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Preparation of 5-formyl- and 5-acetylbarbituric acids, including the corresponding Schiff bases and phenylhydrazones

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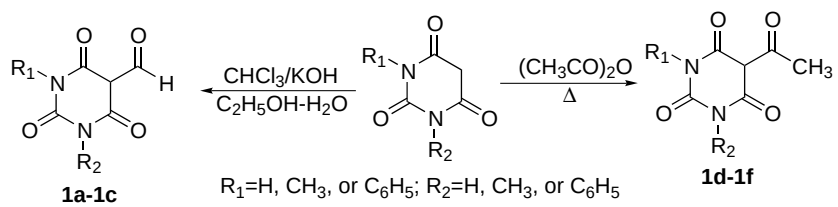
Abstract—Simple, effective, and high yield synthetic procedures for formylation and acetylation of barbituric acid derivatives is described. Generated 5-acylbarbituric acids are transformed into the corresponding Schiff bases in high yield condensation reactions with ω-aminoalkanoic acids and nitrophenylhydrazines.

Barbituric acid derivatives have proven their abilities to attract attention for a long time as 'holy grail' pharmaceuticals with a wide variety of biological activity.[1] Many new drugs are envisioned using the small 5-acylbarbituric moiety as a primary building block in the preparation. Synthetic procedures for the preparation of 5-acylbarbiturates with acyl groups containing phenyl as well as long alkyl groups are well documented in the literature.[2] Direct pharmaceutical and other industrial applications of 5-acylbarbiturates is well documented.[2,3] Unfortunately, there are no good synthetic procedures for the preparation of simple acylbarbiturates, such as formyl and acetylbarbiturates. Here we present very efficient methods for the preparation of a wide variety of 5-formyl-, 5-acetylbarbiturates and their corresponding phenylhydrazones and Schiff bases with ω-aminoalkanoic acids.

There are several very efficient ways to introduce the formyl group to organic molecules.[4] General methods for the introduction of a masked formyl group can be divided into the three classes according to the nature of the reactant (C, $^{-}$C, or $^{+}$C). The first group belong to the Inanaga SmI_2-induced masked-formylation of carbonyl compounds.[5] This reaction has a limited synthetic scope because strong oxidants or SmI_2 must be used. Using a masked nucleophile ($^{-}$C) is probably the most important and widely developed method today.[6] Classical examples of the formyl cation equivalents ($^{+}$C) are reactions of alkyl orthoformates with organometallics.[7] Direct formylation of organic compounds is also well established in organic chemistry. The Vilsmeier or the Vilsmeier–Haack reaction[8] is the most common method for the direct formylation of reactive aromatic rings (anilines and phenols). Another direct formylation that can be applied to phenols and certain heterocyclic compounds such as pyrroles and indoles is the Reimer–Tiemann reaction.[9] The reaction is performed in basic solution and the yields are generally low, seldom rising >50%.[10] This methodology was applied by Panteleimonov and Madrik in preparing 5-formylbarbituric acid in 30% yield.[11] With our modification of this procedure (Scheme 1) we were able to simplify the reaction procedure, obtain higher purity and very good isolated yields of 5-formylbarbiturates. The lowest yield (~45%) is for non-substituted barbituric acids. However, the apparent reactant conversion is more than 80%.[12] We repeated the procedure with slight modifica-



Scheme 1. Paths for direct 5-formylation and 5-acetylation of barbituric acids.

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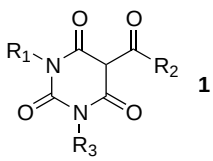
tions and the isolated yield of the product was 45%. With 1-phenyl and 1,3-dimethylbarbituric acids[13] the isolated yields are substantially higher (Table 1).

To our surprise we were not able to find a reliable procedure for the preparation of 5-acetylbarbiturates, although the preparation of higher 5-acylbarbiturates is well known.[14] If 5-acetylbarbiturates are to be used as precursors for the preparation of valuable pharmaceuticals they should be inexpensive and available in large quantities.[15] To meet these requirements, a simple synthetic procedure, preferably one-pot, starting with readily available barbiturates must be developed. Here we are reporting a synthetic procedure for a one-pot preparation of 5-acetylbarbiturates in high yields (Table 1). The reaction involves refluxing the corresponding barbiturates in acetic anhydride for a few hours followed by isolation of the corresponding 5-acetylbarbiturate.[16]

As mentioned previously, the Schiff bases of the 5-acylbarbituric acids show some interesting biological activity,[17] therefore the need for the preparation of these compounds in large quantity using a simple and effective synthetic procedure is apparent. Especially valuable are Schiff bases between ω-aminoalkanoic acids and 5-acylbarbituric acids.[18] Our preliminary results suggest that these compounds might be very potent anticancer agents.[19] We have developed a very simple one-pot synthetic procedure to obtain these compounds in multigram quantities. The procedure involves the condensation between two of the reactants in methanol.[20] These compounds have physical properties that easily set them apart from both starting materials, as well as make them an easy subject of biological evaluation. They have high water solubility, and are similar to the zwitterionic character of amino acids. Considering the different physical properties in comparison to the starting materials, the isolated yields are also very high (Table 2).

Positions of double bonds in the Schiff bases strongly vary with the nature of the solvent, as well as the temperature applied. It is commonly interpreted that Schiff bases are compounds with a carbon–nitrogen double bond,[23] which can move throughout the molecule producing a more thermally stable product and/or this double bond can be moved throughout the molecule via proton exchange with a solvent molecule as well as with another Schiff base. Barbituric acid based Schiff bases are perfect examples of this kind of molecular equilibrium. The equilibrium is temperature sensitive and two isomers, one with a carbon–nitrogen and the other with a carbon–carbon double bond have substantially different NMR shifts, as demonstrated in the example of Schiff base **2a** (Fig. 1). The compound is highly soluble in water and dimethyl sulfoxide (DMSO), but only slightly soluble in methanol. At room temperature more than 90% of compound **2a** has a carbon–carbon double bond.[24] By refluxing a methanol and water solution for 5 min the ratio of the isomers does not change to a degree that can be noticed from NMR analysis. It seems obvious that due to the low boiling point of these two solvents, the equilibrium activation barrier cannot be reached thermally. On the other hand, DMSO has a boiling point of 189°C and its heat capacity is much higher than both methanol and water, thus the higher equilibrium activation barrier can be reached. By heating the DMSO solution, allowing the solvent to reflux for 1 min the amount of the **2a C–N** isomer in solution increased from 18% (A, Fig. 1) to 61% (B, Fig. 1). With prolonged solvent refluxing (3 min) (C, Fig. 1) the amount of the **2a C–N** isomer increased to 89%, and after 5 min the practically pure DMSO solution of **2a C–N** was observed. If the NMR solution is left at room temperature for a long time the carbon–carbon double bond isomer **2a C–C** reappears (D, Fig. 1). Therefore carbon–carbon double bond isomers of type **2a C–C** are more stable and separated by a large activation barrier from the carbon–nitrogen double bond isomer type **2a C–N**. On the other hand, the reaction barrier for transforming the less stable carbon–nitrogen isomer into the more stable carbon–carbon isomer is relatively low and when the Schiff base product of barbituric acids is purified by crystallization, only the carbon–carbon double bond isomer is isolated. This is the case with all of our reported Schiff bases.

Table 1. The isolated yields of 5-formyl- and 5-acetylbarbituric acid

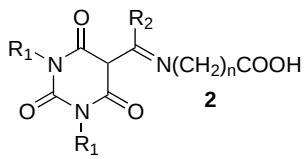


1

	R_1	R_2	R_3	Method	Yield (%)
1a	H	H	H	A	45
1b	C_6H_5	H	H	A	67
1c	CH_3	H	CH_3	A	75
1d	H	CH_3	H	B	95
1e	C_6H_5	CH_3	H	B	65
1f	CH_3	CH_3	CH_3	B	92

A = Reimer–Tiemann formylation reaction; B = reaction in acetic anhydride.

Table 2. Some ω-aminoalkanoic acid Schiff bases of 5-formyl-1,3-dimethylbarbituric and 5-acetylbarbituric acids[21,22]



2

	R_1	R_2	n	Yield (%)
2a	H	CH_3	2	93
2b	H	CH_3	3	91
2c	H	CH_3	5	95
2d	CH_3	H	2	89
2e	CH_3	H	3	85
2f	CH_3	H	5	87

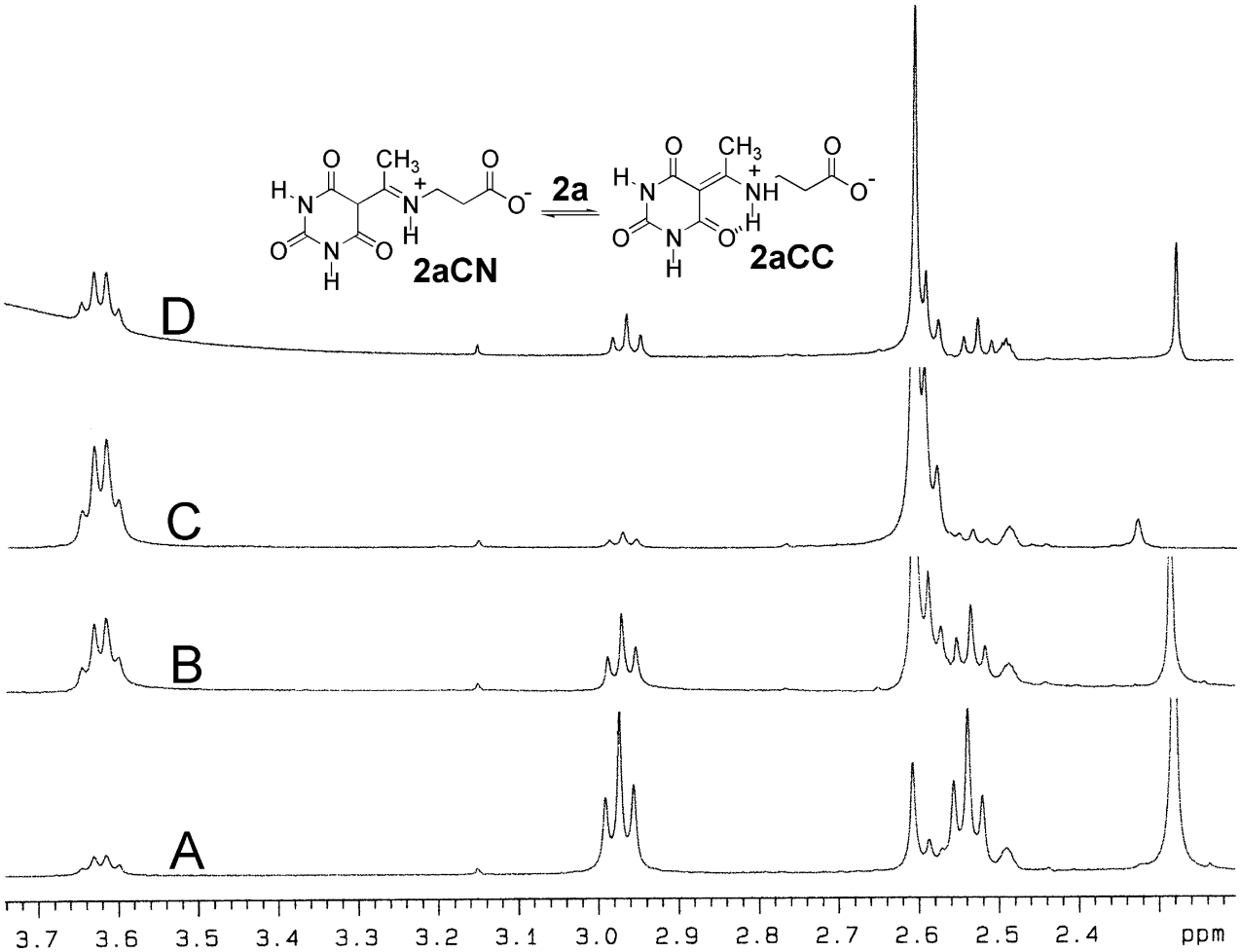
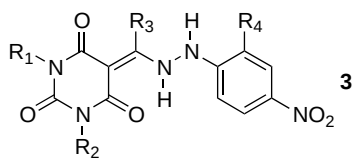


Figure 1. Change of equilibrium for two structural isomers of **2a**. (A) Isomers isolated from methanol reaction mixture. (B) Ratio of isomers after heating DMSO-d_6 NMR solution at 189°C for 1 min. (C) Same as B with heating for 3 min. (D) Solution was heated for 5 min with the solvent refluxing and the left at room temperature for approximately 8 h.

It was recently demonstrated that simple nitrophenylhydrazones of 4-hydroxybenzophenone have strong anticancer properties.[25] In binding capabilities to biomolecules, the barbituric acid moiety is superior to phenols. Therefore, it was of interest to develop a simple procedure for the preparation of phenylhydrazones with 5-formyl- and 5-acetylbarbiturates in relatively large quantities for biological studies (various cell assays an animal models for anticancer activity testing). Several variations of the procedures for the preparation of phenylhydrazones were tested to accomplish this task. The simplest and most effective are the direct condensation of the corresponding phenylhydrazine with 5-acylbarbiturates in methanol at elevated temperatures. After the reaction is completed (after a few hours of methanol refluxing) the isolation and purification of the product depends on the physical properties.[26] The optimized isolated yields for phenylhydrazones of barbituric acid derivatives are presented in Table 3.

In summary, a facile one-step synthetic procedure for the preparation of both formyl and acetyl barbituric

Table 3. Nitrophenylhydrazones of 5-formyl- and 5-acetylbarbiturates



3

	R_1	R_2	R_3	R_4	Yield (%)
3a	H	H	H	H	80
3b	H	H	H	NO_2	88
3d	C_6H_5	H	H	H	92
3e	C_6H_5	H	H	NO_2	93
3f	CH_3	CH_3	H	H	95
3g	CH_3	CH_3	H	NO_2	91
3h	H	H	CH_3	H	73
3i	H	H	CH_3	NO_2	86
3j	C_6H_5	H	CH_3	H	84
3k	C_6H_5	H	CH_3	NO_2	81
3l	CH_3	CH_3	CH_3	H	63
3m	CH_3	CH_3	CH_3	NO_2	84

acid in any desired quantity without protection–deprotection processes involved in the course of the preparation was developed. Very elegant high yield one-step preparations of Schiff bases from these acylbarbiturates, ω-aminoalkanoic acids and phenylhydrazines were developed. All of these compounds have value in medicinal chemistry and are now available as very inexpensive materials in large quantities. It was also demonstrated that barbituric acid-based Schiff bases in the form of the carbon–nitrogen double bond are not stable isomers, but rather the molecules exist in its extended conjugated form as the carbon–carbon double bond isomer.

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12. From a set of small-scale (2 mg of barbituric acid) NMR followed reactions, it is obvious that around 80% of barbituric acid is converted into 5-formylbarbituric acid. Unfortunately, the solubility of barbituric acid and 5-formylbarbituric acid in water and methanol as purification solvents are very similar, therefore to obtain pure 5-formylbarbiturates, a large quantity is lost during the elimination of starting materials through crystallization and washing with water and methanol. In the case of substituted barbituric acids such as 1,3-dimethylbarbituric acid, the conversion is higher than 85% and the lost amount of product during purification is substantially smaller.
13. **Method A**: Typical procedure for formylation of barbituric acid with chloroform: *The Reimer–Tiemann Reaction*. **Preparation of 5-formyl-1,3-dimethylbarbituric acid (1c)**. Into a 50% ethanol (400 mL) solution of potassium hydroxide (84 g; 1.5 mol), the chloroform (50 mL) solution of 1,3-dimethylbarbituric acid (33.6 g; 0.2 mol) was added. The reaction is exothermic and is controlled by an ice-water bath. A yellow precipitate forms almost immediately. The reaction suspension was stirred at room temperature for an additional 3 h, then cooled in ice water (~5°C). The solid was separated by filtration and was slurred in water (~100 mL), and the pH was adjusted to ~3 by adding concentrated hydrochloric acid. After cooling at ~5°C for 1 h, the solid was separated by filtration, washed with acetone (3×20 mL) and dried at 110°C for 0.5 h, resulting in pure product. If necessary, further purification can be performed by crystallization from a small amount of water–ethanol mixture. The yield of the white powdery product is 27.6 g (75%) ^{1}H NMR (DMSO-d_6–D_2O; 5:1) δ 9.639 (1H, s) and 3.049 ppm (6H, s); ^{13}C NMR (DMSO-d_6–D_2O; 5:1) δ 188.220, 148.527, 147.222, 97.092, and 24.052 ppm; MS-EI, m/z 184 (M^+, 20%), 169 ($(M-CH_3)^+$, 28%), 156 ($(M-CO)^+$, 39%), anal. calcd for $C_7H_8N_2O_4$ (MW 184.15): C, 45.66; H, 4.38; N, 15.21. Found: C, 45.34; H, 4.65; N, 15.02.
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15. For instance, 5-acetylbarbituric acid can be purchased from Aldrich Co. as a product in the Rare Chemical Library for the price of $50 for 50 mg.
16. **Method B**: Typical procedure for the preparation of 5-acetylbarbiturates. **Preparation 5-acetylbarbituric acid (1d)**. A mixture of barbituric acid (12.8 g; 0.1 mol) and acetic anhydride (300 mL) with a few drops of concentrated sulfuric acid was refluxed for 1 h. The reaction in the beginning is a suspension but after ~10 min of refluxing it changes color (orange) and becomes a solution. The reaction mixture was concentrated to 1/2 of its original volume and cooled at ~10°C (ice-water bath). The formed solid was separated by filtration, washed with hot water (3×25 mL), then acetone (3×25 mL), and dried

at 80°C for 30 min. The yield of yellow powder was 16.1 g (95%). ^{1}H NMR (DMSO-d_6) δ 11.768 (1H, s, NH), 11.035 (1H, s, NH), and 2.563 ppm (3H, s, CH_3); ^{13}H NMR (DMSO-d_6) δ 191.343, 168.146, 158.736, and 145.502 four different carbonyls, 91.913 (C-5 from barbituric acid), and 20.385 ppm (C from acetyl). MS (electrospray, ES$^+$, in methanol with 0.1% CH_3COOH) 215.2 (M+2Na) and 251.1 (M+Na+HOAc).

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19. Some of the barbituric acid derivatives show encouraging differentiation activity on the human leukemia cancer cell lines. Results will be published elsewhere.
20. Typical procedure for the preparation of Schiff bases with ω-aminoalkanoic acids and 5-acyl barbituric acids. **Preparation of 6-[(1,3-dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-ylmethylene)-amino]-hexanoic acid (2f)**. A mixture of 5-formyl-1,3-dimethylbarbituric acid (0.92 g; 5 mmol) and 5-aminohexanoic acid (0.655 g; 5 mol) in methanol (200 mL) was refluxed for 5 h. Methanol was evaporated to a solid residue and the solid residue was re-dissolved in a small amount of hot methanol ($\sim$50 mL). This solution was left at room temperature to slowly evaporate to 1/5 of the volume. The formed white needles of product were separated by filtration, washed with cold methanol (3×5 mL) and dried at 60°C for 30 min to afford the pure product. The yield is 1.3 g (87%). ^{1}H NMR (DMSO-d_6:D_2O=3:1)[19] δ 8.084 (1H, s), 3.414 (2H, d, J=6.7 Hz, NCH_2), 3.080 (6H, d, J=0.6 Hz, two NCH_3), 2.180 (2H, t, J=7.2 Hz), 1.489 (m, 4H), and 1.215 ppm (m, 2H); ^{13}C NMR (DMSO-d_6:D_2O=3:1) d 173 (-COO), 161.380, 160.484, and 156.653 (three carbonyls carbons from the barbituric acid ring), 149.465 (-CH=N-), 86.793 (C-5 from barbituric acid ring), 47.165 (N**C**H_2), 30.967, 26.714, 22.599, and 21.346 (four carbons of five methylene carbons of hexanoic acid moiety) and 25.068 and 24.412 ppm (two carbons of N-CH_3). MS (electrospray, ES$^+$, in methanol with 0.1% CH_3COOH), 320.1 and 320.3 (M+Na), 617.0 and 618.1 (2M+Na).
21. The ^{1}H NMR spectra of the Schiff base **2** strongly depend on the pH and the capability of the H–D exchange between **2** and the solvent. If ^{1}H NMR spectra are recorded in DMSO-d_6 then the hydrogen–hydrogen splitting signals for the zwitterionic form of the Schiff base **2** are observed. For instance, in the ^{1}H NMR spectra of **2f** at 10.30 ppm there is a double splitting of the triplet for CH=N**H**-CH_2-, at 8.2 ppm a doublet for -C**H**=NH-, and a double triplet for NH-CH_2-CH_2-. Due to the hydrogen–deuterium exchange in DMSO-d_6–D_2O (3:1) as an NMR solvent (NH is now mostly ND) the spectra is changed. There is no NH signal and therefore CH= becomes a singlet and N-CH_2- is a simple triplet.
22. Schiff bases made from 5-acetylbarbituric acids have substantially lower solubility in methanol than ones made from 5-formyl-1,3-dimethybarbituric acid. All three compounds of this series (**2a**, **2b**, and **2c**) are not soluble at 5 mmol concentration per 200 mL of refluxing methanol. These compounds are isolated as crystalline products by filtration of the hot reaction suspension. They are $\sim$98% pure. If necessary, these compounds can be further purified by crystallization from acetic acid.
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24. The structural assignment was based on the chemical shifts for β-alanine in DMSO-d_6 as the NMR solvent. Reference for the chemical shift is the middle signal of the five signals for DMSO as the solvent at 2.49 ppm. β-Alanine is slightly soluble in DMSO. All hydrogens on the nitrogens are exchanged with deuterium from the solvent, therefore besides the two huge signals for the solvent and water, two additional triplets, one at 2.798 ppm (J=4.5 Hz) for -N**C**H_2- and the other at 2.060 ppm (J=4.5 Hz) for -CH_2CO- are observed. With the assumption that the chemical shifts for -N**C**H_2- of **2a** in its carbon–carbon double bond isomer **2a C–C** is similar to β-alanine, the chemical shift at 2.973 ppm is assigned to -N**C**H_2- in the **2a C–C** isomer and the chemical shifts at 3.632 and 3.616 ppm to -NHCH_2- in the **2a C–N** isomer.
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26. Table 3: Usually preparation of nitrophenylhydrazones of barbituric acids involve refluxing the corresponding hydrazine and 5-acylbarbituric acid in methanol, followed by the isolation and purification of the product. Physical properties of the product determine what procedure will be used for the hydrazone isolation and purification. **Preparation of 5-[(4-nitrophenyl)hydrazonomethyl]-pyrimidine-2,4,6-trione (3a)**. A methanol (200 mL) suspension of 5-formylbarbituric acid (1.56 g; 10 mmol) and 4-nitrophenylhydrazine (1.53 g; 10 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water, washed with methanol and crystallized from acetic acid (500 mL) to give 2.3 g (80%) of pure compound. ^{1}H NMR (DMSO-d_6) δ 11.22 (1H, broad singlet), 10.847 (1H, s), 10.749 (1H, s), 9.859 (1H, s), 8.123 (2H, d, J=9.0 Hz), 7.985 (1H, s), and 6.819 (2H, d, J=9 Hz) ppm; ^{13}C NMR (DMSO-d_6) δ 155.488, 150.018, 147.163, 136.005, 122.196, 108.227, 108.227, and 87.062 ppm; anal. calcd for $C_{11}H_9N_5O_5$ (MW 291.2): C, 45.37; H, 3.11; N, 24.05. Found: C, 45.04; H, 3.38; N, 23.88%.