Boron trifluoride supported on nano-SiO₂: an efficient and reusable heterogeneous catalyst for the synthesis of bis(indolyl)methanes and oxindole derivatives

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Abstract Boron trifluoride supported on nano-SiO₂ was used as an efficient and heterogeneous catalyst for the electrophilic substitution reaction of indole with various aromatic aldehydes and isatins in methanol to afford the corresponding bis(indolyl)methanes and oxindole derivatives in high yields at room temperature and under reflux conditions, respectively. The catalyst can be reused several times without loss of its catalytic activity.

Keywords Boron trifluoride \cdot Heterogeneous catalyst \cdot Bis(indolyl)methanes \cdot Oxindole

Introduction

Boron trifluoride-etherate (BF₃.OEt₂) as a homogeneous catalyst is widely used in many organic reactions [1]. Heterogenization of the BF₃ catalyst with solid support has attracted much attention in organic synthesis owing to its easy work-up procedure, easy filtration, and minimization of cost and waste generation, especially during BF₃ recovery, due to its reuse and recycling [2].

The synthesis of oxindoles and their derivatives has been of considerable interest because a large number of natural products and drugs contain this heterocyclic unit [3]. Oxindoles are used as antibacterial, antiflammatory, and laxatives [4, 5]. Furthermore, these heterocyclic compounds have been recently isolated from plants [6].

Bis(indolyl)methanes are important intermediates in organic synthesis and exhibit various physiological properties and pharmacological activities [7], such as

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useful estrogen metabolism promoter [8], inhibitory of human prostate cancer cells [9], and radical scavenging activity associated with cancer cells [10]. A number of natural products containing bis(indolyl)methane moieties have been also isolated from marine sources [11].

Numerous methods have been reported for the synthesis of these compounds. Amongst them, the acid-catalyzed electrophilic substitution reaction of indole with carbonyl compounds is one of the straightforward approaches for the synthesis of oxindole derivatives and bis(indolyl)methanes. A variety of reagents such as protic acids [12], Lewis acids [13], heterogeneous acids [14, 15], and ionic liquids [16] have been employed to achieve these transformations. However, there are still some drawbacks in these catalytic systems such as the requirement for a stiochiometric amount of Lewis acid, an expensive and toxic catalyst, long reaction times, harsh acidic conditions, and in some cases low yields of products and large amounts of catalyst.

In continuation of our interest in the synthesis of heterocyclic compounds and the use of heterogeneous catalysts in organic reactions [17-19], we used boron trifluoride supported on nano-SiO₂ (nano-SiO₂–BF₃⁻CH₃OH₂⁺) as an efficient and reusable heterogeneous catalyst for the synthesis of oxindole derivatives (Scheme 1) and bis(indolyl)methanes (Scheme 2) at room temperature and under reflux conditions.

Experimental

All materials were of commercial reagent grade. Aldehydes, boron trifluorideetherate, isatin, and indole were obtained from Merck. All the products are known compounds and were identified by comparison of their physical and spectroscopic data with those of authentic samples.

Catalyst preparation

The catalyst was synthesized by the reported procedure [2]. In a typical procedure, a mixture of $BF_3.OEt_2$ (3.42 g, 24 mmol) and preheated silica gel (3.0 g) in MeOH



Scheme 1 Nano-SiO₂-BF₃⁻CH₃OH₂⁺-catalyzed synthesis of oxindole derivatives



Scheme 2 Nano-SiO₂-BF₃⁻CH₃OH₂⁺-catalyzed synthesis of bis(indolyl)methanes



Fig. 1 FT-IR spectra of a SiO₂, b nano-SiO₂-BF₃⁻CH₃OH₂⁺

(20 ml) was prepared and stirred for 3 h at room temperature. The slurry was dried slowly at 40 $^{\circ}$ C. The obtained solid was dried in an ambient temperature for 2 h.

For identification of the structure of catalyst, we studied FT-IR spectra of SiO_2 and nano- SiO_2 -BF₃⁻CH₃OH₂⁺ (Fig 1). In both of them, the absorption bands for Si–OH and Si–O–Si appeared at 800 cm⁻¹ and 1,100 cm⁻¹, respectively. In the nano- SiO_2 -BF₃⁻CH₃OH₂⁺ spectrum, the absorption of the B–F and B–O bands was

observed in 700, 900, and $1,520 \text{ cm}^{-1}$, respectively. These observations clearly indicated that the catalyst had been synthesized.

General procedure for the synthesis of oxindole derivatives

In order to synthezise oxindole derivatives, a round-bottomed flask (25 ml) was equipped with a condenser and a magnetic stirrer, and a mixture of indole 1 (1 mmol), isatin 2 (0.5 mmol), catalyst (0.3 g), and methanol (10 ml) was stirred under reflux conditions for the appropriate time (Table 1). The progress of the reaction was monitored by TLC (eluent: ethyl acetate/*n*-hexane, 1/1). After the reaction was completed, the mixture was filtrated, and the methanol was removed under reduced pressure. The resulting solid was recrystallized from ethanol to afford the pure product.

General procedure for the synthesis of bis(indolyl)methanes

For preparation of bis(indolyl)methanes, a mixture of indole 1 (1 mmol), aldehyde 4 (0.5 mmol), catalyst (0.3 g), and methanol (10 ml) was stirred at room temperature for the appropriate time (Table 2). The progress of the reaction was monitored by TLC (eluent: ethyl acetate/*n*-hexane, 1/3). After the reaction was completed, the mixture was filtrated, and the methanol was removed under reduced pressure. The resulting solid was recrystallized from ethanol to afford the pure product.

Results and discussion

For optimizing the reaction conditions, we conducted the reaction of isatin 2a with indole 1 in various solvents such as CH₃OH, CH₃CH₂OH, H₂O, CH₃CN, CH₂Cl₂, CHCl₃, and CCl₄. The results showed that the higher product yield was obtained in methanol and then all reactions were carried out in methanol. Then, the effect of the

Entry	3	\mathbb{R}^1	\mathbb{R}^2	Time (h) ^a	Yield (%) ^b	m.p. (°C)	Lit. m.p. (°C)
1	a	Н	Н	0.33	95, 95, 93, 92, 92 ^c	313–5	312–4 [20]
2	b	Н	Br	0.25	94	310-2	310-1 [21]
3	c	Н	NO_2	0.17	93	297–9	298–9 [21]
4	d	Н	Me	0.45	95	321-3	321–2 [21]
5	e	Me	Н	0.45	96	293-5	292–3 [20]
6	f	PhCH ₂	Н	0.50	97	288–9	288–9 [21]

Table 1 nano-SiO₂-BF₃⁻CH₃OH₂⁺ catalyzed the reaction of indole with isatins

^a Reaction times under reflux

^b Isolated yield under reflux

^c The reusability and recycling of nano-SiO₂–BF₃⁻CH₃OH₂⁺ in the synthesis of compound 3a

Entry	5	R ³	R^4	Time (min) ^a	Yield (%) ^b	m.p. (°C)	Lit. m.p. (°C)
1	a	Н	Н	10	96, 95, 95, 94, 92°	123–5	125–7 [22]
2	b	2-Cl	Н	8	98	72–4	73–5 [23]
3	c	4-Cl	Н	7	97	70–3	70–2 [24]
4	d	2-Cl	4-Cl	5	96	102-5	103–5 [23]
5	e	2-MeO	Н	10	94	134–6	134–6 [23]
6	f	4-MeO	Н	12	98	186–9	187–9 [25]
7	g	4-Me	Н	10	97	95–97	94-6 [25]
8	h	3-NO ₂	Н	7	95	266-8	265-6 [22]
9	i	$4-NO_2$	Н	5	98	221-3	220–2 [23]
10	j	4-OH	Н	15	96	123–5	122–4 [<mark>26</mark>]

Table 2 Nano-SiO₂-BF₃⁻CH₃OH₂⁺ catalyzed the reaction of indole with aldehydes

^a Reaction times at room temperature

^b Isolated yield at room temperature

 $^{\rm c}$ The reusability and recycling of nano-SiO_2-BF_3^-CH_3OH_2^+ in the synthesis of compounds 5a

amount of catalyst on the conversion and the rate of the reaction was studied by varying the amount of nano-SiO₂–BF₃⁻CH₃OH₂⁺ under reflux condition. It was found that 0.3 g of nano-SiO₂–BF₃⁻CH₃OH₂⁺ was sufficient to carry out this reaction smoothly. An increase in the amount of nano-SiO₂–BF₃⁻CH₃OH₂⁺ to more than 0.3 g showed no substantial improvement in the yield, whereas the yield was reduced by decreasing the amount of nano-SiO₂–BF₃⁻CH₃OH₂⁺ to 0.2 and 0.1 g.

On the basis of the results presented in Table 1, the presence of $-CH_3$ as an electron-donating substituent increased the reaction time in comparison with molecule having no substituent (Table 1, entries 1 and 4; 0.33 vs. 0.45 h). On the other hand, a substrate with an electron-withdrawing $-NO_2$ or -Br group on isatin decreased the reaction time. (Table 1, entries 2 and 3, 0.17 vs. 0.25 h). Table 2 shows the condensation reaction of aryl aldehydes in this catalytic system that is dependent on the electron-donating substituents increased the reaction time, but the presence of $-NO_2$ and -Cl as an electron-withdrawing substituents decreased the reaction time (Table 2, entries 2–10, 10–15 vs. 5–7 min). It is worthy of mention that both isatins and aldehydes afforded excellent yields. The results are summarized in Tables 1 and 2.

A plausible mechanism for the condensation reaction of indole with isatins is proposed in Scheme 3. Nano-SiO₂-BF₃⁻CH₃OH₂⁺ coordinates with the oxygen atom of isatins to give intermediate **6**. The electron-rich β -position of the indole ring then attacks the electron-deficient carbon–oxygen double bond of **6** to afford **7**, followed by a hydrogen transfer to yield **8**. The protonation of intermediate **8** is done by nano-SiO₂-BF₃⁻CH₃OH₂⁺ to give **9**. The lone pair electron of nitrogen in **9** causes the exit of the living group (H₂O) and **10** is yielded. The indole ring attacks the electron-deficient conjugated carbon–carbon double bond of **10** to afford **11**, and finally, by a hydrogen transfer, **11** gives the target compound **3** and nano-SiO₂– $BF_3^-CH_3OH_2^+$ catalyzes the next cycle. The similar mechanism can also be proposed for aldehydes.

We also studied the recycling of the nano-SiO₂–BF₃⁻CH₃OH₂⁺ used in the repeated condensation reaction. After the first run, the catalyst was recovered by filtration, followed by washing with methanol, and reused. The catalyst can be reused five sequential times, without loss of its activity (Table 1, entry 1, and Table 2, entry 1).



Scheme 3 A plausible mechanism for the nano-SiO₂–BF₃⁻CH₃OH₂⁺-catalyzed condensation reaction of indole with isatins

Conclusion

In summary, we have described a successful strategy and efficient synthesis for the preparation of oxindole derivatives and bis(indolyl)methanes in reaction of indole with aldehydes and isatins using nano-SiO₂–BF₃⁻CH₃OH₂⁺ heterogeneous catalyst. The method offers several advantages including high yield of products, short reaction time, recyclability of the catalyst, and easy experimental work-up procedure.

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