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RESEARCH ARTICLE

A Simple Reduction of Imines to Biologically Important Secondary Amines Using Sodium Borohydride/Alumina in Solid-Phase

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Abstract The present paper describes a simple reduction of *N*-arylidene- and *N*-heteroarylideneamines from salicylaldehyde, thiophene-2-carboxaldehyde and *N*-methylindole-3-carboxaldehyde to the corresponding secondary amines by a simple method using sodium borohydride on neutral alumina under solvent-free conditions. The new products have been characterized by analytical and spectral data (IR, ^{1}H and ^{13}C NMR, MS). The mass spectra of *N*-substituted benzhydryl amines (alkyl amines) showed the molecular ion peak corresponding to $M^{+} - 2$ and not M^{+} as shown by the *N*-substituted aromatic amines that has been explained by the possibility of formation of a more stable radical in the former type.

Keywords Imines · $NaBH_4$–Al_2O_3 · *sec*-Amines

Introduction

The common method for accessing the secondary amines is the reductive amination of aldehydes or ketones either directly employing the carbonyl compounds and amines or indirectly via preparation of imines followed by reduction [1]. The conversion of imines to amines represents a valuable functional group transformation with wide applicability in synthetic organic chemistry and is an area of current research [2, 3]. Metal hydrides alone [4, 5] or in combination with various transition metal salts [6, 7] are well-known catalysts for the reduction of imines to amines. Greener methodologies for organic synthesis have been developed using non-conventional heating by microwave or ultrasonic irradiations, reactions in aqueous medium, and reactions under solvent-free conditions [8, 9]. Kazemi et al. [10] reported a quick method for the reduction of some *N*-aryl-substituted imines obtained from benzaldehydes to sec-amines in excellent yields by sodium borohydride supported on neutral alumina, and carried out the reduction of *N*-salicylideneaniline, which contains a 2-hydroxyphenyl group on the methine carbon and phenyl group on the nitrogen atom, the methodology for different substituents on the nitrogen atom still remains unexplored.

The *sec*-amines are compounds of biological interest and have also been employed in the synthesis of products that are of interest in pharmaceutical and agricultural industries [11–13]. The *sec*-amines obtained from *N*-aryl imines of salicylaldehyde have been employed in the synthesis of benzoxazines having potential fungicidal activity [14]. The biological activities associated with *sec*-amines include analgesic [15], anti-neuroinflammatory [16], antimicrobial [17], and α-glucosidase inhibition [18]. In particular, the *sec*-amines obtained from *N*-aryl imines of 1-benzylindole-3-carboxaldehyde have recently been evaluated against the $pp60^{c\text{-}Src}$ tyrosine kinase target [19].

The present paper reports the reduction of *N*-salicylideneamines, *N*-(2-thienylidene)amines, and *N*-(1-methylindol-3-ylidene)amines to the corresponding *sec*-amines by simple grinding with alumina-supported sodium borohydride, and the characterization data of the new compounds. The significant spectral characteristics are explained.

Materials and Methods

Melting points have been recorded on a Stuart Scientific melting point apparatus and are uncorrected. The IR

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spectra have been recorded on a Perkin-Elmer-781 IR spectrophotometer using KBr disc of the sample. The ^{1}H and ^{13}C NMR spectra are recorded in a $CDCl_3$ solution at 300 and 75.4 MHz, respectively, on a Brucker™ 300 MHz spectrometer, whereas the mass spectra of the products are on an agilent 597C mass spectrometer.

Aldehydes and amines have been procured from Aldrich products. Imines of salicylaldehyde and thiophene-2-carboxaldehyde have been prepared by the reported methods [20, 21]. The imines of *N*-methylindole-3-carboxaldehyde are prepared by refluxing it with appropriate amine in ethanol.

General Reduction Procedure

To a $NaBH_4/Al_2O_3$ solid-phase prepared in a porcelain mortar by simply grinding neutral alumina (2.0 g) with sodium borohydride (0.34 g, 9.0 mmol) for 5 min, appropriate imine (1.0 mmol) from salicylaldehyde was added followed by addition of five drops of 99 % methanol. The grinding was further continued and the progress of each reaction was monitored by the TLC using chloroform-ether solution. After the complete disappearance of the substrate (15–20 min), the reaction mixture was poured in 20.0 ml of dichloromethane and filtered through a sintered glass funnel. The residue is washed further with two 15.0 ml portions of the same solvent. The solvent from the filtrate containing the product was evaporated to obtain secondary amine products. The same method was employed for the reduction of imines from thiophene-2-carboxaldehyde and *N*-methylindol-3-carboxaldehyde. The analytical and spectral data of the new and some scarce secondary amines (see "Results and Discussion" section) containing 2-hydroxyphenyl, *N*-methylindol-3-yl and 2-thienyl moieties are described below.

*N-(2-Hydroxyphenyl)methyl-4-ethoxyaniline (**2d**)*

Yield: 80 %; m.p. 106–108 °C; mol. formula $C_{15}H_{17}NO_2$; reqd. C 74.05; H 7.04 and N 5.76 %, found C 73.76; H 7.32 and N 5.82 %; IR (KBr, cm^{-1}): 3254 (br, OH and NH); ^{1}H NMR ($CDCl_3$, δ ppm): 7.26–7.19 (m, 1H, arom), 7.13–7.11 (dd, 1H arom), 6.91–6.82 (m, 6H, arom), 6.69 (s, 1H, NH), 4.38 (s, 2H, CH_2), 3.99 (q, 2H, J = 7.2 Hz, OCH_2), 1.42 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 157.2 (OH–*C*), 154.0, 140.3, 129.2, 128.6, 122.8, 119.8, 117.9, 116.7, 115.6, 63.9 (*C*H_2O), 50.3 (*C*H_2), 14.9 (*C*H_3); MS (*m/z*): 243 (M^+), 228, 214, 197, 186, 168, 137, 122, 109, 93, 77, 65.

*N-(2-Hydroxyphenyl)methylbenzhydrylamine (**2f**)*

Yield: 70 %; m.p. 101–102 °C; mol. formula $C_{20}H_{19}NO$; reqd. C 83.01; H 6.62 and N 4.84 %, found C 82.75; H 6.85 and N 4.80 %; IR (KBr, cm^{-1}): 3254 (br), 3027, 1588, 1490, 1252; ^{1}H NMR ($CDCl_3$, δ ppm): 7.50–7.29 (m, 11H, arom), 7.06–7.02 (m, 2H, arom), 6.94–6.89 (t, 1H, arom), 5.31 (s, 1H, D_2O exchangeable, OH or NH), 4.99 (s, 1H,), 3.98 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, δ ppm): 161.28 (OH–*C*), 158.18, 142.77, 142.51, 142.13, 141.73, 132.81, 131.93, 129.41, 128.96 127.98, 122.79, 119.73, 66.28 (*C*–H), 50.76 (*C*H_2); MS (*m/z*): (287, M^+ −2) 167, 152, 115, 91.

*N-(2-Thienyl)methyl-4-ethoxyaniline (**2j**)*

Yield: 79 %; m.p. 70–71 °C; mol. formula $C_{13}H_{15}NOS$; reqd. C 66.92; H 6.48 and N 6.00 %, found C 66.60; H 6.65 and N 6.03 %; IR (KBr, cm^{-1}): 3397, 3185, 2982, 2929, 1509; ^{1}H NMR ($CDCl_3$, δ ppm): 7.27–7.25 (dd, 1H, arom), 7.12–7.00 (m, 2H, arom), 6.86-6.83 (dd, 2H, arom), 6.73–6.69 (dd, 2H, arom), 4.52 (s, 2H, CH_2), 4.03 (q, 2H, J = 7.5 Hz, OCH_2) 3.88 (s, 1H, D_2O exchangeable, NH), 1.45 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 151.9, 143.4, 141.9, 126.8, 124.9, 124.5, 115.8, 114.6, 64.1, 44.5, 15.0; 233 (M^+), 136, 108, 97, 81, 65, 53.

*N-(2-Thienyl)methylbenzhydrylamine (**2l**)*

Yield: 81 %; m.p. 134–136 °C; mol. formula $C_{18}H_{17}NS$; reqd. C 77.38; H 6.13 and N 5.01 %, found C 77.23; H 6.25 and N 4.80 %; IR (KBr, cm^{-1}): 3174 (N–H), 3027, 1598; ^{1}H NMR ($CDCl_3$, δ ppm): 7.49–7.03 (m, 13H, aromatic), 5.10 (s, 1H, CH), 4.65 (bs, 1H, NH), 4.10 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, δ ppm): 144.3, 143.7, 138.3, 137.8, 135.2, 130.1, 129.3, 128.8, 128.7, 128.6, 128.4, 128.0, 71.8, 52.2; MS (*m/z*): 277 (M^+ −2), 202, 194, 182, 167, 152, 139, 128, 115, 97, 89, 77, 63.

*N-(1-Methylindol-3-yl)methylaniline (**2m**)*

Yield: 76 %; m.p. 115–118 °C; mol. formula $C_{16}H_{16}N_2$; reqd. C 81.32; H 6.82 and N 11.85 %, found C 81.10; H 7.05 and N 11.70 %; IR (KBr, cm^{-1}): 3410 (NH); ^{1}H NMR ($CDCl_3$, δ ppm): 7.74–7.71 (dd, 1H, arom), 7.41–7.18 (m, 5H, arom), 7.17 (s, 1H, arom), 6.79–6.75 (m, 3H, arom), 4.52 (s, 2H, CH_2), 3.83 (s, 3H, *N*–CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 148.6, 137.3, 129.3, 129.2, 127.5, 127.1, 121.9, 119.2, 119.1, 112.8, 112.3, 109.4, 39.0, 32.8; MS (*m/z*): 236 (M^+), 220, 144, 118, 77.

*N-(1-Methylindol-3-yl)methyl-4-methylaniline (**2n**)*

Yield: 79 %; m.p. oil; mol. formula $C_{17}H_{18}N_2$; reqd. C 81.56; H 7.25 and N 11.19 %, found C 81.45; H 7.51 and N 11.30 %; IR (KBr, cm^{-1}): 3410 (NH); ^{1}H NMR ($CDCl_3$, δ ppm): 7.72–7.69 (dd, 1H, arom), 7.39–7.01 (m, 6H, arom), 6.71–6.65 (m, 2H, arom), 4.49 (s, 2H, CH_2), 3.82

(s, 3H, *N*–CH_3), 2.31 (s, 3H, CH_3); MS (*m/z*): 250 (M^+), 235, 219, 144, 131, 117, 110, 102, 89, 77.

*N-(1-Methylindol-3-yl)methyl-4-methoxyaniline (**2o**)*

Yield: 79 %; m.p. 93–95 °C; mol. formula $C_{17}H_{18}N_2O$; reqd. C 76.66; H 6.81 and N 10.52 %, found C 76.45; H 7.03 and N 10.60 %; IR (KBr, cm^{-1}): 3420 (NH); ^{1}H NMR ($CDCl_3$, δ ppm): 7.72–7.70 (dd, 1H, arom), 7.39–7.28 (m, 2H, arom), 7.21–7.15 (t, 1H, arom), 7.10 (s, 1H, arom), 6.88-6.84 (dd, 2H, arom), 6.75–6.72 (dd, 2H, arom), 4.47 (s, 2H, CH_2), 3.82 (s, 3H, CH_3), 3.81 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 152.1, 142.9, 137.2, 128.3, 127.2, 121.9, 119.3, 119.2, 114.9, 114.2, 112.6, 109.2, 55.9, 40.9, 32.7; MS (*m/z*): 266 (M^+), 251, 235, 144, 131, 123, 108, 77.

*N-(1-Methylindol-3-yl)methyl-4-chloroaniline (**2p**)*

Yield: 75 %; m.p. 82–84 °C; mol. Formula $C_{16}H_{15}N_2Cl$; reqd. C 70.98; H 5.58 and N 10.35 %, found C 70.65; H 5.80 and N 10.45 %; IR (KBr, cm^{-1}): 3400 (NH); ^{1}H NMR ($CDCl_3$, δ ppm): 7.72–7.70 (dd, 1H, arom), 7.40–7.16 (m, 5H, arom), 7.08 (s, 1H, arom), 6.68–6.63 (m, 2H, arom), 4.48 (s, 2H, CH_2), 3.94 (bs, 1H, NH), 3.82 (s, 3H, *N*–CH_3); MS (*m/z*): 270 (M^+), 268, 257, 217, 156, 144, 129, 115.

*N-(1-Methylindol-3-yl)methylbezhydrylamine (**2q**)*

Yield: 65 %; m.p. oil; mol. formula $C_{23}H_{22}N_2$; reqd. C 84.63; H 6.79 and N 8.58 %, found C 84.40; H 7.02 and N 8.76 %; IR (KBr, cm^{-1}): 3400 (NH); ^{1}H NMR ($CDCl_3$, δ ppm): 7.69–7.67 (dd, 1H, arom), 7.52–7.47 (m, 4H, arom), 7.42–7.13 (m, 9H, arom), 7.03 (s, 1H, arom), 5.0 (s, 1H, CH), 3.98 (s, 2H, CH_2), 3.82 (s, 3H, *N*–CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 144.3, 137.2, 128.5, 127.6, 127.5, 127.4, 127.0, 121.7, 119.3, 119.0, 113.7, 109.3, 66.9, 43.1, 32.7; MS (*m/z*): 324 (M^+ −2), 247, 220, 193, 180, 167, 152, 143, 132, 115, 77.

Results and Discussion

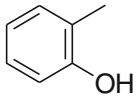
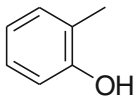
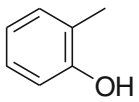
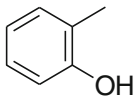
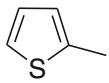
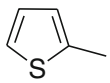
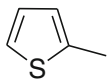
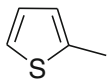
Treatment of imine *N*-salicylideneaniline (1a) with sodium borohydride supported on neutral alumina by grinding in a porcelain mortar for 20 min and usual work-up led to the formation of a white crystalline product in almost quantitative yield that was identified as *N*-(2-hydroxyphenyl)methylaniline (2a) on the basis of reported m.p. (Table 1) and spectral data. IR spectra of the product showed the disappearance of the band at 1,615 cm^{-1} corresponding to the imine linkage. ^{1}H NMR spectra also showed the complete disappearance of the low-field singlet signal corresponding to the azomethine proton (CH=N), and appearance of the methylene proton at δ 4.40 ppm. The progress of the reaction was monitored every 5 min by TLC employing 3.0, 5.0, 7.0, 9.0 and 10 mmol of sodium borohydride in order to optimize the reaction condition. A minimum time of 20 min was recorded for complete reduction of imine using 9.0 mmol of sodium borohydride as against 5 min reported earlier using 3.0 mmol of hydride [10]. A similar treatment of other imines derived from salicylaldehyde and differently substituted amines, also led to the formation of corresponding amines **2b–f** in very good yields (see Table 1). The reaction requires relatively high quantity of the reducing agent sodium borohydride probably because of fewer molecular interactions due to large quantity of the solid support (alumina).

After establishing the versatility of the method for a simple reduction of imines of salicylaldehyde, the study was extended to imines synthesized from thiophene-2-carboxaldehyde and to imines obtained from *N*-methylindole-3-carboxaldehyde because the corresponding secondary amines of these imines are either scarce or not reported at all and may be of potential biological interest. Treatment of the imines with sodium borohydride supported on neutral alumina by grinding in a porcelain mortar for 15–20 min led to the formation of products in good yields, see Table 1. The products were characterized by elemental analysis and spectral data. To the best of our knowledge, the *sec*-amines **2f** and **2l–q** are new amines not reported previously whereas the other *sec*-amines containing 2-thienyl are scarcely known.

A significant difference in the mass spectra of the products was observed when aromatic groups on nitrogen were replaced with the benzhydryl group. All three such amine **2f**, **2l**, and **2q**, instead of showing the molecular ion peak, showed the fragment corresponding to the molecular ion peak equal to M^+ less by 2. This can be explained by possible of formation of a tertiary radical by cleavage of hydrogen atom from the methine carbon in these imines. Such a radical would be stabilized by resonance from the two phenyl groups. This radical may be transformed to imines as shown in Scheme 1. The mass spectra thus show the molecular ion peak corresponding to the benzophenone imines 3.

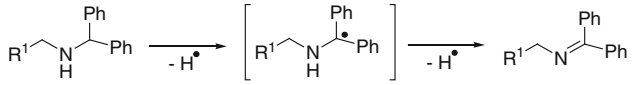
The mechanism for the reaction is shown in Scheme 2. Initially, the azomethine carbon in imines **1** receives a hydride ion from sodium borohydride and changes to intermediate **3** which quickly accepts a proton from the traces of methanol. The reaction did not proceed without a solid alumina support or without adding the traces of methanol.

Table 1 Physical data of product *sec*-amines

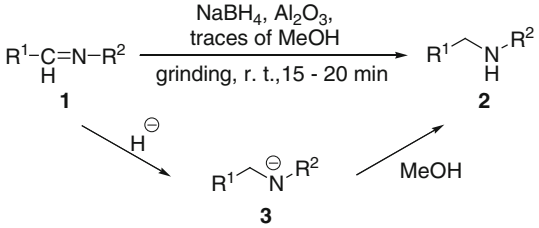
Compd. No.	R^1	R^2	Mol. formula[a]	m.p. (°C)	Yields[b] (%)
2a		Ph	$C_{13}H_{13}NO$	126–128 (129–131) [22]	79
2b		4-MePh	$C_{14}H_{15}NO$	124–126 (122–123) [23]	80
2c		4-MeOPh	$C_{14}H_{15}NO_2$	135–136 (132–134) [22]	81
2e		4-ClPh	$C_{13}H_{12}NOCl$	128–130 (122) [22]	68
2g		Ph	$C_{11}H_{11}NS$	128–130	87
2h		4-MePh	$C_{12}H_{13}NS$	85–86	86
2i		4-MeOPh	$C_{12}H_{13}NOS$	70–72	76
2k		4-ClPh	$C_{11}H_{1O}NSCl$	48–50	96

[a] All compounds showed analysis within ± 0.3

[b] Isolated yields



Scheme 1 Mass fragmentation of *sec*-amines to benzophenone imines



Scheme 2 Reduction of imines to *sec*-amines and the mechanism of reduction

Conclusions

The study reports a simple and versatile method for the simple reduction of imines of salicylaldehyde, thiophene-2-carboxaldehyde, and 1-methylindole-3-carboxaldehyde to biologically important *sec*-amines using sodium borohydride on solid neutral alumina support. Out of seventeen amines synthesized by this method seven compounds are new.

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