Polarized Ketene Dithioacetals; 55:[1] Synthesis of Novel 5-Aryl-2-methylthio-4*H*-pyran-4-ones from Cinnamoylketene Dithioacetals

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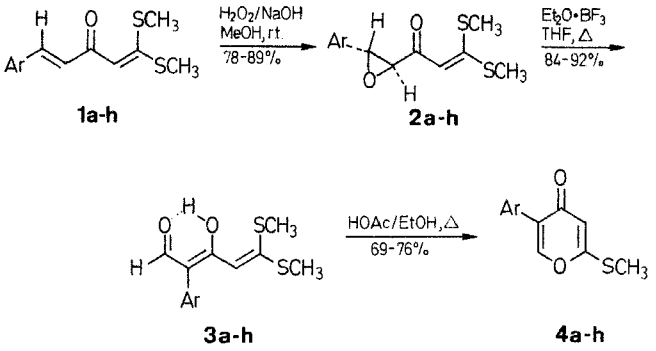
A novel method for the synthesis of 5-aryl-2-methylthio-4*H*-pyran-4-ones **4a–h** has been developed from the corresponding cinnamoylketene dithioacetals **1a–h** in three successive steps. In the first step, **1a–h** were oxidized with alkaline hydrogen peroxide to give the corresponding (β-aryl-α,β-epoxypropanoyl)ketene dithioacetals **2a–h** in 78–89% overall yields. In the second step the epoxyketones **2a–h** were subjected to rearrangement in the presence of ether-boron trifluoride complex to give the corresponding (α-formyl-α-phenylacetyl)ketene dithioacetals **3a–h**, which were then cyclized in the third step by refluxing in acetic acid/ethanol to afford the title compounds in good yields.

During the course of our investigations on polarized ketene dithioacetals, we have shown in our earlier work that cinnamoyl ketene dithioacetals **1**[2] serve as useful precurssors for the synthesis of styrylpyrimidines,[3] methyl 5-aryl-2,4-pentadienoates,[4] substituted 2-arylcyclopentenones[5] and stilbenes.[6] We have also developed recenly a facile method for 2-aryl-6-methylthio-4*H*-pyran-4-ones by base-catalyzed condensation of acylketene dithioacetals with methyl benzoates to give the corresponding (α-aroylacyl)ketene dithioacetals followed by their cyclization in refluxing acetic acid.[7] In the present work, we now report the synthesis of hitherto unknown 5-aryl-2-



1–4	Ar	1–4	Ar
a	C_6H_5	f	$3,4\text{-}(CH_3O)_2C_6H_3$
b	$4\text{-}CH_3C_6H_4$	g	$3,4,5\text{-}(CH_3O)_3C_6H_2$
c	$4\text{-}ClC_6H_4$		
d	$4\text{-}CH_3OC_6H_4$	h	
e	$3\text{-}CH_3OC_6H_4$		

Table 1. 5-Aryl-1,1-bis(methylthio)-4,5-epoxy-1-penten-3-ones **2** Prepared

Product	Yield[a] (%)	m.p. (°C)[b]	Molecular Formula[c]	IR (KBr)[d] δ (cm⁻¹)	¹H-NMR ($CDCl_3$/TMS)[e] δ, J (Hz)	MS (70 eV)[f] m/e (%)
2a	89	82–83	$C_{13}H_{14}O_2S_2$ (266.4)	1630, 1480, 1640	2.41 (s, 3H, SCH_3); 2.42 (s, 3H, SCH_3); 3.49 (d, 1H, J = 2.5, H-4); 3.90 (d, 1H, J = 2.5, H-5); 6.20 (s, 1H, =CH); 7.25 (s, $5H_{arom}$)	266 (M^+, 5); 250 (17); 235 (54); 219 (37); 147 (100)
2b	83	96–97	$C_{14}H_{16}O_2S_2$ (280.4)	1640, 1590, 1480	2.31 (s, 3H, SCH_3); 2.78 (s, 6H, SCH_3, Ar $-CH_3$); 3.50 (d, 1H, J = 2.5, H-4); 3.88 (d, 1H, J = 2.5, H-5); 6.20 (s, 1H, =CH); 7.08–7.28 (m, $4H_{arom}$)	280 (M^+, 4); 264 (5); 249 (13); 233 (51); 147 (100)
2c	80	105–106	$C_{13}H_{13}ClO_2S_2$ (300.8)	1609, 1475	2.50 (s, 3H, SCH_3); 2.51 (s, 3H, SCH_3); 3.45 (d, 1H, J = 2.5, H-4); 3.92 (d, 1H, J = 2.5, H-5); 6.25 (s, 1H, =CH); 7.13–7.55 (m, A_2B_2, $4H_{arom}$)	300, 302 (M^+, 10,5); 284, 286 (51, 20); 269, 271 (9, 4); 253, 255 (8, 3); 147 (38)
2d	86	93–94	$C_{14}H_{16}O_3S_2$ (296.4)	1636, 1609, 1488	2.45 (s, 3H, SCH_3); 2.46 (s, 3H, SCH_3); 3.48 (d, 1H, J = 2.5, H-4); 3.79 (s, 3H, CH_3O); 3.85 (d, 1H, J = 2.5, H-5); 6.20 (s, 1H, =CH); 6.75–7.30 (m, A_2B_2, $4H_{arom}$)	296 (M^+, 18); 280 (6); 265 (10); 249 (100); 147 (80)
2e	78	84–85	$C_{14}H_{16}O_3S_2$ (296.4)	1605, 1480	2.50 (s, 6H, SCH_3); 3.42 (d, 1H, J = 2.5, H-4); 3.74 (s, 3H, CH_3O); 3.88 (d, 1H, J = 2.5, H-5); 6.19 (s, 1H, =CH); 6.72–7.38 (m, $4H_{arom}$)	296 (M^+, 7); 280 (3); 265 (4); 249 (60); 147 (100)
2f	81	120–121	$C_{15}H_{18}O_4S_2$ (326.4)	1620, 1590, 1480	2.50 (s, 3H, SCH_3); 2.51 (s, 3H, SCH_3); 3.55 (d, 1H, J = 2.5, H-4); 3.89 (s, 7H, CH_3O and H-5); 6.16 (s, 1H, =CH); 6.60–6.79 (m, $3H_{arom}$)	M^+ (absent); 310 (17); 295 (20); 279 (15); 263 (100); 147 (82)
2g	80	184–185	$C_{16}H_{20}O_5S_2$ (356.5)	1626, 1590, 1479	2.49 (s, 3H, SCH_3); 2.52 (s, 3H, SCH_3); 3.49 (d, 1H, J = 2.5, H-4); 3.68 (s, 3H, CH_3O); 3.80 (s, 6H, CH_3O); 3.92 (d, J = 2.5 Hz, H-5); 6.28 (s, 1H, =CH); 6.58 (s, $2H_{arom}$)[g]	356 (M^+, 0.5); 309 (12); 147 (92)
2h	83	124–125	$C_{14}H_{14}O_4S_2$ (310.4)	1660, 1600, 1570	2.49 (s, 6H, SCH_3); 3.42 (d, 1H, J = 2.5, H-4); 3.82 (d, 1H, J = 2.5, H-5); 5.96 (s, 2H, CH_2); 6.20 (s, 1H, =CH); 6.62–6.90 (m, $3H_{arom}$)	310 (M^+, 5); 294 (3); 279 (9); 263 (73); 147 (100)

[a] Yield of isolated product **2** based on **1**.
[b] Uncorrected, measured on Thomas Hoover melting point apparatus.
[c] Satisfactory microanalysis obtained: C ±0.29, H ±0.31.
[d] Recorded on Perkin Elmer 297 Infrared spectrophotometer.
[e] Recorded on Varian EM-390 spectrometer.
[f] Measured on Jeol-D 300 Mass spectrometer.
[g] In DMSO-d_6/$CDCl_3$.

Table 2. 2-Aryl-5,5-bis(methylthio)-3-hydroxy-2,4-pentadienals **3** Prepared

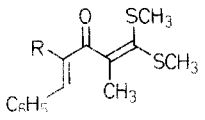
Product	Yield[a] (%)	m.p. (°C)[b]	Molecular Formula[c]	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[e] δ	MS (70 eV)[f] *m/e*
3a	92	158–159	$C_{13}H_{14}O_2S_2$ (266.4)	3200, 2830, 1580, 1500	2.25 (s, 3H, SCH_3); 2.60 (s, 3H, SCH_3); 5.85 (s, 1H, =CH); 7.50–7.55 (m, $5H_{arom}$); 7.80 (s, 1H, CHO)[g]	266 (M^+); 267 ($M^+ + 1$)
3b	86	159–160	$C_{14}H_{16}O_2S_2$ (280.4)	3200, 2830, 1595, 1480	2.26 (s, 3H, SCH_3); 2.40 (s, 3H, SCH_3); 2.63 (s, 3H, CH_3); 5.90 (s, 1H, =CH); 7.05–7.50 (m, $4H_{arom}$); 7.28 (s, 1H, CHO)	280 (M^+); 281 ($M^+ + 1$)
3c	87	164–165	$C_{13}H_{13}ClO_2S_2$ (300.8)	3200, 2840, 1595, 1500, 1480	2.26 (s, 3H, SCH_3); 2.60 (s, 3H, SCH_3); 5.82 (s, 1H, =CH); 7.05–7.50 (m, A_2B_2, $4H_{arom}$); 7.65 (s, 1H, CHO)	300, 302 (M^+); 301, 303 ($M^+ + 1$)
3d	88	140–141	$C_{14}H_{16}O_3S_2$ (296.4)	3210, 2825, 1600, 1520, 1485	2.20 (s, 3H, SCH_3); 2.55 (s, 3H, SCH_3); 3.80 (s, 3H, CH_3O); 5.81 (s, 1H, =CH); 6.75–7.26 (m, A_2B_2, $4H_{arom}$); 7.66 (s, 1H, CHO)	296 (M^+); 297 ($M^+ + 1$)
3e	85	154–155	$C_{14}H_{16}O_3S_2$ (296.4)	3250, 2825, 1590, 1490, 1475	2.14 (s, 3H, SCH_3); 2.50 (s, 3H, SCH_3); 3.70 (s, 3H, CH_3O); 5.83 (s, 1H, =CH); 6.78–7.50 (m, $4H_{arom}$); 7.70 (s, 1H, CHO)	296 (M^+); 297 ($M^+ + 1$)
3f	86	197–198	$C_{15}H_{18}O_4S_2$ (326.4)	3215, 2831, 1590, 1495	2.21 (s, 3H, SCH_3); 2.60 (s, 3H, SCH_3); 3.83 (s, 6H, CH_3O); 5.84 (s, 1H, =CH); 6.65–6.86 (m, $3H_{arom}$); 7.66 (s, 1H, CHO)	327 ($M^+ + 1$)
3g	88	178–179	$C_{16}H_{20}O_5S_2$ (356.5)	3200, 2825, 1590, 1480	2.20 (s, 3H, SCH_3); 2.57 (s, 3H, SCH_3); 3.88 (s, 9H, CH_3O); 5.90 (s, 1H, =CH); 6.49 (s, $2H_{arom}$); 7.74 (s, 1H, CHO)	357 ($M^+ + 1$)
3h	84	174–175	$C_{14}H_{14}O_4S_2$ (310.4)	3200, 2838, 1595, 1498, 1480	2.30 (s, 3H, SCH_3); 2.60 (s, 3H, SCH_3); 5.81 (s, 1H, =CH); 5.99 (s, 2H, CH_2); 6.60–6.82 (m, $3H_{arom}$); 7.67 (s, 1H, CHO)	310 (M^+); 311 ($M^+ + 1$)

[a] Yield of isolated product **3** based on **2**.
[b] Uncorrected, measured on Thomas Hoover melting point apparatus.
[c] Satisfactory microanalysis obtained C ±0.28, H ±0.31.
[d–f] As in Table 2.
[g] ^{13}C-NMR (CDCl$_3$/TMS): δ = 16.38 (q, SCH_3); 17.67 (q, SCH_3); 106.32 (d, =CH); 115.7 (s, Ar–C=); 128.49, 129.07, 130.26 (d, C_{arom}); 132.80 (s, C-1′ of phenyl); 169.70 (d, CHO); 176.50 [s, $=C(SCH_3)_2$]; 181.5 (s, HOC=).

methylthio-4*H*-pyran-4-ones **4** from cinnamoylketene dithioacetals **1** through a sequence of reactions shown in the Scheme.

When **1a** was reacted with alkaline hydrogen peroxide at room temperature, the corresponding (*β*-phenyl-*α*, *β*-epoxypropanoyl)ketene dithioacetal **2a** was obtained in 89% yield, while the bismethylthioenone group remained unaffected under these conditions. The epoxyketone **2a** underwent smooth rearrangement to the corresponding (*α*-formyl-*α*-phenylacetyl)ketene dithioacetal **3a** (92%) on treatment with ether-borontrifluoride complex in refluxing tetrahydrofuran. In a subsequent step, when **3a** was refluxed in ethanol and acetic acid, the corresponding 2-methylthio-5-phenyl-4*H*-pyran-4-one **(4a)** was obtained in 75% yield. The other substituted pyrones **4b–h** were similarly prepared in good yields by the same sequence from the respective **1b–h** *via* **2b–h** and **3b–h**.

The ketene dithioacetals **5a** and **5b** failed to undergo epoxidation with hydrogen peroxide under identical conditions and yielded only intractable reaction mixture at higher temperature (50–60° or under modified conditions.[8])



5a R = H
b R = CH_3

The structures of **2, 3** and **4** were established by their spectral and analytical data (Tables 1–3).

The starting cinnamoyl ketene dithioacetals **1a–h** were prepared according to the reported procedure.[2]

5-Aryl-1,1-bis(methylthio)-4,5-epoxy-1-penten-3-ones 2; General Procedure:
A solution of 30% H_2O_2 (5 mL) in 3 normal aqueous NaOH solution (5 mL) is added dropwise to a well stirred solution of **1** (10 mmol) in MeOH (150 mL) during 5 min. The mixture is stirred at room temperature for 6 h, diluted with water (100 mL), and left overnight in a refrigerator (0 °C). The epoxy compounds **2** are filtered as white solids, which are used as such for subsequent step and crystallyzed from MeOH for spectral and analytical data (Table 1).

2-Aryl-5,5-bis(methylthio)-3-hydroxy-2,4-pentadienals 3; General Procedure:
To a solution of **2** (10 mmol) in THF (50 mL), $Et_2O \cdot BF_3$ (16 mL) is added and the mixture is refluxed for 5 h. The mixture is cooled and poured over ice cold saturated $NaHCO_3$ solution (200 mL). The product is extracted with EtOAc (4 × 50 mL), washed with water (3 × 100 mL), dried (Na_2SO_4) and concentrated to give **3** as bright yellow to orange-red solids. These are used as such for subsequent reaction and crystallyzed from ether/$CHCl_3$ for spectral and analytical data (Table 2).

5-Aryl-2-methylthio-4*H*-pyran-4-ones 4; General Procedure:
A solution of **3** (7.5 mmol) in ethanol (15 mL) and glacial acetic acid (5 mL) is refluxed for 3–5 h, cooled and poured over ice cooled saturated $NaHCO_3$ solution (70 mL). The product is extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), evaporated and the residue is

Table 3. 5-Aryl-2-methylthio-4*H*-pyran-4-ones **4** Prepared

Product	Reaction Time (h)	Yield[a] (%)	m.p.[b] (°C)	Molecular Formula[c]	IR (KBr)[d] $\nu_{C=O}$ (cm^{-1})	^1H-NMR ($CDCl_3$/TMS)[e] δ	MS (70 eV)[f] m/e (%)
4a	6	75	96–97	$C_{12}H_{10}O_2S$ (218.3)	1630	2.40 (s, 3H, SCH_3); 6.10 (s, 1H, H-3); 7.13–7.41 (m, $5H_{arom}$); 7.69 (s, 1H, H-6)	218 (M^+, 53); 203 (13); 146 (38); 118 (28); 102 (100)
4b	7	72	109–110	$C_{13}H_{12}O_2S$ (232.3)	1630	2.33 (s, 3H, CH_3); 2.45 (s, 3H, SCH_3); 6.28 (s, 1H, H-3); 7.10–7.45 (m, A_2B_2, $4H_{arom}$); 7.80 (s, 1H, H-6)	232 (M^+, 48); 217 (11); 160 (48); 132 (14); 116 (100)
4c	5	76	114–115	$C_{12}H_9ClO_2S$ (252.7)	1650	2.47 (s, 3H, SCH_3); 6.28 (s, 1H, H-3); 7.20–7.49 (m, A_2B_2, $4H_{arom}$); 7.78 (s, 1H, H-6)	252, 254 (78, 27); 237, 239 (25, 7); 180, 182 (57, 20); 152, 154 (20.9); 136, 138 (100, 47)
4d	5	73	139–140	$C_{13}H_{12}O_3S$ (248.3)	1632	2.45 (s, 3H, SCH_3); 3.80 (s, 3H, CH_3O); 6.29 (s, 1H, H-3); 6.82–7.56 (m, A_2B_2, $4H_{arom}$); 7.77 (s, 1H, H-6)	248 (100); 233 (15); 176 (69); 148 (10); 132 (63)
4e	4	72	Viscous Semisolid	$C_{13}H_{12}O_3S$ (248.3)	1635[g]	2.48 (s, 3H, SCH_3); 3.80 (s, 3H, CH_3O); 6.19 (s, 1H, H-3); 6.73–7.37 (m, $4H_{arom}$); 7.78 (s, 1H, H-6)	248 (M^+, 100), 233 (17); 176 (39); 148 (80); 132 (65)
4f	5	70	144–145	$C_{14}H_{14}O_4S$ (278.3)	1640	2.45 (s, 3H, SCH_3); 3.82 (s, 6H, CH_3O); 6.19 (s, 1H, H-3); 6.68–7.17 (m, $3H_{arom}$); 7.72 (s, 1H, H-6)	278 (M^+, 100); 263 (7); 206 (4); 178 (30); 162 (25)
4g	3	69	63–64	$C_{15}H_{16}O_5S$ (308.4)	1637	2.45 (s, 3H, SCH_3); 3.71 (s, 3H, CH_3O); 3.81 (s, 6H, CH_3O); 6.15 (s, 1H, H-3); 6.60 (s, $2H_{arom}$); 7.69 (s, 1H, H-6)	308 (M^+, 21); 293 (26); 208 (7); 192 (65)
4h	6	71	144–145	$C_{13}H_{10}O_4S$ (262.3)	1625	2.46 (s, 3H, SCH_3); 5.95 (s, 2H, CH_2); 6.25 (s, 1H, H-3); 6.77–7.05 (m, $3H_{arom}$); 7.72 (s, 1H, H-6)	262 (M^+, 100); 247 (12); 190 (71); 162 (100); 146 (64)

[a] Yield of isolated product **4** based on **3**.
[b] Uncorrected, measured on Thomas Hoover melting point apparatus.
[c] Satisfactory microanalysis obtained: C ±0.27, H ±0.34.
[d–e] As in Table 1.
[g] In chloroform.

chromatographed on a neutral alumina column using EtOAc and hexane (1:20) as eluent to afford **4** as colorless solids which are crystallized from $CHCl_3$/hexane mixture (Table 3).

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