Hard Acid and Soft Nucleophile System. 2.[1] Demethylation of Methyl Ethers of Alcohol and Phenol with an Aluminum Halide–Thiol System

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Aliphatic and aromatic methyl ethers have been easily cleaved on treatment with a hard acid, aluminum halide, and a soft nucleophile, EtSH, to give parent alcohols and phenols, respectively. With compounds possessing both aliphatic and aromatic methyl ether groups, simultaneous demethylation of both types of ethers occurred. The ethereal carbon–oxygen bond in compounds possessing both ether and ester groups was selectively cleaved under mild conditions by using dichloromethane as a cosolvent. Acetoxyl and *N*-acetyl groups were shown to be stable to this reagent system, except for easy hydrolysis of aromatic acetoxyl groups under conditions of workup after the reaction.

Use of the methyl ether function to protect hydroxyl groups has been limited by lack of effective and selective demethylation reagents. Recent reports have shown the cleavage of primary alkyl and phenolic methyl ethers by $(Me)_3SiI$[2a,b] and of phenolic methyl ethers by CH_3SO_3H and methionine.[2c] The combination of $BF_3{\cdot}OEt_2$ and an aliphatic thiol has been shown to be effective in cleaving methyl ethers of primary and secondary alcohols.[3] This cleavage of secondary methyl ethers occurs with retention of configuration, and this reaction was therefore used in the total synthesis of gibberellins A_{15} and A_{37}.[4] We have also shown that this reagent is effective for cleavage of benzyl ethers.[1]

We now report a new, highly active demethylation reagent, an aluminum halide and ethanethiol,[5] characterized by rapid action under mild conditions, easy workup of the reaction products, and high yields. It demethylates methyl ethers of alcohols and phenols and also cleaves aromatic methylenedioxy compounds to catechols.

Results and Discussion

The $BF_3{\cdot}OEt_2$–thiol reagent works well for debenzylation of benzyl ethers but is rather slow in demethylations. In a search for a more active reagent, we explored metal halides as the Lewis acid components. The rate of demethylation of cholestanyl methyl ether (1; see Chart I) was compared by using several combinations of metal halides and ethanethiol, with the results shown in Table I. The order of activity of the metal halides was $ZnCl_2 \ll FeCl_3 < AlCl_3 < AlBr_3$ and is in accord with the order of hardness reported for metal ions.[6] The overall reaction can be explained by the principle of hard and soft acids and bases.[7]

In our studies $AlBr_3$ was used for a few ethers that were difficult to cleave, but $AlCl_3$ was satisfactory for most. The results of demethylation of several ethers by the AlX_3–EtSH reagent are shown in Table II.

The cleavage of methyl ethers of primary (**2**, **3**, **6**) and secondary (**4**, **5**) alcohols proceeded much more rapidly than with the $BF_3{\cdot}OEt_2$–EtSH reagent, and the parent alcohols were generated in good yields. Alcohols derived from secondary alkyl methyl ethers were obtained with

Table I. Demethylation of Cholestanyl Methyl Ether (1) in Ethanethiol at Room Temperature

Lewis acid (molar equiv)	*t*, h	yield of 1a, %	recovery of 1, %
$MnCl_2$ (1.6)	384	0	97.5
$ZnCl_2$ (1.7)	84	6.5	92.5
$FeCl_3$ (1.6)	84	66.3	32.0
$AlCl_3$ (1.8)	5.5	95.9	3.8
$AlBr_3$ (1.8)	3	98.4	0
$BF_3{\cdot}OEt_2$ (8)[a]	96	80	

[a] Data cited from ref 3 (ethanedithiol was used).

Table II. Demethylation of Methyl Ethers in EtSH

compd (mmol)	Lewis acid (molar equiv)	amt EtSH, mL	*t*, h[a]	product	yield, %
2 (0.1)	$AlBr_3$ (3.0)	1.5	14	2a	98.3
3 (0.6)	$AlBr_3$ (1.7)	1.5	4.5	3a	85.1
4 (0.1)	$AlBr_3$ (3.0)	1.0	1	4a	90.0
5 (0.1)	$AlBr_3$ (5.0)	2.0	1	5a	94.3
6 (0.1)	$AlBr_3$ (4.8)	1.0	2.3[b]	6a	96.0
7 (0.4)	$AlCl_3$ (2.0)	2.5	0.5[c]	7a	95.5
8 (0.7)	$AlCl_3$ (2.7)	2.0	0.5	8a	97.5
9 (0.15)	$AlCl_3$ (3.4)	2.0	0.5	5a	97.5
10 (0.1)	$AlCl_3$ (3.2)	1.0	1[c]	6a	95.2
11 (0.5)[d]	$AlCl_3$ (3.0)	0.2	6	11a	98.6
12 (0.2)[d]	$AlCl_3$ (5.0)	1.0	2.5[b]	12a	95.2
14 (0.1)[d]	$AlCl_3$ (5.0)	0.2	2	14a	95.2
15 (0.1)[d]	$AlBr_3$ (5.6)	0.5	3.5[b]	15a	70.4

[a] Reactions run at room temperature except as noted. [b] Reaction run at 0 °C to room temperature. [c] Reaction run at 0 °C. [d] Dichloromethane was used as the cosolvent; 11 and 14, each 3 mL; 12, 2 mL; 15, 0.5 mL.

Table III. Chemical Shifts of Methyl Groups of Estradiol Dimethyl Ether (5) in the Presence of Lewis Acid in $CDCl_3$

Lewis acid (amt)	chemical shift, δ[a] C-3 OCH_3	C-17 OCH_3
none	3.78	3.37
$BF_3{\cdot}OEt_2$ (10 molar equiv)	3.78	3.49
$AlCl_3$ (1 molar equiv)	3.84	3.76

[a] Parts per million from Me_4Si.

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Chart I

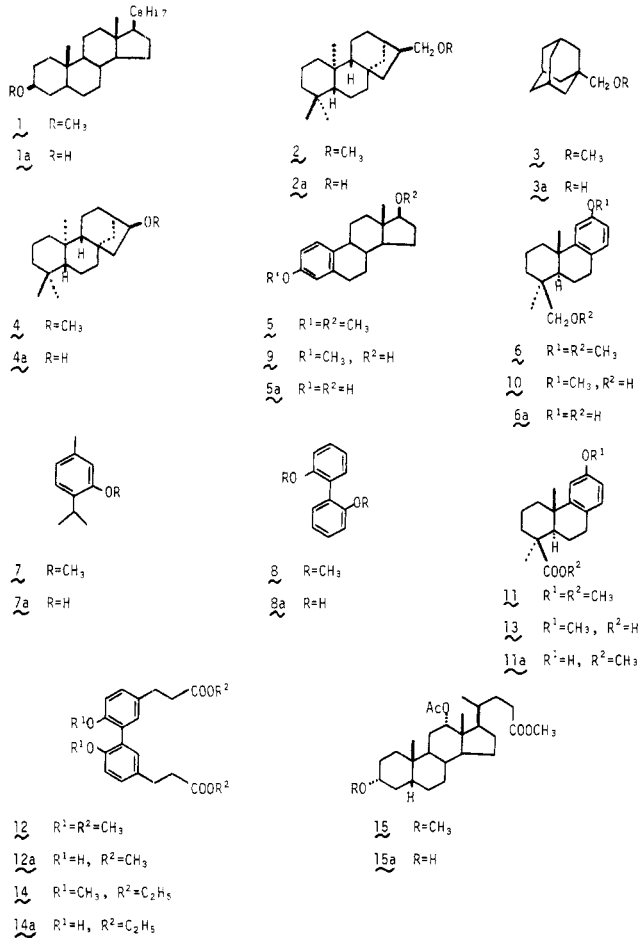
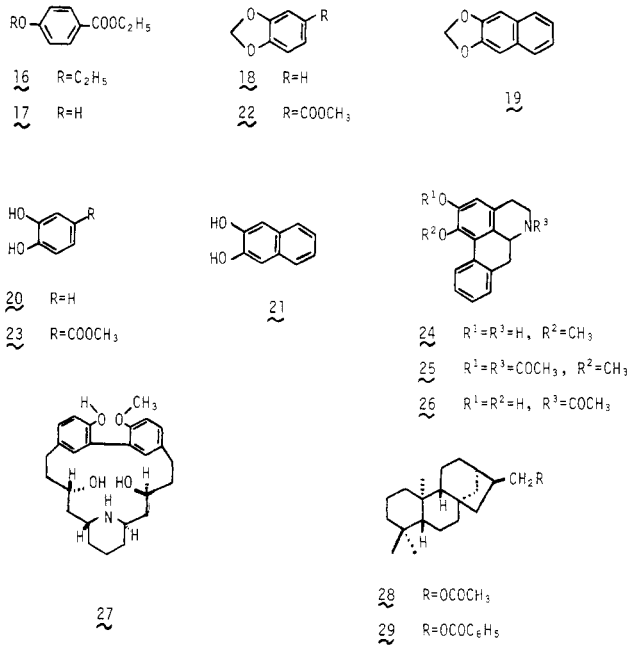


Chart II



retention of configuration, as was observed with the BF_3·OEt_2–EtSH reagent.

Compounds **5** and **6**, which have both alkyl and aryl methyl ether groups, underwent demethylation of both types of ether to give diols **5a** and **6a**, respectively, in high yield. The preferential demethylation of the alkyl ether group that occurs with the BF_3·OEt_2–thiol reagent[3] was not observed. This difference in behavior of the two types of Lewis acids was also shown by the ^1H NMR spectra of **5** in the presence of BF_3·OEt_2 or $AlCl_3$ (Table III). While only a slight paramagnetic shift of the methyl signal of the alkyl methyl ether group was observed with a large excess (10 molar equiv) of BF_3·OEt_2 because of the coordination of the hard acid BF_3 with the alcoholic ether oxygen, the methyl signals of both the aryl and alkyl ether groups shifted significantly downfield with only 1 molar equiv of $AlCl_3$, indicating that both types of ether oxygens coordinate with the hard acid $AlCl_3$. Thus, both aliphatic and aromatic methyl ethers can be cleaved with $AlCl_3$–thiol, while only the former are cleaved with BF_3·OEt_2–thiol.

Demethylation of methyl ethers of simple phenols (**7**–**10**) proceeded rapidly and gave almost quantitative yields of the parent phenols. Presumably the electron-withdrawing effect of the aryl group and/or the stereoelectronic effect due to overlap of the π orbital of the aryl group and the OCH_3 σ orbital contributes to the ease of this reaction.

Selective cleavage of the ester group of **11** with RS^-,[10] RSe^-,[11] and BCl_3[12] has been reported. The very active reagent $AlBr_3$–EtSH cleaves both the ester and ether groups of **11**.[8] However, the less active $AlCl_3$–EtSH, with dichloromethane as cosolvent, cleaves only the ether group of **11** to give **11a** in high yield. Likewise, only the ether linkages of **12** and **14** were cleaved by $AlCl_3$–EtSH, the ester groups remaining intact. Selective deethylation of **16** to **17** (see Chart II) was also achieved with this system.

The AlX_3–EtSH reagent cleaves aromatic methylenedioxy groups (**18**, **19**)[13] to give the corresponding catechols (**20**, **21**) in 70–80% yields. The reagent also effects selective demethylation of methyl 3,4-methylenedioxybenzoate (**22**) to **23**.

An attempt to demethylate the alkaloid asimilobine (**24**)[14] failed because of formation of an insoluble complex of $AlCl_3$ with the basic nitrogen. However, the *N*,*O*-diacetyl derivative **25** was readily cleaved to the *N*-acetyl catechol **26** in 81% yield. The reagent was also used successfully in the recent total synthesis of lythranidine (**27**).[15]

Aldehyde and ketone groups react with AlX_3–EtSH to form thioacetals and thioketals, and aliphatic double bonds add EtSH. On the other hand, hydroxyalkyl (**9**, **10**), acetoxyalkyl (**15**, **28**), *N*-acetyl (**25**), or (benzoyloxy)alkyl (**29**) groups are not affected. We have observed replacement of alkoxy by alkylthio in some naphthalenes and dehalogenation of some aromatic halides; these results will be described elsewhere.

Experimental Section

IR spectra were recorded with a JASCO A-202 diffraction grating infrared spectrophotometer, and ^1H NMR spectra were obtained with a JEOL JNM-FX100 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane. Mass spectra were determined on a JEOL JMS-O1SG double-focusing mass spectrometer.

Materials. Methyl ethers **1**–**8** were prepared from parent alcohols or phenols as previously reported.[3]

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1-(Methoxymethyl)adamantane (3): colorless oil; bp 85–86 °C (2 mm); NMR ($CDCl_3$) δ 2.94 (s, 2 H), 3.32 (s, 3 H). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.92; H, 11.24.

12,19-Dimethoxypodocarpa-8,11,13-triene (6): colorless needles (from methanol); mp 61.5–62.5 °C; NMR ($CDCl_3$) δ 1.03 (s, 3 H), 2.00 (s, 3 H), 3.24 (d, J = 9 Hz, 1 H), 3.33 (s, 3 H), 3.54 (d, J = 9 Hz, 1 H), 3.77 (s, 3 H), 6.66 (dd, J = 8 Hz, 2 Hz, 1 H), 6.81 (d, J = 2 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.14; H, 10.03.

Preparation of 15. To a solution of methyl deoxycholate (0.792 g, 1 .95 mmol) in dichloromethane (4.5 mL) and acetic anhydride (1.0 mL) was added boron trifluoride etherate (0.25 mL). After being stirred for 4 h at room temperature, the reaction mixture was poured into water and extracted with dichloromethane. The organic layer was shaken with brine, dried (Na_2SO_4), and evaporated. The crude material was chromatographed over a silica gel column to give methyl 3,12-diacetoxydeoxycholate (0.735 g, 78.9%), to a solution of which in methanol (30 mL) was added 20% hydrochloric acid (40 drops). After being stirred at room temperature for 4 days, the reaction mixture was poured into brine, extracted with dichloromethane, and worked up as above. Purification by chromatography over a silica gel column afforded **15a**: 166 mg (24.1%); amorphous; NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.81 (d, J = 6 Hz, 3 H), 0.90 (s, 3 H), 2.08 (s, 3 H), 3.66 (s, 3 H), 3.60–3.80 (m, 1 H, CHOH), 5.08 (br t, J = 2 Hz, 1 H, CHOAc); IR (KBr) ν 1735, 1240, 1030 cm^{-1}; high-resolution mass spectrum, calcd for $C_{27}H_{44}O_5$ (M^+) m/e 448.319, found m/e 448.317. Methylation of **15a** according to the standard method[3] gave **15**: amorphous; NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.79 (d, J = 6 Hz, 3 H), 0.88 (s, 3 H), 2.06 (s, 3 H), 3.00–3.30 (m, 1 H, CHOMe), 3.32 (s, 3 H), 3.64 (s, 3 H), 5.04 (br t, 1 H, CHOAc); IR (KBr) ν 1735, 1250, 1170, 1100, 1030 cm^{-1}; high-resolution mass spectrum, calcd for $C_{28}H_{46}O_5$ (M^+) m/e 462.335, found m/e 462.332.

General Procedure for Demethylation. To a stirred solution of aluminum halide in ethanethiol cooled in an ice–water bath was added the substrate under the conditions described in Table II. The reaction was monitored by TLC (aluminum halide was quenched by methanol in the capillary). The reaction mixture was poured into water, acidified with dilute HCl, and extracted with dichloromethane. The organic layer was shaken with brine, dried (Na_2SO_4), filtered, and then evaporated to leave a crude material, which was purified by chromatography over a silica gel column. All products except **11a**, **12a**, and **14a** were identified by comparison with the known parent alcohols or phenols. The yields are given in Table II.

Methyl podocarpate (11a): mp 216–216.5 °C (from methanol); NMR ($CDCl_3$) δ 1.02 (s, 3 H), 1.28 (s, 3 H), 3.64 (s, 3 H), 4.58 (br s, 1 H, OH), 6.55 (dd, J = 8, 2 Hz, 1 H), 6.71 (d, J = 2 Hz, 1 H), 6.87 (d, J = 8 Hz, 1 H); IR ($CHCl_3$) ν 3600, 1720, 1600, 1500, 1230, 1190, 1170, 1150 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.88; H, 8.46.

Dimethyl 2,2′-dihydroxybiphenyl-5,5′-dipropionate (12a): amorphous; NMR ($CDCl_3$) δ 2.54–3.00 (A_2B_2, 8 H), 3.67 (s, 6 H), 6.35 (br s, 2 H, OH), 6.85–7.15 (6 H, aromatic); IR ($CHCl_3$) ν 3560, 1730, 1505, 1440, 1220, 1180 cm^{-1}; high-resolution mass spectrum, calcd for $C_{20}H_{22}O_6$ (M^+) m/e 358.142, found m/e 358.144.

Diethyl 2,2′-dihydroxybiphenyl-5,5′-dipropionate (14a): amorphous; NMR ($CDCl_3$) δ 1.24 (t, J = 8 Hz, 6 H), 2.50–3.00 (A_2B_2, 8 H), 4.12 (q, J = 8 Hz, 4 H), 5.40–6.40 (br s, 2 H, OH), 6.84–7.15 (6 H, aromatic); IR ($CHCl_3$) ν 3550, 1725, 1505, 1230, 1185 cm^{-1}; high-resolution mass spectrum, calcd for $C_{22}H_{26}O_6$ (M^+) m/e 386.173, found m/e 386.170.

Selective Deethylation of 16. To a mixture of dry ethanethiol (1 mL) and dichloromethane (1 mL) was added aluminum chloride (0.40 g, 3.0 mmol) at 0 °C. The resulting solution was warmed to room temperature, and **16** (0.194 g, 1.0 mmol) was added with stirring. After being stirred for 9.5 h, the reaction mixture was poured into water, acidified with dilute HCl, and extracted with dichloromethane. The organic layer was treated as usual to give a crude product. Chromatography over a silica gel column gave **17** (0.157 g, 95.5%) identical with an authentic sample.

Demethylenation of 18. To a solution of aluminum bromide (0.683 g, 2.4 mmol) in dry ethanethiol (2 mL) was added **18** (0.122 g, 1.0 mmol) at 0 °C. After being stirred for 0.5 h, the reaction mixture was poured into water, acidified with 3% HCl, and then extracted with ether. The ethereal layer was shaken with 1% aqueous KOH. The aqueous layer was acidified with 3% HCl and again extracted with ether. The ethereal layer upon the usual workup gave a crude product, which was chromatographed over a silica gel column to afford **20** (86.5 mg, 78.4%).

Demethylenation of 19. The compound **19** (0.173 g, 1.0 mmol) was treated with aluminum bromide (0.655 g, 2.4 mmol) and dry ethanethiol (1.8 mL) under the same conditions as in the above experiment to give **21** (116 mg, 73.0%).

Selective Demethylenation of 22. To a solution of aluminum bromide (0.537 g, 2.0 mmol) in dry ethanethiol (2.3 mL) was added **22** (0.091 g, 0.5 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was poured into water, acidified with 5% HCl, and then extracted with ether. The ethereal layer was treated as usual to give a crude product, and chromatography over a silica gel column gave **23** (61.3 mg, 72.4%), identical with an authentic sample prepared from protocatechuic acid.

Demethylenation of *O*,*N*-Diacetylasimilobine (25). To a solution of aluminum chloride (47 mg, 0.35 mmol) in dry ethanethiol (1 mL) was added **25** (11 mg, 0.03 mmol) at 0 °C. After being stirred for 2.5 h at 0 °C, the reaction mixture was poured into water and extracted with dichloromethane. The usual workup of the organic layer gave **26**: 7.5 mg (81.5%); amorphous; NMR (pyridine-d_5) δ 2.17 (s, 3 H), 7.04 (s, 1 H, aromatic), 7.20–7.50 (m, 3 H, aromatic), 9.22 (br d, 1 H, aromatic); IR (KBr) ν 1605, 1595, 1480 cm^{-1}; high-resolution mass spectrum, calcd for $C_{18}H_{17}O_3N$ (M^+) m/e 295.121, found m/e 295.122.

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Registry No. **1**, 53109-81-2; **1a**, 17608-41-2; **2**, 70094-73-4; **2a**, 13853-46-8; **3**, 29542-63-0; **3a**, 770-71-8; **4**, 62386-12-3; **4a**, 13853-48-0; **5**, 4954-14-7; **5a**, 50-28-2; **6**, 74763-95-4; **6a**, 6690-17-1; **7**, 1076-56-8; **7a**, 89-83-8; **8**, 4877-93-4; **8a**, 1806-29-7; **9**, 1035-77-4; **10**, 16826-86-1; **11**, 1231-74-9; **11a**, 4614-56-6; **12**, 21411-25-6; **12a**, 70094-76-7; **14**, 70094-74-5; **14a**, 70094-77-8; **15**, 74763-96-5; **15a**, 55547-48-3; **16**, 23676-09-7; **17**, 120-47-8; **18**, 274-09-9; **19**, 269-43-2; **20**, 120-80-9; **21**, 92-44-4; **22**, 326-56-7; **23**, 2150-43-8; **25**, 74763-97-6; **26**, 74763-98-7; methyl deoxycholate, 3245-38-3; methyl 3,*O*-diacetoxydeoxycholate, 1181-44-8.