Indian Journal of Chemistry
Vol. 49B, December 2010, pp. 1653-1656

Note

Aluminium nitrate as an efficient and reusable catalyst for the three components one-pot Mannich reaction: Synthesis of β-amino carbonyl compounds

Min Wang*[a], Yan Liang[a] & Zhiguo Song[b]

[a]College of Chemistry and Chemical Engineering, Bohai University, Jinzhou 121000, P. R. China

[b]Center for Science & Technology Experiment, Bohai University, Jinzhou 121000, P. R. China

E-mail: minwangszg@yahoo.com.cn

Received 21 May 2009; accepted (revised) 29 September 2010

Three components one-pot Mannich reaction of aromatic ketones, aromatic aldehydes and aromatic amines has been efficiently catalysed by recyclable aluminium nitrate at ambient temperature to give various β-amino carbonyl compounds in high yields. By simple phase separation, aluminium nitrate could be recycled several times without distinct loss of activity.

Keywords: Mannich reaction, aluminium nitrate, β-amino carbonyl compounds, one-pot synthesis

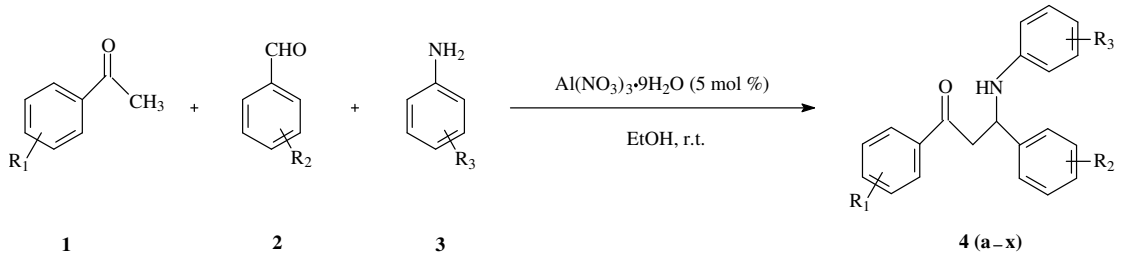
Mannich reactions are one of the most important carbon-carbon bond forming reactions in organic synthesis. They provide β-amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products (ref. 1). The classical synthetic methods rely on the two-component system using preformed electrophiles, such as imines and stable nucleophiles, such as enolates, enol ethers, and enamines (refs. 2-6). But the preferable route is the use of a one-pot three components strategy that allows for a wide range of structural variations. In this context, the development of efficient protocol for one-pot three components Mannich reaction is very valuable.

Recently, a few reported Mannich reactions of aromatic ketones, aromatic aldehydes and aromatic amines have been catalysed by HCl/EtOH (ref. 7), dodecylbenzenesulfonic acid (ref. 8), Ps-SO_3H (ref. 9), $NbCl_5$ (ref. 10), $Re(PFO)_3$ (ref. 11), $Re(OPf)_3$ (ref. 12), ionic liquid (ref. 13), $H_3PW_{12}O_{40}$ (ref. 14), $NaBAr_4^F$ (ref. 15), SiO_2-$OAlCl_2$ (ref. 16), and QAS gemini fluorosurfactant (ref. 17) *etc*. However, most of these methods suffer from drawbacks such as the use of corrosive reagent, expensive and large amount of catalyst, long reaction time, harmful reaction media (fluorous solvent), and low yields. Furthermore, *ortho*-substituted aromatic amines generally gave trace even no products because of large steric hindrance effect. During the course of our studies towards the development of green catalytic processes to synthesize β-amino carbonyl compounds, we found aluminium nitrate ($Al(NO_3)_3{\cdot}9H_2O$) as an inexpensive and commercially available catalyst can efficiently catalyse three components synthesis of β-amino carbonyl compounds via one-pot condensation of aromatic ketones, aromatic aldehydes and aromatic amines in short reaction time (**Scheme I**). After the reaction, $Al(NO_3)_3{\cdot}9H_2O$ could be easily recovered by simple phase separation and could be reused many times without distinct decrease in its catalytic activity. Application of such catalyst will lead to minimal pollution and waste material. To the best of our knowledge, direct Mannich-type reaction catalysed by $Al(NO_3)_3{\cdot}9H_2O$ has not been reported.

Results and Discussion

In order to evaluate the catalytic efficiency of $Al(NO_3)_3{\cdot}9H_2O$, a model reaction was carried out on the synthesis of Mannich base **4a** by the condensation of acetophenone, benzaldehyde and aniline (**Table I**). In the absence of catalyst, the reaction did not proceed (entry 1). Among the tested catalysts, the condensation was best catalysed by 5 mol% $Al(NO_3)_3{\cdot}9H_2O$ (based on aldehyde) in 8 mL EtOH at room temperature (entry 13). It gave the exclusive product **4a** in 85% yield in the shortest reaction time (4 hr). The recycle of $Al(NO_3)_3{\cdot}9H_2O$ was also investigated, and it could be recycled four times without obvious loss of activity (entry 13). The choice of reaction solvent was crucial. The use of CH_3CN furnished poor yield (28%). Other solvents such as THF, CH_2Cl_2, H_2O, and toluene were ineffective for this transformation.

A wide variety of aromatic ketones, aromatic aldehydes and aromatic amines to establish the scope of this catalytic transformation (**Table II**). In all the cases, it was observed that the reactions proceeded smoothly at room temperature. Besides *ortho*-substituted aromatic amine, the aromatic ketones, aromatic aldehydes and aromatic amines bearing both electron



Scheme I

Table I — Mannich reaction of acetophenone, benzaldehyde and aniline catalysed by different catalysts[a]

Entry	Catalyst	Time (hr)	Isolated yield (%)
1	None	30	0
2	HOAc	16	0
3	$ClCH_2COOH$	16	0
4	$Ce(SO_4)_2{\cdot}4H_2O$	16	0
5	$Fe_2(SO_4)_3{\cdot}6H_2O$	16	0
6	$Zn(OAc)_2{\cdot}2H_2O$	16	0
7	$Al_2(SO_4)_3{\cdot}18H_2O$	16	0
8	$CeCl_3{\cdot}7H_2O$	16	52
9	$SnCl_2{\cdot}2H_2O$	16	68
10	$Al(CH_3SO_3)_3{\cdot}4H_2O$	8	84
11	$AlCl_3{\cdot}6H_2O$	5	80
12	$Al(p\text{-}CH_3C_6H_4SO_3)_3$	5	81
13	$Al(NO_3)_3{\cdot}9H_2O$	4	85, 82, 78, 72[b]

[a]Reaction conditions: acetophenone (11 mmoles), benzaldehyde (10 mmoles), aniline (10 mmoles), catalyst (0.5 mmole), EtOH (8 mL), room temperature. [b]Catalyst was reused four times.

donating and electron withdrawing groups underwent this one-pot three components condensation to furnish corresponding Mannich base in high yields within 2-15 hr. Particularly, substituents having weak electron-donating group such as –Cl are favorable for the transformation. *meta*-Substituted and *para*-substituted aromatic amines all gave good results, but *ortho*-substituted aromatic amine afforded corresponding Mannich base in moderate yield after long reaction time because of large steric hindrance (entry **4b**).

In conclusion, we have demonstrated an efficient and environmentally friendly approach for the synthesis of *β*-amino carbonyl compounds *via* one-pot three components condensation of aromatic ketones, aromatic aldehydes and aromatic amines using $Al(NO_3)_3{\cdot}9H_2O$ as a recyclable Lewis acid catalyst. High yields, reduced reaction time, mild reaction condition, easy work-up procedure, inexpensive and commercially available catalyst make this approach as an interesting alternative to the existing methods.

Experimental Section

Melting points were determined by using RY-1 micro melting point apparatus and are uncorrected. Infrared spectra were recorded on Scimitar 2000 series Fourier Transform instrument of Varian. ^{1}H NMR spectra were recorded on Bruker ARX-300 spectrometer in DMSO-d_6 using TMS as an internal standard. Mass spectra were obtained with an Agilent 1100 series LC/MSD VL ESI instrument. Elemental analyses were carried out on EA 2400II elemental analyzer (Perkin-Elmer).

General procedure for the synthesis of β-amino carbonyl compounds, 4: A mixture of aromatic ketone **1** (11 mmoles), aromatic aldehyde **2** (10 mmoles), aromatic amine **3** (10 mmoles) and $Al(NO_3)_3{\cdot}9H_2O$ (0.5 mmole) was stirred in EtOH (8 mL) at room temperature. When the reaction was completed as indicated by TLC, the reaction-mixture was placed at ambient temperature to evaporate EtOH and H_2O, then 60 mL hot CH_2Cl_2 was added to dissolve the solid product. The catalyst was removed by hot filtration and dried for its next use. The organic layer was washed twice with saturated $NaHCO_3$ solution (10 mL), dried (Na_2SO_4), and evaporated to yield the crude product. The crude product was purified via recrystalization from ethanol or ethanol/acetone (v/v=3:2) to give the corresponding pure compound **4**. The pure products were identified by mp, IR, ^{1}H NMR, MS, and elemental analysis.

3-(2-Chlorophenylamino)-3-phenyl-1-phenylpropan-1-one, 4b: White solid; IR (KBr): 3392, 1681, 1594, 1512, 1216 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.55-7.98 (m, 14H, ArH), 5.83 (d, J = 7.8 Hz, 1H, NCH), 5.12 (s, 1H, NH), 3.44 (m, 2H, $COCH_2$); MS (ESI): m/z 336 $(M+H)^+$. Anal. Calcd for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.08; H, 5.40; N, 4.18%.

Table II — $Al(NO_3)_3 \cdot 9H_2O$-catalysed one-pot three components Mannich reaction of aromatic ketone, aromatic aldehyde and aromatic amine[a]

Entry	R_1	R_2	R_3	Isolated Yield/% Time/hr	m.p. °C Found	m.p. °C Reported
4a	H	H	H	85 (4)	166-68	169-70 (ref. 16)
4b	H	H	2-Cl	53 (24)	115-16	-
4c	H	H	3-Cl	88 (2)	134-35	135-37 (ref. 11)
4d	H	H	4-Cl	89 (2)	169-71	170-71 (ref. 16)
4e	H	H	4-CH_3	74 (5)	169-70	167-68 (ref. 10)
4f	H	H	4-OCH_3	65 (9)	123-25	124-25 (ref. 17)
4g	H	H	3-NO_2	80 (10)	141-43	140-42 (ref. 12)
4h	H	H	4-NO_2	75 (10)	180-82	179-80 (ref. 16)
4i	H	H	3-COOH	79 (15)	159-61	162-63 (ref. 11)
4j	H	H	4-COOH	88 (15)	195-97	190-92 (ref. 13)
4k	H	4-Cl	3-Cl	93 (4)	125-27	128-30 (ref. 13)
4l	H	4-NO_2	H	90 (11)	87-88	89-91 (ref. 17)
4m	H	4-NO_2	3-Cl	91 (8)	100-02	-
4n	H	4-NO_2	4-Cl	90 (15)	129-31	-
4o	H	4-OCH_3	H	86 (9)	140-41	142-43 (ref. 16)
4p	4-Cl	H	H	81 (8)	118-19	119-20 (ref. 7)
4q	4-Cl	H	3-Cl	85 (8)	109-11	108-10 (ref. 7)
4r	4-Cl	H	4-Cl	85 (9)	130-32	130-32 (ref. 7)
4s	4-Cl	3-NO_2	H	87 (10)	146-48	152-54 (ref. 18)
4t	4-Cl	3-NO_2	4-Cl	88 (3)	137-39	141-43 (ref. 18)
4u	4-OCH_3	H	H	85 (15)	137-39	-
4v	4-OCH_3	H	4-Cl	84 (8)	174-75	-
4w	4-OCH_3	3-NO_2	4-Cl	98 (9)	124-26	-
4x	4-NO_2	H	4-Cl	94 (7)	144-46	-

[a]The structures of all the products were characterized by m.p., IR, ^{1}H NMR, MS and elemental analysis. The physical and spectroscopic data of our known samples were identical with those reported in the literatures.

3-(3-Chlorophenylamino)-3-(4-nitrophenyl)-1-phenylpropan-1-one, 4m: Yellow solid; IR (KBr): 3408, 1678, 1598, 1515, 1414 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.52-8.19 (m, 13H, ArH), 6.46 (d, J = 7.2 Hz, 1H, NCH), 5.16 (s, 1H, NH), 3.41 (m, 2H, $COCH_2$); MS (ESI): m/z 381 $(M+H)^+$. Anal. Calcd for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.35. Found: C, 66.21; H, 4.49; N, 7.36%.

3-(4-Chlorophenylamino)-3-(4-nitrophenyl)-1-phenylpropan-1-one, 4n: Yellow solid; IR (KBr): 3395, 1673, 1599, 1512, 1224 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.03-8.20 (m, 11H, ArH), 6.58 (d, J = 7.2 Hz, 1H, NCH), 6.51 (d, J = 9.0 Hz, 2H, ArH), 5.12 (s, 1H, NH), 3.40 (m, 2H, $COCH_2$); MS (ESI): m/z 380 (M^+). Anal. Calcd for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.35. Found: C, 66.21; H, 4.49; N, 7.36%.

3-Phenylamino-3-phenyl-1-(4-methoxyphenylpropan)-1-one, 4u: White solid; IR (KBr): 3382, 1657, 1600, 1512, 1259 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.57-7.93 (m, 14H, ArH), 5.09 (d, J = 7.2 Hz, 1H, NCH), 4.97 (s, 1H, NH), 3.86 (s, 3H, OCH_3), 3.41 (m, 2H, $COCH_2$); MS (ESI): m/z 331 (M^+). Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.70; H, 6.39; N, 4.24%.

3-(4-Chlorophenylamino)-3-phenyl-1-(4-methoxyphenylpropan)-1-one, 4v: White solid; IR (KBr): 3379, 1657, 1601, 1512, 1267 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.46-7.91 (m, 13H, ArH), 4.98 (d, J = 7.8 Hz, 1H, NCH), 4.90 (s, 1H, NH), 3.86 (s, 3H, OCH_3), 3.40 (m, 2H, $COCH_2$); MS (ESI): m/z 365 (M^+). Anal. Calcd for $C_{22}H_{20}ClNO_2$: C, 72.22; H, 5.51; N, 3.83. Found: C, 72.24; H, 5.50; N, 3.83%.

3-(4-Chlorophenylamino)-3-(3-nitrophenyl)-(4-methoxyphenylpropan)-1-one, 4w: White solid; IR (KBr): 3369, 1661 1598, 1534, 1267 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.45-8.29 (m, 12H, ArH),

5.03 (d, J = 7.2 Hz, 1H, NCH), 4.98 (s, 1H, NH), 3.86 (s, 3H, OCH_3), 3.47 (m, 2H, $COCH_2$); MS (ESI): m/z 410 (M^+). Anal. Calcd for $C_{22}H_{19}ClN_2O_4$: C, 64.31; H, 4.66; N, 6.82. Found: C, 64.29; H, 4.66; N, 6.83%.

3-(4-Chlorophenylamino)-3-phenyl-1-(4-nitrophenylpropan)-1-one, 4x: Yellow solid; IR (KBr): 3412, 1689, 1598, 1515, 1270 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 6.50-8.34 (m, 13H, ArH), 6.46 (d, J = 7.2 Hz, 1H, NCH), 4.95 (s, 1H, NH), 3.42 (m, 2H, $COCH_2$); MS (ESI): m/z 379 $(M-H)^+$. Anal. Calcd for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.35. Found: C, 66.25; H, 4.50; N, 7.34%.

References

1 Arend M, Westermann B & Risch N, *Angew Chem Int Ed (Engl)* , 37, **1998**, 1044.

2 Matsunaga S, Kumagai N, Harada S & Shibasaki M, *J Am Chem Soc*, 125, **2003**, 4712.

3 Trost B M & Terrell L R, *J Am Chem Soc*, 125, **2003**, 338.

4 Akiyama T, Takaya J & Kagoshima H, *Adv Synth Catal*, 344, **2002**, 338.

5 Kobayashi S, Hamada T & Manabe K, *J Am Chem Soc*, 124, **2002**, 5640.

6 Cobb A J A, Shaw D M, Longbottom D A, Gold J B & Ley S V, *Org Biomol Chem,* 3, **2005**, 84.

7 Yi L, Lei H S, Zou J H & Xu X J, *Synthesis,* **1991,** 717.

8 Manabe K & Kobayashi S, *Org Lett* 1, **1999,** 1965.

9 Iimura S, Nobutou D, Manabe K & Kobayashi S, *Chem Commun*, **2003**, 1644.

10 Wang R, Li B G, Huang T K, Shi L & Lu X X, *Tetrahedron Lett*, 48, **2007**, 2071.

11 Wang L M, Han J W, Sheng J, Tian H & Fan Z Y, *Catal Commun,* 6, **2005,** 201.

12 Yi W B & Cai C, *J Fluorine Chem,* 127, **2006,** 1515.

13 Li J Z, Peng Y Q & Song G H, *Catal Lett,* 102, **2005**, 159.

14 Azizi N, Torkiyan L & Saidi M R, *Org Lett,* 8, **2006**, 2079.

15 Chang C T, Liao B S & Liu S T, *Tetrahedron Lett,* 47, **2006,** 9257.

16 Li Z, Ma X L, Liu J, Feng X, Tian G Q & Zhu A G, *J Mol Catal A: Chem,* 272, **2007,** 132.

17 Shen W, Wang L M & Tian H, *J Fluorine Chem,* 129, **2008,** 267.

18 Zhou J H, *Chin J Org Chem,* 16, **1996,** 218.