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Nitroenediamines (EDAMs), and *N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) 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,[1–3] antibacterial,[4] and antileishmanial.[5] EDAMs as bisnucleophilic reagents could react with various electrophiles to prepare highly functionalized heterocycles.

The reactant *N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) 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. NMSM, 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 α-carbon atom is known as heterocyclic ketene aminals (HAKs).[6] These compounds are generally categorized as good nucleophiles in organic reactions. Furthermore, replacement of nitro group on α-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 **1** 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 nitroenamine 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^1SH from 1,1-bis (methylthio)-2-nitroethene **3** in reaction with diamines affords cyclic nitro-ene-1,1-diamine **6** (Scheme 2).[7,8]

Work in the field of heterocyclic ketene aminals (HKAs) prior to 2014 was reviewed by Wang[6] 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 subsections 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

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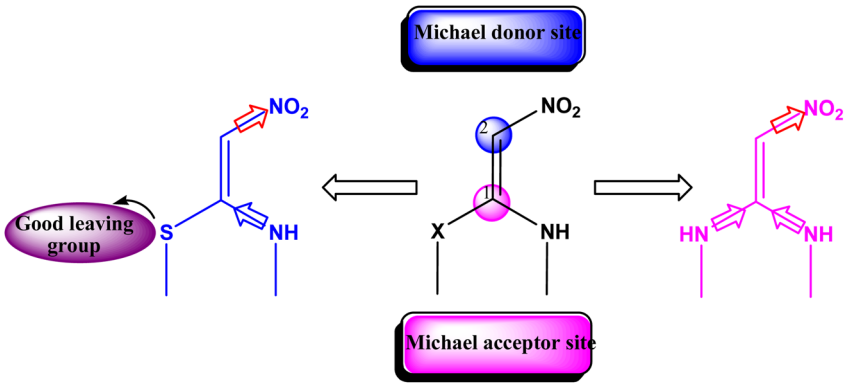
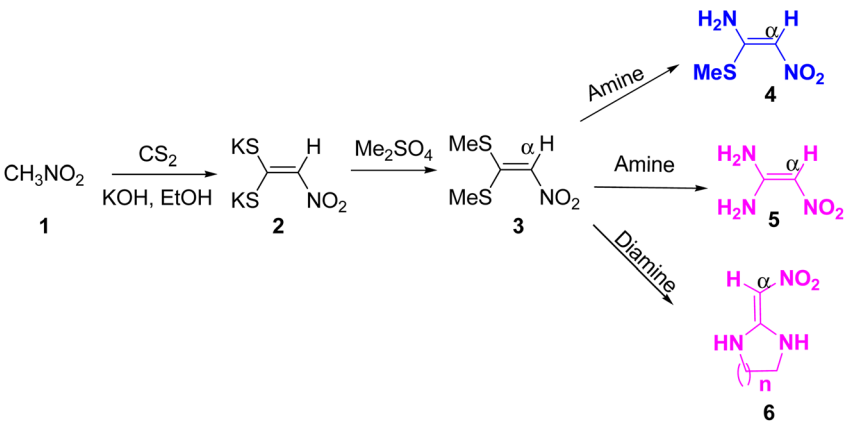


Scheme 1 Structure of nitro-1,1-enediamines and *N*-methyl-1-(methylthio)-2-nitroethenamine.

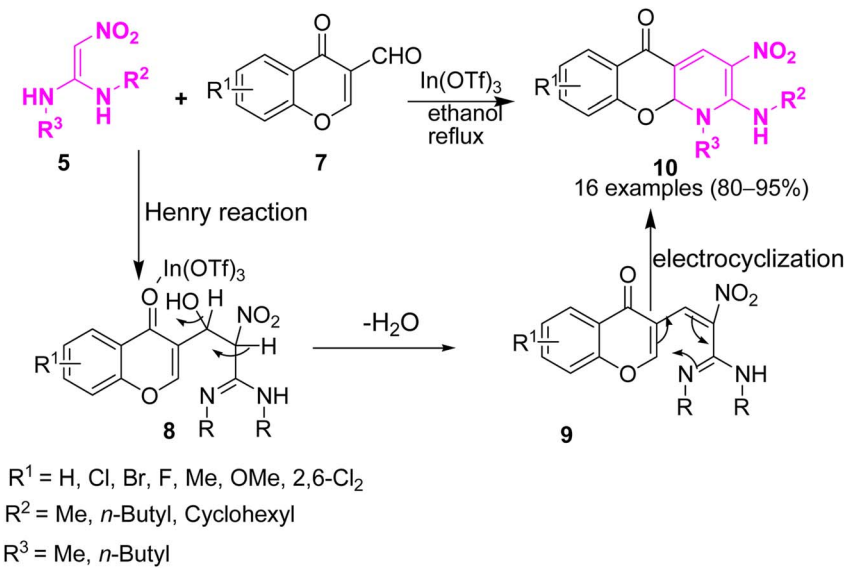
important mechanisms. Since cyclic nitroenediamine is obtained from reactions 1,1-bis(methylthio)-2-nitroethene and diamines, these reactions are also investigated in this section.

2.1. Catalysts-assisted approaches

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



Scheme 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%).[9] 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).

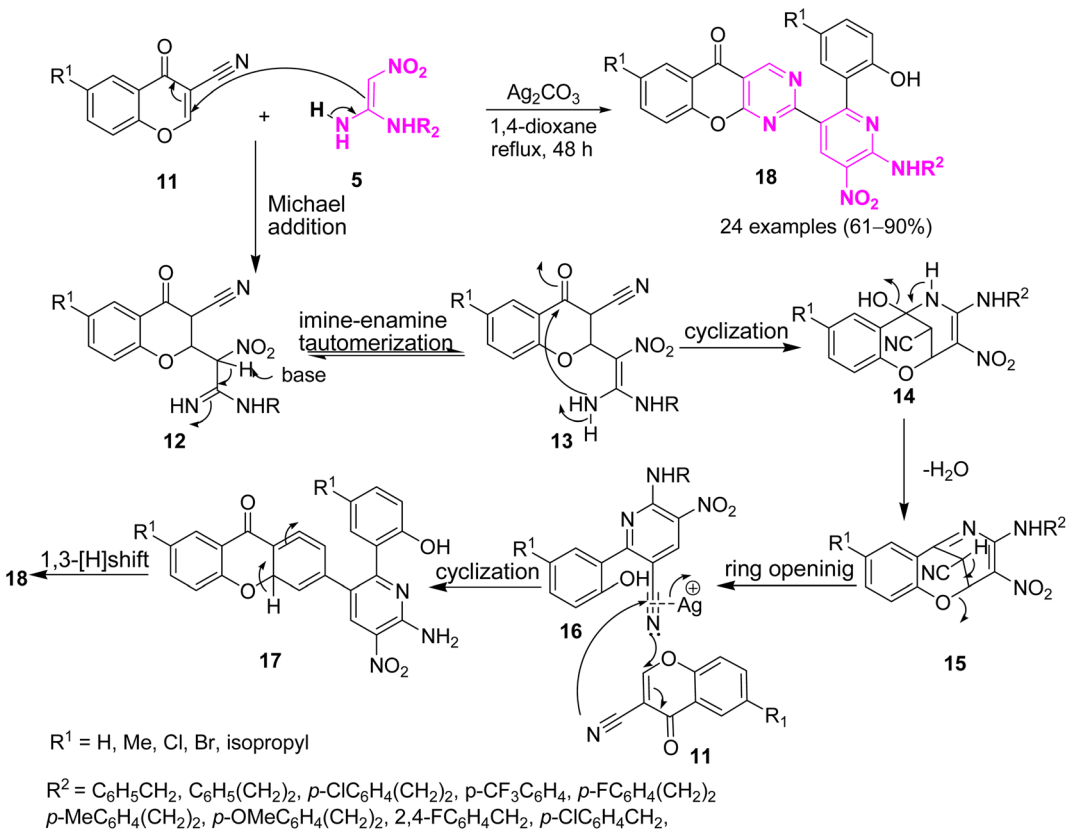
Xiao and coworkers reported the silver-catalyzed synthesis of 2-(pyridin-3-yl)-chromeno[2,3-*d*]pyrimidine derivatives **12** *via* electrocyclization cascade reaction of 3-cyanochromone **11** and 1,1-enediamines **5** under reflux in 1,4-dioxane for 48 hours. Importantly, one C–C bond and three C–N bonds were formed, and one bond was broken in one-pot organic transformation (Scheme 4).[10]

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**.

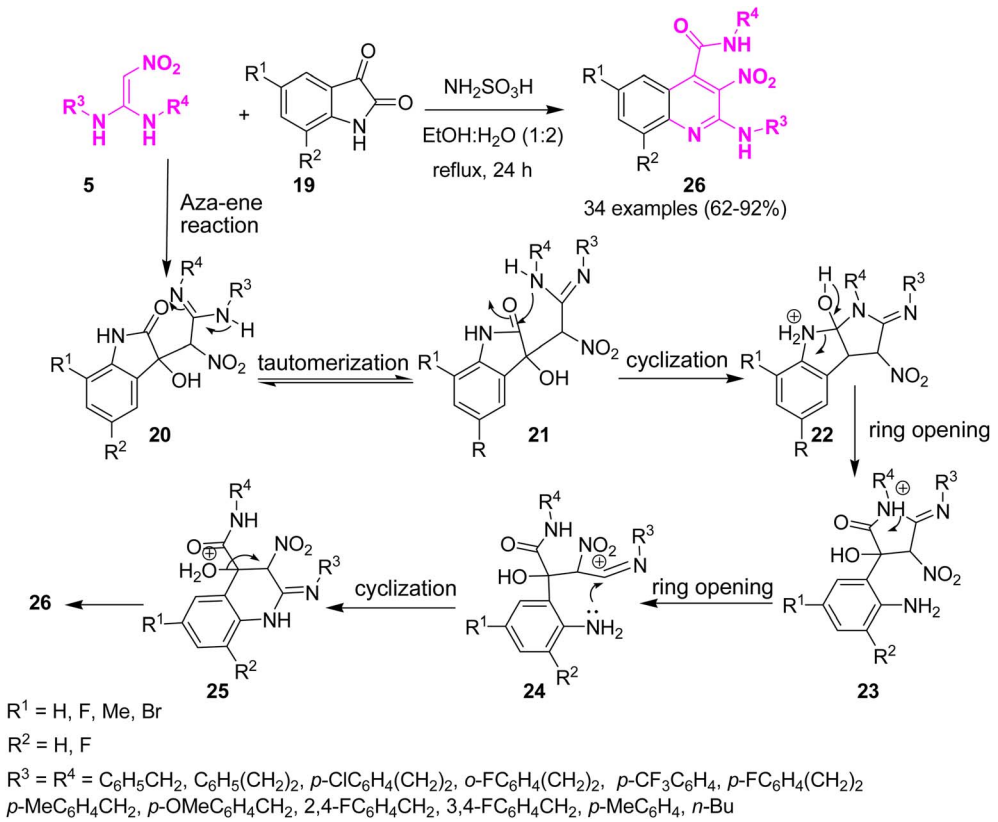
A valuable and efficient reaction of isatins **19** and 1,1-enediamines **5** catalyzed by NH_2SO_3H to synthesize corresponding multisubstituted quinoline-4-carboxamides **26** was reported by Yan and co-workers (Scheme 5).[11] Mechanistically, the aza-ene reaction of EDAMs **5** with isatine **19** 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**.[12] Applying acyclic EDAM substrates **5** in this reaction led to formation of 4-(2-oxoindolin-3-yl)-1*H*-pyrroles **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 (NHCO). 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).

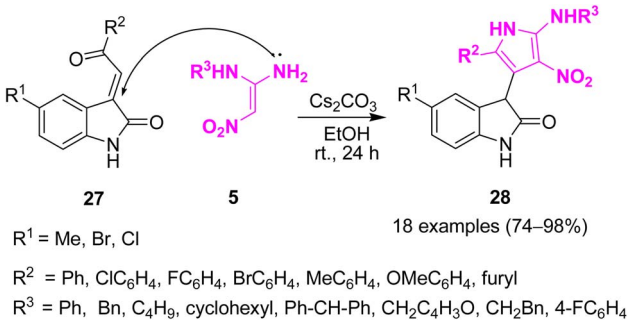
The selective Michael addition of cyclic enediamine **6** to the unsaturated double bond of (*E*)-3-(2-oxo-2-phenylethyl-idene) indolin-2-one derivatives **27** in the presence of Cs_2CO_3 as the base at room temperature after 12 hours makes α-carboline **34** in excellent yields. To the surprise, the 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



Scheme 4 Ag_2CO_3-catalyzed reaction of 3-cyanochromone **11** and 1,1-enediamines **5**.



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



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

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]

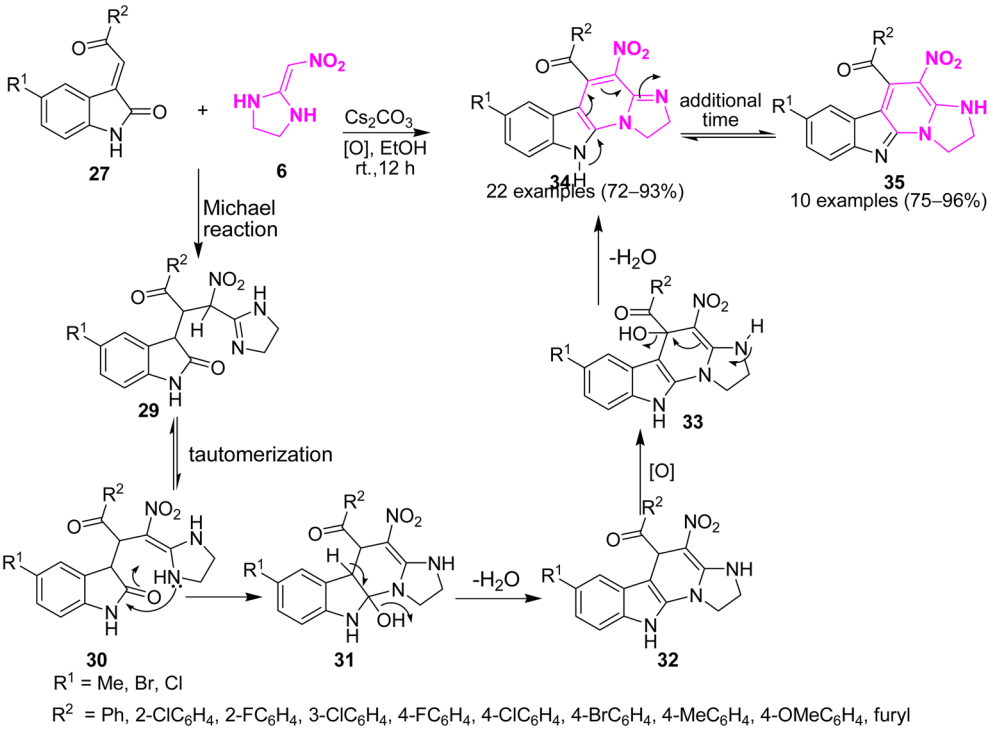
The α-C of EDAMs **5** begins the nucleophilic Michael addition to MBH acetates **36** that is accompanied by the elimination of the acetate group through an S_N2' mechanism to generate intermediate **37**. Imine–enamine tautomerization of intermediate **37** and further intramolecular aza-Michael addition promoted by DBU results in intermediate **38**. Finally, aromatization by elimination of HNO_2 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]

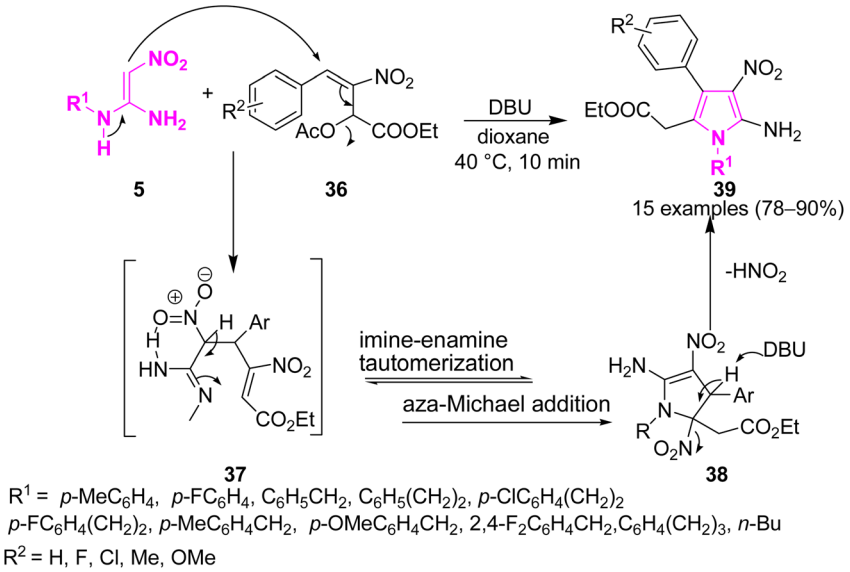
Hasaninejad *et al.* reported the preparation of pyrrolo[1,2-*a*] pyrimidine derivatives **28** *via* the reaction of bromoacetophenone **43** and 2-nitroethene-1,1-diamines **6** in the presence of K_2CO_3 (Scheme 10).[15] The aza-ene reaction between bromoacetophenone **43** and 2-nitroethene-1,1-diamine **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 oxa-aza[3.3.3]propellanes **53**.



Scheme 7 Site-selective synthesis of highly functionalized 2,10-dihydro-1*H*-imidazo[1′,2′:1,6]pyrido[2,3-*b*]indoles **34** and pyrroles **35**.

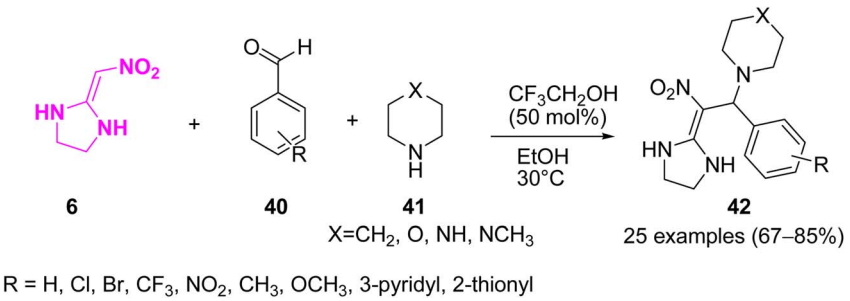


Scheme 8 DBU-promoted tandem reaction of (MBH) acetates **36** with the EDAMs **5**.

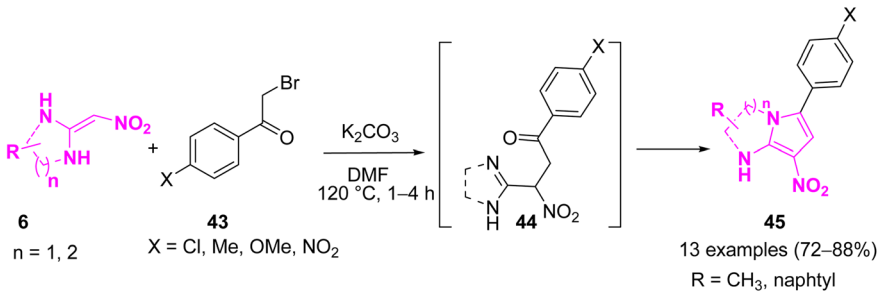
The elimination of two molecules of R^1SH from 1,1-bis(methylthio)-2-nitroethene **3** in presence of diamine **32** affords cyclic nitro ene-1,1-diamine **6**.[8] Alizadeh's group developed an efficient route to synthesis of 1,4-dihydropyridine-fused-1,3-diazaheterocycle derivatives **58** by refluxing a mixture of 1,1-bis(methylthio)-2-nitroethylene **3**, 1,*n*-diamine **32**, arylaldehyde **54**, and malononitrile **47** in ethanol and 10 mol% of piperidine as a basic catalyst (Scheme 12).[17]

Rezvanian reported I_2-promoted reaction of aldehyde **61**, pyruvic acid **60**, aliphatic diamines **59**, and 1,1-bis(methylthio)-2-nitroethylene **3** in synthesis of 1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acids **65** (Scheme 13).[18]

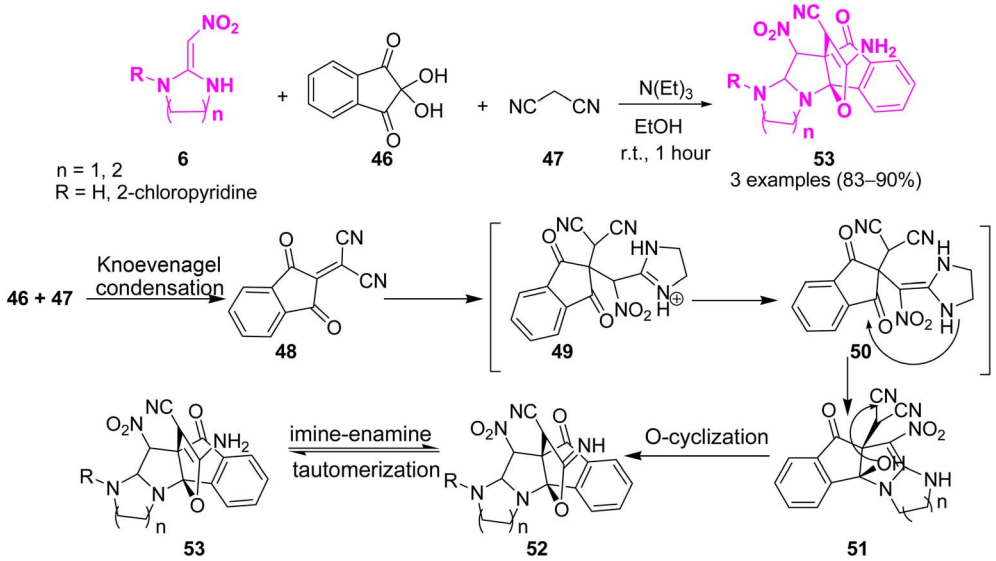
Deep eutectic solvents (DES) consist of halide salt of a quaternary ammonium or phosphonium cation with a hydrogen bond donor (HBD), for example, urea, carboxylic acids, or ethylene glycol. DESs could be used as drug solubilization vehicles for drug delivery research. DES also possess



Scheme 9 TFEA-catalyzed Mannich-like reaction.



Scheme 10 K_2CO_3-promoted synthesis of pyrrolo[1,2-*a*]pyrimidines **28**.



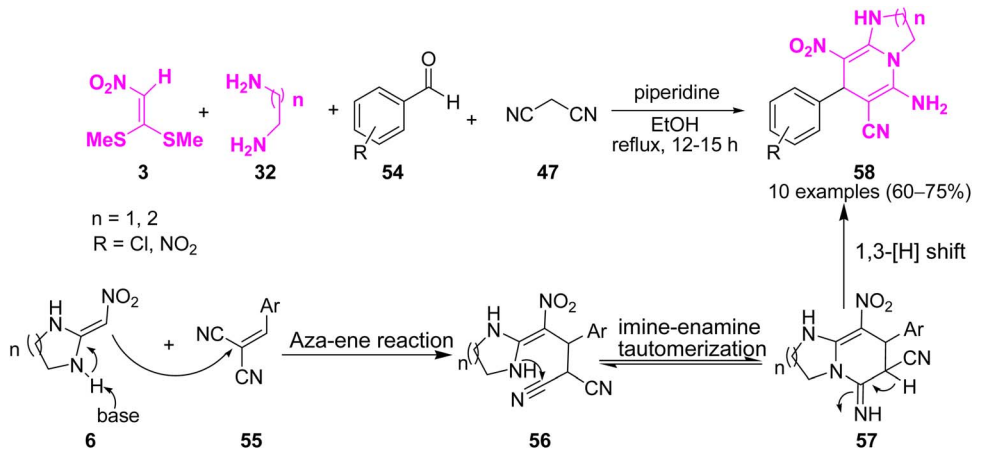
Scheme 11 Bridged-heterocycles synthesis from cyclic nitroenediamines **6**.

several key characteristics as liquids to support a wide variety of substrates and enzymes.[19] 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 **69** (Scheme 14).[20]

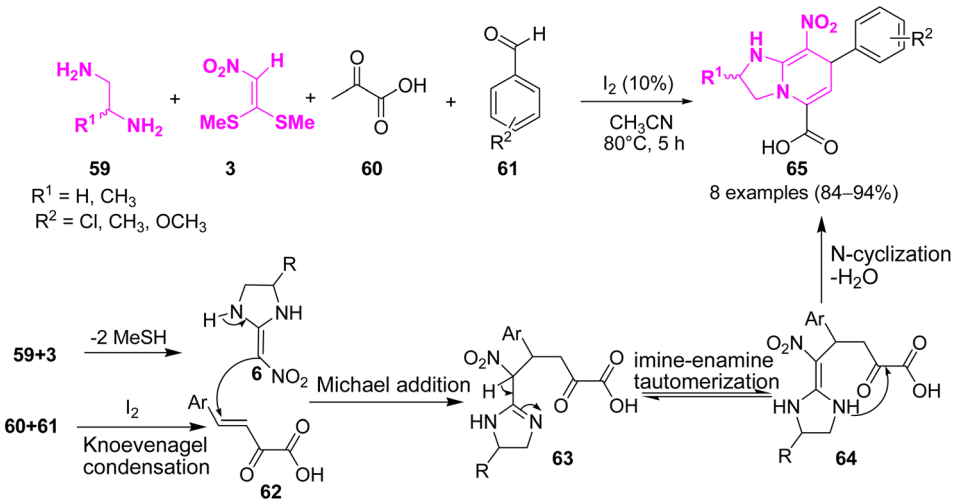
2.2. Catalyst-free approaches

A novel approach was developed for the synthesis of 2-amino-4-coumarinyl-5-arylpyrroles **73** through a metal-free cascade reaction of arylglyoxal monohydrates **71**, 1,1-enediamines (EDAMs) **70** and 4-hydroxy-2*H*-chromen-2-ones **72** (Scheme 15).[21]

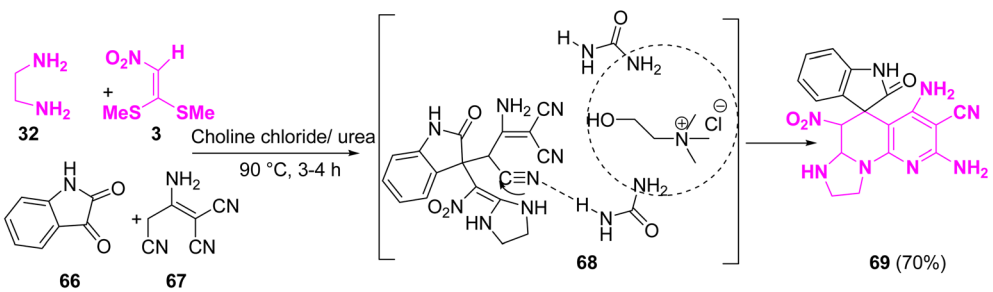
A cascade reaction of 1,1-enediamines **5** with benzylidene-1*H*-indene-1,3(2*H*)-diones **74** in ethanol without any catalysts obtained the products **79**. In this reaction, EDAM **5** attacks the C=C bond of benzylidene to promote the Michael addition reaction. The imine–enamine tautomerization of intermediate **75** makes **76**. Then, the intermediate **77** is obtained through the enol–keto tautomerization of intermediate **76**. The



Scheme 12 Synthesis of 1,4-dihydropyridine-fused-1,3-diazaheterocycle **58** *via* multi-component reaction.



Scheme 13 Iodine-catalyzed MCR reaction.

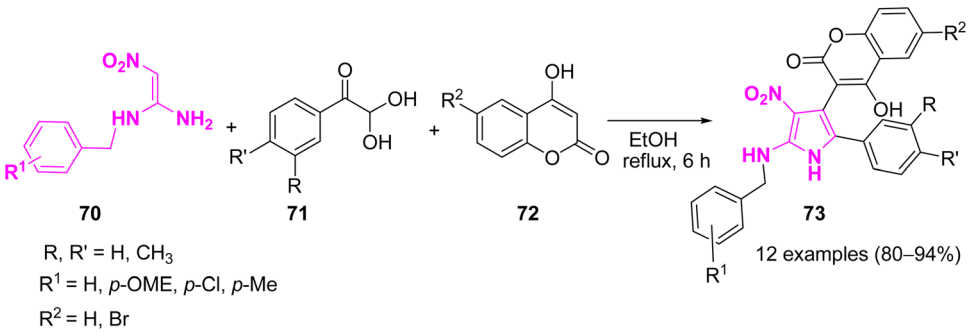


Scheme 14 Synthesis of fully-substituted naphthyridine **69** through domino four-component reaction in deep eutectic solvent.

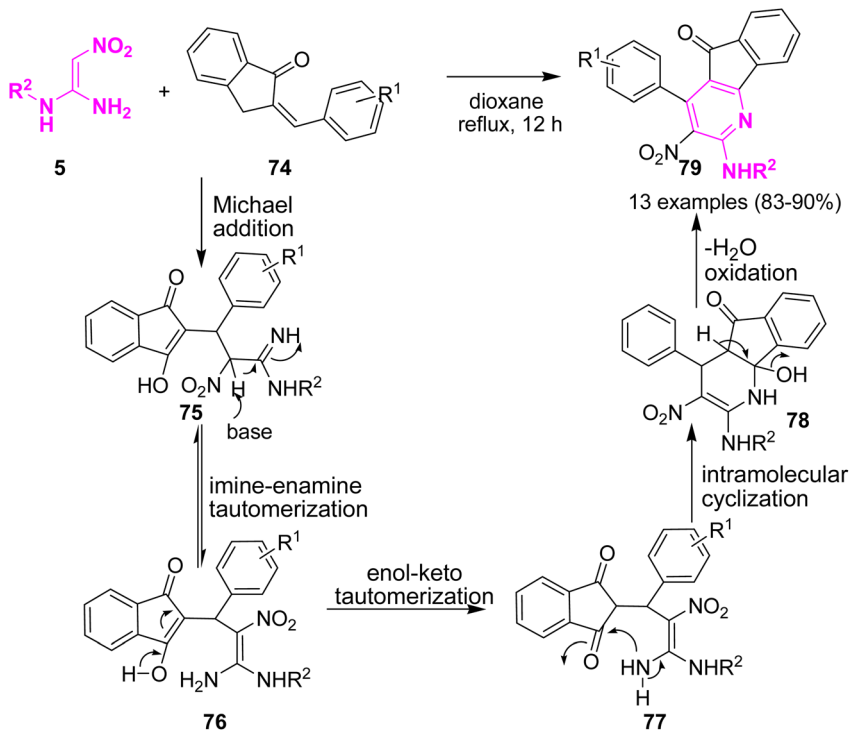
intramolecular cyclization of the intermediates **77** where the amino group attacks the carbonyl provides intermediate **78**. Finally, water removal and oxidation of intermediate **78** affords target **79** (Scheme 16).[22]

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).[23]

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–



Scheme 15 Catalyst-free synthesis of pyrrole derivatives **73** from 1,1-enediamines **70**.



Scheme 16 Synthesis of indenodihydropyridine **79**.

enamine tautomerization followed by cyclization makes desired products **88** (Scheme 18).[24]

Bayat *et al.* synthesized benzo[*g*]imidazo[1,2-*a*]quinoline-dione 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).[25] 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).[26]

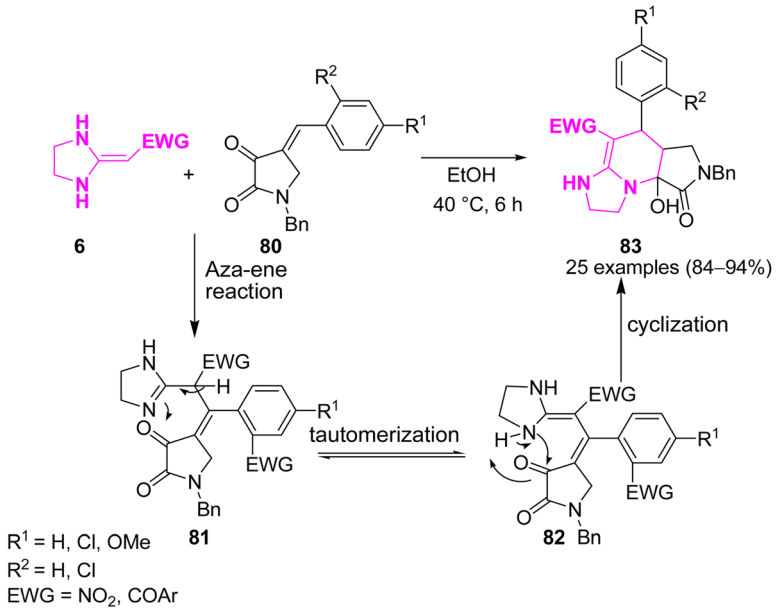
They also used this strategy in stereoselective synthesis of indenone-fused heterocycles **101** (Scheme 21).[27]

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).[28]

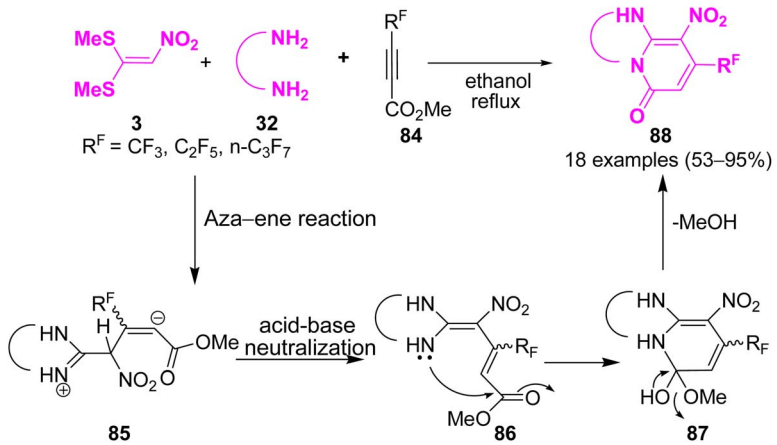
3. (Methylthio)-2-nitroethenamine derivatives (NMSM) in heterocyclization

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



Scheme 17 Catalyst-free synthesis of imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridines **84**.



Scheme 18 Synthesis of perfluoroalkyl-substituted 2-oxopyridine derivatives **88**.

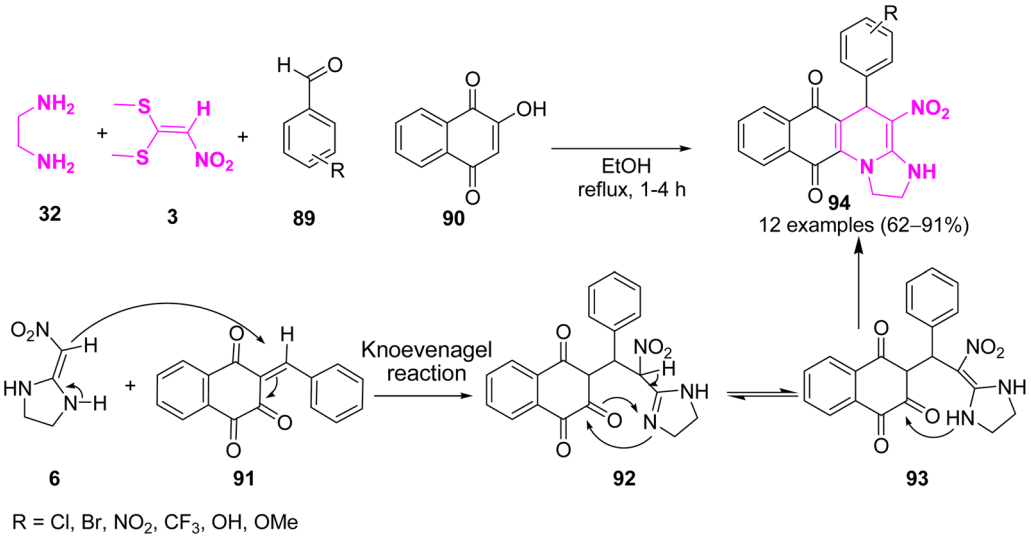
88%). As mentioned earlier, $In(OTf)_3$ promotes the Henry reaction of 3-formylchromone **104** with (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4** (NMSM) to give intermediate **105**. Water removal makes intermediate **106** that undertakes *N*-cyclization, followed by chromone ring opening to provide **108**. At sequence, the elimination of MeSH and $In(OTf)_3$ affords the target **109** (Scheme 23).[9]

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 $InCl_3$ as catalyst (Scheme 24).[29]

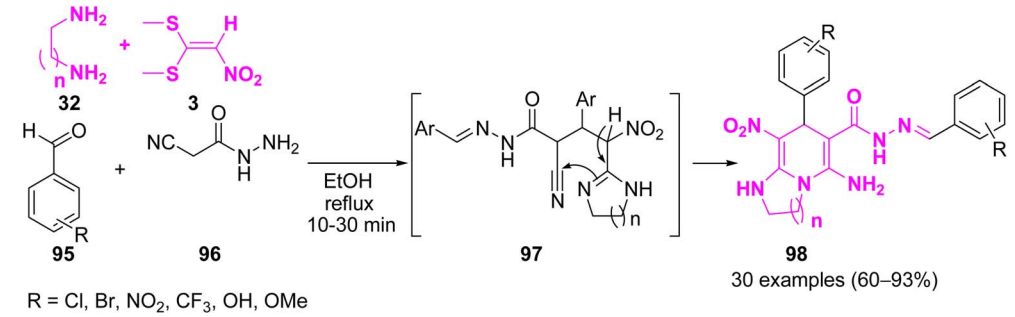
Rong and co-workers established copper-catalyzed construction of various isoxazolines **122** through the 1,3-dipolar cycloaddition reaction of styrene derivatives **116** and 4*H*-1,2-oxazete **118** *in situ* resulting from *N*-alkyl(aryl)-1-(methylthio)-2-nitroethenamine **4**.[30] The tautomerization 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 4*H*-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(1*H*)-one **123** in Knoevenagel condensation domino reaction of aldehydes and *N*,*S*-methylacetal in catalytic amount of $ZnCl_2$ (Scheme 26).[31]

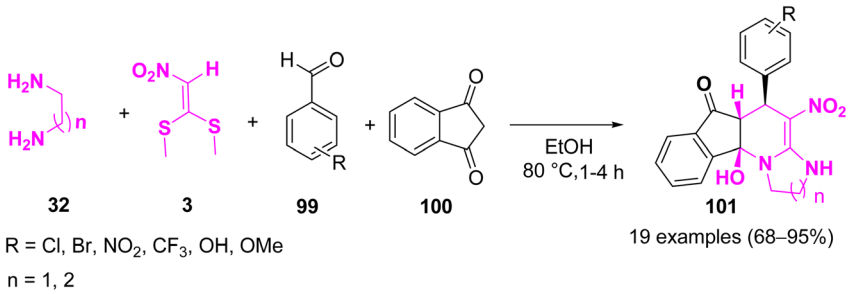
$ZnCl_2$ catalyst was also used in the synthesis of novel 2-methyl-6-(methylamino)-5-nitro-4-(4-aryl)-4*H*-pyran-3-carboxylate derivatives **132**. This domino, one-pot reaction was performed for β-ketoesters **131**, aromatic aldehydes **130**, and



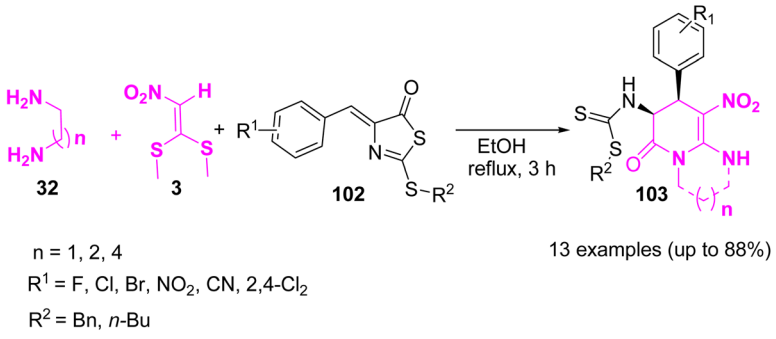
Scheme 19 One-pot synthesis of benzo[*g*]imidazo[1,2-*a*]quinolinedione derivatives **94**.



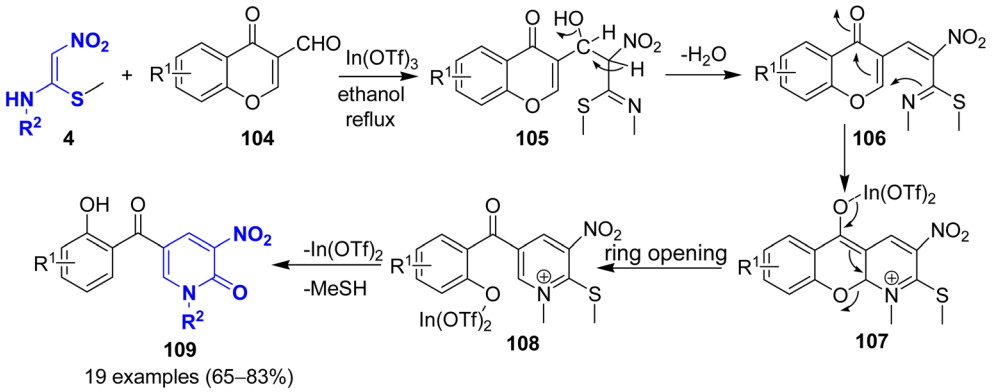
Scheme 20 Synthesis of pyridine-fused *N*-heterocycles **98** *via* multi-component reaction.



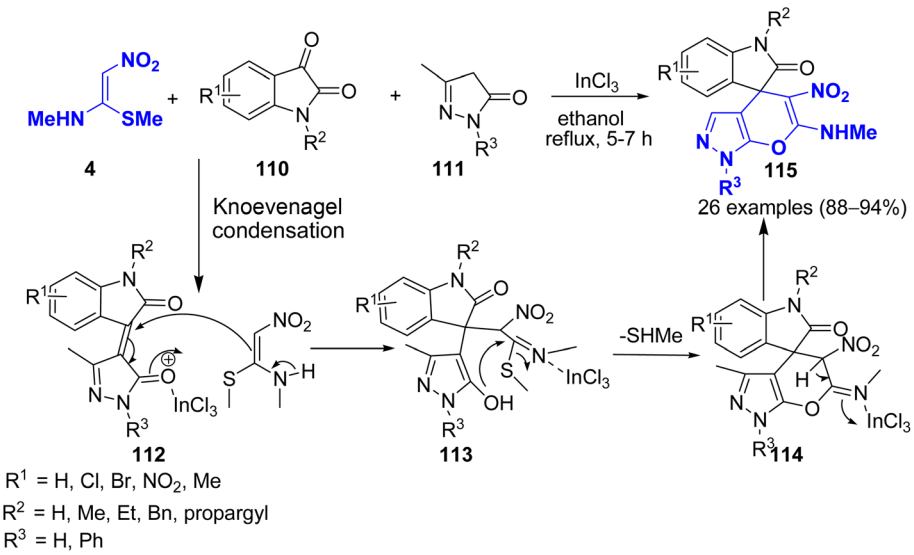
Scheme 21 Synthetic route to indenone-fused heterocycle **101**.



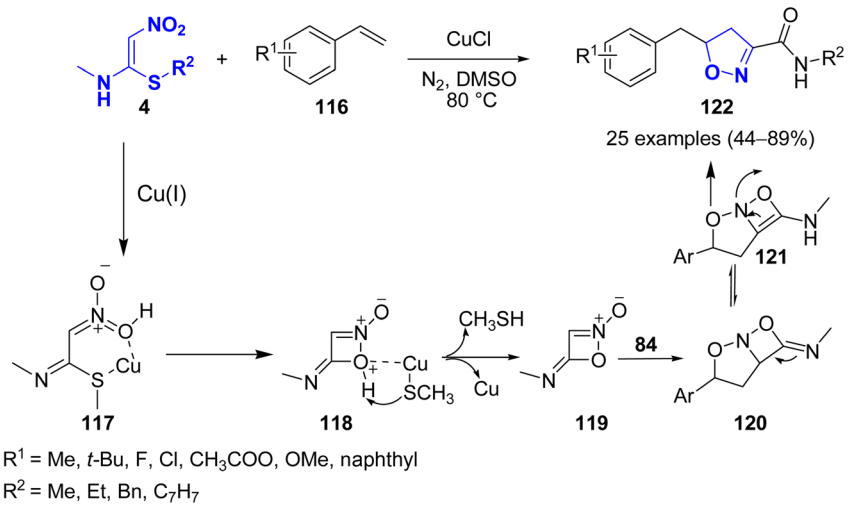
Scheme 22 Synthesis of bicyclic pyridones **103**.



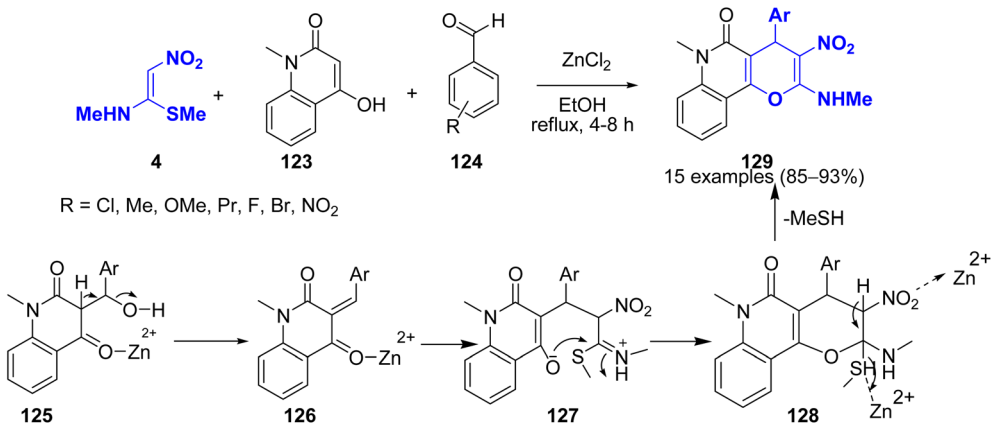
Scheme 23 $In(OTf)_2$-catalyzed Henry reaction of **4** and 3-formylchromone **104**.



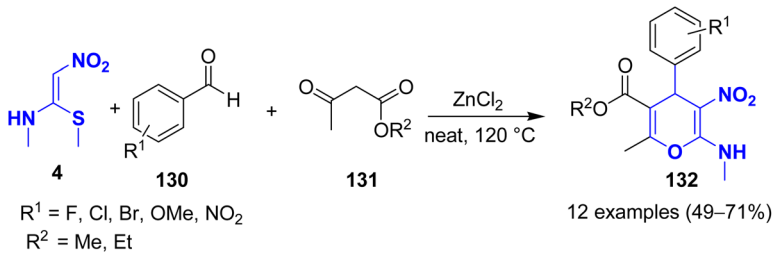
Scheme 24 Synthesis of spiroxindoles **115** through $InCl_3$-catalyzed reaction of *N*-methyl-1-(methylthio)-2-nitroethenamine.



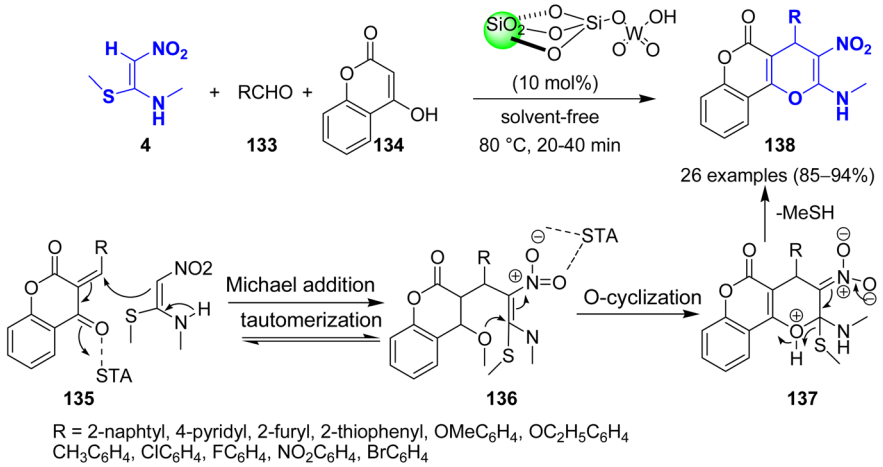
Scheme 25 CuCl-catalyzed reaction of styrene **116** and *N*-methyl-1-(methylthio)-2-nitroethenamine **4**.



Scheme 26 $ZnCl_2$-catalyzed reaction of *N,S*-methylacetal **4**.



Scheme 27 Synthesis of 4*H*-pyran-3-carboxylate derivatives **132** under $ZnCl_2$.



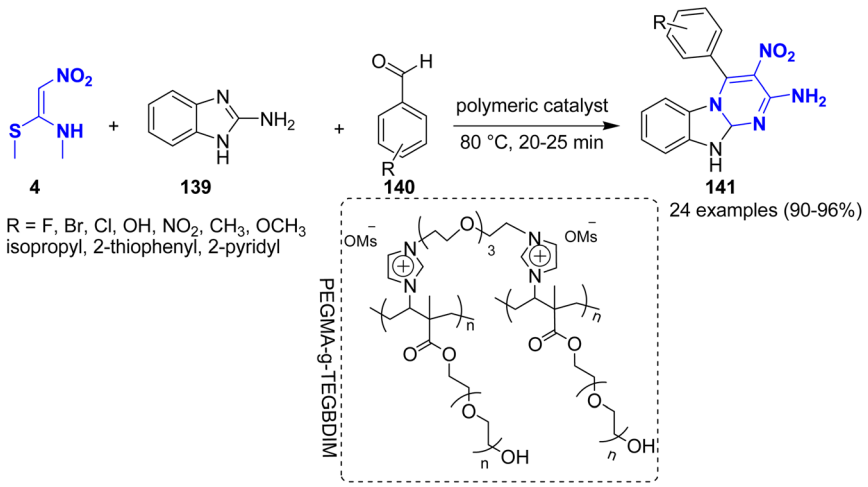
Scheme 28 Solvent-free synthesis of pyrano[3,2-*c*]chromen-5-ones **138**.

(*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) **4** under the neat condition (Scheme 27).[32]

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 tautomerism, intramolecular *O*-cyclization, and elimination of MeSH (Scheme 28).[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 1*H*-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).[34]

The Pot, Atom, and Step Economy (PASE) approach leads to simplicity, high yields and low waste formation in MCR



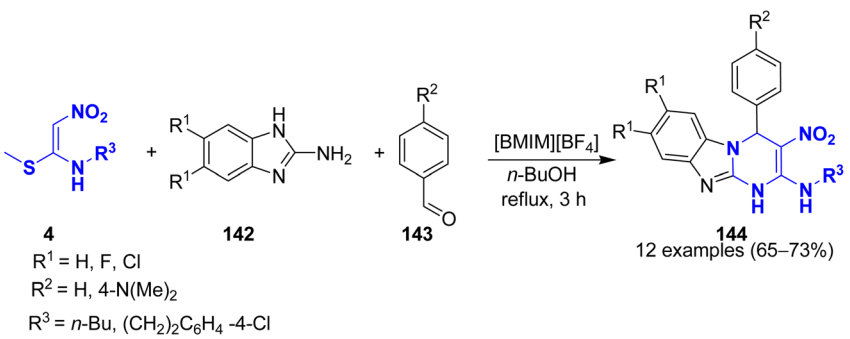
Scheme 29 Synthesis of *N*-methyl-2-nitro-aryl-benzo[4,5]imidazo[1,2-*a*]pyrimidine amines **141**.

chemistry and in the synthesis of heterocycles.[35] This approach was adopted for the synthesis of benz[4,5]imidazo[1,2-*a*]purine derivatives **144** *via* consecutive reduction/auto-aromatization/heterocyclization of 2-aminobenzimidazoles **142**, aromatic aldehydes **143**, and *N*-alkyl-1-(methylthio)-2-nitroethylene-1-amines **4** refluxing in *n*-BuOH for three hours in the presence of 10 mol% [BMIM][BF_4] (Scheme 30).[36]

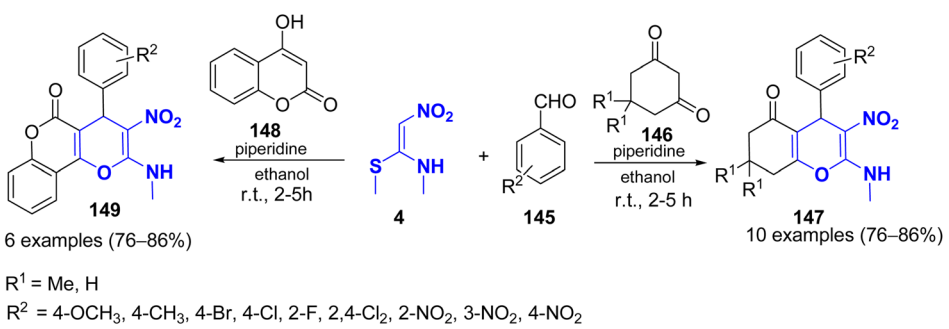
In 2012, chromen-5-ones **149** and pyrano[3,2-*c*]chromen-5-ones **147** were synthesized through tandem reaction of NMSM **4**, aromatic aldehydes **145**, and 4-hydroxycoumarin **148** or dimedone **146** in the presence of catalytic amount of piperidine in ethanol (Scheme 31).[37]

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 4*H*-chromen-5-one derivatives.[38]

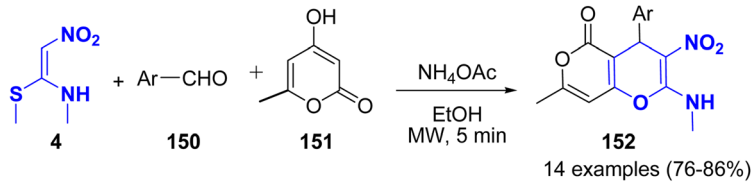
Microwave irradiation facilitated the reaction of aromatic aldehyde **150**, 4-hydroxy-6-methyl-2-pyrone **151** and *N*-methyl-1-(methylthio)-2-nitroethenamine **4** to produce pyrano[4,3-*b*]pyran-5-one derivatives **152**. Ammonium acetate catalyzed the



Scheme 30 [BMIM][BF_4]-assisted synthesis of 3-nitro-imidazo[1,2-*a*]pyrimidin-2-amine derivatives **144**.

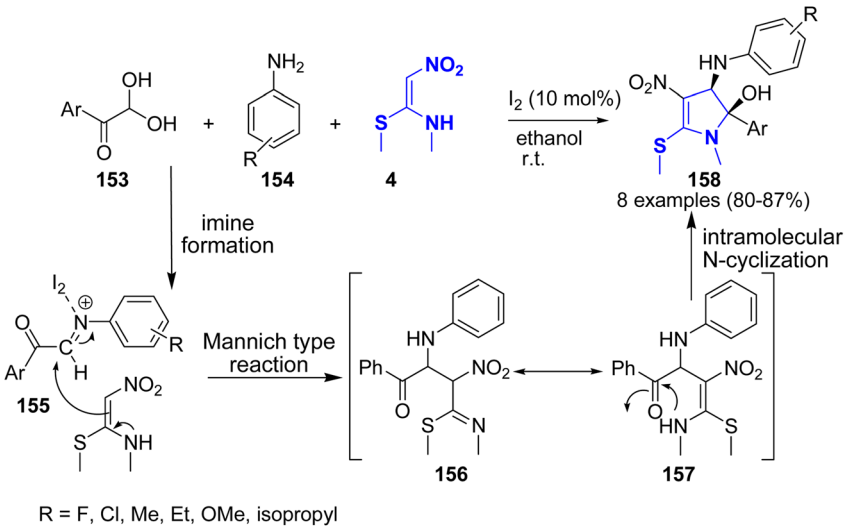


Scheme 31 Synthesis of chromen-5-ones **149** and pyrano[3,2-*c*]chromen-5-ones **147** in presence of piperidine catalyst.



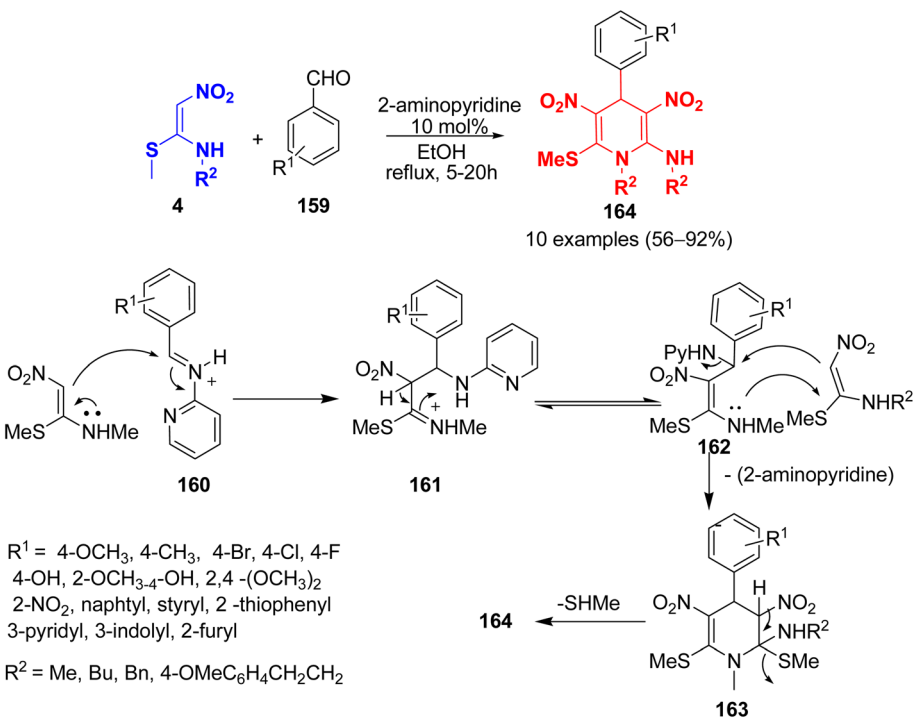
Ar = 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-Br, 4-ClC_6H_4, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2,4-$Cl_2C_6H_3$,2,4-$F_2C_6H_3$, 1-$C_{10}H_7$, 4 -$(CH_3)_2NC_6H_4$, 2-thiophenyl, 2-furyl

Scheme 32 Preparation of pyranopyran derivatives **117** under MW irradiation.



R = F, Cl, Me, Et, OMe, isopropyl

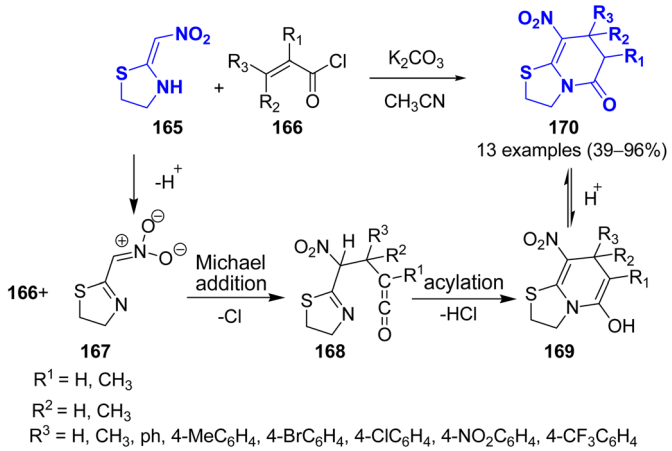
Scheme 33 Iodine-catalyzed reaction of *N*-methyl-1-(methylthio)-2-nitroethenamine, aromatic amines, and phenylglyoxal.



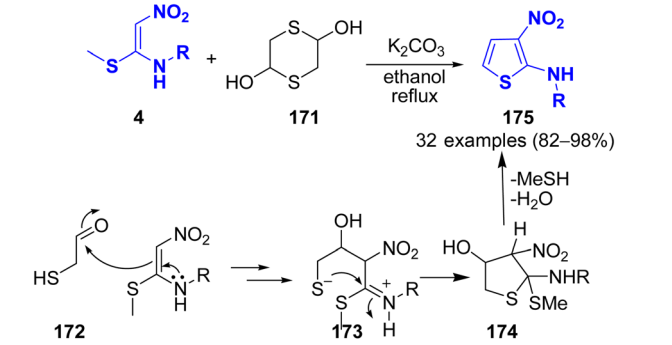
R^1 = 4-OCH_3, 4-CH_3, 4-Br, 4-Cl, 4-F
4-OH, 2-$OCH_{3\text{-}4}$-OH, 2,4 -$(OCH_3)_2$
2-NO_2, naphtyl, styryl, 2 -thiophenyl
3-pyridyl, 3-indolyl, 2-furyl

R^2 = Me, Bu, Bn, 4-$OMeC_6H_4CH_2CH_2$

Scheme 34 Aminopyridine-catalyzed synthesis of highly functionalized dihydropyridines **164**.



Scheme 35 Synthesis of tetrahydrothiazolo[3,2-*a*]pyridinones **170**.



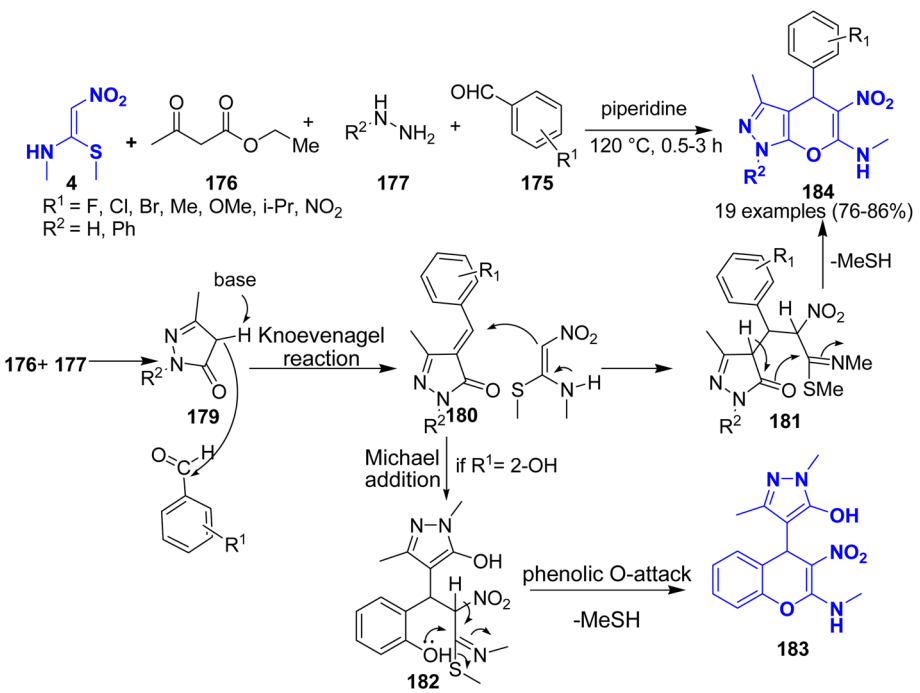
Scheme 36 Synthesis of thiophen derivatives **175** from *N,S*-alkyl amino acetals **4** and 1,4-dithiane-2,5-diol **171**.

reaction in ethanol and the microwave power higher than 200 watts decomposed the substrates (Scheme 32).[39]

N-Methyl-1-(methylthio)-2-nitroethenamine **4**, aromatic amines **154**, and phenylglyoxal monohydrate **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 **120** in excellent yields (Scheme 33).[40] At first, the reaction between aromatic amines **154** and phenylglyoxal monohydrate **153** leads to the imine **155** that is activated in presence of molecular iodine. Mannich type reaction between iodine activated imine **155** and NMSM **4** generates intermediate **156** which undergoes intramolecular cyclization to afford **158**.

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

Aza-Michael annulation of 2-nitromethylene thiazolidine **165** with suitable Michael acceptors **166** using K_2CO_3 as the base afforded tetrahydrothiazolo[3,2-*a*]pyridinones **170** in good



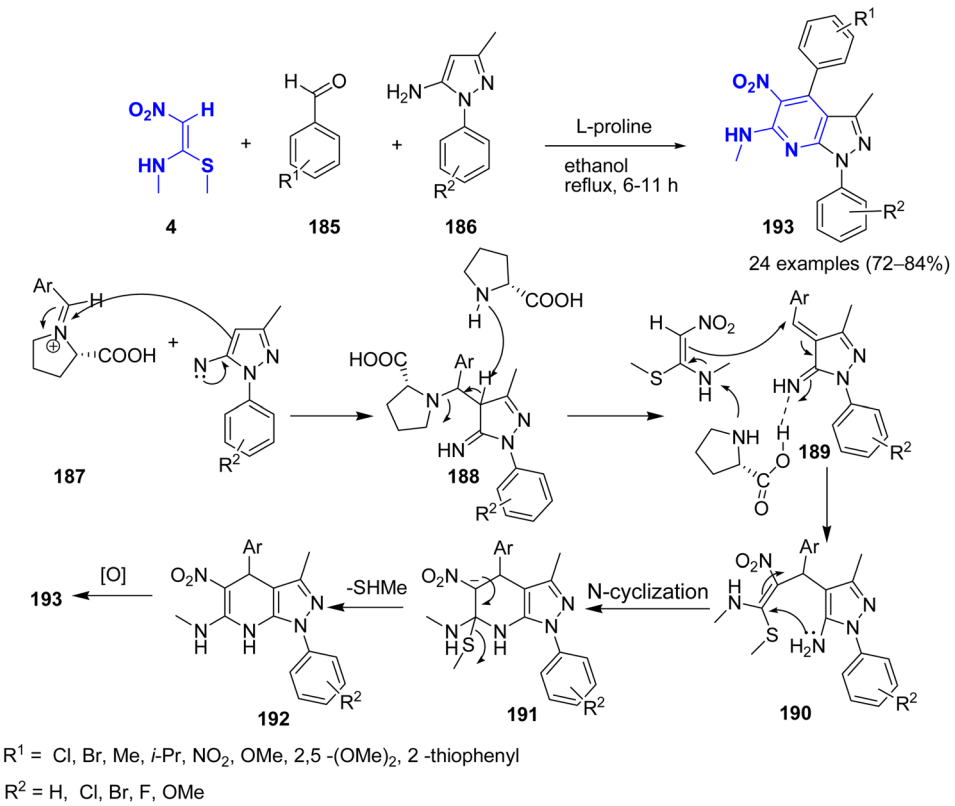
Scheme 37 Synthesis of pyranopyrazoles *via* multi-component reaction.

yields (Scheme 35).[43] Based on proposed mechanism, in the presence of K_2CO_3, 2-nitromethylene thiazolidine **165** forms nitronic acid salt intermediate **167** by tautomerization. Next, Michael addition of **166** with the nitronic acid **167** gives iminoketene intermediate **168**. Then an acylation of imine nitrogen followed by HCl removal results in ring closure and affords thiazolopyridinones **170**.

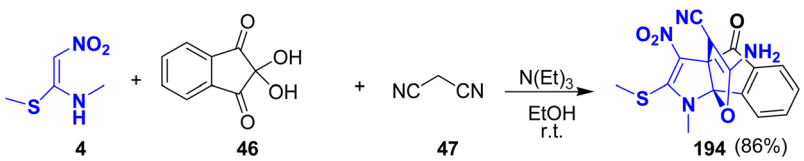
In 2015, Perumal *et al.* recorded the synthesis of 3-nitro-*N*-aryl/alkylthiophen-2-amines through the reactions of α-nitroketene *N*,*S*-alkyl amino acetals **4** and 1,4-dithiane-2,5-diol **171**. Mechanistically, 1,4-dithiane-2,5-diol **171** is decomposed in the presence of K_2CO_3 to generate 2-mercaptoacetaldehyde **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).[44]

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**.[45] 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 chromenopyrazoles **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*-



Scheme 38 Synthesis of *N*,3-dimethyl-5-nitro-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridin-6-amines **193**.

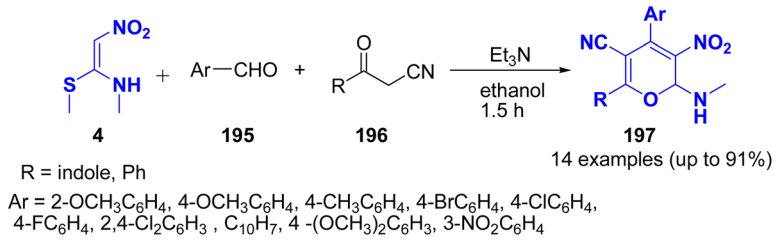


Scheme 39 Synthetic route to bridged-heterocycle-containing neonicotinoids **194**.

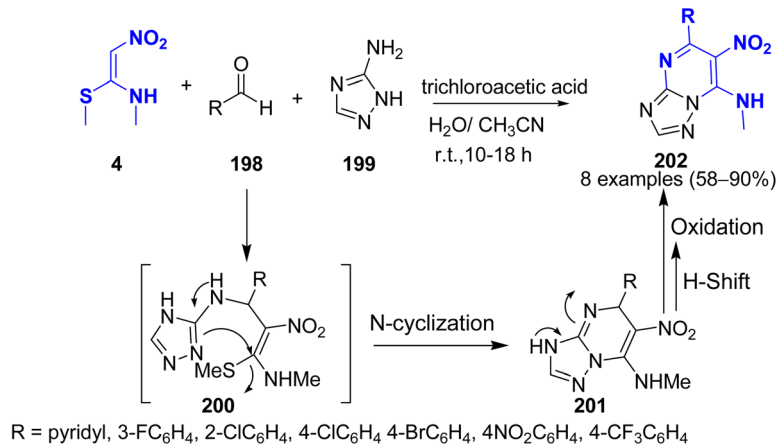
diisopropylethylamine(DIPEA) refluxing in ethanol generated the 1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines *via* domino cyclization Knoevenagel condensation/Michael addition/tautomerism/intramolecular *O*-cyclization/elimination sequences.[46]

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

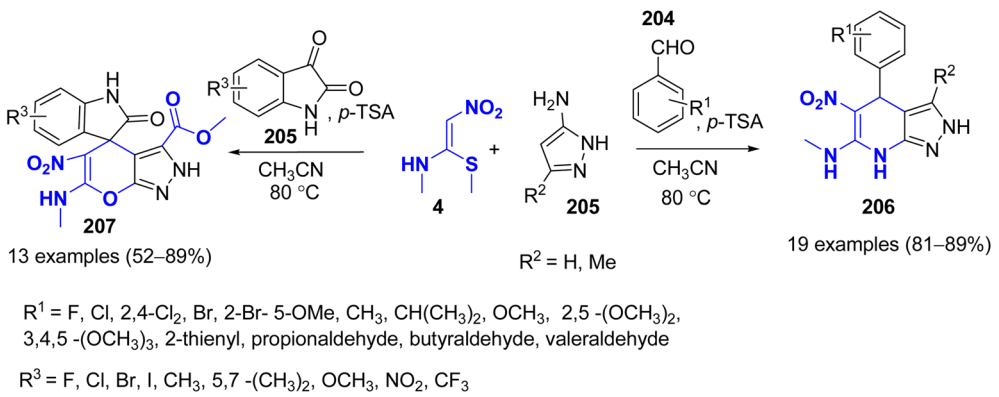
Shao and coworkers prepared bridged heterocycle **195** from one-pot reaction of ninhydrin **46**, malononitrile **47**, and 1-(methylthio)nitroenamine **4** under mild condition (Scheme 39).[16] The mechanism reaction has been mentioned earlier in Scheme 11.



Scheme 40 Synthesis of penta-substituted 4*H*-pyrans **197**.



Scheme 41 Brønsted–Lowry acid-promoted reaction of NMSN 4, aldehydes **198**, and 3-amino-1,2,4-triazole **199**.



Scheme 42 Synthesis of pyrazolo[3,4-*b*]pyridine **206** and pyrano[2,3-*c*]pyrazole **207** from *N*-methyl-1-(methylthio)-2-nitroethen-1-amine **4**.

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 4*H*-pyrans **197** in excellent yield (Scheme 40).[48]

The reaction of *N*-methyl-1-(methylthio)-2-nitroetheneamine **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*-toluenesulfonic acid as the catalyst (Scheme 42).[50]

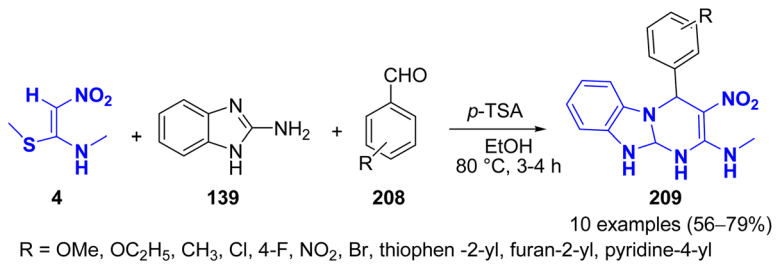
Jeong *et al.* designed three-component reaction of 2-aminobenzimidazole **139**, aldehydes **208**, and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4**, in the presence of catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) for the synthesis of *N*-methyl-3-nitro-aryl-benzo[4,5]imidazo[1,2-*a*]pyrimidin-2-amine 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 CF_3SO_3H an acidic catalyst (Scheme 44).[52]

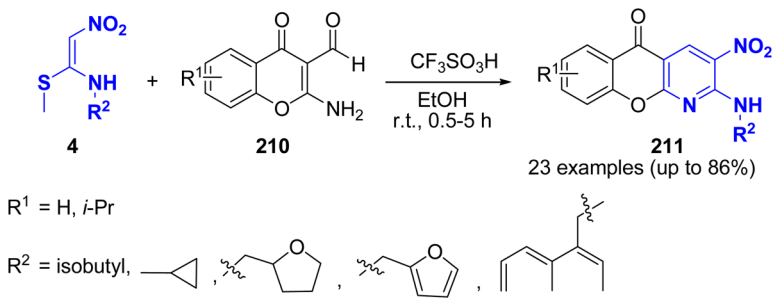
3.2. Catalyst-free approaches

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-(methylamino)-3-nitro-4-aryl-4*H*-benzo[*g*]chromene-5,10-diones **214** in excellent yields (Scheme 45).[46]

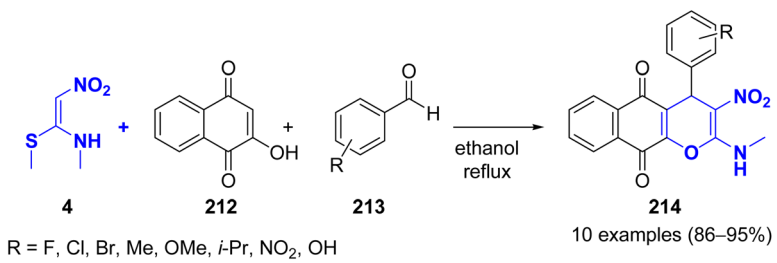
The synthesis of dihydroxyoxoindeno[1,2-*b*]pyrrole derivatives **217** carried out by the simple reaction of ninhydrin **215**, *N*-



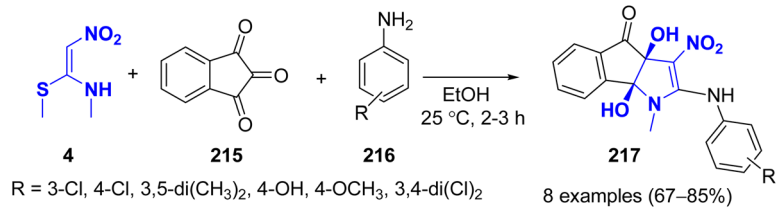
Scheme 43 Synthesis of *N*-methyl-3-nitro-aryl-benzo[4,5]imidazo[1,2-*a*]pyrimidin-2-amine derivatives **209**.



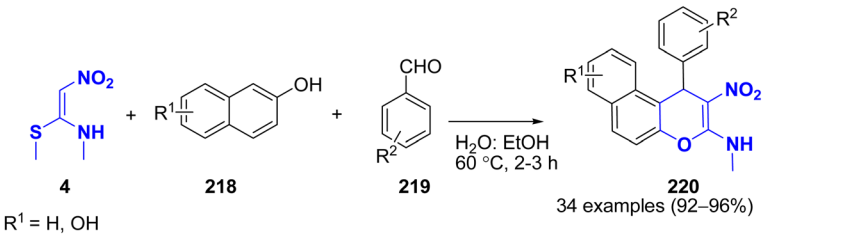
Scheme 44 CF_3SO_3H-catalyzed reaction of 2-amino-3-formylchromones **210** and 1-(methylthio)-2-nitroenamine **4**.



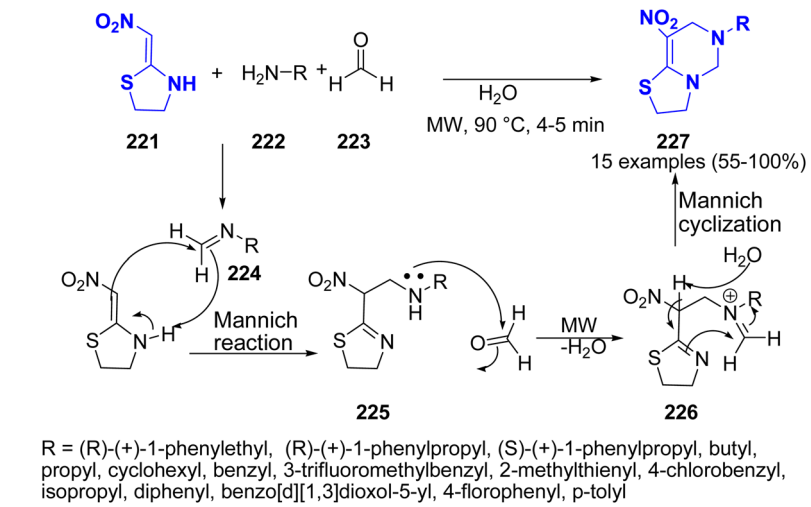
Scheme 45 Catalyst-free synthesis of 3-nitro-benzo[g]chromene-5,10-diones **214**.



Scheme 46 Catalyst-free synthesis of dihydroxyoxoindeno[1,2-*b*]pyrrole **217**.



Scheme 47 Catalyst-free synthesis of *N*-methyl-2-nitro-aryl-1*H*-benzo[*f*]chromen-3-amine **220**.



Scheme 48 MW irradiation-assisted synthesis of tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidines **227**.

methyl-1-(methylthio)-2-nitroethenamine **4**, and various aromatic amines **216** in ethanol without any catalyst at room temperature (Scheme 46).[53] 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).[54]

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).[55]

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

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*-Toluenesulfonic acid
POEGMA-*g*-TEGBDIM	Polyethylene glycol methacrylate-grafted dicationic imidazolium
STA	Silica-supported tungstic acid
TCAA	Trichloroacetic acid
TFEA	2,2,2-Trifluoroethanol

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