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NITROENAMINES

PREPARATION, STRUCTURE AND SYNTHETIC POTENTIAL*†

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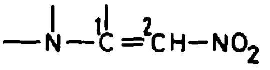
CONTENTS

1. INTRODUCTION

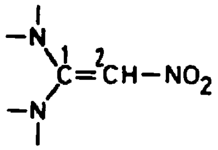
In a recent authoritative review on nitroaliphatic compounds,[1] Seebach *et al.* have concluded that this class of compounds may well turn out to be ideal intermediates in organic synthesis. The emphasis in that article has been on the potential usefulness of the doubly deprotonated species. In the present review, we plan to highlight the chemistry of one sub-group of nitroaliphatic compounds—the nitroenamines.

Olefins with an electron-donating amino group attached to one side of the double-bond, and the strongly electron-withdrawing nitro group at the other, have been known for a long time. However, such compounds have so far remained end-products in themselves. They have not, until recently, attracted the curiosity of theoretical chemists; nor have they been considered suitable starting materials for further synthetic manipulations. It is the purpose of the present article to collate the useful transformations which these substrates can be subjected to. For convenience, nitroenamines are subdivided into 1-amino-2-nitroethylenes (nitrovinylamines) (**1**), and 1,1-diamino-2-nitroethylenes (nitroketeneaminals) (**2**). Throughout this article, the numbering of the carbon atoms in enamines is as indicated in structures **1** and **2**; 1-H and 2-H refer to the H atoms attached to the C atoms 1 and 2 respectively.



$-\overset{|}{N}-\overset{|}{\overset{1}{C}}={}^{2}CH-NO_2$

1



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* Contribution No. 558 from Ciba-Geigy Research Centre.

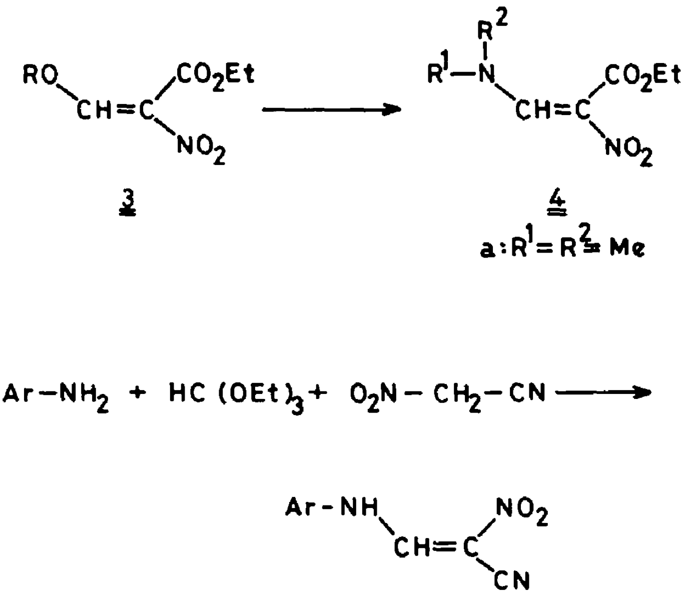
† This article is dedicated to Prof. T. R. Govindachari on the occasion of his 65th birthday.

2. SYNTHESIS OF NITROENAMINES

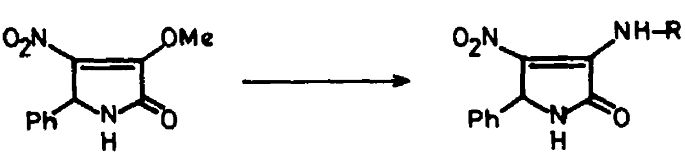
2.1 *Nitrovinylamines*

The methods available for the synthesis of nitrovinylamines prior to 1956 have already been critically reviewed,[2] and need not be further elaborated here. Only the newer synthetic approaches are discussed below.

2.1.1 *Reaction of amines with β-substituted nitrovinyl derivatives.* Nitroacetic esters readily form the alkoxy methylene compounds **3** when heated with alkyl orthoformates in the presence of acetic anhydride. The alkoxy group in **3** can be displaced by amines to form the nitrovinylamines **4**.[3,4] Nitroacetonitrile leads to 3-amino-2-nitroacrylonitriles by this procedure (Scheme 1).[4] Some nitrovinylamines have been generated from enol-ethers of α-nitroketones (Scheme 2).[5]



Scheme 1

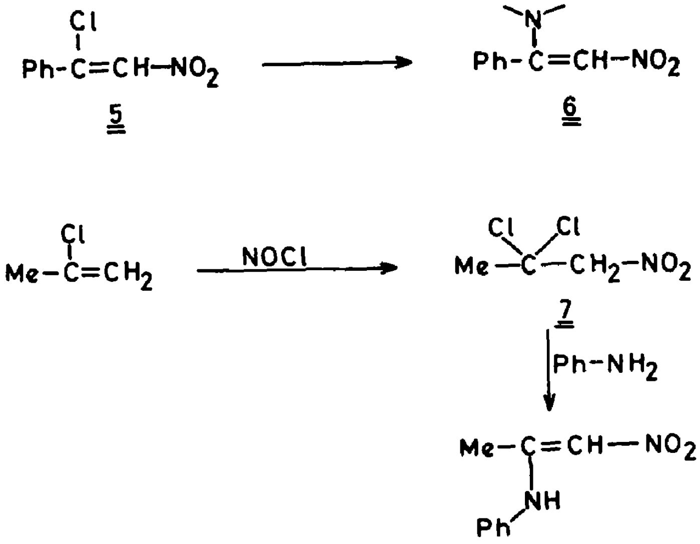


Scheme 2

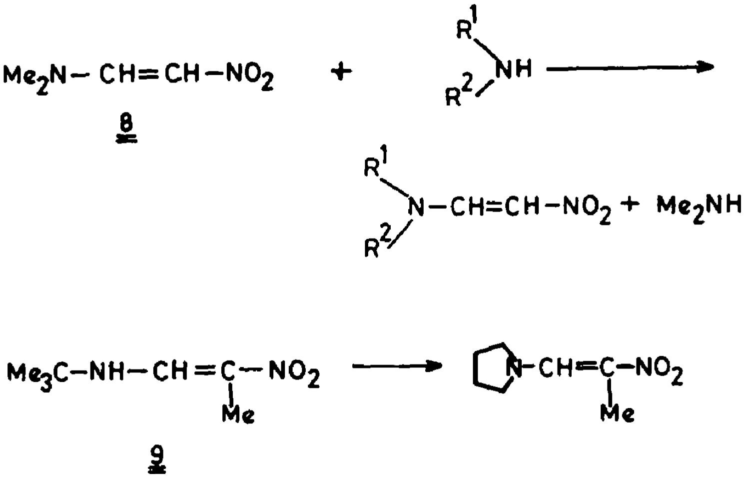
Treatment of the 1-chloro-2-nitroethylenes (**5**) with amines leads to the nitrovinylamines (**6**).[6] However, the difficulty of preparing the starting material makes this method of little preparative value. A related method is the one proceeding via the dichloronitroalkanes (**7**). These are produced when nitrosyl chloride is added to unsaturated compounds containing halogen. Treatment of **7** with aniline in ether leads to nitrovinylamines (Scheme 3).[7] Similar reactions with NOBr have also been reported.

Transamination too has been employed as a preparative procedure; 1-dimethylamino-2-nitroethylene (**8**) is a very useful reagent for this purpose (Scheme 4).[8] Feuer has subjected 1-t-butylamino-2-methyl-2-nitroethylene (**9**) to transamination; but the scope is limited by the poor reactivity of the substrate in this case (Scheme 4).[9]

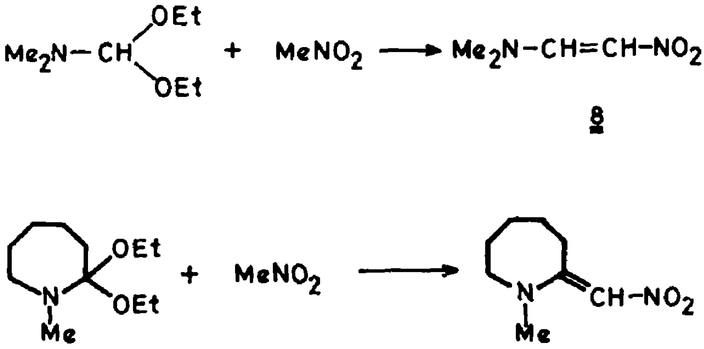
2.1.2 *Reaction of nitroalkanes with derivatives of amides or nitriles.* One of the most common methods of preparing nitrovinylamines is by reaction of amideacetals with nitromethane. Thus DMF diethylacetal gives 1-dimethylamino-2-nitroethylene (**8**) in 85% yield (Scheme 5).[10] Other nitroalkanes and substituted nitroalkanes have been similarly condensed with DMF acetal.[11] A



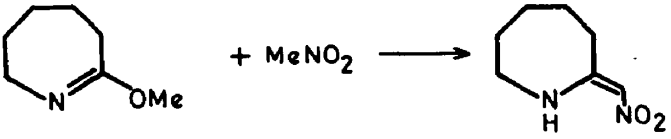
Scheme 3



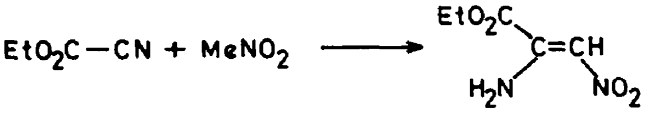
Scheme 4



Scheme 5



Scheme 6



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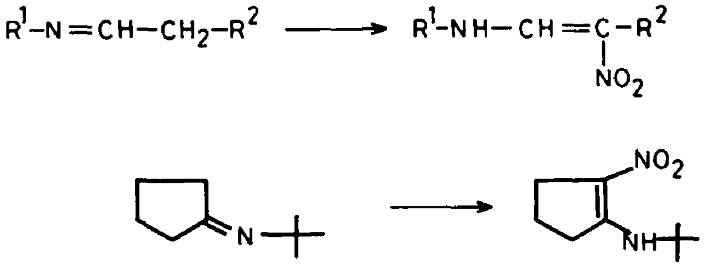
Scheme 7



Scheme 8

variety of substituted amideacetals have been reacted with nitromethane.[12] Lactamacetals also have been successfully used in this reaction (Scheme 5).[13]

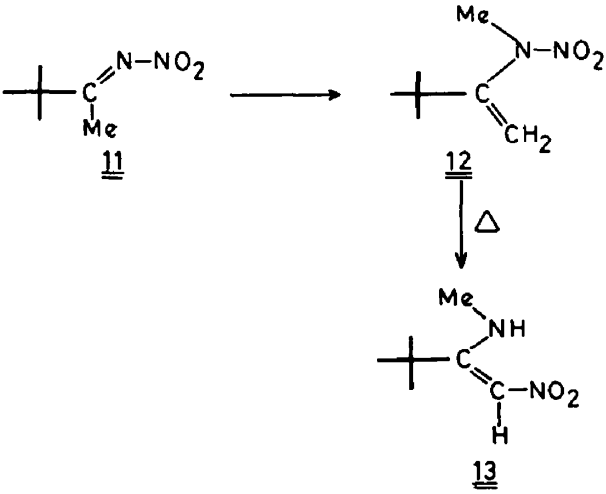
A simplified procedure in some cases makes use of the amide-dimethyl sulphate complex.[14,15]

Lactim ethers react easily with nitromethane to form the corresponding 2-nitromethylene derivatives.[16] An example is given in Scheme 6.

An interesting new reaction is the addition of nitromethane to the nitrile group of ethyl cyanoformate; this is brought about by a combination of Lewis acid and t-amine ($ZnCl_2$–Et_3N). The nitroenamine **10** is obtained in 18% yield (Scheme 7).[17]

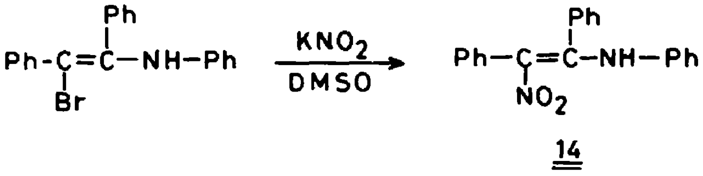
2.1.3 *Nitration of imines.* Feuer has discovered that aldimines can be nitrated by alkyl nitrate (e.g. n-propyl nitrate) in liquid ammonia in presence of potassium amide to give the nitroenamines in about 50% yields (Scheme 8).[18] The reaction has been extended to alicyclic ketimines (Scheme 8).[19]

2.1.4 *Rearrangement of* N-*nitroenamines.* Recently, the thermal rearrangement of the N-methyl-N-nitroenamine (**12**) has been shown to lead to the C-nitro derivative (**13**). The compound **12**



is itself obtained by methylation of pinacolone nitrimine (**11**) with methyl iodide in presence of sodium methoxide.[20]

2.1.5 *From β-halogenoenamines.* The nucleophilic displacement of a halide from a 2-halogenoenamine by nitrite in DMSO to form the nitroenamine **14** in 27% yield has been reported (Scheme 9).[21]

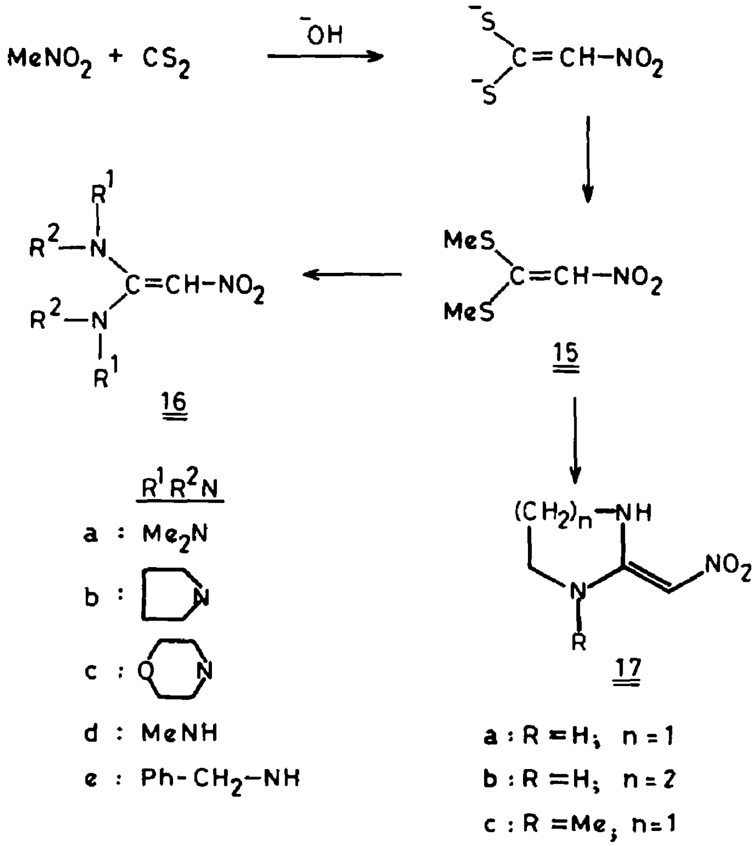


Scheme 9

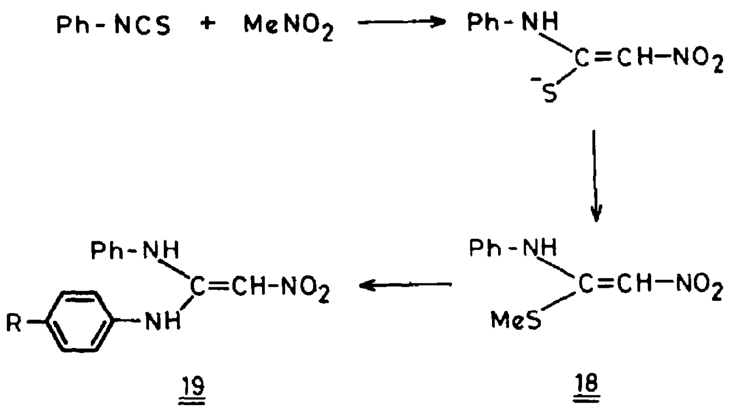
2.2 *Nitroketeneaminals*

The general structure of nitroketeneaminals (**2**) incorporates four easily identifiable fragments: two amines, a nitromethane moiety, and a one-carbon unit bridging these three. These four fragments have been assembled in different sequences in the following synthetic routes to this class of compounds.

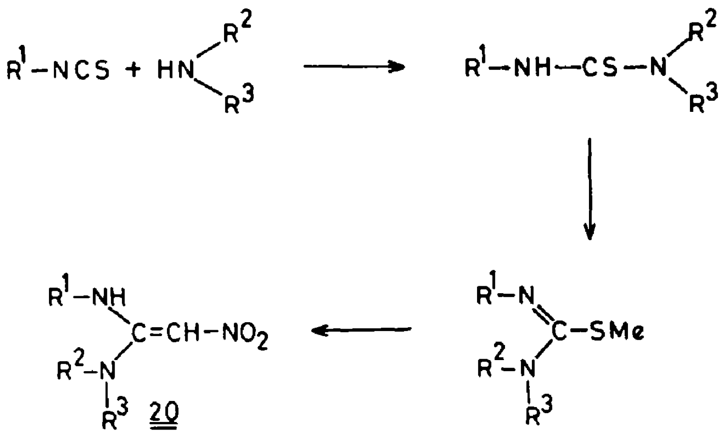
2.2.1. Symmetrical nitroketeneaminals **16** have been obtained by reacting two moles of an amine with one of 1,1-bis methyl-mercapto-2-nitroethylene (**15**). This reagent itself is prepared by condensing nitromethane with carbon disulphide to form the nitrodithioacetic acid salt, followed by methylation (Scheme 10). The reagent **15** can also be reacted with one mole of a suitable diamine to form cyclic nitroketeneaminals (**17**) (Scheme 10).[22,23]



Scheme 10



Scheme 11

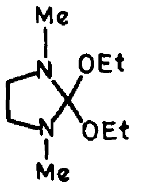


Scheme 12

2.2.2. Nitromethane can be reacted with phenyl isothiocyanate in presence of sodium hydride and then methylated to give **18**.[22] Unsymmetrical nitroketeneaminals (**19**) can be synthesised from **18** by reaction with one mole of a different amine (Scheme 11).[24]

2.2.3. Nitromethane enters the sequence at the last step in the following synthesis, which provides access to unsymmetrical nitroketaneaminals **20**. Here a thiourea is S-alkylated and this S-methyl derivative is condensed with nitromethane (Scheme 12).[23]

To the same general type belongs the condensation of nitromethane with urea acetals. Both **21** and **22** have been used in this reaction.[10]



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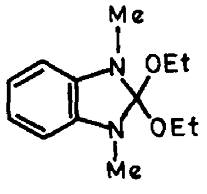
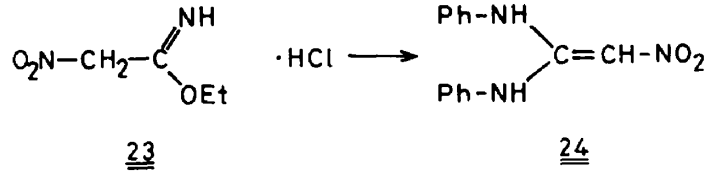


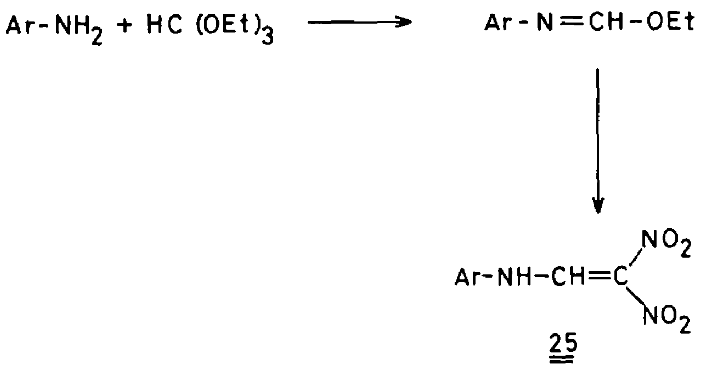
22

2.2.4. Finally, nitroacetimidate (**23**) obtained from nitroacetonitrile is reported to give the nitroketeneaminal (**24**) with excess aniline.[25]

2.3 *Dinitroenamines*

We conclude this section with a brief reference to a special group of compounds—the dinitroenamines. 1-Arylamino-2,2-dinitroethylenes (**25**) have recently been prepared by reacting a





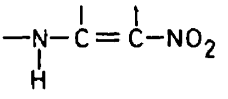
Scheme 13

primary aromatic amine with triethyl orthoformate, followed by treatment with dinitromethane (Scheme 13).[26]

3. NMR STUDIES: STRUCTURE OF NITROENAMINES AND THEIR ANTICIPATED REACTIVITY

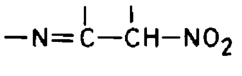
3.1 *Tautomerism*

Nitroenamines (**26**) in which the amino nitrogen carries a hydrogen atom can exist in three tautomeric forms (**a**, **b**, **c**). So far, there has been no evidence for the presence of the nitronic acid tautomer (**26c**) in any nitroenamine. The data available till now had seemed quite conclusive that simple nitroenamines exist only in the tautomeric form **26a** and never as the imino tautomer **26b**. This



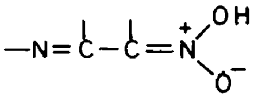
$-\underset{H}{N}-\overset{|}{C}=\overset{|}{C}-NO_2$

26 a



$-N=\overset{|}{C}-\overset{|}{C}H-NO_2$

26b

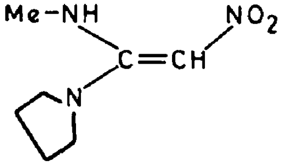


$-N=\overset{|}{C}-\overset{|}{C}=\overset{+}{N}(OH)O^-$

26 c

included earlier IR evidence[2] as well as many recent NMR studies.[18,23] These NMR data provide evidence for two structural features: first is the fact that there is no signal corresponding to a saturated methine (or methylene) as required by structure **26b**; secondly, the location of a H atom on nitrogen is proved in the nitroketeneaminals **27** and **16e** by the fact that they exhibit doublets for the N–CH_3 and N–CH_2 respectively, collapsing to singlets on addition of D_2O.

However, recently the isolation of imino tautomers (**29a** and **b**) has been reported by Büchi and Wüest.[20] Thermal rearrangement of the N-nitro compounds (**28**) gave the C-nitro isomers (**29**). In the



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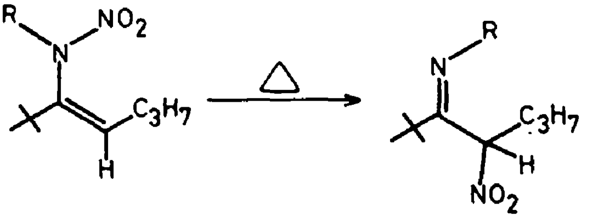


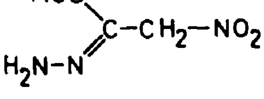
28 29

a : R = H
b : R = Me

UV absorption spectrum, **29a** showed only a low-intensity band at 345 nm (ε 290), ascribable to the presence of approximately 2 % of the enamine tautomer. In the NMR spectrum, the methine signals of **29a** and **29b** were seen at 5.25 and 5.00 ppm respectively. However, as mentioned earlier (Section 2.1.4), rearrangement of the unsubstituted compound **12** gave only the enamine tautomer **13** (UV: λ_{max} 343 nm, ε 16000; NMR: 6.63 ppm).

It appears that the enamine form represents the thermodynamically more stable tautomer; this is the reason why nitroenamines are the end-products in the alkyl nitrate nitration of aldimines in liquid ammonia in presence of potassium amide and ammonium chloride.[18]

1-Hydrazino-2-nitroethylenes seem to exist preferentially in the hydrazone form. Thus **30** (prepared from **15** by reaction with one mole of hydrazine) in $CDCl_3$/DMSO-d_6 shows a two-proton singlet at 5.26 ppm.[27] Interestingly, the amidrazone (**32**) shows the presence of both tautomers [singlets at 6.28 (CH) (**31**) and 5.24 ppm (CH_2) (**32**)] in solution.[27]



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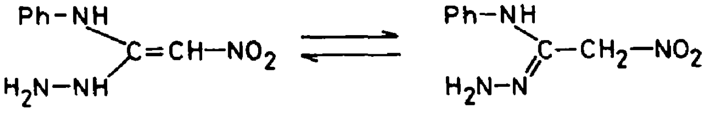
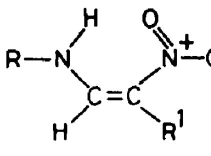
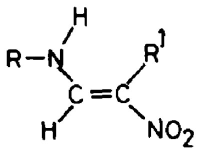


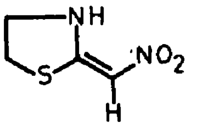
31 32

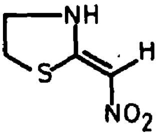
3.2 *Configuration about the double-bond*

Nitrovinylamines (**33**), possessing an NH, seem to prefer the *Z* configuration in non-polar solvents, the stabilising force being the formation of an intramolecular H-bond with the NO_2. As the solvent polarity increases, the amount of E-isomer also increases. Identification of the *E*- and *Z*-isomers is based on the chemical shift of 1-H; there is a marked deshielding of this proton in the *E*-isomer compared to the *Z*-isomer. Thus in **33** (R = t – Bu; R^1 = Me), the $\delta_{1\text{-H}}$ values are 7.09 (Z) and 8.41 (E).[18] NOE experiments have confirmed the H-bonded *E*-form for **18**.[28,29]


33 Z

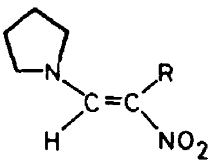

33 E


34 E

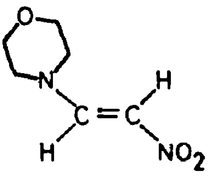

34 Z

The thiazolidine derivative (**34**) occupies a special position as revealed by our NMR studies.[30] In $CDCl_3$ only the *E*-form[29] is observed and in DMSO-d_6, only the *Z*-form; in mixtures of the two solvents, two sets of signals can be seen in both ^1H and ^{13}C spectra. The interesting feature is that in the presumed *Z*-form, the 2-H resonates at about 7.2 ppm, which corresponds to the chemical shift of this proton in 1-nitropropene.[31] This means that in this particular form there is very little overlap of the nitrogen lone-pair with the π-system. We suspect that due to the constraints imposed by being present in a 5-membered sulphur containing ring, the nitrogen exists in the pyramidal form, once the planar *cis*-stabilising H-bond is broken.

Regarding the nitroenamines with no H-atom on the nitrogen, i.e. those nitroenamines which do not derive any stabilization by H-bonding, consensus appears to be that they exist in the *E*-configuration.[9,32] This conclusion is based, in the case of **35** on the chemical shift of 1-H (8.45 ppm)


35 : R=Me

36 : R=H

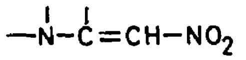

37

which is deshielded by the *cis*-NO_2.[9] This preference for the *E*-configuration is believed to be a consequence of the tendency to minimize steric crowding. In **8**, **36** and **37**, the coupling constant between the two vicinal olefinic protons is of the order of 10.5 Hz.[33] Although this is suggestive of a *trans*-configuration, it is not a reliable criterion, since, as Prof. Büchi has pointed out,[34] the C-1–C-2 double-bond character would be drastically less than in normal olefins. However, the chemical shift of 1-H in these three compounds (8.14, 8.28 and 8.17 respectively)[33] does seem to indicate that such compounds too exist in the *E*-configuration.

The low barrier to rotation around C-1–C-2 in these compounds (see Section 3.5) precludes isolation of pure *E*- and *Z*-forms of nitroenamines; the existence of such isomers has been inferred so far only from NMR data.

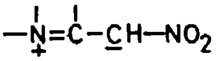
3.3 *Prediction of reactivity from chemical shifts*

Three possible canonical forms (**1a**, **1b**, **1c**) can be written for nitrovinylamines. Nucleophilic activity at C-2, and hence enaminic nature, would be significant if structure **1b** is predominant. On the other hand, if structure **1c** more nearly represents the correct picture, then these compounds should be regarded as "push–pull" ethylenes; their reactivity pattern would then be completely different. Therefore, in trying to predict the reactivity of such compounds, an attempt has to be made to evaluate the relative importance of **1b** and **1c** to the structure.



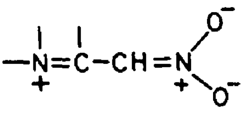
$-\overset{|}{N}-\overset{|}{C}=CH-NO_2$

1a



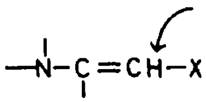
$-\underset{+}{\overset{|}{N}}=\overset{|}{C}-\underline{C}H-NO_2$

1b



1c

3.3.1 ^1H NMR *spectral data*. It has been well recognized that as the electron-density at C-2 in enamines increases, the proton attached to it moves upfield in NMR.[35,36] This will correspond to an increase in the enaminic reactivity. This has been confirmed very neatly in simple cyclic enamines, the predicted order of reactivity coinciding well with the observed order in competition experiments.[37] The basis for the prediction of the degree of enaminic reactivity in nitroenamines by NMR would have to be the comparison of the chemical shift of 2-H in such compounds with those in other types of enamines. In effect, one would have to assume that in molecules represented by structure **38** (X being alkyl, CO, CN, NO_2, etc. the amine being kept unaltered), the relative chemical shift value of 2-H would also reflect their relative efficacy as enamines. Although intuitively this assumption appears valid, it has not yet been verified by actual experiment. Table 1 compares the $\delta_{2\text{-H}}$ values of the nitrovinylamines **8**, **36** and **37** with those of the enaminoester **40** and the enaminoketone **41**.[33] An obvious conclusion from this is that nitrovinylamines would be way down the scale in terms of enaminic reactivity.



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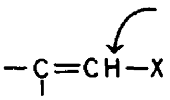

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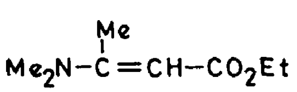
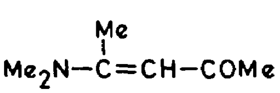


$Me_2N-\overset{Me}{\overset{|}{C}}=CH-CO_2Et$

40



$Me_2N-\overset{Me}{\overset{|}{C}}=CH-COMe$

41

$Me_2N-CH=CH-CO_2Et$

42

We have earlier pointed out[23] that a comparison of the δ values of the indicated proton in the pairs of compounds represented by structures **38** and **39** might be more pertinent in assessing the enaminic nature of the molecule **38**. The upfield shift of the 2-H consequent on introduction of the amine group would provide an indirect measure of the electron-density localised on C-2. One can then grade the

Table 1. ^{1}H and ^{13}C NMR data for enamines. (Reproduced from Ref. 33 with the kind permission of the publishers)

Compound No.	C-2				C-1			$J_{H_1H_2}$ (Hz)	N-CH$_3$ or N-CH$_2$	
	δ_C	corrected δ_C	δ_H	J_{CH} (Hz)	δ_C	δ_H	J_{CH}(Hz)		δ_C	δ_H
37	112.8	112.8	6.85	186.8	149.4	8.17	169.1	10.8	49.2 ($W_{\frac{1}{2}}$ *ca*.68 Hz)	*ca*. 3.36 (overlapping m)
8	111.4	111.4	6.64	188.3	151.0	8.14	172.0	10.5	45.0, 37.5	3.22, 2.90
36	111.1	111.1	6.58	186.8	146.4	8.28	169.1	10.5	52.3, 47.0	3.65, 3.23
16c	102.6	106.2	6.23	185.3	161.4	-	-	-	49.7	3.33
16b	101.6	105.2	6.42	185.3	155.1	-	-	-	49.4	3.50
16a	100.9	104.5	6.30	186	162.0	-	-	-	39.3	2.97
41	93.7	91.9	5.03	151.5	160.3	-	-	-	38.2	2.97
40	84.0	83.7	4.53	152	160.6	-	-	-	38.7	2.92

Table 2. Chemical shift values of 2-H in species 38 and 39 (Reproduced from Ref. 23 with the kind permission of the publishers)

X	δ_H in **39**	δ_H in **38**	$\Delta\delta$
Alkyl	5.73[a]	-	1.31[k]
	5.57[b]	4.17 to 4.50[c]	1.40 to 1.07
CN	5.22[d]	3.77, 4.10[e]	1.45, 1.12
CO_2R	5.76[f]	4.53[g]	1.23
COR	5.97[h]	4.83[i]	1.14
NO_2	7.00[j]	6.64	0.36

[a] in propene : ref. 84

[b] in cyclohexene : ref. 84

[c] in enamines from cyclohexanone : ref. 36

[d] in *trans*-crotononitrile : ref. 84

[e] in *cis*, *trans* mixture of β-aminocrotononitrile : Ref. 85

[f] in methyl *trans*-crotonate : ref. 84

[g] in methyl *trans*-β-aminocrotonate : ref. 86

[h] in mesityl oxide : ref. 84

[i] in 2-methylaminopent-2-en-4-one : ref. 84

[j] in 1-nitropropene : ref. 31

[k] Calculated value : ref. 87

different pairs of compounds according to the $\Delta\delta$ values, $\Delta\delta$ being defined as follows:

$$\Delta\delta = \delta_{2\text{-H}}\ (\text{olefin}) - \delta_{2\text{-H}}\ (\text{enamine})$$

Table 2 presents the $\delta_{2\text{-H}}$ values for some of the common substituted enamines and their parent olefins. On the basis of these figures, it is obvious that nitrovinylamines ($\Delta\delta = 0.36$) would be very poor enamines indeed; they should be more appropriately regarded as "push–pull" ethylenes.

However, if a second amine is now introduced in conjugation with the nitrovinyl system to form nitroketeneaminals (**2**), there seems to be a slightly greater electron-availability at C-2. Table 1 lists the $\delta_{2\text{-H}}$ values of the three symmetrical nitroketeneaminals (**16a**, **16b** and **16c**).[33] Comparison of 1,1-bis-dimethylamino-2-nitroethylene (**16a**) ($\delta_{2\text{-H}}$, 6.30 ppm) with the parent 1-nitropropene results in a $\Delta\delta$ value of 0.70. One would predict then that such nitroketeneaminals would function as enamines, but still much weaker than the enaminones.[23] EH calculations by Summerville and Hoffmann appear to support these conclusions.[23]

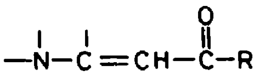
3.3.2 ^{13}C NMR *spectral data.* In Table 1, relevant ^{13}C NMR spectral values of the nitrovinylamines **8**, **36** and **37**, the nitroketeneaminals **16a**, **b** and **c**, the enaminoester **40** and the enaminoketone **41** have been compared.[33] Like the 2-H chemical shifts, the carbon C-2 shifts also indicate greater enamine activity for the nitroketeneaminals compared with the nitrovinylamines. Gratifyingly, the $\delta_{2\text{-H}}$ values and the $\delta_{\text{C-2}}$ values for all the eight compounds listed in the Table fit nicely into the linear regression equation:[33]

$$\delta_{\text{C-2}} = 12.26\,\delta_{2\text{-H}} + 28.87$$

3.4 *Barrier to rotation around* N–C-1

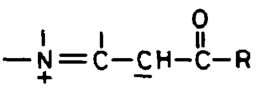
Mannschreck observed in 1967 that the two Me groups attached to the nitrogen in the nitrovinylamine **8** were nonequivalent.[32] In $CDBr_3$ solution, coalescence was observed at 52°, leading to $\Delta G^{\ddagger}_{c}$ 16.5 kcal mol^{-1}.[38] We have found[33] non-equivalence of the two Me's of **8** in both ^{1}H ($^{\delta}$3.22 and 2.90 ppm) and ^{13}C ($^{\delta}$45.0 and 37.5 ppm) spectra in $CDCl_3$ (Table 1). The picture was similar in DMSO-d_6 solution. There was no signal-duplication for other carbons or protons, thereby ruling out the presence of *E*/*Z*-isomers. Hence the phenomenon must be ascribed to a barrier to free rotation around the N–C-1 bond. Similarly, in the pyrrolidino compound (**36**), the N–CH_2 groups give rise to two signals in both ^{1}H and ^{13}C spectra, indicating considerable double-bond character for N–C-1. However, in the morpholino compound (**37**), coalescence starts taking place even at probe temperature, indicating decreased conjugation.

Non-equivalence of N-Me's is not seen at 30° in the nitroketeneaminal (**16a**).[33] This could be explained by invoking amidine-resonance which will cause decreased double-bond character around N-C-1.



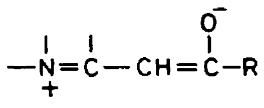
$$-\overset{|}{N}-\overset{|}{C}=CH-\overset{O}{\overset{\|}{C}}-R$$

43a



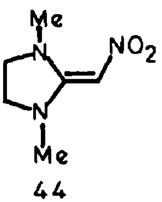
$$-\underset{+}{\overset{|}{N}}=\overset{|}{C}-\underset{-}{C}H-\overset{O}{\overset{\|}{C}}-R$$

43b



$$-\underset{+}{\overset{|}{N}}=\overset{|}{C}-CH=\overset{O^-}{\overset{|}{C}}-R$$

43c



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But the most interesting aspect is the lack of non-equivalence of the N-Me groups of the enaminoester **40** and ketone **41** at probe temperature (Table 1).[33] Mannschreck has reported non-equivalence of the N-Me groups of dimethylaminoacrylate (**42**) in $CHCl_3$ at $-40°$ ($\delta_{2\text{-H}}$ 3.1 and 2.8), but coalescing at 0°; the $\Delta G_c^{\ddagger}$ for this is 13.9 kcal mol^{-1}.[32] It thus transpires that there is greater N–C-1 double-bond character in the nitrovinylamine **8** than in the enaminoester **42**.

This is a paradox since it is known from chemical reactivity, as well as from $\delta_{2\text{-H}}$ values, that enaminoesters are much better enamines than nitrovinylamines. This apparent anomaly has been explained[33] by stressing the importance of charge separated structure **1c** for the nitrovinylamine and of **43a** and **43b**, but not **43c** for the enaminocarbonyl derivatives. This situation will therefore lead to **43** being a better enamine than **1**, although **1** having a greater double-bond character around N–C-1 than **43**, is the better "push–pull" ethylene.

3.5 *Barrier to rotation around* C-1–C-2

The barrier to rotation around C-1–C-2 in the nitroketeneaminal (**44**) is very low, since even at $-63°$, only one signal is observed for N–Me and one for CH_2 in the ^1H NMR spectrum.[39] This can be compared with the spectrum of **15** in which the S–Me signal splits into two at just below 0°. The low barrier to rotation around C-1–C-2 in **44** is in accord with the previous results on the relatively high N–C-1 rotation barriers in nitroenamines.

4. SYNTHETIC POTENTIAL OF NITROENAMINES

A systematic effort to explore the chemical transformations of nitroenamines has been launched only in the last few years. The reactions of nitroenamines can be discussed under four headings:

1. Enaminic reactions
2. Reactions ascribable to the "push–pull" nature of nitroenamines
3. Reactions with nucleophiles
4. Reductive transformations.

The fact that nitroenamines can take part in such diverse reactions, makes them useful intermediates in organic synthesis.

4.1 *Enaminic reactions*

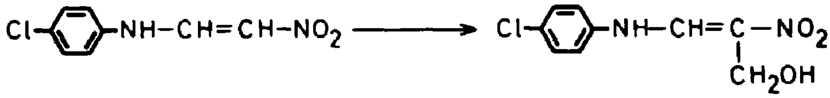
The NMR data presented in the previous section suggest that nitroketeneaminals may possess moderate enaminic reactivity; nitrovinylamines on the other hand, are likely to react only with the more powerful electrophilic reagents. Actual experiments do in fact confirm these predictions. The synthetically useful "enaminic" reactions undergone by nitroenamines are grouped under four broad reaction-types.

4.1.1 *Reaction with electrophiles.* As Stork first pointed out in his classical paper,[40] enamines can react at C-2 with various electrophiles according to Scheme 14. Before we started work in this area, there had been only one published report on the reaction of a nitroenamine with an electrophile.[41] In that paper, the reaction of the nitroenamine (**45**) with formaldehyde to produce the carbinol (**46**) was described. The cyclic products (**47**) were formed if the nitroenamine was reacted with formaldehyde and a primary amine.

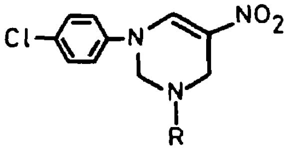
$$-\overset{|}{N}-\overset{|}{C}=CH- \quad + E \longrightarrow -\overset{|}{N}-\overset{|}{C}=\overset{\overset{E}{|}}{C}-$$

Scheme 14

However, there was obviously a need for probing the reaction of nitroenamines with an electrophile that would discriminate between good, moderate and weak enamines. Alkyl and aryl isothiocyanates appeared to us to be a suitable choice for this purpose.[23] The nitrovinylamine **8** did not react with these reagents. But the nitroketeneaminals proved more reactive, as anticipated. Thus **16a** reacted with phenyl, methyl or allyl isothiocyanate to give the adduct (**48**). The bis-pyrrolidino derivative (**16b**) was equally reactive, but the bis-morpholino compound (**16c**) was recovered unchanged after treatment with phenyl isothiocyanate. Nitroketeneaminals in which the two



45 **46**



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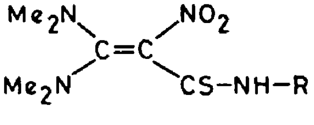

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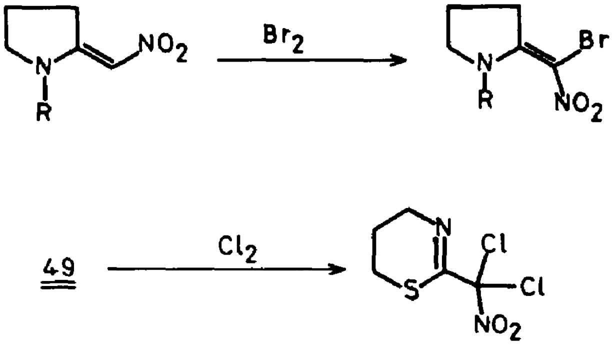
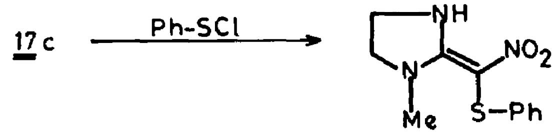
nitrogens carry only one substituent each, seem to be less reactive than the tetrasubstituted analogs. Thus, 1,1-bis-methylamino-2-nitroethylene (**16d**) reacted with phenyl and benzyl isothiocyanates, but not with methyl isothiocyanate. The cyclic analogs (**17a** and **b**) did not react with alkyl or aryl isothiocyanates.[23]

The reaction of nitroenamines with other electrophilic reagents has been reported in several recent patents. For example, **49** reacts with acid anhydrides to give the C-acyl derivative **50**;[42] with DMF acetal, the same nitroenamine gives **51**.[43] With acyl and sulphonyl isocyanates, **52** and **53** are obtained.[44,45] With halogens, mono and bis halogenation have been reported (Scheme 15).[46,47] Phenyl sulphenyl chloride reacts with nitroenamines to form the phenylmercapto compound as shown in Scheme 16.[48]

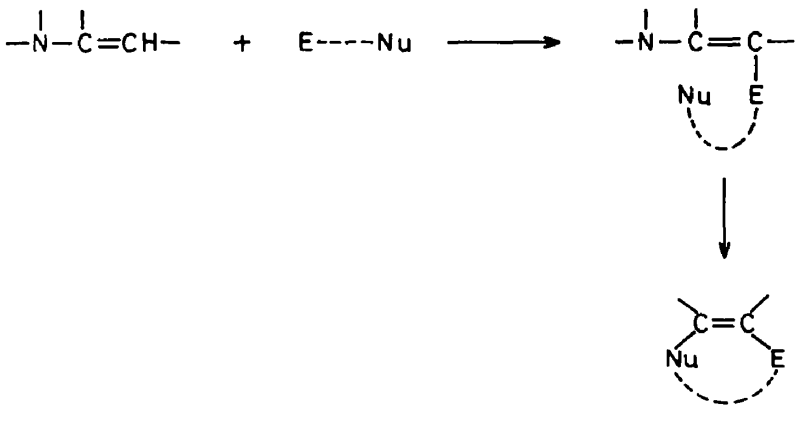


Scheme 15



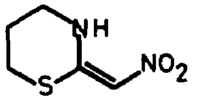
Scheme 16

4.1.2. Heterocyclic ring-closure can be effected by reaction at C-2 of an enamine with an electrophile, followed by displacement of the amine at C-1 by a nucleophile located in the newly introduced chain as in Scheme 17. This principle is exemplified in the novel, albeit serendipitous, synthesis of thiophenes from enamines, described by us a few years back.[49] When nitroenamines were used instead of simple enamines in this reaction, we obtained 3-nitrothiophenes. The electrophile was again an isothiocyanate, the first step thus leading to adducts such as **48**. Condensation of these with



Scheme 17

α-haloketones produced the 3-nitrothiophenes (**54**); obviously, here S-alkylation is followed by attack by the active methylene on C-1 of the nitroenamine system, displacing a (protonated) dimethylamino group (Scheme 18).[50,51] If the α-haloketone is replaced by bromonitromethane as the active methylene component, 2,4-dinitrothiophenes (**55**) result (Scheme 18).[52]



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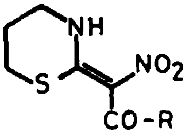

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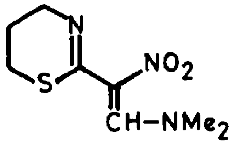

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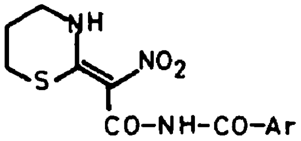

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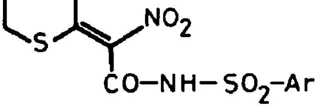

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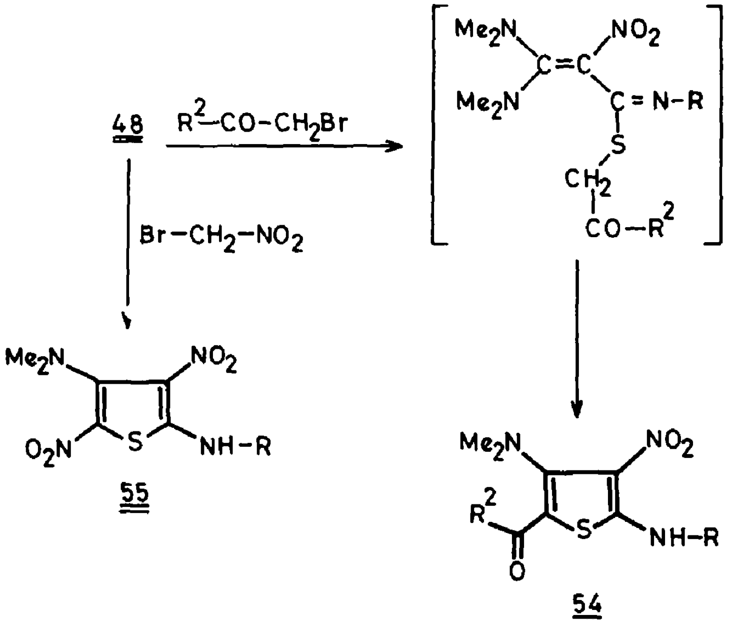
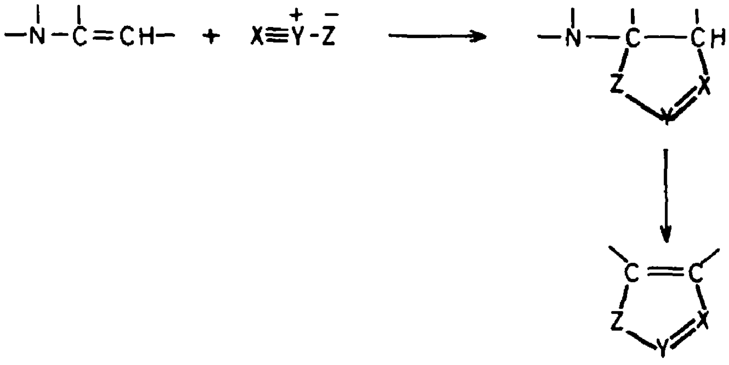
4.1.3 *Cycloaddition with dipolar reagents.* The general reaction of enamines with dipolar reagents is described in Scheme 19. Nitrilimines, generated from α-chlorohydrazones, have been reacted with 1-morpholino-2-nitroethylene (**37**) to give 4-nitropyrazoles (**56**) in low yields.[53] Similarly, nitrileoxides react with nitroketeneaminals to form 5-amino-4-nitroisoxazoles, also in low yields (Scheme 20).[50]

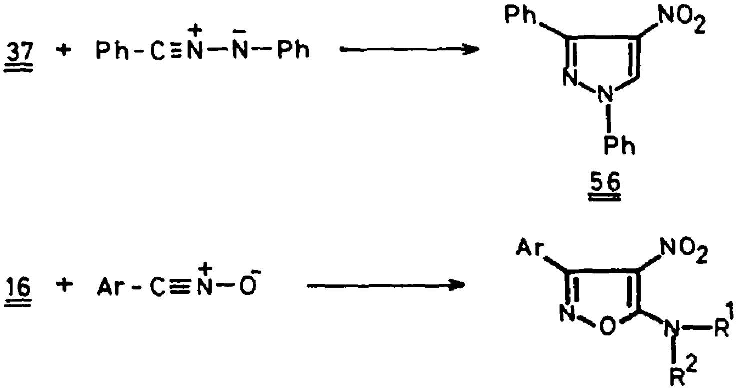
Good yields of 1-aryl-4-nitrotriazoles are obtained on cycloaddition of 1-morpholino-2-nitroethylene (**37**) with aryl azides (Scheme 21).[53,54] The reaction of nitroenamines with sulphonylazides is very interesting. Italian workers have reported[53,54] that nitrotriazoles (**57**) are formed when **37** is condensed with tosylazide (Scheme 21); morpholine and the tosyl group get eliminated in this reaction. However, the reaction takes a different course when nitroketeneaminals carrying at least one NH react with *p*-chlorobenzenesulphonyl azide; cycloaddition seems to be



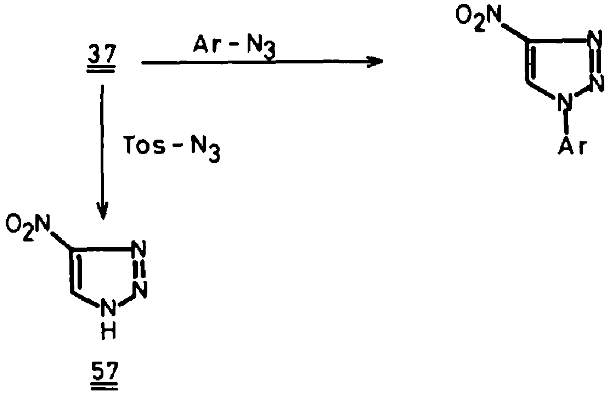
Scheme 18



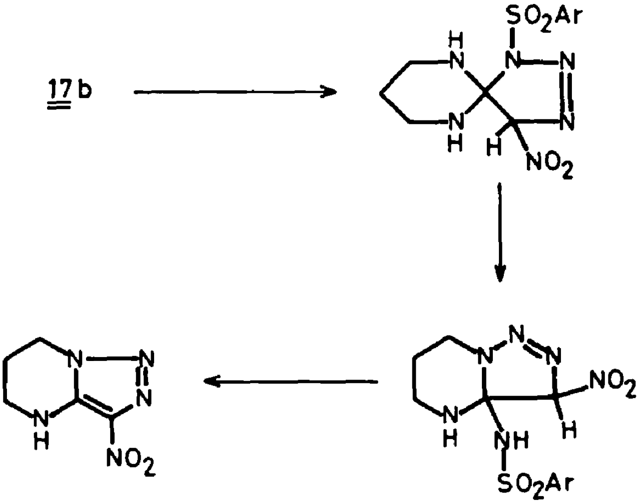
Scheme 19



Scheme 20



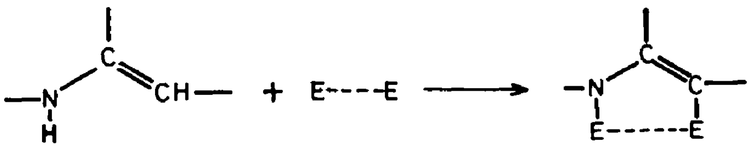
Scheme 21



Scheme 22

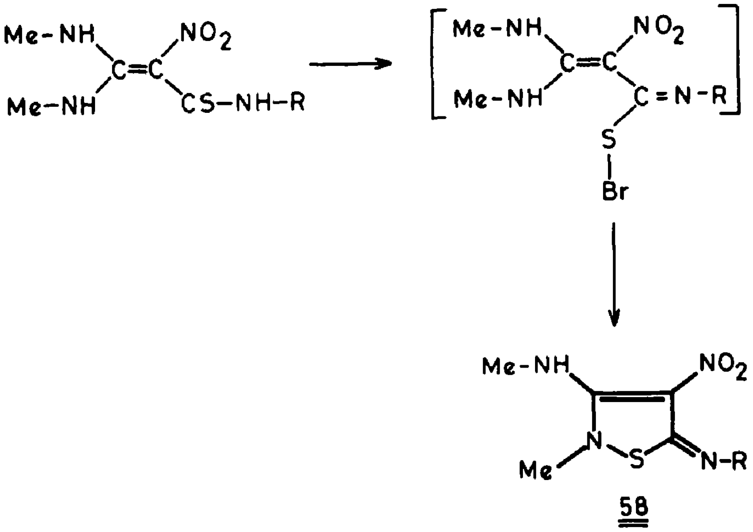
followed by Dimroth rearrangement and elimination of *p*-chlorobenzene sulphonamide, to give, finally, 4-nitro-1,2,3-triazoles (Scheme 22).[55]

4.1.4 *Reaction with bis-electrophiles.* Reaction of enamines, possessing an NH, with suitable bis-electrophiles, leads to heterocyclization by bond-formation at both the nucleophilic sites of the enamine, viz, the carbon C-2 and the N atom (Scheme 23). In our work with nitroenamines, the plan

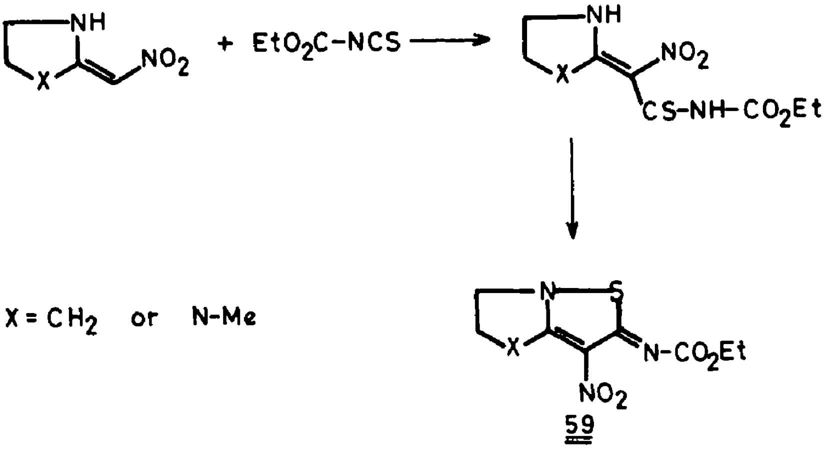


Scheme 23

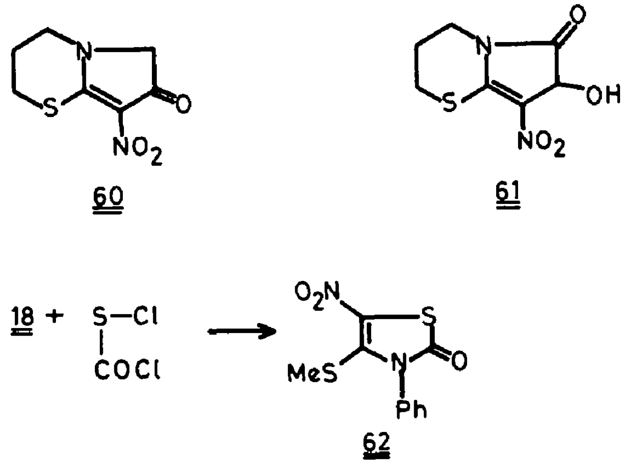
was slightly different in detail: initial reaction with a monoelectrophile at C-2 was to be followed by creation of a second electrophilic centre in a separate step. The primary reactant was an isothiocyanate; subsequently, the S atom in the adduct was converted into the second site of electrophilic activity by reaction with bromine. The N atom then displaced bromide from the sulphenyl bromide to form the isothiazoline (**58**). Overall, the process is an oxidative cyclization (Scheme 24).[56]



Scheme 24



Scheme 25



Scheme 26

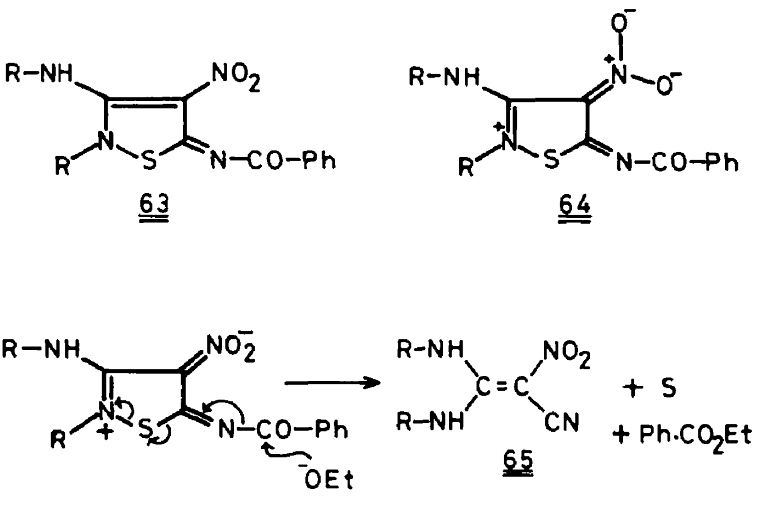
However, as mentioned earlier, nitroketeneaminals bearing only one substituent each on the two N atoms are not very reactive towards alkyl or aryl isothiocyanates. But the more reactive acyl isothiocyanates reacted easily with a variety of nitroketeneaminals, and even with some nitrovinylamines. Thus the condensed isothiazolines (**59**) were prepared by reaction of the nitroenamines with carbethoxy isothiocyanate, followed by bromine oxidation (Scheme 25).[56]

Some bis-electrophilic molecules have also been reacted with nitroenamines. Thus condensation of **49** with glyoxal and glyoxylic acid ester has been reported to give **60** and **61** respectively.[57,58] Similarly, 1-anilino-1-methylmercapto-2-nitroethylene (**18**) and chlorothioformyl chloride give the 5-nitro-3H-2-thiazolone derivative **62** (Scheme 26).[24]

4.2 *Chemical consequences of the "push–pull" effect*

The NMR data reported in Section 3 had led to the conclusion that nitroenamines would be good "push–pull" ethylenes, since they derive considerable contribution to their ground-state from structures like **1c**. Some unique chemical transformations of nitroenamines are reported in this section, which are best explained as being the consequence of this "push-pull" effect. Other enamines do not undergo comparable reactions.

We had in our hands the 5-benzoylimino-4-nitroisothiazoline (**63a**), obtained by the addition of benzoyl isothiocyanate to the nitroketeneaminal (**16e**), followed by bromine oxidation. We argued that the charged amidiniumnitronate structure (**64**) would make the molecule ripe for fragmentation, since it has a sulphur atom linked to a positively charged N atom; consequently, attack by base on the CO should set in motion an interesting series of transformations. In the event, refluxing with sodium ethoxide in ethanol did indeed result in the extrusion of sulphur and formation of the nitrile (**65a**) with loss of ethyl benzoate (Scheme 27).[59]

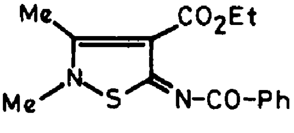


(a : R = Ph–CH$_2$)

Scheme 27

Our next objective was to prove the validity of our assumption that the "push–pull" nature of the nitroenamine system present in **63** was responsible for this novel fragmentation. This was easily done, since no fragmentation could be detected on base-treatment of any of the analogs **66–68**.[59] This is thus in accord with our earlier prediction based on N–C-1 rotation barriers (Section 3.4) that nitroenamines would be better "push–pull" systems than enaminocarbonyl compounds.

Two steps are involved in this novel synthesis of 3,3-diamino-2-nitroacrylonitriles: oxidation of the nitroenamine-acyl isothiocyanate adduct to an isothiazoline and base-initiated fragmentation. The two could be combined in a single operation by taking advantage of another consequence of the "push–pull" effect. The acyl isothiocyanate adducts of enaminoesters and enaminoketones, on treatment with base, cyclise to the corresponding pyrimidinethione (Scheme 28).[60] But when the adducts **69** from nitroenamines are treated with alkali, no such cyclization takes place. Instead, a



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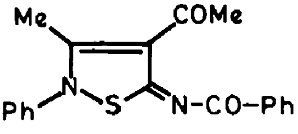

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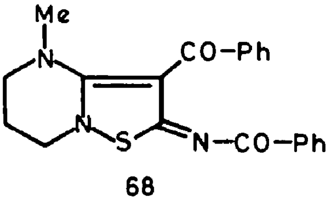

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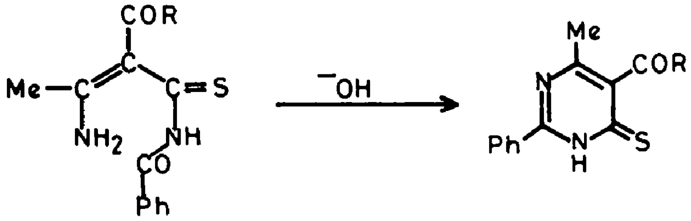
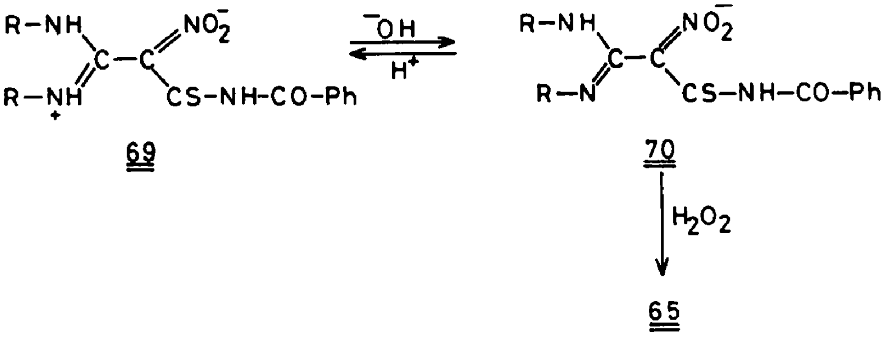
proton from the amidinium group in **69** is abstracted by the base, and the compound goes into solution as the nitronate salt (**70**); acidification regenerates the original compound (**69**). If aqueous hydrogen peroxide is added to the alkaline solution, the required nitrile (**65**) is formed practically instantaneously (Scheme 29).[59] It is impossible to say whether in this case the fragmentation proceeds via an initially formed isothiazoline; but at least in one example of the use of this method, the isothiazoline was isolated along with the nitrile, and could be subsequently induced to fragment by means of sodium methoxide.[59]



Scheme 28



Scheme 29

The transformations reported above have resulted in the conversion in good yield of 1,1-diamino-2-nitroethylenes (**2**) into 3,3-diamino-2-nitroacrylonitriles (**65**), a process which corresponds formally to the introduction of a nitrile at C-2 of nitroenamines. Previously, reagents which have been used for directly introducing a nitrile on simple enamines are those (Cl–CN[61], ArOCN[62]) which are capable of providing $^{+}$CN species. Such reagents need very reactive enamines (pyrrolidine enamines) as substrates. With the less reactive morpholino or piperidino enamines, yields are reported to be extremely low.[61,62]

It is obvious that the reactions of nitroenamines outlined under Sections 4.1 and 4.2 are of great utility in synthesising heteroaromatic nitro compounds.[63]

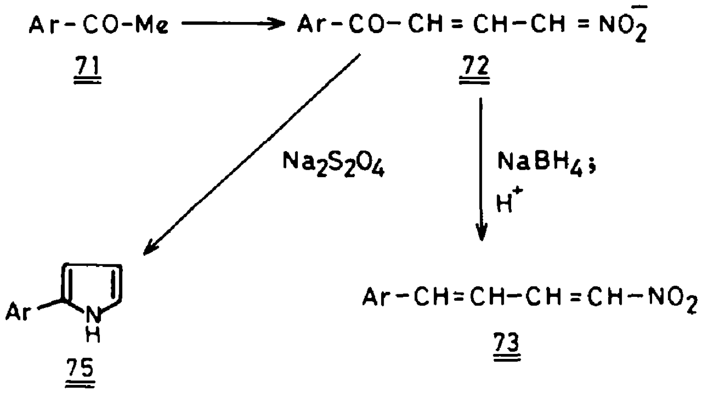
4.3 *Reaction with nucleophiles*

The reaction of nitrovinylamines with various nucleophiles has been extensively investigated.

4.3.1 *Nitrogen nucleophiles.* Transamination as a preparative procedure for nitrovinylamines has already been referred to in Section 2.1.

4.3.2 *Carbon nucleophiles.* (a) 1-Dimethylamino-2-nitroethylene (**8**) reacts with CH-acidic compounds in presence of alkoxides, with elimination of Me_2NH, to give salts of nitronic acids (Scheme 30).[64] The resulting *aci*-nitro compounds undergo a variety of useful transformations. For example, the *aci*-nitro compounds (**72**) derived from aryl and heteryl ketones (**71**) can be reduced with sodium borohydride to give, after acidification, the nitrobutadienes (**73**) (Scheme 31). Benzalacetone has similarly given the nitrotriene (**74**). Sodium dithionite reduction of the *aci*-nitro compound (**72**) gives the pyrrole (**75**) (Scheme 31).[14,65]

Scheme 30



Scheme 31

$$Ph-(CH=CH)_3-NO_2$$

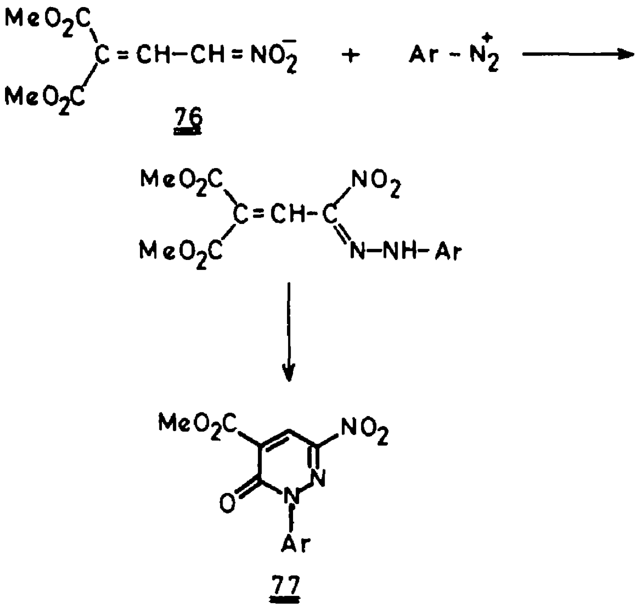
74

Nitroheterocycles and nitrobenzenes can be built from some of these *aci*-nitro compounds. Thus the nitropyridazine (**77**) is obtained by coupling **76** with a diazonium salt and cyclizing the product (Scheme 32).[66] Intramolecular C–C bond formation with suitably located functional groups leads to nitrobenzene derivatives (Scheme 33).[66]

The equivalent of a Nef reaction on the *aci*-nitro compounds (**78**) leads to ene-diones (**79**) (Scheme 34). This can be brought about by ammonium peroxodisulphate[15] or by kieselgel or ascorbic acid.[67] The conversion can also be brought about by decomposition of the O-methyl derivative of the *aci*-nitro compound (Scheme 34).[15] Unsaturated ketoesters (**80**) have been obtained similarly (Scheme 35).[68] The Nef reaction has also been applied directly to a nitroenamine: a patent claims the conversion of **49** to the oxime (**81**).[69]

(b) Grignard reagents have been successfully reacted with nitroenamines to produce nitrovinyl compounds (Scheme 36).[70]

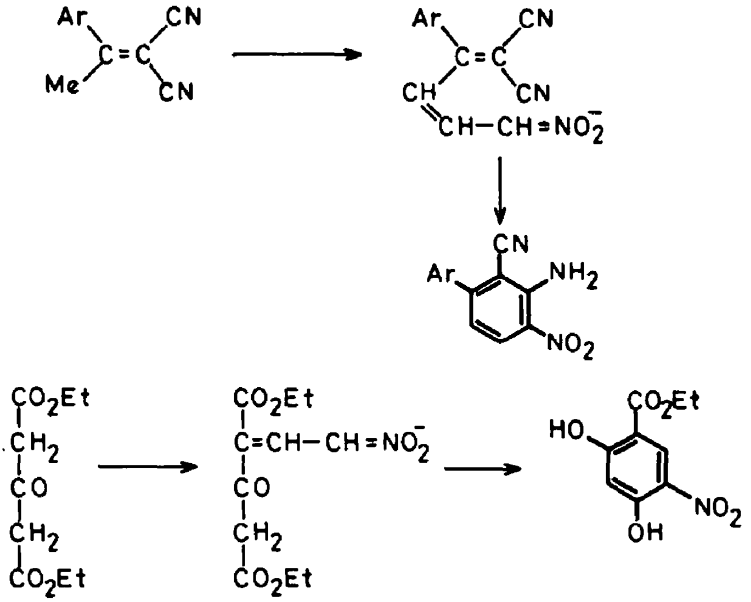
(c) Nitrovinylation of aldehydic carbon has been achieved by reacting the anion derived from aldehyde phenylhydrazone with nitroenamines (Scheme 37).[71]



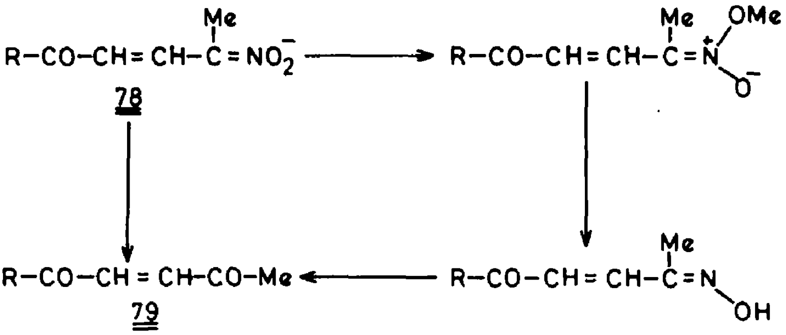
76

77

Scheme 32



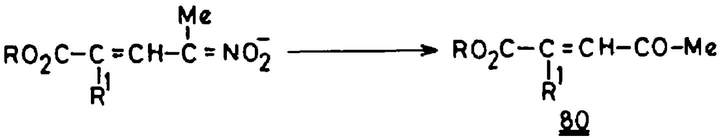
Scheme 33



78

79

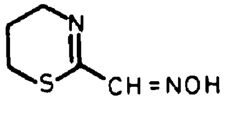
Scheme 34



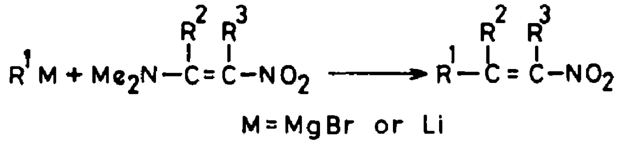
$$RO_2C-\underset{R^1}{C}=CH-\overset{Me}{C}=NO_2^- \longrightarrow RO_2C-\underset{R^1}{C}=CH-CO-Me$$

80

Scheme 35



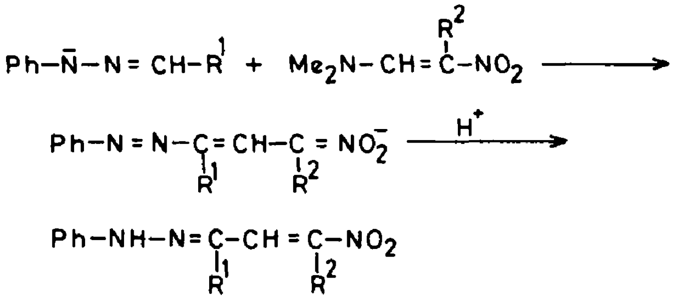
81



$$R^1M + Me_2N-\overset{R^2}{C}=\overset{R^3}{C}-NO_2 \longrightarrow R^1-\overset{R^2}{C}=\overset{R^3}{C}-NO_2$$

M = MgBr or Li

Scheme 36



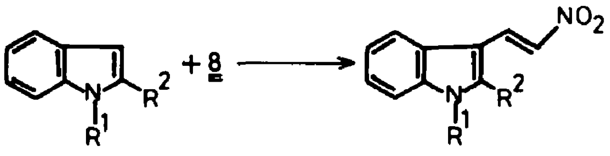
$$Ph-\bar{N}-N=CH-R^1 + Me_2N-CH=\overset{R^2}{C}-NO_2 \longrightarrow$$

$$Ph-N=N-\underset{R^1}{C}=CH-\underset{R^2}{C}=NO_2^- \xrightarrow{H^+}$$

$$Ph-NH-N=\underset{R^1}{C}-CH=\underset{R^2}{C}-NO_2$$

Scheme 37

(d) The nitroenamine (**8**) has been used by Büchi[34] to nitrovinylate indoles. The reaction, carried out in trifluoracetic acid, gives excellent yields of the products (**82**) which are obvious precursors for tryptamines.

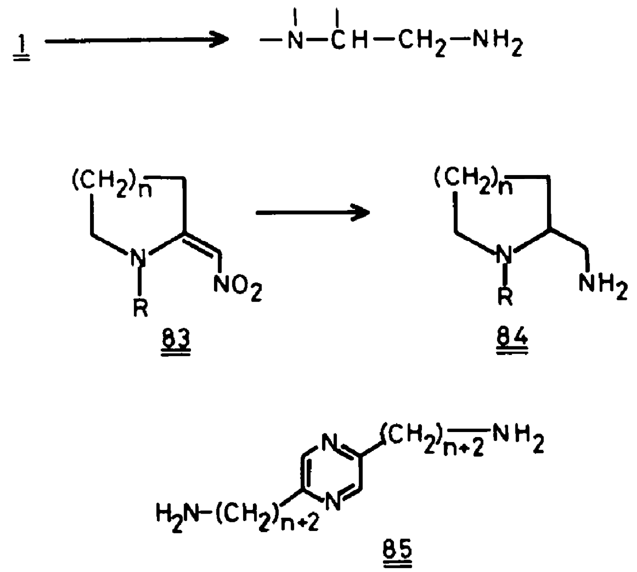


82

4.4 *Reductive transformations*

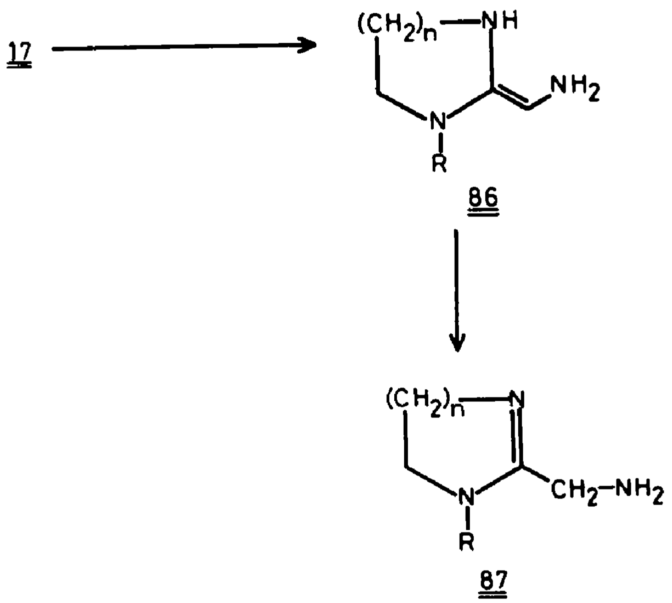
Three main reactions are described in this section, all of which have great synthetic potential; they lead to products which are otherwise difficultly accessible.

4.4.1 *Catalytic reduction of nitrovinylamines.* (a) Catalytic reduction of nitrovinylamines under neutral conditions predictably results in the saturation of the double-bond and the conversion of the nitro to an amino group (Scheme 38).[72] This is perhaps the method of choice for the synthesis of the 2-aminomethyl heterocycles (**84**), which can themselves serve as precursors for a variety of other compounds.[73,74] The reduction can also be brought about by lithium aluminium hydride.[73]



Scheme 38

(b) A more intriguing reaction takes place when the catalytic reduction of **83** (R = H) is carried out under acidic conditions.[75] Absorption of hydrogen ceases after 2.5 moles have been taken up; the product turns out to be the symmetrically substituted pyrazine (**85**). Yields of the pyrazine are very good when n is 3 or 4 (7- or 8-membered ring), and the poorest when n is 2 (6-membered ring). Caprolactam can thus be converted in three simple steps to the pyrazine (**85**; n = 3). The latter therefore appears to be an easily accessible starting material for the construction of cyclophanes and macrocycles incorporating a pyrazine or a piperazine sub-unit. The formation of the pyrazine evidently involves two steps: a cyclodimerization of the immediate reduction product of **83** to a dihydropyrazine, and a dehydrogenation of the dihydropyrazine to the pyrazine (**85**). The latter



Scheme 39

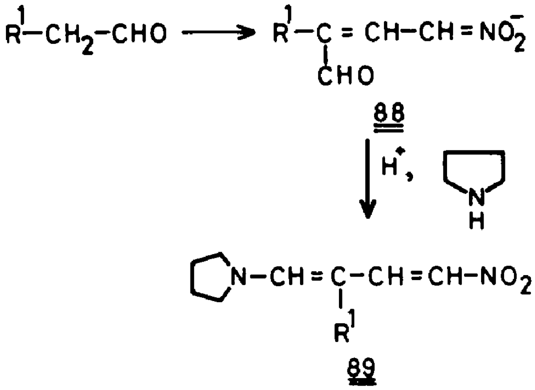
process could take place during work-up (atmospheric oxygen) or through the influence of the catalyst in the reaction medium itself.

4.4.2 *Catalytic reduction of nitroketeneaminals.* Under acidic conditions, catalytic reduction of the nitroketeneaminals (**17**) did not provide any pyrazines. The products were the aminomethyl amidines (**87**). Apparently, the intermediate ene-triamine (**86**) undergoes a prototropic change to the aminomethyl amidine (**87**) faster than it can cyclodimerize (Scheme 39).[76] When this type of prototropy is blocked (tetrasubstituted nitroketeneaminals), no characterisable product is obtained on reduction.

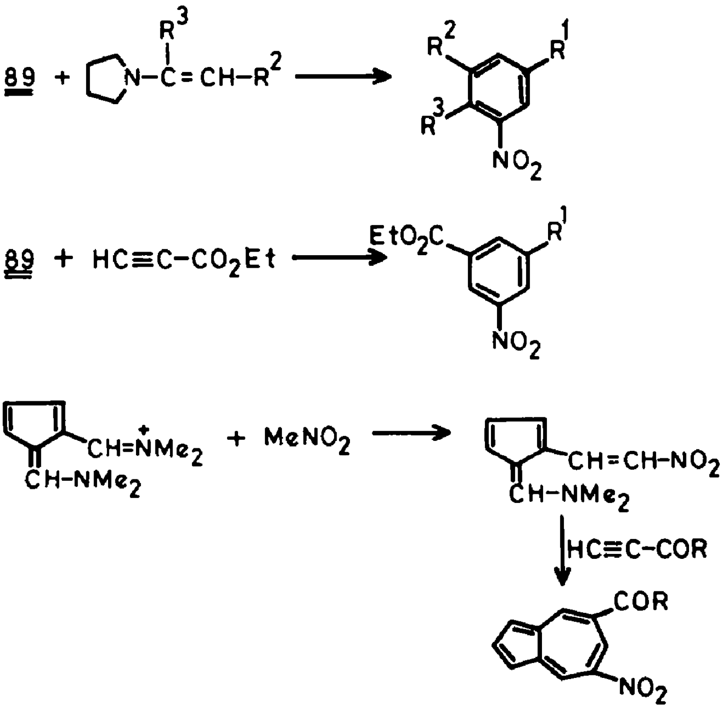
5. NITRODIENAMINES AND NITROPOLYENAMINES

There are reports in the literature on the synthesis and further transformations of a few nitrodienamines and nitropolyenamines; in these compounds, the nitro and amino groups are attached to the two termini of the conjugated olefinic system. This section surveys such compounds.

The 4-*aci*-nitrocrotonic aldehyde derivatives (**88**), obtained from aldehydes and nitroenamines, on subsequent treatment with pyrrolidinium acetate, give the nitrodienamines (**89**) (Scheme 40).[77] The nitrodienamines themselves can be used as reagents for condensation with active methylene compounds, leading to *aci*-nitro derivatives, which can be converted to nitropolyenes etc.[78]



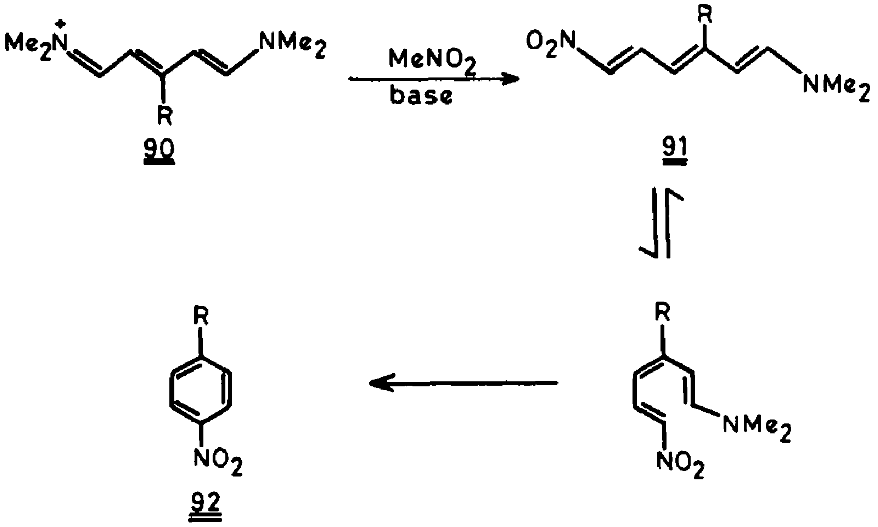
Scheme 40



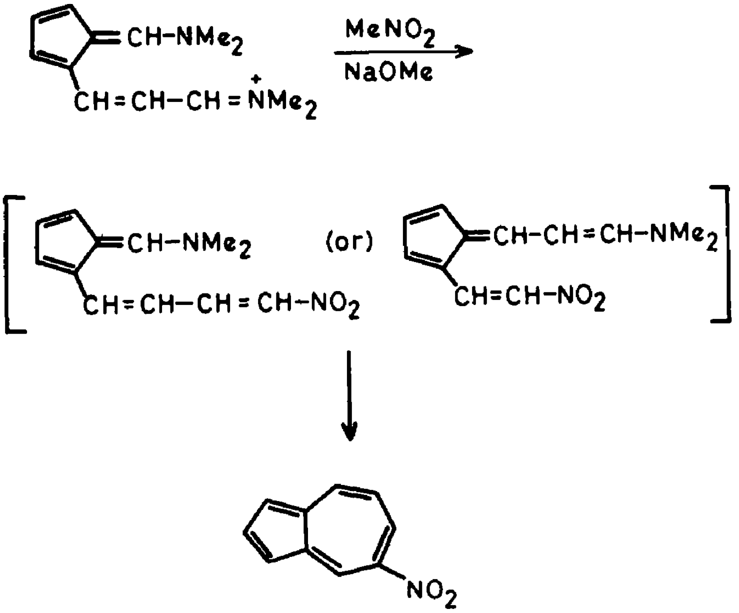
Scheme 41

Nitrodienamines and nitropolyenamines undergo useful (4 + 2)- and (8 + 2)-cycloadditions with substituted olefins and acetylenes; loss of the amine from the adduct leads to aromatic products (Scheme 41).[77,79]

The pentamethinium salt (**90**) reacts with nitromethane to give the 1-dimethylamino-6-nitrohexatriene (**91**). This undergoes thermal electrocyclization followed by elimination of dimethylamine to give the nitrobenzene (**92**) (Scheme 42).[80] A similar route involving electrocyclization and elimination of dimethylamine has been used to prepare nitroazulenes (Scheme 43).[81]

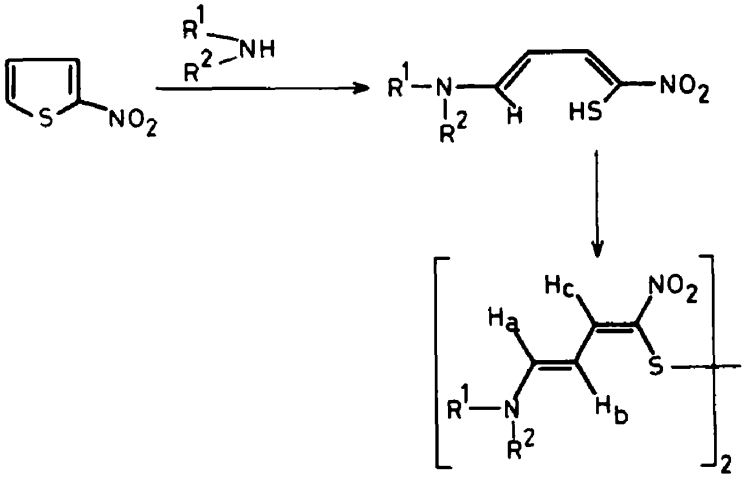


Scheme 42



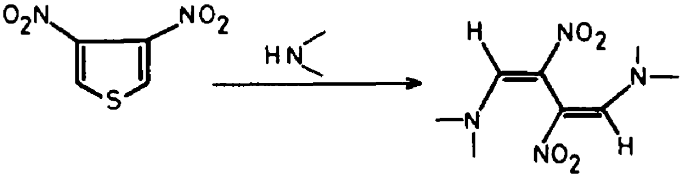
Scheme 43

In an unexpected ring-opening reaction, nitrodienamines (**93**) have been generated in good yield by the reaction of *sec*-amines with 2-nitrothiophen in ethanol at room temperature (Scheme 44).[82] It is believed that the reaction involves addition of the amine at position 5, followed by protonation of the sulphur, ring-opening and oxidative dimerization. The structure of the product is based on its UV (λ_{max} 458 nm; log ε 4.75) and NMR spectral characteristics. Thus the compound **93** ($R^1 = R^2 = Me$) shows the following signals in its ^{1}H NMR spectrum: H_a, 7.88; H_b, 5.48; H_c, 8.22 δ; $J_{ab} = J_{bc} = 12.1$ Hz. These assignments have been confirmed by observing the spectra of the products from the reaction of diethylamine with 3-deutero and 5-deutero-2-nitrothiophens. Interestingly, the compound **93** ($R^1 = R^2 =$ Me) shows nonequivalence of the N-Me groups at 30° (δ 2.97 and 3.20), coalescence taking place at *ca* 70°.



93

Scheme 44



Scheme 45

A related reaction is the ring-opening of 3,4-dinitrothiophen by *sec*-amines in methanol at room temperature (Scheme 45).[83] The sulphur is extruded as hydrogen sulphide and the product molecule contains two nitrovinylamine units coupled to each other at C-2. In the ^{1}H NMR spectrum, the 1-H is seen as a singlet at 8.55 δ, suggesting its *cis* relationship to the nitro group.

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[28] Footnote 8 in ref. 27.

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