

[3+2]-ANNULATION REACTIONS WITH NITROALKENES IN THE SYNTHESIS OF AROMATIC FIVE-MEMBERED NITROGEN HETEROCYCLES

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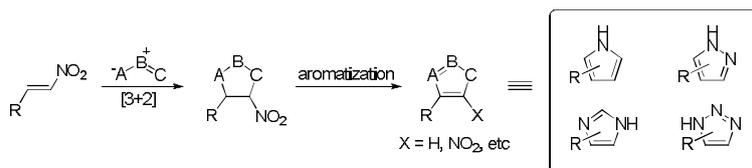
Abstract. [3+2]-Annulation reactions are widely used for the synthesis of aromatic heterocycles. In recent years they have become attractive for the preparation of medicinally relevant heterocycles due to their broad substrate scope and availability of starting materials. Annulations with nitroalkenes may lead to different products due to the ability of the nitro-group to act both as activating group and as leaving group. Ultimately this gives rise to the synthesis of multifunctional heterocyclic compounds, including nitro-substituted ones. The present review covers various annulation reactions with nitroalkenes leading to five-membered nitrogen-containing heterocyclic rings. Oxidative annulation, annulation/elimination and self-oxidative annulation pathways are discussed.

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1. Introduction

Nitroalkenes are useful building blocks for the preparation of a wide variety of heterocyclic compounds, including biologically active substances.¹⁻⁵ Nitroalkenes are known to serve both as nitro group-containing building blocks for the synthesis of nitrated heterocycles, as well as useful synthetic equivalents of alkynes in cycloaddition reactions. The present review focuses on the assembly of 5-membered aromatic nitrogen heterocycles (pyrroles, pyrazoles, imidazoles, triazoles *etc.*) starting with nitroalkenes (Scheme 1).

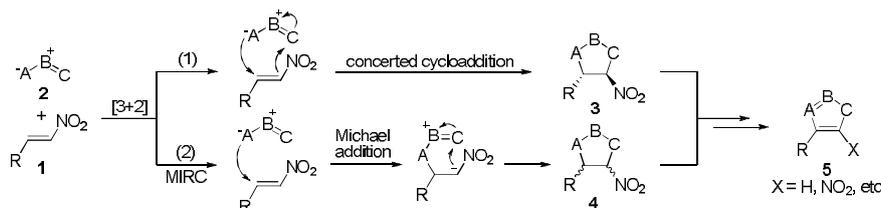


Scheme 1. Assembly of five-membered nitrogen heterocycles from nitroalkenes.

The general approach to this kind of transformation relies on [3+2]-cycloaddition (either true or formal) and subsequent aromatization. Thus, various types of substrates, as well as various cycloaddition and aromatization modes are discussed.

2. Classification of nitroalkene-based annulation reactions

Due to their unique electron-deficient nature, nitroalkenes **1** can undergo [3+2]-annulation reactions with 1,3-dipoles **2** *via* different mechanisms. The major two pathways are concerted 1,3-dipolar cycloaddition^{6,7} (1) and stepwise annulation (2) *via* a Michael addition/cyclization cascade process, often denoted as MIRC (Michael Initiated Ring Closure)^{8,9} (Scheme 2). The most characteristic examples of concerted [3+2]-cycloadditions are annulations of nitroalkenes with azomethine ylides that produce pyrrolidines,^{10,11} and with diazo compounds, that produce pyrazolines. In most cases complete retention of stereochemistry is observed, and the adduct **3** is formed as a single diastereomer. MIRC-involved processes are common for reactions of nitroalkenes with reagents containing strong nucleophilic centers, for example, azide, amidines, *etc.* In this case, the formation of adduct **4** may be not diastereoselective and depends highly on the bulkiness of the substituents and other factors.^{12,13} In depth discussion of this topic lies outside of this review, since the stereochemistry is ultimately lost during the formation of the target heterocycles **5**.



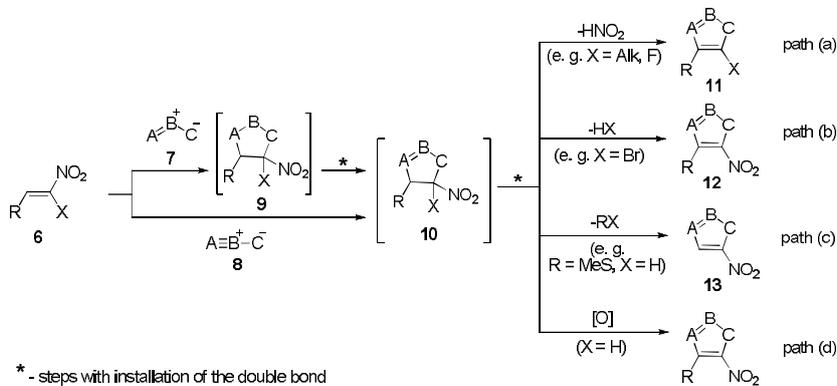
Scheme 2. Mechanisms of [3+2]-annulation involving nitroalkenes.

As mentioned in the introduction, annulations with nitroalkenes may lead to different products due to the high lability of the nitro-group in the resulting saturated adducts and their susceptibility to oxidation. The general scheme of annulation and the different pathways leading to aromatic heterocycles are presented in Scheme 3. As shown, the partially saturated heterocycle **10** is a key intermediate en route to the target aromatic heterocycles **11-13**. The pathway to **10** depends on the type of starting dipole. Allylic type 1,3-dipoles **7** (azomethine ylides, azomethine imines, pyridinium ylides/imines) require [3+2]-cycloaddition with subsequent formation of one double bond (*e.g. via* oxidation) in fully saturated primary adducts **9**. Propargylic type dipoles **7** (azides, diazo compounds) require [3+2]-cycloaddition only. In turn, aromatization of adducts **10** requires installation of one more unsaturated bond in the molecule. Overall, allylic type 1,3-dipoles **7** require two acts of double bond installation (marked with asterisk * in Scheme 3) to form aromatic heterocycles **11-13** (step **9**→**10** and step **10**→**11-13**), while propargylic type dipoles **8** required only one such act (step **10**→**11-13**). Obviously, the aforementioned steps **9**→**10** and **10**→**11-13** have much in common, so we confine our discussion here to the latter; *i.e.* the following discussion regarding step **10**→**11-13** is applicable to step **9**→**10** as well.

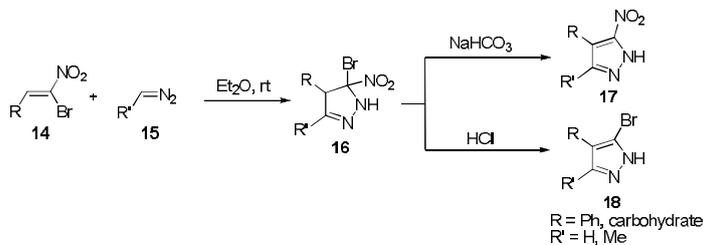
Thus, aromatization of intermediate adducts **10** may be achieved *via* elimination of leaving groups present in the initial substrates or by oxidation. The outcome strongly depends on the nature of the substrates. Generally, the elimination of HNO₂ (Scheme 3, path a) is characteristic for substrates containing a strong C-X bond. Obviously, it applies to carbon substituents (*e.g.* for α -alkylated nitroalkenes **6**, X=Alk). Importantly, α -fluoronitroalkenes (X=F)¹⁴ also serve as useful building blocks for the chemoselective formation of fluorinated heterocycles.¹⁵ In the case of substrates with a labile C-X bond (*e.g.* α -bromonitroalkenes), adducts **10** tend to undergo HX elimination (Scheme 3, path b) leading to nitro-substituted adducts **12**, however, HNO₂ elimination may also be observed. Thus, for α -chloronitroalkenes both types of eliminations are known, but HNO₂ elimination is usually more favored to form chloro-substituted heterocycles (see *e.g.* Scheme 34).¹⁶ The competition between HNO₂ and HBr elimination (path a/path b) was studied for pyrazole formation from nitroalkenes **14** and diazo compounds **15**, and it was found that the reaction medium is crucial for the outcome. In some cases, the intermediate

bromonitropyrazolines **16** were isolated and subjected to different conditions (Scheme 4). When basic conditions (aqueous NaHCO_3) were applied, elimination of less basic bromide was favorable, leading to nitro-substituted pyrazole **17**, whereas in the presence of acid elimination of HNO_2 was predominantly observed to give bromo-pyrazole **18**.^{17,18}

The presence of a labile group R in the β -position of the initial nitroalkene leads to elimination of RH from the unsaturated adduct, as is well-known for β -(methylthio)substituted nitroalkenes (**6**, $\text{RX}=\text{MeSH}$, Scheme 3, path c). Finally, retention of the nitro group is the most characteristic for α -unsubstituted nitroalkenes **6** ($\text{X}=\text{H}$), which serve as useful building blocks for nitro-substituted heterocycles, formed by oxidation as a final step (Scheme 3, path d). Reactions proceeding *via* path (d) are often promoted by addition of external oxidants.



Scheme 3. General scheme for annulations involving nitroalkenes.

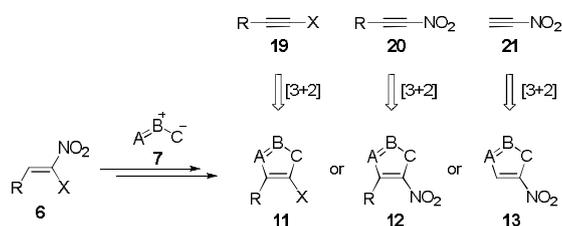


Scheme 4. Dichotomy of annulation/elimination reaction of bromonitroalkenes **14** with diazoalkanes **15**.

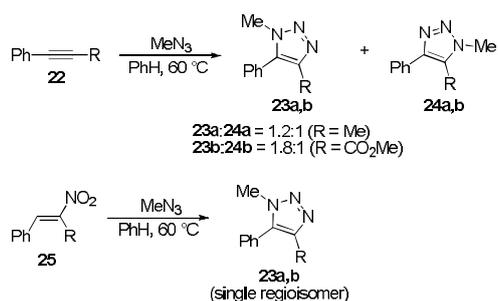
Utilization of nitroalkenes successfully complements other methodologies for the assembly of five-membered heterocycles. Of special note is their use as synthetic equivalents of alkynes in [3+2]-cycloadditions. Firstly, some alkynes containing specific substituents (*e.g.* fluoroalkynes¹⁹ **19** ($\text{X}=\text{F}$) and nitroalkynes²⁰ **20**, **21**, Scheme 5) are highly unstable, which limits the scope of [3+2]-cycloaddition. Another advantage is that the employment of nitroalkenes enables achievement of completely regioselective [3+2]-cycloadditions because of the high polarization of the $\text{C}=\text{C}$ bond. For example, synthesis of trisubstituted triazoles from internal alkynes **22** and azides is not regioselective and leads to a mixture of both isomeric products **23** and **24**. However, azide cycloaddition on nitroalkene **25** proceeds with complete regioselectivity to form a single isomer of product **23** (Scheme 6).²¹

There are some other reactions that do not precisely correspond to any of the pathways described in Scheme 3. Nevertheless, they will be also treated in this review. For example, the Barton-Zard pyrrole synthesis (see 3.1.1.) involves annulation of nitroalkenes with isonitriles. Another pathway which is specific and characteristic for some Lewis acid-catalyzed annulations with nitroalkenes **26** is shown in Scheme 7. It involves Michael addition in the first step, followed by ring closure by attack of the other nucleophilic center

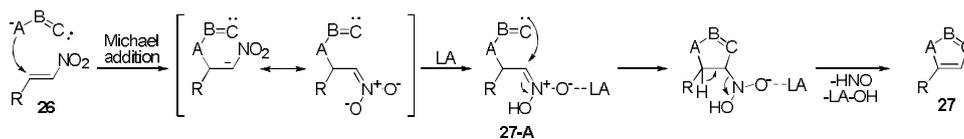
to the incipient activated nitronate (structure **27-A**).²² Afterwards, elimination of nitroxyl (HNO) occurs resulting in the formation of heterocycle **27**. Such peculiarity distinguishes this pathway and path (a) in Scheme 3 since the eliminated species have the nitrogen atom in different oxidation states: N^{+3} in HNO_2 (path a, Scheme 3) and N^{+1} in HNO (Scheme 7). Thus, the pathway shown in Scheme 7 often does not need an external oxidant for the formation of the target aromatic heterocycle **27**. Due to this feature, we will call this type of reactions self-oxidative annulation, because the oxidant involved is actually the nitro group present in substrate. Specific examples can be found in Schemes 14 and 39.



Scheme 5. Nitroalkenes **6** as synthetic equivalents of alkynes **19-21** in [3+2]-cycloaddition.



Scheme 6. Comparison of regioselectivity outcomes of alkyne-azide and nitroalkene-azide cycloadditions.



Scheme 7. Representative mechanism for self-oxidative annulation (LA=Lewis acid).

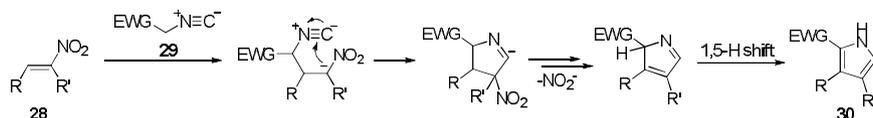
3. Annulations with nitroalkenes in the synthesis of five-membered rings

3.1. Syntheses of pyrroles

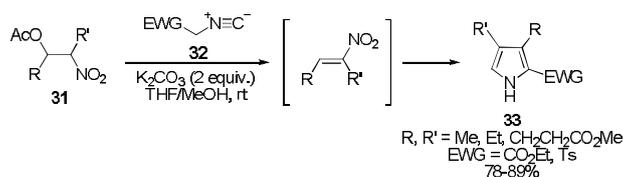
3.1.1. Barton-Zard pyrrole synthesis

Since its initial discovery in 1985 by Barton and Zard,^{23,24} the synthesis of pyrroles from isonitriles **29** containing active methylene group and nitroalkenes **28** became a popular way of pyrrole ring construction, regarding the broad substrate scope of the method. Reviews are available on the topic.^{25,26} The classical conditions for the annulation include utilization of strong amine base (DBU, TMG) to afford pyrroles with one free α -position, making the products useful for the synthesis of multifunctional porphyrines.²⁷ The mechanism involves a typical Michael addition-initiated ring closure followed by elimination of nitrite and formation of pyrrole **30** (Scheme 8).

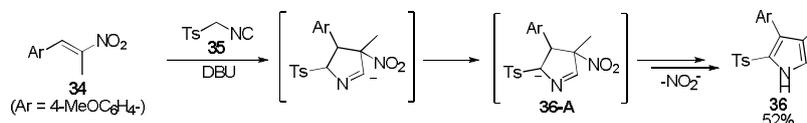
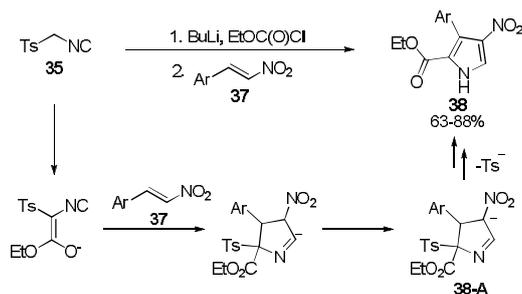
The substrate scope of the method includes nitroalkenes derived both from aromatic and aliphatic aldehydes, α -substituted and α -unsubstituted examples. In one of the protocols pyrroles **33** were prepared from vicinal nitro-acetates **31** (which are direct nitroalkene precursors) and isonitriles **32** with K_2CO_3 as an inexpensive and readily available base (Scheme 9).²⁸



Scheme 8. Barton-Zard reaction.

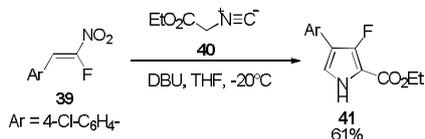
Scheme 9. K₂CO₃-mediated Barton-Zard reaction with vicinal nitroacetates.

In the case of sulfonyl-substituted isonitrile (TsCH₂NC, TosMIC, **35**) the elimination of TsH instead of HNO₂ may happen in the final step.^{24,29} It can be suggested that the reaction pathway is controlled by the substitution pattern of starting materials. Thus, the absence of an acidic CH adjacent to the nitro group while presence of acidic CH adjacent to the sulfonyl function leads to nitrite expulsion in intermediate anion **36-A** (Scheme 10).²⁴ Chemoselectivity may be completely switched to the formation of 3-nitropyrroles. This method involves preliminary acylation of the initial isonitrile with chloroformate. During the subsequent annulation with nitroalkenes **37**, a similar Barton-Zard reaction takes place, accompanied by elimination of sulfinate, possibly *via* anion **38-A** (Scheme 11).³⁰

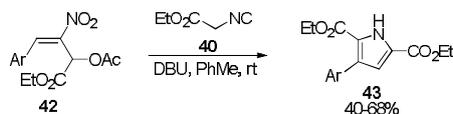
Scheme 10. Synthesis of 2-tosyl-pyrrole **36**.Scheme 11. Chemoselective synthesis of 3-nitropyrroles **38**.

Among the reactions with halonitroalkenes, only the Barton-Zard reaction with α -fluoronitroalkenes was reported. 3-Fluoropyrrole **41** was prepared from α -fluoronitroalkene **39** and ethyl isocynoacetate **40** in the presence of DBU as a base (Scheme 12).¹⁴ Maintaining the low temperature (-20 °C) was important to achieve good yield, as it was found to drop dramatically for the reaction at room temperature.

However, the Barton-Zard reaction was not widely investigated in cases of more complex nitroalkenes. Interestingly, annulation of Morita-Baylis-Hillman acetates **42** with isonitrile **40** under basic conditions results in another mode of [3+2]-annulation, where the nitroalkene acts as component bearing 3 atoms, rather than two in the regular Barton-Zard reaction (Scheme 13). The mechanism of the transformation remains unclear, and the authors did not discuss it in detail.³¹



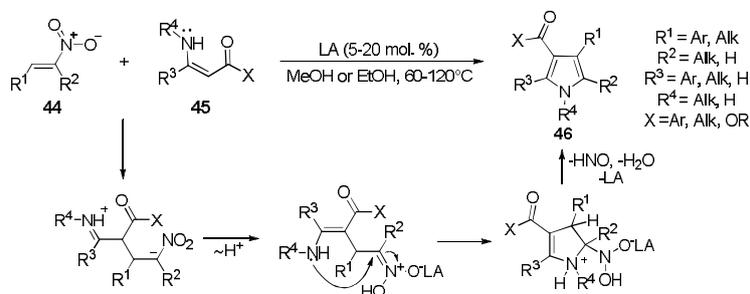
Scheme 12. Synthesis of 3-fluoropyrrole **41** via Barton-Zard reaction.



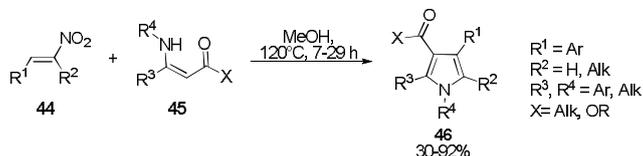
Scheme 13. Annulation of Morita-Baylis-Hillman derived adducts **42** with isocyanide **40**.

3.1.2. Annulation with enamines

Annulation reactions of enamines **45** (enaminones and β -ester substituted enamines) with nitroalkenes **44** are known to be promoted by various Lewis acids and generally proceed as self-oxidative annulations. The first steps involve Michael addition of the enamine to the nitroalkene followed by ring closure of the incipient imino-group to the nitronate. It results in elimination of nitroxyl and formation of target pyrrole **46** (Scheme 14). The most common reaction partners for these reactions are enamines derived from 1,3-dicarbonyl compounds (*e.g.* acetylacetone, acetoacetic ester). The catalysts employed include FeCl_3 ,³² $\text{In}(\text{OTf})_3$,³³ $\text{Ph}_3\text{PAuCl}/\text{AgOTf}$,³⁴ iodine³⁵ and acetic acid.³⁶ The role of the catalyst in these processes is coordination of the nitronate, which causes Nef-like cyclization, a key step in the self-oxidative annulation. However, metal catalyst-free conditions involving simple heating at 120 °C in MeOH has also been developed (Scheme 15).³⁷



Scheme 14. Annulation of nitroalkenes with enamines.

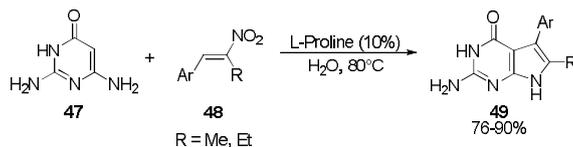


Scheme 15. Catalyst-free procedure for the annulation of nitroalkenes with enamines.

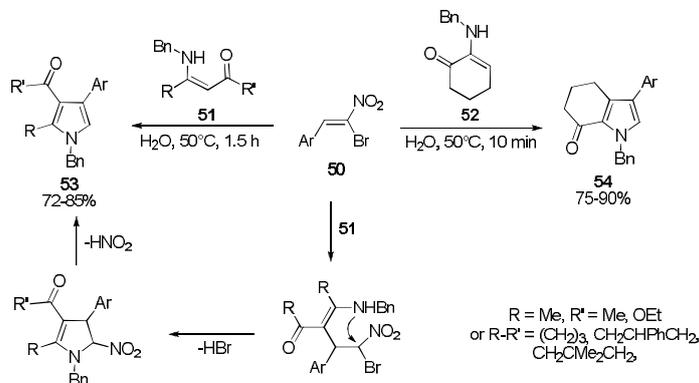
Importantly, this methodology has found several applications in the synthesis of multifunctional pyrroles, including the construction of fused pyrrole ring in pyrrolo[2,3-d]pyrimidine scaffold **49** from cyclic enamine **47** (Scheme 16).³⁸

In the case of α -bromonitroalkenes **50** the reaction with enamines proceeds *via* cyclization/double elimination sequence, resulting in the formation of pyrroles with an unsubstituted 2-position. Water was used as the solvent. This reaction is applicable to both β -substituted **51** and rarer α -substituted enamines **52**

giving different pyrroles **53**, **54** (Scheme 17).³⁹ Importantly, in this case simple nitrite and bromide elimination takes place rather than self-oxidation to afford an aromatic heterocycle.

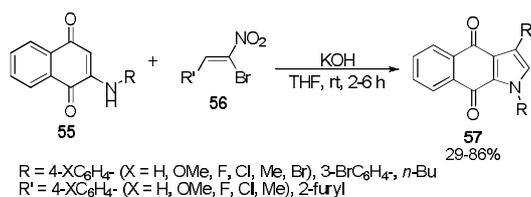


Scheme 16. Construction of pyrrolo[2,3-d]pyrimidines **49** via nitroalkene-enamine annulation.



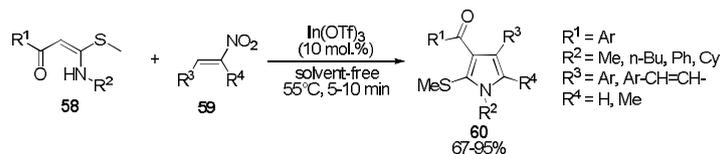
Scheme 17. Annulation of α -bromonitroalkenes **50** with enamines **51-52** in water.

The construction of pyrrolo-fused naphthoquinones was developed based on this methodology of annulation of enamines **55** with bromonitroalkenes **56** (Scheme 18).⁴⁰ The final products **57** were found to possess high anticancer activity.



Scheme 18. Synthesis of pyrrolonaphthoquinones **57**.

In the case of thio-substituted enamines **58**, the reaction proceeds by a similar mechanism of self-oxidative annulation, since the elimination of MeSH does not happen (Scheme 19).³³

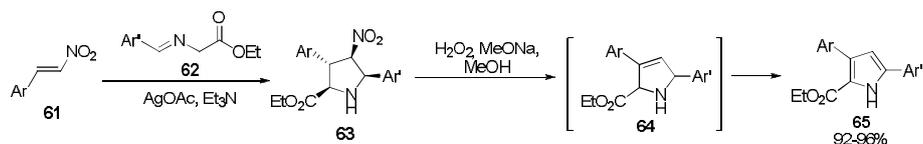


Scheme 19. Annulation of nitroalkenes **59** with thio-substituted enamines **58**.

3.1.3. Annulation with azomethine ylides

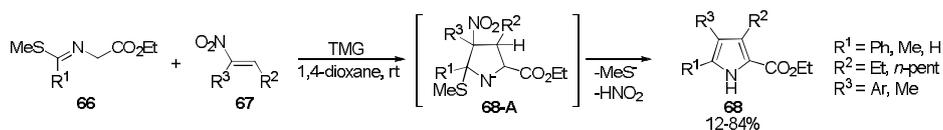
Azomethine ylides are useful substrates frequently employed in [3+2]-cycloaddition reactions.⁷ The most common way to obtain azomethine ylides is their generation from amino acid-derived imines under

basic conditions or in the presence of transition metals. Reactions of simple aromatic nitroalkenes **61** (e.g. β -nitrostyrene) with azomethines **62** under mild conditions often result in the formation of pyrrolidines **63**, which are highly stabilized by bulky aryl groups and hardly susceptible to oxidation. However, in some protocols the further oxidation of pyrrolidines **63** to pyrroles **65** was reported using either aqueous H_2O_2 or manganese dioxide (Scheme 20).^{10,11} In some cases pyrrolines **64** may be isolated as intermediate products.¹¹



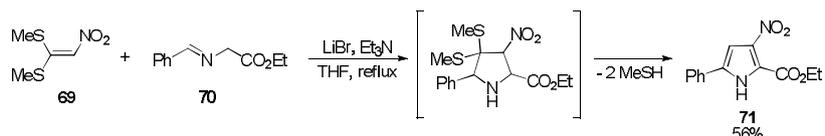
Scheme 20. Two-step synthesis of pyrroles *via* annulation with azomethine ylide/oxidation.

Only in cases when either the azomethine ylide or the nitroalkene contains additional leaving groups, is the direct synthesis of pyrroles known. However, these reactions do not have high synthetic value because the initial reagents are not easily available. *E.g.* imidothiolate **66** was used as a substrate of azomethine ylide. In the presence of tetramethylguanidine annulation with nitroalkenes **67** is accompanied by double elimination resulting in the formation of pyrroles **68** (Scheme 21).⁴¹ The proposed stepwise mechanism involves a MIRC process (intermediate **68-A**) and double elimination of MeS^- and HNO_2 .



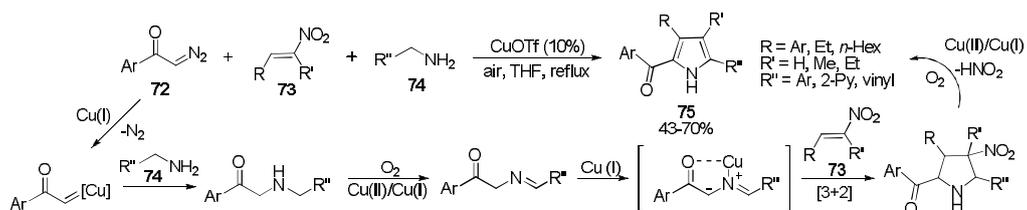
Scheme 21. Annulation of thio-substituted azomethine ylides with nitroalkenes.

Also, β,β -dithiosubstituted nitroalkene **69** in reaction with azomethine ylide generated from imine **70** undergoes double elimination of MeSH , forming 3-nitropyrrole **71** (Scheme 22).⁴²



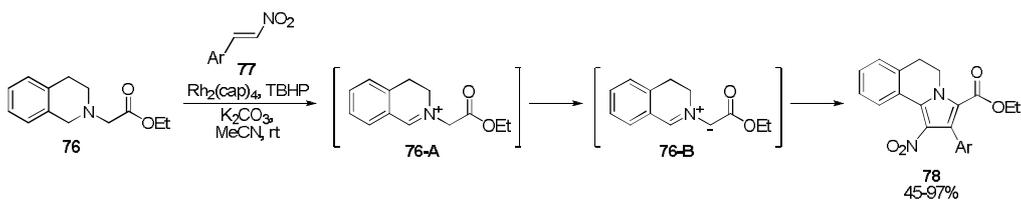
Scheme 22. Annulation of β,β -dithionitroalkene **69** with imine **70**.

Among the non-classical routes to pyrroles, the copper(I)-catalyzed three-component synthesis of multifunctional 2-acylpyrroles from diazoketones **72**, nitroalkenes **73** and primary amines **74** was developed. Intermediate azomethine ylide is generated *via* a carbene insertion into an N-H bond followed by oxidation with $\text{Cu(I)}/\text{O}_2$. Further cycloaddition and aromatization *via* oxidation/ HNO_2 elimination occurs affording target 2-acylpyrroles **75** (Scheme 23).⁴³



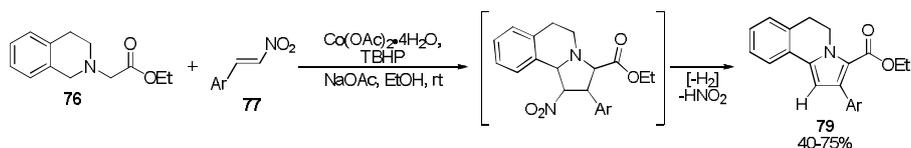
Scheme 23. Copper-catalyzed three-component synthesis of pyrroles.

One of the recent examples of 5,6-dihydropyrrolo[2,1-a]isoquinoline **78** synthesis demonstrates an unusual type of oxidative annulation, where 1,3-dipole **76-B** is generated *via* oxidation of neutral N-substituted tetrahydroisoquinoline **76** by the Rh₂(cap)₄/TBHP system.⁴⁴ The dipole is able to undergo cycloaddition with α -unsubstituted nitroalkenes **77** followed by one more act of oxidation, affording nitro-substituted heterocycles **78** (Scheme 24).



Scheme 24. Synthesis of nitro-derivatives of 5,6-dihydropyrrolo[2,1-a]isoquinoline **78** *via* Rh(II)/TBHP-mediated oxidative annulation; cap=caprolactamate; TBHP-*tert*-butylhydroperoxide.

In another report, it was shown that cheaper cobalt diacetate may be used instead of Rh catalyst to generate the same 1,3-dipole.⁴⁵ The reaction goes *via* nitrite elimination pathway rather than second act of oxidation, and denitrated heterocycles **79** are ultimately formed (Scheme 25).

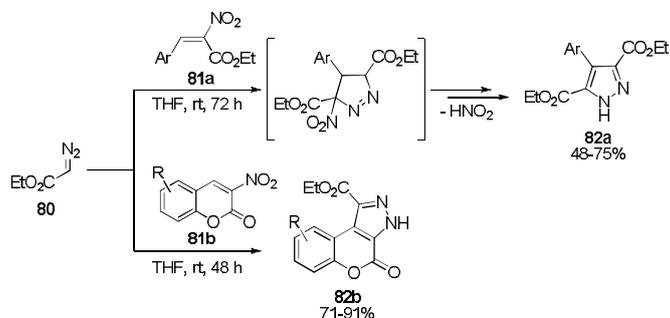


Scheme 25. Synthesis of denitrated derivative of 5,6-dihydropyrrolo[2,1-a]isoquinoline **79** *via* Co(II)/TBHP-mediated oxidative annulation.

3.2. Syntheses of pyrazoles

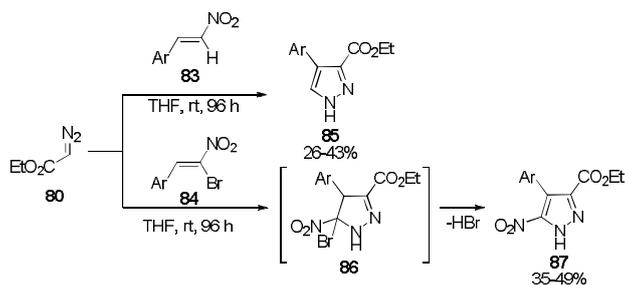
3.2.1. Nitroalkene-diazo [3+2]-cycloadditions

[3+2]-Cycloadditions with diazo compounds are one of the simplest routes for the synthesis of pyrazoles.⁴⁶ The cycloaddition of nitroalkenes and diazo compounds is supposed to be a mixed type of concerted 1,3-dipolar cycloaddition, with a predominant contribution of the HOMO (diazo)-LUMO (nitroalkene) interaction. Ethyl diazoacetate **80** was explored as a model diazo compound, presumably due to its high stability comparatively to diazomethane. In case of highly electron-deficient nitroalkenes **81** (nitrocinnamates **81a** or 3-nitrocoumarine derivatives **81b**) the cycloaddition/elimination reaction sequence proceeded smoothly when the mixture was stirred at r. t. in THF for 2-3 days (Scheme 26).⁴⁷



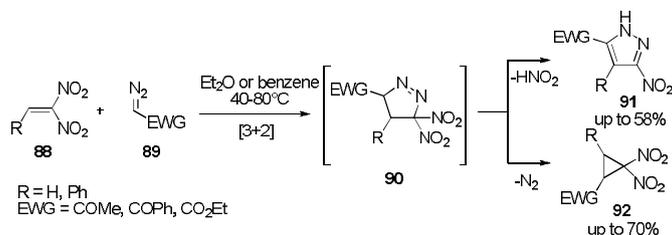
Scheme 26. Annulation of ethyl diazoacetate with electron-deficient nitroalkenes.

The reaction was extended to α -unsubstituted nitroalkenes **83** to give pyrazoles **85** with a free 5-position. Bromonitroalkenes **84** are also known to undergo the reaction, providing 5-nitro-substituted pyrazoles **87** as products of selective HBr elimination. In comparison to the more electron-deficient substrates **81**, these reactions proceed significantly more slowly. Often incomplete conversion of starting nitroalkenes and moderate yields of pyrazoles **85**, **87** were obtained (Scheme 27).⁴⁷



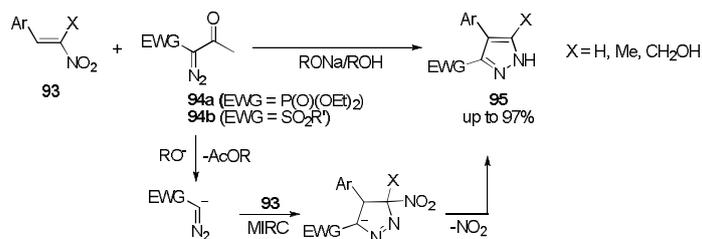
Scheme 27. Annulation of ethyl diazoacetate **80** with α -unsubstituted nitroalkenes **83** and α -bromonitroalkenes **84**.

The reaction between 1,1-dinitroalkenes **88** and diazo compounds **89** gives 3-nitropyrazoles **91** and dinitrocyclopropanes **92** as side-products in comparatively high amounts, especially for β -unsubstituted nitroalkene ($R=H$) (Scheme 28).⁴⁸ Cyclopropanes **92** are formed as a result of nitrogen extrusion from intermediate pyrazolines **90**. It is shown that utilization of 4-10 mol.% of $\text{Mo}(\text{CO})_6$ as a catalyst favors cyclopropane formation, while under catalyst-free conditions nitropyrazoles **91** are obtained as major products.⁴⁸



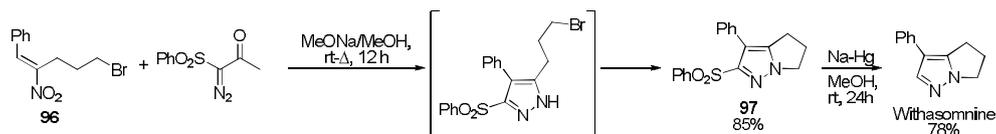
Scheme 28. Dinitroalkene-diazo compounds [3+2]-annulation.

A number of base-mediated annulations between electron-deficient diazo compounds **94** and nitroalkenes **93** were explored in recent times. In the presence of base, Ohira-Bestmann reagent (**94a**, $\text{EWG}=\text{P}(\text{O})(\text{OEt})_2$)⁴⁹ and sulfonyl diazo compounds (**94b**, $\text{EWG}=\text{SO}_2\text{R}'$)⁵⁰ undergo Michael addition to nitroalkenes followed by ring closure. Further elimination of nitrite-anion results in the formation of *NH*-pyrazoles **95** (Scheme 29).



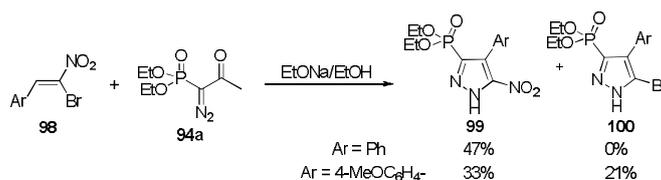
Scheme 29. Base-mediated [3+2]-annulation of electron-deficient diazo compounds with nitroalkenes.

This methodology was used in the total synthesis of the alkaloid withasomnine. One of the routes involved tandem annulation-intramolecular nucleophilic substitution with nitroalkene **96** followed by reductive desulfonation (Scheme 30).⁵⁰



Scheme 30. Synthesis of the alkaloid withasomnine *via* annulation of nitroalkene **96**.

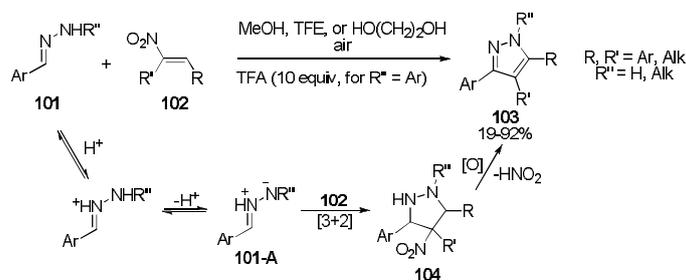
Importantly, in the case of bromonitroalkenes **98**, nitro-substituted *NH*-pyrazole **99** was a major product, but switching the nitroalkene from phenyl- to *p*-anisyl-substituted substrate resulted in the formation of a mixture of products (**99**:**100**=1.6:1, Scheme 31).⁴⁹ This shows, therefore, that the electronic properties of the nitroalkenes may also play a significant role in determining the elimination outcome, even though the reasons of this dependence are unclear.



Scheme 31. Base-mediated [3+2]-annulation of the Ohira-Bestmann reagent with α -bromonitroalkene.

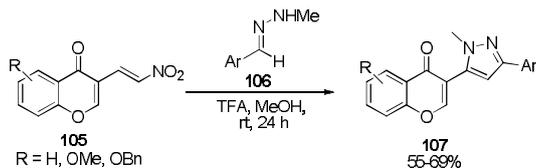
3.2.2. Oxidative annulation of nitroalkenes with hydrazones

Nitroalkenes **102** were also involved in oxidative annulation reactions with hydrazones **101**, which are readily available 1,3-dipole precursors. In the first kind of reactions, acid catalysis is usually used to generate azomethine imine **101-A** *in situ*, which then undergoes cycloaddition with nitroalkene **102**. The oxidation easily proceeds under air as the only oxidant. It is worth noting that utilization of a protic solvent is crucial for this reaction, because the formation of the actual 1,3-dipole, azomethine imine **101-A**, proceeds *via* protonation of the hydrazone. The particular conditions vary depending on the nature of the initial reagents. For more electron-rich *N*-alkylhydrazones, the reaction proceeds under mild conditions (MeOH, rt),⁵¹ while more electron-deficient *N*-arylhydrazones require more acidic trifluoroethanol and TFA as a promoter or harsher conditions (heating in ethylene glycol) (Scheme 32).⁵² Higher yields and reaction rates were observed for electron-rich hydrazones and electron-poor nitroalkenes. Although the mechanism of this annulation is a subject of discussions, according to the stereochemical studies of pyrazolidine **104** formation, a concerted mechanism was excluded due to the lack of stereospecificity at this step (both (*E*)- and (*Z*)-isomers of nitroalkene **102** result in the formation of the same isomer of pyrazolidine).⁵² However, the exact mechanistic details of the stepwise formation of **103** are unclear.



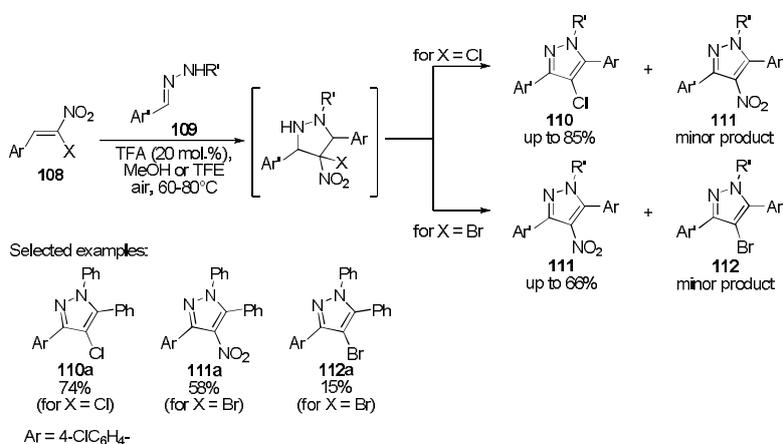
Scheme 32. Oxidative annulation of nitroalkenes **102** with alkyl- and arylhydrazones **101**.

The acid-mediated method has been applied to the multifunctional chromone-derived nitroalkenes **105** and hydrazones **106** (Scheme 33).⁵³ The products **107** were shown to be useful drug candidates possessing good radical scavenging and α -glucosidase inhibitory activity.



Scheme 33. Oxidative annulation of chromone-derived nitroalkenes **105** with alkyhydrazones **106**.

The outcome of the reaction in the case of α -chloro and α -bromonitroalkenes **108** was additionally studied.¹⁶ First, the low reactivity of these nitroalkenes required catalysis by TFA (0.2 equiv). In the case of chloronitroalkenes 4-chloropyrazoles **110** were observed as the main products in the vast majority of cases, while bromonitroalkenes afforded mixtures of both products **111-112** in different ratios (Scheme 34). The more electron-rich nature of hydrazones favors HBr elimination and formation of nitro-substituted pyrazoles **111**. In several cases the reaction was also complicated by formation of 4-unsubstituted pyrazoles, arising by double HBr and HNO_2 elimination accompanied by migration of double bond. As both of these eliminations are highly favorable, these processes are in competition, causing the outcome to be rather unpredictable and strongly dependent on substituents of both reactants.



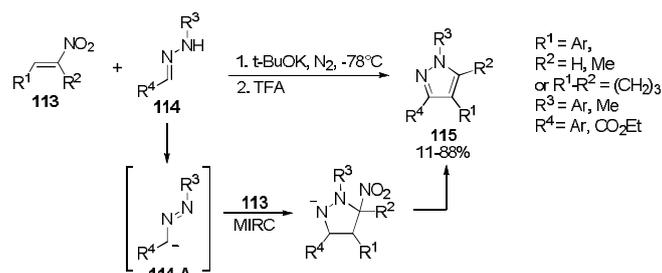
Scheme 34. Oxidative annulation of α -halonitroalkenes **108** with hydrazones under acidic conditions.

The regioselectivity of the process may be switched to the formation of substituted pyrazoles **115** if basic conditions are applied followed by quenching with acid. This peculiar outcome arises from the stepwise mechanism with the Michael addition of carbon-centered hydrazone anion **114-A** to the nitroalkene **113** being the key step (Scheme 35).⁵⁴

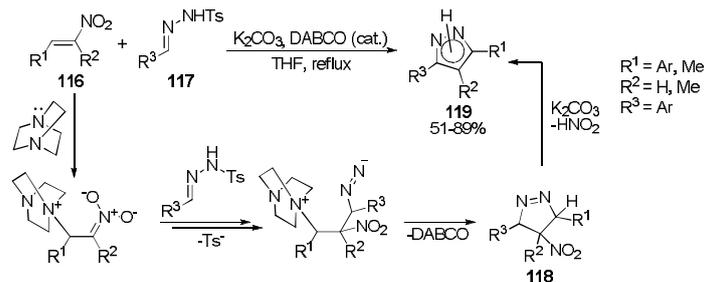
In the presence of DABCO, *N*-tosylhydrazones **117** were successfully applied to the preparation of *NH*-pyrazoles **119**,⁵⁵ the synthesis of which was not reported by acid-mediated methods (Scheme 36). The mechanism of this transformation is different from the previously mentioned base-mediated reaction and resembles the Baylis-Hillman reaction. The Michael addition of DABCO to nitroalkene **116** generates the corresponding anion, which attacks the electrophilic carbon center of the tosylhydrazone, resulting in elimination of tosyl anion and ring closure to form pyrazoline **118**. Elimination of HNO_2 and hydrogen shift leads to the target *NH*-pyrazole **119**.

Interestingly, under mild conditions or in cases where the aromatic hydrazones are derived from electron-deficient aldehydes (*e.g.* ethyl glyoxylate, trifluoroacetaldehyde), the annulation stops at the level of

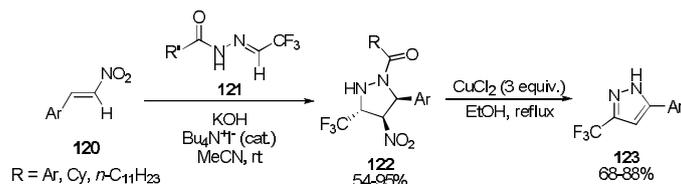
the pyrazolidines, which are relatively stable towards oxidation. Therefore, a few methods for the synthesis of pyrazolidines were reported.^{12,13} CF₃-Substituted *N*-acylpyrazolidines **122** can be converted into 3-trifluoromethylpyrazoles **123** by treatment with CuCl₂ (Scheme 37). In this step, a two-electron oxidation, elimination of HNO₂ and *N*-deacylation of pyrazolidine take place.



Scheme 35. Oxidative annulation of hydrazones **114** with nitroalkenes **113** under basic conditions.

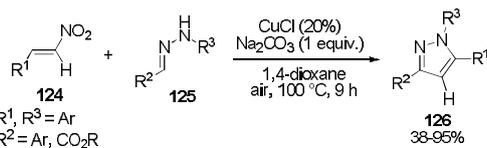


Scheme 36. Synthesis of *NH*-pyrazoles **119** by DABCO-mediated annulation of tosylhydrazones **117** with nitroalkenes **116**.



Scheme 37. Synthesis of trifluoromethylated pyrazolidines **122** and their conversion into pyrazoles **123**.

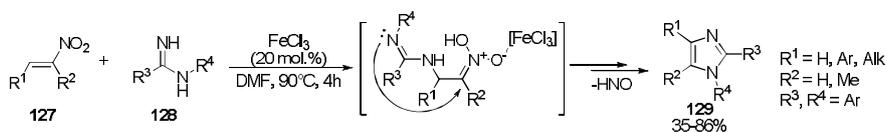
Similarly, the oxidative annulation of hydrazones **125** derived from either aryl- or ester-substituted aldehydes with α -unsubstituted nitroalkenes **124** mediated by CuCl/air oxidative system under basic conditions (Na₂CO₃, 1,4-dioxane) was reported to afford quite pharmaceutically attractive 3-ester-substituted pyrazoles **126** (R²=CO₂R, Scheme 38).⁵⁶



Scheme 38. CuCl-mediated oxidative annulation of nitroalkenes with hydrazones.

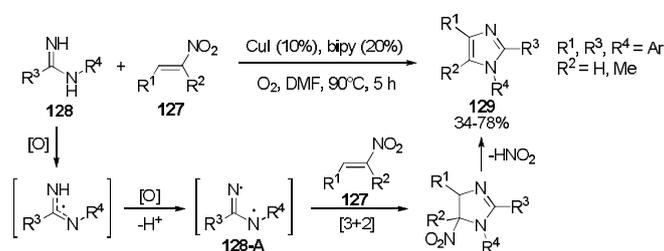
3.3. Synthesis of imidazoles and imidazo[1,2-a]pyridines

Imidazoles and imidazo[1,2-a]pyridines were synthesized from nitroalkenes **127** by several methods. The mechanism of these transformations usually involves oxidative and/or self-oxidative annulation. For the synthesis of imidazole **129**, substituted amidines **128** are the reaction partners. In one of the protocols, the amidine-nitroalkene annulation is catalyzed by 20 mol. % FeCl₃, which acts as a Lewis acid rather than oxidant. The proposed mechanism involves Michael addition followed by self-oxidative ring formation (see Scheme 7) accompanied by elimination of nitroxyl (Scheme 39).⁵⁷



Scheme 39. Nitroalkene-amidine self-oxidative annulation.

Also, the oxidative annulation mechanism rather than the self-oxidative one is known for this type of annulation. Thus, another general method of amidine-nitroalkene cycloaddition involves the rather strong oxidative system CuI/bipy under an oxygen atmosphere in DMF.⁵⁸ This and the related Cu/O₂ systems are frequently employed in oxidative annulation reactions due to the formation of Cu(III) species or copper peroxy complexes under these conditions, which are the active oxidants in copper-mediated aerobic reactions.⁵⁹ Therefore, a double oxidation of amidine **128** to biradical **128-A** was proposed as a key step for this annulation. After that, the biradical undergoes [3+2]-cycloaddition with nitroalkene **127** and elimination of HNO₂ forming product **129** (Scheme 40). Both of these methods of imidazole synthesis are supposed to be universal and tolerate a broad range of variously substituted nitroalkenes and C,N-disubstituted amidines.



Scheme 40. Cu(I)/O₂-mediated oxidative nitroalkene-amidine annulation.

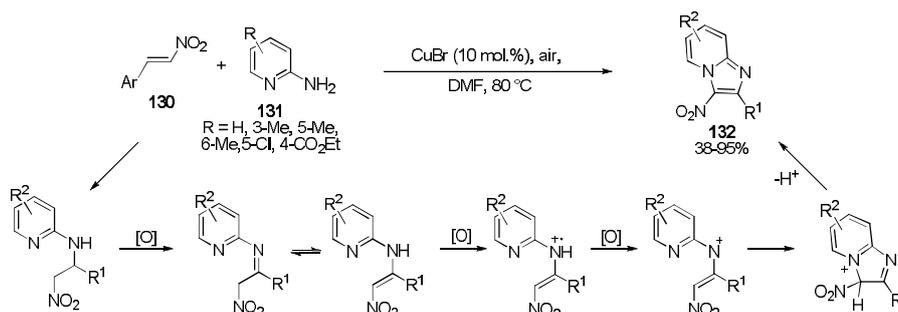
The synthesis of imidazo[1,2-a]pyridines from 2-aminopyridines **131** and nitroalkenes **130** is similar to the previously described amidine-nitroalkene annulation. If strong oxidants without Lewis acid properties are applied, 3-nitro-imidazo[1,2-a]pyridines **132** are formed as products, as a result of excessive oxidation of pre-formed intermediates. The oxidants tested include CuBr/O₂ (Scheme 41),⁶⁰ I₂/H₂O₂⁶¹ and NaClO₂,⁶² all of which are reported to give the target nitrated heterocycles in high yields.

The mechanism in this case involves Michael addition as a first step followed by stepwise four-electron radical oxidation of the exocyclic nitrogen atom to form a nitrenium cation, which undergoes cyclization to the target heterocyclic system. It is worth noting that in these cases the cyclization starts from the Michael addition of exocyclic amino group rather than the pyridinium nitrogen atom.

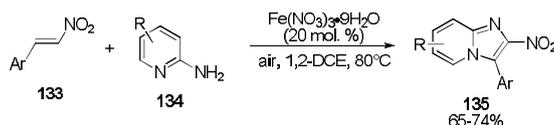
In the case of the Fe(NO₃)₃-mediated protocol, isomeric 2-nitro-imidazo[1,2-a]pyridines **135** are produced from aromatic nitroalkenes (Scheme 42).⁶³

The synthesis of denitrated imidazo[1,2-a]pyridines, proceeding *via* a self-oxidative mechanism without excessive oxidation, has been reported. The FeCl₃-mediated reaction gives 2-substituted heterocycles **137** (Scheme 43)⁶⁴ similarly to the formation of imidazoles **129** (see Scheme 39). In contrast, application of catalytical amounts of Et₃N in the presence of H₂O₂ as the oxidant leads to 3-arylsubstituted imidazo[1,2-a]pyridines **138**.⁶⁵ The regioselectivity outcome of the Et₃N/H₂O₂-mediated process was explained by coordination of Et₃N to the exocyclic amino group, which activates the endocyclic pyridinium

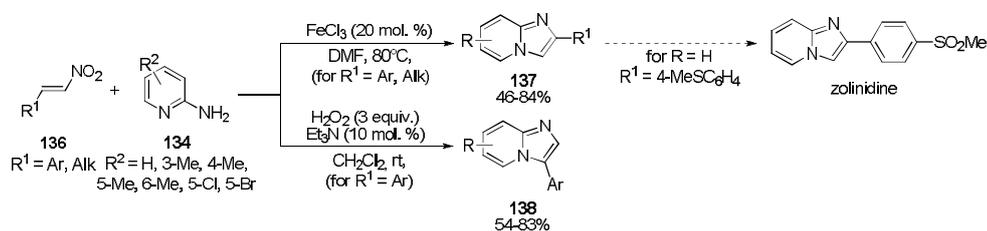
nitrogen and leads to a change in regioselectivity. Specifically substituted product **137** can be used as a direct precursor of the drug zolindine.⁶⁴



Scheme 41. Synthesis of 3-nitro-imidazo[1,2-a]pyridines **132** via nitroalkene-aminopyridine annulation.



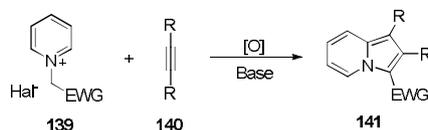
Scheme 42. Fe(NO₃)₃-catalyzed oxidative annulation of nitroalkenes **133** with 2-aminopyridines **134**.



Scheme 43. Synthesis of denitrated imidazo[1,2-a]pyridines from nitroalkenes with different regioselectivity.

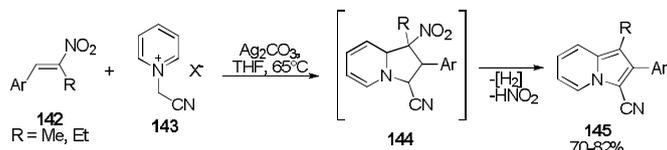
3.4. Synthesis of indolizines and related heterocycles

Indolizines as well as the related aza-heterocycles are available through various routes, including 1,3-dipolar cycloaddition.⁶⁶ For instance, the synthesis of indolizines **141** is widely known for pyridinium salts **139** and alkynes **140** as 2π -components (Scheme 44).



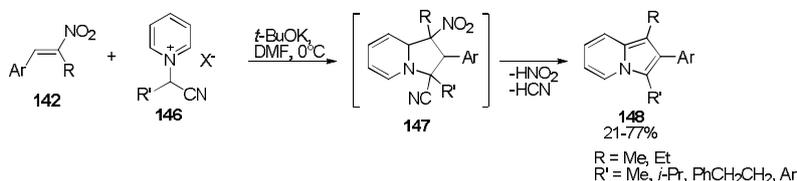
Scheme 44. Oxidative annulation of pyridinium ylides with alkynes for the synthesis of indolizines.

However, the annulation of pyridinium ylides with nitroalkenes is far less studied. This type of oxidative annulation in the presence of an external oxidant is supposed to be a useful route to multifunctional indolizines. In one of the first reports the annulation of cyano-substituted pyridinium salt **143** with α -alkylsubstituted nitroalkenes **142** in the presence of Ag₂CO₃ as a promoter, afforded 3-cyanosubstituted indolizines **145** in good to excellent yields (Scheme 45).⁶⁷ Silver carbonate is a convenient reagent for the reaction, as it acts both as base and oxidant in this reaction; however, its elevated price is a drawback of the method.



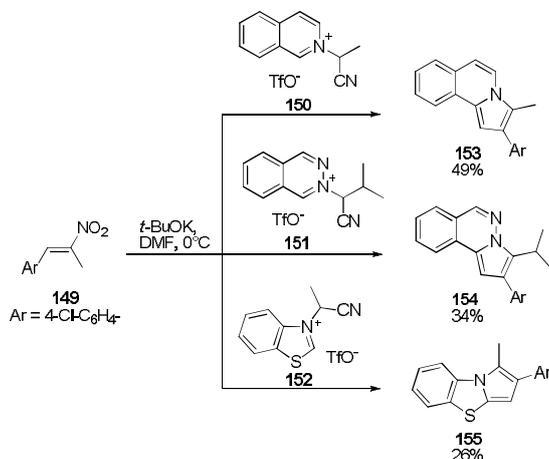
Scheme 45. Ag_2CO_3 -mediated annulation of nitroalkenes with pyridinium ylides.

The same authors⁶⁷ have reported the annulation of nitroalkenes **142** with 1',1'-disubstituted pyridinium salts **146**. In this case, a double elimination of HNO_2 and HCN takes place with no oxidation involved (Scheme 46).



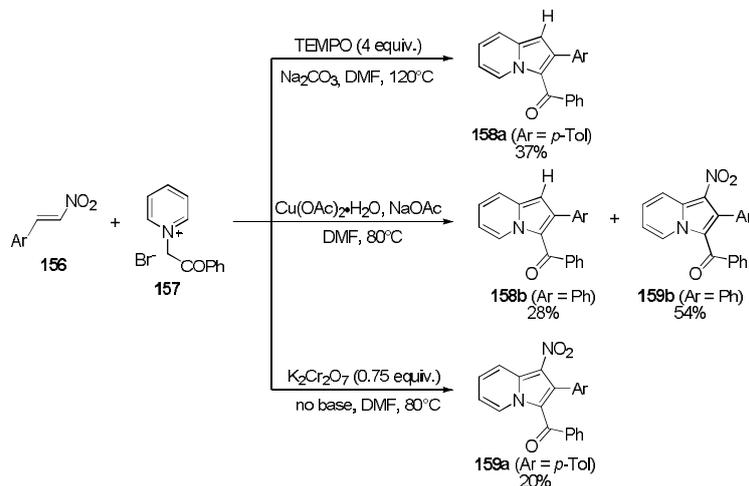
Scheme 46. Annulation of nitroalkenes with 1',1'-disubstituted pyridinium salts.

Furthermore, the scope of the annulation reaction was broadened to fused aza-heterocycles **153-155**, available from the corresponding isoquinolinium **150**, phthalazinium **151** and benzothiazolium **152** salts (Scheme 47).⁶⁷



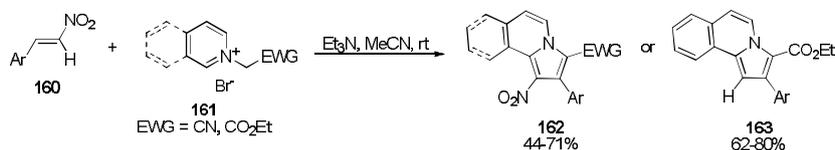
Scheme 47. [3+2]-Annulation of nitroalkenes to fused heterocycles with a bridgehead nitrogen atom.

Several other methods of indolizine synthesis were described on a few nitroalkenes **156**, where $\text{Cu}(\text{OAc})_2$,⁶⁸ $\text{K}_2\text{Cr}_2\text{O}_7$ ⁶⁹ or TEMPO⁷⁰ were used as oxidants. These reactions were not studied on a broad scope of substrates and presented as single occasional examples. In the case of TEMPO-mediated process, 1-unsubstituted indolizine **158a** was obtained chemoselectively. Copper(II) acetate monohydrate-mediated reaction led to a mixture of double oxidation product 1-nitroindolizine **159b** and denitrated derivative **158b** in a 2:1 ratio, whereas application of potassium dichromate as the oxidant led to the formation of nitroindolizine **159a** as a single product, albeit in low yield. The dependence of the outcome on the conditions may be explained both by the different strength of the oxidants and the variation in the bases employed (Scheme 48).



Scheme 48. Oxidative annulation of pyridinium ylides with α -unsubstituted nitroalkenes.

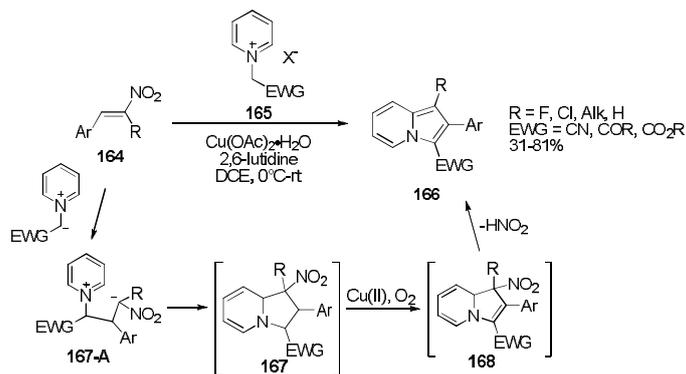
Also, the double oxidative annulation of α -unsubstituted nitroalkenes **160** with pyridinium and isoquinolinium salts **161** bearing cyano- or ethoxycarbonyl- as the electron-withdrawing groups in the presence of Et_3N as a base was reported to lead to 1-nitroindolizines **162** (Scheme 49). Corresponding denitrated pyrrolo[2,1-*a*]isoquinolines **163** were formed in the case of isoquinolinium salts possessing an ethoxycarbonyl group as the EWG.⁷¹



Scheme 49. Oxidative annulation of pyridinium ylides with α -unsubstituted nitroalkenes.

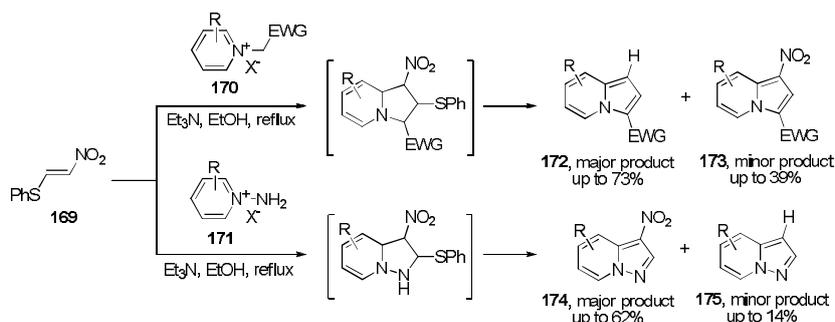
We recently developed a general method for the synthesis of substituted indolizines **166** starting from α -alkyl-, α -fluoro- and α -chloronitroalkenes **164** and various pyridinium salts **165** bearing electron-withdrawing groups (Scheme 50).⁷² Copper(II) acetate was used as a cheap and readily available oxidant and an excess of 2,6-lutidine was employed as a mild base. The latter is necessary to avoid anionic oligomerization, since application of a stronger base leads to dramatic drop in the yield. The usefulness of the Cu(II)/lutidine system for oxidative annulation may be also explained by the coordination of copper with the pyridinium ylide, incidentally similar to that postulated for azomethine ylides.⁷ The procedure is advantageous due to the broad substrate scope of nitroalkenes and pyridinium salts as well as the utilization of cheap and readily available initial reagents. The trends of the oxidative annulation for halogenated nitroalkenes with pyridinium salts are similar to those mentioned previously. Thus, annulation with α -fluoronitroalkenes **164** (R=F) gives 1-fluoroindolizines in good yields, whereas with α -chloronitroalkene **164** (R=Cl) 1-chloroindolizine forms as the product of HNO_2 elimination. In the case of α -bromonitroalkene **164** (R=Br), the reaction does not proceed, probably because of its high sensitivity to the steric hindrance exerted by the large bromine atom. According to both literature data and our own observations, a stepwise rather than a concerted mechanism for tetrahydroindolizine **167** formation is more probable. The rather high dependence of the reaction rate on the nature of the aryl groups in the starting nitroalkenes (with high rates for electron-poor (*e.g.* $\text{Ar}=\textit{p}\text{-NO}_2\text{C}_6\text{H}_4$) and low rates for electron-rich (*e.g.* $\text{Ar}=\textit{p}\text{-MeOC}_6\text{H}_4$) substrates) is in agreement with the dependence observed for Michael additions, which is the rate-determining step in the

process. Further transformations are supposed to involve oxidation of tetrahydroindolizine **167** by Cu(II) to form dihydroindolizine **168** and elimination of nitrous acid to form the final indolizine **166**.



Scheme 50. Cu(II)/2,6-lutidine-mediated oxidative annulation of pyridinium ylides with nitroalkenes.

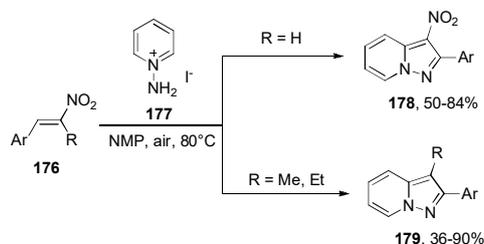
There are also several examples of synthesis of aza-analogs of indolizines, derived from pyridine-*N*-imines (*N*-aminopyridinium ylides), rather than pyridinium ylides. In the first report,⁷³ it was shown that both pyridinium **170** and aminopyridinium **171** salts react with α -thio-substituted nitroalkene **169** to give indolizines **172-173** and pyrazolo[1,5-*a*]pyridines **174-175** respectively (Scheme 51). The difference in chemoselectivity is remarkable in this case. While annulation with pyridinium salts leads to the formation of 1-unsubstituted indolizine **172** as major product in moderate to good yield, aza-annulation preferably gives nitrated pyrazolo[1,5-*a*]pyridine **174**, resulting from oxidation rather than elimination of HNO₂. The difference may be explained by the higher thermodynamic favorability of oxidation of the more electron-rich unsaturated adduct containing two nitrogen atoms.



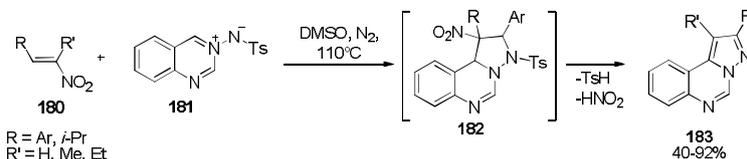
Scheme 51. Dichotomy of annulation of nitroalkene **169** with pyridinium/aminopyridinium salts.

In a recent report, 3-substituted pyrazolo[1,5-*a*]pyridines **179** were synthesized from α -alkylnitroalkenes **176** and aminopyridinium salt **177** under mild conditions (NMP as solvent and air as the only oxidant).⁷⁴ In the case of α -unsubstituted nitroalkenes one more oxidation act takes place, as far as the base-free conditions are concerned, and 3-nitrosubstituted heterocycles **178** are formed (Scheme 52).

The reaction was also studied for quinazoline-derived dipole **181**.⁷⁵ In this case, the sulfonyl group acts both as a stabilizing electron-withdrawing group and as a leaving group. Therefore, under reaction conditions (110 °C, N₂, DMSO) double elimination takes place forming pyrazolo[1,5-*c*]quinazolines **183** (Scheme 53).



Scheme 52. Synthesis of pyrazolo[1,5-a]pyridines **178-179** by oxidative annulation of nitroalkenes with aminopyridinium salts.

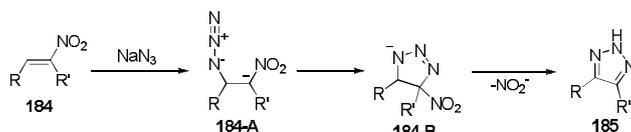


Scheme 53. Synthesis of pyrazolo[1,5-c]quinazolines **183** by annulation of nitroalkenes **180** with *N*-sulfonylimine **181**.

3.5. Synthesis of 1,2,3-triazoles

3.5.1. Synthesis of *NH*-1,2,3-triazoles

Various 1,2,3-triazoles are available by annulation of nitroalkenes with both sodium azide and organic azides. In the first case, the reaction proceeds *via* stepwise mechanism, as the Michael addition of azide-anion to the nitroalkene **184** is highly favorable. The intermediate nitronate-anion **184-A** then cyclizes into triazolone intermediate **184-B**, which undergoes elimination of nitrite thus forming *NH*-1,2,3-triazole **185** (Scheme 54). This annulation is only known to proceed in a non-oxidative manner, as application of oxidative conditions in the presence of free azide-anion may lead to side-reactions. It is important to note that the reaction is highly dependent on the concentration of the reagents, as the yields were found to drop in concentrated solution due to oligomerization of the intermediate anionic species. For most of the examples, good yields of *NH*-triazoles could be achieved in 0.1M or even more diluted medium; in some cases, slow addition of the nitroalkene to the preheated NaN_3 solution proved necessary.⁷⁶

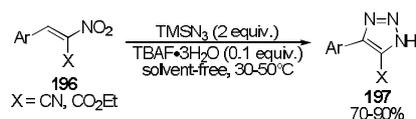


Scheme 54. Mechanism of nitroalkene- NaN_3 [3+2]-annulation

Though the sodium azide-nitroalkene cycloaddition reaction proceeds smoothly without additional catalyst in many cases,^{76,77} it is important to note that the reaction may be significantly promoted by acidic additives. Thus, various Bronsted acids (*p*-TsOH,^{78,79} HSO_3NH_2 ^{80,81}) as well as Lewis acids (ZrCl_4)⁸² were employed for the synthesis of triazoles from nitroalkenes. In recent years, several methodologies suitable for the commercial large-scale preparation of *NH*-1,2,3-triazoles from nitroalkenes with various cheap Bronsted and Lewis acids (AcOH ,⁸³ silica-supported sulfuric acid,⁸⁴ AlCl_3)⁸⁵ used as catalysts, have been developed, making the method applicable for industrial purposes.

The role of the acidic additives is in the decrease in the concentration of anionic species in the medium, known to be responsible for the undesired side-reactions, including oligo- and polymerization of nitroalkenes. One more important role of these additives is the trapping of the liberated HNO_2 . For this purpose, sodium sulfite⁸⁶ and sulfamic acid^{80,81} were used. The presence of nitrous acid can result in both side reactions (*e.g.* nitrosylation of the anionic species) and consumption of the initial azide.

The convenient synthesis of *NH*-triazoles **197** from electron-poor α -cyano and α -ester-substituted nitroalkenes **196** was achieved by reaction with TMSN_3 in the presence of a catalytic amount of TBAF under solvent-free conditions. In the case of cyanonitroalkenes, the reaction proceeds chemoselectively *via* elimination of HNO_2 rather than HCN to form 4-cyano-1,2,3-triazoles **197** (Scheme 59).⁹¹

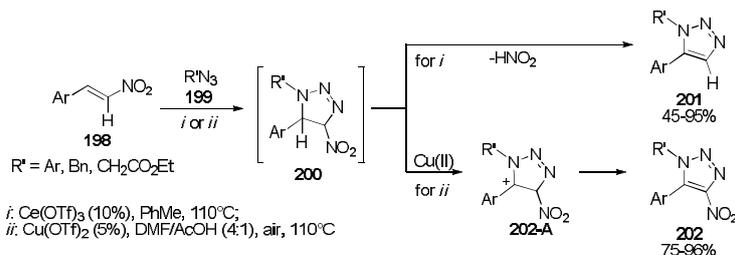


Scheme 59. Reaction of electron-deficient nitroalkenes with TMSN_3 under solvent-free conditions

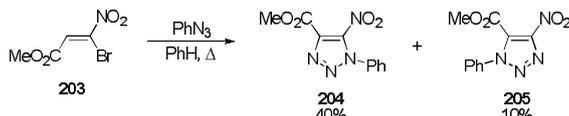
3.5.2. Synthesis of *N*-substituted 1,2,3-triazoles

The reactions of nitroalkenes **198** with organic azides **199** are significantly different comparatively to annulation with sodium azide. In this case, the concerted [3+2]-cycloaddition followed by transformation (elimination or oxidation) of the intermediate triazolone **200** into 1,2,3-triazole is accepted as the general mechanism for these processes. The most important feature of this reaction is the regioselective formation of 1,5-disubstituted 1,2,3-triazoles, which are much less available than the 1,4-disubstituted congeners that are easily prepared by the traditional copper-catalyzed click chemistry approach. This reaction strictly requires elevated temperatures⁹² and/or utilization of a Lewis⁹³ or Bronsted⁷⁸ acid as a catalyst for nitroalkene activation.

In the case of cerium(III) triflate-catalyzed reaction between α -unsubstituted nitroalkene and organic azides (benzyl- or phenylazide), the cycloaddition proceeds *via* a non-oxidative pathway leading to 4-unsubstituted triazoles **201**.⁹³ However, it is possible to completely switch the outcome of the reaction to the chemoselective formation of 4-nitrosubstituted triazoles **202** by employing $\text{Cu}(\text{OTf})_2$ as the catalyst (5 mol. %) under open air conditions.⁹⁴ For this oxidative annulation a two-step radical mechanism for the triazolone oxidation was proposed with the intermediate formation of cation **202-A** in position 5 of triazolone ring (Scheme 60). Reaction with bromonitroacrylate **203** was performed without catalyst and led to selective HBr elimination forming regioisomeric triazoles **204** and **205** (Scheme 61).⁹²



Scheme 60. Dichotomy of annulation/elimination and oxidative annulation in the synthesis of 1,5-disubstituted 1,2,3-triazoles **202,203**.



Scheme 61. Synthesis of triazoles **204** and **205** from bromonitroacrylate **203**.

4. Conclusions

In conclusion, [3+2]-annulation reactions involving nitroalkenes have been reviewed. The methods are classified from the mechanistic point of view according to annulation/elimination, oxidative annulation and self-oxidative annulation processes. Nitroalkenes have been shown to act as synthetic equivalents of alkynes in [3+2]-annulation opening routes to multifunctional nitrogen-containing heterocyclic systems.

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