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Convenient Method for the Preparation of Trityl Ethers from Secondary Alcohols.

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Abstract : The preparation of trityl ethers from secondary alcohols (10 mmol) with triphenylmethyl chloride (1.2 eq.) is carried out at room temperature by using DBU (1.4 eq.) as base in CH_2Cl_2. The high yielding procedure is very simple and its applicability is general.

During the course of our work towards the synthesis of O-protected ethyl lactates, we developed a need for an efficient way to effect the conversion of (S)-ethyl lactate **1a** (Table 1) to the corresponding triphenylmethyl ether **1b** (trityl ether [1]).

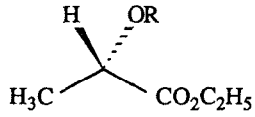
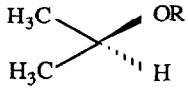
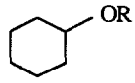
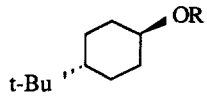
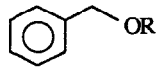
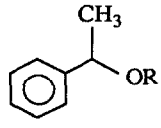
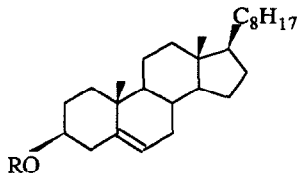
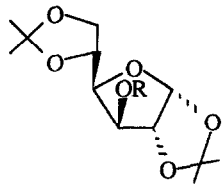
The trityl group is widely used for the protection of hydroxy functions in carbohydrate chemistry [2-6]. The classical method for the preparation of trityl ethers involves reaction of the alcohol substrates with triphenylmethyl chloride in pyridine solution, at temperatures ranging from room temperature up to 100° C [2]. However, tritylation shows a high degree of selectivity for the primary hydroxy groups of polyols and tritylation of secondary hydroxy groups under standard conditions proceeds very slowly or not at all [7,8]. Only a few methods for such operation have been described, i.e. i) the use of triphenylmethylium perchlorate in combination with 2,4,6-tri-tert-butylpyridine at room temperature [4] ii) the use of triphenylmethyl chloride in the presence of 4-N,N-dimethylaminopyridine (DMAP) and triethylamine at 40-45° C [8] iii) the use of triphenylmethylpyridones at 80° C [9].

According to the simpler procedure [8], we first tried to achieve the tritylation of (S)-ethyl lactate **1a** by using triphenylmethyl chloride (1.1 eq.) in combination with DMAP (0.08 eq.) and triethylamine (1.8 eq.). However, even after 6 days in refluxing dichloromethane, the yield in the corresponding trityl ether **1b** was only 35%. We then focused our attention to find a suitable method for this conversion and we report here a new, simple, low-coast and efficient procedure which finds widespread application for the blocking of hydroxy groups. This method avoids the use of sensitive or sophisticated triphenylmethylating agents such as triphenylmethylium perchlorate or triphenylmethylpyridones [4,9]. Moreover, it has definite advantages over the procedure using triphenylmethyl chloride in the presence of DMAP and triethylamine: it proceeds at lower temperatures (room temperature v. 40-45° C) and with better yields (81% v. 35% for compound **1b**, 82% v. 68% for compound **7b**).

During the course of our studies on the synthesis of O-protected ethyl lactates, we observed that the method used for the preparation of tert-butyldimethylsilyl ether [10] was also applicable to the formation of the tert-butyldiphenylsilyl ether [11]. Reaction of (S)-ethyl lactate with 1.2 eq. of tert-butyldimethylchlorosilane (resp. tert-butyldiphenylchlorosilane) and 1.4 eq. of 1,8-diazabicyclo (5.4.0) undec-7-ene (DBU) afforded the corresponding tert-butyldimethylsilyl (resp. tert-butyldiphenylsilyl) derivative in 95% (resp. 100%) yield.

In analogy with this method, we established a convenient procedure for the preparation of trityl ethers (Scheme 1), based on the use of triphenylmethyl chloride in combination with DBU and carried out in dichloromethane solution at room temperature.

Table 1 :

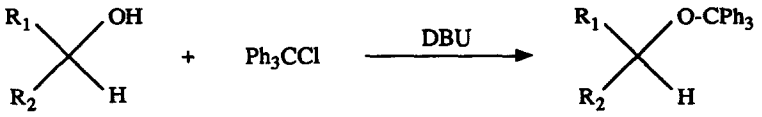
Substrates and Products [i] R = H : **a** ; R = CPh_3 : **b**	Yield , % [ii]	m.p. , °C and $[\alpha]_D$
1 	81	Liq. $[\alpha]_D^{20}$ = - 37 (c=1 ; CH_2Cl_2)
2 	85	114.5 - 115 (Litt. : 115 [9])
3 	85	103 - 104 (Litt. : 105 [9])
4 	96 [iii]	150.5 - 151
5 	88	103 - 104 (Litt. : 105 - 106 [9])
6 	79	118 - 119
7 	82	137.5 - 138 (Litt. : 136 - 138 [9]) $[\alpha]_D^{20}$ = - 28 (c=1 ; $CHCl_3$)
8 	66	121 - 122 (Litt. : 120 - 122 [4]) $[\alpha]_D^{20}$ = - 27 (c=1 ; CH_2Cl_2)

i) Satisfactory ^{1}H-NMR data were obtained for each compound.

ii) Isolated yield after purification.

iii) According to note 15.

Scheme 1 :



A sterically hindered base without nucleophilic properties, 2,4,6-collidin, has already been used for the tritylation of molecules containing weakly activated hydrogens, according to a method involving the use of the tritylium hexafluorophosphate [12].

The general procedure can be considered as follows: to a solution of triphenylmethyl chloride (1.2 eq.) and DBU (1.4 eq.) in dichloromethane, the alcohol substrate (1.0 eq) was added [13] and the mixture was stirred at room temperature for two days. The progress of the reaction was conveniently monitored by TLC or GC analysis of crude reaction mixture. Products were isolated by washing the reaction mixture with cold water, extracting the aqueous layer with dichloromethane and drying the organic extracts with sodium sulfate. Evaporation of the solvent yielded crude triphenylmethyl ethers, which were purified by short column chromatography on silica or basic alumina gel (some compounds may be detritylated on silica gel columns [14]) and solids were recrystallized from ethanol (**2b-6b**) or methanol / ethanol 1:1 (**7b** and **8b**). Representative examples are presented in Table 1 [16].

In summary, our procedure seems to be efficient for the introduction of trityl group in a wide variety of substrates. It avoids the use of sophisticated or sensitive reagents and the mild reaction conditions are particulary suitable for acid-, strong base-, and thermo-sensitive structures. No racemisation was observed with compound **1b** (the (R)-enantiomer was not found by LIS-effect in ^{1}H-NMR spectroscopy with Eu(hfc)$_3$) and no acetal migration (5,6/3,5) occured during tritylation of compound **8a**. Work-up operations are very simple and this new method should be widely exploitable for tritylation of secondary hydroxy groups.

References and Notes :

1. a) L. Fieser and M. Fieser, *Reagents for Organic Synthesis*, John Wiley and Sons, Inc.; Vol.1, 1967, pp.1254-1256; Vol. 5, 1975, p. 742; Vol. 9, 1981, pp. 179-180; Vol. 10, 1982, p.156.
   b) T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley and Sons, Inc., 1981, pp. 34-36.
2. a) L. Hough, M.A. Salam and E. Tarelli, *Carbohydr. Res.*, **1977**, *57*, 97-101.
   b) B.L. Kam and N.J. Oppenheimer, *Carbohydr. Res.*, **1979**, *69*, 308-310.
   c) D. Dupeyre, J.P. Utille and P.J.A. Vottero, *Carbohydr. Res.*, **1979**, *72*, 105-118.
   d) K. Koizumi and T. Utamura, *Chem. Pharm. Bull.*, **1981**, *29*, 3118-3123.
   e) S. Koto, N. Morishima, T. Yoshida, M. Uchino and S. Zen, *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 1171-1175.
   f) K. Koizumi and T. Utamura, *Chem. Pharm. Bull.*, **1983**, *31*, 1260-1266.
3. S. Hanessian and A.P.A. Staub, *Tetrahedron Lett.*, **1973**, *14*, 3555-3558.
4. Y.V.Wozney and N.K. Kochetkov, *Carbohydr. Res.*, **1977**, *54*, 300-303.
5. V. Kohli, H. Blöcker and H. Köster, *Tetrahedron Lett.*, **1980**, *21*, 2683-2686.
6. C. Vicent, J.M. Coteron, J. Jimenez-Barbero, M. Martin-Lomas and S. Penades, *Carbohydr. Res.*, **1989**, *194*, 163-169.
7. O. Hernandez, S.K. Chaudhary, R.H. Cox and J. Porter, *Tetrahedron Lett.*, **1981**, *22*, 1491-1494.
8. S.K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, **1979**, *20*, 95-98.
9. F. Effenberger, W. Brodt and J. Zinczuk, *Chem. Ber.*, **1983**, *116*, 3011-3026.
10. J.M. Aizpurua and C. Palomo, *Tetrahedron Lett.*, **1985**, *26*, 475-476.

11. a) T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley and Sons, Inc., 1981, pp. 47-48.
b) S. Hanessian and P. Lavallee, *Can. J. Chem.*, **1975**, *53*, 2975-2977.
12. G. Bidan, G. Cauquis and M. Genies, *Tetrahedron Lett.*, **1979**, *35*, 177-180.
13. Dichloromethane was distilled from calcium chloride before use. All alcohols were of commercial grade and were distilled (**1a**, **2a**, **3a**, **5a** and **6a**) or sublimated (**4a**, **7a** and **8a**) before use.
14. J. Lehrfeld, *J. Org. Chem.*, **1967**, *32*, 2544-2546.
15. The commercially available 4-tert-butylcyclohexanol **4a** was a 33:67 mixture of cis and trans isomers. From this mixture, trans-4-tert-butylcyclohexanol trityl ether **4b** was selectively obtained (analysis carried out by ^{1}H-^{1}H COSY).
16. *Triphenylmethyl (S)-ethyl lactate ether **1b*** : ^{1}H-NMR (360 MHz, $CDCl_3$, TMS)
δ 1.04 (t, 3H, ^{3}J = 7.1 Hz); 1.34 (d, 3H, ^{3}J = 6.5 Hz); 3.67 (q, 2H), 4.17 (q, 1H); 7.20-7.30 and 7.45-7.49 (m, 15H).
Satisfactory microanalyses ($C_{24}H_{24}O_3$: 360.4) : C : 80.2 and H : 6.5.
*Triphenylmethyl (R,S)-sec-phenethyl ether **6b*** : ^{1}H-NMR (360 MHz, $CDCl_3$, TMS)
δ 1.24 (d, 3H, ^{3}J = 6.3 Hz); 4.80 (q, 1H); 7.25-7.39 and 7.64-7.66 (m, 20H).
Satisfactory microanalyses ($C_{27}H_{24}O$: 364.5) : C : 90.2 and H : 6.5.

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