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Regioselective Acylation of Glycols: Evidence for Organotin-mediated Reversal of Chemoselectivity

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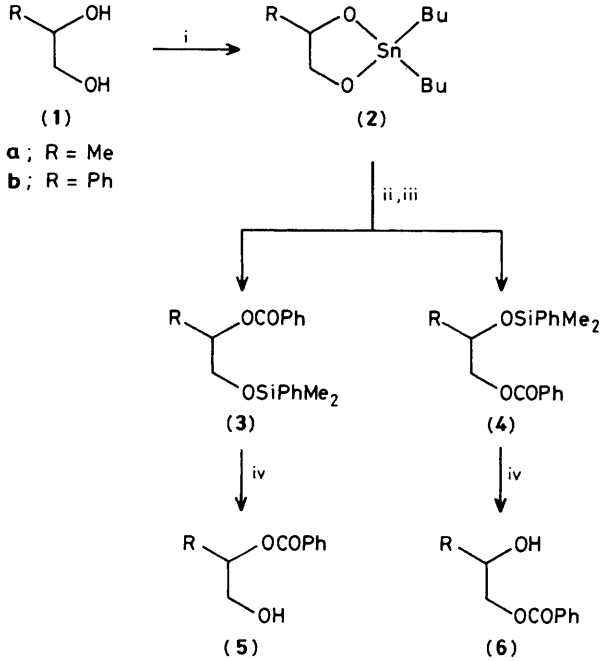
Mono *O*-acylation of unsymmetrical diols *via* their dibutylstannyl derivatives takes place with high reversed chemoselectivity at the most substituted site, the reaction being complementary to standard methods.

The selective 'activation' of hydroxy groups through their stannyl derivatives, in the regiocontrolled *O*-functionalization of diols and polyols, has been proved to be a powerful and efficient alternative to traditional 'protection' methods.[1,2] The activation method has been widely applied with high selectivity in carbohydrate chemistry, although the orientation is strongly dependent on the structure of the reactants. In structurally simpler substrates regioselective monofunctionalization at the primary hydroxy group has been assessed for dialkyltin derivatives of primary and secondary glycols.[2a,3]

In the course of our studies on group 4 organometallic reagents, we have investigated the mono-*O*-acylation of simple unsymmetrically substituted glycols through their dibutylstannyl derivatives. A dramatic reversal of chemoselectivity has been observed, *i.e.* selective esterification at the most substituted hydroxy group, and in this communication we report evidence for this striking reordering of relative reactivity for two examples of glycols with both a primary and a secondary centre.

Propane-1,2-diol (**1a**) and 1-phenylethane-1,2-diol (**1b**) were quantitatively converted into 2,2-dibutyl-1,3,2-dioxastannolanes (**2a,b**) with dibutyltin oxide by azeotropic dehydration in toluene, and subsequently treated with benzoyl chloride (1 equiv.) and phenyldimethylsilyl chloride (1 equiv.), at 0—5 °C in concentrated chloroform solution (see Scheme 1). Mild hydrolysis (cold dilute HCl) of the obtained regioisomeric silyl ether esters (**3**) and (**4**) afforded the corresponding hydroxy esters (**5**) and (**6**). The results are reported in Table 1 (method A).†

It is noteworthy that benzoylation experiments on (**1a, b**) by a conventional method (see Table 1, method B) afforded, as expected, the primary esters (**3**) and (**4**) with completely reversed selectivity, thus showing the complementary nature of the tin-mediated reaction. Direct hydrolysis after the benzoylation step significantly lowers both monoester yields and selectivity (see Table 1, method C).‡



Scheme 1. *Reagents:* i, Bu_2SnO, toluene; ii, PhCOCl (1 equiv.), $CHCl_3$; iii, $Me_2PhSiCl$ (1 equiv.); iv, dilute aq. HCl.

† Although isomeric monoesters of glycols are known to interconvert,[4] silylated products obtained are stable: no scrambling was observed after refluxing for 5 h in chloroform solution.

‡ As in the case of the base catalysed intramolecular transacylation of the diol monoesters,[6] a tetrahedral intermediate can be assumed to be responsible for an intramolecular exchange of the acyl groups in the stannyl monoesters. Fast exchange processes are evident from line broadening in the n.m.r. spectra. Treatment with $Me_2PhSiCl$ quenches this scrambling process, and the product distribution will be dependent on the relative reactivity of isomeric stannoxyesters. Different selectivity values for (**1a**) and (**1b**) are probably due to steric and electronic effects of the substituent.

Table 1. Products yields and isomeric ratios from the monobenzoylation of glycols.[a]

	Method A[b]		Method B[c]		Method C[d]	
	Yield (%)	(3) : (4)	Yield (%)	(3) : (4)	Yield (%)	(3) : (4)
(1a)	84	85 : 15[e] (84 : 16)[f]	78	9 : 91[e] (8 : 92)[f]	70[g]	70 : 30[g] (68 : 32)[f]
(1b)	90	95 : 5[e] (94 : 6)[f]	81	4 : 96[e] (3 : 97)[f]		

[a] Results are averaged over at least two runs. Yields (%) were determined by g.c. analysis on a 30 m capillary column (OV 1) taking into account the bisfunctionalized products. Unequivocal assignments of isomer signals in the ^{13}C n.m.r. spectra were obtained using SEFT pulse sequences,[5] benzoylation induced chemical shifts, spectra of pure compounds (bis-functionalized products), and comparison with spectra of mixtures from the reference reactions (method B). [b] Method described in the text. [c] Standard acylation method in benzene, in the presence of a stoicheiometric amount of pyridine, using (i) PhCOCl, (ii) $Me_2PhSiCl$. [d] Method as in footnote c, using (i) PhCOCl, (ii) dilute HCl. [e] Values determined by g.c. after treatment with aqueous $NaHCO_3$. [f] Values obtained by ^{13}C n.m.r. spectroscopy of the reaction medium. [g] Data obtained by ^1H n.m.r. spectroscopy of the reaction medium.

Product analysis was performed by g.c.; identification of products and direct analysis of the reaction media were carried out by ^1H and ^{13}C n.m.r. spectroscopy.§ Although g.c. analysis required previous work-up of the mixture to eliminate the dibutyltin dichloride formed in the reaction, an excellent agreement was found between the isomeric ratios obtained from both techniques (see Table 1); this proves that no significant change in the composition of the reaction mixture occurred in the treatment.

The synthetic potential of this reversal of chemoselectivity in the *O*-functionalization of glycols is obvious, since it is complementary to available procedures. Moreover, the silyl protected alcohol could allow further manipulation of other functionalities in the molecule and the mild, neutral, anhydrous procedure is suitable for sensitive products.

§ Selected ^{13}C n.m.r. spectroscopic data: (δ, $CHCl_3$ as secondary reference at δ 77.19) (**3a**): CHO 71.66, CH_2O 65.46; (**4a**): CHO 66.76, CH_2O 69.65; (**3b**): CHO 76.88, CH_2O 66.00; (**4b**): CHO 73.25, CH_2O 70.05.

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