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INEXPENSIVE PROTOCOL FOR REDUCTION OF IMINES TO AMINES USING POLYMETHYLHYDROSILOXANE (PMHS)

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Abstract: Amines have been prepared by reduction of imines using inexpensive Polymethylhydrosiloxane (PMHS) as a hydride source activated by $ZnCl_2$.

Amino functionality is present in greater than 75% of drugs and drug candidates[1]. Accordingly generation of this functionality has attracted the interest of organic chemists and various methods have been reported in literature[2]. These include conversion of alcohol functionality to amino via tosylates or mesylates and reduction of nitriles, azides and nitro compounds. Yet another approach wherein aldehydes and ketones are derivatized as imines and further reduced to amines using various hydrides has gained prominence owing to high yields and simplicity in purifications. The hydride sources used includes $NaBH_4$,[3] $LiAlH_4$,[4] and BH_3.DMA.[5] All these reagents are either flammable or expensive. Our continued interest in the utilization of polymeric hydride namely Polymethylhydrosiloxane (PMHS) as a safe and economic hydride source has

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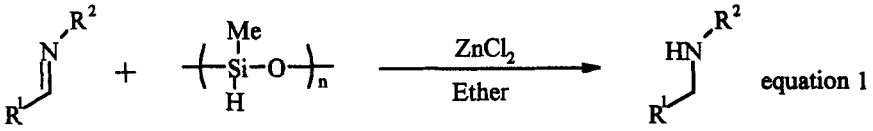


equation 1

prompted us to study the reduction of imines to amines and results pertaining to this study are reported herein[6,7,8] (Table 1).

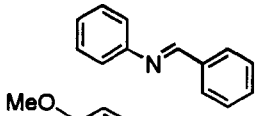
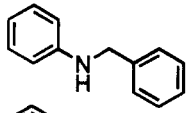
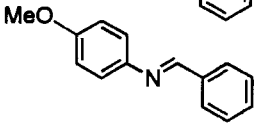
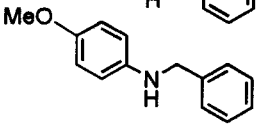
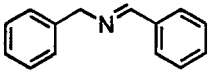
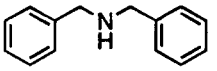
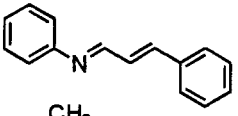
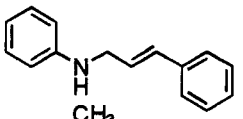
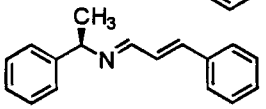
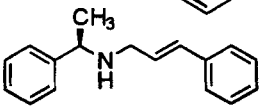
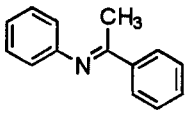
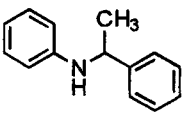
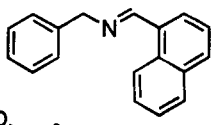
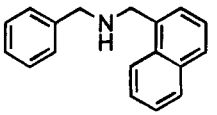
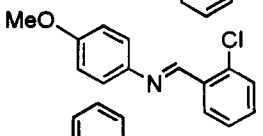
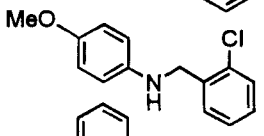
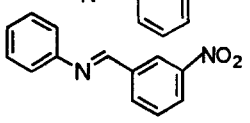
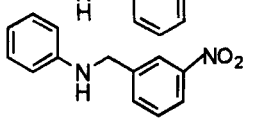
Initially, Benzaldehyde aniline adduct (entry 1) was reacted with PMHS and $ZnCl_2$ in ether at ambient temperature for 10 h to yield benzyl phenyl amine in 67% isolated yield after a standardized workup (*vide infra*). Similarly imine derivatives obtained by condensations of benzaldehyde and *p*-methoxybenzyl amine (entry 2), benzaldehyde and benzylamine (entry 3)[6c], acetophenone-aniline (entry 6), naphthal-benzylamine (entry 7) were reduced to the corresponding amines. Cinnamaldehyde-aniline derivative (entry 4) yielded the corresponding amine without reduction of cinnamyl double bond albeit in moderate yields. Similarly the chiral amine - cinnamaldehyde derivative (entry 5) generated the amino compound without racemization. Entries 8 and 9 demonstrate that the hydride sensitive *o*-chlorobenzaldehyde derivative and *m*-nitrobenzaldehyde derivatives were reduced without affecting chloro and nitro groups.

Experimental

General : All reactions were conducted under an inert atmosphere. ^1H NMR data were recorded on Varian Gemini-200 MHz. Mass measurements were carried out on a CEC-21-110 (double focussing mass spectrometer operating at 70 eV). All products were characterized by ^1H NMR, mass spectrometry and also by comparison with standard samples wherever applicable.

General procedure for the preparation of imines. The carbonyl compound (1.0 equiv.) and amine (1.1 equiv.) were dissolved in dry toluene under nitrogen in a round-bottom flask equipped with a reflux condenser and a Dean-Stark trap. The mixture was heated to reflux for 24-28 hours. The solvent was then removed

Table 1.

Entry	Substrate	Product	Yield (%)[a]
1			67
2			71
3			73
4			55
5			50
6			60
7			63
8			70
9			75

[a] yields are based on isolated chromatographically homogeneous products

under reduced pressure and the imine products obtained were used without further purification.

Preparation of imines (Entry 4, 5 and 6)

To about 1 g of activated molecular sieves (4Å) in 50 ml round bottom flask were added 15 ml of benzene, a carbonyl compound (2 mmol) and an amine

(2.2 mmol) and the mixture was stirred at ambient temperature for 20 h. The molecular sieves were filtered off, the volatiles were removed on a rotary evaporator to yield the imine in quantitative yield. The imines thus obtained were utilized for reduction without further purification.

General procedure for the reduction of imines

To polymethylhydrosiloxane (PMHS) (300mg,) in a 25 ml flask fitted with septum inlet and magnetic stirr bar, was added freshly fused $ZnCl_2$ (270mg, 2 mmol) in 5 ml dry ether under nitrogen atmosphere. After 10 min the imine (1 mmol) was added, and the reaction mixture was allowed to stir at room temperature as specified. The reaction mixture was extracted with 1M HCl (2x15 ml). The aqueous layer was further washed with CH_2Cl_2 (15 ml) to remove non-amine impurities. The purified aqueous layer was basified to pH ~10 with 1N NaOH, and extracted with ethyl acetate (3x15 ml). The combined organic layers were washed with water (1x15 ml) and brine (1x15 ml). After drying over Na_2SO_4, the volatiles were removed on a rotary evaporator to yield the amine (for yields see Table 1).

***N*-benzylaniline**[6c] (Table 1, entry 1). *N*-Diphenylmethanimine (181mg, 1 mmol) was reduced in 10 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40 -7.17 (m, 7H), 6.68(t, 1H, J=7.2 Hz) 6.54 (d, 2H, J=8.2 Hz) 4.30 (s, 2H), 3.90(br, 1H). MS: m/z 183 (M^+), 91, 77, 65, 51.

***N*-(1-benzyl-4-methoxy)-aniline**[5] (Table 1, entry 2). *N*-(4-methoxyphenyl) phenylmethanimine (195 mg, 1 mmol) was reduced in 12 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40-7.25 (m, 5H), 6.75 (d, 2H, J = 8.8 Hz), 6.55 (d, 2H, J = 8.8 Hz), 4.28 (s, 2H), 3.75 (s, 3H), MS: m/z 213 (M^+), 122, 107, 91, 77.

***N*-benzyl phenylmethanamine**[6c] (Table 1, entry 3). *N*-benzylphenylmethanimine (211 mg, 1 mmol) was reduced in 10 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): 7.60-7.20 (m, 10H), 3.8 (s, 4H). MS: m/z 197 (M+), 106, 91, 65, 51.

***N*-1-[(E)-3-phenyl-2-propenyl] aniline** [3a](Table 1, entry 4). *N*-1, 3-diphenyl-(E)-2-propenimine. (207 mg, 1 mmol) was reduced in 20 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6-7.05 (m, 10H), 6.60 (d, 1H, J = 14 Hz), 6.25(dt, 1H, J = 15, 6 Hz), 3.90 (d, 2H, J = 5.5 Hz). MS: m/z 209 (M^+), 117, 106, 91, 77, 51.

***N*-1-phenyl-(1R)-ethyl-3-phenyl-(E)-2-propen-1-amine** (Table 1, entry 5). *N*-1-[phenyl(1R)-ethyl]-3-phenyl-(E)-2-propen-1-imine. (235 mg, 1 mmol) was reduced in 24 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60-7.10 (m, 10H), 6.60 (d, 2H, J = 15.5 Hz), 6.30 (dt, 1H, J = 15.5, 5 Hz), 3.9 (q, 1H, J = 6.2 Hz), 3.3 (br d, 2H, J = 6.8 Hz), 1.45 (d, 3H, J = 6.2 Hz), MS: m/z 237 (M^+), 117, 106, 91, 77, 65; Anal. Calcd. For $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90; Found: C, 86.01; H, 8.08; N, 5.91.

1-(1-anilinoethyl) benzene [6a](Table 1, entry 6). *N*-1,1-diphenylethanimine. (195 mg, 1 mmol) was reduced in 15 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6-7.0 (m, 7H), 6.62 (t, 1H, J = 7.2 Hz), 6.55 (d, 2H, J = 8.8 Hz), 4.45 (q, 1H, J = 6.6 Hz), 1.5 (d, 3H, J = 6.6 Hz) MS: m/z 197 (M^+), 182, 105, 92, 77, 65, 51.

***N*-(1-napthylmethyl)-phenylmethanamine**[4a] (Table 1, entry 7). *N*-benzyl-1-napthylmethanimine (245 mg, 1 mmol) was reduced in 12 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.1 (d, 1H, J = 9 Hz), 7.92-7.75 (m, 2H), 7.50-7.22 (m, 9H), 4.25 (s, 2H), 3.9 (s, 2H), MS: m/z 247 (M^+), 154, 141, 127, 115, 91, 77, 65.

2-chloro-1-(4-methoxyanilinomethyl)benzene[5] (Table 1, entry 8). *N*-(4-methoxyphenyl)-2-chlorophenylmethanimine (245 mg, 1 mmol) was reduced in 12 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20 (m, 2H), 6.82-6.5 (m, 6H), 3.75 (s, 2H), 3.70 (s, 3H), 3.50(br s, 1H), MS: m/z 247 (M^+), 139, 125, 77, 65.

***N*-anilinomethyl-3-nitrobenzene**[5] (Table 1, entry 9). *N*-phenyl-3-nitrophenylmethanimine (225 mg, 1 mmol) was reduced in 12 h, following the general procedure. The amine was purified by column chromatography. ^{1}H NMR

(200 MHz, $CDCl_3$): δ 7.20 (d, 2H, J=7.5 Hz), 7.70-6.50 (m, 7H), 3.50 (s, 2H); MS: m/z 228 (M^+). 136, 106, 91, 77.

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