Preparation of heterocyclic compounds by reaction of dimethyl and diethyl acetylene dicarboxylate (DMAD, DEAD) with thiosemicarbazone derivatives

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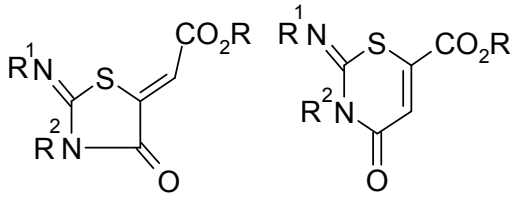
Abstract

Different thiosemicarbazone derivatives react with dimethyl acetylene dicarboxylate (DMAD) and diethyl acetylene dicarboxylate (DEAD) by three different methods: a) in ethyl acetate solvent at ambient temperature, b) one-pot synthesis under microwave irradiation and solvent-free conditions (three-component reaction between thiosemicarbazide, aldehyde/ ketone and DMAD or DEAD), c) a microwave-assisted synthesis under solvent-free conditions, to obtain five-membered S,N-heterocycles thiazolines in good to excellent yields.

Keywords: Thiosemicarbazone, dimethyl acetylene dicarboxylate, diethyl acetylene dicarboxylate, thiazoline

Introduction

Reaction of dimethyl acetylene dicarboxylate (DMAD) with esters and amides of dithiocarboxylic acids are well known methods for preparation of five membered S, and S,N-heterocycles[1,2]. Thioureas possessing more than two N-H bonds react with (DMAD) to give 1:1 molar-methanol adducts[2]. McKillop *et al.* have reported that benzimidazole-2 -thione reacted with DMAD in either methanol or acetic acid to give mixture of two 1:1 molar-methanol one adduct which was identified as [Type (**1**)] by X-ray crystallography but other adduct which was not isolated was only tentatively assigned structure (**2**) from its ^{1}H NMR spectrum[2,5]. The application of microwave irradiation in organic synthesis for conducting reactions at highly accelerated rates is an emerging technique[3]. In fact, in recent years, the use of microwave has become popular among synthetic organic chemists both to improve classical organic reactions (shortening reaction times and /or improving yield) as well as to promote new reactions[6].



(1) (2)

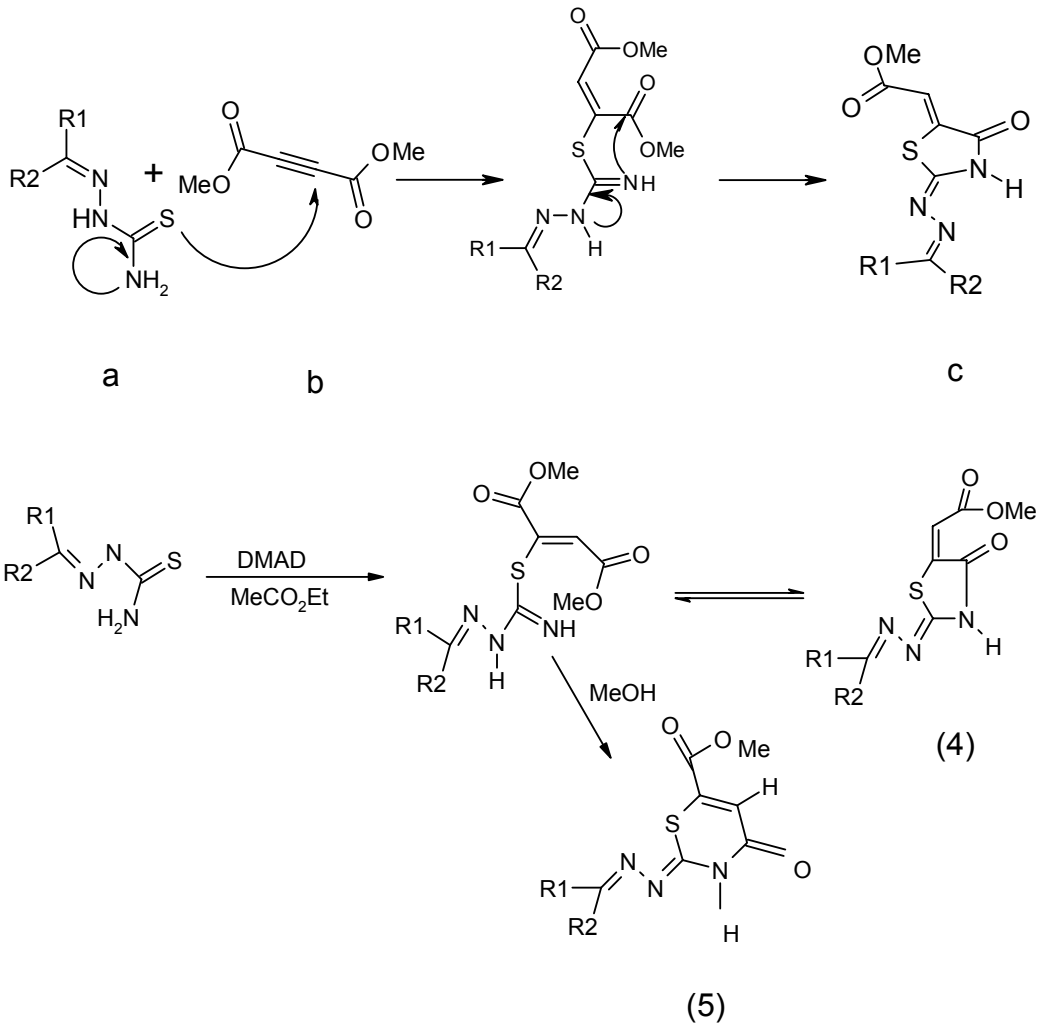
We have considered the reaction of thiosemicarbazone derivatives with dimethyl acetylene dicarboxylate and diethyl acetylene dicarboxylate to synthesis thiazolines, and to find the influence of the nature of electron donor group on the progress of this reaction, in addition on the structure of the resulting products. It should be noted that the reaction of thiosemicarbazone derivatives which contain two N-H, NH_2 and one S-group with DMAD and DEAD have not been described in the literature thus far.

Results and Discussion

In continuing our interest in the synthesis of heterocyclic compounds such as 1,3-thiazinones[7] and other heterocyclic compounds. We would like now to report the synthesis of thiazoline compounds from thiosemicarbazone derivatives possessing two N-H, NH_2 groups and one S=C bond which react with DMAD and DEAD to give thiazoline. In this reaction the sulfur atom attacked the triple bonds and a thiolactam is formed, followed by the aminolyses of an ester group[8]. This reaction can lead to the structures type (**1**), and type (**2**). Both products have been claimed, although structure type 2 has not been confirmed. In this investigation we report three methods for the synthesis of thiazolines: a) thiosemicarbazone is dissolved in ethyl acetate then DMAD or DEAD is added to this solution, reaction was carried out with a stirring for 2.5-5 hr at ambient temperature, b) a facile synthesis via a one-pot three-component reaction between thiosemicarbazide, aldehyde/ketone and DMAD or DEAD in the present of catalytic amounts of acetic acid, thiosemicarbazide and aldehydes are converted in-situ to thiosemicarbazone, next the thiosemicarbazone are reacted with DMAD or DEAD under microwave irradiation and solvent-free condition to produce thiazolin in 95-98% yields, c) in the third method, thiosemicarbazone was mixed with DMAD or DEAD, then the reaction was subject to microwave irradiation under free solvent conditions at short experimental time. The following results were obtained, formation of 1c, after 3 h in method a, 3 min in method b and 5 min in method c. A plausible mechanism is shown below, scheme (1). Compound 1c reveals NH group at 3180 , C-H absorption of thiophene ring at 2780-3081 cm^{-1} ,carbonyl groups at 1741, 1661 cm^{-1} and C=N, C=C at 1666, 1641, 1617 cm^{-1} in the IR spectrum. The ^1H NMR spectrum of 1c indicated one singlet quite down field at (δ 12.60 ppm) which is the proton of NH amide, thiophene ring protons at 7.75, 7.57, 7.18, vinyl proton at 6.64 and methoxy protons at 3.76 ppm. The ^{13}C NMR spectrum of 1c indicated carbonyl group carbons at 165.69, 165.48, 159.16 (C=N), 152.77 (S-

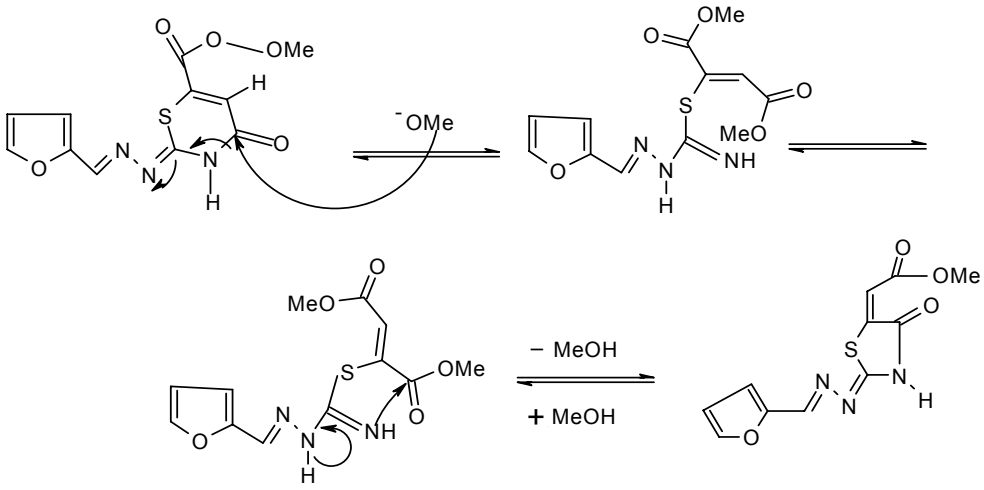
C=CH), 142.58 (C=CH of thiophene ring), 138.06 (CH=N), 132.99, 130.59, 128.03 (C=CH of thiophene ring), 113.48 (C=CH) and methoxy carbon at 52.23 ppm. Mass spectral data and elemental analyses are also in accordance with the proposed structure.

In general all of the spectral data support the structures for the compounds (**1c-10c**), Table 1.

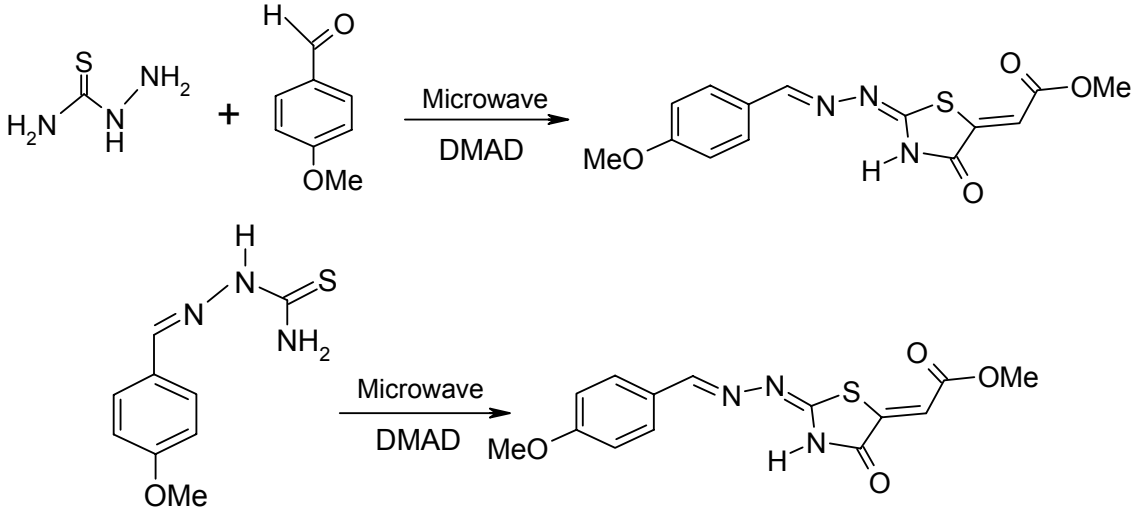


Scheme 1

We have found that the thiosemicarbazone, DMAD and DEAD reacted in ethyl acetate to give only structure (**4**), and when they were reacted in dry methanol only structure (**5**) was formed. The adduct (**4**) was converted to (**5**) by refluxing the reaction mixture in dry methanol. This rearrangement was probably catalyzed by a base. Since, it did not take place if the methanol contained a few drops of acetic acid. A possible mechanism (Scheme 2) involves ring-opening by attack of methoxide on the strained cyclic amide, followed by ring-closure on the other ester group.

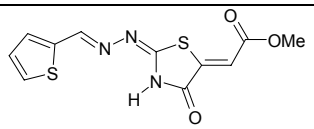
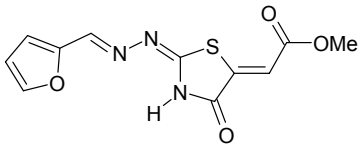
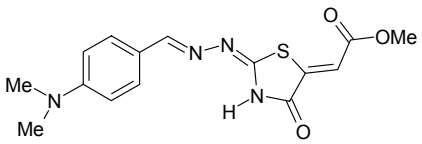
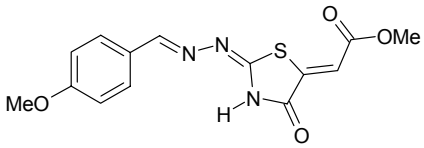
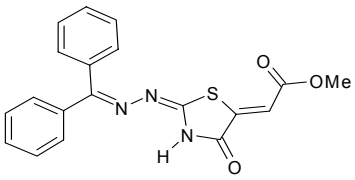
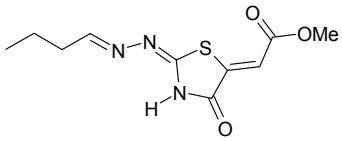
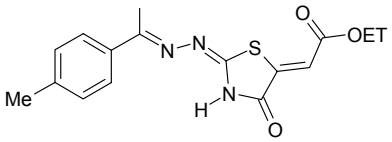
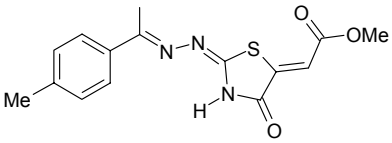
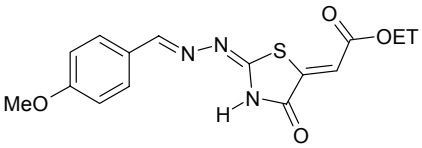


The effect of the electron-donor group on the progress of the reaction and on the structure of the final products was also investigated. When such an electron donor group is present on the benzene ring higher yields were obtained without exerting heat or reflux the reaction mixture, and in addition the reaction rate is much faster.



Scheme 2

Table 1. Compounds and yields

Compound	Structure of compound	Isolated yield (%) method a	Isolated yield (%) method b	Isolated yield (%) method c
1c		78	85	82
2c		80	83	82
3c		80	89	90
4c		93	92	95
5c		87	91	94
6c		86	87	90
7c		87	88	90
8c		90	92	94
9c		85	87	89

Conclusions

Since the use of microwave are playing increasingly pivotal role to synthesis organic compounds, we have developed a microwave-assisted, one-pot, three-component reaction for the preparation of thiazolines with excellent yield. No harsh conditions or cumbersome apparatus are required. Simple purification process, short experimental time for the reaction to be completed and solvent free conditions are the main advantages of these methods, in addition these reactions require the environmentally friendly conditions.

Experimental Section

Furfural, thiofurfural, benzophenone, butanal, *p*-methoxybenzaldehyde, *p*-methylacetophenone, *p*-methyl benzaldehyde, 2-ketoethylbutyrate, *p*-*N,N*-dimethybenzaldehyde, thiosemicarbazide, sodium acetate , dimethyl acetylene dicarboxylate (DMAD), and diethyl acetylene dicarboxylate (DEAD) and all the solvents such as ethyl acetate and ethanol were purchased from Merck chemical co. and were used without further purification. Thiosemicarbazones were prepared according to the procedure in the literature [7]. IR spectra were obtained on a Matson-1000 FT-IR spectrometer. The proton and carbon-13 NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz respectively with Me_4Si as an internal standard. Elemental analyses were performed by National Iranian Oil Company lab (Tehran) using a Heracus CHN-O-Rapid analyzer. Mass spectrometer operating at an ionization potential of 70 eV.

General experimental procedures

(a) To a solution of thiosemicarbazone-2-keto ethyl butyrate (0.76 g, 4 mmol) in ethyl acetate (100 ml) was added a solution of dimethyl acetylene dicarboxylate (0.49 ml, 4 mmol) in small portions. The solution was stirred at ambient temperature for 3 h. The resulting yellow precipitate was filtered, washed with ethyl acetate, a yellow solid was separated which was then recrystallized from ethanol-water. yield (1.04g) 95%.

(b) A mixture of thiosemicarbazide (0.73 g, 8 mmol), p-methoxybenzaldehyde (1.09 g, 8 mmol) and DMAD (0.98 ml, 8 mmol) and a catalytic amount of acetic acid was subject to microwave irradiation under microwave at 80W for 3 min. After cooling the reaction mixture to ambient temperature the solid residue was recrystallized from ethanol-water. The product was obtained as yellow crystals.

c)A mixture of thiosemicarbazone p-methoxybenzaldehyde (0.72 g, 4 mmol) and DMAD (0.49 ml, 4 mmol),was subject to microwave irradiation at 50W for 5 min, after cooling the reaction mixture to room temperature, the solid residue was recrystallized from ethanol-water. The product was obtained as yellow crystals.

[4-Oxo-2-(thiophen-2-ylmethylene-hydrazono)thiazolidine]-acetic acid methyl ester (1c). Yellow solid, 0.92 g, yield 78%, m.p>220 ^{0}C IR (KBr) (υ_{max} ,cm^{-1}): 2780-3081 (CH, thiophene ring), 1741, 1716 (2C=O), 1661, 1641, 1617 (C=N, C=C), ^{1}H NMR (DMSO)δ: 12.60 (1H, s, NH), 8.60 (1H, s, CH=N), 7.75(1H, d), 7.57(1H, d), 7.18 (1H, t), thiophene ring, 6.64 (1H, s, CH=), 3.75 (3H, s, -OMe). ^{13}C NMR (DMSO) δ: 165.69, 165.48 (2C=O), 159.16 (C=N), 152.77 (S-C=CH), 142.58 (thiophene),138.06 (CH=N), 132.99, 130.59, 128.03 (C=CH of thiophene ring), 113.48 (C=CH), 52.23(-OCH_3). MS (m/z, %): 295 (parent peak), 96 (base peak, 100%). Anal. Calcd for $C_{11}H_9N_3O_3S_2$: C, 44.74; H, 3.05; N, 14.24%. Found; C, 44.60; H, 2.95; N, 14.13%.

[**2-(Furan-2-ylmethylene-hydrazono)-4-oxo-thiazolidin-5-ylidene]-acetic acid methyl ester (2c).** Yellow solid, 0.84 g; yield 80%, m.p>220 ^{0}C .IR (KBr) (υ_{max} , cm^{-1}): 2800-3090(CH, furan ring), 1742, 1717 (C=O), 1667, 1645, 1617 (C=N,C=C), ^{1}H NMR (DMSO) δ: 12.75 (1H, s, NH), 8.33 (1H, s, CH=N), 7.90, 7.05 , 6.67 (3H, furan ring), 6.63 (1H, s, CH=C), 3.77 (3H, s,-OMe). ^{13}C NMR (DMSO) δ: 165.85, 165.00 (2C=O), 160.00, 148.88 (C=N), 147.53 (C=CH), 146.55, 142.77, 117.17, 114.5 (furan-ring), 112.56 (C=CH), 52.43 (1C, -OMe). Anal. Calcd for $C_{11}H_9N_3O_4S$: C, 46.64; H, 3.18; N, 14.84%. Found; C, 46.39; H, 3.15; N, 14.49%.

{2-[(4-Dimethylamino-benzylidene)-hydrazono]-4-oxo-thiazolidin-5-ylidene} acetic acid methyl ester (3c). Orange solid, 1.06 g, yield 80 %, m.p >220 ^{0}C. IR (KBr) (υ_{max} ,cm^{-1}): 3020 (C-H, arom), 1735, 1715 (C=O), 1643, 1615 (C=N), ^{1}H NMR (DMSO) δ: 8.23 (1H, s, CH=N), 7.5-6.73 (4H, para, aromatic), 6.40 (1H, CH=), 3.72(3H, s, -OMe), 2.96 (6H, s, 2-CH_3). ^{13}C NMR (DMSO) δ: 172.06, 166.81 (2C=O), 154.77 (C=N), 151.67-111.79(C=C), 51.80 (-OMe), 21.07 (-CH_3). MS (m/z, %): 332 (parent peak), 332 (base peak, 100%), 147, 133, 118, 44. Anal. Calcd for $C_{15}H_{16}N_4O_3S$: C, 54.22; H, 4.82; N, 16.87%. Found; C, 54.16; H, 4.57; N, 16.67%.

{2-[(4-Methoxy-benzylidene)-hydrazono]-4-oxo-thiazolidin-5-ylidene}-acetic acid methyl ester (4c). Yellow solid, 1.19 g, yield 93%, m.p>220 ^{0}C. IR (KBr) (υ_{max} ,cm^{-1}) 2982-3081 (C-H, arom)1741, 1716 (C=O), 1666, 1617 (C=N), ^{1}H NMR (DMSO) δ: 12.40 (1H, s, NH), 9.67 (1H, s, CH=N), 8.23 (1H, s, CH=N), 7.07-7.61 (4H, m, arom), 6.70 (1H, s, CH=C), 3.90, 3.63 (6H, 2-OMe). ^{13} C NMR (DMSO) δ: 172.53, 166.81, (2C=O), 161.20, 160.32 (CH=N), 160.26-117.35 (6C, m, arom), 148.32, 115.02 (C=CH), 55.12, 51.61(2-OMe). MS (m/z, %): 319 (parent peak), 319 (base peak, 100%), 134, 120, 77. Anal. Calcd for $C_{14}H_{13}N_3O_4S$: C, 52.66; H, 4.07; N, 13.17%. Found; C, 52.80; H, 4.01; N, 13.01%.

[2-(Benzhydrylidene-hydrazono)-4-oxo-thiazolidin-5-ylidene]-acetic acid mehyl ester (5c). Yellow solid, 1.27 g, yield 87%, m.p138-140, IR (KBr) (υ_{max} ,cm^{-1}): 2982-3000 (C-H, arom)**,** 1741, 1716 (C=O), 1642, 1617 (C=N), H NMR (DMSO) δ: 8.60 (1H, s, NH), 7.68-7.25 (10H, m, arom), 6.80 (1H, s, CH=C), 3.86 (3H, s, -OMe). ^{13}C NMR (DMSO) δ: 166.42, 165.26 (2C=O), 165.21, 160.74 (2C=N), 150.98 -116.06 (C=CH), 52.52 (-OMe). MS (m/z, %): 365 (parent peak), 165 (base peak, 100%), 180, 77. Anal. Calcd for $C_{19}H_{15}N_3O_3S$: C, 62.46; H, 4.11; N, 11.51%. Found; C, 62.34; H, 11.35; N, 4.11%.

[2-(Butylidene-hydrazono)-4-oxo-thiazolidin-5-ylidene]-acetic acid methyl ester (6c). Yellow solid , 0.88 g, yield 86%, m.p 202-203, IR (KBr) (υ_{max} ,cm^{-1}): 2784-3056 (C-H, aliphatic),

1741, 1666 (C=O), 1641, 1617 (C=N), ^{1}H NMR (DMSO) δ: 12.43(1H, s, NH), , 7.59 (1H, t, CH=N), 6.37 (1H, s, C=CH), 3.52 (3H, s, -OMe), 2.07 (2H, q, -CH_2,) , 1.31 (2H, sext, -CH_2), 0.69 (3H, t, -CH_3), ^{13}C NMR (DMSO) δ: 165.80, 163.83,143.01, 113.98, 52.37 (-OMe), 34.03 (-CH_2-), 18.92 (-CH_2-) 13.57 (-CH_3), MS (m/z, %): 255 (parent peak), 85 (base peak, 100%), 227, 187, 59, 43. Anal. Calcd for $C_{10}H_{13}N_3O_3S$: C, 47.06; H, 5.10; N, 16.47%. Found; C, 46.88; H, 4.90; N, 16.23%.

{4-Oxo-2-[(1-P-tolyl-ethylidene)-hydrazono]-thiazolidin-5-ylidene}-acetic acid ethyl ester (7c). Yellow solid ,1.15 g, yield 87%, m.p >220 ^{0}C, IR (KBr) (ῡ$_{max}$,cm^{-1}): 2956-3081 (CH), 3180 (N-H), 1741, 1716 (C=O), 1641, 1617 (C=N), ^{1}H NMR (DMSO) δ: 11.75 (1H, s, N-H), 7.74-7.23 (4H, 2d, arom), 6.58 (1H, s, CH=C), 4.21 (2H, -CH_2-), 2.47(3H, -CH_3) 2.33(3H, -CH_3), 1.25 (3H, -CH_3), ^{13}C NMR (DMSO) δ:165.31, 165.08 (2C=O), 162.55, 158.28 (2C=N) 142.63 (C=CH), 139.85, 134.44, 128.78, 126.29 (6C, arom), 114.25 (C=CH), 60.95 (-CH_2-), 20.62 (-CH_3-para), 14.47(-CH_3) 13.71 (-CH_3), MS (m/z, %): 331 (parent peak), 118 (base peak, 100%), 316, 91, 65. Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 58.00; H, 5.14; N, 12.69%. Found; C, 58.21; H, 5.19; N, 12.47%.

{4-Oxo-2-[(1-P-tolyl-ethylidene)-hydrazono]-thiazolidin-5-ylidene}-acetic acid methyl ester (8c). Yellow solid ,1.14 g, yield 90%, m.p >220 ^{o}C dec., (KBr) (ῡ$_{max}$, cm^{-1}): 3180 (N-H), 3081(C-H, arom) 1741, 1716 (C=O), 1641, 1617 (C=N), ^{1}H NMR (DMSO) δ: 12.76 (1H, s, N-H), 7.76-7.22 (4H, 2d, arom), 6.61 (1H, s, CH=C), 3.75 (3H, s, -OMe), 2.39 (3H, s, -CH_3), 2.33 (3H, s, -CH_3), ^{13} C NMR (DMSO) δ: 165.88, 165.53, (2C=O), 162.08, 143.14 (2C=N), 140.14, 140.00, 134.48, 129.06, 126.50, 114.00 (C=CH), 52.17, 20.39, 14.74. MS (m/z, %): 317 (parent peak, 100%), 118 (base peak), 302, 91, 65. Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 56.78; H, 4.73; N, 13.25%. Found; C, 56.57; H, 4.67; N, 13.01%.

{2-[(4-Methoxy-benzylidene)-hydrazono]-4- oxo-thiazolidin-5-ylidene}-acetic acid ethyl ester (9c). Yellow solid,1.13 g, yield 85%, m.p >220 ^{o}C dec., (KBr) (ῡ$_{max}$,cm^{-1}): 2982-3000 , 1741, 1716 (C=O), 1666, 1617 (C=N), ^{1}H NMR (DMSO) δ: 8.37 (1H, s, CH=N), 7.74-6.93 (4H, 2d, arom), 6.78, (1H, s, CH=C), 4.31 (2H, q, -CH_2-), 3.85 (3H, s, -OCH_3), 1.35 (3H, t, -CH_3) , ^{13}C NMR (DMSO) δ: 170.94, 166.02, (2C=O), 166.O4, 162.02 (2C=N), 159.48, 158.13 (2C, -S-C=CH), 60.24, (-CH_2-), 55.39 (-OMe), 14.17 (1C, -CH_3). MS (m/z, % :333 (parent peak), 134 (base peak, 100%),120, 91, 77, 57.Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 54.05; H, 4.20; N, 12.61%. Found; C, 53.94; H, 4.17; N,12.48%.

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