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Comparative Studies of the Deprotection of Various Acid Sensitive Protecting Groups with Pyridinium *p*-Toluenesulphonate

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Abstract: Selective deprotection of the various acid sensitive protecting groups e.g. ethoxyethyl (EE) t-butyl dimethylsilyl (TBDMS) and t-butoxycarbonyl (BOC) groups with the inexpensive reagent pyridinium *p*-toulenesulphonate (PPTS), under mild conditions is reported.

Pyridinium *p*-toluenesulphonate (PPTS), an inexpensive and easily prepared reagent, is widely used to deprotect ethoxyethyl (EE), and tetrahydropyranyl (THP) groups[1] under mild conditions. However, it has rarely been used to deprotect other acid sensitive protecting groups e.g. *t*-butyldimethylsilyl (TBDMS) and *t*-butoxycarbonyl (BOC) groups. We required selective deprotection of an EE group in the presence of a TBDMS group during the synthesis of some neurotensin mimetics.[2] We observed that while PPTS in MeOH at room temperature was not selective, a significant degree of selectivity could be achieved by using a less polar solvent, such as *n*-butanol. This prompted us to embark on a study of the use of the PPTS reagent for the selective removal of an EE group in the presence of a TBDMS, and that of a TBDMS in the presence of a BOC.

As a first target, we explored the possibility of achieving selectivity for the deprotection of an EE in the presence of a TBDMS group. Thus, the bis-protected diol **1**[3,4] was reacted with PPTS in various solvents (Figure 1, Eqs. 1 and 2). The result shown in Figure 1 indicates that by changing the polarity of the solvent, selective deprotection of the EE group in the presence of TBDMS can be smoothly achieved.[5] It is to be noted, however, that longer reacion times caused the removal of both the groups.

To assess the effect of PPTS on the presence of EE and TBDMS groups on the primary vs secondary hydroxyl groups, the fully protected 1,2-diol **2** was reacted with PPTS over a period of one hour at room temperature (Figure 1, Eq.3). The PPTS only removed the EE group and spared the TBDMS group even in MeOH thereby providing a way to selectively deblock an EE group from hindered OH group.

t-Butoxycarbonyl (BOC) group is extensively used to protect amino groups in peptide chemistry. The BOC group could be removed with PPTS over 12 hours from the N-BOC-aminoethanol (**3**) (Figure 1, Eq. 4.). These conditions are much milder than the ones normally used (HCl or trifluoroacetic acid). When the bis-protected aminoethanol **4** was subjected to the same reagent/solvent system during shorter reaction times, the

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TBDMS group was selectively removed to furnish N-BOC-aminoethanol (3) (Figure 1, Eq.5) in 75% yield[5], thus providing a method for the selective removal of a TBDMS group in the presence of a BOC. However, a TBDMS group in 1-t-butyldimethylsilyl-2,3-glycerol acetonide could not be selectively removed without concomitant removal of the acetonide functionality.

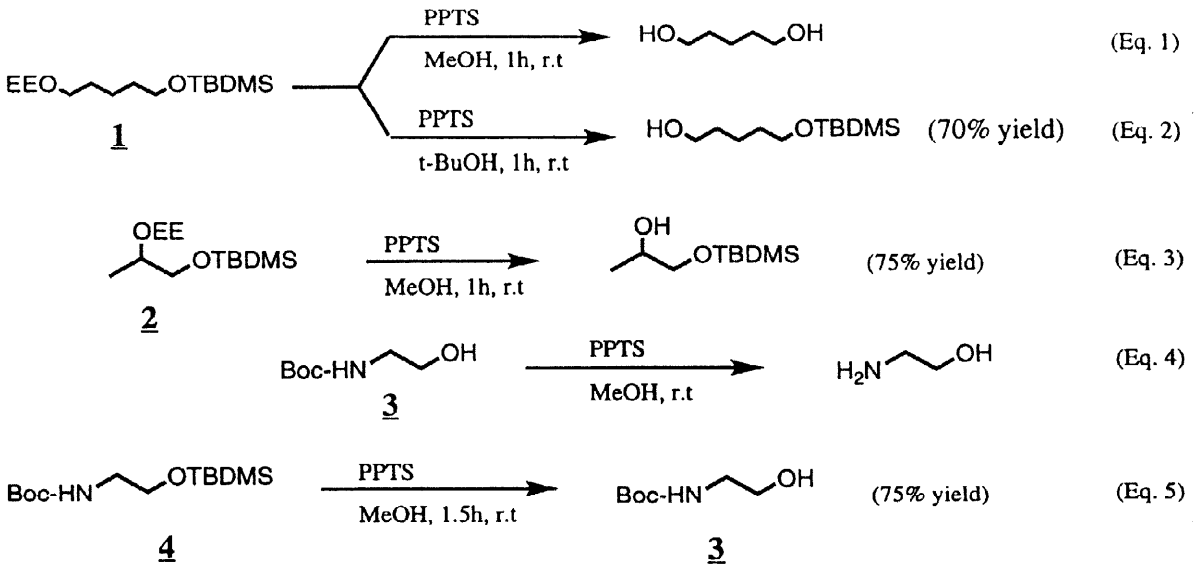

Figure 1

In conclusion, the inexpensive PPTS can be used as a general reagent for the removal of some common acid sensitive protecting groups under very mild conditions. More importantly, selective deprotection of EE in the presence of a TBDMS, and that of TBDMS in the presence of a BOC group can be readily achieved by manipulating solvent polarity and reaction times.

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