Carbohydrate Research, 78(1980) C11–C14

Preliminary communication

Palladium-catalyzed, allylic aminations and alkylations of an unsaturated sugar acetate*

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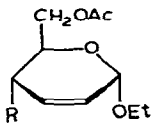
(Received October 15th, 1979; accepted for publication, October 18th, 1979)

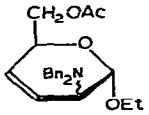
In connection with our interest in the development of methods for the synthesis of unusual amino, deoxy, unsaturated, and branched-chain sugars[1], we considered that the palladium-catalyzed substitution of allylic acetates by amines or reactive methylene compounds[2–5] could prove a valuable asset to carbohydrate chemistry. In the presence of a catalyst such as tetrakis(triphenylphosphine)palladium, an allylic acetate forms an intermediate π-allylpalladium complex that is attacked by an added nucleophile to give an allylically substituted (*e.g.*, aminated or alkylated) product; the palladium species liberated upon collapse of the complex is reconverted into a catalytically active form by the excess of triphenylphosphine. The reaction constitutes one of the numerous applications of organopalladium chemistry that are currently under intensive investigation[6]. It normally proceeds with a high degree of regioselectivity and stereocontrol, although certain deviations from this desirable trend have been observed and discussed[5f–5j].

For an initial evaluation of the potential of the method in the field of carbohydrates, we chose as a substrate the crystalline ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**1**), which is readily prepared[7] from the commercially available D-glucal. Various aliphatic and aromatic amines were employed as nucleophiles, as were several reactive-methylene compounds in the form of their sodio derivatives. Typically, the reactions were performed by stirring **1** (0.5 mmol) with triphenylphosphine (0.4 mmol) and $(Ph_3P)_4Pd^0$ (0.04 mmol) in dry oxolane (30 min at ~25°), whereupon the nucleophile was added, and the mixture heated at reflux temperature until monitoring by t.l.c. indicated the complete disappearance of **1** (1–2 days or, sometimes, less). The products of allylic substitution were isolated by preparative t.l.c. or column chromatography, and high yields (70–90%) were achieved in the majority of cases. Thus, the 4-aminated, 2,3-unsaturated glycosides **2**–**6** were obtained from reactions with diethylamine, piperidine, cyclohexylmethylamine, benzylmethylamine, and benzylamine. Whereas the formation of **2**–**5** appeared to be straightforward, that of **6** was attended by complications stemming from the nature of the nucleophile as a primary amine. The

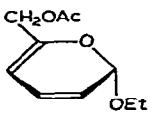
*This work was supported by the Natural Sciences and Engineering Research Council of Canada, and was presented, in part, at the 62nd Canadian Chemical Conference, Vancouver, B.C., June 3–6, 1979.

reaction mixture showed a complex pattern in t.l.c. (2:1 petroleum ether–ethyl acetate), and chromatographic separation gave **6** (R_F 0.6) in 30% yield, and a 1:1 mixture of what was, according to the n.m.r. spectrum, the *O*-deacetylated derivative **6a** (R_F 0.25) of **6** and partially *O*-deacetylated **1** (R_F 0.2), which jointly amounted to 60%. Acetylation of the mixture, followed by chromatography, furnished crystalline **1** and the syrupy, but homogeneous, *N*-acetyl-*O*-acetyl derivative **6b**.

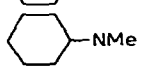




7b



8

1 R = OAc
2 R = Et_2N
3 R = 
4 R = 
5 R = BnNMe
6 R = BnNH
6a R = BnNH ; H instead of Ac
6b R = BnNAc
7a R = Bn_2N
9 R = $CH(CO_2Me)_2$
10 R = $CH(CO_2Et)_2$

Whereas the aminations just described appeared to be nearly regiospecific (as judged from the n.m.r. spectra of the products), dibenzylamine gave two positional isomers in the ratio of 7:3, namely, the 4-aminated analog **7a** (m.p. 78–79°) and its syrupy, 2-aminated, 3,4-unsaturated isomer **7b**. We cannot, at present, offer an explanation for this diminished selectivity. Some reactions of **1** with primary, aromatic amines were examined in a preliminary way. Thus, the incorporation of *p*-aminobenzophenone, *p*-aminoacetophenone, and 2,6-dimethylaniline into the sugar molecule was clearly demonstrated by n.m.r. spectroscopy, but, at least in the last two cases, mixtures of products arose that we have thus far been unable to separate, and that have not yet been fully characterized.

Reaction of **1** with diisopropylamine did not lead to substitution, presumably because of steric hindrance. Instead, elimination occurred, to give the diene **8**. The same happened on prolonged heating of **1** and catalyst in the presence of triethylamine or, indeed, in the absence of any amine. There are precedents in the literature[5j,8], for the formation of dienes from allylic acetates under such circumstances.

The reactions with dimethyl and diethyl sodiomalonate also proceeded well, giving high yields of the branched-chain glycosides **9** and **10**. Use of malononitrile or ethyl cyanoacetate was less satisfactory; only small yields were obtained, and the products have not been characterized, except by their ^{1}H-n.m.r. spectra which, however, did

show the patterns expected for the respective, substitution products. In the case of the product from ethyl cyanoacetate, the multiplicities associated with the signals of the ethyl groups (δ 1.3) and of the olefinic protons (δ 5.7–6.1) suggested the presence of isomers in the ratio of 2:1.

Although the new glycosides **2**–**10** were oils that failed to crystallize (except for **7a**) and tended to incur discoloration unless stored at low temperature, they were obtained in chromatographically homogeneous form, and were characterized by elemental analysis and the following $[\alpha]_D^{25}$ values (*c* 1.0–1.3, chloroform): **2**, +169.8°; **3**, +164.3°; **4**, +149.7°; **5**, +165.4°; **6**, +115.5°; **6b**, +129.1°; **7a**, +171.4°; **7b**, +155.3°; **9**, +93.5°, and **10**, +93.4°. The structures were determined spectroscopically, as will be disclosed in a full paper. In brief, the position of the double bond in **2**–**7a**, **9**, and **10** was revealed by mass spectra showing, in each case, a prominent peak at *m/e* $M^+ - 102$ that originated from loss of *O*-acetylglycolaldehyde due to retrodienic fragmentation, as is typical[9] for 2,3-unsaturated hexopyranosides. By contrast, **7b** gave a peak at *m/e* $M^+ - 74$, resulting from loss of ethyl formate, characteristic[9] for 3,4-unsaturated ethyl hexopyranosides. The ^{13}C-n.m.r. signals attributable to C-1 in the former series of compounds all occurred in the narrow range of 93.89–94.32 p.p.m. (from Me_4Si), whereas the C-1 signal of **7b** stood apart, at 97.40 p.p.m. In the ^{1}H-n.m.r. spectra of **2**–**7a**, **9**, and **10**, the olefinic protons resonated in the δ-6.0 region, as AB quartets ($J_{2,3}$ 10.3–10.8 Hz), with additional splittings from coupling with H-1 and -4. The $J_{4,5}$ values were 9.5–10.3 Hz, indicating diaxial orientations of H-4 and -5, and hence, the D-*erythro* configuration. In **7b**, on the other hand, the olefinic protons gave singlets that coincided at δ 5.88, and the stereochemistry at C-2 was difficult to assign definitively. The fact that coupling between H-1 (virtual singlet at δ 5.08) and H-2 (narrow triplet at δ 3.14) was extremely small is, perhaps, best explained by assuming an equatorial H-2 in the $^0H_1$ conformation, whereby the D-*threo* configuration would tentatively be allocated to **7b**. The diene **8** produced a molecular-ion peak at *m/e* 198 in the mass spectrum, and gave a readily analyzable, first-order, ^{1}H-n.m.r. spectrum.

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