NOVEL SYNTHETIC TRANSFORMATIONS OF 5-(ω-CHLOROALKANOYL)-1,3-DIMETHYLBARBITURIC ACIDS

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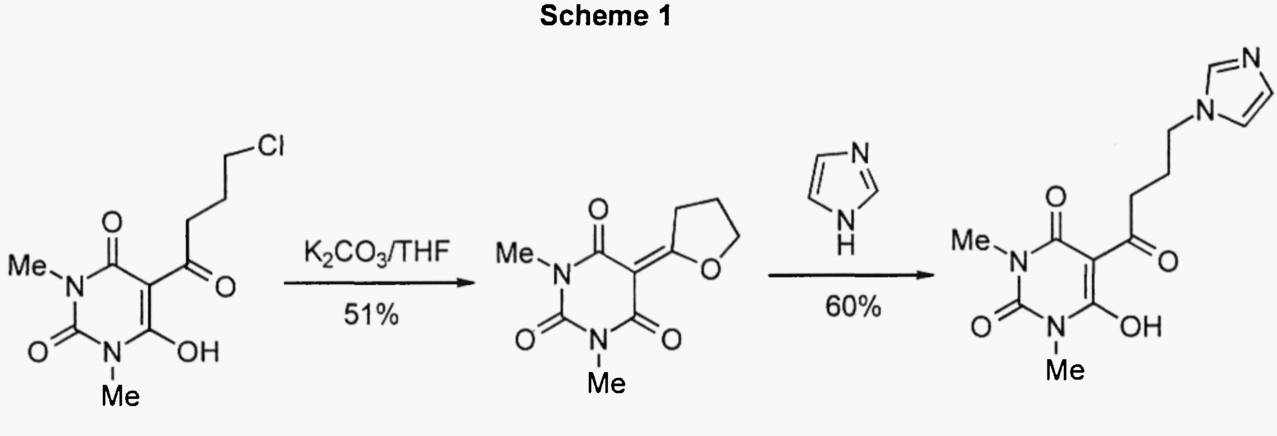
Abstract: The treatment of 5-(4-chlorobutanoyl)-1,3-dimethylbarbituric acid (**1**) with K_2CO_3 furnishes a 5-(tetrahydrofuran-2-ylidene)barbituric acid derivative **2**. A similar reaction of 5-chloroacetyl-1,3-dimethylbarbituric acid (**4**) with Et_3N yields a furanouracil **5**. Synthetic transformations of **2** and **5** to 5-(ω-heteroarylalkanoyl)-1,3-dimethylbarbituric acids and synthesis of other furanouracils from **5** are described.

Recently we have reported an efficient acylation of 1,3-dimethylbarbituric acid (1). In particular, the reaction of a sodium salt of this compound with 4-chlorobutanoyl chloride or chloroacetyl chloride in pyridine provides an easy access to the respective 5-(ω-chloroalkanoyl)-1,3-dimethylbarbituric acids **1** (structure in Scheme 1) and **4** (Scheme 2). In continuation of our work on the synthesis of new pyrimidine derivatives of potential biological activity (1,2) we now describe versatile chemistry of compounds **1** and **4**.

It was reasoned that the chlorine atom in **1** or **4** could be substituted by the reaction with various nucleophiles. In particular, the treatment of **1** with imidazole (1.5 equiv., DMF, reflux for 8h) was expected to give compound **3**. To our surprise this reaction furnished 1,3-dimethylbarbituric acid in an almost quantitative yield and an additional unidentified product that was highly soluble in water under neutral,

Scheme 1



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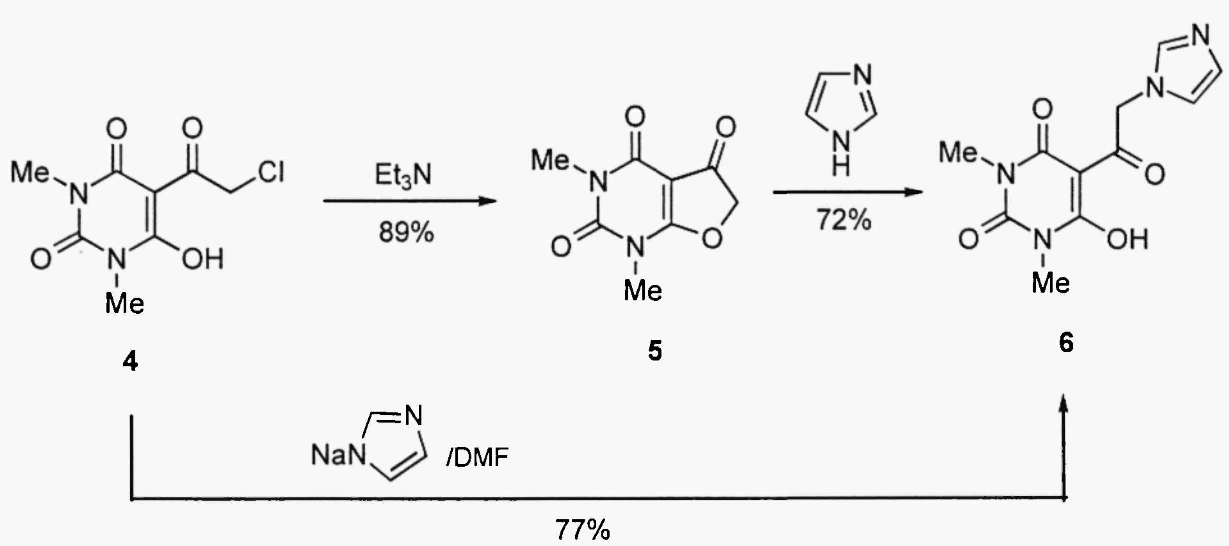
basic, and acidic conditions. Similar results were obtained with other nucleophilic heteroaromatic compounds such as 1,2,4-triazole, benzimidazole or indole and in the presence of their sodium derivatives. The facile loss of the acyl group from **1** can be explained in terms of a nucleophile addition to the acyl carbonyl group of **1** followed by retro aldol-type fragmentation of the resultant adduct (not shown). This suggestion is indirectly supported by the observed intramolecular cyclization of **1** (5 mmol) by treatment with K_2CO_3 which is a non-nucleophilic base (15 mmol in 50 mL of THF, 23 °C, 8h) to give a furylideneuracil derivative **2** (Scheme 1), mp 178-179 °C (from hexanes/benzene).

The tetrahydrofuran-2-ylidene subsystem of **2** underwent ring opening upon treatment with imidazole (2 equiv., no solvent, 125 °C, 2h) to furnish compound **3**, mp 203-205 °C (from H_2O). Thus, the undesired deacylation of **1** in the reaction with imidazole or its sodium salt was eliminated by using the two-step procedure for the preparation of **3**.

A different chemistry of the chloroacetyl analog **4** is given in Scheme 2. Thus, the treatment of **4** with imidazole in EtOH gave a furanouracil **5**, mp 205-206 °C (from EtOH), as the only product, albeit in low yield regardless of conditions. The yield of **5** was greatly improved by conducting the cyclization reaction of **4** (10 mmol) in the presence of Et_3N (1 mL in 60 mL of EtOH, 50 °C, 8h). A subsequent reaction of **5** with imidazole (2 equiv., no solvent, 125 °C, 2h) furnished a ring-opening product **6**, mp 255-256 °C (from H_2O). Interestingly, the treatment of **4** (1 mmol) with a sodium derivative of imidazole (1.5 mmol in 10 mL of DMF, 80 °C, 16h) yielded compound **6** directly. In a similar way, the reaction of **4** with sodium salts of 1,2,4-triazole, benzimidazole, and indole gave the corresponding analogs of **6** in high yields (not shown). All sodium salts were generated *in situ* in a DMF solution by the reaction of imidazole, 1,2,4-triazole, benzimidazole or indole with NaH (1 equiv., 23 °C, 1h).

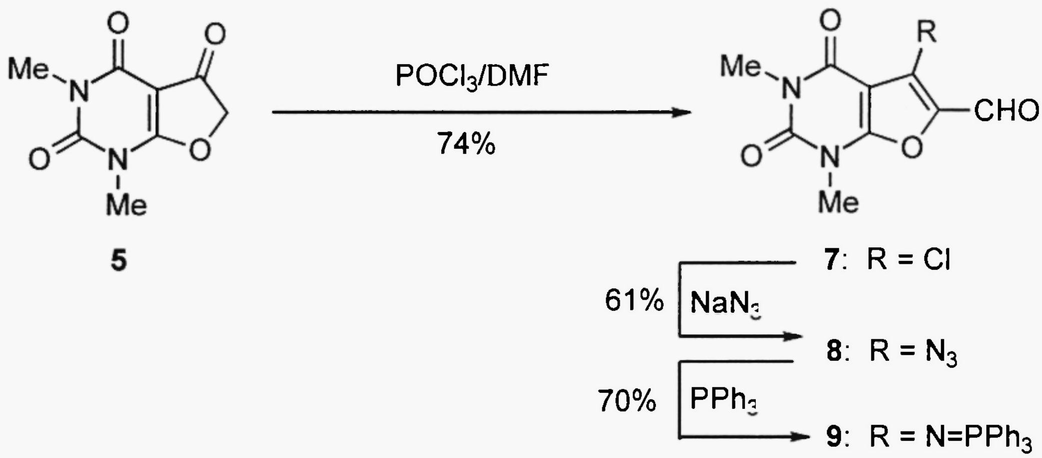
Thus, in contrast to the nucleophile-mediated deacylation of **1**, the reaction of **4** with a nucleophile furnishes the expected substituted derivative such as **6**. These different outcomes can be attributed to the high reactivity of the chloroacetyl functionality in **4**. Two pathways leading to **6** and analogs, namely (i) a direct substitution reaction and (ii) intramolecular cyclization of **4** to **5** followed by ring opening of **5** in the reaction with a nucleophile, are apparently operative.

Scheme 2



In contrast to the facile nucleophile-mediated ring opening reaction of **5**, the ring system of **5** is stable under electrophilic conditions. Thus, the reaction of **5** (1 mmol) with a Vilsmeier reagent (0.6 mL of DMF, 2.3 mL of $POCl_3$, 0 °C; addition of **5**; 100 °C, 45min) yielded the expected product **7** (Scheme 3), mp 147-148 °C (from EtOH). The α,β-unsaturated carboxaldehyde functionality of 7 is an excellent Michael acceptor for nucleophiles and, as such, permits additional functionalization of the furanouracil system. This is illustrated in Scheme 3 by the reaction of 7 (1 mmol) with azide anion (3 mmol of NaN_3, 10 mL of EtOH, 60 °C, 12h) to give **8**, mp 130-131°C (from H_2O). The treatment of **8** (1 mmol) with PPh_3 (1 mmol, 8 mL of benzene, 23 °C, 3h) did not result in the expected cyclization to a fused 1,2,3-triazine (3). Instead, a stable ylid **9**, mp 217-219 °C (from MeOH), was obtained.

Scheme 3



In summary, we have described several synthetically useful transformations of the readily available substrates **1** and **4**. It should be noted that the high yields given in Schemes 1-3 are for analytically pure products. Following a standard workup, all products were purified by crystallization without any chromatographic separation. The given structures were confirmed by elemental analysis results and analysis of ^1H NMR, ^{13}C NMR, and mass spectra. Since there was some uncertainty concerning the structures of **2** and **5**, these compounds were positively identified by x-ray crystallographic analysis. Compounds **1**, **3**, **4**, and **6** exist in solution in a single enol form as shown. This general conclusion is exemplified by analysis of **4** as follows. Thus, inspection of the ^1H NMR spectrum of **4** ($CDCl_3$) revealed the presence of a single tautomer. The one-proton absorption at δ17.9 is strongly indicative of an enol form. In the ^{13}C NMR spectrum of **4** the signal for C5 of the pyrimidine is at δ94.6, which compares favorably with the calculated value of δ94.5. By contrast, the calculated chemical shift for C5 in the alternative tautomer with the acyl carbonyl enolized is δ107.0. The predicted value for the all-carbonyl tautomer is δ79.9.

Full experimental details of this work, also including additional compounds briefly mentioned in the text and our current studies of other 5-(ω-chloroalkanoyl)-1,3-dimethylbarbituric acids, will be published in due course.

Acknowledgments

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