One-pot synthesis of functionalized thiazolidine-4-ones from thiosemicarbazone derivatives and activated acetylenes in water as a green solvent

Sayed Ali Ahmadi*, Dadkhoda Ghazanfari

Department of Chemistry, Faculty of Science, Kerman Branch, Islamic Azad University, Kerman, Iran.

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ABSTRACT

Some 2-iminothiazolidin-4-ones have been synthesized by the reaction of dialkyl acetylenedicarboxylates with thiosemicarbazones. The reaction was performed in the presence of 10 mol% of triphenylphosphine and tetrabutylammonium bromide as a phase transfer catalyst in water as a green solvent. All the synthesized compounds were characterized by their physical and spectral data.

Keywords: Dialkyl acetylenedicarboxylate, Thiosemicarbazone, Thiazolidine-4-ones, Triphenyl phosphine, Tetrabutyl ammonium bromide.

1. Introduction

Reaction of dimethylacetylene dicarboxylate (DMAD) with esters and amides of dithiocarboxylic acids are well known methods for preparation of five membered S, and N heterocycles [1-3]. One of the most important groups of five membered heterocycles is thiazolidinones.

Several methods have been reported in the literature for the preparation of 4-thiazolidinone derivatives. For instance, the reaction between thioureas and thiosemicarbazide derivatives with DMAD is known as a convenient and effective method to prepare 2-amino-5-methoxycarbonyl-thiazolidin-4-ones [4-6]. Most of reported methods use the toxic organic solvents, Hence a more efficient and practical alternative method using an inexpensive and environmentally friendly reagent and solvent is still needed.

In the past years, organic solvents were the most common and perhaps the only choices of solvents among chemists. This scenario has been substantially changed during the last decade or so due to the intensive research towards environmentally benign substitutes for volatile and toxic organic solvents. Now chemists have to deal with the challenge of reducing the environmental impact of the processes without losing their efficiency by using the so-called green solvents under the concepts of Green Chemistry, which has emerged as an important area of chemistry and has achieved outstanding progress towards the development of green reaction processes [7].

A green solvent must ideally have a high boiling point, a low vapor pressure, be non-toxic, dissolve a great range of organic compounds, be inexpensive and of course be recyclable. Water is a solvent with unique physical-chemical properties. Its use as a solvent or co-solvent has unique synthetic advantages leading in some cases to exceptionally high selectivities or reaction rates. Furthermore, organic reactions in water may lead to the development of environmentally friendly chemical processes.

2. Experimental

All chemical compounds were purchased from Merck chemical company and used without further purification. Products 3a-e are known and characterized by comparison of their spectral data with authentic samples [8]. Melting points were recorded on an Electrothermal-9100 apparatus and were uncorrected. IR spectra were recorded on a Brucker Tensor 27 FT-IR spectrometer. NMR spectra were recorded on a BRUKER DRX-500 AVANCE NMR spectrometer using DMSO-d$_6$ as solvent. Mass spectra...
were recorded on an Agilent Technologies MS-5973 (70 eV) mass spectrometer.

2.1. General procedure for the preparation of thiosemicarbazones

Carbonyl compound (2 mmol), thiosemicarbazide (2.2 mmol) and one drop of HCl as catalyst were dissolved in 30 mL of ethanol and refluxed until the reaction was completed (monitored by TLC). Then, the reaction mixture was cooled and poured into crushed ice-water and the resulting precipitate was filtered off and recrystallized from ethanol.

2.2. General procedure for the preparation of 2-thiazolidin-4-ones

A mixture of thiosemicarbazone 1 (1 mmol), acetylenic ester 2 (1 mmol), PPh₃ (0.01 mmol) and TBAB (1 mmol) were mixed in 10 mL of water and refluxed for 2h. The resulting precipitate after filtering was recrystallized from ethanol.

**Spectral data**

*Compound 3a:* Mp 179-181 °C. IR (KBr): 3160, 3075, 2890, 1728, 1715, 1620 cm⁻¹. ¹H NMR (DMSO-d₆) δ (ppm): 3.82 (s, 3H, OCH₃), 6.66 (s, 1H, C=CH), 7.30-7.97 (m, 10H, Ar-H), 8.53 (s, 1H, NH). ¹³C NMR (DMSO-d₆) δ (ppm): 53.3, 114.9, 128.7, 128.8, 129.8, 132.1, 134.6, 143.9, 159.4, 161.6, 166.9. MS (m/z, %): 365 (M, 20), 165 (100), 118 (100), 316 (12), 91 (50).

*Compound 3b:* Mp 210-215 °C. IR (KBr): 3180, 3081, 1741, 1716, 1641 cm⁻¹. ¹H NMR (DMSO-d₆) δ (ppm): 2.33 (3H, s, CH₃), 2.39 (3H, s, CH₃), 3.75 (3H, s, OCH₃), 6.61 (1H, s, CH=C), 7.76-7.22 (4H, 2d, Ar-H), 12.76 (1H, s, N-H). ¹³C NMR (DMSO-d₆) δ (ppm): 14.74, 20.39, 52.17, 114.00, 126.50, 129.06, 134.48, 140.00, 140.14, 143.14, 162.08, 165.53, 165.88. MS (m/z, %): 317 (M, 30), 118 (100), 302 (10), 91 (40), 65 (30).

*Compound 3c:* Mp 222-225 °C. IR (KBr): 3180, 3081, 2956, 1741, 1716, 1641, 1617 cm⁻¹. ¹H NMR (DMSO-d₆) δ (ppm): 1.25 (3H, CH₃), 2.33 (3H, CH₃), 2.47 (3H, CH₃), 4.21 (2H, CH₂), 6.58 (1H, s, CH=C), 7.74-7.23 (4H, 2d, Ar-H), 11.75 (1H, s, N-H). ¹³C NMR (DMSO-d₆) δ (ppm): 13.71, 14.47, 20.62, 60.95, 114.25, 126.29, 128.78, 134.44, 139.85, 142.63, 158.28, 162.55, 165.08, 165.31. MS (m/z, %): 331 (M, 15), 118 (100), 316 (12), 91 (20).

*Compound 3d:* Mp 207-210 °C. IR (KBr): 3180, 3000, 2982, 1741, 1716 (C=O), 1666, 1617 cm⁻¹. ¹H NMR (DMSO-d₆) δ (ppm): 1.35 (3H, t, CH₃), 3.85 (3H, s, OCH₃), 4.31 (2H, q, CH₂), 6.78, (1H, s, CH=CH), 7.74-6.93 (4H, 2d, arom). 8.37 (1H, s, CH=N). ¹³C NMR (DMSO-d₆) δ (ppm): 14.17, 55.39, 60.24, 158.13, 159.48, 162.02, 166.04, 166.02, 170.94. MS (m/z, %): 333 (M, 7), 134 (100), 120 (30), 91 (20).

*Compound 3e:* Mp 180-184 °C. IR (KBr): 3240, 3054, 2910, 1730, 1716, 1617 cm⁻¹. ¹H NMR (DMSO-d₆) δ (ppm): 2.34 (s, 1H, CH₃), 3.78 (s, 3H, OCH₃), 6.66 (s, 1H, C=CH), 7.29-7.31 (d, J = 7.8 Hz, 2H, arom), 7.69-7.71 (d, J = 7.8 Hz, 2H, arom), 8.48 (s, 1H), 11.35 (s, 1H, NH). ¹³C NMR (DMSO-d₆) δ (ppm): 22.0, 53.2, 115.0, 128.1, 128.9, 130.1, 140.2, 143.2, 159.5, 166.7, 178.7. MS (m/z, %): 303 (M, 6), 117 (94), 103 (100).

*Compound 3f:* Mp 193-195 °C. IR (KBr): 3200, 3085, 2890, 1735, 1710, 1625 cm⁻¹. ¹H NMR (DMSO-d₆) δ (ppm): 3.78 (s, 3H, OCH₃), 6.67 (s, 1H, C=CH), 8.00-8.41 (m, 4H, arom), 8.67 (s, 1H), 11.69 (s, 1H, NH). ¹³C NMR (DMSO-d₆) δ (ppm): 53, 115.4, 124.6, 129.0, 129.7, 140.5, 141.6, 148.4, 157.4, 166.7, 179.3. MS (m/z, %): 149 (35), 76 (33), 57 (34), 42 (100).

### 3. Results and Discussion

In this investigation, we would like to report the synthesis of thiazolidinone compounds from thiosemicarbazide derivatives 1 which react with DMAD and DEAD 2 in water as solvent in the presence of 10 mol% of triphenylphosphine and tetrabutyl ammonium bromide (TBAB). The role of TBAB is to dissolve of reactants in water. (Scheme 1). The structures of compounds 3a–3f were assigned by consideration of their IR, ¹H NMR, and ¹³C NMR spectroscopic and mass spectrometric data. For example, the ¹H NMR spectrum of 3a shows a singlet for methoxy protons at 3.82, together with a characteristic signal for the methine proton at 6.66 ppm. In the ¹³C NMR spectrum of 3a, signal corresponding to carbonyl group was observed at 166.9 ppm. The mass spectrum of 3a contained the molecular ion peak at m/z = 365.

![Scheme 1. Synthesis of thiazolidin-4-ones in water.](www.SID.ir)
A plausible rationalization may be advanced to explain the product formation on the basis of the literature report for the synthesis of coumarin derivatives [9]. Presumably, the reaction involves the initial formation of a 1:1 zwitterionic intermediate 4 between the activated acetylenes 2 and Ph$_3$P, which undergoes reaction with 1 to produce the salt pair 5. Combination of this salt pair will produce 6. This intermediate is converted to product 3 via elimination of Ph$_3$P and cyclization (Scheme 2).

To study the generalizability of this process, several examples were studied and are summarized in Table 1. In all cases studied, the reaction proceeded very well to give the corresponding thiazolidinones in good yields.

Ease of recycling of the catalyst is a valuable advantage of this method. After the completion of the reaction, the product separated by filtration and the aqueous solution was used again for the same reaction. For the preparation of 3a (as a model reaction), no significant loss of the catalyst activity was observed when the aqueous solution was used after three times of recycling. Yield of product was 72% at the first run and became 70% at the third run.

In order to assess the efficiency of the present method in comparison with the reported method for the preparation of these compounds, the results of present method were compared with the reported literature method which used ethyl acetate as solvent (Table 2).

The advantages of the present method are the use of water as a green solvent instead of organic solvents and shorter reaction times. However, the yields are slightly lower than the literature.

### 4. Conclusions

In conclusion, a convenient method was described for the preparation of 2-thiazolidin-4-ones in water as a green solvent. This method has several unique merits, such as good yields, efficiency, generality, the use of small amount of the catalyst, simplicity in operation, low cost and the use of water as solvent. To put it differently, the method significantly contributes to the practice of green chemistry.

### Acknowledgement

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### References

Table 1. Synthesis of thiazolidine-4-one derivatives in water.

<table>
<thead>
<tr>
<th>Product 3</th>
<th>Carbonyl compound</th>
<th>Product structure</th>
<th>Yield (%)</th>
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<tr>
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<tr>
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<td><img src="image" alt="Structure D" /></td>
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<tr>
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<tr>
<td>F</td>
<td><img src="image" alt="Structure F" /></td>
<td><img src="image" alt="Structure F" /></td>
<td>85</td>
</tr>
</tbody>
</table>

Thiosemicarbazone (1 mmol), acetylenic ester (1 mmol), PPh₃ (0.01 mmol) and TBAB (1 mmol) in 10 mL of water, refluxed for 2h.

Table 2. Comparison the results of present method with the literatures.

<table>
<thead>
<tr>
<th>Product</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Reference</th>
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<td>r.t.</td>
<td>3h</td>
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<td>[8]</td>
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<tr>
<td></td>
<td>Water</td>
<td>Reflux</td>
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<td>Present work</td>
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<tr>
<td>3b</td>
<td>Ethylacetate</td>
<td>r.t.</td>
<td>3h</td>
<td>90</td>
<td>[8]</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>Reflux</td>
<td>2h</td>
<td>88</td>
<td>Present work</td>
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</table>