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Synthesis of Some 5-[2-Aryl-2-oxoethyl]-1,3-dimethylpyrimidine-2,4,6-trione Derivatives by a One-pot, Three-component Reaction

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ABSTRACT

This study reports the reduction of α,β-unsaturated ketones 4a–g, formed by condensation of arylglyoxals 2a–g with 1,3-dimethylbarbituric acid (3) by L-cysteine (5) in the presence of phosphotungstic acid as a catalyst. This reaction leads to the formation of 5-[2-aryl-2-oxoethyl]-1,3-dimethylpyrimidine-2,4,6-triones 6a–g, with no sign of any heterocyclic product formation. The structure of compound 6f was confirmed by X-ray crystallography.

KEYWORDS

Arylglyoxals, L-cysteine, 1,3-dimethylbarbituric acid, phosphotungstic acid, one-pot, multi-component reaction.

1. Introduction

Multi-component reactions have many advantages over classical reactions, such as low cost and energy consumption, easier isolation and purification, greater atom economy as well as using green solvents with excellent chemo- and regioselectivities.[1–6]

Barbituric acids play an important role in many drugs with biological and pharmaceutical properties.[7–16] They are well-known as anticonvulsants, hypnotics, sedatives, and anxiolytic agents.[17–22] Although barbituric acid itself is hypnotically inactive, its derivatives substituted at C-5 are reported as central nervous system depressants.[23] The synthesis of 5-[2-aryl-2-oxoethyl]-1,3-dimethylpyrimidine-2,4,6-trione derivatives by reaction of arylglyoxal hydrates and 1,3-dimethylbarbituric acid in the presence of guanidine salts has also been reported under reflux or microwave conditions.[24]

Reduction of 5-arylidene-1,3-dimethylbarbituric acid derivatives with a series of thiols has been reported[25] (Scheme 1). In this study, we have investigated whether the amino acid cysteine would lead merely to reduced products, as shown in Scheme 1, or whether conjugate addition of the thiol group might lead to a new series of potential medicinally active compounds.

Herein, we investigate the one-pot, three-component reaction of 1,3-dimethylbarbituric acid, arylglyoxals and L-cysteine in the presence of phosphotungstic acid as a catalyst in H_2O/EtOH under reflux conditions.

2. Experimental

General Procedures

The chemicals used in this work were purchased from Acros Organics or from Merck and were used without purification. Melting points were measured on a Philip Harris C4954718 apparatus. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer at 300 and 75 MHz, respectively. Chemical shifts were measured in $CDCl_3$ as solvent relative to TMS as the internal standard. Infrared spectra were recorded on a Thermo-Nicolet Nexus 670 FT-IR instrument using KBr discs. Elemental analyses were performed using a Leco Analyzer 932. Mass spectra were recorded on an Agilent Technologies (HP) MS Model: 5975C VL MSD mass spectrometer operating at EI 70 eV.

Sample procedure for the synthesis of 5-(2-aryl-2-oxoethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6a–g)

A mixture of 1,3-dimethylbarbituric acid (**3**) (1 mmol) and arylglyoxals **2** (1 mmol) in water (3 mL) was stirred at room temperature for the period of time indicated in Table 1. After compeletion of intermediate formation (tlc, using MeOH: Hexane:$CHCl_3$ / 1:3:15 as eluents, R_f = 0.57–0.62), L-cysteine (2 mmol), phosphotungstic acid (10 % mol) and ethanol (1.5 mL) were added to the reaction mixture, which was refluxed for 1–2 h, during which time the L-cystine was precipitated. The precipitate was filtered and the filtrate was extracted with chloroform. The organic layer was separated, washed with water and dried over Na_2SO_4. Removal of solvent gave the desired products as colourless crystals in 69–77 % yields.

1,3-Dimethyl-5-(2-oxo-2-phenylethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6a): R_f = 0.57. Colourless crystals; 71 %; m.p. 190 °C [lit.,[24] 190–191 °C]; δ_H: 7.96 (2H, d, J = 8.1 Hz, Ar), 7.69 (1H, d, J = 6.6 Hz, Ar), 7.49 (2H, t, J = 8.1 Hz, Ar), 4.05 (2H, d, J = 3.3 Hz, CH_2), 3.61 (1H, t, J = 3.3 Hz, CH), 3.37 (6H, s, 2×NMe) ppm; δ_C: 196.9, 168.0, 151.7, 135.3, 134.0, 129.8, 128.8, 44.5, 37.8, 28.8 ppm; FT-IR υ_{max}: 3427, 2892, 1667, 1463, 139, 1306, 1218, 1113, 1031, 764, 691 cm^{-1}. *m*/z: 274 [M]$^+$ (24), 169 (5), 105 [C_6H_5CO]$^+$ (100), 77 (48), 55 (9), 51 (8).

5-(2-(4-Chlorophenyl)-2-oxoethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3H,5*H*)-trione (6b): R_f = 0.59. Colourless crystals; 75 %; m.p. 166 °C; δ_H: 7.88 (2H, d, J = 8.4 Hz, Ar), 7.45 (2H, d, J = 8.4 Hz,

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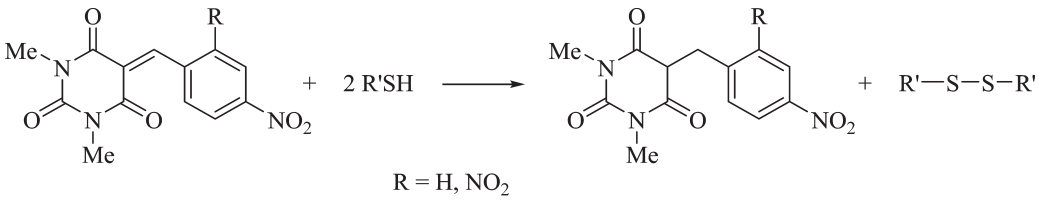


Scheme 1
Reduction of 5-arylidene-1,3-dimethylbarbituric acid derivatives with thiols.

Ar), 3.98 (2H, d, J = 3.9 Hz, CH_2), 3.61 (1H, t, J = 3.9 Hz, CH), 3.35 (6H, s, 2×NMe) ppm; δ_C: 195.8, 167.8, 151.6, 140.5, 133.6, 129.7, 129.1, 44.5, 37.6, 28.8 ppm; FT-IR υ_{max}: 3424, 2883, 1667, 1589, 1463, 1377, 1219, 1097, 1034, 819, 755 cm^{-1}; Found: C, 54.52; H, 4.11; N, 9.16 %. Calc. for $C_{14}H_{13}ClN_2O_4$ (308.72); C, 54.47; H, 4.24; N, 9.07 %. *m/z*: 310 $[M+2]^+$ (20), 308 $[M]^+$ (54), 169 (22), 141 $[4\text{-}^{37}ClC_6H_4CO]^+$ (100), 140 (42), 139 $[4\text{-}^{35}ClC_6H_4CO]^+$ (100), 113 (35), 111 (87), 75 (31), 55 (22).

5-(2-(4-Fluorophenyl)-2-oxoethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6c): R_f = 0.62. Colourless crystals; 69 %; m.p. 162 °C [lit.,[24] 162–163 °C]; δ_H: 7.98 (2H, t, J = 8.4 Hz, Ar), 7.16 (2H, t, J = 8.4 Hz, Ar), 4.02 (2H, d, J = 3.6 Hz, CH_2), 3.60 (1H, t, J = 3.6 Hz, CH), 3.37 (6H, s, 2×NMe) ppm; δ_C: 195.3, 167.9, 164.5, 151.7, 131.8, 131.8, 131.1, 131.0, 116.1, 115.8, 44.5, 37.7, 28.8 ppm. FT-IR υ_{max}: 3389, 3335, 3062, 2930, 2885, 1665, 1606, 1464, 1379, 1312, 1229, 1151, 1111, 1033, 833, 751, 562 cm^{-1}.

1,3-Dimethyl-5-(2-oxo-2-(*p*-tolyl)ethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6d): R_f = 0.58. Colourless crystals; 76 %; m.p. 174 °C; δ_H: 7.84 (2H, d, J = 7.8 Hz, Ar), 7.27 (2H, d, J = 6.6 Hz, Ar), 4.02 (2H, d, J = 3.3 Hz, CH_2), 3.57 (1H, t, J = 3.3 Hz, CH), 3.36 (6H, s, 2×NMe), 2.42 (3H, s, CH_3) ppm; δ_C: 195.5, 168.0, 151.7, 144.9, 130.4, 129.5, 128.4, 43.7, 36.1, 29.7, 27.9, 26.5 ppm; FT-IR υ_{max}: 3429, 2945, 2876, 1669, 1464, 1383, 1233, 1109, 1037, 815, 757, 573, 500 cm^{-1}; Found: C, 62.33; H, 5.68; N, 9.60 %. Calc. for $C_{15}H_{16}N_2O_4$ (288.30); C, 62.49; H, 5.59; N, 9.72 %. *m/z*: 288 (M^+, 88), 169 (13), 120 (99), 119 $[4\text{-}MeC_6H_4CO]^+$ (100), 92 (22), 91 (98), 90 (22), 89 (26), 65 (76), 66 (15), 58 (15), 56 (21), 55 (42).

5-(2-(4-Methoxyphenyl)-2-oxoethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6e): R_f = 0.58. Colourless crystals; 69 %; m.p. 197 °C; δ_H: 7.93 (2H, d, J = 9 Hz, Ar), 6.95 (2H, d, J = 9 Hz, Ar), 4.01 (2H, d, J = 3.9 Hz, CH_2), 3.89 (3H, s, CH_3), 3.56 (1H, t, J = 3.3 Hz, CH), 3.37 (6H, s, 2×NMe) ppm; δ_C: 195.2, 168.1, 164.1, 151.7, 130.6, 128.4, 113.9, 55.5, 44.5, 37.6, 29.7, 28.7 ppm; FT-IR υ_{max}: 3391, 3319, 2942, 2891, 1664, 1604, 1375, 1250, 1167, 1111, 1027, 827, 749, 563 cm^{-1}; Found: C, 59.10; H, 5.42; N, 9.17 %. Calc. for $C_{15}H_{16}N_2O_5$ (304.30); C, 59.21; H, 5.30; N, 9.21 %. *m/z:* 304 $[M]^+$ (20), 136 (16), 135 $[4\text{-}MeOC_6H_4CO]^+$ (100), 107 (10), 92 (18), 77 (24), 55 (11).

5-(2-(3,4-Dimethoxyphenyl)-2-oxoethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6f): R_f = 0.60. Colourless crystals; 77 %; m.p. 181 °C; δ_H: 7.62 (1H, d, J = 8.7 Hz, Ar), 7.43 (1H, s, Ar), 6.90 (1H, d, J = 8.4 Hz, Ar), 4.01 (2H, d, J = 3.6 Hz, CH_2), 3.95 (3H, s, OMe), 3.90 (3H, s, OMe), 3.56 (1H, t, J = 3.6 Hz, CH), 3.36 (6H, s, 2×NMe) ppm; δ_C: 195.5, 168.2, 154.1, 151.7, 149.1, 128.5, 124.5, 111.1, 58.8, 56.8, 55.2, 43.8, 37.5, 29.7, 27.8 ppm; FT-IR υ_{max}: 2949, 2862, 1673, 1587, 1442, 1378, 1264, 1153, 1020, 753 cm^{-1}; Found: C, 57.56; H, 5.30; N, 8.25 %. Calc. for $C_{16}H_{18}N_2O_6$ (334.43); C, 57.48; H, 5.43; N, 8.38 %. *m/z:* 335 $[M+1]^+$ (16), 334 $[M]^+$ (74), 166 (34), 165 $[3,4\text{-}(MeO)_2C_6H_3CO]^+$ (100), 137 (21), 122 (12), 107 (11), 79 (19), 77 (18), 55 (18).

5-(2-(4-Hydroxy-3-methoxyphenyl)-2-oxoethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6g): R_f = 0.61. Colourless crystals; 72 %; m.p. 199 °C; δ_H: 7.60–7.57 (1H, m, Ar), 7.44 (1H, d, J = 0.3 Hz, Ar), 6.97 (1H, d, J = 8.1 Hz, Ar), 6.15 (1H, s, Ar), 4.02 (2H, d, J = 3.6 Hz, CH_2), 3.92 (3H, s, CH_3), 3.56 (1H, t, J = 3.6 Hz, CH), 3.37 (6H, s, 2×NMe) ppm; δ_C: 195.4, 168.1, 151.2, 146.7, 124.0, 114.0, 109.8, 56.0, 44.6, 37.5, 28.8 ppm; FT-IR υ_{max}: 3401, 2947, 2889, 1672, 1593, 1507, 1441, 1389, 1277, 1170, 1114, 1029, 866, 756 cm^{-1}; Found: C, 56.19; H, 5.26; N, 8.67 %. Calc. for $C_{15}H_{16}N_2O_6$ (320.30); C, 56.25; H, 5.04; N, 8.75 %. *m/z:* 320 $[M]^+$ (70), 152 (34), 151 $[3\text{-}MeO\text{-}4\text{-}HOC_6H_3CO]^+$ (100), 123 (35), 108 (18), 77 (9), 55 (23).

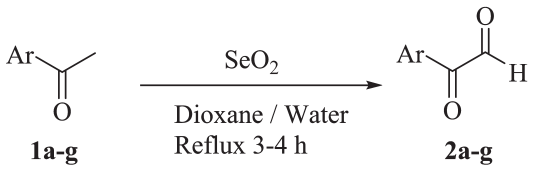
3. Results and Discussion

The arylglyoxals **2a–g** were prepared from the corresponding acetophenones **1a–g** by oxidation with SeO_2 as outlined in Scheme 2.[26–37]

The arylglyoxals **2a–g** were reacted with 1,3-dimethylbarbituric acid (**3**) in H_2O at room temperature to give the corresponding intermediate α,β-unsaturated triones **4a–g**, which were then treated with L-cysteine in presence of phosphotungstic acid under reflux in H_2O/EtOH to form 5-[2-aryl-2-oxoethyl]-1,3-dimethylpyrimidine-2,4,6-trione derivatives **6a–g** as shown in Scheme 3.

The reaction of the intermediate **4a** with L-cysteine (**5**) in the absence of catalyst gave the corresponding product in only 30 % yield after refluxing for 9 h. As expected, in the absence of L-cysteine, no reaction occurred. Seven examples of the conversion of arylglyoxals **2a–g** into the corresponding 5-[2-aryl-2-oxoethyl]-1,3-dimethylpyrimidine-2,4,6-triones **6a–g** at the optimum reaction conditions are listed in Table 1.

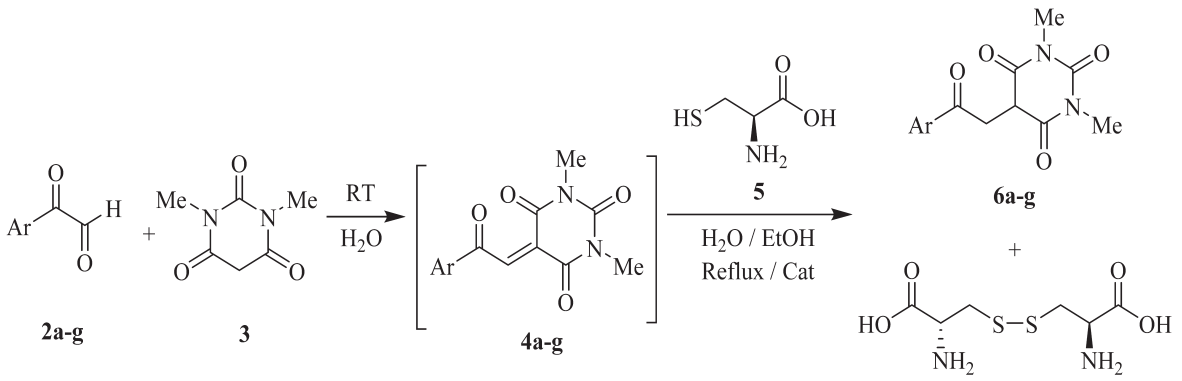
The structures of compounds **6a–g** were elucidated by microanalysis, and their spectral data (FT-IR, ^{1}H-NMR, ^{13}C-NMR). The X-ray crystallographyic analysis of compound **6f**, and the mass spectra of compounds **6a, 6b** and **6d–g** are also reported.



1a-g **2a-g**

a; Ar = C_6H_5 **b**; Ar = 4-ClC_6H_4 **c**; Ar = 4-FC_6H_4 **d**; Ar = 4-MeC_6H_4
e; Ar = 4-$MeOC_6H_4$ **f**; Ar = 3,4-$(MeO)_2C_6H_3$ **g**; Ar = 3-MeO-4-HOC_6H_3

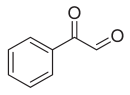
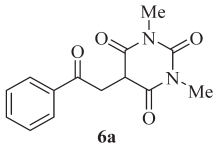
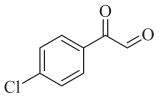
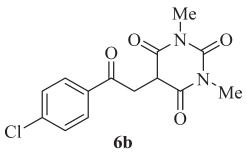
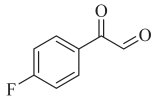
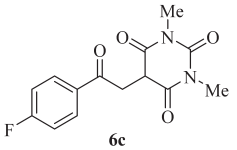
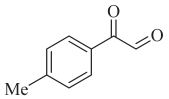
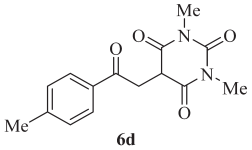
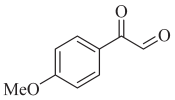
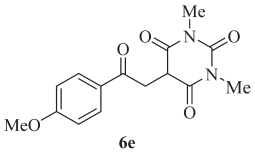
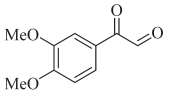
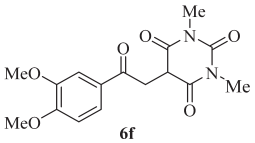
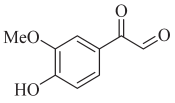
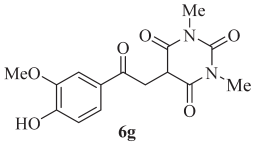
Scheme 2
Preparation of arylglyoxals.



a; Ar = C_6H_5 **b**; Ar = 4-ClC_6H_4 **c**; Ar = 4-FC_6H_4 **d**; Ar = 4-MeC_6H_4
e; Ar = 4-$MeOC_6H_4$ **f**; Ar = 3,4-$(MeO)_2C_6H_3$ **g**; Ar = 3-MeO-4-HOC_6H_3

Scheme 3
Synthesis of 5-[2-aryl-2-oxo-ethyl]-1,3-dimethylpyrimidine-2,4,6-trione derivatives.

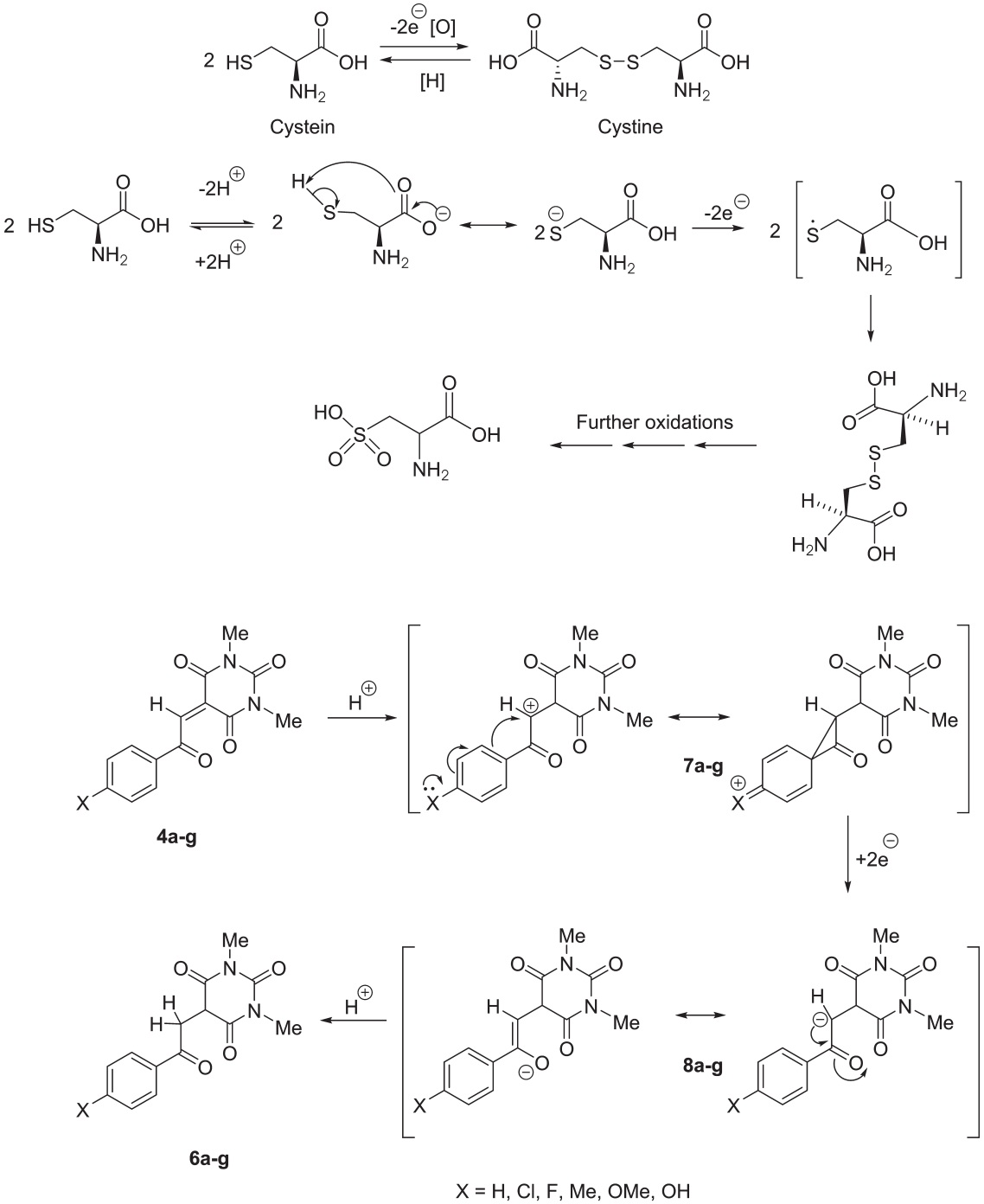
Table 1 The yields, reaction times and melting points of compounds **6a–g**.

Entry	Arylglyoxals	Products	Reaction time/min	Yield/%	M.p./°C
1	 **2a**	 **6a**	115	71	190 [lit.,[24] 190–191 °C]
2	 **2b**	 **6b**	87	75	181
3	 **2c**	 **6c**	90	69	162 [lit.,[24] 162–163 °C]
4	 **2d**	 **6d**	95	76	193
5	 **2e**	 **6e**	75	69	191
6	 **2f**	 **6f**	70	77	177
7	 **2g**	 **6g**	65	72	175

The ^{1}H NMR spectra of all compounds **6a–g** showed a characteristic doublet at around δ 3.98–4.07 ppm, ascribed to the methylene groups, a triplet at around δ 3.56–3.61 ppm due to the CH group and a singlet at around δ 3.35–3.37 ppm due to the methyl groups of the 1,3-dimethylbarbituric acid moiety. In ^{13}C NMR spectra, signals around 195 ppm were ascribed to the ketone carbonyl, and the two singlets around 168 and 153 ppm to the amide carbonyl groups. In the FT-IR spectra, the characteristic absorption bonds at 1664–1673 cm^{-1} could be assigned to the vibrations of the above-mentioned carbonyl groups. The mass spectra of all compounds showed aroyl cations as main fragments with 100 % abundance.

The proposed mechanism for reduction of 5-arylidene-1,3-dimethylbarbituric acid **4a–g** by L-cysteine (**5**) in presence of phosphotungstic acid is shown in Scheme 4. The proton absorption by α,β-unsaturated triketones **4a–g** forms the carbocations **7a–g** with electron-deficient carbon near to aroyl group, which was changed to carbanions **8a–g** by transfer of two electrons from cysteine and finally formed the desired trione **6a–g** by absorption of the second proton. It seems that electron-donating substituents on arylglyoxals stabilizes the carbocations **7a–g** formed in the first step, as the reaction with 4-nitro substituent failed to form the corresponding reduced triketone, due to destabilization of carbocations formation in the first step by electron-withdrawing effect of nitro substituent.

The metal ions in phosphotungstic acid catalyzes the oxidation of L-cysteine to L-cystine.



Scheme 4
The proposed mechanism for reaction.

4. Conclusions

We have synthesized some barbituric acid derivatives *via* the one-pot, three-component reaction of arylglyoxals, 1,3-dimethylbarbituric acid and L-cysteine in H_2O/EtOH. The resulting 5-[2-aryl-2-oxoethyl]-1,3-dimethylpyrimidine-2,4,6-triones synthesized would appear to be suitable synthetic intermediates for a series of new planar polycyclic heterocycles such as pyrimido[4,5-*c*]pyrazines[38] and pyrazolo[2,3-*d*]pyrimidines,[39] with possible pharmaceutical applications.

Supplementary Data

Other supplementary data (^{1}H-NMR, ^{13}C-NMR, IR and mass spectra) associated with this article are available in the online supplement.

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