Nitroenediamines (EDAMs), and \(N\)-methyl-1-(methylthio)-2-nitroethenamine (NMSN) derivatives: scaffolds for heterocycle molecular diversity (update from 2012 to 2021)

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Nitro-1,1-enediamines (EDAMs) and \(1,1\)-bis(methylthio)-2-nitroethene (NMSN) have proven to be a class of attractive and useful synthetic building blocks for use in the synthesis of heterocyclic and fused heterocyclic compounds. The bicyclic or tricyclic heterocycles derived from these frames widely exist in natural and synthetic drugs. To comprehend the reaction properties of EDAMs and NMSN and to design other novel fused heterocycles with biological effects in the future, it is essential to investigate their recent reactions. The current review envisions highlighting some recent and remarkable examples of nitroenediamine reactions categorized by catalyst-assisted and catalyst-free reactions from 2012 onward.

1. Introduction

Nitro-1,1-enediamines (EDAMs) with the formula and structural features illustrated in Scheme 1, are fascinating and versatile building blocks that have been widely applied to synthesize a variety of functionalized fused heterocyclic compounds with diverse pharmacological activities including antitumor, anti-bacterial, and antileishmanial. EDAMs as bisnucleophilic reagents could react with various electrophiles to prepare highly functionalized heterocycles.

The reactant \(N\)-methyl-1-(methylthio)-2-nitroethenamine (NMSN) contains four active sites with three functional groups on an ethene motif, as shown in Scheme 1. A strongly electron-withdrawing nitro group makes the nitroethylene substructure a good Michael acceptor. Besides, the methylthio group acts as a leaving group and electron donor to make the C2 a good Michael donor. Also, the secondary amine group is an electron-donor. Overall, the ethylene moiety is a polarized push–pull alkene with C1 showing electrophilic character and C2 showing nucleophilic character. NMSN, with all these characteristics, is an important reactant that may cause the products more valuable as medical intermediates and in synthesizing a variety of oxygen and nitrogen-containing heterocyclic compounds.

Cyclic enediamine with a carbonyl group on \(\alpha\)-carbon atom is known as heterocyclic ketene aminals (HKAs). These compounds are generally categorized as good nucleophiles in organic reactions. Furthermore, replacement of nitro group on \(\alpha\)-carbon generates a new class of HKAs and will be discussed in this review.

All of ketene aminals, keten thioacetals and nitroenediamines are interesting synthons and readily synthesized through the reaction have been summarized in Scheme 2. The most common method of synthesizing these compounds is the condensation of nitromethane with carbon disulfide in the presence of KOH in ethanol solvent that makes compound 2. The reaction of compound 2 and dimethyl sulfate generates the nitro ketene dithioacetal-1-nitro-2,2-bis(methylthio)ethylene 3 that is a precursor in the synthesis of nitroamine derivatives. The reaction of 3 with various amine (one equivalent or excess amounts) obtains the corresponding mono substituted 4 or keten aminals 5. Also, the elimination of two molecules of \(R^1\)SH from 1,1-bis (methylthio)-2-nitroethene 3 in reaction with diamines affords cyclic nitro-ene-1,1-diamine 6 (Scheme 2).

Work in the field of heterocyclic ketene aminals (HKAs) prior to 2014 was reviewed by Wang and in current review, we will investigate the relevant examples of heterocyclic ketene aminals containing nitro groups. This review summarizes the recent progress in heterocycle synthesis from 2012 to 2021. Its aim is to give an overview of the rich reactivity of nitroenediamines in multi-component reactions. This review is divided into two significant parts according to reagent and divided into sub-sections based on catalytic and non catalytic pathways for further clarification.

2. Nitroenediamine derivatives in heterocyclization

In this section, the reaction of cyclic and acyclic nitroenediamine have been described especially focusing on some
important mechanisms. Since cyclic nitroenediamine is obtained from reactions 1,1-bis(methylthio)-2-nitroethene and diamines, these reactions are also investigated in this section.

2.1. Catalysts-assisted approaches

Indium salts are considered a non-toxic valuable catalyst in organic transformations. An indium triflate-catalyzed reaction

Scheme 1 Structure of nitro-1,1-enediamines and N-methyl-1-(methylthio)-2-nitroethenamine.

Scheme 2 Synthesis of cyclic/acyclic nitro-1,1-enediamines and N-methyl-1-(methylthio)-2-nitroethenamine.

Scheme 3 Synthesis of azaxanthones 10 from via In(OTf)₃-catalyzed reaction.
of (Z)-N-methyl-1-(methylthio)-2-nitroethenamine 5 with 3-formylchromone 7 achieved the azaxanthone derivatives 10 in good yields (up to 88%). Mechanistically, In(OTf)_3 promotes the Henry reaction of 3-formylchromone 7 with N,N-dialkyl-2-nitro-ethene-1,1-diamine 5 to generate intermediate 8. In the following, the removal of water makes the intermediate 9 which undergoes 6π-electrocyclization to afford the final product 10 (Scheme 3).

Xiao and coworkers reported the silver-catalyzed synthesis of 2-(pyridin-3-yl)-chromeno[2,3-d]pyrimidine derivatives 12 via electrocyclization cascade reaction of 3-cyanochromone 11 and 1,1-enediamines 5 under reflux in 1,4-dioxane for 48 hours. Importantly, one C–C bond and three C–N bonds were formed, and one bond was broken in one-pot organic transformation (Scheme 4). Based on proposed mechanism, the nucleophilic Michael addition of nitroenediamine 5 with 3-cyanochromone 11 forms the intermediate 12. The imine–enamine tautomerization of 12 and further intramolecular 1,2-addition involving the primary amine leads to cyclic intermediate 14. Water removal and ring opening of intermediate 15 is promoted by silver carbonate to afford intermediate 16. Finally, the electrocyclization reaction of intermediate 16 with another 3-cyanochromone molecule 11 gives intermediate 17 which undergoes a 1,3-migration of hydrogen to obtain 2-(pyridin-3-yl)-chromeno[2,3-d]pyrimidines 18.

A valuable and efficient reaction of isatins 19 and 1,1-enediamines 5 catalyzed by NH_2SO_3H to synthesize corresponding multisubstituted quinoline-4-carboxamides 26 was reported by Yan and co-workers (Scheme 5). Mechanistically, the aza-ene reaction of EDAMs 5 with isatine 19 gives the intermediates 20. Then, tautomerization followed by intramolecular cyclization makes intermediate 22. Intermediate 22 is converted into intermediate 24 via two ring-opening reactions. The primary amino groups of intermediate 24 attacks the imine ion to produce the intermediate 25 which then undergoes a cyclization reaction and tautomerization to produce 26.

In 2021, Yan and colleagues disclosed the cascade reaction of the (E)-3-[2-oxo-2-phenylethylidene]indolin-2-one derivatives 27 and cyclic and acyclic EDAMs 5 and 6. Applying acyclic EDAM substrates 5 in this reaction led to formation of 4-[2-oxoindolin-3-yl]-1H-pyroles 28 via the selective nucleophilic attack of the amine on the more electron-deficient carbonyl (ArC==O) of compound 27 rather than the amide group (NH.CO). The R1 group greatly affected the yields of 28, such that electron-withdrawing groups manifested higher yield of the products compared to electron-donating groups (Scheme 6).

The selective Michael addition of cyclic enediamine 6 to the unsaturated double bond of (E)-3-[2-oxo-2-phenylethyliene]indolin-2-one derivatives 27 in the presence of Cs_2CO_3 as the base at room temperature after 12 hours makes α-carboline 34 in excellent yields. To the surprise, the methodology for the same reactants in a longer time after 48 hours obtained the more stable α-carbolines 35. Herein, tautomerization followed by intramolecular cyclization provides intermediate 31 that is
transform into 34 under oxygen and losing two water molecules (Scheme 7).

Yan et al. in 2019, explored the DBU-promoted tandem reaction of different Morita–Baylis–Hillman (MBH) acetates 36 with the different EDAMS 5 to access fully substituted-2-amino pyrroles 39. The results revealed that the electron-withdrawing group (F and Cl)-substituted of the MBH acetates can achieve a higher yield than the electron-donating group (MeO) and the reaction with N-phenyl EDAMS and N-alkyl-EDAMS gives higher yields than N-benzyl-EDAMS (Scheme 8).13

The α-C of EDAMS 5 begins the nucleophilic Michael addition to MBH acetates 36 that is accompanied by the elimination of the acetate group through an SN2 mechanism to generate intermediate 37. Imine–enamine tautomerization of intermediate 37 and further intramolecular aza-Michael addition promoted by DBU results in intermediate 38. Finally, aromatization by elimination of HNO2 yields fully substituted 2-aminopyrroles 39.

Li et al. investigated the effect of 2,2,2-trifluoroethanol catalyst on the Mannich-like reaction of β-nitroenamines 6, amines 41, and aromatic aldehydes 40. TFEA was added to establish the hydrogen bond with aromatic aldehydes to increase its electrophilicity (Scheme 9).14

Hasaninejad et al. reported the preparation of pyrrolo[1,2-a]pyrimidine derivatives 28 via the reaction of bromoacetophenone 43 and 2-nitroethene-1,1-diamines 6 in the presence of K2CO3 (Scheme 10).15 The aza-ene reaction between bromoacetophenone 43 and 2-nitroethene-1,1-diamine 6 gives intermediate 44, which is tautomerized and subsequent intramolecularly cyclized to produce 45.

Shao and coworkers prepared bridged heterocycles 53 from one-pot reaction of ninhydrin 46, malononitrile 47, and nitroendiamine 6 in high yields (Scheme 11).16

Knoevenagel condensation of malononitrile 47 with ninhydrin 46 forms intermediate 48 that undergoes Michael addition of the nitro ketene aminal (NKA) 6 to give intermediate 49. The chemoselective nucleophilic attack of the NH of the resulted intermediate 50 at the carbonyl function affords intermediate 51. Then, O-cyclization and tautomerization of imino group to amino group of 51 could lead to fused oxo-aza[3.3.3]propellanes 53.

**Scheme 5** Synthesis of multi-substituted quinoline-4-carboxamides 26.

**Scheme 6** Site-selective synthesis of highly functionalized pyrroles 28.

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The elimination of two molecules of RSH from 1,1-bis(methylthio)-2-nitroethylene in presence of diamine affords cyclic nitro ene-1,1-diamine. Alizadeh’s group developed an efficient route to synthesis of 1,4-dihydropyridine-fused-1,3-diazaheterocycle derivatives by refluxing a mixture of 1,1-bis(methylthio)-2-nitroethylene, 1,1-diamine, arylaldehyde, and malononitrile in ethanol and 10 mol% of piperidine as a basic catalyst (Scheme 12).

Rezvani reported I2-promoted reaction of aldehyde, pyruvic acid, aliphatic diamines, and 1,1-bis(methylthio)-2-nitroethylene in synthesis of 1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-5-carboxylic acids (Scheme 13).

Deep eutectic solvents (DES) consist of halide salt of a quaternary ammonium or phosphonium cation with a hydrogen bond donor (HBD), for example, urea, carboxylic acids, or ethylene glycol. DESs could be used as drug solubilization vehicles for drug delivery research. DES also possess...
several key characteristics as liquids to support a wide variety of substrates and enzymes. Shaabani and co-workers used the DES by mixing choline chloride (ChCl) and urea to activate the carbonyl and cyano groups in a domino four-component reaction to get fully-substituted naphthyridines (Scheme 14).

2.2. Catalyst-free approaches

A novel approach was developed for the synthesis of 2-amino-4-coumarinyl-5-arylpyrroles through a metal-free cascade reaction of aryglyoxal monohydrates, 1,1-enediamines (EDAMs) and 4-hydroxy-2H-chromen-2-ones (Scheme 15). A cascade reaction of 1,1-enediamines with benzylidene-1H-indene-1,3(2H)-diones in ethanol without any catalysts obtained the products. In this reaction, EDAM attacks the C=C bond of benzylidene to promote the Michael addition reaction. The imine–enamine tautomerization of intermediate makes 76. Then, the intermediate 77 is obtained through the enol–keto tautomerization of intermediate 76. The
Intramolecular cyclization of the intermediates 77 where the amino group attacks the carbonyl provides intermediate 78. Finally, water removal and oxidation of intermediate 78 affords target 79 (Scheme 16).

The aza-ene reaction of HKAs 6 and dioxopyrrolidines 80 without any catalysts in ethanol constructed imidazo[1,2-a]pyrrolo[3,4-e]pyridines 83 with good to excellent yield (Scheme 17). Wang et al. devised the synthesis of perfluoroalkyl-substituted 2-oxopyridine-fused 1, 3-diazaheterocycles 88 via one-pot reaction of diamines 32, ketene dithioacetals 3, and 2-perfluoroalkynoates 84. Mechanistically, in situ cyclic ene-1,1-diamine 6 participates in aza-ene reaction with 2-perfluoroalkynoate 84 to give 85. An intramolecular imine-
enamine tautomerization followed by cyclization makes desired products 88 (Scheme 18).

Bayat et al. synthesized benzo[g]imidazo[1,2-a]quinolinedione derivatives 95 from the multi-component reaction of ethylenediamine 32, 1,1-bis(methylthio)-2-nitroethene 3, 2-hydroxy-1,4-naphthoquinone 90 and aromatic aldehydes 89 (Scheme 19). The proposed mechanism reveals that ketene aminal 6 from ethylenediamine 32 and 1,1-bis (methylthio)-2-nitroethene 3 attacks Knoevenagel adduct of the aldehyde 89 and 2-hydroxy-1,4-naphthoquinone 90 to afford intermediate 92. The intermediate 92 under imine–enamine tautomerization and nucleophilic addition of the secondary amino group to the more reactive carbonyl group gives product 94.

In 2017, Bayat’s group applied cyanoacetohydrazide 96 instead of naphthoquinone 90 in similar pathway to produce imidazo[1,2-a]pyridine-6-carbohydrazide derivatives 98 at a short time (Scheme 20). They also used this strategy in stereoselective synthesis of indenone-fused heterocycles 101 (Scheme 21).

In 2021, Ziyaei et al. utilized thioazlactones 102 and ketene aminals for the synthesis of bicyclic pyridone containing the dithiocarbamate group through domino amidation/intramolecular 1,4-addition-type/Friedel–Crafts alkylation reactions (Scheme 22).

3. (Methylthio)-2-nitroethenamine derivatives (NMSM) in heterocyclization

3.1. Catalysts-assisted approaches

An indium triflate-catalyzed reaction of (Z)-N-methyl-1-(methylthio)-2-nitroethenamine 4 with 3-formylchromone 104 achieved the 2-pyridone analogues 109 in good yields (up to
As mentioned earlier, In(OTf)₃ promotes the Henry reaction of 3-formylchromone ¹⁰⁴ with (E)-N-methyl-1-(methylthio)-2-nitroethenamine ⁴ (NMSM) to give intermediate ¹⁰⁵. Water removal makes intermediate ¹⁰⁶ that undertakes N-cyclization, followed by chromone ring opening to provide ¹⁰⁸. At sequence, the elimination of MeSH and In(OTf)₃ affords the target ¹⁰⁹ (Scheme 23).

Perumal et al. developed a novel procedure in spiroxindoles ¹¹⁵ via domino Knoevenagel condensation/Michael addition/intramolecular O-cyclization reaction of isatins ¹¹⁰, pyrazoles ¹¹¹, and (E)-N-methyl-1-(methylthio)-2-nitroethenamine ⁴ in the presence of InCl₃ as catalyst (Scheme 24).

Rong and co-workers established copper-catalyzed construction of various isoxazolines ¹²² through the 1,3-dipolar cycloaddition reaction of styrene derivatives ¹¹⁶ and 4H-1,2-oxazete ¹¹⁸ in situ resulting from N-alkyl(aryl)-1-(methylthio)-2-nitroethenamine ⁴. The tautomerization and combination of substrate ⁴ with CuCl invited by the amino group generates intermediate ¹¹⁷ that smoothly transforms into intermediate ¹¹⁸. Elimination of methanethion from intermediate ¹¹⁸ makes intermediate ⁴H-1,2-oxazete ¹¹⁹ which yields 1,3-dipolar cycloaddition reaction with olefin ¹¹⁶ to obtain target ¹²² (Scheme 25).

Perumal et al. applied 4-hydroxy-1-methylquinolin-2(1H)-one ¹²³ in Knoevenagel condensation domino reaction of aldehydes and N,S-methylacetal in catalytic amount of ZnCl₂ (Scheme 26).

ZnCl₂ catalyst was also used in the synthesis of novel 2-methyl-6-(methylamino)-5-nitro-4-(4-aryl)-4H-pyran-3-carboxylate derivatives ¹³². This domino, one-pot reaction was performed for β-ketoesters ¹³¹, aromatic aldehydes ¹³⁰, and 88%).
Scheme 19  One-pot synthesis of benzo[g]imidazo[1,2-a]quinolinedione derivatives 94.

Scheme 20  Synthesis of pyridine-fused N-heterocycles 98 via multi-component reaction.

Scheme 21  Synthetic route to indenone-fused heterocycle 101.

Scheme 22  Synthesis of bicyclic pyridones 103.
Scheme 23  In(OTf)$_2$-catalyzed Henry reaction of 4 and 3-formylchromone 104.

Scheme 24  Synthesis of spiroxindoles 115 through InCl$_3$-catalyzed reaction of N-methyl-1-(methylthio)-2-nitroethenamine.

Scheme 25  CuCl-catalyzed reaction of styrene 116 and N-methyl-1-(methylthio)-2-nitroethenamine 4.
(E)-N-methyl-1-(methylthio)-2-nitroethenamine (NMSM) 4 under the neat condition (Scheme 27).\textsuperscript{33}

Jeong et al. applied silica-supported tungstic acid (STA) as a catalyst in multi-component reaction to obtain pyrano[3,2-c]chromen-5-ones 136 in green condition through Knoevenagel condensation, Michael addition, imine–enamine tautomeration, intramolecular O-cyclization, and elimination of MeSH (Scheme 28).\textsuperscript{33}

Kim’s research group reported the synthesis of heterogeneous polymeric catalyst based on ion liquids. Polyethylene glycol methacrylate-grafted tetra-ethylene glycol-bridged dicationic imidazolium [POEGMA-g-TEGBDIM], with its terminal hydroxyl groups, not only generates hosting sites for the reactants but also activates the starting materials to promote a three-component reaction of 1H-benzo[d]imidazole-2-amine 139, aryl aldehydes 140, and (E)-N-methyl-1-(methylthio)-2-nitroethenamine 4 to afford corresponding aryl-benzo[4,5]imidazo[1,2-a]pyrimidine amines 141 (Scheme 29).\textsuperscript{34}

The Pot, Atom, and Step Economy (PASE) approach leads to simplicity, high yields and low waste formation in MCR...
chemistry and in the synthesis of heterocycles. This approach was adopted for the synthesis of benzimidazo[1,2-a]purine derivatives via consecutive reduction/auto-aromatization/heterocyclization of 2-aminobenzimidazoles, aromatic aldehydes, and N-alkyl-1-(methylthio)-2-nitroethenylamines in the presence of 10 mol% [BMIM][BF_4] (Scheme 30).

In 2012, chromen-5-ones and pyrano[3,2-c]chromen-5-ones were synthesized through tandem reaction of NMSM, aromatic aldehydes, and 4-hydroxycoumarin or dimedone in the presence of catalytic amount of piperidine in ethanol (Scheme 31).

In 2018, Khan and colleagues reported the similar reaction of cyclic-1,3-diketones, aromatic aldehydes, and NMSM in catalyst-free neat condition at 110 °C to generate 4H-chromen-5-one derivatives.

Microwave irradiation facilitated the reaction of aromatic aldehyde, 4-hydroxy-6-methyl-2-pyrone, and N-methyl-1-(methylthio)-2-nitroethenamine to produce pyrano[4,3-b]pyran-5-one derivatives. Ammonium acetate catalyzed the reaction.

Scheme 29 Synthesis of N-methyl-2-nitro-aryl-benzo[4,5]imidazo[1,2-a]pyrimidine amines.

Scheme 30 [BMIM][BF_4] assisted synthesis of 3-nitro-imidazo[1,2-a]pyrimidin-2-amine derivatives.

Scheme 31 Synthesis of chromen-5-ones and pyrano[3,2-c]chromen-5-ones in presence of piperidine catalyst.
Scheme 32  Preparation of pyranopyran derivatives 117 under MW irradiation.

Scheme 33  Iodine-catalyzed reaction of N-methyl-1-(methylthio)-2-nitroethenamine, aromatic amines, and phenylglyoxal.

Scheme 34  Aminopyridine-catalyzed synthesis of highly functionalized dihydropyridines 164.
reaction in ethanol and the microwave power higher than 200 watts decomposed the substrates (Scheme 32).\textsuperscript{29}

\textit{N}-Methyl-1-(methylthio)-2-nitroethenamine \textsuperscript{4}, aromatic amines \textsuperscript{154}, and phenylglyoxal monohydrate \textsuperscript{153} reacted in the presence of 10 mol\% of iodine as catalyst. Both electron donating and weak withdrawing groups on aromatic amines except for nitro group gave desired products \textsuperscript{120} in excellent yields (Scheme 33).\textsuperscript{40} At first, the reaction between aromatic amines \textsuperscript{154} and phenylglyoxal monohydrate \textsuperscript{153} leads to the imine \textsuperscript{155} that is activated in presence of molecular iodine. Mannich type reaction between iodine activated imine \textsuperscript{155} and NMSM \textsuperscript{4} generates intermediate \textsuperscript{156} which undergoes intramolecular cyclization to afford \textsuperscript{158}.

Prakash Rao and Parthiban developed an easy route to highly functionalized hexa-substituted 1,4-dihydropyridines.\textsuperscript{41} They used one equivalent of aldehydes \textsuperscript{159}, two equivalents of NMSM \textsuperscript{4}, and 10 mol\% of 2-aminopyridine as catalyst reacting in ethanol (Scheme 34). Mechanistically, at the first step, benzaldehyde \textsuperscript{159} reacts with aminopyridine to make the iminium ion \textsuperscript{160}. The reaction of the iminium ion \textsuperscript{160} with one equivalent of NMSM generates intermediate \textsuperscript{161}, which quickly rearranges to the more stable intermediate \textsuperscript{162}. One more unit of NMSM reacts with intermediate \textsuperscript{162} to generate intermediate \textsuperscript{163} and 2-aminopyridine. Finally, an intramolecular elimination of methanethiol from \textsuperscript{163} gives dihydropyridines \textsuperscript{164}. A similar approach was designed to synthesize \textit{N}-methyl-1,4-dihydropyridine derivatives in good yields under microwave irradiation without any solvents within 10 minutes.\textsuperscript{42}

Aza-Michael annulation of 2-nitromethylene thiazolidine \textsuperscript{165} with suitable Michael acceptors \textsuperscript{166} using K\textsubscript{2}CO\textsubscript{3} as the base afforded tetrahydrothiazolo[3,2-\textit{a}]pyridinones \textsuperscript{170} in good yields.

**Scheme 35**  Synthesis of tetrahydrothiazolo[3,2-\textit{a}]pyridinones \textsuperscript{170}.

\begin{align*}
\text{HN} & \quad \text{O} \\
\text{R} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{165} & \quad \text{167} & \quad \text{168} & \quad \text{169} & \quad \text{170} \\
\text{HN} & \quad \text{O} \\
\text{R} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{165} & \quad \text{167} & \quad \text{168} & \quad \text{169} & \quad \text{170}
\end{align*}

**Scheme 36**  Synthesis of thiophen derivatives \textsuperscript{175} from \textit{N},\textit{S}-alkyl amino acetals \textsuperscript{4} and 1,4-dithiane-2,5-diol \textsuperscript{171}.

\begin{align*}
\text{HN} & \quad \text{O} \\
\text{R} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{165} & \quad \text{167} & \quad \text{168} \\
\text{HN} & \quad \text{O} \\
\text{R} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{165} & \quad \text{167} & \quad \text{168}
\end{align*}

**Scheme 37**  Synthesis of pyranopyrazoles via multi-component reaction.

**Scheme 38**  Synthesis of thiophen derivatives \textsuperscript{175} from \textit{N},\textit{S}-alkyl amino acetals \textsuperscript{4} and 1,4-dithiane-2,5-diol \textsuperscript{171}.
yields (Scheme 35). Based on proposed mechanism, in the presence of K$_2$CO$_3$, 2-nitromethylene thiazolidine 165 forms nitronic acid salt intermediate 167 by tautomerization. Next, Michael addition of 166 with the nitronic acid 167 gives imino-ketene intermediate 168. Then an acylation of imine nitrogen followed by HCl removal results in ring closure and affords thiazolopyridinones 170.

In 2015, Perumal et al. recorded the synthesis of 3-nitro-N-aryl/alkylthiophen-2-amines through the reactions of α-nitroketene $N,S$-alkyl amino acetals 4 and 1,4-dithiane-2,5-diol 171. Mechanistically, 1,4-dithiane-2,5-diol 171 is decomposed in the presence of K$_2$CO$_3$ to generate 2-mercaptoacetaldehyde 172. The nucleophilic addition of compounds 4 to the carbonyl of intermediate 172 followed by the addition of the thiolate anion makes the iminium intermediate 173. Addition of thiolate anion to the iminium functionality generates 174. Subsequent, elimination of methylmercaptan and water from 174 produces the thiophene derivatives 175 (Scheme 36).

In 2013, Paramasivan et al. applied a catalytic amount of piperidine in the domino four-component reaction of ethyl acetoacetate 176, hydrazine hydrate 177, substituted aldehydes 178 with the NMSN 4 under solvent-free conditions at 120 °C to achieve pyranopyrazoles derivatives 184 or chromenopyrazoles 183. They proposed two different mechanisms for targets. The condensation of ethyl acetoacetate 176 with hydrazine hydrate 177 gives pyrazolone 179 that undergoes Knoevenagel reaction with aldehydes to give Michael acceptor 180. The adduct 180 immediately undergoes Michael-type addition with nitroketene-$N,S$-acetal (NMSM) 4 to generate the open chain intermediate 181 or 182. If the aldehyde is salicylaldehyde, the oxygen attack of phenol occurs to get 182. Otherwise, the oxygen of pyrazolone attacks imine to generate new intermediate. Finally, the elimination of MeSH from consistent intermediates leads to chroomenopyrazoles 183 or pyranopyrazoles 184 (Scheme 37).

An equimolar mixture of dimethyl acetylenedicarboxylate (DMAD), hydrazine, aromatic aldehyde, and (E)-N-methyl-1-(methylthio)-2-nitroethenamine in the presence of $N,N$-
diisopropylethylamine (DIPEA) refluxing in ethanol generated the 1,4-dihydropyran[2,3-c]pyrazol-6-amines via domino cyclization Knoevenagel condensation/Michael addition/tautomerism/intramolecular O-cyclization/elimination sequences.\textsuperscript{46}

3-Methyl-1-phenyl-1H-pyrazol-5-amine \textbf{187} in the presence of green catalyst, \textsuperscript{L}proline, enabled to react with \textit{N}-methyl-1-(methylthio)-2-nitroetheneamine \textbf{4}, and different aldehydes \textbf{186} to produce \textit{N},3-dimethyl-5-nitro-1-aryl-1H-pyrazolo[3,4-b]pyridin-6-amins \textbf{193} in good yields (Scheme 38).\textsuperscript{47} The reaction of aromatic aldehyde \textbf{185} with \textsuperscript{L}proline generates the iminium species \textbf{187}. Then, the reaction between 3-methyl-1aryl-1H-pyrazol-5-amine \textbf{186} and the iminium species \textbf{187} provides pyrazoloheterodiene \textbf{189} via intermediate \textbf{188}. Subsequently, the Michael addition of the nitroketene \textit{N},S-acetal \textbf{4} to \textbf{189} produces the intermediate \textbf{190}, which under intramolecular annulation affords the tetrahydropyrazolopyridine intermediate \textbf{191}. Elimination of methanethiol from \textbf{191} results in the formation of dihydropyrazolopyridine, \textbf{192}, which undergoes air oxidation to obtain pyrazolopyridine \textbf{193}.

Shao and coworkers prepared bridged heterocycle \textbf{195} from one-pot reaction of ninhydrin \textbf{46}, malononitrile \textbf{47}, and 1-(methylthio)nitroenamine \textbf{4} under mild condition (Scheme 39).\textsuperscript{48} The mechanism reaction has been mentioned earlier in Scheme 11.
The mixture of benzoylacetonitrile 196, aromatic aldehyde 195 and (E)-N-methyl-1-(methylthio)-2-nitroethenamine 4 was refluxed in EtOH in the presence of triethylamine to obtain penta-substituted 4H-pyran 197 in excellent yield (Scheme 40).48

The reaction of N-methyl-1-(methylthio)-2-nitroethenamine 4, different aldehydes (benzaldehydes/heterocyclic aldehydes) 198 and 3-amino-1,2,4-triazole 199 under a mild condition in the presence of trichloroacetic acid (TCAA) as a Brønsted–Lowry acidic promoter generated N-alkyl-6-nitro-3,5-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine 202. The reaction followed via domino Mannich-type reaction, N-cyclization, and oxidation. Anti-tumor activity of the synthetic library was also evaluated (Scheme 41).49

In 2020, Rong et al. suggested a method for the synthesis of pyrazolo[3,4-b]pyridine 206 and pyrano[2,3-c]pyrazole 207 through multi-component condensation of benzaldehyde derivatives 204, isatins 205, N-methyl-1-(methylthio)-2-nitroethen-1-amine 4, 3-aminopyrazole 203, and p-toluene-sulfonic acid as the catalyst (Scheme 42).50

Jeong et al. designed three-component reaction of 2-amino-benzimidazole 139, aldehydes 208, and (E)-N-methyl-1-(methylthio)-2-nitroethenamine 4, in the presence of catalytic amount of p-toluenesulfonic acid (p-TSA) for the synthesis of N-methyl-3-nitro-aryl-benzo[4,5]imidazo[1,2-a]pyrimidin-2-amine derivatives 209 (Scheme 43).51

Recently, Li et al. synthesized chromeno[2,3-b]pyridine derivatives 211 through the annulation of 2-amino-3-formylchromones 210 and various 1-(methylthio)-2-nitroenamines 4 in the presence of CF3SO3H an acidic catalyst (Scheme 44).52

3.2. Catalyst-free approaches

The multi-component coupling reaction of 2-hydroxy-1,4-naphthoquinone 212, aromatic aldehydes 213 and (E)-N-methyl-1-(methylthio)-2-nitroethenamine 4 led to 2-(methyl-amino)-3-nitro-4-aryl-4H-benzo[g]chromene-5,10-diones 214 in excellent yields (Scheme 45).46

The synthesis of dihydroxyoxoindeno[1,2-b]pyrrole derivatives 217 carried out by the simple reaction of ninhydrin 215, N-
methyl-1-(methylthio)-2-nitroethenamine 4, and various aromatic amines 216 in ethanol without any catalyst at room temperature (Scheme 46).\(^{33}\) The spatial relationship between two hydroxy groups was confirmed through NOE studies that revealed the desired 3,8-cis configuration of the substituents on the pyrrole ring.

A catalyst-free three-component reaction using naphthalene-2-ol 218, aromatic aldehydes 219 and \((E)\)-N-methyl-1-(methylthio)-2-nitroethenamine 4 in water–ethanol medium was reported by Jeong and co-workers, leading to a highly functionalized \(N\)-methyl-2-nitro-aryl-1\(H\)-benzo[f]chromen-3-amine derivatives 220 in excellent yields (Scheme 47).\(^{34}\)

Novel tetrahydro-2\(H\)-thiazolo[3,2-c]pyrimidines 227 developed via microwave-mediated Mannich cyclization. The reaction of 2-(nitromethylene)thiazolidine 221, formaldehyde 223, and various aliphatic or aromatic amines 222 in water using microwave irradiation and conventional heating was investigated. Higher yields and shorter reaction time obtained using microwave (Scheme 48).\(^{35}\)

4. Conclusion

Nitro-1,1-enediamines (EDAMs) and \(N\)-methyl-1-(methylthio)-2-nitroethenamine (NMSM) have been applied as versatile synthetic building blocks to synthesize all sorts of heterocycles or fused heterocycles. Relevant contributions of the last ten years with respect the catalysts and catalyst-free approaches have been reviewed. Among these contributions, novel polymeric catalysts and green multi-component reactions for constructing all kinds of biologically active heterocycles have
become of interest to more and more chemists. We believe that this review will stimulate further discussion and research on the synthesis of fused heterocycles.

**Conflicts of interest**

There are no conflicts to declare.

**List of abbreviations**

| Abbreviation | Description                                      |
|--------------|--------------------------------------------------|
| DBU          | 1,8-Diazabicyclo[5.4.0]undec-7-ene              |
| DES          | Deep eutectic solvents                          |
| DIPEA        | N,N-Diisopropylethylamine                       |
| DMAD         | Dimethyl acetylenedicarboxylate                  |
| EDA          | Nitro-1,1-enediamines                           |
| HBD          | Hydrogen bond donor                             |
| HAKs         | Heterocyclic ketene aminals                     |
| MBH          | Morita–Baylis–Hillman                           |
| NMSN         | 1,1-Bis(methylthio)-2-nitroethene               |
| PTSA         | p-Toluensulfonic acid                           |
| POEGMA-g     | Polyethylene glycol methacrylate-grafted        |
| TEGBDIM      | dicationic imidazolium                          |
| STA          | Silica-supported tungstic acid                  |
| TCAA         | Trichloroacetic acid                            |
| TFEA         | 2,2,2-Trifluoroethanol                          |

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