

Nitroalkanes as key building blocks for the synthesis of heterocyclic derivatives

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Abstract

Nitroalkanes constitute a valuable source of stabilized carbanions for carbon–carbon bond formation through reaction with suitable electrophiles. Reduction of the nitro group or its conversion to a carbonyl group readily provides the necessary amino and oxygenated functions suitable for the preparation of various heterocyclic derivatives.

Keywords: Conjugate addition, heterocycles, Nef reaction, nitro-aldol reaction, nitro-alkanes

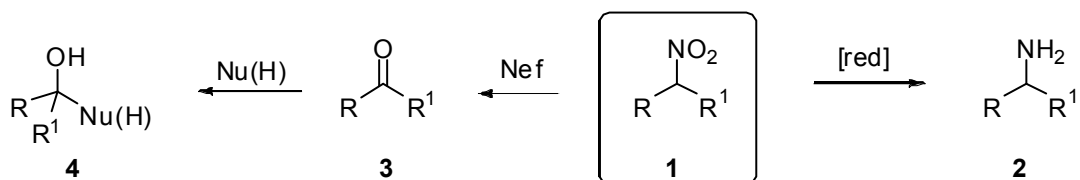
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1. Introduction

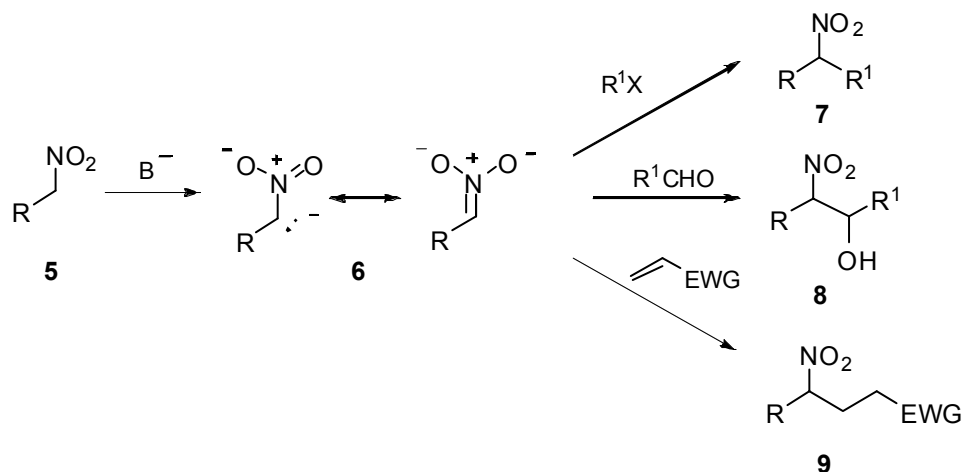
Cyclic frameworks incorporating one or more heteroatoms in their structures are included in a considerable number of compounds which are of practical interest. The nature of the functional

groups present in the reactants used for their preparation depends strongly on the attributes of the heterocyclic system. The preparation of oxygen-containing rings usually requires the presence of hydroxy groups in some key step of their synthesis. Similarly, the introduction of nitrogen atoms in cyclic structures can be realized by starting from amino compounds that can, in turn, be obtained by reduction of various nitrogenated derivatives. In this context, nitroalkanes, **1**, are versatile intermediates since their reduction provides a straightforward entry to amino derivatives, **2** (Scheme 1).^{1,2} Furthermore, the nitro- to carbonyl conversion, also known as the Nef reaction, allows the introduction of an important functional group that, by means of nucleophilic addition or reduction processes, readily affords the hydroxy functionality.³



Scheme 1

From a synthetic standpoint, the transformations cited above usually occur at a stage of the overall process when the assembling of the molecular structure is rather advanced. Therefore, nitro compounds would not be particularly useful if they were not able to assist the carbon-carbon bond formation. Fortunately, nitroalkanes also represent a formidable source of stabilized carbanions since the high electron-withdrawing power of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α -position.⁴ Base-treatment of the nitroalkanes **5** produces the corresponding nitronate anions **6** which can be used as carbon nucleophiles in reactions with haloalkanes,⁵ aldehydes,^{6,7} and Michael acceptors, leading to adducts **7-9** (Scheme 2).⁸



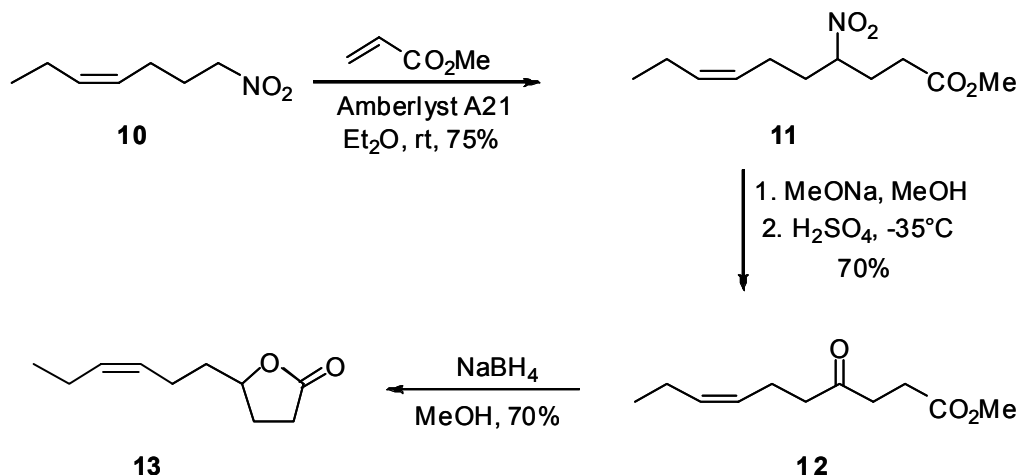
Scheme 2

Dehydration of the β -nitro-alcohols **8** obtained from nitro-aldol reactions affords nitroalkenes that act as efficient Michael acceptors and dienophiles in many reactions directed towards the formation of new carbon-carbon and carbon-heteroatom bonds.⁹⁻¹¹ The aim of this review is to present a selected number of synthetic procedures dealing with the utilization of nitroalkanes as pivotal intermediates for the synthesis of heterocyclic derivatives. The discussion only includes those methods in which the nitro group is directly involved in the formation of the heterocycle.

2. Lactones

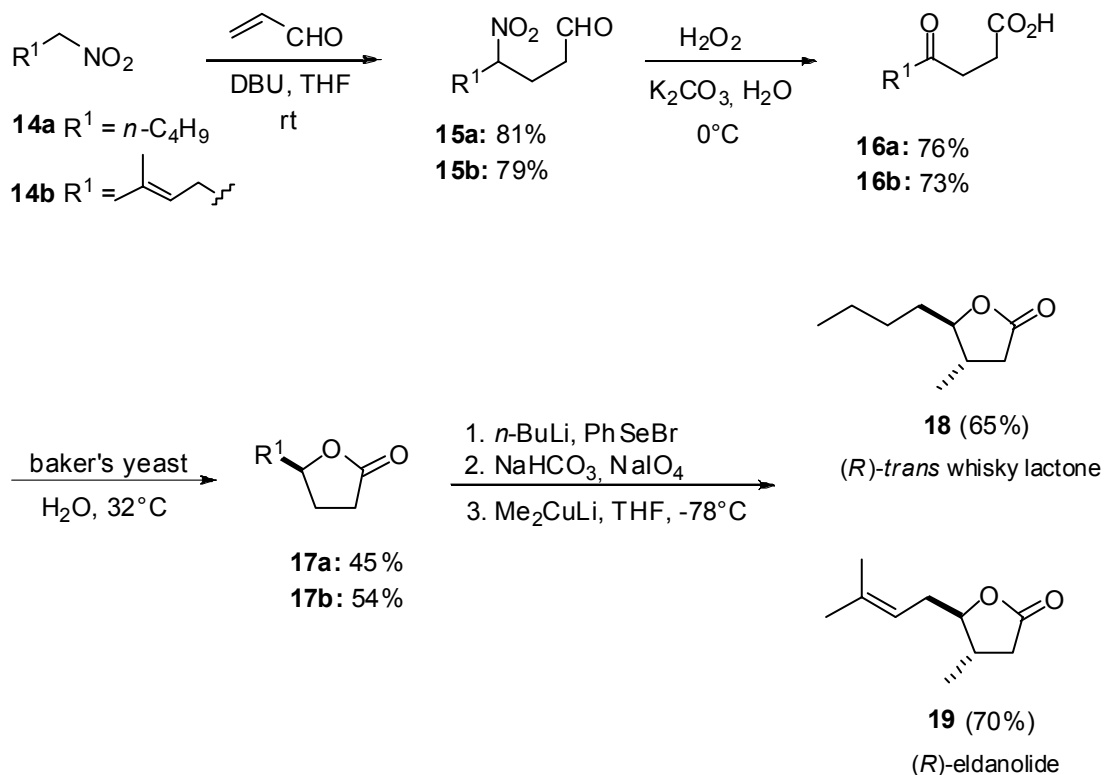
1.1 γ -Lactones

A simple procedure for the preparation of γ -jasmolactone **13**, a constituent of the essential oil of jasmine flowers, entails the utilization of the nitroheptene **10** that can be added to methyl acrylate in the presence of Amberlyst A21 as the basic promoter (Scheme 3).¹² The nitro-ester **11** is then converted into the γ -keto ester **12** which upon chemoselective reduction with NaBH₄ directly affords γ -jasmolactone **13** in satisfactory overall yield.



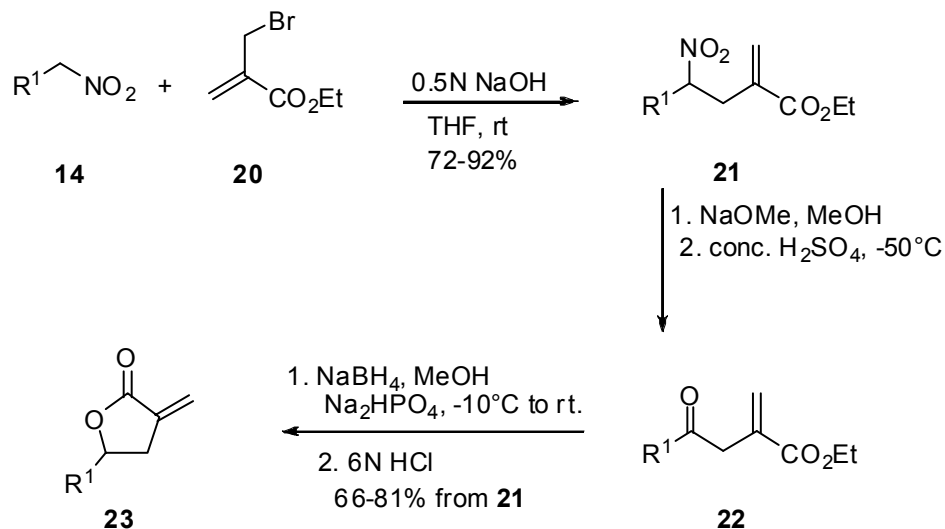
Scheme 3

The carbonyl group in the obtained γ -keto esters can also be reduced enantioselectively, thus forming optically active γ -hydroxy-esters leading to chiral lactones. This approach is outlined for the stereoselective synthesis of (*R*)-*trans* whisky lactone **18**, the key flavor of some alcoholic beverages, and (*R*)-eldanolide **19**, the pheromone of the male African sugarcane stem borer (Scheme 4).¹³ Conjugate addition of nitroalkanes **14** to acrolein provides the corresponding derivatives **15** which by oxidation with hydrogen peroxide are converted into the keto acids **16**. Enantioselective reduction of the carbonyl group using baker's yeast directly affords the lactones **17**. Installation of a double bond into the lactones **17**, and conjugate addition of dimethyl lithium cuprate to the resulting butenolide completes the synthesis of compounds **18** and **19**.



Scheme 4

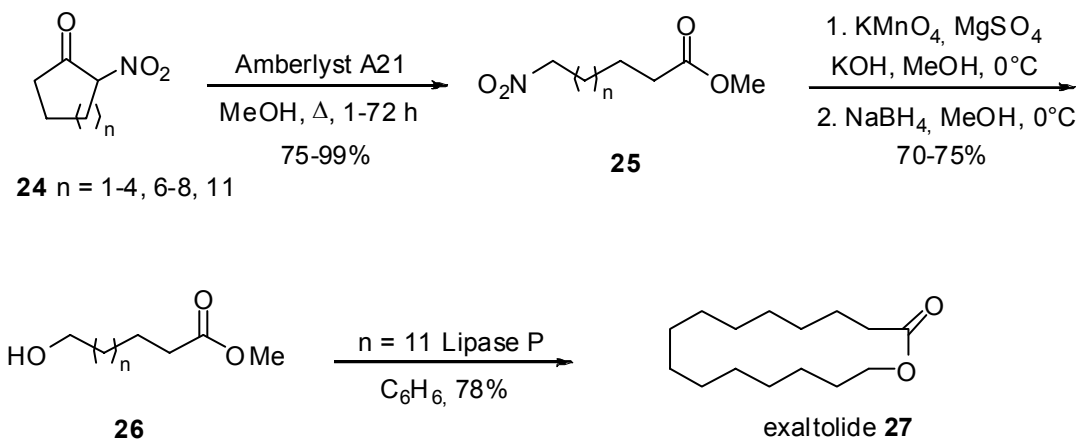
γ -Lactones bearing an exocyclic methylene group are of considerable interest because of their enhanced biological activity. Installation of this *exo*-unsaturation is not a trivial task, since regio-isomerization under a variety of conditions often leads to the more stable endocyclic derivative. Michael addition of primary nitroalkanes **14** with ethyl 2-bromoethyl acrylate **20** leads as usual to an intermediate enolate anion that upon elimination of the bromide anion gives the acrylates **21** (Scheme 5).¹⁴ The compounds **21** are then converted into keto esters, **22**, by a classical Nef reaction and, after a chemoselective reduction of the carbonyl group under controlled conditions, are finally transformed into the lactones **23**.



Scheme 5

2.2 Macrolactones and dilactones

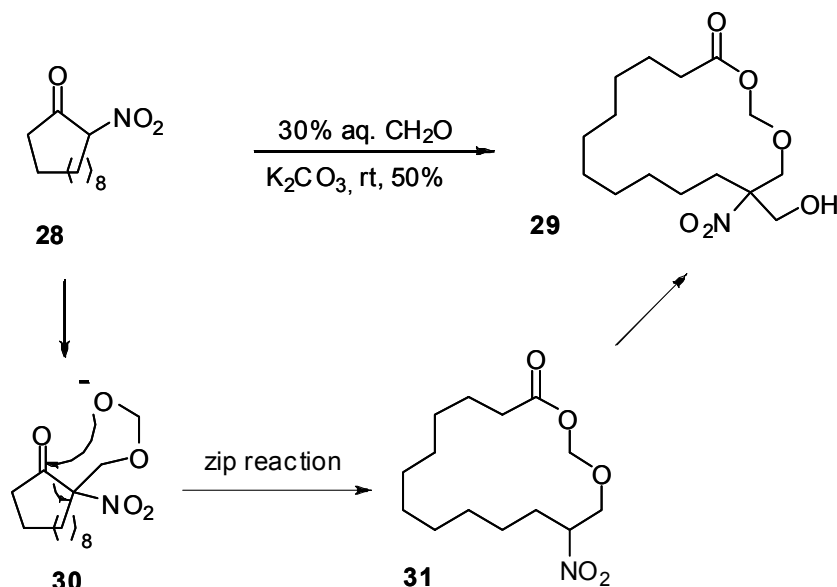
Ring cleavage of cyclic 2-nitro-ketones by external nucleophiles provides rapid entry to ω-nitro-esters.¹⁵ 2-Nitrocycloalkanones **24** of different sizes are opened by methanol at reflux in the presence of Amberlyst A21, to give nitro-esters **25** (Scheme 6).¹⁶ The nitro group is converted into a hydroxy group by a sequential oxidative Nef reaction and reduction leading to hydroxy esters **26**. These compounds can be cyclized to the corresponding macrolactones under different reaction conditions as demonstrated for the C-15 hydroxy ester **26** (*n* = 11) which by Lipase P catalysis is converted into exaltolide **27**, an important perfume isolated from angelica root oil.



Scheme 6

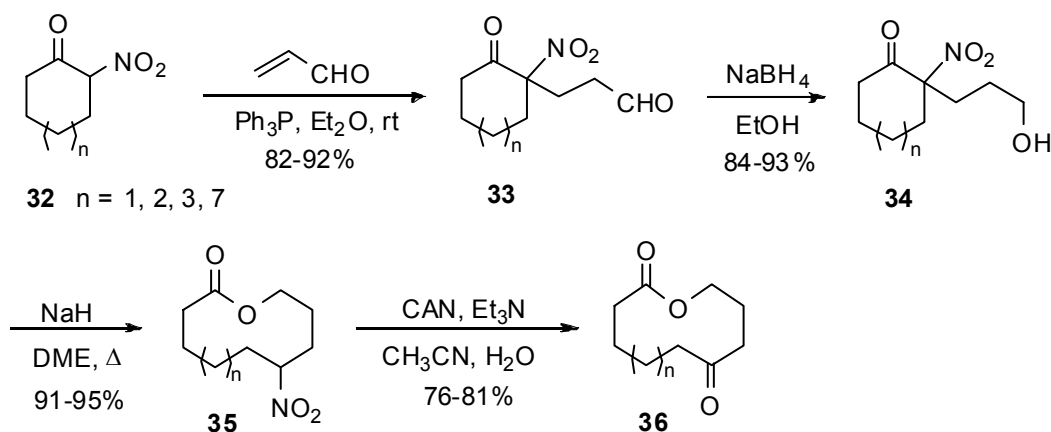
An interesting outcome is observed in the ring cleavage of 2-nitro-cyclododecanone, **28**, by potassium carbonate in a 30% solution of formaldehyde (Scheme 7).¹⁷ The obtained

macrolactone, **29**, is the result of a, “zip reaction”,¹⁸ on the intermediate **30** generated by reaction of the cycloalkanone **28** with two molecules of formaldehyde, followed by further addition of formaldehyde onto compound **31**.



Scheme 7

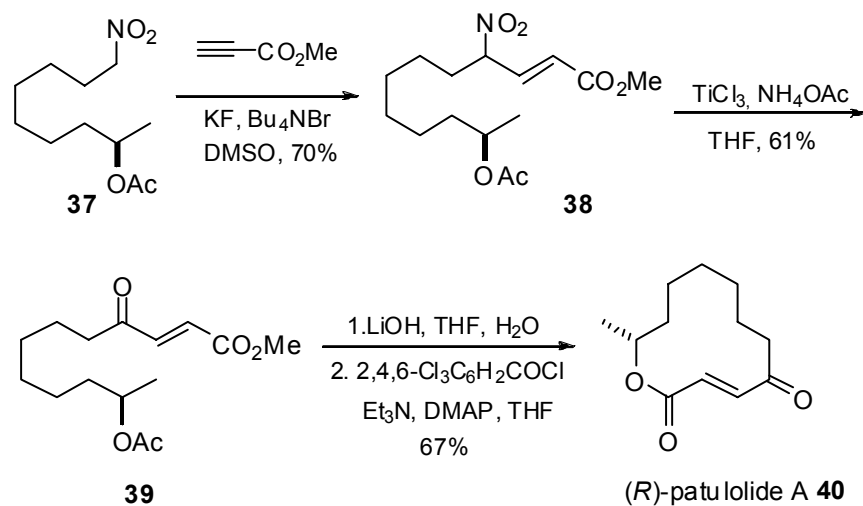
Conjugate addition of the 2-nitro-cycloalkanones **32** to acrolein gives the corresponding aldehydes **33** which upon reduction with NaBH_4 afford the alcohols **34** (Scheme 8).¹⁹



Scheme 8

An intramolecular retro-Claisen cleavage promoted by NaH allows the preparation of macrolactones **35** that are converted into keto-esters **36** by oxidative Nef reaction using cerium ammonium nitrate (CAN). The optically active nitro- acetate **37** can be readily prepared by

enzymatic acylation from the corresponding racemic nitro- alcohol and reacts efficiently with methyl propiolate giving the corresponding adduct (*E*)- **38** (Scheme 9).²⁰ The nitro group is then converted into the keto-ester **39** using the McMurry method,²¹ and after ester hydrolysis the resulting hydroxy acid is lactonized to the macrolide (*R*)- patulolide A, **40**.



Scheme 9

A related strategy is also effective for the total synthesis of optically active (*R,R*)- (-)-pyrenophorin, **42**, an antifungal macrolide dilactone, starting from the nitro- ester **41** (Scheme 10).²²

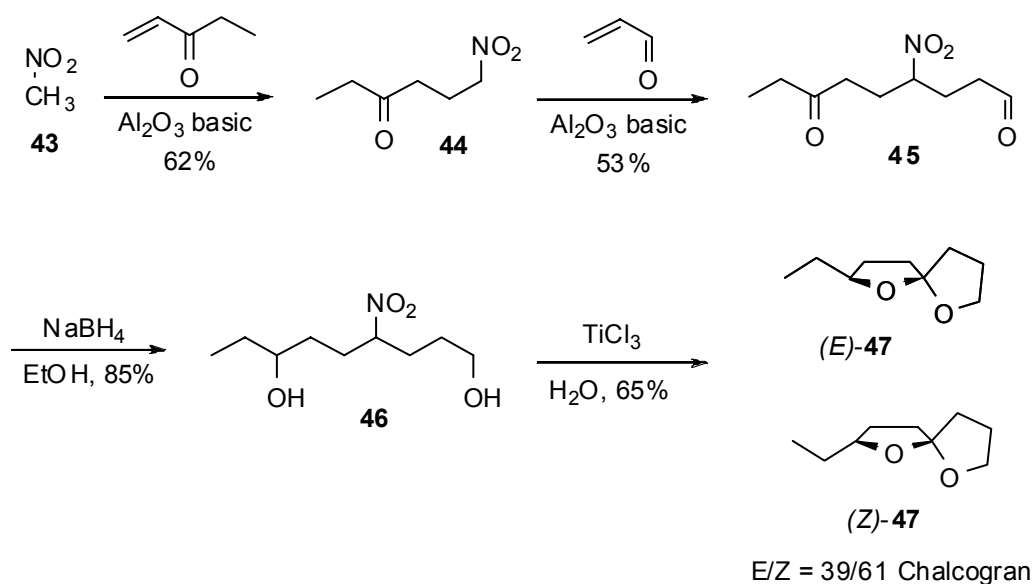


Scheme 10

3. Spiroketal

The spiroketal system is present in a considerable number of natural products obtained from plants, fungi, insect secretions, shellfish toxins, and other living organisms.²³ Many of these bicyclic compounds also show high biological activity as antibiotics and pheromones. Among various practical strategies currently available for assembling the spiroketal unit, the acid-

promoted intramolecular acetalization of dihydroxy-ketone derivatives firmly occupies a central position. Conjugate addition of nitroalkanes to enones provides a rapid entry to 1,4-difunctionalized derivatives. Particularly, nitromethane can be regarded as a multiple coupling reagent corresponding to a carbonyl dianion synthon. A double Michael addition of nitromethane **43** using two different α,β -unsaturated carbonyl derivatives can be used as a key strategy for the preparation of racemic 2-ethyl-1,6-dioxaspiro[4.4]nonane, **47**, known as “Chalcogran”, which is the main component in the aggregation pheromone of the bark beetle *Pityogenes chalcografus* (*L*) (Scheme 11).²⁴ Addition of nitromethane **43** to 1-penten-3-one in the presence of basic alumina under solvent-free conditions affords the corresponding 4-nitro-ketone **44** that is suitable for a subsequent conjugate addition to acrolein under the same conditions, leading to the nitro-diketone **45**. Reduction of the carbonyl groups with NaBH₄ generates the nitro-diol **46**, which upon nitro- to carbonyl- conversion spontaneously produces the spiroketal system of chalcogran **47** as a mixture of stereoisomers in 20% overall yield.

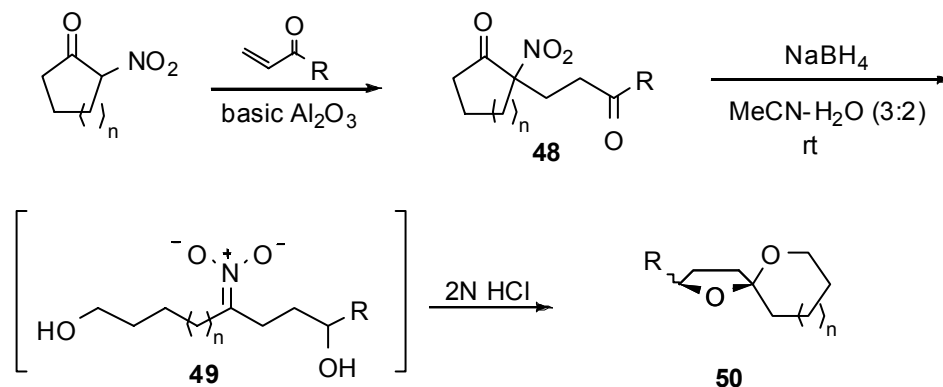


Scheme 11

As shown previously for the synthesis of lactones, 2-nitro-cycloalkanones react with various enones, leading to adducts **48** (Scheme 12).²⁵ The following three synthetic operations, retro-Claisen cleavage, reduction, and nitronate formation, can be carried out on the adducts **48** in a single step using NaBH₄ in a mixture of acetonitrile–water (3:2). The intermediate nitronate **49** upon quick acidic hydrolysis affords directly the spiroketals **50**. In conclusion, this versatile strategy also allows for a rapid entry to 1,6-dioxaspiro[4.6]undecane systems.

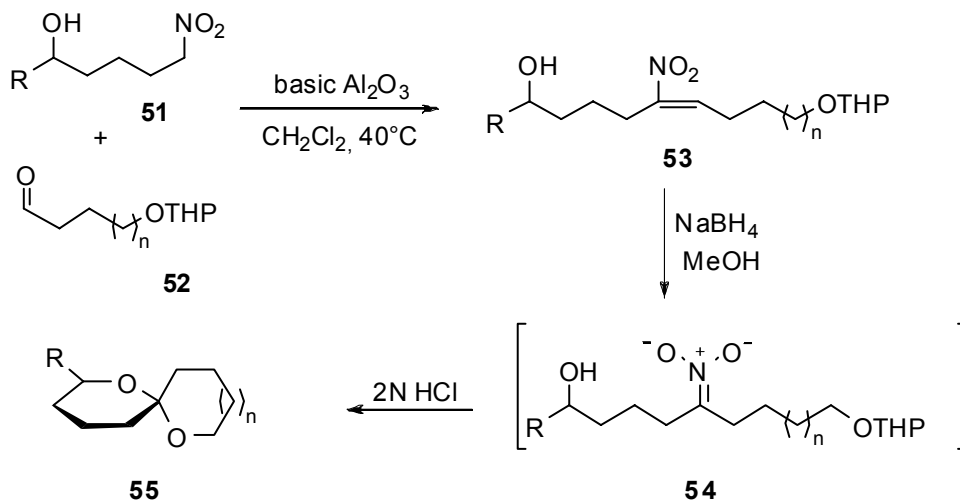
The nitro-aldol (Henry) reaction between the nitro-alcohol **51** and O-protected hydroxy-aldehydes, **52**, occurs efficiently under heterogeneous conditions, leading directly to nitroalkenes **53** (Scheme 13).²⁶ As usual, reduction of the nitroalkene double bond is also coupled with formation of the nitronate anion **54** that upon acidification undergoes a THP deprotection, Nef

reaction, and ketalization, affording the spiroketals **55**. These compounds are the main components of the sex pheromones of the olive fruit fly (*Dacus oleae*) (**55a**) and *Andrena haemorrhhoa* (**55b**). Following a related strategy in which a 5-nitro-ketone and a 4-hydroxy-aldehyde are used for the nitro-aldol reaction, other dialkyl-1,7-dioxaspiro[5.5]undecanes can be readily obtained.²⁷



	n	R	yield (%)	E:Z
a	1	Me	65	3:2
b	1	Et	70	3:2
c	2	Me	75	3:2
d	2	H	60	–

Scheme 12



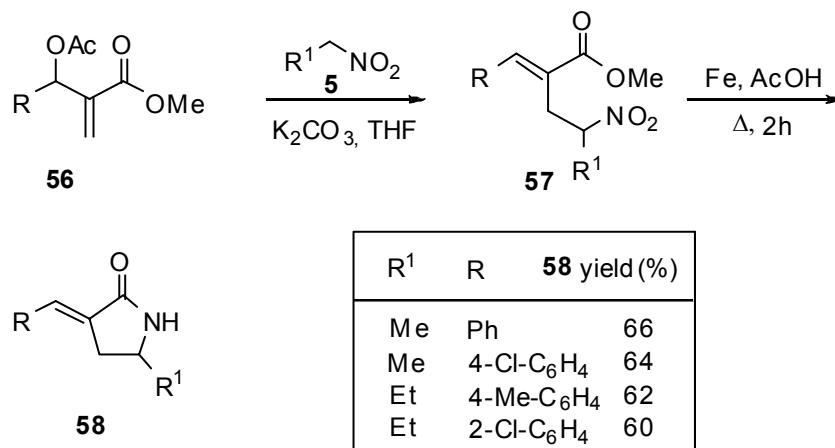
	n	R	53	yield (%)	55
a	1	H	53		64
b	2	Me	54		66

Scheme 13

4. Pyrrolidines and derivatives

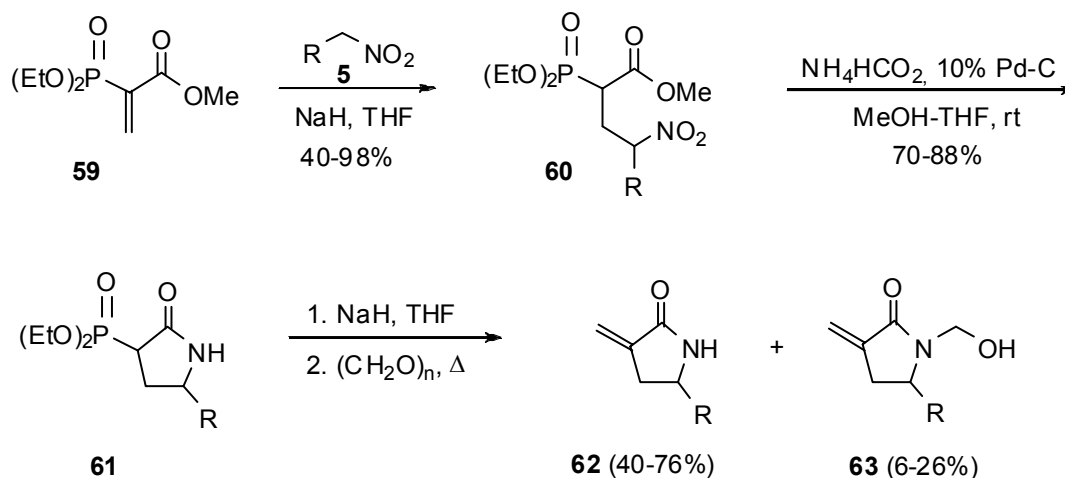
4.1 Pyrrolidin-2-ones

Reduction of the nitrogen atom, thus generating amino derivatives, represents the most obvious transformation of the nitro group. When an ester function is also present in the substrate at the γ -position, a chemoselective reduction of the nitro group directly affords pyrrolidin-2-one derivatives. Addition of nitroalkanes **5** to Baylis–Hillman products **56** gives the corresponding unsaturated nitro-esters **57** that are chemoselectively reduced by a ‘one pot’ procedure to the corresponding 2-alkylidenepyrrolidinones **58** using Fe in boiling AcOH (Scheme 14).²⁸



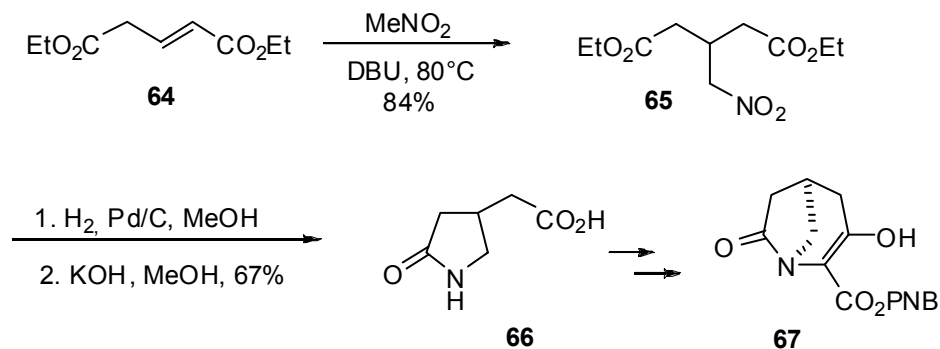
Scheme 14

The introduction of a methylene group at a 2- position is more achievable using 2-diethoxyphosphoryl acrylate **59** that reacts with nitroalkanes **5** and NaH, giving the adduct **60** (Scheme 15).²⁹ Reduction of the nitro group occurs with concomitant lactamization, leading to pyrrolidin-2-ones, **61**. Reaction of **61** with formaldehyde provides a 2-methylenepyrrolidin-2-one, **62**, along with variable amounts of the corresponding 1-hydroxymethyl derivative, **63**.



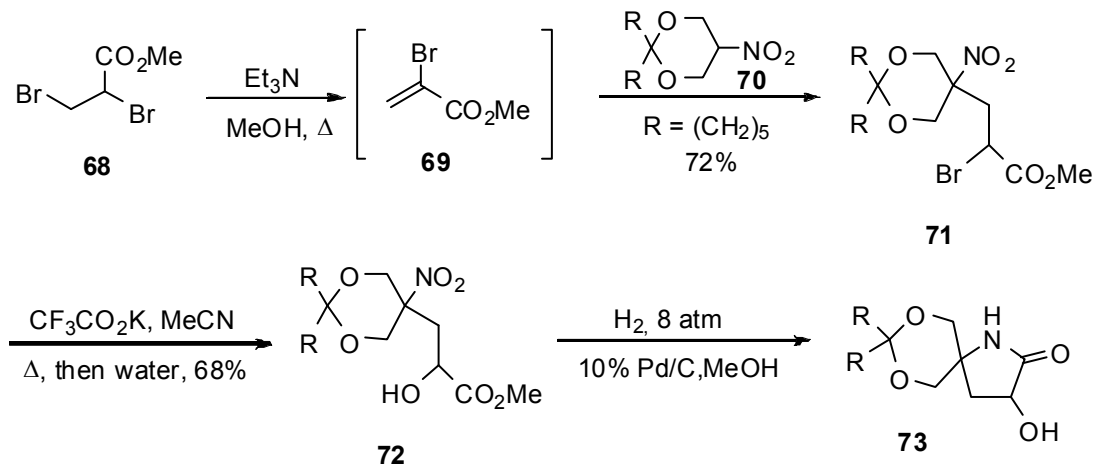
Scheme 15

Nitromethane addition to the diester **64** affords the product **65** which upon reduction of the nitro group and ester hydrolysis gives the pyrrolidinone **66** (Scheme 16).³⁰ The acid **66** can be transformed easily in a few steps into the bicyclo- γ -lactam **67** that acts as an inhibitor of penicillin-binding proteins. Dissymmetric hydrolysis of racemic **66** using two enantiocomplementary enzymes allows the preparation of optically active **66** in both enantiomeric forms.³¹



Scheme 16

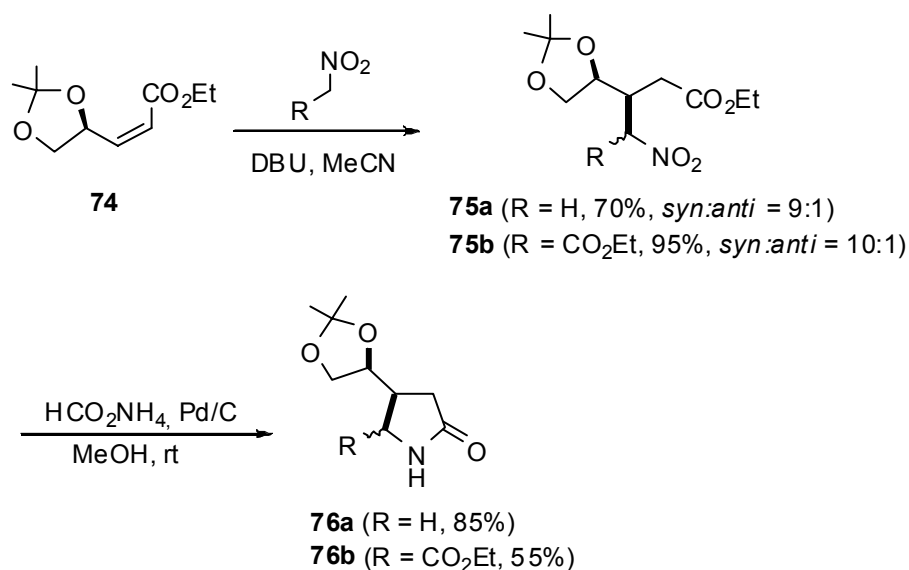
Methyl 2-bromoacrylate **69** can be generated *in situ* from the corresponding dibromo derivative **68** and then made to react with the nitro- compound **70** to give adduct **71** (Scheme 17).³² Substitution of the halogen with an hydroxy group is followed by reduction of the nitro group by catalytic hydrogenation to give the pyrrolidinone **73**. This derivative can be converted into aza-*iso*- nucleotide analogs by further simple synthetic manipulations. 3,4-Dihydroxy pyrrolidinones structurally related to compound **73** can be obtained using the same strategy, by conjugate addition of the nitroalkane **70** to ethyl propynoate, formed *in situ*, followed by dihydroxylation of the resulting unsaturated derivative.³³



Scheme 17

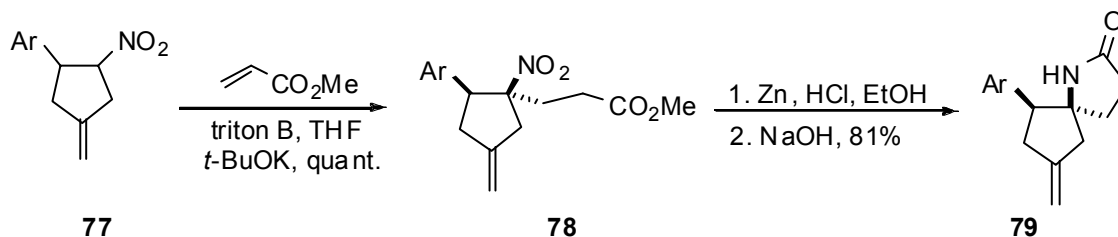
Diastereoselective conjugate addition of nitroalkanes to the chiral (*Z*)- enoate **74** leads to the synthesis of compounds **75** with predominance of the *syn* stereoisomer (Scheme 18).³⁴ Interestingly, the *E* isomer of compound **74** fails to provide good diastereoselection in the same process.³⁵ The stereoselectivity at the carbon atom bearing the nitro group in compound **75b** is rather poor, and this result is probably due to the high acidity of the hydrogen atom between the

nitro and ester groups. Reduction of the nitro group and ring closure affords pyrrolidinones **76** that can be used as synthetic intermediates in the preparation of several interesting compounds.



Scheme 18

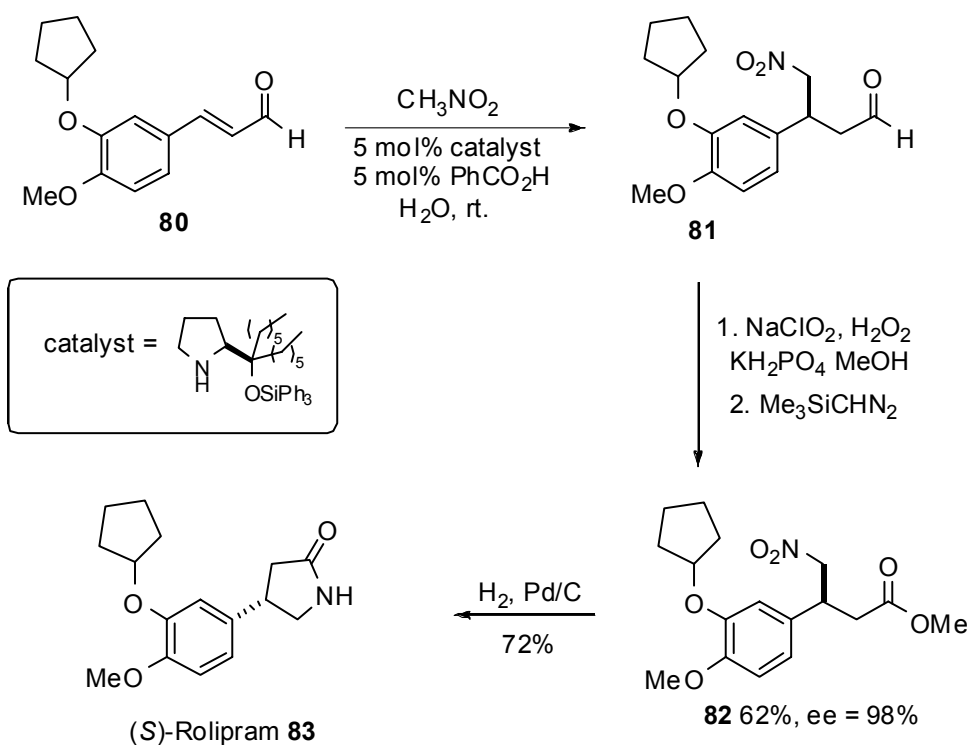
The functionalized nitrocyclopentane **77** reacts with methyl acrylate in quantitative yield to give adduct **78** as a single diastereomer, probably because of the stereo-directing effect of the vicinal phenyl group (Scheme 19).³⁶ Reduction of the nitro group using zinc metal in ethanolic HCl affords spirolactam **79** without any migration of the exocyclic double bond. The lactam **79** is a key intermediate for the synthesis of the alkaloid cephalotaxine.



Scheme 19

Conjugate addition of nitromethane to enals can be carried out under catalytic conditions using chiral pyrrolidines derived from (*S*)-proline in aqueous solutions. The water-compatible iminium catalysis occurs with outstanding enantioselectivity and can be used for the synthesis of the type IV phosphodiesterase inhibitor (*S*)-Rolipram (Scheme 20).³⁷ The unsaturated aldehyde **80** reacts with nitromethane in the presence of a pyrrolidine catalyst giving the adduct **81** which is further oxidized and converted into the corresponding methyl ester **82** in satisfactory yield and

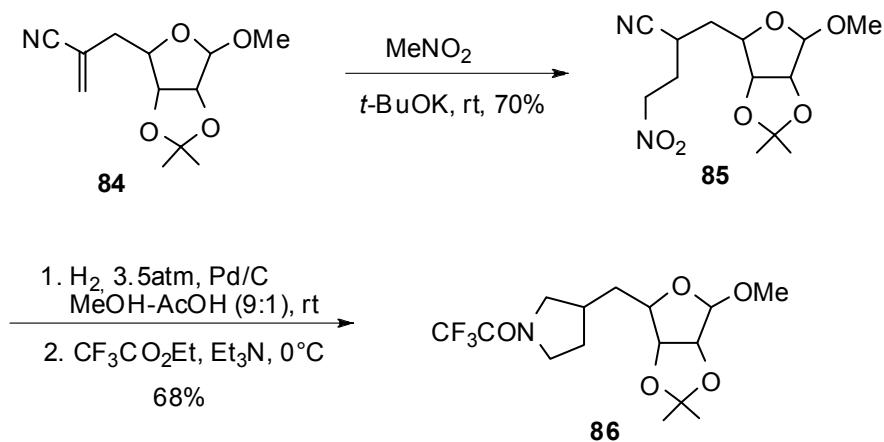
high enantioselectivity. Reduction of the nitro group and spontaneous lactamization complete the synthesis of (*S*)-Rolipram **83**.



Scheme 20

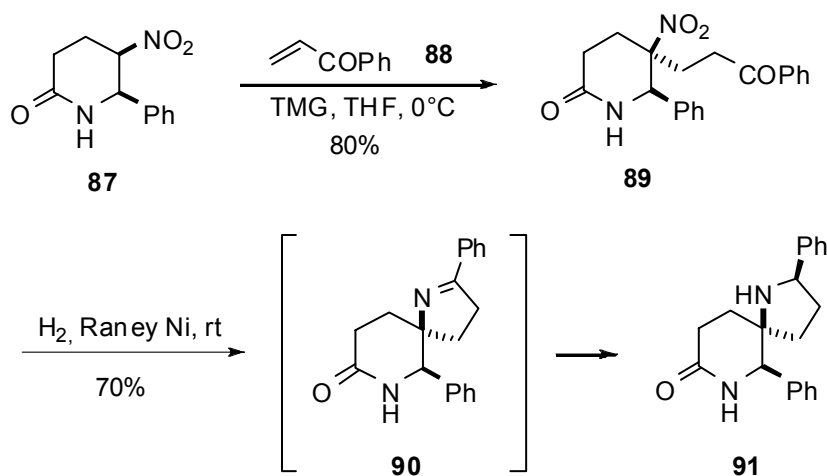
4.2 Pyrrolidines and related bicyclic derivatives

Pyrrolidines can be obtained easily by reduction of the corresponding pyrrolidin-2-ones prepared as discussed in the previous Section. Alternatively, the primary amine obtained by reduction of the nitro group may react with other functional groups (such as carbonyls, giving imino derivatives) that upon further reduction lead to the formation of the pyrrolidine ring. The unsaturated nitrile **84** reacts with nitromethane giving the corresponding adduct **85**, which upon catalytic hydrogenation with 10% Pd/C in MeOH/AcOH (9:1) and acylation furnishes *N*-trifluoroacetylpyrrolidine **86** (Scheme 21).³⁸ It is probable that the primary amine formed by reduction of the nitro group reacts with the intermediate imine formed by reduction of the nitrile to give the intermediate pyrrolidine. Compound **86** is an intermediate for the preparation of synthetic analogues of Sinefungin, a nucleoside active against viruses, fungi and parasites.



Scheme 21

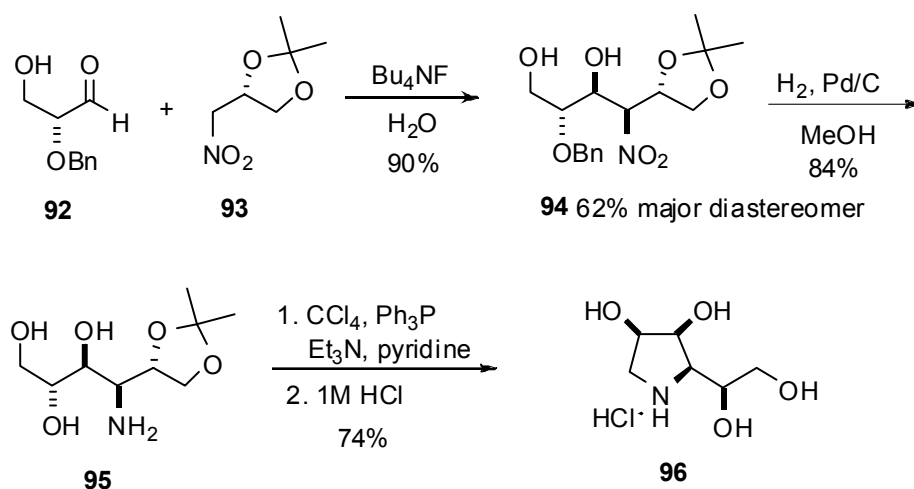
Conjugate addition of the nitrolactam **87** with acrylophenone **88** gives compound **89** with high diastereoselectivity (Scheme 22).³⁹ Catalytic hydrogenation of the nitro-ketone **89** occurs with concomitant formation of an intermediate imine **90** that is reduced in the same conditions to the spiro-pyrrolidine **91**. The presence of the phenyl group in the lactam ring hinders one face of the pyrroline ring in **90**, thus allowing a complete diastereoselection in the imine reduction.



Scheme 22

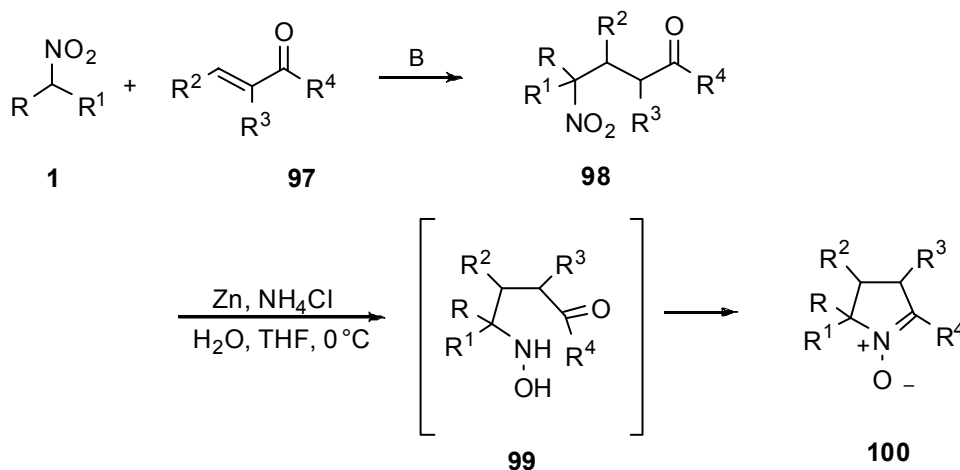
The Henry reaction between the chiral aldehyde **92** and the nitro- derivative **93** gives a mixture of three diastereomers in which compound **94** predominates (Scheme 23).⁴⁰ Reduction by catalytic hydrogenation of the nitro-aldol **94** occurs with retention of the original configuration at the nitro group and at the same time provides debenzoylation of the protected alcohol. Ring closure of the amino-polyol **95** is realized using the Appel reagent⁴¹ that selectively converts the primary hydroxyl into a good nucleofuge. After hydrolysis of the

acetamide group, the hydrochloride salt of polyhydroxylated pyrrolidine **96** is obtained. Derivatives of type **96** are known as strong and selective glycosidase inhibitors.



Scheme 23

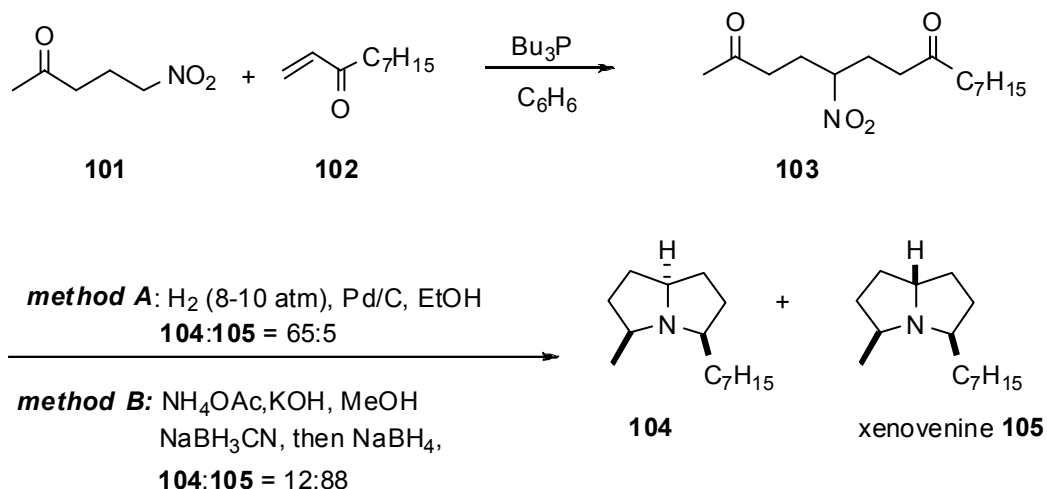
Hydroxylamines are known intermediates in the reduction of nitro- compounds to amines. The adducts **98** obtained by reaction of nitroalkanes, **1**, and enones or enals, **97**, can be reduced using various metals in acidic conditions (Scheme 24).⁴²⁻⁴⁴ The intermediate hydroxylamines **99** produce directly the cyclic nitrones **100** by an intramolecular reaction with the carbonyl group.



Scheme 24

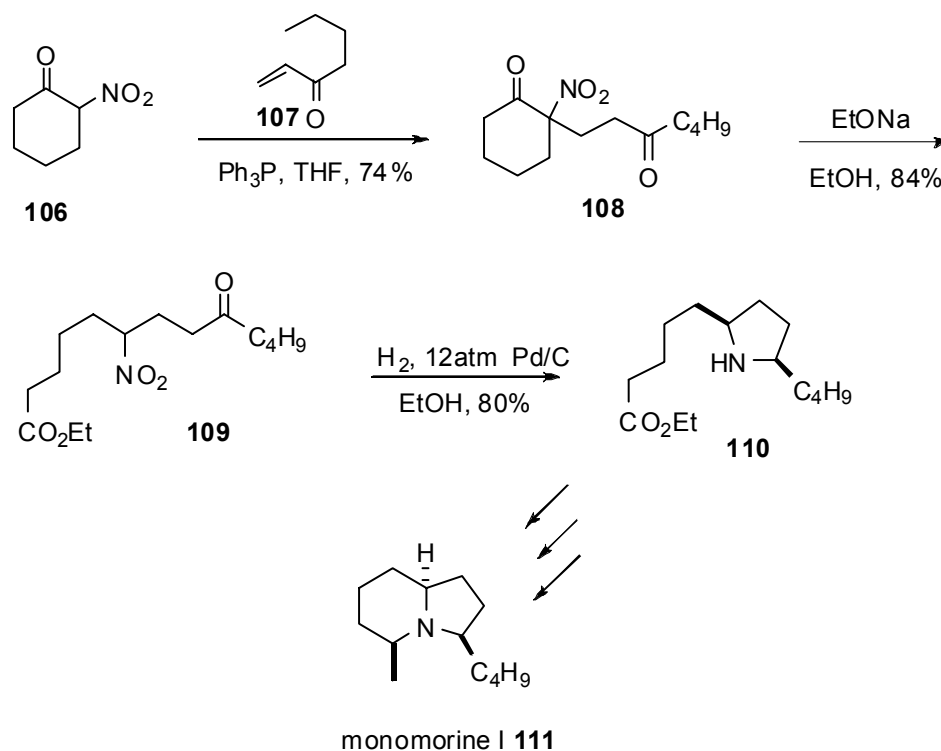
The presence of two carbonyl groups in nitro- diketones, allows the synthesis of pyrrolizidines and indolizidines, which are alkaloid derivatives and can have useful biological activity. The nitro- diketone **103** is readily obtained by addition of nitro-ketone **101** to the vinyl

ketone **102** in the presence of Bu_3P (Scheme 25).⁴⁵ Reduction of compound **103** produces a mixture of stereoisomeric pyrrolizidines **104** and **105** whose diastereomeric composition depends on the reducing system used. Catalytic hydrogenation (method A) favors the formation of compound **104**, while the utilization of complex hydrides (method B) favors the isomer **105**, an alkaloid known as Xenovenine.



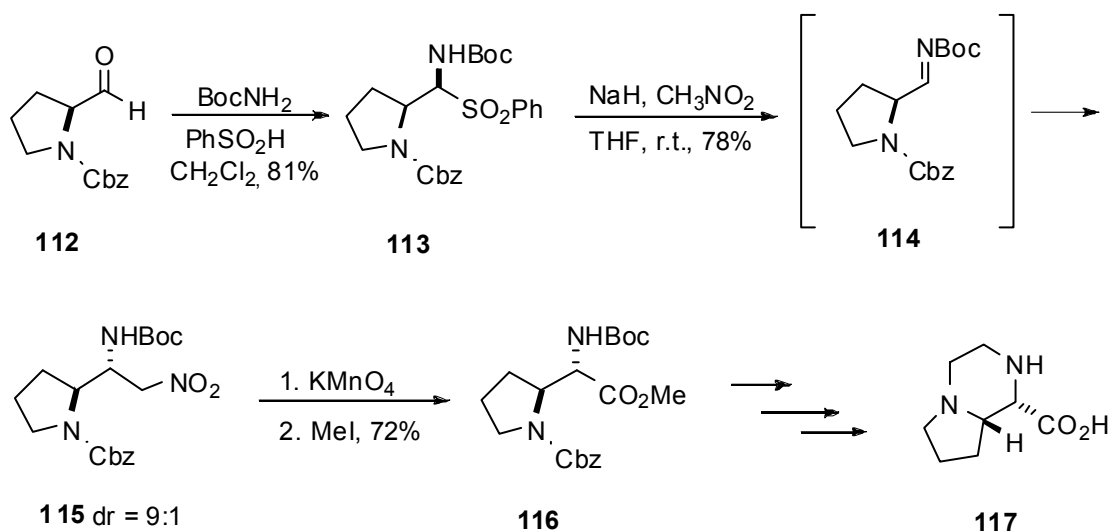
Scheme 25

2-Nitro-ketones usually undergo conjugate additions under milder conditions than do nitroalkanes because of the enhanced acidity of the C-2 hydrogen atom. 2-Nitrocyclohexanone, **106**, reacts with unsaturated ketone **107** in the presence of Ph_3P to give the corresponding adduct **108** (Scheme 26).⁴⁶ The cyclohexanone moiety in **108** suffers a fast base-catalyzed retro-Claisen ring opening, affording the open-chain nitro derivative **109** which under reductive conditions chemoselectively furnishes the *cis*-pyrrolidine **110**. This compound is a central intermediate for the synthesis of the indolizidine alkaloid monomorine I, **111**, a trail pheromone of the Pharaoh Ant, and other similar biologically active substances.⁴⁷



Scheme 26

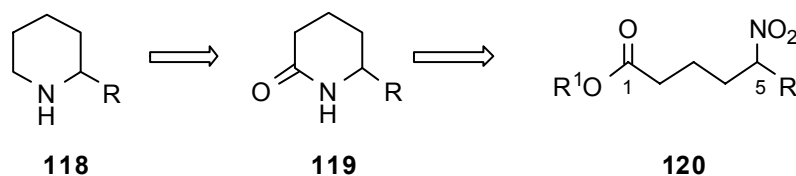
α -Amidoalkyl sulfones are stable precursors of *N*-acylimino derivatives and can be used in the reaction with various nucleophilic reagents.⁴⁸ The chiral α -amido-sulfone **113** can be readily obtained by reaction of (*S*)-prolinal **112** with BocNH₂ and benzenesulfonic acid (Scheme 27).⁴⁹ Reaction of the α -amido-sulfone **113** under basic conditions initially produces the *N*-acylimine **114** that subsequently adds the nitromethane anion leading to the corresponding adduct, **115**, with satisfactory diastereoselectivity. Oxidation of the carbon bearing the nitro group and further alkylation gives the methyl ester **116** that is transformed into the chiral piperazine **117**, an α -amino acid derivative that finds several practical applications as a chiral catalyst as well as a building block for the synthesis of HIV- protease inhibitors.



Scheme 27

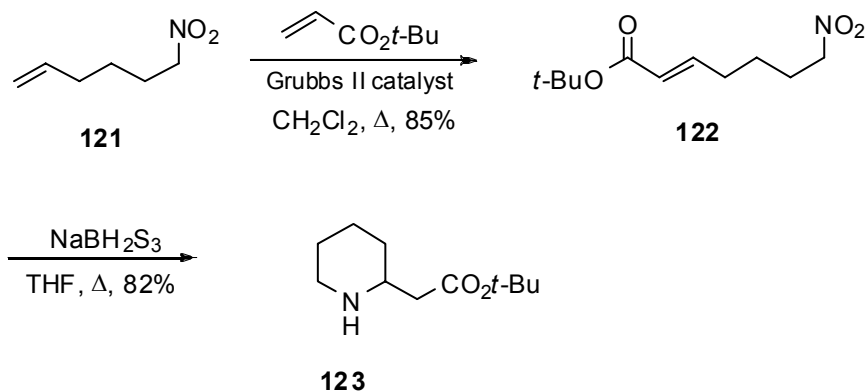
5. Piperidines and Related Derivatives

The synthesis of piperidine derivatives **118**, **119** by reduction of a nitro group and subsequent cyclization would entail a preliminary formation of 1,5-difunctionalized systems **120** which are not directly achievable by conjugate additions or similar processes (Scheme 28).



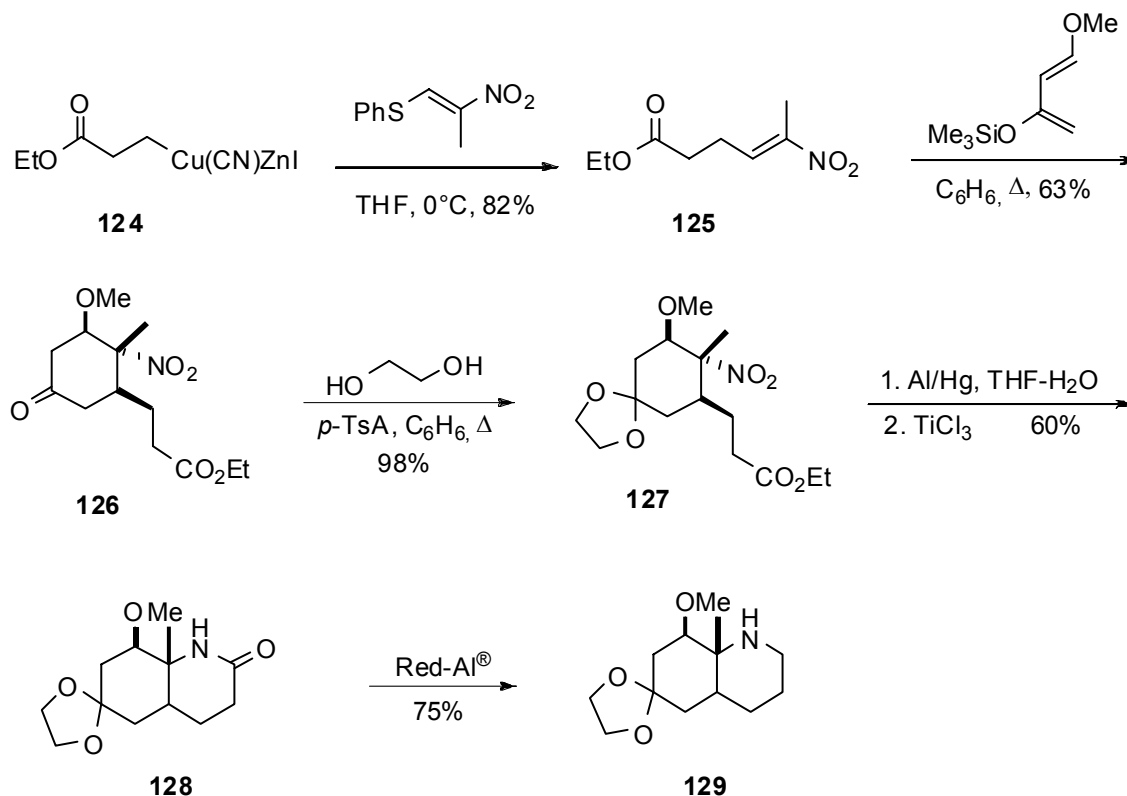
Scheme 28

Various functional groups can be introduced into ω -nitro-1-alkenes by exploiting a cross-metathesis reaction with functionalized alkenes in the presence of Grubbs II catalyst, as illustrated for the synthesis of the nitro-ester **122** from 6-nitrohex-1-ene, **121**, and *t*-butyl acrylate (Scheme 29).⁵⁰ Chemoselective reduction of the nitro group with sulfurated sodium borohydride reagent gives the corresponding amine which, by intramolecular conjugate addition with the unsaturated ester portion, leads to the α -substituted piperidine **123**.



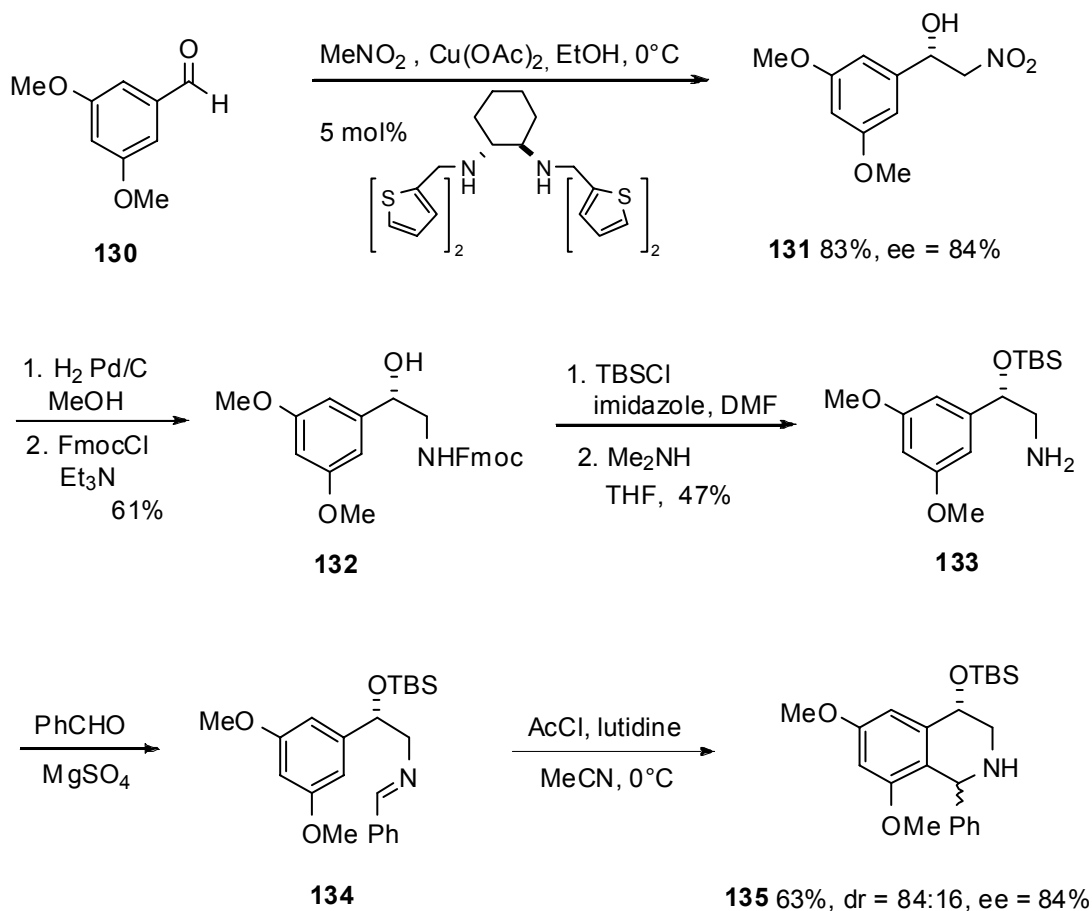
Scheme 29

An interesting procedure to install the nitro and ester groups in a proper 1,5- position consists in the reaction of the functionalized copper–zinc reagent **124** to (*E*)-2-nitro-1-propenyl phenyl sulfide (Scheme 30).^{51,52} The addition–elimination reaction occurs with high *E*- stereoselectivity, allowing the formation of the nitroalkene **125** which is then reacted with Danishefsky’s diene, leading to the nitro- cyclohexanone **126**. After protection of the carbonyl group compound **127** undergoes a partial reduction to the hydroxylamine using Al/Hg amalgam. The partial nature of the reduction is probably caused by the steric hindrance of the nitro group, and can be completed to the amino derivative using TiCl₃. The piperidone derivative **128**, which is isolated after spontaneous lactamization can be further reduced to the piperidine ring using Red-Al[®] under normal conditions.



Scheme 30

Highly functionalized chiral tetrahydro-isoquinolines can be prepared using a Pictet–Spengler reaction on suitable imino derivatives. The generation of a stereo- defined chiral center can be realized by a catalytic enantioselective nitro- aldol reaction of nitromethane on aryl- aldehydes such as **130** in the presence of copper–C₂-symmetrical oligo-thiophene catalyst (Scheme 31).⁵³ The resulting nitro-alcohol **131** is converted into the corresponding amino alcohol and then protected as the fluorenylmethoxycarbamate **132**. This operation is required to carry out silylation of the hydroxy group, since the amine protection is subsequently removed, leading to primary amine **133**. Conversion of amine **133** into the benzylidene imine **134** is followed by a metallo-free ring closure allowing the preparation of the final target in satisfactory diastereo- and enantioselectivities.



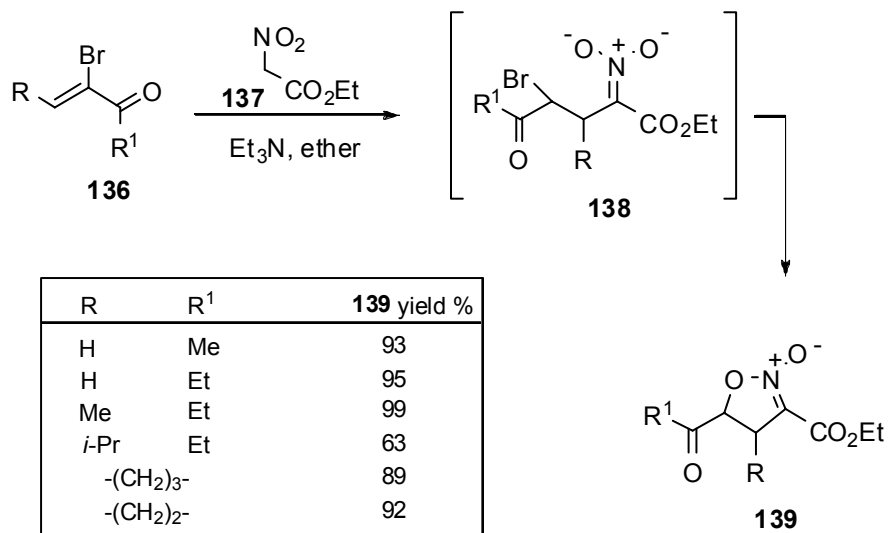
Scheme 31

6. Polyheterocyclic Derivatives

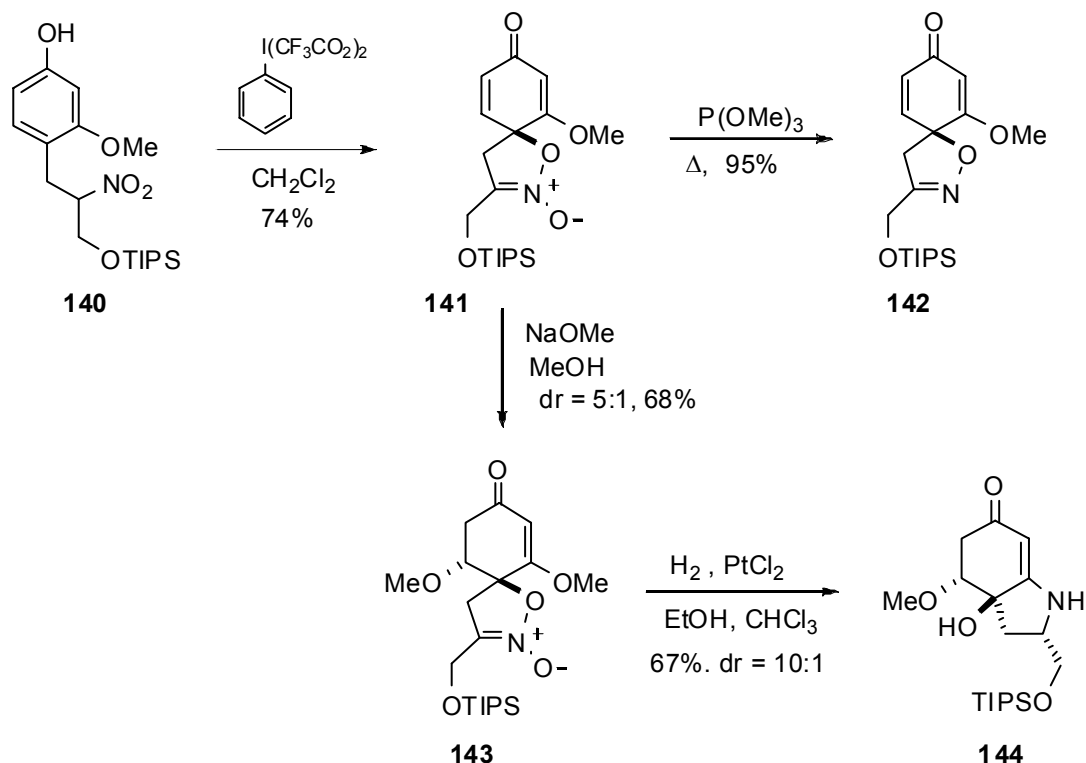
Nitroalkanes can be transformed into silyl nitronates by trapping the nitronate anion with trialkylsilyl halides. Silyl nitronates are useful 1,3- dipoles in cycloaddition reactions with alkenes leading to 2-isoxazolines which can be transformed subsequently into other heterocyclic derivatives.⁵⁴ A new entry to the 2-isoxazoline nucleus makes use of the conjugate addition of ethyl nitroacetate, **137**, with the 2-bromo-ketones, **136** (Scheme 32).⁵⁵ The intermediate adduct **138** undergoes an intramolecular nucleophilic substitution involving the oxygen of the nitronate anion and the bromine atom. The reaction can be realized in homogeneous Et_3N -ether) as well as in heterogeneous conditions (basic alumina), and the 2-isoxazolines **139** are formed predominantly as *trans*- isomers.

Oxidation of the resorcinol derivative **140** with bis-(trifluoroacetoxy)-iodobenzene occurs with concomitant attack of the nitro- group's oxygen to the ring, leading to the spiro-nitronate, **141** (Scheme 33).⁵⁶ Reduction at the nitrogen atom using trimethyl phosphite gives, in high yield, the spiroisoxazoline **142**. Since compound **141** contains a dienone group, it can be made to react

with nucleophiles such as the methoxide anion, leading to the spiro- derivative **143** with satisfactory diastereoselectivity. Catalytic hydrogenation of compound **143** in the presence of PtCl₂ generates a primary amine, which by an intramolecular conjugate addition–elimination produces the pyrrolidine derivative **144** with high diastereoselectivity.

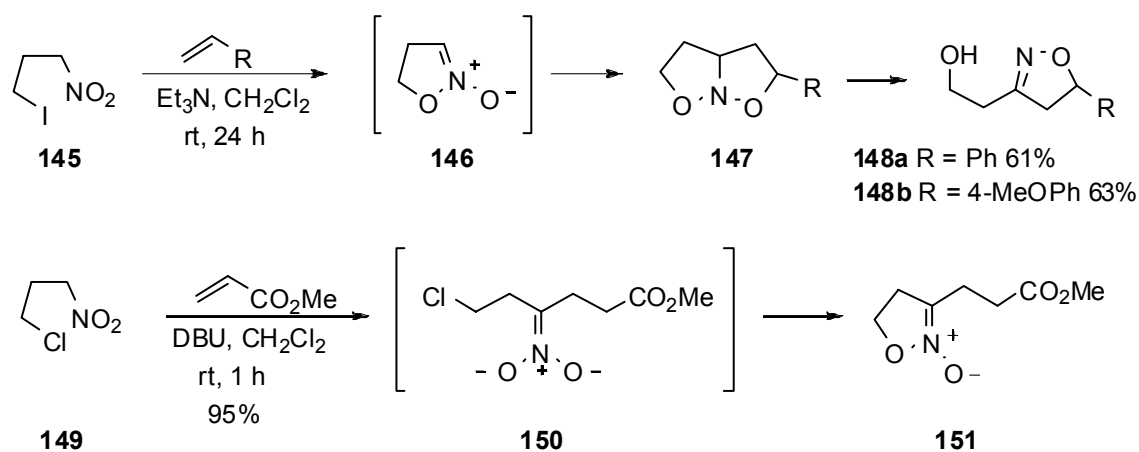


Scheme 32



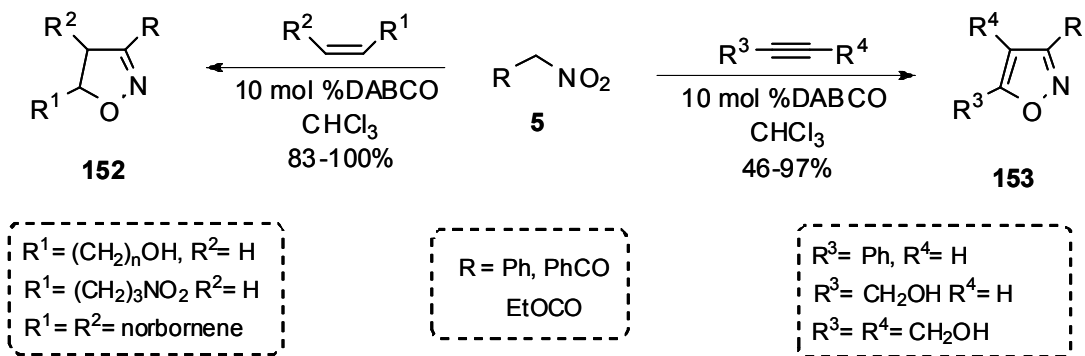
Scheme 33

Cyclic nitronates can be also prepared by intramolecular nucleophilic displacement of ω -halo-nitroalkanes. The nature of the product obtained strongly depends upon from the basic system used to generate the nitronate anion and on the halide atom (Scheme 34).⁵⁷ The iodine atom in compound **145** is readily displaced by oxygen in the presence of triethylamine, leading to a cyclic nitronate, **146**, which in the presence of alkenes undergoes a 1,3-dipolar cycloaddition. The obtained bicyclo derivative **147** promptly decomposes to the hydroxyethyl-isoxazoline, **148**, that is finally isolated in satisfactory yield. The less reactive 3-chloronitropropane, **149**, in the presence of DBU, is converted into the nitronate anion that reacts faster with methyl acrylate in a Michael process than in a ring closure, leading to intermediate **150**. Cyclization follows, giving compound **151** which is isolated in very good yield.



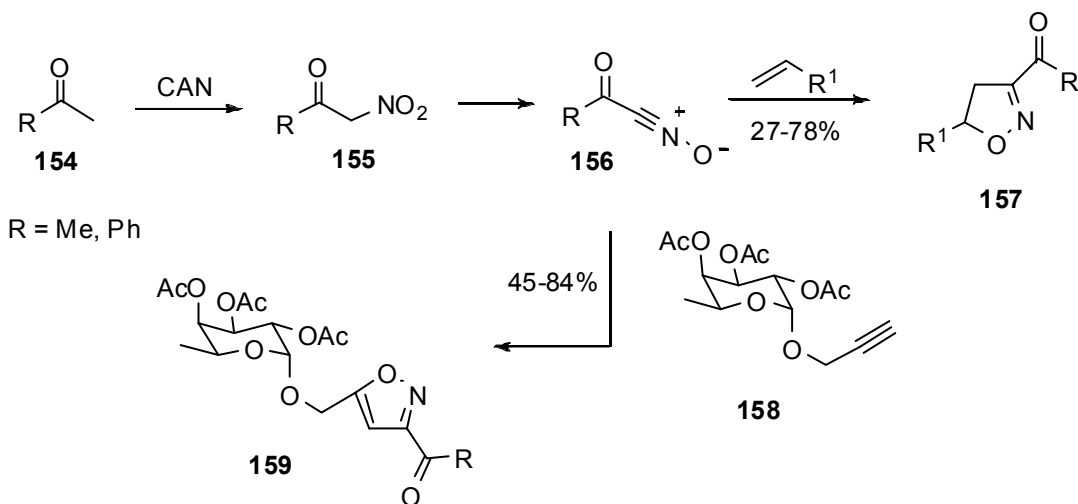
Scheme 34

A tunable synthesis of isoxazolines and isoxazoles can be realized, starting from activated primary nitro compounds (Scheme 35).⁵⁸ Reaction of the nitro compounds **5** with alkenes leads regioselectively to the isoxazoline **152**, while the same process with alkynes produces isoxazoles, **153**. In the proposed catalytic cycle the hydrogen-bonded ion pair formed between the nitronate and the protonated base in chloroform undergoes reversible cycloaddition with the dipolarophile, and then the hydrogen-bonded intermediate adduct releases water by reaction with a second nitro-molecule to give the product and the hydrogen-bonded nitronate. The same process can also be carried out on simple primary nitroalkanes, **5** (R = Et, *n*-Pr, *n*-C₅H₁₁) provided that 1-methylpiperidine is used as a base in the presence of copper (II) acetate.⁵⁹ Nitrile oxides seem not to be involved as intermediates in this process since no furoxans are detected.



Scheme 35

Nitrile oxides are usually generated from nitroalkanes by treatment with phenyl isocyanate under basic conditions.^{54,60} Reaction of ketones **154** with cerium(IV) ammonium nitrate leads to nitro-ketones **155** that, under the same conditions, produce nitrile oxides, **156** (Scheme 36).^{61,62} These 1,3-dipoles react with alkenes to give isoxazolines, **157**, and with alkynes to give isoxazoles. Particularly, reaction of intermediate nitrile oxides **156** with the alkynyl glycosides **158** affords the isoxazoles **159**, which are stable pharmacophores for glycomimetic syntheses.⁶³



Scheme 36

7. Conclusions

Nitroalkanes are versatile intermediates in organic synthesis since they are readily converted into the corresponding nitronate anions that can serve as a source of stabilized carbanions. Conjugate additions, as well as nitro-aldol reactions using nitronate anions, allow relatively easy carbon-carbon bond formation, while the nitro group present in the final product is amenable to further

synthetic transformations. Reduction of the nitro group into the amino group, or conversion into carbonyl groups, provides the necessary heteroatoms for the construction of heterocyclic derivatives. Lactones and spiroketals are usually prepared by exploiting the nitro- to carbonyl conversion (Nef reaction). Pyrrolidines, lactams and other nitrogenated derivatives are obtained by reduction of the nitro group, followed by cyclization. Finally, nitronate anion- cyclization provides a favorable strategy for the assembly of polyheterocyclic compounds featured by both the nitrogen and oxygen atoms.

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