Pyrido[2,3-*b*]pyrazines from Pyrazine C-Nucleosides: An Unusual Intramolecular Rearrangement

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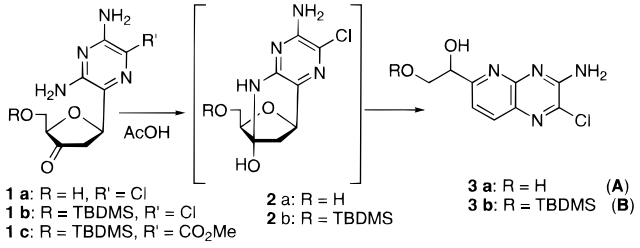
Our synthesis of pyrazine C-nucleosides has involved the use of a palladium-mediated coupling method[1] which provides 3′-keto pyrazine nucleosides as key intermediates.[2] We have found that some of these 3′-keto pyrazine nucleosides undergo an unusual rearrangement to form pyrido[2,3-*b*]pyrazine compounds. We believe that this rearrangement could be a general route to form various other heterocycles via the appropriate 3′-keto nucleosides.

The pyrazine 3′-keto nucleosides **1a**, **1b**, and **1c**[2−4] were prepared via a palladium mediated coupling between fully functionalized pyrazine iodides and a furanoid glycal. These 3′-keto nucleosides were prepared as intermediates for the synthesis of 2′-deoxypyrazine C-nucleosides. We expected to obtain a 2′-deoxypyrazine C-nucleoside by an intramolecular reduction of compound **1a** using sodium triacetoxyborohydride[5] and the free 5′-hydroxyl group. However, when acetic acid was added to facilitate the reduction, instead of the desired 2′-deoxypyrazine C-nucleoside, we obtained an unexpected compound (**A**), as established by ^{1}H-NMR spectra.[6] We subsequently found that the same product could be formed in the absence of a reducing agent. A structurally similar compound (**B**) was obtained when compound **1b** was subjected to the same conditions. Interestingly, nothing happened to the structurally related 3′-keto nucleoside **1c**, when it was subjected to the same conditions. Since compound **B** was more soluble than compound **A**, due to the protecting silyl group, it was used for our initial structural assignment studies. These studies revealed that compound **B** contains[6,7] (1) seven aromatic carbons, of which two have protons attached; (2) an exocyclic side chain with two carbons; (3) one silyl protected hydroxyl group and one unprotected hydroxyl group on the side chain; and (4) a higher UV wavelength. These data suggested that compound **B** may be a pyrido[2,3-*b*]pyrazine compound with a two-carbon side chain attached with protected and unprotected hydroxyl groups. The proposed structure of compound **B** is shown in Scheme 1 as 3-amino-2-chloro-6-[2-(*tert*-butyldimethyl)silyloxy-1-hydroxyethyl]pyrido[2,3-*b*]pyrazine (**3b**). Similar evidence implied that compound **A** was 3-amino-2-chloro-6-(1,2-dihydroxyethyl)-pyrido[2,3-*b*]pyrazine (**3a**). The only structural difference between compound **A** and compound **B** is a silyl protecting group. Elemental analysis[8] supported the proposed structural assignments for compounds **3a** and **3b**. Although these data appeared to be sufficient to support our structural assignments, we elected to conduct some mechanistic studies on this unusual rearrangement.

Scheme 1



It was obvious that the amino group at the 5-position of pyrazine was essential for the rearrangement since compound **1c**, the compound with a less basic amine due to the electron withdrawing carboxylate substituent, did not undergo a similar reaction under these same conditions. The formation of the pyrido[2,3-*b*]pyrazine ring and its side chain can best be explained by an intramolecular cyclization. The cyclization probably formed an aminal intermediate (**2**) first, then the sugar ring of **2** is opened, and the subsequent aromatization will furnish the final product (**3**). Proof of this mechanism could be established by the characterization of an intermediate. After a careful re-examination of the reaction conditions, it was determined that there might be a separable intermediate. Thus, the reaction was performed at a slower rate by adding less acetic acid. Although TLC clearly revealed the presence of a compound with an R_f between the R_f for the starting material and the R_f for the product, the use of flash chromatography to separate this compound only resulted in the isolation of the final product (**3**). This suggested that the intermediate was not stable enough to avoid a conversion to the final product under the workup conditions.

However, the conversion of the starting material to the rearranged product is a high yield reaction, and the conditions are very mild. This would suggest that ^{1}H-NMR spectroscopy might be useful in the identification of an unstable intermediate. Thus, the reaction was conducted in an NMR tube by adding 5 mg of nucleoside **1b** to 0.6 mL of $CDCl_3$ containing one drop of deuterated acetic acid (AcOH-d_4). Spectra were recorded at different time intervals in order to follow the progress of the reaction. The initial spectrum (1) revealed H-2′a and H-2′b[9] of compound **1b** as two quartets at about 2.6 and 2.8 ppm, respectively; H-4′ and H-5′ collapsed together at 4.0 ppm; H-1′ as a quartet at 5.2 ppm; solvent peak at 7.2 ppm and two small broad peaks in the vicinity of the H-1′ peak which were assumed to be the exchangeable protons of the amino group. In spectrum 2 (1 day), some additional peaks had appeared as evidenced by an obvious pseudotriplet[10] at 5.5 ppm and a quartet at 3.3 ppm. A closer examination revealed a small shoulder peak at around 3.9 ppm and a quartet (almost overlapped by the H-2′a peak of compound **1b**) at 2.6 ppm. These additional peaks were ascertained to be from a single intermediate, since they were closely correlated to each other by coupling constants[11] and integration. They also seemed to be peaks characteristic for

(1) Daves, G. D., Jr. *Carbohydrate: Synthetic Methods and Applications in Medicinal Chemistry*; Kodansha Ltd.: Tokyo, 1992; pp 49−65.
(2) Chen, J. J.; Walker, J. A., II; Liu, W.-M.; Wise, D. S.; Townsend, L. B. *Tetrahedron Lett.* **1995**, *33*, 8363−8366.
(3) Compound **1a** is 2-chloro-3,5-diamino-6-(*β*-D-*glycero*-pentofuran-3′-ulos-1′-yl)pyrazine; compound **1b** is 2-chloro-3,5-diamino-6-[*β*-D-*glycero*-pentofuran-5′-*O*-(*tert*-butyldimethylsilyl)-3′-ulos-1′-yl]pyrazine.
(4) Compound **1c** is 3,5-diamino-6-[*β*-D-*glycero*-pentofuran-5′-*O*-(*tert*-butyldimethylsilyl)-3′-ulos-1′-yl]pyrazine-2-carboxylic acid, methyl ester; though it was not reported in ref 2, it was prepared by the same method and fully characterized. For confirmation, please see supporting information for NMR spectra.
(5) Farr, R. N.; Daves, G. D., Jr. *J. Carbohydr. Chem.* **1990**, *9*, 653−660. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.
(6) Please see the supporting information for the NMR spectra of **3a** (**A**) and **3b** (**B**), or Figure 1, spectrum 5[b].
(7) UV (EtOH) (ϵ, M^{-1} cm^{-1}): compound **1b**, 203.5 nm, 3.05 × 10^4; 253.0 nm, 1.44 × 10^4; 342.5 nm, 1.57 × 10^4; compound **3b**, 206.5 nm, 4.28 × 10^4; 235.0 nm, 3.32 × 10^4; 357.0 nm, 1.84 × 10^4.
(8) Anal. for **3a** ($C_9H_9ClN_4O_2 \cdot {}^1/_2H_2O$) C, H, N; for **3b** ($C_{15}H_{23}ClN_4O_2Si$) C, H, N.
(9) The assignments were based on H-decoupling experiments and were compared to similar known compounds (e.g., refs 1 and 2).
(10) If enlarged, it was a quartet.
(11) Its coupling mode was very similar to that of other 3′-keto nucleosides.

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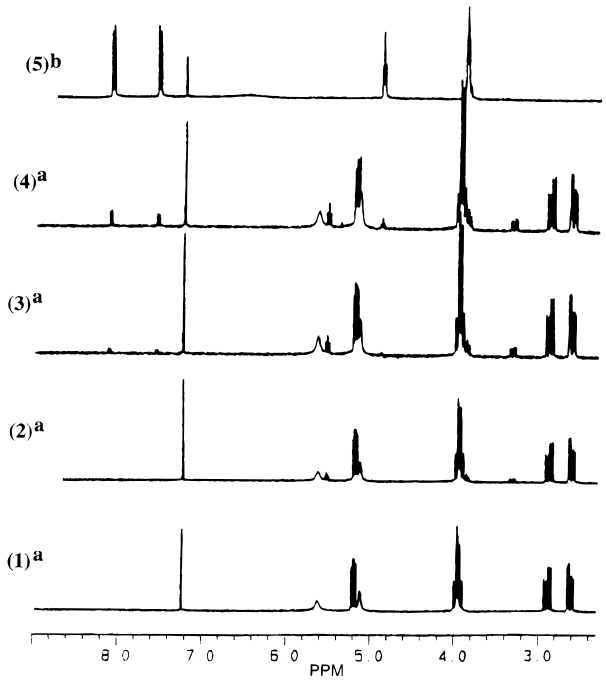

Figure 1. ^{1}H-NMR spectra were recorded with a Bruker AM 360 MHz in $CDCl_3$ (0.6 mL) with one drop of AcOH-d_4. (a) (**1**), (**2**), (**3**), and (**4**) were spectra of **1b** recorded at intervals of 0, 1, 3, 7 days; (b) (**5**) is the spectrum of **3b**.

the sugar moiety of a nucleoside. In spectrum 3 (3 days) we observed three additional peaks as two coupled aromatic peaks at around 8.0 ppm and a triplet at 4.8 ppm. It was established that these peaks were associated with the final product **3b** by a comparison to the corresponding peaks in spectrum 5. In spectrum 4 (7 days), the peaks associated with the intermediate kept increasing, while more final product **3b** was also being formed. An ^{13}C-NMR spectrum was recorded on the mixture at day 4 and provided further proof that the intermediate was a nucleoside since all of the characteristic sugar peaks[12] were present. All of the evidence for this intermediate supported the proposed structure for **2**, which has a similar structure to compound **1**.

These data provide additional information on the products that we obtained from the rearrangement and lend further support of our initial structural assignments for **3**. To the best of our knowledge, this is the first example of a pyrido[2,3-*b*]-pyrazine[13] being formed via an intramolecular aminal formation and should provide some impetus for the application of this approach to other heterocyclic ring systems and their corresponding nucleosides.

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Supporting Information Available: Synthetic procedures for the preparation of compounds **3a** and **3b** and ^{1}H-NMR and ^{13}C-NMR spectra of compounds **1c**, **3a**, and **3b** (7 pages). See any current masthead page for ordering and Internet access instructions.

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(12) ^{13}C-data for the intermediate can be obtained by subtracting known peaks of compound **1b** and **3b** from the mixture ^{13}C-spectrum; they are δ ppm 214.0, 151.5, 148.8, 125.6, 119.1, 80.7, 76.6, 64.0, 39.6 (TBDMS carbons are not listed).

(13) Lunt, E.; Newton, C. G. *Comprehensive Heterocyclic Chemistry Vol. 3*; Pergamon Press: Oxford, 1984; pp 248−262.