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A SIMPLIFIED PROCEDURE FOR THE PREPARATION OF TRIPHENYLMETHYLETHERS

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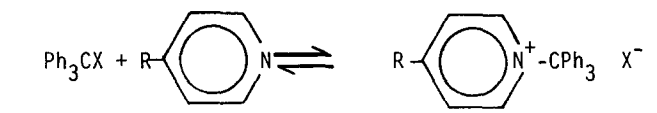
During the course of our work towards a synthesis of thromboxane B_2[1] we developed a need for a simple way to effect the conversion of α-methylglucoside (3a) to the corresponding monotrityl ether (3b). The classical method for the preparation of trityl ethers involves reaction of the alcohol substrate with triphenylmethylchloride in the presence, preferably as solvent, of pyridine at temperatures ranging from room temperature up to 100°[2]. A more recent report describes the application of N-tritylpyridinium fluoroborate as a potent triphenylmethylating agent[3]. This latter method has definite advantages over the classical procedure, although the high cost of reagents involved makes it prohibitive for large scale preparations.

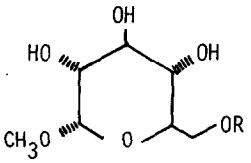
In analogy with the established mechanism for the pyridine catalyzed transfer of acyl groups[4] one can assume that the tritylation reaction proceeds by initial formation of an N-tritylpyridinium salt from which the alkyl group is transfered to the alcohol. The formation of this pyridinium salt (2) is rate determining and consequently the high reactivity of N-



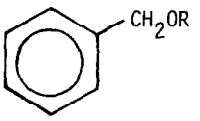
X=Cl⁻, BF_4^- 1 2

R=H, Me_2N

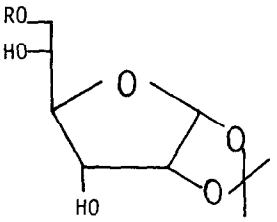
tritylpyridinium fluoroborate (2, X=BF_4) can be explained this way. Electron donating substituents at the para position of the pyridine ring favor formation of intermediates similar to 2[4], a finding which has found synthetic application in acylation reactions[5]. Accordingly, reaction of tritylchloride (1.1 eq) with α-methylglucoside (3a) in N,N-dimethylformamide (DMF) solution overnight at room temperature in the presence of 4-N,N-dimethylaminopyridine (DAP) (0.04 eq) and triethylamine (1.5 eq) cleanly produced 6-O-trityl-α-methylglucoside[6], 3b (88%). By the same procedure tritylethers, 5b and 8b were isolated in 75 and 85% yield after workup[7].



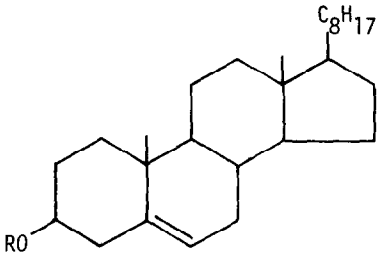
3a, R=H
3b, R=-CPh_3



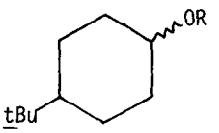
4a, R=H
4b, R=-CPh_3



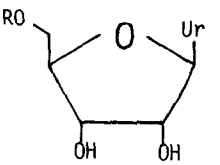
5a, R=H
5b, R=-CPh_3



6a, R=H
6b, R=-CPh_3

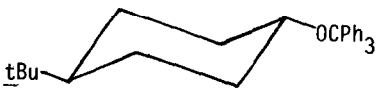


(cis and trans)
7a, R=H
7b, R=-CPh_3

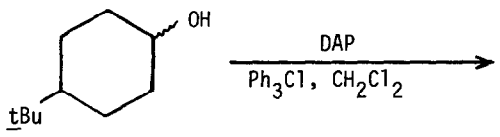


8a, R=H
8b, R=-CPh_3

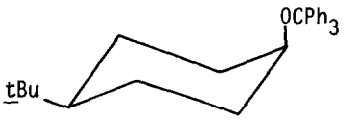
This combination of reagents is also effective in solvents other than DMF as shown by formation of 4b (90%) in dichloromethane solution at room temperature. Reaction of secondary alcohols is considerably slower (18-24 hr) and requires higher temperatures (40-45°), thus the trityl ethers 6b and 7b were prepared in refluxing dichloromethane (68% and 70%) and in DMF solution at 45° (7b, 65%).



>97%



7a



<3%

In the latter case, a unique selectivity was observed in that the tritylether 7b consisted mostly (>97%) of the trans (equatorial) isomer for the reaction carried out in dichloromethane solution[8]. The reaction in DMF solution was slightly less selective affording 7b containing 95% of the equatorial isomer. This rather unexpected event suggests a large steric requirement of 2 (X=Cl) for reaction with alcohols, and consequently the selectivity observed with primary

alcohols would be largely due to a kinetic factor. This same argument applies to the large preference of equatorial versus axial as observed in 7a. Similarly, the ratio of acetylation rates of equatorial and axial 7a by acetic anhydride-pyridine is 3.8[10] and in a related reaction the tosylation of inositol by p-toluensulfonyl chloride-pyridine proceeds with a large preference for the equatorial hydroxyl groups.[11]

This kinetic selectivity potentially may be developed into a practical synthetic tool. However, our immediate need was to develop a simpler and more efficient procedure for the preparation of the title compounds. The role of tritylethers as protective groups in carbohydrate[2] and nucleoside chemistry[9] is well documented, and we feel that the present procedure will stimulate their use in other areas of synthetic organic chemistry. Definite advantages over the classical procedure are increased selectivity, wider choice of solvents, milder reaction conditions, and simplified work-up operations. For comparison, a preparation of 3b by the pyridine-as-solvent procedure was included. Following literature procedures,[6,12] the reaction was carried out at 100° and afforded 3b in 61% yield (lit.[6] 60%) after purification (see experimental). Analysis of crude 3b by high-pressure liquid chromatography (HPLC) on a reverse phase column[13] showed, in addition to product and triphenylmethanol, a substantial amount of pyridine and a compound tentatively identified as a bis-trityl ether (see experimental). Based on the reactivity of the hydroxyl groups in 3a[14] this compound is probably the HO-6 and HO-2 bis-ether. When the reaction was carried at 25° the bis-trityl ether was absent but the yield of 3b was much lower (36%). These experiments illustrate the difficulties encountered in some cases with the pyridine solvent procedure, namely the formation of addition complexes of the product with pyridine and other trityl ethers both of which contaminants are not removed by simple crystallization.[2]

The preparation of triphenylmethylethers by the DAP procedure is illustrated by the following examples:

1-O-Methyl-6-trityl-glucopyranoside (3b): A solution of 3a (11.64 g, 0.06 mol), tritylchloride (18.4 g, 0.066 mol), triethylamine (15 ml), and DAP (0.003 mol, 582 mg) in DMF was stirred overnight at room temperature under nitrogen. After 12 hr stirring, the yellow cloudy solution was poured into ice-water and extracted with dichloromethane. The organic extracts were washed with saturated ammonium chloride solution, water, and dried with sodium sulfate. After removal of the solvents, the yellowish solid was recrystallized from ethanol to give (18.7 g, 71%) pure 3b, mp 154.5-155.5° (lit.[6] mp 151-152°). Concentration of the mother liquors gave additional 4.1 g of product raising the total yield to 88%.

Preparation of 3b using pyridine solvent. (a) At 100°: Reaction of 3a (10 mmol) with tritylchloride (11 mmol) in dry pyridine (20 ml) on a steam bath for 1 hr followed by conventional extractive work-up gave a syrup which was chromatographed on silica gel[8] using 20% $CHCl_3$/ethyl acetate. Two fractions were isolated, the least polar consisted mostly of a bis-trityl ether (0.68 g, 10%); proton nmr (δ, $CDCl_3$), 3.3 ($-OCH_3$), and 7.1-7.7 (aromatic). The second fraction contained 3b and some pyridine. Recrystallization from ethanol gave 2.65 g (two crops, 61%) of white crystals, mp 154-155° (lit.[6] mp 151-152°, 60% yield). (b) At 25°: After 20 hr at room temperature, an experiment as described above afforded 1.68 g (37%) of 3b.

Triphenylmethylbenzylether (4b): Reaction of benzylalcohol (10 mmol) with tritylchloride (11 mmol), triethylamine (2.5 ml) and DAP (0.4 mmol) in dichloromethane at room temperature overnight afforded after work-up as above and recrystallization from hot ethanol, 3.2 g (91%) of pure 4b, mp 95°.

References and Notes

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7. New compounds had C,H analyses. Spectral data obtained on samples were consistent with the structure.
8. Purification of the reaction mixture was carried out on a Waters Associates Prep 500 liquid chromatograph using hexane-dichloromethane eluent mixtures. Unchanged 7a was analyzed by gas liquid chromatography (glc) on a OV-225 column programmed from 70° to 95° at 4°/min. Under these conditions, base line separation of the two isomers was achieved. Relative yields were calculated by measuring peak heights. For comparison, a commercial sample (Aldrich) of 7a analyzed as above gave 69.7% equatorial and 30.3 axial isomer. The trityl group was cleaved (dry HCl, CH_2Cl_2) and the resulting alcohol analyzed by glc as described above. The identity of the individual isomers was confirmed by proton nuclear magnetic resonance.
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13. Analytical HPLC analysis were performed on a Waters Associates ALC 244 liquid chromatograph using a C-8 Chromega column (ES Industries) and a linear gradient from 70 to 90% methanol/water in 15 min at 1 ml/min. Peaks were detected at UV 254 nm and retention times (minutes) were as follows: pyridine, 3; 3b, 6.5; triphenylmethanol, 7; bis-ether, 11.
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