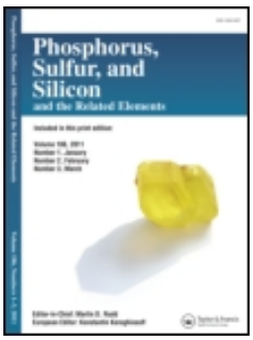

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Efficient "on water" green route heterocyclization of thiosemicarbazones with DMAD

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ABSTRACT

A simple, efficient, and eco-friendly procedure for the synthesis of thiazolidin-4-one derivatives in water from cyclocondensation reaction of thiosemicarbazone derivatives and dimethylacetylene dicarboxylate (DMAD) in good yield is reported. The regiochemistry of the cyclized products is established by elemental analysis, IR, NMR, and mass spectral data. A single crystal X-ray diffraction study of a representative compound, **3f**, is reported.

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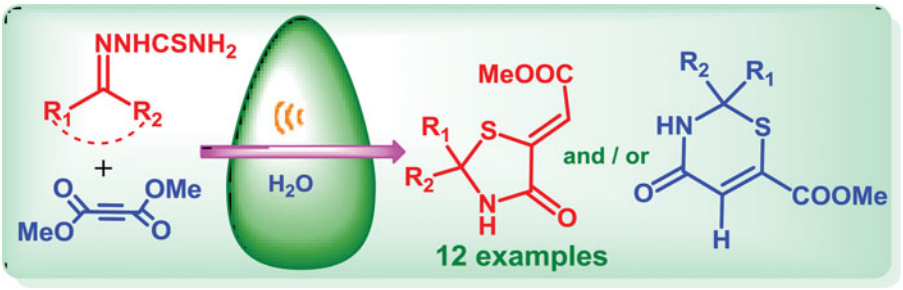
KEYWORDS
Thiazolidin-4-one; thiosemicarbazone; DMAD; X-ray diffraction; eco-friendly

GRAPHICAL ABSTRACT



1. Introduction

The use of water as a reaction medium for chemical transformations has been the subject of organic synthesis due to cost, safety, and environmental concerns.[1–2] Recently, the use of aqueous media in organic reactions has attracted a great deal of attention. The variety of interactions between water and substrates such as hydrogen bonding or interactions related to polarity, acidity and hydrophobicity make water interesting from an industrial as well as laboratory perspective.[3] Sharpless *et al.* recently defined as "on water" conditions, using water as a solvent for the reaction of water insoluble reactants.[4] A number of synthetic protocols for the construction of the thiazolidin-4-one skeleton are available in the literature which used desiccants such as anhyd. NaOAc,[5] DCC,[6] $ZnCl_2$,[7] Dean Stark apparatus[8] and molecular sieves for the removal of water from the reaction mixture. These methods involve expensive and toxic starting materials, harsh reaction conditions, long reaction times, and poor yield of obtained products. Often these reactions are performed in various organic solvents posing a serious threat of fire hazard, especially when they are carried out under microwave irradiation. Several solvent free protocols[9–11] have been developed recently, but still they require toxic organic solvents during product isolation. Therefore, the development of an efficient and versatile method is still required. On the other hand, ultrasonic reactions have been increasingly used as clean, green, and environmentally benign routes for the preparation of organic compounds of synthetic and biological values.[12]

Thiazolidin-4-one framework has emerged as one of the most prolific chemotypes in the recent computational analysis of medicinal chemistry databases due to its multifarious pharmaceutical applications. Thiazolidin-4-one derivatives have been used as synthetic intermediates, dyes and display diverse biological activities such as anticancer,[13] anti-inflammatory,[14] antimicrobial,[15] anticonvulsant,[16] antifungal,[17] antitubercular,[18] anti HIV,[19] analgesic,[20] antimalarial,[21] HIV reverse transcriptase (RT) inhibitory activity,[22] COX-2 inhibitory activity,[23] antihyperglycemic[24], and insulin reversal activity.[25] Prompted by these facts and in continuation to our research program on the synthesis of thiazolidin-4-ones of potential biological relevance[26–28] we envisaged the environmentally benign ultrasound assisted aqueous medium heterocyclization of thiosemicarbazones with DMAD and the structural analysis of new hydrazono thiazolidin-4-ones.

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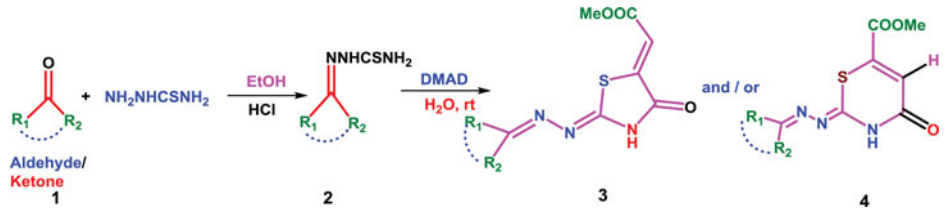
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/gpss.

Supplementary data associated with this article include cif file of compound **3f**, and NMR spectra of the compounds reported in the article. Supplemental data for this article can be accessed on the publisher's website at http://dx.doi.org/10.1080/10426507.2015.1073282



Scheme 1. Synthetic route to synthesis of thiazolidin-4-one derivatives **3**.

2. Result and discussion

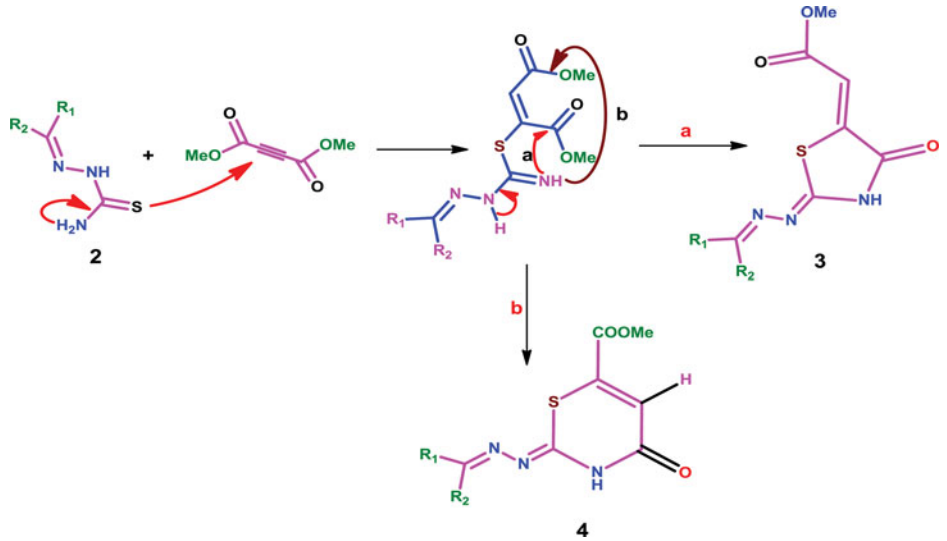
In the present investigations, on-water synthesis of thiazolidin-4-one derivatives **3** has been accomplished from thiosemicarbazones **2** and DMAD (Scheme 1). In one strategy, thiazolidin-4-one derivatives were prepared by stirring a mixture of thiosemicarbazone **2** and DMAD in water at ambient temperature for 24–30 h. In another strategy, thiazolidin-4-ones were obtained in good yield through ultrasonication of the above reaction mixture in water for 30–60 min.

Thiosemicarbazone derivatives **2** of aldehydes or ketones were prepared by stirring a mixture of carbonyl compound **1** and thiosemicarbazide in ethanol containing a catalytic amount of conc. HCl by the reported procedure. [29] Thiosemicarbazone **2**, on stirring with an equimolar amount of DMAD in water at ambient temperature for 24–30 h, furnished a single product (TLC), which was characterized by spectral data as thiazolidin-4-one **3** and not as thiazinan-4-one **4**. The plausible mechanism of formation of **3 (route a)** and **4 (route b)** from condensation of thiosemicarbazone and DMAD in water is shown in Scheme 2.

In the present investigations, thiazolidin-4-one **3** is the only product isolated in all the cases under study (TLC). Compound **4**, if obtained, would behave spectroscopically similar to **3**. To elucidate the isomeric structures and structure of the products obtained as well as to characterize the products, we used spectral (IR, NMR and Mass) data but rigorous proof came from the single crystal X-ray structural analyses of **3f**. In order to test the generality of the method, different aldehydes or ketones (aliphatic, aromatic and heterocyclic) were used and it was found that the reaction can tolerate all different types of carbonyl compounds. The progress of the reaction was monitored by TLC and in some cases the reaction took 30 h for completion. The effect of ultrasound on the reaction was studied with an aim to reduce the time period of the reaction and improve the yield of the product. It was observed that the reaction was completed within 30–60 min under ultrasonication and yield of the products was reasonably improved. The structure of products, time period of reaction and yield of the isolated products is reported in Table 1.

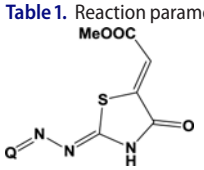
The characterization of all the thiazolidin-4-one derivatives **3a-l** was done by means of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The IR spectrum of compound **3a** showed two peaks at 1720 and 1685 cm^{-1} which was assigned to two carbonyl groups. Appearance of two singlets at δ 3.77 ppm and δ 6.61 ppm in ^{1}H NMR spectrum of **3a** were assigned to OCH_3 group and vinyl proton (=CH), respectively. A broad signal for NH appeared at δ 12.52 ppm. ^{13}C NMR spectrum of **3a** displayed peaks at δ 166.0 (C=O), δ 165.7 (C=O), and δ 165.4 (C=N).

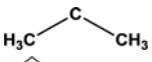
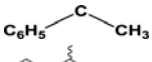
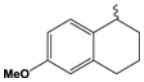
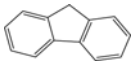
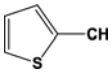
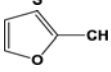
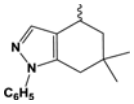
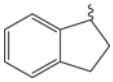
IR spectrum of **3f** exhibited a peak at 1724 cm^{-1} which was assigned to ester carbonyl group. The peak at 1689 cm^{-1} was assigned to CONH group. Two peaks at 1630 cm^{-1} and 1613 cm^{-1} were assigned to two C=N groups. In the ^{1}H NMR spectrum of **3f**, the appearance of a singlet at δ 3.76 ppm was assigned to the methoxy group and that of a singlet at δ 6.63 ppm was assigned to methine (=CH) proton. The ^{13}C NMR spectrum of **3f** displayed peaks at δ 165.8 (C=O), δ 165.5 (C=O), δ 162.3 (C=N), and δ 158.7 (C=N). The mass spectrum of **3f** exhibited a quasi-molecular ion peak at *m/z* 330.2 (27.7%). The structure of compound **3f** was confirmed by a single crystal X-ray crystallographic study, which shows *cis* configuration at C=C and *trans* at C=N. The structure of all other products was



Scheme 2. Plausible mechanism for the formation of thiazolidin-4-one **3** and/or thiazinan-4-one **4**.

Table 1. Reaction parameters for the synthesis of thiazolidin-4-one derivatives **3a-l**.



		Method (a)		Method (b)	
Entry	Compound 3, Q =	Time (h)	Yield (%)	Time (min)	Yield (%)
3a		26	65	40	75
3b		24	68	35	74
3c		25	72	45	78
3d	C_6H_5CH	24	73	30	76
3e		23	71	50	74
3f		25	65	30	68
3g		30	62	35	66
3h		24	64	30	74
3i		28	66	45	71
3j		28	65	30	70
3k		23	58	35	62
3l		24	62	30	68

a = On water synthesis; b = Ultrasound assisted synthesis.

Table 2. Crystal data and the structure refinement parameters of compound **(3f)**.

Compound	3f
CCDC no.	1014085
Empirical formula	$C_{19}H_{21}N_4O_4S$
Formula weight	401.46
Space group	P-1
a (Å)	7.7206(7)
b (Å)	8.5084(5)
c (Å)	15.5819(9)
α (°)	82.116(5)
β (°)	79.399(6)
γ (°)	81.259(6)
Volume (Å^3)	988.12(12)
Z	2
Density (calculated) (Mg/m^3)	1.349
μ (mm^{-1})	0.197
Crystal size (mm)	0.31 × 0.24 × 0.20
Color	Pale yellow
Temperature (K)	293 (2)
Theta range for data collection	3.21 to 29.06
Reflections collected	4,484
Independent reflections	2,860
Data/restraints/parameters	4484/0/256
Goodness-of-fit on F^2	1.030
Final R indices [$I > 2\sigma(I)$]]	$R_1 = 0.0577$, w$R_2 = 0.1191$
R indices (all data)	$R_1 = 0.1013$, w$R_2 = 0.1459$
Largest diff. peak/ hole (eÅ^{-3})	−0.268, 0.458

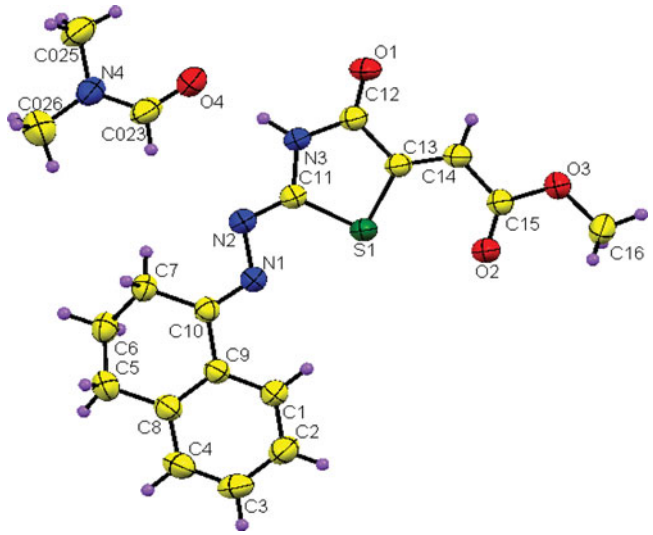


Figure 1. ORTEP diagram of Methyl (*E*)-2-((*Z*)-2-(((*E*)-3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate **(3f)** with non hydrogen ellipsoids drawn at 50% probability level.

similarly assigned by analytical and spectral data. The analytical data of all the synthesized compounds was in accordance with the assigned structures and is in good agreement with calculated values (within range of ±0.4%).

2.1 *Crystallographic study and structural description of compound 3f*

X-ray diffraction measurements were performed on X Calibur EOS OXFORD Diffractometer at 293 (2) K. The intensity data were collected using graphite monochromatic Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct method using the SHELX-97 software package[30] and refined by full-matrix least-squares procedures on F^2. All nonhydrogen atoms were refined with anisotropic thermal parameters. The compound **3f** crystallized in the monoclinic space group P1, with Z = 2 and cell parameters a = 7.7206 (7) Å, b = 8.5084 (5) Å, c = 15.5819 (9) Å, α = 82.116 (5)°, β = 79.399 (6)°, γ = 81.259 (6)°. In the compound, the C11N2 and C12O1 bond distances of 1.280 (3) and 1.212 (3) Å as compared to literature value of 1.27 and 1.22 Å respectively, indicated the double bond character of these bonds. The bond angles N2C11N3 and O1C12C13 are 121.5° (2) and 124.7° (2), respectively, which is consistent with the sp^2 hybrid character of C11 and C12 atoms. The crystallographic data and refinement parameters of **3f** are reported in Table 2. The ORTEP diagram obtained from X-ray structure of **3f** is shown in Figure 1. In the ORTEP diagram, the asymmetric unit of **3f** contains (*E*)-methyl 2-((*Z*)-2-((*E*)-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate and one DMF solvate molecule. DMF solvate is included in the crystal lattice by hydrogen bond between N-H·····O-C with bond length 2.7 Å. The selected bond lengths and bond angles of compound **3f** are listed in Table 3. The crystal packing diagram of **3f** along c axis (Figure S 1) and hydrogen bonding parameters (Table S 1) (Supplemental Materials).

Table 3. Selected bond parameters of compound **3f**.

Entry	Bond Length (Å)	Entry	Bond Angle(°)
S(1)-C(13)	1.742(2)	C(13)-S(1)-C(11)	90.19(11)
S(1)-C(11)	1.761(3)	C(15)-O(3)-C(16)	115.03 (19)
O(3)-C(15)	1.329(3)	C(10)-N(1)-N(2)	115.1 (2)
O(3)-C(16)	1.443(3)	C(12)-N(3)-C(11)	115.0 (2)
O(2)-C(15)	1.210(3)	C(11)-N(2)-N(1)	108.2(2)
O(1)-C(12)	1.212(3)	N(1)-C(10)-C(9)	115.6 (2)
N(1)-C(10)	1.287(3)	N(1)-C(10)-C(7)	125.0 (2)
N(1)-N(2)	1.408(3)	O(1)-C(12)-N(3)	124.9(2)
N(3)-C(12)	1.366(3)	O(1)-C(12)-C(13)	124.7 (2)
N(3)-C(11)	1.381(3)	N(2)-C(11)-N(3)	121.5 (2)
N(2)-C(11)	1.280 (3)	N(2)-C(11)-S(1)	125.27 (18)
C(13)-C(14)	1.330(3)	N(3)-C(11)-S(1)	113.24 (18)

3. Experimental

All the chemicals used were obtained from Sigma and used without further purification. Melting points were determined in open capillaries and are reported uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on BRUKER AVANCE II 400 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported in ppm. IR spectra were recorded on Perkin Elmer (RZX) FTIR spectrometer and the results are reported in cm^{-1}. Mass spectra were recorded on a WATERS, Q-TOF MICROMASS (LC-MS) instrument. The elemental analyses of the compounds were performed on Euro EA 3000 Elemental Analyzer. Thin layer chromatography (TLC) was performed on silica gel G coated plates and using iodine vapor as visualizing agent. Ultrasonication was done on Cole Parmar CPX500, 20 KHz, 500 Watt instrument. X-ray diffraction was performed on X Calibur EOS OXFORD Diffractometer. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for 3a – 3l (Figures S 2 – S 17)

Thiosemicarbazone derivatives **2a-l** were obtained from appropriate aldehyde or ketone and thiosemicarbazone in ethanol by the reported procedure and characterized by their literature[31] melting points.

3.1 *General procedure for the synthesis of 3*

(a) **On water synthesis**
A suspension of thiosemicarbazone **2** (1.0 mmol) and dimethyl acetylene dicarboxylate, DMAD (1.0 mmol) in water (10 mL) was stirred at ambient temperature for 20–30 h. The progress of the reaction was monitored by TLC. After completion of reaction, the solid obtained was filtered, dried and recrystallized from ethanol: DMF (3:1) mixture.

(b) **Synthesis under Ultrasonication**
A suspension of thiosemicarbazone **2** (1.0 mmol) and dimethyl acetylene dicarboxylate, DMAD (1.0 mmol) in water (10 mL) was kept in an ultrasound sonicator (20 KHz) for 30–60 min. The progress of the reaction was monitored by TLC. After completion of reaction, the solid obtained was filtered and recrystallized from ethanol: DMF (3:1) mixture.

3.1.1 *(E)-Methyl 2-((Z)-4-oxo-2-(propan-2-ylidenehydrazono) thiazolidin-5-ylidene)acetate (3a)*

Yellow solid; mp 198–200°C. IR (cm^{-1}) 1720 (C=O), 1685 (C=O), 1620 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6) δ; 1.97–2.02 (m, 6H, 2CH_3), 3.77 (s, 3H, OCH_3), 6.61 (s, 1H, =CH), 12.52 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 166.0 (C=O), 165.7 (C=O), 165.4 (C=N), 143.2 (thiazole-C5), 113.7 (vinyl-CH), 52.0 (OCH_3), 24.6 (CH_3), 18.4 (CH_3). Mass: (M+H$^+$): 242.1 (48%). Anal. Calcd. for $C_9H_{11}N_3O_3S$: C, 44.80; H, 4.60; N, 17.42; S, 13.29; found: C, 44.93; H, 4.72; N, 17.55; S, 13.40.

3.1.2 *(E)-Methyl 2-((Z)-2-(cyclopentylidenehydrazono) -4-oxothiazolidin-5-ylidene)acetate (3b)*

Yellow solid; mp 224–26°C. IR (cm^{-1}) 1716 (C=O), 1688 (C=O), 1612 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 1.72–1.77 (m, 4H, 2CH_2), 2.42–2.51 (m, 4H, 2CH_2), 3.77 (s, 3H, COOMe), 6.61 (s, 1H, =CH), 12.69 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 179.1 (C=O), 165.8 (C=O), 165.5 (C=N), 143.1 (thiazole-C5), 113.8 (vinyl-CH), 52.3 (OCH_3), 32.8 (CH_2), 30.2 (CH_2), 24.2 (CH_2). Mass: (M+H$^+$): 268.0 (17%) .Anal. Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.43; H, 4.90; N, 15.72; S, 12.00; found: C, 49.56; H, 5.01; N, 15.58; S, 12.15.

3.1.3 *(E)-Methyl 2-((Z)-2-(cyclohexylidenehydrazono) -4-oxothiazolidin-5-ylidene)acetate (3c)*

Yellow solid; mp >300°C. IR (cm^{-1}) 1722 (C=O), 1686 (C=O), 1618 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 1.76–1.82 (m, 2H, CH_2), 1.92–1.98 (m, 4H, 2CH_2), 2.46–2.54 (m, 4H, 2CH_2), 3.75 (s, 3H, COOMe), 6.60 (s, 1H, =CH), 12.62 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 179.8 (C=O), 165.1 (C=O), 164.9 (C=N), 145.1 (thiazole-C5), 112.7 (vinyl-CH), 54.4 (OCH_3), 34.9 (CH_2), 31.4 (CH_2), 24.8 (CH_2), 24.2 (CH_2). Mass: (M+H$^+$): 282.1 (12%). Anal. Calcd. for $C_{12}H_{15}N_3O_3S$: C, 51.23; H, 5.37; N, 14.94; S, 11.40; found: C, 51.36; H, 5.48; N, 15.08; S, 11.24.

3.1.4 *(E)-Methyl 2-((Z)-2-((Z)-benzylidenehydrazono) -4-oxothiazolidin-5-ylidene)acetate (3d)*

Yellowish solid; mp 238–240°C. IR (cm^{-1}) 1715 (C=O), 1681 (C=O), 1612 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 3.78 (s, 3H, $COOCH_3$), 6.67 (s, 1H, =CH), 7.48–7.51 (m, 3H, Ph), 7.81–7.83 (m, 2H, Ph), 8.53 (s, 1H, N =CH), 12.91 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 165.8 (C=O), 165.7 (C=O), 160.3 (C=N), 158.6 (C=N), 142.8 (thiazole-C5), 133.6 (C_6H_5), 131.2 (C_6H_5), 128.9 (C_6H_5), 128.0 (C_6H_5), 114.2 (vinyl-CH), 52.4 (OCH_3). Mass: (M+H$^+$): 290.2 (25%). Anal. Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52; S, 11.08; found: C, 54.12; H, 3.94; N, 14.71; S, 11.21.

3.1.5 *(E)-Methyl 2-((Z)-4-oxo-2-((Z)-(1-phenylethylidene) hydrazono)thiazolidin-5-ylidene)acetate (3e)*

Yellowish solid; mp 222–24°C. IR (cm^{-1}) 1718 (C=O), 1688 (C=O), 1618 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 1.98 (s, 3H, CH_3) 3.76 (s, 3H, $COOCH_3$), 6.65 (s, 1H, =CH), 7.52–7.56 (m, 3H, Ph), 7.86–7.89 (m, 2H, Ph), 8.55 (s, 1H, N =CH), 12.86 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 165.6 (C=O),

165.2 (C=O), 160.5 (C=N), 157.5 (C=N), 143.7 (thiazole-C5), 135.6 (C_6H_5), 132.4 (C_6H_5), 128.7 (C_6H_5), 128.3 (C_6H_5), 114.8 (vinyl-CH), 54.6 (OCH_3), 25.7 (CH_3). Mass: ($M+H^+$): 304.1 (100%). Anal. Calcd. for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85; S, 10.57; found: C, 55.58; H, 4.42; N, 13.96; S, 10.70.

3.1.6 *(E)-Methyl 2-((Z)-2-((E)-(3,4-dihydronaphthalen-1(2H) -ylidene)hydrazono)-4-oxothiazolidin-5-ylidene) acetate (3f)*

Yellow shining crystals; mp 206–08°C. IR (ν cm^{-1}): 3157 (NH), 1724 (C=O), 1689 (C=O), 1630 (C=N), 1613 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 1.80–1.86 (m, 2H, CH_2), 2.8 (t, 2H, CH_2, J = 5.7 Hz), 2.87 (t, 2H, CH_2, J = 6.5 Hz), 3.76 (s, 3H, OCH_3), 6.63 (s, 1H, =CH), 7.23 (d, 1H, ArH, J = 7.4 Hz), 7.28–7.38 (m, 2H, ArH), 8.10 (d, 1H, ArH, J = 6.8 Hz), 12.9 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 165.8 (C=O), 165.5 (C=O), 162.3 (C=N), 158.7 (C=N), 143.0 (thiazole-C5), 141.0, 131.6, 130.3, 128.8, 126.2, 124.7 (Ar-C), 113.9 (vinyl-CH), 52.3 (OCH_3), 29.0 (CH_2), 27.0 (CH_2), 21.7 (CH_2). Mass: ($M+H^+$): 330.2 (27.7%). Anal. Calcd. For $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76; S, 9.74; found: C, 58.46; H, 4.72; N, 12.84; S, 9.86.

3.1.7 *(E)-Methyl-2-((Z)-2-((E)-(6-methoxy -3,4-dihydronaphthalen-1(2H)-ylidene)hydrazono) -4-oxothiazolidin-5-ylidene)acetate (3g)*

Yellow shining crystals; mp 198–200°C. IR (ν cm^{-1}): 3160 (NH), 1720 (C=O), 1688 (C=O), 1626 (C=N), 1618 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 1.82–1.87 (m, 2H, CH_2), 2.83 (t, 2H, CH_2, J = 5.7 Hz), 2.91 (t, 2H, CH_2, J = 6.6 Hz), 3.79 (s, 3H, OMe), 3.76 (s, 3H, $COOCH_3$), 6.65 (s, 1H, =CH), 7.18 (d, 1H, ArH, J = 7.0 Hz), 7.29–7.34 (m, 1H, ArH), 7.93 (d, 1H, ArH, J = 7.0 Hz), 12.8 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 166.7 (C=O), 165.3 (C=O), 162.8 (C=N), 159.6 (C=N), 143.5 (thiazole-C5), 142.0, 132.6, 130.6, 128.0, 126.8, 123.9 (Ar-C), 113.7 (vinyl-CH), 54.6 (OCH_3), 52.3 (OCH_3), 29.0 (CH_2), 27.2 (CH_2), 22.6 (CH_2). Mass: (M^+): 359 (85%). Anal. Calcd. for $C_{17}H_{17}N_3O_4S$: C, 56.81; H, 4.77; N, 11.69; S, 8.92; found: C, 56.96; H, 4.89; N, 11.80; S, 9.06.

3.1.8 *(E)-Methyl-2-((Z)-2-((9H-fluoren-9-ylidene)hydrazono) -4-oxothiazolidin-5-ylidene)acetate (3h)*

Yellow shining crystals; mp 232–34°C. IR (ν cm^{-1}): 1720 (C=O), 1682 (C=O), 1628 (C=N), 1618 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 3.79 (s, 3H, OCH_3), 6.70 (s, 1H, =CH), 7.35–7.38 (m, 2H, ArH), 7.47–7.53 (m, 2H, ArH), 7.78–7.85 (m, 3H, ArH), 8.57 (d, 1H, ArH, J = 7.6 Hz), 13.13 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 165.7 (C=O), 165.6 (C=O), 162.9 (C=N), 158.0 (C=N), 142.4 (thiazole-C5), 141.6, 140.5, 135.6, 131.8, 131.4, 130.9, 129.9, 128.3, 128.2, 122.2, 120.5 (Ar-C), 114.8 (vinyl-CH), 52.4 (OCH_3). Mass: ($M+H^+$): 364.1 (100%). Anal. Calcd. For $C_{19}H_{13}N_3O_3S$: C, 62.80; H, 3.61; N, 11.56; S, 8.82; found: C, 62.91; H, 3.75; N, 11.70; S, 9.03.

3.1.9 *(E)-Methyl-2-((Z)-4-oxo-2-((E)-(thiophen -2-ylmethylene)hydrazono) thiazolidin-5-ylidene)acetate (3i)*

Yellow fluffy solid; mp 242–44°C. IR (ν cm^{-1}): 3447 (NH), 1731(C=O), 1696 (C=O), 1640 (C=N), 1626 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 3.79 (s, 3H, OCH_3), 6.67 (s, 1H, =CH), 7.19–7.21 (m, 1H, thiophene), 7.59–7.60 (m, 1H, thiophene), 7.78–7.79 (m, 1H, thiophene), 8.69 (s, 1H, N =CH), 12.84 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 165.8 (C=O), 165.6 (C=O), 162.2 (C=N), 159.3 (C=N), 153.0, 142.8 (thiazole-C5), 138.2, 133.2, 130.8, 128.2 (thiophene-C), 114.1 (vinyl-CH), 52.4 (OCH_3), 35.7, 30.7. Mass: ($M+H^+$): 296.2 (10.6%). Anal. Calcd. For $C_{11}H_9N_3O_3S_2$: C, 44.73; H, 3.07; N, 14.23; S, 21.71; found: C, 44.86; H, 3.19; N, 14.36; S, 21.84.

3.1.10 *(E)-Methyl-2-((Z)-2-((Z)-(furan-2-ylmethylene) hydrazono)-4-oxothiazolidin-5-ylidene)acetate (3j)*

Yellow solid; mp 226–28°C. IR (ν cm^{-1}): 1730 (C=O), 1692 (C=O), 1638 (C=N), 1630 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 3.80 (s, 3H, OCH_3), 6.68 (s, 1H, =CH), 7.22–7.25 (m, 1H, furan), 7.64–7.67 (m, 1H, furan), 7.88–7.89 (m, 1H, furan), 8.76 (s, 1H, N =CH), 12.9 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 166.7 (C=O), 166.3 (C=O), 162.8 (C=N), 158.6 (C=N), 154.1, 143.4 (thiazole-C5), 138.6, 133.9, 131.6, 129.3 (furan-C), 114.7 (vinyl-CH), 52.8 (OCH_3), 35.6, 31.2. Mass: ($M+H^+$): 280.0 (45%). Anal. Calcd. For $C_{11}H_9N_3O_4S$: C, 47.31; H, 3.25; N, 15.05; S, 11.48; found: C, 47.44; H, 3.38; N, 15.15; S, 11.61.

3.1.11 *(E)-Methyl-2-((Z)-2-((Z)-(6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-ylidene) hydrazono) -4-oxothiazolidin-5-ylidene)acetate (3k)*

Dark yellow shining solid; mp 212–14°C. IR (ν cm^{-1}): 3260 (NH), 1728 (C=O), 1692 (C=O), 1636 (C=N), 1620 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 1.07 (s, 6H, $2CH_3$), 2.43 (s, 2H, CH_2), 3.00 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.70 (s, 1H, =CH), 7.43 (m, 1H, ArH), 7.78–7.83 (m, 4H, ArH), 7.95 (s, 1H, N =CH), 12.8 (br, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ; 165.9 (C=O), 158.5 (C=N), 143.6 (C=N), 143.3 (thiazole-C5), 138.6, 136.2, 129.4, 127.5, 123.0 (C_6H_5), 116.5 (pyrazole-CH), 113.7 (vinyl-CH), 52.3 (OCH_3), 36.0 (CH_2), 33.4 (CH_2), 27.9 (CH_3). Mass; ($M+H^+$): 424.3 (96.9%). Anal. Calcd. For $C_{21}H_{21}N_5O_3S$: C, 59.56; H, 5.00; N, 16.54; S, 7.57; found: C, 59.64; H, 5.12; N, 16.62; S, 7.71.

3.1.12 *(E)-methyl-2-((Z)-2-((Z)-(2,3-dihydro-1H-inden-1-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene) acetate (3l)*

Dark yellow solid; mp 214–16°C. IR (ν cm^{-1}): 3186 (NH), 1733 (C=O), 1690 (C=O), 1628 (C=N), 1612(C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 2.92 (t, 2H, CH_2, J = 6.9 Hz), 3.01–3.05 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 6.61 (s, 1H, =CH), 7.33 (t, 1H, ArH, J = 7.7 Hz), 7.41–7.48 (m, 2H, ArH), 7.73 (d, 1H, ArH, J = 7.6 Hz), 12.82 (br, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ; 172.1 (C=O), 165.8 (C=O), 165.5 (C=N), 157.9 (C=N), 150.3, 143.1 (thiazole-C5), 136.9, 131.7, 127.0, 125.9, 121.9 (Ar-C), 113.8 (vinyl-CH), 52.3 (OCH_3), 28.6 (CH_2), 28.0 (CH_2).

Mass; (M+H$^+$): 316.1 (100%). Anal. Calcd. For $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33; S, 10.17; found: C, 57.27; H, 4.28; N, 13.42; S, 10.30.

4. Conclusion

The synthesis of some new 2-hydrazono-4-thiazolidinone derivatives has been accomplished by employing water as a solvent. The reaction completes in 2–3 days time without an energy input. The ultrasound assisted synthesis of 2-hydrazono-4-thiazolidinone derivatives from thiosemicarbazone derivative and DMAD in water occurs within 30–50 min with improved yields. This method of assembling thiazolidin-4-ones from thiosemicarbazone and DMAD using water is green method for synthesis and the products are obtained in good yields.

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