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

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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 thioamides 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 progresse 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

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were recorded on an Agilent Technologies MS-5973 (70 eV) mass spectrometer.

2.1. Genaral procedure for the preparation of thiosemicarbazones

Carbonyl compound (2 mmol), thiosemicarbazide (2.2 mmol) and one drop of HCl as atalyst 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 crashed ice-water and the resulting precipitate was filtered off and recrystalyzed from ethanol.

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

A mixture of thiosemicarbazone **1** (1 mmol), acetylenic ester **2** (1 mmol), PPh_3 (0.01 mmol) and TBAB (1 mmol) were mixed in 10 mL of water and refluxed for 2h. The resulting precipitate after filtering was recrystalized from ethanol.

Spectral data

*Compound **3a**:* Mp 179-181 ^oC. IR (KBr): 3160, 3075, 2890, 1728, 1715, 1620 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 3.82 (s, 3H, OCH_3), 6.66 (s, 1H, C=CH), 7.30-7.97 (m, 10H, Ar-H), 8.53 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) 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), 180 (30).

*Compound **3b**:* Mp 210-215 ^oC. IR (KBr): 3180, 3081, 1741, 1716, 1641 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 2.33 (3H, s, CH_3), 2.39 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 6.61 (1H, s, CH=C), 7.76-7.22 (4H, 2d, Ar-H), 12.76 (1H, s, N-H). ^{13}C NMR (DMSO-d_6) 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 ^oC. IR (KBr): 3180, 3081, 2956, 1741, 1716, 1641, 1617 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 1.25 (3H, CH_3), 2.33(3H, CH_3), 2.47(3H, CH_3), 4.21 (2H, CH_2), 6.58 (1H, s, CH=C), 7.74-7.23 (4H, 2d, Ar-H), 11.75 (1H, s, N-H). ^{13}C NMR (DMSO-d_6) 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 (50).

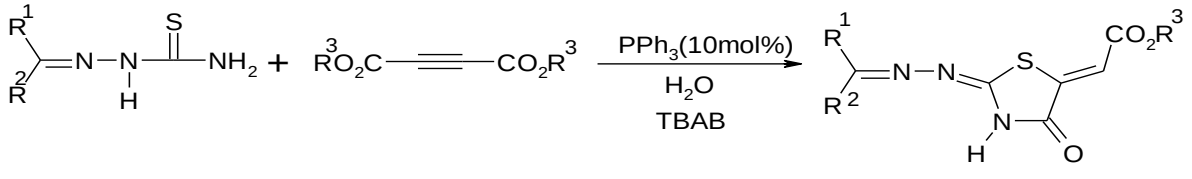
*Compound **3d**:* Mp 207-210 ^oC. IR (KBr): 3180, 3000, 2982, 1741, 1716 (C=O), 1666, 1617 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 1.35 (3H, t, CH_3), 3.85 (3H, s, OCH_3), 4.31 (2H, q, CH_2), 6.78, (1H, s, CH=C), 7.74-6.93 (4H, 2d, arom), 8.37 (1H, s, CH=N). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.17, 55.39, 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 ^oC, IR (KBr): 3240, 3054, 2910, 1730, 1716, 1617 cm^{-1}, ^1H NMR (DMSO-d_6) δ (ppm): 2.34 (s, 1H, CH_3), 3.78 (s, 3H, OCH_3), 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). ^{13}C NMR (DMSO-d_6) δ (ppm): 22.0, 53.2, 115.0, 128.1, 128.9, 130.1, 130.4, 142.2, 143.2, 159.5, 166.7, 178.7. MS (m/z, %): 303 (M, 6), 117 (94), 103 (100).

*Compound **3f**:* Mp 193-195 ^oC, IR (KBr): 3200, 3085, 2890, 1735, 1710, 1625 cm^{-1}, ^1H NMR (DMSO-d_6) δ (ppm): 3.78 (s, 3H, OCH_3), 6.67 (s, 1H, C=CH), 8.00-8.41 (m, 4H, arom), 8.67 (s, 1H), 11.69 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 53, 115.4, 124.6, 129.0, 129.7, 140.3, 141.6, 148.4, 157.4, 166.7, 179.3. MS (m/z, %): 149 (35), 76 (33), 57 (34), 42 (100).

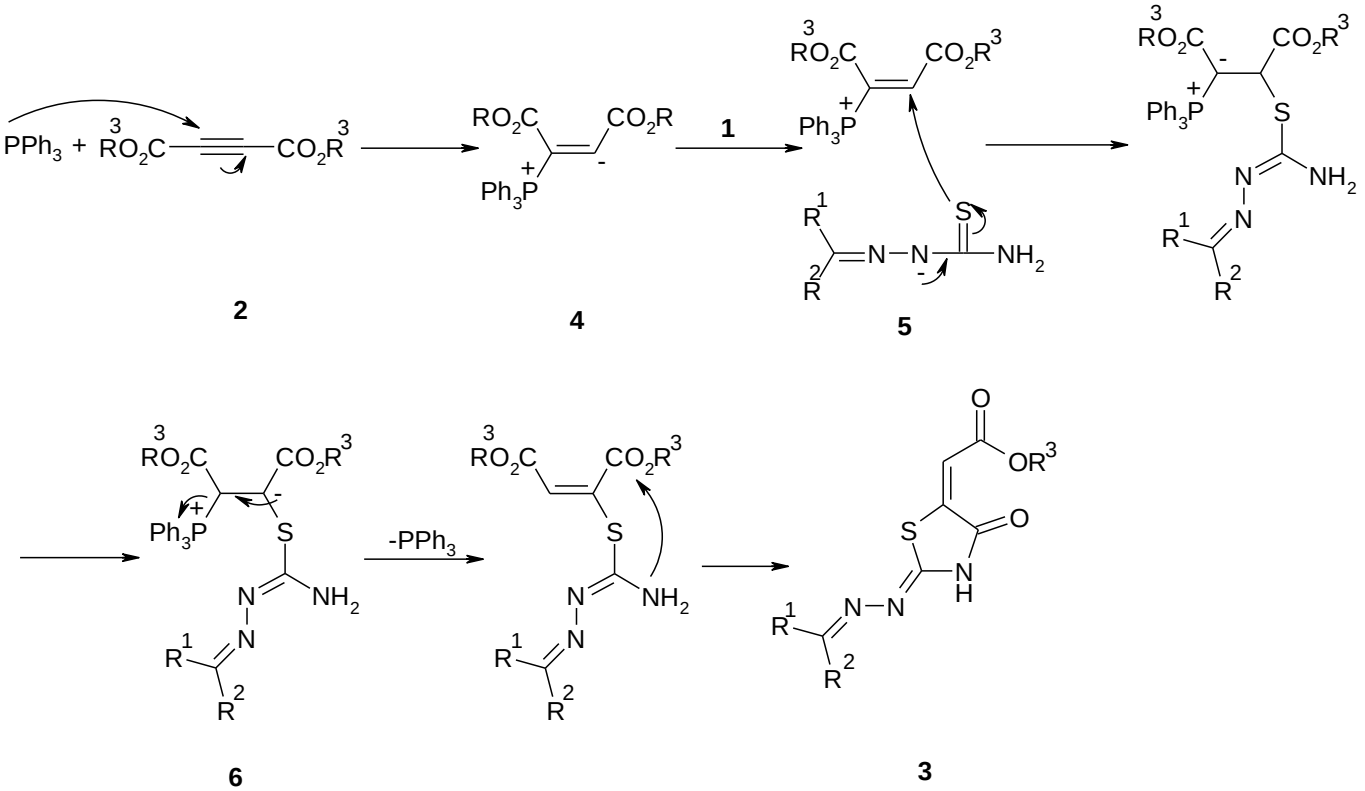
3. Results and Discussion

In this investigation, we would like to report the synthesis of thiazolidinone compounds from thiosemicarbazone 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 ^{13}C 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 ^{13}C 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.



1 **2** **3**

Scheme 1. Syntheis of thiazolodin-4-ones in water.



Scheme 2. A reasonable mechanism for the reaction of thiosemicarbazones with DMAD in the presence of PPh_3 as a catalyst.

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_3P, 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_3P 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 complition 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 ethylacetate 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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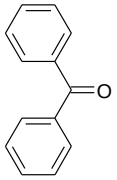
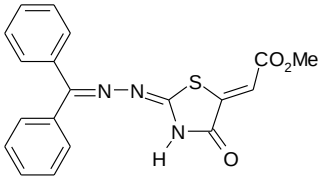
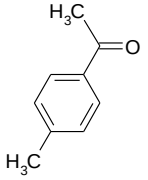
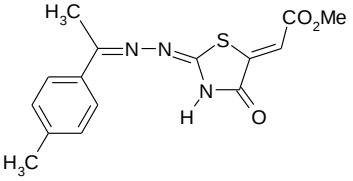
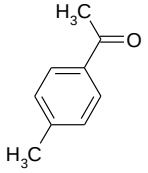
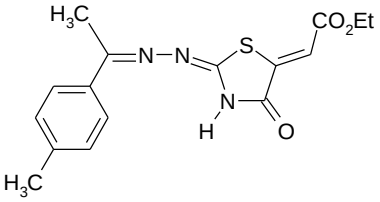
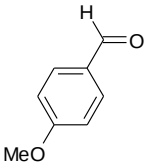
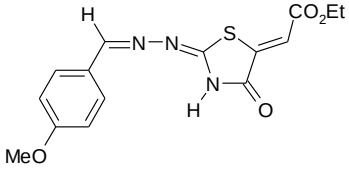
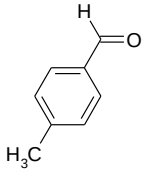
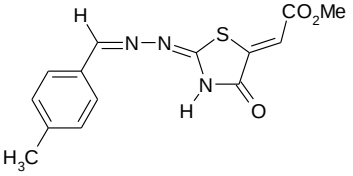
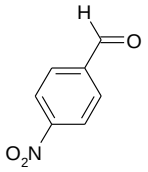
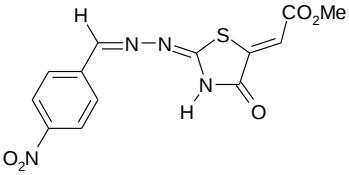
Table1. Synthesis of thiazolidine-4-one derivatives in water.[a]

Product 3	Carbonyl compound	Product structure	Yield (%)[b]
A			72
B			88
C			85
D			86
E			88
F			85

[a]Thiosemicarbazone (1 mmol), acetylenic ester (1 mmol), PPh_3 (0.01 mmol) and TBAB (1 mmol) in 10 mL of water, refluxed for 2h.
[b]Isolated yields

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

Product	Solvent	Conditions	Time	Yield (%)	Reference
3a	Ethylacetate	r.t.	3h	87	[8]
	Water	Reflux	2h	72	Present work
3b	Ethylacetate	r.t.	3h	90	[8]
	Water	Reflux	2h	88	Present work

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