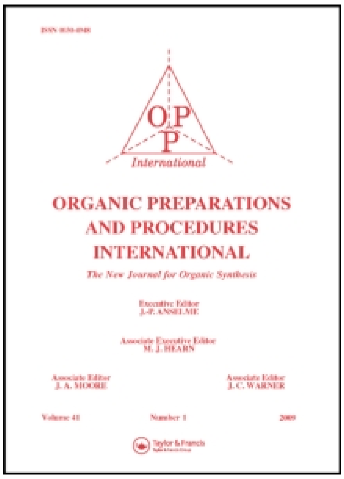

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DEALKYLATION OF ETHERS. A REVIEW

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DEALKYLATION OF ETHERS. A REVIEW

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Dedicated to Professor U. R. Ghatak, IACS, Calcutta, India, on the occasion of his 65th birthday

INTRODUCTION

The dealkylation or cleavage of ethers constitutes an important method in the field of natural products and in the synthesis of polyfunctional molecules. Review articles concerning dealkylation of ethers have already been appeared in the literature in 1954,[1] 1965,[2] 1967,[3] 1983,[4] 1987,[5] and in 1988.[6] The present review therefore concentrates mainly on selected ether cleavage reagents of practical synthetic utility and recent developments concerning the problem of selective dealkylation in molecules containing two or more groups susceptible of dealkylation. Some overlap with the earlier reviews is thus unavoidable although emphasis is given on newer methods.

For convenience, the topic is presented in four main sections: (I) dealkylation of alkyl and aryl ethers; (II) dealkylation of allyl and benzyl ethers; (III) cleavage of cyclic ethers and (IV) selectivity in dealkylation of ethers.

I. DEAKYLATION OF ALKYL AND ARYL ETHERS

1. Acidic Reagents

a) Hydrobromic Acid in the Presence of Phase Transfer Catalyst

The classical methods to hydrolyze ethers involve various protic acids under drastic conditions, e.g. the use of boiling concentrated hydriodic acid,[1] or of a large excess of concentrated hydrobromic acid/hydrochloric acid in acetic acid or acetic anhydride at reflux.[1] A useful modification is the use of hydrobromic acid in presence of phase transfer catalyst.

Alkyl and aryl ethers are efficiently cleaved by 47% hydrobromic acid in the presence of catalytic amounts of phase transfer agents such as hexadecyltributylphosphonium bromide in a heterogeneous aqueous-organic system.[7]

$$\mathrm{R^1\text{-}O\text{-}R^2} + \mathrm{2\ HBr\ aq.} \xrightarrow[-\,\mathrm{H_2O}]{\mathrm{n\text{-}C_{16}H_{33}P^+(C_4H_9\text{-}n)_3Br^-}} \mathrm{R^1\text{-}Br} + \mathrm{R^2\text{-}Br}$$

$$\mathrm{Ar\text{-}O\text{-}R} + \mathrm{HBr\ aq.} \xrightarrow{\mathrm{n\text{-}C_{16}H_{33}P^+(C_4H_9\text{-}n)_3Br^-}} \mathrm{Ar\text{-}OH} + \mathrm{R\text{-}Br}$$

The best results are obtained with 5 and 10 mol of hydrobromic acid for aryl alkyl and dialkyl ethers respectively. On the other hand, the yields and reaction times do not depend on the nature of the phase transfer agent but only on its concentration. An essential requirement for an effective catalyst is its solubility in organic phase. Other than hexadecyltributylphosphonium bromide, tetraoctylammonium bromide and trioctylmethylammonium chloride have been used. In the absence of the catalyst the reaction is about 10-20 times slower. The results are summarized in Table 1.

Typical Procedure. Cleavage of Di-*n*-octyl Ether[7].- Di-*n*-octyl ether (12.1 g, 0.05 mol), 47% aqueous hydrobromic acid (56ml, 0.5 mol), and hexadecyltributylphosphonium bromide (2.5 g, 0.005 mol) are mixed in a flask equipped with a magnetic stirrer and reflux condenser, and heated at 115° (inner temperature) with stirring for 5 hrs. After this time GLC analysis (SE 30, 3% over chromosorb) showed a 92% conversion into 1-bromooctane. The organic layer is separated, dried with sodium sulfate, and distilled to give pure 1-bromooctane; yield: 17.5 g (91%); bp 88°/torr. By treating the distillation residue with hexane, 2.3 g (92%) of pure phosphonium bromide are recovered, mp 54-56°. In the case of aryl alkyl ethers, aqueous alkaline extraction of the organic phase affords the corresponding phenol.

Table 1. Cleavage of Ethers with 47% HBr in Presence of Hexadecyltributylphosphonium Bromide

R^1 or Ar	R^2 or R	Mol of HBr	Mol of Catalyst	Time (hrs)	Yield (%)[a] of R^1Br or RBr	ArOH
n-C_4H_9	*n*-C_4H_9	10	0.1	8	89	
n-C_8H_{17}	*n*-C_8H_{17}	10	0.1	5	91	
n-$C_{16}H_{33}$	CH_3	5	0.1	3	88	
C_6H_5	CH_3	5	0.1	5	—	91
C_6H_5	*n*-C_4H_9	5	0.1	24	85	90
4-*t*-Bu-C_6H_4	CH_3	5	0.1	8	—	90
4-*t*-Bu-C_6H_4	*n*-C_4H_9	5	0.1	24	86	91

a) Yield of isolated product

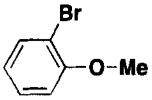
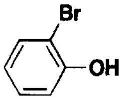
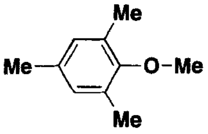
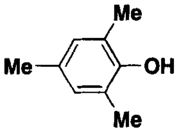
b) Boron Tribromide

Boron tribromide is regarded as one of the reagents of choice for dealkylation of ethers. Despite its efficiency, the primary advantage claimed in favor of boron tribromide is that the cleavage is effected under mild conditions and thus the need for the use of strongly acidic or basic reaction conditions can be avoided.[8-10] Boron tribromide cleaves the ether linkage without affecting ester groups or double bonds. The reaction is conveniently carried out in dichloromethane, benzene or pentane at room temperature. Work-up involves hydrolysis with water and extraction of the product with ether.

Boron tribromide has been used successfully for dealkylation of ethers during the course of synthesis of a variety of natural products.[11-16]

General Procedure for Cleavage of Ether with BBr$_3$[8].- A weighed quantity of the ether (usually 15 to 20 g) is introduced into the reaction flask and cooled in an ice-bath. The calculated quantity of boron tribromide is slowly introduced through a dropping funnel. In all cases boron tribromide and ether are allowed to react in the ratio of 1 mol of boron tribromide to 3 mol of ether. After addition of boron tribromide, the reaction mixture is heated on a water bath for 40 min. The alkyl bromide is distilled directly from the reaction mixture. After removal of the alkyl bromide by distillation, the residue remaining in the flask is hydrolyzed with a minimum amount of 10% sodium hydroxide solution. The resulting solution is acidified with hydrochloric acid and extracted with ether.

Table 2. Cleavage of Ethers by Boron Tribromide

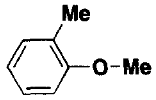
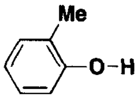
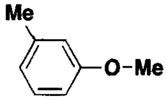
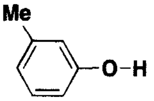
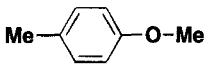
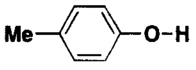
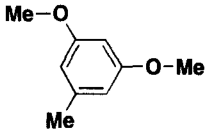
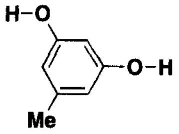
Ether	Alcohol	Yield (%)	Bromide	Yield (%)
Et_2O	EtOH	61	EtBr	86
i-Pr_2O	*i*-PrOH	50	*i*-PrBr	80
n-Bu_2O	*n*-BuOH	62	*n*-BuBr	77
Ph-O-Pr-i	PhOH	64	*i*-PrBr	62
Ph-O-Bu-n	PhOH	75	*n*-BuBr	76
		81	—	—
		87	—	—
$PhCH_2$-O-Pr-n	*n*-PrOH	71	$PhCH_2Br$	75

c) Boron Trihalide-Methyl Sulfide Complex

One of the practical disadvantages in using borontribromide and boron trichloride lies in their tendency to fume profusely in contact with air. This can be avoided when boron trihalide-methyl sulfide addition complex is used. Boron tribromide and boron trichloride form stable complexes with methyl sulfide which are crystalline solids, stable and easy to handle. They can be prepared[17] in gram quantities without any difficulty and stored under a dry, inert atmosphere of nitrogen for a long period of time without any loss of reactivity. They are a ready source of boron halides when used in solution.

High yield dealkylation of several aryl ethers has been observed upon exposure of these compounds to a two-fold to four-fold excess of the boron trihalide-methyl sulfide complex.[18] The results are presented in Table 3.

Table 3. Cleavage of Ethers with $BBr_3.S(CH_3)_2$ Complex

Ether	Ratio of Reagent / Ether	Time[a] (hrs)	Product	Yield (%)
Ph-O-Me	4.0	12	PhOH	86[b]
	3.97	12		67[c]
	3.97	12		50[c]
	3.79	12		78[c]
	3.87	24		64[c]

a) Reaction run at 83°. b) GLC yield. c) Isolated yield.

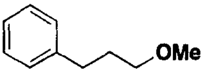
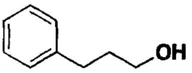
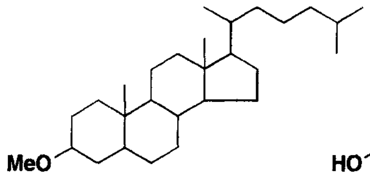
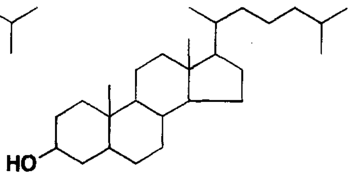
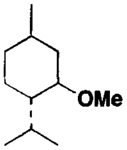
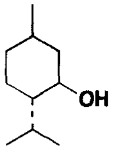
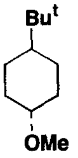
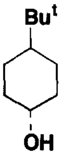
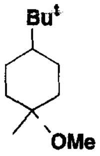
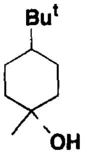
General Procedure for the Cleavage of Ethers with Boron Trihalide-Methyl Sulfide Complex[19].- To a flame-dried 100 mL flask under an atmosphere of nitrogen is added 1,2-dichloroethane (30 mL) and an amount of boron trihalide-methyl sulfide complex as indicated in Table 3. To this solution is added the desired number of equivalents of the aryl ether. The reaction mixture is stirred at reflux and monitored by either TLC or GLC where convenient. When the starting material disappears, the reaction mixture is hydrolyzed by adding water (30 mL), stirring for 20 min and diluting with ether. The organic phase is separated and washed with 1 M $NaHCO_3$ and the phenol is subsequently taken up with 1 N NaOH (3x20 mL). The combined NaOH washings are acidified and the product is subsequently extracted into ether, dried ($MgSO_4$) and the solvent is removed in vacuum.

d) Boron Tribromide-Sodium Iodide-15-Crown-5

An efficient procedure for the cleavage of aliphatic methyl ethers under mild conditions by use of the reagent-system, boron tribromide-sodium iodide-15-crown-5 is described.[19] This reagent system is found to be superior to boron tribromide in cleavage of many methyl ethers. The results are reported in Table 4.

The use of this reagent has been advocated as convenient for deprotection of methyl ethers attached to primary and secondary carbon atoms. However, it either gives poor yields or brings about rearrangements when used with ethers derived from tertiary carbon atoms.

Table 4. Dealkylation of Alkyl Methyl Ethers with BBr_3-NaI-15-crown-5

Methyl Ether	Alcohol	Yield (%)[a]
		100
		100
		75
		93
		10

a) Yield of isolated alcohol.

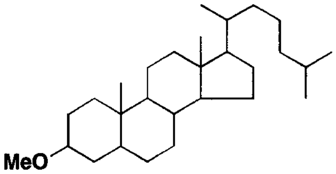
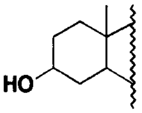
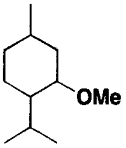
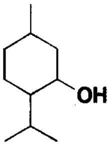
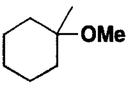
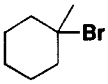
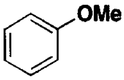
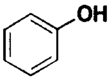
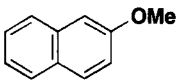
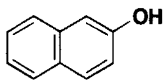
Typical Procedure. Cleavage of 3-Phenylpropanol Methyl Ether[19].- To a stirred solution of 3-phenylpropanol methyl ether (103 mg, 0.687 mmol) in dry methylene chloride (0.5 mL) is added 0.3 M solution of 15-crown-5 (13.7 mL, 6 equiv.) with NaI in methylene chloride followed by addition of 1 M solution of BBr_3 (2.1 mL, 3 equiv.) in methylene chloride at -30° under argon. The reaction mixture is stirred at the same temperature for 3 hrs, quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL) and worked up in the usual manner. Chromatographic purification of the crude product gives the pure alcohol (93 mg, 100%), identical in all respects with an authentic sample.

e) Dimethylboron Bromide

Although boron tribromide readily cleaves aryl methyl ethers to the corresponding phenols in very good yields, it presents certain limitations in case of alkyl methyl ethers producing alkyl halides predominantly (Table 2). Thus competing S_N1 versus S_N2 mechanisms are inherent problems linked to boron halides which restrict their usefulness. Dimethylboron bromide is reported to be an effective and versatile reagent for the cleavage of C-O bonds in a variety of ethers (Table 5).[20] In contrast to boron trihalides, this reagent reacts by a preponderantly S_N2 mechanism, thus allowing the regeneration of an alcohol from the methyl ether.

Typical Procedure. Cleavage of 1-Methoxydecane[20].- To a cold (0°), stirred solution of 1-methoxydodecane (1.03 mmol) and triethylamine (0.21 mmol, to neutralize traces of free acid) in dry methylene chloride (4.1 mL) under argon, is added a solution of dimethylboron bromide (1.34 M,0.99 mL) in methylene chloride. The cooling bath is then removed and the resultant solution is then stirred at room temperature for 3 hrs. The reaction mixture is then cooled to 0°, quenched with saturated aqueous sodium bicarbonate (2 mL) and diluted with ether (30 mL). The organic layer is separated, washed with saturated sodium bicarbonate (2 mL), water (2 mL) and brine (2 mL). The aqueous washings are extracted with ether and the organic layers are combined. After drying the resultant solution is concentrated and subjected to flash chromatography to provide pure 1-dodecanol (89%).

Table 5. Cleavage of Ethers with $(CH_3)_2BBr$

Substrate	Reagent (equiv.)	Temp. (°C)	Time (hrs)	Product	Yield (%)[a]
	3	0-25	18		93
	1.3	0-25	3		75
	1.6	0-25	6		49
	4.0	70	30		72
	4.0	70	36		96

a) Yield of isolated products.

f) Boron Triiodide-N,N-Diethylaniline Complex

Recently, a simple procedure for the cleavage of a variety of ethers using boron triiodide-*N,N*-diethylaniline complex, generated *in situ* from borane: *N,N*-diethylaniline and iodine, has been reported.[21] The mode of dealkylation is presumably analogous to that reported for boron tribromide.

Both alkyl and aryl ethers are dealkylated (Table 6). Alkyl ethers produce iodinated products. Ortho substituents in aryl ethers do not impede the cleavage, but ethers bearing electron withdrawing substituents on the aryl nucleus (2-nitro and 4-nitro) are unreactive.

Table 6. Cleavage of Ethers with Boron Triiodide–*N,N*-Diethylaniline Complex

Substrate	Time (hrs)	Product	Yield (%)[a]
PhOMe	3	PhOH	85
4-BrC_6H_4OMe	4	4-BrC_6H_4OH	86
3,5-$Cl_2C_6H_3OMe$	4	3,5-$Cl_2C_6H_3OH$	67
2-*t*-Bu-5-MeC_6H_3OMe	3	2-*t*-Bu-5-MeC_6H_3OH	71
2-$C_{10}H_7OMe$	3	2-$C_{10}H_7OH$	94
$PhCH_2OCH_2Ph$	2.5	$PhCH_2I$	88

a) Yield of isolated products.

Typical Procedure. Cleavage of Methyl 2-Naphthyl Ether[21].- Addition of a solution of methyl 2-naphthyl ether (3.0 mol) in dry benzene (10 mL) to a complex of boron triiodide-*N,N*-diethylaniline (3.0 mol) (prepared from the borane-*N,N*-diethylaniline complex (3.0 mol) and iodine (9.0 mol)) under an argon atmosphere at room temperature results in a dark reaction mixture. After three hours 2-naphthol is isolated in 94% yield.

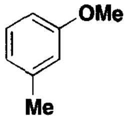
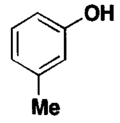
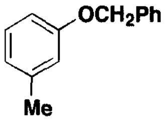
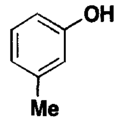
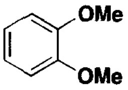
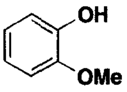
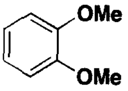
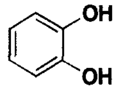
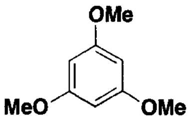
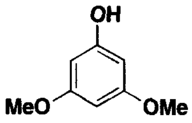
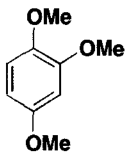
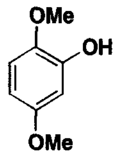
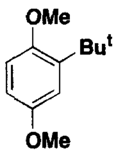
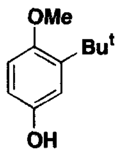
2. Basic Reagents

a) Sodium Salt of N*-Methylaniline*

Aryl alkyl ethers are readily cleaved by the sodium salt of *N*-methylaniline in the presence of HMPT.[22] The salt is prepared from the amine and sodium hydride in xylene/HMPT. The reactions are carried out at temperatures in the range of 60° to 120°, depending on the substrate (Table 7). Monodealkylation of the methyl ethers of polyhydric phenols is easily achieved. 1,2-, 1,3-, and 1,4-dimethoxybenzenes and 1,3,5-trimethoxybenzene are cleaved to the corresponding monophenol. However, it fails to proceed cleanly with substrates containing electronegative substituents such as halogen atoms because of the competing aromatic substitution.

Typical Procedure. Cleavage of 1,2,4-Trimethoxybenzene[22].- *N*-Methylaniline (2.68 g, 25 mmol) is added dropwise at 65° to a stirred suspension of sodium hydride (0.6 g, 25 mmol) in sodium-dried xylene (5 mL) and HMPT (4.26g, 25 mmol, distilled over calcium hydride and stored in dark over molecular sieves,8A°). After 15 min, the ether (12.5 mmol in the minimum amount of xylene) is added and the mixture is heated at 85°. The reaction is monitored by GLC (3 m SE 30 column) and by TLC. When the starting material disappears (6 hrs) the mixture is poured into water, acidified with dilute hydrochloric acid, and the product is extracted with ether. The ether phase is washed with dilute hydrochloric acid (2x90 mL) to remove HMPT and the amines and then the product is extracted with 10% sodium hydroxide solution (2x90 mL). The aqueous phase is acidified with dilute hydrochloric acid and extracted with ether (3x90 mL). The organic phase is dried over calcium chloride and concentrated on a rotary evaporator to give pure 2,5-dimethoxyphenol; yield: 1.9 g (90%). The product may be further purified by column chromatography on silica gel.

Table 7. Dealkylation of Alkyl Aryl Ether with Sodium *N*-Methylanilide in presence of HMPT

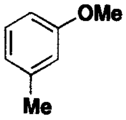
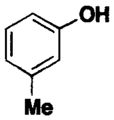
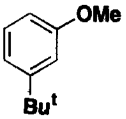
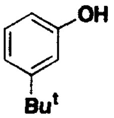
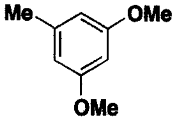
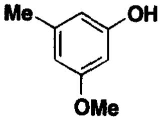
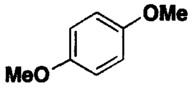
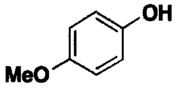
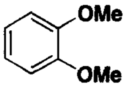
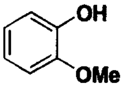
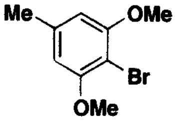
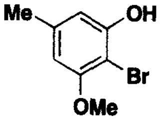
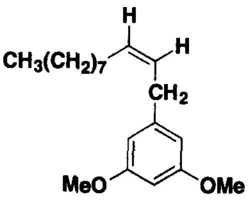
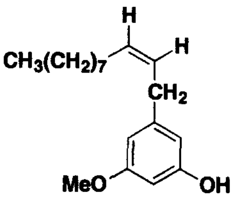
Substrate	Time (hrs)	Temp. (°C)	Product	Yield (%)[a]
	6.5	120		95
	10	120		80
	0.5	95		95
	24	120		90
	9	95		85
	6	85		90
	17	120		70

a) Yield of isolated products.

b) Sodium Ethanethiolate

Sodium ethanethiolate in non-polar aprotic solvents like DMF, has emerged as one of the efficient reagents to dealkylate aromatic ethers.[23] Aromatic bromine substituents or olefinic groups remain unaffected under this procedure. Selective cleavage of one of the ether groups can be achieved in molecules containing more than one such groups (Table 8).

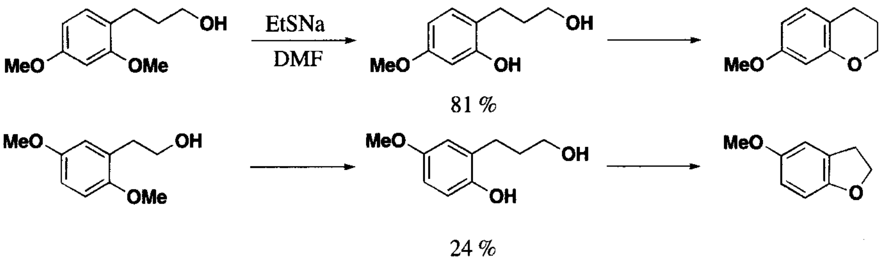
Table 8. Dealkylation of Ethers by Sodium Ethanethiolate

Ether	Equiv. of Reagent	Time (hrs)	Product	Yield (%)
	2.5	3		96
	2.5	3		96
	5	3		84
	5	3		98
	5	3		89
	2.5	20		93
	—	—		—

Typical Procedure. Dealkylation of *m*-Methoxytoluene[23].- Ethanethiol (1.25 g, 11.8 mmol) dissolved in dry DMF (20 mL) is added to a suspension of sodium hydride (1.0 g of a 50% oil dispersion) in dry DMF (10 mL) under an atmosphere of nitrogen. The mixture is stirred for 5 min before a solution of *m*-methoxytoluene (1.09 g) in dry DMF is added. The solution is then refluxed for 3 hrs.

The cooled mixture is acidified with 10% aqueous hydrochloric acid and extracted with ether. The ether layer is washed with water and extracted with 5% sodium hydroxide. The alkaline extracts are then acidified and reextracted with ether. The ethereal solution is washed with water, dried and evaporated to give *m*-cresol as a light brown oil; yield: 0.85 g (78%).

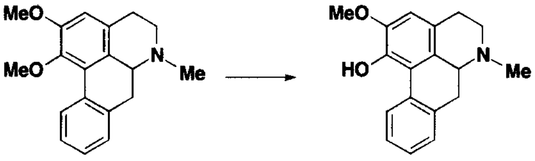
This reagent has gained general acceptance to dealkylate ethers in organic synthesis and its scope has been further extended. It has been observed that methoxyl groups ortho to β-hydroxyethyl or γ-hydroxypropyl substituents in polymethoxybenzene derivatives are regioselectively demethylated with sodium thioethoxide in DMF.[24] Methoxydihydrobenzofurans or methoxychromans are produced by cyclization of the monodemethylated β-hydroxyethyl or γ-hydroxypropyl derivatives, respectively.



Recently, it has been reported[25] that sodium ethanethiolate in DMF provides a convenient and regioselective method for the demethylation of aryl methyl ethers substituted by electron-withdrawing groups. Electronic factors appear to control the observed selectivity; *i.e.*, methyl ethers para to electron-withdrawing functionality react preferentially with the thiol anion. In addition, substituent effects indicate a relationship between the Hammet constant and the efficacy of the reaction, with more electron-poor species providing higher yields of demethylated product. It is also apparent that a variety of these substituents (NO_2, CN, acetyl) provide useful yields of deprotected product, therefore providing additional synthetic utility to this general method.

c) Sodium Benzylselenolate

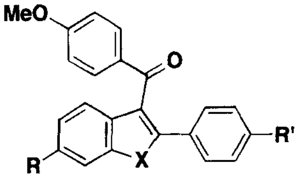
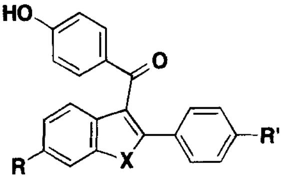
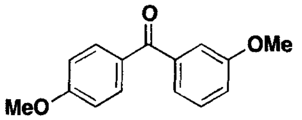
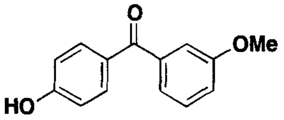
Sodium benzylselenolate in refluxing DMF has been found to be a superior reagent for the demethylation of aryl methyl ethers, as evidenced by a study of its reaction with a number of representative nonphenolic aporphine alkaloids, including nuciferine **1**, apomorphine dimethyl ether **2** and ocopodine **3**.[26]



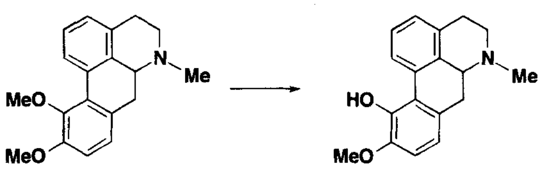
1

General Procedure for Alkaloid Demethylations[26].- To a stirred solution of dibenzyl diselenide (0.222 g, 0.65 mL) in dry DMF (10 mL) is added excess sodium borohydride (ca. 200 mg) under nitrogen. After 15 min the alkaloid (1 mmol) in DMF (10-15 mL) is introduced. The mixture is

Table 9. Regioselectivity in the Thiolate-Mediated Demethylation of Aryl Methyl Ethers

	Ether		Phenol	Conditions[a]	Yield (%)
					
	X	R	R'		
1	CH_2CH_2	CH_3O	H	1.5 eq.[b], 0.5 hr, 85°	87
2	CH_2CH_2	H	CH_3O	1.5 eq., 3.5 hrs, 80°	83
3	CH_2CH_2	CH_3O	CH_3O	1.3 eq., 0.5 hr, 100°	77
4	O	CH_3O	CH_3O	1.5 eq.[b], 4.0 hrs, 80°	75
5	NEt	CH_3O	CH_3O	2.0 eq.[b], 6.0 hrs, 85°	54
				1.5 eq., 3.5 hrs, 80°	80

a) Expressed in terms of EtSNa equivalents, reaction time, and temperature. b) EtSLi employed.



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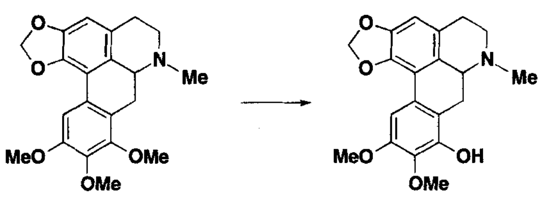


3

refluxed under nitrogen until all the alkaloid is consumed (monitored by TLC). The mixture is cooled and the solvent is evaporated under reduced pressure. The residue is taken up in 5% sulfuric acid and the nonalkaloidal components are extracted with benzene. The acid solution is basified with 10%

ammonium hydroxide (pH 8-9) and exhaustively extracted with chloroform. The combined chloroform extracts are dried (anhydrous sodium sulfate) and evaporated. The product is further purified in the usual manner.

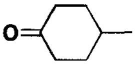
3. *Miscellaneous Reagents*

a) Trimethylsilyl Iodide

Trimethylsilyl iodide has been found to be another useful reagent for ether cleavage and has already gained much popularity.[27-32] An important feature of this reagent is that its cleavage pattern with ethers is somewhat different from that of boron halides. Boron halides usually cleave an alkyl methyl ether to alkyl halide, whereas trimethylsilyl iodide dealkylates it to the corresponding silyl ether which is then hydrolyzed to alcohol. Many functional groups such as double bond, triple bond, keto-carbonyl, amino and aromatic halides are stable under this condition. The results are summarized in Table 10.

Table 10. Dealkylation of Ethers by Trimethylsilyl Iodide

$$R^1\text{–O–}R^2 + (CH_3)_3SiI \longrightarrow R^1\text{–O–}Si(CH_3)_3 + R^2I$$

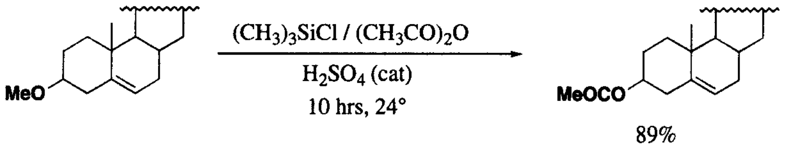
R^1	R^2	Reaction Conditions[a] Time / Temperature	Yield of products (%) R^1–$OSi(CH_3)_3$	R^2I
c-C_6H_{11}	CH_3	6 hrs / 25°	95	5
c-C_6H_{11}	C_2H_5	12 hrs / 25°	49	51
c-C_6H_{11}	t-C_4H_9	0.1 hr / 25°[b]	100	0
c-C_6H_{11}	$C_6H_5CH_2$	0.1 hr / 25°	100	0
	CH_3	2.5 hrs / 25°	100	0
C_6H_5	CH_3	48 hrs / 25°	100	—
3-$CH_3C_6H_4$	C_2H_5	140 hrs / 50°[b]	100	—

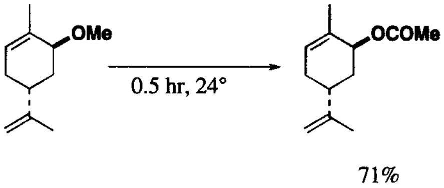
a) Solvent $CDCl_3$, unless otherwise mentioned. b) In CCl_4.

General Procedure for Dealkylation of Ether[29].- To a 2 M solution of ether (1 equiv.) in a suitable solvent (Table 10) is added neat trimethylsilyl iodide (1.3 equiv.) through a dry syringe. The reaction is maintained at temperature indicated in Table 10 and monitored by NMR for completion. Yields are calculated by NMR integration of pertinent peaks. For isolation of the alcohols, at the completion of the reaction, the excess trimethylsilyl iodide is destroyed and the intermediate trimethylsilyl ether formed during the reaction is hydrolyzed to alcohol by pouring the reaction mixture into methanol (4 equiv.). The volatile components are removed at reduced pressure and the residue is taken up in ether, washed with aqueous sodium bisulfite, aqueous sodium bicarbonate and brine and dried. The residue left after evaporation of solvent is further purified (if necessary) by column chromatography on silica gel.

b) Chlorotrimethylsilane and Acetic Anhydride

Methyl and benzyl ethers have been cleaved with a combination of reagents consisting of chlorotrimethylsilane and acetic anhydride containing a catalytic amount of concentrated sulfuric acid.[33] Comparative study with borontrifluoride etherate and acetic anhydride method of ether cleavage[34] suggests that chlorotrimethylsilane and acetic anhydride could be a useful alternative to it. A few representative examples are given below:





General Procedure[33].- To a solution of the substrate (0.5 mmol) in dry ether (0.5 mL) is added acetic anhydride (2 mL) and chlorotrimethylsilane (1 mL) followed by one drop of concentrated sulfuric acid. The reaction mixture is left at room temperature or 0° for a certain period of time. It is diluted with water (200 mL) and extracted with hexane (3x100 mL), washed with water and dried over anhydrous sodium sulfate. Distillation of the solvent under reduced pressure furnishes the crude product which is purified by preparative TLC.

c) Zinc and Acyl Chloride

Alkyl ethers are cleaved very efficiently with a combination of commercial zinc dust and acyl chloride in petroleum ether.[35] The reaction condition is mild enough not to induce any rearrangement even during the cleavage of tertiary and secondary ethers. A wide variety of ethers undergo cleavage by this procedure to produce the corresponding alkyl chlorides and alkanoates. The results are presented in Table 11.

General Procedure for Cleavage of Ether[35].- A suspension of commercial zinc dust (130 mg, 2 mmol, 25 mol%) in petroleum ether (60-80° fraction, 20 mL) is stirred with ether (8 mmol) and acyl chloride (8.8 mmol) at room temperature under nitrogen for a certain period of time as specified in the Table 11 (monitored by TLC). The reaction mixture is then quenched with a drop of water and diluted with ether (40 mL). Zinc dust is filtered off and is washed successively with diethyl ether (5x5 mL). The combined washings and the filtrate are washed with aqueous sodium bicarbonate solution and brine and then dried over sodium sulfate and evaporated to leave the crude product which is separated by column chromatography over silica gel to produce pure alkyl halide and alkyl alkanoate.

Table 11. Cleavage of Ether with Zn / Acyl Chloride

$$R^1\text{–O–}R^2 + R^3COCl \xrightarrow{Zn} R^1\text{–Cl} + R^3COOR^2$$

Ether	Acyl Chloride	Time (hrs)	Yield (%) of Alkyl Halide[a]	Yield (%) of Alkyl Alkanoate[a]
$R^1 = R^2 = Et$	$R^3 = CH_2Ph$	4	—	80
$R^1 = n\text{-}C_6H_{13}$, $R^2 = Me$	$R^3 = CH_2Ph$	4	82	82
R^1 = Cyclohexyl, $R^2 = Me$	$R^3 = CH_2Ph$	4	84	84
$R^1 = Me$, $R^2 = (CH_2)_3Ph$	$R^3 = Me$	15	—	85
$R^1 = CH(Me)(CH_2)_2Ph$, $R^2 = Me$	$R^3 = Me$	5	78	—
$R^1 = C(Me)_2(CH_2)_2Ph$, $R^2 = Me$	$R^3 = Me$	1	80	—
$R^1 = C(Me)_2CH_2Ph$, $R^2 = Me$	$R^3 = Me$	1	82	—

a) Yield of isolated products.

d) Lithium Chloride in DMF

Alkyl aryl ethers having electron-withdrawing substituents in the ortho or para positions are easily cleaved with lithium chloride in DMF.[36] Ethoxy and even isopropoxy groups are easily cleaved when they are ortho to a nitro group. When an aldehydic or an ester carbonyl group is present, the cleavage requires longer reaction times but the yields are reasonably good. The methoxycarbonyl function does not survive these reaction conditions but undergoes demethylation to the carboxy group. Practically no reaction is observed with anisole and methylanisoles. The results are summarized in Table 12.

Typical Procedure. Cleavage of 2.3-Dimethoxybenzaldehyde[36].- 2,3-Dimethoxybenzaldehyde (1.0 g, 6 mmol) and LiCl (0.76 g, 18 mmol) are heated in boiling DMF (10 mL), the reaction being monitored by GLC. When the starting material disappears, 10% aqueous NaOH (30 mL) is added; the solution is washed with ether (2x25 mL), then acidified with 10% aqueous HCl (50 mL), and extracted with ether (2x25 mL). The organic phase is washed with brine (30 mL), dried (sodium sulfate) and concentrated in a rotary evaporator to afford 2-hydroxy-3-methoxybenzaldehyde (0.88 g, 98%).

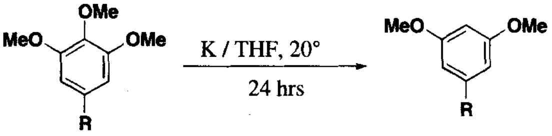
e) Potassium in THF-A Reductive Cleavage Agent

Potassium in THF has been found to be an efficient reagent for the reductive cleavage of aromatic ethers.[37-39] Selective removal of the 4-methoxy group in 1-*n*-alkyl-3,4,5-trimethoxybenzenes is performed with this reagent under electron-transfer conditions.

Table 12. Cleavage of Alkyl Aryl Ethers with LiCl in DMF

R	X^1	X^2	Reaction Time (hrs)	Yield (%)[a]
Me	2-NO_2	H	6	98
Me	3-NO_2	H	6	50
Me	4-NO_2	H	24	98
Et	2-NO_2	H	22	90
i-Pr	2-NO_2	H	24	35
$PhCH_2$	2-NO_2	H	22	98
Et	4-NO_2	H	24	10
Me	2-NO_2	4-Br	4	95
Me	2-Cl	H	72	55
Me	2-Br	H	72	67
Me	2-CHO	H	22	70
Et	2-CHO	H	22	25
i-Pr	2-CHO	H	22	5
Me	2-CO_2Me	H	22	90
CH_2CO_2Me	2-Me	H	22	5

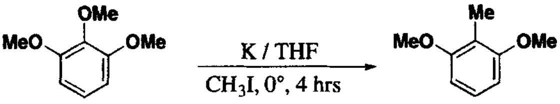
a) Yield of isolated products.



R = H
R = Me
R = n-C_5H_{11}

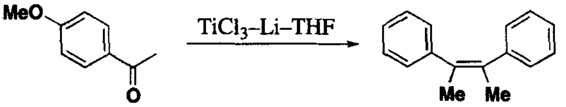
85%
87%
82%

This reagent has also been utilized for the reductive alkylation of trimethoxybenzenes in the presence of alkyl halide in the reaction medium.[39]



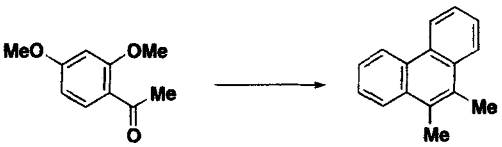
f) Low Valent Titanium in THF-A Reductive Dealkoxylation

Facile dealkoxylation of aryl alkyl ethers is carried out using $TiCl_3$•Li-THF in a one-pot operation.[40] Low valent titanium induced coupling of **4** in THF produces 2,3-diphenylbut-2-ene **5** exclusively. Thus, it is inferred that under the reaction conditions reductive dealkoxylation takes place in tandem with reductive deoxygenation of the carbonyl function.



4 **5**

Application of this methodology to other ortho alkoxy-aromatic aldehydes and ketones as substrates furnished the corresponding phenanthrenes.



g) Metallic Nitrate Supported on Silica Gel - An Oxidative Cleavage Reagent

Metallic nitrates supported on silica gel efficiently cleave and oxidize primary and secondary ethers to the corresponding aldehydes and ketones.[41] Especially, copper nitrate and zinc nitrate are suitable for practical use. Silica gel is essential for efficient oxidation. Overoxidation of the formed aldehydes to carboxylic acids is not observed. Some mechanistic studies suggest that the key step of the process involves the formation of radical species. This oxidative cleavage of ether seems to be useful for organic synthesis because of easy experimental operations, high yields of products and mild reaction conditions. The results of cleavage of several ethers by this procedure are summarized in Table 13.

General Experimental Procedure[41].- *Preparation of Oxidizing Reagent.* To a solution of $Cu(NO_3)_2$•$3H_2O$ (1.69 g, 7 mmol) in water (10 mL) is added 230-400 mesh chromatographic silica gel WB-300 (2 g) in one portion with shaking. Then the solvent is removed in a rotary evaporator. The blue powder formed is dried further at 130° under reduced pressure (5-15 Torr) with stirring until most of the moisture is removed. The reagent has the highest activity just when the color of the powder begins to change from blue to green and loses the activity when it changes to green completely. If the brown gas is evolved during drying the reagent has no activity. Usual drying time is about 30 min. One gram of this reagent (3.5 mmol/g of SiO_2) contains about 2.11 mmol of $Cu(NO_3)_2$.

Table 13. Oxidative Cleavage of Ethers by $M(NO_3)_2$–SiO_2[a]

Ether	M	Solvent	Product, yield, %	Recovery, %
cyclododecyl methyl ether	Zn	CCl_4	cyclododecanone, 87	18
hexyl ether[b]	Zn	isooctane	hexanal, 97	46
hexyl ether[b]	Zn	CCl_4	hexanal, 65; hexyl nitrite, 10	35
butyl ether[b]	Cu	CCl_4	butanal, 64; butyl nitrite, 25	27
2-hexenyl methyl ether	Zn	CCl_4	2-hexenal, 81	2
benzyl methyl ether	Zn	isooctane	benzaldehyde, 94	0
p-methylbenzyl methyl ether	Cu	isooctane	*p*-tolualdehyde, 83	0
p-chlorobenzyl methyl ether	Cu	isooctane	*p*-chorobenzaldehyde, 83	4
m-chlorobenzyl methyl ether	Cu	isooctane	*m*-chlorobenzaldehyde, 81	14
p-fluorobenzyl methyl ether	Cu	isooctane	*p*-fluorobenzaldehyde, 65	0
p-nitrobenzyl methyl ether	Cu	isooctane	*p*-nitrobenzaldehyde, 65	5
benzyl ethyl ether	Zn	isooctane	benzaldehyde	0
benzyl isopentyl ether	Zn	isooctane	benzaldehyde, 84; isopentyl nitrite, 23	0
benzyl hexyl ether	Cu	isooctane	benzaldehyde, 81; hexyl nitrite, 69; hexanal, 1	
benzyl ether[b]	Zn	CCl_4	benzaldehyde, 159	0
1,4-*bis*(methoxymethyl)benzene	Cu	CCl_4	4-(methoxymethyl)benzaldehyde, 70; 1,4-benzenedicarboxaldehyde, 9	24

a) An ether (1 mmol) and $M(NO_3)_n$–SiO_2 (4 mmol) were heated under reflux in a solvent (20 mL) for 1 hr.
b) One mole of the products from 1 mol of the ether was calculated as 100%.

Procedure for Oxidative Cleavage. Benzyl cyclohexyl ether (188 mg, 1 mmol) and $Cu(NO_3)_2$-SiO_2 (1.14 g, 2.4 mmol; 3.5 mmol/g of SiO_2) are heated under nitrogen atmosphere in refluxing CCl_4 (12 mL) while being stirred. The brown gas evolves. The reaction is monitored by TLC. Ten minutes later the brown gas disappears. After 15 min of heating, *n*-pentadecane (0.1 mL), which is an internal standard in GLC analysis, is added and the reaction mixture is transferred to a small glass column with a cotton plug. The solid is separated by filtration and eluted with acetone (3 mL). The filtrate and the eluate are combined and subjected to GLC analysis. Benzaldehyde (0.92 mmol, 92%), cyclohexanone (0.47 mmol. 47%), and cyclohexyl nitrite (0.35 mmol, 35%) are detected. Other oxidation reactions are also carried out in a similar way.

h) Nitrogen Dioxide - An Oxidative Cleavage Reagent

Ethers are efficiently oxidized by nitrogen dioxide to give the corresponding aldehydes and ketones in the presence of silica gel.[42] The cleavage is carried out by stirring an ether (1 mmol) and 230-400 mesh chromatographic silica gel (1 g) in CCl_4 (20 mL) at room temperature or at reflux under an atmosphere of nitrogen dioxide.

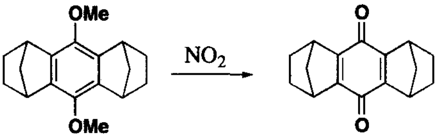
Benzyl and secondary ethers produce the corresponding aldehydes and ketones in high yields, but primary ethers react more slowly (Table 14). In the absence of silica gel the extent of reaction is insignificant.

Nitrogen dioxide also converts hydroquinone dialkyl ethers into the corresponding quinone and alkyl nitrite in dichloromethane at room temperature.[43]

Table 14. Cleavage of Ethers by Nitrogen Dioxide[a]

Ether	Time (min)	Product	Yield (%)
cyclododecyl methyl	30	cyclododecanone	88
benzyl cyclohexyl	15	benzaldehyde cyclohexanone cyclohexyl nitrite	94 36 13
dibenzyl[b]	20	benzaldehyde	194
1-phenylethyl methyl	15	acetophenone	85
dihexyl	60	hexanal	32

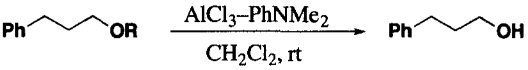
a) Reaction at room temperature. b) At reflux



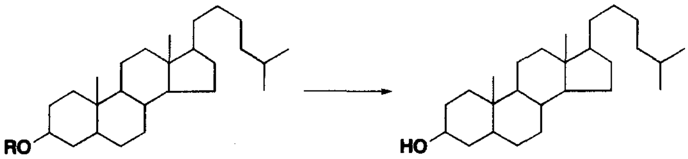
II. DEALKYLATION OF ALLYL AND BENZYL ETHERS

a) Aluminum Chloride - N,N-Dimethylaniline

Allyl and benzyl ethers are cleaved readily on treatment with $AlCl_3$ and N,N-dimethylaniline to give parent alcohols in high yields.[44] Several functionalities such as ester, sulfide and olefinic double bond remain unaffected under this procedure. Ready availability as well as ease of handling of the reagent provides a particular advantage of the present system.



R = allyl 93%
R = benzyl 93%



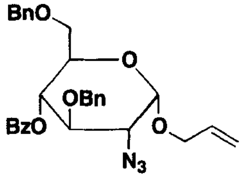
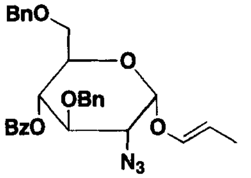
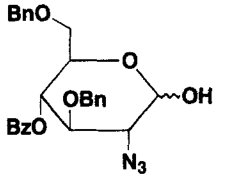
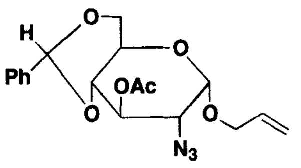
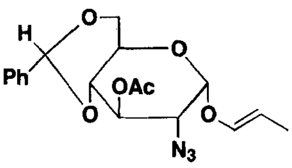
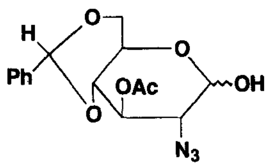
R = alkyl 96%
R = benzyl 96%

General Procedure for Dealkylation[44].- To a solution of ether (0.443 mmol) and N,N-dimethylaniline (1.33 mmol) in methylene chloride (1.0 mL) is added powdered aluminum chloride (239 mg, 1.79 mmol) at room temperature. Stirring is continued at room temperature for benzylic ether and at reflux in case of allylic ether. The reaction mixture is then quenched by addition of 1 N HCl (3 mL) and the aqueous layer is extracted with ethyl acetate (3x7 mL). The combined organic layers are successively washed with 5% $NaHCO_3$ solution and brine, dried over anhydrous sodium sulfate, and the solvent is removed under reduced pressure. The remaining residue is purified by short column chromatography (SiO_2, hexane: ethyl acetate (v/v)= 4:1) to give the alcohol.

b) Cationic Iridium Complex

It has been reported that allyl ethers can be isomerized stereoselectively to give the corresponding *trans*-1-propenyl ethers in high yields using the hydrogen-activated cationic iridium complex.[45,46]

Table 15. Deallylation of Allyl Glycosides

Glycoside	Isomerized Product (yield)	Deprotected Product (yield)
	 (93%)	 (76%)
	 (94%)	 (75%)

Thus, a two step deallylation procedure using 1,5-cyclooctadiene-*bis*(methyldiphenylphosphine)iridium hexafluorophosphate and catalytic amounts of osmium tetroxide with trimethylamine N-oxide is used to protect allyl glycosides in the presence of an azide group at C-2.[47] This method avoids the formation of intramolecular 1,3-dipolar cycloaddition products which are isolated during the deprotection using other procedures.

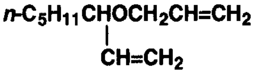
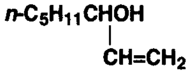
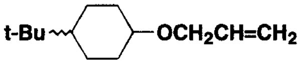
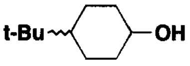
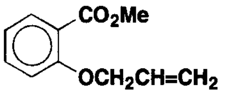
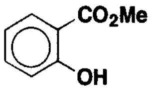
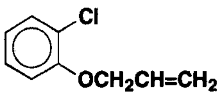
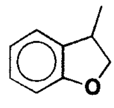
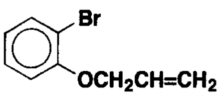
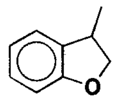
Typical Experimental Procedure[47].- Hydrogen is bubbled for 15 minutes into a suspension of 1,5-cyclooctadiene-*bis*(methyldiphenylphosphine)iridium hexafluorophosphate (100 mg, 0.12 mmol) in THF (20 mL). Immediately the iridium catalyst loses its pink color and starts to dissolve. The mixture is added to a stirred solution of allyl-2-azido-2-deoxy-4-O-benzoyl-3,6-di-O-benzyl-O-α-D-glucopyranoside (2.0 g, 3.8 mmol) in THF (40 mL) and the reaction is stirred for 12 hrs at room temperature under nitrogen. The solvent is removed under reduced pressure and the residual compound is taken up in methylene chloride (50 mL). Trimethylamine N-oxide dihydrate (650 mg, 5.8 mmol) and osmium tetroxide (10 mg, 0.04 mmol) are added and the solution is stirred for 12 hrs at room temperature. The solvent is evaporated and the residue is purified by silica gel chromatography (ether/pentane 1.5:1) to yield the corresponding hydroxy compound (1.4 g, 76%) as an oil.

c) Samarium(III) Chloride - Catalyzed Electrolysis

The allyl-oxygen bond in a series of alkyl and aryl allyl ethers is cleaved in a $SmCl_3$-catalyzed electrochemical reaction.[48] The electrochemical method is based on the use of an undivided cell fitted with a consumable magnesium anode. The reaction condition is mild enough not to affect carboxylic ester and olefinic double bond. The results are presented in Table 16.

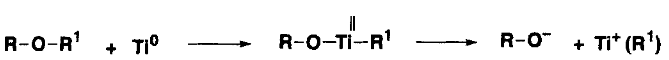
General Electrolysis Condition[48].- A distilled DMF (35 mL)/ammonium salt (0.3 mmol) (eventually KI, 0.3 mmol) solution containing the ether (10 mmol) and anhydrous $SmCl_3$ (10 mmol) is stirred at room temperature and electrolyzed at constant current of 100 mA (current density of 0.5 $A.dm^{-2}$) in a one-compartment electrochemical cell fitted with a central magnesium anode and a nickel foam cathode (20 cm^2). Reactions are followed by GLC and stopped when completed (after 5.5-8 hrs, with consumption of 2-3 Faraday per mol of ether). The DMF solution is acidified with aq. HCl (0.1 M) and extracted with pentane-ether (1:1). The organic layer is washed with water, dried over $MgSO_4$ and evaporated. Products are purified by column chromatography on silica gel with pentane-ether mixture as eluent.

Table 16. $SmCl_3$–Catalyzed Electrochemical Allyl Ether Cleavage

Ether	Supporting Electrolyte	Product	Yield (%)
$PhOCH_2CH=CH_2$	$n\text{-}Bu_4N^+ Br^-$	PhOH	90
$n\text{-}C_8H_{17}OCH_2CH=CH_2$	$n\text{-}Bu_4N^+ BF_4^- + KI$	$n\text{-}C_8H_{17}OH$	85
 $n\text{-}C_5H_{11}\underset{CH=CH_2}{CH}OCH_2CH=CH_2$	$n\text{-}Bu_4N^+ BF_4^- + KI$	 $n\text{-}C_5H_{11}\underset{CH=CH_2}{CH}OH$	60
	$n\text{-}Bu_4N^+ Br^- + KI$		63
	$n\text{-}Bu_4N^+ BF_4^-$		67
	$n\text{-}Bu_4N^+ BF_4^-$		85
	$n\text{-}Bu_4N^+ BF_4^-$		70

d) Low Valent Titanium

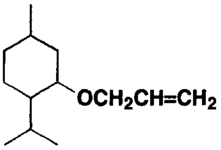
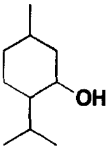
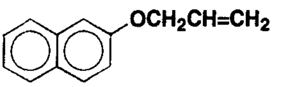
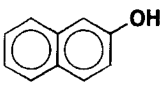
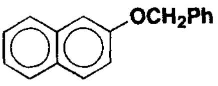
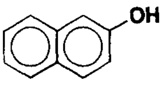
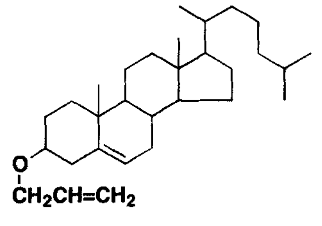
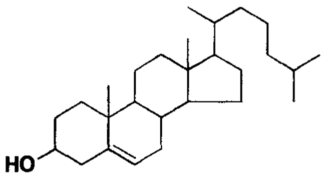
A novel method for deprotection of allyl and benzyl derivatives of alcohols and phenols by low valent titanium is demonstrated.[49] Among several low valent titanium reagents such as $TiCl_3$-Li-DMF, $TiCl_4$-Mg-THF and $TiCl_4$-Zn-THF tested, the first one is found to be the most efficient. It is proposed that deallylation/debenzylation reaction proceeds via oxidative addition of Ti(0) to the substrate followed by the cleavage of the Ti-O bond to form the alkoxide/phenoxide anion.



$$R{-}O{-}R^1 + Ti^0 \longrightarrow R{-}O{-}\overset{\|}{Ti}{-}R^1 \longrightarrow R{-}O^- + Ti^+(R^1)$$

General Procedure for Cleavage[49].- A mixture of $TiCl_3$ (1.55 g, 10 mmol) and Mg (0.410 g, 17 mmol) in dry THF (50 mL) is heated under reflux for 3 hrs in an atmosphere of argon. The resulting black mixture is cooled and a solution of allyl or benzyl ether (5 mmol) in THF (5 mL) is added dropwise to it. The mixture is then refluxed for a certain period of time (Table 17), cooled, diluted with ether, acidified with dilute HCl (1:1) and passed through celite. Finally, it is washed with water, dried (Na_2SO_4) and evaporated to furnish the crude product which is purified by chromatography (SiO_2) to furnish the pure alcohol.

Table 17. Deallylation of Allyl and Benzyl Ethers with Low–valent Titanium[a]

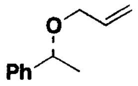
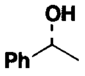
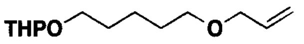
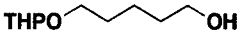
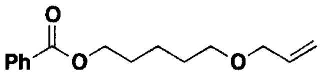
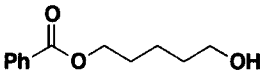
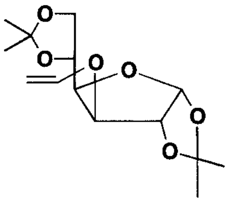
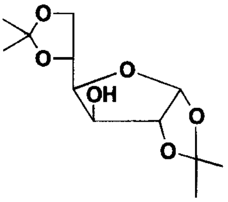
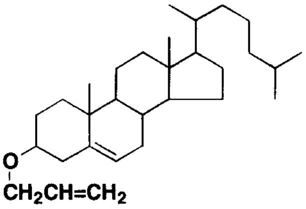
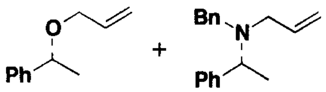
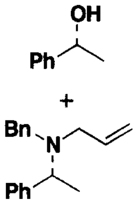
Ether	Time (hrs)	Product	Yield (%)
$CH_3(CH_2)_{15}OCH_2Ph$	14[b]	$CH_3(CH_2)_{15}OH$	85
$CH_2{=}CHCH_2O(CH_2)_{12}OCH_2CH{=}CH_2$	4[b]	$HO(CH_2)_{12}OH$	64
	2.5		88
	5		70
	26		28
	2		90

a) $TiCl_3$–Mg–THF used as a source of low-valent titanium, if not otherwise stated.
b) $TiCl_3$–Li–THF used.

e) Zirconocene Dichloride/n-Butyl Lithium

An efficient zirconium-mediated deprotection of allyl ethers using zirconocene equivalent CP_2Zr is reported recently.[50] The reaction condition is very mild (nearly neutral) and does not affect acid labile protective groups such as O-tetrahydropyranyl and O-isopropylidene. Moreover, the selective deprotection of an allyl group is achieved in the presence of N-allyl protective group. The results of deprotection of several structurally varied allyl ethers are presented in Table 18.

Table 18. Zirconium-Mediated Deprotection of Allyl Ethers

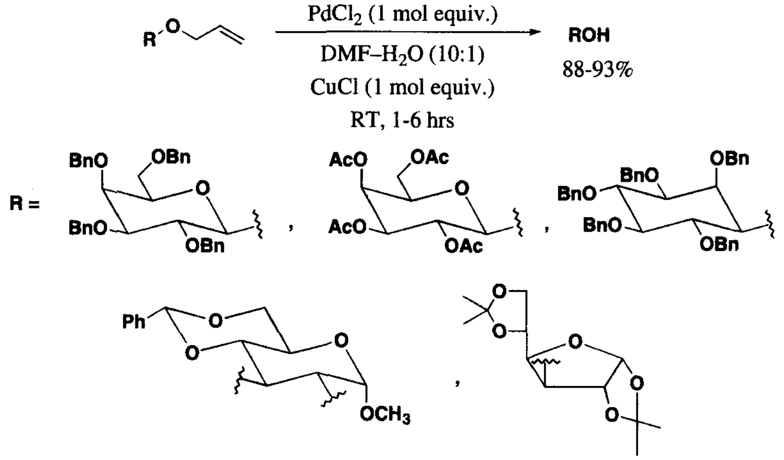
Ether	Product	Yield (%)[a]
		87
		97
		50
		98
	cholesterol	97
		82 95

a) Isolated yield

Typical Procedure. Cleavage of Allyl Cholesteryl Ether[50].- A solution of *n*-butyllithium (1.45 M in hexane, 1.26 mL,1.82 mmol) is added dropwise to a solution of zirconocene dichloride (266 mg, 0.91 mmol) in THF (4 mL) at -78° with stirring. After stirring for 1 hr at -78° a solution of the ether (298 mg, 0.7 mmol) in THF (2 mL) is added, and the acetone-dry ice bath is removed. After the mixture is stirred at ambient temperature, 1 N HCl is added at 0°, and the mixture is extracted with ether. The organic layer is washed with brine and dried over $MgSO_4$. After filtration the solvent is removed in vacuum. The residue is purified by silica gel column chromatography (hexane-ethyl acetate, 3:1) to give cholesterol (263 mg, 97%)

f) $PdCl_2/CuCl/DMF\text{-}H_2O/O_2$

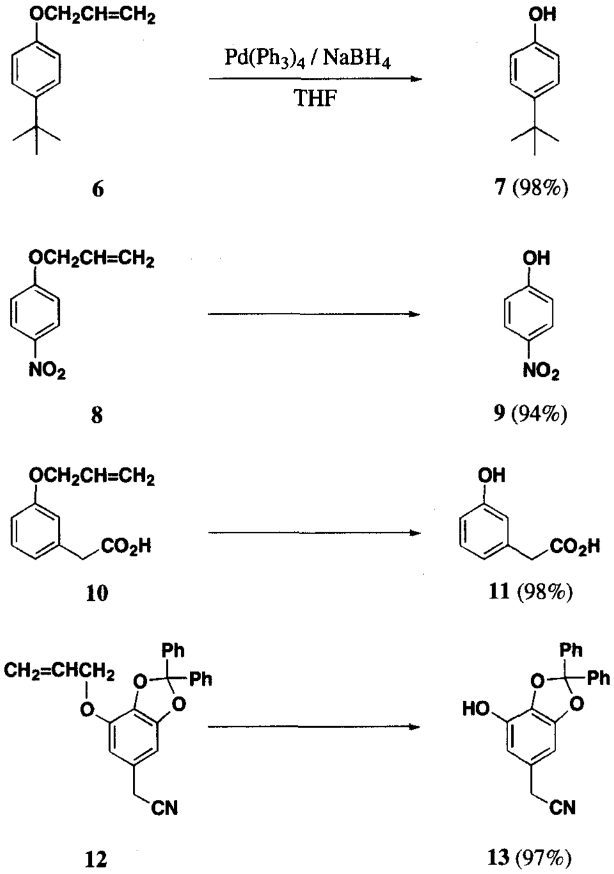
A mild method for the deprotection of diverse O-allyl ethers of glycosides and inositol by use of $PdCl_2/CuCl/DMF\text{-}H_2O/O_2$ is described.[51] Sensitive protective groups also remain unaffected under this procedure. The results of cleavages of different substrates are summarized below:



General Experimental Procedure[51].- To a round bottom flask containing O-allyl derivative (1 mmol) in DMF (2 mL) and water (0.2 mL) (10:1) is added $PdCl_2$ (1 mmol) and CuCl (1 mmol) and stirred for 4 hrs at room temperature while oxygen is continuously bubbled. The reaction mixture is diluted with ether (20 mL) and filtered on a bed of celite. The filtrate is again diluted with ether (50 mL) and washed with water. The organic phase is dried over sodium sulfate, concentrated and filtered on a bed of silica gel to obtain the product.

g) $Pd(Ph_3)_4/NaBH_4$

Another simple method for the deprotection of allyl ether involves treatment of aryl allyl ethers with catalytic amounts of $Pd(Ph_3)_4$ and $NaBH_4$ at room temperature under non-hydrolytic conditions.[52] A range of reducible functional groups including nitro, acetals, carboxylic acids, amides, nitriles, carbamates and imides are compatible with this procedure. It has been assumed that the reaction proceeds via the formation of π-complex rather than the commonly accepted propenyl intermediate and that hydride transfer from $NaBH_4$ to this π-complex affords propene and phenol after aqueous work up. Some representative examples of deallylation are given below:



6 → **7** (98%)

8 → **9** (94%)

10 → **11** (98%)

12 → **13** (97%)

Typical Experimental Procedure. Deallylation of 12[52].- To a solution of compound **12** (70.5 mg, 0.19 mmol) in THF (2 mL) is added a catalytic amount of $Pd(Ph_3)_4$ (4.4 mg, 0.02 equiv.). The slightly yellow solution is stirred for 5 min and $NaBH_4$ (11mg, 0.287 mmol) is introduced. After 1 hr, the excess $NaBH_4$ is destroyed by addition of 1 N HCl. The solvent is removed and the aqueous solution is extracted with methylene chloride. The combined organic extracts are washed with brine, dried over sodium sulfate and evaporated. The crude residue is purified by flash chromatography over silica gel (heptane/ethyl acetate 3:1) to afford product **13** (61 mg, 97%).

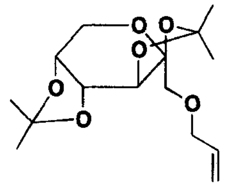
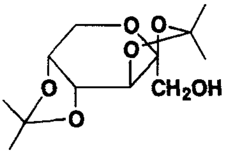
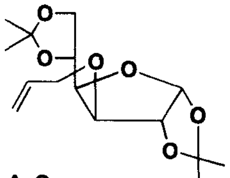
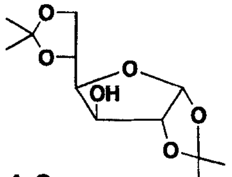
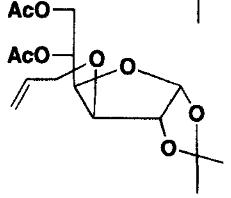
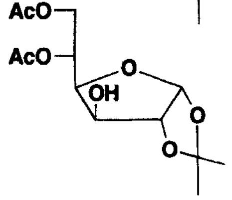
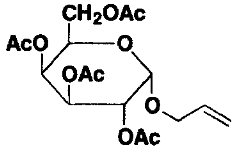
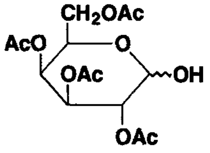
h) N-Bromosuccinimide

A novel approach for deallylation of allylic ether involves the treatment of the ether with N-bromosuccinimide which brominates allylic position under very mild free-radical conditions to afford an α-bromoether which then undergoes hydrolysis to produce the deprotected alcohol and volatile acrolein.[53]

$$\begin{tikzcd}
\mathrm{ROCH_2CH{=}CH_2} + \mathrm{NBS} \arrow[r] & {[\mathrm{RO\dot{C}HCH{=}CH_2}]} \arrow[d] \\
\mathrm{ROH} + \mathrm{CH_2{=}CH\text{-}CHO} & \mathrm{ROCHBrCH{=}CH_2} \arrow[l, "H_2O"']
\end{tikzcd}$$

This method has found application to different carbohydrate derivatives where the allyl group is protecting a primary, secondary and anomeric hydroxyl group in the presence of other acid and base sensitive protecting groups. The findings are summarized in Table 19.

Table 19. Deprotection of Allyl Ether by NBS / H_2O

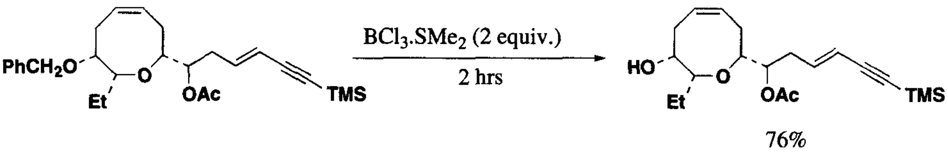
Substrate	Product	Yield (%)[a]
		82
		85
		78
		100

a) Isolated yield

General Experimental Procedure[53].- To a solution of the allyl ether (3 mmol) in freshly distilled carbon tetrachloride (100 mL) is added NBS (3 mmol) and the mixture is refluxed and irradiated with a Tungsgram Halogen 60000 T8 R7-s-15 lamp in a pyrex round bottom flask for 30 min. Reactions are monitored by TLC. After completion, aqueous 3 M NaOH solution (100 mL) is added (in certain cases silica gel is used for hydrolysis) and the mixture is stirred for 1 hr. The organic phase is separated, washed with water, and concentrated and the residue is subjected to column chromatography to yield the corresponding products.

i) Boron Trichloride - Methyl Sulfide Complex

Selective cleavage of benzyl ethers in presence of cyclic and silyl ethers, esters, ketones, alkenes, alkynes and terminal silylated enyne, has been achieved through a simple procedure involving $BCl_3 \cdot SMe_2$ complex.[54]

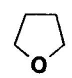
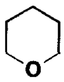
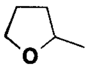
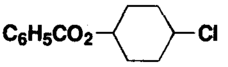


III. CLEAVAGE OF CYCLIC ETHERS

a) Palladium(II) complexes in Presence of Triorganotin Halides

Cyclic ethers are cleaved and acylated in the presence of acyl halide, a catalytic amount of palladium(II) complex and trialkyltin halide under mild conditions.[55] The presence of a catalytic amount of trialkyltin halide enhances the acylation although a slow reaction is detected even in the absence of the compound. Oxiranes are acylated without a catalyst, while tetrahydropyran is much less reactive than tetrahydrofuran. The reaction of 2-methyltetrahydrofuran gives predominantly 4-chloro-4-methylbutyl benzoate, suggesting an S_N1 ring opening process. All these results are presented in Table 20.

Table 20. Cleavage of Cyclic Ethers Catalyzed by Pd(II) Complex[a]

Ether	Pd–catalyst mol %	$(n\text{-}C_4H_9)_3SnCl$ mol %	Product (% yield)
	0.3	15	$C_6H_5CO_2(CH_2)_3CH_2Cl$ (85)
	0.5	15	$C_6H_5CO_2(CH_2)_4CH_2Cl$ (4)
	0.5	15	$C_6H_5CO_2(CH_2)_3CH(CH_3)Cl$ (81)
	0.7	15	 (60)

a) Benzoyl chloride used as acylating agent

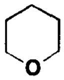
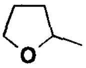
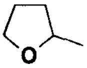
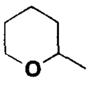
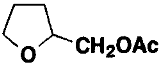
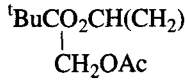
A Typical Experimental Procedure. Cleavage of 2-Methyltetrahydrofuran[55].- A mixture of 2-methyltetrahydrofuran (603 mg, 7 mmol), benzoyl chloride (984 mg, 7 mmol), tributyltin chloride (330 mg, 1.01 mmol) and chlorobenzyl-*bis*(triphenylphosphine)palladium(II) (35 mg, 0.049 mmol) is heated to 63° for 48 hrs. The volatile fractions are transferred by means of a reduced pressure distillation to a cold trap at -180°. The nonvolatile residue is dissolved in ether and extracted with saturated sodium bicarbonate and potassium fluoride aqueous solutions. The ether layer is dried over magnesium sulfate and evaporated to leave 4-chloropentyl benzoate (1.193 g, 81%).

b) Sodium Iodide - Acyl Chloride

Cyclic ethers are regioselectively cleaved at less substituted carbon-oxygen bond in the absence of any Lewis acid by the reagent system of sodium iodide and acyl chlorides.[56]

The cleavage reaction proceeds effectively without the use of an excess amount of acyl chlorides. Results of cleavages of a variety of cyclic ethers are summarized in Table 21.

Table 21. Cleavage of Cyclic Ethers by NaI–RCOCl

Ether	Acyl chloride	Time (hrs)	Products	Yield (%)[a] (ratio)[b]
	MeCOCl	21	$CH_3CO_2(CH_2)_4I$	90
	MeCOCl	44	$CH_3CO_2(CH_2)_5I$	75
	MeCOCl	23	$CH_3CO_2CH(CH_3)(CH_2)_3I$ + $CH_3CO_2(CH_2)_3CH(CH_3)I$	85 (49:51)
	^{t}BuCOCl	22	$^tBuCO_2CH(CH_3)(CH_2)_3I$ + $^tBuCO_2(CH_2)_3CH(CH_3)I$	91 (97:3)
	^{t}BuCOCl	21	$^tBuCO_2CH(CH_3)(CH_2)_4I$ + $^tBuCO_2(CH_2)_4CH(CH_3)I$	59 (80:20)
	^{t}BuCOCl	23	 $^tBuCO_2\underset{CH_2OAc}{CH}(CH_2)_3I$	71

a) Isolated yield. b) Ratio determined by VPC

The regioselectivity observed in these ether cleavage reactions giving the iodide of the less substituted carbon atom is in a marked contrast to other reported ether cleavage reactions with Lewis acid-acyl chloride reagents.[1] However, the present selectivity depends highly on the types of acyl chloride employed; neither acetyl nor benzoyl chloride exhibits any appreciable selectivity, whereas pivaloyl chloride imparts very high selectivity.

A Typical Experimental Procedure. Cleavage of THF[56].- To an acetonitrile (10 mL) solution of THF (0.17 mol) and sodium iodide (0.20 mol) is added acetonitrile (5 mL) solution of acetyl chloride (0.17 mol) at 0°. After 21 hrs of stirring the reaction mixture at an ambient temperature, reaction is quenched by the addition of aqueous sodium bisulfate. After extraction with ether followed by drying over sodium sulfate, the distillation of the solution gives 4-iodobutyl acetate (91%).

A recent study[57] of regiocontrolled ring opening with this reagent reveals that cleavage of 2-methyltetrahydrofuran with bulky acid iodides RCOI gives predominantly the primary iodides (Table 22), while acid chlorides RCOCl lead to secondary chlorides almost exclusively, regardless of the nature of R (Table 23).

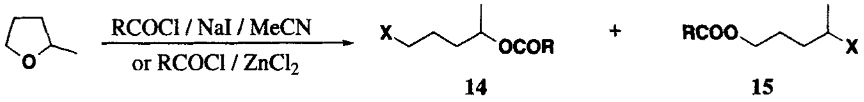


Table 22. Ring Opening of 2-Methyltetrahydrofuran with RCOCl / NaI in MeCN (24 hs, rt).

R	**14 / 15**	Yield (%)
Me	38 / 62	85
Et	44 / 56	82
^{i}Pr	62 / 38	65
^{t}Bu	98 / 2	95
$ClCH_2$	10 / 90	56
Cl_3C	98 / 2	62
C_3F_7	99 / 1	70

Table 23. Ring Opening of 2-Methyltetrahydrofuran with RCOCl / $ZnCl_2$ (cat.) (rt).

R	**14 / 15**	Yield (%)
Me	3 / 97	95
^{t}Bu	2 / 98	92
$ClCH_2$	2 / 97	65
Cl_3C	4 / 96	5
C_3F_7	2 / 98	5

c) Platinum Complexes

Cyclic ethers are readily cleaved under mild conditions by acid halides in the presence of platinum(II) complexes.[58] The reactions are usually exothermic and, when conducted stoichiometrically with respect to ether and acyl halides, sometimes require external cooling. For this reason the ether is generally used in excess to serve as a heat sink. This reaction shows the same kind of regioselectivity expected in an S_N1 reaction as observed in the cleavage of 2-methyltetrahydrofuran to produce 2-chloropentyl acetate in good yield (Table 24). This reaction does not occur with acyclic aliphatic ethers such as diethyl ether or 1,2-dimethoxyethane; thus it can be used for the selective cleavage of cyclic ether in presence of acyclic one.

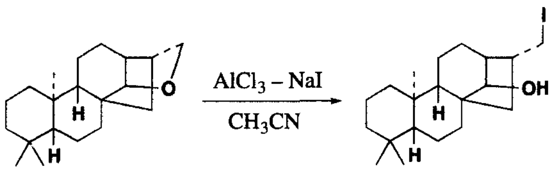
Table 24. Cleavage of Ethers with Pt(II) Complex

Ether	Acyl halide (mol)	Catalyst (mmol)	Product	Yield (%)
THF (0.56)	MeCOCl (0.11)	$K[Pt(C_2H_4)Cl_3]$ (1.3)	$MeCO_2CH_2(CH_2)_3Cl$	72
2-MeTHF (0.35)	MeCOCl (0.08)	$K[Pt(C_2H_4)Cl_3]$ (1.3)	$MeCO_2(CH_2)_3CH(Me)Cl$	70
2,5-(Me)$_2$THF (0.30)	MeCOCl (0.06)	$[Pt(C_2H_4)Cl_2]_2$ (0.61)	$MeCO_2CH(Me)(CH_2)_2CH(Me)Cl$	81
oxetane (0.19)	MeCOCl (0.04)	$K[Pt(C_2H_4)Cl_3]$ (1.4)	$MeCO_2(CH_2)_3Cl$	47
tetrahydropyran	MeCOCl (0.068)	$[Pt(C_2H_4)Cl_2]_2$	$MeCO_2(CH_2)_5Cl$	57

General Procedure for Cleavage Reactions[58].- In a typical procedure acetyl chloride (8.83 g, 0.113 mol) is added dropwise to a stirred tetrahydrofuran (40.0 g, 0.56 mol) solution of $K(Pt(C_2H_4)Cl_3)$ (500 mg, 1.29 mmol). The mixture becomes warm, and after 24 hrs the volatiles are flash distilled in vacuum. Distillation of the residue at reduced pressure yielded 4-chlorobutyl acetate (12.1 g,72%)

d) Aluminum Chloride - Sodium Iodide - Acetonitrile

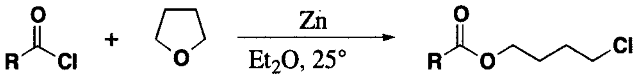
Unsymmetrically substituted 5-membered cyclic ethers are effectively cleaved with the $AlCl_3$-NaI-CH_3CN system at the less hindered carbon atom to afford δ-iodoalcohols.[59] Although the ring opening mode with this reagent system is the same as other methods involving Lewis acids, the advantage exists in obtaining the unprotected δ-iodoalcohol directly. Conversion of ent-14α- and ent-12β-hydroxykaurene is achieved through the ring opening of the cyclic ether with this reagent system as a key step.



e) Zinc-Acyl Chloride

Recently a very simple and efficient cleavage of tetrahydrofuran on reaction with different acyl chlorides in presence of commercial zinc dust leading to 4-chlorobutyl alkanoates in high yields has been demonstrated.[35] In a general typical procedure, a suspension of a catalytic amount of commercial zinc dust (25 mol%) in ether is stirred with THF (1 mmol) and acid chloride (1 mmol) at room temperature for a certain period of time as required for completion. The product is isolated by a simple work up involving filtration of the zinc dust and evaporation of ether.

Table 25. Cleavage of Tetrahydrofuran with Zn / Acyl Chloride

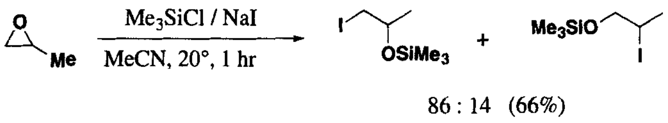


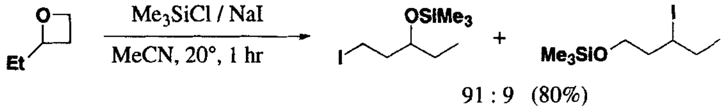
R	Time (hrs)	Yield (%)[a]
CH_3	3	87
C_2H_5	6	80
n-C_3H_7	14	88
i-C_3H_7	14	80
$PhCH_2$	6	90
Cyclohexyl	8	82
Ph	18	70

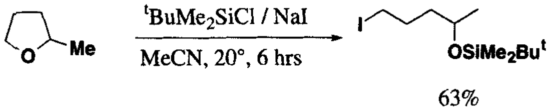
a) Isolated yield

f) Trimethylsilyl Iodide

Trimethylsilyl iodide readily cleaves substituted cyclic ethers under neutral and mild conditions.[60] The primary iodides are formed predominantly indicating S_N2 type cleavage. A few illustrative examples are given below:





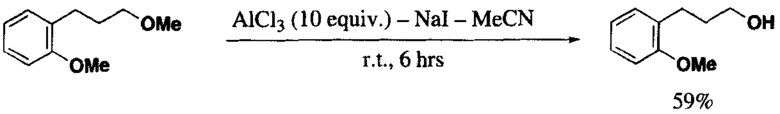


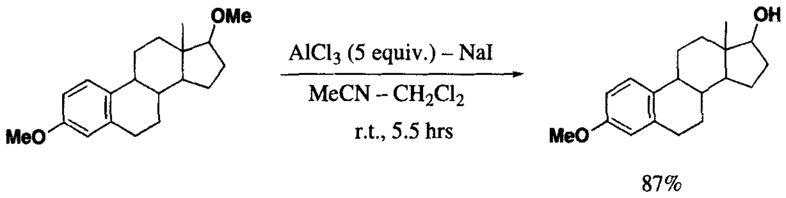
IV. SELECTIVITY IN DEALKYLATION OF ETHERS

The selective dealkylation of one ether moiety without affecting others is of much importance and a frequently desired process in organic synthesis. Although very little systematic study has been made on this specific area, there are a number of reagents available which are capable of doing such transformations.

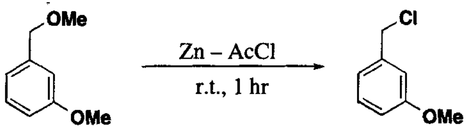
a) Selective Dealkylation of Alkyl Ether

Selective demethylation of aliphatic methyl ether with $AlCl_3$-NaI-CH_3CN reagent system is demonstrated.[61]



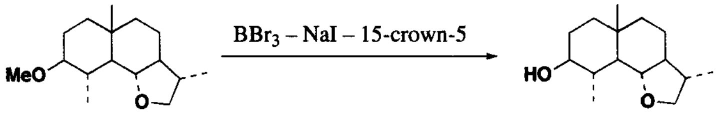


Selective cleavage of dialkyl ether in presence of an aryl alkyl ether is very efficiently achieved using zinc dust and acyl chloride.[35]



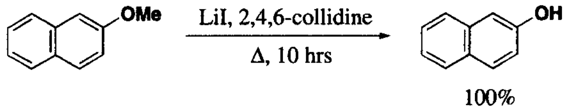
Trimethylsilyl iodide[27-32] cleaves aryl alkyl ethers significantly slower than dialkyl ethers, so that dialkyl ethers are cleaved completely under conditions which cause only 5-10% cleavage of phenolic ethers.

An efficient dealkylation of an aliphatic methyl ether is achieved without affecting the fused tetrahydrofuran ring present in the molecule by BBr_3-NaI-15-crown-5 reagent system.[19]



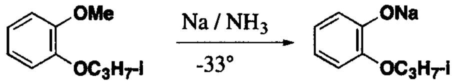
b) Selective Dealkylation of Aryl Ether

Lithium iodide in presence of 2,4,6-collidine very efficiently cleaves an aryl ether whereas, an aliphatic methyl ether remains unaffected under this condition.[62]

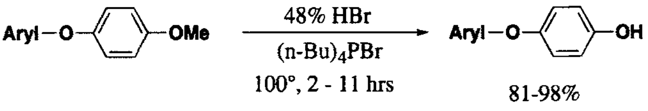


$$C_{16}H_{33}OMe \xrightarrow[\Delta,\ 10\ hrs]{LiI,\ 2,4,6\text{-collidine}} \text{No reaction}$$

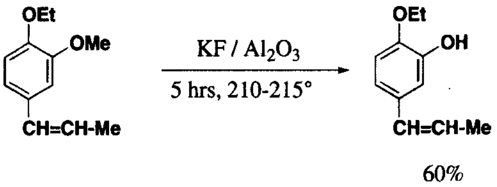
Selective demethylation of a methyl aryl ether in preference to a more highly substituted alkyl aryl ether is achieved with sodium in liquid ammonia.[63]



Hydrobromic acid (48%) in presence of a phase transfer catalyst readily dealkylates a methyl aryl ether without affecting an aryl aryl one present in the molecule.[64]

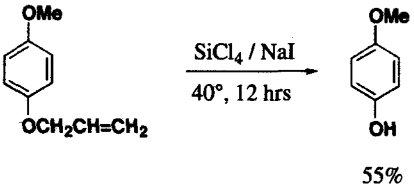


A simple method for the selective demethylation of a methyl aryl ether in preference to an ethyl one is demonstrated using potassium fluoride on alumina.[65]



c) Selective Dealkylation of Allyl Ether

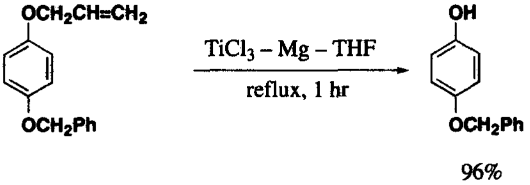
Silicon tetrachloride - sodium iodide reagent system dealkylates an allyl ether selectively in presence of a methyl aryl ether through a simple operation.[66]



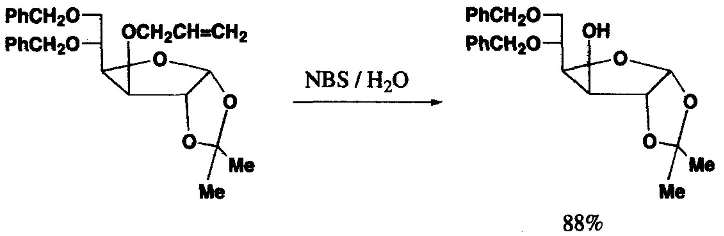
Similar selective cleavage of allyl ether in presence of methyl ether is also achieved with low valent titanium reagents.[49]

$$MeO(CH_2)_{12}OCH_2CH{=}CH_2 \xrightarrow[\text{reflux, 2.5 hrs}]{TiCl_3 - Mg - THF} MeO(CH_2)_{12}OH$$

83%

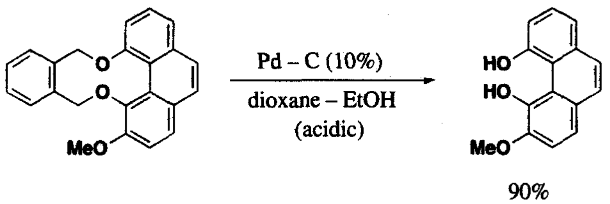


A recent report demonstrates that allylic ethers are dealkylated selectively in preference to benzyl one present in the same molecule with N-bromosuccinimide and water.[53]

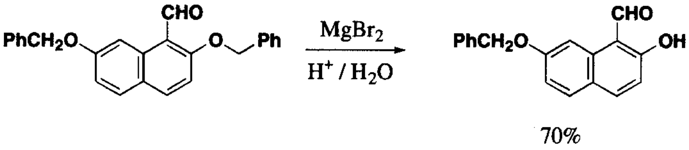


d) Selective Dealkylation of Benzyl Ether

Benzyl ethers are dealkylated very efficiently and selectively in presence of a methyl ether by catalytic hydrogenation over palladium-charcoal in acidic dioxane-ethanol solvent.[67]



The selective cleavage of aromatic benzyl ethers is also achieved with magnesium bromide involving neighboring group effect[68].



V. CONCLUSION

This review attempts to focus the recent progress in dealkylation of ethers including a wide range of useful procedures. Selective dealkylation of one ether moiety in presence of other is also highlighted. General or typical experimental procedure is appended for ready reference of practicing synthetic organic chemists. Although the results presented in this review have not incorporated the applications to natural products or complex structures in details, these methods can certainly be applied to molecules having more complex structures. The present review is hoping to serve the need of synthetic organic chemistry community concerning dealkylation of ethers.

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