# Synthesis of Deoxy Sugars. Deoxygenation by Treatment with *N,N'*-Thiocarbonyldiimidazole/Tri-*n*-butylstannane[1]

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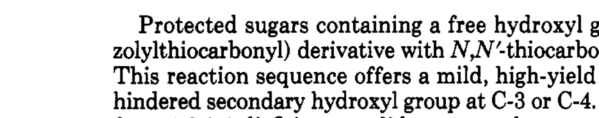
Protected sugars containing a free hydroxyl group have been deoxygenated by conversion to the *O*-(imidazolylthiocarbonyl) derivative with *N,N'*-thiocarbonyldiimidazole followed by treatment with tri-*n*-butylstannane. This reaction sequence offers a mild, high-yield procedure for the deoxygenation of hexose derivatives with a hindered secondary hydroxyl group at C-3 or C-4. The primary 6-*O*-(imidazolylthiocarbonyl) compound obtained from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose reacts with tri-*n*-butylstannane to give a mixture of the 6-deoxy sugar (31%) and starting alcohol (57%).

Deoxy sugars are important constituents of many natural products and synthetic antibiotics. The most direct method for preparing a monodeoxy sugar is usually by the deoxygenation of a free hydroxyl group of a partially protected sugar. Procedures to affect this transformation normally involve one or more substitution reactions,[2] but, unfortunately, activated secondary hydroxyl groups of sugar derivatives often fail for electronic or steric reasons to undergo the desired $S_N2$ or $S_N1$ reaction.[3] For circumvention of this problem, deoxygenation procedures that proceed via free-radical intermediates have been developed in recent years.[4-10]

Barton and McCombie demonstrated that *O*-alkyl thiobenzoates, *O*-alkyl *S*-methyl dithiocarbonates, and (alkoxythiocarbonyl)imidazolides are reduced to deoxy compounds by tri-*n*-butylstannane[4] (eq 1). *O*-(Phenoxythiocarbonyl) derivatives also lead to deoxygenated products.[10] There is little literature precedent to aid in the selection of a thioacyl intermediate for use in a deoxygenation reaction.[4,5,10-14] The ease and conditions of thioacylation and the possibility of competing reaction pathways during the reduction step are important considerations. The imidazolylthiocarbonyl derivative offers the advantage that it is formed in a simple, mild, and high-yield reaction using commercially available *N,N'*-thiocarbonyldiimidazole (TCDI). However, in two reductions where carbon-oxygen bond homolysis to form the alkyl radical was slow, side reactions were observed. In one case, imidazole-catalyzed conversion of tri-*n*-butylstannane to hexabutyldistannane occurred, thereby necessitating the use of excess reducing agent and complicating product isolation.[4] In a second, the reduction of a primary thiocarbonylimidazolide yielded a monothioacetal derivative rather than the deoxygenation product.[4] Side reactions have also been observed during the reduction of other thioacyl compounds.[4,7,12]



(1)

In many cases, deoxygenation via the imidazolylthiocarbonyl derivative would be the method of choice if no problems were encountered during the reductive dethiation. For example, 4-deoxy-D-*lyxo*-hexose was synthesized in excellent yield by TCDI/$SnBu_3H$ treatment of methyl 6-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-mannopyranoside.[13] In order to examine the general utility of this method, we have attempted to deoxygenate a variety of sugar derivatives containing an unprotected hydroxyl group at C-3 or C-4 via the imidazolylthiocarbonyl derivative. The results of this study are contained in the present report.

## Results and Discussion

Treatment of a partially protected sugar possessing a free hydroxyl group with 2 equiv of TCDI in 1,2-dichloroethane (or tetrahydrofuran) gave in most cases an excellent yield of the imidazolylthiocarbonyl derivative (Table I). The (thiocarbonyl)imidazolides were most conveniently isolated by flash chromatography of the crude reaction mixture except for polar sugars or large-scale preparations (>5 g). An initial extractive workup was preferable in these cases. Once isolated, the compounds were stable at room temperature for at least several weeks if stored under an $N_2$ atmosphere and protected from ultraviolet light, which is known to promote photolytic decomposition.[9] Smooth reduction of most imidazolylthiocarbonyl sugars was accomplished by heating them at reflux for several hours with tri-*n*-butylstannane in toluene (Table I). The deoxy sugar derivatives were separated from tin byproducts by partitioning between acetonitrile and hexane[15] and purified by recrystallization or flash

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(5) D. H. R. Barton and W. B. Motherwell, *Pure Appl. Chem.*, **53**, 15 (1981).
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(8) T. Tsuchiya, F. Nakamura, and S. Umezawa, *Tetrahedron Lett.*, 2805 (1979).
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(11) T. S. Fuller and R. V. Stick, *Aust. J. Chem.*, **33**, 2509 (1980).
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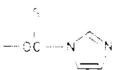
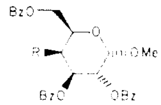
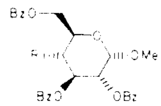
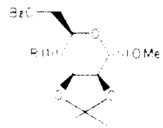
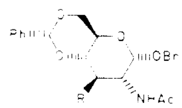
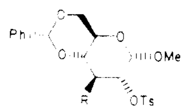
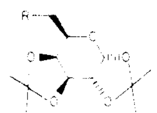
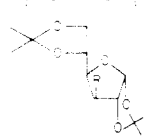
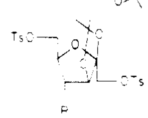
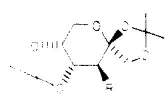
(21) A. L. Raymond and E. F. Schroeder, *J. Am. Chem. Soc.*, **70**, 2785 (1948).

0022-3263/81/1946-4843$01.25/0 

Table I[a]

| | no. for R = OH | no. for R =  | % yield | no. for R = H | % yield from TCDI-sugar |
|---|---|---|---|---|---|
|  | 1[16] | 10 | 94 | 19[25] | 92 |
|  | 2[17] | 11 | 90 | 19[25] | 67 |
|  | 3[18] | 12 | 92 | 20[13] | 87 |
|  | 4[19] | 13 | 59 | 21 | 57 |
|  | 5[20] | 14 | 86 | 22[26] | 68 |
|  | 6[21] | 15 | 82 | 23[7] | 31 |
|  | 7[22] | 16 | 93 | 24[4] | 74 |
|  | 8[23] | 17 | 98 | 25 | 85 |
|  | 9[24] | 18 | 95 | 26 | 65 |

[a] Literature references given by superscripts.

chromatography. Isolated yields of products derived from secondary alcohols were good (60–90%). The one primary compound examined, 6-*O*-(imidazolylthiocarbonyl)-1,2:3,4-di-*O*-isopropylidene-$\alpha$-D-galactopyranose (**15**), gave a mixture of the deoxy product **23** (31%) and starting alcohol **6** (57%). The deoxygenation sequence was performed successfully on compounds containing isopropylidene, benzylidene, *p*-toluenesulfonyl, benzyl, benzoyl, and acetamido groups.

The $^1$H NMR spectra of the imidazolylthiocarbonyl derivatives (Table II) showed characteristic peaks for the three imidazolyl protons ($\delta$ 8.35, 7.65, and 7.05) and for the proton attached to the carbon bearing the thiono substituent. The latter proton was strongly deshielded and resonated in the region of $\delta$ 5.7–6.6. Following the reduction step, a complex splitting pattern generally was observed for the methylene protons of the product in the vicinity of $\delta$ 1.6–2.5. Whenever possible, further proof of the structure was obtained for the deoxy products by comparison of their physical properties with literature values (Table III). Satisfactory elemental analyses were obtained for all new compounds.

To examine the stereoselectivity of the reduction step, methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(imidazolylthiocarbonyl)-$\alpha$-D-galactopyranoside (**10**) and methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(imidazolylthiocarbonyl)-$\alpha$-D-glucopyranoside (**11**) were each treated with tri-*n*-butyltin deuteride. The resonances of the axial ($\delta$ 1.90, $J_{3,4}$ = 11.3 Hz, $J_{4,4'}$ = 12.5 Hz, and $J_{4,5}$ = 11.8 Hz) and equatorial ($\delta$ 2.48, $J_{3,4}$ = 5.2 Hz, $J_{4,4'}$ = 12.5 Hz, and $J_{4,5}$ = 2.0 Hz) protons of methyl 2,3,6-tri-*O*-benzoyl-$\alpha$-D-*xylo*-hexopyranoside (**19**) are sufficiently resolved that the degree of substitution by deuterium at either position can be determined by integration of the $^1$H NMR signals. An identical product mixture was obtained from reduction of each of the epimers. The level of deuterium incorporated into the deoxy sugar **19** was approximately 0.8 per molecule, and the ratio of equatorial to axial deuterium was 5/7. A similar result was obtained by Fuller and Stick in the reduction of a pair of gluco and galacto dithiocarbonate derivatives.[11] The loss of stereochemistry, the absence of molecular rearrangements, the successful reductions of hindered compounds, and the more facile deoxygenation of secondary derivatives than primary ones support the

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(23) J. Pacak, J. Halaskova, V. Stepan, and M. Cerny, *Collect. Czech. Chem. Commun.*, **37**, 3646 (1972).
(24) R. F. Brady, *Carbohydr. Res.*, **15**, 35 (1970).
(25) G. Siewert and O. Westphal, *Justus Liebigs Ann. Chem.*, **720**, 161 (1968).
(26) D. A. Prins, *Helv. Chim. Acta*, **29**, 1 (1946).

Table II. $^1$H NMR Spectral Data of (Alkoxythiocarbonyl)imidazolide and Deoxy Sugar Derivatives[a,b]

| | chemical shifts, $\delta$ | | | | | | |
|---|---|---|---|---|---|---|---|
| compd | H-1 | H-2 | H-3 (H-3a, H-3b) | H-4 (H-4a, H-4b) | H-5 | H-6 | other |
| **10** | 5.34 (d) | 5.75 (dd) | 6.06 (dd) | 6.64 (d) | 4.80-4.25 | | 8.43-7.10 (arom), 3.50 (s, OMe) |
| **11** | 5.55-5.20 | | 6.55-6.15 | | 4.80-4.45 | | 8.30-6.90 (arom), 3.55 (s, OMe) |
| **13** | 5.00 (d) | *c* | 6.25 (t) | | 4.95-3.70 | | 8.38-7.04 (arom and N-H) 5.56 (s, PhCH), 1.83 (Me) |
| **14** | 5.03 (d) | 4.69 (dd) | 6.39 (t) | | 4.32-3.60 | | 7.98-6.97 (arom), 5.46 (s, PhCH), 3.46 (s, OMe), 2.28 (s, TsMe) |
| **15** | 5.52 (d) | | | 4.95-3.95 | | | 8.31, 7.60, 7.00 (Im), 1.35 (6 H), 1.48, 1.50 (Me's) |
| **16** | 6.00 (d) | 4.79 (d) | 5.88 (d, $J$ = 1 Hz) | | 4.40-3.87 | | 8.36, 7.64, 7.07 (Im), 1.62, 1.47, 1.40, 1.33 (Me's) |
| **17** | *c* | | 5.70 (br s) | | 4.00-4.85 | | 8.40, 7.68, 7.10 (Im), 7.9-7.25 ($p$-$C_6H_4$), 2.44 (s, TsMe's) |
| **18** | 4.01 (s) | | 5.93 (d) | 4.51 (dd) | 4.30 (m) | 4.17 (d) | 8.40, 7.68, 7.06, (Im), 1.60, 1.51, 1.41, 1.38 (Me's) |
| **19** | 5.18 (d) | 5.32 (dd) | 5.79 (sx) | 2.48 (dd), 1.90 (q) | 4.49-4.35 | | 8.10-7.34 (arom), 3.45 (OMe) |
| **22** | *c* | *c* | 2.2-1.9, 1.8-1.3 | | 5.04-3.45 | | 8.0-7.3 (arom), 5.5 (s, PhCH), 3.42 (OMe), 2.38 (s, TsMe) |
| **25** | 4.07 (s) | | 4.63 (dd) | 2.4-1.8 | 4.45-3.91 | | 7.9-7.2 (arom), 2.43 (s, TsMe's), 1.31, 1.23, (Me's) |
| **26** | *c* | | 2.06 (s), 2.00 (s) | | 4.57-3.72 | | 1.50 (6 H), 1.40, 1.33 (Me's) |

[a] s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, and m = multiplet. [b] Spectra of compounds **23** and **24** were identical with published spectra.[7] [c] With H-4 to H-6 protons.

Table III. Physical Constants of (Alkoxythiocarbonyl)imidazolide and Deoxy Sugar Derivatives

| | | | anal.,[c] % | | | |
|---|---|---|---|---|---|---|
| compd | mp, °C [lit. value][a] | $[\alpha]_D$ [lit. value][a,b] | C | H | N | S |
| **10** | 66-78 | +150.2 (2.0) | 62.33 (62.22) | 4.58 (4.65) | 4.54 (4.51) | 5.20 (5.03) |
| **11** | 112-116 | +110.8 (1.0) | 62.33 (61.70) | 4.58 (4.59) | 4.54 (4.59) | 5.20 (5.20) |
| **13** | 197.5 | | 61.28 (60.96) | 5.34 (5.51) | 8.25 (8.19) | 6.29 (5.77) |
| **14** | 169.5-170.5 | +69.7 (1.9) | 54.93 (54.92) | 4.79 (4.86) | 5.12 (5.04) | 11.73 (11.64) |
| **15** | | −61.9 (1.0) | 51.88 (51.88) | 5.99 (6.02) | 7.56 (7.46) | 8.65 (8.61) |
| **16** | | −49.6 (0.9) | 51.88 (52.19) | 5.99 (6.06) | | |
| **17** | | +9.0 (1.3) | 50.77 (51.06) | 4.73 (5.03) | | |
| **18** | | −135.0 (1.1) | 51.88 (52.02) | 5.99 (6.15) | 7.56 (7.40) | 8.65 (8.34) |
| **19** | 116-117 [116-117] | +132.6 (2.0) [+133 (1.0)] | | | | |
| **21** | 242-244 dec | | 68.91 (68.31) | 6.57 (6.64) | 3.65 (3.59) | |
| **22** | 115-118 [122] | | | | | |
| **23** | [33-35] | −51.2 (0.8) [−53.6 (1.2)] | | | | |
| **24** | | −6.9 (2.6) [−7.5 (10)] | | | | |
| **25** | 99-100 | +17.4 (1.0) | 53.89 (53.85) | 5.51 (5.69) | | 12.51 (12.56) |
| **26** | 75-76 | −106.5 (1.0) | 59.00 (59.26) | 8.25 (8.30) | | |

[a] See Table I for references. [b] In chloroform; molar concentrations are given in parentheses. [c] Calculated value given with experimental value in parentheses.

postulated free-radical mechanism for the reaction.[4]

In summary, a number of protected sugars containing a free hydroxyl group at C-3 or C-4 have been converted to (alkoxythiocarbonyl)imidazolides and reduced cleanly to the deoxy products in good yield. In view of the ease and mildness of thioacylation and the absence of byproduct formation during the reductions, TCDI/$SnBu_3H$ treatment appears to be an attractive procedure for the deoxygenation of many secondary alcohols.

## Experimental Section

**General Methods.** Melting points were determined with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are expressed in parts per million downfield from $Me_4Si$. Optical rotations were measured in a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc.

TCDI was purchased from Aldrich or synthesized by the procedure of Staab and Walther.[27] Similar results were obtained with reagent from either source. Tri-$n$-butylstannane was obtained from Alfa.

**Synthesis of (Alkoxythiocarbonyl)imidazolides.** Solid TCDI (6 mmol) was added to a solution of the partially protected sugar (3 mmol) in 15 mL of 1,2-dichloroethane (or tetrahydrofuran). The reaction mixture was heated at gentle reflux under

(27) H. A. Staab and G. Walther, *Justus Liebigs Ann. Chem.* **657**, 98 (1962).

an $N_2$ atmosphere until TLC analysis confirmed the disappearance of starting material (1–3 h). After cooling, the solution was concentrated in vacuo and the product isolated by flash chromatography (elution generally with ethyl acetate/hexane, 1:1 v/v).[28] Analytically pure samples of the (thiocarbonyl)imidazolides were obtained following concentration of product fractions and thorough drying.

Polar sugars (e.g., **13**) and products from large-scale preparations were isolated by an extractive workup. Following concentration of the 1,2-dichloroethane solution, the residue was dissolved in methylene chloride (25 mL) and washed with cold 1 N HCl (3 × 20 mL), 5% aqueous sodium bicarbonate (20 mL), and water (20 mL). After being dried ($Na_2SO_4$), the solution was concentrated in vacuo and the crude imidazolylthiocarbonyl compound purified by recrystallization or chromatography.

**Reduction of the (Alkoxythiocarbonyl)imidazolides with Tri-*n*-butylstannane.** A mixture of the (thiocarbonyl)imidazolide (3 mmol) in dry toluene (50 mL) was added dropwise over 30 min to a stirred solution of refluxing toluene (200 mL) and tri-*n*-butylstannane (4.6 mmol) under $N_2$. When TLC analysis indicated the reduction was complete (2–6 h), the solution was cooled and then concentrated in vacuo. The residue was extracted with hot acetonitrile (3 × 50 mL), and the combined extracts were washed with hexane (4 × 50 mL) to remove tin-containing compounds. After concentration of the acetonitrile layer in vacuo, the crude deoxy sugar was purified by flash chromatography or recrystallization.

(28) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

**Acknowledgment** is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

**Registry No.** **1**, 3601-36-3; **2**, 57784-06-2; **3**, 63167-70-4; **4**, 78246-81-8; **5**, 70774-92-4; **6**, 4064-06-6; **7**, 582-52-5; **8**, 32087-60-8; **9**, 25018-67-1; **10**, 79233-80-0; **11**, 79233-81-1; **12**, 73635-97-9; **13**, 79233-82-2; **14**, 79233-83-3; **15**, 79233-84-4; **16**, 79233-85-5; **17**, 79233-86-6; **18**, 79233-87-7; **19**, 19488-41-6; **20**, 73635-98-0; **21**, 79297-67-9; **22**, 79297-68-0; **23**, 4026-27-1; **24**, 4613-62-1; **25**, 79233-88-8; **26**, 67104-35-2; tri-*n*-butylstannane, 688-73-3; TCDI, 6160-65-2.

# Photochemical Additions of Alkenes to Phthalimides To Form Benzazepinediones. Additions of Dienes, Alkenes, Vinyl Ethers, Vinyl Esters, and an Allene

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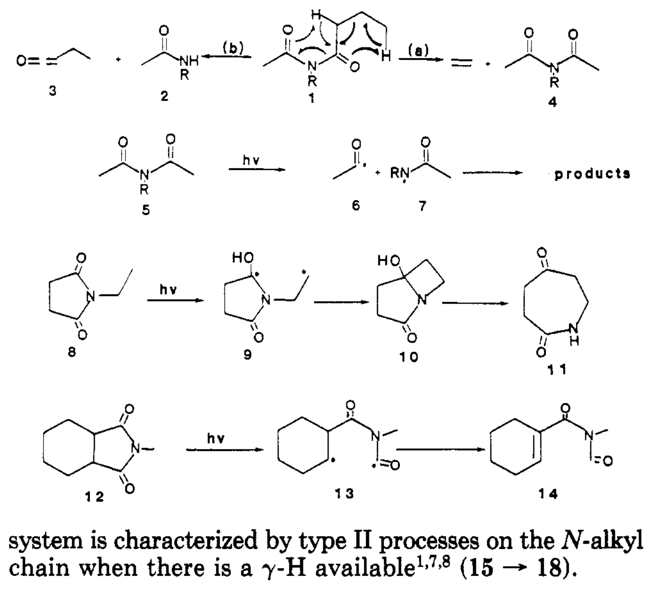
*Received July 20, 1981*

In the presence of certain dienes *N*-methylphthalimide undergoes a novel photochemical addition reaction to give benzazepinediones which corresponds to an addition of the diene across the C(O)–N bond of the imide. The reaction has some generality in that it occurs for selected dienes, alkenes, vinyl ethers, vinyl esters, and an allene. However, the reaction does not take place with electron-poor alkenes such as acrylonitrile and also fails with very electron-rich alkenes such as 2,3-dimethyl-2-butene. In the latter case, failure to react is attributed to a competing electron-transfer reaction.

The photochemistry of imides has developed rapidly over the past 8 years,[1] and from the many studies that have been carried out, it has become clear that there are dramatic differences between the photochemistry of the aliphatic, cycloaliphatic, and aromatic imides (i.e., phthalimides). Whereas aliphatic imides appear to undergo efficient $\alpha$ cleavages of the C(O)–N bond and type II reactions on *C*-alkyl groups (a) and across the imide moiety (b),[2,3] they do not undergo type II abstraction on *N*-alkyl substituents.[4] Conversely the cycloaliphatic imides preferentially undergo $\alpha$ cleavages of the C(O)–C bond with little evidence for C(O)–N cleavage[5] (**12** → **14**, Scheme I) and participate in type II processes on the *N*-alkyl group[5a,6] (**8** → **11**). The chemistry of the phthalimide system is characterized by type II processes on the *N*-alkyl chain when there is a $\gamma$-H available[1,7,8] (**15** → **18**).

Scheme I




(1) For reviews see: (a) Mazzocchi, P. H. "Organic Photochemistry"; Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, p 421. (b) Kanaoka, Y. *Acc. Chem. Res.* **1978**, *11*, 407. (c) Kanaoka, Y. *Yuki Gosei Kagaku Kyokaishi* **1975**, *33*, 949.
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(3) Jameson, C. W. Ph.D. Thesis, University of Maryland, 1975.
(4) Mazzocchi, P. H.; DeCamp,A., unpublished results.
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(7) Kanaoka, Y.; Migita, Y.; Koyama, K.; Sato, Y.; Nakai, H.; Mizoguchi, T. *Tetrahedron Lett.* **1973**, 1193.
(8) The hydrogen abstraction reaction takes place with $\delta$ hydrogens in a number of cases in which there is special stabilization for the incipient radical. Ring closures of medium to very large rings also take place but these generally involve electron-transfer mechanisms.[1]

 