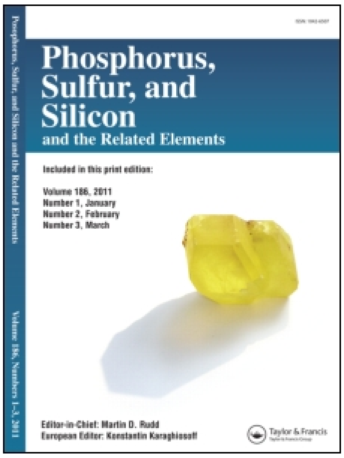

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Amine Exchange Reactions in Ionic Liquid

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Amine Exchange Reactions in Ionic Liquid

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An operationally simple, inexpensive, efficient, and environmentally friendly protocol for the amine exchange reactions of 3-N,N-dimethylaminopropiophenone and N,N-dimethylaminomethylferrocene with primary aryl amines is developed using the ionic liquid [bmim]PF_6 as a solvent. The recovered ionic liquid can be reused for several cycles with constant activity.

Keywords Amine exchange reactions; 1-butyl-3-methyl imidazolium hexafluorophosphate; Mannich bases

INTRODUCTION

Secondary alkyl amines in general are commonly employed for aminomethylation reactions following the early work of Carl Mannich. More recent investigations of the aminomethylation reaction have substantiated that less common alkyl amines,[1] amino acids,[2] or phthalimide[3] can be used effectively as amine components in the classical Mannich reaction. Until the mid-1970s, aryl amines were sporadically reported to react with various functionalities like phenols[4] and heterocyclic compounds.[5,6] More recently, arylaminomethylation of acetophenones has been studied extensively by the addition to a Schiff base generated in situ.[7–9] The amine exchange reaction, which consists of the interaction between an alkyl amine Mannich base and an aryl amine as reported by Singh and Singh,[10] also provides a route to aryl amine Mannich bases.

With green chemistry becoming a central issue in the 21st century, much effort has been made on reducing, recycling, or eliminating

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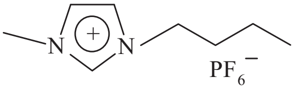


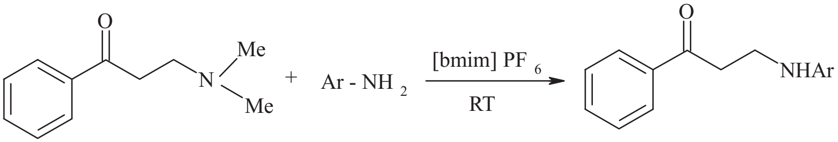
FIGURE 1 [bmim] PF_6.

the use of toxic chemicals in synthetic chemistry. An intriguing line of inquiry in green chemistry is the use of room temperature ionic liquids (RTILs) for organic reactions instead of traditional solvents. The tempting properties of RTILs such as negligible vapor pressure, large liquidus range, high thermal stability, large electrochemical window, and the ability to solvate compounds of varying polarity have made them an environmentally friendly reaction medium for organic synthesis.[11]

Here we report an operationally simple, inexpensive, efficient, and ecofriendly protocol for the amine exchange reaction in an ionic liquid, 1-butyl-3-methyl imidazolium hexafluorophosphate [bmim]PF_6 (Figure 1), as a solvent.

RESULTS AND DISCUSSION

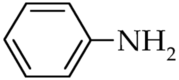
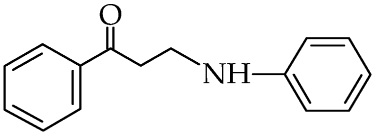
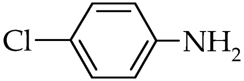
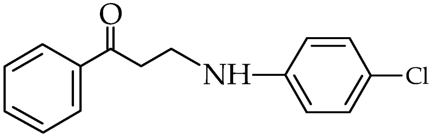
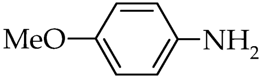
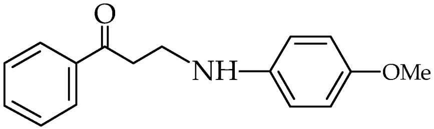
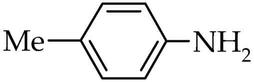
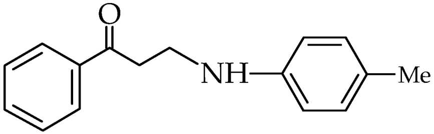
We first focused on the amine exchange reaction between 3-*N*,*N*-dimethylaminopropiophenone **1** and aniline. Since mixtures of products usually are obtained in amine exchange reactions, the outcome of this reaction was of particular interest. The reaction proceeded smoothly in [bmim]PF_6 at room temperature yielding the expected β-anilinopropiophenone **3a** in 92% yield without any side products. Subsequently, the reaction of compound **1** with a variety of aryl amines **2a–h** was investigated (Scheme 1). In most cases, respective products were obtained in good to excellent yields (Table I).

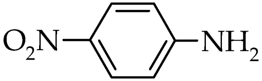
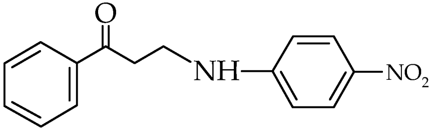
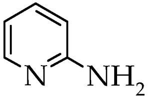
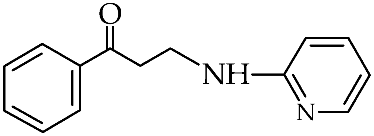
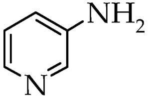
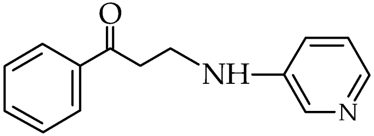
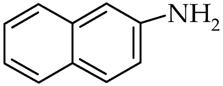
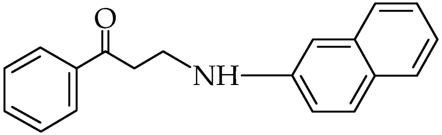


1 2a-h 3a-h

SCHEME 1

TABLE I Amine Exchange Reactions of 3-*N,N*-Dimethylaminopropiophenone with Aryl Amines in [bmim]PF_6^a

	Aryl amine (2)	Product^b(3)	Time (h)	Yield (%)^c	Mp^d (°C)
a			24	92	110–112 (113–114)[12]
b			14	88	136–138 (134–135)[12]
c			14	91	110–111 (111–112)[12]
d			18	88	114–116 (114–115)[12]

e			12	80	172–174 (173–175)[12]
f			11	77	86–88 (88–89)[12]
g			13	89	99–100 (98–99)[12]
h			30	64	150–151 (150–151)[12]

[a] Reactions were carried out at room temperature.

[b] All products were characterized by ^1H NMR and IR spectroscopy as well as by mass spectrometry.

[c] Isolated yields.

[d] Literature values in parenthesis.

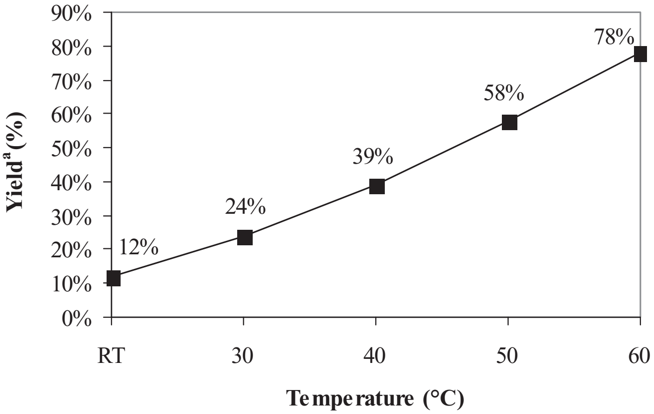
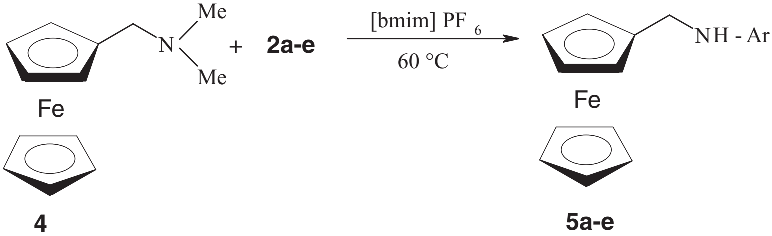


FIGURE 2 Amine exchange reaction of *N,N*-dimethylaminomethylferrocene with aniline in [bmim]PF_6 at different temperatures. Reactions were performed for 48 h. ^{a}Isolatedyields.

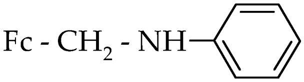
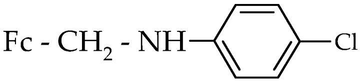
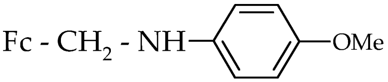
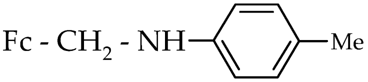
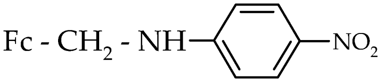
In order to check the general applicability of this protocol, we reacted *N,N*-dimethylaminomethylferrocene **4** with aryl amines in [bmim]PF_6. Preliminary investigations carried out at room temperature did not yield quantitative results. The reaction between **4** and aniline was performed at different temperatures. The best results were obtained when the reaction was carried out at 60 °C (Figure 2). Using the optimized experimental conditions, we checked the feasibility of the method by reacting **4** with the aryl amines **2a–e** (Scheme 2). The results are summarized in Table II and confirm the general applicability of the protocol.



SCHEME 2

For arylamines, the effect of steric demand on the yield appeared to be of greater importance than electronic effects. For instance, the reaction of **1** with *p*-substituted anilines showed comparable results,

TABLE II Amine Exchange Reactions of *N,N*-Dimethylaminomethylferrocene with Aryl Amines in [bmim]PF$_6$[a]

	Product[b] (5)	Time (h)	Yield[c] (%)	Mp[d] (°C)
a		48	78	83–85 (82–84)[13]
b		46	77	126–128 (126–128)[13]
c		49	79	48–50 (50–52)[13]
d		40	73	63–64 (62–64)[13]
e		38	80	123–125 (124–126)[13]

Fc = $C_5H_5FeC_5H_4$

[a] Reactions were carried out at 60°C.

[b] All products were characterized by ^{1}H NMR and IR spectroscopy as well as by mass spectrometry.

[c] Isolated yields.

[d] Literature values in parenthesis.

while the sterically hindered 2-naphthylamine afforded a lower yield of the respective product.

We observed that [bmim]PF$_6$ recovered after the reaction can be recycled and reused without any significant loss in chemical yield of the products. The use of recycled [bmim]PF$_6$ was investigated by the reaction of **1** with aniline. High yields were obtained until the fourth regeneration of [bmim]PF$_6$. The results are shown in Figure 3.

It is noteworthy to mention that the above method provides an alternative ecofriendly and economical route for the synthesis of *N*-arylaminomethylferrocenes, which are otherwise obtained by NaBH$_4$/LiAlH$_4$ reduction of ferrocenylaldimines, resulting from the reaction between ferrocenecarboxyaldehyde and aryl amines (Scheme 3).[13]

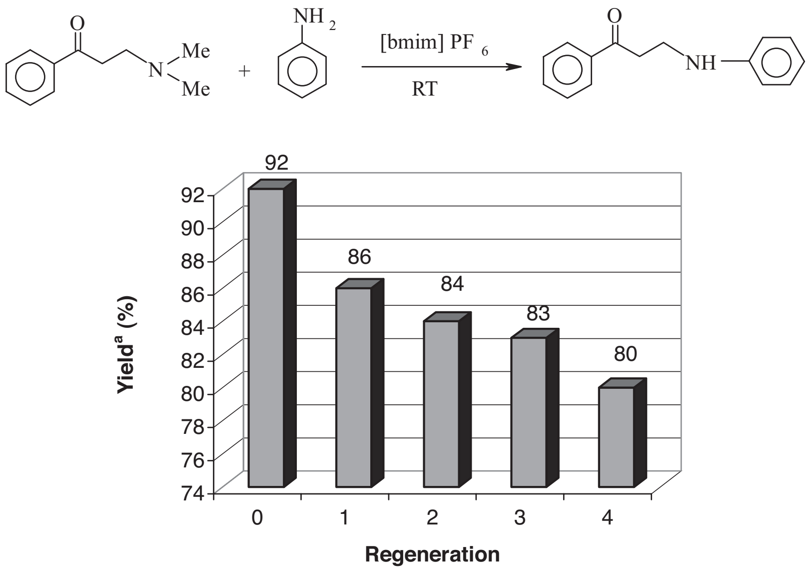
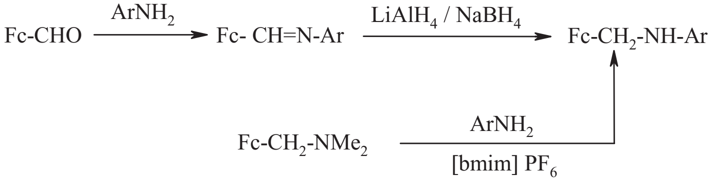


FIGURE 3 Use of recycled [bmim]PF_6. Reactions were performed at room temperature for 24 h. ^{a}Isolated yields.



SCHEME 3 Synthesis of *N*-arylaminomethylferrocenes.

CONCLUSION

We have developed an operationally simple, efficient, and ecofriendly methodology for amine exchange reactions in the ionic liquid [bmim]PF_6. The proposed method is quite general and works with diverse aryl amines. The mild conditions and high yields of the products not only make this protocol an alternative route to the conventional methods, but it also becomes significant under the umbrella of environmentally greener and safer processes.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on Perkin-Elmer Spectrum One FTIR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded with a Varian Mercury YH-300 instrument using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were recorded with a Shimadzu QP2010 GCMS with an ion source temperature of 200°C.

The ionic liquid [bmim]PF_6,[14] 3-*N*,*N*-dimethylaminopropiophenone,[15] and *N*,*N*-dimethylaminomethylferrocene[16] were synthesized following procedures reported in the literature. All other chemicals were obtained from commercial suppliers and used without further purification.

Amine Exchange in [bmim]PF_6: General Procedure

A mixture of 3-*N*,*N*-dimethylaminopropiophenone (1 mmol) or *N*,*N*-dimethylamino-methylferrocene (1 mmol) and the aryl amine (1 mmol) in 1 mL of [bmim]PF_6 was stirred at the appropriate temperature (Tables I and II). After completion of the reaction, as indicated by TLC, the resulting mixture was extracted from the ionic liquid phase using Et_2O (3 × 10.0 mL). Evaporation of the organic solvent afforded the crude product, which was purified by column chromatography on silica gel using petroleum ether (60–80 °C):ethyl acetate (9:1).

Spectral Data of Representative Compounds

1-Phenyl-3-phenylamino-propan-1-one (3a)

White solid; IR (KBr) ($\upsilon_{max,}$cm^1): 3408 (N-H), 1677 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.28$ (t, 2H, CH_2-N), 3.60 (t, 2H, CH_2-CO), 4.11 (bs, 1H, NH), 6.61 (m, 3H, arom-H) 7.18 (m, 3H, arom-H), 7.42 (d, 2H, arom-H), 7.89 (d, 2H, arom-H); MS (EI): m/z - 225 (M^+).

3(4′-chlorophenylamino)-1-phenylpropan-1-one (3b)

White solid; IR(KBr) ($\upsilon_{max,}$cm^1): 3394 (N-H), 1670 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.27$ (t, 2H, CH_2-N), 3.57 (t, 2H, CH_2-CO), 4.12 (bs, 1H, NH), 6.60 (d, $J_{HH} = 8.4$ Hz, 2H, arom-H) 7.12 (m, 3H, arom-H), 7.38 (d, 2H, arom-H), 7.91 (d, $J_{HH} = 8.2$ Hz, 2H, arom-H). MS (EI) : m/z - 259 (M^+).

(N-p-Chlorophenyl)aminomethylferrocene (5b)

Yellow solid; IR(KBr) ($\upsilon_{max,}$cm^1): 3421 (N-H); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.92$ (s, 2H, Fc-CH_2), 4.10 (bs, 1H, NH), 4.15 (s, 2H, Fc), 4.17 (s, 5H, Fc), 4.22 (s, 2H, Fc), 6.56 (d, $J_{HH} = 8.4$ Hz, 2H, arom-H), 7.12 (d, $J_{HH} = 8.1$ Hz, 2H, arom-H); MS (EI): m/z - 326 (M^+).

(N-p-Nitrophenyl)aminomethylferrocene (5e)

Yellow solid; IR(KBr) ($\upsilon_{max,}$cm^1): 3409 (N-H), 1519 $(NO_2)_{asym,}$ 1340 $(NO_2)_{sym}$; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 4.02$ (s, 2H, Fc-CH_2-N), 4.09 (bs, 1H, NH), 4.12 (s, 2H, Fc), 4.27 (s, 5H, Fc), 4.68 (s, 2H, Fc), 7.23 (d, $J_{HH} = 8.8$ Hz, 2H, arom-H), 8.08 (d, $J_{HH} = 8.8$ Hz, 2H, arom-H); MS (EI): m/z - 337 (M^+).

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