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Bismuth(III) chloride-catalyzed one-pot Mannich reaction: three-component synthesis of β-amino carbonyl compounds

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ABSTRACT

A simple and efficient method has been developed for the one-pot Mannich reaction of β-amino carbonyl compounds from aromatic aldehydes, aromatic ketones and aromatic amines in the presence of a catalytic amount of bismuth trichloride.

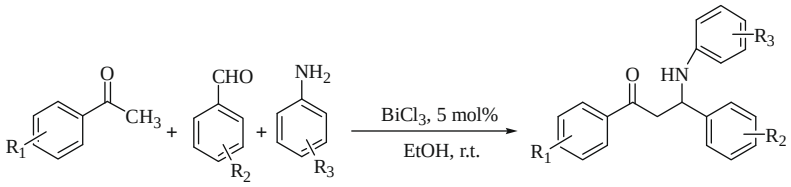
The Mannich reaction is one of the most important carbon–carbon bond forming reactions in organic synthesis[1] because it affords synthetically and biologically important β-amino carbonyl compounds which are important intermediates for the construction of various nitrogen-containing natural products and pharmaceuticals.[2] Due to the drastic reaction conditions, severe side-reactions, substrate limitations and the long reaction time, the classical intermolecular Mannich reaction is plagued.[3] To overcome the drawbacks of the classic method, the Lewis acid-catalyzed condensation between silyl enol ethers or silyl ketene acetals and preformed imines has been developed.[4] Recently, some Bronsted acid or Lewis aicd-catalyzed one-pot Mannich reactions of unmodified aldehydes, ketones and amines have been catalyzed by HCl,[5] proline,[6] *p*-dodecyl benzene sulfonic acid (DBSA),[7] polymer-support sulfonic acid (PS-SO_3H),[8] Lewis acids[9] as well as Silica-$AlCl_3$.[10] However, the long reaction time, costly catalysts and requirement of special effort for catalyst preparation cannot be avoided. Therefore, it has attracted continuous interest to develop methods for the synthesis of β-amino carbonyl compounds.

In recent years, bismuth chloride ($BiCl_3$) has attracted much attention because of its diverse applicability as catalysts in organic synthesis.[11] Compared with transition-metal complexes, bismuth(III) salts are stable in air, relatively nontoxic and inexpensive. In this Letter, we report a rapid and efficient method for one-pot Mannich reaction of aldehydes, ketones and amines in the presence of $BiCl_3$ (Scheme 1).

Initially, we screened different common Lewis acids for their ability to catalyze the three-component Mannich reaction and acetophenone, benzaldehyde and aniline were selected as models. As shown in Table 1, the common Lewis acids such as $ZnCl_2$, $ZnSO_4$, $CuCl_2$, $LaCl_3$ and $FeCl_3$ did not furnish the desired product (Table 1, entries 2–6). $InCl_3$ and *p*-TsOH afforded the desired product but only in moderate yield (Table 1, entries 7 and 8). However, $BiCl_3$ could efficiently catalyze the Mannich reaction to afford the desired products in high yields in relatively short time (Table 1, entries 10–14).

Next, the amount of the catalyst was examined: we found that 5 mol % $BiCl_3$ was sufficient to drive the reaction completely in 95% yield. The less amount gave a low yield even after a prolonged reaction time, and the more amount could not cause the obvious increase for the yield of product but could shorten the reaction time.

In addition, Mannich reaction was very sensitive to the reaction temperature: the high temperature could improve the reaction rate and shorten the reaction time but favour side reactions and the oxygenolysis of aldehyde and amine. It was found that the room temperature was an appropriate condition for $BiCl_3$-catalyzed one-pot three-component Mannich reaction.



Scheme 1.

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Table 1
Conditions optimization of the direct Mannich reaction under different conditions[a]

Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	No cat. (—)	EtOH	48	NR[c]
2	$ZnCl_2$ (10)	EtOH	20	NR
3	$ZnSO_4$ (10)	EtOH	20	NR
4	$CuCl_2$ (10)	EtOH	20	NR
5	$LaCl_3$ (10)	EtOH	20	NR
6	$FeCl_3$ (10)	EtOH	20	NR
7	$InCl_3$ (10)	EtOH	20	56
8	*p*-TsOH (10)	EtOH	20	75
9	I_2 (10)	EtOH	20	80
10	$BiCl_3$ (2)	EtOH	11	75
11	$BiCl_3$ (4)	EtOH	11	84
12	$BiCl_3$ (5)	EtOH	11	95
13	$BiCl_3$ (8)	EtOH	11	88
14	$BiCl_3$ (10)	EtOH	11	79
15	$BiCl_3$ (5)	THF	11	81
16	$BiCl_3$ (5)	DMF	11	62
17	$BiCl_3$ (5)	CH_3CN	11	66
18	$BiCl_3$ (5)	DCM	11	63
19	$BiCl_3$ (5)	H_2O	11	84

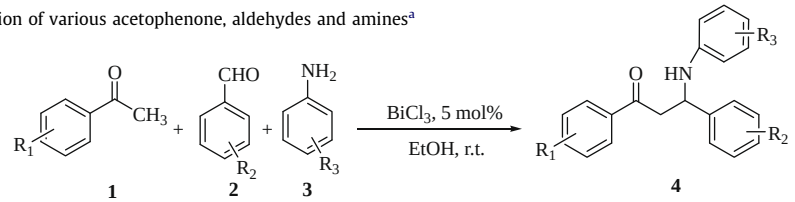
[a] Reaction conditions: acetophenone (2.2 mmol), benzaldehyde (2 mmol), aniline (2 mmol), rt.
[b] Isolated yield.
[c] No reaction.

To explore the scope and generality of the present method, different aromatic ketones, aromatic aldehydes and aromatic amines were selected to undergo one-pot Mannich reaction in the presence of catalytic amount (5 mol %) of $BiCl_3$ in ethanol at room temperature (Scheme 2). The results of this study are summarized in Table 2.

In general, the three-component Mannich reaction proceeded smoothly to give the corresponding products in high yields. Various aldehydes bearing different substitutes, such as *para*-Me, MeO, OH, Me_2N, Cl and NO_2 on the aryl rings were all suitable to the reaction. Aromatic ketones bearing *para*-Me, NO_2 and Cl gave high yields too. In addition, aromatic amines bearing *para*-Me, MeO, NO_2, F, Cl, Br, COOH, NO_2, and *meta*-Me, Br on the aryl rings were also favourable to the reaction. It is worth noting that 4-nitrobenzaldehyde or 4-nitro acetophenone catalyzed by HCl failed to give the desired Mannich base[5] whereas aromatic ketone and aromatic amine bearing electron-withdrawing substituents such as NO_2 could give the desired adducts in good yields (Table 2, entries 15 and 18). Although *meta*- and *para*-substituted aromatic amines both bearing electron-withdrawing substituents and electron-donating substituents gave good results, *ortho*-substituted aromatic amines such as *ortho*-nitroaniline and *ortho*-anisidine (Table 2, entries 25 and 26) failed to yield any products because of large steric hindered effect.[9,10]

In conclusion, we have demonstrated a very simple, efficient and practical method for the one-pot Mannich reaction of β-amino carbonyl compounds from aldehydes, ketones and amines in the presence of catalytic amount of bismuth(III) chloride. The major advantage of this method is that it is truly a one-pot procedure which does not require a separate step to prepare an imine for subsequent use. The significant features of the protocol include operational simplicity, inexpensive reagents, mild condition and high yields of the products.

Table 2
$BiCl_3$-catalyzed direct Mannich reaction of various acetophenone, aldehydes and amines[a]



1 2 3 4

Scheme 2

Entry	R_1	R_2	R_3	Product[b]	Time (h)	Yield[c] (%)	Mp (°C(lit))
1	H	H	H	**4a**	11	95	169–170
2	H	H	4-CH_3	**4b**	12	93	167–168
3	H	H	3-CH_3	**4c**	12	91	131–132
4	H	H	4-OCH_3	**4d**	14	89	166–167
5	H	H	4-F	**4e**	13	95	162–163
6	H	H	4-Cl	**4f**	9	92	170–171
7	H	H	3-Br	**4g**	10	90	128–129
8	H	H	4-NO_2	**4h**	10	88	185–186[9b]
9	H	H	4-COOH	**4i**	11	86	161–162
10	H	4-CH_3	H	**4j**	12	90	129–130
11	H	4-OH	H	**4k**	4	95	220–221
12	H	4-OCH_3	H	**4l**	16	87	142–143
13	H	4-$N(CH_3)_2$	H	**4m**	4	91	202–203
14	H	4-Cl	H	**4n**	12	87	114–115
15	H	4-NO_2	H	**4o**	20	91	105–106[9a]
16	4-CH_3	H	H	**4p**	10	93	139–140[9b]
17	4-Cl	H	H	**4q**	19	88	119–120[9b]
18	4-NO_2	H	H	**4r**	20	87	114–116[9b]
19	H	4-Cl	3-Br	**4s**	16	86	126–127[10]
20	H	4-OCH_3	4-Cl	**4t**	13	85	158–160
21	4-CH_3	H	4-Br	**4u**	11	92	147–149[5b]
22	4-CH_3	4-OCH_3	4-Cl	**4v**	11	90	136–137
23	4-Cl	4-CH_3	4-Cl	**4w**	11	84	146–147
24	4-CH_3	4-Cl	3-Br	**4x**	11	89	74–75
25	H	H	2-NO_2	**4y**	24	—	—
26	H	H	2-OCH_3	**4z**	24	—	—

[a] Reaction conditions: acetophenone (2.2 mmol), benzaldehyde (2 mmol), aniline (2 mmol), ethanol (3 mL), $BiCl_3$ (5 mol %) at rt.
[b] Products are characterized by melting point, IR, ^1H NMR and comparison with literature.
[c] Isolated yield.

Typical procedure for the synthesis of 4. To a mixture of aromatic ketones (2.2 mmol), aromatic aldehydes (2.0 mmol) and aromatic amines (2.0 mmol) in anhydrous ethanol (3 mL) was added $BiCl_3$ (5 mol %). The mixture was stirred at room temperature for the specified time (Table 2) indicated by TLC. After the reaction was completed, saturated $NaHCO_3$ solution (10 mL) was added, and the precipitated solid was collected by filtration, washed with ethanol. The crude product was purified by recrystallization from acetone/ethanol (2:3) to afford the pure products **4a–x**.[12–14]

Acknowledgements

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12. *Compound* **4e**: 3-[(4-fluorophenyl)amino]-1,3-diphenylpropan-1-one: white solid; mp 162–163 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.42 (dd, J = 7.6 Hz, J = 16.3 Hz, 1H), 3.49 (dd, J = 4.9 Hz, J = 16.3 Hz, 1H), 4.91 (dd, J = 7.6 Hz, J = 4.9 Hz, 1H), 6.49–6.52 (m, 2H), 6.78 (t, J = 8.7 Hz, 2H), 7.24 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.41 (m, J = 8.0 Hz, 4H), 7.56 (t, J = 7.4 Hz, 1H), 7.91 (d, J = 7.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 46.3, 55.7, 115.2, 115.5, 115.6, 126.4, 127.5, 128.2, 128.7, 128.9, 133.5, 136.7, 142.6, 143.1, 198.2. IR (KBr) ν = 3386, 1671, 1595, 1511, 1449, 1289, 1220, 815, 701, 684. ESI HRMS exact mass calcd for $(C_{21}H_{18}F_1N_1O_1{}^+Na)^+$ requires m/z 342.1265; found: 342.1268.
13. *Compound* **4v**: 3-(4-chlorophenylamino)-3-(4-methoxyphenyl)-1-*p*-tolylpropan-1-one: white solid; mp 136–137 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.34 (dd, J = 7.6 Hz, J = 16.1 Hz, 1H), 3.43 (dd, J = 5.0 Hz, J = 16.1 Hz, 1H), 3.77 (s, 3H), 4.63 (br s, 1H), 4.87 (dd, J = 5.1 Hz, J = 7.6 Hz, 1H), 6.46 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.6, 46.1, 54.5, 55.2, 114.3, 115.0, 122.4, 127.4, 128.3, 128.8, 129.4, 134.3, 134.5, 144.4, 145.6, 158.9, 197.9; IR (KBr) ν = 3381, 1665, 1603, 1513, 1463, 1370, 1289, 1255, 1175, 1032, 808, 734. ESI HRMS exact mass calcd for $(C_{21}H_{18}F_1N_1O_1{}^+Na)^+$ requires m/z 402.1231; found: 402.1229.
14. *Compound* **4w**: 1-(4-chlorophenyl)-3-(4-chlorophenylamino)-3-*p*-tolylpropan-1-one: yellowish solid; mp 146–147 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.18 (s, 3H), 3.37 (dd, J = 7.3 Hz, J = 16.4 Hz, 1H), 3.41 (dd, J = 5.4 Hz, J = 16.4 Hz, 1H), 4.46 (br s, 1H), 4.93 (t, J = 6.4 Hz, 1H), 6.45 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.81(d, J = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.3, 46.0, 54.4, 114.1, 127.5, 127.8, 128.9, 129.1, 129.5, 129.7, 133.0, 134.9, 140.1, 141.5, 144.2, 196.7; IR (KBr) ν = 3408, 1671, 1617, 1587, 1568, 1520, 1488, 1402, 1365, 1285, 1218, 1093, 991, 825, 804, 722. ESI HRMS exact mass calcd for $(C_{21}H_{18}F_1N_1O_1{}^+Na)^+$ requires m/z 406.0736; found: 406.0728.