



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

Hua Li, Hong-yao Zeng, Hua-wu Shao *

Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, PR China

ARTICLE INFO

Article history:

Received 12 June 2009

Revised 18 September 2009

Accepted 22 September 2009

Available online 25 September 2009

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.

© 2009 Elsevier Ltd. All rights reserved.

The Mannich reaction is one of the most important carbon–carbon bond forming reactions in organic synthesis¹ 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 pre-formed imines has been developed.⁴ Recently, some Bronsted acid or Lewis acid-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-SO₃H),⁸ Lewis acids⁹ as well as Silica-AlCl₃.¹⁰ 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.

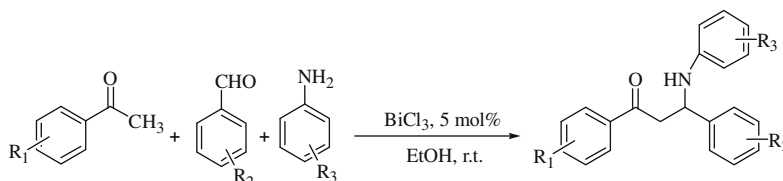
In recent years, bismuth chloride (BiCl₃) has attracted much attention because of its diverse applicability as catalysts in organic synthesis.¹¹ Compared with transition-metal complexes, bismuth(III) salts are stable in air, relatively nontoxic and inexpen-

sive. In this Letter, we report a rapid and efficient method for one-pot Mannich reaction of aldehydes, ketones and amines in the presence of BiCl₃ (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 ZnCl₂, ZnSO₄, CuCl₂, LaCl₃ and FeCl₃ did not furnish the desired product (Table 1, entries 2–6). InCl₃ and *p*-TsOH afforded the desired product but only in moderate yield (Table 1, entries 7 and 8). However, BiCl₃ 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 % BiCl₃ 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 BiCl₃-catalyzed one-pot three-component Mannich reaction.



Scheme 1.

* Corresponding author.

E-mail address: annalee@yeah.net (H. Shao).

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	<i>p</i> -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 ₃ CN	11	66
18	BiCl ₃ (5)	DCM	11	63
19	BiCl ₃ (5)	H ₂ O	11	84

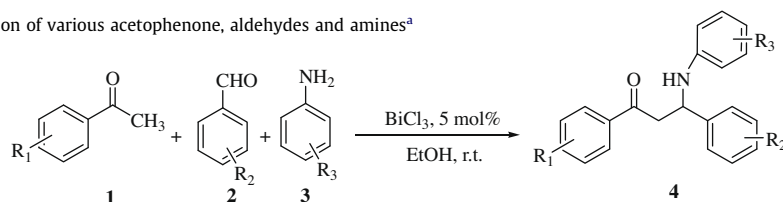
^a Reaction conditions: acetophenone (2.2 mmol), benzaldehyde (2 mmol), aniline (2 mmol), rt.^b Isolated yield.^c No reaction.

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 BiCl₃ in ethanol at room tem-

perature (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, Me₂N, Cl and NO₂ on the aryl rings were all suitable to the reaction. Aromatic ketones bearing *para*-Me, NO₂ and Cl gave high yields too. In addition, aromatic amines bearing *para*-Me, MeO, NO₂, F, Cl, Br, COOH, NO₂, 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 base⁵ whereas aromatic ketone and aromatic amine bearing electron-withdrawing substituents such as NO₂ 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
BiCl₃-catalyzed direct Mannich reaction of various acetophenone, aldehydes and amines^a

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), BiCl₃ (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 BiCl₃ (5 mol %). The mixture was stirred at room temperature for the specified time (Table 2) indicated by TLC. After the reaction was completed, saturated NaHCO₃ 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

We acknowledge the financial support from Chengdu Institute of Biology, Chinese Academy of Sciences. We are also grateful to the Analytical and Testing Center of Chengdu Institute of Biology for supports in NMR and MS analyses.

References and notes

- (a) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112; (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094; (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070; (d) Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 674.
- (a) Müller, R.; Goesmann, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 184–187; (b) Bohme, H.; Haake, M. In Taylor, E. C., Ed.; *Advances in Organic Chemistry*; John Wiley and Sons: New York, 1976; p 107.
- For comprehensive reviews: (a) Tramontini, M.; Angiolini, L. *Mannich-Bases Chemistry and Uses*; CRC: Boca Raton, FL, 1994. and references cited therein; (b) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 355. and references cited therein.
- (a) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640–5641; (b) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143–145; (c) Periasamy, M.; Suresh, S.; Ganesan, S. S. *Tetrahedron Lett.* **2005**, *46*, 5521–5524; (d) Jacobsen, M. F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792–4796; (e) Komoto, I.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 680–688; (f) Chung, W. J.; Omote, M.; Welch, J. T. *J. Org. Chem.* **2005**, *70*, 7784–7787.
- (a) Xu, X. J.; Chen, G. X. *Acta Chem. Sinica* **1982**, *40*, 463–468. in Chinese; (b) Yi, L.; Lei, H. S.; Zou, J. H.; Xu, X. J. *Synthesis* **1991**, *9*, 717–718; (c) Yang, D. C.; Zhang, G. L.; Yang, Y.; Zhong, Y. G. *Chem. J. Chinese U (in Chinese)* **2000**, *21*, 1694–1696.
- (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833; (b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; (c) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978; (d) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677–3680; (e) Kantam, M. L.; Rajasekhar, C. V.; Gopikrishna, G.; Reddy, K. R.; Choudary, B. M. *Tetrahedron Lett.* **2006**, *47*, 5965–5967.
- (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537–2544; (b) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965–1967.
- Imura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 1644–1645.
- (a) Wang, R.; Li, B. G.; Huang, T. K.; Shi, L.; Lu, X. X. *Tetrahedron Lett.* **2007**, *48*, 2071–2073; (b) Yi, W. B.; Cai, C. J. *Fluorine Chem.* **2006**, *127*, 1515–1521; (c) Wang, L. M.; Han, J. W.; Sheng, J.; Tian, H.; Fan, Z. Y. *Catal. Commun.* **2005**, *6*, 201–204; (d) Wang, L. M.; Han, J. W.; Sheng, J.; Fan, Z. Y.; Tian, H. *Chin. J. Org. Chem.* **2005**, *25*, 591–594.
- Li, Z.; Ma, X. L.; Liu, J.; Feng, X.; Tian, G. Q.; Zhu, A. G. *J. Mol. Catal. A: Chem.* **2007**, *272*, 132–135.
- For comprehensive reviews: (a) Postel, M.; Dunach, E. *Coord. Chem. Rev.* **1996**, *155*, 127–144; (b) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373–8397; (c) Vidal, S. *Synlett* **2001**, 1194–1195; (d) Hua, R. M. *Curr. Org. Synth.* **2008**, *5*, 1–27.
- Compound 4e**: 3-[(4-fluorophenyl)amino]-1,3-diphenylpropan-1-one: white solid; mp 162–163 °C; ¹H NMR (600 MHz, CDCl₃): 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). ¹³C NMR (150 MHz, CDCl₃): 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 (C₂₁H₁₈F₁N₁O₁ + Na)⁺ requires *m/z* 342.1265; found: 342.1268.
- Compound 4v**: 3-(4-chlorophenylamino)-3-(4-methoxyphenyl)-1-*p*-tolylpropan-1-one: white solid; mp 136–137 °C; ¹H NMR (600 MHz, CDCl₃): 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); ¹³C NMR (150 MHz, CDCl₃): 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 (C₂₁H₁₈F₁N₁O₁ + Na)⁺ requires *m/z* 402.1231; found: 402.1229.
- Compound 4w**: 1-(4-chlorophenyl)-3-(4-chlorophenylamino)-3-*p*-tolylpropan-1-one: yellowish solid; mp 146–147 °C; ¹H NMR (600 MHz, CDCl₃): 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); ¹³C NMR (150 MHz, CDCl₃): 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 (C₂₁H₁₈F₁N₁O₁ + Na)⁺ requires *m/z* 406.0736; found: 406.0728.