Nano SiO_2 catalyzed 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 Nano SiO_2 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.*

RÉSUMÉ. *Une réaction facile assistée par micro-ondes du bromure de phénacyle et de la 2-amino pyridine est catalysée par du Nano SiO_2 dans des conditions sans solvant pour donner les Imidazo[1,2-a]pyridines correspondantes avec de bons rendements. Les réactions se déroulent avec une efficacité élevée et une bonne tolérance fonctionnelle du groupe. Cette approche fournit un protocole utile pour la préparation de dérivés d'Imidazo[1,2-a]pyridine hautement substitués.*

KEYWORDS: *nano SiO_2, microwave irradiation, Imidazo[1,2-a]pyridines, phenacyl bromide.*

MOTS-CLÉS: *nano SiO_2, irradiation par micro-ondes, Imidazo[1,2-a]pyridines, bromure de phénacyle.*

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1. Introduction

Heterocyclic compounds broadly exist in various natural products and synthetically prepared drugs (Hanson *et al.,* 2008). Imidazo[1,2-a]pyridine derivatives are highly attractive heteroaromatic units because of their diverse biological activity (Kim *et al.,* 2011). Highly popular drugs in medical field like Zolpidem, Alpidem, Zolimidine, Olprinone and SCH28080 containing Imidazo[1,2-a]pyridine as key moiety (Enguehard *et al.,* 2000). It is also reported that Imidazo[1,2- a]pyridine derivatives show excellent biological and pharmaceutical activities such as antiulcer, antiviral, antiapoptotic and anticancer (Bode *et al.,* 2011). In addition to that most of the electronic devices has Imidazo[1,2-a]pyridine as core ligands. 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 (Dai *et al.,* 2005). 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 (Cao *et al.,* 2014).

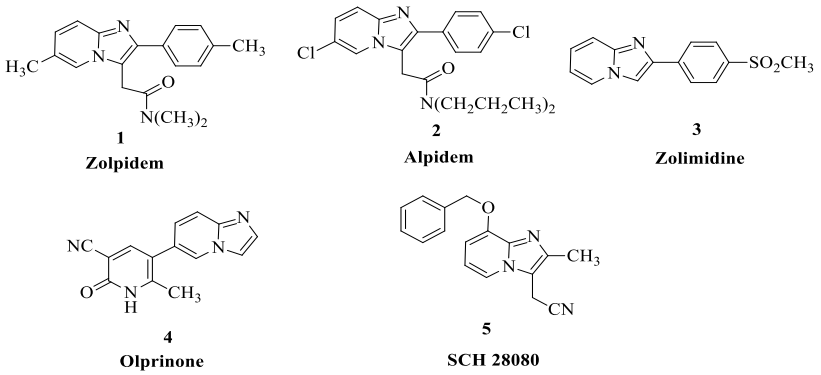


Figure 1. Biologically active Imidazo[1,2-a]pyridine derivatives

On the other hand, microwave-assisted organic synthesis has been applied as an efficient accelerator in many organic reactions (Roberts and Strauss, 2005). 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 PMA-Silica catalyzed reactions (Hassan et al., 2017). The best advantage of microwave irradiation is reduce the time from days or hours to minutes. In this Letter, we developed Nano SiO_2 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.

2. 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 Nano SiO_2were placed in a sealed tube then irradiated at 100°C in a microwave oven for 30sec. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3x10mL) then diluted with water (3×10 ml). The combined ether extracts were concentrated by rotary evaporator. The pure product separated by column chromatography by eluting5% ethyl acetate in hexane. The rest of the Nano SiO_2 was further washed with ether and recycled in subsequent runs.

2.1. Selected spectroscopic data

2-phenyl Imidazo[1,2-a]pyridine (3a): Brown solid, M.P. 130-135°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°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°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°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,

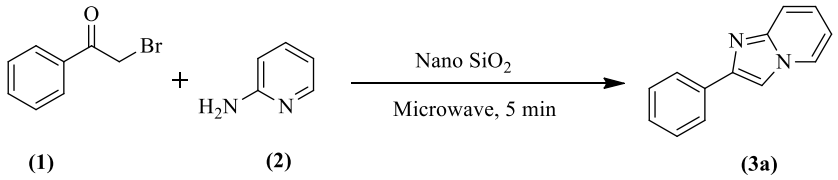
1H, *J* = 6.4 Hz), 2.39 (s, 3H); IR (KBr): 2930, 2844, 1631, 1471 cm^{-1}; ESIMS: m/z: $(M+H)^+$: 209.

2-(4-fluorophenyl) Imidazo[1,2-a]pyridine(3f): Pink color solid, M.P. 162-164ºC; ^1H 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; ^1H 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.

3. Results and discussion

Initially, 2-aminopyridine **1a**, 2-amino pyridine**2a**, were chosen as model substrates to optimize the reaction conditions (Table 1). The desired product 3a was obtained in 98% yield using Nano SiO_2 as catalyst under microwave irradiation at 100º 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 Nano SiO_2. Nano $SiO_2$was superior compared to the above catalysts and increased the yield up to 98%. A higher or lower reaction temperature at 120ºC or 80ºC reduced the yield of the corresponding product **3a** to 76% or 81%. While changing the irradiation time to 5 to 7 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.

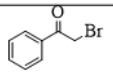
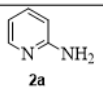
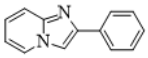
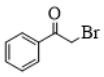
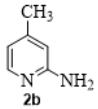
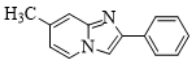
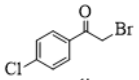
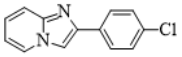
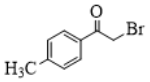
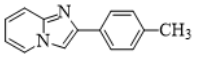
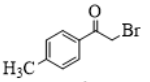
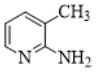
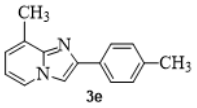
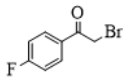
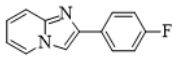
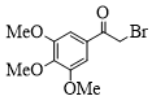
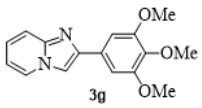
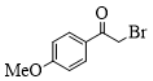
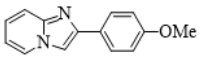
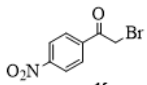
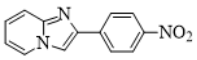


Scheme 1. Synthesis of Imidazo[1,2-a]pyridine

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 and2-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.

Table 1. Nano SiO_2 catalyzed synthesis Imidazo[1,2-a]pyridine derivatives under microwave irradiation and 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 Nano SiO_2 under microwave irradiation at 100 °C and 120W power.
[b] Isolated yields

The experimental procedure has very simple work up to separate desired products also the catalyst. Desired products separated by simple ether extraction and

the rest of the Nano SiO_2reused after by activated at 100ºC 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 Nano SiO_2catalyst was found to be highly stable and reusable under the investigated conditions (up to 4 runs) without any significant loss of its catalytic activity.

Table 2. Reuse of the Nano SiO_2 catalyst in the reaction of 2-Amino aryl ketones with Phenacyl Bromide (2a)

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

4. 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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