

Efficient and Eco-Friendly Process for the Synthesis of Bis(1*H*-indol-3-yl)methanes using Ionic Liquids

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Abstract: Indoles react smoothly with carbonyl compounds in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) ionic liquids under mild reaction conditions to afford the corresponding bis-indolylmethanes in excellent yields. These ionic liquids can be recovered and recycled in subsequent reactions without any apparent loss of activity.

Keywords: aldehydes; bis-indolylmethanes; ionic liquids; ketones

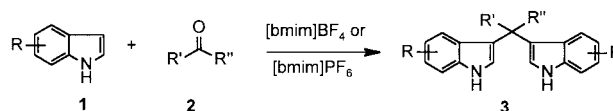
The acid-catalyzed reaction of electron-rich heterocyclic compounds with *p*-dimethylaminobenzaldehyde is known as the Ehrlich test for π -electron excessive heterocycles such as pyrroles and indoles.^[1] The analogous reaction of indoles with other aromatic or aliphatic aldehydes and ketones produces azafulvenium salts. The azafulvenium salts can undergo further addition with a second indole molecule to afford bis(indolyl)methanes.^[2] Generally, Lewis acids^[3,4] as well as protic acids^[5] are employed as catalysts to promote these reactions. However, many of these reagents are deactivated or sometimes decomposed by aqueous work-up and, therefore, they cannot be recycled for further runs. Recently, lanthanide triflates were reported to be efficient for this transformation.^[6] Although metal triflates are reusable, they are strongly acidic and highly expensive. Furthermore, there are no reports on the use of ionic liquids as reaction media for this conversion.

One of the prime principles of green chemistry is to develop an alternative reaction medium, which is the basis for the development of many cleaner chemical technologies. Particularly, ionic liquids have recently gained recognition as possible environmentally safe alternatives to volatile organic solvents. Ionic liquids, especially those based on the 1-*n*-alkyl-3-methylimidazolium cation, have shown great promise as novel reaction media for various catalytic processes.^[8] Due to the great potential of room temperature ionic liquids

as environmentally benign reaction media for catalytic processes, much attention is currently being focused on organic reactions promoted by ionic liquids.^[9] The unique property of ionic liquids is that they have essentially no vapor pressure, which makes them optimal replacements for volatile organic solvents traditionally used as industrial solvents.^[10] A nice feature of ionic liquids is that yields can be optimized by changing the anions or properties of the cation. In addition, several ionic liquids show enhancement in reaction rates and selectivity, compared to organic solvents with the added advantages of ease of recovery and reuse of these ionic solvents. Due to these advantages, ionic liquids can make a significant contribution to green chemistry.

In view of the emerging importance of ionic liquids as novel reaction media, we herein report the synthesis of bis(1*H*-indol-3-yl)methanes from carbonyl compounds and indoles using ionic liquids as reaction media. The treatment of indole with benzaldehyde in [bmim]BF₄ ionic liquid afforded the corresponding bis-indolylmethane in 90% yield (Scheme 1).

A variety of carbonyl compounds reacted smoothly with indoles to produce bis-indolylmethanes under these reaction conditions. The electron deficiency and the nature of the substituents on the aromatic ring show some effects on this conversion. The nitro-substituted arylaldehydes took longer reaction times to produce comparable yields to those obtained with simple and electron-rich counterparts. Electron-rich aldehydes like veratraldehyde etc., reacted rapidly with indole and 2-methylindole to give the products in excellent yields within 4 h whereas aliphatic aldehydes such as hexanal, and cyclohexanecarboxaldehyde afforded 80–90% yields in 5–6 h. Furthermore, the reaction of indole with ketones such as cyclohexanone and cyclopentanone gave the products in good yields. The reaction of ketones with indole took longer when compared to



Scheme 1.

aldehydes. All the products were characterized by ^1H NMR, IR and mass spectral analysis and also by comparison with authentic samples.^[11] The reactions were carried out in both hydrophilic $[\text{bmim}]\text{BF}_4$ as well as in hydrophobic $[\text{bmim}]\text{PF}_6$ ionic liquids. $[\text{Bmim}]\text{BF}_4$ ionic liquid was found to be efficient in terms of conversion and reaction rates. The advantage of the use of ionic liquids as a novel reaction medium for this transformation is that these ionic solvents can be easily recovered and recycled in subsequent reactions. Since the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with ether. The rest of the oily ionic liquid was thoroughly washed with ether and reused in subsequent reactions without further purification. Although the products were obtained in the same purity as in the first run, the yields were gradually decreased in runs carried out using recycled ionic liquid. For example, the reaction of benzaldehyde afforded the corresponding bis-indolylmethane in 90%, 87%, 85%, and 81% yields over four cycles. However, the activity of ionic liquid was consistent in runs and no decrease in yield was obtained when the recycled ionic liquid was activated at 80°C under vacuum in each cycle. The efficiency of various quaternary ammonium salts was studied for the transformation. The reaction did not proceed either in *n*-tetrabutylammonium chloride (*n*- Bu_4NCl) or in 1-*n*-butyl-3-methylimidazolium chloride (BMImCl) molten salts. The reaction probably proceeds through the activation of carbonyl group as well as the indole moiety by ionic liquids as shown in Scheme 2.

However, in the absence of ionic liquids, the reaction did not yield any product even after a long reaction period (10–15 h). Furthermore, we have performed the reactions in polar organic solvents such as DMF and *N*-methylpyrrolidine to compare the efficiency of ionic liquids. The reactions did not proceed in these solvents even under heating conditions (75 – 80°C). This clearly indicates the efficiency of ionic liquids in this transformation. The scope and generality of this process is illustrated with respect to various carbonyl compounds and indoles and the results are presented in Table 1. The use of ionic liquids as promoters for this transformation avoids the use of moisture-sensitive reagents and tedious aqueous work-up to isolate the products. Thus this method is preferable to either protic or Lewis acid promoted procedures.

In summary, the paper describes a simple and highly efficient procedure for the preparation of bis-indolylmethanes through the electrophilic substitution reactions of indoles with aldehydes and ketones in ionic

Table 1 Room temperature, ionic liquid -promoted synthesis of bis-indolylmethanes.^[a]

Entry	indole	carbonyl compound	[bmim]BF ₄		[bmim]PF ₆	
			Time [h]	Yield [%] ^[b]	Time [h]	Yield [%] ^[b]
a			4.5	90	4.5	87
b			3.0	92	4.0	90
c			5.5	85	5.5	84
d			4.0	91	5.0	88
e			3.0	93	4.5	90
f			5.5	87	6.0	84
g			5.0	85	6.5	81
h			4.5	89	6.0	87
i			4.5	85	5.5	82
j			7.5	80	8.0	78
k			5.0	87	6.0	85
l			5.0	87	5.0	79
m			4.5	89	5.5	83
n			5.0	85	6.0	81
o			4.5	90	5.0	87

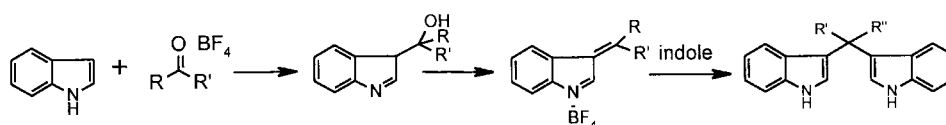
^[a] All the products were characterized by ^1H NMR, IR and mass spectra.
^[b] Isolated and unoptimized yields.

liquids. The notable features of this procedure are mild reaction conditions, improved yields, enhanced rates, cleaner reaction profiles, ease of recovery and reuse of this novel reaction medium making this method simple, convenient, economic and environmentally friendly process for the synthesis of bis-indolylmethanes.

Experimental Section

Methods and Apparatus

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Nicolet-740 FT IR spectrophotometer. ^1H NMR spectra were recorded on a Varian Gem-



Scheme 2.

ini – 200 MHz spectrometer. Mass spectra were recorded on a VG Micromass 7070 H (70 eV). CHN analysis was recorded on a Vario EL analyzer. TLC was performed 0.25 mm E. Merck precoated silica gel plates (60F-254). 1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) ionic liquids were prepared according to the procedures reported in the literature.^[9]

General Procedure

A mixture of indole (2 mmol), aldehyde or ketone (1 mmol) in [bmim]BF₄ or [bmim]PF₆ (2 mL) was stirred at room 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 under vacuum and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (2:8) to afford the pure bis-indole. The rest of the viscous ionic liquid was further washed with ether and reused in subsequent reactions.

Recycling of Ionic Liquid

In case of a hydrophilic ionic liquid, i.e., [bmim]BF₄, the reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with water, dried over anhydrous Na₂SO₄, concentrated under vacuum and the resulting product was purified either by column chromatography or by recrystallization to afford pure product. The ionic liquid can be recovered either by extracting the aqueous phase with ethyl acetate or by evaporating the aqueous layer under vacuum. The ionic liquid thus obtained was further dried at 80 °C under reduced pressure for use in subsequent runs.

Spectroscopic Data for Selected Products

Table 1 entry a: Solid, mp 89–90 °C; ¹H NMR (CDCl₃): δ = 5.90 (s, 1H, CH), 6.60 (d, 2H, *J* = 2.4 Hz), 7.05 (t, 2H, *J* = 8.2 Hz), 7.15 (t, 2H, *J* = 8.2 Hz), 7.30 (m, 9H), 7.85 (brs, 2H, NH); ¹³C NMR (proton decoupled): δ = 40.5, 110.8, 119.5, 119.8, 120.05, 121.7, 123.6, 126.7, 127.3, 128.5, 128.9, 136.6, 144.2; EIMS: *m/z* (%) = 322 (100) M⁺, 245 (60), 204 (45), 122 (35), 105 (20), 77 (10); IR (KBr): ν = 3450, 3020, 1600, 1490, 1220, 1070, 750 cm⁻¹.

Table 1, entry b: Solid, mp 199–200 °C; ¹H NMR (CDCl₃): δ = 3.70 (s, 3H), 3.80 (s, 3H), 5.75 (s, 1H), 6.70 (d, 2H, *J* = 2.4 Hz), 6.80 (d, 2H, *J* = 8.0 Hz), 6.85 (s, 1H), 6.90 (d, 2H, *J* = 8.0 Hz), 7.05 (t, 2H, *J* = 8.0 Hz), 7.30 (t, 4H, *J* = 8.0 Hz), 10.45 (brs, 2H, NH); EIMS: *m/z* (%) = 382 (100) M⁺, 265 (10), 245 (50), 69 (20); IR (KBr): ν = 3450, 3060, 2980, 1620, 1490, 1230, 1005, 760 cm⁻¹.

Table 1, entry c: Solid, mp 153–154 °C; ¹H NMR (CDCl₃): δ = 5.85 (s, 1H), 6.75 (d, 2H, *J* = 2.3 Hz), 6.85 (m, 1H), 6.90 (m, 2H), 6.95–7.05 (m, 4H), 7.2 (s, 1H), 7.25 (t, 2H, *J* = 8.0 Hz), 7.35 (s, 1H), 7.75 (brs, 2H, NH); EIMS: *m/z* (%) = 390 (100) M⁺, 392 (60) (M + 2)⁺, 274 (80), 245 (50), 204 (20), 176 (5), 117 (10); IR (KBr): ν = 3480, 3050, 2970, 1600, 1470, 1250, 1020, 770.

Table 1, entry g: Semisolid; ¹H NMR (CDCl₃): δ = 5.90 (s, 1H), 6.45 (d, 1H, *J* = 16.6 Hz), 6.65 (d, 2H, *J* = 2.3 Hz), 7.05 (t, 2H, *J* = 8.1 Hz), 7.15 (t, 2H, *J* = 8.1 Hz), 7.25 (m, 4H), 7.35 (m, 3H), 7.55 (m, 2H), 7.75 (d, 1H, *J* = 16.6 Hz), 7.85 (brs, 2H, NH); EIMS: *m/z* (%) = 346 (20) M⁺, 321 (100), 244 (80), 205 (30), 122 (15), 77 (10); IR (KBr): ν = 3450, 3100, 2960, 1590, 1470, 1030, 970, 760 cm⁻¹.

Table 1, entry h: Solid, mp 138–140 °C; ¹H NMR (CDCl₃): δ = 1.25 (m, 6H), 1.90 (m, 4H), 2.25 (m, 1H), 4.45 (m, 1H), 6.95 (d, 2H, *J* = 2.4 Hz), 7.05 (m, 2H), 7.15 (m, 2H), 7.25 (d, 2H, *J* = 8.0 Hz), 7.45 (d, 2H, *J* = 8.0 Hz), 7.85 (brs, 2H, NH); EIMS: *m/z* (%) = 328 (30) M⁺, 246 (80), 130 (25), 84 (60), 57 (90), 41 (100); IR (KBr): ν = 3455, 3030, 2980, 1620, 1570, 1285, 1030, 770 cm⁻¹.

Table 1, entry i: Solid, mp 68–70 °C; ¹H NMR (CDCl₃): δ = 0.8 (t, 3H, *J* = 6.8 Hz), 1.25 (m, 6H), 2.25 (m, 2H), 4.60 (t, 1H, *J* = 6.8 Hz), 6.85 (d, 2H, *J* = 2.3 Hz), 7.05 (t, 2H, *J* = 8.0 Hz), 7.15 (t, 2H, *J* = 8.0 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 7.50 (d, 2H, *J* = 8.0 Hz), 7.85 (brs, 2H, NH); EIMS: *m/z* (%) = 316 (70) M⁺, 245 (100), 206 (5), 199 (40), 156 (60), 149 (35), 117 (30); IR (KBr): ν = 3500, 3100, 3030, 2950, 1610, 1580, 1250, 1060, 770 cm⁻¹.

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References and Notes

- [1] a) P. Ehrlich, *Medicin Woche* **1901**, 151; b) L. Morgan, R. Schunior, *J. Org. Chem.* **1962**, 27, 3696; c) D. J. Dolphin, *Heterocycl. Chem.* **1979**, 7, 275.
- [2] W. Remers, *Chem. Heterocycl. Compounds* **1972**, 25, 1.
- [3] a) W. E. Noland, M. R. Venkiteswaran, C. G. Richards, *J. Org. Chem.* **1961**, 26, 4241; b) J. Banerji, A. Chatterjee, S. Manna, C. Pascard, T. Prange, J. Shoolery, *Heterocycles* **1981**, 15, 325.
- [4] a) A. Chatterjee, S. Manna, J. Banerji, T. Prange, J. Shoolery, *J. Chem. Soc. Perkin Trans. I* **1980**, 553; b) G. Babu, N. Sridhar, P. T. Perumal, *Synth. Commun.* **2000**, 30, 1609.
- [5] a) M. Roomi, S. MacDonald, *Can. J. Chem.* **1970**, 48, 139; b) B. Gregorovich, K. Liang, D. Clugston, S. MacDonald, *Can. J. Chem.* **1968**, 46, 3291.
- [6] a) D. Chen, L. Yu, P. G. Wang, *Tetrahedron Lett.* **1996**, 37, 4467; b) S. Kobayashi, M. Araki, M. Yasuda, *Tetrahedron Lett.* **1995**, 36, 5773; c) M. Johannsen, *Chem. Commun.* **1999**, 2223; d) W. Z. Luang, N. Gathergood, R. G. Hazel, K. A. Joergenson, *J. Org. Chem.* **2001**, 66, 1009.
- [7] a) Recent reviews on ionic liquids: T. Welton, *Chem. Rev.* **1999**, 99, 2071; b) P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* **2000**, 39, 3772; c) Catalytic reactions in ionic liquids: R. Sheldon, *Chem. Commun.* **2001**, 2399.
- [8] Ionic liquids have already been described as catalysts: a) C. Wheeler, K. N. West, C. L. Liotta, C. A. Eckert, *Chem. Commun.* **2001**, 887; b) J. Peng, Y. Deng, *Tetrahedron Lett.* **2001**, 42, 5917; c) Brønsted acidic ionic liquids as dual solvent and catalysts: A. C. Cole, J. L.

- Jensen, I. Ntai, K. L. T. Tran, K. J. Weaver, D. C. Forbes, J. H. Davis Jr., *J. Am. Chem. Soc.* **2002**, *124*, 5962.
- [9] Preparation of ionic liquids: a) S. Park, R. J. Kazlauskas, *J. Org. Chem.* **2001**, *66*, 8395; b) P. Bonhote, A. P. Dias, N. Papageorgiou, K. Kalyanasundaram, M. Gratzel, *Inorg. Chem.* **1996**, *35*, 1168.
- [10] Friedel–Crafts alkylation reactions in ionic liquids: a) P. Formentin, H. Garcia, *Catal. Lett.* **2002**, *78*, 155; b) C. D. E. Jong, W. K. J. Shim, E. J. Roo, J. M. Choi, *Chem. Commun.* **2000**, 1695.
- [11] a) H. Chalaye-Mauger, J. N. Denis, M. T. Averbuch-Pouchot, Y. Vallee, *Tetrahedron* **2000**, *56*, 791; b) J. S. Yadav, B. V. S. Reddy, C. V. S. R. Murthy, G. M. Kumar, C. Madan, *Synthesis* **2001**, 783.
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