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Ashraf A. Aly[a], Esam A. Ishak[a] & Alan B. Brown[b]

[a] Chemistry Department, Faculty of Science, Al Jouf University, Sakaka, Al Jouf, KSA

[b] Chemistry Department, Florida Institute of Technology, Melbourne, FL 32901, USA

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Reaction of arylidenehydrazono-4-aryl-2,3-dihydrothiazole-5-carbonitriles with diethyl acetylenedicarboxylate. Synthesis of (*Z*)-ethyl 2-[((*Z*)-2-(*E*)-arylidenehydrazono)-4-oxo-thiazolidine-5-ylidene]acetates. NMR investigation

Ashraf A. Aly[a†,*], Esam A. Ishak[a‡] and Alan B. Brown[b]

[a]*Chemistry Department, Faculty of Science, Al Jouf University, Sakaka, Al Jouf, KSA;*
[b]*Chemistry Department, Florida Institute of Technology, Melbourne, FL 32901, USA*

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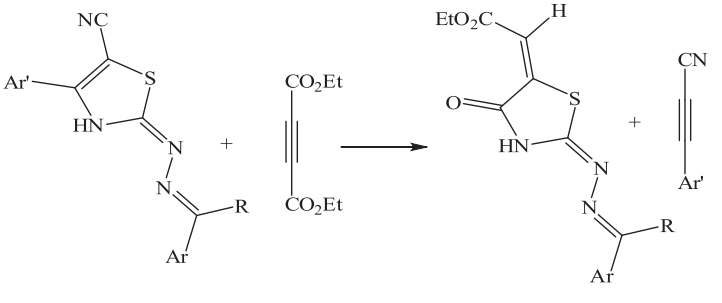
(*Z*)-Ethyl 2-[((*Z*)-2-(*E*)-arylidenehydrazono)-4-oxo-thiazolidine-5-ylidene]acetates were synthesized by three different methods: (a) reaction of arylidenehydrazono-4-aryl-2,3-dihydrothiazole-5-carbonitriles with diethyl acetylenedicarboxylate (DEAD) in acetic acid with prolonged reflux, (b) reaction between thiosemicarbazones, 2-arylidenemalononitriles and DEAD under conventional conditions or microwave irradiation, (c) one-pot three-component reaction of thiosemicarbazone derivatives, ylidene and DEAD. The thiazolinone adducts were obtained in good to excellent yields. NMR of the obtained products was investigated.



Keywords: thiosemicarbazones; thiazolidine; diethyl acetylenedicarboxylate; new conversion; NMR

1. Introduction

Thiazolidin-4-ones are important heterocyclic compounds owing to their biological activities,[1,2] such as anti-tuberculosis,[3] anti-convulsant,[4] and fungistatic.[5] Reactions of dimethyl

*Corresponding author. Email: ashrafaly63@yahoo.com
†Permanent address: Chemistry Department, Faculty of Science, El-Minya University, 61519-El-Minya, Egypt.
‡Permanent address: Chemistry Department, Faculty of Science, Al-Azhar University, Assuit, Egypt.

acetylenedicarboxylate (DMAD) with esters and amides of dithiocarboxylic acids are well-known methods for preparation of five-membered *S*- and *S*,*N*-heterocycles.[6,7] Thioureas react with DMAD to give 1:1 adducts with loss of methanol.[7] In the past, several methods have been reported for the preparation of thiazolidinone derivatives. For example, the reaction of thioamides or thiosemicarbazide derivatives with dialkyl acetylenedicarboxylates is a convenient and effective method to prepare 2-amino-5-methoxycarbonyl-thiazolidin-4-ones.[8,9] Thiosemicarbazones [10–14] and their metal complexes have a broad range of biological applications and medicinal properties, including antiviral, antimalarial, antifungal, and antitumor activity.[15–26] Rakitin reported that an anthraquinonothiazole derivative reacted with triethylamine to give a fused pyrrole derivative.[27] Also, 2-(dimethylamino)-thiazole reacted with DMAD to produce a pyridine derivative *via* extrusion of a sulfur atom.[28] In recent years, the use of microwave irradiation has become popular among synthetic organic chemists, both to improve classic organic reactions (shortening reaction times and/or improving yield), and to promote new reactions.[29] Aly et al. demonstrated a very convenient procedure to synthesize 1,3-thiazines by the reaction of but-2-ynedioic acid, propynoic acid ethyl ester, and (*E*)-1,4-diphenyl-but-2-ene-1,4-dione with aroyl-substituted thioureas in acetic acid.[30] The same group [31] changed the conditions of the reaction by mixing a solution of DEAD and aroylthioureas together with triphenyl phosphine. The products were identified as methyl-(2*Z*)-2-[(2*Z*)-2,3-diaryl-carbonylimino-4-oxo-thiazolidin-5-ylidene]-acetates. Hence, in this paper, we describe the action of DEAD on the thiazole ring (which results from reaction of thiosemicarbazones with 2-arylidenemalononitriles). The one-step three-component system, including thiosemicarbazones, ylidene and DEAD seems to offer an alternative fast and attractive green methodology that saves both solvent and time compared with the multi-step approach.

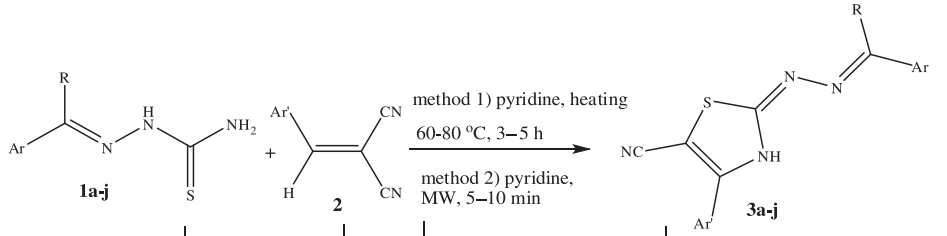
2. Results and discussion

Recently, we reported the synthesis of arylidenehydrazono-4-aryl-2,3-dihydrothiazole-5-carbonitriles **3a–j** by the reaction of pyridine solutions of equimolar amounts of (*E*)-2-arylidenehydrazinecarbothioamides **1a–j** and arylidenemalononitriles **2** under gentle heating (60–80°C) or under microwave irradiation (Scheme 1).[32]

Trials using solvents such as DMF, ethanol/piperidine, ethanol/Et_3N, dioxane/piperidine, DMSO, or solvent-free fusion all failed. It is noteworthy that reactions between **1a–j** and **2** in acetic acid produced low yields of products **3a–j** (Scheme 1). Surprisingly, on reacting compounds **3a–j** with diethyl acetylenedicarboxylate (DEAD, **4**) in acetic acid under prolonged reflux, the reaction produced (*Z*)-ethyl 2-[((*Z*)-2-(*E*)-arylidenehydrazono))-4-oxo-thiazolidine-5-ylidene]-acetates **5a–e** together with 3-aryl-propiolonitriles **6a–d** (Scheme 2). The sequence indicated opening of the thiazolidine ring in **3a–j** during its reaction with DEAD (**4**; Scheme 3).

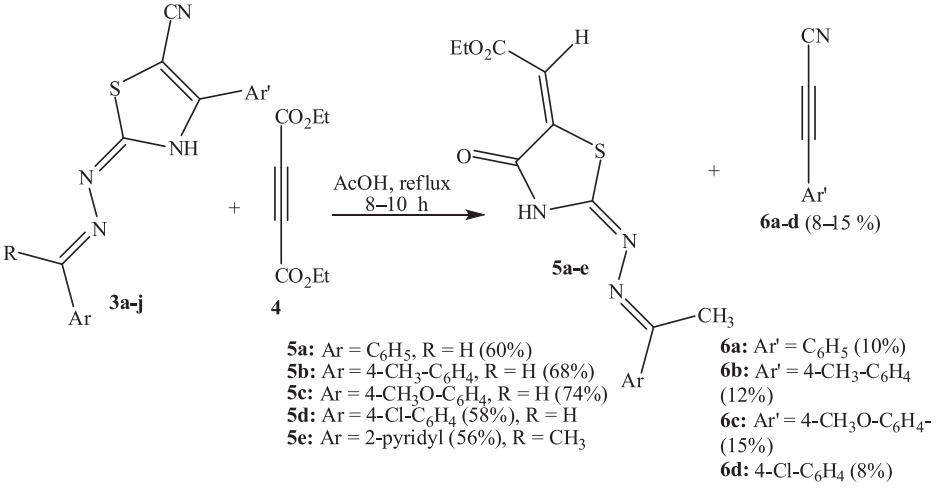
A plausible rationale for the reaction (Scheme 3) begins with attack on the C≡C bond by the *S*-lone pair to form the salt **7**. Neutralization of **7** would cause elimination of 3-aryl-propiolo-nitriles **6** and intermediate **8** (Scheme 3). Tautomerism of **8** into **9** would enable the amidine nitrogen in **9** to attack the carbonyl ester leading to the new thiazolidinone **5** accompanied with elimination of ethanol molecule aided by proton transfer (Scheme 3). In order to prepare **5a–f**, we reacted methanolic solutions of thiosemicarbazones **1a–f** with DEAD **4** under reflux. The synthesis was also achieved by mixing the two starting materials without solvent and exposing the mixture to microwave irradiation. The latter method gave higher yields of the products **5a–f** (Scheme 4).

The third method constitutes a facile synthesis of compounds **5a** and **5b**. It is a one-pot three-component reaction of a mixture of equimolar quantities of thiosemicarbazones **1a, b** with **2a, b** and **4** under prolonged reflux in acetic acid (Scheme 5). We expected that compounds **1** would



	Ar	Ar'	R	Method 1: Yield of **3** (%)	Method 2: Yield of **3** (%)
a	C_6H_5	C_6H_5	H	75	82
b	C_6H_5	4-CH_3-C_6H_4	H	77	86
c	C_6H_5	4-Cl-C_6H_4	H	73	78
d	4-CH_3-C_6H_4	4-CH_3-C_6H_4	H	80	87
e	4-CH_3-C_6H_4	4-CH_3O-C_6H_4	H	84	88
f	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	H	90	96
g	4-CH_3O-C_6H_4	4-Cl-C_6H_4	H	76	84
h	4-Cl-C_6H_4	4-CH_3O-C_6H_4	H	74	80
i	4-Cl-C_6H_4	4-Cl-C_6H_4	H	55	66
j	2-pyridyl	C_6H_5	CH_3	56	65

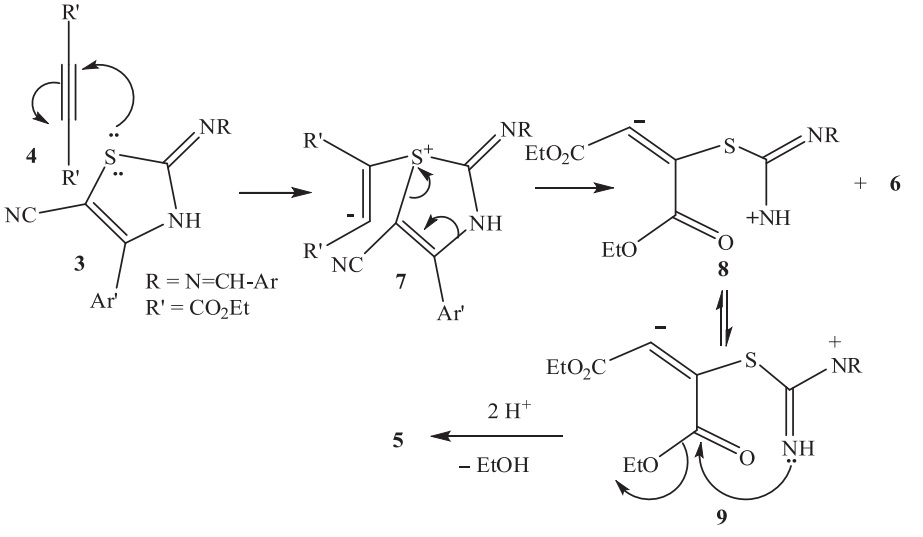
Scheme 1. Synthesis of thiazolidines **3a–j**.



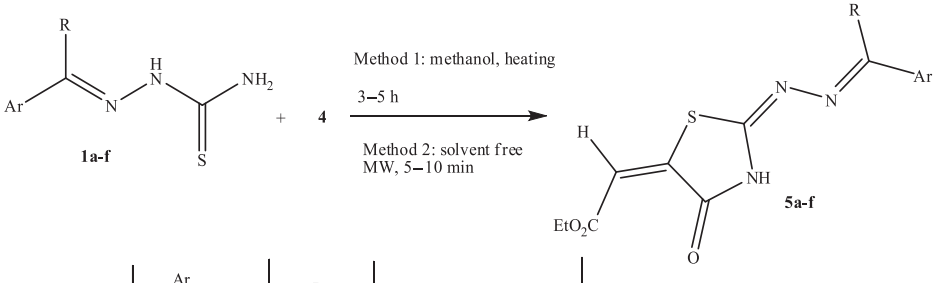
Scheme 2. Conversion of thiazolidines **3a–j** into thiazolidinones **5a–e**.

react more readily with **4** than with **2**. We reacted compounds **1** with **2**, and then in the same reaction vessel we added compound **4** without separation of intermediate compounds **3**. Since, as mentioned before, the reaction of **1** and **2** in acetic acid gave relatively low yield percentages of products **3** [32] that would decrease the overall yields of compounds **5**. Reaction of **1a,b, 2a,b** and **4** in pyridine and/or under microwave irradiation failed.

The structures of compounds **5a–f** were elucidated on the basis of IR, NMR and mass spectra together with elemental analyses. The NMR data of the product obtained from the reaction of



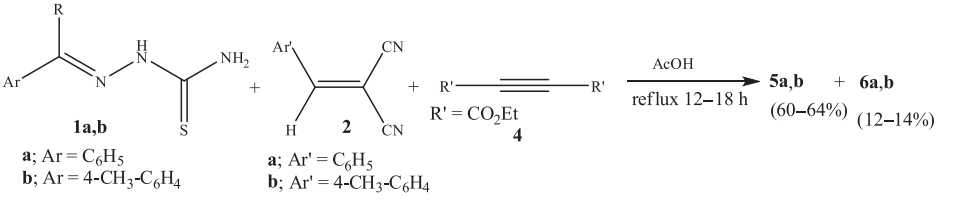
Scheme 3. Plausible mechanism describing formation of thiazolidinones **5**.



1	Ar	R	Method 1: Yield of **5** (%)	Method 2: Yield of **5** (%)
a	C_6H_5	H	75	82
b	4-CH_3-C_6H_4	H	77	86
c	4-CH_3O-C_6H_4	H	82	90
d	4-Cl-C_6H_4	H	71	79
e	2-furyl	H	62	70
f	2-pyridyl	CH_3	66	74

Scheme 4. Synthesis of thiazolidinones **5a**–**f**.

3a with **4** are summarized in Tables 1 and 2. The ethoxy carbons and protons are assigned straightforwardly: CH_2 $\mathbf{C}H_3$, $\delta_C = 13.93$; $CH_2C\boldsymbol{H}_3$, $\delta_H = 1.28$; $\boldsymbol{C}H_2CH_3$, $\delta_C = 61.25$; $C\boldsymbol{H}_2CH_3$, $\delta_H = 4.26$. One carbonyl carbon ($\delta_C = 165.35$) gives HMBC correlation with $C\mathbf{H}_2CH_3$, and is assigned as $\mathbf{C}O_2CH_2CH_3$. The other carbonyl ($\delta_C = 165.63$) is broadened, presumably due to amidine tautomerism; it is assigned as **C**-4, and gives HMBC correlation with the vinylic C***H*** at $\delta_H = 6.66$, assigned as **H**-6. **H**-6 gives HSQC correlation with $\delta_C = 114.48$ and HMBC correlation with $\delta_C = 142.66$, assigned as **C**-6 and **C**-5, respectively. The singlet at $\delta_H = 8.55$ is assigned as C***H***=N; the attached carbon at $\delta_C = 158.62$ is assigned as ***C***H=N. C***H***=N also gives HMBC correlation with a signal at $\delta_C = 133.60$, assigned as ***C**-i*, and a signal at $\delta_C = 127.93$,



Scheme 5. One-pot synthesis of thiazolidinones **5a, b**.

Table 1. The ^{1}H NMR spectral data of the product from the reaction of **3a** with **4**.

^{1}H NMR (DMSO-d_6)	COSY	Assignment
12.90 (b; 1H)		N–***H***
8.55 (s; 1H)		C***H***=N
7.83 (dd, J = 6.6, 2.9 Hz; 2H)	7.52	H-*o*
7.52 (m; 3H)	7.83	H-*m*, ***H*** − *p*
6.66 (s; 1H)		H-5
4.26 (q, J = 7.1; 2H)	1.28	C***H***$_2$CH$_3$
1.28 (t, J = 7.1; 3H)	4.26	CH$_2$C***H***$_3$

Table 2. The ^{13}C NMR spectral data of the product from the reaction of **3a** with **4**.

^{13}C NMR (DMSO-d_6)	HSQC	HMBC	Assignment
165.63 (dd, J = 9.0, 4.9 Hz)		6.66	***C***-4
165.35 (dt, J_d = 1.4, J_t = 2.8 Hz)		4.26	***C***O$_2$CH$_2$CH$_3$
160.26 (“q”, J = 5.7 Hz)		8.55	***C***-2
158.62 (dt, J_d = 166.2, J_t = 2.9 Hz)	8.55	7.85	***C***H=N
142.66 (s)		6.66	***C***-5
133.60 (t, J = 7.4 Hz)		8.55	***C***-*i*
131.18 (dt, J_d = 161.1, J_t = 5.5 Hz)	7.52	7.83	***C***-*p*
128.86 (ddd, J = 164.6, 3.6, 3.6 Hz)	7.52	7.52	***C***-*m*
127.93 (dddd, J = 160.2, 7.4, 3.7, 3.7 Hz)	7.83	8.55	***C***-*o*
114.48 (d, J = 171.2 Hz)	6.66		***C***-6
61.25 (tq, J_t = 148.6, J_q = 4.4 Hz)	4.26	1.28	CO$_2$CH$_2$CH$_3$
13.93 (tq, J_t = 2.5 Hz, J_q = 127.1)	1.28	4.26	***C***H$_3$

assigned as ***C***-*o*. The protons attached to ***C***-*o* appear at δ_H = 7.83; they give HMBC correlation with a signal at δ_C = 131.18, assigned as ***C***-*p*. The proton attached to ***C***-*p* appears at δ_H = 7.52 along with the remaining two aromatic protons, assigned as ***H***-*m*; the remaining aromatic *carbons* appear at δ_C = 128.86, and are assigned as ***C***-*m*. The remaining signal at δ_C = 160.26 is assigned as ***C***-2; like ***C***-*i*, this signal gives HMBC correlation with C***H***=N.

To distinguish between possibilities **5a** and **10a** (Figure 1), a ^{1}H-coupled ^{13}C spectrum was collected. The amide ***C***=O shows doublet couplings of 9.0 and 4.9 Hz, consistent with three-bond coupling to ***H***-6 and two-bond coupling to N-H. The ester ***C***=O shows doublet coupling of 1.4 Hz, consistent with two-bond coupling to ***H***-6, and triplet coupling of 2.8 Hz, consistent with four-bond coupling to C***H***$_2$CH$_3$. ***C***-6 shows no coupling at all. In **10a**, the amide *C*=O would be two bonds from *H*-6 and the ester *C*=O would be three bonds from *H*-6, which should reverse the sizes of the observed couplings. In α,β-unsaturated carbonyl compounds, two-bond coupling constants between ***C***=O and H-α are smaller (3–6 Hz) than three-bond couplings between ***C***=O and ***H***-β(8–16 Hz).[33] The observations that amide *C*=O shows coupling to N-H, but *C*-5 and C-6 do not, also support structure **5a** over isomer **10a**. The observation of coupling between amide

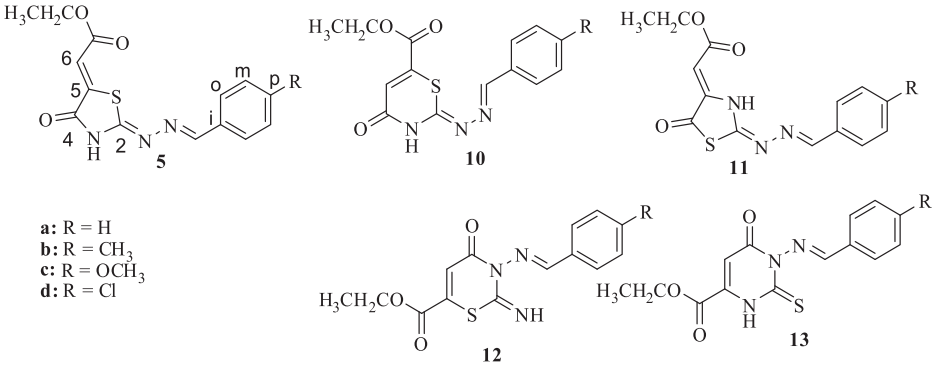


Figure 1. Structures of possible products from the reaction of **3a–d** with **2**.

Table 3. ^{1}H NMR spectral data of **5b**.

^{1}H NMR (DMSO-d_6)	COSY	Assignment
12.83 (b)		N–***H***
8.49 (s, 1H)	7.71	C***H***=N
7.71 (d, J = 7.9; 2H)	8.49, 7.31	***H***-*o*
7.31 (d, J = 7.8; 2H)	7.71, 2.37	***H***-*m*
6.63 (s, 1H)		***H***-6
4.25 (q, J = 7.1 Hz; 2H)	1.28	C***H***$_2$C***H***$_3$
2.37 (s, 3H)	7.31	Ar-CH$_3$
1.28 (t, J = 7.1 Hz; 3H)	4.26	CH$_2$-***CH***$_3$

Table 4. ^{13}C NMR spectral data of **5b**.

^{13}C NMR (DMSO-d_6)	HSQC	HMBC	Assignment
165.69 (dd, J = 9.9, 4.4)		6.66	C-4
165.45 (s)		4.26	***C***O$_2$CH$_2$CH$_3$
161.20 (t, J = 3.3)			C-2
157.39 (dt, J_d = 167.5, J_t = 4.6)	8.56	7.85	***C***H=N
		6.66	C-5
142.80 (s)		7.85,	C-*p*
135.73 (tt, J = 11.3, 9.0)	7.59		
132.62 (dt, J_d = J_t = 8.5)		8.56,	C-*i*
129.59 (ddd, J = 163.7, 6.7, 3.5)	7.59		C-*o*
	7.85	8.56,	C-*m*
129.09 (dd, J = 167.5, 4.6)	7.85		C-6
114.54 (d, J = 171.4)	7.59	7.59	***C***H$_2$CH$_3$
61.32 (tq, J_t = 148.6, J_q = 4.5)	6.66		CH$_2$***C***H$_3$
14.00 (tq, J_t = 2.7, J_q = 126.9)	4.26	1.28	
	1.28	4.26	

C=O and N-*H* also excludes isomer **13a**, in which this would be a five-bond coupling. Structure **13a** can be excluded *via* ^{13}C chemical shifts: structures **5** and **10–12** each have two C=O and two ***C***=N; **13a** would have two ***C***=O, one ***C***=N, and one ***C***=S. Thiocarbonyls typically resonate at $\delta_C > 180$ ppm (cf. tetramethylthiourea 194.8 [34]); in **5b**″, all four ***C***=X appear between δ_C = 157–165, so the structure of **13b**″ is eliminated.

Tables 3 and 4 summarize the NMR data of **5b**. The DEAD-derived signals are assigned by the same logic used for **5a**: CH$_2$**C**H$_3$, δ_C = 14.00; CH$_2$C**H**$_3$, δ_H = 1.28; **C**H$_2$CH$_3$, δ_C = 61.29; C**H**$_2$CH$_3$, δ_H = 4.25; **C**O$_2$CH$_2$CH$_3$, δ_C = 165.44; C-4, δ_C = 165.85; H-6, δ_H = 6.63; C-6,

Table 5. ^{1}H NMR spectral data of **5d**.

^{1}H NMR (DMSO-d_6)	COSY	Assignment
12.94 (b; 1H)		N–***H***
8.56 (s; 1H)		C***H***=N
7.85 (d, $J = 4$; 2H)	7.59	***H***-*o*
7.59 (d, $J = 8.4$; 2H)	7.85	***H***-*m*
6.66 (s; 1H)		***H***-6
4.26 (q, $J = 7.1$; 2H)	1.28	C***H***$_2$CH$_3$
1.28 (t, $J = 7.1$; 3H)	4.26	CH$_2$C***H***$_3$

Table 6. ^{13}C NMR spectral data of **5d**.

^{13}C NMR (DMSO-d_6)	HSQC	HMBC	Assignment
165.85 (d, $J = 5.3$ Hz)		6.63	***C***-4
165.44 (s)		4.25	***C***O$_2$CH$_2$CH$_3$
160.03 (s)	8.49		***C***-2
158.53 (dt, $J_d = 164.6$, $J_t = 4.1$ Hz)	8.49	7.71	*CH*=N
142.93 (s)	6.63		***C***-5
141.29 (tq, $J_t = J_q = 6.8$Hz)		7.71,2.37	***C***-*p*
		8.49,7.31	***C***-*i*
131.03 (dt, $J_d = J_t = 7.8$ Hz)		7.31,2.37	***C***-*m*
129.53 (ddd, $J = 152.9, 5.5, 5.5$ Hz)		8.49, 7.71	***C***-*o*
	6.63		***C***-6
128.00 (ddd, $J = 154.1, 5.7, 4.1$ Hz)	4.25	1.28	***C***H$_2$CH$_3$
	2.37	7.31	Ar-*C*H$_3$
114.33 (d, $J = 171.2$)	1.28	4.25	CH$_2$CH$_3$
61.25 (tq, $J_t = 148.7$, $J_q = 4.4$ Hz)			
21.15 (tq, $J_t = 4.2$, $J_q = 126.8$ Hz)			
14.00 (tq, $J_t = 2.5$, $J_q = 126.9$ Hz)			

$\delta_C = 114.33$; C-5, $\delta_C = 142.93$. C-4 gives a doublet coupling, presumably to H-6. The benzylic methyl carbon and protons appear at $\delta_C = 21.15$ and $\delta_H = 2.37$, respectively; the benzylic protons give HMBC correlation with the carbons at $\delta_C = 141.29$ and 129.53, and the benzylic carbon gives HMBC correlation with the protons at $\delta_H = 7.31$, which in turn give HSQC correlation with $\delta_C = 129.53$. This group of correlations leads to assignment of $\delta_C = 141.29$ and 129.53 as C-*p* and C-*m*, respectively, and of $\delta_H = 7.31$ as H-*m*.

The other aromatic protons at $\delta_H = 7.71$ are assigned as H-*o*, and the attached carbons at $\delta_C = 128.00$ are assigned as C-*o*. C-*o* gives HMBC correlation with a singlet at $\delta_H = 8.49$, assigned as C**H**=N; the attached carbon at $\delta_C = 158.53$ is assigned as **C**H=N. C**H**=N also gives HMBC correlation with a signal at $\delta_C = 131.03$, assigned as C-*i*. The remaining signal at $\delta_C = 160.03$ is assigned as C-2.

Tables 5 and 6 summarize the NMR data of product **5d**. Again, the ethoxy carbons and protons are assigned straightforwardly: CH$_2$***C***H$_3$, $\delta_C = 14.00$; CH$_2$C***H***$_3$, $\delta_H = 1.28$; ***C***H$_2$CH$_3$, $\delta_C = 61.32$; C***H***$_2$CH$_3$, $\delta_H = 4.26$. One carbonyl carbon ($\delta_C = 165.45$) gives HMBC correlation with C***H***$_2$CH$_3$, and is assigned as **C**O$_2$CH$_2$CH$_3$. The other carbonyl ($\delta_C = 165.69$) is broadened, presumably due to amidine tautomerism; it is assigned as ***C***-4, and gives HMBC correlation with the vinylic C***H*** at $\delta_H = 6.66$, assigned as ***H***-6. HSQC correlation with $\delta_C = 114.54$ and HMBC correlation with $\delta_C = 142.80$, assigned as ***C***-6 and ***C***-5, respectively. The singlet at 8.56 is assigned as C***H***=N; the attached carbon at $\delta_C = 157.39$ is assigned as ***C***H=N. C***H***=N also gives HMBC correlation with a signal at $\delta_C = 132.62$, assigned as ***C***-*i*, and a signal at $\delta_C = 129.59$, assigned as ***C***-*o*. The protons attached to ***C***-*o* appear at $\delta_H = 7.85$; they give HMBC correlation with the "other" ***C***-*o* and also with a signal at $\delta_C = 135.73$, assigned as ***C***-*p*. The remaining aromatic

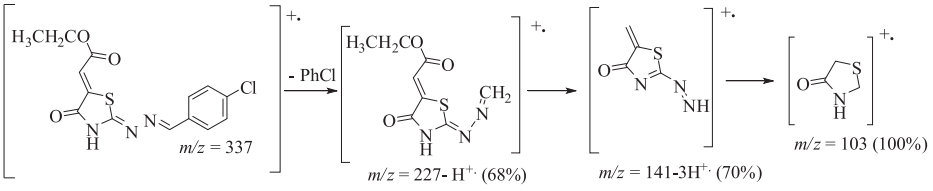


Figure 2. Fragmentation patterns of peak ions in compound **5d**.

carbons and protons appear at $\delta_C = 129.09$ and $\delta_H = 7.59$, and are assigned as ***C***-*m* and $H - m$, respectively; ***C***-*m* gives HMBC correlation with the "other" ***H***-*m*, and ***H***-*m* also gives HMBC correlation with ***C***-*i* and ***C***-*p*.

The remaining signal at $\delta_C = 161.20$ is assigned as ***C***-2; like ***C***-4, this signal is broadened by amidine tautomerism. In the ^{1}H-coupled ^{13}C spectrum, the amide **C**=O shows doublet couplings of 9.9 and 4.4 Hz, consistent with three-bond coupling to H-6 and two-bond coupling to N-H. Neither the ester C=O nor C-5 shows any coupling at all.

The mass spectrum of **5d** contained fragments at $m/z = 337$ (M^+; 100%), 226 (68%), 138 (70%) and 103 (100). Figure 2 shows possible fragmentation pathways. These peaks are repeated in the mass spectra of compounds **5a**–**f**.

Products isolated from the reaction of compounds **3a**–**j** with **4** gave the same physical, spectral and analytical analyses as those isolated from other methods. Yields of products were higher when the aromatic moiety bore electron donating groups such as methyl or methoxy, than when substituents were electron-withdrawing (*e.g.* chloro) in **3c**. Moreover, the reaction can be generalized to heterocyclic rings as in **3j**.

3. Conclusion

In conclusion, we have synthesized a new series of thiazole derivatives in nearly quantitative yields using conventional and microwave-assisted synthetic pathways. A one-pot three-component synthesis could be used under conventional conditions, but was found to be limited under microwave assistance.

4. Experimental

Benzaldehyde, *p*-methylbenzaldehyde, *p*-methoxy-benzaldehyde, *p*-chlorobenzaldehyde, furan-2-carboxyaldehyde, 2-acetylpyridine, thiosemicarbazide, methanol, pyridine, DEAD, and all the solvents such as ethyl acetate and ethanol were purchased from Merck Chemical Co. and were used without further purification. TLC was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with PF_{254} indicator. TLCs were viewed under $\nu = 254$ nm. Melting points (mp) were determined on a Stuart electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr disks on a Shimadzu-408 infrared spectrophotometer, Faculty of Science, El Minia University. NMR spectra were measured on a Bruker AV-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) at Florida Institute of Technology, or in the NMR Laboratory Center, Assiut University, Assiut, Egypt. Electron impact mass spectra were recorded with a JEOL JMS-600 spectrometer at an ionization voltage of 70 eV at the Central Lab, Assiut University, and the Microanalytical Center, Faculty of Science, Cairo University, Cairo, Egypt. Thiosemicarbazones **1a**–**j** were prepared according to the literature.[35]

4.1. *General procedure*

4.1.1. *Method 1: Reactions of thiazolidines **3a–j** with DEAD **4**; synthesis of (arylidenehydrazono-4-oxo-thiazolidin-5-ylidene) acetic acid ethyl esters **5a–e***

A solution of equimolar amounts of **3a–j** (2 mmol) and DEAD, **4** (2 mmol) in acetic acid (50 mL) was heated under reflux at for 8–10 h. The reaction was followed by TLC analysis. The mixture was cooled to room temperature and the precipitate was filtered off to produce **5a–e**. The mother liquor was concentrated to produce compounds **6a–d**. The products **5a–e** were recrystallized from appropriate solvents.

Compounds **6a–c** were identified from their physical properties: **6a** (0.025 g, 10%), 3-phenylpropynenitrile, dark yellow solid, mp 38–40°C (lit. [36] 39°C); **6b** (0.03 g, 12%), 3-(4′-methylphenyl)propynenitrile, mp 63°C (lit. [36] 60–62°C); **6c** (0.04 g, 15%) 3-(4-methoxyphenyl)propynenitrile, mp 77°C (lit. [36] 76–78°C); **6d** (0.025 g, 8%), 3-(4′-chlorophenyl)propynenitrile, mp = 85–86°C (lit. [37] 83–85°C).

4.1.2. *Method 2: Reactions of thiosemicarbazones **1a–f** with DEAD **4**; synthesis of **5a–f** under conventional condition*

A mixture of **1a–f** (2 mmol) and **4** (2 mmol) in MeOH was stirred at reflux for 3–5 h. The mixture was cooled to room temperature; the precipitate was filtered off and the product was recrystallized from the solvent indicated.

4.1.3. *Synthesis of **5a–f** under microwave irradiation*

A mixture of **1a–f** (2 mmol) and **4** (2 mmol) in a beaker was placed in a domestic microwave oven (SUNFLAME) and irradiated at 190 W for 5–10 min. Then, the mixture was cooled to room temperature; the solution was poured into 100 mL of ice water and mixed thoroughly, then allowed to stand for 15 min. The precipitate obtained was filtered, washed with cold ethanol, and recrystallized from the solvent indicated.

4.1.4. *Method 3: Reaction of thiosemicarbazones **1a, b** with **2** and DEAD **4**; one-pot synthesis of **5a, b***

A solution of equimolar amounts of **1a, b,2**, and **4** (2 mmol) in acetic acid (75 mL) was heated under reflux for 12–18 h. The reaction was followed by TLC analysis. The mixture was cooled to room temperature and the precipitate was filtered off to produce **5a–e**. The mother liquor was concentrated to produce compounds **6a, b**. Yields of products **5a–f** reported from microwave conditions refer to in Method 2.

4.1.5. *[4-Oxo-2-(benzylidene)hydrazono)thiazolidine-5-ylidine]acetic acid ethyl ester (**5a**)*

Yellow crystals (ethanol), yield 0.50 g (82%), mp 220°C. IR (KBr) (λ_{max}, cm^{-1}): 3080 (Ar-CH), 2760 (CH=), 1740, 1715 (2 C=O), 1660, 1634, 1600, 1580 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6): Table 1. ^{13}C NMR (100 MHz, DMSO-d_6): Table 2. MS (70 eV, %), m/z: 303 (M^+, 100), 288 (22), 274 (30), 258 (36), 226 (56), 202 (16), 138 (54), 103 (100), 98 (50), 76 (30). Anal. Calcd for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85%. Found; C, 55.40; H, 4.30; N, 14.00%.

4.1.6. *[4-Oxo-2-(4′-methylbenzylidene)-hydrazono)thiazolidine-5-ylidine]acetic acid ethyl ester (**5b**)*

Yellow crystals (methanol), yield 0.53 g (86%), mp 180°C. IR (KBr) (λ_{max}, cm^{-1}): 3090 (Ar-CH), 2080 (Aliph-CH), 1742, 1717 (2 C=O), 1660, 1632, 1600, 1560 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6): Table 3. ^{13}C NMR (100 MHz, DMSO-d_6): Table 4. MS (70 eV, %), m/z: 317 (M^+, 100), 302 (26), 288 (20), 274 (28), 226 (54), 202 (20), 138 (56), 103 (100), 98 (52), 76 (28). Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 56.77; H, 4.76; N, 13.24%. Found; C, 56.60; H, 4.60; N, 13.30%.

4.1.7. *[4-Oxo-2-(4′-methoxybenzylidene)-hydrazono-5-ylidine)thiazolidine-5-ylidine]acetic acid ethyl ester (**5c**)*

Yellow crystals (ethanol), yield 0.43 g (90%), mp 140–142°C. IR (KBr) (λ_{max}, cm^{-1}): 3075 (Ar-CH), 2090–2060 (Aliph-CH), 1740, 1715 (2 C=O), 1658, 1630, 1600, 1560 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 12.86 (b, 1H, N-***H***), 8.50 (s, 1H, C***H***=N), 7.90 (dd, J = 6.7, 2.7 Hz; 2H, ***H***-*o*), 7.04 (m; 2H, ***H***-*m*), 6.25 (s, 1H, ***H***-6), 4.20 (q, J = 7.0 Hz; 2H, C***H***$_2$CH$_3$), 3.90 (s, C***H***$_3$), 1.35 (t, J = 7.1 Hz; 3H, CH$_2$C***H***$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): 167.00 (***C***-4), 165.35 (***C***O$_2$CH$_2$CH$_3$), 162.00 (s, ***C***-*i*, Ar-***C***-OCH$_3$), 160.26 (***C***-2), 158.62 (***C***H=N), 142.66 (s, ***C***-5), 133.60 (***C***-*i*), 128.20 (***C***-*m*), 114.00 (***C***-*o*), 114.48 (***C***-6), 61.20 (***C***H$_2$CH$_3$), 55.40 (s, Ar-O***C***H$_3$) 13.93 (CH$_2$***C***H$_3$). MS (70 eV, %), m/z: 333 (M^+, 100), 318 (40), 302 (46), 272 (34), 258 (30), 226 (58), 138 (64), 103 (98), 98 (62), 76 (30). Anal. Calcd for $C_{15}H_{15}N_3O_4S$: C, 54.04; H, 4.54; N, 12.60%. Found; C, 53.90; H, 4.40; N, 12.50%.

4.1.8. *[4-Oxo-2-(4′-chlorobenzylidene)-hydrazono)thiazolidine-5-ylidine]acetic acid ethyl ester (**5d**)*

Yellow crystals (ethyl acetate), yield 0.53 g (79%), mp 240°C. IR (KBr) (λ_{max}, cm^{-1}): 3060 (Ar-CH), 1740, 1715 (2 C=O), 1660, 1630, 1600, 1558 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6): Table 5. ^{13}C NMR (100 MHz, DMSO-d_6): Table 6. MS (70 eV, %), m/z: 339 (M^{+2}, 40), 338 (M^{+1}, 40), 337 (M^+, 100), 226 (68), 141 (36), 138 (70), 124 (80), 103 (100), 78 (44). Anal. Calcd for $C_{14}H_{12}ClN_3O_3S$: C, 49.78; H, 3.58; Cl, 10.50; N, 12.44%. Found; C, 49.62; H, 3.65; Cl, 10.40; N, 12.30%.

4.1.9. *[4-Oxo-2-(furan-2-ylmethylene)hydrazono)thiazolidine-5-ylidine]-acetic acid ethyl ester (**5e**)*

Pale yellow crystals (acetone), yield 0.41 g (70%), mp > 260°C. IR (KBr) (λ_{max}, cm^{-1}): 3080 (Ar-CH), 1740, 1715 (2 C=O), 1660, 1630, 1600, 1562 (C=N, C=C), 1110 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6): 12.80 (b; 1H, N–*H*), 8.50 (s; 1H, C***H***=N), 7.75 (dd, J = 6.6, 2.9 Hz; 1H, furan-***H***-5), 7.00 (m, 1H, furan-***H***-3), 6.60 (s, 1H, ***H***-6), 6.50 (m, 1H, furan-***H***-4), 4.20 (q, J = 7.4 Hz; 2H, C***H***$_2$CH$_3$), 1.28 (t, J = 7.1 Hz; 3H, CH$_2$C***H***$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): 165.80 (***C***-4), 165.40 (s, ***C***O$_2$CH$_2$CH$_3$), 160.00 (s, ***C***-2), 158.50 (***C***H=N), 150.00 (***C***-2-furan, ***C***-i), 144.00 (***C***-5-furan-***C***-i), 142.90 (s, ***C***-6), 120.00 (***C***H-3-furan), 114.30 (***C***-5), 113.00 (***C***H-4-furan), 61.30 (***C***H$_2$CH$_3$), 14.20 (CH$_2$***C***H$_3$). MS (70 eV, %), m/z: 293 (M^+, 100), 227 (66), 141 (40), 124 (76), 102 (100), 78 (30). Anal. Calcd for $C_{12}H_{11}N_3O_4S$: C, 49.14; H, 3.78; N, 14.33%. Found; C, 49.00; H, 3.65; N, 14.30%.

4.1.10. *[4-Oxo-2-(pyridine-2-ylethylidene)hydrazono)thiazolidine-5-ylidine]-acetic acid ethyl ester (**5f**)*

Orange crystals (ethyl acetate), yield 0.47 g (74%), mp = 198°C. IR (KBr) (λ_{max}, cm^{-1}): 3095 (Ar-CH), 2060 (Aliph-CH), 1740, 1715 (2 C=O), 1668, 1660, 1632, 1600, 1550 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 12.84 (b, 1H, N–*H*), 8.70 (dd, 1H, J = 7.4, 1.2 Hz, pyridine-***H***-6), 8.00 (dd, 1H, J = 7.4, 1.2 Hz, pyridine-***H***-3), 7.80 (m, 1H, pyridine-***H***-4), 7.60 (m, 1H, pyridine-***H***-5), 6.60 (s, 1H, *H*-6), 4.30 (q, J = 7.1 Hz; 2H, C***H***$_2$CH$_3$), 2.80 (s, CH$_3$),1.30 (t, J = 7.1 Hz; 3H, CH$_2$C***H***$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): 166.00 (***C***-4), 165.40 (s, ***C***O$_2$CH$_2$CH$_3$), 164.00 (pyridine-***C***-CH$_3$), 162.00 (s, ***C***-2), 155.00 (pyridine-***Ci***-2), 148.50 (pyridine-***C***H-6), 140.00 (***C***-6), 136.8 (pyridine-***C***H-4), 127.00 (pyridine-***C***H-5), 123.00 (pyridine-***C***H-3), 114.00 (***C***-5), 60.00 (***C***H$_2$CH$_3$), 14.00 (***C***H$_3$), 15.00 (CH$_2$***C***H$_3$). MS (70 eV, %), m/z: 318 (M^+, 100), 302 (14), 240 (24), 226 (60), 141 (38), 124 (74), 102 (100), 80 (34). Anal. Calcd for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60%. Found; C, 52.65; H, 4.55; N, 17.72%.

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