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The Preparation of Isoxazole Derivatives from a Nitro Sugar with Dimethylsulfonium Phenacylide

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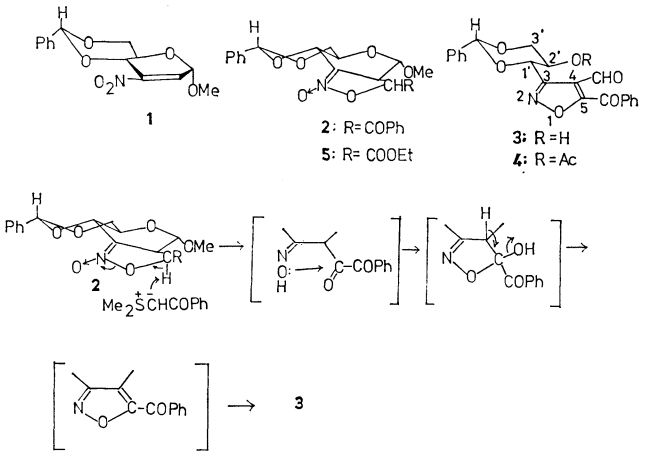
Synopsis. The reaction of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside or 5-benzoyl(methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranosido)[3,2-*c*]isoxazoline *N*-oxide with dimethylsulfonium phenacylide gave 5-benzoyl-3-(1,3-*O*-benzylidene-D-*erthro*-glyceryl)-4-isoxazolecarbaldehyde in a fairly good yield.

Recently we reported that the reaction of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (**1**) (0.2 mmol) with dimethylsulfonium phenacyclide (0.25 mmol) afforded the isoxazoline *N*-oxide **2** in a good yield.[1] However, when this reaction was carried out on a larger scale, the isoxazole, **3**, was formed. The determination of the structure of **3** and the conversion of the isoxazoline *N*-oxide **2** into **3** is described herewith.

The treatment of **1** (293 mg, 1 mmol) with dimethylsulfonium phenacylide (1.5 mmol) in THF (10 ml) at room temperature for 3 h gave a NMR spectroscopically pure syrup, **3** (315 mg), with the odor of dimethyl sulfide. The IR spectrum showed the absorption bands for a hydroxyl (3400 cm^{-1} broad) and α,β-unsaturated carbonyl group (1670 cm^{-1}). The NMR spectrum revealed that **3** had lost the glycosidic methoxyl group, but retained the benzylidene group. The presence of 10-protons in the aromatic region suggested the presence of a benzoyl group. The two 1-proton signals at δ 9.15 and 3.00 (broad) were assigned to the formyl proton and the OH proton respectively. The H-1′ signal appeared as a doublet due to vicinal coupling with H-2′ ($J_{1',2'}$=9 Hz). The acetylation of **3** with acetic anhydride–sodium acetate gave the crystalline acetate, **4**, the NMR spectrum of which showed that the hydroxyl group attached originally at C-2′, since the signal of H-2′ had moved remarkably downfield as a result of the deshielding effect of the acetate group. The results of the elemental analysis of the acetate, **4**, agreed with the formula of $C_{23}H_{19}NO_7$, indicating that the products, **3** and **4**, have not a isoxazoline *N*-oxide ring, but a isoxazole.

The conversion of the isoxazoline *N*-oxide **2** into **3** was observed when **2** was treated with dimethylsulfonium phenacylide at 0 °C for 3 h, whereas the similar treatment of **2** with dimethyl sulfide resulted in the recovery of **2**. The reinvestigation[1] of the reaction between **1** and dimethylsulfonium ethoxycarbonylmethylide under similar conditions gave no evidence for the formation of an isoxazole corresponding to **3**. Furthermore, the treatment of the isoxazoline *N*-oxide, **5**, with dimethylsulfonium ethoxycarbonylmethylide or dimethyl sulfide afforded unchanged **5** in a quantitative yield.

On the basis of the mechanism proposed for the conversion of isoxazoline *N*-oxide into isoxazole[2] and the reports[3] in the literature that the hydrolysis of a pyranose derivative with unsaturated functional groups at the 2 position is facile and that the hydrolyzed product tends to exist in the open-chair aldehyde-form rather than with the pyranoside structure, the route shown in Scheme seems to be most plausible. In this reaction, the abstraction of the proton at C-5 (the isoxazoline ring proton) is probably the crucial step. Dimethylsulfonium phenacylide is basic enough for **2**, but dimethyl sulfide is not, and dimethylsulfonium ethoxycarbonylmethylide is not a sufficient base for **5** because the hydrogen atom (H-5) of **5** is less acidic than that of **2**.



Scheme.

Experimental

The melting point was determined in capillary and is uncorrected. The NMR spectra were determined for solutions in chloroform-*d* (with tetramethylsilane as the internal standard) with a JNM-4H-100 (JEOL) spectrometer.

*5-Benzoyl-3-(1,3-O-benzylidene-*D-erythro-*glyceryl)-4-isoxazolecarbaldehyde (3).* (a) To a solution of **1**[4] (293 mg, 1 mmol) in THF (10 ml), dimethylsulfonium phenacylide (270 mg, 1.5 mmol) was added at room temperature. The mixture was kept at the same temperature for 3 h and then evaporated under reduced pressure to give a dark orange syrup, which was subsequently extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated to give an orange syrup (465 mg). Its MNR spectrum suggested that it was fairly pure; IR (NaCl) 3400 (broad, OH) and 1670 cm^{-1} (α,β-unsaturated CO); NMR δ=9.15 (s, 1, CHO), 5.60 (s, 1, PhCH), 5.20 (d, 1, H-1′), 4.45 (m, 1, H-2′),4.55 (q, 1, H-3e′), 3.76 (t, 1, H-3a′) and 3.00 (broad, s, 1, OH).

Without further purification the syrup was acetylated.

(b) To a solution of dimethylsulfonium phenacylide (13 mg, 0.07 mmol) in THF (0.22 ml) in either the presence

or absence of dimethyl sulfide (0.07 mmol), the isoxazoline *N*-oxide **2** (0.07 mmol) was added at 0 °C. The mixture was kept at 0 °C for 3 h and then evaporated at reduced pressure to give a syrup. Its NMR spectrum showed the complete conversion of **2** into **3**.

The treatment of **2** (0.07 mmol) with dimethyl sulfide in the absence of dimethylsulfonium phenacylide resulted in the recovery of **2**, as judged by NMR spectroscopy.

*3-(2-*O*-Acetyl-1,3-*O*-benzylidene-*D*-erythro-glyceryl)-5-benzoyl-4-isoxazolecarbaldehyde (4).* The crude isoxazole **3** (62 mg) was warmed in a water bath (90 °C) with sodium acetate (62 mg) in acetic anhydride (2 ml) for 1 h. The mixture was then poured into ice water, and the precipitate was collected and washed with water and chromatographed on silica gel (15×70 mm) with benzene. The eluate was evaporated to give a solid residue, which was subsequently recrystallized from ethanol to give 32 mg (46.4%) of colorless crystals of **4**; mp 123.5—124.5 °C; $[\alpha]_D^{20}$ −18.6° (*c* 1, $CHCl_3$); IR (KBr) 1740 (OAc) and 1670 cm^{-1} (α,β-unsaturated COPh and CHO); NMR δ=9.18 (s, 1, CHO), 5.70 (m, 1, H-2′, $J_{1',2'}$=10, $J_{2',3a'}$=10, $J_{2',3e'}$=5.0 Hz), 5.67 (s, 1, PhCH), 5.40 (d, 1, H-1′), 4.55 (q, 1, H-3e′, $J_{3a',3e'}$=10 Hz), 3.79 (t, 1, H-3a′), and 1.97 (s, 3, OAc).

Found: C, 65.60; H, 4.67; N, 3.06%. Calcd for $C_{23}H_{19}NO_7$: C, 65.55; H, 4.54; N, 3.32%.

References

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