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SELECTIVE DEMETHYLATION OF ALIPHATIC METHYL ETHER IN THE PRESENCE OF AROMATIC METHYL ETHER WITH THE ALUMINUM CHLORIDE-SODIUM IODIDE-ACETONITRILE SYSTEM

Manabu Node, Keiichiro Ohta, Tetsuya Kajimoto, Kiyoharu Nishide,
Eiichi Fujita, and Kaoru Fuji*
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

A combination system of aluminum chloride-sodium iodide-acetonitrile effects selective demethylation of aliphatic methyl ethers in the presence of aromatic methyl ether.

KEYWORDS ——— demethylation; methyl ether; aluminum chloride; sodium iodide; hard acid; soft nucleophile

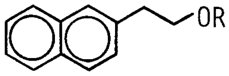
A variety of combination systems of a hard Lewis acid and a thiol or a sulfide as a soft nucleophile have been developed for C-O bond cleavages of methyl ethers,1) benzyl ethers,2) esters,3) and lactones.4) In principle, it is possible with these systems to cleave a specific C-O bond in the presence of an other type of C-O bond by shifting the balance between a hard acid and a soft nucleophile. Here we describe the selective demethylation of aliphatic methyl ether in the presence of aromatic methyl ether with a combination system of aluminum chloride-sodium iodide-acetonitrile, where a thiol or a sulfide is replaced by iodide ion as a soft nucleophile. A key feature of this system involves a decrease in the pulling factor of a hard acid by coordination with acetonitrile.

Results of the demethylation of methyl ethers with this new combination system are listed in the Table. Aliphatic methyl ethers **1a** - **5a** are easily cleaved by the present system at ambient temperature. Though the acetal group was deblocked, ester and lactone moieties remained intact under the reaction conditions, as shown in the case of **5a**. Refluxing temperature was necessary for demethylation of aromatic methyl ethers **6a** and **7a**. This indicates that it is possible to cleave the C-O bond of aliphatic methyl ethers without touching an aromatic methyl ether moiety simply by controlling the reaction temperature. This idea was realized in selective demethylation of dimethyl ethers **8a** - **11a**. No report has been published on the selective demethylation of aliphatic methyl ethers in the presence of the aromatic methyl ether in the same molecule, except for an example of estradiol dimethyl ether (**8a**) with the thiol-boron trifluoride system.1a) In a typical procedure, aluminum chloride (1.0 mmol), sodium iodide (1.0 mmol), and estradiol dimethyl ether (**8a**) (0.1 mmol) were added in this order to a mixture of acetonitrile (4 ml) and dichloromethane (2 ml) at 0°C under nitrogen. After being stirred for 5.5 h at room temperature, the mixture was poured into water and extracted with dichloromethane. After the organic layer was washed with aqueous sodium thiosulfate followed by the usual workup, it afforded **8b** and the starting material **8a** in 87% and 8% yield, respectively.

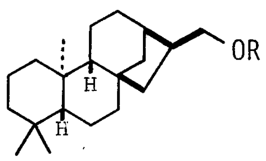
The possible mechanism for this demethylation is shown in Chart 1. Lewis acidity of aluminum chloride is decreased to some extent by the coordination with acetonitrile to form a complex **13** (eq. 1). Addition of a methyl ether into the mixture attains the equilibrium (eq. 2), Table. Cleavage of Methyl Ethers

Compound	Cosolvent	Temp.	Time, h	Product (Yield, %)[a]
1a	non	r.t.	8.0	1b (91)[b]
2a	CH_2Cl_2	r.t.	9.0	2b (90)[b]
3a	CH_2Cl_2	r.t.	6.0	3b (86)[b]
4a	non	r.t.	5.0	4b (86)[c]
5a	non	r.t.	8.0	5b (85)[b]
6a	CH_2Cl_2	reflux	5.0	6b (87)[b]
7a	CH_2Cl_2	reflux	5.5	7b (93)[b]
8a	CH_2Cl_2	r.t.	5.5	8b (87)[c,d]
9a	non	r.t.	5.0	9b (87)[b,e]
10a	non	r.t.	9.0	10b (70)[c]
11a	non	r.t.	6.0	11b (59)[b,f]
12a	non	r.t.	5.0	12b (56), 12c (20)[b]

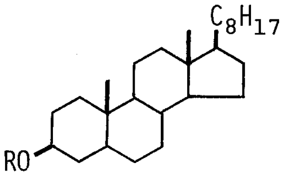
[a] Isolated yield. [b] 10 mol eq of $AlCl_3$ was used. [c] 5 mol eq of $AlCl_3$ was used. [d] An 8% yield of starting material was recovered. [e] A 15% yield of diol was obtained. [f] The corresponding diol was obtained in 16% yield.



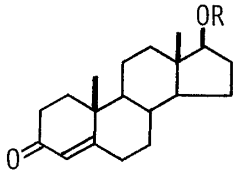
1a, R = Me
1b, R = H



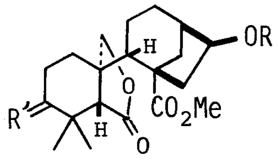
2a, R = Me
2b, R = H



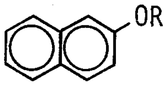
3a, R = Me
3b, R = H



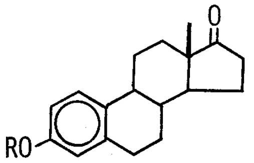
4a, R = Me
4b, R = H



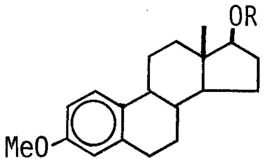
5a, R = Me, R'= O]
5b, R = H, R'= O



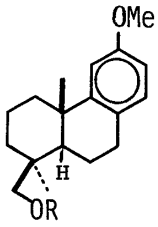
6a, R = Me
6b, R = H



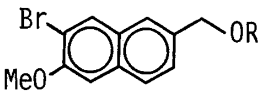
7a, R = Me
7b, R = H



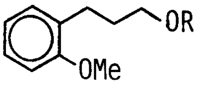
8a, R = Me
8b, R = H



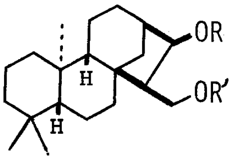
9a, R = Me
9b, R = H



10a, R = Me
10b, R = H

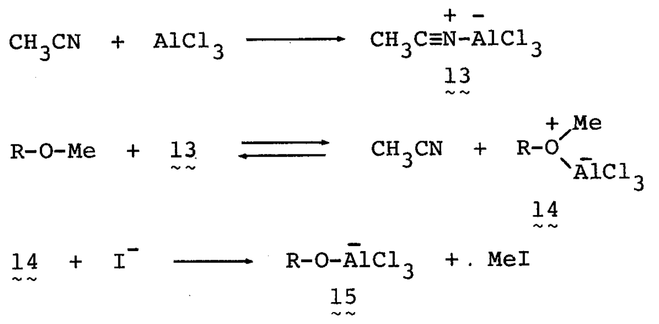


11a, R = Me
11b, R = H



12a, R = R'= Me
12b, R = Me, R'= H
12c, R = H, R'= Me

Chart 1



$$CH_3CN + AlCl_3 \longrightarrow CH_3\overset{+}{C}{\equiv}N\overset{-}{-}AlCl_3 \quad \mathbf{13} \tag{1}$$

$$R{-}O{-}Me + \mathbf{13} \rightleftharpoons CH_3CN + R{-}\overset{+}{O}{<}^{Me}_{\bar{A}lCl_3} \quad \mathbf{14} \tag{2}$$

$$\mathbf{14} + I^- \longrightarrow R{-}O{-}\bar{A}lCl_3 \ (\mathbf{15}) + MeI \tag{3}$$

in which the bias depends upon the basicity of the oxygen atom. Because of the inductive effect of the phenyl ring and delocalization of the lone pair electrons on the oxygen over the aromatic ring, the basicity of the oxygen on the aromatic ring is somewhat decreased as compared to that of aliphatic ethers. As a result, the equilibrium shown in eq. 2 is shifted to the right in aliphatic methyl ethers and to the left in aromatic methyl ethers. The oxonium ion 14 thus formed is attacked by iodide ion at the less hindered methyl group followed by hydrolysis of the resulting 15 to complete demethylation.

It is worthy of note that this system can differentiate the methyl ether of primary alcohol from that of secondary alcohol,$^{5)}$ as illustrated in the partial demethylation of 12a giving 12b. Further studies are currently under way to increase the yield of this partial demethylation by proper choice of a hard acid (pulling factor) and a soft nucleophile (pushing factor) and to apply the method to other compounds possessing dimethyl ethers of primary and secondary hydroxyl groups in the molecule.

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5) There has been only one example of selective demethylation at a primary position in a permethylated thioglycoside. See S. Hanessian and Y. Guindon, *Tetrahedron Lett.* 21, 2305 (1980).

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