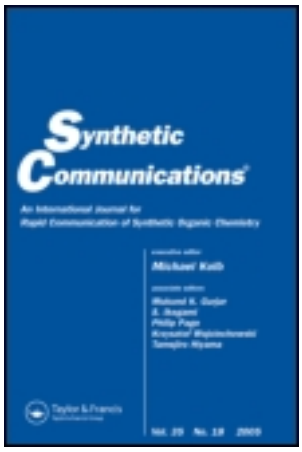

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REDUCTIVE METHYLATION USING DECABORANE IN METHANOL

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REDUCTIVE METHYLATION USING DECABORANE IN METHANOL

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ABSTRACT

Amines (primary and secondary) were methylated to the corresponding tertiary amine using 37% formaldehyde and decaborane in methanol at room temperature under nitrogen in high yields.

The methylation of amines has been achieved by numerous methods.[1] Especially, the reductive methylation has been known as one of the powerful methods for the methylation of amine. These reagents of the reductive methylation are triethylsilane/37% aqueous formaldehyde,[2] formic acid/30%

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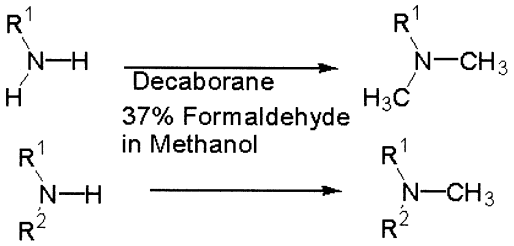
aqueous formaldehyde involving irradiation,[3] sodium borohydride/trifluoroacetic acid/paraformaldehyde,[4] trimethyl orthoformate/sulfuric acid,[5] sodium borohydride/zinc chloride/paraformaldehyde,[6] and sodium cyanoborohydride/aqueous formaldehyde.[7,8] However, these methods have some limitations such as high temperature, strong acidic condition, toxicity or low yield.

As a continuous study on decaborane as a mild, quite stable and nontoxic reducing agent, it was found that primary or secondary amines were reductively methylated to the corresponding tertiary amine using decaborane in the presence of 37% aqueous formaldehyde in methanol at room temperature (Scheme 1). The reaction condition is mild and the reaction is efficient.



Scheme 1.

The amount of 37% formaldehyde and decaborane used in the reaction depended on the starting amines. 3 equiv. of formaldehyde and 60 mole % of decaborane was used for dimethylation of primary amines, and 1.5 equiv. of the formaldehyde and 30 mole % of decaborane was used for the monomethylation of secondary amines.[9] When 37% formaldehyde was added to the solution of 2-methylindoline in methanol (entry 7), the conversion of the amine into the intermediate (carbinolamine) was observed by TLC using a solution of ethyl acetate and hexane (1 : 10). In all the reactions, decaborane was added after stirring the solution of formaldehyde and amines in methanol for a while (30 min). Otherwise, the yields were reduced probably due to the possible competitive reductive etherification of formaldehyde.[10] The yield of the reaction was generally high, but the yield of the electron sufficient amines is relatively low compared to that of the other amines due to the adduct formation with decaborane (or its decomposed stuff) (entries 3, 9, 10). The further studies with other reductive amination reaction *in situ* are underway.

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In conclusion, amines (primary and secondary) were reductively methylated into the corresponding tertiary amines efficiently using 37% formaldehyde and decaborane in methanol.

EXPERIMENTAL

Silica gel 60 (230–400 mesh, Merck) was used for column chromatography, and silica gel $60F_{254}$ plates (0.25 mm, Merck) were used for TLC. Melting point was determined using a Electrothermal IA 9100 (15 v, 50/60 Hz, 40 W) and are uncorrected. ^{1}H-NMR spectra were recorded on a VARIAN at 300 MHz. Elemental analyses were performed on a EAGER 200 analyser. All reagents and substrates were purchased from commercial sources and used without further purification.

GENERAL PROCEDURE FOR *N*-METHYLATION

A representative procedure is as follows (entry 5 of Table 1): A solution of 2-methylindoline (0.097 ml, 0.751 mmol) and 37% aqueous formaldehyde (0.084 ml, 1.126 mmol) in methanol (4 ml) was stirred for 30 min at room temperature under nitrogen. To the solution was added decaborane (27.53 mg, 0.225 mmol) and then the resulting solution was stirred at r.t. The reaction was followed by tlc using a solution of ethyl acetate and hexane (1 : 10). After 30 min, the reaction mixture was then concentrated under reduced pressure and chromatographed on silica gel using a solution of ethyl acetate and hexane (1 : 30) as an eluent to give *N*-methyl-2-methylindoline as a light yellow syrup in quantitative yield.

Methyl 4-(dimethylamino)benzoate (entry 1): yield 94%; white solid 110.9 mg (m.p.: 90.4); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, $J = 7.9$ Hz, 2H), 6.65 (d, $J = 7.9$ Hz, 2H), 3.85 (s, 3H), 3.31 (s, 6H); Anal. Calcd for $C_{10}H_{13}NO_2$, C, 67.02; H, 7.31; N, 7.82. Found, C, 67.01; H, 7.29; N, 7.83.

***N*-Methyl-*N*-isopropyl-(4-nitrophenyl)amine** (entry 5): yield 97%; yellow syrup. 105 mg; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, $J = 9.3$ Hz, 2H), 6.67 (d, $J = 9.3$ Hz, 2H), 4.22 (q, $J = 6.4$ Hz, 1H), 2.88 (s, 3H), 1.24 (d, $J = 6.4$ Hz, 6H); Anal. Calcd for $C_{10}H_{14}N_2O_2$, C, 61.84; H, 7.27; N, 14.42. Found, C, 61.67; H, 7.45; N, 14.59.

Methyl 4-(*N*-methyl-*N*-isopropylamino)benzoate (entry 8): yield 94%; colorless oil 104 mg; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.89 (d, $J = 7.1$ Hz, 2H), 6.70 (d, $J = 7.0$ Hz, 2H), 4.19 (q, $J = 6.6$ Hz, 1H), 3.85 (s, 3H), 2.80

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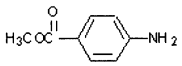
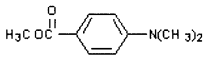
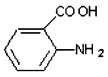
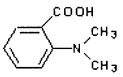
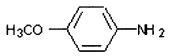
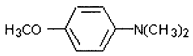
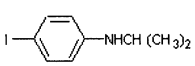
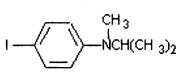
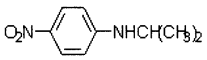
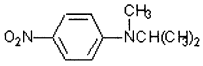
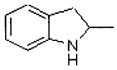
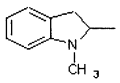
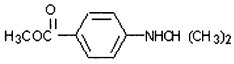
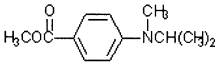
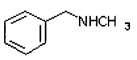
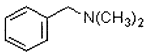
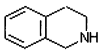
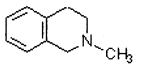
Table 1. The Reductive Methylation Using Decaborane

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1		0.5		94
2		0.5		98.9
3		0.5		83
4		0.5		97
5		12		97
6		0.5		91
7		0.5		89
8		6		96
9		12		82
10		12		77

[a]Isolated yield.

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(s, 3H), 1.19 (d, $J = 6.6$ Hz, 6H); Anal. Calcd for $C_{12}H_{17}NO_2$, C, 69.54; H, 8.27; N, 6.76. Found, C, 69.33; H, 8.44; N, 6.73.

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REFERENCES

1. Klyuev, M.V.; Khidekel, M.L. Russ. Chem. Rev. (Eng. Transl.) **1980**, *49*, 14.
2. Luke, R.W.A.; Boyce, P.G.T.; Dorling, E.K. Tetrahedron Lett. **1996**, *37*, 263.
3. Barbry, D.; Torchy, S. Synth. Commun. **1996**, *26*, 3919.
4. Gribble, G.W.; Nutaitis, C.F. Synthesis **1987**, 709.
5. Padmanabhan, S.; Reddy, N.L.; Durant, G. J. Synth. Commun. **1997**, *27*, 691.
6. Bhattacharyya, S. Synth. Commun. **1995**, *25*, 2061.
7. Borch, R.F.; Hassid, A.I. J. Org. Chem. **1972**, *37*, 1673.
8. Gangjee, A.; Vasudevan, A.; Queener, S.F.; Kisliuk, R.L. J. Med. Chem. **1996**, *39*, 1438.
9. A little excess amount of formaldehyde (2 equiv.) and decaborane (40 mole %) in the case of entry 4 compared to that of other secondary amines (entries 3 and 5–9) was used to complete the reaction.
10. Lee, S.H.; Park, Y.J.; Yoon, C.M. Tetrahedron Lett. **1999**, *40*, 6049.

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