Pergamon

Tetrahedron Letters, Vol. 36, No. 43, pp. 7811-7814, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01654-6

SYNTHESIS OF 1,5-DIDEOXY-1,5-IMINO-D-XYLONOLACTAM *VIA* ACID-CATALYZED INTRAMOLECULAR SCHMIDT REARRANGEMENT

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Summary : 5-Azido-2,3,4-tri-*O*-benzoyl-5-deoxy-D-xylose diethyl dithioacetal (**3**) undergoes smooth Lewis acid-catalyzed demercaptalation (boron trifluoride etherate/HgO) to afford the unstable *aldehydo*-azide **4**, which in the presence of Lewis acids yields the tribenzoate **6** of the title compound (**7**) *via* an apparent intramolecular Schmidt rearrangement.

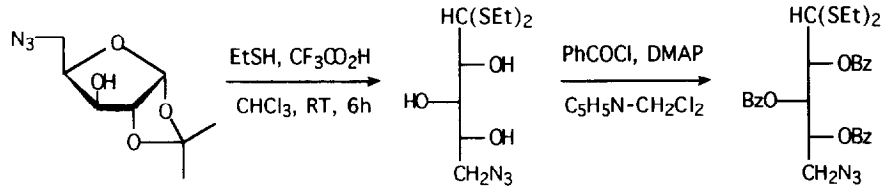
Imino sugars, carbohydrate derivatives containing nitrogen in place of the ring oxygen, possess interesting biological activities, most notably as inhibitors of glycosidases.[1] Both furanose and pyranose imino sugars have been isolated from natural sources[2] and much effort has been expended on the synthesis of both natural and unnatural imino sugars, both by chemical and chemo-enzymatic methods.[3] Several examples have gained attention as potential treatments for such viral infections as HIV,[4] and diseases related to carbohydrate metabolism, such as diabetes.[5] We have a sustained interest in the utility of sugar-derived azides for the preparation of a variety of carbohydrate systems,[6] and now report a new synthesis of a D-xylono-1,5-lactam derivative by means of an acid-catalyzed Schmidt rearrangement of an *aldehydo*-5-azido-5-deoxy-D-xylose precursor.

The Schmidt rearrangement has classically been employed as a method for preparing nitrogen-containing heterocycles by treating a ketone substrate with hydrazoic acid.[7] More recently, the synthetic utility of this reaction has been greatly expanded through the work of Aubé and coworkers, who have shown that lactams are available by either intermolecular[8] or intramolecular[9] acid-catalyzed Schmidt rearrangements of ketones and azides. This methodology has been expanded upon recently as a route to various natural-product skeletons.[10] We have now found that treatment of an ω-azidodeoxy D-xylose-derived aldehyde with Lewis acids leads to similar rearrangement to afford the corresponding D-xylonolactam derivative. Sugar-derived lactams have been shown to exhibit glycosidase inhibitory properties,[11] and are useful intermediates in the synthesis of other imino sugars, such as amidines.[12]

As a precursor for the Schmidt rearrangement we required 5-azido-2,3,4-tri-*O*-benzoyl-5-deoxy-*aldehydo*-D-xylose (**4**) which was expected to be accessible by means of demercaptalation of the corresponding 5-azido-2,3,4-tri-*O*-benzoyl-5-deoxy-*aldehydo*-D-xylose diethyl dithioacetal (**3**, scheme 1). Access to the azide **3**, *via* activation of D-xylose diethyl dithioacetal as its 5-sulfonic ester and subsequent displacement with azide, was precluded because such 5-sulfonates (e.g. the tosylate) in the *xylo* series are known to undergo rapid intramolecular reaction to afford 2,5-anhydro sugars.[13] A less-direct approach to **3** was therefore devised. 5-Azido-5-deoxy-

1,2-*O*-isopropylidene-α-D-xylofuranose (**1**), prepared[14] by a four-step sequence from D-xylose, yielded **1** as a crystalline solid. Treatment of **1** with ethanethiol and trifluoroacetic acid in chloroform at room temperature provided the crystalline diethyl dithioacetal **1** in 62% yield after chromatography (mp 48-50°C, $[\alpha]_D$ +53.5°, $CHCl_3$), and this was converted into a syrupy tribenzoate, identified as 5-azido-2,3,4-tri-*O*-benzoyl-5-deoxy-D-xylose diethyl dithioacetal (**3**, 85%, $[\alpha]_D$ +15.8°, $CHCl_3$), which was expected to be a suitable precursor to the required 5-azido-5-deoxy *aldehydo* derivative.

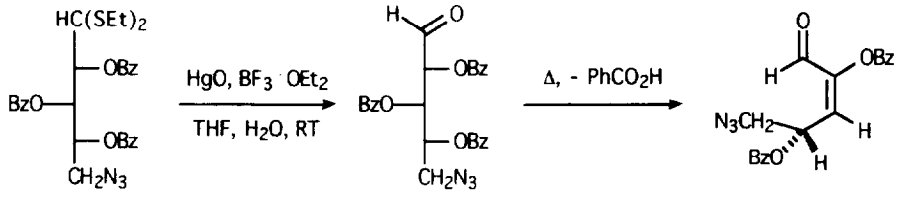
Scheme 1



1 **2** **3**

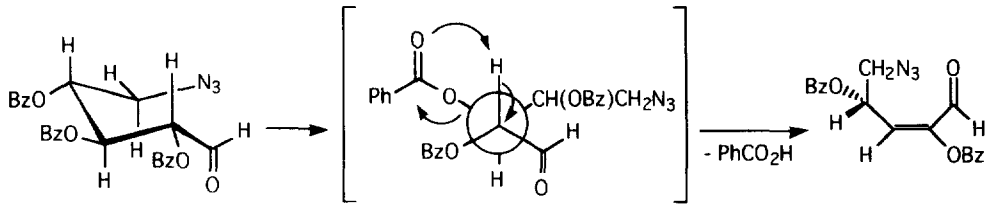
Attempted demercaptalation of **3**, using mercuric chloride and cadmium carbonate in aqueous acetone,[15] gave only low yields of the desired aldehyde, whereas treatment of **3** with mercuric oxide and boron trifluoride etherate according to the method of Vedejs,[16] consistently gave good yields (70-75%) of 5-azido-2,3,4-tri-*O*-benzoyl-5-deoxy-*aldehydo*-D-xylose (**4**) as a colorless oil. Infrared, proton NMR (9.6 ppm, singlet, 1 H, CHO), and ^{13}C NMR (190 ppm, CHO), spectra of a freshly prepared sample of **4** all indicated that the desired aldehyde had been formed; however the compound proved to be unstable upon storage. It was found that refluxing a toluene solution of **4** for 18 hours resulted in conversion into a new compound, isolated by preparative TLC on silica gel. Analysis of NMR spectra (^1H, ^{13}C, ^1H-^1H COSY)[17] proved this compound to be the α,β-unsaturated aldehyde **5** ($[\alpha]_D$ -12.6°, $CHCl_3$), the product of intramolecular syn-elimination of benzoic acid between C-2 and C-3 of **4**. The stereochemistry of the alkene moeity in **5** is considered to be (E)- as shown in scheme 3.

Scheme 2



3 **4** **5**

Scheme 3

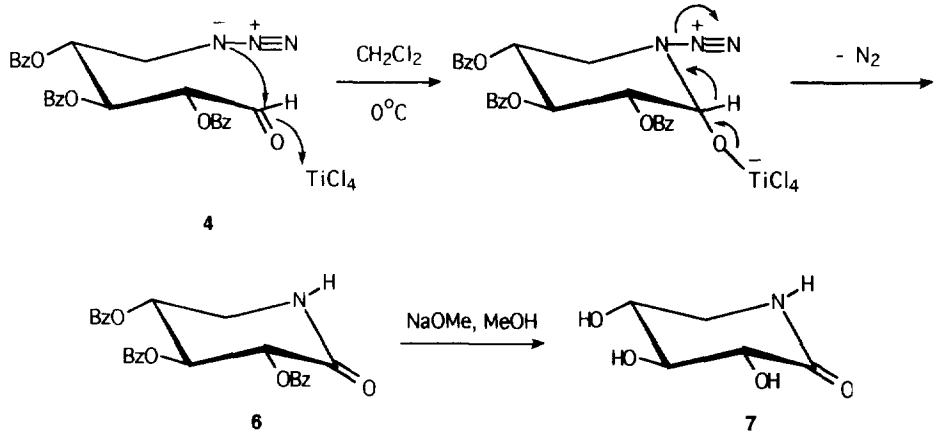


4 **5**

When similar demercaptalation of diethyl dithioacetal **3** was conducted over an extended period of time (16 h, RT), varying amounts of a new, more-polar product were formed. Chromatography afforded this product as a crystalline solid (mp 178-180°C, $[\alpha]_D$ +1.7°, $CHCl_3$) which on the basis of spectral and analytical data,[18] was identified as 2,3,4-tri-*O*-benzoyl-D-xylono-1,5-lactam (**6**), the product of an apparent acid-catalyzed intramolecular Schmidt rearrangement.[9]

To test this hypothesis, a freshly prepared sample of aldehyde **4** was subjected to conditions known to effect the intramolecular Schmidt rearrangement.[9] Thus, treatment of **4** with $TiCl_4$ in dichloromethane solution at 0°C caused an exothermic reaction and evolution of gas. Allowing the mixture to gradually warm to RT and subsequent stirring for 18 h indeed provided lactam **6** (scheme 4), isolated in 84% yield. Conventional debenzoylation (NaOMe/MeOH) afforded 1,5-dideoxy-1,5-imino-D-xylonolactam (**7**) in 80% yield as a colorless solid (mp 68-71°), produced in eight steps from D-xylose in an overall yield of 18%. A possible mechanism for the conversion of **4** into **6**, in line with that proposed by Aubé et. al.,[9] is outlined in scheme 4. These authors suggest that a four-carbon tether between the azide and carbonyl functionalities, as is present in **4**, to be favorable for ring-closure *via* Schmidt rearrangement.

Scheme 4



4 **6** **7**

This reaction of azidodeoxy-*aldehydo* sugars in the presence of Lewis acids offers a promising mode, of general synthetic utility, for the preparation of sugar lactams.

Acknowledgments: We gratefully acknowledge Jack Simpson and Wesley White of the National Institutes of Health (NIMH and NIDDK respectively) for help with mass spectra, and Dr. Herman Yeh and June Yun of the National Institutes of Health (NIDDK) for access to a 300 MHz NMR spectrometer. We are especially grateful to Professor Harold Shechter for helpful discussions on the acid-catalyzed Schmidt rearrangement.

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17. Spectral data for compound **5**: 300 MHz ^{1}H NMR δ ($CDCl_3$) 9.45 (s, 1 H), 8.11-8.02 (m, 4 H), 7.67-7.56 (m, 2 H), 7.59-7.40 (m, 4 H), 6.56 (d, 1 H, *J* 7.3 Hz, H-3), 6.08 (m, 1 H, *J* 7.3, 4.2, 4.2 Hz, H-4), 3.76 (m, 1 H, *J* 4.2, 4.2, 13.1 Hz, H-5,5'); ^{13}C NMR ($CDCl_3$) 184.9, 165.8, 164.1, 149.1, 134.2, 133.6, 131.0, 130.4, 129.2, 129.1, 69.2, 53.6; IR (neat) 3057, 2960, 2928, 2843, 2100, 1714, 1705, 1585, 1490, 1260 cm^{-1}, MS (CI, NH_3) 365, M+.
18. Spectral data for compound **6**: 300 MHz ^{1}H NMR δ ($CDCl_3$) 8.06 (m, 6 H), 7.57 (m, 3 H), 7.44 (m, 6 H), 6.24 (bs, 1 H, N-H), 6.05 (dd, 1 H, *J* 8.2, 5.7 Hz, H-3), 5.78 (d, 1 H, *J* 8.2 Hz, H-2), 5.64 (m, 1 H, *J* 5.7, 6.6, 4.3 Hz, H-4), 3.95 (m, 1 H, *J* 4.3, 12.4 Hz, H-5'), 3.67 (m, 1 H, *J* 6.6, 12.4 Hz, H-5); ^{13}C NMR ($CDCl_3$) 166.9, 165.6, 165.4, 165.2, 133.7, 133.5, 133.4, 130.1, 129.9, 129.8, 128.5, 128.4, 128.3, 71.9, 70.7, 68.9, 42.1; IR ($CHCl_3$) 3020, 1734, 1687, 1438, 1266, 1220, 1094 cm^{-1}, MS (CI, NH_3) 460, M+1.

(*Received in USA* 6 *July* 1995; *revised* 22 *August* 1995; *accepted* 23 *August* 1995)