APPROACHES TO THE SELECTIVE BENZYLATION OF THE PRIMARY HYDROXYL GROUP

N. V. Bovin, L. Yu. Musina,
and A. Ya. Khorlin

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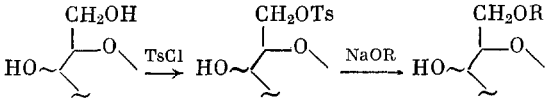
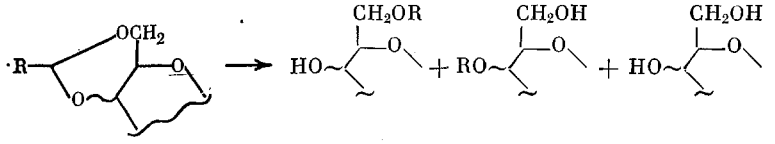
The selective acylation, alkylation, and glycosylation of carbohydrates has received considerable attention [1]. In the case of acylation and glycosylation, some characteristic features of the reactivity of hydroxyl groups have been found, and general methods of selective glycosylation have been proposed for many types of aglycones. The same is true of acylation, but this applies for the most part to acylation of primary hydroxyl groups in the presence of secondary groups. On the other hand, alkylation, and in particular benzylation, of polyols is less selective [1], and seldom affords preparative yields of mono-O-benzyl derivatives. Furthermore, cases are known in which benzylation of the secondary OH group occurs more readily than that of the primary group [2, 3]. Lower selectivity is typical of the classical methods of alkylation (in the presence of NaH, $Ba(OH)_2$, NaOH, or Ag_2O), and of phase-transfer catalyzed alkylations [4]. Two indirect methods have been put forward for the indirect synthesis of 6-O-alkylated hexopyranoses. The first of these [5, 6] involves nucleophilic replacement of the 6-O-tosylates by sodium alkoxide, the tosylates in turn being obtained by selective tosylation.



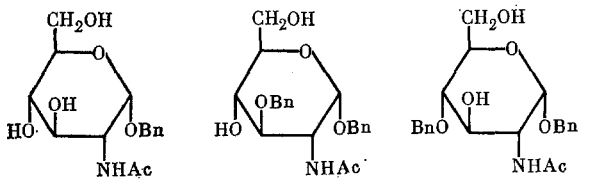
The second method is the reductive fission of 4,6-O-alkylidene derivatives by hydrides ($LiAlH_4$ + $AlCl_3$ [7], $NaBH_3CN$ + HCl [8]) or by $Me_3N{\cdot}BH_3$ + $AlCl_3$ [9], as shown below:



Reductive cleavage has been used preparatively, but the method nevertheless has several drawbacks due to the nonspecificity of the ring opening, and the need to use solvents of low polarity (THF, ether, or toluene) in which the benzylidene derivatives of carbohydrates are sparingly soluble.

Also worthy of mention is a method involving the alkylation of tributyltin alcoholates [10, 11], but this requires severe conditions for the synthesis of the Bu_3Sn derivatives.

There are three more literature methods for the O-alkylation of carbohydrates, namely, with diazo compounds in the presence of Lewis acids [1], by imidates $ROC(=NH)CCl_3$ in the presence of CF_3SO_3H [12], and with alkyl triphthalates [13], but these are of no practical value for selective alkylation. We here examine three approaches to the synthesis of 6-O-benzylpyranoses, taking the alkylation of the triol (I) and the diols (II)-(IV) as examples.



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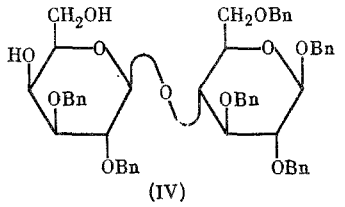


(IV)

Benzylation in the Presence of i-PrONa

If it is assumed that the OH groups in the diol react independently of each other, then the diol may be regarded as a mixture of two alcohols, a primary C^1OH, and a secondary C^2OH. Alkylation in the presence of strong bases appears to proceed under thermodynamic control in the first step, and the outcome of the alkylation is determined by the equilibrium $C^1O^- + C^2OH \rightleftarrows C^1OH + C^2O^-$. In order to direct the reaction towards the preferential formation of C^1OBn, it is necessary to shift the equilibrium to the left, which may be done by adding the alkoxide of a secondary alcohol, for example i-PrONa. The reaction is carried out as follows: to a solution of (II) and BnCl (or BnBr) in DMF is added slowly i-PrONa (up to 2 equiv.). A preparative experiment gave 50% of the 6-O-, 15% of the 4-O-, and 5% of the 4,6-O-benzyl derivatives, together with 30% of the original diol (II), i.e., the selectivity of benzylation of the primary OH group over the secondary group under these conditions is 3.3. In a control experiment, in which benzylation was carried out in the presence of NaH, the selectivity was 1.5. Similar results were obtained in the benzylation of (III).

Hence, the selectivity of benzylation of the primary OH group is increased in the presence of i-PrONa, but from the preparative point of view the outcome cannot be regarded as satisfactory.

Benzylation with Benzyl Trichloroacetylimidate

The alkylation of polyalcohols, which is normally caried out in the presence of strong bases, differs from acylation and glycosylation in being much less regioselective [1]. This could be due to the fact that in acylation and glycosylation the nucleophilic reagent is the alcohol itself, whereas in alkylation it is the alkoxide ion, and if two alcohols differ markedly in their reactivity, then the two corresponding alkoxides, both being strong nucleophiles, will differ in their reactivity to a much lesser degree. It should be emphasized that the latter remarks refer to alkylation in the presence of strong bases (NaH, NaOH, t-BuOK, $Ba(OH)_2$).

There is a group of methods (much less frequently encountered) which do not require the use of strong bases. The nucleophile in these reactions is the alcohol itself, and in these cases, therefore, higher selectivity of alkylation would be expected.

Benzylation with phenyldiazomethane requires the use of a large excess of the reagent [14], and is therefore not very suitable for preparative purposes. Benzylation with benzyl triflate is applicable only to neutral sugars, the acetamido-group under the conditions employed being alkylated in addition to the hydroxyl groups [13]. In this study, an attempt was made to selectively benzylate the primary OH group by the imdate method [12].

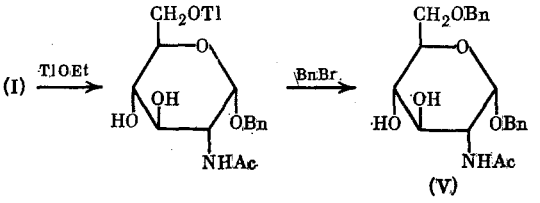
Reaction of the diol (II) with $BnOC(=NH)CCl_3$ (2-2.5 equiv.) in solvents such as chloroform, dichloromethane, and 1,2-dichloroethane in the presence of CF_3SO_3H at 20° and 0°C gave mixtures of the 6-O- and 4-O-Bn derivatives in a ratio of 2:1, in overall yields of 45-60%. Benzylation of the triol (I), which is insoluble in these solvents, in DMSO was somewhat more selective, but the overall yield failed to exceed 20%.

Benzylation by the imidate is in principle very similar to glycosylation with oxazolines, which is highly selective towards primary OH groups [15]. However, attempt to benzylate (I) and (II) under the conditions of the oxazoline synthesis with benzyl trichloroacetimidate, viz., in the presence of TsOH at 60-100°C afforded only trace amounts of the required products.

Finally, benzylation of the diol (IV) (CH_2Cl_2, $BnOC(NH)CCl_3$, CF_3SO_3H, 20°C) took place preferentially in the 4' position, the ratio of 6'-O-Bn- to 4'-O-Bn-isomers under these conditions being 2:3, overall yield 50%. Hence, despite the difference in the alkylation mechanism, in this case an inversion of selectivity was found, such as occurs on other galactose derivatives [2, 3].

Benzylation with Thallium Alkoxides

Thallium alkoxides have been used in carbohydrate chemistry for the benzylation of benzyl-2-acetamido-3,6-di-O-acetyl-2-desoxyglucopyranose [14], and for the preparation of some acyl derivatives [16]. Examples are also known of selective alkylation of noncarbohydrate diols at the primary OH group [17]. Kalinowski et al. [17] carried out the alkylation as follows: to a solution of the diol in MeCN was added TlOEt (up to two equiv.), and the resulting insoluble thallium alkoxide after evaporation (to remove ethanol) was treated with the alkyl halide. This method is unsuitable for compounds (I)-(III), which are sparingly soluble in acetonitrile, and we therefore modified it. To a solution of the triol (I) in DMF was added 1.5 equiv. of TlOEt, and the ethanol was then removed in vacuo (1 mm Hg) together with approximately half of the DMF, at 40°C. The solution was then cooled, and benzyl bromide added. The product (V) was isolated in the pure state by crystallization, isomers and di-O-Bn being formed in only small amounts (<10% in total). The reaction was continued until all the triol had reacted, since (V) is more readily separable from di-O-Bn ethers than from the starting material (I).



EXPERIMENTAL

Melting points were determined on a Boetius apparatus (East Germany), optical rotations were measured at 20°C on a Perkin-Elmer polarimeter, TLC was carried out on Kieselgel F-254 plates (E. Merck) in the systems acetone–toluene and chloroform–methanol, and column chromatography on silica gel 40-100 μm (Chemapol, Czech SSR). The benzylation products were separated preparatively on a column, and compared with authentic samples [18, 19] in respect of the melting points and specific rotations. The solvents after dehydration were finally dried over molecular sieve 4A. Benzyl trichloroacetimidate was prepared as described in [20], and TlOEt as described in [21].

Benzylation of Benzyl-2-acetamido-3-O-benzyl-2-desoxy-α-D-glucopyranoside (II). To a solution of 4 g (10 mmole) of the diol (II) and 2.54 g (20 mmole) of BnCl in 60 ml of DMF was added dropwise at 20°C over 30 min a solution of 20 mmole of i-PrONa (from 480 mg of NaH) in 40 ml of DMFA. After 15 h, the mixture was diluted with 200 ml of dichloromethane, washed twice with water, and evaporated to dryness. Chromatography on silica gel in a 0 → 50% acetone–chloroform gradient gave successively the following glucopyranosides: 3,4,6-tri-O-benzyl- (0.29 g, 5%), 3,4-di-O-benzyl- (0.74 g, 15%), 3,6-di-O-benzyl (2.45 g, 50%), and 3-O-benzyl-2-acetamido-2-desoxy-α-benzyl-D-glucopyranoside (1.20 g, 30%), the melting points and $[\alpha]_D$ values of which agreed with the literature figures [18].

Benzylation of Benzyl-2,3,6,2',3'-penta-O-benzyl-β-lactoside (IV). To a solution of 2.2 g (2.5 mmole) of the disaccharide (IV) [19] and 1.25 g (5 mmole) of benzyl trichloroacetimidate in 100 ml of dichloromethane was added 50 μliter of CF_3SO_3H, followed after 30 min by a further 50 μliter. The mixture was kept at 20°C for 60 min., 1 ml of pyridine added, evaporated, and chromatographed in a 0 → 30% acetone–toluene gradient. There were isolated benzyl-2,3,6-2',3',6'-hexa-O-benzyl-β-lactoside, mp 118°C, $[\alpha]_D^{20}$ +10° (C 1, $CHCl_3$) (cf. [19], syrup, $[\alpha]_D$ +4°, C 0.55), and benzyl-2,3,6-2',3',4'-hexa-O-benzyl-β-lactoside, mp 122-123°C, $[\alpha]_D$ −1°, (C 1, $CHCl_3$) (cf. [19], mp 109-111°C, $[\alpha]_D$ −14°, C 1.29).

Benzyl-2-acetamido-6-O-benzyl-2-desoxy-α-D-glucopyranoside (V). To a solution of 9.3 g (30 mmole) of the triol (I) in 200 ml of DMFA was added with stirring 11.2 g (44 mmole) of TlOEt. When the ethoxide had dissolved completely, the flask was evacuated (to 1 mm Hg), and warmed slowly with stirring to 40°C. When 40-50% of the DMFA had passed into the trap (at −70°C), the solution was cooled to 20°C, and 7.7 g (45 mmole) of BnBr in 50 ml of DMFA was added over 30 min, the disappearance of (I) being followed by TLC. Methanol (10 ml) was added, and after 30 min the TlBr was filtered off, the solution evaporated to dryness, and the residue recrystallized from nitromethane to give 80-90% of (V) (cf. [18]).

CONCLUSIONS

1. The selectivity of benzylation of the primary hydroxyl group in the presence of sodium isopropoxide is greater than in the presence of the hydride.

2. The selectivity of the benzylation of the primary hydroxyl group by benzyl trichloroacetimidate is low.

3. Benzylation of the thallium alkoxide of benzyl-2-acetamido-2-desoxy-α-D-glucopyranoside proceeds readily and selectively in the 6-position.

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