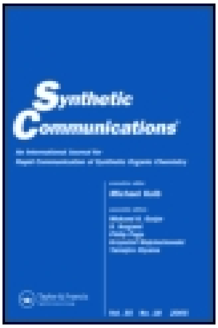

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SELECTIVE CLEAVAGE OF ARYL METHYL ETHER MOIETY OF ARYLOXY ARYL METHYL ETHER BY 48% HBr/TETRA-n-BUTYLPHOSPHONIUM BROMIDE

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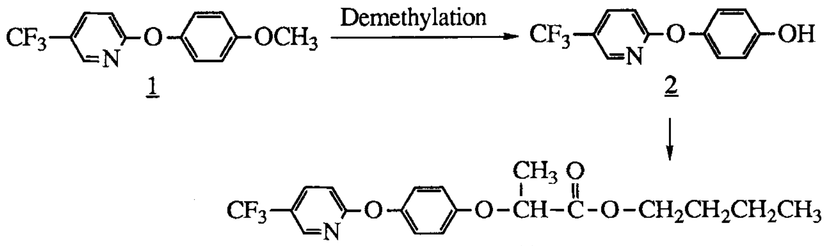
ABSTRACT: Aryl methyl ether moiety in the molecule containing aryl aryl ether part along with aryl methyl ether part is selectively cleaved to give the desired substituted phenol in excellent yield by using 48% HBr in the presence of tetra-n-butylphosphonium bromide

In connection with our work on the synthesis of diaryl ethers like Fluazifop-butyl (3) in agricultural applications as herbicides[1], we required an



1

2

Fluazifop-butyl

3

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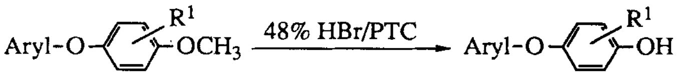
Table 1. Demethylation of the compound (1) with various reagents.



Entry	Reagent	Reaction Temp. (0 °C)	Reaction Time (hr)	Isolated Yield (%)
1	$(CH_3)_3SiCl$, NaI in CH_3CN	80	20	10
2	BBr_3 in CH_2Cl_2	40	8	20
3	48% HBr in AcOH	110	18	35
4	48% HBr, $(n\text{-}Bu)_4PBr$ in AcOH	110	18	65
5	36% HCl, $(n\text{-}Bu)_4PBr$	105	48	11
6	48% HBr, $(n\text{-}Bu)_4PBr$	110	6	94

efficient method for selective cleavage of aryl methyl ether moiety of aryloxy aryl methyl ether (1).

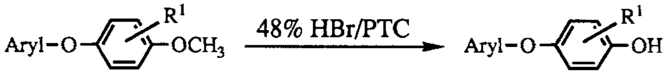
The cleavage of ethers has been considered a versatile reaction in organic synthesis and was comprehensively reviewed.[2] Literature survey indicates that many reagents are capable of cleaving ethers. The selective cleavage of aryl methyl ether part without affecting aryl aryl ether part, however, has not been studied and now we wish to report a useful synthetic method for the selective cleavage of the aryl methyl ether moiety in the presence of aryl aryl ether part. Several known procedures for the demethylation of the compound 1 with various reagents were examined and their results are summarized in Table 1. Thus, the precedent examples that trimethylsilyl iodide[3] and boron tribromide[4] cleave aryl methyl ethers under mild condition prompted us to consider these reagents for the selective cleavage of the aryl alkyl ether (1), but the attempts were not satisfactory (entry 1, 2).

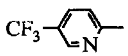
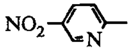
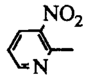
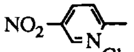
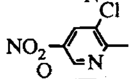
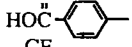
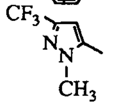
The next experiment was to utilize 48% hydorbromic acid in acetic acid, known as the common method for the cleavage of ethers[2c], but the result was not high yielding process, either (entry 3). Rolla and co-workers[5] have introduced the convenient reagent, 48% hydrobromic acid in the presence of phase transfer catalyst (PTC) for the cleavage of simple dialkyl and aryl alkyl ethers, but it was not studied for the selective cleavage of ethers containing two ether parts. Encouraged by the reasonably good result when the hydrobromic acid with PTC was utilized (entry 4), we paid attention to the 48% HBr/PTC system. Indeed, the desired product 2 was obtained in excellent yield by treatment of the compound 1 with 48% hydrobromic acid in the presence of tetra-n-butylphosphonium bromide (entry 6). In a run which is not included in Table 1, other phase transfer reagents (for example, tetraphenyl phosphoniumbromide, hexadecyl tributylphosphonium bromide) also revealed good results.

To extend the synthetic potential of the 48% HBr/PTC system for the selective cleavage for the other diaryl ethers, we investigated several other compounds as summarized in Table 2. The results reveal that the use of the above reagent enables the compounds with pyrazolyl, phenyl and pyridinyl group as aryl groups to be cleaved selectively to give the corresponding substituted phenols in very good yield. When a nitro group was present in pyridine ring, the lower yield of the product indicates that it is more susceptible to cleavage of the aryl aryl part because of the more electron-withdrawing ability of the nitro group.

In conclusion, although the scope of present reaction has not been thoroughly investigated at this moment, this selective cleavage of

Table 2. Demethylation of aroyl methyl ethers with 48% $HBr(n\text{-}Bu)_4PBr$ at 100 °C



Entry	Aryl	R^1	Reaction Time(hr)	Isolated yield (%)
1		H	6	94
2		H	2	81
3		H	5	80
4		H	11	98
5		H	11	98
6		N	9	90
7		o-NO_2	11	84

aryl methyl ether moiety in the presence of aryl aryl ether part by utilizing 48% hydrobromic acid with a phase transfer catalyst, like tetra-n-butylphosphonium bromide, is believed to provide a useful synthetic potential.

EXPERIMENTAL : The typical experimental procedure is exemplified by the following preparation of* 2-(4-hydroxyphenoxy)-5-trifluoromethylpyridine (2); 2-(4-methoxyphenoxy)-5-trifluoromethyl pyridine (1, 1g, 3.7 mmol), tetra-n-butylphosphonium bromide (0.126 g, 0.37 mmol), and 48% hydrobromic acid (4.2 ml) were heated at 100 °C for 6 hrs. Water (10 ml) was added to the reaction mixture and the mixture was extracted with ethyl acetate (2 x 10 ml). The combined ethyl acetate extracts were washed with brine (10 ml), dried over $MgSO_4$ and then concentrated in vacuo. Purification by flask column chromatography eluting with 20% EtOAc/hexane gave the title compound (0.87 g, 94% yield).

^{1}H NMR ($CDCl_3$) : δ 6.60-7.30(m, 6H), 7.85(q, 1H), 8.4(s, 1H).

MS(70eV) : 255(M^+)

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