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Features of the Synthesis of Thiobarbituric Acid Arylidene Derivatives in the Presence of Triethylamine

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Abstract—The synthesis of thiobarbituric acid arylidene derivatives proceeds in two steps, which include 5-(2-hydroxy-2-phenyl)ethyl derivative formation and dehydration. The triethylamine promotes increase in the negative charge on the 5th carbon atom (from –0.399 to –0.638) and positive charge on the aldehyde CH=O group carbon atom (from 0.288 to 0.300) in the transition state due to associative interaction (analysis by quantum-chemical method AM1), and it also promotes dehydration by "pushing out" the hydroxy group. The yield of thiobarbituric acid arylidene derivatives reaches 92–99%.

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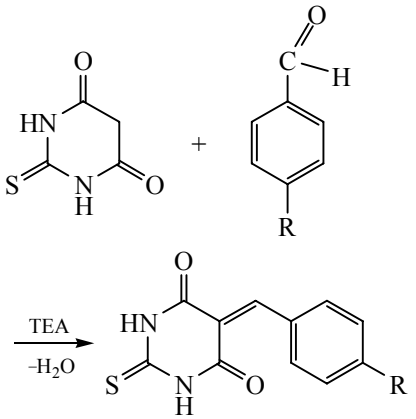
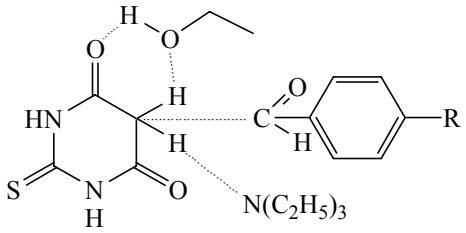
At the condensation of thiobarbituric acid with aromatic aldehydes HCl is commonly used [1]. In that case the reaction mechanism includes the protonation of nucleophilic centers of the initial reagents.

In this communication we show a possibility to apply a base instead of an acid in the synthesis of thiobarbituric acid arylidene derivatives. For this purpose triethylamine was used. The reaction proceeds according to the following scheme:



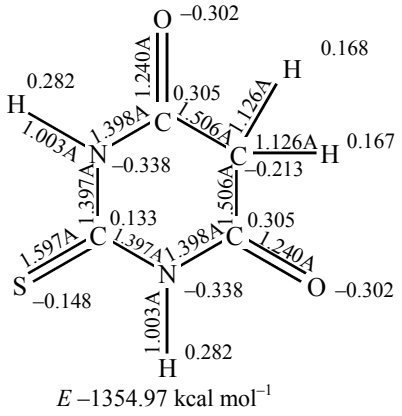
R = H (**I**), CH_3 (**II**), OCH_3 (**III**), F (**IV**), NO_2 (**V**).

In contrast to the data reported in [1] the activation of electrophilic centers by triethylamine can increase the selectivity of the first stage of the process. The reaction course most probably includes the following transition state:



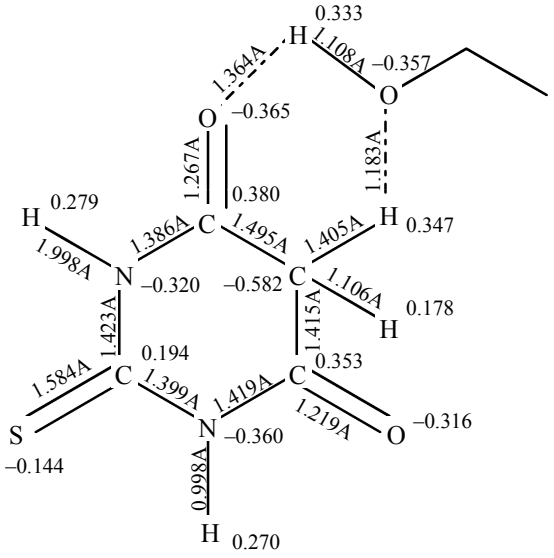
As the reaction medium we used anhydrous ethanol. Apparently, during the first step molecular association occurs of ethanol with the carbonyl group oxygen atom and with the hydrogen atom of methylene group with the formation of the associate with the structure shown in Figs. 1, 2.

As a result of associative interaction of thiobarbituric acid with ethanol increases the negative charge on the 5th carbon atom [from –0.213 (Fig. 1) in the parent molecule to –0.582 (Fig. 2) in the associate]. In the second step the remaining proton of the methylene group associates with the triethylamine molecule and simultaneously the carbon atom approaches the electrophilic carbon atom of the carbonyl group of benzaldehyde molecule with the formation of the transition state shown in Fig. 3.



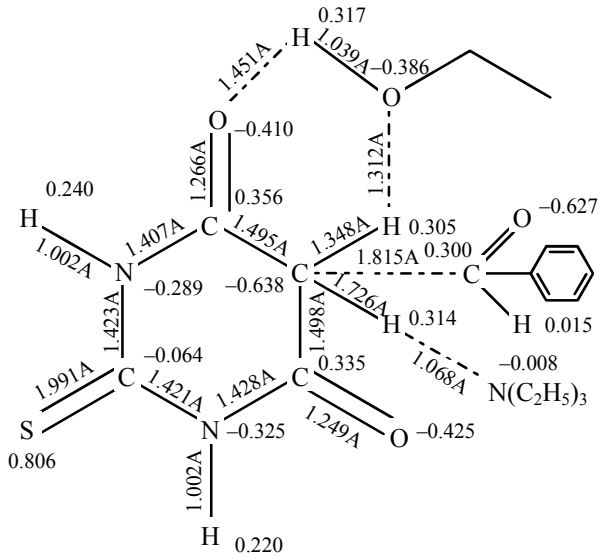
E –1354.97 kcal mol^{-1}

Fig. 1. Electronic structure of thiobarbituric acid.



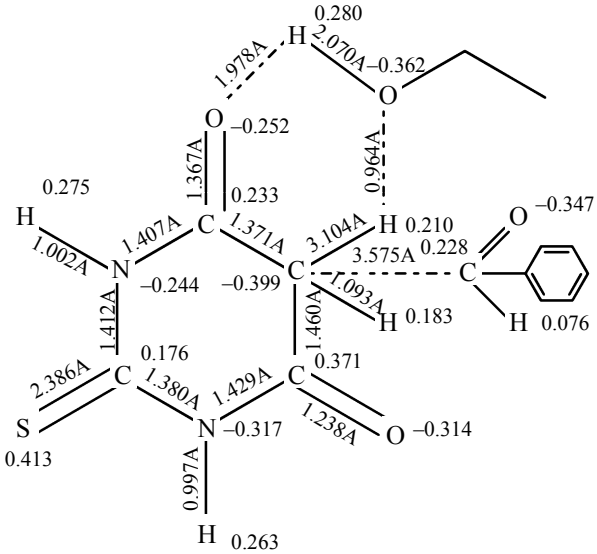
E –2071.34 kcal mol^{-1}

Fig. 2. Electronic structure of thiobarbituric acid associate with ethanol.



E –5412.93 kcal mol^{-1}

Fig. 3. Electronic structure of the transition state in the reaction of thiobarbituric acid with benzaldehyde in the presence of triethylamine.

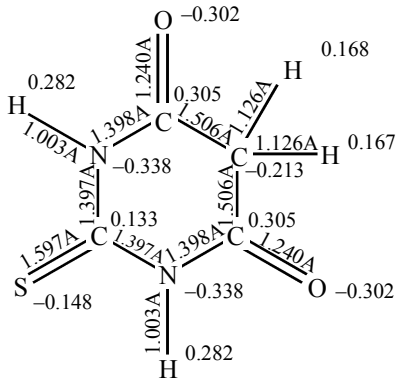


E –3653.11 kcal mol^{-1}

Fig. 4. Electronic structure of the transition state in the reaction of thiobarbituric acid with benzaldehyde in the absence of triethylamine.

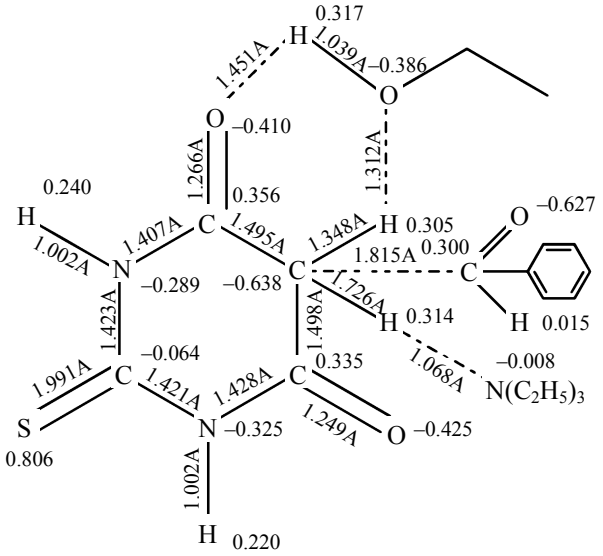
Triethylamine contributes to the proceeding of the condensation reaction (Figs. 3, 4) since it influences the bond polarization C–H···N(C_2H_5)$_3$ and increases substantially the negative charge on the 5th carbon (from –0.399 to –0.638) and also the positive charge on the carbon atom of the benzaldehyde carbonyl group (from 0.228 to 0.300), which undoubtedly favors the electrophilic attack by the benzaldehyde molecule on the nucleophilic center of the thiobarbituric acid. This leads to a considerable decrease in the total energy.

The influence of a substituent on the electronic structure of transition state consists in the contribution of the electron-donor CH_3O group to further bond



E –5787.33 kcal mol^{-1}

Fig. 5. Electronic structure of the transition state in the reaction of thiobarbituric acid with *p*-methoxybenzaldehyde in the presence of triethylamine.

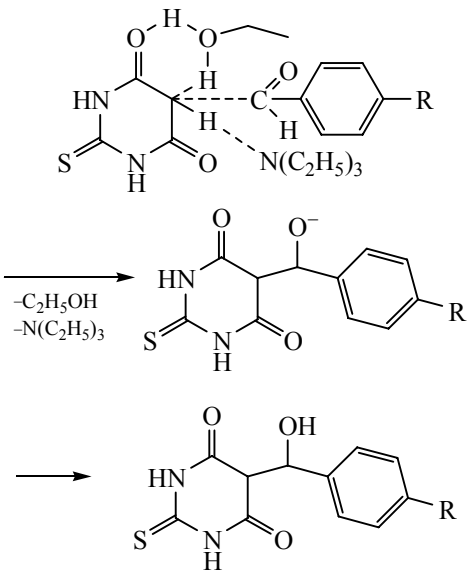


E –5741.63 kcal mol^{-1}

Fig. 6. Electronic structure of the transition state in the reaction of thiobarbituric acid with *p*-nitrobenzaldehyde in the presence of triethylamine.

polarization (charges on the 5th carbon atom of thiobarbituric acid and on the carbon atom of CH=O group become –0.645 and 0.305, respectively) favoring the reaction progress. On the contrary, the introduction of a nitro group leads to the smaller charge on the 5th carbon of thiobarbituric acid (–0.620) and to a significant decrease in the charge on the C=O carbon atom.

Further the transition state is converted into the anion with the negative charge on the of oxygen atom, which under the action of medium forms aldol:

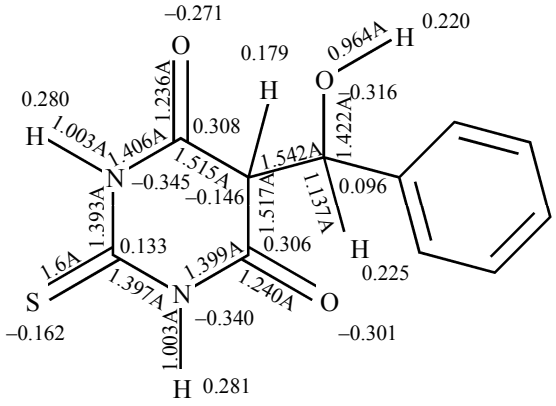


By quantum-chemical calculations using the method AM1 [2] we calculated the electronic structure of the formed aldol (Fig. 7).

Under the action of triethylamine the formed aldol gives a complex (Fig. 8), which finally decomposes affording the reaction product and water.

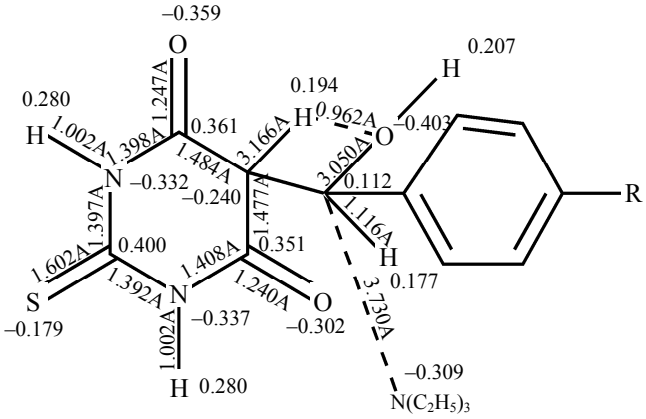
The influence of a substituent on the electronic structure of the aldol–triethylamine complex is seen in the fact that the electron-acceptor group NO_2 to a greater extent contributes to the release of water molecule, since the interatomic distances C(CH_2)···H and C–O increase to favor the reaction course (Fig. 9). On the contrary, the introduction of methoxy group (Fig. 10) results in a decrease in the bond lengths C(CH_2)···H and C–O that to a considerable degree hampers the splitting off of the water molecule and thus decelerates the second step of the reaction.

Thus, at the condensation of thiobarbituric acid with aromatic aldehydes in the presence of triethylamine in the first step the electron-donor substituents in the *para* position of the aldehyde molecule promote the reaction, while they hamper the second step of the reaction. On the contrary, the electron-acceptor substituents in the *para* position of the aldehyde molecule in the first step retard the reaction, while in the second step they promote it.



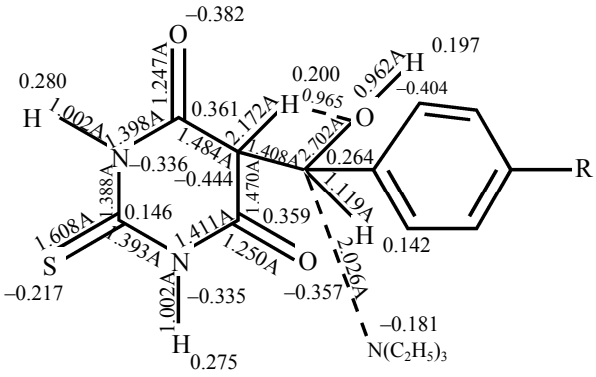
E –2934.05 kcal mol^{-1}

Fig. 7. Electronic structure of aldol obtained in the first stage of the reaction of thiobarbituric acid with benzaldehyde.



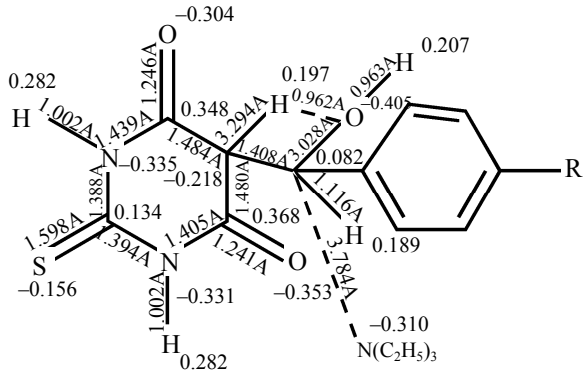
E –4871.32 kcal mol^{-1}

Fig. 8. Electronic structure of the transition state of the complex aldol–triethylamine (R=H).



E –5156.61 kcal mol^{-1}

Fig. 9. Electronic structure of the transition state of the complex aldol–triethylamine (R=OCH_3).



E –5046.69 kcal mol^{-1}

Fig. 10. Electronic structure of the transition state of the complex aldol–triethylamine (R=NO_2).

EXPERIMENTAL

The ^{1}H NMR spectra were registered on a Varian Mercury 300 MHz instrument, internal reference HMDS, solvent DMSO-d_6. Melting point were determined in accordance with the procedure [3].

5-Benzylidene-2-thioxodihydropyrimidine-4,6-(1*H*,5*H*)-dione (I). To a boiling suspension of 6 g (41.6 mmol) of thiobarbituric acid in 50 ml of anhydrous ethanol was poured 2.9 ml (20.8 mmol) of triethylamine and 4.25 ml (41.6 mmol) of freshly distilled benzaldehyde, and the mixture was refluxed at stirring for 15 min. Then the reaction mixture was cooled, the solid phase was washed with water and alcohol, and dried. Yield 9.6 g (99%), mp 271–272°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 5.95 s (1H, C=CH), 6.96–7.36 m (5H, H_{arom}), 11.5 s (1H, NH), 11.8 s (1H, NH). Found, %: N 11.54. $C_{11}H_8N_2O_2S$. Calculated, %: N 12.06.

5-(4-Methylbenzylidene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (II) was obtained analogously from 5 g (34.7 mmol) of thiobarbituric acid, 4.1 ml (34.7 mmol) of *p*-methylbenzaldehyde, and 2.4 ml of triethylamine. Yield 8.0 g (94%), mp >300°C. ^{1}H NMR spectrum, δ, ppm: 2,8 s (3H, CH_3), 5.99 s (1H, C=CH), 6.94–7.39 m (4H, H_{arom}), 11.5 s (1H, NH), 11.8 s (1H, NH). Found, %: N 11.04. $C_{12}H_{10}N_2O_2S$. Calculated, %: N 11.37.

5-(4-Methoxybenzylidene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (III) was obtained analogously from 5 g (34.7 mmol) of thiobarbituric acid, 4.2 ml (34.7 mmol) of *p*-methoxybenzaldehyde, and 2.4 ml of triethylamine. Yield 8.8 g (97%), mp >300°C. ^{1}H NMR spectrum, δ, ppm: 3.8 s (3H, CH_3), 5.96 s (1H, C=CH), 6.91–7.24 m (4H, H_{arom}), 11.6 s (1H, NH), 11.8 s (1H, NH). Found, %: N 10.34. $C_{12}H_{10}N_2O_3S$. Calculated, %: N 10.68.

5-(4-Fluorobenzylidene)pyrimidine-4,6(1*H*,5*H*)-dione (IV) was obtained analogously from 5 g (34.7 mmol) of thiobarbituric acid, 3.7 ml (34.7 mmol) of *p*-fluorobenzaldehyde, and 2.4 ml of triethylamine. Yield 8.0 g (92%), mp >300°C. ^{1}H NMR spectrum, δ, ppm: 5.90 s (1H, C=CH), 6.92–7.44 m (4H, H_{arom}), 11.6 s (1H, NH), 11.8 s (1H, NH). Found, %: N 11.01. $C_{11}H_7FN_2O_2S$. Calculated, %: N 11.19.

5-(4-Nitrobenzylidene)pyrimidine-4,6(1*H*,5*H*)-dione (V) was obtained analogously from 5 g (34.7 mmol) of thiobarbituric acid, 5.2 g (34.7 mmol) of *p*-nitrobenzaldehyde, and 2.4 ml of triethylamine. Yield 9.0 g (94%), mp >300°C. ^{1}H NMR spectrum, δ, ppm: 6.01 s (1H, C=CH), 6.84–7.44 m (2H, H_{arom}), 8.02–8.12 m (2H, $CH_{arom.}$–C_{NO_2}–$CH_{arom.}$), 11.54 s (1H, NH), 11.63 s (1H, NH). Found, %: N 15.02. $C_{11}H_7N_3O_4S$. Calculated, %: N 15.16.

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