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Ultrasound assisted one-pot synthesis of various primary amines

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ABSTRACT

Series of secondary amine derivatives have been prepared by one-pot synthesis of ketones with ammonia ethanol and titanium (IV) isopropoxide, followed by sodium borohydride under ultrasound irradiation. This procedure has the advantages of very short synthesis time with good to excellent yields.

Keywords: Sodium borohydride, Titanium iso propoxide, primary amines, ketones and ultrasound irradiation

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INTRODUCTION

Reductive amination of carbonyl compounds is a very important and powerful tool for chemists to synthesize the structurally diverse primary, secondary and tertiary amines [1]. The sequence proceeds through the formation of an imine or iminium intermediate upon reaction of a carbonyl compound with ammonia, primary amine or secondary amine followed by in situ reduction to an amine of higher order under catalytic conditions[1a, 2]. Sodium cyanoborohydride[1c, 1d and 3], sodium triacetoxy borohydride [1e, 4], pyridine–borane[5], zincborohydride [6], sodium borohydride [7], organosilanes[8], organo tin hydrides[9] and ammonia borane [10] have been utilized to accomplish this transformation. However, most of these reducing agent suffer from drawbacks. Catalytic hydrogenation has effect on other functional groups such as nitro, chloro and alkenes. Also sodium cyanoborohydride produces toxic by products. Amine boranes are more expensive and have to be stored under optimal conditions. Desired primary amines were synthesized using ethanolic ammonia with ketones in the presence of titanium (IV) isopropoxide, followed by sodium borohydride [11]. However, these methods suffer from drawbacks, such as longer time and poor yields.

Recently, ultrasound irradiation technique (UIT) has been largely used in organic syntheses which lead to the reduction in reaction time from hours to minutes, reduce side reactions, increase yields and improve reproducibility [25-32]. In this paper we make use of this UIT for synthesizing primary amines using ethanolic ammonia and ketones in the presence of titanium (IV) isopropoxide, followed by sodium borohydride. The reaction is usually completed in 10 min with good to excellent isolated yields.

MATERIALS AND METHODS

All the chemicals, solvents and reagents procured from Sigma-Aldrich, Merck, Lancaster Chemical and SD fine chemicals and used as such without further purification. All used solvents for spectroscopic and other physical studies were reagent grade and were further purified, employing the reported methods. All the reported melting points in the experiment were determined in open capillary tubes on a Mel-Temp apparatus. All the NMR spectra were recorded on Bruker 400 MHz spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The compounds were dissolved in $CDCl_3$, CD_3OD and DMSO and the chemical shifts were referenced to TMS. Coupling constants were calculated in hertz (Hz). The elemental analysis was performed on a ThermoFinnigan FLASH EA 1112 CHN analyzer and finally the mass spectra were recorded on Agilent LC/MSD SL 1100 instrument.

General procedure for synthesis of various primary amines (1-10)

A mixture of the ketone (1.0 eq), titanium (IV) isopropoxide (1.5 eq) and ammonia in ethanol (5M, 10 vol) were kept under ultrasound (US) irradiation at 30 °C for 5 min. Sodium borohydride (1.5 eq) was added pinch wise over a period for 5 min. After completion of the reaction, excess ethanol was concentrated under reduced pressure to get a residue. The residue was diluted with water and extracted with ethyl acetate, dried with Na_2SO_4, and concentrated under reduced pressure to get the corresponding primary amine. The data below correspond to the entries in **Table 1.** The following compounds were synthesized using the above method.

1-Methyl-3-phenylpropylamine (1)

Off- White solid; IR (KBr); Mp: 181-185 °C; IR (KBr): 2955, 1645, 1492, 1450, 1376 1060, 760, 695,590 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ (ppm): 7.3–7.16 (m, 5H), 2.97–2.9 (m, 1H), 2.8–2.5 (m, 2H), 1.7–1.64 (m, 2H), 1.13–1.12 (d, *J*= 6.4 Hz, 3H); ^{13}C NMR (101.57 MHz, DMSO-d_6) *δ* (ppm): 142.8, 128.6, 127.1, 126.8, 127.4, 128.3, 126.3, 124.1, 124.5, 126.2, 121.9, 120.2, 31.8; MS(ESI): 150.3[(M+H].

4-(4-fluorophenyl) buane-2-amine (2)

Off-White solid; Mp: 182-185 °C; IR (KBr): 2920, 1600, 1502, 1452,.1194 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD) *δ* (ppm): 7.26 - 7.21 (m, 2 H), 7.05 -6.97 (m, 2 H), 3.30 -3.29 (m, 1H), 2.70-2.60 (m, 2H), 2.0 -1.98 (m, 2H), 1.33 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100.57 MHz, DMSO-d_6) *δ* (ppm): 142.4, 129.6, 128.4, 127.9, 127.7, 127.2, 126.9, 125.6, 125.4, 125.3, 122.9, 120.2, 32.5; MS (ESI): 168 [(M+H].

6-bromo-2,3-dihydro-1H-inden-1-amine (3)

Thick liquid; Mp: 183-185 °C; IR (KBr cm^{-1}): 3341, 3060, 3051.8, 2967 ,1554 , 1460, 1248.8, 1213.7; ^1H NMR (400 MHz, DMSO-d_6) *δ* (ppm): 8.34 (bs, 2H), 7.59 (s, 1H), 7.43 (d, *j*= 8.2 Hz, 1H), 7.246 (d, J = 8.2 Hz, 1H), .01 (q, *J* = 8.0 Hz, 1 H 5.01 (q, *J* = 8.0 Hz, 1 H), 2.96-2.90 (m, 1 H), 2.84-2.75 (m, 1 H), 2.41-2.33 (m, 1 H), 1.87-1.80 (m, 1 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ (ppm) : 145,2 142,5 139,3 137,4 130.1, 96.0, 77.8, 54.8, 32.7, 29.7, MS (ESI): 213 $[(M+H]^+$.

6-fluoro-2, 3-dihydro-1H-inden-1-amine (4)

Thick liquid: Mp: 183-185 °C; IR (KBr cm^{-1}): 3351, 3080, 3061.8, 2986 ,1594 , 1470, 1238.8, 1217.9 ; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.8 (bs, 2H)7.25-7.21 (m, 1 H), 7.13 (d d, 1 H, J_1 = 2.2 Hz, J_2 = 9.4 Hz), 7.06 (t d, 1 H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 4.05(t, 1 H, *J* = 7.6 Hz), 2.94-2.76 (m, 2 H), 2.30-2.20 (m, 2 H); ^{13}C NMR (100.57 MHz, DMSO-d_6) δ (ppm): 162.0, 160,0 142.3, 141.4, 139.6, 125.0, 114.2, 111.0, 559, 29.4, 26.9. MS (ESI) 152.08 $[(M+H]^+$.

Phenyl (pyridin-2-yl) methanamine (5)

Thick liquid; Mp: 180-185 °C; IR(KBr): 3310, 2814, 1610, 1521, 141, 1261, 1036 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) *δ* (ppm) 7.78 (d, j = 4.8 Hz, 1H), 7.75 -7.71 (m, 2H), 7.56 (d, J = 1.2 Hz, 2H), 7.42-7.39 (m, 5H) 5.3 (s, 1H) 2.21 (br s, 2H); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ (ppm) : 160.1, 148.8, 142.2, 134.8, 133.2, 129.5, 128.8, 127, 56.6. MS (ESI): 187.1 $[(M+H]^+$.

5-bromo-2,3-dihydro-1H-inden-2-amine (6):

Thick liquid; Mp: 180-185 °C; IR(KBr): 3327, 2985, 2817, 1645, 1509, 1454,1268, 1257, 1137, 1026 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) *δ* (ppm): 8.2 (bs, 2H), 7.58 (s, 1H), 7.41 (d, *j*= 8.2 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 4.0 (m, 1H) 3.25 (m,2H), 2.95 (s, 2H); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ (ppm) : 145, 142, 139, 137, 130., 96,, 43 . MS (ESI): 213 $[(M+H]^+$.

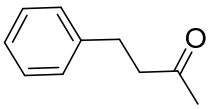
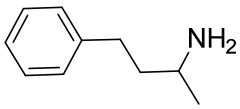
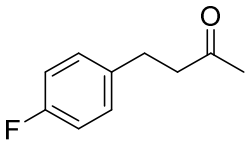
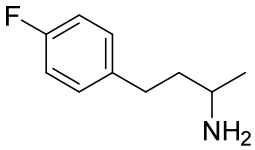
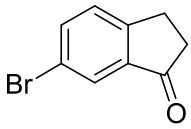
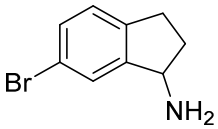
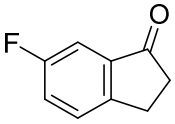
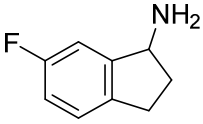
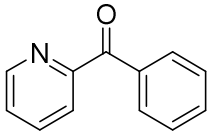
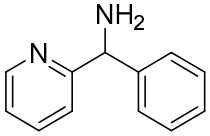
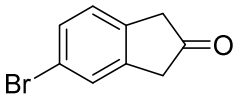
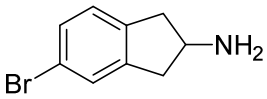
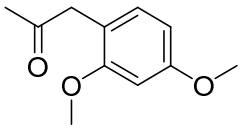
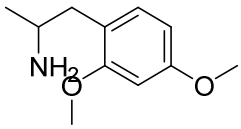
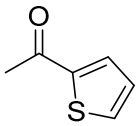
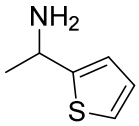
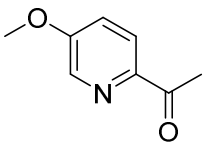
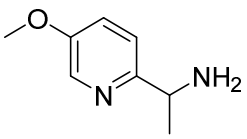
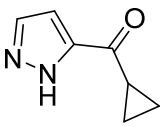
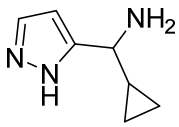
2-(2, 4-Dimethoxyphenyl)-1-methylethylamine (7):

Off-White solid: Mp: 180-185 °C; IR(KBr): 3358, 2960, 2837, 1612, 1508, 1464,1288, 1261, 1157, 1036 cm^{-1}; ^1H NMR400 MHz, $CDCl_3$) *δ* (ppm): 7.02–7.0 (d, *J* = 8 Hz, 1H), 6.45–6.4 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.17–3.08 (m, 1H), 2.68–2.63 (dd, J_1 = 5.4Hz J_2 = 7.9 Hz, 1H), 2.47–2.42 (dd, *J* = 5.3, 7.8 Hz, 1H), 1.09–1.07(d, *J* = 6 Hz, 3H); ^{13}C NMR (100.57 MHz, DMSO-d_6) *δ* (ppm): 158, 157, 130, 126,107, 59, 50, 46, 25; MS(ESI) : 196.2 $[(M+H]^+$

***1-(*thiophen-2-yl) ethanamine (8);**

Light yellow liquid: Mp: 180-185 °C; IR(KBr): 3376, 2965, 1658, 1598, 1437, 1236, 1029; ^1H NMR (400 MHz, DMSO d_6) *δ* (ppm): 7.29 (d, J = 2.0 Hz, 1 H), 6.9 (d, J = 4.4 Hz, 2H), 4.2 (m, 1 H), 1.32 (d, *J* = 6.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 125.4, 123.6, 123.1, 56.2, and 22.30; MS(ESI) : 128.05 $[(M+H]^+$

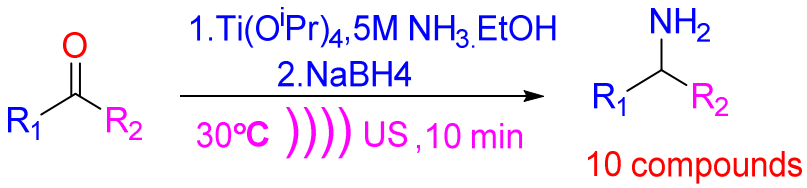
Table 1.Synthesis of various primary amines (1-10)

S.NO	Ketones	product	Time (min)	Yield (%)
01			**9**	**94**
02			**10**	**93**
03			**9**	**92**
04			**9**	**94**
05			**11**	**80**
06			**10**	**90**
07			**10**	**90**
08			**10**	**80**
09			**10**	**87**
10			**9**	**90**

1-(5-methoxypyridin-2-yl) ethan-1-amine (9):
Yellow liquid; Mp: 180-185 °C; IR (KBr, cm^{-1}): 2920, 2609. 1625, 1530, 1325. 1220 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) δ 9ppm) 8.0 (d, *J* = 2.3 Hz, 1 H), 7.30 (d, *J* = 8.6 Hz, 1 H), 7.25 (dd, J_1 = 2.5 Hz, J_2 = 8.3 Hz, 1 H), 4.30 (t, *J* = 6.2 Hz, 1H), 3.6 (s, 3 H), 1.3 (d, J= 9.4 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ: 153, 139 , 131. 130, 124, 52. 45. 16. MS (ESI):153 $[(M+H]^{+})$.

Cyclopropyl (1-ethyl-1H-pyrazol-5-yl) methanamine (10)
Thick liquid: Mp: 181-185 °C; IR (KBr): 3530 , 3420 , 3110 , 2850 , 1560 , 1510 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) : 13.3 (s, `1H) , 7.40 (d, *J* = 2.2 Hz, 1 H), 6.59 (d, *J* = 2.2 Hz, 1 H), 5.20 (s, 2 H) 4.02 (q, *J* = 5.4 Hz, 1 H), 1.41-1.35 (m, 1 H), 0.69-0.63 (m, 1 H), 0.52-0.46 (m, 2 H), 0.43-0.37 (m, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 138, 136, 103, 49, 14.83, and 4.0 3.0; MS (ESI): 138.10[(M+H] $^+$).

RESULTS AND DISCUSSION



The direct reductive amination reactions were carried out in ethanolic ammonia using -titanium isopropoxide (IV) as a Lewis acid, $NaBH_4$ as a reducing agent under ultrasound (US) irradiation. The reductive amination of variety ketones gave the corresponding desired products in good to excellent yields as shown in **Table 1**. The simple phenyl rings contain ketone, 4-(4-fluorophenyl) butan-2-one (**1** and **2**) gave desired product in very good yield (**Table 1,** entry **1** and **2**). Pyridine ring containing ketones also gave good yields (**Table 1,** entries, **5, 9** and **10**). When, 6-bromo-2,3-dihydro-1H-inden-1-one and 5-bromo-1,3-dihydro-2H-inden-2-one (**3** and **6**) was employed under the standard condition, the bromo group was retained during reduction, and the product **3** and **6** was obtained in 92% and 90% yields (entry **3** and **6**). Use of the electron- rich 1-(2,4-dimethoxyphenyl)propan-2-one gave the desired product in very high yields (entry **7**). Interestingly, when using ketone having pyridine ring, reduced C=N bond by product was also formed during the reduction. The reductive amination reaction was also performed with 1-(thiophen-2-yl) ethanone under the standard condition to afford **80** % yield **(**entry **8).** The structures of the products were deduced from their NMR (^1H & ^{13}C) and mass spectra.

CONCLUSION

In summary, a series of variety of biologically active amines was synthesized from easily available starting materials using as a titanium (IV) isopropoxide and sodium borohydride under ultrasound (US) irradiation. The procedure exhibits quite a lot of advantages, such as mild reaction conditions, shorter reaction times, and excellent product yields. Their structures were characterized ^1H NMR, ^{13}C NMR and LCMS.

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REFERENCES

[1] (a) Emerson, W. S. Organic reactions, Wiley, New York, **1948**, 4,174. (b) Moore, M. L. Organic reactions; Wiley, New York, **1949**, 5, 301. (c) Lane, C. F. Synthesis **1975**, 135. (d) Hutchins, R. O, Natale, N. Org. Prep. Proced. Int. **1979**, 11, 201. (e) Gribble, G. W.; Nutaitis, C. F. Org. Prep. Proced, Int.**198**5, 17, 317. (f) Hutchins, R. O, Hutchins, M. K.Comprehensive organic synthesis; Trost, B. M., Fleming, I., Eds, and Pergamon, Oxford, **1991**, 8, 25. (g) Baxter, E. W, Reitz, A. B. Organic reactions, Wiley, New York**, 2002**, 59, 12.
[2] (a) Rylander, P. N. Catalytic hydrogenation in organic synthesis; Academic, New York, **1979,** 165. (b) Klyuev. M. V, Khidekel. M. L. *Russ. Chem. Rev*., **1980**, 49, 14. (c) Tarasevich. V. A, Kozlov, N. G. *Russ. Chem. Rev*., **1999**, 68, 55.
[3] Mattson. R. J, Pham, K. M, Leuck. D. J, Cowen. K. A. *J. Org. Chem.*, **1990**, 55, 2552.
[4] Abdel-Magid. A. F, Carson. K. G, Harris. B. D, Maryanoff.C.A, Shah. R. D. *J. Org. Chem.*, **1996**, 61, 3849.
[5] Bomann. M. D, Guch. I. C, Dimare. M. J.*Org. Chem*., **1995**, 60, 5995.
[6] Ranu. B. C, Majee.A, Sarkar. A..*J. Org. Chem*., **1998**, 63, 370.
[7] (a) Saxena. I, Borah. R, Sarma. J. C. *Chem. Soc. Perkin Trans 1*., **2000**, 503. (b)Bhattacharyya. *Synth. Commun*., **1997,** 27, 4265.
[8] (a) Han. Y, Chorev,.M. A. *J. Org. Chem*., 1999, 64, **1972**. (b) Chandrasekhar. S. R, Ahmed. M. A .*Synlett*., **2000**,1655. (c) Chen. B. C, Sundeen. J. E, Guo, P, Bednarz. M. S, Zhao. R..*Tetrahedron Lett*., **2001**, 42, 1245. (d) Apodaca. R, Xiao. W. *Org. Lett*., 2001, 3, 1745.

(a) Suwa. T, Shibata. I, Nishino. K, Baba. A. *Org. Lett*., **1999**, 1, 1579.(b) Suwa. T, Sugiyama. E, Shibata. I, Baba.A. *Synthesis.*, **2000**, 789.
[10] Ramachandran.V.P, Pravin . G.D, Kaumba. S, Paul. C*Tetrahedron Letters*., **2010**, *51*, 3167-3169.
[11] Bruhaspathy. M. Sukanta. B, John. S.*Tetrahedron.*, **2004,** *60*, 1463–1471.
[12] Ya-Li.S, Yun-Fang.D , Fan.W , Tao. Y, Geng- Liang.Y , *Ultrason Sonochem.*, **2015**, 22,119 .
[13] Wang.L, Keyume.A, Feng.*J Ultrason Sonochem*. , **2015**, 22, 113
[14] Reddy.N.B, R.Rani.C, M. Reddy.S, Pathak.M. *Research on Chemical Intermediates*, **2016** 10, 7533.
[15] Reddy.N.B, R.Rani.C, M. Reddy.S, Pathak.M. *Derpharma Chemica.*, **2015, 7,** 1**.**