A Simple Procedure for the Synthesis of 3-(Substituted-sulfanyl)-4-hydroxy-6-substituted-pyran-2-ones

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A series of 3-(substituted sulfanyl)-4-hydroxy-6-substituted-pyran-2-ones were synthesized for Human immunodeficiency virus-1 protease inhibition. These compounds were synthesized in a simple and convergent fashion to allow us a rapid preparation of many structurally diversified analogues. Thus the condensation of trimethylsilyl enol ethers of corresponding ketones, with 2-(*S*-substituted)propane-1,3-dioates afforded the corresponding pyrones in 24-70% isolated yields.

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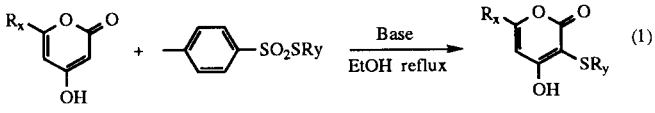
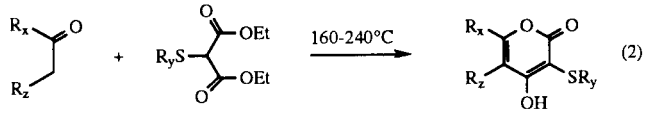
Recently, we have investigated the synthesis of 4-hydroxy-3-thiosubstituted-pyran-2-ones [1] as they have been shown to be potent Human immunodeficiency virus-1 protease inhibitors [2]. A previous report [3] for the synthesis of these compounds describes the reaction of 6-substituted-pyran-2-ones [4] with thiosulphonates in the presence of a base under ethanol refluxing conditions (equation 1). This procedure requires 4 to 5 steps. Another procedure [5],



(1)

which is direct and incorporates a pyran-2-one template synthesis, describes the condensation of dialkyl 2-(arylthio)propane-1,3-dioates with enolizable ketones at high temperatures *viz.*, 160-240° (equation 2). Although this procedure is simple, it suffers from low yields (~5%) as well as difficult isolation of the product.

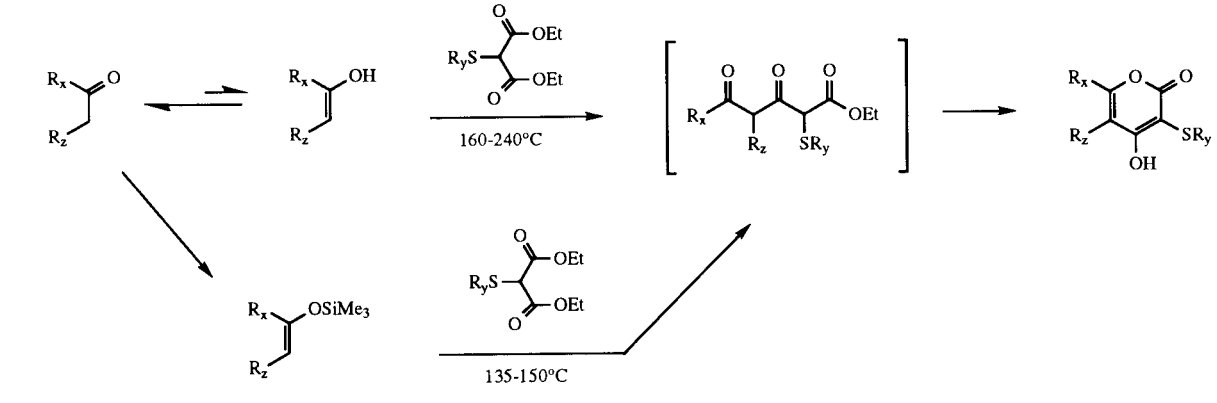


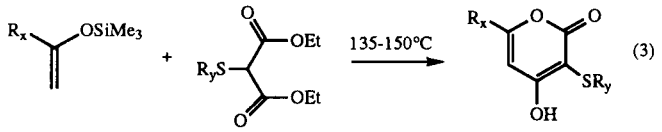
(2)

Mechanistically, it is proposed that the enol, which is in equilibrium with the corresponding ketone, condenses with propane-1,3-dioates to give a diketoester. In the second step, the diketoester cyclizes under the reaction conditions to give pyran-2-one as shown in Scheme I. It was envisioned that prior formation of a silyl enol ether might enhance the formation of diketoester, potentially providing a higher yield of pyran-2-one.

It was found that the condensation of trimethyl silyl enol ethers of ketones with appropriately substituted malonic esters (Scheme I) proceed at 135-150° to provide 4-hydroxy-pyran-2-ones in moderate yields (24-70%), with fewer decomposition products. The presence of heterocyclic rings, for example, benzodioxane and oxazole, on the silyl enol ether portion also afforded the corresponding products, **1** and **2** in 40% and 50% yields respectively (equation 3). The reaction also tolerates polar functional groups such as sulfoxide, ester and cyanide on the silyl enol ether portion, yielding the corresponding products **3**, **4** and **5** (equation 4) in 24%, 60% and 60% respectively. The reaction occurs smoothly with the variations such as benzyl, naphthyl and phenethyl on the propane-1,3-dioate portion give pyrones **6**, **7** and **2** in 52%, 52% and 50%

Scheme I





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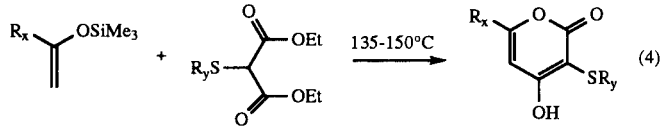

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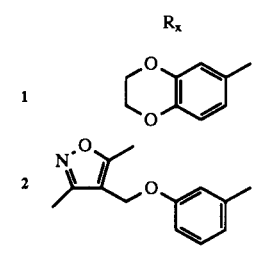
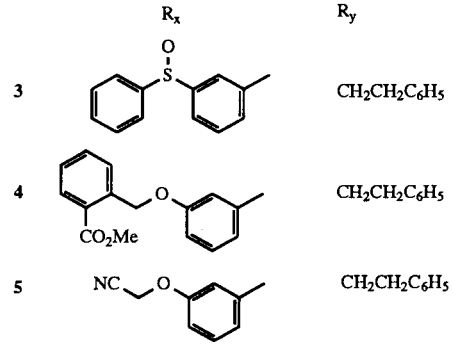
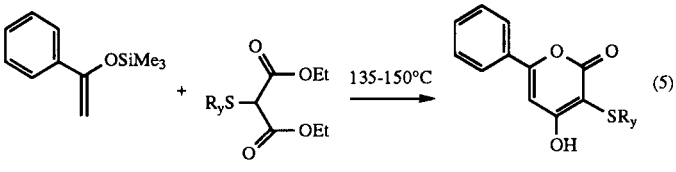




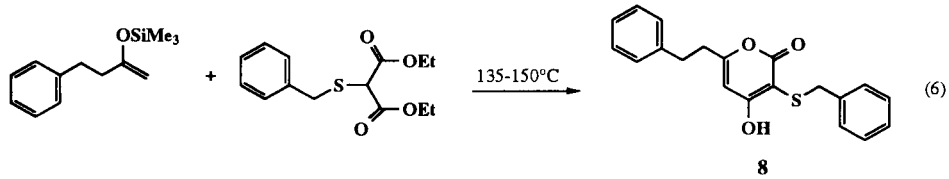


(5)

6 R_y = benzyl
7 R_y = 2-Naphthyl

yields, respectively (equations 5 and 3). In all these reactions the crude silyl enol ether was used, although by using pure silyl enol ether higher yields can be achieved (**6:** 52 *vs.* 70%).

ones. Other non aromatic enolates, for example cyclopenten-1-enyltrimethylsilyl ether, on condensation with diethyl (benzylthio)propane-1,3-dioate also yielded the corresponding pyran-2-one, **10**, in modest yield, 38% (equation 8). The reaction can also be applied to synthesize tricyclic pyrones. Thus, the trimethylsilyl ether of 7-ethyl-1-tetralone on condensation with diethyl (benzylthio)propane-1,3-dioate afforded the corresponding tricyclic pyran-2-one, **11**, in 62% yield. Similarly, other tricyclic pyran-2-ones, **12** and **13**, varying the size of the



(6)

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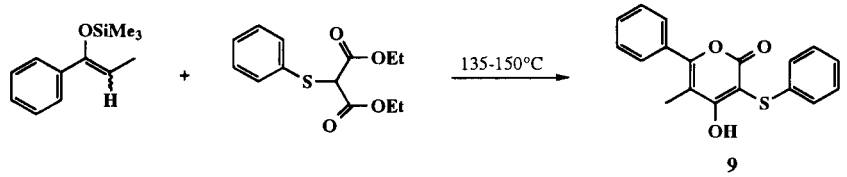
In addition, the reaction of the silyl enol ether of a kinetic enolate with diethyl 2-(benzylthio)propane-1,3-dioate provided the corresponding pyran-2-one, **8** (equation 6) in 24% yield. Similarly, 2-substituted enolate on condensation with appropriately substituted propane-1,3-dioate yielded the expected product (equation 7), **9**, in 33% yield, which leads into 5-substituted 4-hydroxy-pyran-2-

middle ring to 5 and 7, respectively, were also synthesized (equation 9) in 33% and 31% yields. The middle ring could also be an heterocyclic ring as shown in example **14**.

In conclusion, we have developed a very simple and convergent procedure for the synthesis of 4-hydroxy-3-(*S*-substituted)-pyran-2-ones. This procedure allows for the rapid preparation of many structurally diversified ana-



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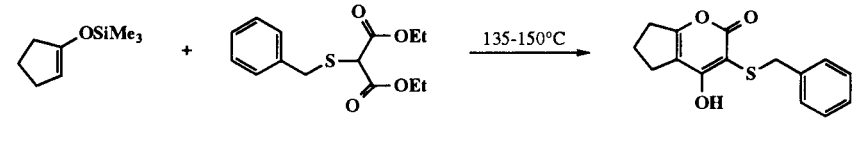

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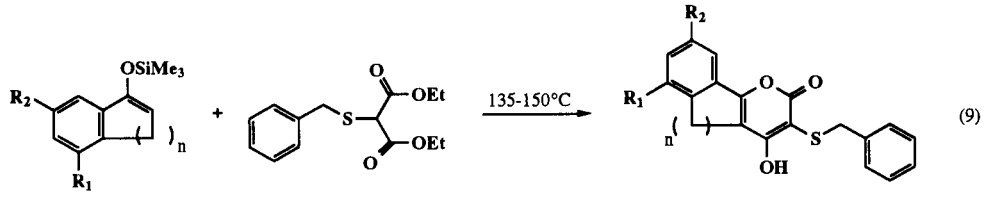
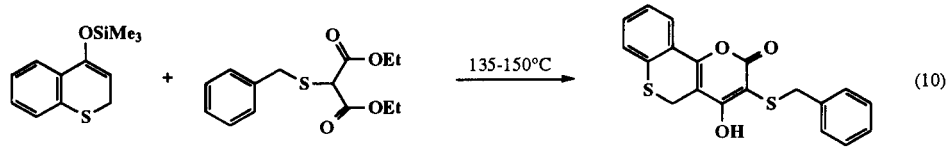


	n	R_1	R_2
12	1	CH_3	H
11	2	H	C_2H_5
13	3	H	H



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logues to further explore their structure-activity relationship as Human immunodeficiency virus protease inhibitors. Though the yields are low to moderate, by using this procedure highly functionalized pyran-2-ones can be synthesized in a simple fashion.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Hoover melting point apparatus and are uncorrected. Infra red spectra were determined on a Nicolet FT IR SX-20 spectrophotometer. Proton magnetic resonance were recorded on a Bruker AM 250 spectrometer and chemical shifts are reported in δ units relative to internal tetramethylsilane. All mass spectra were obtained on a Finnigan 4500 GCMS or a VG analytical 7070E/F spectrometer. Elemental analyses were performed on a Perkin-Elmer Model 240 elemental analyzer, and all compounds had analytical results of ± 0.4% of theoretical values. Flash column or medium pressure chromatography were performed using silica gel (230 to 400 mesh) and concentrations were performed *in vacuo* at 10-30 mm Hg.

General Methods.

Method A.

To a cold solution (-78°) of ketone (10 mmoles) in dry tetrahydrofuran (100 ml) solid lithium hexamethyldisilazide (11 mmoles) was added. The solution was stirred at -78° for 1 hour; followed by -35° for 0.5 hours. To it trimethylsilyl chloride was added dropwise at -78°. The reaction was stirred at -78° for 1 hour, followed by 0° for 0.5 hours. The reaction was quenched with saturated sodium bicarbonate solution; diluted with ethyl acetate (by adding 200-300 ml). The organic layer was washed with saturated sodium bicarbonate solution and brine; dried over anhydrous sodium sulfate. The organic layer was concentrated and the residue was dried *in vacuo* for 1 hour. The crude silyl enol ether (11 mmoles) was mixed with diethyl (2-substituted)propane-1,3-dioate (10 mmoles) and the resultant mixture was heated at 150°, while passing nitrogen gas through the reaction mixture overnight. The reaction mixture was cooled to room temperature and was subjected to column chromatography. Ethyl acetate (10-15%) in hexanes removes unreacted starting material and other impurities; whereas 30-50% ethyl acetate in 5% methylene chloride and 65-45% of hexanes eluents afforded the expected pyrones in 20-75% yield.

Method B.

A solution of ketone (18.8 mmoles) in dichloromethane (50 ml) was cooled to 0° (nitrogen atmosphere) and treated with triethylamine (3.9 ml, 28 mmoles) followed by trimethylsilyltriflate (3.99 ml, 20.6 mmoles). The solution was then warmed to ambient temperature, allowed to stir for 15 minutes, and subsequently quenched into a mixture of diethyl ether (50 ml) and saturated aqueous sodium bicarbonate (20 ml). The layers were separated and the organic layer was washed with a 1:1 mixture of brine and saturated sodium bicarbonate (20 ml). The ethereal solution was then dried (sodium sulfate) and the solvent removed *in vacuo*. The silyl enol ether prepared as described above was then transferred to a flask containing diethyl (2-substituted)propane-1,3-dioate (7.52 mmoles). The mixture was then heated to 160° for 16 hours and allowed to cool to room temperature where it was diluted with diethyl ether (20 ml) and extracted with saturated sodium carbonate(3 x 20 ml). The combined aqueous extracts were acidified with concentrated hydrochloric acid to *p*H 0 and extracted with dichloromethane (3 x 100 ml). The organic layers were combined, dried (sodium sulfate) and the solvent removed *in vacuo*. The resulting residue was then submitted to chromatography (silica gel-230 to 400 mesh, 100% dichloromethane to 0.5% methanol/dichloromethane) to provide the pyrone.

Examples.

3-Benzylsulfanyl-6-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-4-hydroxypyran-2-one (**1**).

The compound was prepared according to Method A using 1,4-benzodioxin-6-yl methyl ketone (2.5 g, 14.25 mmoles),

lithium bis(trimethylsilyl)amide (2.35 g, 14.25 mmoles), chlorotrimethylsilane (2.47 g, 14.25 mmoles), tetrahydrofuran (100 ml), and diethyl 2-(benzylthio)propane-1,3-dioate (1.0 g, 3.55 mmoles). The product, 3-benzylsulfanyl-6-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-4-hydroxypyran-2-one (**1**) was separated by column chromatography in 40% yield, mp 192-193°; ir (potassium bromide): 3435, 2924, 1649, 1624, 1508, 1288, 1066, 698 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 3.99 (s, 2H), 4.17 (m, 4H), 6.8 (s, 1H), 7.0 (d, 1H), 7.2 (m, 1H), 2.28 (m, 7H); ms: 369 (M+H), 277, 233, 163, 107, 91.

Anal. Calcd. for $C_{20}H_{16}O_5S_1$: C, 65.21; H, 4.38. Found: C, 64.80; H, 4.17.

6-[4-(3,5-Dimethylisoxazol-4-ylmethoxy)phenyl]-4-hydroxy-3-phenethylsulfanylpyran-2-one (**2**).

This compound was prepared according to Method A using 4'-(3,5-dimethyl-4-isooxazolyl)acetophenone (1.65 g, 6.74 mmoles), lithium bis(trimethylsilyl)amide (1.13 g, 6.74 mmoles), chlorotrimethylsilane (1.14 ml, 6.74 mmoles), tetrahydrofuran (50 ml), and diethyl 2-(phenethylthio)propane-1,3-dioate (1.0 g, 3.37 mmoles). The product, 6-[4-(3,5-dimethylisoxazol-4-ylmethoxy)phenyl]-4-hydroxy-3-phenethylsulfanylpyran-2-one was separated by column chromatography in 50% yield, mp 152-154°; ir (potassium bromide): 2936, 2979, 1640, 1510, 1406, 1182, 988, 820, 764 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 2.22 (s, 3H), 2.31 (s, 3H), 2.78 (t, 2H), 2.99 (t, 2H), 5.03 (s, 2H), 6.69 (s, 1H), 7.17 (d, 3H), 7.25 (m, 4H), 7.78 (d, 2H); ms: 341, 236, 112, 105.

Anal. Calcd. for $C_{25}H_{23}NO_5S$: C, 66.80; H, 5.16; N, 3.12. Found: C, 66.42; H, 5.20; N, 2.74.

6-(4-Benzenesulfinylphenyl)-4-hydroxy-3-phenethylsulfanylpyran-2-one (**3**).

This compound was prepared according to Method A using 4'-(phenylsulfinyl)acetophenone (2.5 g, 10.24 mmoles), lithium bis(trimethylsilyl)amide (2.57 g, 15.36 mmoles), chlorotrimethylsilane (1.94 ml, 15.36 mmoles), tetrahydrofuran (100 ml), and diethyl 2-(phenethylthio)propane-1,3-dioate (1.0 g, 3.37 mmoles). 6-(4-Benzenesulfinylphenyl)-4-hydroxy-3-phenethylsulfanylpyran-2-one (**3**) was isolated in 24% yield by column chromatography, mp 194-195°; ir (potassium bromide): 3082, 3057, 3026, 2924, 2852, 1718, 1683, 1631, 1550, 1494, 1442, 1415, 1390, 1361, 1180, 1085, 1030, 997, 941, 817, 750, 696, 547, 524 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 2.76 (t, 2H), 3.01 (t, 2H), 6.87 (s, 1H), 7.19 (m, 5H), 7.68 (m, 3H), 8.04 (m, 6H), 12.05 (bs, 1H); ms: 449 (M+H), 433, 344, 190, 109, 105, 91.

Anal. Calcd. for $C_{25}H_{20}O_4S_2$: C, 66.94; H, 4.49. Found: C, 66.85; H, 4.42.

2-[4-(4-Hydroxy-6-oxo-5-phenethylsulfanyl-6*H*-pyran-2-yl)-phenoxymethyl]benzoic Acid Methyl Ester (**4**).

This compound was prepared according to Method B using 4-[methoxyphenyl-(2-carbomethoxy)]acetophenone (2.0 g, 7.04 mmoles), trimethylsilyltrifluoromethylsulfonate (1.57 g, 7.04 mmoles), triethylamine (1.42 g, 14.08 mmoles), dichloromethane (50 ml), and diethyl 2-(phenethylthio)propane-1,3-dioate (1.04 g, 3.52 mmoles). The product, 2-[4-(4-hydroxy-6-oxo-5-phenethylsulfanyl-6*H*-pyran-2-yl)phenoxymethyl]benzoic acid methyl ester (**4**), was isolated in 60% yield, mp 161-162°; ir (potassium bromide): 3028, 2949, 2909, 2675, 1715, 1638, 1510, 1402, 1291, 1267, 1181, 1030, 828, 747 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 2.78 (t, 2H), 2.97 (t, 2H), 3.81 (s, 3H), 5.5 (s, 2H), 6.69 (s, 1H), 7.14 (m, 3H), 7.25 (m, 4H), 7.5 (m, 2H), 7.65 (m, 2H), 7.78 (d, 2H), 7.94 (d, 1H); ms: 489 (M+H), 384, 353, 149, 135, 105.

Anal. Calcd. for $C_{28}H_{24}O_6S$: C, 68.84; H, 4.95. Found: C, 68.5; H, 4.65.

[4-(4-Hydroxy-6-oxo-5-phenethylsulfanyl-6*H*-pyran-2-yl)-phenoxy]acetonitrile (**5**).

This compound was prepared according to Method B using the appropriate acetophenone (3.0 g, 17.12 mmoles), trimethylsilyltrifluoromethylsulfonate (3.8 g, 17.12 mmoles), triethylamine (3.46 g, 17.12 mmoles), dichloromethane (50 ml), and diethyl 2-(phenethylthio)propane-1,3-dioate (2.53 g, 8.56 mmoles). The product, [4-(4-hydroxy-6-oxo-5-phenethylsulfanyl-6*H*-pyran-2-yl)phenoxy]-acetonitrile (**5**) was isolated in 60% yield, mp 157-159°; ir (potassium bromide): 2993, 2577, 1634, 1510, 1404, 1342, 1302, 1226, 1188, 1098, 1051, 833, 717, 505 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 2.92 (t, 2H), 3.11 (t, 2H), 4.86 (s, 2H), 6.56 (s, 1H), 7.08 (d, 2H), 7.19 (t, 3H), 7.3 (m, 3H), 7.86 (d, 2H); ms: 380 (M+H), 275, 205, 105.

Anal. Calcd. for $C_{21}H_{17}O_4SN \cdot 0.2H_2O$: C, 65.8; H, 4.58; N, 3.65. Found: C, 65.71; H, 4.28, N, 3.96.

3-Benzylsulfanyl-4-hydroxy-6-phenylpyran-2-one (**6**).

This compound was prepared according to Method A using 1-phenyl-1-(trimethylsilyloxy)ethylene (6.38 g, 33.0 mmoles) and diethyl 2-(benzylthio)propane-1,3-dioate (7.79 g, 27.64 mmoles). The product, 3-benzylsulfanyl-4-hydroxy-6-phenylpyran-2-one (**6**), was isolated in 70% yield, mp 155-160°; ir (potassium bromide): 3437, 3101, 2925, 2786, 2654, 1721, 1677, 1639, 1594, 1539, 1495, 1453, 1394, 1355, 1105, 764, 695, 527 cm^{-1}; ^1H nmr (250 MHz, dimethyl sulfoxide-d_6): δ 4.00 (s, 2H), 6.74 (s, 1H), 7.23 (m, 5H), 7.53 (m, 3H), 7.78 (m, 2H); ms: 311(M+H), 277, 233, 119, 105, 91.

Anal. Calcd. for $C_{18}H_{14}O_3S$: C, 69.66; H, 4.55. Found: C, 69.34; H, 4.53.

4-Hydroxy-3-(naphthalen-2-ylsulfanyl)-6-phenylpyran-2-one (**7**).

This compound was prepared according to Method A using 1-phenyl-1-(trimethylsilyloxy)ethylene (1.33 g, 6.9 mmoles) and diethyl 2-(2-naphthylthio)propane-1,3-dioate (2.0 g, 6.9 mmoles). The product, 4-hydroxy-3-(naphthalen-2-ylsulfanyl)-6-phenylpyran-2-one (**7**), was isolated by column chromatography in 52% yield, mp 246° dec; ir (potassium bromide): 3435, 3059, 3026, 2922, 1724, 1660, 1628, 1543, 1494, 1452, 1411, 1357, 1190, 1099, 819, 763, 696, 476 cm^{-1}; ^1H nmr (250 MHz, dimethyl sulfoxide-d_6): δ 6.95 (s, 1H), 7.39 (m, 3H), 7.56 (m, 4H), 7.85 (m, 5H); ms: 347 (M+H), 219, 200, 189, 160, 155, 147, 128, 115, 105.

Anal. Calcd. for $C_{21}H_{14}O_3S$: C, 72.81; H, 4.07. Found: C, 72.81; H, 4.30.

3-Benzylsulfanyl-4-hydroxy-6-(phenylethyl)pyran-2-one (**8**).

This compound was prepared according to Method A using 4-phenethylacetophenone (0.786 g, 5.31 mmoles), lithium bis(trimethylsilyl)amide (0.977 g, 5.84 mmoles), chlorotrimethylsilane (0.74 ml, 5.84 mmoles), tetrahydrofuran (58 ml), and diethyl 2-(benzylthio)propane-1,3-dioate (1.0 g, 3.54 mmoles). The product, 3-benzylsulfanyl-4-hydroxy-6-(phenylethyl)pyran-2-one (**8**), was isolated by column chromatography in 24% yield, mp 164-

166°; ir (potassium bromide): 3434, 3030, 2930, 2644, 2604, 1718, 1651, 1622, 1539, 1497, 1454, 1425, 1406, 1373, 997, 754, 705, 466 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 2.75 (t, 3H), 2.85 (t, 2H), 3.92 (s, 2H), 5.92 (s, 1H), 7.23 (m, 9H), 11.69 (bs, 1H); ms: 339 (M+H), 305, 261, 181, 157, 105, 91.

Anal. Calcd. for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36. Found: C, 70.72; H, 5.57.

4-Hydroxy-5-methyl-6-phenyl-3-phenylsulfanylpyran-2-one (**9**).

The title compound was prepared according to Method B using propiophenone (1.5 ml, 11.3 mmoles), triethylamine (3.15 ml, 22.6 mmoles) trimethylsilyltrifluoromethylsulfonate (2.6 ml, 13.5 mmoles), dichloromethane (40 ml) and diethyl 2-(thiophenyl)propane-1,3-dioate (1.0 g, 3.76 mmoles). The product, 4-hydroxy-5-methyl-6-phenyl-3-phenylsulfanylpyran-2-one (**9**), was isolated by column chromatography in 33% yield, mp 166-167°; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 6.31-6.29 (m, 2 H), 6.23-6.21 (m, 3 H), 5.98 (t, 2 H, J = 8 Hz), 5.86 (d, 3 H, J = 8 Hz), 0.71 (s, 3 H); ms: 311 (M + H), 310, 283, 267, 233, 203, 161, 150, 122, 111, 105, 91, 87.

Anal. Calcd. for $C_{18}H_{14}O_3S \cdot 0.3H_2O$: C, 68.46; H, 4.67. Found: C, 68.12; H, 4.38.

3-Benzylsulfanyl-4-hydroxy-5*H*-cyclopentyl[1,2-*b*]pyran-2-one (**10**).

The title compound was prepared according to Method B. The product, 3-benzylsulfanyl-4-hydroxy-5*H*-cyclopentyl[1,2-*b*]pyran-2-one (**10**) was isolated in 38% yield, mp 140-142°; ir (potassium bromide): 3284, 2924, 2860, 1691, 1635, 1558, 1539, 1446, 1421, 1180, 1049, 920, 760, 700 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 11.33 (bs, 1H), 7.29-7.18 (m, 5 H), 3.90 (s, 2 H), 2.72 (t, 2 H, J = 7.5 Hz), 2.55 (t, 2 H, J = 7.5 H), 1.97 (quint., 2 H, J = 7.5 Hz); ms: 275 (M + H), 199, 153, 141, 119, 111, 91.

Anal. Calcd. for $C_{15}H_{14}O_3S \cdot 0.2H_2O$: C, 64.82; H, 5.23; S, 11.51. Found: C, 65.15; H, 5.26; S, 11.51.

3-Benzylsulfanyl-9-ethyl-4-hydroxy-5,6-dihydrobenzo-[*H*]chromen-2-one (**11**).

The title compound was prepared according to Method B using 7-ethyl-1-tetralone (2.0 g, 1.14 mmoles), triethylamine (2.4 ml, 1.72 mmoles), trimethylsilyltrifluoromethylsulfonate (2.4 ml, 1.26 mmoles), dichloromethane (20 ml) and diethyl 2-(thiobenzyl)propane-1,3-dioate (1.0 g, 3.83 mmoles). The product, 3-benzylsulfanyl-9-ethyl-4-hydroxy-5,6-dihydrobenzo-[*H*]chromen-2-one (**11**) was isolated by column chromatography in 62% yield, mp 163-165°; ir (potassium bromide): 3429, 3028, 2970, 1672, 1628, 1602, 1525, 1494, 1454, 1421, 1249, 1207, 1197, 1147, 1095, 761, 705 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 7.49 (s, 1H), 7.28-7.2 (m, 8H), 3.97 (s, 2H), 2.81 (t, 2H, J = 2 Hz), 2.65 (q, 2H, J = 8 Hz), 2.59-2.52 (m, 2H), 1.19 (t, 3H, 8 Hz); ms: 364 (M^+), 273, 245, 172, 141, 128, 115, 105, 91, 84, 77, 66, 44.

Anal. Calcd. for $C_{22}H_{20}O_3S \cdot 0.5H_2O$: C, 70.75; H, 5.67; S, 8.57. Found: C, 70.35; H, 5.26; S, 8.57.

3-Benzylsulfanyl-4-hydroxy-6-methyl-5*H*-indeno[1,2-*b*]pyran-2-one (**12**).

The title compound was prepared according to Method B using 4-methyl-1-indanone (1.0 g, 6.17 mmoles), triethylamine (1.7 ml, 5.62 mmoles), trimethylsilyltrifluoromethylsulfonate (1.3 ml, 6.74 mmoles), dichloromethane (30 ml) and diethyl 2-(thiobenzyl)-propane-1,3-dioate (0.736 g, 2.81 mmoles). The product, 3-benzylsulfanyl-4-hydroxy-6-methyl-5H-indeno[1,2-*b*]pyran-2-one (**12**), was isolated by column chromatography in 33% yield. mp 167-169°; ir (potassium bromide): 3636, 3450, 3063, 3030, 2926, 1691, 1624, 1593, 1543, 1446, 1386, 1172, 754, 702; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 7.48 (d, 1H, J = 7.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.31-7.18 (m, 6H), 3.98 (s, 2H), 3.55 (s, 2H), 2.36 (s, 3H); ms: 336 (M^+), 245, 217, 150, 91, 86, 84, 68, 66, 50, 48, 46.

Anal. Calcd. for $C_{20}H_{16}O_3S \cdot 0.5H_20$: C, 69.54; H, 4.97. Found: C, 69.54; H, 4.86.

3-Benzylsulfanyl-4-hydroxy-6,7-dihydro-5*H*-1-oxa-dibenzo-cyclopenhepten-2-one (**13**).

The title compound was prepared according to Method B using 1-benzosuberone (2.14 g, 13.37 mmoles), triethylamine (2.8 ml, 20.0 mmoles), trimethylsilyltrifluoromethylsulfonate (2.85 ml, 14.7 mmoles), dichloromethane (20.0 ml) and diethyl 2-(thiobenzyl)propane-1,3-dioate (1.17 g, 4.46 mmoles). The product, 3-benzylsulfanyl-4-hydroxy-6,7-dihydro-5*H*-1-oxa-dibenzocyclopenhepten-2-one (**13**), was isolated by column chromatography in 31% yield, mp 108-110°; ir (potassium bromide): 3429, 3290, 3061, 3026, 2928, 2858, 1699, 1624, 1599, 1537, 1452, 1423, 1201, 1178, 1128, 760, 698 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 11.05 (bs, 1H), 7.56 (dd, 1H, J = 1 Hz, 7 Hz), 7.45-7.37 (m, 3H), 7.27-7.2 (m, 5H), 3.98 (s, 2H), 2.55-2.50 (m, 2H), 2.16-2.05 (m, 4H); ms: 350 (M^+), 318, 317, 259, 231, 187, 141, 128, 115, 91, 84, 66.

Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18; S, 9.15. Found: C, 71.99; H, 5.40; S, 9.04.

2-Benzylsulfanyl-1-hydroxy-10*H*-4-oxa-9-thiaphenanthren-3-one (**14**).

The title compound was prepared according to Method B using thiochroman-4-one (3.0 g, 18.27 mmoles), triethylamine (5.10 ml, 3.65 mmoles), trimethylsilyltrifluoromethylsulfonate (3.90 ml, 2.01 mmoles), dichloromethane (35 ml), diethyl 2-(thiobenzyl)propane-1,3-dioate (1.60 g, 6.09 mmoles). The product, 2-benzylsulfanyl-1-hydroxy-10*H*-4-oxa-9-thia-phenanthren-3-one (**14**) was isolated by column chromatography in 31% yield, mp 142-144°; ir (potassium bromide): 3250, 3059, 3032, 1680, 1631, 1531, 1512, 1.19, 1140, 1116, 713 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 7.76 (d, 1H, J = 7.5 Hz), 7.40-7.39 (m, 2H), 7.37-7.22 (m, 6H), 3.99 (s, 2H), 3.84 (s, 2H); ms: 354 (M^+), 263, 235, 191, 91, 66.

Anal. Calcd. for $C_{19}H_{14}O_3S_2 \cdot 0.2H_2O$: C, 63.75; H, 4.06; S, 17.87; Found: C, 63.97; H, 3.96; S, 17.82.

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