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# The Chemistry of 4-Azido-2-pyrimidinone Nucleosides Revisited

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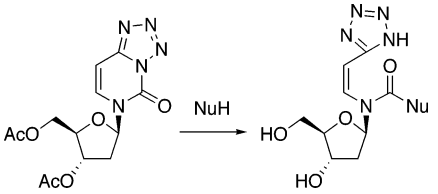
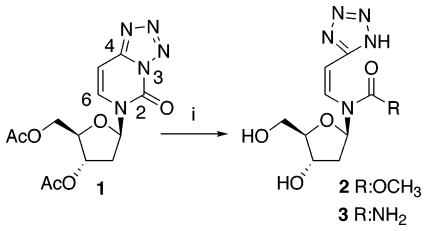



Treatment of 4-azido-2-pyrimidinone nucleoside **1** with MeOH/$K_2CO_3$ or ammonium hydroxide led to derivatives **2** and **3**, respectively. Both compounds derived from a nucleophilic addition at the modified base 2-position. These results contrast with the previously reported sensitivity of the 4-azido-2-pyrimidinone nucleoside 6-position to nucleophiles.

4-Azido-2-pyrimidinone nucleosides have been mostly developed as potential therapeutic agents.[1] They have also been proposed as prodrugs or synthetic intermediates of cytosine derivatives.[2,3] As a part of an ongoing study involving these modified nucleosides, we faced the need to investigate the reactivity of 1-(2-deoxy-3,5-diacetyl-$\beta$-D-ribofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one **1** under alkaline conditions. Our herein reported results are divergent from previously published observations.[2]

Treatment of **1** with methanol/$K_2CO_3$ (1.3 equiv) afforded the deacetylated compound **2** in 94% yield after purification (Scheme 1). Methanol addition was supported by the HR mass data of **2** (*m/z* found 308.0960 (M + Na)$^+$; calcd 308.0971).$^1$H and $^{13}$C NMR signals corresponding to the sugar residue of **2** were rapidly identified by direct comparison with those of 1-(2-deoxy-$\beta$-D-ribofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one.[1c] Resonances of the aglycon moiety consisted of two *vic*-protons at $\delta$ 6.57 (H5) and 6.28 (H6) ($J$ = 8.6 Hz) and three protons of the methoxy group (singlet at $\delta$ 3.46).[4] Carbons attached to these protons resonated at $\delta$ 117.9 (C5), 126.0 (C6), and 53.4 ($OCH_3$). Additionally, two quaternary carbons appeared at $\delta$ 157.5 (C2) and 159.2 (C4). The key NMR argument ascertaining the location of MeO addition on C2, whose chemical shift was in agreement with the value observed for methyl carbamates,[5] was its heteronuclear NMR LR-correlation with the protons of the methoxy group. Consequently, the structure depicted in Scheme 1 was attributed to **2** that results from a nucleophilic attack of the methanolate at the pyrimidinone 2-position of **1** with concomitant cleavage of the C2–N3 bond.

**SCHEME 1**[a]




[a] Key: (i) $K_2CO_3$/MeOH for **2**; $NH_4OH$ for **3**.

According to the literature, the reaction of tetrazolo-[4,5-*c*]pyrimidin-2-one derivatives with ammonium hydroxide leads to amine addition at the 6-position.[2] Treatment of **1** with $NH_4OH$ afforded **3** whose HR mass data (calcd 293.0974 (M + Na)$^+$; found 293.0969) indicated the occurrence of a deacetylation reaction and a $NH_3$ insertion. The $^1$H and $^{13}$C NMR spectrum of **3** was very similar to that of **2**.[4] Indeed, the protons of the aglycon moiety of **3** appeared as two doublets ($\delta$ 6.71 and 6.41, $J$ = 8.8 Hz), and the carbons appeared as resonances at $\delta$ 119.9, 127.6, 159.5, and 158.6 (Table 1). Because of the similarity between the $^1$H and $^{13}$C chemical shifts of **2** and **3** (the chemical shift of C2 of **3** is in total agreement with the $\delta$ value for a *N*,*N*-disubstituted urea type carbon[6]), we propose for **3** the structure depicted in Scheme 1 and believe that its formation mechanism is similar to that of **2**.

Consequently, our results are in disagreement with conclusions published some years ago by the group of Chu and Bartlett who reported, based on NMR[2] and mass data,[7] that in the presence of $NH_4OH$, 4-azido-2-pyrimidinone nucleoside **4** underwent a nucleophilic attack at its 6-position; leading to **5**, an isomer of **3** within its aglycon moiety (Scheme 2). The C6 configuration of **5** was not discussed although it was apparently described as a single diastereomer.

Interestingly, the $^{13}$C NMR data reported for the aglycon moiety of **5** were closely similar to those of **2** and **3**. The only discrepancy was the presence of a resonance

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(4) NMR assignments were made by 2D H–H, H–C, and LR H–C spectra. Particularly, C2 and C6 were assigned from their $^3J$ coupling with H1′.

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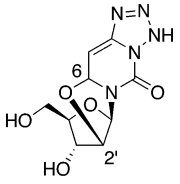
**TABLE 1. $^{13}$C NMR Chemical Shifts ($\delta$, ppm) for Compounds 2, 3, 5,[2] and 6[2]**

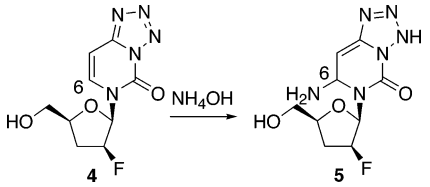


**6**

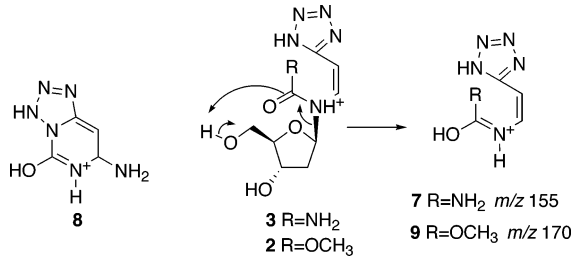
| | **2** | **3** | **5**[2] | **6**[2] |
|---|---|---|---|---|
| C2 | 157.5 | 159.5 | 157.6 | 156.5 |
| C4 | 159.2 | 158.6 | 135.4 | 155.0 |
| C5 | 117.9 | 119.9 | 113.2 | 83.6 |
| C6 | 126.0 | 127.6 | 126.6 | 86.5 |
| C1′ | 88.3 | 87.2* | 87.1 | 119.4 |
| C2′ | 38.0 | 38.2 | 92.6 | 105.2 |
| C3′ | 72.2 | 72.2 | 33.8 | 74.5 |
| C4′ | 87.0 | 86.7* | 75.6 | 86.6 |
| C5′ | 63.7 | 63.5 | 63.3 | 60.7 |

*Interchangeable assignments.

**SCHEME 2**[2,7]



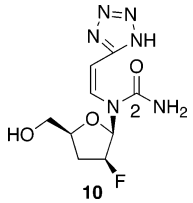
**SCHEME 3**



at $\delta$ 135.4 (assigned to C4) for **5** and not observed for **2** or **3** (C4 appeared at $\delta$ ca. 159 in **2** and **3**) (Table 1). This similarity prompted us to carefully examine the structural analysis proposed for **5**. Such examination indicated that assignment of the resonance at $\delta$ 126.6 to the C6 atom of **5** was particularly doubtful specially considering that, in the same study, the corresponding atom in the 6−2′ anhydro derivative **6** (Table 1) was reported to resonate at $\delta$ 86.5.[2,8]

Study of the mass fragmentation of the base portion of **5** has also been reported to sustain its structure[7] and ion **8** (*m/z* 155) has been proposed as a structural proof. The mass spectrum of **3** displayed also an ion peak at *m/z* 155 (**7**) that was easily explained according to the fragmentation mechanism depicted Scheme 3. Applied to **2**, this mechanism also explained the ion peak observed at *m/z* 170 (**9**) in its mass spectrum.

Therefore, we propose that, as for **2** and **3**, compound **4** is able to undergo a nucleophilic addition at its 2-position and consequently that the most likely structure for the adduct resulting from the treatment of **4** with $NH_4OH$ is **10**.



**10**

Interestingly, it has been reported that in the closely related tetrazolo[1,5-c]pyrimidines/4-azidopyrimidine series the 2-position is susceptible to water addition,[9] leading to ring opening.[10] Our observations are highly consistent with these data, as is the slow cyclization of **2** in neutral conditions giving rise to 1-(2-deoxy-$\beta$-D-ribofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one.[10]

## Experimental Section

**Preparation of Compound 2.** 1-(2-Deoxy-3,5-diacetyl-$\beta$-D-ribofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one **1**[1c] (50 mg, 0.15 mmol) was dissolved in anhydrous methanol (5 mL). Potassium carbonate (30 mg, 0.2 mmol) was added, and the reaction was stirred at room temperature for 45 min. The solvent was then evaporated, and the crude product was purified by silica gel column chromatography (40% MeOH/$CH_2Cl_2$) to yield **2** (40 mg, 94%) as a white solid: $^1$H NMR (400 MHz, $CD_3OD$ + $K_2CO_3$) $\delta$ 6.57 (1H, d, $J$ = 8.6 Hz, H5), 6.28 (1H, d, $J$ = 8.6 Hz, H6), 6.14 (1H, t, $J$ = 6.7 Hz, H1′), 4.18 (1H, dt, $J$ = 6.7; 4.3 Hz, H3′), 3.73 (1H, m, H4′), 3.63 (1H, m, H5′$^a$), 3.50 (1H, m, H5″$^a$), 3,46 (*, s, $OCH_3$), 2.28 (1H, dt, $J$ = 13.7; 6.7 Hz, H2′$^b$), 2.05 (1H, ddd, $J$ = 13.7; 6.7; 4.3 Hz, H2″$^b$); $^{13}$C NMR (75 MHz, $CD_3OD$ + $K_2CO_3$) $\delta$ 159.2 (C4), 157.5 (C2), 126.0 (C6), 117.9 (C5), 88.3 (C1′), 87.0 (C4′), 72.2 (C3′), 63.7 (C5′), 53.4 ($OCH_3$), 38.0 (C2′); HR MS (ESI, MeOH + $H_2O$) $(M + Na)^+$ calcd for $C_{10}H_{15}N_5O_5Na$ 308.0971, found 308.0960. *Partially exchanged with $CD_3OD$.

**Preparation of Compound 3.** 1-(2-Deoxy-3,5-diacetyl-$\beta$-D-ribofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one **1**[1c] (50 mg, 0.15 mmol) was dissolved in concentrated aqueous $NH_4OH$ (5 mL), and the reaction was stirred at room temperature for 24 h. After filtration, the solvent was evaporated, and the crude product was purified by silica gel column chromatography (40% MeOH/$CH_2Cl_2$) to yield **3** (39 mg, 96%): $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 6.71 (1H, d, $J$ = 8.8 Hz, H5), 6.41 (1H, d, $J$ = 8.8 Hz, H6), 6.26 (1H, t, $J$ = 7.3 Hz, H1′), 4.19 (1H, td, $J$ = 3.7; 6.6 Hz, H3′), 3.71 (1H, m, H4′), 3.67−3.53 (2H, m, H5′, H5″), 2.17 (1H, m, H2′$^a$), 2.01 (1H, m, H2″$^a$); $^{13}$C NMR (62.5 MHz, $CD_3OD$) $\delta$ 159.5 (C2), 158.6 (C4), 127.6 (C6), 119.9 (C5), 87.2/86.7 (C1′, C4′), 72.2 (C3′), 63.5 (C5′), 38.2 (C2′); HR MS (ESI, MeOH) $(M + Na)^+$ calcd for $C_9H_{14}N_6O_4Na$ 293.0974, found 293,0969. $^{a,b}$Interchangeable assignments within a compound.

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**Supporting Information Available:** NMR Mass spectra of compound **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The $^{13}$C NMR assignments reported for this compound seem also questionable, particularly, C1′ at $\delta$ 119.4 but we did not attempt to elucidate this point.

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