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A MILD AND VERSATILE METHOD FOR THE TETRAHYDROPYRANYLATION OF ALCOHOLS AND THEIR DETETRAHYDROPYRANYLATION

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Abstract: An efficient and mild method for tetrahydropyranylation of alcohols and their detetrahydropranylation using NH_4Cl is described. This protocol provides a useful alternative tetrahydropyranylation of alcohols and their deprotection at different pH.

Protective groups plays an important role in organic synthesis. Because of this the selective removal of one group leaving the other intact is a challenging task to the organic chemist. However, the success of the methods is determined by their tolerance to a wider variety of groups. Tetrahydropyranylation is one of the most frequently used methods for the protection of hydroxy functionality in synthetic organic chemistry, in particular natural product chemistry[1]. This is because of the ease of formation, stability both in acidic and basic condition, and the easy removal under mild H^+ conditions.

Tetrahydropyranylation is one of the methods of choice to protect a hydroxyl group in multistep organic synthesis[2]. Numerous methods have been reported

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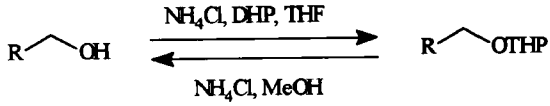
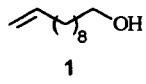
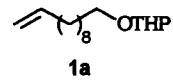
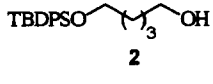
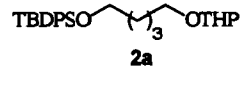
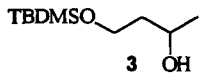
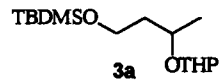
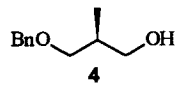
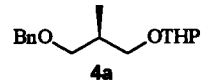
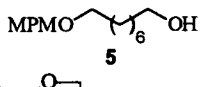
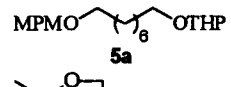
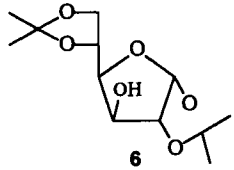
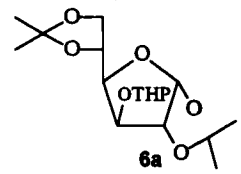
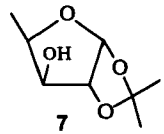
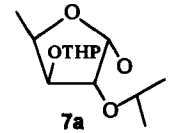
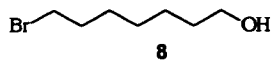
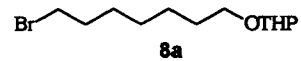
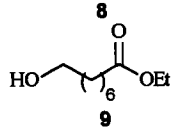
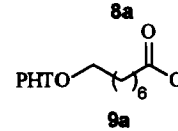
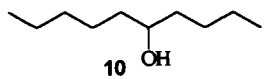
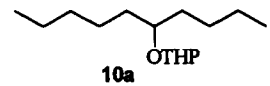
for the tetrahydropyranylation of alcohols[3] and their detetrahydropyranylation[4] such as protic acids[3a] (HCl and PTSA), Lewis acids and pyridinium p-toluenesulfonate[3b]. More recently, ion exchange resins (amberlyst H-15[3c] and Nafion[3d]), clay materials (montmorillonite K-10[3e] and H-Y Zeolite[3f]), $ZnCl_2$[3g], tetra-n-butylammonium peroxydisulfate[3h] and CuCl[3i] have also been employed for the protection of alcohols as THP ethers. Generally, aqueous acids such as acetic acid, HCl, boric acid etc., are used for the cleavage of THP ethers. The weaker acids invariably require higher temperature[3b]. Other known reagents for hydrolysis of THP ethers are Amberlyst H-15[4a], $MgBr_2$[4b], Me_2AlCl[4c], $(NCSBu_2Sn)_2O$[4d], MeOH/HCl[4e], $NaBH_3CN$/ $BF_3.OEt_2$[4f], Ph_3PBr[4g], DDQ[4h] and LiCl in H_2O-DMSO[4i] etc. However, some of these procedures suffer from expensive reagents, high temperature, strongly acidic conditions. Consequently, there is a need to develop alternative methods for the protection as well as deprotection. Herein, we demonstrate (Scheme-1) an interesting useful and mild method for the conversion of alcohols to THP ethers and the cleavage of THP ethers to alcohols using NH_4Cl[5].

Alcohols of different type were subjected to protection in the presence of NH_4Cl in THF (PH 5.93) at reflux conditions to give THP ethers in good yields. The results are summarised in table-1. Deprotection of THP ethers in presence of NH_4Cl in methanol (PH 5.25) at reflux conditions afforded the corresponding alcohols in excellent yields. The results are summarised in table-2. All of the products were purified by column chromatography and the corresponding THP ethers and alcohols were obtained in good yields. It is noteworthy that acid sensitive group like TBDPS (Entry 2), TBDMS (Entry 3), acetonides (Entry 6,7) and bromoalcohols (Entry 8) remain unaffected in these conditions.



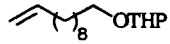
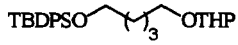
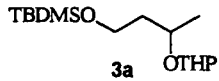
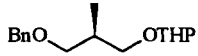
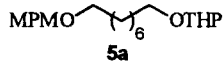
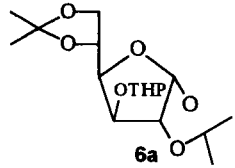
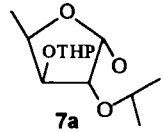
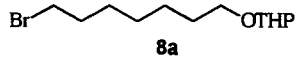
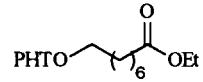
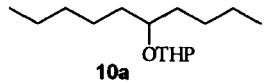
Scheme-1

Table-1 : Tetrahydropyranylation of Alcohols

Entry	alcohol	THP ether	Time (h.)	Yield,[a] %
1.	 1	 1a	3	90
2.	 2	 2a	3	75
3.	 3	 3a	5	65
4.	 4	 4a	4	65
5.	 5	 5a	3	75
6.	 6	 6a	5	60
7.	 7	 7a	5	65
8.	 8	 8a	3	85
9.	 9	 9a	3	85
10.	 10	 10a	4	70

[a] = *Yields after column chromatography purification*

Table-2 : Deprotection of THP Ethers.

Entry	THP ether	Alcohol	Time(h)	Yield,[a] %
1.	 **1a**	1	4	85
2.	 **2a**	2	3	60
3.	 **3a**	3	3	65
4.	 **4a**	4	4	68
5.	 **5a**	5	5	75
6.	 **6a**	6	7	60
7.	 **7a**	7	6	65
8.	 **8a**	8	4	75
9.	 **9a**	9	4	85
10.	 **10a**	10	5	60

[a] = *Yields after column chromatography purification*

In conclusion, our protocol provides a useful alternative for the preparation of tetrahydropyranyl ethers as well as cleavage of tetrahydropyranyl ethers to corresponding alcohols. The notable advantages of this methodology are mild conditions, industrially applicability, tolerance to a wide range of functionalities. We believe this will serve as a useful addition to modern synthetic methodologies.

A) Typical Experimental Procedure for the Protection of alcohols:

To the alcohol (Entry **1**, 1.7 g, 10 mmoles) and DHP (0.84 g, 10 mmoles) in tetrahydrofuran (15 ml), commercial NH_4Cl (0.53 g 10 mmoles) was added and heated at reflux for 3 h. The THF was removed, diluted with water (10 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were dried over Na_2SO_4. Evaporation of solvent, followed by column chromatography (ethyl acetate: pet ether, 2:8) furnished the desired THP ether **1a**. (2.2 g, 90% yield.)

B) Cleavage of THP ether:

To the THP ether (Entry **1a**, 2.5 g, 10 mmoles) in methanol (20 ml), commercial NH_4Cl (1.2 eg, 12 mmoles, 0.64 g) was added and heated at reflux for 4h. Methanol was removed, diluted with water (15 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were dried over Na_2SO_4. Evaporation of solvent, followed by column chromatography (Ethylacetate:pet ether, 4:6) furnished THP cleaved product, **1**. (1.44 g, 85% yield).

Note: All NMR values are concurrent with the reported values.

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