

2-Thioxopyrano[2,3-*d*][1,3]thiazoles by Diels-Alder reaction of arylidenerhodanines under microwave irradiation

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Dedicated on the occasion of the jubilee of academician Irina P. Beletskaya

Abstract

The cycloaddition reaction of 5-arylidene rhodanine derivatives with dienophiles under microwave irradiation afforded the title compounds within short reaction times and in good yields.

Keywords: Rhodanine, benzylidene rhodanines, dienophiles, cycloaddition, microwave irradiation

Introduction

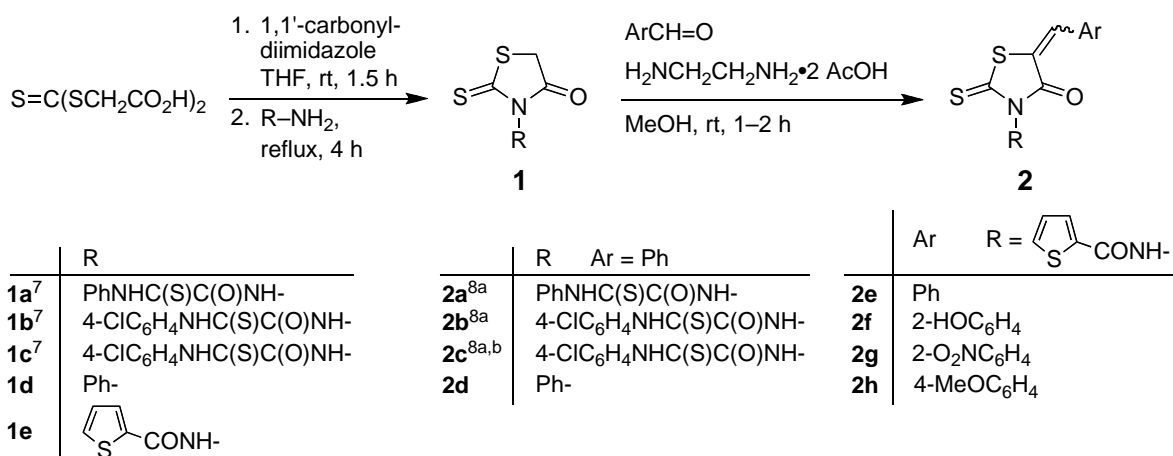
The chemistry of rhodanine and its derivatives has been studied for over half a century because of important chemical and biological applications. Rhodanine derivatives exhibit antibacterial, antiviral, anticonvulsant, antidiabetic and anti-HIV-1 activities,¹⁻⁴ and have been reported as uridine diphospho-*N*-acetylmuramate/L-alanine ligase inhibitors.⁵ Therefore, the synthesis of new rhodanine derivatives is of considerable interest.

Diels-Alder reactions of arylidenerhodanines are a convenient route to fused thiazoles. The reactions of 5-arylidene-1,3-thiazolidine-2,4-dithiones with dimethyl acetylenedicarboxylate (DMAD), maleic anhydride, maleimide, and acrylonitrile in acetic acid at room temperature have been reported to yield thiopyrano[2,3-*d*]thiazolidine-2-thiones.⁶

Results and Discussion

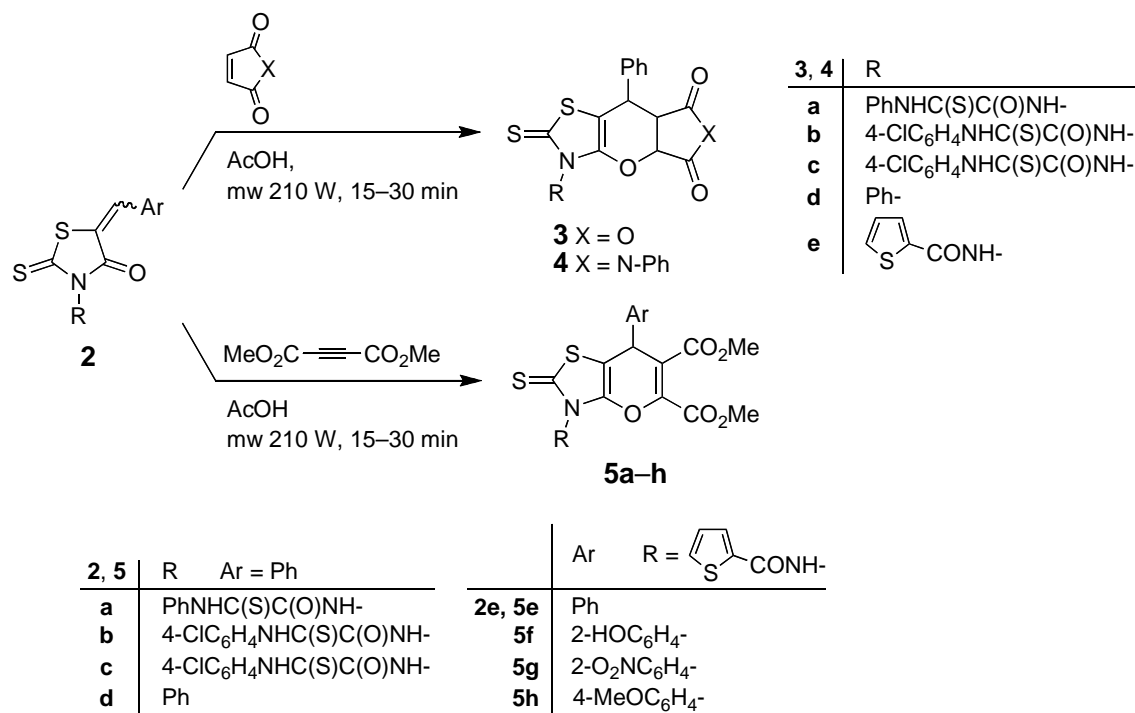
Recently we have reported a convenient method for the synthesis of rhodanines **1**. The reaction of amines, hydrazides, or oxamic acid thiohydrazides with trithiocarbonyldiglycolic acid in the

presence of carbonyldiimidazole affords *N*-substituted rhodanines **1**,⁷ which upon reaction with arylaldehydes form the corresponding arylidene derivatives **2** (Scheme 1).⁸



Scheme 1

We investigated the Diels-Alder reaction of arylidenerhodanines **2** with maleic anhydride, *N*-phenylmaleimide, and DMAD under various conditions: at room temperature, under reflux in various solvents (benzene, toluene, xylenes, acetic acid, acetic anhydride), and under high pressure (10–15 kbar) at various temperatures (from 20 to 150 °C). However, under these reaction conditions either the starting materials were recovered or tarry products were formed.



Scheme 2

The wide applicability of microwave irradiation for chemical reaction enhancement is due to high reaction rates, formation of cleaner products, and operational simplicity.^{9,10} A favorable effect of microwave irradiation on the formation of arylidenerhodanines in the course of the reaction of rhodanines with aromatic aldehydes has been noted previously.^{11,12} So far, microwave-induced cycloaddition reactions of 5-arylidenerhodanines have not been studied.

In fact, we found that the reactions of arylidenerhodanines **2a–e** with maleic anhydride, *N*-phenylmaleimide, and DMAD under 210 W microwave radiation smoothly formed the respective cycloaddition products **3**, **4**, and **5** within 15–30 min in 72–90% yield (Scheme 2).

In conclusion, we developed a facile synthesis of pyrano[2,3-*d*][1,3]thiazoles **3–5** resulting from the cycloaddition reaction of arylidenerhodanines **2** with some dienophiles. Employing microwave irradiation was crucial for the progress of this reaction and provided good yields of pyrano[2,3-*d*][1,3]thiazoles.

Experimental Section

General Procedures. ¹H and ¹³C NMR spectra were recorded on a Bruker AC-200 instrument in DMSO-*d*₆. Mass spectra were obtained with a Kratos instrument using a direct inlet system; the ionization energy was 70 eV, the accelerating voltage was 1.75 kV. Melting points were measured on a Boetius hot-stage apparatus. The reactions were carried out with a microwave oven (Rolsen MS1770SA, 700W) in sealed vessels without external cooling. The purity of the products was checked by TLC (Merck Kieselgel 60 F₂₅₄, EtOAc/hexane).

2-Thioxo-1,3-thiazolidin-4-ones (**1a–c**) have been reported previously;⁷ likewise, starting materials 5-arylidene-4-oxo-2-thioxo-1,3-thiazolidines **2a–c** have been prepared previously.^{8a,b}

2-Thioxo-1,3-thiazolidin-4-ones (**1d,e**). General procedure⁷

A solution of trithiocarbonyldiglycolic acid (0.24 g, 1 mmol) and carbonyldiimidazole (0.32 g, 2 mmol) in tetrahydrofuran (10 mL) was stirred at room temperature for 1.5 h. The appropriate amine or hydrazide (1 mmol) was added, and the reaction mixture was refluxed for 4 h. Then 2 M hydrochloric acid (30 mL) was added, and the mixture was extracted with ethyl acetate (4×15 mL). The organic phases were combined, dried with MgSO₄, and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc/hexane, 1:3 v/v).

3-Phenyl-2-thioxo-1,3-thiazolidin-4-one (1d). The reaction with aniline (93 mg, 1 mmol) furnished yellow crystals **1d** (0.19 g, 91%); mp 192–193 °C (EtOH/hexanes); R_f = 0.47 (EtOAc–hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 7.59–7.45 (m, 3H), 7.39 (d, *J* = 7.3 Hz, 2H), 4.41 (s, 2H). EI-MS: *m/z* (%) 209 (100, M⁺).

***N*-(4-Oxo-2-thioxo-1,3-thiazolidin-3-yl)thiophene-2-carboxamide (1e).** The reaction with 2-thiophenecarboxylic acid hydrazide (0.14 g, 1 mmol) furnished yellow crystals **1e** (0.22 g, 87%); mp 172–173 °C; R_f = 0.55 (EtOAc–hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 11.52 (s, 1H), 8.01–7.92 (m, 2H), 7.27 (t, *J* = 4.3 Hz, 1H), 4.51 (s, 2H). EI-MS: *m/z* (%) 258 [M⁺] (100).

3-Substituted-5-arylidene-2-thioxo-1,3-thiazolidin-4-ones (2d–h). General procedure⁸

A mixture of rhodanine **1** (1 mmol), araldehyde (1 mmol), and ethylenediammonium diacetate (18 mg, 0.1 mmol) in methanol (15 mL) was stirred at room temperature for 1–2 h. After evaporation of the solvent under reduced pressure, and the residue was purified by flash chromatography (silica gel, EtOAc/hexane, 1:3 v/v).

5-Benzylidene-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (2d). The reaction of **1d** (0.21 g, 1 mmol) with benzaldehyde (0.1 g, 1 mmol) furnished yellow crystals **2d** (0.28 g, 95%); mp 185–186 °C; $R_f = 0.69$ (EtOAc/hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 7.82 (s, 1H), 7.63–7.45 (m, 6H), 7.42–7.33 (m, 3H), 7.13 (t, $J = 7.3$ Hz, 1H). EI-MS: m/z (%) 297 (100, M⁺). Anal. calcd. for C₁₆H₁₁NOS₂: C, 64.62; H, 3.73; N, 4.71; S, 21.56. Found: C, 64.66; H, 3.65; N, 4.79; S, 21.50.

N-[5-Benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]thiophene-2-carboxamide (2e). The reaction of **1e** (0.25 g, 1 mmol) with benzaldehyde (0.1 g, 1 mmol) furnished yellow crystals **2e** (0.3 g, 87%); mp 167–168 °C; $R_f = 0.75$ (EtOAc/hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 10.51 (s, 1H), 8.05 (d, $J = 4.7$ Hz, 1H), 7.80 (s, 1H), 7.59 (t, $J = 7.3$ Hz, 2H), 7.51 (d, $J = 7.3$ Hz, 1H), 7.41 (t, $J = 4.1$ Hz, 1H), 7.29 (d, $J = 3.5$ Hz, 1H), 7.14 (t, $J = 7.3$ Hz, 1H). EI-MS: m/z (%) 346 (87, M⁺). Anal. calcd. for C₁₅H₁₀N₂O₂S₃: C, 52.00; H, 2.91; N, 8.09; S, 27.76. Found: C, 52.13; H, 2.83; N, 8.01; S, 27.79.

N-[5-(2-Hydroxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]thiophene-2-carboxamide (2f). The reaction of **1f** (0.25 g, 1 mmol) with salicylic aldehyde (0.1 g, 1 mmol) furnished yellow crystals **2f** (0.3 g, 87%); mp 193–194 °C; $R_f = 0.86$ (EtOAc–hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 10.21 (s, 1H), 9.08 (s, 1H), 8.03 (d, $J = 4.7$ Hz, 1H), 7.95 (s, 1H), 7.49–7.42 (m, 2H), 7.31–7.22 (m, 3H), 6.84 (d, $J = 7.7$ Hz, 1H). EI-MS: m/z (%) 362 (98, M⁺). Anal. calcd. for C₁₅H₁₀N₂O₃S₃: C, 49.71; H, 2.78; N, 7.73; S, 26.54. Found: C, 49.71; H, 2.62; N, 7.79; S, 26.55.

N-[5-(2-Nitrobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]thiophene-2-carboxamide (2g). The reaction of **1g** (0.25 g, 1 mmol) with 2-nitrobenzaldehyde (0.15 g, 1 mmol) furnished yellow crystals **2g** (0.31 g, 79%); mp 201–202 °C; $R_f = 0.72$ (EtOAc/hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 10.55 (s, 1H), 8.25 (d, $J = 7.9$ Hz, 1H), 8.09 (s, 1H), 8.01 (d, $J = 4.7$ Hz, 1H), 7.89–7.80 (m, 2H), 7.44 (t, $J = 4.1$ Hz, 1H), 7.26 (d, $J = 3.5$ Hz, 1H), 7.12 (t, $J = 7.6$ Hz, 1H). EI-MS: m/z (%) 391 (85, M⁺). Anal. calcd. for C₁₅H₉N₃O₄S₃: C, 46.03; H, 2.32; N, 10.73; S, 24.57. Found: C, 46.16; H, 2.27; N, 10.79; S, 24.62.

N-[5-(4-Methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]thiophene-2-carboxamide (2h). The reaction of **1h** (0.25 g, 1 mmol) with 4-methoxybenzaldehyde (0.14 g, 1 mmol) furnished yellow crystals **2h** (0.35 g, 92%); mp 177–178 °C (EtOH/hexanes); $R_f = 0.75$ (EtOAc/hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 10.52 (s, 1H), 8.02 (d, $J = 4.7$ Hz, 1H), 7.80 (s, 1H), 7.52–7.44 (m, 3H), 7.31–7.20 (m, 3H), 3.77 (s, 3H). EI-MS: m/z (%) 376 (88, M⁺). Anal. calcd. for C₁₆H₁₂N₂O₃S₃: C, 51.05; H, 3.21; N, 7.44; S, 25.55. Found: C, 51.15; H, 3.22; N, 7.38; S, 25.59.

2-Thioxopyrano[2,3-*d*][1,3]thiazoles (3 - 5). General procedure

5-Arylidenerhodanine **2** (0.1 mmol), dienophile (0.1 mmol), and acetic acid (2 mL) were mixed in a tightly closed tube with a heat-resistant lid. The tube was placed in a microwave oven and irradiated at 210 W for 15–30 min. The reaction mixture was cooled and poured into water (20 mL). The yellow precipitate formed was filtered off, washed with water and recrystallized from EtOH/hexanes mixtures.

2-[(5,7-Dioxo-8-phenyl-2-thioxo-4a,5,7a,8-tetrahydro-2*H*-furo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazol-3(7*H*)-yl)amino]-*N*-phenyl-2-thioxoacetamide (3a). The reaction of **2a**^{8a} (0.04 g, 0.1 mmol) with maleic anhydride (0.01 g, 0.1 mmol) furnished light yellow crystals **3a** (42 mg, 82%); mp 285–286 °C (EtOH/hexanes); *R*_f = 0.68 (EtOAc/hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 10.38 (s, 1H), 7.75–7.01 (m, 10H), 5.45 (d, *J* = 9.1 Hz, 1H), 4.83 (d, *J* = 6.2 Hz, 1H), 3.75–3.60 (m, 1H). ¹³C NMR (50 MHz, DMSO-*d*₆): δ 187.7, 174.6, 173.1, 170.6, 167.8, 148.3, 141.8, 140.9, 132.3, 127.9, 126.8, 125.0, 125.6, 121.7, 101.9, 79.6, 49.3, 39.5. EI-MS: *m/z* (%) 319 (48), 179 (32). Anal. calcd. for C₂₂H₁₅N₃O₅S₃: C, 53.11; H, 3.04; N, 8.44; S, 19.33. Found: C, 53.21; H, 3.00; N, 8.29; S, 19.48.

***N*-(4-Chlorophenyl)-2-[[5,7-dioxo-8-phenyl-2-thioxo-4a,5,7a,8-tetrahydro-2*H*-furo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazol-3(7*H*)-yl]amino]-2-thioxoacetamide (3b).** The reaction of **2b**^{8a} (43 mg, 0.1 mmol) with maleic anhydride (0.01 g, 0.1 mmol) furnished light yellow crystals **3b** (39 mg, 74%); mp 302–303 °C (EtOH/hexanes); *R*_f = 0.59 (EtOAc/hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 10.03 (s, 1H), 7.68–7.03 (m, 9H), 5.45 (d, *J* = 9.1 Hz, 1H), 4.65 (d, *J* = 6.2 Hz, 1H), 3.73–3.62 (m, 1H). ¹³C NMR (50 MHz, DMSO-*d*₆): δ 187.7, 174.6, 173.1, 170.6, 167.7, 148.3, 140.9, 138.9, 130.6, 129.6, 127.8, 126.8, 125.6, 121.2, 101.9, 79.6, 49.3, 39.5. EI-MS: *m/z* (%) 319 (53), 214 (41). Anal. calcd. for C₂₂H₁₄ClN₃O₅S₃: C, 49.67; H, 2.65; Cl, 6.66; N, 7.90; S, 18. Found: C, 53.35; H, 2.85; N, 8.15; S, 19.63.

2-[[5,7-Dioxo-8-phenyl-2-thioxo-4a,5,7a,8-tetrahydro-2*H*-furo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazol-3(7*H*)-yl]amino]-*N*-(4-methoxyphenyl)-2-thioxoacetamide (3c). The reaction of **2c**^{8a,b} (0.043 g, 0.1 mmol) with maleic anhydride (0.01 g, 0.1 mmol) furnished light yellow crystals **3c** (0.047 g, 89%); mp 257–258 °C (EtOH/hexanes); *R*_f = 0.71 (EtOAc/hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 10.67 (s, 1H), 7.68–6.92 (m, 9H), 5.35 (d, *J* = 9 Hz, 1H), 4.63 (d, *J* = 6.1 Hz, 1H), 3.75–3.61 (m, 1H), 3.75 (s, 3H). ¹³C NMR (50 MHz, DMSO-*d*₆): δ 187.9, 174.6, 173.1, 170.6, 173.06, 167.8, 156.1, 148.3, 140.9, 135.6, 127.8, 126.8, 125.6, 121.3, 116.7, 101.9, 79.7, 55.4, 49.3, 39.5. EI-MS: *m/z* (%) 319 (39), 210 (30). Anal. calcd. for C₂₃H₁₇N₃O₆S₃: C, 52.36; H, 3.25; N, 7.96; S, 18.23. Found: C, 52.49; H, 3.05; N, 7.80; S, 18.46.

3,8-Diphenyl-2-thioxo-3,4a,7a,8-tetrahydro-2*H*-furo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazole-5,7-dione (3d). The reaction of **2d** (0.03 g, 0.1 mmol) with maleic anhydride (0.01 g, 0.1 mmol) furnished light yellow crystals **3d** (35 mg, 90%); mp 237–238 °C (EtOH/hexanes); *R*_f = 0.50 (EtOAc–hexane, 1:1 v/v). ¹H NMR (200 MHz, DMSO-*d*₆): δ 7.88–7.01 (m, 10H), 5.23 (d, *J* = 8.9 Hz, 1H), 4.75 (d, *J* = 6 Hz, 1H), 3.85–3.68 (m, 1H). ¹³C NMR (50 MHz, DMSO-*d*₆): δ 185.3, 174.8, 171.2, 151.7, 142.9, 140.9, 129.9, 128.2, 126.3, 125.2, 123.1, 120.2, 97.6, 78.6, 49.3, 37.5.

EI-MS: m/z (%) 395 (74, M^+). Anal. calcd. for $C_{20}H_{13}NO_4S_2$: C, 60.75; H, 3.31; N, 3.54; S, 16.22. Found: C, 60.91; H, 3.25; N, 3.43; S, 16.38.

***N*-(5,7-Dioxo-8-phenyl-2-thioxo-4a,5,7a,8-tetrahydro-2*H*-furo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazol-3(7*H*)-yl)thiophene-2-carboxamide (3e).** The reaction of **2e** (35 mg, 0.1 mmol) with maleic anhydride (0.01 g, 0.1 mmol) furnished light yellow crystals **3e** (37 mg, 83%); mp 268–269 °C (EtOH/hexanes); R_f = 0.50 (EtOAc/hexane, 1:1 v/v). 1H NMR (200 MHz, DMSO- d_6): δ 9.89 (s, 1H), 7.91–7.05 (m, 8H), 5.15 (d, J = 9 Hz, 1H), 4.83 (d, J = 6.1 Hz, 1H), 3.78–3.65 (m, 1H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 182.4, 174.7, 171.2, 158.3, 154.2, 139.9, 139.2, 137.7, 128.9, 127.1, 126.8, 125.3, 124.8, 103.9, 76.4, 49.3, 36.2. EI-MS: m/z (%) 444 (57, M^+). Anal. calcd. for $C_{20}H_{14}N_2O_5S_2$: C, 56.33; H, 3.31; N, 6.57; S, 15.04. Found: C, 56.30; H, 3.21; N, 6.42; S, 15.28.

2-[(5,7-Dioxo-6,8-diphenyl-2-thioxo-4a,5,6,7,7a,8-hexahydropyrrolo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazol-3(2*H*)-yl)amino]-*N*-phenyl-2-thioxoacetamide (4a). The reaction of **2a**⁸ (0.04 g, 0.1 mmol) with *N*-phenylmaleimide (17 mg, 0.1 mmol) furnished light yellow crystals **4a** (49 mg, 86%); mp 271–272 °C (EtOH/hexanes); R_f = 0.55 (EtOAc/hexane, 1:1 v/v). 1H NMR (200 MHz, DMSO- d_6): δ 10.25 (s, 1H), 7.76–6.82 (m, 15H), 5.38 (d, J = 9.1 Hz, 1H), 4.74 (d, J = 6 Hz, 1H), 4.29–4.05 (m, 1H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 187.2, 174.5, 172.9, 168.5, 167.7, 147.2, 143.2, 141.2, 133.7, 132.2, 129.4, 128.6, 128.2, 126.8, 126.2, 125.7, 124.9, 121.8, 101.0, 87.7, 51.5, 41.6. EI-MS: m/z (%) 394 (25), 179 (37). Anal. calcd. for $C_{28}H_{20}N_4O_4S_3$: C, 58.73; H, 3.52; N, 9.78; S, 16.80. Found: C, 58.89; H, 3.41; N, 9.62; S, 16.95.

***N*-(4-Chlorophenyl)-2-[(5,7-dioxo-6,8-diphenyl-2-thioxo-4a,5,6,7,7a,8-hexahydropyrrolo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazol-3(2*H*)-yl)amino]-2-thioxoacetamide (4b).** The reaction of **2b**⁸ (43 mg, 0.1 mmol) with *N*-phenylmaleimide (17 mg, 0.1 mmol) furnished light yellow colored crystals **4b** (0.048 g, 80%) after recrystallization; mp 292–293 °C (EtOH/hexanes); R_f = 0.50 (EtOAc/hexane, 1:1 v/v). 1H NMR (200 MHz, DMSO- d_6): δ 10.45 (s, 1H), 7.78–7.05 (m, 14H), 5.46 (d, J = 9.0 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.15–4.02 (m, 1H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 187.5, 174.4, 173.1, 168.3, 167.7, 147.0, 143.4, 138.8, 133.7, 130.7, 129.6, 129.2, 128.6, 128.2, 126.9, 126.2, 124.9, 121.2, 100.7, 87.6, 51.6, 41.6. EI-MS: m/z (%) 394 (37), 214 (46). Anal. calcd. for $C_{28}H_{19}ClN_4O_4S_3$: C, 55.39; H, 3.15; Cl, 5.84; N, 9.23; S, 15.84. Found: C, 55.55; H, 3.10; Cl, 5.70; N, 9.11; S, 16.01.

2-[(5,7-Dioxo-6,8-diphenyl-2-thioxo-4a,5,6,7,7a,8-hexahydropyrrolo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazol-3(2*H*)-yl)amino]-*N*-(4-methoxyphenyl)-2-thioxoacetamide (4c). The reaction of **2c**^{8a,b} (43 mg, 0.1 mmol) with *N*-phenylmaleimide (17 mg, 0.1 mmol) furnished light yellow crystals **4c** (47 mg, 78%); mp 267–268 °C (EtOH/hexanes); R_f = 0.55 (EtOAc/hexane, 1:1 v/v). 1H NMR (200 MHz, DMSO- d_6): δ 10.55 (s, 1H), 7.68–6.82 (m, 14H), 5.37 (d, J = 9.0 Hz, 1H), 4.65 (d, J = 6 Hz, 1H), 4.29–4.05 (m, 1H), 3.75 (s, 3H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 187.4, 174.5, 173.2, 168.4, 167.7, 156.1, 147.2, 143.3, 135.7, 133.7, 129.2, 128.6, 128.3, 126.8, 126.4, 124.9, 121.3, 116.7, 100.6, 87.6, 55.4, 51.6, 41.5. EI-MS: m/z (%) 409 (15), 210 (25). Anal. calcd. for $C_{29}H_{22}N_4O_5S_3$: C, 57.79; H, 3.68; N, 9.30; S, 15.96. Found: C, 57.92; H, 3.52; N, 9.19; S, 16.10.

3,6,8-Triphenyl-2-thioxo-3,4a,7a,8-tetrahydropyrrolo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazole-5,7(2*H*,6*H*)-dione (4d). The reaction of **2d** (0.03 g, 0.1 mmol) with *N*-phenylmaleimide (17 mg, 0.1 mmol) furnished light yellow crystals **4d** (0.04 g, 86%); mp 229–230 °C (EtOH/hexanes); R_f = 0.50 (EtOAc/hexane, 1:1 v/v). ^1H NMR (200 MHz, DMSO- d_6): δ 7.78–6.92 (m, 15H), 5.23 (d, J = 8.9 Hz, 1H), 4.37 (d, J = 6.1 Hz, 1H), 4.28–4.12 (m, 1H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 183.2, 174.6, 170.9, 150.9, 143.2, 142.8, 132.9, 129.9, 129.2, 128.9, 128.5, 126.8, 125.6, 124.9, 122.8, 119.8, 96.9, 86.2, 51.5, 38.3. EI-MS: m/z (%) 470 (63, M^+). Anal. calcd. for $\text{C}_{26}\text{H}_{18}\text{N}_2\text{O}_3\text{S}_2$: C, 66.36; H, 3.86; N, 5.95; S, 13.63. Found: C, 66.48; H, 3.75; N, 6.01; S, 13.75.

***N*-(5,7-Dioxo-6,8-diphenyl-2-thioxo-4a,5,6,7,7a,8-hexahydropyrrolo[3',4':5,6]pyrano[2,3-*d*][1,3]thiazol-3(2*H*)-yl)thiophene-2-carboxamide (4e).** The reaction of **2e** (35 mg, 0.1 mmol) with *N*-phenylmaleimide (17 mg, 0.1 mmol) furnished light yellow crystals **4e** (41 mg, 79%); mp 310–311 °C (EtOH/hexanes); R_f = 0.52 (EtOAc/hexane, 1:1 v/v). ^1H NMR (200 MHz, DMSO- d_6): δ 9.82 (s, 1H), 8.05–6.92 (m, 13H), 5.25 (d, J = 8.8 Hz, 1H), 4.62 (d, J = 6.1 Hz, 1H), 4.19–4.01 (m, 1H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 183.1, 174.7, 170.9, 158.4, 153.9, 142.3, 139.3, 137.7, 133.7, 129.5, 128.9, 128.5, 127.6, 126.7, 126.3, 125.2, 124.7, 103.8, 83.3, 51.7, 37.3. EI-MS: m/z (%) 519 (25, M^+). Anal. calcd. for $\text{C}_{25}\text{H}_{17}\text{N}_3\text{O}_4\text{S}_3$: C, 57.79; H, 3.30; N, 8.09; S, 18.51. Found: C, 57.91; H, 3.25; N, 8.19; S, 18.67.

Dimethyl 3-[(2-anilino-2-oxoethanethiyl)amino]-7-phenyl-2-thioxo-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-5,6-dicarboxylate (5a). The reaction of **2a**⁸ (0.04 g, 0.1 mmol) with DMAD (14 mg, 0.1 mmol) furnished light yellow crystals **5a** (43 mg, 81%); mp 182–183 °C (EtOH/hexanes); R_f = 0.63 (EtOAc/hexane, 1:1 v/v). ^1H NMR (200 MHz, DMSO- d_6): δ 10.33 (s, 1H), 7.97–7.02 (m, 10H), 4.66 (s, 1H), 3.87 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 187.3, 167.9, 166.2, 163.3, 159.9, 144.9, 143.2, 142.4, 141.1, 132.4, 130.3, 129.5, 125.7, 123.3, 121.8, 118.1, 96.8, 52.4, 51.6, 42.2. EI-MS: m/z (%) 363 (32), 179 (46). Anal. calcd. for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_6\text{S}_3$: C, 53.03; H, 3.89; N, 7.73; S, 17.69. Found: C, 53.21; H, 3.72; N, 7.61; S, 17.80.

Dimethyl 3-[2-[(4-chlorophenyl)amino]-2-oxoethanethiyl]amino-7-phenyl-2-thioxo-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-5,6-dicarboxylate (5b). The reaction of **2b**⁸ (43 mg, 0.1 mmol) with DMAD (14 mg, 0.1 mmol) furnished light yellow crystals **5b** (43 mg, 76%); mp 204–206 °C (EtOH/hexanes); R_f = 0.60 (EtOAc/hexane, 1:1 v/v). ^1H NMR (200 MHz, DMSO- d_6): δ 10.3 (s, 1H), 7.86–7.01 (m, 9H), 4.55 (s, 1H), 3.85 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 187.2, 167.8, 166.2, 163.3, 159.9, 144.9, 143.2, 142.4, 138.9, 130.7, 130.1, 129.7, 129.3, 123.3, 121.3, 118.1, 96.8, 52.4, 51.6, 42.2. EI-MS: m/z (%) 363 (41), 214 (25). Anal. calcd. for $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_6\text{S}_3$: C, 49.87; H, 3.49; Cl, 6.13; N, 7.27; S, 16.64. Found: C, 49.80; H, 3.35; Cl, 5.96; N, 7.35; S, 16.78.

Dimethyl 3-[2-[(4-methoxyphenyl)amino]-2-oxoethanethiyl]amino-7-phenyl-2-thioxo-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-5,6-dicarboxylate (5c). The reaction of **2c**^{8a,b} (43 mg, 0.1 mmol) with DMAD (14 mg, 0.1 mmol) furnished light yellow crystals **5c** (41 mg, 72%); mp 155–156 °C (EtOH/hexanes); R_f = 0.65 (EtOAc/hexane, 1:1 v/v). ^1H NMR (200 MHz, DMSO- d_6): δ 10.63 (s, 1H), 7.75–6.82 (m, 9H), 4.55 (s, 1H), 3.76–3.65 (s, 9H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 187.4, 167.9, 166.2, 163.3, 159.9, 156.3, 144.9, 143.2, 142.4, 135.7, 130.2, 129.6,

123.3, 121.3, 118.2, 116.7, 96.8, 55.5, 52.4, 51.6, 42.2. EI-MS: m/z (%) 363 (33), 210 (29). Anal. calcd. for $C_{25}H_{23}N_3O_7S_3$: C, 52.34; H, 4.04; N, 7.32; S, 16.77. Found: C, 52.52; H, 3.88; N, 7.20; S, 16.90.

Dimethyl 3,7-diphenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-*d*][1,3]thiazole-5,6-dicarboxylate (5d). The reaction of **2d** (0.03 g, 0.1 mmol) with DMAD (14 mg, 0.1 mmol) furnished light yellow crystals **5d** (0.034 g, 78%); mp 215–216 °C (EtOH/hexanes); R_f = 0.65 (EtOAc/hexane, 1:1 v/v). 1H NMR (200 MHz, DMSO- d_6): δ 7.79–7.01 (m, 10H), 4.55 (s, 1H), 3.75 (s, 3H), 3.62 (s, 3H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 183.5, 166.2, 164.7, 146.4, 145.2, 143.1, 139.8, 130.9, 129.9, 129.2, 123.9, 122.6, 120.8, 120.1, 92.6, 52.5, 51.6, 40.9. EI-MS: m/z (%) 439 (75, M^+). Anal. calcd. for $C_{22}H_{19}NO_5S_2$: C, 59.85; H, 4.34; N, 3.17; S, 14.52. Found: C, 59.99; H, 4.23; N, 3.07; S, 14.64.

Dimethyl 7-phenyl-3-[(2-thienylcarbonyl)amino]-2-thioxo-3,7-dihydro-2H-pyrano[2,3-*d*][1,3]thiazole-5,6-dicarboxylate (5e). The reaction of **2e** (35 mg, 0.1 mmol) with DMAD (14 mg, 0.1 mmol) furnished light yellow crystals **5e** (0.04 g, 82%); mp 257–258 °C (EtOH/hexanes); R_f = 0.63 (EtOAc/hexane, 1:1 v/v). 1H NMR (200 MHz, DMSO- d_6): δ 9.37 (s, 1H), 8.15 (d, J = 4.5 Hz, 1H), 7.45–7.31 (m, 3H), 7.25–7.1 (m, 2H), 7.0 (d, J = 6.9 Hz, 1H) 4.62 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 184.1, 166.2, 163.8, 159.9, 148.9, 143.8, 138.7, 137.6, 137.1, 129.9, 129.4, 128.9, 124.9, 123.3, 118.2, 99.6, 52.4, 51.6, 38.9. EI-MS: m/z (%) 488 (38, M^+). Anal. calcd. for $C_{21}H_{16}N_2O_6S_3$: C, 51.63; H, 3.30; N, 5.73; S, 19.69. Found: C, 51.80; H, 3.25; N, 5.60; S, 19.82.

Dimethyl 7-(2-hydroxyphenyl)-3-[(2-thienylcarbonyl)amino]-2-thioxo-3,7-dihydro-2H-pyrano[2,3-*d*][1,3]thiazole-5,6-dicarboxylate (5f). The reaction of **2f** (36 mg, 0.1 mmol) with DMAD (14 mg, 0.1 mmol) furnished light yellow crystals **5f** (31 mg, 62%); mp 273–274 °C (EtOH/hexanes); R_f = 0.60 (EtOAc/hexane, 1:1 v/v). 1H NMR (200 MHz, DMSO- d_6): δ 10.35 (s, 1H), 9.23 (s, 1H), 8.15 (d, J = 4.7 Hz, 1H), 7.45 (t, J = 4.8 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 3.55 Hz, 1H), 7.03 (t, J = 8.0 Hz, 2H), 6.80 (d, J = 8.3 Hz, 1H), 4.65 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 184.2, 166.2, 163.7, 159.7, 155.8, 148.9, 138.6, 137.6, 137.1, 129.9, 128.9, 127.7, 126.8, 124.8, 124.3, 119.1, 118.0, 100.1, 52.1, 51.6, 30.4. EI-MS: m/z (%) 504 (15, M^+). Anal. calcd. for $C_{21}H_{16}N_2O_7S_3$: C, 49.99; H, 3.20; N, 5.55; S, 19.06. Found: C, 50.12; H, 3.28; N, 5.42; S, 19.26.

Dimethyl 7-(2-nitrophenyl)-3-[(2-thienylcarbonyl)amino]-2-thioxo-3,7-dihydro-2H-pyrano[2,3-*d*][1,3]thiazole-5,6-dicarboxylate (5g). The reaction of **2g** (39 mg, 0.1 mmol) with DMAD (14 mg, 0.1 mmol) furnished light yellow crystals **5g** (0.03 g, 57%); mp 287–288 °C (EtOH/hexanes); R_f = 0.62 (EtOAc/hexane, 1:1 v/v). 1H NMR (200 MHz, DMSO- d_6): δ 9.22 (s, 1H), 8.02 (d, J = 4.7 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 4.1 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 7.13 (t, J = 8.1 Hz, 1H) 4.83 (s, 1H), 3.85 (s, 6H), 3.70 (s, 3H). ^{13}C NMR (50 MHz, DMSO- d_6): δ 184.2, 166.2, 163.4, 159.7, 149.1, 148.7, 143.9, 138.6, 137.7, 137.3, 134.4, 131.4, 128.9, 126.9, 124.8, 122.5, 119.8, 101.1, 52.3, 51.5, 35.7. EI-MS: m/z (%) 533 (31, M^+). Anal. calcd. for $C_{21}H_{15}N_3O_8S_3$: C, 47.27; H, 2.83; N, 7.88; S, 18.03. Found: C, 47.37; H, 2.75; N, 7.99; S, 18.17.

Dimethyl 7-(4-methoxyphenyl)-3-[(2-thienylcarbonyl)amino]-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-5,6-dicarboxylate (5h). The reaction of **2h** (38 mg, 0.1 mmol) with DMAD (14 mg, 0.1 mmol) furnished light yellow crystals **5h** (0.039 g, 68%); mp 287–288 °C (EtOH/hexanes); $R_f = 0.65$ (EtOAc/hexane, 1:1 v/v). $^1\text{H NMR}$ (200 MHz, DMSO- d_6): δ 9.32 (s, 1H), 8.05 (d, $J = 4.7$ Hz, 1H), 7.45 (t, $J = 4.6$ Hz, 1H), 7.23 (d, $J = 3.6$ Hz, 1H), 7.15 (d, $J = 8.2$ Hz, 2H), 6.93 (d, $J = 8.2$ Hz, 2H), 4.82 (s, 1H), 3.85 (s, 6H), 3.70 (s, 3H). $^{13}\text{C NMR}$ (50 MHz, DMSO- d_6): δ 184.2, 166.1, 163.2, 159.8, 148.9, 138.6, 137.7, 137.2, 135.6, 127.6, 124.9, 118.2, 117.1, 99.7, 55.3, 52.4, 51.6, 37.9. EI-MS: m/z (%) 518 (40, M^+). Anal. calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_7\text{S}_3$: C, 50.95; H, 3.50; N, 5.40; S, 18.55. Found: C, 51.12; H, 3.61; N, 5.31; S, 18.60.

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