

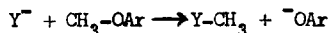
DEMETHYLATION OF ARYL METHYL ETHERS WITH THIOETHOXIDE ION IN DIMETHYL FORMAMIDE

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In connection with other work, we desired to demethylate a brominated aryl methyl ether, which also contained an acid-sensitive group elsewhere in the molecule. The common acidic reagents (1,2) were obviously not applicable and, because Grignard reagents are of limited use in the presence of halogens (3), we turned our attention to cleavage by nucleophilic reagents according to the equation:



A survey of the literature for applications of this reaction was not encouraging. Reagents "Y" such as hydroxide (1,4), methoxide (5), ethoxide (5), sulphite (6), thiophenoxide (7), and thioethoxide (8), each in protic solvents, have required the use of high temperatures, long reaction times, and sealed tube or autoclave conditions to effect even only partial demethylation in some cases. Sodium amide/piperidine (9) (Y = piperidide ion), diphenylphosphide ion/THF (10), and lithium iodide/collidine (11) appeared more promising, but the first reagent attacks many other functional groups including bromides, the second is expensive, not readily accessible, and difficult to remove from unreacted ethers in some cases, and the last appears to react very slowly in the two examples cited.

It occurred to us that, if these reactions were indeed proceeding via  $S_N2$  on methyl (equation), the use of a dipolar aprotic solvent ought to be far more expedient (12). We now report that thioethoxide ion in hot dimethyl formamide (DMF) under nitrogen effects a rapid and clean demethylation of aryl methyl ethers. Our preliminary results are summarised in the Table.

From the limited number of examples studied, it appears that several features make this procedure particularly attractive: (1) High temperatures and long reaction times are not necessary in most cases. The reflux conditions and reaction time of 3 hours were only used in these preliminary studies to ensure complete reaction. Monitoring the demethylation of m-cresol methyl ether (entry 1) by thin layer chromatography indicated that the reaction was complete at reflux after approximately 45 min. This reaction even proceeded slowly at room temperature, and at 100° was complete also after 3 hr. However, the fact that our standard conditions (more severe than necessary) had no detrimental effect on yields, is noteworthy. Nevertheless, milder conditions will be essential in many cases (entry 3).

(2) Products can be isolated virtually quantitatively in a pure state and free from sulphur contaminants (VPC, Lassaignes). Both the excess reagent and the by-product EtSMe were easily removed during evaporation of solvents.

(3) The bromine atom (entry 3) was not affected at lower temperatures. In a 3 hr. run at reflux, however, a complex product was formed.

(4) The hindered ether (entry 2) was demethylated without difficulty.

(5) Ethers of dihydric phenols (entries 4,5) gave selective mono-demethylation in accord with previous observations (5).

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Table. Demethylation of Substituted Anisoles with EtS<sup>-</sup>/DMF

Entry <sup>a</sup>	R	Equivalent of EtS <sup>-</sup>	Yield(%) <sup>b</sup>	<u>Characterised as</u>	
				Deriv.	m.p.(°C)
1	3-methyl-	2.5	94	aryloxyacetic acid	102
2	2- <u>t</u> -butyl	2.5	96 <sup>c</sup>	aryloxyacetic acid	144-5
3 <sup>d</sup>	4-bromo- 3-methyl-	2.6	96	itself	62-63
4	3-methoxy- 5-methyl-	4.9	94	itself	61
5	4-methoxy-	4.9	98	itself	51-52
6	2,3-dimethoxy-	7.6	96 <sup>e</sup>	diacetate	89-90

a All experiments were performed under nitrogen on 1.0 g. of substrate in 40 ml. of DMF for 3 hr. under reflux except for entry 3.

b Yield of isolated phenolic crude product which was recovered from the 1.2N NaOH washings of the total ether extract of the cooled and acidified (3N HCl) reaction mixture (except entry 2). The products appeared homogeneous by TLC, PMR and VPC.

c Isolated by chromatography on silica gel.

d This experiment was conducted at 100°C instead of under reflux.

e This product was 2-hydroxy-3-methoxyphenol.

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