



Scholars Research Library

Der Pharma Chemica, 2015, 7(1):1-4
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis of primary amines by one-pot reductive amination of aldehydes

Bijivemula N. Reddy, S. M. Reddy and Madhavesh Pathak*

Department of Chemistry, Vellore Institute of Technology, Vellore, T.N. India

ABSTRACT

We report here a novel, one-pot, two-step reductive Amination of aldehydes for the atom economical synthesis of primary amine. The Amination step has been carried out with the hydroxyl ammonium chloride and does not require the use of a base. In the subsequent reduction step, a stannous chloride has been used. The operational simplicity, the short reaction times, and the mild reaction conditions add to the value of this method as a practical alternative to the reductive Amination of aldehydes

Keywords: Hydroxyl ammonium chloride; aldehydes; stannous chloride

INTRUDUCION

Primary amines are important in view of their application in a Varsity of chemical industry sectors; hence their introduction processes are of great interest. These compounds are used for the development of pharmaceuticals' and fine chemicals. Among the amines, primary amines are the most useful; however, their synthesis is challenging because of their high reactivity.

Various methods allow the preparation of primary amines. Among those, reductive Amination is the most extensively used. This method, which has been known for a long time, is based on the conversion of aldehydes in to oxime followed by a reduction step.

Primary amines can be selectively synthesized by the reduction of corresponding oxime using low-cost stannous chloride. Here in, we report a new, efficient, one-pot route to primary amines. It is carried out in ethanol at reflux temperature.

MATERIALS AND METHODS

General: All the reagents were obtained commercially (SD fine, India) and used with further purification. Melting points were determined by open capillary method. The IR spectra (in KBr pellets) were recorded on a Perkin-Elmer FTIR spectrophotometer. ¹H NMR (CDCl₃ 400 MHz) and ¹³C NMR (DMSO-d₆, 100.6 MHz) were recorded on spectrometer TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument. The purity of the compounds was checked by TLC on silica gel plates using a mixture of n-hexane and ethyl acetate.

General procedure for the preparation of amines:

To a stirred solution of aldehyde (1.0 eq) in ethanol (20 mL) was added hydroxyl amine hydrochloride (1.2 eq). The resulting reaction mixture was stirred at rt for 3 h. Then, added stannous chloride hydrate (3.0 eq) was added and refluxed for 15 min. After completion of the reaction, solvent was concentrated under reduced pressure to get a crude residue. The residue was basified with 2N NaOH solution and extracted with ethyl acetate, dried over Na₂SO₄ and concentrated in vacuum to afford pure compound

Synthesis of (3-methylisoxazol-5-yl) methanamine(2a)

IR (KBr, cm⁻¹): 3445.64, 2893.02, 2661.68, 2580.66, 1618.0, 1585.92, 1516.81, 1416.95, 1380.44, 1322.41, 1252.23, 1142.91, 1082.51, and 1009.81. ¹H NMR (400 MHz, DMSO d₆) δ: 8.80 (br s, 3H), 6.51 (s, 1H), 4.20 (s, 2H), 2.25 (s, 3H). ¹³C NMR (100.57 MHz, DMSO d₆) δ: 165.20, 159.84, 105.20, 33.79, 10.96. MS: 99.45 % (*m/z* = 113.1, [(M+H)⁺]).

Synthesis of 7-(aminomethyl)-2H-chromen-2-one (2b)

IR (KBr, cm⁻¹): 3425, 3001.8, 1724.75, 1623.66, 1108.23 and 859.62. ¹H NMR (300 MHz, DMSO d₆) δ: 8.64 (s, 1H), 8.08 (d, *J* = 9.3 Hz, 1H), 7.76 (d, *J* = 9.3 Hz, 1H), 7.58 (s, 1H), 7.47 (dd, *J*₁ = 1.5 Hz, *J*₂ = 8.1 Hz, 1H), 6.52 (d, *J* = 9.3 Hz, 1H) 4.196 (s, 2H). ¹³C NMR (100.57 MHz, CD₃OD+NH₄OH) δ: 164.3, 155.5, 149.6, 146.6, 130.2, 125.7, 119.3, 116.6, 116.4, 46.71. LMS: 98.56 % (*m/z* = 176.0, [(M+H)⁺]).

Synthesis of quinoline-5-ylmethanamine(2c)

IR (KBr, cm⁻¹): 3422.90, 2978.60, 2787.10, 2617.16, 1635.86, 1601.16, 1560.98, 1528.54, 1370.93, 1306.51, and 812.33. ¹H NMR (400 MHz, DMSO-d₆) δ: 9.10 (d, *J* = 3.6 Hz, 1H), 8.89 (d, *J* = 8.0 Hz, 1H), 8.52 (br s, 3H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.94 (t, *J* = 7.8 Hz, 1H), 7.85-7.80 (m, 2H), 4.60 (q, *J* = 5.6 Hz, 2H). ¹³C NMR (100.57 MHz, DMSO-d₆) δ: 146.32, 140.68, 140.33, 132.65, 132.17, 130.24, 126.60, 123.55, 121.93, 38.16. MS: 96.12 %, (*m/z* = 159.1 [(M+H)⁺]).

Synthesis of 2-(4-(trifluoromethyl) phenyl ethanamine (2d)

IR (KBr, cm⁻¹): 3459.71, 2997.05, 1602.01, 1484.68, 1472.12, 1328.39, 1165.54, 1129.59, 1117.94, 1069.49, and 822.34. ¹H NMR (400 MHz, DMSO-d₆) δ: 8.14 (br s, 3H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 3.09-2.98 (m, 4H). ¹³C NMR (100.57 MHz, DMSO-d₆) δ: 142.42, 129.57, 128.36, 127.88, 127.56, 127.24, 126.92, 125.65, 125.34, 125.30, 122.95, 120.25, 32.55. MS: 97.46 % (*m/z* = 190.1 [(M+H)⁺]).

Synthesis of 2-(4-bromo-2(trifluoromethoxy) benzyl) isoindoline-1,3-dione(2e)

IR (KBr, cm⁻¹): 3459.71, 2997.05, 1602.01, 1484.68, 1472.12, 1328.39, 1165.54, 1129.59, 1117.94, 1069.49, and 822.34. ¹H NMR (400 MHz, DMSO-d₆) δ: 8.14 (br s, 3H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 3.09-2.98 (m, 4H). ¹³C NMR (100.57 MHz, DMSO-d₆) δ: 142.42, 129.57, 128.36, 127.88, 127.56, 127.24, 126.92, 125.65, 125.34, 125.30, 122.95, 120.25, 32.55. MS: 97.46 % (*m/z* = 190.1 [(M+H)⁺]).

Synthesis of (6-fluoropyridine-3-yl) methanamine(2f)

IR (KBr, cm⁻¹): 3434.60, 3092.80, 3053.68, 255.028, 1614.50, 1477.62, 1291.01 and 1105.01. ¹H NMR (400 MHz, DMSO-d₆) δ: 8.50 (br s, 3H), 8.35 (d, *J* = 2.0 Hz, 1H), 8.18-8.13 (m, 1H), 7.28-7.26 (m, 1H), 4.10-4.06 (m, 2H). ¹³C NMR (100.57 MHz, D₂O) δ: 164.53, 162.12, 147.53, 147.40, 143.67, 143.58, 126.68, 126.65, 110.58, 110.23, 39.53. MS: 99.11 % (*m/z* = 127.0 [(M+H)⁺]).

Synthesis of 2-(2-ethylthiazol-4-yl) ethanamine(2g)

IR (KBr, cm⁻¹): 3437.90, 2866.62, 2466.97, 1602.84, and 1513.13. ¹H NMR (400 MHz, DMSO-d₆) δ: 8.06 (br s, 3H), 7.32 (s, 1H), 3.14-3.06 (m, 2H), 3.00-2.95 (m, 4H) 1.29 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100.57 MHz, DMSO-d₆) δ: 176.22, 145.85, 118.38, 37.49, 26.55, 24.42, 13.78. MS: 98.95 % (*m/z* = 157.0, [(M+H)⁺]).

Synthesis of benzo [d] oxazolo-4 ylmehanamine(2h)

IR (KBr, cm⁻¹): 3436.62, 3148.68, 3068.86, 2849.93, 1681.42, 1657.29, 1593.56, 1499.08, 1450.01, 1388.12, 1290.30, 1231.46, and 1048.45. ¹H NMR (400 MHz, DMSO-d₆) δ: 7.6 (br s, 1 H), 7.09 (s, 1H), 6.74 (t, *J* = 7.8 Hz, 4H), 6.56 (d, *J* = 7.6 Hz, 1H), 6.33 (d, *J* = 7.6 Hz, 1H), 4.43 (s, 2H). ¹³C NMR (75 MHz, TFA) δ: 148.00, 143.99, 129.12, 119.93, 118.19, 112.40, 108.65, 41.15. MS: 92.81 % (*m/z* = 149.1 [M+H]⁺).

Synthesis of (3-(methylthio) phenyl) methanamine(2i)

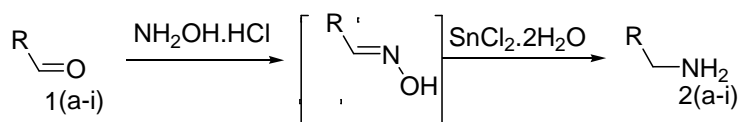
IR (DCM, cm^{-1}): 336.046, 2910.80, 2643.94, 1591.83, 1472.01, 1424.02, 1311.59, 1209.40, 1098.02, 1085.85, 966.95, 956.25, 780.63, and 697.86. ^1H NMR (400 MHz, DMSO-d_6) δ : 7.25-7.21 (m, 2H), 7.08 (dd, $J_1 = 1.4$ Hz, $J_2 = 7.8$ Hz, 2H), 3.68 (s, 2H), 2.46 (s, 3H), 2.04 (br s 2H).. ^{13}C NMR (100.57 MHz, CDCl_3) δ : 143.6, 138.54, 128.88, 125.06, 124.74, 123.74, 46.17, 15.64. LC-MS: 98.80 % ($m/z = 154.0$ $[\text{M}+\text{H}]^+$).

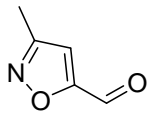
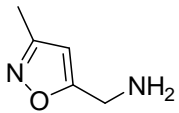
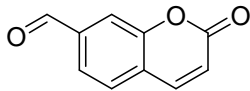
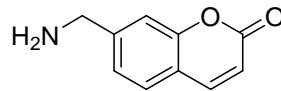
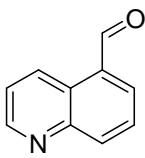
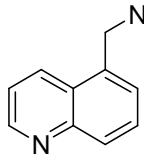
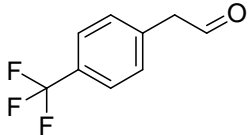
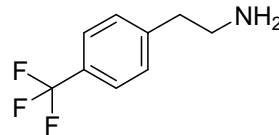
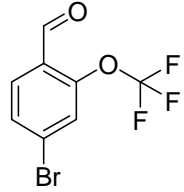
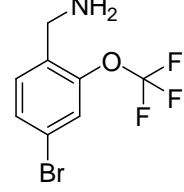
RESULTS AND DISCUSSION

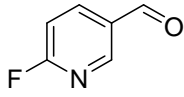
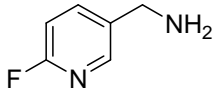
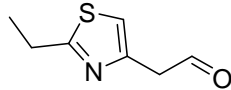
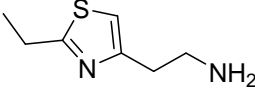
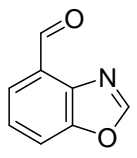
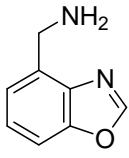
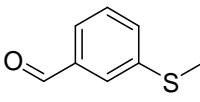
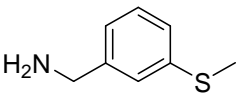
The synthesis of primary amines from the corresponding aldehydes was carried out in two successive steps.

CONCLUSION

This convenient method, which was used at reflux temperature and atmospheric pressure, should prove useful for the synthesis of Variety of primary amines from aldehydes of various structures



Aldehyde 1(a-i)	Product 2(a-i)	Time (min)	Yield (%)
		45	80
		35	92
		40	91
		37	89
		36	92

		55	87
		47	85
		50	91
		45	90

Acknowledgement

This work was financially supported by the Department of chemistry, VIT University, Vellore -6 32014, Tamil Nadu, India

REFERENCES

- [1] E. Riva, S. Gagliardi, C. Mazzoni, D. Passarella, A. Rencurosi, D. Vigo, M. Martinelli, *J. Org. Chem.*, **2009**, *74*, 3540-3543.
- [2] A. Massaro, A. Mordini, G. Reginato, F. Russo, M. Taddei, *Synthesis*, **2007**, 3201-3204.
- [3] L. De Luca, G. Giacomelli, M. Taddei, *J. Org. Chem.*, **2001**, *66*, 2534-2537.
- [4] H. Nemoto, R. Ma, H. Moriguchi, T. Kawamura, M. Kamiya, M. Shibuya, *J. Org. Chem.*, **2007**, *72*, 9850-9853
- [5] I.R. Baxendale, S.V. Ley and F.H. Sneddon, *Synlett*, **775 (2002)** and references therein.
- [6] M.A. Cohen, J. Sawden and N.J. Turner, *Tetrahedron Lett.*, *31*, 7223 (**1990**).
- [7] G.A. Olah, S.C. Narang and A. Garcia-Luma, *Synthesis*, 659 (**1980**).
- [8] S.K. Dewan and R. Singh, *Synth. Commun.*, *33*, 385 (**2003**);
- [9] S.K. Dewan, R. Singh and A. Kumar, *Synth. Commun.*, *34*, 2025 (**2004**).
- [10] J.C. Feng, B. Lin, L. Dai and N.S. Bian, *Synth. Commun.*, *28*, 3765(**1998**).
- [11] D.S. Bose and A.V. Narsaiah, *Tetrahedron Lett.*, *39*, 6533 (**1998**).
- [12] S.K. Dewan and R. Singh, *Orient J. Chem.*, *18*, 601 (**2002**);
- [13] S.K. Dewan and R. Singh, *Indian J Heterocycl. Chem.*, *12*, 287 (**2003**).
- [14] Baldwin, J. J.; Burbaum, J. J.; Henderson, I.; Ohlmeyer, M. H.J. *J. Am. Chem. Soc.* **1995**, *117*, 5588-5589.
- [15] Nestler, H. P.; Bartlett, P. A.; Still, W. C. *J. Org. Chem.* **1994**, *59*, 4723-4724.
- [16] Moran, E. J.; Sarshar, S.; Cargill, J. F.; Shahbaz, M. M.; Lio, A.; Mjalli, A. M. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 10787-10788.
- [17] Nicolaou, K. C.; Xiao, X.-Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2289-2291.
- [18] Ugi, I.; Lohberger, S.; Karl, R. *In Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, **1991**; Vol. 2, pp 1083-1109.
- [19] Moran, E. J.; Tellew, J. E.; Zhao, Z.; Armstrong, R. W. *J. Org. Chem.* **1993**, *58*, 7848.
- [20] Armstrong, R. W.; Tellew, J. E.; Moran, E. J. *J. Org. Chem.* **1992**, *57*, 2208.