

**NITROALKENES IN DIVERSE SYNTHESIS OF HETEROCYCLIC COMPOUNDS  
WITH TWO OR THREE HETEROATOMS: RECENT ADVANCES**

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**Abstract.** This chapter highlights the literature of one of the most privileged substrates in the field of heterocyclic chemistry. Nitroalkenes as versatile organic substrates have been used extensively in direct and diverse synthesis of heterocyclic compounds. We review here the applications of nitroalkenes and their derivatives such as nitrostyrenes, Morita-Baylis-Hillman (MBH) acetates or bromides of nitroalkenes, 1,1-bis(methylthio)-2-nitroethylene, and nitroepoxides in the synthesis of heterocyclic scaffolds with two or three heteroatoms. Following a brief introduction about nitroalkenes, synthetic routes to access heterocyclic scaffolds, exclusively diverse heterocyclic motifs containing two or three heteroatoms such as imidazoles, pyrazoles, triazoles, thiazoles, thiazines, isoxazolines, pyrimidines, imidazopyridines, benzodiazepines as well as bicyclic compounds have been summarized. These significant molecules were synthesized through various synthetic strategies including multi-component reactions, Michael addition reactions, [m+n]-cycloadditions, asymmetric processes, MBH reaction and cascade/domino/tandem protocols.

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### 1. Introduction

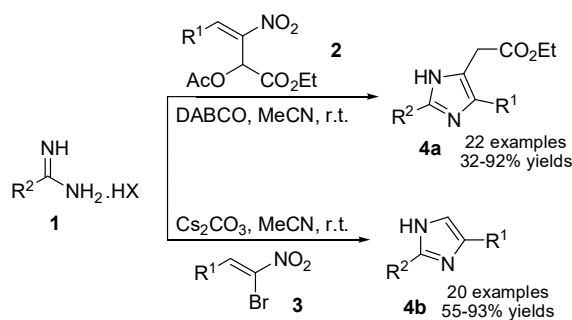
Heterocyclic rings show rich chemistry with a wide range of applications in organic and medicinal chemistry, pharmaceutical and industry.<sup>1</sup> These molecules are widely present in numerous natural products such as vitamins, antibiotics, hormones as well as pigments and dyes. Moreover, a great variety of heterocyclic compounds are found in the structure of several drugs and renewable resources.<sup>2</sup> Among the top 25 best-selling pharmaceuticals from the year 2014, there have been 12 small molecules with heterocyclic scaffolds, by and large nitrogen-containing ones, accounting for more than 50 billion USD in annual revenue.<sup>3</sup> Therefore, organic chemists have been making enthusiastic efforts to produce the novel and applicable heterocyclic compounds by utilizing wide ranges of new reactants and developing efficient synthetic transformations. A simple glance at FDA databases reveals the structural significance of nitrogen-based heterocycles in the drug design and engineering of pharmaceuticals, with nearly 60% of unique small-molecule drugs containing a nitrogen heterocycle. Noteworthy, the average number of nitrogen atoms per drug, being around 2.3, while in those containing a nitrogen heterocycle an increase to 3.1 nitrogen atoms per drug is evidenced.<sup>4</sup> In this context, the compounds with biological properties, molecules bearing five- to seven-membered heterocycles with two or three heteroatoms containing nitrogen, oxygen and sulfur such as imidazoles, pyrazoles, triazoles, thiazoles, thiazines, isoxazolines, pyrimidines, imidazopyridines,

benzodiazepines along with bicyclic moieties exhibit a wide range of outstanding biological and pharmacological activities.<sup>5-8</sup> As a result, it is highly important to design efficient, facile, and straightforward methodologies for the synthesis of heterocyclic rings with two or three heteroatoms. In this context, nitroalkenes and their analogs such as nitrostyrenes, Morita-Baylis-Hillman (MBH) acetates or bromides of nitroalkenes, 1,1-bis(methylthio)-2-nitroethylene, and nitroepoxides as versatile substrates play important roles in a wide range of organic reactions, particularly in a skeletally diverse synthesis of heterocyclic motifs.<sup>9-10</sup> Some examples of these valuable reactions are Mannich reactions, Michael addition reactions, MBH reactions, metal mediated coupling reactions and aldol reactions. The reactivity umpolung of the nitro group as an acyl anion equivalent and nitroalkene as an acyl methyl cation equivalent is well documented in the literature. The combination of nitroalkenes capability to endure Lewis base activation along with the unprecedented efficiency of the nitro moieties to activate electrophiles and stabilize nucleophiles through coordination with Lewis and Bronsted acids have caused nitroalkenes to become effective substrate candidates for asymmetric reactions. The great adaptability of nitro group for the designing of various functional groups has developed the scope of nitro group and particularly nitroalkenes in synthetic organic chemistry strategies. An exact effect of nitro group is common phenomena even in reactions where nitro group undergoes to substitution or elimination. Additionally, nitroalkenes can be easily synthesized *via* nitro-aldol condensation and other direct nitration methods like nitrodecarboxylation which caused spontaneous growth of nitroalkene chemistry in recent years. This book chapter will henceforth focus on the role of the nitroalkenes and their analogs as versatile building blocks for the diverse synthesis of heterocyclic compounds with two or three heteroatoms.

## 2. Imidazoles and their reduced derivatives

One of the most popular five-membered heterocyclic rings with two heteroatoms is imidazole. Compounds containing imidazole rings are known to show broad ranges of pharmaceutically important properties along with biological and medicinal activities.<sup>11</sup> Also, the presence of imidazole scaffolds in the structure of bioactive molecules such as proteins and marine alkaloids have attracted much attention.<sup>12</sup> Furthermore, medicines based on imidazole structures are in use for the treatment of several diseases and disorders. In addition, imidazoles have found widespread applications in the field of polymer science, materials chemistry and coordination chemistry.<sup>13</sup>

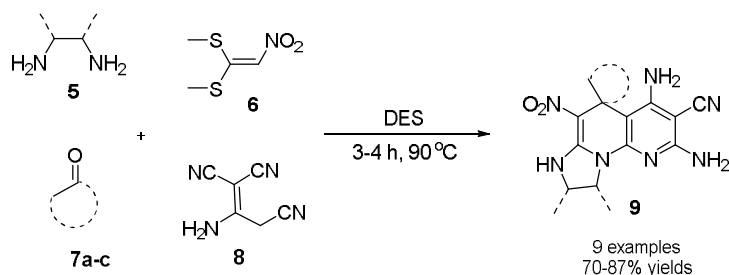
In this regard, Namboothiri and co-workers applied two different kinds of nitroalkenes in the synthesis of substituted imidazoles **4**. The authors developed an efficient and cascade reaction of amidines **1** with nitroallylic acetates **2** and  $\alpha$ -bromonitroalkenes **3** for diversity-oriented synthesis of potentially bioactive imidazoles (Scheme 1).<sup>14</sup> This synthetic strategy is significantly broad in scope, generating a wide range of imidazoles in good to excellent yields. Both of the synthesized imidazole series have been screened against *T. cruzi* bloodstream trypomastigotes, an infective form of the protozoa that causes Chagas disease.



**Scheme 1.** Synthesis of substituted imidazoles.

In another paper, a novel domino four-component strategy for expedient access to imidazonaphthyridines **9** was implemented by Hooshmand and co-workers.<sup>15</sup> The products were achieved by

reacting diamine derivatives **5**, malononitrile dimer **8**, 1,1-bis(methylthio)-2-nitroethylene **6** and various carbonyl compounds **7** such as substituted benzaldehydes **7a**, isatins **7b** and ninhydrin **7c** using deep eutectic solvent (DES) as environmentally benign media (Scheme 2). DES formed by mixing choline chloride with urea was used as a medium and also facilitated the reaction, providing imidazonaphthyridine derivatives in good yields. This one-pot synthetic approach was the most convenient way to prepare a novel type of imidazonaphthyridines **9** with the tandem formation of three new rings along with six  $\sigma$  bonds.



**Scheme 2.** Synthesis of imidazonaphthyridines in DES.

The DES play a dual role in this reaction as a solvent and catalyst, which in the latter case, activates the carbonyl and cyano groups via hydrogen bonding. The proposed mechanism by authors is depicted in Scheme 3. Initially, heterocyclic ketene aminated **10** readily prepared in situ from the addition of diamine **5** and 1,1-bis(methylthio)-2-nitroethylene **6** via a  $S_N2$  reaction followed by loss of 2 equiv of MeSH and in continue involves the nucleophilic attack of heterocyclic ketene aminated **10** to the Knoevenagel adduct **11**. Two consecutive DES-catalyzed cyclizations of intermediates **12** and **13** furnish the desired naphthyridines.

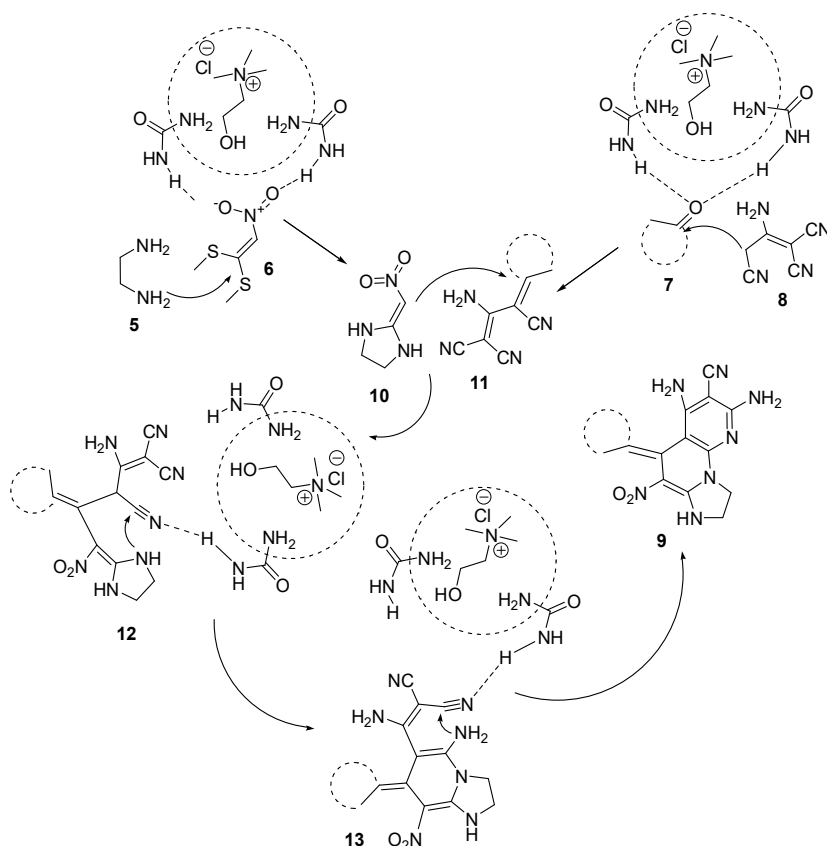
Similarly, Rezvanian executed a highly convergent and direct synthesis of tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acids **15** through a one-pot four-component sequential reaction utilizing benzaldehyde derivatives **7a**, pyruvic acid **14**, diamines **5** and 1,1-bis(methylthio)-2-nitroethylene **6** (Scheme 4). Optimization of this reaction revealed that the best conditions involved carrying out the reaction in the presence of 10 mol% molecular iodine as catalyst in acetonitrile to afford the products in good to excellent yields. According to the proposed mechanism, first heterocyclic ketene aminated **10** was prepared. Next, the formation of second key intermediate **16** occurs through Knoevenagel condensation of benzaldehyde **7a** with enol of pyruvic acid **14** in the presence of iodine. With a strong electron-withdrawing nitro group at the  $\alpha$ -position and electron-donating diamino groups on the diazaheterocycle of heterocyclic ketene aminated **10**, this compound can serve as a nucleophilic component with the electrophilic arylidene pyruvic acid **16** in a Michael-type addition to produce an open chain azaketene type intermediate **17A**, which is in equilibrium with the resonance form **17B** through imine-enamine tautomerization. Subsequently, nucleophilic addition of the secondary amino group to the ketone group in **17**, followed by loss of 1 equiv of  $H_2O$  affords the product **15**.

### 3. Pyrazoles and pyrazolidines

Pyrazole-containing heterocycles are important targets in synthetic and medicinal chemistry due to their presence in the structure of numerous biologically active compounds.<sup>16-17</sup> Pyrazoles have an illustrious history: in 1883, a German chemist Ludwig Knorr was the first one who discovered antipyretic action of pyrazole derivative in man, he named the compound antipyrine. Pyrazole ring exists in the structure of famous commercially available drugs such as Celecoxib, Pyrazofurines, Sildenafil and Acomplia.<sup>18</sup> Due to the positive properties of these heterocyclic compounds, several synthetic routes have been reported in recent decade. In this sense, nitrostyrenes as efficient starting materials have been used in the synthesis of pyrazole scaffolds.

Jørgensen *et al.* demonstrated a new asymmetric synthesis of chiral 4-nitropyrazolidines **20** with three stereogenic centers from ketone-derived hydrazones **19** and nitrostyrenes **18** in the presence of 5 mol% bifunctional thiourea **21** as catalyst (Scheme 5).<sup>19</sup> This efficient catalytic system afforded the corresponding

pyrazolidine **20** in appropriate yields (up to 97%) with high to excellent stereoselectivity (up to 99% ee and >20:1 dr) under metal-free conditions.



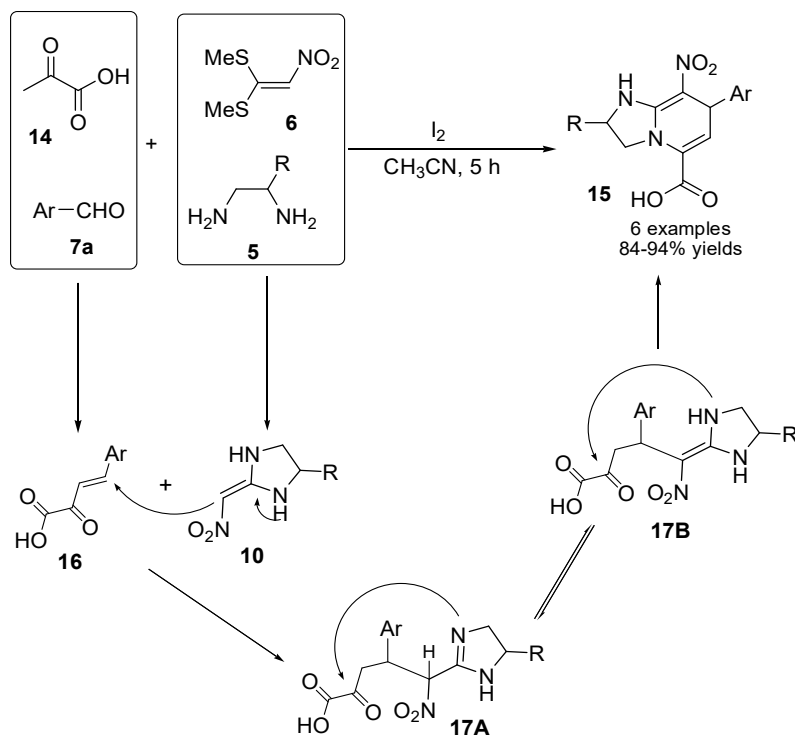
**Scheme 3.** Possible mechanistic pathway for the synthesis of imidazonaphthyridines.

In 2017, Huang and co-workers described a new [3+2]-cycloaddition process between trifluoromethylated *N*-acylhydrazones **22** and a wide range of nitrostyrenes **18** in the presence of potassium hydroxide under phase transfer catalysis (Scheme 6).<sup>20</sup> This strategy provides a straightforward route for the synthesis of trifluoromethylated pyrazolidines **23** with potential bioactive characteristics in good to excellent yields in CH<sub>3</sub>CN at ambient temperature. In a similar way, Lykakis *et al.* reported a one-pot procedure for regioselective synthesis of functionalized pyrazole rings **25** *via* the reaction of in situ prepared benzyl hydrazones **24** and nitrostyrenes **18** (Scheme 6).<sup>21</sup>

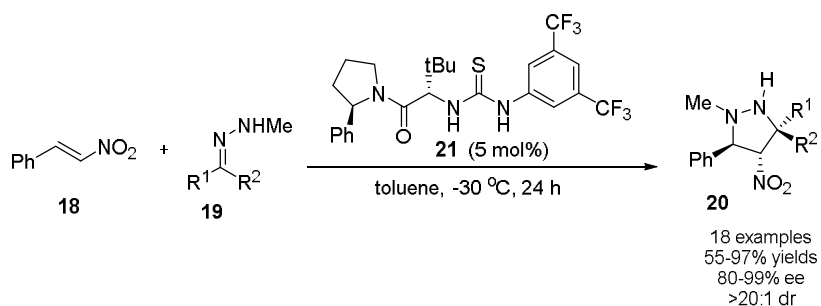
Zhou *et al.* reported a novel protocol for the synthesis of substituted pyrano[2,3-*c*]pyrazoles **27** *via* [3+3] annulation of pyrazolin-5-ones **26** and MBH acetates of nitrostyrenes **2** in acceptable yields, high anti-selectivity, and excellent enantioselectivity catalyzed by bifunctional squaramide **28** (Scheme 7).<sup>22</sup> This synthetic route serves as a versatile tool for the stereocontrolled construction of pyrazole rings with two adjacent tertiary stereogenic centers.

In order to diversify annulated pyrazoles motifs, in 2018, Shibata and co-workers synthesized pyrazole-3-triflones containing a triflyl group at the 3-position **30** using [3+2]-cycloaddition reaction of 2-diazo-1-phenyl-2-((trifluoromethyl)sulfonyl)ethan-1-one **29** with nitroalkenes **18** under basic conditions.<sup>23</sup> This approach is highly compatible to a variety of nitroalkenes in moderate to good yields at room temperature in short reaction time (Scheme 8). With the optimized reaction conditions, the scope of the

cyclization reaction was investigated with diazotriflone and nitroalkene derivatives containing electron-donating, electron-withdrawing, and halogenyl substituents at different positions on the benzene ring.

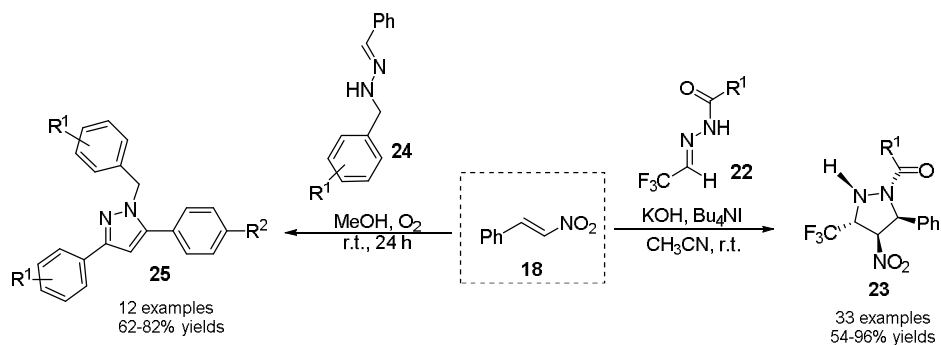


**Scheme 4.** Synthesis of tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acids.

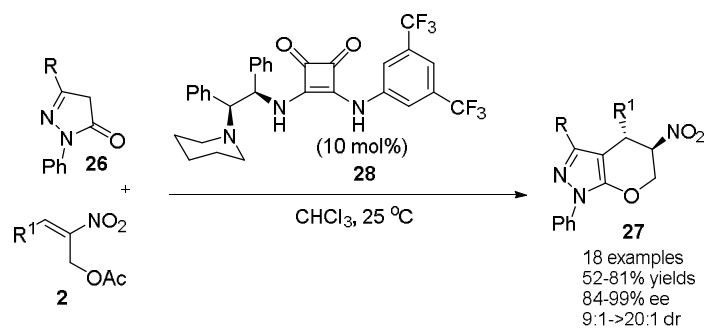


**Scheme 5.** Synthesis of chiral 4-nitropyrrolidines with three stereogenic centers.

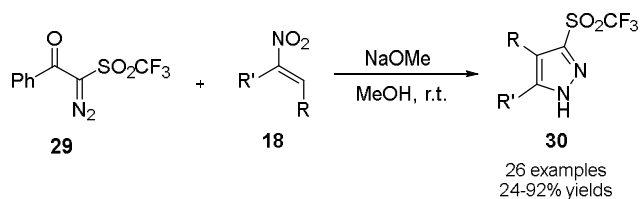
Furthermore, Adimurthy research group developed facile synthesis of pyrazolo[1,5-*a*]pyridine scaffolds **32** via [3+2]-cycloaddition reaction of *N*-aminopyridine **31** along with various nitrostyrenes **18** followed by in situ denitration and oxidation under mild condition.<sup>24</sup> This synthetic route gave good to high yields without using any metal or base (Scheme 9).



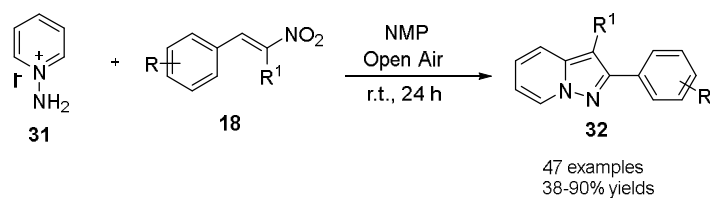
**Scheme 6.** Reaction of nitrostyrenes with *N*-acylhydrazones and benzyl hydrazones.



**Scheme 7.** Synthesis of substituted pyrano[2,3-*c*]pyrazoles via pyrazolin-5-ones and MBH acetates of nitrostyrenes.



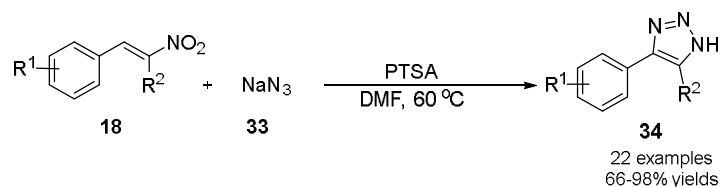
**Scheme 8.** Synthesis of pyrazole-3-triflones containing a triflyl group.



**Scheme 9.** Synthesis of pyrazolo[1,5-*a*]pyridine scaffolds.

#### 4. Triazoles

1,2,3-Triazole derivatives are useful heterocyclic rings due to their broad spectrum of applications and biological activities such as anticancer, anti- HIV and selective  $\beta_3$  adrenergic receptor agonist.<sup>25</sup> Also, they have found wide applications in many other fields of modern chemical sciences including material functionalization, supramolecular chemistry, and polymer sciences.<sup>26</sup> Among the various methods available for the synthesis of 1,2,3-triazoles, copper catalyzed Huisgen 1,3-dipolar cycloaddition reaction of organic azides with substituted alkynes were applied extensively.<sup>27-29</sup> Recently, novel catalysts and reaction mediums are developed for this reaction. In this regards, Guan *et al.* reported a facile and practical procedure for direct synthesis of various 1,2,3-triazole derivatives **34** from the reaction of nitrostyrenes **18** and sodium azide **33** (Scheme 10).<sup>30</sup> They carried out this reaction in the presence of *p*-toluenesulfonic acid as catalyst in DMF with good to excellent yield.

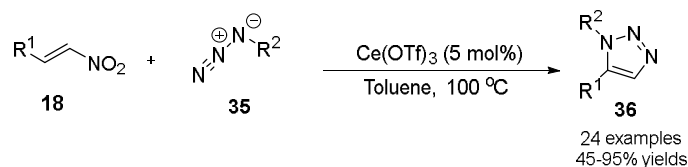


**Scheme 10.** Synthesis of various 1,2,3-triazole derivatives.

In addition, recently, several efficient synthetic methods have been introduced for this reaction using amberlyst-15,<sup>31</sup> sulfamic acid,<sup>32</sup> and acetic acid under flow conditions.<sup>33</sup>

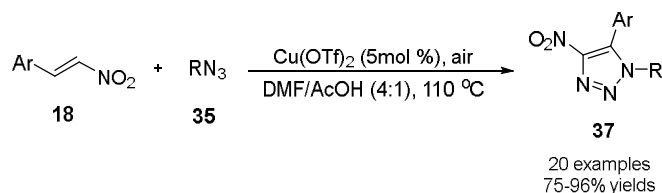
In a parallel report, *via* a re-engineering approach, Dehaen research group reported a three-component reaction to synthesize 1,4,5-trisubstituted-1,2,3-triazoles from aldehydes, nitroalkanes, and organic azides using morpholinium *p*-toluenesulfonate as catalyst, and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as an additive in toluene.<sup>34</sup> Other catalysts such as  $\text{AlCl}_3$ <sup>35</sup> and  $\text{NaHSO}_3/\text{Na}_2\text{SO}_3$ <sup>36</sup> have also been reported for this synthetic method.

In another report, Wang and co-workers described a regioselective metal-catalyzed [3+2]-cycloaddition approach for the synthesis of 1,5-disubstituted-1,2,3-triazoles **36**.<sup>37</sup> In the presence of a catalytic amount of  $\text{Ce}(\text{OTf})_3$ , both benzyl and phenyl azides **35** react selectively with a broad range of aryl nitroalkenes **18** containing a range of functionalities to produce 1,5-disubstituted-1,2,3-triazole motifs in appropriate yields (Scheme 11). This catalytic process did not require dried glassware and an inert atmosphere. Also, in 2016, Elangovan and co-worker reported this reaction by a green synthetic route under catalyst- and solvent-free conditions.<sup>38</sup>



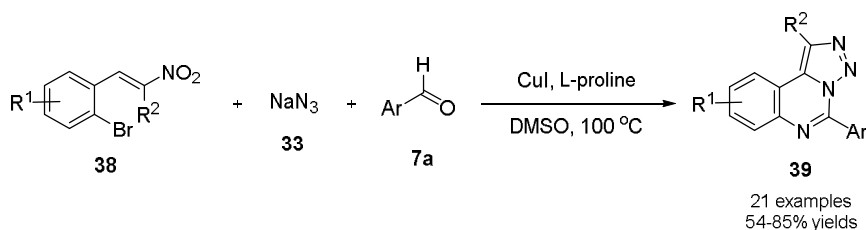
**Scheme 11.** Synthesis of 1,5-disubstituted-1,2,3-triazoles.

Also, Chen and co-workers explored a novel copper-catalyzed [3+2]-cycloaddition/oxidation reaction cascade to access 1,4,5-trisubstituted 1,2,3-triazoles **37** from the reaction of nitrostyrenes **18** with organic azides **35** (Scheme 12).<sup>39</sup> This process cascade affords regioselectively the corresponding nitro-substituted-1,2,3-triazoles with large substrate scope in good to excellent yields. The involved oxidative process overcomes the elimination of  $\text{HNO}_2$  for general cycloaddition of nitrostyrenes with organic azides, which shows a high atom economy.



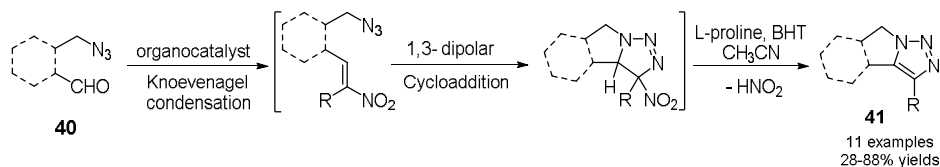
**Scheme 12.** Synthesis of 1,4,5-trisubstituted 1,2,3-triazoles.

Additionally, the similar reaction was investigated by Elangovan and co-workers under solvent-free conditions in the presence and absence of CuO nanoparticles catalyst.<sup>38</sup> In the presence of the catalyst under solvent-free conditions, nitro group is retained in the product while it gets eliminated in the absence of the catalyst. Furthermore, to expand the repertoire of new heterocyclic compounds using nitrostyrenes, Wu and co-workers reported an innovative multicomponent domino approach for the direct synthesis of 5-phenyl-[1,2,3]triazolo[1,5-*c*]quinazolines **39** from simple and readily available (*E*)-1-bromo-2-(2-nitrovinyl)benzenes **38**, aldehydes **7a**, and sodium azide **33** (Scheme 13).<sup>40</sup> The reaction proceeds *via* domino [3+2]-cycloaddition, copper-catalyzed S<sub>N</sub>Ar, reduction, cyclization, and oxidation sequences. Notably, sodium azide acted as a dual nitrogen source in the construction of this novel fused *N*-heterocycle.



**Scheme 13.** Synthesis of 5-phenyl-[1,2,3]triazolo[1,5-*c*]quinazolines.

In another work, Dehaen *et al.* developed efficient synthesis of fused 1,2,3-triazoles **41** by the reaction of an azido aldehyde **40** and a nitroalkane in the presence of *L*-proline as the catalyst, and BHT as an additive in acetonitrile (Scheme 14).<sup>41</sup> This synthetic route has some benefits such as mild conditions, affords high yields, and results in good regioselectivity and excellent substrate scope.



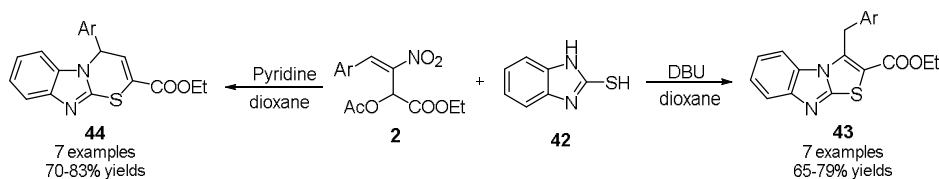
**Scheme 14.** Synthesis of fused 1,2,3-triazoles.

## 5. Thiazoles and thiazines

Among the heterocyclic frameworks with two heteroatoms, those containing nitrogen and sulfur atoms such as thiazoles and thiazines are well-known compounds due to their broad spectrum of biological activities including antimicrobial, anticonvulsant, antifungal, antitumor, and herbicidal properties.<sup>42</sup> These molecules have also been applied as inhibitors of numerous targets for pharmaceutical interventions in various diseases.<sup>43</sup> Because of this, there are several synthetic methods in literature for the synthesis of thiazole and thiazine rings.<sup>44-46</sup> In this regard, nitroalkenes as a magic substrate have been extensively used

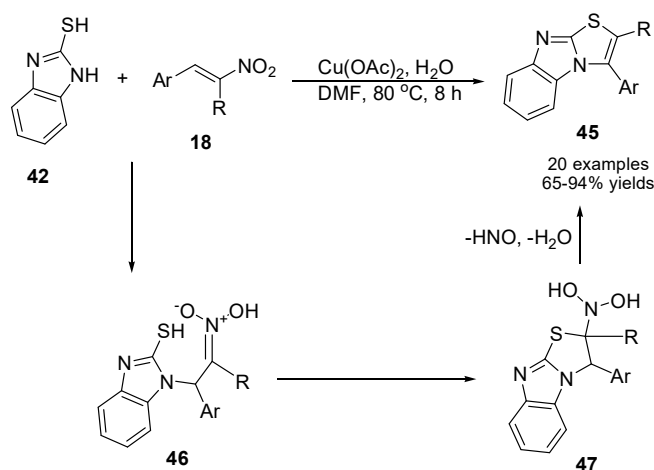


in the synthesis of these useful heterocycles. Zhang and co-workers described a base-controlled regioselective reaction of 2-mercaptobenzimidazole **42** with MBH acetates of nitrostyrenes **2** for preparation of new types of thiazoles **43** and 1,3-thiazines **44** in moderate to good yields.<sup>47</sup> This synthetic method is a catalyst-control strategy. The reaction provided new benzimidazo[2,1-*b*]-1,3-thiazines in the presence of pyridine in dioxane, whereas thiazolo[3,2-*a*]benzimidazole derivatives were obtained in the presence of DBU as base (Scheme 15).



**Scheme 15.** Synthesis of benzimidazo[2,1-*b*]-1,3-thiazines and thiazolo[3,2-*a*]benzimidazole derivatives.

In 2018, the Hajra research group explored an efficient access to benzo[4,5]imidazo[2,1-*b*]thiazole derivatives **45** from a copper(II)-catalyzed thioamination of nitroalkenes **18** with 1*H*-benzo[*d*]imidazole-2-thiol **42** in DMF (Scheme 16).<sup>48</sup> This synthetic strategy showed broad substrate scope and a wide range of functional groups tolerated in this protocol. A structurally diverse nitroalkenes containing electron-donating, electron-withdrawing and halogen substituents as well as 1*H*-benzo[*d*]imidazole-2-thiol were successfully applied to the reaction and afforded the corresponding products in appropriate yields *via* successive carbon-nitrogen and carbon-sulfur bond formations. According to the proposed mechanism by authors, initially the intermediate **46** is formed via the Michael addition of 1*H*-benzo[*d*]imidazole-2-thiol **42** to nitroalkenes **18**. Subsequently, intermediate **47** is generated from the intermediate **46** through intramolecular cyclization via C-S bond formation in the presence of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O. Finally the product **45** was obtained by the elimination of water and HNO.

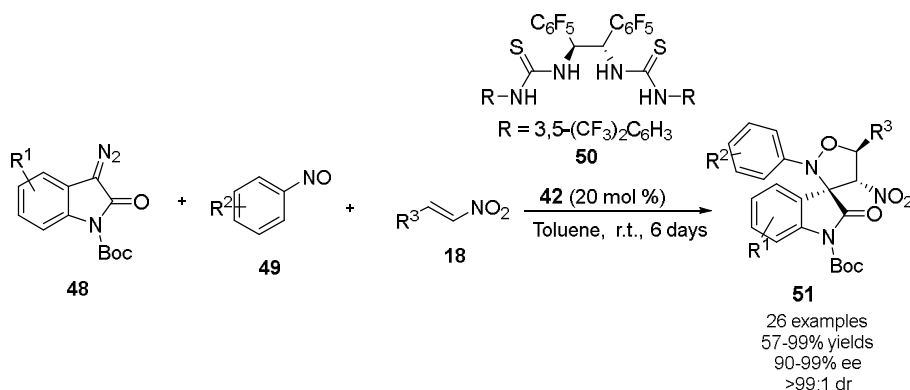


**Scheme 16.** Synthesis of benzo[4,5]imidazo[2,1-*b*]thiazole derivatives.

## 6. Isoxazolines and oxazines

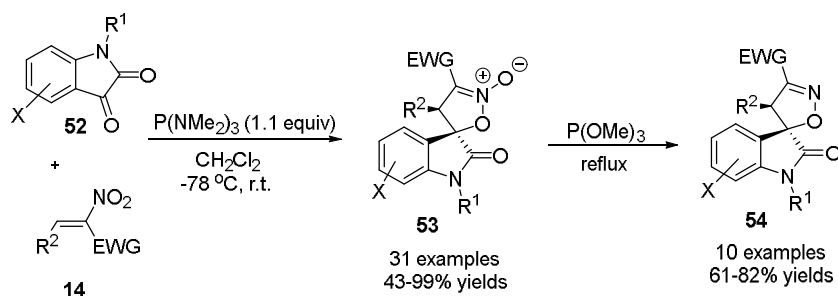
Isoxazolines and oxazines are five-membered and six-membered heterocycles containing nitrogen and oxygen atoms. They are potential targets in many different areas of medicinal chemistry and pharmacological industries for the preparation of anticancer and antimicrobial agents.<sup>49-50</sup> In this context, Liu, Tan and co-workers reported a novel three-component reaction of diazooxindoles **48**, nitrosoarenes **49**,

and nitroalkenes **18** catalyzed by a bis(thiourea) based hydrogen-bond catalyst **50** with high diastereo- and enantioselectivity (Scheme 17).<sup>51</sup> The reaction led to straightforward construction of various spirooxindoles **51** with an isoxazolidine ring *via* readily available substrates with excellent functional-group tolerance. The desired products were produced in good to excellent yields in a long period of time (6 days), and the method demonstrated an unexpected approach for trapping the active intermediate with a nitroalkene to form biologically useful scaffolds containing three contiguous stereogenic centers.



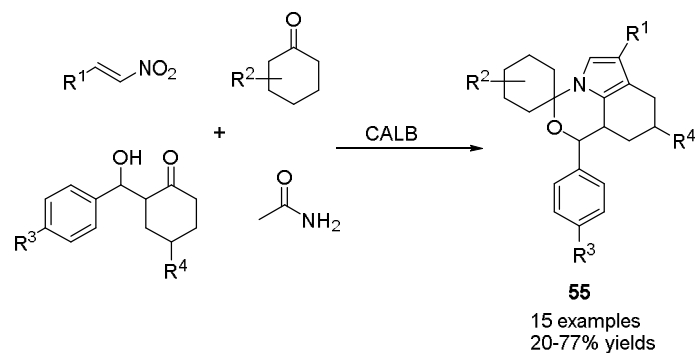
**Scheme 17.** Synthesis of various spirooxindoles with an isoxazolidine ring.

In an interesting work, He *et al.* developed the reductive (1+4) annulation reaction of isatin derivatives **52** and substituted nitroalkenes **18** mediated by a trivalent phosphorus reagent which caused spirooxindolyl isoxazoline *N*-oxides **53** in moderate to excellent yields (Scheme 18).<sup>52</sup> The reaction proceeds through a Michael addition-intramolecular substitution sequence *via in situ* generation of Kukhtin-Ramirez zwitterion intermediates from isatin derivatives and  $\text{P}(\text{NMe}_2)_3$ . Notably, the spirooxindolyl isoxazoline *N*-oxides easily converted to the corresponding isoxazolines **54** in good yields.



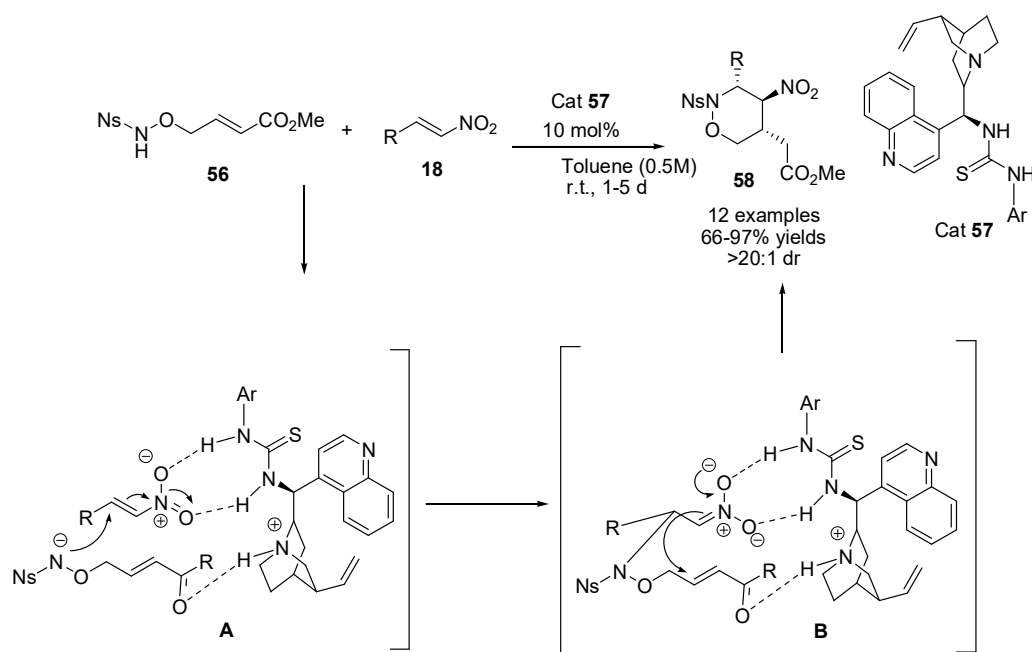
**Scheme 18.** Reaction of isatin derivatives and substituted nitroalkenes.

In another report, Wu *et al.* demonstrated an effective approach for a lipase-catalyzed complicated MCR for the one-pot synthesis of complex spirooxazino derivatives **55** (Scheme 19).<sup>53</sup> 15 various spirooxazino derivatives with different substitutions were synthesized in moderate to high yields. Importantly, chiral spirooxazino were also achieved *via* a further developed two-enzymatic one pot MCR strategy. Additionally, the reaction condition screening for enzymes, enzyme concentration, amides and ratio of substrates were applied. The results showed that only *Candida antarctica* lipase B (CALB) catalyzed this reaction which confirmed the essential role of the specific active site of CALB in the MCR.



**Scheme 19.** The one-pot synthesis of complex spirooxazino derivatives.

In an outstanding paper, in 2018, an efficient asymmetric synthesis of novel tetrahydro-1,2-oxazine motifs **58** *via* bifunctional thiourea catalysis **57** has also been developed by Albrecht research group (Scheme 20).<sup>54</sup> The target products were achieved using nitroalkenes **18** and a recently introduced group of aminoxylation reagents **56** as substrates. The developed cascade reaction proceeds in a sequence of aza-Michael-Michael reaction. The desired products, bearing three contiguous stereocenters have been afforded with good to excellent yields (up to 97%) and with excellent stereocontrol (>20:1 dr, up to 99.5:0.5 er).



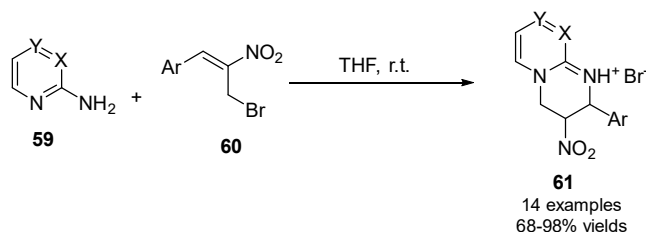
**Scheme 20.** Synthesis of novel tetrahydro-1,2-oxazine motifs.

Theoretical mechanistic studies such as density functional theory (DFT) calculations as well as comprehensive experimental were recently carried out by Jasiński research group to explain the

cycloaddition reactions of nitroalkenes to assess isoxazolines derivatives.<sup>55-56</sup> DFT simulations of reaction paths suggest that these reactions could be considered as polar, “one-step two-stage” cycloadditions.

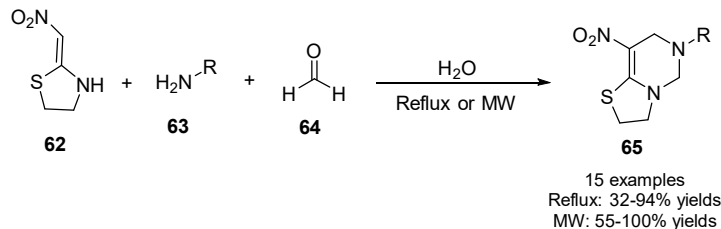
## 7. Dihydropyrimidines

Pyrimidines are significant heterocyclic scaffolds containing two nitrogen atoms. Pyrimidine ring, as an essential part of nucleic acid DNA, shows useful properties in many biological applications. Also, pyrimidine and its derivatives demonstrate a diverse array of pharmacological activities including anticonvulsant, antiviral, antifungal and anticancer properties.<sup>57</sup> In 2017, Namboothiri research group has been demonstrated reactions of 2-aminopyridines **59** and the MBH bromides of nitrostyrenes **60** in THF to access 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **61** (Scheme 21).<sup>58</sup> The reaction of MBH bromides with 2-aminopyridines takes place in the absence of any catalyst or additive in a cascade  $S_N2'$ -6-*endo-trig* fashion and is completely regioselective and highly stereoselective. The products, in their hydrobromide salt form, could be easily isolated and purified by crystallization in  $CHCl_3$ /diethyl ether.



**Scheme 21.** Reaction of 2-aminopyridine and the MBH bromides of nitrostyrenes.

In a similar strategy, Anwar *et al.* reported catalyst-promoted synthesis of dihydro[1,5]-azo-[1,2-*a*]pyrimidine 2-esters at room temperature in appropriate yields *via* one-pot reaction between nitrostyrenes derived MBH acetates and aminoazole derivatives such as 2-aminobenzimidazole, 2-aminoimidazole and 3-amino 1,2,4-triazoles with  $\gamma$ - $\alpha$  cyclisation.<sup>59</sup> Also, Yıldırım and co-workers executed the diverse synthesis of 6-substituted-8-nitrothiazolo[3,2-*c*]pyrimidine compounds **65** *via* a three-component cyclisation of 2-(nitromethylene)thiazolidine **62**, various aliphatic or aromatic amines **63** accompanied by formaldehyde **64** in water, utilizing both microwave (MW) irradiation and conventional heating methods (Scheme 22).<sup>60</sup> Reaction yields were significantly higher and the reaction times considerably reduced using MW heating when compared to conventional heating, resulting in the definition of a quick and effective synthetic strategy.

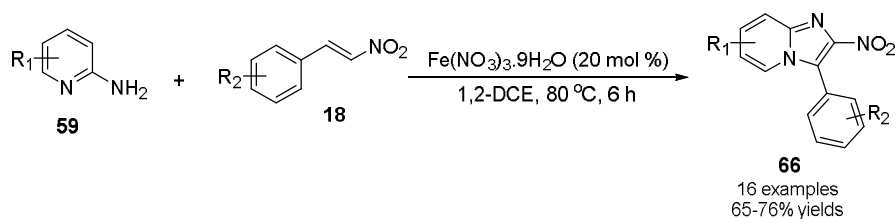


**Scheme 22.** Synthesis of 6-substituted-8-nitrothiazolo[3,2-*c*]pyrimidine compounds.

## 8. Imidazopyridines

Imidazopyridine framework, an imidazole moiety fused with a pyridine ring, is a remarkable class of biologically active heterocycles containing nitrogen. Among the various imidazopyridines, the imidazo[1,2-*a*]pyridine scaffold is one of the most significant and important building blocks in terms of pharmaceuticals, natural products as well as medicinal chemistry. These pharmacologically significant and

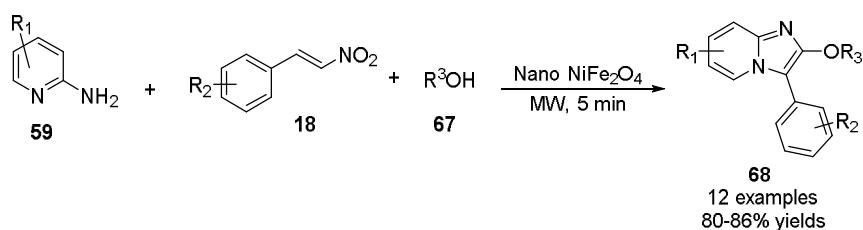
structurally interesting molecules have been synthesized with several methods in recent years. Imidazopyridines exhibit a broad spectrum of biological activities including antibacterial, anthelmintic and antifungal applications.<sup>61</sup> These structures are common in marketed drugs such as Zolpidem, Olprinone, Soraprazan, and several useful molecules in biological testing and preclinical evaluation. Generally, imidazo[1,2-*a*]pyridine derivatives are the end product of Groebke-Blackburn-Bienayme three-component reaction.<sup>62</sup> In addition, more recently, nitroalkenes have been introduced as suitable tools for easy access to imidazo[1,2-*a*]pyridine derivatives. To achieve this important heterocyclic compounds, Hajra and co-workers described an iron-catalyzed oxidative diamination of nitroalkenes **18** with 2-aminopyridines **59**. This approach affords 2-nitro-3-arylimidazo[1,2-*a*]pyridines **66** with excellent regioselectivity under aerobic reaction conditions (Scheme 23).<sup>63</sup> Among the several iron salts such as  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ,  $\text{FeCl}_3$ ,  $\text{FeBr}_3$ ,  $\text{Fe}(\text{OTf})_3$  examined for this reaction, only  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  afforded the acceptable yield. Other metal salts such as  $\text{CuI}$ ,  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ , and  $\text{AgNO}_2$  were also applied in this protocol without desired product. In addition, a broad spectrum of substituted nitroalkenes and aminopyridines were subjected to prove the generality of this synthetic route. This strategy is the first procedure for the synthesis of 2-nitroimidazo[1,2-*a*]pyridines.



**Scheme 23.** Synthesis of 2-nitro-3-arylimidazo[1,2-*a*]pyridines.

Next, in 2016, Singh *et al.* reported an eco-friendly, metal-free, and visible light-catalyzed method for a highly regioselective synthesis of 2-nitro-3-arylimidazo[1,2-*a*]pyridines **66** through the reaction of nitroalkenes **18** with 2-aminopyridines **59**. The reaction was performed under an open atmosphere involving a photoredox catalyst, Eosin Y, which is an efficient and inexpensive organic dye.<sup>64</sup> This synthetic methodology serves the green chemistry protocol, due to the fact that molecular oxygen and visible light have been utilized effectively for this transformation. In 2017, Phan research group developed a straightforward route for the synthesis of 2-nitro-3-arylimidazo[1,2-*a*]pyridines through oxidative amination protocol using indium-based metal-organic frameworks as an efficient heterogeneous catalyst under air.<sup>65</sup> The catalyst could be separated and reused after washing with DMF and dichloromethane and dried at 150 °C for 2 h. This catalyst was applied for seven times without the significant loss of activity. This is the first report on using heterogeneous catalysts for synthesis of 2-nitro-3-arylimidazo[1,2-*a*]pyridines. Moreover, Tachikawa and Itoh and co-workers reported a direct metal-free synthesis of 2-nitro-3-arylimidazo[1,2-*a*]pyridines using a catalytic amount of iodine and aqueous hydrogen peroxide.<sup>66</sup>

Interestingly, Banerjee *et al.* described a convenient and regioselective strategy for the easy synthesis of novel 2-alkoxy-3-arylimidazo[1,2-*a*]pyridines **68** under MW irradiation (Scheme 24).<sup>67</sup>

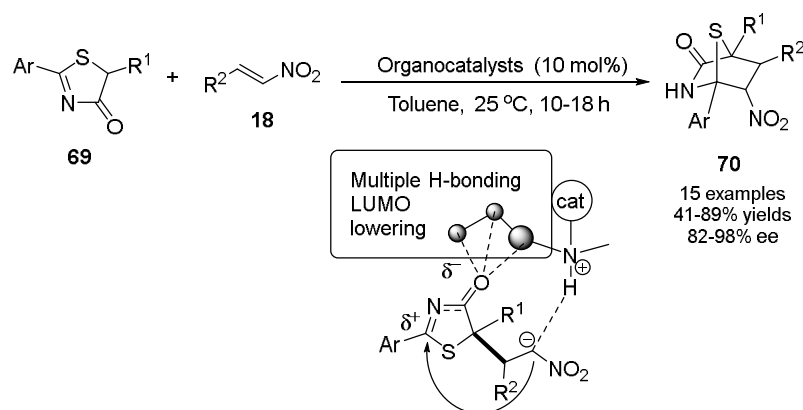


**Scheme 24.** Synthesis of novel 2-alkoxy-3-arylimidazo[1,2-*a*]pyridines.

This synthetic route was carried out *via* a one-pot three-component reaction of 2-aminopyridines **59**, nitroalkenes **18** and alcohols **67** using nano-NiFe<sub>2</sub>O<sub>4</sub> as a recyclable heterogenous catalyst under aerobic conditions. This is the first strategy to access alkoxy functionalized imidazopyridine derivatives *via* cascade single-pot three-component reactions. The MW irradiation expedited the reaction rate and increased the yield of products compared with conventional heating conditions. Different aliphatic alcohols such as ethanol, *n*-propanol and *n*-butanol were participated with good yields, however, tertiary butyl alcohol and phenols were found to be inactive in this protocol. Also, in 2016, the same group reported the synthesis of 2-alkoxyimidazopyridines using mesoporous Fe-SBA-15 as a powerful heterogeneous catalyst.<sup>68</sup>

### 9. Bicyclic compounds

The interest in the synthesis of heteroatom-containing bicyclic compounds is connected with the existence of these molecules in a large number of natural products characterized and identified as active ingredients of medicinal and pharmacological agents.<sup>69</sup> 1,4-Sulfur bridged piperidinones and their analogs are valuable nitrogen and sulfur-containing structural units.<sup>70-71</sup> In a highly innovative report, Lee, Jiang and co-workers demonstrated an efficient synthetic strategy for the direct synthesis of diverse 1,4-sulfur bridged piperidinone frameworks **70** (Scheme 25).<sup>72</sup> The asymmetric synthesis of these products is complicated due to the presence of at least two hetero-quaternary stereocenters in the structure. In order to achieve this goal, the authors have developed a novel asymmetric [4+2] annulation reaction of 5*H*-thiazol-4-ones **69** and nitroalkenes **18** in the presence of a new family of dipeptide-based multifunctional Brønsted base organocatalysts. This approach can be potentially expanded to diverse nitroalkenes, providing an interesting synthetic route to important chiral 1,4-sulfur bridged piperidinones and their derivatives with multiple hetero-quaternary stereogenic centers in good yields and high enantioselectivities. Density functional theory studies involving 5*H*-thiazol-4-one and nitroalkenes propose stereochemical insights into the origin of enantio- and chemo-selectivity.

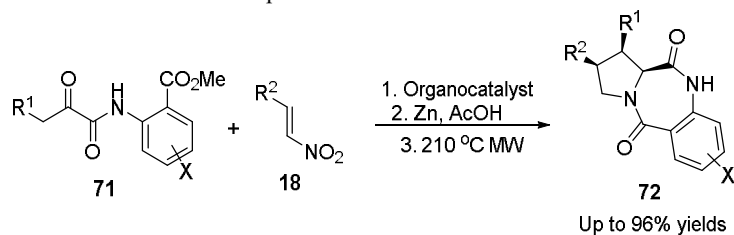


**Scheme 25.** Direct synthesis of diverse 1,4-sulfur bridged piperidinone frameworks.

### 10. Diazepines

Benzodiazepines and their analogs have vital roles in the pharmaceutical industry; their derivatives are known to display a broad spectrum of pharmacological activities such as HIV reverse transcriptase inhibitors, analgesic, antianxiety, anxiolytics, sedative and anti-inflammatory agents.<sup>73</sup> Besides, 1,4-benzodiazepine framework is a highly potent pharmacophore and exists in the structure of various bioactive molecules. Some of them have been clinically utilized as diagnostic markers and drugs for different diseases such as Alprazolam, Cloxazolam, Diazepam and Lopirazepam. Because of the great importance of these seven membered rings containing two nitrogen atoms, several synthetic methodologies have been described in recent years.<sup>74-75</sup> In this regard, Rodriguez, Bonne and co-workers reported an innovative route for the enantioselective synthesis of optically active pyrrolo[1,4]benzodiazepine-2,5-diones

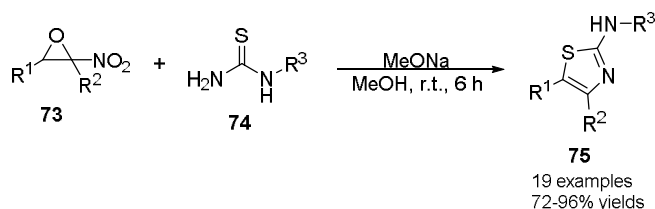
**72** using a chiral thiourea organocatalyst (Scheme 26).<sup>76</sup> This reaction is based on an initial Michael addition of functionalized 1,2-ketoamides **71** on nitroalkenes **18**, followed by reduction-double cyclization sequence to afford the desired substituted benzodiazepine.



**Scheme 26.** Synthesis of optically active pyrrolo[1,4]benzodiazepine-2,5-diones.

### 11. Reactions of nitroepoxides

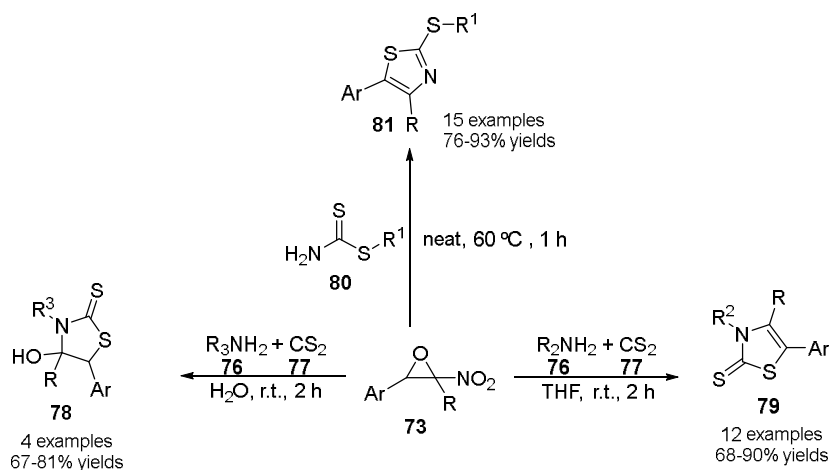
One of the most efficient derivatives of nitroalkenes is nitroepoxides. These versatile substrates have been easily produced by epoxidation of nitroalkenes. Nitroepoxides are an underdeveloped class of compounds with high potential for application in organic reactions, particularly for the synthesis of heterocyclic compounds. In this context, Zhang, Yu and co-workers developed an efficient protocol for the synthesis of 2,4,5-trisubstituted thiazole derivatives **75** by treating easily available  $\alpha$ -nitroepoxides **73** with thioureas **74** (Scheme 27).<sup>77</sup> This efficient process provides desired products in good to excellent yields at ambient temperature with the advantage of operational simplicity and a satisfactory substrate scope.



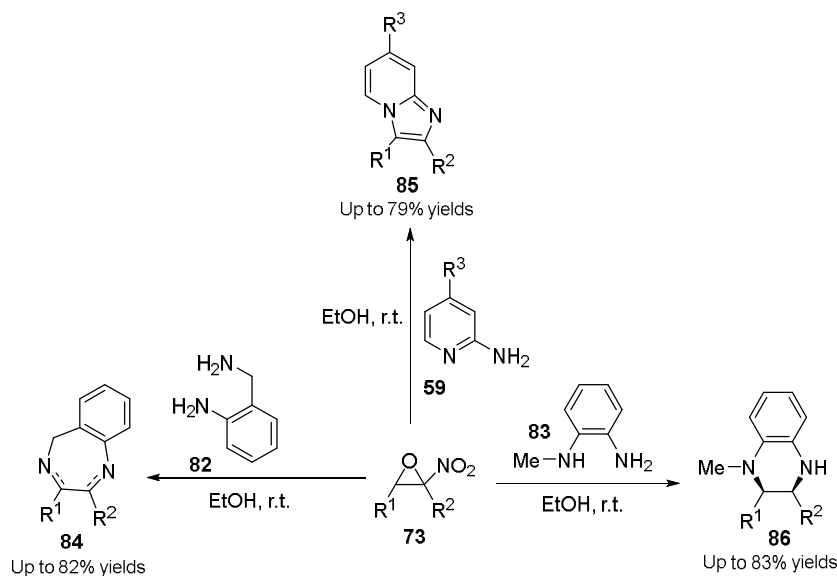
**Scheme 27.** Synthesis of 2,4,5-trisubstituted thiazole derivatives.

In 2017, Ziyaei Halimehjani research group demonstrated a novel, straightforward synthetic route for the expeditious synthesis of substituted thiazole-2(3*H*)-thiones **78** (four new compounds) and thiazolidine-2-thiones **79** (12 new compounds) by the reaction of nitroepoxides **73**, primary amines **76** and carbon disulfide **77** without using any catalyst in water and THF, respectively (Scheme 28).<sup>78</sup> Both of these solvent-control reactions give the corresponding products in good to excellent yields. Under optimized reaction conditions, various primary amines along with nitroepoxides were used to investigate the scope of the reaction. In addition, by using *S*-alkyl dithiocarbamates **80** in this protocol instead of primary amines and carbon disulfide, the corresponding substituted thiazoles **81** were prepared successfully. The advantages of these methods are operational simplicity, mild reaction conditions, short reaction times and high product yields.

Later on, González, Ziyaei Halimehjani and co-worker developed that benzodiazepines **84**, imidazopyridines **85**, and *N*-alkyl tetrahydroquinoxalines derivative **86** can be prepared in high yields and regioselectivity from nitroepoxides **73** along with 2-aminobenzylamines **82**, 2-aminopyridines **59**, and *N*-alkyl-1,2-diaminobenzenes **83** (Scheme 29).<sup>79</sup> This practical method was carried out in EtOH as an eco-friendly solvent and at ambient temperature. Regioselectivity is controlled *via* the attack of the most nucleophilic nitrogen of the unsymmetrical diamine to the  $\beta$  position of the epoxide. In addition, tetrahydrobenzodiazepine scaffolds can be directly achieved with 2-aminobenzylamine as well as sodium borohydride as a reducing agent. These synthetic routes described a facile and efficient way to direct access to pharmacologically notable and structurally interesting scaffolds.



**Scheme 28.** Reaction of nitroepoxides with sulfur nucleophiles.



**Scheme 29.** Synthesis of benzodiazepines, imidazopyridines, and *N*-alkyl tetrahydroquinoxalines derivatives.

## 12. Conclusion

In this updated book chapter, we have shown that the rich chemistry is accessible using nitroalkenes as a privileged reagent in direct synthesis of heterocyclic compounds with two or three heteroatoms through a variety of synthetically remarkable reactions. These synthetic routes led to the novel categories of outstanding heterocyclic compounds such as imidazoles, pyrazoles, triazoles, thiazoles, thiazines, isoxazolines, pyrimidines, imidazopyridines, benzodiazepines as well as bicyclic compounds starting from simple and commercially available reactants. These synthetic compounds were synthesized from nitroalkenes and their derivatives with a broad range of reactants through a wide spectrum of organic transformations such as multi-component reactions, Michael addition reactions, [m+n]-cycloadditions,



asymmetric process, MBH reaction and cascade/domino/tandem protocols. In our opinion, this study will be interesting for scientists from the different field of organic chemistry such as heterocyclic synthesis, combinatorial chemistry and catalytic systems as well as scientists from pharmaceutical and medicinal chemistry.

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