

Silica-supported aluminum chloride: A recyclable and reusable catalyst for one-pot three-component Mannich-type reactions

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Abstract

Silica-supported aluminum chloride was used as an efficient, recyclable and reusable catalyst for the one-pot Mannich-type reactions of acetophenone with aromatic aldehydes and aromatic amines. This protocol has advantages of high yield, mild condition, no environmental pollution, and simple work-up procedure.

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1. Introduction

The Mannich reaction is a classical method for the preparation of β -amino ketones and aldehydes (Mannich bases), and it has been one of the most important basic reaction types in organic chemistry. It is the key step in the synthesis of numerous pharmaceuticals, natural products and versatile synthetic intermediates [1]. Recently, the reported Mannich reactions have been catalyzed by HCl [2], HBF₄ [3–5], InCl₃ [6,7], Y(OTf)₃ [8], Yb(PFO)₃ [9,10], Yb(OⁱPr)₃ [11], Zn(BF₄)₂ [12], Bi(OTf)₃ [13,14], Zn(OTf)₃ [15], PS-SO₃H [16], chiral Brønsted acid [17,18], phosphorodiamidic acid [19], iminodiacetic acid [20], heteropoly acid [21], copper(I)-fesusulphos Lewis acid [22] and dodecylbenzene sulfonic acid [23]. However, most catalysts suffer from drawbacks of difficult separation after the reactions; therefore, they are incapable of recycling and reusing. Furthermore, some of them are corrosive and volatile, and often cause the environment problems.

Silica-supported aluminum chloride, which was prepared by reacting aluminum chloride with conditioned silica gel (Scheme 1), was proved to be solid acid of superacid strength [24]. It has been used as a catalyst of Friedel–Crafts alkylation reactions [25,26] and cationic polymerization of styrene

[27]. In continuation of our investigation of silica-supported environmentally friendly catalysts [28], in this paper, we report the one-pot three-component Mannich-type reactions by using silica supported aluminum chloride as recyclable and reusable catalyst.

2. Experimental

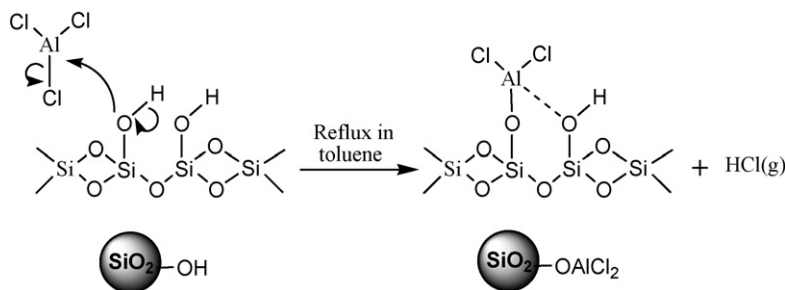
IR spectra were recorded using KBr pellets on a Digilab FTS 3000 FTIR spectrophotometer and ¹H NMR spectra on a Mercury Plus-400 instrument using CDCl₃ as solvent and Me₄Si as internal standard. Elemental analyses were performed on a Vario E1 Elemental Analysis instrument. Melting points were observed in an electrothermal melting point apparatus. The aldehydes and amines were purified by distillation or recrystallization. The solvents were dried prior to use.

2.1. Catalyst preparation

Catalyst was prepared according to literature method [24]. The silica gel (80–200 mesh) was washed with 1 M HCl, followed by deionized water, 30% H₂O₂, and then again deionized water. After being washed, the silica was dried overnight at 373 K in vacuum to give preconditioned silica gel.

1.54 g of preconditioned silica was first refluxed in toluene for 2 h. Then anhydrous aluminum chloride (1.99 g) was added

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Scheme 1. Reaction of AlCl₃ with silica gel to form a highly active catalyst.

to the stirring mixture. This mixture was allowed to react for 1 day under refluxing condition, during which the color of the solution changed into dark purple. Then the mixture was filtered in a drybox, washed three times with absolute ethanol and dried at 373 K to give 2.83 g of product (the loading capacity was ca. 4.28 mmol/g).

2.2. One-pot three-component Mannich-type reactions (typical procedure)

To the mixture of acetophenone (0.30 g, 2.5 mmol), benzaldehyde (0.21 g, 2 mmol) and aniline (0.19 g, 2 mmol) in 3 mL of ethanol, silica supported aluminum chloride (0.05 g, 0.2 mmol of aluminum) was added. The mixture was stirred at room temperature for appropriate time indicated in Table 3 until the reaction was completed as monitored by TLC. The resulting mixture was filtered to recover the catalyst, and the filtrate was evaporated off the solvent to give the crude product. The analytical sample was obtained by recrystallization of crude product from ethanol and acetone (2:3). The recovered catalyst was retested the activity after washed by ethanol and dried in vacuum. The analytical data for represent compounds are shown below.

3-(Phenylamino)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (entry 9). Yield: 89%; white solid; mp 142–143 °C; IR (KBr): $\nu = 3375, 1665$; ¹H NMR (CDCl₃, 400 MHz): $\delta_{\text{H}} = 7.90$ (2H, d, $J = 8.0$ Hz, ArH), 7.56 (1H, t, $J = 8.8$ Hz, ArH), 7.44 (2H, t, $J = 8.0$ Hz, ArH), 7.36 (2H, d, $J = 8.8$ Hz, ArH), 7.10 (2H, t, $J = 8.0$ Hz, ArH), 6.84 (2H, d, $J = 8.8$ Hz, ArH), 6.71 (1H, t, $J = 7.1$ Hz, ArH), 6.62 (2H, d, $J = 7.6$ Hz, ArH), 4.96 (1H, t, $J = 6.0$ Hz, NCH), 3.77 (3H, s, CH₃O), 3.52 (2H, d, $J = 6.0$ Hz, COCH₂). Anal. Calcd. for C₂₂H₂₁NO₂: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.60; H, 6.45; N, 4.15.

3-(3-Bromophenylamino)-3-(4-chlorophenyl)-1-phenylpropan-1-one (entry 18). Yield: 86%; white solid; mp 123–124 °C; IR (KBr): $\nu = 3392, 1676$; ¹H NMR (CDCl₃, 400 MHz): $\delta_{\text{H}} = 7.89$ (2H, d, $J = 7.2$ Hz, ArH), 7.58 (1H, t, $J = 7.6$ Hz, ArH),

Table 1

Mannich reaction of acetophenone, benzaldehyde and aniline catalyzed by different catalysts^a

Entry	Catalyst	Amount of catalyst (mmol%)	Time (h)	Yield of 4 (%) ^b
1	FeCl ₃	10	20	0
2	ZnCl ₂	10	20	0
3	AlCl ₃	10	20	0
4	SiO ₂	10	20	0
5	AlCl ₃ /SiO ₂	10	5	74
6	SiO ₂ -OAlCl ₂	10	5	93

^a All reactions of acetophenone (2.5 mmol), benzaldehyde (2 mmol) and aniline (2 mmol) were carried out in ethanol at room temperature.

^b Yields refer to the isolated products.

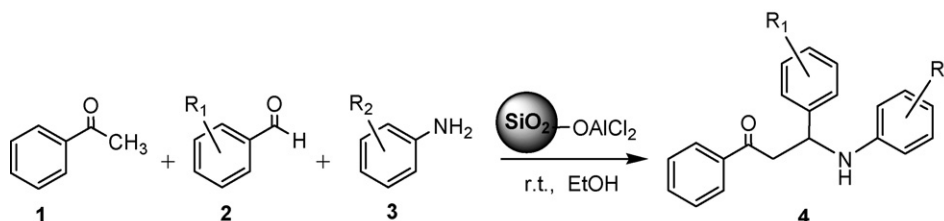
7.46 (2H, t, $J = 7.6$ Hz, ArH), 7.36 (2H, d, $J = 8.4$ Hz, ArH), 7.29 (2H, d, $J = 8.4$ Hz, ArH), 6.93 (1H, t, $J = 8.00$ Hz, ArH), 6.79 (1H, d, $J = 8.0$ Hz, ArH), 6.69 (1H, t, $J = 1.8$ Hz, ArH), 6.44 (1H, dd, $J = 8.2$ Hz, 1.4 Hz, ArH), 4.94 (1H, t, $J = 6.4$ Hz, NCH), 3.45 (2H, d, $J = 6.4$ Hz, COCH₂). Anal. Calcd. for C₂₁H₁₇BrClNO: C, 60.82; H, 4.13; N, 3.38. Found: C, 60.98; H, 4.09; N, 3.47.

3. Results and discussion

3.1. The model reaction under different conditions

To explore the use of silica supported aluminum chloride as a catalyst, Mannich-type reaction of acetophenone (**1**), benzaldehyde (**2**) and aniline (**3**) for the preparation of β -aminocarbonyl compound **4** was investigated under different conditions (Scheme 2).

The effect of different catalysts on the yield of compound **4** is shown in Table 1. The catalytic activities of Lewis acids such as ferrous chloride, zinc chloride and aluminum trichloride were first tested for the Mannich reaction, but no product was observed



Scheme 2. Silica-supported aluminum chloride catalyzed one-pot Mannich reactions of acetophenone, aromatic aldehydes and aromatic amines.

Table 2
Silica-supported aluminum chloride catalyzed Mannich-type reaction in different solvents^a

Entry	Solvent	Yield of 4 (%) ^b
1	MeCN	30
2	EtOH	93
3	Et ₂ O	0
4	CH ₂ Cl ₂	0
5	H ₂ O	0
6	THF	0
7	PhMe	0
8	<i>n</i> -Hexane	0

^a All reactions of acetophenone (2.5 mmol), benzaldehyde (2 mmol) and aniline (2 mmol) were carried out at room temperature for 5 h.

^b Yields refer to the isolated products.

(Table 1, entries 1–3). However, silica supported aluminum chloride could efficiently catalyze Mannich reaction to afford the desired product in high yield (Table 1, entry 6). In contrast, the physical mixture of silica and aluminum trichloride (Table 1, entry 5) exhibited an intermediate level of activity, which was significantly lower than the silica supported aluminum chloride. In the silica gel alone, there was no activity for the reaction (Table 1, entry 4). Furthermore, the silica supported aluminum chloride could be easily separated from the reaction mixture only by filtration and reused three times without obvious loss of activity (product yield: 93% for the first run; 90% for the second run; 88% for the third run).

The effect of amount of silica supported aluminum chloride catalyst on the yield and rate was also investigated. Generally, the reaction rate and yield were increased over the amount of catalyst. It was found that 10 mmol% of catalyst was the appropriate amount for the reaction. The less amount gave a low yield even after long reaction time, and the more amount could not cause the obvious increase for the yield of product. Hence, the optimal amount of catalyst was chosen 10 mmol% in the following reactions.

Mannich reaction was very sensitive to reaction temperature. The high temperature could improve the reaction rate and shorten the reaction time, but favor side reactions and the oxygenolysis of aldehyde and amine. It was found that the room temperature was an appropriate condition for the silica-supported aluminum chloride catalyzed Mannich reaction.

The solvents also played an important role in the Mannich reaction catalyzed by silica supported aluminum chloride. Several solvents were tested for the reaction, such as EtOH, MeCN, CH₂Cl₂, H₂O, THF, Et₂O, PhMe and *n*-hexane. The reaction hardly proceeded in CH₂Cl₂, THF, Et₂O or H₂O. However, the reaction in EtOH afforded product in high selectivity with nearly complete conversion. Therefore, EtOH was selected as the reaction solvent in the following investigation (Table 2).

3.2. One-pot three-component Mannich-type reactions of acetophenone with different aldehydes and amines

To explore the scope and generality of the present method, different aldehydes and amines were tested for the Man-

Table 3
Silica-supported aluminum chloride catalyzed Mannich reactions of acetophenone, aldehydes and amines^a

Entry	R ₁	R ₂	Time (h)	Yield (%) ^b	mp (°C)
1	H	H	5	93	169–170
2	H	4-CH ₃	6	91	167–168
3	H	3-NO ₂	5.5	89	139–140
4	H	4-NO ₂	6	90	179–180
5	H	4-Cl	6	91	170–171
6	H	3-Br	6	87	128–129
7	H	3-COOH	7	78	163–164
8	H	4-COOH	8	84	162–163
9	4-CH ₃ O	H	10	89	142–143
10	4-CH ₃	H	7	92	134–135
11	4-CH ₃	4-CH ₃	8	87	135–136
12	4-Br	4-CH ₃	6	91	126–127
13	4-Cl	4-Cl	7	87	118–119
14	4-Cl	H	8	89	114–115
15	4-Cl	4-NO ₂	6	79	149–150
16	4-Cl	4-COOH	5	84	159–160
17	4-Cl	3-NO ₂	7	77	132–133
18	4-Cl	3-Br	1.5	86	123–124
19	4-OH	4-CH ₃	2	90	172–173
20	4-N(CH ₃) ₂	H	1.5	91	202–203
21	4-N(CH ₃) ₂	4-Cl	2	88	149–150
22	4-N(CH ₃) ₂	4-NO ₂	4	87	206–207
23	4-N(CH ₃) ₂	3-NO ₂	10	85	98–99
24	4-N(CH ₃) ₂	3-Br	3	86	162–163
25	4-N(CH ₃) ₂	4-COOH	1.5	83	219–220
26	3-NO ₂	H	7	84	131–132
27	H	2-Cl	20	Trace	–
28	H	2-NO ₂	20	Trace	–
29	4-CH ₃	2-Cl	20	Trace	–

^a All products were characterized by comparison of their melting points, IR, and ¹H NMR spectra with those of authentic samples.

^b Yields refer to the isolated products.

nich reactions with acetophenone, as shown in Table 3. The three-component Mannich reactions proceeded smoothly in the presence of 10 mmol% of silica-supported aluminum chloride at room temperature to give the corresponding products in high yield (Scheme 2). Various aromatic aldehydes bearing different substitutes, such as *para*-MeO, Me, OH, Br, Cl, Me₂N and *meta*-NO₂, on the aryl rings were all suitable to the reactions. Aromatic amines bearing *para*-Me, NO₂, Cl, COOH and *meta*-NO₂, Br, COOH on the aryl rings were favorable to the reactions. However, the *ortho*-substituted aromatic amines generally gave very low yield, even trace of the products because of large steric hindered effect (Table 3, entries 27–29). It was observed that the catalyst system had no catalytic activity for the reactions when aliphatic aldehydes (such as isovaleraldehyde) and aliphatic amines (such as benzylamine) were used as substrates.

4. Conclusion

The silica supported aluminum chloride was found to be an efficient, recyclable and reusable catalyst for the one-pot three-component Mannich reactions of acetophenone with aromatic aldehydes and aromatic amines. The catalyst is cheap and stable. This protocol has advantages of high yield, mild condition, no environmental pollution, and simple work-up procedure.

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