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REVIEW ARTICLE

Multicomponent Synthesis of Substituted 2-Aminopyridines: A Review

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Abstract

Multicomponent reactions (MCRs) serve as a promising and constructive tool for the efficient synthesis of versatile heterocycles in a one-step fashion. Among the various heterocycles, 2-aminopyridines enjoy a unique position owing to their remarkable biological and pharmacological activities. The present report incorporates an overview of the literature pertaining to the synthesis of 2-aminopyridines employing the multicomponent strategy. The reported results have been classified on the basis of the number and nature of the components. The literature of the last 10 years has been included. This study will be helpful in the development of newer and improved methods for the synthesis of 2-aminopyridines and their analogues.

Keywords: Enamines, Multicomponent reactions, Malononitrile, Substituted 2-aminopyridines

Introduction

Multicomponent reactions (MCRs) constitute a synthetic methodology, wherein three or more commercially available or readily accessible constituents react to form a product, with almost all of the synthons contributing to the newly formed product (Fig.1) (Heravi and Zadsirjan, 2020). Indeed, MCRs play a prominent role in combinatorial chemistry (Mironov, 2010) and drug discovery (Weber, 2002) since they offer fast and easy accessibility to a wide ranging collections of organic compounds with multifaceted substitution patterns. In many cases, MCRs outperform conventional reactions with respect to convenience, efficacy, precision, divergence, and atom economy (Bienayme *et al.*, 2000; Ganem, 2009). Hence, the utilization of MCRs has also been discovered as a promising technique in pharmaceutical industries to make highly functionalized heterocycles.

In the last two decades, 2-aminopyridines have piqued the interest of researchers due to the numerous pharmacological actions associated with their powerful vicinity on target molecules. There are several drugs, such as delavirdine (as an anti-HIV drug), piroxicam, tenoxicam, sulfasalazine (with anti-inflammatory properties), tripelenamine (as an antihistamine), and sulfapyridine (as an antibacterial agent) that contain 2-aminopyridine residue (Marinescu, 2017). Consequently, simplistic or convoluted structures comprising a grafted 2-aminopyridine moiety have shown a diverse array of biological activity, namely antitumoral, antidiabetic, antiviral, anti-inflammatory, antimalarial, anticonvulsant, anti-Alzheimer, antimicrobial, analgesic, antiparasitic as well as antihistaminic properties (Perrier *et al.*, 2000; Anderson *et al.*, 2004; Levy *et al.*, 2005; Chen *et al.*, 2005; Cocco *et al.*, 2005; May *et al.*, 2007; Younis *et al.*, 2012). They also exhibit PKC inhibitory, CXCR1/2 inhibitory, n-NOS-inhibitory, JNK1 inhibitory, Renin-inhibitory, Syk inhibitory and sometimes cardiac action (Hagmann *et al.*, 2000; Murata *et al.*, 2004; Deng *et al.*, 2007; Mantri *et al.*, 2008; Huang *et al.*, 2013). In view of this, there are consistent efforts to develop new protocols to obtain differently substituted 2-aminopyridines.

In this mini review, we aim to report recent literature in a systematized form for the synthesis of 2-aminopyridines employing the MCRs strategy. It is anticipated that the review may induce interest for the development of newer and ameliorated techniques for synthesizing 2-aminopyridines as well as their analogues that could offer better and varied biological activities.

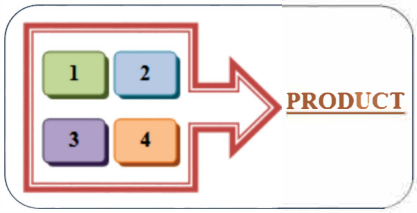

Fig.1. One Pot Synthesis

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Synthetic Approaches

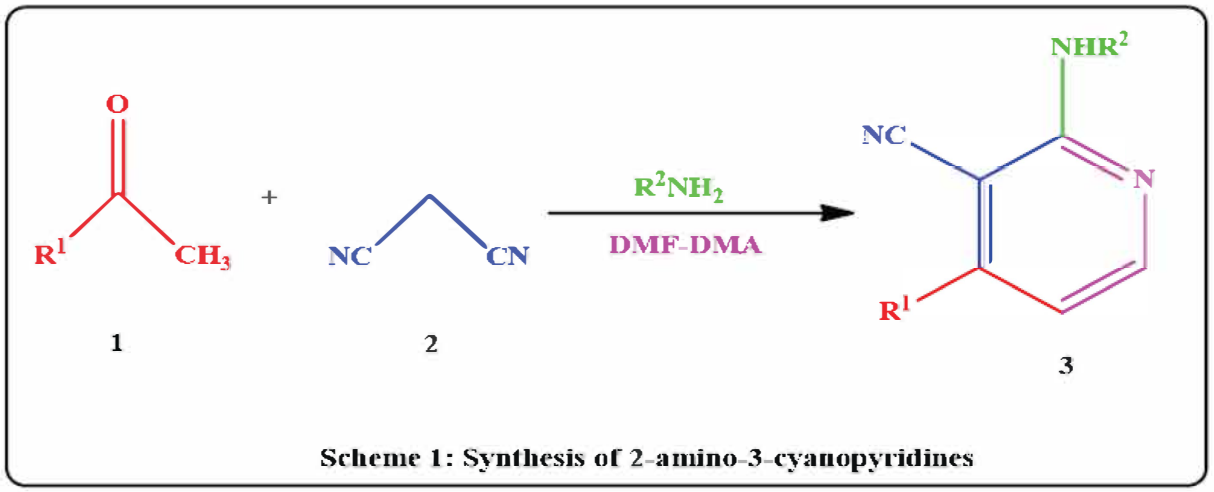
(a) Using Malononitrile as one of the components

Kibou *et al.* (2011) reported the synthesis of 2-amino-3-cyanopyridines (**3**) under solvent-free conditions from condensation of methyl ketones with primary amines to obtain the products in moderate yields (48-73%) (Scheme 1).

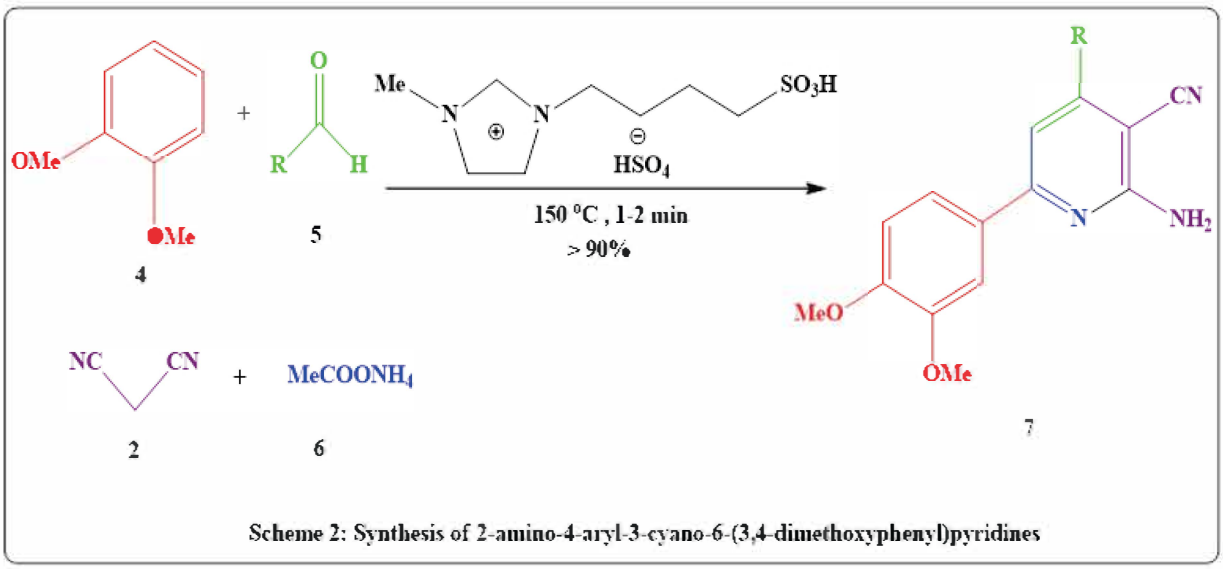
Davoodnia *et al* (2011) obtained 2-amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines in very good yields (90%) by carrying out MCR of an aldehyde, ammonium acetate, malononitrile and 3,4-dimethoxyacetophenone in the presence of 3-methyl-1-(4-sulfonylbutyl) imidazoliumhydrogensulfate $[HO_3S(CH_2)_4MIM][HSO_4]$ as the catalyst (Scheme 2).

A similar strategy was followed for the synthesis of 2-amino-3-cyanopyridine derivatives (**9**) by using ytterbiumperfluorooctanoate $[Yb(PFO)_3]$ as the catalyst (Scheme 3). This methodology was found to tolerate the majority of substrates and has the attributes of simple protocol, excellent yields (77-95%), eco-friendly and recyclable catalyst (Tang *et al.*, 2011). Sheibani *et al* (2011) performed the same reaction with high surface area using MgO in dimethylformamide (DMF) (Scheme 4). The products were obtained in good to high yields (70-87%).

Thimmaiah *et al.* (2012) instead employed a metal-organic framework (MOF) of Zn(II) or a Cd(II) as the heterogeneous catalyst for the MCR of malononitrile, thiophenols and aldehydes for synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines (**11**) in good to excellent yields (61- 88%) (Scheme 5). Ghomi *et al.* (2012) carried out this same reaction in the presence of calcium oxide nanoparticles giving 70-92% yield (Scheme 6).

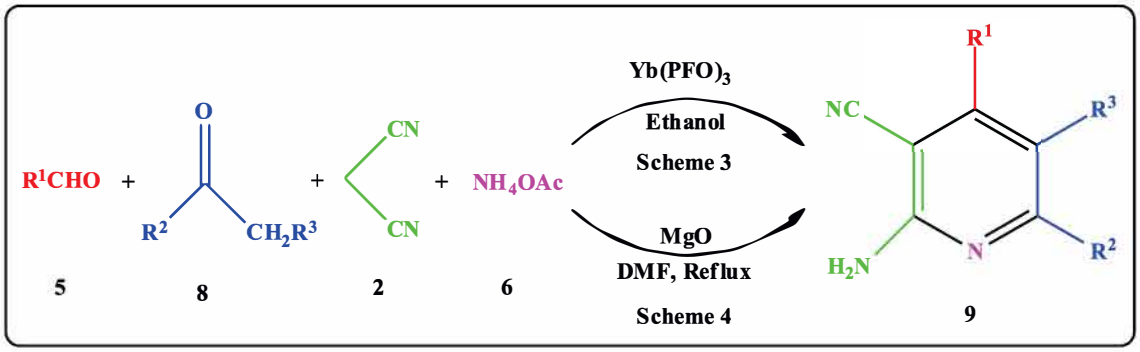


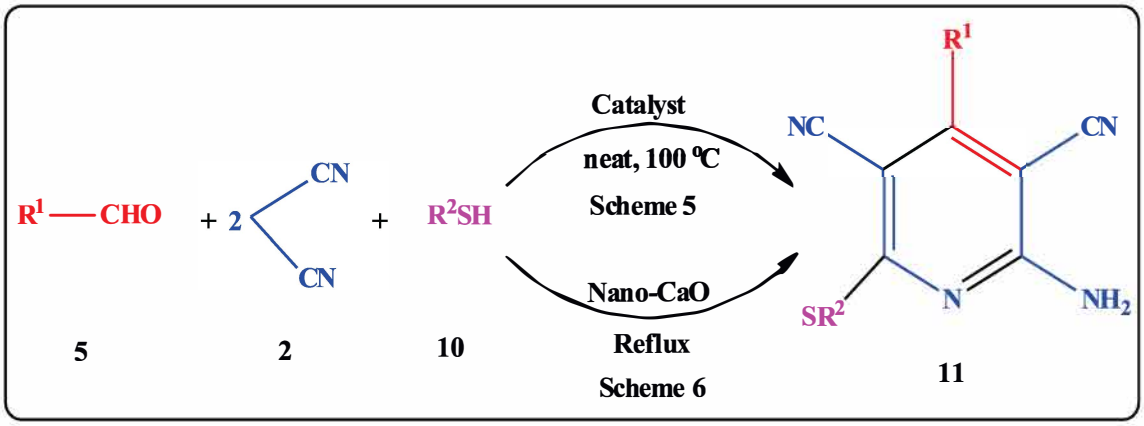
Scheme 1: Synthesis of 2-amino-3-cyanopyridines

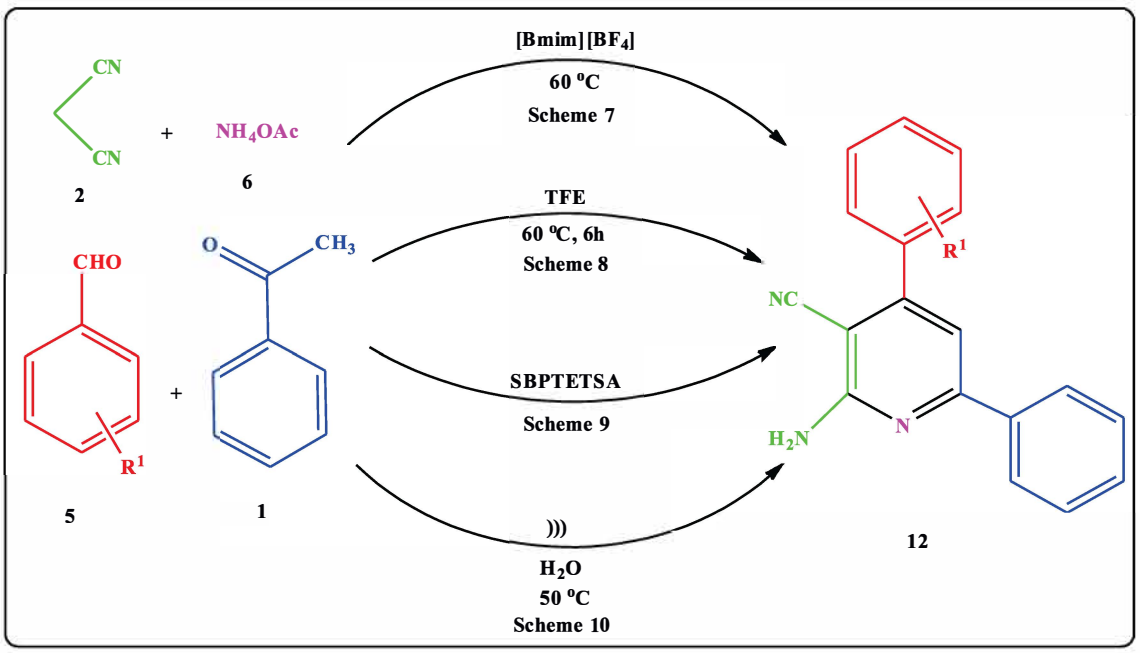


Scheme 2: Synthesis of 2-amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines

Mansoor *et al.* (2012) employed an ionic liquid, 1-butyl-3-methylimidazoliumtetrafluoroborate ([Bmim][BF_4]) as the catalyst for the MCR of malononitrile, ammonium acetate, aromatic aldehyde and methyl ketone to give 2-amino-3-cyanopyridine (**12**) in 78-94% yields (Scheme 7). Khaksar *et al.* (2012) improved the yields to 80-95% by using trifluoroethanol (TFE) as the solvent (Scheme 8), while Niknam *et al.* (2012) obtained the products in 65-90% yields on using silica-bound *N*-propyl triethylenetetraminesulfamic acid (SBPTETSA) as the catalyst (Scheme 9). However, an ultrasound-assisted MCR of the above mentioned four-components under catalyst-free conditions and using water as a green solvent afforded the products in 75-99% yields (Scheme 10) (Safari *et al.*, 2012).



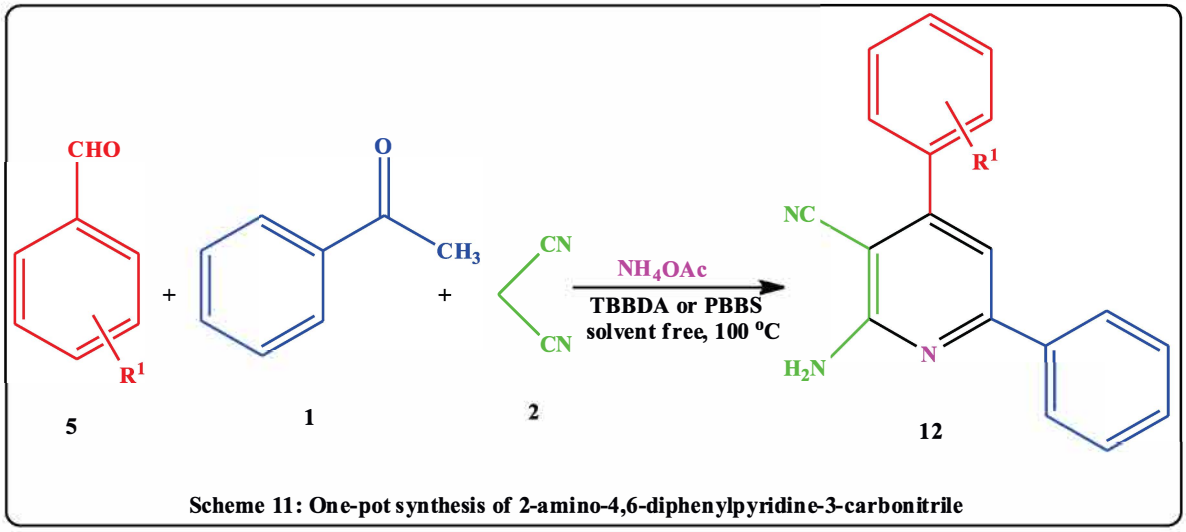




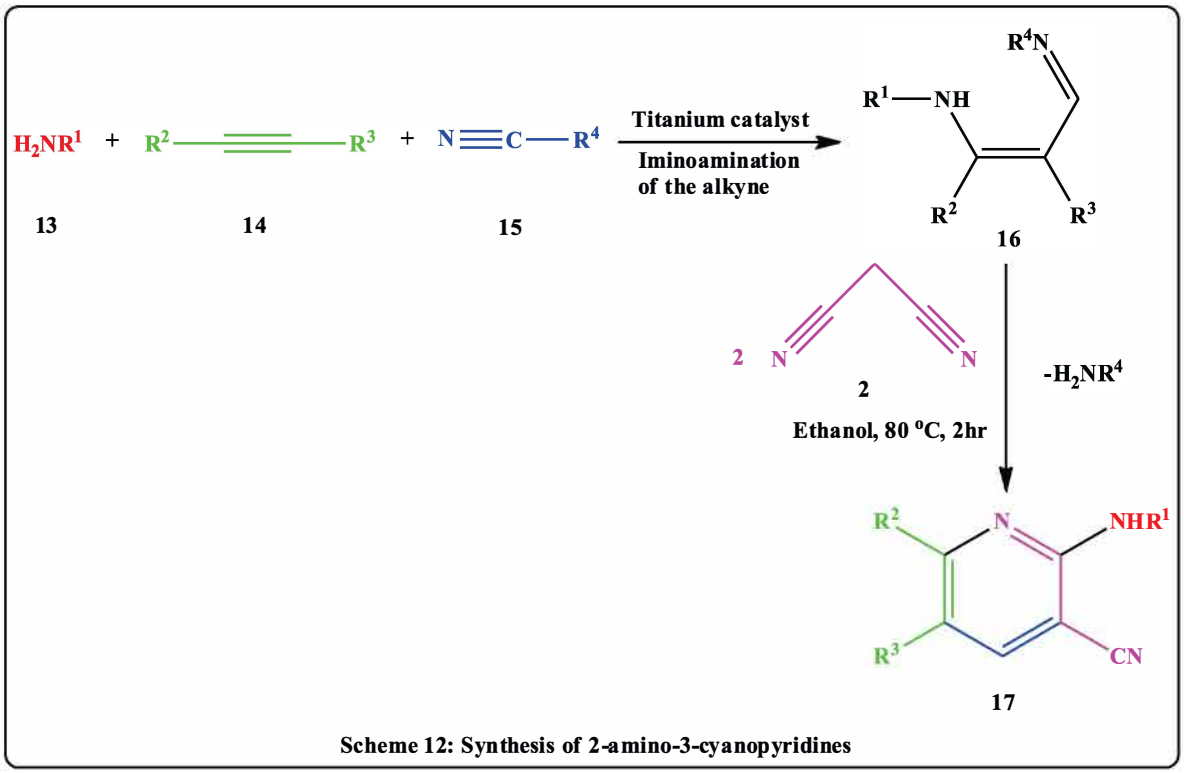
Ghorbani *et al.* (2013) described the synthesis of 2-amino-3-cyanopyridine employing tetrabromobenzene-1,3-disulfonamide (TBBDA) or Poly(N-bromo-N-ethylbenzene-1,3-disulfonamide) (PBBS) without using solvent. Also, the yield obtained by the former method was 85-94% while the latter was79-90% (Scheme 11).

A titanium promoted single-pot synthesis of 2-amino-3-cyanopyridines has been reported in the presence of primary amines, alkynes, malononitrile and isonitriles leading to the formation of isolable 2-imino-1,2-dihydropyridine intermediate giving rise to the rearranged product in 43-68% yield (Scheme 12) (Dissanayake *et al.*, 2014).

Huang *et al.* (2015) revealed $ZnCl_2$-catalyzed explicit cyclization of varied benzylidenemalononitriles and arylamines affording a wide array of novel 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridines. These compounds utilized milder reaction conditions with diverse functional group inclusiveness and reasonable product yields (67-88%) (Scheme13).



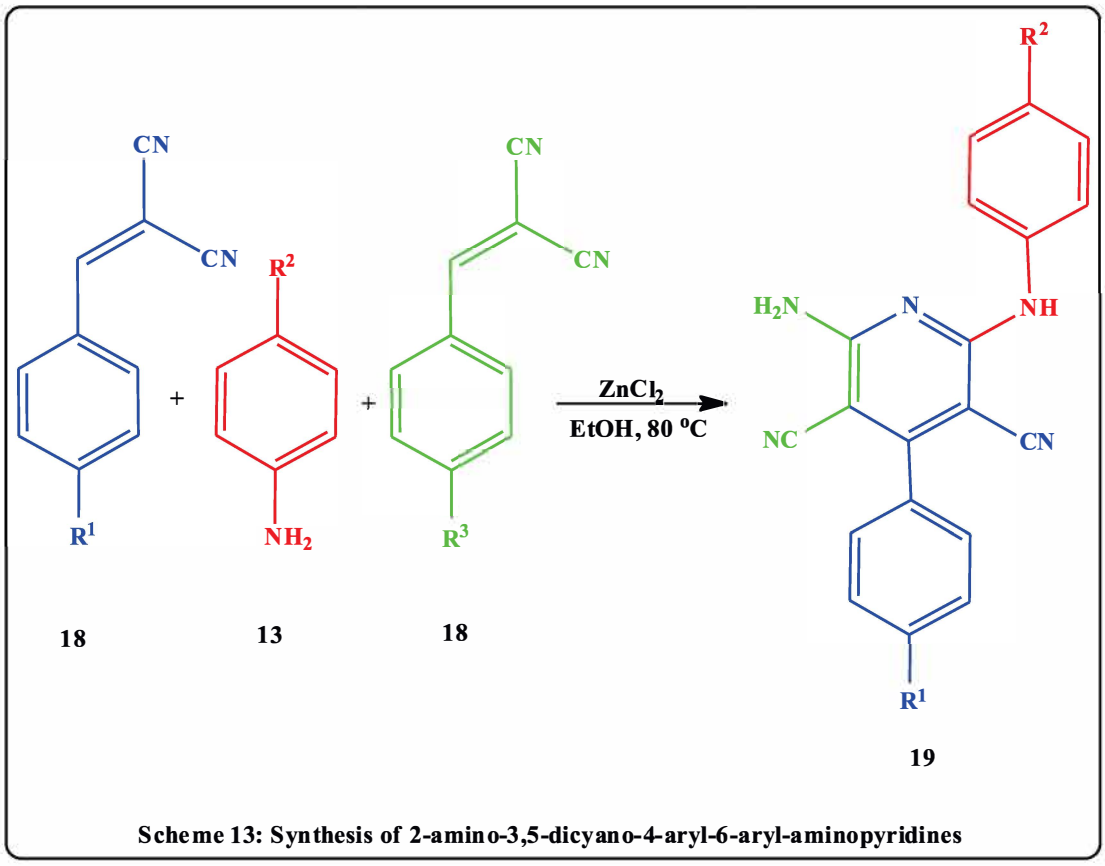
Scheme 11: One-pot synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile



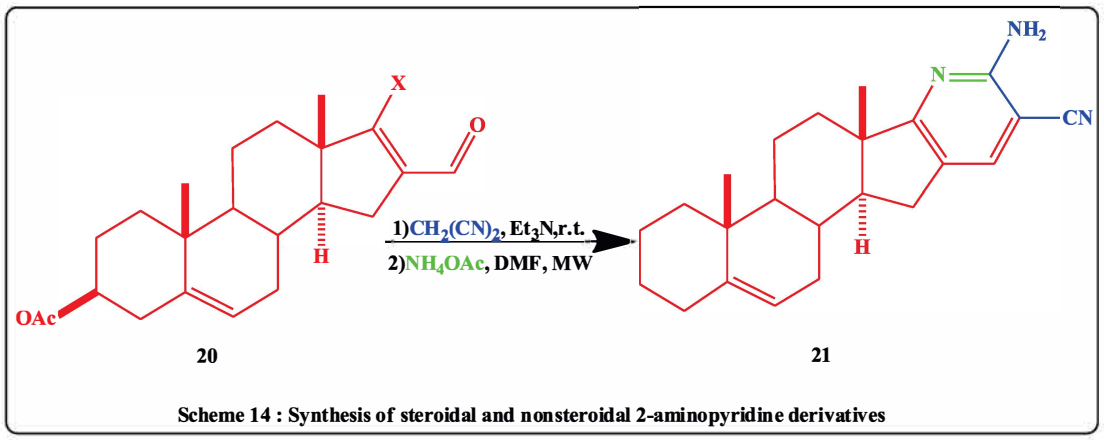
Scheme 12: Synthesis of 2-amino-3-cyanopyridines

A microwave-abetted approach towards the synthesis of steroidal and nonsteroidal 2-aminopyridine derivatives using β-halo-α,β-unsaturated aldehydes via Knoevenagel condensation was developed with 63-83% yield of the product (Scheme 14). A Vilsmeier formylation synthetic pathway had been utilized to proficiently generate the β-halo-α,β-unsaturated aldehydes from their homologous ketones. This methodology even facilitated the formation of 2-aminopyridine-fused steroidal compounds (Gogoi *et al.*, 2015).

Khalifeh and Ghamari (2015) carried out a four-component coupling reaction with 2 mol% copper nanoparticles on charcoal (Cu/C) as a heterogeneous catalyst system and with high yield (83-94%) (Scheme 15). This synthetic protocol was conveniently applicable to a large variety of aldehydes and ketones. It was also observed that the catalyst in the given method was recovered and reused at least eight times with no conspicuous loss in catalytic activity.



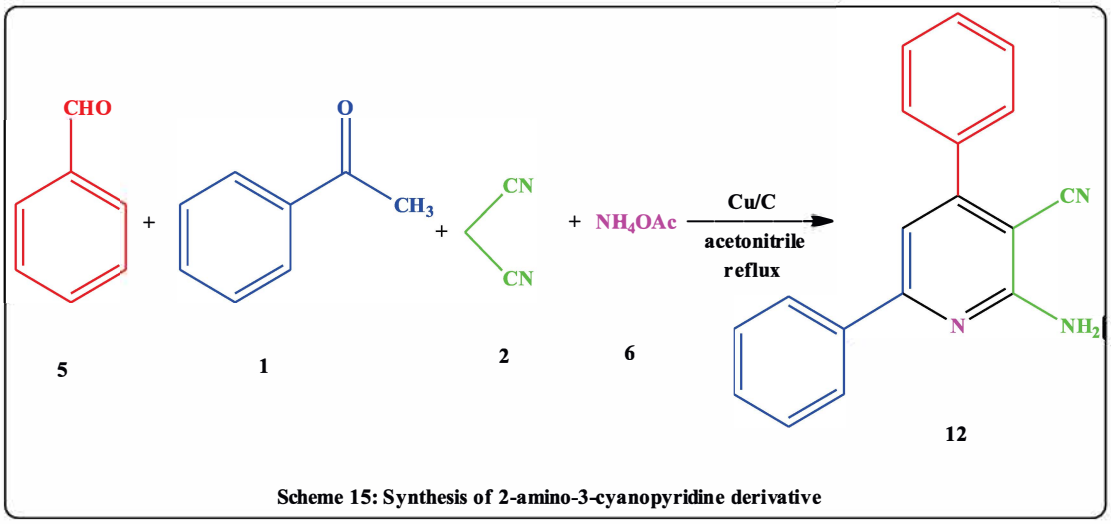
Scheme 13: Synthesis of 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridines



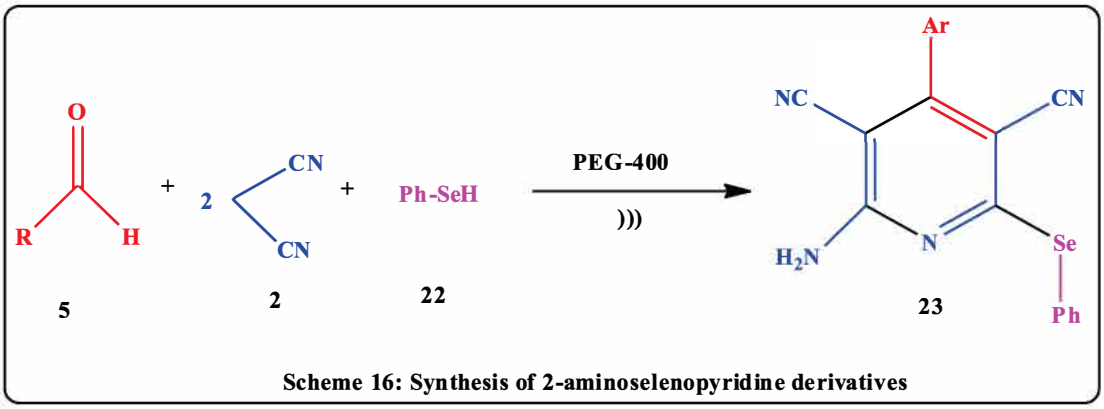
Scheme 14 : Synthesis of steroidal and nonsteroidal 2-aminopyridine derivatives

An ultrasound irradiated MCR of benzeneselenol, aldehydes and malononitrile in polyethylene glycol (PEG-400) was also demonstrated to synthesize 2-aminoselenopyridine derivatives (Scheme 16). A diverse set of aromatic, heteroaromatic and aliphatic aldehydes underwent this MCR affording moderate to good yields i.e., 67-90% (Khan *et al.*, 2015).

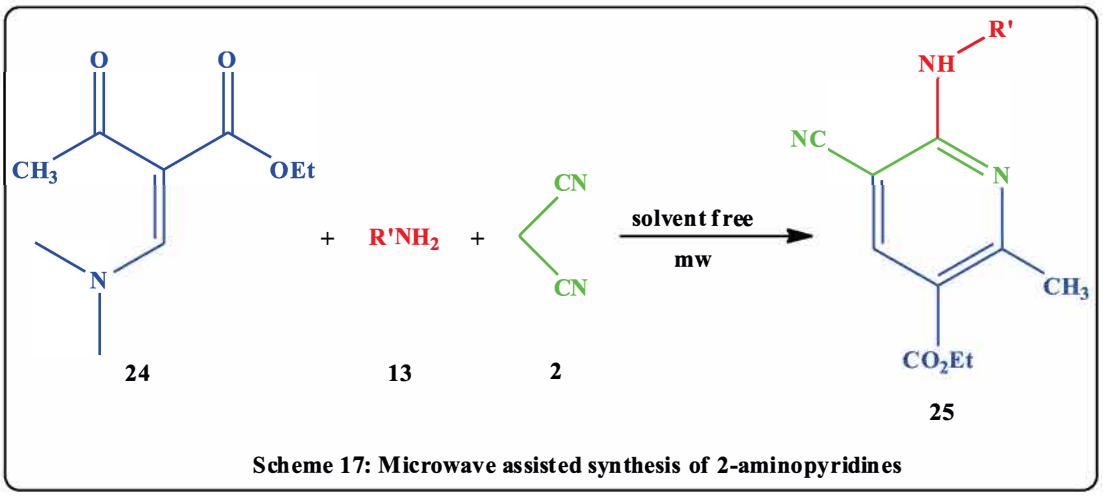
Kibou *et al.* (2016) reported an efficient technique for the synthesis of 2-aminopyridines using a combination of ethyl 2-((dimethylamino)methylene)-3-oxobutanoate, primary amine and malononitrile under microwave irradiations (Scheme 17). This solvent-free technique has several advantages like notably facile manipulation, excellent product yields (80-93%), short reaction durations and avoidance of hazardous solvents.



Scheme 15: Synthesis of 2-amino-3-cyanopyridine derivative



Scheme 16: Synthesis of 2-aminoselenopyridine derivatives



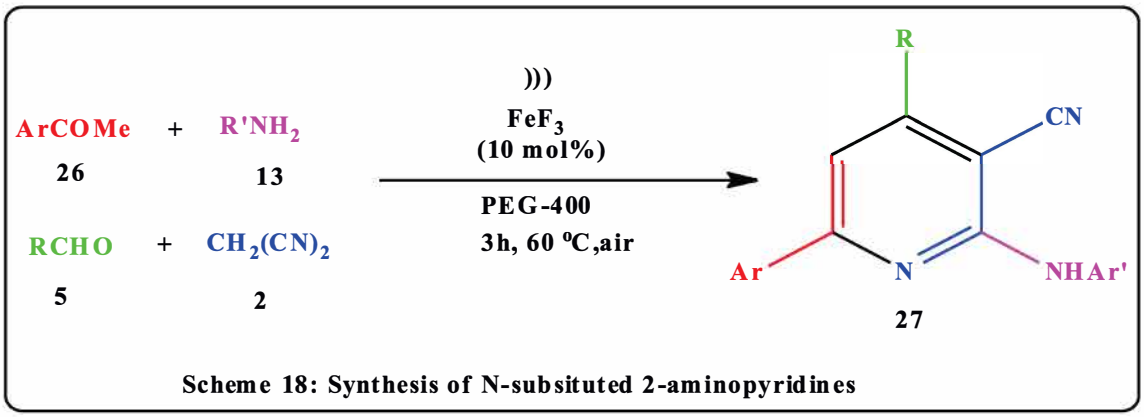
Scheme 17: Microwave assisted synthesis of 2-aminopyridines

Reddy *et al.* (2016) carried out an ultrasound irradiated FeF_3 catalyzed four-component reaction using benzaldehyde, acetophenone, malononitrile and amine to prepare N-substituted 2-aminopyridines conferring 50-92% yield (Scheme 18). The fusion of catalyst FeF_3 and PEG-400 was noticed to be most suitable and the methodology did not require the use of an inert or anhydrous atmosphere.

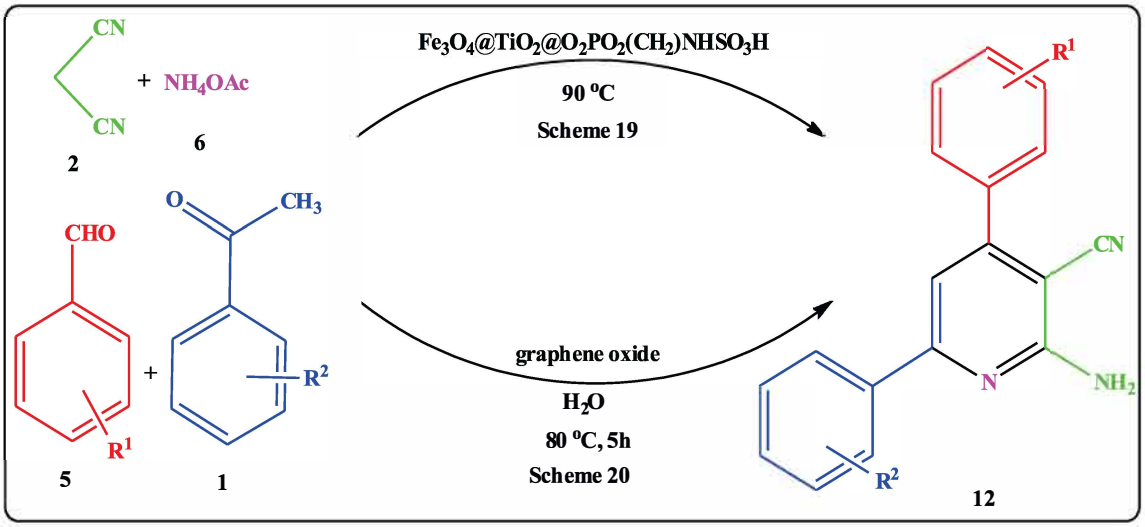
Zolfigol *et al.* (2017) and Kalili *et al.* (2016) individually described MCRs comprising malononitrile, ketones, aldehydes and ammonium acetate under different reaction conditions. The former one carried out this reaction in the presence of a nanomagnetic heterogeneous catalyst, namely $Fe_3O_4@TiO_2@O_2PO_2(CH_2)NHSO_3H$ proffering 82-92% yield (Scheme 19) whereas the latter used graphene oxide as a heterogeneous catalyst and water as a green medium yielding 75-97% product (Scheme 20).

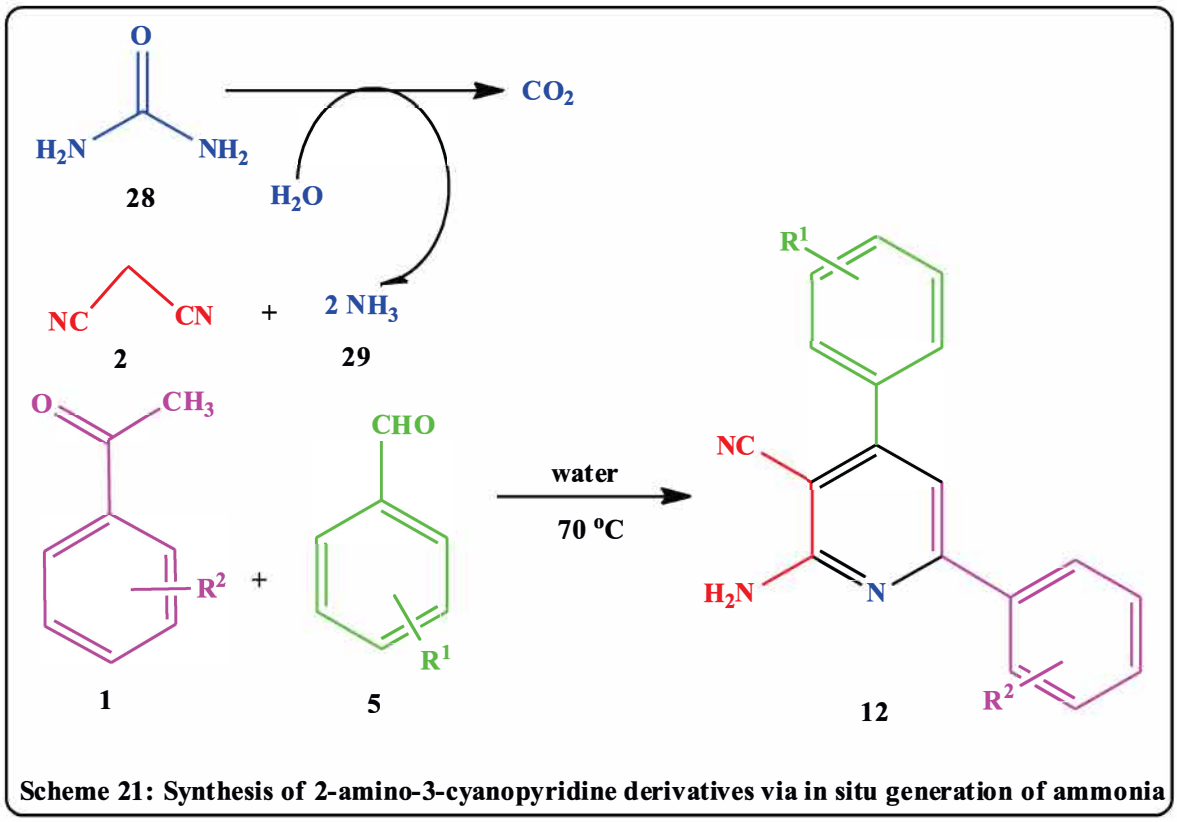
A slightly modified version of the above synthetic route was elaborated, where they synthesized 2-amino-3-cyanopyridines through one-pot condensation of malononitrile, aldehydes and acetophenones with *in situ* generation of NH_3 by the dissociation of urea and the yield obtained was 60-85% (Scheme 21). It was found that ammonium salts supported the enzymatic urease in the bio-production of ammonia, whilst trace amounts of heavy metal ions such as Pb^{2+}, Hg^{2+}, and Ag^{+} hindered these particular reactions and significantly decreased the yields (Tamaddon *et al.*, 2016).

Mobinikhaledi *et al.* (2016) performed a triethylamine catalyzed three-component synthesis of 2,6-diamino-3,5-dicarbonitrilepyridine derivatives via reaction of ammonium acetate, aldehydes and malononitrile without the use of solvent (Scheme 22). Aromatic aldehydes with both electron-rich and electron-deficient groups resulted in good yields (76-91%) whereas the aliphatic aldehydes did not avail yields. An akin three-component condensation reaction was executed in the presence of ZnO nanoparticles. They executed this reaction in the concoction of water and methanol as solvent under classical heating yielding 72-82% product (Scheme 23a) as well as using microwave heating offering 75-88% yield (Scheme 23b) (Patil *et al.*, 2017).

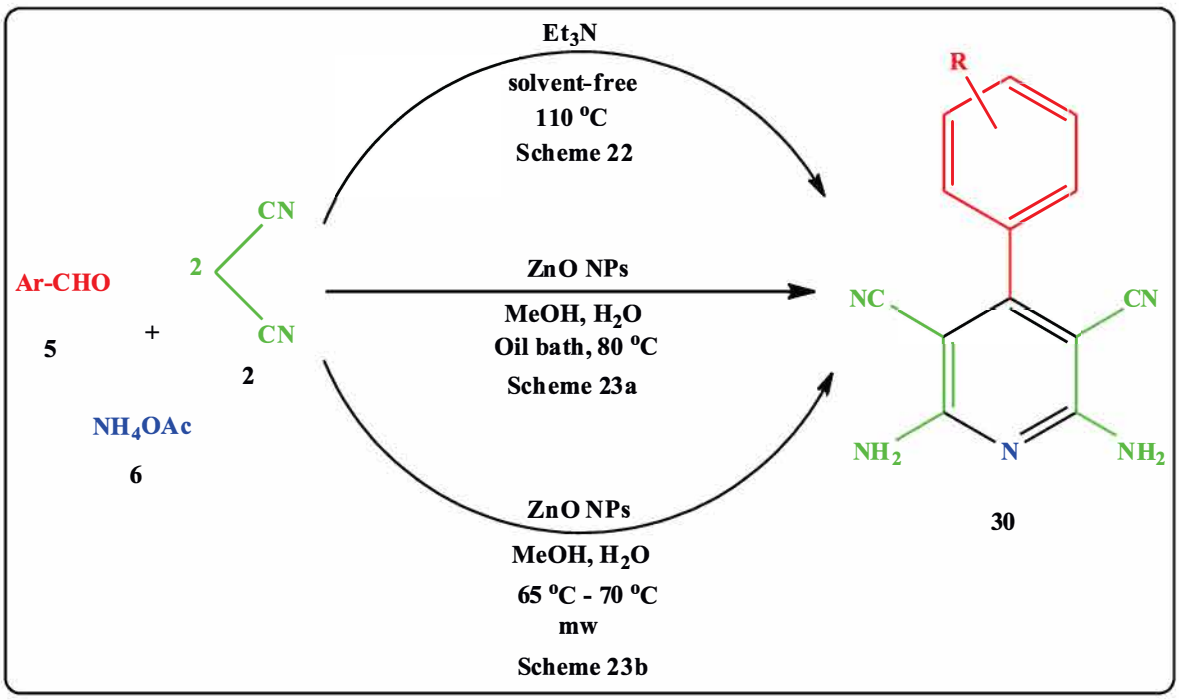


Scheme 18: Synthesis of N-subsituted 2-aminopyridines



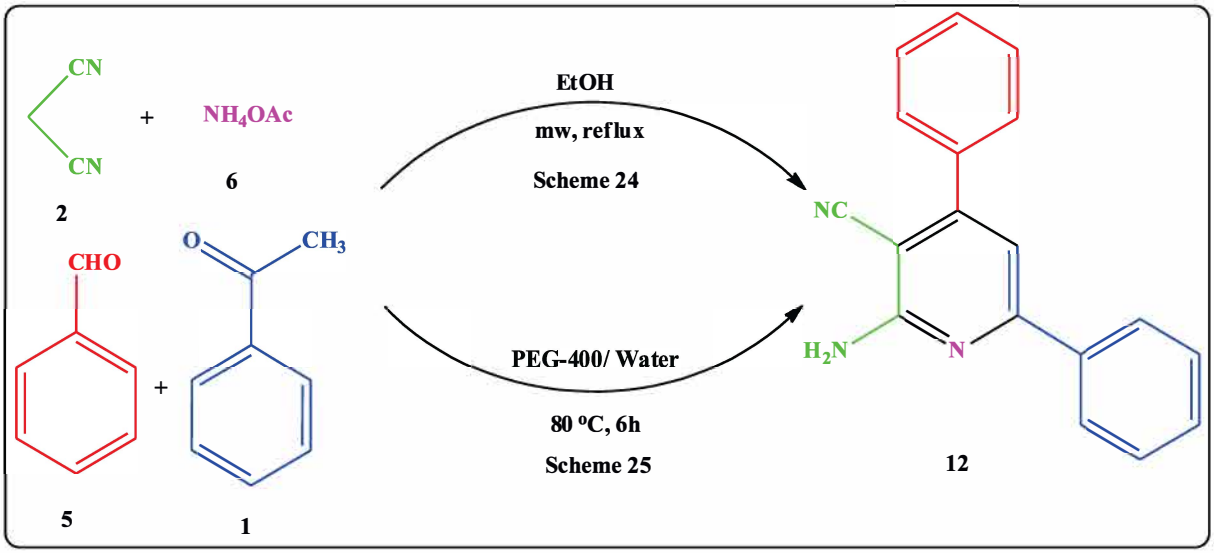


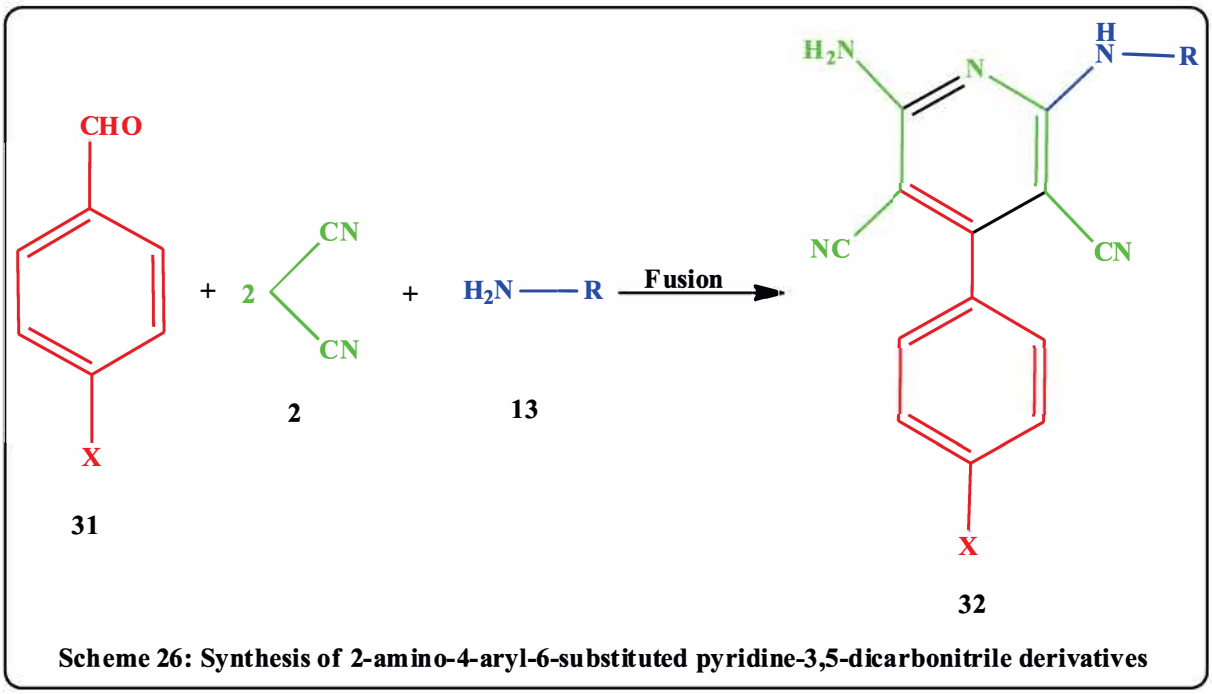
Scheme 21: Synthesis of 2-amino-3-cyanopyridine derivatives via in situ generation of ammonia



Simultaneously, Amer *et al*. (2017) and Balaswamy *et al*. (2017) independently developed a facile method for the synthesis of cyanopyridine derivatives via acetophenones, ammonium acetate, malononitrile and aromatic aldehydes. The former carried out this reaction using ethanol and under both microwave (72-84% yield) and thermal reaction conditions (68-82% yield) (Scheme 24), while the latter used Polyethyleneglycol (PEG-400) as a phase transfer catalyst under aqueous conditions giving 75-86% yield (Scheme 25).

Concurrently, Mahmoud *et al*. (2018) investigated the synthesis of 2-amino-4-aryl-6-substitutedpyridine-3,5-dicarbonitrile derivatives leveraging various primary amines, malononitrile and aromatic aldehydes under the fusion conditions without the use of solvents or catalysts and the yield obtained was about 76-95% (Scheme 26). The synthesized pyridine compounds were rated as good corrosion inhibitors, and also the rate of inhibition was found to be concentration-dependent.





Scheme 26: Synthesis of 2-amino-4-aryl-6-substituted pyridine-3,5-dicarbonitrile derivatives

Maleki *et al.* (2018) revealed a MCR among malononitrile, aldehydes and ammonium acetate in solvent-free conditions at 110°C in the proximity of nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$ as a heterogeneous reusable catalyst and about 79-88% yield was obtained (Scheme 27).

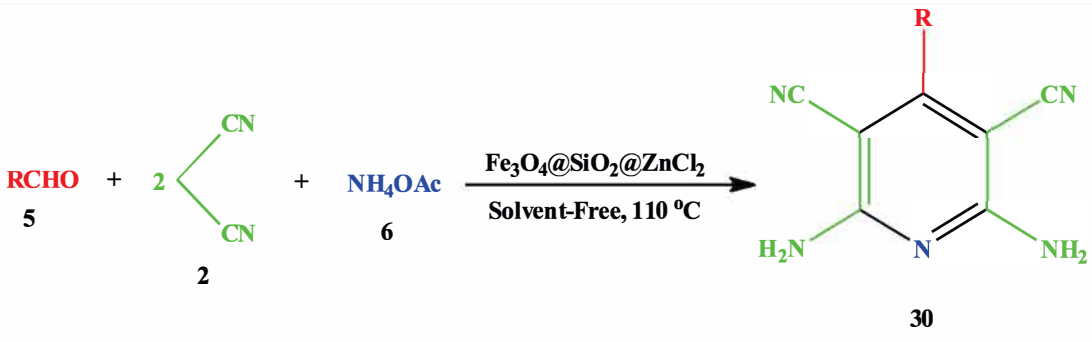
An one-pot four-component reaction for the synthesis of substituted 2-aminopyridines using Cu@imineZCMNPs yielding 85-96% product (Scheme 28) as well as $SrFe_{12}O_{19}$ magnetic nanoparticles (Scheme 29) as a catalyst offering 86-91% yield were elaborated by Yahyazadeh *et al.* (2018) and Kheilkordi *et al.* (2018) respectively where they utilized ammonium acetate, various aldehydes, acetophenone and malononitrile. In the next year, this same reaction was carried out using eggshell nanoFe_3O_4@$Ca(HSO_4)_2$ giving 53-89% yield (Scheme 30). In this protocol, they converted the eggshell that was discarded as hazardous waste by European Union regulations into a valuable catalyst. They even investigated its catalytic property via anomeric-based oxidation (ABO) (Akbarpoor *et al.*, 2019). Similarly, the aforementioned synthetic route has also been demonstrated using magnetic nanoparticles with morpholine tags conferring 81-95% yield (Scheme 31), cobalt(II)nitratehexahydrate obtaining 82-93% yield (Scheme 32) and Fe_3O_4@SiO_2@$(CH_2)_3$-urea-benzimidazole sulfonic acid proffering 70-92% yield (Scheme 33) as catalysts correspondingly (Kalhor *et al.*, 2019; Pejman *et al.*, 2019; Torabi *et al.*, 2019).

A four-component reaction of triethoxymethane, various primary amines, acetophenone, and malononitrile has been developed utilizing several surfactant-possessing mesoporous catalysts such as Si-MCM-41, Al-MCM-41 and Ga-MCM-41 (Scheme 34). According to the catalytic reaction, Si-MCM-41 turned out to be the best one yielding 75-92% product due to the presence of higher density of the siloxy groups (Nouali *et al.*, 2020).

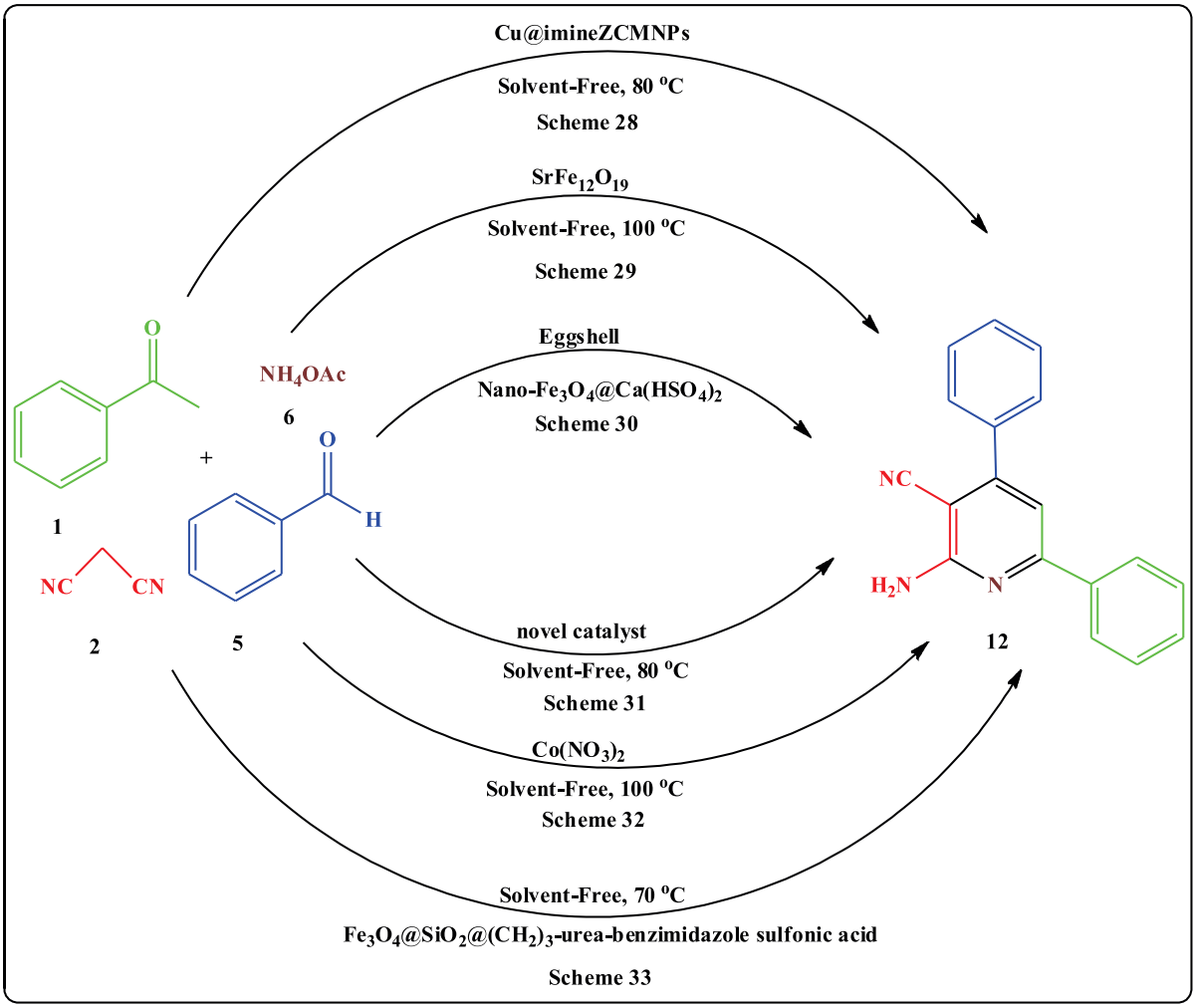
Simultaneously, Benzenine *et al.* (2020) synthesized 2-aminopyridine derivatives by combining acetophenone, aldehydes, malononitrile and ammonium carbonate under solvent-free conditions and without catalyst (Scheme 35). The yield obtained was 80-95%.

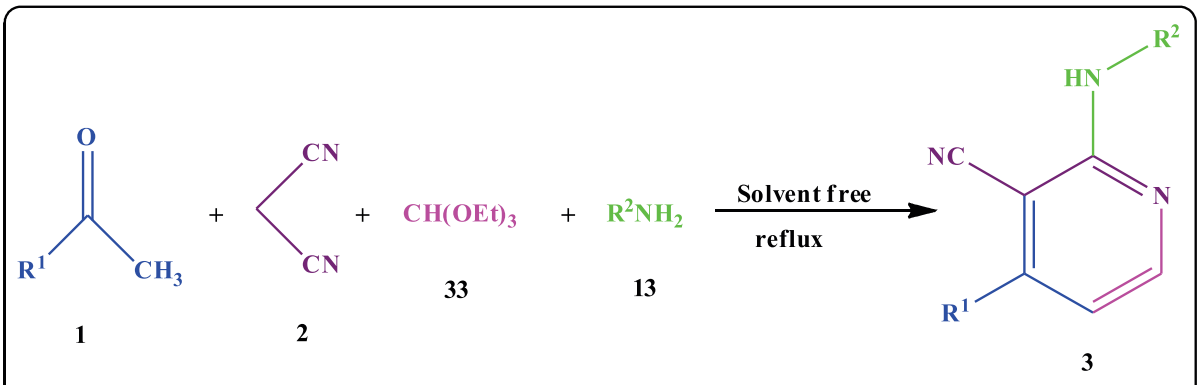
Synthesis of 2-amino-3-cyanopyridine derivatives using aromatic aldehydes, ammonium acetate, malononitrile and acetophenone derivatives in the presence of $Cu(OAc)_2$ has been reported conferring 85-97% yield (Scheme 36). The compounds have also been investigated against a wide spectrum of pathogens including fungi, gram-negative and gram-positive bacteria (Mirjalili *et al.*, 2020).

Allahi and Akhlaghinia (2020) elaborated a water extract of banana peels ash (WEB) catalyzed synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridinesderivatives through condensation of malononitrile, aromatic aldehydes and aromatic or aliphatic thiols offering 80-90% yield (Scheme 37). Aryl and heteroaryl aldehydes including 2-naphthaldehyde (bulky aldehyde) were revealed to be immensely coherent to the present reaction affording excellent yields and short reaction times. It had been also revealed that, since the WEB features a basic nature, so it enables the reaction to progress under moderate circumstances. This same reaction was performed in the following year using Mg-Al hydrotalcite as a solid base catalyst (Scheme 38). In this protocol, aldehyde containing electron donating groups achieved moderate yields whereas electron withdrawing groups imparted good yields because they increase electrophilicity of the carbonyl carbon, which is more susceptible for nucleophilic attack hence enhancement of yield is observed (Kale and Surve, 2021). The yield obtained was 61-82%.

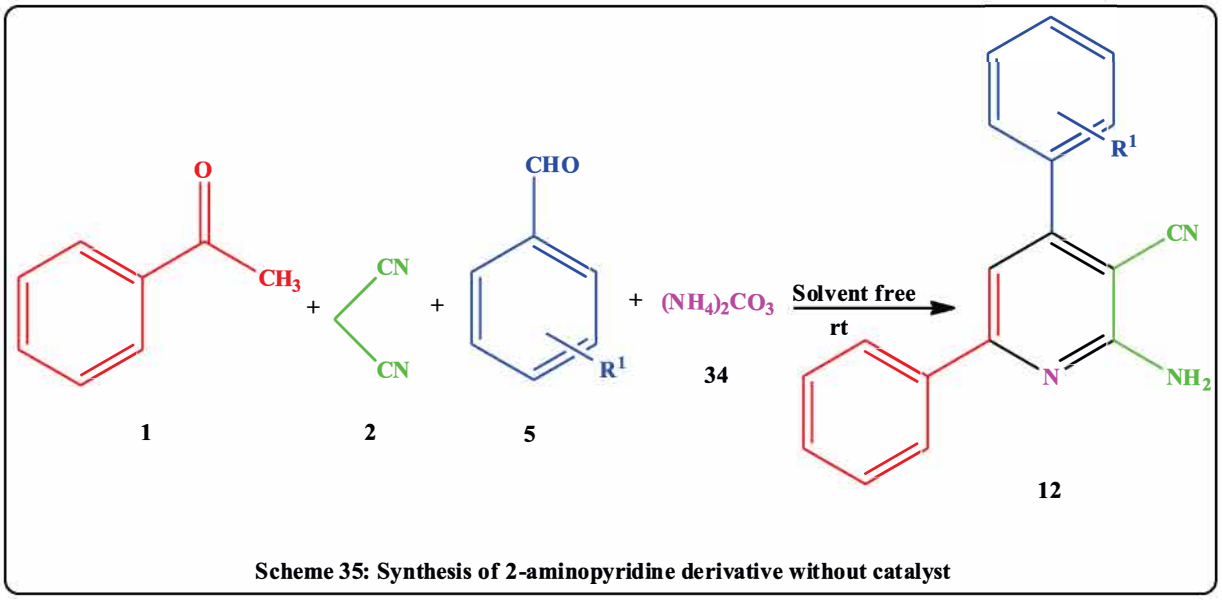


Scheme 27: Synthesis of 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles using nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$

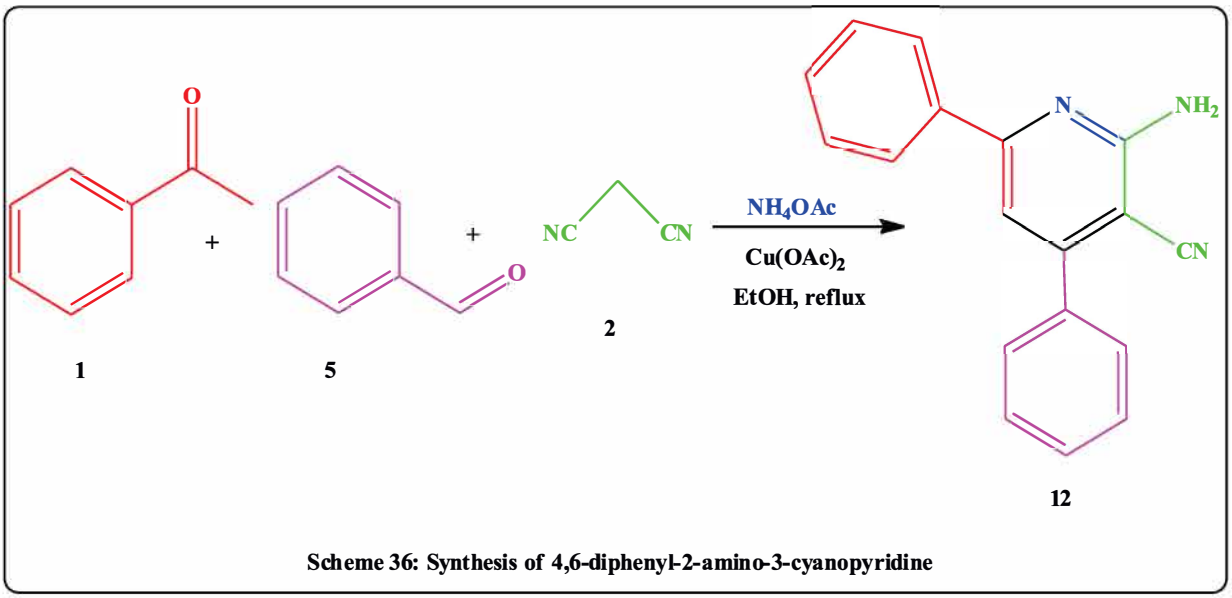




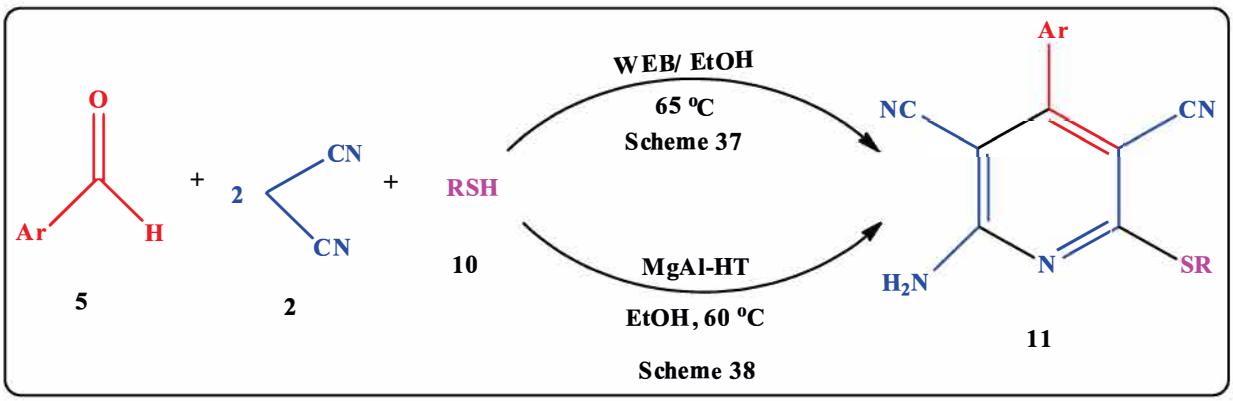
Scheme 34: Synthesis of 2-aminopyridines derivatives via four-component



Scheme 35: Synthesis of 2-aminopyridine derivative without catalyst



Scheme 36: Synthesis of 4,6-diphenyl-2-amino-3-cyanopyridine



(b) ***Using 1,1-enediamines as one of the components***

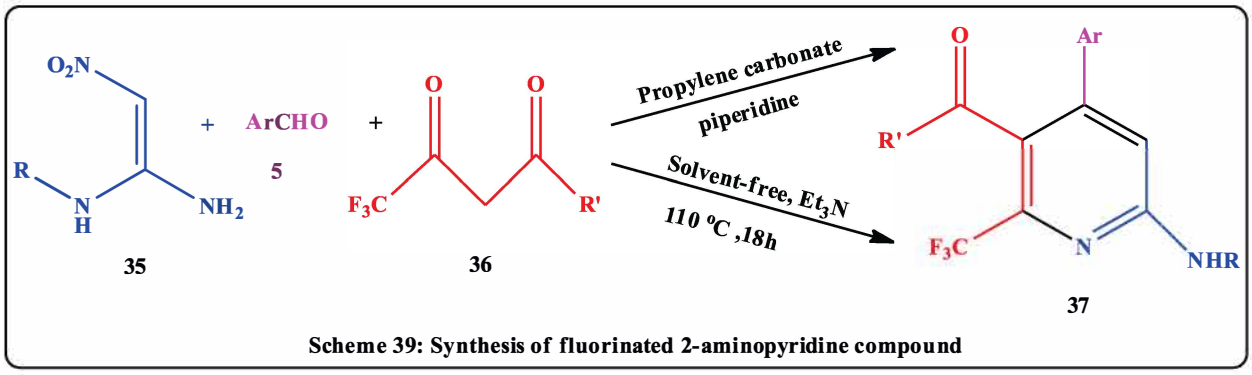
Synthesis of fluorinated 2-aminopyridine compounds have been reported with benzaldehyde derivatives, 1,3-dicarbonyl compounds and 1,1-enediamines (EDAMs). Through this protocol, a wide variety of highly functionalized 2-aminopyridines libraries were reported by carrying out the reaction in by Et_3N at 110°C under solvent-free conditions. Alternatively, use of propylene carbonate stimulated by piperidine at same above temperature has also been reported yielding 80-94% and 70-94% products respectively (Scheme 39). In this method, the nitro group of EDAMs was initially devised as an activating and orienting group to synthesize 2-aminopyridines (Du *et al.*, 2014).

(c) ***Using Cyanoamides or Cyanoacetates as one of the components***

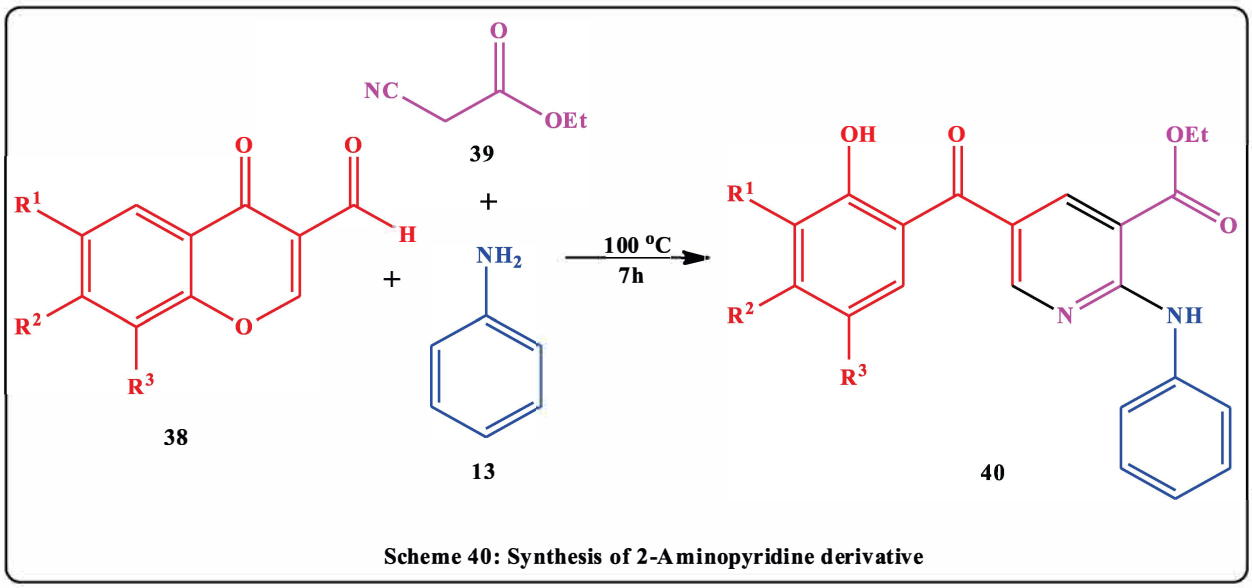
A cascade reaction of easily accessible 4-oxo-4Hchromene-3-carbaldehydes with cyanoamides or cyanoacetates and aromatic or aliphatic amines without solvent and catalyst was also proposed (Scheme 40). Using this protocol, a plethora of multisubstituted 2-aminopyridine analogues were synthesized obtaining 84-92% yields (Baral *et al.*, 2016).

(d) ***Using Enaminonitrile as one of the components***

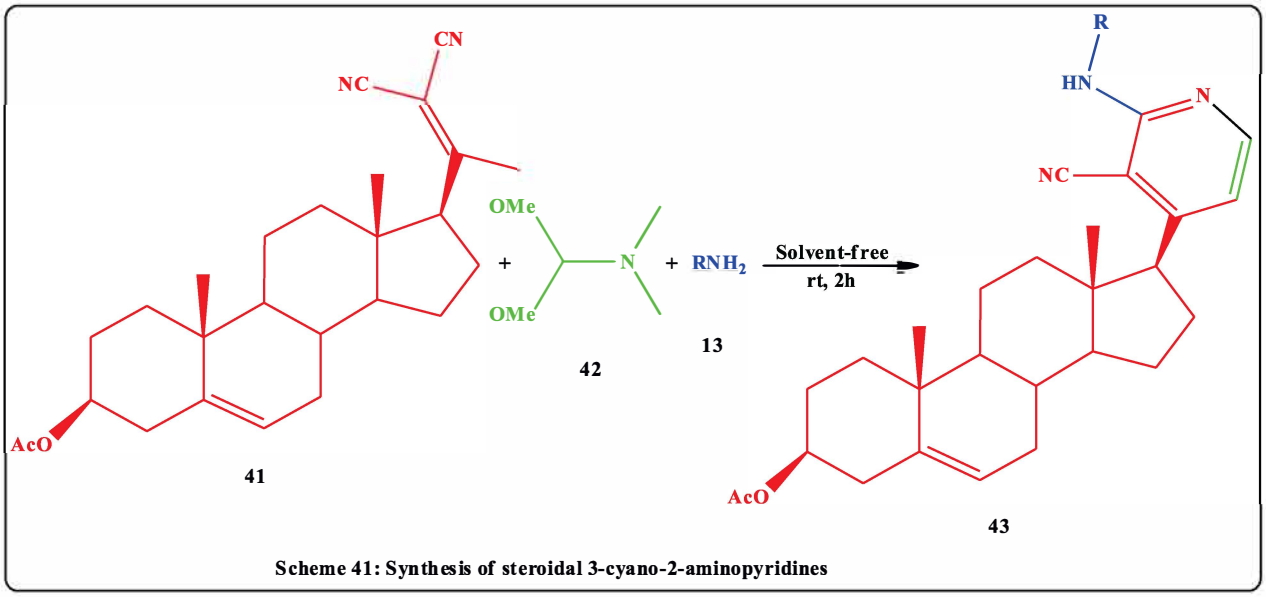
A novel steroidal 3-cyano-2-aminopyridines were synthesized under solvent-free conditions from different primary amines and enaminonitrile offering 45-85% yield (Scheme 41). The adjoining amine and nitrile groups in the end products were found to possess the potency for late-stage functionalization providing a proficient approach to steroidal compound libraries with structural distinctness (Zhang *et al.*, 2016).



Scheme 39: Synthesis of fluorinated 2-aminopyridine compound



Scheme 40: Synthesis of 2-Aminopyridine derivative

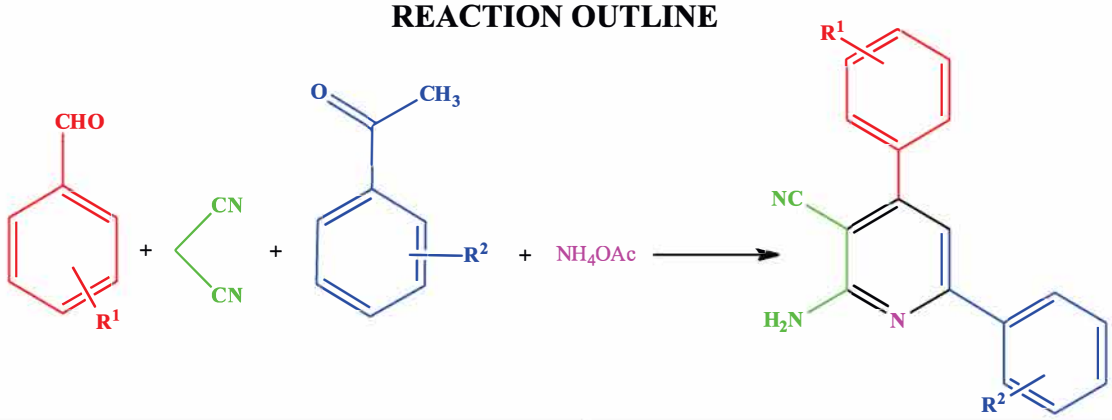


41 42 13 43

Scheme 41: Synthesis of steroidal 3-cyano-2-aminopyridines

Table 1. Synthetic routes employing aldehydes, malononitrile, ammonium acetate and acetophenone derivatives as precursors

REACTION OUTLINE



CATALYST OR REAGENT	REACTION CONDITIONS
[Bmim][BF_4]	60 °C
Catalyst-free	TFE, reflux, 6h
SBPTETSA	Solvent-free, 100 °C
Catalyst-free	Ultrasound, water, 50 °C
TBBDA or PBBS	Solvent-free, 100 °C
Cu/C	Acetonitrile, reflux
Fe_3O_4@TiO_2@$O_2PO_2(CH_2)NHSO_3H$	Solvent-free, 90 °C
Graphene oxide	H_2O, 80 °C, 5h
Catalyst-free	EtOH, mw and reflux
PEG-400	Water, 80 °C, 6h
Cu@imineZCMNPs	Solvent-free, 80 °C
$SrFe_{12}O_{19}$	Solvent-free, 100 °C
Eggshell nano-Fe_3O_4@$Ca(HSO_4)_2$	Solvent-free, 90 °C
Magnetic nanoparticles with morpholine tags	Solvent-free, 80 °C
$Co(NO_3)_2$	Solvent-free, 100 °C
Fe_3O_4@SiO_2@$(CH_2)_3$-urea-benzimidazole sulfonic acid	Solvent-free, 70 °C
$Cu(OAc)_2$	EtOH, reflux

Conclusions

During the last decade a significant development has been made on the MCR synthesis of 2-aminopyridines. The current available reports indicate the preferential reaction pathway employing aromatic aldehydes, malononitrile as well as acetophenone derivatives as the coupling partners in most of the cases (Table 1).

It was also revealed that the use of malononitrile exhibited potent biological activities in the products (Fig.2).

In addition to the above, alkynes, amines, ketoximes and acetate derivatives have also been used as precursors in various methods thus increasing the structural diversity and novelty of 2-aminopyridines. With this mini-review we hope to help readers to discover improved synthetic routes for the synthesis of 2-aminopyridines and its analogues.

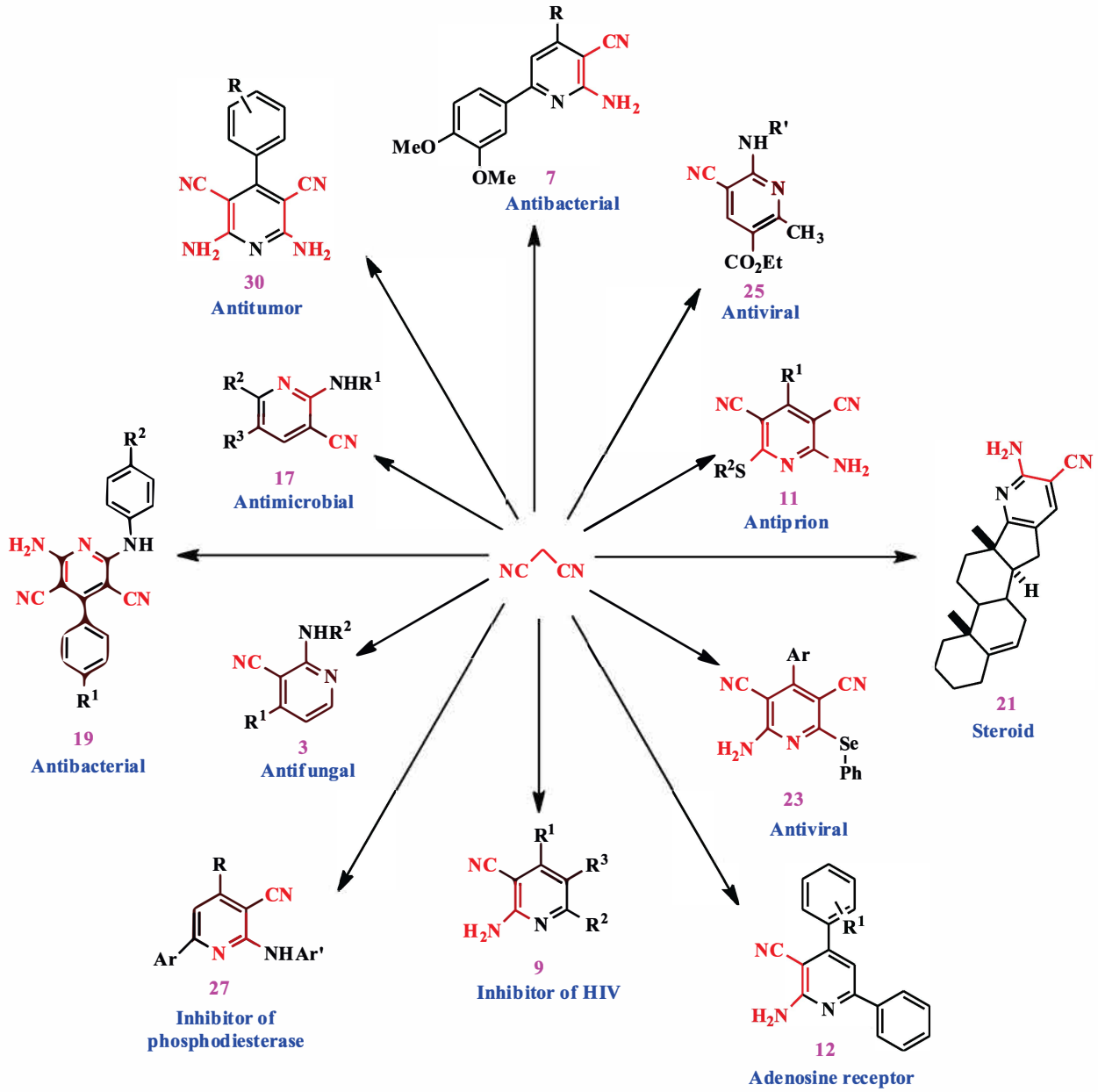


Fig. 2. Malononitrile derivatives exhibiting potent biological activities.

References

Akbarpoor, T., Khazaei, A., Seyf, J.Y., Sarmasti, N., Gilan, M.M. (2019) One-pot synthesis of 2-amino-3-cyanopyridines and hexahydroquinolines using eggshell-based nano-magnetic solid acid catalyst via anomeric-based Oxidation. *Res Chem Intermed* **46**(7): 1-16. doi:10.1007/s11164-019-04049-y.

Allahi, A., Akhlaghinia, B. (2020) WEB (water extract of banana): An efficient natural base for one-pot multi-component synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines. *Phosphorus Sulfur Silicon Relat Elem* **196**(3): 1-9. doi:10.1080/10426507.2020.1835905.

Amer, A. A., Abdelhamid, A. A. (2017) Microwave-Assisted, One-Pot Multicomponent Synthesis of Some New Cyanopyridines. *J Heterocycl Chem* **54**(6): 3126-3132. doi:10.1002/jhet.2926.

Anderson, D. R., Stehle, N. W., Kolodziej, S. A., Reinhard, E. J. (2004) Method of using aminocyanopyridine compounds as mitogen activated protein kinase-activated protein kinase-2 inhibitors. *PCT Int Appl* WO 2004055015 A1 20040701.

Balaswamy, P., Aravind, S., Satyanarayana, B. (2017) Polyethylene glycol-400 used as phase transfer catalyst for one-pot synthesis of 2-amino-3-cyanopyridine derivatives under aqueous conditions. *Rasayan J Chem* **10**(4): 1334-1339. doi:10.7324/RJC.2017.1041903.

Baral, E. R., Sharma, K., Akhtar, M. S., Lee, Y. R. (2016) A catalyst- and solvent-free thermal multicomponent approach for the construction of diverse and polysubstituted 2-aminopyridines and their antibacterial activity. *Org Biomol Chem* **14**(43): 10285–10297. doi:10.1039/c6ob02015a.

Benzenine, D., Kibou, Z., Belhadj, F., Baba-Ahmed, I., Vázquez-Tato, M.P., Seijas, J.A., Choukchou-Braham, N. (2020) Efficient Multicomponent Catalyst Free Synthesis of Substituted 2-aminopyridines. *Chemistry Proceedings* **3**(1): 125-128. doi:10.3390__ecsoc-24-08381.

Bienayme, H., Hulme, C., Oddon, G., Schmitt, P. (2000) Maximizing synthetic efficiency: multi-component transformations lead the way. *Chem Eur J* **6**(18): 3321-3329. doi:10.1002/1521-3765(20000915)6:18<3321::aid-chem3321>3.0.co;2-a.

Chen, H., Zhang, W., Tam, R., Raney, A.K. (2005) Thiazolidinones, oxazolidinones, and pyrrolidinones for HBV. *PCT Int Appl* WO 2005058315 A1 20050630.

Cocco, M. T., Congiu, C., Lilliu, V., Onnis, V. (2005) Synthesis and antiproliferative activity of 2,6-dibenzylamino-3,5-dicyanopyridines on human cancer cell lines. *Eur J Med Chem* **40**(12): 1365-1372. doi:10.1016/j.ejmech.2005.07.005.

Davoodnia, A., Attar, P., Morsali, A., Eshghi, H., Hoseini, N.T., Khadem, S.(2011) Experimental and Theoretical Studies on the Tautomerism in 2-Aminopyridines and 2(1H)-Pyridinones:Synthesis of 2-Amino-4-aryl-3cyano6(3,4dimethoxyphenyl)pyridines and 4-Aryl-3-cyano-6-(3,4-dimethoxyphenyl)-2(1H)-pyridinones. *Bull Korean Chem Soc* **32**(6): 1873-1878. doi:10.5012/bkcs.2011.32.6.1873.

Deng, J., Sanchez, T., Mawsawi, L. Q. A., Dayam, R., Yunes, R. A., Garofalo, A., Bolger, M. B., Neamati, N. (2007) Discovery of structurally diverse HIV-1 integrase inhibitors based on a chalcone pharmacophore. *Bioorg Med Chem* **15**(14): 4985-5002. doi:10.1016/j.bmc.2007.04.041.

Dissanayake, A.A., Staples, R.J., Odom, A.L. (2014) Titanium-Catalyzed, One-Pot Synthesis of 2-Amino-3-cyanopyridines. *Adv Synth Catal* **356**(45): 1811-1822. doi:10.1002/adsc.201301046.

Du, X., Zi, Q., Wu, Y., Jin, Y., Lin, J., Yan,S.(2014) An environmentally benign multi-component reaction: Regioselective synthesis of fluorinated2-aminopyridines using diverse properties of nitro group. *Green Chem* **16**(6): 1-12. doi:10.1039/C8GC03698E.

Ganem, B.(2009) Strategies for Innovation in Multicomponent Reaction Design. *Acc Chem Res* **42**(3): 463–472. doi:10.1021/ar800214s.

Ghomi, J.F., Ghasemzadeh, M.A., Mehrabi, M. (2012) Calcium oxide nanoparticles catalyzed one-step multicomponent synthesis of highly substituted pyridines in aqueous ethanol media. *Scientia Iranica* **20**(3): 549–554. doi:10.1016/j.scient.2012.12.037.

Ghorbani-Vaghei, R.,Toghraei-Semiromi, Z.,Karimi-Nami, R.(2013) One-pot synthesis of 2-amino-3-cyanopyridine derivatives under solvent-free conditions. *Comptes Rendus Chimie* **16**(12): 1111–1117. doi:10.1016/j.crci.2013.06.006

Gogoi, J., Gogoi, P., Goswami, L., Boruah, R.C. (2015) Microwave-Assisted Synthesis of Fused and Substituted 2-Aminopyridinesfrom β-Halo α,β-Unsaturated Aldehydes. *Synthesis* **47**(13): 1905–1912. doi:10.1055/s-0034-1380516.

Hagmann, W. K., Caldwell, C. G., Chen, P., Durette, P. L., Esser, C. K., Lanza, T. J., Kopka, I. E., Guthikonda, R., Shah, S. K., MacCoss, M., Chabin, R. M., Fletcher, D., Grant, S. K., Green, B. G., Humes, J. L., Kelly, T. M., Luell, S., Meurer, R., Moore, V., Pacholok, S. G., Pavia, T., Williams, H. R., Wong, K. K. (2000) Substituted 2-aminopyridines as inhibitors of nitric oxide synthases. *Bioorg Med Chem Lett* **10**(17): 1975-1978. doi:10.1016/s0960-894x(00)00389-9.

Heravi, M.,Zadsirjan, V. (2020) Recent Advances in Applications of Name Reactions in Multicomponent Reactions. *Elsevier*, Amsterdam. doi:10.1016/b978-0-12-818584-1.00007-0.

Huang, H., Guzman-Perez, A., Acquaviva, L., Berry, V., Bregman, H., Dovey, J., Gunaydin, H., Huang, X., Huang, L., Saffran, D., Serafino, R., Schneider, S., Wilson, C., DiMauro, E. F. (2013) Structure-based design of 2-aminopyridine oxazolidinones as potent and selective tankyrase inhibitors. *ACS Med Chem Lett* **4**(12): 1218-1223. doi:10.1021/ml4003315.

Huang, J., Zhou, J., Song, S., Song, H., Chen, Z., Yi, W. (2015) A new and efficient $ZnCl_2$-catalyzed synthesis and biological evaluation of novel 2-amino-3,5-dicyano-4-aryl-6-arylaminopyridines as potent antibacterial agents against *Helicobacter pylori* (HP). *Tetrahedron Lett* **71**(45):8628–8636. doi:10.1155/2018/7958739.

Kale, S., Surve, S. (2021) One-pot multicomponent synthesis of highly substituted pyridines using hydrotalcite as a solid base and reusable catalyst. *Curr Chem Lett* **10**(3): 169-174. doi:10.5267/j.ccl.2021.1.001.

Kalhor, S., Yarie, M., Rezaeivala, M., Zolfigol, M. A. (2019)Novel magnetic nanoparticles with morpholine tags as multirole catalyst for synthesis of hexahydroquinolines and 2-amino-4,6-diphenylnicotinonitriles through vinylogousanomeric-based oxidation. *Res Chem Intermed* **45**(4): 3453–3480. doi:10.1007/s11164-019-03802-7.

Khaksar, S., Yaghoobi, M. (2012) A concise and versatile synthesis of 2-amino-3-cyanopyridine derivatives in 2,2,2-trifluoroethanol. *J Fluor Chem* **142**(2):41-44. doi:10.1016/j.jfluchem.2012.06.009.

Khalifeh, R., Ghamari, M. (2015) A Multicomponent Synthesis of 2-Amino-3-cyanopyridine Derivatives Catalyzed by Heterogeneous and Recyclable Copper Nanoparticles on Charcoal. *J Braz Chem Soc* **27**(4): 759-768. doi:10.5935/0103-5053.20150327.

Khalili, D. (2016) Graphene oxide: a reusable and metal-free carbocatalyst for the one-pot synthesis of 2-amino-3-cyanopyridines in water. *Tetrahedron Lett* **57**(15): 1721-1723. doi:10.1016/j.tetlet.2016.03.020.

Khan, M. N., Karamthulla, S., Choudhury, L. H., HaqueFaizi, M. S. (2015) Ultrasound assisted multicomponent reactions: a green method for the synthesis of highly functionalized selenopyridines using reusable polyethylene glycol as reaction medium. *RSC Advances* **5**(28): 22168–22172. doi:10.1039/c5ra02403j.

Kheilkordi, Z., Ziarani, G.M., Bahar, S., Badiei, A. (2018) The green synthesis of 2-amino-3-cyanopyridines using $SrFe_{12}O_{19}$ magnetic nanoparticles as efficient catalyst and their application in complexation with Hg^{2+} ions. *J Iran Chem Soc* **16**(2):365–372. doi:10.1007/s13738-018-1514-9.

Kibou, Z., Cheikh, N., Choukchou-Braham, N., Mostefa-Kara1, B., Benabdellah, M., Villemin, D. (2011) A new route for the synthesis of 2-aminopyridines. *St Cerc St CICBI* **12**(2): 121–126. doi:1582-540X.

Kibou, Z., Cheikh, N., Villemin, D., Choukchou-Braham, N. (2016) A rapid synthesis of highly functionalized 2-pyridones and 2-aminopyridines via a microwave-assisted multicomponent reaction. *J Mater Environ Sci* **7**(8):3061-3067. doi: 2028-2508/JMESC.

Levy, S.B., Alekshun, M.N., Podlogar, B.L., Ohemeng, K., Verma, A.K., Warchol, T., Bhatia, B., Bowser, T., Grier, M.U.S. (2005) Transcription factor modulating compounds and methods of use thereof. *Patent Appl* 2,005,124,678 A1 20,050,609.

Mahmoud, N.F.H., El-Sewedy, A. (2018) Multicomponent Reactions, Solvent-Free Synthesis of 2-Amino-4-aryl-6-substituted Pyridine-3,5-dicarbonitrile Derivatives, and Corrosion Inhibitors Evaluation. *Hindawi*

Journal of Chemistry **2018**(1):1-9. doi:10.1155/2018/7958739.

Maleki, B., Natheghi, H., Sokhanvaran, V., Ashrafi, S. S. A. (2018) One-Pot-Multicomponent Synthesis of 2,6-Diamino-4-arylpyridine-3,5-dicarbonitrile Derivatives Using Nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$. *Indones J Chem* **18**(4): 639-646. doi:10.22146/ijc.33062.

Mansoor, S. S., Aswin, K., Logaiya, K., Sudhan, S. P. N. (2012) [Bmim]BF_4 ionic liquid: An efficient reaction medium for the one-pot multi-component synthesis of 2-amino-4, 6-diphenylpyridine-3-carbonitrile derivatives. *J Saudi Chem Soc* **20**(5): 517-522. doi:10.1016/j.jscs.2012.07.011.

Mantri, M., de Graaf, O., van Veldhoven, J., Göblyös, A., von FrijtagDrabbeKünzel, J. K., Mulder-Krieger, T., Link, R., de Vries, H., Beukers, M. W., Brussee, J., Ijzerman, A. P. (2008) 2-Amino-6-furan-2-yl-4-substituted nicotinonitriles as A2A adenosine receptor antagonists. *J Med Chem* **51**(15): 4449-4455. doi :10.1021/jm701594y.

Marinescu, M. (2017) 2-aminopyridine – a classic and trendy pharmacophore. *Int J Pharm Bio Sci* **8**(2): 338-355. doi:10.22376/ijpbs.2017.8.2.p338-355.

May, B.C. H., Zorn, J. A., Witkop, J., Sherrill, J., Wallace, A. C., Legname, G., Prusiner, S. B., Cohen, F. E. (2007)Structure–activity relationship study of prion inhibition by 2-aminopyridine-3,5-dicarbonitrile-based compounds: Parallel synthesis, bioactivity and in vitro pharmacokinetics. *J Med Chem* **50**(1): 65-73. doi:10.1021/jm061045z .

Mirjalili, B. B. F., Khabnadideh, S., Gholami, A., Zamani, L., Nezamalhosseini, S. M., Kalantar, N. (2020) $Cu(OAc)_2$ as a green promoter for one-pot synthesis of 2-amino-4,6- diarylpyridine-3-carbonitrile as antibacterial agents. *Bull Chem Soc Ethiop* **34**(1): 149-156. doi:10.4314/bcse.v34i1.14.

Mironov, M. (2010) Multicomponent reactions and combinatorial chemistry. *Russ J Ge Chem* **80**(12): 2628-2646. doi:10.1134/S1070363210120297.

Mobinikhaledi, A., Asadbegi, S., Bodaghifard, M. A. (2016) Convenient, multicomponent, one-pot synthesis of highly substituted pyridines under solvent-free conditions. *Synth Commun* **46**(19): 1605-1611. doi:10.1080/00397911.2016.1218516.

Murata, T., Shimada, M., Sakakibara, S., Yoshino, T., Kadono, H., Masuda, T., Shimazaki, M., Shintani, T., Fuchikami, K., Sakai, K., Inbe, H., Takeshita, K., Niki, T., Umeda, M., Bacon, K. B., Ziegelbauer, K. B., Lowinger, T. B. (2004) Synthesis and structure-activity relationships of novel IKK-beta inhibitors. Part 3: Orally active anti-inflammatory agents. *Bioorg Med Chem Lett* **14**(15): 4019-4022. doi:10.1016/j.bmcl.2004.05.041.

Niknam, K., Jamali, A., Tajaddod, M., Deris, A. (2012) Synthesis of 2-Amino-4,6-diarylnicotinonitriles Using Silica-Bound N-Propyl TriethylenetetramineSulfamic Acid as a Recyclable Solid Acid Catalyst. *Chinese J Catal* **33**(8):1312-1317. doi:10.1016/s1872-2067(11)60421-x.

Nouali, F., Kibou, Z., Boukoussa, B., Choukchou-Braham, N., Bengueddach, A., Villemin, D., Hamacha, R. (2020) Efficient multicomponent synthesis of 2-aminopyridines catalysed by basic mesoporous materials. *Springer Nature BV* **46**(6): 3179-3191. doi:10.1007/s11164-020-04144-5.

Patil, K., Kumbhar, D., Patil, A., Karhale, S., Helavi, V. (2017) Multicomponent, One-pot Synthesis of Highly Substituted Pyridines with Zinc Oxide Nanoparticles as Catalyst. *Indian J Heterocycl Chem* **27**(2): 157-164. doi:res./pub/324824109.

Pejman, H., Hazeri N., Fatahpour, M., Niya, H. F. (2019) A concise route for the one-pot multi-component synthesis of 4,6-disubstituted 2-aminopyridine-3-carbonitriles and pyrano-pyrazoles using cobalt (II) nitrate hexahydrate as catalyst. *Rev Roum Chim* **64**(3): 241-247. doi: 10.33224/rrch.2019.64.3.05.

Perrier, V., Wallace, A. C., Kaneko, K., Safar, J., Prusiner, S. B., Cohen, F. E. (2000) Mimicking dominant negative inhibition of prion replication through structure-based drug design. *Proc Natl Acad Sci U.S.A.* **97**(11): 6073-6078. doi:10.1073/pnas.97.11.6073.

Reddy,D.N.K., Chandrasekhar, K.B., Ganesh, Y.S.S., Reddy, G.R., Kumar, J.P., Kapavarapuc, R.K., Pal, M. (2016) FeF_3-catalyzed MCR in PEG-400: Ultrasound assisted synthesis of N-substituted 2-Aminopyridines. *RSC Advances* **6**(71): 67212–67217. doi:10.1039/c6ra14228a.

Safari, J., Banitaba, S. H., Khalili, S. D. (2012) Ultrasound-promoted an efficient method for one-pot synthesis of 2-amino-4,6-

diphenylnicotinonitriles in water: A rapid procedure without catalyst. *Ultrason Sonochem* **19**(5): 1061-1069. doi:10.1016/j.ultsonch.2012.01.00

Sheibani, H., Saidi, K., Abbasnejad, M., Derakhshani, A., Mohammadzadeh, I. (2011) A convenient one-pot synthesis and anxietic activity of 3-cyano-2(1H)-iminopyridines and halogen derivatives of benzo[h]chromenes. *Arab J Chem* **9**(1): S901–S906. doi:10.1016/j.arabjc.2011.09.006.

Tamaddon, F., Ghazi, S., Noorbala, M. R. (2016) Urease-catalyzed synthesis of aminocyanopyridines from urea under fully green conditions. *J Mol Catal B Enzym* **127**: 89-92. doi:10.1016/j.molcatb.2016.02.015

Tang, J., Wang, L., Yao, Y., Zhang, L., Wang, W. (2011)One-pot synthesis of 2-amino-3-cyanopyridine derivatives catalyzed by ytterbium perflurooctanoate [Yb(PFO)$_3$]. *Tetrahedron Lett* **52**(4): 509–511. doi:10.1016/j.tetlet.2010.11.102

Thimmaiah, M., Li, P., Regati, S., Chen, B., Zhao, J.C.G. (2012) Multi-component synthesis of 2-amino-6-(alkylthio)pyridine-3,5-dicarbonitriles using Zn(II) and Cd(II) metal–organic frameworks (MOFs) under solvent free conditions. *Tetrahedron Lett* **53**(36): 4870–4872. doi:10.1016/j.tetlet.2012.06.139

Torabi, M., Yarie, M., Zolfigol, M. A. (2019) Synthesis of a novel and reusable biological urea based acidic nanomagnetic catalyst: Application for the synthesis of 2-amino-3-cyanopyridines via cooperative vinylogous anomeric based oxidation. *Appl Organomet Chem* **33**(6): 1-15. doi:10.1002/aoc.4933

Weber, L. (2002) The Application of Multi-Component Reactions in Drug Discovery. *Curr Med Chem* **9**(23): 2085-2093. doi:10.2174/0929867023368719

Yahyazadeh, A., Abbaspour-Gilandeh, E., Aghaei-Hashjin, M. (2018) Four-Component synthesis of 2-amino-3-cyanopyridine derivatives catalyzed by CuimineZCMNPs as a novel, efficient and simple nanocatalyst under solvent-free conditions. *Catal Lett* **148**(4): 1254-1262. doi:10.1007/s10562-018-2318-3

Younis, Y., Douelle, F., Feng, T.S., González Cabrera, D., Le Manach, C., Nchinda, A. T., Duffy, S., White, K. L., Shackleford, D. M., Morizzi, J., Mannila, J., Katneni, K., Bhamidipati, R., Zabiulla, K. M., Joseph, J. T., Bashyam, S., Waterson, D., Witty, M. J., Hardick, D., Wittlin, S., Avery, V., Charman, S. A., Chibale, K. (2012) 3,5-Diaryl-2-aminopyridines as a novel class of orally active antimalarials demonstrating single dose cure in mice and clinical candidate potential. *J Med Chem* **55**(7): 3479-3487. doi:10.1021/jm3001373

Zhang, Y.L., Li, Y.F., Shi, X.L., Yu, B., Shi, Y.K., Liu, H.M. (2016) Solvent-free synthesis of novel steroidal 2-aminopyridines. *Steroids* **115**: 147-153. doi:10.1016/j.steroids.2016.09.005

Zolfigol, M. A., Yarie, M. (2017) Fe_3O_4@TiO_2@$O_2PO_2(CH_2)NHSO_3H$ as a novel nanomagnetic catalyst: Application to the preparation of 2-amino-4,6-diphenylnicotinonitriles via anomeric-based oxidation. *Appl Organomet Chem* **31**(5): 1-10. doi:10.1002/aoc.3598