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[Bmim]PF_6 and BF_4 ionic liquids as novel and recyclable reaction media for aromatic amination

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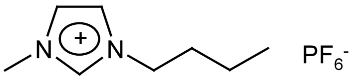
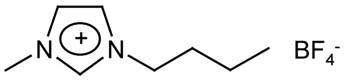
Abstract—Activated aryl halides undergo smooth nucleophilic substitution reactions with secondary amines in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) or 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) ionic liquids (ILs) at room temperature to afford the corresponding arylamines in excellent yields under mild and neutral conditions. © 2003 Elsevier Science Ltd. All rights reserved.

Nucleophilic aromatic substitution has become a very useful and diverse synthetic route for introducing amine functionality onto a benzene ring.[1] Arylamines are very common structural components in biologically active natural products, medicinally important compounds as well as in materials with useful electrical and mechanical properties.[2] Substituted arylamines are widely used clinically as antihistamine, anti-hypertensive and anti-inflammatory drugs. They are also an important class of compounds in neuropharmaceuticals.[3] Classical methods for the synthesis of arylamines typically require a large excess of base, highly polar solvents such as DMF, DMSO at high temperatures with highly activated aryl halides[4] and under high pressure conditions.[5] Hartwig[6] and Buchwald[7] have recently reported the amination of both activated and unactivated aryl halides with amines using Pd or Ni as catalysts under mild conditions. In recent years, ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability, and immiscibility with a number of organic solvents, negligible vapor pressure and recyclability.[8] Their high polarity and the ability to solubilise both inorganic and organic compounds can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents. Accordingly they are emerging as novel replacements for volatile organic solvents in organic synthesis. They are particularly promising, as solvents for various reactions.[9,10] Moreover, ionic liquids are simple and inexpensive to prepare and easy to recycle and their properties can be fine-tuned by changing the anion or the alkyl group attached to cation.

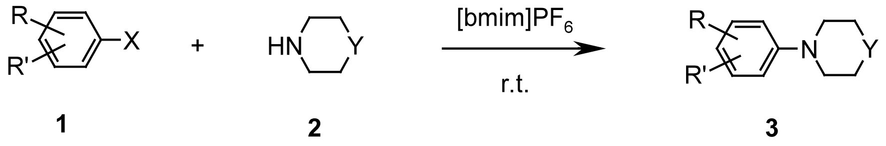


[Bmim]PF_6



[Bmim]BF_4

Because of the distinct advantages of room temperature ionic liquids as environmentally benign reaction media for catalytic processes, much attention has been focused on organic reactions in ionic liquids.



Scheme 1.

Keywords: ionic liquids (ILs); nucleophilic substitution; arylamines.

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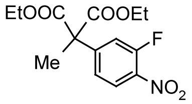
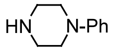
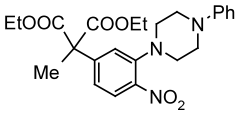
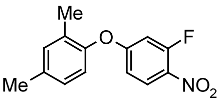
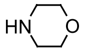
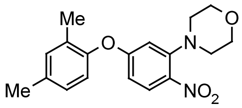
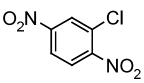
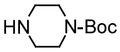
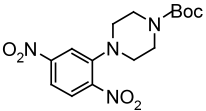
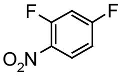
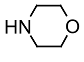
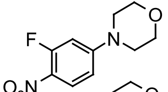
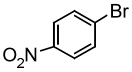
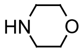
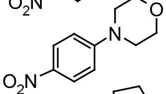
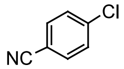
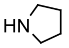
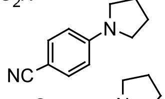
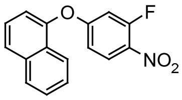
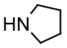
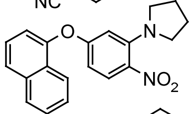
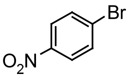
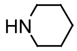
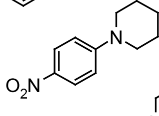
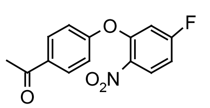
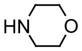
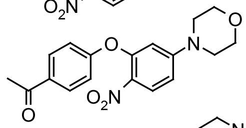
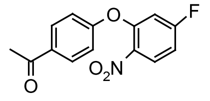
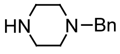
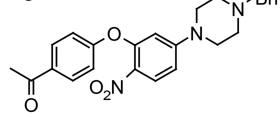
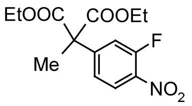
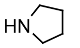
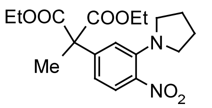
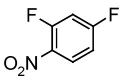
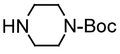
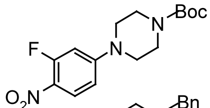
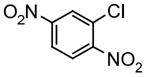
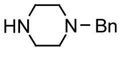
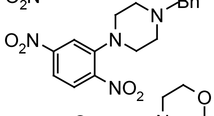
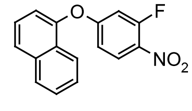
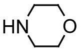
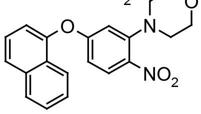
Table 1. *N*-Arylation of amines in 1-butyl-3-methylimidazolium hexafluorophosphate

Entry	Aryl halide	Amine	Product[a]	Time (h)	Yield (%)[b]
a				6.5	89
b				7.5	85
c				6.0	90
d				7.5	87[c]
e				8.0	85
f				10.0	80
g				8.5	89
h				8.0	90
i				9.5	87
j				9.0	85
k				10.0	78
l				8.0	90[c]
m				7.5	92
n				9.0	89

a: All the products were characterized by ^{1}H NMR, IR and mass spectroscopy.
b: Isolated and unoptimized yields.
c: *Para*- and *ortho*- substituted products were obtained in a ratio of 3:1

In view of the emerging importance of imidazolium-based ionic liquids as novel reaction media, we wish to explore the use of ionic liquids as promoters and recyclable solvent systems for the synthesis of arylamines under mild conditions (Scheme 1).

The treatment of *p*-nitrobromobenzene with morpholine in 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid resulted in the formation of 4-(4-nitrophenyl)morpholine in 87% yield. 1-Butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquid was prepared according to reported procedures.[11] In a similar fashion, a variety of aryl halides reacted smoothly with a range of secondary amines under these reaction conditions to give the corresponding arylamines in excellent yields (Table 1). The reactions proceeded efficiently at room temperature in ionic liquids whereas conventional methods require high temperature or microwave activation.[12] The scope and generality of this process is illustrated with respect to various amines and aryl chlorides, bromides and fluorides bearing *ortho*- or *para*-nitro or -cyano groups and the results are presented in Table 1.[13] This method is even effective with sterically hindered and highly functionalized aryl halides (entries a, b, c, g, i). Acid sensitive functionalities such as carbamates, esters and ethers survived under these conditions. Secondary alkyl amines such as morpholine, piperidine, pyrrolidine and piperazine showed higher reactivity than their acyclic counterparts. Furthermore, the reactions proceeded rapidly with *o*- and *p*-nitro substituted benzenes when compared to cyano substituted aryl halides. The experimental procedure is very simple and convenient and in addition, this method did not require any aqueous work-up thereby avoiding the generation of toxic waste. Since the products were weakly soluble in the ionic liquid, they were easily separated by simple extraction with ether. The rest of the viscous ionic liquid was thoroughly washed with ether and recycled in subsequent reactions. Second runs using recovered ionic liquid afforded similar yields to those obtained in the first runs. However, in the third and fourth runs, the yields gradually decreased. For example, *p*-nitrobromobenzene and piperidine in [bmim]PF_6 afforded 90, 90, 81, and 78%, over four cycles. However, the activity of the ionic liquid was consistent in runs and no decrease in yield was obtained when amine was used in slight excess (1.5 equiv.). The products obtained were of the same purity as in the first run. [Bmim]BF_4 ionic liquid was also found to be equally effective for this conversion. Finally, the efficiency of various quaternary ammonium salts was studied. This nucleophilic substitution reaction was not successful when *n*-tetrabutylammonium chloride (*n*-Bu_4NCl) or 1-*n*-butyl-3-methylimidazolium chloride ([bmim]Cl) were used as solvents. This indicated that both cation and anion play an important role in this transformation. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of green strategies for the synthesis of arylamines.

In this paper [bmim]PF_6 ionic liquid is proved to be a useful and novel reaction media for aromatic amination, avoiding the use of basic and highly polar organic solvents such as DMF, DMI or DMSO and high temperature reaction conditions by playing the dual role of solvent and promoter. The substrates show significant increase in reactivity thus improving the yields substantially. The experimental procedure is quite simple, convenient and avoids tedious aqueous work-up procedures for the isolation of products. The use of an easily accessible and recyclable ionic liquid makes this procedure convenient, economic and user-friendly.

Acknowledgements

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13. *General procedure*: A mixture of arylhalide (1 mmol) and secondary amine (1.2 mmol), in 1-butyl-3-methylimidazolium hexafluorophosphate (2 mL) was stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:9) to afford pure arylamine. The rest of the viscous ionic liquid was further washed with ether and recycled in subsequent runs. However, in the case of solids, the products were purified by recrystallization from appropriate solvents. Spectral data for selected products: **3a**: IR (KBr): ν 3328, 2925, 1743, 1542, 1233, 1041, 760. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 6H, $J=6.9$ Hz), 1.85 (s, 3H), 3.20–3.40 (m, 8H), 4.25 (q, 4H, $J=6.9$ Hz), 6.85–6.95 (m, 3H), 7.05 (dd, 1H, $J=1.8$, 8.1 Hz), 7.20–7.30 (m, 3H), 7.80 (d, 1H, $J=8.1$ Hz). FAB Mass: *m/z*: 455 M$^+$, 426, 409, 353, 321, 304, 278, 232, 217, 185, 173, 154, 136, 120, 105.
3b: IR (KBr): ν 3073, 2960, 1449, 1375, 1263, 1149, 1042, 974, 702. ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H), 2.25 (s, 3H), 3.10–3.20 (m, 4H), 3.70–3.80 (m, 4H), 6.10 (brs, 1H), 6.45 (dd, 1H, $J=1.7$, 8.0 Hz), 6.60 (brs, 1H), 6.85 (d, 1H, $J=8.0$ Hz), 7.10 (d, 1H, $J=8.0$ Hz), 8.0 (dd, 1H, $J=1.7$, 8.0 Hz). FAB Mass: *m/z*: 328 M$^+$, 311, 282, 207, 195, 164, 121, 91, 77, 43.
3i: ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H), 3.25 (t, 4H, $J=6.8$ Hz), 3.80 (t, 4H, $J=6.8$ Hz), 6.42 (d, 1H, $J=1.8$ Hz), 6.67 (dd, 1H, $J=1.8$, 8.1 Hz), 6.95 (d, 2H, $J=8.0$ Hz), 7.90 (d, 2H, $J=8.0$ Hz), 8.05 (d, 1H, $J=8.1$ Hz). FAB Mass: *m/z*: 343 M+H$^+$, 327, 313, 307, 294, 207, 191, 178, 165, 154, 136, 119, 107, 95, 81, 69, 55.