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Heterosubstituted Nitroalkenes in Synthesis

By Anthony G. M. Barrett
DEPARTMENT OF CHEMISTRY, COLORADO STATE UNIVERSITY, FORT COLLINS, CO 80523, U S A

1 Introduction

All nitroalkenes are powerful electrophiles that readily undergo conjugate addition reactions with nucleophiles or radicals. In addition, they react as dienophiles in Diels–Alder reactions. These processes may be used readily to assemble molecules with extended carbon frameworks. In addition to these attributes, nitro-compounds are versatile precursors for diverse functionalities. Nitro-compounds may be reduced to provide oximes, hydroxylamines, imines, ketones, amines, or alkanes. They may be converted into carbonyl compounds or derived ketals by the classical Nef reaction. Alternatively nitro-compounds have been converted into ketones or carboxylic acids by oxidative variations of the Nef process. On dehydration, primary nitroalkanes are converted into nitrile oxides, a class of reactive 1,3-dipolar reagents. Clearly both nitroalkanes and nitroalkenes are particularly useful compounds in synthesis.[1] Nitroalkenes that are substituted by heteroatom groups are especially useful for the controlled synthesis of delicate heterocyclic species and related molecules. This review focuses upon the preparation and reactions of nitroalkenes that are substituted with a heteroatom group at C-1 of the alkene unit. Derivatives of β-nitroenamines and related species are not included.

2 1-Alkoxy-nitroalkenes

Several 1-(benzyloxy)nitroalkenes have been prepared by the Henry reaction of (benzyloxy)nitromethane (1) with aldehydes followed by dehydration. Reaction of benzyl chloromethyl ether with silver nitrite in THF and toluene at −25 °C to 0 °C gave (benzyloxy)nitromethane (1) (25%).[2] pK_a measurements of (1) gave a value of about 17.0.[3] The reagent (1) was particularly useful for the synthesis of bicyclic β-lactam systems and has been applied for the construction of an

[1] For earlier reviews on nitro compounds, see H H Bauer, and L Urbas, 'The Chemistry of the Nitro and Nitroso Group', H Feuer, Interscience, New York, 1970, part 2, pp 75–200, S L Ioffe, L M Leont'eva, and V A Tartakovskii, *Russ Chem Rev* (*Engl Transl*), 1977, **46**, 872, D Seebach, E W Colvin, F Lehr, and T Weller, *Chimia*, 1979, **31**, 1, O V Schickh, G Apel, H G Padeken, H H Schwartz, and A Segnitz in 'Houben-Weyl Methoden der Organische Chemie', ed E Muller, Georg Thieme Verlag, Stuttgart, 1971, Vol 10/1, pp 9–462, S Rajappa, *Tetrahedron*, 1981, **37**, 1453, V V Perekalin, *J Org Chem U S S R* (*Engl Transl*), 1985, **21**, 1011, A G M Barrett and G G Graboski, *Chem Rev*, 1986, **86**, 751

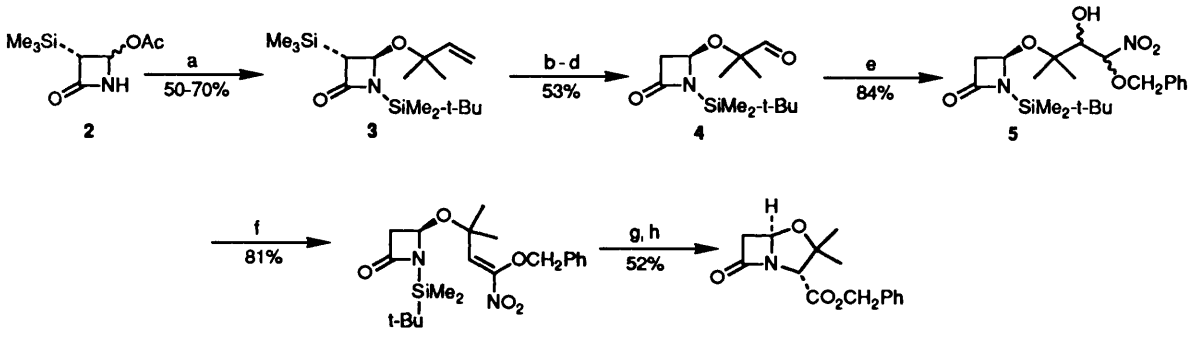
[2] A G M Barrett, M-C Cheng, C D Spilling, and S J Taylor, *J Org Chem*, 1989, **54**, 992

[3] We are indebted to F G Bordwell and A V Satish for these measurements in DMSO solution, see W S Matthews, J E Bares, J E Bartmess, F G Bordwell, F J Cornforth, G E Drucker, Z Margolin, R J McCallum, G J McCollum, and N R Vanier, *J Am Chem Soc*, 1975, **97**, 7006

oxapenam (7), sulbactam (18), and 6-aminopenicillanic acid (27) The oxapenam (7) was prepared from the optically pure 2-azetidinone derivative (2)[4] *via* the alkene (3) and nitroalkene (6) (Scheme 1) Reaction of acetate (2) with 3-methyl-1-buten-3-ol gave the crystalline *trans*-substituted β-lactam (3) This reaction most probably involved the intermediacy of the 2-azetinone derivative (8) or an equivalent zinc-coordinated species and steric approach controlled ether formation [5] Desilylation at C-3, resilylation at N-1, and ozonolysis provided the aldehyde (4) Henry reaction with (benzyloxy)nitromethane (1) was smoothly catalysed by potassium t-butoxide in THF and t-butyl alcohol to provide the β-nitro-alcohol (5) as a mixture of diastereoisomers Dehydration to provide the nitroalkene (6) required mesylation in the presence of triethylamine followed by elimination of the β-nitromesylate using DBU The nitroalkene (6) was obtained only as the *Z*-geometric isomer Indeed all the nitroalkenes bearing C-1 heteroatom substituents that have been prepared in our laboratories were exclusively *Z* On reaction with tetrabutylammonium fluoride, the nitroalkene (6) underwent clean desilylation and cyclization to give a species, probably the nitronate (9) This was not isolated, reaction with ozone *in situ*[6] gave the bicyclic β-lactams (7) and (10) (1 1) Although the kinetic diastereoselectivity was disappointing, the undesired *endo*-isomer (10) was smoothly and cleanly isomerized to the required *exo*-isomer on reaction with DBU Thus, treatment of the crude ozonolysis reaction mixture with DBU gave only (7) (52% from 6) [7] Since the 2-azetidinone derivative (2) is readily available from D-aspartic acid,[4] Scheme 1 represents an effective strategy for the synthesis of optically pure oxapenams The cyclization of (6) to provide (7) is an adaption of earlier elegant work by Shibuya on the cyclization of nitroalkene (11) to produce the carbapenem (12) [8]

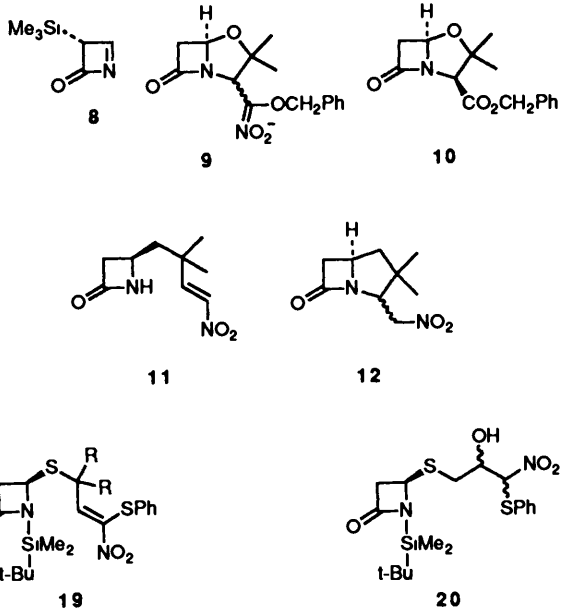
Both benzyl penicillanate (17) and sulbactam (18)[9] were also prepared starting from the Weis intermediate (2)[4] (Scheme 2) [10] Preparation of the sulphide (14) followed exactly the same methods as for ether (3) Ozonolysis proceeded smoothly and without competitive oxidation at sulphur to produce the aldehyde (15) Henry reaction and dehydration gave the crystalline nitroalkene (16) In this case, acetyl chloride and triethylamine were used to eliminate the intermediate β-nitro-alcohol Attempted dehydration using methanesulphonyl chloride resulted in decomposition, possibly due to *S*-chlorination Reaction of nitroalkene (16) with tetrabutylammonium fluoride and ozone resulted in double desilylation, cyclization, and nitronate oxidation to provide the bicyclic β-lactam system Again DBU-catalysed isomerization was employed to ensure clean *exo*-ester stereochemistry In the sequence (14) to (16) the C-3 trimethylsilyl group was retained until bicyclization This is of no particularly preparative significance

[4] H Fritz P Sutter and C D Weis *J Org Chem* 1986 **51** 558
[5] K Clauss D Grimm and G Prossel *Liebigs Ann Chem* 1974 539
[6] J E McMurry J Melton and H Padgett *J Org Chem* 1974 **39** 259
[7] A G Brown D F Corbett and T T Howarth *J Chem Soc Chem Commun* 1977 359
[8] M Shibuya M Kuretani and S Kubota *Tetrahedron Lett* 1981 **22** 4453
[9] A G M Barrett and S Sakdarat *J Org Chem* 1990 **55** 5110
[10] A G M Barrett M C Cheng S Sakdarat C D Spilling and S J Taylor *Tetrahedron Lett* 1989 **30** 2349



Reagents: (a) $Me_2C(OH)CH{=}CH_2$, $Zn(OAc)_2{\cdot}2H_2O$, PhH, Δ; (b) KF, MeOH, pH 7.0; (c) $Pr^i{}_2NEt$, Bu^tMe_2SiCl, DMF; (d) O_3, CH_2Cl_2, −78 °C; Me_2S; (e) $PhCH_2OCH_2NO_2$ (1), Bu^tOK, THF, Bu^tOH; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2; DBU; (g) Bu_4NF, THF, −55 °C, CH_2Cl_2; O_3, −78 °C; (h) DBU, $CDCl_3$, 55 °C

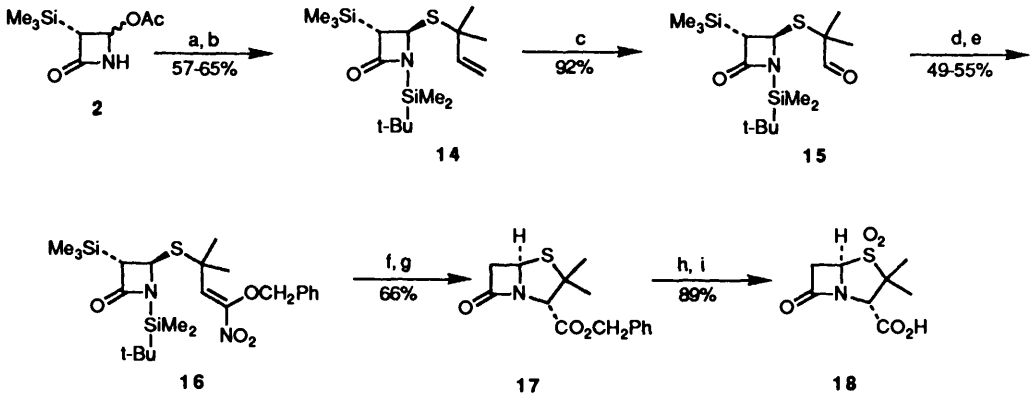
Scheme 1



relative to Scheme 1 Retention of the delicate C-3 $SiMe_3$ group until bicyclization does, however, underscore the mild reaction conditions adopted in preparing the crucial nitroalkene (16) Oxone oxidation of the penam (17) and deprotection gave sulbactam (18) The successful preparation of these penicillin derivatives *via* the 1-(benzyloxy)-1-nitroalkene (16) is noteworthy on two counts First, the nitroalkene (16) was both stable and crystalline All our attempts to prepare the corresponding 1-phenylthio-nitroalkenes (19, R = H or Me) were unsuccessful Although we did succeed in preparing (20),[11] attempted dehydration resulted in decomposition It is possible that (19, R = H) decomposed *via* episulphonium ion formation The nitroalkene (16), which is much less electrophilic, was easily isolated pure Secondly, in the conversion of (16) into (17), ozonolysis of the nitronate intermediate was clean and no competitive *S*-oxidation was observed

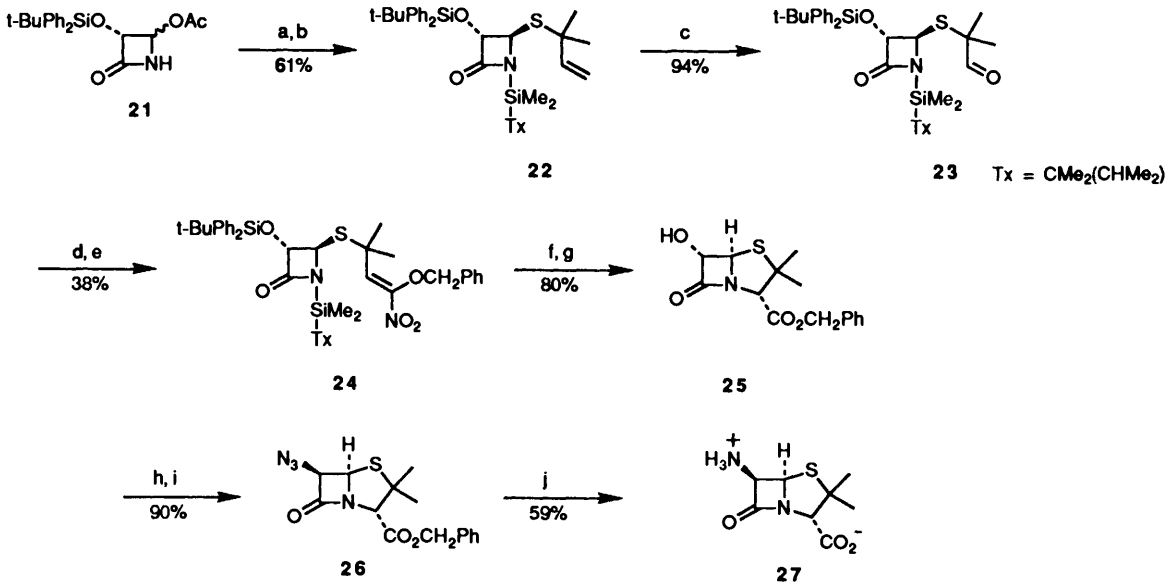
The penam methods were extended to the synthesis of 6-aminopenicillanic acid (Scheme 3) The 2-azetidinone derivative (21) was readily prepared from (*R R*)-tartaric acid using Sharpless cyclic sulphate chemistry [12] Conversion of (21) into (24) directly followed the methods in Scheme 2 In this case a more robust thexyldimethylsilyl group was used for *N*-protection since partial premature desilylation was observed when the t-butyldimethylsilyl group was used Cyclization of nitroalkene (24) proceeded smoothly to provide the penam (25) In this reaction the tetrabutylammonium fluoride mediated both *N*- and *O*-desilylation

[11] S J Taylor Ph D Thesis Northwestern University U S A 1988
[12] Y Gao and K B Sharpless *J Am Chem Soc* 1988 **110** 7538 B M Kim and K B Sharpless *Tetrahedron Lett* 1989 **30** 655 B B Lohray Y Gao and K B Sharpless *ibid* 1989 **30** 2623



Reagents: (a) $Me_2C(SH)=CH_2$ (13), NaOMe, MeOH; (b) Bu^tMe_2SiCl, $(Pr^i)_2NEt$, DMAP, CH_2Cl_2; (c) O_3, CH_2Cl_2, $-78\,^{\circ}C$; Me_2S; (d) $PhCH_2OCH_2NO_2$, $KOBu^t$, Bu^tOH, THF; (e) AcCl, Et_3N, $0\,^{\circ}C$; (f) Bu_4NF, THF, $-78\,^{\circ}C$; CH_2Cl_2, O_3; (g) DBU, $CDCl_3$, $23\,^{\circ}C$; (h) Oxone, MeOH, pH 3; (i) H_2, Pd/C, EtOAc

Scheme 2



Reagents: (a) $Me_2C(SH)CH{=}CH_2$ (13), NaOMe, MeOH; (b) $TxMe_2SiOSO_2CF_3$, 2,6-lutidine, THF, −78 °C; (c) O_3, CH_2Cl_2, −78 °C; Me_2S; (d) $PhCH_2OCH_2NO_2$ (1), Bu^tOK, Bu^tOH, THF; (e) AcCl, Et_3N, CH_2Cl_2; (f) Bu_4NF, THF, −78 °C; O_3, THF, CH_2Cl_2, − 78 °C; (g) DBU, CH_2Cl_2; (h) CF_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (i) LiN_3, DMF; (j) H_2, Pd/C, EtOAc

Scheme 3

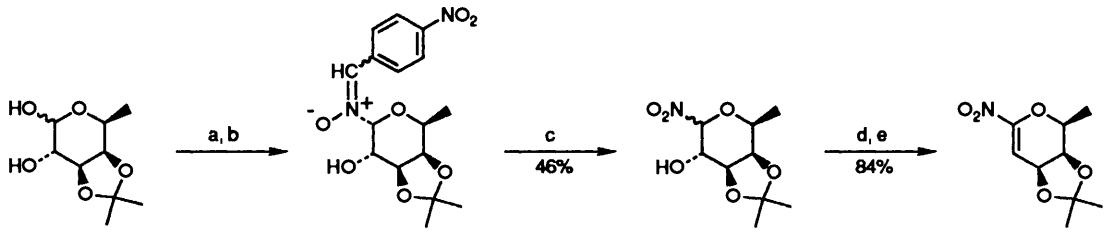
Alcohol (25) was easily converted into 6-aminopenicillanic acid (27) *via* trifluoromethanesulphonylation and azide (26) formation. It is clear from these syntheses that nitroalkenes derived from (benzyloxy)nitromethane (1) are useful intermediates for the construction of delicate polyfunctional β-lactam systems.

Vasella and co-workers have introduced 1-nitro-glycals as versatile reagents for synthesis. Several 1-nitro-glycals have been prepared from the dehydration of 1-nitro-1-deoxy-aldopyranoses and -aldofuranoses. These sugars in turn were prepared from aldose oximes by nitrone formation with 4-nitrobenzaldehyde and ozonolysis. This elegant chemistry is illustrated by the conversion of L-fucose (28) into the nitroalkene (31) (Scheme 4).[13] Nitro-glycals such as (31) are useful electrophiles for further synthetic transformations. The 1-nitro-fucal derivative (31) was readily converted into (−)-cryptosporin (34) by reaction with the lithiated derivative of sulphone (32) to provide (33). This process involved a Michael addition reaction, *C*-acylation, a sulphinate elimination, and the β-elimination of nitrite. Deprotection of (33) gave the target quinone (34) (Scheme 5).

Many other 1-nitro-glycals have been prepared and representative examples are provided by structures (37) to (42).[13,14] These substances were all prepared by dehydration of the 1-deoxy-1-nitro-pyranoses and -furanoses by acetylation. 1-Deoxy-1-nitro-β-D-mannopyranose (35) and the isopropylidene derivative (36) were directly converted into the nitroalkenes (37) and (38) on acetylation. In contrast, the acetates derived from sugars with the glucopyranose, galactofuranose, galactopyranose, and ribofuranose ring systems could be isolated; conversion into the corresponding 1-nitroglycals required treatment with Amberlite IRA-93 resin ($^{-}$OH form) after acetylation.

The nitroalkenes were found to react readily with nucleophiles to produce various Michael adducts. These reactions are exemplified by the transformations in Scheme 6. The addition of nitrogen-centred nucleophiles is especially important for the synthesis of rare sugars. In particular Vasella and co-workers have applied this chemistry in a spectacular and elegant synthesis of *N*-acetylneuraminic acid (52) (Scheme 7).[15] Thus the mannopyranoside derivative (47) was smoothly alkylated to provide (48) and subsequently the ketose (49/50) on hydrolysis. This elegant start to the synthesis of N-acetylneuraminic acid (52) underscores the synthetic potential of the nitro-group. The group controls the stereochemistry of amination in the generation of (47) *via* a Michael addition to a 1-nitro-glucal derivative. Secondly, the nitro-group permits clean *C*-alkylation *via* the nitronate under mildly basic conditions. Thirdly, the nitro-group may be easily lost as nitrite in the release of the ketose functionality. Sodium borohydride reduction of (49/50) proceeded with excellent stereocontrol provided that acetic acid was present thereby ensuring the intermediacy of a hydrogen bonded (amide) keto-group. The product (51) was converted into NANA (52) *via*

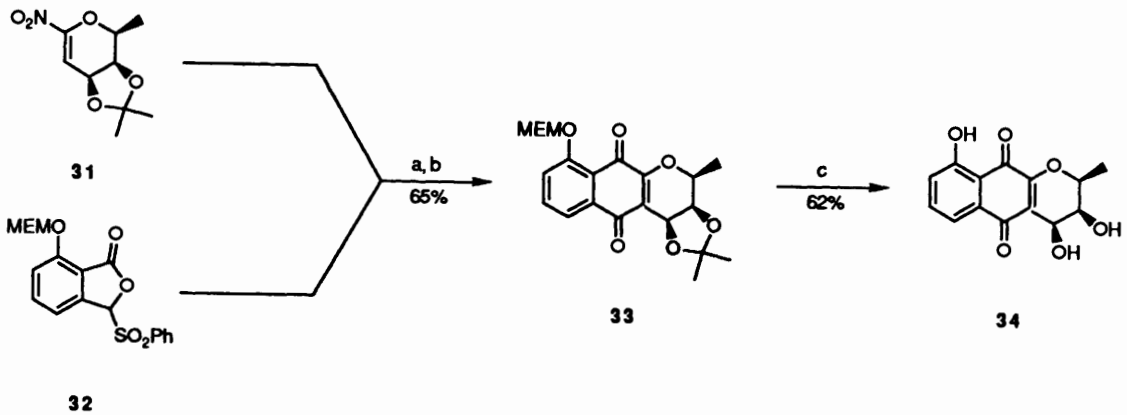
[13] W. Brade and A. Vasella, *Helv. Chim. Acta*, 1989, **72**, 1649; D. Beer, J. H. Bieri, I. Macher, R. Prewo, and A. Vasella, *ibid.*, 1986, **69**, 1172.
[14] F. Baumberger, D. Beer, M. Christen, R Prewo, and A. Vasella, *ibid.*, 1986, **69**, 1191.
[15] F. Baumberger and A. Vasella, *Helv. Chim Acta*, 1986, **69**, 1205.



28 **29** **30** **31**

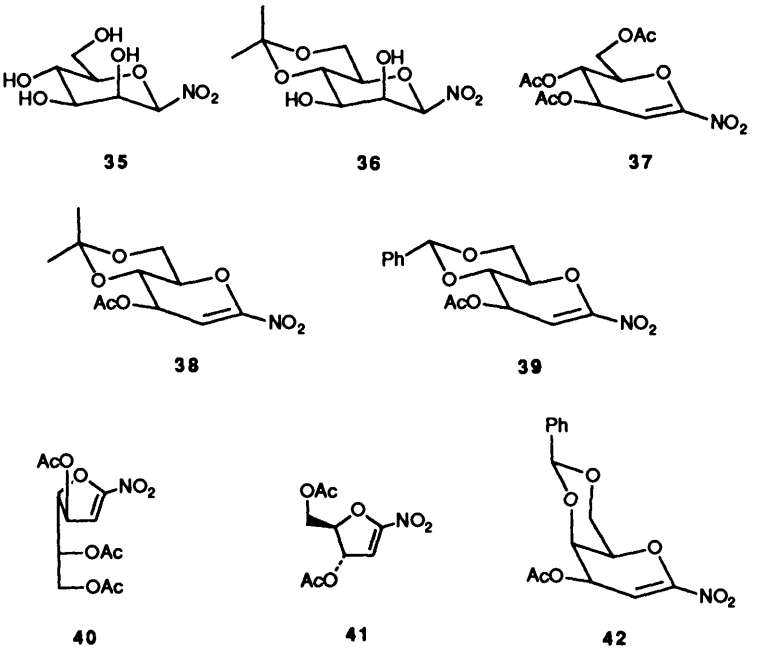
Reagents: (a) $HONH_3Cl$, NaOH, MeOH; (b) $4\text{-}O_2NC_6H_4CHO$, $TsOH.H_2O$, $MgSO_4$, CH_2Cl_2; (c) O_3, $-78\ ^\circ C$; (d) Ac_2O, pyridine, DMAP; (e) Amberlite IRA 93 (^-OH form), $CHCl_3$

Scheme 4



Reagents (a) $LiNPr^{i}_{2}$, THF, $-78\,^{\circ}C$, (b) -78 to 20 C, ultrasound, (c) HCl, THF, Δ

Scheme 5



ozonolysis and deprotection. These studies have been extended to the synthesis of NANA analogues.[16]

3 1-Arylthio-nitroalkenes

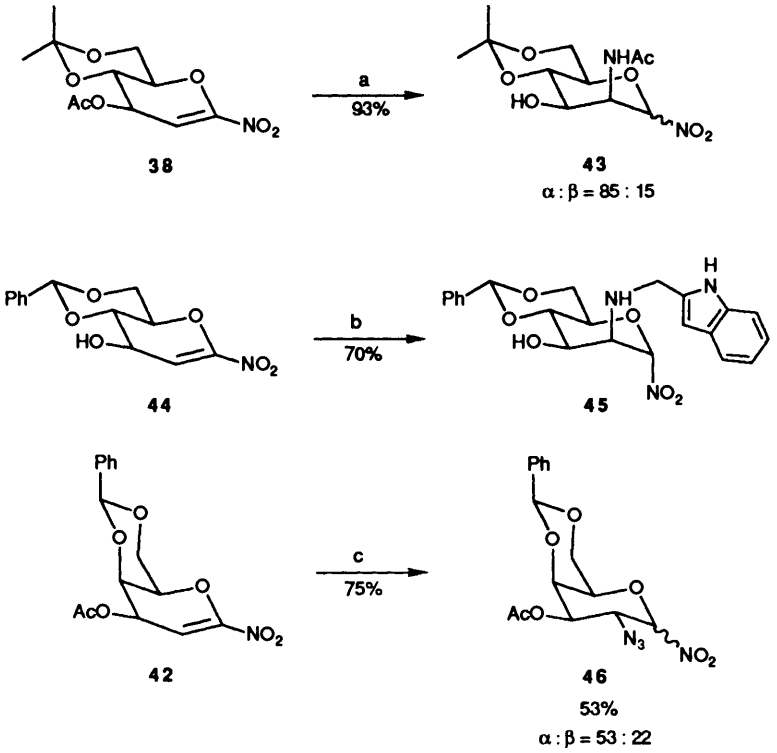
(Phenylthio)nitromethane (53) was readily prepared from benzenesulphenyl chloride and the sodium nitronate of nitromethane, from the nitration of (phenylthio)acetic acid, or from the reaction of ethyl nitroacetate with (phenylthio)morpholine.[17] Yoshikoshi and co-workers have reported that (53) may be readily converted into the *Z*-nitroalkene (55) by Henry reaction with acetaldehyde followed by dehydration of the resultant β-nitro-alcohol intermediate with methanesulphonyl chloride and triethylamine (64%) (Scheme 8).[18] Alternatively, (55) (89%) was prepared using potassium t-butoxide to catalyse the Henry reaction.[19] Nitroalkene (55) is a useful reagent for ring annulation and the preparation of heavily functionalized furan systems.[18] This chemistry is exemplified by the synthesis of the furaneremophilanoid ligularone (59) (Scheme 9). The

[16] F Baumberger and A Vasella, *Helv Chim Acta*, 1986, **69**, 1535

[17] A G M Barrett, D Dhanak, G G Graboski, and S J Taylor, *Org Synth*, 1989, **68**, 8 and references therein For the related selenium reagent see, T Sakakibara, M Manandhar, and Y Ishido, *Synthesis*, 1983, 920

[18] M Miyashita, T Kumazawa, and A Yoshikoshi, *Chem Lett*, 1979, 163, *J Chem Soc*, *Chem Commun*, 1978, 362, *J Org Chem*, 1980, **45**, 2945

[19] B J Banks, A G M Barrett, and M A Russell, *J Chem Soc*, *Chem Commun*, 1984, 670, A G M Barrett, G G Graboski, and M A Russell, *J Org Chem*, 1986, **51**, 1012



Reagents: (a) NH_3, H_2O, THF; (b) tryptamine; (c) NaN_3, HN_3, $CHCl_3$, MeCN, 50 °C

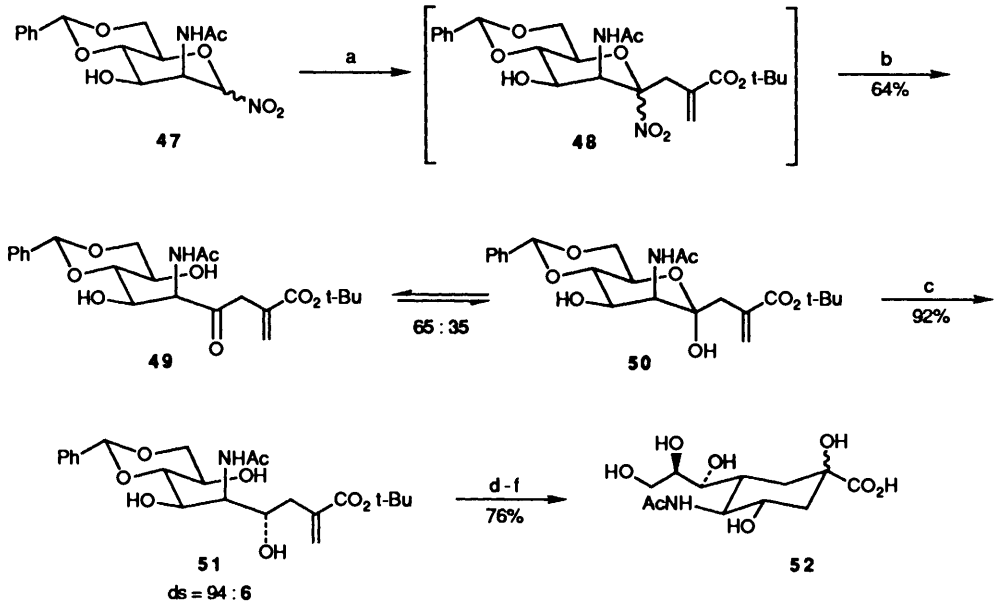
Scheme 6

Table 1 *Preparation of α-substituted* S-*phenyl thio esters*

Precursor	*Product*	*Yield,* %	*Precursor*	*Product*	*Yield,* %
(55)	(66a)	68	(55)	(66g)[a]	51
(55)	(66b)	62	(55)	(66h)	56
(55)	(66c)	67	(55)	(66i)	60
(55)	(66d)	79	(55)	(66j)	39
(55)	(66e)	61	(55)	(66k)	43
(55)	(66f)[a]	55			

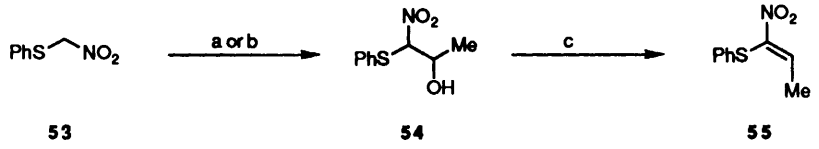
[a] Products obtained as mixtures of diastereoisomers

β-diketone intermediate (56) was condensed with the nitroalkene (55) in the presence of potassium fluoride to produce the dihydrofurans (57) and (58). Subsequent sulphoxide elimination gave the furans ligularone (59) and isoligularone (60). These cyclization reactions involve the conjugate addition of



Reagents (a) DBU, THF, $BrCH_2C(=CH_2)CO_2Bu^t$, 0 °C, (b) THF, urea, pH 6 6 phosphate buffer, (c) $NaBH_4$, dioxane, H_2O, AcOH, (d) O_3, CH_2Cl_2, −78 °C, Ph_3P, (e) H_2, Pd/C, MeOH, H_2O, (f) K_2CO_3, MeOH, H_2O

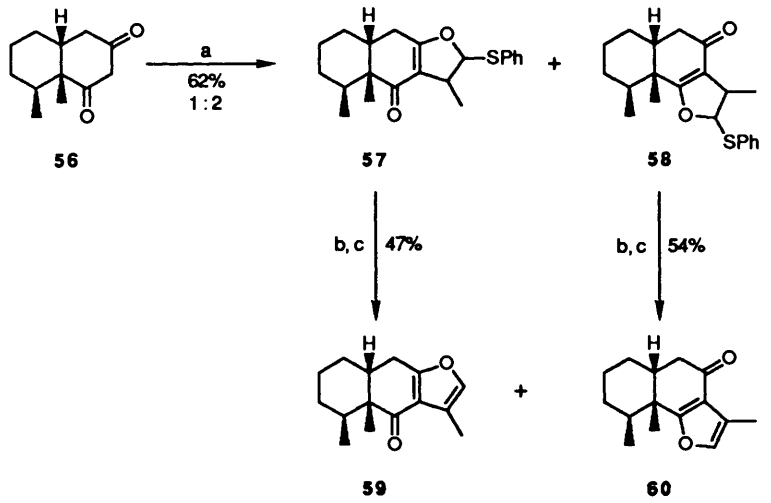
Scheme 7



53 **54** **55**

Reagents (a) 5% KOH, MeCHO, MeOH, AcOH, (b) Bu^{t}OK, Bu^{t}OH, THF, pH 7, (c) MsCl, Et_3N, CH_2Cl_2

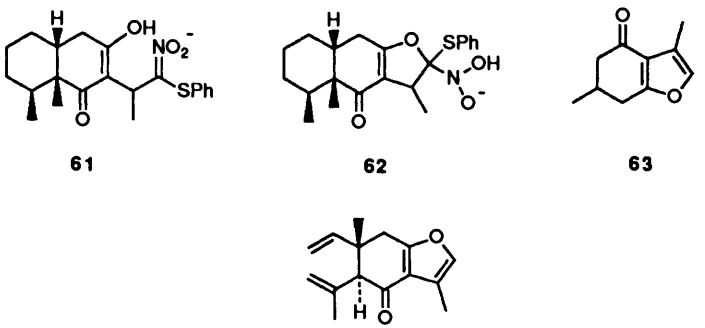
Scheme 8



56 **57** **58** **59** **60**

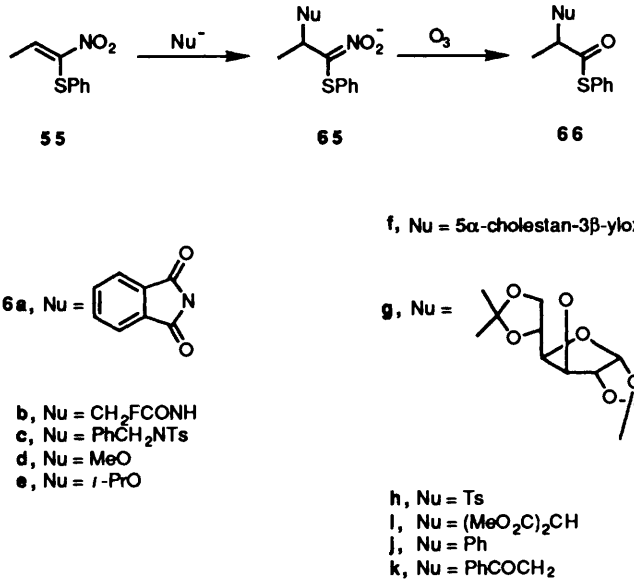
Reagents (a) (55), KF, DME, KF, PhH, (b) $NaIO_4$, H_2O, MeOH, (c) Al_2O_3, pyridine, Δ

Scheme 9



61 **62** **63** **64**

the β-dione enolate to the nitroalkene to provide (61) followed by S_N1 closure or cyclization to provide (62) and loss of nitrous acid These methods were also used



Scheme 10

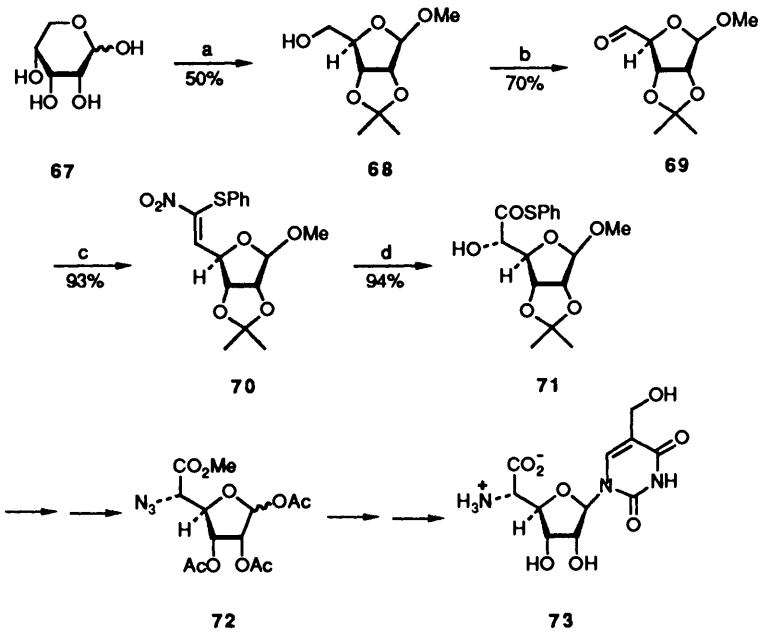
to provide less complex furan systems including racemic evodone (63)[18] and curzerenone (64)[20]

The nitroalkene (55) was also a convenient reagent for the synthesis of diverse α-substituted phenylthio esters[19] These compounds were formed *via* the conjugate addition of nucleophiles to (55) followed by ozonolysis of the intermediate nitronate (65) (Scheme 10 and Table 1) The procedure was applicable for nitrogen-centred nucleophiles (potassium phthalimide, the potassium salt of fluoroacetamide, and *N*-benzyl-*N*-lithio-toluene-4-sulphonamide), oxygen-centred nucleophiles (alkoxides), the sulphinate anion, and carbon-centred nucleophiles (enolates and phenyllithium)

These intermolecular reactions of 1-(phenylthio)-1-nitroalkenes with nucleophiles and ozonolysis has been extended to more highly substituted systems In our laboratories we have used the methods in a stereospecific synthesis of polyoxin C (73) and related nucleosides[21] The key step in these syntheses was the nucleophilic addition of potassium trimethylsilanoate to the ribose derivative (70) (Scheme 11) Nitroalkene (70) was readily prepared from D-ribose (67) *via* protection, oxidation, reaction with (phenylthio)nitromethane (53), and dehydration Potassium trimethylsilanoate smoothly and stereoselectively added to (70) to produce only the phenylthio ester (71) on ozonolysis This substance was transformed into polyoxin C (73) *via* the azide (72) and

[20] M Miyashita T Kumazawa and A Yoshikoshi *Chem Lett* 1981 593 *J Org Chem* 1984 **49** 3728

[21] A G M Barrett and S A Lebold *J Org Chem* 1990 **55** 3853



Reagents: (a) MeOH, acetone, HCl, reflux; (b) CrO_3, pyridine, CH_2Cl_2, 25 °C; (c) $PhSCH_2NO_2$ (53), 1:1 Bu^{t}OH–THF, 0.1 equiv. of Bu^{t}OK, 0 °C to 25 °C; MsCl, Pr$^i_2$NEt, −78 °C to −30 °C, 30 min; (d) KOTMS, DMF, 0 °C, 30 min; MeOH, O_3, −78 °C; 5% methanolic citric acid

Scheme 11

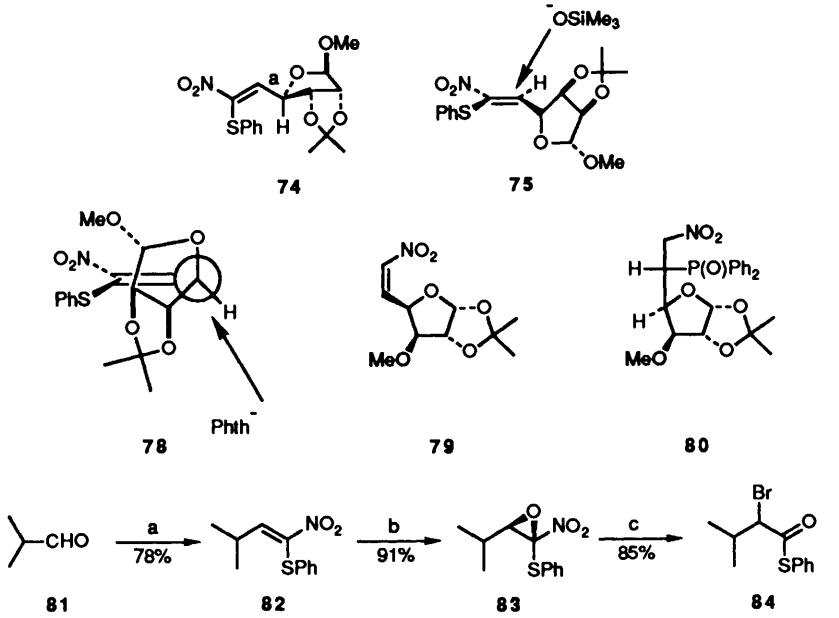
Vorbrüggen glycosidation.[22] The origin of stereocontrol in the conversion of (70) into (71) requires further comment. In the *Z*-nitroalkene (70), the eclipsed conformation (74) is strongly favoured due to the avoidance of 1,3-allylic strain.[23] However, partial rotation ($\approx 30°$) about bond a allows the system to adopt conformation (75). This conformation meets the stereoelectronic requirements for antiperplanar addition of the nucleophile with the result of a high (>50:1) 5(*S*) stereochemical bias in the reactions. However, not all nucleophiles show the same bias on addition to the nitroalkene (70). Indeed potassium phthalimide was found to add to (70) to provide two products (76) and (77) (83%) (Scheme 12). In this case, the major (15:1) product (76) was determined by *X*-ray crystallography to have the 5(*R*)-stereochemistry.[24] Clearly, (76) can not be derived from phthalimide addition to the conformation (75). Examination of molecular models of (75) showed that the addition of phthalimide anion would be disfavoured due to steric congestion between one of the phthalimide carbonyls and the C-3 oxygen substituent. In contrast, addition to conformation (78),

[22] H.Vorbruggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234.
[23] For an excellent review on allylic 1,3-strain see R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.
[24] A. G. M. Barrett, D. Dhanak, and S. A. Lebold, unpublished observations.

70 **76** **77**

Reagent (a) potassium phthalimide, DMF, MeOH, O_3, $-78\,^{\circ}C$

Scheme 12



Reagents (a) $PhSCH_2NO_2$ (53), piperidinium acetate, CH_2Cl_2, Δ, (b) Bu^tOOH, Bu^nLi, (c) $MgBr_2OEt_2$, Et_2O

Scheme 13

which should be higher in energy than (75), should not suffer from such congestion. It is nonetheless remarkable that the nitroalkene (70) underwent two highly stereoselective nucleophilic addition reactions with complete reversal of relative asymmetric induction. The nucleophilic addition of potassium phthalimide to (70) closely follows the stereochemical outcome on the addition of several nucleophiles to the simple *Z*-nitroalkene (79). Yamashita *et al.*[25] have shown that Ph_2POH reacted with (79) to give mostly the (5*S*)-isomer (80) (ds 11:1).

As an alternative to nucleophilic addition to 1-(phenylthio)-nitroalkenes, Jackson and co-workers have studied nucleophilic additions to derived epoxides.[26] The procedure is illustrated by the conversion of the nitroalkene (82) into the corresponding α-bromo-phenylthio ester (84) (Scheme 13). Reaction of iso-butyraldehyde (81) and (phenylthio)nitromethane (53) in the presence of

[25] M Yamashita, M Sugiura, Y Tamada, T Oshikawa, and J Clardy, *Chem Lett*, 1987, 1407, H Yamamoto, A Noguchi, K Torii, K Ohno, T Hanaya, H Kawamoto, S Inokawa, *ibid*, 1988, 1575, M Yamashita, Y Tamada, A Iida, and T Oshikawa, *Synthesis*, 1990, 420

[26] M Ashwell and R F W Jackson, *J Chem Soc, Chem Commun*, 1988, 282, M Ashwell, R F W Jackson, and J M Kirk, *Tetrahedron*, 1990, **46**, 7429

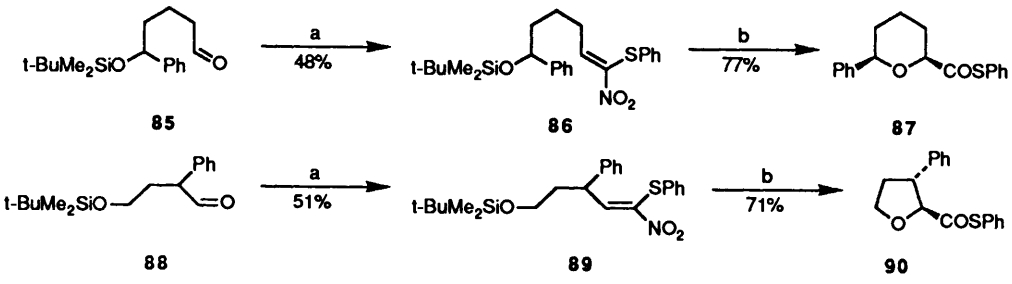
piperidinium acetate directly gave the (*Z*)-nitroalkene (82) and this was smoothly epoxidized The resultant epoxide (83) was allowed to react with magnesium bromide to provide the α-bromo-carboxylic acid derivative (84) Alternatively, (83) and related epoxides, were ring opened with lithium chloride, magnesium iodide, boron trifluoride etherate, trifluoromethanesulphonic acid, or methanesulphonic acid to give the corresponding α-chloro-, α-iodo-, α-fluoro-, α-trifluoromethanesulphonyloxy-, and α-mesyloxy systems These reactions of 1-nitro-1-(phenylthio)oxiranes compliment the chemistry in Scheme 10 The method is most suitable for nucleophiles that are the conjugate bases of strong acids The conversion of (83) into (84) most probably involves C-2 attack followed by loss of nitrous acid

1-(Phenylthio)nitroalkenes are also excellent intermediates for the synthesis of heterocyclic ring systems Protected γ- and δ-hydroxy aldehydes have been converted into tetrahydrofuran- and tetrahydropyran-carboxylic acid derivatives *via* nitroalkene intermediates [27] Examples of these reactions are given in Scheme 14 In both cases, closure of the nitroalkenes (86) and (89) was mediated by reaction with pyridinium hydrogenfluoride followed by ozonolysis of the nitroalkane under basic conditions The tetrahydropyran derivative (87) was formed predominantly as the *cis*-isomer (9 1 1) whereas (90) was obtained exclusively as the *trans*-isomer The highly stereoselective formation of (90) is certainly the result of the minimization of 1,3-allylic strain [23] Cyclization of (86) provided mostly the *cis*-isomer (87) presumably as a result of preferential cyclization *via* the chair-like transition state (91) with two pseudo-equatorial substituents

Nitroalkenes derived from (phenylthio)nitromethane (53) are excellent precursors for the preparation of bicyclic β-lactam ring systems [28] Both hepta-1,6-diene (92) and hexa-1,5-diene (98) have been converted into the carbacepham (96) and carbapenam 100 systems (Scheme 15) Since the methods directly follow the reactions in Scheme 1, they are not discussed in detail here Again in these systems, ring closure of the nitroalkenes (94) and (99) showed a small *endo* bias The major *endo*-isomer (97) was readily isomerized to the *exo*-configuration (96) on treatment with base A related sequence of transformations was used to prepare the oxacephem (106) (Scheme 16) In this case, formation of the nitroalkene (104) was effected in high yield even in the presence of the unprotected tertiary alcohol and the silyloxy group Cyclization of the nitroalkene (104) gave both *exo*-(COSPh) isomers (105) in modest yield and these were dehydrated to the target Δ^3 systems (106) The cyclization of 1-(phenylthio)-1-nitroalkene systems was also used to prepare the two oxapenam thioesters (107) and (108)

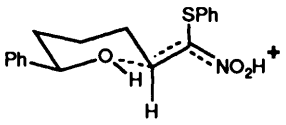
It is clear from all these results and the studies in Section 1 that both (benzyloxy)nitromethane (1) and (phenylthio)nitromethane (53) are very useful reagents for the construction of bicyclic β-lactams Reagent 1 is however superior

[27] A G M Barrett J A Flygare and C D Spilling *J Org Chem* 1989 **54** 4723
[28] A G M Barrett G G Graboski and M A Russell *J Org Chem* 1986 **51** 1012 A G M Barrett G G Graboski M Sabat and S J Taylor *ibid* 1987 **52** 4693



Reagents (a) $PhSCH_2NO_2$ (53), KOBu^t, Bu^{t}OH, THF, MsCl, Et_3N, (b) HF, pyridine, KOBu^t, O_3, $-78\,^\circ C$

Scheme 14



91

since the resultant β-lactam benzyl esters may be readily deprotected to produce the corresponding carboxylic acids.

There are very few studies on the cycloaddition reactions of (phenylthio)nitroalkenes. Reinhoudt and co-workers have reported that the nitroalkene (109) underwent cycloadditions with ynamines to provide nitrones.[29] The process is exemplified by the conversion of (109) and (113) into (112) (Scheme 17).

There are few reported examples of nitroalkenes bearing C-1 selenium substituents. Sakakibara *et al.* have reported the preparation of (phenylselenyl)nitromethane (115) and its conversion into the nitroalkenes (117) (Scheme 18).[17]

4 1-Halogeno-nitroalkenes

There are many examples of 1-bromo- and 1-chloro-nitroalkenes reported by Perekalin's group and by others. These substances are readily prepared by the halogenation of nitroalkenes followed by dehydrohalogenation under basic conditions. Representative examples are given in Table 2. In addition, 1-bromo- and 1-chloronitroalkenes have been prepared from bromo- or chloro-nitromethane, *via* the nitration of halogenoalkenes and *via* the halogenation of some nitronates. Examples of these methods are given in Scheme 19. The versatile 1,1,1-trichloronitroethene (127) was readily prepared from the nitration of trichloroethene (126).[34] Vasil'ev and Burdelev have reported that 1-bromo-1-nitro-2,2-diphenylethene (129) may be prepared from the nitration of the bromide (128).[35] 1,1-Dinitro-2,2-diphenylethene (4%) was a by-product in the reaction. Dauzonne and co-workers have shown that bromonitromethane may

[29] P J S S van Eijk, C Overkempe, W P Trompenaars, D N Reinhoudt, L M Mannmen, G J van Hummel, and S Harkema, *Rec Trav Chim Pays-Bas*, 1988, **107**, 27, P J S S van Eijk, C Overkempe, W P Trompenaars, D N Reinhoudt and S Harkema, *ibid*, 1988, **107**, 40

[30] J M J Tronchet, A P Bonenfant, K D Pallie, and F Habashi, *Helv Chim Acta*, 1979, **62**, 1622, J M J Tronchet, K D Pallie, and F Barbalat-Rey, *J Carbohydr Chem*, 1985, **4**, 29

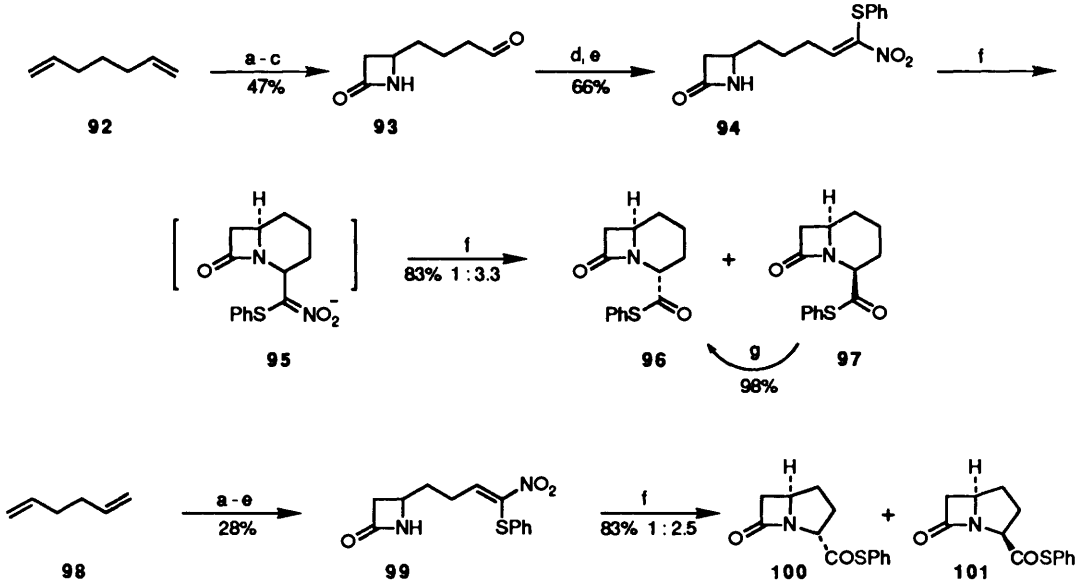
[31] F I Carroll and J A Kepler, *Can J Chem*, 1966, **44**, 2909

[32] F I Carroll, S C Kerbow, and M E Wall, *Can J Chem*, 1966, **44**, 2115, É S Lipina and V V Perekalin, *J Gen Chem U S S R (Engl Transl)*, 1964, **34**, 3693, G L Rowley and M B Frankel, *J Org Chem*, 1969, **34**, 1512 For the preparation of (123) *via* the conrotatory thermal opening of the corresponding cyclobutene system see D B Miller, P W Flanagan, and H Schechter, *ibid*, 1976, **41**, 2112

[33] J P Edasery and N H Cromwell, *J Heterocyclic Chem*, 1979, **16**, 831, A Nakazawa, *Nagaoka Kogyo Tanki Daigaku Kotoo Semmon Gakko Kenkyukyo*, 1967, **3**, 305 (*Chem Abstr*, 1968, **69**, 2398*j*), W E Parnham and J L Bleasdale, *J Am Chem Soc*, 1951, **73**, 4664

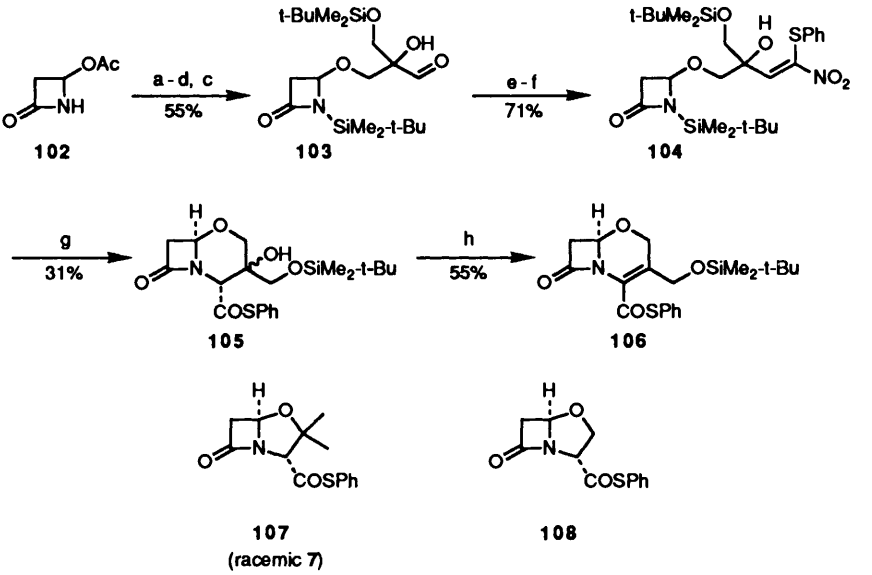
[34] For example see H Johnston, U S Patent 3054828, G B Bachman, T J Logan, K R Hill, and N W Standish, *J Org Chem*, 1960, **25**, 1312

[35] S V Vasil'ev and O T Burdelev, *Izv Vyssh Ucheb Zaved, Khim Tekhnol*, 1970, **13**, 73 (*Chem Abstr*, 1970, **72**, 132199*t*)



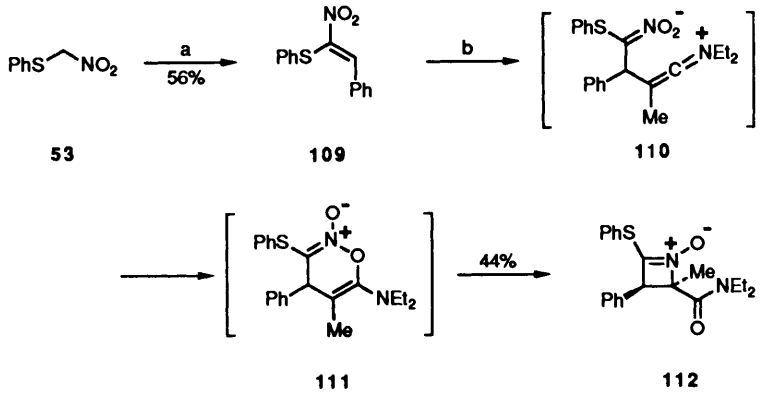
Reagents: (a) $ClSO_2NCO$; $Na_2S_2O_5$; (b) Bu^tMe_2SiCl, Pr^i_2NEt, CH_2Cl_2; (c) O_3, CH_2Cl_2, $-78\,^{\circ}C$; Me_2S; (d) $PhSCH_2NO_2$ (53), $KOBu^t$, Bu^tOH, THF; (e) $MeSO_2Cl$, Et_3N, CH_2Cl_2, $0\,^{\circ}C$; (f) Bu_4NF; THF, $-55\,^{\circ}C$, O_3; $-78\,^{\circ}C$; (g) Pr^i_2NEt

Scheme 15



Reagents: (a) CH_2=C(CH_2OH)CH_2OH, $Zn(OAc)_2$·$2H_2O$, PhH, Δ; (b) Pr'_2NEt, Bu^tMe_2SiCl, CH_2Cl_2; (c) O_3, CH_2Cl_2, −78 °C; (d) CH_2=$CHMgBr$, THF, −78 °C; (e) $PhSCH_2NO_2$ (53), Bu^tOK, THF, Bu^tOH; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2, −10 °C; (g) Bu_4NF, THF, −55 °C; O_3, −78 °C; (h) $MeSO_2Cl$, Et_3N, CH_2Cl_2, −20 °C

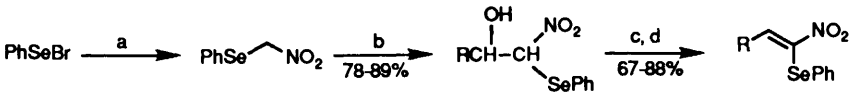
Scheme 16



Reagents: (a) PhCH=NBu, AcOH; (b) MeC≡$CNEt_2$ (113), MeCN

Scheme 17

be used to prepare either 1-bromo- or 1-chloro-1-nitro-2-arylethenes simply by varying the amount of the catalyst dimethylammonium chloride, solvent, and temperature employed. Examples are the conversion of aldehydes (130) and (132)

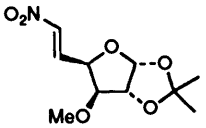
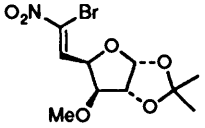
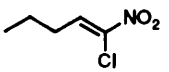
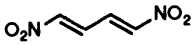
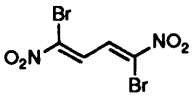
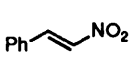
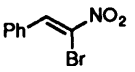


114 **115** **116** **117**

Reagents: (a) $MeNO_2$, NaOEt, $CHCl_3$, (b) RCHO, KF; (c) Ac_2O, $BF_3.OEt_2$; (d) Na_2CO_3, PhH, Δ

Scheme 18

Table 2 *Halogenation–Dehydrohalogenation of nitroalkenes*

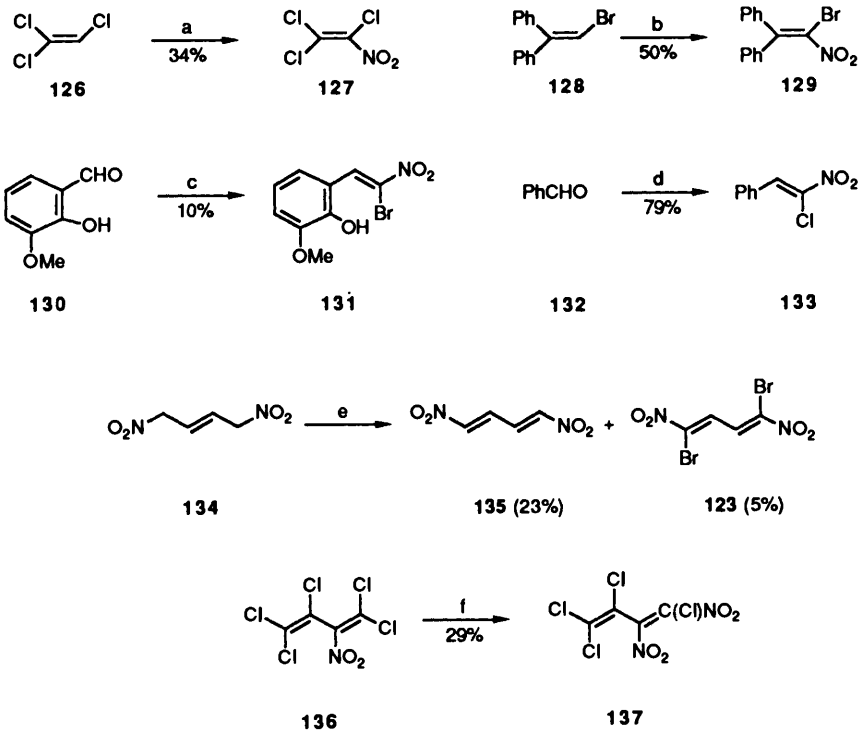
Nitroalkene	*Halogenonitroalkene*	*Method*	*Yield, %*	*Ref.*
 (118)	 (119)	A	90	30
 (120)	 (121)	B	38	31
 (122)	 (123)	C	84	32
 (124)	 (125)	D	75	33

Method: (A) Br_2; Ag_2CO_3; (B) Cl_2, HCl, AcOH; Et_3N, Et_2O; (C) Br_2, $CHCl_3$; PhH, Fluorisil; (D) Br_2; pyridine, c-C_6H_{12}, Δ

into the nitroalkenes (131) and (133).[36,37] The preparation of the dibromide (123) from 1,3-dinitro-2*E*-butene (134) probably involved the intermediacy of the dinitronate dianion of (134).[38] A nucleophilic addition of nitrite and subsequent elimination of chloride was employed in the conversion of pentachloride (136) into the α,β-dinitroalkene (137).[39]

There are several reported syntheses of 1-fluoro-1-nitroalkenes but these are much less common compounds than the chlorine or bromine counterparts.

[36] D. Dauzonne and R. Royer, *Synthesis*, 1987, 1020.
[37] D Dauzonne and P. Demerseman, *Synthesis*, 1990, 66.
[38] G. V. Nekrasova, Ė. S. Lipina, E. E. Boldysh, and V. V. Perekalin, *J. Org. Chem. U.S.S.R.* (*Engl. Transl.*), 1988, **24** 1031. For the synthesis of the corresponding dichloride, see E. H. Braye, *Bull. Soc. Chim. Belg.*, 1963, **72**, 699.
[39] V. I. Potkin, R. V. Kaberdin, and Yu. A. Ol'dekop, *Vestsi Akad. Navuk B.S.S.R.* , *Ser. Khim. Navuk*, 1987, **114**, (*Chem. Abstr.*, 1988, **108**, 130970a)



Reagents (a) 70% HNO_3, 85 °C to 90 °C, (b) N_2O_4, Et_2O, 10 C, H_2O Δ, (c) $BrCH_2NO_2$, Me_2NH_2Cl, KF, Bu^s_2O, Δ, (d) $BrCH_2NO_2$, excess Me_2NH_2Cl, KF, xylene, Δ, (e) BuLi, HMPA, THF, −78 °C, Br_2, (f) KNO_2

Scheme 19

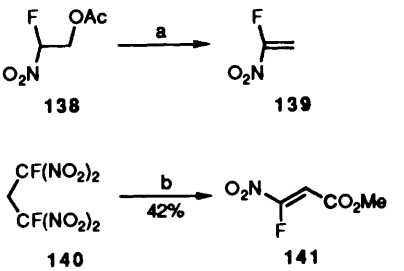
Eremenko and Oreshko[40] have described the preparation and isolation of 1-fluoro-1-nitroethene (139) from the β-elimination of the acetate (138). Methanolysis of the tetranitrodifluoride (140) has been shown to provide the interesting acrylate derivative (141)[41] (Scheme 20). Alternative syntheses of other 1-fluoro-1-nitroalkenes are reported in the Russian literature.[42]

1-Halogeno-1-nitroalkenes are reactive electrophiles that readily undergo Michael addition reactions with nucleophiles. In many cases the halide substituent is displaced after the Michael addition and this process has been used to prepare

[40] L T Eremenko and G V Oreshko, *Bull Acad Sci USSR, Div Chem Sci* (*Engl Transl*), 1969, 660

[41] G V Oreshko, G V Lagodzinskaya, and L T Eremenko, *Bull Acad Sci USSR, Div Chem Sci* (*Engl Transl*), 1989, **38**, 635

[42] L T Eremenko and G V Oreshko, *Bull Acad Sci USSR, Div Chem Sci* (*Engl Transl*), 1987, 1332, L T Eremenko, L O Atovmyan, N I Golovina, G V Oreshko, and M A Fadeev, *ibid*, 1987, 1870 For a report on 1-iodo-1-nitroalkenes, see N V Kondratenko, L A Khomenko, and L M Yagupol'skii, *Zh Org Khim*, 1990, **26**, 740



Reagents (a) NaOAc catalyst, 130 - 140 °C, (b) MeOH, 15– 20 °C

Scheme 20

cyclopropane systems, furans, and other heterocycles 1-Nitro-1,2,2-trichloroethene (127) is a most useful reagent for preparing orthoesters [43] Thus, reactions of (127) with phenols or alcohols under basic conditions has been used to prepare 2-chloro-2-nitro-orthoacetate esters (18—79%). These species were formed *via* a triple Michael addition to (127) and a double loss of chloride The preparation of the orthoacetate (142) is representative These orthoesters should be versatile intermediates for further synthetic transformations Nitrotrichloroethene (127) is also a useful precursor for the synthesis of heterocyclic molecules (Scheme 21) and this chemistry is illustrated by the synthesis of the benzoxazole (143),[44] the 1H-perimidine (144),[45] the furans (145),[46] the methylene-cyclopropane derivative (146),[47] and the indole (147) [48] These reactions proceed *via* double addition–elimination mechanisms [(143) and (144)] with further displacement of the α-chloride [(145), (146), and (147)] Most of these studies were carried out by the Leningrad group

Other 1-bromo- and 1-chloro-1-nitroalkenes show comparable reactivities to trichloronitroethene All the transformations are initiated by Michael addition and this process may be followed by displacement of the halide substituent The transformations of 1-bromo-1-nitro-2-phenylethene (125) (Scheme 22) are

[43] V A Buevich, N Zh Nakova, and V V Perekalin, *J Org Chem U S S R* (*Engl Transl*), 1981, **17**, 1378, 1979, **15**, 1473 V A Buevich and N Zh Nakova, *ibid*, 1977, **13**, 2431, 1978, **14**, 2229, E Francotte, R Verbruggen, H G Viehe, M van Meerssche, G Germain, J P Declercq, *Bull Soc Chim Belg*, 1978, **87**, 693

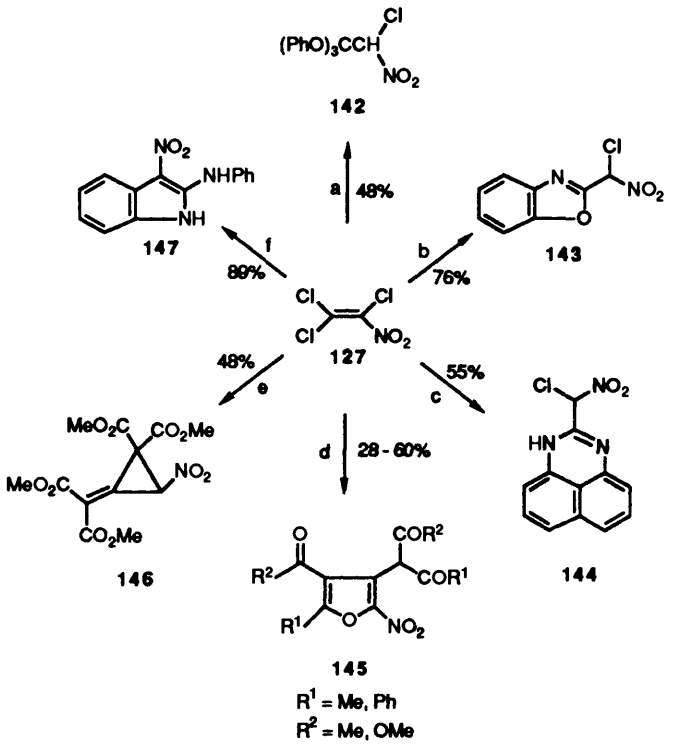
[44] V A Buevich, V V Rudchenko, V S Grineva, and V V Perekalin, *J Org Chem U S S R* (*Engl Trans*), 1978, **14**, 2031, V A Buevich, V S Grineva, and V V Rudchenko, *ibid*, 1975, **11**, 1768

[45] V A Buevich, N Zh Nakova, G Kempter, and V V Perekalin, *J Org Chem U S S R* (*Engl Trans*), 1977, **13**, 2430

[46] V A Buevich, V S Grineva, L I Deiko, and V V Perekalin, *J Org Chem U S S R* (*Engl Transl*), 1975, **11**, 648, V A Buevich, L I Deiko, and V V Perekalin, *ibid*, 1981, **17**, 1175, *ibid*, 1977, **13**, 894, *Khim Geterotsikl Soedin*, 1977, 311 (*Chem Abstr*, 1977, **87**, 22904u), L I Dieko, V A Buevich, V S Grineva, and V V Perekalin, *Khim Geterotsikl Soedin*, 1975, 1148 (*Chem Abstr*, 1976, **84**, 17045*a*)

[47] V A Buevich, L I Deiko, and V E Volynskii, *J Org Chem U S S R* (*Engl Transl*), 1980, **16**, 2055 V A Buevich, L I Deiko, and V V Perekalin, *Khim Dikarbonilnykh Soedin*, *Tezisy Dokl Vses Konf 4th*, 1975, 132 (*Chem Abstr*, 1977, **87**, 53004g)

[48] V A Buevich, V V Rudchenko, and V V Perekalin, *Khim Geterotsikl Soedin*, 1976, 1429 (*Chem Abstr*, 1977, **86**, 72357*v*)



Reagents (a) NaOMe, PhOH, MeOH, (b) 2-$H_2NC_6H_4$-OH, NaOMe, MeOH, (c) 1,8-diaminonaphthalene, Et_2O, 10 °C, (d) $R^1COCH_2COR^2$, NaOMe, (e) $(MeO_2C)_2CH_2$, NaOMe, MeOH, (f) $PhNH_2$

Scheme 21

representative. *N*-Methylpyrrole,[49] the enolate of dimethylacetamide,[50] and sodium sulphite or methoxide[51] have been reported to give simple Michael adducts Under more forcing conditions, enolate intermediates were found to react further to provide cyclopropanes *e g.* (153)[53] or furans *e g* (156)[55] Primary

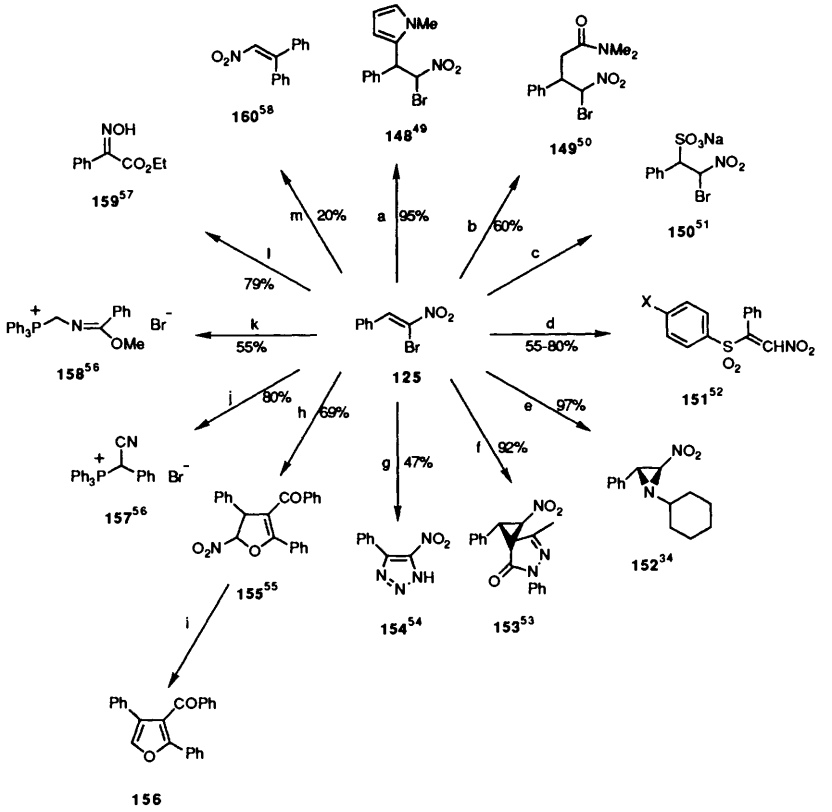
[49] M M Campbell, N Cosford, L Zongli, and M Sainsbury, *Tetrahedron*, 1987, **43**, 1117

[50] D Seebach, H F Leitz, and V Ehrig, *Chem Ber*, 1975, **108**, 1924 For related reactions, see H Neumann and D Seebach, *ibid*, 1978, **111**, 2785, A S Sopova, V V Perekalin, and O I Yurchenko, *J Gen Chem U S S R (Engl Transl)*, 1963, **33**, 2087, A S Sopova, V V Perekalin, V M Lebednova, and O I Yurchenko, *ibid*, 1964, **34**, 1177, A S Sopova, V V Perekalin, and V M Lebednova, *ibid*, 1963, **33**, 2090, 1964, **34**, 2659, A S Sopova, V V Perekalin, and O I Yurchenko, *ibid*, 1964, **34**, 1180

[51] D Aleksiev, *Vestsi Akad Navuk B S S R, Ser Khim Navuk*, 1976, 121 (*Chem Abstr*, 1976, **85**, 5321*v*) For a related addition, see C D Bedford and A T Nielsen, *J Org Chem*, 1978, **43**, 2460

[52] D I Aleksiev, *J Org Chem U S S R (Engl Transl)*, 1975, **11**, 206 and 900

[53] T G Tkhor, A S Sopova, and B I Ionin, *J Org Chem U S S R (Engl Transl)*, 1977, **13**, 777, E L Metelkina, A S Sopova, and B I Ionin, *ibid*, 1973, **9**, 2219, 1972, **8**, 2082, A S Sopova, T G Tkhor, V V Perekalin, and B I Ionin, *ibid*, 1972, **8**, 2347



Reagents: (a) 1-methylpyrrole, ZnI_2; (b) CH_2=C(OLi)NMe_2, THF, −78 °C; (c) $NaHSO_3$, H_2O, dioxane; (d) 4-X-$C_6H_4SO_2Na$ (X = Me, Br, Cl, I); (e) cyclohexylamine; (f) $\overline{CH_2CON(Ph)N{=}C}$(Me), NaOMe, MeOH; (g) NaN_3, EtOH, Δ; (h) $(PhCO)_2CH_2$, NaOMe, MeOH; (i) Et_3N, PhH, Δ; (j) Ph_3P, PhH; (k) Ph_3P, MeOH; (l) *hν*, MeOH; (m) $Pd(OAc)_2$, PhH, AcOH, Δ

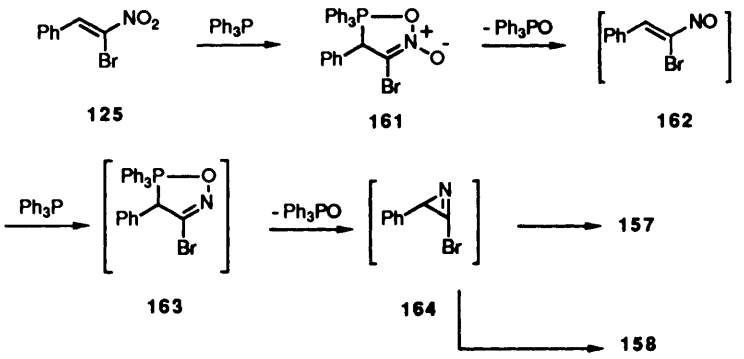
Scheme 22

amines gave aziridines *e.g.* (152),[33] arenesulphinate anions gave the interesting 2-nitrovinyl sulphones (151),[52] and azide anion the triazole (154).[54] Devlin and Walker have reported that (125) gave the phosphonium salts (157) and (158) on reaction with triphenylphosphine in benzene or methanol respectively.[56] These reactions most probably take place *via* Michael addition of the phosphine and

[54] G. Kh. Khisamutdinov, O. A. Bondarenko, L. A. Kupriyanova, V. G. Klimenko, and L. A. Demina, *J. Org. Chem. U.S.S.R.* (*Engl. Transl.*), 1979, **15**, 1168; G. Kh. Krisamutdinov, O. A. Bondarenko, and L. A. Kupriyanova, *ibid.*, 1975, **11**, 2506.

[55] T. G. Tkhor, A. S. Sopova, and B. I. Ionin, *J. Org. Chem. U.S.S.R.* (*Engl. Transl.*), 1976, **12**, 640.

[56] C. J. Devlin and B. J. Walker, *J. Chem. Soc., Chem. Commun.*, 1970, 917; *J. Chem. Soc., Perkin Trans. 1*, 1973, 1428; 174, 453.



Scheme 23

the intermediary of (161)—(164). This mechanistic speculation (Scheme 23), which differs from the authors suggestions,[56] is well founded, at least for intermediate (161), on precedent in the Russian literature.[59,60] Heterocycles related to (161) and equivalent isoxazoline *N*-oxides have been isolated from the reactions of trimethyl phosphite,[59] selenium ylides and the sodium nitronate of nitroacetonitrile with 1-bromo-1-nitroalkenes.[60]

In addition to the reactions of the nitroalkenes (127) and (125) summarized in Schemes 21 and 22, various other heterocyclic systems have been prepared form 1-halogeno-1-nitroalkenes. Dauzonne and co-workers have shown that the reactions of orthohydroxybenzaldehydes with bromonitromethane may be used to prepare benzopyran and -furan ring systems. The dihydrobenzofuran (167) was formed *via* nitroalkene (165) reduction to product (166) and S_N2 ring closure (Scheme 24).[61] Dauzonne found that chloronitroalkenes such as (133) reacted stereoselectively with salicylaldehyde to provide (168);[37] clearly this species was derived from Michael addition of the phenolate anion followed by an intramolecular Henry reaction. The reaction of tetranitrile (171) with nitroalkene (169) to provide (170)[62] presumably followed a related mechanistic pathway.

It is clear from all these reports that 1-halogeno-1-nitroalkenes are reactive electrophiles of considerable use in synthesis. They clearly have very considerable potential for applications in the synthesis of more complex molecular assemblies.

[57] G W Shaffer, *Can J Chem*, 1970, **48**, 1948

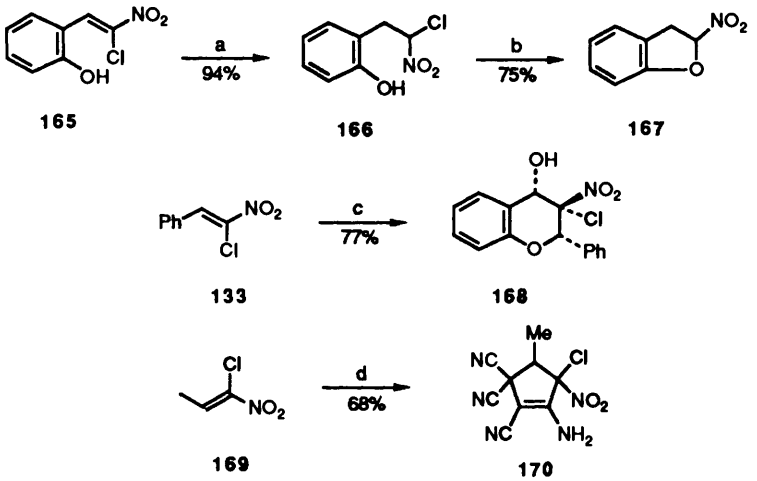
[58] K Yamamura and S Watarai, *Bull Chem Soc Jpn*, 1975, **48**, 3757

[59] R D Gareev, G M Loginova, I N Zykov, and A N Pudovik, *J Gen Chem U S S R* (*Engl Transl*), 1979, **49**, 20, R D Gareev, G M Loginova, and A N Pudovik, *Bull Acad Sci U S S R, Div Chem Sci* (*Engl Transl*), 1978, 400

[60] N N Magdesieva, T A Sergeeva, and R A Kyandzhetsian, *J Org Chem U S S R* (*Engl Transl*), 1985, **21**, 1813, É L Metelkina, A S Sopova, V V Perekalin, and B I Ionin, *ibid*, 1974, **10**, 213

[61] D Dauzonne and R Royer, *Synthesis*, 1988, 339 For related heterocycles see D Dauzonne, H Josien, and P Demerseman, *Tetrahedron*, 1990, **46**, 7359

[62] O E Nasakin, P M Lukin, S P Zil'berg, P B Terent'ev, A Kh Bulai, O A D'yachenko, A B Zolotoi, S V Konovalikhin, and L O Atovmyan, *J Org Chem U S S R* (*Engl Transl*), 1988, **24**, 901



Reagents: (a) $NaBH_4$, Pr'OH, $CHCl_3$, silica; (b) K_2CO_3, Me_2CO; (c) 2-HO-C_6H_4CHO, Et_3N; (d) $(NC)_2CHCH(CN)_2$ (171) Pr'OH, H_2O, Δ

Scheme 24

5 Nitroalkenes Substituted by C-1 Nitrogen Substituents

There are no known nitroalkenes that are substituted by simple amino residues at C-1. Nearly all nitroalkenes bearing C-1 nitrogen substituents are 1,1-dinitroalkenes. In general, 1,1-dinitroalkenes that are C-2 aryl substituted may be isolated whereas aliphatic counterparts are much more reactive and frequently undergo reactions *in situ*. 2-Aryl-1,1-dinitroalkenes have been prepared from the nitration of styrenes or compounds that generate styrenes *in situ*, for example phenethyl alcohols. Representative 2-aryl-1,1-dinitroalkene syntheses are summarized in Table 3. These aryl dinitroalkenes (173), (175), (177), and (179) were easily isolated. In contrast, aliphatic systems were usually trapped as Michael or Diels–Alder adducts. Table 4 lists examples of methods for the generation and trapping of reactive 1,1-dinitroalkenes. The reaction of 1,1,1-trinitroethane (180) with guanidine gave the adduct (182) and this was clearly formed *via* elimination of HNO_2 to produce (181).[67] Reaction of (180) with trimethylamine or diethyl potassiomalonate gave adducts equivalent to (182). However, many other nucleophiles reacted with (180) *via* denitration to produce the anion of 1,1-dinitroethane. On heating, 2,2-dinitroethanol (183) was shown to produce 1,4,6-

[63] E. Bergmann, L. Engel, and H. Meyer, *Chem. Ber.*, 1932, **65**, 446. For a preparation of (173) (87%) from diphenyldiazomethane and $IC(NO_3)_3$ see F. A. Gabitov, A. L. Fridman, and A. D. Nikolaeva, *J. Org. Chem. U.S.S.R.* (*Engl. Transl.*), 1969, **5**, 2182.

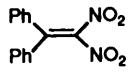
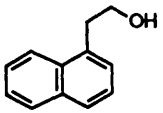
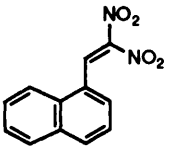
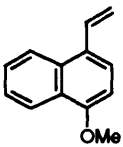
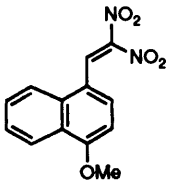
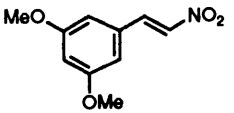
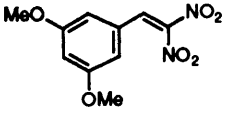
[64] For example, see A. I. Sitkin, O. Z. Safiulina, R. F. Chernyaeva, and A. D. Nikolaeva, *J. Org. Chem. U.S.S.R.* (*Engl. Transl.*), 1975, **11**, 443 and references therein.

[65] For example see A. I. Sitkin, R. F. Chernyaeva, and G. I. Simonova, *Sb. Nauch. Tr. Kuzbas Politekh. Inst.*, 1972, No. 52, 135 (*Chem. Abstr.*, 1974, **81**, 13309e).

[66] P. J. Mulligan and S. LaBerge, *J. Med. Chem.*, 1970, **13**, 1248.

[67] L. Zeldin and H. Schechter, *J. Am. Chem. Soc.*, 1957, **79**, 4708.

Table 3 *Preparation of 2-aryl-1,1-dinitroalkenes via nitration reactions*

Precursor	*Nitroalkene*	*Method*	*Yield, %*	*Ref*
 (172)	 (173)	A		63
 (174)	 (175)	B	41	64
 (176)	 (177)	A	63	65
 (178)	 (179)	C	75	66

Method (A) fuming HNO_3, AcOH, (B) N_2O_4, $(CH_2Cl)_2$, $-10\,^{\circ}C$, (C) $Cu(NO_3)_2$, Ac_2O, $70\,^{\circ}C$

trinitropyridine-*N*-oxide (184)[68] and this was proposed to arise *via* (181), a Michael addition with (183), a retro-Henry reaction, a second Michael addition, and cyclization of the resultant 1,1,3,5-tetranitropentane. Both β-elimination of acetate[69] and flash vacuum pyrolytic loss of nitrogen dioxide[70] have been used to prepare the tetranitro-systems (186) and (189). Both were trapped to produce (187) and (190).

1,1-Dinitroalkenes readily undergo addition reactions with nucleophiles to produce the corresponding Michael adducts. Both compounds (182) and (187) (Table 4) illustrate this reactivity. Besides these examples, simple Michael adducts have been reported to be formed on the addition of thiols *e.g.* cysteine[71] or alcohols.[72] Russell and Dedolph have extensively studied the reaction of

[68] L I Bagel, I V Tselinskii, and I N Shokhor, *J Org Chem U S S R* (*Engl Transl*), 1969, **5**, 2016

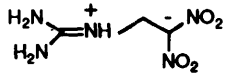
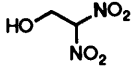
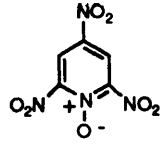
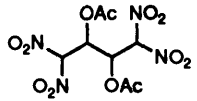
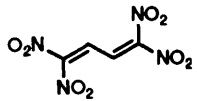
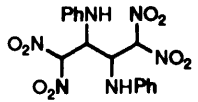
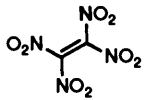
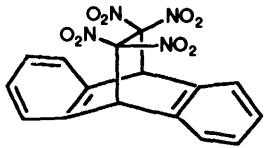
[69] G V Nekrasova, É S Lipina, V P Pozdnyakov, and V V Perekalin, *J Org Chem U S S R* (*Engl Transl*), 1984, **20**, 2277

[70] T S Griffin and K Baum, *J Org Chem*, 1980, **45**, 2880, T S Griffin and D Tzeng, *ibid*, 1985, **50**, 2736

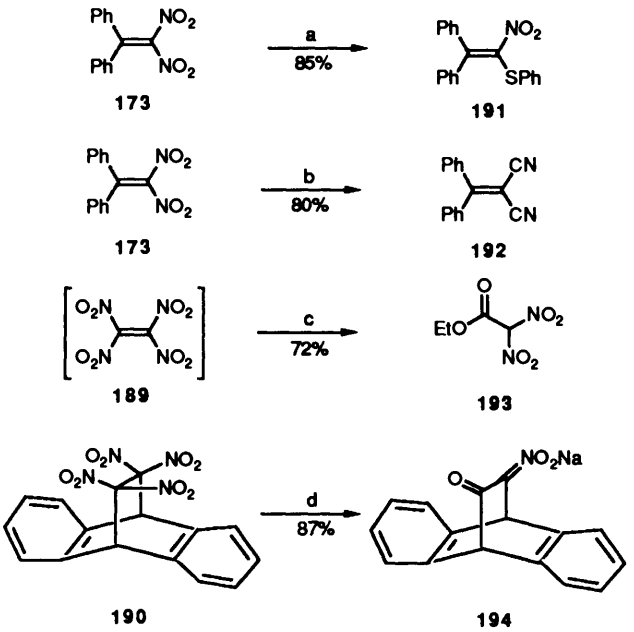
[71] T R Kim, J H Kim, and W S Choi, *Bull Korean Chem Soc*, 1988, **9**, 115 (*Chem Abstr*, 1989, **110**, 39338*f*)

[72] T R Kim, Y H Lee, and W S Choi, *Igong Nonjip*, 1985, **26**, 195 (*Chem Abstr*, 1988, **109**, 169944*r*)

Table 4 *Preparation and trapping of* 1,1-*dinitroalkenes*

Precursor	*Nitroalkene*	*Trapped product*	*Method*[a]	*Yield,* %	*Ref*
$MeC(NO_2)_3$			A	86	67
(180)	(181)	(182)			
			B	24	68
(183)	(181)	(184)			
			C	100	69
(185)	(186)	(187)			
$(O_2N)_3CC(NO_2)_3$			D	50	70
(188)	(189)	(190)			

[a] Reagents (A) guanidine, EtOH, 0 – 25 °C, (B) H_2O, 55 – 60 °C, (C) $PhNH_2$, 5 °C, (D) FVP 260 – 270 °C, anthracene



Reagents (a) PhSK, DMSO, (b) $NCCH_2CN$, Et_3N, EtOH, Δ, (c) EtOH, PhH, (d) NaI, DME, 65 °C

Scheme 25

alkene (173) with diverse nucleophiles in DMSO or THF.[73] Simple Michael adducts were observed with the anions derived from dimethyl or diethyl phosphite or thiophosphite, acetone, t-butyl methyl ketone, acetophenone, DMSO, dimethyl sulphone, and methanol, and cyanide in ethanol solution. In contrast, nitropropane nitronate, nitrite, arene sulphinates, acetate, thioacetate, t-butoxide, ethoxide, hydroxide,[74] and superoxide[75] anions brought about fragmentation, after Michael addition, to produce benzophenone (19—94%). Thiolate anions reacted with (173) to produce 1-nitro-1-[alkyl(or aryl)]thio-2,2-diphenylethene. The formation of adduct (191) is representative (Scheme 25). All products of this type were derived from initial Michael addition followed by rearrangement. In a process reminiscent of benzophenone formation, alkene (173) was also observed to undergo nucleophile addition and fragmentation on reaction with malononitrile, thereby producing dinitrile (192).[76] Tetranitroethene (189) is a very potent electrophile which was found to react with ethanol to produce the dinitroacetic ester (193).[70] The Diels–Alder adduct (190) was

[73] G A Russell and D Dedolph, *J Org Chem*, 1985, **50**, 3878

[74] For a kinetic study of such fragmentations, see C F Bernasconi, D J Carre, and A Kanavariotı, *J Am Chem Soc*, 1981, **103**, 4850

[75] A A Frimer, I Rosenthal, and S Hoz, *Tetrahedron Lett*, 1977, 4631

[76] Z Rappoport and D Ladkani, *J Chem Soc, Perkin Trans 1*, 1974, 2595

reduced by iodide anion to provide the keto-nitronate (194). These reactions which involve nitrite elimination and/or redox chemistry after nitroalkene trapping are of considerable potential for synthesis.

6 Conclusion

It is clear from all these reactions that C-1 heterosubstituted nitroalkenes are reactive electrophiles that have very considerable use in synthesis. Both Michael additions or Diels–Alder reactions are frequently observed. The heteroatom substituent modifies the oxidation level and reactivity profile of the resultant nitroalkane or nitronate anion and thereby permits the synthesis of diverse heterocyclic systems. It is certain that such nitroalkenes will continue to be applied in chemoselective and stereoselective synthesis.

Acknowledgements. I thank all my co-workers who have carried out research with me in the nitroalkene area. They are all acknowledged by name in the various citations. I appreciate their dedication, enthusiasm, and hard work. In addition, I wish to thank the National Institutes of Health for their continued generous support of this research under grants Al-22252 and Al-23034, and G. D. Searle and Company for assistance with microanalyses and unrestricted grant support. Finally I thank Mark L. Boys for help in preparing this manuscript.