Orbital
The electronic journal of chemistry

the electronic journal of chemistry

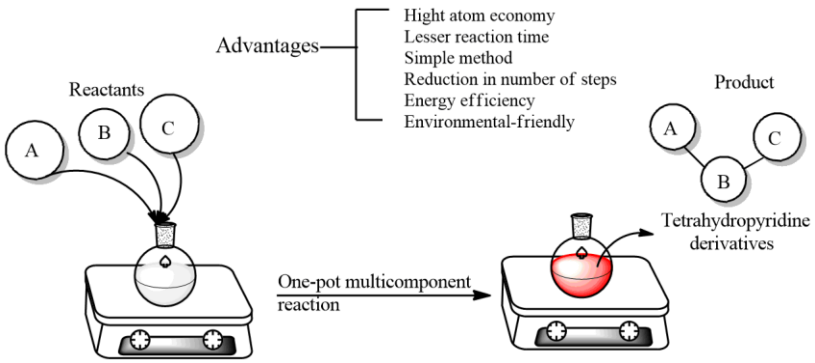
Review | http://dx.doi.org/10.17807/orbital.v13i4.1585

Effect of Methods and Catalysts on the One-pot Synthesis of Tetrahydropyridine Derivatives: A Mini-Review

Ajay Thakur, Ruchi Bharti*, and Renu Sharma

As heterocyclic nitrogen molecules, tetrahydropyridines have been recognized as significant constituents of many natural and synthetic compounds, many of which have interesting biological and pharmacological properties. Tetrahydropyridines (THPs) play a pivotal role in synthesizing a range of remedial compounds. They have exhibited impressive curative efficacy for the treatment of numerous diseases. Due to this reason, they are attractive synthetic targets for organic chemists. Several techniques and schemes have been adopted for the synthesis of these molecules. Among these, multicomponent reactions (MCRs) are proved to be one of the best tools for achieving compounds containing complex diversity in a single step and production of their vast libraries. Along with this, the employment of various catalysts makes this technique more vibrant. This review article discussed different catalysts adopted in the synthesis of tetrahydropyridine derivatives via multicomponent reactions to provide information for the development of new-fangled processes aiming at less reaction time, better yield, and minimum side effects.

Graphical abstract



Keywords

Catalysis
Heterocyclic compounds
Multicomponent reaction
Organic synthesis
Tetrahydropyridine derivatives

Article history

Received 29 December 2020
Revised 03 April 2021
Accepted 14 April 2021
Available online 30 September 2021

Handling Editor: Jamal Rafique

1. Introduction

Recently, tetrahydropyridine-based heterocyclic compounds have received considerable focus due to their excellent ability to act as pharmacophores and emerged as an excellent template for various bioactive molecules [1-2]. The tetrahydropyridine derivatives have been identified as major constituents of natural alkaloids such as arecoline and betanine-III [3-5]. Basically, it has three structural isomers (Figure 1) as 1,2,3,6-tetrahydropyridine (**1**), 1,2,3,4-tetrahydropyridine (**2**) and 3,4,5,6-tetrahydropyridine (**3**).

Amongst these, the tetrahydropyridine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**4**) is a well-known prodrug to

[a] Department of Chemistry, University Institute of Sciences, Chandigarh University, Gharuan, Mohali-140413, Punjab, India. *Corresponding author. E-mail: **ruchi.uis@cumail.in**

neurotoxin MPP+ that induces symptoms like those of Parkinson's disease. Many other tetrahydropyridine derivatives such as (**5**) (1-methyl-4-phenylpyridinium), (**6**) (1-methyl-4-phenoxy-1,2,3,6-tetrahydropyridine), and (4-pyrrole-tetrahydropyridine derivative) (**7**) have been found to inhibit monoamine oxidases (MAO) without exhibiting neurotoxic effects. Apart from this, the oxindole derivative of 1,2,3,6-tetrahydropyridine (**8**) is a potent dopamine autoreceptor agonist, initially synthesized to treat schizophrenic syndrome (Figure 2) [6]. Similarly, Gaboxadol (THIP) (**9**) is a powerful γ-aminobutyric acid (GABA-A) receptor agonist which is used to cure sleeping disorders [7-8].

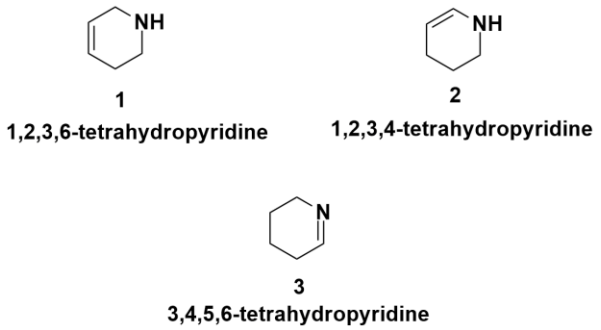


Fig. 1. Three structural isomers of tetrahydropyridines.

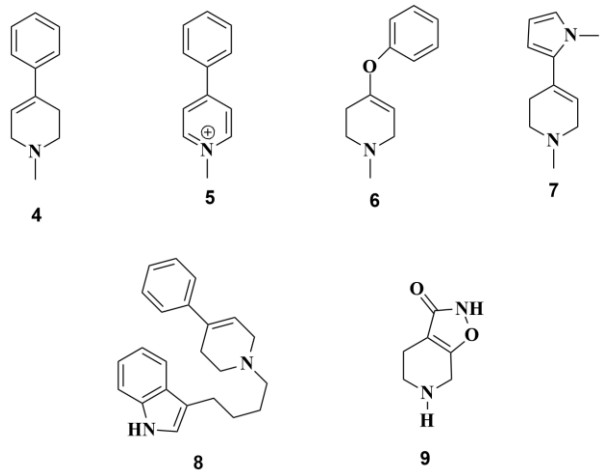


Fig. 2. Pharmaceutically active 1,2,3,6-tetrahydropyridine derivatives.

Besides this, compounds containing other THP structural motifs are profound to show a wide range of biological and medicinal applications such as anti-influenza [9], antimicrobial [10-11], antihypertensive [12], antimalarial [13], antibacterial [14], anti-inflammatory [15], anticancer [16] and anticonvulsant [17], etc. Recently, THP derivatives have also displayed anti-Alzheimer properties [18]. The broad spectrums of activities shown by these motifs have highly attracted the attention of organic and medicinal chemists.

Different types of methods have been adopted for the synthesis of THPs, such as [4+2] cycloaddition reactions [19], multicomponent reactions [20-21], radical cyclization of Baylis-Hillman adducts, and two-component reactions of aldimines and tetrahydropyrandiol [22-24]. Among these methods, multicomponent reactions (MCRs) [25-27] have been recognized as a handy and efficient tool because of their high atom economy, lower costs, and energy-saving features. MCRs have occupied a prominent place in synthetic chemistry for the rapid synthesis of these tetrahydropyridine derivatives.

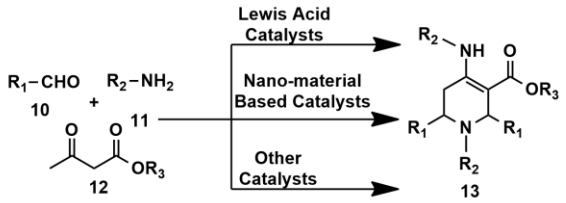
In this review, we have tried to highlight the synthesis of various tetrahydropyridine derivatives reported in the past few years by utilizing different catalysts in one-pot multicomponent reactions to better yield, less reaction time, and minimum side effects.

2. One-Pot Multi-component Synthetic Approaches for 1,2,3,6- or 1,2,5,6-Tetrahydropyridine

1,2,3,6-tetrahydropyridines, also known as 1,2,5,6-tetrahydropyridines, have been found to show various important biological and pharmaceutical activities [28-31] and become the center of attraction for many researchers and scientists. Recently, new multicomponent methodologies have been developed for the synthesis of 1,2,3,6-tetrahydropyridines which are discussed here.

2.1 Five Component One-pot Synthesis of 1,2,3,6-Tetrahydropyridine

One of the best methods for synthesizing 1,2,3,6-tetrahydropyridine derivatives is by using aldehyde (2 mmol), amines (2 mmol), and β-ketoester (1 mmol) as novel substrate via one-pot five-component reaction in the presence of different catalysts under various reaction conditions (Scheme 1).



R_1 = 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-$OCH_3C_6H_4$, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$
R_2 = 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-$OCH_3C_6H_4$, 4-FC_6H_4
R_3 = CH_3 , Et, Allyl

Scheme 1. Synthesis of 1,2,3,6-tetrahydropyridines using various catalysts.

2.1.1 Synthesis of 1,2,3,6-Tetrahydropyridine Using Common Lewis Acids Catalyst

Electron deficient lewis acids activate the substrates by attacking their electron-rich site. Various types of Lewis acid catalysts have been used for the one-pot multicomponent synthesis of 1,2,3,6-tetrahydropyridines which are summarized below:

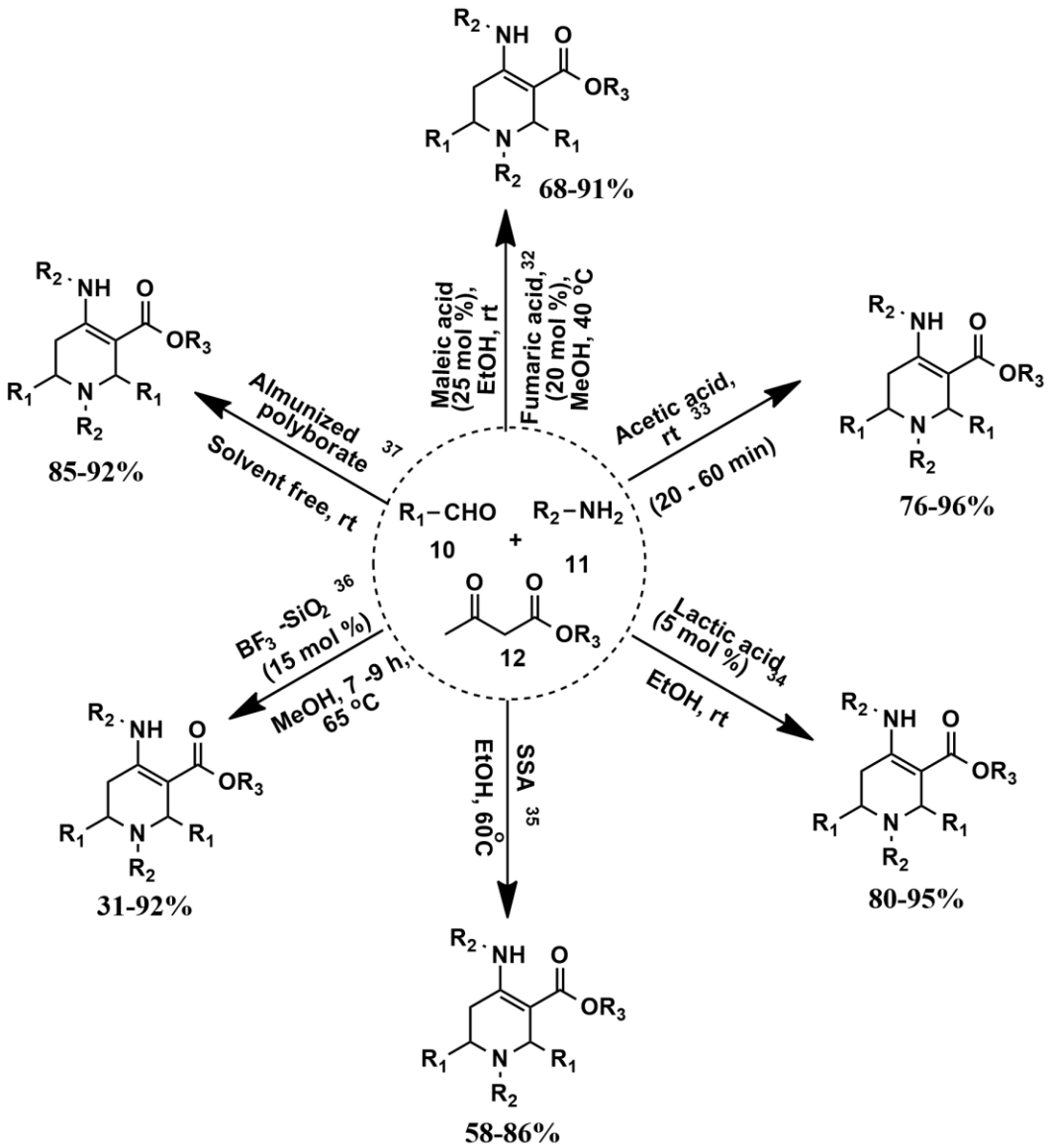
Recently, S. R. Mousavi *et al.* described the catalytic activity of two stereoisomers, i.e., Maleic acid and Fumaric acid, in the one-pot five-component reaction of 2 mmol aldehydes (**10**) with two mmol amines (**11**) and 1 mmol β-ketoester (**12**) for the synthesis of 1,2,5,6-tetrahydropyridine-3-carboxylate derivatives (**13**). As compared to fumaric acid, maleic acid gave more promising results. The desired products with high diastereoselectivity were obtained in moderate to high yield (68-91%) with 25 mol% maleic acids in 5 mL ethanol at room temperature within 30 minutes. However, when 20 mol% of fumaric acid was used as a

catalyst under reflux conditions, the expected product was obtained with a low yield (46-87%) [32] (Scheme 1a).

Afterward, another same one-pot multicomponent reaction was reported by Balijapalli*et al.*, where they explored the dual benefits of acetic acid (AcOH) as a catalyst and solvent at room temperature. The key features of this protocol were short reaction time, mild, clean, and metal-free reaction conditions, [33] which made it an excellent and promising alternative for the production of FTHPs (fully substituted tetrahydropyridines) (**13**) in moderate to good yield (76-96%) (Scheme 1a).

Another effort was made by M. Kangani and his group, where they performed the same reaction in Lactic acid as a green, effective, non–hazardous, and natural catalyst. Lactic acid leads to the generation of highly substituted piperidines (**13**) in lesser time and with high atomic efficiency (80-95% yield). This five-component reaction was carried out in 5 mL ethanol using 5 mol% of lactic acid as a catalyst when allowed to stir for 20 min at ambient temperatures [34] (Scheme1a).

Later, a similar effort was reported by Zhang *et al.* by using silica sulfuric acid (SSA) as catalyst under reflux condition in ethanol and obtained the desired products in moderate to good yield (58-86%). This process is eco-friendly as only water molecules were obtained as a by-product during the synthesis process [35] (Scheme 1a).



Scheme 1a. Synthesis of 1,2,3,6-tetrahydropyridines using Lewis acid catalysts.

Further, Ramachandran and his coworkers reported the same one-pot multicomponent reaction in the presence of ($BF_3.SiO_2$), a silica-based solid lewis acid catalyst in methanol under reflux conditions. This catalyst is inexpensive, convenient to use, eco-friendly, flexible, recyclable, and very effective in synthesizing highly substituted 1,2,5,6- tetrahydropyridine-3-carboxylate derivatives (**13**). Easy work up, less reaction time, high yields (31-92%), environmentally benign reaction conditions are the characteristic features of this reaction [36] (Scheme 1a).

The next attempt was made by Mali *et al.* to synthesize the desired product (**13**) in the presence of Aluminized Polyborate. It is a polymeric Lewis acid form of boric acid supported with aluminum leading to an increase in the overall Lewis acidity of catalyst and hence worked as a promising catalyst for the synthesis of 1,2,5,6-tetrahydropyridine-3-carboxylate derivatives (**13**) at room

temperature in solvent-free conditions with excellent yields (85-92%). The key advantages of this catalyst were its environmental-friendly nature and low cost provided with five times recyclable capability [37] (Scheme 1a).

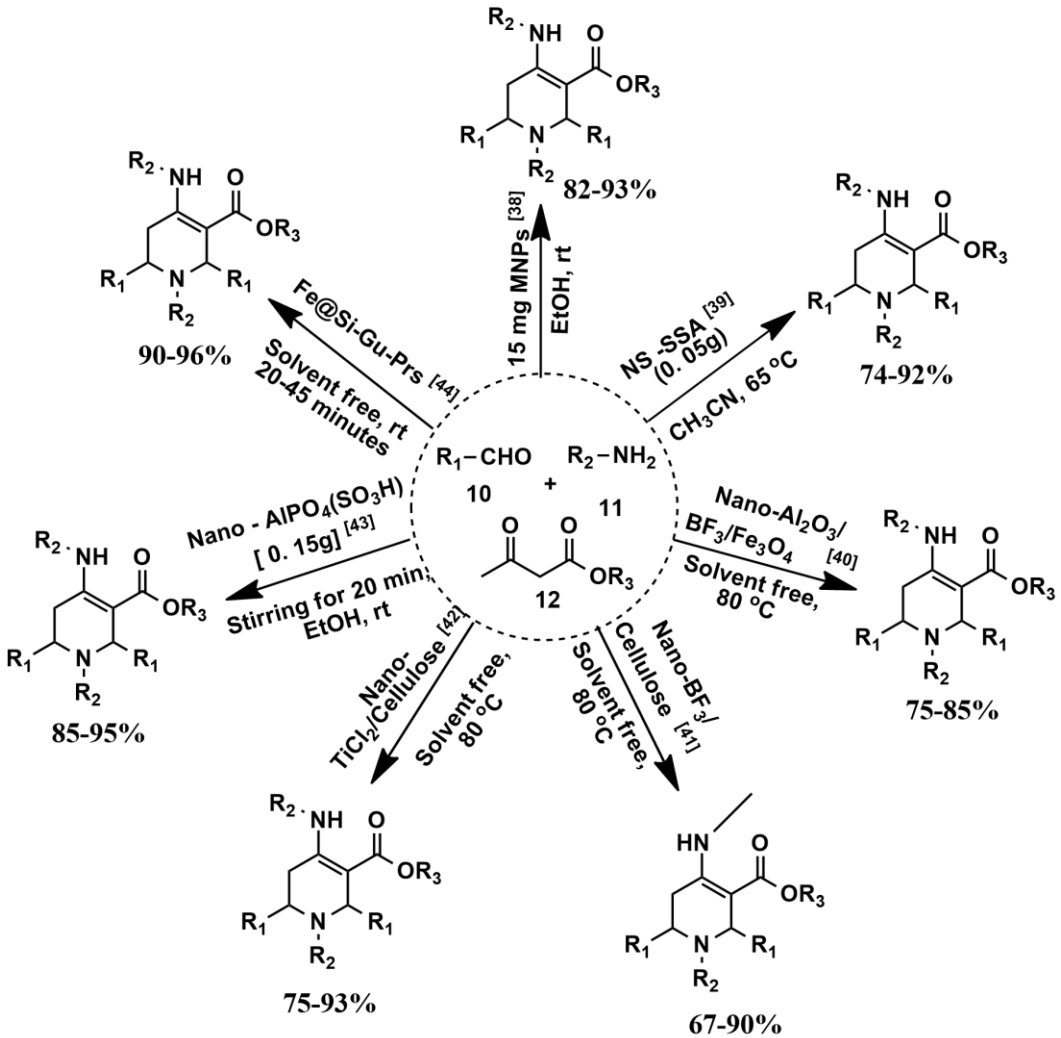
2.1.2 Synthesis of 1,2,5,6-Tetrahydropyridine Derivatives Using Nanomaterial Based- Catalyst

Nanocatalysts are broadly utilized in the engineering and science fields due to enhanced catalytic activities. Moreover, nano-sized catalysts are easier to retrieve, recycle and recover in correlation to bulk dimensions. These nano-sized catalysts perform dual functions; a site for catalysis and support for the catalytic reaction. Various readily available and newly synthesized nanoparticles have been adopted to synthesize highly functionalized tetrahydropyridine (**13**).

In this direction, the magnetic nanoparticle (MNPs) has gained considerable attention both in industrial and scientific research. Very recently, Sajjadifar*et al*. employed MNPs for the synthesis of highly functionalized tetrahydropyridine (**13**). They presented a strategy utilizing Ag, Ni^{2+}, and Fe^{2+} immobilized on hydroxyapatite-core-shell γ-Fe_2O_3 nanoparticles (γ-Fe_2O_3@HAp-Ag, γ-Fe_2O_3@HAp-Ni^{2+}, and γ-Fe_2O_3@HAp-Fe^{2+}), as a recyclable and reusable Lewis acid catalyst in the one-pot multicomponent reaction of aldehyde (**10**), amine (**11**) and β-ketoester (**12**) in ethanol at room temperature, furnishing excellent yields (82-93%) [38] (Scheme 1b).

Another use of nanoparticles as catalysts was reported by M. Daraei*et al*. where he described the use of nano-sphere silica sulfuric acid (NS-SSA) as an effective catalyst in a five-component reaction of aldehydes, amines, and β-ketoesters to get the desired product (**13**) in acetonitrile (CH_3CN) under reflux conditions. Due to its unique properties such as selectivity, efficiency, and detailed workup, it is proved to be a very efficient catalyst in terms of high yields (74-92%), atom economy, selectivity, and environmentally friendly as it reduces the number of synthesis steps [39] (Scheme 1b).

Further, $Al_2O_3/BF_3/Fe_3O_4$ based magnetic nanoparticle (MNPs) has been employed in the one-pot multicomponent synthesis of poly-substituted tetrahydropyridines (**13**) reported by E. Babaei and B. B. F. Mirjalili. This reaction was done in solvent-free condition at 80°C and gave a very high yield (75-85%) of functionalized THPs (**13**). The most attractive feature of this catalyst lies in its easy and less complex preparation. Moreover, no special care is required for its storage as it retained its catalytic activities at ambient temperatures [40] (Scheme1b).



Scheme 1b. Synthesis of 1,2,3,6-tetrahydropyridines using nanoparticles as catalysts.

Based on the effectiveness of nanoparticles as a catalyst, S. A. Fazeli-Attar *et al*. have developed an exciting methodology for the diversified synthesis of THPs (**13**). This methodology developed a nano-BF_3/Cellulose solid acid

catalyst by the chemical interaction of nano cellulose and BF_3 Lewis acid. This nano-BF_3/Cellulose solid acid acts as an excellent biocompatible catalyst permitting an easy and effective route for the one-pot synthesis of highly functionalized tetrahydropyridine (67-90% yield) (**13**) under solvent-free reaction conditions [41] (Scheme 1b).

As a continuation of using nanoparticles as a catalyst, Mirjalilie*t al*. further reported an environmentally benign and productive approach for the synthesis of highly functionalized THPs (75-93%) (**13**) in the presence of nano-$TiCl_2$/Cellulose in the solvent-free reflux conditions [42] (Scheme 1b). This biodegradable catalyst was highly efficient because of the high interaction between OH groups of D-glucose units of cellulose and $TiCl_4$.

Again, a new methodology was described by Sharghie *et al*., where nanosheets of $AlPO_4(SO_3H)$ were used as a solid acid catalyst. These nanosulfonated-$AlPO_4$ nanosheets work efficiently in the synthesis of highly functionalized substituted THPs (**13**) by catalyzing the reaction of aldehyde (**10**), amine (**11**), and β-ketoester (**12**) in acetonitrile under reflux conditions. The use of nanosheets as a catalyst in this methodology provided several advantages such as very high yield (85-95%), easy recovery of product, no use of column chromatography, high yield, and easy management under mild reaction conditions [43] (Scheme 1b).

Further, an efficient protocol was presented by Eshghi and coworkers, where they demonstrated the use of [Fe@Si-Gu-Prs], a new hybrid nanomagnetic catalyst formed by the adsorption of Preyssler heteropoly acid on the surface of Fe_3O_4 magnetic nanoparticles, for the generation of functionalized THPs (**13**). The reaction was performed in the absence of any hazardous solvents under mild reaction conditions at room temperature for 50 minutes to afford the product in high yield (90-96%). This catalyst's high catalytic activity and easy isolation made it highly suitable for this protocol [44] (Scheme1b).

2.1.3 Synthesis of Polysubstituted-1,2,3,6-Tetrahydropyridine Derivatives Using Miscellaneous Catalysts

Along with the use of Lewis acid catalysts and nanomaterial-based catalysts, miscellaneous catalysts were also used for the one-pot multicomponent synthesis of 1,2,3,6-tetrahydropyridine derivatives (**1**).

An effective attempt was made by Patil *et al*. where they used Copper (II) triflate [$Cu(OTf)_2$] as a catalyst in a one-pot five-component reaction of substituted aldehydes (**10**) and aromatic amines (**11**) with β-ketoesters (**12**) at room temperature leading to an excellent yield (84-92%) of the desired product (**13**). The use of mild & clean reaction conditions, less complex workup, and no use of column chromatography were some of the prominent features of this protocol. Moreover, the catalyst shows good reusability, making it further beneficial for the reaction [45] (Scheme 1c).

Further, Khan and coworkers demonstrated the use of 2,6-pyridine dicarboxylic acid (2,6-PDCA) as a catalyst in methanol at room temperature to synthesize THPs (**13**). 2,6-PDCA, also known as dipicolinic acid, is an organo-catalyst and a weak protic acid. It activates the reacting substrate by proton donation as well as by H-bonding. Due to its non-metallic nature, solubility, lower toxicity, air stability, readily available, and cost-effectiveness, it is a significant catalyst for synthesizing THPs. The mentioned strategy offered the desired products with high purity and excellent yields (74-85%) within a short reaction time [46] (Scheme 1c).

Gupta and coworkers demonstrated another essential methodology. This protocol has described an effective and practically applicable route for synthesizing polysubstituted pyridine derivatives (86-94% yield) (**13**) promoted by a potential carbo-catalyst, graphene oxide, under reflux conditions. The attractive features of this protocol include eco-friendly and recyclability of catalyst, easy accessibility of reagents, and simple workup [47] (Scheme 1c).

Further, a proficient and straightforward methodology for forming functionalized tetrahydropyridines (**13**) via multicomponent reaction was developed by Sajadikhah and coworkers. In this process, 20 mol% of an acidic ionic liquid - N^1,N^1,N^2,N^2-tetramethyl-N^1,N^2-bis(sulfo)ethane-1,2-diamine chloride ([TMBSED][Cl]$_2$) in 3 mL of methanol was used at room temperature, providing moderate to good yields (78-94%). The catalyst used gave very high atomic efficiency and can be prepared by easily accessible and less expensive materials [48] (Scheme 1c).

Another effective protocol has been developed by Harichandran*et al*. where they used a mixture of iodine, potassium iodide, and anion exchange Amberlite–resin (Cl) in the reaction system consisting of aldehyde (**10**), amine (**11**) and beta-ketoester, (**12**) in ratio 2:2:1 respectively. This reaction system of resin and reagents was stirred at room temperature in the presence of 10 mL of methanol, leading to the formation of piperidine derivatives (62-85% yield) (**13**) in a facile and effective way [49] (Scheme 1c).

In the direction of using effective catalysts for the synthesis of highly functionalized THPs (**13**), Parvin *et al.* have demonstrated the use of (±)-camphor–10–sulfonic acid as organo-catalyst under neat conditions at room temperature. The catalyst used is advantageous in the sense of being eco-friendly and highly effective in providing good product yields (62-80%) [50] (Scheme 1c).

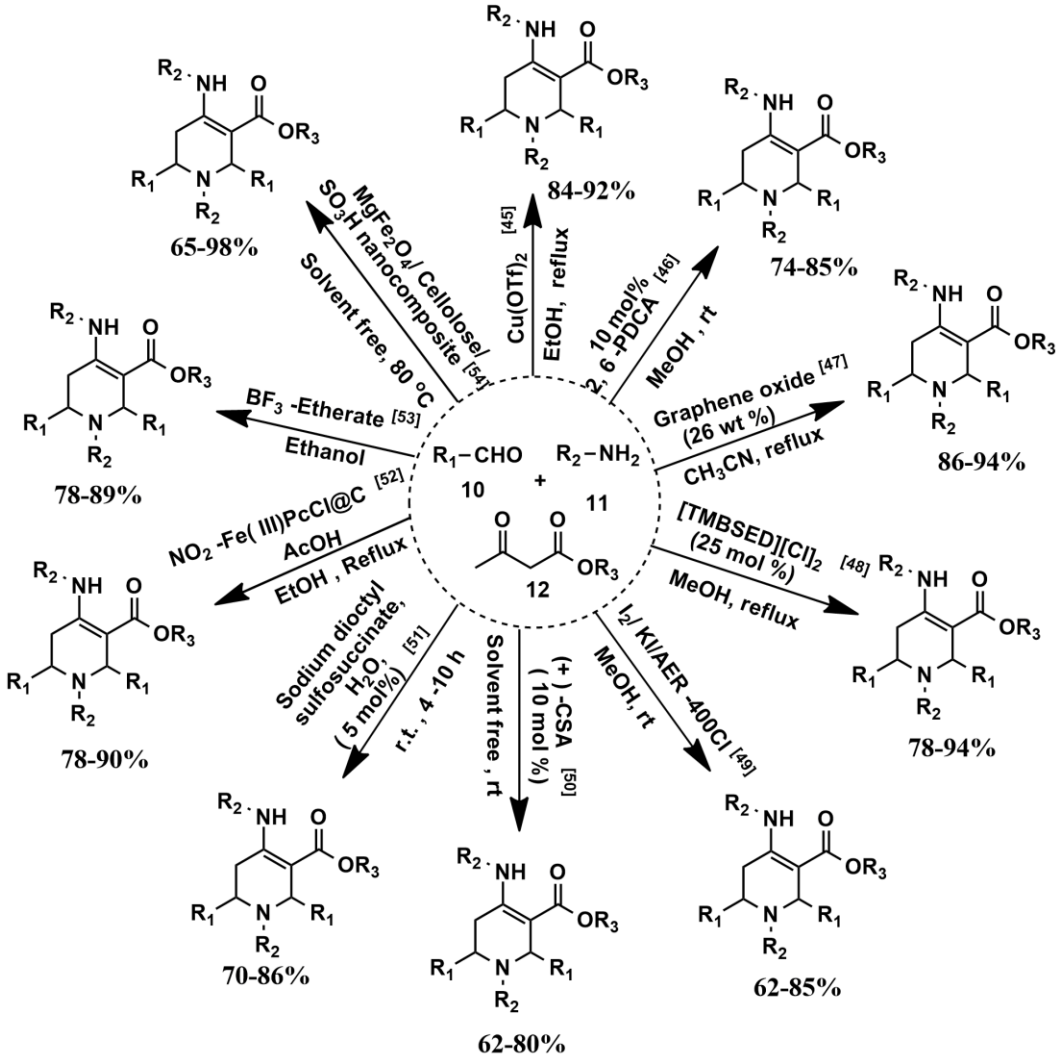
Parikh and his group made the next attempt to report the one-pot synthesis of functionalized tetrahydropyridine derivatives (**13**) through inter and intra-molecular Mannich reaction. For this, they used 5 mol% of sodium dioctyl sulfosuccinate (SDOSS), an anionic surfactant in an aqueous medium at room temperature [51] (Scheme 1c). The anionic surfactant sodium dioctyl sulfosuccinate exhibited very good catalytic activity affording the desired product in moderate to good yields (70-86%). However, another anionic surfactant, sodium dodecyl sulfate (SDS), gave a poor yield.

Further, another synthetic approach for the generation of 1,2,5,6 tetrahydropyridine derivatives (**13**) was given by Wang *et al*., where they used catalytic amount (5-6 mol%) of NO_2–Fe(III)PcCl@C in a solvent mixture of 20 mL anhydrous ethanol and 5 to 6 drops of glacial acetic acid under reflux condition for 2 hours. The desired products are observed in good to high yields (78-90%) [52] (Scheme 1c).

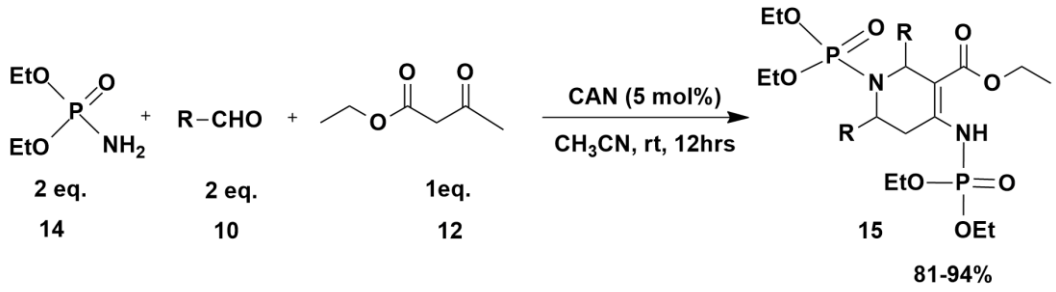
Later, Naidu and his coworkers reported a similar methodology catalyzed by boron trifluoride (BF_3)-etherate furnishing functionalized 1,2,5,6-tetrahydropyridine derivatives (**13**) in good yield (78-89%) under reflux condition in ethanol [53] (Scheme 1c).

Recently, Malekie*t al*. has demonstrated a novel route for synthesizing polysubstituted THPs (**13**) employing in-situ synthesized $MgFe_2O_4$/ cellulose /SO_3H nanocomposite as catalyst under reflux and solvent-free reaction conditions. The desired product was obtained by adding the ethyl acetate, and the catalyst was retrieved using an external magnet [54] (Scheme 1c). It has been observed that the combination of $MgFe_2O_4$, cellulose, and sulfonic acid makes them an attractive solid-supported acid catalyst for the

synthesis of the desired product (**13**). They have also shown that the newly synthesized eco-friendly and magnetically recyclable composite heterogeneous nanocatalyst offers significant advantages, including high yields of products (65-98%), short reaction times, mild conditions, and easy workup procedures, green method, and solvent-free conditions.



Scheme 1c. Synthesis of 1,2,3,6-tetrahydropyridines using various other catalysts.



R = 4-$NO_2C_6H_4$, 4-ClC_6H_4, 3-Br,2-F-C_6H_3, 4-OHC_6H_4, 4-$OMeC_6H_4$, 2,6-$(Me)_2C_6H_3$, 4-N-$(CH_3)_2C_6H_4$, 2-thiol

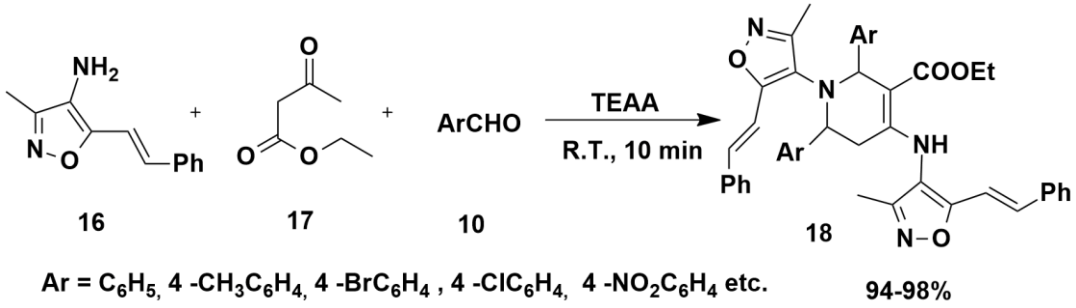
Scheme 2. Synthesis of 1,2,5,6-tetrahydropyridine-3-carboxylate derivatives.

In continuation of the synthesis of 1,2,3,6-THPs (**13**), another efficient effort was made by Reddy and his group, who introduced an inexpensive and environmental friendly ceric ammonium nitrate (CAN) as organocatalyst in the five component reactions of diethylphosphoramidate (2 mmol) (**14**), different aldehydes (2 mmol) (**10**) and 1, 3–dicarbonyl components (1 mmol) (**12**) in acetonitrile at room temperature (**15**). The key features of this reaction were high yield (81-94%), low energy input, readily available starting materials, and no additional requirement of column for purification of derivatives produced [55] (Scheme 2).

2.2 Three-Component Synthesis of 1,2,3,6-Tetrahydropyridines

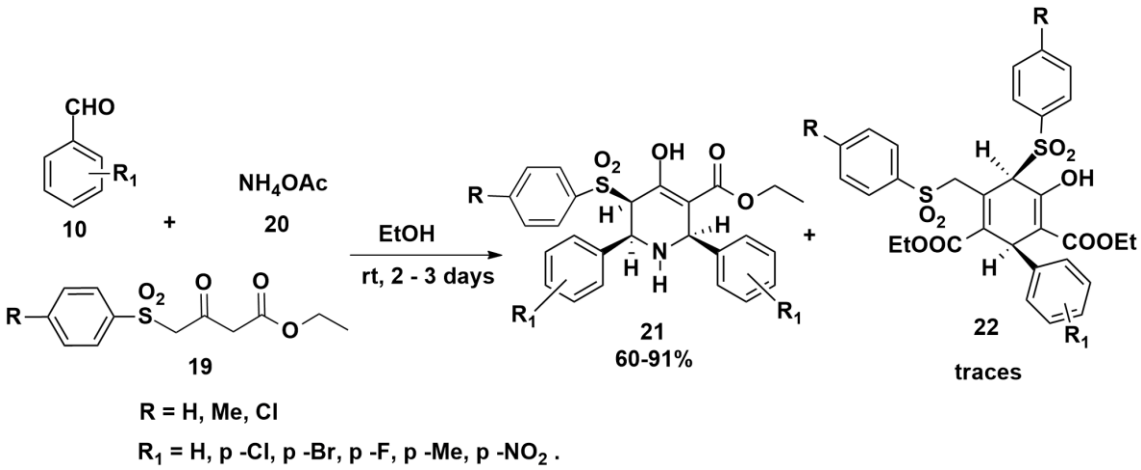
Various synthetic approaches have been reported in the literature to synthesize 1,2,3,6-tetrahydropyridine derivatives via one-pot three-component reactions. I

In this direction, a greener approach for synthesizing highly functionalized tetrahydropyridines was made by Rajanarendar and his group. Here, they did the reaction of isoxazole amine (**16**) with ethyl acetoacetate (**17**) and aldehyde (**10**) in an ionic liquid (ILs) triethylammonium acetate (TEAA) at room temperature leading to the formation of bis-isoxazolyl-1,2,5,6-tetrahydropyridine-3-carboxylates (**18**) in high yields (94-98%) [56] (Scheme 3). Good thermal and mechanical stabilities of supported reagents, easy handling, low toxicity, non-corrosive, easily separable, and reusability of TEAA made it a suitable catalyst for this methodology.



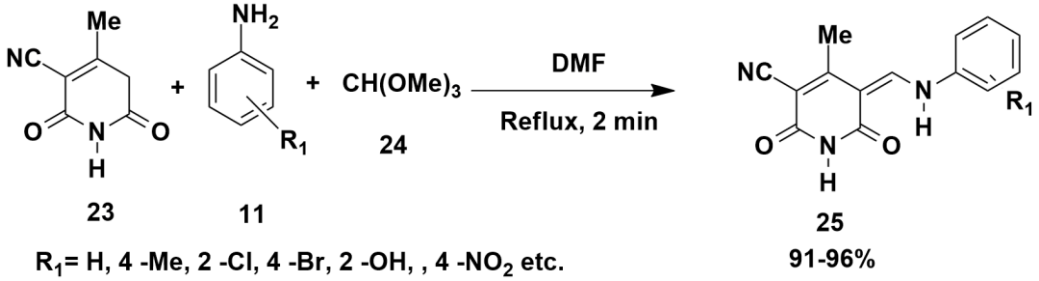
Scheme 3. Synthesis of bis-isoxazolyl-1,2,5,6-tetrahydropyridine-3-carboxylate derivatives.

Further, a very effective stereoselective synthesis of highly functionalized THPs (**21**) was reported by Harikrishnan and his coworkers. In this method, they performed the three-component reaction of aromatic aldehyde **(10**), ethyl-3-oxo-4-(arylsulfonyl) butanoates (**19**), and ammonium acetate (**20**) in a 2:1:2 molar ratio using ethanol at room temperature. They also isolated the traces of cis-cyclohexane-3,6-diene-1,3-dicarboxylate (**22**) along with the desired product (**21**), when **20** were taken in a lesser amount. The amount of **21** highly affects the reaction in terms of yield and product formation. The yield of **21** was only up to 35% when NH_4OAc was taken in 100 mol% [57] (Scheme 4).



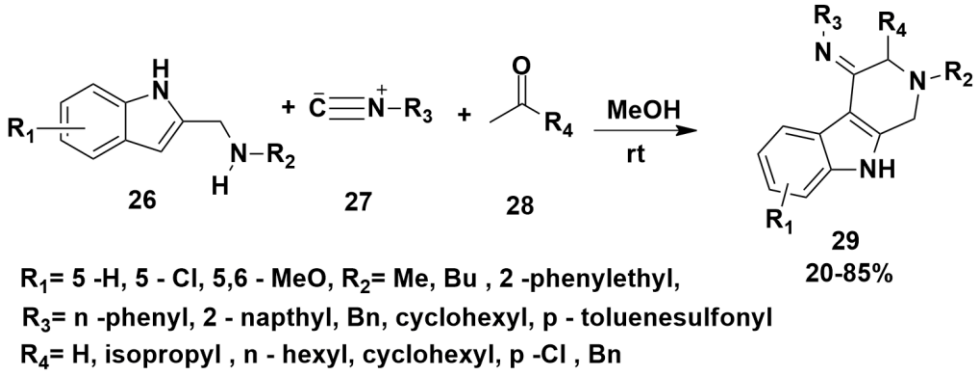
Scheme 4. Synthesis of functionalized 1,2,5,6- tetrahydropyridine derivatives.

The same protocol was further reported by Oshega*et al*. in the absence of catalyst with a slight change in the selection of reaction conditions such as the use of Dimethylformamide under reflux conditions. The use of this reaction condition gave the expected products in good to moderate yield within 2 minutes. Here, the reaction of 4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (**23**) with aromatic amines **(11**) and trimethyl ortho-formate (**24)** was carried out in Dimethylformamide under catalyst-free reflux conditions. This reaction is readily feasible with both electron-donating and electron-withdrawing substituted amines for the synthesis of (Z)-5-(arylamino methylidene)-4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitriles (**25**) in excellent yields (91-96%) with no requirement of further purification [58] (Scheme 5).



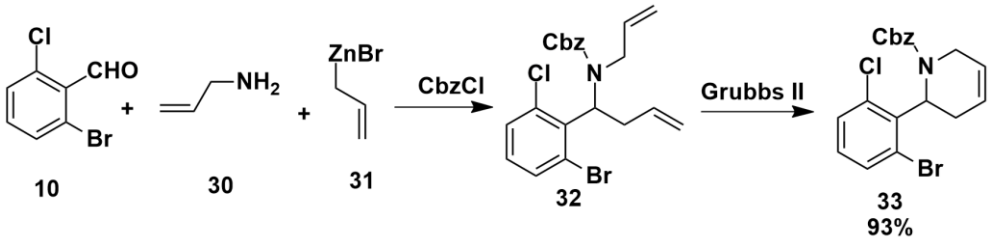
Scheme 5. Synthesis of (Z)-5-(arylaminomethylidene)-4-methyl-2,6-dioxo-1,2,5,6-tetrahydro pyridine-3-carbo-nitriles.

Later, Spisa and his coworkers described a new catalyst-free strategy for the synthesis of functionalized indole derivatives in a catalyst-free atmosphere by a three-component reaction of easily accessible N-alkyl-N-(1*H*-indole-yl methyl) amine (**26**), isocyanide (**27**), and carbonyl compound (**28**) in methanol at room temperature to produce heterologous 1*H*-indole-3-carboxamidines (**29**) in prominent yield (20-85%) [59] (Scheme 6).



Scheme 6. Synthesis of 1*H*-indole-3-carboxamidines.

Further, Sahn *et al.* reported another diversified method for synthesizing high functionalized tetrahydropyridines (93%) (THPs). In this one-pot multicomponent reaction, 2-Bromo-6-chloro benzaldehyde (**10**), allylamine (**30**), allylzinc bromide (**31**) in the presence of an electrophilic substrate Cbz-Cl as a catalyst. The reaction consists of synthesis of a diene (**32**) followed by expected THP-scaffolds (**33**) by cyclization via Mannich reaction and ring-closing metathesis [60] (Scheme 7).



Scheme 7. Synthesis of THPs.

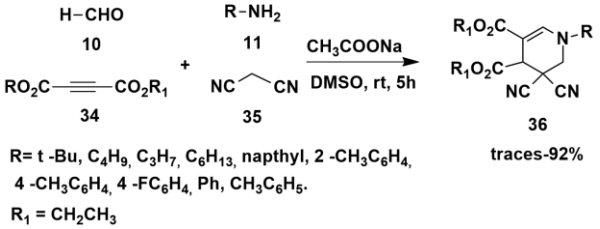
3. Synthesis of 1,2,3,4- or 1,4,5,6-Tetrahydropyridine (THPs)

1,2,3,4-tetrahydropyridine also represented as 1,4,5,6-tetrahydropyridine derivatives. These 1,2,3,4- THPs show significant bioactivities [61] such as anti-arrhythmic agents [62], antibacterial activity [**63**] and insecticidal properties [**64**]. Other than these, 1,2,3,4–tetrahydropyridine derivatives are extensively used in pharmacology and agrology. Due to their wide range of applications, many synthetic approaches have been made to synthesize this class of molecules which are discussed below.

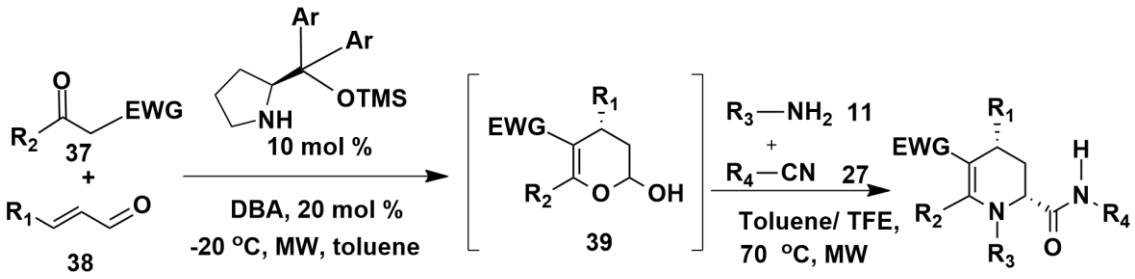
3.1 Four-component Synthesis of Tetrahydropyridine Derivatives

In this direction, a novel attempt was made by Liu and his group, where they described sodium acetate (CH_3COONa) catalyzed four-component reaction of but-2-ynedioic acid diethyl ester (**34**) with malononitrile (**35**), formaldehyde (**10**), and substituted amine (**11**) in DMSO at room temperature. They obtained polysubstituted 1,2,3,4-THPs (**36**) in traces to high yields (traces-92%). This methodology gave the desired products for all the types of substitutions, electron-withdrawing, electron-donating, and electron-neutral except 4-methoxy and 3,4- dimethyl aromatic amines [65] (Scheme 8). Inexpensive, non-toxicity and readily availability of sodium acetate made it a suitable catalyst for this protocol.

Further, an essential four-component reaction for the stereoselective synthesis of penta-substituted THPs (40) was reported by Echemendıa et al. In this methodology, reactions of a carbonyl compound (**37**) and conjugated enol (**38**) with isocyanide (**27**) and amines (**11**) were done in the presence of trifluoroethanol (TFE) or toluene under microwave-assisted irradiation conditions [66] (Scheme 9). Initially, they synthesized the intermediate product hemiacetal (not isolated) (**39**) using 10 mol% organocatalysts and 20 mol% of 3,5-dinitrobenzoic acid via the reaction of carbonyl compounds (**37**) and enol (**38**) at −20°C, then **11** and **12** were added to the reaction mixture to afford the product **40** in moderate to good yield (55-78%).



Scheme 8. Synthesis of polysubstituted 1,2,3,4-tetrahydropyridine derivatives.

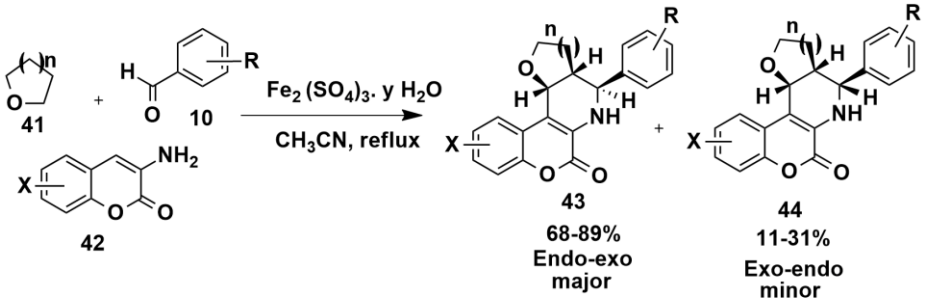


Ar= 3,5 -(CF_3)-C_6H_5, EWG= CN. R_1= Ph, o -$NO_2C_6H_4$, p -BrC_6H_4, o -BrC_6H_4 etc.
R_2= Ph, p -$MeoC_6H_4$, p -BrC_6H_4 etc. R_3= t -Bu, 2 - IC_6H_4.
R_4= t -Bu, -$CH_2CONHAllyl$, Ph, C_6H_{11}

Scheme 9. Synthesis of enantio and diastereoselective penta-substituted pyridine derivatives.

3.2 Three-component Synthesis of Tetrahydropyridines

There have been several methodologies known in the literature for the synthesis of 1,2,3,4-THPs via one-pot three-component reactions. Das and coworkers reported one of the efficient and straightforward strategies in which they synthesized highly substituted THPs ring fused heterocycles **43** (68-89%) and **44** (11-31%). This Povarov reaction involves the reaction of cyclic enol ethers (**41**), aryl aldehydes (**10**), and substituted aryl-3-amino-coumarins (**42**) which were refluxed in the presence 10 mol% of hydrated ferric sulfate [$Fe_2(SO_4)_3$ .y H_2O] catalyst in acetonitrile furnished the desired products in moderate to very high yields [**67**] (Scheme 10). In this methodology, they proved the usefulness of hydrated ferric sulfate [$Fe_2(SO_4)_3$.yH_2O] as an effective heterogeneous, inexpensive, readily available catalyst in terms of reaction time and yield with good diastereoselectivities like other Lewis acids catalyzed Povarov reactions.

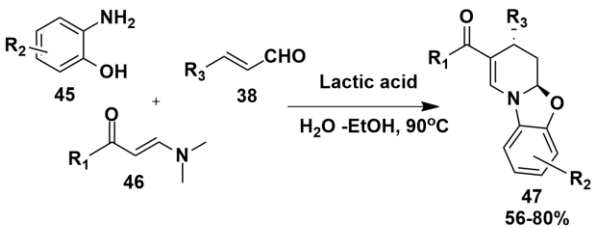


Ar = Ph , 4 - BrC_6H_4, 4 -$OMeC_6H_4$, 4 -MeC_6H_4, 4 -FC_6H_4, 4 -ClC_6H_4, 2 -furfuryl etc.
R = H, Br, NO 2,OMe.
X= H, NO_2, Br, OCH_3

Scheme 10. Synthesis of diastereoselective THPs.

Another convenient three-component approach was described by Wan *et al*. for the synthesis of structurally diversified diastereoselective fused tetrahydropyridine ring (**47**) by using Lactic acid as a non-toxic and bio-available catalyst. In this methodology, they carried out the reaction of *o*-aminophenols (**45**), *α,β*–unsaturated aldehydes (**38**), and enaminone or nitroenones (**46**) in the presence of lactic acid as a sustainable bio-based promoter in ethanol-water solvent mixture under reflux conditions [68] (Scheme 11). Due to the inherent greenness of lactic acid, it proved to be a suitable catalyst for the synthesis of this class of products in good yield (56-80%) in a short reaction time with excellent diastereoselectivities.

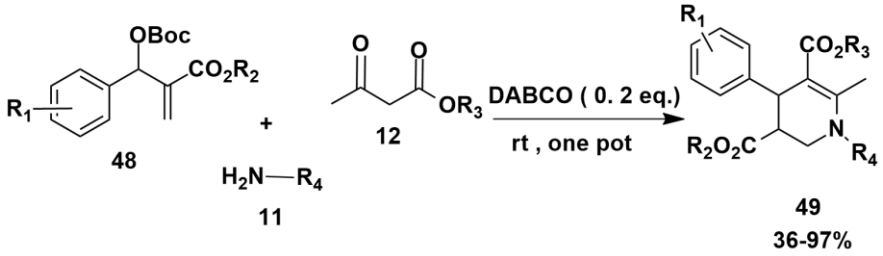
The next attempt for the synthesis of highly functionalized 1,2,3,4-tetrahydropyridine derivatives was prepared by Wei and his group with a diastereomeric ratio (anti: syn = 50:50). Herein, they did the three-component reaction of Morita-Baylis-Hillman carbonate (**48**) with 1,3-ketoesters **(12)** and primary amines (**11**) in the presence of DABCO in dichloromethane at room temperature. The reaction took place via a one-pot [3+2+1] annulations mechanism and gave 4-aryl-1,2,3,4-tetrahydropyridines (**49**) [69] (Scheme 12). DABCO was found suitable for this transformation because the inexpensiveness, eco-friendliness, high reactivity, easy handling, and non-toxic nature lead to affordable products (**49**) in low to excellent yields (36-97%) high selectivity.



R_1 = Me, Ph, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 2-$CH_3C_6H_4$ etc.
R_2= H, 4-Me, 5-Cl R_3 = Ph, 4-$MeOC_6H_4$, 3-MeC_6H_4

Scheme 11. Synthesis of diversified diastereoselective fused tetrahydropyridine ring.

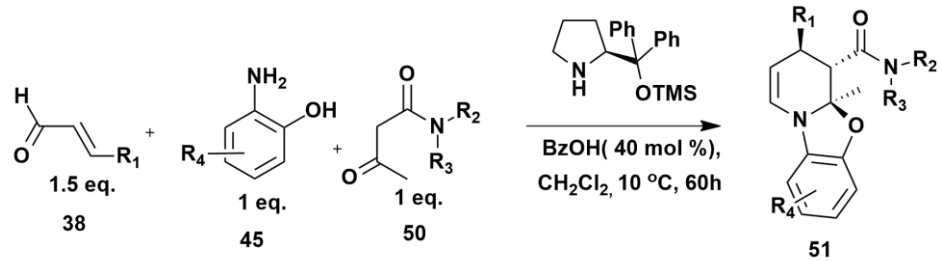
Recently, another efficient three-component reaction of β-ketoamide (1 eq.) (**50**), aromatic aldehydes (1.5 eq.) (**38**), and functionalized aminophenols (1 eq.) (**45**) were described by Bugaut and coworkers. Here, they used 20 mol% of Hayashi-Jørgensen catalyst for synthesizing polycyclic functionalized substituted tetrahydropyridines **51** at 10°C with high enantioselectivity low diastereoselectivity [70] (Scheme 13). However, modifying reaction conditions such as (i) adding benzoic acid (BzOH) as a co-catalyst (ii) increasing the catalyst loading to 20 mol% and extending the reaction time (iii) carrying out the reaction at 10°C, improved the results. In short, they prepared the desired product with good enantioselectivities and high diastereoselectivities under thermodynamic control.



R_1= 4 - NO_2 , 4 -CN, 4 -MeO, 4 -AcHN, 3 -Br, 3 -MeO etc.

R_2= Me, R_3= Et, R_4= Me, Bn, PMB, C_2H_4Ph.

Scheme 12. Synthesis of 4- Aryl-1,2,3,4-tetrahydropyridine.



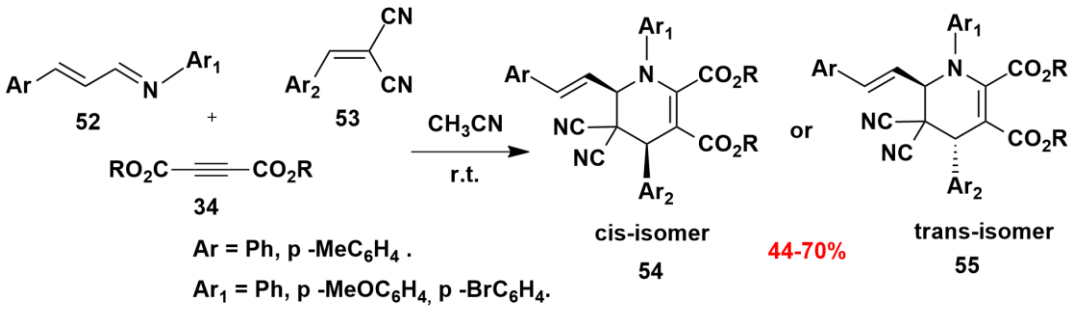
R_1 = Ph, 4 -MeC_6H_4, 4 -$MeOC_6H_4$, 4 -FC_6H_4, 4 -ClC_6H_4, 4 -BrC_6H_4.

R_2 = Me,Bn , R_3 = OMe, Me, Bn .

R_3 = H, 4 -Cl, 5 -Cl, 4 -Me, 5 -Me, 4,5 -$(CH)_4$

Scheme 13. Synthesis of Stereoselective polycyclic 1,2,3,4- tetrahydropyridines.

In another approach, Yan and his group have developed a simple and efficient method to synthesize a new series of 6-styryl-1,4,5,6-THPs (**54, 55**) in excellent cis/trans isomeric ratios. In this strategy, they synthesized styryl-1,4,5,6-THPs derivatives via three-component [2+2+2] cycloaddition reaction occurring among *α,β*-unsaturated-*N*-arylaldimines (1.0 mmol) (**52**), arylidenemalononitriles (1.0 mmol) (**53**) and dialkyl-acetylene-dicarboxylates (1.0 mmol) (**34**) in dry acetonitriles at room temperature within 24 hours [71] (Scheme 14).



Ar = Ph, p -MeC_6H_4 .

Ar_1 = Ph, p -$MeOC_6H_4$, p -BrC_6H_4.

Ar_2 = Ph, p -MeC_6H_4,p -$NO_2C_6H_4$,p -$MeOC_6H_4$,m -$MeOC_6H_4$,m -ClC_6H_4.

R = CH_3

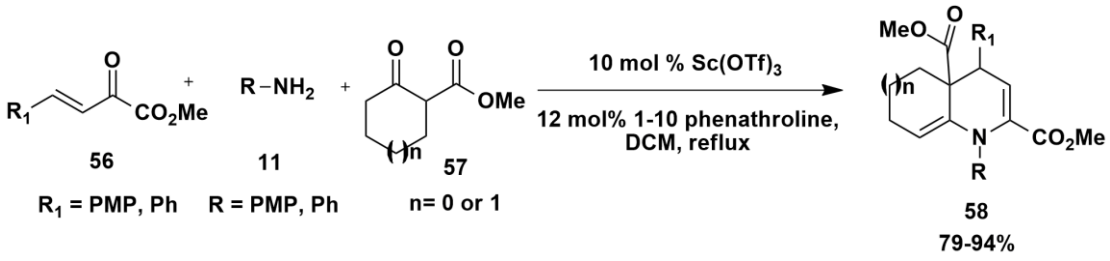
Scheme 14. Synthesis of funtionalized 6- Styryl-1,4,5,6- tetrahydropyridines.

The characteristic feature of this protocol is the production of desired products in satisfactory yield (44-70%) with different isomeric ratios such as 40:60, 25:75, 45:55, 47:53, etc. (Cis: Trans) by using mild reaction conditions.

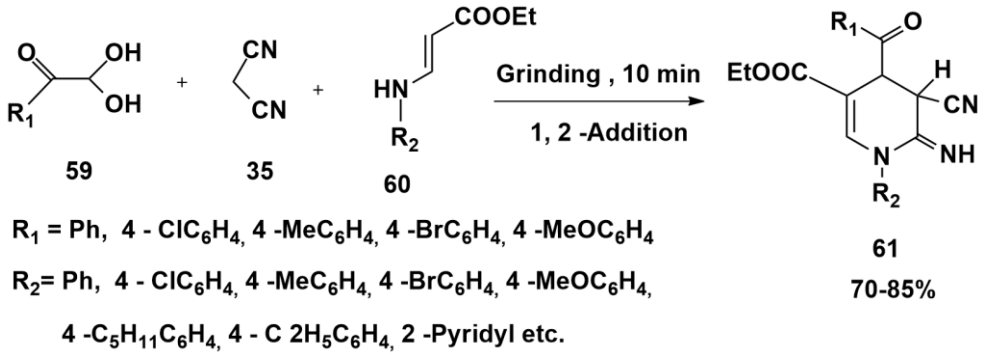
Further effort was made by Liu and his group, which led to the introduction of an important and influential methodology for the synthesis of bicyclic fused tetrahydropyridine derivatives (**58**) via one-pot three-component reaction of *β, Y-* unsaturated α-ketoesters (**56**), arylamines (**11**) and 1,3- dicarbonyl (**57**) compound using Scandium triflate [$Sc(OTf)_3$] as a catalyst. The reaction is catalyzed by refluxing substrates with Scandium triflate in

the presence of 12 mol% of 1-10-phenanthroline and 2 mL DCM in an argon atmosphere. Although this protocol was quite effective as the less expensive starting materials were utilized, providing product in good to high yield (79-94%) but with one drawback that it required column chromatography for purification of product, which made this strategy more complex and time-consuming [72] (Scheme 15). The catalyst Scandium triflate proved to be very active in enhancing the cyclization process during the reaction.

In the efforts of preparing a range of polysubstituted THPs (**61**), Dhinakaran and his group synthesized an effective and chemically selective synthesis with good yields (70-85%) by one-pot multicomponent reaction of ethyl (*E*)-3-(aryl/alkyl amino) acrylates (**60**), malononitrile (**35**) and 2,2-dihydroxy-1-arylethan-1-ones (**59**) under catalyst- and solvent-free grinding conditions. The reaction took place via transformation of products involving Michael addition, Knoevenagel reaction followed by intramolecular cyclization [73] (Scheme 16). However, the reaction scheme selectively produces only the sole type of diastereomers despite two adjacent stereocentres.



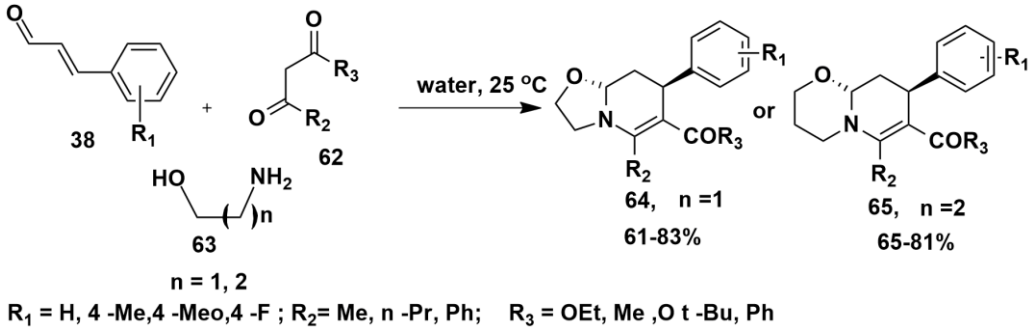
Scheme 15. Synthesis of bicyclic fused 1,2,3,4- tetrahydropyridine derivatives.



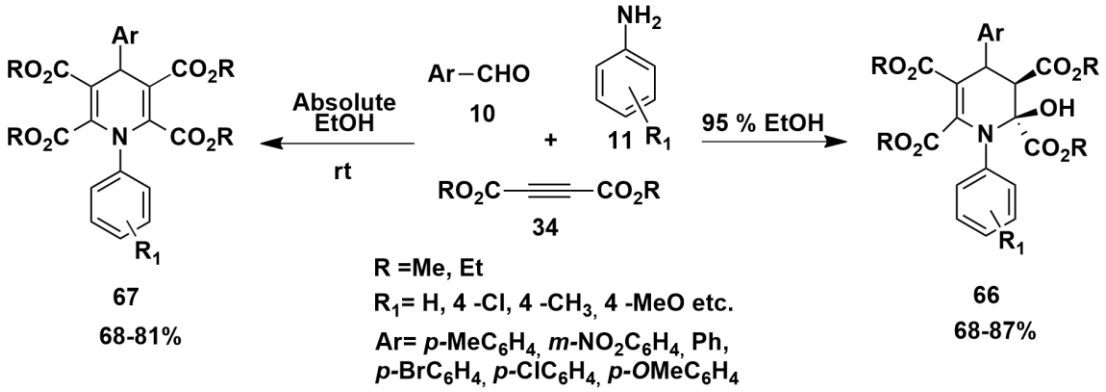
Scheme 16. Synthesis of polysubstituted THPDs.

Another three-component reaction of *α,β*-unsaturated aldehyde (**38**), 1,3-dicarbonyl (**62**), and amino-alcohols (**63**) to produce fused tetrahydropyridines **64** (61-83%) and **65** **(65-81%)** in the presence of water as green solvent at room temperature was reported by Vellaisamy and coworkers. They did a domino series of reactions involving Michael addition and intermolecular cyclization steps producing oxazolo[3,2]pyridine and pyrido[2,1][1,3]oxazines with excellent diastereoselective features along with two heterocyclic rings and four bonds consisting of two C-N, one C-O, and one C-C bond [74] (Scheme 17). The use of water as a catalyst makes this strategy environment-friendly.

A three-component one-pot reaction was further introduced by Yan *et al.* where they did the reaction of aromatic aldehyde (**10**), arylamine (**11**), and dialkylacetylenedicarboxylate (**34**), producing two different pyridine isomers with slight concentration changes of ethanol. The mechanism suggested that the reaction took place via the formation of an intermediate, i.e., hydroamination adduct formed by a nucleophilic attack of amines on alkynes. Absolute ethanol leads to the generation of 1,4−dihydropyridines **67** (68-81%), whereas on using diluted ethanol, tetrahydro-pyridines **66** (68-87%) were obtained [75] (Scheme 18). However, the reaction time was longer, as it took 2 days to complete the reaction at room temperature, but the yield was very high. This reaction shows a broad range of substrate scope.

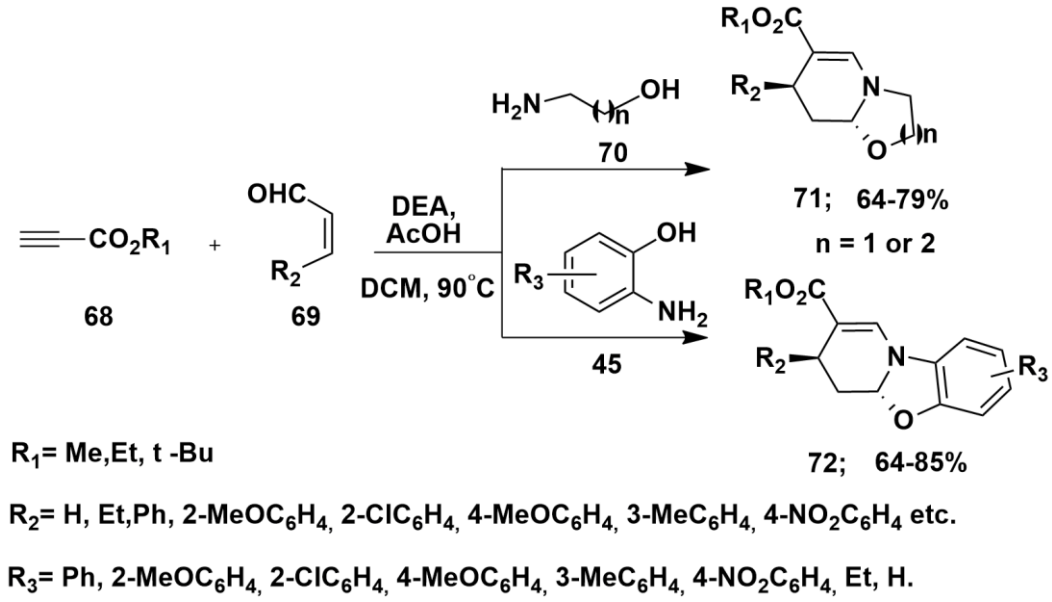


Scheme 17. Synthesis of fused tetrahydro-pyridine derivatives.



Scheme 18. Synthesis of substituted 1,2,3,4- tetrahydropyridines.

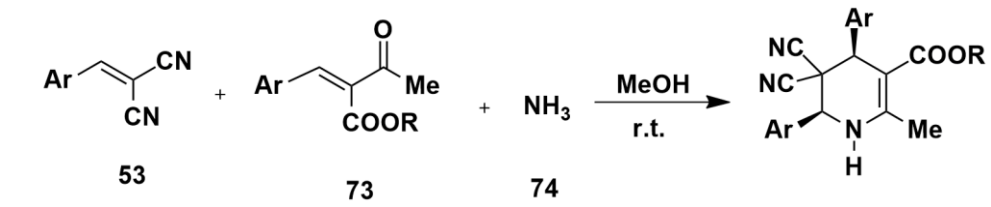
Wan and group have explored a very effective one-pot multicomponent methodology for the synthesis of substituted fused tetrahydropyridines (**72**). In this methodology, they did the reaction of electron-deficient alkynes **68** with enals (**69**) and hydroxyl-functionalized primary amines (**70**, **45**) under reflux conditions in various solvating agents like 1,2 dichloroethane (DCE) and diethanolamine (DEA) at 90°C for 12 hours to synthesize substituted dihydro-3*H*-benzo[4,5]oxazolo[3,2-a] pyridines **71** (64-79%) and tetrahydro-2H-oxazolo[3,2-a]pyridines **72** (64-85%) providing excellent diastereoselective qualities [76] (Scheme 19). Diethanol amine (0.03 mmol) with acetic acid (0.18 mmol) in 2 mL 1,2-dichloroethane (DCE) was proved to be an efficient catalyst for this scheme to generate reactive enamine intermediates during the chemical interaction of DEA with alkynes. The characteristic feature of this method was high yields, less reaction time, readily available starting material and use of cheap catalyst which made this method valuable and economical.



Scheme 19. Synthesis of diverse Ring –fused tetrahydropyridine derivatives.

During the preparation of stereoselective tetrahydropyridines, another facile and straightforward one-pot multicomponent synthesis of (4*RS*, 6*RS*)-4,6-diaryl-5,5-dicyano-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylates (**75**) was reported by Vereshchagin and coworkers, using ammonia. Ammonia used here performed dual functionality, one as a reactant and another as a catalyst. Herein, the starting materials employed were benzylidene-malononitrile (3 mmol) (**53**), 2-acetyl-3-aryl acrylates (3 mmol) (**73**), and aqueous ammonia (6 mmol) (**74**) in methanol at room temperature for 2-4 hours to get stereoselective tetrahydropyridine derivatives in 55 to 87% yield. The observations drawn here indicate that the reaction proceeded smoothly with the substrate having electron-withdrawing groups rather than the electron-donating groups [77] (Scheme 20).

As a next step ahead, another important approach was made by Blumel and his coworkers where they described a quinine-derived squaramide mediated asymmetric organocatalyzed one-pot three-component synthesis of 1,4,5,6–tetrahydropyridines derivatives **78** (55-87%). For this, they did the reaction of *β*-nitro olefin (**76**), 1,3-dicarbonyl (**50**), and aldimines (**77**) via Michael/Aza-Henry/Cyclization process to synthesize the desired products [78] (Scheme 21). The squaramide used as a catalyst efficiently forms the Michael adduct by a Michael addition reaction of dicarbonyl on nitroalkenes followed by aza–henry condensation between the addition adduct formed earlier imine. The key points of this scheme were the formation of product in good diastereoisomeric ratios, significant enantioselectivities, and the presence of neighboring stereogenic centers with extremely low catalytic loading.

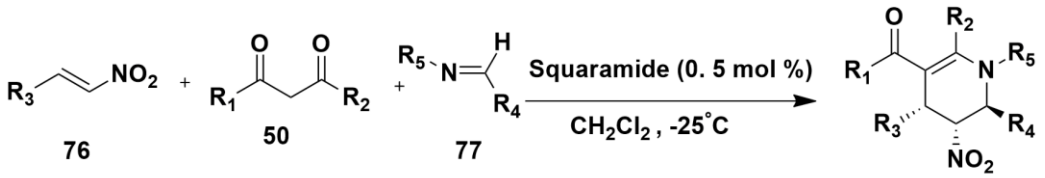


R = Me, Et

Ar = Ph, 4 -FC_6H_4, 4 -MeC_6H_4, 4 -BrC_6H_4, 2 -ClC_6H_4, 4 -$MeOC_6H_4$, 4 -ClC_6H_4, 4 -$NO_2C_6H_4$.

Scheme 20. Synthesis of (4*RS*, 6*RS*-4,6-diaryl-5,5-dicyano-2-methyl-1,4,5,6-tetrahydro pyridine -3-carboxylates.

In exploring multicomponent asymmetric cascade reaction, Yu *et al.* offered an entirely new strategy for synthesizing functionalized THPs utilizing *L*- Proline as an effective organocatalyst. This scheme employed an aldehyde (**10**), amine (**11**), and *β*-ketoester (**12**) as the starting materials for the synthesis of 1,2,3,4-THPs (**79**) (24-65%) using a catalytic amount of organocatalyst *L*-proline subjected to the stirring at 16˚C in THF. The function of the catalyst was to generate a reaction intermediate via the knoevenagel process and then convert it into an iminium ion which further undergoes reaction. The notable features of this protocol were excellent enantioselective properties, less reaction time, and mild reaction conditions. Additionally, the THPs obtained have three C-C bonds and two C-N bonds combined with an all-carbon quaternary stereocenter [79] (Scheme 22). The effectiveness of this reaction lies in the fact that this scheme was practically easy to perform and gave products in a single operation utilizing easily accessible market reagents.

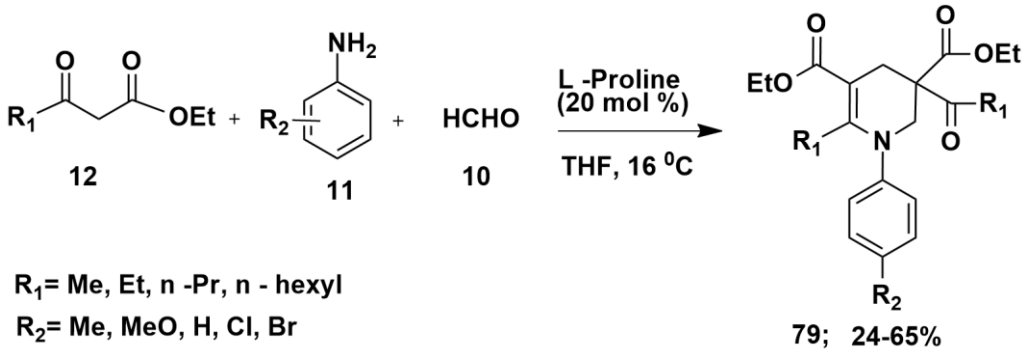


R_1 = Me, OMe, OEt, Ph; R_2= Me

R_3 = Ph, p -MeC_6H_4, p -FC_6H_4, p -ClC_6H_4, 2 -thionyl, Cy

R_4 = Ph, p -MeC_6H_4, p -BrC_6H_4, 2 -furanyl; R_5 = Me, PMB

Scheme 21. Synthesis of organocatalytic one-pot asymmetric 1,4,5,6–tetrahydropyridines derivatives.



R_1= Me, Et, n -Pr, n - hexyl

R_2= Me, MeO, H, Cl, Br

Scheme 22. Synthesis of functionalized THPDs via organocatalytic asymmetric multicomponent cascade reaction.

4. Synthesis of 3,4,5,6- or 2,3,4,5-Tetrahydropyridines

Not many investigations have been reported on the synthesis and analysis of biological activities of 3,4,5,6-tetrahydropyridine (also known as 2,3,4,5-tetrahydro pyridine). However, most of the research in this field showed that these isomeric tetrahydropyridine derivatives work as simulators for Muscarinic receptors.

In 1994, Phillip *et al.* worked on synthesizing 2- amino-(methoxycarbonyl)-3,4,5,6-tetrahydropyridine and evaluated its neurochemical activity. They found that the compounds of these derivatives function as an efficient agonist for M_1 muscarinic receptors [80].

5. Conclusions

This review paper discussed the diverse isomeric forms of highly functionalized tetrahydropyridine being synthesized via multicomponent reactions utilizing various effective and efficient catalysts. A long list of influential and green discoveries regarding the nature of catalysts and significantly more advantageous reaction conditions in the

field of MCRs synthesizing highly functionalized tetrahydropyridines were reported in the past few years and are increasing progressively. All these efforts head towards an eco-friendly and benign path leading to sustainable developments in the future.

Author Contributions

Ajay Thakur: Data-curation, Writing Original-Draft preparation, Ruchi Bharti: Conceptualization, Supervision, Writing-Reviewing and Editing, Project administration, Renu Sharma: Formal Analysis, Validation.

References and Notes

[1] Chen, J.; Cantrell, C. L.; Shang, H. W.; Rojas, M. G. *J. Agric. Food Chem.* **2009**, *57*, 3128. [Crossref]

[2] Kusano, G.; Takahashi, A.; Sugiyama, K.; Nozoe, S. *Chem. Pharm. Bull.* **1987**, *35*, 4862. [Crossref]

[3] Yang, Y. R.; Chang, K. C.; Chen, C. L.; Chiu, T. H. *Chin. J. Physiol.* **2000**, *43*, 23. [Crossref]

[4] Christie, J. E.; Shering, A.; Ferguson, J.; Glen, A. I. *Br. J. Psychiatry* **1981**, *138*, 46. [Crossref]

[5] Harmer, R. A. *Food Chem.* **1980**, *5*, 81. [Crossref]

[6] Barker, D. Pyridines and their Benzo Derivatives: Reactivity of Reduced Compounds. In: Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., eds Oxford: Elsevier, 2008, p. 171.

[7] Glase, S. A.; Akunne, H. C.; Heffner, T. G.; Jaen, J. C.; MacKenzie, R. G.; Meltzer, L. T.; Pugsley, T. A.; Smith, S. J.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 3179. [Crossref]

[8] Ramachandran, P. V.; Burghardt, T. E.; Bland-Berry, L. *J. Org. Chem.* **2005**, *70*, 7911. [Crossref]

[9] Chand, P.; Kotian, P. L.; Dehghani, A.; El-Kattan, Y.; Lin, T. H.; Hutchison, T. L.; Babu, Y. S.; Bantia, S.; Elliott, A. J.; Montgomery, J. A. *J. Med. Chem.* **2001**, *44*, 4379. [Crossref]

[10] Srinivasan, M.; Perumal, S.; Selvaraj, S. *Chem. Pharm. Bull.* **2006**, *54*, 795. [Crossref]

[11] Ramalingan, C.; Park, Y. T.; Kabilan, S. *Eur. J. Med. Chem.* **2006**, *41*, 683. [Crossref]

[12] Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Imbs, J. L. *Eur. J. Med. Chem.* **1991**, *26*, 19. [Crossref]

[13] Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009**, *17*, 625. [Crossref]

[14] Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg, Med. Chem. Lett.* **2007**, *17*, 1206. [Crossref]

[15] Khanum, S. A.; Girish, V.; Suparshwa, S. S.; Khanum, N. F. *Bioorg, Med. Chem. Lett.* **2009**, *19*, 1887. [Crossref]

[16] Aeluri, R.; Alla, M.; Bommena, V. R.; Murthy, R.; Jain, N. *Asian J. Org. Chem.* **2012**, *1*, 71. [Crossref]

[17] Ho, B.; Crider, A. M.; Stables, J. P. *Eur. J. Med. Chem.* **2001,** *36*, 265. [Crossref]

[18] Messer, W. S.; Jr, Abuh, Y. F.; Liu, Y.; Periyasamy, S.; Ngur, D. O.; Edgar, M. A.; El-Assadi, A. A.; Sbeih, S.; Dunbar, P. G.; Roknich, S.; Rho, T.; Fang, Z.; Ojo, B.; Zhang, H.; Huzl, J. J.; Nagy, P. I. *J. Med. Chem.* **1997,** *40*, 1230. [Crossref]

[19] Boger, D. L.; Weinreb, S. M. Hetero Diels-Alder Methodology in Organic Synthesis. Amsterdam: Elsevier, 2012.

[20] Ganem B. *Acc. Chem. Res*. **2009,** *42*, 463. [Crossref]

[21] Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009,** *109*, 4439. [Crossref]

[22] Han, R.-G.; Wang, Y.; Li, Y.-Y.; Xu, P.-F. *Adv. Synth. Catal.* **2008,** *350*, 1474. [Crossref]

[23] Lee, H. S.; Kim, E. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2274. [Crossref]

[24] Takizawa, S.; Inoue, N.; Sasai, H. *Tetrahedron Lett.* **2011**, *52*, 377. [Crossref]

[25] Dömling, A. *Chem. Rev.* **2006,** *106*, 17. [Crossref]

[26] Ahmadi, T.; Mohammadi, Z. G.; Gholamzadeh, P.; Mollabagher, H. *Tetrahedron: Asymmetry* **2017**, *28*, 708. [Crossref]

[27] Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett.* **2010** *51*, 4419. [Crossref]

[28] Aridoss, G.; Amirthaganesan, S.; Kumar, N. A.; Kim, J. T.; Lim, K. T.; Kabilan, S.; Jeong, Y. T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6542. [Crossref]

[29] Brown, B. S.; Keddy, R.; Zheng, G. Z.; Schmidt, R. G.; Koenig, J. R.; McDonald, H. A.; Bianchi, B. R.; Honore, P.; Jarvis, M. F.; Surowy, C. S.; Polakowski, J. S.; Marsh, K. C.; Faltynek, C. R.; Lee, C. H. *Bioorg. Med. Chem.* **2008** *16*, 8516. [Crossref]

[30] Wu, W.; Li, Z.; Yang, G.; Teng, M.; Qin, J.; Hu, Z.; Hou, L.; Shen, L.; Dong, H.; Zhang, Y.; Li, J.; Chen, S.; Tian, J.; Zhang, J.; Ye, L. *Bioorg. Med. Chem. Lett.* **2017,** *27*, 2210. [Crossref]

[31] Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009** *17*, 625. [Crossref]

[32] Mousavi, S. R.; Maghsoodlou, M. T.; Roygar, A.; Lashkari, M. *Res. Chem. Intermed.* **2018**, *44*, 675. [Crossref]

[33] Balijapalli, U.; Munusamy, S.; Sundaramoorthy, K. N.; Iyer, S. K. *Synth. Commun.* **2014** *44*, 943. [Crossref]

[34] Kangani, M.; Hazeri, N.; Yazdani-Elah-Abadi, A.; Maghsoodlou, M.-T. *Polycycl. Aromat. Comp.* **2016,** *38*, 1. [Crossref]

[35] Zhang, X.-X.; Wan, Y.; Pang, L.-l.; Wang, H.-Y.; Zhao, L.-l.; Wang, C.; Wu, H. *J. Heterocycl. Chem*. **2014,** *51*, 442. [Crossref]

[36] Ramachandran, R.; Jayanthi, S.; Jeong, Y. T. *Tetrahedron* **2012,** *68*, 363. [Crossref]

[37] Mali, A. S.; Potnis, C. S.; Chaturbhuj, G. U. *J. Iran. Chem. Soc.* **2018,** *15*, 1399. [Crossref]

[38] Sajjadifar, S.; Rezayati, S.; Shahriari, A.; Abbaspour, S. *Appl. Organometal. Chem*. **2018,** *32*, e4172. [Crossref]

[39] Daraei, M.; Zolfigol, M. A.; Derakhshan-Panah, F.; Shiri, M.; Kruger, H. G.; Mokhlesi, M. *J. Iran. Chem. Soc.* **2015,** *12*, 855. [Crossref]

[40] Babaei, E.; Mirjalili, B. B. F. *Res. Chem. Intermed.* **2018,** *44*, 3493. [Crossref]

[41] Fazeli-Attar, S. A.; Mirjalili, B. B. F. *Iran. J. Catal*. **2019,** *9*, 321. [Link]

[42] Mirjalili, B.; Azad, S.; Bamoniri, A. *Org. Chem. Res*. **2018** *4*, 227. [Link]

[43] Sharghi, H.; Aboonajmi, J.; Aberi, M.; Shiri, P. *J. Iran. Chem. Soc.* **2018,** *15*, 1107. [Crossref]

[44] Eshghi, H.; Khojastehnezhad, A.; Moeinpour, F.; Rezaeian, S.; Bakavoli, M.; Teymouri, M.; Haghbeen, K. *Tetrahedron* **201,** *71*, 436. [Crossref]

[45] Patil, K. N.; Mane, R. A.; Jadhav, S. B.; Mane, M. M.; Helavi, V. B. *Chem. Data Coll.* **2019,** *21*, 100233. [Crossref]

[46] Khan, M. M.; Khan, S.; Iqbal, S.; Saigal; Yousuf, R. *New. J. Chem.* **2016**, *40*, 7504. [Crossref]

[47] Gupta, A.; Kaur, R.; Singh, D.; Kapoor, K. K. *Tetrahedron Lett.* **2017,** *58*, 2583. [Crossref]

[48] Sajadikhah, S. S.; Zare, A.; Hosseini, N. *Org. Chem. Res.* **2019,** *5*, 145. [Crossref]

[49] Harichandran, G.; Amalraj, S. D.; Shanmugam, P. *J. Heterocycl. Chem.* **2013,** *50*, 539. [Crossref]

[50] Bharti, R.; Parvin, T. *J. Heterocycl. Chem.* **2015**, *52*, 1806. [Crossref]

[51] Parikh, N.; Roy, S. R.; Seth, K.; Kumar, A.; Chakraborti, A. K. *Synthesis* **2016,** *48*, 547. [Crossref]

[52] Wang, J.-D.; Lin, Q.-l.; Qiu, J., Gou, X.-F., Hua, C.-W., Zhao, J.-l., Chen, B. *Russ. J. Gen. Chem.* **2017**, *87*, 821. [Crossref]

[53] Naidu, A. A.; Sharma, G. V. R. *Chem. Sci*. **2018,** *7*, 240. [Crossref]

[54] Maleki, A.; Jafari, A. A.; Yousefi, S. *J. Iran. Chem. Soc.* **2017,** *14*, 1801. [Crossref]

[55] Reddy, K. M. K.; Peddanna, K.; Varalakshmi, M.; Reddy, N. B.; Sravya, G.; Zyryanov, G. V.; Reddy, C. S. *Phosphorus Sulfur Silicon Relat. Elem.* **2019,** *194*, 812. [Crossref]

[56] Rajanarendar, E.; Thirupathaiah, K.; Krishna, S. R.; Kishore, B. *Green Sustain. Chem.* **2013**, *3*, 9. [Crossref]

[57] Harikrishnan, P. S.; Rajesh, S. M.; Perumal, S. *Tetrahedron Lett.* **2012,** *53*, 3880. [Crossref]

[58] Oshega, J. S.; Paponov, B. V.; Omelchenko, I. V.; Shishkin, O. V. *Mendeleev Commun*. **2015,** *25*, 133. [Crossref]

[59] La Spisa, F.; Meneghetti, F.; Pozzi, B.; Tron, G. C. *Synthesis* **2015,** *47*, 489. [Crossref]

[60] Sahn, J. J.; Su, J. Y.; Martin, S. F. *Org. Lett.* **2011,** *13*, 2590. [Crossref]

[61] Mohsın, N.; Ahmad, M. *Turk. J. Chem*. **2018,** 42, 1191. [Crossref]

[62] Krauze, A.; Vītoliņa, R.; Garaliene, V.; Sīle, L.; Kluša, V.; Duburs, G. *Eur. J. Med. Chem.* **2005,** *40*, 1163. [Crossref]

[63] Srivastava, B. K.; Solanki, M.; Mishra, B.; Soni, R.; Jayadev, S.; Valani, D.; Jain, M.; Patel, P. R. *Bioorg. Med. Chem. Lett*. **2007,** *17*, 1924. [Crossref]

[64] Zhang, W.; Chen, Y.; Chen, W.; Liu, Z.; Li, Z. *J. Agric. Food Chem*. **2010,** *58*, 6296. [Crossref]

[65] Liu, W.-B.; Jiang, H.-F.; Zhu, S.-F.; Wang, W. *Tetrahedron* **2009,** *65*, 7985. [Crossref]

[66] Echemendía, R.; da Silva, G. P.; Kawamura, M. Y.; de la Torre, A. F.; Corrêa, A. G.; Ferreira, M. A. B.; Rivera, D. G.; Paixão, M. W. *Chem. Commun.* **2019,** *55*, 286. [Crossref]

[67] Das, D. K.; Sarkar, S.; Khan, A. T.; Saravanan, P.; Patra, S. *RSC Adv.* **2014,** *4*, 3581. [Crossref]

[68] Wan, J.-P.; Zhong, S.; Liu, Y. *Synthesis* **2015,** *47*, 3611. [Crossref]

[69] Wei, J.; Li, Y.; Tao, C.; Wang, H.; Cheng, B.; Zhai, H.; Li, Y. *J. Org. Chem.* **2018,** *83*, 835. [Crossref]

[70] Dudognon, Y.; Du, H.; Rodriguez, J.; Bugaut, X.; Constantieux, T. *Chem. Commun. (Cambridge, England)*. **2015,** *51*, 1980. [Crossref]

[71] Zhang, J.; Yang, W.-J.; Sun, J.; Yan, C.-G. *Eur. J. Org. Chem.* **2015,** *2015*, 7571. [Crossref]

[72] Liu, L.; Sarkisian, R.; Deng, Y.; Wang, H. *J. Org. Chem.* **2013,** *78*, 5751. [Crossref]

[73] Dhinakaran, I.; Padmini, V.; Bhuvanesh, N. *ACS Comb. Sci*. **2016,** *18*, 236. [Crossref]

[74] Vinoth, P.; Prasad, P. S. R.; Vivekanand, T.; Maheswari, C. U.; Nagarajan, S.; Menéndez, J. C.; Sridharan, V. *RSC Adv.* **2015,** *5*, 81881. [Crossref]

[75] Sun, J.; Wu, Q.; Xia, E.-Y.; Yan, C.-G. *Eur. J. Org. Chem.* **2011,** *2011*, 2981. [Crossref]

[76] Wan, J. P.; Lin, Y.; Huang, Q.; Liu, Y. *J. Org. Chem.* **2014,** *79*, 7232. [Crossref]

[77] Vereshchagin, A. N.; Karpenko, K. A.; Iliyasov, T. M.; Elinson, M. N.; Dorofeeva, E. O.; Fakhrutdinov, A. N.; Egorov, M. P. *Russ. Chem. Bull.* **2018,** *67*, 2049. [Crossref]

[78] Blümel, M.; Chauhan, P.; Hahn, R.; Raabe, G.; Enders, D. *Org. Lett*. **2014,** *16*, 6012. [Crossref]

[79] Yu, D.-F.; Wang, Y.; Xu, P.-F. *Tetrahedron* **2011,** *67*, 3273. [Crossref]

[80] Dunbar, P. G.; Durant, G. J.; Rho, T.; Ojo, B.; Huzl, J. J.; Smith, D. A.; El-Assadi, A. A.; Sbeih, S.; Ngur, D. O.; Periyasamy, S. *J. Med. Chem*. **1994,** *37*, 2774. [Crossref]

How to cite this article

Thakur, A.; Bharti, R.; Sharma, R. *Orbital: Electron. J. Chem.* **2021**, *13*, 335. DOI: http://dx.doi.org/10.17807/orbital.v13i4.1585