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A NEW METHOD FOR CLEAVAGE OF ALIPHATIC METHYL ETHERS

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Abstract: A new efficient procedure for the cleavage of aliphatic methyl ethers under the mild conditions by the use of the reagents system, boron tribromide - sodium iodide - 15-crown-5 is described.

Among the various kinds of protecting groups of aliphatic hydroxyl groups, methyl ethers might be the most stable ones that resist to the reaction conditions widely used for the synthetic works.[1] Nevertheless, there are only few examples[2] employing the methyl ethers as protecting groups of hydroxyl ones in the synthesis of complex natural products because of the difficulty of cleaving the ethereal (Me-O) bond to regenerate the corresponding hydroxyl groups. Recent publications showed the development of new methodology for the cleavage of the ethereal (Me-O) bond with various kinds of reagent combinations.[3] In this communication, we wish to report a new, mild method for the cleavage of the methyl ethers in the aliphatic compounds.

After several unsatisfactory trials of cleavage reactions with boron tribromide itself, we have found that the reagents system consisting of BBr_3 - NaI - 15-crown-5 in dry methylene chloride cleaved very efficiently primary and secondary aliphatic methyl ethers under mild conditions to give the corresponding alcohols as shown below.

$$\text{RO-Me} \xrightarrow[CH_2Cl_2,\ -30\ ^\circ C]{BBr_3 - NaI - 15\text{-crown-5}} \text{ROH}$$

Table 1 shows several examples of the cleavage reactions of methyl ethers. The following procedure is illustrative. To a stirred solution of 3-phenylpropanol methyl ether 1 (103 mg, 0.687 mmol) in dry CH_2Cl_2 (0.5 ml) was added 13.7 ml of 0.3 M solution (6 equiv) of 15-crown-5 saturated with NaI in CH_2Cl_2 followed by the addition of 2.1 ml of 1 M solution (3 equiv) of BBr_3 in CH_2Cl_2 at -30 °C under argon.[4] The reaction mixture was stirred at the same temperature for 3 h, quenched by the addition of 2 ml of a saturated aqueous $NaHCO_3$ solution and worked up in the usual manner. Chromatographic purification of the crude products gave the pure alcohol 2 (93 mg, quantitative yield) identical in all respects with the authentic sample (IR, ^{1}H-NMR and MS).

In order to investigate the effect of NaI and 15-crown-5 for the above cleavage reactions, the following control experiments were carried out. When the compound 3 was treated with BBr_3 alone in the absence of the crown ether and NaI, none of the desired alcohol 4 but 3-bromo-5α-cholestane was obtained in high yield as reported previously.[5] Similarly, treatment of the compound 13 with BBr_3 gave a complex mixture, from which only brominated compounds were obtained, without formation of the desired alcohol 14. Treatment of 13 with any combination of two reagents (BBr_3 - NaI, BBr_3 - crown ether, NaI - crown ether) gave none of the desired alcohol 14 but resulted in the formation of a complex mixture or the recovery of the starting methyl

ether 13. Thus, only the condition using three reagents described above gave satisfactory results.

In spite of clean cleavage of primary and secondary aliphatic methyl ethers, there are certain limitations in case of tertiary ethers [17 → 18 (10%) and 19 → 20 (rearrangement)].

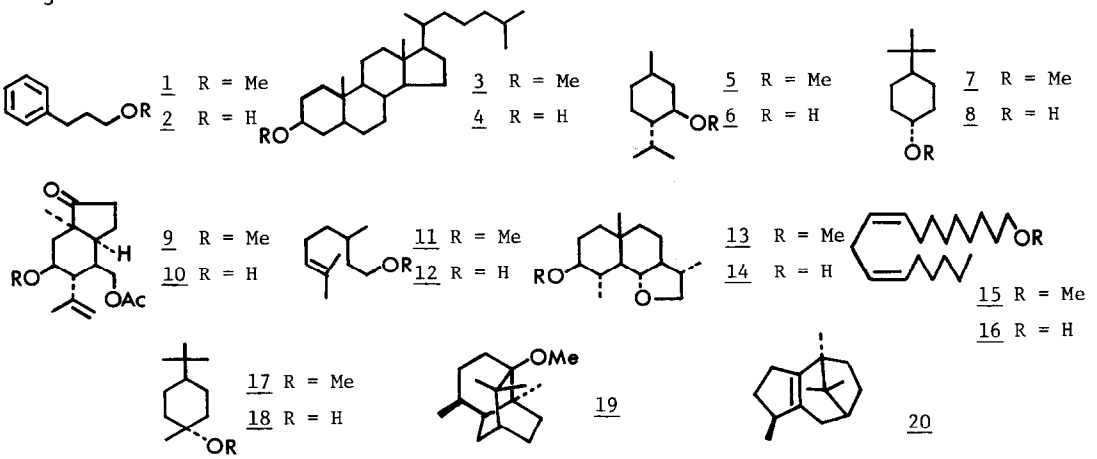
While the actual course of this reaction is not clear as yet, we believe initial coordination of trivalent boron to the ethereal oxygen and subsequent nucleophilic attack of an iodide or bromide anion onto the methyl group to generate the corresponding alcohol.

Further application of this reagents system toward synthesis of natural products is in progress.

Table 1. Cleavage of aliphatic methyl ethers[a]

Methyl ether[b]	Alcohol	Yield (%)[c]
1	2	100
3	4	100
5	6	75
7	8	93
9[d]	10	75
11	12	73
13[e]	14	61
15[f]	16	91
17	18	10
19[f]	20	-

a) Unless otherwise stated, the cleavage reaction was performed at -30 °C with BBr_3 (3 equiv) and 15-crown-5 (6 equiv) - NaI for 3 h. b) All compounds employed in the reaction exhibited satisfactory IR, ^{1}H-NMR and MS spectra. c) All yields refer to isolated alcohol. d) Preparation of this compound will be reported elsewhere. e) Performed with 4 equiv of BBr_3 and 8 equiv of 15-crown-5 - NaI for 4 h. f) Performed for 2 h.



References and Note

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4. The addition sequence of the reagents is very important. BBr_3 should be added to a solution of substrate containing the crown ether - NaI complex in CH_2Cl_2.
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