A GENERAL METHOD FOR ACYLATION OF 1,3-DIALKYL-SUBSTITUTED BARBITURIC AND 2-THIOBARBITURIC ACIDS

Lucjan Strekowski,[*§] Mohamed A. Ismail[§‡] and Hanafi H. Zoorob[*‡]
[§] Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, USA
[‡] Chemistry Department, Faculty of Science, Al-Mansoura University, Egypt

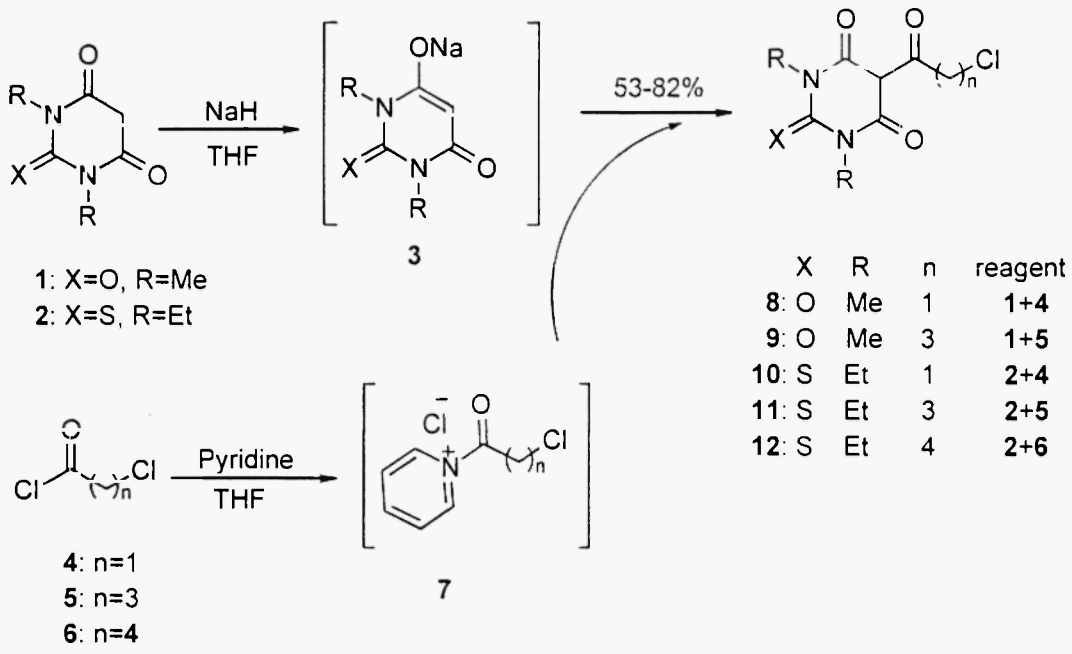
Abstract: A sodium derivative of 1,3-dimethylbarbituric acid or 1,3-diethyl-2-thiobarbituric acid undergoes an efficient acylation reaction at the position 5 by treatment with an acyl chloride in the presence of pyridine.

There is a continuing interest in development of new methodologies for the introduction of a substituent at the position 5 of barbituric acids, which is due to the wide spectrum of biological activity of the 5-functionalized derivatives (1-3). Surprisingly, however, only a few reports have described acylation of 1,3-dimethylbarbituric acid (**1**). Benzoylation can be accomplished by treatment of **1** with benzoyl chloride in the presence of triethylamine and zinc cyanide (3) or by the reaction of a sodium derivative of **1** with benzoyl chloride (4). Compound **1** can also be acetylated by treatment with a large excess of acetic anhydride (5), but similar preparations of higher alkanoyl derivatives have not been reported. As a part of this work we have found that a prolonged heating of (i) **1** with an alkanoyl chloride in the presence of triethylamine or (ii) a sodium salt of **1** with the alkanoyl chloride in various solvents produced only traces of the desired 5-alkanoyl derivative of **1**. In many cases the starting material **1** has been isolated in high yield from the crude mixtures.

We found, however, that efficient acylation of **1** is achieved by the reaction of its sodium derivative **3** with an alkanoyl chloride in the presence of pyridine. This is illustrated in Scheme by the preparation of 5-(ω-chloroalkanoyl)-substituted 1,3-dimethylbarbituric acids **8** and **9** from **1** and the respective ω-chloroalkanoyl chlorides **4** and **5**. 1,3-Diethyl-2-thiobarbituric acid (**2**) is also efficiently acylated by this method, as shown by the synthesis of compounds **10-12**. Obviously, pyridine undergoes a reaction with acid chloride to generate an intermediate product, such as **7**, that is more reactive than the starting acid chloride.

In a typical run, a solution of **1** or **2** (10 mmol) in THF (10 mL) was added to a suspension of NaH (0.3 g, 95%, 12 mmol) in THF (50 mL), and the mixture was heated under reflux and a nitrogen atmosphere for 2.5h. After cooling the resultant solution of **3** was treated with an acid chloride (15 mmol) and then pyridine (1 mL), and the mixture was stirred at 40 °C until a GC analysis showed the absence of **1** or **2** (24-36h). Concentration on a rotary evaporator was followed by treatment of the residue with water (5 mL) and then extraction of the mixture with chloroform (3x20 mL). Drying of the extract ($MgSO_4$) and concentration was followed by crystallization of the residue from an appropriate solvent (6).

Scheme



	X	R	n	reagent
8:	O	Me	1	**1+4**
9:	O	Me	3	**1+5**
10:	S	Et	1	**2+4**
11:	S	Et	3	**2+5**
12:	S	Et	4	**2+6**

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References and Notes

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(6) All compounds gave satisfactory elemental analyses and the given structures are fully consistent with ^{1}H and ^{13}C NMR data. Compound, yield, mp: **8**, 82%, 101-102 °C (from EtOH); **9**, 67%, 56-57 °C (from ether/hexanes); **10**, 65%, 91-92 °C (from ether/hexanes); **11**, 57%, 48-49 °C (from ether/hexanes); **12**, 53%, 50-51 °C (from ether/pentanes)

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