Synthesis of Methyl 5-Aryl-3-oxo-4-pentenoates and Novel Substituted Cyclopentenones[1]

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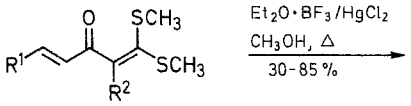
The cinnamoyl- (**1a–j**) and (5-phenyl-2,4-pentadienoyl)- (**1k**) ketene dithioacetals are shown to undergo methanolysis in the presence of ether-boron trifluoride complex and mercury(II) chloride to the corresponding methyl 5-aryl-3-oxo-4-pentenoates **2a–j** and 3-oxo-7-phenyl-4,6-heptadienoate (**2k**), respectively, in good yields. However, the corresponding (2-methylcinnamoyl)ketene dithioacetals **3a–f**, under identical reaction conditions, undergo Nazarov cyclization to give the corresponding substituted cyclopentenones **4a–f**.

Recently we have reported that cinnamoylketene dithioacetals (5-aryl-1,1-bis(methylthio)penta-1,4-diene-3-ones) react with allylmagnesium bromide to give 1,2-adducts, which on cycloaromatization in the presence of ether-boron trifluoride complex yield the corresponding stilbenes in good yields.[2] Similarly, these dithioacetals were also converted to novel 2-methylthio-5-aryl-4*H*-pyran-4-ones.[3] We further contemplated that these acetals, under suitable reaction conditions, should yield the corresponding 3-oxo-4-pentenoates **2**, and our results are reported in this communication.

When the dithioacetal **1a** was refluxed in the presence of ether-boron trifluoride complex in methanol, the reaction mixture showed formation of several products along with unreacted **1a** even after prolonged refluxing (22 h). However, treatment of **1a** with boron trifluoride and mercury(II) chloride in refluxing methanol yielded only one product after work-up, which was identified as 3-oxo-5-phenyl-4-pentenoate (**2a**) (70%). The reaction was found to be general and the other oxoesters **2b–g** and the corresponding 2-methyl derivatives **2h–j** were similarly obtained from the respective **1b–j** in 65–85% overall yields (Scheme **A**). Similarly methanolysis of the corresponding (5-phenyl-2,4-pentadienoyl)ketene dithioacetal (**1k**) yielded the corresponding methyl 3-oxo-4,6-heptadienoate (**2k**), though in low yield (30%). The esters **2a–j** were found to exist in keto-enol equilibrium in solution, and their ratio has been determined by ^{1}H-NMR data (Table 1).



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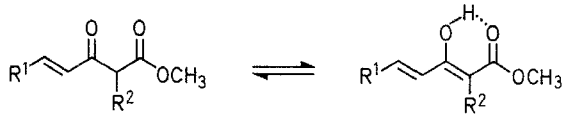
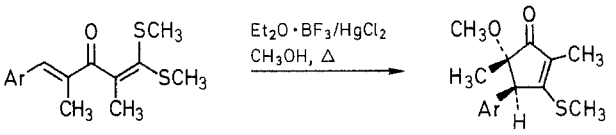


2A **2B**

1, 2	R^1	R^2	1, 2	R^1	R^2
a	C_6H_5	H	**g**	3,4-Methylenedioxy-C_6H_3	H
b	4-$CH_3C_6H_4$	H	**h**	C_6H_5	CH_3
c	4-ClC_6H_4	H	**i**	4-ClC_6H_3	CH_3
d	4-$CH_3OC_6H_4$	H	**j**	4-$CH_3OC_6H_4$	CH_3
e	3,4-$(CH_3O)_2C_6H_3$	H	**k**	C_6H_5–CH=CH–	H
f	3,4,5-$(CH_3O)_3C_6H_2$	H			

Scheme **A**

The dithioacetal **3a** obtained by condensation of propanoyl-(methyl)ketene dithioacetals and benzaldehyde was similarly subjected to methanolysis, but the expected methyl 5-aryl-2,4-dimethyl-3-oxo-4-pentenoate was not detected. The product was characterized as 2,5-dimethyl-5-methoxy-3-methylthio-4-phenyl-2-cyclopentene-1-one (**4a**) on the basis of spectral and analytical data. When the other substituted ketene dithioacetals **3b–f** were reacted under identical conditions, the corresponding cyclopentenones **4b–f** were isolated in 55–73% overall yields (Scheme **B**).

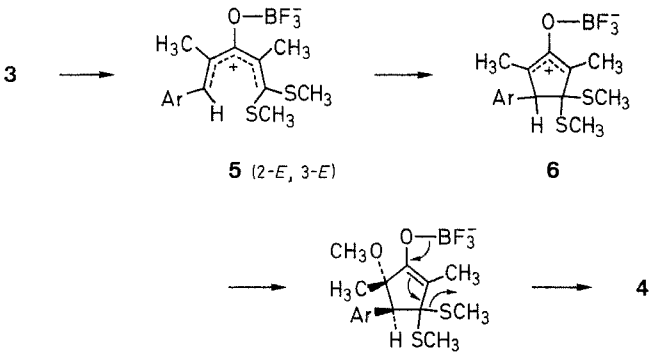


3 **4**

3, 4	Ar	3, 4	Ar
a	C_6H_5	**d**	4-$CH_3OC_6H_4$
b	4-$CH_3C_6H_4$	**e**	3-$CH_3OC_6H_4$
c	4-ClC_6H_4	**f**	3,4-Methylenedioxy-C_6H_3

Scheme **B**

Evidently, the cyclopentenones **4** are formed by ether-boron trifluoride catalyzed Nazarov type cyclization[4] of the dithioacetals **3** and subsequent methanolysis and elimination of methanethiolate, presumably involving intermediate cations **5** and **6** (Scheme **C**). Apparently, the presence of methyl groups at 2- and 4-positions forces the carbenium ion **5** to a twisted non-planar 2-*E*, 3-*E*-configuration[5], thus creating a favorable geometry for cyclization to the corresponding cyclopentenyl cation **6**, which is further stabilized by the two methyl groups.



3 **5** (2-*E*, 3-*E*) **6** **7** **4**

Scheme **C**

The relative stereochemistry at C-4 and C-5 atoms and positions of substituents in **4** were ascertained by their spectral and analytical data. Thus **4a** exhibited in its ^{1}H-NMR spectrum singlets at $\delta = 0.71$, 2.02 and 3.18 for methyl groups at position 5, SCH_3 and OCH_3 groups, respectively, while the signal due to methyl group at position 2 appeared as a sharp doublet at $\delta = 1.82$ ($J = 2.5$ Hz), due to allylic coupling with H-4 proton. The higher field chemical shift of 5-methyl group is apparently due to shielding by phenyl group, thus showing the *cis*-stereochemical relationship between the two groups. The structure of **4a** was further supported by its ^{13}C-NMR spectrum (Table 2).

Table 1. Products **2a–k** Prepared

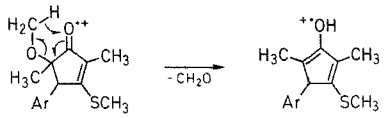
Product	Yield (%)	Keto-Enol Ratio[a] (2A : 2B)	mp (°C)	Molecular Formula[c]	IR (KBr/Film)[d] ν(cm^{-1})	^{1}H-NMR (CCl_4/TMS)[e,f] δ, J(Hz)	MS (70eV)[g] m/z (M^+, %)
2a	70	20 : 80	79–80	$C_{12}H_{12}O_3$ (204.2)	1632, 1532[h]	3.42 (s, 0.4H, CH_2); 3.60 (s, 3H, CH_3O); 5.04 (s, 0.8H, =CH); 6.31 (d, 0.8H, J = 15, =CH); 6.70–7.68 (m, 6.2H$_{arom+olefin}$); 11.90 (s, 0.8H, OH)	204 (65)
2b	72	33 : 67	78–79	$C_{13}H_{14}O_3$ (218.2)	1630, 1590[h]	2.31 (s, 3H, CH_3); 3.52 (s, 0.66H, CH_2); 3.62 (s, 3H, CH_3O); 5.00 (s, 0.67H, =CH); 6.23 (d, 0.66H, J = 15, =CH); 6.60 (d, 0.33H, J = 15, =CH); 6.88–7.60 (m, 5H$_{arom+olefin}$); 11.68 (s, 0.67H, OH)	218 (40)
2c	69	22 : 78	83–84	$C_{12}H_{11}ClO_3$ (238.7)	1645, 1628, 1588[h]	3.48 (s, 0.44H, CH_2); 3.68 (s, 3H, CH_3O); 5.08 (s, 0.78H, =CH); 6.28 (d, 0.78H, J = 15, =CH); 6.68 (d, 0.22H, J = 15, =CH); 7.00–7.50 (m, 5H$_{arom+olefin}$); 11.70 (s, 0.78H, OH)	240 (18); 238 (53)
2d	65	75 : 25	91–92	$C_{13}H_{14}O_4$ (234.2)	1642, 1622, 1588[h]	3.58 (s, 1.5H, CH_2); 3.64 (s, 3H, CH_3O); 3.71 (s, 3H, CH_3O); 5.02 (s, 0.25H, =CH); 6.19 (d, 0.25H, J = 15, =CH); 6.58 (d, 0.75H, J = 12, =CH); 6.71–7.66 (m, 5H$_{arom+olefin}$); 11.62 (s, 0.25H, OH)	234 (77)
2e	68	40 : 60	82–83	$C_{14}H_{16}O_5$ (264.3)	1744 (w), 1644, 1622, 1593[i]	3.60 (s, 0.8H, CH_2); 3.67 (s, 3H, CH_3O); 3.80 (s, 6H, CH_3O); 5.06 (s, 0.6H, =CH); 6.21 (d, 0.6H, J = 15, =CH); 6.59 (d, 0.4H, J = 15, =CH); 6.71–7.10 (m, 3H$_{arom}$); 7.27 (d, 0.6H, J = 15, =CH); 7.52 (d, 0.4H, J = 15, =CH); 11.66 (s, 0.6H, OH)	264 (49)
2f	66	67 : 33	94–95	$C_{15}H_{18}O_6$ (294.3)	1738, 1640, 1625, 1590[j]	3.63 (s, 1.34H, CH_2); 3.68 (s, 3H, CH_3O); 3.83 (s, 9H, CH_3O); 5.10 (s, 0.67H, =CH); 6.23 (d, 0.33H, J = 15, =CH); 6.61 (d, 0.67H, J = 15, CH); 6.62–6.81 (m, 2H$_{arom}$); 7.28 (d, 0.33H, J = 15, 0.33H, =CH); 7.51 (d, 0.67H, J = 15, 0.67H, =CH); 11.66 (s, 0.67H, OH)	294 (86)
2g	64	40 : 60	91–92	$C_{13}H_{12}O_5$ (248.2)	1740 (w), 1630, 1590[i]	3.57 (s, 0.8H, CH_2); 3.68 (s, 3H, CH_3O); 5.02 (s, 0.6H, =CH); 5.88 (s, 2H, OCH_2O); 6.18 (d, 0.6H, J = 15, 0.6H, =CH); 6.51 (d, 0.4H, J = 15, 0.4H, =CH); 6.65–7.10 (m, 3H$_{arom}$); 7.30 (d, 0.6H, J = 15, 0.6H, =CH); 11.65 (s, 0.6H, OH)	248 (77)
2h	85	80 : 20	viscous liquid	$C_{12}H_{14}O_3$ (218.2)	1740, 1688, 1660, 1610[j]	1.37 (d, 2.4H, J = 7, CH_3); 1.88 (s, 0.6H, CH_3); 3.67 (s, 3H, CH_3O); 3.69 (q, 0.8H, J = 7, $CH_3C\underline{H}$); 6.81 (d, 0.8H, J = 15, =CH); 7.16–7.81 (m, 6.2H$_{arom+olefin}$); 12.50 (s, 0.19H, OH)	218 (39)
2i	84	20 : 80	viscous liquid	$C_{13}H_{13}ClO_3$ (252.7)	1640, 1620, 1590[h]	1.44 (d, 0.6H, J = 7, CH_3); 1.93 (s, 2.4H, CH_3); 3.73 (q, 0.2H, J = 7, $CH_3C\underline{H}$); 3.82 (s, 3H, CH_3O); 6.80 (d, 0.2H, J = 15, =CH); 6.82 (d, 0.8H, J = 15, =CH); 7.21–7.71 (m, 5H$_{arom+olefin}$); 12.60 (s, 0.8H, OH)	254 (7); 252 (21)
2j	83	100 : 0	viscous liquid	$C_{14}H_{16}O_4$ (248.3)	1730, 1682, 1595[j]	1.32 (d, 3H, J = 7, CH_3); 3.68 (s, 3H, CH_3O); 3.80 (s, 3H, CH_3O); 3.81 (q, 1H, J = 7, $C\underline{H}CH_3$); 6.55 (d, 1H, J = 15, =CH); 6.81 (d, 2H$_{arom}$, J = 12); 6.82–7.76 (m, 3H$_{arom+olefin}$)	–
2k	30	30 : 70	89	$C_{14}H_{14}O_3$ (230.2)	1638, 1620, 1588, 1560[h]	3.63 (s, 0.6H, CH_2); 3.80 (s, 3H, CH_3O); 5.10 (s, 0.7, =CH); 6.00 (d, 0.7H, J = 15, =CH); 6.71–7.83 (m, 8.3H$_{arom+olefin}$); 11.88 (s, 0.7, OH)	230 (63)

[a] Keto-enol ratio in CCl_4, estimated by ^{1}H-NMR spectra.
[b] Uncorrected, measured on Thomas Hoover melting point apparatus.
[c] Satisfactory microanalyses obtained: C ±0.31, H ±0.29.
[d] Recorded on Perkin-Elmer 297 Infrared Spectrophotometer.
[e] Recorded on Varian EM-390 Spectrometer.
[f] The styryl olefinic protons of keto and enol forms in **2a–k** appear at different δ values.
[g] Measured on Jeol-D 300 Mass Spectrometer.
[h] The products **2a**, **2b**, **2c**, **2d**, **2i** and **2k** exist in enol forms in solid or neat liquid phase as evident from the absence of peak above 1700 cm^{-1} due to free ester carbonyl group in thier IR spectra.
[i] The products **2e** and **2g** exist in enol form in solid phase, but show presence of small amount of keto form (~5%) as indicated by the presence of weak intensity peaks at 1744 and 1740 cm^{-1}, respectively, in their IR spectra.
[j] The products **2f**, **2h** and **2j** exist in keto form in solid or neat liquid phase, as they show a strong intensity peak between 1730–1740 cm^{-1} in their IR spectra.

Table 2. Cyclopentenones **4** Prepared

Product	Reflux Time (h)	Yield (%)	mp[a] (°C)	Molecular Formula[b]	IR (KBr/Film)[c] ν (cm^{-1})	^{1}H-NMR (CCl_4/TMS)[d] δ, J (Hz)	MS (70eV)[e,f] m/z (%)
4a	3	73	52	$C_{15}H_{18}O_2S$ (262.4)	1674, 1568	0.71 (s, 3H, 5-CH_3); 1.82 (d, 3H, J = 2.5, 2-CH_3); 2.02 (s, 3H, SCH_3); 3.18 (s, 3H, CH_3O); 4.0 (q, 1H, J = 2.5, H-4); 7.00–7.40 (m, 5H_{arom})[g]	262 (M^+, 4); 232 (100)
4b	3	65	oil	$C_{16}H_{20}O_2S$ (276.4)	1690, 1595	0.70 (s, 3H, CH_3); 1.80 (d, 3H, J = 2.5, CH_3); 2.03 (s, 3H, SCH_3); 2.32 (s, 3H, ArCH_3); 3.16 (s, 3H, CH_3O); 4.02 (q, 1H, J = 2.5, ArC$\underline{H}$); 6.81–7.22 (m, 4H_{arom})	276 (M^+, 3); 246 (100)
4c	3	60	oil	$C_{16}H_{20}O_3S$ (292.4)	1680, 1580	0.71 (s, 3H, CH_3); 1.71 (d, 3H, J = 2.5, CH_3); 1.95 (s, 3H, SCH_3); 3.10 (s, 3H, CH_3O); 3.70 (s, 3H, CH_3O); 3.90 (q, 1H, J = 2.5, ArC$\underline{H}$); 6.70–7.01 (m, 4H_{arom})	292 (M^+, 37); 262 (100)
4d	3	68	oil	$C_{15}H_{17}ClO_2S$ (296.8)	1682, 1583	0.70 (s, 3H, CH_3); 1.83 (d, 3H, J = 2.5, CH_3); 2.06 (s, 3H, SCH_3); 3.21 (s, 3H, CH_3O); 4.01 (q, 1H, J = 2.5, ArC$\underline{H}$); 6.90–7.51 (m, 4H_{arom})	296 (M^+, 1); 266 (100); 268 (36)
4e	4	60	oil	$C_{16}H_{20}O_3S$ (292.4)	1680, 1580	0.65 (s, 3H, CH_3); 1.82 (d, 3H, J = 2.5, CH_3); 2.06 (s, 3H, SCH_3); 3.22 (s, 3H, CH_3O); 4.01 (q, 1H, J = 2.5, ArC$\underline{H}$); 6.5–7.21 (m, 4H_{arom})	292 (M^+, 1); 262 (100)
4f	6	55	oil	$C_{16}H_{18}O_4S$ (306.4)	1681, 1580	0.75 (s, 3H, CH_3); 1.81 (d, 3H, J = 2.5); 2.10 (s, 3H, SCH_3); 3.15 (s, 3H, CH_3O); 3.91 (q, 1H, J = 2.5, ArC$\underline{H}$); 5.90 (s, 2H, OCH_2O); 6.41–6.90 (m, 3H_{arom})	306 (M^+, 59); 276 (100)

[a] Uncorrected, measured on Thomas Hoover melting point apparatus.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.30.
[c–e] Refers to footnotes d, e, g in Table 1.
[f] Mass spectra of all **4a–f** show base peak at $M^+ - 30$, which is due to elimination of formaldehyde through McLafferty rearrangement involving transfer of γ-hydrogen[5].



[g] ^{13}C-NMR ($CDCl_3$/TMS): δ = 8.72 (5-CH_3); 13.49 (2-CH_3); 18.14 (SCH_3); 51.74 (OCH_3); 57.94 (C-5); 127.58, 128.86 (C_{arom}); 133.10 (C-2), 137.77 (C-1'$_{arom}$); 171.93 (C-3), 204.0 (C=O).

γ,δ-Unsaturated β-ketoesters are highly versatile and useful synthetic intermediates[6–11] and a number of methods are reported for their synthesis. The most general methods[6,12–15] involve condensation of either dianions or Wittig reagents derived from acetoacetic esters with appropriate carbonyl compounds.[9] The present method is a simple alternative route for these compounds involving easily accessible acylketene dithioacetals with a latent β-ketoester functionality. Similarly, Nazarov cyclization of **3** affords novel substituted cyclopentenones.

Methyl 5-Aryl-3-oxo-4-pentenoates 2a–j, Methyl 3-Oxo-7-phenyl-4,6-heptadienoate (2k) and 4-Aryl-2,5-Dimethyl-5-methoxy-3-methyl-2-cyclopentene-1-ones 4a–f; General Procedure:

A suspension of acylketene dithioacetal **1** or **3** (0.01 mol) and $HgCl_2$ (2.70 g, 0.01 mol) in dry MeOH (30 mL) is stirred at room temperature vor 10 min and distilled $Et_2O \cdot BF_3$ (1.5 mL, 0.01 mol is added and the mixture is refluxed for 2 h **(2a–k)** of 3–6 h **(4a–f)**. The mixture is filtered through a sintered funnel to remove traces of $HgCl_2$ and the filtrate diluted with $CHCl_3$ (100 mL), washed with sat. $NaHCO_3$ solution (2 × 50 mL) and water (2 × 50 mL), dried (Na_2SO_4) and evaporated to give crude products, which are purified by column chromatography on silica gel. Elution with hexane/EtOAc (95:5) gives pure esters **2a–k** and cyclopentenones **4a–f** (Table).

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(1) Part 64 of the series on Polarized Ketene *S,S*- and *S,N*-Acetals. Part 63: Datta, A., Ila, H., Junjappa, H. *Tetrahedron* , in press.
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