Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Thiation of new 5-(2-aryl-2-oxoethyl)-2,4-dioxo-1, 3-thiazolidines

Nadia K. El-Aasar[a]; Khaled F. Saied[a]
[a] Department of Chemistry, Faculty of Science Ain Shams University, Abbassia, Cairo, Egypt

To cite this Article El-Aasar, Nadia K. and Saied, Khaled F.(2008) 'Thiation of new 5-(2-aryl-2-oxoethyl)-2,4-dioxo-1, 3-thiazolidines', Journal of Sulfur Chemistry, 29: 1, 43 — 52
To link to this Article: DOI: 10.1080/17415990701784642
URL: http://dx.doi.org/10.1080/17415990701784642

Journal of Sulfur Chemistry
Vol. 29, No. 1, February 2008, 43–52

Taylor & Francis
Taylor & Francis Group

Thiation of new 5-(2-aryl-2-oxoethyl)-2,4-dioxo-1, 3-thiazolidines

Nadia K. El-Aasar* and Khaled F. Saied

Department of Chemistry, Faculty of Science Ain Shams University, Abbassia, Cairo, Egypt

(*Received 08 May 2007; final version received 21 October 2007*)

The hitherto unknown 5-(2-aryl-2-oxoethyl)-3-substituted-2,4-dioxo-1,3-thiazolidines **2** and 5-(2-aryl-2-oxoethylidene)-3-aryl-2,4-dioxo-1,3-thiazolidines **4** have been prepared from their 2-thioxo- homologues **1** and **3**, respectively, via treatment with CrO_3. Compound **4** has also been obtained by treating **1** and/or **2** with bromine at different experimental conditions. Thiation of **2** and/or **4**, gave a mixture of 3,5-di-substituted-2,3-dihydro-2-oxothieno[2,3-*d*]thiazoles **5** and the respective 2-thioxo derivatives **6**. Reactions of hydrazine hydrate with **1c**, **d**, were carried out at room temperature as well as under reflux, affording *di*-(3-oxo-6-aryl-4,5-dihydropyridazin)disulfides **7c**, **d** and *di*-(3-oxo-6-arylpyridazin)disulfides **8c**, **d**, respectively, together with 4-arylthiosemi carbazides **9c**, **d**, under both conditions. Structures of the above products have been elucidated based on their microanalytical and spectroscopic data. Compound **2e** exhibited pronounced antischistosomal activity.

Keywords: transformation; 2,4-thiazolidinones; thieno-thiazoles; antischistosomal

1. Introduction

The substituted 2-thioxo-4-oxo-, and 2,4-dioxo-1,3-thiazolidines are two classes of interesting biological activity (*1, 2*). Conversion of the 2-thioxo-1,3-thiazolidines into the respective 2-oxo derivatives is well known (*3*). Different reagents have been reported to effect this process; aqueous chloroacetic acid, hydrogen peroxide, and bromine (*3–7*). In attempted synthesis of 3-substituted-5-(2-aryl-2-oxoethyl)-2,4-dioxo-1,3-thiazolidines **2**, we found that chromium trioxide could be used to achieve the preceding conversion. The biological activity which was tested for **2e** showed the utility of this derivative as an antischistosomal drug (*8*).

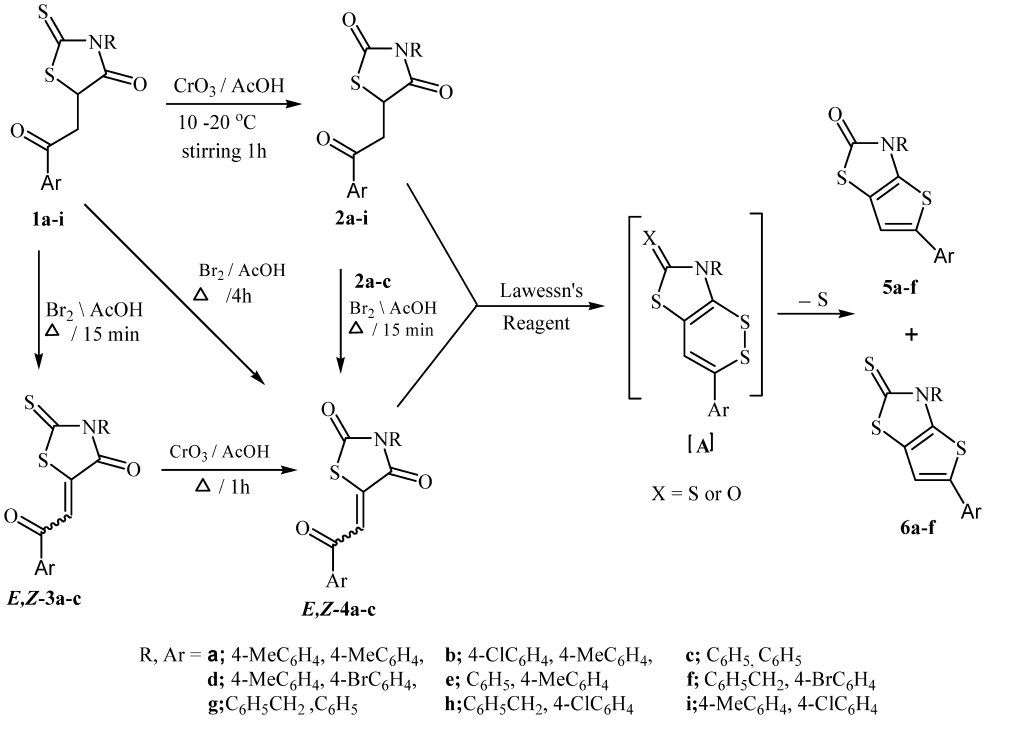
2. Chemistry

Treatment of 3-aryl-5-(2-aryl-2-oxoethyl)-4-oxo-2-thioxo-1,3-thiazolidines **1a–c** (*9, 10*) gently with hot Br_2/AcOH solution, resulted in easy bromination simultaneously with dehydrobromination (*7*), affording *E*, *Z*-5-(2-aryl-2-oxethylidene)-3-aryl-4-oxo-2-thioxo-1, 3-thiazolidines **3a–c** (*9, 10*). However, under reflux for longer time, thiono transformation

*Corresponding author. Email: nadia.alaasar@yahoo.com

ISSN 1741-5993 print/ISSN 1741-6000 online

DOI: 10.1080/17415990701784642
http://www.informaworld.com



Scheme 1.

(*7*) was then achieved, providing the respective 5-(2-aryl-2-oxoethylidene)-3-aryl-2,4-dioxo-1, 3-thiazolidines **4a–c** (Scheme 1).

Herein, we developed a new method concerns the previous transformation, by the use of chromium trioxide. Thus, treatment of the 2-thiono **1a–i** (*9–12*) with this reagent in cold AcOH afforded the respective 2-oxy homologues **2a–i**. Furthermore, similar treatment of **3a–c** in boiled AcOH, provided **4a–c** (Scheme 1).

The advantage of this method appears in synthesis of **2** from **1**; this treatment successfully performed the required conversion and affected neither H-5 of the hetero ring nor the neighboring methylene protons.

The 1H NMR spectrum of **2a** exhibited the characteristic pattern of the $-CH-CH_2-$ moiety; at δ ppm 4.67 dd, 1H (H-5), 4.13, 3.53 each dd, 1H for the CH_2 (Ph-CO-$\underline{CH_2}-$) (Table 1). The mass spectrum showed a correct molecular ion peak m/e 339 (24%) and a base peak m/e 119 (100%) corresponding to the stable ionic radical C_8H_7O [A]. Also, intense peaks m/e 220 (42%) and m/e 91(50%) corresponding to [B] and [C] fragments were exhibited (Table 1 and Figure 1). The IR spectrum showed three $\nu_{C=O}$ absorptions at 1754, 1690, and 1674 cm^{-1}. Furthermore, the structure of **2** was further supported when the behavior of **2a–c** with bromine was investigated, providing the expected **4a–c**.

The structure of **4** has been confirmed when it was prepared via the preceding different methods. Moreover, the structure was elucidated based on analytical and spectral evidences. The EI-MS of **4a** displayed the expected molecular ion peak m/e 337 (9.1%, Table 1) showing its formation from **2a** by elimination of a hydrogen molecule; from **3a** via replacement of sulfur atom by oxygen and from **1a** through these two processes together. The IR spectrum of **4a** exhibited $\nu_{C=O}$ at 1752, 1699, and 1644 cm^{-1}. The 1H NMR spectrum showed a singlet for the olefinic proton at $\sim\delta$ 8.22, while the $-CH-CH_2-$ pattern exhibited in the spectrum of **2a** disappeared.

Table 1. IR, elemental analysis and mass spectroscopic data of prepared compounds.

Compound No.	IR Cm^{-1} $\nu_{C=O}$	Mol. for (M. wt.)	Analysis% (required/found) C	H	N	Ms (m/z)
2a	1754, 1690, 1674	$C_{19}H_{17}NO_3S$ (339)	67.24, 67.26	5.05, 5.07	4.1, 4.34	339 (24.1%), 220 (42.4%) 119 (100%), 91 (50%)
2b	1755, 1695, 1672	$C_{18}H_{14}ClNO_3S$ (359)	60.08, 59.35	3.92, 3.86	3.89, 3.84	359 (13.6%), 240 (14.7%) 119 (100%) · 91 (59.4%)
2c	1753, 1674(br)	$C_{17}H_{13}NO_3S$ (311)	65.58, 65.56	4.21, 4.27	4.50, 4.63	311 (34.1%), 206 (59. 1) 105 (100%), 77 (67.8%)
2d	1754, 1684(br)	$C_{18}H_{14}BrNO_3S$ (404)	53.46, 53.54	3.49, 3.44	3.46, 3.47	404 (16.9%), 220 (100%) 183 (40.3%),155 (17.9%)
2e	1755, 1706, 1675	$C_{18}H_{15}NO_3S$ (325)	66.44, 66.53	4.65, 4.75	4.46, 4.38	325 (19.4%), 206 (31.1%) 119 (100%), 91 (69.4%)
2f	1743, 1681 (br)	$C_{18}H_{14}BrNO_3S$ (404)	53.46, 53.52	3.49, 3.45	3.46, 3.55	404 (25.8%), 220 (46.9%) 183 (36.7%),155 (18.8%)
2g	1744, 1681 (br)	$C_{18}H_{15}NO_3S$ (325)	66.44, 66.51	4.65, 4.7	4.30, 4.33	325 (42.4%), 220 (67.1%), 105 (100), 91 (89.7%)
2h	1745, 1683 (br)	$C_{18}H_{14}ClNO_3S$ (359)	60.08, 61.0	3.92, 4.11	3.89, 4.17	359 (100%), 220 (14.7%) 105 (4%) · 91 (49.4%)
2i	1745, 1676 (br)	$C_{18}H_{14}ClNO_3S$ (359)	60.08, 60.21	3.92, 3.94	3.89, 4.17	359 (29.6%), 220 (100%) 139 (83.1%), 111 (38.4%)
4a	1752, 1699, 1644	$C_{19}H_{15}NO_3S$ (337)	67.64, 67.57	4.48, 4.37	4.15, 4.17	337 (9.2%), 309 (24.4%) 119 (100%), 91 (45%)
4b	1755, 1696, 1640	$C_{18}H_{12}ClNO_3S$ (357)	60.42, 60.46	3.38, 3.46	3.91, 3.42	119 (100%), 91 (47. 3%) 357 (2.8%), 329 (15.8%)
4c	1750, 1689, 1640	$C_{17}H_{11}NO_3S$ (309)	66.01, 66.13	3.58, 3.50	4.53, 4.54	309 (9.2%), 281 (15.9%) 105 (100%), 77 (53.7%)
5a	1714	$C_{19}H_{15}NOS_2$ (337)	67.63, 67.71	4.48, 4.44	4.15, 4.20	337 (43.1%), 294 (100%) 135 (28.6%)
5b	1696	$C_{18}H_{12}ClNOS_2$ (357)	60.41, 60.48	3.38, 3.36	3.91, 4.12	357 (38.1%), 294 (100%) 135 (39.7%)
5c	1676	$C_{17}H_{11}NOS_2$ (309)	65.99, 66.32	3.58, 3.63	4.53, 4.55	309 (68.2%), 281 (36.9%) 280(100%), 121 (79.7%)

(*continued*)

Table 1. Continued.

Compound No.	IR Cm^{-1} $\nu_{C=O}$	Mol. for (M. wt.)	Analysis% (required/found) C	H	N	Ms (m/z)
5d	1674	$C_{18}H_{12}BrNOS_2$ (402)	53.73, 53.79	3.01, 3.22	3.48, 3.52	402 (61.6%), 360 (100%) 358 (86.1%), 199 (35.8%)
5e	1678	$C_{18}H_{13}NOS_2$ (323)	66.84, 66.99	4.05, 4.21	4.33, 4.46	323 (61.6%), 294 (100%) 135 (35.8%)
5f	1678	$C_{18}H_{12}BrNOS_2$ (402)	53.73, 53.77	3.01, 3.03	3.48, 3.54	402 (8.9%), 91 (100%)
7c	3330; ν O−H	$C_{20}H_{18}N_4O_2S_2$ (410)	58.52, 57.7	4.42, 4.32	13.65, 13.9	410 (14.2%), 205 (25,1%), 172 (80.4%), 115 (100%)
7d	1650	$C_{20}H_{16}Br_2N_4O_2S_2$ (568)	42.26, 42.48	2.84, 2.77	9.86, 10.2	282 (8.8%), 223 (100%), 144 (68%)
8c	1620	$C_{20}H_{14}N_4O_2S_2$ (406)	59.10, 60.4	3.47, 3.51	13.78, 13.88	406 (14.2%), 204 (100%) 203 (4.3%)
8d	1640	$C_{20}H_{12}Br_2N_4O_2S_2$ (564)	42.57, 42.67	2. 14, 1.95	9.93, 9.78	282 (20.7%), 183 (8.9%)

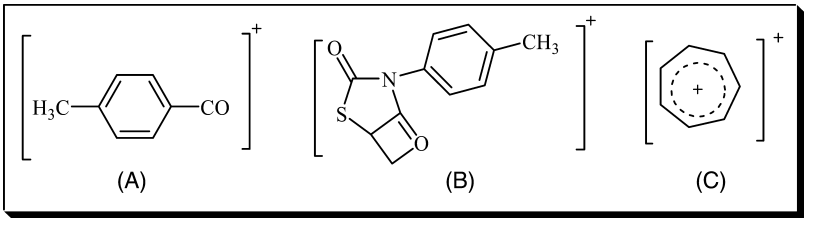


Figure 1. The base peak [A] and the major fragments [B] and [c] of **2a**.

Presentation of one singlet for the olefinic proton in the 1H NMR spectra, indicated that **4a** and **4b** are pure isomers. This interpretation was based on the PNMR spectroscopic data of 3-ethylidenesuccinimides(*13*), which exhibited two singlets for the olefinc proton as a mixture of *E* and *Z* isomers. The configuration assignment of these isomers was based on the assumption that the vinylic proton in isomer (*Z*) is more deshielded by the 4-oxo group compared with the counterpart (*E*).

According to our reported work (*9*), thiation of either **2a–f** or **4a–c** was studied. When the starting materials were treated with one equivalent of Lawesson's reagent (*14*), 3,5-disubstituted-2,3-dihydro-2-oxothieno[2,3-*d*]thiazoles **5** was obtained together with traces of the respective 2-thioxo- derivatives **6**. However, when two equivalents of the reagent were applied, compound **6** was obtained in a good yield at the expense of **5**.

The EI-MS of **5a–f** showed perfect molecular ion peaks and fragmentation patterns which confirmed the expected structure (Table 1, Figure 2). The absorption bands of the three C=O groups of **2** as well as **4** have been collapsed in the IR spectra of **5** into one ν_{CO}, corresponding to a thiolactone group. The 1H NMR spectra showed neither the olefinic proton of **4** nor the $-CH-CH_2-$ pattern of **2**, while a singlet concerning H-6 of the thiophene ring was displayed at $\delta \approx 7.1$. The structure of **6** was confirmed by matching m.p. and T.L.C. with authentic specimens previously prepared (*9*).

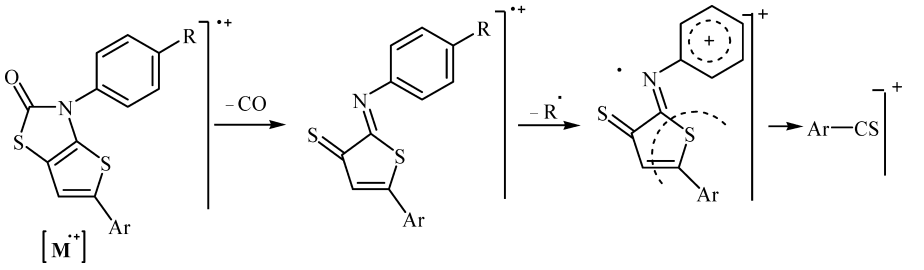


Figure 2. Ion peaks and fragmentation patterns of 6.

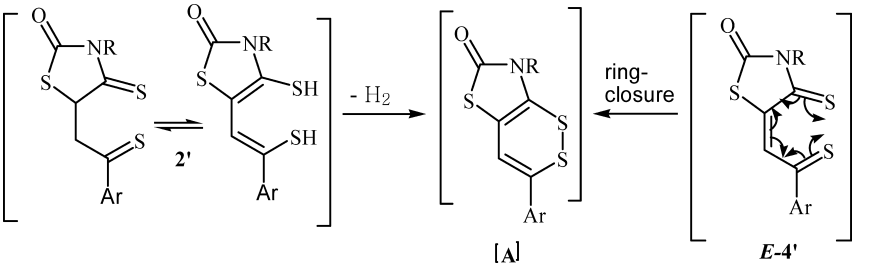
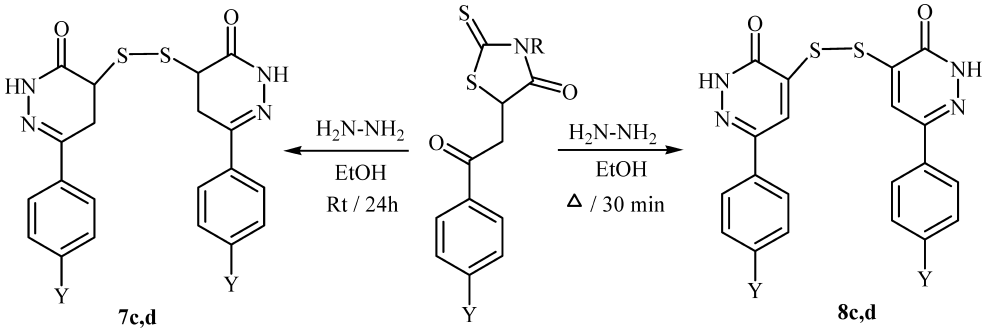


Figure 3. Hypothetically formed 1,4-dithioxo **2′** and ***E*-4′**.

Conversion of **2** and **4** into the respective **5** has occurred via the sextet 1,2-dithiane [**A**] by sulfur extrusion. The intermediate [**A**] was first generated from the hypothetically formed 1,4-dithioxo **2′** and *E*-**4′** (Scheme 1, Figure 3). The proposed mechanism for this transformation has been previously discussed for synthesis of **6** (*9, 15*).

Reactions of **1c**, **d** (*9, 10*) with hydrazine hydrate in ethanol were also studied. When the reactions were carried out at room temperature, afforded *di*-(3-oxo-6-aryl-4,5-dihydro-pyridazin)disulfides **7c**, **d** together with 4-arylthiosemicarbazides **9c**, **d**, via cleaving the hetero ring along 1,2 as well as 3,4 bonds. On the other hand, when these reactions were repeated under reflux; *di*-(3-oxo-6-aryl-pyridazin)disulfides **8c**, **d** were obtained, in addition to **9c**, **d** (Scheme 2).



1c; R = Ph, Y = H
1d; R = 4-MeC_6H_4 ,Y = Br

7, 8c; Y = H
7, 8d; Y = Br

9c; R = Ph
9d; R = 4-MeC_6H_4

Scheme 2.

The 1H NMR spectrum of the disulfide **7c** displayed at δ 11.25 s 1H (NH), 7.76–7.7 m, 2H (aromatic H), 7.44–7.40 m, 3H (aromatic H), 4.05 dd 1H, (H-4), 3.34 and 3.16 ppm each dd 1H ($-\underline{CH_2}-$) of the hetero ring methylene protons (H-5). The IR spectrum which was devoid of any C=O absorption, showed an intense ν_{O-H} at 3330 cm^{-1} revealing the presence of **7c** in the enol form. The EI-MS displayed the expected molecular ion peak m/e 410 (13%) besides a base peak m/e 115 (100) and an intense peak m/e 206.

The 1H NMR spectrum of **8c** exhibited at δ 13.58 s 1H (NH), 7.87 s 1H (olefinic H), 7.78–7.74 m, 2H (aromatic H), 7.46–7.42 m, 3H (aromatic H). The mass spectrum exhibited a correct molecular ion peak m/e 406 (16%) and a base peak corresponding to the mercapto ion radical m/e 204. The structure of **9** was confirmed by matching (m.p and IR) with authentic samples (*16, 17*).

3. Biological activity

For antischistosomal study (*8*), 40 albino CDI male mice were supplied by the Schistosome Biological supply Program at Thoedor Bilharz Research Institute, Giza Egypt. Each mouse was experimentally infected with 80 cercariae of *Schistosoma mansoni* by tail immersion method. The mice were housed with controlled temperature, light environment and fed on standard diet and normal drinking water.

One month post-infection, the mice were randomly divided into four equal groups; group **I** was the infected non-treated group, while groups **II**, **III**, and **IV** were treated with **2e** 50, 100, and 200 mg/kg body/weight, respectively, in a single oral dose suspended in distilled water. Choice of these doses was based on the LD_{50} of thiazolidine derivatives previously investigated as 100 mg/kg body weight, so, the half and double values of the LD_{50} were tested. Administration of these doses to the infected groups resulted in reduction of the worm burden. Granuloma number and diameters in the infected livers of the three groups have also been reduced. Few weeks after administration, **2e** caused severe tegumental alterations and loss or shortening of the spines in *S. mansoni*. Swelling, vacuolization, erosion, cracks, peeling, and fusion of the tegumental ridges were also observed. The most effective and recommended dose was found to be **2e** 50 mg/kg body/weight.

4. Experimental

All melting points are uncorrected. IR Spectra were measured on a Perkin–Elmer 1600 FT.IR spectrophotometer as KBr discs. The 1H NMR spectra were measured in $CDCl_3$ solution on Varian Gemini 200 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS. Mass spectra were recorded on Shimadzu GC-MS-QP 1000EX Instruments operating at 70 eV. The spectroscopic measurements were carried out in the microanalytical center, Faculty of Science, Cairo University, Egypt. Column chromatography and TLC were run on Silica Gel Voeim, activity III/30 mm according to Brockmann and Schodder and TLC aluminum sheet Silica GEL 60 F_{254} (Merck). Light petroleum is referred to the fraction B.P. (60–80). The starting material **1a**–**i** and **3a–c** were prepared according to previously reported methods (*9–12*).

4.1. *Synthesis of 3-substituted-5-(2-aryl-2-oxoethyl)-2,4-dioxo-1,3-thiazolidines 2a–i*

A suspension of each of **1a**–**h** or **i** (10 mmol) in AcOH (50 ml) was stirred for 30 min at 15–20 °C. During this time, CrO_3 1.0 g (30 mmol) was added portion-wise. The stirring was continued for another 30 min at room temperature. The reaction mixture was then heated (90 °C), cooled and

diluted with H_2O (5 ml). The precipitated solid was filtered off, washed, dried, and recrystallized with charcoal (toluene/light petroleum) to give the following.

4.1.1. *3-(4-Tolyl)-5-(2-(4-tolyl)-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2a)*

2.7 g (79.2%), m.p: 188–190 °C; 1H NMR: $\delta = 7.87$ (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.32, 7.29 two central peaks Abq, 4 H, H_{arom}), 7.24 (d, 2H, $J = 8.4$ Hz, H_{arom}), 4.76 (dd, $1H_A$, $J_{AX} = 9.8$ $J_{AM} = 2.8$ Hz,), 4.13 (dd, 1H M, $J_{MX} = 18.60$, $J_{AX} = 2.80$ Hz), 3.63 (dd, $1H_X$, $J_{MX} = 18.60$, $J_{AX} = 9.80$ Hz), 2.24, 2.03 each (s, 3H, CH_3).

4.1.2. *3-(4-Chlorophenyl)-5-(2-(4-tolyl)-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2b)*

2.7 g (75.2%), m. p. 208–210 °C; 1H NMR $\delta = 7.87$ (d, 2H, H_{arom}, $J = 8.0$ Hz), 7.49 (d, 2H, H_{arom}, $J = 8.6$ Hz), 7.32–7.27 (m, 4H, H_{arom}), 4.71 (dd, $1H_A$, $J_{AX} = 9.40$, $J_{AM} = 3.0$ Hz), 4.11 (dd, $1H_M$, $J_{MX} = 18.4$, $J_{AM} = 3.0$ Hz) 3.69 (dd, $1H_X$, $J_{MX} = 18.40$, $J_{AX} = 9.40$ Hz), 2.44 (s, 3H, CH_3).

4.1.3. *3-Phenyl-5-(2-phenyl-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2c)*

2.3 g (74.1% 0; m.p: 117–118 °C ; 1H NMR: $\delta = 7.98$ (d, 2H, H_{arom}, $J = 7.8$ Hz), 7.65 (appt.t, 1H, H_{arom}, $J = 7.2$ Hz), 7.45–7.57 (m, 5H, H_{arom}), 7.33 (d, 2H, H_{arom}, $J = 6.7$ Hz), 4.74 (dd, $1H_A$, $J_{AX} = 9.9$, $J_{AM} = 3.0$ Hz), 4.16 (dd, $1H_M$, $J_{MX} = 18.7$, $J_{AM} = 3.0$ Hz) 3.7 (dd, $1H_X$, $J_{MX} = 18.7$, $J_{AX} = 9.9$ Hz).

4.1.4. *3-(4-Tolyl)-5-(2-(4-bromophenyl)-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2d)*

3.1 g (76.9%), m.p: 199–201 °C; 1H NMR : $\delta = 7.84$,7.65 (2 d, 2H, H_{arom}, $J = 8.6$ Hz), 7.32, 7.19 (2 d, 2H, H_{arom}, $J = 8.0$ Hz), 4.71 (dd, $1H_A$, $J_{AX} = 9.8$, $J_{AM} = 3.0$ Hz), 4.11 (dd, $1H_M$, $J_{MX} = 18.6$, $J_{AM} = 3.0$ Hz), 3.65 (dd, $1H_X$, $J_{MX} = 18.4$, $J_{AX} = 9.8$ Hz), 2.40 (s, 3H, CH_3).

4.1.5. *3-Phenyl-5-(2-(4-tolyl)-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2e)*

2.5 g (76.9%); m.p: 185–187 °C ; 1H NMR $\delta = 7.87$ (d, 2H, H_{arom}, $J = 8.2$ Hz), 7.52–7.48 (m, 3H, H_{arom}), 7.35–7.28 (m, 4H, H_{arom}), 4.72 (dd, $1H_A$, $J_{AX} = 9.8$, $J_{AM} = 3.0$ Hz), 4.13 (dd, $1H_M$, $J_{MX} = 18.4$, $J_{AM} = 3.0$ Hz), 3.67 (dd, $1H_X$, $J_{MX} = 18.4$, $J_{AX} = 9.8$ Hz), 2.44 (s, 3H, CH_3).

4.1.6. *3-Benzyl-5-(2-(4-bromophenyl)-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2f)*

3.3 g (80.2%), m.p: 134–136 °C ; 1H NMR: $\delta = 7.80$, 7.63 each (d, 2H, H_{arom}, $J = 8.8$ Hz), 7.44–7.31 (m, 5H, H_{arom}), 4.80 (s, 2H, Ph-CH_2), 4.58 (dd, $1H_A$, $J_{AX} = 10.6$, $J_{AM} = 3.0$ Hz), 4.05 (dd, $1H_M$, $J_{MX} = 18.6$, $J_{AM} = 3.0$ Hz), 3.43 (dd, $1H_X$, $J_{MX} = 18.6$, $J_{AX} = 10.6$ Hz).

4.1.7. *3-Benzyl-5-(2-phenyl-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2g)*

0.43 g (86.0%); m.p: 105–106 °C; 1H NMR: $\delta = 7.94$ (d, 2H, H_{arom}, $J = 7.80$ Hz), 7.63 (appt.t,1H, H_{arom}, $J = 7.60$ Hz), 7.53 (appt.t, 2H, H_{arom}, $J = 7.6$ Hz), 4.81 (s, 2H, Ph$\underline{CH_2}$), 4.598 (dd, 1H, H_A, $J_{AX} = 10.8$, $J_{AM} = 3.0$ Hz), 4.10 (dd, 1H, H_M, $J_{MX} = 18.6$, $J_{AM} = 3.0$ Hz), 3.47 (dd, 1H, H_X, $J_{MX} = 18.8$, $J_{AX} = 3.0$ Hz).

4.1.8. *3-Benzyl-5-(2-(4-chlorophenyl)-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2h)*

0.81 g (81.0%); m.p. 130–132 °C; 1H NMR: $\delta = 7.92$ (d, 2H, $2H_{arom}$, $J = 8.4$ Hz), 7.50 (d, 2H, H_{arom}, $J = 8.4$ Hz), 7.36–7.46 (m, 5H, H_{arom}), 4.84 (s, 2H, $Ph\underline{CH_2}$), 4.62 (dd, 1H, H_A, $J_{AX} = 10.6$, $J_{AM} = 3.0$ Hz), 4.10 (dd, 1H, H_M, $J_{MX} = 18.6$, $J_{AM} = 10.6$ Hz), 3.48 (dd, 1 H, H_X, $J_{MX} = 18.6$, $J_{AX} = 10.6$ Hz).

4.1.9. *3-(4-Tolyl)-5-(2-(4-chlorophenyl)-2-oxoethyl)-2,4-dioxo-1,3-thiazolidine (2i)*

3.11 g (76.8%), m. p: 190–192 °C; 1H NMR : $\delta = 7.82$, 7.37 (2 d, 2H, H_{arom}, $J = 8.6$ Hz), 7.20, 7.08 (2d, 2H, H_{arom}, $J = 8.8$ Hz), 4.62 (dd, 1H, H_A, $J_{AX} = 9.4$, $J_{AM} = 3.0$ Hz), 4.11 (dd, 1H, H_M, $J_{MX} = 18.6$, $J_{AM} = 3.0$ Hz), 3.65 (dd, 1H, H_X, $J_{MX} = 18.6$, $J_{AX} = 9.4$ Hz), 2.28 (s, 3H, CH_3).

4.2. *Synthesis of 3-substituted-5-(2-aryl-2-oxoethylidene)-2,4-dioxo-1,3-thiazolidines 4a–c*

4.2.1. *Method A (from 3a–c)*

A mixture of **3a**, **b** or **c** (1.0 g, $\approx$ 3 mmol) and CrO_3 (0.3 g, 10 mmol) was refluxed in 15 ml of glacial acetic acid for an hour. The reaction mixture was cooled and diluted with 5 ml of H_2O. The precipitated solid was filtered off, washed, dried, and recrystallized (toluene/ethanol) with charcoal to give **4a–c**.

4.2.2. *Method B (from 1a–c)*

A mixture of **1a**, **b**, or **c** (3 mmol) and bromine (2 ml, 2.2 mmol) was refluxed in glacial acetic acid (25 ml) for 4 h. The reaction mixture was concentrated and left to cool. The separated product was filtered off, dried, and recrystallized from toluene/ethanol to give **4a–c** (matched m.p. and i.r with the samples previously obtained from Method A).

4.2.3. *Method C (from 2a–c)*

A stirred hot solution of glacial acetic acid (25 ml) containing 3 mmol of **2a**, **b**, or **c** was treated drop-wise with bromine (2 ml, 2.2 mmol). The reaction mixture was heated for 15 min till HBr was ceased to evolve and worked out as in method B to give **4a–c** (matched m.p. and i.r with the samples previously obtained from Method A and B).

4.2.4. *3-(4-Tolyl)-5-(2-(4-tolyl)-2-oxoethylidene)-2,4-dioxo-1,3-thiazolidine (4a)*

0.83 g (80%), m.p: 199–201 °C; 1H NMR $\delta = 8.23$ (s, 1H, $H_{olefinic}$) 7.10 (d, 2H, H_{arom}, $J = 7.4$ Hz), 7.36–7.09 (m, 6H, H_{arom}), 2.45, 2.411 each (s, 3H, CH_3).

4.2.5. *3-(4-Chlorophenyl)-5-(2-(4-tolyl)-2-oxoethylidene)-2,4-dioxo-1,3-thiazolidine (4b)*

0.87 g (81%), m.p: 223–225 °C; 1H NMR $\delta = 8.25$ (s, 1H, $H_{olefinic}$) 8.01, 7.36 (2d, 2H, H_{arom}, $J = 8.2$ Hz), 7.519–7.3 (2d, 2H, H_{arom}, $J = 8.8$ Hz) 2.47 (s, 3H, CH_3).

4.2.6. *3-Phenyl-5-(2-phenyl-2-oxoethylidene)-2,4-dioxo-1,3-thiazolidine (4c)*

0.75 g (80%), m.p: 188–190 °C.

4.3. *Synthesis of 3,5-disubistituted-2,3-dihydro-2-oxothieno[2,3-d]thiazoles 5a–f*

A solution of dry toluene (25 ml) containing Lawesson's reagent (2.5 mmol) was refluxed for 4 h with (3 mmol) each of **2a–d** or **f** (Method I) and/or with **4a**, **b**, or **c** (Method II). The reaction mixture was washed with H_2O (25 ml). The organic layer was separated, dried ($CaCl_2$) anhydrous and concentrated. The residue was chromatographed over silica gel and eluted with (4:3:1 V/V) light petroleum/carbon tetrachloride/ethyl acetate to afford **6a–f** followed by **5a–f,** which was recrystallized from toluene/ethanol.

Note: when two equivalent of Lawesson's reagent were applied, the product was **6** only matched m.p. and i.r with samples previously obtained (*9*).

4.3.1. *3,5-Di-(4-tolyl)-2,3-dihydro-2-oxothieno[2,3-d]thiazole (5a)*

0.4 g (40% Method 1), 0.43 g (42% Method 2); m.p: 159–161 °C; 1H NMR $\delta = 7.48$ (d, 2H, H_{arom}, $J = 8.0$ Hz), 7.36–7.25 (m, 4H, H_{arom}), 7.18 (d, 2H, H_{arom}, $J = 8.2$ Hz), 7.13 (s, 1H, H-6) 2.44, 2.36 each (s, 3H, CH_3).

4.3.2. *3-(4-Chlorophenyl)-5-(4-tolyl)-2,3-dihydro-2-oxothieno[2,3-d]thiazole (5b)*

0.41 g (38% Method 1), 0.44 g (40% Method 2); m.p: 182–184 °C; 1H NMR $\delta = 7.56$, 7.539 (two central peaks Abq, 4H, H_{arom}), 7.387, 7.189 (2d, 2H, H_{arom}, $J = 8.0$ Hz), 7.13 (s, 1H, H-6), 2.37 (s, 3H, CH_3).

4.3.3. *3,5-Diphenyl-2,3-dihydro-2-oxothieno[2,3-d]thiazole (5c)*

0.41 g (45% Method 1), 0.40 g (42% Method 2); m.p: 151–153 °C; 1H NMR $\delta = 7.60-7.34$ (m, 10 H, H_{arom}), 7.13 (s, 1H, H-6).

4.3.4. *3-(4-Tolyl)-5-(4-bromophenyl)-2,3-dihydro-2-oxothieno[2,3-d]thiazole (5d)*

0.44 g (38% Method 1); m.p: 233–235 °C; 1H NMR $\delta = 7.13 - 7.25$ (m, 8 H, H_{arom}), 7.17 (s, 1H, H-6), 2.436 (s, 3H, CH_3).

4.3.5. *3-Phenyl-5-(4-tolyl)-2,3-dihydro-2-oxothieno[2,3-d]thiazole (5e)*

0.35 g (38% Method 1); m.p: 158–160 °C; 1H NMR $\delta = 7.64 - 7.49$ (m, 5H, H_{arom}), 7.39, 7.18 each (d, 2H, H_{arom}, $J = 8.2$ Hz), 7.134 (s, 1H, H-6), 2.367 (s, 3H, CH_3).

4.3.6. *3-Benzyl-5-(4-bromophenyl)-2,3-dihydro-2-oxothieno[2,3-d]thiazole (5f)*

0.5 g (42% Method 1); m.p:156–158 °C; 1H NMR $\delta = 7.46$ (d, 2H, H_{arom}, $J = 8.6$ Hz), 7.43–7.38 (s br, 5H, H_{arom}), 7.1 (s, 1H, H-6), 5.05 (s, 2H, Ph-$\underline{CH_2}$).

4.4. *Synthesis of di-(3-oxo-6-aryl-4,5-dihydropyridazin)disulfides 7c, d and di-(3-oxo-6-arylpyridazin)disulfides 8c, d*

A solution of ethanol (50 ml) containing 3 mmol of **1c** (*10*) or **1d** (*9*) and hydrazine hydrate (2.5 mmol) was stirred at room temperature for 24 h (Method I) and/or heated for 30 min.

(Method II). The solid product from method I was filtered off, dried and recrystallized (cold chloroform/light petroleum) to give *di*-(3-oxo-6aryl-4,5-dihydro-pyridazin)disulfides **7c**, **d**. The product of Method II was filtered off, dried, and recrystallized (dioxane/toluene) to give *di*-(3-oxo-6-arylpyridazin)disulfides **8c**, **d**. The mother liquor of both methods was concentrated and left to cool providing 4-arylthio semicarbazide **9c**, **d** (*16, 17*).

4.4.1. *Di-(3-oxo-6-phenyl-4,5-dihydropyridazin)disulfides (7c)*

0.4 g (40% Method I), m.p: 150–152 °C. 1H NMR $\delta = 11.25$ (s, 1H, OH), 7.76–7.70 (m, 2H, H_{arom}), 7.44–7.4 (m, 3H, H_{arom}), 4.05 (dd, $1H_A$, $J_{AX} = 4.4$, $J_{AM} = 5.8$ Hz), 3.34 (dd, $1H_M$, $J_{MX} = 16.4$, $J_{AM} = 5.8$ Hz), 3.16 (dd, $1H_X$, $J_{MX} = 16.4$, $J_{AX} = 4.4$ Hz).

4.4.2. *Di-(3-oxo-6-(4-bromophenyl)-4,5-dihydropyridazin)disulfides (7d)*

0.44 g (44% Method I), m.p: 188–191 °C. 1H NMR: $\delta = 8.08$ (s, 1H, NH), 7.51 (s, 4H, H_{arom}), 4.48 (deformed t., $1H_A$, $J_{AX} = J_{AM} = 11.2$ Hz), 3.61 (dd, $1H_M$, $J_{MX} = 17.1$, $J_{AM} = 11.2$ Hz), 3.11 (dd, $1H_X$, $J_{MX} = 17.1$, $J_{AX} = 11.2$ Hz).

4.4.3. *Di-(3-oxo-6-phenylpyridazin)disulfides (8c)*

0.45 g (45% Method II), m.p: 188–190 °C. 1H NMR: $\delta = 13.58$ (s, 1H, NH), 7.87 (s 1H, $H_{olefinic}$), 7.78–7.74 (m, 2H, H_{arom}), 7.46–7.42 (m, 3H, H_{arom}).

4.4.4. *Di-(3-oxo-6-(4-bromophenyl)-pyridazin)disulfides (8c)*

0.43 g (43% Method II), m.p: 191 °C. 1H NMR: $\delta = 13.63$ (s, 1H, NH), 7.85 (s, 1H, $H_{olefinic}$), 7.76, 7.65 each, (d, 2H, $J = 8.6$ Hz, H_{arom}).

References

(1) Brown, F.C. *Chem. Rev*. **1961,** *61,* 463.
(2) Singh, S.P.; Parmers, S.S.; Raman, K.K.; Stenberg, V.I. *Chem. Rev*. **1981,** *81,* 175.
(3) Croxall, W.J.; Lo, C.P.; Shropshire, E.Y. *J. Am. Chem. Soc.* **1953,** *75,* 4519.
(4) Vladzimirskaya, E.V. *Zh. Obshch. Khim*. **1959,** *29,* 2795; Vladzimirskaya, E.V. *Chem. Abst*. **1960,** *54,* 10997c.
(5) Kitamura, R. *J. Pharm. Soc. Jpn*. **1938,** *58,* 804; Taniyama, H.; Hagiwara, K.; Okada, H.; Uchida, H. *Yakugaku Zasshi* **1957,** *77,* 1236; Taniyama, H.; Hagiwara, K.; Okada, H.; Uchida, H. *Chem. Abst*. **1958,** *52,* 6322.
(6) Suesse, M., Dehne, H. *Z. Chem*. **1975,** *15,* 303; Suesse, M., Dehne, H. *Chem. Abstr*. **1976,** *84,* 43923e.
(7) Omar, M.T.; Fouli, F.A.; EL-Garhi, M.Z. *Bull. Chem. Soc. Jpn*. **1991,** *64,* 750; Nagase, H. *Chem. Pharm. Bull*. **1974,** *22,* 1661.
(8) Taha, H.A., Soliman, M.I. *Int. J. Agri. Boil*. **2007,** *9,* 87.
(9) Omar, M.T.; EL-Aasar, N.K.; Saied, K.F. *Synthesis* **2001,** *3,* 413.
(10) Omar, M.T.; Youssef, A.S.A.; Kandeel, K.A. *Phosporus Sulfur Silicon* **2000,** *162,* 25.
(11) Kinugawa, J., Nagase, H. *Takeda Chemical Industries, Ltd. Japan* **1964,** *11,* 342; Kinugawa, J., Nagase, H. *Chem. Abstr*. **1966,** *65,* 13717e.
(12) Omar, M.T.; Kandeel, K.A.; Youssef, A.S.A. *Monatsh. Chem*. **1995,** *126,* 439.
(13) Brochmann, H., Knobloch, G. *Tetrahedron Lett.* **1970,** *11,* 267.
(14) Scheibye, S.; Kristensen, J.; Lawesson, S.O. *Tetrahedron* **1979,** *35,* 1339.
(15) Omar, M.T.; EL-Khamry, A.; Youssef, A.M.; Ramadan, S. *Sulfur Lett.* **2002,** *25,* 173.
(16) Bost, R.W., Smith, W.F. *J. Am. Chem. Soc.* **1931,** *53,* 652.
(17) Pulvermacher, G. *Ber* **1893,** *26,* 2821.