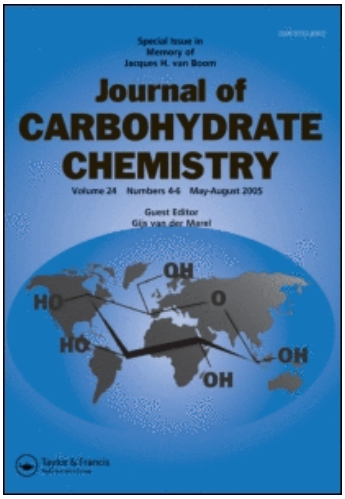

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Neirabeyeh, Mamdouh Al and Rollin, Patrick(1990) 'A New Approach for the *C*-Alkylation of Unsaturated Sugars Involving the Benzothiazol-2-Ylthio Leaving Group', Journal of Carbohydrate Chemistry, 9: 4, 471 — 478
To link to this Article: DOI: 10.1080/07328309008543847
URL: http://dx.doi.org/10.1080/07328309008543847

J. CARBOHYDRATE CHEMISTRY, 9(4), 471-478 (1990)

A NEW APPROACH FOR THE *C*-ALKYLATION OF UNSATURATED SUGARS INVOLVING THE BENZOTHIAZOL-2-YLTHIO LEAVING GROUP[1]

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Received August 12, 1989 - Final form January 17, 1990

ABSTRACT

The leaving ability of the benzothiazol-2-ylthio group was applied to the *C*-alkylation of a 2,3-enopyranoside model structure. Coordination of the organometallic reagent to the thio-heterocyclic moiety was responsible for a stereospecific *syn* conjugate alkyl attack.

INTRODUCTION

The prominent role of sugars in enantiospecific synthesis for elaboration of chiral molecules[2] requires efficient methods for C-C *sigma*-bond creation on carbohydrate templates. This can often be accomplished by interaction of an organometallic reagent with a saccharidic substrate comprising a suitably activated electrophilic carbon site.[3] Particularly, the S_N reactivity of unsaturated sugar structures have been studied with the contribution of sulfonate[4] and carboxylate[5] allylic leaving groups.[6]

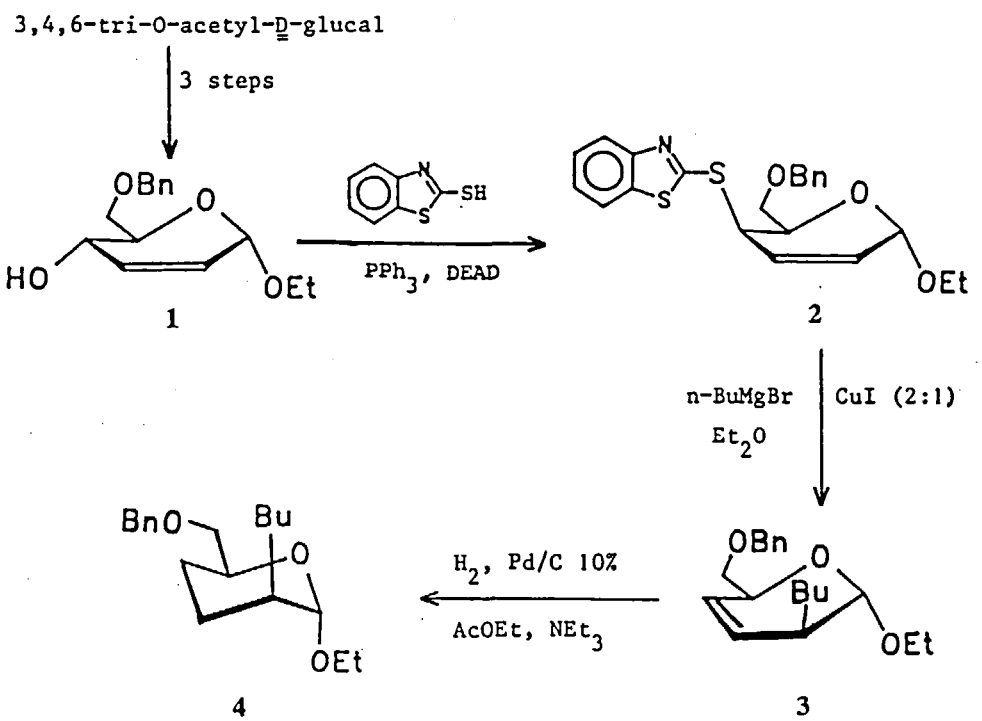
In connection with a program centered on the development in enantiospecific synthesis of new methods based on the manipulation of thio-functions, we have taken advantage of earlier findings about the nucleophilic substitution of benzothiazol-2-yl

allyl sulphides by copper(I) salt-catalyzed Grignard reagents. The results of Calo et al.[7] clearly demonstrated that the reactivity and the selectivity of such reagents were associated with the anchimeric coordination aptitude of the heterocyclic nucleus towards the metallic center involved.

RESULTS AND DISCUSSION

Our preliminary approach consisted of selecting a readily available pair of epimeric structures in order to study the regio- and stereochemical outcome of the reaction. Suitably protected 2,3-dideoxy-D-*erythro* and *threo*-hex-2-enopyranosides were chosen for this purpose.

Thus, the D-*erythro* allylic alcohol **1** was prepared in three steps from 3,4,6-tri-*O*-acetyl-D-glucal according to Valverde et al.[8] Conversion of **1** to the activated *threo* thiosugar **2** was smoothly effected using a Mitsunobu-type procedure already in development in our laboratory.[9] 2-Mercaptobenzothiazole reacted with **1** in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) to give a 88% yield of ethyl 4-*S*-(benzothiazol-2'-yl)-6-*O*-benzyl-2,3-dideoxy-4-thio-α-D-*threo*-hex-2-enopyranoside (**2**).



The *C*-alkylation step was performed with *n*-butylmagnesium bromide as the model nucleophilic species according to the procedure established by Calo et al. (*n*-BuMgBr/CuI 2:1 ratio in ethereal solution)[7] and produced an 81% yield of a *C*-branched product which was proven to be ethyl 6-*O*-benzyl-2-*C*-butyl-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside (3).

The structure of 3 was elucidated on the grounds of ^{1}H NMR observations in agreement with related spectroscopic data[4a-b] :

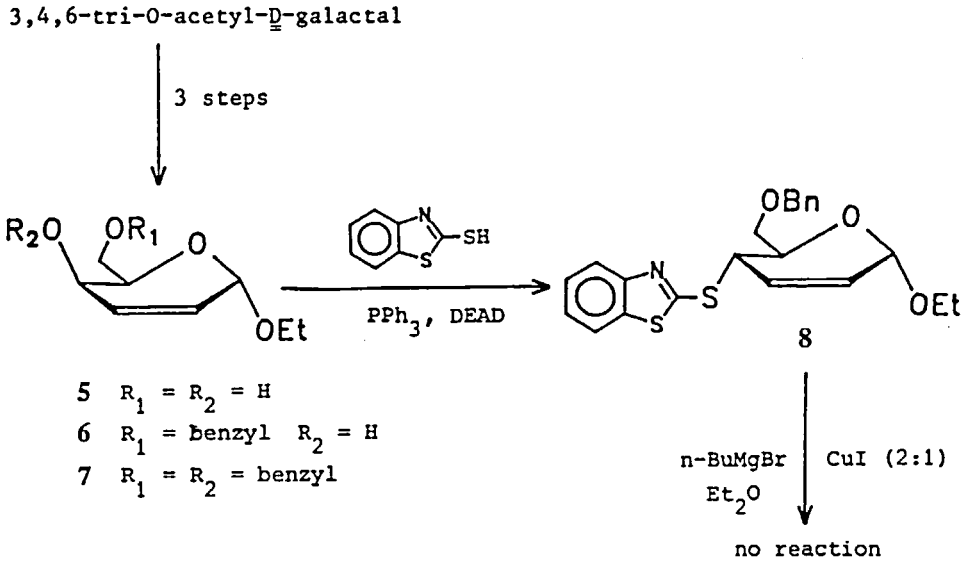
- the large vicinal coupling associated with an *anti* orientation of H-4 and H-5 is missing, precluding a D-*erythro*-type 2,3-enopyranoside.
- the very weak (less than 1 Hz) $J_{1,2}$ coupling is characteristic for 3,4-enopyranosides having an α-*threo* configuration.
- the 3,4-location of the double bond is confirmed by the $^4J_{2,4}$ and $^4J_{3,5}$ allylic couplings and the $^5J_{2,5}$ homo-allylic coupling.

Decisive proof for the structure of 3 was brought out by examination of the ^{1}H NMR spectrum of its 2,3-dihydro-derivative 4 in which the H-1 singlet at 4.60 ppm rules out the presence of a vicinal methylene group and indicates an axial 2-*C*-alkyl substituent.[5]

The high S_N2' regioselection observed is in total agreement with anterior results and particularly with the conclusions of Calo et al.[7] about the crucial role played by anchimeric coordination of the organometallic species with both the 2,3-double bond and the C=N bond of the benzothiazole nucleus. Moreover, the *pi*-complex intermediacy is consistent with a *syn* attack on C-2, thus inducing a *threo* configuration of the resulting 3,4-enopyranoside.

Such a rationalization of the former results would lead one to anticipate a clearly different behaviour for compound 8, the C-4 epimer of 2, which can be obtained in four steps from 3,4,6-tri-*O*-acetyl-D-galactal. The *threo* allylic alcohol 6 was prepared in 75% yield through a similar stannylidene-assisted regioselective benzylation of the known[10,11] corresponding ethyl 2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside 5. Conversion of 6 into the *erythro* thio-derivative 8 was carried out in 80% yield via a Mitsunobu inversion of the type previously mentioned.[9]

Finally, compound 8 was submitted to the *C*-alkylation conditions already described for its C-4 epimer 2. In all attempts effected, no *C*-butylation reaction took place and the starting material was recovered unchanged. This contrasting result again speaks for the mediation of a *N*-coordinated *pi*-complex which compels the nucleophilic species to a *syn* approach on the α-face of the 2,3-enopyranoside unit. Under such conditions, the α-ethoxy anomeric substituent would probably hinder strongly a C-2 attack.



In order to check the preceding assumptions, a comparative conformational analysis of epimeric compounds **2** and **8** was performed using the refined MMPM I version of Allinger's MM2 force field.[12,13] Computation of the geometry and the energy of the epimers infers $^{0}H_{5}$ initial conformation in both cases and precludes any decisive difference in the accessibility of the electrophilic C-4.

Therefore it is concluded that the S_N2' displacement of the allylic benzothiazol-2-ylthio group in sugar epimers is regio- and stereo-controlled by the coordination ability and the anomeric configuration of the substrate. Further work is in progress in our laboratory to explore the scope of this sugar *C*-alkylation.

EXPERIMENTAL

General procedures. Melting points were determined with a Kofler-block apparatus and are uncorrected. Optical rotations were measured with a Jobin-Yvon Digital type 71 polarimeter at 25 °C. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AM 300 WB spectrometer with samples in $CDCl_3$ solution containing 1% TMS. High resolution mass spectra were measured on a VG Analytical 70-250 S spectrometer. Thin layer chromatography was run on aluminum sheets precoated with silica gel 60 (0.2 mm, F-254, E.Merck); detection was effected by observation under short wavelength UV light, then dipping the chromatograms into a solution of ceric ammonium nitrate $[Ce(NH_4)_2(NO_3)_6]$ in 20% sulfuric acid and charring them with a heat gun. Column chromatography was performed using Kieselgel 60 (70-230 mesh ASTM, Merck).

Ethyl 4-S-(benzothiazol-2'-yl)-6-O-benzyl-2,3-dideoxy-4-thio-α-D-threo-hex-2-enopyranoside (2). To a stirred solution of **1** (1.31 g, 4.95 mmol) and triphenylphosphine (1.56 g, 1.2 equiv.) in dry toluene (20 mL) was suspended 2-mercaptobenzothiazole (0.91 g, 1.1 equiv.). DEAD (0.94 mL, 1.2 equiv.) was then added dropwise and stirring was continued until complete consumption of the starting alcohol (ca. 2h) was observed (TLC petroleum ether-ethyl acetate 4:1) The mixture was concentrated *in vacuo* then directly chromatographed (100 g SiO_2) with petroleum ether-ethyl acetate (9:1) as the eluent to give 1.8 g (88% yield) of crystalline compound **2** : mp 66 °C, $[\alpha]_D$ -150° (*c* 0.31, chloroform); ^{1}H NMR δ 1.25 (t, 3H, $J_{Me,CH2}$ = 6.8 Hz, $\underline{Me}CH_2$), 3.57 and 3.90 (2dq, 2H, J_{gem} = 9.8 Hz, $O\underline{CH_2}Me$), 3.76 (dd, 1H, $J_{6,6'}$ = 10.6 Hz, $J_{6,5}$ = 6.6 Hz, H-6), 3.84 (dd, 1H, $J_{6',5}$ = 5.3 Hz, H-6'), 4.42 and 4.51 (2d, 2H, J_{gem} = 12.0 Hz, $O\underline{CH_2}Ph$), 4.65 (ddd, 1H, $J_{5,4}$ = 2.6 Hz, H-5), 4.78 (dd, 1H, $J_{4,3}$ = 5.8 Hz, H-4), 5.08 (d, 1H, $J_{1,2}$ = 2.9 Hz, H-1), 5.89 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 6.35 (dd, 1H, H-3), 7.20 (s, 5H, $CH_2\underline{Ph}$), 7.30 and 7.41 (2t, 2H, J_{vic} = 7.6 Hz, benzothiazole H-6 and H-5), 7.74 and 7.81 (2d, 2H, J_{vic} = 7.6 Hz, benzothiazole H-7 and H-4).

Exact mass calculated for $C_{22}H_{23}NO_3S_2$: 413.1119, found : 413.1134.

Ethyl 6-O-benzyl-2-C-butyl-2,3,4-trideoxy-α-D-threo-hex-3-enopyranoside (3). A butylmagnesium bromide solution in diethyl ether (5 mL) was prepared from Mg (73.7 mg, 3.03 mmol) and 1-bromobutane (0.32 mL, 2.97 mmol). After 1 h, the solution was cooled to -30 °C and CuI (286.8 mg, 1.5 mmol) was rapidly added under argon and the suspension was stirred at -30 °C for 0.5 h. An ethereal solution of compound **2** (441 mg, 1.06 mmol) was then added, and the stirred mixture was allowed to warm up slowly to room temperature. After stirring for 5 h more, the reaction medium was diluted with diethyl ether (15 mL) and treated with saturated aqueous NH_4Cl containing a few drops of concentrated NH_4OH. After extraction, the almost colorless ethereal phase was filtered over anhydrous Na_2SO_4 and concentrated to dryness *in vacuo*. Purification was achieved on a silica gel column, using a 9:1 mixture of hexane-ethyl acetate as the eluent and 261 mg (81% yield) of the glycoside **3** were obtained in the form of a fluid, colorless oil, $[\alpha]_D$ +53° (*c* 1.30, chloroform); ^{1}H NMR δ 0.89 (t, 3H, $J_{Me,CH2}$ = 7.1 Hz, Me in *n*-butyl), 1.23 (t, 3H, $J_{Me,CH2}$ = 7.3 Hz, Me in OEt), 1.25-1.55 (m, 6H, $(CH_2)_3$ in *n*-butyl), 2.02 (m, 1H, H-2), 3.55 and 3.85 (2dq, 2H, J_{gem} = 9.8 Hz, $O\underline{CH_2}Me$), 3.52 (dd, 1H, $J_{6,6'}$ = 10.5 Hz, $J_{6,5}$ = 4.7 Hz, H-6), 3.58 (dd, 1H, $J_{6',5}$ = 6.2 Hz, H-6'), 4.36 (m, 1H, H-5), 4.57 and 4.64 (2d, 2H, Jgem = 12.0 Hz, $O\underline{CH_2}Ph$), 4.76 (bs, 1H, H-1), 5.68 (bd, 1H, $J_{4,3}$ = 10.5 Hz, H-4), 5.82 (bdd, 1H, $J_{3,2}$ = 4.7 Hz, H-3), 7.25-7.40 (m, 5H, Ph).

Exact mass calculated for $C_{19}H_{28}O_3$: 304.2038, found : 304.2035.

Ethyl 6-O-benzyl-2-C-butyl-2,3,4-trideoxy-α-D-threo-hexopyranoside (4). Compound 3 (68 mg, 0.22 mmol) was dissolved in ethyl acetate (5mL) containing 4 drops of triethylamine and 10% Pd/C (20 mg) was added. The mixture was then stirred overnight under a hydrogen atmosphere. TLC (9:1 hexane-ethyl acetate) showed no starting material and the presence of a slightly faster-moving product. After filtration of the catalyst through a pad of Celite and removal of the solvent *in vacuo,* purification by rapid silica gel column chromatography yielded pure 4 as a colorless oil (60 mg, 89%), $[\alpha]_D$ +45° (*c* 1.05, chloroform); ^{1}H NMR δ 0.90 (t, 3H, $J_{Me,CH2}$ = 7.1 Hz, Me in *n*-butyl), 1.23 (t, 3H, $J_{Me,CH2}$ = 7.3 Hz, Me in OEt), 1.25-1.70 (m, 10H, $(CH_2)_3$ in *n*-butyl,H-2,H-3,H-4,H-4'), 1.98 (m, 1H, H-3'), 3.47 and 3.77 (2dq, 2H, J_{gem} = 9.9 Hz, O$\underline{CH_2}$Me), 3.42 (dd, 1H, $J_{6,6'}$ = 10.1 Hz, $J_{6,5}$ = 4.3 Hz, H-6), 3.49 (dd, 1H, $J_{6',5}$ = 6.0 Hz, H-6'), 3.95 (m, 1H, H-5), 4.55 and 4.59 (2d, 2H, Jgem = 12.1 Hz, O$\underline{CH}$2Ph), 4.60 (bs, 1H, H-1),7.20-7.40 (m, 5H, Ph).

Exact mass calculated for $C_{19}H_{30}O_3$: 306.2195, found : 306.2184.

Ethyl 6-O-benzyl-2,3-dideoxy-α-D-threo-hex-2-enopyranoside (6). A mixture of diol 5 (274 mg, 1.57 mmol) and dibutyltin oxide (391 mg, 1 equiv.) in dry benzene (10 mL) was refluxed overnight in a Dean-Stark apparatus. Tetrabutylammonium bromide (506 mg, 1 equiv.) and benzyl bromide (0.23 mL, 1.2 equiv.) were then added and reflux was continued for 24 h. After concentration *in vacuo*, the mixture was chromatographed on silica gel with petroleum ether-ethyl acetate (gradient from 9:1 to 1:1) to give 310 mg (75% yield) of syrupy 6, $[\alpha]_D$ -79° (*c* 2.66, chloroform); ^{1}H NMR δ 1.23 (t, 3H, $J_{Me,CH2}$ = 7.1 Hz, Me in OEt), 2.18 (bs, 1H, OH), 3.55 and 3.85 (2dq, 2H, J_{gem} = 9.9 Hz, O$\underline{CH_2}$Me), 3.73 (dd, 1H, $J_{6,6'}$ = 10.4 Hz, $J_{6,5}$ = 6.6 Hz, H-6), 3.79 (dd, 1H, $J_{6',5}$ = 5.6 Hz, H-6'), 3.87 (m, 1H, H-4), 4.23 (m, 1H, H-5), 4.60 (s, 2H, O$\underline{CH_2}$Ph), 5.03 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1), 5.90 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 6.13 (dd, 1H, $J_{3,4}$ = 5.6 Hz, H-3), 7.35 (m, 5H, Ph).

Exact mass calculated for $C_{15}H_{20}O_4$: 264.1362, found : 264.1353.

The syrupy 4,6-di-*O*-benzyl derivative 7 was isolated in 19% yield, $[\alpha]_D$ -106° (*c* 0.90, chloroform); ^{1}H NMR δ 1.25 (t, 3H, J_{MeCH2} = 7.2 Hz, Me in OEt), 3.57 and 3.88 (2dq, 2H, J_{gem} = 9.9 Hz, O$\underline{CH_2}$Me), 3.72 (dd, 1H, $J_{4,5}$ = 2.4 Hz, H-4), 3.79 (m, 2H, H-6 and H-6'), 4.29 (ddd, 1H, H-5), 4.59 and 4.60 (two AB systems, 4H, J_{gem} = 12.0 Hz, O$\underline{CH_2}$Ph), 5.08 (d, 1H, $J_{1,2}$ = 2.8 Hz, H-1), 5.98 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 6.12 (dd, 1H, $J_{3,4}$ = 5.4 Hz, H-3), 7.31 (m, 10H, Ph).

Exact mass calculated for $C_{22}H_{26}O_4$: 354.1831, found : 354.1820.

Ethyl 4-S-(benzothiazol-2'-yl)-6-O-benzyl-2,3-dideoxy-4-thio-α-D-erythro-hex-2-enopyranoside (8). Starting from compound 6 (160 mg, 0.60 mmol), the same experimental conditions as those used for the preparation of 2 [triphenylphosphine

(189 mg, 1.2 equiv.), 2-mercaptobenzothiazole (110 mg, 1.1 equiv.) in toluene (3 mL), DEAD (0.115 mL, 1.2 equiv.)] gave 198 mg (80%) of syrupy 8, $[\alpha]_D$ +87° (*c* 3.30, chloroform); ^{1}H NMR δ 1.25 (t, $J_{Me,CH2}$ = 6.8 Hz, Me in OEt), 3.59 and 3.88 (2dq, 2H, J_{gem} = 9.8 Hz, O$\underline{CH_2}$Me), 3.77 (dd, 1H, $J_{6,6'}$ = 11.1 Hz, $J_{6,5}$ = 2.4 Hz, H-6), 3.86 (dd, 1H, $J_{6',5}$ = 4.3 Hz, H-6'), 4.18 (ddd, 1H, $J_{5,4}$ = 10.6 Hz, H-5), 4.49 and 4.58 (2d, 2H, J_{gem} = 12.1 Hz, O$\underline{CH_2}$Ph), 4.88 (ddd, 1H, $J_{4,3}$ = 1.4 Hz, $J_{4,2}$ = 2,4Hz, H-4), 5.11 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1), 5.88 (ddd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 6.17 (dd, 1H, H-3), 7.20 (m, 3H) and 7.32 (m, 2H, Ph), 7.32 and 7.43 (2t, 2H, J_{vic} = 7.6 Hz, benzothiazole H-6 and H-5), 7.78 and 7.86 (2d, 2H, J_{vic} = 7.6 Hz, benzothiazole H-7 and H-4).

Exact mass calculated for $C_{22}H_{23}NO_3S_2$: 413.1119, found : 413.1122.

Reaction of 8 with the n-butylmagnesium bromide/ CuI complex. Compound 8 was tentatively submitted to the same experimental conditions as for the *C*-alkylation of its epimer 2. In all attempts made, the starting material was recovered unchanged.

ACKNOWLEDGMENT

We wish to thank Prof.G. Guillaumet for multiform support and P. Stangier (Universität Münster, FRG) for the drawings.

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