Preparation of Unsubstituted Dipyridine-Dibarbituric Acid Ylide through Dimerization of Pyridin-2-ylmethylenepyrimidinetrione as a Reactive Intermediate

Branko S. Jursic

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148
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Preparation of 5,5'-(pyridin-2-ylmethylene)dipyrimidinetrione from barbituric acid and 2-pyridinecarboxaldehyde in any polar solvent is a straightforward synthetic procedure, while preparation of the dipyridine-dibarbituric acid ylide from the same starting materials is sensitive to the reaction media, pH, and temperature. For both products, the formation of the reactive intermediate 2-pyridin-2-ylmethylenepyrimidinetrione is certain and this intermediate is a cross road for the reaction to be directed in one way or other. The experimental evidence for the formation of this important intermediate, as well as synthetic procedures for the preparation of both condensation products are presented.

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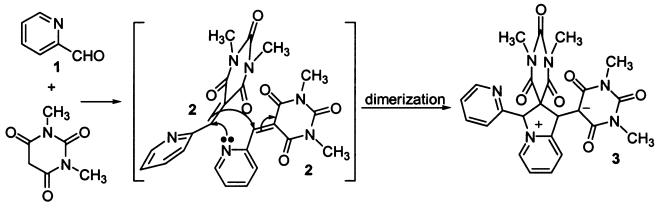
Previously, we have successfully developed methods for the preparations of both the double addition product **5** and the tetramethylated dipyridine-dibarbituric acid ylide **3** from 1,3-dimethylbarbituric acid and 2-pyridinecarboxaldehyde [1] (Scheme 1). We have been determined to develop a synthetic procedure for the preparation of the unsubstituted dipyridine-dibarbituric acid ylide **4** (Scheme 2). This ylide has acidic (barbituric NH groups) and basic (pyridine) moieties which enable it to be soluble in both acidic and basic aqueous media. The ylide **4** should be stable in basic aqueous media at room temperature unlike the structurally similar tetramethylated ylide **3**, in which upon heating in basic solution one of the barbituric acid moieties is decarbonylated [2]. Structurally, ylide **3** is built from two Knoevenagel condensation products between 2-pyridinecarboxaldehyde and 1,3-dimethylbarbituric acid (compound **2** Scheme 1) [3]. In strong acidic media, such as stomach acid (HCl), the pyridine moiety should be protonated and ylide **3** should fall apart to generate free intermediate **2** [4]. This compound is very reactive and cannot be isolated as a product of the 2-pyridinecarboxaldehyde and 1,3-dimethylbarbituric acid condensation. It has been indicated that condensation product of this type, containing the pyridine moiety, is very important either as an intermediate for the preparation other biologically active compounds or by itself due to valuable biological activity [5]. Therefore, special attention is given to pyridinecarboxaldehyde Knoevenagel condensation products with unsubstituted barbituric acid.

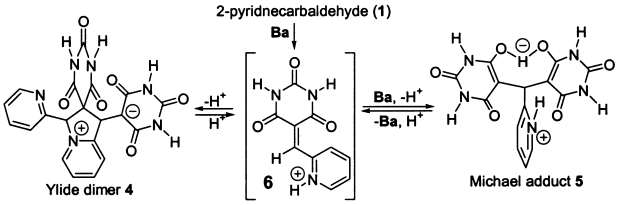
Scheme 1



Synthetic route for preparation of **3** in multigram quantities.

Logical starting materials for the preparation of unsubstituted ylide **4** are 2-pyridinecarboxaldehyde (**1**) and barbituric acid (**Ba**) as illustrated in Scheme 2. When the reaction is performed in polar solvents, such as methanol or DMSO with a 1:1 molar ratio, barbituric acid is fully consumed while 2-pyridinecarboxaldehyde is still present in the reaction media. This holds true even if the reaction is performed at elevated temperatures (refluxing methanol temperature). It seems that condensation products with 1:2 molar ratio of the reactants are formed.

Scheme 2



Product of 2-pyridinecarboxaldehyde (**1**) condensation with barbituric acid (**Ba**).

To better explore the reaction conditions and the reaction outcome, the condensation reaction is monitored by ^{1}H-NMR. Six different solvents (pyridine, acetic acid, trifluoroacetic acid, methanol, tetrahydrofuran, and dimethyl sulfoxide) were used as reaction media at room temperature. Regardless of the solvent used, the reaction is complete in several minutes, producing only one product with quantitative conversion (Figure 1). Spectroscopic properties for this product are very similar to spectroscopic properties of the previously prepared and x-ray characterized tetramethylated derivative of **5** [6]. Under this reaction condition, we were not able to detect even a trace amount of ylide dimer **4**.

One can assume that compound **5** is the Michael adduct formed by the barbituric acid addition to the reactive intermediate **6**, as it is presented in Scheme 2. If this is true then

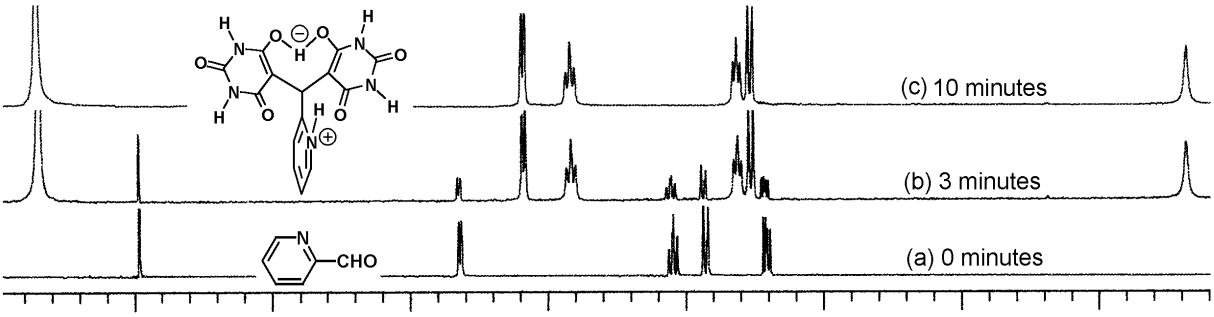


Figure 1. ^{1}H-NMR (DMSO-d_6, 500 MHz) reaction following of 2-pyridinecarboxaldehyde condensation with barbituric acid in dimethyl sulfoxide.

by careful control of the reaction conditions, it should be possible to direct reactive intermediate **6** toward the ylide dimer **4** or toward Michael adduct **5** (Scheme 2). Because formation of the Michael adduct is very fast in a majority of the reactions, it is the only product obtained from the condensation. From a practical standpoint, it is not possible to control the reaction toward the formation of **4** if the equilibrium between the reactive intermediate **6** and the adduct **5** is nonexistent. To establish that relationship between reactive intermediate **6** and Michael adduct **5** we have monitored the decomposition process of **5** in concentrated sulfuric acid and DMSO (1:1) (Figure 2, spectra I). Almost instantaneously signals of **6** are formed and in about 3 hours at 80 °C compound **5** is fully converted into reactive intermediate **6** (Figure 2). It also seems obvious that in strong acid reaction conditions, as in concentrated sulfuric acid, intermediate **6** is fully protonated and therefore its dimerization into the desirable ylide **4** is prevented. The acidity of the barbituric acid might be sufficient to produce a trace of the reactive intermediate that might isomerize. If this is true then with prolonged reaction (for several days of methanol refluxing) times, the ylide product can be accumulated. An equimolar methanol mixture of barbituric acid and 2-pyridinecrabaldehyde was refluxed for several days. The formed solid material was the subject of the ^{1}H-NMR analysis (Figure 2. Spectra II). Two products were always present in the white precipitate, both ylide **4** and the adduct **5**. After seven days of refluxing the methanol suspension, the solid material contains approximately 50% of **4** and 50% of **5** (Figure 2). With prolonged refluxing the ratio of the desirable product is increased up to 90% and this procedure was used for preparation of compound **4**.

Our spectroscopic studies, performed in exceptionally strong acidic media (concentrated sulfuric acid), support the notion that reactive intermediate **6** can exist as a pyridinium salt. Hence, it is reasonable to speculate that it should be possible to prepare and isolate some form of the salt of **6**.

In this paper we have demonstrated that the Knoevenagel condensation product between barbituric acid and 2-pyridinecarboxaldehyde (pyridin-2-ylmethylenepyrimidinetrione) is a reactive intermediate that can either add one molecule of barbituric acid to form the Michael-type adduct and/or dimerize into the thermally more stable dipyridine-dibarbituric acid ylide. Formation of the Michael-type adduct is a kinetically controlled reaction and is occurring almost instantaneously after the two reagents come into contact with each other. The formed adduct is sensitive to strong acid, such as concentrated sulfuric acid, and one molecule of barbituric acid can be eliminated. Solubility of the dimer is very low and it becomes a major product of the 2-pyridinecarboxaldehyde-barbituric acid condensation if the reaction suspension is refluxed for a long period of time. A very efficient synthetic procedure

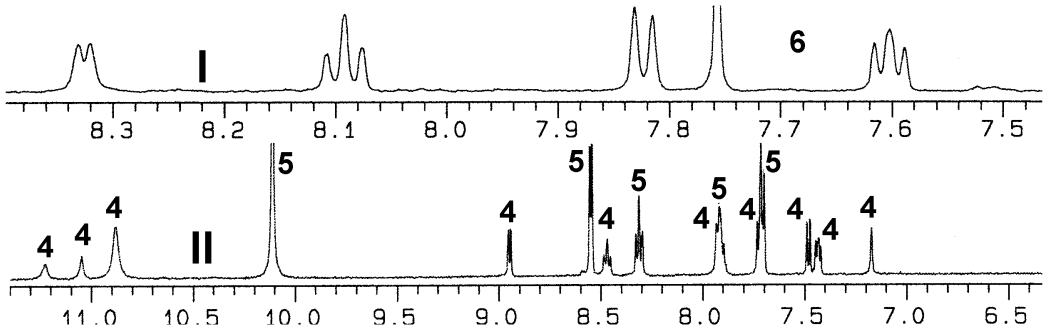


Figure 2. ^{1}H-NMR (500 MHz) of (I) the Michael adduct **5** in H_2SO_4-DMSO (1:1) at 80 ºC after 3 hours and (II) solid product obtained after seven days refluxing of 2-pyridinecarboxaldehyde-barbituric acid methanol suspension.

was developed for the preparation of large quantities of both adduct **5**, the Michael-type, and the ylide **4**.

EXPERIMENTAL

Melting points were acquired on an Electrothermal IA 9000 Digital Melting Point Apparatus and are uncorrected. All reported compounds decompose at high temperatures (above 280 ºC). The ^{1}H and ^{13}C NMR spectra were run on Varian INOVA 500 MHz spectrophotometer with DMSO-d_6 as a solvent and internal standard (2.50 and 36 ppm for ^{1}H and ^{13}C NMR respectively). The mass spectra were recorded on a Micromass Quattro 2 Triple Quadropole Mass Spectrometer; Elemental Analysis was performed by Atlantic Microlab, Inc., Norcross, GA.

Improved Procedure for Preparation of Ylide **3** [1].

Refluxing methanol (200 mL) solution of 2-pyridinecarboxaldehyde (21.4 g; 0.2 mol) and refluxing methanol (200 mL) solution of 1,3-dimethylbarbituric acid (31.2 g; 0.2 mol) were mixed together. The volume of the resulting reaction mixture was reduced to 100 mL by evaporation of methanol at atmospheric pressure. The resulting suspension was cooled to room temperature and white solid was separated by filtration, washed with methanol (3x20 mL), and dried at 80 ºC for one hour to afford pure **3** (46.2g; 94.1%).

Preparation of 5,5'-(Pyridin-2-ylmethylene)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5**).

Into clear trifluoroacetic acid (100 mL) solution of barbituric acid (640 mg; 5 mmol) trifluoroacetic acid (10 mL) solution of 2-pyridinecarboxaldehyde (270 mg; 2.5 mmol) was added. The resulting clear pale green solution was stirred at room temperature for one hour. After ~5 minute white precipitate starts to form. The solid product was separated by filtration, washed with trifluoroacetic acid (3x5 mL) and dried at 80 ºC in vacuum to afford 845 mg (98%) of pure product. The product decomposes at temperatures over 275 °C. In an alternative procedure barbituric acid (12.8 g; 0.1 mol) was dissolved in methanol (1400 mL) with stirring at room temperature. Into this clear methanol solution 2-pyridinecarboxaldehyde (5.35 g; 0.05 mol) was added dropwise. Immediately a white precipitate formed. Reaction suspension was stirred at room temperature for thirty minutes. Solid precipitate was separated by filtration, washed with methanol (3x50 mL) and dried at 80 ºC for two hour to afford pure product in 97% yield (16.7 g). Mp 275 °C with decomposition. ^{1}H-NMR (DMSO-d_6): δ 10.33 (4H, s, NH), 8.57 (1H, d, *J*=5.5Hz), 8.38 (1H, t, *J*=2.5 Hz), 7.78 (1H, t, *J*=6.5 Hz), 7.73 (1H, d, *J*=8.5 Hz), 6.15 (1H, s, CH benzyl); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 161.3, 156.8 (two different carbonyls), 147.2, 142.2, 137.9, 122.1, 120.4 (five pyridine carbons), 83.2 (benzyl carbon), and 29.0 ppm (barbituric C-5). Enolization of the 4,4' and 6,6' carbonyl pairs renders them equivalent on the NMR time scale.

Anal. Calcd. For $C_{14}H_{11}N_5O_6$: C, 48.70; H, 3.21; N, 20.28. Found: C, 48.22; H, 3.32; N, 20.03.

Preparation of 2',4',6'-Trioxo-3-pyridin-2-yl-1-(2,4,6-trioxohexahydropyrimidin-5-yl)-1,1',3,3',4',6'-hexahydro-2'*H*-spiro[indolizine-2,5'-pyrimidine] (Ylide **4**).

Into refluxing methanol solution (100 mL) of 2-pyridinecarboxaldehyde (1.07 g; 0.01 mol) barbituric acid (1.28 g; 0.01 mol) was added. A small amount of solid material was used to follow the reaction by. After refluxing the reaction for forty days (~90% **4** present in the solid) the white powder was separated by filtration, slurred in methanol (50 mL), refluxed for one hour and separated from the liquid by hot filtration. This procedure was repeated an additional three times to remove traces of byproduct. The yield of the reaction is 1.37 g (63 %). Mp 320 ºC with decomposition; the compound has very low solubility in DMSO, methanol, water, etc. To prepare an NMR sample the white product (50 mg) was mixed with the NMR solvent prepared from 1 mL of D_2O and 100 mg sodium hydroxide. After about 30 minutes the suspension becomes a solution, which was used for recording the ^{1}H-NMR spectrum. For the ^{13}C-NMR spectra ^{13}C-NMR DMSO-d_6 was also added as an internal NMR reference. Reference signals for ^{1}H-NMR is water at 4.80 ppm and for ^{13}C-NMR DMSO at 39.5 ppm. ^{1}H-NMR (D_2O-NaOH): δ 8.81 (1H, d, J=6.0 Hz), 8.53 (1H, t, J=6 Hz), 8.52 (1H, d, J=6Hz), 7.97 (1H, d, J=8Hz), 7.95 (1H, t, J=8 Hz), 7.93 (1H, t, 6Hz), 7.49 (1H, t, J=6.0Hz), 7.40 (1H, d, J=8Hz), 7.17 (1H, s), and 5.54 ppm (1H, s). ^{13}C-NMR (DMSO-d_6): δ 167.1, 162.9, 161.8, and 161.7 (four different carbonyl carbons), 154.6, 152.1, 150.6, 147.7, 141.8, 139.9, 126.9, 126.4, 125.5, and 125.0 ppm (10 aromatic carbons), 87.1, 78.9, 62.8, and 53.0 ppm (four aliphatic carbons). Electrospray AutoSpec ES$^+$ (CH_3COOH) strong signal at 435 (M+1).

Anal. Calcd. For $C_{20}H_{14}N_6O_6$ (MW 434.10): C, 55.30; H, 3.25; N, 19.36. Found: C, 55.18; H, 3.38; N, 19.13.

Acknowledgement.

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[2] For decarbonylation of *N,N'*-disubstituted barbituric acid derivatives see: B. S. Jursic, *Tetrahedron Lett.* **41**, 5325 (2000).

[3] For the Knoevenagel condensation of aromatic aldehydes with barbituric acid see B. S. Jursic, *J. Heterocyclic Chem.* **38**, 655 (2001) and references therein.

[4] In fact we have followed the decomposition **3** by ^{1}H-NMR using **3** (2 mg) in sulfuric acid (0.5 mL) and DMSO-d_6 (0.3 mL) as reaction media at 80 ºC. After approximately 40 minutes, the ylide **3** was quantitatively transformed in **2**. This can be judged by transformation of two sets of pyridine signals (two doublets and two triplets) into one set of the pyridine signals as well as three singlets for **3** into two singlets for **2**. For details of NMR spectra of **3** see reference 1. ^{1}H-NMR (500 MHz) signals for *in situ* generated **2** in its protonated form is 8.44 (1H, d, *J*=6.0 Hz, H-6 of pyridine ring), 8.20 (1H, t, *J*=8.0 Hz, H-5 of pyridine ring), 7.89 (1H, d, *J*=9.0 Hz, 3-H of the pyridine ring), 7.81 (1H, s, benzylidene hydrogen), 7.70 (1H, t, *J*=8.0 Hz, 4-H of pyridine ring), 2.81 (3H, s, CH_3), and 2.79 ppm (3H, s, CH_3).

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[6] 5,5'-(Pyridin-2-ylmethylene)di[1,3-dimetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione] as tetramethylated derivative of **5** was prepared by 2,2'-pyridil condensation with 1,3-dimethylbarbituric acid in refluxing methanol. The structure was confirmed by X-ray single crystal analysis, obtained by slow crystallization of the reaction product from acetic acid. For details of the preparation procedure and structural analysis see: B. S. Jursic, D. M. Neumann, K. Martin, and E. D. Stevens, *Org. Lett*. **4**, 811 (2002).