One pot synthesis of amino-ethanethiol derivatives of aromatic aldehydes by the catalytic action of DBU

R Rejithamol, S Beena, Midhina Krishnan, Megha T Dharan and Anusree L

Department of Chemistry, Amrita School of Arts and Sciences, Amrita Vishwa Vidyapeetham, Amritapuri Campus, Clappana P. O. Kollam, India, 690525.

E-mail id: rejithamol01@gmail.com

Abstract: A facile and effective one pot organic synthesis of benzylidene amino-ethanethiols from the condensation reaction between 2-aminoethanethiol and aromatic aldehydes by the catalytic action of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) at mild reaction conditions. For the best our knowledge there is no report on the organic synthesis of benzylideneamino-ethanethiols

1. INTRODUCTION

Cysteamine (CA) or 2-mercaptoethylamine is an aminothiol compound used for the treatment of cystinosis [1]. Cystinosis is a disease related to the excess of cystine accumulation in the lysosomal tissues. The treatment with cysteamine substantially decreases intracellular cystine accumulation and thereby the curing of disease [2-5]. So, it is necessary to quantify the amount of cysteamine in patients suffering from cystinosis. In addition to this CA have radiation protective effects on the nucleobases adenine, cytosine, guanine, thymine and the water soluble vitamin ascorbic acid in aqueous solutions [6]. There are several methods reported for the detection and quantification of CA including gas chromatography[7], capillary electrophoresis [8], high performance liquid chromatography[9] and electroanalytical methods [10-12].

1,8-Diazabicyclo [5.4.0] undec-7-ene (DBU), is considered as a non-nucleophilic base and catalyst complexing ligand in a wide variety of reactions. DBU is commercially available, cheap, non-hazardous, homogenous, green and recyclable catalyst which makes the organic reaction more effective and environmental friendly [13]. Recently, there is a report on the DBU mediated condensation reaction between 2-nitro-phenylacetetonitrile with aromatic aldehydes for the synthesis of phenylacrylonitrile derivatives [14-16] (scheme 1).

Herein represent a facile and effective one pot method for the synthesis of benzylidene amino-ethanethiols from the condensation reaction between 2-amino-ethanethiols and aromatic aldehydes by
the catalytic action of DBU at room temperature (scheme 2). This organic synthetic approach is the first time report on the chemical synthesis of benzylideneamino-ethanethiols.

\[
\text{SH} \quad \text{NH}_2 \quad \overset{\text{CHO}}{\rightarrow} \quad \text{SH} \quad \overset{\text{N=}}{\longrightarrow} \quad \text{N} \quad \text{CHO} \\
1 \quad 2 \quad \text{DBU} \quad \text{Methanol, rt, 24hrs, 39\%} \quad 3a
\]

Scheme 2

2. RESULTS AND DISCUSSIONS

2.1. Characterisation

The structural identification of the product 3a was done by the nuclear magnetic resonance (NMR) and attenuated total infrared (FT-IR) spectroscopic techniques. In the IR spectra, the aromatic C-H signals displayed in between 2921.6-2851.6 cm\(^{-1}\). The weak S-H, strong C-N, C=\(\equiv\)N and C=C stretching vibrations were observed to be at 2550, 1596.24 and 1289.6 cm\(^{-1}\) respectively. The -CH\(_2\) bending vibrations are absorbed to be in between 652-1000 cm\(^{-1}\) (figure 1A). In the \(^1\)H NMR spectrum, C-H absorbed at δ 8.4, the aromatic protons were occurred in between δ 7.31 to 7.59, aliphatic CH\(_2\) protons are at δ 3.0 and δ 3.9 and the S-H protons at δ 1.5 (figure 1B). The melting point of the compound 3a was found to be in between 94-96°C.

![Figure 1](image1.png)

Figure 1. (A) IR spectrum of the compound 3a and (B) \(^1\)H-NMR spectrum of 3a

2.2. Mechanism

The proposed mechanism for the formation of benzylidene ethane-aminothiols is shown in scheme 3. Initially the lone pairs on the nitrogen atom of the ethane- amino thiol can be bonded to the carbonyl group of the aldehyde to form an ammine-aldehyde adduct. Then the nucleophilic base DBU abstract one of the protons from the adduct and to form substituted amino methanol. The mercaptoethylaminophenyl methanol is stabilized by the removal of a molecule of water and to form the corresponding benzylidene ethane-aminothiol (scheme 3).
3. EXPERIMENTAL SECTION

3.1. Materials and Measurements

Bruker Advance DPX-400-megahertz (MHz) NMR spectrometer was used for recording the NMR spectra. Chemical shifts are described (δ) relative to TMS (1H) and coupling constants (J) are expressed in Hertz (Hz). IR spectra were recorded on Perkin Elmer FT-IR spectrophotometer. Melting points were recorded on a Büchi melting point apparatus. Analytical grade solvents were used for the entire synthetic approach.

3.2. Synthesis and isolation of substituted ethane-aminothiols

General method for the synthesis of substituted ethane-aminothiols (3a-e): A solution of cysteamine HCl (1, 1mmol) and DBU (1 mmol) in methanol (5 mL) was stirred at room temperature. To this solution, the aromatic aldehyde (1 mmol) was added and the reaction mixture stirred for 24 hours at the same temperature. After the completion of the reaction, the solvent was then removed by distillation under vacuum and the product was separated from the crude residue by column chromatography (silica:100-200 mesh, hexane-ethyl acetate: 80:20). The reaction was generalized by changing the aromatic aldehyde and in all the reactions the corresponding substituted ethane-aminothiols were successfully isolated and characterized (Table 1).

| Entry | Aldehyde   | Product   | Yield (%) |
|-------|------------|-----------|-----------|
| 3b    |            |           | 72        |
| 3c    |            |           | 63        |
| 3d    |            |           | 57        |
| 3e    |            |           | 43        |

Table 1: Synthesis of substituted ethane-aminothiols (3b-e)

Scheme 3: Mechanism of the reaction
3b: $^1$H NMR: $\delta$ 8 (d, 2H), 7.35-7.33 (m, 2H), 5.6 (s, 1H), 3.16-3.07 (m, 4H), 1.6(s, 1H). IR:1641.9,1599.09,1514.3,1335.15,1289.66,1105.17,1026.93,1010.32,993.48,948.82,812.06,853.69,83.20,748.35,687.50,628.62,547.74,518.88,418.48,55.489,27.404.26 cm$^{-1}$. MP: 94-96°C.

3c: $^1$H NMR: $\delta$ 7.13 - 6.84 (m, 4H), 5.3 (s, 1H), 3.8 (s, 3H), 2.98-2.75 (m, 4H), 1.8(s, 1H). IR: 2927.47, 1658, 1605.92, 1507.80, 1242.98, 1173.55, 1028.54, 825.86, 703.63, 530.33 cm$^{-1}$. MP: 99-101°C.

3d: $^1$H NMR: $\delta$ 8(d, 2H), 7.44-7.41(m, 2H), 6.98(s, 1H), 3.85 (s, 3H), 1.3 (m, 4H), 0.84 (s, 1H). IR:2851.6,2921.64,1629,1572,1596,1508,1462,1418.3,1301.56,1248.98,1172,1029.93,979.66,824,540 .25,517.21 cm$^{-1}$. MP: 180-182°C.

3e: $^1$H NMR: $\delta$ 3.84(s, 3H), 7.04(d, 1H, J=8Hz), 7.71(d, 1H, J=8Hz), 7.71-7.79(m, 1H), 8.13 (d, 1H, 4Hz), 8.20(d, 1H, J=8Hz), 9.04(s, 1H). IR:3272.35,2963.98,2929.45,1524.38,1446.40,1405.37,1367.92,1264.98,1280.71,1239.01,11 83.11. 1130.28,1084.32,1034.1,937.92,931.92,860.59,823.85,800.09,753.47,690.91,556.36,521.79,494.32,46 6.91 cm$^{-1}$. MP: 160-162°C.

4. CONCLUSIONS

Herein reported an effective and effortless organic synthesis of substituted ethane- amino thiols by the catalytic action of DBU in a conciliatory approach. As far as we know there is no literature report on the organic synthesis of benzylidene ethane-amino thiols.

ACKNOWLEDGMENTS

Authors acknowledge Sophisticated Test and Instrumentation Centre, Cochin University of Science and Technology, Ernakulum for the NMR characterization and School of Chemical Sciences, Mahatma Gandhi University, Kottayam for the infrared spectroscopy of the synthesized compounds.

REFERENCES

[1]. William Gahl A, Jess Thoene G and Jerry Schneider A 2002 J.Med. 22347
[2]. Besouw M , Masereeuw R, and Van den Heuvel L2013 Drug Discovery Today 18 785-92
[3]. Cairns and Anderson 2002 Current Pharmaceutical Design8 69
[4]. Stachowicz M, Lehmann B, Tibi A, P Progon, Daurat Vand Pradeau D1998 J. Pharm. Biomed. Anal.17 767
[5]. Kataoka H, Lmamura Y, Tanaka H and Makita M 1993J. Pharm. Biomed. Anal.111963
[6]. Vahid A and Hassan K M 2016 Anal. Methods, 8 5604-10
[7]. Kataoka H, Tanaka H and Makita M 1994 J Chromatogr. B Biomed. Appl.6579
[8]. Jonas A J and Schneider J A 1981 Anal. Biochem.114 429
[9]. Hsiung M,Yeo Y, Itiaba K and Crawhall J C 1978 Biochem. Med.19 305
[10]. Raoof J B,Ojani R and Chekin F 2009J. Mater. Sci.,44 2688
[11]. Ojani R,Raoof J B and Zarei E 2009Electroanalysis,21 1189
[12]. Ensafi A and Karimi-Maleh H 2010 Electroanalysis,22 25
[13]. BhaskaraN, Garima G, Ankitha C, Anshika L and Jitender M K 2015 Current organic chemistry19790-812
[14]. Rejithamol R, Aparna K, Swetha S, Gayathri A and Jisha S 2017Asian journal of chemistry291963-65
[15]. Rejithamol R,Beena S,Santhy A and AshaBN 2018 Materials Today: Proceedings5 17694–17698
[16]. Rejithamol R, Beena S, Sajitha C S, Malavika Dileep N K, Drisya A and Keerthi P R 2019 IOP Conf. Ser.: Mater. Sci. Eng.561 012017