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SELECTIVE SYNTHESIS OF 2-ARYL-1-ARYLMETHYL-1*H*-1,3-BENZIMIDAZOLES PROMOTED BY IONIC LIQUID

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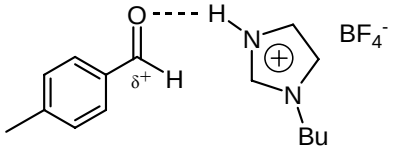
Abstract –Ionic liquid is used to promote the condensation of *o*-phenylenediamine with aldehydes and afford corresponding 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles efficiently. The absence of a catalyst and recyclability on the non-volatile IL make this an environment friendly methodology for selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles.

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest. Benzimidazole derivatives exhibit significant activity against several viruses such as HIV,[1] herpes (HSV-1),[2] RNA,[3] influenza,[4a] and human cytomegalovirus (HCMV)[1]. The widespread interest in benzimidazole-containing structures has promoted extensive studies for their synthesis. While many strategies are available for benzimidazole synthesis,[7-16] there are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamines and carboxylic acids[4b] or their derivatives (nitriles, imidates, or orthoesters),[5] which often requires strong acidic conditions, and sometimes combines with very high temperatures or the use of microwave irradiation.[6] The other way involves a two-step procedure that includes the oxidative cyclo-dehydrogenation of Schiff 's bases, which are often generated from the condensation of phenylenediamines and aldehydes. Various oxidative and catalytic reagents such as sulfamic acid,[7] I_2,[8] DDQ,[9] Air,[10] Oxone,[11] $FeCl_3 \cdot 6H_2O$,[12] $In(OTf)_3$,[13] $Yb(OTf)_3$,[14] $Sc(OTf)_3$,[15] $KHSO_4$,[16] have been employed. Because of the availability of a vast number of aldehydes, the latter method has been extensively used. While many published methods are effective, some of these methods suffer from one or more disadvantages such as high reaction

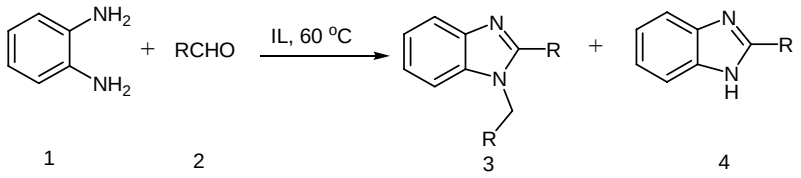
temperature, prolonged reaction time, and toxic solvents etc. Therefore, the discovery of mild and practical routes for synthesis of 2-substituted benzimidazoles continues to attract the attention of researchers.

In recent times, the use of non-aqueous room temperature ionic liquids(IL) as green solvents in organic synthetic processes has gained considerable importance due to their negligible vapour pressure, solvating ability and easy recyclability.[17] It is reported that a significant shift of 3 ppm (^{13}C-NMR) for the carbonyl carbons of aldehyde by their interaction with IL were observed. Additional evidence was obtained by recording their IR spectra (neat) wherein also a significant shift to a lower wave number by 18 cm^{-1} was observed. (Scheme1).[18]



Scheme 1

So we tried to synthesize 2-substituted benzimidazoles using IL as solvent, but failed. However, we found that IL was a efficient promoter in synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles by the condensation of arylaldehyde with *o*-phenylenediamine (Equation 1).



Equation 1

In order to establish the optimum condition for this reaction, various solvents were examined. Using *o*-phenylenediamine and *p*-chlorobenzaldehyde as a model, different solvents might cause different yields. As shown in Table 1, the reaction carried out in IL (Entry 14) was the most successful compared to those with other solvents. Little products were obtained when the reaction was carried out in H_2O, DMF, or CH_3CH_2OH. While the reaction was carried out in a mixture of IL/H_2O or IL/EtOH, both 2-(4-chlorophenyl)benzimidazole and 1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1*H*-1,3-benzimidazole were obtained.

To test the general scope and versatility of this procedure in the synthesis of a variety of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles, we examined a number of differently substituted arylaldehydes. We are pleased to find that good to high yields were obtained in the condensation of *o*-phenylenediamine with aldehydes. As Table 2 shows, arylaldehydes without substituents gave desired benzimidazoles in excellent yields (**3a**, **3g**). Aldehydes bearing electron-donating substituents gave more

desired benzimidazoles than electron-withdrawing substituents except for **3i**. To extend the scope of this method, we also examined the condensation of alkyl aldehyde with *o*-phenylenediamine, but failed.

Table 1**.** Effect of solvent in condensation of *o*-phenylenediamine with 4-chlorobenzaldehyde

Entry	Aldehyde (equiv.)	Solvent	Time [d](min)	Yield [a] (%) of **3**	Yield [a] (%) of **4**
1	A[b](1)	H_2O	25	trace	trace
2	A(1)	DMF	25	trace	trace
3	A(1)	EtOH	25	trace	trace
4	A(1)	IL[c]	25	32	25
5	A(1)	IL/H_2O(V/V=1:1)	25	30	25
6	A(1)	IL/H_2O(V/V=1:2)	25	30	24
7	A(1)	IL/H_2O(V/V=1:10)	25	28	23
8	A(1)	IL/H_2O(V/V=1:20)	30	25	21
9	A(1)	IL/EtOH(V/V=(1:2)	25	34	25
10	A(1)	IL/EtOH(V/V=(1:10)	25	33	25
11	A(1)	IL/EtOH(V/V=(1:20)	30	33	25
12	A(2)	IL/H_2O(V/V=1:1)	25	40	31
13	A(2)	IL/EtOH(V/V=(1:2)	25	41	31
14	A(2)	IL	25	83	trace

[a]All yields refer to isolated product. [b]A= 4-chlorobenzaldehyde. [c]IL= 1-methylimidazolium tetrafluoroborate [Hmim]BF_4. [d]Reaction temperature:60 °C.

Table 2**.** Synthesis of various 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in IL

Entry	R	Time (min)	Yield [a] (%)
1	a: C_6H_5	25	92
2	b: 4-ClC_6H_4	35	83
3	c: 4-$NO_2C_6H_4$	60	70
4	d: 3-$NO_2C_6H_4$	60	72
5	e: 4-$H_3CC_6H_4$	45	82
6	f: 4-$CH_3OC_6H_4$	30	84
7	g: 2-Furanyl	30	88
8	h: 2-ClC_6H_4	60	75
9	i: 4-$(CH_3)_2NC_6H_4$	60	trace
10	j: CH_3 (CH_2)$_5$	60	trace
11	k: $CH_3CH_2CH_2$	60	trace
12	l: CH_3CH_2	60	trace

[a] All yields refer to isolated product, characterized by melting points, IR, ^{1}H NMR

In conclusion, we have developed a simple, one-pot synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles by the condensation of *o*-phenylenediamine with arylaldehyde in IL. For this procedure, there was no need for any additional catalyst. The absence of a catalyst and recyclability on the non-volatile IL make this an environment friendly methodology for selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles.

EXPERIMENTAL

All melting points were determined on a Kofler micro melting point apparatus and were uncorrected. IR spectra were recorded on a SP3-300 spectrophotometer using KBr discs. ^{1}H NMR spectra were measured on a Bruker DPX-400M spectrophotometer using TMS as internal standard and $CDCl_3$ or CD_3COCD_3 as solvent.

Typical procedure for synthesis of benzimidazoles: Aldehyde (1 mmol) and *o*-phenylenediamine (0.5 mmol) were mixed in IL (2 mL) thoroughly. Then the mixture was heated and stirred at 60 °C for appropriate time (monitored by TLC). When the reaction was finished, the solution was cooled to rt. The reaction mixture was added with H_2O (20 mL). In cases where the product precipitated as a free flowing solid, it was collected by filtration, washed with H_2O and dried. In cases where gummy material precipitated the product was extracted into EtOAc, the organic phase was washed with H_2O, brine and dried (Na_2SO_4). Evaporation of solvent gave the crude product, which was recrystallised or purified by column chromatography over silica gel (petroleum ether/EtOAC, 3:1) to afford the corresponding 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles. The aqueous layer containing IL was subjected to distillation (80 °C at 10mmHg) for 2h to remove water, leaving behind the IL [Hmim]BF_4, which was recycled.

All the compounds are known compounds. They were identified from their ^{1}H NMR spectroscopic data and by comparing their mps with those reported in the literature (references cited). **3a:** mp 129-130 °C (lit.,[19b] 132 °C); **3b:** mp 138-139 °C (lit.,[19b] 136 °C); **3c:** mp 212-214 °C (lit.,[19b] 192 °C); **3d:** mp 158-160 °C (lit.,[7] 168-170 °C); **3e:** mp 121-123 °C (lit.,[19b] 128-130 °C); **3f:** mp 115-117 °C (lit.,[7] 126-128 °C); **3g:** mp 88-90 °C (lit.,[19b] 94 °C); **3h:** mp 160-162 °C (lit.,[19b] 163 °C).

1-Benzy-2-phenyl-1*H*-1,3-benzimidazole ^{1}H NMR(CD_3COCD_3): δ 7.78-7.76 (m, 3H) ; 7.54-7.52 (m, 3H) ; 7.40 (d, J= 7.2,1H) ; 7.34-7.22 (m, 5H) ; 7.11 (d, J= 7.2, 2H); 5.63 (s, 2H).

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-1,3-benzimidazole (3b) ^{1}HNMR($CDCl_3$): δ 7.91 (d, *J* = 8 Hz,1H); 7.63 (d, 2H); 7.47 (d, 2H); 7.39–7.20 (m, 4H); 7.23 (d, *J* = 8 Hz, 1H); 7.04 (d, *J* = 8 Hz, 2H); 5.43 (s, 2H).

1-(4-Nitrobenzyl)-2-(4-nitrophenyl)-1*H*-1,3-benzimidazole (3c) ^{1}HNMR(CD_3COCD_3): δ 8.38 (d, *J* = 8 Hz,2H); 8.20 (d, *J* = 8 Hz, 2H); 8.07 (d, *J* = 8, 2H); 7.84 (d, *J* = 7.2 Hz, 1H); 7.51 (d, *J* = 7.2 Hz, 1H);7.40 (d, *J* = 8, 2H); 7.35 (t, 2H); 5.90 (s, 2H).

1-(3-Nitrobenzyl)-2-(3-nitrophenyl)-1*H*-1,3-benzimidazole (3d) ^{1}HNMR($CDCl_3$): δ 8.52 (s, 1H); 8.39 (d, *J*= 7.6 Hz, 1H); 8.23 (d, *J*= 8.0 Hz, 1H); 8.11 (d, *J*= 7.6 Hz, 2H); 8.06 (s, 1H); 7.97 (d, *J*= 8.0 Hz, 1H); 7.72 (t, *J*= 8.0 Hz, 1H); 7.58 (t, *J*= 8.0 Hz, 1H); 7.46-7.31 (m, 4H); 5.62 (s, 2H);

1-(4-Methylbenzyl)-2-(4-methylphenyl)-1*H*-1,3-benzimidazole (3e) ^{1}HNMR($CDCl_3$): δ 7.91 (d, 1H);7.63 (d, *J* = 7.6 Hz, 2H); 7.34 (m, 1H);7.31 (d, *J*=7.6, 2H); 7.24 (m, 2H); 7.16 (d, *J* = 7.6 Hz,2H);

7.02 (d, *J* = 7.6 Hz, 2H); 5.45 (s, 2H); 2.44 (s, 3H); 2.36 (s, 3H).

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-1,3-benzimidazole (3f) ^{1}HNMR(CD_3COCD_3): δ 7.74-7.72(d, 3H); 7.38 (d, 1H); 7.23 (m, 2H) ; 7.08(d, *J* = 8 Hz, 2H); 7.06 (d, *J* = 8 Hz, 2H); 6.87 (d, *J* = 8.8 Hz, 2H); 5.54 (s, 2H);3.88 (s, 3H); 3.76 (s, 3H).

2-(2-Furyl)-1-(2-furylmethyl)-1*H*-1,3-benzimidazole (3g) ^{1}HNMR(CD_3COCD_3): δ 7.92 (s, 1H); 7.68 (m, 2H); 7.45 (s, 1H); 7.30 (m, 3H); 6.73 (s, 1H); 6.45(d, 1H); 6.37 (d, 1H); 5.83 (s, 2H).

1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1*H*-1,3-benzimidazole (3h) ^{1}HNMR(CD_3COCD_3): δ 7.80 (d, *J* = 7.2 Hz,1H); 7.62-7.54 (m, 3H); 7.46-7.27 (m, 6H); 7.18 (t, *J* = 7.2 Hz, 1H); 6.72 (d, *J* = 8 Hz, 1H); 5.48 (s, 2H).

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REFERENCES

1. a) A. R. Porcari, R. V. Devivar, L. S. Kucera, J. C. Drach, and L. B. Townsend, *J. Med. Chem*., 1998, **41**, 1251. b) M. Roth, M. L. Morningstar, P. L. Boyer, S. H. Hughes, R. W. Bukheit, and C. J. Michejda, *J. Med. Chem*., 1997, **40**, 4199.
2. M. T. Migawa, J. L. Giradet, J.A. Walker, G. W. Koszalka, S. D. Chamberlain, J. C. Drach, and L. B. Townsend, *J. Med. Chem*., 1998, **41**, 1242.
3. I. Tamm and P. B. Seghal, *Adv. Virus Res*., 1978, **22**, 187.
4. a) I. Tamm, *Science*, 1957, **126**, 1235. b) T. Hisano, M. Ichikawa, K. Tsumoto, and M. Tasaki, *Chem. Pharm. Bull.*, 1982, **30**, 2996.
5. a) A. Czarny, W. D. Wilson, and D. W. Boykin, *J. Heterocycl. Chem*., 1996, **33**, 1393. b) R. R. Tidwell, J. D. Geratz, O. Dann, G. Volz, D. Zeh, and H. Loewe, *J. Med. Chem*., 1978, **21**, 613.
6. G. V. Reddy, V. V. V. N. S. R. Rao, B. Narsaiah, and P. S. Rao, *Synth. Commun*., 2002, **32**, 3703.
7. M. Chakrabarty, S. Karmakar, A. Mukherji, S. Arim, and Y. Harigayab, *Heterocycles*, 2006, **68**, 967
8. P. Gogoi and D. Konwar, *Tetrahedron Lett.*, 2006, **47**, 79.
9. K. J. Lee and K. D. Janda, *Can. J. Chem*., 2001, **79**, 1556.
10. S. Lin and L. Yang, *Tetrahedron Lett.*, 2005, **46**, 4315.
11. P. L. Beaulieu, B. Hache, and E. von Moos, *Synthesis*, 2003, **11**, 1683.
12. M. P. Singh, S. Sasmal, W. Lu, and M. N. Chatterjee, *Synthesis*, 2000, **10**, 1380.
13. R. Trivedi, S. K. De, and R. A. Gibbs, *J. Mol. Cat. A: Chem.*, 2005, **245** , 8.
14. C. Massimo, E. Francesco, and M. Francesca, *Synlett,* 2004, **10**, 1832.
15. a) T. Itoh, K. Nagata, H. Ishikawa, and A. Ohsawa, *Heterocycles*, 2004, **63**, 2769.

b) K. Nagata, T. Itoh, H. Ishikawa, and A. Ohsawa, *Heterocycles*, 2003, **61**, 93.

16. H. Q. Ma, Y. L. Wang, and J. Y Wang, *Heterocycles*, 2006, **68**, 1669.
17. J. Dupont, R. F. D. Souza, and P. A. Suarez, *Chem. Rev.*, 2002, **102**, 3667.
18. A.R. Gholap, K. Venkatesan, T. Daniel, R. J. Lahoti, and K. V. Srinivasan, *Green Chem.*, 2004, **6**, 147.
19. a) S. Perumal, S. Mariappan, and S. Selvaraj, *ARKIVOC*, 2004, **8**, 46. b) P. Salehi, M. Dabiri, M. A. Zolfigol, S. Otokesh, and M. Baghbanzadeh, *Tetrahedron Lett.*, 2006, **47**, 2557.