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FURO[3,4-b]FURAN FORMATIONS FROM ALKYNOLS OF XYLOSE

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Abstract Treatment of iodoalkynol derivatives of xylose with iodonium-producing reagents afforded β,β-diiodoenol ethers contained in furo[3,4-b]furan cores.

Haloalkynol reactions of synthetic utility with iodonium species generated by combinations of N-iodosuccinimide and catalytic quantities of acid involve either group shifts that lead to β-iodoenones or oxygen shifts that lead to α-iodoenones.[1] The group shift reactions are of greater interest because they are stereospecific with the migrating group *anti* to the iodine atom. For cyclic systems ring expansions are also stereospecific for bromoalkynols to (Z)-bromoiodoenones.[2] The mechanistic differences between the group shift reactions and the oxygen shift reactions have been described, and the nature of the stereochemical shifts has been delineated.[3,4] These stereochemically defined arrays in linear and cyclic systems can serve as templates for the selective replacements of halogens by aryl or alkyl radicals through palladium-catalyzed reactions with organotin or organoboron compounds.[5,6] A broad range of novel analogues are at hand for pharmacologically significant compounds such as tamoxifen used widely in the treatment and prevention of breast cancer and clomiphene used as a fertility agent.[7,8] In an effort to convert haloalkynylfuranoses to ketopyranoses we encountered a third reaction which is the main concern of this report.

The commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose was treated with tosyl chloride and pyridine to give the 5-*O*-tosylate whose melting point of 133-134°C and 1HNMR matched those in the literature[9] and which was converted by methoxide to the 5-*O*-methyl ether **1** whose spectral values agreed with previous reports.[10] The latter was oxidized with PDC in acetic anhydride to give 1,2-*O*-isopropylidene-5-*O*-methyl-α-D-pent-3-ulofuranose (**2**) in 89%

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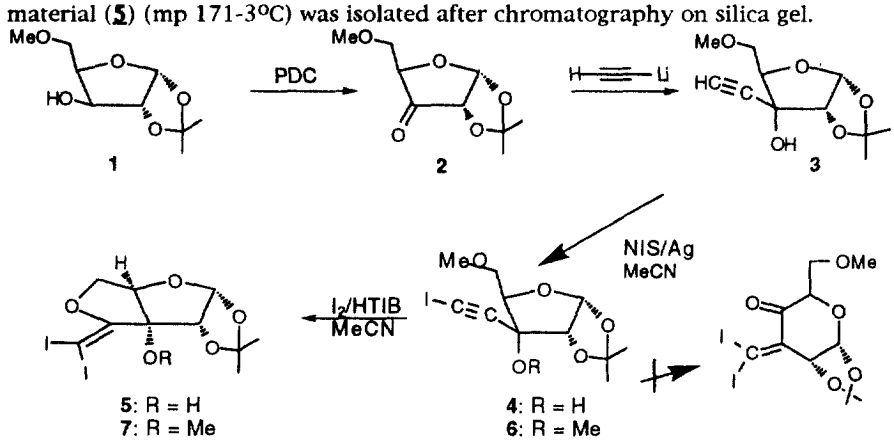
yield. Reaction of that 3-ketose with lithium acetylide or ethynyl magnesium bromide in THF afforded 3-ethynyl-1,2-*O*-isopropylidene-5-*O*-methyl-α-D-pentofuranose(**3**). Only one isomer was isolated in 70% yield and was assumed to be that isomer whose alkynyl group was *anti* to the bulky isopropylidene group. The alkynyl hydrogen was replaced with iodine by the action of NIS and catalytic amounts of silver nitrate in acetone or acetonitrile in 83% yield to give **4**, the 3-iodoethynyl derivative of **3**.[11] Its 13CNMR had an upfield signal at 7.3 ppm, an indication of the iodoalkyne carbon. Compounds **2** through **7** had spectral data and elemental analyses consistent with their assignments.

The attempt to form a diiodomethylene-hexulopyranose was carried out with NIS and catalytic TsOH in 5% aqueous acetonitrile as well as with equimolar quantities of iodine and hydroxy(4-methylbenzenesulfonato-*O*)phenyliodine (HTIB) in acetonitrile. The ketopyranose was not formed. A material (**5**) (mp 171-3°C) was isolated after chromatography on silica gel.



The main product's IR, 1HNMR and 13CNMR displayed no evidence of a carbonyl or methoxy group. The molecular weight by MS was 466 m/z rather than the expected 480 supporting the loss of the methyl group present in **2**, **3** and **4**. The presence of a hydroxyl group was noted in the IR (sharp band at 3500 cm^{-1} and in the 1HNMR (signal at 3.54 ppm). The striking feature of the 13CNMR was an upfield signal at -16.4 ppm and a downfield signal at 160 ppm. The usual position for the β-vinyl carbons bearing two iodines in the β,β-diiodoenones is around 14 ppm.[2d] A model compound that exhibits this

interesting heavy atom effect is 2-(diiodomethylene)tetrahydrofuran whose signal is at -26.02 ppm for the diiodomethylene carbon and 163 ppm for the other half of the alkene.[12] The proposed structure for **5** is (*cis*)-3a-hydroxy-4-diiodomethylene-2,3-*O*-isopropylidene-2,3,3a,4,6,6a-hexahydro-furan[3,4-b]furan. Further support in the MS was a peak at 350 m/z (80-100%) indicative of a loss of 116 from the mass peak, an effect observed in all the other 1,2-*O*-isopropylidene-xylofuranoses.

Further supportive data resided in the 1HNMR whose full spectrum was as follows: 1.45(s, 3H), 1.60(s,3H), 3.54(s, 1H), 4.31(d, J=2.3 Hz, 1H), 4.32(s, 1H), 4.77(d,J=2.3 Hz, 1H), 4.99(d, J=4.1 Hz, 1H), 5.98(d, J=4.1 Hz, 1H). The latter two peaks are characteristic of the protons on C-1 and C-2 of the furanose ring with an isopropylidene attachment. The lack of splitting between the *anti* proton on C-6 and the angular proton on C-6a has been reported by Tsuchiya and colleagues for a furo[3,4-b]furan from a ring contraction of a glucopyranoside.[13] The geminal coupling between the C-6 protons is not observed due to their almost identical chemical shifts.

The formation of this cyclic ether and the fate of the missing methyl group was connected by GC/MS results which showed peaks of methyl tosylate - 186 m/z (M^+), 155, 91. Thus the vinyl cation formed by iodonium attack on the alkynyl portion of **4** was proximate to the terminal ether's oxygen and reinforces the assignment of the C-3 alkyne as *anti* to the isopropylidene group. That vinyl cations can cleave ethers intramolecularly can be substantiated by the report of benzofuran formation in the solvolyses of 1-aryl-2,2-bis(o-methoxyphenyl)vinyl halides.[14]

The methyl ether of **4** was prepared by NaH/CH_3I. This compound **6** (mp 96-98°C) was treated with the NIS/TsOH system as well as the I_2/HTIB duo. The chief product (mp 156-7°C) was shown to be the 3a - methoxy form of **5** by a simple conversion of **5** to **7** with NaH/CH_3I. It too had the remarkable signal at -16 ppm in the 13CNMR along with 157.1 (C-4 alkene) and 54.9 (methoxyl on C-3a). Its MS was as follows: 480 m/z (M^+, 35), 364 (M^+-116, 100). The IR displayed neither hydroxyl nor carbonyl bands. The 1HNMR had the methoxyl protons at 3.38 ppm (s,3H) as well as these peaks: 1.42 (s, 3H), 1.59 (s, 3H), 4.21 (dd, J= 10.6, 2.6 Hz, 1H), 4.31 (d, J=10.6 Hz, 1H), 5.02 (d, J=2.6 Hz, 1H), 5.16 (d, J=3.7 Hz, 1H) and

5.85 (d, J=3.7 Hz, 1H). Since there were differences in the chemical shifts of the C-6 protons, their geminal splitting of 10.6 Hz was seen, but as in **5** only the C-6 proton (4.21) *syn* to the angular proton 6a (5.02) was split by 2.6 Hz. The geminal splitting is close to the value of 10.5 Hz reported by Tsuchiya.[13]

The isolated yields of **5** and **7** ranged from 55 to 65 %. They and any bromoiodo analogues would serve as templates for novel tamoxifen-like compounds after aryl exchanges of the halogens. Shift reactions to ketopyranoses may be possible for those stuctures whose haloalkynyl groups are *anti* to the 5-*O*- methoxyls of pentofuranoses.

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