxycarbonyl)cyclopentadiene (0.50 g, 1.43 mmol), Ag_2O (0.16 g, 0.73 mmol), and benzene (9 mL) were stirred for 2 hours at room temperature. The halide (2.38 mmol) was then added and the mixture was stirred for 2 hours. The solution was filtered and most of the benzene was removed by rotary evaporation. Crude product solutions of **148a** and **148b** were subjected to centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate). For crude product solutions of **148c** and **148d**, CH_2Cl_2 was added and the solution was washed three times with 10% $NaHCO_3$. The CH_2Cl_2 layer was dried with $MgSO_4$ and filtered. The CH_2Cl_2 was removed by rotary evaporation and the residues were subjected to centrifugal chromatography (silica gel, 7:3 hexane/ethyl acetate) except in the cases of **148e** and **148f**, which were recrystallized from methanol. The isolated percentage yields of **148a-f** were not optimized. Pentakis(methoxcarbonyl)cyclopentadiene, silver (I) oxide, and the following halides were purchased from Aldrich Chemical Co. and used as supplied: bromodiphenylmethane (for **148a**), chloromethyl methyl ether (for **148b**), 1-bromoadamantane (for **148c**), 4-methoxybenzyl chloride (for **148d**), benzyl bromide (for **148e**), and iodomethane (for **148f**).

1,2,3,4,5-pentakis(Methoxycarbonyl)-5-(1,1-diphenylmethyl)cyclopentadiene, (148a): 25% yield; mp 108-110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.17 (m, 10 H, 2 Ph), 5.60 (s, 1 H, CH), 3.81 (s, 6 H, 2 COOMe), 3.63 (s, 3 H, COOMe), 3.36 (s, 6 H, COOMe); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.70, 162.66 (2), 161.48 (2), 143.76 (2), 142.67 (2), 139.12 (2), 129.27 (4), 128.00 (4), 127.11 (2), 71.45, 53.30, 52.80, 52.65 (2), 52.06 (2); MS *m/z* (M^+) for $C_{28}H_{26}O_{10}$ calcd 522.1526 found, 522.1514.

1,2,3,4,5-pentakis(Methoxycarbonyl)-5-methoxymethylcyclopentadiene, (148b): 39% yield; mp 119-120 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.23 (s, 2 H, CH_2), 3.88 (s, 6 H, 2 COOMe), 3.83 (s, 6 H, 2 COOMe), 3.68 (s, 3 H, COOMe), 3.26 (s, 3 H, OMe); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.76, 162.55 (2), 161.92 (2), 141.78 (2), 141.67 (2), 71.84, 68.71, 59.87, 53.21, 52.72 (2), 52.56 (2); *m/z* (M^+) for $C_{17}H_{20}O_{11}$ calcd 400.1006, found 400.0995.

5-(1-Adamantyl)-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadiene, (148c): 22% yield; mp 124-125°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.86 (s, 6 H, 2 COOMe), 3.81 (s, 6 H, 2 COOMe), 3.64 (s, 3 H, COOMe), 1.95 (bs, 3 H, CH), 1.88 (bs, 6 H, 3 CH_2), 1.65 (bs, 6 H, 3 CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.65, 163.31 (2), 162.61 (2), 144.51 (2), 140.70 (2), 74.77, 52.60 (2), 52.46 (2), 52.21, 42.55, 38.09 (3), 36.35 (3), 28.94 (3); MS *m/z* (M^+) for $C_{25}H_{30}O_{10}$ -H calcd 489.1761 found 489.1756.

1,2,3,4,5-pentakis(Methoxycarbonyl)-5-(4-methoxybenzyl)cyclopentadiene, (148d): 31% yield; mp 88.5-89.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.92 (d, J = 8.7 Hz, 2 H, CH_{ortho}), 6.69 (d, J = 8.7 Hz, 2 H, CH_{meta}), 3.87 (s, 6 H, 2 COOMe), 3.77 (s, 6 H, 2 COOMe), 3.74 (s, 3 H, COOMe), 3.71 (s, 2 H, CH_2), 3.69 (s, 3 H, OMe); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.33, 162.34 (2), 162.11 (2), 158.60, 142.87 (2), 141.70 (2), 130.19 (2), 125.45, 113.18 (2), 68.48, 55.06, 53.30, 52.66 (4), 37.26; *m/z* (M^+) for $C_{23}H_{24}O_{11}$ calcd 476.1319, found 476.1296.

5-Benzyl-1,2,3,4,5-pentakis(methoxycarbonyl)cyclopentadiene, (148e): 45% yield; mp 116-117 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19-7.00 (m, 5H, Ph), 3.87 (s, 6 H, 2 COOMe), 3.76 (s, 8 H, 2 COOMe, CH_2), 3.70 (s, 3 H, COOMe); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.29, 162.30 (2), 162.06 (2), 142.70 (2), 141.82 (2), 133.40, 129.09 (2), 127.81 (2), 127.28, 68.13, 53.35, 52.69 (2), 52.67 (2), 38.01; MS *m/z* (M^+) for $C_{22}H_{22}O_{10}$ calcd 446.1213, found 446.1218.

1,2,3,4,5-pentakis(Methoxycarbonyl)-5-methylcyclopentadiene, (148f): 50% yield; mp 99-100 °C (lit. 101-102 °C);[205] ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 6 H, 2 COOMe), 3.83 (s, 6 H, 2 COOMe), 3.66 (s, 3 H, COOMe), 1.69 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.40, 162.62 (2), 161.82 (2), 144.86 (2), 139.65 (2), 65.60, 53.24, 52.75 (2), 52.59 (2), 17.35.

5.21 Rearrangement of 148a-f in methanol or methanol-d_4.

Rearrangement of 148a in methanol-d_4. Cyclopentadiene **148a** (0.0124 g, 0.0240 mmol) and toluene (2.52 μL, internal standard) were dissolved in 0.5 mL of methanol-d_4. After 3 minutes at ambient temperature ^{1}H NMR spectroscopy (200 MHz) revealed **148a** (49%), **152** (D analogue, 51%), and **154f** (D analogue, 51%). After 20 minutes at ambient temperature, ^{1}H NMR spectroscopy (200 MHz) revealed **152** (D analogue, 100%) and **154a** (D, analogue 100%). In another experiment, cyclopentadiene **148a** (0.200 g, 0.038 mmol) was dissolved in methanol (1.0 mL) for 20 minutes. The volatiles were removed in vacuo and the residue was dissolved in $CDCl_3$. ^{1}H NMR spectroscopy revealed **152** (100%) and benzhydryl methyl ether (100%). The $CDCl_3$ was removed in vacuo and the residue was subjected to centrifugal chromatography (silica gel, 3:2 hexane/ethyl acetate) to give **152** (77%) and **154f** (82%). Compound **154f** was confirmed by the comparison of its spectroscopic data to those reported in the literature for benzhydryl methyl ether.[192]

Rearrangement of 148b in methanol-d_4. Cyclopentadiene **148b** (0.0076 g, 0.0189 mmol) and toluene (2.00 μL, internal standard) were dissolved in methanol-d_4 and placed in an nmr tube. The tube was then heated at 40 °C and the rate of disappearance of **148b** was monitored by ^{1}H NMR spectroscopy (200 MHz). Concentration vs. time data (7 points) were obtained by normalizing the integrated intensity of the methyl singlet of toluene against the integrated intensity of the CH_2 singlet of **148b** for 2 half lifes. The resultant plot of ln{(A-x)/A} vs. t yielded an observed rate constant of

(5.2 ± 0.3) x 10^{-4} s^{-1} (correlation coefficient = 0.9934) for the decrease in concentration of **148b**. After 2 hours at 40 °C, ^{1}H NMR spectroscopy (200 MHz) revealed **154b** (D analogue, 100%) and **152** (D analogue, 100%). Bulb to bulb distillation (0.01 mm Hg) separated the volatiles from **152**. The presence of dimethoxymethane-d_3 in the volatiles was confirmed by gas chromatography and ^{1}H NMR spectroscopy spiking experiments with an authentic sample of dimethoxymethane.

Rearrangement of 148c in methanol and methanol-d_4. Cyclopentadiene **148c** (0.0085 g, 0.0174 mmol) and toluene (1.75 μL, internal standard) were dissolved in methanol-d_4 (0.5 mL) and placed in a nmr tube. The tube was then heated at 50 °C and the rate of disappearance of **148c** was monitored by ^{1}H NMR spectroscopy (200 MHz). Concentration vs. time data (6 points) were obtained by normalizing the integrated intensity of the methyl singlet of toluene against the integrated intensity of the COOMe singlet of **148c** at 3.5 ppm for 2.6 half lifes. The resultant plot of ln{(A-x)/A} vs. t yielded an observed rate constant of (5.2 ± 0.2) x 10^{-4} s^{-1} (correlation coefficient = 0.9966) for the decrease in concentration of **148c**. After 3 hours at 50 °C the solution consisted of **152** (D analogue, 100%) and **154c** (D analogue, 100%). In another experiment, cyclopentadiene **148c** (0.0100 g, 0.0205 mmol) was dissolved in 0.5 mL of methanol. After 2 hours at 65 °C, the solvent was removed in vacuo and the residue was subjected to centrifugal chromatography (silica gel, 4:1 hexane/ethyl acetate) to give **152** (67%) and 1-adamantyl methyl ether (73%). The spectral data for 1-adamantyl methyl ether were identical to those of a sample prepared by another route.[193]

Rearrangement of 148d in methanol. Cyclopentadiene **148d** (0.0104 g, 0.0219 mmol) and toluene (1.75 μL, internal standard) were dissolved in methanol-d_4 (0.5 mL) and placed in a nmr tube. The tube was then heated at 100 °C and the rate of disappearance of **148d** was monitored by ^{1}H NMR spectroscopy (200 MHz). Concentration vs. time data (9 points) were obtained by normalizing the integrated intensity of the methyl singlet of toluene against the integrated intensity of the COOMe singlet of **148d** at 3.77 ppm for 2.5 half lifes. The resultant plot of ln{(A-x)/A} vs. t yielded an observed rate constant of (3.14 ± 0.08) x 10^{-4} s^{-1} (correlation coefficient = 0.9980) for the decrease in concentration of **148d**. After 4 hours at 50 °C the solution consisted of **152** (D analogue, 100%) and **154d** (D analogue, 100%). In another experiment, cyclopentadiene **148d** (.0200 g, .0420 mmol) was dissolved in methanol (1.0 mL) and sealed in a tube. The tube was heated at 100 °C for 4 hours. The solvent was removed in vacuo and the residue dissolved in chloroform-d. ^{1}H NMR spectroscopy revealed **152** (100%) and **154d** (100%). The solvent was removed in vacuo and the residue was subjected to centrifugal chromatography (silica gel, 3:2 hexane/ethyl acetate) to give **152** (71%) and **154d** (82%). The spectral data for p-methoxybenzyl methyl ether were identical to those of a sample prepared by another route.[194]

Rearrangement of 148e in methanol-d_4. Cyclopentadiene **148e** (0.030 g, 0.063 mmol) was dissolved in methanol-d_4 (0.5 mL). The solution was then degassed (three freeze-pump-thaw cycles), and sealed in an nmr tube. The tube was heated at 140 °C for 3 hours after which ^{1}H NMR spectroscopy (200 MHz) revealed **148e** (63%), **149e** (29%),

and **150e** (8%). The carbomethoxy and methylene signals from the ^{1}H NMR spectra of **149e** and **150e** could be identified in that solution. This mixture of isomers could not be separated by column chromatography.

4-Benzyl-1,2,3,5,5-pentakis(methoxycarbonyl)cyclopentadiene, (149e): ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.37 (s, 2 H, CH_2), 3.95 (s, 3 H, COOMe), 3.83 (s, 3 H, COOMe), 3.74 (s, 3 H, COOMe), 3.36 (s, 6 H, 2 COOMe).

3-Benzyl-1,2,4,5,5-pentakis(methoxycarbonyl)cyclopentadiene, (150e): ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.24 (s, 2 H, CH_2), 3.38 (s, 3 H, COOMe), 3.79 (s, 6 H, 2 COOMe), 3.77 (s, 3 H, COOMe), 3.51 (s, 3 H, COOMe).

Rearrangement of 148f in methanol-d_4. Cyclopentadiene **148f** (0.0262 g, 0.0707 mmol) was dissolved in methanol-d_4 (0.5 mL). The solution was then degassed (three freeze-pump-thaw cycles), and sealed in an nmr tube. The tube was heated at 140 °C for 35 minutes and ^{1}H NMR spectroscopy (90 MHz) revealed **148f** (62%) and **149g** (38%). After the nmr tube was heated for an additional period of 1 hour and 25 minutes, ^{1}H NMR spectroscopy (200 MHz) revealed **148f** (60%) and **149f** (40%). After the nmr tube was heated at 140 °C for an additional 1 hour period, ^{1}H NMR (200 MHz) spectroscopy revealed **148f** (57%) and **149f** (43%). These two isomers could not be separated by centrifugal chromatography. The volatiles were removed in vacuo and the residue dissolved in chloroform-*d*. Signals corresponding to the ^{1}H NMR and ^{13}C NMR spectra

of **149f** could be identified from this solution.

1,2,3,5,5-pentakis(Methoxycarbonyl)-4-methylcyclopentadiene, (149f): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.93 (s, 3 H, COOMe), 3.82 (s, 3 H, COOMe), 3.78 (s, 3 H, COOMe), 3.75 (s, 6 H, 2 COOMe), 2.42 (s, 3 H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.77, 164.11 (2), 161.90, 161.38, 158.47, 147.55, 132.08, 131.55, 74.51, 53.68 (2), 52.67 (overlap with isomer assumed), 52.28 (2), 14.58.

APPENDIX I

Observed Rate Constant Data

Plot of the first order rate of disappearance of **111e** in C_6D_6 at 20 °C (sample plot).

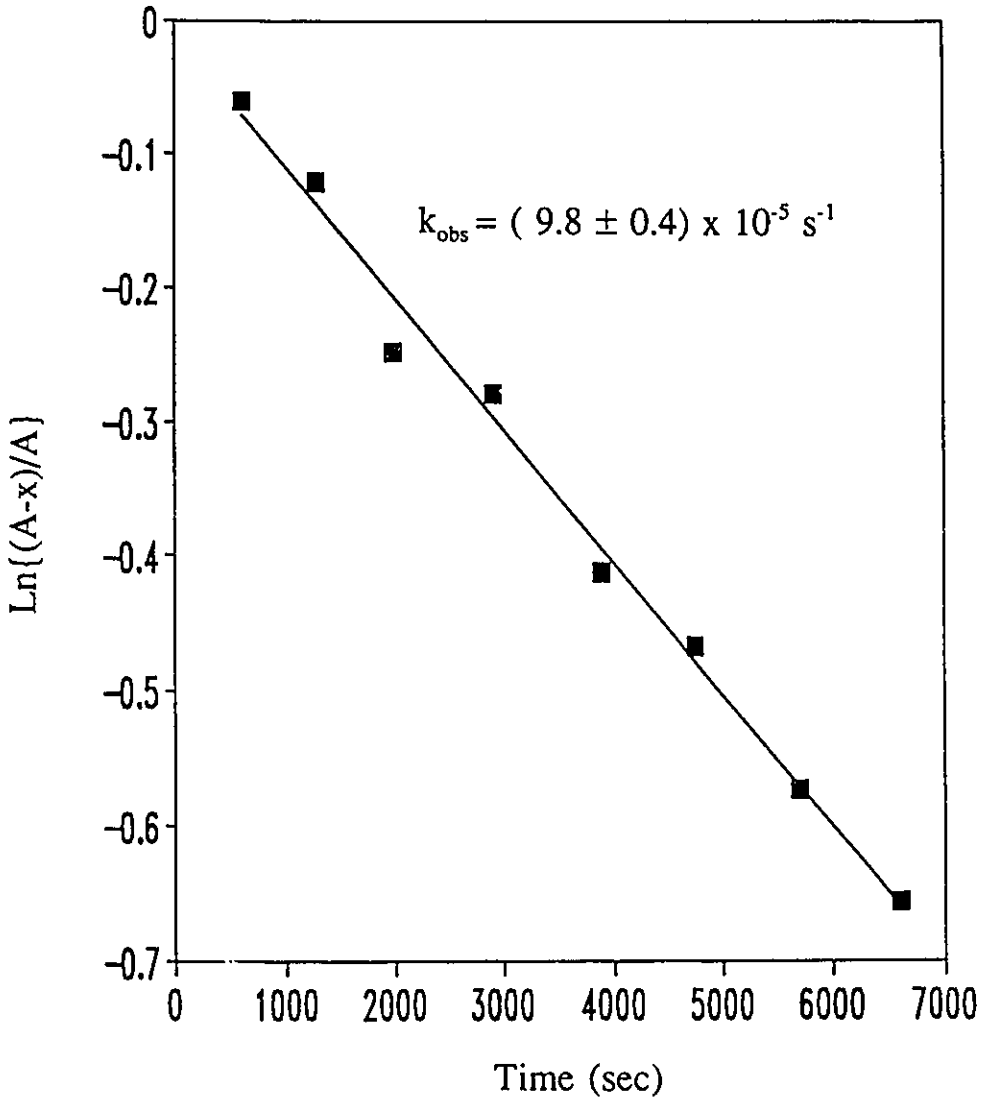


Table 27. Determination of k_{obs} for **111e** in C_6D_6 at 20 °C.

Time (sec)	Ln{(A-x)/A}
605	-0.061
1278	-0.121
1984	-0.248
2904	-0.279
3893	-0.412
4746	-0.467
5699	-0.574
6608	-0.657
Slope (m) = (-9.8 ± 0.4) x 10^{-5} s^{-1} Correlation Coefficient (R) = 0.9953	

Table 28. Determination of k_{obs} for **111c** in C_6D_6 with 2.5 equivalents of triethylenediamine at 35 °C.

Time (sec)	Ln {(A-x)/A}
987	0
1920	-0.069
5950	-0.246
7082	-0.280
8205	-0.374
9489	-0.465
10749	-0.562
11970	-0.562
13320	-0.667
14752	-0.752
16194	-0.836
18542	-1.050
21007	-1.200
24005	-1.451
m = (-6.2 ± 0.2) x 10^{-5} s^{-1} R = 0.9941	

Table 29. Determination of k_{obs} for **111d** in C_6D_6 at 35 °C.

Time (sec)	Ln{(A-x)/A}
5173	1.377
5941	1.422
6563	1.448
7771	1.542
8988	1.591
9641	1.576
10644	1.728
11576	1.781
12730	1.883
13808	1.907
15013	1.960
16346	1.981
17572	2.100
18865	2.167
20045	2.166
m = (5.6 ± 0.2) x 10^{-5} s^{-1} R = 0.9912	

Table 30. Determination of k_{obs} for **120b** in C_6D_6 at 90 °C.

Time (sec)	Ln{(A-x)/A}
1171	0
2034	-0.205
2835	-0.244
4635	-0.290
5559	-0.375
7667	-0.683
8900	-0.786
11934	-1.264
13219	-1.299
14900	-1.550
$m = (-1.10 \pm 0.05) \times 10^{-4}\ s^{-1}$ $R = 0.9905$	

Table 31. Determination of k_{obs} for **120e** in C_6D_6 at 130 °C.

Time (sec)	Ln{(A-x)/A}
2755	1.511
3369	1.578
3985	1.668
4581	1.771
5172	1.891
6380	2.011
$m = (1.45 \pm 0.08) \times 10^{-4}\ s^{-1}$ $R = 0.9939$	

Table 32. Determination of k_{obs} for **128c** in C_6D_6 at 90 °C.

Time (sec)	Ln{(A-x)/A}
0	0
1796	-0.113
3599	-0.276
5298	-0.474
6904	-0.625
8642	-0.788
10142	-0.890
11774	-1.248
13462	-1.382
15242	-1.555
$m = (-1.06 \pm .03) \times 10^{-4}\ s^{-1}$ $R = 0.9975$	

Table 33. Determination of k_{obs} for **128c** in acetone-d_6 at 90 °C.

Time (sec)	Ln{(A-x)/A}
0	0
608	-0.061
845	-0.205
909	-0.220
1476	-0.362
3212	-0.391
5055	-0.581
6899	-0.799
8707	-0.922
11071	-1.141
13035	-1.310
16027	-1.684
18097	-1.834
$m = (-9.7 \pm 0.3) \times 10^{-5} s^{-1}$ $R = 0.9954$	

Table 34. Determination of k_{obs} for **128c** in CD_3OD at 50 °C.

Time (sec)	Ln{(A-x)/A}
0	0
911	-0.368
1805	-0.793
2757	-1.280
3580	-1.648
m = (-4.7 ± 0.1) x 10^{-4} s^{-1} R = 0.9993	

Table 35. Determination of k_{obs} for **128d** in C_6D_6 at 90 °C.

Time (sec)	Ln{(A-x)/A}
0	0
975	-0.116
3463	-0.270
4393	-0.567
7388	-0.898
10001	-1.203
12602	-1.279
m = (-1.10 ± 0.09) x 10^{-4} s^{-1} R = 0.9850	

Table 36. Determination of k_{obs} for **128d** in acetone-d_6 at 90 °C.

Time (sec)	Ln{(A-x)/A}
608	0
1453	-0.172
2362	-0.218
3838	-0.385
5574	-0.490
7417	-0.795
9261	-0.890
11069	-0.944
13433	-1.097
20459	-1.889
m = (-8.9 ± 0.4) x 10^{-5} s^{-1} R = 0.9924	

Table 37. Determination of k_{obs} for **128e** in C_6D_6 at 60 °C.

Time (sec)	Ln{(A-x)/A}
0	0
922	-0.116
2019	-0.355
2998	-0.710
4021	-0.957
4957	-1.360
5958	-1.688
6964	-2.166
7939	-2.601
m = (-3.3 ± 0.2) x 10^{-4} s^{-1} R = 0.9898	

Table 38. Determination of k_{obs} for **128e** in C_6D_6 at 60 °C.

Time (sec)	Ln{(A-x)/A}
0	0
601	-0.160
1205	-0.352
2057	-0.632
2823	-0.825
3470	-1.239
3986	-1.439
4521	-1.633
5066	-1.789
5638	-2.135
$m = (-3.8 \pm 0.1) \times 10^{-4}$ s^{-1} $R = 0.9952$	

Table 39. Determination of k_{obs} for **128e** in acetone-d_6 at 60 °C.

Time (sec)	Ln{(A-x)/A}
0	0
465	-0.018
1096	-0.169
1771	-0.237
2704	-0.420
4497	-0.826
5361	-1.065
6376	-1.402
7403	-1.354
$m = (-2.1 \pm 0.1) \times 10^{-4}$ s^{-1} $R = 0.9990$	

Table 40. Determination of k_{obs} for **128f** in C_6D_6 at 90 °C.

Time (sec)	Ln{(A-x)/A}
975	0
3463	-0.558
4461	-0.752
5484	-1.130
6420	-1.418
7421	-1.797
8427	-2.037
9402	-2.294
$m = (-2.8 \pm 0.1) \times 10^{-4}$ s^{-1} $R = 0.9955$	

Table 41. Determination of k_{obs} for **128f** in acetone-d_6 at 90 °C.

Time (sec)	Ln{(A-x)/A}
608	0
1453	-0.134
2362	-0.441
3285	-0.641
4205	-0.962
5063	-1.187
5694	-1.378
6334	-1.537
6996	-1.714
7759	-1.980
$m = (-2.80 \pm 0.05) \times 10^{-4}$ s^{-1} $R = 0.9988$	

Table 42. Determination of k_{obs} for **148b** in CD_3OD at 40 °C.

Time (sec)	Ln{(A-x)/A}
0	0
271	-0.142
549	-0.286
831	-0.400
1462	-0.760
1805	-1.110
2199	-1.360
$m = (-6.2 \pm 0.3) \times 10^{-4}\ s^{-1}$ $R = 0.9935$	

Table 43. Determination of k_{obs} for **148c** in CD_3OD at 50 °C.

Time (sec)	Ln{(A-x)/A}
0	0
1162	-0.627
2002	-1.068
2634	-1.346
3053	-1.681
3443	-1.720
$m = (-5.2 \pm 0.2) \times 10^{-4}\ s^{-1}$ $R = 0.9966$	

Table 44. Determination of k_{obs} for **148d** in CD_3OD at 100 °C.

Time (sec)	Ln{(A-x)/A}
0	0
600	-0.072
1307	-0.315
2019	-0.545
2621	-0.733
3346	-1.026
4043	-1.184
4766	-1.448
5427	-1.631
$m = (-3.14 \pm 0.08) \times 10^{-4}\ s^{-1}$ $R = 0.9980$	

APPENDIX II

Calculation of the maximum value for k_r that would not give detectible Line Broadening

The width of a relevant NMR line has a broadening contribution, at half height ($\Delta\upsilon_{1/2}$) as follows:

$$\Delta\upsilon_{1/2} = (\tau_A\pi)^{-1} \quad (\tau_A = \text{the lifetime of a nucleus in environment A})$$

Therefore,

$$\Delta\upsilon_{1/2} = k_r/\pi \quad (k_r = \text{rate of rearrangement})$$

For detectible line broadening:

$$k_r > (\Delta\upsilon_{1/2})\pi$$

Since, $1.0 \text{ Hz} < \Delta\upsilon_{1/2} < 1.5 \text{ Hz}$

Then, $k_r > 3.1 - 4.7 \text{ s}^{-1}$

APPENDIX III

Infrared Spectra

General Experimental: Infrared (IR) spectra were recorded on a Bio-Rad FTS-40 spectrometer and are reported as λ_{max} in cm^{-1}. IR spectra were measured in CCl_4 on NaCl plates and absorptions are reported as weak (w), medium (m), or strong (s).

113b: IR ν (N-H) 3194 (w), (N-H) 3108 (w), 2990 (w), 2929 (w), 2823 (w), 1717 (m), 1679 (s), 1637 (w), 1457 (w), 1373 (m), 1337 (w), 1326 (w), 1261 (w), 1194 (w), 1103 (m) cm^{-1}.

113d: IR ν (N-H) 3195 (w), 2927 (s), 2908 (s), 2851 (m), 1735 (w), 1710 (m), 1676 (s), 1654 (w), 1452 (w), 1417 (w), 1377 (w) 1314 (w), 1242 (w), 1128 (w), 993 (w), 909 (m) cm^{-1}.

114b: IR ν 2997 (m), 2943 (m), 2889 (m), 2834 (m), 2817 (w), 2738 (w), 1574 (w), 1468 (m), 1454 (m), 1376 (m), 1303 (w), 1275 (w), 1233 (s), 1206 (s), 1196 (s), 1157 (s), 1121 (s), 1062 (s), 992 (m), 911 (s), 871 (w), 857 (w) cm^{-1}.

114e: IR ν 3001 (w), 2943 (w), 2913 (w), 2836 (w), 1614 (m), 1515 (s), 1464 (w), 1442 (w), 1376 (m), 1322 (w), 1303 (w), 1251 (s), 1188 (m), 1181 (m), 1152 (s), 1060 (m), 1041 (m), 969 (w), 909 (m), 833 (w) cm^{-1}.

118a: IR ν 2952 (w), (C=O) 1745 (m), (C=O) 1720 (m), 1556 (w), 1307 (w), 1238 (w), 1216 (m), 1174 (w), 1085 (w) cm^{-1}.

119a: IR ν 3033 (w), 2952 (w), 2841 (m), (C=O) 1723 (s), 1544 (m), 1495 (w), 1450 (m), 1304 (m), 1239 (s), 1193 (w), 1107 (s), 1068 (m), 1014 (w), 960 (w), 822 (w), 700 (m) cm^{-1}.

119d: IR ν 2913 (s), 2854 (m), (C=O) 1723 (s), 1485 (w), 1450 (m), 1420 (w), 1353 (w), 1308 (w), 1241 (s), 1205 (s), 1108 (m), 1035 (w), 1023 (m), 950 (w), 701 (w), 625 (w) cm^{-1}.

134c: IR ν 2965 (s), 2872 (w), 2843 (w), 1762 (s), (C=C) 1736 (s), (C=O) 1699 (s), 1473 (w), 1436 (m), 1365 (w), 1292 (w), 1253 (m), 1232 (s), 1171 (w) cm^{-1}.

134d: IR ν 2909 (s), 2852 (s), (C=C) 1732 (s), (C=O) 1701 (m), 1450 (m), 1437 (m), 1363 (w), 1310 (w), 1251 (m), 1203 (m), 1167 (m), 1034 (w), 909 (m) cm^{-1}.

128c: IR ν 2970 (s), 2956 (m), 1752 (s), (C=O) 1730 (s), (C=C-N=N) 1621 (m), 1458 (m), 1435 (m), 1370 (m), 1266 (s), 1219 (m), 1197 (w), 1114 (m), 1076 (m), 1056 (m), 982 (m), 925 (w), 668 (w), 551 (w) cm^{-1}.

128f: IR ν 3112 (w), 1752 (m), (C=O) 1732 (s), (C=C-N=N) 1609 (w), 1454 (m), 1304 (w), 1271 (s), 1073 (w), 1046 (w), 702 (w), 625 (w) cm^{-1}.

131b: IR ν (N-H) 3455 (m), (N-H) 3197 (w), 2960 (m), 2823 (w), (C=O) 1723 (s), 1463 (m), 1440 (m), 1304 (m), 1261 (s), 1245 (w), 1196 (m), 1096 (s), 1015 (s), 957 (w) cm^{-1}.

131c: IR ν (N-H) 3465 (m), (N-H) 3196 (w), 2987 (w), 2955 (m), 2918 (w), 2872 (w), (C=O) 1742 (s), 1444 (m), 1361 (m), 1266 (m), 1216 (m), 1201 (m), 1169 (m), 1106 (w), 1032 (m) cm^{-1}.

132c: IR ν 2984 (m), 2952 (m), 1742 (m), (C=O) 1722 (s), 1448 (m), 1351 (w), 1270 (w), 1224 (s), 1170 (m), 1110 (m), 1032 (w), 1020 (w), 951 (w) cm^{-1}.

132e: IR ν 3001 (w), 2954 (m), 2912 (w), 2837 (w), 1743 (m), (C=O) 1723 (s), 1614 (m), 1587 (w), 1515 (s), 1459 (m), 1424 (m), 1382 (w), 1295 (w), 1250 (s), 1227 (s), 1177 (m), 1040 (m), 1023 (m), 951 (w), 909 (m), 827 (w) cm^{-1}.

139b: IR ν 2996 (w), 2952 (m), 2932 (m), 2855 (w), (C=O) 1733 (s), 1456 (m), 1256 (s), 1194 (w), 1153 (w), 1109 (w), 1086 (m), 1005 (w), 921 (w) cm^{-1}.

135c: IR ν (N-H) 3467 (w), 2960 (m), 2929 (m), 2860 (w), (C=O) 1737 (s), 1717 (m), 1458 (w), 1374 (w), 1259 (w), 1230 (m), 1019 (w), 909 (s) cm^{-1}.

148e: IR ν 3033 (w), 2953 (m), 2846 (w), (C=O) 1748 (s), (C=C) 1625 (w), 1455 (m), 1436 (s), 1344 (m), 1287 (m), 1254 (s), 1222 (s), 1180 (m), 1145 (w), 1132 (w), 1067 (w), 999 (m), 702 (m) cm^{-1}.

148b: IR ν 3029 (w), 2953 (w), 2828 (w), (C=O) 1747 (s), (C=C) 1627 (w), 1436 (m), 1344 (w), 1247 (m), 1211 (m), 1171 (w), 1118 (w), 981 (w), 937 (w), 625 (w), 474 (w) cm^{-1}.

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