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Journal of Molecular Catalysis A: Chemical 249 (2006) 201–206
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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N-Arylation of imidazoles, imides, amines, amides and sulfonamides with boronic acids using a recyclable $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system

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Received 31 October 2005; received in revised form 6 January 2006; accepted 9 January 2006
Available online 17 February 2006

Abstract

N-Arylation of imidazoles, imides, amines, amides and sulfonamides with arylboronic acids using a recyclable $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system has been developed in the absence of a base or additive to afford the corresponding *N*-arylated products in good to excellent yields.

Keywords: *N*-Arylation; Copper salt; Ionic liquid; *N*-Nucleophiles; Arylboronic acids

1. Introduction

C(aryl)–N bond formation plays an important role in organic synthesis since the resultant *N*-arylated products have wide spread use in pharmaceutical and agrochemical industries [1–3]. Ullmann and Goldberg arylation of amines, amides, anilines with aryl halides using copper catalysts are popular methodologies [4] before the Pd and Ni catalyzed protocols by Hartwig and Buchwald [5,6]. Chan et al. [7], Evans et al. [8], Lam et al. [9] and others [10] reported the preparation of arylamines, *N*-arylheterocycles using boronic acids and cupric acetate under mild conditions compared to that of conventional methods. There are reports describing arylsiloxanes [11], arylstannanes [9b], diaryliodonium salts [12], arylbismuth[13] or aryllead triacetates [3b] as aryl donors using cupric acetate and a base. Some of the above stated methods include use of stoichiometric quantities of $Cu(OAc)_2$, excess arylboronic acid or base and longer reaction times. Collman has demonstrated the first catalytic version using $[Cu(OH){\cdot}TMEDA]_2Cl_2$ [14] and later by Antella and Buchwald [15] and Lam et al. [3a] using $Cu(OAc)_2$ as catalyst in presence of base and additive. Recently, *N*-arylation is reported using copper salts in the absence of base in protic solvents [16]. Chiang et al. reported the heterogeneous protocol for C–N cross-coupling reactions with arylboronic acids using a polymer supported copper catalyst [17].

Ionic liquids (ILs) are acknowledged as eco-benevolent alternatives to the volatile organic solvents and have also other useful properties like very low vapour pressure, wide liquid range, high thermal stability and possess highly conductive solvation ability for a variety of organic substrates and catalysts including Lewis acids and enzymes [18,19]. The emerging importance of the imidazolium based ionic liquids in organic synthesis, motivated us to test the efficacy of ionic liquids for C–N coupling reactions. Herein, we report *N*-arylation of *N*-nucleophiles with arylboronic acids in the absence of a base using a recyclable $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system (Scheme 1).

2. Experimental

1-Methyl imidazole, *n*-butyl bromide, $NaBF_4$, $NaPF_6$, *n*-tetrabutylammonium bromide and arylboronic acids were purchased from Aldrich or Fluka and used without further purification. $Cu(OAc)_2{\cdot}H_2O$, imidazole, amines and imides were purchased from S.D. Fine Chemicals, Mumbai. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F_{254} plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

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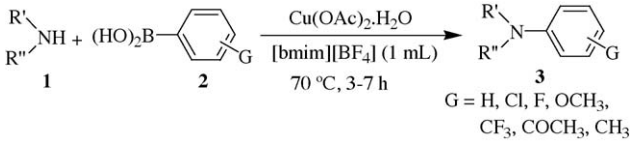
doi:10.1016/j.molcata.2006.01.012

2.1. Synthesis of ionic liquids

[bmim][BF_4] and [bmim][PF_6] were synthesized according to the procedures reported in the literature and the purity was confirmed by ^{1}H NMR and TGA-DTA analysis [20].

2.2. Typical experimental procedure for the N-arylation of N-nucleophiles with arylboronic acids

To a mixture of $Cu(OAc)_2{\cdot}H_2O$ (0.020 g, 10 mol%) in [bmim][BF_4] (1 mL), *N*-nucleophile (1 mmol), arylboronic acid (1 mmol) were added successively and stirred at 70 °C for appropriate time. After completion of the reaction, as monitored by TLC, the product was extracted with diethyl ether or ethyl acetate:*n*-hexane [(1:1), (3 × 10 mL)]. The combined extracts were concentrated in vacuum and the resulting product was purified by column chromatography on silica gel with ethyl acetate and *n*-hexane as eluent to afford *N*-arylated product. All the products gave satisfactory ^{1}H NMR and mass spectral data in accordance with literature [14,15,17]. The ionic liquid containing the catalyst was dried under vacuum and preserved for the next run.



Scheme 1.

Table 1
Optimization of catalytic conditions in *N*-arylation of imidazole with phenylboronic acid using $Cu(OAc)_2{\cdot}H_2O$ under various solvent systems

Entry	Base	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	None	[bmim][BF_4]	25	24	NR[b]
2	Et_3N	[bmim][BF_4]	25	24	40
3	None	[bmim][BF_4]	70	3	95, 80[c]
4	None	DMF	70	3	40
5	None	THF	70	3	45
6	None	CH_2Cl_2	70	3	50
7	None	CH_3OH	70	3	85, 95[d]

Reaction conditions: Imidazole (1 mmol), phenylboronic acid (1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%) and solvent (1 mL).
[a] Isolated yield after column chromatography.
[b] No reaction observed.
[c] Reaction using anhydrous $Cu(OAc)_2$.
[d] Isolated yield after 4 h.

3. Results and discussion

Preliminary experiments were carried out with imidazole as a typical *N*-nucleophile and phenylboronic acid as aryl donor using 10 mol% of $Cu(OAc)_2{\cdot}H_2O$ in [bmim][BF_4] (1 mL) under diverse reaction conditions and the results are summarized in Table 1. No reaction occurred in the absence of a base and the use of Et_3N as a base gave 40% yield of the cross-coupled product

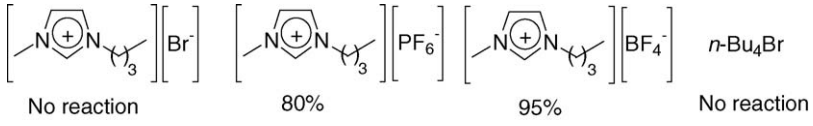
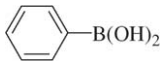
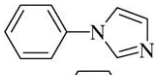
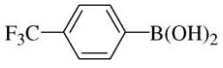
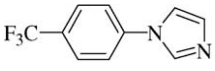
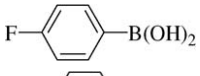
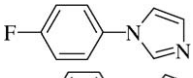
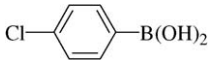
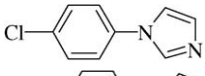
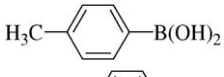
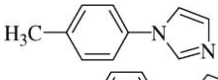
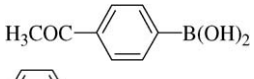
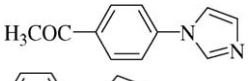
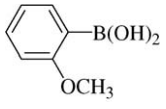
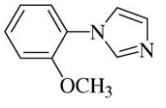


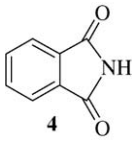
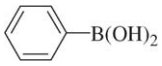
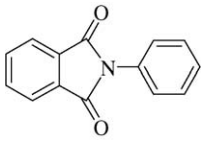
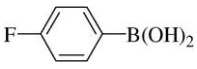
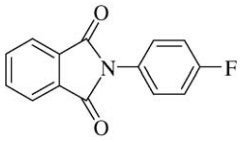
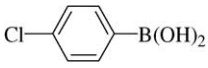
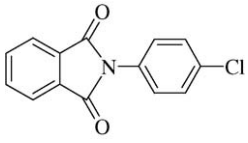
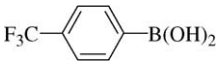
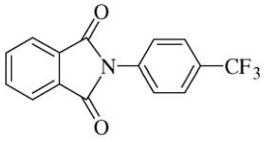
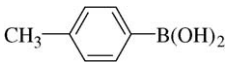
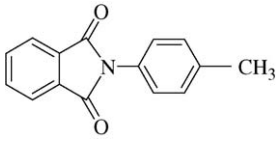
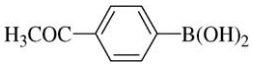
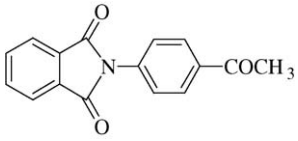
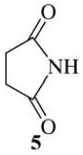
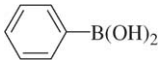
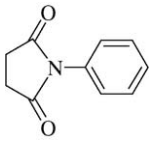
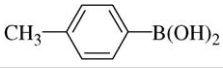
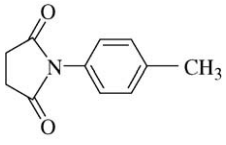
Fig. 1. Screening of ILs for the *N*-arylation of imidazole (1 mmol) with phenylboronic acid (1 mmol) using 10 mol% $Cu(OAc)_2{\cdot}H_2O$ at 70 °C in 3.0 h.

Table 2
N-Arylation of imidazole with various arylboronic acids using $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system

Entry	Arylboronic acid	Time (h)	Product	Yield (%)[a]
1		3.0		95, 90[b]
2		4.0		90
3		4.0		85
4		4.0		85
5		4.5		88
6		5.0		80
7		5.0		80

Reaction conditions: Imidazole (1 mmol), arylboronic acid (1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%) and [bmim][BF_4] (1 mL).
[a] Isolated yield.
[b] Isolated yield after fourth cycle.

Table 3
N-Arylation of imides with various arylboronic acids using $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system

Entry	Imine	Arylboronic acid	Time (h)	Product	Yield (%)[a]
1	 **4**		3.0		92, 85[b]
2	**4**		5.0		85
3	**4**		4.0		90
4	**4**		5.0		88
5	**4**		6.0		90
6	**4**		7.0		80
7	 **5**		4.0		90
8	**5**		5.0		88

Reaction conditions: Imide (1 mmol), arylboronic acid (1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%) and [bmim][BF_4] (1 mL).
[a] Isolated yield.
[b] Isolated yield after fourth cycle.

at room temperature (Table 1, entries 1 and 2). However, when the reaction was performed at 70 °C in the absence of a base, the corresponding product, *N*-phenylimidazole was obtained in excellent yield in 3 h (Table 1, entry 3). To evaluate the effect of solvent, we conducted a series of experiments in various organic solvents under the same conditions and results are presented in Table 1. The reaction in dimethylformamide (DMF), tetrahydrofuran (THF) and dichloroethane gave the *N*-phenylimidazole in 40–50% yield (Table 1, entries 4–6) and in methanol 95% isolated yield after 4 h (Table 1, entry 7). It is interesting to note that the activity in ionic liquids is superior over the classical organic solvents in the absence of a base [18i].

Similarly, the cross-coupling reaction between imidazole and phenylboronic acid was performed with different ILs and results are grouped in Fig. 1. Among the ILs tested, hydrophilic [bmim][BF_4] was found to be superior (95% yield) than that of hydrophobic [bmim][PF_6] (80% yield), whereas the cross-coupling reaction was not successful in other molten salts such as *n*-tetrabutylammonium bromide (*n*-Bu_4Br) and 1-*n*-butyl-3-methylimidazolium bromide ([bmim][Br]) under similar reac-

Table 4
N-Arylation of various *N*-nucleophiles with various arylboronic acids using $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system

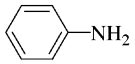
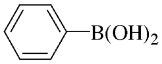
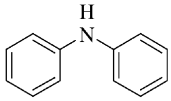
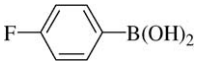
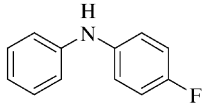
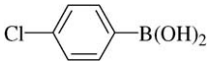
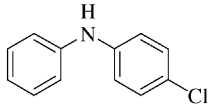
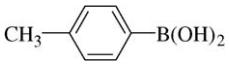
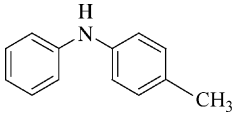
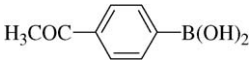
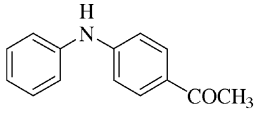
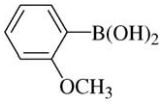
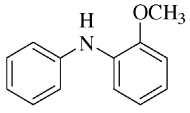
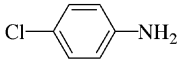
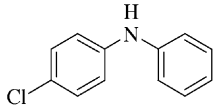
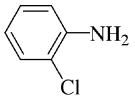
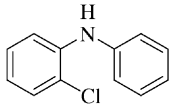
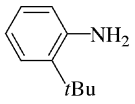
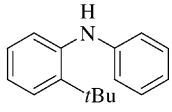
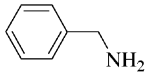
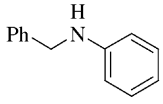
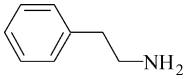
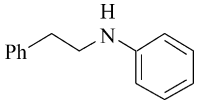
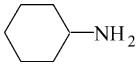
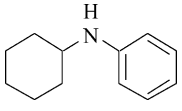
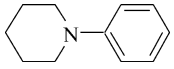
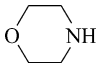
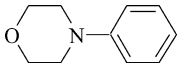
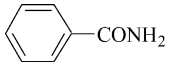
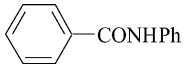
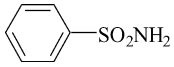
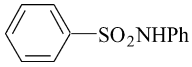
Entry	Amine	Arylboronic acid	Time (h)	Product	Yield (%)[a]
1	 **6**	 **7**	4.0		75, 70[b]
2	**6**		4.0		72
3	**6**		4.0		70
4	**6**		4.5		75
5	**6**		5.0		65
6	**6**		5.0		68
7		**7**	5.0		70
8		**7**	5.0		65
9		**7**	5.0		60
10		**7**	4.0		60
11		**7**	4.0		60
12		**7**	5.0		55
13		**7**	5.0		60

Table 4 (*Continued*)

Entry	Amine	Arylboronic acid	Time (h)	Product	Yield (%)[a]
14		**7**	5.0		60
15		**7**	6.0		30
16		**7**	6.0		30

Reaction conditions: Amine (1 mmol), arylboronic acid (1 mmol), $Cu(OAc)_2$ (10 mol%) and [bmim][BF_4] (1 mL).
[a] Isolated yield.
[b] Isolated yield after fourth cycle.

tions conditions. These results clearly indicate that both the cation and anion play a significant role in this cross-coupling reactions. Similar observations were reported by Welton and coworkers for Pd catalyzed Suzuki reactions in ionic liquids [21].

Under optimized reaction conditions, a wide range of structurally diverse arylboronic acids were coupled with imidazole (Table 2, entries 1–7) using $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system to produce the corresponding substituted *N*-aryl imidazoles in good to excellent yields. Finally, upon completion of the reaction, the ionic liquid phase containing [bmim][BF_4] and catalyst was almost quantitatively recovered by simple extraction of the product with Et_2O. The recovered ionic liquid phase containing the catalyst was reused for several cycles with consistent activity (Table 2, entry 1).

In an endeavor to expand the scope of the above methodology, the catalytic system was applied to imides, amines, amides and sulfonamides. A series of substituted arylboronic acids were coupled with phthalimide (Table 3, entries 1–6) and succinamide (Table 3, entries 7 and 8) under the generalized reaction conditions to afford the corresponding *N*-aryl imides in good to excellent yields. The yields are comparable to the literature values using the homogeneous catalyst [16b].

Similarly, aniline was subjected to cross-coupling with substituted arylboronic acids and *o*-, *p*-substituted anilines with phenylboronic acid and the corresponding *N*-aryl amines were obtained in satisfactory yields (Table 4, entries 1–9). The coupling of alkyl amines with phenylboronic acid gave the *N*-alkyl anilines in moderate yields (Table 4, entries 10–14). However, the reaction of amides and sulfonamides with phenylboronic acid afforded the corresponding products albeit in lower yields (Table 4, entries 15 and 16).

In general, the reactions are facile, clean for the synthesis of a variety of *N*-arylated products. Several functional groups, such as Cl, CF_3, F, CH_3, $COCH_3$ and OCH_3 remain unaffected under the present reaction conditions.

4. Conclusions

In summary, we have developed a simple and recyclable protocol for the cross-coupling reaction of arylboronic acids with a wide range of *N*-nucleophiles to afford the *N*-arylated products using inexpensive $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system in the absence of a base or additive.

Acknowledgments

We wish to thank the CSIR for financial support under the Task Force Project CMM-0005. B.N., Ch.V.R. and V.N. thank the Council of Scientific and Industrial Research (CSIR), India, for research fellowships.

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