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Study of an efficient conversion of 1,3-dimethyl-5-(Arylazo)-6-Amino-Uracils to 1,3-dimethyl-8-(Aryl)-Azapurin-2,6-Diones

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ABSTRACT

6-Aminouracils have extensively been used as precursors for synthesizing numerous uracil derivatives of biological and pharmaceutical significance. This study describes an application of 1,3-dimethyl-5-(arylazo)-6-aminouracils (Uazo: Uazo1-Uazo4, precursors) for an efficient synthesis of a series of 8-substituted-azapurins (AP), namely 1,3-dimethyl-8-(aryl)-azapurin-2,6-diones (aryl = *p*-HC_6H_4 (**AP1**), -MeC_6H_4 (**AP2**), $-ClC_6H_4$ (**AP3**), and $-SO_2NH_2C_6H_4$ (**AP4**)) following an oxidation method in the presence of copper (II) nitrate and in alkaline medium. The obtained compounds were isolated in good yields as crystalline air-stable products and have been fully characterized in the solution by UV–vis and NMR spectroscopy, as well as in the solid state by FT-IR spectroscopy, elemental analysis, and single-crystal X-ray diffraction (for **AP2** and **AP4**). UV–vis study evidences that the conversion of the 6-aminouracil precursors occurs *via* an intermediate, Cu(II)-complex and a plausible mechanism for the formation of **AP1**-**AP4** has been proposed. Unlike **AP2** the crystal structure of **AP4** reveals the formation of interdigitated 1D H-bonded chains that has been topologically classified within the 2C1 type. The ^{1}H NMR spectra of the products have proton signals that completely devoid of hydrazone (–NH–) and imine (=NH) signals of their parent Uazo derivatives, thus confirming their full conversion and a stability of the **AP1**-**AP4** in solution. The excitation and emission spectra of **AP1**-**AP4** were also recorded in solution, revealing electronic transitions between similar vibrational energy levels of S_0 (singlet ground state) and S_1 (singlet first excited state).

1. Introduction

Purine (adenine and guanine) and pyrimidine (cytosine, thymine, and uracil) bases are the two different important hydrolysis products of nucleic acids. These bases have widely been studied from diverse perspectives, particularly their interactions with metals and chemical modification [1–16], aiming at understanding in their *vivo* functioning and tuning pharmacological behavior. Chemical modification of natural nucleobases (*i.e.*, purines and pyrimidine bases) in search of new drugs for effective antiviral and antitumour therapy has extensively been explored [4–16]. In particular, the modification in purines (see Scheme 1(A)) has generally been accomplished at its imidazole ring, resulting in the substitution of CH by N in position 8 of the purine ring and forming 8-azapurines [6–8] (see Scheme 1(B)). Such a conversion of purines to 8-azapurines leads to an effective decrease of the electron density at this position [17] and thus can significantly influence their chemical and biological properties [18], including their recognized activity as anti-tumour drugs [18a]. Moreover, 8-azapurine family includes 8-azaadenines (6-amino-8-azapurine), 8-azaguanines (2-amino-8-azapurin-6-one), 8-azainosine (9-β-D-ribofuranosyl-8-azapurin-6-one), 8-azahypoxanthines (8-azapurin-6-one), and 8-azaxanthines (8-azapurin-2,6-dione, Scheme 1C), which differ from each other by the presence of amino and/or hydroxyl substituents in the positions 2 and 6 [9,19].

The present work deals with the derivatives of 1,3-dimethyl-8-azapurin-2,6-dione (Scheme 1D). The synthesis of 8-azapurine

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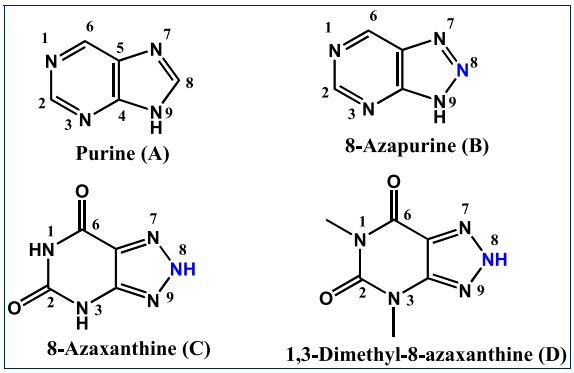

Scheme 1. Molecular structures of purine derivatives (**A**–**D**).

derivatives generally starts with the starting materials based on either pyrimidine or 1,2,3-triazole derivatives. The first of 8-azapurines, 1,3-dimethyl-8-azapurin-2,6-dione (Scheme 1D), was made by Traube [20] *via* cyclization of the corresponding 4,5-diaminopyrimidine with nitrous acid. Later on, the Traube synthesis has proved to be compatible with many kinds of groups in the starting pyrimidine moiety for synthesizing 8-azapurines [21–24]. The mobile hydrogen atom at the 8-position in 1,3-dimethyl-8-azapurin-2,6-dione (Scheme 1D) can, theoretically, be attached to any one of the three triazole-nitrogen atoms, giving the possibility to synthesize different N-substituted derivatives. A notable deficiency of the Traube synthesis concerns its inability to produce 7- or 8- substituted 8-azapurines starting from amino-pyrimidine derivatives [25,26] and such difficulty could be overcome using triazole derivatives [27]. It is noteworthy to mention that the bond arrangement in 8-azapurine (Scheme 1B) might suggest instability.

Nevertheless, the 6-aminouracils are extensively used as precursors for synthesizing numerous uracil derivatives of biological and pharmaceutical importance [28–30]. For example, Sulfadimethoxine [30], a sulphanilamide or sulfa-drug, is prepared from 6-aminouracil and is used to inhibit the uracil-DNA glycosylase [31] and the dihydropyrimidine dehydrogenase enzymes [32]. Our laboratory has been engaged in synthesizing 5-(arylazo)-6-aminouracils and exploring their chemistry [33]. From literature it is found that there are several effective methods [34,35] converting 2-amino-azo compounds to 2-substituted v-triazole derivatives; these are heating, chromic acid oxidation, lead tetraacetate oxidation, oxidation with alkaline copper sulfate, and oxidation with copper sulfate in pyridine-water. In particular, Islam and Nagamatsu [36] demonstrated the synthesis of some derivatives of 1,3-dimethyl-8-(aryl)azapurin-2,6-diones *via* the oxidation with copper sulfate in pyridine-water medium.

Inspired by these results and following our general interest in this area of synthetic organic chemistry, we report in the present study an efficient conversion of a series of 1,3-dimethyl-5-(arylazo)-6-aminouracils (Uazo1-Uazo4) to 1,3-dimethyl-8-(aryl)azapurin-2,6-diones (**AP1**-**AP4**), by applying a procedure for the oxidation with alkaline copper nitrate in DMF-water mixture. As a base, $NaHCO_3$ was used. The present report thus includes the synthesis, full characterization, and detailed spectroscopic studies of the **AP1**-**AP4** products, crystal structures of **AP2** and **AP4**, as well as a topological analysis of the identified 1D H-bonded network in the crystal packing pattern of **AP4**. The sulfonamide derivative, in particular, can potentially constitute a promising pharmaceutically active agent, as the sulfonamide ($-SO_2NH_2$) group is an integral part of various sulfa-drugs [37–39]. In addition, the molecules containing sulfonamide functionality can exhibit interesting solid state properties [40–44].

2. Experimental

2.1. Materials and instruments

All chemicals were commercially available (reagent grade) and were used without any further purification. All solvents were of A. R. grade. 1,3-Dimethyl-6-aminouracil and 1,3-dimethyl-5-(arylazo)-6-aminouracil were prepared following reported procedures [33].

Melting points were determined on a Labtech Digital melting point apparatus with a heating rate of 2 °C/min and not corrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer (model RX-1) in the region 4000–400 cm^{-1} (KBr pellets). The ^1H NMR and ^{13}C NMR spectra in DMSO-D_6 were recorded on a JEOL DELTA2 spectrometer at 500 MHz and 125 MHz, respectively. The electronic spectra were recorded on a Shimadzu UV–*vis*-1800 spectrophotometer. Excitation and emission spectra of all the compounds were recorded on a Perkin Elmer LS 55 Fluorescence Spectrometer. Excitation and emission slits were set to 10 and 2.5 nm. Elemental analyses were made on a Perkin Elmer 2400 series-II analyzer and the obtained results are in good agreement with the calculated values.

2.2. Synthesis of 1,3-dimethyl-8-(aryl)-azapurin-2,6-dione derivatives (*AP1*-*AP4*)

General procedure. The compounds **AP1**-**AP4** were synthesized *via* an alkaline copper sulfate method [34] with some modifications. Typically, 1,3-dimethyl-5-(phenylazo)-6-aminouracil (Uazo1, 103.6 mg, 0.4 mmol) was dissolved in DMF, followed by the addition of an aqueous solution of $NaHCO_3$ (33.6 mg, 0.4 mmol). The obtained mixture was heated at 70 °C with continuous stirring over 20 min. Then, to this warm mixture a DMF solution of $Cu(NO_3)_2{\cdot}3H_2O$ (48.4 mg, 0.2 mmol) was added slowly with continuous stirring for further 1 h at the same temperature. An intense yellow powder of the product started to precipitate in the course of cooling the reaction mixture down to room temperature. The product was filtered off, washed with water, and dried in vacuum. X-ray quality single crystals can be obtained by re-dissolving the product in DMF-water (3:1 v/v) mixture, followed by slow evaporation for two weeks. Single crystals of **AP2** and **AP4** were analyzed for molecular structure of the products.

Physical and spectral data of the obtained products are given as follows.

2.2.1. 1,3-Dimethyl-8-(phenyl)-azapurin-2,6-dione (*AP1*)

Yellow square-plate crystals (yield: 53%) with a melting point of 265 ± 1 °C. FT-IR (KBr pellet, υ/cm^{-1}): 2817 (bw, Ar–H), 1726, 1676 (s, >C=O), 1606, 1592 (bs, >C=N-), 1493 (sw, –C–C), 1384, 1351, 1295 (s, –N–C), 1061 (s, –N–N), 990, 961, 764, 744, 692, and 652 (other bands). ^1H NMR (DMSO-D_6, δ/ppm): 8.08–8.06 (d, 2H, Ar–H), 7.64–7.49 (m, 3H, Ar–H), 3.49 (s, 3H, N(3)–CH_3), and 3.28 (s, 3H, N (1)–CH_3). ^{13}C NMR (125 MHz, DMSO-D_6, δ/ppm): 155.91 (>C=O), 155.77 (>C=O), 150.74 (>C=N), 150.06 (>C=N), 138.54 (Ar–C), 131.40 (Ar–C), 129.91 (Ar–C), 129.04 (Ar–C), 126.68 (Ar–C), 118.89 (Ar–C), 30.80 (N–CH_3), 28.17 (N–CH_3). Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22, Found: C, 56.12; H, 4.26; N, 27.02.

2.2.2. 1,3-Dimethyl-8-(p-Me-phenyl)-azapurin-2,6-dione (*AP2*)

Yellow square-plate crystals (yield: 58%) with a melting point of 271 ± 1 °C. FT-IR (KBr pellet, υ/cm^{-1}): 2822 (bw, Ar–H), 1726, 1677 (s, >C=O), 1595 (bs, >C=N-), 1508 (sw, –C–C), 1384, 1353, 1297 (s,