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Tetrabutylammonium tribromide (TBATB)-promoted tetrahydropyranylation/depyranylation of alcohols†

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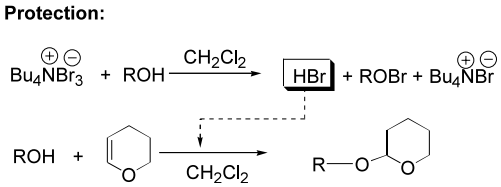
Abstract—Alcohols are tetrahydropyranylated rapidly in high yields in the presence of a catalytic amount of TBATB in dichloromethane at room temperature. Depyranylation to their parent alcohol is achieved in quantitative yields by merely changing the solvent to methanol.

THP ethers are one of the most widely used protecting groups employed during a multi step organic synthesis because of low cost and stability towards various reaction conditions such as strong bases, Grignard reagents, hydrides, redox reagents, alkylating, acylating agents and catalytic hydrogenation and easy removal under mild acidic conditions. Numerous methods have been reported for tetrahydropyranylation[1–3] and detetrahydropyranylation.[1,2,4] Protection is normally achieved with a mild acidic reagent in an aprotic solvent such as CH_2Cl_2, THF, acetone etc.; and deprotection also with an acidic reagent but in a polar or protic solvent such as methanol, ethanol, isopropanol, acetonitrile, etc. Commonly used catalysts are potassium dodecatangestocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$),[5] $ZrCl_4$,[6] I_2-microwave irradiation,[7] LiBr,[8] acetonyltriphenylphosphonium bromide,[9] I_2,[10] NH_4Cl,[11] heteropoly acids,[12] which catalyse both these transformations effectively by merely changing the solvent system. However, some of these procedures suffer due to the use of expensive and toxic reagents, high temperature, longer reaction times and incompatibility with other acid-sensitive functional groups.

Therefore there is a need to develop an alternative method for the protection as well as deprotection of alcohols under mild reaction conditions. Recently, tetrabutylammonium tribromide (TBATB) has been used as a brominating agent[13] and for the cleavage of *tert*-butyldimethylsilyl ethers,[14] cleavage of dithioacetals[15] and acetalisation of carbonyl compounds.[16] In this letter we report a mild and efficient method for the tetrahydropyranylation of alcohols using tetrabutylammonium tribromide (0.025 equiv.) as a promoter in the presence of 3,4-dihydro-2*H*-pyran (1.1 equiv.) in methylene chloride at room temperature, whereas the detetrahydropyranylation could be readily achieved using the same quantities of the reagent in methanol at room temperature.

Tetrahydropyranylation did not occur when the blank runs were performed in the absence of TBATB. Despite the use of an aprotic solvent during pyranylation, the occurrence of this reaction may be attributed to the in situ formation of HBr by the interaction of alcohol with TBATB, as shown in Scheme 1. It has been shown that organic ammonium tribromide such as benzyltrimethylammonium tribromides generate HBr and MeOBr in methanol.[17] Taking cues from this and our earlier observations[14,16] the following mechanism has been proposed for the deprotection, as shown in Scheme 2. Gas chromatographic co-injection analysis unequivocally established the formation of 2-methoxytetrahydropyran as a transacetalisation product and in turn the mechanism. 2-Methoxytetrahydropyran was prepared by reacting methanol with 3,4-dihydro-2*H*-pyran in the presence of I_2.[10] Other alcoholic solvents such as ethanol and isopropanol can also be used for the deprotection.



Scheme 1. Proposed mechanism of protection.

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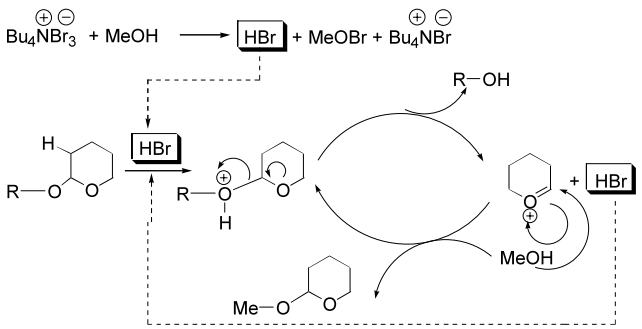


Scheme 2. Proposed mechanism of deprotection.

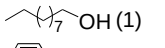
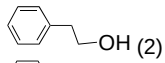
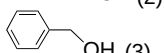
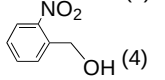
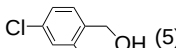
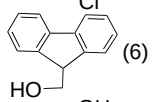
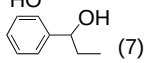
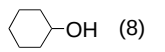
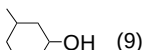
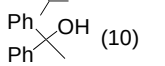
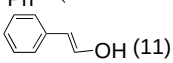
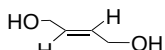
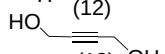
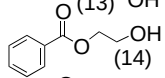
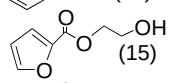
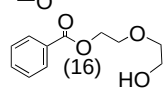
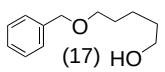
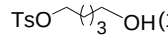
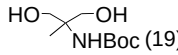
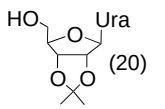
Several examples illustrating this novel and rapid procedure for tetrahydropyranylation of alcohols and their successive deprotection are presented in Table 1. The general applicability of this methodology can be seen from the wide spectrum of hydroxyl compounds ranging from primary, secondary, tertiary, benzyl alcohols, which are protected/deprotected as THP ethers in high yields with TBATB as the promoter. The tolerance of various protecting groups under the reaction conditions has been examined by reacting substrates bearing substituents such as nitro, alkene, alkyne, esters, OBn, Boc, isopropylidine, OTs, etc. and the reaction conditions were compatible both in the protection and deprotection stages.

In conclusion, this methodology provides a useful alternative for the preparation as well as cleavage of tetrahydropyranyl ethers to the corresponding alcohols. The main advantages of our methodology are mild reaction conditions, high efficiencies, quick and clean, economic viability of the reagent, industrial applicability and tolerance to a wide range of functionalities. We believe that this will be a useful addition to modern synthetic methodologies. The possibility of deprotection using the same catalyst with slight change in experimental protocol makes this method an attractive strategy, offering advantages over other methods, which use different catalysts.

(a) **General procedure for the tetrahydropyranylation of alcohols**: To a solution of alcohol (5 mmol) in dichloromethane (10 mL) was added 3,4-dihydro-2*H*-pyran (5.5 equiv.) and tetrabutylammonium tribromide (TBATB) (0.125 mmol) and the resulting solution was left at room temperature. The progress of the reaction was monitored by GC/TLC. On completion, a saturated solution of sodium bicarbonate (10 mL) was added and the product was extracted with CH_2Cl_2 (2×25 mL). The organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed to give crude THP ether, which was purified through a short column of silica to obtain a pure sample of the THP ether. GC retention time was identical with that of an authentic sample. IR and ^1H NMR data were in good agreement with the spectral data published.

(b) **Detetrahydropyranylation of OTHP ethers of alcohol**: To a solution of THP ether (5 mmol) in methanol (10 mL) was added TBATB (0.50 mmol) and the resulting solution was left at room temperature. The progress of the reaction was monitored by GC/TLC. On completion of the reaction, methanol was removed

Table 1. Tetrahydropyranylation/depyranylation of alcohols in the presence of TBATB

Substrate	Protection		Deprotection	
	Time / h	Yield/%[a,b]	Time / h	Yield/%[a,b]
 (1)	0.50	87	0.08	95
 (2)	0.75	88	0.66	95
 (3)	1.00	85	0.16	95
 (4)	2.00	79	0.50	95
 (5)	1.00	85	0.50	95
 (6)	1.00	78	2.00	90
 (7)	0.41	85	1.00	97
 (8)	1.00	75	0.08	92[c]
 (9)	1.00	74	0.08	92
 (10)	0.50	50	1.00	75
 (11)	2.00	65	0.16	98
 (12)	0.5	95[d]	0.16	95
 (13)	0.33	91[d]	0.33	92
 (14)	1.00	71	0.16	97
 (15)	1.00	75	0.16	96
 (16)	1.00	76	0.16	92
 (17)	1.00	73	0.20	92
 (18)	1.50	80	0.50	93
 (19)	2.00	74	1.00	95
 (20)	0.41	88	1.5	75

[a]Reactions were monitored by TLC, GC. [b] Confirmed by comparision with IR and ^1H NMR. [c]Determined by GC. [d]Double amounts of THP were used.

under vacuum and product was purified through a short column of silica gel to obtain pure alcohol. GC retention time was identical with that of an authentic sample and IR and ^{1}H NMR data were in good agreement with the spectral data published.

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References

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; (b) Kocieński, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, 1994.
2. Jarowicki, K.; Kocieński, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2495.
3. (a) Deka, N.; Sarma, J. C. *J. Org. Chem.* **2001**, *66*, 1947; (b) Branco, L. C. *Tetrahedron* **2001**, *57*, 4405; (c) Babu, B. S.; Balasubramanian, K. K. *Synlett* **1999**, *8*, 1261; (d) Nishiguchi, T.; Hayakawa, S.; Hirasaka, Y.; Saitoh, M. *Tetrahedron Lett*. **2000**, *41*, 9843; (e) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Costantino, U. *Tetrahedron Lett*. **1998**, *28*, 8159; (f) Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett*. **1998**, *39*, 9287.
4. (a) Davis, K. J.; Bhalerao, U. T.; Rao, B. V. *Synth. Commun*. **2000**, *30*, 2301; (b) Markó, I. S.; Ates, A.; Augustyns, B.; Gautier, A.; Quesnel, Y.; Turet, L.; Wiaux, M. *Tetrahedron Lett*. **1999**, *40*, 5613; (c) Ramasamy, K. S.; Averett, D. *Synlett* **1999**, *6*, 709; (d) Lee, A. S.-Y.; Su, F.-Y.; Liao, Y.-C. *Tetrahedron Lett*. **1999**, *40*, 1323; (e) Ramasamy, K. S.; Bandaru, R.; Averett, D. *Synth. Commun*. **1999**, *29*, 2881.
5. Habibi, M. H.; Tangestaninejad, S.; Baltork, I. M.; Mirkhani, V.; Yadollahi, B. *Tetrahedron Lett*. **2001**, *42*, 2851.
6. Rezai, N.; Meybodi, F. A.; Salahi, P. *Synth. Commun*. **2000**, *30*, 1799.
7. Deka, N.; Sarma, J. C. *Synth. Commun*. **2000**, *30*, 4435.
8. Reddy, M. A.; Reddy, L. R.; Bhanumathi, N.; Rao, K. R. *Synth. Commun*. **2000**, *30*, 4323.
9. Hon, Y.-S.; Lee, C.-F. *Tetrahedron Lett*. **1999**, *40*, 2389.
10. Kumar, H. M. S.; Reddy, B. V. S.; Reddy, E. J.; Yadav, J. S. *Chem. Lett*. **1999**, 857.
11. Jadav, J. S.; Srinivas, D.; Reddy, G. S. *Synth. Commun*. **1998**, *28*, 1399.
12. Molnar, A.; Beregszaszi, T. *Tetrahedron Lett*. **1996**, *37*, 8597.
13. (a) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett*. **1998**, *39*, 8163; (b) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett*. **2000**, *2*, 247; (c) Bose, G.; Bhujarbarua, P. M.; Chaudhuri, M. K.; Kalita, D.; Khan, A. T. *Chem. Lett*. **2001**, 290.
14. Gopinath, R.; Patel, B. K. *Org. Lett*. **2000**, *2*, 4177.
15. Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2001**, 785.
16. Gopinath, R.; Haque, Sk. J.; Patel, B. K., unpublished results.
17. Kajigaeshi, S.; Kakinami, T.; Hirakawa, T. *Chem. Lett*. **1987**, 627.