Synthesis of Bis(indolyl)methanes Catalyzed by Acidic Ionic Liquid Immobilized on Silica (ILIS)

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Abstract: A new organocatalytic procedure for the synthesis of bis(indolyl)methanes with acidic ionic liquid immobilized on silica gel (ILIS-SO_2Cl) has been developed. The reaction condition is applicable to a variety of aryl and aliphatic aldehydes and indoles. The mild nature of the reaction conditions showed that the acetoxy or TBDMS group in the aldehyde was maintained intact. The catalyst was reused four times in 93% average yield.

Key words: catalysis, condensation, indoles, ionic liquids, supported catalysis

Room temperature ionic liquids have played important roles not only as environmentally benign and recyclable reaction media, but also as support for organomolecular catalysts for purposes of recycling, owing to their immiscibility with other organic solvents as well as with water.[1] We recently anchored a sulfonic acid residue on an ionic liquid to afford **6** and demonstrated its capability as a supported and recyclable organomolecular catalyst for Beckmann rearrangement, Friedel–Crafts alkylation and nitration.[2]

An additional method for the immobilization of liquid catalysts for easy recycling and better handling is to graft the organomolecular moiety of the catalyst on solid surface.[3] To this end, the acidic ionic liquid catalysts **7** and **8** were grafted onto a silica surface. The resulting catalysts (ILIS = ionic liquid immobilized on silica) **4** and **5** exhibited better reactivity for esterification and nitration.[4]

Bis(indolyl)methanes **3** are found widely distributed in the bioactive metabolites of terrestrial and marine organisms.[5] Some compounds have potent pharmaceutical activities such as tranquilizers[6] or anticarcinogen.[7] Due to their intriguing physiological activities, many synthetic procedures have been reported so far,[8] in which development of the environmentally benign aspect is of current interest from the standpoint of process chemistry by employing Lewis acid in ionic liquid[9] or task-specific acidic ionic liquid.[10]

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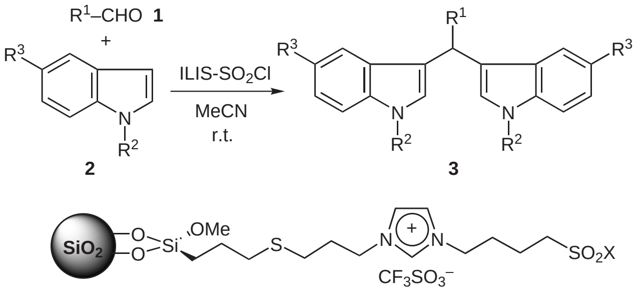

4 ILIS–SO_2Cl: X = Cl
5 ILIS–SO_3H : X = OH

Scheme 1 Synthesis of bis(indolyl)methanes **3** catalyzed by ILIS-SO_2Cl (**4**)

In this paper, we report an efficient, mild and recyclable procedure for nucleophilic condensation of indoles **2** with aldehydes **1** leading to bis(indolyl)methanes **3** catalyzed by the acidic ILIS **4** (Scheme 1).

Optimized reaction conditions were investigated employing a reaction of benzaldehyde (**1**, R^1 = Ph) and indole (**2**, $R^2 = R^3$ = H), and the results are shown in Table 1. Among the solvents investigated, acetonitrile gave the best result (Table 1, entry 1) in the reaction catalyzed by ILIS-SO_2Cl (**4**), which afforded higher yield than Brønsted acid, ILIS-SO_3H (**5**), silica or HCl (Table 1, entries 5–7). Other acidic catalysts, *p*-toluenesulfonyl chloride, acidic ILs **7** and **8** or acidic silica **9** and **10** (Figure 1) resulted in lower yields (Table 1, entries 8–12). It is noteworthy that the reaction proceeded smoothly at ambient temperature.

6 R = Me, X = OH or Cl
7 R = allyl, X = Cl
8 R = allyl, X = OH

9 X = Cl
10 X = OH

Figure 1

Based on the optimized reaction conditions (Table 1, entry 1), the present protocol was applied to a variety of aldehydes **1**. As shown in Table 2 (entries 1–6), aryl aldehydes **1** with both electron-withdrawing and electron-donating characteristics provided bis(indolyl)methane **3** in good to high yields. The mild nature of the reaction conditions was exemplified in the reaction of aryl

Table 1 Investigation of Optimum Reaction Conditions of Benzaldehyde (**1**, R^1 = Ph) and Indole (**2**, R^2 = R^3 = H)[a]

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	ILIS-SO_2Cl (**4**)	MeCN	5.5	97
2[c]			6.5	88
3		EtOH	5.0	88
4		H_2O	4.0	80
5	ILIS-SO_3H (**5**)	MeCN	5.5	45
6	silica	EtOH	5.5	0
7[d]	HCl	MeCN	2.0	0
8	TsCl		5.5	44
9	acidic IL **7**			60
10	acidic IL **8**			45
11	acidic silica **9**			87
12	acidic silica **10**			75
13[e]	ILIS-SO_2Cl (**4**)		6.0	45

[a] Reaction was carried out as described in ref. 11 in the presence of catalyst (0.1 equiv).
[b] Isolated pure product yield based on indole **2**.
[c] ILIS-SO_2Cl **4** (0.05 equiv) was used.
[d] *p*-Chlorobenzaldehyde was used.
[e] Powdered molecular sieves were added.

aldehydes **1** having base- or acid-sensitive substituents (Table 2, entries 4 and 6), which might be deprotected by other previously known reaction conditions. Not only aryl aldehydes **1** but also aliphatic aldehydes **1** provided the desired bis(indolyl)methanes **3** (Table 2, entries 7–9).

Table 2 Reaction of a Variety of Aldehydes **1** with Indole (**2**, R^2 = R^3 = H)[11]

Entry	Aldehyde **1**	Time (h)	Yield (%)[a]
1	benzaldehyde	5.5	97
2	*p*-nitrobenzaldehyde	4.5	97
3	*p*-chlorobenzaldehyde	2.0	90
4	*p*-acetoxybenzaldehyde	4.0	64
5	*p*-methoxybenzaldehyde	9.0	97
6	*p*-(*tert*-butyldimethylsilyloxy)benzaldehyde	3.0	95
7	hydrocinnamaldehyde	4.0	98
8	*n*-decanal	19.5	67
9	*n*-heptanal	1.5	65

[a] Isolated pure product yield based on indole (**2**).

The present protocol was also applicable to various substituted indoles **2** (Table 3), in which even the electron-poor bromoindole **2** provided the product **3** (entry 1).

Table 3 Reaction of Benzaldehyde (**1**, R^1 = Ph) with Various Indoles **2**[11]

Entry	Substituted indole **2**	Time (h)	Yield (%)[a]
1	R^2 = H, R^3 = Br	3.5	81
2	R^2 = H, R^3 = OMe	17.5	93
3	R^2 = Me, R^3 = H	5.5	88

[a] Isolated pure product yield based on indole derivative **2**.

In order to increase stability and to diminish loss of the catalyst in recycle use, the catalyst was immobilized on cylindrical silica pellets (3 × 2.5 mm OD, loading of sulfonylchloride moiety: 0.30 mmol/g), which was superior to a powdery catalyst and could be recycled four times in 93% average yield simply after trituration of the product with Et_2O followed by evacuation of the catalyst in vacuo (Table 4). Handling of the viscous acidic ionic liquid catalyst[2] in recycle use was improved by immobilization on silica pellets, though slight decrease of catalytic activity was observed as shown in cycle 4.

Table 4 Recycling of ILIS-SO_2Cl (**4**) in the Reaction of *p*-Chlorobenzaldehyde (**1**, R^1 = *p*-ClC_6H_4) with Indole (**2**, R^2 = R^3 = H)[11]

Cycle	Time (h)	Yield (%)[a]
1	2.5	86 (82)[b]
2	5.0	97 (95)[b]
3	12.0	92 (98)[b]
4	24.0	96 (78)[b]

[a] Isolated pure product yield based on indole **2**.
[b] In parentheses: yield after 2.5 h.

Although the reaction pathway is yet to be clarified, the sulfonylchloride moiety of ILIS-SO_2Cl (**4**) might work as a mild Lewis acid[12] to activate aldehyde **1** and other electrophilic intermediates, since Brønsted acid ILIS-SO_3H (**5**), IL **8** and acidic silica **10** gave unsatisfactory results (Table 1, entries 5–7, 10 and 12). It was considered that the catalysis by HCl generated by hydrolysis of ILIS-SO_2Cl (**4**) takes place during the reaction, but this hypothesis was ruled out based on the negative result in Table 1 (entry 7). Lower catalytic activities of sulfonyl chlorides such as *p*-toluenesulfonyl chloride, ionic liquid **7**, and silica **9** (Table 1, entries 8, 9 and 11) suggest the importance of the ionic liquid tether on silica for the higher catalytic activity of ILIS-SO_2Cl (**4**). Addition of molecular sieves powder disturbed the reaction (Table 1, entry 13). An ionic liquid, 1-*n*-hexyl-3-methylimidazolium tetrafluoroborate ([hmim]BF_4), is known to have no catalytic activity.[10]

In summary, we have developed a new protocol for the synthesis of bis(indolyl)methanes **3** from aldehydes **1** and indoles **2** catalyzed by Lewis acidic ionic liquid immobilized on silica, ILIS-SO$_2$Cl (**4**), which exhibited an efficient, mild, practical and recyclable nature.

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(11) **Typical Experimental Procedure**: A suspension of the benzaldehyde (**1**) (30 mL, 0.3 mmol), indole(**2**) (60 mg, 0.5 mmol) and ILIS-SO$_2$Cl(**4**) (143 mg, loading of sulfonyl chloride: 0.35 mmol/g, 0.05 mmol) in MeCN (3 mL) was stirred gently at ambient temperature under nitrogen atmosphere for 5.5 h. The product was triturated with Et$_2$O and the combined organic layer was evaporated to dryness. Medium pressure LC of the residue (eluent: EtOAc–*n*-hexane, 3:1) afforded bis(indolyl)methane(**3**) (79 mg, 97% based on **2**).

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