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DIRECT CONVERSION OF TETRAHYDROPYRANYLATED ALCOHOLS TO THE CORRESPONDING BROMIDES

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Summary : Various tetrahydro-2 pyranyl protected alcohols are converted into the corresponding bromides by PPh_3 / CBr_4, with inversion of configuration, and in high yield.

The conversion of protected alcohols into the corresponding bromides, suitable for further chemical elaboration, is a useful synthetic transformation, especially for polyfunctional molecules. Various methods are currently available for this purpose[1]. In the course of a synthesis of a precursor of C-1 labeled arachidonic acid[2] involving a THP protected ether (entry 1), we found that treatment of 1 with PPh_3 / CBr_4 yielded directly the corresponding bromide in good yield. This is a mild and very efficient general method of bromination of various THP protected alcohols.

$$\text{R-OTHP} \xrightarrow[CH_2Cl_2]{2\,PPh_3\,/\,CBr_4} \text{R-Br}$$

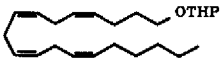
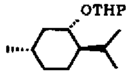
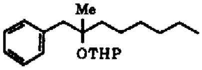
The conversion is conveniently accomplished by the following general procedure : CBr_4 (1.4 mmol) was added under argon, at room temperature, to a solution of THP ether[3] (1 mmol) in anhydrous CH_2Cl_2 (5ml). After stirring for 10 min the solution was cooled to 0°C and PPh_3 (2.8 mmol) was added. The mixture was stirred overnight at room temperature and filtered through silica gel to eliminate the undesired by-products. Evaporation of the solvent provides the corresponding bromide[4].

The results are summarised in the table. The reaction appears to be general, to convert primary, secondary, and tertiary as well as allylic, benzylic and α-cyano THP-protected alcohols into bromides.

The stereochemistry of the reaction was investigated using the THP protected (-) menthol (entry 2) which was converted to neomenthyl bromide ($[\alpha]_D = +60°$, c=1.38, EtOH)[5]. There was complete inversion of configuration, indicating that a S_N2 process is induced. The reaction mechanism is probably similar to the one proposed for the conversion of THP ethers into bromides using PPh_3Br_2[1a].

Further applications of this reaction will be reported in due course.

Table

Entry	Substrate	solvent	% yield of bromide[a]
1		CH_2Cl_2	76
2		CH_2Cl_2	85
3		CH_2Cl_2[b] CH_3CN[c]	44 62
4		CH_2Cl_2	80
5		CH_2Cl_2	87
6		CH_2Cl_2[d]	82

[a]Isolated yield of pure product. [b]40% of elimination was observed. [c]The best results for the bromination of tertiary protected THP alcohols were obtained with 1.2 eq CBr_4 and 2.4 eq PPh_3 in CH_3CN and by adding 1.5 eq of LiBr to the overnight stirred reaction mixture. 15-25% of elimination was observed. [d]With addition of 1 eq of Bu_4NBr.

References and notes.

1. (a) Sonnet, P.E. Synth. Comm. 1976, 6, 21. (b) Mattes, H. and Benezra, C. Tetrahedron Lett. 1987, 28, 1697. (c) Schmidt, S.P. and Brooks, D.W. Tetrahedron Lett. 1987, 28, 767 and references therein.

2. Heitz, M.-P.; Wagner, A.; Mioskowski, C., J. Org. Chem., accepted for publication.

3. The THP ethers were prepared following the general procedure published by Bolitt, V.; Mioskowski, C.; Shin, D.-S. and Falck, J.R., Tetrahedron Lett. 1988, 29, 4583. All products were characterised by ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR, IR and gave satisfactory microanalyses.

4. The new bromides showed IR, 200 MHz ^{1}H NMR, 50 MHz ^{13}C NMR, and mass spectra consistent with their assigned structures.

5. The optical rotations reported by (a) Oshikawa, T. and Yamashita, M., Bull. Chem. Soc. Jpn. 1984, 57, 2675 and (b) Yamashita, M.; Soeda, Y.; Susuki, N. ; Yamada, M., Bull. Chem. Soc. Jpn. 1983, 56, 1871, are discordant ($[\alpha]_D = -7.26°$ (c=1.01, EtOH) and $[\alpha]_D = -49.8°$ (c=1.04, EtOH)) and do not correspond with our value. Thus we prepared neomenthyl bromide by two known routes implying inversion of configuration : treatment of (-) menthol either with PPh_3/CBr_4 (see Hooz, J. and Gilani, S.S.H. Can. J. Chem. 1968, 46, 86) or $DIPHOSBr_2$[1c] gave the corresponding bromide $[\alpha]_D = +59°$ (c=1.38, EtOH) and $[\alpha]_D = +58°$ (c=1.44, EtOH).

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