Oxonium Salt Alkylation of Structurally and Optically Labile Alcohols

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Received October 26, 1976

We recently required a general method for the transformation of a number of alcohols into their methyl and ethyl ethers in good yield and with intact structure of the alcohol moiety. Several common methods of effecting alcohol alkylation were deemed to be inappropriate to meet our needs. For example, the familiar Williamson reaction[1] between alkyl halides and metal alkoxides of primary and secondary alcohols having hydrogens at chiral centers located either α or β to the hydroxyl group frequently yields ethers which are extensively racemized.[2-5] The alternate Purdie procedure[1] using alcohols and alkyl halides in the presence of silver oxide apparently proceeds without racemization,[6,7] but may prove ineffective in the case of sterically hindered alcohols.[8]

We felt that the use of Meerwein's triethyloxonium (**1**) and trimethyloxonium (**2**) tetrafluoroborate salts[9] might offer an improved synthetic route to the ethers since optically active ether has been produced by the action of **1** on optically active pinacolyl alcohol.[8]

$$(C_2H_5)_3O^+ \, BF_4^- \qquad (CH_3)_3O^+ \, BF_4^-$$
$$\textbf{1} \qquad\qquad\qquad \textbf{2}$$
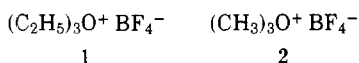
Our major concern with this approach was that the tetrafluoroboric acid produced (eq 1) might promote structural

$$ROH + R'_3O^+BF_4^- \xrightarrow{-R'_2O}$$

$$R-\overset{+}{\underset{H}{O}}\diagup\overset{R'}{} \; BF_4^- \rightleftharpoons ROR' + HBF_4 \quad (1)$$
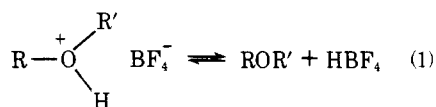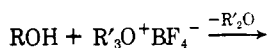
isomerization, racemization, and/or polymerization in systems prone to undergo carbenium ion formation. Indeed, when a dichloromethane solution of 1-phenylethanol and freshly prepared triethyloxonium tetrafluoroborate[10] (1.6 equiv) was stirred at room temperature for 1 week, only polymeric material was obtained. As 1-ethoxy-1-phenylethane is known to retain its optical activity in the presence of **1**,[11] a cationic polymerization process induced by the liberated tetrafluoroboric acid seems the most likely cause of this behavior. Similar treatment of 2,2-dimethyl-1-propanol with **1** (1.2 equiv) produced a 55% yield of ethers consisting of a mixture of 2,2-dimethyl-1-ethoxypropane (83%) together with the methyl-shifted isomeric ether 2-ethoxy-2-methylbutane (17%) (eq 2).
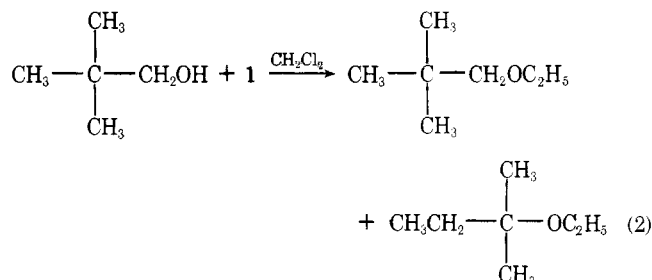
It seemed to us that a reasonable way to avoid such undesired carbenium ion processes would be through the introduction of a sterically hindered Bronsted base of low nucleophilicity to remove acid as it forms. As *N,N*-diisopropylethylamine[12] (**3**)

$$[(CH_3)_2CH]_2NC_2H_5$$
$$\textbf{3}$$
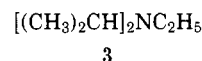
has reportedly been used successfully for this purpose during esterifications of carboxylic acids by either **1** or **2**,[13] we explored its use in alcohol alkylation. The effect of added amine was dramatic (see Table I). Introduction of amine **3** (2 equiv) into a solution of (*R*)-(+)-1-phenylethanol and **1** (1.5 equiv) produced (*R*)-(+)-1-ethoxy-1-phenylethane in good synthetic and optical yields. Good yields were also obtained using **1** and **3** for ethylation of 2,2-dimethyl-1-propanol and (*S*)-(−)-2-methyl-1-butanol, both systems prone to undergo isomerization in the presence of protic acids. However, treatment of a dichloromethane solution of 2-*tert*-butyl-2-adamantanol with **1** and **3** for 1 week gave only unreacted alcohol upon workup. Apparently this alcohol, chosen for study because of its extreme propensity to undergo acid-catalyzed dehydration with rearrangement,[14] is too sterically hindered around the

Table I. Alkylation of Various Alcohols with Trimethyl- and Triethyloxonium Tetrafluoroborates in the Presence of Sterically Hindered Amines[a]

Alcohol	Registry no.	Oxonium salt[b]	Amine[b]	Ether product	Isolated yield, %	Registry no.
2,2-Dimethyl-1-propanol	75-84-3	1 (1.2)	None	2,2-Dimethyl-1-ethoxypropane (83%)	55[c]	17348-57-1
				2-Ethoxy-2-methylbutane (17%)		919-94-8
		1 (1.0)	3 (2.9)	2,2-Dimethyl-1-ethoxypropane	70	
(*R*)-(+)-1-Phenylethanol	1517-69-7	1 (1.6)	None	None[d]		
[α]^{25}D +40.33° (neat)		1 (1.5)	3 (3.0)	(*R*)-(+)-1-Ethoxy-1-phenylethane	65	61587-06-2
				[α]^{30}D +84.8° (neat)		
		2 (2.1)	4 (2.1)	(*R*)-(+)-1-Methoxy-1-phenylethane	69	52224-89-2
				[α]^{26}D +125.9° (neat)		
(*S*)-(−)-2-Methyl-1-butanol	1565-80-6	1 (1.0)	3 (1.2)	(*S*)-(+)-1-Ethoxy-2-methylbutane	89	1767-83-5
[α]^{23}D −5.69° (neat)				[α]^{24}D +0.92° (neat)		
		2 (1.0)	3 (1.5)	None[e]		
		2 (1.0)	4 (1.2)	(*S*)-(+)-1-Methoxy-2-methylbutane	57[f]	1565-78-2
				[α]^{25}D +0.57° (neat)		
2-*tert*-Butyl-2-adamantanol	38424-20-3	1 (2.2)	3 (3.3)	None[g]		
		2 (2.1)	4 (2.5)	None[h]		

[a] Unless otherwise specified, reactions were allowed to proceed in dichloromethane at room temperature for 1 week. [b] Number in parentheses represents molar ratio of this reagent relative to alcohol. [c] Isolated yield of ether mixture. [d] Only polymeric product obtained. [e] Exclusive amine quaternization occurred. [f] Reaction time 3 days. [g] Alcohol recovered. [h] After 1 week ca. two-thirds of the alcohol had been converted to 2-methyl-2-(2'-propenyl)adamantane.

hydroxyl oxygen to serve as an effective nucleophile toward triethyloxonium ion.

Attempts to form methyl ethers through use of amine 3 and trimethyloxonium tetrafluoroborate (2) were unsuccessful as the amine proved more nucleophilic toward trimethyloxonium ion than did the alcohol. Thus, when 2 (1 equiv)[15] was suspended in a dichloromethane solution of 3 (1.5 equiv) and 2-methyl-1-butanol and stirred for 1 week, a white precipitate of diisopropylethylmethylammonium tetrafluoroborate was obtained. The unreacted alcohol was recovered.

The sterically more hindered, less nucleophilic base 1,8-bis(dimethylamino)naphthalene (4)[16,17] did prove effective

(CH₃)₂N   N(CH₃)₂

4
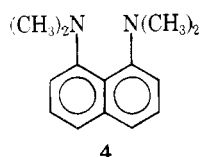
in the methylation of alcohols with 2. In the presence of this amine, the methyl ethers of both (S)-(−)-2-methyl-1-butanol and (R)-(+)-1-phenylethanol were obtained in good synthetic yields and with excellent optical purities (Table I). Although no 2-*tert*-butyl-2-methoxyadamantane was obtained by the addition of 2 and 4 to 2-*tert*-butyl-2-adamantanol, over a period of several weeks the alcohol slowly disappeared and was replaced by the methyl-shifted elimination product 2-methyl-2-(2'-propenyl)adamantane. This suggests that, unlike the case with 1, this alcohol may slowly attack the less hindered trimethyloxonium ion to yield an intermediate secondary oxonium ion (protonated ether) which then loses methanol to form products of diminished internal steric strain.[14,18]

The number of alcohols studied to date has not been great and the yields of products have not been optimized, but it would appear that the use of trialkyloxonium salts in conjunction with nonnucleophilic amine bases to effect alkylation of labile alcohols is an attractive, general synthetic route to ethers which may be difficult to obtain by other means.

Experimental Section

General. NMR spectra were obtained on a Varian T-60A instrument using tetramethylsilane as an internal standard. Optical rotations were measured on neat samples using a Rudolph Model 26202 automatic digital polarimeter. VPC analyses were performed on a Varian Aerograph 90-P chromatograph using 0.25-in. columns. All glassware was oven dried and assembled while hot.

Materials. Reagent grade dichloromethane was dried over Linde 4A molecular sieves prior to use. Triethyloxonium tetrafluoroborate and trimethyloxonium tetrafluoroborate were prepared according to previously reported procedures[10,15] and were washed several times with anhydrous diethyl ether just prior to use.

General Alkylation Procedures. (S)-(+)-1-Ethoxy-2-methylbutane. The preparation of this compound is representative of all successful ethylations. Into a 100-mL, round-bottomed flask fitted with a condenser, drying tube, and magnetic stirring bar were placed 20.0 g (0.16 mol) of N,N-diisopropylethylamine (Aldrich), 25.2 g (0.13 mol) of triethyloxonium tetrafluoroborate, 40 mL of dichloromethane, and 14.0 mL (0.13 mol) of (S)-(−)-2-methyl-1-butanol [Eastman, [α]²³_D −5.69° (neat), optical purity 96.8%[19]]. The resulting solution was stirred at room temperature for 7 days before it was quenched with ice water and extracted with two 50-mL portions of diethyl ether. The combined ether extracts were washed twice with 5% aqueous sodium bicarbonate solution and once with water prior to drying (MgSO₄). Distillation produced 13.3 g (89%) of colorless product which was pure by VPC (20-ft Carbowax 20M, 140 °C), NMR, and IR analyses: bp 105–106.5 °C; [α]²⁴_D +0.92° (neat) [lit.[19] bp 109–110 °C; [α]²⁰_D +0.89° (neat)].

(S)-(+)-1-Methoxy-2-methylbutane. Procedures for methylation were essentially the same as those used in ethylation except that the reduced solubility of trimethyloxonium tetrafluoroborate in dichloromethane resulted in a suspension rather than a solution of reactants. After 3 days of stirring, workup of a mixture of 7.0 mL (0.06 mol) of (S)-(−)-2-methyl-1-butanol, 9.5 g (0.06 mol) of trimethyloxon-

ium tetrafluoroborate, and 15.0 g (0.07 mol) of 1,8-bis(dimethylamino)naphthalene[17] in 20 mL of dichloromethane yielded 3.5 g (57%) of pure product: bp 89.5–90.5 °C; [α]²⁵_D +0.57° (neat) [lit.[19] bp 90 °C; [α]²⁰_D +0.61° (neat)].

In a similar experiment using N,N-diisopropylethylamine instead of 1,8-bis(dimethylamino)naphthalene, workup yielded only unreacted alcohol together with a white, crystalline precipitate which could be recrystallized from hot water. This material had microanalytical and spectral properties consistent with diisopropylethylmethylammonium tetrafluoroborate: NMR (CD₃CN) δ 3.60 (2 H, septet), 3.05 (2 H, q), 2.50 (3 H, s), and 1.10 (15 H, m). Careful examination of the upfield multiplet region showed it to consist of a 12-proton doublet ($J = 6.7$ Hz), each line of which was split into a triplet of equal intensity ($J = 1.7$ Hz), which partially overlapped a three-proton doublet ($J = 7.5$ Hz), each line of which was further split into a triplet of equal intensity ($J = 1.8$ Hz). This pattern is consistent with three-bond coupling between nitrogen and the isopropyl group methyl protons with J_{NH} equal to 1.7 Hz and with the ethyl group methyl protons with J_{NH} equal to 1.8 Hz. These values compare closely with analogous couplings reported in the cases of other tetraalkylammonium salts.[20]

References and Notes

(1) H. Feuer and J. Hooz in "The Chemistry of the Ether Linkage", S. Patai, Ed., Interscience, New York, N.Y., 1967, pp 445–498.
(2) P. G. Stevens, *J. Am. Chem. Soc.*, **54**, 3732 (1932).
(3) W. von E. Doering and T. C. Aschner, *J. Am. Chem. Soc.*, **71**, 838 (1949).
(4) K. Mislow, *J. Am. Chem. Soc.*, **73**, 3954 (1951).
(5) H. M. Peters, D. M. Feigl, and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968).
(6) A. Streitwieser, Jr., and A. C. Waiss, Jr., *J. Org. Chem.*, **27**, 290 (1962).
(7) K. Mislow, *J. Am. Chem. Soc.*, **73**, 4043 (1951).
(8) J. Jacobus, Z. Majerski, K. Mislow, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **91**, 1998 (1969).
(9) H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. Prakt. Chem.*, **147**, 257 (1937).
(10) H. Meerwein, *Org. Synth.*, **46**, 113 (1966).
(11) R. A. Moss and C. E. Powell, *J. Am. Chem. Soc.*, **98**, 283 (1976).
(12) S. Hünig and M. Kiessel, *Chem. Ber.*, **91**, 380 (1958).
(13) D. J. Raber and P. Gariano, *Tetrahedron Lett.*, 4741 (1971).
(14) J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 4628 (1972).
(15) T. J. Curphey, *Org. Synth.*, **51**, 142 (1971).
(16) R. W. Alder, P. S. Bowman, W. R. S. Steele, and D. R. Winterman, *Chem. Commun.*, 723 (1968).
(17) Supplied by the Aldrich Chemical Co. under the name "Proton Sponge".
(18) J. L. Fry and R. C. Badger, *J. Am. Chem. Soc.*, **97**, 6276 (1975).
(19) C. Blomberg and J. Coops, *Recl. Trav. Chim. Pays-Bas*, **83**, 1083 (1964).
(20) P. G. Gassman and D. C. Heckert, *J. Org. Chem.*, **30**, 2859 (1965).

Unsaturated Carbenes from Primary Vinyl Triflates. 6. Competitive Addition of Isopropylidene Carbene to Olefins[1]

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Unsaturated carbenes[2], 1, have been shown to be singlets,[3] electrophilic,[4] and at least in the case of the vinyl triflate, 2, derived species,[5] free rather than carbenoid.[4a] In order to as-

1   2, OTf = OSO₂CF₃   3