Carbohydrate Research, 94 (1981) 101–107
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

The thiocyanate route to derivatives of 3-thio-D-glucose and 3-thio-D-allose

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(Received September 30th, 1980; accepted for publication, November 25th, 1980)

SN2 displacements of sugar sulfonate groups by thioacetate, thiobenzoate, and thiocyanate ions provide one of the most efficient approaches to thiosugar synthesis[1]. Of these three nucleophiles, thiocyanates are the least expensive, most easily available, and most stable, but, unfortunately, are ordinarily also the poorest nucleophiles and thus are useful only when relatively easily displaceable groups are involved. Accordingly, this approach to the preparation of derivatives of 3-thio-D-glucose and -D-allose required the use of thioacetate or thiobenzoate displacements of the 3-*O*-tosyl esters of 1,2:5,6-di-*O*-isopropylidene-D-allofuranose[2,4] and 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose[3,4]; efforts to effect displacement of the *O*-tosyl group of the D-allose derivative with the thiocyanate ion in *N*,*N*-dimethylformamide at high temperature were unsuccesful[5]. However, recent access to the 3-triflates of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose and -D-allofuranose[6,7], with their markedly improved, leaving-group ability, suggested an investigation of the SN2 reactions of the thiocyanate ion with these esters as an approach to derivatives of 3-thio-D-glucose and -D-allose. This study, and certain complications that can result from the use of the triflate leaving-group, are described herein.

The reaction of the D-glucofuranose triflate[6,7] **1** with potassium thiocyanate in hot acetonitrile gave a rather low yield of the crystalline D-allofuranose thiocyanate **3**. A substantial proportion of a polymeric oil and some of the partially deblocked derivative **4** were other reaction products. The polymer seemed to originate from polymerization of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**15**), the elimination product from **1**. Compound **1** is known to undergo facile elimination in the presence of bases[8], and we could show that the preformed, crystalline, unsaturated compound **15**, when treated in acetonitrile under the conditions of the reaction and in the presence of potassium triflate (potassium thiocyanate caused little change), was transformed into a polymeric material that qualitatively

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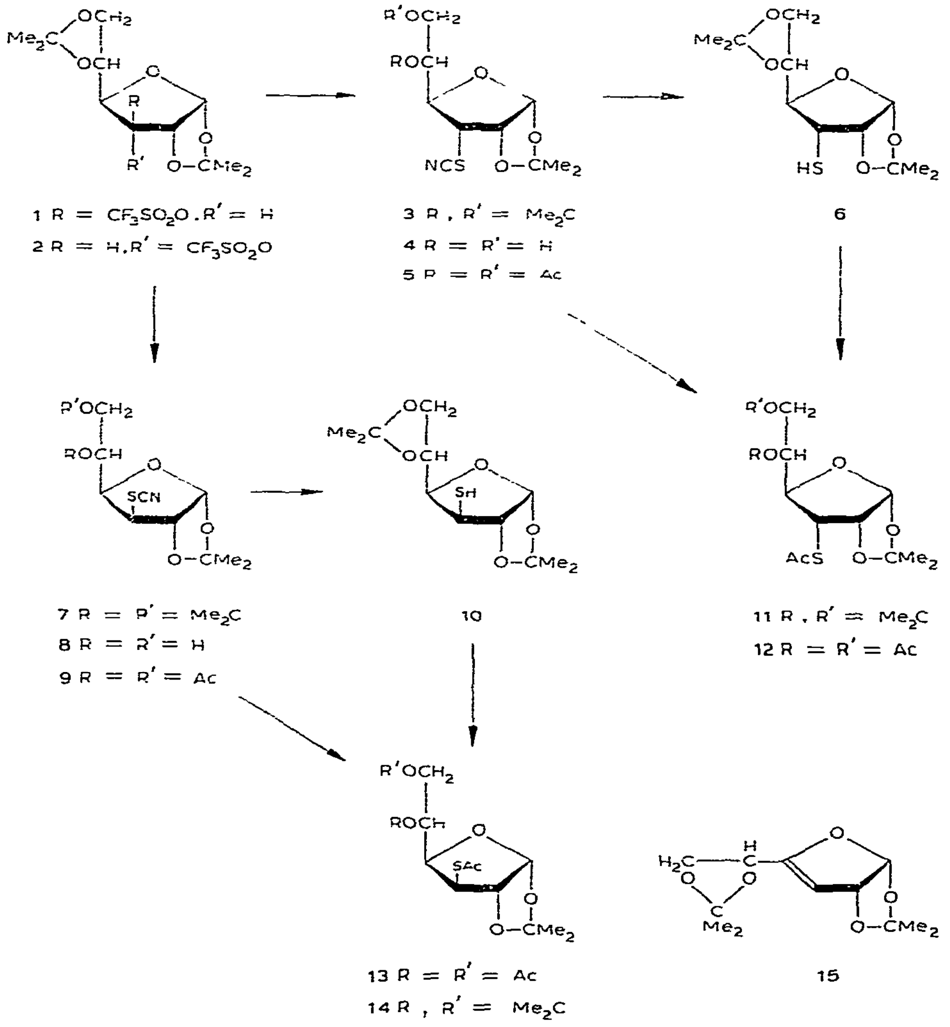
resembled the material that accompanied **3** in the reaction product. The presence of potassium triflate in the reaction mixture was also responsible for the partial deblocking to form **4**, as was shown by control experiments. It is clear that the intrinsic acidity of potassium triflate, at least in acetonitrile, can have important effects on certain reactions.

Cleavage of **3** with methanolic sodium methoxide gave, after neutralization, mainly the thiol **6**, but both t.l.c. and the n.m.r. spectrum suggested the presence of another material. Reaction of **3** with lithium aluminum hydride, however, produced, without complications, the thiol **6**, which formed the *S*-acetyl derivative **11**, previously reported by Nayak and Whistler[3]. Sodium methoxide has been employed previously to convert sugar thiocyanates to the free thiol[9], but it is evident that, in at least some cases, the thiol is accompanied by other products; addition of a molecule of methanol



to the nitrile triple bond is one possibility. Hydrolysis of the 5,6-*O*-isopropylidene group of **3** was accomplished with Amberlyst 15 (H^+) resin, in water at room temperature, to give **4**, characterized as the diacetate **5**. Sodium methoxide cleavage of **4** gave a partially deblocked thiol, characterized as the crystalline triacetate **12**, the physical properties of which agreed with those described by Nayak and Whistler[3].

Reaction of the D-allofuranose triflate **2** with potassium thiocyanate in hot acetonitrile gave a good yield of the crystalline D-glucofuranose thiocyanate **7**. None of the partially deblocked compound **8** was present in the reaction mixture, nor was there any evidence for material derived from the elimination product from **2**. Authentic **8** was obtained as an oil by hydrolysis of **7** with an acidic ion-exchange resin; it was characterized as the diacetate **9**. Again, methanolic sodium methoxide converted **7** to a product that was mainly the thiol **10**, but which contained other compounds. Lithium aluminum hydride treatment of **7** produced pure thiol **10**, the n.m.r. spectrum of which was in accord with that described by Heap and Owen[10] and by Stout *et al.*[11], and which could be acetylated to the known *S*-acetyl derivative[10] **14**. Reaction of **8** with sodium methoxide gave a thiol that was characterized as the triacetate **13**.

EXPERIMENTAL

General methods. — Organic solutions were dried in the presence of magnesium sulfate and were evaporated *in vacuo*, generally <40°. N.m.r. spectra were recorded at 60 MHz with a Varian EM-360 spectrometer, usually for solutions in chloroform-*d* with tetramethylsilane as internal standard. Optical rotations were measured for chloroform solutions at 28°, unless otherwise noted, with a Perkin–Elmer Model 141 automatic polarimeter. I.r. spectra were recorded with a Beckman Aculab 4 spectrometer, usually for chloroform or carbon tetrachloride solutions. Column chromatography employed SilicAR CC-7 (Mallinckrodt) silica gel at atmospheric pressure, and t.l.c. was performed on Brinkmann Polygram Sil G/UV_{254} plates in 1:4 to 1:1 (v/v) ethyl acetate–hexane, unless otherwise noted, with a sulfuric acid spray for detection. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Micro-Analysis, Inc., Wilmington, DE 19808, or Guelph Chemical Laboratories Ltd., Guelph, Ontario, NIE 3J4.

3-S-Cyano-1,2:5,6-di-O-isopropylidene-3-thio-α-D-allofuranose (3). — A stirred mixture of the D-glucose triflate **1** (9.0 g, 23 mmol), potassium thiocyanate (21 g, 214 mmol), and acetonitrile (150 mL) was heated at 78° for 36 h. The acetonitrile was evaporated, water (200 mL) added to the residue, and the aqueous mixture extracted with dichloromethane (3 × 200 mL). The dried extracts were evaporated to give an oily residue (7.4 g) which was triturated with three 300-mL portions of boiling hexane. Upon evaporation, the hexane extracts left **3** (3.9 g) as an oil that could be crystallized from ether–hexane to give 3.7 g (53%), m.p. 48–50°, $[\alpha]_D^{28}$ +63.9° (*c* 1, chloroform); $\nu_{max}^{CCl_4}$ 2200 cm^{-1} (SCN); n.m.r.: δ 5.90 (d, $J_{1,2}$ 4 Hz, H-1), 4.83 (t, $J_{2,3}$ 5 Hz, H-2), 4.13 (m, 4 H), 3.43 (dd, $J_{3,4}$ 9 Hz, H-3), 1.56, 1.50, and 1.33 (3 s, 12 H, CH_3).

Anal. Calc. for $C_{13}H_{19}NO_5S$: C, 51.81; H, 6.35; N, 4.65; S, 10.63. Found: C, 51.86; H, 6.34; N, 4.61; S, 10.51.

The residue remaining after the hot hexane extraction (2.3 g) was acetylated. N.m.r. and t.l.c. of the resulting product indicated that ~30% was the diacetate of **4** and the remainder the polymeric material described in the Discussion. Crystalline **4** had been directly isolated in small amounts from the residues of other reactions.

Effect of potassium triflate on the reaction products from **1** *and KSCN.* — (*a*) *3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-*D-erythro-*hex-3-enofuranose* (**15**). A stirred mixture of the elimination product[8] **15** (1.5 g) from **1**, potassium thiocyanate (4.0 g), and acetonitrile (75 mL) was heated at 78° for 36 h. The solution had become red at the end of this time, but t.l.c. showed a strong spot for the starting alkene **15**, together with weaker spots for other materials, presumably decomposition products. Potassium triflate (0.5 g) was added to the mixture and heating at 78° was continued for 24 h, at which time the solution was black and t.l.c. showed the absence of the starting alkene **15**. The black polymeric oil isolated from the mixture qualitatively (i.r. and n.m.r.) resembled the material isolated from the reaction of **1** and potassium thiocyanate.

(*b*) *3-*S*-Cyano-1,2:5,6-di-*O*-isopropylidene-3-thio-α-*D*-allofuranose* (**3**). — A stirred solution of **3** (0.3 g) in acetonitrile (10 mL) was heated for 18 h at 80°. T.l.c. showed no change and, particularly, no formation of **4**. Potassium thiocyanate (1.0 g) was added, and heating was continued for 24 h, after which time t.l.c. showed no formation of **4**. Potassium triflate (0.175 g) was added, and the mixture heated for 24 h, after which time t.l.c. showed complete conversion to **4**. A good yield of **4** identical with that described, in the next paragraph, was obtained from the reaction mixture.

*3-*S*-Cyano-1,2-*O*-isopropylidene-3-thio-α-*D*-allofuranose* (**4**). — To a mixture of 1,2-dimethoxyethane (10 mL) and water (8 mL) was added **3** (0.50 g) and Amberlyst 15 (H^+) resin (2.5 g). The mixture was stirred for 18 h at room temperature, and then filtered, and the resin washed with dichloromethane (100 mL). The filtrate was diluted with water (50 mL) and extracted with two 100-mL portions of dichloromethane. Evaporation of the dried extracts gave a residue that was recrystallized from dichloromethane–hexane to yield **4** (0.35 g, 85%), m.p. 109–110°, $[\alpha]_D^{28}$ +66.0 (*c* 1, chloroform); n.m.r.: δ 5.90 (d, $J_{1,2}$ 4 Hz, H-1), 4.83 (t, $J_{2,3}$ 4 Hz, H-2), 3.90 (m, 5 H), 3.03 (b, 1 H) and 2.46 (b, 1 H) (probable OH), 1.56, and 1.36 (2 s, 6 H, CH_3).

Anal. Calc. for $C_{10}H_{15}NO_5S$: C, 45.98; H, 5.74; N, 5.36; S, 12.27. Found: C, 45.78; H, 5.71; N, 5.48; S, 12.36.

*5,6-Di-*O*-acetyl-3-*S*-cyano-1,2-*O*-isopropylidene-3-thio-α-*D*-allofuranose* (**5**). — A mixture of **4** (0.30 g), acetic anhydride (1.0 mL), and pyridine (5 mL) was stirred overnight at room temperature, and then processed in the usual fashion to afford, after crystallization from dichloromethane–hexane, **5** (0.36 g, 90%) m.p. 99–100°, $[\alpha]_D^{28}$ +79.6° (*c* 1, chloroform); n.m.r.: δ 5.83 (d, $J_{1,2}$ 4 Hz, H-1), 5.26 (sextet, H-5), 4.80 (t, $J_{2,3}$ 4 Hz, H-2), 4.30 (m, 3 H), 3.46 (dd. $J_{3,4}$ 9 Hz, H-3), 2.20, 2.13 (2 s, 6 H, Ac), 1.56, and 1.40 (2 s, 6 H, CH_3).

Anal. Calc. for $C_{14}H_{19}NO_7S$: C, 48.68; H, 5.54; S, 9.28. Found: C, 49.12; H, 5.58; S, 9.38.

1,2:5,6-Di-O-isopropylidene-3-thio-α-D-allofuranose (**6**). — (*a*) *By hydride reduction.* A mixture of **3** (0.40 g), lithium aluminum hydride (0.60 g), and ether (150 mL) was heated for 1 h at reflux, and then the excess hydride was decomposed with ethyl acetate (5 mL), followed by water (5 mL) and 5% aqueous acetic acid (200 mL). The ether layer was separated, and the aqueous layer extracted with ether (2 × 200 mL). The combined extracts were washed with water (100 mL), dried, and evaporated to give crude **6** (0.25 g), which was chromatographed on silica to give chromatographically homogeneous **6** (0.21 g, 57%), m.p. 35–36°, $[\alpha]_D^{28}$ +70.9° (*c* 1, chloroform); $\nu_{max}^{CCl_4}$ 2600 cm^{-1} (SH); n.m.r.: δ 5.76 (d, $J_{1,2}$ 4 Hz, H-1), 4.60 (t, $J_{2,3}$ 4 Hz, H-2), 4.10 (m, 4 H), 2.96 (sextet, H-3), 2.03 (d, $J_{3,SH}$ 9 Hz, S*H*), 1.53, 1.46, and 1.36 (3 s, 12 H, CH_3).

Anal. Calc. for $C_{12}H_{20}O_5S$: C, 52.17; H, 7.25: S, 11.59. Found: C. 52.13: H, 7.26; S, 12.17.

(*b*) *By sodium methoxide cleavage.* A solution of **3** (2.0 g) and sodium methoxide (0.6 g) in methanol (50 mL) was stirred for 4 h under a nitrogen atmosphere, and then neutralized with Amberlite IRC 50 (H^+) resin (4.5 g). The mixture was filtered, the resin washed with dichloromethane (100 mL), and the filtrate evaporated. The residue was triturated with dichloromethane (200 mL), and the extract washed with water (100 mL), dried, and evaporated. The residue was distilled to give a liquid (0.30 g) b.p.$_{0.1\,mm}$ 114–118°, $[\alpha]_D^{28}$ +71° (*c* 1, chloroform), the n.m.r. spectrum of which was in good agreement with that of the material described under (*a*), except that the SH signal appeared as a singlet, and the H-3 signal as a double doublet.

Anal. Calc. for $C_{12}H_{20}O_5S$: C, 52.17; H, 7.25; S, 11.59. Found: C. 52.86; H, 7.26; S, 11.30.

3-S-Acetyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-allofuranose (**11**). — Conventional acetylation of **6** (70 mg) gave, after crystallization from ether–hexane, **11** (50 mg), m.p. 88–89° (lit.[3] m.p. 88°), and its n.m.r. spectrum was in accord with that reported by Nayak and Whistler[3].

5,6-O-3-S-Triacetyl-1,2-O-isopropylidene-3-thio-α-D-allofuranose (**12**). — A mixture of **4** (0.20 g), sodium methoxide (0.60 g), and methanol (20 mL) was stirred for 4 h at room temperature under nitrogen, and then the base was neutralized with Amberlite IRC-50 (H^+) resin (1.0 g). The mixture was filtered, the resin washed with dichloromethane (50 mL), and the filtrate evaporated. The residue was acetylated with acetic anhydride and pyridine in the usual fashion to give **12** (0.16 g, 57%), m.p. 102–104°, $[\alpha]_D^{28}$ +97.4° (*c* 1, chloroform); n.m.r.: δ 5.90 (d, $J_{1,2}$ 4 Hz, H-1), 5.23 (m, H-5), 4.73 (t, $J_{2,3}$ 4 Hz, H-2), 4.20 (m, 4 H), 2.40 (s, 3 H, 5Ac), 2.10 and 2.06 (2 s, 6 H, OAc), 1.50, and 1.33 (2 s, 6 H, CH_3); lit.[3] m.p. 99°, $[\alpha]_D^{25}$ +102.16° (chloroform).

3-S-Cyano-1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose (**7**). — A stirred mixture of **2*** (ref. 6, 2.0 g, 8.0 mmol), potassium thiocyanate (3.1 g, 32 mmol) and acetonitrile (75 mL) was heated for 20 h at 70°, and processed according to the procedure described for the preparation of **3**. Compound **7** (1.10 g, 71%) was obtained as a white, crystalline solid after crystallization from hexane,m.p. 43–44°, $[\alpha]_D^{28}$ —75.5° (*c* 1, chloroform); $\nu_{max}^{CCl_4}$ 2160 cm^{-1} (SCN); n.m.r.: δ 5.96 (d, $J_{1,2}$ 4 Hz, H-1), 4.90 (d, $J_{1,2}$ 4 Hz, H-2), 4.16 (m, 4 H), 3.80 (d, 1 H), 1.55, 1.42, and 1.34 (3 s, 12 H, CH_3).

Anal. Calc. for $C_{13}H_{19}NO_5S$: C, 51.81; H, 6.35; N, 4.65; S, 10.63. Found: C, 51.64; H, 6.57; N, 4.38; S, 10.39.

3-S-Cyano-1,2-O-isopropylidene-3-thio-α-D-glucofuranose (**8**). — A mixture of **7** (0.5 g), 1,2-dimethoxyethane (15 mL), water (10 mL), and Amberlyst 15 (H^+) resin (2.5 g) was stirred for 18 h at room temperature, and the mixture was processed as in the procedure described for **4**. The product (0.38 g, 88%) was a yellow oil, $[\alpha]_D^{28}$ —76.6° (*c* 1, chloroform); $\nu_{max}^{CHCl_3}$ 3500 (OH) and 2160 cm^{-1} (SCN); n.m.r.: δ 6.00 (d, $J_{1,2}$ 4 Hz, H-1), 4.90 (d, H-2), 4.30 (dd, 1 H), 3.83 (m, 6 H), 1.53, and 1.33 (2 s, 6 H, CH_3).

Anal. Calc. for $C_{10}H_{15}NO_5S$: C, 45.98; H, 5.74; N, 5.36; S, 12.27. Found: C, 46.62; H, 6.21; N, 5.17; S, 12.13.

5,6-Di-O-acetyl-3-S-cyano-1,2-O-isopropylidene-3-thio-α-D-glucofuranose (**9**). — Conventional acetylation of **8** (0.38 g) gave **9** (0.42 g, 85%) as an oil which was further purified by thick-layer chromatography, $[\alpha]_D^{28}$ —29.4° (*c* 1, chloroform); $\nu_{max}^{CCl_4}$ 2180 cm^{-1} (SCN); n.m.r.: δ 5.96 (d, $J_{1,2}$ 4 Hz, H-1), 5.03 (m, 2 H), 4.60 (m, 2 H), 4.00 (m, 2 H), 2.13 (s, 6 H, OAc), 1.56, and 1.36 (2 s, 6 H, CH_3).

Anal. Calc. for $C_{14}H_{19}NO_7S$: C, 48.68; H, 5.54; N, 4.05; S, 9.28. Found: C, 48.85; H, 5.51; N, 4.17; S, 9.68.

1,2:5,6-O-isopropylidene-3-thio-α-D-glucofuranose (**10**). — (*a*) *By hydride reduction.* Reduction of **7** (0.3 g) was accomplished by the procedure described for **6**. The crude product (0.23 g) was purified by silica gel chromatography to give **10** (0.17 g, 60%) the n.m.r. spectrum of which agreed with that reported by Heap and Owen[10]; ν_{max}^{film} 2600 cm^{-1} (SH).

(*b*) *By sodium methoxide cleavage.* Crude **10** (0.18 g) was isolated from **7** (0.2 g) by use of the procedure described for **6**. Good general agreement with the n.m.r. spectrum observed for **10** obtained by procedure (*a*) was observed but extra signals were present; the SH group appeared as a singlet at δ 2.20, and H-3 as a doublet at δ 3.30.

3-S-Acetyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose (**14**). — The thiol **10** (70 mg) was acetylated conventionally to give **14** (75 mg, 92%) as a chromatographically homogeneous oil; n.m.r.: δ 5.76 (d, $J_{1,2}$ 4 Hz, H-1), 4.50 (d, $J_{1,2}$ 4 Hz,

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*Compound **2** was prepared by triflation[6] of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose, which was prepared according to the general directions of Baker *et al.*[12], except that the initial oxidation was much more conveniently done and in higher yield by the method of Garegg and Samuelson[13].

H-2), 4.0 (m, 5 H), 2.36 (s, 3 H, SAc), 1.50, 1.40, and 1.30 (3 s, 12 H, CH_3); in good agreement with the spectrum reported by Heap and Owen[10].

5,6-O-3-S-Triacetyl-1,2-O-isopropylidene-3-thio-α-D-glucofuranose (**13**).—Cleavage of **8** (1.0 g) was accomplished by the procedure used in the preparation of **12**, to give an oil (0.85 g) that was conventionally acetylated. The product (0.90 g, 65%) was an oil that was purified by thick-layer chromatography, $[\alpha]_D^{28}$ +52.2° (*c* 1, chloroform); n.m.r.: δ 5.76 (d, $J_{1,2}$ 4 Hz, H-1), 5.16 (d, of d, H-5), 4.50 (m, 3 H), 4.10 (m, 2 H), 2.36 (s, 3 H, SAc), 2.10 and 2.00 (2 s, 6 H, OAc), 1.56 and 1.33 (2 s, 6 H, CH_3).

Anal. Calc. for $C_{15}H_{22}O_8S$: C, 49.71; H, 6.11; S, 8.84. Found: C, 49.99; H, 6.26; S, 9.06.

ACKNOWLEDGMENTS

This work was supported by a grant (AM-20219) from the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health. Some of the work was performed during the tenure of an Eleanor Roosevelt International Cancer Fellowship awarded by the American Cancer Society. L.G. wishes to acknowledge the support and encouragement of Dr. M. Hubert-Habart, in whose laboratory at the Fondation Curie, Institut du Radium, Paris, France, the work was done.

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