NITROALKENES IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Abstract - The utility of nitroalkenes in the synthesis of a variety of heterocyclic compounds is described.

CONTENTS

INTRODUCTION

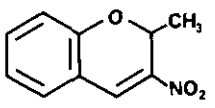
The versatility of nitro compounds in organic synthesis is demonstrated by the proliferation of their use in recent years. The electron deficient nitro group can be easily converted into a number of useful functional groups via a variety of classical organic reactions. Excellent reviews[1-4] cover some of the recent chemistry of nitro groups. As an example, Yoshikoshi reviewed condensation reactions of nitroalkenes with enol silanes, ester enolates and anions derived from β-dicarbonyl compounds etc.[5] Nitroalkenes have also proven to be powerful dienophiles in Diels-Alder reactions[6,7] and undergo addition reactions with a wide range of nucleophiles. Nitroalkenes also provide access to useful synthetic precursors like nitroalkanes[8], N-substituted hydroxylamines[9], amines[10], ketones[11], α-substituted oximes[12], and α-substituted ketones[13]. However, syntheses of heterocyclic compounds via nitroalkenes have not been reviewed.

This article addresses the recent application of nitroalkenes to the syntheses of heterocyclic compounds; some significant earlier contributions are also included. Reactions of nitroenamines were covered in a recent review[14] and are not included except for some newer applications. The use of related nitroalkanes and nitroalcohols in the synthesis of heterocyclic compounds[15] and the role of nitroalkenes in typical cyclenone annulation[16] and bicycloannulation reactions[17] are also excluded. Similarly, the cycloaddition reactions of related nitrosoalkenes[18] are not included.

I. OXYGEN HETEROCYCLES

A. Benzopyrans

Although 2-methyl-3-nitrochromene[19] (1) was first synthesized in 1948, along with the corresponding hydrated analog (2), for use in the preparation of pharmacologically important 3-aminochroman derivatives (3), revival of interest in this class of compounds did not take place until the late seventies.



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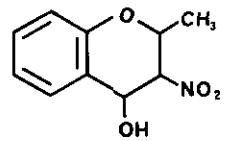

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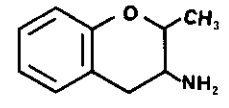

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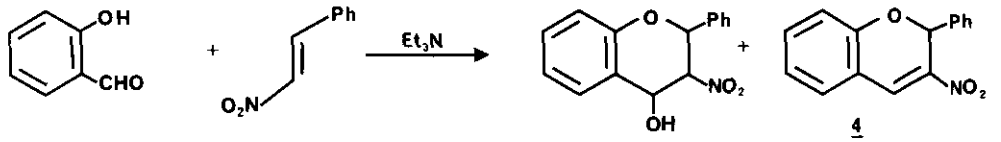
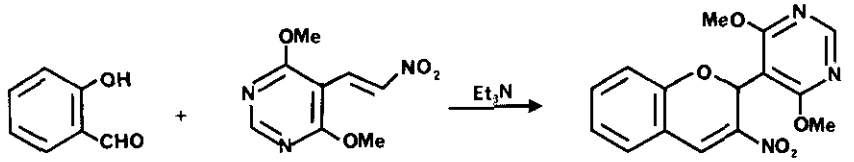
Sakakibara developed a method for synthesizing 2-phenyl-3-nitrochromene (4) and the corresponding C-nucleosides derivatives (5) by condensation of salicylaldehyde with β-nitrostyrenes in the presence of triethylamine.[20]



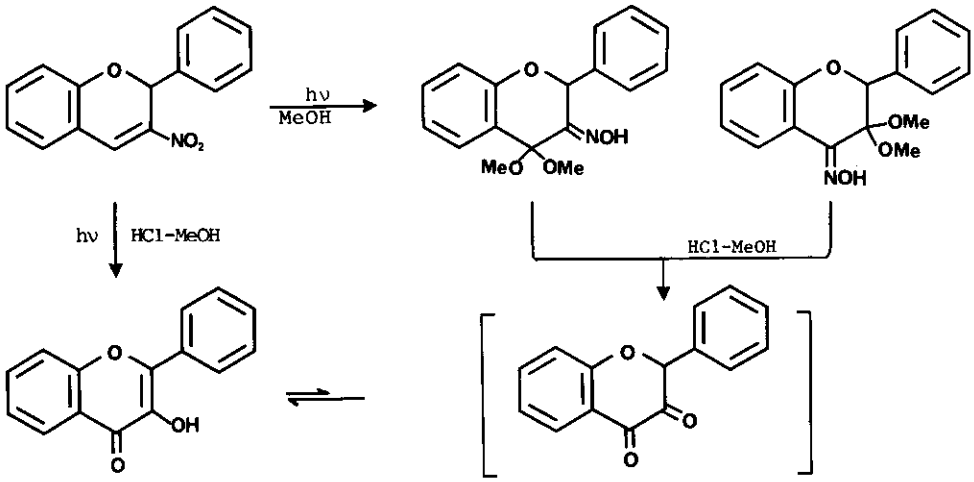


In a comprehensive study directed toward the synthesis of Δ^3-chromenes carrying electron-withdrawing substituents at the 3-position, Royer prepared 3-nitrochromenes from o-hydroxybenzaldehydes and β-nitrostyrene derivatives in pyridine.[21] The yields reported are modest. A variety of Δ^3-nitrochromenes, mono- or disubstituted at the 2-position, were shown to possess radioprotecting properties.[22] A series of 2-alkyl-3-nitro-2H-chromenes, close analogs of 2-nitrobenzofurans, were examined for their biological activity.[23] The ready accessibility of nitroenamines[24] (one-pot synthesis) was promptly utilized by the French group for the synthesis of 2-dialkylamino-3-nitro-2H-chromenes[25] which unfortunately did not exhibit any activity against bacteria, protozoa, and helminths.

Varma and Kabalka reported that the condensation of o-hydroxyarylaldehydes with β-nitrostyrene derivatives on basic alumina surfaces in the absence of solvent yielded 3-nitrochromenes.[26] Improved yields could be obtained using sonic acceleration when the reactants were solids. The corresponding 2-naphthyl-3-nitrochromene derivatives[27] were also synthesized via an improved work-up procedure which involves the removal of the excess unreacted o-hydroxybenzaldehydes on basic alumina.

Trivedi and his group demonstrated the use of 2-phenyl-3-nitrochromenes in the preparation of flavonols,[28] another biologically important class of compounds.[29] This conversion was achieved by photolysis of nitrochromenes in acidic methanol or, alternatively, by acid hydrolysis of the photo products obtained in methanol. The

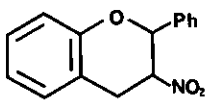
reaction presumably proceeds via an oxime intermediate [Scheme 1].



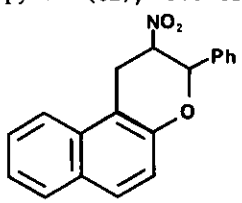
Scheme 1

The oxidation of 3-nitrochromenes with alkaline hydrogen peroxide[30] or divalent chromium[31] also provides an alternative route to flavanols.

Although the chemistry of 3-nitrochromenes has been the subject of extensive investigations, the corresponding saturated analogs, nitrochromans, are virtually unknown.[32,33] The simplest approach to this class of compounds involves the reduction of chromenes.[34,35] However, reduction reactions have always resulted in the formation of chromanamines.[19,36] Consequently, most of the nitrochromans described to date have the nitro group attached to the aromatic ring[32]; the only exception being some intermediates formed in the synthesis of 3-aminoflavans[33] and a 2-methyl-3-nitrochroman.[37] 2-Phenyl-3-nitro-2H-1-benzopyrans (4) has been chemoselectively reduced to the corresponding 3,4-dihydro-2H-1-benzopyran derivative (6a) using sodium borohydride in a mixed solvent system of methanol-tetrahydrofuran (1:10, v/v).[38] Methanol apparently reacts with sodium borohydride to form methoxyborohydride species[39] which effectively reduce the nitrochromene. A series of 2-phenyl-3-nitrochromans[38] and the corresponding 2-naphthyl derivatives[40], including a 3-phenyl-2-nitro-dihydronaphtho[2,1-b]pyran (6b), were obtained in good yield via this sequence.

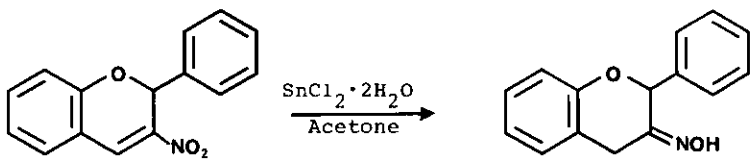


6a



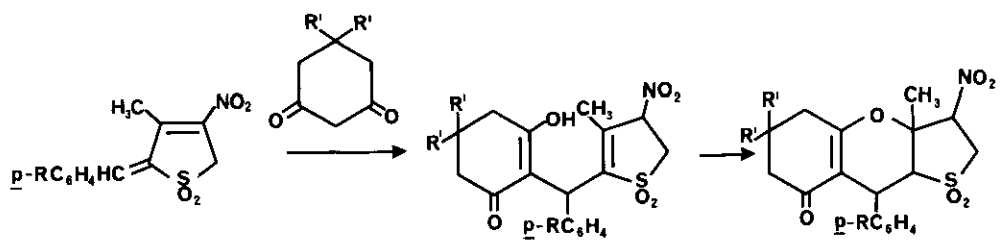
6b

A useful application of the 3-nitrochromenes involves their stannous chloride reduction to stable, crystalline 3-chromanone oxime derivatives[40] (7). It is anticipated that the ready accessibility of these oximes will stimulate interest in



7

the chemistry of 3-chromanones which have not been studied in detail to date because of their inherent instability.[41] Reduction of these oxime derivatives may also provide an alternative route to chromanamines.[42] The synthesis of new tricyclic chroman systems (9a-c) was described recently[43] which involves the reaction of 2-benzylidene(anisylidene)-3-methyl-4-nitro-3,3-thiolene 1,1-dioxides (8a-b) with 1,3-cyclohexanediones (dimedone, dihydroresorcinol) in the presence of sodium alkoxides.

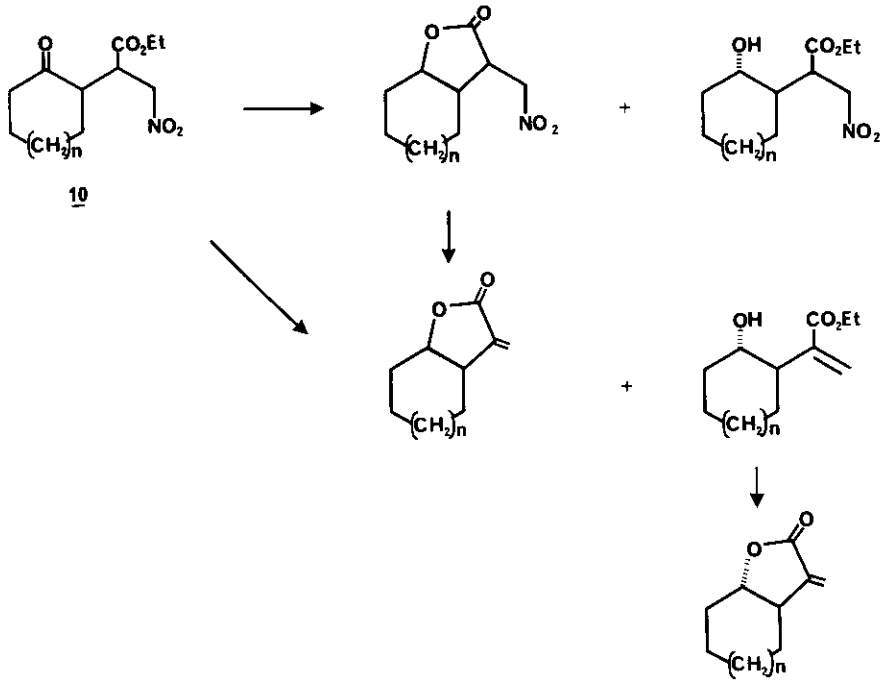


8 a. R=H
b. R=OCH_3

9 a. R=R'=H
b. R=H, R'=CH_3
c. R=OCH_3, R'=CH_3

B. Butyrolactones

Michael addition of the morpholine enamines of cycloalkanones to ethyl β-nitroacrylate, afforded adducts(10) which have been utilized in an overall three-step synthesis of α-methylenebutyrolactones.[44] Sodium borohydride reduction, with simultaneous lactonization and elimination of the nitro-group, provides an efficient method for introducing the lactone moiety in the syntheses of complex sesquiterpene lactones [Scheme 2].



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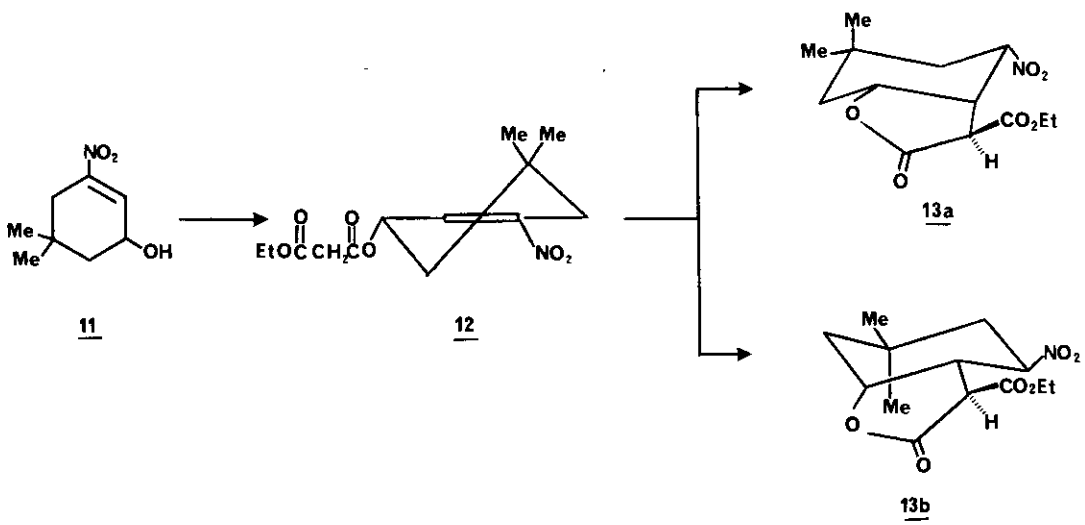
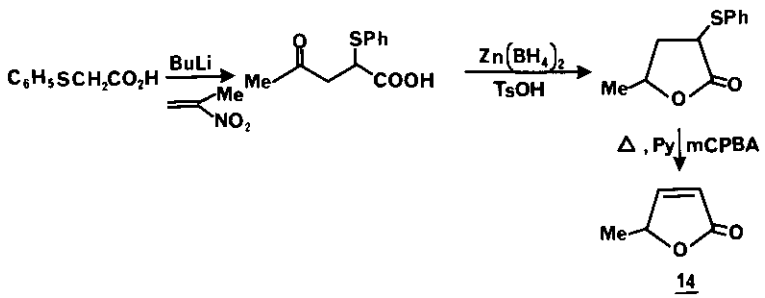
Scheme 2

γ-Hydroxy-α-nitroalkenes, readily prepared from α,β-unsaturated ketones,[45] have been utilized by Sakakibara and his group in a highly stereoselective preparation of γ-butyrolactone derivatives.[46] Treatment of 5,5-dimethyl-3-nitrocyclohex-2-en-1-ol (11) with a solution of monoethyl malonate and p-toluenesulfonyl chloride in pyridine afforded an ester (12) which under mild alkaline conditions, underwent a ring closure to give lactones (13a) and (13b) in 55% and 27% yields respectively.



11 12 13a 13b

The one-pot synthesis of γ-keto acids from carboxylic acid dianions and nitroalkenes was used in an elegant synthesis of β-angelica lactone[16] (14).



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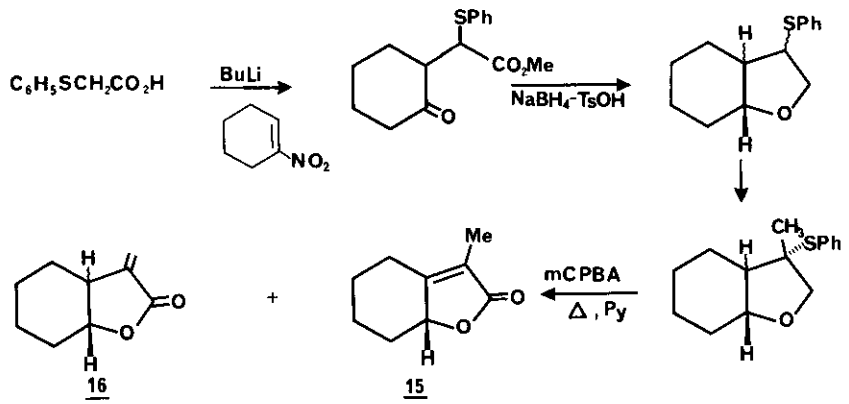
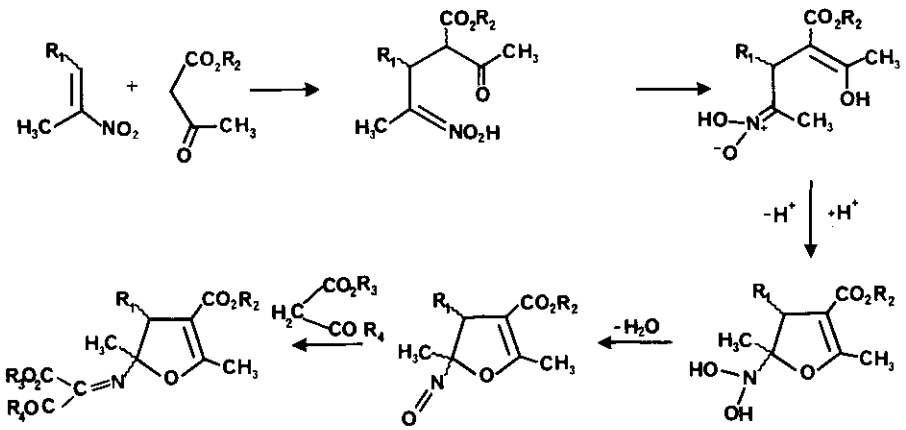
This methodology was successfully extended to the synthesis of fused lactones[16] (15) and (16) as shown in the following reaction schemes.



16 15

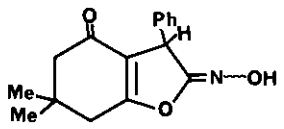
C. Furans and Furanones

Boberg and co-workers obtained 4,5-dihydro-5-(methylenamino)-3-furancarboxylates[47] by treating the adducts of α-nitroalkenes and acetoacetate (nitronic acids) with active methylene compounds [Scheme 3].



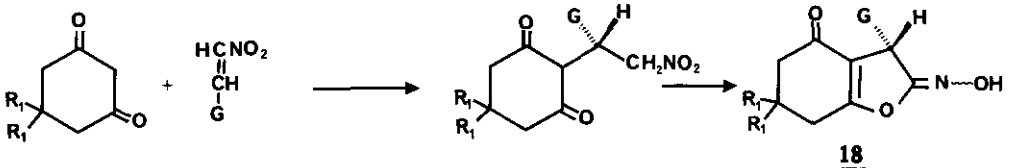
Scheme 3

The corresponding 2-methyl-3-furancarboxylates[48] were also obtained from α-nitroalkenes, acetoacetates, and other compounds with an active methylene group.
Michael adducts obtained from the reaction of cyclohexane-1,3-diones with 2-alkyl- or 2-aryl-1-nitroethylenes under basic conditions are known to undergo cyclization to yield benzofuran-4-(5H)-one derivatives[49-51] (17).



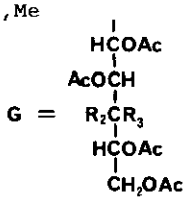
17

Gomez-Sanchez and co-workers, in their extensive investigations on sugar nitroolefins[52-54], have used the above approach to prepare (3,5,6,7-tetrahydro-2-hydroxyimino-3-pentaacetoxyalditol-1-yl)benzofuran-4(2H)-ones (18) and, subsequently, C-(alditol-1-yl) derivatives of other heterocycles.



18

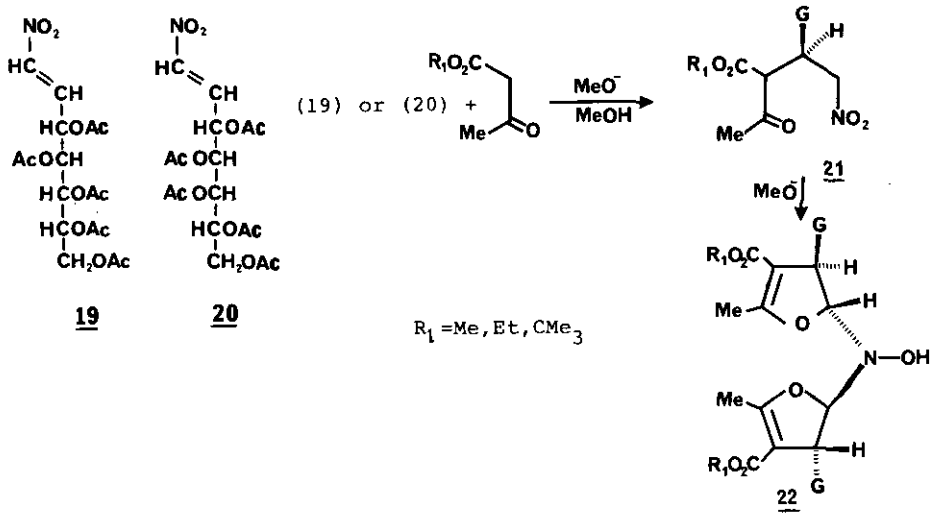
R_1=H,Me



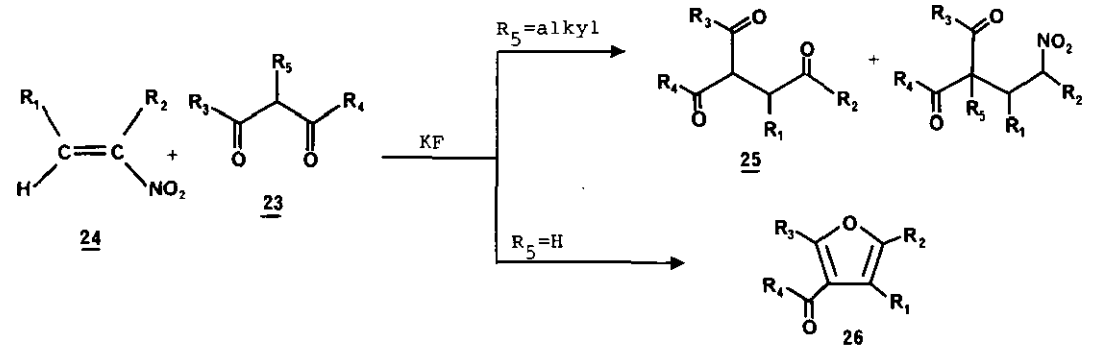
R_2=OAc, R_3=H

R_2=H, R_3=OAc

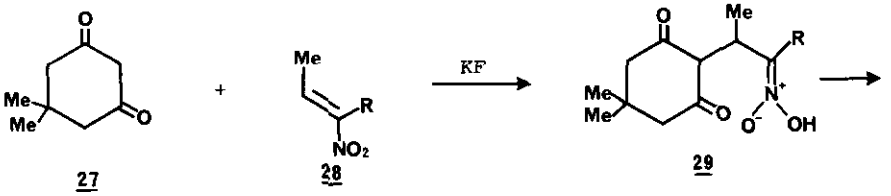
The addition reactions of sugar nitroalkenes with 3-aminocrotonic esters appear to follow a complex pathway[55,56] in which pyrrole derivatives are formed along with the normal, Michael adducts. Similar complexities were observed[57] in the reaction of 1,3-dicarbonyl compounds with a model nitroalkene (β-nitrostyrene); an abnormal product possessing a dimeric, 2,3-dihydro-2-(hydroxyamino)furan structure was obtained which readily transformed into a pyrrole derivative.
The addition reactions of some acetoacetic esters with acyclic 1-nitrohept-1-enitols having D-gluco (19) and D-galacto (20) configuration gave, besides normal Michael adducts (21), some "abnormal" bicyclic compounds such as (22).

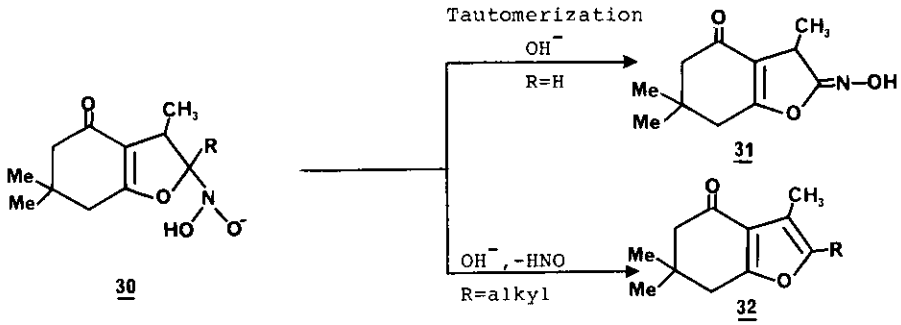


1,3-Dicarbonyl compounds(23) react with nitroalkenes(24) in the presence of potassium fluoride, as a base, to afford either tricarbonyl compounds[58,59] (25) or acylfurans[58,60] (26) depending on the presence (or absence) of 2-alkyl substituents on the substrates. Thus, 2-unsubstituted, 1,3-dicarbonyl compounds (R_5=H) afforded 3-acylfurans[60] (26) directly in an essentially one-pot reaction involving a conjugate addition Nef-reaction-furan ring forming sequence.



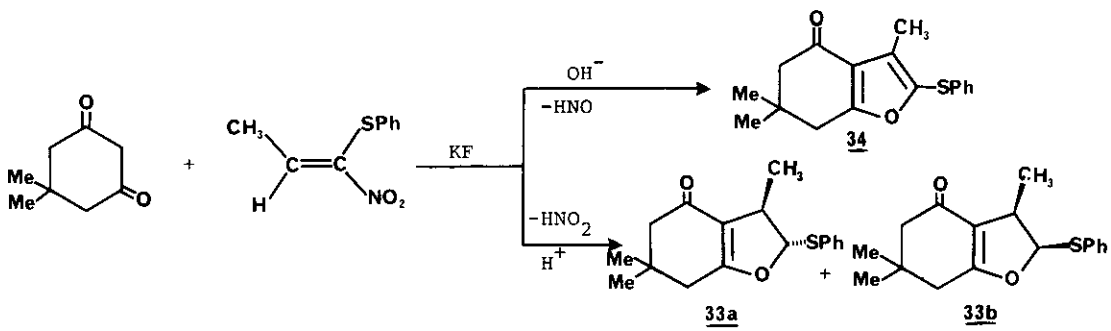
However, the reaction of dimedone (27) with 1-nitropropene (28) (R=H) gave stereoisomeric mixture of (hydroxyimino)dihydrofurans (31) and not the 3-methylfuran[61] (32;R=H).

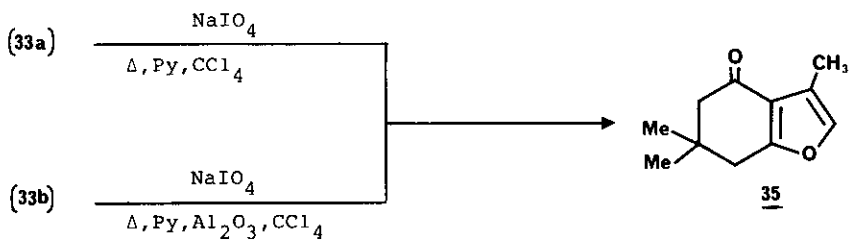




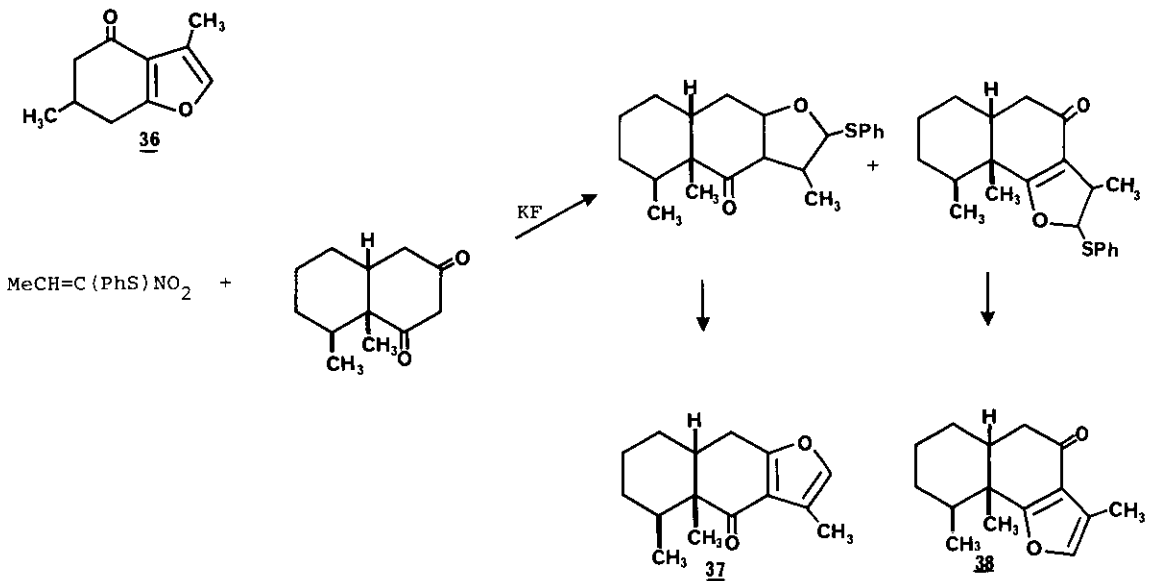
The adduct (29) (conjugate addition) cyclizes to give (30). When R in (30) is hydrogen, elimination of hydroxide anion followed by nitroso-oxime tautomerization, results in the formation of (31). An alkyl substituent in (30) prevent such a tautomerization, resulting in the formation of the acylfuran (32) upon elimination of the hydroxide and nitroxyl moieties.

Yoshikoshi and his group continued their fruitful research by investigating the reaction of a new nitroalkene reagent, 1-nitro-1-(phenylthio)propene[62], with 1,3-diones. The reaction afforded a 1:4 diastereomeric mixture of dihydrofurans (33a and 33b) instead of expected furan derivative[61] (34). This may be due to the anion-stabilizing effect of the sulfur substituent which accelerates the elimination of nitrous acid rather than nitroxyl. The dihydrofurans (33a) and (33b) were converted into 3-methylfuran derivative (35) via conventional procedures[61].

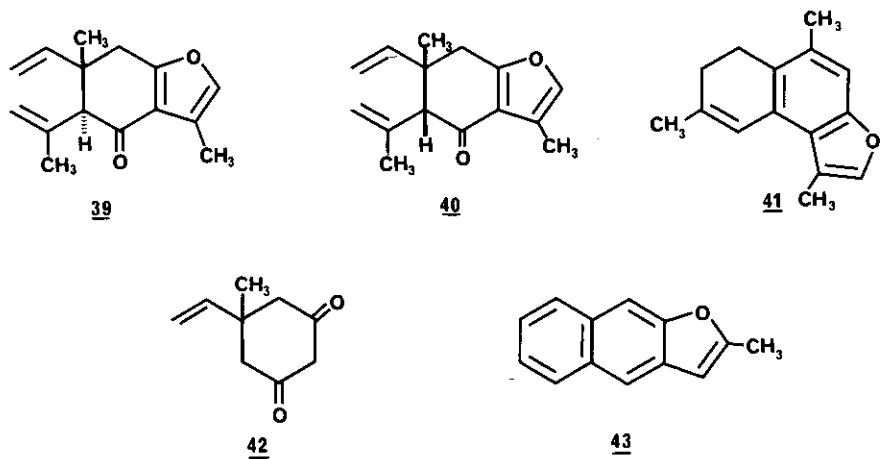




The above sequence, leading to 3-methylfuran derivatives, provided a straightforward strategy for the synthesis of a variety of naturally occurring furanoterpenoids such as evodone (36), ligularone (37) and isoligularone[61] (38).



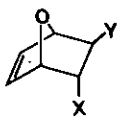
The versatility of this 3-methylfuran annulation reaction was demonstrated recently in the total syntheses of three furanoelemanoids[63] namely curzerenone (39), epicurzerenon (40) and pyrocurzerenone (41) from 1-nitro-1-(phenylthio)propene and the cyclic 1,3-dione (42).



Phenols in general do not react with 2-nitropropene with the exception of β-naphthol which gave naphtha[2,3-b]furan[5] (43).

D. C-Nucleosides and Amino Sugars

The dienophilic character of nitroalkenes has been used in the synthesis of C-nucleoside derivatives, racemic showdomycin and related compounds. The Diels-Alder adduct (44) of methyl β-nitroacrylate with furan was elaborated in several steps to the desired 2'-epi-showdomycin[64] (45)



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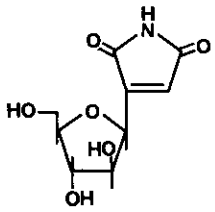
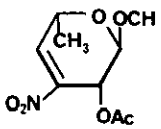
X=NO_2, Y=$COOCH_3$

X=$COOCH_3$, Y=NO_2



45

The sodium borohydride reduction of the 2-O-acetyl-3-enoside (46) to the corresponding nitro sugar played a key role in the synthesis of amino sugars, 4-deoxydaunosamine (47) and 4-deoxyristosamine[65] (48), from readily available methyl-α-L-rhamnopyranoside.



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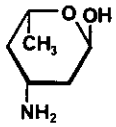

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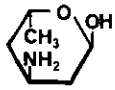

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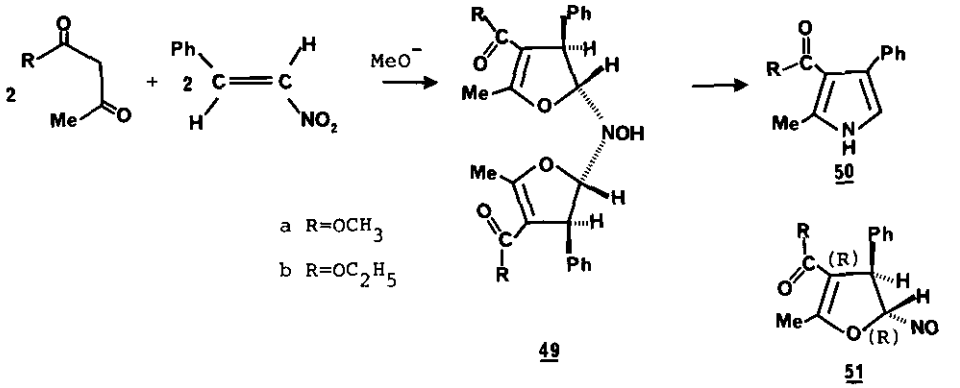
II. NITROGEN HETEROCYCLES

A. Pyrroles

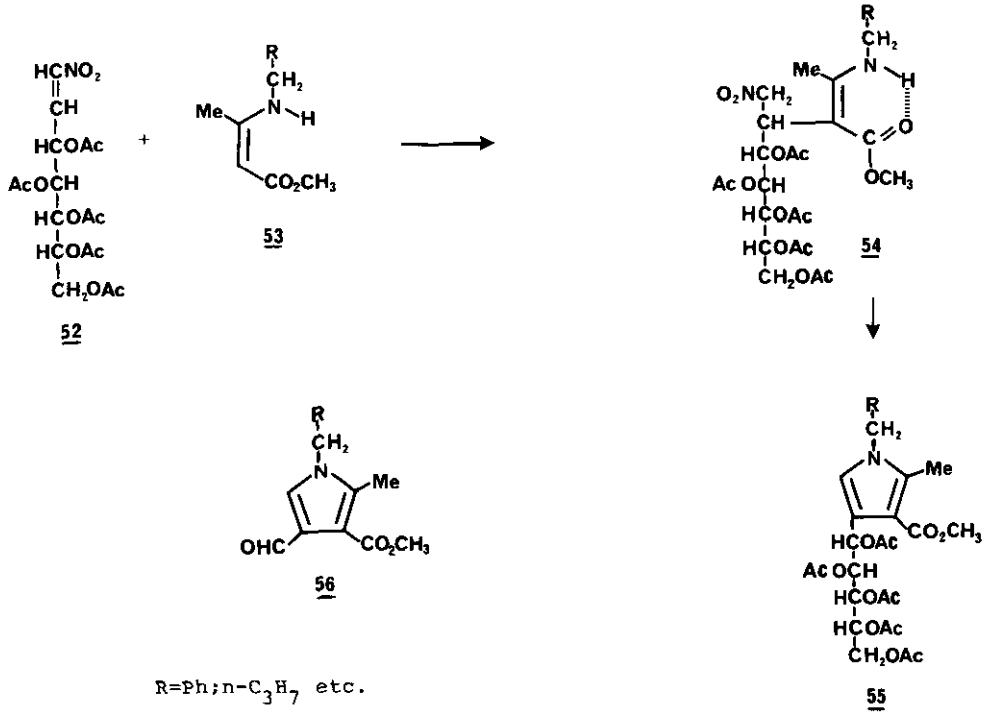
There are several routes to pyrroles originating from nitroalkenes. The Michael reactions of 1,3-dicarbonyl compounds with nitroalkenes in methanol containing sodium methoxide produced unusual cyclic aminoacetal derivatives (49) which afforded 3-acylpyrroles (50) in high yields on reaction with ammonia or amines.[57] The reactions can be carried out in one-pot.

The mechanism of the formation of the unusual Michael products (49) presumably involves the nitrosointermediate (51) which is similar to those proposed to explain the formation of 3-acylfurans[58,60] and 2-hydroxyiminobenzofuranones (17)[50].



49 50 51

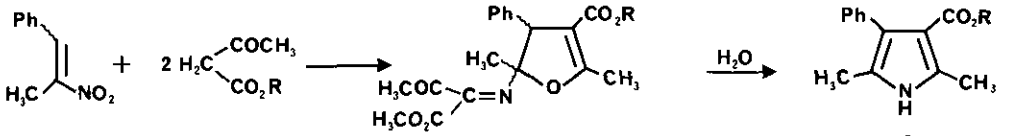
Gomez-Sanchez and co-workers used this chemistry in the syntheses of sugar pyrroles[55] (55) and their corresponding polyols by a Michael-type addition of 3-(alkylamino)crotonic esters (53) to penta-acetoxy-1-nitrohept-1-enes (52). The adducts (54) undergo cyclization to pyrroles, and the process is favored by either increased polarity or temperature. The deacetylated pyrroles (polyols) were oxidized by periodate or lead tetracetate to pyrrole-3-carbaldehyde (56).



52 53 54 55 56

R=Ph;n-C_3H_7 etc.

Boberg reported a similar approach involving the condensation of β-methyl-β-nitrostyrene with methyl acetoacetate followed by an acid hydrolysis of the furan intermediate (57) to the 3-acylpyrrole[66] (58).

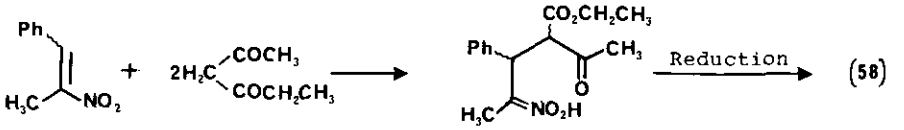


57 58

a R=CH_3

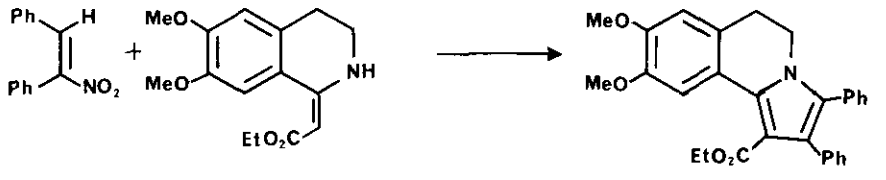
b R=C_2H_5

Alternatively, the aci-nitro adduct (59), obtained from the same styrene with ethyl acetoacetate, was reduced with a variety of reducing agents to pyrrole (58).

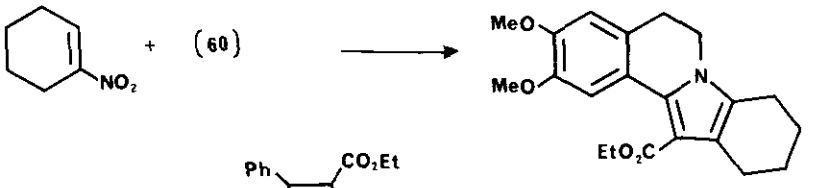


59

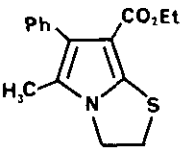
Meyer also used similar methodology in the syntheses of a variety of pyrroles[67] via cyclization of the Michael addition products of enamines with nitroalkenes. The scope of the reaction is exemplified by the preparation of pyrrolo[2,1-a]isoquinoline (61) and pyrrolo[2,1-b]thiazole (62) derivatives in addition to some other pyrrole derivatives such as (63).



60 61



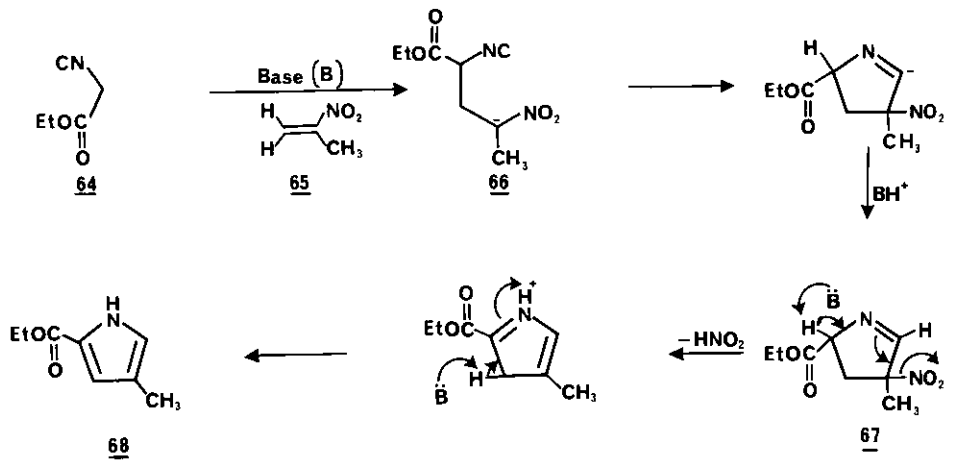
62



63

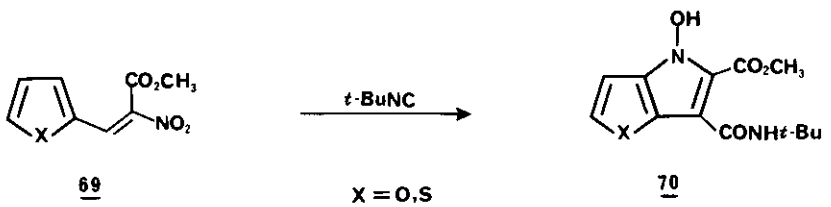
More recently, Barton and Zard[68] disclosed a unique pyrrole synthesis using nitroalkenes, or their β-acetoxynitro precursors, and α-isocyanoacetate esters in the presence of a base. Some important pyrroles unsubstituted in 5 position are easily obtainable by this route which makes it particularly relevant to the porphyrin field.

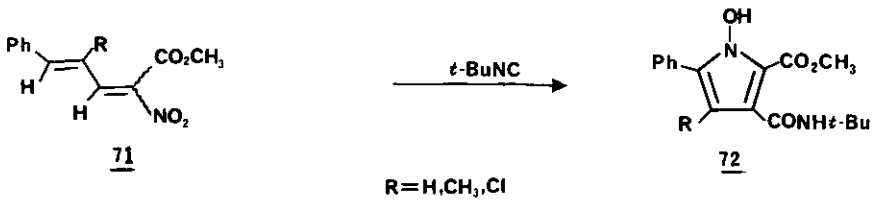
Base catalyzed Michael addition of an α-isocyanoacetate (64) to a nitroalkene (65), followed by cyclization of the nitronate anion (66) onto the isocyano group, led to the pyrroline (67). Base catalyzed removal of nitrite from the pyrroline accompanied by a double bond rearrangement provided the pyrrole (68).



Utilizing this approach, a variety of pyrroles, which constitute basic building blocks for various natural porphyrins and bile pigments, are now easily accessible. The mild reaction conditions make this procedure easily adaptable to the syntheses of labeled substrates useful for biosynthetic studies.

Foucaud[69,70], in an investigation dealing with the [1+4] cycloaddition reactions of isocyanides with thienyl or furyl nitroalkenes (69), discovered the formation of fused 1-hydroxypyrroles (70). Methyl 2-nitro-2,4-pentadienoates (71), in similar cycloaddition reactions, also afforded 1-hydroxypyrroles (72).



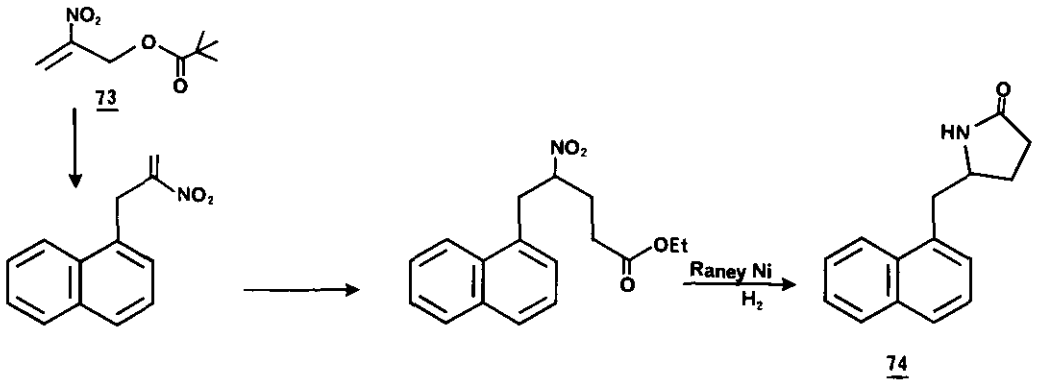


71 72

R=H,CH3,Cl

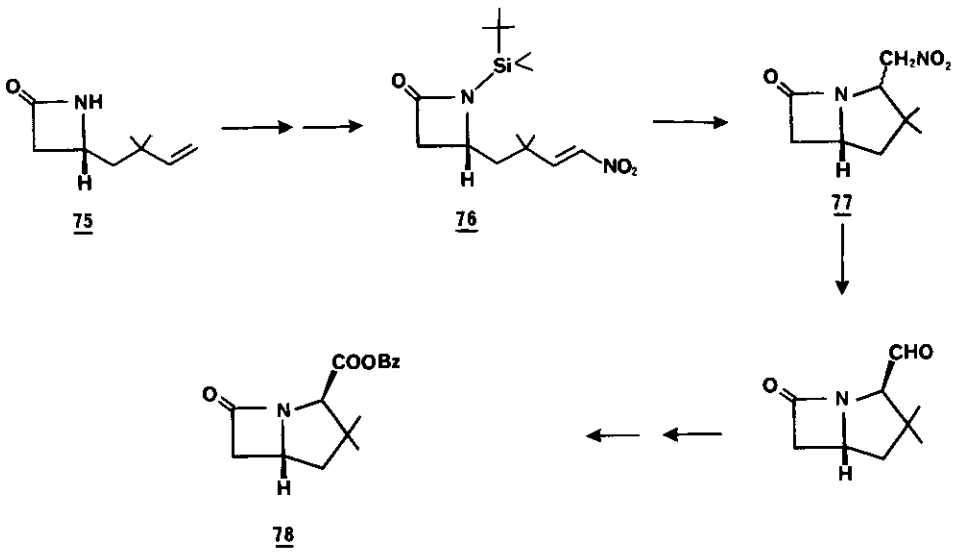
B. Lactams

Seebach prepared 2'-nitro-2'-propen-1'-yl 2,2-dimethylpropanoate (73), a multicomponent coupling reagent for convergent syntheses.[71] It was shown to be a versatile nitroallylating reagent, combining with nucleophiles as diverse as anilines, indoles, enolates and organolithium compounds. The formation of a lactam derivative (74) demonstrates the utility of this reagent which can also undergo in situ reactions with two different substrate nucleophiles.



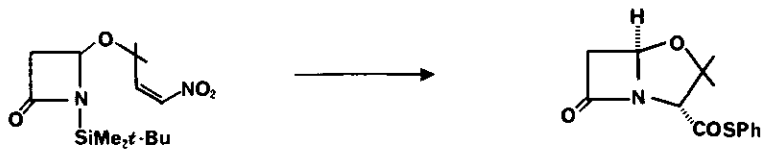
73 74

A synthetic approach towards 2,2-dimethyl-1-carbapenam (78) derivative has been reported by Shibuya and his group.[72] The key intermediate, an α,β-unsaturated nitroalkene (76), was prepared from azetidinone (75). A fluoride assisted desilylation, followed by simultaneous cyclization, provided the epimeric mixture of bicyclic nitro compound (77) which was converted to the corresponding benzyl ester (78) via aldehyde and carboxylic acid intermediates.



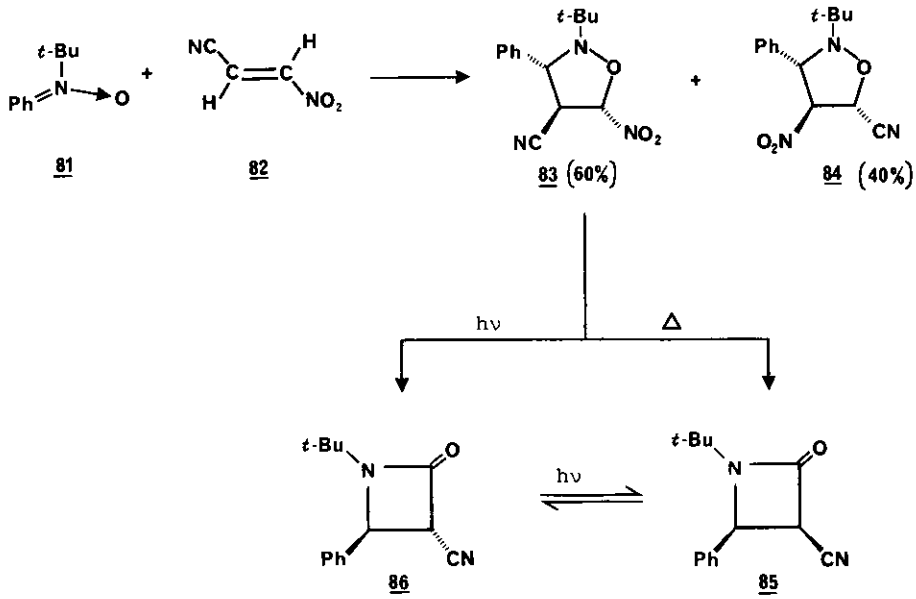
75 76 77 78

Recently, Barrett and co-workers demonstrated the use of Z-1-nitro-1-phenylthio-1-alkene derivative (79) in the preparation of bicyclic β-lactams[73] of type (80), a methodology that can be applied to both the dethiapenam and dethiacepham nuclei. The fluoride mediated desilylation, smooth cyclization of nitrogen centered anion to the nitronate, and the McMurray's oxidative Nef reaction take place in one-pot.

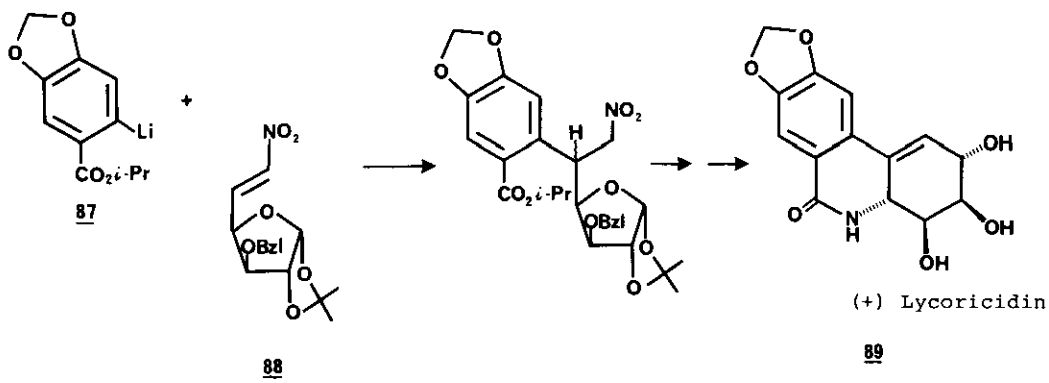


79 80

Padwa[74-76] developed a synthesis of β-lactams which involves a 1,3-dipolar cycloaddition of a nitrone to a nitroalkene followed by a photochemical (or thermal) reorganization of the resulting 5-nitroisoxazolidine. For example phenyl-n-tert-butylnitrone (81) reacted with trans-1-cyano-2-nitroethylene (82) to give a mixture of two regioisomeric isoxazolidines (83) and (84) in quantitative yields. When heated, the major regioisomer (83) was converted into cis-β-lactam (85). However, upon photolysis, only the trans-β-lactam(86) was obtained.



Paulsen and Stubbe have employed the addition of carbanion (87) to the nitroalkene (88) to yield an adduct which provided (+)-lycoricidin[77] (89) from D-glucose via the lactam intermediate.

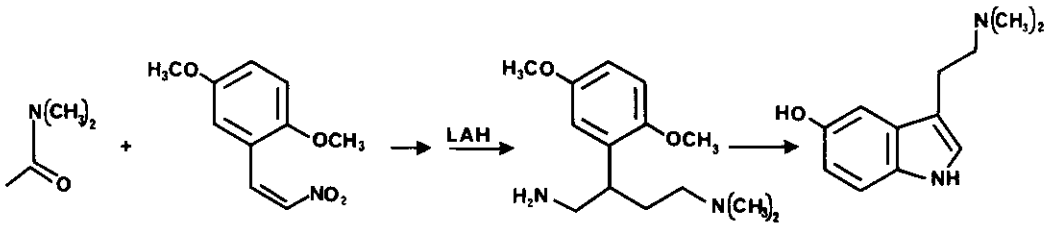


Seebach investigated stereochemical control in the condensation of chiral enolates or enamines with nitroalkenes.[78] The condensation product obtained from nitroethylene and the enolate dianion of ethyl (S)-(+)-3-hydroxybutyrate afforded the nitroester (90) with a diastereoselectivity of 95:5. Stereochemical control at centers, other than those α to the carbonyl, was totally absent. Raney nickel catalyzed hydrogenation of the nitro ester (90) produced lactam (91) in high yields.

90 91

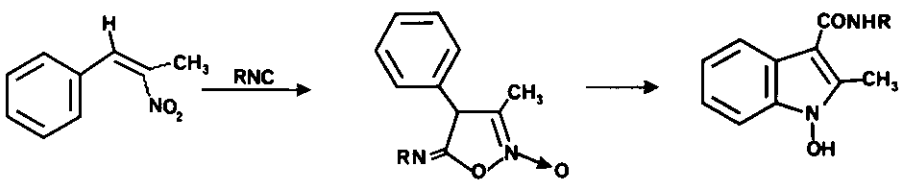
C. Indoles

Seebach[79] prepared derivatives of 1,3- and 1,4-dicarbonyl systems from the Michael adducts of masked acyl anion equivalents (or enolates) to nitroalkenes using Nef-type reactions. The adducts were reduced with lithium aluminum hydride to give amines which are convenient precursors to indoles as demonstrated in the synthesis of bufotenin (92).



92

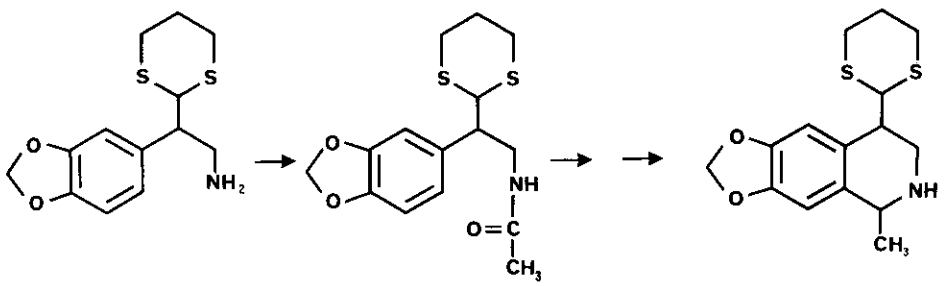
The ring opening reactions of unstable 3-substituted isooxazoline N-oxides[80] (93) obtained from isocyanides and aryl nitroalkenes were utilized by Foucaud and co-workers in the synthesis of 1-hydroxyindoles.[69] Aryl nitroalkenes with a free ortho position on the aryl ring afforded 1-hydroxyindoles derivatives (94) when allowed to react with a small excess of isocyanide in benzene or acetonitrile.



93 94

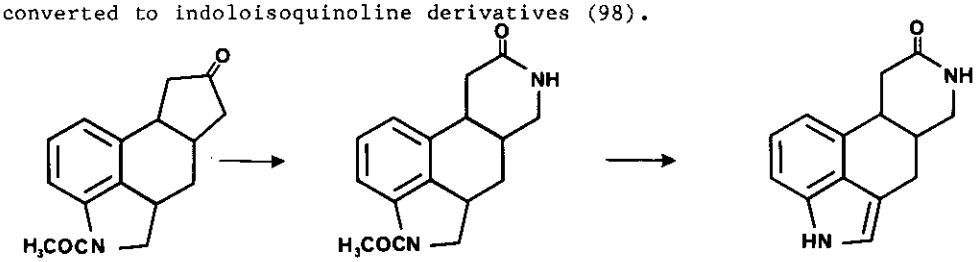
D. **Isoquinolines**

Dithianylisoquinoline derivatives such as (95) were obtained when amine precursors accessible from the corresponding nitroalkenes, were subjected to standard reactions such as Bischler-Napieralski and Pictet-Spengler reaction and oxidative indole ring closures.[79]



95

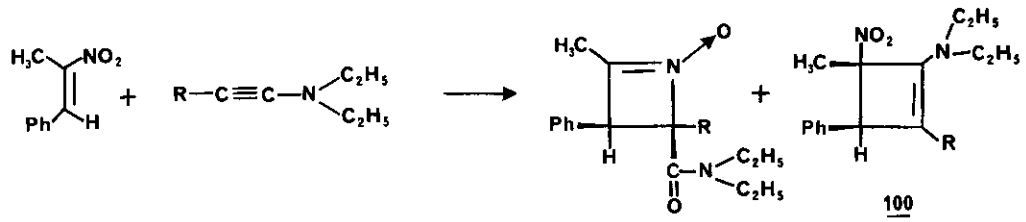
A central nervous system active indoloisoquinoline (98) was prepared recently.[81] 1-Benzoyl-2,2a,3,4-tetrahydrobenz[cd]indol-5-(4H)-one was lithiated, alkylated with $H_2C{=}C(CH_3)NO_2$, and hydrolyzed to afford the 4-acetonyl derivative which upon base catalyzed cyclization and acetylation gave indenoindole derivative (96). The Beckmann rearrangement of its oxime derivative gave indoloisoquinolinone (97). By sequential deacetylation, dehydrogenation, and reduction reactions of (97) was converted to indoloisoquinoline derivatives (98).



96 97 98

E. **Nitrones**

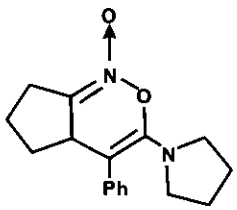
Reinhoudt[82,83] and co-workers obtained 2,3-dihydroazete 1-oxide (99), the stable, four-membered cyclic nitrone, from the facile reaction of nitroalkenes with ynamines; 3-nitrocyclobutenes (100) were the other reaction product.



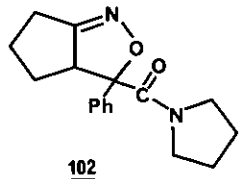
99 100

F. 1,2-Oxazine oxides

A thermally unstable cyclic nitronic ester derivative (101) was similarly obtained when 1-nitrocyclopentene was reacted with 1-phenyl-2-(1-pyrrolidinyl)acetylene. This 4H-1,2-oxazine 2-oxide derivative[84] isomerized in dilute chloroform solution, and in the solid state, to an isoxazole derivative (102).

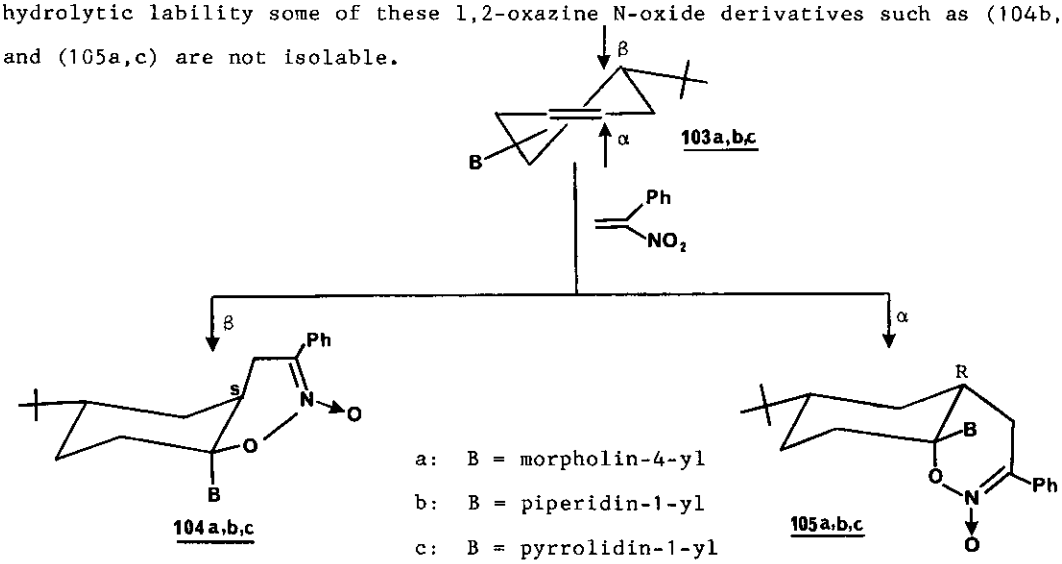


101



102

The reactivity of α-nitrostyrene towards conformationally locked enamines such as (103) was examined by Valentin and his co-workers[85]. In contrast to β-nitrostyrene, which generally gives nitroalkylated enamines, α-nitrostyrene leads to the formation of 1,2-oxazine N-oxide derivatives as the products of kinetic control. The relatively low stereoselectivity in the attack results in the formation of two diastereoisomeric heterocycles (104a-c) and (105a-c). Due to their inherent hydrolytic lability some of these 1,2-oxazine N-oxide derivatives such as (104b,c) and (105a,c) are not isolable.



103a,b,c

104a,b,c

105a,b,c

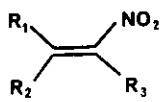
a: B = morpholin-4-yl

b: B = piperidin-1-yl

c: B = pyrrolidin-1-yl

G. Oxazoles, Isoxazoles and Isoxazolines

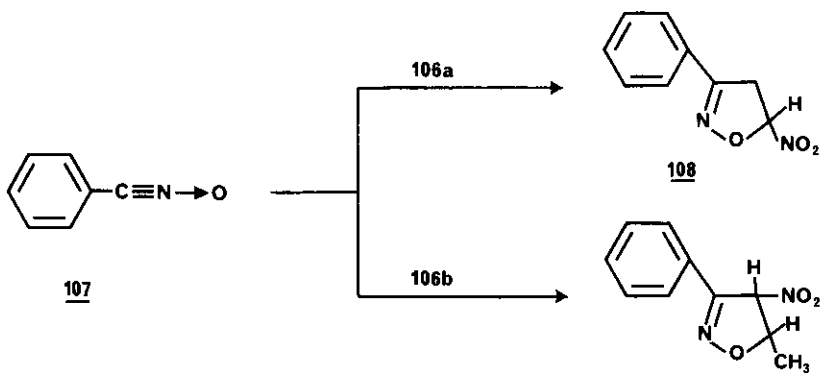
Baranski and co-workers have investigated the 1,3-dipolar cycloaddition of various unconjugated[86] and conjugated nitroalkenes[87-89] with aliphatic and aromatic nitrile oxides. Whereas unconjugated nitroalkenes afforded only 5-nitroalkyl-4,5-dihydro-1,2-oxazoles, conjugated nitroalkenes gave 4- or 5-nitro-4,5-dihydro-1,2-oxazoles (or 1,2-oxazoles not containing a nitro group) depending on the structure of nitroalkenes[87] (106a-e).



106

	R_1	R_2	R_3
a	H	H	H
b	H	CH_3	H
c	CH_3	CH_3	H
d	H	H	CH_3
e	H	CH_3	CH_3

Thus, the reaction of benzonitrile oxide (107) with nitroethylene (106a) gave 5-nitro-3-phenyl-4,5-dihydro-1,2-oxazole (108) whereas the analogous reaction with 1-nitro-1-propene (106b) led to 5-methyl-4-nitro-3-phenyl-4,5-dihydro-1,2-oxazole (109).

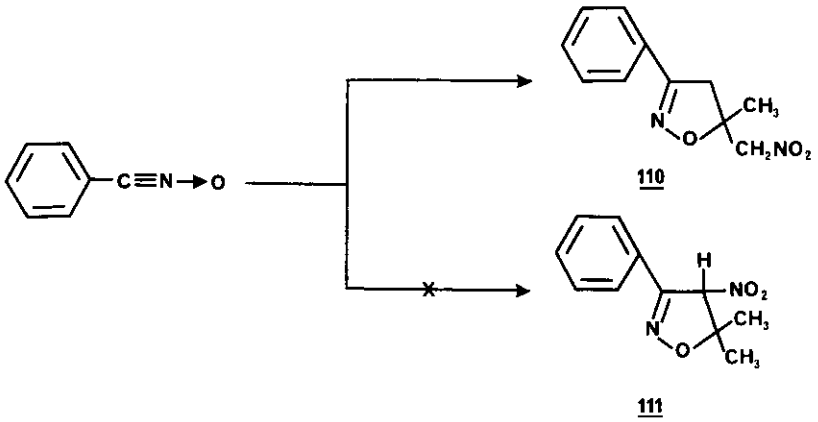


107

108

109

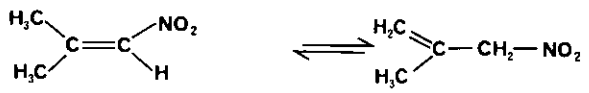
Under the same conditions, 2-methyl-1-nitropropene (106c) gave 5-methyl-5-nitromethyl-3-phenyl-4,5-dihydro-1,2-oxazole (110) instead of the expected product (111), presumably due to isomerization of 2-methyl-1-nitropropene (106c) to



110

111

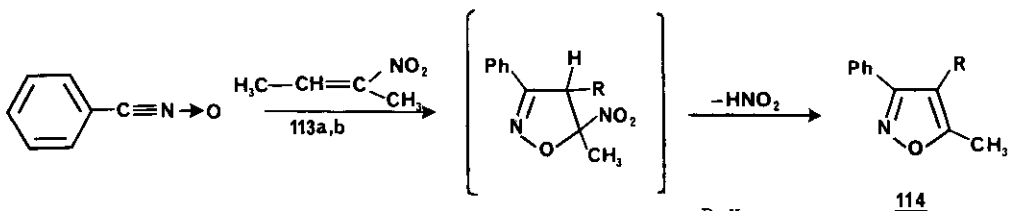
2-methyl-3-nitro-propene (112) by a hydrogen shift.



106c

112

The addition of 2-nitropropene (113a) and 2-nitro-2-butene (113b) to benzonitrile oxide, proceeds beyond the 1,2-oxazoline stage to afford the corresponding 1,2-oxazoles (114a,b) with elimination of nitrous acid. Alternatively, 1,2-oxazole (114a) could be obtained by dehydronitration of 4,5-dihydro-1,2-oxazole (109) in boiling xylene.



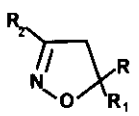
113a,b

114

a R=H

b R=CH_3

Preparation of isoxazoline derivatives (115) was also achieved by thermal condensation of arylhydroxamic acid chlorides ($R_2CCl{=}NOH$) with nitroalkenes ($CH_2{=}CRR_1$) at 135-40°C.[90]

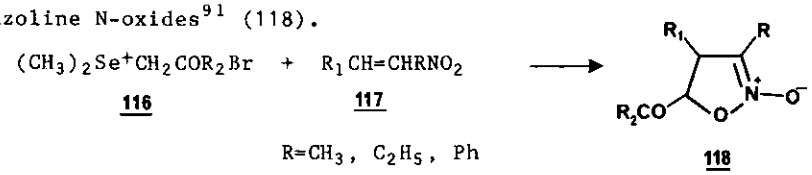


115

R = H,Me; R_1 = CH_2NO_2, p-$O_2NC_6H_4$, 2,4,6-$(O_2N)_3C_6H_2$;

R_2 = Ph, m-$O_2NC_6H_4$, p-$O_2NC_6H_4$, p-$MeOC_6H_4$

Selenium oxo ylides (116) react with nitroalkenes (117) in aqueous chloroform in the presence of sodium hydroxide under inert atmosphere to give substituted isoxazoline N-oxides[91] (118).



$(CH_3)_2Se^+CH_2COR_2Br$ + $R_1CH{=}CHRNO_2$ →

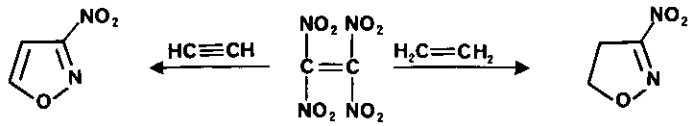
116 117 118

R=CH_3, C_2H_5, Ph

R_1=Ph, 2-thienyl, 3-pyridyl

R_2=Ph, 2-thienyl

A recent preparation of tetranitroethylene, by flash vacuum pyrolysis of hexanitroethane, was utilized by Baum and Tzeng[92] for the synthesis of 3-nitroisoxazoles and 3-nitro-2-isoxazolines from acetylenes and olefins respectively.

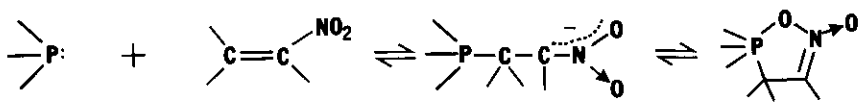


A diradical mechanism has been proposed in which the electron-deficient dinitromethyl radical abstracts an oxygen from an adjacent nitro group, loss of $O{=}C(NO_2)_2$ and ring closure gives the observed product.

IV. PHOSPHORUS HETEROCYCLES

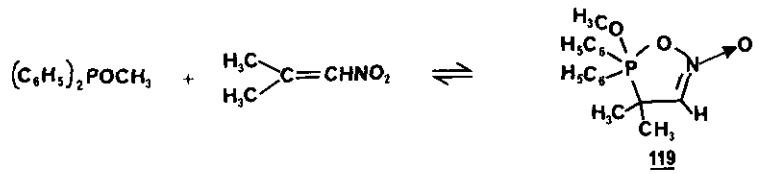
1,2,5,λ^5-Oxazaphospholine 2-Oxides

Russian research groups have made detailed studies of the addition reactions of diverse phosphorus(III) and (V) reagents with nitroalkenes to prepare a variety of phosphacycles[93-95]. In essence, the reactions of esters of trivalent phosphorus (PIII)acids with conjugated nitroalkenes appear to follow the general scheme outlined below.



The overall direction of the process is determined by the position of the equilibrium (PIII $\rightleftarrows$ PV) and the relative reactivities of the components. In a simple case, the reaction of 2-methyl-1-nitropropene with methyl diphenylphosphinite resulted in the formation of crystalline, 5-methoxy-4,4-dimethyl-5,5-di-

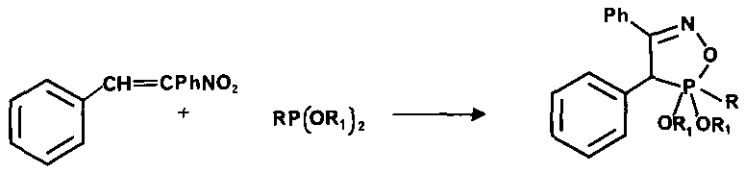
phenyl-Δ^2-1,2,5 λ^5-oxazaphospholine 2-oxide (119) which is unstable to water or heating.



119

The phosphorane structure was unambiguously established by detailed spectral investigations.

In a continuing study of the reactivity of organophosphorus compounds, Cadogan and co-workers[95] have reported formation of 1,2,5-oxazaphosph(V)ole derivatives (120) by reaction of 1,2-diaryl-1-nitroethenes with phosphorus(III) esters.



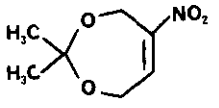
120

R=Ph, OCH_3; $R_1=CH_3$

R=OC_2H_5; $R_1=C_2H_5$

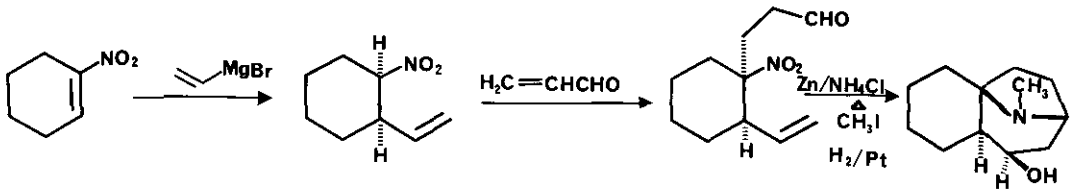
V. MISCELLANEOUS HETEROCYCLIC DERIVATIVES

Corey described two new approaches to conjugated nitrocycloalkenes,[7,97] which are versatile precursors in a variety of reactions. A synthesis involving nitromercuration of an olefin followed by the base-catalyzed elimination of mercury from the resulting nitromercurial was utilized in the preparation of the nitrocycloalkene (121).



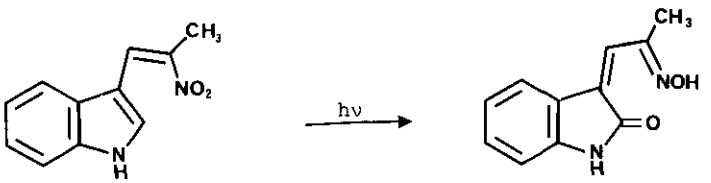
121

1-Nitrocyclohexene was used to prepare a tricyclic system (122) as described in the following scheme.



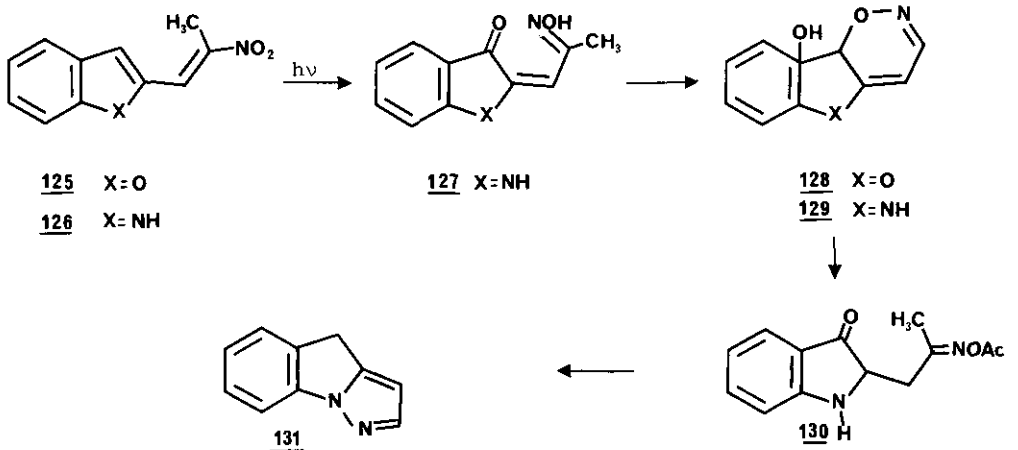
122

Reid and co-workers examined the photorearrangement of heterocyclic nitroalkenes.[97,99] Thus 3-(2-nitroprop-1-enyl)indole (123) was converted to 3-(2-hydroxyiminopropylidene)-2-oxindole [98] (124) presumably due to the dipolar character of the starting indole.



123 124

In an analogus process, a fused 6-hydroxy-1,2-oxazine (128) was obtained by irradiation of 2-(2-nitroprop-1-enyl)benzofuran (125) in acetone solution.[99] The acetylation of oxazine (129) lead to the formation of 2-methyl-4H-pyrazolo[1,5-a]-indol-4-one (131) formed presumably via the oxime acetate (130). Similar reactions were observed with furan derivatives.



125 X=O
126 X=NH

127 X=NH

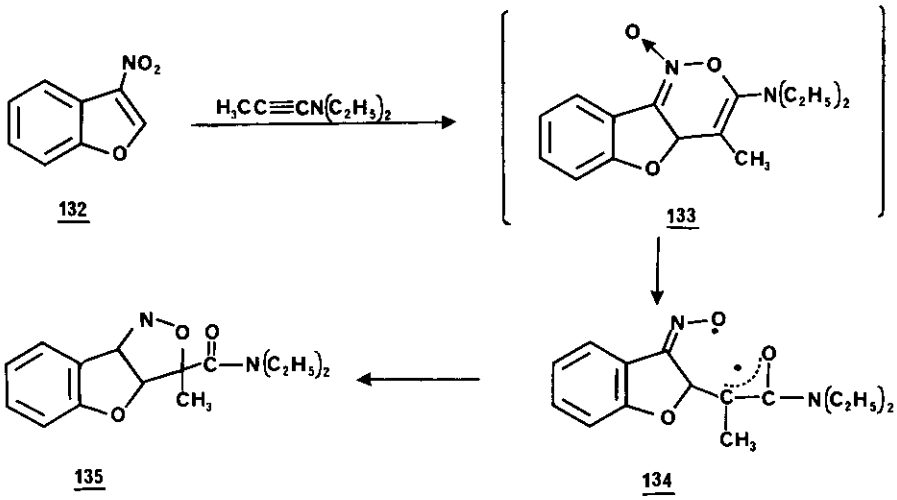
128 X=O
129 X=NH

130

131

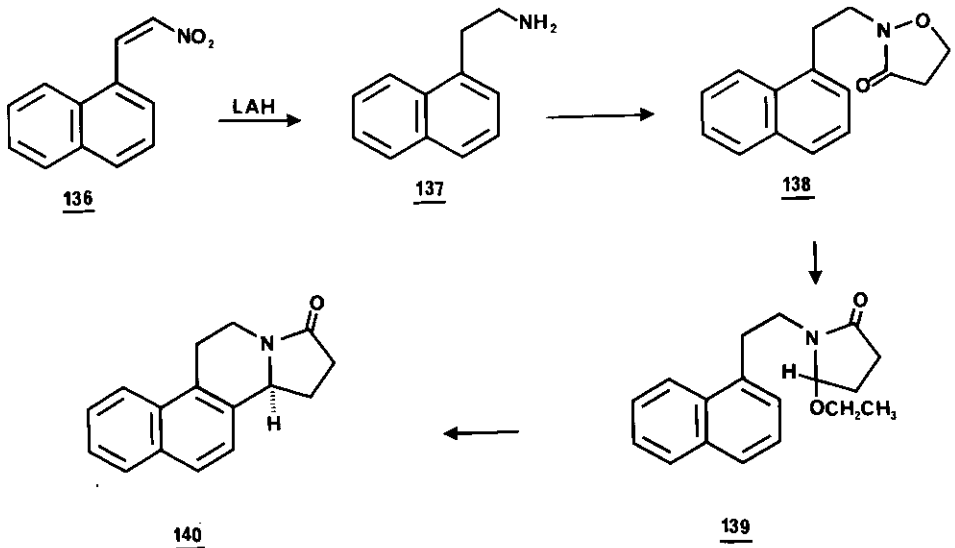
Reinhoudt[100] achieved the reduction of nitro group using an ynamine. Thus, 3-nitrobenzo[b]furan (132) reacted thermally with 1-diethylaminopropyne to afford a

novel 1:1 addition product, benzofuro[3,2-c]isoxazole in which one of the oxygen atoms of the nitro group is transferred to C-1 of the acetylene. The structure of (135) was determined by X-ray crystallography and its formation was explained by a

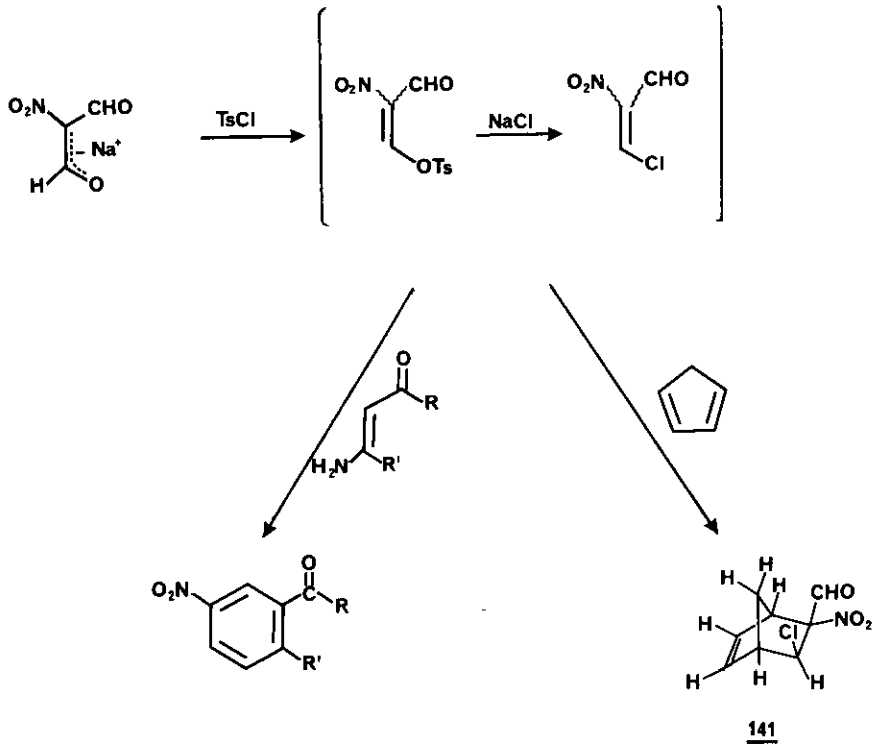


(4+2) cycloaddition followed by rearrangement of the cyclic nitronic ester (133) via the diradical (134).

Trehan[101] synthesized 13-aza-3-desoxy-18-nor-equilenin (140) starting from 2-(1'-naphthyl)-1-nitroethylene (136). The amine (137), obtained by reduction of (136), was converted to a succinimide derivative (138). The sodium borohydride reduction of (138) and subsequent cyclization of (139) with tosyl chloride afforded 18-nor-equilenin derivative (140).



Hoffman and co-workers developed a convenient synthesis of 3-nitro-5-acyl-pyridines[102] starting with sodium nitromalonaldehyde which obviated the need for elaborate functional group manipulations on the pyridine ring. The intermediacy of 3-chloro-2-nitro-acrolein formed from sodium nitromalonaldehyde and tosyl chloride, was confirmed by the characterization of a Diels-Alder adduct (141).



ACKNOWLEDGEMENT

We wish to thank the Department of Energy for the support of our research.

REFERENCES

1. H. H. Bauer and L. Urbas, 'The Chemistry of the Nitro and Nitroso Groups,' part 2, Ed. by H. Feuer, Interscience, New York, N.Y. 1970, p. 75.
2. O. Schickh, G. Apel, H. G. Padeken, H. H. Schwarz and A. Segnitz, 'Methoden der Organischen Chemie (Houben-Weyl),' Ed. by E. Müller, Georg Thieme Verlag, Stuttgart, 1971, vol. 10/1, p. 9.
3. J. Kochani, Wiad. Chem., 1978, 32, 723; Chem. Abstr., 1979, 90, 103287m.
4. D. Seebach, E. W. Colvin, F. Lehr and T. Weller, Chimia, 1979, 33, 1.

5. A. Yoshikoshi and M. Miyashita, Acc. Chem. Res., 1985, 18, 284.
6. N. Ono, H. Miyake and A. Kaji, J. Chem. Soc. Chem. Commun., 1982, 33.
7. E. J. Corey and H. Estreicher, J. Am. Chem. Soc., 1978, 100, 6294.
8. R. S. Varma and G. W. Kabalka, Synth. Commun., 1984, 14, 1093.
9. M. S. Mourad, R. S. Varma and G. W. Kabalka, J. Org. Chem., 1985, 50, 133; R. S. Varma and G. W. Kabalka, Org. Prep. Proced. Int., 1985, 17, 254.
10. M. S. Mourad, R. S. Varma and G. W. Kabalka, Synth. Commun., 1984, 14, 1099; R. S. Varma and G. W. Kabalka, Synth. Commun., 1985, 15, 843.
11. M. S. Mourad, R. S. Varma and G. W. Kabalka, Synthesis, 1985, 654; R. S. Varma, M. Varma and G. W. Kabalka, Tetrahedron Lett., 1985, 26, 3777.
12. R. S. Varma and G. W. Kabalka, Chem. Lett., 1984, 243.
13. R. S. Varma and G. W. Kabalka, Synth. Commun., 1985, 15, 443.
14. S. Rajappa, Tetrahedron, 1981, 37, 1453.
15. T. Urbanski, Synthesis, 1974, 613.
16. M. Miyashita, R. Yamaguchi and A. Yoshikoshi, J. Org. Chem., 1984, 49, 2857.
17. R. M. Cory, P. C. Anderson, M. D. Bailey, F. R. McLaren, R. M. Renneboog and B. R. Yamamoto, Can. J. Chem., 1985, 63, 2618; R. M. Cory, P. C. Anderson, F. R. McLaren and B. R. Yamamoto, J. Chem. Soc. Chem. Commun., 1981, 73.
18. S. E. Denmark, M. S. Dappen and J. A. Sternberg, J. Org. Chem., 1984, 49, 4741.
19. G. B. Bachman and H. A. Levine, J. Am. Chem. Soc., 1948, 70, 599.
20. T. Sakabibara, M. Koezuka and R. Sudoh, Bull. Chem., Soc. Jpn., 1978, 51, 3095.
21. L. Rene and R. Royer, Eur. J. Med.-Chem.-Chim. Ther., 1975, 10, 72.
22. M. Fatome, L. Andrieu, J. D. Laval, R. Royer and L. Rene, Eur. J. Med. Chem.-Chim. Ther., 1976, 11, 81.
23. L. Rene, L. Blanco, R. Royer, R. Cavier and J. Lemoine, Eur. J. Med. Chem.-Chim. Ther., 1977, 12, 385.
24. M. Faulques, L. Rene and R. Royer, Synthesis, 1982, 260.
25. L. Rene and R. Royer, Eur. J. Med. Chem.-Chim. Ther., 1982, 17, 89.
26. R. S. Varma and G. W. Kabalka, Heterocycles, 1985, 23, 139.
27. R. S. Varma, M. Kadkhodayan and G. W. Kabalka, Synthesis (in press).
28. T. S. Rao, A. K. Singh and G. K. Trivedi, Heterocycles, 1984, 22, 1377.
29. R. Bognar and M. Rakosi, Proc. 5th Hungarian Bioflavonoid Symp., Matrafured, Hungry, 1977, pp. 138-142.

30. T. S. Rao, S. Deshpande, H. H. Mathur and G. K. Trivedi, Heterocycles, 1984, 22, 1943.
31. T. S. Rao, H. H. Mathur and G. K. Trivedi, Tetrahedron Lett., 1984, 25, 5561.
32. I. M. Lockhart, 'Chromans and Tocopherols,' Eds. by G. P. Ellis and I. M. Lockhart, John Wiley and Sons, Inc., New York, N.Y. 1981, p 189.
33. P. K. Arora and A. P. Bhaduri, Ind. J. Chem., 1981, 20B, 951.
34. E. E. Schweizer, C. J. Berninger, D. M. Crouse, R. A. Davis and R. S. Logothetis, J. Org. Chem., 1969, 34, 207.
35. E. E. Schweizer and D. M. Nycz, 'Chromenes, Chromanones and Chromenes,' Ed. by G. P. Ellis, John Wiley and Sons, Inc., New York, N.Y. 1977, p 70.
36. H. Booth, D. Huckle, I. M. Lockhart, J. Chem. Soc., Perkin Trans. II, 1973, 227.
37. I. M. Lockhart, British Patent, 1,168,228 (1969); Chem. Abstr., 1970, 72, 31618y.
38. R. S. Varma, M. Kadkhodayan and G. W. Kabalka, Heterocycles (in press).
39. R. S. Varma and G. W. Kabalka, Synth. Commun., 1985, 15, 151.
40. R. S. Varma, M. Varma, Y.-Z. Gai and G. W. Kabalka, Unpublished work.
41. F. Baranton, G. Fontaine and P. Maitte, Bull. Soc. Chim. Fr., 1968, 4203.
42. CIBA Ltd., French Patent 1465839 (1968); Chem. Abstr., 1968, 68, 68884a.
43. M. V. Vasil'eva, V. M. Berestovitskaya and V. V. Perekalin, J. Org. Chem. USSR, 1985, 21, 1439.
44. J. W. Patterson and J. E. McMurry, J. Chem. Soc. Chem. Commun., 1971, 488.
45. T. Takamoto, Y. Ikeda, Y. Tachimori, A. Seta and R. Sudoh, J. Chem. Soc. Chem. Commun., 1978, 350.
46. T. Sakakibara, Y. Ikeda, T. Miura and R. Sudoh, Chem. Lett., 1982, 99.
47. F. Boberg, M. Ruhr and A. Garming, Liebigs Ann. Chem., 1984, 223.
48. F. Boberg, K.-H. Garburg, K.-J. Görlich, E. Pipereit and M. Ruhr, Liebigs Ann. Chem., 1984, 911.
49. A. T. Nielsen and T. G. Archibald, Tetrahedron, 1969, 25, 2993.
50. G. B. Ansell, D. W. Moore and A. T. Nielsen, J. Chem. Soc. B, 1971, 2376.
51. S. J. Dominiami, M. O. Chaney and N. D. Jones, Tetrahedron Lett., 1970, 4735.
52. A. Gomez-Sanchez, M. Mancera and F. Rosado, Carbohydr. Res., 1984, 134, 63.
53. A. Gomez-Sanchez, M. Mancera and F. Rosado, Carbohydr. Res., 1984, 134, 75.

54. A. Gomez-Sanchez, J. Galan, M. Rico and J. Bellanato, J. Chem. Soc. Perkin Trans. I, 1985, 2695.

55. A. Gomez-Sanchez, M. Mancera, F. Rosado and J. Bellanato, J. Chem. Soc. Perkin Trans. I, 1980, 1199.

56. A. Gomez-Sanchez, M. Mancera, F. J. Caballero and J. Bellanato, An. Quim., 1983, 79, 175.

57. A. Gomez-Sanchez, B. M. Stiefel, R. Fernandez-Fernandez, C. Pascual and J. Bellanato, J. Chem. Soc. Perkin Trans. I, 1982, 441.

58. T. Yanami, M. Kato and A. Yoshikoshi, J. Chem. Soc. Chem. Commun., 1975, 726.

59 T. Yanami, A. Ballatore, M. Miyashita, M. Kato and A. Yoshikoshi, Synthesis, 1980, 407.

60. T. Yanami, A. Ballatore, M. Miyashita, M. Kato and A. Yoshikoshi, J. Chem. Soc., Perkin Trans. I, 1978, 1144.

61. M. Miyashita, T. Kumazawa and A. Yoshikoshi, J. Org. Chem., 1980, 45, 2945.

62. M. Miyashita, T. Kumazawa and A. Yoshikoshi, J. Chem. Soc. Chem. Commun., 1978, 362.

63. M. Miyashita, T. Kumazawa and A. Yoshikoshi, J. Org. Chem., 1984, 49, 3728.

64. G. Just, T. J. Liak, M.-I. Lim, P. Potvin and Y. S. Tsantrizos, Can. J. Chem., 1980, 58, 2024.

65. H. H. Baer and H. R. Hanna, Can. J. Chem., 1980, 58, 1751.

66. F. Boberg, K.-H. Garburg, K.-J. Görlich, E. Pipereit and M. Ruhr, Liebigs Ann. Chem., 1985, 239; idem, ibid., 1984, 911.

67. H. Meyer, Liebigs Ann. Chem., 1981, 1534.

68. D. H. R. Barton and S. Z. Zard, J. Chem. Soc. Chem. Commun., 1985, 1098.

69. A. Foucaud, C. Razorilalana-Rabearivony, E. Loukakou and H. Person, J. Org. Chem., 1983, 48, 3639.

70. A. Foucaud, Bull. Soc. Chim. Belg., 1981, 90, 545.

71. D. Seebach and P. Knochel, Helv. Chim. Acta , 1984, 67, 261.

72. M. Shibuya, M. Kuretani and S. Kubota, Tetrahedron Lett., 1981, 22, 4453.

73. A. G. M. Barrett, G. G. Graboski and M. A. Russell, J. Org. Chem., 1985, 50, 2603.

74. A. Padwa, K. F. Koehler and A. Rodriguez, J. Am. Chem. Soc., 181, 103, 4974.

75. A. Padwa, L. Fisera, K. F. Koehler, A. Rodriguez and G. S. K. Wong, J. Org. Chem., 1984, 49, 276.

76. A. Padwa, K. F. Koehler, and A. Rodriguez, J. Org. Chem., 1984, 49, 282.
77. H. Paulsen and M. Stubbe, Tetrahedron Lett., 1982, 23, 3171.
78. M. Züger, T. Weller and D. Seebach, Helv. Chim. Acta , 1980, 63, 2005.
79. D. Seebach, V. Ehrig, H. F. Leitz and R. Henning, Chem. Ber., 1975, 108, 1946.
80. T. Saegusa, S. Kobayashi, Y. Ito, I. Morino, Tetrahedron, 1972, 28, 3389.
81. Lilly Industries Ltd., U. K., Austrian Patent, AT 374,201 (1984); Chem. Abstr., 1984, 101, 38443p.
82. A. D. de Wit, M. L. M. Pennings, W. P. Trompenaars, D. N. Reinhoudt, S. Harkema and O. Nevestveit, J. Chem. Soc. Chem. Commun., 1979, 993.
83. M. L. M. Pennings and D. N. Reinhoudt, J. Org. Chem., 1982, 47, 1816.
84. M. L. M. Pennings and D. N. Reinhoudt, Tetrahedron Lett., 1980, 21, 1781.
85. P. Bradamante, G. Pitacco, A. Risaliti and E. Valentin, Tetrahedron Lett., 1982, 23, 2683.
86. A. Baranski, G. A. Shvekhgeimer and N. I. Kirilova, Pol. J. Chem., 1980, 54, 23.
87. G. A. Shvekhgeimer, A. Baranski and M. Grzegozek, Synthesis, 1976, 612.
88. A. Baranski, Pol. J. Chem., 1982, 56, 257, 1585.
89. A. Baranski and G. A. Shvekhgeimer, Pol. J. Chem., 1982, 56, 459.
90. G. A. Shvekhgeimer and A. Baranski, Tezisy Vses. Soveshch. Khim. Nitrosoedinenii, 5th; Chem. Abstr., 1977, 87, 53126y.
91. N. N. Magdesieva, T. A. Sergeeva and R. A. Kyandzhetsian, Zh. Org. Khim., 1985, 21, 1980; Chem. Abstr., 1985, 103, 215232h.
92. K. Baum and D. Tzeng, J. Org. Chem., 1985, 50, 2736.
93. R. D. Gareev, A. V. Il'yasov, Ya. A. Levin, E. I. Gol'dfarb, V. I. Morozov, I. M. Shermergorn and A. N. Pudovik, J. General Chem. USSR, 1982, 1123.
94. R. D. Gareev, G. M. Loginova, E. E. Barisova, A. V. Il'yasov, A. N. Pudovik, and I. M. Shermergorn, J. General Chem. USSR, 1982, 2265.
95. R. D. Gareev, A. N. Pudovik and I. M. Shermergorn, J. General Chem. USSR, 1983, 27.
96. J. I. G. Cadogan, R. A. North and A. G. Rowley, J. Chem. Res. (S), 1978, 1.
97. E. J. Corey and H. Estreicher, Tetrahedron Lett., 1980, 21, 1113.
98. J. S. Cridland and S. T. Reid, J. Chem. Soc. Chem. Commun., 1969, 125.
99. R. Hunt, S. T. Reid and K. T. Taylor, Tetrahedron Lett., 1972, 2861.

100. A. D. de Wit, W. P. Trompenaars, D. N. Reinhoudt, S. Harkema and G. J. van Hummel, Tetrahedron Lett., 1980, 21, 1779.

101. I. R. Trehan, K. Bala and J. B. Singh, Ind. J. Chem., 1979, 18B, 295.

102. J. M. Hoffman, B. T. Phillips and D. W. Cochran, J. Org. Chem., 1984, 49, 193.

Received, 3rd April, 1986