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Received August 8, 1985

The reaction of diethyl ethoxymethylenemalonate (**1**) and 6-amino-1,3-dimethyluracil (**2**) was determined to be regioselective. Under acidic conditions the product was the previously isolated 7-oxopyrido[2,3-*d*]pyrimidine (**3**), while in the presence of one equivalent of base followed by thermal cyclization, the isomeric 5-oxopyrido[2,3-*d*]pyrimidine (**5**) is formed.

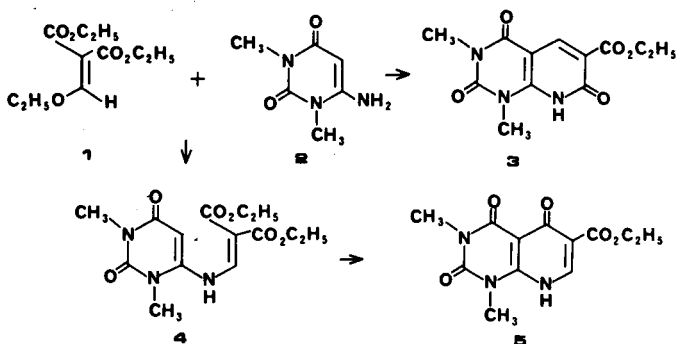
J. Heterocyclic Chem., **22**, 1469 (1985).

The pyrido[2,3-*d*]pyrimidine ring system is contained in a number of biologically active compounds including antitumor [1], antibacterial [2], and anticonvulsive [3] agents. The reaction of diethyl ethoxymethylenemalonate (**1**) with 6-aminopyrimidines has been widely used for the synthesis of 5-oxo-6-carbethoxy-pyrido[2,3-*d*]pyrimidines [4,5]. An unusual exception to the normal pathway of the Gould-Jacobs reaction was reported for the reaction of 6-amino-1,3-dimethyluracil (**2**) with **1** to give the unexpected 7-oxopyrido[2,3-*d*]pyrimidine (**3**) rather than the expected intermediate **4** [6]. This report describes reaction conditions which allow the regioselective alkylation of **2** by **1** at either the nitrogen or at the carbon in good yields.

The direct formation of the 7-oxopyrido[2,3-*d*]pyrimidine from **1** and **2** suggested that the resonance form of **2** in which a negative charge at C-5 and a positive charge on the amino group played a substantial role in directing alkylation to the carbon rather than the nitrogen of **2** as expected. If this is the case, the presence of base to neutralize the positive charge on the nitrogen should allow the reaction to proceed in the normal Gould-Jacobs manner. Wawzonek has previously reported that **2** undergoes regioselective attack by cinnamaldehyde to produce either the 5-phenyl or 7-phenyl pyrido[2,3-*d*]pyrimidine in low yields depending upon the reaction conditions [7]. When **1** and **2** are refluxed overnight in ethanol containing one equivalent of sodium ethoxide, a quantitative yield of **4** is indeed obtained.

Structural assignment of **4** is based on pmr spectroscopy and the conversion of **4** to **5**. The pmr spectrum of **4** revealed a singlet at δ 5.53, indicative of the typical pyrimidine C-5H signal and two doublets at δ 8.17 and δ 11.3. Upon addition of deuterium oxide, the signal at δ 8.17 collapsed to a singlet while the signal at δ 11.3 disappeared. These latter two signals are characteristic for the vinylic proton and adjacent NH [5]. These results are consistent with the mechanism of the reaction being the attack at the ethoxy carbon of **1** by the most nucleophilic center of **2**. Thermal cyclization of **4** in refluxing phenyl ether afforded the 5-oxopyrido[2,3-*d*]pyrimidine (**5**) in excellent yield.

A complete reversal of the regioselectivity in the reaction of **1** with **2** was achieved by altering the reaction conditions. Refluxing of **1** and **2** in acetic acid overnight afforded the 7-oxopyrido[2,3-*d*]pyrimidine (**3**) in almost double the yield of the previously reported fusion reaction [6]. More importantly, there was no indication by silica gel chromatography of the formation of either **4** or **5** in the reaction mixture. Attempts to isolate the uncyclized intermediate from attack of C-5 of **2** on the ethoxy carbon of **1** proved unsuccessful. This method may be applicable to the regioselective synthesis of other 5-oxo and 7-oxopyridopyrimidines. Studies along this line are now in progress in our laboratory.



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The pmr spectra were recorded on a Varian EM-360 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are reported as values in parts per million (ppm). The uv absorption spectra data were obtained on a Cary Model 15 spectrometer. Microanalyses were performed by Baron Consulting Co.

6-Carboethoxy-1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**3**).

Compound **2** (7.75 g, 50 mmoles) and compound **1** (11.8 g, 55 mmoles) were refluxed overnight in glacial acetic acid (75 ml). The solvent was removed *in vacuo* and the residue crystallized from ethanol/chloroform to afford 7.85 g (56%) of **3**. The melting point, uv, ^1H nmr, and tlc were identical with those of **3** prepared by the fusion method [6].

-Diethyl *N*-(1,3-Dimethyl-2,4-dioxo-6-pyrimidinyl)aminomethylenemalonate (**4**).

Compound **1** (11.8 g, 55 mmoles) and compound **2** (7.75 g, 50 mmoles) were added to ethanol (200 ml) in which sodium (1.15 g, 50 mmoles) was previously dissolved. The mixture was refluxed overnight, cooled and filtered to afford 16.1 g (99%) of **4** as white crystals. Recrystallization from ethanol/chloroform gave an analytically pure sample: mp 176-177°; uv (*pH* 1): 320 nm (ϵ 23,700), (*pH* 11): 270 nm (ϵ 34,500); ¹H nmr: δ 11.3 (d, NH, 1, *J* = 12 Hz), 8.17 (d, NH-CH, 1, *J* = 12 Hz), 5.53 (s, C-5H, 1), 4.43 (d of q, CH₂, 4), 3.55 (s, NCH₃, 3), 3.33 (s, NCH₃, 3) and 1.33 (d of t, CH₂CH₃, 6).

Anal. Calcd. for C₁₄H₁₉N₅O₆: C, 51.69; H, 5.89; N, 12.92. Found: C, 51.77; H, 6.08; N, 12.63.

6-Carboxy-1,3-dimethyl-2,4,7-trioxypyrido[2,3-*d*]pyrimidine (**5**).

Compound **4** (1.3 g, 4 mmoles) was added to refluxing phenyl ether (10 ml). After 1 hour the solution was cooled and diluted with 30 ml of ethyl ether and stirred overnight. The white solid was filtered and washed with ethyl ether to afford 998 mg (89%) of **5**. Recrystallization from ethanol/chloroform afforded an analytically pure sample, mp 171°; uv (*pH* 1): 319 nm (ϵ 12,500), (*pH* 11): 298 nm (ϵ 6,000); ¹H nmr: δ 13.5 (s, NH, 1), 8.99 (s, C-7H, 1), 4.42 (q, CH₂, 2), 3.70 (s, NCH₃, 3), 3.47 (s, NCH₃, 3),

and 1.42 (t, CH₂CH₃, 3).

Anal. Calcd. for C₁₂H₁₃N₅O₅: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.86; H, 4.98; N, 14.90.

Acknowledgement.

Technical Assistance from Miss Jana Cox is appreciated. This work was supported by grant GM-29767 from the National Institute of General Medical Sciences.

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