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A CONVENIENT NEW METHOD FOR CONVERTING AROMATIC METHYL ETHERS TO PHENOLS WITH SODIUM CYANIDE-DIMETHYL SULFOXIDE

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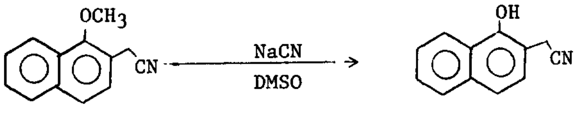
The importance of deblocking aromatic methyl ethers in synthetic organic chemistry is illustrated by the number of methods that have been developed for this purpose.[1-7] We wish to report that sodium cyanide-dimethyl sulfoxide is an excellent reagent for this transformation and is very advantageous for aromatic methoxy nitriles.

In the course of synthetic work on metabolites of DL-588,[8] an antidepressant of clinical interest, we needed a convenient method for demethylating 1-methoxy-2-naphthaleneacetonitrile (1). Treatment of this nitrile with lithium iodide in collidine according to the general procedure of Harrison[5] for the cleavage of aromatic methyl ethers gave a multi-component mixture as judged by thin layer chromatography (tlc). At this point several methods for deblocking aromatic methyl ethers were evaluated. It was felt that classical acidic deblocking reagents[2] would prove unacceptable because of the cyano group in the molecule. It has been reported[9] that sodium cyanide-dimethyl sulfoxide deblocks certain methyl and ethyl esters which undergo simultaneous decarboxylation. The postulate that sodium cyanide-dimethyl sulfoxide would likewise deblock aromatic methyl ethers was verified when 1 was treated with a five-fold excess of sodium cyanide in dimethyl sulfoxide at 180° for five hours. Under these conditions, 1-hydroxy-2-naphthaleneacetonitrile (2) was isolated in 79% yield. This deblocking procedure proved to be very advantageous for other aromatic methoxy nitriles as shown by examples 2-4 in the Table.



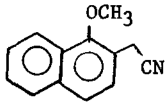
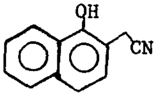
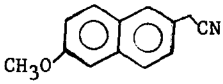
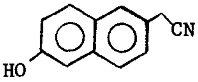
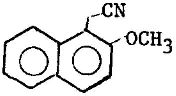
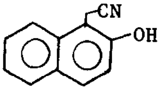
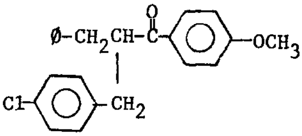
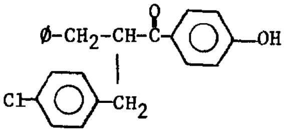
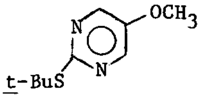
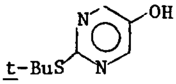
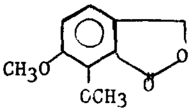
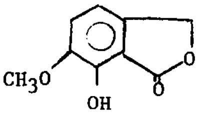
1 2

The generality of this procedure was investigated and the results are presented in the Table. As can be seen, yields are generally high. It should be noted that the reaction proceeds in good yield for the heterocycle, 2-*tert*-butylthio-5-methoxypyrimidine (example 9) and 6-methoxyquinoline (example 8), whereas the reaction does not work for the electron-rich indole in example 14. The deblocking procedure failed to proceed cleanly with nitro-substituted aromatics as would be expected because of the occurrence of the von Richter reaction. However, the reaction proved very useful for deblocking aromatic methoxy ethers containing ketones, amides and carboxylic acids. In example 6, it was found that boron tribromide failed to cleave the ether even under forcing conditions.

Substitution of dimethylformamide for dimethyl sulfoxide led to unreacted starting material with 2-methoxynaphthalene, even after refluxing with excess sodium cyanide for 48 hours. In 1933, Rodionow, *et al.*[10] reported that the fusion of potassium cyanide with meconin (example 13) for three hours at 180-185° led to a 45-47% yield of the 7-monodemethylated product along with crude unreacted starting material. By our procedure monodemethylation occurred quantitatively by tlc in one hour at 125° (bath temp.) and a 76% yield of crystalline product was isolated.[11]

In a typical experiment, 1-methoxy-2-naphthaleneacetonitrile (6.0 g, 30 mmol) and sodium cyanide (7.5 g 150 mmol) were added to A.R. DMSO (40 ml) and heated at 180° (bath temp.) under nitrogen. The reaction was followed by tlc and after 5 hours poured into ice water.

TABLE: Deblocking of Aromatic Methyl Ethers with Sodium Cyanide-DMSO

Example	Substrate	Phenol	Reaction Time/Temp, °C	Isolated [a] Yield %
1			5 hr/180	79
2			24 hr/170	69
3			6 hr/160	66
4	3,4-dimethoxybenzonitrile	3,4-dihydroxybenzontrile	24 hr/180	44
5	4-methoxyacetophenone	4-hydroxyacetophenone	16 hr/165	81
6			14 hr/165	81
7	4-methoxybenzamide	4-hydroxybenzamide[b]	24 hr/165	91
8	6-methoxyquinoline	6-hydroxyquinoline	48 hr/165	82
9			3.5 hr/180	83
10	2-methoxynaphthalene	2-naphthol	24 hr/180	77
11	1-methoxynaphthalene	1-naphthol	5 hr/180	77
12	2-methoxybenzoic acid	salicylic acid	8 hr/180	89
13			1 hr/125	76
14	5-methoxyindole	-	48 hr/180	No Rxn

a. Known products were identified by comparison of mp and spectral data with authentic samples. New compounds had satisfactory CHN analyses. [b] Isolated by continuous liquid-liquid extraction with ether.

The solution was acidified with 6N HCl (caution: HCN evolution). The resulting precipitate was collected by filtration,[12] washed with water and dried (5.2 g, 95%). Recrystallization from benzene gave white crystals in two crops (4.4 g 79%); mp 126-8°.

ACKNOWLEDGEMENT

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11) W. M. Rodionow, *et al*. in ref. 10 report a small unspecified quantity of 6-monodemethylated product from 60 g of meconin. We did not isolate any of this isomer.

12) When the product does not precipitate, extraction with ether or ethyl acetate proved satisfactory. Ethyl acetate did not extract DMSO from the water layer.

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