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Dealkylation of Alkyl and Aryl Ethers with $AlCl_3$ - NaI in the Absence of Solvent

Mehran Ghiaci [a] & Jila Asghari [a]

[a] Department of Chemistry, Isfahan University of Technology, Isfahan, 84156, Iran

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Dealkylation of Alkyl and Aryl Ethers with $AlCl_3$ - NaI in the Absence of Solvent

Mehran Ghiaci* and Jila Asghari

Department of Chemistry,
Isfahan University of Technology,
Isfahan, 84156, Iran.

A facile synthetic procedure, for dealkylation of alkyl and aryl ethers with $AlCl_3$ - NaI in the absence of solvent is developed. We have been able to deprotect different methyl ethers in excellent yields.

The dealkylation of ethers provides an important method in the field of natural products and in the synthesis of polyfunctional molecules. A number of review articles concerning dealkylation of ethers have already been appeared.[1-3] The classical methods to hydrolyze ethers involve various protic acids under drastic conditions, eg. the use of boiling concentrated hydroiodic acid, or of a large excess of concentrated hydrobromic acid/ hydrochloric acid in acetic acid or acetic anhydride at reflux. A useful modification is the use of hydrobromic acid in the presence of phase transfer catalyst.[4] Boron tribromide is regarded as one of the reagents of choice for dealkylation of ethers.[5-8] Some of the other reagents of choice are: $BX_3/(CH_3)_2S$[9], BBr_3-NaI-15-crown-5[10],

$(CH_3)_2BBr$[11], BI_3 - N,N-diethylaniline[12], sodium salt of N-methylaniline[13], NaSEt-DMF[14], sodium benzylselenoate.[15]

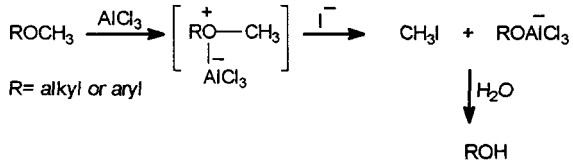
Recently, while exploring the scope and utility of solid-phase condition in organic synthesis, we observed that the no solvent conditions are also effective in some cases.[17] Although the cleavage reagent Lewis acid-NaI is aknown cleavage reagent, herein we report our results on a new and convenient procedure to dealkylation of alkyl and aryl ethers.

In order to examine the Lewis acid property of $AlCl_3$ in the solid state, anisole was mixed with $AlCl_3$-NaI (1:1) in a ratio of 1:2 in an agate mortor and heating the mixture to 70-80°C for 15 min. A small amount of the mass was simply quenched by the addition of an aqueous solution of 5% $Na_2S_2O_3$. After the extraction with ether followed by drying over $MgSO_4$, monitoring the ether extract by TLC showed only one spot that was characterised as phenol.

The cleavage of cyclic ethers through the employment of the reagent system of NaI and acyl chloride has been reported as an efficient method.[18] We report here that THF was cleaved by $AlCl_3$-NaI (1:1) at 70°C in 45 min to give 4-iodobutanol quantitatively.

Adopting the above method, various alkyl and aryl ethers have been deprotected to the corresponding alcohols or phenols in excellent yields, and the method is much simpler than all the methods known so far for its simplicity and high conversion. The list of different alkyl and aryl ethers that have been dealkylated are given in Table 1. This method is not useful for converting cholestryl methyl ether to cholesterol (entry 16), and in the case of 1-methyl naphthalene, which sublime in the reaction condition (entry 18).

A practical disadvantage of this method could be the liberation of small amount of iodine that would harm a sensitive functional group (entry 20).



In a most convincing demonstration of this dealkylation, the possibility of formation of the adduct **1** is not ruled out that in the next step iodide ion as the nucleophile attacks to the less hindered site of this adduct to generate methyl iodide and the salt **2**.

Solvents were used directly as obtained from the suppliers. Reagents were employed as purchased from Fluka or Merck. Thin layer chromatography (TLC) was carried out using glass sheets precoated with silica gel 60F. Melting points were determined on an Electrothermal Galler Kamp apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (60 MHz). IR spectra were obtained using a Shimatzo IR-435 spectrometer. The purity of the products were determined by GC and ^{1}H NMR spectroscopy, and comparing with authentic samples.

General Procedure.- A mixture of alkyl or aryl ether (1 equivalent), $AlCl_3$ (2 equivalent) and NaI (2 equivalent) was thoroughly ground in an agate mortor for a few minutes. The softened mass was ground by heating (70-80°C) for 1-3 hrs. The reaction mixture was diluted with the aqueous solution of $Na_2S_2O_3$ (5%) and extracted with ether. The ether

Table 1. Dealkylation of Alkyl or Aryl Ethers to corresponding Alcohol or Phenol.

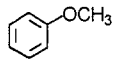
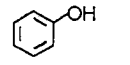
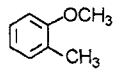
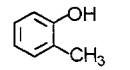
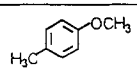
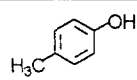
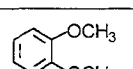
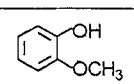
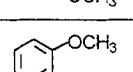
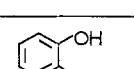
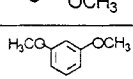
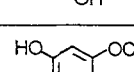
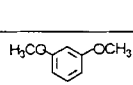
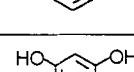
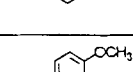
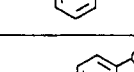
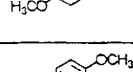
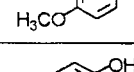
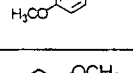
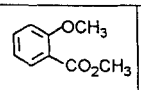
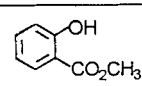
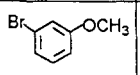
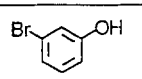
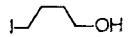
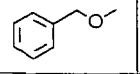
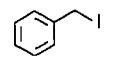
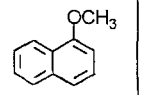
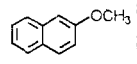
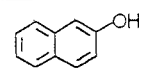
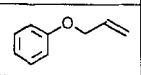
Entry	Substrate	Time (hrs)	$AlCl_3$:NaI:)	Temp. (°C)	Products	Yield based on TLC (%)[a]
1	$(n\text{-}C_4H_9)_2O$	15 min	2:2:1	70-80	$n\text{-}C_4H_9OH$	100 (95)
2	$n\text{-}C_{16}H_{33}OCH_3$	15 min	2:2:1	70-80	$n\text{-}C_{16}H_{33}OH$	100 (97)
3		15 min	2:2:1	70-80		100 (98)
4		3.5	2:2:1	70-80		100 (97)
5		2	2:2:1	70-80		100 (97)
6		8	2:2:1	70-80		- (65)
7		24	2:2:1	70-80		100 (95)
8		4	2:2:1	70-80		- (70)
9		24	2:2:1	70-80		100 (95)
10		2	2:2:1	70-80		100 (96)
11		2 weeks	2:2:1	25		100 (95)
12		24	2:2:1	70-80	no reaction	-

Table 1. Continued.

13		2	2:2:1	70-80		100 (95)
14		3	2:2:1	70-80		100 (96)
15		45 min	2:2:1	70-80		100 (90)
16	$C_{28}H_{46}OCH_3$	4	2:2:1	70-80	no reaction	-
17		1	2:2:1	70-80		100 (60)
18		3	2:2:1	70-80	-	-
19		3	2:2:1	70-80		- (20)
20		1	2:2:1	70-80	mixture of products	-

a) numbers in the parentheses are isolated yields

extract was dried over $MgSO_4$. The solvent was removed in vacuum to give the product.

Methylsalicylate.- A mixture of methyl 2-methoxybenzoate (1.66 g, 10 mmol), anhydrous aluminium chloride (2.66 g, 20 mmol) and sodium iodide (2.89 g, 20 mmol) was thoroughly ground in an agate mortor for a few minutes. The reaction mixture was ground by heating (70-80°C) for 2hr. The reaction mixture was diluted with 20 mL of aqueous $Na_2S_2O_3$ (5%) and extracted with 2x20 mL Et_2O. After drying the organic layer over anhydrous $MgSO_4$, the solvent was removed on a rotary evaporator, providing 1.45 g, 95% of methyl salicylate.

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