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Synthesis and Photochemical Behavior of the Tetrazolo Tautomer of 2-Azido-4-pyrimidinone-2′-deoxyriboside

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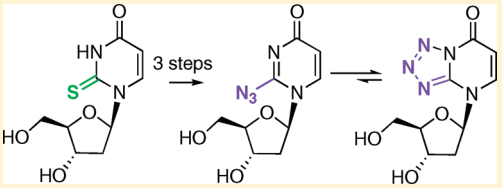
Supporting Information

ABSTRACT: The 2-azido analogue of 2′-deoxyuridine was prepared in three steps from 2′-deoxy-2-thiouridine. The sulfur atom of the 2-thio nucleoside was methylated and then displaced by hydrazine to furnish the corresponding 2-hydrazino derivative. After diazotization, the 2-azido compound that exists as its tetrazolo tautomer was obtained. Upon UV irradiation in aqueous solution, the title compound led to isocytosine.



Azidopyrimidine nucleosides are synthetic molecules endowed with diverse and highly valuable (photo)chemical and pharmacological properties. The azido group can substitute the C2-, C4-, C5-, or C6-position of the pyrimidine moiety. 4-Azidopyrimidine nucleosides are more stable under their tetrazolo tautomer form. They have been mostly developed as potential therapeutic agents[1,2] but are also useful as synthetic intermediates.[3] They are also able to give rise to ring-expanded or -contracted derivatives upon UV excitation.[4] 5-Azidonucleosides are widely used in photo-cross-linking experiments.[5] In addition, their use in the preparation of fluorescent probes by click chemistry has recently been reported.[6] 6-Azidonucleosides initially prepared to be photochemical tools[7] are employed as synthetic intermediates.[8,9] Surprisingly, the synthesis of 2-azidonucleosides has never been reported, even though the synthesis of 2-azido-4-pyrimidinones is known.[10]

We herein report the first synthesis of **1**, the 2-azido analogue of 2′-deoxyuridine, and its preliminary photochemical study.

We initially attempted to adapt our recently reported synthesis of 5-azido-2′-deoxyuridine[11] and to prepare **1** by diazotization of 2′-deoxyisocytidine and then azide treatment using mild conditions. Being unsuccessful, we devised another strategy in which the azido group would be formed by diazotization of a 2-hydrazino compound prepared by hydrazinolysis of a 2-thio derivative as reported in the 2-azidopyrimidine aglycon series.[10b−10d] Accordingly, we would need 2′-deoxy-2-thiouridine **2**. Compound **2** can be prepared by Lewis acid catalyzed condensation of 2,4-bis(trimethylsilyl)-2-thiouracil with 1-chloro-2-deoxy-di-*O*-*p*-toluyl-α-D-ribofuranose.[12] However, this method suffers from several drawbacks: (1) the acute sensitivity of the reaction to the experimental conditions, (2) the need to prepare the α-chlorosugar, and (3) the variable yield of the *p*-toluyl deprotection. Another method to prepare **2** involves the sulfhydrolysis of 2′-deoxy-2-*O*-methyluridine.[13] Although this method has been reported to be lengthy and inefficient,[12b] the recently reported successful synthesis of other 2-thionucleosides using H_2S treatment of 2-*O*-ethyl precursors[14] prompted us to evaluate it to synthesize **2** (Scheme 1). 2′-Deoxy-2-*O*-ethyluridine **4** was obtained in 69% yield by refluxing 5′-*O*-tosyl-2′-deoxyuridine **3**[15] in anhydrous ethanol in the presence of 2.9 equiv of anhydrous $NaHCO_3$ under nitrogen atmosphere. Derivative **4** was then heated with saturated H_2S in anhydrous pyridine at 70 °C for 7 days to afford **2** in 74% yield after purification.

Treatment of **2** with K_2CO_3 (1 equiv) and CH_3I (2.4 equiv) in anhydrous acetone and under inert atmosphere regioselectively and quantitatively led to the activated *S*-methyl derivative **6** (Scheme 2) whose instability precluded its purification by chromatography.

As a consequence, the reaction mixture was filtrated, and the concentrated filtrate was immediately reacted with 4.4 equiv of hydrazine monohydrate in acetonitrile at −10 °C for 9 h. This protocol quantitatively afforded the hydrazino derivative **5** as inferred from the examination of the ^{1}H NMR spectrum of the crude reaction mixture. Low temperature and hydrazine monohydrate stoichiometry were crucial to avoid the formation of side products including pyrazol-3-one resulting from hydrazine attack at position C6.[16] After removal of the solvent and excess of hydrazine under vacuum, compound **5** was directly used in the next step without purification. Reaction of **5** with 2.9 equiv of $NaNO_2$ in 10% aqueous acetic acid at 0 °C for 15 min afforded the azido derivative **1** that was isolated in 40% overall yield from **2** (three steps) after chromatography (Scheme 2).

Compound **1** may exist as its azide and/or tetrazolo form,[10a,10e,17] **1a** and/or **1b**, respectively. The ^{1}H NMR spectrum of **1** recorded in D_2O displayed one single set of signals. Since the rate of the azidoazomethine−tetrazole tautomerism is sufficiently slow to afford two distinct species observable by ^{1}H NMR,[10a,10e,17] in

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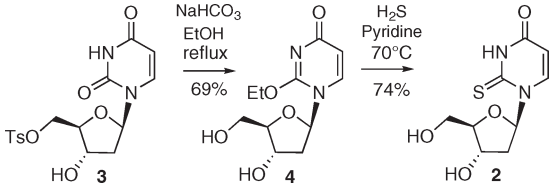
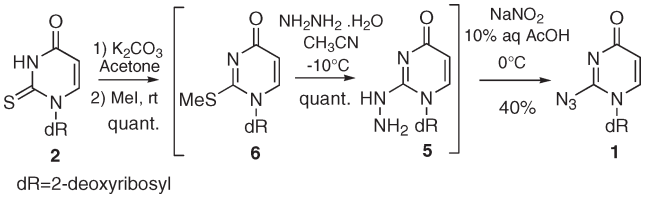
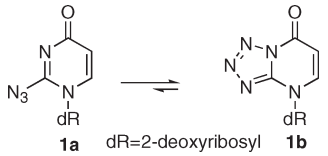
Scheme 1



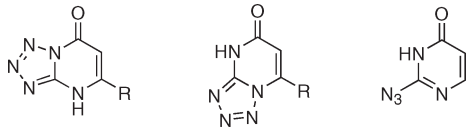
Scheme 2



aqueous solution only one tautomer of **1** is present. The absence of a strong azido absorption band in the IR spectrum of **1** suggested that **1** is in the tetrazolo (**1b**) form as observed in 4-azidonucleosides.[1−3]



Compound **1** is relatively unstable in aqueous solution. After one month at 5 °C or 2 days at room temperature, it gives rise to 7_{maj} and 7_{min} in a ratio of approximately 7:3. Concomitant release of 2-deoxyribose was observed by ^{1}H NMR. Analytical samples of 7_{maj} and 7_{min} were obtained by reversed-phase HPLC. The ^{1}H NMR spectrum of each product consisted of two doublets at δ 8.61 and 6.39, J = 7.5 Hz and δ 8.18 and 6.15; J = 7.0 Hz for 7_{min} and 7_{maj}, respectively, confirming the absence of a deoxyribose moiety. The electrospray mass spectrum of each compound displayed an ion peak at m/z 182 (M + 2Na − H), indicating that 7_{maj} and 7_{min} are either one of the two tetrazolo forms **7a**,**b** or the azido tautomer **7c**. Absence of a strong azide band absorption in the IR spectrum of 7_{maj} and 7_{min} indicated that they correspond to the tetrazolo tautomers **7a** and **7b**. The similarity of the carbon chemical shifts of C4 and C5 of 7_{maj} and **1** (δ C4 157.3; C5 99.4 for 7_{maj} and δ C4 157.3 C5 102.2 for **1**) (for comparison, δ C4 163.8; C5 111.5 for 7_{min}) allows assignment of the tetrazole structure tetrazolo[5,1-*b*]pyrimidin-4(1*H*)-one **7a** for 7_{maj} and hence **7b** for 7_{min}.



Interestingly, **8**, the 6-methyl analogue of **7**, is a known product.[10a] It exists as the two tetrazolo isomers **8a** and **8b** in DMSO solution. The major difference between the ^{1}H NMR spectrum of these two tautomers is the deshielding of H5 in **8b** compared to the one of **8a** (δ 6.28 versus 5.92, respectively). A similar behavior is observed between H5 of **7b** and **7a** (δ 6.39 versus 6.15, respectively), additionally supporting the assigned tautomer structures.

Previously known azidopyrimidine nucleosides give rise to intramolecular nitrene insertion products upon photoexcitation.[4,7b,18] This prompted us to study the photochemical behavior of **1**. Unexpectedly, preliminary studies (λ>290 nm) performed in aqueous solution indicated that **1** is only slightly photoreactive. The only photoproduct detected in the crude irradiation mixture is isocytosine. Some amount of degradation product **7** was also present. A control experiment performed in the dark indicated that the formation of **7** is not accelerated by UV exposure. Therefore, isocytosine is likely produced from the photoreduction of **7**,[19] the latter being thermally produced during UV exposure.

In conclusion, the tetrazolo tautomer of 1-(2-deoxy-β-D-ribofuranosyl)-2-azidopyrimidin-4-one was prepared in three steps with a 40% overall yield after purification starting from 2′-deoxy-2-thiouridine. Despite its relative instability, introduction of the azido group at the 2-position of pyrimidine nucleosides could open perspectives in the development of new nucleosides based on the versatility of the azide chemistry.[20,21]

EXPERIMENTAL SECTION

General Procedures. Acetone, acetonitrile and pyridine were dried by heating, under reflux, with CaH_2. Dry methanol and ethanol were obtained by distillation from sodium methoxide and sodium ethoxide, respectively. 5′-*O*-Tosyl-2′-deoxyuridine and $NaHCO_3$ were dried by standing under vacuum in a desiccator containing P_2O_5. ^{1}H chemical shifts are reported in ppm relative to residual undeuterated solvent (D_2O, δ_H = 4.80; methanol-d_4, δ_H = 3.30). ^{13}C chemical shifts are reported in ppm in D_2O relative to an external capillary standard of dioxane (δ_C = 67.8) or in methanol-d_4 (δ_C = 49.0).

2′-Deoxy-2-*O*-ethyluridine (4). A mixture of dry 5′-*O*-tosyl-2′-deoxyuridine[15] (2.03 g, 5.31 mmol) and dry $NaHCO_3$ (1.3 g, 15.59 mmol) was refluxed in anhydrous ethanol (112 mL) under nitrogen for 2 days. After being cooled to room temperature, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of methanol (5 to 10%) in dichloromethane to give **4** as a white powder (944 mg, 69% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 8.19 (d, J = 7.7 Hz, 1H), 6.22 (t, J = 6.4 Hz, 1H), 6.01 (d, J = 7.7 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 4.38 (ddd, J = 3.3; 3.8; 6.4 Hz, 1H), 3.97 (td, J = 3.3; 3.7 Hz, 1H), 3.80 (dd, J = 3.3, 12.1 Hz, 1H), 3.72 (dd, J = 3.7, 12.1 Hz, 1H), 2.39 (ddd, J = 3.8, 6.4, 13.6 Hz, 1H), 2.24 (td, J = 6.4; 13.6 Hz, 1H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.2, 157.2, 140.9, 107.9, 89.6, 88.5, 71.8, 66.6, 62.5, 42.2, 14.3; HRMS (ESI) m/z calcd for $C_{11}H_{16}N_2O_5Na$ $[M + Na]^+$ 279.0957, found 279.0963.

2′-Deoxy-2-thiouridine (2). Compound **4** (944 mg, 3.69 mmol) was solubilized in H_2S-saturated anhydrous pyridine (70 mL) at 0 °C, and the solution was transferred into a steel bomb that was sealed and heated at 70 °C for 7 days. Compressed air was bubbled through the reaction, and then pyridine was evaporated and coevaporated under reduced pressure with ethanol and toluene. The residue was purified by flash silica gel column chromatography using 5% of methanol in dichloromethane. Appropriate fractions were concentrated to dryness to afford **2** as a white powder (663 mg, 74% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 8.21 (d, J = 8.1 Hz, 1H), 6.90 (t, J = 6.3 Hz, 1H), 5.94 (d, J = 8.1 Hz, 1H), 4.36 (ddd, J = 3.7, 4.0, 6.3 Hz, 1H), 3.96 (ddd, J = 3.0, 3.4, 3.7 Hz, 1H), 3.83 (dd, J = 3.0, 12.1 Hz, 1H), 3.75 (dd, J = 3.4, 12.1 Hz, 1H), 2.50 (ddd, J = 4.0, 6.3, 13.7 Hz, 1H), 2.12 (td, J = 6.3, 13.7 Hz, 1H);

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^{13}C NMR (75 MHz, CD_3OD) δ 177.2, 162.7, 142.6, 106.8, 91.2, 89.4, 71.6, 62.3, 41.7; MS (ESI) m/z 267, $[M + Na]^+$.

2′-Deoxy-2-*S*-methylthiouridine (6). 2′-Deoxy-2-thiouridine **2** (60 mg, 0.25 mmol) and K_2CO_3 (32 mg, 0.25 mmol) were suspended in anhydrous acetone (1.3 mL). The suspension was stirred under nitrogen at room temperature for 20 min. Then CH_3I (38 μL, 0.369 mmol) was added, and the suspension was stirred at rt for 3 h. The reaction mixture was filtered and the precipitate washed with anhydrous acetone (5 mL). The filtrate and acetone wash were combined and evaporated under reduced pressure to quantitatively afford **6** as an oil. Compound **6** was used for the next step without purification: ^{1}H NMR (300 MHz, D_2O) δ 8.12 (d, J = 7.7 Hz, 1H), 6.34 (t, J = 6.3 Hz, 1H), 6.25 (d, J = 7.7 Hz, 1H), 4.48 (td, J = 4.3, 6.5 Hz, 1H), 4.10 (dt, J = 3.4, 4.3 Hz, 1H), 3.87 (dd, J = 3.4, 12.6 Hz, 1H), 3.78 (dd, J = 4.3, 12.6 Hz, 1H), 2.59 (s, 3H), 2.56 (ddd, J = 4.3, 6.3, 14.2 Hz, 1H), 2.39 (ddd, J = 6.3, 6.5, 14.2 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 171.7, 165.0, 141.1, 108.2, 88.6, 87.3, 70.1, 60.8, 39.7, 14.3; HRMS (ESI) m/z calcd for $C_{10}H_{14}N_2O_4SK$ $[M + K]^+$ 297.0311, found 297.0310.

1-(2-Deoxy-β-D-ribofuranosyl)-2-hydrazinopyrimidin-4-one (5). To a solution of **6** (100 mg, 0.39 mmol) in anhydrous acetonitrile (3.9 mL) cooled at −10 °C was added hydrazine monohydrate (84 μL, 1.73 mmol). The solution was stirred at −10 °C for 9 h. The reaction mixture was then concentrated under reduced pressure to give **5** in nearly quantitative yield. Crude **5** was used for the next step without purification: ^{1}H NMR (300 MHz, D_2O) δ 7.75 (d, J = 7.7 Hz, 1H), 5.97 (t, J = 6.7 Hz, 1H), 5.87 (d, J = 7.7 Hz, 1H), 4.50 (td, J = 4.1, 6.7 Hz, 1H), 4.07 (dt, J = 3.2, 4.1 Hz, 1H), 3.86 (dd, J = 3.2, 12.5 Hz, 1H), 3.78 (dd, J = 4.1, 12.5 Hz, 1H), 2.53 (td, J = 6.7, 14.1 Hz, 1H), 2.41 (ddd, J = 4.1, 6.6, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, D_2O)[22] δ 173.1, 154.6, 141.4, 103.6, 88.5, 86.8, 70.0, 60.6, 37.8; HRMS (ESI) m/z calcd for $C_9H_{14}N_4O_4K$ $[M + K]^+$ 281.0652, found 281.0651.

1-(2-Deoxy-β-D-ribofuranosyl)tetrazolo[5,1-*b*]pyrimidin-4-one (1b). $NaNO_2$ (75 mg, 1.09 mmol) was added to a stirred solution of crude **5** (ca. 0.39 mmol) in 10% aqueous acetic acid (10 mL) at 0 °C and in the dark. After 15 min, the reaction mixture was concentrated and coevaporated with toluene under reduced pressure at room temperature. The residue was purified by flash chromatography using 4% of methanol in dichloromethane. Appropriate fractions were collected and concentrated to dryness under vacuum without heating to yield **1b** as a white powder (40 mg, 40% from **2**, three steps): UV (H_2O) λ_{max} = 283 nm; IR (film, cm^{-1}): 1713, 1660, 1556; ^{1}H NMR (500 MHz, D_2O) δ 8.41 (d, J = 8.0 Hz, 1H), 6.50 (t, J = 6.3 Hz, 1H), 6.29 (d, J = 8.0 Hz, 1H), 4.58 (ddd, J = 4.0; 4.8; 6.3 Hz, 1H), 4.17 (ddd, J = 3.3, 4.0, 4.9 Hz, 1H), 3.89 (dd, J = 3.3, 12.6 Hz, 1H), 3.81 (dd, J = 4.9, 12.6 Hz, 1H), 2.69 (td, J = 6.3, 14.3 Hz, 1H), 2.62 (ddd, J = 4.8, 6.3, 14.3 Hz, 1H); ^{13}C NMR (125.7 MHz, D_2O) δ 157.3, 151.5, 143.4, 102.2, 91.8, 88.9, 71.3, 62.2, 40.1; HRMS (ESI) m/z calcd for $C_9H_{12}N_5O_4$ $[M + H]^+$ 254.0889, found 254.0886.

Analytical Purification of 7_{maj} and 7_{min}. A D_2O solution of **1** was allowed to sit for 1 month at 5 °C. The mixture was purified on an Atlantis T3 (5 μm, 4.6 × 250 mm) column using 0.05 M aqueous ammonium acetate as eluent for 10 min followed by a gradient of acetonitrile (0−1% in 5 min) and then an isocratic at 1% for 5 min at a flow rate of 1 mL/min. A photodiode array and an ELS detectors were used. Compound 7_{min} eluted at 12 min and compound 7_{maj} at 20 min.

Tetrazolo[5,1-*b*]pyrimidin-4(1*H*)-one 7_{maj}: UV (H_2O) λ_{max} = 293 nm; IR (film, cm^{-1}) 1645, 1505; ^{1}H NMR (300 MHz, D_2O) δ 8.18 (d, J = 7.0 Hz, 1H), 6.15 (d, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, D_2O)[22] δ 157.3, 151.6, 145.9, 99.4; MS (ESI) m/z 182 $[M + 2Na - H]^+$.

Tetrazolo[1,5-*a*]pyrimidin-4(3*H*)-one 7_{min}: UV (H_2O) λ_{max} = 279 nm; IR (film, cm^{-1}) 1640; ^{1}H NMR (300 MHz, D_2O) δ 8.61 (d, J = 7.5 Hz, 1H), 6.39 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, D_2O)[22] δ 163.8, 150.7, 134.3, 111.5; MS (ESI) m/z 182 $[M + 2Na - H]^+$.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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