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Dissolving Metal Reduction with Crown Ether ---Reductive Demethylation of Mono-, Di- and Trimethoxybenzene Derivatives with Toluene Radical Anion

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Abstract: Toluene radical anion generated from potassium metal and toluene with the assistance of crown ether has been proved effective for reductive demethylation of methoxybenzene derivatives.

Alkalides and electrides are ionic salts consisting of alkali metal cation complexed by cyclic polyethers and alkali metal anion or electron as the anion, respectively[1]. These are generated by complexing alkali metal with cyclic polyethers as complexants. Since the first preparation and characterization of $Na^+C222Na^-$ by Dye in 1974[1], crystal structures have been obtained for 25 alkalides and 4 electrides[1].
When the complexation is carried out in aromatic solvents, the arene radical anions are formed as the secondary species through the electron transfer from the initially produced alkalides or electrides to the solvent molecules.

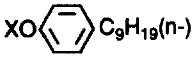
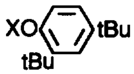
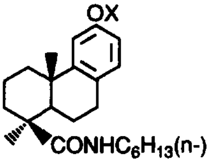
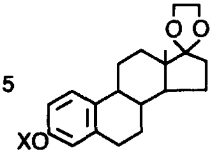
In order to elucidate the chemical reactivity as reducing agents of these curious chemical species, especially potassium anion and toluene radical anion, various types of organic functionalities have been subjected to the reduction by these uncommon species. Potassium anion in combination with alcohol(isopropanol) was shown to be effective for cleavage of sulfonamides[2b] and reduction of conjugated dienes or acetylenes[2e]. Toluene radical anion was proved useful for hydrogenolysis of aliphatic and aromatic fluoro or chloro compounds[2a] and also for reductive removal of aliphatic nitrile[2c] and isonitrile[2d] groups. Sulfides, sulfoxides, sulfones and dithioacetals can be cleaved with toluene radical anion[2e].

The applicability of the toluene radical anion system to the demethylation of methoxybenzene derivatives will be reported in the present communication.

General experimental conditions are as follows: A solution of a substrate (0.5 mmol) and dicyclohexano-18-crown-6 (1.0 mmol) in toluene (20 ml) is agitated with a lump of excess potassium metal (ca 7 mm cube) under nitrogen at ambient temperature for 2-3 hrs. The reaction mixture is then transferred to a round bottom flask containing isopropanol (0.5 ml) for quenching by a long needle through a rubber septum.

Table 1 summarizes the results from the reduction of anisole derivatives. In general, anisoles give the corresponding phenols in high to quantitative yields. The amide and acetal groups are shown to be stable to the reaction conditions (entry 4,5).

Table 1. DEMETHYLATION OF ANISOLE DERIVATIVES

Entry	Substrate		Product	Yield %
1		X=Me	X=H	90
2		X=Me	X=H	quant.
3		X=Me	X=H	96
4		X=Me	X=H	quant.
5		X=Me	X=H	quant.

It is a matter of interest to see the effect of the proton source on the reduction of anisoles with the present system. As is widely recognized, the presence of alcohol is crucial for the conversion of anisoles into the enol ethers or ketones with alkali metal in liquid ammonia[3].

Table 2 clearly shows that addition of isopropanol (ca 7 mol eq.) totally suppresses the demethylation reaction with toluene radical anion and the substrate was recovered unchanged (entry 2). This tells about the difference between the Birch type reducing system and ours.

In tetrahydrofuran without alcohol, namely with the potassium anion as the active species for the reduction, the demethylation proceeds in the same manner as in toluene (entry 3). Nevertheless with the alcohol added, the demethylation goes to some extent (26 %) and an unidentified hydrocarbon is obtained besides the substrate recovered (35 %)(entry 4). Neither enol ether nor carbonyl compound is detected.

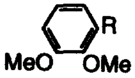
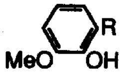
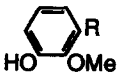
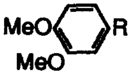
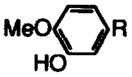
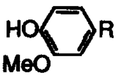
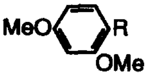
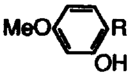
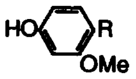
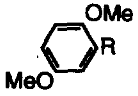
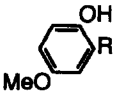
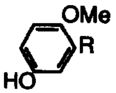
Table 2. EFFECT OF SOLVENT AND PROTON SOURCE
— Reduction of p-Nonylanisole (R= nC_9H_{19})

			Product, Yield %	
Entry	Solvent	H^+ a)		
1	toluene	–	0	99
2	toluene	+	95	0
3	THF	–	0	quant.
4 b)	THF	+	35	26

a) + : with isopropanol ; – : without isopropanol.
b) Accompanied with an unidentified hydrocarbon.

On reduction with toluene radical anion, dimethoxybenzenes give isomers of monomethoxyphenols in high yields (81-96 %)(Table 3). Moderate selectivity in the cleavage of the two methoxy groups is observed (75:25, entry 1; 75:25, entry 2; 84:16, entry 3), with an exception (49:51, entry 4). The major products are generated from the cleavage reaction of the methoxy groups closer to the alkyl chains on the aromatic rings (entry 1, 2 and 3).

Table 3 DEMETHYLATION OF DIMETHOXYBENZENES

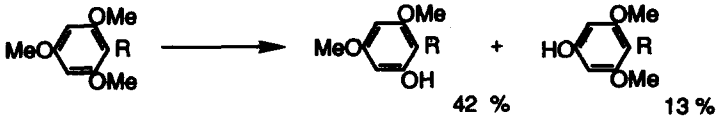
Entry	Substrate ($R=nC_{23}H_{47}$)	Product, Yield, % a)	
1		 62 %	 21 %
2		 61 %	 20 %
3 b)		 78 %	 15 %
4		 47 %	 48 %

a) Isolated yields by silica gel column are shown in entry 1, 2 and 4.
b) Two isomers were inseparable on TLC. Yields were calculated from the combined yields and NMR peak intensities.

The general tendency of preferential cleavage of the closer methoxy group to the alkyl chain is observed also with a trimethoxybenzene derivative. That is , 2,4,6-trimethoxytricosanylbenzene gave 2-hydroxy-4,6-dimethoxy and 4-hydroxy-2,6-dimethoxy derivatives in 42 and 13 % yield, respectively. The ortho methoxy group seems to be more susceptible to the cleavage than the para methoxy group.

Table 4. DEMETHYLATION OF TRIMETHOXYBENZENE DERIVATIVE

(R = $nC_{23}H_{47}$)



Conclusively speaking, the toluene radical anion generated from K metal and toluene with the assistance of crown ether can be an alternative synthetic tool for the demethylation of aromatic methoxy groups[4]. In connection with the present study, the results from the investigation of the reactivities of toluene radical anion as a reducing agent for the hydrogenolysis of alkyl-aryl or aryl-aryl ethers and methylenedioxy compounds will be reported separately.

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