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GREEN CHEMISTRY APPROACHES TO THE SYNTHESIS OF 5-ARYLIDENETHIOBARBITURIC ACIDS BY A CONDENSATION REACTIONS BETWEEN AROMATIC ALDEHYDES AND THIOBARBITURIC ACID: COMPARISON OF WATER, MICROWAVE IRRADIATION, AND GRINDING

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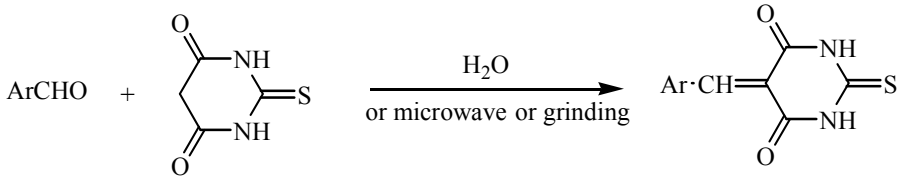
Abstract– A general and practical green chemistry route to the synthesis of 5-arylidenethiobarbituric acids is described from aromatic aldehydes and thiobarbituric acid under three different sets of reaction conditions: water without catalyst conditions, microwave irradiation, and grinding method using NH_4OAc as a catalyst at room temperature.

INTRODUCTION

Eco-benign version of organic reactions is potential candidates for the synthesis of biologically active compounds.[1] At the beginning of the new century, green chemistry approaches hold out significant potential not only for reduction of byproducts, a reduction in the waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies.[2] For organic reactions, there is an urgent need for improvement in reducing toxic volatile solvents. So, methods without solvent or replacing organic solvent by water have been studied for the synthesis of a wide variety of organic molecules. Recently, microwave assisted synthesis, sonication, solid-phase methods and other environmentally friendly reactions in organic

synthesis have been paid considerable attention.[3] Of all existing areas of green chemistry, utilization of water as solvent in organic chemistry, microwave assisted synthesis, and grinding reactions under solvent-free conditions are the most ripe for greening. The use of water as solvent in organic chemistry under uncatalyzed conditions was particularly eco-friendly because of cheapness, uninflammability and nontoxicity. This technique was proposed by Breslow[4] in the 1980s and has already become one of the most promising approaches in organic synthesis.[5] Microwave irradiation or the grinding method under solvent-free conditions is a new and convenient synthetic method and has increasingly been used in organic synthesis during these years.[6] Compared with traditional methods, these two methods are more efficient, and provide unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and ease of manipulation. Therefore, microwave irradiation and grinding method in organic synthesis have become an increasingly popular technology.[7]

The derivatives of the barbituric and thiobarbituric are important class of biological activities such as antibacterial, hypotensive, and sedative.[8] Arylidenebarbituric and thiobarbituric acids are widely used as precursors for the synthesis of bioactive derivatives[9] and their derivatives are also the very important intermediates in organic reactions.[10] Therefore, preparation of arylidene barbituric and thiobarbituric acids has attracted considerable attention in recent years. Cross aldol-type condensation of barbituric acid or thiobarbituric acid with aldehydes is available for this preparation. Generally, this reaction was carried out by condensing barbituric acid or thiobarbituric acid with aldehydes by using acetic acid as a catalyst under conventional refluxing conditions in aqueous medium (Scheme 1).[11] This method requires longer reaction time and tedious work-up. In 1990, Villemin[12] prepared the barbiturates in the presence of Montmorillonite KSF clay being a catalyst under microwave irradiation. Recently, Dewan[13] reported the synthesis of 5-arylidenebarbiturates using a variety of catalysts – NH_4OAc/AcOH, Montmorillonite K-10, silica gel, basic alumina, NaCl, Montmorillonite KSF and KSF/NaCl in dry media under microwave irradiation. 5-Arylidenethiobarbituric acids were also prepared by using grinding method, but it took long time.[14] In this paper, we described a rapid and convenient method for the synthesis of 5-arylidenethiobarbituric acids under three different sets of reaction conditions: water without catalyst, microwave irradiation, and grinding method using NH_4OAc as a catalyst at room temperature. The reaction conditions and experimental results were summarized in Table 1.



1 **2** **3**

Scheme 1

RESULTS AND DISCUSSION

It is interesting that the reaction easily occurs in water although the mechanism involves a net dehydration to the alcoholic intermediate obtained by nucleophilic attacking neighboring active methylene to the carbonyl group. We propose that water helps the dissociation of thiobarbituric acid due to its high ε value,[15] 78, which generates the nucleophilic species being able to attack the carbonium of the aldehyde. Besides, water is in low cost and safety. It also makes the product easily to be isolated and it can be employed in many kinds of aromatic aldehydes, either in liquid or solid forms.

Table 1. Synthesis of 5-arylidenethiobarbituric acid (**3**)

Entry	Ar	Mp (℃)	Yield (%)				
			H_2O	Microwave irradiation			Grinding
				Time(min)[a]		Power(W)[a]	
3a	C_6H_5	>300	67	88	10	162	78
3b	4-$(CH_3)_2NC_6H_4$	259-260	87	92	4	522	91
3c	4-ClC_6H_4	291-292	82	90	4	350	82
3d	4-HOC_6H_4	>300	87	83	5	522	81
3e	3,4-$(CH_2O_2)C_6H_3$	>300	62	96	2	162	94
3f	4-$CH_3OC_6H_4$	>300	95	87	3	350	84
3g	2,4-$Cl_2C_6H_3$	263-264	83	76	12	522	63
3h	2-HOC_6H_4	>300	50	78	6	162	77
3i	(η^5-C_5H_5)Fe(η^5-C_5H_4)	260(dec.)	85	86	6	162	87

[a] Reactions under microwave irradiation.

On the same conditions as described above, 5-arylidenethiobarbituric acid (**3**) can not be obtained from the condensation reactions when aromatic ketone substituted for aromatic aldehydes (**1**). Obviously, the activity of aromatic ketone is quite lower than aromatic aldehydes largely due to electronic effect and steric effect. As a consequence, it is difficult for aromatic ketone to condensate with thiobarbituric acid (**2**) to form 5-arylidenethiobarbituric acid (**3**).

In the case of microwave irradiation, the product with high yield and good purity can be obtained when the irradiation output is in the range of 162~522 W and the reaction was irradiated intermittently. High output of microwave and long time irradiation could result in carbonization. So in this experiment all experimental conditions used were optimized, and listed in Table 1.

Without the catalyst of NH_4OAc, it takes long time for the condensation between aromatic aldehydes (**1**) and thiobarbituric acid (**2**) under the condition of solid grinding, in line with the results described elsewhere.[13] With the catalyst of NH_4OAc, however, the reaction can complete within 10 min under grinding. This observation indicates that NH_4OAc exhibits excellent catalyst effect in this condensation reaction.

In conclusion, a simple synthetic route for 5-arylidenethiobarbituric acids by the condensation reaction of aromatic aldehydes with thiobarbituric acid is described in three different sets of reaction conditions: water without catalyst conditions, microwave irradiation, and grinding method using NH_4OAc as a catalyst at room temperature. This new method is a simple, good-yielding and environmentally friendly process.

EXPERIMENTAL

General: All reported yields are isolated yields. TLC was carried out on silica gel GF254 (20-40 μ). Microwave assisted organic reactions were performed in Galanz oven (WD900SL23-2, 2450 Hz, output power 900W). ^{1}H NMR and ^{13}C NMR spectra were recorded on an INOVA-400 NMR spectrometer using TMS as internal standard. Elemental analyses and IR spectra were measured on an EL-III microanalyser and EQUINOX55 spectrophotometer as KBr pellets, respectively. Mps were determined in a capillary tube and are uncorrected. Formylferencene[16] and thiobarbituric acid[17] was prepared according to the literature. Other chemicals were purchased and used without any further purification.

General Procedure for the Preparation of the 5-Arylidenethiobarbituric Acids in Water (Typical

Procedure).

A mixture of benzaldehyde (1.06 g, 10 mmol) and thiobarbituric acid (1.44 g, 10 mmol) in water (40 mL) is stirred at 95-100℃ for 45 min. Then the solid was filtered and washed subsequently with boiling water and ether. After drying in vacuum, the 5-phenylmethylenethiobarbituric acid **(3a)** was obtained as a yellow solid (1.55 g, 67%).

General Procedure for the Preparation of the 5-Arylidenethiobarbituric Acids by Microwave Irradiation.

A mixture of benzaldehyde (1.06 g, 10 mmol) and thiobarbituric acid (1.44 g, 10 mmol) was irradiated in the MW oven five times at the 18% full output power (162 W) for 10 min with 2 min cooling period after irradiation cycle. Then, the mixture was treated as above and the 5-phenylmethylenethiobarbituric acid **(3a)** was obtained as a yellow solid (2.04 g, 88%).

General Procedure for the Preparation of the 5-Arylidenethiobarbituric Acids by Grinding.

A mixture of benzaldehyde (1.06 g, 10 mmol), thiobarbituric acid (1.44 g, 10 mmol) and NH_4OAc (0.77 g, 10 mmol) was grinded in mortar for 10 min. The solid was washed subsequently with ether and boiling water. After drying in vacuum, the 5-phenylmethylenethiobarbituric acid **(3a)** was obtained as a yellow solid (1.81 g, 78%).

5-Phenylmethylenethiobarbituric acid **(3a)**: Yellow solid, mp > 300 ℃ (ethanol-water); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.48~8.15 (m, 5H), 8.31 (s, 1H), 12.35 (s, 1H), 12.47 (s, 1H); IR (KBr) υ: 3065, 2910, 1536, 1653, 1204 cm^{-1}; Anal. Calcd for $C_{11}H_8N_2O_2S$: C 56.90, H 3.45, N 12.07. Found C 56.71, H 3.66, N 12.28.

5-(4-Dimethylamino)phenylmethylenethiobarbituric acid **(3b)**: Ferrugineous solid, mp 259-260 ℃ (ethanol-water); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.16 (s, 6H), 6.83 (d, J = 9.2 Hz, 2H), 8.16 (s, 1H), 8.47 (d, J = 9.2 Hz, 2H), 12.03 (s, 1H), 12.13 (s, 1H); IR (KBr) υ: 3455, 3114, 1646, 1493, 1233 cm^{-1}; Anal. Calcd for $C_{13}H_{13}N_3O_2S$: C 56.73, H 4.73, N 15.27. Found C 56.96, H 4.46, N 15.20.

5-(4-Chlorophenyl)methylenethiobarbituric acid **(3c)**: Yellow solid, mp 291-292 ℃ (ethanol-water); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.55 (d, J = 8.4 Hz, 2H), 8.13 (d, J = 8.4 Hz, 2H), 8.26 (s, 1H), 12.37 (s, 1H), 12.48 (s, 1H); IR (KBr) υ: 3113, 3059, 1656, 1569, 1205 cm^{-1}; Anal. Calcd for $C_{11}H_7N_2O_2ClS$: C 49.53, H 2.63, N 10.51. Found C 49.86, H 2.46, N 10.72.

5-(4-Hydroxyphenyl)methylenethiobarbituric acid **(3d)**: Orange-red solid, mp > 300 ℃ (ethanol-water); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.90 (d, J = 9.2 Hz, 2H), 8.23 (s, 1H), 8.39 (d, J = 9.2 Hz, 2H),

10.97 (s, 1H), 12.25 (s, 1H), 12.34 (s, 1H); IR (KBr) υ: 3211, 1655, 1608, 1580, 1521, 1213 cm^{-1}; Anal. Calcd for $C_{11}H_8N_2O_3S$: C 53.22, H 3.22, N 11.29. Found C 53.51, H 3.20, N 11.54.

5-(3,4-Methenedioxyphenyl)methylenethiobarbituric acid **(3e)**: Orange-red solid, mp > 300 ℃ (ethanol-water); ^1H NMR（DMSO-d_6, 400 MHz）δ: 6.20 (s, 2H, CH_2), 7.10 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 8.23 (s, 1H), 8.29 (s, 1H), 12.31 (s, 1H), 12.40 (s, 1H); IR (KBr) υ: 3230, 3164, 1668, 1527, 1452, 1206 cm^{-1}; Anal. Calcd for $C_{13}H_8N_2O_4S$: C 54.17, H 2.78, N 9.72. Found C 54.39, H 2.98, N 9.70.

5-(4-Methoxyphenyl)methylenethiobarbituric acid **(3f)**: Orange solid, mp > 300 ℃ (ethanol-water); ^1H NMR（DMSO-d_6, 400 MHz）δ: 3.85 (s, 3H), 7.08 (d, J = 8.4 Hz, 2H), 8.27 (s, 1H), 8.42 (d, J = 8.4 Hz, 2H), 12.29 (s, 1H), 12.39 (s, 1H); IR (KBr) υ: 3451, 3061, 1650, 1508, 1210 cm^{-1}; Anal. Calcd for $C_{12}H_{10}N_2O_3S$: C 54.96, H 3.82, N 10.69. Found C 55.24, H 3.71, N 10.88.

5-(2,4-Dichlorophenyl)methylenethiobarbituric acid **(3g)**: Yellow solid, mp 263-264 ℃ (ethanol-water); ^1H NMR（DMSO-d_6, 400 MHz）δ: 7.49 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 12.38 (s, 1H), 12.55 (s, 1H); IR (KBr) υ: 3090, 1673, 1570, 1216 cm^{-1}; Anal. Calcd for $C_{11}H_6N_2O_3Cl_2S$: C 41.64, H 1.89, N 8.83. Found C 41.85, H 1.76, N 8.59.

5-(2-Hydroxyphenyl)methylenethiobarbituric acid **(3h**): Orange-red solid, mp > 300 ℃ (ethanol-water); ^1H NMR（DMSO-d_6, 400 MHz）δ: 6.89-6.91 (m, 2H)；8.23 (s, 1H)；8.37~8.40 (m, 2H)；12.25 (s, 1H)；12.34 (s, 1H). IR (KBr) υ: 3211, 1655, 1520, 1212 cm^{-1}; Anal. Calcd for $C_{11}H_8N_2O_3S$: C 53.22, H 3.22, N 11.29. Found C 53.40, H 3.38, N 11.25.

5-Ferrocenylmethylenethiobarbituric acid **(3i)**: Purple solid, mp 260 ℃ (dec.) (EtOAc-isohexane); ^1H NMR（DMSO-d_6, 400 MHz）δ: 4.33 (s, 5H), 5.04 (s, 2H), 5.39 (s, 2H), 8.26 (s, 1H), 12.09 (s, 1H), 12.21 (s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ: 70.92, 75.97, 76.39, 111.06, 158.07, 159.89, 161.98, 177.84; IR (KBr) υ: 3092, 2896, 1743, 1693, 1646, 1512, 1367, 1154, 1046, 522, 469 cm^{-1}; Anal. Calcd for $C_{15}H_{12}N_2O_2FeS$: C 52.94, H 3.53, N 8.24. Found C 52.68, H 3.76, N 8.51.

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