

Recent advances in the chemistry of two-carbon nitro-containing synthetic equivalents

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To date, nitro-containing compounds form one of the most important classes of organic compounds. The chemistry of these molecules attracts attention primarily due to their use as high-energy reagents and drugs. Also, the introduction of a nitro group is a popular synthetic strategy for constructing new organic molecules. The present review summarizes the latest research findings of compounds bearing a nitro group on a two-carbon moiety such as aminonitroethylenes, α, α -bis(alkyl-sulfanyl)nitroalkenes and their amino derivatives, α -nitroketones, alkyl nitroacetates and nitroacetonitrile. The literature data are systematized according to the type of chemical reactions such as reactions between nucleophiles and electrophiles, various cyclization reactions, reactions at the C–H bond, *etc.* The reactivities of the said nitro compounds and the conditions of chemical transformations are compared to assess the prospects of their application. The bibliography includes 314 references.

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1. Introduction

For over one hundred and fifty years ago, organic chemists all over the world work with nitro-containing compounds. Initially, such compounds were considered as intermediates in the production of azo dyes, and were directly used as explosive materials. Currently, the use of nitro-containing structures as high-energy compounds has also not lost its relevance,¹ although modern studies of the properties of nitro derivatives are focused mostly on nitrogen-containing nitroheterocycles,^{2–5} rather than on polynitrobenzenes.⁶

For example, there are monographs and reviews on nitroazoles^{7–9} and nitroazines¹⁰ devoted to chemical properties and biological activities of the corresponding nitro compounds. Moreover, many nitro derivatives have found application as drugs.^{3, 11–14} In 2019, Nepali *et al.*¹⁵ published a detailed review on nitro compounds used in medicine, focusing on the uniqueness of the biological activity of the nitro group.

Nevertheless, the chemistry of nitro compounds is the most studied research subject for synthetic chemists. Scientists such as Henry, Konovalov, Nef, Zinin, Meyer, *etc.*,

have studied organics since their university years. Thanks to them and other scientists, we know that nitro compounds are not only an aim in themselves for synthesis but are also key intermediates in the preparation of numerous other organic molecules. At the turn of XX–XXI centuries, the frequently cited book by Noboru Ono¹⁶ entitled *The Nitro Group in Organic Synthesis* was published, which details the methods for introducing a nitro group into molecules and also chemical properties of nitro compounds.

At the same time, modern reviews are often focused on specific classes of compounds that can be represented as nitro-containing synthetic equivalents (NSEs), e.g., nitroalkenes,^{17–23} nitrodienes,²⁴ nitroalkanes,²⁵ γ -nitrocarbonyl compounds,²⁶ nitroaziridines²⁷ and nitroalkynes.²⁸ This is not surprising, since the introduction of the nitro group into molecules, not *via* direct nitration or oxidation, makes available products containing substituents that are sensitive to harsh reaction conditions. Consequently, understanding the chemical properties of such NSEs as well as their synthetic possibilities provides access to a various new approaches and compounds.

The present review considers groups of two-carbon NSEs such as α -aminonitroethylenes (**1**), α,α -di(alkylthio)-

nitroalkenes and their amino derivatives (**3**, **4**), α -nitroketones (**5**), alkyl nitroacetates (**6**) and nitroacetonitrile (**7**) (Fig. 1), and shows their diverse synthetic opportunities. Particular attention is paid to similarities and differences in the chemical behaviour of these groups. As mentioned above, the study on the synthetic potential of such compounds is necessary, first of all, to understand how to implement the related synthetic strategies, since in some cases the simplest or the only approach to the target molecule requires the use of these NSEs. Accordingly, with new methods for the modification of low-molecular-weight nitro compounds, the analysis of modern trends in the chemistry of such structures is very relevant, especially considering that these compounds, until now, have never been explored within a single study.^{16, 29–32}

It should be noted that the definition two-carbon for a fragment of a molecule is not canonical. In this review, this term is proposed to be applied to those structures whose central fragment contains two carbon atoms linked by a single or double bond. One of these atoms contains an NO₂ moiety, which causes a special distribution of electrons in the molecule.

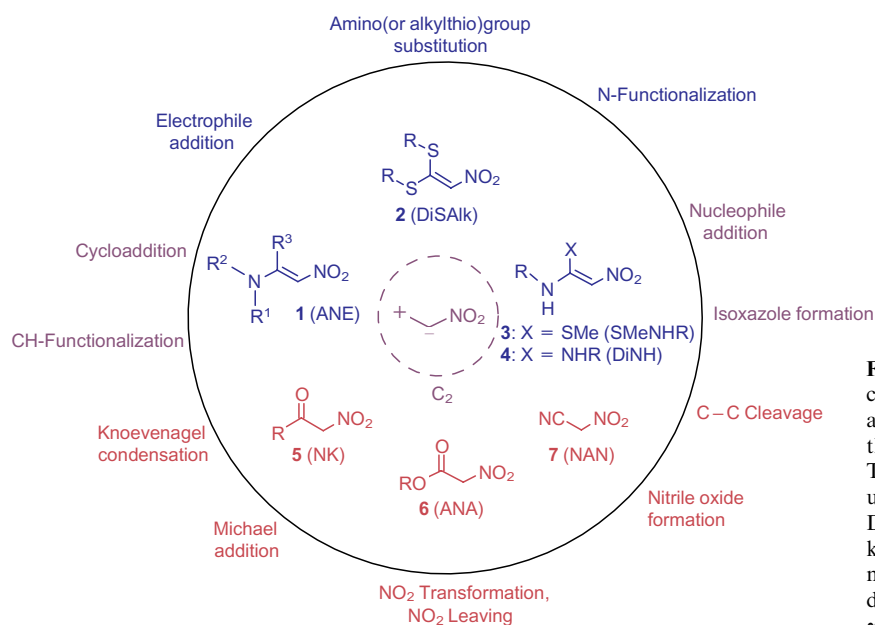


Figure 1. Structures of nitro-containing synthetic equivalents and possible transformations with their participation.

The following abbreviations are used: ANE is aminonitroethylene, DiSAIk is α,α -di(alkylthio)nitroalkene, SMeNHR is (alkylthio)aminonitroalkene, DiNH is α,α -di(amino)nitroalkene, NK is α -nitroketone, ANA is alkyl nitroacetate, NAN is nitroacetonitrile.

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2. Conjugated nitroalkenes

2.1. α -Aminoethylenes

α -Aminonitroethylenes, like nitroacetonitrile, form rather underexplored group of NSEs. Apparently, this is due to the few available methods for the synthesis of such push–pull structures. At the same time, α -aminonitroethylenes have great synthetic potential; the main routes for their modification are depicted in Fig. 2, and the most common methods for the synthesis of these compounds can be found in publications.^{33–35}

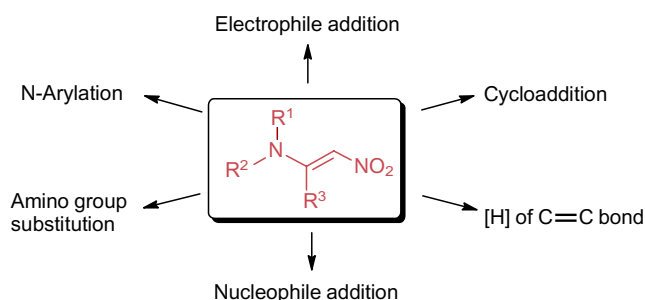


Figure 2. Possible ways to modify α -aminonitroethylene.

A key factor governing the chemical properties of ANEs and DiSAIk, is the possibility of imine–enamine tautomerism at $R^1 = H$. In this case, the carbon atom adjacent to the nitro group, and the NH moiety become available to the reaction with various electrophiles. Moreover, when using transition metal catalysis or oxidizing systems, the CH bond is modified.

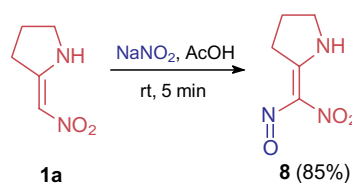
2.1.1. Reactions with electrophiles

In 2020, Pilipecz *et al.*³⁶ carried out nitrosation of (nitromethylene)pyrrolidin-2-yl **1a** to study chemical properties of 2-[nitro(nitroso)methylene]pyrrolidine (**8**). The reaction is completed in just a few minutes. The authors also noted that product **8** decomposes in a day when stored at room temperature (rt), however, it can be stored in the refrigerator for over a week (Scheme 1).

Alekszi-Kaszás *et al.*³⁷ studied the Mannich reaction of the same compound **1a** with C-electrophiles. The use of a double excess of formaldehyde (as 35% formaline) and primary aromatic amine provided 4-nitro-1,2,3,5,6,7-hexa-

Pilipecz (2020)

Scheme 1



hydropyrrolo[1,2-*c*]pyrimidines **9a–d** (Scheme 2). Initially, it is the C-atom bound to the nitro group that is attacked by the electrophile. This was demonstrated by the reaction of NSE **1a** with an alkylated benzotriazole yielding product **10** (see Scheme 2).

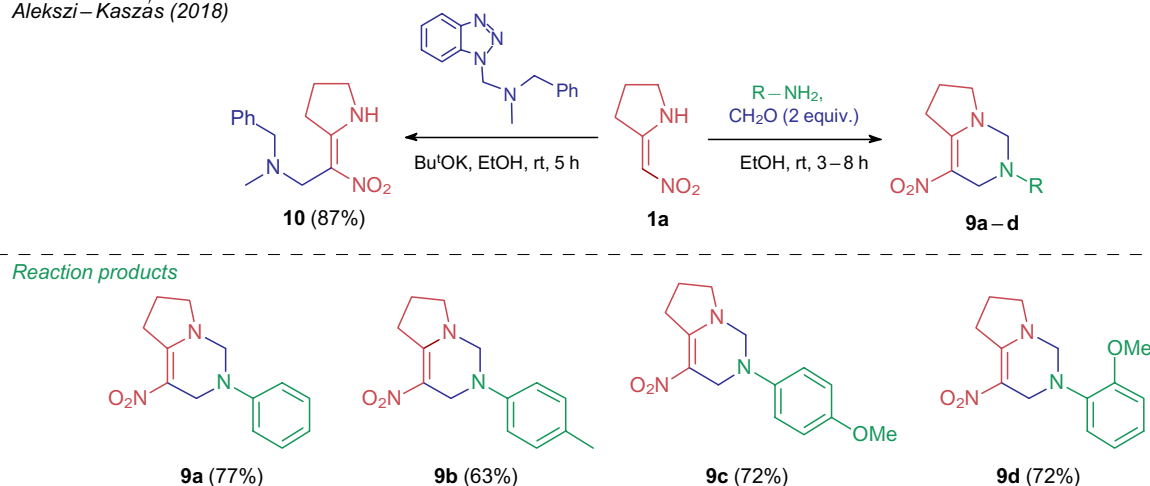
In 2019, Lyapustin *et al.*^{38,39} found that 1-morpholino-2-nitroalkenes **1** react with boron trifluoride etherate in alcohol to give the corresponding nitroalkynes **11** (Scheme 3). These products were reacted *in situ* with aminoazoles **12** to afford azolylenamines **13**, capable of heterocyclization with aldehydes **14** when heated in the same reaction system. The resultant 4,7-dihydro-6-nitroazolo[1,5-*a*]pyrimidines **15** were also produced using a multicomponent procedure when refluxing the starting compounds in *n*-butanol in the presence of the same Lewis acid. The plausible reaction pathway includes the formation of morpholino-containing intermediates **16** and **17**.

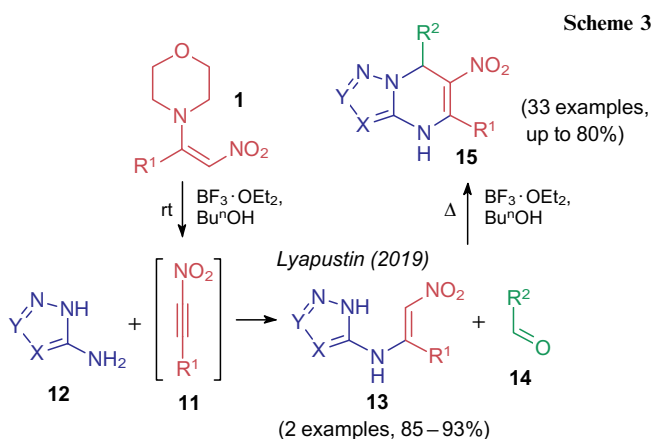
The same multicomponent reaction (MCR), when carried out in acetic acid, follows an alternative pathway. In 2020, the same research group⁴⁰ found that acetic acid disfavours the formation of nitroalkyne **11**, and the reaction can occur only if all three reactants are present. In this way, several 6-nitro-4,5,6,7-tetrahydroazolo[1,5-*a*]pyrimidines (**18a–d**) were obtained. The reaction pathway under the catalysis with Brønsted acid through formation of intermediate compounds **19**, **20** was proposed (Scheme 4).

In 2020, Zhang *et al.*⁴¹ found that the reaction of aminonitroethylenes **1** with the carbonyl moiety of substituted isatins **21** under acidic conditions leads to the cleavage of both C–N bonds, unprecedented for this NSE group, and formation of products **22** (Scheme 5). The authors suggested that the reversible addition, *e.g.*, of aminonitroethylene **1b** to protonated isatin **23** catalyzed by sulfamic acid first occurs to give adduct **24**. Further, under the action of an acid, a water molecule adds to the imine fragment of adduct **25**. Then, intermediate **26** undergoes a loss of a

Alekszi–Kaszás (2018)

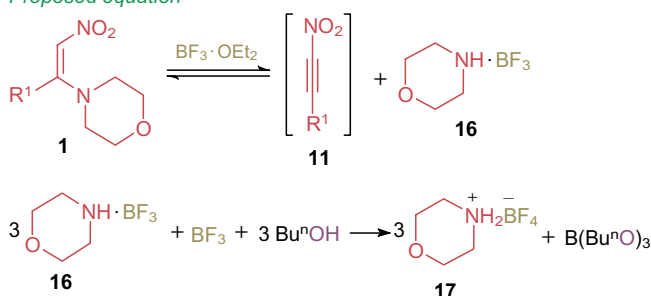
Scheme 2





R¹ = Alk; R² = Alk, Ar, Het

Proposed equation



nitrous acid molecule and an 1,2-amine migration to give a rearrangement product **27**. Finally, intermediate **27** is deprotonated and dehydrated to afford product **22**.

In 2017, Siddaraju and Prabhu⁴² described the only example of the reaction of 1-dimethylamino-2-nitroethene

(**1c**) with the *in situ* generated species containing the S–I bond. The authors argue that compound **1c** reacts with 1-phenyltetrazole-5-thiol (**28**) when heated in DMSO in the presence of iodine with the formation of sulfide **29** (Scheme 6).

Based on the control experiments, the authors found that 1-phenyltetrazole-5-thiol (**28**) first reacts with iodine to give dimer **30** and HI. The resultant dimer then reacts with iodine to afford intermediate **31** containing the S–I bond. Nucleophilic displacement of an iodide group by enamine **1c** affords product **29**. Further, iodine is regenerated by the reaction of HI with DMSO and the catalytic cycle is repeated.

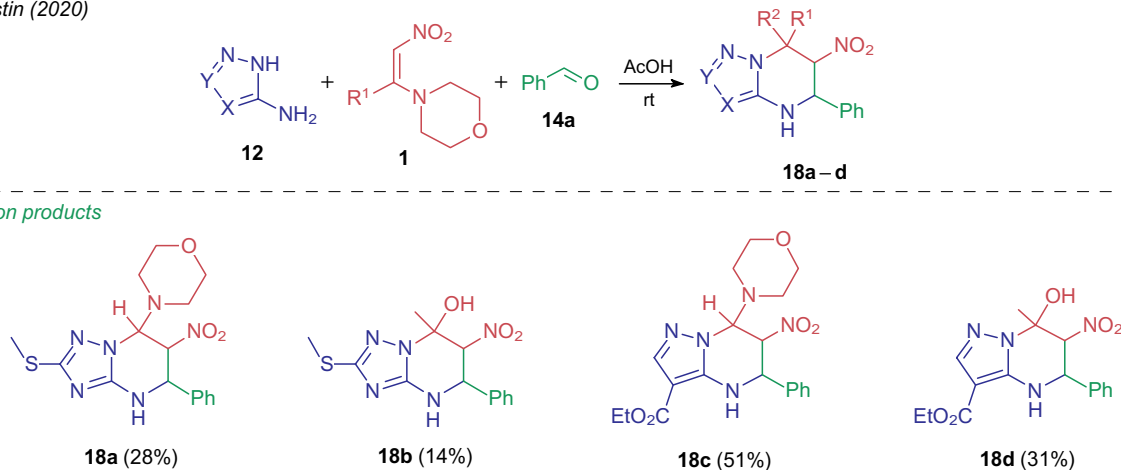
2.1.2. Reactions with nucleophiles

One reaction demonstrating the interconversion between aminonitroethylenes and α -nitroketones, is the reaction of the former compounds with alkalis. Rusinov *et al.*³³ showed that 1-morpholino-2-nitroalkenes **1** react with alcoholic solutions of sodium or potassium hydroxides at room temperature to yield the salts of α -nitrocarbonyl compounds **32a–c** (Scheme 7). Numerous methods for the preparation of such ketones are available in the literature; however, the synthesis from ANE is relatively recent.³³ This way is among the easiest approaches to produce a stable form of nitroacetic aldehyde, though the disadvantage of this method is a limitation in structural modifications of compounds **1**.

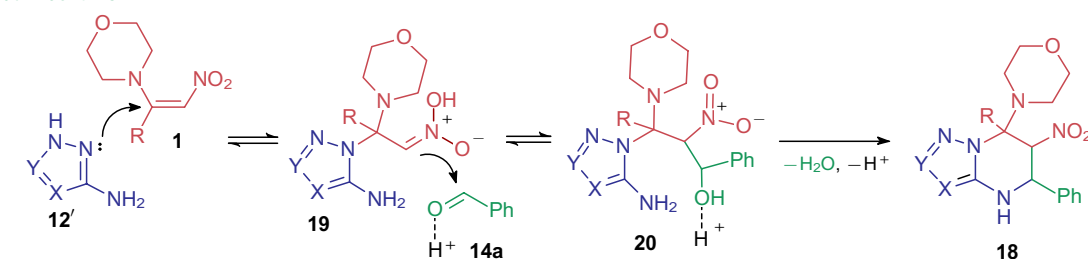
An electrophilic centre in aminonitroethylenes is prochiral, and nucleophile addition reactions imply the appearance of at least one chiral centre in the molecule. Therefore, investigations of such reactions often include the development of stereoselective synthetic approaches. For example, Ogasawara and Hayashi⁴³ improved a method to produce the antiviral drug Tamiflu [(–)-Oseltamivir, **35**] from substrates **1d** and **33** in a flow reactor. Scheme 8 illustrates

Lyapustin (2020)

Scheme 4

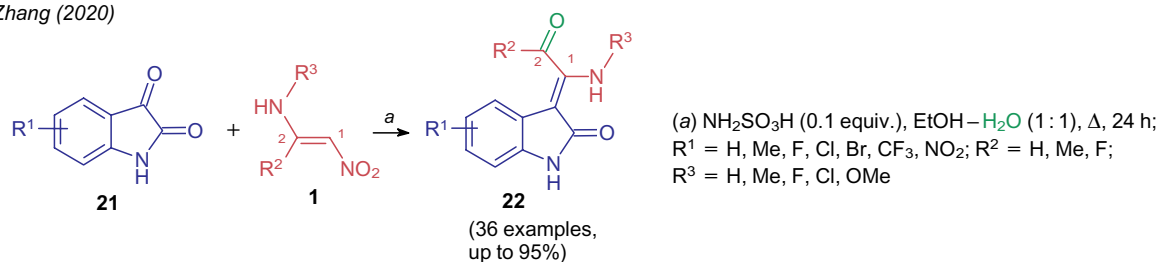


Proposed mechanism

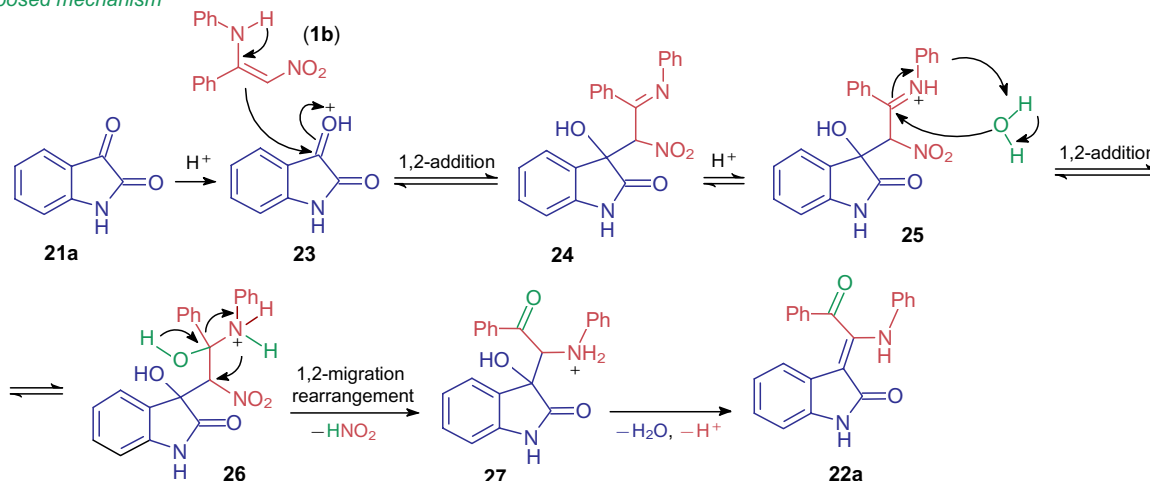


Zhang (2020)

Scheme 5

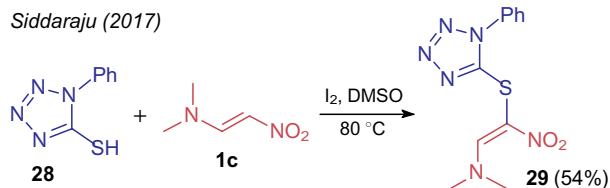


Proposed mechanism

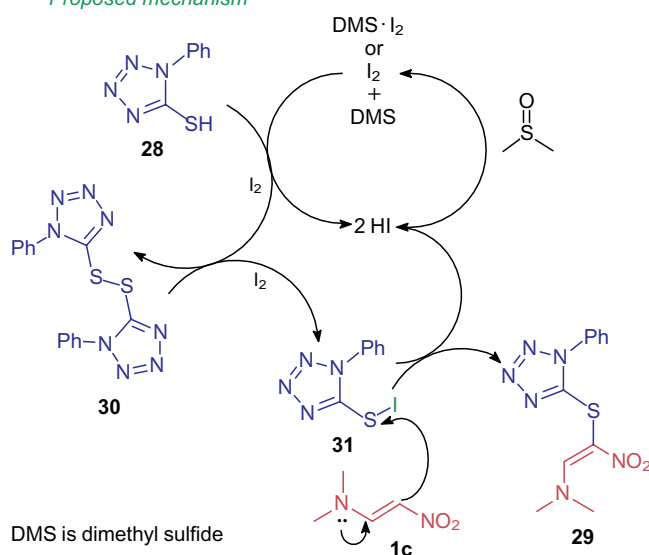


Siddaraju (2017)

Scheme 6

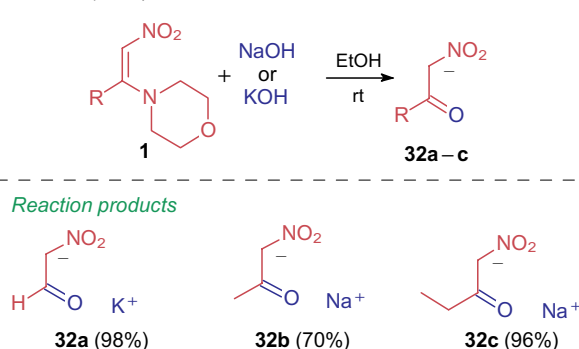


Proposed mechanism



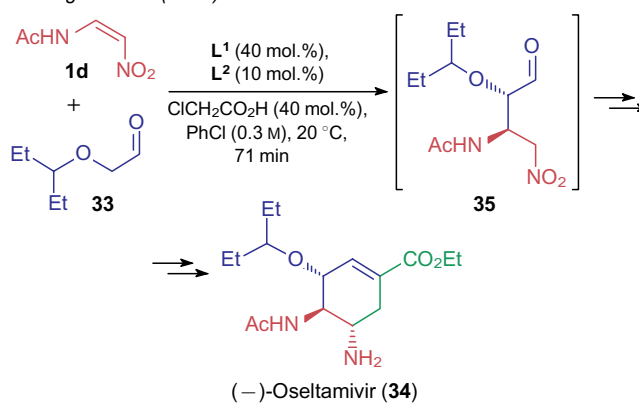
Rusinov (2020)

Scheme 7

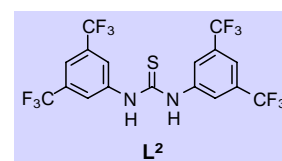
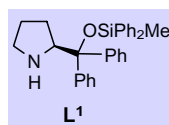


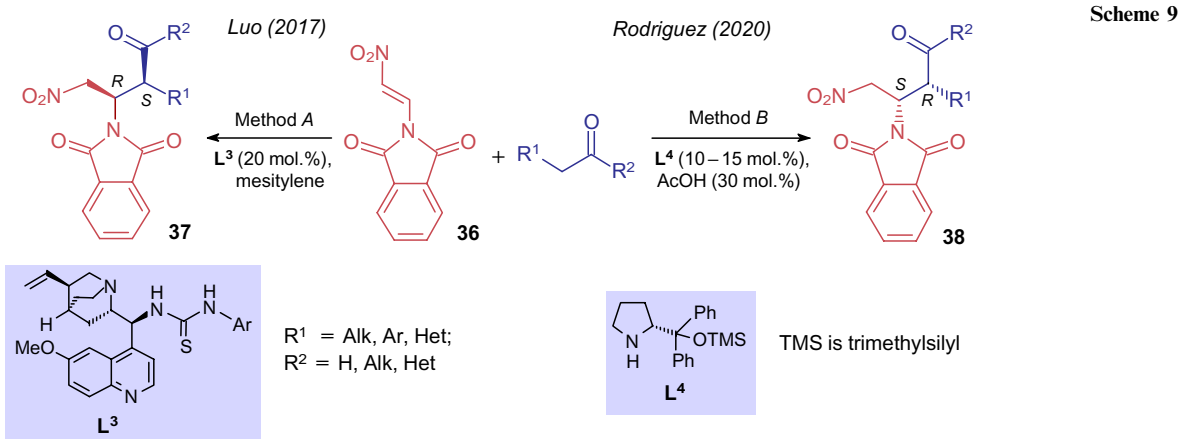
Ogasawara (2017)

Scheme 8



only the first step of this transformation, directly related to the subject of this review. Although all steps in the above scheme occur sequentially without isolation of intermediate products, the authors explored each reaction separately. It was found that the use of a modified Hayashi–Jørgensen catalyst (L^1) and 1,3-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (L^2) provides *N*-[(2*R*,3*S*)-1-nitro-4-oxo-3-(pentan-

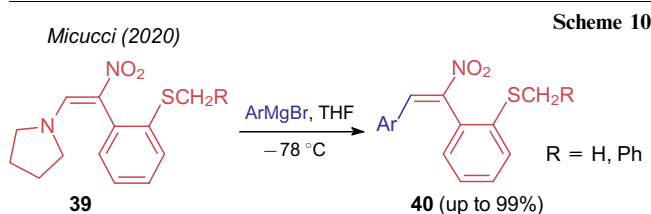




3-yloxy)butan-2-yl]acetamide (**34**) with a 97% enantiomeric excess in the first step.

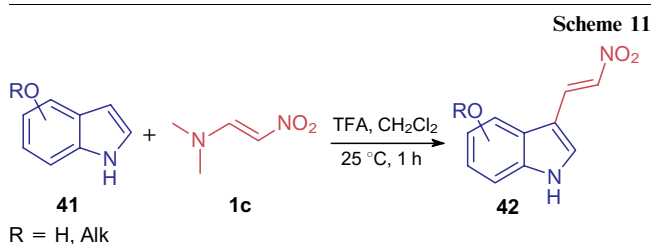
The Michael reaction involving the α -CH-acidic atom of carbonyl compounds was also studied for preparing stereoselective adducts with optically active thiourea **L**³ (method *A*)⁴⁴ as in the previous example, and pyrrolidine catalyst **L**⁴ (method *B*)⁴⁵ (Scheme 9). 2-(2-Nitrovinyl)isoindoline-1,3-dione (**36**) reacts with aldehydes and ketones to afford, depending on the reaction conditions, different stereoisomers **37** (14 examples, yields up to 99%, diastereomeric ratio (*dr*) > 20 : 1, enantiomeric excess (*ee*) (80–99%) and **38** (6 examples, yields up to 84%, *dr* from 3 : 1 to 80 : 1, 85–99% *ee*).

The reaction of compounds **39** with Grignard reagents in tetrahydrofuran is reported,⁴⁶ in which an amino moiety is almost quantitatively displaced with a C-nucleophile to give 2-(1-nitro-2-arylviny)phenyl sulfides **40** (Scheme 10).



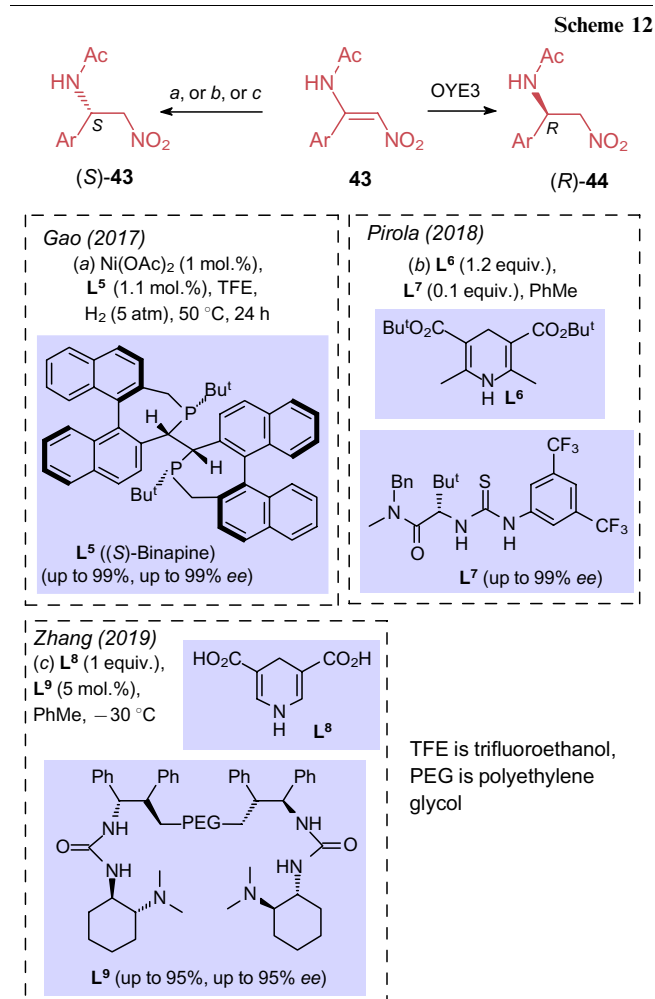
One of the common applications of ANEs is the introduction of a nitrovinyl group into indoles **41** for the further synthesis of the corresponding biologically active compounds from derivatives **42**.^{47–50} Such procedure is mainly carried out in methylene chloride in the presence of trifluoroacetic acid (TFA) (Scheme 11).

The role of trifluoroacetic acid in this reaction is likely to activate ANE. However, the cited publications did not provide any data on the use of other acids in this transformation or detailed studies on the mechanism of the process.



2.1.3. Reduction of the double bond

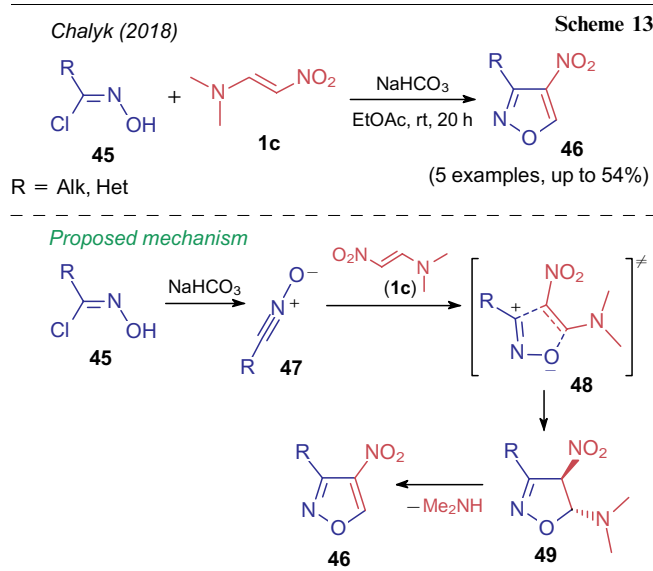
Hydrogenation of the double bond of aminonitroalkenes, similar to the addition of nucleophiles, results in the formation of a chiral centre. Accordingly, depending on the structure, this can produce both *R*- or *S*-isomers and also a racemate if there is no need for a stereoselective product. Thus, in 2017, Brenna *et al.*³⁵ pioneered in bio-reduction of ANE in the presence of an enzyme (reductase) in high yields (up to 88%) and with high enantioselectivity (up to 99%). When reducing the substrates **43** with Old Yellow Enzymes 3 (OYE3), isomers (*R*)-**44** were the major products (Scheme 12). A few publications addressed the



synthesis of their epimers (*S*)-**44**. For example, Gao *et al.*⁵¹ carried out hydrogenation with hydrogen gas using nickel acetate and (*S*)-Binapine ligand (**L**⁵). This procedure features excellent stereoselectivity and high conversion rates. Pirola *et al.*⁵² described in detail the use of a flow reactor to reduce ANE in the presence of an organocatalyst based on dihydropyrimidine (**L**⁶) and thiourea (**L**⁷). The authors optimized the protocol and further reduced the nitro group under the same continuous-flow conditions. Zhang and Shi⁵³ accomplished the reduction of nitroenamines in the presence of dihydropyrimidine (**L**⁸) and polyethylene glycol organocatalyst (**L**⁹). However, the authors evaluated the enantiomeric purity of the products without establishing the absolute configuration.

2.1.4. Cycloaddition reactions

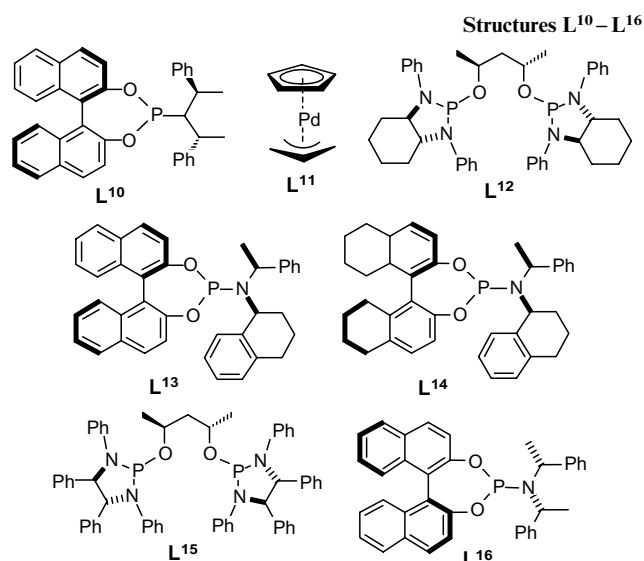
In 2018, Chalyk *et al.*⁵⁴ reported their findings on cycloaddition of ANEs to halooxime **45** to prepare 4-nitroisoxazoles **46** (Scheme 13). The plausible mechanism suggests the reaction of halooxime **45** with sodium hydrocarbonate to deliver nitrile oxide **47**. Then, intermediate **47** enters the pericyclic reaction with 1-dimethylamino-2-nitroalkene **1c**, which leads to the aromatization of the system *via* intermediate state **48** and intermediate **49**.



In the present review, the synthesis of isoxazoles from NSE is discussed below in the relevant sections, however, this example is the only one, in which the nitro group is not directly involved in the formation of the heterocycle.

A series of works of the research group led by Trost^{55–60} concerns the synthesis of 2-amino-1-nitrocyclopentanes (Table 1, lines 1–6) and -cyclohexanes (see Table 1, lines 7–9) from the appropriate allyl (*tert*-butyl) carbonates and aminonitroethylenes. The authors mainly consider the variability of substrates and the effect of the catalyst on the stereoselectivity of the process. In all cases, palladium catalysts [e.g., in the form of complexes with dibenzylideneacetone (dba) or cyclopentadiene (Cp)] and phosphorus-containing ligands **L**¹⁰–**L**¹⁶ were used.

To prepare spiroindoles **51** from oxindoles **50** and aminonitroethylene **1d**, Du *et al.*⁶¹ used an optically active catalyst based on thiourea **L**¹⁷. Depending on substrates in choice, enantioselectivity of the process varied over a wide



range, while diastereoselectivity, on the contrary, was quite high (Scheme 14).

In 2019, two publications of the Shuvalov's group^{62,63} appeared on the reaction of ANEs with 1,3-dicarbonyl compounds furnishing 3-nitropyridines **52**, **53** (Scheme 15). The study⁶² concerned only the reaction between nitroenamines **1** and hydroxymethylenecyclohexanone when heated without solvent, while in the publication,⁶³ the scope of the starting carbonyl compounds was significantly expanded. The synthesis was carried out in acetic acid to improve the yield of the product. Moreover, the reaction of nitroenamines **1** with β,γ -diketocarboxylate was carried out.

Lukashenko *et al.*⁶⁴ described the reaction of compound **1a** with an intermediate diene **54** generated by heating 1-[(dimethylamino)methyl]naphthalen-2-ols **55** in acetic acid (Scheme 16). According to the authors, the reaction follows the [4+2]-cycloaddition route, however, the resulting ring system **56** eventually undergoes ring-opening to give the Mannich product **57**.

In 2021, Lindsay *et al.*⁶⁵ showed that *N*-aryl-substituted aminonitroethylenes are prone to intramolecular cyclization under oxidative conditions. To carry out this reaction, the authors developed an oxidative system, in which arylaminonitroethylenes **1** produced 3-nitroindoles **58** in an electrochemical cell in the presence of KI catalyst (Scheme 17). Through a series of 13 control experiments, on the example of substrate **1e**, the authors proposed a reaction mechanism, in which the process is initiated by electron transfer from nitroenamine to an iodine atom at the anode to generate a cation radical **59**. Further, after the formation of a new C–C bond and deprotonation of a species **60**, the radical intermediate **61** at the cathode transforms into the anionic form **62**, which is protonated to give 3-nitro-2-phenyl-2,3-dihydroindole (**63**). Under electrochemical cell conditions, semiproduct **63** undergoes autoaromatization to afford product **58a**.

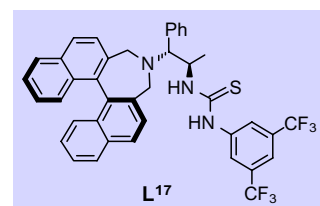
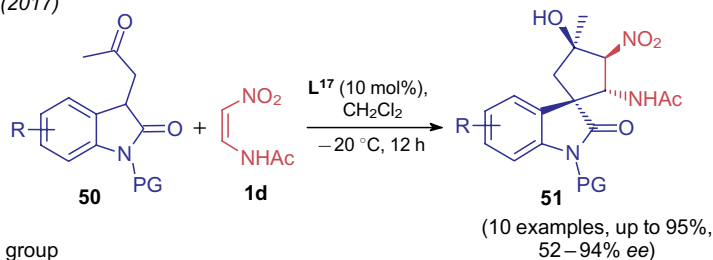
2.1.5. Other reactions

This subsection include reactions that do not formally fall into the above-mentioned classifications, and can not be grouped in any way, since they are rarely mentioned in the literature. For example, Cheng *et al.*⁶⁶ demonstrated the possibility of oxidative coupling of (*E*)-*N,N*-dimethyl-2-nitroetheneamine (**1c**) with 1,3-diphenylprop-1-ene (**64**) in

Table 1. Synthesis of nitro-containing cyclopentanes and cyclohexanes based on aminonitroethylenes.

No.	Substrate	Aminonitroethylene	Product	Catalyst	Reaction conditions	Yield (%) (selectivity)	Ref.
1	 (Boc = C(O)OBu ^t)			Pd ₂ (dba) ₃ (2.5 mol.%), L ¹⁰ (10 mol.%)	PhMe, argon, 4 °C, 4 h	up to 95 (<i>dr</i> = >20 : 1, up to 92% <i>ee</i>)	55
2				L ¹¹ (5 mmol.%), L ¹² (6 mmol.%)	1,4-dioxane, 50 °C, 12 h	73 (<i>dr</i> = >20 : 1, 94% <i>ee</i>)	56
3	 R = Alk, Ar, Het			Pd ₂ (dba) ₃ ·CHCl ₃ (2.5 mol.%), L ¹² (6 mol.%)	1,4-dioxane, 50 °C, 12 h	up to 94 (<i>dr</i> = >15 : 1, up to 99% <i>ee</i>)	57
4				[Pd(cinnamyl)Cp] (2 mol.%), L ¹² (3 mol.%)	B(OEt) ₃ (15 mol.%), Et ₂ BOMe (15 mol.%), 1,4-dioxane, 60 °C, 1 h	95 (<i>dr</i> = 13 : 1, 88% <i>ee</i>)	58
5	 R = Alk, Ar, Het			[CpPd(η ³ -C ₃ H ₅)] (5 mol.%), L ¹² (6 mol.%)	PhMe, 23 °C, 20 h	< 90 (<i>dr</i> from 3.7 : 1 to 20 : 1 up to 99% <i>ee</i>)	59
6	 R = CN, CO ₂ Me			Pd ₂ (dba) ₃ (2.5 mol.%), L ¹³ (12 mmol.%)	PhMe, rt, 24 h	up to 80 (<i>dr</i> = >15 : 1, up to 91% <i>ee</i>)	60
7	 R ¹ , R ² = CN, CO ₂ Alk, N=CPh ₂			Pd ₂ (dba) ₃ (1.0–2.5 mol.%), L ¹³ (12 mmol.%) or L ¹⁴ (4 mmol.%)	PhMe, 4 °C, 24 h	up to 94 (<i>dr</i> from 2.0 : 1 to 15 : 1, up to 95% <i>ee</i>)	60
8				Pd ₂ (dba) ₃ (2.5 mol.%), X = O: L ¹² (6 mol.%), X = NAlk: L ¹⁵ (6 mol.%)	PhMe, rt, 24 h	up to 81 (<i>dr</i> from 2.3 : 1 to 15 : 1, up to 93% <i>ee</i>)	60
9	 2-Py (pyridyl), quinolin-2-yl, isoquinolin-1-yl, etc.			Pd ₂ (dba) ₃ (2.5 mmol.%), L ¹⁶ (12 mmol.%)	PhMe, 4 °C, 24 h	up to 92 (<i>dr</i> from 1.2 : 1 to 15 : 1, up to 95% <i>ee</i>)	60

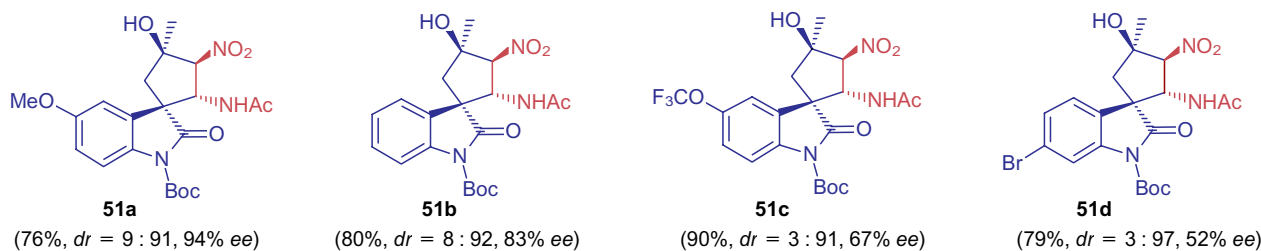
Du (2017)



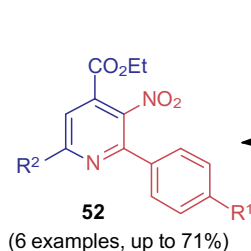
Scheme 14

PG is protecting group

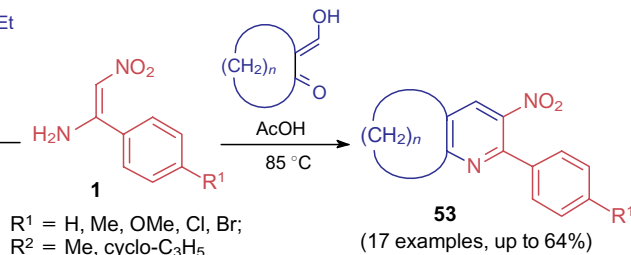
Selected examples



Shuvalov (*SynLett* 2019)



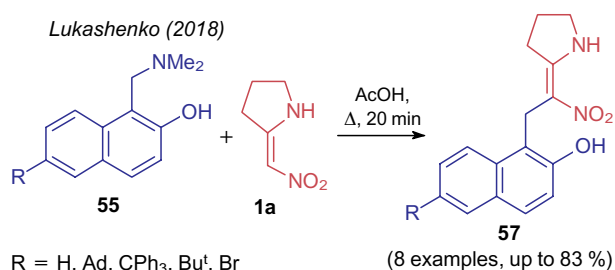
Shuvalov (*Chemistry Select* 2019)



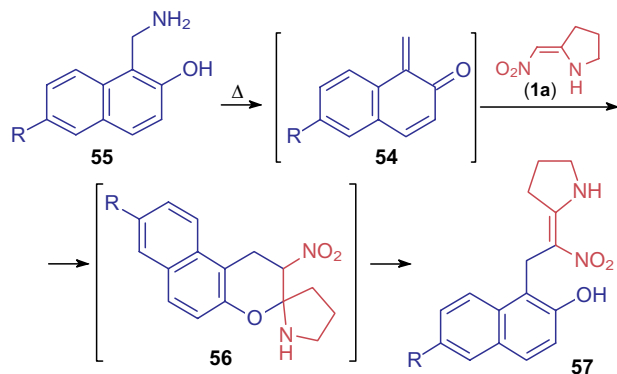
Scheme 15

Scheme 16

Lukashenko (2018)



Proposed mechanism



Ad is adamantyl

dichloroethane (Scheme 18). The authors considered a combination of various EWG-alkenes (EWG is an electron-withdrawing group), however, the amino group hydro-

lyzed only in compound **1c**, and the intermediate most likely oxidized to a carboxylic acid with further decarboxylation to product **65**.

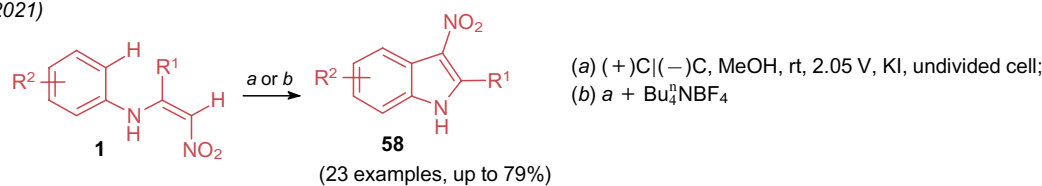
Compounds **1**, bearing the monosubstituted amino group, can be arylated in dimethylformamide in the presence of 2 equiv. of a base and catalytic amounts of copper(I) chloride. Aradi *et al.*⁶⁷ described the procedure of the reaction of ANE with diaryliodonium triflate **66**, which might be formally considered as amination of iodine-containing (hetero)aromatic compounds. The proposed reaction pathway implies the formation of *cis*- and *trans*-isomers **67** in non-stoichiometric amounts *via* copper-containing intermediates **68** and **69** (Scheme 19).

In 2020, Verma *et al.*⁶⁸ developed an elegant atom-economical approach to the synthesis of various nitro-substituted aromatic and heteroaromatic compounds bearing sensitive functional groups. The method includes regioselective annulation of 2-alkenylbenzonitriles **70** with nitromethane **71** in dimethylsulfoxide in the presence of 2 equiv. of potassium hydroxide to afford fused systems **72** (Scheme 20). Based on control experiments and the findings on using a deuterated solvent, the authors proposed a reaction pathway as illustrated on the example of 2-(phenylethynyl)benzonitrile (**70a**). The aza-Henry addition of the nitromethane potassium salt **71'** to a nitrile group of the substrate gives anion **73**, which reacts with deuterated DMSO to afford intermediate **74**. The key structure of this mechanism is ANE **75**, which cyclizes to compound **76** when reacting with a solvent.

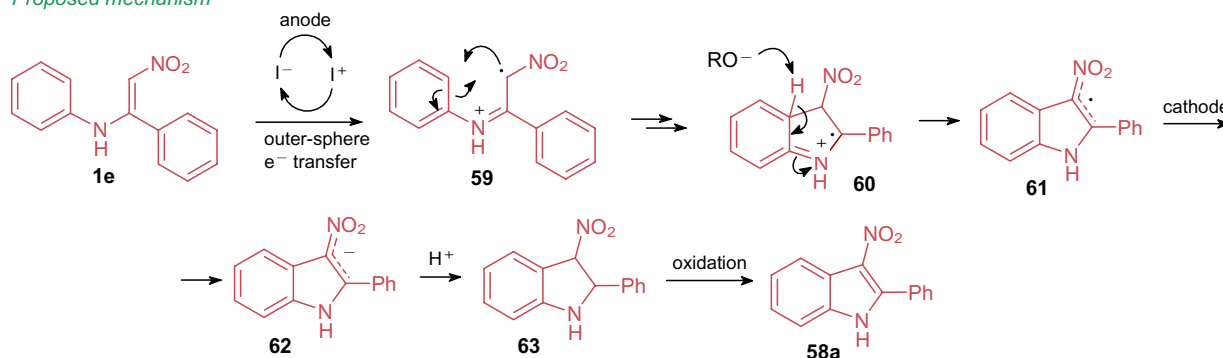
In the same year, Zalte *et al.*⁶⁹ employed the similar reaction to prepare fused compounds, 9-amino-

Lindsay (2021)

Scheme 17

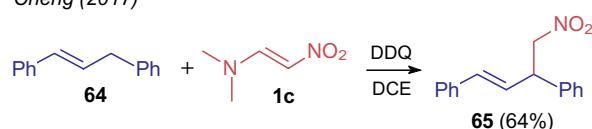


Proposed mechanism



Cheng (2017)

Scheme 18

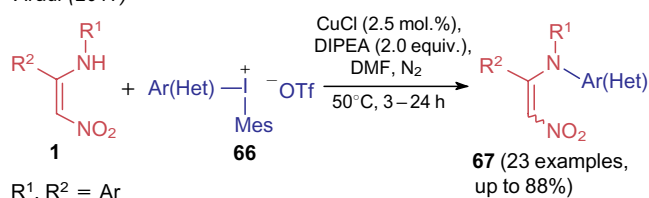


DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DCE is 1,2-dichloroethane

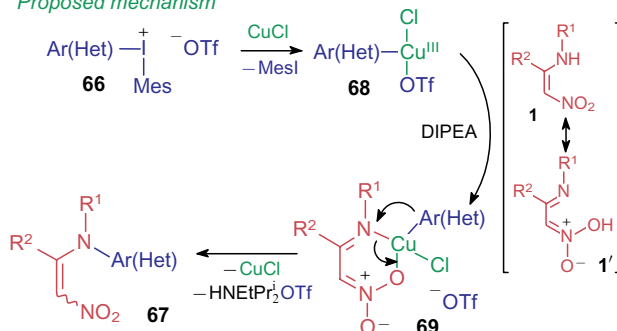
When considering methods for the preparation of ANE **1**, it can be concluded that over the past five years, the chemical properties of such NSEs have been enriched by a significant number of new and nontrivial examples. These transformations show good prospects for their application to the synthesis of a variety of hetero- and carbocyclic compounds, and other acyclic molecules necessary to construct more complex organic skeletons.

Aradi (2017)

Scheme 19

R¹, R² = Ar

Proposed mechanism



Tf is trifluoromethanesulfonyl (triflyl), Mes is 2,4,6-trimethylphenyl (mesityl), DIPEA is diisopropylethylamine

2.2. 1-Nitro-2,2-disubstituted ethylenes

The chemical behaviour and a pool of reactions of disubstituted nitroethylenes **2–4** are generally similar to those for the above-mentioned NSEs (Fig. 3). Significant differences are evident in that compounds **2–4** are much more likely to react with the leave of the nitro group. This is mainly due to the need to form an aromatic system during cyclization. As for NSEs **3, 4**, they tend to form isoxazole rings through the transformation of the nitro group. Compound **2** and **3, 4** are noticeably different: since imine-enamine tautomerism is impossible for DiSalk, such derivatives do not interact with electrophiles either. To functionalize the C-atom adjacent to the nitro group, palladium catalysts should be used (see Section 2.2.4). Therefore, various primary amines are used in the reactions involving compounds **2** to allow the electrophile to react with the *in situ* generated SMEnH. Interestingly, no studies are available on the chemical properties of (alkylthio)aminonitroalkenes substituted with a Salk fragment and a secondary amino group. The most common methods for producing such compounds are available in the studies.^{70, 71}

2.2.1. Cycloaddition reactions

The overwhelming majority of transformations described for NSEs **2–4** are heterocyclization reactions affording polysubstituted 3-nitropyridines (Table 2, lines 1–31), 3-nitropyranes (see Table 2, lines 32–45) (**2**, 32–45) or 5-nitropyrimidines (see Table 2, lines 46, 47). 3-Nitropyridines are accessible *via* the [3 + 3]-cycloaddition reaction involving NSEs and di-C-electrophiles, and also [3 + 2 + 1]-type reactions using NSE, C-electrophiles and various 1,2-bifunctional structures. In the case of 2,2-dimethylthio-1-nitroethylene (**2a**), mono- or diamines are added to the

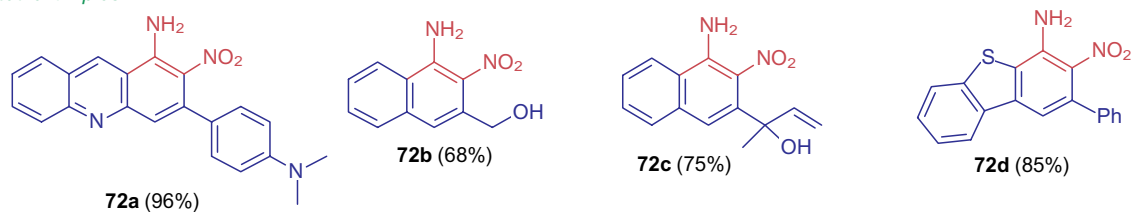
pyrido[1,2-*a*]indoles **78**, from indoles **77**. As in the previous case, the reaction mechanism comprised the formation of a push–pull enamine (Scheme 21). However, in this example, the reaction began with the formation of anion **79** and was completed presumably *via* the alkyne-allene rearrangement **80** → **81** followed by an intramolecular cyclization.

Verma (2020)

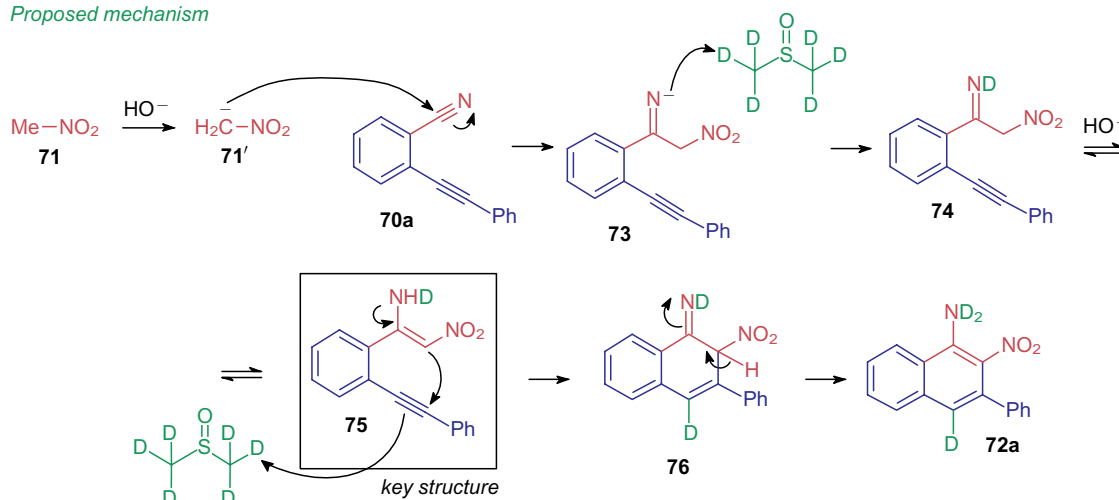


Scheme 20

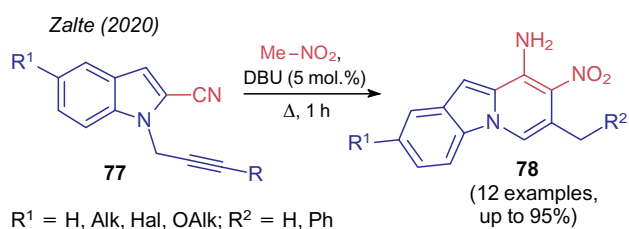
Selected examples



Proposed mechanism



Scheme 21



Proposed mechanism

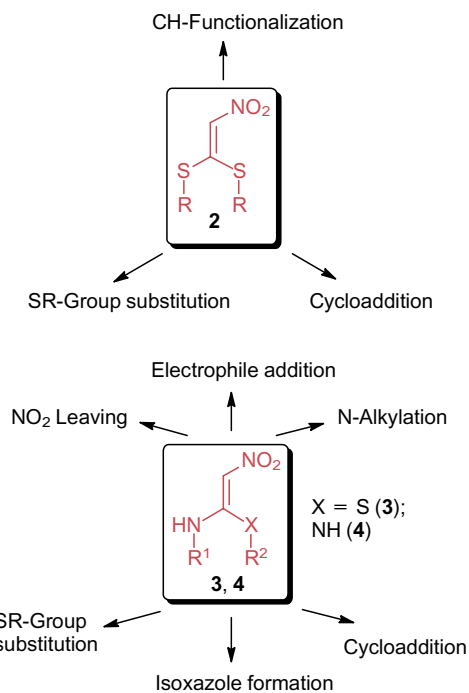
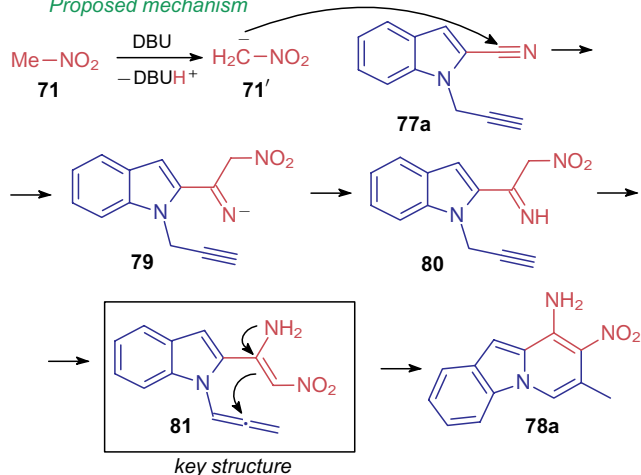


Figure 3. Possible ways to modify compounds 2–4.

DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

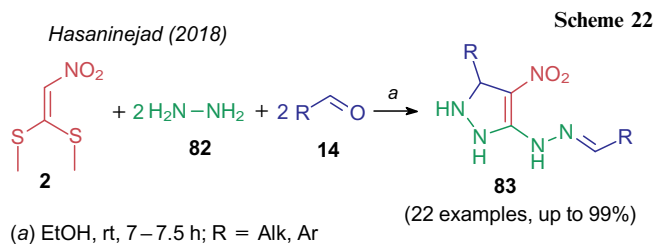
reaction mixture, which initially generate *in situ* mono- or diamino-1-nitroethylenes **3** or **4** to be cyclized. To produce nitropyranes, NSEs, C-electrophiles and bifunctionalized O,C-nucleophiles are mainly used in the [3+2+1]-cyclization or NSE, while NSEs and bifunctionalized compounds (O-nucleophile, C-electrophile) are employed in the [4+2]-addition reaction. In these cases, the methylthio group is displaced with an O-nucleophile, and the effect of the NH-alkyl group is noted only in the reaction pathway of tautomeric transformations. Nitropyrimidines are commonly produced *via* the [3+2+1]-type reaction of aminoazoles, aromatic aldehydes and 2-alkylamino-2-methylthio-1-nitroethylenes.

For all these transformations, no clear relationship between the cyclization type or the features of certain substrates and the preferred reaction conditions or the type of catalysis was revealed. Nevertheless, these multi-component processes are carried out mainly in polar solvents in the presence of catalytic amounts of acid or base, or on heating without a catalyst. Fusion, microwave irradiation, ionic liquids or electrolysis conditions are less commonly used. The data on cycloaddition reactions producing six-membered rings are summarized in Table 2.

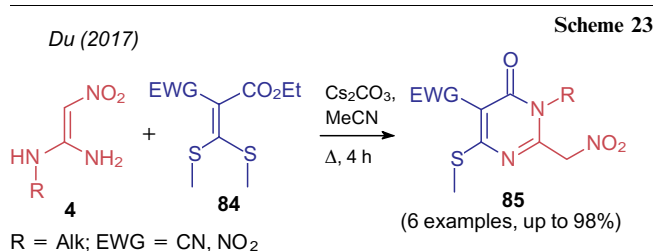
The authors often point out the beneficial properties of the resultant compounds, primarily their biological activities and photophysical characteristics, or use these structures as scaffolds to create practically valuable compounds. Note that in a review of 2019, Saigal *et al.*²⁹ highlighted some transformations related to the reactions of 1-nitrosubstituted 2-alkylthio-2-alkylaminoalkenes. However, in the present review, the chemical properties of this group of NSE are presented in more detail. Often there are cases of two-, three- and four-component reactions affording poly-substituted 3-nitropyrrroles (Table 3). The process in general is the reaction between an 1,2-dielectrophile and nitroalkene **3** bearing at least one unsubstituted NH group. The dielectrophile can be both generated in the reaction and used in a finished form. In this process, as in the formation of six-membered rings, it was problematic to identify the general dependence of the reaction conditions on particular substrates. Nevertheless, in most cases, the reaction is carried out in polar solvents without any catalyst.

The cyclization ability of α,α -di(alkylthio)nitroalkenes **2** is not limited to the examples shown above. Based on such nitroenamines, other five-six-membered heterocycles as well as seven- and eight-membered compounds can also be produced. For example, Hasaninejad *et al.*¹⁵¹ carried out the three-component consecutive reaction involving compounds **2**, hydrazine (**82**) and aldehydes **14** in ethanol at room temperature to obtain 4-nitro-2,3-dihydropyrazoles **83** in nearly quantitative yields (Scheme 22). First, methylthio moieties are displaced with hydrazine molecules, while an intermediate is converted to product **83** *via* the [4+1]-cyclization with a molecule of aldehyde **14**.

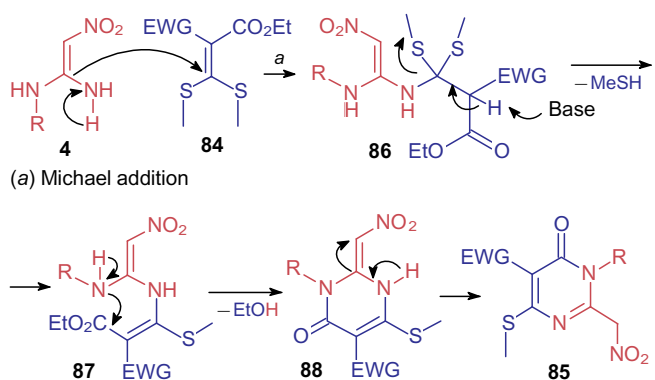
As was shown above, α,α -di(amino)nitroalkenes **4** react with 2,2-di(methylthio)ethylene **84**, bearing two electron-withdrawing groups, in boiling acetonitrile in the presence of cesium carbonate to furnish nitropyrimidines (see Table 2, line 21). However, as noted in the cited publication,¹⁰⁴ formally the same reaction but involving NSE **4**, containing one unsubstituted amino group, and 1-EWG-1-ethoxycarbonyl-2,2-di(methylthio)ethylenes **84** affords the products of an alternative heterocyclization, 5-EWG-substituted 6-methylthio-2-nitromethylpyrimidin-4-ones **85**. The authors propose two different mechanisms for these proc-



esses (the second one implying the formation of structures **86–88**), from which it can be concluded that regioselectivity is governed by the spatial availability of the unsubstituted amino group (Scheme 23).



Proposed mechanism



The reaction of nitroaminoalkenes **3** or **4** with an aromatic amine [2,5-dimethylaniline (**89**)] and succinaldehyde (**90**) was used to synthesize compounds **91** based on the 3-nitroazepine core (Scheme 24).¹⁵² Note that in the absence of the aromatic amine, the reaction stops at the step of formation of azepine with a bridging oxygen atom, while the addition of 2,5-dimethylaniline gives an aza derivative **91**.

In 2021, Zhang *et al.*^{153, 154} showed two pathways for the reaction of α,α -di(amino)nitroalkenes **4** with glutaraldehyde (**92**) depending on the type of acid catalyst (Scheme 25). In the first case (pathway *a*), oxabridged 10-nitro-5,9-epoxy-1,2,3,4,5,6,7,8-octahydroimidazo[1,2-*a*]azocines **93** were formed.¹⁵³ The reaction occurred in acetonitrile in the presence of Brønsted acid catalyst (HCl) and was in fact the condensation of a dinucleophile with a dielectrophile. Catalysis with Lewis acid [B(OH)₃] unexpectedly led to 8,10-dinitro-1,2,3,5,6,7-hexahydroimidazo[1,2-*a*]azocin-5-ol **94** (pathway *b*).¹⁵⁴ The low yield of the product may indicate that the second nitro group is incorporated in a molecule **94** due to the destruction of the starting NSE **4**. However, the authors did not propose any reaction pathway.

Table 2. Synthesis of six-membered nitroheterocycles based on compounds 2–4.

No	Nitroalkene	Electrophile	Nucleophile	Other reactants	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
1		 R ¹ = H, Hal, OMe, NO ₂ (cm. ^a)		 H ₂ N-CH ₂ -CH ₂ -XH X = NH (for a–c, e), S (for c, d); n = 1, 2; R ² = Cl, Br, NO ₂ ; R ³ = Me		a) EtOH, H ₂ O, Δ, 4–7 h b) EtOH, Δ c) EtOH–H ₂ O, Δ, 10–60 min d) Et ₃ N, EtOH, 8–10 h, rt → Δ e) AcOH, EtOH, Δ, 8–12 h	up to 90 up to 90 up to 91 up to 95 up to 87	72 73 74 75 76
2		(Het)Ar-CHO		H ₂ N-CH ₂ -CH ₂ -XH X = NH (for a, c), S (for b); n = 1–3		a) EtOH, Δ, 7–9 h b) H ₂ O–EtOH (3 : 1), Δ c) EtOH, 80 °C, 1–3 h	up to 94 up to 87 up to 95	77 78 79
3		 R = H, OMe	NC-CH ₂ -CN	H ₂ N-CH ₂ -CH ₂ -NH ₂ n = 1, 2		EtOH, Δ, 3 h	up to 90	80, 81
4		 R = Bu ⁿ , Bn	–	H ₂ N-CH ₂ -CH ₂ -NH ₂ (= (CH ₂) _n (n = 2, 3), CH ₂ CMe ₂ CH ₂)		EtOH, Δ, 3 h	up to 89	82
5		 R ¹ = H, Me; R ² = H, Hal, Me, NO ₂		H ₂ N-CH ₂ -CH ₂ -NH ₂ n = 1, 2		KAl(SO ₄) ₂ · 12 H ₂ O, EtOH, Δ, 7–8.5 h	up to 98	83
6		 R = H, OMe	–	H ₂ N-CH ₂ -CH ₂ -NH ₂ n = 1–3		EtOH, Δ, 3 h	up to 93	84
7		 or R ¹ = H, Hal, OMe, NO ₂ ; R ² = H, Me, Hal, OMe, NO ₂	 R ³ = H, Me	H ₂ N-CH ₂ -CH ₂ -CH ₂ -NH ₂		Piperidine (5 mol.%), EtOH, MW, 80 °C, 5 min	up to 94	85

Table 2 (continued).

No	Nitroalkene	Electrophile	Nucleophile	Other reactants	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
8		 R = H, Hal, OMe, NO ₂ , etc.		H ₂ NCH ₂ SH		EtOH, 80 °C, 1–8 h	up to 95	86
9			—	H ₂ N(CH ₂) _n NH ₂	 n = 2, X = OR; n = 1, X = SMe	ROH, Δ > rt, 3 h (R = Me, Et)	up to 76	87
10		 R = H, Hal, OMe, NO ₂		H ₂ N(CH ₂) _n XH X = NH, S		1) EtOH, Δ, 5 h; 2) AcOH (70%), 70 °C, 0.2–12 h	up to 95	88
11		 R = H, Alk, Hal, OMe, NO ₂ , etc.		H ₂ N(CH ₂) ₃ NH ₂		EtOH, 80 °C, 10–15 min	up to 89	89
12			NCCH ₂ CN	H ₂ N(CH ₂) ₃ NH ₂		Piperidine (10 mol.%), EtOH, Δ, 20 h	70	90
13	 or 			NH ₂ –R R = Alk		EtOH, Δ, 7–10 h	up to 90	91

Table 2 (continued).

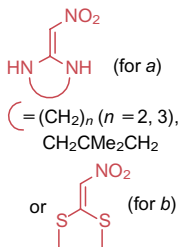
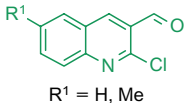

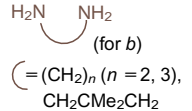
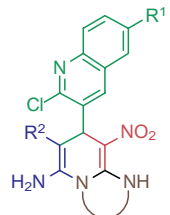
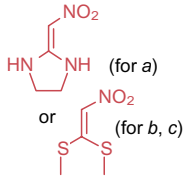
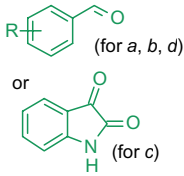
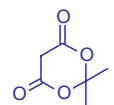
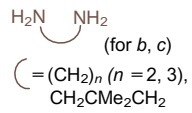
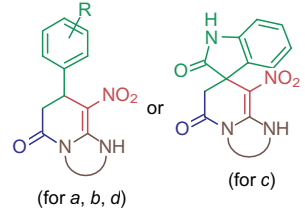
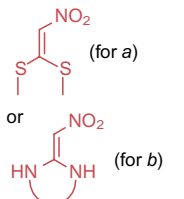
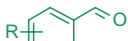
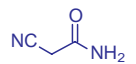
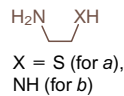
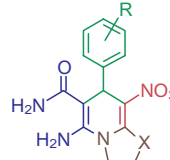
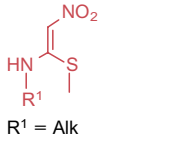
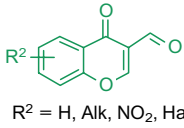
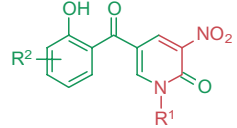
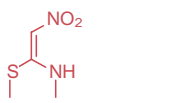
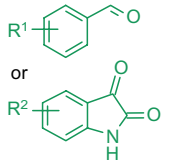
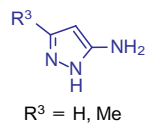
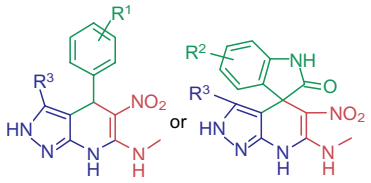
No	Nitroalkene	Electrophile	Nucleophile	Other reactants	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
14	 <p>(for a) $(= (\text{CH}_2)_n (n = 2, 3), \text{CH}_2\text{CMe}_2\text{CH}_2)$ or (for b)</p>	 <p>$\text{R}^1 = \text{H}, \text{Me}$</p>	 <p>$\text{R}^2 = \text{CN}, \text{CO}_2\text{Me}$</p>	 <p>(for b) $(= (\text{CH}_2)_n (n = 2, 3), \text{CH}_2\text{CMe}_2\text{CH}_2)$</p>		<p>a) Piperidine (11 mol.%), EtOH, rt, 3–4 h b) H₂O, Δ, 4 h</p>	<p>up to 90 up to 90</p>	<p>92 93</p>
15	 <p>(for a) or (for b, c)</p>	 <p>(for a, b, d) or (for c)</p> <p>$\text{R}^1 = \text{H}, \text{Me}, \text{OMe}, \text{Hal}, \text{etc.}$</p>		 <p>(for b, c) $(= (\text{CH}_2)_n (n = 2, 3), \text{CH}_2\text{CMe}_2\text{CH}_2)$</p>	 <p>(for a, b, d) or (for c)</p>	<p>a) NaBr (50 mol.%), PrⁿOH, 80–120 min, $I = 0.5 \text{ A}$ b) <i>p</i>-TsOH, H₂O, Δ, 5 h c) <i>p</i>-TsOH, EtOH, 80 °C, 0.15 h d) EtOH, Δ, 3 h</p>	<p>up to 96 up to 90 up to 87 67</p>	<p>94 95 96 81</p>
16	 <p>(for a) or (for b)</p>	 <p>$\text{R} = \text{H}, \text{Hal}, \text{OH}, \text{CO}_2\text{Me}$</p>		 <p>X = S (for a), NH (for b)</p>		<p>a) Et₃N, EtOH, H₂O, Δ, 1–5 h b) EtOH, Δ, 2–5 h</p>	<p>up to 93 up to 93</p>	<p>97 98</p>
17	 <p>$\text{R}^1 = \text{Alk}$</p>	 <p>$\text{R}^2 = \text{H}, \text{Alk}, \text{NO}_2, \text{Hal}$</p>	—	—		<p>In(OTf)₃, EtOH, Δ, 1 h</p>	<p>up to 88</p>	<p>99</p>
18		 <p>or</p> <p>$\text{R}^1 = \text{Alk}, \text{OMe}, \text{Hal}, \text{etc.};$ $\text{R}^2 = \text{H}, \text{Me}, \text{OMe}, \text{Hal}, \text{CF}_3, \text{etc.}$</p>	 <p>$\text{R}^3 = \text{H}, \text{Me}$</p>	—	 <p>or</p>	<p><i>p</i>-TsOH, MeCN, 80 °C, 5–9 h</p>	<p>up to 91</p>	<p>100</p>

Table 2 (continued).

No	Nitroalkene	Electrophile	Nucleophile	Other reactants	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
19			—	—		a) MW, neat, 110 °C, 10–15 min b) <i>p</i> -TsOH (10 mol.%), H ₂ O, rt, 15 min	up to 94 up to 98	101 102
20			NC-CH ₂ -CN	—		Et ₃ N (50 mol.%), MeCN, Δ, 3 h	up to 53	103
21			—	—		Cs ₂ CO ₃ , MeCN, Δ, 8 h	up to 97	104
22			—	R ³ -OH R ³ = Alk		HClO ₄ , R ³ OH or Me ₂ CO, 50 °C, 24 h	up to 92	105
23			—	—		NH ₂ SO ₃ H (10 mol.%), EtOH-H ₂ O (1 : 2), Δ, 24 h	up to 96	106
24			—	—		a) In(OTf) ₃ , EtOH, Δ, 1 h b) EtOH, Δ, 20 min	up to 95 up to 98	99 107
25			NC-CH ₂ -CN	Hal-CH ₂ -Y-CH ₂ -Hal Y = (CH ₂) _m (m = 2, 4), <i>p</i> -phenylene		K ₂ CO ₃ , PEG-400, rt, 9–13 h	up to 77	108

Table 2 (continued).

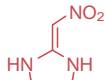
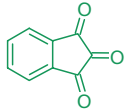
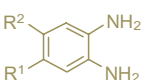
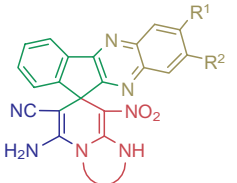
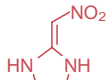
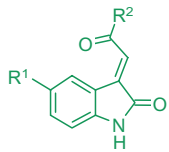
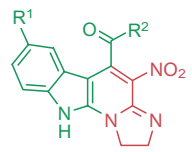
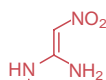
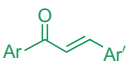
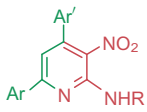
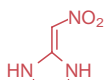
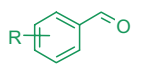
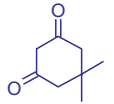
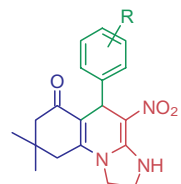
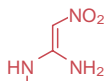
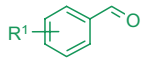
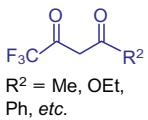
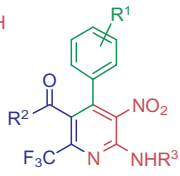
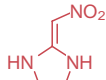
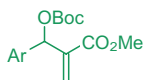
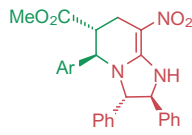
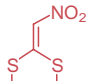
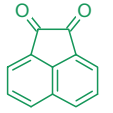
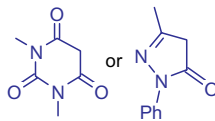
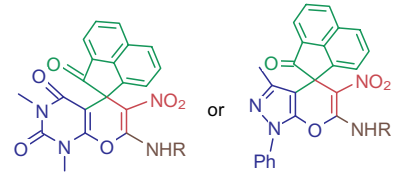
No	Nitroalkene	Electrophile	Nucleophile	Other reactants	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
26	 $(\text{CH}_2)_n$ ($n = 2, 3$), $\text{CH}_2\text{CMe}_2\text{CH}_2$		$\text{NC-CH}_2\text{-CN}$	 $\text{R}^1 = \text{R}^2 = \text{H, Me};$ $\text{R}^1 = \text{H, R}^2 = \text{NO}_2$		PEG-400, 130 °C, 10–14 h	up to 81	109
27		 $\text{R}^1 = \text{H, Me, Hal};$ $\text{R}^2 = \text{Alk, Ar}$	—	O_2		Cs_2CO_3 , EtOH, rt, 12 h	up to 93	110
28	 $\text{R} = (\text{CH}_2)_n\text{Ar}$ ($n = 0-2$)		—	O_2		Cs_2CO_3 , 1,4-dioxane, 130 °C, 9 h	up to 95	111
29		 $\text{R} = \text{Me, Cl, NO}_2$		—		a) Et_3N , EtOH, Δ b) Electrolysis, NaBr (0.5 mol.%), Pr^iOH – DMSO (95 : 5)	up to 56 up to 96	112 113
30	 $\text{R} = (\text{CH}_2)_n\text{Ar}$ ($n = 0-2$)	 $\text{R}^1 = \text{H, Me, Hal, OMe}$	 $\text{R}^2 = \text{Me, OEt, Ph, etc.}$	O_2		Et_3N (1 equiv.), neat, 110 °C, 18 h	up to 55	114
31	 Ph		—	—		DABCO (20 mol.%), CH_2Cl_2 , 2 h	up to 87 (<i>dr</i> from 10 : 1 to 19 : 1)	115
32				$\text{H}_2\text{N-R}$ $\text{R} = \text{Me, Et, Pr}^i$		EtOH, Δ , 3.5–8.5 h	up to 95	116


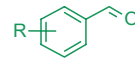
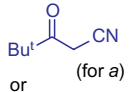
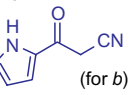
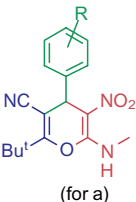
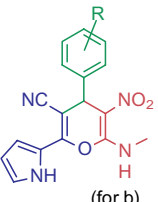

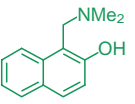
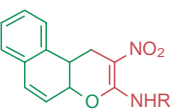

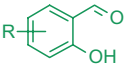
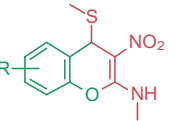

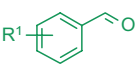
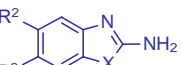
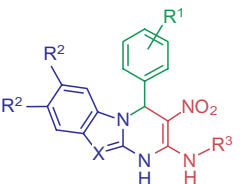

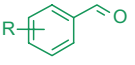

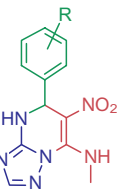
Table 2 (continued).

No	Nitroalkene	Electrophile	Nucleophile	Other reactants	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
33		 R ¹ = Hal, OMe, NO ₂ , OH, CF ₃		H ₂ N-R ² R ² = Et, Pr ⁱ , Bn		MeCN, rt, 6–7 h	up to 90	117
34				H ₂ N-R R = Me, Et, Pr ⁱ , Pr ⁱ		EtOH–H ₂ O (85:15), 89 °C, 6 h	up to 91	118
35	 or 	 R ¹ = H, Cl, Br; R ² = H (for a); R ¹ = H; R ² = H, Me, Bn (for b); R ¹ = H, Cl; R ² = H, Me, Et (for c)		H ₂ N-R ³ (for a, c) R ³ = Alk	 for a: for b: for c: R ⁴ = Me, CF ₃ ; R ⁵ = Me, Ar	a) EtOH, rt or H ₂ O, Δ b) H ₂ O, Δ, 7–10 h c) EtOH, Δ, 10–12 h	up to 86 up to 81 up to 84	119 120 121
36		 R ¹ = H, Me, OMe, NO ₂ ; or R ² = H, Me, All, propargyl; R ³ = H, Me, Cl, NO ₂		–	 or 	Dimethyl urea–L-tartaric acid (2:1), 0 °C, 30–45 min or H ₂ O, 80 °C, 30–60 min	up to 95	122

Table 2 (continued).

No	Nitroalkene	Electrophile	Nucleophile	Other reactants	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
37		 R = H, Me, Hal, OMe, NO ₂		—		Neat, 110 °C	up to 94	123
38		 R = H, Alk, Hal, NO ₂ , etc.		—		Neat, 110 °C, 20–55 min	up to 92	124
39		 R = H, F, NO ₂ , CF ₃ , etc.		—		MW, 150 °C, 5 min	up to 89	125, 126
40	 R = Me			—		MW, neat, 150 °C, 10–15 min	up to 94	127
41		 R ¹ = OMe, Hal, NO ₂ , etc.	 R ² = Me, Et	—		ZnCl ₂ (30 mol.%), neat, 120 °C, 30–50 min	up to 70	128
42		 R = H, Hal, OH, OMe, etc.		—		Et ₃ N, [bmim][BF ₄], 80 °C, 7–10 h	up to 89	129

Table 2 (continued).

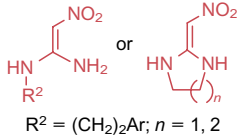
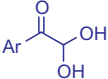
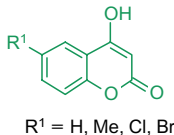
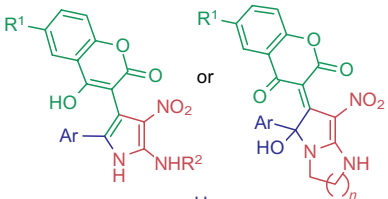
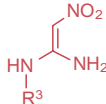
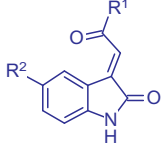
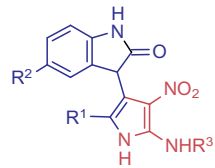
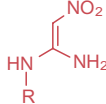
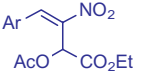
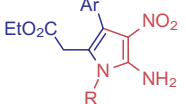
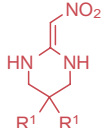
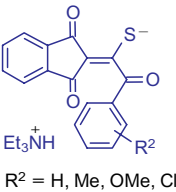
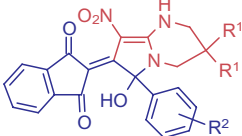
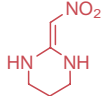

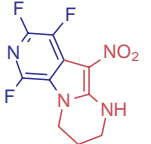
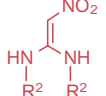
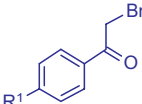

No	Nitroalkene	Electrophile	Nucleophile	Other reactants	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
43		 R = H, Hal, OMe, etc.	 (for a) or  (for b)	—	 (for a) or  (for b)	a) NH ₄ OAc, EtOH, MW, 80 °C, 5 min b) Piperidine, EtOH, MW, 90 °C, 15–20 min	up to 81 up to 93	130 131
44			—	—		MeCN, 80 °C, 8 h	up to 72	132
45		 R = H, Alk, Hal, OAlk, NEt ₂	—	—		Choline hydroxide (10 mol.%), H ₂ O, rt, 5–6 h	up to 96	133
46		 R ¹ = H, Alk, Hal, OAlk, NMe ₂	 X = NH (for a–c), S (for d); R ² = H, F, Cl	—		a) [bmim][BF ₄], Bu ⁿ OH, Δ, 3 h b) PEGMA-g-TEGBDIM, neat, 80 °C, 20–25 min c) <i>p</i> -TsOH, EtOH, 80 °C, 3–4 h d) FeF ₃ , neat, 80 °C, 1–1.5 h	up to 73 up to 96 up to 98 up to 91	134 135 136 137
47		 R = H, Hal, NO ₂ , CF ₃		—		Cl ₃ CCO ₂ H (20 mol.%), MeCN or H ₂ O, 18–24 h	up to 90	138

Note. The following abbreviations are used: MW is microwave irradiation, *p*-Ts is *p*-toluenesulfonyl (tosyl), DABCO is 1,4-diazabicyclo[2.2.2]octane, bmim is 1-n-butyl-3-methylimidazolium, PEGMA-g-TEGBDIM is polyethylene glycol methacrylate-grafted tetra-ethylene glycol-bridged dicationic imidazolium based ionic liquid, Cy is cyclohexyl. ^a Here and below, the absence of a locant in a benzene ring means that it can be in different positions.

Table 3. Illustrative syntheses of 3-nitropyrrols from compounds 2–4.

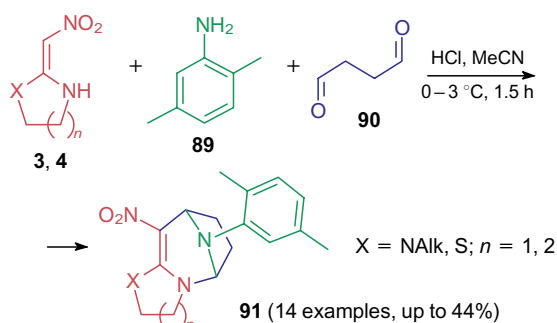
No	Nitroalkene	Electrophile	Nucleophile (other reactants)	Product	Reaction conditions	Yield (%)	Ref.
1			 X = O, S; R = H, Me (H ₂ N-CH ₂) _n -NH ₂)		EtOH, Δ, 6 h	up to 90	81, 139
2		 R = Me, Ph, 4-ClC ₆ H ₄	 (H ₂ N-CH ₂) _n -NH ₂) n = 1–3		H ₂ O–EtOH (3 : 1), 60 °C, 5–60 min	up to 98	140
3			NC-CH ₂ -CN or NC-CH ₂ -CO ₂ Me		PEG-400 (10 mol.%), H ₂ O, Δ, 40 min or neat, 80 °C, 1 h	up to 95	141
4			 R = H, Alk, Hal, OMe		I ₂ (10 mol.%), EtOH, rt, 3–8 h	up to 87	142
5					H ₂ O, 60 °C, 20–30 min	up to 93	143
6			 R = H, Hal, OMe, OH		a) EtOH, rt, 1–3 h b) BSA, Si@Fe ₂ O ₃ , 20–30 min	up to 85 up to 94	144 145

Table 3 (continued).

No	Nitroalkene	Electrophile	Nucleophile (other reactants)	Product	Reaction conditions	Yield (%)	Ref.
7	 R ² = (CH ₂) ₂ Ar; n = 1, 2		 R ¹ = H, Me, Cl, Br		EtOH, Δ, 6 h or 1,4-dioxane, Δ, 10 h	up to 94	146
8	 R ³ = H, Ph, Bn, etc.	 R ¹ = Ar; R ² = H, Me, Hal	—		EtOH, Δ, 12 h	up to 96	110
9	 R = (CH ₂) _n Ar (n = 0–2)		—		DBU, 1,4-dioxane, 40 °C, 10 min	up to 90	147
10	 R ¹ = H, Me	 R ² = H, Me, OMe, Cl	(MeI)		DMF, rt, 24 h	up to 86	148
11			—		1) K ₂ CO ₃ , 1,4-dioxane, 80 °C, 2 h; 2) Cs ₂ CO ₃ , 1,4-dioxane, Δ, 3 h	up to 95	149
12	 R ² = Alk; R ² –R ² = (CH ₂) _n (n = 2, 3), etc.	 R ¹ = H, Me, OMe, Cl, NO ₂	—		K ₂ CO ₃ , DMF, 80 °C, 50–220 min	up to 88	150

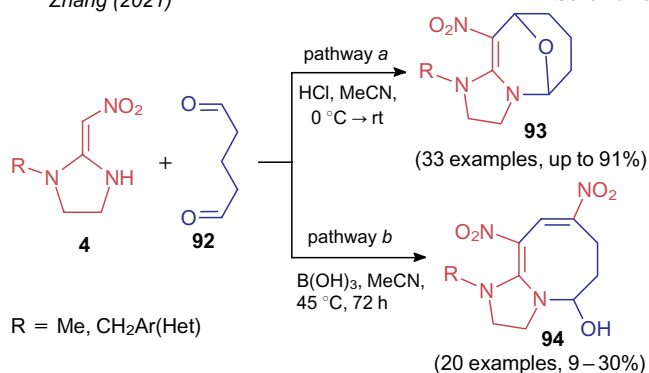
Chen (2021)

Scheme 24



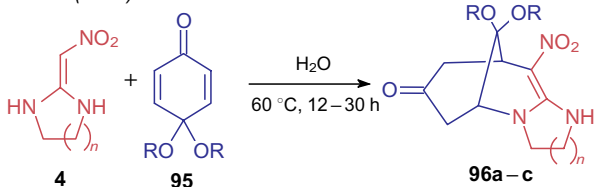
Zhang (2021)

Scheme 25

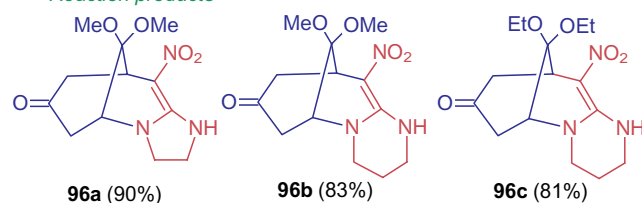


Ma (2017)

Scheme 26



Reaction products



To construct an azocine ring, Ma *et al.*¹⁵⁵ used quinone-based dielectrophiles **95**. Thus, reactions of compounds **4** with ketones **95** provides 10-nitro-2,3,5,6,8,9-hexahydro-5,9-methanoimidazo[1,2-*a*]zocin-7-one (**96a**) and 11-nitro-1,2,3,4,6,7,9,10-octahydro-6,10-methanopyrimido[1,2-*a*]zocin-8-ones **96b,c** in high yields (Scheme 26). Noteworthy that unlike the previous similar examples, the process occurs in water under catalyst-free conditions, thus being consistent with the principles of green chemistry.

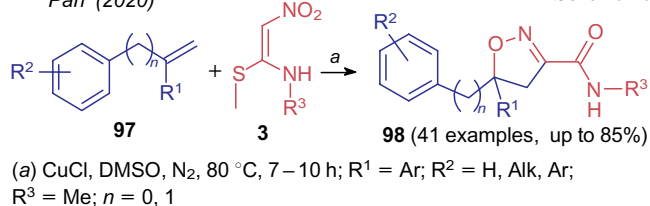
2.2.2. Synthesis of isoxazoles

Recently, two approaches to prepare isoxazoles based on NSE **3** have been reported. In the first case, in 2020, Pan *et al.*¹⁵⁶ carried out the reaction between 2-alkyl(aryl)-amino-2-methylthio-1-nitroethylenes **3** and olefins **97** in

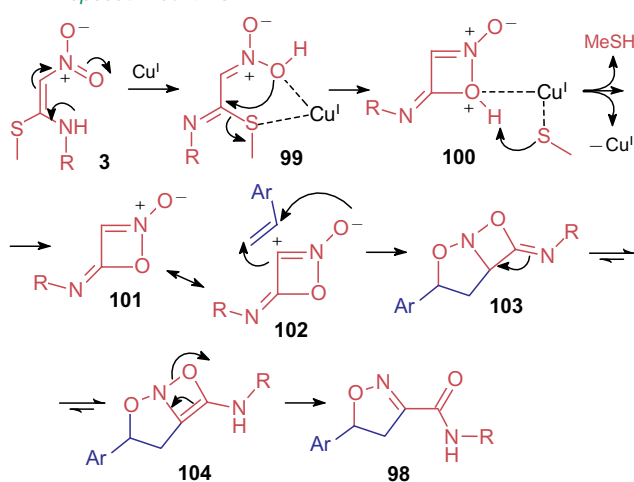
dimethylsulfoxide in the presence of copper(I) chloride to obtain 3,5-disubstituted 4,5-dihydroisoxazoles **98** (Scheme 27). According to the authors, NSE activated by the catalyst first coordinates to the metal atom to generate species **99**, and then, *via* intermediate **100**, forms an oxazetidine ring **101**, which further undergoes cycloaddition to the starting olefin as a zwitterion **102**. Intermediate isoxazolidinoxazetidine bicycle **103** transforms into its tautomer **104**, followed by the ring-opening of the four-membered heterocycle to afford 4,5-dihydroisoxazole **98**. Simple procedure, availability of the catalyst and high regioselectivity of the process allow considering NSE **3** as a versatile synthon for the construction of such isoxazoles. An alternative approach had been used a few years before to prepare 3,4,5-trisubstituted isoxazoles **105**.

Pan (2020)

Scheme 27



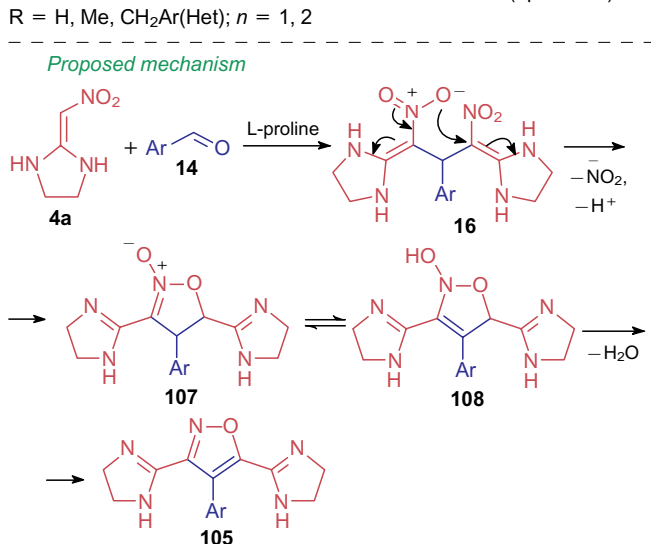
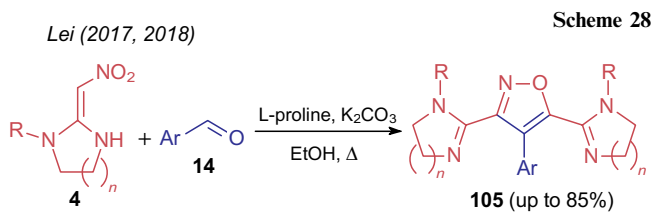
Proposed mechanism



Lei *et al.*^{157,158} carried out the reaction between 2,2-diamino-1-nitroalkenes **4** and aromatic aldehydes **14** in alcohol in the presence of potassium carbonate and L-proline (Scheme 28). In this case, two molecules of NSE, *e.g.*, compound **4a**, cross-link with a molecule of aldehyde **14** to generate intermediate **106**, which then undergoes intramolecular nucleophilic substitution of the nitro group to afford finally isoxazoline-*N*-oxide **107**. The following tautomeric transformations and dehydration yield polysubstituted isoxazoles **105**.

2.2.3. Reactions with the elimination of a nitro group

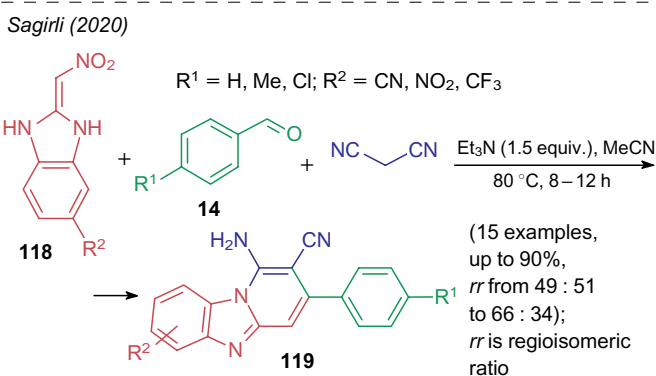
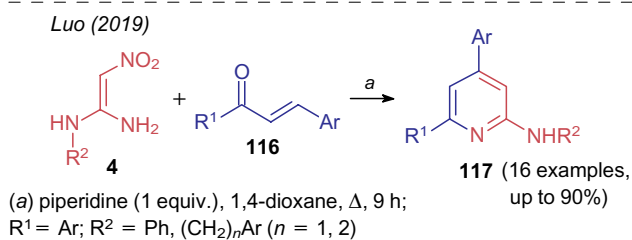
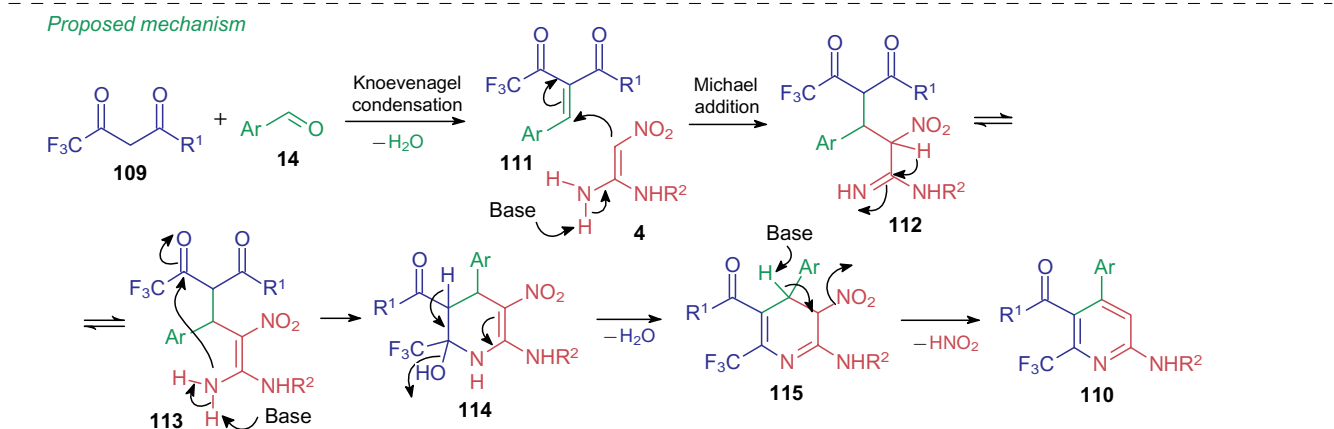
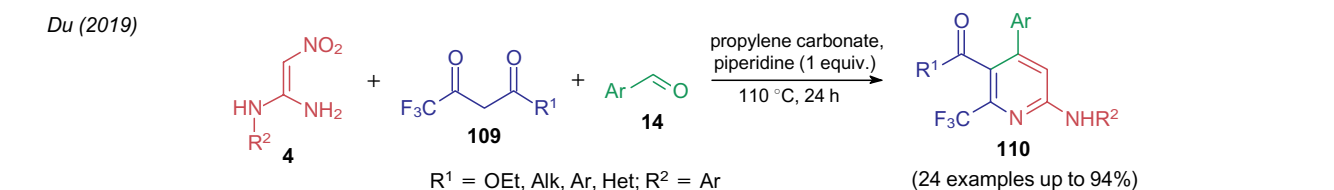
The structural features of a nitro group are not limited only to its ability to enter cycloaddition reactions. The nitro group can often serve as a leaving group, generally, as a nitrite ion or nitrous acid. However, under certain conditions, some multicomponent processes affording 3-nitropyridines (see Table 1) can follow an alternative reaction path. For example, in 2019, Du *et al.*¹¹⁴ studied the base-promoted reaction of 2-aryl-amino-substituted 2-amino-1-nitroalkenes **4**, trifluoroacetoacetates **109** and aromatic

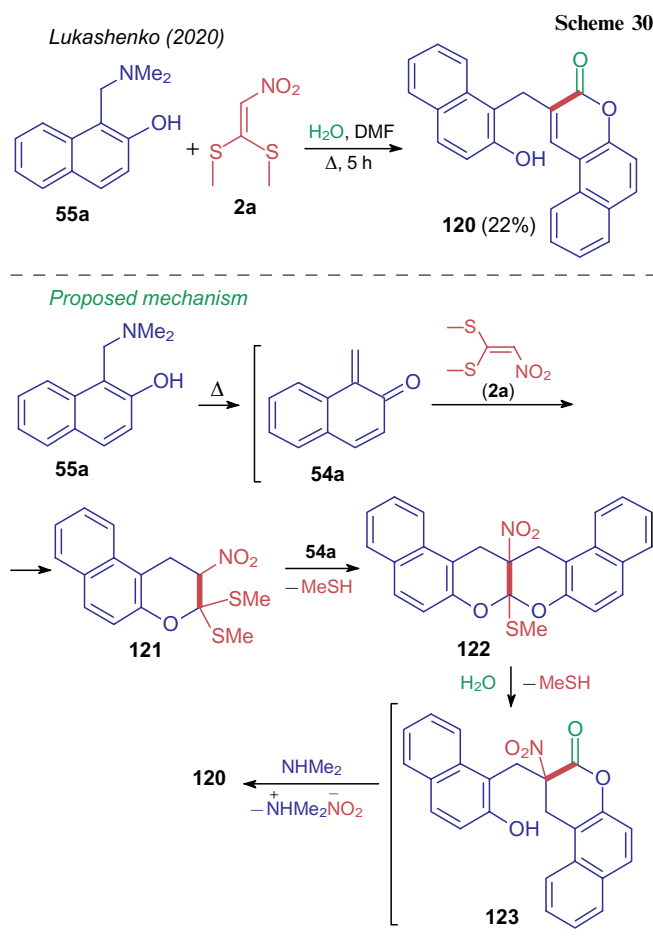


aldehydes **14** (Table 2 and Scheme 29). When melting the starting compounds together with an equivalent amount of triethylamine, a mixture of 3-nitropyrimidine (see line 30) and pyridine **110** is obtained (see Scheme 29). Carrying out this reaction in propylene carbonate with an equivalent amount of piperidine provides the regioselective synthesis of pyridines **110**. The plausible reaction pathway suggests the formation of intermediates **111–114** and implies aromatization of dihydronitropyridine **115** in two ways, namely, under the action of oxygen (see line 30) or by the loss of a nitrous acid molecule (see Scheme 29).

The same year, Luo *et al.*¹¹¹ carried out a similar process involving α,β -unsubstituted ketones. The reaction mechanism provided in the cited publication¹¹¹ is similar to that illustrated in Scheme 29, however, by varying the reaction conditions, the authors succeeded in obtaining two alternative products in the individual state. Refluxing 2-alkyl(aryl)amino-substituted 2-amino-1-nitroalkenes **4** with chalcones **116** in the presence of a strong inorganic base (Cs₂CO₃) promotes aromatization of the intermediate under the action of atmospheric oxygen and furnishes diaryl-substituted 2-amino-3-nitropyridines (see line 28 in Table 2). On the contrary, refluxing with piperidine leads to the loss of a molecule of nitrous acid and affords pyrimidines (see Scheme 29). Findings of Sagiri¹⁵⁹ add to these examples: in this case, NSE **118**, benzaldehydes and malononitrile construct the heterocyclic system **119**.

Scheme 29





An uncharacteristic transformation is observed when α,ω -di(methylthio)nitroethylene (**2a**) reacts with the *in situ* formed diene **54a** (Scheme 30). Lukashenko *et al.*¹³² carried out the synthesis of benzo[*f*]chromen-3-one **120**, in which NSE served as an ‘acetylene’ source. When heated, 1-[(dimethylamino)methyl]-2-naphthol (**55a**) forms 1-methylenenaphthalen-2-one (**54a**), which enters the Diels–Alder reaction twice: first, it reacts with DiSalk **2a** and then with intermediate **121** releasing a molecule of methanethiol. Under the action of water present in the reaction mixture, symmetric dimer **122** underwent ring-opening, displacement of the methylthio group with a hydroxyl group and aromatization, accompanied by the loss of a molecule of nitrous acid from intermediate **123** to form product **120**.

2.2.4. Reactions at the C–H bond

The C–H bond in NSEs is often modified through reactions with nucleophiles. However, such reactions do not always produce cyclic structures. For example, reactions of 2,2-diamino-1-nitroethylenes **4** and **124** with *p*-quinone methide **125** in acetone in the presence of cesium carbonate occur as an addition of NSE to a C-electrophile.¹⁶⁰ The subsequent dehydrogenation lead to conjugated compounds **126** and **127**, respectively (Scheme 31). The plausible reaction pathway (via the formation of intermediates **128** and **129**) is provided for the second process.

As mentioned in the beginning of this review, the key factor in all such processes is the possibility of enamine-imine tautomerism, which promotes further addition reac-

tions. The research groups of Bayat^{80,81} and Peytam¹⁶¹ carried out multicomponent reactions, also involving 2,2-diamino-1-nitroethylenes derived from α,ω -di(methylthio)nitroethylene (**2a**) and amines, and C-electrophiles as the key interacting intermediates. Although these reactions proceeded on heating in ethanol without a catalyst, they were completed mainly with dehydrogenation to afford the corresponding conjugated structures. Scheme 31 illustrates the examples of MCRs with compounds **130**–**133** to produce products **134**, **135** (see Scheme 31).

In turn, chemical properties of DiSalk **2** differ somewhat from those of the above-mentioned compounds. Since tautomerism, which fundamentally changes the chemical properties of the C-atom adjacent to the nitro group, is not possible in such structures, the reaction with electrophiles is not typical for this NSEs. Therefore, in 2021, Li *et al.*¹⁶² developed a procedure for the preparation of regioisomers **136** and **137**, which included the activation of the C–H bond of compounds **2** with palladium(II) acetate (Scheme 32). The mechanism of the reaction as illustrated on the example of substrate **2b** suggests the divergent addition of a molecule of the terminal alkene to the activated complex **138** to afford Pd-derivatives **139** and(or) **140**. Nevertheless, in practice, the process selectivity turns towards the formation of linear isomers **136** (ratio from 1.4:1 to 45:1 with a total yield of 11–92%).

2.2.5. Other reactions

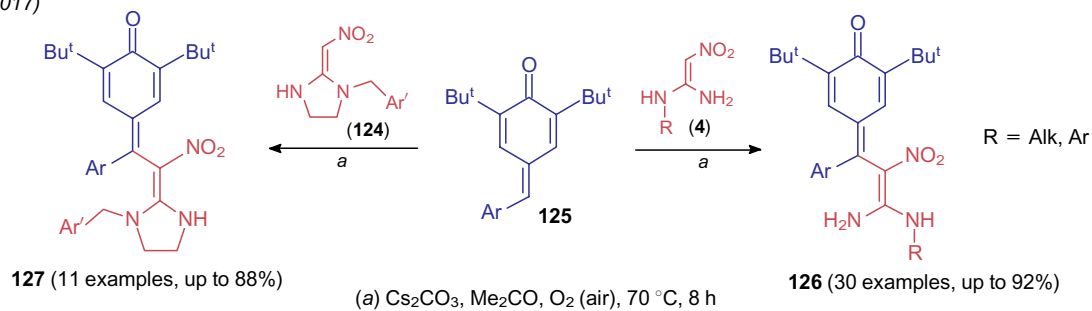
If the substitution of alkylthio groups in DiSalk **2a** by various primary amines is not a specific procedure and is used both directly and as part of multicomponent transformations, a similar substitution by C-nucleophiles is much less common. In 2018, Rogacki *et al.*¹⁶³ developed a multistep procedure to prepare compounds having antitubercular activity, which starts from the condensation of substrate **2a** with the CH-acidic *p*-bromophenylacetonitrile (**141**) in the presence of sodium hydroxide in dimethyl sulfoxide (Scheme 33). The generated push–pull alkene **142** was further used *in situ* in the Nef reaction to produce product **143**.

As with aminonitroethanes, DiNH **4**, bearing the secondary amine group, enters the alkylation reaction. However, contrary to the example given in Scheme 19, in 2021, Chen *et al.*¹⁵² carried out alkylation with halides **144** to afford monoalkyl derivatives **145** under conditions close to standard for reactions of this type. When using alkyl chlorides, the reaction was conducted in dimethyl sulfoxide in the presence of potassium hydroxide at room temperature, while with alkyl bromides, cesium carbonate in acetonitrile was used with the addition of a phase transfer catalyst, tetra-*n*-butylammonium bromide (TBAB) (Scheme 34).

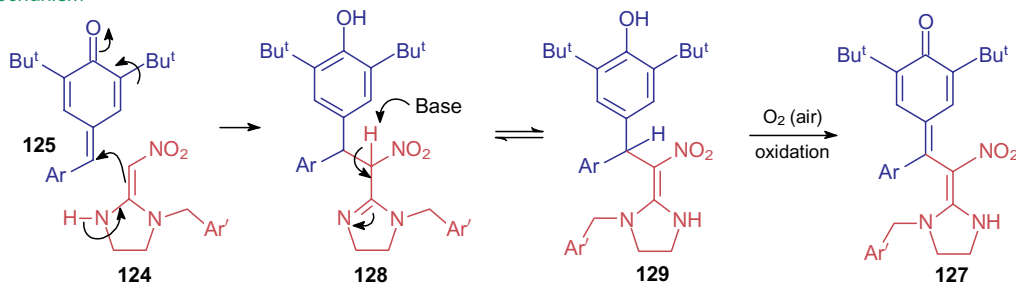
Thus, in contrast to the above-mentioned ANE **1**, compounds **2**–**4** were explored much better. At the same time, the variability of their chemical properties is mostly limited to transformations resulting in the heterocycle formation. This is not surprising, since NSE **2**–**4** are strongly pronounced push–pull compounds and contain two leaving groups at once, which promote heterocyclization. Nevertheless, an in-depth study of methods for modifying the C–H bond attached to the nitro group creates prerequisites for the development of new synthetic approaches to complex organic molecules based on such compounds.

Scheme 31

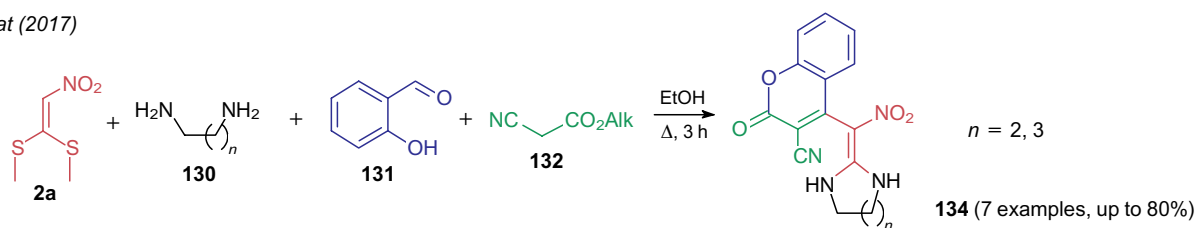
Wang (2017)



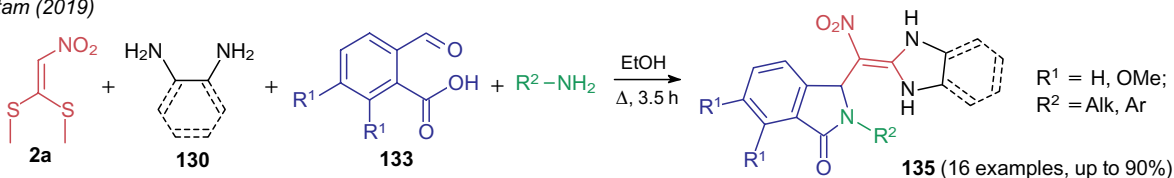
Proposed mechanism



Bayat (2017)

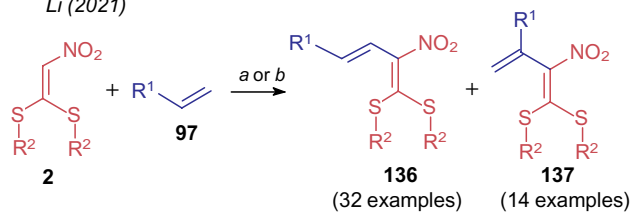


Peytam (2019)

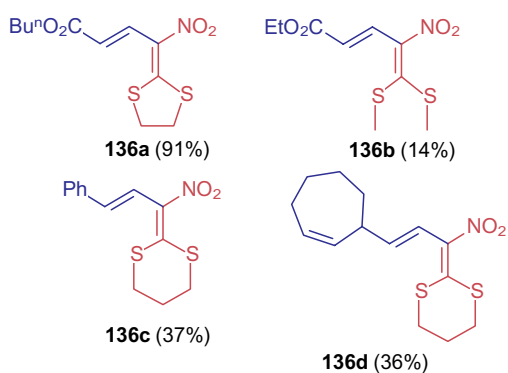


Scheme 32

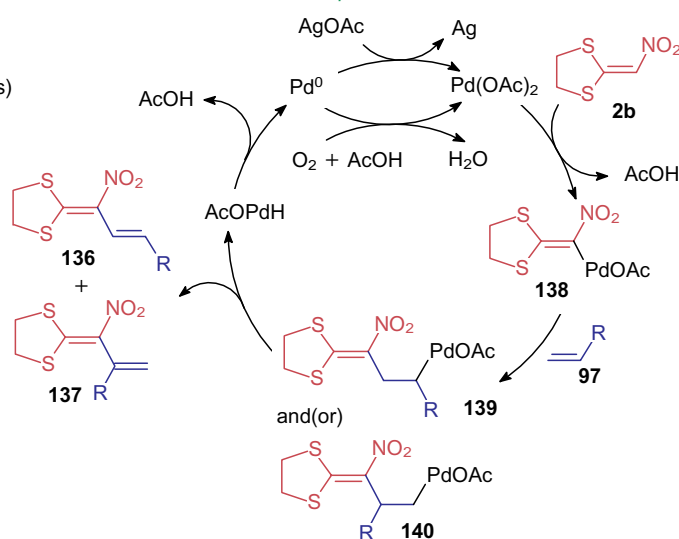
Li (2021)

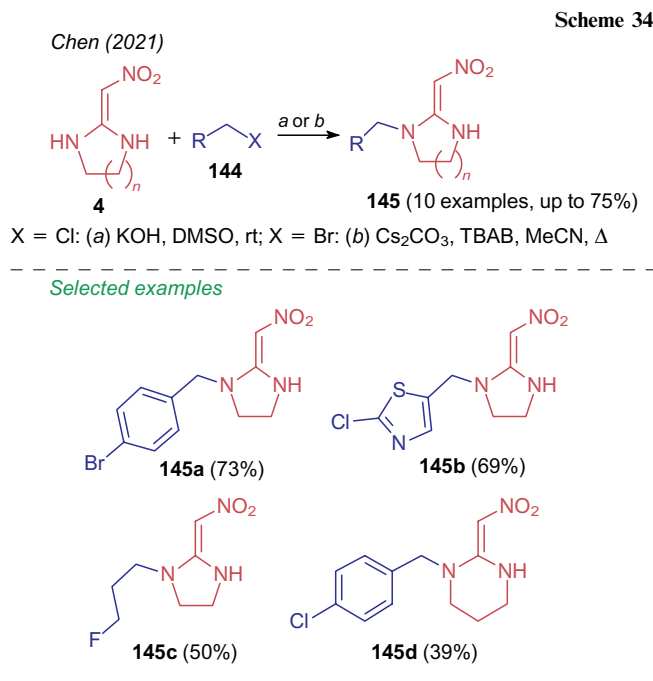
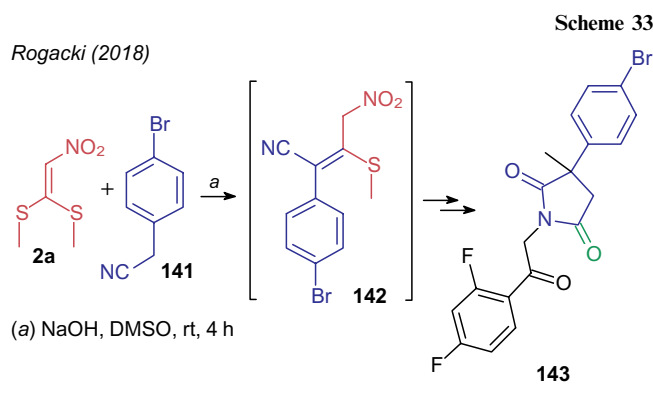


Selected examples

(a) $\text{Pd}(\text{OAc})_2$ (10 mol.%), AcOH-DMSO (4 : 1), $50-110\text{ }^\circ\text{C}$, 15–23 h;
(b) a + AcOAg (2 equiv.), N_2 or benzoquinone (20 mol.%)

Proposed mechanism





3. Structures of the $\text{O}_2\text{N}-\text{CH}_2-\text{EWG}$ type

The next three groups of NSEs: α -nitroketones (**5**), alkyl nitroacetates (**6**) and nitroacetonitrile (**7**) have similar structural features, which indicates their similar chemical behaviour (Fig. 4). The main affinity element is the $\text{C}(\text{sp}^3)$ -hybridized atom conjugated with two electron-withdrawing groups and allowing these compounds to enter the Knoevenagel and Michael reactions. In addition, NSEs **5–7** are often used in the synthesis of isoxazoles bearing the appropriate electron-withdrawing substituents. Compounds **2–4**, described in the previous Section, found application in such transformations much less frequently, while aminonitroethylenes were not used at all during the considered period. A common feature of NSEs **5–7** is also their participation in the cycloaddition reactions. Of these three groups of compounds, nitroacetonitrile (**7**) is the least represented in the literature, which is due to its low availability and low stability. Certain chemical properties described above for nitro derivatives **1–3**, e.g., the reaction at the $\text{C}-\text{H}$ bond, modification of the nitro group and transformations with its elimination are also typical of ANA and NK. Moreover, new properties appear such as the possibility to deliver nitrile oxides, and also the $\text{C}-\text{C}$ bond cleavage, which give, due to the presence of an α -CH acidic atom and a

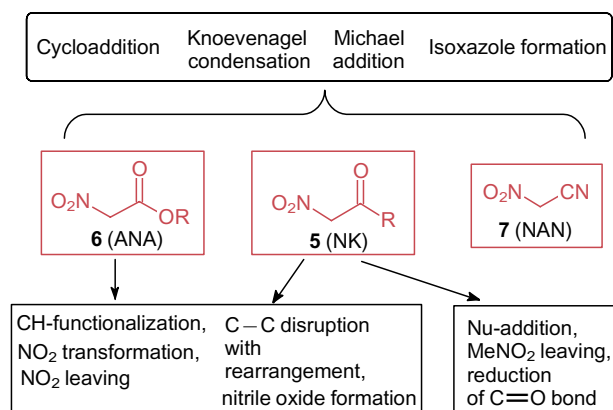


Figure 4. Possible ways to modify compounds **5–7**.

carbonyl group, four–six-membered rings, which further undergo ring-opening. Note that nitroketones can enter reactions characteristic of carbonyl compounds, e.g., the addition of nucleophile and reduction. Moreover, NKs can eliminate not only nitro group but also a molecule of nitromethane, as discussed in detail below.

Considering similar trends in chemical behaviour of nitro derivatives **5–7**, the examples of the Knoevenagel and Michael reactions, as well as the synthesis of isoxazoles for these compounds were combined and represented in the form of the corresponding Tables.

3.1. General reactions

3.1.1. Knoevenagel condensation

α -Nitroketones (**5**), alkyl nitroacetates (**6**) and nitroacetonitrile (**7**) are excellent examples of compounds having an active methylene centre to react with carbonyl compounds by the Knoevenagel reaction. Such transformations, found in the literature during the reporting period, are summarized in Table 4.

Despite the variety of protocols of the Knoevenagel reaction, due to numerous theoretical and practical studies for the NSEs of this group, several features of this transformation can be highlighted: the use of methyl thioimine as the electrophilic substrate instead of carbonyl compound (see Table 4, line 3), a two-step synthesis to produce an alkene bearing four electron-withdrawing substituents (see Table 4, line 5), and also an unusual catalyst in the reaction between ANA and isatin (see Table 4, line 8). Zhu *et al.*¹⁷³ showed that the use of piperidine as the catalyst results in the replacement of a nitro group in the product by a piperidine moiety. Therefore, Lewis acids are recommended for use in such processes along with a non-nucleophilic organic base. Compound **7**, as the strongest CH-acid of the three groups under consideration, can react with aldehydes without any catalyst in anhydrous ethanol (see Table 4, lines 17, 18).

3.1.2. Michael reaction

An active methylene centre of NSEs **5–7** is also often involved in the Michael reaction. Examples of such transformations are shown in Table 5. The addition of NSEs **5–7** is mainly catalyzed by bases (see Table 5, lines 1, 2, 4, 6, 15, 16), although the use of bacteria *Aspergillus niger* in the stereospecific reaction is also known (see Table 5, line 7). In addition to the biocatalyst, optically active catalysts **L**¹⁸ and **L**¹⁹ derived from diaminocyclobu-

Table 4. Illustrative Knoevenagel reactions involving nitro compounds 5–7.

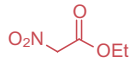
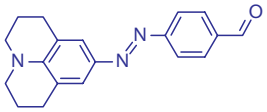
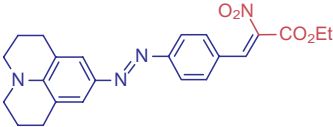
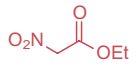

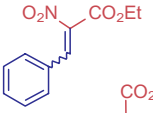
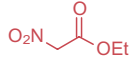
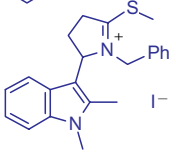
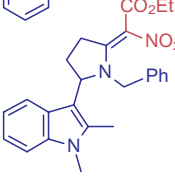
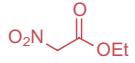
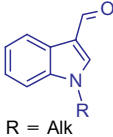
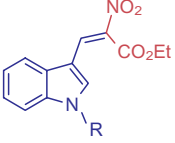
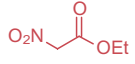
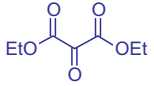
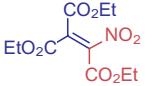
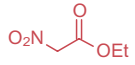

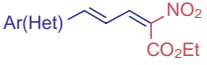
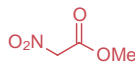
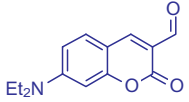
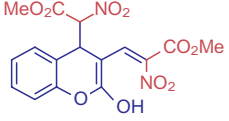
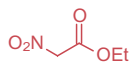
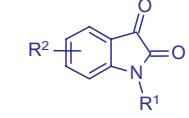

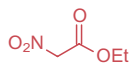
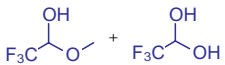
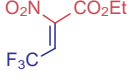
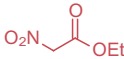
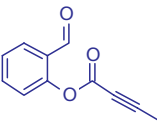
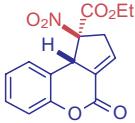
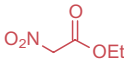
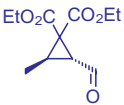
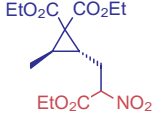
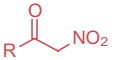

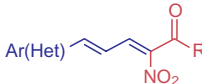
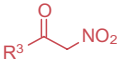
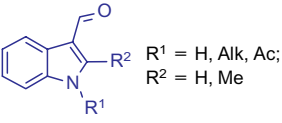
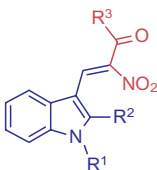
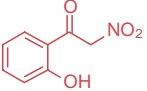
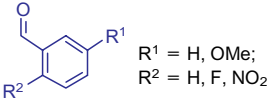
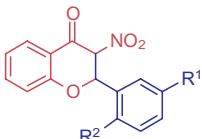
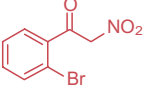

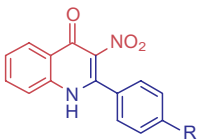
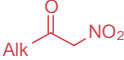

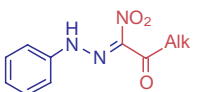
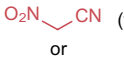
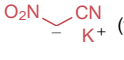

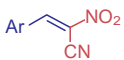

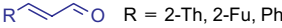
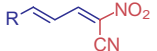
No	Nitro compound	Carbonyl compound	Product	Reaction conditions	Yield (%)	Ref.
1				β -Alanine (20 mol.%), AcOH, PhH, MS 3A, Δ , 10 h	48	164
2				TiCl ₄ , THF, $-10 \rightarrow 25$ °C, 18 h	—	165
3				Et ₃ N (2 equiv.), CH ₂ Cl ₂ , rt, 6 h	—	166
4		 R = Alk		a) AcOH (5 mol.%), piperidine (5 mol.%), PhMe, Dean–Stark trap, 6 h b) β -Alanine (20 mol.%), AcOH, PhH (abs), Dean–Stark trap, 5 h	— 81	167 168
5				1) K ₂ CO ₃ (0.1 equiv.), CH ₂ Cl ₂ , Δ , 3 h; 2) Et ₃ N (1.2 equiv.), MeSO ₂ Cl, CH ₂ Cl ₂ , 0 °C, 3 h	24	169
6				β -Alanine (20 mol.%), AcOH, PhH, Dean–Stark trap, 4 h	up to 71	170, 171
7				Piperidine, MeOH, Δ , 5 h	70	172
8		 R ¹ = H, Alk, Boc; R ² = H, Me, Hal, NO ₂ , etc.		TiCl ₄ (2 equiv.), DMAP (3 equiv.), THF, 0 °C \rightarrow rt, 8–24 h	up to 95	173
9				1) DBU (4.5 mol.%), rt, 24 h; 2) P ₂ O ₅ , 150 °C	53 (<i>E</i> : <i>Z</i> = 1.8:1.0)	174

Table 4 (continued).

No	Nitro compound	Carbonyl compound	Product	Reaction conditions	Yield (%)	Ref.
10				(4-MeOC ₆ H ₄) ₃ P (30 mol.%), 1,4-dioxane, 25 °C, 24 h	50	175
11				Hantzsch ester, (S)-proline (10 mol.%), CH ₂ Cl ₂ , 25 °C, 240 min	78% (<i>de</i> > 98%)	176
12	 R = Me, Ph, OEt			β -Alanine (20 mol.%), AcOH, PhH, Dean–Stark trap, 2 h or EtOH (abs.), rt, 7 days	up to 74	170, 171
13	 R ³ = Me, Ph	 R ¹ = H, Alk, Ac; R ² = H, Me		β -Alanine, AcOH, PhH, Dean–Stark trap, 2 h or POCl ₃ (2 drops), EtOH (abs.), $\Delta \rightarrow$ rt, 24 h	up 93	168
14		 R ¹ = H, OMe; R ² = H, F, NO ₂		Na ₂ CO ₃ (1.5 equiv.), L-proline (0.5 equiv.), EtOH (abs.), rt, overnight	up to 68	177
15		 R = H, Me, Ph		CuCl ₂ (5 mol.%), K ₂ CO ₃ (2 equiv.), NH ₃ (aq.) (5 equiv.), L-proline (10 mol.%), H ₂ O, Δ	up to 46	178
16				AcONa, H ₂ O, rt, 30 min	up to 73	33
17	 (for a, c) or  (for b)			a) 1- <i>n</i> -Butyl-3-methyl-1 <i>H</i> -imidazol-3-ium chloride, MS 4A, rt, 5 min b) TFA (2 equiv.), EtOH, rt, 3 h c) EtOH (abs.), rt, 24 h	up to 98 up to 62 87	179 180 168
18		 R = 2-Th, 2-Fu, Ph		EtOH (abs.), rt, 24 h	up to 88	170, 171

Note. Here and in Table 5, a dash in the yield column means that the product yield was not indicated in the original publication. MS are molecular sieves, DMAP is 4-(*N,N*-dimethylamino)pyridine, *de* is diastereomeric excess.

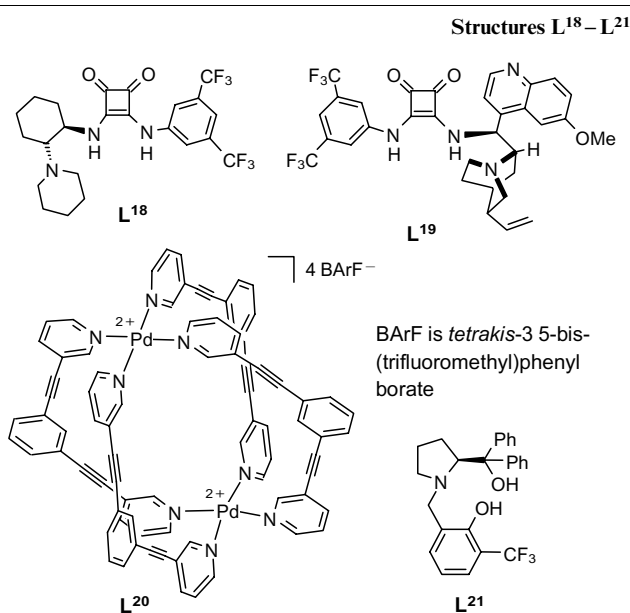
tenediones (see Table 5, lines 3, 5, 12 and 14) and pyrrolidine (see Table 5, line 11) can also be used for the stereoselective implementation of the process. An interesting case is the Michael reaction using a coordination compound Pd_2L_4 (L^{20}) in combination with 18-crown-6 (see Table 5, lines 10 and 13). This catalytic system provides not only a significant improvement in the reaction rate, but also makes the process highly stereoselective.

3.1.3. Synthesis of isoxazoles

The most common applications of NSEs **5**–**7** also include their use as starting materials in the synthesis of various isoxazoles and isoxazole N-oxides. Both the active methylene centre of the subject compounds and the nitro group *per*

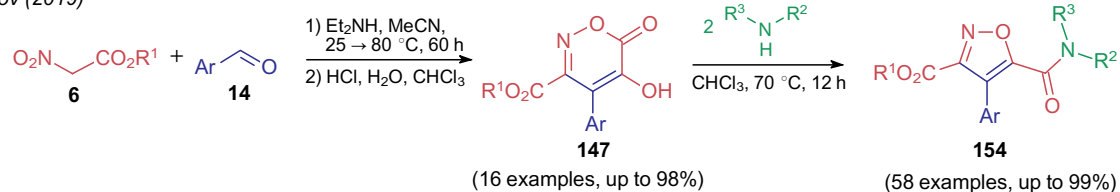
se are involved in the construction of the five-membered ring. Various alkenes, alkynes and carbonyl compounds are typical substrates for such process (Table 6). Noteworthy that the current ideas about the formation of (dihydro)isoxazoles suggest the initial generation of the corresponding (dihydro)isoxazole N-oxides, which are either dehydrated under more harsh conditions or reduced in boiling trimethyl phosphite. The only reaction that occurs in the presence of an asymmetric catalyst L^{21} is shown in line 8 of this Table (conditions *a*).

In 2019, Smirnov *et al.*²¹³ revised the classical mechanism of the Dornow–Wiehler reaction. The authors found that aromatic aldehydes **14** can react with 2 equiv. of nitro compounds **6** to produce not only 3,5-alkoxy-4-arylisoxazoles **146** but also 4-aryl-5-hydroxy-6-oxo-6*H*-1,2-oxazine-3-carboxylates **147** (Scheme 35). However, the formation of six-membered rings directly depends on the reaction conditions: this requires the use of a polar aprotic solvent, as well as an unusual temperature mode. The starting compounds are first stirred at room temperature for two days, and then the reaction mixture is heated at 80 °C for 3 h. Using aliphatic aldehydes, a mixture of products **146** and **147** is obtained, and in the case of aromatic aldehydes with strong electron-withdrawing groups, only isoxazoles **146** are isolated. It is assumed that this process starts from the reaction of one NSE molecule with an aldehyde to give intermediate **148**, which adds the second molecule of the nitro compound. 3,5-Dinitroglutaric ester **149** cyclizes into isoxazoline N-oxide **150**. When treated with a base, intermediate **150** delivers the corresponding salt **151**, which is ring-opened to form oxime **152** capable of cyclizing into products **146** and **147** (see Scheme 35, paths *a* and *b*, respectively). The authors²¹³ was also showed that oxazines **147** react with various amines and water to afford intermediates **153**, cyclizing into unsymmetrical isoxazoles **154**, which is a significant contribution to the study of such structures.



Smirnov (2019)

Scheme 35



Proposed mechanism

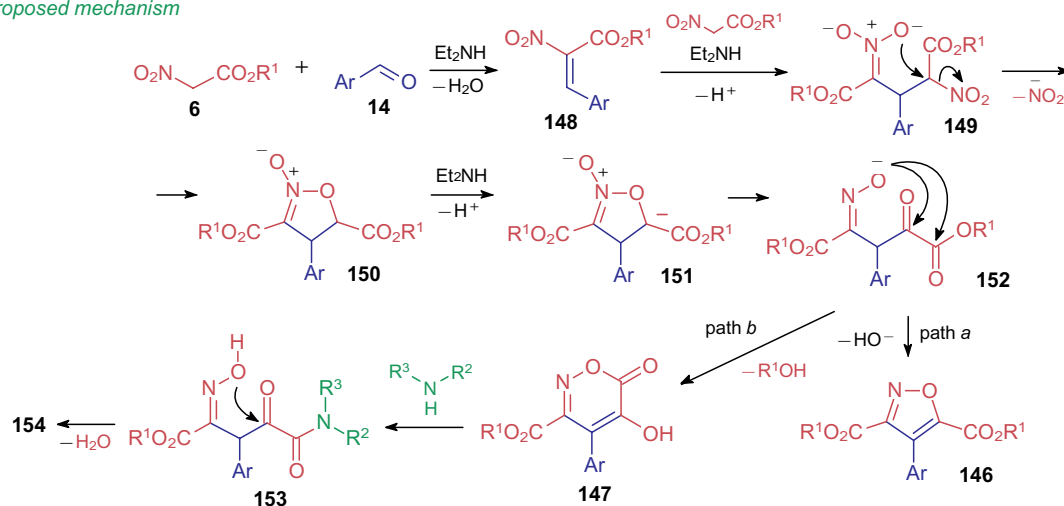


Table 5. Illustrative Michael reactions involving nitro compounds **5**, **6**.



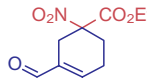


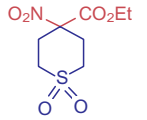
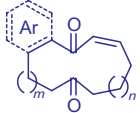
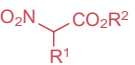
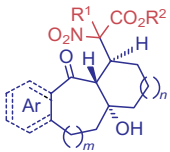
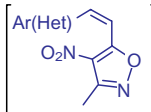
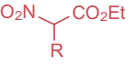
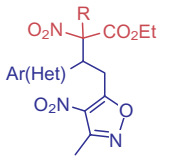
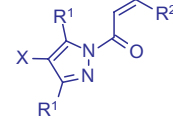
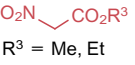
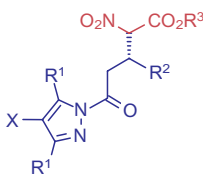


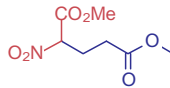
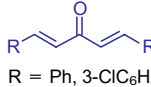

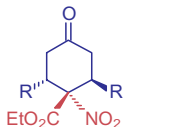
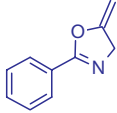

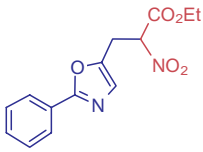
No	Substrate	Alkyl nitroacetate	Product	Asymmetric catalyst	Reaction conditions	Yield (%) (selectivity)	Ref.
1				—	K ₃ PO ₄ (1 equiv.), 1,4-dioxane, 50 °C, 24 h	—	181
2				—	DBU (1.1 equiv.), CH ₂ Cl ₂ , 23 °C, 16 h	68	182
3	 <i>n</i> = <i>m</i> = 1; <i>n</i> = 2, <i>m</i> = 0	 R ¹ = H, Me; R ² = Me, Et, Bu ^t , Bn		L¹⁸ (10 mol.%)	PhMe, 25 °C, 48–72 h	< 5–99 (82–92% <i>ee</i>)	183
4		 R = H (for a), Me (for b)		—	a) Et ₃ N (10 mol.%), rt, 3–5 min, grinding b) LiBr (1 equiv.), DBU (10 mol.%), THF, rt, 24 h	up to 93 19 (<i>dr</i> = 1 : 1)	184 185
5	 X = H, Hal; R ¹ = H, Me; R ² = Ar	 R ³ = Me, Et		L¹⁹ (20 mol.%)	PhMe, rt, 48–168 h	up to 98 (<i>dr</i> = 1 : 1, up to 99% <i>ee</i>)	186
6				—	K ₂ CO ₃ (30 mol.%), neat, 90 °C, 17 h	46	187
7	 R = Ph, 3-ClC ₆ H ₄			—	<i>Aspergillus niger</i> , MeCN, 40 °C, 48 h	74 (<i>dr</i> = >99 : 1)	188
8				—	CAN (4 equiv.), DMF, CH ₂ Cl ₂ , 0 °C, 4.3 h	22	189

Table 5 (continued).

No	Substrate	Alkyl nitroacetate	Product	Asymmetric catalyst	Reaction conditions	Yield (%) (selectivity)	Ref.
9				—	Pd(dba) ₂ (5 mol.%), DPEPhos (10 mol.%), MeCN, rt, 5 h	80 (<i>Z</i> : <i>E</i> = 70:30)	190
10				L²⁰ (2 mol.%)	18-crown-6 (10 mol.%), CH ₂ Cl ₂ , rt, 0.7–9 h	98	191
11				L²¹ (10 mol.%)	Et ₃ N, Cu(OAc) ₂ ·H ₂ O, PhMe, 0 °C, 24 h	up to 99 (<i>dr</i> = 1:1, up to 96% <i>ee</i>)	192
12				L¹⁹ (10 mol.%)	CH ₂ Cl ₂ , 0 °C, 48 h	80 (<i>dr</i> = 1:1, 53% <i>ee</i>)	193
13				L²⁰ (2 mol.%)	18-crown-6 (10 mol.%), CH ₂ Cl ₂ , rt, 0.7–9 h	up to 100	191
14				L¹⁹ (10 mol.%)	PhMe, rt, 48 h	73 (<i>dr</i> = 1:0.8, 96% <i>ee</i>)	194
15				—	K ₂ CO ₃ , Bu ₄ NOH, PhMe, rt, 1 h	91	195
16	—			—	Bu ^t OK (10 mol.%), THF, −40 °C, 4–18 h	up to 95 (<i>dr</i> from 9:1 to >20:1)	196

Note. TBS is *tert*-butyldimethylsilyl, CAN is cerium(IV)-ammonium nitrate, DPEPhos is bis[(2-diphenylphosphino)phenyl]ether.

Table 6. Synthesis of isoxazoles based on nitro compounds **5** and **6**.


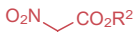
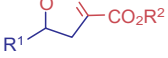


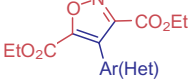


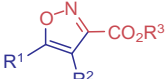
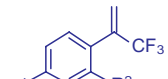

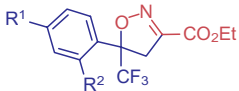


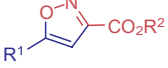
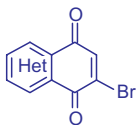

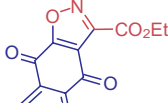
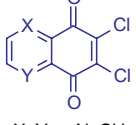

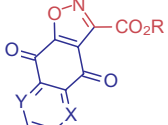


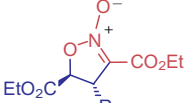
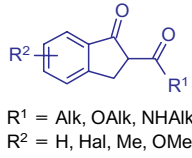

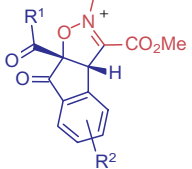


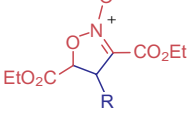


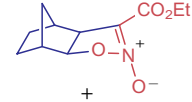
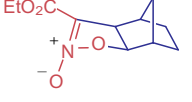
No	Substrate	Nitro compound	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
1	 $R^1 = \text{Ar}, \text{CO}_2\text{Me}$	 $R^2 = \text{Me}, \text{Et}$		a) DABCO, EtOH, Δ , overnight	up to 75	197
				b) TEMPO (10 mol.%), H ₂ O, air, 60 °C, 4 h	up to 78	198
				c) DABCO (10 mol.%), EtOH, 80 °C, 100 h	72	189
				d) Chloramine-T (0.5 equiv.), MeCN, 80 °C	30	199
2				DABCO (20 mol.%), H ₂ O, US, 80 °C, 24 h	up to 92	200
3	 $R^1 = \text{H}, R^2 = \text{Ph};$ $R^1 = R^2 = \text{CO}_2\text{Alk}$	 $R^3 = \text{Me}, \text{Et}$		a) DABCO (0.2 equiv), MeOH, 80 °C, 3 days	94	201
				b) DABCO (50 mol.%), CuO(nano) (5 mol.%), ZrO ₂ (balls), zirconia grinding jar, 1 h	up to 93	202
				c) NaHSO ₄ /SiO ₂ , PhMe or <i>o</i> -dichlorobenzene, Δ , 6 h	up to 66	203
4	 $R^1 = \text{H}, \text{Me}, \text{Hal};$ $R^2 = \text{H}, \text{Cl}$			d) TEMPO (10 mol.%), H ₂ O, air, 60 °C, 4 h	up to 96	198
				DABCO, EtOH (abs), 80 °C, 80 h, sealed tube	up to 75	204
5	 $R^1 = \text{Alk}, \text{CH}_2\text{OH},$ $\text{OC}_5\text{H}_{11-n}, 2\text{-Py}$	 $R^2 = \text{Me}, \text{Et}$		DABCO (50 mol.%), CuO(nano) (5 mol.%), ZrO ₂ (balls), zirconia grinding jar, 60 °C, 1h	up to 92	202
6				Mn(OAc) ₃ , MeCN, Δ , 12 h	up to 33	205
7	 $X, Y = \text{N}, \text{CH}$	 $R = \text{Alk}$		K ₂ CO ₃ , MeCN, Δ , 3 h	5–8	205
8	 $R = \text{Ar}, 1\text{-Naph}, 2\text{-Fu}$			a) Cs ₂ CO ₃ (4 equiv.), L ²¹ (10 mol.%), CHCl ₃ , rt, 7 days	up to 80 (<i>dr</i> = >20: 1, <i>er</i> up to 95%)	206
				b) Et ₃ N, MeCN, rt, 0.5 h	95	207
9	 $R^1 = \text{Alk}, \text{OAlk}, \text{NHAlk};$ $R^2 = \text{H}, \text{Hal}, \text{Me}, \text{OMe}, \text{etc.}$			AIBX (2.5 equiv.), AcOH (1 equiv.), MeCN–H ₂ O (1 : 3 (vol.)), 0 °C → rt 50 min–24 h	up to 98	208
10	 $R = \text{Bn}, \text{Ar}, 2\text{-Th}, 3\text{-Th}$			DABCO (20 mol.%), H ₂ O, US, 40 °C, 24 h	up to 92	200
11			 	NaHCO ₃ (1.5 equiv.), CAN (1.5 equiv.), EtOH, argon, 5 °C	65 (racemate)	209

Table 6 (continued).

No	Substrate	Nitro compound	Product	Reaction conditions	Yield (%) (selectivity)	Ref.
12				NaHCO ₃ (1.5 equiv.), CAN (1.5 equiv.), EtOH, argon, 5 °C	48	209
13	 R ¹ = H; R ² = Alk, CH ₂ Ar; R ¹ -R ² = (CH ₂) ₄			a) Chloramine-T (0.5 equiv.), MeCN, 80 °C, 18 h b) NaHSO ₄ /SiO ₂ , PhMe, Δ, 6 h c) AgNO ₂ (2 equiv.), Cu(MeCN) ₄ PF ₆ (10 mol.%), Zn(OTf) ₂ (50 mol.%), AcOK, MeCN, argon, MS 4 A, 80 °C, 24 h	up to 89 89 79	199 203 210
14	 R ¹ = H; R ² = Alk, CO ₂ Et; R ¹ = R ² = CO ₂ Alk			a) Chloramine-T (0.5 equiv.), MeCN, 80 °C, 18 h b) PPA, 110 °C, 2 h c) TEMPO (10 mol.%), H ₂ O, air, 60 °C, 4 h d) NaHSO ₄ /SiO ₂ , PhMe, Δ, 6 h e) DABCO (50 mol.%), CuO(nano) (5 mol.%), ZrO ₂ (balls), zirconia grinding jar, 60 °C, 1 h	up to 64 up to 38 up to 96 up to 96 up to 73	199 211 198 203 202
15	 R = Ar			DABCO (50 mol.%), CuO(nano) (5 mol.%), ZrO ₂ (balls), zirconia grinding jar, 60 °C, 1 h	up to 94	202
16	 R ¹ = Ar, 2-Th, 2-Fu			DIPEA (2 equiv.), MeCN, rt, 36–72 h	up to 72	206
17	 R ¹ = Me; R ² = Alk, Ph; R ¹ = R ² = Ph			NaHSO ₄ /SiO ₂ , PhMe, 80 °C, 8 h	up to 97	212

Note. TEMPO is (2,2,2,6-tetramethylpiperidin-1-yl)oxyl, Naph is naphthyl, Fu is furyl, Th is thienyl, US is ultrasonication, AIBX is 5-trimethylammonio-2-iodoxybenzoate, *er* is enantiomeric ratio, PPA is polyphosphoric acid.

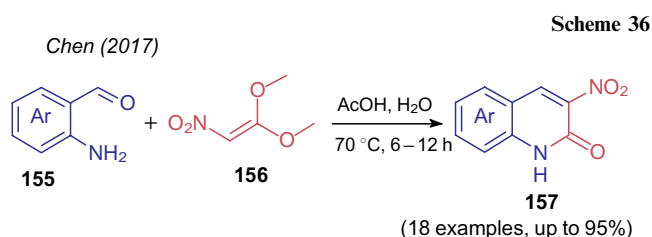
3.2. Alkyl nitroacetates

The following are the most specific properties of alkyl nitroacetates. Quite often, these compounds are considered as latent analogues of glycine alkyl esters. This determines the ways of their modifications, which were discussed in detail in the review by Hervin *et al.*³⁰ The methods for the synthesis of such compounds can be found in publications.^{214, 215}

3.2.1. Cycloaddition reactions

The presence of a nitro group, which significantly increases the acidic properties of the methylene carbon atom, as well as the ethoxycarbonyl group, turns ethyl nitroacetate (**6a**) into a pronounced bifunctional NSE, which is often used in the synthesis of six-membered rings. Several examples demonstrating the involvement of compound **6a** in the construction of a ring of nitroquinolones and nitrocoumarins are presented in Table 7. In general, these transformations are a modification of the Friedländer reaction, which can involve both *o*-aminobenzaldehydes and salicylic aldehydes.^{216–222}

An interesting example is the use of 1,1-dimethoxy-2-nitroethylene (**156**) instead of alkyl nitroacetate in the reaction with *o*-aminobenzaldehydes **155** (Scheme 36). Chen *et al.*²²² pointed out that such NSE was first deve-



loped so as to introduce the CH=CHNO₂ fragment into molecules to design biologically active compounds. Despite the structural similarity of nitroalkene **156** with dimethyl carbonate, the authors failed to use this NSE as an alkylating agent, but this compound found application in the preparation of 3-nitroquinolin-2-ones **157** on heating in dilute acetic acid. Apparently, in the presence of water, 1,1-dimethoxy-2-nitroethylene (**156**) hydrolyzes to methyl nitroacetate, which is involved in the cycloaddition reaction by known mechanisms.

Of particular interest is the synthesis of 3-nitroazolo[5,1-*c*]triazines **158**^{10, 13, 14, 223–227} from ethyl nitroacetate (**6a**) and diazoles **159** generated *in situ* during diazotization of the corresponding amino azoles **12** (Scheme 37). The reaction tolerates a wide range of amino-substituted pyr-

Table 7. Cycloaddition reactions involving ethyl nitroacetate (**6a**).

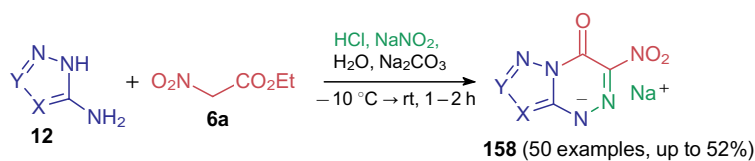
No	Aldehyde	Product	Reaction conditions	Yield (%)	Ref.
1			Piperidine, AcOH, Bu ⁿ OH, Δ, 24 h	73	216
2			Bu ⁿ OH, Δ, overnight	63	217
3			Piperidine, AcOH, Bu ⁿ OH, Δ, 5 h	85	218
4			Piperidine, PhH, Dean–Stark trap, Δ, 6 h	92–93	219
	R = Me, Bn				
5			L-Proline (30 mol. %), EtOH, rt, 4 h	84	220
6			Piperidine, PhMe (abs.), MW, 140 °C, 10 min	45	221
7			AcOH, H ₂ O, 70 °C, 12 h	92	222

azoles, imidazoles, triazoles and tetrazoles. Note that hydrazones **160** resulting from azo coupling can heterocyclize to products **158** without being isolated from the reaction mixture.^{225, 227}

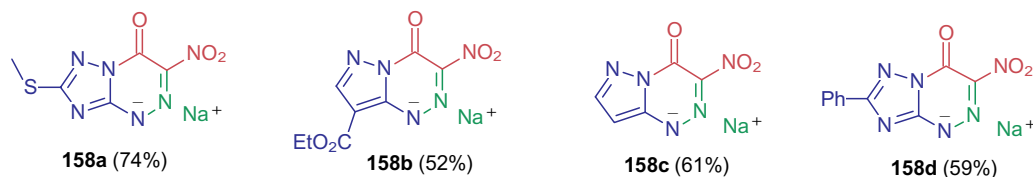
3-Nitroazolo[5,1-*c*][1,2,4]-triazin-4-ones **158** thus obtained form a new class of antiviral agents effective in the treatment and prevention of influenza, SARS, tick-borne encephalitis, as well as COVID-19 and a number of other viral infections. An antiviral drug Triazavirin (Riami-

Rusinov (2017)

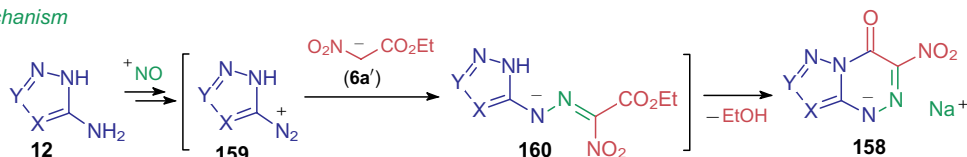
Scheme 37



Selected examples



Proposed mechanism



lovir),^{228,229} 6-methylthio-3-nitro[1,2,4]triazolo[5,1-c][1,2,4]triazin-4-one sodium salt dihydrate (**158a**), is produced in Russia on an industrial scale and are used in medical practice. Compounds **158** are also of interest as antidiabetic drugs.^{223,225} Moreover, the synthesis of Triazavirin labeled with several stable isotopes was reported, since incorporation of deuterium, ¹³C and ¹⁵N atoms into its structure provides unique opportunities for studying its metabolic processes and mechanism of action in the body.²³⁰

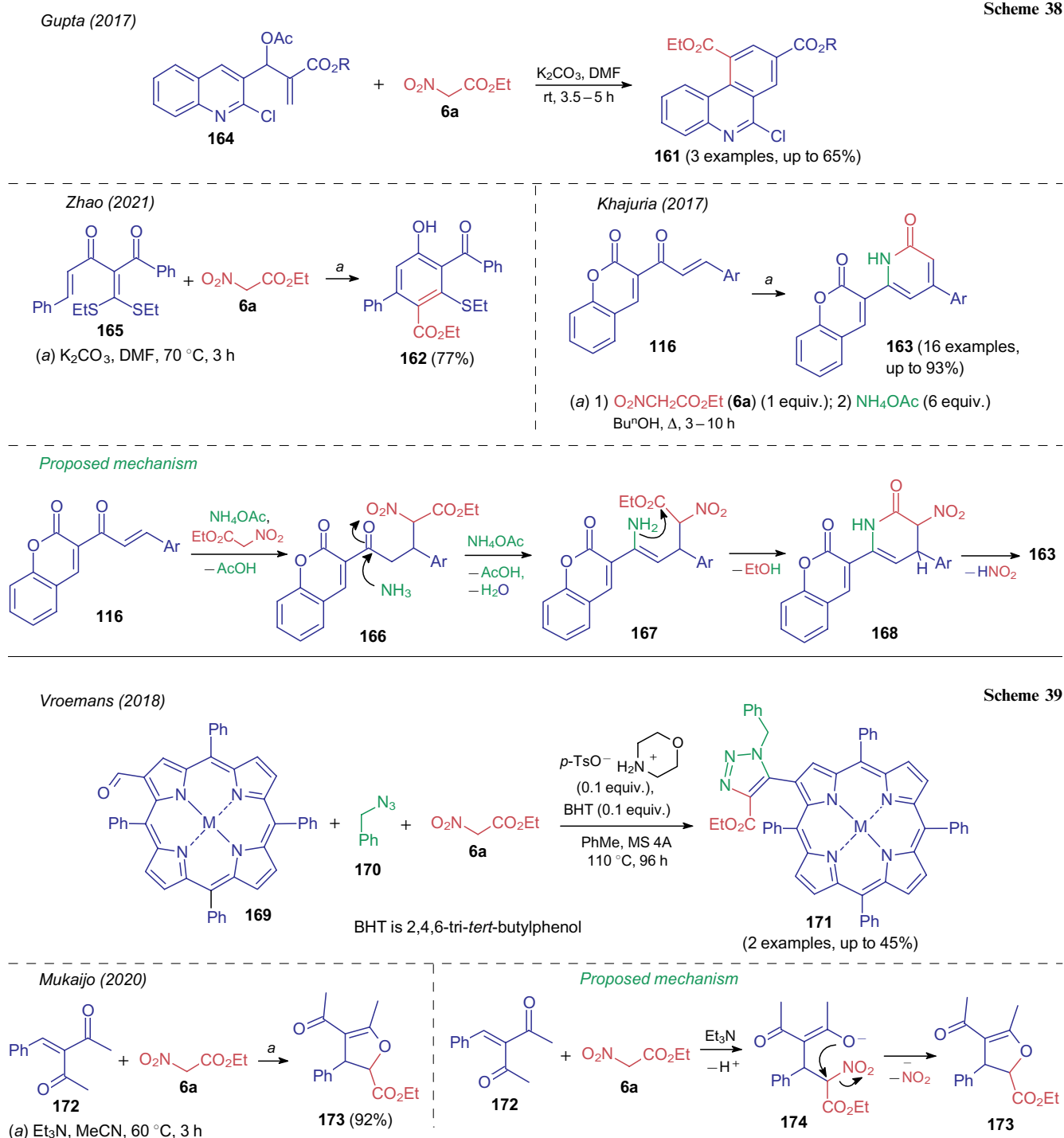
3.2.2. Transformations involving the elimination of the nitro group

Similar to NSEs outlined in the previous Section, alkyl nitroacetates enter the cycloaddition reactions, which lead

to aromatization *via* the expulsion of the nitrite anion. Thus, a number of publications^{231–233} deal with the synthesis of six-membered and heteroaromatic compounds **161–163** from substrates **116**, **164**, **165** and ethyl nitroacetate (**6a**) (Scheme 38). In general, such processes often requires the use of polar solvents and base catalysts. Despite the structural features of substrates **116**, **164**, **165**, the cyclization follow the similar mechanisms. For example, for products **163**, the formation of intermediates **166–168** is assumed.

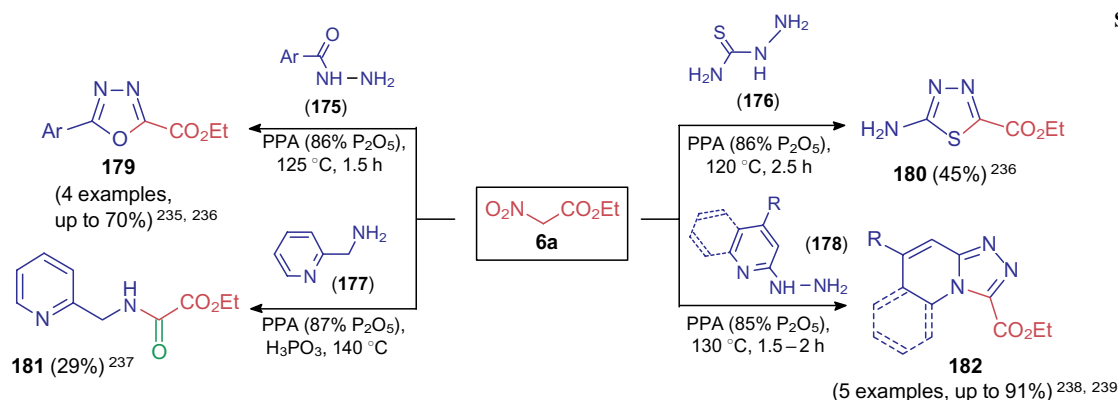
The synthesis of five-membered heterocycles using ANAs is also possible. Starting from complexes **169**, benzyl azide (**170**) and ethyl nitroacetate (**6a**), triazole-containing

Scheme 38

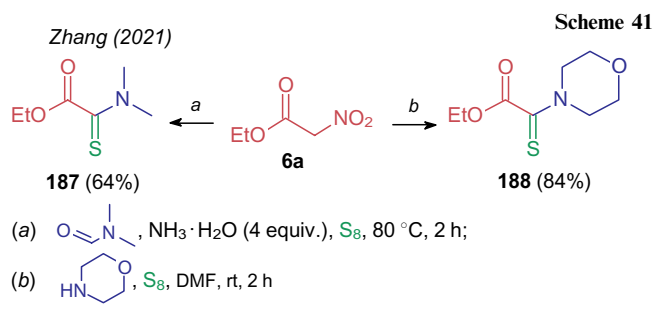
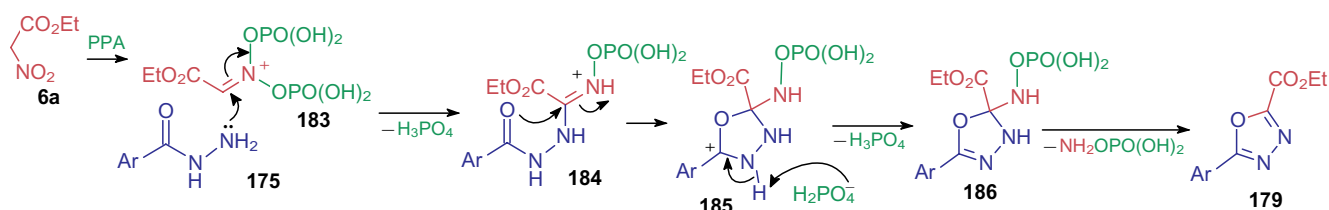


Scheme 39

Scheme 40



Proposed mechanism



porphyrins **171**²³⁴ were obtained, whereas 3-benzylidene-pentane-2,4-dione (**172**) and the nitro compound **6a** afforded dihydrofuran **173**.²⁰⁷ However, the mechanism of expulsion of the nitro group differs somewhat from that described in the previous examples. In reactions as illustrated in Scheme 39, the nitrite anion was not eliminated leading to aromatization of the molecule, but an intramolecular substitution occurs, *e.g.*, in structure **174** to form a heterocycle.

Aksenov *et al.*^{235–239} described a special type of nitro group substitution in ANAs. It was shown that the reaction between ethyl nitroacetate (**6a**) and polyphosphoric acid affords a diphosphorylated intermediate, which can further react with various N-nucleophiles, *e.g.*, with compounds **175**–**178** (Scheme 40). As a result, products **179**–**182** are formed. The authors suggest that N-nucleophile (*e.g.*, hydrazide **175**) attacks diphosphorylated intermediate **183** to generate species **184**, which further cyclizes into oxadiazolidine **185**. In the final step, the nitrogen atom of the nitro group leaves intermediate **186** in the form of aminoxyphosphoric acid.

In 2021, the research group of Zhang²⁴⁰ carried out the simultaneous thionation of ethyl nitroacetate (**6a**) on the CH-acidic carbon atom and displacement of the nitro group with dimethylamine (compound **187**) or morpholine (**188**) moieties (Scheme 41). (This process will be detailed in Section 3.3.5 on nitrocarbonyl compounds.)

3.2.3. Reactions at the C–H bond

This subsection covers the reactions of alkyl nitroacetates, in which an active methylene fragment is modified in ways other than those discussed above in the Knoevenagel and Michael reactions (Table 8). Among such processes, one can single out the addition of ethyl nitroacetate (**6a**) to heptene in the presence of ligand **L**²² and stereoselective aza-Henry conversion of imines and alkyl nitroacetates under the action of optically active quinoline catalyst **L**²³ (see Table 8, line 4). Also known is the regioselective reaction of ANAs with alkynes catalyzed by palladium or rhodium complexes with (2-biphenyl)dicyclohexylphosphine (Cy-Johnphos) or ligand **L**²⁴ (see Table 8, lines 5, 6), which is likely to occur *via* an intermediate allene structure. The reaction of ANA with alkylating agents containing various leaving groups (see Table 8, lines 7–13), such as

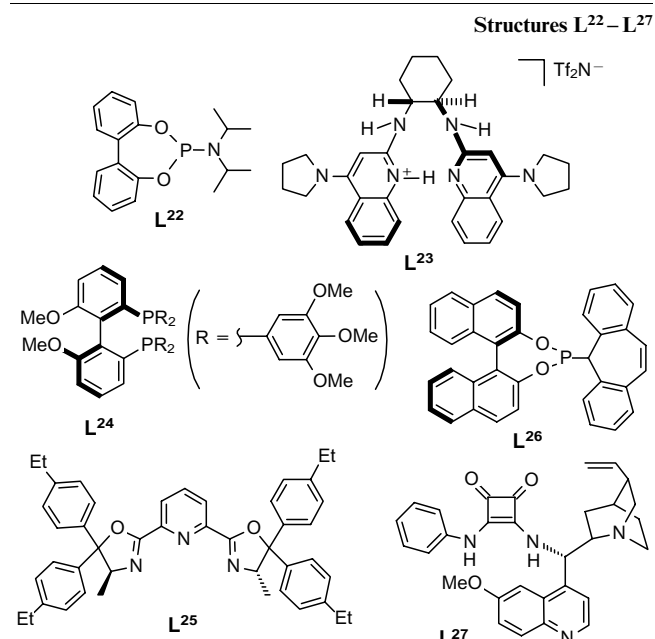
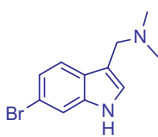
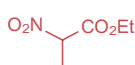
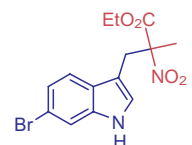
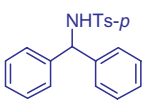
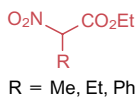
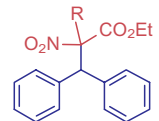
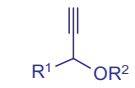
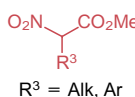

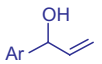

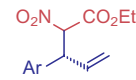
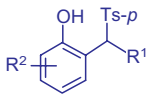
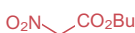
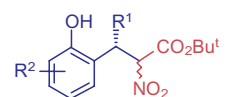


Table 8. Reactions involving the CH bond of nitro compounds **6**.

No	Substrate	Nitro acetate	Product	Catalys	Reaction conditions	Yield (%) (selectivity)	Ref.
1				PdCl ₂ –BINAP (10 mol.%), Ag ₃ PO ₄ (1 equiv.)	Na ₂ HPO ₄ · 12 H ₂ O (2 equiv.), DMA, 120 °C	24 (<i>dr</i> = 1 : 1.3)	241
2				Pd(OAc) ₂ (5 mol.%), PPh ₃ (15 mol.%)	Et ₂ O, rt, 1–5 h	up to 71	242
3				Pd ₂ (dba) ₃ (2.5 mol.%), L ²² (5 mol.%)	2,5-DTBQ (1.1 equiv.), 1,4-dioxane, 50 °C, 24 h	73	243
4				L ²³ (5 mol.%)	PhMe or CH ₂ Cl ₂ , –20 °C, 2 days	up to 76 (<i>dr</i> from 1 : 1 to > 20 : 1, up to 99% <i>ee</i>)	244–246
5				Pd(PPh ₃) ₄ (10 mol.%), Cy-Johnphos (20 mol.%)	PhCO ₂ H (10 mol.%), H ₂ O, argon, 100 °C, 24 h	–	247
6				[Rh(cod)Cl] ₂ (4 mol.%), L ²⁴ (8 mol.%)	(PhO) ₂ P(O)OH (20 mol.%), DCE, 80 °C, 24 h	up to 96 (<i>dr</i> = > 20 : 1, up to 98% <i>ee</i>)	248
7				TBAI (10 mol.%)	DIPEA, DMF, argon, 0 °C → rt, overnight	35	249
8				–	NaH, DMF, N ₂ , rt, overnight	79	250

Table 8 (continued).

No	Substrate	Nitro acetate	Product	Catalys	Reaction conditions	Yield (%) (selectivity)	Ref.
9				—	PhMe, N ₂ , 105 °C, 24 h	24	251
10		 R = Me, Et, Ph		AlCl ₃ (100 mol.%)	CHCl ₃ , 80 °C, 12 h	up to 56	252
11	 R ¹ = Alk, Ar; R ² = Boc, C(O)C ₆ F ₅	 R ³ = Alk, Ar		Cu(MeCN) ₄ BF ₄ (5 mol.%), L ²⁵ (6 mol.%)	<i>N</i> -Ethylmorpholine (2 equiv.), CH ₂ Cl ₂ , −40 °C, 48–72 h	up to 97 (<i>dr</i> from 1.5 : 1 to 20 : 1, up to 97% <i>ee</i>)	253
12				[Ir(cod)Cl] ₂ (4 mol.%), Zn(OTf) ₂ (20 mol.%), L ²⁶ (16 mol.%)	CH ₂ Cl ₂ , 50 °C, 6–11 h	up to 73 (>99% <i>ee</i>)	254
13	 R ¹ = Me, Ar; R ² = Alk, OMe, etc.			L ²⁷ (10 mol.%), rt, 72 h	NaHCO ₃ (5% aq.) (50 equiv.), CHCl ₃	up to 99 (<i>dr</i> from 1 : 1 to 5 : 1, up to 99% <i>ee</i>)	255

Note. BINAP is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, DMA is dimethylamide, 2,5-DTBQ is 2,5-di-*tert*-butyl-*p*-hydroquinone, cod is cycloocta-1,5-diene, TBAI is tetra-*n*-butylammonium iodide.

bromide, tosyl, hydroxide, alkoxide, and amines, was studied. As ligands, compounds **L**²⁵–**L**²⁷ can be used. It is also worth noting that in the presence of metal complexes, the alkylation reaction prevails in the competitive processes of addition of ANAs to alkynes (see Table 8, line 11) and alkenes (see Table 8, line 12).

3.2.4. Other reactions

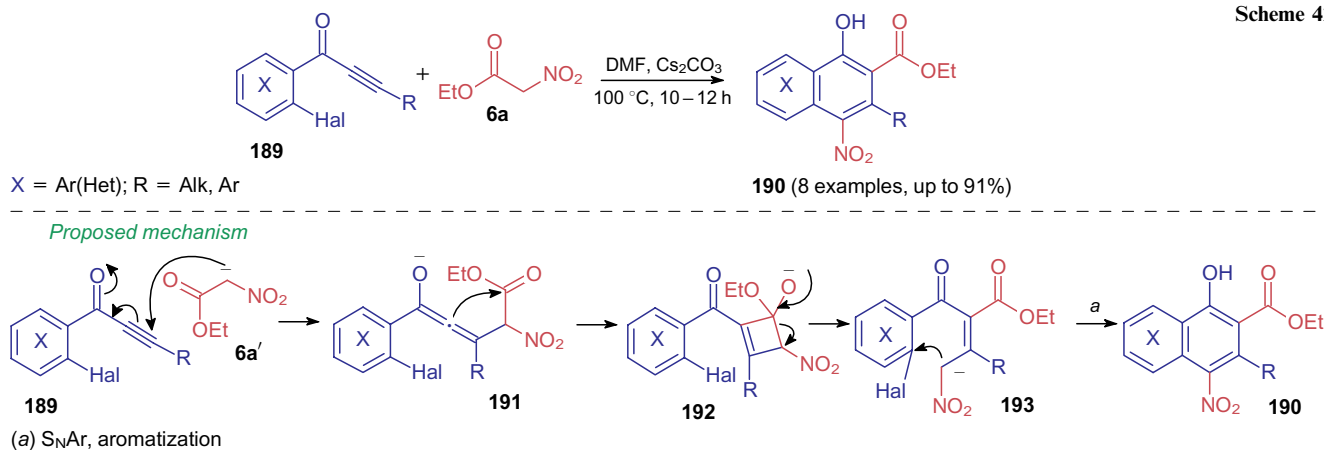
Ethyl nitroacetate (**6a**) undergoes an unusual C–C bond cleavage when reacting with ketoalkynes **189** in the presence of cesium carbonate at elevated temperatures to produce nitro(het)arenes **190**.^{256, 257} The authors note that activated NSE **6a'** first adds across a triple bond of substrate **189** to yield allene **191**, which then undergoes an intramolecular cyclization to afford nitro-containing cyclobutene **192** (Scheme 42). Further, the C–C bond, which previously belonged to the starting compound **6a**, is cleaved in the intermediate **192** to generate anion **193**. Given the halogen atom *ortho*-positioned to the alkynylcarbonyl substituent in substrate **189**, the final reaction step is aromatization with nucleophilic aromatic substitution of that halogen atom.

Noteworthy that similar reaction of 3-alkynyloxy-substituted indoles **194** devoid of the 2-positioned halogen atom delivers products **195a–c** containing no nitro group.²⁵⁸ In this case, the generation of intermediates **196** and **197** is followed by the final aromatization of an intermediate anion **198** *via* the loss of a molecule of nitrous acid (Scheme 43).

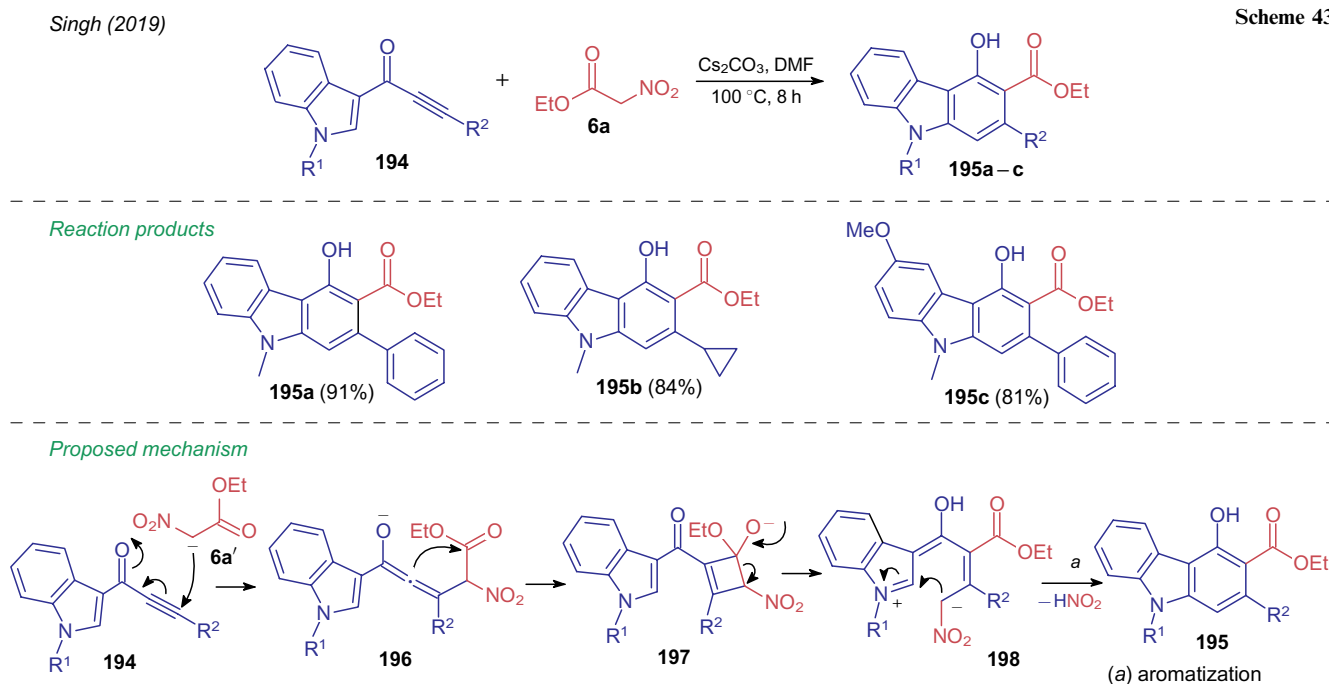
In 2020, Roscales and Csáky²⁵⁹ described the protocol for a simultaneous reduction of a nitro group and its modification in alkyl nitroacetates. Thus, a prolonged heating of compounds **6** with arylboronic acids **199** and trialkyl phosphites **200** furnishes aminoacetic acid esters **201** in satisfactory-to-good yields (Scheme 44). The plausible mechanism suggests the formation of a four-membered ring intermediate **202**, which attacks arylboronic acid **199**. Next, two molecules of trialkyl phosphate are released sequentially from intermediate compounds **203** and **204**. The newly formed boramide acid **205** is alkylated with trialkyl phosphate to give aminodisubstituted product **201**.

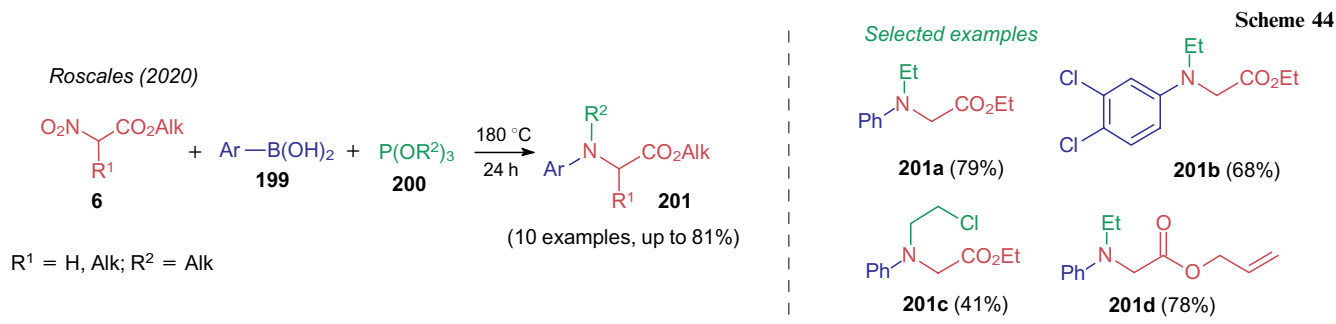
Alkylation and arylation are not the only reactions of the nitro group reductive modification. Qu *et al.*²⁶⁰ showed the possibility of acylating ethyl nitroacetate (**6a**) with

Scheme 42

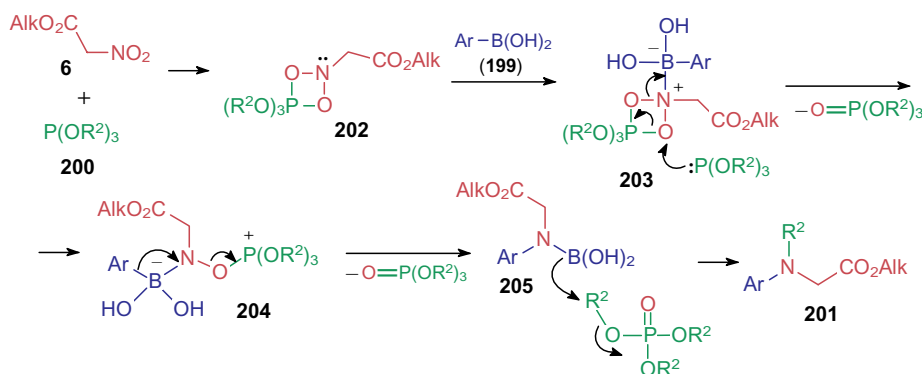


Scheme 43



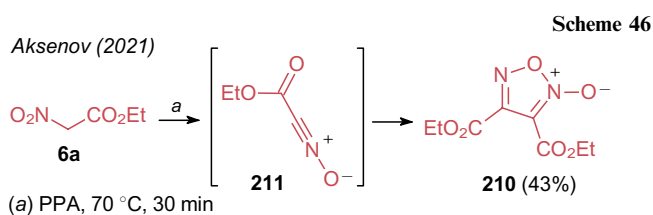


Proposed mechanism



benzotriazole **206** on reduction with zinc in the presence of phenanthroline **L²⁸**, which delivered product **207** followed heating in dioxane (Scheme 45). Based on the control experiments, the author proposed the mechanism including the initial formation of azodicarboxylate **208**, which further converts to a nitrene intermediate **209** under the action of Ni^0 .

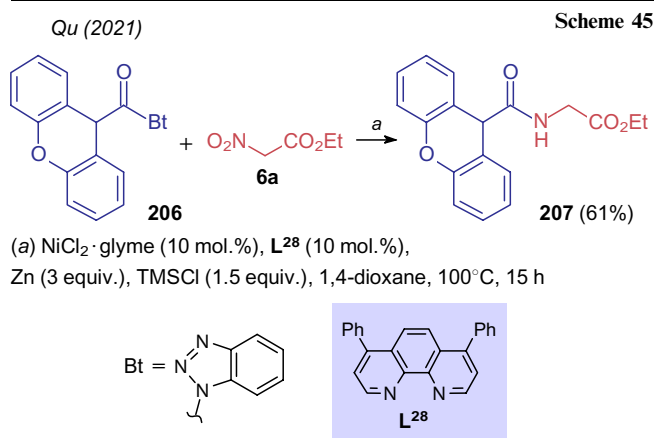
Cited above publications of Aksenov *et al.*^{235–239} describe a special influence of polyphosphoric acid on the reactions of alkyl nitroacetates **6** with nucleophiles (see Scheme 40). At the same time, under certain conditions,²¹¹ polyphosphoric acid reacts with ANAs as a conventional mineral acid, *i.e.*, it does not provoke the expulsion of the



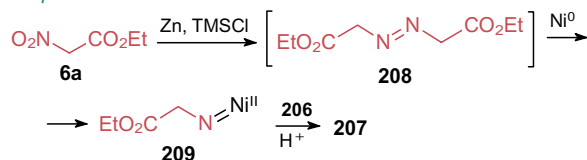
nitro group, but promotes dehydration. Thus, compound **6a** delivers disubstituted furoxan *N*-oxide **210** in the presence of polyphosphoric acid at 70 °C (Scheme 46). This reaction was carried out to study the influence of PPA on NSEs. Nitrile oxide **211** is proposed to be the key intermediate; however, it was not possible to isolate it because of its high reactivity.

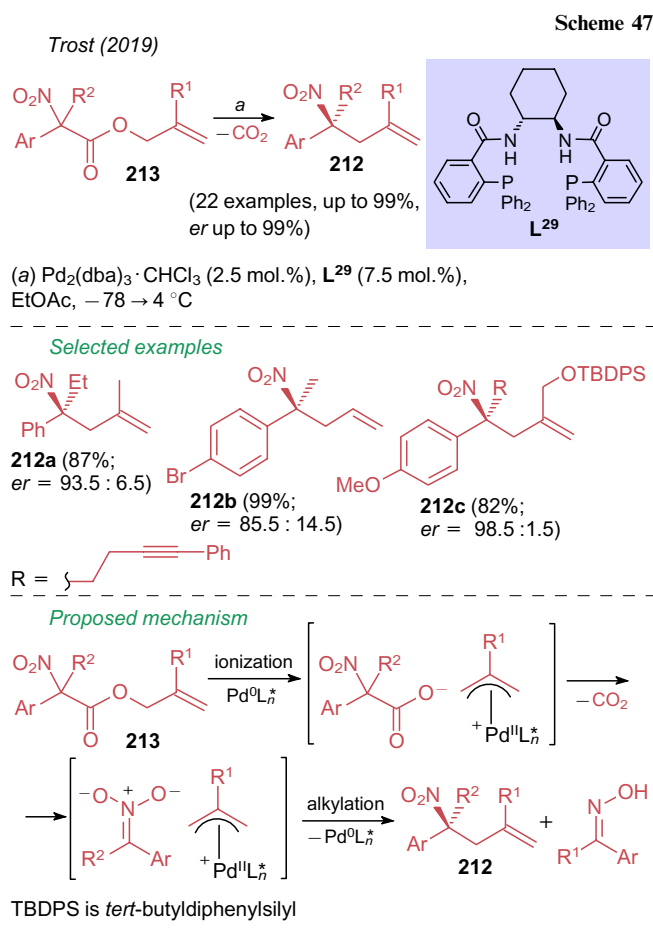
An interesting example of enantioselective palladium-catalyzed decarboxylation was reported by Trost *et al.*²⁶¹ in 2019. The use of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ complex and optically active ligand **L²⁹** in ethyl acetate at low temperature makes available the synthesis of tetrasubstituted nitroalkanes **212** from allyl nitroacetates **213** (Scheme 47). The authors note that this synthetic approach to nitroalkanes **212**, referred to as decarboxylative asymmetric allylic alkylation (DAAA), has several advantages over the alternative strategy involving allylation of disubstituted nitroalkanes. The main advantages of this reaction are high stereoselectivity and an insignificant effect of steric factors.

To summarize this Section, it can be said that the difference in chemical behaviour between conjugated NSEs and nitroalkane-type structures is already evident in the example of alkyl nitroacetates. The C–H bond in nitroacetates has a strong acidic character, providing a variety of simple transformations with the formation of a new C–C bond. Moreover, compounds **6** are much more likely to enter reactions with direct involvement of the nitro group,



Proposed mechanism





thereby providing an access to both new heterocyclic compounds and polysubstituted amines.

3.3. α -Nitrocarbonyl compounds

As mentioned above, α -nitroketones (**5**) and alkyl nitroacetates (**6**) have similar chemical behaviour patterns. Their most distinctive features are the reactions arising from the

presence of a carbonyl rather than an ester moiety, such as addition of nucleophiles and reduction. In general, α -nitroketones are quite ubiquitous compounds and methods for their preparation are detailed in a monograph.¹⁶

3.3.1. Cycloaddition reactions

Similar to ANAs, α -nitroketones, due to their bifunctional nature, enter cyclization reactions. These can be cyclocondensations involving only nitroketones, as well as nitroketones and other bifunctional substrates with various carbonyl compounds or their latent forms (Table 9).

Like ethyl nitroacetate (**6a**), salts of nitroacetaldehyde and α -nitroketones **32** are versatile substrates for the construction of nitro-1,2,4-triazine core in the synthesis of 4-hydroxy-3-nitro-1,4-dihydroazolo[5,1-*c*]-1,2,4-triazines **214** (Scheme 48).^{265–267} This transformation, as that depicted in Scheme 37, suggests diazotization at -10 °C without isolation of an intermediate hydrazone.

3.3.2. Reactions with the cleavage of the C(NO₂)–C(O) bond

A distinctive feature of α -nitroketones is the C–C bond cleavage in reactions with various bifunctional compounds (Table 10). Several examples of such interaction were observed for ANAs (see Schemes 42, 43), however, for

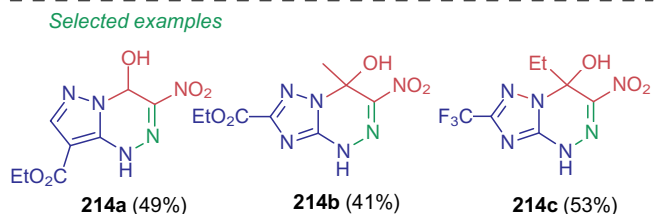
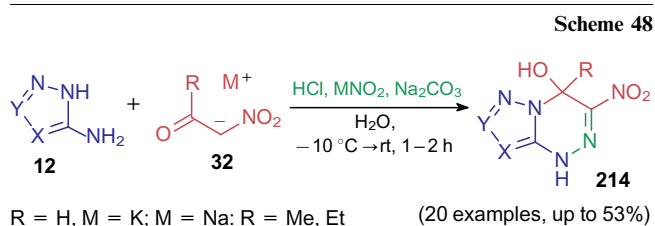


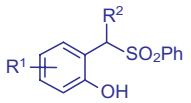
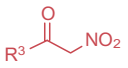
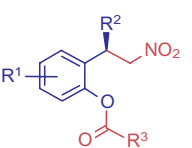
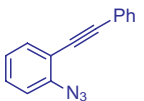
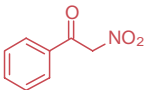
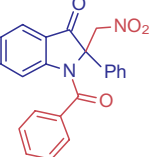
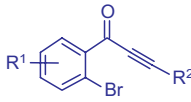
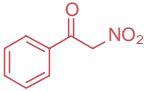
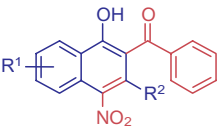
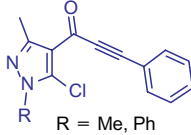
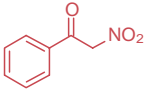
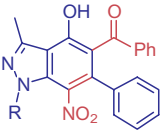
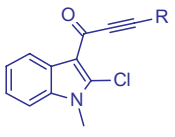
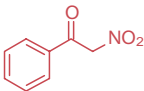
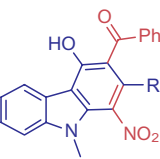
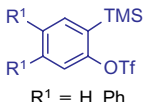
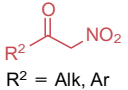
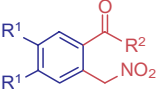
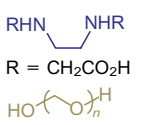

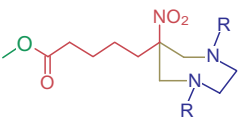
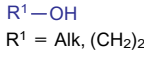
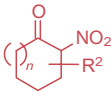
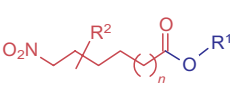
Table 9. Cycloaddition reactions involving compounds **5**.

No	Nitro ketone	Substrate	Other reactants	Product	Reaction conditions	Yield (%)	Ref.
1			CH(OEt) ₃ EWG = Ac, CO ₂ Et		a) AcOH, 80 °C, 5 days b) AcOH, N ₂ , 65 °C, 48 h	up to 48 up to 77	262 62
2			 NH ₄ OAc		AcOH, 50–60 °C, 0.5–1 h	up to 45	263
3					HCl, EtOH, Δ , 7 h	up to 89	33
4			 NH ₄ OAc		AcOH, 60 °C, 3–10 min	up to 63	264

Table 10. Reactions with the cleavage of the C(NO₂)–C(O) bond in compounds 5.

No	Substrate	Nitro ketone	Product	Asymmetric catalyst	Reaction conditions	Yield (%) (stereoselectivity)	Ref.
1	 X = O, NBn			L¹⁹ (10 mol.%)	CH ₂ Cl ₂ , 0 °C, 48 h	up to 91 (up to 50% <i>ee</i>)	193
2	 X = O, NBn; R ¹ = Ar, 2-Th	 R ² = Ar, (CH ₂) ₂ Ph, Cy		L³⁰ (10 mol.%)	DCE, 25 °C, 12 h	up to 85 (up to 90% <i>ee</i>)	268
3	 R ¹ = Me, Bn, Ph; R ² = H, Me, Hal, OMe, OCF ₃			–	DBU (20 mol.%), CHCl ₃ , 30 °C, 1–2 days	up to 99	269
4	 R ¹ = H, Me, Cl, CF ₃ ; R ² = Ar	 R ³ = Me, Ar, 2-Th		L³¹ (5 mol.%)	EtOAc, 0 °C, 24 h	up to 98 (up to 95% <i>ee</i>)	270
5	 R ¹ , R ² = Ar	 R ³ = Ar, 2-Th		L³² (10 mol.%),	PhCF ₃ , 0 °C, 5 days	up to 94 (up to 99% <i>ee</i>)	271
6	 R ¹ = Ar, (CH ₂) ₂ Ph, 2-Th; n = 1, 2	 R ² = Ar, 2-Th, Cy		L¹⁹ (10 mol.%)	PhMe, rt, 2–5 days	up to 93 (up to 99% <i>ee</i>)	194
7	 R ¹ = Me, Ar, Het; R ² = H, Me, Cl, OMe, NO ₂	 R ³ = Me, Ar, 2-Th		L¹⁹ (20 mol.%)	THF, rt, 168 h	up to 99 (up to 97% <i>ee</i>)	272
8	 R ¹ = Alk, Ph; R ² = H, Me, Cl, OMe, OEt	 R ³ = Ar		L³³ (20 mol.%)	PhCO ₂ H (20 mol.%), DCE, rt, 5 days	up to 82 (up to 99% <i>ee</i>)	273
9	 R ¹ = Me, Hal, OMe, NO ₂	 R ² = Ph		L³⁴ (20 mol.%)	PhCO ₂ H (20 mol.%), DCE, 20 °C, 7 days	up to 93 (<i>dr</i> = > 20 : 1, up to 96% <i>ee</i>)	274
10	 R = H, Me, Hal, OMe	 Ar(Het)		L³⁵ (10 mol.%)	DCE, rt, 2–7 days	up to 92 (up to 98% <i>ee</i>)	275

Table 10 (continued).

No	Substrate	Nitro ketone	Product	Asymmetric catalyst	Reaction conditions	Yield (%) (stereoselectivity)	Ref.
11	 R ¹ = H, Alk, Hal, etc.; R ² = Ar	 R ³ = Bu ⁿ , Ar, 2-Th		L ³⁶ (10 mol.%)	NaHCO ₃ (10% aq.) (50 equiv.), rt, 3 days	up to 99 (98% <i>ee</i>)	276
12				—	1) Pd(OAc) ₂ (5 mol.%), <i>p</i> -TsOH (3 equiv.), 1,4-dioxane, rt, 10 min; 2) Cs ₂ CO ₃ (3.5 equiv.), 90 °C, 2 h	68%	277
13	 R ¹ = H, OCH ₂ O; R ² = Ph, cyclo-C ₃ H ₅			—	Cs ₂ CO ₃ (2 equiv.), DMF, 100 °C, 12 h	up to 82	256
14	 R = Me, Ph			—	Cs ₂ CO ₃ (2 equiv.), DMF, 100 °C, 10 h	up to 75	257
15	 R = Ph, 4-Bu ^t C ₆ H ₄			—	Cs ₂ CO ₃ (2 equiv.), DMF, 100 °C, 8 h	up to 80	258
16	 R ¹ = H, Ph	 R ² = Alk, Ar		—	KF (2.5 equiv.), MeCN, 80 °C, 8 h	up to 96	278
17	 R = CH ₂ CO ₂ H HO-(O) _n -H			—	Amberlyst A21, MeOH, 80–90 °C, 16 h	up to 85	279– 282
18	 R ¹ = Alk, (CH ₂) ₂ OH	 R ² = H, Me, Me ₂ ; n = 0–2		—	PS-BEMP (25 mol.%), ^a rt, 2–29 h	up to 98	283

^a PS-BEMP is 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene.

compounds **5**, a much larger number of such reactions are known. Ligands L¹⁹ (see the structure above), L³⁰–L³⁶ were used as asymmetric catalysts.

3.3.3. Reactions with nucleophiles

Reactions of nitrocarbonyl compounds with C- and N-nucleophiles generally affect the carbonyl moiety by the addition or A_NE patterns (*i.e.*, with the loss of a water molecule). Thus, examples of the reaction of nitroketones **5a,b** with the Grignard reagent to afford nitro derivatives **215**, **216** are known (Scheme 49).^{284,285}

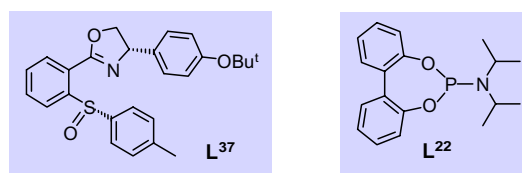
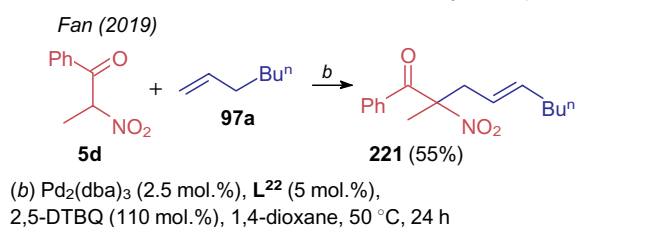
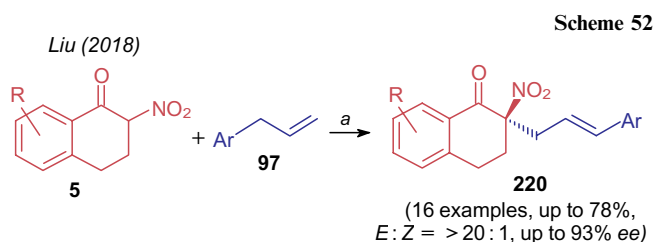
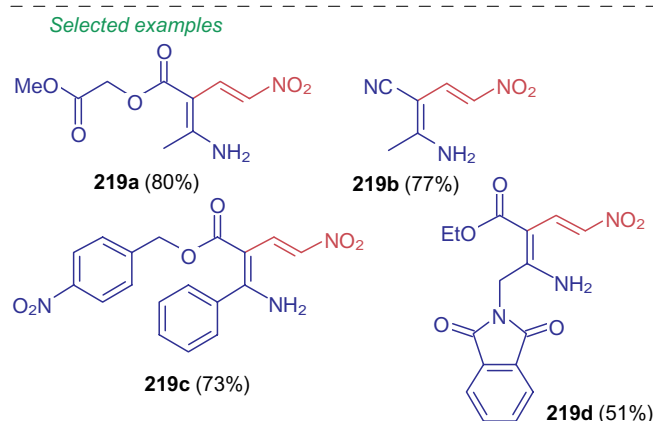
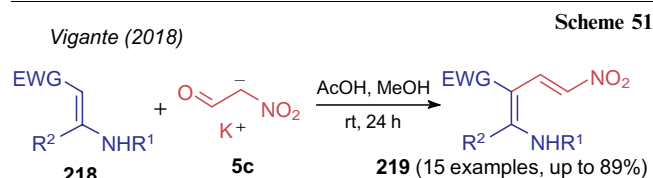
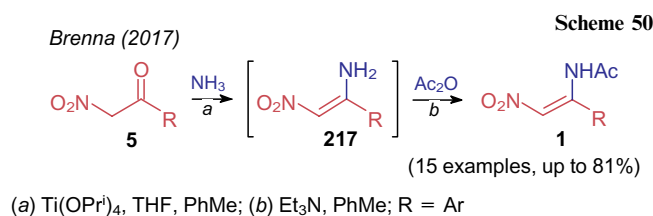
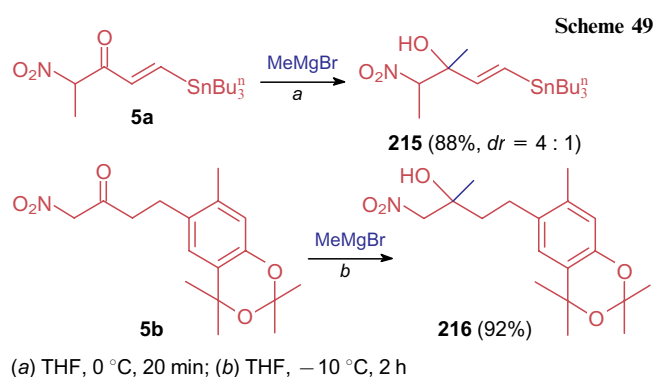
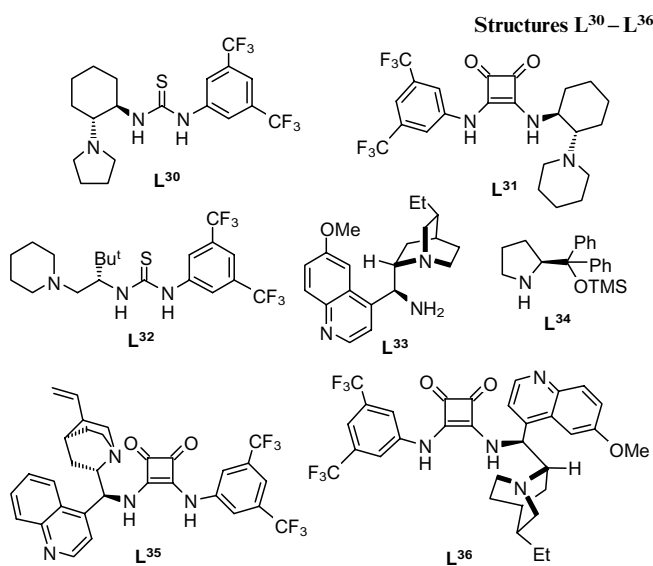
Brenna *et al.*³⁵ described the preparation of N-acylated aminonitroethylenes **1** by treating nitroketones **5** with

ammonia in the presence of titanium isopropoxide followed by acylation of intermediate **217** (Scheme 50).

Potassium salt of nitroacetic aldehyde **5c** can react with push–pull pre-nucleophiles **218** in a methanol–acetic acid mixture (Scheme 51).²⁸⁶ This process can also be considered as an incorporation of a nitrovinyl fragment into a molecule.

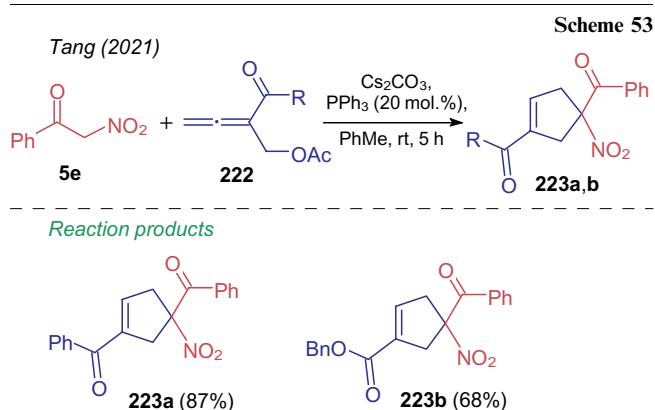
3.3.4. Reactions at the C–H bond

Modification of the C(sp³)-hybridized atom in nitro-containing carbonyl compounds is mainly represented by their reactions with unsaturated hydrocarbons. Thus, Liu *et al.*²⁸⁷ and Fan *et al.*²⁴³ reported alkylation of terminal



olefins using palladium catalysts and appropriate ligands L³⁷ and L²² (Scheme 52). Using aryl sulfoxide–oxazoline catalyst L³⁷, (*R*)-2-(3-aryllallyl)-3,4-dihydro-2-nitronaphthalen-1-ones **220** were produced with high enantioselectivity. The similar reaction involving nitroketone **5d** and heptene **97a** in the presence of ligand L²² furnished product **221** in moderate yield.

When treated with a base and triphenyl phosphine, nitroacetophenone (**5e**) reacts with allenes **222** to give 1-benzoyl-1-nitrocyclopent-3-ene-3-carboxylates **223a,b** in high yields (Scheme 53).²⁸⁸



In 2018, An *et al.*²⁸⁹ pioneered in carrying out α -C-arylation of nitroketones **5** with diaryliodonium salts under metal-free conditions to afford a wide range of nitro compounds **224** (Scheme 54).

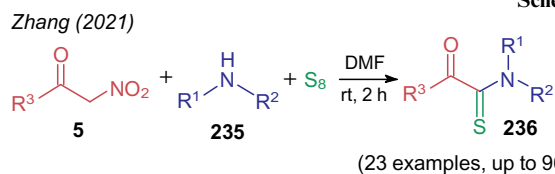
3.3.5. Transformations with elimination of the nitro group

In 2017, Reddy *et al.*²⁹⁰ showed an example of the Henry reaction between nitroketones and nitrosocarboxylic acid esters **226** generated *in situ* from alkyl-*N*-hydroxycarbamates **225**, which ends up with elimination of a nitrite ion (Scheme 55). The reaction pathway differs for unsubstituted

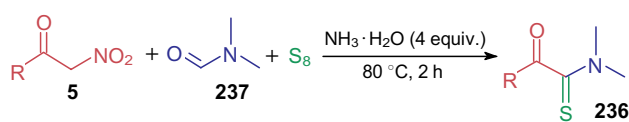
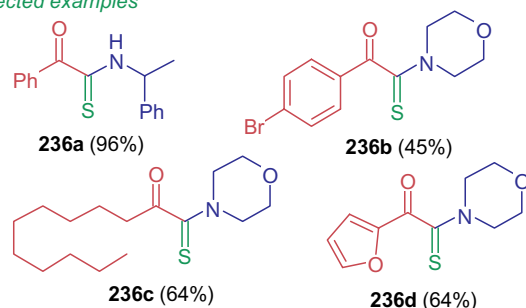
α -nitroketones (**5**) and their analogues **227** substituted at the CH-acidic atom: in the first case, the reaction affords α -ketoamides **228** [see Scheme 55, reaction (1)], while substrates **227** deliver α -ketoximes **229** [see Scheme 55, reaction (2)]. The plausible mechanism of both processes include the formation of intermediates **230**–**234**.

For nitro carbonyl compounds, a process was also described similar in conditions to the Willgerodt–Kindler reaction. Zhang *et al.*²⁴⁰ noted that thionation of nitroketones **5** with elemental sulfur in dimethylformamide in the presence of various amines **235** occurs with the displacement of a nitro group to give products **236** in good yields (Scheme 56). If ammonia is used as the amine, the products are dimethylamine derivatives of ketothioamides **236** ($R^1 = R^2 = \text{Me}$), since dimethylformamide **237** acts as a reactant under reaction conditions and decomposes into carbon monoxide and dimethylamine. The mechanism of

Scheme 56

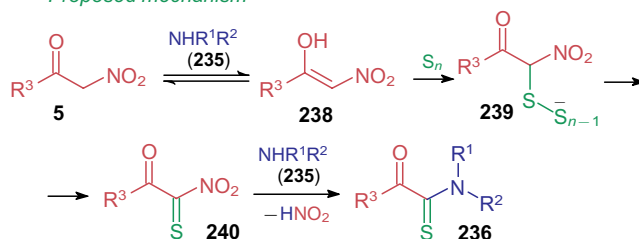


Selected examples



R = Ar, Het

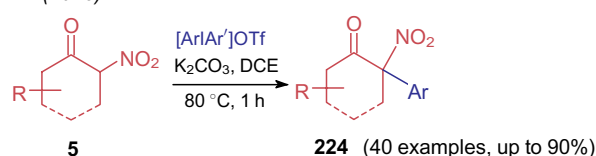
Proposed mechanism



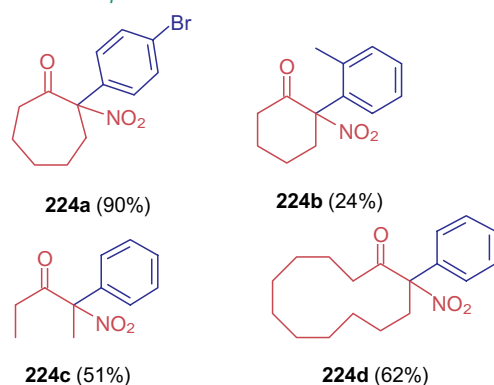
this process suggests the initial thionation of the CH-acidic atom of the enol form **238** to afford adduct **239**, which significantly facilitates the subsequent nucleophilic substitution of the nitro group in intermediate **240**.

An (2018)

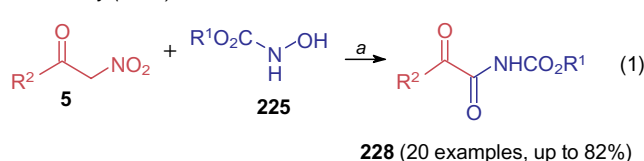
Scheme 54



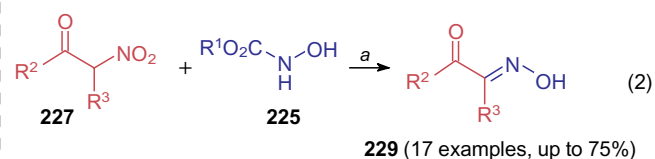
Selected examples



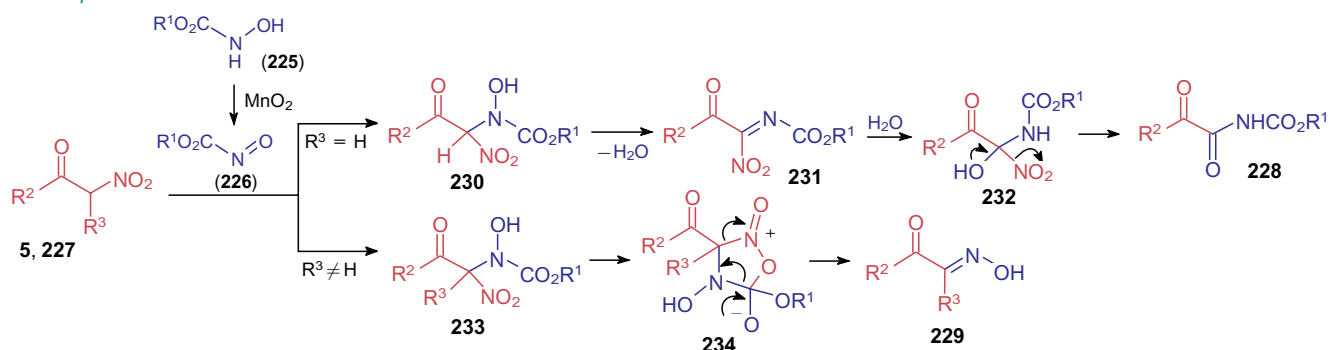
Reddy (2017)

(a) quinidine (10 mol.%), MnO₂ (5 equiv.), THF, rt, 48 h; R¹ = CH₂Ar, (–)-menthyl; R² = Ar, Het; R³ = H, Me

Scheme 55

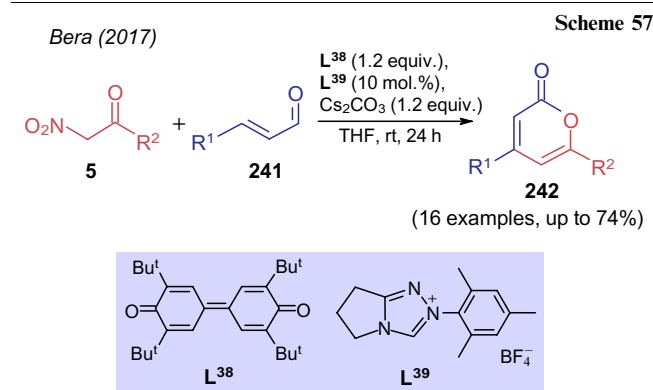


Proposed mechanism



In nitrocarbonyl compounds as in alkyl nitroacetates, the nitro group often serves as a leaving group, leading to the formation of aromatic compounds. Thus, the reaction of β -arylcinnamaldehydes **241** with nitroketones **5** in the presence of oxidant **L**³⁸ and triazolium salt **L**³⁹ generating

the carbene catalyst affords α -pyrones **242** (Scheme 57).²⁹¹ According to the authors, NK **5** adds to the activated species **243** followed by the loss of nitrous acid by salt **244**. Then, intermediate **245** undergoes lactonization to yield α -pyrone **242** and carbene **246**, to complete the catalytic cycle.



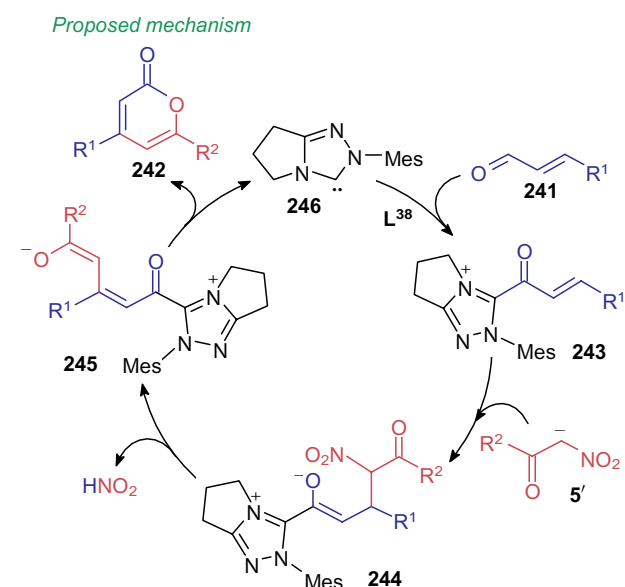
Starting from compounds **247** prepared by the Morita–Baylis–Hillman reaction, Reddy *et al.*²⁹² synthesized in 2020 a number of 2*H*-pyranes **248**. The reaction with nitroketones **5** was carried out in THF using 3 mol.% of DABCO (Scheme 58). Based on quantum chemical calculations and isolation of intermediate **249** in the individual form, the authors proposed the mechanism of the process, in which DABCO initially adds to substrate **247**, while cation **250** reacts, *e.g.*, with the anion of nitroacetophenone **5e** to form a novel C–C bond (see Scheme 58).

Elimination of DABCO from compound **251** gives intermediate **249**, which was characterized by spectral methods. Under reaction conditions, the loss of a molecule of nitrous acid occurs, and then compound **252** cyclizes to 4-alkynylpyrane-3-carboxylate **248**.

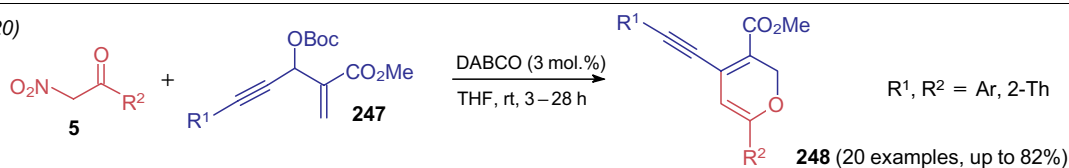
In addition to pyranes and other heterocycles, nitroacetophenone **5e** can deliver compounds containing an aromatic benzene ring. For instance, heating of acylated *N*-methyl indole **194** with nitroketone **5e** in DMF in the presence of cesium carbonate gives 4-hydroxy-9-methylcarbazol-3-ylphenylmethanones **253a–c** in good yields (Scheme 59).²⁵⁸ The mechanism of this reaction was presented above (see Scheme 43).

Five-membered heterocycles were prepared by a procedure, which is a modification of the Nazarov reaction, denitrative imino-diaza-Nazarov cyclization (DIDAN) (Scheme 60). Aegurla *et al.*²⁹³ reacted nitroketones **5** with the *in situ* formed hydrazones **254** in the presence of iodine in ethanol to afford 3,5-disubstituted pyrazoles **255**. It is assumed that the resulting enamine-imine **256** reacts with iodine to undergo, after tautomeric transformations, 4*p*-electrocyclization to generate diazaallyl cation **257**, which is aromatized through the loss of a molecule of nitrous acid from intermediate **258**.

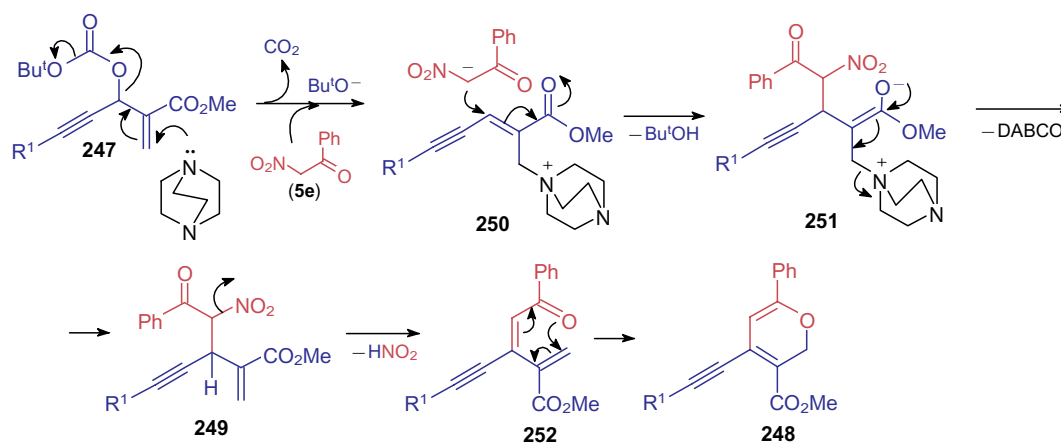
An interesting example was described by Mukaijo *et al.*,²⁰⁷ who studied the reaction of nitroketone **5f** with 2-nitro-3-phenylacrylate **259** (Scheme 61). The

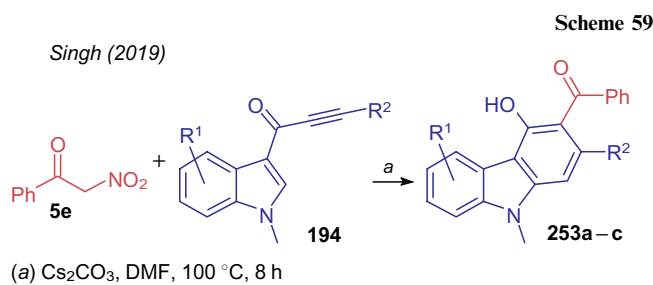


Reddy (2020)

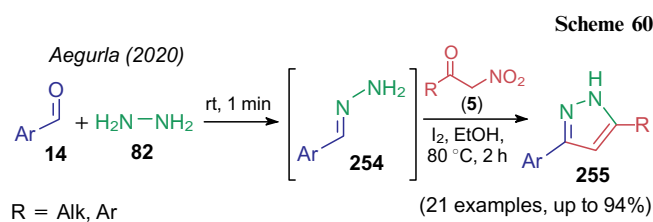
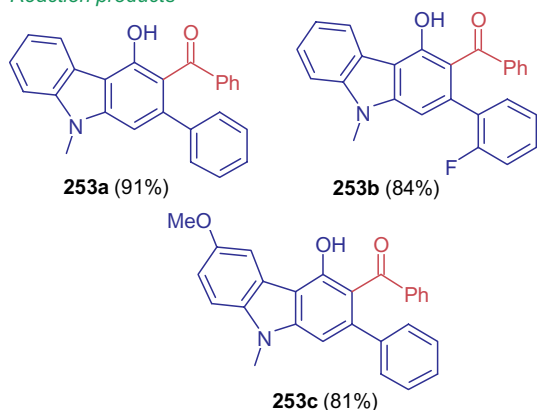


Proposed mechanism

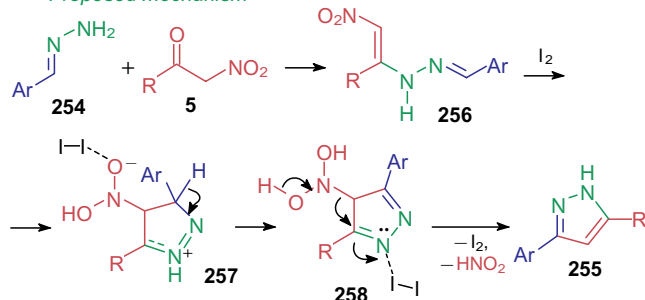




Reaction products



Proposed mechanism



major product of the reaction catalyzed by triethylamine is 5-(4-methylbenzoyl)-4-phenyl-3-ethoxycarbonylisoxazole-2-oxide (**260**), which includes a nitro group from acrylate **259**. The authors note that adduct **261** formed in this reaction can cyclize in three ways, however, since the tolyl substituent lowers the nucleophilicity of the nitronate ion and increases the electrophilicity of the α -CH acidic atom compared to ethoxycarbonyl substituent, it is isoxazole **260** that is predominantly formed from intermediate **262**.

3.3.6. Transformation with elimination of nitromethane

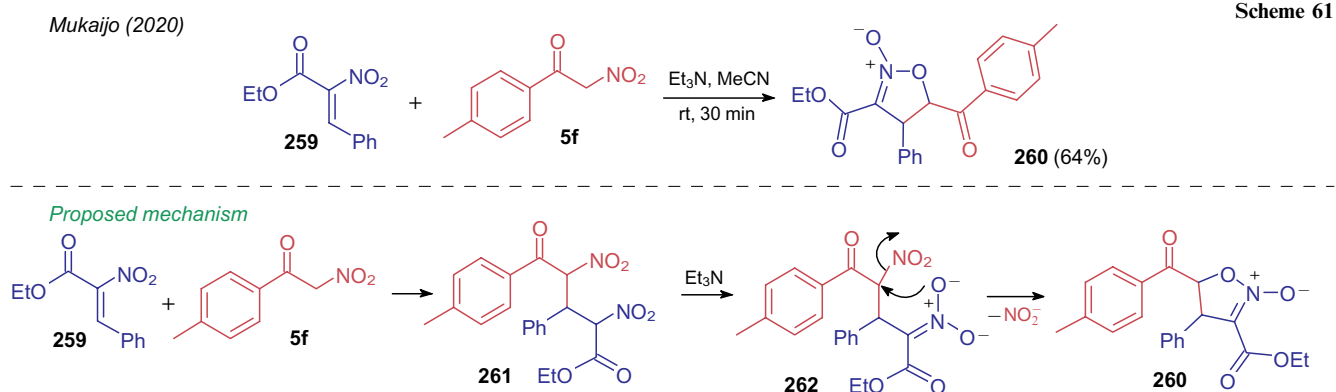
As noted above, the scientific group led by Aksenov^{237–239, 294, 295} studied the reactions of alkyl nitroacetates with various nucleophiles promoted by polyphosphoric acid (see Scheme 40). The same authors also explored the reaction of nitroketones **5** with dinucleophiles **177**, **178**, **263–266** under similar conditions, which delivered products **267–272** (Scheme 62). These reactions show a major difference between chemical behaviour of alkyl nitroacetates and nitroketones — in nitro-containing esters **6**, aminoxyphosphoric acid acts as a leaving group, while in nitrocarbonyl compounds **5**, the leaving group is a nitromethane molecule. The authors provide no explanation of eliminating just this small molecule. The mechanism suggesting the formation of intermediates **273** and **274** is exemplified by the reaction of nitroacetophenone (**5e**) with 2-(aminomethyl)anilines **266** in 87% PPA.

The C–C bond cleavage in nitroketones **5** and their substituted analogues **227** was also observed^{296, 297} in their base-promoted reactions with alcohols affording esters **275** (Scheme 63). The reaction with alcohols is catalyzed with potassium carbonate (reaction *a*) or *tert*-butoxide (reaction *c*), while such acylation of free amines is considered impossible due to high nucleophilicity of the latter. Therefore, Sarma and Phukan²⁹⁶ carried out the reaction *b* with bromamine-T (**276**) to furnish tosyl amides **277**.

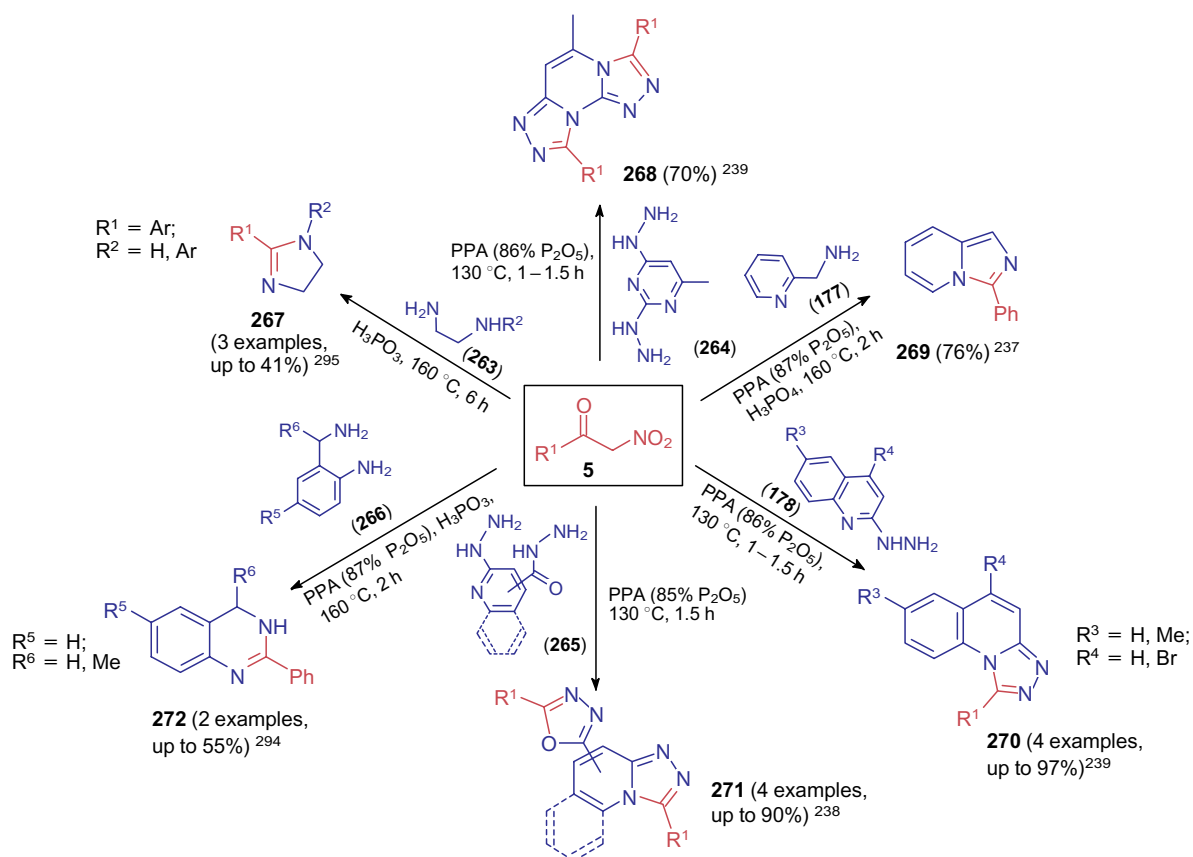
3.3.7. Other reactions

Wang *et al.*²⁹⁸ carried out a reaction characteristic of carbonyl compounds such as the reduction of a keto group in compounds **5** and **278** to the corresponding alcohols **279** and **280** (Scheme 64). The authors explored the stereoselective bioreduction of ketones with ketoreductases (KRED). At pH 5, the use of YGL039w afforded *S*-isomer, while in the presence of RasADH/SyADH, *R*-isomer was obtained. The yields of the products and enantioselectivity reached 99%.

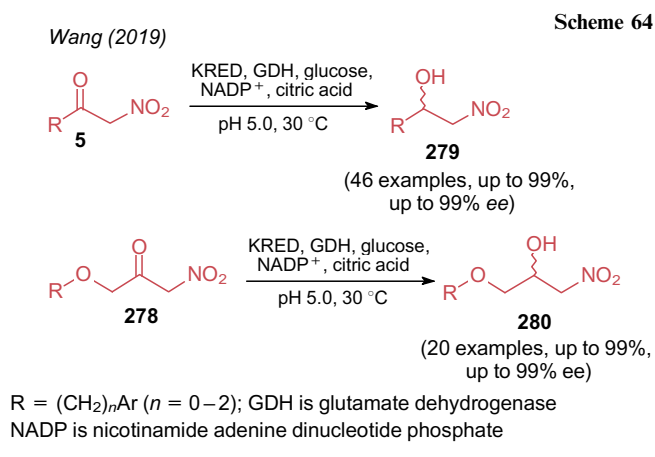
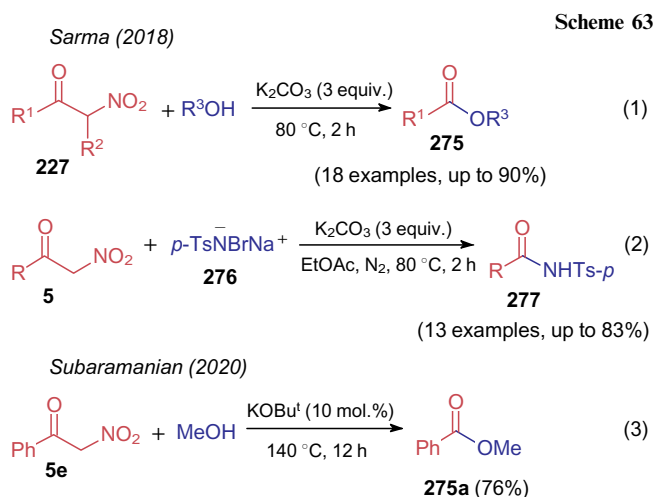
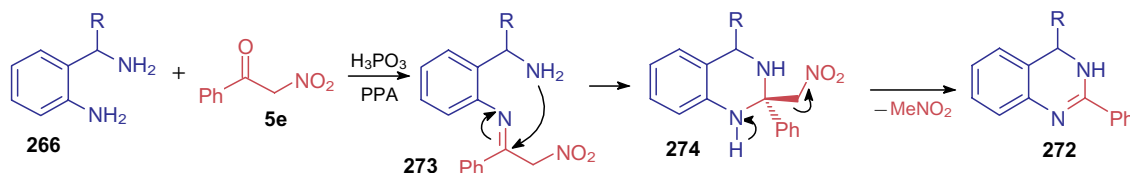
Stereoselectivity of the process was also studied²⁹⁹ on the example of the Mannich reaction between nitroketones



Scheme 62



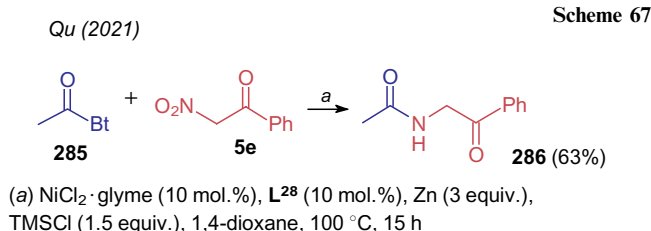
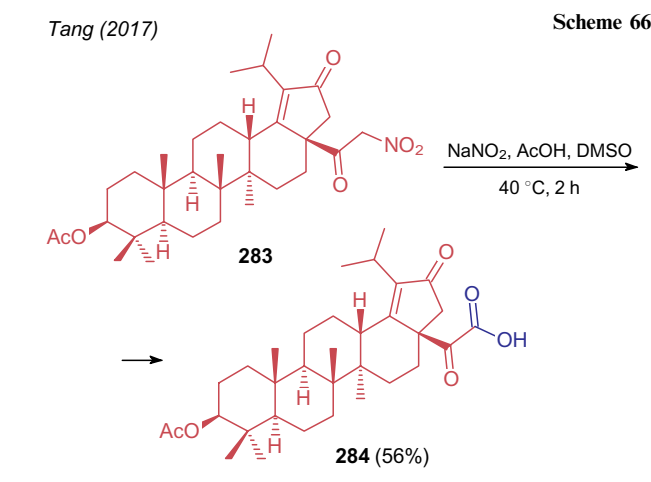
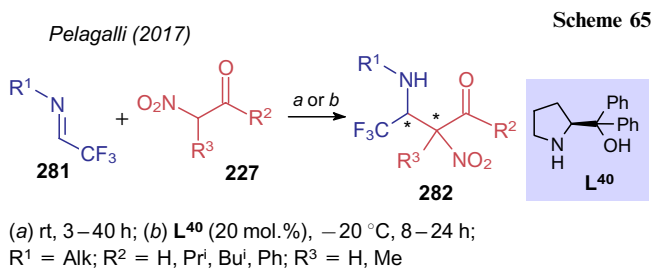
Proposed mechanism



227 and trifluoromethyl aldimines **281** (Scheme 65). The authors found that structures of both substrates play a pivotal role in increasing stereoselectivity. With a certain substituent R^1 , it is possible to shift the direction of the reaction towards the formation of an *anti*-isomer **282**. The

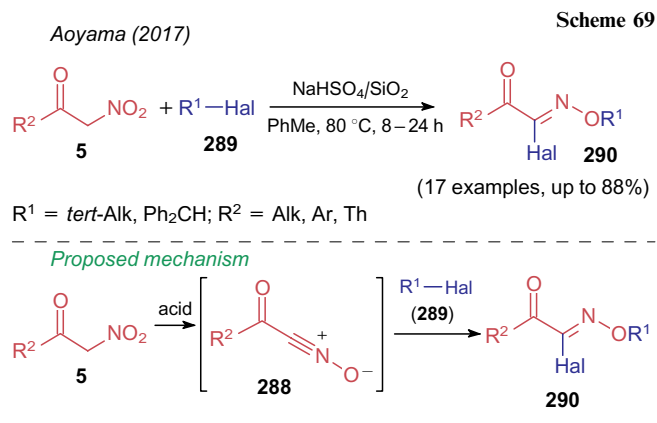
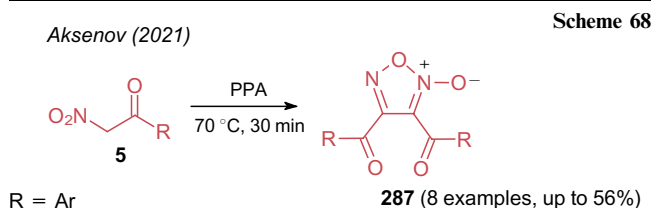
use of (*S*)- α,α -diphenylprolinol (**L**⁴⁰) also favours the formation of this isomer.

Tang *et al.*³⁰⁰ carried out the conversion of betulin derivative **283** to α -ketocarboxylic acid **284** (Scheme 66). Although this transformation resembles the Nef reaction, the intermediate compound seems to be nitrolic acid, which under the reaction conditions gives product **284** with releasing nitrous oxide.



One more property combining nitroketones and alkyl nitroacetates is acid-catalyzed dimerization. Thus, Aksenov *et al.*²¹¹ developed a straightforward method for the synthesis of furoxan *N*-oxides **287** intended to elucidate the mechanism of the reaction between nitroketones **5** and polyphosphoric acid (Scheme 68). Similarly to the reaction in Scheme 46, nitrile oxide **288** acts as an intermediate.

Disubstituted furoxans **287** are not the only product that can be derived from intermediate nitrile oxides **288**. Even though this intermediate has an explicit dipole structure, its modification should not necessarily lead to the formation of a ring structure. For example, in 2017, Aoyama *et al.*³⁰¹



showed the possibility of carrying out the addition of alkyl halides **289** to intermediates **288** to furnish ketoximes **290** (Scheme 69). In this study, nitrile oxides *per se* were generated *in situ* in the presence of NaHSO₄/SiO₂.

Thus, it can be noted that over the past five years, among all the considered NSEs, α -nitroketones have been studied in the most detail in terms of the diversity of their chemical properties. This is mainly due to the availability and high reactivity of these compounds. Their main difference from alkyl nitroacetates includes the reactions at the carbonyl group. Due to this, compounds **5** are characterized by reactions with nucleophiles, as well as the C–C bond cleavage reactions resulting in a wide range of cyclic and acyclic molecules.

3.4. Nitroacetonitrile

Nitroacetonitrile (**7**) is the least studied of the above-mentioned NSEs. The scope of its application relates primarily to energetic materials with low impact sensitivity and biologically active compounds. Despite the small number of studies related to it, two reviews^{31,32} have been devoted to nitroacetonitrile and its derivatives over the past few years. Moreover, methods for the synthesis of nitroacetonitrile can also be found in publications.^{302,303} This review discusses works on nitroacetonitrile published since 2016.

3.4.1. Cycloaddition reactions

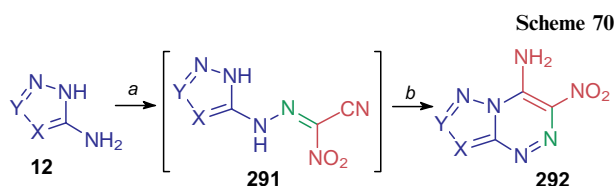
As mentioned above, one of the main applications of compound **7** is the synthesis of nitrogen-containing high-energy heterocyclic compounds bearing a nitro group. These transformations are generally diazotization of various aminopyrazoles,³⁰⁴ triazoles^{226,305–309} and tetrazole³¹⁰ followed by azo coupling with nitroacetonitrile. Scheme 70 and Table 11 illustrate the reactions described for the period under consideration. Generally, diazotization was carried out using hydrochloric or diluted sulfuric acids and sodium nitrite served as a nitrosating agent in almost all cases. Tang *et al.*³⁰⁷ employed methanolic hydrogen chloride for the diazotization of 3,5-diamino-1,2,4-triazole followed by the addition of *tert*-butyl nitrite. The azo coupling process first delivers hydrazone **291**, which in some cases can be isolated and identified. The target azolo-1,2,4-triazines **292** can also be accessible *via* thermal cyclization.

A curious example of similar azo coupling reaction was demonstrated by the Feng's research group³¹¹ in 2021. It was found that coupling of 5-amino-4-nitro-1,2,3-triazole **12a** with compound **7** gives the corresponding hydrazone **291a**, however, its further intramolecular cyclization fur-

Table 11. Cycloaddition reactions involving aminoazoles **12** (see Scheme 70).

No	Product	Reactants	Conditions <i>a</i>	Conditions <i>b</i>	Yield (%)	Ref.
1		$\text{O}_2\text{N}-\text{CH}_2-\text{CN}$ NaOH	H_2SO_4 (20%), NaNO_2 , H_2O , 5 °C, 1 h	rt, 3 days	54	305
2		$\text{O}_2\text{N}-\text{CH}_2-\text{CN}$ K^+	HCl, NaNO_2 , H_2O , -2 °C, 2 h ^a	rt, 1.5 h	19	310
3		$\text{O}_2\text{N}-\text{CH}_2-\text{CN}$ NaOH	H_2SO_4 (20%), NaNO_2 , H_2O , 5 °C, 30 min	rt, 3 h	70	304
4		$\text{O}_2\text{N}-\text{CH}_2-\text{CN}$ NaOH	1) HCl (gas), Bu^tONO , MeOH, 0 °C, 1 h; 2) H_2SO_4 (20%), H_2O , 0–5 °C	rt, 1 day	40	307
5		$\text{O}_2\text{N}-\text{CH}_2-\text{CN}$ NaOH	<i>a</i>) H_2SO_4 (20%), NaNO_2 , H_2O , 5 °C, 30 min <i>b</i>) H_2SO_4 (20%), NaNO_2 , H_2O , 0–2 °C to rt, 3–4 h ^b	rt, 3 days H_2O , MeOH, 70 °C, 3 h	48 84	306, 308 309

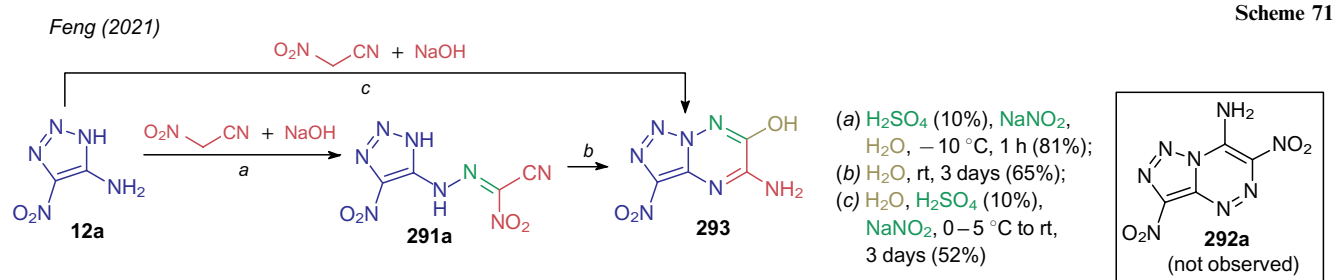
^a To avoid the risk of an explosion of the reaction mixture, concentration of substrate **12** and its diazonium salt should not exceed 3%; ^b yield 78%, in other cases, intermediate **291** was not isolated.



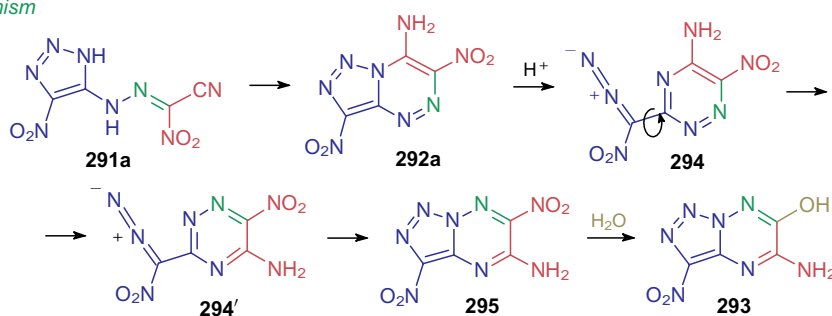
nishes 5-amino-3-nitro-1,2,3-triazolo-[1,5-*b*][1,2,4]triazin-6-ol (**293**) rather than 3,6-dinitro-1,2,3-triazolo[5,1-*c*][1,2,4]triazine-7-amine (**292a**) (Scheme 71). Nitro-containing product **292a** can not be obtained either *via*

the azo coupling–cyclization sequence or by cyclization of an intermediate hydrazone **291a** in water. The authors argue that initially, cyclization of hydrazone **291a** does afford nitrotriazolotriazine **292a**, however, further it undergoes the Dimroth rearrangement *via* the triazole ring-opening to give diazo-intermediate **294**, which converts to nitro compound **295**, furnishing the observed product upon hydrolysis.

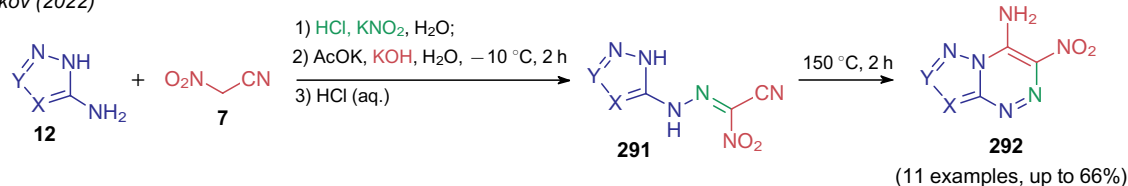
If in the above examples the resulting azolotriazines **292** were mainly considered as nitrogen-containing high-energy compounds, then by changing the azole component, Voinkov *et al.*³¹² prepared a number of heterocycles possessing antimicrobial activity. Versatile and environmentally



Proposed mechanism

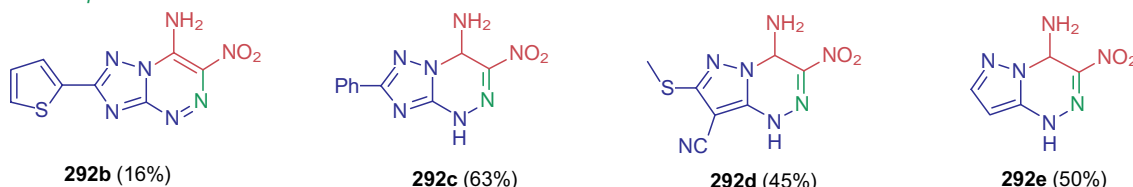


Voinkov (2022)



Scheme 72

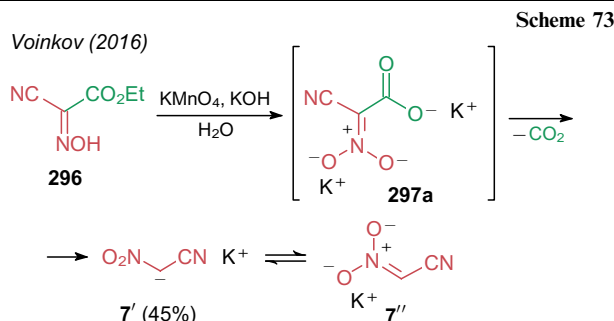
Selected examples



friendly protocol has been proposed comprising isolation of hydrazones **291** and their thermal cyclization under solvent-free conditions (Scheme 72).

3.4.2. Reactions with a latent form of nitroacetonitrile

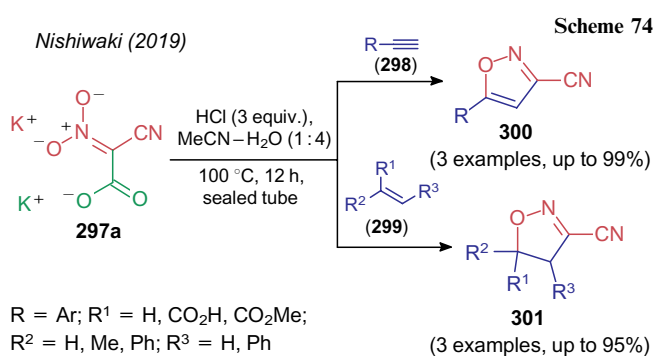
In 2016, Voinkov *et al.*¹⁸⁰ developed a convenient synthetic procedure to obtain potassium salt of nitroacetonitrile (**7'**) via oxidation of ethyl 2-hydroxyimino-2-cyanoacetate (**296**) with potassium permanganate in the presence of potassium hydroxide (Scheme 73). The intermediate under these conditions is the dipotassium salt of nitrocyanoacetic acid **297a**, which undergoes decarboxylation to form NSE. Note the potassium salt **7'** is in an *aci*-nitro form **7''**, as confirmed by X-ray diffraction analysis.¹⁸⁰



Scheme 73

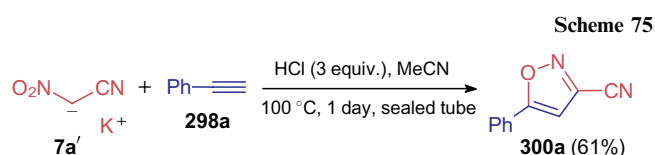
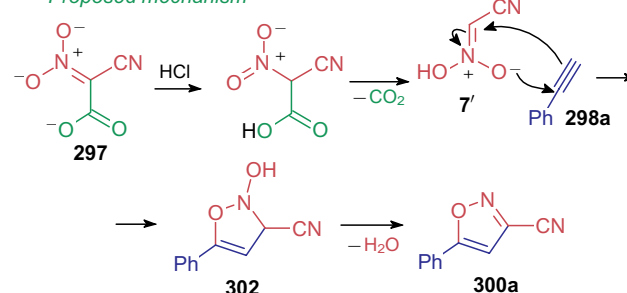
In the following publications, dianion **297** was used as a starting compound for various reactions, since the monopotassium salt **7'** is explosive. Nishiwaki *et al.*³¹³ implemented the reaction of dipotassium salt **297a** with alkynes (**298**) and alkenes (**299**) in an acetonitrile–water mixture to prepare 3-cyanoisoxazoles **300** and 3-cyano-4,5-dihydroisoxazoles **301**, respectively. The process was carried out in the presence of 3 equiv. of hydrochloric acid on heating in a sealed tube (Scheme 74). The reaction with phenylacetylene (**298a**) is probably mediated by intermediate **302**.

In the same work, the model reaction of phenyl acetylene (**298a**) with potassium salt **7'** was carried out to gain insight into the mechanism of the process (Scheme 75). Based on this reaction, the authors suggest that when treated with an acid, dipotassium salt **297a** is decarboxylated to give nitroacetonitrile, which serves as a 1,3-dipole in the cycloaddition reaction with phenylacetylene. According to the authors, an excess hydrochloric acid can indicate the presence of cyanonitrile oxide **303** in the reaction

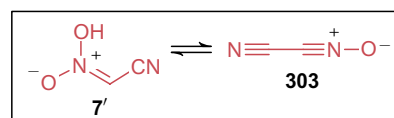


Scheme 74

Proposed mechanism

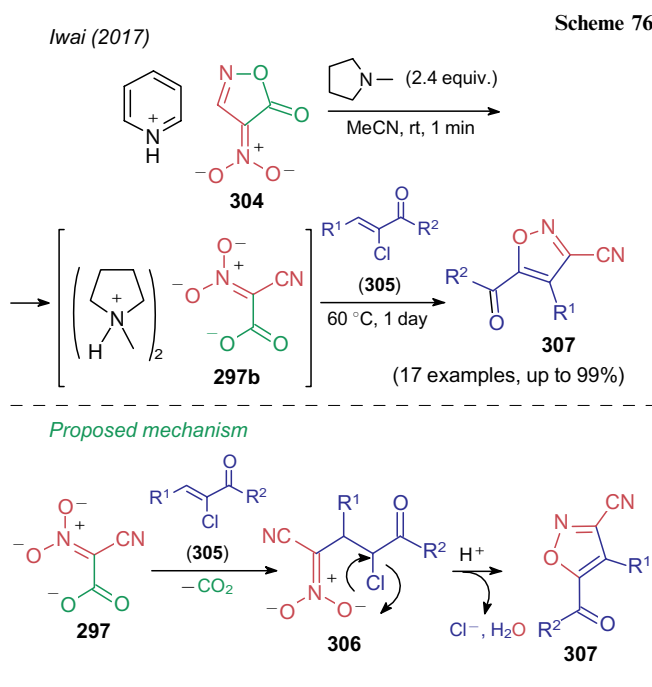


Scheme 75



mixture, and dipotassium salt **297a**, like compound **7**, can be considered as its masked form.

Di(*N*-methylpyrrolidinium) salt of nitrocyanoacetic acid **297b** is an alternative to dipotassium salt **297a**. Its main advantage over potassium salt **7'** and dipotassium salt **297a** is its solubility in organic media. Thus, Iwai *et al.*³¹⁴ reported the synthesis of dianion **297b** from the salt of nitroisoxazolone **304** and its subsequent reaction with α -chloro- α,β -unsaturated ketones **305** (Scheme 76). The reaction pathway suggests decarboxylation of intermediate



297 followed by the Michael addition of substrate **305**. The final stage of the process is an intramolecular cyclization of intermediate compound **306** to yield 5-acyl-3-cyanoisoxazoles **307**.

It is obvious that the search for the methods to produce stable forms of nitroacetonitrile and the development of novel approaches to modify its latent forms should significantly increase the synthetic potential of this NSE, which will be reflected in an increase in the number of publications devoted to nitroacetonitrile over time.

4. Conclusion

Summing up the literature survey, it can be concluded that over the past five years, interest in the NSE chemistry has increased significantly. This is largely due to the search for new ways to functionalize such structures. For example, for nitro-containing alkenes, the functionalization of the C–H bond adjacent to the nitro group appears to be quite indicative but yet little-studied trend. For derivatives in which imine-enamine tautomerism is impossible, functionalization methods are just beginning to be developed, which, with due attention of scientists, can become very useful for the practical and theoretical study of this subject. This also includes reactions involving the cleavage of the C–C and(or) C–NO₂ bonds, as well as the accompanying rearrangements. Some reactions of this type were described for the first time precisely in the period under consideration, which indicates the relevance of further study of these processes so as to obtain more accurate ideas about their capabilities. However, the bulk of the transformations associated with nitroalkenes falls on cycloaddition reactions in multicomponent and sequential fashions. This is not surprising, since the use of such NSEs offers access to a wide range of polysubstituted heterocycles, either of independent interest or intended for further modification, often due to the presence of a nitro group in the molecule.

In turn, nitroalkanes are also used mainly to construct heterocycles. On the other hand, in their case, the tendency to heterocyclization is more pronounced, resulting in the

loss of nitrous acid or nitromethane molecules to form an aromatic structure. Undoubtedly, this indicates the uniqueness of such NSEs as synthetic units in the construction of complex organic structures. Accordingly, the use of the features of the reactivity of such compounds, as well as the elucidation of conditions allowing an easy change in the cyclization course, will become a relevant task in the near future. Moreover, for nitroalkanes, processes (for example, the Michael reaction) are increasingly being considered, which, depending on the type of catalyst, proceed stereoselectively or stereospecifically. Given that such NSEs are often used when creating medicinal drugs, it can be argued that the development of conditions for obtaining enantiomerically pure products using such substrates will also be a promising area of research.

The reactions discussed in this review are mostly implemented to prepare potential biologically active molecules and high-energy compounds. Of course, these are not the only fields of practical application of NSEs, but even they are enough to demonstrate the high relevance of the ongoing research. The authors of many of the cited works made a great contribution to the description of new reaction mechanisms, as well as to the addition of theoretical ideas about the course of known processes. To conclude, it should be noted that based on the discovery of new reactions involving low-molecular-weight NSEs, the chemical potential of these compounds is limited only by the imagination of synthetic chemists.

This work was funded by the Ministry of Science and the Higher Education of the Russian Federation [State contract No. FEUZ-2023-0021 (H687/42B.325/23)].

5. List of acronyms

Following acronyms are used in the review:

- Δ — boiling point,
- 2,5-DTBQ — 2,5-di-*tert*-butyl-*p*-hydroquinone,
- Ad — adamantyl,
- AIBX — 5-trimethylammonium-2-iodoxybenzoate,
- ANA — alkyl nitroacetate,
- ANE — aminonitroethylene,
- BARf — *tetrakis*-3,5-bis(trifluoromethyl)phenyl borate,
- BHT — 2,4,6-tri-*tert*-butylphenol,
- BINAP — [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl],
- bmim — 1-*n*-butyl-3-methylimidazolium,
- Boc — *tert*-butyloxycarbonyl,
- CAN — cerium(IV)-ammonium nitrate,
- cod — cycloocta-1,5-diene,
- Cp — cyclopentadiene,
- Cy — cyclohexyl,
- Cy-Johnphos — (2-biphenyl)dicyclohexylphosphine,
- DAAA — decarboxylative asymmetric allylic alkylation,
- DABCO — 1,4-diazabicyclo[2.2.2]octane,
- dba — dibenzylideneacetone,
- DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
- DCE — 1,2-dichloroethane,
- DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
- DIPEA — diisopropylethylamine,
- DiNH — α,α-di(amino)nitroalkene,
- DiSAIk — (α,α-di(alkylthio)nitroalkene),
- DMA — dimethylacetamide,
- DMAP — 4-(*N,N*-dimethylamino)pyridine,
- DMBQ — 2,6-dimethoxybenzoquinone,
- DMS — dimethyl sulfide,
- DPEPhos — bis[(2-diphenylphosphino)phenyl] ether,

de — diastereomeric excess,
dr — diastereomeric ratio,
er — enantiomeric ratio,
 EWG — electron withdrawing group,
 Fu — furyl,
 GDH — glutamate dehydrogenase,
 KRED — keto reductases,
 MCR — multicomponent reaction,
 Mes — 2,4,6-trimethylphenyl (mesityl),
 MS — molecular sieves,
 MW — microwave irradiation,
 Naph — naphthyl,
 NADP — nicotinamide adenine dinucleotide phosphate,
 NAN — nitroacetonitrile,
 NK — α -nitroketone,
 NSE — nitro synthetic equivalents,
 PEG — polyethylene glycol,
 PEGMA-g-TEGBDIM — polyethylene glycol methacrylate-grafted tetraethylene glycol-bridged dicationic imidazolium based ionic liquid,
 PG — protecting group,
 PPA — polyphosphoric acid,
 PS-BEMP — 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene,
 Py — pyridyl,
p-Ts — *p*-toluenesulfonyl (tosyl),
 rt — room temperature,
rr — regioisomeric ratio,
 SMeNHR — (alkylthio)aminoalkene,
 TBAB — tetra-*n*-butylammonium bromide,
 TBAI — tetra-*n*-butylammonium iodide,
 TBDPS — *tert*-butyldiphenylsilyl,
 TBS — *tert*-butyldimethylsilyl,
 TEMPO — 2,2,6,6-tetramethylpiperidin-1-yl)oxyl,
 TFA — trifluoroacetic acid,
 Tf — trifluoromethanesulfonyl (triflyl),
 TFE — trifluoroethanol,
 Th — thienyl,
 TMS — trimethylsilyl,
 US — ultrasonication.

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