Efficient Fe^{III}-Catalyzed Synthesis of Bis(indolyl)methanes in Ionic Liquids

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An efficient synthesis of bis(indolyl)methanes through Fe^{III} catalyzed electrophilic substitution reactions of indoles with various aldehydes in ionic liquid is described. It was found that the ionic liquids involving $FeCl_3\text{-}6H_2O$ were the most

Introduction

Room-temperature ionic liquids have attracted steady attention as green media in organic synthesis, mainly because of their unique properties such as good solvating capability, wide liquid range, negligible vapor pressure, and ease of recycling. Moreover, their hydrophobicity/hydrophilicity can be tuned by appropriate modification of the cation or anion, which has earned them the sobriquet of "designer solvents".^[1] Studies of ionic liquids, especially those based on the 1-(*n*-alkyl)-3-methylimidazolium cation (Scheme 1), have had an important impact on organic reactions, ^[3] Heck reactions,^[4] Mannich reactions,^[5] bromination of alkynes,^[6] and so on.



Scheme 1. The structure of ionic liquids

Since bis(indolyl)methanes possess a wide range of biological activity, their synthesis has received a considerable amount of interest.^[7] Generally, bis(indolyl)methanes are efficient catalytic systems, and could be simply recycled without significant loss of activity.

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prepared by the condensation of indoles with various aldehydes or ketones in the presence of either protic^[8] or Lewis acids^[9] such as LiClO₄ ^[10] or I₂.^[11] More recently, ionic liquids in conjunction with In(OTf)₃ were employed for the first time as novel and eco-friendly reaction media for this transformation in our laboratory.^[12] Not only is In(OTf)₃ expensive, however, but some deactivation of In(OTf)₃ also obviously occurred during the recycling procedure. As a result, it was essential for us to continue our study into more practical and efficient catalytic systems.

On the other hand, Fe^{III} salts are well known to catalyze many organic transformations, including oxidation of sulfides,^[13] the Michael reaction,^[14] the thia-Fries rearrangement,^[15] and the synthesis of diphenylmethane^[16] and 1,6anhydroglucopyranoses.^[17] Recently, Suranna et al.^[18] reported that several metal complexes, including FeCl₃·6H₂O, catalyzed the Michael addition of acetylacetone to methyl vinyl ketone in ionic liquids and that their catalytic activity was strongly dependent on the presence of halide impurities of ionic liquids. In view of their commercial availability, ease of handing, and remarkably low toxicity, we wish to report here an efficient and recycling-friendly synthesis of bis(indolyl)methanes with the aid of Fe^{III} salts in ionic liquids (Scheme 2). To the best of our knowledge, this is the first report on the use of Fe^{III} salts as catalysts for the condensation of indoles with various aldehydes.





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Results and Discussion

Treatment of 4-chlorobenzaldehyde with indole in the presence of FeCl₃·6H₂O in 1-methyl-3-octylimidazolium hexafluorophosphate ([omim]PF₆) afforded the corresponding 4-chlorophenyl-3,3'-bis(indolyl)methane in 96% yield (Table 1, Entry 1). The activity of FeCl₃·6H₂O was shown to be no lower than that exerted by In(OTf)₃ (Table 1, Entry 9). We also examined other Fe^{III} salts such as $Fe(NO)_3 \cdot 9H_2O$ and $Fe_2(SO_4)_3 \cdot xH_2O$. As shown in Table 1, the reaction between indole and 4-chlorobenzaldehyde mediated by Fe(NO)₃·9H₂O was slow, but gave a high yield (Entry 2). The catalytic reaction did not proceed on changing from FeCl₃·6H₂O to Fe₂(SO₄)₃·xH₂O. In addition, we also tested the catalytic activity of different transition metal chlorides, such as CoCl₂·6H₂O, NiCl₂·6H₂O, and CuCl₂·2H₂O. A yield of only 55% was obtained when FeCl₃·6H₂O was replaced with CoCl₂·6H₂O (Entry 4), while the reaction was unsuccessful when the other Lewis acids indicated in Table 1 were used (Entries 5-8).

Table 1. Synthesis of 4-chlorophenyl-3,3'-bis(indolyl)methane by use of Fe^{III} and other Lewis acids in [omim]PF₆

Entry	Lewis acid (mol %)	Time [h]	Yield ^[a] [%] 96	
1	$FeCl_3 \cdot 6H_2O(5)$	0.5		
2	$Fe(NO_3)_3 \cdot 9H_2O(5)$	6.5	95	
3	$Fe_2(SO_4)_3 \cdot xH_2O(5)$	48	0	
4	$CoCl_2 \cdot 6H_2O(5)$	48	55	
5	$NiCl_2 \cdot 6H_2O(5)$	48	0	
6	$CuCl_2 \cdot 2H_2O(5)$	48	0	
7	$SmCl_3 \cdot 5H_2O(5)$	48	0	
8	LiCl (10)	48	0	
9	$In(OTf)_3$ (5)	0.25	96	

^[a] Isolated yields.

To examine the influence of the nature of the ionic liquid, we also carried out the reaction in various air-/moisturestable ionic liquids. The results are summarized in Table 2. It was found that [omim]PF₆ was a more effective medium than other ionic liquids in terms of yield (Entry 3). However, the reaction did not proceed when some $[BF_4^-]$ - or $[Cl^-]$ -type ionic liquids were used. The reaction mixture unavoidably produces water as well as the corresponding bis-

Table 2. FeCl₃·6H₂O-catalyzed synthesis of 4-chlorophenyl-3,3'-bis(indolyl)methane in various ionic liquids

Entry	Ionic liquid	Time [h]	Yield ^[a] [%]	
1	[bmim]PF ₆	0.5	87	
2	[hmim]PF ₆	0.25	95	
3	[omim]PF ₆	0.5	96	
4	[dmim]PF ₆	24.5	78	
5	[hmim]BF ₄	24	0	
6	[omim]BF ₄	24	0	
7	[bmim]Cl	24	0	

[a] Isolated yields.

Encouraged by these results, we studied various aldehydes under optimized conditions, and Table 3 summarizes the results. In all cases, both aromatic and aliphatic aldehydes reacted smoothly with indoles in high yields when catalyzed by FeCl₃·6H₂O in [omim]PF₆, most of the reactions proceeding nearly quantitatively. Moreover, this method is highly chemoselective, as ketones do not participate in the reaction. For example, when a 1:1 mixture of 4-chlorobenzaldehyde and acetophenone was allowed to react with indole with catalysis by FeCl₃·6H₂O in [omim]PF₆, it was found that only 4-chlorophenyl-3,3'-bis(indolyl)methane (**3a**) was obtained, while acetophenone did not give the corresponding product **3j** (Entry 10). This selectivity might be useful to differentiate aldehydes from ketones through the synthesis of bis(indolyl)methanes.

Table 3. FeCl₃·6H₂O-catalyzed synthesis of bis(indolyl)methanes with various aldehydes with use of $[\text{omim}]\text{PF}_6$

Entry ^[a]	R	R′	Product	Time [h]	Yield ^[b] [%]
1	4-ClC ₆ H₄	Н	3a	0.5	96
2	C ₆ H ₅	Н	3b	1.5	98
3	$4-CH_3C_6H_4$	Н	3c	4	85
4	4-CH ₃ OC ₆ H ₄	Н	3d	5	78
5	$4-NO_2C_6H_4$	Н	3e	2.5	82
6	$2-ClC_6H_4$	Н	3f	0.25	96
7	(CH ₂) ₅ CH	Н	3g	1.25	96
8	$2-C_4H_3S$	Н	3h	4	95
9	$CH_3(CH_2)_5$	Н	3i	0.75	98
10	C_6H_5	CH_3	3j	10	0

^[a] All products were characterized by ¹H NMR, IR, and HRMS data. ^[b] Isolated yields.

One of the main aims of our study was to investigate the reuse and recycling of FeCl₃·6H₂O in the ionic liquid. The products were easily separated by simple extraction with diethyl ether. After removal of the diethyl ether fraction, the



Figure 1. The recycle of the In(OTf)_3 and FeCl_3·6H_2O in [om-im]PF_6

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rest of the viscous ionic liquid was directly recycled in subsequent runs. As shown in Figure 1, treatment of 4-chlorobenzaldehyde with indole with catalysed by In(OTf)₃ afforded 96, 87, 42, and 0% yields. Unlike the In(OTf)₃-promoted recycling, however, which resulted in a dramatic decrease in the yields of product, FeCl₃·6H₂O immobilized by ionic liquid was reused for four cycles, and afforded yields similar to those obtained in the first run, although increases in reaction times were observed.

Conclusion

In brief, we report that Fe^{III} salts have been employed for catalysis of electrophilic substitution reactions between indoles and various aldehydes in ionic liquids to afford the corresponding bis(indolyl)methanes. It is noteworthy that the FeCl₃·6H₂O/[omim]PF₆ catalytic system can be reused at least four times without significant loss of activity. The simple procedures as well as the easy reuse of this novel catalytic system are expected to contribute to the development of more benign syntheses of bis(indolyl)methanes.

Experimental Section

General Remarks: Ionic liquids were prepared as described previously.^[19] Melting points were recorded with an Electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded with a Nicolet FT-IR500 spectrophotometer with KBr optics. ¹H NMR (400 MHz) spectra were recorded with a Varian Mercury MHz spectrometer in CDCl₃. CHN analyses were recorded with a Carlo–Erba EA1110 CNNO-S analyzer. High resolution mass spectra were obtained with a GCT-TOF instrument.

General Procedure: A mixture of indole (0.5 mmol), FeCl₃·6H₂O (5 mol %), and aldehyde (0.25 mmol) in the ionic liquid (0.5 mL) was stirred at room temperature for the appropriate time (Table 2). After completion of the reaction as indicated by TLC, the ionic liquid was extracted with Et₂O. The solvent was concentrated in vacuo and purified by column chromatography (ethyl acetate/petroleum ether, 1:9) to afford the pure products.

4-Chlorophenyl-3,3'-bis(indolyl)methane (3a): Solid, m.p. 76–77 °C (85.6 mg, 96% yield). IR (KBr): $\tilde{v} = 1089$, 1455, 1487, 3054, 3410 (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 5.86$ (s, 1 H, Ar-CH), 6.66 (s, 2 H), 7.02 (t, J = 8.3 Hz, 2 H), 7.18 (t, J = 7.9 Hz, 2 H), 7.26–7.38 (m, 8 H), 7.98 (br. s, 2 H, NH) ppm. HRMS: calcd. C₂₃H₁₇ClN₂ (356.11): 356.1080; found 356.1069.

3,3'-Bis(indoly1)phenylmethane (3b): Solid, m.p. 151-152 °C (77.6 mg, 98% yield). IR (KBr): $\tilde{v} = 744$, 1093, 455, 1600, 1618, 3055, 3412 (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 5.89$ (s, 1 H, Ar-CH), 6.67 (s, 2 H), 7.00 (t, J = 6.8 Hz, 2 H), 7.19 (m, 3 H), 7.29 (m, 2 H), 7.35 (m, 6 H), 7.94 (br. s, 2 H, NH) ppm. C₂₃H₁₈N₂ (322.14): calcd. C 85.68, H 5.63, N 8.69; found C 85.75, H 5.56, N 8.56.

3,3'-Bis(indolyl)-4-methylphenylmethane (3c): Solid, m.p. 94–96 °C, (71.5 mg, 85% yield). IR (KBr): $\tilde{v} = 775$, 1050, 1215, 1510, 1600, 2930, 3040, 3410 (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 2.32$ (s, 3 H, Ar-CH3), 5.86 (s, 1 H, Ar-CH), 6.68 (s, 2 H), 7.02 (t, J = 7.2 Hz, 2 H), 7.1 (d, J = 7.2 Hz, 2 H), 7.23–7.27 (m, 6 H),

7.4 (d, J = 7.2 Hz, 2 H), 7.93 (br. s, 2 H, NH) ppm. $C_{24}H_{20}N_2$ (349.45): calcd. C 85.68, H 5.99, N 8.33; found C 85.37, H 5.95, N 8.04.

3,3'-Bis(indolyl)-4-methoxyphenylmethane (3d): Solid, m.p. 187–189 °C, (68.7 mg, 78% yield). IR (KBr): $\tilde{v} = 1220$, 1244, 1455, 1508, 1609, 2928, 3410 (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 3.78$ (s, 3 H, CH3), 5.84 (s, 1 H, Ar-CH), 6.66 (s, 2 H), 6.82 (d, J = 8.3 Hz, 2 H), 7.00 (t, J = 7.3 Hz, 2 H), 7.17 (t, J = 7.3 Hz, 2 H), 7.19 (s, 2 H), 7.35–7.40 (m, 4 H), 7.94 (br. s, 2 H, NH) ppm. C₂₄H₂₀N₂O (352.43): calcd. C 81.79, H 5.72, N 7.95; found C 81.72, H 5.82, N 7.98.

3,3'-Bis(indolyl)-4-nitrophenylmethane (3e): Solid, m.p. 217–219 °C, (75.3 mg, 82% yield). IR (KBr): $\tilde{v} = 1340$, 1456, 1507, 1592, 3052, 3422 (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 6.00$ (s, 1 H, Ar-CH), 6.70 (s, 2 H), 7.00–7.05 (m, 3 H), 7.35 (d, J = 8.0 Hz, 3 H), 7.40 (d, J = 8.0 Hz, 2 H), 7.52 (d, J = 8.8 Hz, 2 H), 8.04 (br. s, 2 H, NH), 8.15 (d, J = 8.8 Hz, 2 H) ppm. C₂₃H₁₇N₃O₂ (367.40): calcd. C 75.19, H 4.66, N 11.44; found C 75.28, H 4.51, N 11.60.

2-Chlorophenyl-3,3'-bis(indolyl)methane (3f): Solid, m.p. 72–74 °C. (85.6 mg, 96% yield). IR (KBr): $\tilde{v} = 1010, 1037, 1093, 1337, 1417, 1455, 1616, 3052, 3412 (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): <math>\delta = 6.34$ (s, 1 H, Ar-CH), 6.66 (s, 2 H), 7.02 (t, J = 8.0 Hz, 2 H), 7.11–7.23 (m, 6 H), 7.36–7.43 (m, 4 H), 7.96 (br. s, 2 H, NH) ppm. HRMS: calcd. for C₂₃H₁₇ClN₂ 356.1080; found 356.1071.

Cyclohexyl-3,3'-bis(indolyl)methane (3g): Solid, m.p. 184–186 °C. (78.8 mg, 96% yield). IR (KBr): $\tilde{v} = 741$, 1094, 1338, 1455, 1617, 3052, 3412 (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.52$ (m, 6 H), 1.83 (m, 4 H), 2.25 (m, 1 H), 4.27 (d J = 9.6 Hz, 1 H), 7.03–7.18 (m, 6 H), 7.33 (d, J = 5.6 Hz, 2 H), 7.54 (d, J = 7.2 Hz, 2 H), 7.94 (br. s, 2 H, NH) ppm. C₂₃H₂₄N₂ (328.19): calcd. C 84.11, H 7.37, N 8.53; found C 84.17, H 7.77, N 8.03.

3,3'-Bis(indolyl)-2-thienylmethane (3h): Solid, m.p. 151–153 °C. (78.0 mg, 95% yield). IR (KBr): $\tilde{\nu} = 1260, 1450, 1715, 3410$ (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 6.18$ (s, 1 H, Ar-CH), 6.87 (s, 2 H), 6.92–7.48 (m, 11 H), 7.98 (br. s, 2 H, NH) ppm. C₂₁H₁₆N₂S (328.10): calcd. C 76.80, H 4.91, N 8.53; found C 76.62, H 5.04, N 8.54.

3,3'-Bis(indolyl)heptane (3i): Solid, m.p. 66–68 °C. (81.0 mg, 98% yield). IR (KBr): $\tilde{v} = 799$, 1092, 1337, 1455, 1618, 3052, 3414 (NH) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 0.83$ (t, J = 6.8 Hz, 3 H), 1.23–1.36 (m, 8 H), 2.19 (m,2 H), 4.66 (t, J = 7.2 Hz, 1 H), 7.00–7.04 (m,4 H), 7.13 (t, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.57 (d, J = 7.2 Hz, 2 H), 7.90 (br. s, 2 H, NH) ppm. C₂₃H₂₆N₂ (330.47): calcd. C 83.39, H 7.93, N 8.48; found C 83.46, H 8.17, N 8.06.

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