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An Efficient and Expeditious Method for the Synthesis of Alkyl Oxo-1, 3-Thizolan-5-Yliden Acetate Derivatives

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Abstract: Series of alkyl oxo-1, 3-thiazolane-5-ylidene acetate derivatives were synthesized from monothiosemicarbazone 1, 3 or 1, 2-bicarbonyl compounds and dimethyl or diethyl acetylenedicarboxylate. The product yield was rate from good to excellent by any of three methods, such as ethyl acetate or methanol at ambient temperature' microwave irradiation under solvent-free conditions, heating in an oil bath under solvent-free conditions. Even though various methods for synthesis of thiazoline compounds may exist in literature but synthesis of the new 1, 3-thiazolane compound which contain additional carbonyl group was successfully carried out in this study. The new approach may be preferable once the use solvent was eliminated. The obtained yield was quite acceptable and lied in the reported range.

Key words: Thizolane · Alkyl acethylenic ester · Thiazoline · Monothiosemicarbazone · Microwave irradiation

INTRODUCTION

Over the past decades, thiazolidine compounds have prominent place in heterocyclic chemistry largely due to the wide ranging biological activities demonstrated by this class of compounds [1, 2]. Reaction of dialkyl acethylenedicarboxylate with esters and amides of dithiocarboxylic acid are well known synthetic routes to prepare five and six members of S and S, N heterocyclic compounds [3]. Several substituted thiazolidones have been found to possess hypnotic, anaesthetic, sedative, anticonvulsant and microbiological activities [4-7]. Thiazole derivatives, thiazolidine-4-one and organic compounds containing thiazole and thiazolidinone ring system are used as antiviral agent and some are used as pesticides [6, 8-10], anti-tumor, cytotoxic [1, 4, 10], anti-fungal [7, 8], anti-bacterial [6, 8, 11], anti-parasitic, anti tubercular [7, 12], analgesic [6, 13-15] , anti-cancer [5, 6, 12, 14, 16].

In view of their extensive physiological activities of thiazolidinone, many thiazolidinone derivatives have been prepared. The reaction of thiourea with acetylenic ester has been widely reported by number of research scientists to give a thiazoline-4-one 1, an imidazolinthion 2, or a 1, 3-thiazine-4-one 3 (Scheme 1) [9, 15, 17].

However, recent studies have shown that the thiazoline-4-one 1 that is formed in this reaction [19]. Recently, it was noticed and has been reported the synthesis of a series of thiazoline compounds from the reaction of aldehydes and ketones thiosemicarbazone derivatives with alkyl acethylenic esters (compounds 5 and 6 are demonstrated in Scheme 2) [8, 18, 19].

The purpose of present work is to demonstrate a convenient strategy for the synthesis alkyl oxo-1, 3-thizolan-5-yliden acetate derivaties from reaction of monothiosemicarbazone derivatives of 1, 3-dicarbonyl compounds and 3, 4-dihyroxycyclobuta-3-ene-1, 2-dione with dimethyl and diethyl acetylenedicarboxylate. The synthesized products of thiazoline derivatives were successful and resulted high product yield. Thus, there are limited sources on synthesis and pharmacology of the alkyl oxo-1, 3-thiazolane-5-ylidene acetate derivatives from monothiosemicarbazone 1, 3 or 1, 2-bicarbonyl compounds. Special attention was paid for the synthesis of thiazolane derivatives. Additional investigation may be required on biological activities of thiazolane derivatives. In order to make use of the synthesized chemicals for the production of new formulated drugs; further research on developed synthetic drug structural-activities may be required.

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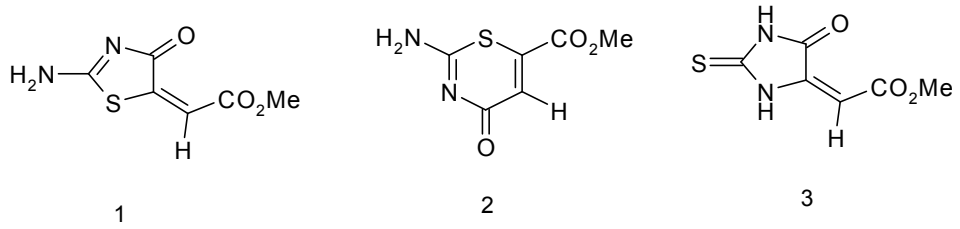
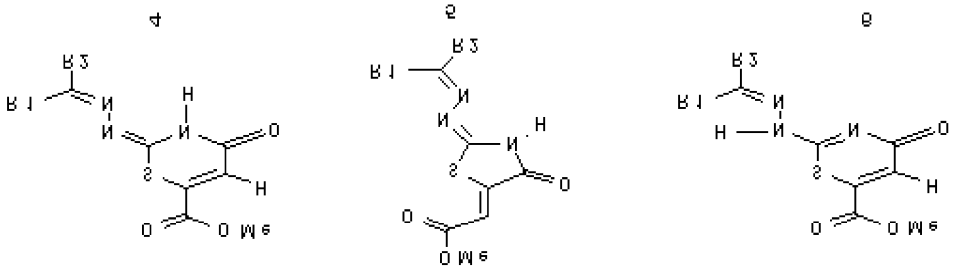


Scheme 1: Reaction of thiazoline compounds



Scheme 2: Thiosemicarbazone derivatives synthesized with alkyl acethylenic esters

MATERIALS AND METHODS

All chemicals (3, 4-Dihyroxycyclobuta-3-ene-1, 2-dione pentane-2, 4-dione, 3-oxo-butyric acid ethyl ester, cyclohexane-1, 3-dione, 5, 5-dimethylcyclohexane-1, 3-dione and solvents for example ethyl acetate, methanol, ethanol, diethyl ether) used for the experiments were analytical grades and supplied by Merck (Darmstadt, Germany). Monothiosemicarbazone derivatives, 1, 3-dicarbonyl compounds and 3, 4-dihyroxycyclobuta-3-ene-1, 2-dione were prepared according to the procedure in the literature [7, 15, 18]. 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 125.7 MHz, respectively. Me_4Si was used as an internal standard in DMSO-d_6. Mass spectrometer was operated at an ionization potential of 70 ev. Element analyses (C, H, N) were performed with a Heracus CHN-O-Rapid analyzer. The microwave induced reactions were carried out in an open borosil glass vessel under atmospheric pressure in BMO-700T domestic oven; which was equipped with magnetic stirrer, manufactured by BPL multimode Sanyo utilities and appliances Ltd. Operation was performed at 700 W generating 2450 MHz frequency.

The general procedure for the reaction of thiosemicarbazone-2-oxo ethyl butyrate with dimethyl acetylene dicarboxylate (4c):

- A solution of thiosemicarbazone-2-oxo ethyl butyrate (0.81 g, 4 mmol) in ethyl acetate (15 ml) was added into a solution of dimethyl acetylene dicarboxylate (0.49 ml, 4 mmol) in a small portion. The solution was mixed thoroughly by stirring at ambient temperature for 5 h. The resulting yellow precipitate was filtered and then washed with ethyl acetate. The yellow solid was separated which then recrystallized from ethanol-water, the product yield (1.19g) was 90%.
- A mixture of thiosemicarbazone 2-oxo ethyl butyrate (0.81 g, 4 mmol) and DMAD (0.49 ml, 4 mmol) was irradiated under microwave at 80W for 5 min, cooled to room temperature and then solid residue was recrystallized from ethanol-water. The obtained product was yellow powder.
- A mixture of thiosemicarbazone 2-oxo ethyl butyrate (0.81 g, 4 mmol) and DMAD (0.49 ml, 4 mmol) was heated in an oil bath at 70-80°C under solvent-free condition for a 15 minute and then the reacted mixture was cooled to room temperature. The solid residue was recrystallized from ethanol-water. Also the obtained product was yellow powder.

***Methyl 2-(2-{2-[1-methyl-3-oxobutylidene]hydrazon}-4-oxo-1,3-thiazolane-5-yliden) acetate (1c)*:** Yellow powder, yield: 1.09 g (92%), m.p. 198°C. IR (KBr): 3369 (N-H), 2955-3081(CH, aliphatic), 1766, 1698, 1687, (3C=O), 1611, 1630 (C=N). Tatomer A: H-NMR: δ = 9.80 (1H, s, NH), 6.90(1H, s, CH=C), 4.20(2H, s, CH_2), 3.65 (3H, s, OCH_3), 2.51 (3H, s, -CH_3), 2.15 (3H, s, CH_3). ^{13}C-NMR: δ = 179.50 (C=O), 177.30, 176.80, (2C=O), 158.34, 145.27, 119.32, (2C=C, C=N), 58.02 (CH_2) 52..47 (OCH_3), 31.24 (CH_3), 14.77 (CH_3). Anal Calcd for $C_{11}H_{13}N_3O_4S$ (283.30): C 46.64; H 4.63; N 14.83. Found: C 46.34; H 4.87; N 15.08.

***Methyl 2-(2-{2-[(1-methyl-3-oxo-1-butenyl]hydrazon}-4-oxo-1,3-thiazolane-5-yliden) acetate*:** Tatomer B: H-NMR: δ = 6.50 (CH=C). ^{13}C-NMR: δ =147.03 (C=NH), 115.35 (CH=C) .

***Ethyl 2-(2-{2-[1-methyl-3-oxobutylidene]hydrazon}-4-oxo-1,3-thiazolane-5-yliden) acetate (2c)*:** Yellow powder, yield: 1.09 g (87%), m.p 151-152°C. IR (KBr): 3368 (N-H), 2950- 3081, (CH, aliphatic), 1765,1693, 1666 (3C=O), 1617 (C=N).

Tatomer A: H-NMR: δ 9.5 (1H, s, NH), 6.87 (1H, s, CH=C), 4.12 (2H, s, CH_2), 4.24 (2H, q, CH_2), 2.50 (3H, s, CH_3), 2.11(3H, s, CH_3), 1.25 (3H, t, CH_3). ^{13}C-NMR: δ = 179.74 (C=O), 178.66, 178.60 (2C=O)157.64, 144.046, 144.94, 121.33 (C=C, C=N), 57.88, 60.15(2CH_2), 14.77, 14.36 (2CH_3). Anal Calcd for $C_{12}H_{15}N_3O_4S$ (297.327): C 48.48; H 5.08; N 14.13. Found: C 48.18; H 4.82; N 14.42.

***Ethyl 2-(2-{(2-[1-methyl-3-oxo-1-butenyl]hydrazon}-4-oxo-1,3-thiazolane-5-yliden) acetate*:** Tatomer B: H-NMR: δ = 6.48 (1H, s, CH=C). ^{13}C-NMR: δ = 146.06 (C=NH), 115.55 (CH=C).

***Ethyl3-(2-{5-[2-ethoxy-2-oxoethylidiene]-4-oxo-1,3-thiazolane-2 yliden} hydrazono) butanoate (3c)*:** Yellow solid, yield: 1.30 g (95%), m.p 154-157°C. IR (KBr) (υ_{max}, cm^{-1}): 3372 (NH), 2858, 2933 (CH,aliphatic), 1741, 1691, 1668, (3C=O), 1617, 1592 (C=N). ^{1}H NMR (DMSO) δ: 12.72 (1H, s, NH), 6.61 (1H, s, CH=C), 4.1 (2H, q, CH_2), 3.95 (2H, q, CH_2), 3.61 (2H, s, CH_2), 2.07 (3H, s, CH_3), 1.28 (3H, t, CH_3), 1.27 (3H, t, CH_3). ^{13}C NMR (DMSO) δ: 169.00, 165.60, 165.00 (3C=O), 164.20, 163.00 (2C=N), 142.91, 114.14 (C=CH), 60.0, 62.20 (2C, CH_2), 43.68 (CH_2), 17.63, 15.25 (2C, CH_3). MS (m/z, %): 343 (parent peak, 100%), 41 (base peak), 265, 65.

***Methyl 3-(2-{5-[(E)-2-ethoxy-2-oxoethylidiene]-4-oxo-1,3-thiazolane-2-yliden}hydrazono) butanoate (4c)*:** Yellow solid, yield: 1.19 g (90%), IR (KBr) (υ_{max}, cm^{-1}): 3385 (NH), 2870, 2930 (CH,aliphatic),1740, 1698, 1690 (3C=O), 1615, 1592 (C=N).^{1}H NMR (DMSO) δ: 12.32 (1H, s, NH), 6.71 (1H, s, CH=C), 4.21 (2H, q, CH2), 3.75 (3H, s. CH3), 3.61 (2H, s, CH_2), 2.12 (3H, s, CH3), 1.28 (3H,t, CH_3). ^{13}C NMR (DMSO) δ: 169.00, 165.60, 165.00 (3C=O), 164.20, 163.00 (2C=N), 142.91, 114.14 (C=CH), 61.12 (1C, CH2), 52.35 (1C, Ome), 43.68 (CH_2), 16.43 (1C, CH_3). MS (m/z, %):327 (parent peak, 100%), 41 (base peak), 265, 65.

***Ethyl 2-{4-oxo-2-[2-(3-oxocyclohexyliden)hydrazono]-1,3-thiazolane-5-yliden} actate (5c)*:** Yellow powder, yield: 0.91 g (70%), IR (KBr) (υ_{max}, cm^{-1}): 3378 (NH), 1780,1710, 1692 (3C=O), 1650, 1635 (2C=N), 1325, 1222 (C-N).^{1}H NMR (DMSO) δ : 10.34 (1H, s, NH), 6.75 (1H, s, CH=C), 4.31 (2H, q, CH_2), 2.50 (2H, s, CH_2), 2.45 (2H, t, CH_2), 2.36 (2H, t, CH_2), 2.04 (2H, m, CH_2), 1.30 (3H, t, CH_3). ^{13}C NMR (DMSO) δ: 188.32 (C=O), 178.55, 176.22, 169.35, 167.18 (3C=O, C=N), 119.11 (CH=C), 63.14, 61.10, 49.05, 44.77, 24.33 (5CH_2), 16.17 (CH_3). Anal Calcd for $C_{13}H_{15}N_3O_4S$ (297.327): C 50.48; H 4.89; N 13.58. Found: C 50.70; H 4.82; N 13.44.

***Methyl 2-{4-oxo-2-[2-(3-oxocyclohexyliden)hydrazono]-1,3-thiazolane-5-yliden} actate (6c)*:** Yellow powder, yield: 0.91 g (73%), m.p 231-232°C. IR (KBr) (υ_{max}, cm^{-1}): 3377 (NH), 1780,1715, 1691 (3C=O), 1652, 1632 (2C=N), 1322, 1223 (C-N). ^{1}H NMR (DMSO) δ : 10.40 (1H, s, NH), 6.79 (1H, s, CH=C), 3.79 (3H, s, OCH_3), 2.52 (2H, s, CH_2), 2.41 (2H, t, CH_2), 2.36 (2H, t, CH_2), 2.04 (2H, m, CH_2), . ^{13}C NMR (DMSO) δ: 188.05(C=O), 177.25, 177.08, 168.98, 167.66 (3C=O, C=N), 118.69 (CH=C), 61.10, 55.47, 49.05, 44.77, 24.33 (4CH_2, OCH_3). Anal Calcd for $C_{12}H_{13}N_3O_4S$ (295.32): C 48.81; H 4.44; N 14.23. Found: C 48.98; H 4.32; N 14.42.

***Ethyl 2-{2-[2-(3,3-dimethyl-5-oxocyclohexyliden) hydrazono]-4-oxo-1,3-thiazolane-5-yliden} acetate (7c)*:** Yellow powder, yield: 1.13 g (80%), m.p 205-206°C, IR (KBr) (υ_{max}, cm^{-1}): 3369 (NH), 1778,1700, 1690 (3C=O), 1650, 1631 (2C=N), 1327, 1218 (C-N). ^{1}H NMR (DMSO) δ: 10.121 (1H, s, NH), 6.63 (1H, s, CH=C), 4.28 (2H, q, CH2), 2.37 (2H, s, CH2), 2.27 (2H, s, CH2), 2.04 (2H, s, CH2), 1.28 (3H, t, CH3), 1. 051 (6H, s, 2CH3). ^{13}C NMR (DMSO) δ: 180.30 (C=O), 170.25, 171.70, 166.35, 165.12 (2C=O, C=N), 116.10 (CH=C), 62.10, 60.10, 48.00, 42.30 (4CH2), 37.5 (C), 27.15 (2CH3) 14.40 (CH3). Anal Calcd for $C_{15}H_{19}N_3O_4S$ (337.40): C 53.40; H 5.68; N 12.45. Found: C 53.94; H 5.82; N 12.22.

***Methyl 2-{2-[2-(3,3-dimethyl-5-oxocyclohexyliden) hydrazono]-4-oxo-1,3-thiazolane-5-yliden} acetate (8c)*:** Yellow powder, yield: 1.15 g (85%), m.p 201-203°C, . IR (KBr) (υ_{max}, cm^{-1}): 3371 (NH), 1784,1700, 1695 (3C=O), 1642, 1630 (2C=N), 1330, 1220 (C-N).). ^{1}H NMR (DMSO) δ: 10.162 (1H, s, NH), 6.65 (1H, s, CH=C), 3.74 (3H, s, OCH_3), 2.38 (2H, s, CH_2), 2.25 (2H, s, CH_2), 2.01 (2H, s, CH_2), 1. 052H, s, 2CH_3). ^{13}C NMR (DMSO) δ: 182.29 (C=O), 171.25, 170.00, 166.51, 165.42 (2C=O, C=N), 115.00 (CH=C), 62.10, 60.10 (2CH_2) 56.89 (OCH_3), 48.17, 42.86 (2CH_2), 38.48 (C), 28.10 (2CH_3) . Anal Calcd for $C_{14}H_{17}N_3O_4S$ (323.37): C 52.00; H 5.30; N 12.99. Found: C 51.85; H 5.45; N 13.12.

***Methyl 2-{2-[2-(2,3-dihydroxy-4-oxo-2-cyclobutenylliden) hydrazono]-4-oxo-1,3-thizolane-5-yliden} acetate (1e)*:** PaleYellow powder, yield: 1.21 g

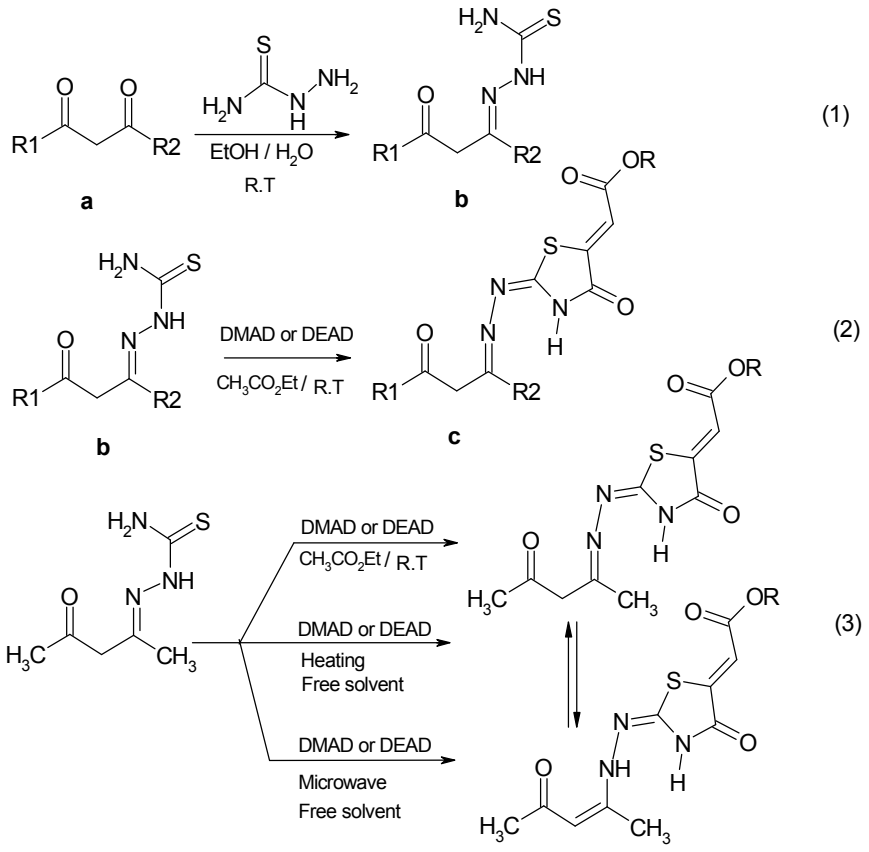
(97%), m.p> 230°C . IR (KBr) (υ_{max}, cm^{-1}): 3385 (NH), 3300-3550 (O-H), 1787, 1696,1688, (3C=O), 1648, 1635, 1617 (C=N.C=C) ^{1}H NMR (DMSO) δ : 15.45, 15.42 (2H, OH), 10.12 (1H, s, NH), 7.74 (1H, s, CH=C), 3.75 (3H, s, OCH3). ^{13}C NMR (DMSO) δ: 196.17, 187.74, 184.57, 182.80, 178.88, 175.00, 174.33 (3C=O, 2C=N, HO-C=C-OH), 166.12 (C=C), 128..46 (CH=C), 49.50 (OCH_3). Anal Calcd for $C_{10}H_7N_3O_6S$ (297.25): C 40.41; H 2.37; N 14.14. Found: C 40.35; H 2.60; N 14.32.

***Ethyl 2-{2-[2-(2,3-dihydroxy-4-oxo-2-cyclobutenylliden) hydrazono]-4-oxo-1,3-thizolane-5-yliden} acetate (2e)*:** PaleYellow powder, yield: 1.19 g (90%), m.p>230°C. IR (Kbr) (υ_{max}, cm^{-1}): 3384 (NH), 3300-3550 (O-H), 1787, 1696,689 (3C=O), 1645, 1630, 1617 (C=N, C=C). ^{1}H NMR (DMSO) δ : 15.45, 15.42 (2H, OH), 10.10 (1H, s, NH), 7.72 (1H, s, CH=C), 4.5 (2H, q, CH2), 1.32 (3H, t, CH3). ^{13}C NMR (DMSO) δ: 195.50, 187.34, 184.60, 183.00, 178.32, 175.12, 174.02 (3C=O, 2C=N, HO-C=C-OH), 166. 15 (C=C), 126.17 (CH=C), 67.20 (CH_2), 17.10 (CH_3). Anal Calcd for $C_{11}H_9N_3O_6S$ (311.27): C 42.45; H 2.91; N 13.50. Found: C 42.72; H 3.12; N 13.25.

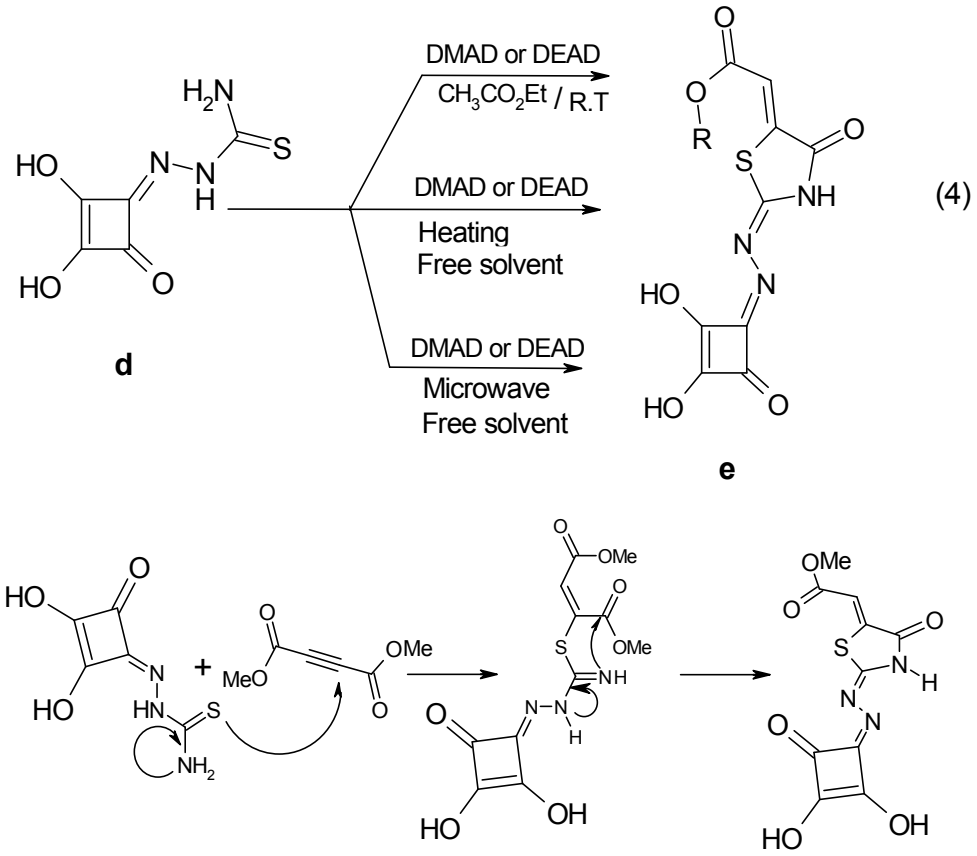
RESULTS AND DISCUSSION

The preparation of thiazoline compounds were developed [20] over the past years [1, 8, 9, 12, 16, 21]. There is a few report about synthesis of thiazoline compound from monothiosemicarbazone derivatives 1, 3-dicarbonyl and 1, 2-dihyroxy-3, 4-cyclobutenedione in literature [5, 11, 12, 14, 22-27]. In continuation and extended development of new synthesized thiazoline; present synthesis of five members of thiazoline such as S, N-heterocyclic thiazoline. In addition present work discuss about methods for the synthesis of heterocyclic thiazoline from monothiosemicarbazone derivatives 1, 3-dicarbonyl and 1, 2-dihyroxy-3, 4-cyclobutenedione. DMAD and DEAD were reacted with different monothiosemicarbazone 1, 3-dicarbonyl and 3, 4-dihyroxycyclobuta-3-ene-1, 2-dione via three methods as defined below:

- Monothiosemicarbazone was dissolved in ethyl acetate or methanol solution, then DMAD or DEAD was added to the solution and stirred for 3-4 hr at ambient temperature.



Scheme 3: Synthesis of alkyl oxo-1, 3-thizolan-5-yliden acetate derivative



Scheme 4: Synthsis and mechanism of alkyl 2-{2-[2-(2,3-dihydroxy-4-oxo-2-cyclobutenylliden)hydrazono]-4-oxo-1,3-thizolane-5-yliden} acetate

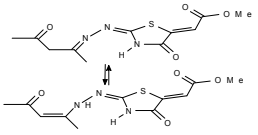
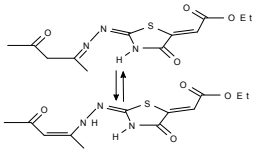
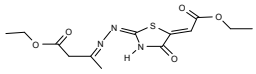
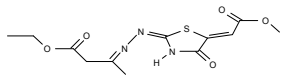
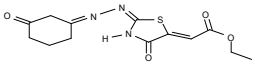
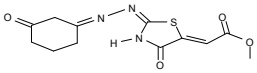
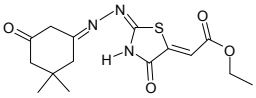
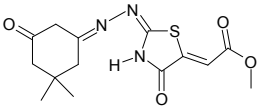
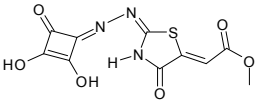
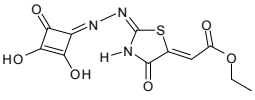
- Monothiosemicarbazone was mixed with acetylenic ester and then the reaction was subjected to microwave irradiation under free solvent condition.
- Monothiosemicarbazone was mixed with acetylenic ester. The reaction was then heated in an oil bath under solvent-free condition.

The reactions for the synthesis of alkyl oxo-1, 3-thizolan-5-yliden acetate derivative are summarized as Scheme 3 shown as follows:

The reaction is mainly condensation followed by cyclization. Initially the sulfur atom from monothiosemicarbazone attacks to the carbon triple bond of acetylenic ester compound which is the prone to nucleophilic attack then cyclization proceed onto the esteric (CO_2R) function to give products alkyl oxo-1, 3-thizolan-5-yliden acetate derivatives in appreciably high yield (Scheme 4) [4, 11, 21].

Table 1 summarized all synthesized thiazoline derivatives with resulted yields obtained in 3 methods (A, B and C), formula 1c-8c and 1e-2e. The structure of compound 4c was deduced from their elemental analysis and their IR, ^{1}H- and ^{13}C-NMR spectra. The mass spectra of this compound displayed molecular ion peak at the appropriate m/z-values. Compound 4c showed NH group at 3385, carbonyl groups at 1740, 1690, 1698 and C=N, C=C at 1615, 1592 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum of compound 4c indicated one singlet quiet down field at δ=12.32 ppm which is the proton of NH amide, Vinyl proton at 6.71 ppm and methoxy proton at 3.75 ppm. This compound also showed one quartet signal at 4.21, one triplet signal at 1.28 ppm which is the protons of ethyl group and two singlet signals for methyl and methylene groups at 3.61, 2.12 ppm. The ^{13}C-NMR spectrum of 4c indicate that the carbonyl group carbons are at 169.00, 165.60, 165.00, (C=N), 164.20, 163.00, (CH=C), 142.91, 114.14, (methoxy carbon), 52.35, (ethoxy carbon), 61.12, 16.43; also the methyl and methylene carbons are at 43.68 ppm. The mass spectra revealed that the molecular ion peak was at m/z = 317 and the base peak was at m/z = 41 (100%).

Table 1: compounds and yield of alkyl oxo-1, 3-thizolan-5-yliden acetate derivaties (1c to 2e)

Synthesized Compounds	Structure of compounds	Yield (%) Method A	Yield (%) Method B	Yield (%) Method C
1c		92	94	90
2c		87	90	90
3c		95	94	92
4c		90	90	89
5c		70	75	73
6c		73	76	75
7c		80	77	75
8c		85	80	77
1e		97	98	97
2e		90	92	95

CONCLUSIONS

It was concluded that the developed three different simple synthesized methods were used for the preparation of the new 1, 3-thiazolane compounds which contain additional carbonyl group in ethyl acetate or methanol at ambient temperature. The synthesized methods were experimented with microwave irradiation under solvent-free conditions and heated in an oil bath under solvent-free conditions. Although there are various methods presented on synthesis of thiazoline compounds; but there was no distinct method reported in literature about synthesis of these compounds as the present paper has demonstrated. All of these discussed synthesized methods have led to high product yields. Microwave irradiation and heating in an oil bath display dramatically reduced in reaction time as it was compared to conventional batch experiment using magnetic stirrer method. Also, the present data showed great effort to obtain the desired products with high purities and yields.

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