Demethylation of Aliphatic Methyl Ethers with a Thiol and Boron Trifluoride

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Treatment of primary and secondary alkyl methyl ethers with boron trifluoride–ether complex in several thiols gave the corresponding alcohols in good yields and, in the case of secondary alkyl methyl ethers, with retention of the original stereochemistry.

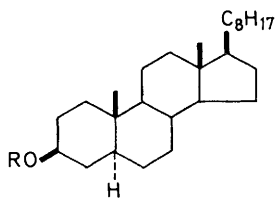
METHYL ethers of primary and secondary alcohols are stable under both basic and acidic conditions; hence *O*-methylation is regarded as one of the most effective alcohol-protecting groups. De-*O*-methylation, however, is difficult, which is the most important reason why *O*-methylation is not a usual method of protection of these alcohols.

Much work has appeared on the ether cleavage reaction,[1] but de-*O*-methylation of aliphatic methyl ethers has received little attention. The most important de-*O*-methylations reported so far are probably the reactions of methyl ethers with boron halides, *i.e.* boron trifluoride–ether and acetic anhydride,[2] boron trichloride,[3] and boron tribromide.[4,5] With regard to secondary alkyl methyl ethers, boron trifluoride and acetic anhydride have been reported to convert Δ^4- and Δ^5-3-methoxycholestenes into the corresponding 3β-acetoxy-compounds,[2] but products from 3-methoxycholestanes consisted of mixtures of epimeric 3-acetates and cholest-2-ene.[2] Similar results were recently reported in reactions with anhydrous iron(III) chloride in acetic anhydride.[6] On the other hand, the reactions[5] of cholestanyl methyl ether (1) with boron trichloride or boron tribromide gave epimeric chlorides or bromides, no alcohol being obtained. Transformations of the methyl group in secondary alkyl methyl ethers into a formyl group by chromic anhydride and acetic acid[7] and into a trimethylsilyl group by bis(trimethylsilyl)-mercury[8] seem unsatisfactory with regard to yields.

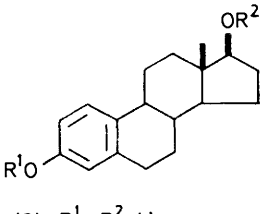
[1] E. Staude and F. Patat, 'The Chemistry of the Ether Linkage,' ed. S. Patai, Interscience, London, 1967, p. 21.
[2] C. R. Narayanan and K. N. Iyer, *J. Org. Chem.*, 1965, **30**, 1734.
[3] S. D. Géro, *Tetrahedron Letters*, 1966, 591.
[4] W. A. Ayer, W. R. Bowman, T. L. Joseph, and P. Smith, *J. Amer. Chem. Soc.*, 1968, **90**, 1648.
[5] R. D. Youssefyeh and Y. Mazur, *Chem. and Ind.*, 1963, 609.
[6] B. Ganem and V. R. Small, jun., *J. Org. Chem.*, 1974, **39**, 3728.
[7] I. T. Harrison and S. Harrison, *Chem. Comm.*, 1966, 752.

Thus no useful demethylating agent for secondary alkyl methyl ethers has yet been reported.

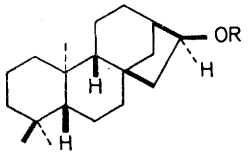
We have recently found that primary and secondary alkyl methyl ethers can be converted into the corresponding alcohols in good yields by treatment with a thiol and boron trifluoride–ether, and also that the



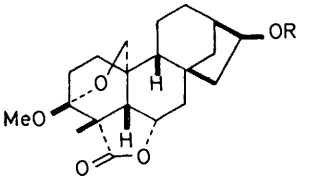
(1) R = Me
(7) R = H



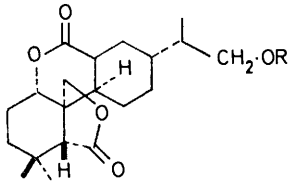
(2) $R^1 = R^2 = Me$
(8) $R^1 = Me$, $R^2 = H$
(9) $R^1 = R^2 = H$



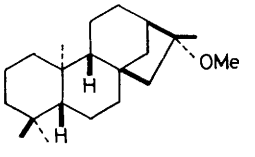
(3) R = Me
(10) R = H



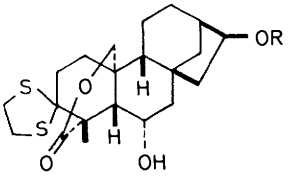
(4) R = Me
(11) R = H



(5) R = Me
(14) R = H



(6)



(12) R = Me
(13) R = H
(15) R = Ac

demethylation proceeds with retention of stereochemistry in a secondary alkyl methyl ether. We now report the details of this reaction.

The substrates studied were cholestan-3β-yl methyl ether (1),[2] 17β-estradiol dimethyl ether (2),[9] *ent*-16α-methoxy-17-norkaurane (3), *ent*-3β,20-epoxy-3,16α-dimethoxy-17-norkauran-19,6β-olide (4),* *ent*-16-methoxy-B-secoabietane-7,1β;6,20-diolide (5), and *ent*-16-methoxykaurane (6).[10] The thiols, propane-1-thiol, 2-methylpropane-1-thiol, benzenethiol, and ethane-1,2-dithiol were employed. The reaction conditions and the results are shown in the Table.

Cholestanyl methyl ether (1) was converted into cholestanol (7) in 70—80% yields; in a similar experiment with ethylene glycol instead of a thiol almost all the starting material (1) was recovered, even after 20 days. 17β-Estradiol dimethyl ether (2) was converted into 17β-estradiol 3-methyl ether (8) [9] in good yield in the presence of a relatively small quantity of boron trifluoride. In the presence of larger quantities of the Lewis acid, demethylation of the aliphatic *O*-methyl group (8) was complete within a shorter time, and on further treatment for a long time some demethylation of the aromatic *O*-methyl group occurred to yield 17β-estradiol (9) [9,11] as a minor product. The reaction with *ent*-16α-methoxy-17-norkaurane (3) gave *ent*-16α-hydroxy-17-norkaurane (10),[12] with some unchanged starting material. On the other hand, the reaction of (3) with boron tribromide is known to afford a mixture of rearranged products containing bromine.[13] The reaction with compound (4) proceeded with competing of acetal exchange accompanied by recyclisation to a new lactone ring and demethylation to give the products (11)—(13), but further treatment for a long time gave (13) in almost quantitative yield. In the reaction with methyl ether (5) of a primary alcohol, a high yield of the parent alcohol (14) [14] was obtained. In the reaction with the methyl ether (6) of a tertiary alcohol, however, many products were obtained and no detailed investigation was carried out.

The retention of the original stereochemistry in the secondary alcohols derived from compounds (1)—(3) was proved by direct comparisons with authentic samples [(7)—(10), respectively]. The retention of the original stereochemistry also in the alcohols (11) and (13) was established by reconversion of (11) into (4) by treatment with methyl iodide and sodium hydride, and by the n.m.r. coupling pattern of H-16 of the acetate (15), derived from (13), respectively.

Finally treatment of 2,2′-dimethoxybiphenyl (16) [15] with boron trifluoride–ether in high concentration in phenylmethanethiol for a long time gave the demethylation product (17) [15] in good yield, accompanied by the methyl sulphide (18).

The present findings may be summarised as follows. (i) Alcohols derived from secondary alkyl methyl ethers showed retention of the original configuration. (ii) The

* This compound will be described in detail in a later paper on the synthesis of some C_{20} gibberellins.

[8] C. Eaborn, R. A. Jackson, and R. W. Walsingham, *J. Chem. Soc.* (*C*), 1967, 2188.
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[10] J. R. Hanson, *J. Chem. Soc.* (*C*), 1963, 5061.
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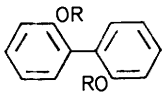
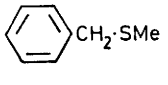
[13] Unpublished results obtained in our laboratory.
[14] E. Fujita, T. Fujita, H. Katayama, M. Shibuya, and T. Shingu, *J. Chem. Soc.* (*C*), 1970, 1674.
[15] G. Aulin-Erdtman and R. Sanden, *Acta Chem. Scand.*, 1963, **17**, 1991.

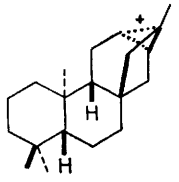
rates of demethylation were in the order: $-CH_2-OMe$ > $-CH-OMe$ ≫ Ph–OMe. (iii) The effectiveness of the



(16) R = Me
(17) R = H

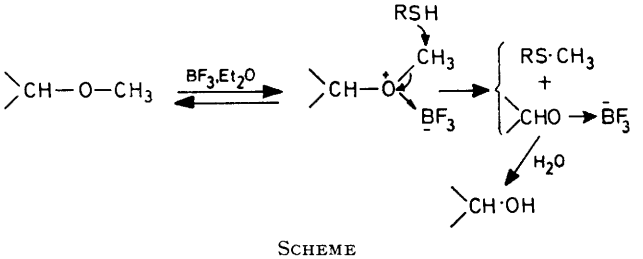


(18)



(19)

thiols in promoting demethylation was in the order: aliphatic dithiol > aliphatic monothiol > aromatic thiol. (iv) The rate increased with increasing concentration of boron trifluoride–ether. This reaction is therefore considered to proceed *via* nucleophic attack of the thiol on the less hindered and more electron-deficient carbon atom, that is the methyl carbon atom, of the oxonium species formed initially, as shown in the Scheme.



SCHEME

The unsuccessful result with the tertiary alkyl methyl ether (6) is probably attributable to easy elimination of the methoxy-group co-ordinated to the boron trifluoride to form a non-classical carbocation (19). The low rate of cleavage of the aromatic methyl ether may be due to the $-I$ effect of the phenyl group, pushing the equilibrium shown in the Scheme to the left. The rate difference between benzenethiol and aliphatic thiols is believed to be due to differences in their nucleophilicity. The sole disadvantage in these reactions is the long reaction time, but this can be minimised by use of a large concentration of boron trifluoride.

In conclusion, we have developed a versatile method of application of methyl ethers for the protection of primary and secondary alcohols. We have applied this method in the synthesis of C_{20} gibberellins.[16] The large rate difference between aromatic and aliphatic methyl ethers has potential for selective and stepwise demethylation.

EXPERIMENTAL

M.p.s were taken with a micro hot-stage apparatus. Unless otherwise stated, i.r. spectra were recorded for KBr discs with a Hitachi EPI-S2 spectrometer and n.m.r. spectra with a Varian T-60 spectrometer for solutions in [^{2}H]chloroform (tetramethylsilane as internal standard). Mass spectra were determined with a JEOL JMS-OISG double-focusing spectrometer. Extracts were dried over Na_2SO_4. Mallinckrodt silicic acid or Kieselgel (0.06—0.2 mm; Merck) was used for column chromatography, and Kieselgel G (Merck) for t.l.c.

Demethylation reaction: conditions and results

Material; mg	Thiol;* ml	BF_3–Et_2O (ml)	Reaction time (days)	Product; yield (%) †	Recovery of material (%)
(1); 20	a; 1	0.05	4	(7); 80	
(1); 20	b; 1	0.05	8	(7); 73	10
(1); 20	c; 1	0.05	8	(7); 75	5
(1); 20	a; 1	2.00	1	(7); 75	0
(2); 30	a; 1	0.05	8	(8); 60	27
(2); 30	a; 1	0.10	3	(8); 93	4
(2); 30	a; 1	0.30	0.4	(8); 77 and (9); 9	6
			8	(8); 80 and (9); 18	0
(2); 20	c; 1	0.10	5	(8); 80	0
(2); 20	d; 1	0.10	2	(8); 60	34
(3); 14	a; 0.5	0.03	4	(10); 75	21
(4); 33	a; 1	0.03	4	(11); 26 and (12); 22; (13); 43	
(4); 98	a; 3	0.15	12	(13); 92	0
(5); 20	a; 0.5	0.03	3	(14); 92	
(6); 40	a; 1	0.03	1	Many products	
(16); 50	e; 1	0.50	6	(17); 84 and (18) (7 mg) ‡	12

* a, ethanedithiol; b, 2-methylpropane-1-thiol; c, propane-1-thiol; d, benzenethiol; e, phenylmethanethiol. † Isolated yield. ‡ δ 1.53 (3 H, s, SMe), 3.82 (2 H, s, CH_2·S), and 7.83br (5 H, s, ArH).

Synthesis of Substrates.—(i) *Estradiol dimethyl ether* (2). To a solution of sodium hydride (100 mg) (53% in mineral oil; washed with dry ether) in dimethylformamide (DMF) (5 ml) was added estradiol (9) (100 mg) at 0 °C under nitrogen. After stirring for 10 min, methyl iodide (0.2 ml) was added. The solution was stirred overnight, then poured into ice–water and extracted with ether. The usual work-up gave a crystalline product (103 mg), which was recrystallised from CH_2Cl_2–MeOH to yield the *dimethyl ether* (2) (82.5 mg) as needles, m.p. 161—163°, $\nu_{max.}$ 1 605, 1 500, 1 232, 1 101, and 1 030 cm^{-1}, δ 0.79 (3 H, s), 3.16—3.47 (1 H, m, 17-H), 3.40 (3 H, s, 17-OMe), 3.80 (3 H, s, 3-OMe), 6.63 (1 H, s, 4-H), and 6.92 and 7.17 [each 1 H, AB type, *J* 9 Hz, 1- and 2-H; the higher field signal showed long-range coupling (*J* 3 Hz) with 9-H] (Found: C, 79.9; H, 9.5. $C_{20}H_{28}O_2$ requires C, 79.95; H, 9.4%).

(ii) ent-16α-*Methoxy*-17-*norkaurane* (3). To a solution of *ent*-16α-hydroxy-17-norkaurane (10) (18 mg) in dry

[16] M. Node, H. Hori, and E. Fujita, *J.C.S. Chem. Comm.*, 1975, 898.

ether (5 ml) was added diazomethane (in ether dried over KOH) (5 ml) at −15 °C. Boron trifluoride–ether (3 drops) was then added with stirring. After stirring for 30 min, the mixture was poured into water and extracted with ether. The usual work-up gave a crystalline product (18 mg), which was recrystallised from MeOH–Me_2CO to yield the methyl ether (3) (14 mg) as leaflets, m.p. 77—78°, $\nu_{max.}$ 1 005 cm^{-1}, δ 0.81, 0.84, and 1.02 (each 3 H, s, 3 × tert. Me), 3.32 (3 H, s, OMe), and 3.76 (1 H, quint, *J* 5.5 Hz, 16-H), M^+, 290.

(iii) ent-16-*Methoxy*-B-*secoabietane*-7,1β;6,20-*diolide* (5). To a solution of *ent*-16-hydroxy-B-secoabietane-7,1β;6,20-diolide (14) [14] (57 mg) in dry ether–chloroform (1 : 1) (5 ml) was added an excess of diazomethane (in ether dried over KOH) (5 ml) at −10 °C. Boron trifluoride–ether (3 drops) was then added with stirring. After 30 min, the mixture was poured into water and extracted with ether. The usual work-up gave a mixture, which was chromatographed (SiO_2; CH_2Cl_2) to separate the alcohol (14) (21 mg) and the *methyl ether* (5) (32 mg), obtained as needles, m.p. 168—172° (from MeOH), $\nu_{max.}$ 1 775, 1 748, 1 176, and 1 048 cm^{-1}, δ 0.88 (3 H, d, *J* 7 Hz, 15-Me), 1.10 and 1.24 (each 3 H, s, 4-Me_2), 2.35 (1 H, s, 5-H), 3.30 (2 H, d, *J* 5 Hz, 16-H_2), 3.33 (3 H, s, OMe), 3.79 and 4.45 (each 1 H, AB-type, *J* 9 Hz, 20-H_2), and 4.32 (1 H, t, *J* 8 Hz, 1-H) (Found: C, 69.35; H, 8.85. $C_{21}H_{32}O_5$ requires C, 69.2; H, 9.15%).

Demethylation of Aliphatic Methyl Ethers.—(i) *General procedure.* To a solution of the methyl ether in the thiol was added boron trifluoride–etherate with stirring at room temperature. After a few days, extraction with CH_2Cl_2 and treatment as usual gave a crude product, which was chromatographed (SiO_2; n-hexane–CH_2Cl_2–acetone) to yield pure material (Table).

(ii) *Physical data of new products. ent*-3β,20-Epoxy-16α-hydroxy-3-methoxy-17-norkauran-19,6β-olide (11), amorphous, $\nu_{max.}$ 3 500, 1 760, and 1 070 cm^{-1}, δ (C_5D_5N) 1.41 (3 H, s, 4-Me), 3.56 (3 H, s, 3-OMe), and 3.7—4.9 (4 H, m, 6-H, 16-H, and 20-H_2) M^+ 348; *ent*-3,3-ethylenedithio-6β-hydroxy-16α-methoxy-17-norkauran-19,20-olide (12), needles, m.p. >300° (from MeOH), $\nu_{max.}$ 3 500 and 1 710 cm^{-1}, δ 1.57 (3 H, s, 4-Me), 3.30 (4 H, s, S·CH_2·CH_2·S), 3.34 (3 H, s, OMe), 3.80 (1 H, m, 16-H), 4.17 and 5.43 [each 1 H, AB-type, *J* 11.5 Hz, 20-H_2; lower field signal showed long-range coupling (*J* 2.5 Hz)], and 4.33 (1 H, m, 6-H), M^+ 424; *ent*-3,3-ethylenedithio-6β,16α-dihydroxy-17-norkauran-19,20-olide (13), amorphous, $\nu_{max.}$ 3 400, 3 350, 1 705, and 1 020 cm^{-1}, M^+, 410.

Methylation of the Alcohol (11).—To a solution of sodium hydride (5 mg) (53% in mineral oil, washed with dry ether) in DMF (1 ml) was added the alcohol (11) (9 mg) at 0 °C, followed by methyl iodide (4 drops). After being stirred for 1 h at room temperature, the mixture was poured into water and extracted with ether. The usual work-up gave a crude product (11 mg), which was chromatographed (SiO_2; CH_2Cl_2) to give the *methyl ether* (4) (5 mg) as needles, m.p. 217.5—218.5° (from MeOH), $\nu_{max.}$ 1 768, 1 102, 1 075, and 1 038 cm^{-1}, δ 1.33 (3 H, s, 4-Me), 3.30 and 3.44 (each 3 H, s, 2 × OMe), *ca.* 3.80 (1 H, m, 16-H), 3.90 and 4.46 [each 1 H, AB-type, *J* 9 Hz, 20-H_2; lower field signal showed long-range coupling (*J* 3 Hz)], and 4.70 (1 H, t, *J* 5.5 Hz, 6-H) (Found: C, 69.5; H, 8.4. $C_{21}H_{30}O_5$ requires C, 69.6; H, 8.35%).

Acetylation of the Diol (13).—A mixture of the diol (13) (29 mg) and Ac_2O–pyridine (1 : 1) (1 ml) was kept at room temperature overnight. After addition of MeOH to decompose the excess of Ac_2O, the solution was evaporated under reduced pressure and the product was chromatographed (SiO_2; CH_2Cl_2–Me_2CO) to afford the monoacetate (15) (30 mg) as needles, m.p. >300° (from MeOH), $\nu_{max.}$ 3 500, 1 730, 1 720, and 1 260 cm^{-1}, δ 1.57 (3 H, s, 4-Me), 2.06 (3 H, s, OAc), 3.29 (4 H, s, S·CH_2CH_2·S), 4.18 and 5.43 [each 1 H, AB-type, *J* 11 Hz, 20-H_2; lower field signal showed long-range coupling (*J* 3 Hz)], 4.33 (1 H, m, 6-H), and 5.0 (1 H, quint, *J* 5.5 Hz, 16-H); M^+ 452.

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