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CLEAVAGE OF METHYL AND BENZYL ETHERS WITH THIOTRIMETHYLSILANES

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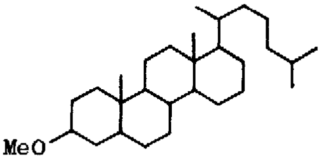
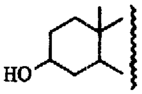
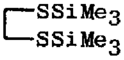
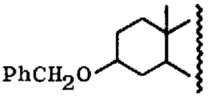
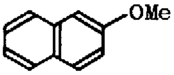
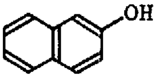
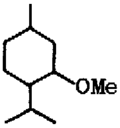
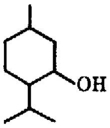
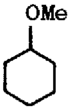
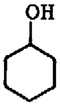
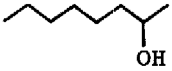
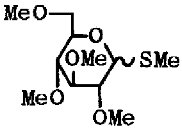
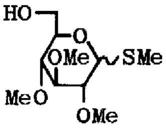
Abstract: The reagents methylthio-, phenylthio- or 1,2-ethanedithiobis- trimethylsilane in combination with zinc iodide and tetra n-butylammonium iodide effect de-O-alkylation of methyl and benzyl ethers under relatively mild conditions. Ester functions are unaffected and no iodides are formed in the cases studied.

Several recent reports concerned with the cleavage of C-O bonds of the ether type with organosilane reagent combinations [1a-e] as well as with Lewis acid - thiol systems [1f], prompt us to disclose a relatively mild method for the cleavage of methyl and benzyl ethers in the aliphatic and aromatic series. Based on the reasonable mechanistic premise that cleavage of an ether bond could be brought about by the presence of a strong oxygenophile and a good nucleophile, and taking into account the relatively large difference in bond energies between S-Si (~70 Kcal/mol)[2] and O-Si (~108 kcal/mol)[3] bonds, we considered the use of various thiosilanes [4] which combine the functional requirements for such a reaction, particularly in conjunction with a Lewis acid [5]. Preliminary experiments indicated that the inclusion of tetra n-butylammonium iodide greatly enhanced the de-O-alkylation process. The overall reaction can be summarized as follows:

$$\text{RO-Me} + \text{R'S-SiMe}_3 \xrightarrow{\text{ZnI}_2,\ n\text{-Bu}_4\text{NI}} \text{ROH} + \text{R'-SMe}$$

Table 1 shows several examples of demethylation and debenzylation. As expected, the latter reaction takes place particularly readily. In a typical procedure, β-dihydrocholesterol 3-methyl ether (0.16 g, 0.4 mmole) was added to 8 ml of a 0.5 M solution (10 equiv.) of phenylthiotrimethylsilane [6] in 1,2-dichloroethane, followed by zinc iodide (0.64 g, 2 mmoles) and tetra n-butylammonium iodide (0.22 g, 0.6 mmole). The suspension was stirred at 60° for 6 h and the reaction mixture was processed by filtration and washing the filtrate successively with 5% aq. barium hydroxide then with water. Processing the organic phase as usual gave a residue consisting mainly of β-dihydrocholesterol. Chromatographic purification gave the crystalline alcohol (0.13 g, 84%), identical in all respects with an authentic sample (mp, mixture mp).

Similar results were obtained with methylthiotrimethylsilane and 1,2-ethanedithiobis (trimethylsilane)[2], although the reaction times were somewhat shorter. Both primary and secondary ethers (methyl and benzyl) are readily cleaved and the major product is the

ETHER	REAGENT	TEMP.	TIME	PRODUCT[a]	YIELD[b]
	$PhSSiMe_3$	60°	6-8 h		84%
"	$MeSSiMe_3$	40°	4-5 h	"	81%
"	 $SSiMe_3$ $SSiMe_3$	60°	4-5 h	"	75%
	$PhSSiMe_3$	"	2-3 h	"	86%
	"	"	18 h		87%
	$MeSSiMe_3$	40°	9 h		~97%[c,d]
	$PhSSiMe_3$	60°	8 h		~97%[c]
	"	"	1.5 h		~98%[c]
	"	"	4 h		~98%[c]
	$MeSSiMe_3$	40°	6 h		71%[e]

a). All products were identified by comparison with authentic samples. b). Isolated yields c). Identified by G.C. d). Methylthiotrimethylsilane was much more effective in this case. e). This product was easily converted into a trityl ether (TrCl, pyr.); it was further characterized by ^{13}C nmr spectroscopy.

expected alcohol. In one run (entry 1, Table 1), thioanisole was isolated in over 80% yield and characterized (GC, mass spec.). Demethylation of aromatic ethers as exemplified by β-naphthol methyl ether (also p-bromoanisole and anisole) is also possible under relatively mild conditions. The last entry in Table 1 shows an example of selective de-O-methylation at a primary position in a permethylated thioglycoside. Prolonged treatment (60°, 36 h) effected further demethylation and led to an as yet unidentified monomethyl thioglycoside thus demonstrating the possibility to demethylate permethylated polyols.

While the mechanism of this reaction is not entirely clear as yet, it is useful to report on several experiments aimed at ascertaining whether or not the demethylations are caused by hydrogen iodide[8], trimethylsilyl iodide[1a,b,c], or iodine[1c,d], produced individually or in combinations in the reaction mixture. Because of the relative stability of the reagents, and the possibility to rigorously exclude moisture, adventitious formation of hydrogen iodide can be discounted. Furthermore, no iodides[8] were detected and the demethylations took place in the presence of an acid scavenger (suspended barium carbonate[9]). The formation of iodine and/or trimethylsilyl iodide with the combination of reagents used cannot be excluded *a priori*. In a recent paper, Detty[10] reported that admixture of iodine with phenylthiotrimethylsilane did not produce trimethylsilyl iodide. We have found that treatment of β-dihydrocholesterol 3-methyl ether with phenylthiotrimethylsilane (10 equiv.) and iodine (1.5 equiv.) results in partial demethylation (60°, 24 h). However, addition of zinc iodide (2 equiv.) greatly accelerated the process as judged by the formation of the alcohol (60°, 1-2 h). From these results, others discussed below, and the nature of the products formed, it is unlikely that the dealkylations with the thiosilane-ZnI_2-n-Bu_4NI combination proceeds by iodine or trimethylsilyl iodide-mediated processes. In this regard, we have also made the preparatively useful observation that demethylation of the β-dihydrocholesterol 3-methyl ether with trimethylsilyl iodide[1a] (7 equiv., CH_2Cl_2) is complete *within a few minutes at 25°, in the presence of zinc iodide* (5 equiv.), with or without added tetra n-butylammonium iodide. Had the demethylations with the thiosilane reagent been caused by *in situ* formation of trimethylsilyl iodide, one would have expected much faster reactions than those shown in Table 1. Moreover, no iodides were formed in our reactions (compare ref. 11)[11]. The most practical combination of reagents was found to be the thiosilane-ZnI_2-n-Bu_4NI system in dichloromethane or 1,2-dichloroethane[12]. Individually, or in pairs, the reagents do not effect dealkylation. A synthetically useful and mechanistically revealing feature is the finding that esters (acetates, benzoates) are unaffected under the reaction conditions even when they are primary (compare with trimethylsilyl iodide[13] and silane-iodine cases[1c,d]). For example, β-dihydrocholesterol acetate was recovered mostly unchanged when subjected to the conditions of demethylation even after 24 h.

Other synthetic applications of reagents comprising relatively weak heteroatom-oxygenophile bonds are presently under study in our laboratory.

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References:

1. For some recent examples, see a). M.E. Jung and M.A. Lyster, J. Org. Chem., 42, 3761 (1977). b). T.-L. Ho and G.A. Olah, Angew Chem. internat. ed., 15, 774 (1976). c). T.-L. Ho and G.A. Olah, Proc. Natl. Acad. Sci. U.S.A., 75, 4 (1978). d). G.A. Olah, S.C. Narang, B.G. Balaram Gupta and R. Malhotra, J. Org. Chem., 44, 1247 (1979). e). T. Morita, Y. Okamoto and H. Sakurai, J. Chem. Soc. Chem. Comm., 874 (1978). f). M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji and E. Fujita, Chem. Lett., 97 (1979) and previous papers; see also H.G. Fletcher, Jr., and H.W. Diehl, Carbohydr. Res., 17, 383 (1971).

2. D.A. Evans, L.K. Truesdale, K.G. Grimm and S.L. Nesbitt, J. Am. Chem. Soc., 99, 5009 (1977); cf. ref. 11 in the Evans paper.

3. C.R. Kruger and E.G. Rochon, J. Organomet. Chem., 1, 476 (1964).

4. For preparatively useful applications of thiosilanes see ref. 2 and other references cited therein.

5. E.W. Abel and D.J. Walker, J. Chem. Soc., A 2338 (1968).

6. R.S. Glass, J. Organomet. Chem., 61, 83 (1973); see also I. Ojima, M. Nihonyangi and T. Nagai, ibid., 50, C26 (1973).

7. Available from Petrarch Systems, Levittown, Pa.

8. C.A. Smith and J.D. Grutzner, J. Org. Chem., 41, 367 (1976).

9. S. Hanessian and N.P. Plessas, J. Org. Chem., 34, 1035 (1969); S. Hanessian, Methods Carbohyd. Chem., 6, 183 (1972).

10. M.R. Detty, Tetrahedron Lett., 4189 (1979).

11. M.E. Jung and T.A. Blumekopf, Tetrahedron Lett., 3657 (1978).

12. Several other Lewis acids, ex. $ZnBr_2$, $ZnCl_2$, $AlCl_3$, $SnCl_4$, BF_3. Et_2O, were ineffective Also reaction did not take place in the following solvents: MeCN, DMSO, THF, DMF, toluene. The role of tetra n-butylammonium iodide is not clear as yet, but it may produce new zinc species (ZnI_3 among others) which may provide more effectively coordinated intermediates. These aspects are under study.

13. M.E. Jung and P.L. Ornstein, Tetrahedon Lett., 2659 (1977).

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