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Recent advances in metal-free catalysts for the synthesis of N-heterocyclic frameworks focusing on 5- and 6-membered rings: a review

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The tremendous potential of transition metal-free multi-component reactions (MCR) in the synthesis of N-heterocyclic frameworks is examined in this review, offering a complete overview of this subject matter. The discussion on the mechanistic rationale of the reaction routes and intermediates provides profound insights into the underlying changes, encouraging deeper investigation into various molecular frameworks. This review serves as a doorway to study the practicality of exploiting these reactions for the efficient and uncomplicated synthesis of specific nitrogen heterocycles. Specifically, we reveal the potential of transition metal-free catalysts in this field. Because of their extensive scope and diversity, these reactions enable the synthesis of various heterocycles that contain nitrogen, which include 5-membered (carbazole, pyrimidines, and pyrroles) and 6-membered rings (piperidine, pyridine, quinoline, diazine, pyrazine, quinoxaline, and 1,2,3-triazine). In addition, the compatibility of transition metal-free catalysts with various functional groups and substrates not only increases the synthetic value of these compounds but also broadens their relevance in the domains of medical chemistry, materials science, and other relevant areas of study. To motivate future study and development in this field, the successful examples described in this review highlight the potential of transition metal-free catalysts as powerful instruments for the quick and efficient synthesis of nitrogen heterocycles. In general, this review provides a thorough and insightful examination of transition metal-free catalysts, highlighting the relevance of these compounds in contemporary organic synthesis and their potential to revolutionize the field of nitrogen heterocycle synthesis.

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1 Introduction

The study of heterocyclic compounds holds great significance within the realm of organic chemistry, and it has garnered considerable interest from the scientific community. The appeal of heterocyclic compounds stems from their pronounced electron-donating properties and robust coordination capabilities, making them highly bioactive.

Recent advancements in synthetic methodologies have provided rapid access to a variety of functionalized heterocyclic compounds, which are essential for medicinal chemists.^{1–3} This is due to the capacity to broaden the accessible drug-like chemical space and promote more effective drug development programs.⁴ As a result, medicinal chemists are now able to discover new drugs more quickly. Additionally, the discovery of dependable synthetic pathways capable of producing large amounts of the required molecule contributes to speeding up the drug development processes.⁵ During a drug discovery

program, it is a common practice to utilize established synthetic methodologies. Nevertheless, the pharmaceutical industry has witnessed significant advantages as a result of the development of novel heterocyclic syntheses that enable alternative methods of bond formation. This review examines the application of recent advancements in C–H activation, photoredox chemistry, hydrogen-borrowing catalysis, MCR, regioselective and stereoselective synthesis, and other innovative methodologies for the generation of ring structures in actual project delivery.⁶ In addition, emphasis is placed on the significance and the value of collaborative efforts between the pharmaceutical industry and academic institutions in helping to shape the advancement of novel synthetic methodologies for the functionalization of heterocycles, garnering significant attention from the pharmaceutical sector.⁷

The creation of novel compounds and composites has received much research attention in heterocyclic chemistry, which is a significant and distinctive class among the applied areas of organic chemistry.^{8–10} Over the past two decades, these compounds have attracted increasing interest. They have helped in the creation of many different organic synthesis procedures and widely used in chemical sciences.

One of the most basic classes of organic compounds is known as N-heterocycles. These molecules contain nitrogen atoms in their ring structures. Their relevance stems from the fact that they are found in a broad variety of physiologically active compounds, medicines, agrochemicals, and functional materials.¹¹ As a result of the wide range of chemical characteristics that N-heterocycles possess, they have been used as essential building blocks in organic synthesis processes. This makes it possible to create novel pharmaceuticals, catalysts, and electronic materials.^{12,13} Consequently, researchers have extensively investigated a wide range of synthetic techniques for the purpose of effectively constructing N-heterocycles, with particular emphasis on enhancing the reaction efficiency, selectivity, and preservation of the environment. Herein, we



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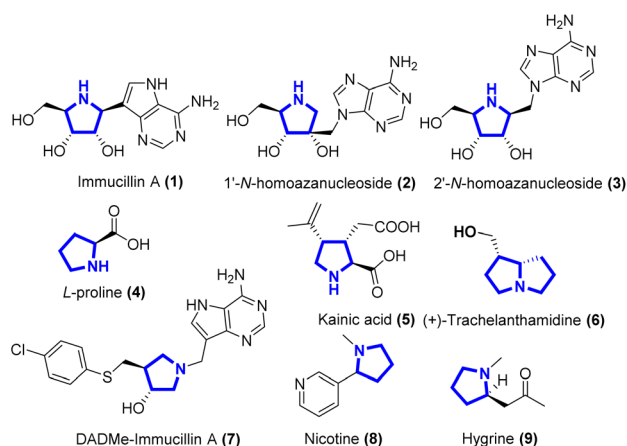
provide an overview of various compounds belonging to the N-heterocyclic class, encompassing both 5- and 6-ring systems synthesized using metal-free catalysts under green reaction conditions.

2. 5-Membered rings

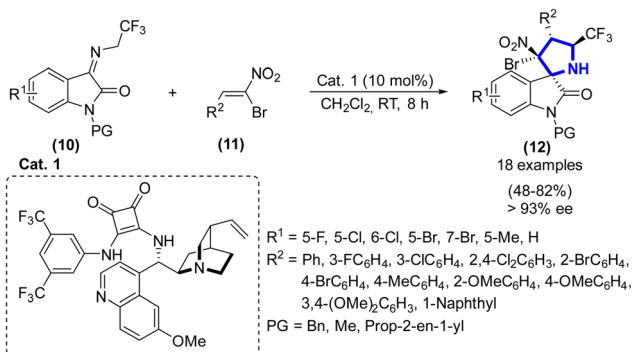
2.1. Five-membered heterocycle containing one nitrogen atom

2.1.1. Pyrrolidine. Pyrrolidine is a saturated, five-membered heterocycle containing nitrogen, which plays an essential role in several biological and pharmacological applications.¹⁴ It functions as a structural core in several natural alkaloids, including nicotine, hygrine, and kakuol, which demonstrate a variety of biological actions. Pyrrolidine derivatives have been extensively used in medicinal chemistry owing their capacity to improve pharmacokinetic parameters and influence biological targets (such as nicotine, L-proline, and hygrine) (Scheme 1).^{15–18}

F.-Y. Chen *et al.* (2020) synthesized pyrrolidinyl spirooxindoles (**3**) using cinchonidine-derived squaramide (10 mol%) as the catalyst from isatin-derived ketamine and (*Z*)- α -bromo-nitroalkene in the presence of CH₂Cl₂ (2 mL) at r.t. in 8 h (Scheme 2).¹⁹ The researchers analyzed the unrefined reaction



Scheme 1 Chemical structures of bioactive compounds containing a pyrrolidine framework.



Scheme 2 Synthesis of pyrrolidinyl spirooxindoles catalyzed by Cat. 1.

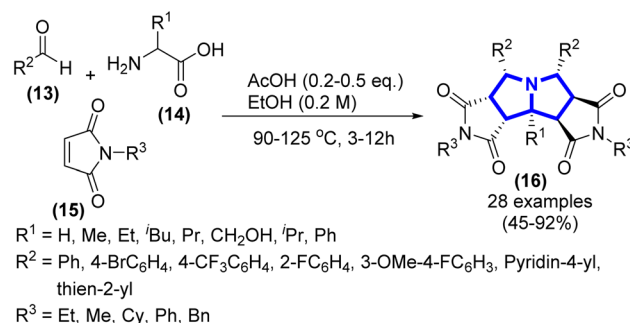
mixture using ¹H NMR spectroscopy, resulting in the determination of the *dr* value, which exceeded 20 : 1. The determination of the *ee* value was conducted using chiral HPLC analysis, specifically using a Chiralpak AD-H column with a mobile phase consisting of 20% 2-propanol and *n*-hexane at a flow rate of 1 mL min^{−1}. A wavelength of 254 nm was used for the UV measurement. The analysis focused on the primary diastereoisomer, which exhibited an *ee* value exceeding 93%. Additionally, the efficacy of the catalyst was successfully exhibited in relation to the quantity of product in grams, resulting in a yield of 70%.

In the study by X. Zhang *et al.* (2019), they employed acetic acid as a catalyst to facilitate the synthesis of tetracyclic compounds with pyrrolidine rings. The synthesis was accomplished by exploiting oxazolidin-5-ones as the initial substrates and leveraging the 1,3-dipolar cycloaddition process of azomethine ylides (Scheme 3).²⁰ A new and effective one-pot five-component method was described in this study for the selective synthesis of N-bridged bicyclic pyrrolidines with different types of side chains. Also, CO₂ and H₂O were produced as by-products, which were seen as the highlight of this reaction process.

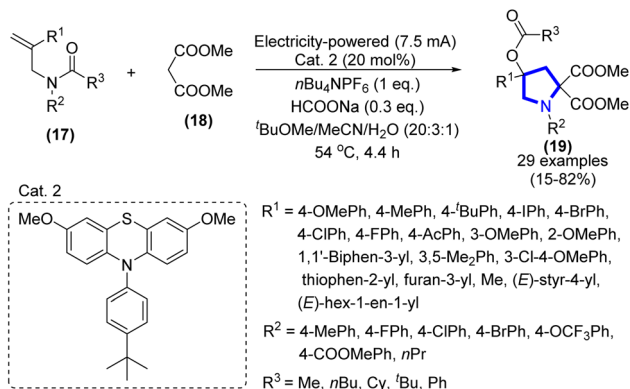
In a recent study conducted by Z.-J. Wu *et al.* (2018), a novel organocatalyzed electrochemical approach was devised for the efficient synthesis of pyrrolidine frameworks. In this process, *N*-allyl amides are dehydrogenated, and then joined with 1,3-dicarbonyl compounds (Scheme 4).²¹ This method was demonstrated using an RVC-anode (100 PPI, 1 cm × 1 cm × 1.2 cm) and Pt-cathode at 7.5 mA (*j*_{anode} ~ 0.1 mA cm^{−2}), in 4.4 h under argon.

In a recent study conducted by D. Kowalczyk *et al.* (2017), they investigated the methodology employed for synthesizing pyrrolidine derivatives that incorporate a benzofuran-3(2*H*)-one framework (Scheme 5).²² The [3 + 2]-cycloaddition process was conducted using 2-arylidene-benzofuran-3(2*H*)-ones and imines produced from salicylaldehyde and diethyl aminomalonates. The experiment was conducted with the inclusion of cinchona alkaloid quinine as the organocatalyst, with a loading of 10 mol%. The identification of the primary products was accomplished through ¹H NMR analysis conducted on the unrefined reaction mixture. The *er* value of the primary products was determined using chiral stationary phase HPLC.

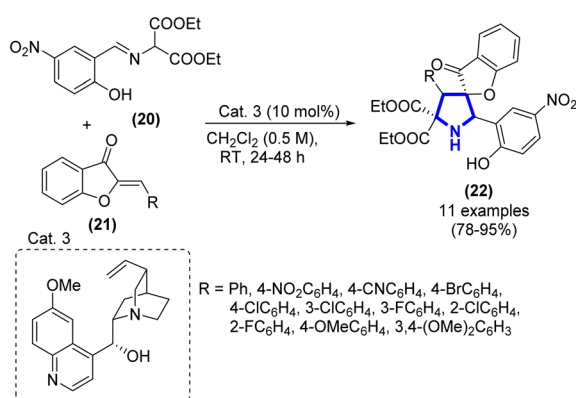
In a recent study conducted by Azomethine Ylides Z. Huang *et al.* (2017), they focused on the utilization of phosphine as



Scheme 3 Synthesis of pyrrolidine-containing tetracyclic compounds catalyzed by AcOH/EtOH.

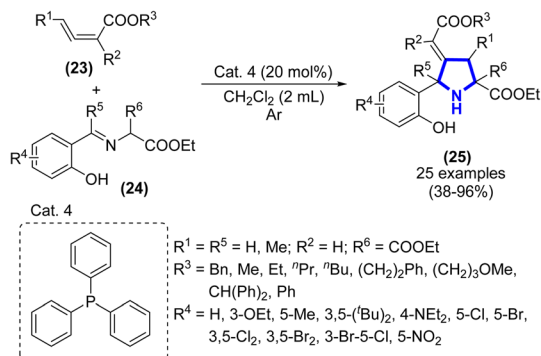


Scheme 4 Synthesis of pyrrolidine and tetrahydropyridine derivatives catalyzed by Cat. 2.

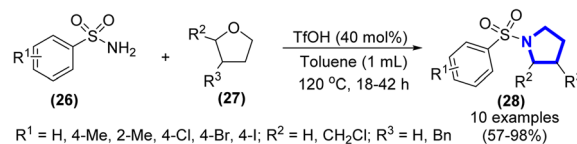


Scheme 5 Synthesis of pyrrolidine derivatives catalyzed by Cat. 3.

a catalyst for the [3 + 2]-cycloaddition reaction between allenates and *o*-hydroxyaryl. Their objective was to synthesize functionalized 4-methylenepyrrolidine derivatives using this catalytic process (Scheme 6).²³ In this research, triphenylphosphine (20 mol%) acted as an efficient catalyst in the presence of dichloromethane solvent (2 mL), and a high yield of the major products was recorded of over 78%. Moreover, the reaction could be performed on a gram scale with 76% yield. Also, the functionalized 4-methylenepyrrolidines were used as precursors to synthesize other derivatives for pharmaceutical applications.



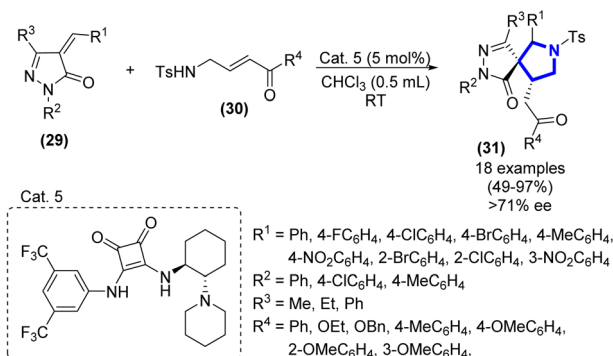
Scheme 6 Synthesis of 4-methylenepyrrolidine derivatives catalyzed by Cat. 4.



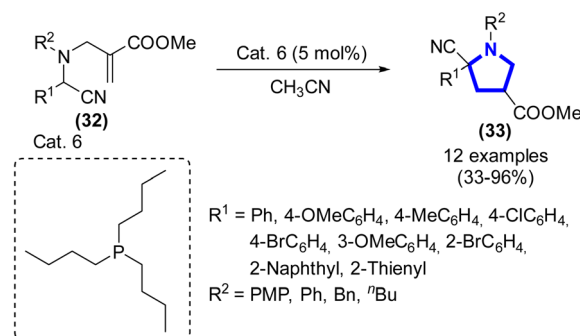
Scheme 7 Synthesis of pyrrolidine catalyzed by TfOH.

The use of cyclic ethers as alkylation reagents for the *N*-alkylation of sulphonamides to synthesize pyrrolidine was reported by W. Shi *et al.* (2014) (Scheme 7).²⁴ The reaction was conducted with trifluoromethanesulfonic acid (TfOH) as the catalyst and toluene as the solvent at 120 °C for 18–42 h. The predominant product yields were evidenced using ¹H-NMR spectroscopy, exhibiting favorable to outstanding outcomes.

A study focusing on the diastereo- and enantio-selective synthesis of spiro-pyrrolidine-pyrazolones *via* the aza-Michael/Michael addition process was introduced by J.-H. Li *et al.* (2016) (Scheme 8).²⁵ The process was performed between pyrazolone and tosyl aminomethyl enone with 5 mol% catalyst Cat. 5. The required product was achieved in good to exceptional yield (49–97%) when dichloromethane was utilized at r.t. together with excellent enantioselectivities (over 71% ee, based on chiral HPLC analysis). This method demonstrated efficacy during a gram-scale trial, which resulted in a yield of 85% of the starting material.



Scheme 8 Synthesis of spiro-pyrrolidine-pyrazolones catalyzed by Cat. 5.

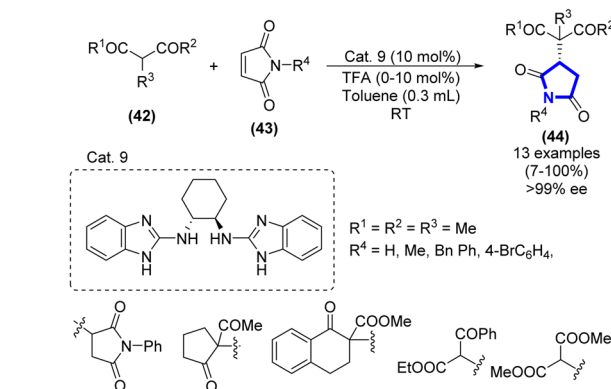


Scheme 9 Synthesis of 2,4-disubstituted pyrrolidines catalyzed by Cat. 6.

E. Da *et al.* (2014) published a method for the synthesis of 2,4-disubstituted pyrrolidines from *N*-allylic-substituted α -amino nitriles *via* intramolecular Michael reactions (Scheme 9).²⁶ The 5-*endo*-trig cyclization reaction afforded the best results when carried out using chloroform as the solvent in the presence of **Cat. 6** (5 mol%) at r.t. The investigation involved the examination of the reactions using both electron-donating and electron-withdrawing groups. The determination of significant product yields was accomplished through ¹H NMR measurement, reaching up to 96%.

G. Talavera *et al.* (2013) introduced the process of synthesizing α -amino- δ -keto esters or β -substituted δ -oxoamides from α,β -unsaturated aldehydes through the Michael reaction under iminium activation (Scheme 10).²⁷ The process was demonstrated with a chiral secondary amine catalyst in toluene. In the second oxidation step of the process, the reaction was carried out in pyridinium chlorochromate (PCC) and dichloromethane at r.t. after 16 h. The *cis/trans* ratio was measured *via* NMR analysis, while the ee value was determined *via* HPLC analysis.

C. Guo *et al.* (2013) invented a technique for the synthesis of pyrrolidine frameworks from β -ketoesters and benzylamine *via* a three-component reaction (Scheme 11).²⁸ In the presence of **Cat. 7** (10 mol%), a yield of pyrrolidine was obtained at 50 °C in 8 days. The principal chemicals were identified *via* HPLC and



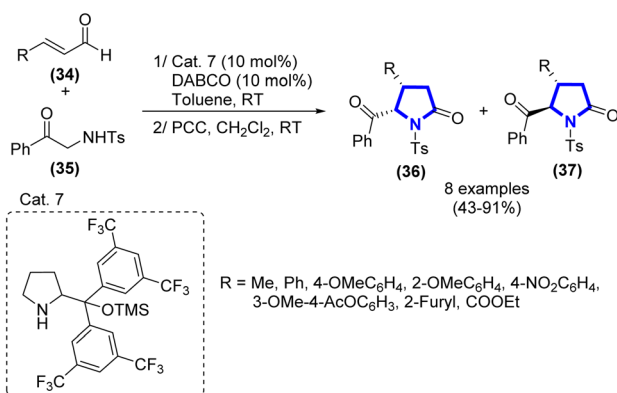
Scheme 12 Synthesis of pyrrolidines catalyzed by **Cat. 9**.

acquired with yields ranging from moderate to exceptional (up to 90%).

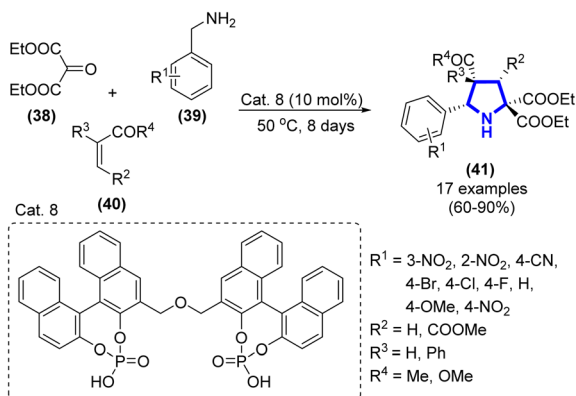
In the study conducted by E. Gomez-Torres *et al.* (2011), they reported the synthesis of pyrrolidine frameworks using the process of adding 1,3-diketones, β -ketoesters, and malonates to maleimide and *N*-substituted maleimides (Scheme 12).²⁹ At r.t. and in toluene as the solvent, the application of organocatalyst **Cat. 9** at a concentration of 10 mol% was shown to produce the best results. The pyrrolidines of interest were synthesized with satisfactory to outstanding efficiency. The catalytic activity of the chiral 2-aminobenzoimidazole-derived organocatalyst was evaluated on the gram scale.

In a study conducted by Yu *et al.* (2010), they successfully demonstrated the application of Michael addition reaction for the conjugate addition of ketones to maleimides. This reaction was catalyzed by a bifunctional monosulfonyl DPEN salt (Scheme 13).³⁰ The experiment was conducted using a catalyst, specifically 10 mol% of **Cat. 10**, and benzoic acid in the same concentration. The reaction took place at r.t. in a toluene solution with a volume of 0.5 mL. The reaction was permitted to continue for 48 h. The initial products were subjected to a screening process, which led to substantial yields (reaching up to 99%) and remarkable enantioselectivities (reaching up to 99%).

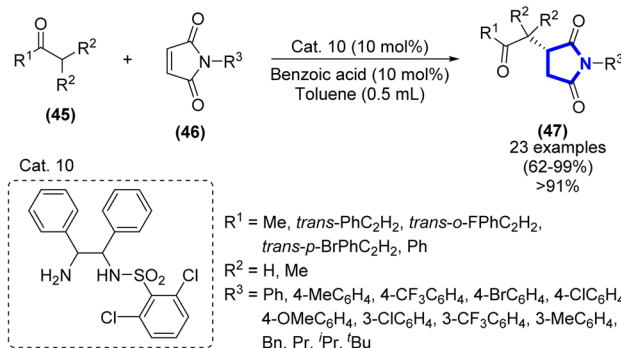
Ankita Chaudhary *et al.* (2018) developed a catalyst-free three-component domino reaction characterized and applied



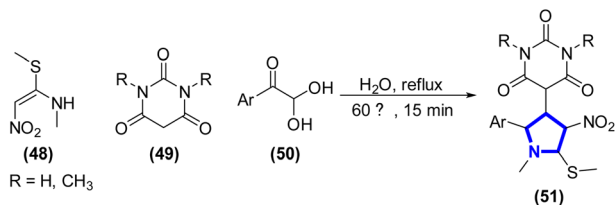
Scheme 10 Synthesis of α -amino- δ -keto esters or β -substituted δ -oxoamides catalyzed by **Cat. 7**.



Scheme 11 Synthesis of pyrrolidine derivatives catalyzed by **Cat. 8**.



Scheme 13 Synthesis of pyrrolidines catalyzed by **Cat. 10**.

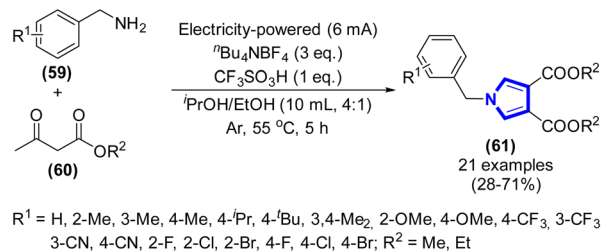


Scheme 14 Catalyst-free chemoselective synthesis of pyrrolidine derivatives.

for synthesis of pyrimidinetriones. The compounds were synthesized in aqueous medium with chemoselectivity. This technology is distinguished by its rapid reaction time, high yield, operational simplicity, and absence of column chromatographic purification (Scheme 14).³¹

2.1.2. Pyrrole. Pyrrole is a substance belonging to a group of compounds called the heterocycles. Specifically, it is a heterocyclic aromatic organic molecule possessing a ring structure consisting of four carbon atoms and one nitrogen atom.³² Proline and hydroxyproline are examples of amino acids that have a pyrrole ring structure. In medicinal chemistry, one of the most pressing challenges is the development of new synthetic molecules having drug-like characteristics. The majority of pharmaceutically useful compounds have their origins in natural products, and these compounds are typically based on N-heterocyclic motifs. Many pharmacological features of commercially available medications with pyrrole rings are known, including antipsychotic,³³ anticancer,³⁴ antifungal,³⁵ antiprotazoal,³⁶ and antimalarial (Scheme 15).³⁷

A synthetic technique for producing poly-substituted pyrroles from 1,3-dicarbonyl compounds and primary amines was disclosed by M. Xiong *et al.* (2021) (Scheme 16).³⁸ The

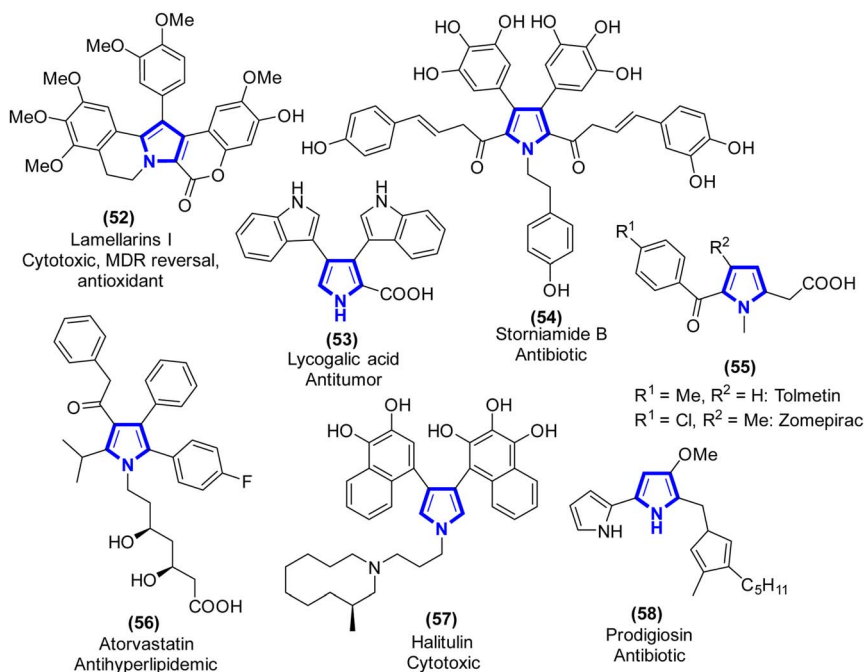


Scheme 16 Synthesis of poly-substituted pyrroles using electro-oxidative intermolecular annulation.

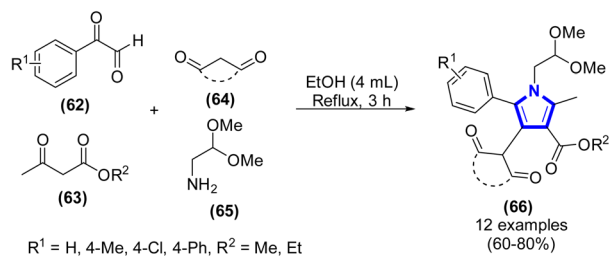
experiment was conducted using electro-oxidative intermolecular annulation. This was accomplished by employing a graphite rod as the anode and a platinum plate as the cathode, with a steady current of 6 mA. The reaction was performed in *n*-Bu₄NBF₄ and CF₃SO₃H, and a volume of 10 mL *i*PrOH and EtOH in a 4 : 1 ratio v/v was introduced in the reaction system. The reaction proceeded for a duration of 5 h at a temperature of 55 °C under argon. The major products were obtained in moderate yields *via* intermolecular cyclization.

A study focusing on the synthesis of novel tricyclic pyrrolo [2,1-*a*]isoquinolines was published by M. Ghandi *et al.* (2021) (Scheme 17).³⁹ The experimental procedure involved the utilization of ethanol in an intramolecular acid-catalyzed cyclization process. The duration of the reaction was 3 h. The target products were obtained in yields ranging from modest to excellent.

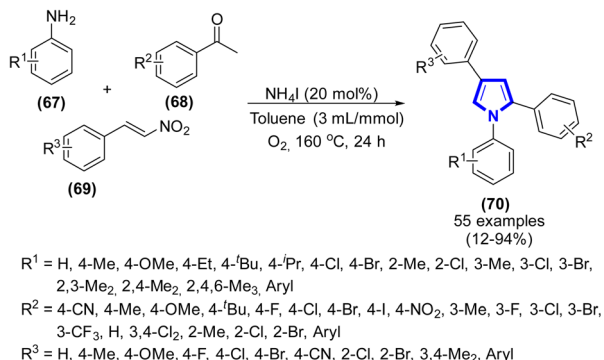
D. Chang *et al.* (2021) pioneered a novel approach for the preparation of multiaryl-substituted pyrrole frames from arylketones, amines, and nitrovinylarenes (Scheme 18).⁴⁰ The experiment was conducted for a duration of 24 h at 160 °C,



Scheme 15 Chemical structures of bioactive compounds containing a pyrrole framework.



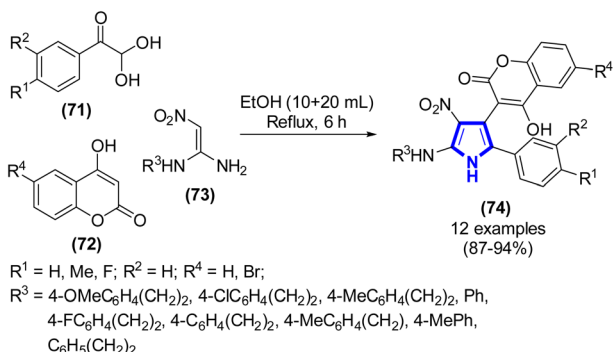
Scheme 17 Synthesis of tricyclic pyrrolo[2,1-a]isoquinolines in ethanol.



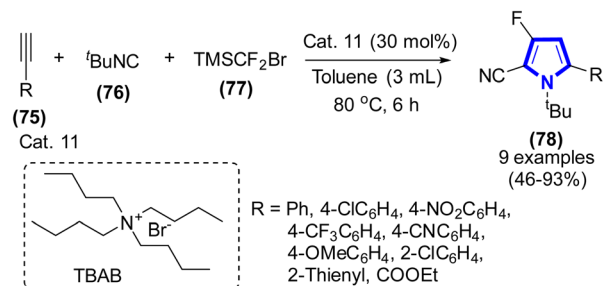
Scheme 18 Synthesis of multiaryl-substituted pyrrole catalyzed by ammonium iodide.

utilizing ammonium iodide as the catalyst and toluene as the solvent. The principal compounds were obtained in favorable to excellent yields (up to 94%). Also, 2,3,5-triaryl-substituted pyrroles were recorded in the absence of nitrovinylarenes. The yield of the reaction was about 77% under the optimal conditions.

A novel procedure was developed by Q.-X. Zi *et al.* (2020) to show the preparation of 2-amino-4-coumarinyl-5-arylpyrrole derivatives (Scheme 19).⁴¹ The oxidation reaction of arylglyoxal monohydrates, 1,1-enediamines, and 4-hydroxy-2*H*-chromen-2-ones was conducted in ethanol under reflux conditions for a duration of 6 h. The primary products were synthesized in the absence of metal catalysts, resulting in yields varying from satisfactory to exceptional, exceeding 87%.



Scheme 19 Synthesis of 2-amino-4-coumarinyl-5-arylpyrroles in ethanol.

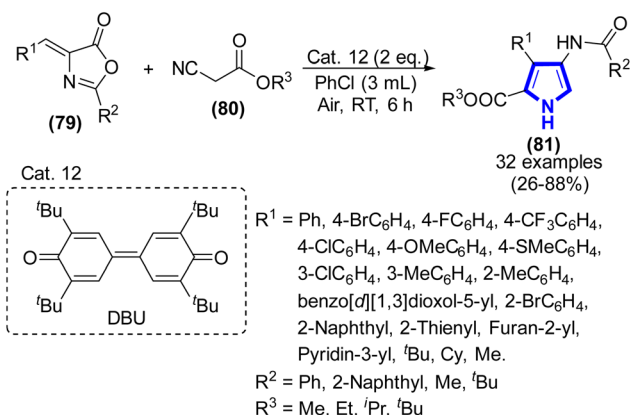


Scheme 20 Synthesis of mono-fluorinated pyrroles catalyzed by Cat. 11.

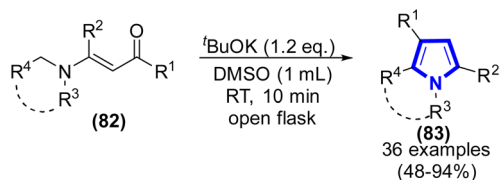
In the presence of TBAB (Cat. 11), the reaction of alkynes, 2-isocyano-2-methylpropane, and (bromodifluoromethyl) trimethyl-silane was stirred at 80 °C for 6 h to form mono-fluorinated pyrrole derivatives, which was demonstrated by R. Zhang *et al.* (2020) (Scheme 20).⁴² The mono-fluorinated pyrroles of interest were successfully synthesized by a [3 + 2]-cycloaddition reaction. The reaction proceeded under an N_2 environment, with toluene serving as the solvent. The yields achieved ranged from moderate to good.

In the study by Zhang *et al.* (2020), they successfully synthesized 2,3,4-trisubstituted pyrrole frameworks *via* a [3 + 2]-reaction. The process of cyclization involving activated methylene isocyanides with 4-(arylidene) compounds was considered. The compounds referred to are oxazol-5(4*H*)-ones having a substituent at the 2-position (Scheme 21).⁴³ The [3 + 2]-cyclization reaction occurred at r.t. to form 2,3,4-trisubstituted pyrroles in the presence of DBU (Cat. 12) and chlorobenzene for 6 h. The intended product could be achieved in yields ranging from 26% to 88%, depending on the substrate scope.

L. Xu *et al.* (2020) successfully devised a method utilizing a superbase catalyst to facilitate the $\text{N-}\alpha\text{-sp}^3\text{C-H}$ functionalization of tertiary enamines, enabling the synthesis of pyrroles with various substituents (Scheme 22).⁴⁴ The experimental procedure was conducted at ambient temperature with the addition of $^t\text{BuOK}$ and DMSO. It was observed that this method was highly effective for the synthesis of substituted



Scheme 21 Preparation of 2,3,4-trisubstituted pyrroles catalyzed by Cat. 12.



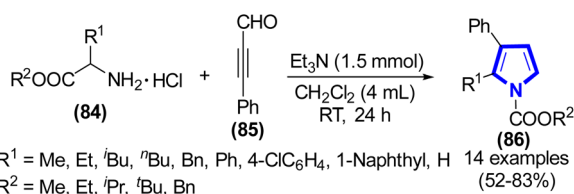
R^1 = Ph, 4-MeC₆H₄, 2-MeC₆H₄, 4-OMeC₆H₄, 4-^tBuC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 3-Naphthyl, 2-Furanyl,
 R^2 = Ph, 4-MeC₆H₄, 3-MeC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 2-Thienyl,
 R^3 = Me, Et, ⁱPr, ⁿBu, Bn, Ph
 R^4 = Ph, 4-OMeC₆H₄, 4-MeC₆H₄, 3-MeC₆H₄, 2-MeC₆H₄, 2-OMeC₆H₄, 4-FC₆H₄, 2-FC₆H₄, 4-ClC₆H₄, 4-CF₃C₆H₄, 4-CNC₆H₄, 2-Furanyl, 3-Pyridinyl, 2-Naphthyl

Scheme 22 Synthesis of substituted pyrroles catalyzed by ^tBuOK.

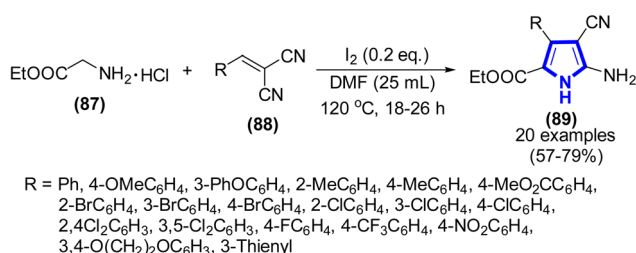
pyrrole derivatives. This study concentrated on evaluating the impact of various substituents on the substrate, resulting in a very favorable yield of the desired product, which accounted for about 48–94%.

L. Wei *et al.* (2020) devised a methodology for the synthesis of functionalized pyrroles by a sequential process involving condensation and intramolecular cyclization (Scheme 23).⁴⁵ This reaction process was employed to synthesize pyrrole frames from α -amino acid esters hydrochloride and alkynals in the presence of triethylamine and dichloromethane at ambient temperature for 24 h. To validate the efficacy of this approach, the reaction was conducted on a significant scale, utilizing a quantity of 10 mmol.

L. Su *et al.* (2020) presented a new method for synthesizing 5-amino-1*H*-pyrrole-2-carboxylates. This was achieved using the [3 + 2]-cycloaddition process involving benzyldenemalononitriles and ethyl glycinate hydrochloride, utilizing iodine and DMF as catalysts. The reaction was conducted at 120 °C and prolonged reaction times of 18–36 h (Scheme 24).⁴⁶ The geometric



Scheme 23 Synthesis of pyrroles catalyzed by triethylamine.

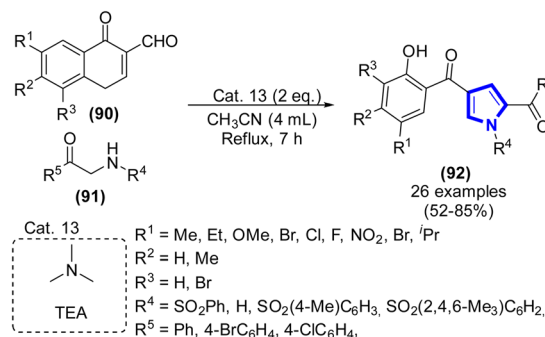


Scheme 24 Synthesis of 5-amino-1*H*-pyrrole-2-carboxylates catalyzed by iodine.

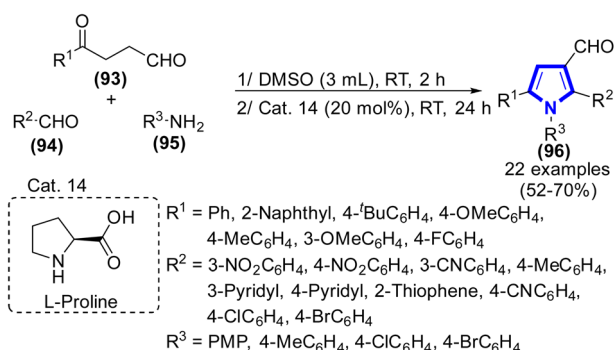
structure of the target substance was determined through X-ray crystallographic analysis.

In a recent publication by R. Shrestha *et al.* (2020), a novel and highly efficient one-pot methodology for the synthesis of polyfunctionalized pyrroles was elucidated (Scheme 25).⁴⁷ The reaction was carried out by a series of chemical transformations, namely Knoevenagel condensation, intramolecular Michael addition, and ring opening, which occurred as a result of *N*-annulation of 3-formylchromones and α -amino ketones. This reaction was conducted in the presence of Cat. 13. The employed methodology shows notable benefits, including its ability to accommodate diverse functional groups and its utilization of moderate reaction circumstances. The reaction was conducted using acetonitrile as the solvent, resulting in a high yield of main products after a duration of 7 in the range of 52–85%.

The preparation of pyrrole-3-carboxaldehydes from aldehydes, amines, and 1,4-ketoaldehydes through chemoselective Mannich reaction-cyclization, which was published by N. A. Mir *et al.* (2020) (Scheme 26).⁴⁸ This reaction was performed in two steps, where a mixture of aldehydes and amines was reacted with each other in DMSO for 2 h, in the presence of *L*-proline (Cat. 14), and then 1,4-ketoaldehydes was added to form pyrrole-3-carboxaldehyde products for 24 h at r.t. The principal products were evaluated for their *in vitro* antibacterial and antifungal characteristics, with the most positive results noted at an MIC of 16 $\mu\text{g mL}^{-1}$, particularly for bacterial strains.



Scheme 25 Synthesis of polyfunctionalized pyrroles catalyzed by Cat. 13.

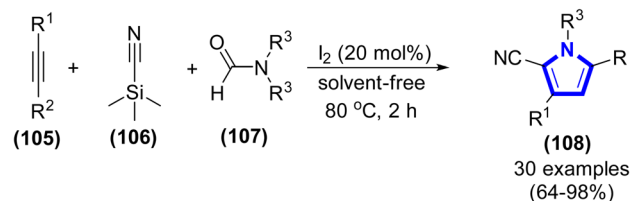


Scheme 26 Synthesis of pyrrole-3-carboxaldehydes catalyzed by Cat. 14.

Three-component domino reactions to synthesize multi-functionalized pyrroles were established by V. A. Mamedov *et al.* (2020) (Scheme 27).⁴⁹ The experimental procedure involved the combination of 3-arylquinoxalin-2-ones, malononitrile, secondary cyclic amine (or primary alcohols), and an alcohol solution in acetic acid. The mixture was subjected to heating for a duration of 7 h. The quinoxalinone-benzimidazolone rearrangement was employed to initiate the pathways, resulting in the formation of pyrrolocarbonitriles in significant yields. The yield reached about 25–83%, depending on the substrate scope.

In the recent study by H. Jia *et al.* (2020), they devised a highly effective approach for synthesizing substituted dihydropyrrole and pyrrole frameworks by the process of [3 + 2]-cyclization and subsequent aromatization (Scheme 28).⁵⁰ The cyclization of β -chloro-vinyl dithianes with imines was carried out under the reaction conditions of an argon atmosphere using ^tBuOK and THF as the solvent at ambient temperature for a duration of 30 min. The pure products were acquired in satisfactory yields.

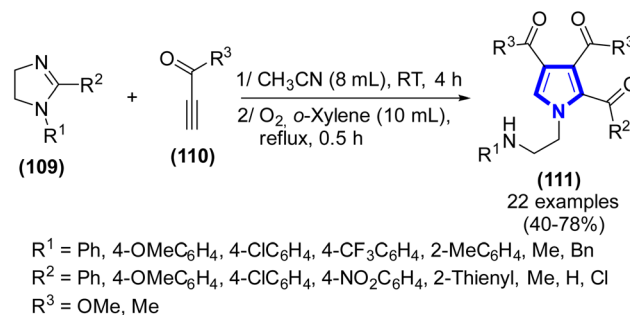
Q.-W. Gui *et al.* (2020) discovered a sustainable method for the synthesis of multi-substituted pyrroles using a metal- and solvent-free approach (Scheme 29).⁵¹ This investigation involved the utilization of alkynes, TMS-CN, and *N,N*-disubstituted formamides in the presence of iodine at a concentration of 20 mol%. Under the ideal reaction conditions, the major compounds were determined in good yields (up to 98%). Importantly, in the gram-scale preparation of pyrroles (under 8 products), the targeted compounds were separated in outstanding yields (64–98%).



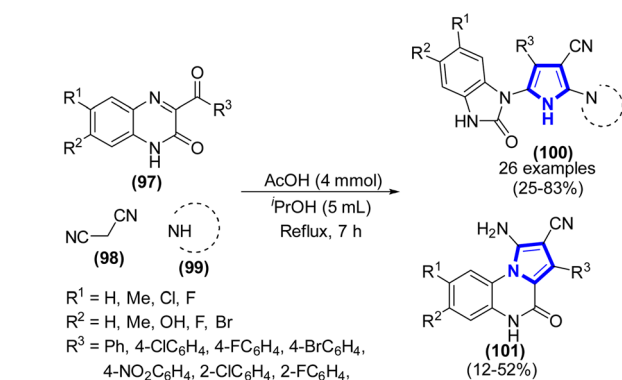
$R^1 = \text{Ph, 4-MeC}_6\text{H}_5, 4\text{-EtC}_6\text{H}_5, 4\text{-}^i\text{PrC}_6\text{H}_5, 4\text{-}^t\text{BuC}_6\text{H}_5, 4\text{-OMeC}_6\text{H}_5, 4\text{-PhC}_6\text{H}_5, 4\text{-FC}_6\text{H}_5, 4\text{-ClC}_6\text{H}_5, 4\text{-BrC}_6\text{H}_5, 4\text{-IC}_6\text{H}_5, 4\text{-CF}_3\text{C}_6\text{H}_5, 4\text{-CNC}_6\text{H}_5, 4\text{-COOMeC}_6\text{H}_5, 4\text{-NO}_2\text{C}_6\text{H}_5, 3\text{-MeC}_6\text{H}_5, 3\text{-FC}_6\text{H}_5, 2\text{-ClC}_6\text{H}_5, 2\text{-Naphthyl, 2-Pyridyl, 2-Thienyl, Alkyl, Bn, COOMe}$
 $R^3 = \text{Me, Et, } ^i\text{Bu, Ph; R = H, Me,}$

Scheme 29 Synthesis of multi-substituted pyrroles catalyzed by iodine.

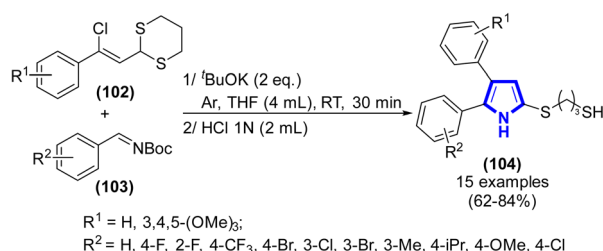
A methodology for synthesizing poly-substituted pyrroles by the reaction of 1,2-disubstituted 2-imidazolines with alkynes was executed by Golantsov *et al.* (2020) (Scheme 30).⁵² The aza-Claisen rearrangement or/and transannular nucleophilic addition ring-opening reactions were performed in two steps to form the major products. During the initial stage, the reaction involved the combination of 2-imidazolines and alkynes in acetonitrile, which was maintained at ambient temperature for a duration of 4 h. Subsequently, poly-substituted pyrroles were synthesized in xylene medium.



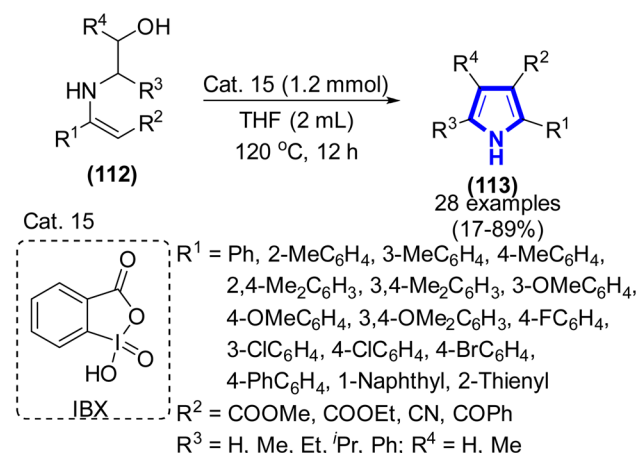
Scheme 30 Synthesis of polysubstituted pyrroles.



Scheme 27 Synthesis of pyrroles catalyzed by acetic acid.

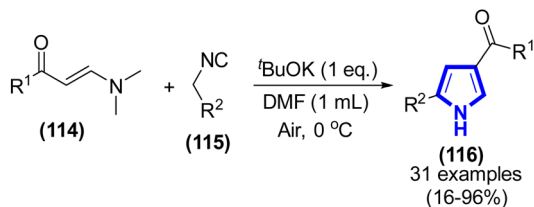


Scheme 28 Synthesis of pyrrole scaffolds catalyzed by ^tBuOK.



Scheme 31 Synthesis of 2,3-disubstituted pyrroles catalyzed by Cat. 15.





$R^1 = \text{Ph}, 2\text{-MeC}_6\text{H}_4, 3\text{-MeC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 3,4\text{-OMe}_2\text{C}_6\text{H}_3, 3\text{-ClC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 4\text{-BrC}_6\text{H}_4, 2\text{-Naphthyl}, 1\text{-Naphthyl}, 2\text{-Pyridyl}$
 $R^2 = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4$

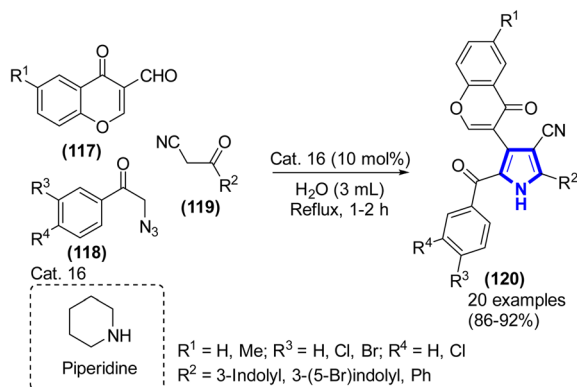
Scheme 32 Synthesis of 2,4-disubstituted pyrroles catalyzed by $t\text{BuOK}$.

P. Gao *et al.* (2020) carried out a study on a metal-free methodology for the synthesis of 2,3-disubstituted pyrroles using *N*-hydroxyalkyl enamines (Scheme 31).⁵³ The primary products were obtained with good selectivity through the conversion of *N*-hydroxyalkyl enamines *via* oxidative cyclization using Cat. 15 (IBX) in THF. The experiment was conducted at a temperature of 120 °C for a duration of 12 h.

A novel approach for the preparation of 2,4-disubstituted pyrroles from isocyanides was reported by I. V. Efimov *et al.* (2020) (Scheme 32).⁵⁴ The authors demonstrated the [3 + 2] cycloaddition reaction of isocyanides and enamines and/or enaminones to form 2,4-disubstituted pyrroles in the presence of $t\text{BuOK}$ and DMF in air at 0 °C. The major products were obtained in moderate yields (up to 96%).

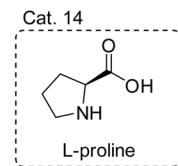
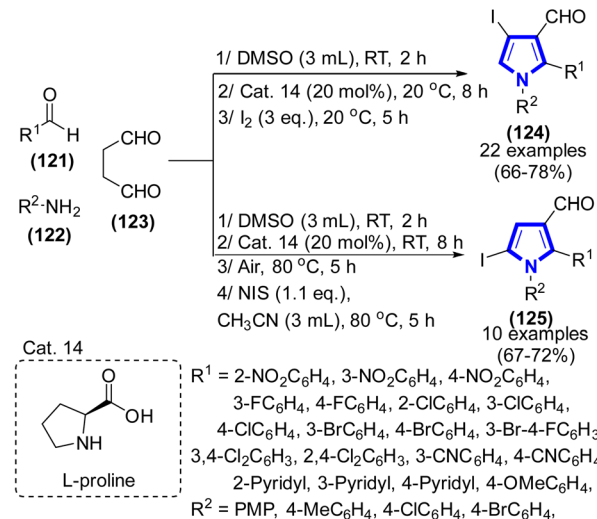
A study proposed an environmentally friendly method for the synthesis of chromenopyrrole frameworks. The reaction is facilitated by the presence of a piperidine catalyst, as described by E. Dhanasekar *et al.* (2020) (Scheme 33).⁵⁵ The experimental procedure was conducted in an aqueous solution using a domino Knoevenagel–Michael addition–cyclization–rearrangement sequence. This approach exhibits several advantages, including a rapid reaction time, simple of operation, and high yield. The reaction was investigated on a gram scale with the objective of synthesizing the desired molecule in high yield.

The synthesis of iodopyrrole-3-carboxaldehydes using succinaldehyde and imines was investigated by S. Choudhary *et al.* (2020) using the aforementioned methods (Scheme 34).⁵⁶ The straightforward method was demonstrated to form 4- or 5-



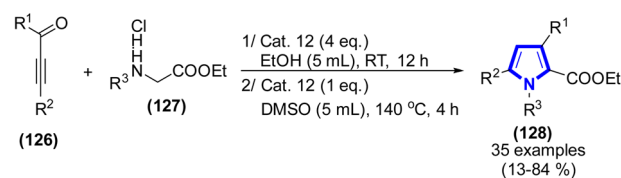
$R^1 = \text{H}, \text{Me}; R^3 = \text{H}, \text{Cl}, \text{Br}; R^4 = \text{H}, \text{Cl}$
 $R^2 = 3\text{-Indolyl}, 3\text{-(5-Br)indolyl}, \text{Ph}$

Scheme 33 Synthesis of chromenopyrrole catalyzed by Cat. 16.



$R^1 = 2\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-FC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 3\text{-BrC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 3\text{-Br-4-FC}_6\text{H}_3, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 3\text{-CNC}_6\text{H}_4, 4\text{-CNC}_6\text{H}_4, 2\text{-Pyridyl}, 3\text{-Pyridyl}, 4\text{-Pyridyl}, 4\text{-OMeC}_6\text{H}_4$
 $R^2 = \text{PMP}, 4\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4$

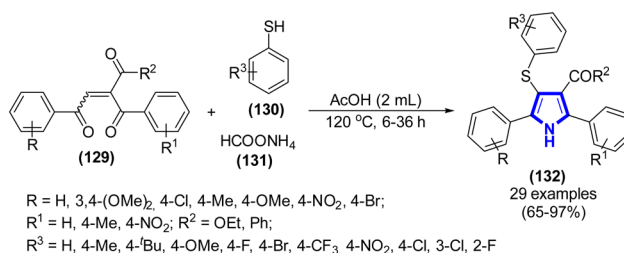
Scheme 34 Synthesis of iodopyrrole-3-carboxaldehydes catalyzed by Cat. 14.



Scheme 35 Synthesis of polysubstituted pyrroles catalyzed by Cat. 12.

iodopyrrole-3-carboxaldehydes using Cat. 14 in the presence of I_2 through Mannich reaction–cyclization.

T. Yang *et al.* (2019) introduced a highly effective approach to produce polysubstituted pyrroles using α,β -unsaturated yrones and *N*-substituted ethyl glycine ethyl ester hydrochlorides (Scheme 35).⁵⁷ Cat. 12 was employed as the catalyst in a two-step process for the synthesis of pyrrole frameworks. The initial procedure involved the reaction between a combination of α,β -unsaturated yrones and *N*-substituted ethyl glycine ethyl ester hydrochlorides. This reaction took place in the presence of Cat. 12 under ambient conditions for a duration of 12 h, followed by the removal of ethanol after the reaction. Subsequently, dimethyl sulfoxide (DMSO) was introduced in the solution, and the resulting mixture was subjected to stirring at 140 °C for a duration of 4 h. The primary products were acquired in favorable yields. This approach exhibits several advantages,



$R = \text{H}, 3,4\text{-(OMe)}_2, 4\text{-Cl}, 4\text{-Me}, 4\text{-OMe}, 4\text{-NO}_2, 4\text{-Br};$
 $R^1 = \text{H}, 4\text{-Me}, 4\text{-NO}_2; R^2 = \text{OEt}, \text{Ph};$
 $R^3 = \text{H}, 4\text{-Me}, 4\text{-}^i\text{Bu}, 4\text{-OMe}, 4\text{-F}, 4\text{-Br}, 4\text{-CF}_3, 4\text{-NO}_2, 4\text{-Cl}, 3\text{-Cl}, 2\text{-F}$

Scheme 36 Synthesis of 4-thioarylpyrroles catalyzed by ammonium formate.

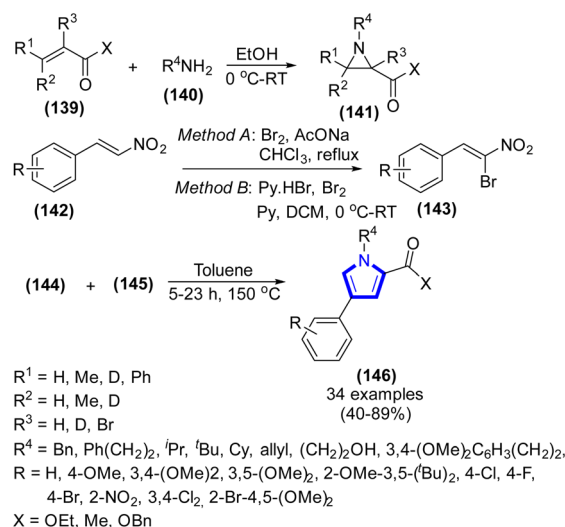
including the utilization of a non-metallic catalyst and the employment of mild reaction conditions.

In the study by V. Rajeshkumar *et al.* (2019), they devised a novel methodology for the synthesis of 4-thioarylpyrroles using a one-pot three-component approach (Scheme 36).⁵⁸ The experimental procedure involved the utilization of 1,4-enediones, thiols, and ammonium formate in a consecutive thiol-Michael/Paal-Knorr reaction for the purpose of synthesizing C-S and C-N bonds.

An organocatalytic technique for synthesizing functionalized pyrroles by the cycloisomerization of *Z*-1-iodo-4-*N*-methylbenzenesulfonyl-1,6-enynes was described by L. Meng *et al.* (2019) (Scheme 37).⁵⁹ The chemical reactions were performed in the presence of organomolecule **Cat. 17** and ^tBuOK for a period of 10 min.

An effective procedure for the synthesis of tetrahydrocyclopenta[*b*]pyrroles was provided by J. A. Malone *et al.* (2019) (Scheme 38).⁶⁰ The reaction was conducted using α' -hydroxy silylenol ether and a silylenol ether generated from acetophenone. This reaction was performed *via* the [2 + 2 + 1] annulation reaction mechanism, employing a Brønsted acid as a catalyst. Utilizing this method, they could successfully produce high yields of these biologically important N-heterocycles. The application of this method to access heterocycles and complex molecules that are structurally related is currently underway in the laboratory.

V. Kumar *et al.* (2019) described a unique one-pot method for the synthesis of 1,2,4-trisubstituted pyrroles (Scheme 39).⁶¹ This reaction proceeds *via* a chain reaction involving aziridines and β -bromo- β -nitrostyrenes. Initially, *N*-substituted-aziridine-2-

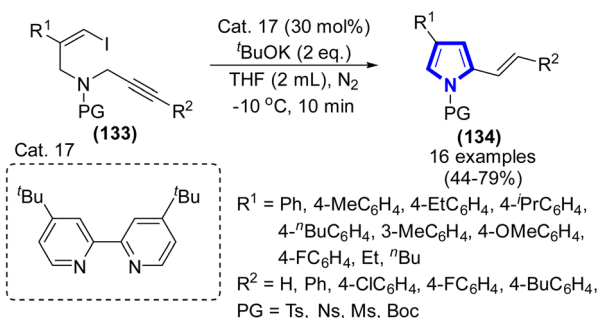


Scheme 39 Synthesis of 1,2,4-trisubstituted pyrroles.

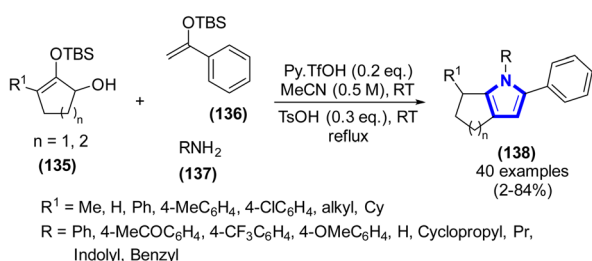
carboxylates are produced using dibrominated-compounds and ethanolamine as the starting materials. Similarly, β -bromo- β -nitrostyrene can be derived from β -nitrostyrene *via* synthesis. The desired product was obtained in satisfactory to outstanding yields. The protocol for the formal preparation of ningalin B was delineated, encompassing the utilization of the established approach.

According to B. S. Karki *et al.* (2019), under the conditions of visible light photoredox catalyzed reactions, a formal [3 + 2] cycloaddition reaction involving 2*H*-azirines and nitroalkenes led to the metal-free synthesis of trisubstituted pyrroles (Scheme 40).⁶² This technique involved a base-mediated denitration reaction, followed by the Michael addition of the 2*H*-azaallenyl radical to the β -nitrostyrenes. The direction of the nitro group influence regulates the regiochemistry of the reaction. The notable characteristics of the reaction include its perfect regioselectivity, and in the majority of situations, excellent product yields.

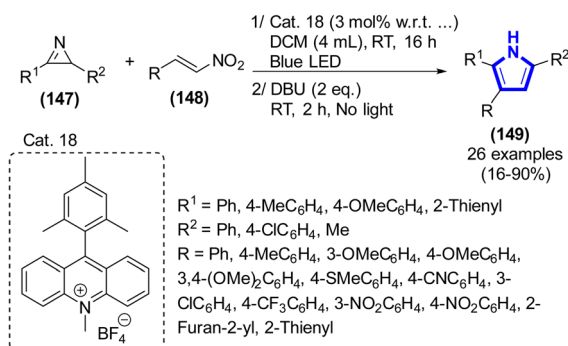
By using electrooxidation annihilation to create polypotent pyrroles from amines and aldehydes or ketones, a generic and useful method was developed by X. Gao *et al.* (2019) (Scheme 41).⁶³ Arylacetaldehyde and primary amines may favorably



Scheme 37 Synthesis of functionalized pyrroles catalyzed by Cat. 17.

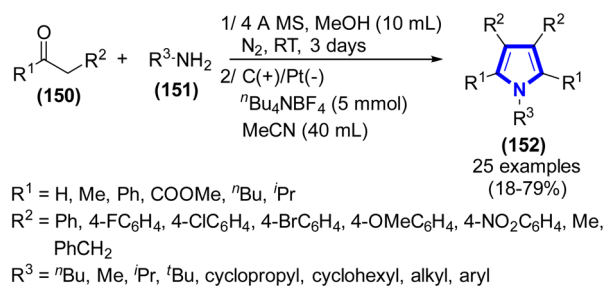


Scheme 38 Synthesis of tetrahydrocyclopenta[*b*]pyrroles catalyzed by Py TfOH.



Scheme 40 Synthesis of trisubstituted pyrroles *via* a visible-light photoredox-catalyzed reaction.





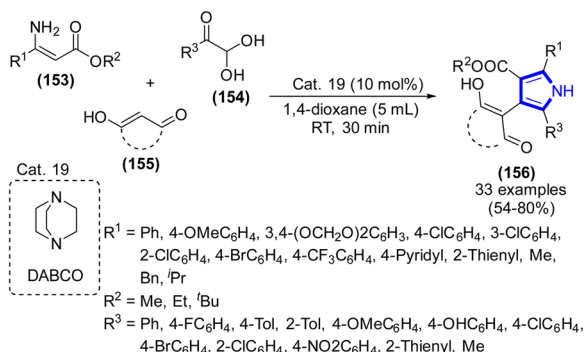
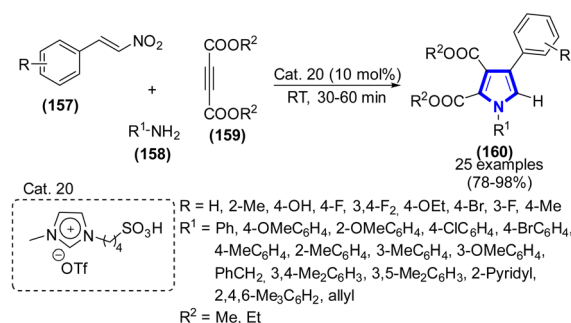
Scheme 41 Synthesis of polypotent pyrroles via electrooxidation.

engage in this metabolism to produce β -substituted pyrroles without the need for extra oxidants. Using imines as a substrate was a highly effective way to acquire tetrasubstituted pyrroles. This reaction was tolerant to functional groups under moderate conditions and may be scaled up to large quantities.

A mild and efficient three-component domino-catalyzed **Cat. 19** was developed by X. Chang *et al.* (2019) for the synthesis of highly functional NH-pyrroles from arylglyoxal monohydrates, enzymatic esters, and 1,3-dicarbonyl cyclic compounds in 1,4-dioxane at r.t. for 0.5 h (Scheme 42).⁶⁴ The current work used a domino-catalyzed method to synthesize a variety of substituted NH-pyrroles, resulting in moderate to favorable yields, of 54–80%.

Tetrasubstituted pyrroles were synthesized utilizing one-pot, three-component methodologies and an exceptionally efficient, transition metal-free Brønsted acidic IL, which was introduced by A. Balu Atar *et al.* (2019) (Scheme 43).⁶⁵ The present approach uses **Cat. 20** for the solvent-free, efficient synthesis of amines, dialkyl acetylenedicarboxylates, and β -nitrostyrenes. The tetrasubstituted pyrrole was synthesized using **Cat. 20**. Many functionalized tetrasubstituted pyrrole derivatives could be synthesized in high yields under transition metal- and solvent-free conditions. Furthermore, the reuse of **Cat. 20** in successive processes did not decrease the product yield. In one pot, this eco-friendly approach produces a variety of tetrasubstituted pyrroles with various therapeutic uses.⁶⁶

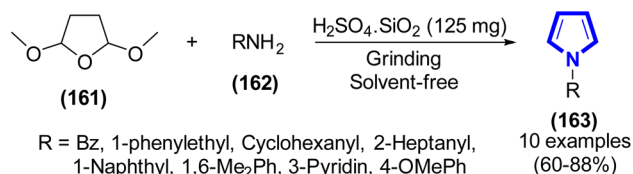
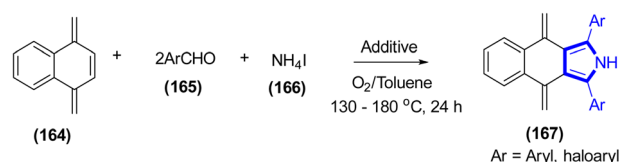
Recently, A. J. Khammas *et al.* (2019) developed a method for the production of *N*-substituted pyrrole derivatives, where a sulfuric acid catalyst immobilized on silica gel (SSA) was

Scheme 42 Synthesis of tetrasubstituted NH-pyrroles catalyzed by **Cat. 20**.Scheme 43 Synthesis of tetrasubstituted pyrroles catalyzed by **Cat. 20**.

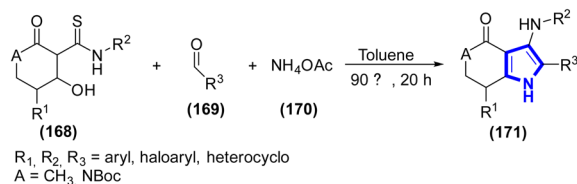
found to be extremely efficient (Scheme 44).⁶⁷ They established the optimized reaction conditions to produce a high yield, including simple grinding of the reactants, absence of a solvent, and short reaction time. Additionally, this reaction satisfies the majority of green chemistry criteria.

C. Zhou *et al.* (2023) documented the establishment of a four-component reaction for the synthesis of tetrasubstituted pyrroles under metal-free conditions. The pyrrole ring was synthesized in a single vessel *via* [2 + 1 + 1 + 1] condensation with ammonium salt as the nitrogen source. Substituted benzo [f]isoindole-4,9-diones and pyrrolo[3,4-*c*]pyrrole-1,3-diones were synthesized from 1,4-naphthoquinones and maleimides as versatile C2 fragments. This study employed ammonium salt as a nitrogen source, utilized readily available starting materials, and synthesized two carbon–carbon and two carbon–nitrogen bonds in a single process (Scheme 45).⁶⁸

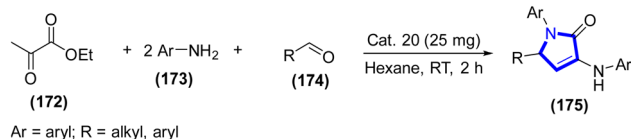
In the study reported by K. Afratis *et al.* (2023), they aimed to synthesized substituted fused pyrroles through MCR among thioamides, aldehydes, and ammonium acetate. Intercepting the cyclic intermediate with compounds in the required oxidation state eliminated the requirement of harmful oxidizing agents. This reaction is advantageous due to several diversification points that may be readily used, given the accessibility of commercially available aldehydes and anilines, and may have

Scheme 44 Synthesis of *N*-substituted pyrroles catalyzed by H_2SO_4 SiO_2 (SSA).

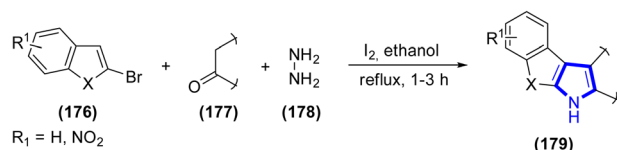
Scheme 45 Synthesis of tetrasubstituted pyrroles.



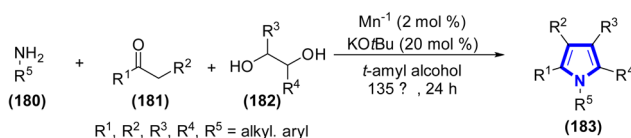
Scheme 46 Synthesis of fully substituted fused pyrroles through an MCR.



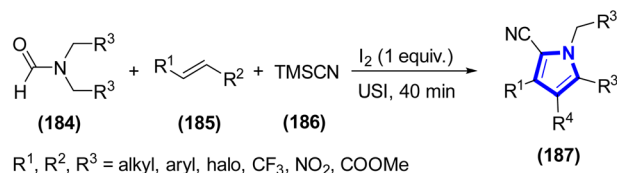
Scheme 47 Synthesis of 1H-pyrrol-2(5H)-ones.



Scheme 48 Synthesis of benzofuro/thieno[2,3-b]pyrroles.



Scheme 49 Manganese-catalysed multicomponent synthesis of pyrroles.



Scheme 50 Synthesis of pyrroles using ultrasound-assisted method.

extensive applications in the synthesis of physiologically significant pyrrole-containing molecules (Scheme 46).⁶⁹

Tajbakhsh *et al.* (2023) established an efficient method for the acid-catalyzed synthesis of 1H-pyrrol-2(5H)-ones. This was achieved using a unique *N*-sulfonic acid modified poly(styrene-

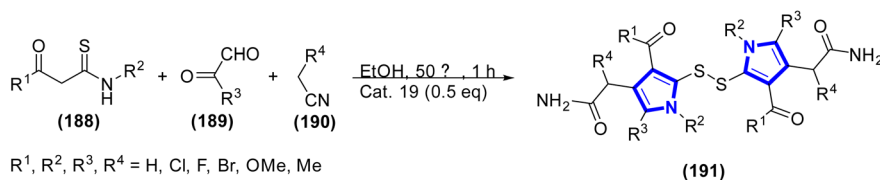
diethylenetriamine) *via* a three-component reaction including aldehydes, amines, and ethyl pyruvate. The reaction was conducted within a short, producing elevated yield promptly (Scheme 47).⁷⁰

Kalegowda Shivashankar and colleagues (2018) published a study on the development of a novel I_2 -catalyzed one-pot multi-component approach for the synthesis of a broad variety of elusive benzofuro[2,3-*b*]pyrroles. To date, there has been no investigation on the possibility of cyclization occurring in one pot among alkanones, hydrazine, and 2-bromobenzofuran or 2-bromobenzothiophene. Considering this, the described single-step procedure offers a flexible alternative to the current pathways for access to relevant benzofuro/thieno [2,3-*b*]pyrroles (Scheme 48).⁷¹

Borghs *et al.* (2019) reported the detailed synthesis of around thirty-five substituted pyrrole derivatives using multicomponent reactions under distinctive base metal-catalyzed conditions (Scheme 49). PNP (*N,N'*-bis(diphenylphosphine)-2,6-diaminopyridine) served as a ligand integrated into the metal catalyst, which was a magnesium complex characterized by air stability and cost-effectiveness. A substantial quantity of water and hydrogen gas was generated as by-products of the operation. The computational analysis indicated the participation of an acceptor dehydrogenation hydrogen auto-transfer mechanism in this process. The metal-ligand combination has a dual function in the dehydrogenation of ethylene glycol by the acceptor, followed by an unusual hydrogen auto-transfer mechanism.⁷²

Under moderate reaction conditions, L. Kumar S and colleagues (2024) developed an ultrasound-assisted, one-pot tandem MCR assay for various tri- and tetra-substituted pyrroles (Scheme 50). In addition to having excellent chemo- and regio-selectivity, their process does not involve the use of metals or solvents. Additionally, the reaction makes it possible to produce a wide range of substrates with a high tolerance for functional groups, resulting in excellent to exceptional yields. In this context, iodine serves as both a catalyst and an oxidant, facilitating a significant reduction in chemical waste. In comparison to traditional heating, this method, together with ultrasonic irradiation, enhanced the reaction efficiency and speed, while concurrently reducing the occurrence of side reactions. This approach enables the synthesis of several poly-substituted pyrrolocarbonitriles, many of which are challenging to obtain using conventional procedures.⁷³

In 2017, Xiang Li and colleagues developed a strategy for synthesizing pyrrole analogs *via* a one-pot method, yielding disulfide-tethered pyrrole (Scheme 51). This reaction involves a sequence of transformations, including sequential Knoevenagel condensation, Michael addition, *N*-*O*-cyclization, ring



Scheme 51 Synthesis of pyrrole analogs using Cat. 19.



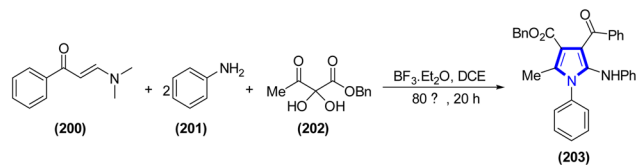
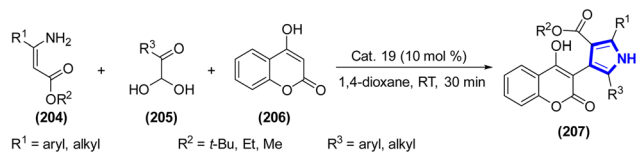
Review

opening, double tautomerization, and oxidative coupling. These reactions provide two new pyrrole rings and nine chemical bonds. The published approach enables the synthesis of products with high formation efficiency and atom economy, while also exhibiting notable attributes including the absence of transition metals, simple reaction conditions, shorter reaction time, and uncomplicated synthesis process. This technique is an extension of a feasible method for synthesizing disulfides linked to pyrroles.⁷⁴

Thangavel Pavithra and colleagues (2023) successfully synthesized tetrasubstituted pyrroles without the need for any solvent or catalyst, at ambient temperature and under the influence of white light. Overall, the product was successfully obtained *via* intermolecular cyclization and aromatization. According to previous reports, this method is also incredibly affordable and exceptionally beneficial to the environment. Additionally, early *in vitro* cytotoxic experiments were carried out on compounds against hepatocellular carcinoma cells (HepG2) to determine their potential cytotoxicity. One of the compounds showed significant activity, which had an IC₅₀ value of 17.82 M (Scheme 52).⁷⁵

The group led by Sridhar Pervaram (2020) aimed to produce poly-substituted pyrrolidinone derivatives *via* a green multi-component reaction. Polyethylene glycol-400 was employed as the solvent, and 1-butyl-3-methylimidazolium tetrafluoroborate as an IL. Because ILs are inexpensive and can be reused, they are regarded as superior catalysts for phase transfer given that they do not cause toxicity. Consequently, an approach that is simple, very effective, and environmentally friendly was developed (Scheme 53).⁷⁶

Tongyan Yu and colleagues (2021) successfully designed a method employing enaminone as a substrate for the precise capture of carbocation intermediates. This allowed them to produce highly functionalized pyrroles and pyrrole-fused piperidine-4-ones in yields ranging from modest to good. This four-component reaction, mediated by BF₃·Et₂O, has several benefits, including gentle reaction conditions, absence of metals, and availability of practically relevant pathways to create

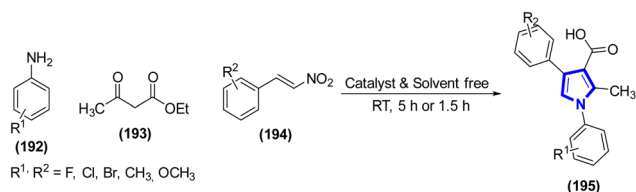
Scheme 54 Synthesis of pyrroles *via* a four-component reaction.

Scheme 55 Synthesis of pyrroles catalyzed by Cat. 19.

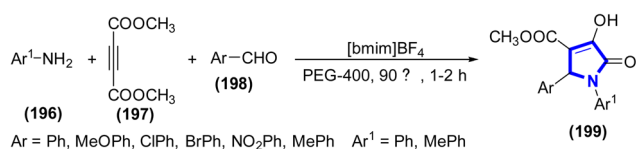
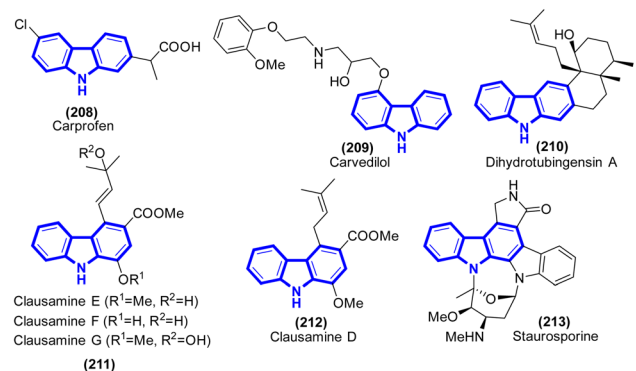
highly functionalized pyrroles, making it a scheme appealing (Scheme 54).⁷⁷

The group of researchers led by Xiangqing Chang (2019) devised a three-component reaction AS an effective and innovative multicomponent reaction. To produce highly functionalized NH-pyrroles, the reaction was supported by a solvent composed of 1,4-dioxane and catalyzed with the assistance of Cat. 19 at the appropriate temperature. The reaction tolerated various functional groups, which resulted in moderate to excellent yields of different substituted NH-pyrroles. The reaction was carried out under conditions that are not particularly harsh, the components that were used to initiate it are not difficult to obtain, and it could tolerate a wide variety of functional groups (Scheme 55).⁶⁴

2.1.3. Carbazole. Carbazole is a tricyclic aromatic heterocycle with a core pyrrole ring joined by two benzene rings. The term “carbazole” encompasses tricyclic molecular frameworks and diverse fused carbazoles, including tetracyclic (comprising 5-, 6-, and 7-membered rings), pentacyclic, hexacyclic, and heptacyclic structures.⁷⁸ This distinctive structure endows carbazole and its derivatives with considerable chemical stability, electrical characteristics, and biological activity, making them advantageous in several scientific and commercial applications. Carbazole derivatives are prevalent in both



Scheme 52 Three-component synthesis of tetra-substituted pyrroles without solvents and catalysts.

Scheme 53 Synthesis of pyrrolidinone derivatives using PEG-400 and [bmim]BF₄.

Scheme 56 Chemical structures of bioactive compounds containing a carbazole framework.



natural and manufactured substances, including alkaloids such as murrayanine and ellipticine, which have significant anticancer and antibacterial activities. Carbazoles have demonstrated a diverse range of biological activities including anticancer,⁷⁹ antiepileptics,⁸⁰ antibacterial,⁸¹ anti-inflammatories,⁸² antioxidative,⁸³ analgesic,⁸⁴ antidiarrheal,⁸⁵ antihistaminic,⁸⁶ neuroprotective,⁸⁷ and pancreatic lipase inhibitory⁸⁸ characteristics (Scheme 56).

In the study by P. Zhang *et al.* (2020), they successfully synthesized clausine and glycozoline, alkaloids produced from carbazole, *via* a transition-metal and exogenous-oxidant-free C–H bond amination method (Scheme 57).⁸⁹ This work presented a methodology for conducting environmentally sustainable electrochemical C–H bond dehydrogenative amination. This method has potential to be employed for the production of favored carbazole moieties, which are useful in various contexts. It was underlined that this approach has an eco-friendly and sustainable nature due to its scalability, relatively moderate conditions, and widespread applicability.

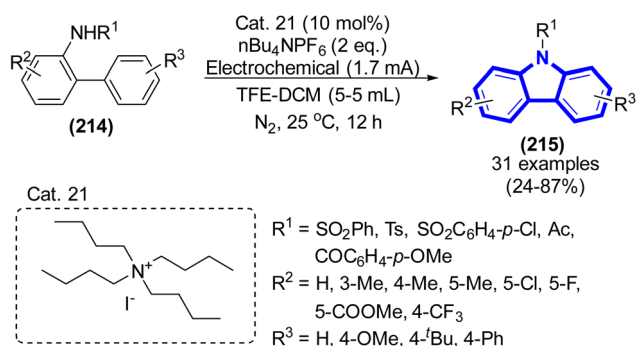
C. Gioia *et al.* (2008) published a protocol for the preparation of carbazole frames from 3-vinylindoles *via* a Diels–Alder reaction in the presence of an acid-base organo-catalyst (Scheme 58).⁹⁰ The activation of 3-vinylindoles for catalytic asymmetric processes can potentially be facilitated by the interaction between a base and the N–H moiety. This was the case if the substrate was used correctly. Diels–Alder reactions

use a wide variety of 1-amino-substituted dienes as the diene substrate.

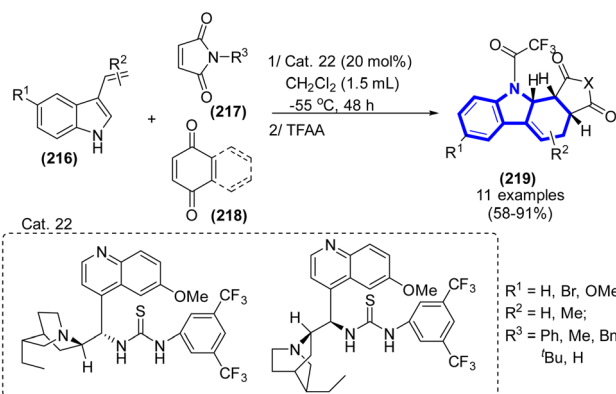
In the study by J. Wang *et al.* (2015), they introduced a novel and comparatively less harmful approach for the production of carbazoles *via* tandem iodocyclization, involving 1,2-alkyl migration and subsequent aromatization. This methodology focused on the synthesis of carbazoles (Scheme 59),⁹¹ providing an approach for the synthesis of iodocarbazoles. This strategy involves performing tandem iodocyclization in conjunction with migration and aromatization. This technique of successive cascading may be carried out quickly at ambient temperature and in a very short period.

S. Yaragorla *et al.* (2018) first reported the production of 3-iodocarbazoles *via* the iodo-cycloisomerization of 1-(indol-3-yl)-1-arylbut-3-yn-2-ols (Scheme 60).⁹² The synthesis commenced with a cascade 5-*endo*-spirocyclization, and subsequently selective 1,2-alkyl migration as the second step in the synthesis process. The solvent employed in this study was AcOEt, and the researchers conducted their work with a focus on atom and step economy.

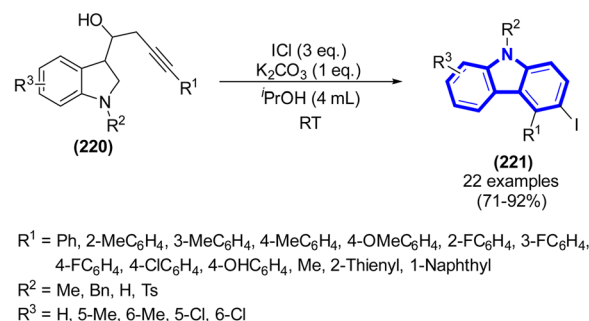
The production of 1,3-dihydroxy-2-carboxycarbazole from the reaction between indole-3-acetic acid and Meldrum acid has undergone significant enhancements through the implementation of an innovative and very efficient methodology, which was introduced by K. Liu *et al.* (2015) (Scheme 61).⁹³



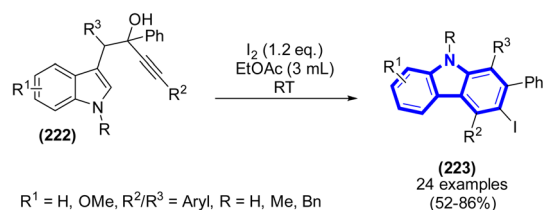
Scheme 57 Synthesis of carbazole-derived alkaloids catalyzed by Cat. 21.



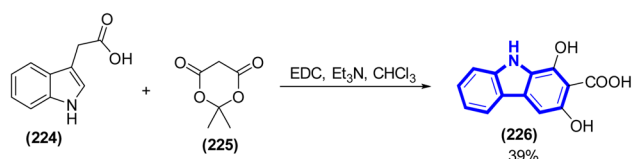
Scheme 58 Synthesis of carbazole frameworks catalyzed by Cat. 22.



Scheme 59 Synthesis of carbazoles catalyzed by ICl and K_2CO_3 .

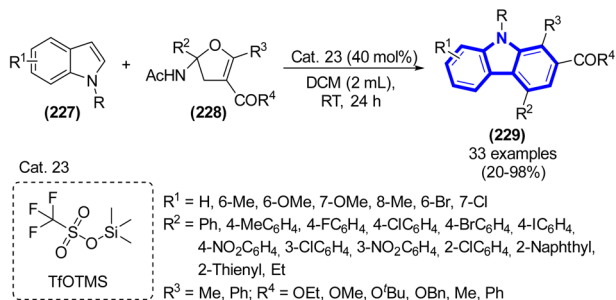


Scheme 60 Synthesis of 3-iodocarbazoles catalyzed by I_2 .



Scheme 61 Synthesis of 1,3-dihydroxy-2-carboxycarbazole.



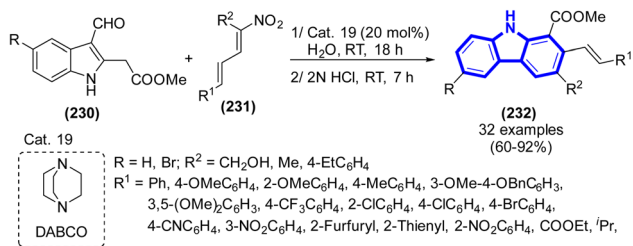


Scheme 62 Synthesis of trisubstituted carbazoles catalyzed by Cat. 24.

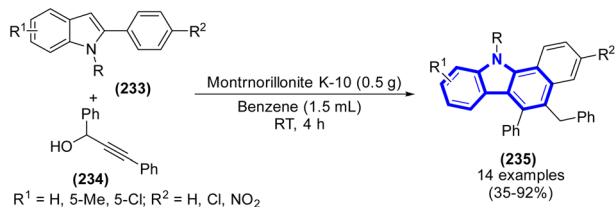
Using the **Cat. 23**-catalyzed ring-opening and annulation of 2-amidodihydrofurans, a safe and efficient method for synthesizing carbazoles was established by J. Zhao *et al.* (2015) (Scheme 62).⁹⁴ This method was based on the ring-opening of 2-amidodihydrofurans at r.t. Synthesis with strong chemical selectivity and regioselectivity may be successfully scaled up using this method.

S. Biswas *et al.* (2015) presented a methodology for the synthesis of multi-substituted carbazoles by reacting α,β -substituted nitro olefins with 2-(3-formyl-1*H*-indol-2-yl)acetates in an aqueous environment, utilizing **Cat. 19** as the catalyst (Scheme 63).⁹⁵ This all-in-one, oxidant-free, mild, environmentally friendly technique may prove to be an effective alternative synthetic strategy for fast access to 3-alkyl-substituted carbazole frameworks that are structurally similar to physiologically active natural carbazoles.

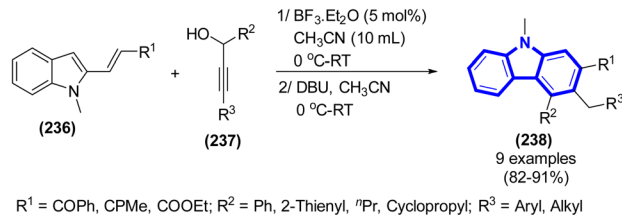
The development of an effective two-step synthesis method to benzo[*a*]carbazoles starting from 2-arylimidoles was accomplished by J. W. Lim *et al.* (2015) (Scheme 64).⁹⁶ Through a series of consecutive propargylations, propargyl-allenyl isomerization,



Scheme 63 Synthesis of substituted carbazoles catalyzed by Cat. 19.



Scheme 64 Synthesis of benzo[*a*]carbazoles catalyzed by montmorillonite K-10.



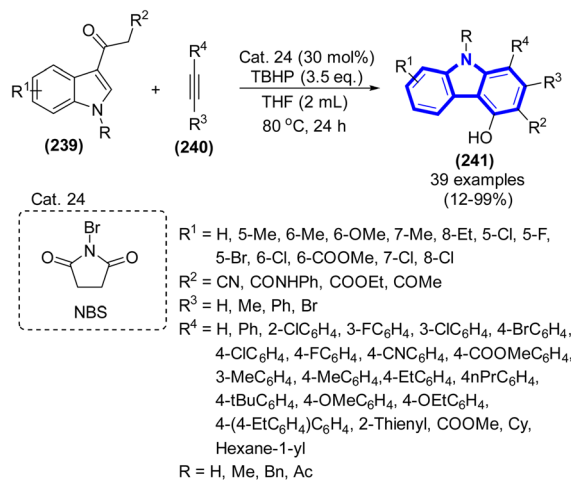
Scheme 65 Synthesis of substituted carbazoles.

and simultaneous 6 π -electrocyclization procedure, it was possible to achieve the effective synthesis of benzo[*a*]carbazoles using 2-arylimidoles as the starting material.

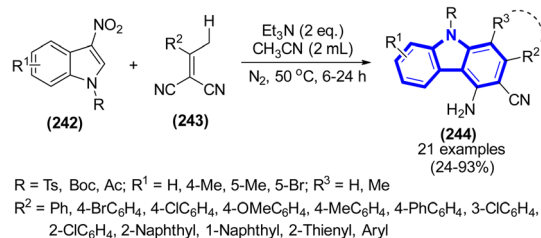
This innovative one-pot [4 + 2]-benzannulation technique was employed to obtain substituted carbazoles, which was illustrated by C. Raji Reddy *et al.* (2016) (Scheme 65).⁹⁷ The aforementioned technique has numerous advantages, including the utilization of moderate and metal-free reaction conditions, a wide range of applicable substrates, and the availability of easily accessible starting materials, ensuring its accessibility.

An intermolecular annulation of acetyl indoles with alkynes catalyzed by **Cat. 24** was created by H. Wang *et al.* (2017) (Scheme 66).⁹⁸ Conditions that were mild and devoid of metals allowed the formation of carbazoles smoothly.

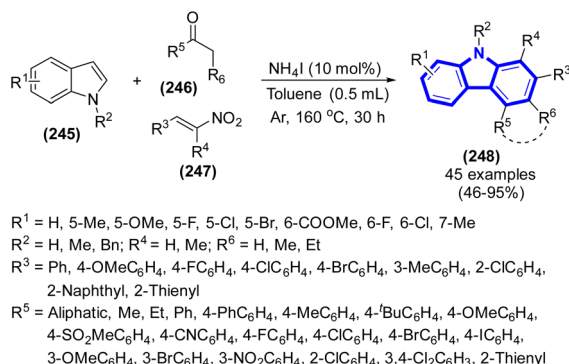
D. Cao *et al.* (2018) devised a broad methodology for the synthesis of 4-carbazolamine derivatives by employing a vinyl-ogous Michael addition/cyclization/isomerization/elimination reaction between 3-nitroindoles and alkylidene malononitriles



Scheme 66 Synthesis of carbazoles catalyzed by Cat. 24.



Scheme 67 Synthesis of multi-substituted 4-carbazolamine derivatives.

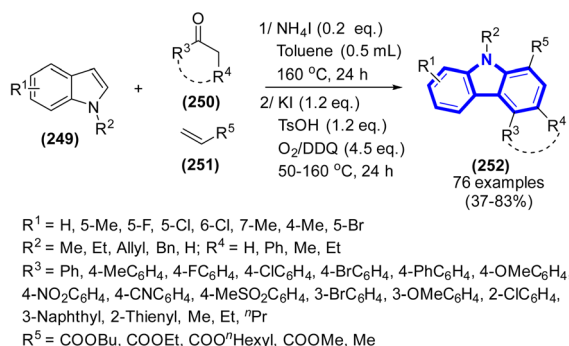
Scheme 68 Synthesis of carbazoles catalyzed by NH_4I .

(Scheme 67).⁹⁹ This method did not require the use of transition metals in any step of the process.

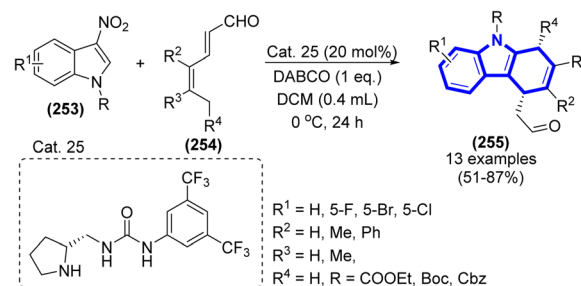
Under metal-free conditions, an effective method for the conversion of indole to carbazole was created by S. Chen *et al.* (2016) (Scheme 68).¹⁰⁰ In this method, indoles, ketones, and nitroalkenes are assembled into a single compound using a three-component technique. The manufacture of a varying range of functionalized carbazoles was demonstrated by the implementation of the indole-to-carbazole process, with yields ranging from satisfactory to outstanding. This method has several advantages, such as metal-free reaction condition, excellent regioselectivity, wide functional group tolerance, and readily available starting materials.

An effective one-pot method for converting indole-to-carbazole that only requires two steps was discovered by S. Chen *et al.* (2017) (Scheme 69).^{101,102} The very efficient tri-component synthesis of multi-substituted carbazoles commences with the use of indoles, ketones, and alkenes, with oxygen serving as the oxidizing agent in the reaction. Oxygen was the only oxidant that was used in this process, which did not include any transition metals. The current approach makes it possible to assemble a wide range of substituted carbazole products virtually. It also has a high degree of regioselectivity and can tolerate several functional groups.

Y. Li *et al.* (2016) presented the formal $[4 + 2]$ cycloaddition of 3-nitroindoles, which resulted in the formation of chiral dihydrocarbazole frames (Scheme 70).¹⁰³ Chiral dihydrocarbazole scaffolds could be produced in yields ranging from good to



Scheme 69 Synthesis of carbazole frameworks.

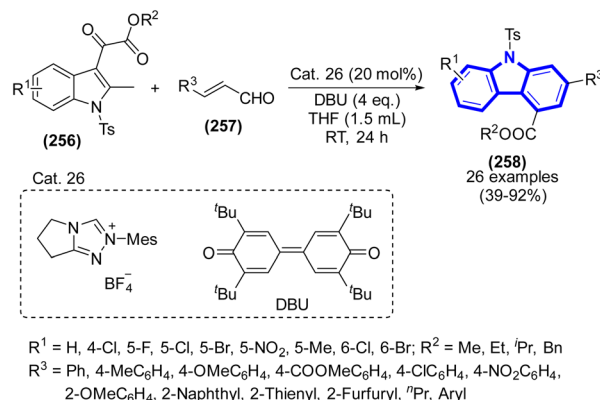


Scheme 70 Synthesis of chiral dihydrocarbazole frameworks catalyzed by Cat. 25.

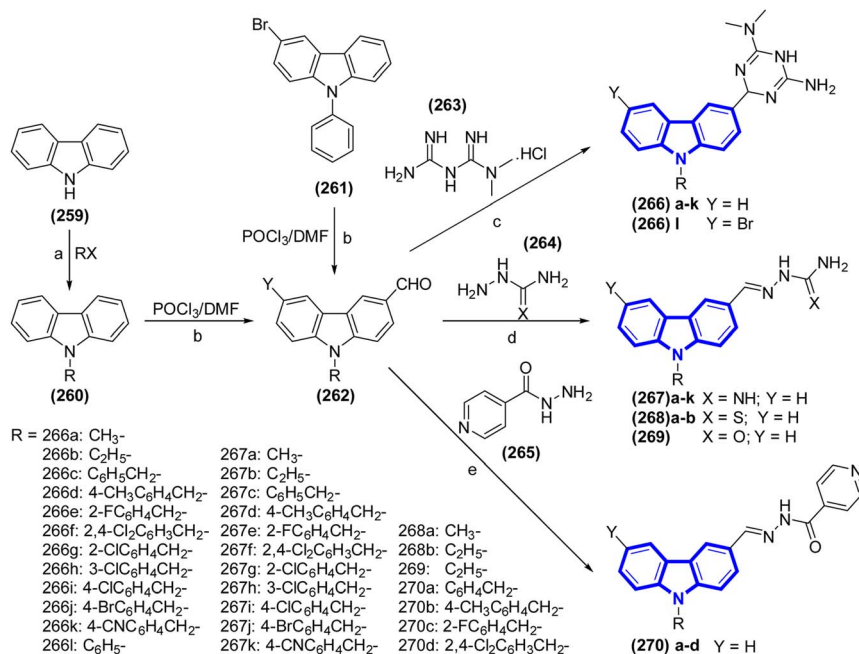
outstanding (up to 87%) and enantioselectivities ranging from modest to high (up to 97% ee) when 3-nitroindoles were used in conjunction with an organocatalyst. Under moderate reaction conditions, a $[4 + 2]$ cycloaddition/elimination cascade occurred throughout the reaction.

The synthesis of carbazoles *via* carbene-catalyzed oxidative formal $[4 + 2]$ -annulation of enals with 2-methyl-3-oxoacetate indoles has been established as an efficient method. This technique, introduced by D. Liu *et al.* (2018), provides a direct and swift pathway for the synthesis of carbazoles (Scheme 71).¹⁰⁴ Also, this metal-free reaction has a wide substrate tolerance under moderate conditions.

Hu-Ri Piao *et al.* (2021) proposed a method for the design, synthesis and evaluation of carbazole derivatives as potential antimicrobial agents (Scheme 72).¹⁰⁵ Most of the compounds had significant inhibitory effects against several bacterial strains, including a multidrug-resistant clinical isolate and one fungal strain, with MICs ranging from 0.5 to 16 mg mL^{−1}. Compounds **266f** and **267d** exhibited the highest inhibitory effects, with MICs ranging from 0.5 to 2 mg mL^{−1}. Structure–activity relationship analysis and docking experiments indicated that the dihydro triazine moiety enhances the antibacterial efficacy and diminishes the toxicity of the carbazole derivatives. *In vitro* enzyme activity studies indicated that the binding of compound **266f** to dihydrofolate reductase may explain the antibacterial action.



Scheme 71 Synthesis of carbazoles catalyzed by Cat. 26.



Scheme 72 Synthesis and evaluation of carbazole derivatives.

Wu *et al.* (2017) described a novel transition metal-free one-pot approach for the synthesis of *N*-arylcarbazoles (Scheme 73). In the presence of atmospheric oxygen, anilines were reacted with cyclohexanones using KI as a promoter, CH₃SO₃H as an acid, and toluene as the solvent. Subsequently, iodine was added and the mixture heated at 160 °C to get *N*-arylcarbazoles. In this transformation, the nitrogen sources were aniline and cyclohexanone, with the aryl ring and the additional two aryl rings specified accordingly. A series of derivatives was synthesized, with yields in the range of 41% to 90%. A potential mechanism for this transformation was also suggested.¹⁰⁶

Guo and colleagues (2012) successfully developed a metal-free and direct approach for the *N*-arylation of carbazoles using diaryliodonium salts. The reaction occurred between carbazoles and diaryliodonium salts to obtain the desired products. In this reaction, KO^tBu was used as the base and toluene as the solvent at 50 °C. A series of derivatives was synthesized, with yields ranging from traces to 92% (Scheme 74).¹⁰⁷

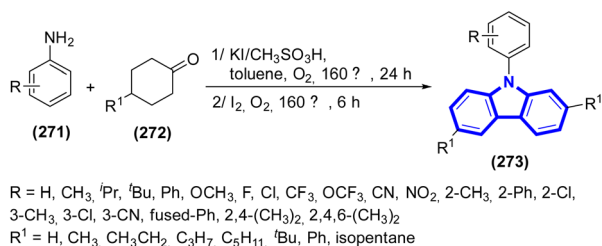
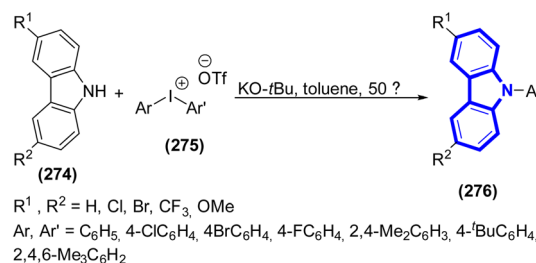
Chakrabarty *et al.* (2013) suggested a methodology for synthesizing carbazoles using aryne and nitrosoarenes. The major product was treated with nitrosoarenes to get

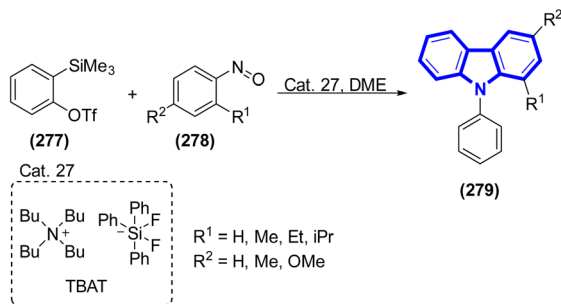
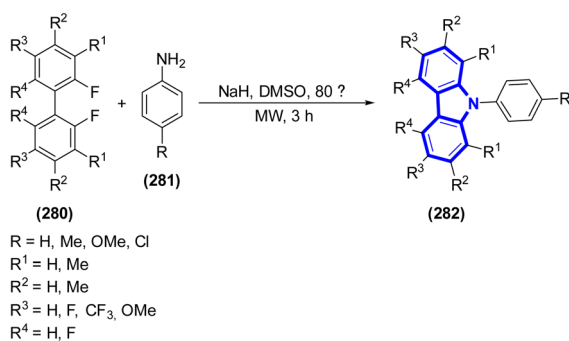
N-arylcarbazoles. The procedure used Cat. 27 and dimethyl ether (DME) solvent, yielding the major products in yields of 51–76% (Scheme 75).¹⁰⁸

In 2021, Feofanov and colleagues reported a technique for the synthesis of *N*-arylated carbazole that did not involve the use of transition metals. In the absence of transition metals, 2,2'-difluoro-1,1'-biphenyls were subjected to treatment with *para*-substituted anilines, generating the products with a yield in the range of 22–85%. NaH was used in dimethyl sulfoxide solvent at a temperature of 80 °C to carry out the reaction (Scheme 76).¹⁰⁹

2.2. Five-membered heterocycles containing two nitrogen atoms

2.2.1. Imidazolidine. Imidazolidine is a saturated five-membered heterocyclic molecule including two nitrogen atoms located at positions 1 and 3. It is structurally similar to imidazoline and imidazole, although it diverges owing to its completely saturated ring structure, which affects its chemical reactivity and biological activity.¹¹⁰ Imidazolidine and its derivatives have attracted considerable attention in medicinal chemistry owing to their diverse pharmacological

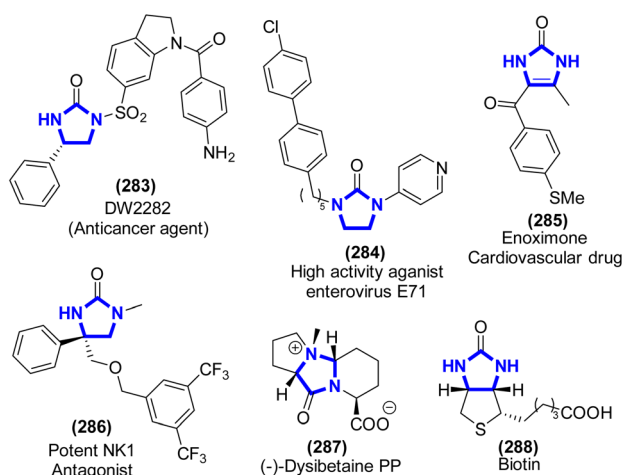
Scheme 73 Synthesis of *N*-arylcarbazoles using transition metal-free one-pot reaction.Scheme 74 Synthesis of *N*-arylcarbazoles using diaryliodonium salts.

Scheme 75 Synthesis of *N*-arylcarbazoles catalyzed by Cat. 27.

Scheme 76 Synthesis of arylated carbazoles.

characteristics. Imidazolidines participate in a variety of crucial biological processes, including fungicidal,¹¹¹ antibacterial,¹¹² tyrosine phosphatase inhibitors,¹¹³ and antiviral¹¹⁰ activities, which together with *N,N'*-dibenzyl-2-arylimidazolidines, *N,N'*-bisaminoalkylimidazolidines, and *N,N*-dihydroxyphenylimidazolidines have attracted significant interest (Scheme 77).^{114,115}

A. N. Komogortsev *et al.* (2021) published a simple procedure for synthesizing new imidazole-2-thione derivatives

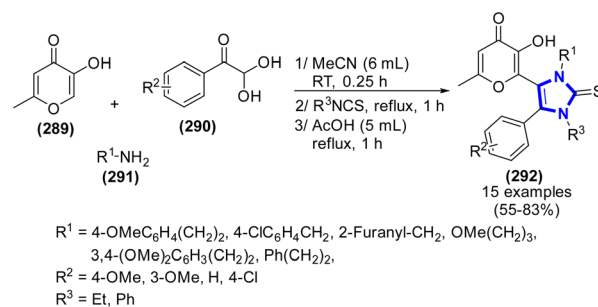


Scheme 77 Chemical structures of bioactive compounds containing an imidazolidine framework.

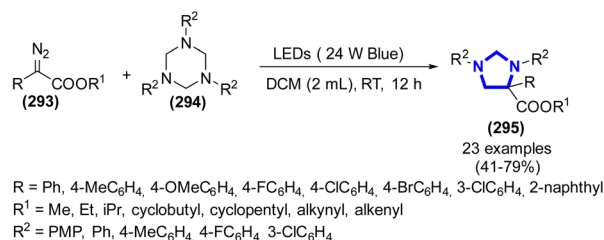
incorporating allomaltol fragments *via* a one-pot three-step reaction among allomaltol, arylglyoxals, primary amines, and alkyl or aryl isothiocyanates (Scheme 78).¹¹⁶ In addition to moderate reaction conditions, atom economy, and rapid workup technique that does not need any purification, this procedure offers several other advantages. Moreover, XRD was used to identify the structures of an intermediate and one of the products.

Simple modification of the reaction solvent for the preparation of a variety of imidazolidine frameworks under blue LED irradiation, leading too good to excellent yields, was researched by X. Cheng *et al.* (2021) (Scheme 79).¹¹⁷ The formation of the products was achieved through the cycloaddition reaction between α -diazo esters and hexahydro-1,3,5-triazines in dichloromethane (DCM) at ambient temperature for a duration of 12 h, without the use of any catalyst. More importantly, based on the findings of the control tests and density functional theory calculations, a viable reaction mechanism was presented.

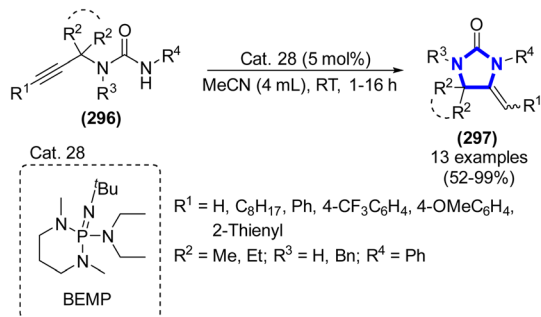
A. Casnati *et al.* (2019) employed phosphazene base Cat. 28 as an organo-catalyst for the synthesis of imidazolidin-2-ones and imidazole-2-ones from propargylic urea through an intramolecular hydroamidation (Scheme 80).¹¹⁸ When 5 mol% of Cat. 28 and 4 mL of MeCN were used and the reaction was conducted at r.t., the target product were obtained in moderate to excellent yields. Based on the findings of density functional theory (DFT), it was determined that the predominant pathway for the production of imidazole-2-ones involves a base-mediated isomerization process, leading to the formation of an allenamide intermediate.



Scheme 78 Synthesis of imidazole-2-thione derivatives.



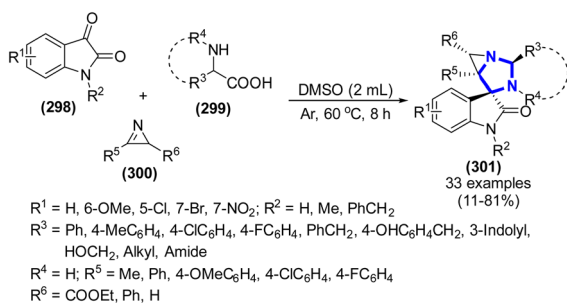
Scheme 79 Visible light-promoted synthesis of imidazolidine frameworks without a catalyst.



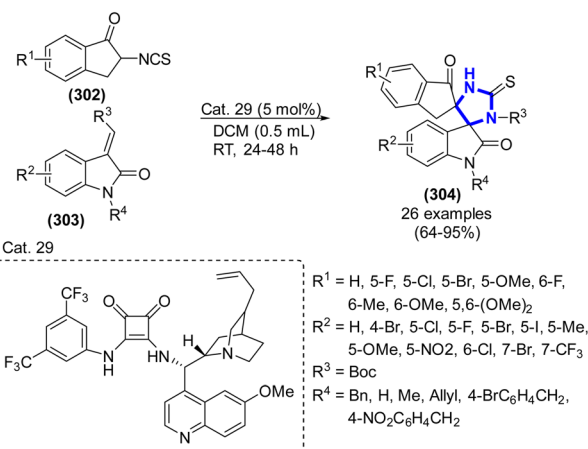
Scheme 80 Synthesis of imidazole-2-ones catalyzed by Cat. 28.

A. Angyal *et al.* (2019) documented a one-step three-component reaction involving α -amino acids, isatins, and 2H-azirines, resulting in the synthesis of a range of 1,3-diaspiro[bicyclo[3.1.0]hexane]oxindole frameworks (Scheme 81).¹¹⁹ When DMSO was employed as the solvent at a temperature of 60 °C and the reaction time of 8 h, the products were obtained in moderate to high yields. This methodology showed several advantages such as endoselectivity, compatibility of a wide range of substrates, gentle reaction conditions, and high yields.

In a study conducted by B. Zhao *et al.* (2018), a novel catalyst derived from 1-indanone-derived isothiocyanate was



Scheme 81 Synthesis of 1,3-diaspiro[bicyclo[3.1.0]hexane]oxindole frameworks.



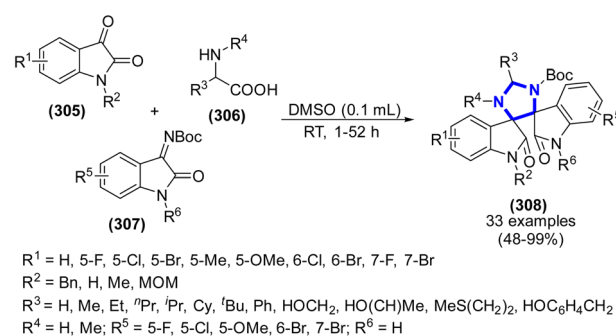
Scheme 82 Synthesis of bispirocyclic indanone-thioimidazolidine-oxindoles catalyzed by Cat. 29.

investigated for its application in the diastereo- and enantio-selective Mannich/cyclization reaction. The objective of this research was to synthesize a series of bispirocyclic indanone-thioimidazolidine-oxindoles, which possess two neighboring spiro-quaternary stereocenters (Scheme 82).¹²⁰ With **Cat. 29** (5 mol%), DCM as the solvent, and r.t., the desired product yields were good to outstanding after 24–48 h. Moreover, the effectiveness of the reaction was assessed through a large-scale reaction, giving 82% yield (>25 : 1 dr, >99% ee).

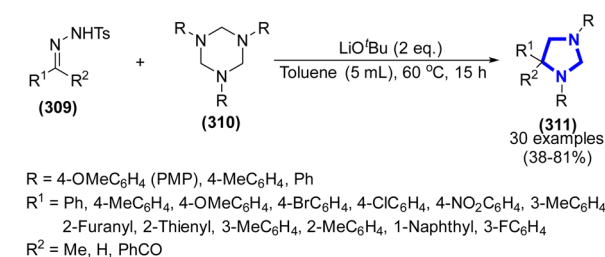
Y.-L. Qian *et al.* (2017) conducted a 1,3-dipolar cycloaddition reaction using isatin, amino acid, and isatin-derived ketimine, resulting in the synthesis of dispirooxindole-imidazolidine frameworks. This reaction, which does not involve the use of additives, allows the formation of a diverse array of frameworks containing vicinal quaternary carbon centers (Scheme 83).¹²¹ This transformation possesses several advantages, including a wide range of applicable substrates, mild reaction conditions, and high product yields ranging from good to extraordinary. The synthesis was also performed on the gram scale, resulting in a product yield of 94% and a diastereomeric ratio of 85 : 15.

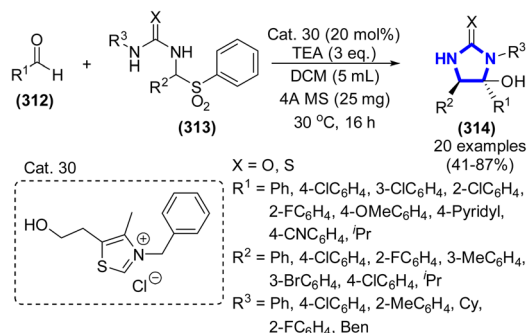
P. Liu *et al.* (2017) reported a new technique to synthesize imidazolidines *via* the [2 + 1 + 2]-cycloaddition process between tosylhydrazones and hexahydro-1,3,5-triazines using LiO^tBu as the catalyst and toluene as the solvent (Scheme 84).¹²² The advantageous features of this method are metal-free, modest to fine yields, and no need to separate the tosylhydrazones. Notably, the dual functions of LiO^tBu were demonstrated to either liberate the diazo or boost the cycloaddition.

A combination of thiazolium salt/triethylamine (**Cat. 30**) was found to be effective for initiating the domino process to prepare a variety of imidazolidine-2-thiones by G. Di Carmine



Scheme 83 Synthesis of various dispirooxindole-imidazolidine frameworks.

Scheme 84 Synthesis of imidazolidines catalyzed by LiO^tBu.

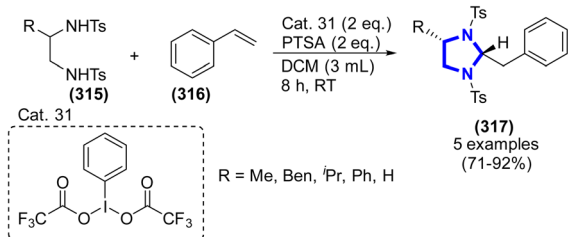


Scheme 85 Synthesis of imidazolidine-2-thiones catalyzed by Cat. 30.

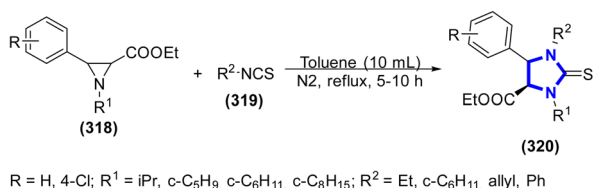
et al. (2017) (Scheme 85).¹²³ The reaction was performed *via* the intramolecular aza-acetalization reaction between aldehydes and benzylidenethioureas, leading to good to outstanding product yields. Moreover, this approach is considered diastereoselective (up to 99 : 1 dr) and effective because of the excellent yield of up to 95% in the gram-scale reaction.

P. V. Balaji *et al.* (2016) investigated the aminooxygenation between 1,2-diamine derivatives and styrene to form geminal diaminated imidazolidine utilizing Cat. 31 as the catalyst (Scheme 86).¹²⁴ The target compounds were obtained in high yields after an 8 h reaction at r.t. in *p*-TSA and DCM as the solvent. This protocol is advantageous because of its high diastereoselectivity, good yields, and absence of metal.

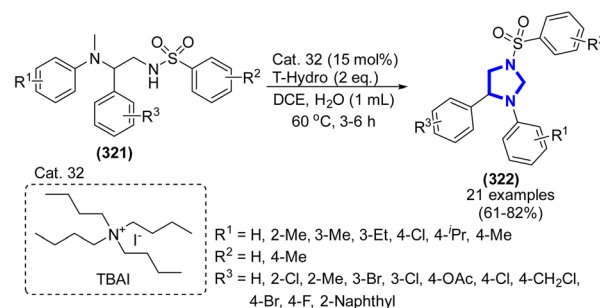
M. A. Tabarki *et al.* (2016) reported the application of a series of *N*-substituted isothiocyanates for the ring opening of *N*-alkylaziridine-2-carboxylates to create *trans*-imidazolidine-2-thiones without a catalyst (Scheme 87).¹²⁵ This methodology showed many advantages such as regio- and stereo-selectivity, without additives, and high product yields. Furthermore, it was shown that the generation of the products was determined



Scheme 86 Synthesis of geminal diaminated imidazolidine catalyzed by Cat. 31.



Scheme 87 Synthesis of *trans*-imidazolidine-2-thiones without a catalyst.

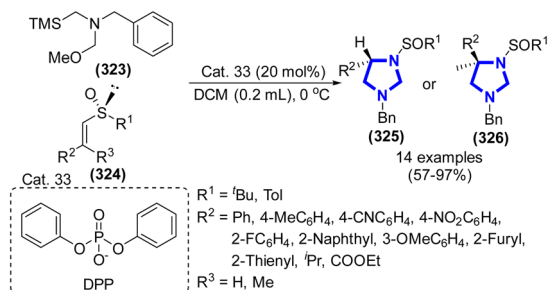


Scheme 88 Synthesis of imidazolidines catalyzed by Cat. 32.

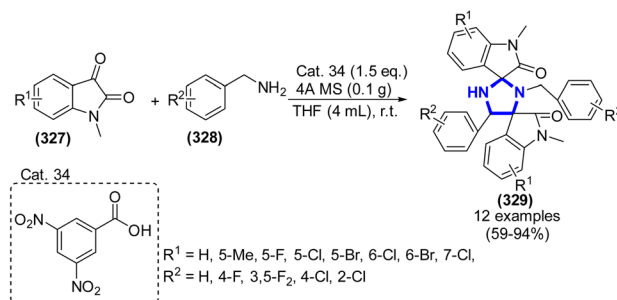
by the steric hindrance and electronic influence of the *N*-substituents in the substrates.

V. Satheesh *et al.* (2016) employed Cat. 32 as a catalyst and 'BuOOH in water (T-Hydro) as an oxidizing agent for the preparation of imidazolidines (Scheme 88).¹²⁶ Numerous *N*-aryl and 2-aryl substituted compounds were examined, resulting in the synthesis of products with favorable yields. The method in question exhibits several notable characteristics, including the use of water as the solvent, the absence of metals, regioselectivity, ease of product separation, and a wide range of applicable substrates.

Under the catalysis of Cat. 33, DCM as a solvent, and a temperature of 0 °C, the asymmetric 1,3-dipolar reaction between methanamines and methyl aryl ketimines to form *N*-sulfinylaldimines with modest to outstanding yields was reported by C. Izquierdo *et al.* (2016) (Scheme 89).¹²⁷ Importantly, in the gram-scale of 5.3 mmol, the products were produced in high yields (83%) with high diastereoselectivity (>98 : 2).



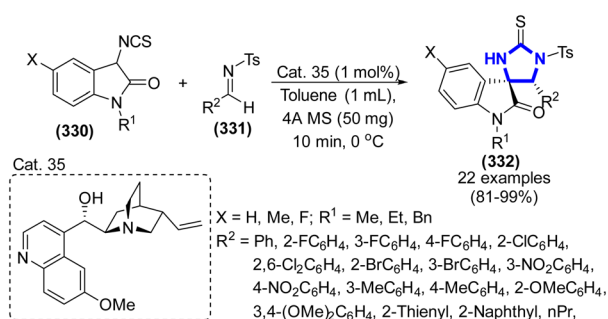
Scheme 89 Synthesis of *N*-sulfinylaldimines catalyzed by DPP.



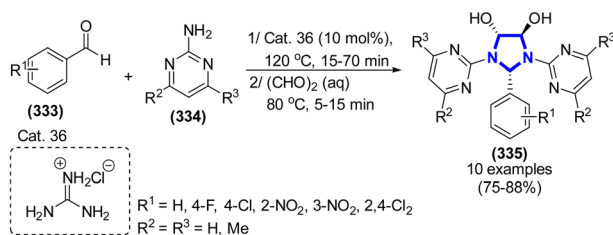
Scheme 90 Synthesis of dispirooxindole-imidazolidines catalyzed by Cat. 34 in the presence of 4 Å MS.

Y.-H. Sun *et al.* (2015) reported the preparation of a wide range of dispirooxindole-imidazolidine frameworks *via* the self-1,3-dipolar cycloaddition of *N*-methylisatins and benzylamines in the presence of 3,5-dinitrobenzoic acid and 4 Å MS in THF as the solvent at r.t. (Scheme 90).¹²⁸ It was also the first time that a range of new dispirooxindole-imidazolidines with two quaternary carbons and three stereogenic centers were synthesized in high yields and with exceptional stereoselectivities.

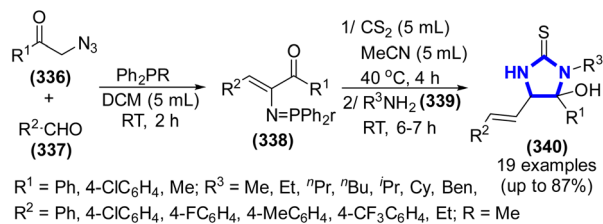
M. Bai *et al.* (2015) employed commercial quinine as a catalyst for the domino Mannich-cyclization reactions of 3-isothiocyanato oxindoles and imines to synthesize spiro [imidazolidine-2-thione-4,30-oxindole] skeletons



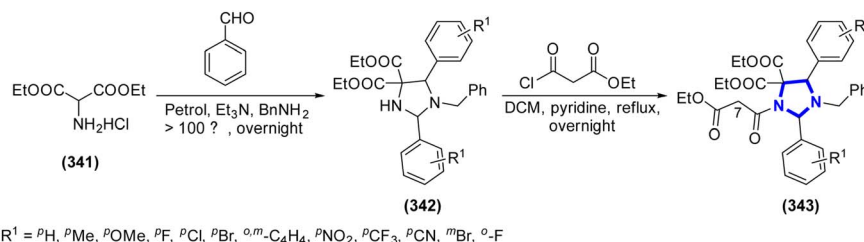
Scheme 91 Synthesis of spiro[imidazolidine-2-thione-4,30-oxindole] skeletons catalyzed by Cat. 35.



Scheme 92 Synthesis of imidazolidines catalyzed by Cat. 36.



Scheme 93 Synthesis of imidazoline-2-thione derivatives.



Scheme 94 Synthesis of imidazoline-2-thione derivatives.

(Scheme 91).¹²⁹ The intended products were obtained in high yields under ideal reaction conditions. This method exhibited notable characteristics, including remarkable diastereo- and enantio-selectivity (achieving ratios of up to 99:1 dr and 97% ee), the ease of obtaining the catalyst, and the low amount of catalyst required (1 mol%).

A cyclo-condensation reaction between heteroarylamines and benzaldehyde derivatives to form imidazolidines with guanidinium chloride in glyoxal was reported by A. Olyaei *et al.* (2013) (Scheme 92).¹³⁰ This methodology, which is now being used, has several advantages, including high efficiency and universality, distinct reaction profiles, and a one-pot two-step synthetic procedure. Additionally, this was the first time that heteroarylamines, arylaldehydes, and glyoxal were used in a reaction to obtain products that were needed.

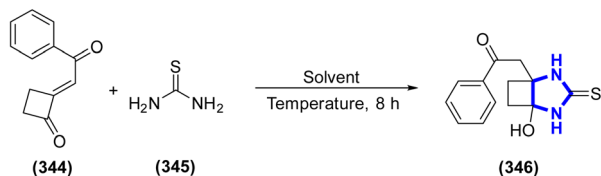
A wide range of imidazoline-2-thiones derivatives created by aliphatic primary amines and vinyliminophosphorane, which was the product of the reaction between α -azidoketone with aromatic aldehydes, were reported by H. Xie *et al.* (2012) (Scheme 93).¹³¹ The advantages of this method are its simple procedure, moderate reaction conditions, excellent yields, and readily available starting material.

In a kinetically regulated method, the Dieckmann ring closure of hemiaminal ether and imidazolidines efficiently yields bicyclic substrates using a chemoselective ring closure. Additionally, hemiaminal and amination heterocyclic systems containing $-NCH(Ar)X-$ ($X = O$ and NR) are accessible. According to the findings by Moloney *et al.* (2023), this procedure was not unsuccessful. The activity of these systems is at its highest in a particular well-defined region of chemical space (Scheme 94). These systems demonstrate significant antibacterial activity, at least against Gram-positive pathogens.¹³²

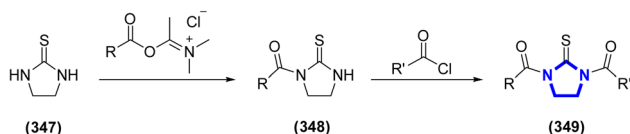
Angelo Frongia and colleagues (2024) indicated that the $[3 + 2]$ -annulation process involving thiourea, an ambident dinucleophile, and cyclobutanone, which features a new pull-pull alkene system, theoretically exhibits various chemo- and regio-selectivity profiles. Their report outlined the efficient synthesis of cyclobutanones and demonstrated their reaction with thioureas, which was mechanistically explained by the relevant steric and electronic effects. The $[3 + 2]$ -annulation occurs under moderate, additive-free conditions, yielding previously unreported cyclobutane-fused imidazolidine-2-thione and thiazolidine-2-imines in satisfactory yields (Scheme 95).¹³³

Andrea Spallarossa and colleagues (2022) demonstrated that imidazolidine-2-thione interacted with atypical Vilsmeier adducts derived from dimethylacetamide and other acyl





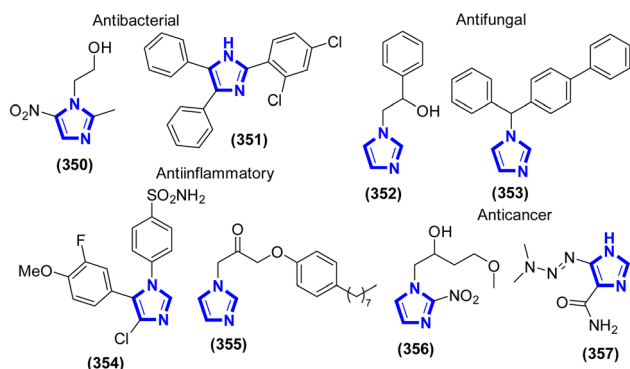
Scheme 95 Synthesis of 2-(phenacylethylidene)cyclobutanones.



Scheme 96 Synthesis of mono- and di-acylated imidazolidine-2-thione derivatives.

chlorides exhibiting distinct electronic and steric properties (Scheme 96). The type of acyl chloride reagent influences the synthesis of mono- or di-acylated thiourea derivatives. Semi-empirical computer simulations were used to identify the influencing component of the reaction. The reaction of benzoylimidazolidin-2-thiones with acyl chlorides was performed to evaluate the chemical versatility of mono-acylated derivatives, which have therapeutic significance. The derivatives of a restricted library of asymmetric di-acyl thioureas did not exhibit cytotoxic effects on SKOV-3 and MCF-7 cancer cell lines. Furthermore, *in silico* analyses demonstrated robust pharmacokinetics and drug-like characteristics for mono- and di-acylated thioureas. These features indicate that the synthesized compounds are attractive non-cytotoxic chemical frameworks for medicinal chemistry.¹³⁴

2.2.2. Imidazole (imidazoline). Imidazole, also known as 1,3-diaza-2,4-cyclopentadiene, is a flat cyclic structure composed of five atoms, consisting of three carbon (C) atoms and two nitrogen (N) atoms, located at the 1 and 3 positions in the ring. Some representatives of this framework are histidine and histamine. Imidazoles have many applications because of their antifungal,¹³⁵ anti-protozoan,¹³⁶ and anti-hypotensive¹³⁷



Scheme 97 Chemical structures of bioactive compounds containing an imidazole framework.

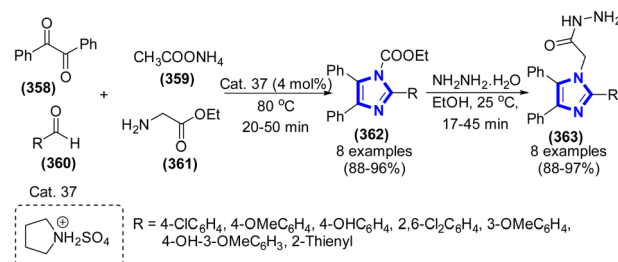
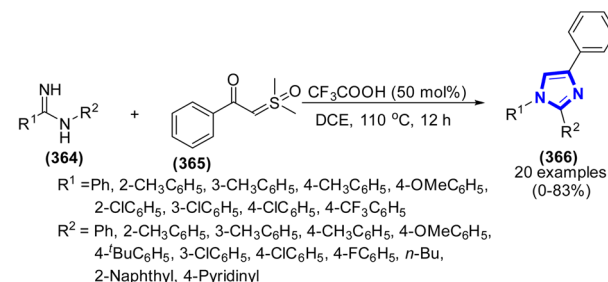
properties. Moreover, imidazole derivatives are also used in photography and electronics (Scheme 97).¹³⁸

A. A. Abdelhamid *et al.* (2020) employed IL pyrrolidinium hydrogen sulfate as a catalyst for the one-pot preparation of 1*H*-imidazole-1-carboxylates from a multi-component mixture of 1,2-diphenylethane-1,2-dione, NH_4OAc , aromatic aldehydes, and ethyl glycinate hydrochloride (Scheme 98).¹³⁹ After 20–50 min of reaction at 80 °C, the desired product yields were good to outstanding. Then, the intermediate was used to react with hydrazine hydrate to form 1*H*-(imidazole-1-yl)acetohydrazides at 25 °C in EtOH after 17–45 min, leading to good to excellent yields. This protocol is highly advantageous due to its short reaction time, ease of implementation, nonchromatographic approach, and high yields. Moreover, the *in vivo* experiment demonstrated the antioxidant action of the products.

Y. Tian *et al.* (2019) published a report on the acid-catalyzed synthesis of imidazole derivatives from amidines and sulfoxonium ylides in DCE at 110 °C after 12 h (Scheme 99).¹⁴⁰ When CF_3COOH was employed as the catalyst, the product yields were boosted. The advantages of this method are its large scope of aromatic functional groups, strong regioselectivity, cost-effectiveness, and ecologically benign property.

M. R. Albayati *et al.* (2019) described a method to use Cat. 38 as the catalyst for the preparation of a series of multi-substituted imidazole derivatives through the mixing of benzil, NH_4OAc , phenethylamine, or $\text{C}_4\text{H}_9\text{NH}_2$ with various aromatic aldehydes (Scheme 100).¹⁴¹ The main advantages of this approach are its relatively rapid reaction times, high yield, and simplicity of stabilization.

A [3 + 2] heterocycloaddition approach for the synthesis of cyanoaryl-imidazoles from cyanobenzene derivatives and

Scheme 98 Synthesis of ethyl-4,5-diphenyl-2-(substituted)-1*H*-imidazole-1-carboxylate catalyzed by Cat. 37.

Scheme 99 Synthesis of imidazole derivatives catalyzed by trifluoroacetic acid.

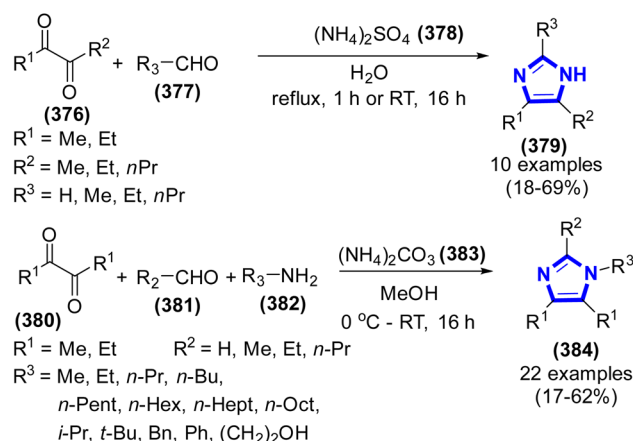
Review

azomethine ylides catalyzed by trifluoroacetic acid, followed by the *in situ* oxidation of the crude product to form 4-arylimidazole frameworks was demonstrated by M. Beuvin *et al.* (2018) (Scheme 101).¹⁴² Computational results indicated that the heterocycloaddition process was preferred from both a kinetic and thermodynamic standpoint.

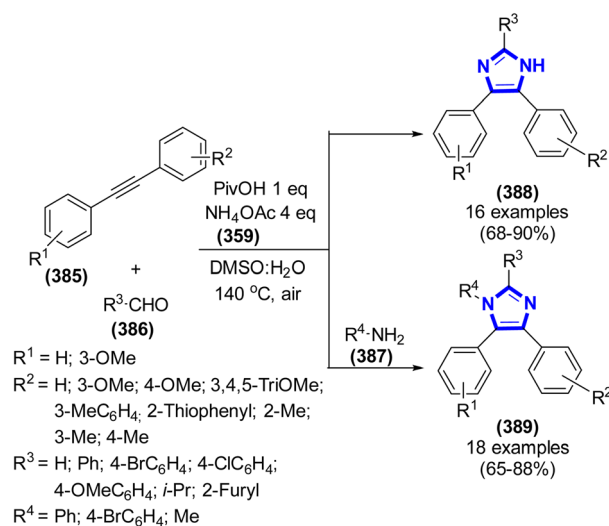
S. Evjen *et al.* (2017) showed a report about the combination of alkyldicarbonyl compounds, as well as appropriate alkyl aldehydes and ammonia to create a series of polyalkylated N-H and N-alkyl imidazoles (Scheme 102).¹⁴³ The main advantages of this approach are its readily available starting materials, high yield, and adaptability for mass production at a reasonable cost.

In the study reported by C.-Y. Chen *et al.* (2013), they demonstrated a multicomponent reaction among internal alkynes, aldehydes, and anilines. The reaction was facilitated by pivalic acid and conducted in a combination of water and DMSO. The outcome of this reaction was the formation of imidazole moieties (Scheme 103).¹⁴⁴ This approach is a feasible alternative to the classic transition metal-catalyzed procedures because of its ambient conditions, easy work-up technique, and excellent product yields. Furthermore, some of the products outperformed their analogs in terms of fluorescence emission and UV absorption.

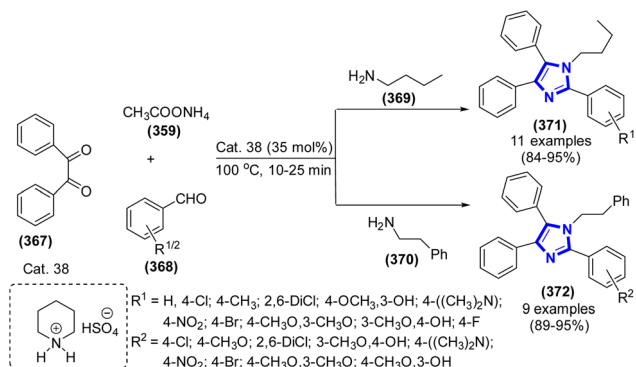
G. Mloston *et al.* (2011) introduced the synthesis of two imidazoline-frameworks *via* the reaction of ethyl 2-hydroxyimino-3-oxobutanoate, racemic amino alcohols, and formaldehyde in EtOH as the solvent (Scheme 104).¹⁴⁵ The experimental procedure employed in this study was devoid of



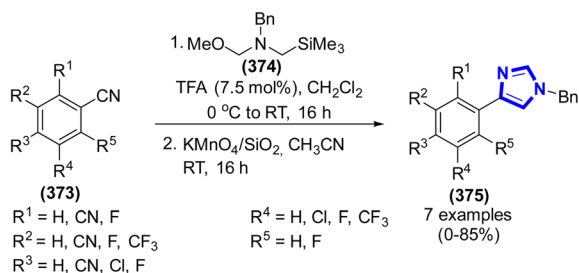
Scheme 102 Synthesis of N-alkyl/aryl imidazoles.



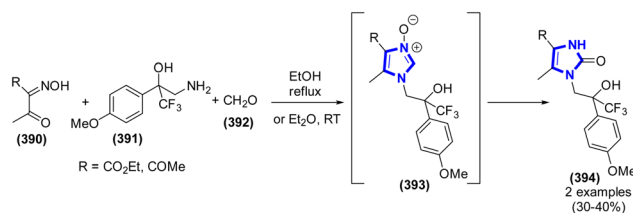
Scheme 103 Synthesis of imidazole moieties catalyzed by pivalic acid.



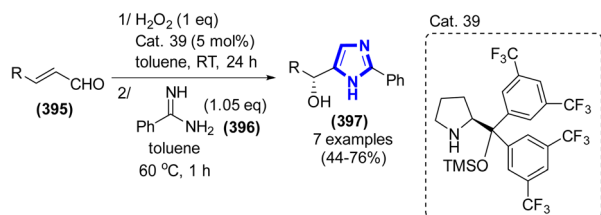
Scheme 100 Synthesis of multi-substituted imidazole derivatives catalyzed by Cat. 38.



Scheme 101 Synthesis of 4-aryl imidazole frameworks catalyzed by trifluoroacetic acid.



Scheme 104 Synthesis of imidazolone frameworks in ethanol.



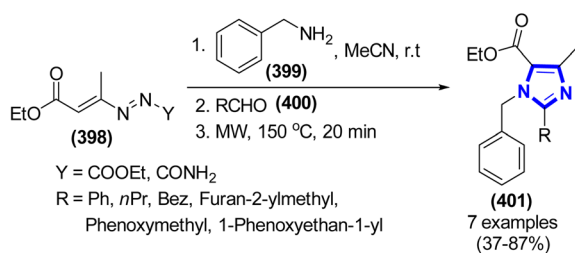
Scheme 105 Synthesis of optically active 2,5-disubstituted imidazoles catalyzed by Cat. 39.

annulation. The technique detailed in the study has several advantages, including the utilization of low catalyst loadings, commercially and readily available starting materials, and the implementation of moderate reaction conditions.

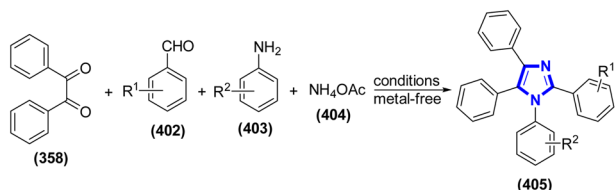
L. Preti *et al.* (2010) reported the microwave-assisted 1,5-electrocyclization of azavinyl azomethine ylides using 1,2-diaza-1,3-dienes, which led to the formation of a diverse range of 3*H*-imidazole-4-carboxylates (Scheme 106).¹⁴⁷ It is worth noting that this procedure is simple and effective without isolating the intermediates and it can be conducted in a multicomponent manner.

Owing to the efficacy and simplicity of the four-component reaction involving 1,2-diketones, aldehydes, primary amines, and ammonium acetate, it has been recognized as a viable approach for synthesizing 1,2,4,5-tetrasubstituted imidazoles (Scheme 107). This method had received significant attention from scientists around the world. Many research works have been published using various catalysts such as silica gel/ NaHSO_4 support,¹⁴⁸ silica-supported perchloric acid,¹⁴⁹ mercaptopropylsilica,¹⁵⁰ poly(AMPS-co-AA),¹⁵¹ and zeolite BEA,¹⁵² and catalyst-free procedure.¹⁵³

1-Substituted, 2-aryl, 4,5-phenylimidazole was synthesized by Bourissou *et al.* (2000) utilizing benzil, benzonitrile, and primary amines on the surface of silica gel under solvent-free



Scheme 106 Synthesis of 2-substituted 3*H*-imidazole-4-carboxylates under MW.



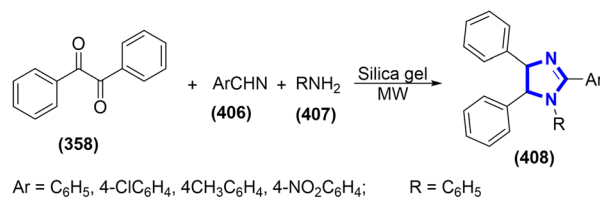
Scheme 107 Synthesis of 1,2,4,5-polyimidazoles catalyzed by metal-free catalysts.

conditions. The MW was used to produce modest efficiencies (Scheme 108).¹⁵⁴

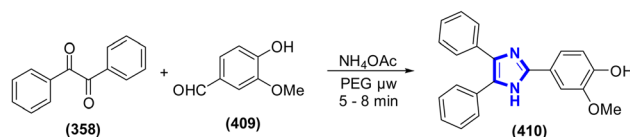
Benzyl, 3-methoxy-4-hydroxybenzaldehyde, and ammonium acetate were used in the synthesis of triaryl-imidazole by Nalage *et al.* (2010). The synthesis was carried out in the presence of polyethylene glycol and subjected to MW for a period of 5 min. These researchers achieved yields of up to 71% (Scheme 109).¹⁵⁵

Acetic acid, aromatic aldehydes, phenylglyoxal, and ammonium acetate were utilized as components in the synthesis of disubstituted imidazole by Husain *et al.* (2009). Next, the 1,2,4-disubstituted imidazoles were combined with chlorobenzene in the presence of triethylamine and tetrahydrofuran (THF), which resulted in the production of a new product, which had a yield of 74% (Scheme 110).¹⁵⁶

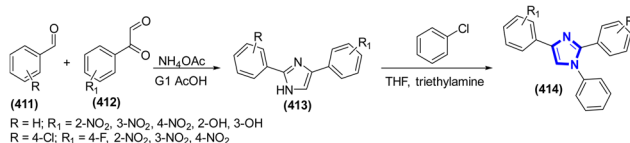
Sharma *et al.* (2024) documented the SAR-guided synthesis of powerful, selective, and artemisinin-synergistic imidazole derivatives with potential *in vitro* antiparasmodial and *in vivo* antimalarial efficacy. The findings indicated that the compound with 4,5-triphenyl and 2-naphthalene substitution on the imidazole ring had the most significant antiparasmodial action (0.5 μM), although Im2 demonstrated favorable resistance indices (1.06–1.72) and selectivity indices (>133.3). Despite Im22 demonstrating elevated resistance indices (4–4.6), it showed significant synergistic efficacy with ART against PfINDO. Im2 and Im5 demonstrated significant *in vivo* antimalarial efficacy, prolonging the lifespan of infected mice to 28.6 ± 4.2 and 27.4 ± 4 days, respectively, in contrast to the untreated control group, which survived 21.3 ± 3.5 days (Scheme 111).¹⁵⁷



Scheme 108 Synthesis of substituted, 2-aryl, 4,5-phenylimidazoles.

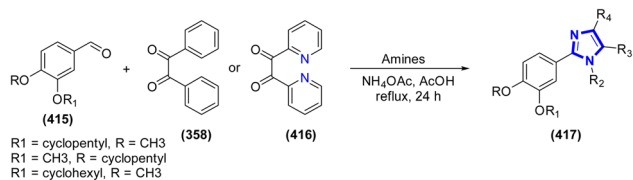


Scheme 109 Synthesis of triaryl-imidazole in the presence of polyethylene.



Scheme 110 Synthesis of disubstituted imidazoles.



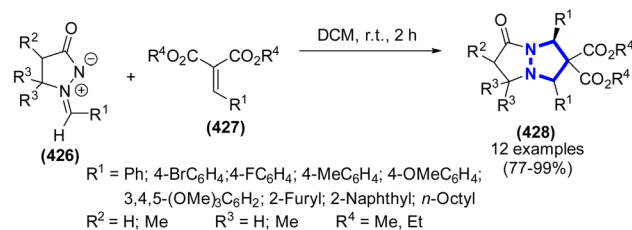


Scheme 111 A novel series of 2,4,5-triphenyl-1*H*-imidazole derivatives.

2.2.3. Pyrazolidine. Formed from three carbon atoms and two neighboring nitrogen atoms, pyrazolines (sometimes called dihydropyrazole) are mono-unsaturated 5-membered heterocyclic compounds.¹⁵⁸ Three tautomeric forms of pyrazoline exist, *i.e.*, 1-, 2-, and 3-pyrazoline. Many pyrazolidine frameworks display substantial anti-inflammatory, antidepressant, anticancer, antibacterial, and antiviral properties such as oxyphenbutazone and acetylpyrazoline derivatives (Scheme 112).^{159–162}

T. Gieshoff *et al.* (2017) discovered a new way to get 1,2-diarylpyrazolidin-3,5-diones from easily available dianilides without using harmful hydrazine building blocks (Scheme 113).^{163,164} This strategy is a viable alternative to the traditional methods because of sustainability, affordable starting materials, large substrate scope, and moderate to good yields.

D. Wang *et al.* (2013) described the [3 + 2] annulation of azomethine imine with trifluoroethylidene malonate to create trifluoromethyl-containing pyrazolidine scaffolds (Scheme 114).¹⁶⁵ Under the optimal conditions of DCM as the solvent, ambient temperature, and reaction time of 2 h, the target

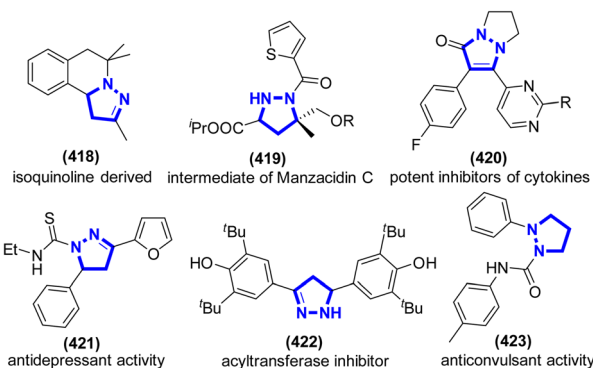


Scheme 114 Synthesis of trifluoromethyl-containing pyrazolidine scaffolds in DCM.

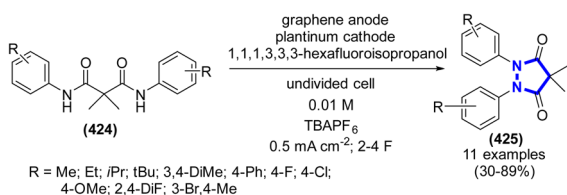
products were obtained in good to exceptional yields. This is a method with high diastereoselectivity (up to 99 : 1) and mild conditions. On a larger scale of 0.5 mmol, an excellent yield of 98% and >99 : 1 dr was achieved.

A domino aza-Michael/hemiacetal reaction between di-substituted hydrazine and α,β -unsaturated aldehydes to form pyrazolidine derivatives under the catalysis of pyrrolidine in CH₂Cl₂ was demonstrated by Z.-C. Geng *et al.* (2012) (Scheme 115).¹⁶⁶ The desired products were acquired in substantial yields under the optimal reaction conditions. This process was regioselectively regulated, had a broad substrate scope, and was devoid of any additives.

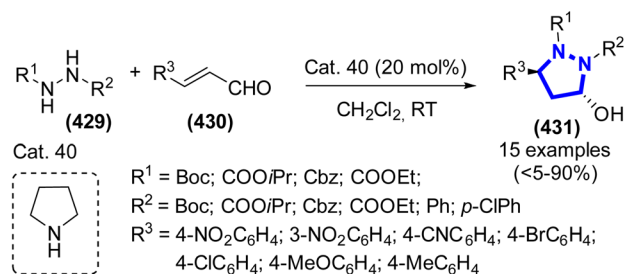
M. Fernandez *et al.* (2012) introduced an aza-Michael/hemiaminalization reaction between α,β -unsaturated aldehydes and *N,N'*-disubstituted hydrazides to form pyrazolidines with the catalysis of readily available silyl diarylprolinol ether in



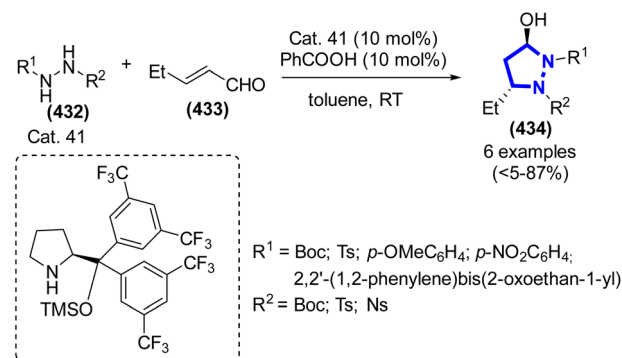
Scheme 112 Chemical structures of bioactive compounds containing a pyrazolidine framework.



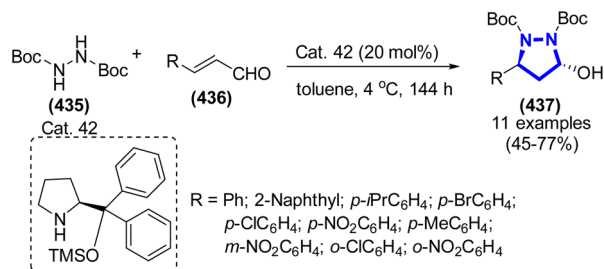
Scheme 113 Synthesis of 1,2-diarylpyrazolidin-3,5-diones *via* electrochemical method.



Scheme 115 Synthesis of pyrazolidine derivatives catalyzed by Cat. 40.



Scheme 116 Synthesis of pyrazolidines catalyzed by Cat. 41.



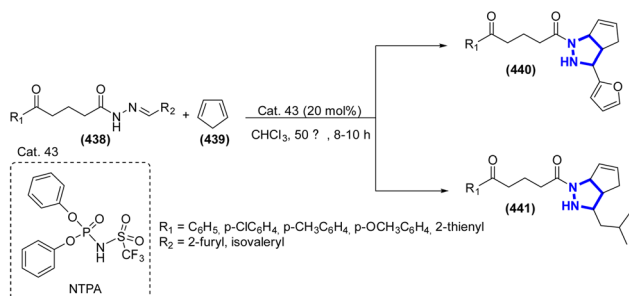
Scheme 117 Synthesis of 3-hydroxypyrazolidines catalyzed by Cat. 42.

toluene solvent (Scheme 116).¹⁶⁷ Although the product yields were quite low, this was a regioselective and metal-free protocol.

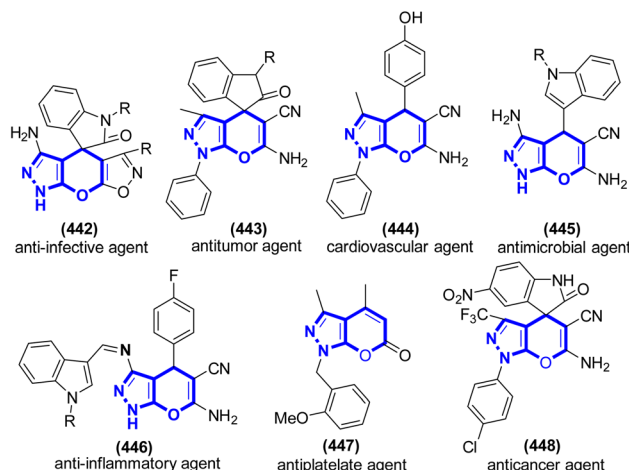
The 1,3-diamination between cinnamic aldehydes and di-1,2-*N*-*tert*-butoxycarbonyl (Boc)-protected hydrazine to form 3-hydroxypyrazolidines catalyzed by easily accessible chiral amines Cat. 42 was introduced by L. Deiana *et al.* (2012) (Scheme 117).¹⁶⁸ This was a chemo- and enantio-selective-controlled (>99% ee) aza-Michael/hemiaminal domino sequence, leading too good to exceptional yields.

Remziye Azra Kartop and colleagues (2023) documented the design and synthesis of a series of new pyrazolidine derivatives from *N*-acyl hydrazones using *N*-triflylphosphoramidate (NTPA)-catalyzed [3 + 2] cycloaddition (Scheme 118). The structural elucidation of the produced compounds was performed using several spectroscopic techniques, including IR, NMR, MS, and elemental analysis. The cytotoxic efficacy of the pyrazolidine derivatives was assessed against human lung cancer (A549), pancreatic cancer (PANC 1), prostate cancer (DU-145), breast cancer (MCF-7), and human dermal fibroblasts (HDF) using the MTS test. Compounds 440 and 441 (IC₅₀ = 12.5–21.8 μM) exhibited superior antiproliferative activity compared to all other compounds against the A549 human lung cancer cell line and the PANC1 pancreatic cancer cell line, respectively (Scheme 119).¹⁶⁹

2.2.4. Pyrazole (pyrazoline). Pyrazoles are five-membered heterocyclic compounds with two contiguous nitrogen atoms at positions 1 and 2. This distinctive structure confers considerable chemical stability and biological activity to pyrazole derivatives, making them advantageous in medicinal chemistry, agrochemicals, and materials science.¹⁷⁰ Many pyrazole moieties exhibit antitubercular, antimicrobial, anti-consulant,



Scheme 118 Creation of novel pyrazolidines through [3 + 2] cycloaddition.

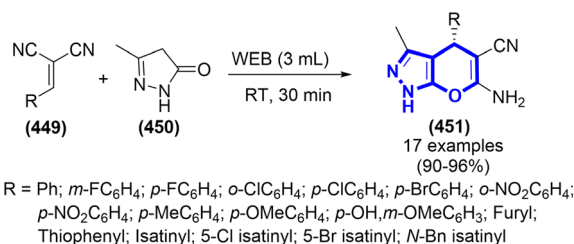


Scheme 119 Chemical structures of bioactive compounds containing a pyrazole framework.

anticancer, and antiviral activities and act as selective COX-2 inhibitors such as celecoxib and eprizole.^{171–175}

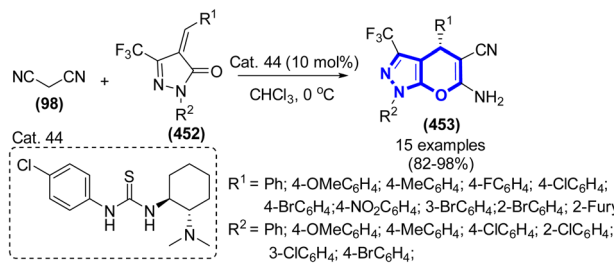
K. D. Dwivedi *et al.* (2020) employed water extract from banana peels (WEB) as a catalyst for the preparation of pyrano [2,3-*c*]pyrazoles from the reaction between arylidene malononitriles and pyrazolone at r.t. after 30 min (Scheme 120).¹⁷⁶ This was a green and broad synthesis technique that did not use any harmful organic solvents and ligands. Also, this methodology is versatile and may be effectively employed for a diverse array of substrates, resulting in yields ranging from high to exceptional. This approach offers several advantages, including quick reaction, environmentally favorable reaction conditions, and facile product separation without the need for column chromatography.

In the study conducted by H. F. Zhang *et al.* (2014), they presented a comprehensive analysis on the synthesis of a diverse array of functionalized fluorinated dihydropyrano[2,3-*c*]pyrazoles. The synthesis of pyrazoles from the (*Z*)-isomer was discussed. The reaction between 1*H*-pyrazol-5(4*H*)-ones and malononitrile was conducted in chloroform as the solvent at 0 °C (Scheme 121).¹⁷⁷ The application of Cat. 44 as the catalyst resulted in the successful synthesis of the desired products through a domino Michael addition and Thorpe-Ziegler type cyclization. The reaction exhibited high yields, reaching up to 98%, and satisfactory enantioselectivity, with enantiomeric excess values of up to 90%.

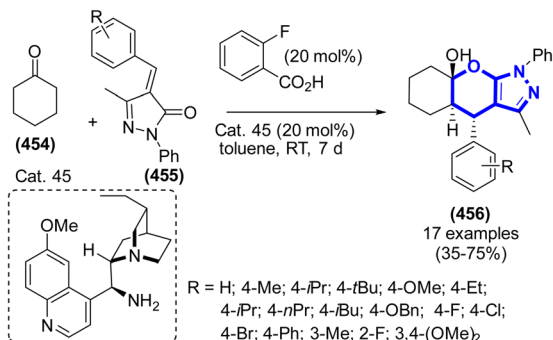


Scheme 120 Synthesis of pyrano[2,3-*c*]pyrazoles catalyzed by WEB.





Scheme 121 Synthesis of functionalized dihydropyrano[2,3-c]pyrazoles catalyzed by Cat. 44.



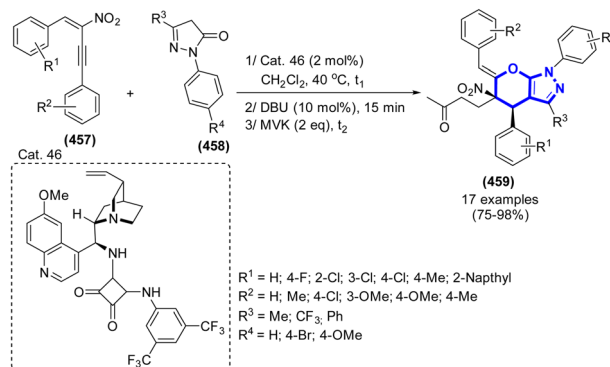
Scheme 122 Synthesis of tetrahydropyrano[2,3-c]pyrazoles catalyzed by Cat. 45.

With the catalytic activity of readily accessible primary amine produced from hydroquinine and 2-FC₆H₄CO₂H, a series of tetrahydropyrano[2,3-c]pyrazoles was synthesized *via* the reaction between alkylidene pyrazolones and cyclic ketones/pentanal, which was reported by R. Maity *et al.* (2017) (Scheme 122).¹⁷⁸ This enantioselective cascade Michael-hemiketalization reaction led to moderate to high yields of products containing three adjacent stereogenic centers.

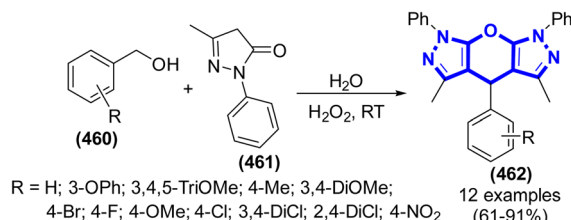
Y. Wu *et al.* (2018) reported the utilization of quinine-derived squaramide as a catalyst for the successful synthesis of tetrahydropyrano[2,3-c]pyrazoles. This technique involved the reaction of 1,3-enynes, 1-aryl-3-substituted pyrazolones, and methyl vinyl ketone (Scheme 123).¹⁷⁹ This protocol produced the desired products in good to exceptional yields from easily accessible starting materials without the isolation of the intermediate. The diastereomeric ratios were determined to be >20 : 1 dr by ¹H-NMR analysis and the ee value by HPLC analysis was in the range of 82–95%.

A. Dandia *et al.* (2018) described the succession of oxidation, Michael addition, cyclization, and dehydration reaction between benzyl alcohol and 1*H*-pyrazol-5(4*H*)-one to prepare pyrano-2-one derivatives in water at r.t. (Scheme 124).¹⁸⁰ It was also concluded that water was necessary for the production of C–C bonds and other phases of the reaction. The intrinsic benefits of this protocol include chemoselectivity, reduced reaction time, high yields, easy work-up approach, no need for chromatographic purification, and the use of green solvents, namely water.

V. Ramesh *et al.* (2016) reported a five-component method using various aromatic aldehydes, thiophenols, 3-



Scheme 123 Synthesis of tetrahydropyrano[2,3-c]pyrazoles catalyzed by Cat. 46.

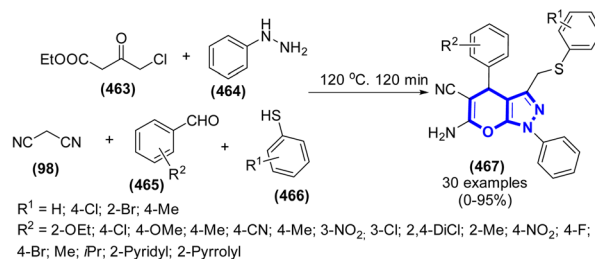


Scheme 124 Synthesis of pyrano-2-one derivatives in water.

oxobutanoates, phenylhydrazine, and malononitrile for the synthesis of thioether-containing dihydropyrano[2,3-c]pyrazoles after 20 min at 120 °C (Scheme 125).¹⁸¹ The aforementioned synthetic approach exhibited several advantages, such as its expeditious establishment, absence of purification protocols, swift reaction kinetics with favorable atom efficiency, and notable product yields ranging from 81% to 86%.

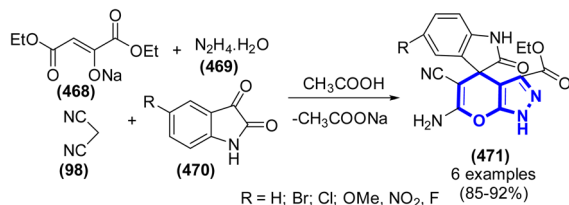
This study encompasses a diverse array of pyrano[2,3-c]pyrazoles. The synthesis of 3'-carboxylate derivatives was elucidated by V. L. Gein *et al.* (2017) through a multi-component reaction involving diethyl oxalacetate sodium salt, isatin, malononitrile, and hydrazine hydrate. The reaction was conducted in the presence of acetic acid within ethanol as the solvent (Scheme 126).¹⁸² The yields of the required goods exhibited favorable to exceptional performance.

A. Alizadeh *et al.* (2014) devised a facile regioselective MCR comprised of ninhydrin, malononitrile, hydrazine derivatives,

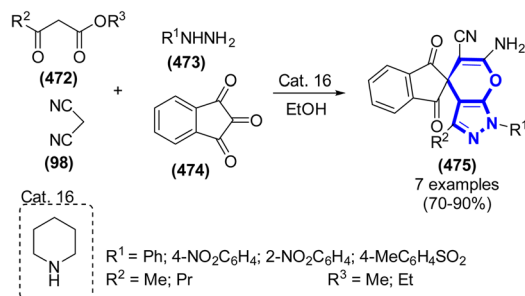


Scheme 125 Synthesis of dihydropyrano[2,3-c]pyrazoles under solvent-free conditions.





Scheme 126 Synthesis of pyrano[2,3-c]pyrazole derivatives catalyzed by CH₃COOH.



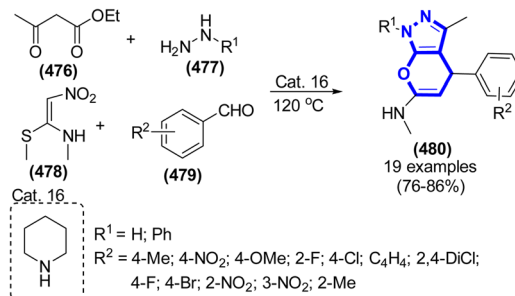
Scheme 127 Synthesis of spiro-pyranopyrazoles and oxa-aza-[3.3.3]propellanes catalyzed by Cat. 16 in ethanol.

and β -keto esters or dimethyl acetylene dicarboxylate to synthesize spiro-pyranopyrazoles and oxa-aza[3.3.3]propellanes in the presence of the catalytically active piperidine (Scheme 127).¹⁸³ The simplicity, regioselectivity, without metal catalyst or column chromatography purification, and high yields of this approach make it valuable.

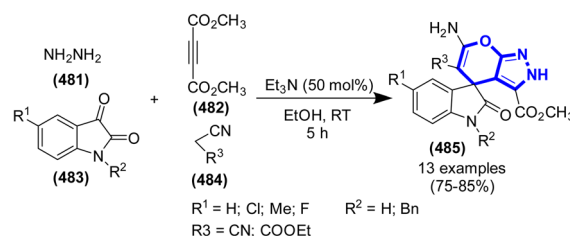
A four-component cascade reaction involving *N*-phenyl hydrazine, various aromatic aldehydes, ethylacetoacetate, and nitroketene-*N,S*-acetal to produce pyranopyrazole frameworks catalyzed by piperidine at 120 °C under solvent-free conditions was introduced by K. Jayabal *et al.* (2014) (Scheme 128).¹⁸⁴ Through a sequence of condensation-Knoevenagel-Michael-annulation reaction, the products were obtained in high yields, ranging from good to outstanding. This technology is notable owing to its rapid response time, great yield, low cost, simple operation, and huge structural variety.

In EtOH as the solvent and triethylamine as the catalyst, a cascade multicomponent reaction of hydrazine, dimethyl acetylene dicarboxylate, isatin, and malononitrile or ethyl cyanoacetate to form pyrano[2,3-*c*]pyrazole derivatives was accomplished by C. Wang *et al.* (2015) (Scheme 129).¹⁸⁵ Additionally, this reaction has the benefits of utilizing an easily accessible starting material, applying mild reaction conditions, and exhibiting a straightforward operational procedure.

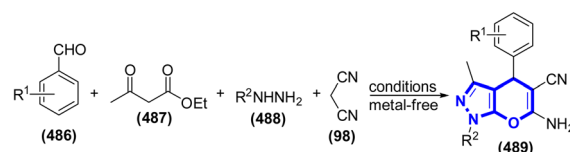
Singh and colleague (2017) detailed an environmentally friendly and efficient method, *i.e.*, the one-pot, multi-component synthesis of pyrano[2,3-*c*]pyrazoles facilitated by visible light, achieved without the use of catalysts or solvents (Scheme 130). This protocol is characterized by its cost-effectiveness, nontoxic nature, absence of catalysts and solvents, accessible reactants, and lack of requirement for specialized glassware and a photo-reactor system. The current



Scheme 128 Synthesis of pyranopyrazole frameworks catalyzed by Cat. 16.



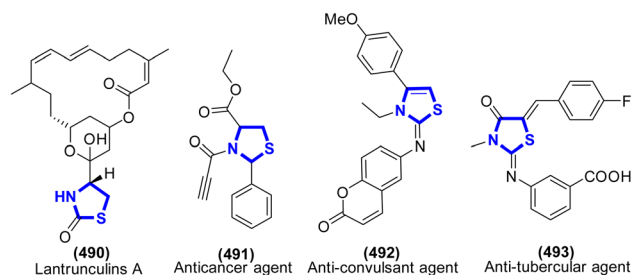
Scheme 129 Synthesis of pyrano[2,3-*c*]pyrazole derivatives catalyzed by Et₃N.



Scheme 130 Synthesis of pyrano[2,3-*c*]pyrazoles catalyzed by metal-free catalysts.

methodology was further broadened by employing diethyl acetylene dicarboxylate as the reactant instead of ethylacetoacetate (Scheme 131).¹⁸⁶

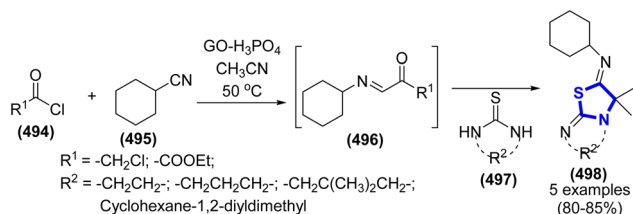
2.2.5. Thiazolidine/isothiazolidine. Thiazolidine is a cyclic molecule consisting of five members, wherein a thioether group is located at position 1 and an amine group is located at position 3. Thiazolidine and its derivatives have demonstrated antibacterial, anti-inflammatory, anticonvulsant, antimalarial, analgesic, anti-HIV, and anticancer activities.^{187–191}



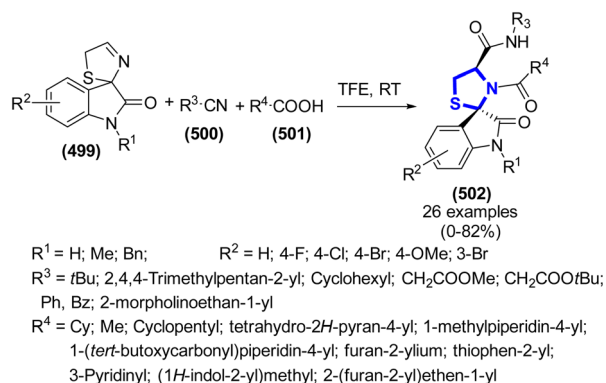
Scheme 131 Chemical structures of bioactive compounds containing a thiazolidine/isothiazolidine framework.



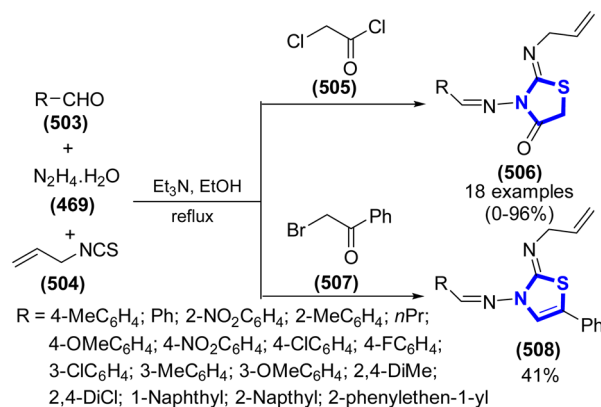
A. Daghlavi *et al.* (2020) reported a Nef-isocyanide multi-component reaction employing alkyl chloroglyoxalates, cyclohexyl isocyanide, and cyclic thiourea derivatives in the presence of graphene oxide-supported phosphoric acid to synthesize some hydroxy-thiazolidine-4-carboxylate derivatives (Scheme 132).¹⁹² The advantages of this method include the utilization of widely accessible chemicals, reusability of the catalyst, high yields, few environmental dangers, no requirement for stereo-isomer separation, and as a result, a reduced number of total stages. The catalyst was employed for a series of five consecutive reactions without any decrease in the overall reaction yield observed.



Scheme 132 Synthesis of hydroxy-thiazolidine-4-carboxylate derivatives catalyzed by phosphoric acid supported on graphene oxide.



Scheme 133 Synthesis of spirooxindole-fused thiazolidine derivatives.



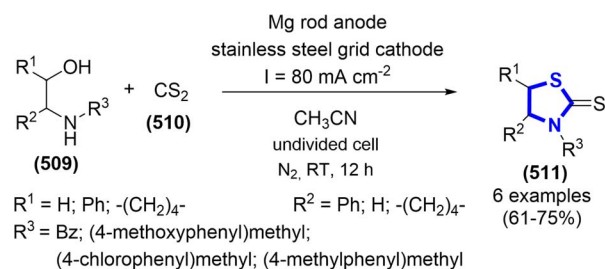
Scheme 134 Synthesis of a wide range of thiazolidine-4-one and 3H-thiazoles catalyzed by Et_3N .

G. Rainoldi *et al.* (2018) conducted a Ugi-type three-component reaction involving oxindole-based thiazolines, various isocyanides, and carboxylic acids in fluorinated solvents at ambient temperature. This reaction resulted in the formation of functionalized spirooxindole-fused thiazolidines (Scheme 133).¹⁹³ The required compounds were obtained in satisfactory to favorable yields, exhibiting significant diastereoselectivity, efficient separation, and straightforward workup techniques.

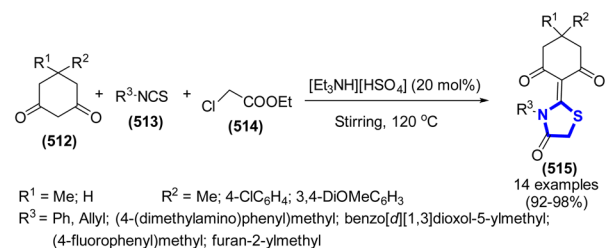
In the study by B. Kaboudin *et al.* (2018), they utilized Et_3N as the catalyst and EtOH as the solvent to facilitate a multi-component condensation-cyclization process. This reaction involved the combination of hydrazine, allyl isothiocyanate, α -haloketone, and various aldehydes to produce thiazolidine-4-one and 3H-thiazole derivatives (Scheme 134).¹⁹⁴ This approach is notable for its excellent yields, easy set-up, easily accessible starting ingredients, and simple reaction procedure without the isolation of the intermediate.

H. Medini *et al.* (2015) introduced a synthetic route for a series of thiazoline-2-thione derivatives from secondary β -amino alcohols *via* electrolysis using carbon disulfide under the catalysis of an electrogenerated base (Scheme 135).¹⁹⁵ The resulting compounds were obtained in yields of varying degrees, ranging from minor to significant.

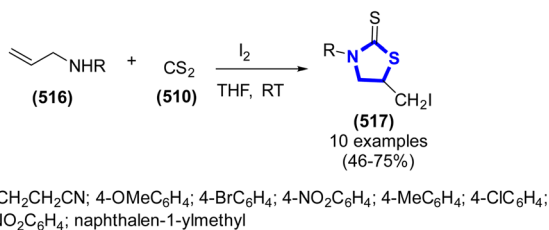
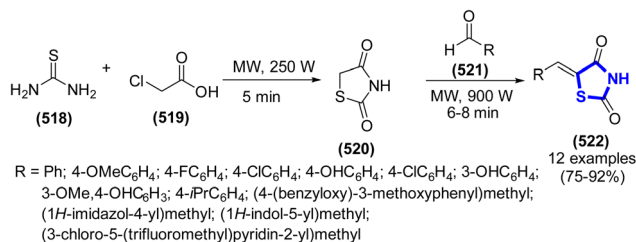
A one-pot three-component reaction among 1,3-diketones, cyanates, and ethyl chloroacetate to synthesize a wide range of thiazolidine/oxazolidine derivatives in $[Et_3NH][HSO_4]$ IL (20 mol%) was described by A. M. Malla *et al.* (2015) (Scheme 136).¹⁹⁶ Moreover, the IL in this technique has both catalytic and medium engineering capabilities, which is a unique aspect of this approach. The advantages of this protocol include its outstanding yield, moderate reaction conditions, large substrate scope, decreased chemical waste, short reaction time,



Scheme 135 Synthesis of thiazoline-2-thione derivatives in the presence of CS_2 .



Scheme 136 Synthesis of thiazolidine/oxazolidine derivatives catalyzed by $[Et_3NH][HSO_4]$.

Scheme 137 Synthesis of thiazolidine-2-thiones catalyzed by I₂.

Scheme 138 Synthesis of thiazolidine-2,4-dione or 2-thioxothiazolidine-4-one derivatives under MW.

easy operating method, straightforward catalyst manufacture, and retained catalytic activity even after being recycled up to four times.

A. Ziyaei-Halimehjani *et al.* (2012) reported the reaction among allyl amines, carbon disulfide, and iodine to synthesize thiazolidine-2-thiones through regiospecific iodocyclization in tetrahydrofuran at ambient temperature (Scheme 137).¹⁹⁷ This protocol is easy, effective, and regiospecific, with good to high product yields.

B. R. P. Kumar *et al.* (2006) reported the microwave-induced reaction between thiazolidine-2,4-dione or thiazolidine-2-

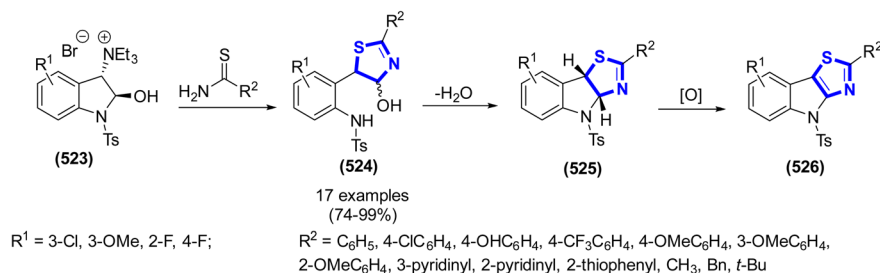
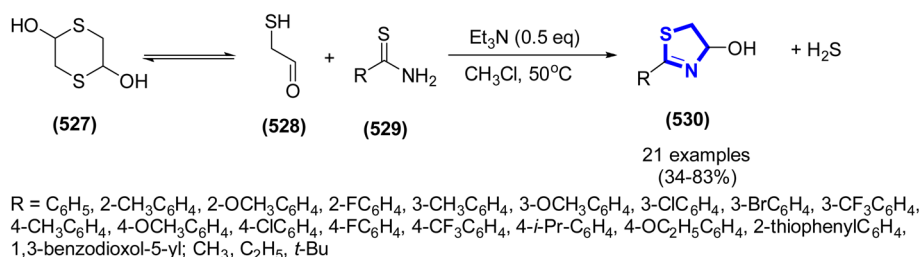
thioxo-thiazolidine-4-one and different aryl and heteroaryl aldehydes *via* Knoevenagel condensation in the presence of piperidine, activated silica gel, and acetic acid at the MW power of 900 W for 6–8 min to produce a wide range of thiazolidine-2,4-diones or 2-thioxothiazolidine-4-ones, respectively (Scheme 138).¹⁹⁸ This protocol is advantageous because of its quick reaction speeds, high yields, no use of solvent, and no pollutants generated. Moreover, compared to conventional heating, microwave heating showed comparatively higher yields.

Takumi Abe *et al.* showed that indoline hemiaminals yield 2,5-diaryl-4-hydroxythiazolines *via* a thioamidation/ring-switch sequence (2024). The effectiveness of this transformation hinges on the use of thioamide as a thiazoline precursor under transitory tautomeric regulation. This transformation involves gentle reaction conditions with favorable yields and extensive functional group tolerance (17 samples, up to 99% yield) (Scheme 139).¹⁹⁹

Xiantao Ma *et al.* disclosed an innovative approach for synthesizing 2-substituted-4,5-dihydrothiazol-4-ols *via* the cyclization of thioamides and 1,4-dithiane-2,5-diol in the presence of Et₃N (2025). Stable hydroxy-substituted thiazole compounds were obtained from substituted thioamides. The reaction conditions are straightforward, the substrate scope is extensive, and the target compounds were acquired in yields of up to 82% (Scheme 140).²⁰⁰

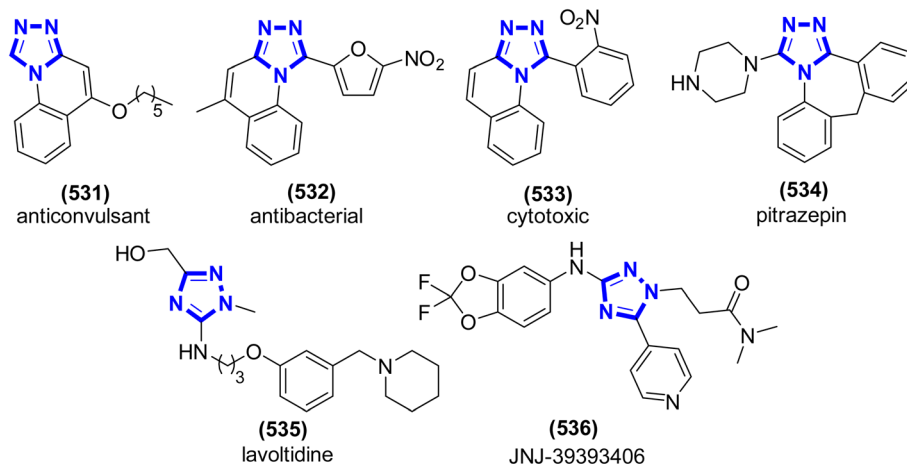
2.3. Five-membered heterocycles containing at least three nitrogen atoms

2.3.1. Triazole. In the class of nitrogen-containing heterocyclic compounds, triazoles stand out as having particularly advantageous therapeutic uses. The structure of five-membered triazoles may be broken down into two distinct categories, *i.e.*, 1,2,3-triazole

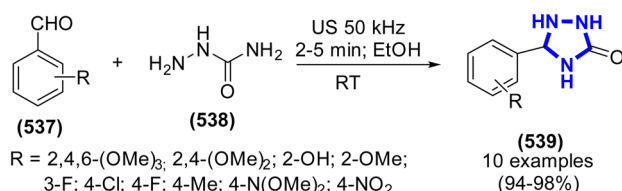
Scheme 139 Synthesis of thiazolo[4,5-*b*]indoles.

Scheme 140 Synthesis of 2-substituted-4,5-dihydrothiazol-4-ols.

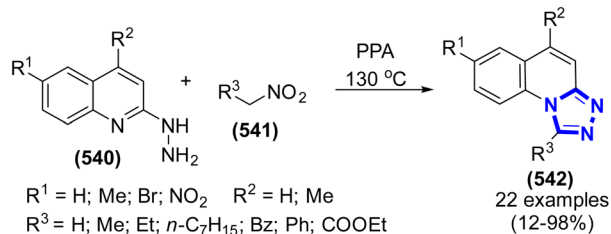




Scheme 141 Chemical structures of bioactive compounds containing a triazole framework.



Scheme 142 Synthesis of triazole derivatives in the absence of a catalyst.

Scheme 143 Synthesis of 1,2,4-triazolo[4,3-*a*]quinoline derivatives catalyzed by PPA.

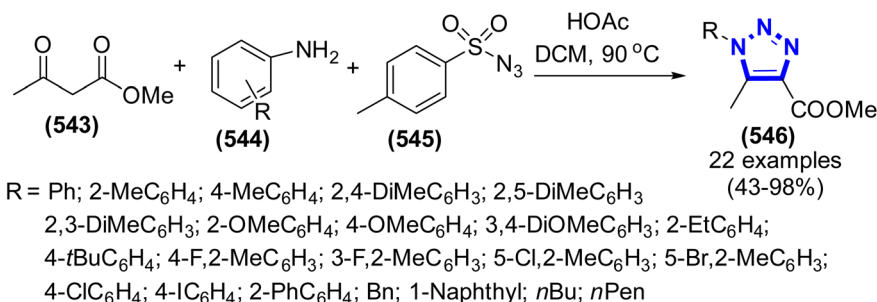
and 1,2,4-triazole. Both 1,2,3- and 1,2,4-triazoles have structural features that allow them to support a wide variety of substituents around their core structures. This presents an opportunity for the advancement of several novel bioactive products. Triazole

compounds have a broad range of pharmacological activities, including antibacterial,^{201,202} analgesic,^{203,204} anti-inflammatory, local anesthetic,^{205,206} antineoplastic,^{207,208} antiviral,²⁰⁹ anti-proliferative,²¹⁰ and anticancer²¹¹ activities (Scheme 141).

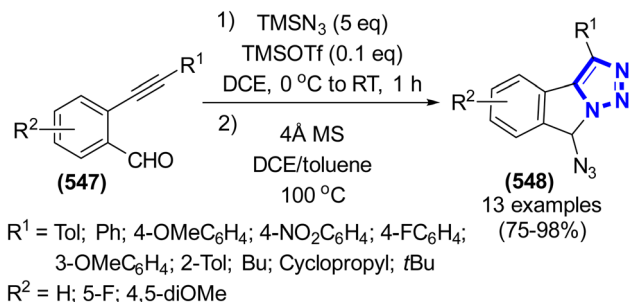
In a study conducted by Venigalla *et al.* (2020), an ultrasonic-assisted reaction was employed to synthesize a range of triazole derivatives using aldehydes and semicarbazide in EtOH at r.t. Notably, the reaction proceeded without the use of a catalyst (Scheme 142).²¹² This Knoevenagel-cyclic condensation has many advantages such as ecological friendliness, clean and simple operation, cost-effectiveness, fast reaction time, easy set-up, high output, and reduced waste generation.

In the study conducted by A. Aksenov *et al.* (2020), the utilization of polyphosphoric acid (PPA) as a catalyst was investigated for the purpose of synthesizing 1,2,4-triazolo[4,3-*a*]quinolines. This synthesis involved the reaction between 2-hydrazinylquinolines and nitroalkanes, which was carried out at 130 °C (Scheme 143).²¹³ This synthetic route resulted in good to outstanding product yields. In addition, several triazoloquinolines showed intriguing action in promoting the differentiation of neuroblastoma cancer cells.

N. Guo *et al.* (2019) developed a method for the preparation of 1,2,3-triazole derivatives *via* the multicomponent reaction among primary amines, 1,3-dicarbonyls, and tosyl azide catalyzed by AcOH in DCM at 90 °C (Scheme 144).²¹⁴ The present cycloaddition reaction, employing readily accessible starting



Scheme 144 Preparation of 1,2,3-triazole derivatives catalyzed by acetic acid.



Scheme 145 Synthesis of 1,2,3-triazole-fused isoindoles catalyzed by TMSOTf.

materials, resulted in satisfactory to outstanding yields of the respective products.

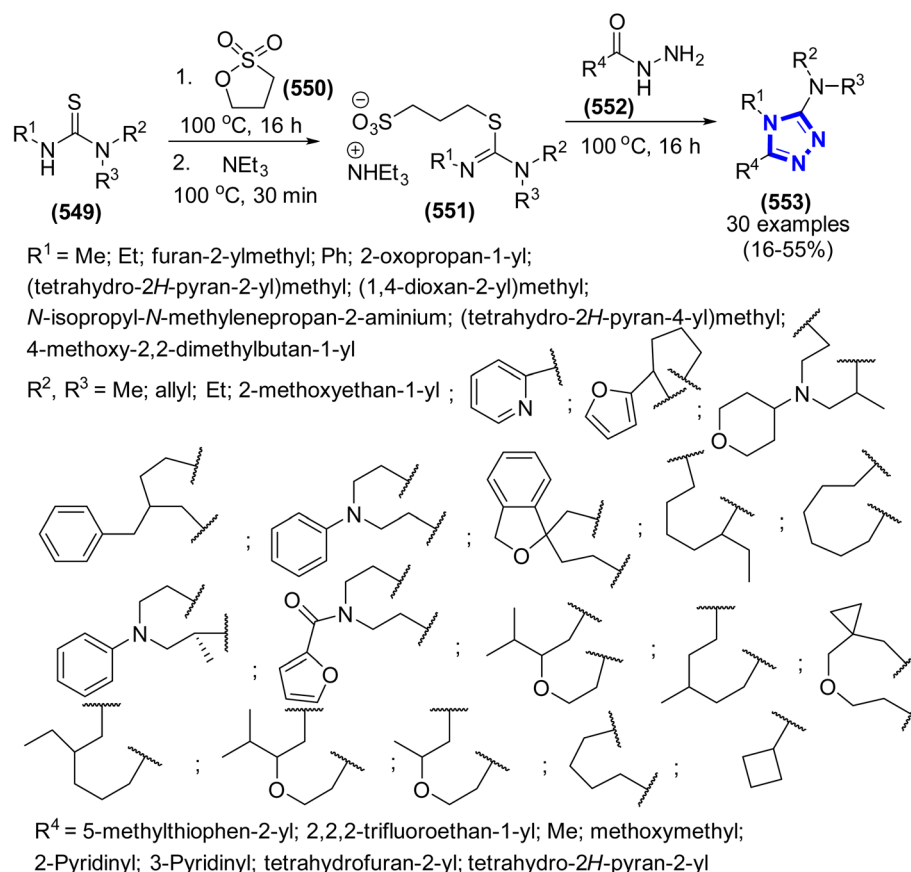
A wide variety of 1,2,3-triazole-fused isoindoles produced by a one-pot two-step intramolecular azide-alkyne cycloaddition was published by N. Okamoto *et al.* (2018) (Scheme 145).²¹⁵ The first step was the creation of a *gem*-diazide intermediate from *o*-alkynylbenzaldehydes and trimethylsilyl azide under the catalysis of trimethylsilyl trifluoromethanesulfonate in DCE at 0 °C to r.t. Following a reaction period of one hour, 4 Å molecular sieves and toluene were introduced, accompanied by an increase in temperature to 100 °C. This process resulted in the formation of the intended products, with yields ranging from good to outstanding.

A. V. Bogolyubsky *et al.* (2018) conducted a one-pot two-step conversion of various thioureas to 1,2,4-aminotriazoles derivatives (Scheme 146).²¹⁶ The first step was the *S*-alkylation of thioureas using 1,3-propanesultone in NEt₃, followed by consecutive ring closure with hydrazides to form 3-amino-1,2,4-triazoles. The advantages of this protocol include its cost- and time-effective manner, readily available starting ingredients, and no need for poisonous and volatile solvents but it has moderate yields.

In the study conducted by V. O. Filimonov *et al.* (2017), they synthesized a range of 1,2,3-triazoles employing 2-cyanothioacetamides and sulfonyl azides using EtONa as the catalyst and EtOH as the solvent. The reaction took place at −10 °C (Scheme 147).²¹⁷ The synthetic route used in this investigation yielded the intended compounds with results ranging from good to exceptional.

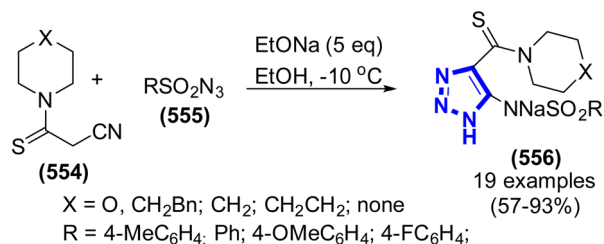
W. Li *et al.* (2013) demonstrated the 1,3-dipolar cycloaddition of a wide range of α,β -unsaturated aldehydes and azides to form triazole-olefin derivatives in the presence of diethylamine and DBU in DMSO solvent at 60 °C and reaction time of 2 h (Scheme 148).²¹⁸ The advantages of this approach include the use of a simple and low-cost catalyst, large substrate scope, easily accessible starting ingredients, simple operation, and high product yields.

2.3.2. Oxadiazole. Oxadiazoles are five-membered heterocyclic compounds including one oxygen atom and two nitrogen atoms in their ring structure, which exist in four isomeric forms

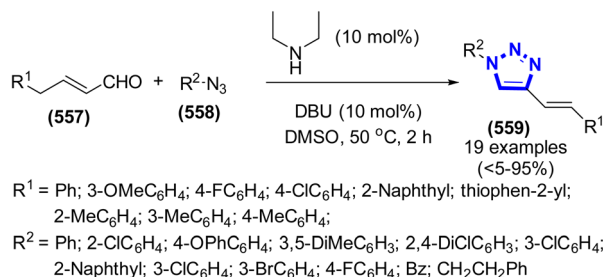


Scheme 146 Synthesis of 3-amino-1,2,4-triazole moieties catalyzed by NEt₃.





Scheme 147 Synthesis of 1,2,3-triazoles catalyzed by EtONa.



Scheme 148 Synthesis of triazole-olefin scaffolds catalyzed by amine.

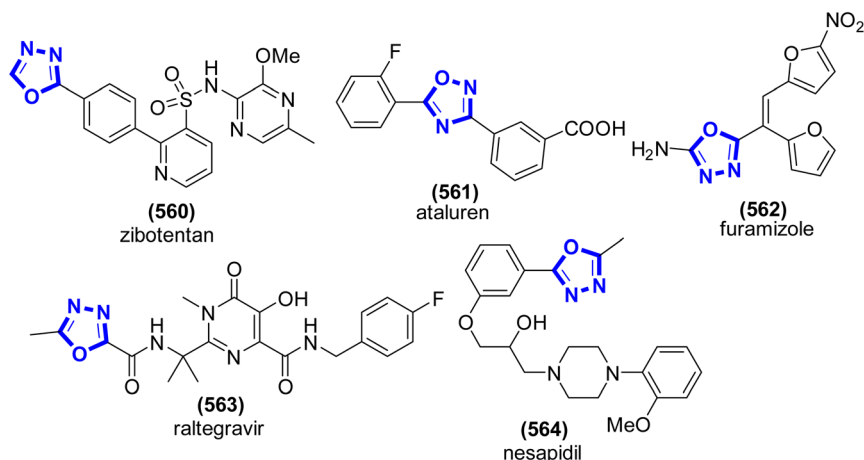
including 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, and 1,2,5-oxadiazole. Among them, 1,3,4-oxadiazole is the most extensively researched owing to its notable biological and

pharmacological attributes.²¹⁹ Oxadiazole derivatives have a wide variety of biological properties, including anti-cancer,²²⁰ anti-inflammatory,²²¹ fungicidal,²²² herbicidal,²²³ anti-HIV,²²⁴ antibacterial,²²⁵ and plant growth regulator actions (Scheme 149).²²⁶

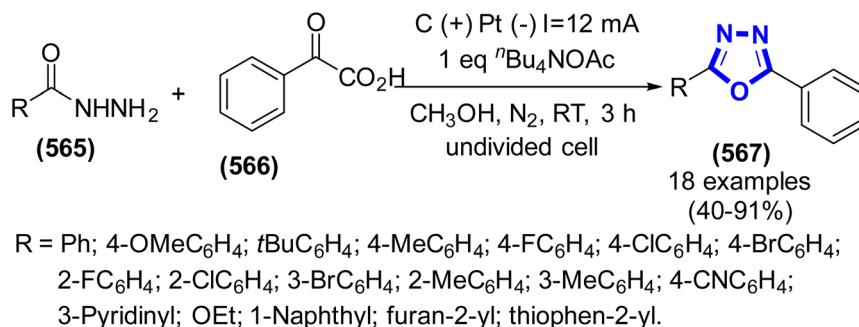
The intermolecular electrochemical cyclization of various α -keto acids and acylhydrazines was developed for the preparation of 1,3,4-oxadiazoles in $n\text{Bu}_4\text{NOAc}$ and methanol by F. Lu *et al.* (2020) (Scheme 150).²²⁷ This protocol is advantageous because of the absence of transition metals or other oxidants, gentle reaction conditions, large substrate scope and great yields. The practicality of this methodology was examined using a 5-mmol-scale reaction, and the yield was shown to have no difference compared to the scale of 0.5 mmol.

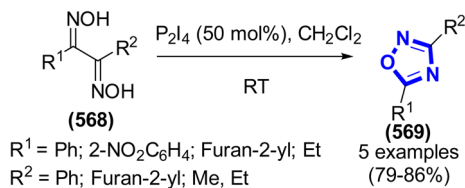
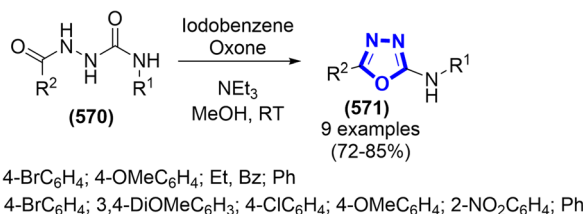
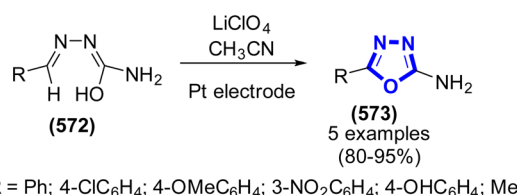
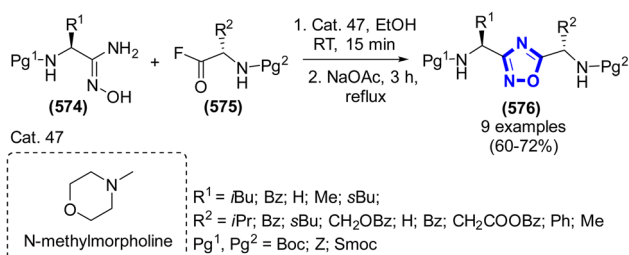
V. N. Telvekar *et al.* (2013) reported the rearrangement of 1,2-dioximes of α -diketones to Beckmann product 1,2,4-oxadiazoles using diphosphorus tetraiodide in DCM at r.t. (Scheme 151).²²⁸ This procedure using a new, gentle agent afforded the products in outstanding yields.

Under the oxidative effect of oxone and catalytic activity of NEt_3 , the oxidative desulfurization of various thiosemicarbazides to oxadiazole moieties using iodobenzene was examined by K. N. Patel *et al.* (2012) (Scheme 152).²²⁹ This synthetic route using easily accessible oxidants afforded matching compounds in high to exceptional yields.



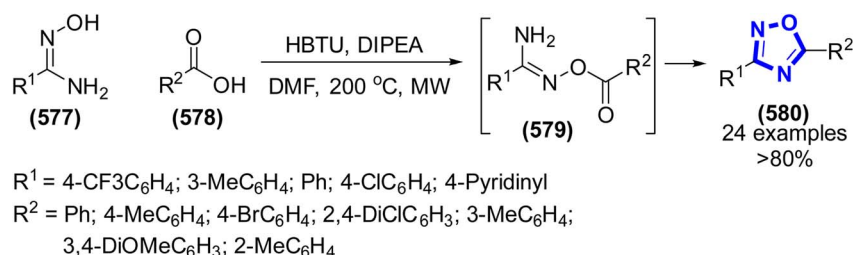
Scheme 149 Chemical structures of bioactive compounds containing an oxadiazole framework.

Scheme 150 Synthesis of 1,3,4-oxadiazole ring systems catalyzed by $n\text{Bu}_4\text{NOAc}$.

Scheme 151 Synthesis of 1,2,4-oxadiazole derivatives catalyzed by P_2I_4 .Scheme 152 Synthesis of oxadiazole moieties catalyzed by NEt_3 .Scheme 153 Synthesis of oxadiazole frameworks catalyzed by LiClO_4 via an electrolysis method.

Scheme 154 Synthesis of 1,2,4-oxadiazole-linked orthogonally urethane-protected dipeptides catalyzed by Cat. 47.

The electrocyclization process involving the reaction of semicarbazone, formed from semicarbazide hydrochloride and various aldehydes, in the presence of sodium ethoxide, results



Scheme 155 Synthesis of six 1,2,4-oxadiazole derivatives catalyzed by TBTU/HOBt and DIPEA.

in the formation of oxadiazoles. This reaction takes place in acetonitrile with lithium perchlorate as the electrolyte, with a platinum electrode serving as the catalyst. This methodology was first reported by L. K. Sharma *et al.* (2010) (Scheme 153).²³⁰ The implementation of this environmentally sustainable approach led to favorable outcomes in terms of product yields, ranging from satisfactory to exceptional.

V. V. Sureshbabu *et al.* (2008) presented a method for the synthesis of various 1,2,4-oxadiazole-linked orthogonally urethane-protected dipeptides *via* a two-step reaction between *N*-protected amino acyl fluoride and amino acid-derived amidoxime (Scheme 154).²³¹ The first step was catalyzed by *N*-methylmorpholine in EtOH as the solvent at r.t. after 15 min and NaOAc was used as the catalyst in the second stage. This protocol afforded products with average to great yields.

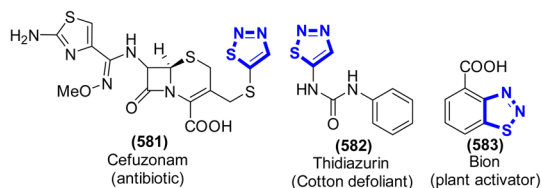
The microwave-assisted coupling of amidoximes with carboxylic acids to prepare 1,2,4-oxadiazoles catalyzed by *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU)/1-hydroxybenzotriazole hydrate (HOBt) and excess *N,N*-diisopropylethylamine (DIPEA) in >80% yield was reported by M. D. Evans *et al.* (2003) (Scheme 155).²³² Subsequently, employing a statistical design methodology, the optimal reaction conditions were predicted.

2.3.3. Thiadiazole. Thiadiazole is a five-membered ring consisting of two nitrogen atoms, two carbon atoms, and a sulfur atom. Thiadiazole and its derivatives show numerous bioactivities such as antimicrobial,^{233,234} anti-inflammatory,²³⁵ anti-cancer,^{236,237} anticonvulsant,²³⁸ antidepressant,²³⁹ antioxidant,²⁴⁰ radioprotective,²⁴¹ and anti-leishmanial.^{242,243} Also, several medications on the market contain a thiadiazole ring system, including acetazolamide, methazolamide, and sulfamethazole (Scheme 156).

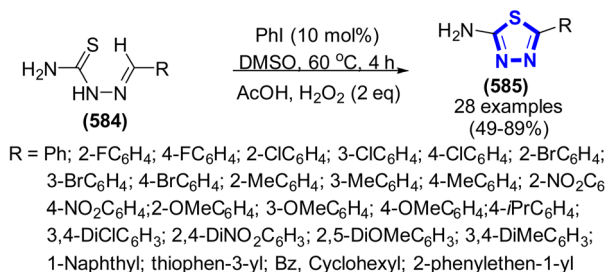
Y. Han *et al.* (2018) developed an approach for the synthesis of various 2-amino-1,3,4-thiadiazole derivatives from thiosemicarbazide through intramolecular oxidative coupling in the presence of phenyl iodide and H_2O_2 with AcOH (Scheme 157).²⁴⁴ The current approach used readily available starting materials with moderate reaction conditions, adequate to exceptional product yields, and the exclusion of metal catalysts, hence improving the environmental sustainability of the process.

A synthetic route to various 4,5-functionalized 1,2,3-thiadiazoles from triazole catalyzed by a strong base in either protic (such as water, with or without acid) or aprotic (such as ethyl acetate) solvent at ambient temperature was described by V. O. Filimonov *et al.* (2017) (Scheme 158).²¹⁷ This metal-free





Scheme 156 Chemical structures of bioactive compounds containing a thiadiazole framework.



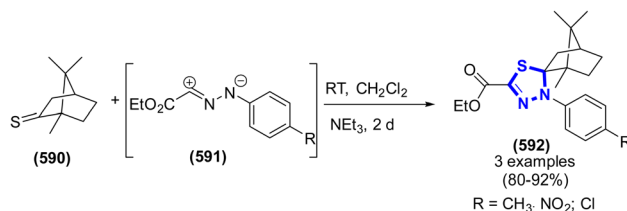
Scheme 157 Synthesis of 2-amino-1,3,4-thiadiazole catalyzed by PhI.

Cornforth-type rearrangement generated the products in great to outstanding yields. Based on DFT calculations, the process of rearrangement proceeds by initially generating a diazo molecule as an intermediate species. This rearrangement can be facilitated by acids, which catalyze the reaction through the protonation of the oxygen atom in the sulfonamide group.

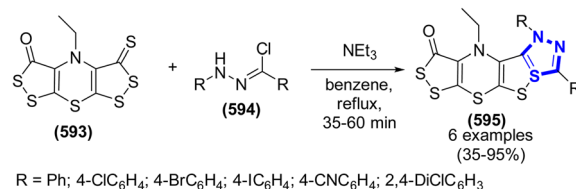
A. Feddoui *et al.* (2004) introduced the 1,3-dipolar cycloaddition of nitrilimines created by the *in situ* reaction between α -bromoglyoxalates and triethylamine with (1R)-thiocamphor to form various camphane-2-carboxylic acid ethyl esters in DCM at ambient temperature (Scheme 159).²⁴⁵ The structures of the pure 1,3,4-thiadiazoles diastereoisomers were thoroughly determined using spectroscopic methods, and based on the X-ray investigations, it was deduced that the absolute configuration of the C5 sporadic carbon is (R).

The reaction between ketothione and hydrazonoyl chlorides to synthesize dithiolo[1,4]thiazine derivatives in the presence of NEt₃ was introduced by S. Barriga *et al.* (2001) (Scheme 160).²⁴⁶ This 1,3-dipolar cycloaddition approach gave the products in high yields.

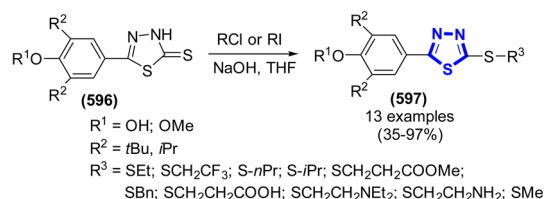
Y. Song *et al.* (1999) demonstrated the alkylation of thiadiazolethiones with alkyl chloride or alkyl iodide in the presence of NaOH in THF to form 1,3,4-thiadiazoles (Scheme 161).²⁴⁷ This protocol gave the desired products in modest to high yields. Moreover, following mass screening and SAR tests, 1,3,4-



Scheme 159 Synthesis of 1,3,4-thiadiazole frameworks.



Scheme 160 Synthesis of dithiolo[1,4]thiazines catalyzed by NEt₃.

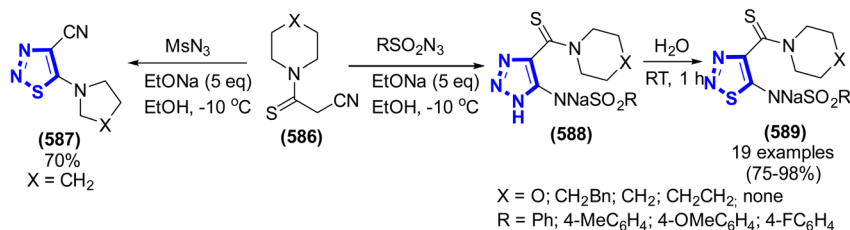


Scheme 161 Synthesis of 1,3,4-thiadiazole derivatives catalyzed by NaOH.

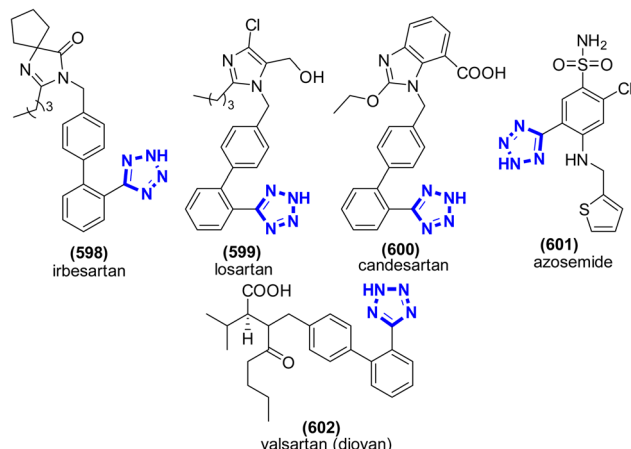
thiadiazole was found to be a powerful, selective, and orally active COX-2 inhibitor.

2.3.4. Tetrazole. Tetrazoles are five-membered heterocyclic compounds characterized by the presence of four nitrogen atoms in their ring structure. They have considerable chemical stability, acidity equivalent to carboxylic acids, and robust hydrogen bonding potential, making them advantageous in medicines, materials science, and coordination chemistry.²⁴⁸ Tetrazole derivatives are extensively used in medicinal chemistry as bioisosteres of carboxylic acids, enhancing metabolic stability and membrane permeability in drug design. Tetrazole moieties display many bioactivities such as antiviral,^{249,250} anticancer,^{251,252} antibacterial,²⁵³ antifungal,²⁵⁴ antioxidant,²⁵⁵ and inhibitors of metabolic processes.²⁵⁶

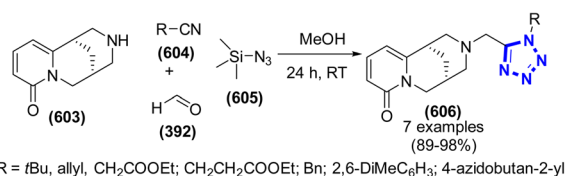
D. P. Zarezin *et al.* (2018) reported the azido-Ugi multicomponent reaction of trimethylsilyl azide, cytosine, formaldehyde, and various isocyanides in the presence of MeOH solvent to



Scheme 158 Synthesis of 4,5-functionalized 1,2,3-thiadiazoles.



Scheme 162 Chemical structures of bioactive compounds containing a tetrazole framework.



Scheme 163 Synthesis of tetrazole derivatives of cytosine.

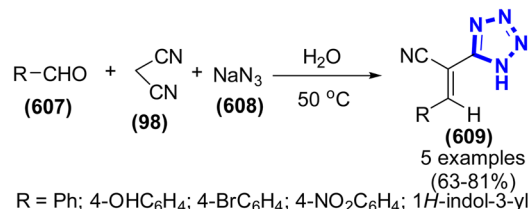
synthesize tetrazole derivatives of cytosine (Scheme 163).²⁵⁷ This was a useful synthetic route because either aliphatic, aromatic, functionalized, or sterically hindered isocyanides could be employed, and the product yields were excellent.

Z. N. Tisseh *et al.* (2012) developed a synthetic route for catalyst-free cascade Knoevenagel condensation/1,3 dipolar cycloaddition, producing various 5-substituted-tetrazoles (Scheme 162).²⁵⁸ The experimental procedure involved the execution of a three-component reaction utilizing aromatic aldehydes, malononitrile, and NaN_3 in an aqueous environment at 50 °C. This reaction yielded high quantities of products. Because there was no catalyst or additional agent, this innovative method allowed the use of water and avoided ecologically hazardous traditional organic solvents, as well as quick set-up and minimal waste generation.

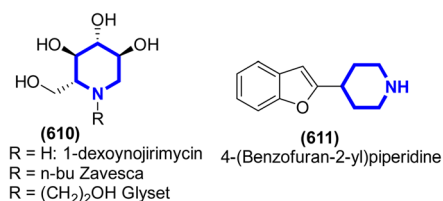
3. 6-Membered rings

3.1. Six-membered heterocycles containing one nitrogen atom

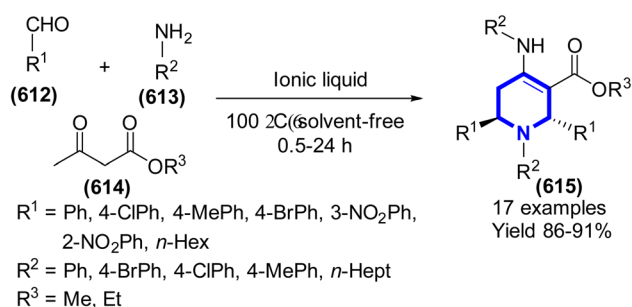
3.1.1. Piperidine. Piperidine is a saturated heterocyclic molecule with six rings and one nitrogen atom. Its adaptable and non-aromatic configuration confers substantial chemical and biological attributes, establishing it as a crucial scaffold in pharmaceutical chemistry, organic synthesis, and materials research.²⁵⁹ Piperidine derivatives are prevalent in bioactive compounds and pharmacological agents in medical chemistry. They demonstrate a wide range of pharmacological actions, including analgesic, antihypertensive, depressive,



Scheme 164 Synthesis of 5-substituted-tetrazole moieties without a catalyst.



Scheme 165 Chemical structures of bioactive compounds containing a piperidine framework.



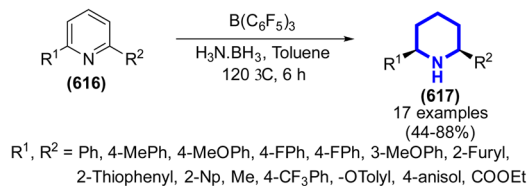
Scheme 166 Synthesis of functionalized piperidine catalyzed by an ionic liquid.

antipsychotic, antiviral, and anticancer properties. Numerous prominent pharmaceuticals, including Risperidone (antipsychotic), Loperamide (antidiarrheal), and Paroxetine (antidepressant), contain a piperidine ring, underscoring its significance in drug design and optimization (Scheme 164 and 165).^{260,261}

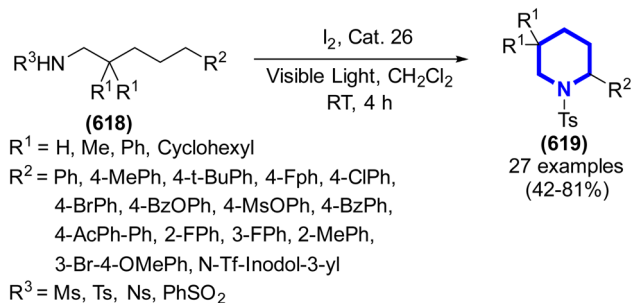
Hamid Reza Shaterian and Kobra Azizi (2013) reported a green procedure for the synthesis of highly functionalized piperidine derivatives (Scheme 166).²⁶² The five-component reactions of aromatic aldehydes, aniline, and β -ketoester were conducted under the catalysis of an acidic IL. A range of acidic ILs was examined, including [Hmim]HSO₄, [TMG]ClO₄, and [TMG]TFA. The reaction mixture was stirred at 100 °C for 10 min in the absence of any solvent, resulting in the desired outcome. In particular, the IL has potential to be efficiently removed from the reaction media, and subsequently utilized in many cycles. The employed procedure demonstrated efficacy, diastereoselectivity, and convenience as a one-pot method.

In the study conducted by Zhou *et al.* (2016), they documented the utilization of borane as a catalyst for the metal-free

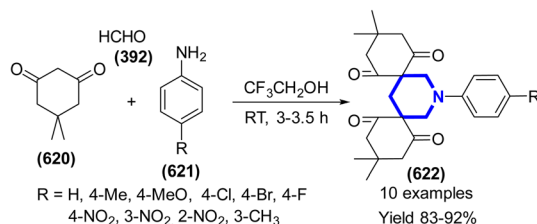




Scheme 167 Synthesis of piperidine derivatives catalyzed by tris(perfluorophenyl)-borane.



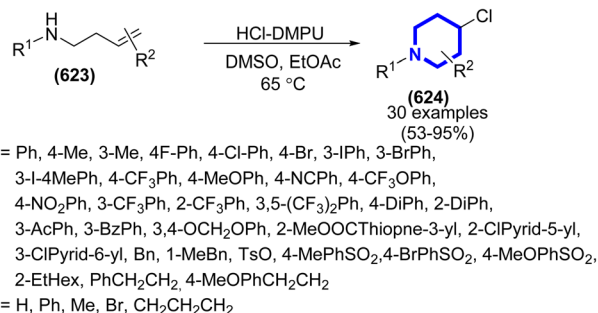
Scheme 168 Synthesis of piperidines catalyzed by iodine and N-bromosuccinimide (NBS) (Cat. 26).



Scheme 169 Synthesis of piperidines catalyzed by 2,2,2-trifluoroethanol.

transfer hydrogenation of pyridines (Scheme 167).²⁶³ A diverse range of pyridines was produced through the utilization of piperidine derivatives, ammonia borane as the hydrogen source, and tris(perfluorophenyl)borane as the catalyst. The reactions were conducted using toluene as the solvent at 120 °C for 6 h, generating products in yields ranging from 44% to 88%, accompanied by *cis*-selectivity that varied from moderate to outstanding.

Hongwei Zhang and Kilian Muniz (2017) described a way to selectively create piperidine *via* intramolecular catalytic C_{sp^3} -H amination (Scheme 168).²⁶⁴ In the experimental procedure, the reactions were performed in the presence of molecular iodine and NBS, utilizing a visible light source, over a duration of 4 h at ambient temperature. The reaction was investigated using sulfonimides, trimethyl-silylethylsulfonyl, and 2-bromophenyl sulfonyl under the optimized conditions. The corresponding piperidination products were obtained in medium to high yield.



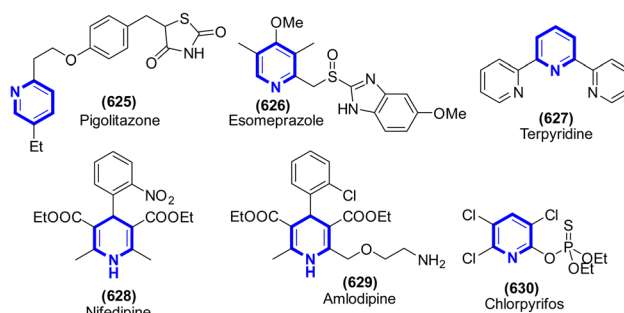
Scheme 170 Synthesis of piperidines catalyzed by HCl/DMU.

The experimental procedure showcased a technique characterized by gentle and consistent conditions, enabling the targeted synthesis of 2-arylsubstituted piperidines.

Audumbar Patil *et al.* (2018) developed a metal-free green procedure for the preparation of piperidine scaffolds from formaldehyde, aromatic aniline, and 1,3-dicarbonyl compounds (Scheme 169).²⁶⁵ 2,2,2-Trifluoroethanol was used as the catalyst with a strong acidic property, which played a crucial function in increasing the rate of the reaction and initiating it.

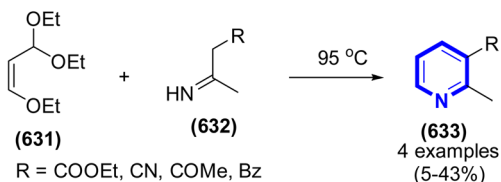
Rene Ebule *et al.* (2019) published an aza-Pummerer protocol for the synthesis of piperidines from homoallylic (Scheme 170).²⁶⁶ The present investigation demonstrated that the combination of hydrochloric acid (HCl) and *N,N*-dimethylpropyleneurea (DMPU) facilitates the generation of the (thiomethyl)methyl carbenium ion from dimethyl sulfoxide (DMSO) under mild conditions. High yields of 4-chloropiperidines were obtained through the cyclization of aromatic and aliphatic amines using the HCl/DMPU reagent. The aza-Pummerer method, facilitated by a combination of 5 + 1 protic acids, demonstrates a broad substrate scope. Under these conditions, the reaction exhibits high chemical yields, while effectively accommodating diverse functional groups. Furthermore, the scalability of this approach is noteworthy (Scheme 171).

3.1.2. Pyridine. Pyridine is a six-membered aromatic heterocycle with one nitrogen atom in its ring. The structural resemblance of pyridine to benzene, together with the electron-withdrawing characteristics of nitrogen, bestows it and its derivatives distinct chemical and electronic qualities, making them exceedingly desirable in many scientific and commercial



Scheme 171 Chemical structures of bioactive compounds containing a pyridine framework.





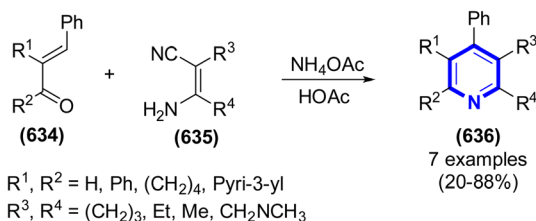
Scheme 172 Synthesis of pyridines under catalyst-free conditions.

applications.²⁶⁷ Pyridine serves as a crucial scaffold in medicinal chemistry, significantly improving bioavailability, metabolic stability, and target binding in several pharmaceutical medicines. Drugs containing pyridine have a diverse array of pharmacological effects. In contemporary medicine, pyridine derivatives are also becoming an increasingly important class of compounds with antimicrobial,²⁶⁸ antiviral,²⁶⁹ antioxidant,²⁷⁰ and anticancer²⁷¹ activities.

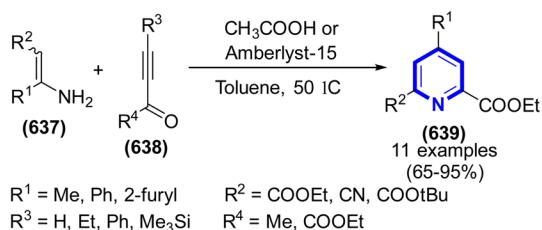
P. Baumgarten and A. Dornow (1939) reported a process for the synthesis of 2,3-disubstituted pyridine derivatives (Scheme 172).²⁷² The reactions were performed *via* the condensation of alkyl or vinyl amines with 1,3-dicarbonyl derivatives.

Michael Robinson *et al.* (1992) prepared pyridines from enamino nitriles (Scheme 173).²⁷³ Under acidic conditions (using $\text{NH}_4\text{OAc}/\text{HOAc}$), the target pyridine compounds were afforded in about 42% yield from the cyclization of chalcones and 1-amino-2-cyanocyclopentenes.

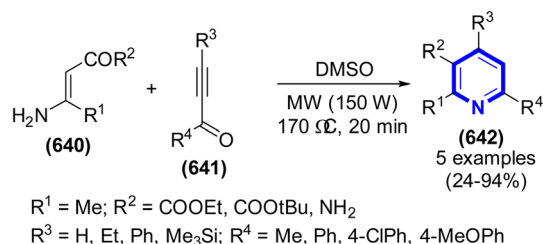
Bagley *et al.* (2001) described a unique adaptation of the Bohlmann–Rahtz pyridine synthesis method (Scheme 174).²⁷⁴ In this method, the catalyst employed was either AcOH or Amberlyst-15. In a single synthetic step conducted at 50 °C, a diverse array of functionalized pyridines was derived through the cyclization reaction between enamino esters and alkynone substrates.



Scheme 173 Synthesis of pyridines catalyzed by AcOH.



Scheme 174 Synthesis of pyridines catalyzed by Amberlyst-15 ion exchange resin or HOAc.

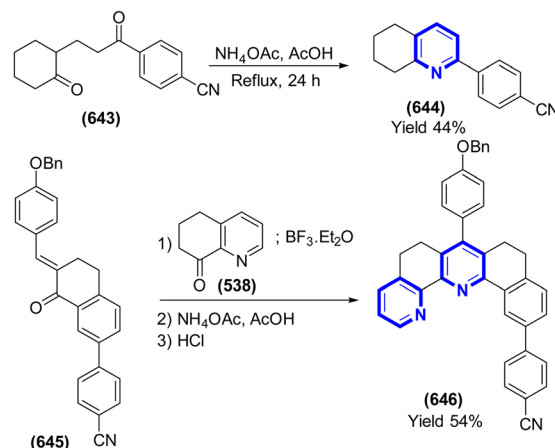


Scheme 175 Synthesis of pyridines under catalyst-free conditions.

In the study by Bagley *et al.* (2002), they developed a novel MW approach for the preparation of pyridines, employing the Bohlmann–Rahtz reaction (Scheme 175).²⁷⁵ Under microwave irradiation, the ethyl aminocrotonate reacted with various alkynones throughout a two-step procedure including Michael addition of enamine and alkynone and cyclodehydration to pyridine. The experiment was performed at 170 °C in toluene solvent, utilizing irradiation at either 150 or 160 W for a duration of 20 min.

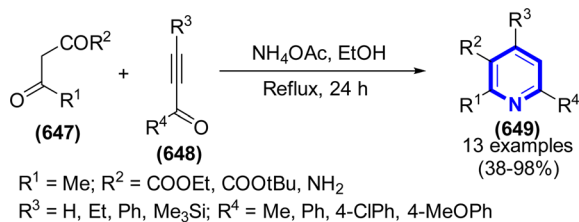
In 2002, Kelly and Lebedev proposed a methodology for synthesizing a selection of unsymmetrical bridged terpyridines (Scheme 176).²⁷⁶ The synthesis of the pyridines was achieved through the condensation reaction between amine and carbonyl molecules. The present methodology employed intra- and inter-molecular Michael reactions as crucial steps.

Xin Xiong *et al.* (2004) showed a novel mild condensation approach for the preparation of poly-substituted pyridines (Scheme 177).²⁷⁷ The reaction involving alkynones, 1,3-dicarbonyl compounds, and NH_4OAc was conducted under reflux in alcoholic solvents for a duration of 24 h, in the absence of a catalyst. The present study showcased a novel hetero-annulation reaction involving three components, which was successfully conducted using highly efficient and gentle reaction conditions. The pyridines that corresponded to the given conditions were obtained in yields ranging from modest to good and obtained as single regioisomers.

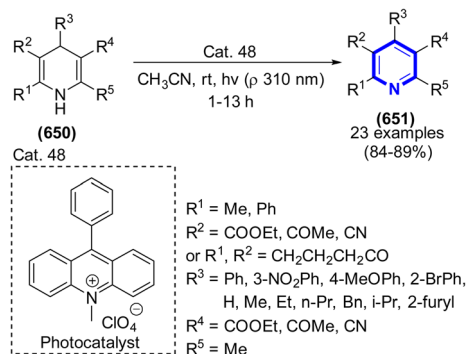


Scheme 176 Synthesis of unsymmetrical bridged terpyridines catalyzed by AcOH.





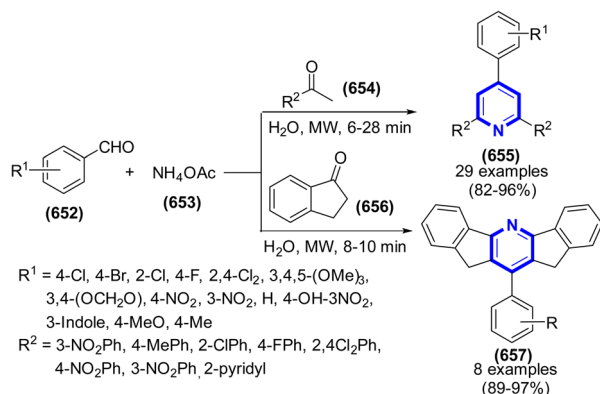
Scheme 177 Synthesis of pyridines under catalyst-free conditions.



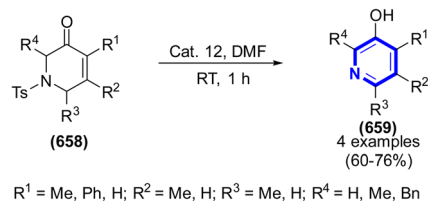
Scheme 178 Synthesis of pyridines catalyzed by Cat. 48.

The mild aromatization of 1,4-dihydropyridines under metal-free conditions was reported by Xinqiang Fang *et al.* (2007) (Scheme 178).²⁷⁸ This method for the oxidation aromatization of 1,4-dihydropyridines to symmetrical and unsymmetrical pyridines was performed at r.t. in the presence of Cat. 48 as the organocatalyst. The reaction mixture was refluxed in anhydrous acetonitrile solvent under an oxygen atmosphere, while exposed to irradiation from a 150 W high-pressure mercury lamp. The light emitted from the lamp was filtered to exclude wavelengths below 310 nm. This study showcases the efficacy of 9-phenyl-10-methylacridinium as a very efficient photocatalyst. This organocatalyst has a significant level of recoverability and reusability.

In the study by Shujiang Tu *et al.* (2007), they documented the utilization of a Krohnke reaction as a means to synthesize terpyridines (Scheme 179).²⁷⁹ The experimental protocol



Scheme 179 Synthesis of terpyridines under catalyst-free conditions.



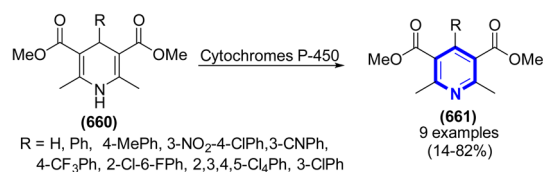
Scheme 180 Synthesis of 3-hydroxypyridines catalyzed by Cat. 12.

involved a one-pot reaction using 2-acetylpyridines, aromatic aldehydes, and ammonium acetate, employing either MW or conventional heating. Various terpyridines were afforded in aqueous medium. This protocol is a convenient, economic, and environmentally friendly process.

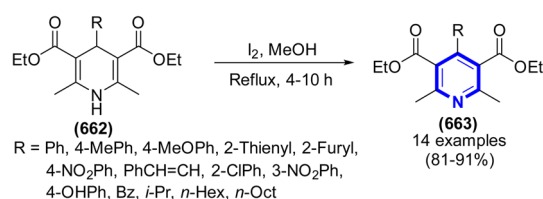
Kazuhiro Yoshida *et al.* (2009) reported the discovery of a novel synthesis pathway for the production of 3-hydroxypyridines (Scheme 180).²⁸⁰ The reactions were conducted by treating pyridin-3-ones with Cat. 12 in dimethylformamide at ambient temperature for a duration of 1 h. The corresponding products were generated in high yields. The primary advantages of this approach are its simplicity, flexibility, and ability to prevent the production of inseparable regioisomers.

In the study by Boecker *et al.* (1986), they successfully synthesized derivatives of pyridines with 4-aryl and 4-alkyl substitutions *via* the enzymatic oxidation of 1,4-dihydropyridines (Scheme 181).²⁸¹ Cytochrome P-450 enzyme was used as an efficient oxidase biocatalyst in this process.

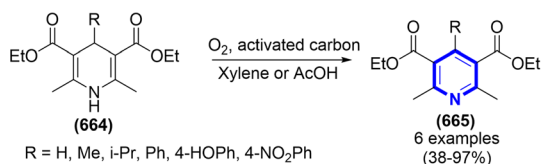
Jhillu S. Yadav *et al.* (2000) synthesized pyridines *via* the aromatization of Hantzsch 1,4-dihydropyridines (Scheme 182).²⁸² The aromatization method was performed by refluxing Hantzsch 1,4-dihydropyridines with iodine in methanol. Various alkyl, benzyl, aryl, and heterocyclic 4-substituted pyridines were afforded in high yields. This protocol is highly advantageous over existing methods because of its simple and mild reaction conditions.



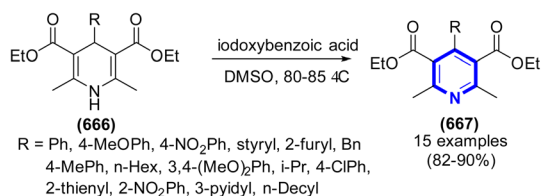
Scheme 181 Synthesis of 4-substituted pyridines catalyzed by cytochrome P-450 enzyme.



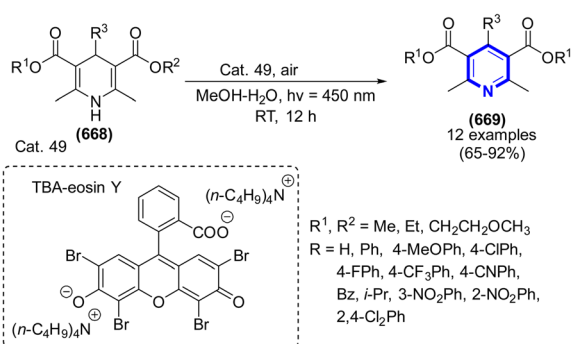
Scheme 182 Synthesis of pyridines catalyzed by molecular iodine.



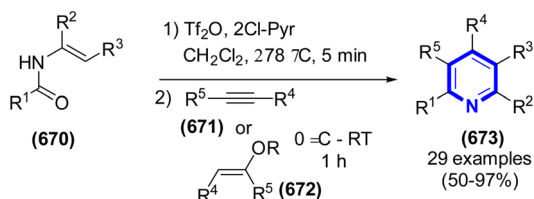
Scheme 183 Synthesis of pyridines catalyzed by activated carbon.



Scheme 184 Synthesis of pyridines catalyzed by iodoxybenzoic acid.

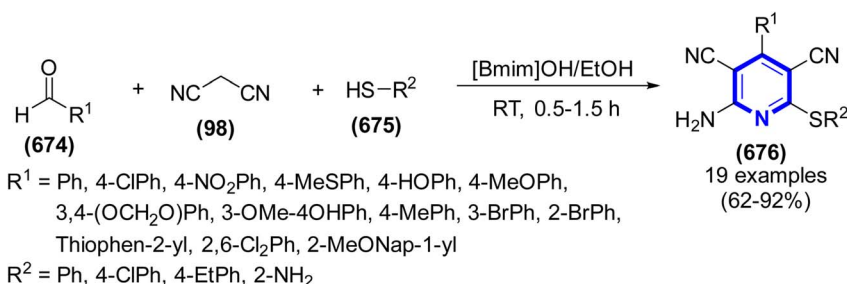


Scheme 185 Synthesis of pyridines catalyzed by Cat. 49.



R¹ = H, Ph, 2-Thienyl, N(CH₂CH₂)₂O
 R², R³ = Me, (CH₂)₄
 R²C=CHR³ = Ph, 3,5-(OMe)₂Ph, 4-COOMePh, 3-DHP, 3-Thienyl, 4-NO₂Ph
 R⁴, R⁵ = H, OEt, t-Bu, OSiPr₃, Ph, Morpholine, 4-MeOPh,
 R⁴C=CR⁵ = (CH₂)₃, (CH₂)₄, Indene; R = Et, OSiPh₃, OSiMe₃, OSiMe₂Bu

Scheme 186 Synthesis of pyridines catalyzed by 2-chloropyridine.



Scheme 187 Synthesis of pyridines catalyzed by [Bmim]OH.

Natsuki Nakamichi *et al.* (2004) developed a method for the activated carbon-promoted oxidative aromatization of Hantzsch 1,4-dihydropyridines (Scheme 183).²⁸³ In the presence of molecular oxygen, 1,4-dihydropyridines were treated in xylene or AcOH using activated carbon as the catalyst. The reaction mixture was placed in a three-necked flask and subjected to stirring at 120 °C for 30 min. The corresponding pyridine derivatives were obtained from a series of Hantzsch 1,4-dihydropyridines with substituents on their 4-position. This is a simple, environmentally friendly, economical, and operationally simple procedure without the use of metal oxides or organic oxidizing agents.

J. S. Yadav *et al.* (2006) aromatized 1,4-dihydropyridines using iodoxybenzoic acid as an efficient oxidant (Scheme 184).²⁸⁴ The experiment was conducted using DMSO as the solvent, at a temperature in the range of 80–85 °C. The reaction mixture was heated for a period of 2–4 h depending on the structure of the substrate. A wide variety of pyridine derivatives was produced in elevated yields. The advantages of this approach include the use of inexpensive oxidants, mild reaction conditions, and easy workup.

Xiaojing Wei *et al.* (2014) proposed a novel metal-free-mediated oxidation aromatization technique for the conversion of 1,4-dihydropyridines to pyridines (Scheme 185).²⁸⁵ The process of aromatization of 1,4-dihydropyridines was facilitated through the use of **Cat. 49** as a photosensitizer. Instead of using a photoredox catalyst and inorganic oxidant, the advantages of this protocol are the use of the organic dye eosin-Y and molecular oxygen.

In the study by Mohammad Movassaghi *et al.* (2007), they presented a technique enabling the synthesis of pyridine derivatives *via* a single-step and convergent approach (Scheme 186).²⁸⁶ The cyclization reactions were conducted under controlled conditions in dichloromethane at temperatures ranging from –78 °C to 0 °C. These reactions involved the direct condensation of N-vinyl/aryl amides with several π -nucleophile reagents, including ynamide, ynamine, alkyl vinyl ether, and silyl ether. The combinations were subjected to heating with trifluoromethanesulfonic anhydride (Tf₂O) in the presence of 2-chloropyridine (2-ClPyr) as a base additive. A range of poly-substituted pyridines was synthesized in high yields.

Brindaban C. Ranu *et al.* (2007) developed an improved process for the three-component synthesis of pyridines using task-specific ILs (Scheme 187).²⁸⁷ Stirring was used to execute the three-component condensations of aromatic aldehydes,



malononitrile, and thiophenols, in the presence of 1-butyl-3-methylimidazolium hydroxide ion liquid ([Bmim]OH). A wide range of aromatics, as well as heteroaromatic pyridines, yielded good to exceptional results. The reactions were very clean, simple, and easy to work up. This is a green protocol because of the absence of hazardous organic solvents in the reaction and the reusability of ILs.

A general and efficient method for the 2-amination of pyridines was reported by Jingjun Yin *et al.* (2007) (Scheme 188).²⁸⁸ The pyridine *N*-oxide derivatives were treated with *tert*-butylamine in the presence of *p*-toluenesulfonic anhydride. This mixture was mixed in trifluorotoluene at 5–20 °C, followed by deprotection with trifluoroacetic acid (70 °C, 2–6 h). High yields of substituted pyridines were achieved under improved one-pot conditions.

Yaojia Jiang *et al.* (2014) researched a new strategy for the synthesis of pyridines *via* ring expansion of 2-allyl-2*H*-azirines (Scheme 189).²⁸⁹ It was claimed that the initial stage involved the formation of 1-azatrienes through the opening of 2-allyl-2*H*-azirines using Cat. 12 as a catalyst under metal-free conditions. Subsequently, the 1-azatrienes obtained were subjected to 6*π*-

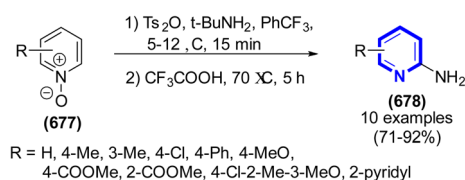
electrocyclization, resulting in the formation of pyridines. A diverse range of pyridines, bearing aryl, alkyl, and heterocyclic substituents, was synthesized with excellent efficiency, resulting in high to exceptional yields.

A new method for the synthesis of pyridines through a one-pot metal-free route was described by Hongbo Wei *et al.* (2015) (Scheme 190).²⁹⁰ The investigated technique is predicated on the utilization of cascade reactions involving aldehydes, phosphorus ylides, and propargyl azide. This approach occurred in three steps involved a Wittig reaction, Staudinger reaction, aza-Wittig reaction, 6*π*-3-azatriene electrocyclization, and 1,3-hydrogen shift. The present study described a novel and highly efficient metal-free one-pot synthetic protocol for the preparation of polysubstituted pyridines. This approach demonstrates several benefits, such as operational simplicity and the capacity to accept various functional groups.

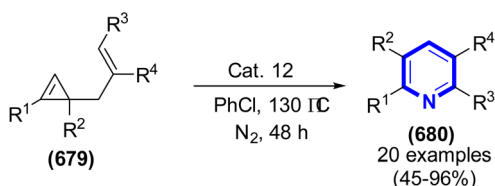
Huawen Huang *et al.* (2016) published a method for the transition-metal-catalyzed preparation of polysubstituted pyridines (Scheme 191).²⁹¹ The reactions were conducted using *O*-acetylketoimes and acroleins in the presence of iodine and triethylamine. A diverse array of functional *N*-heterocycles was synthesized in moderate to excellent product yields with favorable chemo-selectivity. The investigation and proposal of the probable reaction mechanism for the metal-free synthesis of pyridines were conducted *via* mechanistic experiments. This comprehensive mechanism elucidated the function of iodine and triethylamine as activating agents for the *N*-O bond in the heterocyclization of oximes, thereby facilitating the process.

Shen *et al.* (2015) developed a method for the synthesis of polysubstituted pyridines *via* the direct β -C(sp³)-H functionalization of enamines, which offers a practical approach (Scheme 192).²⁹² The two-step process in the one-pot annulation of 1-arylethylamines and ynone consists of an intermolecular Michael addition reaction followed by an intramolecular condensation. A wide range of pyridines was prepared under metal-free conditions in excellent yield and high regioselectivity. This technique exhibited compatibility with a wide range of substrates, demonstrated excellent atom efficiency, and showcased the significant synthetic potential of the resulting compounds.

Debashis Majee *et al.* (2016) proposed an innovative synthetic approach to produce 4,6-diarylpicolinates. This method involves a domino reaction between cyclic sulfamidate imines and Morita–Baylis–Hillman acetates derived from

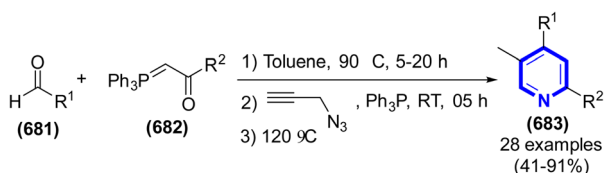


Scheme 188 Synthesis of pyridines catalyzed by *p*-toluenesulfonic anhydride.



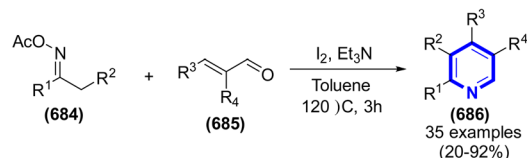
R¹ = Ph, 4-MeOPh, 4-NO₂Ph, 2-furyl, 2-thienyl, Me, *n*-Pr, PhCH₂CH₂, *i*-Pr, Cyclohexyl, cyclopropyl, cyclohex-1-enyl
 R² = COOEt, COO*t*-Bu, Ph, H, PO(OEt)₂
 R³ = Ph, 3-MeOPh, 4-H, 4-NO₂Ph, Me; R⁴ = H, Me

Scheme 189 Synthesis of pyridines catalyzed by Cat. 12.



R¹ = Ph, 4-MePh, 3,4-Me₂Ph, 3-MeOPh, 2-FPh, 2-ClPh, 3-ClPh, 4-ClPh, 2-BrPh, 4-MeOOCPh, 2,5-Br₂Ph, 4-CF₃Ph, 4-NO₂Ph, 4-NCPH, 4-Me₂NPh, 2-Furyl, 4-Pyridyl, 4-BisPh, 2-naphthyl, PhCH=CH-, PhCH₂CH₂
 R² = Me, *n*-Bu, *i*-Pr, Cyclopropyl, Ph, 4-MeOPh, 4-BrPh

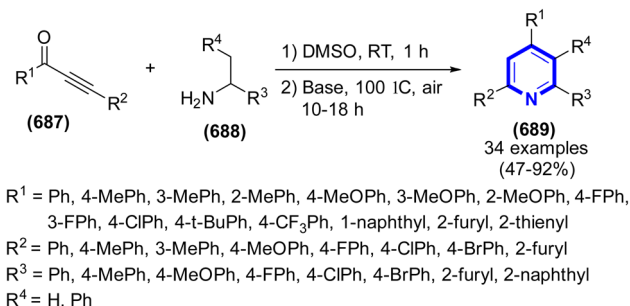
Scheme 190 Synthesis of pyridines under catalyst-free conditions.



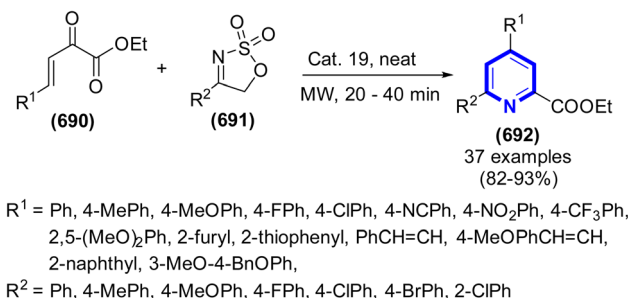
R¹ = Ph, 4-MePh, 4-*t*-BuPh, 4-*i*-BuPh, 4-BisPh, 4-MeOPh, 4-FPh, 4-ClPh, 4-BrPh, 4-IPh, 4-MeSO₂Ph, 4-NO₂Ph, 3-MeOPh, 3-BrPh, 3-NO₂Ph, 3-CF₃Ph, 2-ClPh, 2-NO₂Ph, 3,4-Cl₂Ph, 1-naphthyl, 2-furyl, 2-thienyl, 3-pyridyl
 R² = H, Me, Ph, (CH₂CH₂)
 R³ = Ph, 4-MeOPh, 4-NO₂Ph, 4-FPh, 2-MeOPh, 2-furyl, *n*-Pr, H
 R⁴ = H, Me

Scheme 191 Synthesis of pyridines catalyzed by iodine.





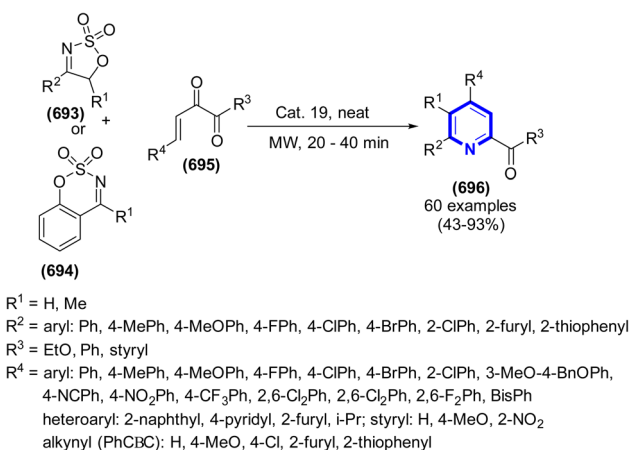
Scheme 192 Synthesis of pyridines catalyzed by an organic base.



Scheme 193 Synthesis of pyridines catalyzed by Cat. 19.

nitroolefins/nitrodienes (Scheme 193).²⁹³ The 5-membered cyclizations were performed using **Cat. 19** as an organobase under metal-free conditions at 55 °C. A range of 4,6-diaryl-picolinate compounds was synthesized in high to outstanding yields.

Similarly, other metal-free and solvent-free protocols for the synthesis of diversely substituted picolinates were developed by Soumen Biswas *et al.* (2017) (Scheme 194).²⁹⁴ The formation of picolinate derivatives was achieved through a sequential reaction involving five- or six-membered cyclic sulfamidate imines and β,γ -unsaturated α -ketocarboxyls. This reaction was conducted under neat conditions and facilitated by MW. Under the optimized reaction conditions, the annulations were promoted



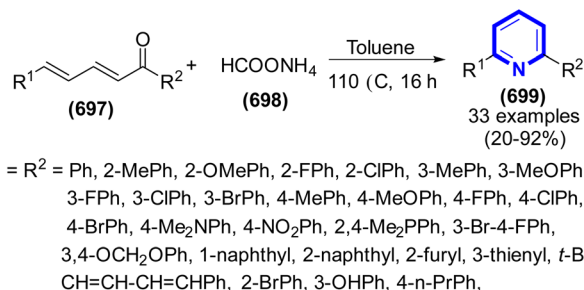
Scheme 194 Synthesis of pyridines catalyzed by Cat. 19.

by **Cat. 19** as a solid organic base. The corresponding products were obtained including 4,6-disubstituted-picolinates, picolinates, and 4,6-diaryl-2-benzoyl/cinnamoyl-pyridines in good yields.

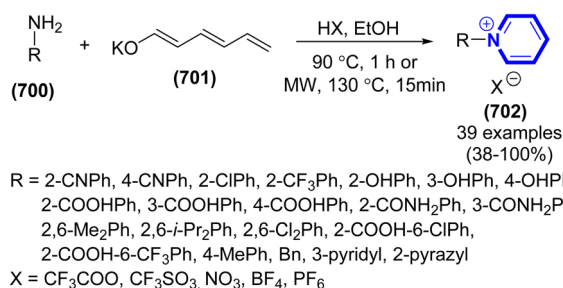
In a study conducted by Yejun Gao *et al.* (2019), a method for synthesizing asymmetrical 2,6-diarylpyridines from $\alpha,\beta,\gamma,\delta$ -unsaturated ketones was demonstrated. This process involved the Michael addition of ammonium formate, followed by annulation (Scheme 195).²⁹⁵ The cyclization process was performed in toluene solvent in ambient air at 110 °C for 16 h. A range of aliphatic and aromatic 2,4-dien-1-one substrates was employed to explore the annulation process. The corresponding products were obtained in high yields. This method offers numerous significant benefits, such as a simple and expedited work-up procedure, a wide range of substituents, lack of additives, outstanding yields, and a high level of regioselectivity.

Ghada Asskar *et al.* (2019) demonstrated the conversion of primary amines into pyridinium salts (Scheme 196).²⁹⁶ In this experimental procedure, glutacanaldehyde was employed as a substitute reagent for the zinc salt. In the present investigation, the degradation was effectively inhibited in the presence of amines. The conversion of primary amines to pyridinium salts was conducted using a Brønsted acid catalyst at 90 °C for 1 h. To synthesize a wide range of pyridines, a variation in the counterion and aniline was surveyed, resulting in excellent conversions.

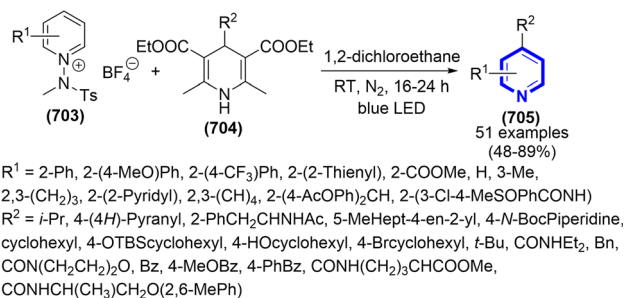
Inwon Kim *et al.* (2020) successfully devised a method for functionalizing the C4-pyridine scaffold using 1,4-dihydropyridines *via* photoinduced charge transfer (Scheme 197).²⁹⁷ The present study investigated the utilization of electron donor-



Scheme 195 Synthesis of 2,6-diarylpyridines under catalyst-free conditions.



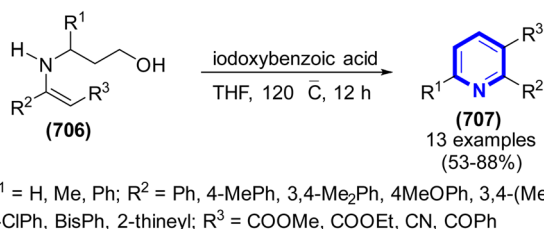
Scheme 196 Synthesis of pyridinium salts catalyzed by a Brønsted acid.



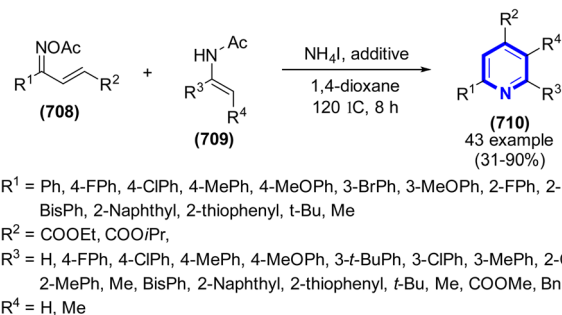
Scheme 197 Synthesis of pyridines under the catalyst-free conditions.

acceptor complexes formed between *N*-amidopyridinium salts and 1,4-dihydropyridine derivatives, employing visible light irradiation as the primary stimulus. The resultant compounds were derived from different radicals of 1,4-dihydropyridines, including alkyl, acyl, and carbamoyl groups. This technique shows notable advantages, particularly in terms of superior regiocontrol, as well as the utilization of mild and metal-free settings. Notably, this strategy does not necessitate the use of a photocatalyst and may be effectively implemented under visible-light-promoted conditions.

A new metal-free strategy for the synthesis of 2,3-disubstituted pyridines was reported by Peng Gao *et al.* (2020) (Scheme 198).⁵³ The production of 2,3-disubstituted pyridines was achieved by means of a specific oxidative cyclization process involving *N*-hydroxyalkyl enamines and iodoxybenzoic acid. The process of synthesizing pyridines can be achieved using a two-step procedure, which entails the oxidation of alcohols and the subsequent condensation of aldehydes with the α -carbon of enamines. The reaction was conducted in



Scheme 198 Synthesis of pyridines catalyzed by iodoxybenzoic acid.

Scheme 199 Synthesis of pyridines catalyzed by NH_4I .

tetrahydrofuran at 120 °C for 12 h. This is an efficient metal-free protocol for the synthesis of pyridines due to the use of environment-friendly substrates, wide reagent scope, mild conditions, and good efficiency.

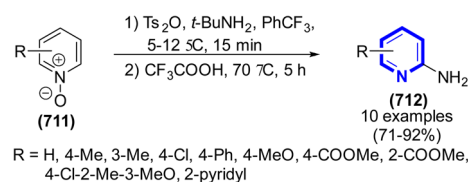
Jindian Duan *et al.* (2020) researched NH_4I -triggered [4 + 2] cyclization for the synthesis of pyridines under metal-free conditions (Scheme 199).²⁹⁸ The strategy development in this study involved the annulation of α,β -unsaturated ketoxime acetates with *N*-acetyl enamides. The reaction mixture of ketoxime-enoate and *N*-acetyl enamide was heated in tetrahydrofuran with a certain amount of ammonium iodide and additive ($\text{Na}_2\text{S}_2\text{O}_4$, NaHSO_3 , triethyl amine, or pyridine) at 120 °C for 8 h under a nitrogen atmosphere. A variety of poly-substituted pyridine derivatives was synthesized using an array of substrates, yielding adequate to outstanding results. A credible mechanism was suggested for this reaction based on the experimental results.

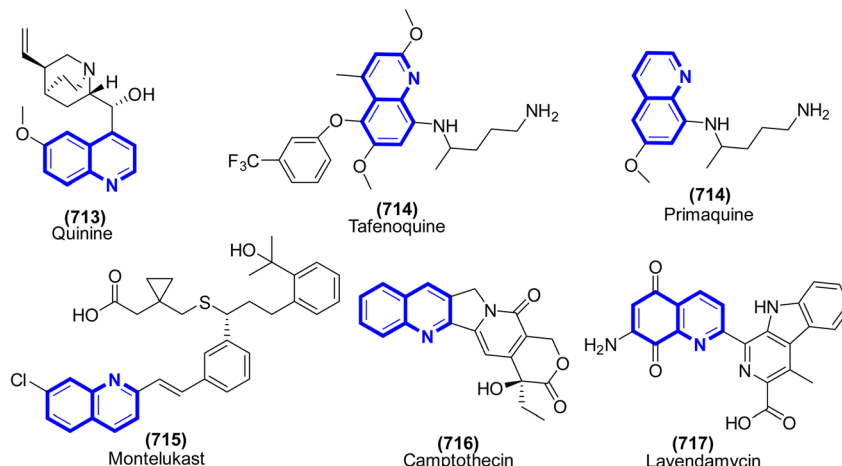
Jingjun Yin *et al.* (2007) synthesized 2-aminopyridines from pyridine *N*-oxides (Scheme 200).²⁸⁸ The products were obtained *via* a one-pot reaction using Ts_2O and $t\text{-BuNH}_2$. The crude reaction mixture was treated with trifluoroacetic acid, which provided the *tert*-butyl group. This protocol is an efficient procedure for the 2-amination of 2-unsubstituted pyridine derivatives (Scheme 201).

3.1.3. Quinoline and isoquinoline. Quinoline/isoquinoline are members of a class of organic compounds in the aromatic heterocyclic series. The compounds have a distinctive double-ring configuration including a benzene ring and a pyridine ring, which are joined at two neighboring carbon atoms. The ring that makes up benzene is composed of six carbon atoms, whereas the ring that makes up pyridine is composed of five carbon atoms and one nitrogen atom.²⁹⁹ These compounds are present in a wide variety of bioactive natural ingredients, medications that are now utilized in clinical practice, and pharmaceuticals, including anticancer,³⁰⁰ antibacterials,³⁰¹ antitumor,³⁰² and anti-inflammatory drugs.³⁰¹

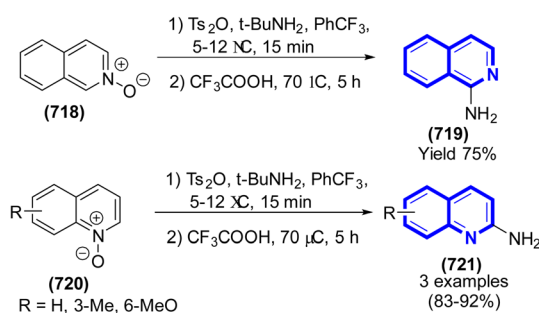
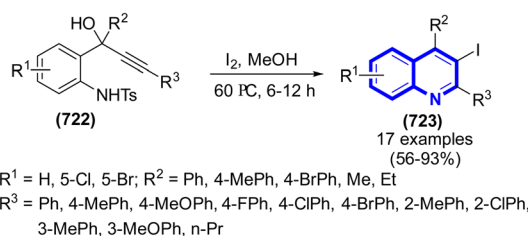
Jingjun Yin *et al.* (2007) synthesized (iso)quinolones through a simple method (Scheme 202).²⁸⁸ In a single-step procedure, quinoline/isoquinoline *N*-oxide were transformed into 2-amino(iso)quinolines by employing Ts_2O and $t\text{-BuNH}_2$. Subsequently, the unrefined reaction mixture was subjected to treatment with trifluoroacetic acid, resulting in the introduction of the *tert*-butyl group. This procedure enabled the highly effective one-pot 2-amination of 2-unsubstituted quinolones.

A simple and free-metal protocol for the preparation of 3-iodoquinolines was reported by Shaukat Ali *et al.* (2011) (Scheme 203).³⁰³ Their investigation involved the utilization of

Scheme 200 Synthesis of 2-aminopyridines using Ts_2O and $t\text{-BuNH}_2$.

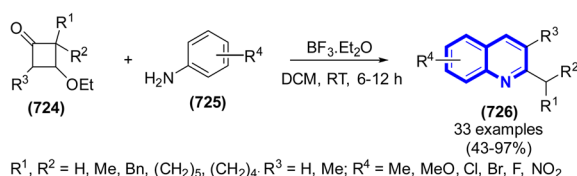


Scheme 201 Chemical structures of bioactive compounds containing a quinoline/isoquinoline framework.

Scheme 202 Synthesis of (iso)quinolones using Ts_2O and $t\text{-BuNH}_2$.

Scheme 203 Synthesis of 3-iodoquinolones catalyzed by iodine.

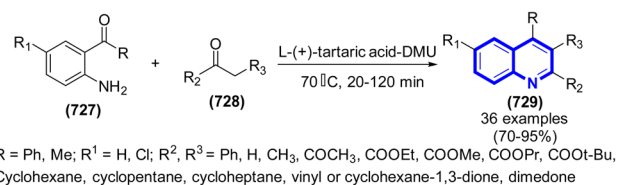
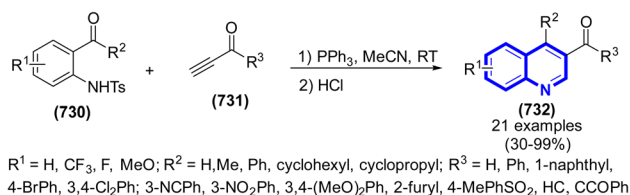
the 6-*endo*-dig iodocyclization methodology, employing mild reaction conditions. The reaction included the agitation of 2-tosylaminophenylprop-1-yn-3-ols and molecular iodine in methanol, followed by heating at 60 °C for an appropriate period. The target quinolones were achieved in modest to

Scheme 204 Synthesis of quinolines catalyzed by $\text{BF}_3 \cdot \text{OEt}_2$.

exceptional yields through this efficient and highly regioselective methods.

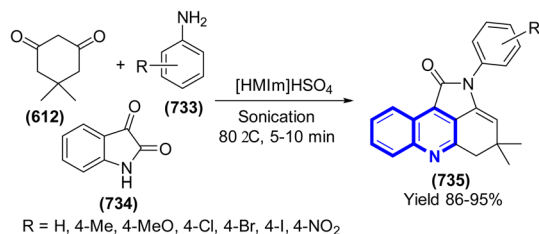
Gang Shan *et al.* (2011) illustrated a novel one-step methodology for the preparation of 2-substituted quinolines *via* [3 + 3]-cyclization (Scheme 204).³⁰⁴ The experimental procedure involved the reaction between 3-ethoxycyclobutanones and aromatic amines, which took place in dichloromethane solvent under ambient conditions. To promote the reaction, $\text{BF}_3 \cdot \text{OEt}_2$ was added to the reaction mixture. A broad functional group tolerance was observed under the optimized reaction conditions.

In the study by Fei-Ping Ma *et al.* (2012), they devised a very effective and environmentally friendly approach to produce quinoline derivatives (Scheme 205).³⁰⁵ The Friedlander heteroannulation process was employed to carry out this approach, resulting in the synthesis of 2-aminoaryl ketones and α -methylene ketones in high yields. This process utilized a deep eutectic solvent that was non-toxic, making it both unique and very successful in an environmentally friendly manner.

Scheme 205 Synthesis of quinoline catalyzed by $L\text{-(+)-tartaric acid-DMU}$.

Scheme 206 Synthesis of quinolones catalyzed by triphenylphosphine.



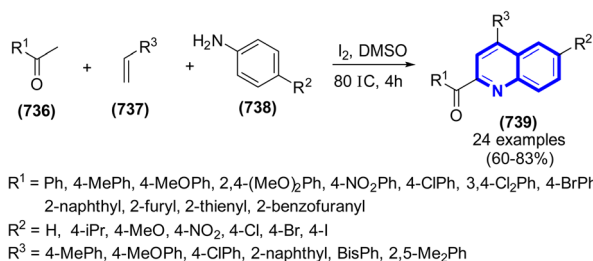


Scheme 207 Synthesis of acridin-1(2H)-ones catalyzed by [HMIIm]HSO₄.

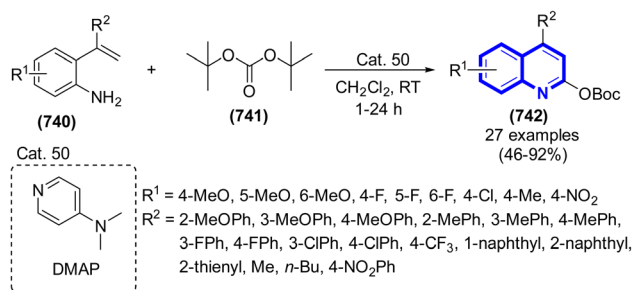
A novel one-pot route for the synthesis of quinolones using a phosphine catalyst was described by San Khong *et al.* (2012) (Scheme 206).³⁰⁶ The process of annulating activated acetylenes with *o*-tosylamidobenzaldehydes or *o*-tosylamidophenones was carried out *via* Michael addition and aldol cyclization. The solution was agitated in acetonitrile at r.t. in triphenylphosphine. Then, the dihydroquinoline intermediates were treated with an HCl solution, leading to detosylated products. A variety of 3-substituted and 3,4-disubstituted quinolones was produced in high yield.

In the study conducted by Hassan Kefayati *et al.* (2012), they investigated the synthesis of acridin-1(2H)-ones in ILs (Scheme 207).³⁰⁷ The synthesis of a three-component condensation process involving 5,5-dimethyl-1,3-cyclohexadione, anilines, and isatin was conducted using 1-hexyl-3-methylimidazolium hydrogen sulfate ([HMIIm]HSO₄) as the solvent. The reaction was carried out under the influence of US for brief periods. The employed approach demonstrated a high level of efficiency and environmental friendliness in the synthesis of pyrroloacridine derivatives, resulting in significant yields and a straightforward process for isolating the desired products.

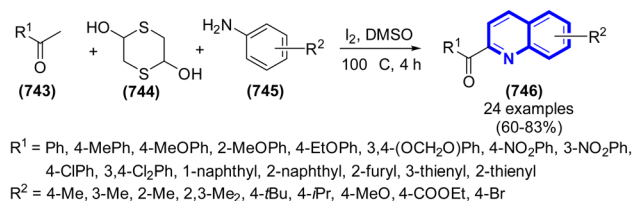
Qinghe Gao *et al.* (2014) reported in detail the utilization of a formal [3 + 2 + 1] annulation strategy for the synthesis of quinolines by a Povarov-type reaction (Scheme 208).³⁰⁸ The three-component reactions of methyl ketones, arylamines, and styrenes were performed in dimethyl sulfoxide at 100 °C for 4 h. In this study, molecular iodine played an important role as the catalyst. The corresponding products were afforded with various groups on the phenyl ring, such as electron-rich, bearing electron-neutral, and electron-deficient groups in the phenyl ring of methyl ketone and aniline.



Scheme 208 Synthesis of quinolines catalyzed by iodine.



Scheme 209 Synthesis of quinolinones catalyzed by Cat. 50.

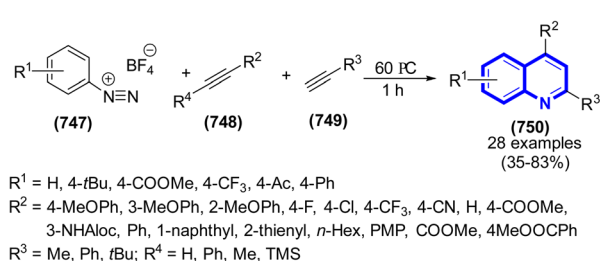


Scheme 210 Synthesis of quinolones catalyzed by iodine.

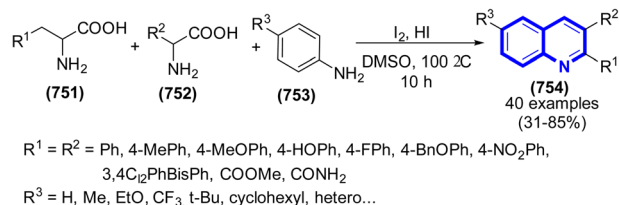
Ya-Nan Huang *et al.* (2016) illustrated a protocol for the synthesis of quinolinones and 2-(pseudo)haloquinolines using 4-dimethylaminopyridine as an organocatalyst (Scheme 209).³⁰⁹ 2-Alkenyl-anilines were treated with di-*tert*-butyl dicarbonate in dichloromethane with 4-dimethylaminopyridine at ambient temperature. Under mild conditions, a variety of quinolines was afforded through 6 π -electron cyclization.

In the study by Xia Wu *et al.* (2017), they developed a new formal [4 + 2] pathway for the production of quinolones (Scheme 210).³¹⁰ The reaction involving the formation of cyclic compounds from methyl ketones and arylamines was carried out using 1,4-dithiane-2,5-diol as the ethylene source. This process was performed in dimethyl sulfoxide using a molecular iodine catalyst at 100 °C for 4 h. The target 2-acylquinolines were provided from various substrates in good yield. The authors presented a hypothesized mechanism that encompasses four distinct steps, namely iodination, Kornblum oxidation, Povarov reaction, and aromatization, based on the findings obtained from control trials.

A novel method for the synthesis of quinolone derivatives through a three-component was described by Hao Wang *et al.* (2017) (Scheme 211).³¹¹ The process of cyclization involving aryl



Scheme 211 Synthesis of quinolines under catalyst-free conditions.

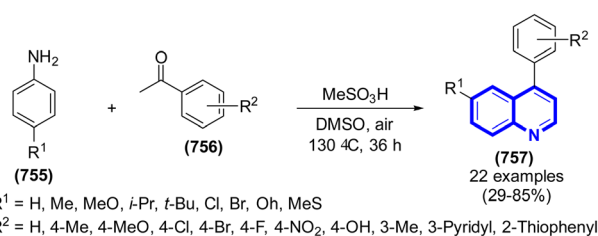
Scheme 212 Synthesis of quinolines catalyzed by I_2/HI .

diazonium compounds, nitriles, and alkynes was conducted at a temperature of 60 °C in the absence of any additives and catalyst. This straightforward and quick approach yielded a collection of quinoline derivatives in high yield.

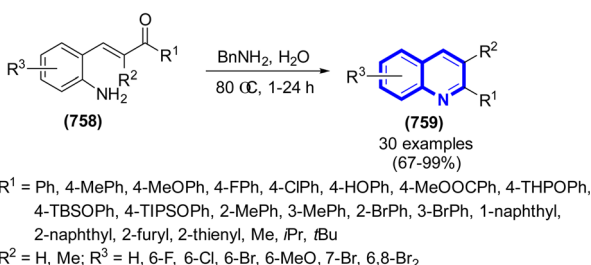
Jia-Chen Xiang *et al.* (2017) presented a detailed procedure for the synthesis of functionalized quinolines *via* a three-component reaction conducted in the absence of metal catalysts (Scheme 212).³¹² The annulation of aniline and two amino acids was performed in dimethyl sulfoxide with the assistance of HI. In addition, the mixture was subjected to the addition of molecular iodine, followed by agitation at 100 °C for 10 h. Under the optimum conditions, various mono- and di-substituted products were obtained in good yields.

Tao-Shan Jiang *et al.* (2018) synthesized quinolines from anilines, acetophenones, and dimethyl sulfoxide in air (Scheme 213).³¹³ The one-pot reaction for the synthesis of quinolone derivatives was facilitated by the utilization of methanesulfonic acid as a catalyst in this procedure. This process had an excellent substrate and functional group tolerance, generating the products in high yields.¹⁷⁹

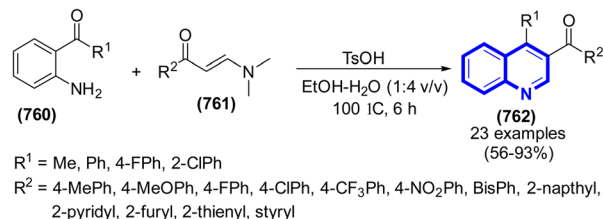
In the same year, So Young Lee *et al.* (2018) prepared 2-substituted quinolines using a nucleophilic organic catalyst (Scheme 214).³¹⁴ The cyclization of 2-aminochalcone occurred



Scheme 213 Synthesis of quinolines catalyzed by methanesulfonic acid.



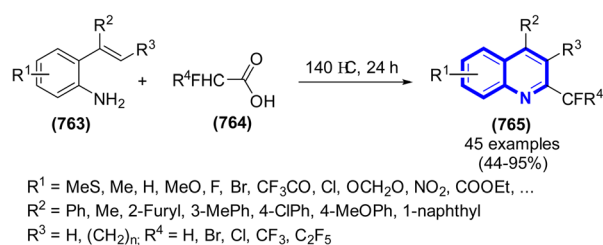
Scheme 214 Synthesis of quinolines catalyzed by benzylamine.

Scheme 215 Synthesis of 3-arylquinolines catalyzed by *p*-toluenesulfonic acid.

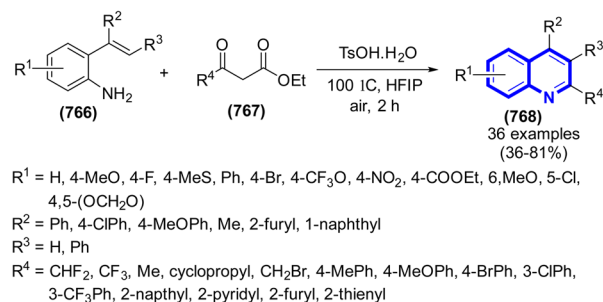
in the presence of a benzylamine catalyst in water as a green solvent. A wide substrate scope was studied, leading to the corresponding products in good yield. The advantages of the approach include its simple workup, easy product isolation, and available substrates.

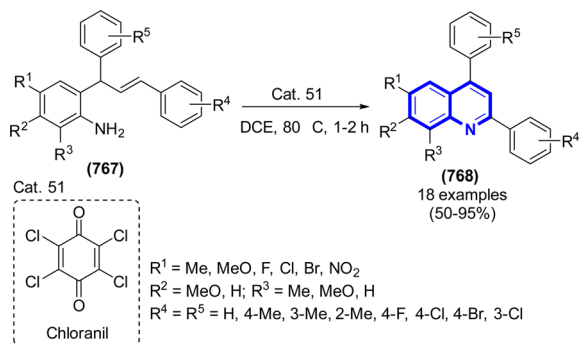
A simple and efficient route for the chemoselective synthesis of 3-arylquinolines was developed by Pan Zhou *et al.* (2018) (Scheme 215).³¹⁵ The process of cyclization involving 2-aminoaryl ketones and *N,N*-dimethylenaminones was seen to take place in a solvent mixture comprised of water and ethanol. The utilization of PTSA as a very effective catalyst was employed, with the reaction mixture being subjected to a temperature of 100 °C for 6 h. The benefits associated with employing this particular methodology include favorable reaction conditions, a wide applicability, abundant substrate availability, straightforward procedural steps, and significant product yields.

Jiang Nan *et al.* (2019) prepared 2-fluoroalkylated quinolines *via* [5 + 1] annulation under metal-free conditions (Scheme 216).³¹⁶ 2-Vinylanilines reacted with polyfluoroalkanoic



Scheme 216 Synthesis of 2-fluoroalkylated quinolines under catalyst-free conditions.

Scheme 217 Synthesis of quinolones catalyzed by *p*-toluenesulfonic acid.



Scheme 218 Synthesis of 2,4-diarylquinolines catalyzed by Cat. 51.

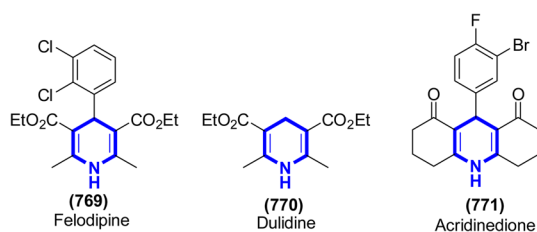
acids at 140 °C. Additional types of fluoroalkylated quinolones were produced in good yield. This process was demonstrated to be an efficient synthetic route for fluoro-containing organic compounds under catalyst- and additive-free conditions.

Next, Jiang Nan *et al.* (2020) provided a detailed account of a methodology for the synthesis of quinolone derivatives under metal-free conditions (Scheme 217).³¹⁷ This approach was performed *via* domino condensation and aza-Prins cyclization. 2-Alkenylanilines reacted with β -dicarbonyl compounds in hexafluoroisopropanol at 100 °C for 2 h using *p*-toluenesulfonic acid as the catalyst. Various products were prepared from a wide substrate scope.

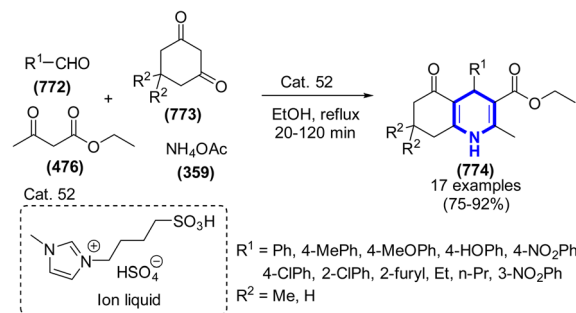
Dongping Cheng *et al.* (2020) reported an alternative method for synthesizing 2,4-diarylquinoline compounds (Scheme 218).³¹⁸ The experimental procedure involved the utilization of oxidative cyclization, employing chloranil as the oxidizing agent. The reaction mixture was heated to a temperature of 80 °C using dichloroethane as the solvent. A diverse array of *o*-allylaniline derivatives was utilized in the synthesis of 2,4-diarylquinolines (Scheme 219).

3.1.4. Dihydropyridine. Dihydropyridines, also referred to as DHPs, are a class of extremely small chemical compounds that have a structure derived from pyridine. The pyridine structure can exist in a total of five isomeric forms, among which the 1,2-dihydro- and 1,4-dihydro-pyridine structures are the most common ones.³¹⁹ Because of their pharmacological and biological properties, such as antihypertensive,³²⁰ anti-anginal, and calcium channel blocker for cardiovascular disease,³²¹ these precursors are significant.

Polyhydroquinoline derivatives were developed by Majid M. Heravi *et al.* (2010). The synthesis of a Brønsted acid IL was



Scheme 219 Chemical structures of bioactive compounds containing a dihydropyridine framework.



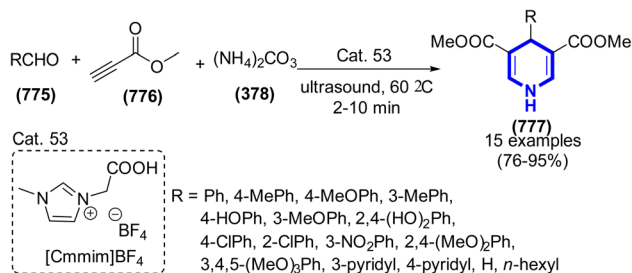
Scheme 220 Synthesis of polyhydroquinolines catalyzed by Cat. 52.

achieved *via* a four-component Hantzsch reaction (Scheme 220).³²² The solution containing aldehyde, ethylacetoacetate, dimedone, and ammonium acetate was subjected to reflux in ethanol with the aid of Cat. 52. Various polyhydroquinoline derivatives, including aromatic, aliphatic, and heterocyclic compounds, were obtained using the aforementioned processes. The employed technique demonstrated a straightforward, effective, and environmentally benign approach.

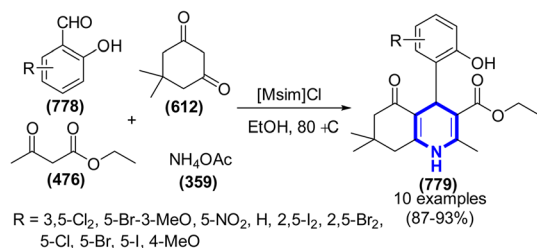
Jing-Yu He *et al.* (2015) synthesized 1,4-dihydropyridine-3,5-dicarboxylates under the catalysis of a Brønsted IL (Scheme 221).³²³ Under ultrasonic irradiation, the three-component reaction of aromatic aldehydes, methyl propionate, and ammonium carbonate was carried out in Cat. 53. Under the optimized reaction conditions, various 1,4-dihydropyridine derivatives were prepared at 60 °C for 2 to 10 min in good yield. This simple experimental procedure is considered a green approach with reusing and recycling abilities.

In the study conducted by Jadhvar *et al.* (2015), a novel environmentally friendly approach was proposed for the synthesis of polyhydroquinoline frameworks. This method involved the utilization of a Brønsted acidic IL as a catalyst (Scheme 222).³²⁴ The polyhydroquinoline frameworks were synthesized *via* the condensation of substituted salicylaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate. The reaction mixture was subjected to heating at a temperature of 80 °C with stirring, in the presence of [Msm]Cl. The corresponding polyhydroquinoline derivatives were produced from a wide range of substrates.

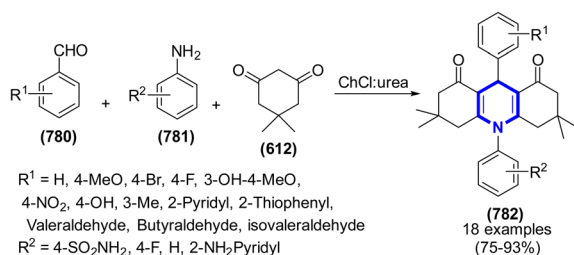
Manisha R. Bhosle *et al.* (2018) investigated a novel methodology for the synthesis of *N*-substituted decahydroacridine-



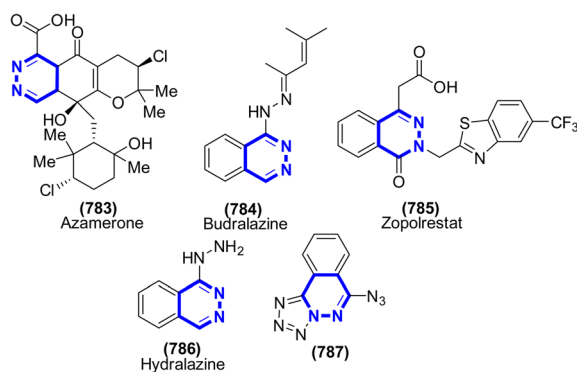
Scheme 221 Synthesis of 1,4-dihydropyridine catalyzed by Cat. 53.



Scheme 222 Synthesis of polyhydroquinolines catalyzed by [Msim]Cl.



Scheme 223 Synthesis of decahydroacridine-1,8-diones catalyzed by a ChCl: urea mixture.

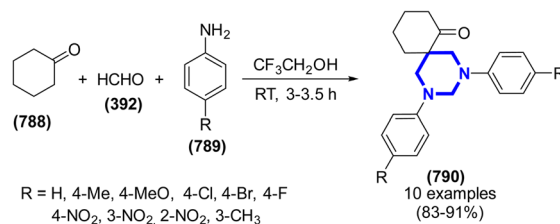


Scheme 224 Chemical structures of bioactive compounds containing a diazinane framework.

1,8-dione derivatives (Scheme 223).³²⁵ A choline chloride: urea deep eutectic mixture was prepared and used as a recyclable organocatalyst and medium/solvent. The procedure was executed by a multicomponent reaction including a diverse array of aromatic aldehydes, dimedone, and aromatic amines under gentle conditions. The combination of choline chloride and urea has the potential to function as an environmentally friendly catalyst. The advantages of this protocol are catalytic activity, quick catalyst synthesis, straightforward workup protocol, and environmentally friendly conditions (Scheme 224).

3.2. Six-membered rings with two nitrogen-atom-containing heterocycles

3.2.1. Diazinane. Diazinanes feature a cyclohexane-like six-membered ring structure, with two of their carbons substituted

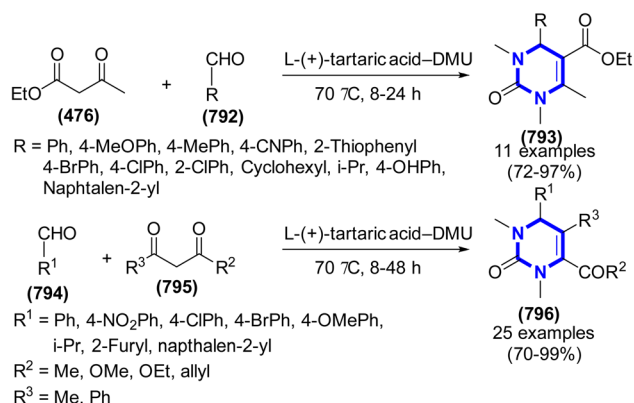


Scheme 225 Synthesis of 1,3-diazinane under catalyst-free conditions.

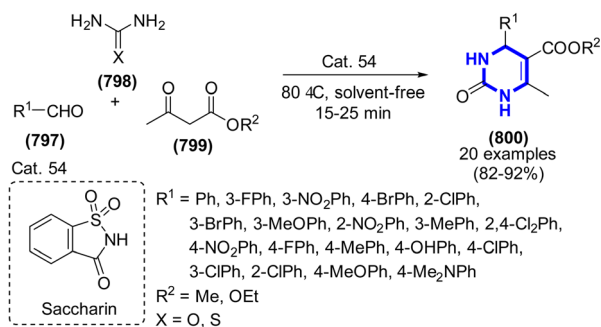
by nitrogens. Diazinanes exist as three distinct isomers, which are characterized by the spatial arrangement of the nitrogen atoms in their respective molecular structures. The three isomers are denoted as 1,2-diazinane, 1,3-diazinane, and 1,4-diazinane. It has been shown that some diazinane derivatives exhibit anticonvulsant,³²⁶ anticancer,³²⁷ anti-inflammatory,³²⁸ and vasorelaxant properties.³²⁹

Audumbar Patil *et al.* (2018) described an effective process for the preparation of 1,3-diazinane derivatives (Scheme 225).²⁶⁵ This protocol was conducted at ambient temperature in 2,2,2-trifluoroethanol. It has the advantages of gentle reaction conditions, no column chromatographic purification, and good yield.

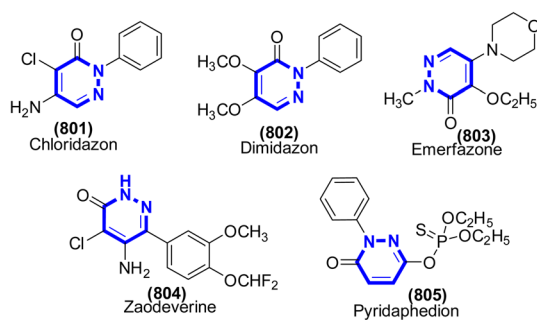
Sangram Gore *et al.* (2011) reported a study on a sustainable methodology for the synthesis of dihydropyrimidinone derivatives using a green approach, namely through the utilization of the Biginelli reaction (Scheme 226).³³⁰ The multicomponent condensation procedures were executed using a one-pot method, employing low melting combinations of L-(+)-tartaric acid and urea, all under moderate conditions. Additionally, several additional melts were examined, including citric acid-DMU, D-(-)-fructose-DMU, sorbitol-DMU-NH₄Cl, and D-(+)-mannose-DMU. This work presented a process that demonstrates ecologically favorable qualities, therefore providing a way for synthesizing dihydropyrimidinone. The deep eutectic solvents played many roles in this approach, acting as the solvent, catalyst, and reactant.



Scheme 226 Synthesis of dihydropyrimidinones catalyzed by a deep eutectic solvent.



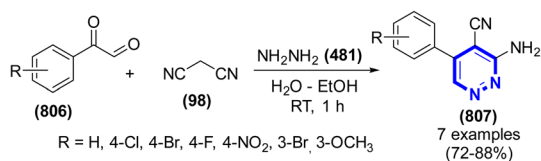
Scheme 227 Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones catalyzed by Cat. 54.



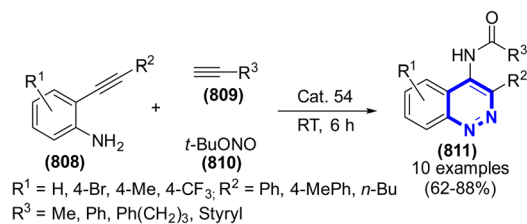
Scheme 228 Chemical structure of bioactive compounds containing a pyridazine framework.

In 2016, Farzaneh Mohamadpour *et al.* prepared 3,4-dihydro-pyrimidin-2-(1H)-one *via* a saccharin (Cat. 54)-catalyzed multiple component reaction (Scheme 227).³³¹ The reaction involving a combination of aromatic aldehydes, alkyl acetoacetate, and urea was conducted by subjecting the mixture to heating at 80 °C for a certain duration, while utilizing saccharin as an effective organic catalyst. Following the optimization of the reaction conditions, a diverse array of 3,4-dihydropyrimidin-2-(1H)-one scaffolds was obtained in high yields within a short reaction period (Scheme 228).

3.2.2. Pyridazine (1,2-diazine) and cinnoline. Pyridazine is a six-membered aromatic heterocycle including two nitrogen atoms located at positions 1 and 2. This distinctive nitrogen configuration greatly affects the electrical characteristics, making pyridazine and its derivatives essential in pharmaceutical chemistry, agrochemicals, and materials research.³³² Pyridazine-based compounds have been extensively investigated in medicinal chemistry for their pharmacological



Scheme 229 Synthesis of arylpyridazine-4-carbonitriles under catalyst-free conditions.



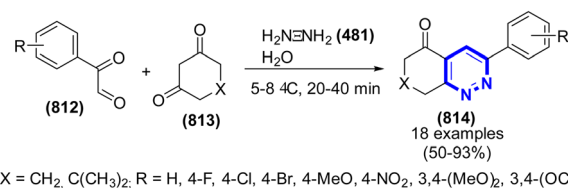
Scheme 230 Synthesis of 4-amidocinnolines catalyzed by Cat. 54.

potential. They demonstrate diverse biological actions, including anticancer, antihypertensive, anti-inflammatory, antidiabetic, and antibacterial properties. These derivatives exhibit a broad spectrum of biological activities, including cardiovascular,³³³ antidiabetic,³³⁴ anti-AIDS,³³⁵ anticancer,³³⁶ and anticonvulsant.³³⁷

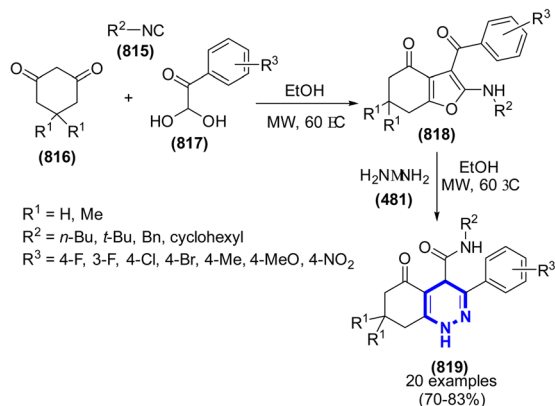
3-Amino-5-arylpyridazine-4-carbonitriles were synthesized by J. Khalafy *et al.* (2013) (Scheme 229).³³⁸ The one-pot three-component reactions were performed between malononitrile and arylglyoxals in with $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ at ambient temperature in H_2O and EtOH for 1 h. This was a simple process for synthesizing various 3-amino-5-arylpyridazine-4-carbonitriles with biological and pharmaceutical applications.

Nader Ghaffari Khaligh *et al.* (2018) devised a highly efficient methodology for the synthesis of 4-amidocinnolines utilizing a metal and halogen-free approach (Scheme 230).³³⁹ The investigation involved the utilization of a one-pot reaction method, whereby *o*-alkynylaniline and nitrile were subjected to 'butyl nitrite, a metal-free diazotization reactant. Especially, saccharin was utilized as a green catalyst, playing a significant role in this reaction. The reaction mixture was refluxed for a duration of 6 h. The scope of this technique was investigated under the optimal reaction conditions, wherein a diverse set of 2-alkynylanilines and nitrile substrates was employed to obtain the corresponding 4-amidocinnoline derivatives. This method was demonstrated to be a systematic protocol with several advantages such as a metal-free conditions and environment-friendly workup.

A green regioselective method for the assembly of novel 7,8-dihydrocinnoline-5(6H)-ones was shown by Jabbar Khalafy *et al.* (2012) (Scheme 231).³⁴⁰ The experimental procedure involved the execution of a one-pot three-component reaction, whereby arylglyoxals, 1,3-cyclohexanedione, and dimedone were combined. The mixture was supplemented with hydrazine hydrate, serving as a catalyst. The reaction mixture was stirred in water, which served as a green solvent, at a temperature in



Scheme 231 Synthesis of 7,8-dihydrocinnoline-5(6H)-ones under catalyst-free conditions.

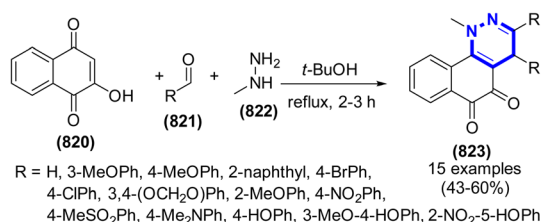
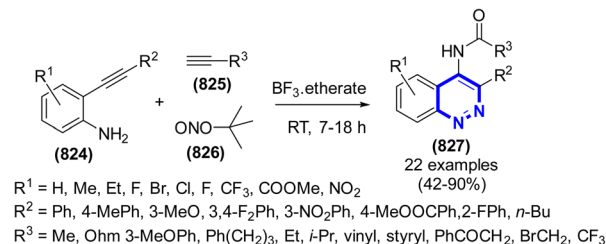


Scheme 232 Synthesis of cinnolines under catalyst-free conditions.

the range of 5–8 °C (using an ice bath) for a duration of 20–40 min. A series of target cinnoline derivatives was obtained from various substrates after recrystallization from ethanol. The present study described a novel and environmentally friendly procedure for the synthesis of 7,8-dihydrocinnolin-5(6*H*)-one derivatives, characterized by their green and efficient protocol, which offers the advantage of a straightforward workup process.

Guan-Hua Ma *et al.* (2014) prepared polyfunctionalized cinnoline-4-carboxamides under microwave irradiation (Scheme 232).³⁴¹ The experiment involved the implementation of a regioselective ring-opening process on 6,7-dihydrobenzofuran-4(5*H*)-ones, followed by cyclization with hydrazine hydrate. The mixture was subjected to microwave irradiation at 60 °C for 25 min. In addition, the synthesis of benzofuran-4(5*H*)-one derivatives *via* a three-component domino reaction was conducted using cyclic-1,3-dione molecules, arylglyoxals, and alkyl isocyanides under identical reaction conditions. Thus, this is an eco-friendly two-step domino synthesis of cinnoline derivatives avoiding the use of transition metal catalysts.

Tuyet-Anh Dang Thi *et al.* (2015) synthesized novel functionalized dihydro-benzo[*h*]cinnoline-5,6-diones *via* a one-pot multi-component reaction (Scheme 233).³⁴² A mixture of hydrazines, aromatic aldehydes, and naphthoquinone was heated in *tert*-butanol for 30–60 min. A series of naphthoquinones was provided in this study. The detailed mechanism for the formation of naphthoquinones was proposed including Knoevenagel condensation, Michael addition, keto-

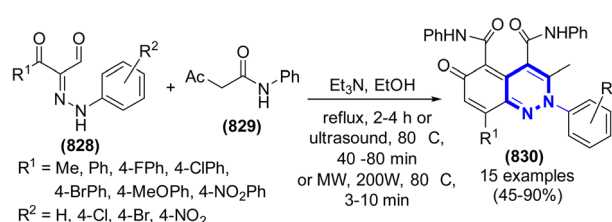
Scheme 233 Synthesis of dihydrobenzo[*h*]cinnoline-5,6-diones under catalyst-free conditions.Scheme 234 Synthesis of 4-amido-cinnolines catalyzed by BF_3 -etherate.

enol tautomerization, and elimination. Besides, the cytotoxic activity of the target products was surveyed and described.

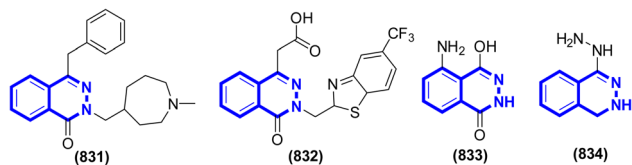
Gopal Chandru Senadi *et al.* (2016) developed a protocol for the synthesis of 4-amido-cinnolines *via* a one-pot cascade reaction (Scheme 234).³⁴³ The construction of 4-amido-cinnoline derivatives was performed employing 2-alkynylanilines, *t*-butyl nitrite, and nitriles in the presence of BF_3 -etherate at ambient temperature. Based on the data obtained from control experiments, the reaction mechanism was proposed to explain the creation of two novel C–N bonds. This mechanism involves a sequential process of diazotization using *t*-BuONO and the subsequent nucleophilic addition of the alkyne to the BF_3 -coordinated diazonium ion. Subsequently, the nitrile compound was introduced into the intermediate vinyl cation, resulting in the formation of the desired end product. A range of 4-amido-cinnoline derivatives was synthesized with satisfactory to excellent yields using a metal-free approach.

A simultaneous one-pot protocol for the preparation of 2-arylcinnolin-6-one moieties was described by Hamad M. Al-Matar *et al.* (2018) (Scheme 235).³⁴⁴ The experimental procedure involved the cyclization of 3-oxo-2-arylhydrazonopropanal derivatives with acetoacetanilide and triethylamine in an ethanol solvent. This study examined three distinct methodologies in the experimental procedure, namely refluxing for a duration of 2–4 h, microwave irradiation at 80 °C at a power output of 200 W for a period of 3–10 min, and US at 80 °C for a duration of 40–80 min. In this study, a variety of 2-arylcinnolin-6(2*H*)-one derivatives was prepared following the optimization of the method. Additionally, a comprehensive mechanistic route was proposed (Scheme 236).

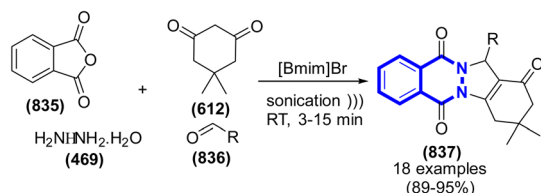
3.2.3. Phthalazine. Phthalazine is a fused bicyclic heterocyclic molecule with a pyridazine ring fused to a benzene ring. This structural framework confers distinctive electrical and



Scheme 235 Synthesis of 2-arylcinnolin-6-one catalyzed by triethylamine.



Scheme 236 Chemical structures of bioactive compounds containing a phthalazine framework.

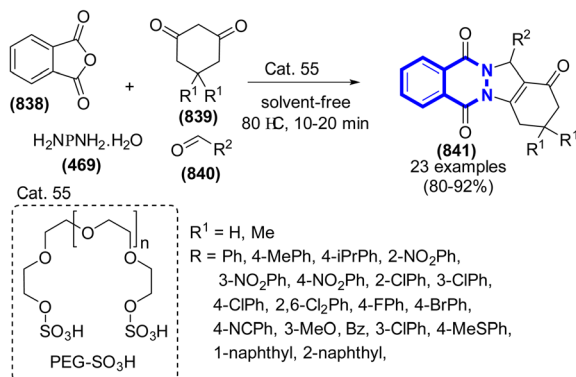


R = Ph, 4-ClPh, 4-BrPh, 4-FPh, 4-NO₂Ph, 2-ClPh, 3-NO₂Ph, 4-MePh, 2-MePh, 3-ClPh, 2-MeO, 4-CF₃, 4-MeO, 3-PhOPh, 4-*i*PrPh, 3-indolyl, 2-thienyl, 2-naphthyl

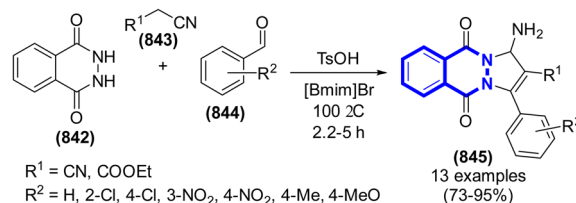
Scheme 237 Synthesis of phthalazinetriones catalyzed by 1-butyl-3-methylimidazolium bromide.

chemical characteristics, making phthalazine derivatives significant in pharmaceutical chemistry, materials research, and industrial applications.³⁴⁵ Phthalazine-based compounds in medicinal chemistry exhibit a variety of pharmacological properties, such as anticancer, anti-inflammatory, antibacterial, antihypertensive, anticonvulsant, and enzyme inhibitory effects. Many medications displaying pharmacological effects, in particular antidiabetic,³⁴⁶ anticancer,³⁴⁷ antithrombotic,³⁴⁸ anti-inflammatory,³⁴⁹ and analgesic³⁵⁰ properties, possess the phthalazine scaffold as a pharmacophoric characteristic.

Mohsen Shekouhy and Alireza Hasaninejad (2012) published a one-pot strategy for the preparation of 2*H*-indazolo[2,1-*b*]phthalazinetriones under catalyst-free conditions (Scheme 237).³⁵¹ The four-component reactions among dione, benzaldehyde, hydrazinium hydroxide, and phthalic anhydride were carried out at r.t. under US. An IL, specifically 1-butyl-3-methylimidazolium bromide, was employed as an environmentally friendly solvent, which exhibited the advantageous characteristic of facile reusability. Many organic transformations for the synthesis of phthalazinetriones derivatives



Scheme 238 Synthesis of phthalazinetriones catalyzed by Cat. 55.



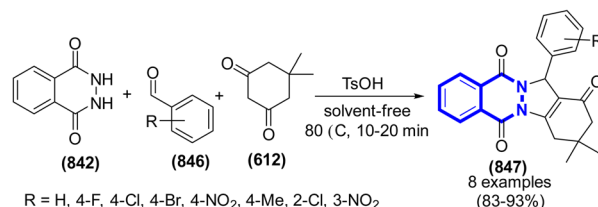
Scheme 239 Synthesis of phthalazine-5,10-dione catalyzed by PTSA.

were studied, which were obtained in yields ranging from fair to outstanding.

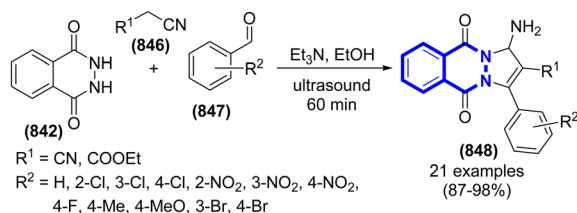
Similarly, Alireza Hasaninejad *et al.* (2012) conducted the synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetrione derivatives using a one-pot four-component condensation approach, employing biodegradable polymeric catalysts (Scheme 238).³⁵² A combination of aromatic aldehydes, phthalic anhydride, hydrazinium hydroxide, and 1,3-diketone compounds, namely 1,3-cyclohexanedione and 5,5-dimethyl 1,3-cyclohexanedione, was heated to 80 °C in the absence of a solvent. The current study used sulfuric acid-modified polyethylene glycol-6000 (PEG-OSO₃H) as an effective and eco-friendly catalyst, demonstrating significant reusability. A series of target phthalazine compounds was obtained in high yields after recrystallization from hot ethanol.

In addition, phthalhydrazide was used as a reactant in an approach for the synthesis of pyrazolo[1,2-*b*]phthalazine-5,10-dione (Scheme 239).³⁵³ For example, R. Ghahremanzadeh *et al.* (2008) prepared 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones *via* a one-pot three-component reaction in IL as the solvent. The experimental procedure involved conducting multiple component reactions using phthalhydrazide, aromatic aldehydes, and malononitrile/ethyl cyanoacetate. A catalytic quantity of PTSA was employed as the catalyst, and the reactions were performed at 100 °C. In this study, the 1-butyl-3-methylimidazolium bromide IL ([Bmim]Br) was employed as an environmentally friendly solvent. Notably, this IL was efficiently recovered and reused in subsequent cycles. This cyclocondensation was demonstrated as an efficient synthetic approach to obtain phthalazine compounds.

In the same year, a one-pot synthetic protocol to obtain 2*H*-indazolo[2,1-*b*]phthalazine-triones was described by Maryam Sayyafi *et al.* (2008) (Scheme 240).³⁵⁴ The condensation reaction involving aromatic aldehydes, phthalhydrazide, and dione was conducted in the absence of a solvent. The reaction mixture was subjected to heating at 80 °C in the presence of a PTSA



Scheme 240 Synthesis of phthalazine-triones catalyzed by *p*-toluenesulfonic acid.



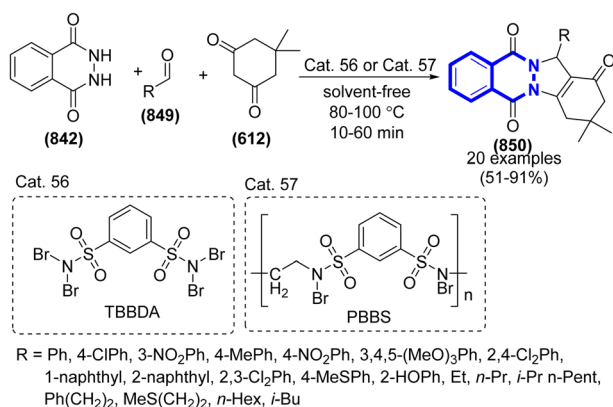
Scheme 241 Synthesis of phthalazine-5,10-diones catalyzed by triethylamine.

catalyst for a duration of several minutes. A variety of the matching products was produced in outstanding yield without any by-product.

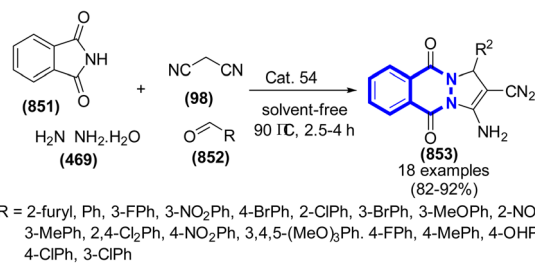
An US one-pot methodology for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones was reported by Mohammad Reza Nabid *et al.* (2010) (Scheme 241).³⁵⁵ Under US, triethylamine was demonstrated as an effective catalyst in the annulation of aromatic aldehydes, phthalhydrazide, and malononitrile/ethyl cyanoacetate. The process was conducted in ethanol at 50 °C for 60 min, furnishing the respective compounds in excellent yields.

Ramin Ghorbani-Vaghei *et al.* (2011) described a method for the one-pot preparation of 2*H*-indazolo[2,1-*b*]phthalazinetrione derivatives under solventless conditions (Scheme 242).³⁵⁶ Aldehydes, phthalhydrazide, and dimedone compounds were subjected to a three-component reaction under reflux conditions at a temperature in the range of 80–100 °C. This reaction was facilitated by the use of *N*-halosulfonamide catalysts, namely **Cat. 56** and **Cat. 57**. A diverse range of aliphatic and aromatic 2*H*-indazolo[2,1-*b*]phthalazinetrione derivatives was synthesized with high efficiency, resulting in outstanding yields.

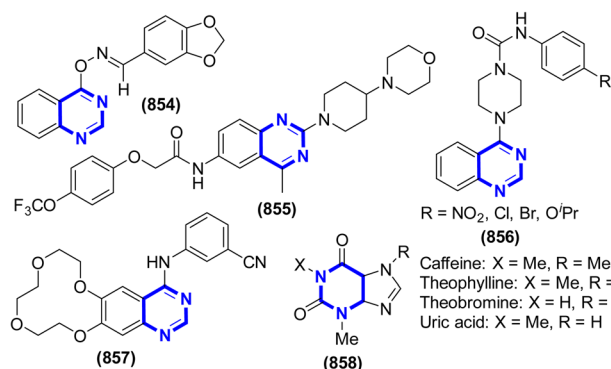
In the study conducted by Farzaneh Mohamadpour *et al.* (2016), they introduced an alternative and cost-effective method for synthesizing 3,4-dihydro-pyrimidin-2-(1*H*)-one derivatives (Scheme 243).³³¹ The synthesis of phthalimide condensate was carried out with the application of heat at 90 °C for 2.5–4 h, using hydrazine monohydrate, benzaldehyde, and malononitrile as the reactants. This technique employed saccharin as an environmentally sustainable and ecologically friendly



Scheme 242 Synthesis of phthalazinetriones catalyzed by **Cat. 56** or **Cat. 57**.



Scheme 243 Synthesis of pyrimidin-2-(1*H*)-ones catalyzed by **Cat. 54**.

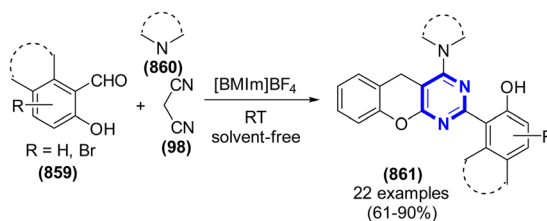


Scheme 244 Chemical structures of bioactive compounds containing a pyrimidine framework.

organocatalyst. A range of pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives was successfully synthesized in satisfactory yield using aldehyde derivatives possessing electron-donating and electron-withdrawing groups (Scheme 244).

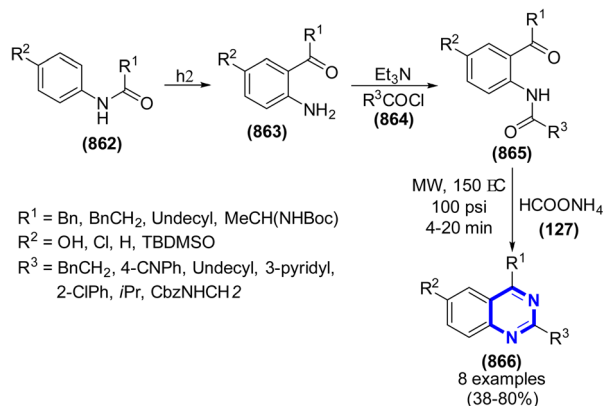
3.2.4. Pyrimidine (1,3-diazine) and quinazoline. Pyrimidine, also known 1,3-diazine, is formed by the substitution of two meta-oriented CH units in benzene with nitrogen atoms. The replacement nomenclature refers to quinazoline as 1,3-diazanaphthalene, whereas the fusion nomenclature refers to it as benzo[*d*]pyrimidine. The reported biological effects of pyrimidines include antibacterial,³⁵⁷ antitumor,³⁵⁸ and tyrosine kinase inhibitory effects.³⁵⁹ Quinazoline is a benzo-fused pyrimidine, which is classified by the fusion nomenclature as benzo[*d*]pyrimidine. Quinazoline derivatives have been identified to exhibit anticancer,³⁶⁰ anti-inflammation,³⁶¹ and antibacterial³⁶² therapeutic activities.

Krishna Nand Singh *et al.* (2012) developed the protocol for the synthesis of benzopyranopyrimidines (Scheme 245). The experimental procedure involved the utilization of 1-butyl-3-



Scheme 245 Synthesis of benzopyranopyrimidines catalyzed by [Bmim]BF₄.





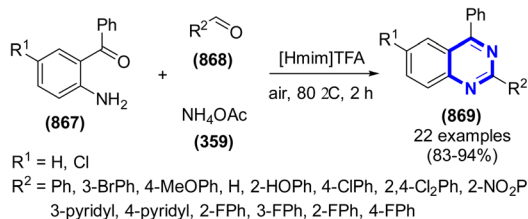
Scheme 246 Synthesis of 2,4-disubstituted quinazolines.

methylimidazolium tetrafluoroborate IL ([Bmim]BF₄) as a catalyst, conducted at ambient temperature in the absence of any solvent. The IL was successfully employed for up to five consecutive cycles without experiencing any substantial decrease in quantity or effectiveness.³⁶³

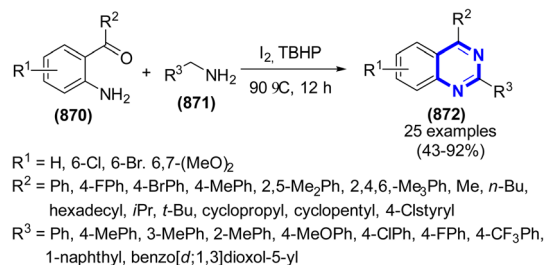
In 2006, Serena Ferrini *et al.* showed an efficient three-step synthetic approach to prepare 2,4-disubstituted quinazolines (Scheme 246).³⁶⁴ The Fries rearrangement of anilides occurred *via* a photochemical reaction, affording 2-aminoacylbenzene. Cyclization of 2,4-disubstituted quinazolines was achieved under MW conditions in ammonium formate. In this study, a range of 2,4-dialkyl/aryl quinazolines and benzoquinazolines was synthesized using the described methodology, resulting in significant yields.

Minoo Dabiri *et al.* (2010) outlined a methodology for the synthesis of quinazolines *via* a one-pot reaction, employing a Brønsted acidic IL as the catalyst (Scheme 247).³⁶⁵ The condensation process was carried out using a three-component system consisting of 2-aminobenzophenones, formaldehyde or aromatic aldehydes, and ammonium acetate. The reaction mixture was subjected to thermal treatment at 80 °C for 2 h, while being exposed to 1-methylimidazolium trifluoroacetate ([Hmim]TFA). The catalyst composed of an IL demonstrated a high degree of ease in its separation and subsequent reuse, with the capability of being employed multiple times. The investigation encompassed a wide range of substrates, resulting in the successful synthesis of the desired compounds in high yields.

Jintang Zhang *et al.* (2011) reported a procedure that demonstrates high efficiency and novelty for the synthesis of 2-



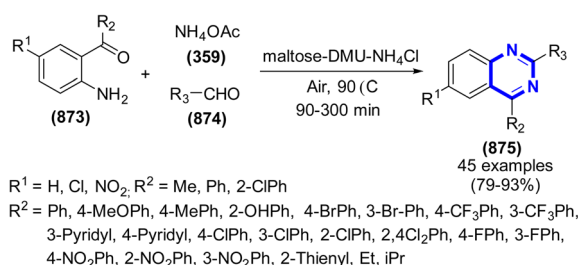
Scheme 247 Synthesis of quinazoline catalyzed by [Hmim]TFA.

Scheme 248 Synthesis of 2-phenylquinazolines catalyzed by I₂/TBHP.

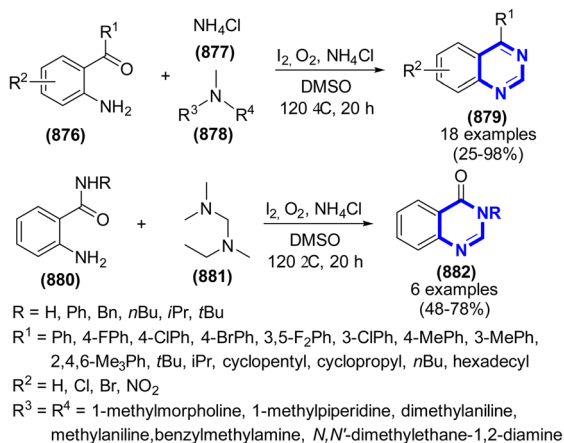
phenylquinazoline derivatives (Scheme 248).³⁶⁶ The process of combining 2-aminobenzophenones and benzylic amines was carried out using a sequential reaction that involved sp³C-H functionalization. The substrate mixture was supplemented with aqueous ^tbutyl hydroperoxide and iodide. The procedure involved subjecting the sample to heating at 90 °C for 12 h. A variety of 2-phenylquinazolines was produced from 2-aminobenzoketones with benzylic amines.

Zhan-Hui Zhang *et al.* (2012) synthesized quinazoline derivatives under catalyst-free conditions (Scheme 249).³⁶⁷ The experimental procedure involved conducting a one-pot three-component reaction using 2-aminoaryl ketones, aldehyde, and ammonium acetate as reactants. The reaction took place in a solvent composed of a low melting sugar-urea-salt mixture under aerobic oxidation conditions. A range of deep eutectic solvents (DESSs) was examined, including citric acid-DMU, L-(+)-tartaric acid-choline chloride, mannose-DMU-NH₄Cl, lactose-DMU-NH₄Cl, maltose-DMU-NH₄Cl, and D-(−)-fructose-DMU, L-(+)-tartaric acid-DMU. The advantage of the protocol include its simple work-up, eco-friendly method, and green reaction medium.

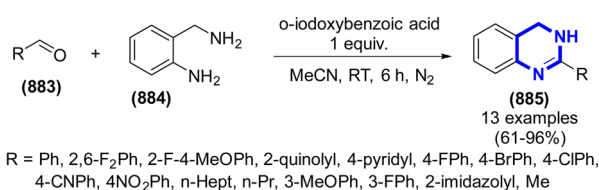
Yizhe Yan *et al.* (2015) developed an innovative procedure for synthesizing quinazolines and quinazolinones (Scheme 250).³⁶⁸ The experimental procedure involved the utilization of iodine as a catalyst for the oxidative C(sp³)-H amination/C-N cleavage of tertiary amines. The domino ring annulation was conducted under an oxygen atmosphere. The reaction mixtures of alkyl amine and 2-aminobenzophenone or 2-aminobenzamide were heated in DMSO at 120 °C for 20 h. The advantage of this protocol is its simple workup, peroxide- and metal-free conditions, wide substrate scope, and high yield.



Scheme 249 Synthesis of quinazolines catalyzed by a low melting point mixture.



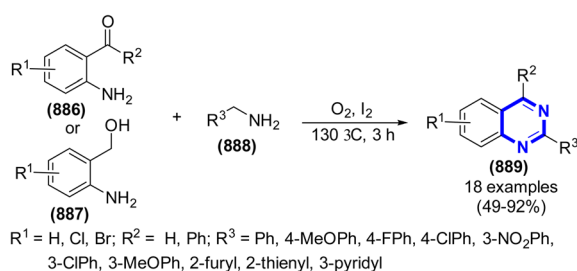
Scheme 250 Synthesis of quinazolines and quinazolinones catalyzed by iodine.



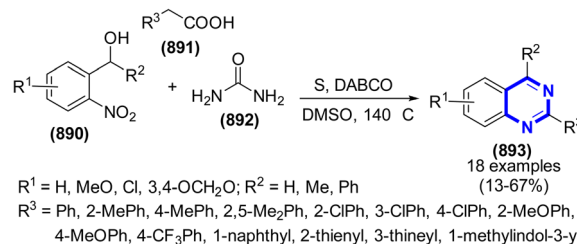
Scheme 251 Synthesis of quinazolines and dihydroquinazolines catalyzed by *o*-iodoxybenzoic acid.

A protocol for the synthesis of quinazolines and dihydroquinazolines was reported by Santanu Hati and Subhabrata Sen (2016) (Scheme 251).³⁶⁹ The reaction involved the utilization of *o*-aminobenzylamine and aliphatic, aromatic, and hetero-aromatic aldehydes and conducted in the presence of **Cat. 15** and acetonitrile as the solvent. The corresponding quinazolines and dihydroquinazolines were obtained with 2 equivalents or 1 equivalent of *o*-iodoxybenzoic acid, respectively. This is an efficient approach with several benefits including accessible starting ingredients, easy workup, high yield, and mild reaction conditions.

Dewal S. Deshmukh *et al.* (2018) synthesized 2-arylquinazolines through benzylic sp³ H–C bond amination under the catalysis of I₂ (Scheme 252).³⁷⁰ The reaction occurred between benzylamines and 2-aminobenzaldehydes, 2-aminobenzophenones, or 2-aminobenzyl alcohols with O₂ as a green



Scheme 252 Synthesis of 2-arylquinazolines catalyzed by iodine.



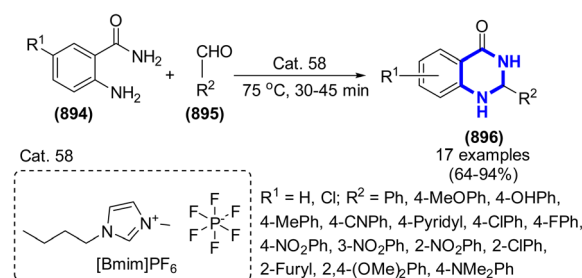
Scheme 253 Synthesis of quinazolines catalyzed by elemental sulfur.

oxidizing agent. Besides, molecular iodine was added to the mixture under solvent-free conditions. Various matching 2-arylquinazolines were prepared in fair to outstanding yields.

D. S. Deshmukh and B. M. Bhanage (2020) prepared substituted quinazolines *via* a sulfur-mediated decarboxylative coupling method (Scheme 253).³⁷⁰ The reaction involving the condensation of 2-nitrobenzyl alcohols and arylacetic acids was carried out by refluxing in DMSO, with urea serving as the nitrogen source. In addition, a promoter consisting of **Cat. 19** base and elemental sulfur was included in the mixture. This study successfully synthesized a range of quinazoline derivatives with excellent efficiency.

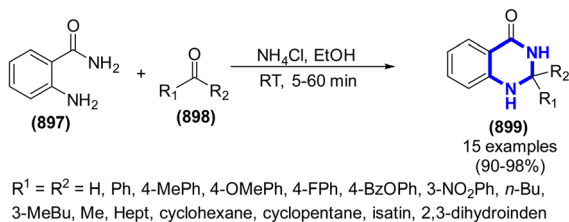
Jiuxi Chen *et al.* (2007) presented a novel approach to the synthesis of 2,3-dihydroquinazolin-4(1*H*)-on derivatives. This process involved the utilization of ILs, specifically **Cat. 58**, or water-ion liquids, under catalyst-free conditions (Scheme 254).³⁷¹ The aforementioned reactions were conducted by means of direct cyclocondensation of anthranilamides and aldehydes, as well as a one-pot three-component cyclocondensation involving isatoic anhydrides, ammonium acetate, and aldehydes. The green technique employed in this study involved the integration of straightforward experimental protocols, as well as the facilitation of efficient recovery and reusability of the newly developed reaction media. This approach was characterized by moderate reaction conditions and demonstrated favorable yields.

Ahmad Shaabani *et al.* (2008) conducted the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives. This was achieved using a condensation reaction involving 2-aminobenzamide and a range of alkyl, aryl, and alicyclic aldehydes/ketones. The process was carried out at ambient temperature (Scheme 255).³⁷² The experiment was conducted with the addition of a catalytic quantity of ammonium chloride in ethanol. The

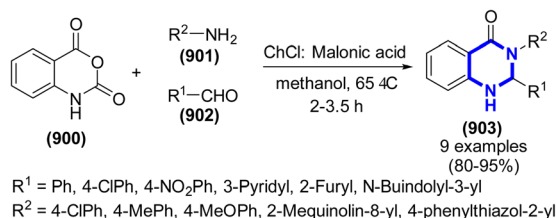


Scheme 254 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-on in ILs.





Scheme 255 Synthesis of 2,3-dihydroquinazolin-4(1H)-one catalyzed by ammonium chloride.

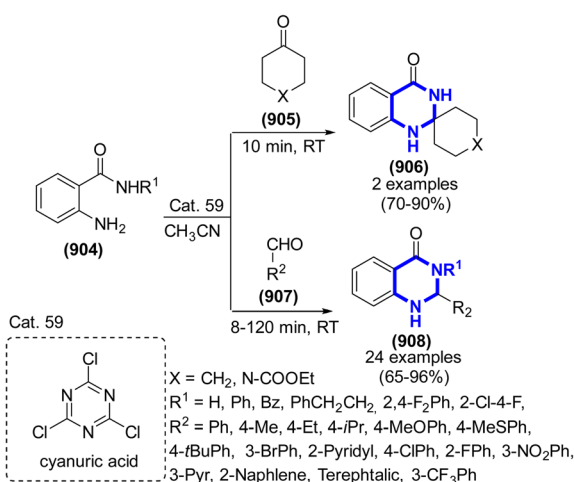


Scheme 256 Synthesis of 2,3-dihydroquinazolin-4(1H)-one catalyzed by a deep eutectic solvent.

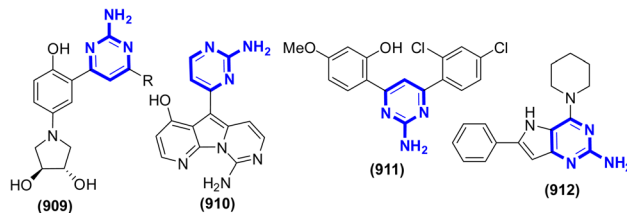
condensation reaction demonstrated excellent efficiency due to its ability to produce significant yields and achieve rapid reaction times.

Lobo *et al.* (2012) employed an acidic eutectic combination to synthesize a diverse range of 2,3-dihydroquinazolin-4(1H)-one derivatives (Scheme 256).³⁷³ The synthesis involving the combination of isatoic anhydride, aldehydes, and aromatic amines was conducted in methanol solvent at 65 °C. High yields were obtained for the aromatic and heterocyclic substitution at the 2,3-positions of quinazolinone.

Moni Sharma *et al.* (2011) developed an efficient procedure for the synthesis of dihydroquinazolinones and spiroquinazolinone (Scheme 257).³⁷⁴ This protocol was performed *via* the cyclocondensation reaction of anthranilamide and aldehyde at r.t. with a cyanuric chloride catalyst to provide



Scheme 257 Synthesis of dihydroquinazolinones and spiroquinazolinone catalyzed by cyanuric chloride.



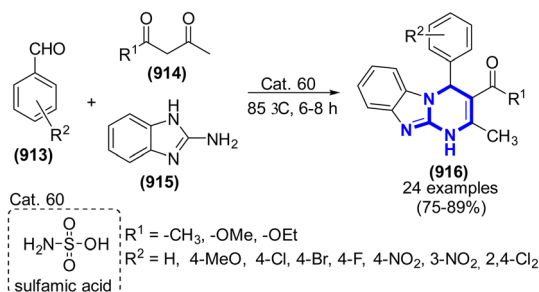
Scheme 258 Chemical structures of bioactive compounds containing a benzo[4,5]imidazo[1,2-a]pyrimidine framework.

products in high yield. This procedure was demonstrated to be a highly succinct, effective, gentle, and straightforward technique (Scheme 258).

3.2.5. Benzo[4,5]imidazo[1,2-a]pyrimidine. Benzimidazole-fused pyrimidines belong to a class of N-heterocyclic compounds, and the N-fused hybrid structures of these compounds typically exhibit unique biological activities that are not present in the majority of homonuclear scaffolds. Benzimidazole-fused pyrimidines, also known as benzo[4,5]imidazo[1,2-a]pyrimidines, were discovered to exhibit distinct fluorescence characteristics as well as diverse biological activities. Their biological effects include antibacterial,³⁷⁵ antiviral,³⁷⁶ antiulcer,³⁷⁷ anti-HIV,³⁷⁸ anticancer,³⁷⁹ antiproliferative,³⁸⁰ and anti-inflammatory³⁸¹ capabilities.

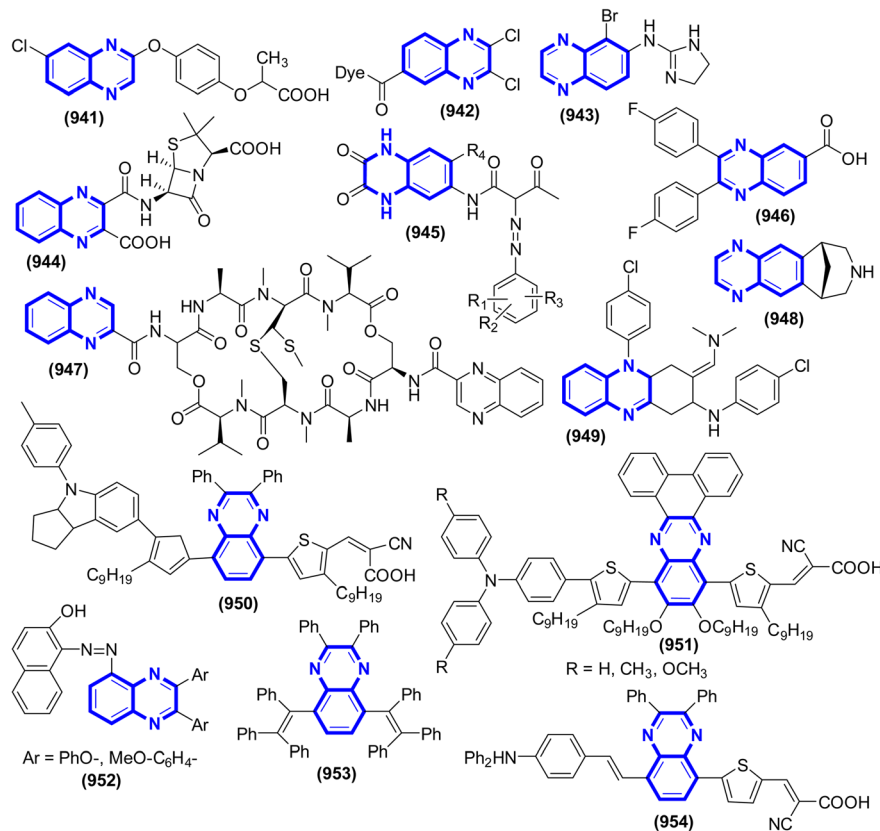
C. S. Yao *et al.* (2008) illustrated a straightforward simple protocol for the preparation of benzo[4,5]imidazo[1,2-a]pyrimidine scaffolds (Scheme 259).³⁸² The researchers conducted a three-component reaction involving aldehydes, a β -dicarbonyl compounds, and 2-aminobenzimidazole. This reaction was catalyzed by sulfamic acid and performed under solvent-free conditions. A range of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives was successfully synthesized in favorable yields under the optimal reaction conditions and using different reagents.

Next, C. Yao *et al.* (2009) synthesized 1H-pyrimido[1,2-a]benzimidazole frameworks from aryl aldehydes, 1,3-dicarbonyl compounds and 1H-benzo[d]imidazole-2-amine solvent at 90 °C (Scheme 260).³⁸³ The methodology employed in this study can be classified as environmentally friendly, given that it utilizes an IL known as [Bmim][BF₄], which possesses green characteristics. This IL could be recycled and reused several times without considerable degradation in its catalytic efficacy. The developed

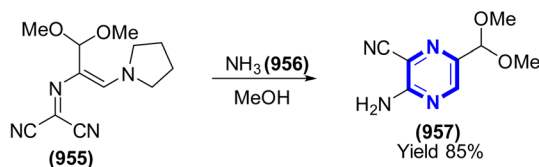


Scheme 259 Synthesis of benzo[4,5]imidazo[1,2-a]pyrimidines catalyzed by Cat. 60.





Scheme 264 Chemical structures of bioactive compounds containing a pyrazine and quinoxaline framework.

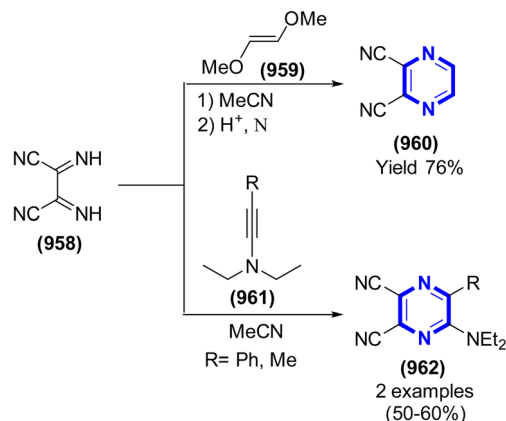


Scheme 265 Synthesis of pyrazine catalyzed under catalyst-free conditions.

(Scheme 265).³⁹⁰ A mixture of (prop-1-en-2-yl)carbonimidoyl dicyanide and ammonia was refluxed in methanol. 2-Amino-3-cyano-5-(dimethoxymethyl)pyrazine was obtained in 85% yield.

The [4 + 2] cycloaddition of diiminosuccinonitrile with 1,2-dimethoxyethylene and ynamines for the synthesis of pyrazine was reported by Fukunaga *et al.* (1984) (Scheme 266).³⁹¹ Tetrahydropyrazine was obtained in high yield. 1,2-Dimethoxyethylene, phenyl(diethylamino)acetylene, and diethyl-amino-1-propyne were the ynamines used in this protocol.

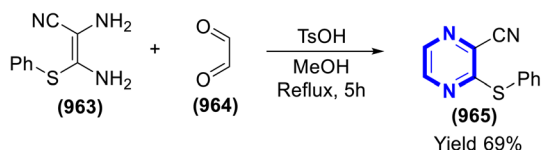
N. Sato *et al.* (1992) reported a protocol for the synthesis of 3-phenylthiopyrazinecarbonitrile by condensing 2,3-diamino-3-phenylthioacrylonitrile with glyoxal (Scheme 267).³⁹² The reaction mixture was subjected to reflux in methanol for a duration of 5 h under PTSA. The resultant compounds were produced in high yield upon recrystallization using methanol as the solvent.



Scheme 266 Synthesis of pyrazine.

This was an important step in the synthetic method for 3 alkoxy- and 3-aminopyrazinecarbonitriles.

Weijiang Zhang (2001) conducted a study on the regioselective synthesis of thieno-[2,3-*b*]pyrazine (Scheme 268).³⁹³ Phenylglyoxal was substituted under Sato's experimental conditions, resulting in the formation of a mixture of 5-phenyl-3-phenylthiopyrazinecarbonitrile and 6-phenyl-3-phenylthiopyrazinecarbonitrile, without exhibiting any regioselectivity. Thus, to solve this problem, the authors added



Scheme 267 Synthesis of 3-phenylthiopyrazinecarbonitrile catalyzed by PTSA.

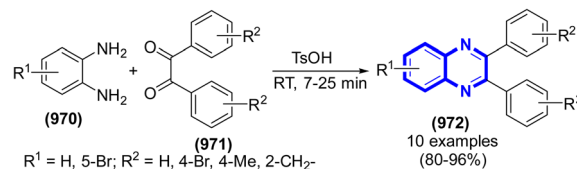
excess trifluoroacetic acid (TFA) to a mixture of 2,2-diethoxyacetophenone and 2,3-diamino-3-phenylthioacrylonitrile instead of PTSA. The reaction mixture was refluxed in propan-2-ol at r.t. for a duration of 22–24 h. The result of the experiment showed that 6-phenyl-3-phenylthio-pyrazinecarbonitrile was obtained in good yield. Especially, this catalyst exhibited high selectivity, where the ratio of 6-phenyl and 5-phenyl derivatives was 15.5 : 1.

A novel process for the synthesis of quinoxalines using Brønsted acid hydrotrope-combined catalyst was developed by Arjun Kumbhar *et al.* (2012) (Scheme 269).³⁹⁴ The combination of 1,2-diketones and 1,2-diamines was subjected to agitation with PTSA in an aqueous solution at r.t. The catalyst could be reused for the next cycles. Thus, this approach is considered an efficient and green protocol with a straightforward work-up, producing a good yield of quinoxaline compounds.

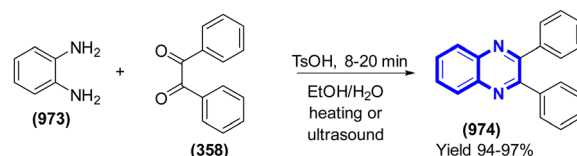
Another environmentally friendly procedure for the preparation of 2,3-diphenyl quinoxaline was reported Pranita Mahadik (2014) (Scheme 270).³⁹⁵ 2,3-Diphenyl quinoxalines also were synthesized from *o*-phenylenediamine and benzil with PTSA within a short reaction time under mild conditions. Three different practical techniques were surveyed including ultrasound and stirring in ethanol or water. Compared with traditional methods, this approach is a more convenient such as avoiding the use of harmful solvents, simple workup, cleaner reactions, and being highly efficient.

Similarly, Zeyuan Zhang *et al.* (2016) also prepared quinoxaline derivatives using PTSA as a catalyst (Scheme 271).³⁹⁶ The one-pot reaction of benzene-1,2-diamines with 2-hydroxyethanone was performed using DMSO as the oxidant. This was a two-step process including oxidation and annulation to obtain the target compounds in high yield.

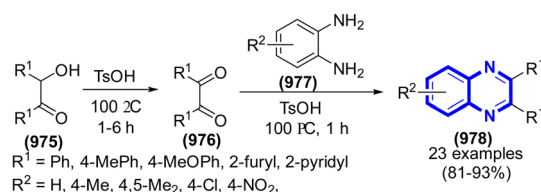
The one-pot preparation of quinoxaline scaffolds using a natural Brønsted acid was published by Radhakrishnan Mahesh *et al.* (2011) (Scheme 272).³⁹⁷ The reaction was based on the condensation between *o*-phenylenediamines and 1,2-dicarbonyl compounds with a certain amount of citric acid as a catalyst. The reaction mixture was agitated in ethanol for



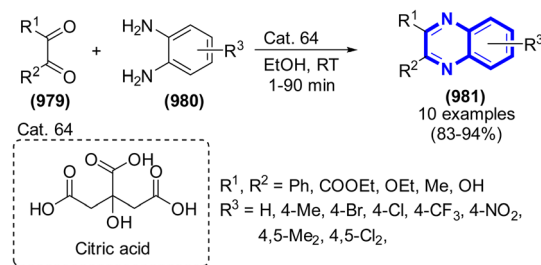
Scheme 269 Synthesis of quinoxalines catalyzed by PTSA.



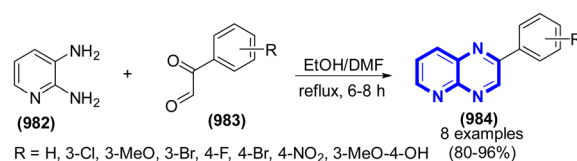
Scheme 270 Synthesis of 2,3-diphenyl quinoxaline catalyzed by PTSA.



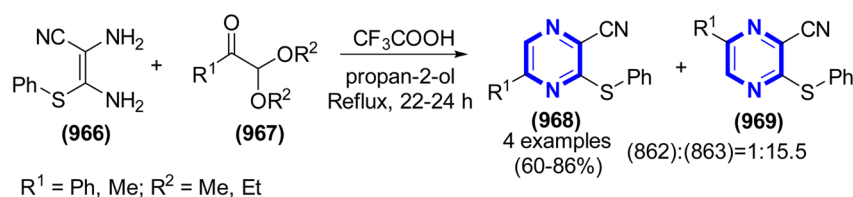
Scheme 271 Synthesis of quinoxalines catalyzed by PTSA.



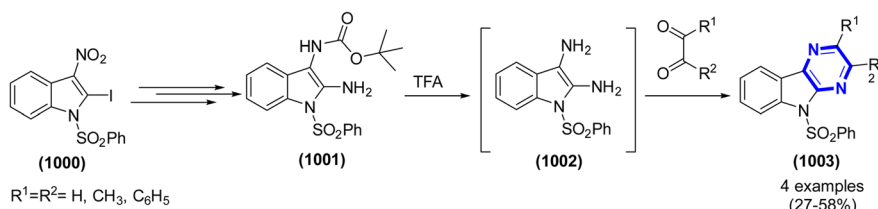
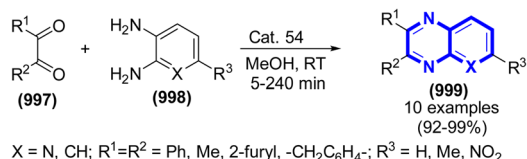
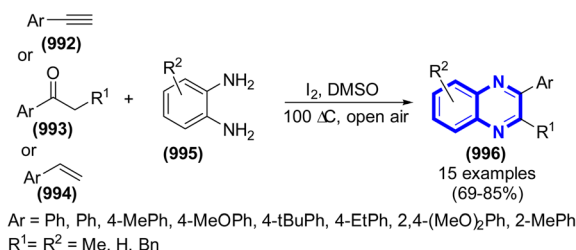
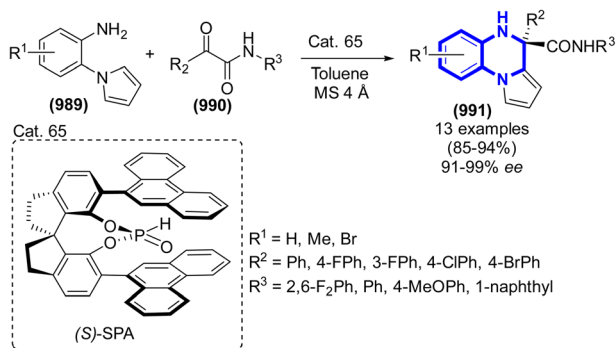
Scheme 272 Synthesis of quinoxalines catalyzed by Cat. 64.



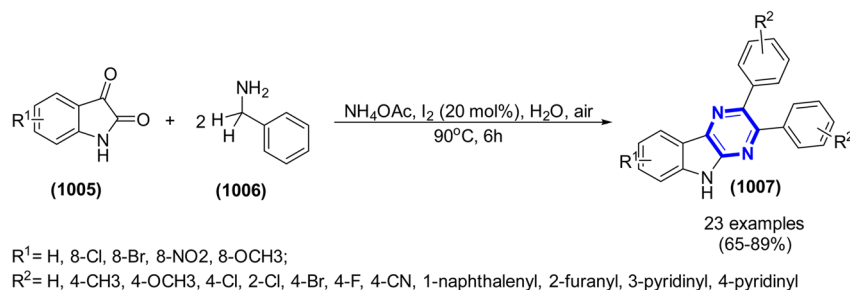
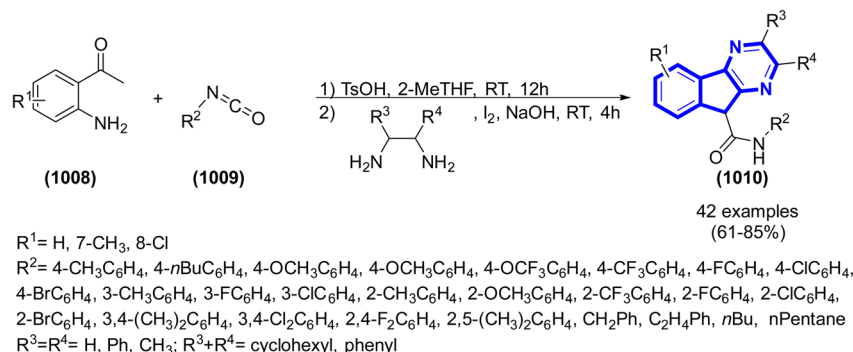
Scheme 273 Synthesis of 3-arylpyrido[2,3-*b*]pyrazines.



Scheme 268 Synthesis of thieno[2,3-*b*]pyrazines catalyzed by trifluoroacetic acid.



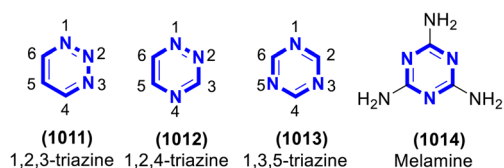
Frédéric Lassagne *et al.* (2014) reported a protocol for the synthesis of quinoxalines and pyrido[2,3-*b*]pyrazines using saccharin as an organic catalyst (Scheme 277).⁴⁰² The experiment involved conducting a cyclocondensation reaction between 1,2-arylenediamines and 1,2-dicarbonyl compounds in methanol at r.t., with relatively brief reaction durations. A series of target heterocycle products was obtained after completion of

Scheme 279 Synthesis of 5H-pyrazino[2,3-*b*]indole.Scheme 280 Synthesis of dihydropyrazino[2,3-*b*]indoles in 2-MeTHF.

the reaction with high regioselectivity. Saccharin was demonstrated as an efficient organocatalyst for this strategy.

Gordon W. Gribble and co-workers discovered method for the three-step synthesis of masked 2,3-diaminoindole from 2-iodo-3-nitro-1-(phenylsulfonyl)indole (2016). Treatment with trifluoroacetic acid produced the unstable 2,3-diamino-1-(phenylsulfonyl)indole, which could be captured by α -dicarbonyl compounds to provide 5H-pyrazino[2,3-*b*]indoles. This methodology enhances the established syntheses of 5H-pyrazino[2,3-*b*]indoles and analogous fused indoles by the condensation of isatins with phenylenediamines (Scheme 278).⁴⁰³

Chhanda Mukhopadhyay and colleague reported the development of an exceptional oxidative coupling/cyclization technique for the synthesis of 5H-pyrazino[2,3-*b*]indole compounds (2023). This technique involves two sequential cross-coupling reactions, C–N coupling followed by C–C coupling, both catalyzed by molecular iodine under aerobic conditions. Electron-rich and electron-deficient benzylamines were used with various isatins to synthesize a range of 5H-pyrazino[2,3-*b*]indoles in good to exceptional yields (Scheme 279).⁴⁰⁴

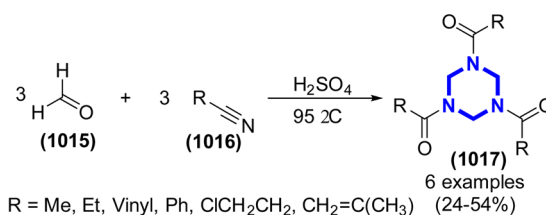


Scheme 281 Various isomers of triazine.

Yongmin Ma and colleague described a metal-free method for the synthesis of dihydropyrazino[2,3-*b*]indoles in 2-MeTHF, using a green solvent at r.t (2024). A collection of functionalized dihydropyrazino[2,3-*b*]indoles (42 instances, 61–85%) was synthesized from widely accessible 2-aminoacetophenones, isocyanates, and 1,2-diamines in favorable yields, even on a gram scale, by straightforward filtering without the need for column chromatography purification. The current technology employs organocatalysts, an environmentally benign solvent, a domino approach, moderate conditions, easily obtainable substrates, large-scale synthesis, and wide substrate range (Scheme 280).⁴⁰⁵

3.3. Six-membered heterocycles containing three nitrogen atoms

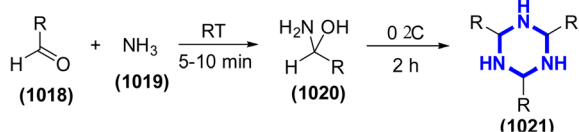
3.3.1. Triazinane. The synthesis of nitrogen-containing heterocyclic compounds has attracted significant attention due to their efficacy in interacting with diverse biological receptors, exhibiting high binding affinity.⁴⁰⁶ This article highlighted the triazine moiety, which has a wide range of biological



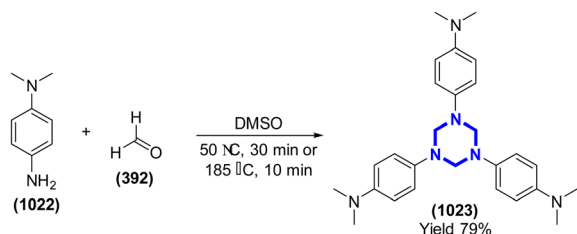
Scheme 282 Synthesis of triazine catalyzed by sulfuric acid.



Review



Scheme 283 Synthesis of 2,4,6-trialkyl-1,3,5-hexahydrotriazine.



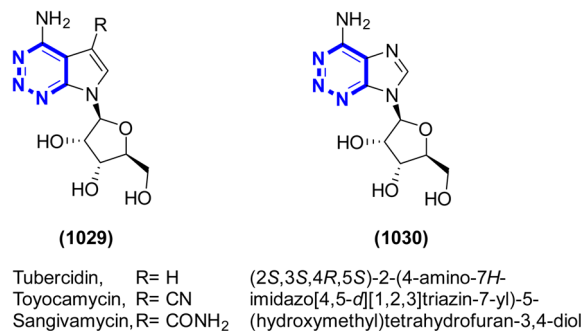
Scheme 284 Synthesis of hexahydro-1,3,5-triazines.

properties and has evolved into a crucial heterocyclic scaffold, making it one of the most thoroughly researched heterocycles. The triazine structure is a heterocyclic ring analogous to the six-membered benzene ring, with three carbon atoms substituted by nitrogen atoms. The isomers of triazine are differentiated by the arrangement of their nitrogen atoms, designated as 1,2,3-triazine (994), 1,2,4-triazine (995), and 1,3,5-triazine (996) (Scheme 281).⁴⁰⁷

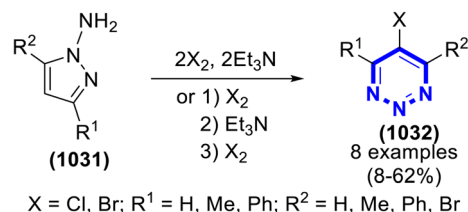
The condensation of formaldehyde with nitriles was researched by M. A. Gradsten and M. W. Pollock in 1948 (Scheme 282).⁴⁰⁸ The reaction was performed under the catalysis of sulfuric acid. Similarly, M. A. Gradsten *et al.* (1950) synthesized hexahydro-1,3,5-tripropionyltriazine *via* the condensation of aldehyde and propionitrile. The reaction mixture was heated at a temperature in the range of 95 °C to 105 °C. The triazine compound was synthesized, resulting in a yield of 62%.⁴⁰⁹ Two years later, propionitrile, acrylonitrile, and benzonitrile were used as reagents in this condensation by Villiam Emmon *et al.*, where solvent systems for this reaction were studied.⁴¹⁰

A. T. Nielsen *et al.* (1973) researched this reaction *via* a condensation reaction (Scheme 283).⁴¹¹ Firstly, aldehyde ammonia hydrates were prepared *via* the nucleophile addition of aldehyde and ammonia. Next, amino-1-alkanols were converted to triazines after 2 h. A wide range of 2,4,6-trialkyl-1,3,5-hexahydrotriazine derivatives was prepared in a high yield.

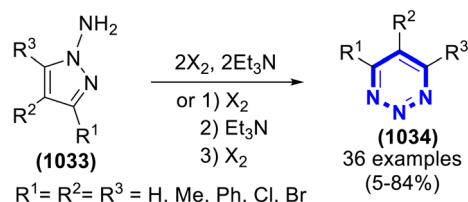
Paraformaldehyde condensation with diamine was described by Jeannette M. García *et al.* (2014) (Scheme 284).⁴¹² The reaction was conducted in dimethyl sulfoxide at 50 °C or



Scheme 286 Chemical structures of bioactive compounds containing a 1,2,3-triazine-framework.



Scheme 287 Synthesis of halo-1,2,3-triazines.

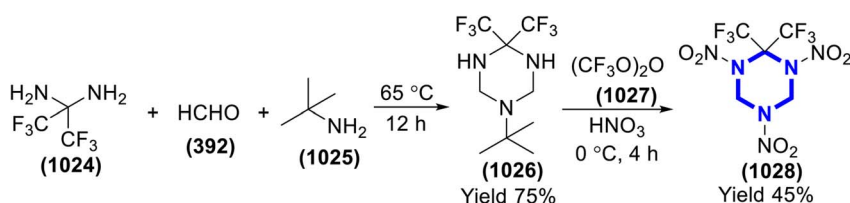


Scheme 288 Synthesis of halogenated and unhalogenated 1,2,3-triazines.

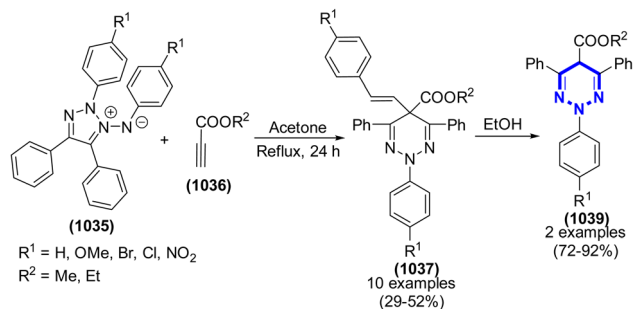
185 °C, leading to the formation of 1,3,5-substituted hexahydro-1,3,5-triazines in 70% yield.

Tongtong Yang *et al.* (2019) reported a unique approach for the synthesis of 1,3,5-triazine derivatives (Scheme 285).⁴¹³ The condensation of hexafluoro-2,2-propanediamine and formaldehyde with *tert*-butylamine was carried out at 65 °C for 12 h. Specifically, 1-(*tert*-butyl)-4,4-bis(trifluoromethyl)-1,3,5-triazine was obtained in high yield without further purification (Scheme 286).

3.3.2. 1,2,3-Triazine. The 1,2,3-triazine heterocyclic system is composed of three carbon atoms and three nitrogen atoms



Scheme 285 Synthesis of 1,3,5-triazine.



Scheme 289 Synthesis of 2,5-dihydro-1,2,3-triazine.

arranged asymmetrically within a six-membered ring structure, one of which is composed of three nitrogen atoms arranged symmetrically at the 1, 2, and 3 positions. 1,2,3-Triazine is an important ingredient in many different types of medications, including antitumor,⁴¹⁴ antibacterial,⁴¹⁵ and antifungal drugs.⁴¹⁶

Terumitsu Kaihoh *et al.* (1987) synthesized halo-1,2,3-triazines (Scheme 287).⁴¹⁷ 1-Aminopyrazoles were treated with chlorine and bromine. Especially, triazines or halogenated 1-aminopyrazoles were not observed in this process. Various halo-1,2,3-triazines were obtained in high yields through this simple one-pot reaction.

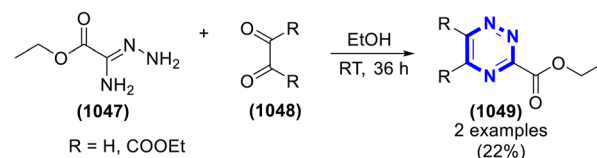
Similarly, Akio Ohsawa *et al.* (1988) continuously researched the synthesis of 1,2,3-triazines using the same method (Scheme 288).⁴¹⁸ The reactions were conducted between *N*-aminopyrazoles with various halogenating reagents such as Cl_2 , Br_2 , I_2 , Br-Cl , I-Cl , I-Br , *N*-chlorosuccinimide, and *N*-bromosuccinimide. Under the optimized conditions, many halogenated and unhalogenated 1,2,3-triazines were produced using this approach.

The one-pot synthesis of fluorescent 2,5-dihydro-1,2,3-triazine frameworks was established by Richard N. Butler *et al.* (2006) (Scheme 289).^{419,420} The corresponding triazines were afforded *via* the reaction of 1,2,3-triazolium-1-aminides and propiolate esters involving Huisgen cycloaddition and rearrangements. The reaction mixture was refluxed in anhydrous acetone for a duration of 24 h. A diverse array of 1,2,3-triazine derivatives was synthesized in satisfactory yields (Scheme 290).

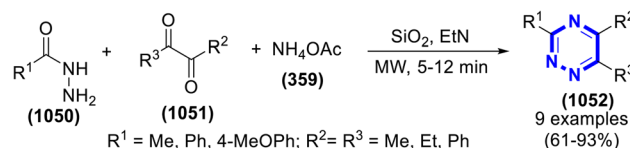
3.3.3. 1,2,4-Triazine. The 1,2,4-triazine heterocyclic system is comprised of a six-membered ring structure consisting of three carbon atoms and three nitrogen atoms arranged asymmetrically, one of which is composed of three nitrogen atoms arranged symmetrically at the 1, 2, and 4 positions. 1,2,4-Triazines and their oxo derivatives show a wide variety of biological activities, including antibacterial,⁴²¹ antifungal,⁴²² anticancer,⁴²³ and anti-inflammatory⁴²⁴ properties.

W. W. Paudler and J. M. Barton (1966) synthesized 1,2,4-triazine-3-carboxylate *via* a simple condensation reaction (Scheme 291).⁴²⁵ A mixture of glyoxal with ethyl oxalamidrazonate was stirred in ethanol at r.t. for 36 h, affording the target compounds.

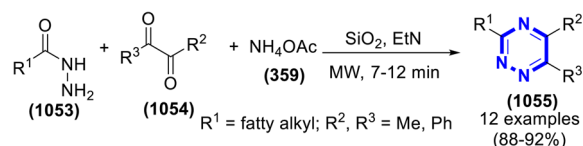
Shahnaz Rostamizadeh and Kamran Sadeghi (2002) prepared 1,2,4-triazines through a one-pot three-component



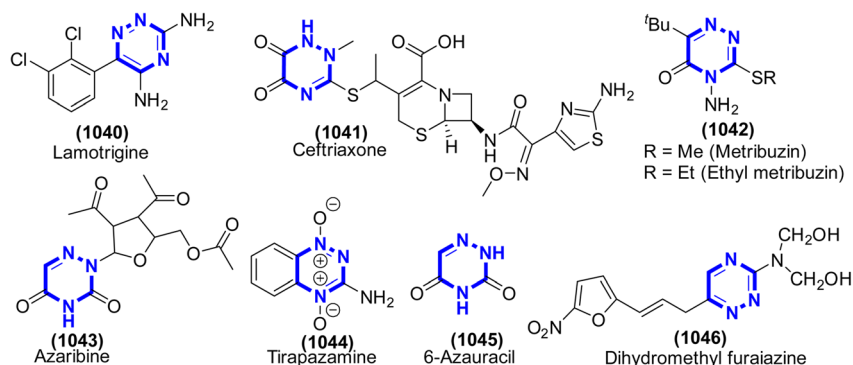
Scheme 291 Synthesis of 1,2,4-triazine-3-carboxylate.



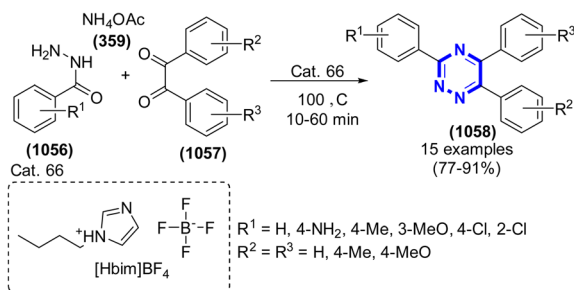
Scheme 292 Synthesis of 1,2,4-triazines catalyzed by silica gel.



Scheme 293 Synthesis of 3,5,6-trisubstituted-1,2,4-triazines catalyzed by silica gel.



Scheme 290 Chemical structures of bioactive compounds containing a 1,2,4-triazine framework.



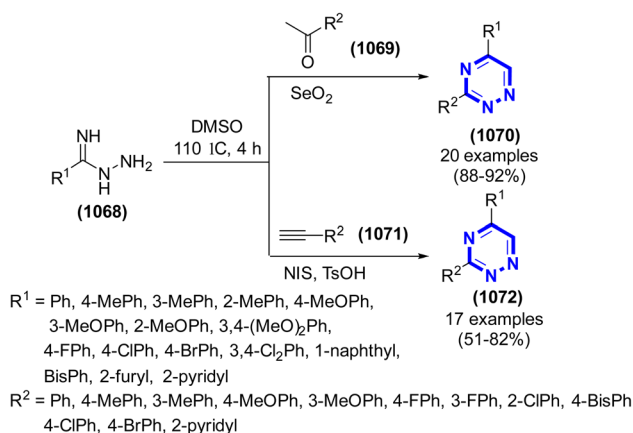
Scheme 294 Synthesis of 1,2,4-triazines catalyzed by Cat. 66.

reaction (Scheme 292).⁴²⁶ A mixture of acid hydrazide, 1,2-diketones, and ammonium acetate was irradiated under a microwave source. The reaction was conducted on the surface of silica gel in the presence of a tertiary amine for the appropriate time. This protocol is efficient due to its rapid reaction rate, simple workup, and good yield.

A similar protocol for the preparation of 1,2,4-triazines from fatty acid hydrazides was studied by Abdul Rauf *et al.* (2007) (Scheme 293).⁴²⁷ The condensation of 1,2-diketones with MW was conducted on solid inorganic substrates under solvent-free conditions. The fatty-substituted triazine compounds were obtained in excellent yield and screened for antimicrobial activity.

In 2007, a green one-pot synthesis protocol of 1,2,4-triazines in the Brønsted acidic IL was reported by T. M. Potewar *et al.* (Scheme 294).⁴²⁸ A mixture of hydrazide acids, 1,2-diketone compounds, and ammonium acetate was stirred at 100 °C for short reaction times. Cat. 66 ([Hbim]BF₄) was used as the catalyst and solvent. Various 1,2,4-triazine compounds were afforded in excellent isolated yields.

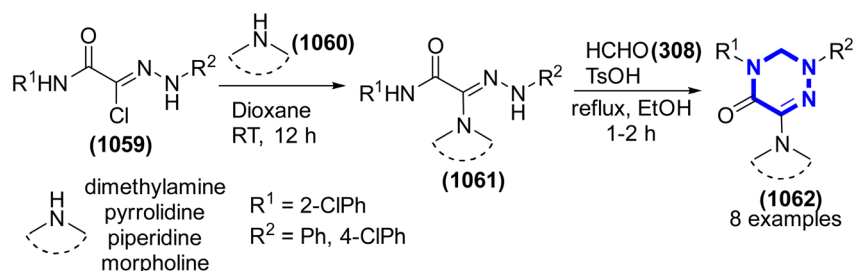
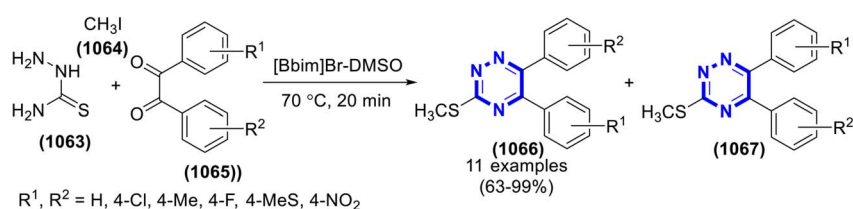
Fabian Krauth *et al.* (2010) synthesized 1,2,4-triazine derivatives *via* cyclization (Scheme 295).⁴²⁹ Firstly, hydrazoneyl chlorides were reacted with amines such as dimethylamine,

Scheme 297 Synthesis of 1,2,4-triazine catalyzed by SeO₂ or NIS-TsOH systems.

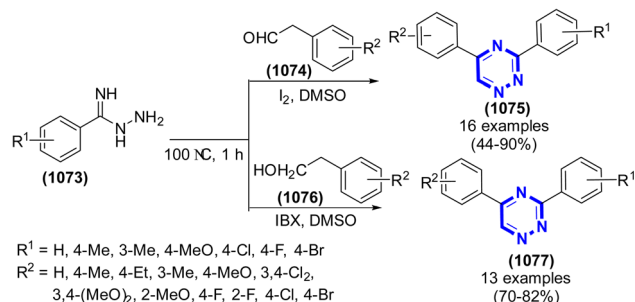
pyrrolidine, piperidine, and morpholine in dioxane at r.t. for 12 h. Next, a mixture of amidrazone intermediate compounds and formaldehyde was refluxed in ethanol using PTSA as a catalyst for 1–2 h. Finally, the target product was recrystallized and surveyed for antiproliferative and cytotoxic activity.

Riyaj S. Tamboli *et al.* (2014) prepared 5,6-diaryl-1,2,4-triazines through a one-pot reaction (Scheme 296).⁴³⁰ A mixture of diketones, thiosemicarbazides, and methyl iodide was stirred at 70 °C for 20 min. A mixture of DMSO and 1,3-dibutylimidazolium bromide (1:10 w/w) was used as the solvent in this process. A regioisomeric mixture of target 1,2,4-triazines was obtained from unsymmetrical diketone compounds. In particular, the IL exhibited a high degree of recoverability and was successfully reused multiple times.

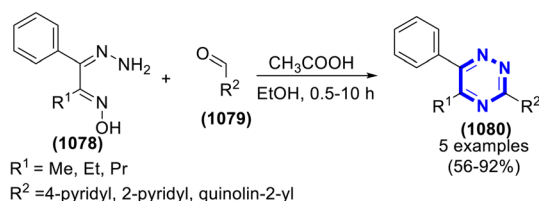
In the publication by Tang *et al.*, they presented a concise and effective approach towards the synthesis of 1,2,4-triazine derivatives using domino cyclization (Scheme 297).⁴³¹ The

Scheme 295 Synthesis of 1,2,4-triazine catalyzed by *p*-toluenesulfonic acid.

Scheme 296 Synthesis of 5,6-diaryl-1,2,4-triazines in an ionic liquid.



Scheme 298 Synthesis of 1,2,4-triazine catalyzed by *o*-iodoxybenzoic acid.

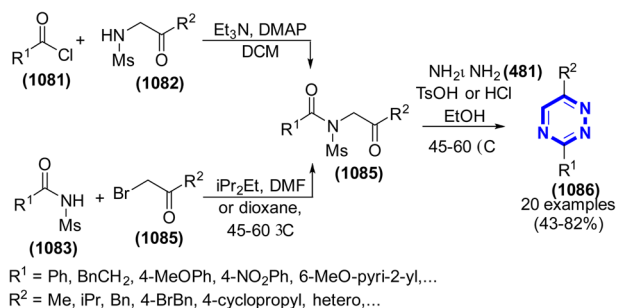


Scheme 299 Synthesis of 1,2,4-triazines catalyzed by glacial AcOH.

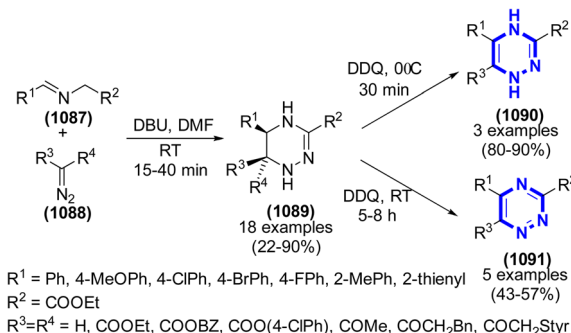
condensation was conducted between amidrazones and ketone or alkyne compounds in the presence of SeO_2 or NIS-TsOH systems (*N*-iodosuccinimide and PTSA) as oxidants. The reaction mixture was subjected to thermal treatment at 110 °C for 4 h. A series of corresponding 1,2,4-triazines was prepared in moderate to high yield.

Yafeng Liu *et al.* (2017) presented an innovative approach for the production of 1,2,4-triazine compounds by utilizing of two interconnected domino reactions (Scheme 298).⁴³² A mixture of *N*-aminobenzamidine and arylacetaldehydes or aryethyl alcohols was heated at 100 °C for 2 h in the presence of iodine and **Cat. 15** additive, respectively. This study focused on investigating high functional group tolerance, which resulted in the production of the desired compounds in exceptional yields. The employed approach, devoid of transition metals, exhibited characteristics of simplicity, environmental friendliness, and high efficiency in the realm of heterocyclic synthesis.

A one-pot protocol for the synthesis of 1,2,4-triazines was described by O. V. Shabunina *et al.* (2018) (Scheme 299).⁴³³ This



Scheme 300 Synthesis of 3,6-disubstituted-1,2,4-triazines catalyzed by Brønsted acid solution.

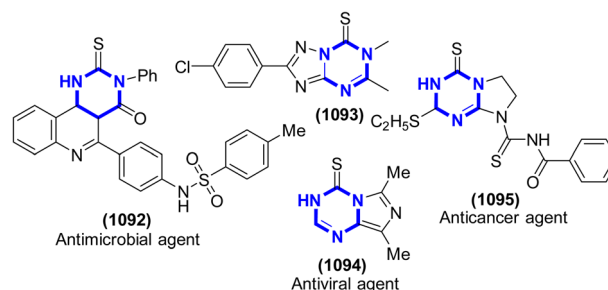


Scheme 301 Synthesis of dihydro-1,2,4-triazines and 1,2,4-triazines.

process was conducted *via* the condensation of different hydrazones and aldehydes, with the addition of glacial AcOH to the reaction mixture. The annulation reaction occurred at ambient conditions, specifically at r.t., for the designated duration. The aforementioned methodology was deemed advantageous due to its practicality, straightforward experimental procedure, accessible substrates, and notable efficiency in terms of product yield.

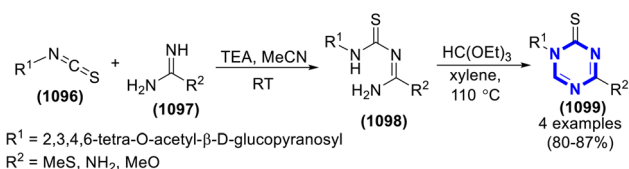
In the same year, Matthew S. Dowling *et al.* prepared 3,6-disubstituted-1,2,4-triazine scaffolds *via* an annulation reaction (Scheme 300).⁴³⁴ A mixture of β -keto-*N*-acylsulfonamide and hydrazine was mixed with Brønsted acid solution (HCl or TsOH) and heated at 45–60 °C for 18–24 h. Especially, two approaches were studied with different starting materials. Consequently, a diverse array of 3,6-disubstituted-1,2,4-triazines was synthesized by including various sp^3 -linked substituents at both the C-3 and C-6 positions.

Lu Zhang *et al.* (2018) described a novel protocol for the synthesis of 2,5-dihydro-1,2,4-triazines and 1,2,4-triazines (Scheme 301).⁴³⁵ The initial step was the [3 + 3] cyclization reaction between ethyl diazoacetate and imine, which was carried out with the assistance of **Cat. 12** as the catalyst. The combination was subjected to stirring at ambient temperature for a duration of 15 to 40 min in the presence of *N,N*-dimethylformamide. Then, tetrahydro-1,2,4-triazine was treated with 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) as an oxidant and continuously stirred for the appropriate time and temperature. Dihydro-1,2,4-triazines and 1,2,4-triazines were synthesized under different reaction conditions. The former was obtained



Scheme 302 Chemical structures of bioactive compounds containing a 1,3,5-triazine framework.





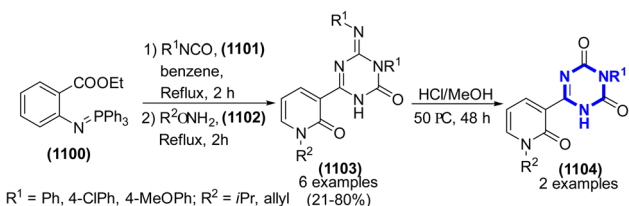
Scheme 303 Synthesis of triazinethione.

by conducting the reaction at 0 °C for 30 min, while the latter was created by carrying out the reaction at r.t. for a period of 8 h. The technique employed in this study demonstrated high efficiency, showcasing several advantageous features such as a streamlined one-pot process, a wide range of applicable substrates, excellent tolerance towards various functional groups, and mild reaction conditions (Scheme 302).

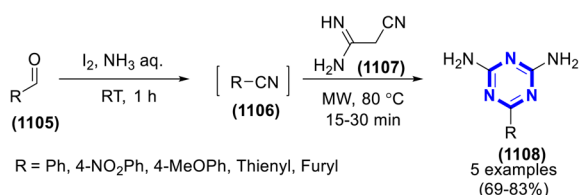
3.3.4. 1,3,5-Triazine. The 1,3,5-triazine heterocyclic system consists of a six-membered ring structure of three carbon atoms and three nitrogen atoms. The nitrogen atoms are positioned asymmetrically within the ring, with a symmetrical arrangement of three nitrogen atoms at 1, 3, and 5 positions. 1,3,5-Triazine and its derivatives have been shown to be efficient antibacterial,⁴³⁶ antimalarial,⁴³⁷ anticancer,⁴³⁸ antimicrobial,⁴³⁹ and antitubercular⁴⁴⁰ agents.

Haruo Ogura *et al.* (1981) illustrated a strategy for the synthesis of triazinethione analogues (Scheme 303).⁴⁴¹ The reaction of a carboximidamide with isothiocyanate was performed in acetonitrile at r.t. Then, triethyl orthoformate and xylene were added to the mixture and heated, and the desired triazinethiones were obtained *via* the cyclization of isothiobiuret.

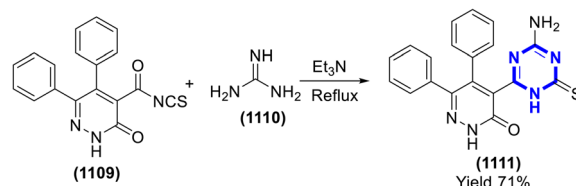
The one-pot preparation of (2-oxo-1,2-dihydropyridin-3-yl)-1,3,5-triazines was shown by Tomohiro Okawa *et al.* (1997) (Scheme 304).⁴⁴² This is an approach with multiple steps including the intermolecular aza-Wittig reaction of methyl 2-(*N*-triphenylphosphoranylidene)amino-nicotinate with aryl



Scheme 304 Synthesis of (2-oxo-1,2-dihydropyridin-3-yl)-1,3,5-triazines.



Scheme 305 Synthesis of triazines.



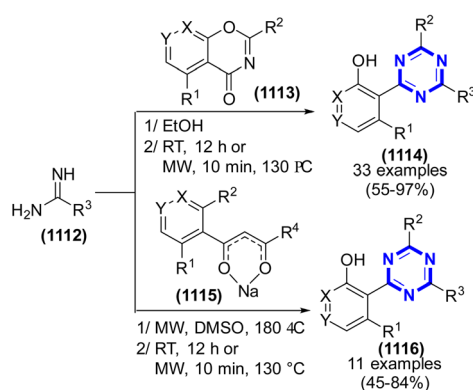
Scheme 306 Synthesis of 1,3,5-triazines catalyzed by triethyl amine.

isocyanates and heterocyclization by primary amines. Pyrido [1,2-*a*][1,3,5]triazines, the key intermediates, were isolated and characterized. Therefore, the transformation mechanism was proposed to elucidate the process by which the desired products are formed.

Shie and Fang (2006) employed the microwave-assisted technique to manufacture triazines through the cycloaddition of intermediate nitriles with dicyandiamide (Scheme 305).⁴⁴³ A mixture of aromatic aldehyde and iodine dissolved in ammonia water and tetrahydrofuran (THF) was introduced in a round-bottom flask and subjected to stirring for a duration of 1 h at ambient temperature. This reaction yielded the desired nitrile compound. Subsequently, the inclusion of dicyandiamide in the amalgamation ensued, followed by subjecting the amalgamation to irradiation in a microwave reactor operating at 80 °C for 15–30 min. Diamino-1,3,5-triazines were synthesized in a significant yield.

M. Hemdan and M. Elshahawi (2007) synthesized 1,3,5-triazines from 3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonyl isothiocyanate (Scheme 306).⁴⁴⁴ A mixture of isothiocyanate and guanidine HCl was refluxed, furnishing 1,3,5-triazine derivatives. This reaction was catalyzed by a certain amount of triethyl amine. The corresponding products were obtained in a yield of 71%.

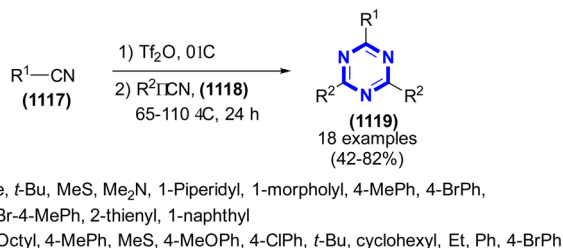
A cyclocondensation process for the synthesis of pyridyl-substituted 1,3,5-triazines was developed by Laetitia Le Falher *et al.* (2014) (Scheme 307).⁴⁴⁵ The reaction between 4*H*-pyrido [1,3]oxazin-4-ones and amidines was carried out at ambient temperature or using MW. A diverse array of triazine



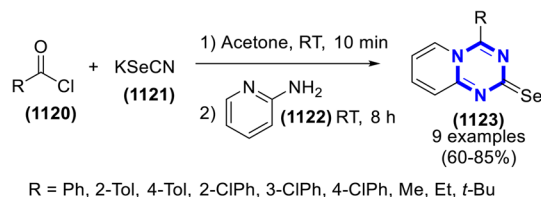
X, Y = CH, N; $R^1 = \text{H, Br}$; $R^2 = \text{Ph, 4-MeOPh, 4-FPh, 1-methylpyrrol-2-yl, 4-ClPh, 2-furyl}$; $R^3 = \text{Ph, 4-FPh, morpholinyl, NH}_2$; $R^4 = \text{Ph, 4-MeOPh, 4-FPh}$

Scheme 307 Synthesis of pyridyl-substituted 1,3,5-triazines under catalyst-free conditions.





Scheme 308 Synthesis of 1,3,5-triazine.

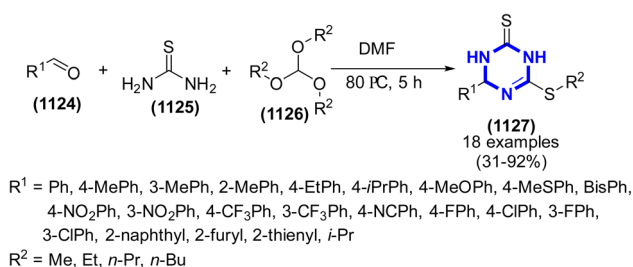


Scheme 309 Synthesis of 2H-pyrido[1,2-a][1,3,5]triazine-2-selenones.

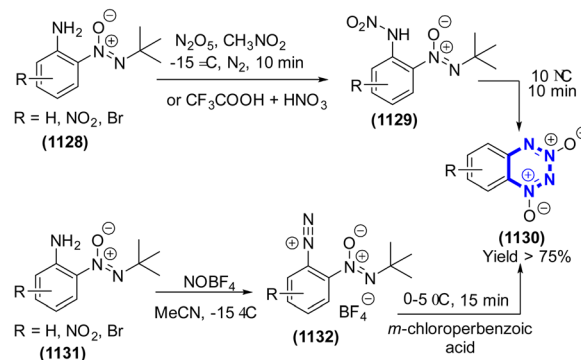
compounds with varying properties was successfully synthesized from three distinct derivatives of 4H-pyrido[1,3]oxazin-4-one, yielding satisfactory to exceptional results. The hypothesized reaction mechanism for this change is considered to be feasible. This protocol is a rapid, efficient, and economic one-step synthetic preparation.

Antonio Herrera *et al.* (2014) reported a one-pot approach for the synthesis of 1,3,5-triazine derivatives through the controlled cross-cyclotrimerization of nitriles (Scheme 308).⁴⁴⁶ The formation of 2,4-disubstituted-6-substituted 1,3,5-triazines was achieved through the reaction between a nitrile compound and either triflic anhydride or triflic acid. The one-pot reaction was conducted by subjecting the mixture to a temperature in the range of 65–110 °C for a duration of 24 h. A diverse range of triazine derivatives was synthesized from two distinct nitriles, resulting in yields varying from moderate to high.

Issa Yavari and Shabnam Mosaferi (2017) prepared 2H-pyrido[1,2-a][1,3,5]triazine-2-selenones *via* a one-pot reaction (Scheme 309).⁴⁴⁷ Initially, acyl chlorides were subjected to a reaction with potassium selenocyanate in acetone under ambient conditions for a duration of 10 min, resulting in the formation of acyl isoselenocyanates. Subsequently, pyridin-2-



Scheme 310 Synthesis of 4-aryl-6-(alkylthio)-3,4-dihydro-1,3,5-triazine-2(1H)-thiones.



Scheme 311 Synthesis of benzo-1,2,3,4-tetrazine-1,3-dioxides.

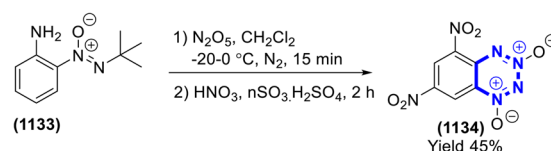
amine was introduced in the solution, which was then subjected to continuous stirring at ambient temperature for 8 h, resulting in the formation of pyrido[1,2-a][1,3,5]triazines. The operational simplicity, variety of reactants, easy workup, and potential diversity are advantages of this protocol.

A catalyst-free methodology for the preparation of 1,3,5-triazine-2,4-dithione scaffolds was developed by Gui-Feng Kang and Gang Zhang (2020) (Scheme 310).⁴⁴⁸ The implementation of this approach involved the utilization of three-component processes involving arylaldehydes, thiourea, and trialkyl orthoformates. The combination of substrates was subjected to thermal treatment in *N,N*-dimethylformamide at 80 °C for 1 h. A range of targeted substituted triazinethione compounds was synthesized in moderate to high yields *via* a one-pot process involving substituted aldehydes and thiourea. The investigation and proposal of a comprehensive plausible mechanism were based on control experiments. The method employed in this study is a direct and efficient strategy for synthesizing 4-aryl-6-(alkylthio)-3,4-dihydro-1,3,5-triazine-2(1H)-thione derivatives.

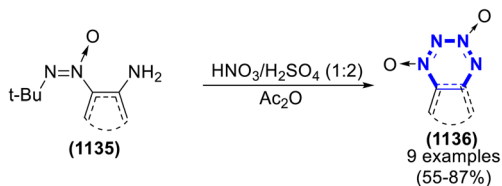
3.4. Six-membered rings with four nitrogen-atom-containing heterocycles

3.4.1. 1,2,3,4-Tetrazine. Tetrazine is a chemical compound characterized by a six-membered aromatic ring with four nitrogen atoms incorporated within its structure. In many cases, 1,2,3,4-tetrazines were obtained by fusing them into an aromatic ring system. Once this was done, the tetrazines were then stabilized as the dioxide derivatives, which were also referred to as v-tetrazines.⁴⁴⁹

Aleksandr M. Churakov *et al.* prepared benzo-1,2,3,4-tetrazine-1,3-dioxides (Scheme 311).⁴⁵⁰ The annulation of 2-(*tert*-butyl-azoxy)aniline derivatives and oxodiazonium ion could be carried out *via* two different methods such as nitration



Scheme 312 Synthesis of 5,7-dinitrobenzo-1,2,3,4-tetrazine-1,3-dioxide catalyzed by nitric acid and oleum solution.



Scheme 313 Synthesis of 1,2,3,4-tetrazine-1,3-dioxides catalyzed by nitric acid–sulfuric acid–anhydride acetic system.

of *N*-nitroamines or treatment of diazonium salts with peracids under basic conditions.

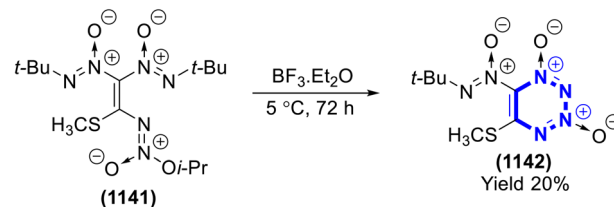
Similarly, Thomas M. Klapotke *et al.* (2012) described a process for the synthesis of 5,7-dinitrobenzo-1,2,3,4-tetrazine-1,3-dioxide (Scheme 312).⁴⁵¹ Initially, a combination of 2-*tert*-butyl-1-(2-anilino)-diazine-1-oxide and dinitrogen pentoxide was subjected to treatment in dichloromethane at $-20\text{ }^{\circ}\text{C}$. Subsequently, the mixture was agitated for 15 min at $0\text{ }^{\circ}\text{C}$ under a controlled nitrogen environment. The reaction mixture was subjected to heating at $80\text{ }^{\circ}\text{C}$ for 2 h subsequent to the addition of nitric acid and oleum solution. The tetrazine-1,3-dioxide of interest was acquired in a yield of 45%.

A novel protocol for the synthesis of 1,2,3,4-tetrazine 1,3-dioxides was described by Alexey A. Voronin *et al.* (2014) (Scheme 313).⁴⁵² The annulation was carried out between 4-amino-5-(*tert*-butyl-*NNO*-azoxy)-2 *R*-2*H*-1,2,3-triazoles or their 1-oxides in a nitric acid–sulfuric acid–anhydride acetic system. The mixture was heated to ambient temperature and agitated for a duration of approximately one hour.

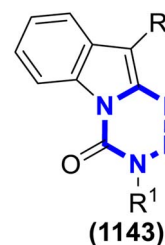
In addition, similar research was also performed by Alexey A. Voronin *et al.* (2017) (Scheme 314).⁴⁵³ A range of *N*-alkyl and *N*-aryl substituted derivatives of 1,2,3,4-tetrazine-1,3-dioxides was synthesized *via* an annulation process involving *N*-aryl-1,2,3-triazoles.

In another four-step process, Michael S. Klenov *et al.* (2015) reported the synthesis of 6-(*tert*-butyl-*NNO*-azoxy)-5-methylthio-1,2,3,4-tetrazine-1,3-dioxide (Scheme 315).⁴⁵⁴ This reaction was performed *via* the treatment of azoxyalkene with excess $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at $5\text{ }^{\circ}\text{C}$. After 72 h, the 1,2,3,4-tetrazine-1,3-dioxide product was obtained in 20% yield with by-products (Scheme 316).

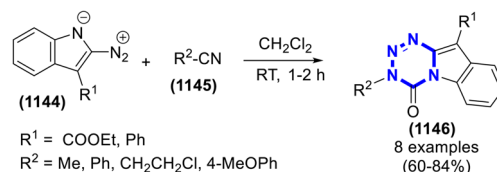
3.4.2. 1,2,3,5-Tetrazine. Tetrazine is a chemical compound characterized by a six-membered aromatic ring with four nitrogen atoms incorporated within its structure. 1,2,3,5-



Scheme 315 Synthesis of 6-(*tert*-butyl-*NNO*-azoxy)-5-methylthio-1,2,3,4-tetrazine-1,3-dioxide catalyzed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$.



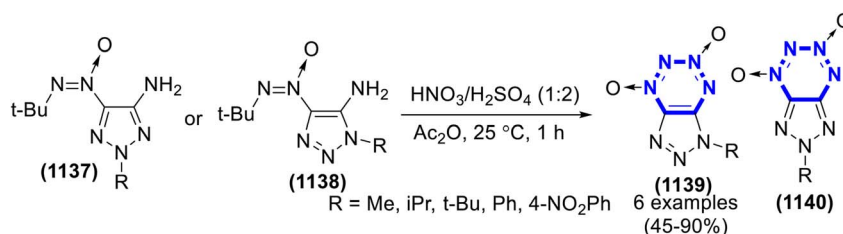
Scheme 316 Chemical structure of a bioactive compound containing a 1,2,3,5-tetrazine framework.



Scheme 317 Synthesis of [1,2,3,5]tetrazino[5,4-*a*]indole-4-one catalyzed under catalyst-free conditions.

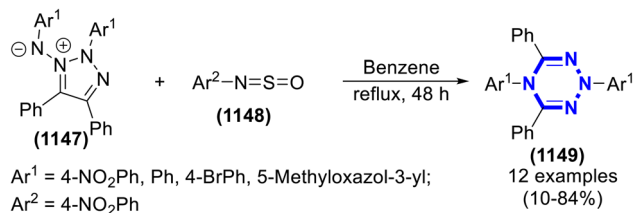
Tetrazines, commonly referred to as tetrazines, have demonstrated notable biological activity as antiproliferative agents.⁴⁵⁵

Paola Barraja *et al.* (2004) showed a strategy for the synthesis of [1,2,3,5]tetrazino-[5,4-*a*]indole-4-one (Scheme 317).⁴⁵⁵ A mixture of 2-diazoindoles and alkyl or aryl isocyanates was dissolved in anhydrous dichloromethane at $0\text{ }^{\circ}\text{C}$ and agitated at ambient temperature for 1–2 h. A diverse array of target products was successfully synthesized in high yields following the purification process involving column chromatography and recrystallization.

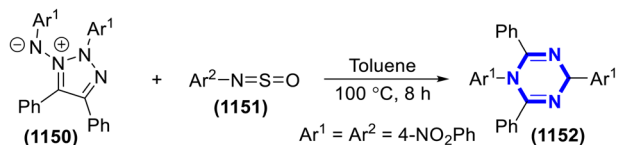


Scheme 314 Synthesis of *N*-alkyl and *N*-aryl substituted 1,2,3,4-tetrazine-1,3-dioxides catalyzed by nitric acid–sulfuric acid–anhydride acetic system.

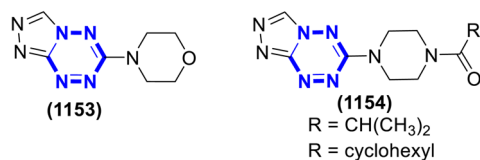




Scheme 318 Synthesis of 1,2,3,5-tetrazine under catalyst-free conditions.



Scheme 319 Synthesis of N²,4,6,N⁵-tetrasubstituted 2,5-dihydro-1,2,3,5-tetrazines under catalyst-free conditions.



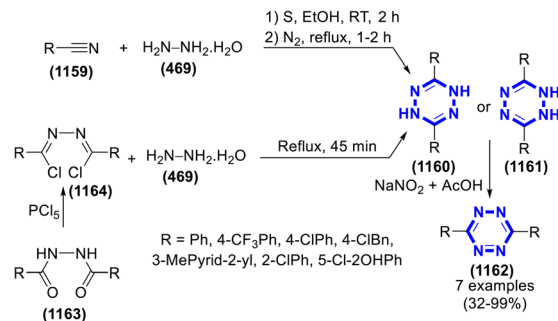
Scheme 320 Chemical structures of bioactive compounds containing a 1,2,4,5-tetrazine framework.

A novel protocol for preparing 1,2,3,5-tetrazines was reported by Richard N. Butler *et al.* (1988 and 1990) (Scheme 318).^{456,457} This method is based on the cycloadditions of aryl *N*-sulphonyl amines with substituted triazolium imides. The mixture reaction was refluxed in benzene for 48 h.

Then, Zhi-Chen Wu *et al.* (2019) also applied this reaction for the multi-gram scale preparation of N²,4,6,N⁵-tetrasubstituted 2,5-dihydro-1,2,3,5-tetrazines (Scheme 319).⁴⁵⁸

3.4.3. 1,2,4,5-Tetrazine. Tetrazine is a chemical compound with a six-membered aromatic ring with the inclusion of four nitrogen atoms. The 1,2,4,5-tetrazines have been extensively utilized in several fields and have gained significant recognition. The existence of a class of chemicals known as 3,6-disubstituted 1,2,4,5-tetrazines, alternatively referred to as *s*-tetrazines, has been documented. Studies on the particular biological activity of 1,2,4,5-tetrazines as an antitumor agent have been conducted (Scheme 320).⁴⁵⁹

M. D. Coburn *et al.* (1991) prepared 1,2,4,5-tetrazine *via* the condensation of hydrazinecarbohydrazonhydrazide chloride

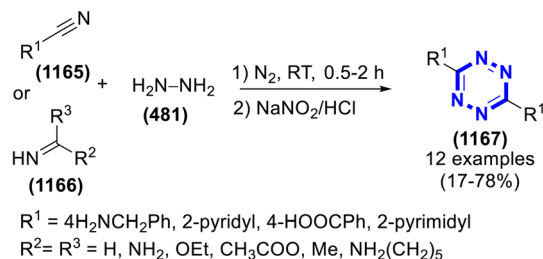


Scheme 322 Synthesis of various 1,2,4,5-tetrazines under catalyst-free conditions.

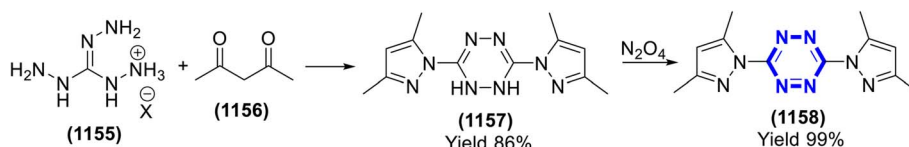
and acetylacetone (Scheme 321).⁴⁶⁰ Similarly, Jochen Kerth *et al.* (2002) also synthesized 1,2,4,5-tetrazine *via* the same two-step process. Firstly, a dihydrotetrazine derivative was synthesized *via* the condensation of pentan-2,4-dione giving nitrile and the salt of hydrazinecarbohydrazonhydrazide. Then, it was oxidized by gaseous N₂O₄, affording 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine in 99% yield.⁴⁶¹

Guo-Wu Rao *et al.* (2006) synthesized various 1,2,4,5-tetrazine derivatives (Scheme 322).⁴⁶² In this study, two routes were used the preparation of 1,2,4,5-tetrazine. The first method was performed *via* the annulation of nitrile and hydrazine hydrate in the presence of elemental sulfur and ethanol. Besides, the azine compound was refluxed with hydrazine hydrate, leading to tetrazine. 3,6-Disubstituted-1,4-dihydro-1,2,4,5-tetrazines were treated *via* the oxidation of a mixture of sodium nitrite in an acetic acid solution.

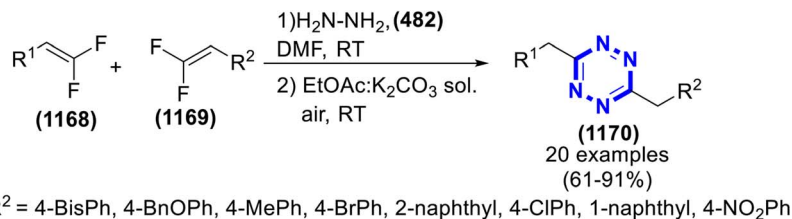
In the study by Karver *et al.* (2011), they presented a straightforward approach for the production of 1,2,4,5-tetrazines through [4 + 2] cycloaddition (Scheme 323).⁴⁶³ In the first step, carbonitrile, imidate ester, or amidine pair reacted in hydrazine at r.t. for the appropriate time. Then, the oxidation of dihydrotetrazine intermediates was performed by adding a mixture of sodium nitrite in an HCl solution.



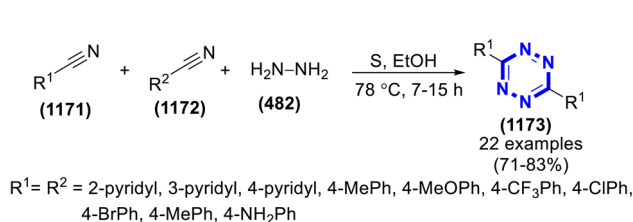
Scheme 323 Synthesis of 1,2,4,5-tetrazines under catalyst-free conditions.



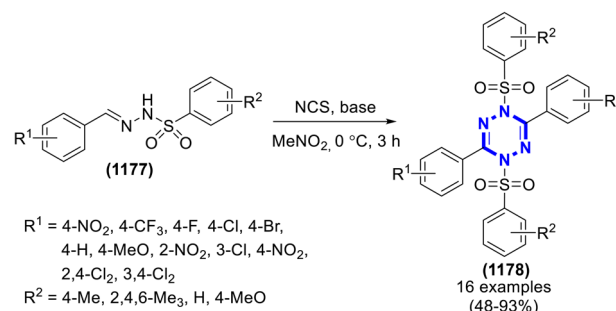
Scheme 321 Synthesis of 1,2,4,5-tetrazine under catalyst-free conditions.



Scheme 324 Synthesis of tetrazines under catalyst-free conditions.



Scheme 325 Synthesis of 1,2,4,5-tetrazines catalyzed by elemental sulfur.

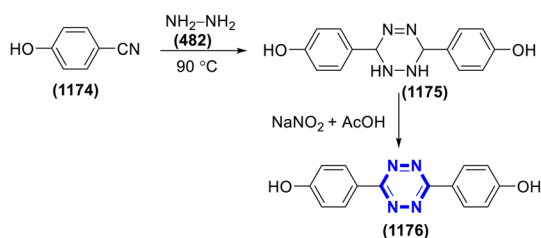


Scheme 327 Synthesis of 1,2,4,5-tetrazines.

A green protocol for the preparation of tetrazines was described by Zheng Fang *et al.* (2013) (Scheme 324).⁴⁶⁴ Briefly, *gem*-difluoroalkenes were treated with hydrazine in *N,N*-dimethylformamide. Subsequently, ethyl acetate and a base were added to the mixture. The experimental procedure involved studying the reaction under an oxygen atmosphere, at a temperature consistent with the ambient conditions. The symmetric and asymmetric 3,6-disubstituted 1,2,4,5-tetrazines were synthesized in excellent yields.

In a study conducted by Chen Li *et al.* (2015), a novel methodology was developed for the synthesis of 3,6-unsymmetrically disubstituted 1,2,4,5-tetrazines through a one-pot process (Scheme 325).⁴⁶⁵ The cyclization of nitriles and hydrazine hydrate was performed by refluxing in ethanol at 78 °C. Especially, elemental sulfur was used as the catalyst. A series of target 3,6-unsymmetrically disubstituted 1,2,4,5-tetrazines was successfully produced in good yield.

A novel *sym*-tetrazine was prepared by Tawfik A. Khattab (2018) through the condensation of nitrile with hydrazine (Scheme 326).⁴⁶⁶ The reaction was carried out between 4-hydroxybenzonitrile and hydrazine at 90 °C for 16 h, leading to 4,4'-(1,2,3,6-tetrahydro-1,2,4,5-tetrazine-3,6-diyl)diphenol. The intermediate underwent oxidation when exposed to a combination of sodium nitrite and acetic acid. This procedure successfully yielded 4,4'-(1,2,4,5-tetrazine-3,6-diyl)diphenol.



Scheme 326 Synthesis of tetrazines under catalyst-free conditions.

Y.-Z. Ji *et al.* (2019) synthesized 1,2,4,5-tetrazine derivatives *via* the NCS-mediated chlorination of arylaldehyde-derived *N*-tosylhydrazones (Scheme 327).⁴⁶⁷ The arylaldehyde-derived arylsulfonyl-hydrazones underwent a reaction with *N*-chlorosuccinimide in the presence of a base. A diverse array of 1,2,4,5-tetrazine derivatives was synthesized in high yields using a wide range of hydrazone substrates, all in the absence of any metal catalysts.

4 Conclusions and outlook

This review summarized the current progress in the synthesis of N-heterocyclic frameworks, namely 5- and 6-membered rings, using one-pot methodologies devoid of transition metal catalysts. These techniques facilitate the synthesis of several valuable N-heterocyclic frameworks of significant interest using efficient, time-saving, and atom-economical procedures.

Despite the extensive applicability of N-heterocyclic frameworks, particularly 5- and 6-membered rings, several hurdles and untapped potential persist in the pursuit of developing more universal, efficient, sustainable, and practical synthetic methodologies. We provide a compilation of suggestions for further endeavors. The restricted substrate range can be broadened under moderate and environmentally friendly reaction conditions. Emphasis should be placed on the installation of potentially transformable groupings in effective medications and pharmaceuticals. Recent results on the electrochemical oxidative annulation of N-heterocycles indicate that this area still offers significant opportunities for synthetic advancements and noteworthy enhancements. The deliberate amalgamation of efficient chemical synthesis and enzymatic methods for the creation of various heterocyclic molecules signifies a promising

future trajectory. Enzymatic methods, especially biocatalysis and enzyme-mediated cyclization, have distinct benefits including elevated regio- and stereo-selectivity, gentle reaction conditions, and little environmental effect. Recent progress in enzyme engineering and directed evolution has broadened the capabilities of enzymatic techniques for the synthesis of heterocycles, facilitating the development of new scaffolds with improved pharmacological attributes. Advancing further, in-depth investigations of enzyme-catalyzed processes, with chemical techniques, will be crucial in formulating sustainable and adaptable synthetic solutions. The ongoing advancement of N-heterocyclic chemistry will undoubtedly provide significant prospects for synthetic and medicinal chemists, fostering innovation in drug development and materials research. Undoubtedly, the advancement of enriched N-heterocyclic chemistry will persist, providing many prospects for both synthetic and medicinal chemists in the development of diverse heterocyclic frameworks of pharmacological significance.

Data availability statements

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Appendix

Abbreviation

DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
dr	Diastereomeric ratio
ee	Enantiomeric excess
er	Enantiomeric ratio
HPLC	High-performance liquid chromatography
IL	Ionic liquid
MCR	Multi-component reaction
MIC	Minimum inhibitory concentration
MW	Microwave irradiation
NBS	N-Bromosuccinimide
PTSA	p-Toluenesulfonic acid
r.t.	Room temperature
SAR	Specific absorption rate
US	Ultrasonic irradiation

Notes and references

- 1 N. Kerru, S. V. Bhaskaruni, L. Gummidi, S. N. Maddila, S. Maddila and S. B. Jonnalagadda, *Synth. Commun.*, 2019, **49**, 2437–2459.
- 2 N. Kerru, P. Singh, N. Koorbanally, R. Raj and V. Kumar, *Eur. J. Med. Chem.*, 2017, **142**, 179–212.

- 3 B. Eftekhari-Sis, M. Zirak and A. Akbari, *Chem. Rev.*, 2013, **113**, 2958–3043.
- 4 A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones and O. Fadeyi, *Org. Biomol. Chem.*, 2016, **14**, 6611–6637.
- 5 M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.*, 2013, **9**, 2265–2319.
- 6 N. Holmberg-Douglas and D. A. Nicewicz, *Chem. Rev.*, 2022, **122**, 1925–2016.
- 7 J. D. Hayler, D. K. Leahy and E. M. Simmons, *Organometallics*, 2019, **38**, 36–46.
- 8 X. Li, L. He, H. Chen, W. Wu and H. Jiang, *J. Org. Chem.*, 2013, **78**, 3636–3646.
- 9 C. M. Santos, M. Freitas and E. Fernandes, *Eur. J. Med. Chem.*, 2018, **157**, 1460–1479.
- 10 P. N. Kalaria, S. C. Karad and D. K. Raval, *Eur. J. Med. Chem.*, 2018, **158**, 917–936.
- 11 X. Li, J. Xu and Z.-G. Xu, *Org. Chem. Front.*, 2024, **11**, 4041–4053.
- 12 P. A. Wiczorkiewicz, T. M. Krygowski and H. Szatyłowicz, *Phys. Chem. Chem. Phys.*, 2024, **26**, 19398–19410.
- 13 K. H. Nguyen, T. H. Nguyen, H. B. Phan, H. T. Nguyen and P. H. Tran, *Next Mater.*, 2025, **8**, 100536.
- 14 A. A. Bhat, N. Tandon, I. Singh and R. Tandon, *J. Mol. Struct.*, 2023, **1283**, 135175.
- 15 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.
- 16 A. V. Smolobochkin, A. S. Gazizov, A. R. Burilov and M. A. Pudovik, *Chem. Heterocycl. Compd.*, 2016, **52**, 753–765.
- 17 A. S. Gazizov and A. V. Smolobochkin, *Chem. Heterocycl. Compd.*, 2018, **54**, 683–685.
- 18 J. Li, Y. Ye and Y. Zhang, *Org. Chem. Front.*, 2018, **5**, 864–892.
- 19 F.-Y. Chen, L. Xiang, G. Zhan, H. Liu, B. Kang, S.-C. Zhang, C. Peng and B. Han, *Tetrahedron Lett.*, 2020, **61**, 151806.
- 20 X. Zhang, W. Qiu, J. Evans, M. Kaur, J. P. Jasinski and W. Zhang, *Org. Lett.*, 2019, **21**, 2176–2179.
- 21 Z. J. Wu, S. R. Li and H.-C. Xu, *Angew. Chem., Int. Ed.*, 2018, **130**, 14266–14270.
- 22 D. Kowalczyk, J. Wojciechowski and Ł. Albrecht, *Synthesis*, 2017, **49**, 880–890.
- 23 Z. Huang, Y. Bao, Y. Zhang, F. Yang, T. Lu and Q. Zhou, *J. Org. Chem.*, 2017, **82**, 12726–12734.
- 24 W. Shi, C.-M. Bai, K. Zhu, D.-M. Cui and C. Zhang, *Tetrahedron*, 2014, **70**, 434–438.
- 25 D. Chen, F. Liang, D. Feng, M. Xian, H. Zhang, H. Liu and F. Du, *Chem. Eng. J.*, 2016, **300**, 177–184.
- 26 D. En, G.-F. Zou, Y. Guo and W.-W. Liao, *J. Org. Chem.*, 2014, **79**, 4456–4462.
- 27 G. Talavera, E. Reyes, J. L. Vicario, L. Carrillo and U. Uria, *Adv. Synth. Catal.*, 2013, **355**, 653–658.
- 28 C. Guo, J. Song and L.-Z. Gong, *Org. Lett.*, 2013, **15**, 2676–2679.
- 29 E. Gómez-Torres, D. A. Alonso, E. Gómez-Bengoia and C. Najera, *Org. Lett.*, 2011, **13**, 6106–6109.
- 30 F. Yu, X. Sun, Z. Jin, S. Wen, X. Liang and J. Ye, *Chem. Commun.*, 2010, **46**, 4589–4591.



- 31 A. Chaudhary, J. M. Khurana, G. Khanna and M. Saroha, *ChemistrySelect*, 2018, **3**, 6334–6337.
- 32 L. D. Nguyen, K. H. Nguyen, P. N. Nguyen, K. N. Tran, D. D. Le, P. H. Tran and H. T. Nguyen, *J. Chem. Technol. Biotechnol.*, 2025, **100**, 121–137.
- 33 M. K. Scott, G. E. Martin, D. L. DiStefano, C. L. Fedde, M. J. Kukla, D. L. Barrett, W. J. Baldy, R. J. Elgin, Jr., J. M. Kesslick, J. R. Mathiasen, *et al.*, *J. Med. Chem.*, 1992, **35**, 552–558.
- 34 E. Mateev, M. Georgieva and A. Zlatkov, *J. Pharm. Pharm. Sci.*, 2022, **25**, 24–40.
- 35 M. S. El-Gaby, A. M. Gaber, A. A. Atalla and K. A. Abd Al-Wahab, *Farmaco*, 2002, **57**, 613–617.
- 36 P. S. Vieira, T. Souza, R. V. Honorato, L. M. Zanthorlin, K. U. Severiano, S. A. Rocco, A. H. C. de Oliveira, A. T. Cordeiro, P. S. L. Oliveira, P. O. de Giuseppe and M. T. Murakami, *Biochem. Biophys. Res. Commun.*, 2017, **488**, 461–465.
- 37 M. J. Palmer, X. Deng, S. Watts, G. Krilov, A. Gerasuto, S. Kokkonda, F. El Mazouni, J. White, K. L. White, J. Striepen, J. Bath, K. A. Schindler, T. Yeo, D. M. Shackleford, S. Mok, I. Deni, A. Lawong, A. Huang, G. Chen, W. Wang, J. Jayaseelan, K. Katneni, R. Patil, J. Saunders, S. P. Shahi, R. Chittimalla, I. Angulo-Barturen, M. B. Jiménez-Díaz, S. Wittlin, P. K. Tumwebaze, P. J. Rosenthal, R. A. Cooper, A. C. C. Aguiar, R. V. C. Guido, D. B. Pereira, N. Mittal, E. A. Winzeler, D. R. Tomchick, B. Laleu, J. N. Burrows, P. K. Rathod, D. A. Fidock, S. A. Charman and M. A. Phillips, *J. Med. Chem.*, 2021, **64**, 6085–6136.
- 38 M. Xiong, X. Liang, Y. Zhou and Y. Pan, *J. Org. Chem.*, 2021, **86**, 4986–4993.
- 39 M. Ghandi, M. Khodadadi and A. Abbasi, *J. Heterocycl. Chem.*, 2021, **58**, 478–487.
- 40 D. Chang, J. Chen, Y. Liu, H. Huang, A. Qin and G.-J. Deng, *J. Org. Chem.*, 2020, **86**, 110–127.
- 41 Q.-X. Zi, C.-L. Yang, K. Li, Q. Luo, J. Lin and S.-J. Yan, *J. Org. Chem.*, 2019, **85**, 327–338.
- 42 R. Zhang, Z. Zhang, K. Wang and J. Wang, *J. Org. Chem.*, 2020, **85**, 9791–9800.
- 43 J. Zhang, M. Liu, C. Li, Y.-J. Xu and L. Dong, *Org. Chem. Front.*, 2020, **7**, 420–424.
- 44 L. Xu, L. Wu, T. Chen, S. Xu, C. Huang, Y. Wang, Q. You and J. Shen, *ChemistrySelect*, 2020, **5**, 655–659.
- 45 L. Wei, S.-M. Xu, Z. Jia, H.-Y. Tao and C.-J. Wang, *Chem. Commun.*, 2020, **56**, 9691–9694.
- 46 Z. Su, S. Wang, N. Luo and C. Wang, *Synlett*, 2020, **31**, 1022–1026.
- 47 R. Shrestha, H. D. Khanal, W. G. Yang, S. H. Kim, J. J. Shim and Y. R. Lee, *Asian J. Org. Chem.*, 2020, **9**, 1070–1075.
- 48 N. A. Mir, P. Ramaraju, S. Vanaparthi, S. Choudhary, R. P. Singh, P. Sharma, R. Kant, R. Singh, M. Sankaranarayanan and I. Kumar, *New J. Chem.*, 2020, **44**, 16329–16339.
- 49 V. A. Mamedov, E. A. Khafizova, N. E. Algaeva, S. K. Latypov and O. G. Sinyashin, *J. Org. Chem.*, 2020, **85**, 9887–9904.
- 50 H. Jia, D. Min, T. Guo, M. Wu, X. Wang, J. Liu and S. Tang, *J. Org. Chem.*, 2020, **85**, 14847–14857.
- 51 Q.-W. Gui, X. He, W. Wang, H. Zhou, Y. Dong, N. Wang, J.-X. Tang, Z. Cao and W.-M. He, *Green Chem.*, 2020, **22**, 118–122.
- 52 N. E. Golantsov, A. S. Golubenkova, A. A. Festa, A. V. Varlamov and L. G. Voskressensky, *Org. Lett.*, 2020, **22**, 4726–4731.
- 53 P. Gao, H.-J. Chen, Z.-J. Bai, M.-N. Zhao, D. Yang, J. Wang, N. Wang, L. Du and Z.-H. Guan, *J. Org. Chem.*, 2020, **85**, 7939–7951.
- 54 I. V. Efimov, M. D. Matveeva, R. Luque, V. A. Bakulev and L. G. Voskressensky, *Eur. J. Org. Chem.*, 2020, **2020**, 1108–1113.
- 55 E. Dhanasekar, T. Kannan, R. Venkatesan, P. T. Perumal and J. Kamalraja, *J. Org. Chem.*, 2020, **85**, 9631–9649.
- 56 S. Choudhary, J. Yadav, A. P. Pawar, S. Vanaparthi, N. A. Mir, E. Iype, R. Sharma, R. Kant and I. Kumar, *Org. Biomol. Chem.*, 2020, **18**, 1155–1164.
- 57 T. Yang, K.-H. Wang, D. Huang, P. Li, Z. Deng, Y. Su and Y. Hu, *Tetrahedron*, 2019, **75**, 2291–2297.
- 58 V. Rajeshkumar, C. Neelamegam and S. Anandan, *Synthesis*, 2019, **51**, 4023–4033.
- 59 L. Meng, X. Chi, X. Sun, C. Cao, B. Ai, Q. Liu, P. Zhao, Z. Zhao, Y. Dong and H. Liu, *Org. Biomol. Chem.*, 2019, **17**, 7669–7673.
- 60 J. A. Malone, C. E. Toussel, F. R. Fronczek and R. Kartika, *Org. Lett.*, 2019, **21**, 3610–3614.
- 61 V. Kumar, A. Awasthi, A. Metya and T. Khan, *J. Org. Chem.*, 2019, **84**, 11581–11595.
- 62 B. S. Karki, L. Devi, A. Pokhriyal, R. Kant and N. Rastogi, *Chem. – Asian J.*, 2019, **14**, 4793–4797.
- 63 X. Gao, P. Wang, Q. Wang, J. Chen and A. Lei, *Green Chem.*, 2019, **21**, 4941–4945.
- 64 X. Chang, X. Yang, Z. Chen and W. Zhong, *Synlett*, 2019, **30**, 1431–1436.
- 65 A. Balu Atar, E. Han, D. H. Sohn and J. Kang, *Synth. Commun.*, 2019, **49**, 1181–1192.
- 66 E. Ghabraie, S. Balalaie, M. Bararjanian, H. R. Bijanzadeh and F. Rominger, *Tetrahedron*, 2011, **67**, 5415–5420.
- 67 A. Khammas, C. Yolacan and F. Aydogan, *Russ. J. Gen. Chem.*, 2018, **88**, 2680–2683.
- 68 C. Zhou, H. Zheng, Y. Chen, G. Mao and G.-J. Deng, *J. Org. Chem.*, 2023, **88**, 1533–1544.
- 69 K. Afratis, J. M. Bateman, B. F. Rahemtulla, O. Hughes, B. C. Milgram, T. A. Mulhern and E. P. A. Talbot, *Org. Lett.*, 2023, **25**, 461–465.
- 70 T. Abbaspour, G. Firouzzadeh Pasha and M. Tajbakhsh, *Appl. Organomet. Chem.*, 2023, **37**, e6933.
- 71 P. Chacko and K. Shivashankar, *Tetrahedron*, 2018, **74**, 1520–1526.
- 72 J. C. Borghs, L. M. Azofra, T. Biberger, O. Linnenberg, L. Cavallo, M. Rueping and O. El-Sepelgy, *ChemSusChem*, 2019, **12**, 3083–3088.
- 73 L. Kumar S, A. Servesh, S. J. Chundattu, S. Tabassum and S. Govindaraju, *Mol. Diversity*, 2024, **29**, 1761–1787.



- 74 C.-X. Li, R.-J. Liu, K. Yin, L.-R. Wen and M. Li, *Org. Biomol. Chem.*, 2017, **15**, 5820–5823.
- 75 T. Pavithra, D. B. Rajkumar, K. Gnanaoli, S. N. Sunil Gowda, N. Devipriya and C. U. Maheswari, *ChemistrySelect*, 2023, **8**, e202204564.
- 76 S. Pervaram, D. Ashok, C. V. R. Reddy, M. Sarasija and A. Ganesh, *Chem. Data Collect.*, 2020, **29**, 100508.
- 77 T. Yu, F. Ji, D. Huang, Y. Gao, Z. Shi, X. Sha, J. Xu, S. You, M. Zhang and Q. Sha, *Org. Chem. Front.*, 2021, **8**, 5716–5721.
- 78 H. T. Nguyen, P. N. Nguyen, T. Van Le, T. H. Nguyen, L. D. Nguyen and P. H. Tran, *RSC Adv.*, 2023, **13**, 28623–28631.
- 79 G. Wang, S. Sun and H. Guo, *Eur. J. Med. Chem.*, 2022, **229**, 113999.
- 80 X. Zhu, Y. He, Z. Liu, Z. Zhu, Y. He, J. Qiu, D. Liu, M. Mo, P. Wang, X. Tian and P. Xu, *Appl. Mater. Today*, 2020, **19**, 100559.
- 81 Y. J. Xue, M. Y. Li, X. J. Jin, C. J. Zheng and H. R. Piao, *J. Enzyme Inhib. Med. Chem.*, 2021, **36**, 295–306.
- 82 Y. Chen, N. Cao, H. Lv, K. Zeng, J. Yuan, X. Guo, M. Zhao, P. Tu and Y. Jiang, *Phytochemistry*, 2020, **170**, 112186.
- 83 Y. Tachibana, H. Kikuzaki, N. H. Lajis and N. Nakatani, *J. Agric. Food Chem.*, 2003, **51**, 6461–6467.
- 84 J. A. Scatina, D. R. Hicks, M. Kraml and M. N. Cayen, *Xenobiotica*, 1989, **19**, 991–1002.
- 85 S. Mandal, A. Nayak, M. Kar, S. K. Banerjee, A. Das, S. N. Upadhyay, R. K. Singh, A. Banerji and J. Banerji, *Fitoterapia*, 2010, **81**, 72–74.
- 86 J. H. Burckhalter, V. C. Stephens and L. A. Hall, *J. Am. Pharm. Assoc.*, 1950, **39**, 271–273.
- 87 Y.-P. Liu, J.-M. Guo, Y.-Y. Liu, S. Hu, G. Yan, L. Qiang and Y.-H. Fu, *J. Agric. Food Chem.*, 2019, **67**, 5764–5771.
- 88 R. Birari, S. K. Roy, A. Singh and K. K. Bhutani, *Nat. Prod. Commun.*, 2009, **4**, 1089–1092.
- 89 P. Zhang, B. Li, L. Niu, L. Wang, G. Zhang, X. Jia, G. Zhang, S. Liu, L. Ma and W. Gao, *Adv. Synth. Catal.*, 2020, **362**, 2342–2347.
- 90 C. Gioia, A. Hauville, L. Bernardi, F. Fini and A. Ricci, *Angew. Chem., Int. Ed.*, 2008, **47**, 9236–9239.
- 91 J. Wang, H.-T. Zhu, Y.-F. Qiu, Y. Niu, S. Chen, Y.-X. Li, X.-Y. Liu and Y.-M. Liang, *Org. Lett.*, 2015, **17**, 3186–3189.
- 92 S. Yaragorla, D. Bag, R. Dada and K. J. Jose, *ACS Omega*, 2018, **3**, 15024–15034.
- 93 K. Liu and S. Zhang, *ACS Med. Chem. Lett.*, 2015, **6**, 894–897.
- 94 J. Zhao, P. Li, C. Xia and F. Li, *Chem. - Eur. J.*, 2015, **21**, 16383–16386.
- 95 S. Biswas, A. Dagar, A. Srivastava and S. Samanta, *Eur. J. Org. Chem.*, 2015, **2015**, 4493–4503.
- 96 J. W. Lim, S. H. Kim, J. Kim and J. N. Kim, *Bull. Korean Chem. Soc.*, 2015, **36**, 1351–1359.
- 97 C. Raji Reddy, R. Rani Valleti and U. Dilipkumar, *Chem. - Eur. J.*, 2016, **22**, 2501–2506.
- 98 H. Wang, Z. Wang, Y.-L. Wang, R.-R. Zhou, G.-C. Wu, S.-Y. Yin, X. Yan and B. Wang, *Org. Lett.*, 2017, **19**, 6140–6143.
- 99 D. Cao, A. Ying, H. Mo, D. Chen, G. Chen, Z. Wang and J. Yang, *J. Org. Chem.*, 2018, **83**, 12568–12574.
- 100 S. Chen, Y. Li, P. Ni, H. Huang and G.-J. Deng, *Org. Lett.*, 2016, **18**, 5384–5387.
- 101 S. Chen, Y. Li, P. Ni, B. Yang, H. Huang and G.-J. Deng, *J. Org. Chem.*, 2017, **82**, 2935–2942.
- 102 S. Chen, L. Wang, J. Zhang, Z. Hao, H. Huang and G.-J. Deng, *J. Org. Chem.*, 2017, **82**, 11182–11191.
- 103 Y. Li, F. Tur, R. P. Nielsen, H. Jiang, F. Jensen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2016, **55**, 1020–1024.
- 104 D. Liu, Y. Gao, J. Huang, Z. Fu and W. Huang, *J. Org. Chem.*, 2018, **83**, 14210–14217.
- 105 Y.-J. Xue, M.-Y. Li, X.-J. Jin, C.-J. Zheng and H.-R. Piao, *J. Enzyme Inhib. Med. Chem.*, 2021, **36**, 296–307.
- 106 J. Wu, X. Chen, Y. Xie, Y. Guo, Q. Zhang and G.-J. Deng, *J. Org. Chem.*, 2017, **82**, 5743–5750.
- 107 F. Guo, L. Wang, P. Wang, J. Yu and J. Han, *Asian J. Org. Chem.*, 2012, **1**, 218–221.
- 108 S. Chakrabarty, I. Chatterjee, L. Tebben and A. Studer, *Angew. Chem.*, 2013, **52**, 2968–2971.
- 109 M. Feofanov, V. Akhmetov, R. Takayama and K. Amsharov, *Org. Biomol. Chem.*, 2021, **19**, 7172–7175.
- 110 S. P. Swain and S. Mohanty, *ChemMedChem*, 2019, **14**, 291–302.
- 111 Y. A. Ammar, M. A. El-Sharief, M. M. Ghorab, Y. A. Mohamed, A. Ragab and S. Y. Abbas, *Curr. Org. Synth.*, 2016, **13**, 466–475.
- 112 G. S. de Carvalho, R. M. Dias, F. R. Pavan, C. Q. Leite, V. L. Silva, C. G. Diniz, D. T. de Paula, E. S. Coimbra, P. Retailleau and A. D. da Silva, *Med. Chem.*, 2013, **9**, 351–359.
- 113 X. Liang, H. Fu, P. Xiao, H. Fang and X. Hou, *Bioorg. Chem.*, 2020, **103**, 104124.
- 114 M. C. Caterina, I. A. Perillo, L. Boiani, H. Pezaroglo, H. Cerecetto, M. González and A. Salerno, *Bioorg. Med. Chem.*, 2008, **16**, 2226–2234.
- 115 V. Sharma and M. Khan, *Eur. J. Med. Chem.*, 2001, **36**, 651–658.
- 116 A. N. Komogortsev, V. G. Melekhina, B. V. Lichitsky and M. E. Minyaev, *J. Heterocycl. Chem.*, 2021, **58**, 864–872.
- 117 X. Cheng, B.-G. Cai, H. Mao, J. Lu, L. Li, K. Wang and J. Xuan, *Org. Lett.*, 2021, **23**, 4109–4114.
- 118 A. Casnati, A. Perrone, P. P. Mazzeo, A. Bacchi, R. Mancuso, B. Gabriele, R. Maggi, G. Maestri, E. Motti and A. S. Stirling, *J. Org. Chem.*, 2019, **84**, 3477–3490.
- 119 A. Angyal, A. Demjén, V. Harmat, J. n. Wolfling, L. G. Puskás and I. Kanizsai, *J. Org. Chem.*, 2019, **84**, 4273–4281.
- 120 B.-L. Zhao and D.-M. Du, *Org. Lett.*, 2018, **20**, 3797–3800.
- 121 Y.-L. Qian, P.-J. Xia, J. Li, Q.-L. Zhao, J.-A. Xiao, H.-y. Xiang and H. Yang, *Org. Biomol. Chem.*, 2017, **15**, 8705–8708.
- 122 P. Liu, G. Xu and J. Sun, *Org. Lett.*, 2017, **19**, 1858–1861.
- 123 G. Di Carmine, D. Ragno, C. De Risi, O. Bortolini, P. P. Giovannini, G. Fantin and A. Massi, *Org. Biomol. Chem.*, 2017, **15**, 8788–8801.
- 124 P. V. Balaji and S. Chandrasekaran, *Tetrahedron*, 2016, **72**, 1095–1104.
- 125 M. A. Tabarki and R. Besbes, *Tetrahedron Lett.*, 2016, **57**, 3832–3836.



- 126 V. Satheesh, M. Sengoden and T. Punniyamurthy, *J. Org. Chem.*, 2016, **81**, 9792–9801.
- 127 C. Izquierdo, F. Esteban, J. L. G. Ruano, A. Fraile and J. Aleman, *Org. Lett.*, 2016, **18**, 92–95.
- 128 Y.-H. Sun, Y. Xiong, C.-Q. Peng, W. Li, J.-A. Xiao and H. Yang, *Org. Biomol. Chem.*, 2015, **13**, 7907–7910.
- 129 M. Bai, B.-D. Cui, J. Zuo, J.-Q. Zhao, Y. You, Y.-Z. Chen, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Tetrahedron*, 2015, **71**, 949–955.
- 130 A. Olyaei, M. K. Karimi and R. Razeghi, *Tetrahedron Lett.*, 2013, **54**, 5730–5733.
- 131 H. Xie, J.-C. Liu, L. Wu and M.-W. Ding, *Tetrahedron*, 2012, **68**, 7984–7990.
- 132 L. Saney, T. Panduwawala, X. Li, K. E. Christensen, M. Genov, A. Pretsch, D. Pretsch and M. G. Moloney, *Org. Biomol. Chem.*, 2023, **21**, 4801–4809.
- 133 S. Barranco, A. Pagnanini, F. Cuccu, P. Caboni, R. Guillot, D. J. Aitken and A. Frongia, *Org. Biomol. Chem.*, 2024, **22**, 8048–8053.
- 134 A. Scarsi, M. Ponassi, C. Brullo, C. Rosano and A. Spallarossa, *Mol. Diversity*, 2023, **27**, 1285–1295.
- 135 S. H. Bae, J. H. Park, H. G. Choi, H. Kim and S. H. Kim, *Biomol. Ther.*, 2018, **26**, 494–502.
- 136 J. S. de Araújo, A. García-Rubia, V. Sebastián-Pérez, T. D. Kalejaiye, P. Bernardino da Silva, C. R. Fonseca-Berzal, L. Maes, H. P. De Koning, M. N. C. Soeiro and C. Gil, *Antimicrob. Agents Chemother.*, 2019, **63**, e02156.
- 137 H. Karppanen, P. Paakkari, A. L. Orma and I. Paakkari, *Agents Actions*, 1979, **9**, 84–86.
- 138 A. Bhatnagar, P. Sharma and N. Kumar, *Int. J. PharmTech Res.*, 2011, **3**, 268–282.
- 139 A. A. Abdelhamid, H. A. Salah and A. A. Marzouk, *J. Heterocycl. Chem.*, 2020, **57**, 676–685.
- 140 Y. Tian, M. Qin, X. Yang, X. Zhang, Y. Liu, X. Guo and B. Chen, *Tetrahedron*, 2019, **75**, 2817–2823.
- 141 M. R. Albayati, A. A. Marzouk and A. A. Abdelhamid, *J. Heterocycl. Chem.*, 2019, **56**, 1514–1519.
- 142 M. Beuvin, M. Manneveau, S. Diab, B. Picard, M. Sanselme, S. R. Piettre, J. Legros and I. Chataigner, *Tetrahedron Lett.*, 2018, **59**, 4487–4491.
- 143 S. Evjen and A. Fiksdahl, *Synth. Commun.*, 2017, **47**, 1392–1399.
- 144 C.-Y. Chen, W.-P. Hu, P.-C. Yan, G. C. Senadi and J.-J. Wang, *Org. Lett.*, 2013, **15**, 6116–6119.
- 145 G. Mlostóń, E. Obijalska and H. Heimgartner, *J. Fluorine Chem.*, 2011, **132**, 951–955.
- 146 L. Albrecht, L. K. Ransborg, A. Albrecht, L. Lykke and K. A. Jørgensen, *Chem. - Eur. J.*, 2011, **17**, 13240–13246.
- 147 L. Preti, O. A. Attanasi, E. Caselli, G. Favi, C. Ori, P. Davoli, F. Felluga and F. Prati, *Eur. J. Org Chem.*, 2010, **2010**, 4312–4320.
- 148 A. R. Karimi, Z. Alimohammadi, J. Azizian, A. A. Mohammadi and M. R. Mohammadzadeh, *Catal. Commun.*, 2006, **7**, 728–732.
- 149 S. Kantevari, S. V. N. Vuppapapati, D. O. Biradar and L. Nagarapu, *J. Mol. Catal. A: Chem.*, 2007, **266**, 109–113.
- 150 C. Mukhopadhyay, P. K. Tapaswi and M. G. B. Drew, *Tetrahedron Lett.*, 2010, **51**, 3944–3950.
- 151 A. Mohammadi, H. Keshvari, R. Sandaroos, B. Maleki, H. Rouhi, H. Moradi, Z. Sepehr and S. Damavandi, *Appl. Catal.*, 2012, **429**, 73–78.
- 152 J. J. Gabla, S. R. Mistry and K. C. Maheria, *Catal. Sci. Technol.*, 2017, **7**, 5154–5167.
- 153 A. Khodairy, A. M. Ali and M. T. El-Wassimy, *J. Heterocycl. Chem.*, 2017, **54**, 3342–3349.
- 154 D. Bourissou, O. Guerret, F. P. Gabbaï and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39–92.
- 155 S. V. Nalage, M. B. Kalyankar, V. S. Patil, S. V. Bhosale, S. U. Deshmukh and R. P. Pawar, *Open Catal. J.*, 2010, **3**, 58–61.
- 156 A. Husain, S. Drabu and N. Kumar, *Acta Pol. Pharm.*, 2009, **66**, 243–248.
- 157 M. Ratanlal, D. Mohankrishnan, V. Jayaram, D. Sahal and G. V. M. Sharma, *ChemistrySelect*, 2024, **9**, e202302636.
- 158 A. A. Bhat, I. Singh, N. Tandon and R. Tandon, *Eur. J. Med. Chem.*, 2023, **246**, 114954.
- 159 B. Marshall and J. R. Warren, *Lancet*, 1984, **323**, 1311–1315.
- 160 A. Nomura, G. N. Stemmermann, P.-H. Chyou, G. I. Perez-Perez and M. J. Blaser, *Ann. Intern. Med.*, 1994, **120**, 977–981.
- 161 J. Labenz and G. Börsch, *Gut*, 1994, **35**, 19–22.
- 162 J. Parsonnet, G. D. Friedman, D. P. Vandersteen, Y. Chang, J. H. Vogelmann, N. Orentreich and R. K. Sibley, *N. Engl. J. Med.*, 1991, **325**, 1127–1131.
- 163 T. Gieshoff, A. Kehl, D. Schollmeyer, K. D. Moeller and S. R. Waldvogel, *J. Am. Chem. Soc.*, 2017, **139**, 12317–12324.
- 164 T. Gieshoff, D. Schollmeyer and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2016, **55**, 9437–9440.
- 165 D. Wang, H. P. Deng, Y. Wei, Q. Xu and M. Shi, *Eur. J. Org Chem.*, 2013, **2013**, 401–406.
- 166 Z.-C. Geng, J. Chen, N. Li, X.-F. Huang, Y. Zhang, Y.-W. Zhang and X.-W. Wang, *Beilstein J. Org. Chem.*, 2012, **8**, 1710–1720.
- 167 M. Fernandez, E. Reyes, J. L. Vicario, D. Badia and L. Carrillo, *Adv. Synth. Catal.*, 2012, **354**, 371–376.
- 168 L. Deiana, G. L. Zhao, H. Leijonmarck, J. Sun, C. W. Lehmann and A. Córdova, *ChemistryOpen*, 2012, **1**, 134–139.
- 169 Y. Biliz, B. Hasdemir, H. B. Küçük, S. Yıldırım, F. Kocabaş and R. A. Kartop, *J. Mol. Struct.*, 2024, **1295**, 136813.
- 170 H. T. Nguyen, T. V. Le and P. H. Tran, *J. Environ. Chem. Eng.*, 2021, **9**, 105228.
- 171 N. Nayak, J. Ramprasad and U. Dalimba, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 5540–5545.
- 172 N. C. Desai and D. V. Vaja, *Int. Lett. Chem., Phys. Astron.*, 2018, **77**, 35–52.
- 173 N. D. Amnerkar and K. P. Bhusari, *Eur. J. Med. Chem.*, 2010, **45**, 149–159.
- 174 A. Balbi, M. Anzaldi, C. Macciò, C. Aiello, M. Mazzei, R. Gangemi, P. Castagnola, M. Miele, C. Rosano and M. Viale, *Eur. J. Med. Chem.*, 2011, **46**, 5293–5309.



- 175 O. I. El-Sabbagh, M. M. Baraka, S. M. Ibrahim, C. Pannecouque, G. Andrei, R. Snoeck, J. Balzarini and A. A. Rashad, *Eur. J. Med. Chem.*, 2009, **44**, 3746–3753.
- 176 K. D. Dwivedi, B. Borah and L. R. Chowhan, *Front. Chem.*, 2020, **7**, 944.
- 177 H.-F. Zhang, Z.-Q. Ye and G. Zhao, *Chin. Chem. Lett.*, 2014, **25**, 535–540.
- 178 R. Maity and S. C. Pan, *Org. Biomol. Chem.*, 2017, **15**, 8032–8036.
- 179 C. Y. Wu and K. Chen, *ChemistrySelect*, 2018, **3**, 3500–3504.
- 180 A. Dandia, S. Bansal, R. Sharma and V. Parewa, *ChemistrySelect*, 2018, **3**, 9785–9789.
- 181 V. Ramesh, S. Shanmugam and N. S. Devi, *New J. Chem.*, 2016, **40**, 9993–10001.
- 182 V. L. Gein, T. M. Zamaraeva and P. A. Slepukhin, *Tetrahedron Lett.*, 2017, **58**, 134–136.
- 183 A. Alizadeh and F. Bayat, *Helv. Chim. Acta*, 2014, **97**, 694–700.
- 184 K. Jayabal and T. P. Paramasivan, *Tetrahedron Lett.*, 2014, **55**, 2010–2014.
- 185 C. Wang, Y.-H. Jiang and C.-G. Yan, *Chin. Chem. Lett.*, 2015, **26**, 889–893.
- 186 B. P. Tripathi, A. Mishra, P. Rai, Y. K. Pandey, M. Srivastava, S. Yadav, J. Singh and J. Singh, *New J. Chem.*, 2017, **41**, 11148–11154.
- 187 S. Pandeya, D. Sriram, G. Nath and E. DeClercq, *Eur. J. Pharm. Sci.*, 1999, **9**, 25–31.
- 188 V. Gududuru, E. Hurh, J. T. Dalton and D. D. Miller, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5289–5293.
- 189 S. Bhattacharya, B. Roy, S. Mana and S. Kumar, *Pharma Res.*, 2009, **2**, 79–83.
- 190 J. Balzarini, B. Orzeszko, J. K. Maurin and A. Orzeszko, *Eur. J. Med. Chem.*, 2007, **42**, 993–1003.
- 191 M.-H. Shih and F.-Y. Ke, *Bioorg. Med. Chem.*, 2004, **12**, 4633–4643.
- 192 A. Daghlavi, E. Kowsari, M. Abdouss, M. H. Ghasemi and E. Asadi, *Res. Chem. Intermed.*, 2020, **46**, 3593–3605.
- 193 G. Rainoldi, F. Begnini, M. De Munnik, L. Lo Presti, C. M. Vande Velde, R. Orru, G. Lesma, E. Ruijter and A. Silvani, *ACS Comb. Sci.*, 2018, **20**, 98–105.
- 194 B. Kaboudin and J. Abbasi Shiran, *J. Sulfur Chem.*, 2018, **39**, 633–645.
- 195 H. Medini, N. H. Mekni and K. Boujlel, *J. Sulfur Chem.*, 2015, **36**, 653–659.
- 196 A. M. Malla, M. Parveen, F. Ahmad, S. Azaz and M. Alam, *RSC Adv.*, 2015, **5**, 19552–19569.
- 197 A. Ziyaei-Halimehjani, K. Marjani and A. Ashouri, *Tetrahedron Lett.*, 2012, **53**, 3490–3492.
- 198 B. P. Kumar, M. Nanjan, B. Suresh, M. Karvekar and L. Adhikary, *J. Heterocycl. Chem.*, 2006, **43**, 897–903.
- 199 K. Yamada, T. Tsubogo, H. Kanazawa, S. Ishizuka, K. Ohyama, M. Kaida and T. Abe, *Eur. J. Org. Chem.*, 2024, **27**, e202301130.
- 200 M. Zhang, Y. Chen, J. Liu, X. Yan, K. Huang and X. Ma, *Asian J. Org. Chem.*, 2025, **14**, e202400558.
- 201 M. Chen, S. Lu, G. Yuan, S. Yang and X. Du, *Heterocycl. Commun.*, 2000, **6**, 421–426.
- 202 E. A. Sheremet, R. I. Tomanov, E. V. Trukhin and V. M. Berestovitskaya, *Russ. J. Org. Chem.*, 2004, **40**, 594–595.
- 203 H. N. Hafez, H.-A. S. Abbas and A.-R. B. A. El-Gazzar, *Acta Pharm.*, 2008, **58**, 359–378.
- 204 K. M. Banu, A. Dinakar and C. Ananthanarayanan, *Indian J. Pharm. Sci.*, 1999, **61**, 202.
- 205 L. P. Guan, Q. H. Jin, G. R. Tian, K. Y. Chai and Z. S. Quan, *J. Pharm. Pharm. Sci.*, 2007, **10**, 254–262.
- 206 A. Passannanti, P. Diana, P. Barraja, F. Mingoia, A. Lauria and G. Cirrincione, *Heterocycles*, 1998, **6**, 1229–1235.
- 207 R. Gujjar, A. Marwaha, F. El Mazouni, J. White, K. L. White, S. Creason, D. M. Shackelford, J. Baldwin, W. N. Charman and F. S. Buckner, *J. Med. Chem.*, 2009, **52**, 1864–1872.
- 208 B. A. Johns, J. G. Weatherhead, S. H. Allen, J. B. Thompson, E. P. Garvey, S. A. Foster, J. L. Jeffrey and W. H. Miller, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1802–1806.
- 209 S. Manfredini, C. B. Vicentini, M. Manfrini, N. Bianchi, C. Rutigliano, C. Mischiati and R. Gambari, *Bioorg. Med. Chem.*, 2000, **8**, 2343–2346.
- 210 A. Duran, H. Dogan and S. Rollas, *Il Farmaco*, 2002, **57**, 559–564.
- 211 Z. Xu, S. J. Zhao and Y. Liu, *Eur. J. Med. Chem.*, 2019, **183**, 111700.
- 212 L. S. Venigalla, S. Maddila and S. B. Jonnalagadda, *J. Iran. Chem. Soc.*, 2020, **17**, 1539–1544.
- 213 N. A. Aksenov, A. V. Aksenov, N. K. Kirilov, N. A. Arutiunov, D. A. Aksenov, V. Maslivets, Z. Zhao, L. Du, M. Rubin and A. Kornienko, *Org. Biomol. Chem.*, 2020, **18**, 6651–6664.
- 214 N. Guo, X. Liu, H. Xu, X. Zhou and H. Zhao, *Org. Biomol. Chem.*, 2019, **17**, 6148–6152.
- 215 N. Okamoto, T. Sueda, H. Minami and R. Yanada, *Tetrahedron Lett.*, 2018, **59**, 1461–1464.
- 216 A. V. Bogolyubsky, O. Savych, A. V. Zhemera, S. E. Pipko, A. V. Grishchenko, A. I. Konovets, R. O. Doroshchuk, D. N. Khomenko, V. S. Brovarets and Y. S. Moroz, *ACS Comb. Sci.*, 2018, **20**, 461–466.
- 217 V. O. Filimonov, L. N. Dianova, K. A. Galata, T. V. Beryozkina, M. S. Novikov, V. S. Berseneva, O. S. Eltsov, A. T. Lebedev, P. A. Slepukhin and V. A. Bakulev, *J. Org. Chem.*, 2017, **82**, 4056–4071.
- 218 W. Li, Q. Jia, Z. Du and J. Wang, *Chem. Commun.*, 2013, **49**, 10187–10189.
- 219 M. Taha, N. H. Ismail, S. Imran, M. Q. B. Rokei, S. M. Saad and K. M. Khan, *Bioorg. Med. Chem.*, 2015, **23**, 4155–4162.
- 220 T. Glomb, K. Szymankiewicz and P. Świątek, *Molecules*, 2018, **23**, 3361.
- 221 G. Chawla, B. Naaz and A. A. Siddiqui, *Mini-Rev. Med. Chem.*, 2018, **18**, 216–233.
- 222 D. R. Faria, R. C. Melo, G. S. Arita, K. M. Sakita, F. A. V. Rodrigues-Vendramini, I. R. G. Capoci, T. C. A. Becker, P. S. Bonfim-Mendonça, M. S. S. Felipe, T. I. E. Svidzinski and E. S. Kioshima, *Pathogens*, 2021, **10**, 314.
- 223 Y.-E. Wang, D. Yang, L. Dai, J. Huo, L. Chen, Z. Kang, J. Mao and J. Zhang, *J. Agric. Food Chem.*, 2022, **70**, 2510–2519.



- 224 W. A. El-Sayed, F. A. El-Essawy, O. M. Ali, B. S. Nasr, M. M. Abdalla, A. A. Abdel-Rahman and Z. Naturforsch C, *J. Biosci.*, 2009, **64**, 773–778.
- 225 T. Glomb and P. Świątek, *Int. J. Mol. Sci.*, 2021, **22**, 6979.
- 226 M. Luczynski and A. Kudelko, *Appl. Sci.*, 2022, **12**, 3756.
- 227 F. Lu, F. Gong, L. Li, K. Zhang, Z. Li, X. Zhang, Y. Yin, Y. Wang, Z. Gao and H. Zhang, *Eur. J. Org. Chem.*, 2020, **2020**, 3257–3260.
- 228 V. N. Telvekar and B. S. Takale, *Synth. Commun.*, 2013, **43**, 221–227.
- 229 K. N. Patel, N. C. Jadhav, P. B. Jagadhane and V. N. Telvekar, *Synlett*, 2012, **23**, 1970–1972.
- 230 L. Sharma, S. Kumar, S. Singh and R. Singh, *Russ. J. Electrochem.*, 2010, **46**, 34–40.
- 231 V. V. Sureshbabu, H. P. Hemantha and S. A. Naik, *Tetrahedron Lett.*, 2008, **49**, 5133–5136.
- 232 M. D. Evans, J. Ring, A. Schoen, A. Bell, P. Edwards, D. Berthelot, R. Nicewonger and C. M. Baldino, *Tetrahedron Lett.*, 2003, **44**, 9337–9341.
- 233 S. Jazayeri, M. H. Moshafi, L. Firoozpour, S. Emami, S. Rajabalian, M. Haddad, F. Pahlavanzadeh, M. Esnaashari, A. Shafiee and A. Foroumadi, *Eur. J. Med. Chem.*, 2009, **44**, 1205–1209.
- 234 S. N. Swamy, B. Priya, B. Prabhuswamy, B. Doreswamy, J. S. Prasad and K. S. Rangappa, *Eur. J. Med. Chem.*, 2006, **41**, 531–538.
- 235 U. Salgın-Gökşen, N. Gökhan-Kelekçi, Ö. Göktaş, Y. Köysal, E. Kılıç, Ş. Işık, G. Aktay and M. Özalp, *Bioorg. Med. Chem.*, 2007, **15**, 5738–5751.
- 236 A. T. Mavrova, D. Wesselinova, Y. A. Tsenov and P. Denkova, *Eur. J. Med. Chem.*, 2009, **44**, 63–69.
- 237 K. B. Zheng, J. He and J. Zhang, *Chin. Chem. Lett.*, 2008, **19**, 1281–1284.
- 238 A. Gupta, P. Mishra, S. Pandeya, S. K. Kashaw, V. Kashaw and J. P. Stables, *Eur. J. Med. Chem.*, 2009, **44**, 1100–1105.
- 239 N. Ö. Can, Ö. D. Can, D. Osmaniye and Ü. Demir Özkay, *Molecules*, 2018, **23**, 716.
- 240 I. Khan, S. Ali, S. Hameed, N. H. Rama, M. T. Hussain, A. Wadood, R. Uddin, Z. Ul-Haq, A. Khan, S. Ali and M. I. Choudhary, *Eur. J. Med. Chem.*, 2010, **45**, 5200–5207.
- 241 C. Kuş, G. Ayhan-Kılıçgil, S. Özbey, F. B. Kaynak, M. Kaya, T. Çoban and B. Can-Eke, *Bioorg. Med. Chem.*, 2008, **16**, 4294–4303.
- 242 M. Behrouzi-Fardmoghdam, F. Poorrajab, S. K. Ardestani, S. Emami, A. Shafiee and A. Foroumadi, *Bioorg. Med. Chem.*, 2008, **16**, 4509–4515.
- 243 A. Foroumadi, S. Emami, S. Pournourmohammadi, A. Kharazmi and A. Shafiee, *Eur. J. Med. Chem.*, 2005, **40**, 1346–1350.
- 244 Y. Han, Y. Sun, A. Abdulkader, B. Liu and D. Wang, *Catal. Lett.*, 2018, **148**, 3486–3491.
- 245 A. Feddoui, M. Y. A. Itto, A. Hasnaoui, D. Villemin, P. A. Jaffrès, J. S. D. O. Santos, A. Riahi, F. Huet and J. C. Daran, *J. Heterocycl. Chem.*, 2004, **41**, 731–735.
- 246 S. Barriga, P. Fuertes, C. F. Marcos, D. Miguel, O. A. Rakitin, C. W. Rees and T. Torroba, *J. Org. Chem.*, 2001, **66**, 5766–5771.
- 247 Y. Song, D. T. Connor, A. D. Sercel, R. J. Sorenson, R. Doubleday, P. C. Unangst, B. D. Roth, V. G. Beylin, R. B. Gilbertsen and K. Chan, *J. Med. Chem.*, 1999, **42**, 1161–1169.
- 248 C. Gao, L. Chang, Z. Xu, X.-F. Yan, C. Ding, F. Zhao, X. Wu and L.-S. Feng, *Eur. J. Med. Chem.*, 2019, **163**, 404–412.
- 249 D. C. Crosby, X. Lei, C. G. Gibbs, B. R. McDougall, W. E. Robinson Jr and M. G. Reinecke, *J. Med. Chem.*, 2010, **53**, 8161–8175.
- 250 P. Zhan, H. Liu, X. Liu, Y. Wang, C. Pannecouque, M. Witvrouw and E. De Clercq, *Med. Chem. Res.*, 2010, **19**, 652–663.
- 251 T. V. Serebryanskaya, T. Yung, A. A. Bogdanov, A. Shchebet, S. A. Johnsen, A. S. Lyakhov, L. S. Ivashkevich, Z. A. Ibrahimava, T. S. Garbuzenco and T. S. Kolesnikova, *J. Inorg. Biochem.*, 2013, **120**, 44–53.
- 252 M. Arshad, A. R. Bhat, S. Pokharel, J.-E. Kim, E. J. Lee, F. Athar and I. Choi, *Eur. J. Med. Chem.*, 2014, **71**, 229–236.
- 253 M. Y. Wani, A. R. Bhat, A. Azam, D. H. Lee, I. Choi and F. Athar, *Eur. J. Med. Chem.*, 2012, **54**, 845–854.
- 254 A. B. Salake, A. S. Chothe, S. S. Nilewar, M. Khilare, R. S. Meshram, A. A. Pandey and M. Kathiravan, *J. Chem. Biol.*, 2014, **7**, 29–35.
- 255 J. Figueiredo, M. Ismael, J. Pinheiro, A. Silva, J. Justino, F. Silva, M. Goulart, D. Mira, M. Araújo and R. Campoy, *Carbohydr. Res.*, 2012, **347**, 47–54.
- 256 K. Pegklidou, C. Koukoulitsa, I. Nicolaou and V. J. Demopoulos, *Bioorg. Med. Chem.*, 2010, **18**, 2107–2114.
- 257 D. P. Zarezin, A. M. Kabyl'da, V. I. Vinogradova, P. V. Dorovatovskii, V. N. Khrustalev and V. G. Nenajdenko, *Tetrahedron*, 2018, **74**, 4315–4322.
- 258 Z. N. Tisseh, M. Dabiri, M. Nobahar, H. R. Khavasi and A. Bazgir, *Tetrahedron*, 2012, **68**, 1769–1773.
- 259 R. P. Wurz and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 12234–12235.
- 260 M. De Angelis, C. Sappino, E. Mandic, M. D'Alessio, M. G. De Dominicis, S. Sannino, L. Primitivo, P. Mencarelli, A. Ricelli and G. Righi, *Tetrahedron*, 2021, **79**, 131837.
- 261 S. R. Chowdhury, J. Gu, Y. Hu, J. Wang, S. Lei, M. S. Tavallaie, C. Lam, D. Lu, F. Jiang and L. Fu, *Eur. J. Med. Chem.*, 2021, **222**, 113541.
- 262 H. R. Shaterian and K. Azizi, *J. Mol. Liq.*, 2013, **180**, 187–191.
- 263 Q. Zhou, L. Zhang, W. Meng, X. Feng, J. Yang and H. Du, *Org. Lett.*, 2016, **18**, 5189–5191.
- 264 H. Zhang and K. Muñiz, *ACS Catal.*, 2017, **7**, 4122–4125.
- 265 A. Patil and R. Salunkhe, *Res. Chem. Intermed.*, 2018, **44**, 3337–3348.
- 266 R. Ebule, S. Mudshinge, M. H. Nantz, M. S. Mashuta, G. B. Hammond and B. Xu, *J. Org. Chem.*, 2019, **84**, 3249–3259.
- 267 P. N. Nguyen, L. H. T. Nguyen, T. L. H. Doan, P. H. Tran and H. T. Nguyen, *RSC Adv.*, 2024, **14**, 7006–7021.
- 268 V. Chavan, S. Sonawane, M. Shingare and B. Karale, *Chem. Heterocycl. Compd.*, 2006, **42**, 625–630.
- 269 E. Abele, R. Abele and E. Lukevics, *Chem. Heterocycl. Compd.*, 2003, **39**, 825–865.



- 270 A. A. Fadda, M. A. Berghot, F. A. Amer, D. S. Badawy and N. M. Bayoumy, *Arch. Pharm.*, 2012, **345**, 378–385.
- 271 M. El-Naggar, H. Almahli, H. S. Ibrahim, W. M. Eldehna and H. A. Abdel-Aziz, *Molecules*, 2018, **23**.
- 272 P. Baumgarten and A. Dornow, *Ber. Dtsch. Chem. Ges.*, 1939, **72**, 563–566.
- 273 J. M. Robinson, L. W. Brent, C. Chau, K. A. Floyd, S. L. Gillham, T. L. McMahan, D. J. Magda, T. J. Motycka and M. J. Pack, *J. Org. Chem.*, 1992, **57**, 7352–7355.
- 274 M. C. Bagley, J. W. Dale and J. Bower, *Synlett*, 2001, **2001**, 1149–1151.
- 275 M. C. Bagley, R. Lunn and X. Xiong, *Tetrahedron Lett.*, 2002, **43**, 8331–8334.
- 276 T. R. Kelly and R. L. Lebedev, *J. Org. Chem.*, 2002, **67**, 2197–2205.
- 277 X. Xiong, M. C. Bagley and K. Chapaneri, *Tetrahedron Lett.*, 2004, **45**, 6121–6124.
- 278 X. Fang, Y.-C. Liu and C. Li, *J. Org. Chem.*, 2007, **72**, 8608–8610.
- 279 S. Tu, R. Jia, B. Jiang, J. Zhang, Y. Zhang, C. Yao and S. Ji, *Tetrahedron*, 2007, **63**, 381–388.
- 280 K. Yoshida, F. Kawagoe, K. Hayashi, S. Horiuchi, T. Imamoto and A. Yanagisawa, *Org. Lett.*, 2009, **11**, 515–518.
- 281 R. H. Boecker and F. P. Guengerich, *J. Med. Chem.*, 1986, **29**, 1596–1603.
- 282 J. S. Yadav, B. V. S. Reddy, G. Sabitha and G. S. K. K. Reddy, *Synthesis*, 2000, **2000**, 1532–1534.
- 283 N. Nakamichi, Y. Kawashita and M. Hayashi, *Synthesis*, 2004, **2004**, 1015–1020.
- 284 J. Yadav, B. Reddy, A. Basak, G. Baishya and A. V. Narsaiah, *Synthesis*, 2006, **2006**, 451–454.
- 285 X. Wei, L. Wang, W. Jia, S. Du, L. Wu and Q. Liu, *Chin. J. Chem.*, 2014, **32**, 1245–1250.
- 286 M. Movassaghi, M. D. Hill and O. K. Ahmad, *J. Am. Chem. Soc.*, 2007, **129**, 10096–10097.
- 287 B. C. Ranu, R. Jana and S. Sowmiah, *J. Org. Chem.*, 2007, **72**, 3152–3154.
- 288 J. Yin, B. Xiang, M. A. Huffman, C. E. Raab and I. W. Davies, *J. Org. Chem.*, 2007, **72**, 4554–4557.
- 289 Y. Jiang, C.-M. Park and T.-P. Loh, *Org. Lett.*, 2014, **16**, 3432–3435.
- 290 H. Wei, Y. Li, K. Xiao, B. Cheng, H. Wang, L. Hu and H. Zhai, *Org. Lett.*, 2015, **17**, 5974–5977.
- 291 H. Huang, J. Cai, L. Tang, Z. Wang, F. Li and G.-J. Deng, *J. Org. Chem.*, 2016, **81**, 1499–1505.
- 292 J. Shen, D. Cai, C. Kuai, Y. Liu, M. e. Wei, G. Cheng and X. Cui, *J. Org. Chem.*, 2015, **80**, 6584–6589.
- 293 D. Majee, S. Biswas, S. M. Mobin and S. Samanta, *J. Org. Chem.*, 2016, **81**, 4378–4385.
- 294 S. Biswas, D. Majee, S. Guin and S. Samanta, *J. Org. Chem.*, 2017, **82**, 10928–10938.
- 295 Y. Gao, R. Chen and Y. Ma, *Synthesis*, 2019, **51**, 3875–3882.
- 296 G. Asskar, M. Rivard and T. Martens, *J. Org. Chem.*, 2019, **85**, 1232–1239.
- 297 I. Kim, S. Park and S. Hong, *Org. Lett.*, 2020, **22**, 8730–8734.
- 298 J. Duan, L. Zhang, G. Xu, H. Chen, X. Ding, Y. Mao, B. Rong, N. Zhu and K. Guo, *J. Org. Chem.*, 2020, **85**, 8157–8165.
- 299 M. Hassani, W. Cai, K. H. Koelsch, D. C. Holley, A. S. Rose, F. Olang, J. P. Lineswala, W. G. Holloway, J. M. Gerdes and M. Behforouz, *J. Med. Chem.*, 2008, **51**, 3104–3115.
- 300 J. Iqbal, S. A. Ejaz, I. Khan, E. Ausekle, M. Miliutina and P. Langer, *Daru*, 2019, **27**, 613–626.
- 301 S. S. Zhang, Q. W. Tan and L. P. Guan, *Mini-Rev. Med. Chem.*, 2021, **21**, 2261–2275.
- 302 Y.-T. Duan, Y.-F. Yao, D.-J. Tang, N. j. Thumar, S. B. Teraiya, J. A. Makawana, Y.-L. Sang, Z.-C. Wang, X.-X. Tao, A.-Q. Jiang and H.-L. Zhu, *RSC Adv.*, 2014, **4**, 20382–20392.
- 303 S. Ali, H.-T. Zhu, X.-F. Xia, K.-G. Ji, Y.-F. Yang, X.-R. Song and Y.-M. Liang, *Org. Lett.*, 2011, **13**, 2598–2601.
- 304 G. Shan, X. Sun, Q. Xia and Y. Rao, *Org. Lett.*, 2011, **13**, 5770–5773.
- 305 F.-P. Ma, G.-T. Cheng, Z.-G. He and Z.-H. Zhang, *Aust. J. Chem.*, 2012, **65**, 409–416.
- 306 S. Khong and O. Kwon, *J. Org. Chem.*, 2012, **77**, 8257–8267.
- 307 H. Kefayati, F. Narchin and K. Rad-Moghadam, *Tetrahedron Lett.*, 2012, **53**, 4573–4575.
- 308 Q. Gao, S. Liu, X. Wu and A. Wu, *Org. Lett.*, 2014, **16**, 4582–4585.
- 309 Y.-N. Huang, Y.-L. Li, J. Li and J. Deng, *J. Org. Chem.*, 2016, **81**, 4645–4653.
- 310 X. Wu, X. Geng, P. Zhao, J. Zhang, X. Gong, Y.-d. Wu and A.-x. Wu, *Org. Lett.*, 2017, **19**, 1550–1553.
- 311 H. Wang, Q. Xu, S. Shen and S. Yu, *J. Org. Chem.*, 2017, **82**, 770–775.
- 312 J.-C. Xiang, Z.-X. Wang, Y. Cheng, S.-Q. Xia, M. Wang, B.-C. Tang, Y.-D. Wu and A.-X. Wu, *J. Org. Chem.*, 2017, **82**, 9210–9216.
- 313 T.-S. Jiang, X. Wang and X. Zhang, *Tetrahedron Lett.*, 2018, **59**, 2979–2982.
- 314 S. Y. Lee and C.-H. Cheon, *J. Org. Chem.*, 2018, **83**, 13036–13044.
- 315 P. Zhou, B. Hu, K. Rao, L. Li, J. Yang, C. Gao, F. Wang and F. Yu, *Synlett*, 2018, **29**, 519–524.
- 316 J. Nan, Y. Hu, P. Chen and Y. Ma, *Org. Lett.*, 2019, **21**, 1984–1988.
- 317 J. Nan, P. Chen, Y. Zhang, Y. Yin, B. Wang and Y. Ma, *J. Org. Chem.*, 2020, **85**, 14042–14054.
- 318 D. Cheng, X. Yan, J. Shen, Y. Pu, X. Xu and J. Yan, *Synthesis*, 2020, **52**, 1833–1840.
- 319 W. A. Carroll, K. A. Agrios, R. J. Altenbach, S. A. Buckner, Y. Chen, M. J. Coghlan, A. V. Daza, I. Drizin, M. Gopalakrishnan and R. F. Henry, *J. Med. Chem.*, 2004, **47**, 3180–3192.
- 320 M. De Luca, G. Ioele and G. Ragno, *Pharmaceutics*, 2019, **11**, 85.
- 321 D. J. Triggle, *Cell. Mol. Neurobiol.*, 2003, **23**, 293–303.
- 322 M. M. Heravi, M. Saeedi, N. Karimi, M. Zakeri, Y. S. Beheshtiha and A. Davoodnia, *Synth. Commun.*, 2010, **40**, 523–529.
- 323 J.-Y. He, H.-Z. Jia, Q.-G. Yao, S.-J. Liu, H.-K. Yue, H.-W. Yu and R.-S. Hu, *Ultrason. Sonochem.*, 2015, **22**, 144–148.



- 324 S. Jadhvar, H. Kasraliker, S. Goswami, A. Chakrawar and S. Bhusare, *Res. Chem. Intermed.*, 2017, **43**, 7211–7221.
- 325 M. R. Bhosle, D. Nipte, J. Gaikwad, M. A. Shaikh, G. M. Bondle and J. N. Sangshetti, *Res. Chem. Intermed.*, 2018, **44**, 7047–7064.
- 326 Z. Quan, X. Sun and L. Guan, *Chem. Biol. Drug Des.*, 2009, **73**, 313–319.
- 327 M. C. Cardia, S. Distinto, E. Maccioni, A. Plumitallo, L. Sanna, M. L. Sanna and S. Vigo, *J. Heterocycl. Chem.*, 2009, **46**, 674–679.
- 328 M. I. Hegab, N. A. A. Taleb, S. M. Hasabelnaby and A. Goudah, *Eur. J. Med. Chem.*, 2010, **45**, 1267–1277.
- 329 F. M. Awadallah, W. I. El-Eraky and D. O. Saleh, *Eur. J. Med. Chem.*, 2012, **52**, 14–21.
- 330 S. Gore, S. Baskaran and B. Koenig, *Green Chem.*, 2011, **13**, 1009–1013.
- 331 F. Mohamadpour, M. T. Maghsoodlou, R. Heydari and M. Lashkari, *J. Iran. Chem. Soc.*, 2016, **13**, 1549–1560.
- 332 H. T. Nguyen and P. H. Tran, *RSC Adv.*, 2016, **6**, 98365–98368.
- 333 M. Szumilak and A. Stanczak, *Molecules*, 2019, **24**, 2271.
- 334 R. M. Butnariu and I. I. Mangalagiu, *Bioorg. Med. Chem.*, 2009, **17**, 2823–2829.
- 335 E. M. Flefel, W. A. Tantawy, W. I. El-Sofany, M. El-Shahat, A. A. El-Sayed and D. N. Abd-Elshafy, *Molecules*, 2017, **22**, 148.
- 336 D. Mantu, D. Maftai, D. Iurea, C. Ursu and V. Bejan, *Med. Chem. Res.*, 2014, **23**, 2909–2915.
- 337 R. Sivakumar, N. Anbalagan, V. Gunasekaran and J. T. Leonard, *Biol. Pharm. Bull.*, 2003, **26**, 1407–1411.
- 338 J. Khalafy, M. Rimaz, S. Farajzadeh and M. Ezzati, *S. Afr. J. Chem.*, 2013, **66**, 179–182.
- 339 N. G. Khaligh, T. Mihankhah, M. R. Johan and J. J. Ching, *Monatsh. Chem.*, 2018, **149**, 1083–1087.
- 340 J. Khalafy, M. Rimaz, M. Ezzati and R. H. Prager, *Bull. Korean Chem. Soc.*, 2012, **33**, 2890–2896.
- 341 G.-H. Ma, X.-J. Tu, Y. Ning, B. Jiang and S.-J. Tu, *ACS Comb. Sci.*, 2014, **16**, 281–286.
- 342 T. A. D. Thi, L. Decuyper, H. T. Phuong, D. V. Ngoc, H. T. Nguyen, T. T. Nguyen, T. Do Huy, H. H. Nguyen, M. D'hooghe and T. Van Nguyen, *Tetrahedron Lett.*, 2015, **56**, 5855–5858.
- 343 G. C. Senadi, B. S. Gore, W.-P. Hu and J.-J. Wang, *Org. Lett.*, 2016, **18**, 2890–2893.
- 344 H. M. Al-Matar, K. M. Dawood and W. M. Tohamy, *RSC Adv.*, 2018, **8**, 34459–34467.
- 345 J. Sangshetti, S. K. Pathan, R. Patil, S. Akber Ansari, S. Chhajed, R. Arote and D. B. Shinde, *Bioorg. Med. Chem.*, 2019, **27**, 3979–3997.
- 346 B. L. Mylari, E. R. Larson, T. A. Beyer, W. J. Zembrowski, C. E. Aldinger, M. F. Dee, T. W. Siegel and D. H. Singleton, *J. Med. Chem.*, 1991, **34**, 108–122.
- 347 K. M. Amin, F. F. Barsoum, F. M. Awadallah and N. E. Mohamed, *Eur. J. Med. Chem.*, 2016, **123**, 191–201.
- 348 A. Sugimoto, H. Tanaka, Y. Eguchi, S. Ito, Y. Takashima and M. Ishikawa, *J. Med. Chem.*, 1984, **27**, 1300–1305.
- 349 A. Khalil, M. Berghot and M. Gouda, *Eur. J. Med. Chem.*, 2009, **44**, 4448–4454.
- 350 M. Van der Mey, H. Boss, D. Couwenberg, A. Hatzelmann, G. J. Sterk, K. Goubitz, H. Schenk and H. Timmerman, *J. Med. Chem.*, 2002, **45**, 2526–2533.
- 351 M. Shekouhy and A. Hasaninejad, *Ultrason. Sonochem.*, 2012, **19**, 307–313.
- 352 A. Hasaninejad, M. R. Kazerooni and A. Zare, *Catal. Today*, 2012, **196**, 148–155.
- 353 R. Ghahremanzadeh, G. I. Shakibaei and A. Bazgir, *Synlett*, 2008, **2008**, 1129–1132.
- 354 M. Sayyafi, M. Seyyedhamzeh, H. R. Khavasi and A. Bazgir, *Tetrahedron*, 2008, **64**, 2375–2378.
- 355 M. R. Nabid, S. J. T. Rezaei, R. Ghahremanzadeh and A. Bazgir, *Ultrason. Sonochem.*, 2010, **17**, 159–161.
- 356 R. Ghorbani-Vaghei, R. Karimi-Nami, Z. Toghræi-Semiromi, M. Amiri and M. Ghavidel, *Tetrahedron*, 2011, **67**, 1930–1937.
- 357 A. Bhat, R. Dongra and R. Selokar, *Int. J. Pharma Bio Sci.*, 2014, **5**, 422–430.
- 358 E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch and C. A. Nichol, *J. Med. Chem.*, 1980, **23**, 327–329.
- 359 A. M. Thompson, A. J. Bridges, D. W. Fry, A. J. Kraker and W. A. Denny, *J. Med. Chem.*, 1995, **38**, 3780–3788.
- 360 A. E. Wakeling, S. P. Guy, J. R. Woodburn, S. E. Ashton, B. J. Curry, A. J. Barker and K. H. Gibson, *Cancer Res.*, 2002, **62**, 5749–5754.
- 361 A. Baba, N. Kawamura, H. Makino, Y. Ohta, S. Taketomi and T. Sohda, *J. Med. Chem.*, 1996, **39**, 5176–5182.
- 362 R. Rohini, P. M. Reddy, K. Shanker, A. Hu and V. Ravinder, *Eur. J. Med. Chem.*, 2010, **45**, 1200–1205.
- 363 A. K. Gupta, K. Kumari, N. Singh, D. S. Raghuvanshi and K. N. Singh, *Tetrahedron Lett.*, 2012, **53**, 650–653.
- 364 S. Ferrini, F. Ponticelli and M. Taddei, *Org. Lett.*, 2007, **9**, 69–72.
- 365 M. Dabiri, P. Salehi and M. Bahramnejad, *Synth. Commun.*, 2010, **40**, 3214–3225.
- 366 J. Zhang, D. Zhu, C. Yu, C. Wan and Z. Wang, *Org. Lett.*, 2010, **12**, 2841–2843.
- 367 Z.-H. Zhang, X.-N. Zhang, L.-P. Mo, Y.-X. Li and F.-P. Ma, *Green Chem.*, 2012, **14**, 1502–1506.
- 368 Y. Yan, Y. Xu, B. Niu, H. Xie and Y. Liu, *J. Org. Chem.*, 2015, **80**, 5581–5587.
- 369 S. Hati and S. Sen, *Synthesis*, 2016, **48**, 1389–1398.
- 370 D. S. Deshmukh and B. M. Bhanage, *Synlett*, 2018, **29**, 979–985.
- 371 J. Chen, W. Su, H. Wu, M. Liu and C. Jin, *Green Chem.*, 2007, **9**, 972–975.
- 372 A. Shaabani, A. Maleki and H. Mofakham, *Synth. Commun.*, 2008, **38**, 3751–3759.
- 373 H. R. Lobo, B. S. Singh and G. S. Shankarling, *Catal. Commun.*, 2012, **27**, 179–183.
- 374 M. Sharma, S. Pandey, K. Chauhan, D. Sharma, B. Kumar and P. M. Chauhan, *J. Org. Chem.*, 2012, **77**, 929–937.
- 375 O. Algul, A. Meric, S. Polat, N. Didem Yuksek and M. S. Serin, *Cent. Eur. J. Chem.*, 2009, **7**, 337–342.



- 376 T. CHIBA, S. SHIGETA and Y. NUMAZAKI, *Biol. Pharm. Bull.*, 1995, **18**, 1081–1083.
- 377 K. TERASHIMA, O. MURAOKA and M. ONO, *Chem. Pharm. Bull.*, 1995, **43**, 1985–1991.
- 378 S. M. Sondhi, R. P. Verma, V. K. Sharma, N. Singhal, J. L. Kraus, M. Camplo and J.-C. Chermann, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1997, **122**, 215–225.
- 379 H. T. Abdel-Mohsen, F. A. Ragab, M. M. Ramla and H. I. El Diwani, *Eur. J. Med. Chem.*, 2010, **45**, 2336–2344.
- 380 A. Nowicka, H. Liszkiewicz, W. P. Nawrocka, J. Wietrzyk, K. Kempńska and A. Dryś, *Cent. Eur. J. Chem.*, 2014, **12**, 1047–1055.
- 381 S. M. Sondhi, S. Rajvanshi, M. Johar, N. Bharti, A. Azam and A. K. Singh, *Eur. J. Med. Chem.*, 2002, **37**, 835–843.
- 382 C. S. Yao, S. Lei, C. H. Wang, C. X. Yu, Q. Q. Shao and S. J. Tu, *Chin. J. Chem.*, 2008, **26**, 2107–2111.
- 383 C. Yao, S. Lei, C. Wang, T. Li, C. Yu, X. Wang and S. Tu, *J. Heterocycl. Chem.*, 2010, **47**, 26–32.
- 384 G. D. Rao, B. Acharya, S. Verma and M. Kaushik, *Tetrahedron Lett.*, 2011, **52**, 809–812.
- 385 J. Liu, M. Lei and L. Hu, *Green Chem.*, 2012, **14**, 840–846.
- 386 R. Gupta, A. Jain, Y. Madan and E. Menghani, *J. Heterocycl. Chem.*, 2014, **51**, 1395–1403.
- 387 D. P. Singh, S. K. Deivedi, S. R. Hashim and R. G. Singhal, *Pharmaceuticals*, 2010, **3**, 2416–2425.
- 388 M. Montana, V. Montero, O. Khoumeri and P. Vanelle, *Molecules*, 2020, **25**, 2784.
- 389 M. M. Alanazi, H. Elkady, N. A. Alsaif, A. J. Obaidullah, W. A. Alanazi, A. M. Al-Hossaini, M. A. Alharbi, I. H. Eissa and M. A. Dahab, *J. Mol. Struct.*, 2022, **1253**, 132220.
- 390 E. C. Taylor and D. J. Dumas, *J. Org. Chem.*, 1981, **46**, 1394–1402.
- 391 T. Fukunaga and R. W. Begland, *J. Org. Chem.*, 1984, **49**, 813–821.
- 392 N. Sato, N. Matsui and J. Heterocyclic, *Chem*, 1992, **29**, 1689–1692.
- 393 W. Zhang, A. R. Haight, K. L. Ford and S. I. Parekh, *Synth. Commun.*, 2001, **31**, 725–730.
- 394 A. Kumbhar, S. Kamble, M. Barge, G. Rashinkar and R. Salunkhe, *Tetrahedron Lett.*, 2012, **53**, 2756–2760.
- 395 P. Mahadik, D. Jagwani and R. Joshi, *Int. j. Innov. Res. Sci. Eng. Technol.*, 2014, **1**, 482–490.
- 396 Z. Zhang, C. Xie, L. Feng and C. Ma, *Synth. Commun.*, 2016, **46**, 1507–1518.
- 397 R. Mahesh, A. K. Dhar, T. S. TVNV, S. Thirunavukkarasu and T. Devadoss, *Chin. Chem. Lett.*, 2011, **22**, 389–392.
- 398 J. Khalafy, A. Marjani and M. Haghipour, *Curr. Chem. Lett.*, 2013, **2**, 21–26.
- 399 L. Moradi, M. Piltan, H. Rostami and G. Abasi, *Chin. Chem. Lett.*, 2013, **24**, 740–742.
- 400 X. Shen, Y. Wang, T. Wu, Z. Mao and X. Lin, *Chem. - Eur. J.*, 2015, **21**, 9039–9043.
- 401 K. D. R. Viswanadham, M. P. Reddy, P. Sathyanarayana, O. Ravi, R. Kant and S. R. Bathula, *Chem. Commun.*, 2014, **50**, 13517–13520.
- 402 F. Lassagne, F. Chevallier and F. Mongin, *Synth. Commun.*, 2014, **44**, 141–149.
- 403 P. Z. Mannes, E. O. Onyango and G. W. Gribble, *J. Org. Chem.*, 2016, **81**, 12478–12481.
- 404 D. Bera, R. Sarkar, P. Saha, P. Ghosh and C. Mukhopadhyay, *Chem. Commun.*, 2023, **59**, 7771–7774.
- 405 J. Fang, J. Fang, Y. Rao, H. Qiu, Z. Pan and Y. Ma, *Org. Biomol. Chem.*, 2024, **22**, 2043–2048.
- 406 J. Sharma and R. Kaushal, *Russ. J. Gen. Chem.*, 2024, **94**, 1794–1814.
- 407 B. Groenendaal, D. J. Vugts, R. F. Schmitz, F. J. J. de Kanter, E. Ruijter, M. B. Groen and R. V. A. Orru, *J. Org. Chem.*, 2008, **73**, 719–722.
- 408 M. Gradsten and M. Pollock, *J. Am. Chem. Soc.*, 1948, **70**, 3079–3081.
- 409 W. O. Teeters and M. A. Gradsten, in *Organic Syntheses*, 2003, pp. 51.
- 410 W. D. Emmons, H. A. Rolewicz, W. N. Cannon and R. M. Ross, *J. Am. Chem. Soc.*, 1952, **74**, 5524–5525.
- 411 A. T. Nielsen, R. L. Atkins, D. W. Moore, R. Scott, D. Mallory and J. M. LaBerge, *J. Org. Chem.*, 1973, **38**, 3288–3295.
- 412 J. M. García, G. O. Jones, K. Virwani, B. D. McCloskey, D. J. Boday, G. M. ter Huurne, H. W. Horn, D. J. Coady, A. M. Bintaleb and A. M. Alabdulrahman, *Science*, 2014, **344**, 732–735.
- 413 T. Yang, Z. Xu, Z. Meng and L. Zhai, *ChemistrySelect*, 2019, **4**, 6338–6341.
- 414 S. Cascioferro, B. Parrino, V. Spanò, A. Carbone, A. Montalbano, P. Barraja, P. Diana and G. Cirrincione, *Eur. J. Med. Chem.*, 2017, **142**, 74–86.
- 415 K. Kobari, I. Takakura, M. Nakatomi, S. Sogame and C. Uylangco, *Bull. W. H. O.*, 1970, **43**, 365–371.
- 416 J. C. A. Hunt, E. Briggs, E. D. Clarke and W. G. Whittingham, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5222–5226.
- 417 T. Kaihoh, T. Itoh, A. Ohsawa, M. Okada, C. Kawabata and H. Igeta, *Chem. Pharm. Bull.*, 1987, **35**, 3952–3954.
- 418 A. Ohsawa, T. Kaihoh, T. Itoh, M. Okada, C. Kawabata, K. Yamaguchi and H. Igeta, *Chem. Pharm. Bull.*, 1988, **36**, 3838–3848.
- 419 R. N. Butler, A. M. Fahy, A. Fox, J. C. Stephens, P. McArdle, D. Cunningham and A. Ryder, *J. Org. Chem.*, 2006, **71**, 5679–5687.
- 420 R. N. Butler, A. M. Fahy, A. Fox, J. C. Stephens, P. McArdle, D. Cunningham and A. G. Ryder, *Tetrahedron Lett.*, 2006, **47**, 1721–1724.
- 421 K. Sztanke, A. Sidor-Wójtowicz, J. Truchlińska, K. Pasternak and M. Sztanke, *Ann. Univ. Mariae Curie-Skłodowska Sect. D Med.*, 2004, **59**, 342–345.
- 422 L. X. Li, J. Jiao, X. B. Wang, M. Chen, X. C. Fu, W. J. Si and C. L. Yang, *Molecules*, 2018, **23**, 746.
- 423 A. Gornowicz, A. Szymanowska, M. Mojzych, R. Czarnomysy, K. Bielawski and A. Bielawska, *Molecules*, 2021, **26**, 2045.
- 424 P. Mullick, S. A. Khan, T. Begum, S. Verma, D. Kaushik and O. Alam, *Acta Pol. Pharm.*, 2009, **66**, 379–385.
- 425 W. W. Paudler and J. M. Barton, *J. Org. Chem.*, 1966, **31**, 1720–1722.



- 426 S. Rostamizadeh and K. Sadeghi, *Synth. Commun.*, 2002, **32**, 1899–1902.
- 427 A. Rauf, S. Sharma and S. Gangal, *Arkivoc*, 2007, **16**, 137–147.
- 428 T. Potewar, R. Lahoti, T. Daniel and K. Srinivasan, *Synth. Commun.*, 2007, **37**, 261–269.
- 429 F. Krauth, H.-M. Dahse, H.-H. Rüttinger and P. Froberg, *Bioorg. Med. Chem.*, 2010, **18**, 1816–1821.
- 430 R. S. Tamboli, R. Giridhar, H. M. Mande, S. R. Shah and M. R. Yadav, *Synth. Commun.*, 2014, **44**, 2192–2204.
- 431 D. Tang, J. Wang, P. Wu, X. Guo, J.-H. Li, S. Yang and B.-H. Chen, *RSC Adv.*, 2016, **6**, 12514–12518.
- 432 Y. Liu, X. Guo, D. Tang, J. Wang, P. Wu, J. Han and B. Chen, *Chin. J. Chem.*, 2017, **35**, 1222–1226.
- 433 O. Shabunina, A. Krinochkin, D. Kopchuk, G. Zyryanov, V. Rusinov and O. Chupakhin, *Russ. J. Org. Chem.*, 2018, **54**, 812–814.
- 434 M. S. Dowling, W. Jiao, J. Hou, Y. Jiang and S. Gong, *J. Org. Chem.*, 2018, **83**, 4229–4238.
- 435 L. Zhang, J. J. Chen, S. S. Liu, Y. X. Liang and Y. L. Zhao, *Adv. Synth. Catal.*, 2018, **360**, 2172–2177.
- 436 S. Singh, M. K. Mandal, A. Masih, A. Saha, S. K. Ghosh, H. R. Bhat and U. P. Singh, *Arch. Pharm.*, 2021, **354**, e2000363.
- 437 P. Gogoi, A. Shakya, S. K. Ghosh, N. Gogoi, P. Gahtori, N. Singh, D. R. Bhattacharyya, U. P. Singh and H. R. Bhat, *J. Biochem. Mol. Toxicol.*, 2021, **35**, e22682.
- 438 S. Cascioferro, B. Parrino, V. Spanò, A. Carbone, A. Montalbano, P. Barraja, P. Diana and G. Cirrincione, *Eur. J. Med. Chem.*, 2017, **142**, 523–549.
- 439 K. M. Al-Zaydi, H. H. Khalil, A. El-Faham and S. N. Khattab, *Chem. Cent. J.*, 2017, **11**, 39.
- 440 N. Sunduru, L. Gupta, V. Chaturvedi, R. Dwivedi, S. Sinha and P. M. Chauhan, *Eur. J. Med. Chem.*, 2010, **45**, 3335–3345.
- 441 H. Ogura, H. Takahashi and O. Sato, *Chem. Pharm. Bull.*, 1981, **29**, 1838–1842.
- 442 T. Okawa, N. Osakada, S. Eguchi and A. Kakehi, *Tetrahedron*, 1997, **53**, 16061–16082.
- 443 J.-J. Shie and J.-M. Fang, *J. Org. Chem.*, 2007, **72**, 3141–3144.
- 444 M. M. Hemdan and M. M. Elshahawi, *J. Chem. Res.*, 2009, **2009**, 75–77.
- 445 L. L. Falher, O. Ben Ayad, O. Ziyaret, A. Mamontov, C. Botuha, S. Thorimbert and F. Slowinski, *J. Org. Chem.*, 2014, **79**, 6579–6589.
- 446 A. Herrera, A. Riano, R. Moreno, B. Caso, Z. D. Pardo, I. Fernandez, E. Saez, D. Molero, A. Sanchez-Vazquez and R. Martinez-Alvarez, *J. Org. Chem.*, 2014, **79**, 7012–7024.
- 447 I. Yavari and S. Mosaferi, *Monatsh. Chem.*, 2017, **148**, 963–966.
- 448 G.-F. Kang and G. Zhang, *Beilstein J. Org. Chem.*, 2020, **16**, 1447–1455.
- 449 W.-X. Hu, G.-W. Rao and Y.-Q. Sun, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1177–1181.
- 450 A. M. Churakov, O. Y. Smirnov, S. L. Ioffe, Y. A. Strelenko and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2002, **2002**, 2342–2349.
- 451 T. M. Klapötke, D. G. Piercey, J. Stierstorfer and M. Weyrauther, *Propellants, Explos. Pyrotech.*, 2012, **37**, 527–535.
- 452 A. A. Voronin, V. P. Zelenov, A. M. Churakov, Y. A. Strelenko, I. V. Fedyanin and V. A. Tartakovsky, *Tetrahedron*, 2014, **70**, 3018–3022.
- 453 A. A. Voronin, A. M. Churakov, M. S. Klenov, Y. A. Strelenko, I. V. Fedyanin and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2017, **2017**, 4963–4971.
- 454 M. S. Klenov, O. V. Anikin, A. M. Churakov, Y. A. Strelenko, I. V. Fedyanin, I. V. Ananyev and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2015, **2015**, 6170–6179.
- 455 P. Barraja, P. Diana, A. Lauria, A. Montalbano, A. M. Almerico, G. Dattolo and G. Cirrincione, *Bioorg. Med. Chem.*, 2005, **13**, 295–300.
- 456 G. A. áO'Halloran and P. D. áO'Shea, *J. Chem. Soc. Perkin Trans. I*, 1990, 2527–2536.
- 457 R. N. Butler, D. Cunningham, P. McArdle and G. A. O'Halloran, *J. Chem. Soc., Chem. Commun.*, 1988, 232–234.
- 458 Z.-C. Wu and D. L. Boger, *J. Am. Chem. Soc.*, 2019, **141**, 16388–16397.
- 459 F. Xu, Z.-z. Yang, J.-r. Jiang, W.-g. Pan, X.-l. Yang, J.-y. Wu, Y. Zhu, J. Wang, Q.-Y. Shou and H.-g. Wu, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 3042–3047.
- 460 M. Coburn, G. Buntain, B. Harris, M. Hiskey, K. Y. Lee and D. Ott, *J. Heterocycl. Chem.*, 1991, **28**, 2049–2050.
- 461 J. Kerth and S. Löbbecke, *Propellants, Explos. Pyrotech.*, 2002, **27**, 111–118.
- 462 G.-W. Rao and W.-X. Hu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3702–3705.
- 463 M. R. Karver, R. Weissleder and S. A. Hilderbrand, *Bioconjug. Chem.*, 2011, **22**, 2263–2270.
- 464 Z. Fang, W.-L. Hu, D.-Y. Liu, C.-Y. Yu and X.-G. Hu, *Green Chem.*, 2017, **19**, 1299–1302.
- 465 C. Li, H. Ge, B. Yin, M. She, P. Liu, X. Li and J. Li, *RSC Adv.*, 2015, **5**, 12277–12286.
- 466 T. A. Khattab, *Helv. Chim. Acta*, 2018, **101**, e1800009.
- 467 Y.-Z. Ji, H.-J. Li, Y. Liu and Y.-C. Wu, *Synthesis*, 2020, **52**, 69–74.

