Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 10331–10338

TETRAHEDRON

An efficient conversion of nitroaromatics and aromatic amines to tertiary amines in one-pot way

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Received 28 September 2002; revised 17 September 2003; accepted 17 September 2003

Abstract—Reductive alkylation and reductive methylation of aromatic primary amines with carbonyls and 37% formaldehyde using decaborane in one-pot way gave the corresponding tertiary amines in high yields. The reaction condition was extended for the reduction of nitroaromatic using decaborane and Pd/C followed by the reductive alkylation and reductive methylation using decaborane to give the corresponding tertiary amines in high yields.

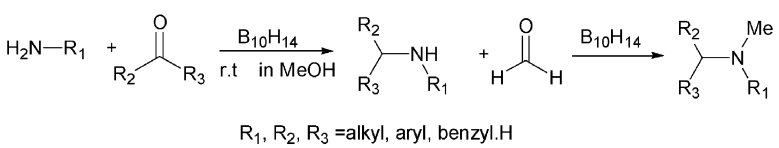
1. Introduction

Consecutive reactions[1] have received much attention because they efficiently give complex molecules from simple starting materials. The ideal case for these consecutive reactions is the one-pot synthesis, in which all these processes occur in a consecutive way by addition of reagents successively without isolation of intermediates.[2,3] It is necessary that the yield of each step should be quantitative (at least high) for consecutive reactions in one-pot way to be successful. One of the synthetic methods of secondary amines and tertiary amine is the reductive alkylation of primary amines and secondary amines with carbonyls using a variety of reducing reagents.[4]

Decaborane ($B_{10}H_{14}$)[5,6] is a commercially available white solid that decompose only slowly in air. Decaborane was reported as a reducing reagent in organic synthesis, but inefficient in synthetic point of view due to its low reducing power in a polar solvents.[7] By changing solvent to protic solvents and/or adding additives, decaborane was found to be quite mild reducing agent in reduction reactions such as reductive alkylation,[8] reductive methylation,[9] reductive etherification,[10] reduction of nitro groups and nitro reduction followed by reductive alkylation.[11] As a continuous study on decaborane, we exteneded decaborane to two one-pot reactions: the reductive alkylation[5] followed by reductive methylation (so-called double reductive alkylation) as well as the reduction of nitroaromatics followed by reductive alkylation and reductive methylation. Here we are going to report the synthesis of the corresponding tertiary amines from primary amines as well as the synthesis of the corresponding aromatic tertiary amines from nitroaromatics in methanol using decaborane in a one-pot way, and their scope and limitation.

2. Result and discussion

The consecutive reactions were conducted in methanol using decaborane as a reducing agent (Scheme 1 and 2). One is the double reductive alkylation of aromatic primary amine with various carbonyl and formaldehyde using decaborane to give aromatic tertiary amine and the other is the reduction of nitroaromatics using decaborane (Table 1) and 10% Pd/C system followed by the double reductive alkylation to give the corresponding aromatic tertiary amines (Table 2).



Scheme 1.

Keywords: reductive alkylation; reduction; nitroaromatic; decaborane; amines; one-pot reaction.
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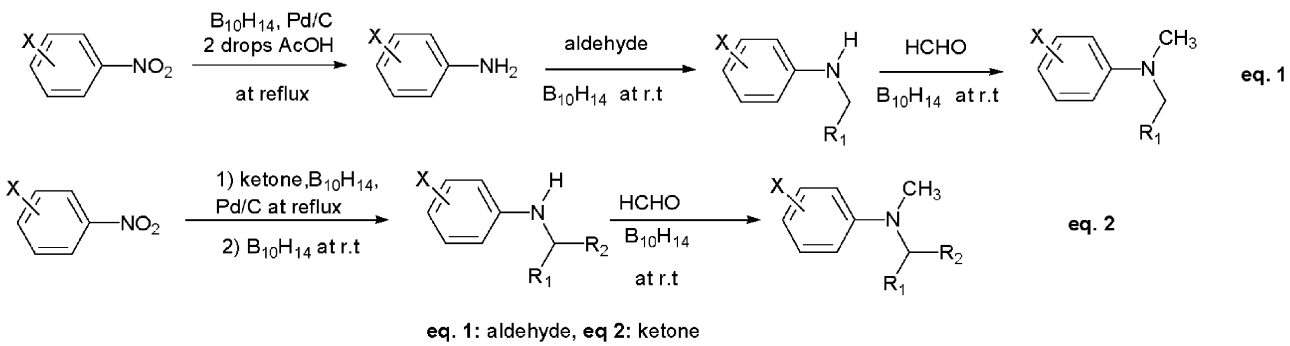
doi:10.1016/j.tet.2003.09.054



Scheme 2.

Table 1. Reductive alkylation of anilines followed by methylation

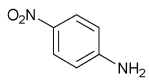
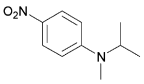
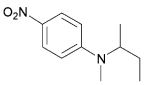
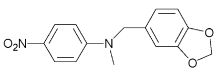
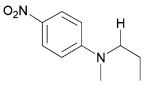
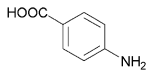
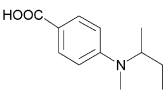
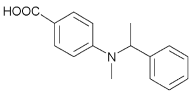
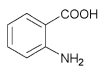
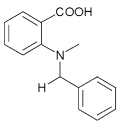
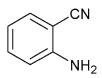
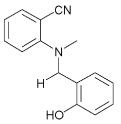
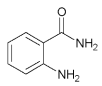
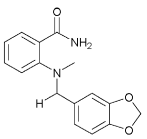
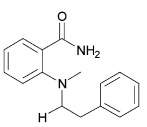
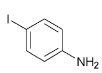
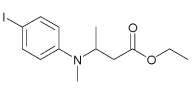
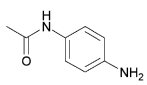
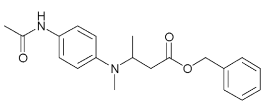
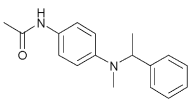
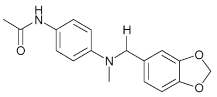
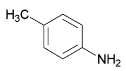
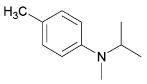
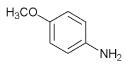
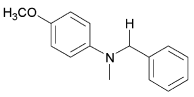
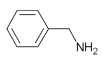
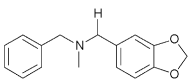
Entry	Substrates	Carbonyls (equiv.) decaborane (equiv.)/ time (h)	Formaldehyde[a] (equiv.)/ decaborane (equiv.)/ time (h)	Product	Yield (%)[b]
1		Acetone (1.1) 0.3/0.5	2/0.3/10		93
2		Butanone (1.1) 0.3/0.5	2/0.3/12		85
3		Piperonal (1.1) 0.3/8	2/0.3/3.3		96
4		Propanal (1.1) 0.3/15	2/0.3/2		64
5		Butanone (1.1) 0.3/1	1.5/0.2/1		97
6		Acetophenone (1.1) 0.3/12	2/0.3/1		90
7		Benzaldehyde (1.1) 0.3/0.5	1.5/0.2/0.5		98
8		Salicylaldehyde (1) 0.3/1	1.5/0.2/4		99
9		Piperonal (1) 0.3/0.5	2/0.3/9		98
10		Phenylacetaldehyde (1) 0.3/0.5	2/0.3/6		58
11		Ethyl acetoacetate (1.1) 0.3/3	1.5/0.2/0.5		98

Table 1 (*continued*)

Entry	Substrates	Carbonyls (equiv.) decaborane (equiv.)/ time (h)	Formaldehyde[a] (equiv.)/ decaborane (equiv.)/ time (h)	Product	Yield (%)[b]
12		Benzyl acetoacetate (1.1) 0.3/2	1.5/0.2/5		86
13		Acetophenone (1.2) 0.4/24	2/0.3/1.5		90
14		Piperonal (1.1) 0.3/0.5	1.5/0.2/1.5		98
15		Acetone (1.1) 0.3/0.5	1.5/0.2/0.5		91
16		Benzaldehyde (1) 0.3/0.5	1.5/0.2/0.5		95
17		Piperonal (1.1) 0.3/0.5	1.5/0.2/0.5		92

[a] 37% Aqueous formaldehyde.
[b] Isolated yields.

2.1. Reductive alkylation and reductive methylation

The reductive alkylation and reductive methylation of anilines with various substituents with carbonyls and 37% aqueous formaldehyde using decaborane in methanol gave the corresponding aromatic tertiary amine in high yield (Scheme 1). The amounts of decaborane used are 30 or 40 mol% for the first step and 20 or 30 mol% for the second step depending on the reactivities of substrates and secondary amine intermediates. The amount of carbonyl and formaldehyde used in the reaction was also dependent on the reactivities of each starting substrate and secondary amine intermediates. After completion of the first step, which was identified by TLC using ethyl acetate and hexane (1:4), 37% aqueous formaldehyde and decaborane was added to the reaction mixture. The amount of decaborane, carbonyl and 37% formaldehyde, and reaction time necessary in each step of the reactions and results are shown in Table 1. The yields of the reaction are generally high except for propanal, aliphatic aldehyde (entries 4 and 10), due to the reduction of aldehyde[12] or/and irreversible acetal formation[13] under the reaction conditions. Aromatic nitro and cyano group and aromatic iodide are stable under the reaction conditions (Table 1, entries 1–4, 8 and 11).

The double reductive alkylation of basic aliphatic amine was not successful due to the basicity of amine. The reason is that decaborane could not be acted as a catalyst in the formation of imine from amine and carbonyl probably because reaction solution become basic in the presence of basic amine. Decaborane solution in methanol is acidic. While less basic benzyl amine underwent the double reductive alkylation with piperonal and formaldehyde to give tertiary amine in 92% yield (entry 17), butylamine with carbonyls did not give any expected product amine.

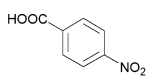
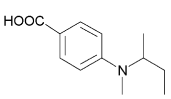
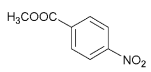
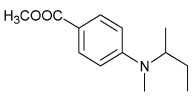
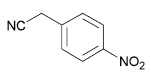
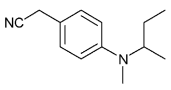
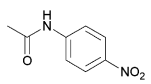
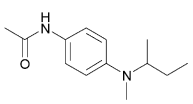
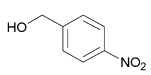
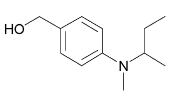
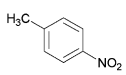
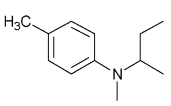
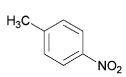
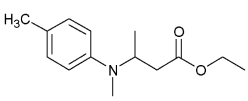
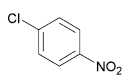
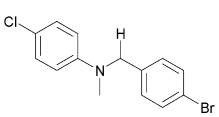
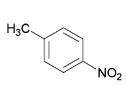
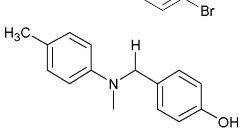
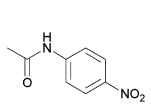
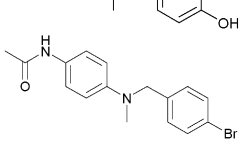
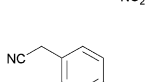
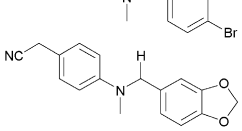
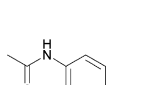
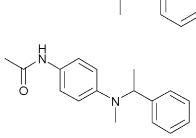
2.2. Reduction of nitroaromatics followed by reductive alkylation and reductive methylation

As an extension of reduction of nitro group and double reductive alkylation, the direct conversion of nitroaromatics into tertiary amine was tried by reduction of nitro group followed by double reductive alkylation in one-pot way. The substrates were confined to nitroaromatics with substituents. 30% Pd/C (w/w) of substrate was used in the nitro group reduction step of nitroaromatics. Decaborane was added in each step in all of the examples. 30 mol% of decaborane ($B_{10}H_{14}$) was used in the reduction of the nitro group and 30 or 20 mol% of decaborane for reductive alkylation and reductive methylation respectively. The amount of decaborane, reaction time and results are shown in Table 2. While ketones were added to the reaction solution from the beginning of the reaction (Eq. 2, Scheme 2), aldehydes were added after the completion of the nitro group reduction due to possible reductive etherification[10] (Eq. 1, Scheme 2). Under the mentioned conditions, the consecutive reactions were completed in several hours and gave the corresponding tertiary amines in high yields. The other reducible functional groups such as halogen (entries 3 and 6) and benzylic group (entry 5) was remained intact under our consecutive reaction conditions.

3. Conclusion

Anilines were converted into the corresponding tertiary

Table 2. Reduction of nitroaromatics followed by reductive alkylation and reductive methylation

Entry	Substrates	Decaborane (equiv.)/ time (h)	Carbonyl (equiv.) decaborane (equiv.)/ time (h)	Formaldehyde[a] (equiv.)/decaborane (equiv.)/time	Product	Yield (%)[b]
1		0.3/1	Butanone (1.5) 0.2/1	1.5/0.2/1		95
2		0.3/0.5	Butanone (1.5) 0.3/2	1.5/0.2/3		92
3		0.3/2.5	Butanone (1.5) 0.2/2	1.5/0.2/2		87
4		0.3/0.5	Butanone (1.5) 0.2/2	2/0.3/1.5		95
5		0.3/3	Butanone (1.5) 0.2/2.5	1.5/0.2/3		86
6		0.3/1.5	Butanone (1.5) 0.2/2	1.5/0.2/3		93
7		0.3/1.5	Ethyl acetoacetate (1.5) 0.2/2	1.5/0.2/3		98
8		0.3/0.5	4-Bromobenzaldehyde (1.2) 0.2/0.5	1.5/0.2/0.5		72
9		0.3/1.5	4-Hydroxy benzaldehyde (1.5) 0.2/2	1.5/0.2/3		84
10		0.3/0.5	4-Bromobenzaldehyde (1.5) 0.2/0.5	1.5/0.2/0.5		99
11		0.3/2.5	Piperonal (1.1) 0.2/1.5	1.5/0.2/0.5		96
12		0.3/0.5	Acetophenone (1.5) 0.2/0.5	1.5/0.2/0.5		87

[a] 37% Aqueous formaldehyde.
[b] Isolated yields.

amine by reductive alkylation and reductive methylation with carbonyls and 37% of formaldehyde in one-pot way generally in high yields. The yield of reaction with aliphatic aldehydes was relatively low due to their reduction or/and their irreversible acetal formation under reaction condition. The efficient conversion of nitroaromatic into tertiary amine was developed by reduction of nitroaromatics followed by double reductive alkylation in one-pot way. The two reactions were limited to the electron deficient amine such as aromatic amines as a substrate.

4. Experimental

4.1. General

All solvents and reagents were used as purchased. All of substrates used are commercially available. Purification by flash column chromatography were performed using silica gel 60 0.04–0.063 nm (230–400 mesh) (Merck re: 9385), and TLC using silica gel 60F254, layer thickness 0.2 nm on glasses. ^{1}H NMR spectra were recorded on a Bruker AM

200 spectrometer using $CDCl_3$ as a solvent and chemical shifts are reported as δ values (ppm). Mp was measured on Electrothermal Melting Point Apparatus and uncorrected. Elemental analysis was measured on EA1110 (CE Instrument Italy) machine.

4.2. Double reductive alkylation: reductive alkylation and reductive methylation (Table 1). A typical procedure of double reductive alkylation

4.2.1. *N*-Isopropyl-*N*-methyl-4-nitroaniline (entry 1). To a solution of 4-nitroaniline (100 mg, 0.72 mmol) in methanol (3.6 ml) was added acetone (58 μl, 0.796 mmol), decaborane (27 mg, 0.22 mmol). The solution was stirred at rt for 0.5 h and 37% formaldehyde (109 μl, 1.45 mmol) and decaborane (27 mg, 0.217 mmol) was added. The resulting solution was stirred at rt under nitrogen for 10 h. The mixture was concentrated under reduced pressure, chromatographed on silica gel column using a solution of ethyl acetate and *n*-hexane (1:10) and concentrated to give a tertiary amine in 93% yield as a yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, 2H, J=9.3 Hz, aromatic H), 6.67 (d, 2H, J=9.3 Hz, aromatic H), 4.21–4.25 (m, 1H, CH), 2.87 (s, 3H, NCH_3), 1.24 (d, 6H, J=6.6 Hz, $(-CH_3)_2$). Anal. calcd: C, 61.84; H, 7.27; N, 14.42. Found: C, 62.13; H, 7.01; N, 14.71.

4.2.2. *N*-Isobutyl-*N*-methyl-4-nitroaniline (entry 2). The double reductive alkylation of 4-nitroanilne with butanone and 37% formaldehyde gave a tertiary amine as yellow syrup in 83% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, 2H, J=9.9 Hz, aromatic H), 6.68 (d, 2H, J=9.9 Hz, aromatic H), 3.95–4.03 (m, 1H, CH), 2.85 (s, 3H, NCH_3), 1.57 (m, 2H, CH_2), 1.20 (d, 3H, J=6.6 Hz, $-CH_3$), 0.87 (t, 3H, J=6.9 Hz, $-CH_3$). Anal. calcd: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.54; H, 7.53; N, 13.79.

4.2.3. *N*-Methyl-*N*-piperonyl-4-nitroaniline (entry 3). The double reductive alkylation of 4-nitroaniline with piperonal and 37% formaldehyde gave a tertiary amine in 96% yield as a yellow solid. Mp: 113.1°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, 2H, J=9.6 Hz, aromatic H), 6.77 (d, 1H, J=8.1 Hz, aromatic H), 6.76 (d, 2H, J=9.6 Hz, aromatic H), 6.64–6.68 (m, 4H, aromatic H), 5.95 (s, 2H, CH_2), 4.57 (s, 2H, benzyl H), 3.16 (s, 3H, NCH_3). Anal. calcd: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.34; H, 4.71; N, 9.63.

4.2.4. *N*-Methyl-*N*-propyl-4-nitroaniline (entry 4). The double reductive alkylation of 4-nitroaniline with propanal and 37% formaldehyde gave a tertiary amine in 64% yield as a yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, 2H, J=9.3 Hz, aromatic H), 6.58 (d, 2H, J=9.3 Hz, aromatic H), 3.39 (t, 2H, J=7.5 Hz, CH_2), 3.07 (s, 3H, NCH_3), 1.62–1.70 (m, 2H, $-CH_2$), 0.95 (t, 3H, J=7.5 Hz, $-CH_3$). Anal. calcd: C, 61.84; H, 7.27; N, 14.24. Found: C, 62.63; H, 7.31; N, 14.43.

4.2.5. 4-(*N*-Isobutyl-*N*-methylamino)benzoic acid (entry 5). The double reductive alkylation of 4-aminobenzoic acid with 2-butanone and 37% formaldehyde gave a tertiary amine in 97% yield as a white solid. Mp: 119°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (d, 2H, J=9.6 Hz, aromatic H), 6.73 (d, 2H, J=9.6 Hz, aromatic H), 3.94–3.97 (m, 1H, J=7.5 Hz, CH_2), 2.80 (s, 3H, NCH_3), 1.54–1.64 (m, 2H, J=7.5 Hz, CH_2), 1.17 (d, 3H, J=6.6 Hz, $-CH_3$), 0.87 (t, 3H, J=7.2 Hz, $-CH_3$). Anal. calcd: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.73; H, 8.11; N, 6.54.

4.2.6. 4-(*N*-Methyl-*N*-1-phenethylamino)benzoic acid (entry 6). The double reductive alkylation of 4-aminobenzoic acid with acetophenone and 37% formaldehyde gave a tertiary amine in 90% yield as a white solid. Mp: 154°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.98 (d, 2H, J=9.6 Hz, aromatic H), 7.38–7.26 (m, 5H, aromatic H), 6.80 (d, 2H, J=9.6 Hz, aromatic H), 5.28 (q, 1H, J=6.6 Hz, CH), 2.77 (s, 3H, NCH_3), 1.62 (d, 3H, J=6.6 Hz, $-CH_3$). Anal. calcd: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.11; H, 6.84; N, 5.54.

4.2.7. 2-(*N*-Benzyl-*N*-methylamino)benzoic acid (entry 7). The double reductive alkylation of anthranilic acid with benzaldehyde and 37% formaldehyde gave a tertiary amine in 98% yield as a light yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.29 (dd, 2H, J=9.6 Hz, aromatic H), 7.64–7.33 (m, 7H, aromatic H), 4.11 (s, 2H, $-CH_2$), 2.72 (s, 3H, NCH_3). Anal. calcd: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.98; H, 6.31; N, 5.67.

4.2.8. *N*-(2-Hydroxybenzyl)-*N*-methylanthranilonitrile (entry 8). The double reductive alkylation of anthranilonitrile with and 37% formaldehyde gave a tertiary amine in 98% yield as a yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65–6.80 (m, 8H, aromatic H), 4.36 (s, 2H, $-CH_2$), 2.88 (s, 3H, NCH_3), 1.62 (d, 3H, J=7.2 Hz, $-CH_3$). Anal. calcd: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.04; H, 5.79; N, 11.69.

4.2.9. *N*-Methyl-*N*-piperoylanthranilamide (entry 9). The double reductive alkylation of 4-anthranilamide with piperonal and 37% formaldehyde gave a tertiary amine in 98% yield as a white syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.2 (d, 1H, J=7.8 Hz, aromatic H), 7.45 (t, 1H, J=7.2 Hz, aromatic H), 7.22 (m, 2H, aromatic H), 6.76–6.66 (m, 3H, aromatic H), 5.95 (s. 2H, $-CH_2-$), 4.02 (s, 2H, $-CH_2$), 2.62 (s, 3H, NCH_3). Anal. calcd: C, 67.59; H, 5.67; N, 9.85. Found: C, 68.77; H, 5.59; N, 9.78.

4.2.10. *N*-Methyl-*N*-propylanthranilamide (entry 10). The double reductive alkylation of 4-anthranilamide with phenylacetaldehyde and 37% formaldehyde gave a tertiary amine in 58% yield. Mp: 127.8°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18–7.12 (m, 9H, aromatic H), 5.39 (s, 2H, amide NH_2), 3.29 (t, 2H, J=6.9 Hz, $-CH_2$), 2.73 (s, 3H, NCH_3). Anal. calcd: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.29; H, 7.08; N, 10.95.

4.2.11. Ethyl 3-(*N*-4-iodophenyl-*N*-methylamino)-butanoate (entry 11). The double reductive alkylation of 4-iodoaniline with ethyl acetoacetate and 37% formaldehyde gave a tertiary amine in 98% yield as a light yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45 (dd, 2H, J=7.2 Hz, aromatic H), 6.61 (dd, 2H, J=7.2 Hz, aromatic H), 4.36–4.43 (m, 1H, C–H), 4.05 (q, 2H, J=7.2 Hz, O–CH_2–**), 2.69 (s, 3H, NCH_3), 2.61 (q, 1H, J=6.9 Hz; CH_2), 2.42 (q, 1H, J=6.9 Hz, NCH_2-), 1.15–1.20 (m, 6H,

$-(CH_3)_2$). Anal. calcd: C, 44.97; H, 5.23; N, 4.03. Found: C, 45.16; H, 5.34; N, 4.11.

4.2.12. Benzyl 3-(*N*-4-acetylaminophenyl-*N*-methyl-amino)-butanoate (entry 12). The double reductive alkylation of 4-aminoacetanilide with benzyl acetoacetate and 37% formaldehyde gave a tertiary amine in 86% yield as a pale lemon syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.04 (m, 7H, aromatic H), 6.80 (d, 2H, J=9.6 Hz, aromatic H), 5.04 (d, 2H, J=5.4 Hz, $-CH_2-$), 4.39–4.44 (m, 1H, CH), 2.67 (s, 3H, NCH_3), 2.15 (s, 3H, $COCH_3$), 1.15 (d, 3H, J=6.6 Hz, $-CH_3$). Anal. calcd: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.72; H, 7.02; N, 8.49.

4.2.13. *N*-Methyl-*N*-(1-phenethyl)-4-acetamidoaniline (entry 13). The double reductive alkylation of 4-amino-acetanilide with acetophenone and 37% formaldehyde gave a tertiary amine in 91% yield as a pale gray syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.18 (m, 7H, aromatic H), 6.71 (d, 2H, J=9 Hz, aromatic H), 4.97 (q, 1H, J=9 Hz, –CH), 2.57 (s, 3H; NCH_3), 2.06 (s, 3H, $COCH_3$), 1.44 (s, 3H, J=6.9 Hz, $-CH_3$). Anal. calcd: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.18; H, 7.54; N, 10.42.

4.2.14. *N*-Methyl-*N*-piperoyl-4-acetamidoaniline (entry 14). The double reductive alkylation of 4-aminoacetanilide with piperonal and 37% formaldehyde gave a tertiary amine in 98% yield as a white solid. Mp: 141.6°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32 (s, 1H, NH), 7.22 (d, 2H, J= 8.7 Hz, aromatic H), 6.68–6.59 (m, 5H, aromatic H), 5.84 (s, 2H, $-CH_2-$), 4.31 (s, 2H, CH_2), 2.87 (s, 3H, NCH_3), 2.04 (s, 3H, $-COCH_3$). Anal. calcd: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.20; H, 6.15; N, 9.05.

4.2.15. *N*-Isopropyl-*N*-methyl-*p*-toluidine (entry 15). The double reductive alkylation of *p*-toluidine with acetone and 37% formaldehyde gave a tertiary amine in 91% yield as a pale yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.05 (d, 2H, aromatic H), 6.83 (d, 2H, J=9 Hz), 6.74 (d, 2H, J=9 Hz) 4.03 (m, 1H, C–H), 2.70 (d, 3H, J=0.9 Hz, NCH_3), 2.26 (s, 3H, CH_3), 1.14 (m, 6H, $(-CH_3)_2$). Anal. calcd: C, 80.93; H, 10.50; N, 8.58. Found: C, 81.14; H, 10.69; N, 8.84.

4.2.16. *N*-Benzyl-*N*-methyl-4-anisidine (entry 16). The double reductive alkylation of *p*-anisidine with benz-aldehyde and 37% formaldehyde gave a tertiary amine in 95% yield as a pale yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.23 (m, 5H, aromatic H), 6.83 (d, 4H, J=9 Hz, aromatic H), 4.43 (s, 2H, benzyl $-CH_2$), 3.75 (s, 3H, O–CH_3), 2.92 (s, 3H, N–CH_3). Anal. calcd: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.95; H, 7.79; N, 6.31.

4.2.17. *N*-Benzyl-*N*-methyl-*N*-piperoylamine (entry 17). The reaction of benzylamine with piperonal and 37% formaldehyde gave a tertiary amine in 92% yield as a colorless syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.29 (m, 5H, aromatic H), 6.91 (s, 1H), 6.75 (d, 2H, J=1.2 Hz, aromatic H), 5.94 (s, 2H, benzyl $-CH_2$), 3.50 (s, 2H, $-CH_2$), 3.42 (s, 2H, $-CH_2$), 2.16 (s, 3H, NCH_3). Anal. calcd: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.51; H, 6.98; N, 5.69.

4.3. Reduction of nitro group followed by double reductive alkylation using ketones and 37% formaldehyde (Table 2, entries 1–7). A typical procedure

4.3.1. 4-(*N*-Isobutyl-*N*-methylamino)benzoic acid (entry 1). To a solution of 4-nitrobenzoic acid (50 mg, 0.299 mmol) in methanol (5 ml) was added 2-butanone (40 μl, 0.448 mmol), decaborane (11 mg, 0.089 mmol) and 10% Pd/C (15 mg). The resulting solution was stirred at ca. 40°C for 1 h. The mixture was then cooled to rt and decaborane (11 mg, 0.089 mmol) was added. The resulting solution was stirred at rt under nitrogen for 1 h. And then 37% formaldehyde (33 μl, 0.448 mmol) and decaborane (7.3 mg, 0.059 mmol) were added to the mixture. The resulting solution was stirred at rt under nitrogen for 2 h. The mixture was concentrated under reduced pressure, chromatographed on a short pad of silica gel using a solution of ethyl acetate and *n*-hexane (1:6) and concentrated to give tertiary amine (59 mg, 95%) as a crystalline white solid. Mp: 119.7°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (d, 2H, J=9.6 Hz, aromatic H), 6.73 (d, 2H, J=9.6 Hz, aromatic H), 3.94–3.97 (m, 1H, CH), 2.80 (s, 3H, NCH_3), 1.54–1.67 (m, 2H, CH_2), 1.17 (d, 3H, J=6.6 Hz, CH_3), 0.87 (t, 3H, J=7.5 Hz, CH_3). Anal. calcd: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.83; H, 8.12; N, 6.51.

4.3.2. Methyl 4-(*N*-isobutyl-*N*-methylamino)benzoate (entry 2). The reduction of methyl 4-nitrobenzoate followed by double reductive alkylation with 2-butanone and 37% formaldehyde gave a tertiary amine in 92% yield as a pale yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.87 (dd, 2H, J=7.2, 2.1 Hz, aromatic H), 6.70 (dd, 2H, J=7.2, 2.1 Hz, aromatic H), 3.89–3.96 (m, 1H, CH), 3.84 (s, 3H, $COOCH_3$), 2.78 (s, 3H, NCH_3), 1.53–1.61 (m, 2H, CH_2), 1.15 (d, 3H, J=6.6 Hz, $-CH_3$), 0.86 (t, 3H, J=7.2 Hz, $-CH_3$). Anal. calcd: C, 70.56; H, 8.65; N, 6.33. Found: C, 10.23; H, 8.73; N, 6.14.

4.3.3. 4-(*N*-Isobutyl-*N*-methylamino)phenylacetonitrile (entry 3). The reduction of 4-nitrophenylacetonitrile followed by double reductive alkylation with 2-butanone and 37% formaldehyde gave a tertiary amine in 87% yield as a yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.07 (d, 2H, J=8.7 Hz, aromatic H), 6.67 (d, 2H, J=8.7 Hz, aromatic H), 3.75 (m, 1H, CH), 3.56 (s, 2H, benzyl-CH_2), 2.63 (s, 3H, NCH_3), 1.52 (m, 2H, $-CH_2$), 1.04 (d, 3H, J=6.6 Hz, $-CH_3$), 0.80 (t, 3H, J=7.5 Hz, $-CH_3$). Anal. calcd: C, 77.18; H, 8.97; N, 13.85. Found: C, 76.95; H, 9.11; N, 13.69.

4.3.4. (*N*-Isobutyl-*N*-methyl)-4-acetamidoaniline (entry 4). The reduction of 4-nitroacetanilide followed by double reductive alkylation with 2-butanone and 37% formal-dehyde gave a tertiary amine in 95% yield as a white solid. Mp: 109.4°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (d, 2H, J=8.7 Hz, aromatic H), 6.72 (d, 2H, J=8.7 Hz, aromatic H), 3.73–3.75 (m, 1H, CH), 2.67 (s, 3H, NCH_3), 2.13 (s, 3H, $-COCH_3$), 1.64–1.44 (m, 2H, $-CH_2$), 1.08 (d, 3H, J= 6.6 Hz, $-CH_3$), 0.85–0.91 (m, 3H, $-CH_3$). Anal. calcd: C, 70.87; H, 9.15; N, 12.72. Found: C, 71.11; H, 9.23; N, 12.79.

4.3.5. 4-(*N*-Isobutyl-*N*-methylamino)benzyl alcohol (entry 5). The reduction of 4-nitrobenzyl alcohol followed

by double reductive alkylation with 2-butanone and 37% formaldehyde gave a tertiary amine in 86% yield as a light yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.07 (d, 2H, J=8.7 Hz, aromatic H), 6.67 (d, 2H, J=8.7 Hz, aromatic H), 3.75 (m, 1H, CH), 3.56 (s, 2H, benzyl-CH_2), 2.63 (s, 3H, NCH_3), 1.45–1.57 (m, 2H, $-CH_2$), 1.04 (d, 3H, J=6.6 Hz, $-CH_3$), 0.80 (t, 3H, J=7.5 Hz, $-CH_3$). Anal. calcd: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.35; H, 9.80; N, 7.02.

4.3.6. *N*-Isobutyl-*N*-methyl-*p*-toluidine (entry 6). The reduction of 4-nitrotoluene followed by double reductive alkylation of 2-butanone and 37% formaldehyde gave a tertiary amine in 93% yield as a light yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.03 (d, 2H, J=8.7 Hz, aromatic H), 6.71 (d, 2H, J=8.7 Hz, aromatic H), 3.71–3.78 (m, 1H, CH), 2.67 (s, 3H, NCH_3), 2.24 (s, 3H, $-CH_3$), 1.56–1.63 (m, 2H, $-CH_2$), 1.08 (d, 3H, J=6.6 Hz, $-CH_3$), 0.88 (t, 3H, J=7.2 Hz, $-CH_3$). Anal. calcd: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.02; H, 10.48; N, 8.12.

4.3.7. Ethyl 3-(*N*-methyl-*N*-4-tolylamino)butanoate (entry 7). The reduction of 4-nitrotoluene followed by double reductive alkylation with ethyl acetoacetate and 37% formaldehyde (30 μl, 1.09 mmol) gave a tertiary amine in 98% yield as a light yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04 (d, 2H, J=8.4 Hz, aromatic H), 6.78 (d, 2H, J=8.4 Hz, aromatic H), 4.37–4.39 (m, 1H, CH), 4.07 (q, 2H, J=7.2 Hz, $COOCH_2$), 2.68 (s, 3H, NCH_3), 2.60 (dd, 1H, J=7.5 Hz, CH_2), 2.40 (dd, 1H, J=7.5 Hz, CH_2), 2.24 (s, 3H, $-CH_3$), 1.16–1.22 (m, 6H, $-(CH_3)_2$). Anal. calcd: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.14; H, 9.13; N, 5.71.

4.4. Reduction of nitro group followed by double reductive alkylation using aldehydes and 37% formaldehyde (Table 2, entries 8–11)

4.4.1. *N*-4-Bromobenzyl-*N*-methyl-4-chloroaniline (entry 8). To a solution of 1-chloro-4-nitrobenzene (50 mg, 0.317 mmol) in methanol (5 ml) was added two drops of acetic acid, decaborane (11 mg, 0.095 mmol) and 10% Pd/C (15 mg). The resulting solution was heated to reflux under nitrogen for 0.5 h and the mixture was cooled to room temperature. 4-Bromobenzaldehyde (70.5 mg, 0.380 mmol) and decaborane (7.7 mg, 0.063 mmol) were then added to the reaction mixture. The solution was stirred at rt under nitrogen for 0.5 h. And then 37% formaldehyde (35 μl, 0.475 mmol), decaborane (7.7 mg, 0.063 mmol) was added to the mixture. The resulting solution was stirred at rt under nitrogen for 0.5 h. The mixture was concentrated under reduced pressure, chromatographed on a short pad of silica gel using a solution of methylene chloride and *n*-hexane (1:20) and concentrated to give a tertiary amine (71 mg, 72%) as a pale yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43 (d, 2H, J=8.4 Hz, aromatic H), 7.14 (d, 2H, J=9 Hz, aromatic H), 7.06 (d, 2H, J=8.4 Hz, aromatic H), 6.61 (d, 2H, J=9 Hz, aromatic H), 4.44 (s, 2H, benzyl-CH_2), 2.99 (s, 3H, NCH_3). Anal. calcd: C, 54.13; H, 4.22; N, 4.51. Found: C, 54.38; H, 4.05; N, 4.78.

4.4.2. *N*-Methyl-*N*-4-hydroxybenzyl-4-toluidine (entry 9). The reduction of 4-nitrotoluene followed by double reductive alkylation with 4-hydroxybenzaldehyde and 37% formaldehyde and chromatography on silica gel column using a solution of ethyl acetate and *n*-hexane (1:7) gave a tertiary amine in 84% yield as a pale yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10 (d, 2H, J=8.4 Hz, aromatic H), 7.03 (d, 2H, J=6.6 Hz, aromatic H), 6.76 (d, 2H, J=6.6 Hz, aromatic H), 6.68 (d, 2H, J=8.4 Hz, aromatic H), 2.92 (s, 2H, benzyl-CH_2), 2.27 (s, 3H, NCH_3). Anal. calcd: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.51; H, 7.41; N, 6.31.

4.4.3. *N*-(4-[Methyl-(1-(4-bromobenzyl)-4-acetamido-aniline (entry 10). The reduction of 4-nitroacetanilide followed by double reductive alkylation with 4-bromobenzaldehyde and 37% formaldehyde (31 μl, 0.416 mmol) and chromatography on silica gel column using a solution of ethyl acetate and *n*-hexane (1:1) gave a tertiary amine (92 mg, 99%) as a pale white solid. Mp: 117°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 (d, 2H, J=8.7 Hz, aromatic H), 7.28 (d, 2H, J=9 Hz, aromatic H), 7.08 (d, 2H, J=8.7 Hz, aromatic H), 6.66 (d, 2H, J=9 Hz, aromatic H), 4.43 (s, 2H, benzyl-CH_2), 2.97 (s, 3H, NCH_3), 2.13 (s, 3H, $-COCH_3$). Anal. calcd: C, 57.67; H, 5.14; N, 8.41. Found: C, 57.39; H, 4.01; N, 8.68.

4.4.4. *N*-Piperoyl-*N*-methyl-4-aminophenylacetonitrile (entry 11). The reduction of 4-nitrophenylacetonitrile followed double reductive alkylation with piperonal and 37% formaldehyde and chromatography on silica gel column using a solution of ethyl acetate and *n*-hexane (1:4) gave a tertiary amine in 96% yield as a pale yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.13 (d, 2H, J=8.7 Hz, aromatic H), 6.77–6.65 (m, 5H, aromatic H), 5.93 (s, 2H, $-CH_2$), 4.43 (s, 2H, benzyl-CH_2), 3.63 (s, 2H, benzyl-CH_2), 3.00 (s, 3H, NCH_3). Anal. calcd: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.66; H, 5.97; N, 9.67.

4.4.5. *N*-4-[Methyl-(1-phenylethyl)-amino]-phenylacetamide (entry 12). The reduction of 4-nitroacetanilide followed double reductive alkylation with acetophenone and 37% formaldehyde and chromatography on silica gel column using a solution of ethyl acetate and *n*-hexane (1:4) gave a tertiary amine in 87% yield as a white solid. Mp: 128–129°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.25 (m, 7H, aromatic H), 7.01 (s, 1H), 6.80–6.77 (d, 2H, J=9.0 Hz), 5.09–5.02 (q, 1H, J=6.6 Hz), 2.65 (s, 3H), 2.14 (s, 3H), 1.53 (d, 3H, J=6.6 Hz). Anal. calcd: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.82; H, 7.39; N, 10.69.

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