Montmorillonite K10 Clay Catalyzed One Pot Synthesis of 2,4,6-Tri Substituted Pyridine under Solvent Free Condition

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ABSTRACT
Montmorillonite K10 catalyzed synthesis of 2,4,6 triaryl pyridine under solvent free condition is described. Montmorillonite effectively catalyzed the reaction in good to excellent yields. Using this solid catalyst, the reactions could be carried out in a short period of time with very good yield of triaryl pyridines, up to 97% under solvent free condition. This catalyst could be recycled very easily, which makes this methodology environmentally benign. The catalyst is active over three cycles.

Keywords: Clay Catalyst; Solvent Free Synthesis; Substituted Pyridine

1. Introduction
One-pot multicomponent coupling reactions (MCRs), where several organic moieties are coupled in one step, for carbon-carbon and carbon-heteroatom bond formation is an attractive synthetic strategy for the synthesis of small-molecule libraries with several degrees of structural diversities [1]. Multiaryl substituted pyridine derivatives are recently reported as electron transport materials [2]. The highly substituted pyridine derivatives, like 2-amino-4aryl-3,5-dicyano-6-sulfanylpyridines have significant and diverse medicinal utility. Essentially, these compounds serve as high-potency agonists for the human adenosine receptors and act as potential therapeutic agents for the treatment of Creutzfeldt-Jacob disease, Parkinson’s disease, hypoxia, asthma, cancer, kidney disease and prion disease [3-5]. Due to their n-stacking ability, some pyridines are used in supramolecular chemistry [6-8]. Previously, 2,4,6-triarylpyridines have been prepared by the condensation of 1,5-diketones with formamide-formic acid [9], reaction of (arylmethylene) isoquinolinium ylide with α,β-unsaturated ketones [10,11], and reaction of N-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate [12]. More recently, many improved methods for preparation of 2,4,6-triaryl pyridines have been reported such as reaction of α-ketoketene dithioacetals with methyl ketones in the presence of ammonium acetate [13], reaction of N-phosphinylethenamides with aldehydes [14], addition of lithiated β-enaminophosphonates to chalcones [15], condensation of acetophenones, benzaldehydes and NH₂OAc in the presence of NaOH under solvent free condition [16], one pot reaction of acetophenones, benzaldehydes and NH₂OAc without catalyst under microwave irradiation [17] etc. Due to the non corrosive, easy to handle, thermally robust, inexpensive and environmental friendly nature of clays have gained importance in organic synthesis as solid acid catalysts. Montmorillonite K10 has proved to be an efficient catalyst in promoting various organic reactions such as addition reaction [18], Knoevenagel condensation [19], Aza-Diels Alder reaction [20], Esterification [21], isomerisation reaction [22] etc. However, the utility of this catalyst for the synthesis of trisubstituted pyridines under solvent free condition has not been explored before. In continuation of our efforts to explore the catalytic activity of clays for various organic transformations, a one-pot solvent free synthesis of 2,4,6trisubstituted pyridines by condensation of various aldehydes, ketones and ammonium acetate have been attempted.

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2. Experimental Procedure

Commercial clay K10 was purchased from Sigma-Aldrich India. The clay was activated at 200°C for 3 h before use. The reactants were purchased from Merck Ltd. India and were used as such. The products were characterized by FT-IR, NMR spectral methods and m. p. FT-IR spectra were recorded by the KBr pellet method on a JASCO FT-IR spectrometer in the range of 400 to 4000 cm$^{-1}$. High-resolution mass spectra were obtained with a LC-MS (Q-TOFF) LC (Waters). 1H NMR spectra were recorded on a Bruker 400 MHZ instrument with tetra methyl silane (TMS) as internal standard in CDCl3.

2.1. Synthesis of 2,4,6 Triaryl Pyridines

A mixture of aldehyde (1 mmol), acetophenone (2 mmol), 1.3 mol% (NH4OAc) and activated K10 clay (0.2 g) was stirred at 120°C. The progress of the reaction was monitored by TLC. After the completion of the reaction, hot ethanol was added to the mixture and the insoluble catalyst was filtered off. The pure product was obtained by recrystallisation from the solvent.

2.2. Reusability of the Catalyst

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 1.

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.

3. Results and Discussion

The catalytic efficiency of K10 was evaluated for the synthesis of triaryl pyridines by a one pot condensation of aldehyde, ketone and NH4OAc under solvent free condition (Scheme 1). High yield (97%) was obtained with benzaldehyde and acetophenone. To evaluate the scope and limitations of the methodology, reactions were carried out with various substituted benzaldehydes including both electron-donating and electron-withdrawing substituents at para position of the aromatic ring (Table 2). The results showed that there is no adverse effect of substituents, either electron-donating or electron-withdrawing, on the aromatic ring of benzaldehyde or acetophenone on the product yield. In the case of all the aldehydes, very high yields (>88%) were obtained in comparatively less time (2 - 6.5 h). All the products were characterized by comparing melting points with those of the reported compounds. The reaction conditions such as temperature, time and amount of catalyst were optimized. The effect of catalyst loading was studied by increasing the catalyst concentration from 0.05 g to 0.3 g with an increment of 0.05 g selecting benzaldehyde and acetophenone as substrates for 3 h, the formation of product was found to increase up to 0.2 g further increase did not appreciably affect the yield of the product, optimum catalyst concentration of 0.2 g was selected for further studies, similarly temperature was also optimized by varying the temperature from 40°C - 130°C, optimum temperature obtained was 120°C.

Spectral Data of Selected Products

| Product | mp (°C) | 1H NMR (CDCl3, 400 MHZ) | FT-IR (KBr) | LC-MS (m/z) |
|---------|--------|----------------|-------------|-------------|
| 2,4,6-triphenylpyridine | 130°C - 132°C | δ 7.2 - 8.2 (m, 17H) | 308.1 (M + 1) | 324.3 (M + 1) |
| 4-phenyl-2,6-dip-tolylpyridine | 156°C - 158°C | δ 7.2 - 8.2 (m, 15H), 2.4 (s, 6H) | 336.2 (M + 1) | 324.3 (M + 1) |
| 4-(2,6-diphenylpyridin-4-yl) phenol | 197°C | 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) | 324.3 (M + 1) | 3038, 1598, 1517, 1602, 1207, 1109 cm$^{-1}$ |

Table 1. Results of recycling studies.

| No. of recycling steps | % Yield |
|-----------------------|---------|
| 1                     | 97      |
| 2                     | 92      |
| 3                     | 88      |

Table 2. Results of recycling studies.

Reaction condition: benzaldehyde (1 mmol), acetophenone (2 mmol), NH4OAc (1.3 mol%), 0.2 gm catalyst reaction time 4 h. Isolated yield.

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NH$_4$OAc. Results are summarized in Table 3.

The mechanism of triaryl pyridine synthesis is as shown in Scheme 2 [25]. First step involves the condensation of ammonia with a molecule of chalcone and Michael addition of ammonia to the second molecule of chalcone leads to the formation of 2,4-diaryl-1-azadiene 3 and the 1:1 adduct 4 probably undergoes a formal [4 + 2] cycloaddition to form tetrahydropyridine intermediate 5. Dehydration to dihydropyridine intermediate 6 and then oxidative aromatization with removal of the benzyl side chain would yield 2,4,6-triarylpyridine. According to the mechanism, the role of NH$_4$OAc is as nitrogen source and acetic acid is formed as by-product, the reaction is catalyzed by acid, the presence of acetic acid increases the acidity of the medium.

The main advantages of the present method in the synthesis of triarylpyridines are that they are clean reactions without any side product under solvent free condition and workup does not require column chromatography. The catalyst could be recycled efficiently for three cycles without any appreciable loss in the yield.

4. Conclusion

A mild, efficient and environmentally friendly approach for the synthesis of 2,4,6-trisubstituted pyridines via cyclocondensation of aromatic ketones with aromatic aldehydes and ammonium acetate in the presence of Montmorillonite K10 clay as a recyclable solid acid 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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