Green chemistry 1: Simple and Efficient Synthesis -in Water- and Antibacterial Activity of 5-Arylidene Derivatives of Thiobarbituric and Barbituric acids.

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Abstract: An efficient Knovenagel condensation of thiobarbituric and barbituric acids **1a, b** with aromatic aldehydes **2a-f**, in water, using ethanolamine as catalyst, afforded 5-arylidene derivatives **3a-f** of **1a, b** in 10-15 minutes reaction times, with 88-95% isolated yields and high purity. Derivatives **3b-f** showed reasonable activity against gram **(+ve)** and gram **(-ve)** bacteria.
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1. Introduction.

Thiobarbituric **1a** and barbituric acids **1b** are reported to have applications in the biological and industrial fields [1-4]. Certain compounds analogous to **1a** in containing -in their structure- nitrogen and sulphur as electron-donor atoms, have been reported to show anti-cancer and anti-viral activities [5]. Thiobarbituric acid **1a** is, also, used in pharmacological and analytical fields [3, 6-11]. Thiobarbital (5,5-diethyl -2- thiobarbituric acid) [2b]; and thiobutabarbital (5-(2-butyl)-5-ethyl-2-Thiobarbituric acid) [2c] are used as antihyperthyroid; and anesthetic agents, respectively. Barbituric acid **1b** is used in the manufacture of plastics and pharmaceuticals [2a, 3, 12]. Barbital (5,5-diethyl barbituric acid) possesses sedative and hypnotic activity [2d]. Reposal, 5-bicyclo[3.2.0]octen-2-yl-5-ethylbarbituric acid [2e], is medically reported as short acting hypnotic.

Since substitution in thiobarbituric **1a** and barbituric **1b** acids at the position 5 creates notable therapeutic activity in certain respective 5-substituted systems -as indicated to above- it was prompting to us to synthesize and investigate the antibacterial activity of certain 5-arylidene derivatives **3a-f** of **1a, b** (Scheme 1 and Tables 1 & 2).

The desirability of a safer, simpler, faster and more economic synthetic procedure had encouraged us to investigate water as a *green chemical* agent for replacing the usual hazardous organic solvents in the synthesis of the planned 5-arylidene derivatives **3a-f** (Scheme 1). This *green chemistry* trend is supported by applying the efficient and economic technique of one-pot three-component reaction (**C**, Scheme 1).

2. Results and Discussion.

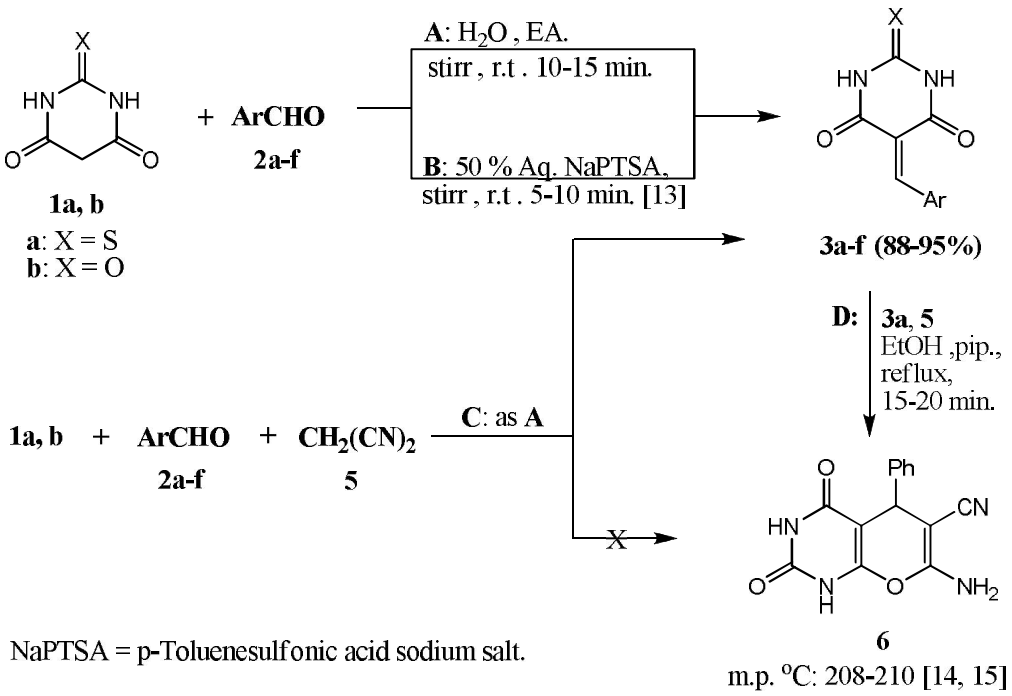
2.1. Chemistry

The reaction of thiobarbituric **1a** or barbituric **1b** acids with aromatic aldehyde **2a-f,** in stirred distilled water, at room temperature, in the presence of ethanolamine, EA, as catalyst, afforded the corresponding 5-arylidene derivatives **3a-f**, in excellent isolated yields of 88-95% and high purity, within 10-15 minutes reaction times (**A**, Scheme 1, Table 1).

Carrying out the above mentioned reaction, under the conditions of a related work [13] on barbituric acid **1b**, where –in the present work- stirring **1a, b** and **2a-f**, at room temperature, in aqueous 50% solution of sodium p-toluene sulfonate (NaPTSA) (**B, Scheme 1),** afforded the same 5-arylidene derivatives **3a-f** (m.p. and mixture m.p.).

This unambiguous synthesis of **3a-f** proves their structures.

The one-pot three-component reaction of the appropriate of **1**, **2** and malononitrile **5**, under the above mentioned experimental conditions (**C,** Scheme 1), did not afford the expected reported [14, 15] pyrano [2,3-d] pyrimidine derivative **6**; it -instead- afforded **3a-f** (Scheme 1), (m.p. and mixture m.p.).Compound **6** could, however, be obtained *via* the reaction of **3a** with **5** in refluxing ethanol, in the presence of piperidine, pip., as catalyst, for 15-20 minutes (**D,** Scheme 1). The detected melting point of **6** agreed with reported data on preparing **6** *via* a fusion -type- reaction within 70 minutes [14, 15].



Scheme 1

Table 1: 5-Arylidene derivatives (3a-f) of thiobarbituric 1a, barbituric 1b acids and pyrano [2,3-d] pyrimidine derivative 6 (Scheme 1).

Deriv. **3**	X	Ar	M.p.°C detect. / report.	Mix m.p.°C	Ref.
a	S	4-$CH_3OC_6H_4$	>300 / >300	>300	[19]
b	S	3,4-$(CH_3O)_2C_6H_3$	274-6 /	.....	.....
c	S	3,4,5-$(CH_3O)_3C_6H_2$	271-3 /	.....	.....
d	O	C_6H_5	264-5 / 264	264-6	[13, 16-18]
e	O	3,4-$(CH_3O)_2C_6H_3$	>300 /	.....	.....
f	O	3,4,5-$(CH_3O)_3C_6H_2$	240-2 / 264	240-2	[13]
6	O	C_6H_5	208-210 / 206-9, 208-210	.....	[14, 15]

Derivatives **3a-f** and **6** gave satisfactory results in elemental and spectral (**IR** and **^{1}H NMR**) analyses (cf. Experimental).

As an example, the **^{1}H NMR** spectrum of **3b** showed singlet signals at the δ regions of 12.38 and 12.27 ppm for the two thioimidic NH functional groups; and at the δ 8.35 ppm for the ylidenic proton (Ar-**CH**=C) (cf. Experimental).

2.2. Antibacterial activity

The antibacterial activity of derivatives **3b-f** were tested against gram-positive (Bacillus cereus) and gram-negative (Escherichia coli) bacteria and was determined by the disc -cup plate agar- diffusion method [20-23]. Measuring the inhibition zone radius by centimeters, after 24h of incubation, at 37^{o}C, revealed that the tested derivatives **3b-f** showed reasonable activities against the tested bacteria (Table 2). The stock solutions (10µg/ml) were prepared in dimethyl sulfoxide (DMSO); and the DMSO had no effect on the tested bacteria under the applied experimental conditions. The antibiotic **Ampicillin** was used as a standard reference in this study.

Table 2: Antibacterial activity of derivatives **3b-f**

Compound	Ar	X	Antibacterial activity (inhibition zone radius by cm) at 10µg/ml	
			B. cereus (G +ve)	E. coli (G -ve)
3b	3,4-$(CH_3O)_2C_6H_3$	S	0.95	1.075
3c	3,4,5-$(CH_3O)_3C_6H_2$	S	0.85	1.15
3d	C_6H_5	O	1.05	1
3e	3,4-$(CH_3O)_2C_6H_3$	O	0.4	0.575
3f	3,4,5-$(CH_3O)_3C_6H_2$	O	0.525	0.625
Control	DMSO	-	0	0
Standard	Ampicillin	-	0.775	1.025

3. Experimental.

Melting points were obtained on a Gallenkamp melting point apparatus (open capillary tubes) and were uncorrected; IR spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet) at the Department of Chemistry, Faculty of Science at (New) Damietta, Mansoura University, Damietta branch, Egypt. ^{1}H NMR spectra were performed on a BRUKER (600 MHz) ultra shield Avence III Spectrometer at the Faculty of Science, King Abdulaziz University, Jeddah, K.S.A, using (TMS) as an internal stander, DMSO and DMSO: $CDCl_3$ as a solvents. Chemical shifts were expressed as δ ppm. Micro analytical data were performed on a PERKIN-ELMER 2400 C, H, N Elemental Analyzer at the Micro analytical Unit, Cairo University, Egypt, and in the Faculty of Science, King Abdulaziz University, Jeddah, K.S.A.

Synthesis of the 5-arylidene derivatives (3a-f) (Scheme 1).

General procedure A:

A mixture of thiobarbituric or barbituric acids **1a, b** (0.01 mol), the appropriate aromatic aldehyde **2a-f** (0.01 mol) and 2 drops of ethanolamine, EA, in 30 ml of distilled water was stirred for 10-15 min., at room temperature. The deposited solid product was collected by filtration and recrystallized from 95% ethanol.

General procedure B:

A mixture of thiobarbituric or barbituric acids **1a, b** (0.01 mol), the appropriate aromatic aldehyde **2a-f** (0.01 mol), in 20 ml of aqueous 50% sodium p-toluene sulfonate (NaPTSA) solution, was stirred, at room temperature, for 5-10 min. The deposited solid product was collected by filtration and recrystallized from 95% ethanol [13].

General procedure C: (Although it was initially intended to synthesize **6**):

A mixture of thiobarbituric or barbituric acid **1a, b** (0.01 mol), the appropriate aromatic aldehyde **2a-f** (0.01 mol) and malononitrile **5** (0.01 mol), 2 drops of ethanolamine, in 30 ml of distilled water, was stirred for 10-15 min., at room temperature. The deposited solid product was treated as in procedure **A**.

5-(4-methoxybenzylidene)-2-thiobarbituric acid (3a).

Yellow crystals: Yield: 95%; reported m.p. >300 ^{o}C [19]; m.p: >300 ^{o}C; mix.m.p: >300 ^{o}C; **IR** (KBr, cm^{-1}): γ = 3429 (NH), 3066 (CH aromatic), 2915 (CH aliphatic), 1699, 1652 (CO, CS).

Anal. Calcd for $C_{12}H_{10}N_2O_3S$ (M. Wt: 262.28): C, 54.95; H, 3.84; N, 10.68%; Found: C, 54.91; H, 3.78; N, 10.60%.

5-(3,4-dimethoxybenzylidene)-2-thiobarbituric acid (3b).

Orange crystals: Yield: 92%; m.p: 274-6 ^{o}C; **IR** (KBr, cm^{-1}): γ = 3363, 3200 (NH), 3139 (CH aromatic), 2946, 2896 (CH aliphatic), 1720, 1681 (CO, CS). **^{1}H NMR** (600 MHz, DMSO: $CDCl_3$), δ, ppm = 12.38 (1H, s, N**H**), 12.27 (1H, s, N**H**), 8.53 (1H, s, Ar-**H**), 8.35 (1H, s, Ar-**CH**=C), 7.88 (1H, d, Ar-**H**), 7.08 (1H, d, Ar-**H**), 3.96 (3H, s, C**H**$_3$), 3.90 (3H, s, C**H**$_3$).

Anal. Calcd for $C_{13}H_{12}N_2O_4S$ (M. Wt: 292.31): C, 53.42; H, 4.14; N, 9.58%; Found: C, 53.33; H, 4.01; N, 9.46%.

5-(3,4,5-trimethoxybenzylidene)-2- thiobarbituric acid (3c).

Orange crystals: Yield: 93%; m.p: 271-3 ^{o}C; **IR** (KBr, cm^{-1}): γ = 3200 (NH), 3116 (CH aromatic), 2908 (CH aliphatic), 1700, 1654 (CO, CS); **^{1}H NMR** (600 MHz, DMSO: $CDCl_3$), δ, ppm = 12.43 (1H, s, N**H**), 12.31 (1H, s, N**H**), 8.35 (1H, s, Ar-**CH**=C), 7.94 (1H, s, Ar-**H**), 7.85 (1H, s, Ar-**H**), 3.91(3H, s, CH_3), 3.89 (6H, s, 2C**H**$_3$).

Anal. Calcd for $C_{14}H_{14}N_2O_5S$ (M. Wt: 322.34): C, 52.17; H, 4.38; N, 8.69%; Found: C, 52.03; H, 4.21; N, 8.56%.

5-benzylidenebarbituric acid (3d).

White crystals: Yield: 92%; reported m.p. 264 ^{o}C [13, 16-18]; m.p: 264-5 ^{o}C; mix.m.p: 264-6 ^{o}C; **IR** (KBr, cm^{-1}): γ = 3212 (NH), 3066 (CH aromatic), 1751, 1677 (CO).

Anal. Calcd for $C_{11}H_8N_2O_3$ (M. Wt: 216.19): C, 61.11; H, 3.73; N, 12.96%; Found: C, 61.08; H, 3.67; N, 12.87%.

5-(3,4-dimethoxybenzylidene)barbituric acid (3e).

Yellow crystals: Yield: 88%; m.p:>300 ^{o}C; **IR** (KBr, cm^{-1}): γ = 3224, 3139 (NH), 3073 (CH aromatic), 2954 (CH aliphatic), 1743, 1693 (CO); **^{1}H NMR** (600 MHz, DMSO), δ, ppm = 11.32 (1H, s, N**H**) , 11.2 (1H, s, N**H**) , 8.4 (1H, s, Ar-**CH**=C) , 8.23 (1H, s, Ar-**H**), 7.89 (1H, d, Ar-**H**), 7.1 (1H, d, Ar-**H**), 3.86 (3H, s, C**H**$_3$), 3.79 (3H, s, C**H**$_3$).

Anal. Calcd for $C_{13}H_{12}N_2O_5$ (M. Wt: 276.24): C, 56.52; H, 4.38; N, 10.14%; Found: C, 56.43; H, 4.21; N, 10.07%.

5-(3,4,5-trimethoxybenzylidene)barbituric acid (3f).

Yellow crystals: Yield: 95%; reported m.p. 264 ^{o}C [13]; m.p: 240-2 ^{o}C; mix. m.p: 240-2 ^{o}C; **IR** (KBr, cm^{-1}): γ = 3206 (NH), 3016 (CH aromatic), 2840 (CH aliphatic), 1756, 1736, 1668 (CO).

Anal. Calcd for $C_{14}H_{14}N_2O_6$ (M. Wt: 306.27): C, 54.90; H, 4.61; N, 9.15%; Found: C, 54.83; H, 4.58; N, 9.11%.

Synthesis of derivative 6 (Scheme 1).

A mixture consisting of (0.01 mol) of each of **3a** and malononitrile **5**, in 15 ml of 95% ethanol, in the presence of two drops of piperidine as catalyst, was refluxed for 15-20 min. The solid product that was deposited on hot was filtered off and recrystallized from DMF/ Ethanol.

7-Amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (6) (scheme 1).

Yellowish fine crystals: Yield: 94%; m.p: 208-210 ^{o}C; reported m.p. 206-9 ^{o}C [14], 208-210 ^{o}C [15]; **IR** (KBr, cm^{-1}): γ = 3380-3300 (NH, NH_2), 3187, 3077 (CH aromatic), 2836 (CH aliphatic), 2194 (CN), 1718, 1683 (CO).

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