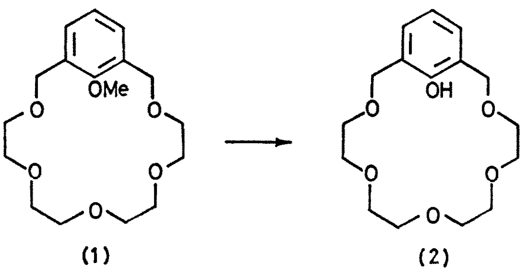
Reactions of Lithium Aluminium Hydride in Hydrocarbon Solvents. Selective Demethylation of Some Substituted Methyl Phenyl Ethers

By John F. Carroll, Sunanta Kulkowit, and M. Anthony McKervey*
(*Department of Chemistry, University College, Cork, Ireland*)

Summary Lithium aluminium hydride in benzene or heptane is an effective reagent for selective demethylation of methyl phenyl ethers having additional ether functions in the immediate vicinity of the reaction site.

Lithium aluminium hydride, a versatile organic reducing agent, is customarily used in ethereal solvents in which it is moderately soluble.[1] Nothing appears to be known about the reducing power of this reagent in hydrocarbon solvents. We now report the useful finding that although lithium aluminium hydride is completely insoluble in benzene or heptane, its reducing power in these liquids is such that it is possible to demethylate certain substituted methyl phenyl ethers having additional ether functions in the immediate vicinity of the reaction site. This discovery followed recent work[2] in which we found that demethylation of crown ether anisoles of type (**1**) using anhydrous lithium iodide in pyridine is much facilitated by the proximate oxygen atoms of the crown ether ring. Thus conditions whereby lithium iodide brought about rapid demethylation of (**1**) to (**2**) left 2,6-dimethylanisole totally unchanged. A similar synergism has now been observed in the lithium aluminium hydride cleavage of some substituted methyl phenyl ethers when benzene or heptane is used as solvent.



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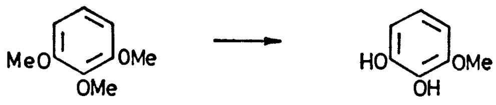

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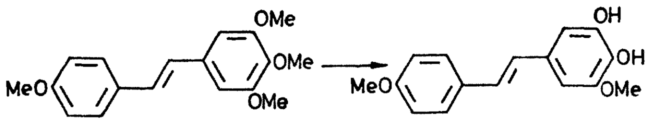
Whereas a mixture of anisole and lithium aluminium hydride (1:2 molar ratio) in boiling benzene, heptane, or tetrahydrofuran exhibited no change after 48 h, 1,2,3-trimethoxybenzene (**3**) under identical conditions in benzene or heptane was transformed, in 6 h, into 1,2-dihydroxy-3-methoxybenzene (**4**) in 81% yield, constituting a very con-



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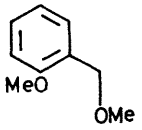

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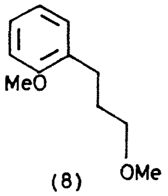

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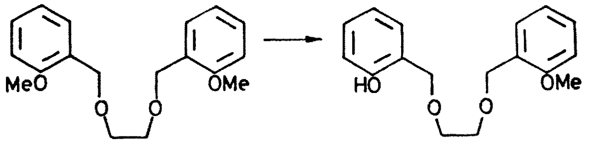

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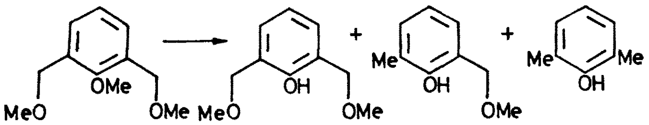

(11) (12) (13) (14)

venient route to this pyrogallol derivative Conversion of (**3**) into (**4**) in tetrahydrofuran was very much slower (*ca* 5% in 6 h), emphasising the solvation aspect of this ether cleavage

Some idea of the type of vicinal substitution likely to facilitate demethylation by lithium aluminium hydride is revealed by the behaviour of veratrole and the ethers (**5**), (**7**), (**8**), (**9**), and (**11**) in boiling benzene (1.2 molar ratio of substrate: $LiAlH_4$) Thus veratrole gave guaiacol (55%) and catechol (17%) after 24 h, but 1,3- and 1,4-dimethoxybenzene were recovered unchanged The inertness of isolated methoxy groups and the potential of the method for regioselective demethylation in polyfunctional molecules is further illustrated by the behaviour of the tetramethoxystilbene derivative (**5**) which, in 6 5 h with lithium aluminium hydride in boiling benzene, gave the dihydroxy compound (**6**) in 80% yield This contrasting behaviour suggests that demethylation in hydrocarbon solvents is facilitated by neighbouring methoxy groups, the synergism being due to co-ordination between the reagent and ethereal oxygen atoms However, the manner in which the neighbouring groups are arranged is also important Thus the monosubstituted anisole (**7**) and its homologue (**8**) suffered little or no demethylation after 48 h in boiling benzene, but the structurally related bisanisole (**9**) gave the monophenol (**10**) in 67% yield after 8 h When the anisyl group is flanked by two benzyl ether groups as in (**11**) demethylation to (**12**) (38%) does occur, but (**13**) (11%) and 2,6-dimethylphenol (**14**) (15%) are also produced, demonstrating that lithium aluminium hydride cleavage of benzyl ethers is also possible in benzene

These results indicate that there is a new dimension to reductions with lithium aluminium hydride in organic synthesis through the use of non-co-ordinating solvents

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[1] For a comprehensive recent survey of the reducing power of lithium aluminium hydride and related reagents in ethereal solvents see H C Brown and S Krishnamurthy, *Tetrahedron*, 1979, **35**, 567

[2] M A McKervey and L D Mulholland, *J Chem Soc*, *Chem Commun*, 1977, 438

[3] The hydrogenolytic cleavage of some strained cyclic ethers using lithium triethylborohydride has been reported by H C Brown, S Krishnamurthy, and R A Coleman, *J Am Chem Soc*, 1972, **94**, 1750