Asian Journal of Chemistry; Vol. 25, No. 6 (2013), 2953-2955

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.12595

Synthesis and Theoretical Investigation of 5-(4-Dimethylaminobenzylidene)thiobarbituric Acid

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(*Received*: 11 November 2011; *Accepted*: 3 December 2012) AJC-12494

In this study, synthesis of 5-benzylidene thiobarbituric acid derivative has been described. The route of preparation involved the uses of thiobarbituric acid as starting material and treated with 4-dimethylaminobenzaldehyde compound to give required derivative. This compound was identified by spectroscopic methods; H NMR, FTIR and CHNS analysis and also by measuring its melting point. A theoretical investigation is performed using hybrid Beck model (B3LYP), ESP showed regular distribution of charge density of whole molecule when one of the two proton is removed from α-carbon, the ESP for HOMO electron density is heavily localized on α negative carbon, reflect the reactivity of thiobarbituric molecule and show it as highly effective nucleophile when act into nucleophilic substitution reactions.

Key Words: Synthesis, 5-(4-Dimethylaminobenzylidene)thiobarbituric acid.

INTRODUCTION

Active hydrogen compounds condense with aldehydes and ketones kown as Knoevenagel condensations. These aldol-like condensations usually catalyzed with weak bases. Iminium ions are intermediates which from α,β-unsaturated compounds having structures corresponding to these formed by mixed aldol condensations followed by dehydration. These reactions are catalyzed by amines or buffer systems containing an amine and an acid are referred to as Knoevenagel condensations[1]. Cross aldol-type condensation of thiobarbituric acid with aromatic aldehydes using acetic acid as a catalyst is available for the preparation[2]. In this paper, we described a rapid and convenient method for the synthesis of 5-arylidene thiobarbituric acids under uncatalyzed conditions using water as the solvent. It is interesting that the reaction easily occurs in water although the mechanism involves a net dehydration to the alcoholic intermediate obtained by nucleophilic attack of the active methylene neighboring to the carbonyl groups[3].

EXPERIMENTAL

Solvents and materials were obtained from Fluka (Taufkirchen, Germany). Electro thermal 1A melting point apparatus was used to measure the melting point of prepared compound. Infrared spectra were recorded as KBr discs using Fourier transform infrared spectrophotometer FTIR-8400s SHIMADZU. ^{1}H NMR spectra were recorded by Brukur, Ultra Shield 300 MHz, Switzerland with TMS as internal standard in DMSO-d_6. Elemental analysis, E.A.G.E.R. -100, Carlo Erba strumentazione, Italy.

Synthesis of thiobarbituric acid: Thiobarbituric acid was prepared according to the literature[4].

Synthesis of 5-(4-dimethylaminobenzylidene)thiobarbituric acid (3a): A mixture of 4-dimethylaminobenzaldehyde (10 mmol) and thiobarbituric acid (10 mmol) in water (40 mL) was stirred at 95-100 ºC for 2 h. Then the solid was filtered and washed subsequently with boiling water and finally with ether and drying in vacuum. The residue was dissolved in warm ethanol and recrystallized (76.92 % yield) as a red solid, m.p. 256 ºC; ^{1}H NMR (DMSO-d_6) δ: 2.6 [s, 6H, N(CH_3)$_2$], δ 6.1 (s, 1H, CH), δ 6.78-7.26 (m, 4H), δ 12.3 (s, 1H, NH); FTIR (KBr, ν_{max}, cm^{-1}) 3122 (NH), 3066 (CH), 1689 (C=O), 1647 (C=S), 1606 (C=C). Anal. calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26; S, 11.65 Found: C, 58.37; H, 5.01; N, 15.57; S, 10.91.

Synthesis of 5-(4-hydroxy-2-methoxybenzylidene)-thiobarbituric acid (3b): According to the preparation of **3a**, **3b** was prepared from thiobarbituric acid and 4-hydroxy-2-methoxybenzylidene as a yellow solid, m.p. 223 ºC; FTIR (KBr, ν_{max}, cm^{-1}) 3184 (NH), 3385 (OH),3066 (CH),1670 (C=O),1647 (C=S), 1606 (C=C). Anal. calcd. for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07; S, 11.52 Found: C, 52.17; H, 3.51; N, 10.57; S, 11.89.

Synthesis of 5-(4-bromobenzylidene)thiobarbituric acid (3c): According to the preparation of **3a**, **3c** was prepared

from thiobarbituric acid and 4-bromobenzylidene as a white solid, m.p. 198 ºC; ^{1}H NMR (DMSO-d_6); δ 6.5 (s, 1H, CH), δ 6.78-7.26 (m, 4H), δ 12.1 (s,1H, NH); FTIR (KBr, ν_{max}, cm^{-1}) 3223 (NH), 3070 (CH), 1688 (C=O),1649 (C=S), 1600 (C=C). Anal. calcd. for $C_{11}H_7BrN_2O_2S$: C, 42.46; H, 2.27; N, 9.00; S, 10.31 Found: C, 42.67; H, 2.54; N, 9.38; S, 9.98.

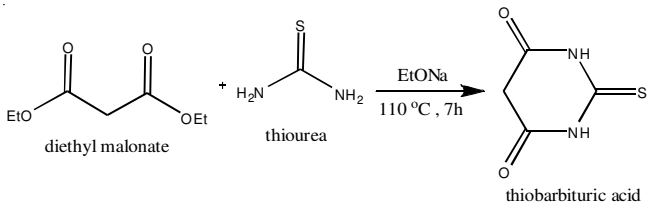
Synthesis of 5-(2-bromobenzylidene)thiobarbituric acid (3d): According to the preparation of **3a**, **3d** was prepared from thiobarbituric acid and 2-bromobenzylidene as a white solid, m.p. 203 ºC; FTIR (KBr, ν_{max}, cm^{-1}) 3223 (NH), 3070 (CH), 1653 (C=O), 1638 (C=S), 1598 (C=C). Anal. calcd. for $C_{11}H_7BrN_2O_2S$: C, 42.46; H, 2.27; N, 9.00; S, 10.31 Found: C, 42.78; H, 2.59; N, 9.28; S, 10.12.

Synthesis of 5-(3-methoxybenzylidene)thiobarbituric acid (3e): According to the preparation of **3a**, **3e** was prepared from thiobarbituric acid and 3-methoxybenzylidene as a yellow solid, m.p. 204 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3211 (NH), 3066 (CH), 1680 (C=O), 1647 (C=S), 1606 (C=C). Anal. calcd. for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84; N, 10.68; S, 12.23 Found: C, 54.37; H, 3.61; N, 10.58; S, 12.52.

Synthesis of 5-(2-hydroxybenzylidene)thiobarbituric acid (3f): According to the preparation of **3a**, **3f** was prepared from thiobarbituric acid and 2-hydroxybenzylidene as a yellow solid, m.p. 243 ºC; FTIR (KBr, ν_{max}, cm^{-1}) 3345 (OH), 3219 (NH), 3065 (CH), 1675 (C=O), 1649 (C=S), 1606 (C=C). Anal. calcd. for $C_{11}H_8N_2O_3S$: C, 53.22; H, 3.25; N, 11.28; S, 12.92 Found: C, 53.67; H, 3.60; N, 10.98; S, 12.72.

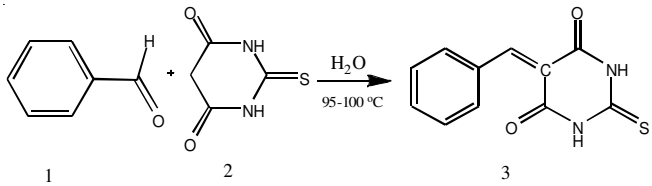
RESULTS AND DISCUSSION

The present investigation involved the application of thiobarbituric acid as starting material which was readily accessible from diethylmalonate and thiourea as shown on (**Scheme-I**).



Scheme-I: Synthesis of thiobarbituric acid

In this paper, we describe a rapid and convenient method for the synthesis of 5-arylidene thiobarbituric acids under uncatalyzed conditions using water as the solvent (**Scheme-II**).



Scheme-II: Synthesis of 5-(4-dimethylaminobenzylidene)thiobarbituric acid

The electronic structure of (thiobarbituric acid) and 5-(4-dimethylaminobe-nzylidene) thiobarbituric acid was calculated by density functional theory using the Gaussian09[5] program package. The theoretical investigation are performed by using one of more effective hybrid Beck[6] model [B3LYP/6-31G(d)] model chemistry in calculation the optimized structures, the difference density plots were prepared using Gauss view software.

TABLE-1
SYNTHESIS OF 5-BENZYLIDENETHIOBARBITURIC ACID DERIVATIVES

Compound	Ph	Yields (%)
3a	*p*-N(CH_3)$_2$	76.92
3b	*o*-OCH_3, *p*-OH	74.56
3c	*p*-Br	85.78
3d	*o*-Br	83.45
3e	*m*-OCH_3	77.87
3f	*o*-OH	53.54

Fig. 1 shows how the *p*-electron resonance is spreading and distributed around larger regions on six member ring of thiobarbitic acid anion(III) where the corresponding free radical(II) and neutral(I) molecules the electron no localization region is aggregate on one side, so the negative charge add to molecular system more stability than the parent molecule, then attend to be favourite to remove the first acidic hydrogen from α-carbon.

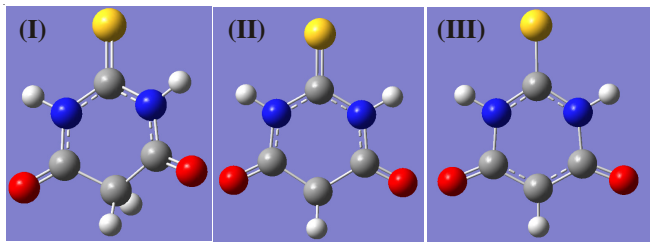


Fig. 1. Show the optimized structures of (thiobarbituric acid) molecule in different (I) the neutral molecules and (II) and (III) free radical and negative ones calculated by DFT methods [B3LYP/6-31G(d)] level theory

Fig. 2 shows a representation of electrostatic potential of total electron density to thiobarbituric acid molecule, the red region corresponding the high electron density locations, ESP surface confirm the regular distribution of charge density of whole molecules when one of the two proton are removed from α-carbon atom.

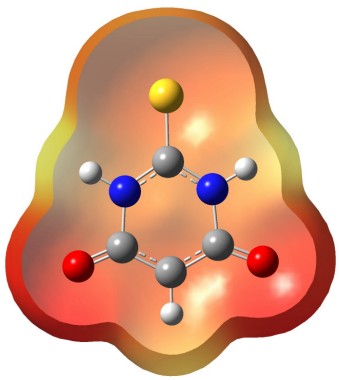


Fig. 2. Electrostatic potential surface for total electron density of (thiobarbituric acid) anion calculated by DFT methods [B3LYP/6-31G (d)] level theory

The highest occupied molecular orbital (HOMO) (Fig. 3) show electron density are heavily localized on α-negative carbon atom, reflect the reactivity of thiobarbituric acid molecule, and show it as highly effective nucleophile when act onto nucleophilic substitution reactions.

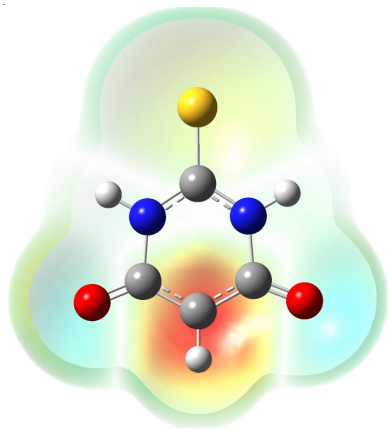


Fig. 3. Electrostatic potential surface of HOMO electron density for molecules calculated by DFT methods [B3LYP/6-31G(d)] level theory for (thiobarbituric acid) anion

The electrostatic potential (Fig. 4) show of total electron density of product compound, is clear that molecular system have high dipole moment and that make the molecules is polar one, because the highly density localized on lone pairs region of oxygen and sulfur atoms (red colour) in one side where the electron defiecent is clear (blue colour) on another side of molecule, this polarity make 5-(4-dimethylaminobenzylidene) thiobarbituric acid molecule tend to be soluble in polar solvent.

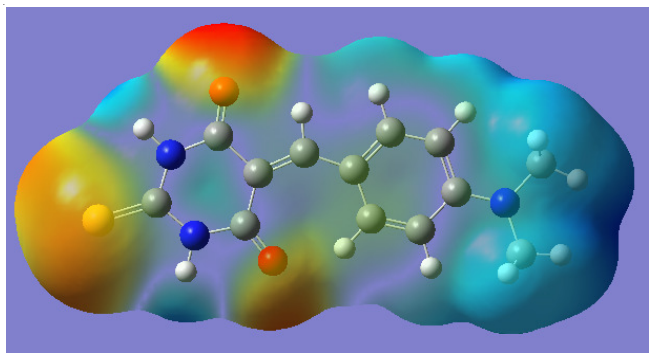


Fig. 4. Electrostatic potential surface for total electron density of 5-(4-dimethylaminobenzylidene)thiobarbituric acid molecule calculated by DFT methods [B3LYP/6-31G(d)] level theory

Conclusion

A simple synthetic route for 5-(4-dimethylaminobenzylidene)thiobarbituric acid by the condensation reaction of 4-dimethylaminobenzaldehyde with thiobarbituric acid in water without catalyst is described.

ACKNOWLEDGEMENTS

The authors thank Central Laboratory in Kufa University for the research facilities.

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