Tetrahedron Letters,Vol.28,No.47,pp 5853-5856,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS OF C-GLYCOSYL COMPOUNDS BY THE ADDITION OF GLYCOSYL RADICALS TO OLEFINS[1]

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Abstract : The Bu_3SnH - AIBN induced radical additions of 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl derivatives, bearing α-Br (1), α-I (5), β-OCSSMe (7), and β-SePh (8) groups on the anomeric carbon, with olefins such as dimethyl maleate, methyl vinyl ketone, dimethyl acetylenedicarboxylate, butyl vinyl ether, and N-ethylmaleimide were examined for a synthesis of C-glycosyl compounds.

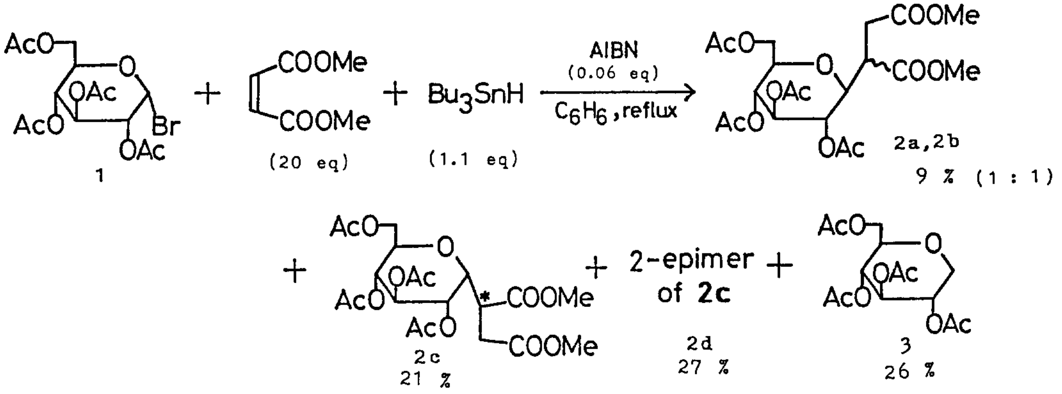
Various types of C-glycosyl compounds with interesting biological properties are found in nature[3]. C-Glycosyl compounds have also been recognized as partial structures of many natural products and thus they attract the interest of synthetic organic chemists as chiral building blocks in natural product synthesis[4]. There have been many researches concerning the synthesis of C-glycosyl compounds[5]. We have reported the syntheses of C-glycosyl compounds by photochemically-induced[6] and peroxide-induced[7] radical additions of alcohols and ethers to glycals. In this communication, the tributyltin hydride (Bu_3SnH) - α,α'-azobisisobutyronitrile (AIBN) induced additions of a glucopyranosyl radical to olefins are described. In the course of our investigation[1], similar glycosyl radical addition reactions have been published[8-10]. In these works, however, the olefins used were restricted to a few simple ones such as allyltributyltin, methyl acrylate, and acrylonitrile.

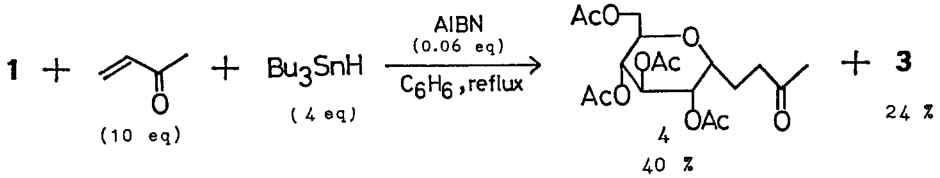
Dropwise addition of a solution of Bu_3SnH (1.1 eq) in benzene to a refluxing solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1) (1.0 eq), dimethyl maleate (20 eq), and AIBN (0.06 eq) in benzene gave a diastereomeric mixture of dimethyl 2-glucopyranosylsuccinate derivatives (**2a** - **d**) in a good yield (68%), and a reduced product, 2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-glucitol (**3**), in a 26% yield. Rechromatography of the mixture of **2a** - **d** gave the mixture of equal amounts of two β-anomers (**2a**, **2b**) (9% yield), the less polar (having a lager Rf-value) α-anomer (**2c**)[11] (21% yield) and the more polar (having a smaller Rf-value) α-anomer (**2d**)[11] (27% yield). Configurations at 2-position of **2c** and **2d** remain to be established. The high stereoselectivity at 1'-position ($\alpha : \beta$ = 5.3 : 1) may be rationalized by the anomeric effect in the glycopyranosyl radical intermediate[12]. The low stereoselectivity at 2-position (**2a** : **2b** = ca. 1 : 1, **2c** : **2d** = 1 : 1.3) causes no problems on the case of conversion of them to heterocyclic compounds analogous to showdomycin.

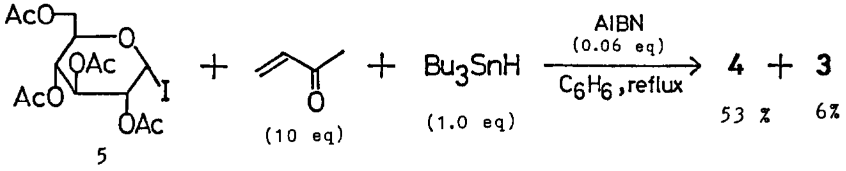
A similar reaction of 1 with methyl vinyl ketone (10 eq) gave 4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-2-butanone (4) (40% yield) and 3 (24% yield). In this case, four equivalents of Bu_3SnH was needed for the disappearance of the starting bromide 1 on t.l.c. analyses of the reaction mixture. Thus, it was suggested that Bu_3Sn either abstracted the bromine atom from 1 or added to methyl vinyl ketone comparably. An attempted reaction of 1 with dimethyl acetylenedicarboxylate gave no *C*-glycosyl compounds and the bromide 1 was recovered quantitatively (91% recovery yield); Bu_3Sn did not abstract bromine from 1 but almost completely added to the acetylene. On the other hand, a reaction of 1 with butyl vinyl ether gave 3 quantitatively (98% yield); the intermediate glycosyl radical did not add to the olefin but completely abstracted the hydrogen atom from Bu_3SnH. From these results, it is clearly seen that the glycosyl radical behaves as a typical nucleophilic carbon radical.

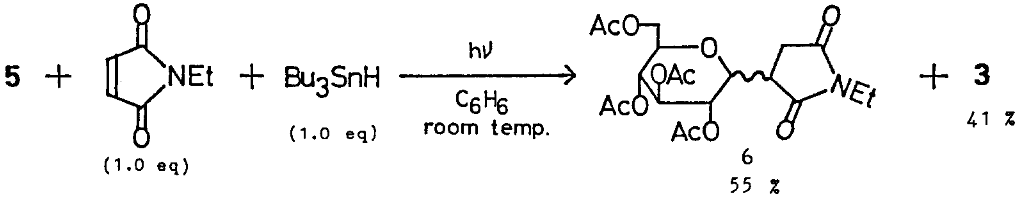
Because it is known that Bu_3Sn abstracts an iodine atom more preferably than a bromine atom[13], 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide (5)[14] was then examined. The reaction of 5 with dimethyl maleate similarly gave a mixture of 2a and 2b (6% yield), a mixture of 2c and 2d (45% yield), and 3 (25% yield). The reaction of 5 with methyl vinyl ketone smoothly proceeded by the use of 1.0 equivalent Bu_3SnH to give 4 (53% yield) and 3 (6% yild), while the reaction with dimethyl acetylenedicarboxylate gave no *C*-glycosyl compounds and almost all of the iodide 5 remained unchanged (on t.l.c. examination). Thus, the abstraction of the iodine atom from 5 by Bu_3Sn occurs much faster than the addition of Bu_3Sn to methyl vinyl ketone, but still much slower than the addition of Bu_3Sn to dimethyl acetylenedicarboxylate. U.v. irradiation of a solution of 5, dimethyl maleate, and Bu_3SnH (1 eq.) afforded a mixture of 2c and 2d (30% yield), and 3 (*ca*. 70% yield). Higher yield of the reduced product 3 compared to the AIBN-induced reaction, was due to the presence of all the used Bu_3SnH in the reaction mixture from the initial stage of the reaction. In the case of the reaction of 5 with *N*-ethylmaleimide, however, u.v. irradiation was proved to be very effective to give a diastereomeric mixture of *N*-ethyl-2-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-succinimides (6)[15] in a good yield (55% yield) along with 3 (41% yield).

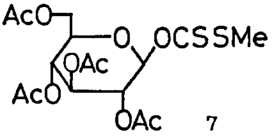
Two other glycosyl derivatives, 2,3,4,6-tetra-*O*-acetyl-1-*O*-methylthiothiocarbonyl-β-D-glucopyranose (7)[16] and phenyl 2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranoside (8)[17], were also tested as precursors of the glycosyl radical. Attempted reduction of 7 by Bu_3SnH - AIBN system proceeded very slowly : after the mixture had been refluxed for 4.5 hour, although the formation of the reduced product 3 was observed, large amounts of the starting material 7 were remained unchanged (t.l.c. examination). Thus, 7 was decided not to be applied to radical addition reactions. The reaction of 8 with methyl vinyl ketone (10 eq) by the use of 4 equivalents of Bu_3SnH gave no *C*-

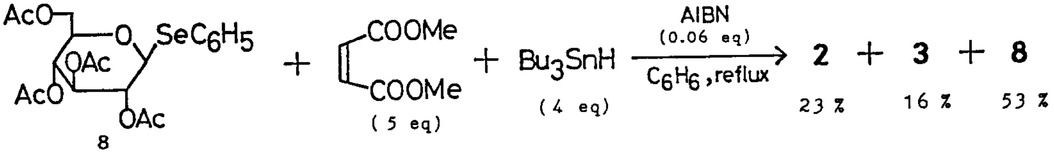

1
(20 eq)
Bu3SnH
(1.1 eq)
AIBN
(0.06 eq)
C6H6, reflux
2a,2b
9 % (1 : 1)
2c
21 %
2-epimer of 2c
2d
27 %
3
26 %


1
(10 eq)
Bu3SnH
(4 eq)
AIBN
(0.06 eq)
C6H6, reflux
4
40 %
3
24 %


5
(10 eq)
Bu3SnH
(1.0 eq)
AIBN
(0.06 eq)
C6H6, reflux
4
3
53 %
6%


5
(1.0 eq)
Bu3SnH
(1.0 eq)
hν
C6H6
room temp.
6
55 %
3
41 %


7


8
(5 eq)
Bu3SnH
(4 eq)
AIBN
(0.06 eq)
C6H6, reflux
2
3
8
23 %
16 %
53 %

glycosyl compounds but **8** in a 76% recovery yield. In the case of the reaction with dimethyl maleate (20 eq) by the use of 1.1 equivalents of Bu$_3$SnH, trace amounts of C-glycosyl compounds **2** were detected by t.l.c. along with recovered **8**. Thus, the abstraction of the PhSe group by Bu$_3$Sn is rather slower than the addition of Bu$_3$Sn to dimethyl maleate. Therefore, by the reduction of the amount of dimethyl maleate down to 5 equivalents and by the increase of the amount of Bu$_3$SnH up to 4 equivalents, the C-glycosyl compounds **2** were obtained in a 23% yield along with reduced compound **3** (16% yield) and **8** (53% recovery yield). Thus, it is clear that **8** is a less suitable precursor of glycosyl radicals than both bromide **1** and iodide **5**.

From the results mentioned above, it was concluded that these glycosyl radical additions to olefins provide a useful methodology for the synthesis of C-glycosyl compounds, especially C-glycosyl heterocycles such as C-nucleoside analogues.

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(Received in Japan 25 June 1987)