# ONE-POT SYNTHESIS OF SUBSTITUTED PYRIDINES THROUGH MULTICOMPONENT REACTION

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## ABSTRACT:

Multi-component reactions (MCRs) are composed of three or more reagents with the final product comprising of all or most of the carbon atoms from its substrates. They provide an attractive entry into pyridine derivatives, which is a very important class of heterocyclic chemistry from a variety of perspectives including medicinal, electrochemical, agrochemical and pharmaceutical. The aim of this review is to provide a comprehensive overview of literature on one-pot multicomponent synthesis of substituted pyridines.

## 1. INTRODUCTION

Due to its widespread usage in the synthesis of physiologically active chemicals in heterocyclic, medicinal, and combinatorial chemistry, the development of multi-component reactions (MCRs) has gotten a lot of attention. By virtue of its environmental considerations, productivity, atom- economy, ease of execution, and high yields, one-pot multi-component synthetic techniques give significant advantages over standard linear-type creating products[1]. These characteristics make MCRs ideal for quickly constructing a wide range of heterocyclic scaffolds, such as useful heterocyclic scaffolds.

The first major synthesis of pyridine derivatives was described in 1881 by **Arthur Rudolf Hantzsch**.. **Anderson**'s remarkable experiment in 1846, when he was examining the pyrolysis of bones and was able to separate picoline as the first identified pyridine, is associated to the discovery of the pyridine core (Pyr, meaning fire in Greek, and idine, a suffix used for aromatic bases). Since **Körner (1869)** and **Dewar (1871)** proposed the proper structure, this ring has become one of the most researched aromatics, and there are various reasons why the pyridine nucleus seems to be so appealing[2].

Pyridine derivatives are an important class of heterocyclic motifs in a variety of areas of organic chemistry, widely found in the core of alkaloids, biologically active compounds, chiral ligands, clinical drugs, exist in many active pharmaceuticals and functional materials[3,4]. Among them, 2-amino-3-cyano pyridine derivatives are known to have multiple biological activities, such as anti-inflammatory, analgesic and antipyretic properties. As a result, establishing methods for preparing polysubstituted pyridine derivatives is crucial for medicinal chemistry and is a good target for organic synthesis [3]. Besides pyridine synthesis, the oxidation of Hantzsch 1,4- dihydropyridines seems to be of considerable interest, because 1,4-dihydropyridine-based calcium channel blockers are oxidatively transformed to pyridine derivatives by cytochrome P-450 in the liver[5].

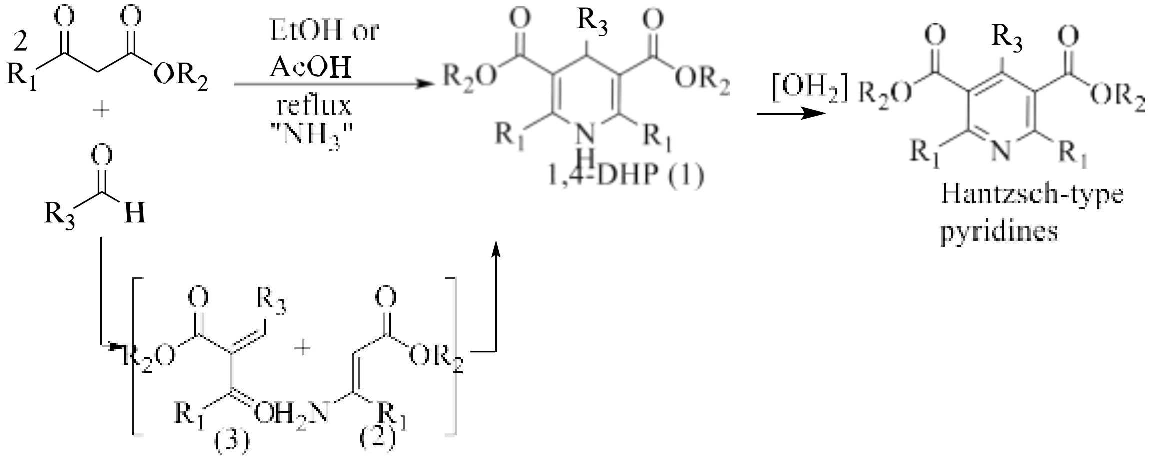
The transition-metal-catalyzed C-C cross-coupling reaction has been used in a wide range of applications in recent years. Peter recently reported by using Suzuki–Miyaura reaction to achieve site-selective arylation of widely viable 2,3,5,6-tetrachloropyridine, permitting the selective synthesis of mono-, di-, tri-, and tetraarylated pyridines in good to quantifiable yields[6].

We ’re focusing in this article on current selected advancements in the production of one- pot multicomponent approaches towards pyridines, because establishing "green chemistry" strategies has never been an emergency in our economical and environmental scenario. The existing literature has been arranged according to the major reaction involved in each procedure, with an emphasis on the pyridine ring synthesis.

## 2. HANTZSCH PYRIDINE SYNTHESIS

The two-step approach is one of the most popular methods for pyridine synthesis developed by **Hantzsch** in **1881**, which involves the oxidation of 1,4-dihydropyridines **1** (DHPs), earlier formed via one-pot pseudo-four-component reaction of 2 equiv of a 1,3-dicarbonyl derivative, an aldehyde and a source of ammonia (Scheme 1).

A cyclodehydration between in situ produced enamino ester **2** and alkylidene malonate **3** intermediates yields the corresponding symmetrical heterocycles. The aromatized products are obtained after further oxidation[7].



**Scheme 1**. General Hantzsch Pyridine Synthesis

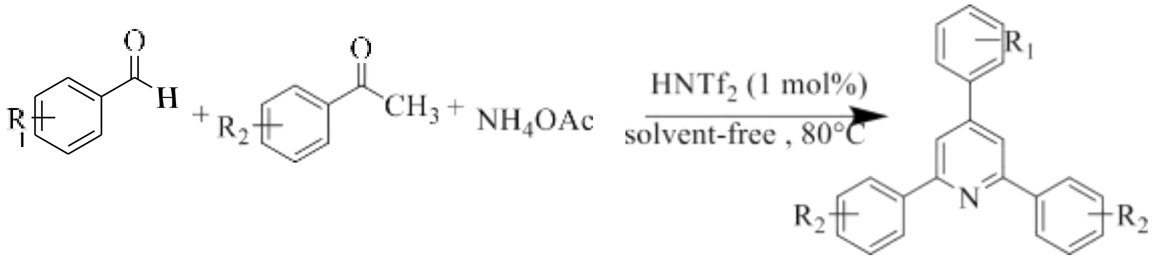
## 3. PYRIDINE SYNTHESIS BASED ON THE MICHAEL ADDITION

The two methods for synthesising pyridines have been detailed in this section, both of which need a key step of michael addition. The two strategies are presented in contrast to one another because one is catalysed while the other is not.

### 3.1 HNTf$_2$ catalyzed synthesis

The versatile super Bronsted acid triflimide (HNTf$_2$) serves as an effective catalyst in the synthesis of 2,4,6-triarypyridines from aromatic aldehydes, substituted acetophenones, and ammonium acetate in this simple and efficient approach.With both electron-donating and electron- withdrawing substituents on the aromatic ring, reactions are equally facile, and all products are produced in high yields.

**Advantages and limitations:** The use of a metal-free, commercially accessible catalyst, a concise experimental and work-up technique, excellent yields, gentle reaction conditions, and lower catalyst loading are all merits of this procedure. The method requires a 1 mol% $HNTf_2$ catalyst, but it is not reused. This is a major constraint[8].



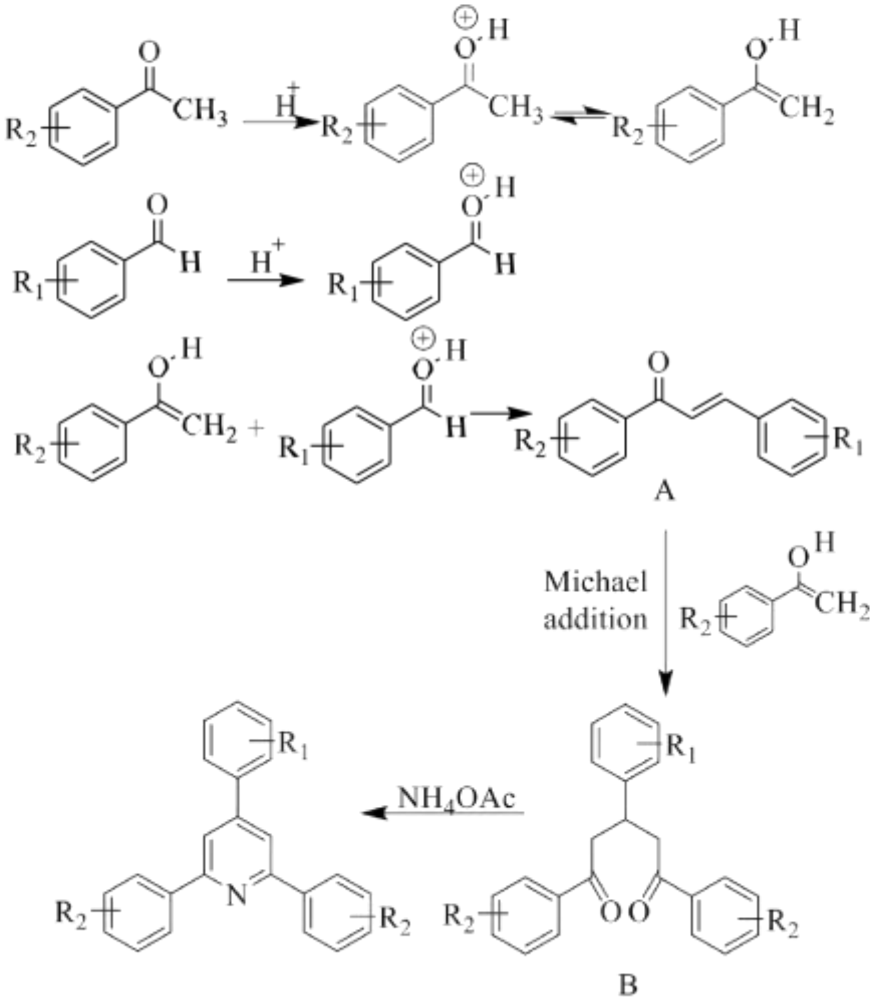
**Scheme 2.** $HNTf_2$ catalyzed one pot three-component synthesis of 2,4,6-triarylpyridines

**Reaction Condition:** benzaldehyde (1 mmol), acetophenone (2 mmol), ammonium acetate (1.5 mmol), solvent (3 mL), $HNTf_2$ (1 mol%) at 80 ˚˚C for 50 min.
Best performance was obtained when 1 mol% of catalyst was used at 80 C˚ under solvent-free conditions[8].

**Mechanism:**

In Scheme 3, a possible mechanism for the synthesis of 2,4,6-triarylpyridines has been proposed. $HNTf_2$ works as an efficient Bronsted acid catalyst by activating the carbonyl group of an aromatic aldehyde and a substituted acetophenone, leading to aldol condensation to generate a 1,3-diaryl-2-propen-1-one **A**, which then underwent Michael addition to yield an intermediate **B**.

The required product is then obtained by cyclization and dehydrogenation of Intermediate **B**[8].

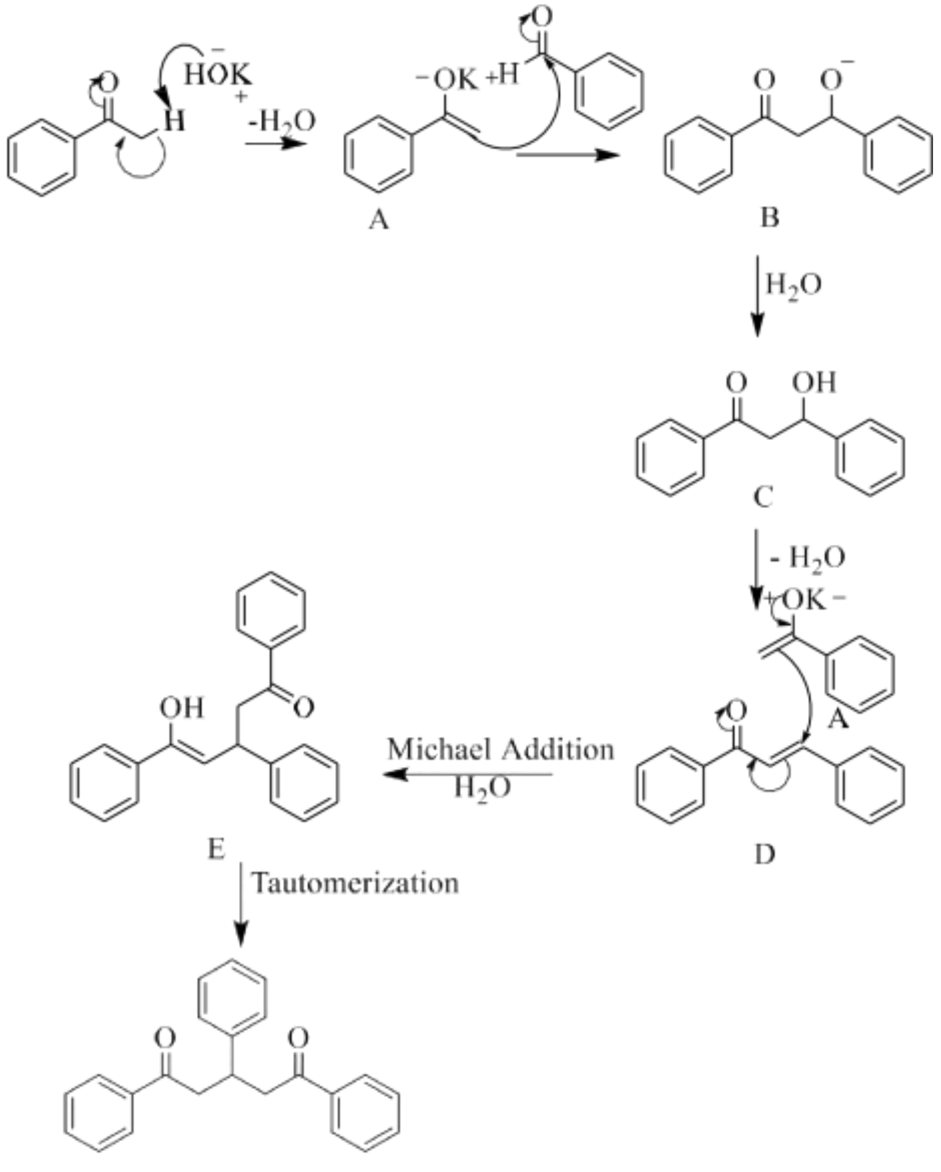


Scheme 3. Plausible reaction mechanism

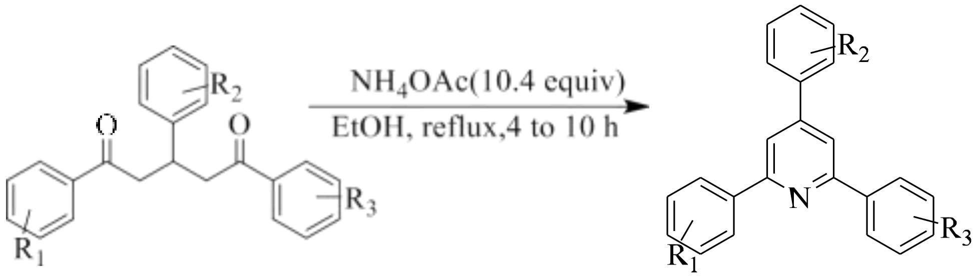
### 3.2 Catalyst free synthesis under transition- metal- free condition

Claisen Schmidt condensation followed by Michael addition of aryl ketones and aryl aldehydes under a transition-metal-free condition is a simple and green one-pot procedure for the synthesis of substituted 1,3,5-triaryl-1,5-diketones. Ammonium acetate was used as a nitrogen source in the synthesis of 2,4,6-triaryl pyridine in a catalyst-free system.

**Advantages:** a shorter reaction time, transition-metal-free, a high isolated yield, no extra additives or reagents, a broad substrate scope, a low amount of base employment, the use of cheaper starting materials, cost-effectiveness and environmental friendly, simple workup and reaction procedure[9].



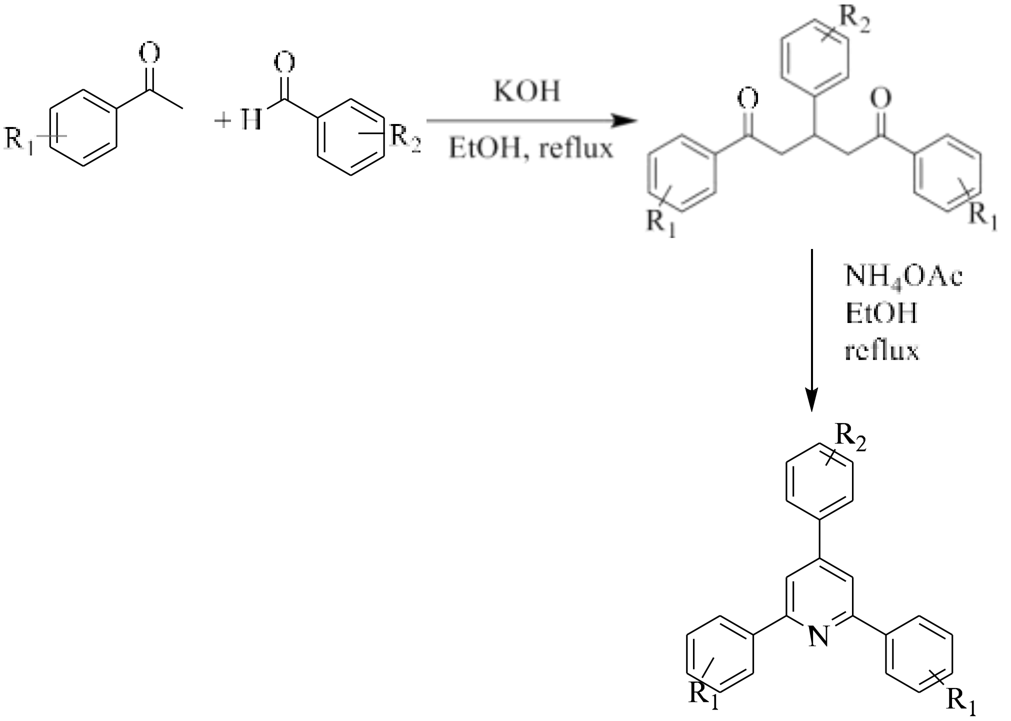
**Scheme 5.** Plausible mechanism for one-pot synthesis of 1,5- diketone



**Scheme 6.** Catalyst free cyclization of 1,5- diketones to give 2,4,6- triaryl pyridine derivatives

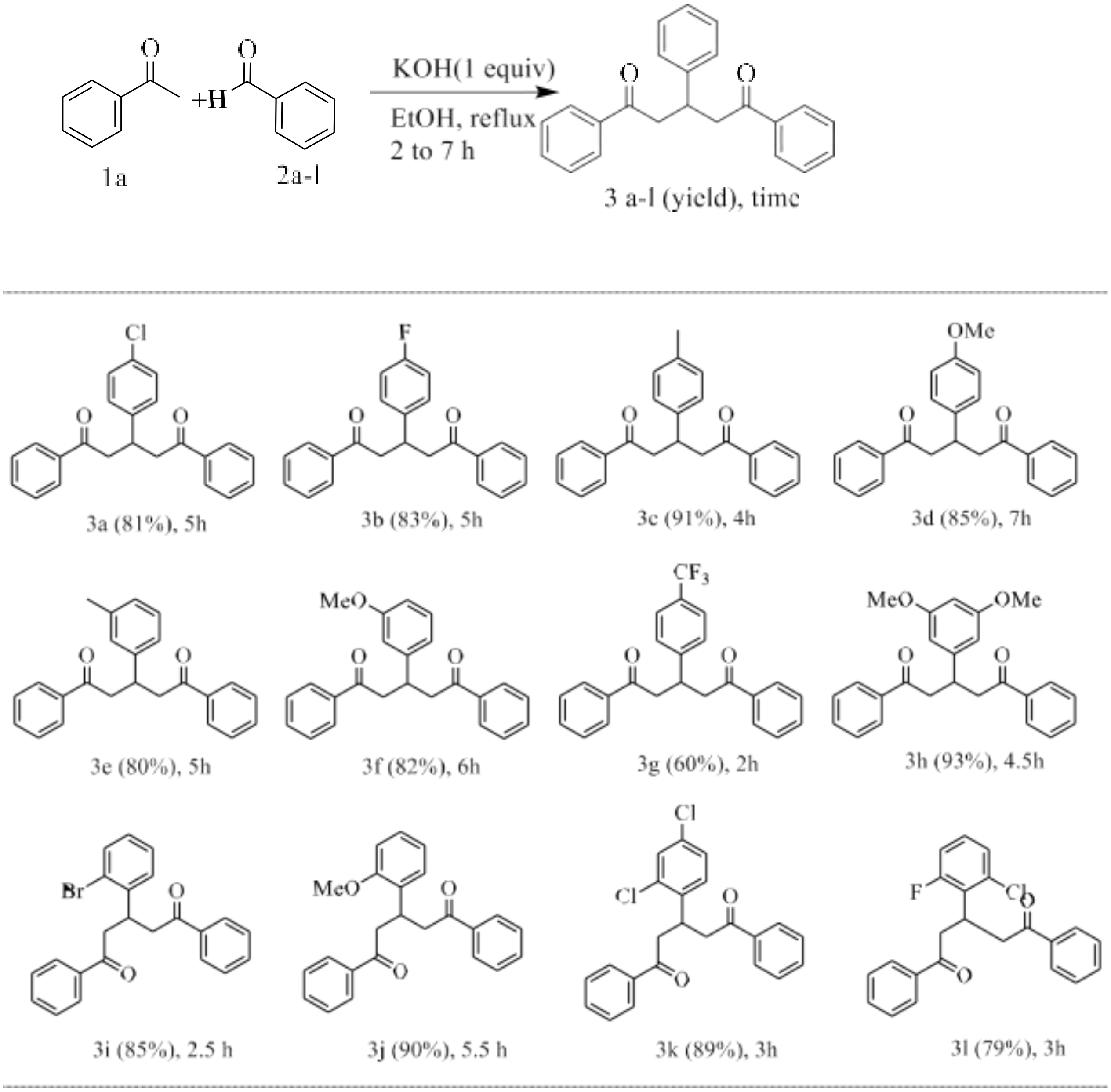
On optimization, best suited reaction conditions for the one-pot synthesis of 1,3,5-triphenylpentane-1,5-dione using acetophenone (1.88 mmol, 2.0 equiv) and benzaldehyde (0.94 mmol, 1.0 equiv) as substrates were taken to be 1 equiv of KOH as base, ethanol as solvent and refluxing.

1,5-diones with weak electron-donating groups on the aromatic ring, such as methyl and chloro groups, could provide higher yields of 2,4,6-triaryl-substituted pyridines than those with strong electron-donating groups, such as the methoxy group. These findings are consistent with those of **Chen et. al.,** who used a one-pot protocol with $Cu(OTf)_2$ as the catalyst to synthesis a large number of polysubstituted pyridines[9].



**Scheme 4.** Transition-metal-free synthesis of 2,4,6-triarylpyridines

**Table 1. Substrate Scope with Respect to Aryl Aldehydes 2**



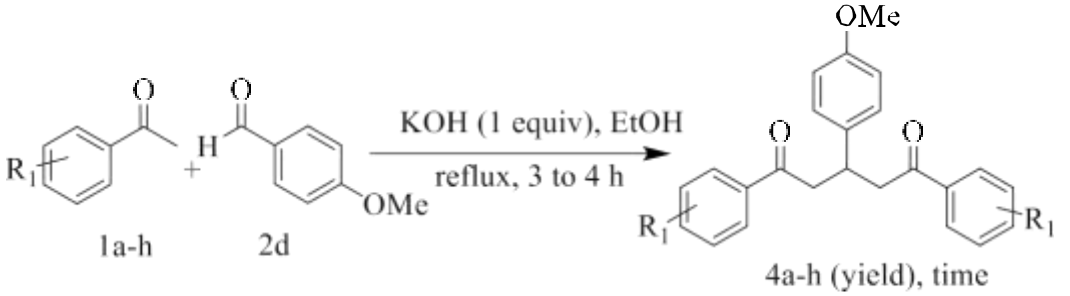
3a (81%), 5h
3b (83%), 5h
3c (91%), 4h
3d (85%), 7h
3e (80%), 5h
3f (82%), 6h
3g (60%), 2h
3h (93%), 4.5h
3i (85%), 2.5 h
3j (90%), 5.5 h
3k (89%), 3h
3l (79%), 3h

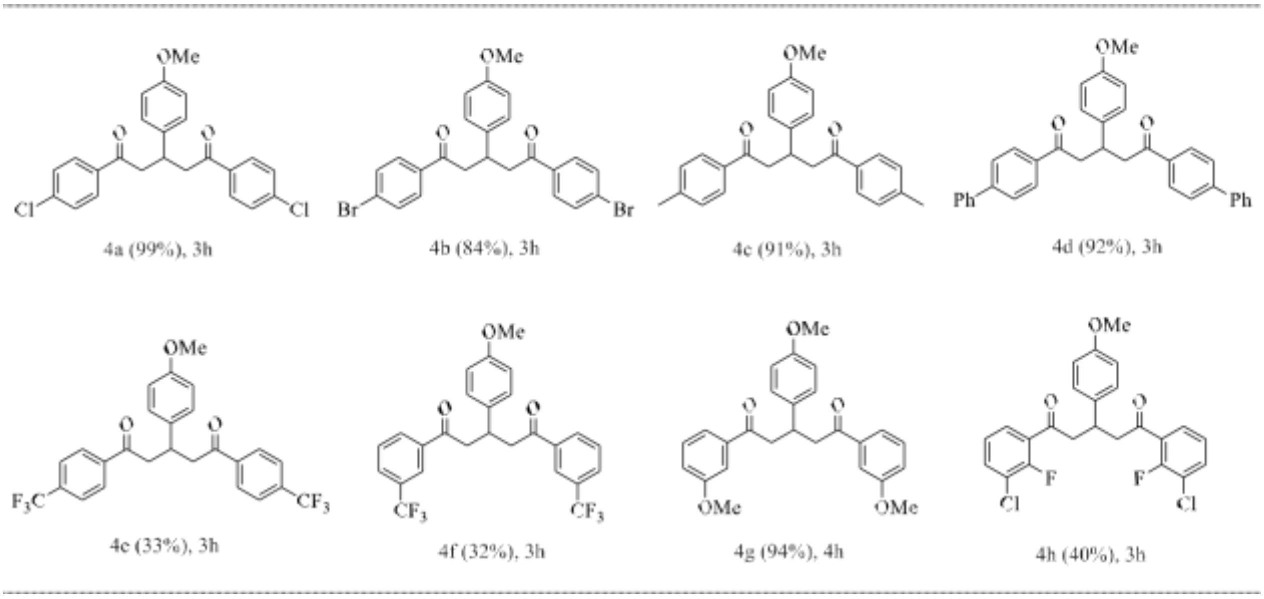
Table 1 summarized the results of a study of the substrate scope of KOH-mediated reactions employing different substituted aryl aldehydes (**2a-l**) and acetophenone (**1a**). Thus, under the same reaction conditions, the Claisen Schmidt condensation-Michael addition reaction of aryl methyl ketone (**1a**) with aryl aldehydes (**2a-f)** and **3h-l**), reacted smoothly to give the corresponding 1,5- diketones **3a-f** and **3h-l** in good yields of **79-93%**.

The benzaldehyde derivatives possessing an electron-withdrawing group were observed to possess shorter (2−3 h) reaction time than those which contained electron-donating substituents (4−7h).

**Kamble** and **Shankarling** also supported this observation[9].

**Table 2. Substrate Scope of Substituted Aryl Ketones 1**





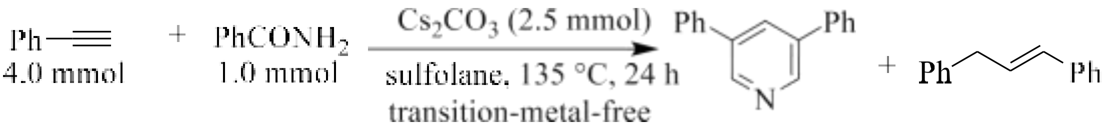
Reaction of substituted acetophenone occured efficiently with aldehyde **2d** to give the corresponding 1,5-diketones **4a-d, 4g** in very good to excellent yields (**84% to quantitave**) regardless of the substituents positions. The high electron-withdrawing nature of the substituents on the aryl substrates may explain the lower yields of products **4f-h**[9].

## 4. METAL-FREE MULTICOMPONENT SYNTHESIS

### 4.1 BASE PROMOTED SYNTHESIS VIA AROMATIC ALKYNE

### ANNULATION USING BENZAMIDES AS NITROGEN SOURCE

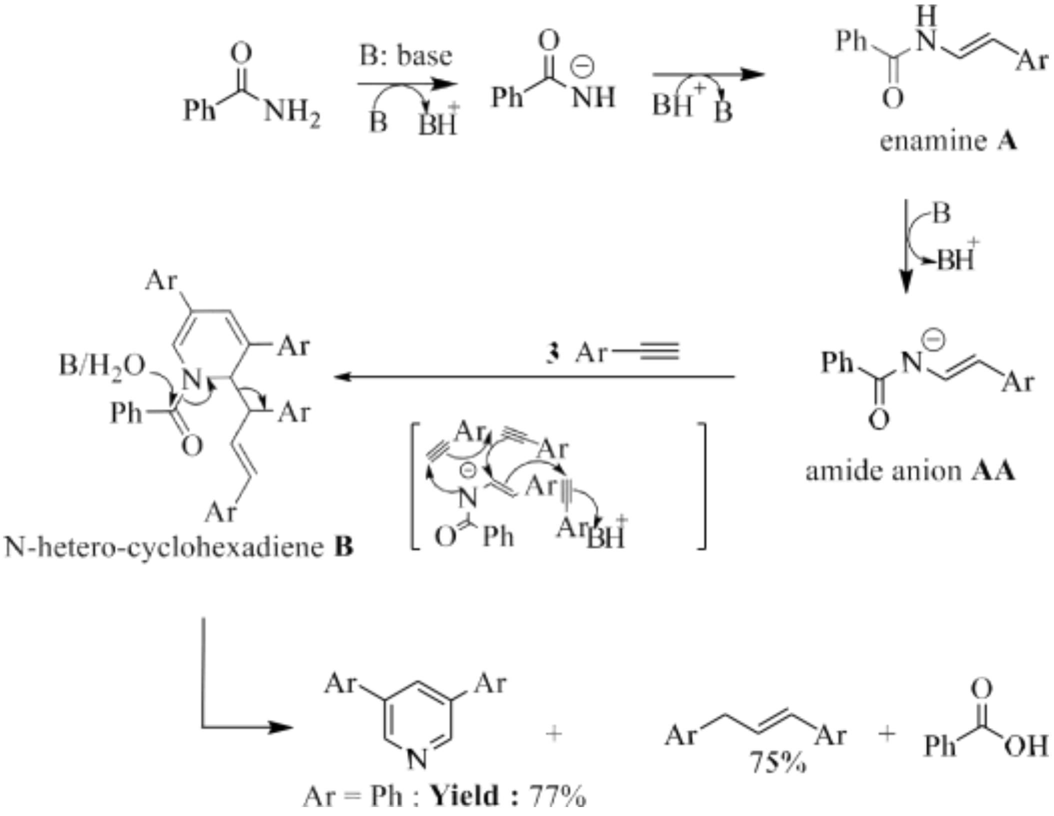
This method is of keen interest, since there has never been a report on the synthesis of 3,5-disubstitued pyridines in one-pot manner starting from alkynes; in addition, it is also a new transformation of alkynes. Here, the by-product i.e. 1,3-diphenyl propene, which has wide range of application and is difficult to prepare by traditional organic synthesis, was isolated in good yield (75%)[10].



Scheme 7. One-pot synthesis of pyridines by alkyne annulation reported by Hua's group.

The above mentioned reaction conditions were best suited and produced 77% yield of the disubstituted pyridine.The reaction worked best when benzamide was used as N-source. On replacement with acetamide, no desired product was formed which is maybe due to its more basic nature.

A proposed mechanism for the base-promoted annulation of alkynes with benzamides to form pyridine ring is depicted in Scheme 8. Enamine intermediate **A** is formed by the base promoted addition reaction, which then forms amide anion **AA.** Further, cycloaddition occurs to give intermediate **B**, which ultimately gets converted into pyridine and propene under basic conditions and with a small amount of water via cleavage of C-N and C-C bonds[10].



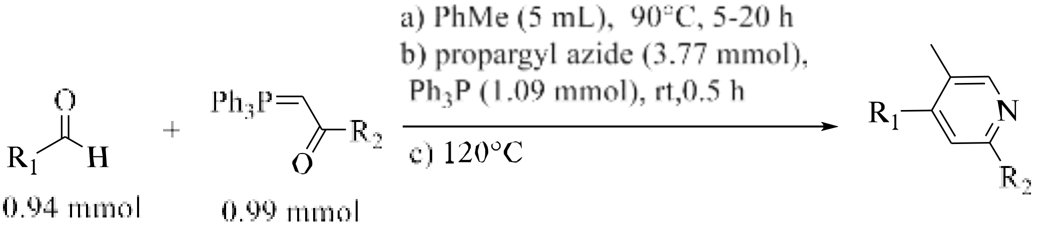
Scheme 8. Probable mechanism for pyridine synthesis by alkyne annulations.

### 4.2 Synthesis via Cascade reaction

It is still of keen interest to develop an effective and generic approach for the production of substituted pyridines from commonly available substrates using mild reaction conditions.

**Cascade reactions** comprising basic operational techniques and equipment are often utilised to save time and energy, prevent intermediates isolation, and to enhance reaction efficiency, which is in agreement with what green chemistry promotes.

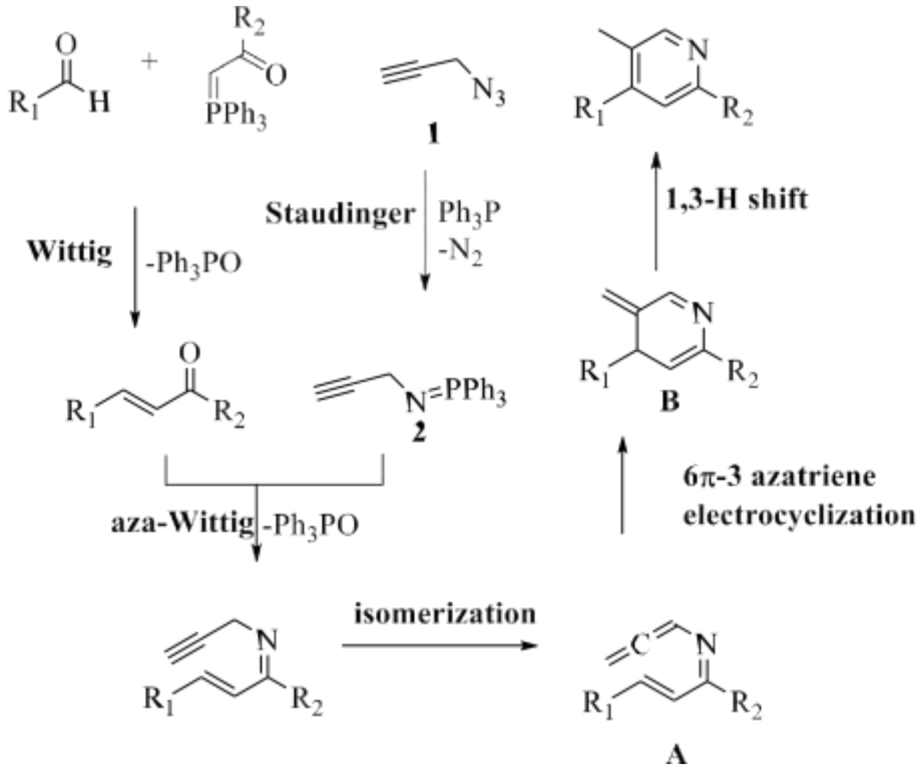
A metal-free, multicomponent, one-pot sequence that included a Wittig reaction, a Staudinger reaction, an aza-Wittig reaction, a 6□-3-azatriene electrocyclization reaction, and a 1,3-H shift has been presented in Scheme 9 for the efficient one-pot formation of substituted pyridines from an aldehyde, phosphorus ylide[11].



Scheme 9. Synthesis of pyridines using metal-free strategy

Reaction worked well with aldehydes containing one or two electron-releasing groups (Me or MeO) or moderately weak electron withdrawing group (halogen or $CO_2Me$) on the phenyl ring which resulted in good yields (78−90%) of pyridines. Whereas, aldehydes bearing more electron- deficient phenyl ring slowed the reaction and produced remarkably low yields for the pyridine products (63–74%). Phosphorus ylides containing a bulky alkyl group could also be used in this method, but the yields were significantly lower. Moreover, no predicted product was obtained when the R2 group was H, most likely due to poor imine synthesis via a Staudinger reaction. Moreover, no predicted product was obtained when the $R_2$ group was substituted by H, most likely due to poor imine synthesis via a Staudinger reaction.

The probable reaction mechanism has been provided in Scheme 10, where Wittig reaction lead to the formation of □□□□unsaturated ketone **A.** Azide(**1**) reacted independently with triphenylphosphine to give phosphazene (**2**) via Staudinger reaction. Then, aza- Wittig reaction produced imine which on isomerization gave rise to intermediate **A**, which has an allene moiety conjugated to □□□□unsaturated imine. Lastly, trisubstituted pyridine was obtained by triggering 6□-3-azatriene electrocyclization of **A** , followed by a 1,3-H shift[11].

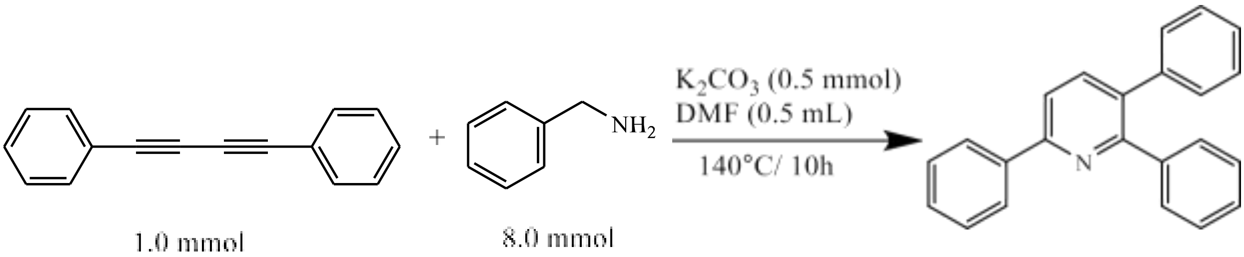


**Scheme 10.** Proposed reaction mechanism

## 5. BASE CATALYSED SYNTHESIS FROM CONJUGATED ACETYLENES AND BENZYLAMINES

Chalk's research yielded just 70% of 2,3,6-triphenylpyridine from solutions of 1,4-diphenylbutadiyne in benzylamine (1:6.13 mmol) after 2 to 3 hours at 180°C under nitrogen, which stimulated our interest in improving the synthetic yield of arylated pyridines from conjugated acetylenes and substituted benzylamines under ideal conditions.

Conjugated acetylenes and substituted benzylamines reacted smoothly to produce tri-aryl substituted pyridines in good to excellent yields in N,N-dimethylformamide (DMF) under air at 140 °C in presence of $K_2CO_3$ as catalyst[6].



**Scheme 11.** Synthesis of arylated pyridines from conjugated acetylenes and substituted benzylamines

The catalyst K2CO3 gave nearly quantitative yield (99 percent). Other bases, like Na2CO3, NaOH, KOH, and KHCO3, yielded good results as well. Cs2CO3, NaF, NaH2PO4, KH2PO4, and CH3COONa produced only low yields under identical reaction conditions.

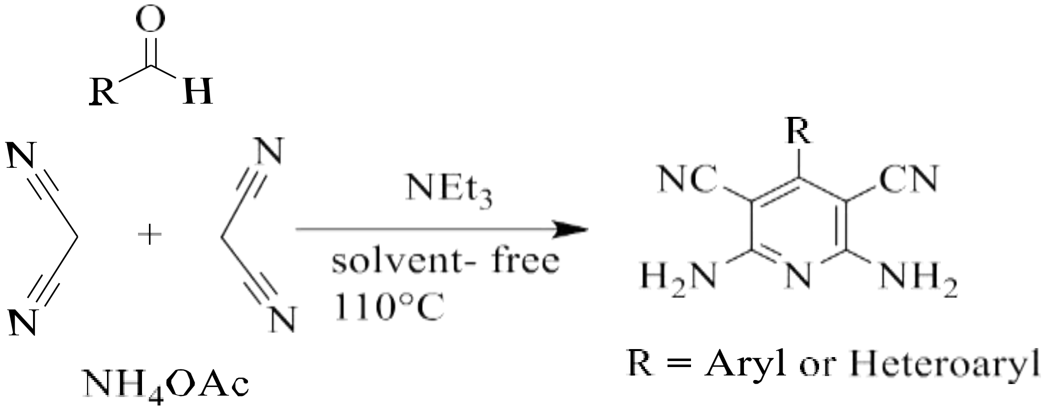
The substituted benzylamine containing an electron-donating group reacted smoothly, producing a nearly quantitative yield (99%). Various substituted benzylamines with electron-withdrawing groups, such as -F, -Cl, and -CF3, gave moderate to good yields of the respective products. The substrate containing an electron-withdrawing substituent in the 3-position of benzylamine had a significant impact on the reaction yield, which was only around 50% due to steric and electronic effects.

When compared to Chalk's method, the pros of this protocol included the absence of byproducts, even when the reaction performed in the air[6].

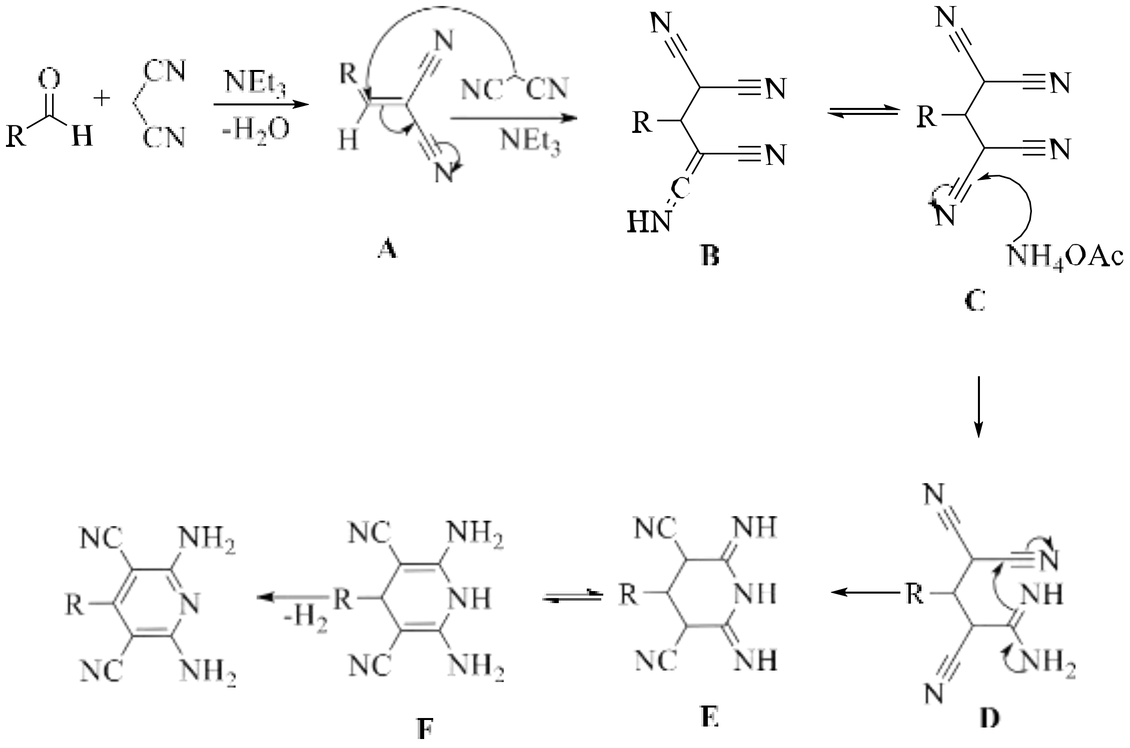
## 6. SOLVENT FREE SYNTHESIS OF HIGHLY SUBSTITUTED PYRIDINES

This method incorporates aldehydes, malononitrile and ammonium acetate under solvent-free conditions catalysed by triethylamine into the desired highly substituted pyridine derivatives. It yields high purity compounds and has several strengths including shorter reaction time, high yields and concise workup treatment.

The mechanism is depicted in Scheme 12[1].



**Scheme 12.** Multicomponent solvent- free synthesis of pyridine derivatives.



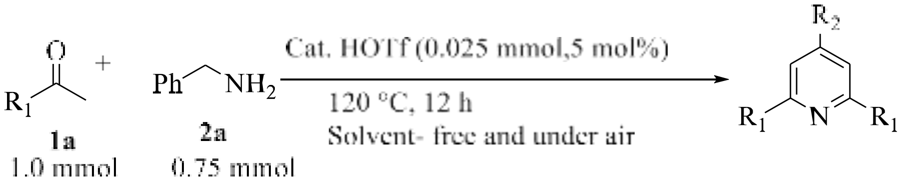
**Scheme 13.** Plausible mechanism for the solvent-free synthesis of substituted pyridine

## 7. HOTf-CATALYZED AND SOLVENT-FREE SUSTAINABLE SYNTHESIS

Conventional thermal condensation of carbonyl compounds is a common approach for the preparation of pyridines, among a variety of diverse methodologies. High temperatures and extreme circumstances, but at the other hand, are mainly encountered in these reactions.

One current emerging approach to overcome the aforementioned shortcomings is to synthesize it via a transition-metal-catalyzed cycloaddition procedure. However, in terms of activity, selectivity, reaction condition, substrate scope, as well as functional group tolerance, such an approach could replace known techniques. For an instance, Cheng, Ellman, and Rovis groups independently revealed the Rh catalysed C-H functionalization of, □□□□unsaturated oximes/imines with alkynes or alkenes, allowing easy access to pyridine products. Wang and colleagues recently described an effective Ru-catalyzed dehydrative [4+2] cycloaddition of enamides and alkynes that yielded highly substituted pyridines. These diverse reactions, on the other hand, frequently demanded the introduction of external oxidants and/or additives, resulting in stoichiometric levels of associated transition-metal byproducts and the application potential too got limited due to certain reasons. As a result, establishing a more generic, practically concise, and versatile pyridine scaffold synthesis approach is very desirable.

Using ketones along with amines as simple reagents, a diverse HOTf-catalyzed and solvent-free method for extremely efficient one-pot synthesis of pyridine derivatives has been established. Good to high yields, exclusive chemoselectivity, solvent-free and wide range of substrate/functional group tolerance are all notable aspects of this "green" reaction[12].



**Scheme 12.** One-pot construction of pyridine derivatives via HOTf-catalyzed chemoselective condensation reaction

In the absence of solvent, the reaction of reagents **1a** and **2a** produced the desired product with a remarkable yield of **87%.** Both substrates tolerated substitutes at the para- and meta-positions well.

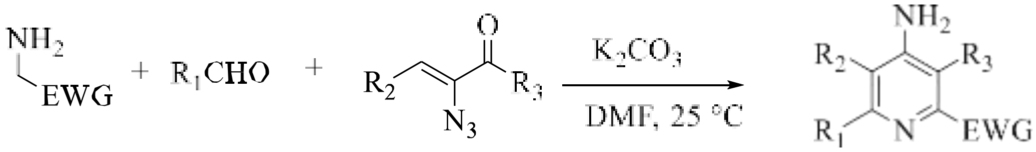
It must be highlighted that the electronic behavior of the substituent on the benzene ring in the precursors had a significant impact on the reaction yield, with the substrates having electron-releasing groups offering better yields than those having electron-withdrawing groups. An important fact about the synthesis is that the active catalyst HOTf is recoverable[12].

## 8. SYNTHESIS OF POLYSUBSTITUTED 4-AMINOPYRIDINES

Some conventional synthetic methods need not just a long reaction time, elevated temperature, costlier transition metal additives, or complex substrates, but also low yields in addition to isomers.

Domino reactions have turned out to be extremely powerful by meeting the green chemistry criteria of being both environment friendly and atom-cost-effective, for the formation of complex compounds by forming multiple bonds in one-pot reactions. The domino process, which uses □□□□azidovinylketone to synthesize polysubstituted 4-aminopyridines in a "one-pot" three- component approach, has been explored here. The fact that three molecules could be directly assembled into the desired compounds in a highly efficient and atom-economic manner under mild conditions is an interesting feature of this methodology.

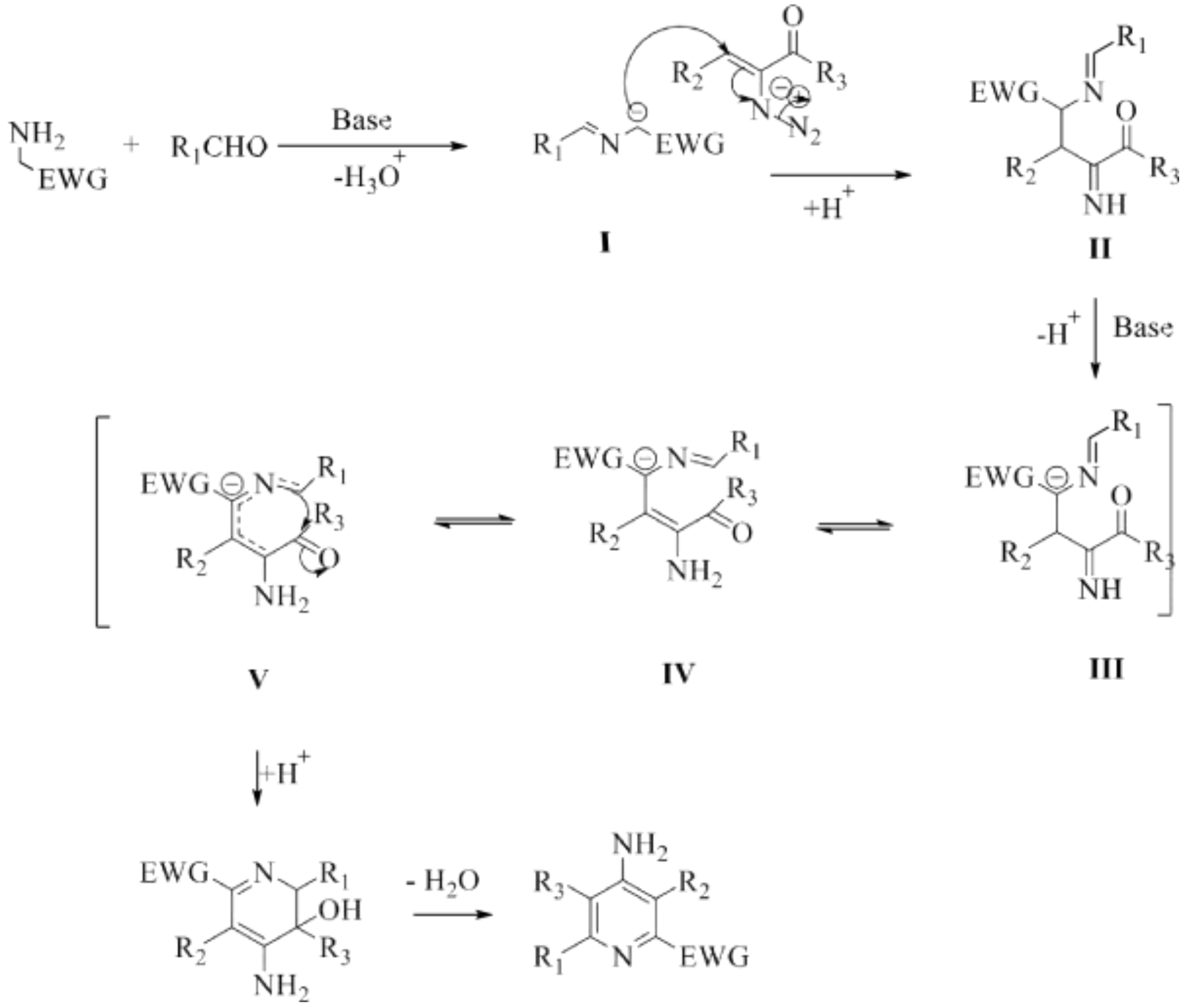
It's worth noting that literature on the direct synthesis of 4-aminopyridine derivatives is scarce. COX-2 inhibitors and acetylcholine-releasing agents are among the biological functions of several 4-aminopyridine derivatives[3].



**Scheme 13.** Synthesis of polysubstituted 4-aminopyridines

Electron-deficient benzaldehydes produced the desired products in less time and with higher yields over electron-rich benzaldehydes. To attain intermediate yields, some of the electron-rich benzaldehydes even required a higher temperature. Performance of methylamines having a cyano group was found to be better than the ones with an ester group.

The probable mechanism has been depicted in Scheme 14 where in the first step, condensation took place to give the corresponding imine (**I**), which underwent intermolecular Michael addition with □□□□azidovinylketone and nitrogen elimination resulting in intermediate (**II**). Base further attacked (**II**) to afford intermediate (**III**). Eventually, intramolecular cyclization took place to yield the desired product[3].



**Scheme 14.** Proposed reaction mechanism

In terms of atom count, this synthesis is economical because only nitrogen and water molecules are released in this one-pot synthesis. Overall, this reaction's ability to insert functional groups into the pyridine ring system, 9makes it a promising method for pharmaceutical building blocks and medicinal chemistry applications[3].

## 9. CONCLUSION

This compilation of diverse one-pot multicomponent reactions applied to the synthesis of substituted pyridines includes some strategies that are highly economical and environmental benign. When it comes to deciding a method, there is no such thing as the ideal multicomponent pyridine synthesis; instead, it is a matter of substitution pattern. These highly substituted pyridine compounds could be useful chemotypes in molecular design studies.

In a section of this review paper, the synthesis of 3,5-diaryl pyridines by $Cs_2CO_3$-promoted annulation of aromatic terminal alkynes using benzamides as nitrogen providers in sulfolane has been discussed. Noteworthy, it is of considerable interest, since this approach has never been reported starting with alkynes, in a one-pot manner with exceptional chemoselectivity. In addition, it is a new alkyne transformation.

Multiple improvements to well-known methods to synthesize the pyridine ring have been added to the organic chemist's toolkit over many decades. Scientists are especially interested in this field because heterocyclic building blocks are quite useful as intermediaries in medication development.

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