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Microwave Assisted-Solvent Free Synthesis of Imidazo[1,2-a]pyridines

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ABSTRACT

A facile microwave assisted reaction of phenacyl bromide and 2-amino pyridine is catalyzed by an ionic liquid 1-(4-sulfonic acid) butylpyridinium hydrogen sulfate under solvent free conditions to give corresponding imidazo[1,2-a]pyridines in good yields. Reactions proceed with high efficiency and good functional group tolerance. This approach provides a useful protocol for the preparation of highly substituted imidazo[1,2-a]pyridine derivatives.

Keywords: 1-(4-sulfonic acid) butylpyridinium hydrogen sulfate, Microwave irradiation, Imidazo[1,2-a]pyridines, Phenacyl bromide

INTRODUCTION

Heterocyclic compounds broadly exist in various natural products and synthetically prepared drugs [1,2]. Imidazo[1,2-a]pyridine derivatives are highly attractive hetero aromatic units because of their diverse biological activity [3,4]. Highly popular drugs in medical field like Zolpidem, Alpidem, Zolimidine, Olprinone and SCH28080 containing imidazo[1,2-a]pyridine as key moiety [5]. It is also reported that imidazo[1,2-a]pyridine derivatives show excellent biological and pharmaceutical activities such as antiulcer, antiviral, antiapoptotic and anticancer [6,7]. In addition to that most of the electronic devices has imidazo[1,2-a]pyridine as core ligands [8]. Many synthetic approaches have been reported for the development of imidazo[1,2-a]pyridine derivatives. Best methods for the construction of imidazo[1,2-a]pyridine are multicomponent reactions, one-pot condensation, metal catalyzed C–H activation by metal catalyzed reactions [9-11]. The chemical and pharmaceutical industries are always under pressure to build up more environmentally friendly organic reaction methodologies the synthesis of imidazo[1,2-a]pyridine derivatives. Therefore, it is highly attractive to explore metal free, short reaction time and environmentally benign synthesis to form those heterocycles (Figures 1 and 2) [12,13].

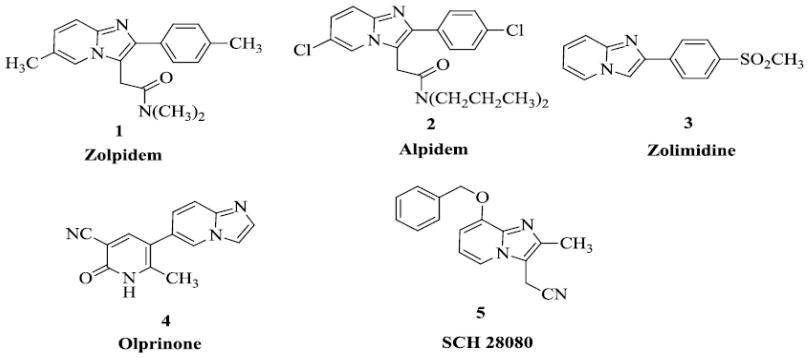


Figure 1: Biologically active Imidazo[1,2-a]pyridine derivatives

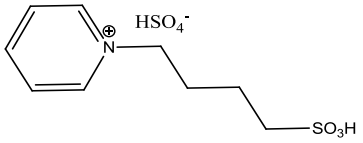


Figure 2: Structure of bronsted acidic ionic liquid 1-(4-sulfonic acid) butylpyridinium hydrogen sulfate

On the other hand, microwave-assisted organic synthesis has been applied as an efficient accelerator in many organic reactions [14]. This technology facilitates the organic reactions with high yields, short reaction times, and cleaner reactions. The benefits offered by microwave irradiation have also been widely used in the field of ionic liquid catalyzed reactions [15-17]. The best advantage of microwave irradiation is reduce the time from days or hours to minutes. In this Letter, we developed an ionic liquid catalyzed, simple, and efficient procedure to synthesize imidazo[1,2-a]pyridine derivatives via a coupling reaction between phenacyl bromide and 2-amino pyridine under microwave irradiation and solvent free conditions.

MATERIALS AND METHODS

Melting points were recorded by using Buchi R-535 instrument and are uncorrected. NMR spectra were recorded on either a Bruker Advance 300 or Advance 400 spectrometer. Chemical shifts (δ) are given in ppm using internal references or TMS as external reference for $CDCl_3$. Mass spectra were recorded on Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General reaction procedure

A mixture of phenacyl bromide (1 mmol) and 2-amino pyridine (1.2 mmol) and 1-(4-sulfonic acid) butylpyridinium hydrogen sulfate (3 mL) were placed in a sealed tube then irradiated at 100^{o}C in a microwave oven for 30 sec. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethylether (3 × 10 mL) then diluted with water (3×10 ml). The combined ether extracts were concentrated by rotary evaporator. The pure product separated by column chromatography by eluting 5% ethyl acetate in hexane. The rest of the viscous ionic liquid was further washed with ether and recycled in subsequent runs.

Selected spectroscopic data

2-phenyl Imidazo[1,2-a]pyridine (3a)

Brown solid, M.P. 130-135^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J=6.7 Hz, 1H), 7.89 (d, J= 7.5 Hz, 2H), 7.84 (s, 1H), 7.63 (d, J=9.0 Hz, 1H), 7.40 (t, J=7.5 Hz, 2H), 7.30 (d, J=7.5 Hz, 1H), 7.14 (dd, J=6.7, 9.0 Hz, 1H), 6.74 (t, J=6.7 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ 145.6, 131.9, 128.7, 127.9, 126.0, 125.5, 124.7, 117.4, 116.2, 108.1; IR (KBr): 2924, 2854, 1740, 1629, 1500, 1471, 1366, 1073 cm^{-1}; ESIMS: m/z: $(M+H)^+$: 195; HRMS calcd for $C_{13}H_{11}N_2$ $(M+H)^+$: 195.0922; found, 195.0921.

7-methyl-2-phenyl Imidazo[1,2-a]pyridine (3b)

White solid, M.P. 163-165^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, 1H, J=1.51 Hz), 7.87 (d, 2H, J=7.55), 7.72 (s, 1H), 7.45-7.25 (m, 4H), 6.57 (d, 1H, J=7.55Hz), 2.41 (s, 3H); IR (KBr): 2955, 2865, 1629, 1478, 1370, 1073 cm^{-1}; ESIMS: m/z: $(M+H)^+$: 209.

2-(4-chlorophenyl) Imidazo[1,2-a]pyridine (3c)

Brown solid, M.P. 206-207^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, J=6.79), 7.91 (t, 1H, J=2.26Hz), 7.83 (s, 1H), 7.80 (d, 1H, J=8.30 Hz), 7.61 (d, 1H, J=9.06), 7.34 (t, 1H, J=8.30), 7.27 (d, 1H, J=2.26 Hz), 7.16 (dt, 1H, J=1.51, 6.79 Hz) 6.77 (dt, 1H, J=1.51, 6.79 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 145.6, 144.5, 133.6, 132.1, 128.8, 127.2, 125.5, 124.9, 117.4, 112.5, 108.1; IR (KBr) : 2924, 2854, 1740, 1629, 1500, 1471 cm^{-1}; ESIMS: m/z: $(M+H)^+$: 229.

2-p-tolyl Imidazo[1,2-a]pyridine (3d)

White solid, M.P. 143-145^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, 1H, *J*=6.4 Hz), 7.86 (d, 2H, *J*=8.0 Hz), 7.83 (s, 1H), 7.65 (d, 1H, *J*=8.0 Hz), 7.24-7.27 (m, 2H), 7.17 (t, 1H, *J*=8.2 Hz), 6.78 (t, 1H, *J*=6.4 Hz), 2.39 (s, 3H); IR (KBr): 2930, 2844, 1631, 1471 cm^{-1}; ESIMS: m/z: $(M+H)^+$: 209.

2-(4-fluorophenyl) Imidazo[1,2-a]pyridine(3f)

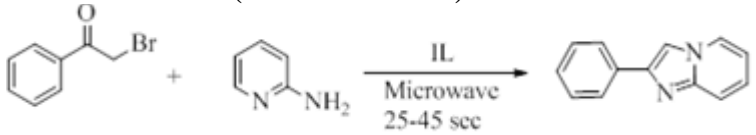
Pink color solid, M.P. 162-164^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (td, 1H, *J*=1.2, 6.8 Hz), 7.90-7.97 (m, 2H), 7.83 (s, 1H), 7.69 (d, *J*=9.2 Hz, 1H), 7.19-7.24 (m, 1H), 7.12-7.18 (m, 2H), 6.83 (dt, 1H, *J*=0.8, 6.8 Hz); IR (KBr): 2955, 2823, 1642, 903 cm^{-1}; ESIMS: m/z: $(M+H)^+$: 212.

2-(3,4,5-trimethoxyphenyl) Imidazo[1,2-a]pyridine (3g)

Semi solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, 1H, J=9.4Hz), 7.64-7.36 (m, 3H), 7.36-7.18 (m, 2H), 6.80-6.67 (m, 1H), 6.54-6.41 (m, 1H), 2.84 (s, 9H); IR (KBr): 2922, 2835, 1625, 1095 cm^{-1}; ESIMS: m/z: $(M+H)^+$: 285.

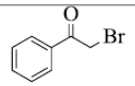
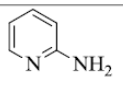
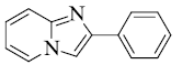
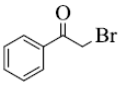
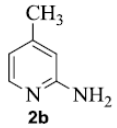
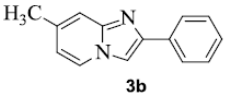
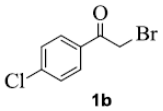
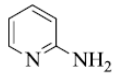
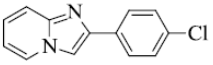
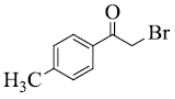
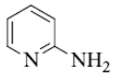
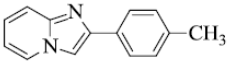
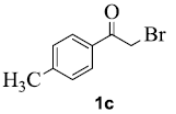
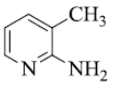
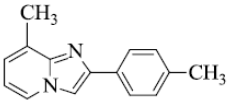
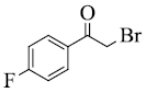
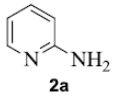
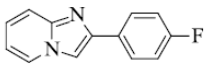
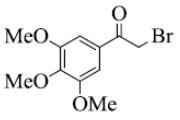
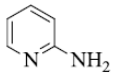
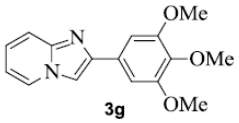
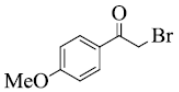
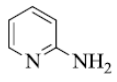
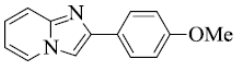
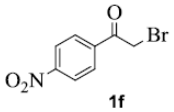
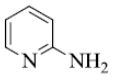
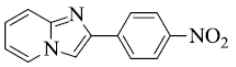
RESULTS AND DISCUSSION

Initially, 2-aminopyridine 1a, 2-amino pyridine 2a, were chosen as model substrates to optimize the reaction conditions. The desired product 3a was obtained in 98% yield using ionic liquid 1-(4-sulfonic acid) butyl-3-methylimidazolium hydrogen sulphate as catalyst under microwave irradiation at 100^{o}C. Encouraged by this result, various bronsted acids such as H_2SO_4, $HClO_4$, H_2CO_3 and CF_3COOH were subsequently examined. H_2SO_4 and CF_3COOH afforded lower yields compared to ionic liquid. Ionic liquid was superior compared to the above catalysts and increased the yield up to 98%. A higher or lower reaction temperature at 120 or 80^o C reduced the yield of the corresponding product 3a to 76% or 81%. While changing the irradiation time to 10 or 30 min also led to a decreased yield. In comparison, using the same conditions under conventional oil heating, the desired product 3a was obtained in a yield of 78% after an extended reaction time of 3 h (Scheme 1 and Table 1).



Scheme 1: Synthesis of Imidazo[1,2-a]pyridine

Table 1: Ionic liquid catalyzed synthesis imidazo[1,2-a]pyridine derivatives under microwave irradiation ans solvent free conditions[a]

Entry	Phenacyl bromide	2-Amino pyridine	Product	Time(Sec)	Yield(%)[b]
1	 **1a**	 **2a**	 **3a**	25	95
2	 **1a**	 **2b**	 **3b**	30	92
3	 **1b**	 **2a**	 **3c**	30	91
4	 **1c**	 **2a**	 **3d**	30	87
5	 **1c**	 **2c**	 **3e**	40	90
6	 **1d**	 **2a**	 **3f**	40	91
7	 **1e**	 **2a**	 **3g**	40	92
8	 **1f**	 **2a**	 **3h**	40	92
9	 **1f**	 **2a**	 **3h**	45	92

[a] Reaction condition: **1a** (1 mol), **2a** (1 mol) and Ionic liquid (3 mL) under microwave irradiation at 100 °C and 120W power.
[b]Isolated yields

With the optimized multicomponent protocol in hand, we next explored the scope of this reaction (Table 2). To our delight, we found this method to be very general for a wide range of phenacyl bromides and 2-amino pyridines provided easy access to the desired imidazo[1,2-a]pyridine derivatives. Phenacyl bromide with a variety of functional groups, such as methyl, fluoro, chloro, bromo, methoxy, nitro were tolerated, and led to the desired products 3a-h in good yields. We are pleased to find that 3-methyl-2-amino pyridine and 4-methyl-2-amino were smoothly reacted under the same conditions, which produce the corresponding imidazo[1,2-a]pyridine derivatives 3a-3h in generally moderate to good yields (87–92%). These results indicated that this metal-free condensation reaction for the construction of substituted imidazo[1,2-a]pyridines was efficient and reliable.

The experimental procedure has very simple work up to separate desired products also the products are weakly soluble in ionic liquid. Desired products separated by simple ether extraction and the rest of the viscous ionic liquid reused after by activated at 100^{o}C under reduced pressure without loss of its activity. Reused runs were carried out under similarly optimized conditions using phenacyl bromide react with 2-aminopyridine. The catalyst showed excellent recoverability and reusability over 4 successive runs under the same conditions as the first run. The ionic liquid catalyst was found to be hsighly stable and reusable under the investigated conditions (up to 4 runs) without any significant loss of its catalytic activity.

Table 2: Reuse of the PMA-Silica catalyst in the reaction of 2-Amino aryl ketones with Aliphatic ketone (2a)

Run No.	**1**	**2**	**3**	**4**
Yield	95	95	93	93

CONCLUSION

In conclusion, a solvent-free and microwave-enhanced reaction for generation of imidazo[1,2-a]pyridine derivatives has been developed. Various phenacyl bromides and 2-amino pyridines can be tolerated in this reaction to afford the desired products in good yields. Reaction time noticeably decreases from days or hours to seconds under microwave irradiation. Further studies to expand the substrate scope and detail reaction mechanism are currently underway in our lab.

ACKNOWLEDGEMENTS

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