A Simple, Effective and Highly Selective Cleavage of 3-Methylbut-2-enyl (prenyl) Ethers Using *p*-Toluenesulfonic Acid

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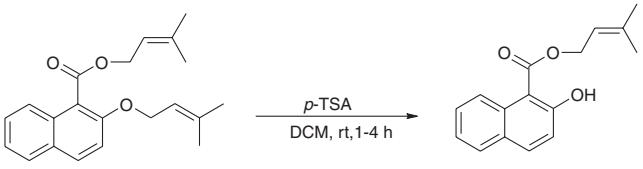
A highly selective cleavage of prenyl ethers has been achieved in high yields using *p*-toluenesulfonic acid under extremely mild conditions. This method is compatible with a wide variety of functional groups such as methyl, benzyl, allyl ethers and benzyl, methyl, prenyl esters present in the molecules.

Deprotection of the functional group[1] is one of the most important and widely carried out synthetic transformations in preparative organic chemistry. In the synthesis of multifunctional molecules often the problem arises that a given functional group has to be deprotected in the presence of others. Of many functional groups requiring synthetic manipulation involving deprotection, one encounters prenylethers due to the ease of formation, removal and their stability to a wide range of reagents and reaction conditions.[2] Recently a few methods have been developed for the deprotection of prenyl ethers under different conditions which include *n*-Bu_4NI-$TiCl_4$,[3] I_2,[4] $Sc(OTf)_3$[5] and DDQ.[6]

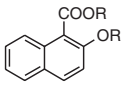
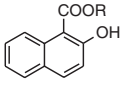
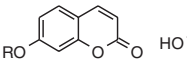
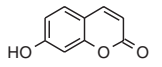
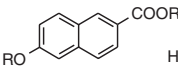
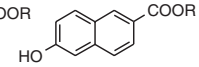
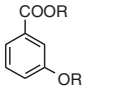
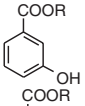
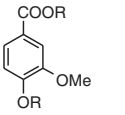
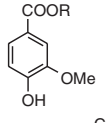
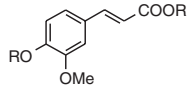
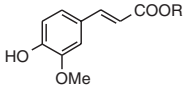
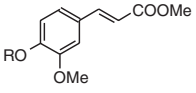
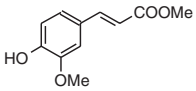
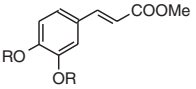
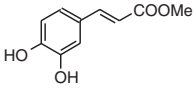
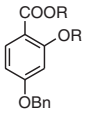
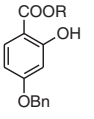
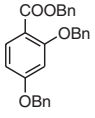
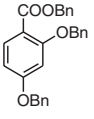
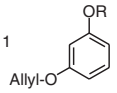
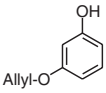
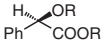
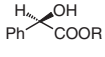
However, many of the existing methods suffer from drawbacks such as lack of selectivity, unsatisfactory yields, and usage of costly and toxic reagents. Also, the yields in respect of the substrates having carbonyl group in position para to the ethers are low. These limitations prompted us to investigate further new and convenient methodology for the selective cleavage of prenyl ethers over a wide range of functional groups. During the development of new methods for the deprotection of prenyl ethers,[7] we observed that *p*-Toluenesulfonic acid can smoothly and rapidly cleave prenyl ethers within 1-4 h with high chemoselectivity.

In this communication, we wish to report that *p*-TSA is an efficient catalyst[8] for the deprotection of prenyl ethers (Scheme 1). The cleavage was effected at room temperature in dichloromethane. The added advantage of this method includes simple reaction conditions, several ether and ester functionalities remain intact under these reaction conditions. It is note worthy that the yields of the deprotected alcohols where in there is a carbonyl functionality is in position para with respect to the ethers are high (Entry 5). The treatment of prenyl ether of umbelliferone (Entry 2) with *p*-TSA in dichloromethane under mild conditions gave the corresponding phenol (umbelliferone) in 98% yield in 1 h.[9] In order to establish the chemoselectivity of the method, we have examined the deprotection of ethers in presence of several ethereal and ester functional groups and these results were tabulated in Table. As can be seen in table deprotection proceeded very cleanly in high yields in all cases.



Scheme 1.

Table 1. Selective cleavage of prenyl ethers using *p*-TSA

Entry	substrate [A]	Product [B]	Time	% Yield [b]
1			1.5	96
2			1	98
3			1.5	90
4			2	80
5			1.5	86
6			2.5	92
7			2	90
8			4	80
9			2.5	88
10			---	
11			1.5	70
12			3	76

R = 3-Methylbut-2-enyl, [b]Isolated yields.

It is noteworthy that allyl protected alcohols (Entry 11) were unreacted in our reaction conditions even after 4 hours, pointing to the great potential use of this method in selectively deprotecting the prenyl (2-methylbut-2-enyl) ethers.

In conclusion, *p*-TSA was demonstrated to be a simple and convenient deprotecting agent for prenyl group. The advantages of the method are (i) inexpensive nature of the reagent, (ii) coreagents are not needed, (iii) extremely simple experimental procedures (anhydrous, inert (or) dry atmosphere conditions are not required), (iv) high selectivity towards the deprotection of prenyl ethers and high yields. These advantages are very useful in complex multistep syntheses, which require sequential protection and deprotection of various functionalities.

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References and Notes

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9 Typical experimental procedure: To a solution of prenyl ether (0.1 g, 0.3 mmol) in DCM (5 mL), *p*-TSA (0.058 g, 0.3 mmol) was added and stirred at room temperature. Stirring was continued for appropriate time (Table 1) by monitoring the reaction with TLC. After completion, the reaction was quenched by adding water (5 mL). The aqueous layer was extracted with DCM (10 mL) and the organic layer was separated and dried over anhydrous Na_2SO_4. After removal of the solvent the crude product was purified by column chromatography (60-120 mesh). The structures of phenols thus obtained were confirmed by ^{1}H NMR, IR and mass spectral analysis. Compound (**6A**): ^{1}H NMR ($CDCl_3$, 200 MHz, δ): 1.78 (br s, 12H, 4 × CH_3), 3.84 (s, 3H, OMe), 4.58 (d, 2H, $J = 7$ Hz, $\underline{CH_2}$-CH), 4.64 (d, 2H, $J = 7$ Hz, $\underline{CH_2}$-CH), 5.38 (br t, 1H, $J = 7$ Hz, CH_2-$\underline{CH}$), 5.50 (br t, 1H, $J = 7$ Hz, CH_2-$\underline{CH}$), 6.24 (d, 1H, $J = 12$ Hz, olefinic), 6.80 (d, 1H, $J = 8$ Hz), 7.00 (s, 1H), 7.02 (d, 1H, $J = 8$ Hz), 7.58 (d, 1H, $J = 12$ Hz, olefinic). Mass: m/z 330. Compound (**6B**): ^{1}H NMR ($CDCl_3$, 200 MHz, δ): 1.78 (br s, 6H, 2 × CH_3), 3.90 (s, 3H, OMe), 4.64 (d, 2H, $J = 7$ Hz, $\underline{CH_2}$-CH), 5.40 (br t, $J = 7$ Hz, CH_2-$\underline{CH}$), 6.26 (d, 1H, $J = 12$ Hz, olefinic), 6.98 (d, 1H, $J = 8$ Hz), 7.02 (s, 1H), 7.04 (d, 1H, $J = 8$ Hz), 7.64 (d, 1H, $J = 12$ Hz, olefinic). Mass: m/z 262. Compound (**7A**): ^{1}H NMR ($CDCl_3$, 200 MHz, δ): 1.78 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 3.78 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.58 (d, 2H, $J = 7$ Hz, $\underline{CH_2}$-CH), 5.46 (t, 1H, $J = 7$ Hz), CH_2-$\underline{CH}$), 6.24 (d, 1H, $J = 12$ Hz, olefinic), 6.80 (d, 1H, $J = 8$ Hz), 7.02 (s, 1H), 7.04 (d, 1H, $J = 8$ Hz), 7.58 (d, 1H, $J = 12$ Hz, olefinic). Mass: m/z 276. Compound (**7B**): ^{1}H NMR ($CDCl_3$, 200 MHz, δ): 3.78 (s, 3H, OMe), 3.86 (s, 3H, OMe), 6.24 (d, 1H, $J = 12$ Hz, olefinic), 6.86 (d, 1H, $J = 8$ Hz), 7.00 (s, 1H), 7.04 (d, 1H, $J = 8$ Hz), 7.60 (d, 1H, $J = 12$ Hz, olefinic). Mass: m/z 208. IICT Communication No: 030509.

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