Rapid Stereospecific Methylation of Alcohols and Glycols with Sodium Hydride/Methyl Iodide[1]

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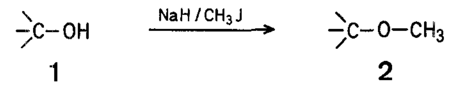
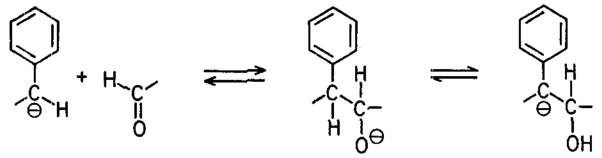
Addition of an alcohol (**1**) or glycol to mixtures of sodium hydride and methyl iodide or dimethyl sulfate in tetrahydrofuran at 50° results in vigorous evolution of hydrogen accompanied by rapid quantitative permethylation (**2**) of the substrate. Methylation is stereospecific without epimerization, as revealed in alkylations of *cis* and *trans*-2-methylcyclohexanol and *threo*-3-phenyl-2-butanol.

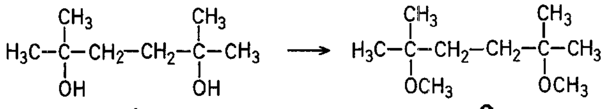


Of the wide variety of procedures described for methylation of alcohols[2], those most frequently employed are based upon reactions of the methylating agent with either preformed metal alkoxide or with alcohol and bases such as silver oxide or sodium hydroxide[3]. Recently, methylation of alcohols and phenols has been reported with mixtures of sodium hydride and methyl iodide in various solvents[4,5,6].

A major complication of alkylation via alkoxides (Williamson synthesis) is racemization and epimerization[7,8], shown by Doering and Aschner[9] to be catalyzed by traces of carbonyl compounds, oxygen, and other oxidizing agents. In α- and β-phenyl carbinols, mechanisms involving proton abstraction from carbon or retro-aldol reactions are also possible.



Reaction of 2,5-dimethylhexan-2,5-diol (**1a**) with excess sodium hydride/methyl iodide at 50° for 1–1.5 h resulted in complete conversion to the bis-methyl ether (**2a**); complete methylation of both functions occurred in one step.



$$H_3C-C(CH_3)(OH)-CH_2-CH_2-C(CH_3)(OH)-CH_3 \longrightarrow H_3C-C(CH_3)(OCH_3)-CH_2-CH_2-C(CH_3)(OCH_3)-CH_3$$

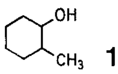
1a **2a**

Similarly, 3-methyl-3-pentanol, benzyl alcohol, and 2,5-dimethyl-3-hexyn-2,5-diol were methylated in greater than 90% yield (G.L.P.C.); in the latter case, no evidence of retro-ethynylation was observed.

Methylation of *cis*- and *trans*-2-methylcyclohexanol was completely stereospecific. In contrast, a more conventional procedure involving conversion of the alcohol to alkoxide with sodium metal in refluxing toluene followed by methylation yielded incomplete conversion; both ether and recovered alcohol were partly epimerized (Table 1).

A more critical test is provided by 3-phenyl-2-butanol which may be epimerized by C-deprotonation and retro-aldol reactions as well as by the oxidation – reduction mechanism. Methylation of L(+)-*threo*-3-phenyl-2-butanol[10] was used to compare the sodium hydride/methyl iodide system with two mild basic stereospecific methylating reagents: silver oxide/methyl iodide[11] and butyllithium/methyl iodide. In tetrahydrofuran at 50–65°, sodium hydride/methyl iodide provided higher conversion in considerably less time than the other two, and yielded L(+)-*threo*-3-phenyl-2-methoxybutane with the highest specific rotation (Table 2).

Table 1. Methylation of 2-Methylcyclohexanol

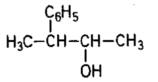


1b

Purity[a]	Reaction Conditions	Conversion (%)[a]	Product Stereochemistry Ether[a]	Recovered Alcohol[a]
>99.5% *cis*[b]	NaH/CH_3J/50°/ THF/1 h	100%	>99.5% *cis*[b]	—
99% *trans*	NaH/CH_3J/50°/ THF/1 h	100%	99% *trans*	—
>99.5% *cis*[b]	1. Na/$C_6H_5CH_3$/115°/ 18 h 2. CH_3J/50°/1 h	85%	96% *cis*	70% *cis*

[a] By G.L.P.C.
[b] No *trans* detectable

Table 2. Methylation of L(+)-*threo*-3-Phenyl-2-butanol[a]



$H_3C-CH(C_6H_5)-CH(OH)-CH_3$

1c

Reaction Conditions	Conversion (%)[b]	Products, $[\alpha]_D^{27}$ (benzene) Ether	Recovered Alcohol
NaH/CH_3J/THF/1 h/50°	100	+25.18°	—
NaH/CH_3J/THF/0.3 h/50°	60	+25.18°	+39.80°
Ag_2O/CH_3J/acetone/36 h/50°	50	+23.04°	+37.21°
n-C_4H_9Li/CH_3J/THF/30 h/65°	70	+24.04°	+35.22

[a] $[\alpha]_D^{27} = +39.80°$
[b] By G.L.P.C.

The above reactions were all carried out under nitrogen atmosphere, but no attempt was made to rigorously deoxygenate solvents; pure reagent solvents from freshly opened bottles were employed.

The above results clearly indicate that sodium hydride/methyl iodide in tetrahydrofuran represents not only a simple, direct, rapid method for effecting permethylation but also a convenient, highly stereospecific new methylating reagent.

Benzyl Methyl Ether (General Procedure):

In a dry 250 ml round bottom flask (equipped with an injection port, reflux condenser with inlet for dry nitrogen, and a Teflon-clad magnetic stirring bar) was placed sodium hydride (100 mmol, 4.4 g of 58% dispersion in oil, Alfa Products Div. of Ventron Corp.). The reactor was purged with nitrogen and dry tetrahydrofuran (60 ml) was added with a syringe. With stirring, the slurry was heated at 45–50° in an oil bath and methyl iodide (17.0 g, 120 mmol, 7.5 ml) was added. Benzyl alcohol, (80 mmol, 8.65 g, 8.7 ml), in tetrahydrofuran (20 ml) was added dropwise over 30 min; hydrogen evolution accompanied the addition. (With diols such as **1a**, 40 mmol, 80 meq of OH, was used.) After a further 30 min heating, the reaction mixture was cooled and hydrolyzed by dropwise addition of sufficient water to dissolve any precipitate (vigorous hydrogen evolution initially!). The aqueous layer was separated and extracted twice with ether; then the combined organic solutions were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. A portion of the dried soln. (5% by wt) was analyzed by G.L.P.C.; it was free of benzyl alcohol and contained a 94% yield of the ether (against added internal standard). Distillation of the remaining solution gave benzyl methyl-ether; yield: 7.9 g (81%); b.p. 169–171° (ref.[12] b.p. 170°); n_D^{24} 1.5006 (ref.[12] n_D^{20} 1.5031).

L(+)-*threo*-3-Phenyl-2-methoxybutane:

In a 25 ml flask (magnetic stir bar, injection port, condenser with nitrogen inlet) was placed sodium hydride (0.45 g, 58% w/w dispersion in oil, Alfa Products Div. of Ventron Corp.). The oil was removed with two successive washes of dry pentane (2 × 5 ml). Dry tetrahydrofuran (10.0 ml) was added and the suspension was heated in an oil bath at 45–50°. A solution of L(+)-*threo*-3-phenyl-2-butanol (1.0 g, 6.7 mmol) and methyl iodide (0.63 ml, 10 mmol) in tetrahydrofuran (5.0 ml) was added dropwise over 20 min, followed by further heating for 40 min. With cooling, the reaction mixture was carefully hydrolyzed by dropwise addition of water (5 ml). The mixture was treated with ether (25 ml), and the ether layer was separated, extracted with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification by G.L.P.C. (12′ × $\frac{1}{2}$″ od. column packed with 10% Carbowax 20M on 100/120 mesh Chromosorb W) yielded *threo*-3-phenyl-2-methoxybutane: yield: 0.90 g, 82%; $n_D^{20} = 1.4926$, $[\alpha]_D^{27} = +25.18°$ ($c = 5$, benzene), $\alpha_D^{27} = +15.18°$ (neat, 1.0 dm), OH absent in I.R. spectrum.

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[1] Saline Hydrides and Superbases in Organic Reactions. IV.

[2] H. Meerwein in Houben-Weyl, „*Methoden der Organischen Chemie*", E. Müller, Ed., 4th edit. Georg Thieme Verlag, Stuttgart, 1965, Vol. VI/3, p. 1.
C. A. Buehler, D. E. Pearson, "*Survey of Organic Syntheses*", Wiley-Interscience, New York, 1970, p. 174.

[3] The use of hydroxides is reported limited to relatively acidic alcohols: J. Braun, E. Anton, K. Weissbach, *Ber. dtsch. chem. Ges.* **63**, 2847 (1930).
Recently, methyl sulfate/hydroxide methylations have been carried out on less reactive alcohols using phase transfer catalysis: A. Merz, *Angew. Chem.* **85**, 868 (1973); *Angew. Chem. Internat. Edit.* **12**, 846 (1973).

[4] B. A. Stoochnoff, N. L. Benoiton, *Tetrahedron Lett.* **1973,** 21.

[5] U. E. Diner, F. Sweet, R. K. Brown, *Can. J. Chem.* **44,** 1591 (1966).

[6] E. D. M. Eades, D. H. Ball, L. Long, Jr., *J. Org. Chem.* **30,** 3949 (1965).

[7] K. Mislow, *J. Amer. Chem. Soc.* **73,** 3954 (1951).

[8] E. D. Hughes, C. K. Ingold, A. D. Scott, *J. Chem. Soc.* **1937,** 1201.

[9] W. von E. Doering, T. C. Aschner, *J. Amer. Chem. Soc.* **71,** 838 (1949).

[10] D. J. Cram, *J. Amer. Chem. Soc.* **71,** 3863 (1949).

[11] A. Streitwieser, Jr., A. C. Waiss, *J. Org. Chem.* **27,** 290 (1962). K. Mislow, *J. Amer. Chem. Soc.* **73,** 4044 (1951).

[12] V. N. Ipatieff, R. L. Burwell, *J. Amer. Chem. Soc.* **63,** 969 (1941).