Reactions of Dimethyl Ethynedicarboxylate with (Substituted Ethylidene) hydrazinecarbothioamides

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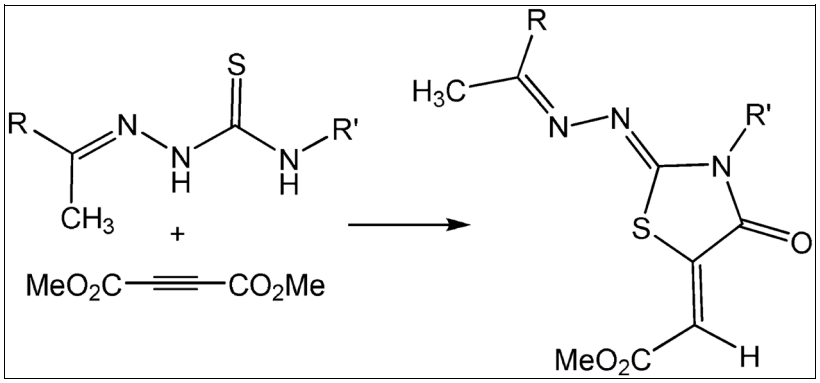

The reaction of (substituted ethylidene)hydrazinecarbothioamides **4a–g** with dimethyl ethynedicarboxylate (**DMAD, 2**) gave [(substituted ethylidene)hydrazono)-4-oxothiazolidine-5-ylidene]acetates **7a–g** (71–88 %). The structure of the new compounds was established by infrared spectroscopy, mass spectrometry, and NMR spectroscopy.

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INTRODUCTION

Reaction of unsubstituted thiourea with acetylene dicarboxylic methyl and ethyl esters could give rise to five- and six-membered heterocycles [1–3]. Unlike thioureas, the molecule of thiosemicarbazide contains four nucleophilic centers; therefore, the number of possible products that could be formed by the reactions of thiosemicarbazide derivatives with acetylene mono- and acetylene di-carboxylic acid esters increases [4,5].

Thiazolidinones and thiazinones were obtained by the reaction of thioureas and thiosemicarbazides with dimethyl ethynedicarboxylate (DMAD) [3,6–17]. The presence of an N-C-S linkage is believed to account for the amoebicidal, anticonvulsant, fungicidal [18], and antiviral [19] activities. Thiazolidin-4-one ring systems are known to act as analgesic, antibacterial, anticonvulsant, antiparasitic, anti-inflammatory, herbicidal [20–25], and potent anti-HIV agents [26].

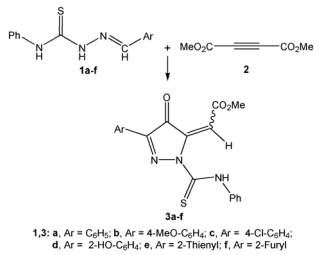
Recently, we reported the reaction of various arenealdehyde 4-phenylthiosemicarbazones **1a–f** with DMAD (**2**) that gave methyl [3-aryl-4-oxo-1-(phenylthiocarbamoyl)-4, 5-dihydro-1*H*-pyrazol-5-ylidene]ethanoates **3a–f** [27]. Both the azomethine carbon and N2 of **1a–f** had taken part in the heterocyclization. Because DMAD (**2**) can offer only electrophilic sites for attack, the methine carbon of **1a–f** had act as a nucleophile in sense of an "umpolung". This behavior is not unexpected, because aldehyde hydrazones are known to react as azaenamines toward suitable electrophiles [28]. This reactivity requires the availability of methine proton; the reactions reported are thus not open to ketone thiosemicarbazones. This fascinating versatility in the reaction of **1a–f** with **2** justifies of further investigation of the reactivity of ketone 4-unsubstituted and substituted thiosemicarbazones **4a–g** toward DMAD (**2**) (Scheme 1).

RESULTS AND DISCUSSION

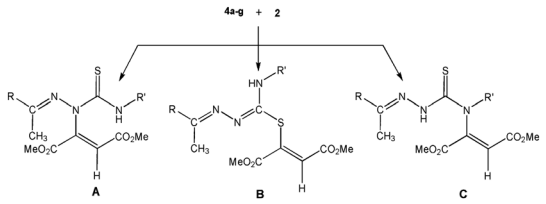
Now we have reacted 2-(1-substituted ethylidene)-hydrazinecarbothiamides **4a–g** (Fig. 1) with DMAD (**2**); the reactions gave mainly one single product each in 71–88% yield. From the elemental analyses and the mass spectra a net release of methanol (MW 32) had occurred.

In the infrared (IR) spectra, two carbonyl bands were observed in the ranges 1725–1715 cm^{-1} and 1705–1680 cm^{-1}, and a band between 1640 and 1620 cm^{-1} was assigned to C=N vibration. In the ^1H NMR spectra of all the compounds series **7a–d**, a NH proton appears at 13.06–12.92 ppm, accounting for lactam proton but not for imine proton, which is expected at upfield shift. This was considered to be a strong confirmation for the ring closure shown below in Scheme 4. The ^1H NMR spectra showed three singlets at 2.50–2.36, 3.89–3.83, and 6.94–6.73 ppm, because of

Scheme 1



Scheme 2



CH_3, methoxy protons, and vinyl-CH, respectively, in addition to the aromatic protons.

The *Z*-configuration of the exocyclic C═C bond, in the 5-benzylidene derivatives **7a–d** and **7e–g**, was attributed on the basis of ^{1}H-NMR spectral analysis, because the methine proton resonated as expected at higher chemical shift values 6.94–6.73 [11,29] because of the deshielding effect of the adjacent C═O than it would do in *E*-isomers.

In all cases of compounds **7a–g**, the ^{13}C NMR have been obtained showing signals at 166.34–165.63, 165.99–164.0, 163.74–158.02, 159.34–153.66, 144.56–141.25, and 115.48–114.06 ppm because of (C═O, ring), (C═O, ester), (C-2), (external-C═N), (C-5), and (vinyl-CH), respectively. The ^{1}H-NMR spectrum of **7g** (R = phenyl, R′ = allyl) clearly showed the presence of allyl group, which resonated at 4.57, 5.34, and 5.98 ppm because of (allyl-CH_2N), (allyl-CH_2═), and (allyl-CH═), respectively. The presence of allyl group is evident from the ^{13}C-DEPT-NMR spectrum, exhibiting positive signal at 135.94 ppm (allyl-CH═) and negative signals at 44.96 and 118.27 ppm because of (allyl-CH_2N) and (allyl-CH_2═), respectively. The mass spectrometry fragmentations of the isolated compounds were studied under electron ionization. The mass spectra showed the following fragments common to all compounds [M^+-15], 145 ($C_5H_5SO_3$), 72 ($HCCO_2Me$) and *m/z* 59 (CO_2Me). The composition listed may be reached in the following ways: it is likely that all products observed are formed from one of the three labile (1:1) adducts (**A**, **B**, and **C**) of **2** to **4a–g** (Scheme 2).

Likely isomeric products **5** and **6**, if the reaction took place through the intermediate (**A**), are shown in Scheme 3.

The products **7** and **8** could be isolated, if the reaction involved the participation of SH and formation of intermediate (**B**) (Scheme 4).

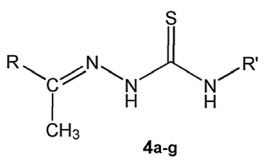
If N4 attached the triple bond of **2** followed by intramolecular nucleophilic attach of N2 at ester group, the products **9** and **10** were formed *via* the intermediate (**C**) (Scheme 5).

The alternative structures **5**, **6**, **9**, and **10** could be ruled out on the basis of ^{13}C NMR and the absence of C═S in the isolated products. The ring C═O resonances observed rule out the thiazine-4-one [6, 11] structure **8**, whereas they are agreeable for thiazolidin-4-ones **7** (Table 1).

However, only structures **7a–g** accommodates all spectral data listed above, especially the ^{13}C-chemical shifts for ring carbonyl atoms, (C-2), (C-5), and vinyl-CH (Table 1) for comparison with all relevant and alternatives [10].

CONCLUSION

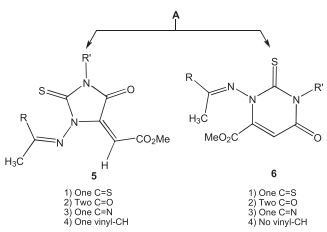
The products obtained from the reaction of (substituted ethylidene)hydrazinecarbothioamides **4a–g** with dimethyl ethynedicarboxylate (**2**), followed by heterocyclization are neither imidazolidinethione nor pyrimidinethione. Neither the N2-C(S)-N4 + C2 (intermediate **A**) nor the N4-C(S)-N2 + C2 (intermediate **C**) is observed due to the increased negative charge on sulfur atom, and S-C-N4 + C2 mode of cyclization is favored. Comparison of ^{13}C NMR chemical shifts for the possible sets of isomers may serve as a useful supplementary tool in finding the correct structure of a heterocycle.



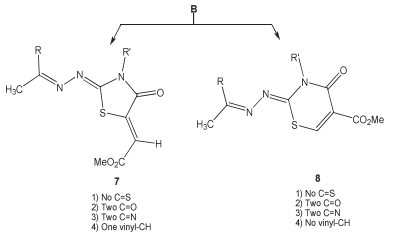
a, R = C_6H_5; R' = H: **b**, R = 4-HO-C_6H_4; R' = H
c, R = 2-Furyl; R' = H: **d**, R = 3-pyridyl; R' = H
e, R = C_6H_5; R' = C_6H_5: **f**, R = C_6H_5; R' = $C_6H_5CH_2$
g, R = C_6H_5; R' = CH_2=CH-CH_2

Figure 1. Substituted ethylidene hydrazinecarbothioamides **4a–g**.

Scheme 3



Scheme 4



EXPERIMENTAL

Melting points were determined on using open capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded with Shimadzu 408 instrument using potassium bromide plats. Spectra of 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR were recorded on Mercury-300BB spectrometers. Chemical shifts are expressed as δ (ppm) with reference of tetramethylsilane as internal standard, br = broad, s = singlet, dd = doublet of doublet, and m = multiplet. ^{13}C assignments (q = quaternary carbon atoms) were made with the aid of DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on Shimadzu Qp-2010 Plus instruments. Elemental analyses were carried out at the Microanalytiacl Center, Cairo University, Egypt. Thin-layer chromatography (TLC) was performed on analytical Merck 9385 Silica aluminum sheets (Kieselgel 60) with Pf_{254} indicator. TLCs were viewed at λ_{max} = 254 nm UV.

Starting materials. (Substituted ethylidene)hydrazinecarbothioamides **4a–g** were prepared by the reaction of thiosemicarbazide or 4-substituted thiosemicarbazides with the proper ketone, according to published procedures [30,31]. Dimethyl ethynedicarboxylate (DMAD, **2**) was bought from Fluka.

Reactions of (substituted ethylidene)hydrazinecarbothioamides 4a–g with dimethyl ethynedicarboxylate (DMAD, 2). ***General procedure.*** To a solutions of (substituted ethylidene) hydrazinecarbothio-amides **4a–g** (2 mmol) in ethanol (25 mL) was added a solution of dimethyl ethynedicarboxylate (DMAD, **2**; 0.284 g, 2 mmol) in small portions. The mixture was stirring under reflux for 2–3 h (the reaction was followed by TLC). The solvent was evaporated and the residue was crystallized from suitable solvent to give compounds **7a–g**.

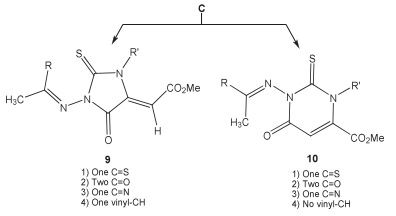
Methyl 2-[(*Z*)-2-((*Z*)-(1-phenylethylidene)hydrazono)-4-oxothiazolidin-5-ylidene]acetate (7a). This compound was obtained as yellow crystals (acetonitrile), mp 254–256 °C; ir: NH 3210–3150, CO 1720,

Table 1

^{13}C NMR shifts data in products **7a–g** (this work) and literature data of compounds comparable to **7a–g** and their structural alternatives.

Compound	C-2	C-4	C-5	Vinyl-CH	CO-ester	Literature data related to **8**	C-2	C-4	C-5	CO-ester
7a–g	163.74 –158.02	166.34 –165.63	144.56 –141.25	115.99 –114.06	165.99 –164.00	Substituted thiazin-4-one [11]	166.80	164.00	121.60	165.60
Literature data related to **7a–g** (4-oxothiazo-lidin-5-ylidene) acetate [10]	160.95	166.80	144.10	115.42	164.47	Benzimadazo-thiazin-4-one-2-carboxylate [6]	142.70	159.00	121.30	161.60

Scheme 5



1685, C=N 1640, Ar and C=C 1600, 1580 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.4 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.79 (s, 1H, vinyl-CH), 7.39 (m, 3H, Ar-H), 7.9 (m, 2H, Ar-H), 12.96 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.98 (CH_3), 52.27 (OCH_3), 114.67 (vinyl-CH), 126.74, 128.31, 130.16 (Ar-CH), 137.57 (Ar-C), 143.45 (C-5), 159.22 (acyclic-C=N), 162.98 (C-2), 165.99 (ester-CO), 166.34 (cyclic-CO); ms: *m/z* 303 (M^+, 100), 288 (40), 244 (10), 216 (42), 186 (14), 145 (18), 118 (14), 77 (28), 72 (12), 59 (12). Anal. Calcd. for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85; S, 10.57. Found: C, 55.61; H, 4.17; N, 14.03; S, 10.69.

Methyl 2-[(*Z*)-2-((*Z*)-(1-(4-hydroxyphenyl)ethylidene)-hydrazono)-4-oxothiazolidin-5-ylidene]acetate (7b). This compound was obtained as yellow crystals (acetonitrile), mp 272–274 °C; ir: HO 3495, NH 3195–3120, CO 1715, 1680, C=N 1635, Ar and C=C 1605, 1595 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.82 (s, 1H, vinyl-CH), 6.91 (dd, 2H, Ar-H), 7.81 (dd, 2H, Ar-H), 9.69 (s, 1H, OH), 12.92 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.26 (CH_3), 51.76 (OCH_3), 114.89 (vinyl-CH), 127.88, 128.04 (Ar-CH), 131.14 (Ar-C), 143.15 (C-5), 159.34 (acyclic-C=N), 162.50 (C-2), 165.50 (ester-CO), 165.80 (cyclic-CO); ms: *m/z* 319 (M^+,80), 304 (100), 232 (30), 227 (13), 134 (26), 145 (32), 92 (22), 77 (31), 72 (21), 59 (61). Anal. Calcd. for $C_{14}H_{13}N_3O_4S$: C, 52.66; H, 4.10; N, 13.16; S, 10.04. Found: C, 52.52; H, 4.19; N, 13.34; S, 9.91.

Methyl 2-[(*Z*)-2-((*Z*)-(1-(furan-2-yl)ethylidene)hydra-zono)-4-oxothiazolidin-5-ylidene]acetate (7c). This compound was obtained as orange crystals (acetonitrile), mp 278–280 °C; ir: NH 3205–3150, CO 1715, 1690, C=N 1630, Ar and C=C 1610, 1595, C-O-C 1085 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.53 (m, 1H, furan-CH), 6.80 (s, 1H, vinyl-CH), 6.98 (m, 1H, furan-CH), 7.71 (m, 1H, furan-CH), 13.06 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.04 (CH_3), 51.87 (OCH_3), 111.64 (furan-CH), 114.06 (vinyl-CH), 112.29, 142.81 (furan-CH), 144.56 (C-5), 151.42 (furan-C), 154.03 (acyclic-C=N), 158.02 (C-2), 165.36 (ester-CO), 165.63 (cyclic-CO); ms: *m/z* 293 (M^+, 56), 278 (33), 206 (23), 145 (18), 145 (22), 72 (42), 67 (21), 145 (18), 59 (30). Anal. Calcd. for $C_{12}H_{11}N_3O_4S$: C, 49.14; H, 3.78; N, 14.33; S, 10.93. Found: C, 48.95; H, 3.86; N, 14.51; S, 11.12.

Methyl 2-[(*Z*)-4-oxo-2-((*Z*)-(1-(pyridine-3-yl)ethylidene) hydrazono)thiazolidin-5-ylidene]acetate (7d). This compound was obtained as yellow crystals (acetonitrile), mp 256–258 °C; ir: NH 3230–3170, CO 1720, 1695, C=N 1625, Ar and C=C 1605, 1595 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.5 (br, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.73 (s, 1H, vinyl-CH), 7.57 (m, 1H, pyridin-H), 8.26 (m, 1H, pyridin-H), 8.71 (m, 1H, pyridin-H), 9.09 (m, 1H, pyridin-H), 13.02 ppm (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.04 (CH_3), 51.87 (OCH_3), 114.06 (vinyl-CH), 143.36 (C-5), 142.2 (pyridine-C), 142.81, 144.56 (pyridine-CH), 151.42, 154.02 (pyridine-CH), 154.03 (acyclic-C=N), 159.14 (C-2), 165.37 (ester-CO), 165.63 (cyclic-CO); ms: *m/z* 304 (M^+, 34), 289 (15), 217 (24), 159 (29), 145 (18), 85 (52), 119 (32), 78 (45), 72 (22), 59 (100). Anal. Calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.31; H, 3.97; N, 18.41; S, 10.54. Found: C, 51.19; H, 4.08; N, 18.57; S, 10.36.

Methyl 2-[(*Z*)-4-oxo-3-phenyl-2((*Z*)-(1-phenylethylidene) hydrazono)thiazolidin-5-ylidene]acetate (7e). This compound was obtained as yellow crystals (acetonitrile), mp 198–200 °C; ir: Ar-CH 3100, CO 1725, 1695, C=N 1620, Ar and C=C 1605, 1585 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 6.94 (s, 1H, vinyl-CH), 7.41–7.58 (m, 8H, Ar-H), 7.85–7.91 ppm (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 14.6 (CH_3), 51.95 (OCH_3), 115.48 (vinyl-CH), 126.36, 126.95, 127.85, 128.42, 129.90 (Ar-CH), 133.62, 136.82 (Ar-C), 141.25 (C-5), 158.12 (acyclic-C=N), 163.91 (C-2), 164.35 (ester-CO), 165.84 (cyclic-CO); ms: *m/z* 379 (M^+,95), 364 (20), 320 (16), 292 (16), 261 (8), 234 (100), 135 (22), 145 (22), 118 (30), 77 (36), 72 (18), 59 (12). Anal. Calcd. for $C_{20}H_{17}N_3O_3S$: C, 63.31; H, 4.52; N, 11.07; S, 8.45. Found: C, 63.47; H, 4.41; N, 10.88; S, 8.34.

Methyl 2-[(*Z*)-3-benzyl-4-oxo-2-((*Z*)-(1-phenylethylidene) hydrazono)thiazolidin-5-ylidene]acetate (7f). This compound was obtained as yellow crystals (acetonitrile), mp 154–156 °C; ir: Ar-CH 3090, Ali-CH 2950, CO 1715, 1690, C=N 1620, Ar and C=C 1605, 1585 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 5.14 (s, 2H, CH_2), 6.89 (s, 1H, vinyl-CH), 7.36–7.49 (m, 8H, Ar-H), 7.90–7.92 ppm (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 14.46 (CH_3), 45.56 (CH_2), 51.76 (OCH_3), 114.92 (vinyl-CH), 126.32, 127.86, 127.91, 128.1, 128.22 (Ar-CH), 134.87, 136.72 (Ar-C), 141.83 (C-5), 153.66 (acyclic-C=N), 158.12 (C-2), 164.53 (ester-CO), 166.12 (cyclic-CO); ms: *m/z* 393 (M^+,56), 378 (31), 306 (52), 248 (33), 145 (100), 91 (71), 72 (18), 59 (21). Anal. Calcd. for $C_{21}H_{19}N_3O_3S$: C, 64.10; H, 4.87; N, 10.68; S, 8.15. Found: C, 63.94; H, 4.98; N, 10.82; S, 7.97.

Methyl 2-[(*Z*)-3-allyl-4-oxo-2-((*Z*)-(1-phenylethylidene) hydrazono)thiazolidin-5-ylidene]acetate (7g). This compound was obtained as yellow crystals (acetonitrile), mp 132–134 °C; ir: Ar-CH 3110, Ali-CH 2920, CO 1725, 1705, C=N 1630, Ar and C=C 1610, 1580 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.49 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.57 (m, 2H, allyl-CH_2N), 5.34 (m, 2H, allyl-CH_2=), 5.98 (m, 1H, allyl-CH=), 6.85 (s, 1H, vinyl-CH), 7.40–7.48 (m, 3H, Ar-H), 7.87–7.93 ppm (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 14.57 (CH_3), 44.96 (allyl-CH_2N), 51.95 (OCH_3), 115.12 (vinyl-CH), 118.27 (allyl-CH_2=), 126.35, 126.56, 127.95 (Ar-CH), 129.94 (Ar-C), 135.94 (allyl-CH=), 141.56 (C-5), 157.14 (acyclic-C=N), 163.74 (C-2), 164.00 (ester-CO), 165.66 (cyclic-CO); ms: *m/z* 343 (M^+,100), 328 (58), 256 (32), 198 (28), 145 (22), 118 (26), 77 (81), 72 (18), 59 (25), 41 (44). Anal. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24; S, 9.34. Found: C, 59.61; H, 5.07; N, 12.12; S, 9.41.

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