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Three-Component Mannich Reaction of Aromatic Ketones, Aldehydes and Amines Catalyzed by Reusable Aluminium Methanesulfonate

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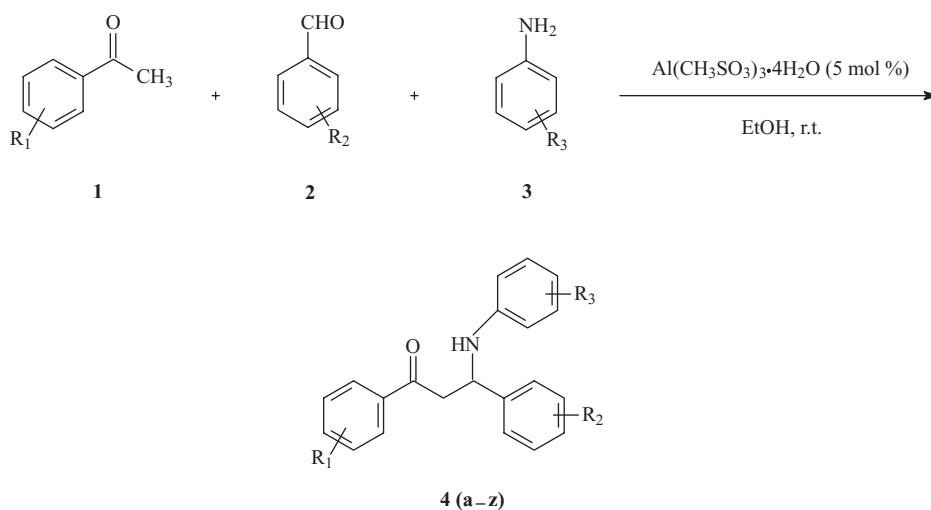
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Mannich type reactions are very important carbon-carbon bond forming reactions in organic synthesis and one of the most useful methods for the preparation of β -aminocarbonyl compounds, which are valuable synthetic intermediates for pharmaceuticals and natural products.¹ Among the three-component reactions, the Mannich processes have elicited enormous interest and several procedures for the synthesis of β -aminocarbonyl compounds have been widely described in the literature.² Earlier literature reported that β -aminocarbonyl compounds derived from aromatic ketones, aldehydes and amines can only be realized indirectly by “amine exchange reaction” or “the addition of ketones to Schiff bases”.^{3,4} Yi and co-workers described the three-component Mannich reaction of aromatic ketones, aldehydes and amines could be catalyzed by HCl/EtOH in 1991.⁵ Since then, the Mannich reaction has been expanded to include various ketones, aldehydes and amines using HCl/EtOH.⁶ However, the hydrochloride salts of the Mannich bases using HCl/EtOH are unstable on standing.⁵ Furthermore, hydrochloric acid is environmentally unfriendly. Therefore, more practical synthetic methods for these multiply-substituted Mannich bases have been reported, using dodecylbenzenesulfonic acid,⁷ polystyrene-SO₃H,⁸ NbCl₅,⁹ Re(PFO)₃,¹⁰ Re(OPf)₃,¹¹ an acidic ionic liquid,¹² H₃PW₁₂O₄₀,¹³ NaBAR₄^F,¹⁴ SiO₂-OAlCl₂,¹⁵ QAS gemini fluorosurfactant,¹⁶ *etc.* However, several drawbacks such as large excesses of catalyst, expensive reagents, long reaction time, and low yields still exist. Moreover, the Mannich reaction of *ortho*-substituted aromatic amine gave none of desired product due to steric effects. In addition, conventional Lewis acid cannot be used because of the presence of free amines and water produced in the imine formation. Thus, from atom-economy and environmental standpoints, it is desirable to develop a new efficient system for the direct one-pot Mannich reaction.

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Recently, the use of methanesulfonates as Lewis acid catalysts has been well documented.^{17–20} Properties such as low toxicity, moisture and air stability, and their recyclability make them attractive alternatives to conventional Lewis acids. As a part of our studies to explore the utility of methanesulfonates, we found that aluminium methanesulfonate ($\text{Al}(\text{CH}_3\text{SO}_3)_3 \cdot 4\text{H}_2\text{O}$) can catalyze the one-pot three-component Mannich reaction of aromatic ketones, aldehydes and amines efficiently at ambient temperature (*Scheme 1*).



Scheme 1

First, we compared the catalytic activity of $\text{Al}(\text{CH}_3\text{SO}_3)_3 \cdot 4\text{H}_2\text{O}$ with other protic acids and Lewis acids in the model condensation of acetophenone, benzaldehyde and aniline (*Table 1*). Screening of different catalysts revealed that $\text{Al}(\text{CH}_3\text{SO}_3)_3 \cdot 4\text{H}_2\text{O}$ was the most effective catalyst for this transformation since it resulted in the highest conversion to the desired product. Some traditional Lewis acids such as $\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$, $\text{Fe}_2(\text{SO}_4)_3 \cdot 6\text{H}_2\text{O}$, $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ and $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ did not furnish the product **4a** at all. The recyclability of $\text{Al}(\text{CH}_3\text{SO}_3)_3 \cdot 4\text{H}_2\text{O}$ was also investigated, and it could be recycled four times without any loss of activity (*Table 1*, Entry 10). Encouraged by above results, the effect of solvents on the yield of acetophenone, benzaldehyde and aniline was investigated (*Table 2*). EtOH provided excellent yield and proved to be the choice, whereas CH_3CN afforded lower yield. The reactions carried out in THF, toluene, CH_2Cl_2 , Et_2O , cyclohexane, and H_2O all failed to yield any product.

Next, we determined for the optimized reaction conditions using the same model reaction. The effect of different molar ratio of reactants, amount of catalyst, and solvent on the yields was studied. The best result (86% yield) was obtained by carrying out the reaction with 1.1:1:1 molar ratio of acetophenone, benzaldehyde, aniline at ambient temperature in the presence of 5 mol% (based on benzaldehyde) of $\text{Al}(\text{CH}_3\text{SO}_3)_3 \cdot 4\text{H}_2\text{O}$ in 5 mL EtOH for 8 h. The amount of catalyst affected the reaction significantly. We observed that 5 mol% $\text{Al}(\text{CH}_3\text{SO}_3)_3 \cdot 4\text{H}_2\text{O}$ could catalyze the reaction efficiently and increasing the amount of catalyst did not lead to better yields.

Table 1
Mannich Reaction of Acetophenone, Benzaldehyde and Aniline Catalyzed by Different Catalysts^a

Entry	Catalyst	Time (h)	Isolated yield (%)
1	None	30	0
2	HOAc	16	0
3	ClCH ₂ COOH	16	0
4	Ce(SO ₄) ₂ ·4H ₂ O	16	0
5	Fe ₂ (SO ₄) ₃ ·6H ₂ O	16	0
6	Zn(OAc) ₂ ·2H ₂ O	16	0
7	CeCl ₃ ·7H ₂ O	16	56
8	SnCl ₂ ·2H ₂ O	16	71
9	Al ₂ (SO ₄) ₃ ·18H ₂ O	8	0
10	Al(CH ₃ SO ₃) ₃ ·4H ₂ O	8	86, 82, 76, 70 ^b

^aReaction conditions: acetophenone (11 mmol), benzaldehyde (10 mmol), aniline (10 mmol), catalyst (0.5 mmol), EtOH (5 mL), room temperature.

^bCatalyst was reused four times.

Using these optimized reaction conditions, the one-pot three-component Mannich reactions of various aromatic ketones, aldehydes and amines were investigated and the results are shown in Table 3. In all cases except entry **4b**, the reactions proceeded smoothly within 0.5–20 h and good yields (82–99%) of β -aminocarbonyl compounds were obtained. Aromatic aldehydes and aromatic amines carrying either electron-withdrawing or electron-donating groups were all suitable to the reactions. The position of *meta*-substituent or

Table 2
Al(CH₃SO₃)₃·4H₂O-catalyzed Mannich Reaction of Acetophenone, Benzaldehyde and Aniline in Different Solvents^a

Entry	Solvent	Isolated Yield (%)
1	EtOH	86
2	CH ₃ CN	25
3	THF	0
4	Toluene	0
5	CH ₂ Cl ₂	0
6	Et ₂ O	0
7	Cyclohexane	0
8	H ₂ O	0
9	None	0

^aReaction conditions: acetophenone (11 mmol), benzaldehyde (10 mmol), aniline (10 mmol), Al(CH₃SO₃)₃·4H₂O (0.5 mmol), solvent (5 mL), room temperature, 8 h.

Table 3

Al(CH₃SO₃)₃·4H₂O-catalyzed One-pot Three-component Mannich Reaction of Aromatic Ketones, Aldehydes and Amines^a

Entry	R ₁	R ₂	R ₃	Time (h)	Yield (%) ^b	mp. (°C)	lit. mp. (°C)
4a	H	H	H	8	86	169–170	169–170 ¹⁵
4b	H	H	2-Cl	24	50	115–116	—
4c	H	H	3-Cl	7	90	130–131	135–137 ¹⁰
4d	H	H	3-NO ₂	10	93	140–142	140–142 ¹¹
4e	H	H	4-CH ₃	7	86	163–166	167–168 ⁹
4f	H	H	3-COOH	20	87	159–161	162–163 ¹⁰
4g	H	H	4-COOH	13	92	193–195	190–192 ²¹
4h	H	H	4-OCH ₃	12	87	127–129	124–125 ¹⁶
4i	H	4-Cl	H	7	97	109–111	114–115 ¹⁵
4j	H	4-Cl	3-Cl	3	92	119–122	128–130 ²¹
4k	H	4-Cl	4-Cl	10	98	121–123	118–119 ¹⁵
4l	H	4-Cl	4-CH ₃	8	90	112–114	118–119 ²¹
4m	H	4-Cl	4-COOH	12	94	162–165	159–160 ¹⁵
4n	H	4-NO ₂	H	8	95	80–82	89–91 ¹⁶
4o	H	4-NO ₂	3-Cl	20	91	99–102	—
4p	H	4-NO ₂	4-COOH	0.5	87	190–192	—
4q	H	3-NO ₂	4-Cl	8	90	155–156	153–155 ²²
4r	H	4-OCH ₃	H	10	90	137–139	142–143 ¹⁵
4s	H	4-OCH ₃	3-Cl	2	99	117–119	116–118 ⁶
4t	H	4-OCH ₃	4-CH ₃	15	86	153–155	160–161 ¹²
4u	4-Cl	H	H	14	87	115–116	119–120 ⁶
4v	4-Cl	H	3-Cl	14	87	109–110	108–110 ⁶
4w	4-Cl	H	4-Cl	13	82	128–130	130–132 ⁶
4x	4-Cl	H	4-CH ₃	13	87	135–137	141–142 ⁶
4y	4-Cl	3-NO ₂	4-Cl	10	95	136–138	141–143 ²²
4z	4-NO ₂	H	4-Cl	12	92	146–148	—

^aThe structures of all the products were characterized by mp., ¹H NMR, IR, MS and elemental analysis. The physical and spectroscopic data of our known samples were identical with those reported in the literatures.

^bIsolated yields.

para-substituent on the aromatic ring shows little effects on this conversion. One of the outstanding advantages of this method is its efficiency for the conversion of *ortho*-substituted aromatic amine to the corresponding Mannich base in moderate yield (Entry **4b**), a reaction that generally fails to yield any product in the presence of the previously reported catalysts because of steric hindrance. In addition, 4-chloroacetophenone and 4-nitroacetophenone were also used and provided good yields.

In summary, a novel procedure for one-pot three-component Mannich reactions of aromatic ketones, aldehydes and amines have been developed. It is notable that the catalyst

is easy to prepare, stable and storable, easily recycled and reused without substantial loss of catalytic activity, which make them attractive and environmental friendly. This approach could make a valuable contribution to the existing processes in the field of β -aminocarbonyl compounds synthesis.

Experimental Section

Melting points were determined using RY-1 micromelting point apparatus and are uncorrected. Infrared spectra were recorded on Scimitar 2000 series Fourier Transform instrument of VARIAN. ^1H NMR spectra were determined on Bruker ARX-600 spectrometer in $\text{DMSO-}d_6$ 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).

Representative Procedure for the Synthesis of 4

A mixture of aromatic ketone **1** (11 mmol), aromatic aldehyde **2** (10 mmol), aromatic amine **3** (10 mmol) and 0.192 g $\text{Al}(\text{CH}_3\text{SO}_3)_3 \cdot 4\text{H}_2\text{O}$ (5 mol%) was stirred in EtOH (5 mL) at room temperature. When the reaction was completed as indicated by TLC, the reaction mixture was allowed to evaporate at ambient temperature, then 60 mL hot CH_2Cl_2 was added to dissolve the solid product. The catalyst was removed by hot gravity filtration and dried for its next use. The organic filtrate 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 by recrystallization from ethanol or ethanol/acetone ($v/v = 3:2$) to give the corresponding pure compound **4**. The pure products were identified by their mp., IR, ^1H 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} ; ^1H NMR (600 MHz, $\text{DMSO-}d_6$): δ 3.44 (dd, $J = 4.2, 4.2$ Hz, 1H, COCH_2), 3.98 (dd, $J = 8.4, 8.4$ Hz, 1H, COCH_2), 5.12 (s, 1H, NH), 5.83 (d, $J = 7.8$ Hz, 1H, NCH), 6.55 (t, $J = 7.8$ Hz, 1H, ArH), 6.61 (d, $J = 8.4$ Hz, 1H, ArH), 7.01 (t, $J = 8.4$ Hz, 1H, ArH), 7.22 (dd, $J = 7.8, 7.2$ Hz, 2H, ArH), 7.31 (t, $J = 12.0$ Hz, 2H, ArH), 7.53–7.48 (m, 4H, ArH), 7.65 (t, $J = 7.2$ Hz, 1H, ArH), 7.98 (d, $J = 7.8$ Hz, 2H, ArH); MS (ESI): m/z 336 ($\text{M}+\text{H}$) $^+$.

Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{ClNO}$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.08; H, 5.40; N, 4.18.

3-(3-Chlorophenylamino)-3-(4-nitrophenyl)-1-phenylpropan-1-one (4o), yellow solid. IR (KBr): 3408, 1679, 1598, 1515, 1414 cm^{-1} ; ^1H NMR (600 MHz, $\text{DMSO-}d_6$): δ 3.41 (dd, $J = 4.2, 4.2$ Hz, 1H, COCH_2), 3.72 (dd, $J = 9.0, 9.0$ Hz, 1H, COCH_2), 5.16 (s, 1H, NH), 6.46 (d, $J = 7.2$ Hz, 1H, NCH), 6.52 (d, $J = 7.8$ Hz, 2H, ArH), 6.71 (d, $J = 7.2$ Hz, 1H, ArH), 7.17 (t, $J = 8.4$ Hz, 1H, ArH), 7.54 (t, $J = 8.4$ Hz, 2H, ArH), 7.66 (t, $J = 7.2$ Hz, 1H, ArH), 7.77 (d, $J = 9.0$ Hz, 2H, ArH), 7.98 (d, $J = 7.2$ Hz, 2H, ArH), 8.19 (d, $J = 9.0$ Hz, 2H, ArH); MS (ESI): m/z 381 ($\text{M}+\text{H}$) $^+$.

Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{ClN}_2\text{O}_3$: C, 66.23; H, 4.50; N, 7.35. Found: C, 66.21; H, 4.49; N, 7.36.

3-(4-Carboxylphenylamino)-3-(4-nitrophenyl)-1-phenylpropan-1-one (4p), pale yellow solid. IR (KBr): 3389, 1661, 1600, 1519, 1124 cm^{-1} ; ^1H NMR (600 MHz, DMSO- d_6): δ 3.45 (dd, $J = 4.8, 4.8$ Hz, 1H, COCH₂), 3.78 (dd, $J = 9.0, 9.0$ Hz, 1H, COCH₂), 5.24 (s, 1H, NH), 6.55 (d, $J = 9.0$ Hz, 2H, ArH), 7.13 (d, $J = 7.2$ Hz, 1H, NCH), 7.55 (t, $J = 7.8$ Hz, 2H, ArH), 7.61 (d, $J = 9.0$ Hz, 2H, ArH), 7.66 (t, $J = 7.2$ Hz, 1H, ArH), 7.76 (d, $J = 9.0$ Hz, 2H, ArH), 7.99 (d, $J = 7.2$ Hz, 2H, ArH), 8.21 (d, $J = 9.0$ Hz, 2H, ArH), 8.43 (s, 1H, COOH); MS (ESI): m/z 389 (M-H)⁺.

Anal. Calcd for C₂₂H₁₈N₂O₅: C, 67.68; H, 4.65; N, 7.17; Found C, 67.66; H, 4.66; N, 7.17.

3-(4-Chlorophenylamino)-3-phenyl-1-(4-nitrophenylpropan)-1-one (4z), yellow solid. IR (KBr): 3412, 1689, 1598, 1515, 1270 cm^{-1} ; ^1H NMR (600 MHz, DMSO- d_6): δ 3.42 (dd, $J = 4.2, 4.2$ Hz, 1H, COCH₂), 3.71 (dd, $J = 9.0, 9.0$ Hz, 1H, COCH₂), 4.95 (s, 1H, NH), 6.46 (d, $J = 7.2$ Hz, 1H, NCH), 6.50 (d, $J = 8.4$ Hz, 2H, ArH), 7.01 (t, $J = 7.2$ Hz, 2H, ArH), 7.22 (t, $J = 7.2$ Hz, 1H, ArH), 7.32 (t, $J = 7.2$ Hz, 2H, ArH), 7.45 (d, $J = 7.2$ Hz, 2H, ArH), 8.20 (d, $J = 7.2$ Hz, 2H, ArH), 8.34 (d, $J = 7.2$ Hz, 2H, ArH); MS (ESI): m/z 379 (M-H)⁺.

Anal. Calcd for C₂₁H₁₇ClN₂O₃: C, 66.23; H, 4.50; N, 7.35; Found C, 66.25; H, 4.50; N, 7.34.

References

1. M. Tramontini, *Synthesis*, 703 (1973).
2. M. Syamala, *Org. Prep. Proced. Int.*, **37**, 103 (2005); **41**, 1 (2009).
3. A. H. Blatt and N. Gross, *J. Org. Chem.*, **29**, 3306 (1964).
4. J. C. Craig, M. Moyle and L. F. Johnson, *J. Org. Chem.*, **29**, 410 (1964).
5. L. Yi, H. S. Lei, J. H. Zou and X. J. Xu, *Synthesis*, 717 (1991).
6. J. H. Zou, *Org. Prep. Proced. Int.*, **28**, 618 (1996).
7. K. Manabe and S. Kobayashi, *Org. Lett.*, **1**, 1965 (1999).
8. S. Iimura, D. Nobutou, K. Manabe and S. Kobayashi, *Chem. Commun.*, 1644 (2003).
9. R. Wang, B. G. Li, T. K. Huang, L. Shi and X. X. Lu, *Tetrahedron Lett.*, **48**, 2071 (2007).
10. L. M. Wang, J. W. Han, J. Sheng, H. Tian and Z. Y. Fan, *Catal. Commun.*, **6**, 201 (2005).
11. W. B. Yi and C. Cai, *J. Fluorine Chem.*, **127**, 1515 (2006).
12. D. Fang, J. Luo, X. L. Zhou and Z. L. Liu, *Catal. Lett.*, **116**, 76 (2007).
13. N. Azizi, L. Torkiyan and M. R. Saidi, *Org. Lett.*, **8**, 2079 (2006).
14. C. T. Chang, B. S. Liao and S. T. Liu, *Tetrahedron Lett.*, **47**, 9257 (2006).
15. Z. Li, X. L. Ma, J. Liu, X. Feng, G. Q. Tian and A. G. Zhu, *J. Mol. Catal. A: Chem.*, **272**, 132 (2007).
16. W. Shen, L. M. Wang and H. Tian, *J. Fluorine Chem.*, **129**, 267 (2008).
17. M. Wang, Z. C. Wang, Z. L. Sun and H. Jiang, *React. Kinet. Catal. Lett.*, **84**, 223 (2005).
18. M. Wang, Z. C. Wang, Z. L. Sun and H. Jiang, *Transition Met. Chem.*, **30**, 792 (2005).

19. M. Wang, H. Gong, H. Jiang and Z. C. Wang, *Synth. Commun.*, **36**, 1953 (2006).
20. M. Wang, Z. G. Song, H. Gong and H. Jiang, *Chin. Chem. Lett.*, **18**, 799 (2007); *Chin. Chem. Lett.*, **149**, 355199.
21. J. Z. Li, Y. Q. Peng and G. H. Song, *Catal. Lett.*, **102**, 159 (2005).
22. J. H. Zhou, *Chin. J. Org. Chem.*, **16**, 218 (1996); *Chem. Abstr.*, **149**, 355199 (2007).