SHORT PAPER

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Protection of phenols as *t*-butyl ethers under mild conditions[†‡]

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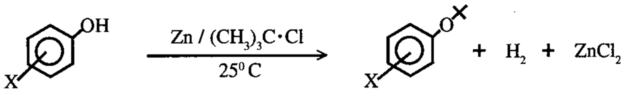
Zinc mediated selective O-*y*-butylation of phenols has been carried out in good to excellent yields under mild conditions. No trace of C-*t*-butylation was observed.

A phenolic hydroxyl group is present in many compounds of biological interest (*e.g.* tyrosine, thyroxine, estrone, codeine, terramycin and catechol). Protection of phenols is often required. Unfortunately phenols react readily either at oxygen or carbon (or both) with oxidizing agents and electrophiles, and as the phenoxide ion with even mild alkylating and actylating agents.[1] A phenol, link an alcohol, can be protected either as an ether or ester. Aromatic ethers and esters are more readily cleaved than the corresponding aliphatic compounds.

Simple *n*-alkyl ethers, formed in basic solution from a phenol and a halide or sulfate are very stable. Formerly, drastic conditions (*e.g.* refluxing HBr) were required for their cleavage.[1] More recently, several types of ether have been investigated for the protection of phenols, generally involving milder methods for deblocking (*e.g. via* nucleophilic displacement, hydrogenolysis of benzyl ethers and mild acid hydrolysis of acetal-type ethers[1]). An aryl *t*-butyl ether can be prepared either by acid-catalysed[2] or, more commonly, base-catalysed[3] reactions. Therefore, aryl *t*-butyl ethers are stable towards acidic and basic conditions and making the *t*-butyl group an important protecting group compared with other protecting groups for phenols. We now report for the first time a rapid and efficient zinc-mediated method for the protection of phenols as *t*-butyl ethers under mild conditions (Scheme 1).



Scheme 1

Various substituted phenols are converted into the corresponding O-*t*-butyl ethers using zinc dust and an excess of *t*-butyl chloride. The results are summarized in Table 1. It is interesting to note that the *t*-butoxy group tolerates the acidic conditions generated by the by-products. It is worth commenting that *t*-butylation took place selectively on the oxygen atom of phenol and not the ring carbon atom under these reaction conditions. Further more, *t*-butylation of the phenolic-OH is carried out in the presence of a benzylic hydroxy group (entry 9), aromatic and aliphatic primary amino groups (entries 10,14), a carboxy group (entry 11), an aldehyde group (entries 12,13) and a thiol group (entries 15,16). Therefore, this method is suitable for selective O-*t*-butylation of phenols under mild conditions.

Attempts have been to study whether zinc or zinc chloride is the actual catalyst acting for the *t*-butylation of phenols. When a mixture of 4-chlorophenol, 4-nitrophenol or 4-methylphenol, zinc chloride and excess of *t*-butyl chloride was stirred at 25 °C for 6 h, only 25–30% of corresponding *t*-butylated phenol was formed as a product of 65–70% of starting material was recovered. This indicated that zinc and not zinc chloride acted as the effective catalyst for the reaction.

Deprotection of 4-chlorophenyl *t*-butyl ether, 4-nitrophenyl *t*-butyl ether and 4-fluorophenyl *t*-butyl ether as 25 °C by the reported method[2] gave the corresponding phenols in 50 – 60% yields and required a very long time (15–20 H). Work on the development of a mild and fast method for deprotection of aryl *t*-butyl ethers is in progress.

Experimental

All chemicals were of analytical grade. IR and ^{1}HNMR spectra were recorded on a Bomem MB 104 FTIR spectrometer and a Perkin Elmer 90 MHz NMR instruments, respectively.

General procedure: A mixture of phenol (5 mmol), Zn dust (5 mmol) and *t*-butyl chloride (10 ml) was stirred at 25 °C for 1 h. After completion of the reaction, the mixture was filtered and the residue washed with ether (3×5 cm^3). To this filtrate 10% NaOH (20 cm^3) was added and the products extracted with ether (3×5 cm^3). The ether layer was dried with anhydrous sodium sulfate and the removal of solvent under reduced pressure gave the products in good yield (65–97%). When necessary some products were purified by column chromatography.

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References

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3 H. Masada and Y. Oshi, *Chem. Lett*. 1978, 57.
4 (a) *Dictionary of Organic Compounds,* 6th Edn. Chapman and Hall, London 1995; (b) F. Camps. J. Coll and J.M. Moreto, *Synthesis*, 1982, 146.

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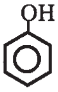
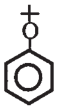
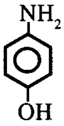
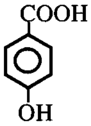
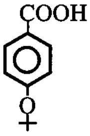
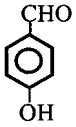
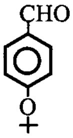
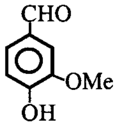
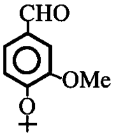
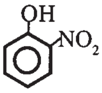
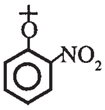
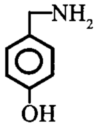
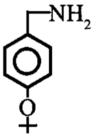
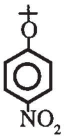
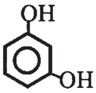
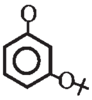
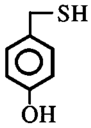
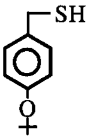
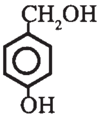
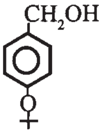
[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

[‡] This paper is dedicated to Dr J.M. Waghmare, Founder Vice-Chancellor of SRTM University, Nanded, on the occasion of his 65th birthday.

Table 1 Protection of phenols as *t*-butyl ethers under mild conditions

Entry	Phenol	Product[4]	Yield[a,b] (%)	Entry	Phenol	Product[4]	Yield[a,b] (%)
1			65	10			78
2			93	11			82
3			88	12			72
4			83	13			78
5			80	14			87
6			87	15			91
7			94	16			93
8			85				
9			82				

[a]Yields are of isolated products. [b]Products were characterized by either their physical constance[4], IR, ^1H NMR and comparison with authentic samples.