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Tetrahydropyridines: a recent update for their multicomponent synthesis

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Tetrahydropyridines (THPs) are important nitrogen-based ring compounds found in many natural and synthetic molecules with wide biological importance. Their simple structure and chemical flexibility make them valuable in drug design and organic synthesis. Among different synthetic methods, multicomponent reactions (MCRs) have become a fast, efficient, and eco-friendly approach for preparing a large variety of THP derivatives in a single step. This review focuses on recent developments in the synthesis of tetrahydropyridines using MCRs with different nitrogen sources such as amines, enamines, imines, ammonia, ammonium acetate, *etc.* It also highlights green and sustainable methods like solvent-free, microwave-assisted, photoinduced, and catalyst-free reactions. Overall, this review explains how multicomponent reactions provide an easy, economical, and environmentally friendly route for building diverse tetrahydropyridine structures useful in chemical and medicinal research.

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Faiz Ahmad Faiz

Faiz Ahmad Faiz is currently a fourth-year BSc Research student in the Department of Chemistry at Aligarh Muslim University, Aligarh, India. He was born in the district of Samastipur, Bihar. His research interests focus on the synthesis of organic compounds, especially nitrogen-containing heterocycles and drug-like molecules. He recently completed a research project titled "Efficient One-Pot Five-Component Synthesis of Piperidine Derivatives" under the Indo-US STEM APJ Abdul Kalam STEM Education and Research Program jointly conducted by The Ohio State University and Aligarh Muslim University under mentorship of Dr Md. Musawwer Khan. His long-term goal is to contribute to the development of new and efficient synthetic methods for medicinally important organic drugs.

1 Introduction

Tetrahydropyridine (THP) scaffolds are a significant group of nitrogen-containing heterocycles because they are widely incorporated in natural bioactive compounds and are highly useful in synthetic chemistry. Their simple ring system, together with broad biological activities, makes THP derivatives valuable in drug discovery. Among the various synthetic approaches, multicomponent reactions (MCRs) are especially attractive since they are easy to carry out, save time, and allow the rapid preparation of many structurally diverse THP derivatives.[1] The biological value of this scaffold is also seen in nature, as several alkaloids contain the THP ring. Some notable examples include bis-benzyl-isoquinoline alkaloids (BBIQAs, **I**) isolated from the Menispermaceae and Berberidaceae families,[2] solacongestidine (**II**) isolated from *Solanum congestiflorum* which exhibits antifungal activity against *Candida albicans*, *Trichophyton rubrum* and *Cryptococcus albidus*[3] and (+)-cannabisativine (**III**) from *Cannabis sativa*,[4] and (−)-sedacrine (**IV**) from *Sedum* species,[5] all of which show important biological effects as shown in Fig. 1. These natural products provide a strong base for designing synthetic analogues with potential pharmacological importance.

Over the years, tetrahydropyridine derivatives have gained considerable attention in medicinal chemistry due to their broad spectrum of pharmacological activities.[6] Numerous studies have reported that compounds containing the THP ring exhibit diverse bioactivities like -antimicrobial,[7] anticonvulsant,[8] antiproliferative,[9] anti-inflammatory,[10] antimalarial,[11] antidiabetic[12] *etc.* Some medicinally important compounds containing the tetrahydropyridine skeleton are shown in Fig. 2. In recent findings, tetrahydropyridine containing compound **V** has also emerged as a biologically relevant scaffold, demonstrating CDK2 kinase inhibition associated with anticancer activity, as well as DprE1 inhibition, which is important in antitubercular drug discovery.[13] Additionally, thiazole-based tetrahydropyridines (**VI**) showed promising biological activity: several compounds exhibited strong insecticidal effects against *Aphis laburni*, and even resistant strains, thereby suggesting potential in resistance management.[14] Furthermore, 4-aryl-1,2,3,6-tetrahydropyridines (**VII**) were studied as 5-HT$_2$C receptor agonists, positioning them as potential agents for appetite suppression and obesity treatment.[15]

Mohd Sufiyan Khan

Mr Mohd Sufiyan Khan, born on February 10, 2005, in Aligarh, India, is currently a fourth-year BSc Research student at Aligarh Muslim University. He recently completed a research project under supervision of Dr Md. Musawwer Khan on "Green One-Pot Synthesis of Pyranopyrazole Derivative Using Deep Eutectic Solvent" under the Indo–US STEM APJ Abdul Kalam STEM Education and Research Program, jointly conducted by The Ohio State University (USA) and Aligarh Muslim University (India). His research interests focus on green chemistry, heterocyclic synthesis, computational chemistry and sustainable organic transformations. He aims to develop environmentally friendly and efficient methodologies in synthetic organic chemistry to support sustainable scientific innovation.

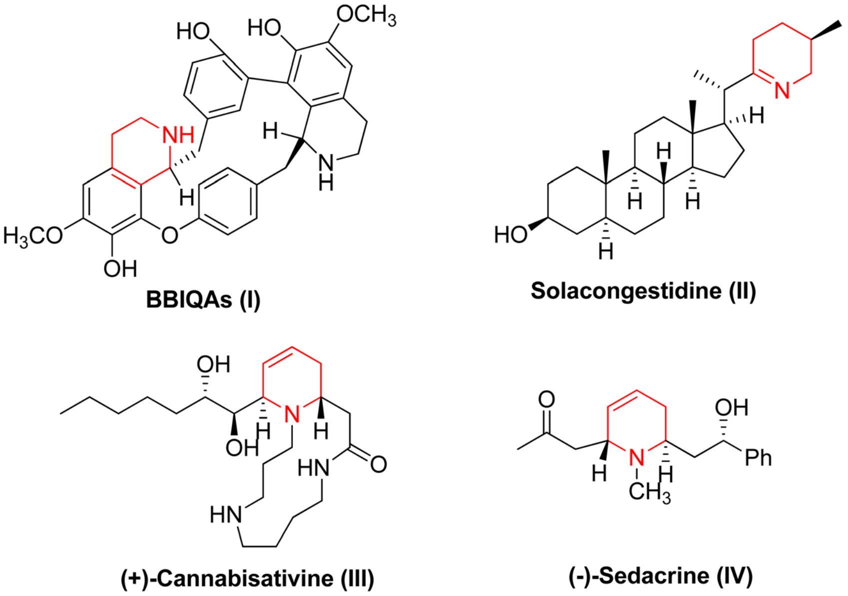
Tetrahydropyridine derivatives (**VIII**) also represent a class of muscarinic acetylcholine receptor ligands, with several compounds showing agonist activity at the M1 subtype involved in cognition and memory. The tetrahydropyridine ring contributes to effective receptor binding and functional activation. These compounds typically activate M1 receptors through Gq/11-mediated calcium signaling. Some tetrahydropyridine-based M1 agonists also stimulate ERK1/2 pathways and promote non-amyloidogenic amyloid precursor protein processing, supporting their relevance in Alzheimer's disease research.[16] Tetrahydropyridine (THP) derivatives (**IX**) also represent a novel class of ligands with high affinity and selectivity for central nicotinic acetylcholine receptors (nAChRs), showing notable subtype selectivity, especially toward the α4β2 subtype of nAChRs, which is dominant in the brain. These compounds offer potential as central nervous system (CNS) therapeutics, with uses in studying nicotinic receptor function and possibly addressing neurological disorders like Alzheimer's or Parkinson's disease due to their selective cholinergic modulation.[17]

Moreover, THP derivatives (**X**) are particularly well recognized for their monoamine oxidase (MAO) inhibitory activity. Several substituted tetrahydropyridines effectively inhibit MAO-A and MAO-B enzymes, which are responsible for the metabolic degradation of key neurotransmitters such as dopamine, serotonin, and norepinephrine. MAO-A inhibition is mainly associated with antidepressant and anxiolytic effects, whereas MAO-B inhibition is relevant to the treatment of neurodegenerative disorders, especially Parkinson's disease. Subtle structural variations on the tetrahydropyridine ring strongly influence enzyme selectivity and inhibitory potency.[18]

Due to the above properties of THP, diverse synthetic approaches have been developed worldwide using multicomponent reactions (MCRs). MCRs serve as an efficient approach for rapidly assembling structurally diverse and complex molecules in a single synthetic operation. Compared to traditional stepwise methods, MCRs[19] offer several advantages such as reduced cost, shorter reaction times, improved atom economy, and eco-friendly protocols. Additionally, they enable rapid exploration of structural diversity, making them highly suitable for combinatorial synthesis.

1.1. Recent progress for synthesis of tetrahydropyridines using multicomponent reaction

Tetrahydropyridine (THP) rings are widely studied N-heterocycles because of their valuable biological properties and practical applications, so chemists have focused on



BBIQAs (I)

Solacongestidine (II)

(+)-Cannabisativine (III)

(-)-Sedacrine (IV)

Fig. 1 Natural alkaloids having tertrahydropyridine ring system.

developing faster, cheaper, and greener synthetic method. One-pot multicomponent reactions (MCRs) have emerged as especially powerful tools for constructing diverse THP libraries by combining a few simple building blocks in a single operation; varying the amine component and other partners provides easy access to many substituted derivatives. In 2016, our group published a review summarized work up to 2015,[20] and since then numerous research reports have extended and refined MCR strategies. In, this review therefore we cover a decade literature published after 2015 to the present and organizes the methods primarily by the type of amino building block employed in the multicomponent routes.

1.2. Synthesis of THP using amine as amino source

Using *tert*-butyl alcohol as a solvent, Ishmiyarov *et al.* described a one-pot, three-component synthesis of compound **4** by condensation of ethyl acetoacetate, methoxymethanol (formed *in situ* from paraformaldehyde), and primary amines or diamines in methanol.[21] The reaction proceeds through an intermediate **2a**, which then undergoes intramolecular cyclization to form the tetrahydropyridine core. High yields of mono and bicyclic tetrahydropyridine derivatives, up to 98%, were produced during the five-hour reaction at 65 °C. Depending on the amine's structure, the reaction produced compounds like diethyl 3-acetyl-1-isopropyl-6-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate, diethyl 3-acetyl-1-benzyl-6-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate, and diethyl 3-acetyl-1-(2-hydroxyethyl)-6-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate. *Tert*-butyl alcohol was essential for the product selectivity. Intramolecular cyclization made possible by the use of diamines resulted in fused bicyclic systems. Under mild conditions, this multicomponent method offers a quick and easy way to obtain structurally varied tetrahydropyridine derivatives (Scheme 1).

A one-pot method was established for the preparation of tetrahydropyridine-3-carboxylate derivatives **9** using a green and efficient approach. The reaction involves a four-component condensation of Meldrum's acid, ethyl cyanoacetate, aryl aldehydes, and aromatic amines in ethanol, promoted by nano nickel oxide (NiO) nanoparticles under ultrasound irradiation.[22] This method provided high yields up to 95% in a short time and avoided the use of toxic reagents or harsh conditions. The process benefits from energy efficiency, catalyst reusability, and eco-friendly conditions. This innovative protocol was reported by Fathima shows the effective combination of nanocatalysis and sonochemistry in the green preparation of pharmacologically important tetrahydropyridine-3-carboxylates passing through an intermediate **8a** (Scheme 2).

Yang *et al.* developed an efficient Ru(II)-catalyzed one-pot synthesis of 1,2-dihydropyridines (DHPs) **13**, which were subsequently converted into tetrahydropyridines (THPs) through an intermediate **12a.**[23] The reaction proceeds *via* a three-component strategy, employing cinnamaldehyde, *p*-anisidine, and diphenylacetylene as the starting materials. The catalytic system showed wide applicability to various substrates and was compatible with different functional groups, accommodating various aryl and heteroaryl aldehydes, amines, and internal alkynes. Notably, the use of $RuCl_2(COD)$ as a simple and accessible catalyst, in combination with additives such as $Mg(OAc)_2$, TiO_2, and BTBAC, significantly enhanced the reaction efficiency (Scheme 3).

Zanatta and co-workers reported a very fast, one-pot method to make 1-arylethyl-2-arylethylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridines **16** in excellent yields.[24] They started from 2-alkoxy-5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans and simply added two equivalents of a 2-arylethanamine and related 2-ethanamines in methanol or ethanol at room temperature (Scheme 4). In just five minutes, the mixture cleanly converts into the target tetrahydropyridine products, each bearing a trifluoroacetyl ketone at C-5 and an arylethylamino group at C-2 in 90–98% isolated yield. The reactions proceeded rapidly,

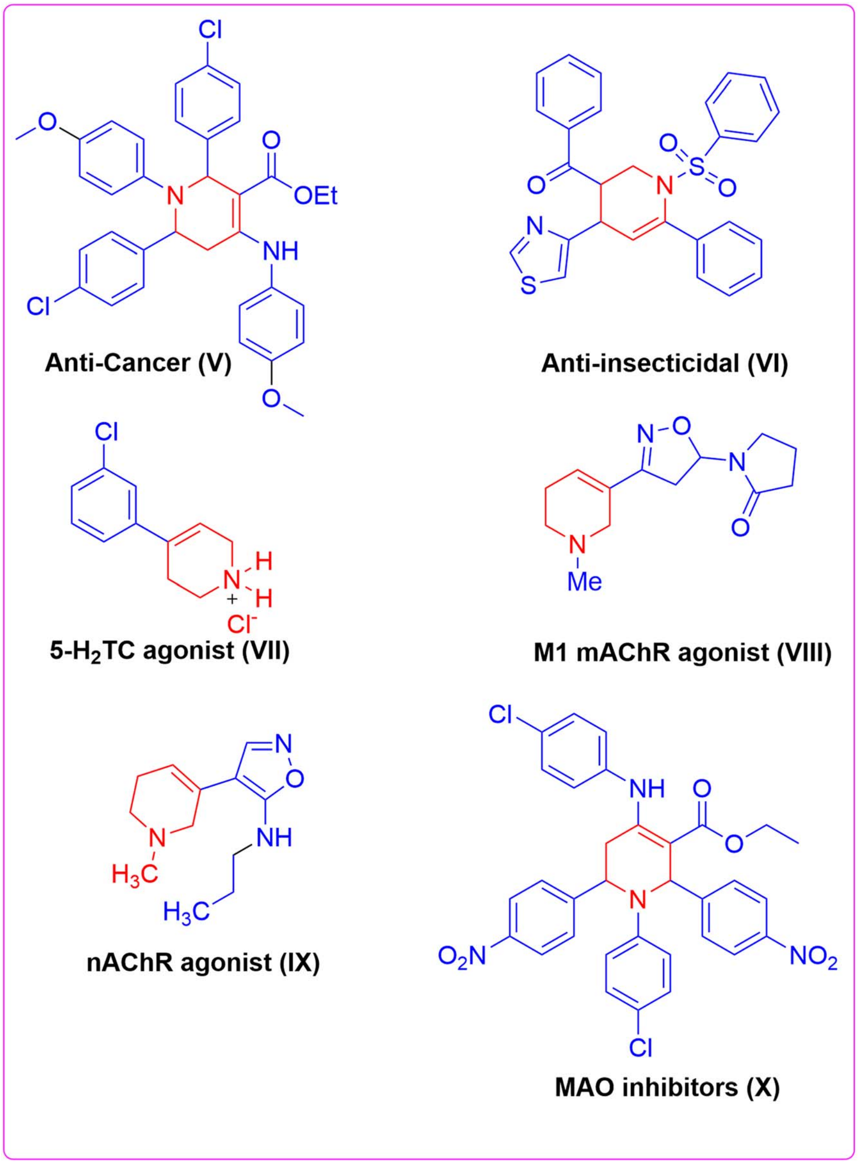
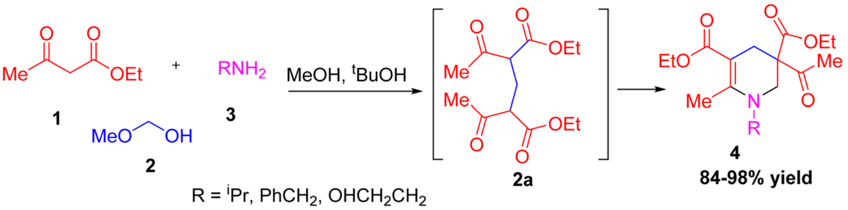


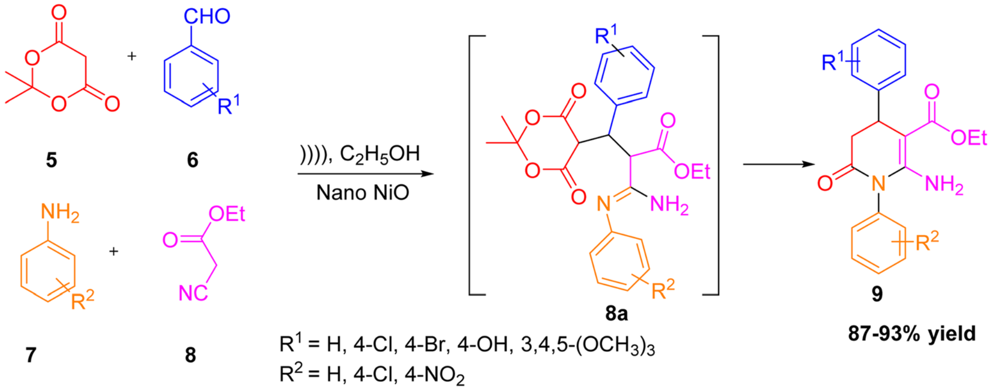
Fig. 2 Some medicinally important compound containing tetrahydropyridine skeleton.

occurred at room temperature, afforded high yields, and were easy to purify and isolate. They have used many types of ethanamines, making this method useful for making many different compounds in the future. Furthermore, the same group also prepared these derivatives using an ionic liquid ([BMIM]BF_4)[25] in combination with microwave irradiation and achieved yield up to 97%.

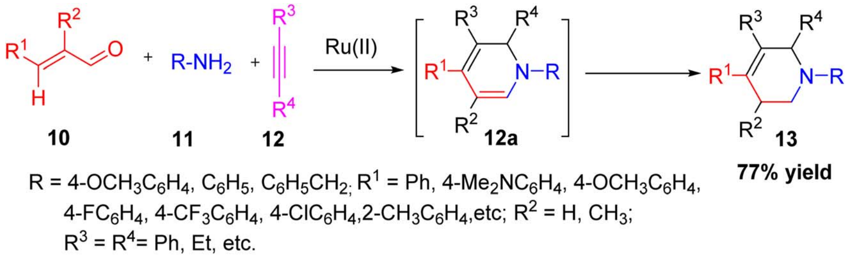
Dudognon *et al.* reported a new and simple method to make enantioenriched polycyclic 1,2,3,4-tetrahydropyridines **20**, which are important in drug research.[26] They used a three-component reaction that combined β-ketoamides, (*E*)-cinnamaldehydes, and 2-aminophenols under the influence of a chiral iminium-based organocatalyst. This method forms the product 1,2,3,4-tetrahydropyridine derivatives *via* an



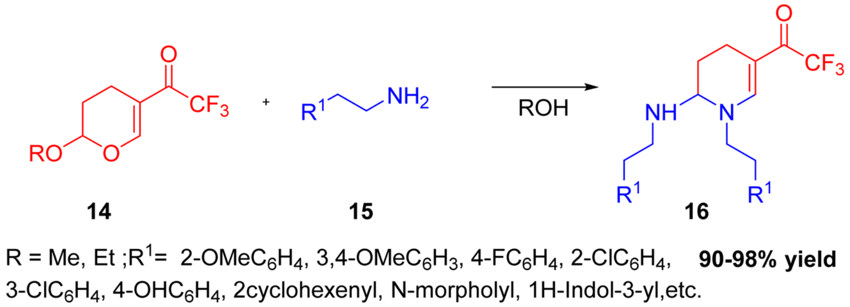
Scheme 1 Solvent selective multicomponent synthesis of monocyclic 1,2,3,4-tetrahydropyridine derivatives.



Scheme 2 Formation of tetrahydropyridine-3-carboxylates by using ultrasound irradiation.



Scheme 3 One-pot three component formation of THPD using Ru(II).

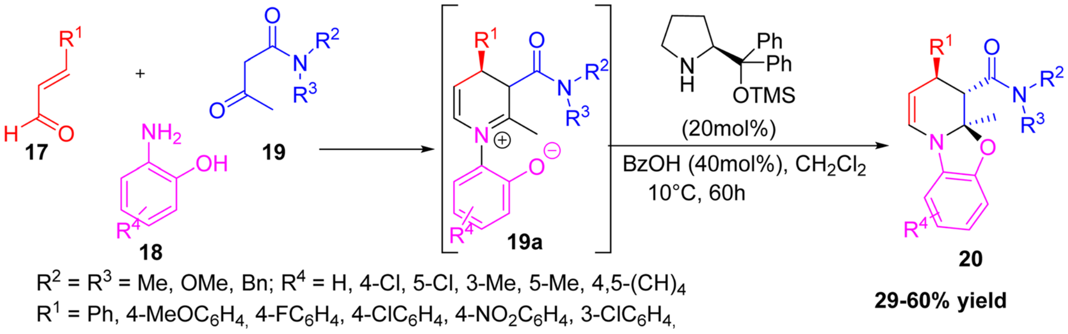


Scheme 4 One-pot formation of 1-arylethyl-2-arylethylamino-5-trifluoroacetyl-1,2,3,4 tetrahydropyridines.

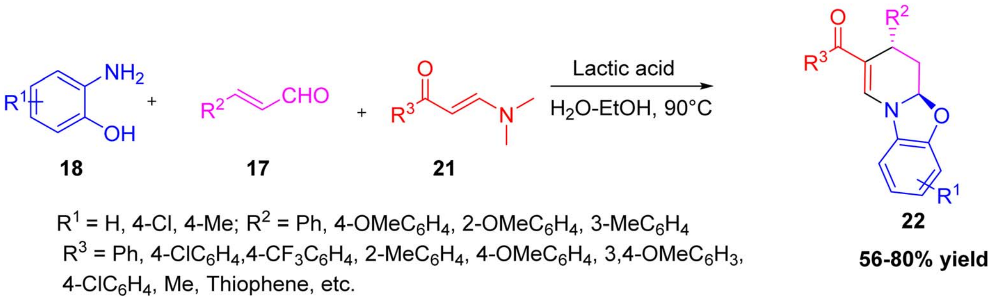
intermediate **19a** with three connected chiral centres and four new bonds formed in a single step. The reaction showed high regio-, diastereo-, and enantioselectivity. Although the yields were moderate, the stereocontrol and structural complexity obtained in one step show the synthetic value of this MCR approach (Scheme 5).

Wan and co-workers developed a simple one-pot reaction using an enaminone (or nitroenamine), *o*-aminophenol, and cinnamaldehyde in the presence of lactic acid and an ethanol–water mixture to make fused tetrahydropyridines.[27] The product, phenyl(3-phenyl-4,4a-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridin-2-yl)methanone **22**, was obtained in 76% yield as a single diastereomer (Scheme 6). The reaction goes through transamination of the enaminone, Michael addition to cinnamaldehyde, ring closure, and dehydration as shown in mechanism (Scheme 7). This method is efficient and sustainable, using a green solvent, a non-toxic bio-based catalyst, and air atmosphere at 90 °C to produce various tetrahydropyridine derivatives.

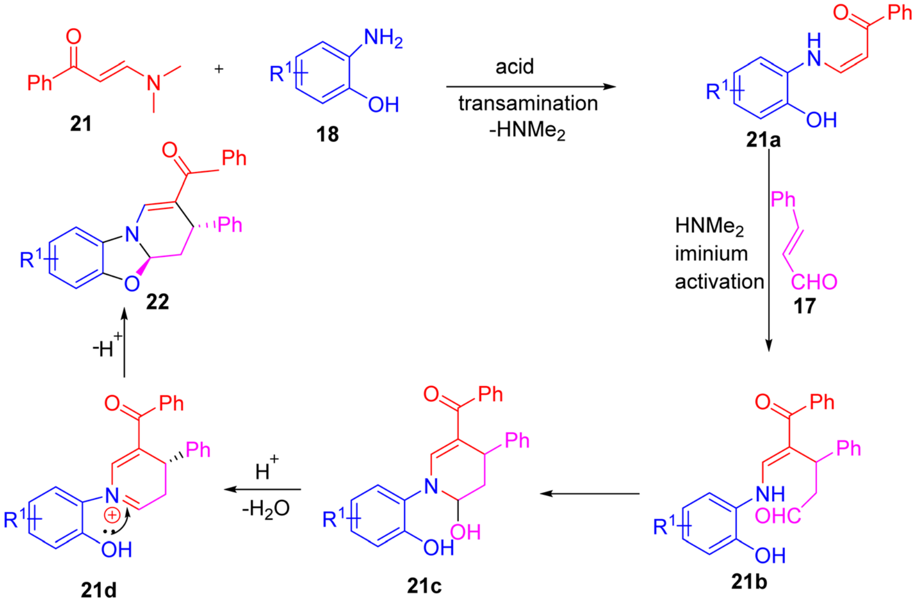
Mohammadi *et al.* reported a simple and efficient one-pot, four-component reaction to synthesize new tetrahydropyridine derivatives.[28] The target product, 10*b*-hydroxy-4-nitro-5-phenyl-2,3,5,5*a*-tetrahydro-1*H*-imidazo[1,2-*a*]indeno[2,1-*e*]pyridin-6(10*bH*)-one **27**, was synthesized using ethylenediamine, 1,1-bis(methylthio)-2-nitroethylene, various aldehydes, and 1,3-indandione in ethanol without using any catalyst (Scheme 8). The reaction involves a Knoevenagel condensation, Michael addition, tautomerization, and cyclization steps. The reaction provides high yields and exhibits excellent stereoselectivity in the formation of the final products. Additionally, molecular docking analysis revealed that several of these compounds exhibit strong binding affinity toward the active site of the HIV



Scheme 5 Formation of polycyclic 1,2,3,4-tetrahydropyridines using organocatalyst.



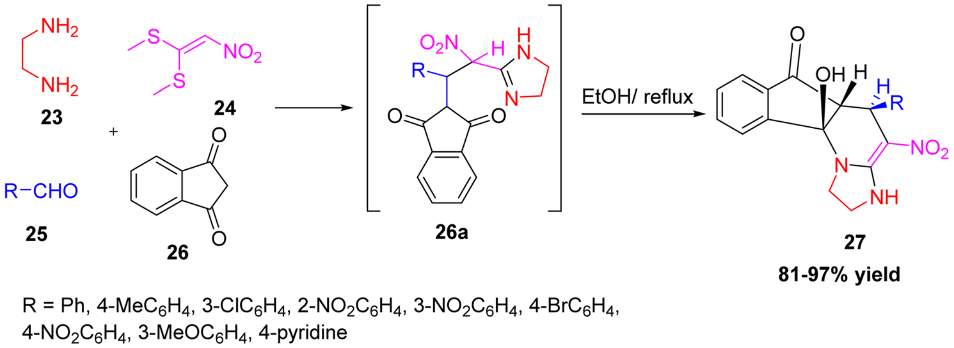
Scheme 6 One-pot three component formation of fused tetrahydropyridine by lactic acid.



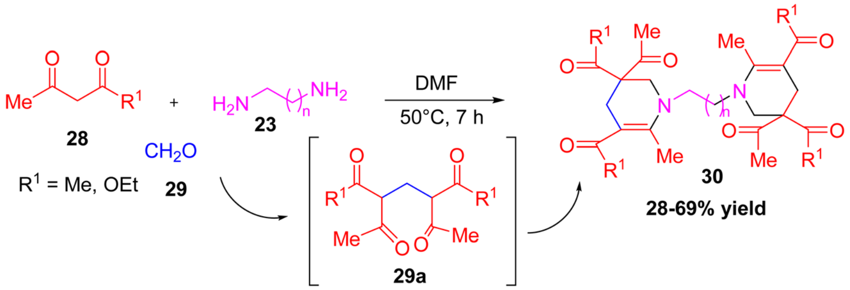
Scheme 7 Mechanistic approach to explain for synthesis of fused tetrahydropyridine.

protease enzyme with binding energies comparable to the standard drug saquinavir. The synthesized tetrahydropyridine compounds exhibit potential for further development as HIV protease inhibitors.

Gibadullina *et al.* reported a convenient one-pot multicomponent synthesis of 1,1′-(α,ω-alkanediyl)bis(1,2,3,4-tetrahydropyridines), **30** recognized for exhibiting diverse biological activities.[29] The method involves 1,3-dicarbonyl compounds (acetylacetone or acetoacetic ester), aqueous 33% formaldehyde, and various α,ω-diamines such as ethylenediamine, 1,3-diaminopropane, and 1,5-diaminopentane. The reaction proceeded efficiently in DMF at 50 °C over 7 hours, yielding the bis-tetrahydropyridine derivatives in 28–69% yields. Notably, the process follows a multicomponent



Scheme 8 Synthesis of 10*b*-hydroxy-4-nitro-5-phenyl-2,3,5,5*a*-tetrahydro-1*H*-imidazo[1,2-*a*]indeno[2,1-*e*]pyridin-6(10*bH*)-one *via* MCR.

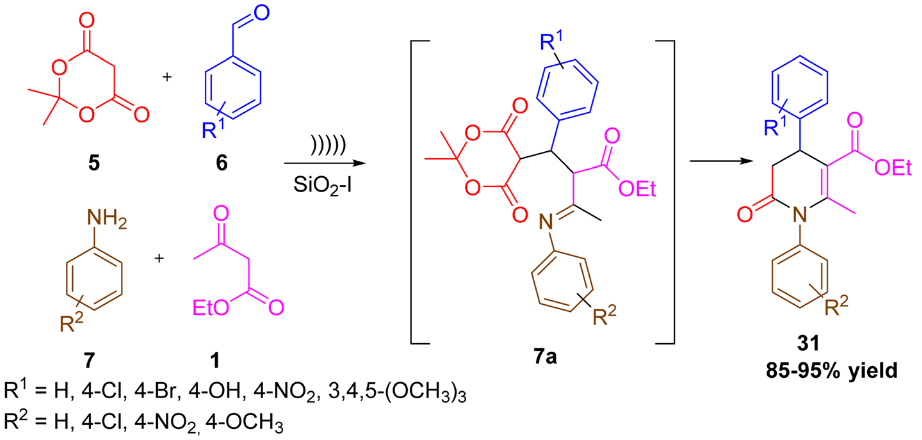


Scheme 9 Multicomponent preparation of polyfunctionalized tetrahydropyridine.

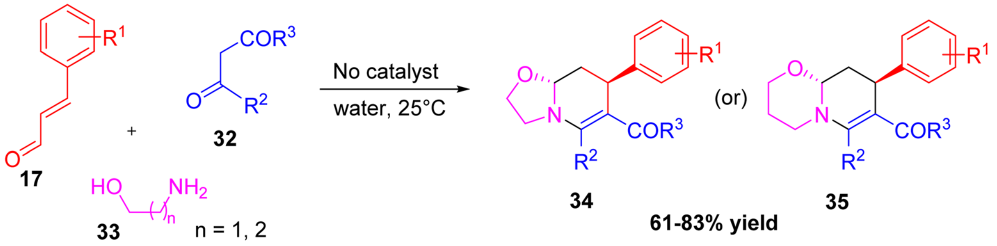
cyclocondensation mechanism, where the intermediate **29a** formed from formaldehyde and 1,3-diketones undergoes nucleophilic addition with imines and intramolecular cyclization (Scheme 9).

Govindaraju *et al.* reported the ultrasound-assisted, silica iodide (SiO_2-I)-catalyzed one-pot four-component synthesis of novel 1,4,5,6-tetrahydropyridine-3-carboxylate derivatives **31**, passes through an intermediate **7a.**[30] The reaction involved Meldrum's acid, substituted aryl aldehydes, aromatic amines, and ethyl acetoacetate, carried out under solvent-free conditions and ultrasonic irradiation. This green and efficient methodology afforded different products with excellent yields, notably ethyl-1-(4′-chlorophenyl)-2-methyl-6-oxo-4-(3′,4′,5′-trimethoxyphenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate in 95% yield under optimized conditions. Compared to conventional methods, this approach offers a shorter reaction time, mild reaction conditions, reusability of the catalyst, and high product purity without the need for chromatographic purification (Scheme 10).

Vinoth and co-workers developed a green and efficient approach for the synthesis of tetrahydropyridine derivatives, specifically fused tetrahydropyridines like oxazolo[3,2-*a*]pyridines (Scheme 11).[31] The method involves a three-component reaction of amino alcohols, 1,3-dicarbonyl compounds, and α,β-unsaturated aldehydes in water, without using any catalyst. This simple, one-pot procedure allows the construction of the tetrahydropyridine core in good yields through a sequence of enamine formation,

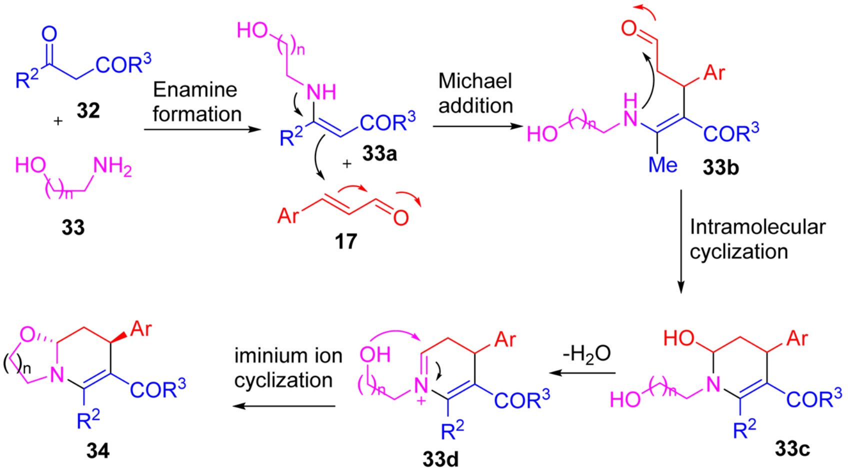


Scheme 10 Ultrasound assisted formation of 1,4,5,6-tetrahydropyridine-3-carboxylate derivatives.

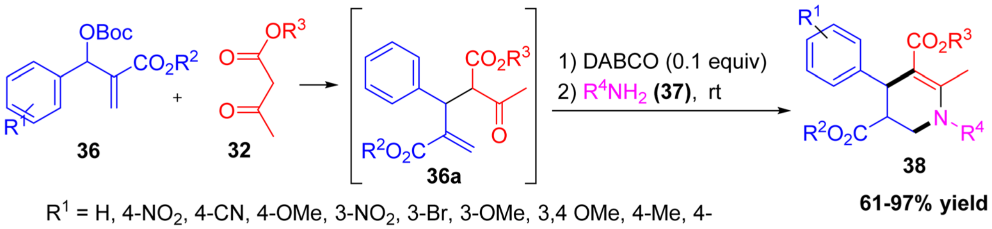


R^1 = H, 4-CH_3, 4-OMe, 4-F; R^2 = CH_3, Ph, $CH_3CH_3CH_2$; R^3 = OEt, Ph, CH_3, O^tBu

Scheme 11 A catalyst free one-pot synthesis of tetrahydropyridine derivative.



Scheme 12 Probable mechanism to explain synthesis of tetrahydropyridine derivative.



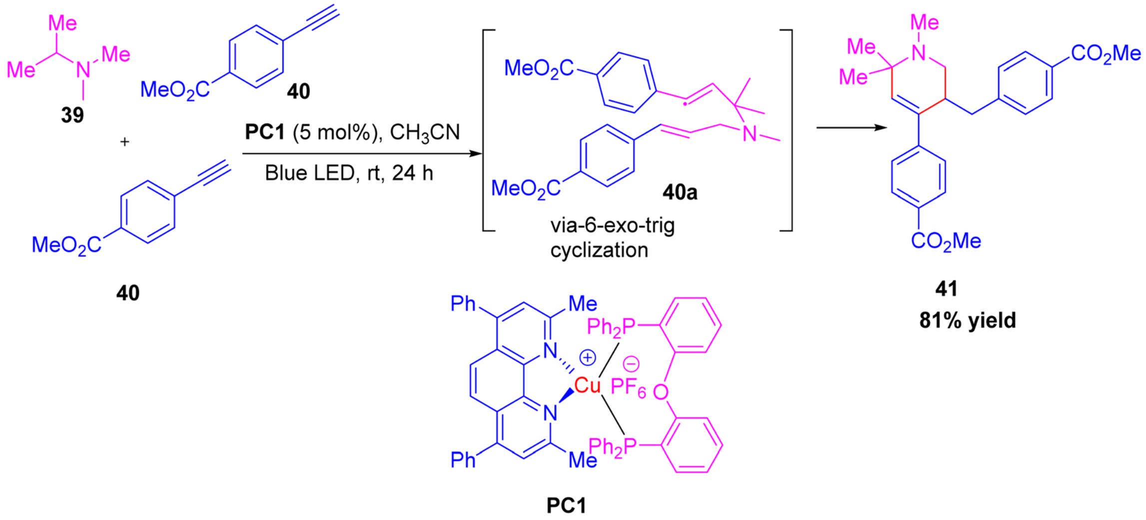
R^1 = H, 4-NO_2, 4-CN, 4-OMe, 3-NO_2, 3-Br, 3-OMe, 3,4 OMe, 4-Me, 4-Br,etc.
R^2 = Me, ^{t}Bu, ^{n}Bu; R^3 = Et, ^{t}Bu; R^4 = Me, Bn, PMB, Et, n-Bu

Scheme 13 Multicomponent synthesis of 4-aryl-1,2,3,4-tetrahydropyridines catalysed by DABCO.

Michael addition, and intramolecular cyclization steps (Scheme 12). The reaction showed excellent control over stereochemistry, mainly producing the trans isomers in most cases. It also followed principles of atom and step economy, as it generated only water as a by-product. Impressively, the process formed two fused rings and four new bonds, including one carbon–carbon, two carbon–nitrogen, and one carbon–oxygen all in a single step.

Wei *et al.* reported an efficient one-pot, three-component formation of 4-aryl-1,2,3,4-tetrahydropyridines **38** using Morita–Baylis–Hillman (MBH) carbonates **36**, 1,3-ketoesters, and primary amines as starting materials.[32] The reaction is catalyzed by DABCO, a Lewis base, and follows a formal [3 + 2 + 1] cyclization mechanism. This organocatalytic method provides a variety of tetrahydropyridine derivatives under mild conditions and in excellent yields. The reaction is compatible with various aromatic groups, amines, and esters, offering a simple and rapid route to construct complex molecular frameworks (Scheme 13).

Li *et al.* reported an easy and effective approach for the synthesis of multisubstituted tetrahydropyridine derivatives **41** using a photoinduced copper-catalyzed multicomponent reaction.[33] The reaction uses readily available starting materials like alkyl amines, alkynes, and aldehydes and proceeds under mild conditions using visible light. The product was formed through an interesting [3 + 2 + 1] radical cyclization, which creates three carbon–carbon (C–C) bonds and one carbon–nitrogen (C–N) bond in a single step. The method shows excellent regio- and



Scheme 14 Photoinduced multicomponent synthesis of highly substituted tetrahydropyridine.

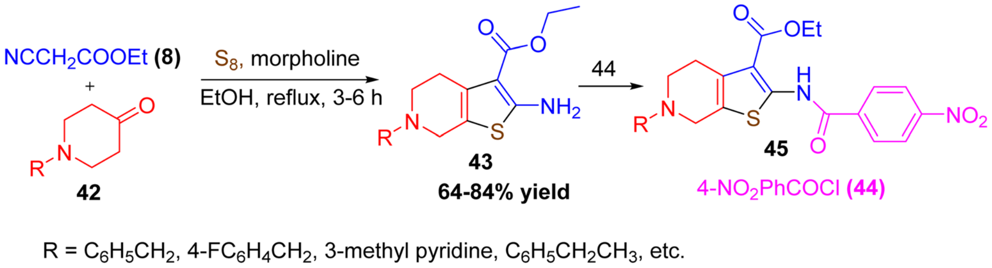
diastereoselectivity, and the reaction occurs through an α-aminoalkyl radical intermediate. This new approach offers a green and economical way to prepare complex bicyclic and spirocyclic tetrahydropyridines, which are important in pharmaceutical and chemical research (Scheme 14).

Rossetti *et al.* reported a simple one-pot three-component Gewald reaction to synthesize a series of novel chiral derivatives of 2-amino-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine, a type of fused tetrahydropyridine compound **45**.[34] The main starting materials used in the reaction were *N*-substituted piperidones, ethyl cyanoacetate, and sulfur, followed by reaction with 4-nitrobenzoyl chloride. The main aim was to introduce chiral amine substituents on the nitrogen atom of the tetrahydropyridine ring to study their impact on antimicrobial activity. The synthesized compounds were tested against two bacterial strains: *Sarcina lutea* (Gram-positive) and *Escherichia coli* (Gram-negative). The results showed that only Gram-positive bacteria were inhibited, and notably, the (*R*)-enantiomers had stronger activity than their (*S*)-counterparts. This shows the significance of chirality in biological activity and supports the potential of these tetrahydropyridine derivatives as new antibacterial agents (Scheme 15).

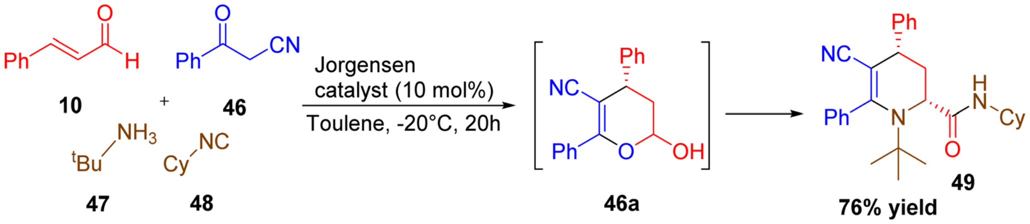
A novel and highly stereoselective multicomponent reaction (MCR) for the synthesis of penta substituted tetrahydropyridines was developed by Echemendia and co-workers.[35] This one-pot, organocatalytic procedure involved the combination of benzoylacetonitrile, cinnamaldehyde, a primary or secondary amine, and an isocyanide, catalyzed by the Jørgensen–Hayashi catalyst and 3,5-dinitrobenzoic acid. The reaction proceeded under microwave irradiation in trifluoroethanol. This strategy also allowed the incorporation of peptide, sugar, and steroid moieties, resulting in complex chimeric tetrahydropyridine hybrids (Scheme 16).

Tang and co-workers reported the diastereoselective synthesis of two fused tetrahydropyridine derivatives **51** and **52** *via* a one-pot multicomponent reaction.[36] The synthesis was achieved by using cinnamaldehyde, *o*-aminophenol, with starting materials **32** and **50** in refluxing ethanol using acetic acid (AcOH) as a catalyst proceeds *via* an intermediate **32a** and **50a** respectively. The reaction proceeded efficiently to deliver the trans isomer in high yield and with excellent stereoselectivity (Scheme 17).

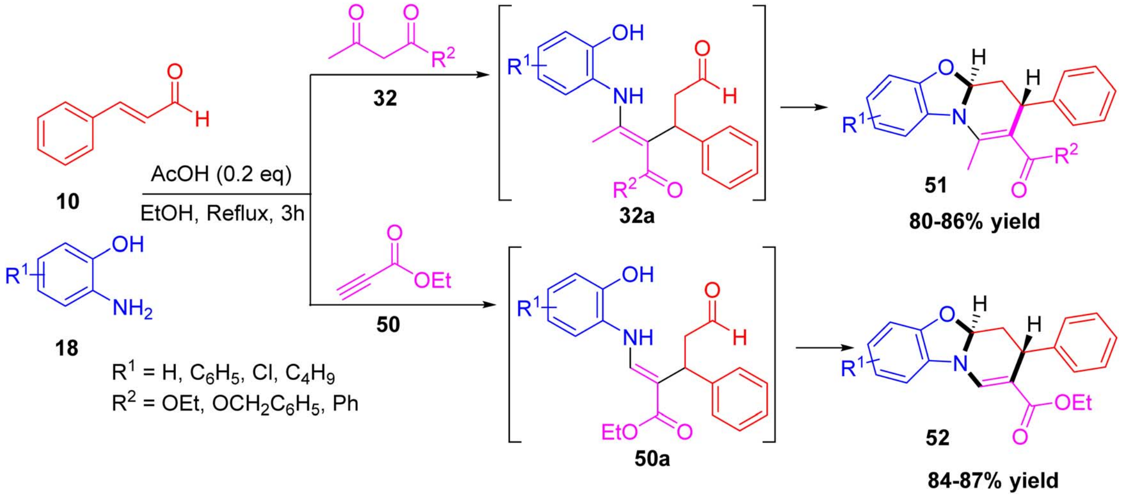
Zhu *et al.* developed a simple and effective method to prepare indol-3-yl-substituted tetrahydropyridines using a three-component reaction.[37] In this reaction, 1-amino-3,3-diethoxypropane, diethyl acetylenedicarboxylate, and indole derivatives were combined in acetonitrile at 60 °C with Al(OTf)$_3$ as the catalyst. The reaction proceeds through an intermediate **55a,** which then cyclizes to form the tetrahydropyridine core. The process gave a wide range of products in moderate to good yields. Different indoles, including 5-methoxyindole, 6-nitroindole, 2-methylindole, and *N*-substituted indoles, worked well, showing the broad scope of



Scheme 15 Three component synthesis of 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine.

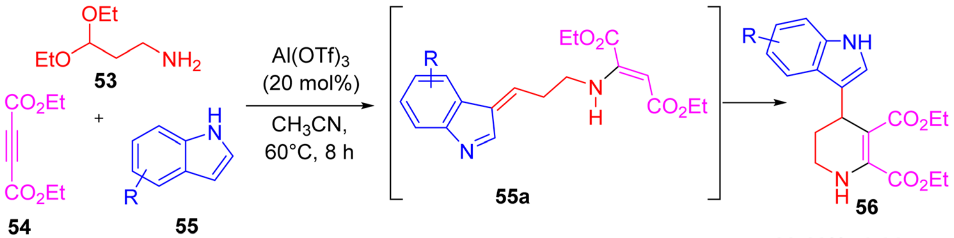


Scheme 16 Organocatalytic multicomponent synthesis of pentasubstitued tetrahydropyridine.



R^1 = H, C_6H_5, Cl, C_4H_9
R^2 = OEt, $OCH_2C_6H_5$, Ph

Scheme 17 Diastereoselective synthesis of ethyl 3-phenyl-4,4*a*-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-2-carboxylate.

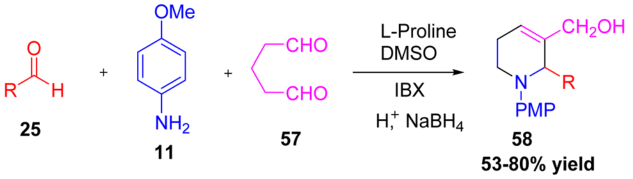


R = H, Cl, Me, OMe, Br, CO_2Et, Me, etc.

Scheme 18 Al(OTf)$_3$ catalysed three component synthesis of indol-3-yl-substituted tetrahydropyridines

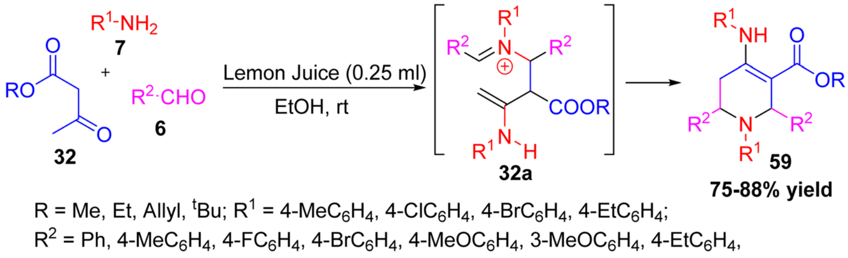
the method. This one-pot reaction is attractive because it uses easily available starting materials and a low-cost catalyst to make biologically valuable tetrahydropyridine derivatives in a straightforward way (Scheme 18).

Ramaraju *et al.* reported an efficient enantioselective multicomponent synthesis of 1,2,5,6-tetrahydropyridines (THPs) through a one-pot domino sequence. The reaction involved the proline-catalyzed Mannich reaction and cyclization of glutaraldehyde with *in situ* generated imines, which were prepared from aromatic aldehydes and *p*-anisidine, followed by site-selective oxidation using IBX (2-iodoxybenzoic acid) and $NaBH_4$ reduction under mild conditions.[38] The reaction was carried out in DMSO as the solvent, giving chiral THPs in good yields (up to 80%) and excellent enantioselectivity. The method was also applied for the synthesis of several medicinally important nitrogen heterocycles, including hexahydrochromeno[4,3-*b*]pyridine, polyhydroxylated piperidines, guvacine, and nipecotic acid derivatives. This simple, environmentally friendly, and economical one-pot strategy demonstrates the efficiency of L-proline catalysis in constructing biologically significant tetrahydropyridine derivatives (Scheme 19).

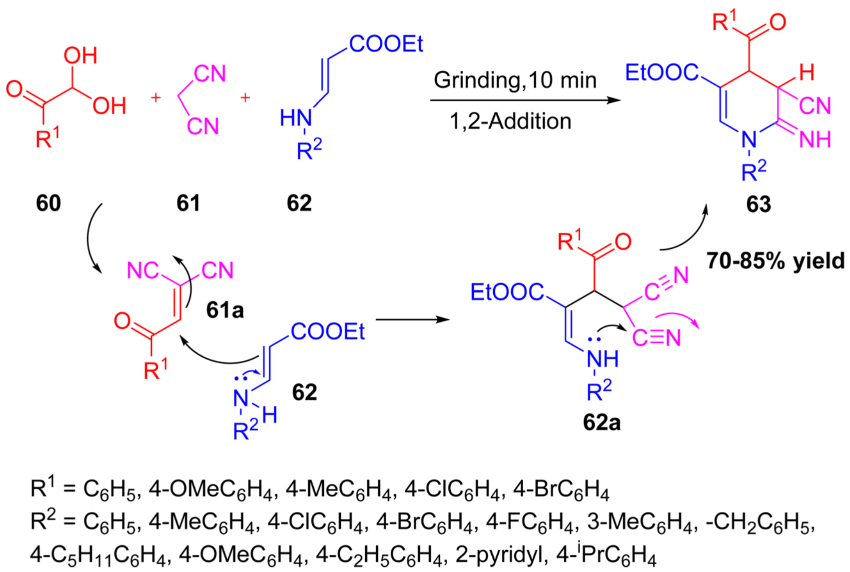


R = C6H5, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 3-ClC_6H_4, 2-ClC_6H_4, 3-FC_6H_4, 2-FC_6H_4, 3-CNC_6H_4 etc.

Scheme 19 Enantioselective formation of 1,2,5,6-tetrahydropyridines by L-proline catalyzed.



Scheme 20 Five-component synthesis of tetrahydropyridine using lemon juice as a green catalyst.



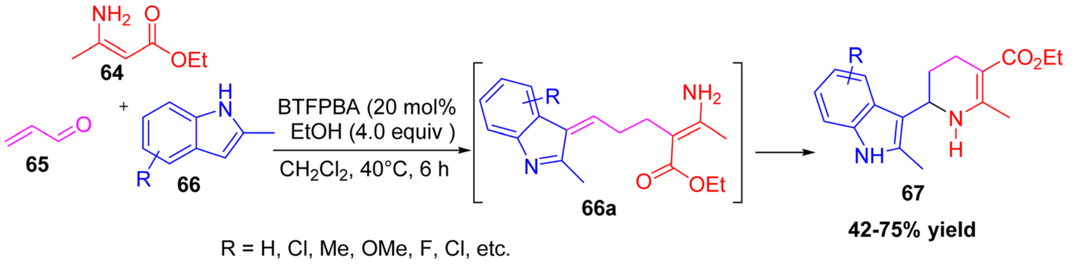
Scheme 21 A catalyst free three component synthesis of tetrahydropyridine-3-carboxylate.

Khan *et al.* reported a green and efficient multicomponent synthesis of functionalized tetrahydropyridine (THPD) derivatives using lemon juice as a natural, biodegradable, and eco-friendly catalyst. The reaction involved β-ketoesters, aromatic aldehydes and its substituted derivatives, and aromatic amines in ethanol at room temperature. Using only 0.25 mL of lemon juice as a catalyst, the reaction proceeded *via* intermediate **32a** to give the desired tetrahydropyridine products in good to excellent yields (76–86%) within a few hours.[39a] This green protocol eliminates the need for toxic reagents, harsh conditions, and column chromatography, offering a simple, cost-effective, and sustainable approach for synthesizing biologically significant tetrahydropyridine derivatives with high atom economy and operational ease (Scheme 20). Several methods have also been reported by L-proline,[39b] Ni(Salen),[39c] Fe_3O_4@S–TiO_2,[39d] *N*-methyl pyridinium tosylate (NMPyTs) ionic liquid,[39e] ammonium trifluoroacetate,[39f] phosphomolybdic acid,[39g] nano-Fe_3O_4@walnut shell,[39h], [Cu(2-pic)$_2$]2H_2O}*n*],[39i] *etc.*

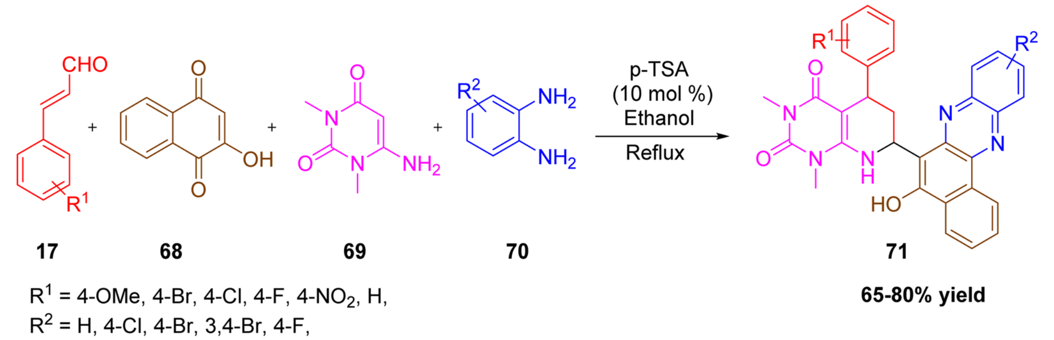
1.3. Synthesis of THP using enamine as amino source

Dhinakaran *et al.* developed an efficient and eco-friendly method for the multicomponent synthesis of ethyl 5-cyano-1-(4-ethylphenyl)-6-imino-4-(4-methoxybenzoyl)-1,4,5,6-tetrahydropyridine-3-carboxylate **63** (Scheme 21).[40] The reaction proceeds *via* an intermediate **62a** formed during the domino Knoevenagel condensation and Michael addition, which then undergoes intramolecular cyclization to give the tetrahydropyridine product. The process uses ethyl (*E*)-3-(arylamino) acrylates **62**, 2,2-dihydroxy-1-arylethan-1-ones **60**, and malononitrile in a single step under solvent-free and catalyst-free grinding conditions, offering high yields and excellent selectivity. Importantly, the selective formation of tetrahydropyridine depends on the presence of electron-donating groups on the *N*-aryl ring of the acrylate. This green synthesis protocol provides a practical and sustainable method for preparing bioactive tetrahydropyridine compounds.

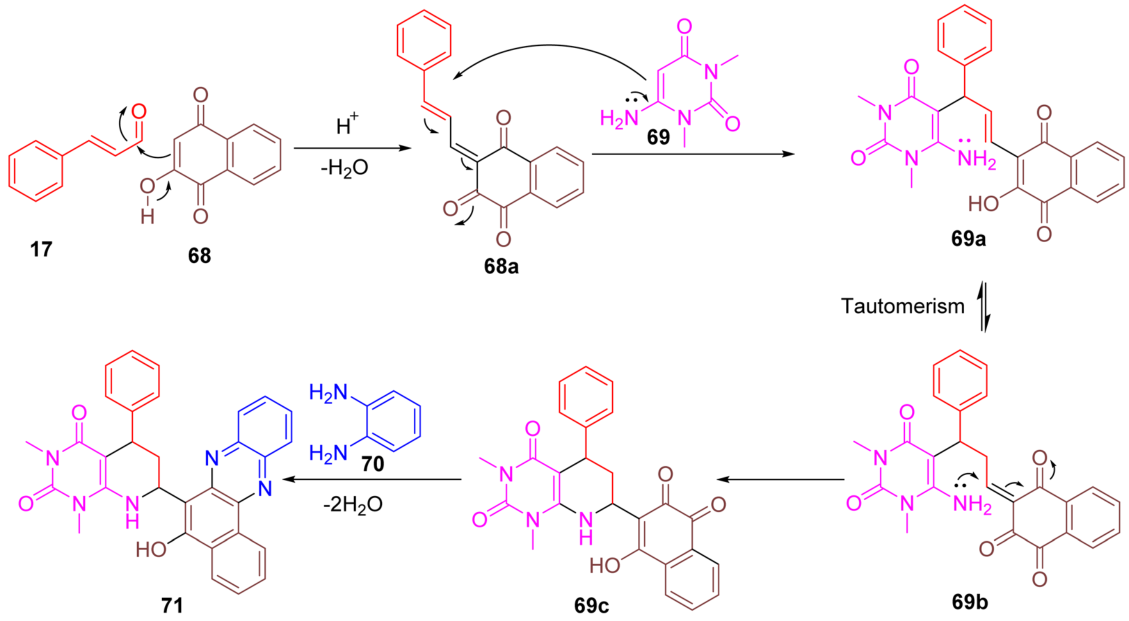
Zhu *et al.* introduced a BTFPBA-catalyzed three-component reaction to make C6-(indol-3-yl)-substituted tetrahydropyridines **67**.[37] This reaction used ethyl 3-aminocrotonate **64**, acrolein **65**, and 2-methylindole derivatives **66** in dichloromethane at 40 °C, with 2,4-bis(trifluoromethyl)phenylboronic acid (BTFPBA) as the catalyst. The reaction proceeds *via* an intermediate **66a**, which then cyclizes to give the desired products in moderate to good yields. It worked well with different indoles such as 5-methylindole, 5-methoxyindole, 2-phenylindole, and *N*-substituted indoles. This approach is notable because it provides an easy one-pot way to build diverse indole-tetrahydropyridine hybrids, which are valuable scaffolds in medicinal chemistry (Scheme 22).



Scheme 22 One pot three component synthesis of indol-3-yl-substituted tetrahydropyridines using BTFPBA as a catalyst.

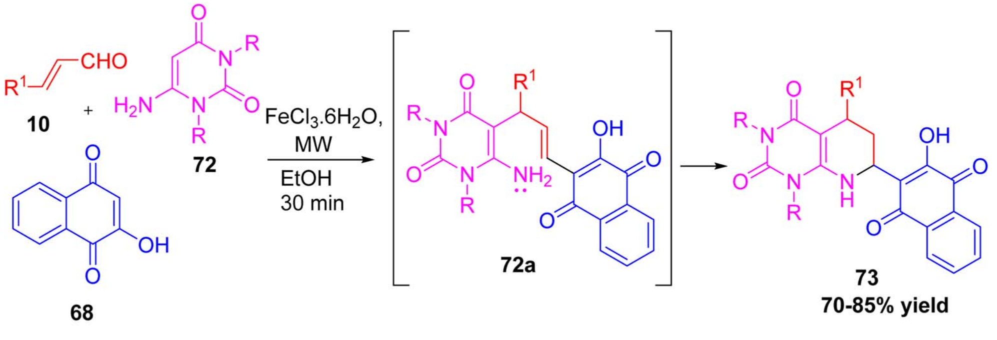


Scheme 23 *p*-TSA catalysed synthesis of benzophenazine containing THPD *via* MCR.



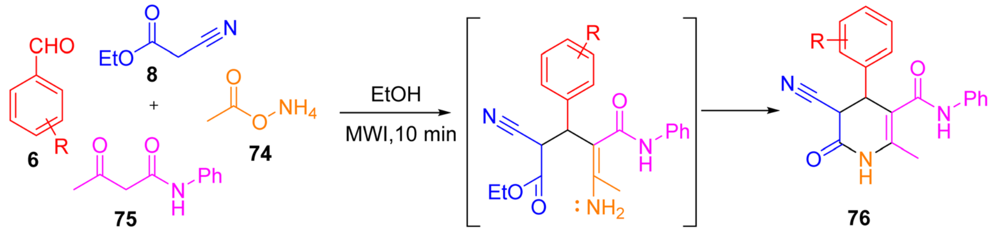
Scheme 24 Probable mechanism to explain synthesis of benzophenazine containing THPD *via* MCR.

Darakshan and Parvin developed a simple and eco-friendly method to synthesize benzophenazine tethered tetrahydropyridopyrimidine derivatives using a one-pot four-component reaction (Scheme 23).[41] The reaction involves cinnamaldehyde or crotonaldehyde **17**, 2-hydroxy-1,4-naphthoquinone **68**, 6-amino-1,3-dimethyl uracil **69**, and *o*-phenylenediamine **70** in ethanol with *p*-toluenesulfonic acid (*p*-TSA) as a catalyst. The reaction proceeds *via* a Knoevenagel condensation, followed by nucleophilic attack, tautomerization, and intramolecular cyclization, ultimately leading to the selective formation of product **71** through sequential addition of the reactants (Scheme 24). The final products combine three bioactive structures: benzophenazine, tetrahydropyridine, and pyrimidine, which makes them promising for medicinal use. The advantages of this method include simple procedure,



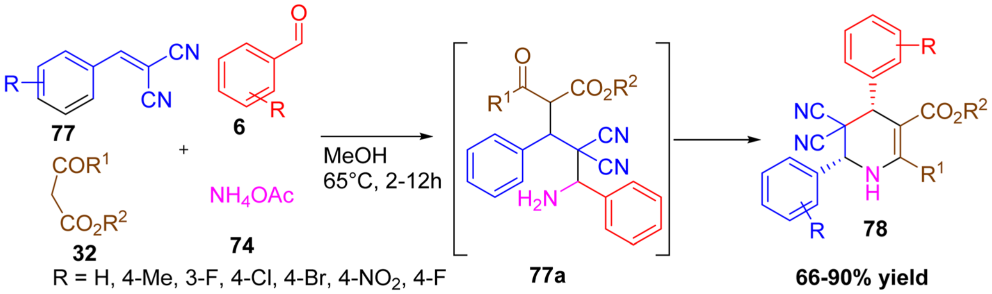
R = H, CH$_3$; R^1 = C$_6$H$_5$, 4-OMeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-NO$_2$C$_6$H$_4$,etc.

Scheme 25 Regioselective microwave irradiation multicomponent synthesis of tetrahydropyridine derivative.



R = 2-OMe, 2,4-Cl, 3,4,5,-OMe, 4-OH, 3-Cl, 2,5-OMe,
2-Me, 2,4,5-Me, 2-CF$_3$, 2-Cl, 2-thionyl

Scheme 26 Microwave irradiation one-pot catalysed formation of tetrahydropyridine-3-carboxamide.



R = H, 4-Me, 3-F, 4-Cl, 4-Br, 4-NO$_2$, 4-F
R^1 = Me, Et, Ph, 4-BrPh R^2 = Me, Et

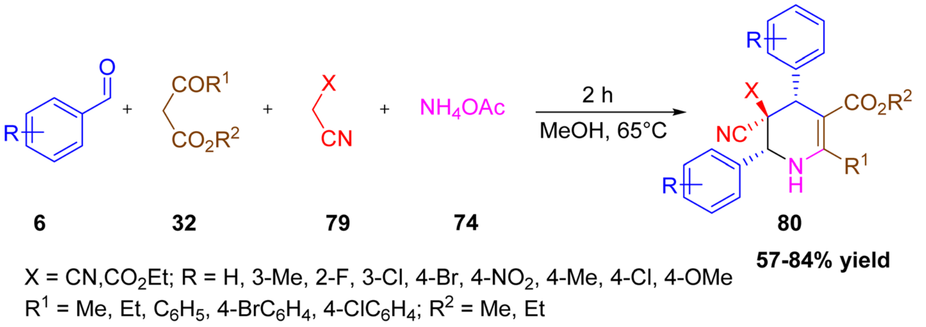
Scheme 27 Multicomponent synthesis of 1,4,5,6-tetrahydropyridine derivatives by Mannich reaction.

metal-free conditions, availability of reactants, and easy purification.

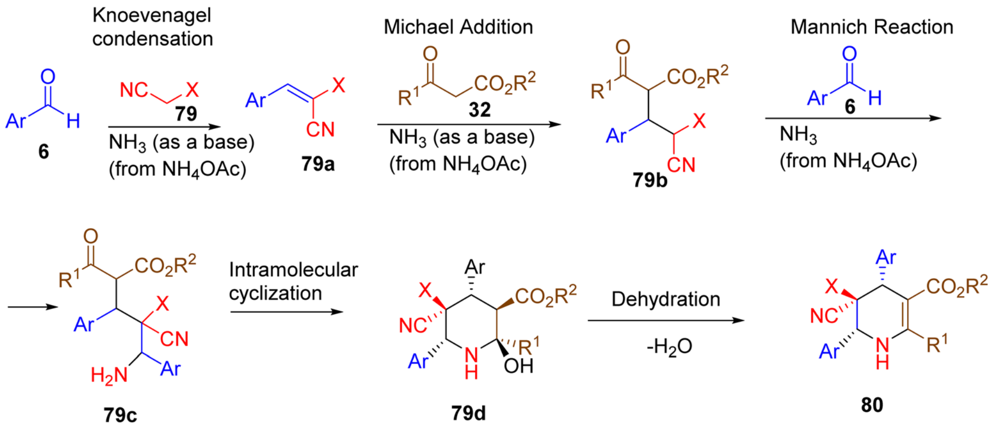
The product **73** was successfully synthesized through a three-component reaction using cinnamaldehyde (α,β-unsaturated aldehyde), 2-hydroxy-1,4-naphthaquinone (a cyclic 1,3-dicarbonyl compound), and 1,3-dimethyl-6-aminouracil. Kumari *et al.* demonstrated a microwave-assisted, regioselective one-pot method in ethanol using FeCl$_3$·6H$_2$O as a green and inexpensive catalyst.[42] The reaction proceeds *via* an intermediate **72a**, which then cyclizes to give the desired product in high yield (up to 85%) under mild conditions within 30 minutes. The developed method is simple, environmentally friendly, and useful for synthesizing pyrimidine-fused tetrahydropyridine derivatives, which show biological and medicinal applications (Scheme 25).

1.4. Synthesis of THP using ammonia and ammonium acetate as amino source

Khumalo *et al.* presented a clean and eco-friendly method for synthesizing tetrahydropyridine-3-carboxamide derivatives through a microwave-assisted, catalyst-free one-pot reaction.[43a] The reaction involves a combination of aromatic aldehydes, ethyl cyanoacetate, acetoacetanilide, and ammonium acetate, using ethanol as a green solvent (Scheme 26). Under microwave irradiation, the products were formed rapidly within 10 minutes, with high yields ranging from 91% to 97%. This protocol avoids the use of toxic catalysts and lengthy purification, as the products can be easily isolated without column chromatography. The method also benefits from short reaction times, energy efficiency, and operational simplicity. Furthermore, another method using a CeO$_2$/MWCNT nanocomposite



Scheme 28 Stereoselective five-component synthesis of highly substituted tetrahydropyridine.



Scheme 29 Plausible mechanism to explain synthesis of highly substituted tetrahydropyridine.

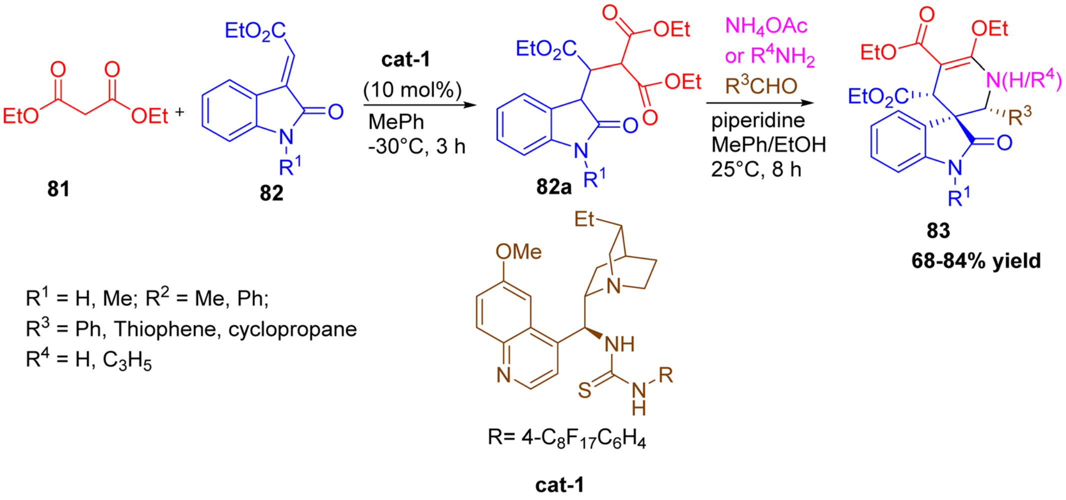
catalyst, also reported for achieving the same product up to 97% yield in 15 minutes.[43b]

A novel and efficient four-component synthesis of 1,4,5,6-tetrahydropyridine derivatives was developed by Vereshchagin *et al.*, involving benzylidenemalononitriles, aromatic aldehydes, esters of 3-oxocarboxylic acids, and ammonium acetate.[44] The reaction proceeds through a cascade sequence passing through an intermediate **77a** formed during the Michael addition and Mannich reaction, followed by cyclization and dehydration in methanol, to afford highly diastereoselective 2-substituted alkyl (4*SR*,6*RS*)-4,6-diaryl-5,5-dicyano-1,4,5,6-tetrahydropyridine-3-carboxylates **78**. This method achieves excellent yields (66–92%) in a single step and eliminates the need for column chromatography. Ammonium acetate plays a dual role as a base and a nitrogen source (Scheme 27).

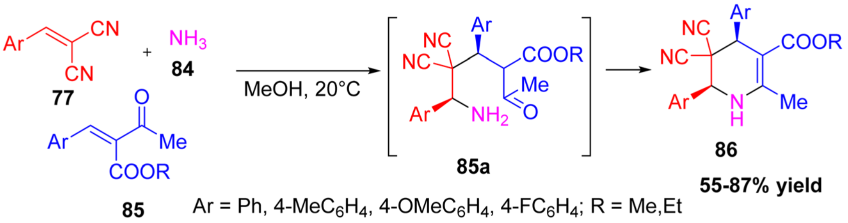
Iliyasov *et al.* reported the stereoselective one-pot five-component synthesis of substituted 1,4,5,6-tetrahydropyridines, particularly 2-substituted alkyl (4*SR*,6*RS*)-4,6-diaryl-5,5-dicyano-1,4,5,6-tetrahydropyridine-3-carboxylates and 3,5-dialkyl (4*RS*,5*SR*,6*RS*)-5-cyano-2,4,6-triaryl-1,4,5,6-tetrahydropyridine-5,3-carboxylates (Scheme 28).[45] The method involves a series of Knoevenagel condensation, Michael addition, Mannich reaction, cyclization, and dehydration using aromatic aldehydes, malononitrile or ethyl cyanoacetate, esters of 3-oxocarboxylic acids, and ammonium acetate as the key reactants (Scheme 29). Ammonium acetate plays a dual role as a base and a nitrogen source. The reaction proceeds under mild reflux conditions in methanol and leads to high yields (57–84%).

Spirooxindole derivatives containing 2-piperidinone and 1,2,3,4-tetrahydropyridine[46] rings were synthesized *via* a one-pot asymmetric multicomponent reaction developed by Huang *et al.* This four-component cascade proceeds through an intermediate **82a** formed during the Michael/Mannich sequence, followed by cyclization, and is catalyzed by a recyclable fluorous Cinchona alkaloid/thiourea-based organocatalyst. The key reactants include electron-deficient olefinic oxindoles, diethyl malonate or 1,3-diketones, aromatic or heteroaromatic aldehydes, and ammonium acetate or amines. The optimized method yielded products with up to 99% enantiomeric excess and excellent diastereoselectivity. The catalyst could be easily recovered and reused without loss of efficiency. This environmentally friendly synthesis provides valuable spirooxindole–tetrahydropyridine hybrids, which are of great interest in drug discovery due to their structural similarity to biologically active molecules like MDM2 inhibitors (Scheme 30).

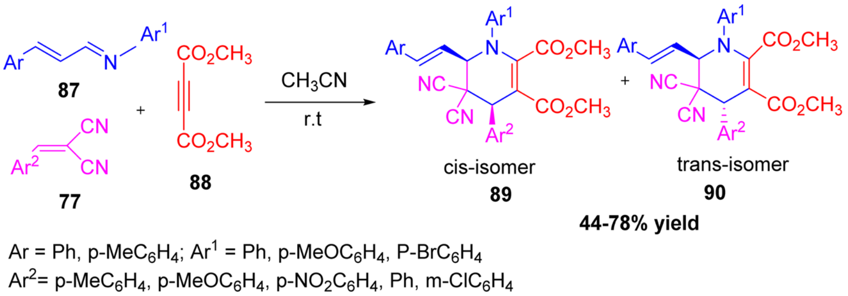
Vereshchagin *et al.* reported a simple and efficient method for synthesizing (4*RS*,6*SR*)-4,6-diaryl-5,5-dicyano-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylates, a type of tetrahydropyridine derivative with a wide range of biological activity.[47] Method is multicomponent reaction involving three key reactants: benzylidenemalononitrile, 2-acetyl-3-arylacrylate, and aqueous ammonia in methanol at room temperature. The reaction proceeds through an intermediate **85a**, leading to high



Scheme 30 Four component synthesis of 1,2,3,4-tetrahydropyridine derivative using organocatalyst.



Scheme 31 Diastereoselective multicomponent synthesis of 1,4,5,6-tetrahydropyridine-3-carboxylates.



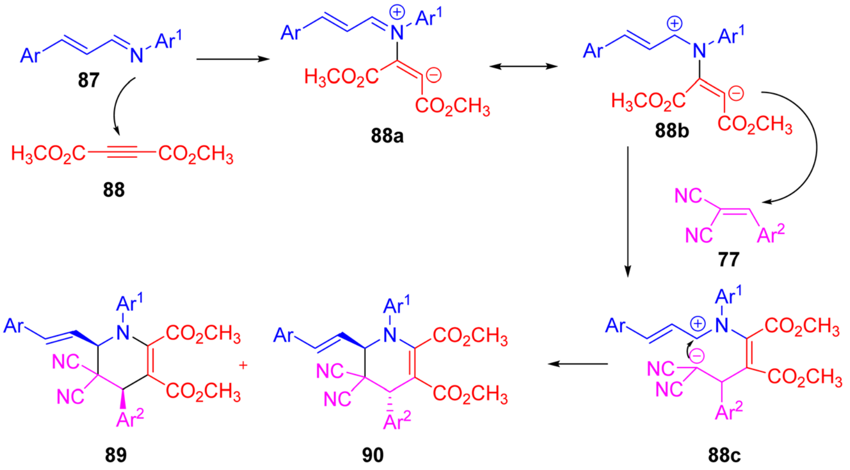
Scheme 32 Three component synthesis of 6-styryl-1,4,5,6-tetrahydropyridines *via* cycloaddition reaction.

diastereoselectivity and yields ranging from 55% to 87%. Ammonia plays a dual role, acting as both a nitrogen source and a base. This method offers a mild, clean, and simple synthetic route to complex nitrogen-containing heterocycles (Scheme 31).

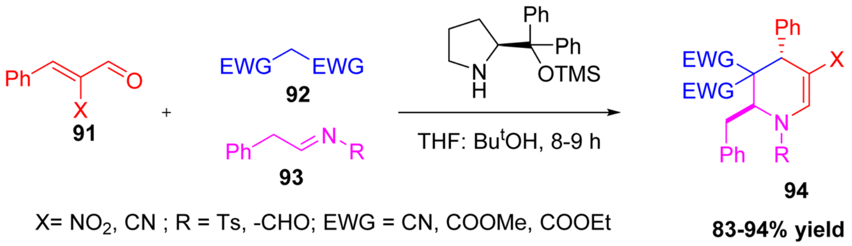
1.5. Synthesis of THP using imine as amino source

Zhang *et al.* describe a very simple three-component reaction was developed using α,β-unsaturated *N*-arylaldimines, dialkyl acetylenedicarboxylates, and arylidenemalononitriles in dry acetonitrile at room temperature (Scheme 32).[48] This reaction leads to the formation of 6-styryl-1,4,5,6-tetrahydropyridines with different cis/trans forms in good yields. Similar results were obtained when using other reactants like ethyl arylidenecyanoacetates or arylidene pivaloylacetonitriles. The reaction works through a domino [2 + 2 + 2] cycloaddition involving 1,4-dipolar intermediates (Scheme 33). These intermediates form when α,β-unsaturated imines react with electron-poor alkynes. This method allows easy access to functionalized tetrahydropyridines under mild conditions. It offers advantages such as simple setup, good yields, and broad substrate scope. The process is useful for making nitrogen-containing heterocycles and shows promise for applications in organic and medicinal chemistry.

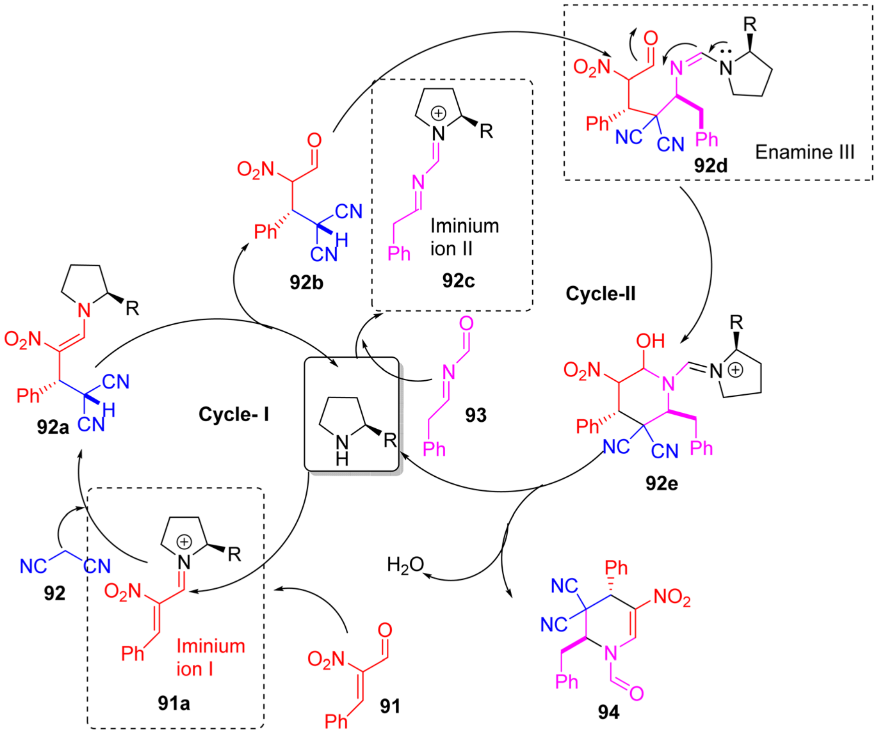
Rai *et al.* reported a novel one-pot three-component synthesis of highly substituted tetrahydropyridines (THPs) using a Morita–Baylis–Hillman (MBH) enal-based triple cascade strategy (Scheme 34).[49] The reaction involves [*E*]-α-cyano/nitro cinnamaldehyde, malononitrile (an active methylene compound), and aldimines or phenyl-*N*-tosyl-methanimines as reactants. This method uses iminium-enamine catalysis facilitated by a secondary amine catalyst and proceeds through a sequential cascade forming C–C and C–N bonds in one pot



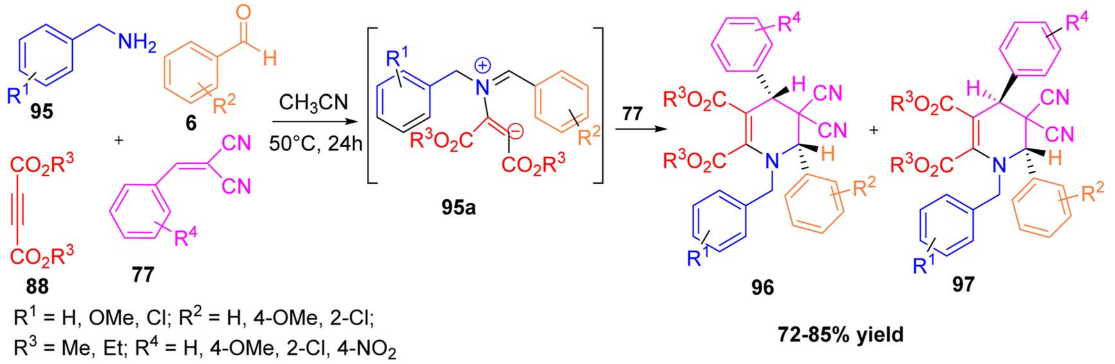
Scheme 33 Probable mechanism to represent the synthesis of 6-styryl-1,4,5,6-tetrahydropyridines.



Scheme 34 Three component synthesis of tetrahydropyridine derivative *via* cascade reaction.

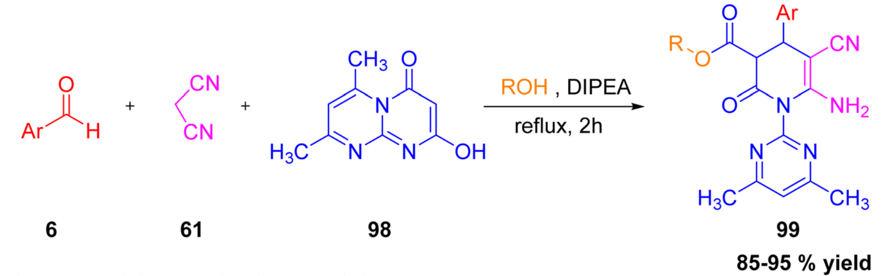


Scheme 35 Mechanistic way to show the formation of highly substituted tetrahydropyridines



R^1 = H, OMe, Cl; R^2 = H, 4-OMe, 2-Cl;
R^3 = Me, Et; R^4 = H, 4-OMe, 2-Cl, 4-NO$_2$

Scheme 36 One-pot synthesis of highly substituted tetrahydropyridine without using catalyst.



Ar = C_6H_5, 4-MeOC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 4-ClC$_6$H$_4$,
2,6-Cl$_2$C$_6$H$_3$, 3-MeOC$_6$H$_4$, 4-NCC$_6$H$_4$, 2-naphthyl,
4-MeC$_6$H$_4$, 3-ClC$_6$H$_4$; R = Me, Et, ^{i}Pr

Scheme 37 Four-component synthesis of tetrahydropyridine derivative using DIPEA as a catalyst.

(Scheme 35). The reaction provides the THP products in high yields (83–94%) and with excellent diastereoselectivity (95–99%) favouring the anti-isomer. This method is a useful and selective way to make complex THP compounds and shows the role of MBH adducts in making complicated heterocycles.

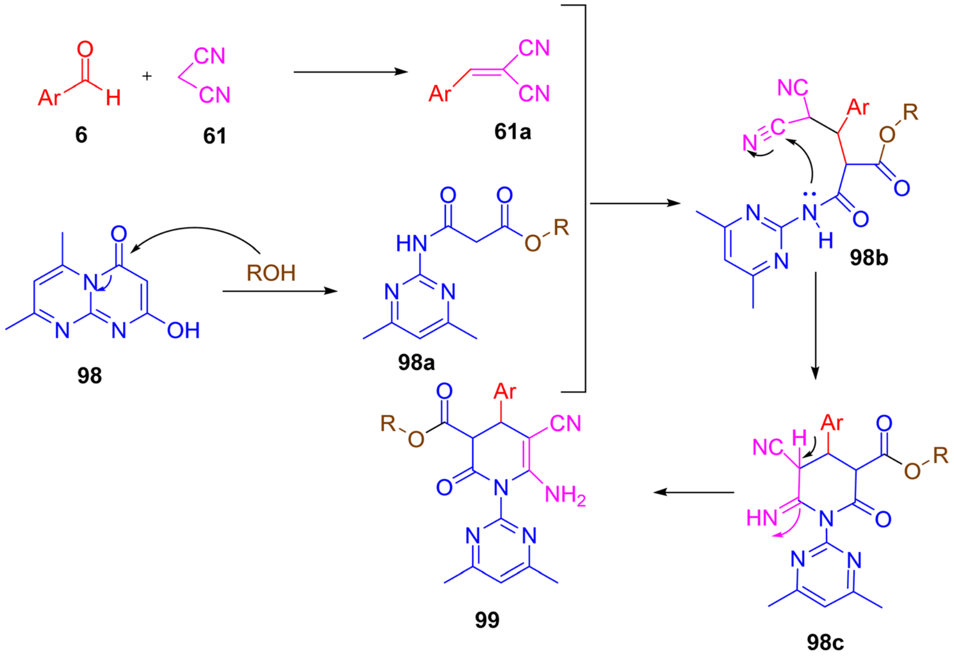
Mehrabi and Mohebbi reported a simple and efficient one-pot, two-step synthesis of highly substituted tetrahydropyridines.[50] The method involves the initial formation of *N*-benzylidene-methanamines from benzylamines and benzaldehydes in the presence of acetic acid, followed by cyclization with dialkyl acetylenedicarboxylates and benzylidenemalononitriles in acetonitrile at 50 °C under catalyst-free condition. This multicomponent process efficiently yields products like dimethyl 1-benzyl-5,5-dicyano-1,4,5,6-tetrahydro-4,6-diphenylpyridine-2,3-dicarboxylate in good yields (up to 85%). This method is easy to use, uses inexpensive starting materials, works well under mild conditions, and gives good yields (Scheme 36).

1.6. Synthesis of THP using miscellaneous reactions

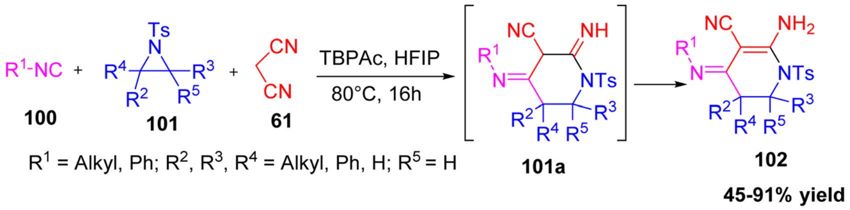
Zangouei *et al.* developed a new and efficient one-pot, four-component method for the synthesis of alkyl 6-amino-5-cyano-1-(4,6-dimethylpyrimidin-2-yl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylates **99** (Scheme 37).[51] The reaction combines aromatic aldehydes **6,** malononitrile **61,** 6,8-dimethyl-2-hydroxy-4*H*-pyrimido[1,2-*a*]pyrimidine-4-one **98,** and alcohols in the presence of diisopropylethylamine (DIPEA) under reflux (Scheme 38). This unexpected transformation produced the target compounds **99** with excellent diastereoselectivity and in high yields ranging from 85% to 95%. The stereochemistry of the products was confirmed by single-crystal X-ray analysis. The advantages of this method include mild reaction conditions, short reaction times, and simple purification. Optimization experiments showed that ethanol and DIPEA were essential for achieving good results, while other solvents or solvent-free systems failed to produce the desired product. The mechanism of product formation is given in Scheme 38, which revealed that the key intermediate **98a** obtained by reaction of alcohol with compound **98.**

A simple and efficient multicomponent method was developed for synthesizing tetrahydropyridine derivatives through a domino ring-opening and cyclization reaction.[52] Kermani used aziridines, isocyanides, and malononitrile as reactants, with tetrabutylphosphonium acetate (TBPAc) as the catalyst in hexafluoroisopropanol (HFIP) under mild conditions. The reaction proceeds *via* an intermediate **101a,** which subsequently undergoes cyclization to afford products **102** in good to excellent yields with high atom economy and regioselectivity. This approach allows rapid construction of structurally diverse tetrahydropyridines, which are known for their biological and pharmaceutical relevance. This approach demonstrates the effectiveness of TBPAc as an organocatalyst and provides a useful strategy for building nitrogen-containing six-membered heterocycles (Scheme 39).

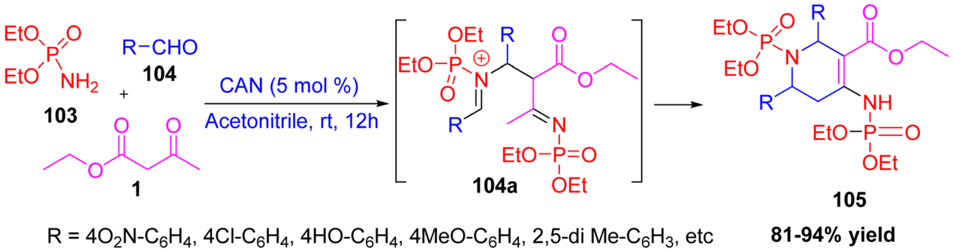
A novel and efficient one-pot multicomponent synthesis of tetrahydropyridine phosphonate derivatives has been reported using diethylphosphoramidate, aromatic aldehydes, and ethyl acetoacetate as starting materials in the presence of ceric



Scheme 38 Mechanism proposed to explain the synthesis of tetrahydropyridine derivative *via* MCR.



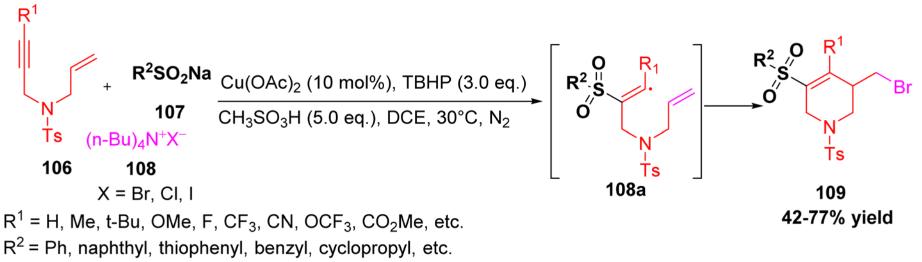
Scheme 39 Multicomponent synthesis of diverse tetrahydropyridine using TBPAc catalyst through domino ring opening.



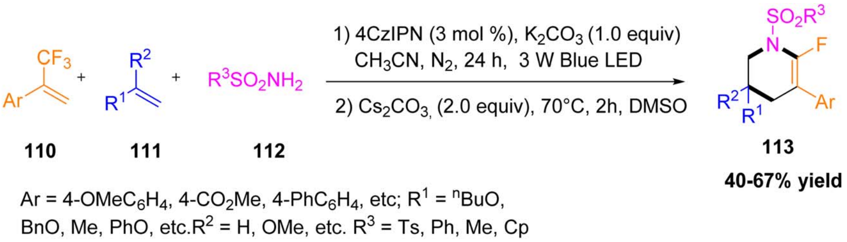
Scheme 40 Multicomponent synthesis of tetrahydropyridine phosphonate derivatives using CAN as a catalyst.

ammonium nitrate (CAN) as a catalyst in acetonitrile at room temperature.[53] The reaction passes *via* an intermediate **104a** to afford the tetrahydropyridine products under mild conditions with good yields and high atom economy. The main product synthesized was ethyl 1-(diethoxyphosphoryl)-4-((diethoxyphosphoryl)amino)-2,6-diaryl-1,2,5,6-tetrahydropyridine-3-carboxylate. Molecular docking studies were carried out for the synthesized tetrahydropyridine phosphonate derivatives to evaluate their interaction with the α-glucosidase enzyme, a key target in the treatment of type II diabetes mellitus. Since this enzyme plays a crucial role in carbohydrate digestion, its inhibition can help regulate blood sugar levels. The docking analysis helped to understand the probable binding mechanisms between the synthesized compounds and the enzyme's active site. Reddy *et al.*, demonstrated an environmentally friendly and effective approach for the synthesis of bioactive tetrahydropyridines (Scheme 40).

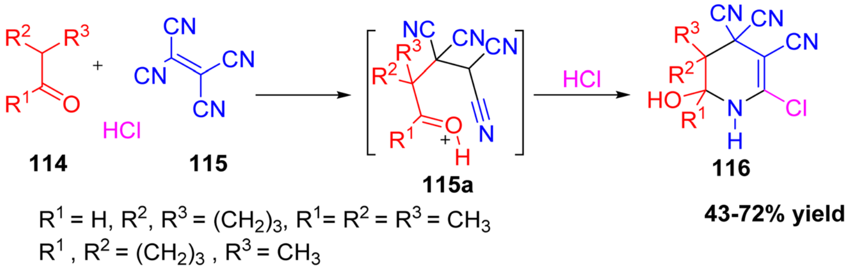
Kang *et al.* reported a simple one-pot method to make 3-(halomethyl)-4-aryl-5-(aryl or alkylsulfonyl)-1-tosyl-1,2,3,6-tetrahydropyridine derivatives **109** using a three-component reaction.[54] The starting materials were N-centered 1,6-enynes, sodium sulfinates, and tetrabutylammonium halides **108** (TBAX). In the presence of a copper catalyst, sulfonyl radicals are generated, which add to the triple bond to form an



Scheme 41 Three-component synthesis of tetrahydropyridine derivative *via* ring formation.



Scheme 42 Photoinduced multicomponent synthesis of 6-fluoro-1,2,3,4-tetrahydropyridines



Scheme 43 One-pot synthesis of 6-hydroxy-2-chloro-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile derivatives.

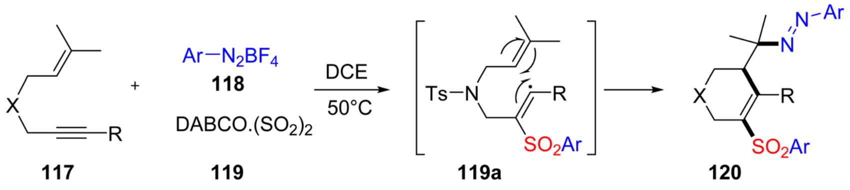
intermediate **108a** that subsequently undergoes 6-*endo*-dig cyclization and halogenation to afford the desired products. This method works well with many types of reactants, including aromatic and aliphatic ones, and gives good yields (Scheme 41).

Zhang *et al.* developed a new and easy one-pot method to make useful fluorinated compounds called mono fluorocyclohexenes and 6-fluoro-1,2,3,4-tetrahydropyridines **113** which are important building blocks in synthetic chemistry and the pharmaceutical industry.[55] They used three starting materials: α-CF_3 alkenes, electron-rich alkenes and dimethyl esters or sulfonamides. These react together in the presence of light and a base to break two C–F bonds and form a ring structure. When dimethyl malonate is used, the product is monofluorocyclohexene. When sulfonamides are used, the product is 6-fluoro-1,2,3,4-tetrahydropyridine. These functional products can be used for synthetic applications such as decarboxylation, cyclization, reduction, and oxidation (Scheme 42).

Ershov *et al.* developed a simple and efficient multicomponent method to synthesize 6-hydroxy-2-chloro-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile derivatives **116** through a three-component reaction involving tetracyanoethylene, various ketones, and hydrogen chloride (HCl) in 1,4-dioxane at 30–40 °C.[56] The reaction follows a domino mechanism, where an intermediate **115a** is formed and then converted to the final product. The yields of the final compounds ranged from 43% to 72%. These tetrahydropyridine derivatives are significant because they are part of many biologically active compounds (Scheme 43).

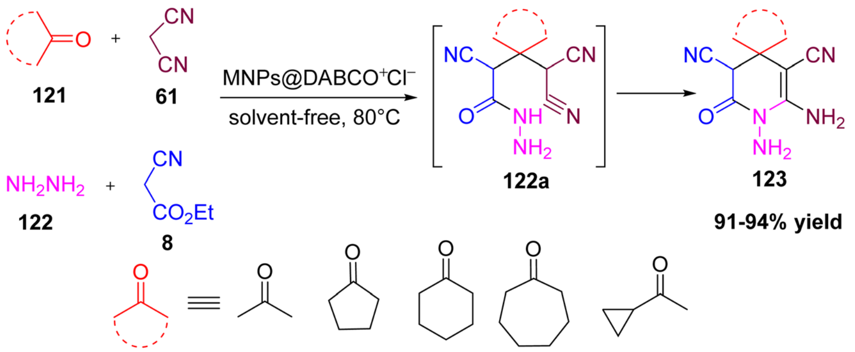
An and Wu reported a mild and catalyst-free multicomponent method to make sulfonated tetrahydropyridine derivatives **120**.[57] The reaction uses 1,6-enynes, sulfur dioxide (from DABCO·$(SO_2)_2$), and aryldiazonium tetrafluoroborates as the main starting materials (Scheme 44). It works through a radical cyclization process started by arylsulfonyl radicals passing through an intermediate **119a** formed during the reaction. Two molecules of the aryldiazonium salt are involved in this transformation. The best results were obtained by heating the mixture in dichloroethane at 50 °C under nitrogen, without any catalyst, giving moderate to good yields. This metal-free method is an efficient way to make functional tetrahydropyridine compounds, which are useful in medicinal and synthetic chemistry.

Rigi and Shaterian reported a straightforward, green four-component synthesis of 1,6-diamino-2-oxo-1,2,3,4-

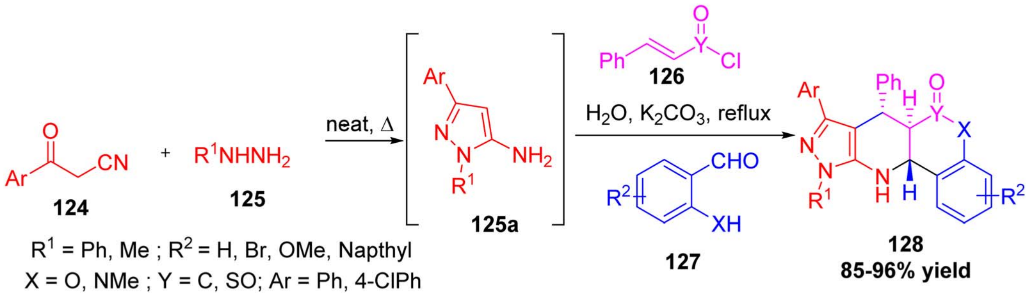


R = p-MeC$_6$H$_4$, p-FC$_6$H$_4$, p-ClC$_6$H$_4$, p-OMeC$_6$H$_4$, m-OMeC$_6$H$_4$, p-NO$_2$C$_6$H$_4$, **32-75% yield**
p-COMeC$_6$H$_4$, p-BrC$_6$H$_4$, etc. ; X = NTs, O, C(CO$_2$Me)$_2$
Ar = p-FC$_6$H$_4$, Ph, p-MeC$_6$H$_4$, p-OMeC$_6$H$_4$, p-ClC$_6$H$_4$, o-MeC$_6$H$_4$, m-MeC$_6$H$_4$,
p-CF$_3$C$_6$H$_4$, p-NO$_2$C$_6$H$_4$, etc.

Scheme 44 Multicomponent synthesis of sulfonated tetrahydropyridine derivatives *via* cyclization process.



Scheme 45 A four-component synthesis of 1,6-diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitriles.

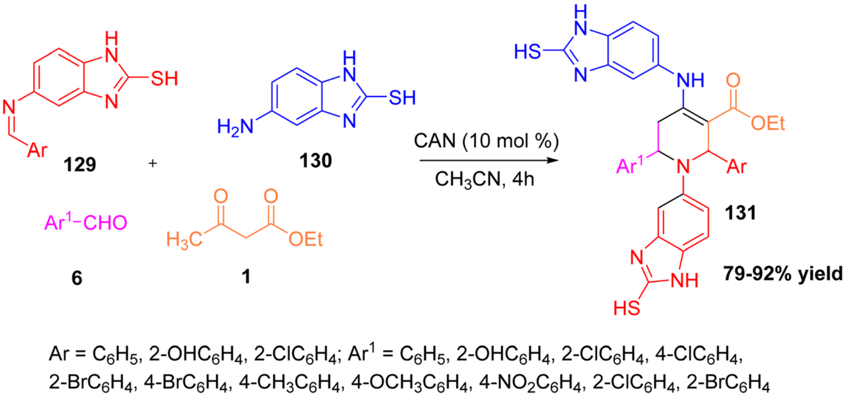


R^1 = Ph, Me ; R^2 = H, Br, OMe, Napthyl
X = O, NMe ; Y = C, SO; Ar = Ph, 4-ClPh

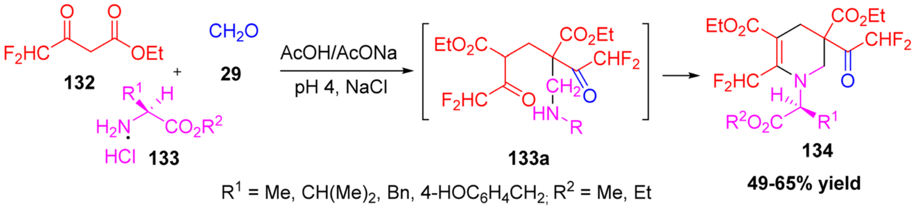
Scheme 46 One-pot synthesis of pyrazolo-tetrahydropyridines derivatives *via* Aza–Diels–Alder reaction.

tetrahydropyridine-3,5-dicarbonitriles **123** by reacting hydrazine hydrate, malononitrile, ethyl cyanoacetate, and ketones at 80 °C under solvent-free conditions (Scheme 45).[58a] The reaction proceeds *via* an intermediate **122a**, which subsequently undergoes cyclization to afford the desired tetrahydropyridine products. Using a magnetic nanoparticle-supported ionic liquid catalyst (MNPs@DABCO·Cl) enables easy product separation with an external magnet, high isolated yields, and catalyst reuse for at least four cycles without loss of activity. Overall, this work gives a high yield, short reaction time, efficient, and recyclable protocol for making tetrahydropyridine derivatives in an environmentally friendly manner. Some other methods, such as ultrasonication and the use of 4-(dimethylamino)pyridine (DMAP) and nano-Fe$_2$O$_3$ as catalysts, have also been reported, offering advantages such as high yields, a broader substrate scope, and short reaction times.[58b–d]

Nazeri *et al.* reported an environmentally friendly and simple one-pot multicomponent approach has been developed for producing pyrazolo-tetrahydropyridine derivatives **128** through a chemo- and diastereoselective intramolecular Aza–Diels–Alder reaction (ADAR). In this approach, four key starting materials; benzoylacetonitrile derivatives, phenylhydrazine, salicylaldehyde derivatives, and styrenesulfonyl or cinnamoyl chloride **126** react in water as an environmentally friendly solvent (Scheme 46).[59] The reaction proceeds smoothly with good yields and avoids traditional purification steps such as recrystallization and column chromatography methods by employing the Group-Assisted Purification (GAP) chemistry technique. This approach enables the quick formation of complex heterocyclic structures that incorporate pharmacologically significant components.



Scheme 47 Formation of benzo[*d*]imidazolyl tetrahydropyridine carboxylates using CAN as a catalyst.



Scheme 48 One pot synthesis of 1,2,3,4-tetrahydropyridine-3,5-dicarboxylate.

Ravindernath and Reddy reported an efficient one-pot multicomponent synthesis of benzo[*d*]imidazolyl tetrahydropyridine carboxylates using (*E*)-5-(benzylidene amino)-1*H*-benzo[*d*]imidazole-2-thiol, 5-amino-2-mercaptobenzimidazole, aromatic aldehydes, and ethyl acetoacetate as reactants in acetonitrile solvent with ceric ammonium nitrate (CAN) as a Lewis acid catalyst.[60] The reaction proceeds smoothly at room temperature to afford the desired tetrahydropyridine derivatives in good yields. The synthesized compounds were evaluated for anti-inflammatory, antioxidant, antibacterial, and antifungal activities. Most of the synthesized derivatives showed significant biological properties, with several compounds exhibiting comparable or better activity than standard drugs such as diclofenac sodium, ciprofloxacin, and fluconazole. This study highlights that combining benzimidazole and tetrahydropyridine frameworks within a single molecule enhances pharmacological potential. Overall, this multicomponent approach offers a simple, economical, and environmentally friendly route to biologically active benzo[*d*]imidazolyl tetrahydropyridine carboxylates (Scheme 47).

Gibadullina *et al.* reported an efficient one-pot multicomponent synthesis of difluoromethyl-containing 1,2,3,4-tetrahydropyridine derivatives. The reaction involved ethyl 4,4-difluoroacetoacetate, formaldehyde, and various primary amine hydrochlorides or α-amino acid ester hydrochlorides as reactants.[61] The process proceeds through an intermediate **133a** formed during the Mannich-type condensation, which subsequently cyclizes to afford the tetrahydropyridine framework. The optimized conditions employed an acetate buffer (pH 4) as the reaction medium in the presence of sodium chloride (NaCl) as an electrolyte additive, which significantly enhanced the selectivity and yield of the desired products. Under these conditions, diethyl 3-(difluoroacetyl)-6-(difluoromethyl)-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate was obtained in good to excellent yield (Scheme 48).

2 Conclusion

In conclusion, multicomponent reactions (MCRs) have proven to be a powerful, efficient, and eco-friendly approach for the synthesis of tetrahydropyridine (THP) derivatives. Over the past decade, various MCR strategies using different nitrogen sources such as amines, enamines, imines, ammonia, and ammonium acetate, *etc.* have enabled the rapid and diverse construction of THP frameworks with wide biological and pharmaceutical importance. These methods often proceed under mild, solvent-free, or green conditions, with high yields and excellent selectivity. The development of catalyst-free, microwave-assisted, photoinduced, and nanocatalytic systems further highlights the progress toward sustainable and atom-economical chemistry. Overall, the advances summarized in this review show that MCR-based synthesis provides a simple, versatile, and environmentally responsible route for designing structurally complex THP derivatives, paving the way for their future applications in medicinal and organic chemistry.

Conflicts of interest

There are no conflicts to declare.

Data availability

This is a review article, therefore no additional data is available.

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