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Note

Benzoyl cyanide as a selective acylating agent

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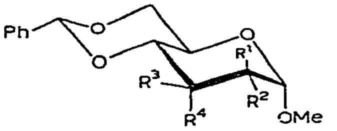
Recently, *N*-benzoylimidazole has been shown to be a highly selective acylating agent in carbohydrate chemistry. Thus, methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside[1] (**1**), methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-altropyranoside[2] (**2**), and benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside[3] (**8**) have been prepared from the parent diols (**3**, **4**, and **9**) in yields of 78, 48, and 89–93%, respectively. In the preparation of **2**, the starting diol was recovered in 44% yield.



1 R^1 = R^4 = H ; R^2 = OBz ; R^3 = OH
2 R^2 = R^3 = H ; R^1 = OBz ; R^4 = OH
3 R^1 = R^4 = H ; R^2 = R^3 = OH
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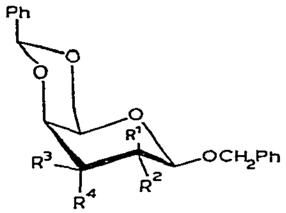
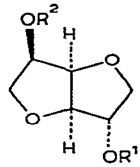
5 R^2 = R^4 = H ; R^1 = R^3 = OH
6 R^2 = R^4 = H ; R^1 = OBz ; R^3 = OH
7 R^2 = R^4 = H ; R^1 = OH ; R^3 = OBz



8 R^1 = R^4 = H ; R^2 = OH ; R^3 = OBz
9 R^1 = R^4 = H ; R^2 = R^3 = OH



10 R^1 = R^2 = H
11 R^1 = Bz ; R^2 = H
12 R^1 = H ; R^2 = Bz
13 R^1 = R^2 = Bz

We recently attempted the mono-benzoylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**5**) using *N*-benzoylimidazole in chloroform. However, little selectivity between HO-2 and HO-3 was observed since the imidazole formed during the acylation is capable of catalysing a facile ester migration between the two *cis*-hydroxyl groups, and the product consisted of a nearly 1:1 equilibrium mixture of 2- and 3-benzoates **6** and **7**, respectively. This contrasts to the mono-benzoylation of the *trans* 2,3-diol group in the *gluco*-derivative **3**; in this system, acyl migration is much slower under the reaction conditions, and the product (**1**) is apparently formed under kinetic control.

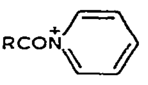
It seemed probable that an acylating agent which reacted in a neutral, nonhydroxylic solvent with the production of a weak acid might decrease the possibility of ester migration subsequent to acylation, and benzoyl cyanide, which has recently found application in nucleoside chemistry[4], seemed to be a suitable reagent. Treatment of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**5**) with one molar equivalent of benzoyl cyanide in acetonitrile in the presence of a catalytic quantity of triethylamine for 5–30 min, followed by preparative layer chromatography, yielded the 2- and 3-benzoates in the ratio 2.3 to 1. It is noteworthy that benzoyl chloride in pyridine has recently been reported[5] to yield the 3-benzoate **7** in 90% yield. The 2-benzoate **6**, which does not appear to have been described previously, was not crystalline, but was readily characterised as its 3-*O*-tosyl derivative.

In view of this ester ratio, the selectivity of benzoyl cyanide was compared to that of *N*-benzoylimidazole, and we now draw attention to the selectivity exhibited in benzoylations using this reagent.

Reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**) under similar conditions to that for the *manno*-isomer gave the 2-benzoate **1** in 62% yield, and benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**9**) gave the 3-benzoate **8** in 74% yield. Methyl 4,6-*O*-benzylidene-α-D-altropyranoside (**4**) was converted into the 2-benzoate **2** (62%), an improvement over the previous synthesis using the imidazolide[2]*.

Intramolecular hydrogen bonding has often been invoked to rationalise enhanced reactivity of hydroxyl groups towards esterification. Thus, it has been shown that 1:4,3:6-dianhydro-D-glucitol (**10**) is preferentially tosylated[6] and acylated[7,8] by acid chlorides in pyridine at the relatively hindered *endo*-5-OH group, and it is this group which exhibits strong intramolecular hydrogen bonding in dilute solution in carbon tetrachloride. The previous observations on the selectivity of acid chlorides were confirmed by using benzoyl chloride, when the 5-ester **12** and 2-ester **11** were isolated in the ratio 3.8:1. Neither *N*-benzoylimidazole or benzoyl cyanide, however, showed any appreciable selectivity for either of the hydroxyl groups in **10**.

An alternative explanation to hydrogen bonding has been forwarded for the enhanced reactivity of certain hydroxyl groups towards esterification. It has been suggested[9] that acyl pyridinium ions (**14** and **15**) are the effective acylating agents in reactions involving acid chlorides in pyridine, and that polar interactions, especially between oxygen atoms capable of acting as hydrogen-bond acceptors and the posi-



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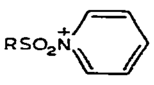

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*T.l.c. showed these compounds to be accompanied by only minor amounts of the other esters and starting materials.

tively charged nitrogen in the pyridinium ring, may be responsible for holding the acylating agent in the proximity of the hydroxyl group showing enhanced reactivity (see structure **8** in ref. 9); it is just this hydroxyl group which is capable of hydrogen bonding to the acceptor atoms in dilute solution. Our present results are not in disagreement with such a mechanistic interpretation. Thus, both *N*-benzoylimidazole and benzoyl cyanide lack an atom with a formal positive charge*, as is present in **14** and **15**, and they show no enhanced reactivity towards the 5-OH group in **10**. The selectivity shown by *N*-benzoylimidazole and benzoyl cyanide would therefore seem to be a result of other stero and/or electronic factors.

Benzoyl cyanide is commercially available, and recently a simplified synthesis has been reported[10]. The simplicity of the acylation procedure, together with its selectivity towards the pyranoside diols, suggest that this reagent may have considerable potential for selective benzoylation of carbohydrates. This possibility is being actively investigated.

EXPERIMENTAL

Preparative layer chromatography (p.l.c.) was carried out on Kieselgel PF_{254}. The following solvent combinations (v/v) were utilised as developers for t.l.c. and p.l.c.: *A* benzene–methanol (10:1), *B* benzene–ethyl acetate (2:1), *C* benzene–ethyl acetate (4:1). N.m.r. spectra were measured on a Varian HA-100 instrument with Me_4Si as internal reference, and chemical shifts are accurate to δ ± 0.02. Rotations were measured on a Perkin–Elmer 141 polarimeter in chloroform solutions.

Chloroform used for the preparations involving *N*-benzoylimidazole was washed with water, dried over calcium chloride, and distilled. Organic solutions were dried with anhydrous sodium sulphate.

Benzoylations with N-*benzoylimidazole.* — (*a*) *Methyl 4,6-*O*-benzylidene-α-*D*-mannopyranoside* (**5**). — A solution of *N*-benzoylimidazole in chloroform, prepared[3] by reaction of imidazole (2.1 g) and benzoyl chloride (2.1 g) in purified chloroform (30 ml), was added to a solution of **5** (4.12 g) in purified chloroform, and the mixture was heated under reflux for 10 h. The cooled mixture was filtered, washed with saturated, aqueous sodium hydrogen carbonate (15 ml) and saturated, aqueous sodium chloride (2 × 15 ml), and then dried. T.l.c. (solvent *A*) showed four components (*W*–*Z*, in order of increasing R_F values). *W* and *Z* were the starting diol **5** and the 2,3-dibenzoate, respectively. The components *X* and *Y*, which were shown to be the 3-benzoate **7** and the 2-benzoate **6**, respectively (see below), were present in nearly equal proportions. Components *X* and *Y* were isolated by p.l.c. (solvent *A*). Both showed i.r. absorption for ester carbonyl and hydroxyl groups. Re-examination of the separated components by t.l.c. showed the onset of acyl migration, and they were therefore immediately subjected to tosylation using tosyl chloride in pyridine.

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*Resonance between the canonical forms $R{-}CO{-}C{\equiv}N$ and $R{-}CO{-}\overset{+}{C}{=}\overline{N}$, and electronegativity differences between C and N will, of course, lead to bond polarization of the cyano group.

Component *Y* gave methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-tosyl-α-D-mannopyranoside, m.p. 187–189° (from ethyl acetate–light petroleum), $[\alpha]_D^{25}$ −34° (*c* 0.5); the m.p. was undepressed on admixture with an authentic sample prepared by benzoylation of the known[11] methyl 4,6-*O*-benzylidene-3-*O*-tosyl-α-D-mannopyranoside; ν_{max} (Nujol) 1725 (C=O) and 1170 cm^{-1} (R–SO$_2$–O–). N.m.r. data ($CDCl_3$): δ 2.28 (s, CH_3–Ar), 3.38 (s, OMe), 3.76–4.40 (complex, H-4,5,6,6′), 4.84 (d, H-1), 5.04 (dd, H-3), 5.44–5.56 (m, H-2), 5.52 (s, benzylic-H), 6.80–8.14 (complex, Ar-H).

Anal. Calc. for $C_{28}H_{28}O_9S$: C, 62.2; H, 5.2; S, 5.9. Found: C, 62.2; H, 5.2; S, 6.0.

Tosylation of component *X* gave methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-mannopyranoside, m.p. 213–215°, $[\alpha]_D^{25}$ −51° (*c* 0.1); ν_{max} (Nujol) 1715 (C=O) and 1175 cm^{-1} (R–SO$_2$O). N.m.r. data ($CDCl_3$): δ 2.12 (s, CH_3–Ar), 3.42 (s, OMe), 3.80–4.40 (complex, H-4,5,6,6′), 4.90–4.98 (m, H-1,2), 5.46 (dd, H-3), 5.60 (s, benzylic-H), 6.80–7.90 (Ar-H); lit.[5], m.p. 214–215°, $[\alpha]_D^{25}$ −35° (chloroform).

Anal. Calc. for $C_{28}H_{28}O_9S$: C, 62.2; H, 5.2; S, 5.9. Found: C, 62.3; H, 5.2; S, 5.9.

(*b*) *1,4:3,6-Dianhydro-*D*-glucitol* (**10**). — A solution of diol **10** and an equimolar amount of *N*-benzoylimidazole in chloroform (25 ml) was heated under reflux for 10 h and the reaction products were isolated by p.l.c. (solvent *B*). The 5- and 2-benzoates, and 2,5-dibenzoate (order of increasing R_F values) were isolated in the weight ratios of 1:1.35:1.35.

1,4:3,6-Dianhydro-2-*O*-benzoyl-D-glucitol (**11**), crystallised from ether–light petroleum, had m.p. 69–71°, $[\alpha]_D^{22}$ +70° (*c* 0.32), ν_{max} (*c* 4mM, carbon tetrachloride) 3563 cm^{-1} (bonded OH).

Anal. Calc. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.1; H, 5.6.

1,4:3,6-Dianhydro-5-*O*-benzoyl-D-glucitol (**12**), crystallised from ether–light petroleum, had m.p. 115–117°, $[\alpha]_D$ +52.2° (*c* 0.4), ν_{max} (4mM, carbon tetrachloride) 3630 (free OH) and 3610 cm^{-1} (shoulder)*.

Anal. Calc. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.2; H, 5.7.

1,4:3,6-Dianhydro-2,5-di-*O*-benzoyl-D-glucitol had m.p. 101–102°, $[\alpha]_D$ +27° (*c* 0.2); lit.[12] m.p. 102–103°, $[\alpha]_D^{18}$ +24.5° (chloroform).

Benzoylations using benzoyl cyanide. — General procedure. Equimolar quantities of the diol and benzoyl cyanide (approx. 2 to 4 mmoles) were stirred in acetonitrile (10 ml). One or two drops of triethylamine were then added, resulting in rapid dissolution of the diol, which was often not completely soluble in the initial mixture. The reaction was followed by t.l.c. and was generally complete in 5 to 30 min. The resulting, light-yellow solution was diluted with methanol (5 ml) and stirred for a

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*Although a similar shoulder on the peak for free OH in 5-*O*-acetyl-1,4:3,6-dianhydro-D-glucitol has been attributed to contamination[8], it is still present in the spectrum of rigorously purified material, and a similar pattern is found for 1,4:3,6-dianhydro-5-*O*-methyl-D-glucitol[13]. That the HO-2 in **10** can be involved in intramolecular hydrogen bonding is suggested by the fact that tetrahydrofuran-3-ol also exhibits[14] a minor absorption due to bonded OH.

further 30 min, after which the solution was concentrated. Methanol (5 ml) was added to the residue and the solution re-concentrated.

For the *gluco-*, *altro-*, and *galacto*-diols, a pure product was obtained directly by crystallisation of the final residue. The products from the *manno-* and anhydro-diol were subjected to chromatography.

(*a*) *Methyl 4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**3**). The diol **3** (1.13 g) and benzoyl cyanide (0.52 g) gave (t.l.c., solvent *C*) the 2-benzoate **1** with only traces of the slower moving 3-benzoate and faster moving 2,3-dibenzoate. Crystallisation from methanol gave methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1**; 0.96 g, 62%), m.p. and mixture[1] m.p. 167–169°; lit.[15] m.p. 169–170°; lit.[1] m.p. 166.5–168.5°.

(*b*) *Methyl 4,6-*O*-benzylidene-α-*D*-altropyranoside* (**4**). The diol **4** (0.56 g) gave (t.l.c., solvent *C*) predominantly one product, and crystallisation from methanol yielded methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-altropyranoside (**2**; 0.48 g, 62%), m.p. 137–138.5°, $[\alpha]_D^{24}$ $-5.2°$ (*c* 2.0); lit.[2] m.p. 138–139°, $[\alpha]_D^{19}$ $-5 \pm 1°$ (chloroform).

(*c*) *Benzyl 4,6-*O*-benzylidene-β-*D*-galactopyranoside* (**9**). The diol **9** (0.78 g) and benzoyl cyanide gave (t.l.c., solvent *C*) the 3-benzoate with only traces of the 2-iosmer, the 2,3-dibenzoate, and starting material. Crystallisation from methanol yielded benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**8**; 0.75 g, 74%), m.p. 179–181°, $[\alpha]_D$ $+61.5°$ (*c* 0.2); lit.[3] m.p. 178–179°, $[\alpha]_D$ $+64.4°$ (chloroform).

(*d*) *Methyl 4,6-*O*-benzylidene-α-*D*-mannopyranoside* (**5**). Reaction of the diol (1.13 g) with benzoyl cyanide yielded a mixture of benzoates which was separated by p.l.c. (solvent *C* containing a few drops of 2M acetic acid to suppress acyl migration). The 3- and 2-benzoates and 2,3-dibenzoate (order of increasing R_F values) were isolated in weight ratios of 1.5:3.5:1.0.

The 2-benzoate **6** was obtained as an amorphous solid (the 2-toluene-*p*-sulphonate is also amorphous[5]), $[\alpha]_D$ $-45.1°$ (*c* 0.3); ν_{max} (Nujol) 3460 (OH) and 1730 cm^{-1} (C=O). N.m.r. data (C_6D_6): δ 2.94 (s, OMe), 3.5–4.4 (complex, H-3,4,5,6,6′), 4.70 (d, H-1), 5.40 (s, benzylic-H), 5.61 (dd, H-2), 7.00–8.40 (complex, Ar-H).

Anal. Calc. for $C_{21}H_{22}O_7$: C, 65.3; H, 5.7. Found: C, 65.3; H, 6.0.

Compound **6** was characterised as its 3-toluene-*p*-sulphonate, m.p. 186–188° (see above).

The 3-benzoate, on crystallisation from hexane, had m.p. 132–133°, $[\alpha]_D^{22}$ $-26.1°$ (*c* 0.13); lit.[5] m.p. 131–132°, $[\alpha]_D$ $-24°$ (chloroform).

(*e*) *1,4:3,6-Dianhydro-*D*-glucitol* (**10**) — The diol **10**, reacted with benzoyl cyanide in the usual manner, gave after separation of the products by p.l.c. (solvent *B*), the 5- and 2-benzoates and 2,5-dibenzoate in the weight ratios 1.0:1.16:1.57.

*Benzoylation of 1,4:3,6-dianhydro-*D*-glucitol* (**10**) *with benzoyl chloride in pyridine.* — A solution of the diol **10** (1.46 g) in pyridine (15 ml) was cooled to 0° and a solution of benzoyl chloride (1.40 g) in pyridine (15 ml) was added dropwise during 15 min. After storage at 5° overnight and then at room temperature for 10 h, work up in the usual manner, followed by p.l.c. (solvent *B*), gave the 5- and 2-benzoates and 2,5-dibenzoate in the weight ratios 3.8:1:3.3.

Equilibration of diol monobenzoates catalysed by imidazole in chloroform. — (*a*) *Methyl 3-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside.* The title compound (0.28 g), prepared[16] by base-catalysed isomerization of the 2-benzoate **1**, was heated under reflux with imidazole (0.14 g) in chloroform (10 ml). The progress of reaction was monitored by t.l.c. (solvent *C*). After 12 h, the estimated isomerization to the 2-benzoate was ~10%. Only after 35 h did the ratio of mono-benzoates approach equality.

(*b*) *Methyl 3-O-benzoyl-4,6-O-benzylidene-α-D-mannopyranoside.* The title compound (0.04 g) was heated under reflux in chloroform (2 ml) in the presence of imidazole (15 mg), and the isomerization was monitored by t.l.c. (solvent *C*). After 1 h, approximately equal quantities of the 2- and 3-benzoates were present, and this ratio remained virtually unaltered on further reflux for a total of 16 h.

ACKNOWLEDGMENTS

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