Efficient Synthesis of Bis(indolyl)methanes Catalyzed by Lewis Acids in Ionic Liquids

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Abstract: Efficient electrophilic substitution reactions of indoles with various aldehydes proceed smoothly in ionic liquids using Lewis acids, $In(OTf)_3$, $YbCl_3$, $InCl_3$, $BiCl_3$, and $ZnCl_2$, to afford the corresponding bis(indolyl)methanes in high yields.

Key words: ionic liquids, $In(OTf)_3$, Lewis acids, indoles, bis(indolyl)methanes

The biologically active indoles and their derivatives have long been of interest as pharmaceuticals.[1] Bisindolylalkanes and their derivatives have received more attention because of their existence in bioactive metabolites of terrestrial and marine origin.[2] The simple method for the synthesis of this class of compounds involves the electrophilic substitution of indoles with various aldehydes and ketones in the presence of either protic[3] or Lewis acids.[4,5] However, more than stoichiometric amounts of the Lewis acids are required because they are trapped by nitrogen.[6] Recently, $LiClO_4$,[7] $In(OTf)_3$[8] and I_2[9] were also found to catalyze these reactions. Although these catalysts are very useful and efficient, the long reaction time (4–10h) and complicated manipulation, along with the use of environmentally harmful organic solvents, (particularly their recovery and reuse) limited their development from the viewpoint of green chemistry.

In recent years, owing to their interesting chemical and physical properties, such as being non-flammable, nontoxic, reusable, inexpensive, having no measurable vapour pressure and high thermal stability, ionic liquids are attracting increasing interest as potential cleaner solvents.[10] Furthermore, utilization of ionic liquids, particularly in metal-catalyzed reactions, allows easy recovery and reuse of the catalysts.[11] In addition to the polar properties of ionic liquids, they are non-coordinating, which avoids the undesired solvent binding in the pre-transition states, and hence offers great advantages for asymmetric synthesis. More recently, an asymmetric Mannich-type reaction catalyzed by immobilized In(III) complexes in ionic liquids has been developed in our laboratory.[12] As a result, we decided to prepare the bis(indolyl)methanes catalyzed by Lewis acids in ionic liquids.

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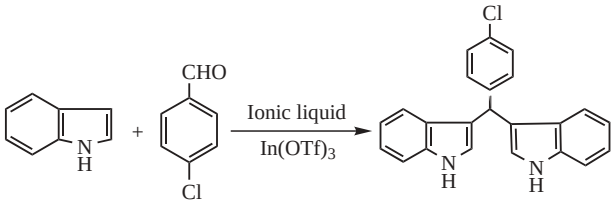
Firstly, we studied the effect of different ionic liquids on this reaction using $In(OTf)_3$. Six different ionic liquids were used in our investigation, i.e. butylmethylimidazolium tetrafluoroborate ([bmim][BF_4^-]), butylmethyl imidazolium hexafluorophosphate ([bmim][PF_6^-]), hexylmethylimidazolium chloride ([hmim][Cl^-]), hexyl methylimidazolium hexafluorophosphate ([hmim][PF_6^-]), octylmethylimidazolium hexafluorophosphate ([omim][PF_6^-]) and decylmethylimidazolium hexafluoro phosphate ([dmim][PF_6^-]). The results are shown in Table 1. It was found that in [BF_4^-] or [PF_6^-]-type ionic liquids the electrophilic substitution reactions of indoles with 4-chlorobenzaldehyde proceeded smoothly in high yields. It is interesting that no desired products were obtained ever after 48 hours when [hmim][Cl^-] was used.

Table 1 $In(OTf)_3$-Catalyzed Synthesis of 3,3′-Bis(indolyl)-4-chloro Phenylmethane in Various Ionic Liquids



Entry	Ionic liquid	Time (min)	Yield (%)[a]
1	[bmim][PF_6^-]	15	89
2	[hmim][PF_6^-]	15	95
3	[omim][PF_6^-]	15	96
4	[dmim][PF_6^-]	60	82
5	[bmim][BF_4^-]	15	81
6	[hmim][Cl^-]	720	0

[a] Isolated yields.

Prompted by these results, we then examined the catalytic activity of different Lewis acids in [omim][PF_6^-]. As shown in Table 2, all catalysts examined were very effective in this reaction in ionic liquid [omim][PF_6^-]. Among the catalysts, $In(OTf)_3$ showed the highest catalytic activity, the reaction being completed in 15 min (Table 2, entry 1). It was also found when a weaker Lewis acid such as $ZnCl_2$ (Table 2, entry 5) was utilized, it always required longer reaction times and an increase of

the amounts of catalyst. Moreover, study continued to be done using [omim][PF_6^-] with various aldehydes in presence of $In(OTf)_3$. Results shown in Table 3 indicated both aliphatic and aromatic aldehydes underwent smooth reaction with indoles giving high yields of products as well as **3a** (96%).

Table 2 Synthesis of 3,3′-Bis(indolyl)-4-chlorophenylmethane Using Lewis Acids in [omim][PF_6^-]

Entry	Lewis acid (mol%)	Time (h)	Yield (%)[a]
1	$In(OTf)_3$ (5)	0.25	96
2	$YbCl_3$ (5)	4	87
3	$BiCl_3$ (10)	1.5	93
4	$InCl_3$ (10)	1	71
5	$ZnCl_2$ (10)	7	79

[a] Isolated yields.

Table 3 $In(OTf)_3$-Catalyzed Synthesis of Bis(indolyl)methanes with Various Aldehydes Using [omim][PF_6^-]

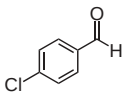
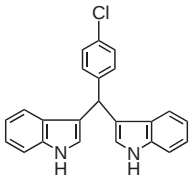
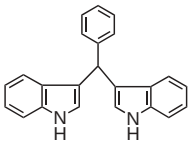
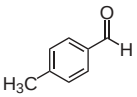
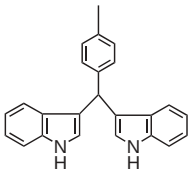
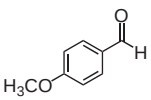
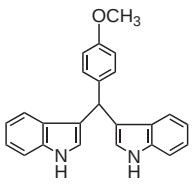
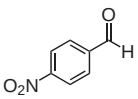
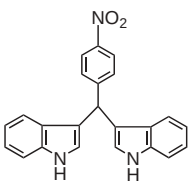
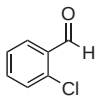
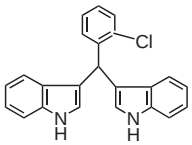
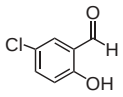
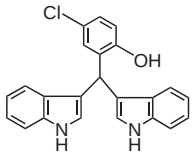
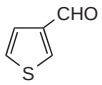
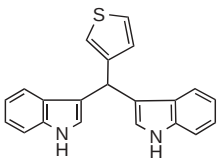
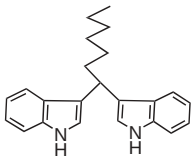
Entry	RCHO	Products[a]	Time (min)	Yield (%)[b]
1		**3a** 	15	96
2		**3b** 	15	90
3		**3c** 	20	73
4		**3d** 	15	76
5		**3e** 	70	78

Table 3 $In(OTf)_3$-Catalyzed Synthesis of Bis(indolyl)methanes with Various Aldehydes Using [omim][PF_6^-] (continued)

Entry	RCHO	Products[a]	Time (min)	Yield (%)[b]
6		**3f** 	30	95
7		**3g** 	75	86
8		**3h** 	15	92
9		**3i** 	15	89

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

Finally, the reuse of $In(OTf)_3$ in [omim][PF_6^-] was carried out (Table 4). The catalytic activity of $In(OTf)_3$ which was immobilized in [omim][PF_6^-] gradually decreased in the second and third cycles (entries 2 and 3). In the fourth cycle we did not gain the desired product. However, following the addition of another 0.05 equivalents of $In(OTf)_3$ in the recycled [omim][PF_6^-], the reaction proceeded as in the first cycle.

Table 4 Synthesis of 3,3′-Bis(indolyl)-4-chlorophenylmethane in [omim][PF_6^-] Using Recycled $In(OTf)_3$

Cycle	Time (h)	Yield (%)[a]
1	0.25	96
2	48	87
3	48	42
4	48	0

[a] Isolated yields.

In conclusion, we have developed an efficient electrophilic substitution reaction of indoles with various aldehydes catalyzed by Lewis acids in ionic liquids. $In(OTf)_3$, $YbCl_3$, $InCl_3$, $BiCl_3$, and $ZnCl_2$ all exhibited high catalytic activity in ionic liquids in this reaction.

Efforts to develop more active and available catalytic system are currently in progress.

Typical Experimental Procedure: To a stirred solution of $In(OTf)_3$ (5 mol%) and 4-chlorobenzaldehyde (0.5 mmol) in the ionic liquid (1 mL) at room temperature was added indole (1 mmol). The mixture was stirred at room temperature for 15 min. After completion of the reaction as indicated by TLC, the ionic liquid was extracted with Et_2O. The ether layer was dried (Na_2SO_4), concentrated under vacuum and purified by column chromatography (ethyl acetate:petroleum ether = 1:9) to afford the pure product.

3,3′-Bis(indolyl)-4-chlorophenylmethane: IR (KBr): υ 1089,1455, 1487, 3054, 3410 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (s, 1 H, Ar-CH), 6.66 (s, 2 H), 7.02 (t, 2 H, *J* = 8.3 Hz), 7.18 (d, 2 H, *J* = 7.9 Hz), 7.23–7.38 (m, 8 H), 7.4 (d, 2 H, *J* = 8.1 Hz), 7.85 (br, s, 2 H, NH).

HRMS: *m*/*z* calcd for $C_{23}H_{17}ClN_2$: 356.1080; found: 356.1005.

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