



ONE-POT SYNTHESIS OF 2,4,6-TRIARYL PYRIDINES USING MAGNESIUM ACETATE AS ORGANOMETALLIC CATALYST UNDER SOLVENT FREE CONDITION

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ABSTRACT

A simple, efficient, rapid method has been developed for synthesis of 2,4,6-triarylpyridines derivatives by the condensation reaction of aromatic aldehyde derivatives acetophenone derivatives and ammonium acetate with Magnesium acetate as organometallic catalyst. This approach offers many advantages such as good product yield, short reaction time, easy isolation of products, mild reaction conditions and environmentally benign reaction conditions.

KEY WORDS: Magnesium acetate; multi-component reaction; Triarylpyridine; Solvent-free.

INTRODUCTION

The development of simple, efficient and economically viable chemical process or methodologies for widely used organic compounds are in great demand¹. Multicomponent reactions (MCRs) via one-pot reaction have received a great deal of interest because of their atom-economy and straightforward reaction design due to substantial minimization of waste, labour, time, and cost.²⁻⁴ Nowadays, exploration of solvent-free conditions in reactions as a central tenet of Green Chemistry has gained importance due to several advantages, including experimental simplicity, less energy requirement, and almost quantitative reactivity of the substrates.^{5,6} N-heterocyclic compounds, such as pyridines have a unique position in synthetic chemistry. The pyridyl heterocyclic nucleus is a building block in molecules of natural products, pharmaceuticals such as vasodilator, anticonvulsant, antiepileptic, anaesthetic and agrochemicals such as pesticides and herbicides⁷⁻¹⁰. Due to their π -stacking ability, they are prominent synthons in supramolecular chemistry.¹¹⁻¹³ Their excellent thermal stabilities have investigated their use as monomeric building blocks in thin films and organometallic polymers.^{14,15} Pyridines (Kröhnke pyridines) have been synthesized using various methods and procedures. Traditionally, these compounds have been synthesized through the reaction of *N*-phenacylpyridinium salts with α,β -unsaturated ketones in the presence of

NH_4OAc .^{16, 17} Recently, several new improved methods have been developed for the synthesis of 2,4,6-triaryl pyridines. Among all these methods, one pot synthesis of poly-substituted pyridines from acetophenones, aryl aldehydes, and NH_4OAc is the well-established protocol. These protocols include: using NaOH in PEG,^{18–20} catalytic amount of HOAc ,²¹ $\text{HClO}_4\text{-SiO}_2$,²² preyssler type heteropolyacid $\text{H}_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]$,²³ wet 2,4,6-trichloro-1,3,5-triazine (TCT)²⁴ and Bronsted acidic ionic liquids²⁵ etc.

However, these protocols are related with some disadvantages like hazardous reaction condition, extended reaction time and also use of harmful catalyst and organic solvent. Since, 2,4,6-triarylpyridines having great significance in pharmaceutical and medicinal fields.

Thus, there is still necessity to develop an efficient protocol for the synthesis of 2,4,6-triarylpyridines. Recently Magnesium acetate have been employed as an efficient organometallic catalyst in synthetic organic chemistry.

2. Experimental

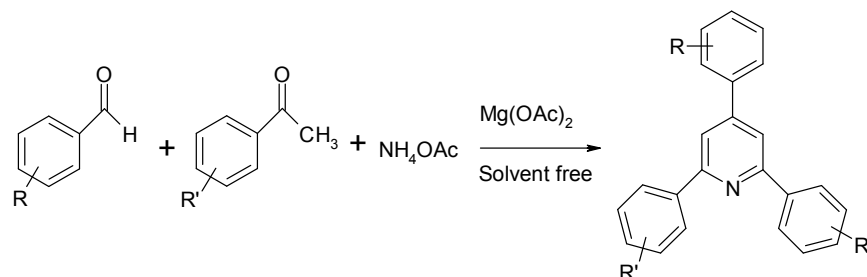
2.1 Materials & methods

The reaction was monitored by TLC using 0.25 mm E-Merck silica gel plates, which were visualized in Iodine Chamber. Melting points were taken in open capillaries. ^1H NMR in d_6on 300 MHz using TMS as an internal standard.

2.2 General procedure for synthesis of 2,4,6 Triaryl Pyridines

A mixture of aromatic aldehyde (1 mmol), Acetophenone (2mmol), Ammonium acetate (1.3 mmol) and Magnesium acetate 0.1 g was stirred at 120°C . The reaction progress was monitored by TLC. After the completion of the reaction, hot ethanol was added to the mixture and the catalyst was filtered off. After drying it was purified by recrystallization from hot ethanol, pure products were obtained. Spectral data of some products are given below.

Scheme-I



RESULTS AND DISCUSSION

The optimum condition for the synthesis of 2,4,6-Tri substituted pyridine derivatives was established by considering a reaction between benzaldehyde, acetophenone and ammonium acetate as model reaction. It was performed in the presence of anhydrous $\text{Mg}(\text{OAc})_2$ as a catalyst under solvent free condition. (Scheme 1)

The efficiency of anhydrous $\text{Mg}(\text{OAc})_2$ as a catalyst was determined with respect to its amount to be loaded in reaction mixture. There was no improvement in yield with increment in loading amount of catalyst from 0.01 mmol to 0.05 mmol. A satisfactory yield in short reaction time was obtained with 0.1 mmol of catalyst. There was no appreciable improvement in yield even if loading amount was increased to 0.2 mmol.

Table 1. Investigation of catalytic effect of anhydr. Mg(OAc)₂ on synthesis of 2,4,6-Tri substituted pyridine

Entry	anhydrous Mg(OAc) ₂ (mmol)	Time (min)	Yield ^b (%)
1	0.01	45	52
2	0.05	40	58
3	0.1	45	97
4	0.2	40	97

^bIsolated yields

Thus, the most appropriate loading amount for anhydrous Mg(OAc)₂ as a catalyst was found to be 0.1 mmol as per results summarized in Table 1.

The effect of various ammonia sources were studied. Effect of the different ammonia derivatives on yield of the product were checked, maximum yield was obtained for NH₄OAc. Results are summarized in **Table 2**

Table 2. Effect of various ammonia sources on the yield of product^a

Entry	Ammonia Source	Time (min)	Yield ^b (%)
1	NH ₄ OAc	45	97
2	NH ₂ CONH ₂	72	54
3	NH ₂ COCH ₃	55	68
4	NH ₂ CSNH ₂	68	48

^bIsolated yields

In order to establish the generality of this method, the synthesis of various triarylpyridines derivatives was studied using different aldehydes and acetophenones under optimized reaction conditions (**Table 3**). Aromatic aldehydes tolerated well in this reaction and varieties of aldehydes with electron-donating (Table 3, entries 2-4,6-10, 12-13). or electron-withdrawing (Table 3, entries 5,11). groups on the aromatic ring had little effect on the reaction rate and desired products were formed in good yields. All the products were characterized by comparing melting points with those of the reported compounds

Table 3. Magnesium acetate^a catalysed synthesis of tri-aryl pyridines

Entry	R ₁	R ₂	Time(h)	Yield ^b (%)	M.P(⁰ C)	Observed
1	H	H	1	97	133-136	135
2	H	H-CH ₃	3	94	156-158	158
3	H	4-Br	2	93	194-196	194
4	4-OH	H	2	97	197-198	198

5	4-NO ₂	H	3	92	203-205	203
6	2-Cl	H	1.5	94	113-114	113
7	4-Cl	H	1	95	126-127	129-130
8	4-OCH ₃	H	4	96	101-102	99
9	4-CH ₃	H	3.5	95	116-118	117
10	4-CH ₃	4-CH ₃	2	91	177-178	178-180
11	3-NO ₂	4-Br	2	90	>200	----
12	4-Cl	4-CH ₃	1	92	199-201	200
13	4-Cl	4-Br	2	95	>200	-----

^aaldehyde (1 mmol), Acetophenone (2 mmol), Ammonium acetate (1.3 mmol) and Magnesium acetate 0.1 g was stirred at 120°C under solvent free conditions.

^b Isolated yields

At the end of the reaction the catalyst was filtered, washed with diethyl ether, dried at 130°C for 1 h, and reused. The recycled catalyst was found to be active over three cycles without appreciable loss in catalytic activity. Results are given in **Table 4**. All the products are known compounds and were characterized by comparing IR and ¹H NMR spectral data as well as melting points with those reported in the literature. All yields refer to that of isolated pure products.

Table- 4. Reuse of catalyst in synthesis of tri-aryl pyridines

Entry	1	2	3	4	5
Yield ^a (%)	97	97	95	92	90

^a Isolated yield of corresponding product

Compound characterization

2,4,6-triphenylpyridine (Entry 1, **Table 3**) . ¹H NMR (CDCl₃, 400MHz): δ 7.2 - 8.2 (m, 17H), FT-IR (KBr): 3032, 1604, 1544, 1232, 1025 cm⁻¹, LC-MS (m/z): 308.1 (M + 1).

4-phenyl-2,6 -dip-tolylpyridine (Entry 2, **Table 3**) ¹H NMR (CDCl₃, 400 MHz): δ 7.2 - 8.2 (m, 15H), 2.4 (s, 6H), FT-IR (KBr): 3030, 1654, 1593, 1330, 1180 cm⁻¹, LC-MS (m/z): 336.2 (M + 1).

4 -(2,6-diphenylpyridin-4-yl) phenol (Entry 4, **Table 3**) ¹H NMR (CDCl₃, 400 MHz): δ 8.2 (dd, 4H, J = 1.2 Hz), 7.8(s, 2H), 7.68(d, 2H, J = 4.4 Hz), 7.4 - 7.6 (m, 6H), 7 (d, 2H, J = 8.4 Hz), 5 (s, 1H) FT-IR (KBr): 3038, 1598, 1517, 1602, 1207, 1109 cm⁻¹, LC-MS (m/z): 324.3 (M + 1).

4 -(4-nitrophenyl) -2,6-diphenylpyridine (Entry 5, **Table 3**). ¹H NMR (CDCl₃, 400MHz): 7.42 - 7.89 (m, 17H), FT-IR (KBr): 3069, 1608, 1528, 1351, 1218 cm⁻¹, LC-MS (m/z): 353.3 (M + 1).

CONCLUSION

A mild, efficient and environmentally friendly approach for the synthesis of 2,4,6-trisubstituted pyridines via cyclocondensation of aromatic aldehydes, with ketones and ammonium acetate in the presence of Magnesium acetate as a recyclable catalyst has been developed. The trisubstituted pyridines were produced with 100% selectivity without formation of any other side product. The green context of the reaction is the use of non-corrosive catalyst under solvent free reaction condition and workup procedure does not require column chromatography.

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