Available online at www.sciencedirect.com

ScienceDirect

Chinese Chemical Letters 21 (2010) 31–34

CHINESE CHEMICAL LETTERS

www.elsevier.com/locate/cclet

$CeCl_3{\cdot}7H_2O$ as an efficient catalyst for one-pot synthesis of β-amino ketones by three-component Mannich reaction

Yan Dai [a], Bin Dong Li [a], Heng Dao Quan [b], Chun Xu Lü [a,*]

[a] *School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China*
[b] *National Institute of Advanced Industrial Science and Technology, Ibaraki 3058565, Japan*

Received 13 May 2009

Abstract

Cerium trichloride heptahydrate ($CeCl_3{\cdot}7H_2O$) was found to be an efficient and recyclable catalyst for the three-component direct Mannich reaction of anilines and benzaldehydes with acetophenone. This protocol has advantages of high yield, no environmental pollution, mild condition, and simple work-up procedure.

Keywords: Cerium trichloride heptahydrate; Mannich reaction; β-Amino ketones; Lewis acid

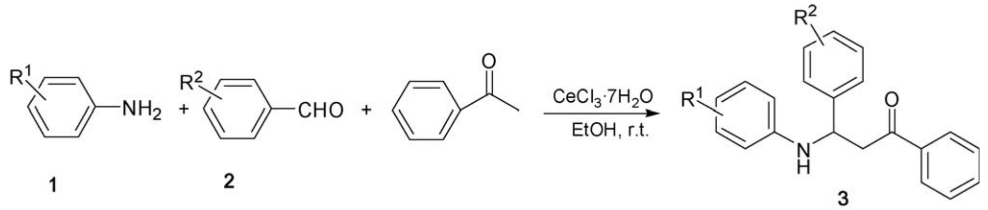
The development of promoted organic reactions using air-stable and water-tolerant lanthanide salts as Lewis acid catalyst is one of the most important and challenging subjects in organic synthesis chemistry [1]. In the last years, cerium trichloride heptahydrate ($CeCl_3{\cdot}7H_2O$) as a moisture and air tolerant Lewis acid has attracted considerable attention because of its high abundance in the Earth's crust, high catalytic activity, low toxicity and the easy work-up. It has been used for various organic transformations [2] such as epoxide opening reaction, elimination reaction, carbon–carbon and carbon–heteroatom bonds forming reactions, selective deprotection reactions and so on. However, the use of $CeCl_3{\cdot}7H_2O$ in Mannich-type reaction has rarely been reported.

Mannich reactions are important carbon-carbon bond forming reactions in organic synthesis [3]. They provide β-amino ketones, β-amino esters and other β-amino carbonyl compounds, which are useful building blocks for important molecules with applications in various pharmaceuticals and in the field of material science [4]. Traditionally, Mannich reactions have been achieved by using proton acids or Lewis acids as catalysts [5]. However, these procedures are not entirely satisfactory and suffer from some limitations including use of toxic reagents, atmosphere sensitive reagents or catalysts, a large amount of expensive and non-recoverable catalyst, requirement of special effort for catalyst preparation. Therefore, the development of new catalysts with more efficiency is of interest. To our knowledge, the use of $CeCl_3{\cdot}7H_2O$ as catalyst for three-component direct Mannich reaction has not been described in the literature. Herein we describe a mild, convenient, and simple procedure for effecting the one-pot, three-component reaction of anilines and benzaldehydes with acetophenone for the preparation of β-amino ketones using $CeCl_3{\cdot}7H_2O$ as catalyst (Scheme 1).

---

[*] Corresponding author.
E-mail address: lucx@mail.njust.edu.cn (C.X. Lü).

1001-8417/$ – see front matter © 2009 Chun Xu Lü. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.
doi:10.1016/j.cclet.2009.08.011



Scheme 1.

1. Results and discussion

Initially, we chose the reaction of aniline and benzaldehyde with acetophenone as a reaction model in ethanol [6]. As a preliminary study, several common Lewis acids and Brønsted acids were used as catalysts (Table 1). As for the non-metal Lewis acids or Brønsted acids such HCl, CH_3SO_3H, p-TsOH, I_2, [Hmim][HSO_4] and $H_3PW_{12}O_{40}$, due to their shortcoming of difficult recovery or special efforts for preparation, they could not be considered as economic and green catalysts even if some of them displayed good catalytic capacity (Table 1, entries 1–6). Although Yb(OTf)$_3$ and Zn(OTf)$_2$ displayed as effective catalysts for such reaction, their expensive cost limited their practical usage on a large scale (Table 1, entries 7 and 8). In cases of $FeCl_3$, $ZnCl_2$, $AlCl_3$ and $CuCl_2$, they did not furnish the desired products even the reaction time was prolonged to 24 h (Table 1, entries 9–12). In contrast, $CeCl_3·7H_2O$ could be easily separated from the reaction mixture only by filtration and reused three times without obvious loss of activity (product yield: 91% in the first run; 89% in the second run; 85% in the third run) (Table 1, entries 13 and 14). Thus, in view of excellent catalytic capacity, outstanding stability and ready reutilization, $CeCl_3·7H_2O$ was chosen as the effective catalyst for the Mannich reaction of aniline and benzaldehyde with acetophenone.

Then, the $CeCl_3·7H_2O$-catalyzed Mannich reaction was examined in various solvents (Table 2). $CeCl_3·7H_2O$-catalyzed Mannich reactions in organic solvents such as CH_3CN, CH_2Cl_2, PhMe, n-hexane and gave the desired products in low yield with the formation of imine side products. Although the reaction in water could afford desired product, the yield was only moderate because of the low solubility of aldehydes, ketones, and amines in water. Among

Table 1
Mannich reaction of aniline and benzaldehyde with acetophenone in ethanol catalyzed by different catalysts[a].

Entry	Catalyst	Time (h)	Yield [b] (%)	Entry	Catalyst	Time (h)	Yield[b] (%)
1	HCl	24	75	8	Zn(OTf)$_2$	12	85
2	CH_3SO_3H	14	92	9	$FeCl_3$	24	0
3	p-TsOH	24	88	10	$ZnCl_2$	24	0
4	I_2	12	82	11	$AlCl_3$	24	0
5	[Hmim][HSO_4]	10	90	12	$CuCl_2$	24	0
6	$H_3PW_{12}O_{40}$	24	87	13	$CeCl_3·7H_2O$	10	91
7	Yb(OTf)$_3$	12	86	14	$CeCl_3·7H_2O$	10	91, 89, 85[c]

[a] Reaction conditions: $PhNH_2$ (2.1 mmol), PhCHO (2 mmol), $PhCOCH_3$ (2.4 mmol), catalyst (0.1 mmol), EtOH (3 mL), r.t.

[b] Isolated yield.

[c] Catalyst was reused in three times.

Table 2
Synthesis of β-amino ketone in different solvents[a].

Entry	Solvent	Yield[b] (%)	Entry	Solvent	Yield[b] (%)
1	None	46	5	CH_2Cl_2	53
2	H_2O	68	6	PhMe	20
3	EtOH	91	7	n-Hexane	Trace
4	CH_3CN	63			

[a] Reaction conditions: $PhNH_2$ (2.1 mmol), PhCHO (2 mmol), $PhCOCH_3$ (2.4 mmol), $CeCl_3·7H_2O$ (0.1 mmol), EtOH (3 mL), time (10 h), r.t.

[b] Isolated yield.

Table 3
Synthesis of β-amino ketone under different conditions[a].

Entry	$PhNH_2$ (mmol)	$PhCOCH_3$ (mmol)	$CeCl_3{\cdot}7H_2O$ (mmol)	Yield[b] (%)	Entry	$PhNH_2$ (mmol)	$PhCOCH_3$ (mmol)	$CeCl_3{\cdot}7H_2O$ (mmol)	Yield[b] (%)
1	1.8	2	0.1	70	8	2.3	2.3	0.1	95
2	2	2	0.1	79	9	2.3	2.4	0.1	92
3	2.1	2	0.1	84	10	2.3	2.3	0	0
4	2.3	2	0.1	85	11	2.3	2.3	0.04	86
5	2.4	2	0.1	81	12	2.3	2.3	0.08	92
6	2.3	1.8	0.1	77	13	2.3	2.3	0.12	95
7	2.3	2.2	0.1	91	14	2.3	2.3	0.2	93

[a] Reaction conditions: PhCHO (2.0 mmol), EtOH (3 mL), time (10 h), r.t.
[b] Isolated yield.

the screened solvent systems, ethanol was the solvent of choice, since in this solvent the Mannich-type reaction proceeded smoothly and afforded the desired adducts in high yields at mild temperature.

In order to optimize the reaction condition, experiments focused on the effect of the amount of aniline and acetophenone were explored (Table 3, entries 1–9). Interestingly, when the amount of aniline or acetophenone was less than benzaldehyde, the reaction gave low yield with formation of enol and imine side products, respectively. The best result was obtained when the ratio of aniline, benzaldehyde and acetophenone was 1.15:1.0:1.15. Thereafter, the effect of amount of $CeCl_3{\cdot}7H_2O$ catalyst on the three-component reaction was also investigated. Generally, there was no reaction in the absence of catalyst, indicating that this was indeed a $CeCl_3{\cdot}7H_2O$-catalyzed reaction and the yield were increased over the amount of catalyst. It was found that 5 mol% of $CeCl_3{\cdot}7H_2O$ (based on benzaldehyde) could effectively catalyze the reaction. No substantial improvement in the yield was found with further increase of the catalyst. Hence, the optimal amount of catalyst was chosen as 5 mol% based on benzaldehyde in the following reactions.

To study the effectiveness of $CeCl_3{\cdot}7H_2O$, we extended the range to a series of anilines and benzaldehydes (Table 4). The yields of products varied depending upon the types and positions of substitutions. The results showed that substituted anilines with both electron-withdrawing and electron-donating groups at the meta and para positions

Table 4
$CeCl_3{\cdot}7H_2O$-catalyzed direct Mannich reaction with acetophenone[a].

Entry	R^1	R^2	Time (h)	Product	Yield [b] (%)	mp (°C)	Ref. Mp (°C)
1	H	H	10	**3a**	95	169–171	168–170 [5a]
2	4-NO_2	H	8	**3b**	96	184–186	184–186 [5b]
3	4-OCH_3	H	14	**3c**	87	165–168	
4	2-CH_3	H	16	**3d**	Trace	–	
5	4-CH_3	H	14	**3e**	88	168–170	165–167 [5a]
6	4-Cl	H	10	**3f**	96	169–170	170–171 [5b]
7	H	4-OCH_3	15	**3g**	92	148–150	147–149 [5a]
8	3-Cl	H	8	**3h**	93	132–134	
9	2-Cl	H	16	**3i**	Trace	–	
10	2-NO_2	H	16	**3j**	0	–	
11	3-COOH	H	14	**3k**	87	162–163	163–164 [5c]
12	4-COOH	H	13	**3l**	92	160–162	162–163 [5c]
13	H	4-NO_2	18	**3m**	86	106–108	107–110 [5d]
14	H	4-Cl	13	**3n**	93	115–117	114–115 [5c]
15	3-Br	4-Cl	3	**3o**	97	122–123	123–124 [5c]
16	2-Cl	4-CH_3	16	**3p**	Trace	–	
17	4-CH_3	4-OH	5	**3q**	98	171–173	172–173 [5c]
18	4-CH_3	4-CH_3	10	**3r**	91	134–135	135–136 [5c]
19	H	4-CH_3	10	**3s**	97	129–130	131–132 [5a]

[a] Reaction conditions: $PhNH_2$ (2.3 mmol), PhCHO (2.0 mmol), $PhCOCH_3$ (2.3 mmol), $CeCl_3{\cdot}7H_2O$ (0.1 mmol), EtOH (3 mL), r.t.
[b] Isolated yield, all products were characterized by comparison of their melting points, MS and ^1H NMR spectra with those of authentic samples.

produced the corresponding β-amino ketones in excellent yields. However, the ortho-substituted anilines generally gave very low yield, even trace of the products. This could be attributed to the steric hindrance caused by ortho group on the approaching electrophilic reagents (as was also claimed by Li and Wang [5c,h]). The effect of substitution related to benzaldehydes was also briefly studied. It was observed that the strong electron-withdrawing groups decrease the yield of products, whereas weak electron-donating groups increase it. This can be explained from the stability of intermediate "$[ArNHCHArR^2]+$": When R^2 owns strong electron-withdrawing capacity, the carbon cation is not easy to form due to its instability; but if R^2 owns strong electron-donating capacity, the reaction activity to participate in the next step reaction is weak due to the high stability of the intermediate.

2. Conclusion

In conclusion, three-component Mannich-type reaction of anilines and benzaldehydes with acetophenone was efficiently catalyzed by $CeCl_3 \cdot 7H_2O$ in ethanol. The noteworthy features of the reported protocol include: (a) simple procedure; (b) air-stable and water-tolerant catalyst; (c) cheap and non-toxic solvent; (d) the reuse of the catalytic system. Furthermore, this protocol is adaptive for synthesis of a diverse set of β-amino ketones.

Acknowledgment

We are grateful for the financial support from Nanjing University of Science and Technology.

References

[1] F. Fringuelli, F. Pizzo, L. Vaccaro, J. Org. Chem. 66 (2001) 4719.
[2] X.S. Fan, Y.Z. Li, Y.M. Zhang, Chin. J. Org. Chem. 25 (2005) 1029.
[3] (a) M. Arend, B. Westermann, N. Risch, Angew. Chem. Int. Ed. 37 (1998) 1044;
  (b) S. Kobayashi, H. Ishitani, Chem. Rev. 99 (1999) 1069;
  (c) M.M.B. Marques, Angew. Chem. Int. Ed. 45 (2006) 348.
[4] (a) A.T. Khan, T. Parvin, L.H. Choudhury, J. Org. Chem. 73 (2008) 8398;
  (b) R. Muller, H. Goesmann, H. Waldmann, Angew. Chem. Int. Ed. 38 (1999) 184;
  (c) W. Notz, F. Tanaka, S.I. Watanabe, J. Org. Chem. 68 (2003) 9624;
  (d) M. Suginome, L. Uehlin, M. Murakami, J. Am. Chem. Soc. 126 (2004) 13196.
[5] (a) M.A. Bigdeli, F. Nemati, G.H. Mahdavinia, Tetrahedron Lett. 48 (2007) 6801;
  (b) L. Yi, H. Lei, J. Zou, Synthesis 9 (1991) 717;
  (c) Z. Li, X. Ma, J. Liu, J. Mol. Catal. A: Chem. 272 (2007) 132;
  (d) T. Akiyama, J. Takaya, H. Kagoshima, Adv. Synth. Catal. 344 (2002) 338;
  (e) W.G. Shou, Y.Y. Yang, Y.G. Wang, Tetrahedron Lett. 47 (2006) 1845;
  (f) T.P. Loh, S.L. Chen, Org. Lett. 4 (2002) 3647;
  (g) L. Ming, J. Han, J. Sheng, Chin. J. Org. Chem. 25 (2005) 591.
[6] General procedure: $CeCl_3 \cdot 7H_2O$ (0.1 mmol) was added to a mixture of anilines (2.3 mmol), benzaldehydes (2.0 mmol) and acetophenone (2.3 mmol) in ethanol (3 mL). The mixture was stirred at room temperature for a certain time (Table 4) and monitored by TLC, then the contents of the flask had solidified. The reaction mixture was cooled in refrigerator for one night. The solid was filtered off and the cake was washed with H_2O. Finally, the crude products were purified by crystallization from ethanol affording **3a**–**3s**. The catalyst-containing ethanol was reused in subsequent runs without further purification. The structures of all the products were unambiguously established on the comparison of their melting points, MS, IR, and ^1H NMR spectra data with those of authentic samples. Selective data: **3a**: m.p. 169–171 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.42 (d, 2H, $J = 4.8$ Hz), 4.95 (t, 1H, $J = 6.1$ Hz), 6.52 (s, 2H), 6.65 (s, 1H), 7.05 (s, 2H), 7.24 (s, 2H), 7.31 (s, 2H), 7.42 (s, 4H), 7.55 (s, 1H), 7.88 (d, 2H, $J = 4.8$ Hz). IR (KBr, ν_{max}): 3200, 1681, 1612, 1511, 1300, 759, 510 cm^{-1}. MS (EI) *m/z* 301 (M^+).