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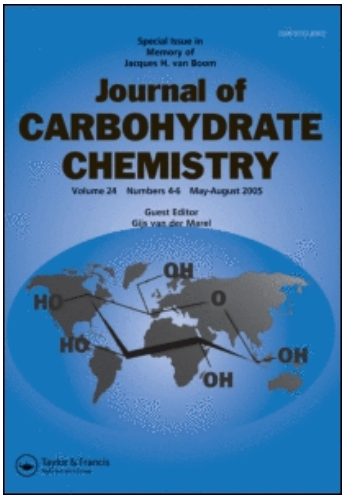

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Practical Synthesis of Sinigrin

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COMMUNICATION

PRACTICAL SYNTHESIS OF SINIGRIN

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Sinigrin (**1**), the most commonly known glucosinolate, is a naturally occurring thiosugar, widely distributed in the botanic family Cruciferae. Sinigrin was first isolated in 1839 from seeds of black mustard in the form of its potassium salt.[1] Commercially available sinigrin is obtained by extraction from horseradish.[2] So far a number of natural glucosinolates and their analogs have been synthesized.[3-10] The only synthesis of compound **1**, leading to a crystalline product on the miligram scale, has been reported by Benn and Ettlinger[3] (Scheme 1). Their procedure has been applied by Kjaer and Jensen[4] for the synthesis of the higher homologue of sinigrin (**1**), but no information of the overall yield has been provided.

We now report the first practical synthesis of sinigrin, which is suitable for preparation on a ten-gram-scale.[11] The general scheme of the preparation is close to that reported by Benn and Ettlinger;[3] we have introduced, however, significant changes which raise the overall yield of the synthesis. Preparation of hydroxamoyl chloride **3**, followed by condensation with 1-mercaptoglucose **4**, is the key step of the synthesis. The conventional route, in which the sodium salt of 4-nitrobut-1-ene (**2**)[12] was converted into

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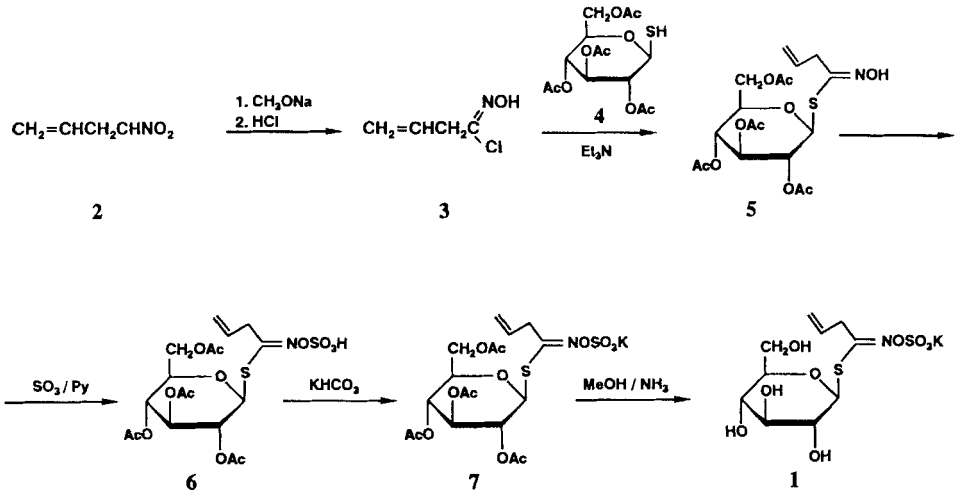

Scheme 1

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3 using a lithium chloride - hydrochloric acid mixture, afforded a low yield of the product.[3] On the other hand, the presence of a double bond in the olefin precludes formation of **3** from the corresponding oxime by direct chlorination.[5,7-9] We eventually succeeded in preparing **3** using a slight modification of the method of Gil and MacLeod.[5] A solution of HCl in ethyl ether was used instead of gaseous HCl and the product was not isolated by filtration at -60 °C, but used without isolation for condensation with **4**[13] as the crude post-reaction mixture. This procedure modification raised the overall yield of hydroximoyl chloride formation and condensation to 77%. The next two steps, sulphation and formation of the potassium salt **7** according to the standard procedure,[5] were slightly modified in order to avoid use of water and subsequent freeze-drying. Crystallization of synthetic sinigrin differs from the procedure applied to the extracted natural compound because of contamination of the crude product with acetamide released in the last step of the synthesis.[14] Therefore, the procedure used in carrying out deacetylation is important in maximizing the overall yield of sinigrin. We found that the concentration of ammonia in methanol should vary within the range of 0.01-0.18%, providing about 1 molar equivalent of ammonia, i.e. ¼ th of the amount necessary for deacetylation of acetyl groups, if acetamide would be formed as the deacetylation product.

Owing to this low concentration, ammonia only played the role of a catalyst in the transesterification process. The crude sinigrin (**1**) thus obtained is almost uncontaminated with acetamide. Crystallization of **1** was done by slow addition of ethanol to a saturated aqueous solution of **1**, followed by lowering of the temperature. The overall yield of sinigrin monohydrate, starting from **2**, amounted to 42 %.

EXPERIMENTAL

Melting points are uncorrected. Optical rotation was measured with a JASCO Dip-360 digital polarimeter. ^{1}H NMR spectra were recorded with a Bruker AM 500 spectrometer. IR spectra were obtained in a FT-IR-1600 Perkin-Elmer spectrophotometer. 4-Nitrobut-1-ene was synthesized according to Kornblum et al.,[12] and 1-mercapto-2,3,4,6-tetra-*O*-acetyl-ß-D-glucose (**4**) according to Ref. 13.

***S*-(2,3,4,6-Tetra-*O*-acetyl-ß-D-glucopyranosyl)-but-3'-ene-thiohydroximate** (**5**). To a solution of 4-nitrobut-1-ene (**2**; 24 g, 0.24 mol) in methanol (80 mL), sodium methoxide in methanol (5.46 g of sodium in 160 mL of methanol) was added at room temperature. The mixture was stirred for 5 min and then anhydrous ethyl ether (800 mL) was added. The precipitate of the sodium salt of **2** was filtered, washed with anhydrous ether, and dried to afford a crystalline salt (27 g). This salt was suspended in anhydrous ether (600 mL), cooled to -70 °C and treated with a cold ethyl ether solution of HCl (535 mL of 3.3 M solution). The mixture was stirred at -70 °C for 30 min and subsequently triethylamine (400 mL) in ethyl ether (800 mL) was added at a temperature not exceeding -40 °C. To the reaction mixture, a solution of thiol **4** (87 g) in ethyl ether (1.6 L) was added, and the temperature was raised to 15 °C. The mixture was stirred for 30 min at 15 °C and then was poured into a solution of sulfuric acid (300 mL) in water (4 L) cooled to 4 °C. The product was extracted with ethyl acetate (1.6 L). The extract was washed with water (3 x 2 L) until neutral, dried over magnesium sulfate, and concentrated. Crude product was washed with 96% ethanol (150 mL) to give **5** (75.0 g, 77%): mp 165-166 °C, lit. Ref. 3 164-165 °C; $[\alpha]_D$ -13° (*c* 1.0, chloroform), lit. Ref. 3 $[\alpha]_D$ -13° (*c* 0.14, chloroform); IR (KBr) 3310, 1747, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01, 2.04, 2.05, 2.09 (4s, 12H, 4xAc), 3.33 (m, 1H, J_{gem} 16.7 Hz, J_{vic} 6.9 Hz, -C**H**$_A$H$_B$-), 3.39 (m, 1H, J_{vic} 5.4 Hz, -CH$_A$**H**$_B$-), 3.75 (ddd, 1H, *J* 3.0, 5.3 and 10.1 Hz, H-5), 4.16 (dd,

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1H, *J* 3.0 and 12.3 Hz, H-6), 4.18 (dd, 1H, *J* 5.3 and 12.3 Hz, H-6'), 5.03 - 5.10 (m, 2H, H-2, 4), 5.12 (d, 1H, *J* 10.1 Hz, H-1), 5.21 - 5.26 (m, 2H, $=CH_2$), 5.25 (t, 1H, *J* 9.2 Hz, H-3), 5.94 (m, H, -CH=).

Anal. Calcd for $C_{18}H_{25}NO_{10}S$ (447.46): C, 48.32; H, 5.63; N, 3.13. Found: C, 48.33; H, 5.81; N, 3.26.

Potassium *S*-(2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranosyl)-but-3'-ene-thio-*O*-sulfoximate (2,3,4,6-Tetra-*O*-acetyl-allylglucosinolate) (7). Thiohydroximate **5** (74.5 g) was dissolved in dry pyridine (740 mL), treated with a freshly prepared pyridine-sulfur trioxide complex (83 g) and stirred for 48 h at room temperature. Subsequently the mixture was neutralized with an aqueous solution of $KHCO_3$ (105 g in 600 mL of water) and then extracted three times with ethyl ether (4.5 L, 1.5 L, and 1,5 L). The precipitate was filtered, washed with a saturated solution of K_2SO_4 (2 x 90 mL) and then with ethanol (150 mL). The residue was extracted with hot 85 % ethanol (900 mL and 300 mL). The solution was cooled, and crystals were filtered to give **7** (60.1 g, 68 %), mp 193-194 °C, lit. Ref. 3 193-195 °C; $[\alpha]_D$ -16° (*c* 1.0, water), lit. Ref. 3 $[\alpha]_D$ -16° (*c* 0.14, water); IR (KBr) 1753 cm^{-1}; ^1H NMR (D_2O) δ 2.11, 2.14, 2.15, 2.17, (4s, 12H, 4xAc), 3.55 (m, 2H, $-CH_2-$), 4.21 (ddd, 1H, *J* 2.2, 4,5 and 10.1 Hz, H-5), 4.28 (dd, 1H, *J* 2.2 and 12.7 Hz, H-6), 4.41 (dd, 1H, *J* 4.5 and 12.7 Hz, H-6'), 5.18 - 5.24 (m, 2H, H-2, 4), 5.33 - 5.40 (m, 2H, $=CH_2$), 5.48 (t, 1H, *J* 9.2 Hz, H-3), 5.49 (d, 1H, *J* 10.1 Hz, H-1), 6.07 (m, 1H, -CH=).

Anal. Calcd for $C_{18}H_{24}KNO_{13}S_2$ (565.62): C, 38.22; H, 4.28; N, 2.48. Found: C, 37.78; H, 4.49; N, 2.34.

Sinigrin monohydrate (1). Compound **7** (60.0 g) was suspended in methanol (2.4 L), treated with methanolic ammonia (20.0 mL of 6.7 M solution), and stirred for 24 h. Subsequently activated charcoal (10 g) was added and the mixture was stirred for 10 min. The charcoal was filtered off, and the solvent was removed under reduced pressure. The glassy residue was dissolved in water (100 mL), treated slowly with 96 % ethanol (750 mL), and left at 0 °C for 3 h. The crystals of **1** (35.1 g) mp. 128-129 °C were separated by filtration. The filtrate was concentrated under reduced pressure, dissolved in water (10 mL), and treated with 96% ethanol (150 mL) to afford additional 3.1 g of **1**. Total yield of **1** was 38.2 g, 83 %, mp 128-129 °C, lit. Ref. 3 mp 125-127 °C; $[\alpha]_D$ -17° (*c* 1.0, water), lit. Ref. 3 $[\alpha]_D$ -17° (*c* 0.2, water); ^1H NMR (D_2O) δ 3.43-

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3.57 (m, 6H, H-2, 3, 4, 5, -CH_2-), 3.72 (dd, 1H, *J* 5.9 and 12.6 Hz, H-6), 3.92 (dd, 1H, *J* 2.6 and 12.6 Hz, H-6'), 5.06 (d, 1H, *J* 9.9 Hz, H-1), 5.29 (dq, 1H, =C$\mathbf{H}_A$$H_B$), 5.33 (dq, 1H, =$CH_A$$\mathbf{H}_B$), 6.04 (m, 1H, J_{vicA}10.3, J_{vicB} 17.3 Hz, -CH=).

Anal. Calcd for $C_{10}H_{18}KNO_{10}S_2$ (415.49): C, 28.91; H, 4.37; N, 3.37. Found: C, 29.00; H, 4.42; N, 3.46.

Spectral and analytical data of **1** were found to be identical with respective data of natural sinigrin provided by Aldrich.

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