Tetrahedron Vol 32, pp 2109 to 2111 Pergamon Press 1976. Printed in Great Britain

ESTERFICATION OF ALLYLIC ALCOHOLS WITH BENZOIC ACID IN THE PRESENCE OF DIETHYL AZODICARBOXYLATE AND TRIPHENYLPHOSPHINE

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(*Received in the UK* 24 *December* 1975; *Accepted for publication* 13 *January* 1976)

Abstract—Stereoselectivity of esterification reaction of some allylic alcohols, mainly unsaturated pyranosides, with benzoic acid in the presence of diethyl azodicarboxylate and triphenyl phosphine was investigated. The reaction was found to proceed with inversion, without allylic rearrangement.

Preparation of carboxylic and phosphoric acid esters via quaternary phosphonium salts, using diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP)[1] has been shown to proceed with inversion of configuration,[2] thus providing a useful synthetic tool, which has successfully been applied in steroid[3] and deoxysugar[4] chemistry. Replacing the acid by phthalimide allows the stereospecific conversion of alcohols into phthalimido derivatives and eventually into amines, which facilitates the synthesis of amino-acids[5] and amino-sugars.[6]

In this paper the application of the DEAD–TPP system to inversion of configuration of allylic alcohols through benzoate esters is described.

$$\mathrm{R{-}OH + PhCOOH + Ph_3P + EtO_2C{-}N{=}N{-}CO_2Et \rightarrow}$$
$$\mathrm{R{-}OCOPh + EtO_2C{-}NHNH{-}CO_2Et + Ph_3PO}$$

The alcohols **1–8** were treated with excess benzoic acid, TPP and DEAD in tetrahydrofuran solution at ambient temperature to give the benzoates (Table 1). The choice of substrates resulted from following considerations. The unsaturated alcohols **1–6** are key intermediates in the total synthesis of methyl aldopyranosides[7] and methyl ketopyranosides.[8] They are obtained by reduction of the corresponding α,β-unsaturated ketones, and because of the marked stereoselectivity of this process conversion of configuration becomes a necessary step in numerous syntheses. This has usually been achieved in a classical manner, through sulphonate esters, with subsequent S_N2 type displacement by benzoate anion. The overall yield of this transformation did not exceed 40% in the case of 2,3-unsaturated sugars.[7,9] Low yields, difficulty in purification of sulphonate esters and side reactions, for example formation of the 4-chloro-4-deoxy derivative on treatment with tosyl chloride,[9] limited the applicability of the method.

RESULTS AND DISCUSSION

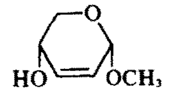
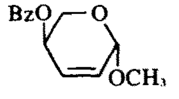
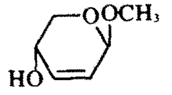
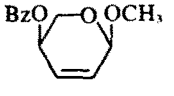
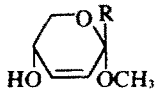
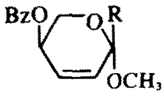
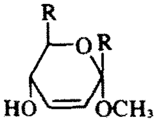
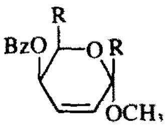
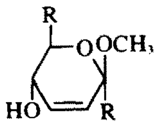
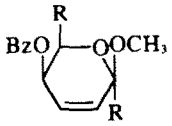
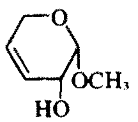
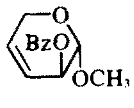
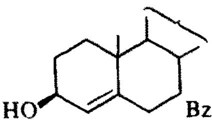
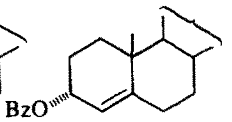
When methyl 2,3 - dideoxy - α - DL - glycero - pent - 2 - enopyranoside **1** was subjected to esterification with benzoic acid in the presence of DEAD and TPP only one reaction product could be detected (TLC, GLC, PMR). It was easily identified on examination of its ^{1}H-NMR spectrum as methyl 2,3 - dideoxy - β - DL - glycero - pent - 2 - enopyranoside benzoate **9** and finally compared with an authentic sample.[10] The conversion was virtually quantitative as shown by analytical means (TLC, GLC) and more than 90% of the product could be isolated chromatographically. Similarly, methyl 2,3 - dideoxy - β - DL - glycero - pent - 2 - enopyranoside **2** was selectively converted into its C-4 epimeric benzoate, indicating that the pseudo-axial hydroxy group reacts with equal ease. Other allylic alcohols converted into epimeric benzoates were; methyl 1 - O - benzyl - 3,4 - dideoxy - α - DL - glycero - hex - 3 - enopyranosid - 2 - ulose **3**, methyl 1,7 - di - O - benzyl - 3,4 - dideoxy - α - DL - erythro - hept - 3 - enopyranosid - 2 - ulose **4**, methyl 1,7 - di - O - benzyl - 3,4 - dideoxy - β - DL - erythro - hept - 3 - enopyranosid - 2 - ulose **5** and methyl 3,4 - dideoxy - α - DL - glycero - pent - 3 - enopyranoside **6**. Benzoates of 3,4-unsaturated ketosugars (**11–13**) were subsequently saponified, acetylated and compared with samples of the acetates of known configuration.

To demonstrate the wider applicability of the described transformation we reacted cholest - 4 - en - 3β - ol with benzoic acid, DEAD and TPP. The benzoate was formed in high yield. It had different physical properites and ^{1}H NMR spectrum from cholest - 4 - en - 3β - ol benzoate[11] and on saponification afforded completely pure α-alcohol, which was identified by comparison with an authentic sample.

In all cases analytical methods indicated complete consumption of the starting alcohol and did not reveal the presence of other products, except traces of cholestadiene obtained from **7**. The results are collected in Table 1. ^{1}H NMR data of the products are presented in Table 2.

The efficiency of the esterification procedure in the case of allylic alcohols is noteworthy. The DEAD–TPP system is recognized as a dehydrating agent[12] and can also bring about replacement of activated –OH groups (e.g. anomeric, benzyl or allyl –OH groups) by the 1,2-dialkoxycarbonylhydrazino residue.[13] Both reactions are in principle possible for the substrates examined, but in the presence of benzoic acid they evidently can not compete effectively with esterification, allylic benzoates being obtained in high yields. Even more striking is the regio- and stereoselectivity of the reaction. Recent investigation of the hydroxyl group exchange for the phthalimido residue in allylic systems of 2,3- and 3,4-unsaturated sugars[14] revealed that the stereochemistry of the transformation depends rather strongly on the substrate structure. Thus, inversion or rearrangement with and without inversion was encountered, suggesting the

Table 1. Formulae, yields and characteristic features of obtained benzoates

Substrate[a]	Product	Yield (%)	b.p. (°C/torr.)	Characteristic IR bands (cm^{-1})	Found C%	Found H%	Calc. C%	Calc. H%
 **1**	 **9**	94	120/0.3	1715, 1270 (ester) 1600, 700 (aromatic) 1090, 1060, 1040 (acetal)				
 **2**	 **10**	90	120/0.3	1715, 1270 (ester) 1600, 700 (aromatic) 1100, 1050 (acetal)				
 **3**	 **11**	87		1700, 1270 (ester) 1600, 720, 705 (aromatic) 1120, 1060 (acetal)	71.1	6.4	71.2	6.3
 **4**	 **12**	82		1720, 1260 (ester) 3050, 1600, 740, 700, 690 (aromatic) 1100, 1040 (acetal)	73.5	6.6	73.4	6.4
 **5**	 **13**	70		1720, 1265 (ester), 1660 (C=C) 3080, 1600, 740, 705, 695 (aromatic) 1100, 1070 (acetal)	73.6	6.5	73.4	6.4
 **6**	 **14**	88	120/0.2	1720, 1270 (ester) 3080, 1600, 705 (aromatic) 1100, 1060 (acetal)	66.6	6.0	66.6	6.0
 **7**	 **15**	81	oil, not distilled	1710, 1270 (ester) 1650 (C=C) 1600, 1580, 700 (aromatic)	83.0	10.2	83.2	10.3
$CH_2{=}CH{-}CHDOH$ **8**	$CH_2{=}CH{-}CHDOBz$ **16**	92	85/12	3100, 1605, 700 (aromatic) 2200, 2100 (C—D) 1715, 1280 (ester) 1660 (C=C)				

Bz = C_6H_5CO–; R = $C_6H_5CH_2$–OCH_2–

[a] Racemic substrates **1–6** are conventionally represented by the formulae of the *D*-series.

[b] Not determined. The compound was purified by molecular distillation.

[c] Compared directly with an authentic sample.

formation of thermodynamically controlled products via allylic carbonium ions. Very high regio- and stereoselectivity was consistently observed in the case of benzoylation indicating that its course is not thermodynamically controlled. To prove this point we examined the regioselectivity of the benzoylation reaction carried out on a basically symmetric allylic system. Deuterated allyl alcohol **8** was taken as the substrate, assuming that the distortion from complete symmetry in the ionic transition species, introduced by the presence of deuterium, would be negligible and yet the terminal carbon atoms could easily be distinguished. Treatment of the alcohol **8** according to the described procedure (see Experimental) yielded an ester, which on examination by ^{1}H NMR spectroscopy showed no deuterium scrambling, all the deuterium was found in the -CHD–OBz group, within the accuracy of the integration. This result appears to be of theoretical as well as practical significance. It has been demonstrated[15] that reactions of the DEAD–TPP system start with the formation of a betaine; $EtO_2C{-}N(Ph_3P^+){-}N^-{-}CO_2Et$, and are ionic in character. Results of phthalimidation of allylic alcohols[14] are consistent with this assumption. Our experiments, on the other hand indicate clearly that free allyl carbonium ions are not available during benzoylation. We

Table 2. ^{1}H NMR data of compounds **11–16**

Compound	Chemical shifts (δ) ppm	Coupling constants (Hz)
11	3.22 (s, 3H) OCH$_3$; 3.50 (dd, 2H) H-1, H-1′; 3.78–4.22 (m, 2H) H-6, H-6′; 4.48 (dd, 2H) OCH$_2$Ph; 5.08 (m, 1H) H-5; 5.92–6.22 (m, 2H) H-3, H-4; 7.0–7.4, 7.9–8.1 (m, 10H) aromatic.	$J_{11'} = 10.5$; $J_{66'} = 12.5$ $J_{gem} = 12.0$ (-OCH$_2$Ph) $J_{56} = 3.0$; $J_{56'} = 0.8$ $J_{34} = 10.2$; $J_{45} = 4.2$
12	3.27 (s, 3H) OCH$_3$; 3.34–4.00 (m, 4H) H-1, H-1′; H-7, H-7′; 4.1–4.5 (m, 5H) 2x OCH$_2$Ph, H-6 5.35 (dd, 1H) H-5; 6.10 (dd, 1H) H-4; 6.30 (d, 1H) H-3; 7.0–7.3, 8.0–8.2 (m, 15H) aromatic.	$J_{11'} = 10.2$; $J_{67} = 6.5$ $J_{56} = 2.5$; $J_{45} = 5.2$ $J_{34} = 10.0$
13	3.31 (s, 3H) OCH$_3$; 3.58 (s, 2H) H-1, H-1′; 3.62–3.71 (d, 2H) H-7, H-7′; 4.40–4.47 (d, 2H) OCH$_2$Ph; 4.57 (s, 2H) OCH$_2$Ph; 4.38–4.50 (m, 1H) H-6 5.28 (dd, 1H) H-5; 5.91 (d, 1H) H-3; 6.50 (dd, 1H) H-4; 7.0–7.3, 8.0–8.2 (m, 15H) aromatic.	$J_{34} = 10.4$; $J_{45} = 5.7$ $J_{56} = 2.1$; $J_{67} = 6.4$
14	3.45 (s, 3H) OCH$_3$; 4.16 (m, 2H) H-5, H-5′; 4.80 (s, 1H) H-1; 5.15 (m, 1H) H-2; 6.00 (m, 2H) H-3, H-4; 7.2–7.6, 8.0–8.2 (m, 5H) aromatic.	$J_{34} = 10.4$
15	5.35 (broad s, 1H); 5.53 (d, 1H); 7.2–7.5, 8.0–8.1 (m, 5H) aromatic.	$J = 5.5$
16	4.75 (m, 1H) CHDOBz; 5.15, 5.25, 5.42 (m, 2H) H$_2$C = ; 6.0 (m, 1H) =CH— 7.3–7.5, 8.0–8.2 (m, 5H) aromatic.	

therefore feel inclined to describe the reaction of a carboxylic anion with an alkoxy phosphonium salt ROP$^+$Ph$_3$ as proceeding through an intimate ion pair rather than a free charged species. From the practical point of view the esterification of allylic alcohol with benzoic acid in the presence of TPP and DEAD is an excellent procedure for inversion of configuration and protecting hydroxy groups in substrates susceptible to allylic rearrangement.

EXPERIMENTAL

B.ps of the microdistillations refer to the air bath temperature and are uncorrected. IR spectra were recorded with a Unicam SP-200 spectrophotometer. ^{1}H NMR spectra were recorded on Varian HA-60/IL (60 MHz) and Jeol JNM-4H-100 (100 MHz) spectrometers in CDCl$_3$ solutions using TMS as internal standard. Gas chromatography was performed on a W. Giede G.Ch.F. 18.3 apparatus, equipped with a 1 m × 3 mm stainless steel column packed with 15% Reoplex on 60–80 mesh chromosorb W. TLC was carried out on silica gel G (Merck), and silica gel (Merck) was used for column chromatography. All reactions and chromatographic separations were monitored by TLC. Methyl 2,3 - dideoxy - α - DL - glycero - pent - 2 - enopyranoside **1**, methyl 2,3 - dideoxy - β - DL - glycero - pent - 2 - enopyranoside **2**[10] and methyl 3,4 - dideoxy - α - DL - glycero - pent - 3 - enopyranoside **6**[16] were obtained as described in the literature. Details of the preparation of methyl 1 - O - benzyl - 3,4 - dideoxy - α - DL - glycero - hex - 3 - enopyranosid - 2 - ulose **3**, methyl 1,7 - di - O - benzyl - 3,4 - dideoxy - α - DL - erythro - hept - 3 - enopyranosid - 2 - ulose **4** and methyl 1,7 - di - O - benzyl - 3,4 - dideoxy - β - DL - erythro - hept - 3 - enopyranosid - 2 - ulose **5** will be given elsewhere.[8] Cholest - 4 - en - 3β - ol **7** was obtained as described in the literature.[17] Deuterated allyl alcohol **8** was prepared by reduction of commercially available acroleine with lithium-aluminum deuteride.

Preparation of benzoates (general procedure). An alcohol (1 mmol), triphenylphosphine (2 mmol) and benzoic acid (2 mmol) were dissolved in dry tetrahydrofuran (10 ml). A solution of diethyl azodicarboxylate (2 mmol) in tetrahydrofuran (2 ml) was added dropwise with stirring at room temperature. After 1 h the solvent was removed by evaporation and the residue taken into methylene chloride (20 ml), washed with a solution of sodium bicarbonate and water, dried (MgSO$_4$), filtered and evaporated to dryness. The residue was chromatographed on a silica gel column eluted with petroleum ether–ethyl acetate mixture.

Analytical samples were obtained by vacuum (**9**, **10**, **14**, **18**) and molecular (**11–13**) distillation.

Acknowledgements—The authors are most greateful to Prof. O. Achmatowicz Jr. for many stimulating discussions and would also like to thank Dr. M. Chmielewski for furnishing us with a sample of methyl 3,4 - dideoxy - α - DL - glyceropent - 3 - enopyranoside.

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