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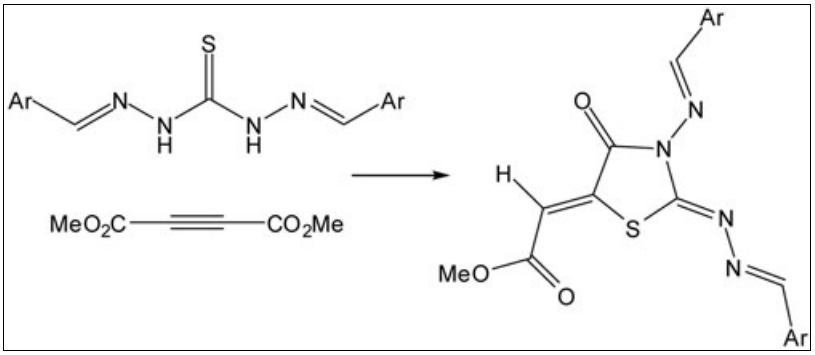

(*Z*)-Methyl 2-[3-(arylideneamino)-2-(arylidenehydrazono)-4-oxothiazolidin-5-ylidene]acetate prepared during the reaction between thiocarbonohydrazides and dimethyl acetylene dicarboxylate. Rational for there conversations involving the nucleophilic addition on C/C triple bond of dimethyl acetylenedicarboxylate are presented.

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INTRODUCTION

The pronounced reactivity of thioureas and thiosemicarbazides toward dimethyl acetylenedicarboxylate (DMAD) is well documented [1–7]. Different thiosemi-carbazone derivatives reacted with DMAD and diethyl acetylenedicarboxylate (DEAD) by three different methods [8]: (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 condition, to obtain five-membered *S,N*-heterocycles thiazolines [8]. The reaction of DMAD with heterocyclic thioamides has been carried out and a number of thiazoline derivatives have been reported [4]. Facial DMAD-mediated cyclization reactions of easily available thiosemicarbazones of formyl- and acetyl-ferrocene and *S*-methyl derivatives affording biologically promising sulfur heterocycles (thiazolone, thiazole, 1,3-thiazine-4-one), carrying at least one carbomethoxy group [9]. Cyclization of 1,5-bis (ferrocenylmethylidene)thio-carbonohydrazide with DMAD afforded diastereomeric dimethylthiazole-4,5-dicarboxylates (*cis* and *trans*) [10].

On the other hand, the reaction of arenaldehyde thiosemicarbazones with DMAD gave methyl [3-aryl-4-oxo-1-(phenylthiocarbamoyl)-4,5-dihydro-1*H*-pyrazol-5-ylidene] ethanoate due to the azaenamine reactivity shown by thiosemicarbazones and the availability of the methine proton [11].

Recently, it has been reported that, the reaction of diacyl thiocarbohydrazides with DMAD (**1**) in refluxing ethanol led to (4-oxathiazolidine-5-ylidene)acetates [12], whereas (*Z*)-methyl-2-arylhydrazide-4-oxo-3-(propan-2-ylideneamino)thiazolidine-5-ylidene)acetates formed during the reaction of DMAD (**1**) with *N*-[2-(propan-2-ylidene) hydrazinecarbonothioyl]arylhydrazides [12].

Thiazolidine-4-one ring systems are known to possess antibacterial [13, 14], antituberculosis [15, 16], antiviral [16, 17], anticancer [18–20], and antioxidant [21].

On the basis of aforementioned encouraged results, we investigated the reaction of 1,5-bis(substituted arylmethylidene)thiocarbohydrazides **2a–d** with dimethyl acetylenedicarboxylate (**1**).

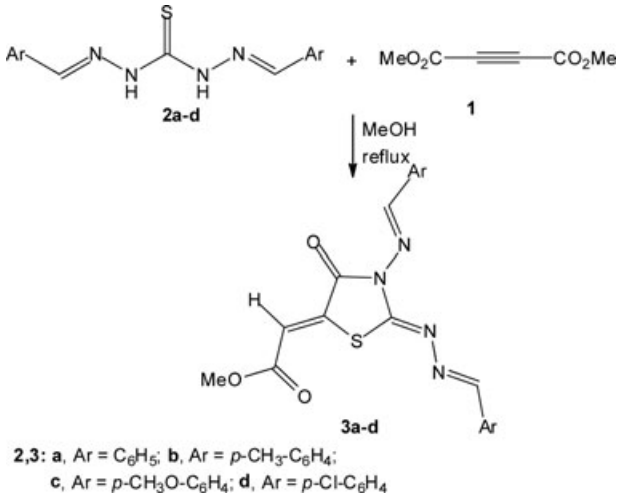
RESULTS AND DISCUSSION

In methanol and reflux temperature, the thiocarbo -hydrazides **2a–d** reacted with DMAD (**1**) to give one single product each in 75–95% yield (Scheme 1).

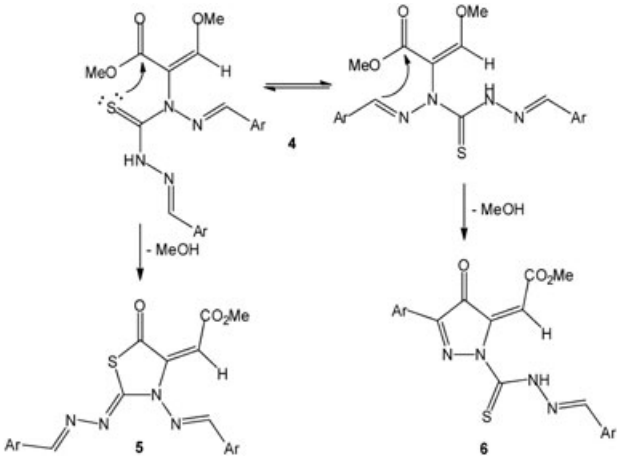
From elemental analyses and the mass spectra, a net release of methanol had occurred. The mass spectra showed the following five fragments common to all products [M^+-31], [M^+-Ar-CH N], [M^+-Ar-CH N NC], [M^+-Ar-CH N N C S], and [MeO_2C CH C S].

In IR spectra, two carbonyl bands were seen in the ranges 1715–1730 cm^{-1} and 1690–1705 cm^{-1} in addition

Scheme 1



Scheme 2



to a band between 1625 and 1635 cm^{-1} was assigned to C N vibration.

The ^{1}H-NMR spectra showed the presence of vinylic-CH between 6.85 and 7.00 ppm and methoxy protons at about 3.85–3.90 ppm as two singlets. All the new compounds synthesized contain a carbomethoxy methylidene side chain ($CHCO_2Me$). In the ^{1}H-NMR signals, one of CH N is downfield shifted (δ_H = 9.05–9.30 ppm) due to the formation of hydrogen-bond with lactam-CO, the other CH N showed one singlet at δ_H = 8.50–8.65 ppm due to the anisotropy of the N (sp^2) atom [22].

In all cases, the ^{13}C-NMR spectra have been obtained showing six downfield lying lines at 165.41–166.48 (C O, ring), 164.33–165.35 (C O, ester), 160.25–163.26 (CH N), 156.31–160.24 (C-2, C N), 140.29–141.65 (C-5) and 115.91–116.86 (vinyl-CH).

Compounds **2a–d** may react either with their sulfur atom, N^2 as nucleophilic sites. On the other hand, it has been reported that the azomethine carbon and N^2 of **2a–d** had taken part in the heterocyclization [11]. The methine carbon of **2** had to act as a nucleophile in the sense of an "umpolung" [11]. Thus, several options for interaction between **2a–d** and DMAD (**1**) may be expected as will be outlined later.

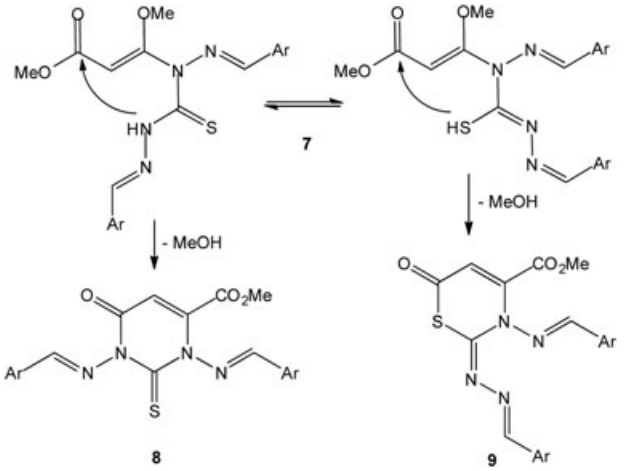
If the reaction took place through N^2 and azomethine-CH or N^2 and SH of **2**, the most likely isomeric products would be **5** and **6**, respectively (Scheme 2).

If N^2 attached the triple bond of **1** followed by interamolecular nucleophilic attack of N^4 or SH at α- and β-ester group, the products **8** and **9** were observed (Scheme 3).

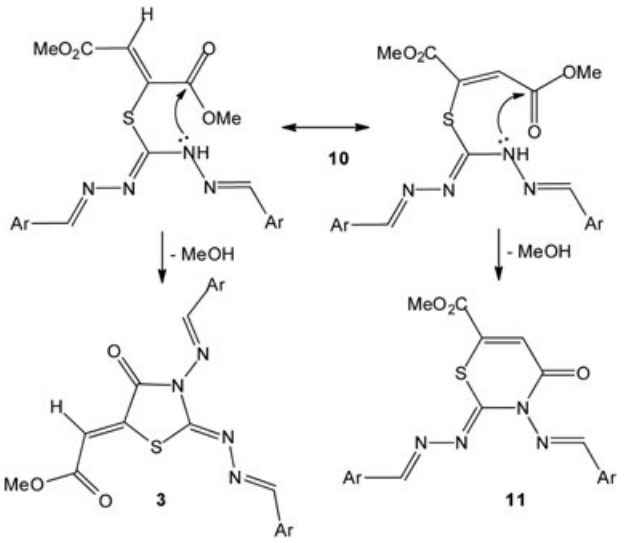
The products **3** and **11** could be isolated if the reaction involve the participation of SH and N^4, respectively (Scheme 4).

The structures **6** and **8** can be immediately ruled out, no signal is far enough down field for a C S. On the other hand, compounds **5** and **9** have been already eliminated

Scheme 3



Scheme 4



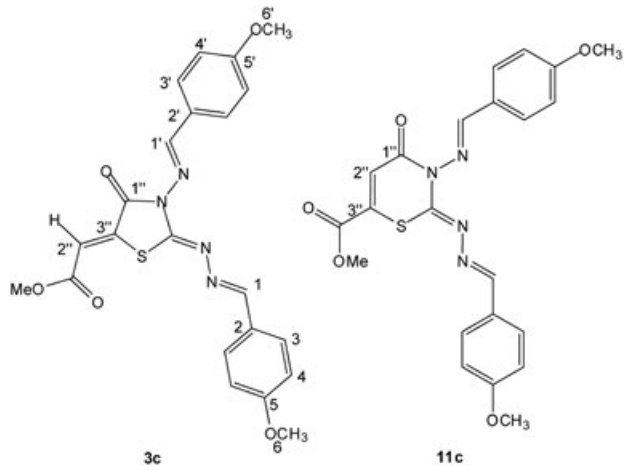


Figure 1.

based on the ring carbonyl ^{13}C-resonance, should occur considerably down-field to those which have been observed. We will concentrate between the alternative structures **3** and **11**. In each DMAD-derived structure **3** and **11**, C-1″ is the lactam carbonyl, C-2″ is the proton-bearing carbon and C-3″ is the "quaternary" carbon (Fig. 1). The spectra of compound **3c** show two *p*-anisyl units: one isolated methoxy group and one isolated vinyl-CH proton (Table 1).

The signals between δ_C = 166.48–156.79 ppm (Table 2) must represent two C O, three C N, and two methoxy-bearing aryl carbons. Of the three sets of methoxy protons, the signals at δ_H = 3.89 ppm is assigned as the ester methoxyl; this signal gives HSQC correlation with the attached carbon at δ_C = 52.53 ppm (Table 2) and HMBC correlation with the ester carbonyl at δ_C = 166.48 ppm. The signal (δ_C = 161.32 ppm) giving HMBC correlation to H-2″ (δ_H = 6.97 ppm) is assigned as the lactam carbonyl C-1″. Under gated decoupling, C-1″ couples to H-2″ with *J* = 5.4 Hz, a value which require a three-bond coupling not two-bond coupling [23]. Thus, structure **11** can also be ruled out. The magnitude of this coupling further argues that C-1″ and H-2″ are mutually cis [23] as depicted in structure **3c**. The carbon (δ_C = 116.38 ppm) giving HSQC correlation to H-2″ is assigned as C-2″. The carbon resonating at δ_C = 140.68 does not give any HMBC correlations, but is assigned as C-3″ by analogy with other structures [12].

The two *p*-anisylidene units can be unambiguously differentiated based on the coupling networks, except for C-6,6′. Each *p*-anisylidene subunit is spectroscopically isolated, but ^{13}C-NMR simulation predicts that C-1 will resonate downfield of C-1′ (predicted δ_C = 163.7 *vs.* 154.7); therefore, the downfield of the two (experimental δ_C = 164.99 *vs.* 160.23) is assigned as C-1 and the rest of the assignment follow.

Table 1

^{1}H NMR data for compound **3c**.

^{1}H NMR (CDCI3)	COSY	Assignment
9.06 (s; 1H)		H-1
8.49(s; 1H)		H-1′
7.88 (d, *J* = 8.8; 2H)	6.99	H-3
7.78 (d, *J* = 8.8;2H)	6.95	H-3′
6.99 (d, *J* = 9.3; 2H)	7.88	H-4
6.97 (s; 1H)		H-2″
6.95 (d, *J* = 8.8; 2H)	7.78	H-4′
3.893 (s; 3H)		$C0_2CH_3$
3.887 (s; 3H)		H-6
3.87 (s; 3H)		H-6′

CONCLUSIONS

The presented synthesis is provides insight into the reactions between the electron donating thiocarbo-hydrazides **2a–d** and dimethyl acetylenedicarboxylate (**1**). Oxothiazolidine derivatives **3a–d** are formed from **2** and **1**. The results reported herein supplement the rich chemistry of dimethyl acetylenedicarboxylate.

EXPERIMENTAL

Melting points were determined with a Gallenkamp melting point apparatus and were uncorrected. The IR spectra were recorded with a Shimadzu 408 instrument using potassium bromide pellets. The 400 MHz ^{1}H- and 100 MHz ^{13}C-NMR were measured in $CDCl_3$ using Bruker AV 400 spectrometer. Chemical shifts are expressed at δ (ppm) using tetramethylsilane (TMS) = 0. The ^{13}C-NMR assignments (*q* = quaternary carbon atoms) were made with aid of DEPT 135/90 spectra. Coupling constants are stated in Hz; ^{1}H-coupled ^{13}C spectra were measured using gated decoupling. Correlations were established using ^{1}H-^{1}H COSY, HMBC, and HSQC experiments. The mass spectra (70 eV, electron impact mode) were recorded on a Finnigan MAT instrument. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt.

Starting materials. Dimethyl acetylenedicarboxylate (DMAD, **1**) was bought from Fluka. 1,5-Bis(substituted arylmethylidene)-thiocarbohydrazide **2a–d** were prepared according to the literatures as 1,5-bis(phenylmethylidene)thiocarbohydrazide **2a** [24], 1,5-bis (4-methylphenylmethylidene)thiocarbohydrazide **2b** [25] 1,5-bis (4-methoxyphenylmethylidene)thiocarbo-hydrazide **2c** [24], and 1,5-bis(4-chlorophenylmethylidene)-thiocarbohydrazide **2d** [24,26].

Reactions of 1,5-bis(substituted arylmethylidene) thiocarbohydrazide 2a–d and dimethyl ethynedicarboxylate (1). A mixture of 1,5-bis(substituted arylmethylidene) thiocarbohydrazide **2a–d** (1 mmol) and dimethyl acetylenedicarboxylate (**1**, 1 mmol) in methanol was refluxed for 30 min (for compound **2a**), 1 h (for compound **2b**), 1.5 h (for compound **2c**), and 2 h (for compound **2d**). The solvent was evaporated and the obtained precipitate was recrystallized to give **3a–d**.

(Z)-Methyl 2-[(Z)-3-((E)-benzylideneamino)-2-((E)-benzylidenehydrazono)-4-oxothiazolidin-5-ylidene]acetate (3a). This compound was obtained as yellow crystals (ethanol) (85%), mp 166–168°C; IR: Ali-CH 2960, CO 1725,1705, C N 1625, Ar-C C 1605, 1590 cm^{-1}; ^{1}H-NMR: δ 3.960 (s, 3H, CO_2CH_3), 7.0 (s, 1H, vinyl-CH, C-2″), 7.45–7.60 (m, 6H, Ar-H), 7.80–7.95 (m, 4H, Ar-H), 8.60 (s, 1H, C-1′-H), 9.30 (s, 1H, C-1-H); ^{13}C-NMR: δ

Table 2

^{13}C NMR, HSQC, and HMBC data for compound **3c**.

^{13}CNMR ($CDCl_3$)[a]	HSQC	HMBC	Assignment
166.48 (dq, J_d = 1.3, J_q = 4.0)		3.893	CO_2CH_3
164.99 (dt, J_d = 166.6, J_t = 5.2)	9.06[b]		C-1
163.26 (m)		7.88, 3.887	C-5
162.36 (m)		7.78,3.87	C-5′
161.32 (d, J = 5.4)		6.97	C-1″
160.23 (dt, J_d = 163.5, J_t = 4.2)	8.49[c]		C-1′
156.79 (s)			C ( ) N
140.68 (s)			C-3″
131.02 (ddd, J = 160.9, 7.1, 4.2)	7.88	9.06, 7.88, 6.99	C-3
130.35 (ddd, J = 160.5, 7.3, 4.0)	7.87	8.49, 7.78, 6.95	C-3′
126.55 (dt, J_d = J_t = 7.8)		8.49, 6.95	C-2′
125.20 (dt, J_d = J_t = 7.4)		9.06,6.99	C-2
116.38 (d, J = 172.6)	6.97		C-2″
114.36 (dd, J = 161.2, 4.7)	6.99	7.88, 6.99	C-4
114.27 (dd, J = 160.2, 4.8)	6.95	7.78, 6.95	C-4′
55.51 (q, J = 144.3), 55.45 (q, J = 144.4)	3.887, 3.87		C-6,6′
52.53 (q, J = 147.6)	3.893		CO_2CH_3

[a]Carbon multiplicities were measured via a gated decoupling experiment.
[b]Detected via one-bond coupling in HMBC.
[c]Detected via one-bond coupling in ^{1}H-coupled ^{13}C spectrum.

52.61 (CO_2CH_3), 116.86 (vinyl-CH), 128.65 (Ar-CH), 128.80, 128.91, 129.07, 131.50, 132.57, 133.69 (Ar-CH), 140.29 (C-5 (3″)), 157.83 (C-2, C N), 160.31 (CH N, C-1′), 161.42 (C-5, C-1″), 162.43 (C OCH$_3$, C-5′), 163.35 (C OCH$_3$, C-5), 165.08 (CH N, C-1), 166.57 ppm (CO, ester); ms: *m/z* 392 (M^+, 15), 288 (22), 230 (8), 146 (100), 116 (81), 90 (79), 77 (85), 72 (32), 59 (24). *Anal. Calcd. for* $C_{20}H_{16}N_4O_3S$: C, 61.21; H, 4.11; N, 14.28; S, 8.17. Found: C, 61.37; H, 4.03; N, 14.18; S, 8.32.

(Z)-Methyl 2-[(Z)-3-((E)-(4-methylbenzylidene)amino)-2-((E)-(4-methylbenzylidene)hydrazono)-4-oxothiazolidin-5-ylidene] acetate (3b). This compound was obtained as yellow crystals (ethanol) (90%), mp 178–180°C; IR: Ali-CH 2975, CO 1720,1690, C N 1635, Ar-C C 1600, 1585 cm^{-1}; ^{1}H-NMR: δ 2.40 (s, 3H, CH_3), 3.90 (s, 3H, CO_2CH_3), 6.97 (s, 1H, vinyl-CH, C-2″), 7.30 (d, J = 8.86, 2H, H-4′), 7.33 (d, J = 9.34, 2H, H-4), 7.81 (d, J = 8.86, 2H, H-3′), 7.90 (d, J = 8.86, 2H, H-3), 8.55 (s, 1H, C-1′-H), 9.18 (s, 1H, C-1-H); ^{13}C-NMR: δ 21.28 (CH_3), 52.07 (CO_2CH_3), 116.09 (vinyl-CH, C-2″), 128.14 (Ar-C), 128.61, 129.06, 129.14, 129.37, 129.86, 130.51 (Ar-CH), 141.65 (C-5 (C-3″)), 156.31 (C-2, C N), 160.27 (CH N, C-1′), 161.38 (C-1″), 162.37 (C-5′), 163.31 (C-5), 165.02 (C-1), 166.53 ppm (CO, ester); ms: *m/z* 420 (M^+, 19), 302 (27), 144 (11), 144 (100), 116 (61), 91 (42), 77 (36), 59 (35). *Anal. Calcd. for* $C_{22}H_{20}N_4O_3S$: C, 62.84; H, 4.79; N, 13.32; S, 7.63. Found: C, 63.02; H, 4.71; N, 13.49; S, 7.48.

(Z)-Methyl 2-[(Z)-3-((E)-(4-methoxybenzylidene)amino)-2-((E)-(4-methoxybenzylidene)hydrazono)-4-oxothiazolidin-5-ylidene] acetate (3c). This compound was obtained as yellow crystals (ethanol) (95%), mp 190–192°C; IR: Ali-CH 2967, CO 1715,1700, C N 1630, Ar-C C 1610, 1590 cm^{-1}; ^{1}H and ^{13}C-NMR (see table 1,2); ms: *m/z* 452 (M^+, 14), 421 (12), 319 (77), 292 (39), 191 (19), 134 (100), 116 (25), 77 (27), 59 (65). *Anal. Calcd. for* $C_{22}H_{20}N_4O_3S$: C, 58.40; H, 4.46; N, 12.38; S, 7.09. Found: C, 58.26; H, 4.55; N, 12.22; S, 6.92.

(Z)-Methyl 2-[(Z)-3-((E)-(4-chlorobenzylidene)amino)-2-((E)-(4-chlorobenzylidene)hydrazono)-4-oxothiazolidin-5-ylidene]acetate (3d). This compound was obtained as yellow crystals (ethanol) (75%), mp 208–210°C; IR: Ali-CH 2985, CO 1730,1705, C N 1630, Ar-C C 1610, 1595 cm^{-1}; ^{1}H-NMR: δ 3.85 (s, 3H, CO_2CH_3), 6.85 (s, 1H, vinyl-CH), 7.50–7.68 (m, 4H, Ar-H), 7.76–7.92 (m, 4H, Ar-H), 8.65 (s, 1H, C-1′-H), 9.30 (s, 1H, C-1-H); ^{13}C-NMR: δ 115.91 (vinyl-CH), 128.87, 136.62 (Ar-C), 129.18, 129.39, 129.82, 130.30, 130.56, 130.14 (Ar-CH), 141.08 (C-5 (3″)), 159.57 (C-2, C N), 160.56 (CH N, C-1′), 161.69 (C-1″), 165.21 (CH N, C-1), 166.50 ppm (CO, ester); ms: *m/z* 460/464 (M^+, 12), 389 (21), 226 (32), 182 (73), 116 (100), 77 (64). *Anal. Calcd. for* $C_{20}H_{14}Cl_2N_4O_3S$: C, 52.07; H, 3.06; Cl, 15.37; N, 12.14; S, 6.95. Found: C, 51.89; H, 2.97; Cl, 15.48; N, 11.96; S, 7.08.

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