Tetrahedron Letters 53 (2012) 2316–2318

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Photochemistry of 6-azidopurine ribonucleoside in aqueous solution

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ARTICLE INFO

Article history:
Received 28 November 2011
Revised 12 February 2012
Accepted 23 February 2012
Available online 3 March 2012

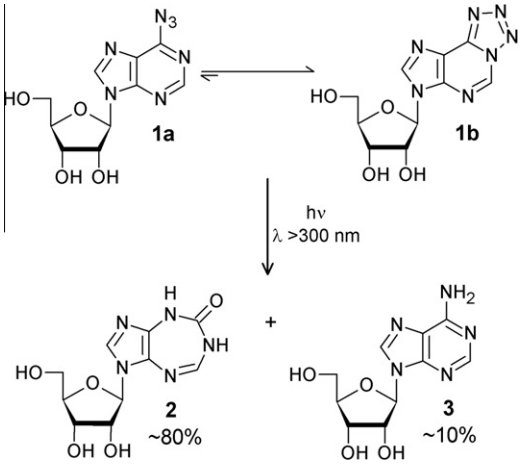
Keywords:
6-Azidopurine
Photochemistry
Ring expansion
1,3,5-Triazepinone nucleoside

ABSTRACT

In aqueous solution, 6-azido-9-β-D-ribofuranosylpurine undergoes an efficient photoinduced purine ring expansion to give a novel imidazole-fused 1,3,5-triazepinone nucleoside and partial conversion into adenosine. The structure of the major product was established as 1-(β-D-ribofuranosyl)-4,6-dihydroimidazo[4,5-*f*][1,3,5]triazepin-5(1*H*)-one based on HRMS and NMR spectral data.

Azido derivatives of nucleobases have long been used as photoaffinity labeling agents in the studies of nucleic acid–protein interactions via a photocross-linking technique.[1,2] So far, among purine derivatives, 8-azidoadenosine has been the most frequently utilized analogue, whereas the other azidopurines (8-azidoguanosine, 2-azidoadenosine and 2,6-diazidopurine) have been used to a much lesser extent.[1–3] Nearly 30 years ago, 6-azidopurine ribonucleoside was proposed as a photoaffinity probe for ribosomal peptidyltransferase.[4] It has been shown that the 6-azidopurine moiety is readily photolyzed by UV irradiation, however, to date, no reports concerning the structure of the photoproducts formed, are available.[4] Apart from their use as photoaffinity reagents, azidonucleosides, as with other aryl azides, are also good candidates for creating ring-expanded, unsaturated azepine products via nitrogen insertion.[5] Indeed, an efficient photochemical ring expansion of 4-azidouracil nucleosides to 1,3,5-triazepine-2,4-dione nucleosides has been reported.[6] In the above context, the photochemistry of 6-azidopurine nucleoside appeared worthy of more detailed investigation. Herein, we demonstrate that in aqueous solution, compound **1** undergoes efficient photochemical purine ring expansion leading to the novel imidazole-fused 1,3,5-triazepinone nucleoside **2** (Scheme 1).

The synthesis of 6-azidopurine nucleoside **1** was carried out according to a reported procedure.[7] As indicated in Scheme 1, 6-azidopurine nucleoside can exist in an azide-tetrazole equilibrium, and in aqueous solution this equilibrium is shifted almost entirely to the tetrazolyl isomer.[8] Thus, an aqueous solution of **1a**,**b**



Scheme 1. Azide-tetrazole tautomeric equilibrium of 6-azidopurine, **1a**, in aqueous solution and structures of photoproducts of its irradiation with near UV light under aerobic conditions.

(5×10^{-4} M) was irradiated under aerobic conditions in a 0.2 cm UV cell with a high pressure mercury lamp (HBO 200) equipped with a 313 nm interference filter. The progress of the reaction was monitored by the disappearance of the absorption band in the UV spectra of **1a**,**b** (λ_{max} ~290 nm, Fig. 1) and by HPLC. The formation of two photoproducts, **2** and **3**, was observed by HPLC (Fig. 2) with ca. 50% conversion of **1**.

The minor photoproduct **3** was identified as adenosine by comparison (HPLC, MS, UV) with an authentic sample. The molecular

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http://dx.doi.org/10.1016/j.tetlet.2012.02.103

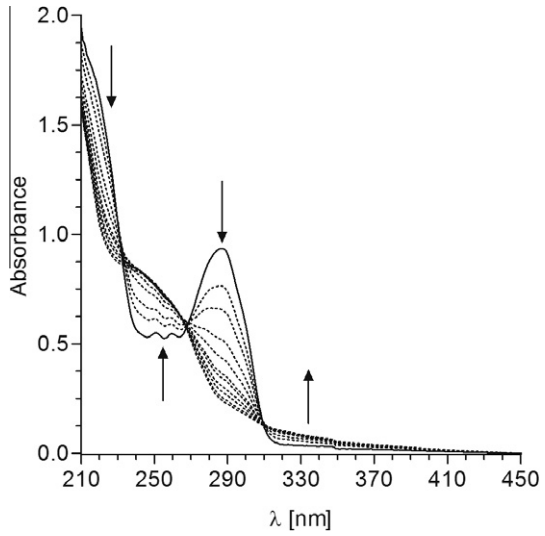


Figure 1. Changes in the absorption spectrum of an aqueous solution of **1** during irradiation at λ >300 nm. The spectra were taken at 15 min increments.

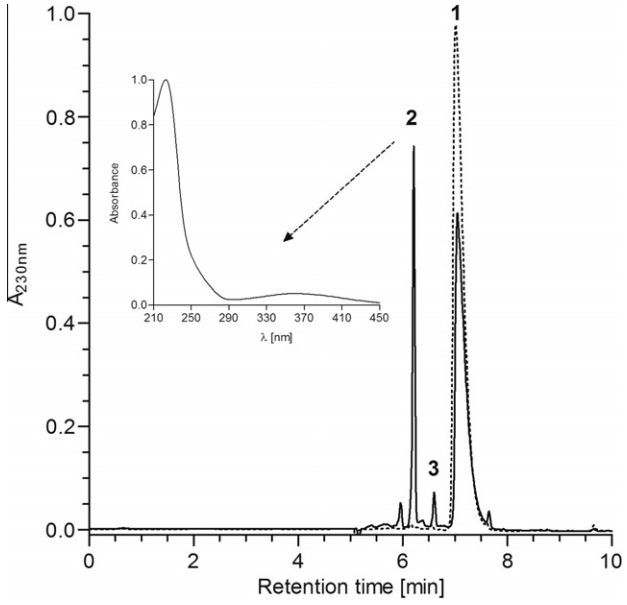
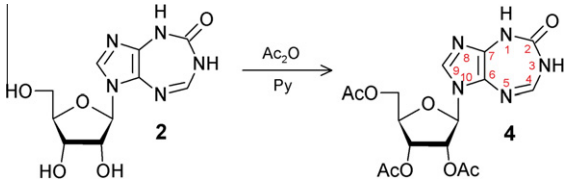


Figure 2. HPLC analysis of an aqueous solution of **1** before (dotted line) and after 30 min irradiation (solid line). The column was a Waters XBridge™ OST C18 2.5 μm 4.6 × 50 mm, eluted with acetonitrile/water using a linear gradient of 18–50% of acetonitrile over 15 min at a flow rate of 1.0 mL/min. The inset shows the UV absorption spectrum of the major photoproduct **2**.

formula of the major photoproduct **2**, $C_{10}H_{13}N_5O_5$, determined by HR-LSIMS, indicated that its formation involved the loss of an N_2 molecule and addition of H_2O. Furthermore, the characteristic UV spectrum of this photoproduct (Fig. 2, inset) exhibiting a low intensity, broad absorption band centered at 358 nm indicated that a major structural change occurred within the chromophore unit of **1** upon irradiation. These observations suggested the possible formation of a purine ring expanded triazepine product **2** (Scheme 1) via the generally accepted mechanism involving formation of an intermediate nitrene, followed by its rearrangement into the seven-membered ring carbodiimide and addition of a water molecule.[5,6]

To isolate and fully characterize the photoproduct **2** by NMR spectroscopy, preparative scale irradiation of **1** was performed in



Scheme 2. Synthesis of 2′,3′,5′-tri-O-acetylated nucleoside **4** and numbering of multiple ring system.

a 200 mL photoreactor with an immersed high pressure mercury lamp equipped with a cut-off Pyrex filter (λ >300 nm). The photoproduct was isolated from the reaction mixture by semi-preparative reversed-phase HPLC and subjected to acetylation with acetic anhydride in anhydrous pyridine to give 2′,3′,5′-tri-O-acetylated nucleoside **4** (Scheme 2).

The proposed structure of **4** was confirmed from HRMS and NMR spectral data.[9] Its high-resolution mass spectrum revealed a molecular mass of 409.12335, which corresponded to the formula $C_{16}H_{19}N_5O_8$. Both the ^{1}H and ^{13}C NMR spectra showed typical signal patterns corresponding to the intact ribose part of the molecule, which confirmed that the transformations occurred on the aglycone. In the aromatic region of the ^{13}C NMR spectrum of **4** there were five signals, two due to the methine carbons and three from quaternary carbons (at 137.56, 131.23 ppm and 154.40, 128.40, 121.62 ppm, respectively). In the ^{1}H MNR spectrum, apart from the resonances due to the ribose unit, two C–H and two exchangeable N–H signals were detected, at 7.27, 6.31 ppm, and 7.84, 6.76 ppm. The position of the latter two N–H signals shifted considerably with temperature (up to 1 ppm over a range of 50 °C). The chemical shift of the carbon signal at 154.4 ppm suggests that it was due to a urea C2 carbonyl. All the remaining carbon signals appeared within the range expected for the postulated structure, but it was impossible to assign them on the basis of their chemical shift alone. Several two-dimensional multiple resonance experiments were performed (Fig. 3) and revealed correlations of atoms corresponding to the following signals: ^{1}H TOCSY revealed the signals H(7.84), H(6.76) and H(6.31) (two N–H and one C–H) as a one spin system, omitting the H(7.27) signal.

Heteronuclear carbon–proton correlation revealed one-bond contacts between signals C(131.23) and H(7.27) as well as C(137.56) and H(6.31). HMBC was detected between the following signals: proton signal H(7.27) correlates with carbon signals C(128.40), C(121.62) and C(86.54) (anomeric carbon atom); the proton signal H(7.84) correlates with C(121.62); the anomeric

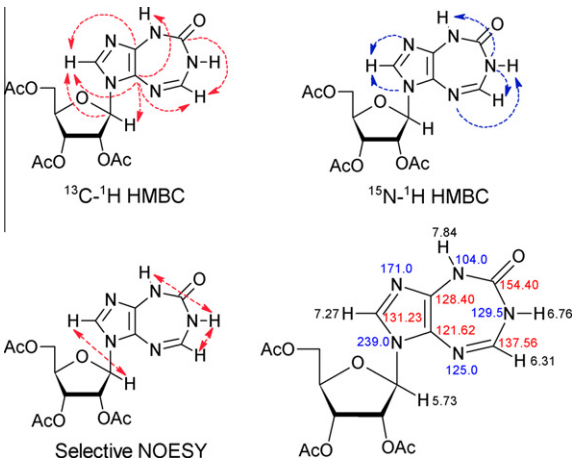


Figure 3. HMBC, NOEs and signal assignments for photoproduct **4**.

proton H(5.73) shows correlation with C(131.23) and C(121.62); proton H(6.31) correlates with carbon signals C(121.62) and C(154.40). Heteronuclear nitrogen–proton correlations not only provided clues as to the inter-atom relations, but also allowed detection of the ^{15}N resonance positions, that were too weak to be detected directly. Five nitrogen signals appeared at 104, 125, 129.5, 171, and 239 ppm (relative to NH_3 gas as a reference). One bond (N–H) correlations were detected between N(104)–H(7.84) and N(129.5)–H(6.76). Multiple bond correlations were present between H(7.84) with N(129.5); H(6.76) with N(125); H(7.27) with both N(171) and N(239), and H(6.31) with N(129.5). The final set of correlations was provided by selective NOESY which showed contacts between H(7.84)–H(6.76); H(6.76)–H(6.31), and H(5.73, anomeric)–H(7.27). All the above data agree very well with the structure of the nucleoside **2** having the aglycone which contains fused imidazole and 1,3,5-triazepin-2-one rings.

In conclusion, the photochemistry of 6-azidopurine nucleosides provides opportunities for the synthesis of potentially valuable imidazole-fused 1,3,5-triazepinone nucleosides.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.103. These data include MOL files and InChiKeys of the most important compounds described in this article.

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9. Compound **4**: ^1H NMR: ($CDCl_3$) δ 7.84 (s, 1H, H1), 7.27 (s, 1H, H9), 6.76 (s, 1H, H3), 6.31 (s, 1H, H4), 5.73 (m, 1H, H1′), 5.70 (m, 1H, H2′), 5.48 (m, 1H, H3′), 4.38 (m, 1H, H5′), 4.34 (m, 1H, H4′), 4.29 (m, 1H, H5″), 2.12–2.10 (s, 9H, Ac). ^{13}C NMR: ($CDCl_3$) δ 170.31–169.16 (C=O-Ac), 154.40 (C2), 137.56 (C4), 131.23 (C9), 128.40 (C7), 121.62 (C6), 86.54 (C1′), 79.67 (C4′), 73.33 (C3′), 70.30 (C2′), 63.10 (C5′), 20.87–20.55 (CH_3-Ac). ^{15}N NMR: ($CDCl_3$) δ 239.0 (N10), 171.0 (N8), 129.5 (N3), 125.0 (N5), 104.0 (N1). HR MS calcd for $C_{16}H_{19}N_5O_8$: 409.12335, found: 409.12347.