HL ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)
http://heteroletters.org Vol. 3: (3), 2013, 325-329

ONE POT SYNTHESIS OF THIAZOLIDINONES IN MOLTEN $(ET_3NH)HSO_4$

Maryam Kalantari

Department of Chemical Engineering, Faculty of Engineering, Shahid Bahonar University of Kerman, Kerman, Iran
E-mail: Kalantari@mail.uk.ac.ir

Abstract:

Some thiazolidinones have been synthesized by the reaction of semicarbazones with acetylenic esters in molten $(Et_3NH)HSO_4$ as an acid ionic liquid. This method provides several advantages such as operational simplicity, higher yield, safety and environment friendly protocol.

Keywords: Thiosemicarbazone; thiazolidinone; acetylenic ester; triethyl ammonium hydrogen sulfate;

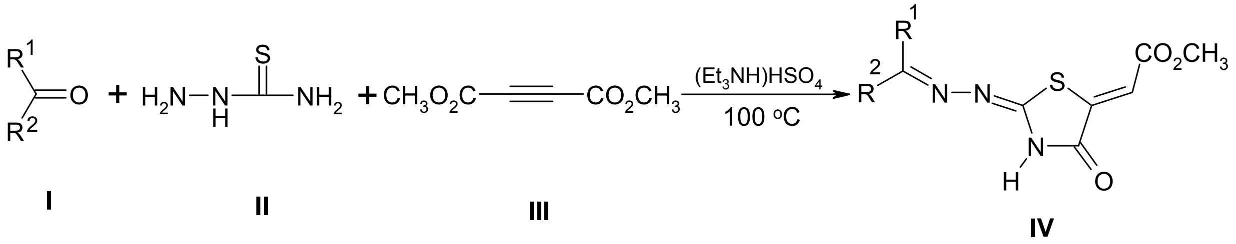
Introduction

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been done in the past [i]. Numerous reports have appeared in the literature highlighting the chemistry and use of these compounds [ii]. Thiazolidinone derivatives have been investigated for a range of pharmacologic indications such as anti-inflammatory [iii], antimicrobial [iv], antiviral [v], antifungal [vi], and antibacterial [vii] activities.

Results and Discussion:

In the present work, an attempt has been made to undertake the synthesis of thiazolidinone derivatives from thiosemicarbazones in molten triethyl ammonium hydrogen sulfate as an acidic ionic liquid.

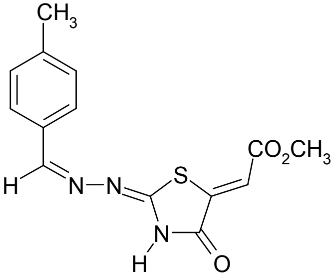
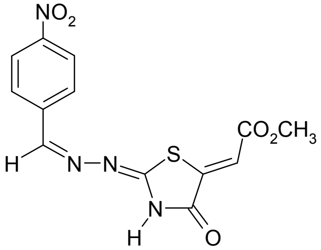
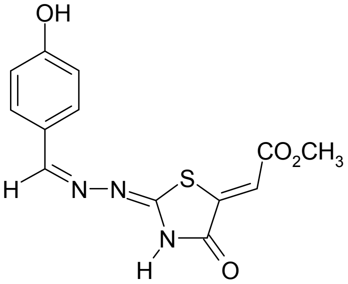
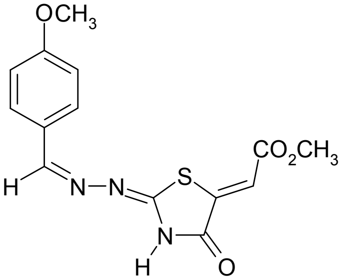
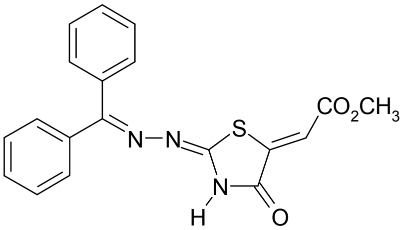
In the first part of this investigation the synthesis of thiazolidin-4-ones via the reaction of dimethylacetylene dicarboxylate (DMAD) with thiosemicarbazide and carbonyl compounds was performed. Treatment of equimolar quantities of a carbonyl compound **I** and thiosemicarbazide **II** with DMAD **III** in $(Et_3NH)HSO_4$ afforded exclusively thiazolidinone **IV** (Scheme 1).



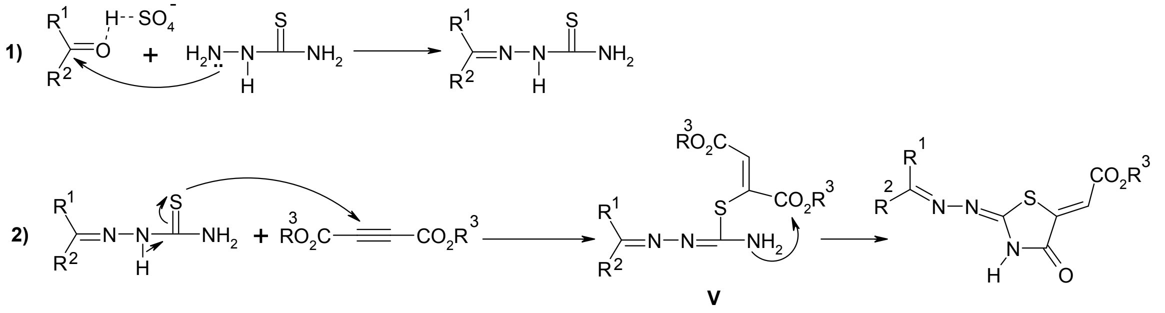
Scheme 1. one pot synthesis of thiazolidinones from thiosemicarbazide, DMAD and carbonyl compounds.

Several carbonyl compounds consisting of both electron withdrawing and electron-donating groups reacted smoothly with thiosemicarbazide and DMAD in $(Et_3NH)HSO_4$ as solvent to give 4-thiazolidinone in good yields within 5–15 minutes at 100 °C. The results are summarized in Table 1.

Table 1. Three component synthesis of thiazolidinones

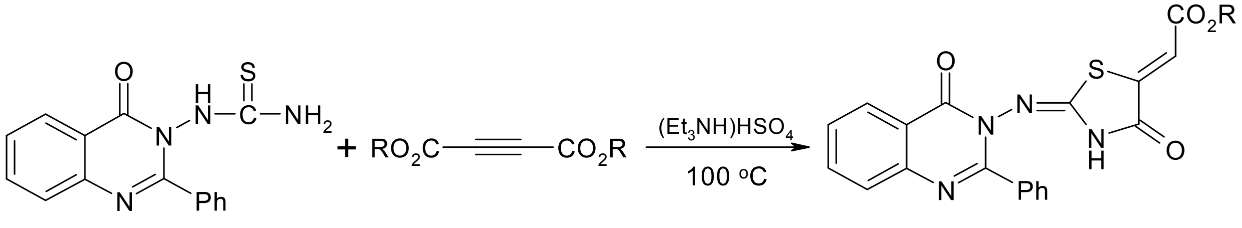
Entry	R^1	R^2	Product	Time (min)	Yield (%)
IVa	4-CH_3-C_6H_5	H		15	85
IVb	4-NO_2-C_6H_5	H		5	84
IVc	4-HO-C_6H_5	H		5	77
IVd	4-OCH_3-C_6H_5	H		10	57
IVe	Ph	Ph		15	52

A plausible mechanism is given in scheme 2. In the first step the carbonyl group activates by ($Et_3NH)HSO_4$ then it reacts with thiosemicarbazide to give a thiosemicarbazone. In the second step sulfur atom of thiosemicarbazone gives Michael addition with DMAD. Then the intermediate (**V**) undergoes an intramolecular cyclization to afford exclusively a thiazolidin-4-one.



Scheme 2.

After successfully synthesizing a series of thiazolidinones from one pot reaction of thiosemicarbazide, carbonyl compounds and DMAD, we turned our attention towards the synthesis of thiazolidinone derivatives **VII** via reaction of quinazolinyl thiourea **VI** with acetylenic ester **VII** under similar reaction conditions (Scheme 2).



VI **VII** **VIII**

VIII	R	Time (min)	Yield(%)
a	Me	15	80
b	Et	20	85

Scheme 2. Synthesis of quinazolinyl thiazolidnone

Experimental:

Dimethyl acetylenedicarboxylate (DMAD), diethyl acetylenedicarboxylate (DEAD), thiosemicarbazide were obtained from Merck chemical company and were used without further purification. Melting points were obtained on an Electrothermal-9100 melting point apparatus and were uncorrected. Mass spectra were recorded on a Shimadzu QP-2000A Mass spectrometer operating at an ionization potential of 70 eV. IR spectra data were recorded on a Brucker Tensor-27 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were reported on a Bruker DRX-500 AVANCE spectrometer at 500.13MHz and 125.76MHz, respectively. quinazolinyl thiourea **VI** was prepared according to the literature procedure [viii].

General procedure for the preparation of (IV)

Carbonyl compound **I** (1 mmole), thiosemicarbazide (1 mmole) and DMAD (1 mmol) was dissolved in 2 mmol of $(Et_3NH)HSO_4$. Reaction mixture was heated at 100 °C and progress was monitored by TLC. After completion of the reaction the mixture was dissolved in ethanol and poured into crashed ice-water to give a precipitate. It was filtered and recrystallized from ethanol to yield desired product.

{2-[(4-Methyl-benzylidene)-hydrazono]-4-oxo-thiazolidin-5-ylidene}-acetic acid methyl ester (**IVa**).

Yellow solid, m.p. 180 °C(dec), IR (KBr) v_{max} : 3240, 3054, 2910, 1730, 1716, 1617 cm^{-1}, ^{1}H NMR (DMSO-d6) 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-d6) 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).

{2-[(4-Nitro-benzylidene)-hydrazono]-4-oxo-thiazolidin-5-ylidene}-acetic acid methyl ester (**IVb**).

Yellow solid, m.p. 194 °C(dec), IR (KBr) v_{max} : 3200, 3085, 2890, 1735, 1710, 1625 cm^{-1}, ^{1}H NMR (DMSO-d6) 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-d6) 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).

{2-[(4-hydroxy-benzylidene)-hydrazono]-4-oxo-thiazolidin-5-ylidene}-acetic acid methyl ester (**IVc**). Yellow solid, m.p. 201 °C(dec), IR (KBr) v_{max} : 3250, 3015, 2920, 1730, 1715, 1620 cm^{-1}, ^{1}H NMR (DMSO-d6) δ (ppm): 3.75 (s, 3H, OCH_3), 6.62 (s, 1H, C=CH), 6.87 (d, J = 7.4 Hz, 3H, arom and OH), 7.64 (d, J = 7.5 Hz, 2H, arom), 8.37 (s, 1H), 10.18 (s, 1H, NH). ^{13}C NMR (DMSO-d6) δ (ppm): 53.2, 114.6, 116.7, 125.5, 130.6, 130.8, 144.0, 159.2, 161.4, 166.7, 166.7. MS (m/z, %): 305 (M, 23), 304 (100), 212 (17), 105 (80).

{2-[(4-methoxy-benzylidene)-hydrazono]-4-oxo-thiazolidin-5-ylidene}-acetic acid methyl ester (**IVd**). Yellow solid, m.p. 185 °C(dec), IR (KBr) v_{max} : 3150, 3065, 2880, 1733, 1720, 1625 cm^{-1}, ^{1}H NMR (DMSO-d6) δ (ppm): 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.65 (s, 1H, C=CH), 7.05 (d, 2H, J = 8.2 Hz, arom), 7.76 (d, 2H, J = 8.1 Hz, arom), 8.45 (s, 1H), 11.29 (s, 1H, NH). ^{13}C NMR (DMSO-d6) δ (ppm): 53.3, 56.3, 114.9, 115.0, 115.3, 127.2, 129.8, 130.7, 143.1, 143.9, 159.1, 166.8. MS (m/z, %): 318 (M-1, 78), 133 (100), 119 (51), 90 (43).

[2-(Benzhydrylidene-hydrazono)-4-oxo-thiazolidin-5-ylidene]-acetic acid mehyl ester (**IVe**). Yellow solid, m.p. 179 °C, IR (KBr) v_{max} : 3160, 3075, 2890, 1728, 1715, 1620 cm^{-1}, ^{1}H NMR (DMSO-d6) δ (ppm): 3.82 (s, 3H, OCH_3), 6.66 (s, 1H, C=CH), 7.30-7.97 (m, 10H, arom), 8.53 (s, 1H, NH). ^{13}C 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, %): 288 (43), 178 (33), 104 (35), 89 (100), 76 (93).

General procedure for the preparation of (VIII)

Quinazolinyl thiourea **VI** and DMAD (1 mmol) was dissolved in 2 mmol of $(Et_3NH)HSO_4$. Reaction mixture was heated at 100 °C and progress was monitored by TLC. After completion of the reaction the mixture was dissolved in ethanol and poured into crashed ice-water to give a precipitate. It was filtered and recrystalized from ethanol to yield desired product.

[4-Oxo-2-(4-oxo-2-phenyl-4H-quinazolin-3-ylimino)-thiazolidin-5-ylidene]-acetic acid methyl ester (**VIIIa**). Yellow solid, m.p. 200 °C (dec), IR (KBr) ν_{max} : 3200, 3056, 2940, 1732, 1718, 1690, 1615 cm^{-1}, ^1H NMR (DMSO-d6) δ (ppm): 3.77 (s, 1H, CH_3), 6.80 (s, 1H, C=CH), 7.22-8.20 (m, 9H, arom), 10.85 (s, 1H, NH). ^{13}C NMR (DMSO-d6) δ (ppm): 53.8, 116.2, 122.5, 126.2, 126.7, 127.8, 128.8, 129.2, 130.0, 131.4, 134.3, 140.7, 147.2, 148.8, 158.8, 160.9, 161.6, 166.7. MS (m/z, %): 406 (M, 10), 222 (50), 186 (30), 173 (100), 146 (20).

[4-Oxo-2-(4-oxo-2-phenyl-4H-quinazolin-3-ylimino)-thiazolidin-5-ylidene]-acetic acid ethyl ester (**VIIIb**). Yellow solid, m.p. 215 °C (dec), IR (KBr) ν_{max} : 3210, 3090, 2930, 1740, 1720, 1690, 1616 cm^{-1}, ^1H NMR (DMSO-d6) δ (ppm): 1.28 (3H, t, J = 7.0 Hz, CH_3), 4.25 (2H, q, J = 7.0, OCH_2), 6.77 (s, 1H, C=CH), 7.20-8.06 (m, 9H, arom), 11.02 (s, 1H, NH). ^{13}C NMR (DMSO-d6) δ (ppm): 15.7, 60.4, 115.3, 120.7, 126.2, 126.8, 127.4, 128.6, 129.1, 131.0, 131.4, 133.3, 141.1, 147.3, 148.7, 158.7, 161.1, 161.5, 165.8. MS (m/z, %): 420 (M, 8), 222 (40), 200 (40), 187 (100), 146 (40).

Acknowledgments

The author gratefully acknowledges the financial support from the Research Council of Shahid Bahonar University of Kerman.

References:

i. Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175–203.
ii. Brown, F. C. Chem. Rev. **1961**, *61*, 463–521.
iii. Ottana, R.; Maccari, R.; Barreca, M. L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Di Paola, R.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M. G. *Bioorg. Med. Chem.* **2005**, *13*, 4243–4252.
iv. Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. *Bioorg. Med. Chem.* **2006**, *14*, 3859–3864.
v. Elbarbary, A. A.; Khodair, A. I.; Pedersen, E. B.; Nielsen, C. *Monatsh. Chem.* **1994**, *125*, 593–598.
vi. Liu, H. L.; Li, Z. C.; Anthonsen, T. *Molecules* **2000**, *5*, 1055–1061.
vii. Kalaiya, S. B.; Parikh, A. R.. *J. Indian Chem. Soc.* **1987**, *64*, 172–175.
viii. U. Ameta, S. Ojha, D. Bhambi, G. L. Talesara, ARKIVOC **2006** (xiii) 83-89.

Received on April 25, 2013.