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Barbituric Acid Initiated Rearrangement of 2,2′-Pyridil into 5,5′-(2-pyrilidine)bisbarbituric Acid

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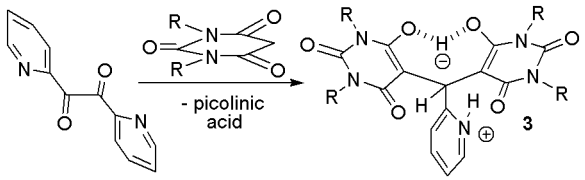
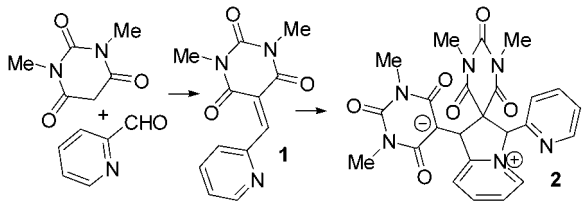
ABSTRACT



In the study of the barbituric acid initiated 2,2′-pyridil rearrangement, a very efficient synthetic procedure (isolated yield 80−90%) for the preparation of useful 2-pyrilidenes 3 was developed.

Derivatives of barbituric acid have attracted the attention of researchers in synthetic organic chemistry, as well as medicinal chemistry, for a long time as a result of their exceptionally diverse biological activity.[1] It was demonstrated that some barbituric acid derivatives have new and very interesting biological activities that stand apart from previous medical utilization of barbituric acid derivatives.[2] An even higher interest in this research area was elevated by a recent discovery that aromatic pyrilidenes, which structurally resemble 5,5′-pyrilidenebisbarbituric acids, have very potent immuno-modulating activity.[3] To be able to fully evaluate these inhibitory activities, a general synthetic route for the preparation of these compounds must be developed. While the preparation of a wide variety of 5,5′-(3-pyrilidene) and 5,5′-(4-pyrilidene)bisbarbituric acids and their ammonium salts[4] can be accomplished through the condensation of pyridinecarbaldehyde and the corresponding barbituric acid, the condensation between 2-pyridinecarbaldehyde and barbituric acid yields unique pyridinium-barbiturate ylides. The reaction is unique in many ways because of the fact that ylide **2**[5] is prepared by the dimerization of the condensation intermediate **1**[6] (Scheme 1).

Scheme 1. Preparation of Ylide **2**



Considering that 5,5′-(2-pyrilidene)bisbarbituric acid **3** cannot be prepared in this way, we have searched for a 2-pyridinecarbaldehyde synthetic equivalent. In many chemi-

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(1) There are many diseases that are treated with barbituric acid derivatives alone or in combination with some other chemotherapeutics. (a) Goth, A. *Medical Pharmacology*, 4th ed.; C. V. Mosby Company: St. Louis, 1968. *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Ed.; Wiley: New York, 1997; Vols. 1−5. (b) Rastaldo, R.; Penna, C.; Pagliaro, P. *Life Sci.* **2001**, *69*, 729. (c) Aiken, S. P.; Brown, W. M. *Front. Biosci.* **2000**, *5*, 124. (d) Ghansah, E.; Weiss, D. S. *Neuropharmacology* **2001**, *40*, 327. (e) Levine, B. *Princ. Forensic Toxicol.* **1999**, 185.

(2) (a) Oliva, A.; Zimmermann, G.; Krell, H.-W. *Barbituric Acid Derivatives with Antimetastatic and Antitumor Activity*; International Patent WO 98/58925, 1998. (b) Gulliya, K. S *Uses for Barbituric Acid Analogues*; U.S. patent 943,385, 1997.

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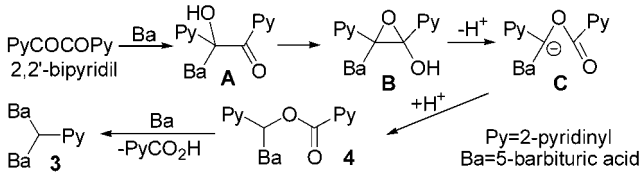
cal reactions the phenyl moiety of a molecule can be substituted with pyridine without altering the side chain reaction. If this is true for benzil (PhCOCOPh), then the corresponding pyridine synthetic equivalent (PyCOCOPy) might be used for the preparation of **3**. There is an abundance of literature reports indicating the transformation of benzyl benzoates or even benzaldehydes into benzil derivatives.[7] If it is possible to enforce the reverse benzil reaction of a pyridine analogue, then 2,2′-bipyridil can be used as a synthetic equivalent for 2-pyridinecarbaldehyde.[8]

Based on the benzil model, the acid-catalyzed rearrangement mechanism proposed for the conversion of 2,2′-pyridil into 5,5′-(2-pyrilidene)bisbarbituric acid **3** is presented in Scheme 2. It is expected that the most energy-demanding

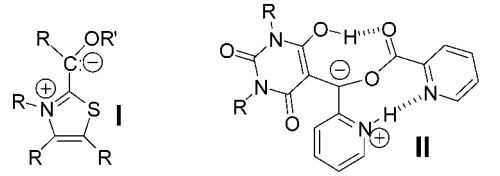
Scheme 2. Preparation of Pyrilidene **3**



transformation should be the rearrangement of keto alcohol **A** into ester **3**. The third step in the transformation (**4** → **3**) is nucleophilic substitution by barbituric acid on ester **4**.

Ester **4** (Scheme 2) can also be represented in its Zwitterionic structure **II**[9] (Scheme 3), which in many ways

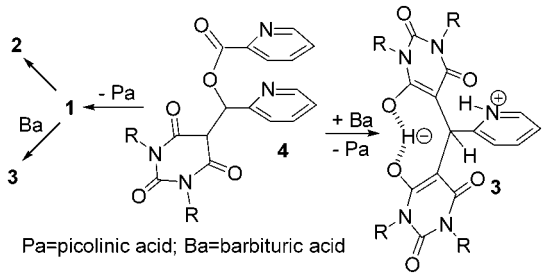
Scheme 3. Zwitterionic Thiamin and Barbiturate Models



resembles the thiamin model **I** often present in nature.[10] We believe that this model is also involved as an intermediate in the preparation of 5,5′-(2-pyrilidene)bisbarbituric acid.

One can envision at least two pathways in the preparation of 5,5′-(2-pyrilidene)bisbarbituric acid; one through elimination of picolinic acid and formation of intermediate **1**, followed by the addition of barbituric acid to the newly formed double bond, and the other by simple nucleophilic substitution of the picolinic acid moiety of ester **3** with barbituric acid (Scheme 4). Depending on solvent and

Scheme 4. Proposed Reaction Scheme for Preparation of **3**



temperature, both of these reactions occur. If the reaction is performed for a few hours in refluxing methanol, the only product of the condensation is 5,5′-(2-pyrilidene)bisbarbituric acid **3** in more than 80% isolated yield.[11] In the extended time experiment at room temperature it seems that the reaction goes through either elimination−addition, or the elimination−addition and nucleophilic substitution reactions compete, because both **2** and **3** are isolated from the reaction mixture.[12]

To determine the validity of our reaction mechanism we performed NMR reaction-following experiments at room

(3) For instance, see: Veniaminovich, V. *Salts of 5,5′-Arylidenebisbarbituric and 5,5′-Arylidenebis(2-thiobarbituric) Acid and 5,5′-Arylidenebis-(2-thiobarbituric) Acid Having an Antibacterial, Anti-Chlamydial, Antiviral and Immuno-Modulating Activity*; International Patent WO 99/25699, 1999.

(4) Neumann, D. M.; Jursic, B. S.; Stevens, E. D. Manuscript in preparation

(5) Jursic, B. S.; Neumann, D. M.; Moore, Z.; Stevens, E. D. *J. Org. Chem.* Manuscript submitted.

(6) Jursic, B. S. *J. Heterocycl. Chem.* **2001**, *38*, 655 and references therein.

(7) (a) *O*-Benzoylbenzaldehyde cyanohydrin has been found to form benzil in DMF in a base-catalyzed reversible reaction. Zheng, Z.-R.; Kjaer, N. T.; Lund, H. *Acta Chem. Scand.* **1998**, *52*, 362. (b) For base-catalyzed rearrangement of symmetrically substituted benzils, see: Bowden, K.; Williams, K. D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 77 and references therein.

(8) It is interesting to note that there is a lack of benzil−benzylic acid rearrangements. We believe that this is due to the fact that the base present is too weak to promote rearrangement, but with the addition of a strong base the rearrangement might occur.

(9) Zwitterion **II** might be prepared through the rearrangement of reactive intermediate **B** as shown in Scheme 2.

(10) For thiamin action in biological systems, see: (a) Bruce, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*; W. A. Benjamin: New York, 1966; Vol. 2, Chapter 8. (b) Reed, L. J. *Acc. Chem. Res.* **1974**, *7*, 40. (c) Nakanishi, I.; Itoh, S.; Fukuzumi, S. *Chem. Eur. J.* **1999**, *5*, 2810. (d) Nakanishi, I.; Itoh, S.; Suenobu, T.; Fukuzumi, S. *Chem. Commun.* **1997**, 1927. (e) Shinkai, S.; Yamashita, Kusano, Y.; Manabe, O. *J. Am. Chem. Soc.* **1982**, *104*, 563.

(11) **Typical Procedure for Preparation of Pyrilidenes 3.** Preparation of 5,5′-(2-pyrilidene)bis(1,3-dimethylbarbituric acid). A methanol (400 mL) solution of 2,2-pyridil (212 mg; 1 mmol) and 1,3-dimethyl barbituric acid (468 mg; 3 mmol) was refluxed for 5 h. The dark reaction mixture was concentrated (∼50 mL volume) at atmospheric pressure and left at room temperature in an open beaker overnight. The crystalline product was slurred in cold methanol (∼10 mL), separated by filtration, washed with cold methanol (3 × 10 mL), and dried at 90 °C for 30 min to afford 350 mg (87%) of pure product. If necessary, further purification of the product can be accomplished by crystallization from acetic acid. ^{1}H NMR (DMSO-d_6) δ 8.587 (1H, d, J = 5.2 Hz), 8.411 (1H, t, J = 7.1 Hz), 7.885 (1H, d, J = 5.4 Hz), 7.818 (1H, t, J = 7.1 Hz), 6.334 (1H, s), 3.133 ppm (12H, s); ^{13}C NMR (DMSO-d_6) δ 159.384, 155.976, 147.913, 142.451, 137.564, 122.386, 120.609, 81.156, 32.045, 24.514 ppm. ES 424 $(M + Na)^+$. Anal. Calcd For $C_{18}H_{19}N_5O_6$ (MW 401.37): C, 53.75; H, 4.83; N, 17.33. Found: C, 53.86; H, 4.77; N 17.45.

(12) From a closed-bottle mixture of 2,2-pyridil (2 mg) and 1,3-dimethybarbituric acid (5 mg) in methanol (1 mL) after standing at room temperature for 30 days a single crystal was grown. The crystal (1.7 mg) contains both **2** and **3**. Through comparison of the ^{1}H NMR signals for **2** (doublet at 9.003 ppm) and **3** (doublet at 8.587 ppm) the ratio of products is 32:68.

temperature in solvents such as methanol, tetrahydrofuran, acetic acid, chloroform, and dimethyl sulfoxide. Only in DMSO is the reaction mixture a solution. In all other cases a precipitate forms. From this experiment it is obvious that the formation of ester **4** is required for high yield transformation of 2,2′-pyridil and barbituric acid into pyrilidine **3** and picolinic acid (Figure 1). In prolonged DMSO experiments,

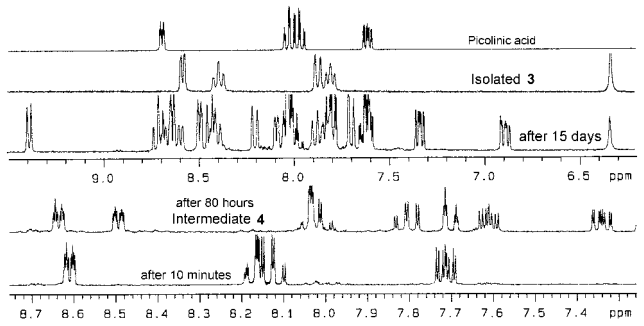


Figure 1. ^{1}H NMR (DMSO-d_6) spectra over the course of the reaction time.

a low field NMR aromatic compound is formed, which is not detected when the preparation of compound **3** is performed in methanol as a solvent.

To confirm the general applicability of this method in preparation of a wide variety of useful 2-pyrilidenes, preparations of derivatives with 1-phenylbarbituric acid, 1-methylbarbituric acid, 1-butylbarbituric acid, and barbituric acid were performed. In all cases, the corresponding pyrilidine **3** was isolated in higher than 80% yield (we were not able to detect any other side products). Structural properties of **3** with R = CH_3 were determined using the usual analytical methods as well as X-ray analysis. The X-ray single crystal was obtained by slow crystallization from acetic acid. The structure of compound **3** shows very interesting structural properties (Figure 2).

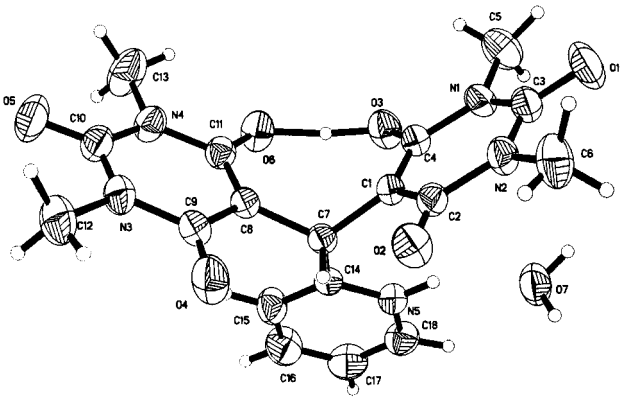


Figure 2. ORTEP of X-ray structure of **3**.

In the crystalline state compound **3** has a Zwitterionic structure with the positive charge located on the pyridinium cation and the negative charge located almost equally on both barbituric acids. In solution, both hydrogens in the 5- and 5′-positions of the two barbituric acids were not located because one is on the pyridine ring and the other is involved in hydrogen bonding interactions between two barbituric acid moieties. The plane with the pyridinium ring is almost perpendicular to the plane that separates the two barbituric acid moieties. The C(1)−C(4) bond distance is 1.365 Å in comparison with the C(1)−C(2) distance of 1.4275 Å and the (C1)-C(7) distance of 1.5201 Å, indicating the strong double bond character of the first two bonds and delocalization of the negative charge. All atoms in the ring and ones attached to the ring are basically in the ring plane.

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