Pergamon

Tetrahedron 55 (1999) 7065–7114

TETRAHEDRON

Tetrahedron report number 493

Nitroenamines : An update

Srinivasachari Rajappa*

B-1, Melody Apartments, ICS Colony,
Pune 411 007, India

Received 26 April 1999

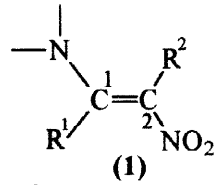
Contents

* e-mail : rajappa@pn2.vsnl.net.in

PII: S0040-4020(99)00384-1

1. Introduction

The first major review of the chemistry of nitroenamines was published in 1981[1] and covered the available preparative methods for this class of compounds, NMR spectral studies particularly with reference to the configuration around the C(1)-C(2) double bond, and the synthetic potential of nitroenamines. Since that time, research has progressed in several directions in this field. Firstly, more detailed spectroscopic studies, coupled with the elucidation of bond-lengths and bond angles in the solid state through X-ray crystallography and theoretical calculations have provided greater insight into the structure of these molecules. Secondly, chiral nitroenamines have been used as synthons in asymmetric synthesis, resulting in the enantioselective synthesis of several complex natural products, and lastly novel molecules containing the nitroenamine unit have been designed and constructed for use as drugs or pesticides.



(1)

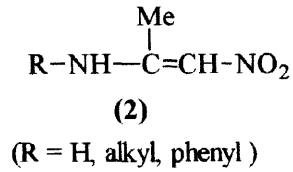
a : R^1, R^2 = H, alkyl, aryl
b : R^1 = NR_2; R^2 = H, alkyl, aryl
c : R^1 = OR; R^2 = H, alkyl, aryl
d : R^1 = SR; R^2 = H, alkyl, aryl
e : R^1 = H, alkyl, aryl, NR_2; R^2 = NO_2, CN, COR

By definition, the term nitroenamines includes nitrovinylamines (**1a**), nitroketeneaminals (**1b**), nitroketene O,N-acetals (**1c**) and nitroketene S,N-acetals (**1d**). All these constitute push-pull ethylene systems with a donor (amine) at one end and an acceptor (nitro) at the other end of the ethylene. As in the earlier review, the present article also includes molecules with further conjugation (nitropolyenamines), as well as push-pull ethylenes with a second acceptor group (NO_2, COR, CN) at C(2) (**1e**). The numbering of the two carbon atoms is as shown in (**1**).

2. Synthesis

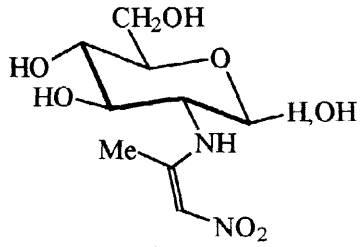
2.1 *Nitrovinylamines* (1a)

The classical enamine synthesis from carbonyl compounds has been extended to nitroenamines as well.[2] Reaction of nitroacetone with ammonia or primary amines using $TiCl_4$ as the catalyst is reported to give good yields of the nitroenamines (**2**). Nitroacetone also reacts with aminosugars to form chiral nitroenamines.[3] Thus, 2-amino-2-deoxy-D-glucose reacts with nitroacetone in the presence of acetic acid to give an almost quantitative yield of the nitroenamine (**3**).

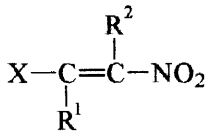


(2)

(R = H, alkyl, phenyl)

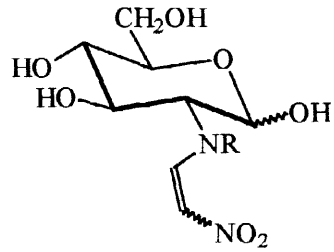


(3)

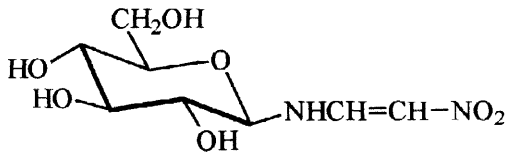


(4)

a : X = EtO—
b : X = PhS—



(5) a : R = H
b : R = ^{n}Bu



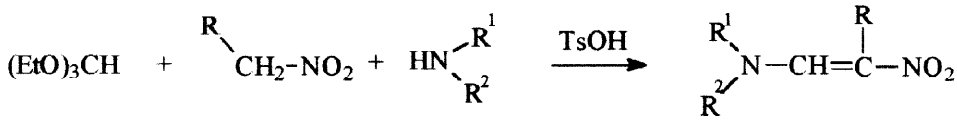
(6)

Nitroenamines can be prepared by displacement of the X group in (**4**) by amines; X can be alkoxy, alkyl/arylthio, or another amine. 1-Ethoxy-2-nitroethene (**4a**; R^1=R^2=H), prepared according to the procedure of Royer,[4] has been reacted with various amines to give nitroenamines.[5] This procedure has been extended to the synthesis of chiral nitroenamines by treating aminosugars with (**4a**). Thus, reaction of 2-amino-2-deoxy-D-glucose and its N-butyl derivative with an equimolar amount of the reagent in MeOH at 0°C gave almost quantitative

yields of the chiral nitroenamines (**5**) as anomeric mixtures.[6] Similarly, β-D-glucopyranosylamine gave the nitroenamine (**6**).

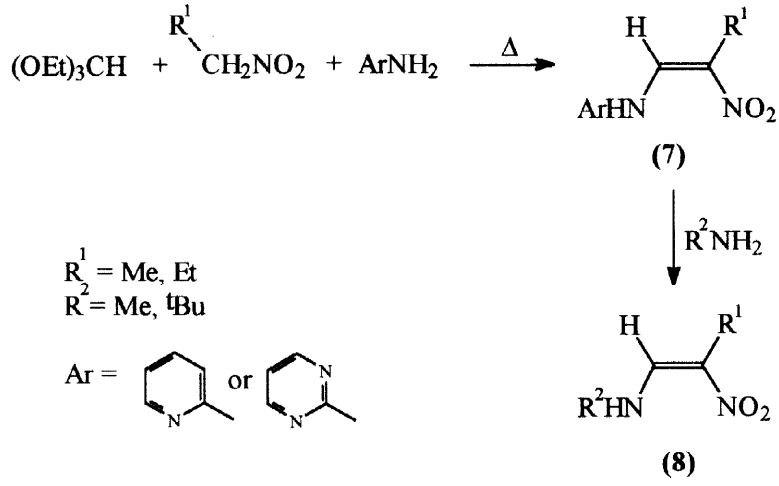
A modification of this leads to a one-pot synthesis of nitroenamines in moderate yields. The procedure consists of boiling a mixture of triethyl orthoformate, nitromethane and a secondary amine (Scheme 1).[7] Yields range from 9 to 70%; highest yields were obtained with N-methylaniline and morpholine. Extension to higher nitroalkanes was reported to give poor yields of 2-alkyl nitroenamines. A subsequent report, however, states that the procedure has been successfully used for the synthesis of 1-morpholino-2-methyl-2-nitroethene (71%) and 1-morpholino-2-ethyl-2-nitroethene (58%).[8]

Scheme 1



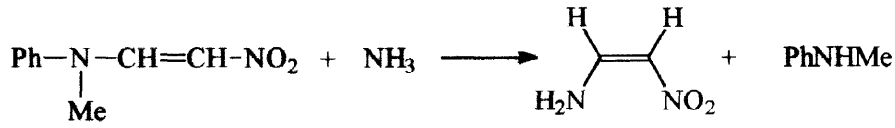
However, **warning:** when this procedure is used for the synthesis of 1-pyrrolidino-2-nitroethene, the carcinogenic 1-nitrosopyrrolidine is formed to the extent of 3% as indicated by NMR and mass spectroscopy.[9]

Scheme 2



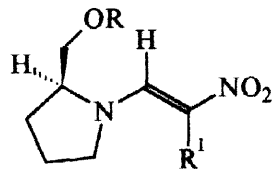
A modification of the triethyl orthoformate method can be utilised for the synthesis of 2-alkyl-1-amino-2-nitroethenes. The strategy is to react 2-aminopyridine or 2-aminopyrimidine with the 1-nitroalkane and triethyl orthoformate to give (**7**) in 50 to 65% yields. Subsequent transamination with primary aliphatic amines leads to quantitative yields of the desired products (**8**) (Scheme 2).[10] Similarly, the N-unsubstituted nitroenamine (**9**) could be formed by transamination from the N-methylaniline derivative (Scheme 3).[10]

Scheme 3



(9)

Chiral nitroenamines **(10,11)** have also been prepared by transamination. Thus, reaction of 1-morpholino-2-nitroolefins with (*S*)-2-(methoxymethyl) pyrrolidine or (*S*)-prolinol leads to **(10)** and **(11)** respectively.[11,12] The latter can be converted to either the trityl derivative **(12)** or the t-butyldimethylsilyl derivative **(13)** in order to provide steric bulk in the side-chain.

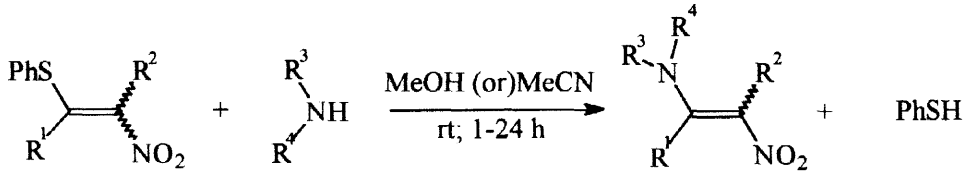


a : R^1 = H
b : R^1 = Me

(10) : R = Me **(12)** : R = Ph_3C
(11) : R = H **(13)** : R = $^tBuMe_2Si$

The displacement of thiophenol by amines from 2-nitro-1-phenylthioalkenes **(4b)** has been developed into a general synthesis of nitroenamines (Scheme 4).[13] The reaction proceeds at room temperature and the products are obtained in 48-85% yields. The amine can be aliphatic or aromatic, primary or secondary.

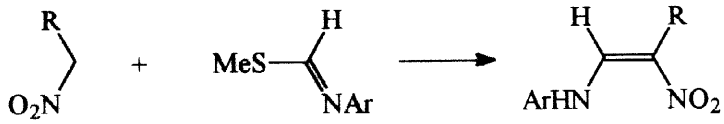
Scheme 4



R = H or Me; R = H or Me

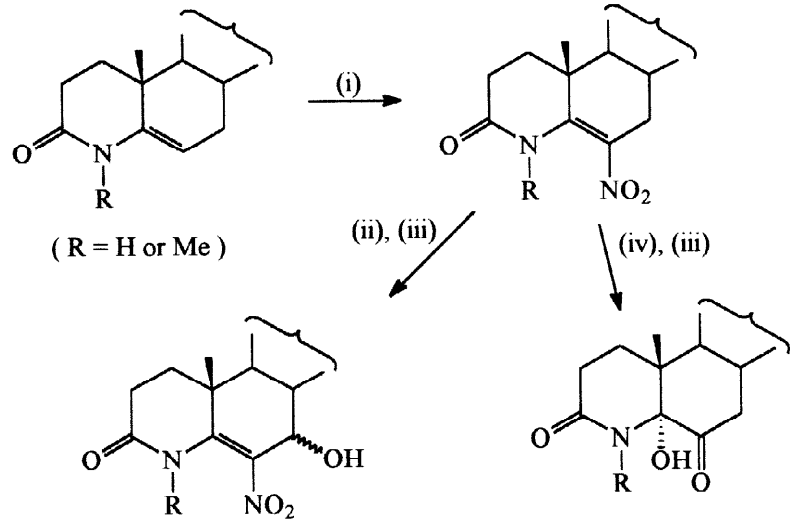
Nitroenamines bearing an aryl group or a heteroaryl group on C(2) can be easily prepared from substituted nitromethanes and S-methyl methaneimidothioates (available *via* thioformamides).[14] The reaction is carried out in the absence of solvent, at room temperature, and appears to be quite general for the preparation of 1-arylamino-2-aryl-2-nitroethenes **(14a)** from aryl nitromethanes (Scheme 5), with excellent yields. However, the condensation of nitroethane with the iminothioether takes much longer, and gives only modest yields of **(14b)**.

Scheme 5



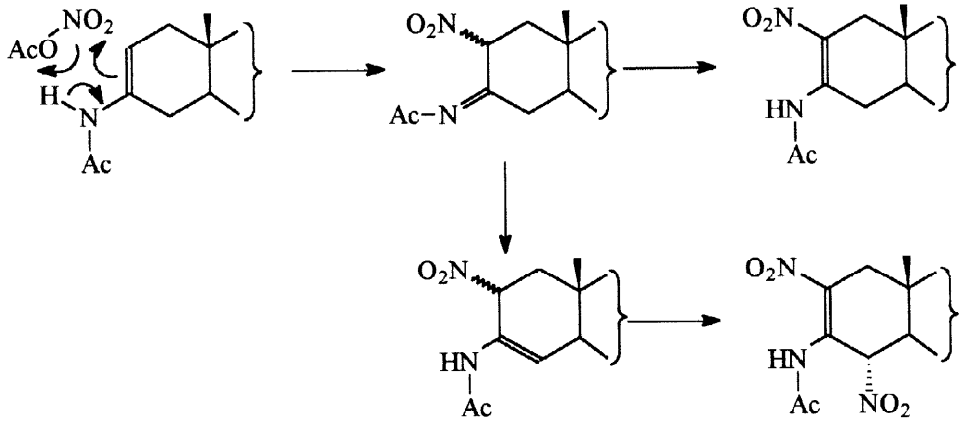
(14) a : R = Ar'
b : R = Me

Scheme 6



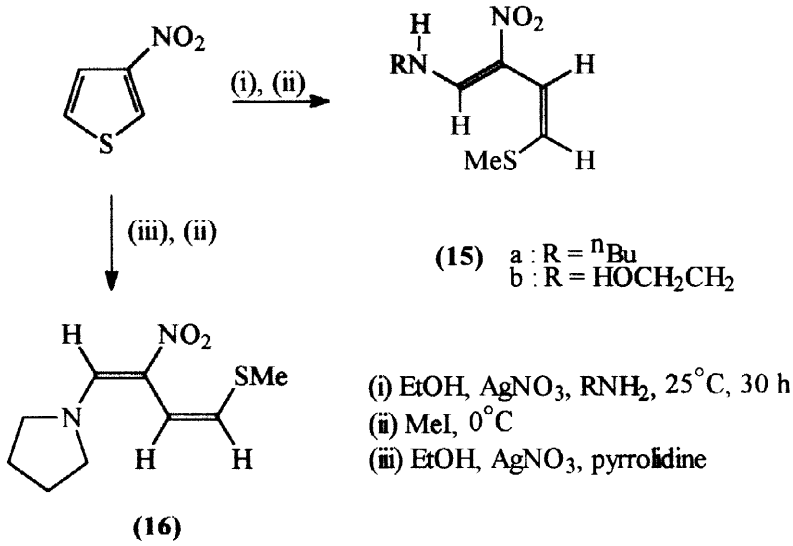
(R = H or Me)

(i) $AcONO_2$ (ii) $AcONO_2$, allylic oxidation (iii) H_2O
(iv) Ac_2O, followed by H_2O; Nef reaction.



A recent method of synthesising nitroenamines in certain special substrates[15,16] consists of the nitration of N-acyl enamines (enamides), the preferred nitrating agent being acetyl nitrate, prepared by adding 65% nitric acid to acetic anhydride. The initial product of nitration seems to be an N-acyl imine, presumably formed *via* a six-membered transition state. One pathway for this imine involves a prototropic shift leading to an N-acyl nitroenamine which can undergo further allylic oxidation or Nef reaction (Scheme 6).

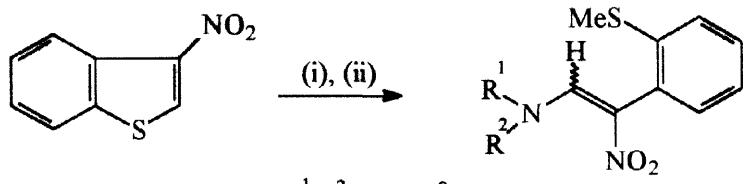
Scheme 7



Ring-opening of 2-nitrothiophene by means of *sec* amines has been discussed in the earlier review.[1] The amine attacks position 5 of the thiophene ring with concomitant cleavage of the C-S bond, leading to a 1-amino-4-nitrobutadiene. In contrast to this, it has been reported that 3-nitrothiophene reacts with N-lithiopiperidide to give low yields of 3-nitro-2-piperidinothiophene and 3,3′-dinitro-2,2′-bithienyl; no ring-opened products have been observed in this reaction.[17] However, it has now been found that 3-nitrothiophene also undergoes facile ring-opening with primary and secondary amines with subsequent methylation leading to 1-amino-4-methylthio-2-nitro-1,3-butadienes (**15**).[18] Thus, treatment of 3-nitrothiophene in EtOH with $nBuNH_2$ and $AgNO_3$ at 25°C for 30h gives the silver salt of the mercaptobutadiene. Methylation by excess MeI at 0°C leads to **(15a)** in 57% yield. Other primary amines react similarly, the product (**15b**) from ethanolamine being crystalline. Pyrrolidine gives a lower yield (24%) of (**16**) (Scheme 7).

Similarly, reaction of 3-nitrobenzo [b] thiophene with primary or *sec* amines in the presence of $AgNO_3$, followed by methylation with MeI gives the nitroenamines (**17**) by ring-opening (Scheme 8).[19]

Scheme 8

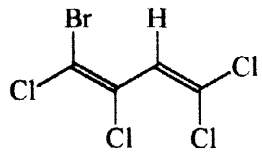


(i) EtOH, $AgNO_3$, R^1 R^2 NH, 30°C
(ii) MeI

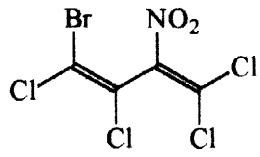
(17)

2.2 *Nitroketeneaminals* (1b)

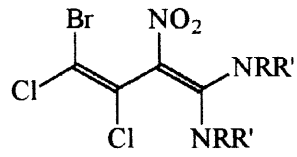
Nitration of 1-bromo-1,2,4,4-tetrachlorobutadiene (**18**) (*E* and *Z* isomers) with HNO_3/H_3PO_4 or HNO_3/H_2SO_4 has given the *E* and *Z* isomers of (**19**). Reaction of the *E*-isomers with amines leads to the nitroketeneaminals (**20**).[20]



(18 *E*)



(19 *E*)

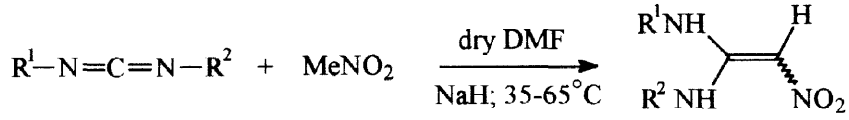


(20)

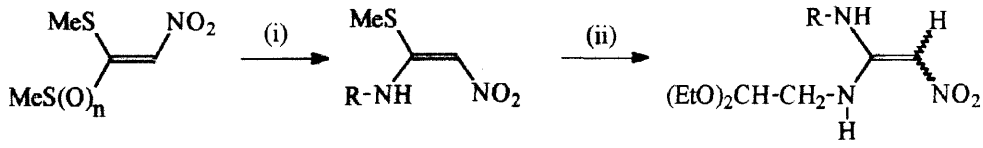
A common method for the synthesis of nitroketeneaminals consists of nitromethylation of carbondisulfide, followed by bis-methylation to give 1,1-bis(methylthio)-2-nitroethene (**21a**) and final substitution of the two methylthio groups by amines.[1] Analogously, it has now been shown that nitromethane can add to suitably substituted carbodiimides to give nitroketeneaminals directly;[21] yields are in the range of 35-65% (Scheme 9). This has also led to a new synthesis of the anti-ulcer drug ranitidine (See Section 7).

The monosulfoxide (**21b**) of 1,1-bis(methylthio)-2-nitroethene had been synthesised earlier.[22] This compound is particularly useful for the preparation of unsymmetrical nitroketeneaminals such as (**22**) (Scheme 10).[23]

Scheme 9



Scheme 10



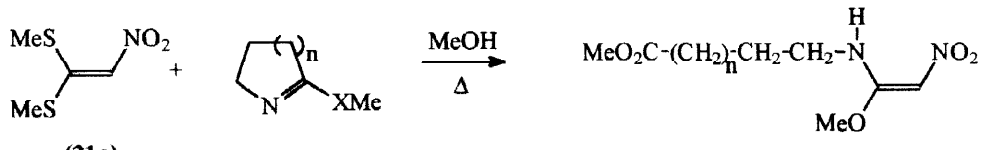
(21) a : n = 0
b : n = 1

(22)

(i) RNH_2 (ii) $(EtO)_2CHCH_2NH_2$

2.3 *Nitroketene O,N-acetals* (**1c**)

There appear to be very few reports in the literature on the synthesis of N-substituted 1-alkoxy-2-nitroethenamines. The best way to make such compounds is by displacement of methanethiol from the corresponding 1-methylthio derivatives by the appropriate alcohol. A novel variant has been reported in which 1-[ω-(alkoxycarbonyl) alkyl]-amino-1-methoxy-2-nitroethenes (**24**) are formed by reaction of lactim ethers (**23a**) or sulfides (**23b**) with 1,1-bis (methylthio)-2-nitroethene (**21a**) in refluxing methanol.[24] The enaminic protons in the products (**24**) resonate between 6.60 and 6.70 ppm. Use of dioxan as the solvent instead of MeOH, of course, leads to the corresponding methylthio derivative (see Section 2.4)



(21a)

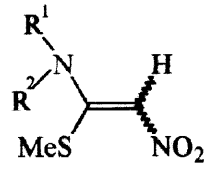
n = 1,2,3

(23) a : X = O
b : X = S

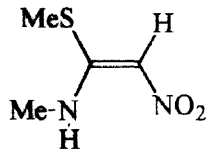
(24)

2.4 *Nitroketene S,N-acetals* (**1d**)

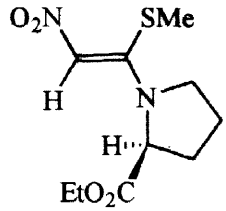
Reaction of 1,1-bis (methylthio)-2-nitroethene (**21a**) with one equivalent of several primary or secondary amines at 30°C has given the corresponding N-substituted 1-methylthio-2-nitroethenamines. (**25**). The product, however, is likely to be contaminated with traces of the corresponding nitroketeneaminal formed by the displacement of the second methylthio group.[25-28] This procedure has been used to synthesise 1-methylamino-1-methylthio-2-nitroethene (**26**), a crucial intermediate for the manufacture of ranitidine (See Section 7). The monosulfoxide (**21b**) has also been used for this purpose.[29] The esters of (*S*)-proline, (*S*)-valine and (*S*)-phenylalanine have similarly yielded (**27**),(**28**) and (**29**) respectively on reaction with (**21a**).[30] The enaminic proton is seen at 6.2 to 6.6 ppm in the ^1H NMR spectra of these compounds.



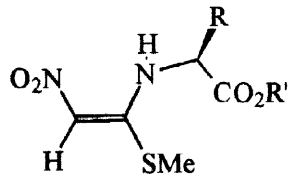
(25)



(26)



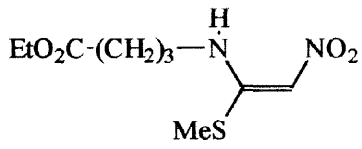
(27)



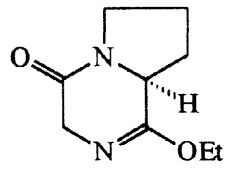
(28) R = Me_2CH; R' = Me

(29) R = $PhCH_2$; R' = Et

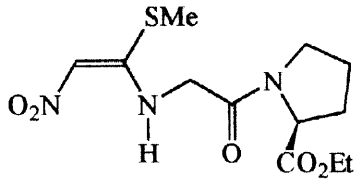
As mentioned in the previous section, reaction of γ-butyrolactim ether with 1,1,-bis(methylthio)-2-nitroethene (**21a**) in dioxan-water gives (**30**). Similarly the cyclodipeptide monoiminoether (**31**) leads to (**32**).[24]



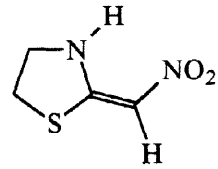
(30)



(31)



(32)



(33)

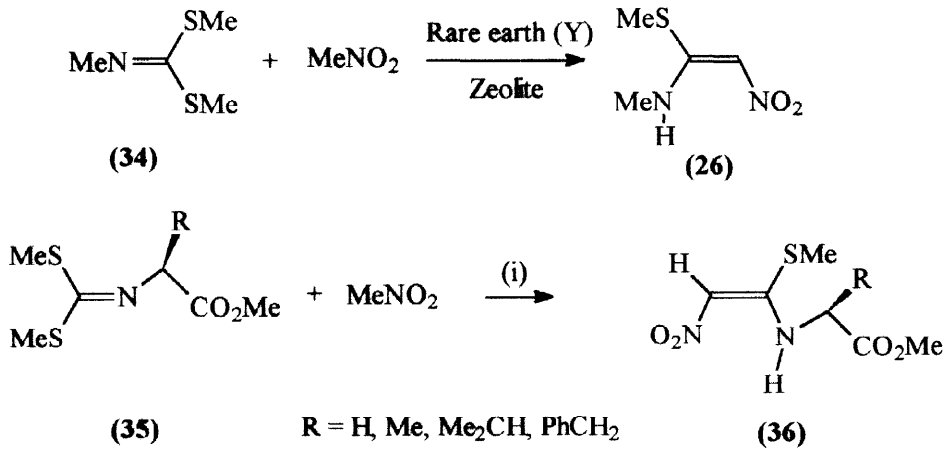
The thiazolidine derivative (**33**) has been made by reacting 2-mercaptoethylamine with (**21a**).[31]

A second approach to the synthesis of 1-methylamino-1-methylthio-2-nitroethene (**26**) depends upon the addition of nitromethane anion to methyl isothiocyanate; this is brought about by KOH in DMSO.[32] Subsequent S-methylation gives the required product (**26**).

In a totally new approach, nitromethane has been condensed with bis (methylthio) methaneimine (**34**) in the presence of a rare-earth exchanged NaY zeolite to give (**26**) (Scheme 11).[33] This specific zeolite catalyst appears to be uniquely suited for such a condensation. Other Lewis or Bronsted acid catalysts are ineffective. Since carbonimidodithioates such as (**34**) are easily accessible from primary amines and carbondisulfide, this constitutes a general

synthesis of N-substituted 1-methylthio-2-nitroethenamines. The carbonimidodithioates (**35**) derived from the esters of (*S*)- α-aminoacids have been converted by this method into the products (**36**) in good yields (Scheme 11). [34] This is an alternative pathway to the nitroketene S,N-acetals such as (**28**) and (**29**) reported earlier.[30]

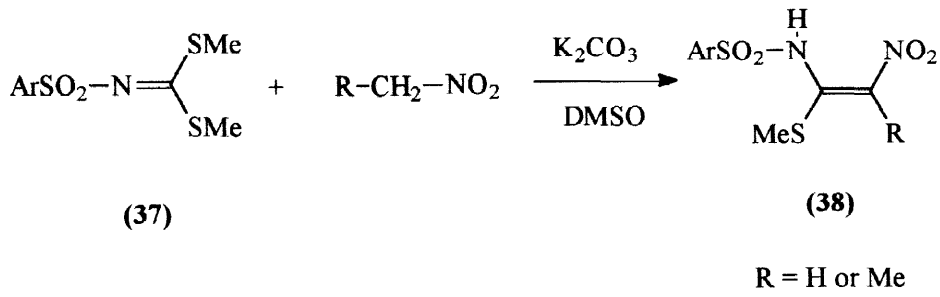
Scheme 11



(i) Na Y zeolite (faujasite group) ion-exchanged by treatment with a 5 % aq. soln. of a mixture of rare-earth chlorides (mixture of La, Pr, Sm along with heavier ones under the commercial name didymium chloride) nutil it corresponded to 70% exchange of Na^+.

The uniqueness of the rare-earth exchanged Y zeolite in bringing about such condensations between nitromethane and carbonimidodithioates has been sought to be understood through force field calculations and computer simulation studies.[35]

N-Sulfonyl carbonimidodithioates (**37**) have been condensed with nitromethane or nitroethane in DMSO to provide 1-methylthio-1-sulfonamido-2-nitroethenes (**38**). In this case, the condensation is brought about by anhydrous K_2CO_3.[36]

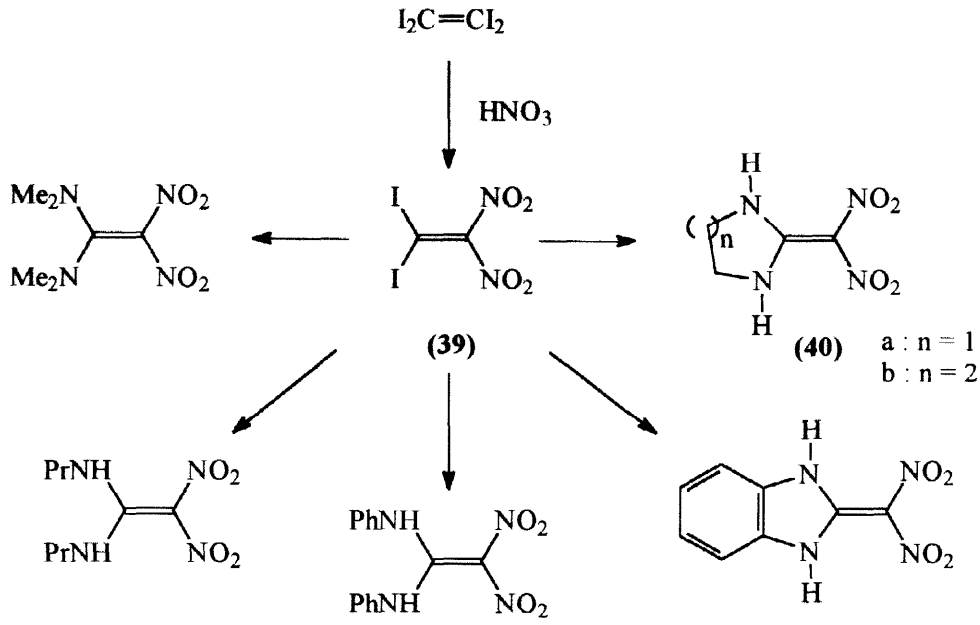


2.5 *Nitroenamines with a second acceptor group at C (2).* (**1e**)

The synthesis of 1-arylamino-2,2-dinitroethene has been noted in the earlier review.[1] Since then, a number of 1,1-diamino-2,2-dinitroethenes have been synthesised in good to excellent yields by reacting 1,1-diiodo-2,2-dinitroethene (**39**) prepared by nitration of tetraiodoethene with amines[37] (Scheme 12). Several aliphatic and aromatic, primary and

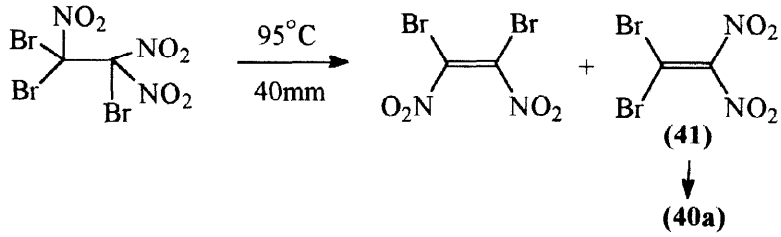
secondary amines, as well as diamines have been reacted with (**39**) at 0°C in CH_2Cl_2 to give the corresponding diaminodinitroethenes (Scheme 12).

Scheme 12



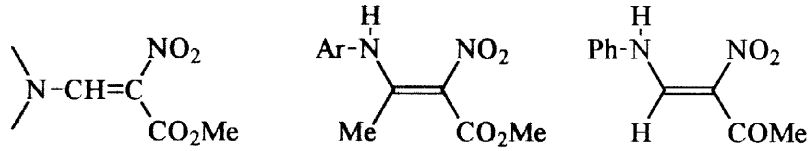
The imidazolidine derivative (**40a**) has also been prepared from the dibromo compound (**41**). Bromination of the dipotassium salt of tetranitroethane gave 1,1,2-tribromo-1,2,2-trinitroethane and thermolysis of this at 95°C/40 mm gave a 10% yield of 1,2-dibromo-1,2-dinitroethene as a solid, along with an isomer whose structure was established as (**41**) from the ^{13}C NMR spectrum. Reaction of this with ethylenediamine at 0°C gave (**40a**) (Scheme 13).[38]

Scheme 13



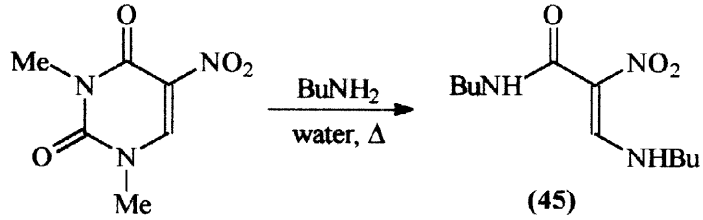
The synthesis of nitroenamines from 1-ethoxy-2-nitroethene has been extended for the preparation of enamines with two acceptor groups at C(2). Thus, methoxymethylene nitroacetic ester, methyl 3-ethoxy-2-nitrocrotonate and ethoxymethylenenitroacetone, on treatment with amines, lead to products such as (**42**), (**43**) and (**44**).[5,39] Similar compounds have also been obtained by ring-opening reactions. Hydrolytic ring opening of 1,3-dialkyl-5-nitrouracil led to the nitroenamine (**45**) (Scheme 14)[40] while treatment of 3-methyl-5-

nitropyrimidin-4(3H)-one with primary amines resulted in moderate to excellent yields of (**46**) (Scheme 15).[41] Surprisingly, *sec.* amines do not give the expected products. Instead, dipropylamine afforded the unsubstituted amino (38%) and methylamino (28%) derivatives; the mechanism has not been elucidated (Scheme 15). Aryl hydrazines react with pyrimidinone at room temperature to give good yields of the nitroenamines (**47**) bearing a methanimidoyl substituent at the carbamoyl group (Scheme 15).



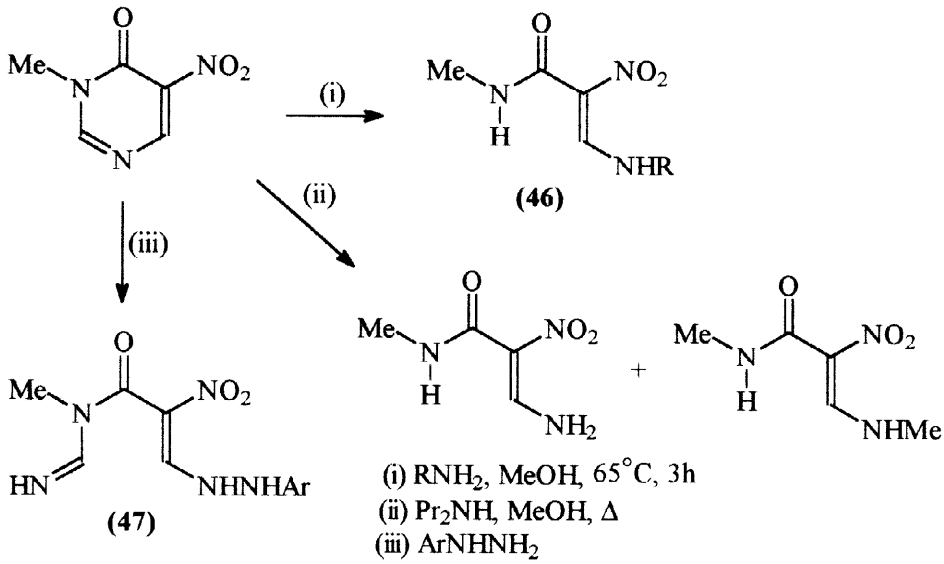
(**42**) (**43**) (**44**)

Scheme 14



(**45**)

Scheme 15



(**46**)

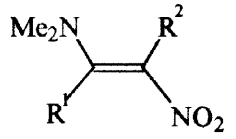
(**47**)

(i) RNH_2, MeOH, 65°C, 3h
(ii) Pr_2NH, MeOH, Δ
(iii) $ArNHNH_2$

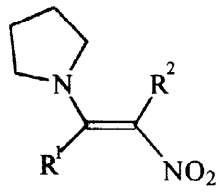
3. Structure and configuration : Spectroscopy, Dipole moments and X-ray crystallography

3.1 *Electronic spectra*

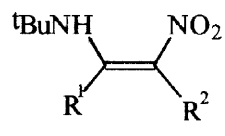
Detailed investigations have been carried out on the electronic spectra of the nitroenamines **48, 49 and 50.**[42] In water, (**48a**) shows λ_{max} at 361 nm (ε 24,900). The introduction of a methyl group on C(2) results in a drop of 20% in the intensity of the band (λ_{max} 380 nm) of compound (**48b**). In contrast, there is little change in the C(1) methyl derivative (**48c**). This has been attributed to considerable loss of planarity in (**48b**), but not in (**48c**) due to the twisting of NMe_2 as a result of steric crowding. In the corresponding pyrrolidinyl compounds, the drop in intensity for (**49b**) compared to (**49a**) is much less, suggesting that steric hindrance is less in these compounds compared to that in the dimethylamino analogs.



(48)



(49)



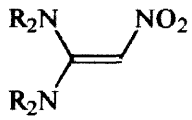
(50)

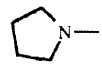
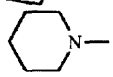
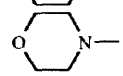
a : $R^1 = R^2 = H$
b : $R^1 = H$; $R^2 = Me$
c : $R^1 = Me$; $R^2 = H$

The UV of (**48a**) also shows a large solvent effect; λ_{max} in cyclohexane is 336 nm (ε 17,300) (see above for the values in water). A similar solvent effect is also seen in the UV of the *sec.* nitroenamine (**50a**) (λ_{max} water, 355 nm; λ_{max} cyclohexane, 336 nm). Since it is known from other studies that in non-polar solvents (**48a**) exists in the *E* configuration and (**50a**) as *Z*, the solvent induced change in λ_{max} in these compounds cannot be attributed to a change in the geometry of the molecule. In general, λ_{max} of simple nitroenamines is barely affected by isomerization; but the intensity is roughly halved in the *cis*-form compared to the *trans*-isomer.

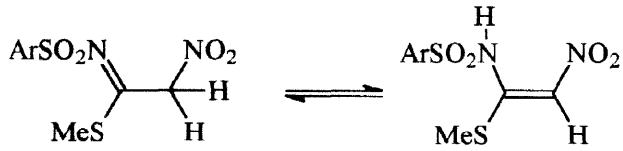
In recent times, considerable attention has been focused on the non-linear optical properties (NLO) of organic molecules. Molecules which have large second order polarizabilities are extremely useful in second harmonic generation (SHG) at a particular wavelength. Several organic molecules having electron donor and acceptor groups, separated by a conjugated system, have been investigated for this purpose. With this in view, the SHG coefficients of the four nitroketeneaminals (**51** to **54**) have been determined and compared with that of the simple nitroenamine (**48a**).[43] The UV absorption maxima of all the four nitroketeneaminals have been determined in different solvents and show that they have a broad absorption band in the 320-380 nm region [λ_{max} in cyclohexane is 334 nm for (**51**) and 344 nm for the other three]. Excepting the pyrrolidine derivative (**52**), with all the others, the

maximum is highly sensitive to solvent polarity, the absorption band shifting to longer wavelengths by about 10 nm when the polarity of the solvent is increased. This is indicative of excitation leading to a substantial amount of charge transfer with the excited state being stabilized more compared to the initial state, in polar solvents.



	R_2N—
51:	Me_2N—
52:	
53:	
54:	

SHG efficiency of the above five compounds (**48a, 51-54**) has been experimentally determined in the powdered state. Only the 1,1-bispiperidino-2-nitroethene (**53**) exhibits a second harmonic intensity, 0.2 times that of urea. All the other molecules are inactive.



(38A) **(38B)**

To date there are very few reports on the observation of the imine tautomer of nitroenamines.[1] Normally it appears that the enamine form represents the thermodynamically more stable tautomer. It has now been reported that the N-sulfonamido nitroenamines (**38**) exhibit solvent-dependent tautomerism as determined by UV and ^1H NMR spectroscopy.[36] In non-polar solvents, the compound (**38**; R=H) exists almost completely in the imine form (**38A**) [weak absorption band at 364 nm (ε 600); two-proton singlet at δ 5.70], but in polar solvents, (**38B**) predominates. In MeOH the compound exhibits strong UV absorption at 364 nm (ε 6200), and in [$^2H_6$] DMSO it exhibits a one-proton singlet at δ 6.0 due to the enaminic proton.

3.2 *Vibrational spectra*

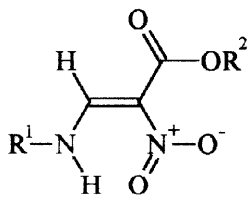
In contrast to the situation in 1981,[1] sufficient data is now available on the vibrational spectra of nitroenamines. Extensive studies have been carried out on the IR and Raman spectra of the nitroenamines **48**, **49** and **50**.[42,44] The salient features are the following: there is usually a very strong band at 1650-1550 cm^{-1}, ascribed to the asymmetrical coupling of C=C and C(1)-N stretching modes; the N-O stretchings do not contribute to the "enamine band", but couple

with other vibrations to give a weak IR and Raman band at 1530 - 1480 cm^{-1}; and there is also a strong IR (medium or weak Raman) band at 1280-1230 cm^{-1}, mainly due to $\nu_s(NO_2)$.

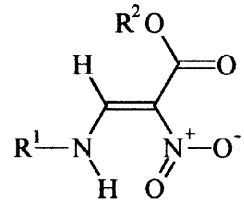
The different geometric isomers of the nitroenamines can also be distinguished by their vibrational spectra. The "enamine band" (at 1650-1550 cm^{-1}) is seen at a higher frequency in the *Z* form than in the *E* form.[44] In the case of nitroenamines having a *sec.* amine, the presence or absence of intramolecular hydrogen bonds can be inferred from the frequency of the NH band in the IR spectrum.[6] Thus the tetraacetate of (**5a**) exists in the *E*-configuration in the solid state, with the NH band appearing at 3430 cm^{-1} (w), indicating the absence of an intramolecular hydrogen bond. But in solution ($CDCl_3$), this band moves to 3005 cm^{-1}, indicating the intramolecularly hydrogen-bonded *Z*-configuration.

IR spectroscopy plays a crucial role in determining the configuration and conformation of nitroenamines of the type (**55**) in which the amino group is monosubstituted.[45,46] In such molecules, both *Z* and *E* forms can have intramolecular hydrogen bonds. The barrier to rotation around the C(1)-C(2) double bond is low ($\Delta G^{\neq}$17-20 kcal.mol^{-1}). In solution, these compounds exist as equilibrium mixtures of the three forms *s-cis*, *Z* (**55A**), *s-trans*, *Z* (**55B**) and *s-cis*, *E* (**55C**), the ratios depending on the polarity of the solvent. This can be deduced from the IR spectra, in which each isomer has easily distinguishable absorption bands. For instance, when R^1=Me, the molecule shows the following IR bands in the carbonyl region (in CH_2Cl_2 solution); 1731 cm^{-1} (**55B**), 1696cm^{-1} (**55A**) and 1668 cm^{-1} (**55C**). However, in both ^1H and ^{13}C NMR spectra ($CDCl_3$), only two species (*Z* and *E*) are observed in the ratio 57:43; obviously the rotamers (**55A**) and (**55B**) are rapidly interconverting on the NMR time-scale.

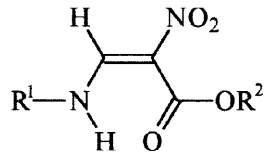
If an additional methyl group is introduced onto the double-bond, the molecule becomes sterically even more crowded. This leads to a loss of planarity and hence a decrease in conjugation. Thus in (**56Z**), the ester group is twisted out of the plane of the nitroenamine moiety. The deduction is based on a study of both vibrational and NMR spectra.



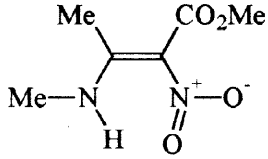
(55A)



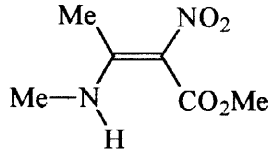
(55B)



(55C)

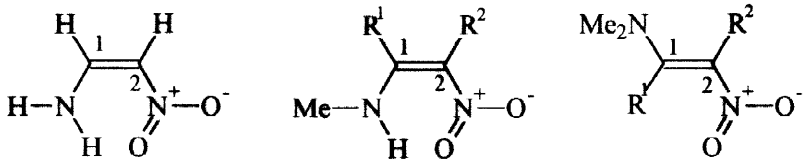


(56*Z*)



(56*E*)

3.3 *NMR Spectra*

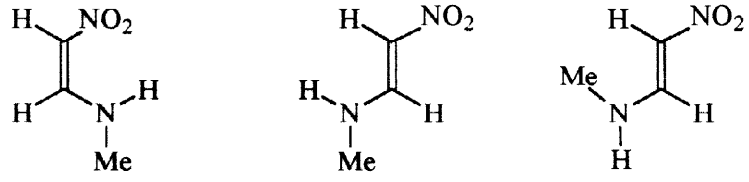


(9) (57) (48)

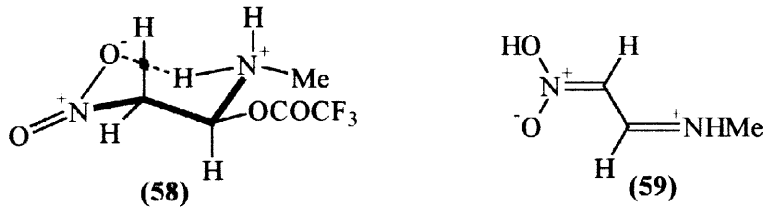
a : $R^1 = R^2 = H$
b : $R^1 = H$; $R^2 = Me$
c : $R^1 = Me$; $R^2 = H$

Extensive NMR (^1H, ^{13}C) spectroscopic studies have been carried out on the nitroenamines **9, 48** and **57**. Together with theoretical studies, these provide a fairly complete picture of the configuration of these nitroenamines in solvents of differing polarity as well as in the solid state [44,47] corroborating the conclusions presented in the previous review[1]. The energy barriers for rotation around the C(1)-C(2) and N-C(1) bonds have also been estimated.

In both (**9**) and (**57a**), the *Z* isomer with an intramolecular hydrogen bond is predominant in $CDCl_3$. With (**57a**), the proportions of the different rotamers about the C=C and N-C (1) bonds are solvent-dependent. At 34°C, in $CDCl_3$, only one conformer is present, having the *Z* configuration about the C(1)-C(2) double bond and the *sE* conformation with respect to the N-C(1) bond. $J_{HC(1),HC(2)}$ is 5.5 Hz and $J_{HN,HC(1)}$ is 14.0 Hz. However, in [$^2H_6$] DMSO, a mixture of three rotamers is seen in the ratio 23.5:7.7:68.8. The C(1)-C(2)/N-C(1) geometries in these have been determined to be *Z, sE; E, sE;* and *E,sZ* respectively. Thus in this solvent, almost 75% of the compound has the *E* configuration about the C=C double bond. In trifluoracetic acid, two species are seen in about equal amounts (47.5:52.5) and it has been suggested that these are (**58**) and (**59**) (protonated at C(2) and oxygen respectively).[47]

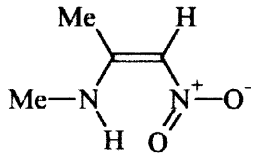


(57a) (*Z, sE*) (*E, sE*) (*E, sZ*)

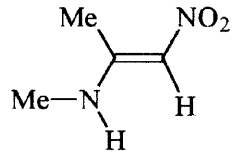


(58) (59)

The nitroenamine (**57c**) with a methyl group at C(1) also exists in the *Z* form in $CDCl_3$ and in [$^2H_6$] DMSO, (*Z*) is still favoured over (*E*). Similarly, the *Z* form of 1-*t*-butylamino-1-methyl-2-nitroethene (**50c**) predominates even in [$^2H_6$] DMSO and it is likely to have this configuration even in water.[42] A methyl group at C(1) thus seems to stabilize the *Z*-form. This may be due to the strengthening of the intramolecular hydrogen bond by a buttressing effect, and the steric interaction between the *cis* Me and NO_2 in the *E* configuration. The NH proton chemical shifts of the three related compounds (**50a**) (δ9.35), (**50b**) (9.7 ppm) and (**50c**) (10.7 ppm) indicate the following order of intramolecular H-bond strength: **(50c)** >> **(50b)** > **50a**



(57c) ***Z***



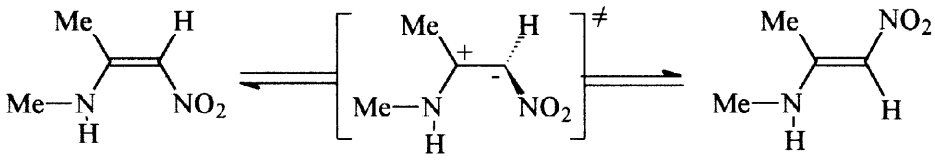
E

The stabilization of the *E*-isomer with increasing polarity of the medium can be attributed to the larger dipole moment of the more extended *E* -isomer relative to that of the *Z*-isomer, and the formation of intermolecular H-bonds between the NH of the *E*-isomer and the solvent molecules.

In the dimethylamino compounds (**48a** and c), the *E*-isomer is the only one seen in NMR. The two compounds also show restricted rotation around N-C(1) as indicated by the chemical shift anisochrony of the protons of the Me_2N group.

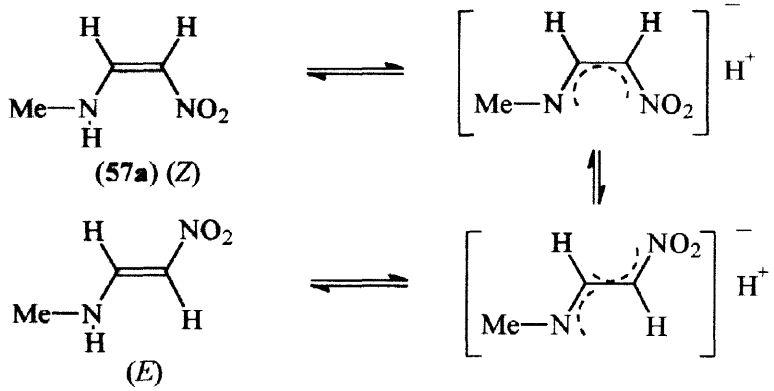
Dynamic ^1H NMR studies have been performed on some of these compounds in order to determine the activation parameters for the $Z \rightleftharpoons E$ equilibrium.[44] Comparison of these with the activation energies for the exchange of the protons of the amino group has resulted in the suggestion that there may be two different mechanisms for the isomerization process. Thus in 2-methylamino-1-nitropropene (**57c**), the couplings of the NH proton were observed even at 425K showing the absence of ionization indicating a thermal mechanism for the isomerization (Scheme 16). On the other hand, for 1-methylamino-2-nitroethene (**57a**), the $\Delta G^{\neq}$ value for the exchange of NH proton was lower than that for the $Z \rightleftharpoons E$ isomerization. Hence, in this case, an anionic mechanism may also be operating (Scheme 17).

Scheme 16



(57c) (*Z*) (*E*)

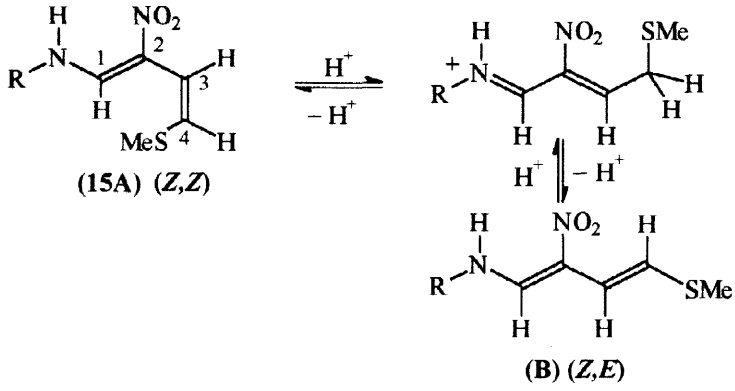
Scheme 17



In the case of the chiral, *tert.* nitroenamine (**10b**), the chemical shift of H-C(1) and NOE studies have shown that, in solution, the molecule exists in the configuration shown. The 3.88 ppm H-C(α) and the 8.54 ppm H-C(1) exhibit considerable NOE on each other (8-9%). The chemical shift of H-C(1) shows that it is *cis* to the NO_2 group and the same configuration persists in the solid state as shown by X-ray crystallography.[48,49]

In compound (**15a**), obtained from the ring-opening of 3-nitrothiophene by primary amines,[18] the ^1H NMR spectrum showed the presence of a major species (A) together with traces of a second isomer (B). The major isomer has been assigned the (*Z,Z*) configuration at the two double bonds on the basis of the following evidence. The chemical shift of H-C(1) is 7.45 ppm, indicating that this is located *trans* to the NO_2 group; $J_{H\text{-}C(3),H\text{-}C(4)}$ is 10Hz proving that they are *cis* related. In contrast, the pyrrolidine derivative (**16**) has the (*E,Z*) configuration, with the C(1)-H proton resonating at 8.35 ppm, being *cis* to the NO_2 group. Acid-catalysed equilibration of [**15a**(A)] gave a product consisting of the (*Z,Z*) and (*Z,E*) isomers in the ratio 3:1. The newly generated isomer (*Z,E*) corresponded to the trace component (B) present in the original sample of (**15a**), with a coupling constant $J_{H\text{-}C(3),H\text{-}C(4)}$ of 15Hz. Equilibration must have occurred by protonation-rotation-deprotonation (Scheme 18).

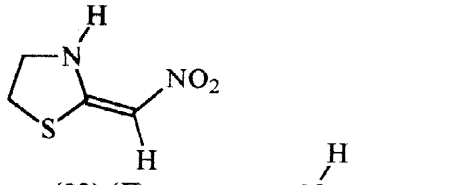
Scheme 18

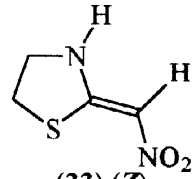


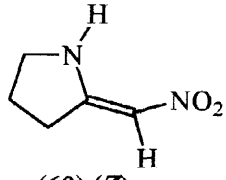
Solvent dependent $E \rightleftharpoons Z$ isomerism of the thiazolidine derivative (**33**) mentioned in the earlier review,[1] has been confirmed by a study of the ^{15}N NMR spectra.[50] In a carefully dried solvent mixture of $[^2H_6]$DMSO/$CDCl_3$ (1:2 v/v) at 25°C, using 40.5MHz and under conditions of gated ^1H-decoupling the compound showed two ^{15}N signals of comparable intensity at -264.1 and -275.4 ppm (both corresponding to C=C-NH). Signals corresponding to -N= could not be observed in the region between -60 and -120 ppm [referring to $MeNO_2$ as external standard].

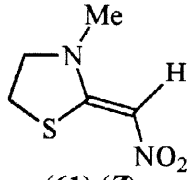
Other analogs of (**33**), however, do not exhibit this type of behaviour. Thus the pyrrolidine derivative (**60**) exists only in the *Z* configuration (NH, NO_2 *cis*) both in $CDCl_3$ and in $[^2H_6]$ DMSO, and the two N-methyl derivatives (**61**) and (**62**) exist exclusively in the configuration with NMe, NO_2 *trans*-related in both solvents. Even more surprising, the 6-membered homologue (**63**) as well as the open-chain analogue (**26**) continue to exist as the *E*-isomers (NH, NO_2, *cis*) on going from $CDCl_3$ to $[^2H_6]$DMSO, as seen in both the ^1H and ^{13}C spectra.[51] This is in contrast to the behaviour of (**33**).

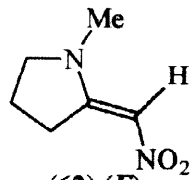
These experimental results, together with the short S...O contact in the solid state in (**33**) (see section 3.5) suggest the existence of a non-covalent, direction-dependent attractive interaction between the oxygen of the NO_2 and the divalent ring sulfur. This attraction may be the consequence of a favourable, nucleophile-like approach of the lone-pair of electrons on the oxygen along the back of the S-C bond. This corresponds to a HOMO (p type oxygen lone pair) -LUMO (σ^*on S-C) interaction. The geometrical requirement is apparently met particularly well in the 5-membered case (**33**), but not in (**63**) or in (**26**).[51]

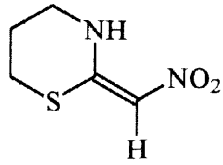

(**33**) (*E*)

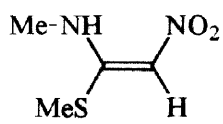

(**33**) (*Z*)


(**60**) (*Z*)


(**61**) (*Z*)

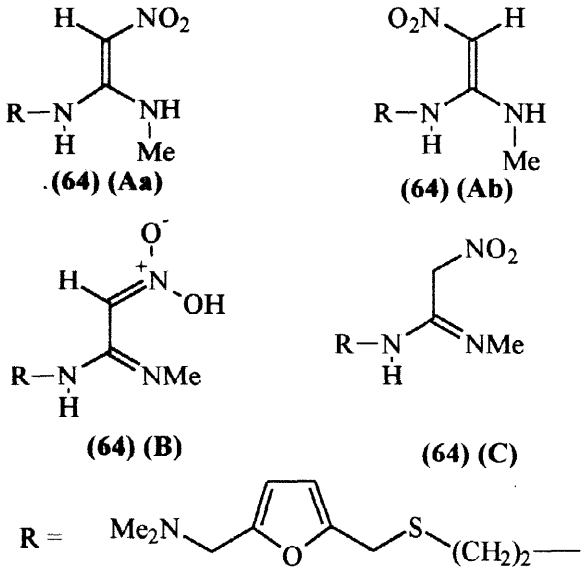

(**62**) (*E*)


(**63**) (*E*)


(**26**) (*E*)

Ranitidine is a selective histamine H_2 antagonist, used extensively as an anti-ulcer drug. A key feature of this molecule (**64**) is the presence of the 1,1-diamino-2-nitroethene moiety. The structure of the base and the hydrochloride, as well as the configuration and barrier to rotation around C(1)-C(2) have been extensively investigated.[52] Three tautomeric structures are possible nitroenamine (A), nitronic acid (B) and nitromethylamidine (C) and since the two amino substituents are different, two geometrical isomers (Aa, Ab) can be written for the nitroenamine. Of the three possible tautomers, the nitromethylamidine (C) could be rejected since there is no signal due to the CH_2 group in the ^1H NMR spectrum; only a one-proton singlet is seen in the olefinic region.

The ^1H NMR spectra of both ranitidine and its monohydrochloride (protonated on the Me_2N-side-chain) show temperature dependent variations consistent with a low barrier to rotation around C(1)-C(2). At 328K in $CDCl_3$, the base shows only one set of time-averaged signals due to the fast interconversion of the two geometrical isomers (Aa) and (Ab). At 271 K, the interconversion is much slower and two sets of signals are observed. The coalescence temperature is approximately 314K. The barrier to rotation, $\Delta G^{\neq}$ has been estimated to be 15.7± 0.1 kcal mol^{-1} and is the same as that for 1,1-bis(methylamino)-2-nitroethene. In CD_3OD, this value is further lowered to 13.0 kcal mol^{-1} being due to the disruption of the intramolecular H-bond in the polar solvent.



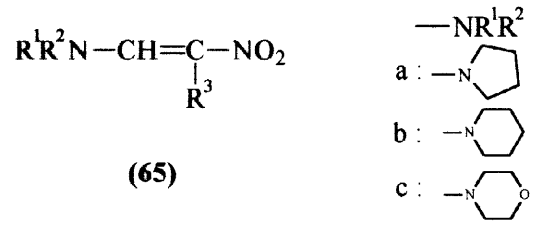
(64) (Aa) (64) (Ab) (64) (B) (64) (C)

At 271K, the two N*H* Me signals ($CDCl_3$) are seen as quartets and the two N*H*CH_2 signals as triplets and on this basis, the presence of the nitronic acid tautomer (B) can be ruled out.

The monohydrochloride shows only one set of signals in D_2O at 278K and above but in CD_3OD at 240K, separate NMe signals are observed, with the coalescence temperature of 262 K. The calculated energy barrier to rotation around C(1)-C(2) is 13.1 kcal mol^{-1}, the same as for the base in this solvent.

3.4 *Dipole moments*

Dipole moments of several nitroenamines have been measured,[53] confirming the existence of extensive conjugation as is also inferred from NMR studies. The magnitude of the dipole moment varies significantly with the different amine moieties, which is in contrast to the situation with simple enamines. Thus, the dipole moments of (**65**a, R^3=H) and (**65**b, R^3=H) are greater than that of the morpholinoenamine (**65**c, R^3=H). This is also in accord with the NMR data.[1]



(65)

3.5 *X-ray crystallography*

The X-ray crystal structures of several nitroenamines have been determined and relevant bond-lengths are given in Table 1. The configuration around C(1)-C(2) in the solid state need not necessarily be the same as in solution. Thus 1-methylamino-2-nitroethene (**57a**) exists in the *E*-configuration in the solid state with the MeNH and NO_2 disposed *trans* to each other. The molecule is planar, with the amine nitrogen being trigonal and the configuration about the N-C(1) bond is *s-Z*.[47]

The crystal structure of the pyrrolidine (**62**) and the thiazolidine (**33**) have been determined.[50] and surprisingly, in both cases the NO_2 and the ring nitrogen are *trans*-related to each other [**62**(*E*) and **33**(*Z*)]. From the data, it is difficult to decide whether in fact there is significantly more pyramidality at the ring nitrogen in (**33**) compared to (**62**) (as had been suggested previously).[1]

The most significant aspect of the crystal structure of (**33***Z*) is the existence of an intramolecular short distance between the sulfur atom and one of the oxygen atoms of the NO_2 of only 2.68 Å, well below the sum of their van der Waals radii.

The crystal structure of the ethanolamine derivative (**15b**) has been determined,[18] and the C-C bond-lengths of the butadiene chain are 1.385, 1.458 and 1.315 Å. The surprising feature of this molecule is that the butadiene moiety has assumed a configuration close to *cisoid* but it is not completely planar. There is a significant twist about the central single bond, thereby leading to a disruption of the conjugation.

The crystal structure of several nitroketeneaminals have also been elucidated, including ranitidine (**64**) (as its hydrogen oxalate),[57] and the structurally related hydrazone (**67**).[58] In the former, NO_2 is *cis* to the MeNH, while in the latter it is *cis* to the hydrazine group.

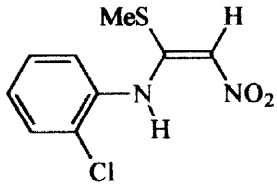
Crystal structures of several 2,2-dinitroethene-1,1-diamines have also been determined including the imidazolidine (**40a**) and its higher homologue (**40b**).[37] The former is essentially

planar, but the latter has a twist of 89° around the double bond. The planarity of (**40a**) is probably due to reduced crowding or more favourable hydrogen-bonding. Finally, the crystal structure of the 2,2-diamino-1-nitroacrylonitrile derivative (**68**) has also been determined,[59] with the NO_2 *cis* to the MeNH group as shown.

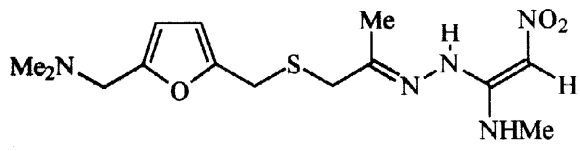
Table 1

Bond-lengths Å determined from X-ray crystallographic studies of nitroenamines.

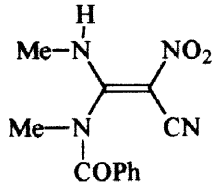
Compound	Configuration	N - C(1)	C(1) - C(2)	C(2) - NO_2	Ref.
57a	*E*	1.303	1.356	1.378	47
48a	*E*	1.334	1.345	1.394	54
		1.325	1.35	1.39	55
65c	*E*	1.323	1.368	NA	53
62	*E*	1.318	1.357	1.377	50
33	*Z*	1.317	1.405	1.342	50
15b	*Z*	1.302	1.385	1.396	18
66	*E*	1.338	1.378	1.378	56
51	-	1.349; 1.356	1.412	1.375	56
64	-	1.321; 1.315	1.433	1.353	57
67	-	1.335; 1.343	1.406	1.354	58
40a	-	1.322; 1.321	1.430	1.415; 1.404	37
40b	-	1.297; 1.306	1.473	1.383; 1.383	37
68	-	1.315; 1.409	1.402	1.404	59



(66)



(67)



(68)

3.6 *Theoretical calculations*

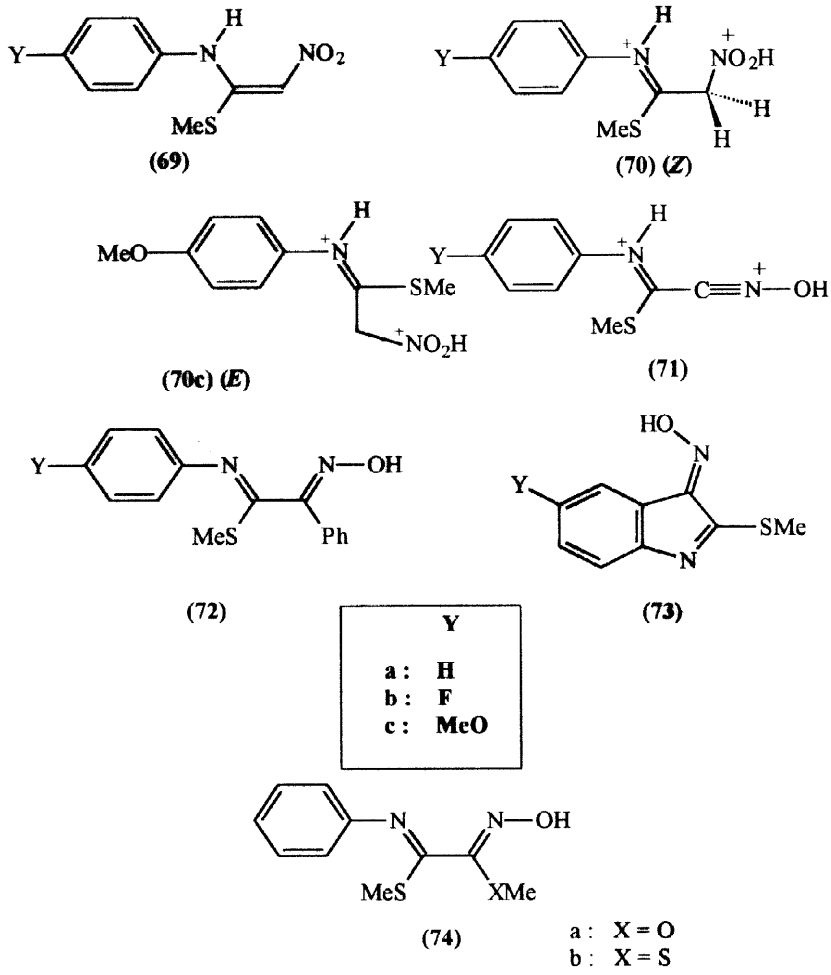
Theoretical calculations have been carried out on the simple unsubstituted nitroenamine molecule in solution, using the self-consistent reaction field approach.[60] This provides some insight into the effect of solvents on the $E \rightleftharpoons Z$ equilibrium, as well as on the barrier to rotation and the results seem to agree with the experimental observations. Previously, geometries, rotational barriers and isomer populations had been studied by the MNDO/H and AM1 methods[61] with attempts to include the crucial solvent effects. An effort has also been made to correlate the observed vibrational spectral characteristics of nitroenamines with the calculated values.[62] Calculations have been performed both by *ab initio* and semi-empirical techniques.

4. Reactivity

4.1 *Protonation and hydrolysis*

The behaviour of 1-methylthio-2-nitro-N-phenylethenamines (**69**) in superacids has been investigated both by NMR studies and by quenching experiments.[63] The nitroenamines were dissolved in triflic acid at 0° C and quickly cooled to -18°C and the ^1H and ^{13}C NMR spectra were monitored. The olefinic signal quickly disappeared and signals due to a CH_2 [δ_H 5.4 (s) and δc 75 ppm], indicating the formation of the C,O-diprotonated species (**70**) appeared. Only one set of signals was seen in the NMR in each case, assuredly due to the *Z* isomer formed as the kinetic product of protonation. Only in the case of the 4-methoxyphenyl derivative (**70c**) at 0°C, did a second set of bands appear slowly [δ_H 5.10 (s); δ_c 74.45 ppm] which was attributed to the formation of the *E* isomer. Configurational assignment was made on the basis of differences in chemical shifts and by analogy to the protonated forms of related compounds like imines and oximes. The final *Z/E* ratio in the case of (**70c**) was almost 1:1.

At low temperatures, cations (**70**) are slowly converted to the hydroxynitrilium ions (**71**), as indicated by the disappearance of the NMR signals due to CH_2. The iminium carbon signal moves upfield from about 185 ppm in (**70**) to about 166 ppm in (**71**) due to conjugation while the hydroxynitrilium carbon is seen as a broad, weak signal near 26.5 ppm, similar to that of aromatic nitrile oxides.

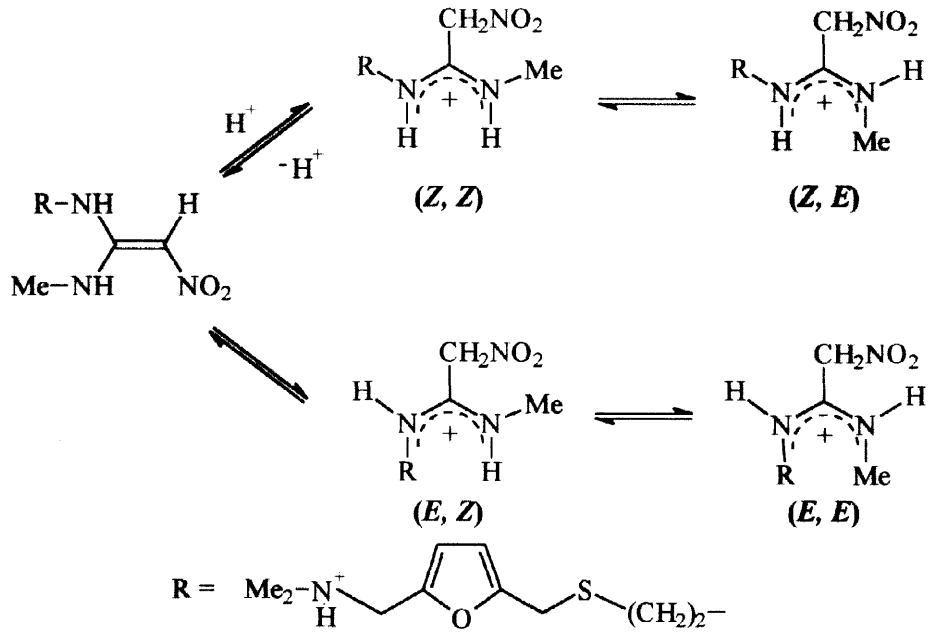


The structure of (**71**) has been confirmed by trapping experiments. Thus, if (**69**) is dissolved in benzene along with triflic acid, the hydroxynitrilium ion (**71**) formed *in situ* reacts with benzene to form (**72**) in good yields. In the case of the methoxy derivative (**69c**), intramolecular cyclization also takes place, leading to a mixture of (**72**) and (**73**). Compounds (**72**) have been isolated and fully characterised. Similarly, the quenching of ion (**71a**) with either MeOH or MeSH leads to (**74a**) or (**74b**) respectively.

The site of protonation as well as behaviour on hydrolysis of ranitidine (**64**) have been studied.[52,64] The pKa of ranitidine is 8.2 and the basic centre corresponding to this, is the side-chain NMe_2 group. The UV spectrum of the base in water at pH 6.5 shows a long wave-length λ_{max} at 315 nm (ε 15,400) mainly due to the nitroketeneaminal unit. [1,1-Bis(methylamino)-2-nitroethene has λ_{max} at 226 (ε4200) and 313 nm (ε15,200)]. In stronger acid (M, HCl) the 315 nm band disappears, indicating that the second protonation leads to loss of conjugation. The pKa for this is 2.3 suggesting that in this process, C(2) protonation of the nitroenamine has taken place. In the corresponding ^1H NMR, the olefinic proton at 6.83 has disappeared and is replaced by the CH_2NO_2 signal at δ5.80. At the same time, two sets of signals are seen for

NMe [3.13, 3.03 ppm (d)], NCH_2 (q) and SCH_2 (t). The second protonation - deprotonation is a slow exchange process on the NMR time-scale in contrast to the first protonation at NMe_2, since signals due to mono- and di- protonated ranitidine can be seen simultaneously. The two sets of signals of the diprotonated species are likely to be due to the presence of two geometrical isomers of the amidinium group, and on the basis of NOE experiments, it has been suggested that these are the (*E,Z*) and (*Z,E*) isomers (Scheme 19).

Scheme 19



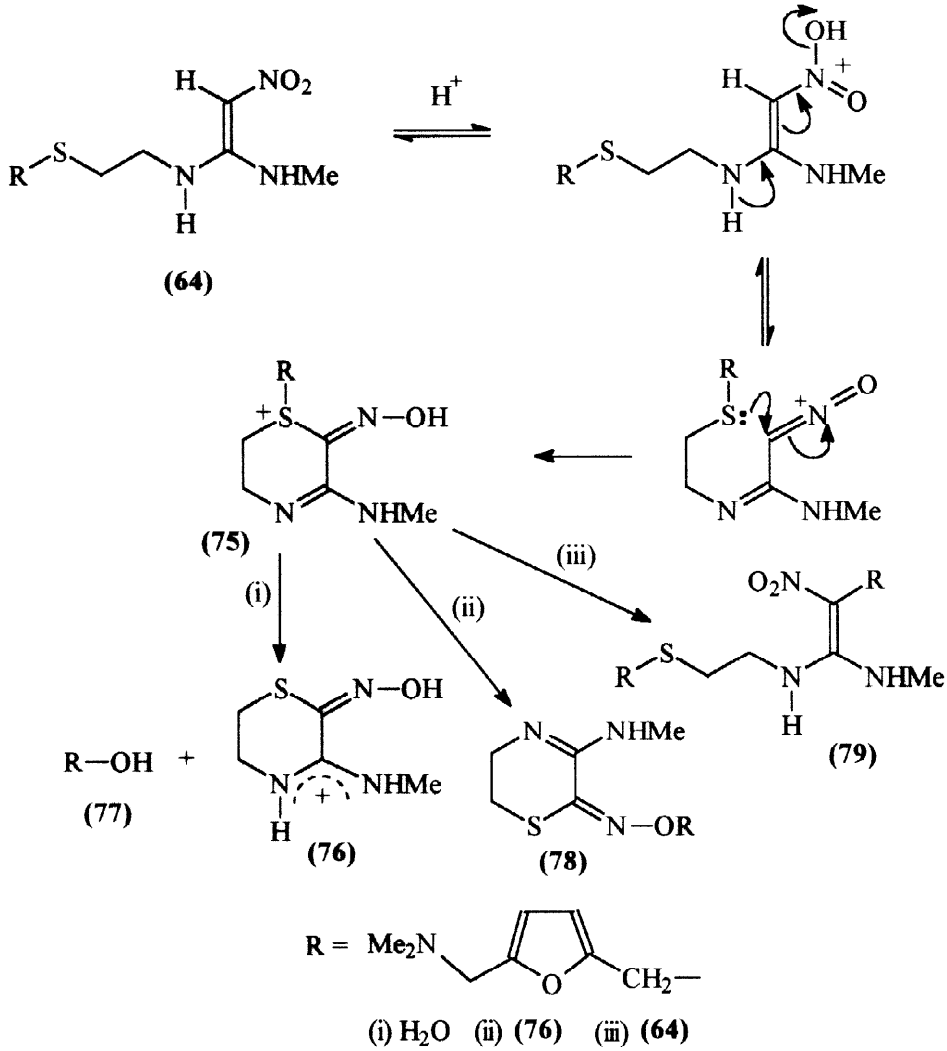
At pH7, the ranitidine molecule is quite stable, hydrolysis occurring to an extent of <5% after 2 years at 30°C. Likewise, at very low pH (<1), ranitidine hydrochloride appears to be resistant to hydrolysis, even on prolonged heating. This is in accord with the results of the protonation experiments, when it was shown that the second proton is attached to the carbon, resulting in the formation of the nitromethyl amidinium ion.

Hydrolysis of ranitidine takes place rapidly in the pH range 2-4 and is complete after 6h at reflux temperature. The products formed are shown in Scheme 20 with the crucial intermediate being (**75**). Attack on this intermediate by water would lead to the major products (**76**) and (**77**) and the former (as its free base) can also act as the nucleophile on (**75**) leading to the compound (**78**). Finally, if ranitidine itself is the nucleophile acting on (**75**), the product would be (**79**).

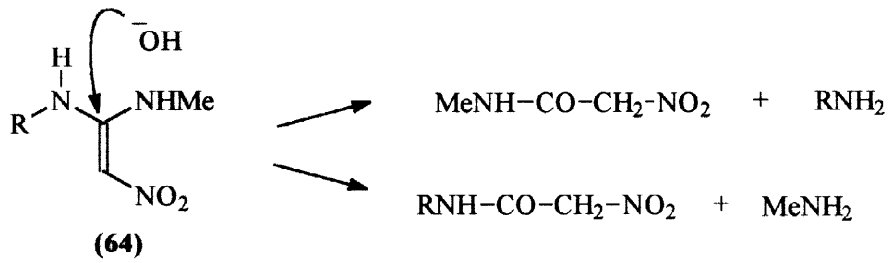
Hydrolysis at pH values >9 is also rapid, as 4h at reflux temperature completes the hydrolysis. In this case, the products are formed by an addition of OH^- at C(1) of the

nitroenamine, followed by elimination of either of the two amine moieties, resulting in an N-substituted nitroacetamide (Scheme 21).

Scheme 20

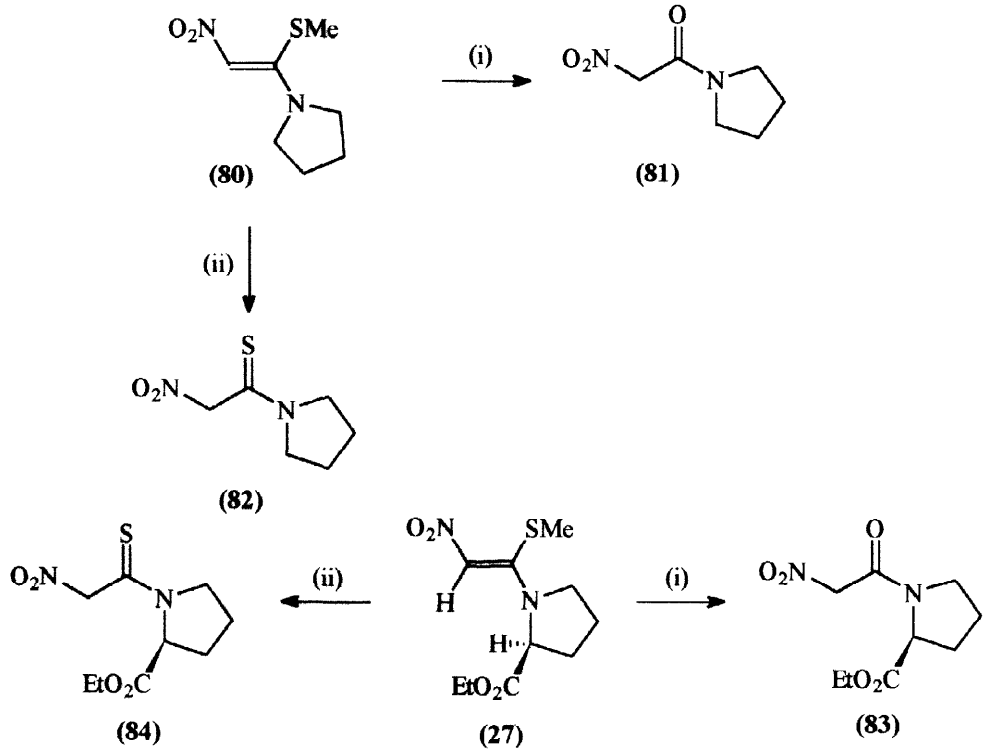


Scheme 21



1-Methylthio-2-nitro-N-arylethenamines have been hydrolysed by aq.KOH to provide nitroacetanilides.[65] In general, N-substituted 1-methylthio-2-nitroethenamines are excellent

precursors for N-nitroacetyl and N-nitrothioacetyl derivatives of various amines and amino acid esters.[28] Thus Hg^{2+}-catalysed hydrolysis (MeCN-H_2O, 3:1, 30°C), of 1-methylthio-1-pyrrolidino-2-nitroethene (**80**) gave N-nitroacetyl pyrrolidine (**81**) whereas, treatment of (**80**) with dry Na_2S in de-oxygenated EtOH containing acetic acid for 3h at 30°C, led to the thioamide (**82**) in 68% yield. The nitroenamine (**27**) from ethyl (*S*)-prolinate similarly gave (**83**) and (**84**).[28] N-Nitroacetyl derivatives of other (*S*)-α-amino acid esters have similarly been prepared[30] and N-Nitroacetyl sulfonamides could also be obtained in 60-75% yields by Hg^{2+}-catalysed hydrolysis of (**38**).[36]



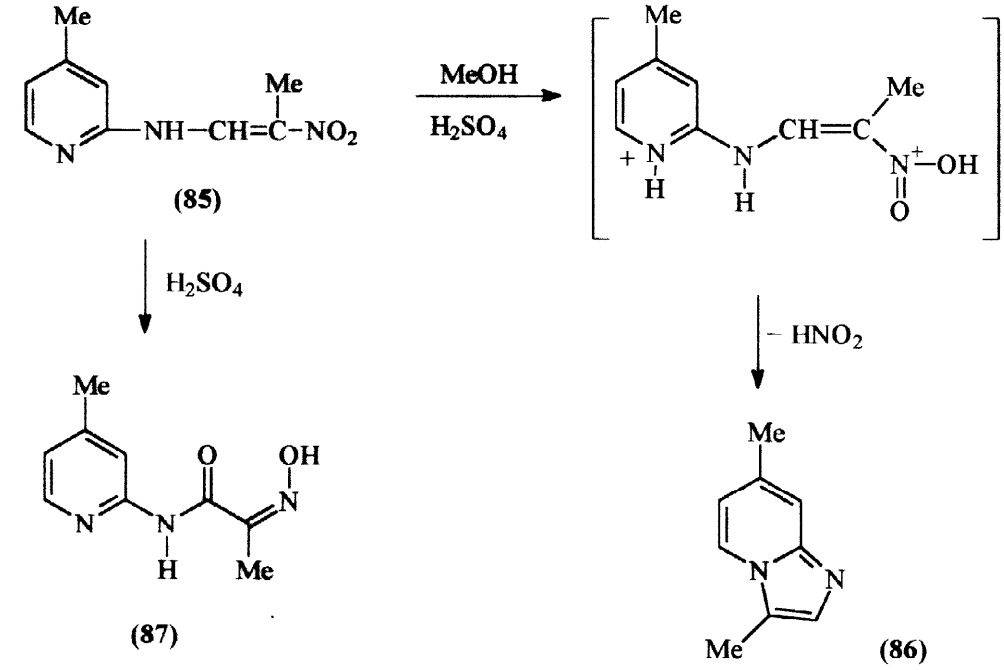
(i) $MeCN-H_2O$, Hg^{2+} (ii) Na_2S, EtOH–HOAc

4.2 *Acid-induced cyclizations*

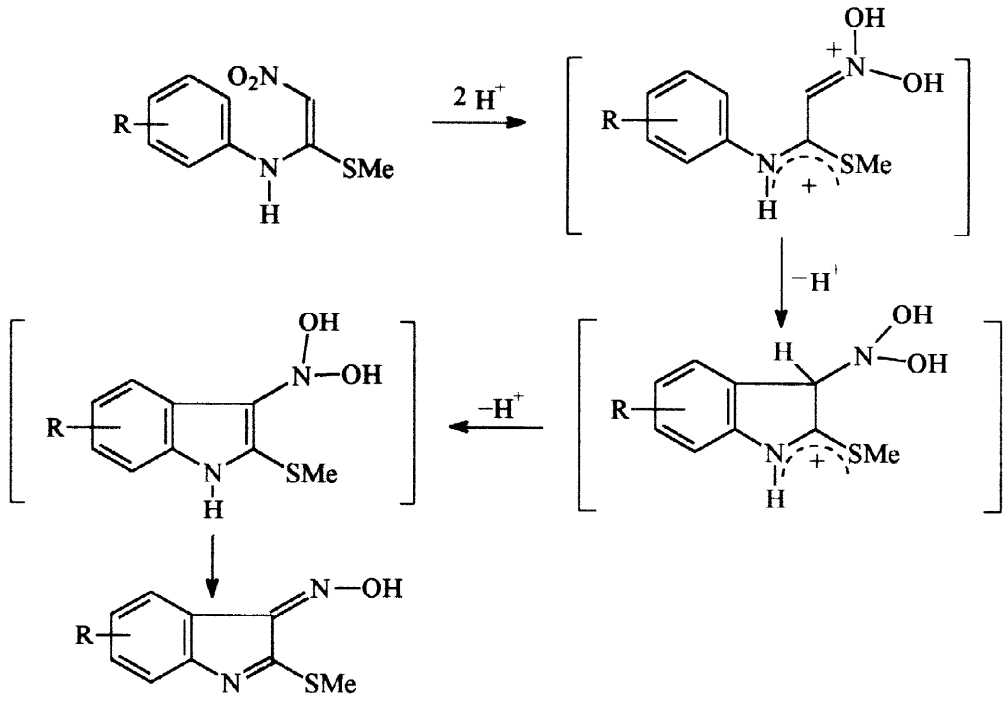
There are a few reports on the formation of heterocycles by acid-induced cyclization of nitroenamines in which the NO_2 group takes part or is eliminated. For example, the nitroenamine (**85**) bearing a 2-pyridyl substituent on the amine cyclises to (**86**) in 70% yield on heating with MeOH-H_2SO_4. With conc.H_2SO_4 at 0°C, the oxime (**87**) results (Scheme 22).[66,67]

Several 1-methylthio-2-nitro-N-aryl ethenamines have been cyclized in low yields to 3H-indol-3-one 3-oximes by means of triflic acid at room temperature (Scheme 23).[68]

Scheme 22



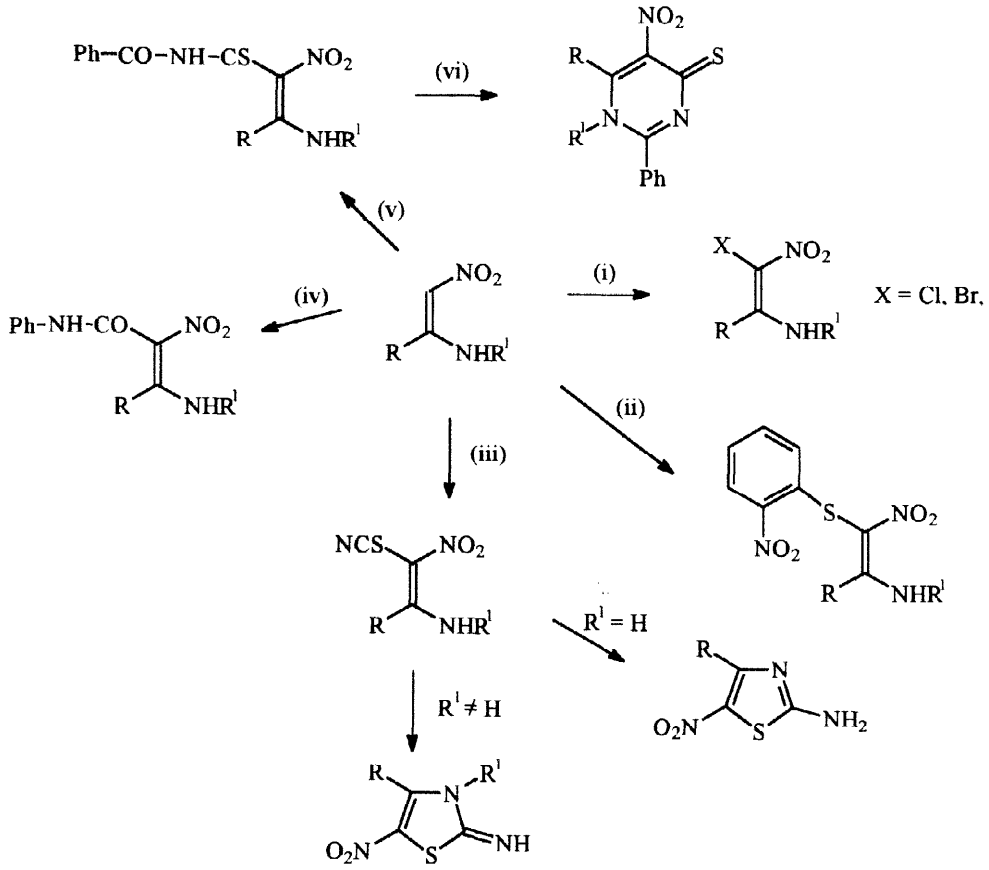
Scheme 23



4.3 *Reaction with electrophiles*

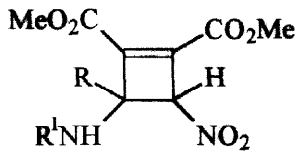
The reaction of nitroenamines with several electrophiles occurs at C(2) as expected. The electrophiles that have been reacted thus far include N-halosuccinimides, *o*-nitrobenzenesulfenyl chloride, thiocyanogen, phenyl isocyanate and benzoyl isothiocyanate (Scheme 24)[2,69]. Acetylene dicarboxylic ester undergoes cycloaddition with nitroenamines in refluxing THF and thermolysis of the resulting cyclobutene derivatives (**88**) leads to the 1-amino-4-nitrobutadiene-2,3-dicarboxylates (**89**).[69] Typical spectral data for (**89**; R=R^1=Me) are; UV :λ_{max} 322 nm (ε64,00);^{1}H NMR ($CDCl_3$): H-C(4) 6.84 ppm.

Scheme 24

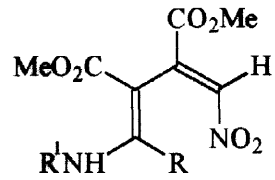


(i) N- halosuccinimide (ii) *o*-nitrobenzenesulfenyl chloride
(iii) thiocyanogen (iv) phenyl isocyanate, Δ, MeCN
(v) benzoyl isothiocyanate (vi) DMF, Δ

It has been found that the use of acetone as solvent for the addition of phenyl isothiocyanate to nitroketeneaminals results in better yields (70-96%) of the 3,3-diamino-2-nitrothioacrylamides than those reported previously using EtOH or toluene as solvent.[70]



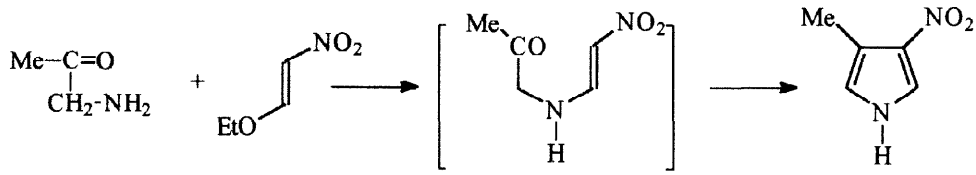
(88)

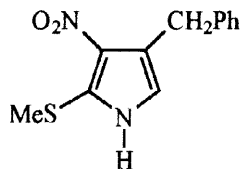


(89)

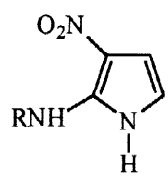
Intramolecular attack by the nitroenamine on a suitably located carbonyl group results in the formation of heterocycles. Several such examples have come to light in which the site of nucleophilic activity is the enaminic carbon atom C(2). α-Aminoketones react with 1-ethoxy-2-nitroethene (**4a**; R^1=R^2=H) to give 3-nitropyrroles in high yields. Probably, the reaction proceeds *via* a nitroenamine (Scheme 25).[3,6] 2-Amino-2-deoxy-D-glucose thus leads to 4-nitro-2-(D-arabinotetritol-1-yl) pyrrole and similarly, reaction of 1-amino-3-phenylpropan-2-one hydrochloride with 1-(methylsulfinyl)-1-methylthio-2-nitroethene (**21b**), in the presence of NaOMe in refluxing MeOH, gives the 3-nitropyrrole (**90**) in 52% yield.[23] The initial displacement of the methylsulfinyl group is followed by enamine cyclization on the carbonyl. The aminoacetaldehyde derivatives (**22**) likewise cyclize to 3-nitropyrroles (**91**) under mildly acidic conditions.

Scheme 25





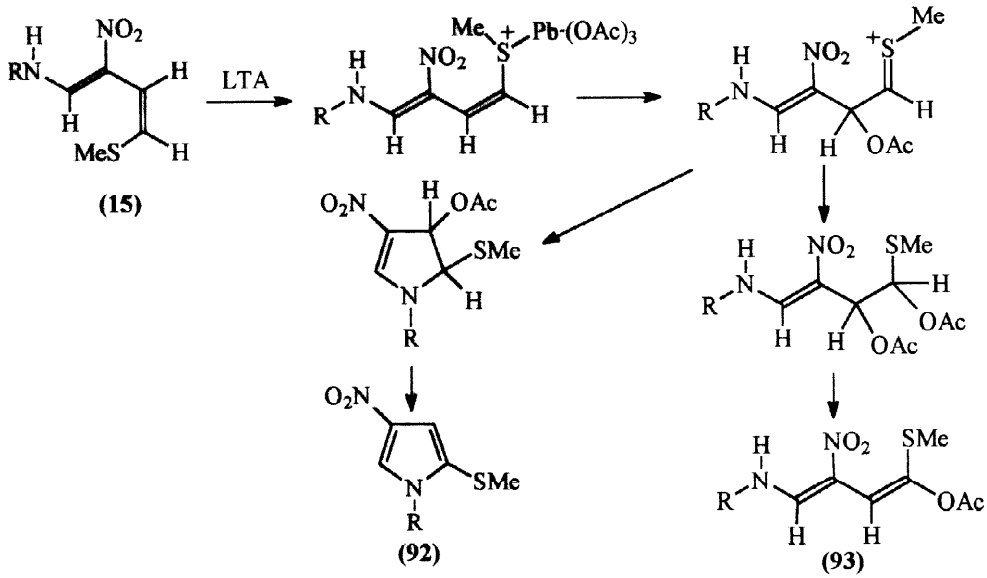
(90)



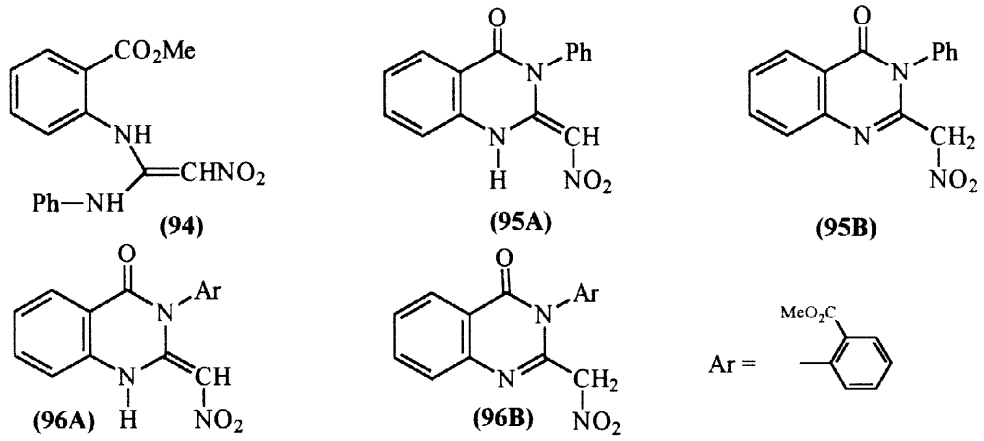
(91)

Lead tetraacetate oxidation of the 1-amino-4-methylthio-2-nitrobutadienes (**15**) gives the pyrroles (**92**) (14% yield) along with the acetoxy compounds (**93**) (51%) (Scheme 26).[18] In this cyclization to the pyrrole (**92**), the nitrogen of the nitroenamine has acted as the nucleophilic centre.

Scheme 26

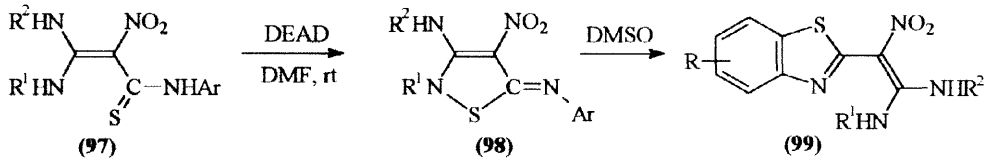


The reaction of 1-methylthio-2-nitro-N-phenyl ethenamine with methyl anthranilate provides another example in which the site of nucleophilic activity is the nitrogen and not C(2) of the nitroenamine[71], since the intermediate 2-nitro-N,N'-bisarylethylene-1,1,-diamines (**94**) is not expected to be a good enamine. The product exists as a mixture of the two tautomers (**95A**) [^{1}H NMR signal at δ5.92 (s) for = $CHNO_2$] and (**95B**) [δ5.50 ppm (s) for CH_2NO_2] in the ratio 5:4 in [$^2H_6$] DMSO solution. Signals due to both species are also seen in ^{13}C NMR. Similarly, the reaction of two moles of methyl anthranilate with one of 1,1-bis(methylthio)-2-nitroethene (**21a**) gives (**96**) seen in [$^2H_6$] DMSO solution as a mixture of the two tautomers (A) and (B).



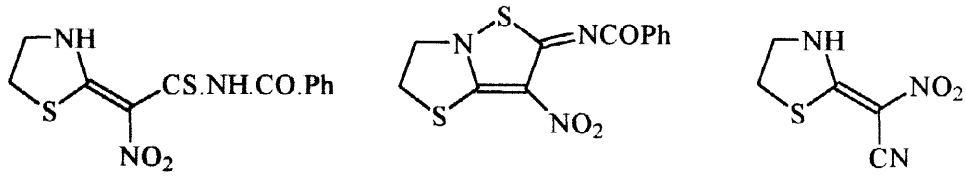
4.4 *Further transformations of the isothiocyanate adducts*

The reaction of nitroketeneaminals with isothiocyanates had been discussed earlier.[1] The 3,3-diamino-2-nitrothioacrylamides (**97**) thus formed, could subsequently be oxidised by bromine to the 4-nitroisothiazol-5-(2H)-imines (**98**), but it has now been found that diethyl azodicarboxylate is a better reagent for bringing about the oxidative conversion of (**97**) to (**98**). Furthermore, an extremely interesting rearrangement of (**98**) to the benzothiazole derivatives (**99**) brought about by dissolution in DMSO has been uncovered.[72] and a plausible mechanism has been suggested for this rearrangement.



(**97**) (**98**) (**99**)

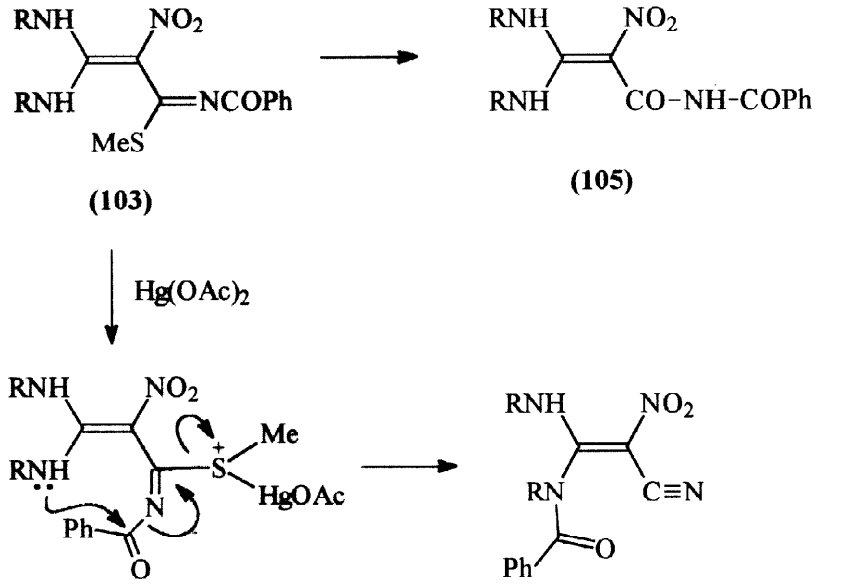
Oxidative conversion of benzoyl isothiocyanate adducts of nitroketeneaminals to 2,2-diamino-1-nitroacrylonitriles had also been previously mentioned.[1] Now this has been extended to the thiazolidine derivative (**33**). This nitroenamine is less reactive than the corresponding imidazolidine derivative as it does not form an adduct with phenyl isothiocyanate, but, with the more reactive acyl isothiocyanates, it does form the expected adducts. The benzoyl derivative (**100**) could be oxidatively cyclized to the 2-benzoylimino-3-nitro-5,6-dihydro-(2H)-isothiazolo[3,2-b] thiazole (**101**), which in turn, undergoes the characteristic alkoxide-induced fragmentation[1] to give the push-pull ethylene (**102**).[31] Benzoyl isothiocyanate adducts of nitroketeneaminals could be carefully S-methylated by means of MeI in DMF at room temperature[59] and these S-methyl derivatives (**103**) undergo interesting transformations. Treatment with mercuric acetate in DMF at room temperature leads to two products, the nitrile (**104**) (major product, 46 to 85% yields), and the hydrolysis product (**105**)[59] with the conversion probably proceeding as shown in Scheme 27. This fragmentation is reminiscent of the oxidative fragmentation referred to above.



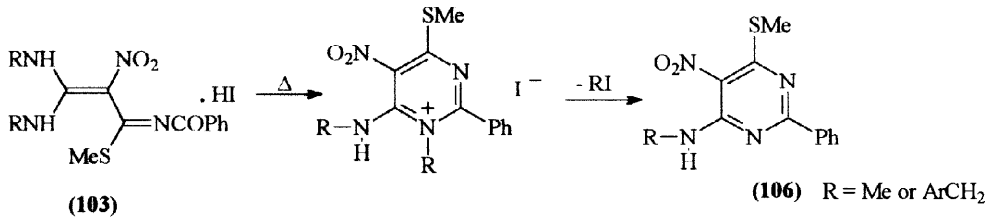
(**100**) (**101**) (**102**)

The S-methyl derivatives (**103**) also undergo an interestisng thermal cyclization. Thus, heating the benzoyl isothiocyanate adducts with MeI in EtOH leads to the pyrimidine derivatives (**106**). Initial cyclization by the attack of the amine on the carbonyl is followed by N-dealkylation by the iodide ion (Scheme 28).[73,74,75]

Scheme 27



Scheme 28

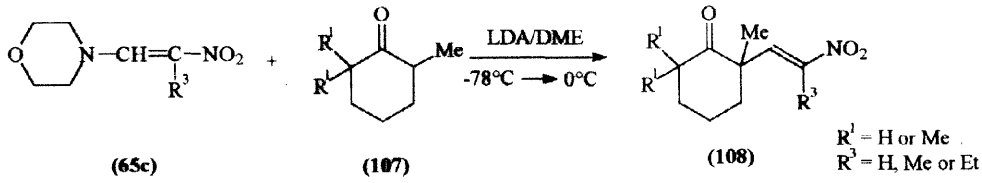


4.5 *Reaction with nucleophiles*

The reaction of 1-dimethylamino-2-nitroethene with aryl ketones in the presence of alkoxides had been referred previously[1] but the full synthetic potential of this type of displacement by carbon nucleophiles had not been explored.

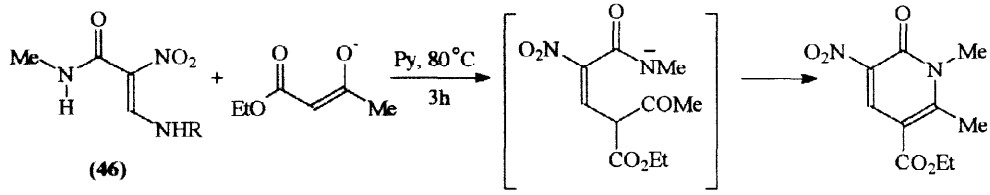
It has now been found that 1-morpholino-2-nitroethenes (**65c**; R^3=H, Me or Et) are ideal substrates for reaction with lithium enolates of ketones and aldehydes.[8] Thus, for example, cyclohexanones (**107**) lead to the products (**108**) in 50-99% yields, mostly having *E*-stereochemistry, and only occasionally the *Z*-isomer is formed as a minor component. Aldehyde enolates also undergo the nitroolefination reaction, but the products are unstable. Other carbonyl compounds which have been successfully subjected to this reaction are esters, lactones and lactams. The synthetic potential of this reaction will be dealt with in section 5.

The aminomethylene derivatives (**46**) of nitroacetic acid amides react with the enolate of acetoacetic ester to give a polysubstituted pyridone (Scheme 29).[41]



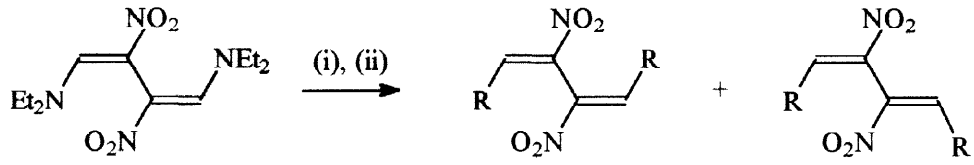
(65c) (107) (108)

Scheme 29



(46)

It has been reported earlier [1] that ring-opening of 3,4-dinitrothiophene by means of primary or secondary amines leads to 1,4-diamino-2,3-dinitro 1,3-butadienes (**109**). Reaction of these with Grignard reagents in THF at 0°C results in addition-elimination, leading to the 2,3-dinitro-1,3-butadienes (**110**) in almost quantitative yields.[76]. The main component of the product is the *(E,E)* isomer, along with minor amounts of the (*E,Z*) isomer. The ^{1}H NMR spectrum of the (*E,E*) isomer (**110**; R=Et) shows the vinylic protons at about 7.65δ, whereas in the (*E,Z*) isomer, two peaks are seen at δ7.53 and 6.27 ppm.

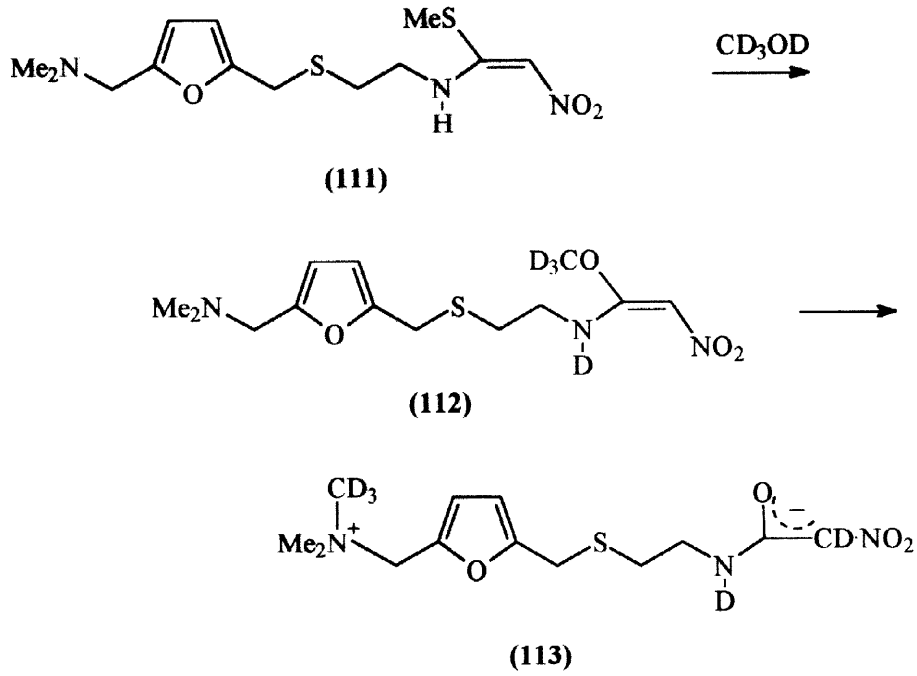


(**109**) (**110**) (***E,E***) (**110**) (***E,Z***)

(i) RMgBr, THF, 0°C (ii) quenching with 3%HCl

1-Methoxy-2-nitro-N-alkylethenamine can apparently function as a methylating agent, and the evidence can be seen in ranitidine chemistry. When the methylthio derivative (**111**) was kept in CD_3OD at room temperature for several weeks, the final product isolated was (**113**), having a CD_3 group attached to the side-chain nitrogen. It is reasonable to assume that the transformation had occurred *via* the initially formed (**112**).[77]

Reaction of 1-diethylamino-2-nitroolefins with ethyl isocyanoacetate in the presence of DBU at room temperature, followed by quenching with HCl, leads to 1-hydroxypyrazoles in good yields (Scheme 30).[78]

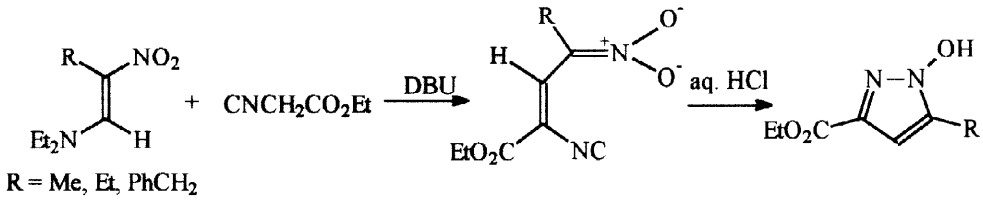


(111)

(112)

(113)

Scheme 30



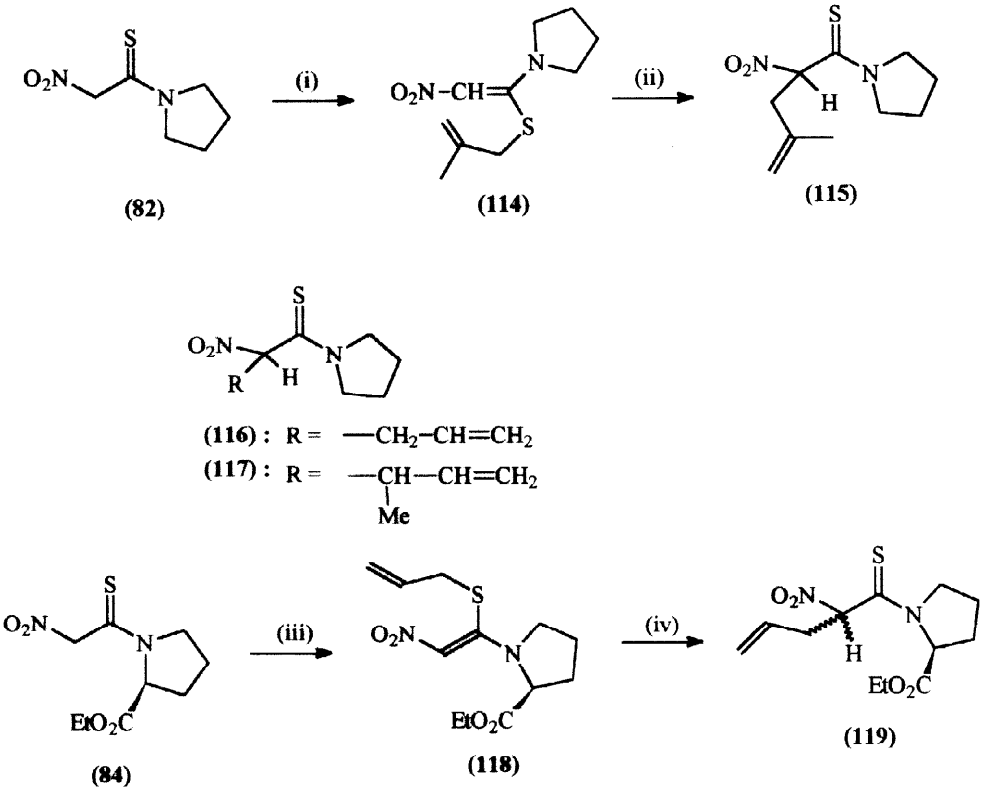
4.6 *Pericyclic reactions*

Thio-Claisen rearrangements of N-substituted 1-allylthio-2-nitroethenamines occur in an unexpectedly facile manner. The S-methallyl derivative (**114**) obtained from N-nitrothioacetyl pyrrolidine (**82**) undergoes thermal [3,3] sigmatropic rearrangement at 45°C to give the C-methallyl derivative (**115**) in 51% yield (Scheme 31). The vinyl proton singlet at 6.83 ppm of (**114**) vanishes and is replaced by a multiplet at 5.67 ppm. Similar reaction of (**82**) with allyl bromide and crotyl bromide leads to (**116**) and (**117**) respectively.[79]

There are two surprising features in these transformations, the first being the facility with which the thio-Claisen rearrangement takes place while the second is the degree of stereoselectivity observed in the corresponding rearrangement of the (*S*)-proline ester derivative (**118**). This S-allyl derivative was obtained by treating the thioamide (**84**) with allyl bromide at 30°C and it shows the vinyl proton signal at 6.80 ppm in the ^{1}H NMR spectrum. At 45-50°C, it is transformed in 90% yield to the C-allyl derivative (**119**) as a mixture of two diastereomers (Scheme 31). The *de* is estimated to be 66%. The major diastereomer appears to have the thermodynamically less favoured configuration, since deliberate base-catalysed (or even

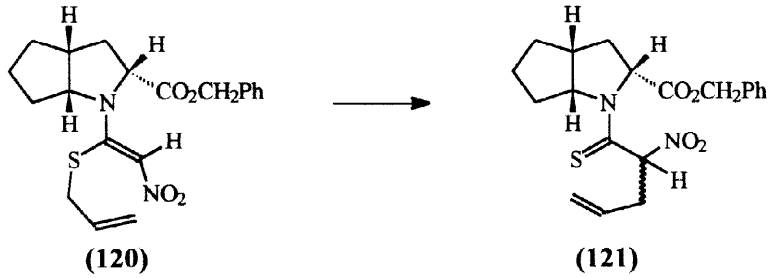
thermal) equilibration results in the preponderance of the other diastereomer. The induction of chirality by an asymmetric centre located two atoms away from the C(2) carbon of the [3,3] framework is quite surprising.[79]

Scheme 31



(i) methallyl chloride (ii) 45°C (iii) allyl bromide (iv) 45-50°C

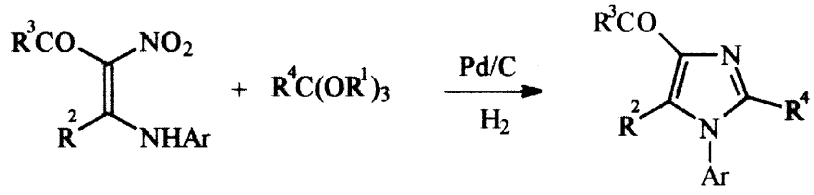
The benzyl ester of the bicyclic analogue of proline with the (all-*R*) configuration has given the maximum diastereoselectivity so far in this series.[80] The C-allyl derivative (**121**) is obtained from (**120**) with a *de* of 70%. The rearrangement takes place at room temperature in 3h to give (**121**) in 52% yield.



4.7 *Reductive transformations*

Reductive acylation of 1-anilino-2-nitroethenes leads to 1-arylimidazoles.[39] Thus catalytic hydrogenation (Pd/C) of the esters (**43**) or ketone (**44**) in the presence of excess carboxylic acid orthoester leads to 1-arylimidazoles in moderate yields (Scheme 32).

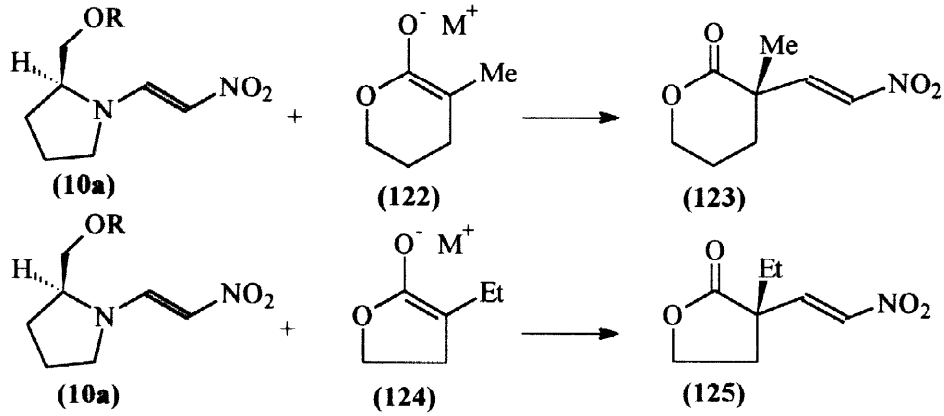
Scheme 32



R^3 = OMe or Me

5. Chiral nitroenamines in asymmetric synthesis

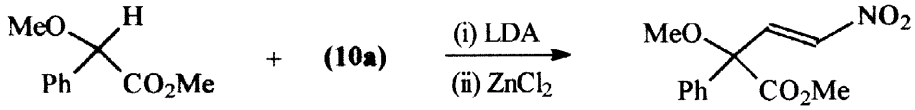
As discussed in section 4.5, nitroenamines can react with a variety of carbon nucleophiles by an addition-elimination process in which the amine is expelled. With a chiral nitroenamine, this may result in asymmetric induction with the advantage that it will not be necessary to remove the chiral auxiliary at a later stage in the synthetic sequence.



Fuji, Node and their coworkers have effectively used this strategy in several stereo and enantioselective syntheses. In the first example, it was demonstrated that high enantioselectivity could, in fact, be obtained in the construction of chiral quaternary carbons.[11] Thus, reaction of the lithium enolate (**122**) of the six-membered lactone with the chiral nitroenamine (**10a**) gave the product (**123**) with 41% *ee*. If Zn^{2+} was used as the counterion instead of Li^+ in the above reaction, the *ee* rose dramatically to 86%. However, under the same conditions, the zinc enolate of the five-membered lactone (**124**) gave the product (**125**) with only 63% *ee*.

Three remarkable facts have emerged from an extensive study of such nitroolefinations of for example, lactones, esters and lactams.[11,12,48,49,81,82] Firstly, zinc enolates have enhanced

reactivity over the corresponding lithium enolates in asymmetric nitroolefination. In addition, or as a consequence, the enantioselectivity is increased dramatically by the use of the zinc enolates. Thus, the reaction of the lithium enolate of the ester (**126**) with the chiral nitroenamine (**10a**) at -78°C gives (*S*) (**127**) in 88% yield with only 6% *ee*, while addition of 1 mol eq. of $ZnCl_2$ results in 96% yield of (*R*) (**127**) with 69% *ee*.[81]



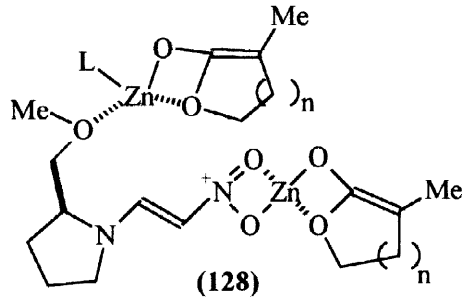
(126) **(127)**

Secondly, such nitroolefination invariably leads to exclusive or preferential formation of the *E*-nitroolefin.

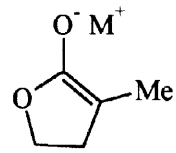
Finally, the reaction of the enolates of the lactones (**122**) and (**124**) with the chiral nitroenamine (**10**) derived from (*S*)-prolinol, the newly created chiral quaternary carbon has the (*S*)-configuration.[48]

Quenching and cross-over experiments have been carried out in order to provide a reasonable explanation for the above observations. The higher reactivity of the zinc enolates is ascribed to the stronger Lewis acidity of Zn^{2+} towards the nitroenamine compared to that of Li^{+}. Based on this, a catalytic cycle has been postulated in which the zinc enolate reacts preferentially in the presence of the lithium enolate and the zinc enolate is subsequently regenerated by metal-metal exchange.[81]

The first step in the sequence is the addition of the zinc enolate to the zinc complex (**128**) with the adduct formation being irreversible, as shown by cross-over experiments.[49] Of the four possible ways in which the two reactants can approach each other the *re-re* approach would lead to the (*S*)-configuration of the product, whereas the *si-si* approach would lead to the (*R*)-configuration. At -78°C, the methoxyl group in the nitroenamine also functions as a chelating site for the metal cation to make the *si*-face bulkier. The *si-si* approach is thus hindered by the bulkiness of the side-chain on the pyrrolidine,[82] whereas the *si-re* and *re-si* approaches would lead to transition states with higher energy. It is assumed that the original *s-E* conformation about the N-C(1) bond in the nitroenamine is preserved.



(128)
n = 1 or 2
L = Cl (or) solvent



(129)

Quenching experiments prove that the reaction stays at the adduct stage in the medium and elimination of the chiral amine takes place only during work-up.[49] The preferred conformation of the transition state for this elimination is such that the formation of the *E*-olefin is favoured as the transition state leading to the *Z*-olefin suffers from severe A-strain.[48] The implication of the irreversibility of the adduct formation is that the asymmetric induction is controlled kinetically.[49]

It has been mentioned above that metal-complexation at the side-chain oxygen of the prolinol moiety increases the steric bulk at the *si*-face of the nitroenamine. Confirmation of this is provided by reacting the zinc enolate of the γ-lactone (**129**) with the series of nitroenamines (**10-13**) derived from (*S*) prolinol. The enantioselectivity increases in the following order :

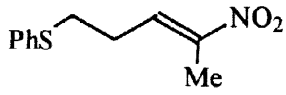
10a (*ee*, 56%)<**11a**, **12a** (*ee*, 83%)<**13a**(*ee*, 88%)

Introduction of a methyl substituent on C(2) of the nitroenamine increases the *ee* further, with (**13b**) leading to an *ee* of 93%. Thus, the use of this methodology for the asymmetric nitroolefination of γ-lactones has also been established.[12,82]

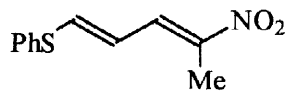
The above nitroolefins (such as **123,125**) of defined stereochemistry have been used as starting materials for the enantioselective synthesis of several natural products, for example, indole alkaloids, [83,84] diterpenoids,[85,86] and physostigmine [87,88].

6. Nitrodienamines and nitropolyenamines

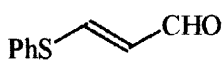
A practical route for the synthesis of 1-dialkylamino-4-nitro-1,3-butadienes has been described recently[89] and is similar to the earlier reported one for nitroenamines.[13] Michael addition of thiophenol to acrolein is followed by an aldol condensation with nitroethane and elimination of water to give (**130**). Chlorination of this with sulfuryl chloride and elimination of HCl by base gives the diene (**131**). The phenylthio group in this can be displaced by *secondary* amines to yield the nitrodienamines (**133**). An alternative route to (**131**) is the reaction of the aldehyde (**132**) with nitroethane in the presence of DBU, followed by alumina-mediated dehydration.



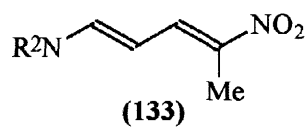
(130)



(131)



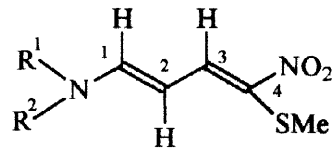
(132)



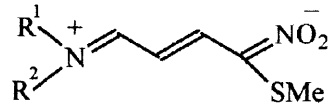
(133)

The nitrodienamines (**133**) appear to consist of only one isomer in each case, from their NMR spectra and the *(E,E)* geometry has been assigned on the basis of the coupling constants in the ^{1}H NMR spectra. The X-ray crystal structure of (**133**; R_2N- = 1-piperidinyl) has confirmed this geometry and the molecule is essentially planar. The C-C bond-lengths of the butadiene moiety are : 1.37 [C(1)-C(2)], 1.42 [C(2)-C(3)] and 1.35 Å [C(3)-C(4)]. In MeOH, the compounds exhibit long wavelength absorption maxima at around 460 nm (log ε 4.46).

Further investigations have been carried out on the structure and configuration of the push-pull butadienes (**134**) obtained by the ring-opening of 2-nitrothiophene.[90] These compounds result from the action of primary and secondary amines on 2-nitrothiophene in the presence of $AgNO_3$, followed by methylation.[1] The intriguing feature in the ^{1}H NMR spectrum of these compounds is the chemical shift of H-C(2), which is unexpectedly downfield [δ5.72 (**134a**); 5.60 (**134b**); 5.80 ppm (**134c**)] compared to that of the similar proton in (**133**) [4.99 ppm]. One possible explanation for this is based on the results of the x-ray crystal structure of (**134b**) (see below),[90] as the downfield shift of H-C(2) may result from its spatial proximity to the S atom in solution as well as in the solid.



(134)



(135)

a : $R^1 = R^2 = Et$
b : $R^1, R^2 =$ —$(CH_2)_4$—
c : $R^1 = n$Bu; $R^2 = H$

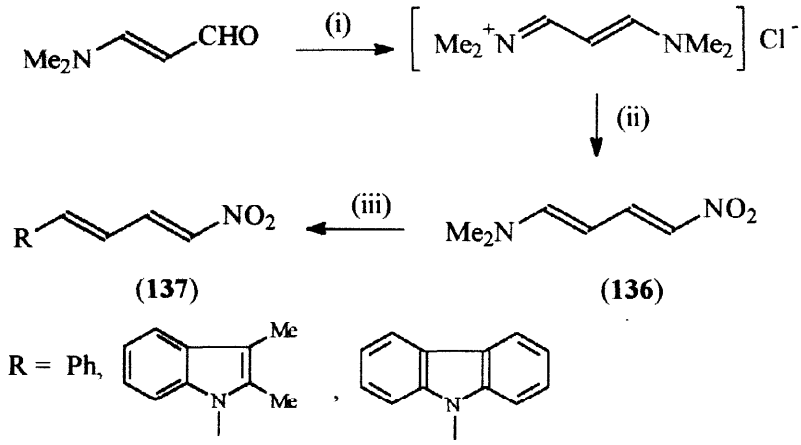
Extended conjugation over the entire molecule as shown in (**135**) is indicated by the magnetic non-equivalence of the α-CH_2 groups of (**134b**) both in ^{1}H and ^{13}C NMR spectra [δ_H : 3.40, 3.60 ppm; δ_C: 47.33, 52.74 ppm].

The x-ray crystal structure of (**134b**) reveals that the C-C bond-lengths are 1.380 [C(1)-C(2)], 1.380 [C(2)-C(3)] and 1.371 Å [C(3)-C(4)] and that there is a close contact between S and H-C(2), in which the hydrogen approaches S at an angle of 27° from the perpendicular to the plane through atoms C(4)-S-CH_3. This is very close to the predicted approach of electrophiles to divalent sulfur. The positioning of the hydrogen atom along a sulfur lone-pair orbital may contribute to the stability of this conformation and may constitute an example of H-bonding of the type C-H...S.

The nitrodienamine (**136**) has been synthesised from dimethylaminoacrolein as shown in Scheme 33. This undergoes cycloaddition with dienophiles, followed by elimination of dimethylamine to yield fused nitrobenzene derivatives.[91] The nitrodienamine has also been reacted with several Grignard reagents. The reaction takes the expected course, leading to

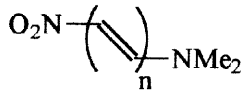
products (**137**) by addition-elimination (Scheme 33).[92] The condensation of (**136**) with indole derivatives in trifluoroacetic acid leads to several dimeric products in low yields.[93]

Scheme 33



(i) $Me_2NH.HCl$ (ii) NaH, $MeNO_2$; Et_3N (iii) RMgBr

Polyenes containing electron-donors and acceptors at either end of the chain are attracting current interest because of their possible non-linear optical properties. The effect of conjugation on the hyperpolarizability of such compounds [including compounds of the type (**138**)] has now been studied systematically.[94,95]



(**138**)

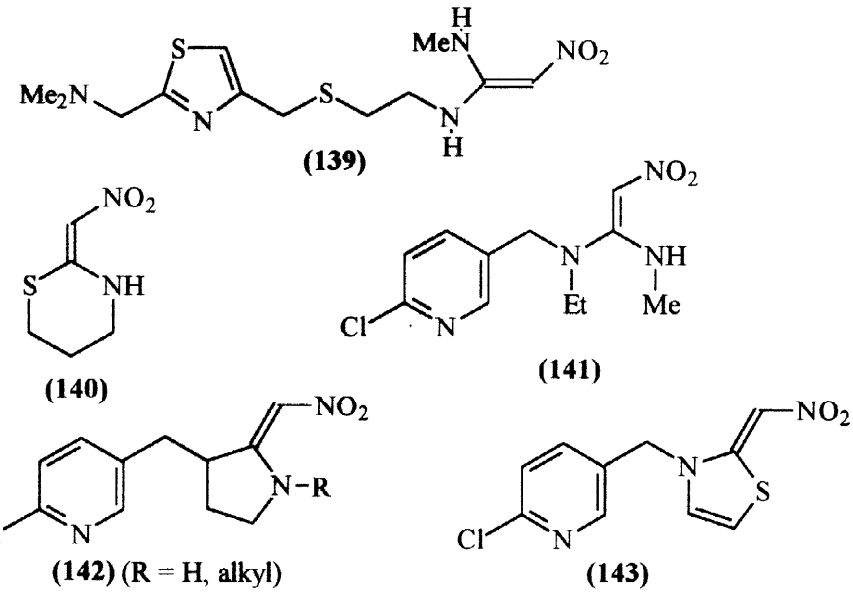
7. Nitroenamines as drugs and pesticides

Several compounds having a nitroenamine unit in their structure are already on the market as drugs or pesticides.

Ranitidine (**64**) has been one of the largest selling drugs of recent times. It is a potent histamine H_2-receptor antagonist and hence useful in the treatment of clinical conditions associated with hypersecretion of gastric acid, such as duodenal and gastric ulcer, and reflux oesophagitis. The molecule possesses a nitroketeneaminal unit.[96] Nizatidine (**139**), in which a thiazole ring replaces the furan ring of ranitidine, is reported to be quite potent.[97] Several related structures having the nitroketeneaminal unit have also been evaluated for their efficacy as histamine H_2-receptor antagonists.

The nitroenamine moiety also figures in several molecules claimed to have insecticidal properties.[98] One of the earliest such compounds was nithiazin (**140**) reported by Shell. In

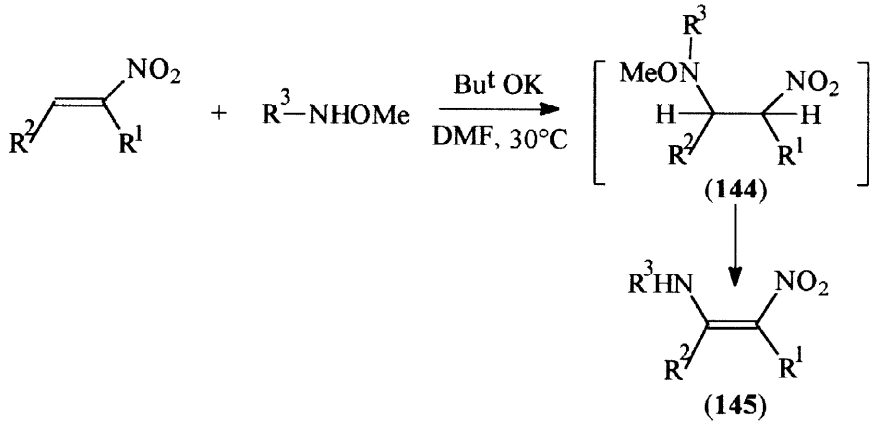
1995, Takeda introduced nitenpyram (**141**) onto the market for the treatment against sucking insect pests.[99] Several other companies are also involved in synthesising molecules containing the nitroenamine unit for pesticidal application and two such promising lead structures are (**142**) (Novartis) and (**143**) (Nihon-Bayer).[98]



8. Addendum

In the interim between the compilation of the first draft of this review and its despatch to the Editor in its final format, several interesting publications on nitroenamines have to light. These have been grouped together in this section.

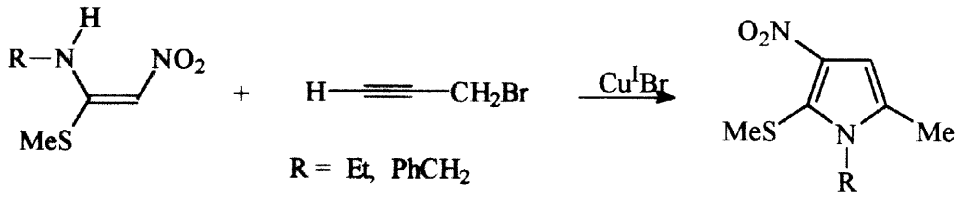
Scheme 34



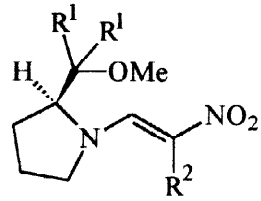
Nitroolefins have been directly converted to nitroenamines (**145**) by reaction with methoxyamines in the presence of potassium *t*-butoxide (Scheme 34).[100] This is an example of vicarious nucleophilic substition. The yields are generally good to excellent. The intermediate adducts (**144**) have been isolated in several cases; treatment of these with excess base leads to the products (**145**).

The reaction of 1-alkyl (or aryl)- 1-methylthio-2-nitroethenes with aminoacetaldehyde dimethylacetal to produce the corresponding nitroenamines, and their subsequent acid-catalysed cyclization to 3-nitropyrroles[1] has been developed into a facile general synthesis of this class of compounds.[101] Earlier, it has been shown that reaction of N-substituted 1-methylthio-2-nitroethenamines with prop-2-ynyl bromide in the presence of cuprous bromide leads to 1-alkyl 2-methylthio-5-methyl-3-nitropyrroles in good yields[102] Initial electrophilic attack at C(2) is followed by intramolecular nucleophilic attack by the NH on the allenic central carbon (Scheme 35).

Scheme 35



Several new chiral nitroenamines (**146**) with bulky substituents in the side-chain have been found to be useful for the asymmetric nitro-olefination of the zinc enolates of lactones.103 The products, possessing a sterogenic quaternary carbon atom, (absolute configuration *S*), were obtained with excellent *ee*'s (>95%).



(**146**) a : R^1 = Ph; R^2 = H
b : R^1 = Ph; R^2 = Me

Acknowledgement

I am deeply indebted to Surekha Deshpande and Smita Gadre for their help in preparing this manuscript. I thank the CSIR for a grant under the Emeritus Scientist Scheme.

References

1. Rajappa S. *Tetrahedron*, **1981**, *37* ,1453-1480.
2. Tokumitsu T. Hayashi T. *J.Org.Chem.*, **1985**, *50* , 1547-1550.
3. Chiara, J.-L. Gomez-Sanchez A., Hidalgo F.-J. Yruela I., *Carbohydrate Res.* **1989**, *188*, 55-62.
4. Rene L. Royer R. *Synthesis*, **1981**, 878.
5. Gomez-Sanchez, A., Hidalgo-Garcia F.-J., Chiara J.-L. Bellanato J. *An Quim., Ser.C.* **1985**, *81*, 139. *Chem.Abstr.* **1986**, *105* , 24542.
6. Gomez-Sanchez A. Hidalgo F.-J. Chiara J.-L. *Carbohydrate Res.* **1987**, *167* , 55-66.
7. Faulques M, Rene L. Royer R. *Synthesis*, **1982**, 260-261.
8. Node M, Nagasawa H. Naniwa Y. Fuji K. *Synthesis*, **1987**, 729-732.
9. Ciganek E. *Synthesis*, **1986**, 871-872.
10. Krowczynski A. Kozerski L. *Synthesis*, **1983**, 489-491.
11. Fuji K, Node M, Nagasawa H, Naniwa Y. Terada S. *J.Am.Chem.Soc.*, **1986**, *108* , 3855-3856.
12. Node M, Kurosaki R, Hosomi K, Inoue T, Nishide K, Ohmori T. Fuji K. *Tetrahedron Lett.*, **1995**, *36* , 99-102.
13. Kamimura A. Ono N. *Synthesis*, **1988**, 921-922.
14. Turner K.A. *Synthesis*, **1998**, 139-141.
15. Morzycki J.W, Wilczewska A.Z. Lotowski Z. *Tetrahedron Lett.*, **1996**, *37* , 2079-2082.
16. Morzycki J.W, Lotowski Z, Stepniowska M, Gryszkiewicz A. Wilczewska A.Z. *Tetrahedron*, **1997**, *53* , 16161-16168.
17. Dell'Erba C, Novi M, Guanti G. Spinelli D. *J.Heterocycl Chem.*, **1975**, *12* , 327-331.
18. Surange S.S, Kumaran G, Rajappa S, Rajalakshmi K. Pattabhi V. *Tetrahedron*, **1997**, *53*, 8531-8540.
19. Surange S.S. Rajappa S. *Tetrahedron Lett*, **1998**, *39* , 7169-7172.
20. Potkin V.I, Gogolinskii V.I, Nechai N.I, Zapolskii V.A. Kaberdin R.V. *Zh.Org.Khim*, **1995**, *31*, 1816. *Chem.Abstr.*, **1996**, *125* : 113914.
21. Moimas F. Angeli C, Comisso G, Zanon P. Decorte E. *Synthesis*, **1985**, 509-510.

22. White G.R. *U.S.Patent* 4028379 **(1977)**.

23. Young R.C, Mitchell R.C, Brown T.H, Ganellin C.R, Griffiths R, Jones M, Rana K.K, Saunders D, Smith I.R, Sore N.E. Wilks T.J. *J.Med.Chem.*, **1988**, *31*, 656-671.

24. Anbazhagan M, Dixit A.N. Rajappa S. *J.Chem.Soc.,Perkin Trans.I.*, **1997**, 2421-2424.

25. CRC Comp. Belg. BE 888,747 (1981), *Chem.Abstr.*, **1982**, *96* , 181127x.

26. Price B.J, Jack D. *Eur.Pat.Appl.* EP 58,492 **(1982)**, *Chem.Abstr.*, **1983**, *98* , 16574z.

27. Price B.J, Clitherow J.W, Bradshaw J. USP 4,128,658 **(1978)**.

28. Manjunatha S.G, Reddy K.V, Rajappa S. *Tetrahedron Lett.*, **1990**, *31* , 1327-1330.

29. White G.R, Ger.Offen. 2621092 **(1976)**, *Chem.Abstr.*, **1977**, *86* , 72655r.

30. Manjunatha S.G, Chittari P, Rajappa S. *Helv.Chim.Acta.* **1991**, *74* , 1071-1080.

31. Rajappa S, Advani B.G. *Proc.Indian Acad.Sci. (Chem.Sci).*, **1982**, *91* : 463-466.

32. Seager J.F, Dansey R. *Brit Pat.* GB 2 160 204A **(1985)**.

33. Deshmukh A.R.A.S, Reddy T.I, Bhawal B.M, Shiralkar V.P, Rajappa S. *J.Chem.Soc., Perkin Trans.I.* **1990**, 1217-1218.

34. Reddy T.I, Bhawal B.M, Rajappa S. *Tetrahedron,* **1993**, *49,* 2101-2108.

35. Bhawal B.M, Vetrivel R, Reddy T.I, Deshmukh A.R.A.S, Rajappa S. *J.Phys.Org.Chem.* **1994**, *7* , 377-384.

36. Maybhate S.P, Deshmukh A.R.A.S, Rajappa S. *Tetrahedron,* **1991**, *47,* 3887-3894.

37. Baum K, Bigelow S.S, Nguyen N.V, Archibald T.G, Gilardi R, Flippen-Anderson J.L, George C. *J.Org.Chem.*, **1992**, *57*, 235-241.

38. Nguyen N.V, Baum K. *Tetrahedron Lett.*, **1992**, *33*, 2949-2952.

39. Gomez-Sanchez A, Hidalgo F.J, Chiara J.L. *J.Heterocycl.Chem.*, **1987**, *24,* 1757-1763.

40. Hirota K, Kitade Y, Sajiki H, Maki Y. *Tetrahedron Lett.*, **1986**, *27,* 3263-3266.

41. Nishiwaki N, Mizukawa Y, Ohta M, Terai R, Tohda Y, Ariga M. *Heterocycl.Commun.*, **1996**, *2,* 21-24.

42. Ostercamp D.L, Taylor P.J. *J.Chem.Soc., Perkin Trans.II.*, **1985**, 1021-1028.

43. Mohanalingam K, Das P.K, Rajappa S. *Spectrochim.Acta.*, **1992**, *48A,* 1647-1656.

44. Chiara J.-L, Gomez-Sanchez A, Bellanato J. *J.Chem.Soc.,Perkin Trans.II*, **1992**, 787-798.

45. Chiara J.-L, Gomez-Sanchez A, Hidalgo F.-J, Bellanato J. *J.Chem.Soc.,Perkin Trans.II.*, **1988**, 1691-1698.

46. Chiara J.-L, Gomez-Sanchez A, Marcos E.S, Bellanato J. *J.Chem.Soc., Perkin Trans.II*, **1990**, 385-392.

47. Gate E.N, Meek M.A, Schwalbe C.H, Stevens M.F.G, Threadgill M.D. *J.Chem.Soc., Perkin Trans.II.* **1985**, 251-255.

48. Fuji K, Node M. *Synlett*, **1991**, 603-610.

49. Fuji K, Node M, Nagasawa H, Naniwa Y, Taga T, Machida K, Snatzke G. *J.Am.Chem.Soc.*, **1989**, *111*, 7921-7925.

50. Rajappa S, Nagarajan K, Venkatesan K, Kamath N, Padmanabhan V.M, von Philipsborn W, Chen B.C, Muller R. *Helv.Chim.Acta.*, **1984**, *67*, 1669-1680.

51. Rajappa S, Bhawal B.M, Deshmukh A.R.A.S, Manjunatha S.G, Chandrasekhar J. *Chem.Commun.*, **1989**, 1729-1730.

52. Cholerton T.J, Hunt J.H, Klinkert G, Martin-Smith M. *J.Chem.Soc.,Perkin Trans.II.* **1984**, 1761-1766.

53. Schlueter J.A, Cook A.G. *J.Org.Chem.*, **1989**, *54*, 2255-2258.

54. Hazell A, Mukhopadhyay A, *Acta Cryst.*, **1980**, *B36*, 747-748.

55. Dianez M.J, Lopez-Castro A, Marquez R. *Acta Cryst.*, **1985**, *C41*, 981-983.

56. Ganazzoli F, Meille S.V, Gronchi P. *Acta Cryst.*, **1986**, *C42*, 1385-1390.

57. Kojic-Prodic B. Ruzic-Toros Z. Toso R. *Acta Cryst.*, **1982**, *B38*, 1837-1840.

58. Chiari G, Viterbo D. J.*Chem.Soc.Perkin Trans II.* **1983**, 1815-1820.

59. Garcia Trimino M.I, Linden A. Heimgartner H. Macias Cabrera A. *Helv.Chim.Acta.* **1993**, *76*, 2817-2829.

60. Pappalardo R.P, Maarcos E.S, Ruiz-Lopez M.F, Rinaldi D, Rivail J.-L. *J.Am.Chem.Soc.*, **1993**, *115*, 3722-3730.

61. Marcos E.S, Maraver J.J, Chiara J.L, Gomez-Sanchez A. *J.Chem.Soc.Perkin Trans II*, **1988**, 2059-2064.

62. Chiara J.L, Gomez-Sanchez A, Marcos E.S. *J.Chem.Soc.Perkin Trans.II.*, **1990**, 1627-1636.

63. Coustard J.-M. *Tetrahedron*, **1996**, *52*, 9509-9520.

64. Haywood P.A, Martin-Smith M, Cholerton T.J, Evans M.B. *J.Chem.Soc.Perkin Trans.I*, **1987**, 951-954.

65. Kearney T. Harris P.A, Jackson A, Joule J.A. *Synthesis*, **1992**, 769-772.

66. Krowczynski A, Kozerski L. *Heterocycles*, **1986**, *24*, 1209-1213.

67. Krowczynski A, Kozerski L. Bull Polish *Acad.Sci.Chem*, **1986**, *34*, 341-349.

68. Kearney T. Joule J.A, Jackson A. *Heterocycles*, **1992**, *33*, 757-762.

69. Tokumitsu T. *Bull.Chem.Soc.Jpn.*, **1986**, *59*, 3871-3876.

70. Moya Argilagos D. Macias Cabrera A. Garcia Trimino M.I, Velez Castro H. *Synth.Commun.* **1996**, *26*, 1187-1197.

71. Rajappa S, Sreenivasan R, *Indian J.Chem.*, **1985**, *24B*, 795-796.

72. Moya Argilagos D, Garcia Trimino M.I, Macias Cabrera A, Linden A, Heimgartner H. *Helv.Chim.Acta.* **1997**, *80*, 273-292.

73. Linden A, Heimgartner H, Garcia Trimino M.I, Macias Cabrera A. *Acta Crystallogr.Section C*, **1994**, *50*, 421-424.

74. Garcia Trimino M.I, Macias Cabrera A, Velez Castro H. *Synth.Commun*, **1992**, *22*, 1319-1331.

75. Pomes Hernandez R, Duque Rodriguez J, Garcia Trimino M.I, Novoa de Armas H, Alfredo Toscano R. *Acta Crystallogr.Section C.*, **1995**, *51*, 1392-1394.

76. Dell'Erba C, Mele A, Novi M, Petrillo G, Stagnaro P. *Tetrahedron Lett.* **1990**, *31*, 4933-4936.

77. Herzig J, Antebi A, Nudelman A, Gottlieb H.E. *J.Org.Chem.* **1986**, *51*, 730-732.

78. Uno H, Kinoshita T, Matsumoto K, Murashima T, Ogawa T, Ono N. *J.Chem.Res.(S).* **1996**, 76-77.

79. Reddy K.V, Rajappa S. *Tetrahedron Lett.*, **1992**, *33*, 7957-7960.

80. Wilken J, Wallbaum S, Saak W, Haase D, Pohl S, Patkar L.N, Dixit A.N, Chittari P, Rajappa S, Martens J. *Liebigs Ann.* **1996**, 927-934.

81. Fuji K, Kawabata T, Naniwa Y, Ohmori T, Node M. *Chem.Pharm.Bull.*, **1994**, *42*, 999-1001.

82. Nishide K, Kurosaki R, Hosomi K, Imazto H, Inoue T, Node M, Ohmori T, Fuji K. *Tetrahedron.* **1995**, *51*, 10857-10866.

83. Node M, Nagasawa H, Fuji K. *J.Am.Chem.Soc.*, **1987**, *109*, 7901-7903.

84. Node M, Nagasawa H, Fuji K. *J.Org.Chem.*, **1990**, *55*, 517-521.

85. Node M, Hao X.-J, Nagasawa H, Fuji K. *Tetrahedron Lett.*, **1989**, *30*, 4141-4144.

86. Hao X, Node M, Fuji K. *J.Chem.Soc.Perkin Trans.I.*, **1992**, 1505-1509.

87. Node M, Hao X, Fuji K. *Chem.Lett.*, **1991**, 57-60.

88. Node M, Itoh A, Masaki Y, Fuji K. *Heterocycles.*, **1991**, *32*, 1705-1707.

89. Ono N, Matsumoto K, Ogawa T, Tani H, Uno H. *J.Chem.Soc.Perkin Trans.I.*, **1996**, 1905-1910.

90. Surange S.S, Kumaran G, Rajappa S, Pal D, Chakrabarti P. *Helv.Chim.Acta.*, **1997**, *80*, 2329-2336.

91. Takeuchi N, Ohki J, Tobinaga S. *Chem.Pharm.Bull.*, **1988**, *36*, 481-487.

92. Koike T, Hagiwara M, Takeuchi N, Tobinaga S. *Heterocycles*, **1997**, *45*, 1271-1280.

93. Takeuchi N, Tanabe M, Hagiwara M, Goto K, Koike T, Tobinaga S. *Heterocycles*, **1994**, *38*, 613-627.

94. Morley J.O, Docherty V.J, Pugh D. *J.Chem.Soc.Perkin Trans.II*, **1987**, 1351-1355.

95. Tsunekawa T, Yamaguchi K. *J.Phys.Chem*, **1992**, *96*, 10268-10275.

96. Daly M.J, Price B.J. in *Progress in Medicinal Chemistry. G.P.Ellis, G.B.West (Eds). Elsevier, Amsterdam.* **1983**, *Vol 20*, pp 337-368.

97. Cooper D.G, Young R.C, Durant G.J, Ganellin C.R. in *"Comprehensive Medicinal Chemistry", Vol.3,* (Eds) C.Hansch, P.G.Sammes and J.B.Taylor, *Pergamon Press*; **1990**, pp 323-421.

98. Pachlatko J.P. *Chimia*, **1998**, *52*, 29-47.

99. Minamida I, Iwanaga K, Tabuchi T, Aoki I, Fusaka T, Ishizuka H, Okauchi T. *J.Pest.Sci.Int.Ed.***1993**, *18, 41. Chem. Abstr.* **1993**, *119*, 139023.

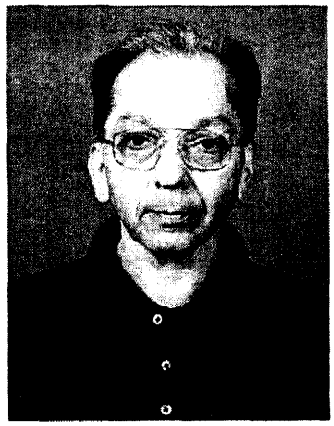
100. Seko S, Komoto I. *J. Chem. Soc. Perkin Trans. I.*, **1998**, 2975-2976.

101. Terang N, Mehta B.K, Ila H, Junjappa H. *Tetrahedron*, **1998**, *54*, 12973-12984.

102. Gupta A.K, Reddy K.R, Ila H, Junjappa H. *J.Chem.Sco. Perkin Trans.I*, **1995**, 1725-1727.

103. Yang X, Wang R. *Tetrahedron Asymmetry*, **1997**, *8*, 3275-3281.

Biographical sketch



Srinivasachari Rajappa

Dr.S.Rajappa (born 22.2.1934), graduated from the University of Madras in 1954. He obtained his Ph.D. from the Presidency College, Madras as a post-doctoral research associate at the Florida State University and then worked with Prof.R.B.Woodward at Harvard University for two years. Dr.Rajappa returned to India in Nov. 1964, and joined Ciba-Geigy Research Centre as a Scientist. He became Head of Chemistry Research at Ciba-Geigy Res. Centre in 1984. After a brief stint as the Head of Research in Rhone-Poulenc (India) at Bombay, Dr.Rajappa was invited to join NCL as Head of the Division of Organic Synthesis in 1988. He retired from this position in 1994, and was an Emeritus Scientist at the same institution until March 1999.