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 aryglyoxals 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

Aryglyoxals, 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.7−10 They are well-known as anticonvulsants, hypnotics, sedatives, and anxiolytic agents.11−14 Although barbituric acid itself is hypnotically inactive, its derivatives substituted at C-5 are reported as central nervous system depressants.15−16 The synthesis of 5-[2-aryl-2-oxoethyl]-1,3-dimethylpyrimidine-2,4,6-triones by reaction of aryglyoxal 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 reported25 (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, aryglyoxals and L-cysteine in the presence of phosphotungstic acid as a catalyst in H2O/EtOH under reflux conditions.

2. Experimental Procedures

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 C8954718 apparatus. 1H and 13C-NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer at 300 and 75 MHz, respectively. Chemical shifts were measured in CDCl3 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-(2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (6a–g)

A mixture of 1,3-dimethylbarbituric acid (3) (1 mmol) and aryglyoxals 2 (1 mmol) in water (3 mL) was stirred at room temperature for the period of time indicated in Table 1. After completion of intermediate formation (tlc, using MeOH:water and dried over Na2SO4. 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(1H,3H,5H)-trione (6a–g)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
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<tbody>
<tr>
<td>6a</td>
<td>H</td>
<td>4-Chloro</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>6b</td>
<td>4-Chloro</td>
<td>H</td>
<td>2-NO2</td>
<td>H</td>
</tr>
<tr>
<td>6c</td>
<td>H</td>
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<td>H</td>
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<td>6f</td>
<td>H</td>
<td>4-Chloro</td>
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<td>H</td>
</tr>
<tr>
<td>6g</td>
<td>H</td>
<td>4-Chloro</td>
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</tr>
</tbody>
</table>

Avance AQS 300 MHz spectrometer at 300 and 75 MHz, respectively. Chemical shifts were measured in CDCl3 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.
Reduction of 5-arylidene-1,3-dimethylbarbituric acid derivatives with thiols.

5-(2-(Fluoro-3-methoxyphenyl)-2-oxoethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (6c): R<sub>e</sub> = 0.56. Colourless crystals; 76 %; m.p. 178 °C [lit., 161–164 °C]; δ<sub>δ</sub>: 7.50 (1H, d, J = 8 Hz, Ar), 7.15 (2H, d, J = 6 Hz, Ar), 4.02 (2H, d, J = 3.3 Hz, CH<sub>2</sub>), 3.57 (1H, t, J = 3.3 Hz, CH<sub>3</sub>), 3.36 (6H, s, 2×NMe<sub>2</sub>), 1.28 (3H, s, CH<sub>3</sub>) ppm; δ<sub>δ</sub>: 159.5, 168.2, 164.9, 150.9, 141.4, 134.7, 128.6, 128.0, 125.6, 128.0, 124.7, 129.5, 118.6, 117.7, 110.3, 108.9, 76.4, 38.8, 32.0 ppm; FT-IR vmax: 3429, 2954, 2876, 1769, 1664, 1430, 1379, 1219, 1151, 1111, 1033, 833, 753, 573 cm<sup>–1</sup>. 

3. Results and Discussion

The arylglyoxals 2a–g were prepared from the corresponding acetophenones 1a–g by oxidation with SeO<sub>2</sub> as outlined in Scheme 2.3–7

The arylglyoxals 2a–g were reacted with 1,3-dimethylbarbituric acid (3) in H<sub>2</sub>O 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<sub>2</sub>O/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. Several 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, 1H-NMR, 13C-NMR). The X-ray crystallographic analysis of compound 6f, and the mass spectra of compounds 6a, 6b, and 6d–g are also reported.
Table 1. The yields, reaction times and melting points of compounds 6a–g.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylglyoxals</th>
<th>Products</th>
<th>Reaction time/min</th>
<th>Yield/%</th>
<th>M.p./°C</th>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>6a</td>
<td>115</td>
<td>71</td>
<td>190 [lit., 24 190–191 °C]</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>6b</td>
<td>87</td>
<td>75</td>
<td>181</td>
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<tr>
<td>3</td>
<td>2c</td>
<td>6c</td>
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<td>69</td>
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<tr>
<td>6</td>
<td>2f</td>
<td>6f</td>
<td>70</td>
<td>77</td>
<td>177</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>6g</td>
<td>65</td>
<td>72</td>
<td>175</td>
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</table>

Scheme 3
Synthesis of 5-[2-aryl-2-oxo-ethyl]-1,3-dimethylpyrimidine-2,4,6-trione derivatives.
The $^1$H NMR spectra of all compounds 6a–g showed a characteristic doublet at around $\delta$ 3.98–4.07 ppm, ascribed to the methylene groups, a triplet at around $\delta$ 3.56–3.61 ppm due to the CH group and a singlet at around $\delta$ 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 aryl 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 $\alpha,\beta$-unsaturated triketones 4a–g forms the carbocations 7a–g with electron-deficient carbon near to aryl 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.
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 H₂O/ETOH. The resulting 5-[2-arylidene-2-oxoethyl]-1,3-dimethylpyrimidine-2,4,6-triones synthesized would appear to be suitable synthetic intermediates for a series of new planar poly cyclic heterocycles such as pyrimido [4,5-c]pyrazines and pyrazolo[2,3-í]pyrimidines, with possible pharmaceutical applications.

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

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