A CONVENIENT APPROACH FOR REDUCTION OF SOME FLUORO IMINES USING $NaBH_4$

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Fluoroimines have been reduced to their corresponding amines by means of $NaBH_4$ using MeOH as a solvent at room temperature. The reaction time and yield are 1-1.5 hr and 77-90%, respectively. Reduction process is very effective, inexpensive and clean for synthesis of fluoroamines in good yield. The structures of the compounds are supported by FTIR, mass spectrometry ^1H and ^{13}C NMR spectral data.

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Introduction

The chemistry of fluorine containing compounds has been tremendously developed. Intrinsic properties of fluorine atom, such as high electro negativity, small atomic radius, and low polarisability of the C-F bond, impart significant improvement on the biological activity of fluorinated molecules.[1] Fluorine has played pivotal role in novel drug discovery for modulating physical and biological properties of the molecules.[2-3] Thus, fluorine substitution remains an attractive means in the development of more active and selective pharmaceutical drug molecule.

Schiff bases constitute an area of rapidly growing interest because they form the basis of novel chemistry[4,5] interesting physical properties[6,7] and important biological activity.[8,9] Imines can be effectively reduced to amines by several reducing agents.[10-11] Sodium borohydride is a powerful reducing agents and has been employed in the reduction of a range of functional groups.[12,13] In the present work an effect has made to reduce some fluoro schif bases by $NaBH_4$, which is simple, safe and inexpensive reagent, and reduction can be achieved within 1-1.5 hrs.

Material and Methods

Instrumentation

Melting points were determined in an open capillary tube and are uncorrected. The chemicals and solvents were of laboratory grade and were purified. Completion of the reaction was monitored by thin layer chromatography using hexane/ethyl acetate as mobile phase on pre coated sheets of silica gel-G (Merck, Germany) using iodine vapor for detection. IR spectra recorded in KBr on a Perkin-Elmer spectrometer. ^1H and ^{13}C NMR (70MHz) spectra were recorded in DMSO-d_6 with an Avance spectrometer (Bruker, Germany) at 400-MHz frequency using TMS as an internal standard. The mass spectra were recorded on EISHIMADZU-GC/MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

Synthesis

The reaction scheme for the reduction of fluoro Schiff bases is presented in **Scheme-1**. Into a 100mL flask 0.01 mole fluoro Schiff base (**1a-l**)[14] and 20mL MeOH were placed in an ice bath and 0.015 mole $NaBH_4$ was added pinch wise during 10 min. with stirring. After complete addition of $NaBH_4$, the reaction mixture was further stirred at RT for 1-1.5hr. The progress of the reaction was monitored by TLC. The solid separated on evaporation of solvent was filtered, washed with cold water and recrystalized from ethanol to get **2a-l.**

2-[(4-Fluorophenylamino)methyl]phenol (2a)

White solid, Yield 90 %, m.p.125 ^oC. IR KBr):3540 cm^{-1} (OH), 3248 cm^{-1} (NH), 2947 cm^{-1} (-CH). ^1H NMR (DMSO d_6): δ 4.01 (s, 1H, NH), δ 4.12 (s, 2H, -CH_2), δ 6.90-7.31 (m, 8H, Ar-H), δ 10.20 (s, 1H, Ar-OH); ^{13}C NMR; 156.2,153.1,145.3,143.4,136.1,134.3,130.7, 115.0, 113.6, 43.3. Anal Calcd for $C_{13}H_{12}FNO$ (217): C, 77.41; H, 5.52; N, 6.45. Found: C, 77.40; H, 5.31; N, 6.75

2,4-Dibromo-6-[(4-fluorophenylamino)methyl]phenol (2b)

Yellow solid, Yield 85 %, m.p.140 ^oC. IR (KBr):3550 cm^{-1} (OH), 3240 cm^{-1} (NH), 2930 cm^{-1} (-CH). ^1H NMR (DMSO d_6): δ 4.03 (s, 1H, NH), δ 4.20 (s, 2H, -CH_2), δ 6.90-7.31 (m, 6H, Ar-H), δ 10.30 (s, 1H, Ar-OH); ^{13}C NMR; δ 157.4, 154.2, 145.8, 144.1, 136.9, 132.6, 116.3, 114.6, 110.0, 105.6, 44.7. Anal Calcd for $C_{13}H_{10}Br_2FNO$ (374.18): C, 41.71; H, 2.67; N, 3.74. Found: C, 41.40; H, 2.31; N, 3.55.

4-Chloro-2-[(4-fluorophenylamino)methyl]phenol (2c)

White solid, yield 80 %, m.p. 120 ^oC. IR KBr): 3545cm^{-1} (OH), 3245cm^{-1}(NH), 2940cm^{-1}(-CH). ^1H NMR (DMSO d_6): δ 4.05 (s, 1H, NH), δ 4.20 (s, 2H, -CH_2), δ 7.00-7.45 (m, 7H,

Ar-H), δ 10.31 (s, 1H, Ar-OH); ^{13}C NMR; 158.4, 151.1, 144.1, 142.6, 137.0, 136.4, 130.7, 128.5, 115.3, 114.9, 43.3. Anal Calcd for $C_{13}H_{11}ClFNO$ (251.5): C, 62.00; H, 4.37; N, 5.30. Found: C, 62.02; H, 4.25; N, 5.30.

2-[(4-Fluorophenylamino)methyl]-2,6-diiodophenol (2d)

Yellow solid, Yield 85 %, m.p.110 ºC. IR (KBr):3535 cm^{-1} (OH), 3225 cm^{-1} (NH), 2915 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ 4.01 (s, 1H, NH), δ 4.13 (s, 2H, -CH_2), δ 6.85-7.25 (m, 6H, Ar-H), δ 10.12 (s, 1H, Ar-OH); ^{13}C NMR; δ 155.2, 152.3, 143.7, 142.1, 136.9, 131.0, 114.1, 111.6, 105.0, 102.9, 44.7. Anal Calcd for $C_{13}H_{10}F\ I_2NO$ (467): C, 32.26; H, 2.13; N, 2.99. Found: C, 32.55; H, 2.10; N, 3.01.

4-[(4-Fluorophenylamino)methyl]benzene-1,3-diol (2e)

White solid, Yield 85 %, m.p.135 ºC. IR KBr):3430 cm^{-1} (OH), 3235 cm^{-1} (NH), 2920 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ 4.05 (s, 1H, NH), δ 4.20 (s, 2H, -CH_2), δ 6.40-6.85 (m, 7H, Ar-H), δ 10.01 (s, 2H, 2Ar-OH); ^{13}C NMR; 158.0, 156.1, 143.4, 140.7, 137.0, 130.2, 115.3, 114.9, 110.0, 105.8, 43.3. Anal Calcd for $C_{13}H_{12}FNO_2$ (233): C, 66.95; H, 5.15; N, 6.00. Found: C, 67.02; H, 5.10; N, 6.05.

2-Ethoxy-4-[(4-fluorophenylamino)methyl]phenol (2f)

White solid, Yield 85 %, m.p.148 ºC. IR KBr): 3510 cm^{-1} (OH), 3240 cm^{-1} (NH), 2890 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ1.35 (t, 3H, CH_3) δ3.90 (q, 2H, CH_2), δ 4.13 (s, 1H, NH), δ 4.20 (s, 2H, -CH_2), δ 7.10-7.90 (m, 7H, Ar-H), δ 10.01 (s, 1H, Ar-OH); ^{13}C NMR; 158.3, 156.1, 150.8, 134.7, 133.5, 130.0, 123.6, 116.5, 112.3, 114.9, 65.2, 56.4, 18.0. Anal Calcd for $C_{15}H_{16}FNO_2$ (261): C, 68.96; H, 6.13; N, 5.36. Found: C, 68.56; H, 6.05; N, 5.45.

2-Bromo-6-ethoxy-4-[(4-fluorophenylamino)methyl]phenol (2g)

Brown solid, Yield 85 %, m.p.152 ºC. IR KBr):3515 cm^{-1} (OH), 3252 cm^{-1} (NH), 2920 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ1.37 (t, 3H, CH_3) δ3.96 (q, 2H, CH_2), δ 4.09 (s, 1H, NH), δ 4.15 (s, 2H, -CH_2), δ 7.15-7.95 (m, 6H, Ar-H), δ 10.10 (s, 1H, Ar-OH); ^{13}C NMR; 158.7, 156.1, 151.0, 135.2, 134.1, 131.0, 124.5, 117.2, 113.3, 115.0, 65.8, 56.9, 18.8. Anal Calcd for $C_{15}H_{15}BrFNO_2$ (339.5): C, 53.01; H, 4.41; N, 4.12. Found: C, 53.00; H, 4.35; N, 4.20.

2-Ethoxy-4-[(4-fluorophenylamino)methyl]-6-iodophenol (2h)

Yellow solid, yield 77 %, m.p.135 ºC. IR KBr):3505 cm^{-1} (OH), 3210 cm^{-1} (NH), 2910 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ1.30 (t, 3H, CH_3) δ3.85 (q, 2H, CH_2), δ 4.10 (s, 1H, NH), δ 4.15 (s, 2H, -CH_2), δ 7.09-7.80 (m, 7H, Ar-H), δ 10.03 (s, 1H, Ar-OH); ^{13}C NMR; 158.1, 156.1, 149.8, 134.3, 133.0, 130.7, 122.9, 117.1, 111.8, 113.2, 64.1, 56.1, 18.0. Anal Calcd for $C_{15}H_{15}FINO_2$ (387): C, 46.51; H, 3.87; N, 3.61. Found: C, 46.70; H, 3.05; N, 3.80.

4-[(4-Fluorophenylamino)methyl]-2-methoxyphenol (2i)

White solid, Yield 85 %, m.p. 141 ºC. IR KBr): 3510 cm^{-1} (OH), 3260 cm^{-1} (NH), 2925 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ 3.70(s, 3H, CH_3) δ 4.22 (s, 1H, NH), δ 4.32 (s, 2H, -CH_2), δ 6.40-6.80 (m, 7H, Ar-H), δ 10.05 (s, 1H, Ar-OH); ^{13}C NMR; 158.5, 153.0, 145.1, 139.1, 136.0, 120.8, 116.8, 115.9, 114.3, 113.9, 61.2, 46.2. Anal Calcd for $C_{14}H_{14}FNO_2$ (247): C, 68.01; H, 5.66; N, 5.67. Found: C, 68.10; H, 5.75; N, 5.70.

2-Bromo-4-[(4-fluorophenylamino)methyl]-6-methoxyphenol (2j)

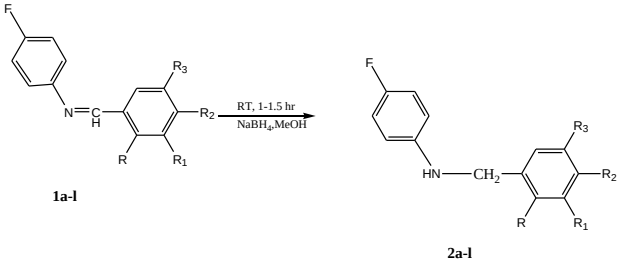
Faint yellow solid, yield 80 %, m.p.145 ºC. IR KBr):3513 cm^{-1} (OH), 3275 cm^{-1} (NH), 2940 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ3.80(s, 3H, CH_3) δ 4.25 (s, 1H, NH), δ 4.36 (s, 2H, -CH_2), δ 6.45-6.90 (m, 6H, Ar-H), δ 10.10 (s, 1H, Ar-OH); ^{13}C NMR; 158.7, 153.3, 145.5, 139.2, 136.6, 121.0, 117.1, 116.0, 114.7, 114.3, 61.8, 44.1. Anal Calcd for $C_{14}H_{13}BrFNO_2$ (325.5): C, 51.61; H, 3.99; N, 4.30. Found: C, 51.40; H, 4.01; N, 4.25.

2-Chloro-4-[(4-fluorophenylamino)methyl]-6-methoxyphenol (2k)

White solid, Yield 78 %, m.p. 138 ºC. IR KBr):3515 cm^{-1} (OH), 3265 cm^{-1} (NH), 2940 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ3.75(s, 3H, CH_3) δ 4.3 (s, 1H, NH), δ 4.40 (s, 2H, -CH_2), δ 6.50-7.00 (m, 6H, Ar-H), δ 10.16 (s, 1H, Ar-OH); ^{13}C NMR; 159.1, 153.8, 146.0, 139.7, 137.3, 121.8, 117.7, 117.1, 115.0, 114.9, 62.0, 44.5. Anal Calcd for $C_{14}H_{13}ClFNO_2$ (281.5): C, 59.68; H, 4.61; N, 4.97. Found: C, 59.40; H, 4.72; N, 4.60

4-[(4-Fluorophenylamino)methyl]-2-iodo-6-methoxyphenol (2l)

Yellow solid, Yield 77 %, m.p. 130 ºC. IR KBr):3500 cm^{-1} (OH), 3215 cm^{-1} (NH), 2904 cm^{-1} (-CH). ^{1}H NMR (DMSO d_6): δ 3.80(s, 3H, CH_3) δ 4.17 (s, 1H, NH), δ 4.20 (s, 2H, -CH_2), δ 6.55-7.10 (m, 6H, Ar-H), δ 10.10 (s, 1H, Ar-OH); ^{13}C NMR; 159.0, 153.2, 145.8, 137.1, 137.0, 121.5, 116.6, 116.3, 114.4, 114.0, 62.5, 44.0. Anal Calcd for $C_{14}H_{13}FINO_2$ (373): C, 5.01; H, 3.48; N, 3.75. Found: C, 45.51; H, 3.62; N, 3.50



1a, 2a: R=OH; R_1, R_2, R_3=H; **1b, 2b**: R=OH; R_1, R_3=Br, R_2=H; **1c, 2c:** R=OH; R_1, R_2=H, R_3=Cl; **1d, 2d**: R=OH; R_1, R_3=I, R_2=H; **1e, 2e:** R, R_2=OH; R_1, R_2=H; **1f, 2f:** R, R_3=H; R_1=OEt, R_2=OH; **1g, 2g**: R=H; R_1=OEt; R_2=OH; R_3=Br **1h, 2h**: R=H; R_1=OEt; R_2=OH; R_3=I; **1i, 2i**: R, R_3=H; R_1=OMe, R_2=OH; **1j, 2j**: R=H; R_1=OMe, R_2=OH, R_3=Br; **1k, 2k:** R=H; R_1=OMe, R_2=OH, R_3=Cl; 1l, 2l: R=H; R_1=OMe, R_2=OH

Scheme1. Reduction of fluoroimines.

Results and discussion

This paper describes very simple methodologies developed for effective reduction of fluoro schif bases using sodium borohydride as a reducing agent. Similar methodologies have been found effective in reducing ketones to alcohols in an aprotic solvents[15]. Several structurally varied Schiff bases underwent reduction by this procedure to produce the corresponding secondary amines in high yields[16,19]. Sodium borohydride thus appears to be very efficient reagent for the reduction of imines to the corresponding amines in high yields. Moreover, the easy availability of reagent, operational simplicity and generality makes this procedure extremely attractive. The procedure does not require anhydrous condition is inexpensive and avoids the use of inert atmosphere.

Conclusion

We have described a convenient procedure by means of $NaBH_4$ has shown to convert fluoro imines into corresponding amines. The structures of all the amines are supported by FTIR, ^1H and ^{13}C NMR and mass spectroscopic techniques. The developed method is simple, inexpensive and safe for the one-pot reduction of imines.

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