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Three-Component, One-Flask Synthesis of Rhodanines (Thiazolidinones)

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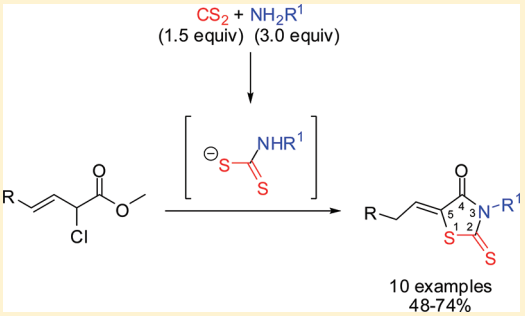
Supporting Information

ABSTRACT: 5-(*Z*)-Alkylidene-2-thioxo-1,3-thiazolidin-4-ones (rhodanine derivatives) were prepared by reaction of in situ generated dithiocarbamates with recently reported racemic α-chloro-β,γ-alkenoate esters. This multicomponent sequential transformation performed in one reaction flask represents a general route to this medicinally valuable class of sulfur/nitrogen heterocycles. Using this convergent procedure, we prepared an analogue of the drug epalrestat, an aldose reductase inhibitory rhodanine.



Sequentially linking several different components in one reaction vessel has been studied intensively as a rapid way to increase molecular complexity while avoiding costly and environmentally unfriendly isolation and purification of intermediates.[1−4] Such efficient multicomponent reactions, such as the Ugi reaction,[5] often produce privileged scaffolds of considerable medicinal value. Rhodanines (2-thioxo-1,3-thiazolidin-4-ones) are five-membered ring sulfur/nitrogen heterocycles some of which have antimalarial, antibacterial, antifungal, antiviral, antitumor, anti-inflammatory, or herbicidal activities.[6]

5-*Arylidene* rhodanines are common,[7−14] whereas 5-*alkylidene* rhodanines are rare.[15−17] In one direct comparison, 5-alkylidene rhodanine **A** was more potent as a class C β-lactamase inhibitor than the corresponding vinylogous 5-arylidene rhodanine **B** (Figure 1).[16]

Three-component, one-flask preparation of 5-arylidene rhodanines from aryl propiolates and dithiocarbamates has been reported,[18] as well as three-component preparation of 5-hydrazinoalkylidene rhodanines,[19] 5-acyl rhodanines,[20] 5-carboxymethyl rhodanines,[21] and 2-amino 4-thiazolones[22] and also two-component rhodanine syntheses.[23] 5-Alkylidenation of rhodanine-3-acetic acid at 75−100 °C has been achieved.[15] 5-Alkylidenation of 3-NH rhodanine, however, proceeds in only 11−19% yields.[17] We report here a synthetic approach to these heterocycles involving three-component, one-flask, sequential 1 + 2 + 2 atom construction of five-membered ring 5-alkylidene rhodanines **3**−**5** (Scheme 1). Our multicomponent protocol involves amine addition to carbon disulfide followed in situ by exclusive S_N2 displacement of chloride from recently reported α,β,γ-trifunctional ester allylic chloride **2**, carbon−carbon double bond isomerization into conjugation with the ester group (β,γ-enoate → α,β-enoate), and finally 5-*exo*-*trig*[24] cyclization to produce 5-(*Z*)-alkylidene rhodanines **3**−**5** in 48−74% yields with diverse R and R^1 groups (Scheme 1).

We recently described gram scale synthesis and various transformations of versatile and diverse α-chloro-β,γ-alkenoate esters **2**, with R groups including benzyl, *n*-pentyl, cyclohexyl, 9-nonenyl, and 4-benzyloxybutyl, prepared from γ-selenyl α,β-enoate esters **1** (Scheme 1).[25−27] A new transformation of multifunctional enoate esters **2**, occurring in 2-propanol solvent under mild (25 °C) conditions, produces various 5-alkylidene rhodanine derivatives typically favoring *Z* over *E* olefins by 30:1 to 7:1 ratios; routine silica gel column chromatography afforded the pure 5-(*Z*)-alkylidene rhodanines in the yields shown in Scheme 1. The (*Z*)-geometry of the 5-alkylidene rhodanines **3**−**5** is consistent with literature analogies[28−31] and was confirmed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of the crude reaction mixtures contained two distinct triplets for the single olefinic proton, the major triplet at 6.98−7.02 ppm and the minor triplet at 6.47−6.52 ppm. These ^{1}H NMR data are consistent with the *Z*-isomer olefinic proton being further downfield than the *E*-isomer olefinic proton, because of deshielding from the carbonyl group.[28−31]

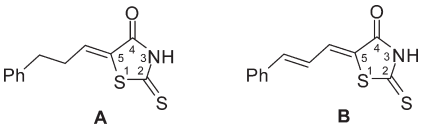


Figure 1. 5-Alkylidene rhodanine **A** and vinylogous 5-arylidene rhodanine **B**.

The second step in this one-flask process is an S_N2 displacement of chloride by in situ generated dithiocarbamate; in a closely related system we have isolated some of the uncyclized S_N2 product with β,γ-unsaturation. Next, probably excess amine induces migration of the β,γ-carbon−carbon double bond into

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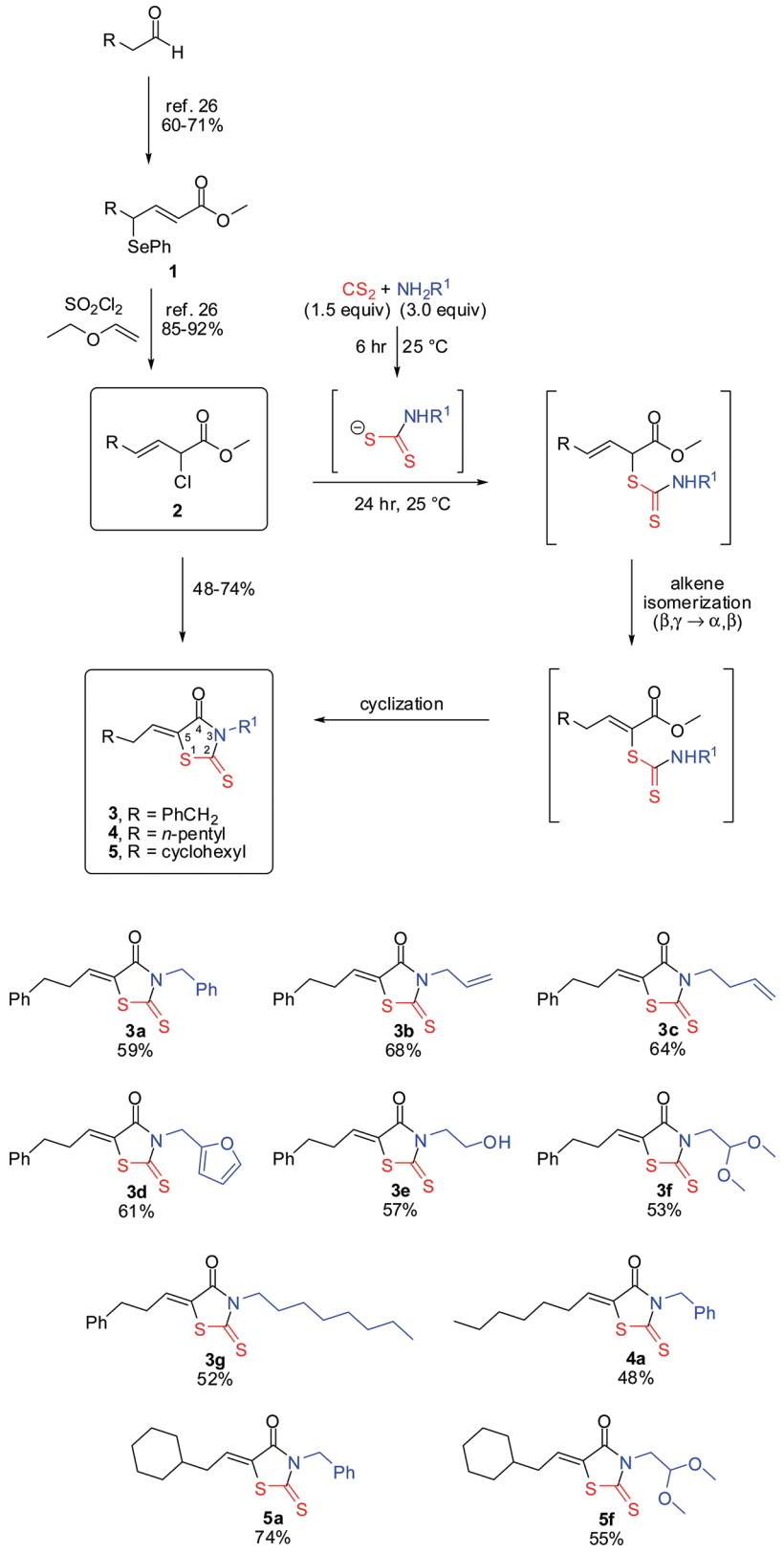
Scheme 1. Formation of 5-(*Z*)-Alkylidene Rhodanines 3−5



conjugation with the ester group, forcing the dithiocarbamate nitrogen atom and the ester carbonyl group into close proximity, thereby assisting cyclization into lactams **3**−**5**.

We have successfully achieved synthesis of rhodanine **3e** on a 250 mg scale. Various simple as well as functionalized (olefinic, alcoholic, acetal, and furyl) commercial primary amines

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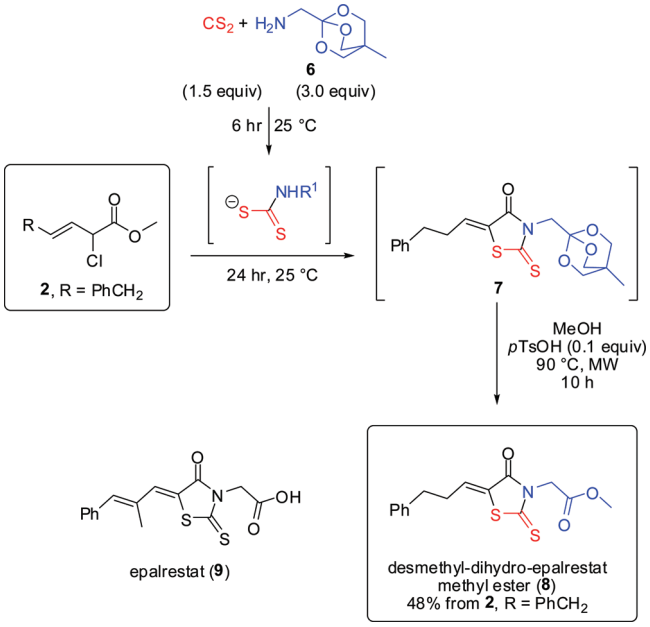
Scheme 2. Synthesis of Desmethyl-dihydro-epalrestat Methyl Ester 8



(although not less nucleophilic anilines)[32] participated in forming the rhodanines **3**−**5** shown in Scheme 1. Several amines failed to produce rhodanines via Scheme 1, including propargylamine, aminoacetonitrile, 2-(aminomethyl)pyridine, 6-aminohexanoic acid, glycine, and glycine ethyl ester.

Primary amine orthoester **6**[33] was utilized to give fragile rhodanine orthoester **7**, which was treated immediately with methanol and a catalytic amount of *p*-toluenesulfonic acid (Scheme 2). In this three-component, one-flask protocol, the desired desmethyl-dihydro-epalrestat methyl ester **8** was produced chromatographically pure in 48% yield as a close analogue of the aldose inhibitory drug epalrestat (**9**).[34,35] Short syntheses of carboxylic acid analogues of methyl ester **8**, although not of epalrestat, have been reported.[15]

In conclusion, convergent syntheses of *N*-alkyl 5-(*Z*)-alkylidene rhodanine derivatives have been achieved using recently reported racemic α-chloro-β,γ-alkenoate ester **2** building blocks.[27] The formation of these rhodanine derivatives involves a three-step, one-flask protocol that provides quick access to biologically valuable sulfur−nitrogen heterocycles. The method is mild and versatile, working successfully with a variety of simple as well as functionalized primary amines and with several different α-chloro esters **2**,[26,27] allowing preparation of a small library of new *N*-alkyl 5-alkylidene rhodanines.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using the residual solvent peak as the internal standard. FAB mass spectra were obtained using a double focusing magnetic sector mass spectrometer equipped with a Cs ion gun (28 kV @ 2 μA), an off-axis electron multiplier and an MSS data system. The resolution of the instrument was set at 10,000 (100 ppm peak width). Samples were mixed with *m*-nitrobenzyl-alcohol matrix deposited on the target of a direct insertion probe for introduction into the source. Spectra were acquired under control of the data system. Nominal mass scan spectra were acquired with a mass scan range of 10−1000 amu using a magnet scan rate of 25 s/dec. For accurate mass measurements, a narrower mass scan range was employed, with the matrix containing 10% PEG or PEGMME mass calibrant. Fourier transform-infrared (FT-IR) experiments were obtained from 4000 to 600 cm^{-1}. Microwave reactions were run sealed tubes in a Biotage Initatior with an external contact temperature probe. Thin-layer chromatography was performed with glass-backed 20 cm × 20 cm extra-hard layer 250 μm thickness 60 Å plates with F_{254} indicator cut down to 20 mm × 50 mm for analytical purposes. Compounds purified via preparative TLC were performed with glass-backed 20 cm × 20 cm extra-hard layer 1000 μm thickness 60 Å plates with F_{254} indicator.

(±)-Seleno Acrylate 1 (R = Cyclohexyl). An oven-dried, single-necked 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with dichloromethane (10 mL), DL-proline (0.07 g, 0.57 mmol, 0.2 equiv), and 2-cyclohexylacetaldehyde (0.36 g, 2.84 mmol, 1.0 equiv) and was allowed to stir at room temperature under argon. After 10 min, *N*-(phenylseleno)phthalimide (1.00 g, 3.11 mmol, 1.1 equiv) was added and allowed to stir at room temperature under argon. After 2 h, hexanes (15 mL) were added, and the slurry was gravity filtered and concentrated into a 50-mL round-bottomed flask on a rotary evaporator. The resultant seleno-aldehyde was dissolved in THF (10 mL), and methyl (triphenylphosphoranylidene)acetate (1.23 g, 3.68 mmol, 1.3 equiv) was added to the flask. The solution was allowed to stir at room temperature under argon. After 16 h, the reaction was quenched with NH_4Cl (20 mL), extracted with diethyl ether (3 × 25 mL), dried over $MgSO_4$, gravity filtered, and concentrated on a rotary evaporator. The yellow oil was purified via column chromatography (hexanes flush of initial yellow band followed by 50:1, hexanes/ethyl acetate) to afford the desired product (**1**) as a yellow oil (0.55 g, 1.70 mmol, 60%). IR (thin film) 3056, 2926, 2852, 1722, 1644, 1578, 1476, 1436, 1331, 1310, 1268, 1233, 1216, 1199, 1171, 1143, 1073, 1036, 1021, 978, 910, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2H), 7.30−7.21 (m, 3H), 6.91 (dd, J = 15.6, 11.2 Hz, 1H), 5.15 (d, J = 15.6 Hz, 1H), 3.65 (s, 3H), 3.54 (dd, J = 11.2, 7.6 Hz, 1H), 2.01 (d, J = 12.8 Hz, 1H), 1.79−1.69 (m, 3H), 1.60−1.69 (m, 2H), 1.28−1.05 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 146.7, 136.2, 128.9, 128.7, 128.2, 119.1, 54.4, 51.4, 41.5, 32.1, 31.4, 26.2, 26.2, 26.1. HRMS (FAB) m/z calcd for $C_{17}H_{23}O_2Se$ [M + H$^+$] 339.0863, found 339.0852.

(±)-α-Chloro Ester 2 (R = Cyclohexyl). An oven-dried, single-necked 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with seleno-acrylate **1** (0.48 g, 1.42 mmol, 1.0 equiv), hexanes (3 mL), and ethyl vinyl ether (4.85 mL, 50.6 mmol, 6.0 equiv). Sulfuryl chloride (0.23 mL, 2.84 mmol, 2.0 equiv) was added dropwise as a solution in hexanes (7 mL) over 30 min, and the reaction was allowed to stir at room temperature under argon. After 30 min TLC analysis confirmed completion of reaction, the solution was concentrated on a rotary evaporator, and the dark oil was purified immediately via column chromatography (1% ethyl acetate in hexanes) to afford the desired product (**2**) as a colorless oil (0.28 g, 1.30 mmol, 92%). IR (thin film) 2926, 2852, 2360, 1748, 1653, 1558, 1436, 1270, 1160, 967, 664 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dd, J = 15.6, 6.4 Hz, 1H), 5.59 (ddd, J = 14.8, 8.4, 0.8 Hz, 1H), 4.71 (d, 8.8 Hz, 1H), 3.74 (s, 3H), 2.03−1.92 (m, 1H), 1.74−1.65 (m, 4H), 1.58−1.65 (m, 1H), 1.29−0.99 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 143.5, 122.2, 58.1, 52.9, 40.2, 32.2, 32.1, 25.9, 25.8. HRMS (FAB) m/z calcd for $C_{11}H_{18}ClO_2$ [M + H$^+$] 217.0995, found 217.0996.

General Procedure for Synthesis of 5-(*Z*)-Alkylidine Rhodanines 3−5. An oven-dried, 2 dram vial, equipped with a magnetic stir bar, under a stream of argon through a needle was charged with carbon disulfide (0.17 mmol, 1.5 equiv), amine (0.33 mmol, 3.0 equiv), and 2-propanol (1.0 mL) and was stirred at room temperature under argon. After 6 h, α-chloro ester **2** (0.11 mmol, 1.0 equiv) was added as a solution in 2-propanol (0.5 mL), and the reaction was allowed to stir at

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room temperature under argon. After 24 h, the reaction was quenched with saturated ammonium chloride (1 mL) and extracted with diethyl ether (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, gravity filtered, and concentrated on a rotary evaporator. The crude mixtures were purified via silica gel column chromatography (5% ethyl acetate in hexanes) or alternatively via preparative silica TLC (5% ethyl acetate in hexanes).

Rhodanine 3a. 22.0 mg, 59% yield as a yellow oil. IR (thin film) 3062, 3029, 2926, 2857, 2368, 2345, 2092, 1717, 1628, 1603, 1495, 1454, 1425, 1375, 1348, 1197, 1080, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.33−7.17 (m, 8H), 6.97 (t, J = 7.6 Hz, 1H), 5.25 (s, 2H), 2.85 (t, 7.6 Hz, 2H), 2.55 (q, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 166.1, 139.7, 136.9, 134.8, 128.9, 128.7, 128.5, 128.2, 128.0, 127.6, 126.6, 47.3, 33.8. 33.6. HRMS (FAB) m/z calcd for $C_{19}H_{17}NOS_2$ 339.0752, found 339.0758.

Rhodanine 3b. 21.6 mg, 68% yield as a yellow oil. IR (thin film) 3061, 3026, 2924, 2853, 1720, 1626, 1495, 1453, 1417, 1365, 1337, 1213, 1136, 989, 934 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.13 (m, 5H), 6.97 (t, J = 7.2 Hz, 1H), 5.87−5.70 (m, 1H), 5.32−5.22 (m, 2H), 4.67 (d, J = 5.6 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.56 (q, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 165.7, 139.7, 136.9, 129.6, 129.5, 128.7, 128.3, 127.7, 119.3, 46.2, 33.9, 33.7. HRMS (FAB) m/z calcd for $C_{15}H_{15}NOS_2$ 290.0668, found 290.0663.

Rhodanine 3c. 21.3 mg, 64% yield as a yellow oil. IR (thin film) 3061, 3026, 2925, 2359, 2341, 1718, 1628, 1496, 1430, 1350, 1328, 1273, 1202, 1136 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.17 (m, 5H), 6.95 (t, J = 8.0 Hz, 1H), 5.83−5.72 (m, 1H), 5.11−5.07 (m, 2H), 4.15 (dd, J = 6.0, 2.8 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.46 (q, J = 7.2 Hz, 2H), 2.43−2.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 166.2, 139.9, 136.8, 134.0, 128.9, 128.5, 127.8, 126.8, 117.9, 43.7, 34.1, 33.8, 31.4. HRMS (FAB) m/z calcd for $C_{16}H_{18}NOS_2$ [M + H^+] 304.0830, found 304.0829.

Rhodanine 3d. 22.1 mg, 61% yield as a yellow oil. IR (thin film) 3734, 3609, 3583, 3026, 2924, 2854, 2360, 1721, 1626, 1496, 1453, 1413, 1338, 1243, 1180, 1077, 1010, 939, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.28 (m, 3H), 7.22−7.15 (3H), 6.98 (t, J = 7.7 Hz, 1H), 6.38 (d, J = 3.6 Hz, 1H), 6.30−6.29 (m, 1H), 2.84 (t, J = 7.7 Hz, 2H), 2.54 (q, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 165.8, 148.1, 142.8, 139.9, 137.3, 128.9, 128.5, 127.6, 126.8, 110.6, 110.5, 40.3, 34.1, 33.9. HRMS (FAB) m/z calcd for $C_{17}H_{15}NO_2S_2$ 329.0544, found 329.0545.

Rhodanine 3e. 18.4 mg, 57% yield as a yellow oil. IR (thin film) 3445, 3026, 2941, 1721, 1628, 1496, 1454, 1427, 1329, 1276, 1197, 1093, 729, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H), 7.27−7.23 (m, 1H), 7.20−7.18 (m, 2H), 6.99 (t, 7.8 Hz, 1H), 4.30 (t, J = 5.4 Hz, 2H), 3.90 (t, J = 5.4 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.59 (q, J = 7.5 Hz, 2H), 1.93 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 166.8, 139.7, 137.5, 128.7, 128.3, 127.4, 126.7, 60.1, 46.4, 33.9, 33.7. HRMS (FAB) m/z calcd for $C_{14}H_{16}NO_2S_2$ [M + H^+] 294.06225, found 294.06231.

Rhodanine 3f. 19.7 mg, 53% yield as a yellow oil. IR (thin film) 3025, 2935, 2835, 2090, 1723, 1628, 1496, 1454, 1419, 1359, 1324, 1219, 1187, 1127, 1102, 1066, 988, 822, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H), 7.23−7.18 (m, 3H), 6.97 (t, J = 7.6 Hz, 1H), 4.87 (t, J = 5.6 Hz, 1H), 4.19 (d, J = 6.0 Hz, 2H), 3.37 (s, 6H), 2.86 (t, J = 7.2 Hz, 2H), 2.55 (q, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 165.9, 139.7, 137.1, 128.7, 128.3, 127.4, 126.6, 99.3, 53.8, 44.9, 33.9. 33.7. HRMS (FAB) m/z calcd for $C_{16}H_{19}NO_3S_2$ 337.08064, found 337.08056.

Rhodanine 3g. 20.7 mg, 52% yield as a yellow oil. IR (thin film) 2925, 2854, 2181, 2101, 1726, 1575, 1495, 1454, 1437, 1347, 1266, 1230, 1174, 1137, 1065, 1020, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.24−7.22 (m, 1H), 7.21−7.17 (m, 2H), 6.95 (t, J = 7.6 Hz, 1H), 4.04−4.01 (m, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.55 (q, J = 7.6 Hz, 2H), 1.68−1.55 (m, 2H), 1.33−1.23 (m, 10H), 0.89−0.85 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 166.1, 139.8, 136.5, 128.7, 128.3, 127.8, 126.6, 44.6, 33.9, 33.7, 31.8, 29.1, 26.9, 26.7, 22.6, 14.1. HRMS (FAB) m/z calcd for $C_{20}H_{28}NOS_2$ [M + H^+] 362.1612, found 362.1614.

Rhodanine 4a. 16.9 mg, 48% yield as a yellow oil. IR (thin film) 3032, 2953, 2926, 2855, 2359, 1718, 1627, 1604, 1494, 1455, 1425, 1375, 1348, 1319, 1300, 1194, 1108, 1080, 949, 821, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.42 (m, 2H), 7.32−7.28 (m, 3H), 6.97 (t, J = 7.6 Hz, 1H), 5.25 (s, 2H), 2.23 (q, J = 7.2 Hz, 2H), 1.57−1.52 (m, 4H), 1.28−1.32 (m, 6H), 0.91−0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 166.2, 138.8, 134.9, 128.9, 128.6, 128.1, 126.9, 47.4, 32.1, 31.5, 28.9, 27.9, 22.5, 14.0. HRMS (FAB) m/z calcd for $C_{17}H_{21}NOS_2$ 319.1065, found 319.1068.

Rhodanine 5a. 26.9 mg, 74% yield as a yellow oil. IR (thin film) 2921, 2850, 2362, 1718, 1626, 1494, 1447, 1424, 1375, 1347, 1318, 1298, 1193, 1079, 1029, 939, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.42 (m, 2H), 7.32−7.27 (m, 3H), 7.0 (t, 8.0 Hz, 1H), 5.26 (s, 2H), 2.12 (dd, J = 8.0, 6.8 Hz, 2H), 1.76−1.68 (m, 5H), 1.26−1.14 (m, 4H), 1.12−0.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 166.1, 137.8, 134.9, 129.0, 128.5, 128.1, 127.6, 47.3, 39.9, 37.7, 33.2, 26.1. HRMS (FAB) m/z calcd for $C_{18}H_{22}NOS_2$ [M + H^+] 332.1143, found 332.1135.

Rhodanine 5f. 19.9 mg, 55% yield as a yellow oil. IR (thin film) 2924, 2851, 2360, 2341, 1723, 1628, 1557, 1540, 1506, 1447, 1419, 1359, 1323, 1217, 1187, 1127, 1103, 1010, 985, 890, 750, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (t, 8 Hz, 1H), 4.87 (t, 5.2 Hz, 1H), 4.19 (d, 4.4 Hz, 2H), 3.38 (s, 6H), 2.12 (dd, J = 14.8, 7.6 Hz, 2H), 1.75−1.63 (m, 5H), 1.28−1.18 (m, 4H), 1.12−0.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 166.1, 138.1, 127.5, 99.5, 53.9, 45.0, 40.1, 37.9, 33.4, 26.3, 26.2. HRMS (FAB) m/z calcd for $C_{15}H_{23}NO_3S_2$ 329.1119, found 329.1105.

Epalrestat Analogue 8. An oven-dried, 2 dram vial, equipped with a magnetic stir bar, under argon was charged via syringe with carbon disulfide (25.0 mg, 0.33 mmol, 1.5 equiv), amine orthoester **6** (105.0 mg, 0.66 mmol, 3.0 equiv), and 2-propanol (2.0 mL) and was stirred at room temperature, under argon. After 6 h, α-chloro ester **2** (R = $PhCH_2$) (50.0 mg, 0.22 mmol, 1.0 equiv) was added as a solution in 2-propanol (1.0 mL), and the reaction was allowed to stir at room temperature under argon. After 24 h, the reaction was quenched with saturated ammonium chloride (1 mL) and extracted with diethyl ether (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, gravity filtered, and concentrated on a rotary evaporator at room temperature. The crude oil was dissolved in methanol (1.5 mL), transferred to a microwave vial, charged with *p*-toluenesulfonic acid (3.8 mg, 0.02 mmol, 0.1 equiv), sealed, and heated at 90 °C for 10 h. Dichloromethane (5 mL) was added, washed with water (3 × 5 mL), dried over $MgSO_4$, and concentrated. The residue was purified via silica gel column chromatography (10% ethyl acetate in hexanes) to afford 33.9 mg of **8** as a yellow oil in 48% yield. IR (thin film) 3024, 2924, 2851, 2362, 1750, 1718, 1625, 1578, 1495, 1454, 1435, 1400, 1364, 1321, 1265, 1198, 1054, 1008, 954, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.22−7.17 (m, 3H), 7.02 (t, J = 7.6 Hz, 1H), 4.79 (s, 2H), 3.76 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 2.58 (q, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 166.4, 166.3, 139.6, 137.8, 128.8, 128.3, 127.4, 126.7, 52.8, 44.5, 33.9, 33.8. HRMS (FAB) m/z calcd for $C_{15}H_{16}NO_3S_2$ [M + H^+] 322.0572, found 322.0571.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Magedov, I. V.; Frolova, L.; Manpadi, M.; Bhoga, U.; Tang, H.; Evdokimov, N., M.; George, O.; Georgiou, K. M.; Renner, S.; Getlik, M.; Kinnibrugh, T. L.; Fernandes, M. A.; Van Slambrouck, S.; Steelant, F. A.; Shuster, C. B.; Rogelj, S.; van Otterlo, W. A. L.; Kornienko, A. *J. Med. Chem.* **2011**, *54*, 4234–4246.
(2) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2977–2978.
(3) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634.
(4) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831–844.
(5) Ugi, I. *Angew. Chem., Int. Ed.* **1982**, *21*, 810–819.
(6) Tomašić, T.; Mašić, L. P. *Curr. Med. Chem.* **2009**, *16*, 1596–1629.
(7) Opletalova, V.; Dolezel, J.; Kralova, K.; Pesko, M.; Kunes, J.; Jampilek, J. *Molecules* **2011**, *16*, 5207–5227.
(8) Bernardo, P. H.; Sivaraman, T.; Wan, K.-F.; Xu, J.; Krishnamoorthy, J.; Song, C. M.; Tian, L.; Chin, J. S. F.; Lim, D. S. W.; Mok, H. Y. K.; Yu, V. C.; Tong, J. C.; Chai, C. L. L. *J. Med. Chem.* **2010**, *53*, 2314–2318.
(9) Chen, Z.-H.; Zheng, C.-J.; Sun, L.-P.; Piao, H.-R. *Eur. J. Med. Chem.* **2010**, *45*, 5739–5743.
(10) Dolezel, J.; Hirsova, P.; Opletalova, V.; Dohnal, J.; Marcela, V.; Kunes, J.; Jampilek, J. *Molecules* **2009**, *14*, 4197–4212.
(11) Sing, W. T; Lee, C. L.; Yeo, S. L.; Lim, S. P.; Sim, M. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 91–94.
(12) Lee, C. L.; Sim, M. M. *Tetrahedron Lett.* **2010**, *41*, 5729–5732.
(13) Sortino, M.; Delgado, P.; Juárez, S.; Quiroga, J.; Abonía, R.; Insuasty, B.; Nogueras, M.; Rodero, L.; Garibotto, F. M.; Enriz, R. D.; Zacchino, S. A. *Bioorg. Med. Chem.* **2007**, *15*, 484–494.
(14) Bourahla, K.; Derdour, A.; Rahmouni, M.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2007**, *48*, 5785–5789.
(15) Ohishi, Y.; Mukai, T.; Nagahara, M.; Yajima, M.; Kajikawa, N.; Miyahara, K.; Takano, T. *Chem. Pharm. Bull.* **1990**, *38*, 1911–1919.
(16) Grant, E. B.; Guiadeen, D.; Baum, E. Z.; Foleno, B. D.; Jin, H.; Montenegro, D. A.; Nelson, E. A.; Bush, K.; Hlasta, D. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2179–2182.
(17) Russell, A. J.; Westwood, I. M.; Crawford, M. H. J.; Robinson, J.; Kawamura, A.; Redfield, C.; Laurieri, N.; Lowe, E. D.; Davies, S. G.; Sim, E. *Bioorg. Med. Chem.* **2009**, *17*, 905–918.
(18) Gabillet, S.; Lecerclé, D.; Loreau, O.; Carboni, M.; Dézard, S.; Gomis, J.-M.; Taran, F. *Org. Lett.* **2007**, *9*, 3925–3927.
(19) Attanasi, O. A.; Crescentini, L. D.; Gavi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Behalo, M. S. *Org. Lett.* **2009**, *11*, 2265–2268.
(20) Yavari, I.; Hajinasiri, R.; Sayyed-Alangi, S. Z.; Iravani, N. *Monatsh. Chem.* **2008**, *139*, 1029–1031.
(21) Alizadeh, A.; Zohreh, N. *Synlett.* **2009**, *13*, 2146–2148.
(22) Anderluh, M.; Jukič, M.; Petrič, R. *Tetrahedron* **2009**, *65*, 344–350.
(23) Radi, M.; Botta, L.; Casaluce, G.; Bernardini, M.; Botta, M. *J. Comb. Chem.* **2010**, *12*, 200–205.
(24) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
(25) Hess, L. C.; Posner, G. H. *Org. Lett.* **2010**, *12*, 2120–2122.
(26) Genna, D. T.; Hencken, C. P.; Siegler, M.; Posner, G. H. *Org. Lett.* **2010**, *12*, 4694–4697.
(27) Hencken, C. P.; Genna, D. T.; Siegler, M.; Posner, G. H. *J. Org. Chem.* **2011**, *76*, 5149–5155.
(28) Kandeel, K. A. *Chem. Pap.* **2004**, *58*, 334–340.
(29) Ottaná, R.; Maccari, R.; Barreca, M. L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Di Paola, R.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M. G. *Bioorg. Med. Chem.* **2005**, *13*, 4243–4252.
(30) Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. *Bioorg. Med. Chem.* **2006**, *14*, 3859–3864.
(31) Kasmi-Mir, S.; Djarfri, A.; Paquin, L.; Hamelin, J.; Rahmouni, M. *Molecules* **2006**, *11*, 597–602.
(32) Kamila, S.; Ankati, H.; Biehl, E. R. *Tetrahedron Lett.* **2011**, *52*, 4375–4377.
(33) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571–5574.
(34) Miyamoto, S. *Chem-Bio Inf. J.* **2002**, *2*, 74–85.
(35) Demopoulos, V. J.; Nicolaou, I.; Alexiou, P.; Zika, C.; Sturm, K.; Kristl, A. *Brilliant Light in Life and Material Sciences*; Tsakanov, V., Wiedemann, H., Eds.; Springer: New York, 2007; p 241.