[Omim][BF_4] ionic liquid, a green and recyclable medium for one-pot aminomethylation of electron-rich aromatic compounds

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An efficient catalyst-free procedure has been developed for one-pot aminomethylation of some electron-rich aromatic compounds such as 1- and 2-naphthols, indole, N-methylindol and benzamide, in [omim][BF_4] ionic liquid at room temperature. The ionic liquid can be recovered and reused without any noticeable loss of performance.

Keywords: aminomethylation, electron-rich aromatic compounds, one-pot reaction, green chemistry, [omim][BF_4] ionic liquid, Mannich reaction

The aminomethylation of electron-rich aromatic compounds by the Mannich reaction is of value in the chemistry of drugs, pesticides, pharmaceutical and natural products.[1,2] In addition, the reaction has found applications in plant protection and in paint and polymer chemistry.[3] The utilisation of Mannich bases in cancer treatment is another interesting area of research.[4] The reaction also affords a facile access to many versatile synthetic building blocks which can easily be converted into a range of useful and valuable derivatives. Such derivatives consist of Michael acceptors, 1,3-amino alcohols and functionalised carbonyl compounds.[5] Different substrates have been used as the CH-acidic component in Mannich reaction, such as ketones, β-ketoesters, malonates and nitro compounds.[4]

With increasing concerns over pollution and serious environmental mandates enforced on industry and academia, ionic liquids have attracted extensive interest in recent years as excellent alternatives to conventional organic solvents. Their favourable properties and applications make them be both catalysts and solvents in chemical research and industry.[6,7] Ionic liquids have become very useful solvents for synthetic organic transformations as a result of their simplicity of recovery, very low vapour pressure, thermal stability, and their ability to dissolve a broad range of organic compounds.[8–11]

The use of three component one-pot strategies is preferred for the synthesis of a diverse array of Mannich bases. This involves the *in-situ* formation of iminium intermediates from paraformaldehyde and secondary amines which are readily available with a wide range of structural variations. So far, a few three-component related procedures involving electron-rich aromatic compounds have been reported using different media or catalysts such as acidic alumina (Al_2O_3),[12–14] *p*-toluene sulfonic acid (*p*-TSA) under microwave irradiation,[15,16] dry benzene at reflux,[17] conc. HCl or NaOH,[18,19] and functionalised ionic liquids.[20–22] Some of these methods suffer from the use of strong acidic or basic conditions, long reaction times, toxic reagents, low yields, and cumbersome preparation of the catalysts. Hence, there is an increasing interest in developing environmentally benign and atom-economic catalytic processes for the synthesis of Mannich bases.

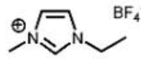
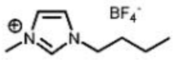
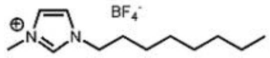
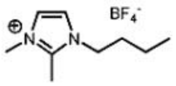
Here we report a three-component aminomethylation of various electron-rich aromatic compounds in the presence of [Omim][BF_4] ionic liquid at room temperature. The process leads to an efficient synthesis of some Mannich bases under mild conditions using no additive nor catalyst.

Results and discussion

Effect of different ionic liquids

Initially, the effect of different ionic liquids 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF_4]), 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), 1-octyl-3-methylimidazolium tetrafluoroborate ([omim][BF_4]), and 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim][BF_4])

Table 1 Mannich reaction of paraformaldehyde, pyrrolidine and β-naphthol in the presence of different ionic liquids[a]

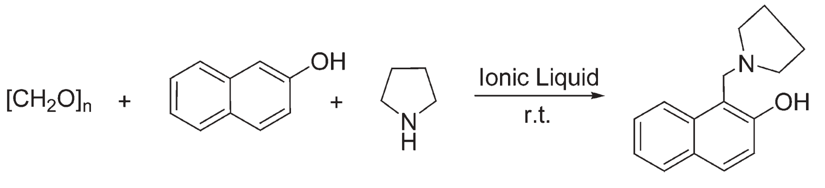
Entry	Ionic liquid	Time/h	Yield/%
1		1.5	92
2		3	88
3		1	95
4		2.5	75

[a] The reaction was carried out at room temperature.

Table 2 Investigation of the amount of [omim][BF_4][a]

Entry	mmol of [omim]BF_4	Time/h	Yield/%[b]
1	2.5	1	86
2	2.8	1	95
3	3.5	1	93
4	4.5	1	80

[a] The reaction conditions: paraformaldehyde (1.5 mmol), pyrrolidine (1.5 mmol), β-naphthol (1.0 mmol).
[b] Isolated yield.



Scheme 1

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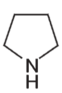
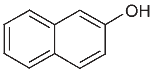
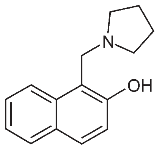
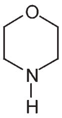
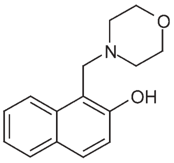
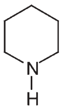
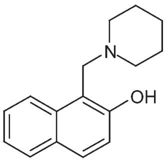
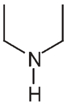
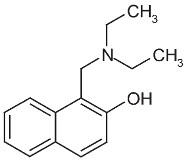
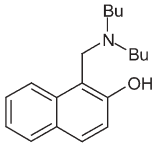
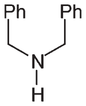
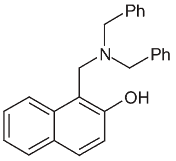
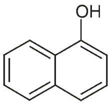
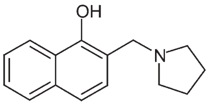
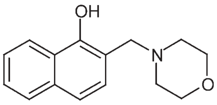
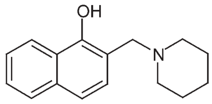
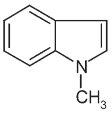
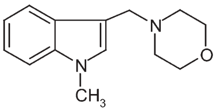
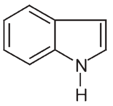
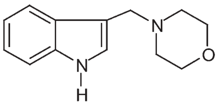
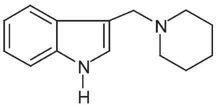
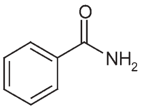
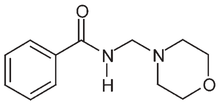
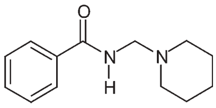
Table 3 Room-temperature, [omim][BF_4] mediated Mannich reactions with CH_2O, amines and electron-rich aromatic compounds

Entry	Amine (**1**)	Aromatic compound (**2**)	Product (**3**)	Time /h	Yield/%	M.p./°C
1	 **1a**	 **2a**	 **3a**	1	93	87–88 [86–88][23]
2	 **1b**	**2a**	 **3b**	2	70	115–116 [114–116][15]
3	 **1c**	**2a**	 **3c**	1.5	80	94.5–95 [94.5–95.5][24]
4	 **1d**	**2a**	 **3d**	1.5	99	Oil[12]
5	$NH(Bu)_2$ **1e**	**2a**	 **3e**	1.5	70	Oil[12]
6	 **1f**	**2a**	 **3f**	6	75	117–118 [117–117.5][19]
7	**1a**	 **2b**	 **3g**	1.5	60	Oil[25]
8	**1b**	**2b**	 **3h**	4	65	Oil[17]
9	**1c**	**2b**	 **3i**	3	54	135–136 [133.5–134.5][24]
10	**1b**	 **2c**	 **3j**	24	34	Oil[5]
11	**1b**	 **2d**	 **3k**	12 3	69 87[a]	120–121 [118–119][26]
12	**1c**	**2d**	 **3l**	12	72	161–162 [162–163][26]
13	**1b**	 **2e**	 **3m**	5.5 3	80 90[a]	66–68 [67–68][14]
14	**1c**	**2e**	 **3n**	4	84	125–127 [128][14]

[a] The reaction was carried out at 80 °C.

on the three-component Mannich reaction of paraformaldehyde, pyrrolidine and β-naphthol as the model reaction (Scheme 1) was examined in order to find the ionic liquid with the best catalytic effects. The results in Table 1 show that among various ionic liquids used in the model reaction, [omim][BF_4] had the best performance in respect to the reaction time and the yield of the product (Table 1, entry 3).

Effect of amounts of [omim][BF_4]

In order to optimise the reaction condition, the use of different amounts of [omim][BF_4] was evaluated in the model reaction. From the data presented in the Table 2, it is obvious that the optimum result was obtained when the reaction was carried out in 2.8 mmol of the ionic liquid (Table 2, entry 2).

The optimised conditions were then employed to evaluate the generality of the procedure (Table 3). In the reactions of 2-naphthol with formaldehyde and cyclic or acyclic amines, the Mannich bases were obtained in good to excellent yields within short times (entries 1–6). 1-Naphthol (entries 7–9), indole derivatives (entries 10–12), and benzamide (entries 13 and 14) also reacted well under the same conditions to give their respective products, although lower yields were obtained in some cases.

Reusability and recovery

The reusability of the ionic liquid was investigated in consecutive Mannich reactions of paraformaldehyde and pyrrolidine with 2-naphthol. The reactions were carried out by following the typical procedure. At the end of each reaction and after extraction of the products, the ionic liquid was recovered by removing the volatile solvent under reduced pressure using a rotary evapourator. The results of the reuse of the ionic liquid are summarised in the Fig. 1. As it is shown, the ionic liquid can be used for at least four consecutive runs without considerable loss of its catalytic activity.

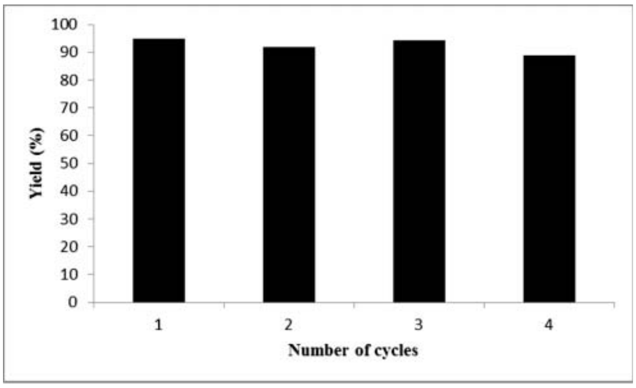


Fig. 1 Efficient recycling of the catalyst [omim][BF_4].

Conclusion

In conclusion, we have described a simple and efficient procedure for the three-component one-pot aminomethylation of various aromatic electron-rich compounds using ionic liquids as the catalyst and solvent at room temperature. Whereas all the ionic liquids which were studied catalysed the model reaction, it has been found that [omim][BF_4] was the most effective. The method has several advantages including mild reaction conditions, high yields of the products, simple work-up procedure, short reaction times, use of green and recoverable medium, and presence of no other extra additives or catalysts, and specially room temperature reaction conditions.

Experimental

^{1}H NMR spectra were measured on a Bruker DRX 500 Avance (500MHz) and Bruker Ultra Shield, 80 MHz spectrometers in $CDCl_3$ solutions with TMS as the internal standard. Infrared spectra were recorded using KBr pellets on a FT-IR Shimadzu 8400S spectrometer. Melting points were determined using an Electrothermal 9100 apparatus. All chemicals and reagents were purchased from Merck Company and used without further purification except for benzaldehyde which was distilled prior to being used. Analytical TLC was carried out using Merck 0.2 mm silica gel 60 F-254 Al-plates. All yields refer to the isolated products after purification. The ionic liquids [emim]BF_4 and [bmim]BF_4[27], [omim]BF_4[28], and [bdmim]BF_4[29] were prepared using available procedures. All the products were known and were identified by comparison of their melting points and/or spectroscopic data with those reported in the literature.

Typical procedure

A mixture of paraformaldehyde (1.5 mmol), a secondary amine (1.5 mmol), and an aromatic compound (1.0 mmol) in [omim][BF_4] (2.8 mmol) was stirred at room temperature for the appropriate length of time (Table 3). After completion of the reaction, based on TLC monitoring, the reaction mixture was extracted with Et_2O (3 × 10 mL). The extract was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel and EtOAc/hexane as the eluent (if necessary) or recrystallised from hexane and ethanol. The products were dried under vacuum at 40° C.

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