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Mono *C*-alkylation and mono *C*-benzylation of barbituric acids through zinc/acid reduction of acyl, benzylidene, and alkylidene barbiturate intermediates

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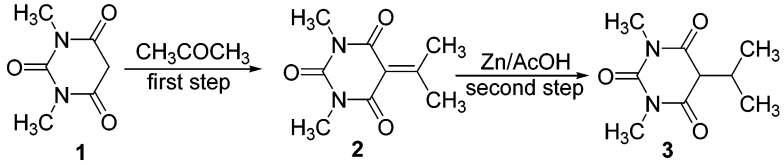
Abstract—Through systematic exploration of reaction conditions, very efficient preparative procedures for obtaining large quantities of substituted 5-alkyl and 5-benzylbarbituric acids were developed. The procedure involves a two step preparation in which the second step is zinc dust/acid reduction. For preparation of 5-alkylbarbiturates, the first step is the preparation of either 5-acyl or 5-alkylidenebarbiturate. If 5-benzylbarbiturate is the target product, then the first step includes the preparation of 5-benzylidene. Regardless of the nature of the first step, all reactions presented synthetic yields around 90% and isolation and purification involves only crystallization.

5-Alkylated and benzylated barbituric acid derivatives are proven to be valuable pharmaceuticals or important intermediates in the preparation of other pharmaceuticals.[1] Subsequently, there are many available synthetic procedures for their preparations.[2] One of the main targets of preparative organic chemistry is to develop simple, safe, environmentally friendly, and inexpensive procedures for synthesis of valuable organic compounds. Our major research is to utilize barbituric acid and 1,3-disubstituted barbituric acid to obtain new structurally diverse heterocycles with the barbituric acid moieties incorporated. Unsubstituted barbituric acid (pyrimidine-2,4,6-trione) are ideal starting materials for the preparation of a diverse number of heterocyclic compounds. They are inexpensive and readily available, or if necessary are quite easily prepared.

An ideal synthetic approach in the preparation of any derivative of barbituric acid is by substitution of one or all of its four protons (two on nitrogen in 1 and 3-positions, and two on the carbon atom in the 5-position). In the past, we have successfully developed procedures for *N*-alkylation of 5,5-disubstituted barbituric acid[3] and reductive *C*-alkylation[4] of barbituric acid analogs by catalytic (palladium or platinum) hydrogenation of barbituric acid benzylidenes. Now we are reporting a much more simplified procedure for the reductive 5-benzylation and 5-alkylation of barbituric acid derivatives with zinc in acetic acid.

The source of alkylation on C5 of barbituric acid should be aliphatic aldehydes or ketones, as reported in the cases of Pt/C catalytic alkylation of barbituric acids. To explore the Zn/AcOH approach for the 5-alkylation of barbituric acid we used the catalytic H_2/Pt-C conversion of 1,3-dimethylbarbituric acid and acetone into 5-isopropyl-1,3-dimethylbarbituric acid (**3**)[5] as a standard reaction for comparison. Our attempts to perform the two step preparation of **3**, first by generating 5-isopropylidene-1,3-dimethylbarbituric acid (**2**) followed by its Zn/AcOH reduction as demonstrated in Scheme 1, was not successful. Reduction of



Scheme 1. An example of two step reductive alkylation of barbituric acid.

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the CC double bond by Zn/AcOH was not accomplished. During the course of the realization of the synthetic path in Scheme 1, several procedures for the preparation of **2** in acid conditions were investigated.[6] To the best of our knowledge, there are no reported literature procedures for the preparation of isopropylidene **2.**

By monitoring the H_2/Pt-C reaction by NMR spectroscopy, it was determined that both isopropanol and diisopropylether are byproducts of the hydrogenation. Due to their physical properties, they can easily be separated from the target product **3** therefore, the preparation procedure was not complicated. This finding suggested that isopropanol in the presence of a strong acid, such as sulfuric acid, might be an alkylating reagent for barbituric acid derivatives. Unfortunately, our attempts to *C*-alkylate barbituric acid and 1,3-dimethyl barbituric acid with isopropanol in the presence of sulfuric acid, trifluoromethanesulfuric acid, and polyphosphoric acid were not successful. Instead, a small amount of *O*-alkylation product ($\sim$30%) was isolated in sulfuric acid. The same results were obtained with zinc dust used as a catalyst.

It is reasonable to use 5-acylbarbiturates, as precursors for the preparation of 5-alkylbarbiturates pending that 5-acylbarbiturates are readily available. Previously, we developed procedures for inexpensive large quantity preparations of both 5-formyl and 5-acetylbarbituric acid derivatives.[7] Therefore, through the reduction of these compounds, one should be able to obtain the corresponding 5-alkylbarbituric acid. Under 5%Pd/C catalytic hydrogenation in an acetic acid-sulfuric acid media we were not able to detect any of the product of reduction. About 5% of the reduction product was detected after 24 hours if the reduction was performed with hydrogen and 5%Pt/C in same reaction media. Even when the reaction time (three days) was prolonged, there was not a substantial increase in the percentage of the product of reduction. If 5-acylbarbituric acid derivatives were to be precursors for the preparation of 5-alkylbarbituric acid, then other simple reducing reagents must be explored.

Clemmensen reduction of carbonyl groups of ketones to methylene groups with zinc amalgam and hydrochloric acid is well documented in literature.[8] Our attempts to reduce 5-acetyl-1,3-dimethylbarbituric acid with zinc dust in acetic acid, in acetic acid with concentrated hydrochloric acid and in acetic acid with sulfuric acid was not successful. Therefore, we have performed the NMR reaction following for the 5-acetyl-1,3-dimethylbarbituric acid reduction. Many different solvents and reduction conditions were explored, and the best results were obtained by zinc dust reduction in D_2O-concentrated hydrochloric acid (Fig. 1).[9] Due to the proton exchange with D^+ of the media, two singlets (one for NCH_3 and one for $COCH_3$) of **4d** were observed. The reaction is exceptionally fast and is practically over after 10 minutes, producing only one product. In the course of the reduction in the D_2O-H_2O reaction media, deuterium is partially incorporated into the ethyl moiety of **5d**. The results are that the methyl group is actually a doublet and methylene group is a low intensity triplet. Nevertheless, the course of the reaction is clearly demonstrated by the shifting NCH_3 singlet of **4d** from 3.27 to 3.24 ppm of **5d** (Fig. 1). Almost identical reaction conditions were used for the preparation of 5-alkylbarbituric acid **5** by zinc dust- hydrochloric acid reduction of acylbarbiturate **4**.[10] It is interesting to mention that under the same reaction conditions (zinc dust in concentrated hydrochloric acid at room temperature) we were not able to reduce the keto group of 1-benzoylbarbituric acid. Instead, the unchanged starting material was isolated from reaction mixture. It seems that under these conditions, aromatic barbituric acid ketones are more resistant to reduction (Table 1).

In some of our previous synthetic applications of barbituric acid derivatives, we have demonstrated that condensation of barbituric acid derivatives with aromatic aldehydes is a simple and straightforward synthetic procedure.[11] In the majority of cases the corresponding benzylidenes are obtained. If it is possible to use simple zinc dust in combination with a modest acid to reduce the benzylidene double bond, then these compounds might become viable starting materials for the preparation 5-benzylbarbituric acid derivatives. Many reaction conditions (zinc dust in combination with hydrochloric acid, trifluoroacetic acid, acetic acid, acetic acid/sulfuric acid, acetic acid/hydrochloric acid) were explored through NMR reaction following. The optimized reaction conditions are shown in Figure 2 for benzylidene

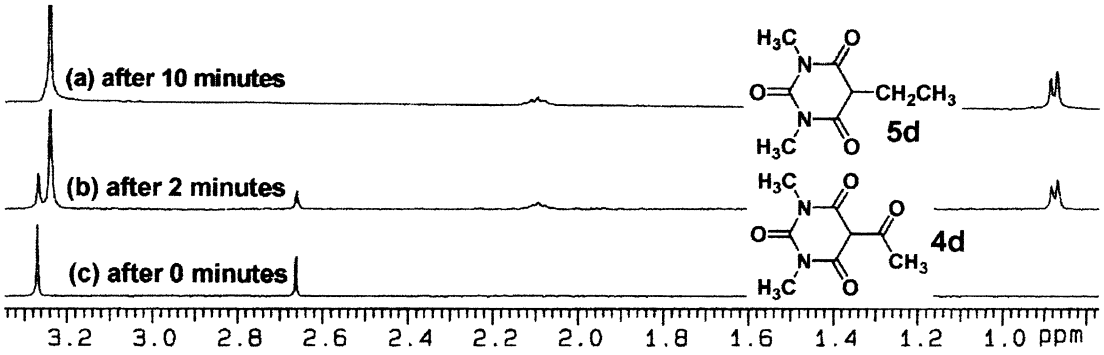
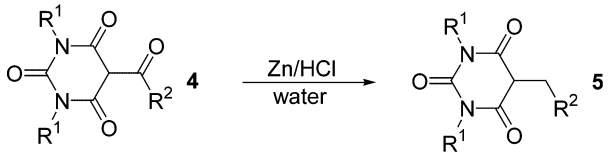


Figure 1. NMR reaction following of **4d** reduction with zinc dust in aqueous hydrochloric acid.

Table 1. Isolated yields of 5-acetylbarbituric acid **5**



Entry	R^1	R^2	5-Acylbarbiturate	5-Acetylbarbiturate	Yield (%)
1	H	H	**4a**	**5a**	87
2	CH_3	H	**4b**	**5b**	91
3	H	CH_3	**4c**	**5c**	88
4	CH_3	CH_3	**4d**	**5d**	96
5	H	$-(CH_2)_8CH_3$	**4e**	**5e**	93
6	CH_3	$-(CH_2)_8CH_3$	**4f**	**5f**	97

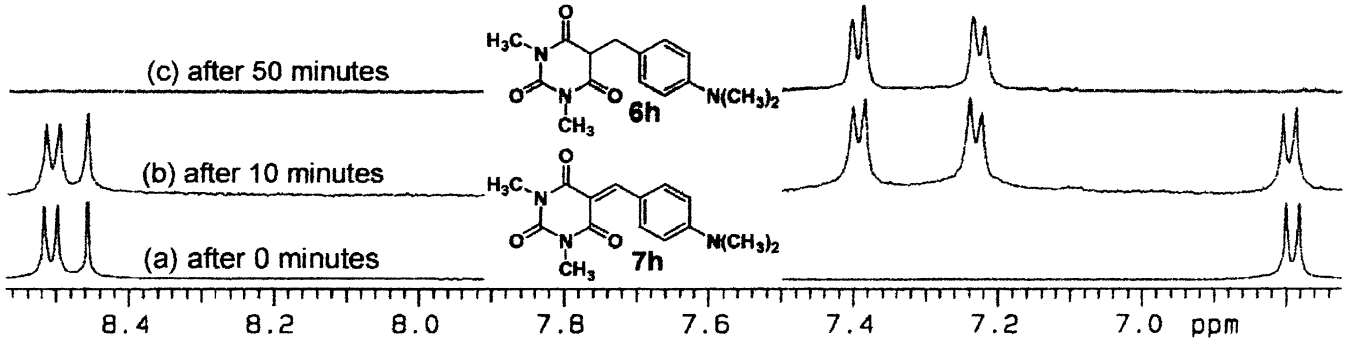


Figure 2. The NMR (CD_3CO_2D, 500 MHz) reduction monitoring of **6h** with Zn-CD_3CO_2D at room temperature.[12]

6h NMR reaction following. It appears that room temperature zinc-acetic acid reduction over a period longer than one hour is optimal for the preparation of benzylbarbiturates. After approximately 10 minutes, reduction is 50% completed and after approximately one hour the reaction is practically completed.

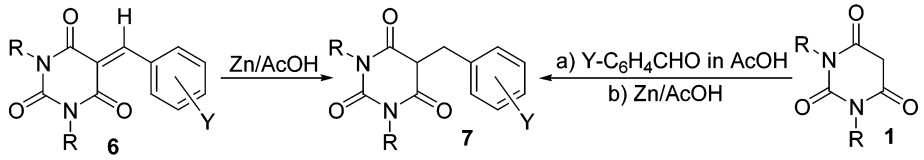
The first step in the preparation of 5-benzylbarbituric acid derivatives **7** involves the preparation of barbituric acid benzylidene **6**.[13] The formed benzylidene is then subjected to zinc dust reduction in acetic acid.[14] It is not necessary to isolate the intermediate barbituric acid benzylidene **6** from the reaction mixture (acetic acid solution for $R=CH_3$ or acetic acid suspension for $R=H$, Table 2). After the condensation is accomplished, zinc dust is added into the acetic acid mixture for completion of the one pot synthesis.[15] Regardless of the way the reduction is performed, the isolation of the product includes a simple filtration, evaporation of the reaction solvent, and crystallization of the solid residue from either methanol or ether. Isolated yields are almost quantitative (Table 2).

As mentioned above, we were not able to utilize neither aliphatic aldehydes nor aliphatic ketones for the 5-alkylation of barbituric acids due to difficulties in the transformation into the alkylidene of barbituric acid. We believed that once the barbituric acid alkylidene was formed, then zinc dust-acetic acid reduction should yield to 5-alkylbarbituric acid. Obviously, aliphatic aldehydes have too low reactivity in the condensations with barbituric acids. This is not true for α,β-unsaturated aldehydes. Once the condensation product with two conjugated double bonds **8** is formed, its zinc-acetic acid reduction should provide 5-alkylated barbituric acid. To establish this synthetic approach, the condensation reaction between cinnamaldehyde and barbituric acid, followed by the zinc-acetic acid reduction was followed by NMR spectroscopy. The reaction was performed in acetic acid and few drops of this reaction mixture was used for NMR reaction following.[16] The NMR reaction following for this condensation is presented in Figure 3. After twelve hours at room temperature *trans*-cinnamaldehyde is fully converted into alkylidene barbituric acid **9d**. Reduction with zinc dust in acetic acid is practically over after three hours.

The isolated yields some of the 5-alkylbarbituric acid **9** prepared by zinc dust-acetic acid reduction are presented in Table 3. All of the synthetic procedures combined two step reactions with isolation of the intermediate conjugated alkylidene **8** in 80–95% yield.[17] The isolated yields for the second step in the reaction for the preparation of **9** are between 83 and 94% (Table 3).[18]

Finally, we decided to test our synthetic approach on barbituric acid derivatives with the two separated double bonds of barbituric acid dibenzylidenes **10** (Table 4). The starting double benzylidenes **10** were prepared from 1,ω-benzenedicarbaldehydes and the correspond-

Table 2. Isolated yields of 5-benzylbarbituricacid derivatives **7**



Entry	R	Y	Benzylidine **6**	Benzyl **7**	Yield (%)[a]	Yield (%)[b]
1	H	H	**6a**	**7a**[c]	92	88
1	CH_3	H	**6b**	**7a**[c]	94	84
2	H	4-OH	**6c**	**7c**[c]	88	81
3	CH_3	4-OH	**6d**	**7d**[c]	86	82
4	H	4-OCH_3	**6e**	**7e**[c]	88	84
5	CH_3	4-OCH_3	**6f**	**7f**[d]	90	84
6	H	4-$N(CH_3)_2$	**6g**	**7g**[e]	95	86
7	CH_3	4-$N(CH_3)_2$	**6h**	**7h**[e]	97	88
8	H	2,4-Di-OCH_3	**6i**	**7i**[d]	98	84
9	CH_3	2,4-Di-OCH_3	**6j**	**7j**[e]	96	92
10	H	3,4,5-Tri-OCH_3	**6k**	**7k**[d]	95	86
11	CH_3	3,4,5-Tri-OCH_3	**6l**	**7l**[e]	94	89

[a] Starting with benzylidene **6**.
[b] Starting with substituted benzaldehyde.
[c] Purified by refluxing and washing with hot methanol.
[d] Purified by crystallization from methanol.
[e] Purified by crystallization from ether.

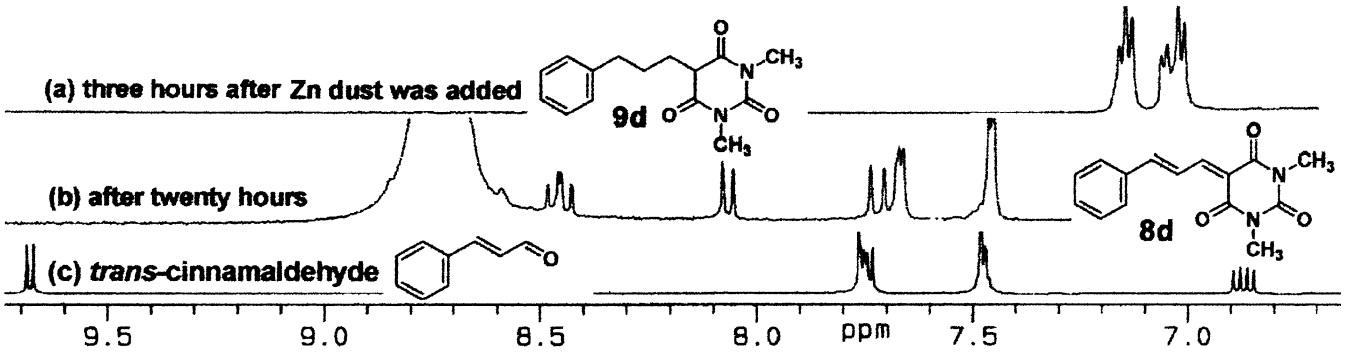
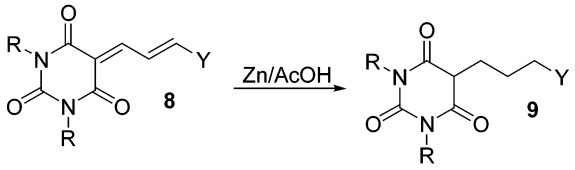


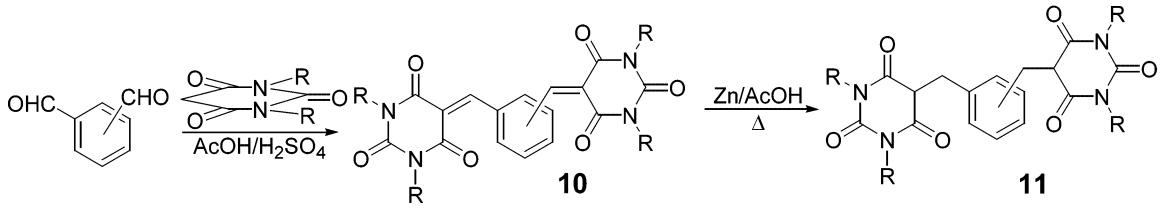
Figure 3. Step by step NMR reaction following of formation and zinc-acetic acid reduction of **8d**.

Table 3. Preparation of 5-alkylbarbituric acid **9** by reducing conjugated alkylidenes **8**



Entry	R	Y	Alkylidene **8**	Product **9**	Yield (%)
1	H	CH_3	**8a**	**9a**	83
2	CH_3	CH_3	**8b**	**9b**	88
3	H	C_6H_5	**8c**	**9c**	91
4	CH_3	C_6H_5	**8d**	**9d**	94
5	H	4-$(CH_3)_2NC_6H_4$	**8e**	**9e**	90
6	CH_3	4-$(CH_3)_2NC_6H_4$	**8f**	**9f**	93
7	H	2-$CH_3OC_6H_4$	**8g**	**9g**	91
8	CH_3	2-$CH_3OC_6H_4$	**8h**	**9h**	94

Table 4. Isolated yields for **10** and **11**



Entry	R	Position	Alkylidene **10**	Yield (%) of **10**	Alkyl **11**	Yield (%) of **11**
1	H	1,3	**10a**	92	**11a**	87
2	CH_3	1,3	**10b**	94	**11b**	92
3	H	1,4	**10c**	93	**11c**	91
4	CH_3	1,4	**10d**	95	**11d**	90

ing barbituric acids in acetic acid-sulfuric acid as the reactive media. Due to the low solubility of the condensation product in the reaction media, isolation yields are higher than 90%.[19] Low solubility of both **10** and **11** in acetic acid is also the reason why the reaction was performed with **10** not fully soluble in acetic acid (suspension), accounting for why the reaction mixture was refluxed.[20]

To fully characterize the prepared compounds by zinc dust reduction we have selected the largest molecule, product **11d** for X-ray structural analysis.[21] The single crystal for the X-ray analysis was grown by slow crystallization from methanol. The obtained structure fully agrees with our determined structure by NMR and elemental analysis. This structure has several very interesting characteristics. The molecule seems to be 'squeezed' into a ball conformation to occupy as little space as possible. This is perfectly demonstrated in that both barbituric acid rings are not planar. They have a slight boat conformation to bring both -NCON- (urea) moieties closer to the middle of 1,4-phenylene ring (Fig. 4), indicating weak nonbonding interactions between barbituric acid and phenyl moieties of **11d**.

It can be concluded that during the systematic exploration of the reaction conditions by the NMR reaction following experiments, it was possible to develop a very efficient synthetic procedure for the preparation of large quantities of 5-substituted barbituric acid derivatives. Regardless of the nature of the reaction intermediate, 5-acyl, 5-benzylidene, or 5-alkylidenebarbituric acid, the second step in the two step preparation involves high yield and high purity zinc dust acid reduction. Considering that starting materials (barbituric acid, acid chlorides, and aldehydes) are inexpensive and readily available and that purification of the product is accomplished by crystallization, the presented synthetic procedures are applicable to large scale (industrial) preparations of this compounds.[22]

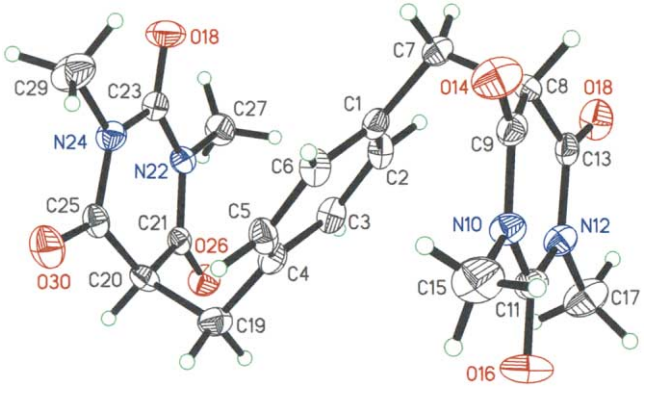


Figure 4. X-ray determined structure of **11d**.

Acknowledgements

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References

1. Barbituric acid derivatives (barbiturates) are a family of drugs that depress nerve activity in the brain producing changes in mental activity ranging from mild sedation and sleep, to deep coma. Commonly they are used to treat anxiety, insomnia, seizure disorders, migraine headaches, and use is surgery as general anesthetics. For general information see: Olin, B. R., Ed.; Central Nervous System Drugs, Sedatives and Hypnotics, Barbiturates. In *Facts and Comparisons Drug Information*. St. Louis, MO: Facts and Comparisons, 1993; pp. 1398–413.
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4. Jursic, B. S.; Neumann, D. M. *Tetrahedron Lett*. **2001**, *42*, 4103.
5. **Preparation of 5-isopropyl-1,3-dimethybarbituric acid (3)**. Although we have previously mentioned this product in Table 1 of Ref. 2, the exact procedure, isolation and characterization of this compound was not mentioned.

Therefore, here we are presenting detailed synthetic procedure and characterization of 5-isopropyl-1,3-dimethylbarbituric acid. 1,3-Dimethylbarbituric acid 1.56 g (0.01 mol) was dissolved in acetone (200 ml) and 5%Pt/C with 50% water was added (0.3 g). Into the black suspension concentrated sulfuric acid was added and the reaction suspension was shaken at 75 psi hydrogen pressure for 48 hours. Catalyst was separated by filtration and washed with acetone (3×20 ml). Combined acetone filtrates were evaporated to dryness and solid product was crystallized from methanol (50 ml). Formed white crystals were separated by filtration giving 1.82 g (92%) product. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.414 (1H, d, $J=4$ Hz, CH), 3.132 (6H, s, NCH_3), 2,418 (1H, m, C**H**$(CH_3)_2$) and 0.966 ppm (6H, d, $J=7.5$ Hz, $C(CH_3)_2$); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 168.4 and 151.8 (two different CO), 54.5, 32.6, 27.8, and 19.3 ppm (four different aliphatic carbons). Anal. calcd. For $C_9H_{14}N_2O_3$ (MW 198.22): C, 54.53; H, 7.12; N, 14.13. Found: C, 54.32; H 7.25, N 14.06.

6. Acetone was used as a solvent (large excess) for isopropylidene formation with acid in 10 fold excess such as acetic acid, trifluoroacetic acid, sulfuric acid, trifluoromethanesulfonic acid, and in polyphosphoric acid. Even strongly acidic DOWEX 50W-X8 was used as a catalyst after it was dried by continuos benzene evaporation. In the last case through NMR study of the reaction mixture, we were able to detect traces of isopropylidene barbituric acid.
7. Jursic, B. S.; Neumann, D. M. *Tetrahedron Lett*. **2001**, *42*, 8435.
8. (a) Clemmensen *Ber*. **1913**, *46*, 1837; (b) Martin, E. L. *Org*. *React*. **1942**, *1*, 155.
9. 5-Acetyl-1,3-dimethylbarbituric acid **4d** is soluble in concentrated hydrochloric acid. 2 mg (0.01 mmol) of acetylbarbituric acid **4d** was dissolved in 1 ml of concentrated hydrochloric acid. This solution was diluted with 2 ml of D_2O and used to record NMR spectra on 500 MH Varian UNITY as a starting point in NMR following experiment through water suppression signal. Proton in 5-postion of barbituric acid ring is exchanged by deuterium from the reaction media therefore two singlets were observed. Chemical shift for higher intensity singlet (NCH_3) were placed to 3.27 ppm to correspond it to chemical shift in pure $CDCl_3$. Reaction mixture was poured over zinc dust (100 mg) with the immediate formation of hydrogen bubbles noted. Clear solution over zinc dust occured after 2 minutes and after 10 minutes was pipetted for NMR reaction following.
10. General procedure for reduction of 5-acylbarbiturates. **Preparation of 5-ethyl-1,3-dimethylbarbituric acid (5d)**. Concentrated hydrochloric acid (50 ml) solution of 5-acetyl-1,3-dimethylbarbituric acid (1.98 g; 0.01 mol) was slowly added into water (50 ml) suspension of zinc dust (2 g). Reaction suspension was vigorously stirred at room temperature for thirty minutes and extracted with chloroform (4×50 ml). Combined chloroform extracts were dried over anhydrous sodium carbonate and evaporated. Oily residue was crystallized from methanol (20 ml) to allow methanol to slowly evaporate at room temperature and atmospheric pressure. The yield of **5d** is 1.77 g (96%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.419 (t, 1H, $J=5$ Hz, CH), 3.243 (6H, s, N-CH_3), 2.123 (2H, d-t, $J_1=5$ Hz, $J_2=7.5$ Hz, CH_2), and 0.867 ppm (3H, t, $J=7.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 168.71, 151.76 (two different carbonyls), 50.08, 28.52, 24.86 and 10.41 ppm (four different sp^3 carbons). Anal. calcd. For $C_8H_{12}N_2O_3$ (184.19): C, 52.17; H, 6.57; N, 15.21. Found: C, 52.05; H 6.83, N 15.12.
11. Jursic, B. S. *J. Heterocyclic Chem*. **2001**, *38*, 655.
12. The NMR sample is prepared by mixing 2.5 mg (0.01 mmol) of **6h** in 1 ml CD_3CO_2D. This solution was used for recording reference spectra (0 time in Fig. 1). In this solution zinc (6.5 mg; 0.1 mmol) was added and the zinc addition time was used as 0 time for monitoring the reaction.
13. Typical procedure for preparation of barbituric acid benzylidenes **6**. **Preparation of 5-(4-methoxybenzylidene)-1,3-dimethylpyrimidine-2,4,6-trione (6f)**. Acetic acid (150 ml) solution of 4-methoxybenzaldehyde (2.72 g; 0.02 mol) and 1,3-dimethylbarbituric acid (3.12 g; 0.02 mol) was refluxed for two hours. Yellow reaction mixture was concentrated to ~30 mL and the resulting yellow suspension left at room temperature overnight. Solid was separated by filtration, washed with ice-cold methanol (3×10 ml) and dried at 110°C for one hour. The yield of the product is 4.8 g (93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.449 (1H, s, CH), 8.291 (2H, d, $J=9$ Hz, *o*-CH), 6.941 (2H, d, $J=9.0$ Hz, *m*-CH), 3.875 (3H, s, OCH_3), 3.368 (3H, s, NCH_3), and 3.350 ppm (3H, s, NCH_3). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 164.39, 163.17, 161.05, 158.79, 151.49, 138.06, 125.65, 114.43, 114.06, 55.72, 29.12, and ppm 28.45 (twelve different carbon atoms). Anal. calcd. For $C_{14}H_{14}N_2O_4$ (274.27): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.12; H 5.22, N 10.08.
14. Typical procedure for zinc dust-acetic acid reduction of barbituric acid benzylidenes. **Preparation 5-(4-methoxybenzyl)-1,3-dimethylpyrimidine-2,4,6-trione (7f)**. Acetic acid (150 ml) suspension of benzylidene **6f** (2.74 g, 0.01 mol) and zinc dust (6.4 g; 0.1 mol) was stirred at room temperature for three hours. Acetic acid solution was separated by filtration. Gray solid was washed with acetic acid (3×20 ml). Combined filtrates were evaporated and solid residue was crystallized from methanol. The yield of **7f** is 2.47 g (90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.931 (2H, d, $J=8$ Hz, *o*-CH), 6.738 (2H, D, $J=8$ Hz, *m*-CH), 3.742 (3H, s, OCH_3), 3.717 (1H, t, $J=5$ Hz, CH), 3.393 (2H, d, $J=5$ Hz), and 3.118 ppm (6H, s, NCH_3). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 159.22, 151.15 (two different carbonyl carbons), 139.50, 130.09, 127.15, 114.05 (four aromatic carbons), 55.28 (methoxy carbon), 50.97 (5-C of barbituric acid ring), 37.21 (methylene carbon), and 28.29 ppm (NCH_3 carbon). Anal. calcd. For $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14. Found: C, 60.64; H, 5.96; N, 10.02.
15. Typical one pot preparation procedure of **7**. **Preparation of 5-(4-methoxybenzyl)pyrimidine-2,4,6-trione (7e)**. Acetic acid (200 ml) solution of barbituric acid (1.28 g; 0.01 mol) and 4-methoxybenzaldehyde (1.36 g; 0.01 mol) was refluxed for three hours. Reaction mixture was allowed to cool to room temperature. Benzylidene **6e** product partially precipitates from the reaction mixture. Into this reaction suspension zinc dust was added (6.4 g;0.1 mol) and resulting suspension was stirred at room temperature. Solution over gray (zinc) sediment is colorless. Liquid was separated by filtration and solid was washed

with acetic acid. Combined filtrates were evaporated under reduced pressure. Solid residue was refluxed with methanol (30 ml). Insoluble solid was separated by filtration, washed with methanol (3×20 ml) and dried at 110°C for one hour to afford 2.08 g (84% yield) pure product. ^{1}H NMR (DMSO-d_6, four drops of H_2SO_4, 400 MHz) δ 11.08 (2H, NH), 6.89 (2H, d, $J=8.0$ Hz), 6.72 (2H, d, $J=8.0$ Hz), 3.72 (1H, t, $J=4.0$ Hz), 3.59 (3H, s, OCH_3), and 3.10 ppm (2H, d, $J=4.0$ Hz, CH_2). ^{13}C NMR (DMSO-d_6, four drops of H_2SO_4, 400 MHz) δ 167.41, 155.36 (two different carbonyls), 147.89, 127.35, 126.08, 111.04 (four different aromatic carbons), 52.30, 46.79 and 30.28 ppm (three different aliphatic carbons).

16. Acetic acid (100 ml) solution of cinnamaldehyde (26.4 mg; 0.1 mmol) and 1,3-dimethylbarbituric acid (15.6 mg) was stirred at room temperature. Every hour two drops of the reaction mixture were dissolved in 0.6 ml of DMSO-d_6. To make this prepared NMR sample a clear solution, a few drops of CF_3SO_3H were added. After all starting aldehyde is transferred into condensation product **8d** zinc dust (640 mg; 10 mmol) was added into reaction mixture and reaction progress is again monitored by NMR spectroscopy in DMSO-d_6–CF_3SO_3H.
17. All barbituric acid alkylidenes **8** are prepared from corresponding α,β-unsaturated aldehyde and barbituric acid following typical procedures for preparation of **8d**. **Preparation of 1,3-Dimethyl-5-(3-phenylallylidene)pyrimidine-2,4,6-trione (8d)**. Acetic acid (200 ml) solution of cinnamaldehyde (2.64g; 0.02 mol) and 1,3-dimethylbarbituric acid (3.12 g; 0.02 mol) was refluxed for one hour. Formed yellow suspension was concentrated to volume of about 30 ml and cooled to room temperature. Solid was separated by filtration, washed with ice-cold methanol (3×15 ml) and dried at 110°C for one hour to afford 4.9 g (91%) of pure product. ^{1}H NMR ($CDCl_3$, 500Mz) δ 8.456 (1H, d+d, $J_1=12.5$ Hz, $J_2=11.5$), 8.060 (1H, d, $J=11.5$), 7.542 (2H, m), 7.29 (4H, m), and 3.249 (3H, s, NCH_3), 3.247 ppm (3H, s, NCH_3). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 162.33, 161.75, 157.32, 154.29, 151.52, 135.44, 131.60, 129.22, 127.82, 125.20, 114.68, 28.80, and 28.17 ppm (twelve different carbon atoms). Anal. calcd. For $C_{15}H_{14}N_2O_3$ (270.28): C, 66.66; H, 5.22; N, 10.36. Found: C, 66.41; H, 5.38; N, 10.24.
18. Typical procedure for zinc-acetic acid reduction of barbituric acid alkylidenes **8**. **Preparation 1,3-dimethyl-5-(3-phenylpropyl)pyrimidine-2,4,6-trione (9d)**. Acetic acid suspension (200 ml) of alkylidene **8d** (2.7 g 0.01 mol) and zinc dust (6.4 g; 0.1 mol) was stirred at room temperature overnight. Liquid over gray sediment of the reaction suspension is colorless. Solid was separated by filtration and washed with acetic acid (3x50 ml). Combined filtrates were evaporated to solid residue. Solid residue was crystallized from methanol to afford 2.58 g (94%) pure product. ^{1}H NMR($CDCl_3$, 500 MHz) δ 7.234 (2H, t, $J=7.0$ Hz, *m*-H), 7.052 (1H, t, $J=7.5$ Hz, *p*-H), 6.987 (2H, t, $J=6.5$ Hz, *o*-H), 3.258 (1H, t, $J=5$ Hz, CH), 2.457 (2H, t, $J=7.5$ Hz, CH_2Ph), 1.783 (2H, d+t, $J_1=7.5$, $J_2=5$ Hz, $CHCH_2$), and 1.544 ppm (2H, m, CH_2). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 170.79, 150.83, 140.83, 128.50, 128.33, 126.19, 76.37, 41.38, 35.07, 29.03, and 24.40 ppm (eleven different carbon atoms). Anal. calcd. For $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.52; H, 6.72; N, 10.11.
19. Preparation of alkylidenes **10** is very simple but due to their low solubility in most common organic solvents, the NMR spectroscopic determination of their purity is carried out in concentrated sulfuric acid with three drops of DMSO-d_6. When a drop of DMSO was added, immediately orange precipitate was formed. **Typical procedure for preparation of 10, preparation of 5,5′-[1,4-phenylenedi-(methylylidene)]bis(1,3 - dimethylpyrimidine - 2,4,6 - trione (10d)**. Acetic acid (400 ml) solution of 1,4-benzenedicarbaldehyde (0.67 g; 5 mmol), 1,3-dimethylbarbituric acid (1.56 g; 10 mmol), and sulfuric acid (0.3 ml) was refluxed for one hour. Immediately color of the reaction mixture changes to orange and an orange precipitate starts to form. Reaction suspension was reduced to $\frac{1}{4}$ of its original volume and solid was separated from hot reaction suspension by filtration. Solid yellow product was washed hot acetic acid (3×20 ml), hot methanol (3×20 ml) and dried at 110°C for two hours to afford 1.95 g (95%). ^{1}H NMR (H_2SO_4, three drops of DMSO-d_6, 500 MHz) δ 8.262 (2H, s, vinyl CH), 7.316 (4H, s, aromatic H), 2.913 (6H, s, NCH_3), and 2.810 ppm (6H, s, NCH_3); ^{13}C NMR (H_2SO_4, three drops of DMSO-d_6, 500 MHz) δ 166.04, 165.90, 165.82 (three different carbonyls), 162.36, 151.50 137.13, 132.51, 116.80 (five different CC double bond carbons), 30.86 and 30.04 ppm (two different NCH_3 carbons). Anal. calcd. For $C_{20}H_{18}N_4O_6$ (410.38): C, 58.53; H, 4.42; N, 13.65 Found: C, 58.36; H, 4.57; N, 13.41.
20. Typical procedure for reduction of dimethylidenes **10**. **Preparation 5,5′-[1,4-phenylenedi(methylene)]bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (11b)**. Acetic acid (500 ml) suspension of 5,5′-[1,4-phenylenedi(methylylidene)]bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (**10d**) (1.025 g; 0.0025 mol) and zinc (3.2g; 0.05 mol) was refluxed for three hours. From still refluxing suspension solid residue was separated by filtration and washed with hot acetic acid (3×50 ml). Combined acetic acid filtrates were evaporated to solid residue. White solid product was crystallized from methanol to afford 0.93 g (90%) pure product. ^{1}H NMR (DMSO-d_6, four drops of H_2SO_4, 400 MHz) δ 6.81 (4H, s), 3.91 (2H, t, $J=4.4$ Hz), 3.15 (4H, d, $J=4.4$ Hz), and 2.90 ppm (12H, s, NCH_3). ^{13}C NMR (DMSO-d_6, four drops of H_2SO_4, 400 MHz) δ 165.43 and 148.20 (two different carbonyl carbons), 132.40 and 125.86 (two different aromatic carbons), 47.24 32.21, and 24.92 ppm (three different aliphatic carbons). Anal. calcd. For $C_{20}H_{22}N_4O_6$ (414.41): C, 57.97; H, 5.35; N, 13.52. Found: C, 57.87; H, 5.45; N, 13.43.
21. X-Ray structure determination was performed on Bruker SMART 1KCCD automated diffractometer. Crystals of compound **11d** were obtained by crystallization from methanol by allowing slow solvent evaporation. All reagents and solvents were purchased from Aldrich and used without prior purification. X-Ray Single Crystal Structure Determination of Compound **11d** at 150(2) K *Crystal Data*: C_{20} H_{22} N_4 O_6 0.71073 Å [CH_3OH], $M_r=297.08$, monoclinic, space group $P2_1/n$, $a=7.9926(4)$ Å, $b=18.5230(9)$ Å, $c=13.6506(7)$ Å, $\beta=93.399(1)°$, $V=2017.37(18)$ Å^3, $Z=4$, ρ_{calcd} 1.364 Mgm^{-3}, $F_{000}=872$, Wavelength (λ) = 0.71073 Å, Absorption coefficient (μ) = 0.103 mm^{-1}.

   Data collection and reduction: Crystal size: 0.15×0.15×0.30 mm, Theta range: 2.20–26.43°, Index ranges: $-9\leq h\leq 10, -23, \leq k\leq 23, -17\leq 1\leq 17$, Reflections collected:

22381, Independent reflections: 4130 [$R_{int}=0.0588$], Refinement method: Full-matrix least-squares on F^2, Data/restraints/parameters: 4130/110/372. Final R indices [$I>2\sigma(I)$]: $R_1=0.0423$, w$R_2=0.1074$, Goodness-of-fit on F^2: 0.953. R indices (all data) $R_1=0.0808$, w$R_2=0.1074$, Largest diff. peak and hole: 0.189 and −0.222 eÅ^{-3}. *Measurement*, *Computing and Graphics*: *SMART 1K CDD* (Bruker, 2000); cell refinement: *SMART*; data reduction *SAINT-Plus* (Bruker, 2000); programs(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELX97* (Sheldrick, 1997); molecular graphics: *SHELXTL97* (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL97*. (a) Bruker. *SMART* (Version 5.060) and *SMART-Plus* (Version 6.02); Bruker AXS Inc., Madison, WI, USA, 2000; (b) Sheldick, G. M. *SHELXTL* DOS/Windows/NT; Version 5.1. Bruker AXS Inc., Madison, WI, USA, 1997; (c) Sheldrick, G. M. *SHELXL-97*, University of Göttingen, Göttingen, Germany, 1997.

22. Patent application in preparation.