PALLADIUM CATALYZED REACTIONS OF UNSATURATED CARBOHYDRATES – A ROUTE TO C–GLYCOSIDES

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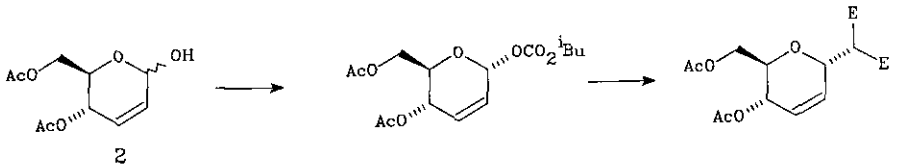
Abstract– Glycosyl carbonates are shown to be excellent substrates to effect palladium catalyzed stereoselective C–glycosidations in good yields under mild conditions.

C–Glycosides are important chiral building blocks in the synthesis of natural products[1] and several methods for their preparation have been developed.[2] Due to the stereocontrol offered by transition metal mediated transformations, several groups have recently investigated these methods to afford C–glycosidation.[3] Although the use of palladium catalyzed allylic substitution[4] has received limited attention in this context,[5] it would provide an easy, stereo– and regioselective route for the preparation of C–glycosides. Since glycals are generally unreactive under the conditions employed to obtain palladium catalyzed allylic substitution,[6] attention has been given to the use of pseudoglycals as possible substrates.[7] Recently Brakta *et al.*[7] reported the palladium catalyzed introduction of a limited number of carbon nucleophiles into the anomeric position of the phenyl glycoside (**1**) in moderate to excellent yields. This reaction requires drastic conditions and the use of *O*–benzyl protecting groups at the 4– and 6–positions of the starting material. As part of our continuing investigation into the palladium catalyzed reactions of unsaturated sugars,[8] we now report the fast and efficient introduction of nucleophiles into glycosyl carbonates[9] (cf. Scheme 1) under neutral conditions at room temperature.[10]

The glycosyl carbonate (**3**), which was favored as starting material,[11] was obtained by treatment of

di–*O*–acetylpseudoglucal[12] (**2**) with isobutyl chloroformate in the presence of pyridine. The α–anomer was obtained in an isolated yield of 75% (*Scheme* 1).[13] Treatment of **2** with di–*tert*–butyl dicarbonate in the presence of pyridine yielded both the α– and β–anomers (**4**) and (**5**) respectively.

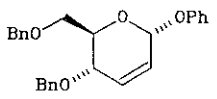


E = Electron withdrawing group

Scheme 1

Reaction of the glycosyl carbonate (**3**) with 4 equivalents of diethyl malonate in the presence of catalytic amounts of $Pd(PPh_3)_4$ and PPh_3,[14] however, furnished only the acetal (**6**) in a yield of 72%. This can be rationalized in terms of the attack of *in situ* generated isobutoxide (after the loss of CO_2) on the π–allyl palladium complex. Use of a large excess (*10* eq.) of nucleophile did, however, give the sought after C–glycoside (**7**) in a yield of 81%. Compounds (**8**) (in a 60:40 mixture of isomers) and (**9**) were prepared in similar reactions. This method, in contrast to the reaction reported by Brakta *et al.*[7] allows the direct introduction of enolisable substituents into the 1–α–position. Reactions of the α– and β–carbonates (**4**) and (**5**) also afforded the C–glycosides (**7**) and (**11**), respectively, in good yields. **10** was prepared from **5** in a similar reaction. In all cases regioselective substitution proceeded with retention of configuration at C–1. It may also be noted that although the substrates also contain an allylic acetate group, the allylic substitution proceeds in a chemoselective way and no products of C–4 substitution were observed under these conditions. The reactions were complete at room temperature within minutes after the introduction of the nucleophile into the reaction mixture. Surprisingly use of the alkyl cyanoacetates (**12**) and (**13**), even in large excess, gave only the products of double substitution (**14**) and (**15**), respectively. The reason for this facile double substitution is not yet clear and is still under investigation. Tertiary nucleophiles other than methyl Meldrum's acid (**16**) gave no reaction under these conditions and heating of the mixture gave only the acetal (**6**). Since the use of large excesses of nucleophile is uneconomical and complicates the purification of the reaction products, we turned attention to the development of reaction conditions that do not impose these

limitations. A solution to the problem involves the use of only 2 equivalents of nucleophile. In this case the final step of the procedure involves addition of the palladium catalyst resulting in the complete suppression of acetal formation. The best results were however achieved by the use of anions of carbon nucleophiles in these allylic substitution reactions, prepared prior to addition by deprotonation with sodium hydride.



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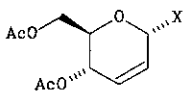
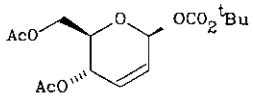


3. X = $OCO_2{}^iBu$
4. X = $OCO_2{}^tBu$



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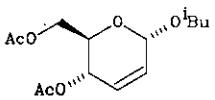

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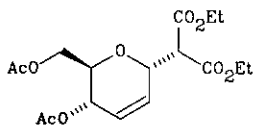

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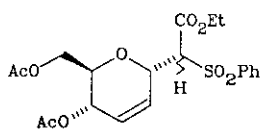

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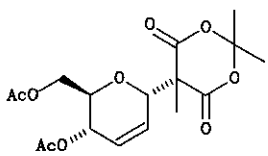

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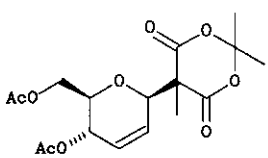

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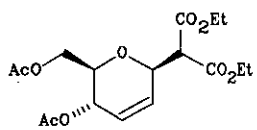

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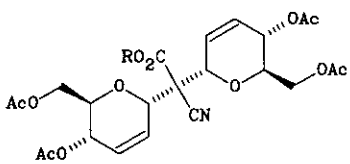
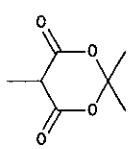
12. R = Me
13. R = ^tBu



14. R = Me
15. R = ^tBu



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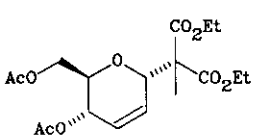

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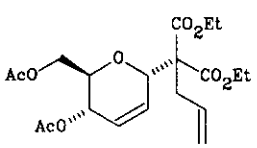

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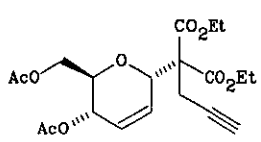

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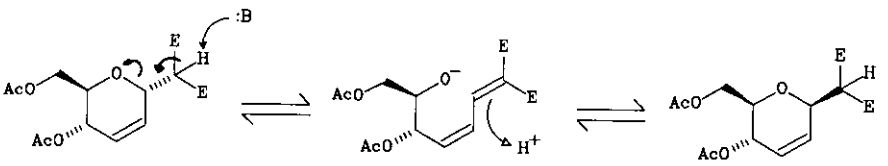
Surprisingly, use of the anion of diethyl malonate as nucleophile in these reactions gave two products which were later identified as the α– and β–isomers (7) and (11), respectively. Further experiments indicated that isomerization takes place under the basic reaction conditions after completion of the palladium catalyzed allylic substitution. Treatment of the C–glycoside (7) with bases such as triethylamine and N,N–dimethylguanidine also resulted in isomerization to the β–isomer. The isomerization of these glycosides under basic conditions is ascribed to the acidity of the H–1' of this type of compound and probably proceeds by the mechanism depicted in Scheme 2.



Scheme 2

The C–glycosides obtained by Brakta *et al.*[7] can also be rationalized in a similar way rather than the mechanism suggested by the authors.

As expected, the use of the anions of tertiary nucleophiles such as diethyl methylmalonate did not result in isomerization of the products of allylic substitution. Thus reaction of the carbonate (3) with the anion of diethyl methylmalonate (4 eq.) in the presence of $Pd(PPh_3)_4$ and PPh_3 gave the C–glycoside (17) in excess of 70% yield. Similar reactions also afforded the products (18) and (19) in more than 70% yields. It was later found that 1 equivalent of anion was sufficient to result in C–glycosidation under these conditions.

This method therefore provides a fast and efficient route for the introduction of enolate type nucleophiles into the anomeric position of carbohydrates. In addition this reaction allows the introduction of a C–substituent containing an acidic 1–H hydrogen into the 1 β–position of a pseudoglycal. The use of an ester protecting group at the 4–position of the pseudoglycal starting materials allows the subsequent palladium catalyzed introduction of different nucleophiles into the 4–position under basic conditions and we are currently investigating this possibility.[10]

ACKNOWLEDGEMENT

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11. The use of the corresponding acetate requires drastic conditions and the use of anions as nucleophiles which leads to isomerization of the reaction products in all cases.
12. (a) E. Fischer *Ber.*, 1914, **47**, 196; (b) M. Bergmann and W. Freudenberg, *Ber.*, 1931, **64**, 158.

13. The structures and stereochemistry of all products were in accord with proton and carbon nmr , mass spectra and micro analyses, The structures of **9** and **10** were confirmed with X–ray crystallography. Selected data of some key compounds are cited. **3** $[\alpha]_D^{21}$ +55^0 (c = 2.0, $CHCl_3$); ^{13}C nmr ($CDCl_3$) δ 18.84, 20.71, 20.89, 27.74, 62.37, 64.47, 68.88, 74.39, 91.11, 125.12, 131.14, 153.99, 170.07, 170.72; ^1H nmr ($CDCl_3$) δ 3.93 (dd, J = 6.8, 10.2 Hz), 3.96 (dd, J = 6.6, 10.2 Hz), 4.12 (ddd, J = 2.6, 4.7, 9.4 Hz), 4.18 (dd, J = 2.6, 12.2 Hz), 4.23 (dd, J = 4.8, 12.2 Hz), 5.36 (dq, J = 9.8, 1.6 Hz), 5.86 (ddd, J = 2.0, 2.8, 10.2 Hz), 6.03 (d, J = 10.2 Hz), 6.17 (m); m/z 271 ($M^+ - OCOCH_3$, 8.3%); **9** (preferred conformation):mp. 148–150^{0}C, $[\alpha]_D^{24}$ +111^0 (c = 2.8, $CHCl_3$); ^{13}C nmr ($CDCl_3$) δ 21.35, 21.53, 21.86, 29.28, 30.59, 53.95, 61.98, 64.30, 73.33, 76.29, 106.55, 124.57, 129.17, 167.96, 169.88, 171.31, 171.52; ^1H nmr ($CDCl_3$) δ 3.97 (m 3H), 4.68 (q, J = 2.1 Hz), 4.90 (m), 6.03 (ddd, J = 2.2, 4.4, 10.6 Hz), 6.25 (ddd, J = 1.0, 1.7, 10.6 Hz); m/z 369 (M^+ 1.0 %); **10** (preferred conformation) ^1H nmr δ 3.72 (ddd, J = 2.8, 5.6, 9.0 Hz), 4.09 (dd, J = 5.6, 12.2 Hz), 4.17 (dd, J = 5.6, 12.2 Hz), 4.73 (m), 5.30 (m, J = 9.8 Hz), 5.85 (dt, J = 10.4, 2.2 Hz), 6.12 (dt, J = 10.6, 1.6 Hz).

14. Palladium catalyzed allylic substitution is generally carried out as follows: $Pd(PPh_3)_4$ (10 mol %) , PPh_3 (20 mol %) and the substrate (1 mmol) are stirred together in THF (10 ml) after which the nucleophile (10 mmol) is added. It is of interest to note that under these conditions the acetal is not obtained before the introduction of the nucleophile to the reaction mixture.

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