Pergamon

Tetrahedron Letters, Vol. 38, No. 50, pp. 8749-8752, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10342-2

Chemoselective Aryl Alkyl Ether Cleavage by Thiophenolate Anion Through its *In Situ* Generation in Catalytic Amount[†]

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Abstract *: Catalytically in situ generated alkali metal thiophenoxide in NMP (1-methyl-2-pyrrolidinone) chemoselectively cleaves aryl alkyl ethers in high yields.*
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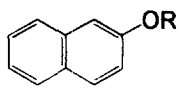
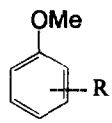
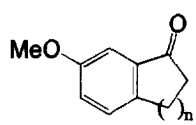
Ether cleavage is a versatile transformation in organic chemistry considering its importance for the deprotection of hydroxy groups and its involvement in the manufacture of a number of pharmaceuticals, drugs and other fine chemicals. A variety of nucleophilic (both under acidic and alkaline conditions), reductive and oxidative methods for the cleavage of aryl alkyl ethers are available in the literature[1] but these are not always satisfactory for molecules having sensitive functionalities. Thus there is continuous interest in developing new reagents which dealkylate ethers chemoselectively. Since the introduction by Feutrill and Mirrington[2] alkaline thiolates are the commonly employed reagents for this purpose[3]. Hwu *et al*[4] later introduced sodium trimethylsilanethiolate (Me_3SiSNa) for aryl alkyl ether cleavage. In all these protocols the effective thiolate reagent is generated in stoichiometric amount or more. Stoichiometric use of thiolate is often associated with the nucleophilic displacement of nitro group[5] and halogen[6] rather than the usual ether cleavage. Furthermore thiol anions are not only powerful nucleophiles but also strong reducing agents due to RS^- to $RS^{\cdot}$ transformation[7]. Thus the chance of radical process is always high when carrying out reaction of thiol anions with nitro compounds[4b,c] and α,β-unsaturated ketones[8]. Moreover these protocols employ excess of the reagent (1.5 - 8 eq. in case of alkane thiolates and 2 - 3.5 eq. in case of Me_3SiSNa) and require longer reaction period (0.5 - 3.4 h at 80 - 120 ^{0}C for alkane thiolates and 24 h at 170 ^{0}C for Me_3SiSNa).

In this communication we report an efficient method for chemoselective cleavage of aryl alkyl ethers by thiophenol in presence of catalytic amount of K_2CO_3 through *in situ* catalytic generation of the thiophenolate anion as nucleophile. The reaction takes place under virtually neutral condition. The reaction is carried out in dry NMP at 190^{0}C for 10 - 30 min. (see Table) with decreased product yields at lower temperature. The reaction proceeds equally well with hexamethylphosphoramide as solvent but other dipolar aprotic solvents like dimethylformamide, N,N-dimethylacetamide, formamide, dimethylsulfoxide, acetonitrile and morpholine are not effective. Although most of the reactions have been carried out using K_2CO_3 as the catalyst the ether cleavage proceeds smoothly with alkali metal carbonates, bicarbonates and hydroxides in general. The presence of the catalyst is essential since no ether cleavage is detected in its absence. In a typical experiment the magenetically stirred mixture of the ether (5 mmol), PhSH (5 mmol) and K_2CO_3 (2 - 5 mol %) in dry NMP (2.5 ml) was heated at 190^{0}C under N_2 for the requisite period of time (see Table). The cold reaction mixture was made alkaline with 5% aq. NaOH and extracted with Et_2O to remove the neutral components. The aqueous part was acidified with dil. HCl and extracted with Et_2O to afford the desired phenol which may be purified further through crystallisation or chromatography (silica gel, eluent Et_2O - hexane). The unreacted starting material may be recycled without purification increasing the yield to virtually quantitative in most of the cases. Methyl ethers are relatively more facile to be cleaved than the corresponding benzyl ether which in turn is more reactive than the ethyl ether. Substrates containing electron wthdrawing group (entries 6,8,9,11,13) react at a faster rate as is reflected by the shorter reaction time in accord with the earlier observations[3c,9]. The reactions with *p*-nitro- and *p*-chloro anisoles (entries 5,6) need special attention because stoichiometric use of thiolates are associated with the replacement of the nitro group and halogen rather than the usual ether cleavage. Use of Me_3SiSNa on the other hand converts *p*-nitrophenol to *p*-amino phenol as a result of concommitant reduction of the nitro group[4b]. Methoxystilbene (entry 10) and ethers containing α,β-unsaturated carbonyl function (entries 12,13) are smoothly cleaved without competitive addition to styrenoid double bond[10] or Michael addition[11].

It occured to us that the use of dipolar aprotic solvent ought to be more expedient[12] for this reaction to proceed *via* S_N2 attack on the alkyl group as well as in making the proton exchange between the generated aryloxide and PhSH in a counterattack mode[13] because of better solvation of PhS^- compared to that of ArO^-[14]. Lack of proton exchange in case of thioalkanes (e.g. EtSH), due to their weak acidic character, with ArO^- make them ineffective for the ether cleavage under this condition.

In summary the reported procedure constitutes an excellent method for the cleavage of aryl alkyl ethers under virtually neutral condition without affecting other functionality present in the molecule.

Table 1. Chemoselective Cleavage of Aryl Alkyl Ethers by Catalytically Generated PhS^-

Entry	Ether	Time (min)	Yield (%)
			
1	R = Me	30	97
2	OBz	30	76
3	OEt	30	60
			
4	R = 2-NH_2	30	80
5	4-Cl	30	70
6	4-NO_2	10	68
7	3-CHO	30	85
8	4-CHO	10	90
9	4-$COCH_3$	10	85
10	4-CH=CHPh(*E*)	30	80
11	4-COCOPh	10	85
12	4-CH=CHCOPh(*E*)	30	90
13	4-COCH=CHPh(*E*)	10	83
			
14	n = 1	30	75
15	2	30	90

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! Dedicated to Prof. U. R. Ghatak.

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13. The *in situ* catalytic generation of thiophenolate anion may be realised as follow :

$$PhSH \xrightarrow{K_2CO_3} PhS^-K^+ \xrightarrow{ROAr} PhSR + ArO^-K^+ \quad \text{--- ---} \quad \text{(i)}$$

$$ArO^-K^+ + PhSH \rightleftharpoons ArOH + PhS^-K^+ \quad \text{--- ---} \quad \text{(ii)}$$

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(*Received in UK* 12 *August* 1997; *revised* 2 *September* 1997; *accepted* 10 *October* 1997)