

One-Pot Three-Component Synthesis of Imidazo[1,5-*a*]pyridines

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Abstract

A one-pot three component condensation synthesis of imidazo[1,5-*a*]pyridines using of various aromatic aldehydes and dipyrindil ketone with ammonium acetate in the presence of Lithium chloride as catalyst in good yields under microwave irradiation has been described.

Keywords: Lithium Chloride, Imidazo[1,5-*a*]pyridine, Microwave Irradiation

1. Introduction

Imidazo[1,5-*a*]pyridines and their derivatives with a nodal nitrogen atom, an important class of ring fused heterocyclic compounds exhibit a wide spectrum of biological activities [1]. Therefore development of new and efficient synthetic method for the synthesis of these compounds is of importance in both synthetic organic chemistry and medicinal chemistry [2]. In addition, other applications of these compound in organic light-emitting diodes (OLEDs) [3] and organic thin-layer field effect transistors (FETs) [4] have been reported.

The classical method for synthesis of imidazo[1,5-*a*]pyridines mainly involves the use of 2-pyridylalkylamines with acylchlorides [5-15] and/or organic acids derivatives [16,17] in two step addition and cyclization. Besides these reactions, pereparation of imidazo[1,5-*a*]pyridines from 2-pyridylalkylamines with α,β -unsaturated compounds [18], and/or aldehydes [19] have been reported. Other approaches include the use of imine derivatives [20], 2-cyanopyridine [21] and benzotriazoles [22]. Recently, the generation these compounds by a three component condensation reaction using pyridilketons, aldehyds and ammonium acetate were reported [23-25]. Most syntheses require harsh reaction conditions because of the use of highly sensitive reagents. In addition, the syntheses of these heterocycles have been usually carried out in polar organic solvents such as methanol, ethanol, DMF and DMSO leading to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed of.

During the course of our studies towards the development of new routes to the synthesis of nitrogen containing heterocyclic compounds [26,27], we wish to introduce an efficient procedure for the synthesis of imidazo[1,5-*a*]pyridine via one-pot three component condensation of dipyrindyl ketone 1 with aldehyde 2 and NH_4OAc in the presence of lithium chloride as an inexpensive mild Lewis acid using microwave irradiation (Scheme 1).

2. Results and Discussion

In synthesis of imidazo[1,5-*a*]pyridines, *p*-methoxybenzaldehyde, dipyrindyl ketone and ammonium acetate were selected as model reactants during the optimization conditions. Initially in order to, in this condensation reaction different solvents such as DMF, EtOH and HOAc in the presence and absence of LiCl salt were utilized (**Table 1**). Studies indicated that among the solvents, HOAc is the best solvent at 3 min (**Table 1**). However, the results of various times of irradiation show that in all solvents the best yield was obtained in during 3 min by medium power at 300 W. Then, the reactions were performed in the presence of different salts such as Li_2SO_4 , Li_2CO_3 , LiHSO_4 , Na_2SO_4 , NaBr and NaCl under microwave irradiation in HOAc. Among the various salts, LiCl was identified to be the best salts for this three-component reaction in HOAc under the microwave irradiation as illustrated in **Table 1** (Entry 10). In all cases molar ratio of reactant was used based on previous report [21]. After good consideration we found that these ratios are the best.

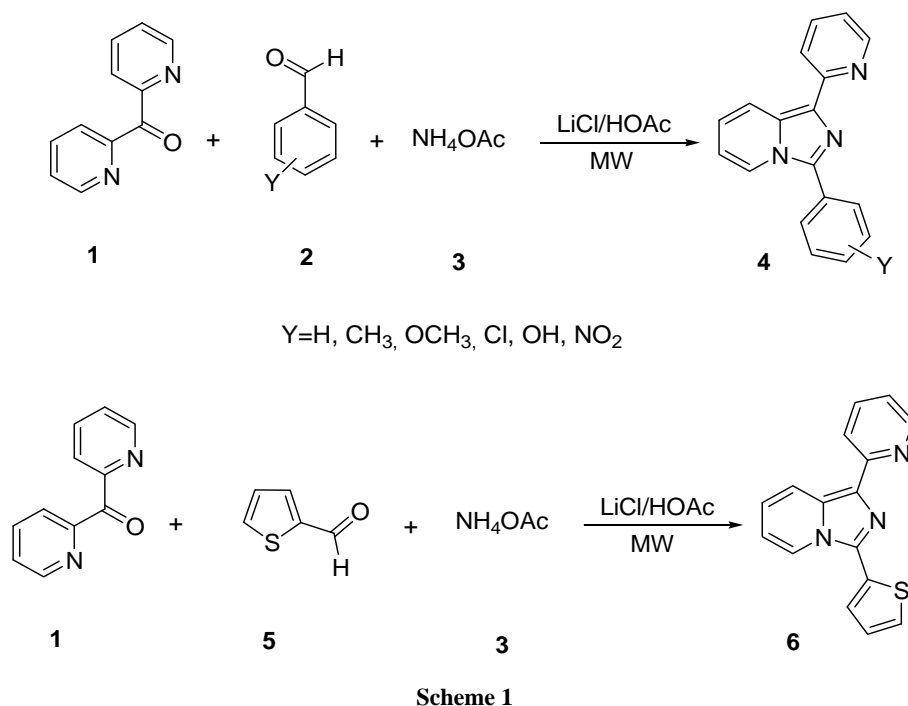


Table 1. One-pot synthesis of imidazo[1,5-*a*]pyridines in the presence of various salts in different solvents under microwave irradiation^a.

| Experimental number | Solvent and Catalyst ^b | Yield (%) (Time (min : sec)) MW ^c |
|---------------------|--------------------------------------|--|
| 1 | DMF | 21(3:00) |
| 2 | EtOH | 46(3:00) |
| 3 | HOAc | 53(2:00) |
| 4 | HOAc | 72(3:00) |
| 5 | HOAc | 72(4:00) |
| 6 | DMF/LiCl | 39(3:00) |
| 7 | EtOH/LiCl | 65(3:00) |
| 8 | HOAc/LiCl | 81(2:00) |
| 9 | HOAc/LiCl | 93(3:00) |
| 10 | HOAc/LiCl | 93(4:00) |
| 11 | HOAc/Li ₂ SO ₄ | 77(3:00) |
| 12 | HOAc/Li ₂ CO ₃ | 70(3:00) |
| 13 | HOAc/LiHSO ₄ | 73(3:00) |
| 14 | HOAc/NaCl | 69(3:00) |
| 15 | HOAc/NaBr | 69(3:00) |
| 16 | HOAc/Na ₂ SO ₄ | 68(3:00) |
| 17 | LiCl | 61(3:00) |
| 18 | - | 22(5:00) |

^aDipyridyl ketone (1 mmol), para-methoxybenzaldehyde (2 mmol) and ammonium acetate (6 mmol); ^bCatalyst (0.1 g, 2 mmol), Solvent (0.5 mL); ^c360 W.

It is important to note in the presence of only LiCl or HOAc the reaction yield is considerably decreased (**Table 1**, Entries 4 and 17).

The optimum amount of lithium chloride was 2 equivalents and lithium chloride of more than 2 equivalents was identified to give the similar results (**Table 2**).

To explore the scope and limitations of this reaction, we extended the reaction of dipyridyl ketone with various aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the meta and para positions. As indicated in **Table 3**, the reaction pro-

ceeded very efficiently in all cases, however with 4-nitrobenzaldehyde no reaction took place. In addition, we have repeated the reaction with dipyridyl ketone instead of phenylpyridyl ketone and the desired product has been efficiently produced (**Table 3**).

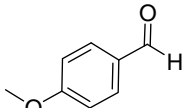
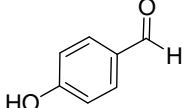
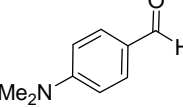
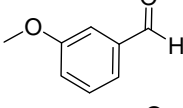
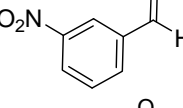
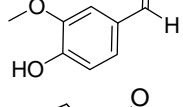

The conceivable mechanism of the reaction is as following: lithium cation is coordinated with phenylpyridyl ketone to make carbonyl group as an activated group to nucleophilic attack by the in situ generated imine. The subsequent intramolecular interaction leads to the cyclization and finally to the formation of the desirable imi-

Table 2. Optimization of amounts of LiCl in the one-pot synthesis of imidazo[1,5-*a*]pyridines in HOAc (0.5 mL) under microwave irradiation^a.

| Experimental number | Catalyst (mmol) LiCl | Time (min) | Yield (%) |
|---------------------|----------------------|------------|-----------|
| 1 | - | 3 | 22 |
| 2 | 0.5 mmol | 3 | 39 |
| 3 | 1 mmol | 3 | 65 |
| 4 | 2 mmol | 3 | 93 |
| 5 | 2 mmol | 2 | 62 |
| 5 | 2 mmol | 1 | 34 |
| 6 | 4 mmol | 3 | 93 |

^aPyridilphenyl ketone (1 mmol), para-methylbenzaldehyde (2 mmol) and ammonium acetate (6 mmol).

Table 3. One-pot synthesis of imidazo[1,5-*a*]pyridines in the presence of lithium chloride as a Lewis acid under solvent-free conditions using microwave irradiation.^a

| Entry | Aldehyde | Product | Yield (%) | M.P. (°C) | |
|-------|---|-----------|-----------|-----------|-----------------------|
| | | | | Found | Reported ^b |
| 1 |  | 4a | 94 | 119 - 120 | 120 - 121 |
| 2 |  | 4b | 88 | 195 - 196 | 195 - 196 |
| 3 |  | 4c | 82 | 180 - 181 | 180 - 182 |
| 4 |  | 4d | 83 | 94 - 96 | 92 - 93 |
| 5 |  | 4e | 81 | 91 - 92 | 96 - 97 |
| 6 |  | 4f | 89 | 129 - 131 | 132 - 133 |
| 7 |  | 6 | 71 | 127 - 130 | 131 - 132 |

^aUsing microwave irradiation HOAc/LiCl at 3 min; ^bref [25].

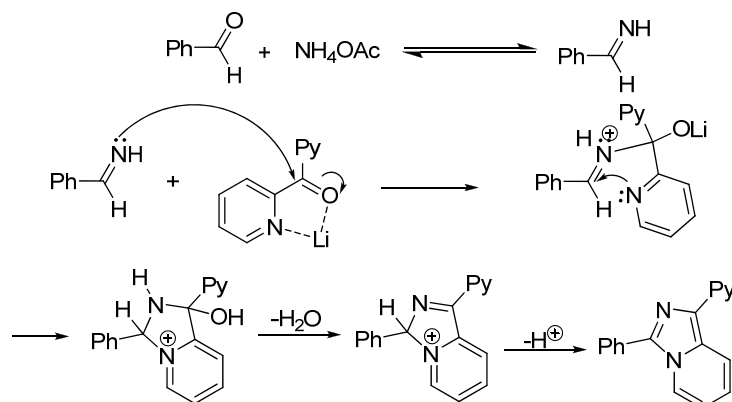
dazo[1,5-*a*]pyridine. (Scheme 2)

In conclusion, we have introduced an efficient and environmentally friendly approach for the synthesis of biologically active imidazo[1,5-*a*]pyridines via condensation of dipyrindyl ketone with various aromatic aldehydes and ammonium acetate using lithium chloride as a neutral Lewis acid catalyst. Corrosiveness safety, less waste and ease of separation are all among desirable factors for the chemical industry which we have considered in our

green chemistry approach.

3. Experimental

Melting points were measured with an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded with a Shimadzu IR-470 spectrometer. ¹H and ¹³C NMR spectra were recorded with a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47



Scheme 2

MHz, respectively. NMR spectra were obtained on solutions in DMSO-d₆. All the products are known compounds, which were characterized by IR and ¹H NMR spectral data and their mp's compared with literature reports. The microwave apparatus that used for these experiments is APEX, EU-CHEMICAL apparatus. This apparatus is a scientific microwave that designed for chemical experiments.

General procedure for the preparation of imidazo[1,5-a]pyridines

A mixture of pyridyl ketone (1 mmol), aldehyde (2 mmol), ammonium acetate (0.462 g, 6 mmol), lithium chloride (0.1 g, 2 mmol) and acetic acid (0.5 mL) was irradiated in a microwave oven for 3 min. The solid materials residue was then washed with water and to give the crude product. For further purification it was crystallized from ethanol:acetone mixture or by column chromatography to afford pure products.

4. Acknowledgements

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