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Short communication

Ionic liquid [Dabco-C_8][$FeCl_4$] as an efficient and recyclable catalyst for direct C3 alkylation of indoles with electron-deficient olefins

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ABSTRACT

In this paper, a simple and highly efficient Friedel–Crafts Michael–type addition of indoles to electron-deficient olefins was achieved by a new magnetic ionic liquid catalyst ([Dabco-C_8][$FeCl_4$]). This catalyst system is applicable to a variety of electron-deficient olefins, including chalcones, enones, and nitro-olefins, and affords the corresponding 3-alkylindole derivatives in good to excellent yields under mild conditions within short times. The catalyst can be recycled four times without considerable activity loss.

1. Introduction

Indole derivatives are currently explored as privileged structures in a large number of natural products and therapeutic agents [1–3]. Among them, 3-substituted indoles are important building blocks for the synthesis of biologically active compounds and drug discovery [4]. The C3-selective alkylation of indoles is one of the most important organic transformations for the synthesis of 3-substituted indole derivatives [5–6]. The simple and direct method for the synthesis of 3-alkylated indoles involves the Friedel–Crafts Michael–type addition of indoles to electron-deficient olefins in the presence of different catalysts, such as protic acids [7–8], Lewis acids [9–10], supported catalysts [11–12], and other catalysts [13–18]. Although considerable progress has been made by these protocols, many of them still suffer drawbacks such as strong acidic conditions, expensive reagents and solvents, limited substrate scope, lower yield of products, and longer reaction times. Therefore, a simple, efficient and general synthetic protocol for the synthesis of 3-substituted indoles with a reusable catalyst remains a major challenge in synthetic organic chemistry.

In recent years, green chemistry has been deeply rooted in people's hearts. It is playing an important role in meeting the fundamental scientific challenges of protecting the living environment [19]. Ionic liquids (ILs), as green solvents and reusable catalysts, have attracted increased interest in chemical and biochemical transformations [20–21]. Recently, another new class of IL, namely magnetic ILs, has shown more advantages and a wider range of applications than conventional ILs [22–25]. Here, as our ongoing interest is on highly efficient IL-catalyzed organic reactions [26–33], we wish to disclose a general synthetic protocol for the synthesis of 3-substituted indoles in good to excellent yields by using a highly efficient and recyclable magnetic IL [Dabco-C_8][$FeCl_4$].

2. Results and discussion

Three kinds of Dabco-base IL catalysts were prepared following the synthetic route shown in Scheme 1. The synthetic procedure for [Dabco-C_8]Cl was quite straightforward, which could be obtained just by one step from the reaction between 1,4-diazobicyclo[2.2.2]octane (DABCO) and 1-chlorooctane in methanol under reflux conditions for 7 h. The magnetic IL catalyst [Dabco-C_8][$FeCl_4$] was prepared by simple mixing of [Dabco-C_8]Cl with $FeCl_3$ in methanol after stirring for 12 h at room temperature, and the anion of the catalyst Cl^- was changed to $[FeCl_4]^-$. Another IL catalyst [Dabco-C_2OH][$FeCl_4$] was synthesized in a similar way (Fig. 1).

The Raman spectra of the Dabco-base magnetic IL catalysts are shown in Fig. 2. The spectra of [Dabco-C_2OH][$FeCl_4$] and [Dabco-C_8][$FeCl_4$] show strong bands at 340 and 332 cm^{-1} which are assigned to the totally symmetric Fe–Cl stretch vibration of [$FeCl_4$] anion [34]. These assignments confirm the presence of [$FeCl_4$] anion.

Initially, the reaction between indole (**1a**) and chalcone (**2a**) was used as the model reaction to screen the catalysts, solvent, and temperature to develop appropriate reaction conditions. The results of these studies are summarized in Table 1. The Dabco-base IL catalysts could promote the reaction, and afford the corresponding C3 alkylation of indole product **3a** with moderate to good yields in CH_2Cl_2 at room temperature (Table 1, entries 1 and 2). In addition, product **3a** was

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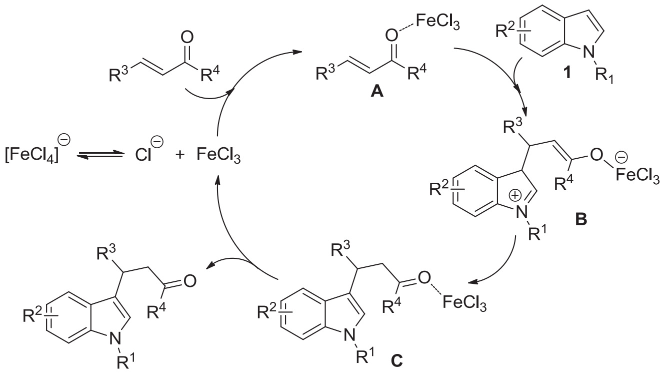


Scheme 1. A plausible mechanism for the conjugate addition of indoles to electron-deficient olefins.

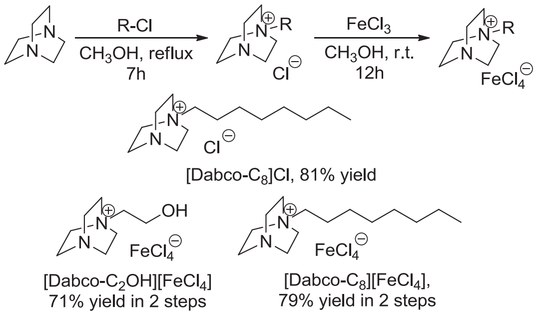
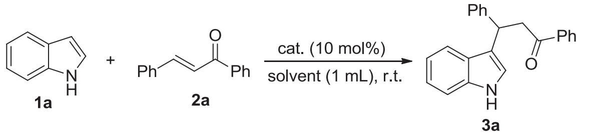


Fig. 1. Synthesis of the Dabco-base ionic liquid catalysts.

obtained in a good yield of 85% in the presence of 10 mol% of [Dabco-C_8][$FeCl_4$] IL catalyst (Table 1, entry 2). Furthermore, the catalyst [Dabco-C_8]Cl, which does not contain Fe, was used in the same reaction, which afforded product **3a** in a low yield of 19% (Table 1, entry 3). [Dabco-C_8][$FeCl_4$], as the catalyst of choice, was evaluated in different solvents, such as DCE (1,2-dichloroethane), CH_3CN, THF, toluene, C_2H_5OH, and DMF, and the yields of **3a** differed considerably (Table 1, entries 4–9). It is clear that DCE was the best solvent for this reaction, and a high yield of 91% was obtained (Table 1, entry 4). We then tried to raise the reaction temperature. To our delight, the reaction was completed in 1.5 h when it was performed at above 50 °C (Table 1, entries 10 and 11). Finally, we found that the C3 alkylation of indole product **3a** could be obtained in an excellent yield of 98% within only 1.25 h under the conditions of 50 °C in 0.3 mL DCE (Table 1, entry 12).

Table 1
Optimization of reaction conditions.[a]



Entry	Cat	Solvent (mL)	Time (h)	Yield (%)[b]
1	[Dabco-C_2OH][$FeCl_4$]	CH_2Cl_2	12	42
2	[Dabco-C_8][$FeCl_4$]	CH_2Cl_2	12	85
3	[Dabco-C_8]Cl	CH_2Cl_2	12	19
4	[Dabco-C_8][$FeCl_4$]	DCE	12	91
5	[Dabco-C_8][$FeCl_4$]	CH_3CN	12	50
6	[Dabco-C_8][$FeCl_4$]	THF	12	61
7	[Dabco-C_8][$FeCl_4$]	Toluene	12	35
8	[Dabco-C_8][$FeCl_4$]	C_2H_5OH	12	58
9	[Dabco-C_8][$FeCl_4$]	DMF	12	Trace
10[c]	[Dabco-C_8][$FeCl_4$]	DCE	1.5	92
11[d]	[Dabco-C_8][$FeCl_4$]	DCE	1.5	92
12[c,e]	[Dabco-C_8][$FeCl_4$]	DCE	1.25	98
13[c,e,f]	[Dabco-C_8][$FeCl_4$]	DCE	1.5	96
14[c,e,g]	[Dabco-C_8][$FeCl_4$]	DCE	1.5	95
15[c,e,h]	[Dabco-C_8][$FeCl_4$]	DCE	2	91

[a] Conditions: indole (**1a**, 1 mmol) and chalcone (**2a**, 1 mmol), IL catalyst (0.1 mmol, 10 mol%), and solvent 1 mL at room temperature.
[b] Isolated yield.
[c] The reaction temperature was 50 °C.
[d] The reaction temperature was 80 °C.
[e] Solvent 0.3 mL was used.
[f] The second cycle.
[g] The third cycle.
[h] The fourth cycle.

The recyclability of the catalyst is a very important parameter, which was examined for the synthesis of **3a**. After completion of the reaction, first, the solvent under vacuum was removed, and then the reaction mixture was extracted with diethyl ether (3 × 10 mL). The residue was dried under vacuum at 50 °C for 6 h, yielding the IL in its activated form. It was then reused in the next recycling run under the same conditions. This IL catalyst could be recovered and reused at least four times in the alkylation reaction for the synthesis of **3a** (Table 1, entries 13–15).

Under the optimized conditions, the scope of indoles and chalcones was explored, and the results are listed in Table 2. The reaction of indole and its derivatives with chalcones proceeded smoothly and afforded the C3 alkylation of indole product **3** with good to excellent yield (82–98%) in the presence of 10 mol% of [Dabco-C_8][$FeCl_4$] IL catalyst in DCE at 50 °C. Both the substrates with different substituents, such as methyl, methoxyl, and halide, were tolerated in the present protocol. In particular, excellent yields were achieved when 1-methylindole and 2-methylindole were used in the reaction (Table 2, entries

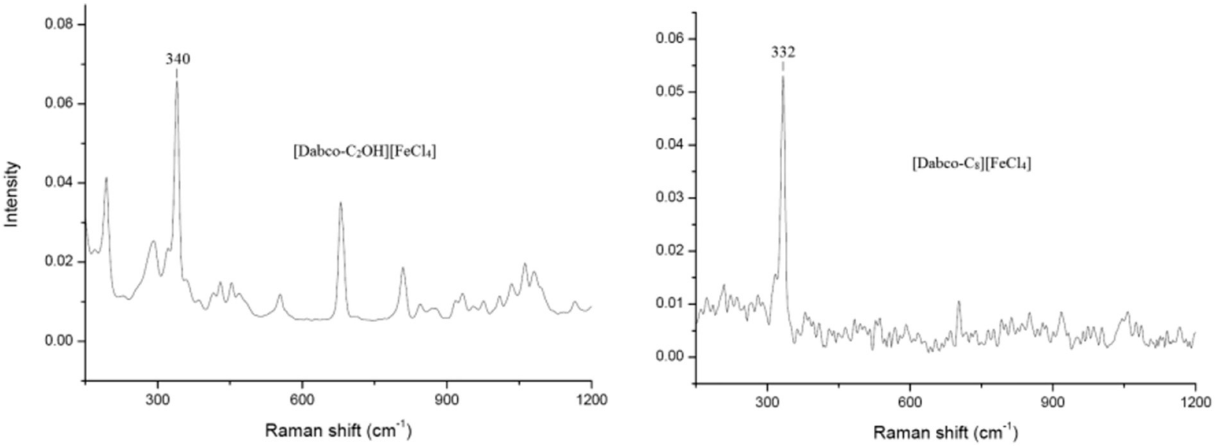


Fig. 2. Raman spectra of the catalysts.