Synthesis of some trisubstituted thiazolidin-4-ones

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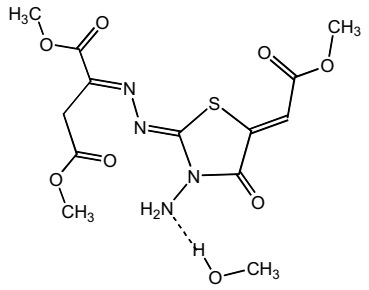
The addition of dimethyl acetylenedicarboxylate (DMAD) to thiocarbohydrazide and aldehyde dithiocarbohydrazones afforded new substituted thiazolidines.

Keywords: thiocarbohydrazide, thiocarbohydrazones, aldehydes, dimethyl acetylenedicarboxylate, thiazolidines

Thiazolidines and thiazoles are an important group of heterocyclic systems, found in many bio–active molecules, specifically in vitamin B_1.[1] Compounds containing this heterocyclic nucleus are also found in many bio–active substrates such as thiazole natural products,[2] thiazole based amino acids [3] and peptide antibiotics,[4] *etc.*

As a part of a research program on the synthesis of heterocyclic system containing nitrogen and sulfur, and with a view to extending the synthetic utility of dimethyl acetylenedicarboxylate,[5] we have investigated the addition of the latter to thiocarbohydrazide and dithiocarbohydrazones in methanol.

We first carried out the reaction of dimethyl acetylenedicarboxylate with thiocarbohydrazide in methanol to obtain a single compound which was characterised to be dimethyl 2-[3-amino-5-(methoxycarbonylmethylene)-4-oxothiazolidin-2-ylidenehydrazono]succinate (**1**) in 85% yield. The structure of **1** was determined by ^{1}H NMR, IR, MS and microanalysis (Scheme 1). For confirmation, we obtained the compound as a single crystal suitable for X–ray diffraction. A diffraction study confirmed the structure of compound **1**. An ORTEP diagram of **1** is shown in Fig. 1. Selected crystal data, bond lengths and bond angles are listed in Tables 1–3.[6]



(**1**)

The C–C, C–N, N–N, and C–S distances are in the expected range. The sequence C7/C10/C11/O6/O7 is perpendicular to the C–N–O–S skeleton of the rest of the molecule. There is hydrogen bonding between **1** and the methanol molecule (O8···N2 distance 2.912(9) Å).[6]

Further, thiocarbonodihydrazones **2a–h** were prepared as reported,[7, 8] and treated with DMAD in methanol. Theoretically, four possible products can be obtained from this reaction. They are **3,** and the isomers **4**, **5** and **6**. For these compounds the methyl [3-arylmethylenamino-2-(arylmethylenehydrazono)-4-oxothiazolidin-5-ylidene]acetate structure (**3**) was assigned, based on the NMR, Mass and IR spectra and microanalyses. The ^{1}H NMR spectra of **3a–h** exhibited methylene protons (s, δ 6.79 – 7.05 ppm). If the reaction products were **5** or **6** one would expect aromatic ring protons to be more deshielded than the methylene (Scheme 2).

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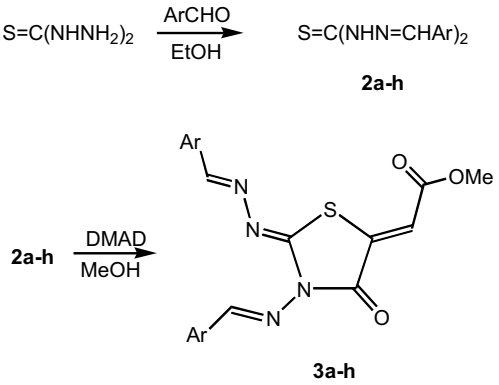

Scheme 1

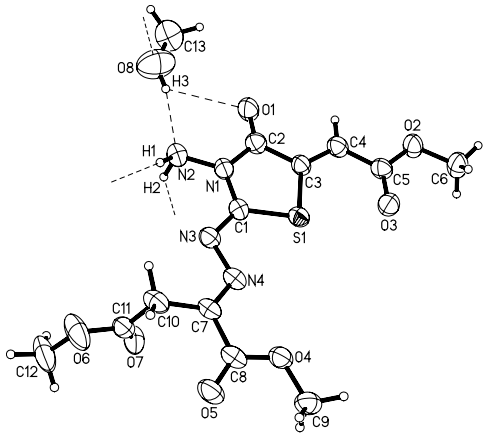

Fig. 1 ORTEP drawing of **1.** MeOH (30% probability for thermal ellipsoids).

Experimental

The melting points were obtained using an Electrothermal IA 9100 digital melting point apparatus. The FT–IR spectra (KBr discs) were recorded on a Bruker (400–4000 cm^{-1}) spectrometer. NMR spectra were recorded on a 300 MHz spectrometer using TMS as internal standard. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system. The X–ray structure determination was performed with an IPDS II (Stoe) instrument using Mo–K_α radiation.

Dimethyl 2-[3-amino-5-(methoxycarbonylmethylene)-4-oxo-thiazolidin-2-ylidenehydrazono]succinate (**1**): Thiocarbohydrazide (1 mmol) and DMAD (2 mmol) were heated at reflux in MeOH (10 ml) for 20 min. The solution was cooled and the crystals that separated were collected: yellow crystalline solid. m.p. 166–167°C (82%). IR: ν_{NH_2} 3497; ν_{CO} 1721, 1718, 1682 cm^{-1}. ^{1}H NMR: δ (ppm)

Table 1 Crystallographic data for compound **1**

Formula	$C_{13}H_{18}N_4O_8S$
Formula weight (g/mole)	780.73
Crystal size (mm)	0.31 × 0.08 × 0.03
a (Å)	4.773(1)
b (Å)	13.351(3)
c (Å)	15.417(3)
α (°)	65.28(2)
β (°)	89.99(2)
γ (°)	84.99(2)
Unit cell volume (Å)	888.3(3)
Z	2
d_{calc} (g/cm^3)	1.46
Crystal system	Triclinic
Space group (No.)	P–1 (2 [ ])
Absorption correction	Numerical
μ (cm^{-1})	2.3
Temperature (K)	173
$2\theta_{max}$ (°)	51.92
hkl values	$-5\leq h\leq 5$, $-16\leq k\leq 16$, $-18\leq l\leq 18$
Measured reflections	10144
Unique reflections	3449
R_{int}	0.1123
Reflections with $F_o>4\sigma(F_o)$	1329
Parameter	247
Structure solution	Direct methods (SIR–92 [ ])
Refinement against F^2	SHELXL–97 [ ]
H atoms	Calculated positions with Common displacement Parameter. Free refinement For H1 and H2
Flack parameter	–
R_1	0.0662
wR_2 (all data)	0.1744
max. residual electron density	0.32 (e/Å^3)

[a] $w = 1/[\sigma^2(F_o^2) + (0.0791\cdot P)^2]$; $P = [\max(F_o^2, 0) + 2\cdot F_c^2]/3$

Table 2 Selected[6] bond lengths (Å) for compound **1**

S(1) – C(1)	1.760(5)	S(1) – C(3)	1.747(6)
O(1) – C(2)	1.214(6)	O(2) – C(5)	1.336(5)
O(2) – C(6)	1.453(6)	O(3) – C(5)	1.205(6)
O(4) – C(8)	1.316(6)	O(4) – C(9)	1.456(6)
O(5) – C(8)	1.203(5)	O(6) – C(11)	1.346(6)
O(6) – C(12)	1.441(8)	O(7) – C(11)	1.172(6)
N(1) – N(2)	1.421(6)	N(1) – C(1)	1.372(6)
N(1) – C(2)	1.372(6)	N(3) – N(4)	1.412(5)
N(3) – C(1)	1.283(5)	N(4) – C(7)	1.278(5)
C(2) – C(3)	1.488(7)	C(3) – C(4)	1.343(6)
C(4) – C(5)	1.464(7)	C(7) – C(8)	1.506(7)
C(7) – C(10)	1.517(7)	C(10) – C(11)	1.503(8)
N(2) – H(1)	0.95(7)	N(2) – H(2)	0.90(6)
C(4) – H(41)	0.95	C(6) – H(61)	0.98

($CDCl_3$) 2.08 (s, 2H, CH_2); 3.78 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 4.73 (s, 2H, NH_2); 6.88 (s, 1H, C =CH). MS: *m/z* 358 (M^+) ($C_{12}H_{14}N_4O_7S^+$), 116 ($C_4H_4O_2S^+$). Anal. Calcd. for $C_{13}H_{18}N_4O_8S$: C, 40.00; H, 4,62; N, 14.36. Found: C, 39.98; H, 4.65; N, 14.32%.

Methyl [3-arylmethylenamino-2-(arylmethylenehydrazono)-4-oxothiazolidin-5-ylidene]acetates (**3a–f**)*: general procedure*

A solution of thiocarbonodihydrazone[7,8] (**2**) (1 mmol) and DMAD (1 mmol) in 10 ml of MeOH was heated at reflux for 20 min. The solution was cooled and the crystals that separated were collected.

Dibenzylidene compound (**3a**): Obtained from the reaction of bis(benzaldehyde) 1,5-thiocarbonodihydrazone (**2a**) with DMAD, as a yellow powder, m.p. 77–78ºC (92%). IR: ν_{CO} 1739, 1690 cm^{-1}. ^{1}H NMR: δ (ppm) ($CDCl_3$) 3.90 (s, 3H, OCH_3); 7.01 (s, 1H, C=CH exo methylene); 7.52 (m, 6H, Ar–H); 7.85 (m, 4H, Ar–H); 8.57 (s, 1H, N=CH); 9.25 (s, 1H, N=CH). MS: *m/z* 392 (M^+), 118 ($C_7H_6N_2^+$), 116 ($C_4H_4O_2S^+$). Anal. Calcd. for $C_{20}H_{16}N_4O_3S$: C, 61.22; H, 4.08; N, 14.28. Found: C, 61.17; H, 4.07; N, 14.32%.

Bis-(4-methylbenzylidene) compound (**3b**): From 1,5-bis-(*p*-methylbenzaldehyde) thiocarbonodihydrazone (**2b**) as a yellow powder, m.p. 177–178°C (92%). IR: ν_{CO} 1710, 1691 cm^{-1}. ^{1}H NMR: δ (ppm) ($CDCl_3$) 2.42 (s, 3H, CH_3); 2.44 (s, 3H, CH_3); 3.91 (s, 3H, OCH_3); 7.00 (s, 1H, C =CH exo methylene); 7.25 (d, 2H, *J* = 8 Hz, Ar–H); 7.30 (d, 2H, *J* = 8 Hz, Ar–H); 7.72 (d, 2H, *J* = 8 Hz, Ar–H); 7.83 (d, 2H, *J* = 8 Hz, Ar–H); 8.53 (s, 1H, N=CH); 9.17 (1H, s, N=CH). MS: *m/z* 420 (M^+), 132 ($C_8H_8N_2^+$), 116 ($C_4H_4O_2S^+$). Anal. Calcd. for $C_{22}H_{20}N_4O_3S$: C, 62.85; H, 4.76; N, 13.33. Found: C, 62.92; H, 4.87; N, 13.45%.

Table 3 Selected[6] bond angles (deg) for compound **1**

C(1)–S(1)–C(3)	90.2(3)	C(5)–O(2)–C(6)	114.4(5)
C(8)–O(4)–C(9)	116.7(5)	C(11)–O(6)–C(12)	114.9(6)
N(2)–N(1)–C(1)	123.2(5)	N(2)–N(1)–C(2)	119.8(5)
C(1)–N(1)–C(2)	116.9(4)	N(4)–N(3)–C(1)	108.8(4)
N(3)–N(4)–C(7)	114.2(4)	S(1)–C(1)–N(1)	112.0(4)
S(1)–C(1)–N(3)	127.0(4)	N(1)–C(1)–N(3)	121.0(4)
O(1)–C(2)–N(1)	125.4(5)	O(1)–C(2)–C(3)	125.6(5)
N(1)–C(2)–C(3)	109.0(5)	S(1)–C(3)–C(2)	111.8(4)
S(1)–C(3)–C(4)	126.4(4)	C(2)–C(3)–C(4)	121.7(5)
C(3)–C(4)–C(5)	120.7(5)	O(2)–C(5)–O(3)	123.6(5)
O(2)–C(5)–C(4)	112.7(5)	O(3)–C(5)–C(4)	123.7(5)
N(4)–C(7)–C(8)	117.5(5)	N(4)–C(7)–C(10)	125.5(5)
C(8)–C(7)–C(10)	116.9(5)	O(4)–C(8)–O(5)	125.2(5)
O(4)–C(8)–C(7)	113.0(5)	O(5)–C(8)–C(7)	121.8(5)
C(7)–C(10)–C(11)	110.9(5)	O(6)–C(11)–O(7)	122.0(5)
O(6)–C(11)–C(10)	111.3(6)	O(7)–C(11)–C(10)	126.7(6)
N(1)–N(2)–H(1)	112.(4)	N(1)–N(2)–H(2)	105.0(4)
		H(1)–N(2)–H(2)	95.(6)

Bis-(4-nitrobenzylidene) compound (**3c**): From 1,5-bis-(*p*-nitrobenzaldehyde) thiocarbonodihydrazone (**2c**), as an orange crystalline solid, m.p. 160–161°C (91%). IR: ν_{CO}: 1735, 1697 cm^{-1}. ^{1}H NMR: δ (ppm) (DMSO–d_6) 3.82 (s, 3H, OCH_3); 6.95 (s, 1H, C =CH exo methylene); 8.17 (d, 4H, *J* = 7 Hz, Ar–H); 8.42 (d, 4H, *J* = 7 Hz, Ar–H); 8.59 (s, 1H, N=CH); 9.46(s, 1H, N=CH). MS: *m/z* 482 (M^+), 163 ($C_7H_5N_3O_2^+$), 116 ($C_4H_4O_2S^+$). Anal. Calcd. for $C_{20}H_{14}N_6O_7S$: C, 49.79; H, 2.90; N, 17.42. Found: C, 49.68; H, 2.88; N, 17.41%.

Bis-(3-nitrobenzylidene) compound (**3d**): From 1,5-bis-(*m*-nitrobenzaldehyde) thiocarbonodihydrazone (**2d**), with DMAD as a yellow powder, m.p. 130–131°C (87%). IR: ν_{CO}: 1721, 1698 cm^{-1}. ^{1}H NMR: δ (ppm) (DMSO–d_6) 3.85 (s, 3H, OCH_3); 6.79 (s, 1H, C =CH exo methylene); 7.73 (m, 2H, Ar–H); 8.23 (d, 1H, *J* = 7 Hz, Ar–H); 8.26 (d, 1H, *J* = 7 Hz, Ar–H); 8.35 (m, 2H, Ar–H); 8.58 (d, 1H, *J* = 2 Hz, Ar–H); 8.64 (d, 1H, *J* = 7 Hz, Ar–H); 8.67 (s, 1H, N=CH); 8.92 (s, 1H, N=CH). MS: *m/z* 482 (M^+), 163 ($C_7H_5N_3O_2^+$), 116 ($C_4H_4O_2S^+$). Anal. Calcd. for $C_{20}H_{14}N_6O_7S$: C, 49.79; H, 2.90; N, 17.42. Found: C, 49.68; H, 2.85; N, 17.40%.

Bis-(trans-3-phenyl-2-propenylidene) derivative (**3e**): Formed from the reaction of 1,5-bis(cinnamaldehyde) thiocarbonodihydrazone (**2e**) with DMAD as an orange powder, m.p. 230–231°C (88%). IR: ν_{CO}: 1702, 1699 cm^{-1}. ^{1}H NMR: δ (ppm) (DMSO–d_6) 3.64 (s, 3H, OCH_3), 7.05 (s, 1H, C =CH exo methylene), 7.51 (m, 4H, Ar–H), 7.63 (m, 6H, Ar–H), 7.91 (dd, 2H, *J* = 16, 9 Hz, C =CH), 7.98 (d, 1H, *J* = 16 Hz, C =CH), 8.00 (d, 1H, *J* = 16 Hz, C =CH), 8.65 (d, 1H, *J* = 9 Hz, N=CH), 9.17 (d, 1H, *J* = 9 Hz, N=CH). MS: *m/z* 444 (M^+), 144 ($C_9H_8N_2^+$), 116($C_4H_4O_2S^+$). Anal. Calcd. for $C_{24}H_{20}N_4O_3S$: C, 64.86; H, 4.50; N, 12.61. Found: C, 64.85; H, 4.42; N, 12.55%.

Bis-(2-hydroxybenzylidene) derivative (**3f**): From 1,5-bis (salicylaldehyde) thiocarbonodihydrazone (**2f**), orange powder, m.p. 244–245°C (91%). IR: ν_{CO} 1739, 1698 cm^{-1}. ^{1}H NMR: δ (ppm) (DMSO–d_6) 3.80 (s, 3H, OCH_3); 6.84 (s, 1H, C =CH exo methylene); 6.94 (m, 4H, Ar–H); 7.43 (m, 2H, Ar–H); 7.74 (dd, 2H, *J* = 7, 2 Hz, Ar–H,); 8.83 (s, 1H, N=CH); 9.40 (s, 1H, N=CH); 10.53 (s, 1H, OH); 10.73 (s, 1H, OH). MS, *m/z* 424 (M^+), 134 ($C_7H_6N_2O^+$), 116 ($C_4H_4O_2S^+$). Anal. Calcd. for $C_{20}H_{16}N_4O_5S$: C, 56.60; H, 3.77; N, 13.20. Found: C, 56.60; H, 4.00; N, 13.20%.

Bis(pyrrol-2-ylmethylene) derivative (**3g**): From the reaction of 1,5-bis(pyrrole-2-carbaldehyde) thiocarbonodihydrazone (**2g**) with DMAD as an orange powder. m.p. 82–84°C (94%). IR: ν_{NH}: 3486; ν_{CO}: 1721, 1703 cm^{-1}. ^{1}H NMR: δ (ppm) ($CDCl_3$) 3.92 (s, 3H, OCH_3); 6.35 (m, 2H, Py–H); 6.81(m, 2H, Py–H); 6.99 (s, 1H, C =CH exo methylene); 7.28 (m, 2H, Py–H); 8.91 (s, H, N=CH); 9.01 (s, 1H, N=CH); 9.53 (br 1H, N=CH); 10.38 (br, 1H NH). MS: *m/z* 370 (M^+), 107($C_5H_5N_3^+$), 116($C_4H_4O_2S^+$). Anal. Calcd. for $C_{16}H_{14}N_6O_3S$: C, 51.89; H, 3.78; N, 22.70. Found: C, 51.76; H, 3.67; N, 22.68%.

Bis-furfurylidene derivative (**3h**): Obtained from the reaction of 1,5-bis(furan-2-carbaldehyde) thiocarbodihydrazone (**2h**), orange powder. M.p. 212–213°C (96%). IR: ν_{CO}: 1701, 1699 cm^{-1}. ^{1}H NMR: δ (ppm) (DMSO–d_6) 3.92 (s, 3H, OCH_3); 6.82 (s, 1H, C =CH exo methylene); 6.92 (dd, 2H, *J* = 2, 13 Hz, Ar–H); 7.46 (dd, 2H,

J = 4, 8 Hz, Ar– H); 8.18 (dd, 2H, *J* = 8, 13 Hz, Ar–H); 8.24 (s, 1H, N=CH); 9.21 (s, 1H, N=CH). MS: *m/z* 372 (M^+), 108 ($C_5H_4N_2O^+$), 116 ($C_4H_4O_2S^+$). Anal. Calcd. for $C_{16}H_{12}N_4O_5S$: C, 51.61; H, 3.22; N, 15.05. Found: C, 51.58; H, 3.10; N, 15.02%.

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8 Fuller information is available at the Cambridge Crystallographic Data Centre by quoting the publication number CCDC 290358. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: + 44(0) 1223 336033 or e–mail: deposit@ccdc.cam.ac.uk].