Ethane-1,2-diaminium hydrogen sulfate: recyclable organocatalyst for one-pot synthesis of β-amino ketones by a three-component Mannich reaction

Kiumars Bahrami[a,b]*, Mohammad Mehdi Khodaei[a,b], Masoumeh Mohammadi[a] and Nasrin Babajani[a]

[a]*Department of Chemistry, Razi University, Kermanshah 67149-67346, Iran*

[b]*Nanoscience and Nanotechnology Research Center (NNRC), Razi University, Kermanshah, 67149-67346, Iran*

Ethane-1,2-diaminium hydrogen sulfate was synthesised and characterised by NMR and elemental analysis techniques, and found to exhibit high catalytic efficiency towards one-pot Mannich-type reactions of ketones with aromatic aldehydes and aromatic amines in ethanol. This method has the advantages of mild conditions, availability of starting materials, compatibility with a variety of functionalities, and simple work-up procedures. This catalyst also shows good recyclability and reusability.

Keywords: Mannich reaction, β-amino ketones, ethane-1,2-diaminium hydrogen sulfate

With new pharmacological targets continuously being discovered, novel biologically active leads are urgently needed, resulting in a search for techniques capable of providing many medicinally interesting compounds.

Mannich-type reactions are one of the most classical and useful methods for the preparation of β-amino ketones and aldehydes, which constitute various pharmaceuticals, natural products, and versatile synthetic intermediates.[1–4]

The catalysts traditionally used in the direct Mannich reactions of aldehydes, ketones and aryl amines are Lewis acids[5–8] and Brønsted acids.[9–12] Although other catalysts such as proline,[13] Brønsted ionic liquids,[14–17] and rare earth perfluorooctanoates[18–19] have also been used for this purpose. However, in most cases these protocols use hazardous organic solvents, have long reaction times with low yields, and use large amounts of catalysts. Toxicity and difficulties in separating conventional catalysts from the product are coupled with poor selectivity are other important issues. Owing to the versatile biological activity of β-amino ketones, development of an alternative synthetic methodology is of importance.

In continuation of our research programme to develop selective and efficient methods in organic synthesis,[20–22] we describe here an eco-friendly and economical approach to direct Mannich reactions catalysed by ethane-1,2-diaminium hydrogen sulfate (EDAHS) as a new acidic organic catalyst (Scheme 1).

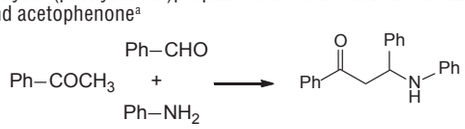
In order to optimise the reaction conditions, the condensation of benzaldehyde and aniline with acetophenone was studied as a model reaction in the presence of varying amounts of EDAHS in EtOH at room temperature. It was found that, using benzaldehyde (1 mmol), aniline (1 mmol), acetophenone (1 mmol) and EDAHS (0.1 mmol) in EtOH, the reaction proceeded very cleanly at room temperature and the corresponding β-amino ketone was obtained in 95% yield (Table 1, entry 4).

Lower loadings of the catalyst gave a low yield even after a prolonged reaction time, whilst higher loadings did not cause any obvious increase in the yield of product but could shorten the reaction time.

In addition, high temperatures improved the reaction rate and shortened the reaction time but favoured side reactions. It was found that room temperature was most suitable for the reaction. Although the reaction in water afforded the desired product, the yield was only moderate because of the low solubility of aldehydes, ketones and amines in water.

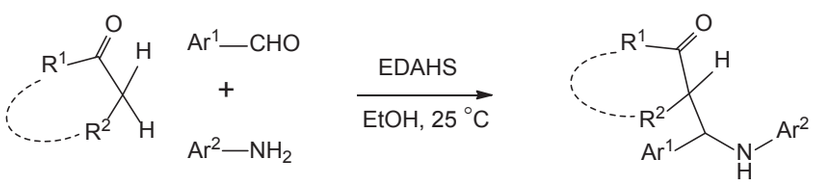
The activity of the recycled catalyst was also examined under the optimised conditions. Thus, after the first run, which gave

Table 1 Effect of increasing amount of EDAHS on synthesis of 1,3-diphenyl-3-(phenylamino)propan-1-one from reaction of benzaldehyde, aniline and acetophenone[a]



Entry	EDAHS/mmol	Yield/%[b]
1	0.005	Trace
2	0.07	70
3	0.09	85
4	0.1	95

[a]Reaction conditions: The reactions were performed with benzaldehyde (1 mmol), aniline (1 mmol) and acetophenone (1 mmol) for 22 min in EtOH at room temperature.
[b]Isolated yield.



EDAHS = Ethane-1,2-diaminium hydrogen sulfate

$H_3\overset{+}{N}CH_2CH_2\overset{+}{N}H_3 .\ 2HSO_4^-$

4a-k R^1 = aryl, R^2 = H
4l-p R^1-R^2 = -$(CH_2)_4$-

Scheme 1 EDAHS catalysed Mannich reaction of ketones, aryl aldehydes and aryl amines.

* Correspondent. E-mail: kbahrami2@hotmail.com

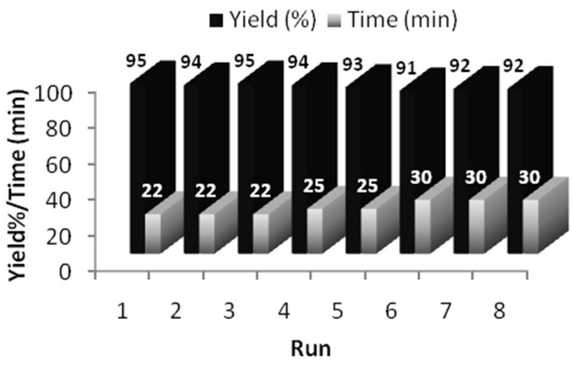


Fig. 1 Recyclability of EDAHS for the preparation of 1,3-diphenyl-3-(phenylamino)propan-1-one.

the desired β-amino ketone in 95% yield, the recovered catalyst was subjected to a second Mannich-type reaction from which it gave the desired product in 94% yield; the average isolated yield for eight consecutive runs was 93%, which clearly demonstrates the practical recyclability of this catalyst (Fig. 1).

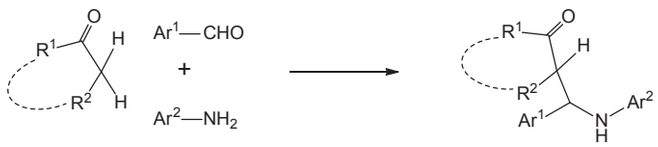
The results for the preparation of β-amino ketones are summarised in Table 2. As shown, a wide variety of structurally diverse β-amino ketones were synthesised with EDAHS according to optimised reaction conditions. In order to show the generality and scope of the new protocol, various aromatic aldehydes with either electron-withdrawing or electron-donating groups were tested. It is clear that the aldehydes react readily to generate the products in very good yields. In the present investigation, the aldehydes with electron-withdrawing groups showed slightly higher reactivity than the aldehydes with electron-donating groups (Table 2, entries 13 and 16). Aromatic amines bearing *p*-Me, *p*-Cl, and *p*-NO_2 groups were favourable to the reactions. Moreover, aromatic amines with electron-donating groups were significantly more nucleophilic and thus determined the reaction rate. Various acetophenones bearing different substituents such as *p*-Cl and *p*-NO_2 were all suitable for the reactions. Furthermore, acetophenone was less reactive than cyclohexanone and required longer reaction times to afford the desired products (Table 2, entries 12–16).

^{1}H NMR spectroscopy of the products indicated that these substrates were converted into the corresponding β-amino ketones without undergoing further structural changes in their functional groups. For example, amino, nitro, halo, and hydroxy functional groups were compatible with the reaction conditions. In the case of β-amino-cyclohexanones, the stereochemistry was determined by ^{1}H NMR analysis and by comparison with known compounds. The reaction proceeded smoothly to afford the Mannich condensation products in excellent yield with the *anti*-isomer as the major product. Unfortunately, it was observed that the catalyst system had no catalytic activity for the reactions when aliphatic aldehydes (such as butyraldehyde) and aliphatic amines (such as propylamine) were used as substrates.

A comparison of the catalytic efficiency of EDAHS with selected, previously known catalysts is shown in Table 3 to demonstrate that the present protocol is indeed superior to several of the existing protocols.

In conclusion, we have shown that EDAHS can promote the preparation of a variety of β-amino ketones from ketones, aryl aldehydes, and amines. Although the literature reports a number of procedures for the preparation of β-amino ketones, the excellent yields, simplicity, good availability of starting materials, compatibility with a variety of functionalities and ease of isolation of the products make our procedure a practical alternative. This procedure also overcomes the formation of unwanted by-products and should open new possibilities for medicinal chemistry and material science applications.

Table 2 Direct Mannich-type reaction of aromatic aldehydes, anilines, and ketones[a]



Entry	Ketone	Aldehyde	Amine	Product	Time/min (Yield/%)[b]	*Anti*/*syn*[c]	M.p./°C	Lit. m.p./°C
1	$C_6H_5COCH_3$	C_6H_5CHO	$C_6H_5NH_2$	**4a**	22 (95)	–	169–170[19]	170–171[19]
2	$C_6H_5COCH_3$	4-MeC_6H_4CHO	4-$MeC_6H_5NH_2$	**4b**	10 (90)	–	132–134[6]	134–135[6]
3	$C_6H_5COCH_3$	4-MeC_6H_4CHO	$C_6H_5NH_2$	**4c**	22 (92)	–	130–132[19]	131–132[19]
4	$C_6H_5COCH_3$	4-$MeOC_6H_4CHO$	$C_6H_5NH_2$	**4d**	24 (90)	–	148–149[6]	148–150[6]
5	$C_6H_5COCH_3$	4-$MeOC_6H_4CHO$	4-$ClC_6H_5NH_2$	**4e**	25 (93)	–	156–158[7]	158–160[7]
6	$C_6H_5COCH_3$	4-$Me_2NC_6H_4CHO$	4-$ClC_6H_5NH_2$	**4f**	28 (86)	–	149–151[8]	149–150[8]
7	$C_6H_5COCH_3$	4-ClC_6H_4CHO	4-$ClC_6H_5NH_2$	**4g**	23 (90)	–	119–120[8]	118–119[8]
8	$C_6H_5COCH_3$	4-ClC_6H_4CHO	4-$O_2NC_6H_5NH_2$	**4h**	27 (89)	–	147–148[8]	149–150[8]
9	4-$ClC_6H_4COCH_3$	4-MeC_6H_4CHO	4-$ClC_6H_5NH_2$	**4i**	21 (91)	–	146–148[7]	146–147[7]
10	4-$ClC_6H_4COCH_3$	C_6H_5CHO	$C_6H_5NH_2$	**4j**	19 (95)	–	117–118[7]	119–120[7]
11	4-$O_2NC_6H_4COCH_3$	C_6H_5CHO	$C_6H_5NH_2$	**4k**	18 (93)	–	114–115[7]	114–116[7]
12	Cyclohexanone	C_6H_5CHO	$C_6H_5NH_2$	**4l**	14 (90)	75/25	137–138[18]	139–140[18]
13	Cyclohexanone	4-$MeOC_6H_4CHO$	4-$ClC_6H_5NH_2$	**4m**	20 (89)	80/20	131–133[18]	133–134[18]
14	Cyclohexanone	4-HOC_6H_4CHO	$C_6H_5NH_2$	**4n**	17 (88)	70/30	191–193[27]	191–191.7[23]
15	Cyclohexanone	4-MeC_6H_4CHO	4-$ClC_6H_4NH_2$	**4o**	20 (90)	79/21	104–106[27]	105.3–105.9[23]
16	Cyclohexanone	3-$O_2NC_6H_4CHO$	$C_6H_5NH_2$	**4p**	12 (87)	80/20	164–165[28]	163–165[24]

[a]The products were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures.
[b]Yields refer to pure isolated products.
[c]*Anti*/*syn*-ratio measured by ^{1}H NMR spectroscopy analysis of the crude reaction mixture.

Table 3 Comparison of some of the results obtained with this work and the some reported systems

Substrate	Conditions[Ref.]	Time/min	Yield/%
	This work	22 min	95
4a	$CeCl_3$–$7H_2O$/EtOH/r.t.[6]	10 h	95
	$BiCl_3$/EtOH/r.t.[7]	11 h	95
	This work	20 min	90
4b	$CeCl_3$–$7H_2O$/EtOH/r.t.[6]	10 h	91
	SiO_2–$OAlCl_2$/EtOH/r.t.[8]	8 h	87
	This work	22 min	92
4c	$CeCl_3$–$7H_2O$/EtOH/r.t.[6]	10 h	97
	$BiCl_3$/EtOH/r.t.[7]	12 h	93

Experimental

The materials were purchased from Sigma-Aldrich and Merck and were used without any purification. Melting points were determined in a capillary tube and are not corrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer using TMS as internal standard.

Ethane-1,2-diaminium hydrogen sulfate (EDAHS)

Ethylenediamine (6.67 mL, 0.1 mol) was placed in a two-necked flask equipped with a reflux condenser and a dropping funnel. The flask was cooled in an ice bath. Under vigorous magnetic stirring, 98% H_2SO_4 (10.7 mL, 0.2 mol) was added dropwise to the flask in about 20 minutes to afford a brown powder. The salt was filtered off and the filter paper and salt were placed on a watch glass and dried using another piece of filter paper. The salt was then covered with a piece of clean filter paper and allowed to dry at room temperature to yield ethane-1,2-diaminium hydrogen sulfate (24.1 g, 94%) as a brownish solid, m.p. 85–89 °C. ^{1}H NMR (D_2O, 400 MHz) δ 3.08 (s, 4 H, –CH_2–N); ^{13}C NMR (D_2O, 100 MHz) δ 36.4. Anal. calcd for $C_2H_{12}N_2O_8S_2$: 256; C, 9.37; H, 4.72; N, 10.93; S, 25.03; found: C, 9.30; H, 4.80; N, 10.85; S, 25.25%

Synthesis of β-amino ketones; general procedure

EDAHS (0.1 mmol, 0.026 g) was added to a mixture of acetophenone (1 mmol) or cyclohexanone (1 mmol), aryl aldehyde (1 mmol) and aryl amine (1 mmol) in EtOH (5 mL). The mixture was stirred at room temperature for the desired time as indicated in Table 2. The progress of the reaction was monitored by TLC. After the reaction was completed, the precipitated solid was filtered off, washed three times with water and recrystallised from anhydrous ethanol. The products were identified by their ^{1}H NMR spectra and their physical data (m.p.) and by comparison with those described in the literature. The catalyst, EDAHS was recovered by evaporation of the aqueous washings and was reused in the next run.

3-(Phenylamino)-1,3-diphenylpropan-1-one (**4a**): White solid; m.p. 169–170 °C (lit.[19] 169–170 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (1H, dd, *J*=7.8, 16 Hz), 3.53 (1H, dd, *J*=5.5, 16 Hz), 4.58 (1H, br), 4.96 (1H, t, *J*=7.2 Hz), 6.68–6.52 (3H, m), 7.92–7.07 (12 H, m).

3-(4-Chloro-phenylamino)-3-(4-methoxy-phenyl)-1-phenyl-propan-1-one (**4e**): White solid; m.p. 156–158 °C (lit.[7] 158–160 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.36 (1H, dd, *J*=7.5, 15.7 Hz), 3.45 (1H, dd, *J*=5.8, 15.7 Hz,), 4.60 (1H, br), 3.78 (3H, s), 4.90 (1H, t, *J*=7.5 Hz), 6.86–6.50 (4H, m), 7.31–7.08 (4H, m), 7.90–7.42 (5H, m).

2-(Phenyl(phenylamino)methyl)cyclohexanone (**4l**): White solid; m.p. 137–138 °C (lit.[18] 135–137 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72–1.61 (3H, m), 1.93–1.80 (3H, m), 2.45–2.28 (2H, m), 2.81–2.73 (1H, m), 4.62 (0.75 H, d, *J*=7.2 Hz), 4.80 (0.25 H, d, *J*=4.2 Hz), 6.64–6.51 (3H, m), 7.36–7.04 (7H, m).

We are thankful to the Razi University Research Council for partial support of this work.

Received 13 December 2013; accepted 11 February 2014
Paper 1302340 doi: 10.3184/174751914X13939287092503
Published online: 2 April 2014

References

1 M. Tramontini, *Synthesis*, 1973, 703.
2 E.F. Kleinman, in *Comprehensive organic synthesis*. Pergamon Press, New York, 1991, Vol. 2, p. 893.
3 M. Arend, B. Westermann and N. Risch, *Angew. Chem. Int. Ed*., 1998, **37**, 1044.
4 S. Kobayashi and M. Ueno, *Comprehensive asymmetric catalysis*. Springer, Berlin, 2004.
5 B. Eftekhari-Sis, A. Abdollahifar, M.M. Hashemi and M. Zirak, *Eur. J. Org. Chem*., 2006, 5152.
6 Y. Dai, B.D. Li, H.D. Quan and C.X. Lu, *Chin. Chem. Lett*., 2010, **21**, 31.
7 H. Li, H.-Y. Zeng and H.-W. Shao, *Tetrahedron Lett*., 2009, **50**, 6858.
8 Z. Li, X. Ma, J. Liu, X. Feng, G. Tian and A. Zhu, *J. Mol. Catal. A: Chem*., 2007, **272**, 132.
9 S. Iimura, D. Nobutou, K. Manabe and S. Kobayashi, *Chem. Commun*., 2003, 1644.
10 T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem. Int. Ed*., 2004, **43**, 1566.
11 Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu and L.-Z. Gong, *J. Am. Chem. Soc*., 2007, **129**, 3790.
12 T. Akiyama, K. Matsuda and K. Fuchibe, *Synlett*, 2005, 322.
13 J.M. Janey, Y. Hsiao and J.D. Armstrong, *J. Org. Chem*., 2006, **71**, 390.
14 G. Zhao, T. Jiang, H. Gao, B. Han, J. Huang and D. Sun, *Green Chem*., 2004, **6**, 75.
15 F. Dong, L. Jun, Z. Xin-Li and L. Zu-Liang, *Catal. Lett*., 2007, **116**, 76.
16 J.Z. Li, Y.Q. Peng and G.H. Song, *Catal. Lett*., 2005, **102**, 159.
17 S. Sahoo, T. Joseph and S.B. Halligudi, *J. Mol. Catal. A: Chem*., 2006, **244**, 179.
18 W.B. Yi and C. Cai, *J. Fluorine Chem*., 2006, **127**, 1515.
19 L.M. Wang, J.W. Han, J. Sheng, H. Tian and Z.Y. Fan, *Catal. Commun*., 2005, **6**, 201.
20 K. Bahrami, M.M. Khodaei and F. Naali, *J. Org. Chem*., 2008, **73**, 6835.
21 K. Bahrami, M.M. Khodaei and M. Soheilizad, *J. Org. Chem*., 2009, **74**, 9287.
22 K. Bahrami, M.M. Khodaei and A. Nejati, *Green Chem*., 2010, **12**, 1237.
23 H. Wu, X.-M. Chen, Y. Wan, L. Ye, H.-Q. Xin, H.-H. Xu, C.-H. Yue, L.-l. Pang, R. Ma and D.-Q. Shi, *Tetrahedron Lett*., 2009, **50**, 1062.
24 W. Shen, L.-M. Wang and H. Tian, *J. Fluorine Chem*., 2008, **129**, 267.