Simple Preparation of 4-Aryl- and 4-Alkyl-2(5*H*)-furanones from β-Substituted Crotonic Esters

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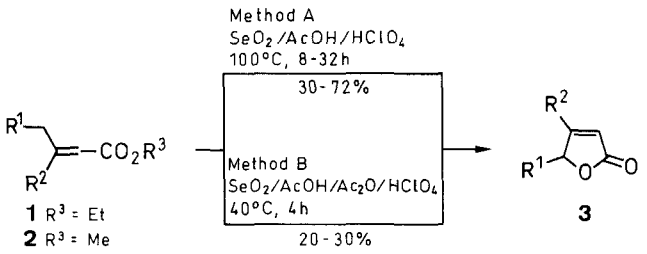
Treatment of β-aryl- or β-alkylcrotonic esters with selenium dioxide in acetic acid in the presence of a catalytic amount of perchloric acid gave 4-substituted 2(5*H*)-furanones in moderate to good yields.

2(5*H*)-Furanones are widespread in a variety of biologically important natural products, and are used as versatile synthetic intermediates. For their preparation, the classic Reformatsky reaction and many other methods have been developed and reviewed.[1-3] Recently, palladium(II)- or silicon-assisted methods have been elaborated.[4,5] However, surprisingly no attention has been payed to the method developed by Sondheimer et al., who prepared a steroidal lactone by allylic oxidation with selenium dioxide.[6,7] We have examined this method and found it to be generally suitable for the synthesis of 4-aryl-2(5*H*)-furanones, simply by modifying the reaction conditions.

We tried to optimize the reaction conditions with the easily available ethyl β-phenylcrotonate (**1a**).[8] The phenyl derivative **1a** was actually converted to 4-phenyl-2(5*H*)-furanone (**3a**) in 20–34% yield under known conditions, i.e., in refluxing benzene and acetic acid. Sulfuric acid is reported to enhance the oxidation potential of selenium dioxide by protonation on the Se=O bond.[9] By adding perchloric acid to the acetic acid solution, we could improve the yield of **3a** to 42%. Further, in contrast to ethyl ester, the methyl ester underwent condensation more readily; **3a** was formed from **2a** in a preparatively satisfactory yield of 60% after 20 hours of heating at 100 °C. (Method A. Table 1). Here, it is worth noting that the corresponding β-phenylcrotonic acid was not converted to **3a** and that adding acetic anhydride to the acetic acid solvent (1:1, w/w) improved the yield of **3a** to 50%. By the modified procedure, the methyl β-phenylcrotonates in which the phenyl ring is substituted with various groups and their naphthyl, as well as thienyl derivatives, were converted to the corresponding unsaturated lactones in one step.

Also an alkyl butenolide, 4-*tert*-butyl-2-(5*H*)-furanone (**3m**) was obtained in good yield from β-*tert*-butylcrotonic ester (**2m**). However methyl cyclohexylideneacetate (**2o**) gave a complex product mixture under the above conditions. Lactone **3o** was isolated in 30% yield in acetic acid/acetic anhydride containing perchloric acid as catalyst at 40 °C (Method B, Table 1). The yield of 4-methylfuranone (**3n**) was poor even under these mild conditions.

Application of the present method may be restricted to the preparation of 4-aryl- and 4-tertiaryalkyl-2(5*H*)-furanones. However, our simple procedure starting with easily accessible materials is an alternative choice to the existing methodologies.



1–3	R^1	R^2	1–3	R^1	R^2
a	H	Ph	**i**	H	3,4-$(MeO)_2C_6H_3$
b	H	4-ClC_6H_4	**j**	H	1-naphthyl
c	H	4-BrC_6H_4	**k**	H	2-naphthyl
d	H	4-MeC_6H_4	**l**	H	2-thienyl
e	H	4-$MeOC_6H_4$	**m**	H	*t*-C_4H_9
f	H	4-$O_2NC_6H_4$	**n**	H	Me
g	H	4-$PhOC_6H_4$	**o**	$-(CH_2)_4-$	
h	H	4-(2′,4′-$Cl_2C_6H_3$)OC_6H_4			

Table 1. 4-Substituted 2(5*H*)-Furanones **3** Prepared

Product	Method	Reaction Time (h)	Yield (%)	mp (°C) or bp (°C/Torr)	Molecular Formula[a] or Lit. mp (°C) or bp (°C/Torr)
3a	A	20	60	87	92.5[4]
3b	A	20	51	162	171–173[10]
3c	A	20	55	169	163[4]
3d	A	12	62	117	116[4]
3e	A	8	72	121	120[4]
3f	A	32	30	262	270[11]
3g	A	20	67	121	$C_{16}H_{12}O_3$ (252.3)
3h	A	20	50	130	$C_{16}H_{10}Cl_2O_3$ (321.1)
3i	A	8	59	136	$C_{12}H_{12}O_4$ (220.2)
3j	A	30	35	99	$C_{14}H_{10}O_2$ (210.2)
3k	A	20	60	131	$C_{14}H_{10}O_2$ (210.2)
3l	A	16	68	100	$C_8H_6O_2S$ (166.2)
3m	A	30	52	136–140/15	53/0.07[1]
3n	B	4	20	105–110/12	115–130/35[12]
3o	B	4	30	138–145/13	100–120/0.1[13]

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.30, S ±0.22.

Table 2. Conversion of Ethyl Ester **1** to Methyl Ester **2**

Product	Time (h)	Yield (%)	mp (°C) or bp (°C/Torr)
2a	14	79	138–142/18
2b	6	88	163–168/15
2c	6	91	173–181/15
2d	16	70	160–164/16
2e	18	66	179–181/16
2f	10	90	123–126 (EtOH)
2i	24	65	140–145/0.1
2k	12	77	163–177/0.1
2l	14	60	148–153/16
2m	24	58	116–122/50
2o	24	55	100–101/15

Table 3. Spectroscopic Data of **3**

Product	MS (M^+, base ion) *m/e* (rel. int.)	IR (KBr/film) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS), δ	
				Lactone Ring	Others
3a	160 (51), 131 (100)	1790, 1750, 1710, 1610	5.20 (d, 2H, J = 1.8), 6.37 (t, 1H, J = 1.8), 7.4–7.6 (m, 5H)	71.0, 112.9, 163.9, 173.8	126.4, 129.3, 129.6, 131.8
3b	194 (69), 165 (100)	1780, 1750, 1720, 1610	5.21 (d, 2H, J = 1.8), 6.37 (t, 1H, J = 1.8), 7.46 (brs, 4H)	70.8, 113.6, 162.5, 173.5	127.7, 128.1, 129.6, 137.9
3c	240 (63), 209 (100)	1780, 1750, 1710, 1610	5.21 (d, 2H, J = 1.5), 6.39 (t, 1H, J = 1.5), 7.38 (d, 2H, J = 8.9), 7.62 (d, 2H, J = 8.9)	70.8, 113.8, 162.6, 173.4	126.3, 127.9, 128.8, 132.7
3d	174 (90), 145 (100)	1780, 1740, 1710, 1610	2.41 (s, 3H), 5.19 (d, 2H, J = 1.1), 6.31 (t, 1H, J = 1.1), 7.27 (d, 2H, J = 8.4), 7.40 (d, 2H, J = 8.4)	71.0, 111.9, 163.9, 174.1	21.5, 126.4, 126.9, 129.9, 142.5
3e	190 (100)	1785, 1720, 1620	3.87 (s, 3H), 5.19 (d, 2H, J = 1.5), 6.24 (t, 1H, J = 1.5), 6.98 (d, 2H, J = 9.2), 7.46 (d, 2H, J = 9.2)	70.9, 114.7, 163.6, 174.3	55.5, 110.7, 122.3, 128.2, 162.5
3f[a]	205 (41), 176 (100)	1780, 1720, 1620	5.45 (d, 2H, J = 1.9), 6.99 (t, 1H, J = 1.9), 7.99 (d, 2H, J = 8.8), 8.34 (d, 2H, J = 8.8)	71.1, 116.2, 162.4, 173.1	124.0, 128.4, 135.6, 148.7
3g	252 (100)	1790, 1740, 1620	5.19 (d, 2H, J = 2.0), 6.28 (t, 1H, J = 2.0), 7.04 (d, 2H, J = 8.9), 7.45 (d, 2H, J = 8.9), 7.0–7.5 (m, 5H)	70.9, 111.6, 163.2, 174.0	118.4, 120.0, 124.1, 124.6, 128.3, 130.1, 155.5, 160.8
3h	320 (100)	1785, 1735, 1618	5.19 (d, 2H, J = 1.5), 6.30 (t, 1H, J = 1.5), 6.98 (d, 2H, J = 8.9), 7.05 (d, 1H, J = 8.9), 7.28 (dd, 1H, J = 8.9, 2.5), 7.48 (d, 2H, J = 8.9), 7.50 (d, 1H, J = 2.5)	70.9, 112.1, 162.9, 173.9	117.5, 123.1, 124.7, 127.7, 128.4, 128.5, 130.8, 130.9, 150.0, 159.8
3i	220 (100)	1790, 1720, 1620	3.94 (s, 3H), 3.95 (s, 3H), 5.20 (d, 2H, J = 1.8), 6.25 (t, 1H, J = 1.8), 6.92 (d, 1H, J = 8.5), 7.00 (d, 1H, J = 2.0), 7.08 (dd, 1H, J = 8.5, 2.0)	70.9, 109.2, 163.7, 174.1	56.0, 56.1, 110.9, 111.2, 120.0, 122.5, 149.6, 152.3
3j	210 (45), 152 (100)	1780, 1760, 1720, 1640	5.26 (d, 2H, J = 1.8), 6.45 (t, 1H, J = 1.8), 7.5–8.2 (m, 7H)	73.2, 118.9, 163.9, 173.6	124.2, 125.0, 125.5, 126.8, 127.7, 128.5, 129.0, 130.3, 131.2, 134.0
3k	210 (100)	1790, 1720, 1610	5.30 (d, 2H, J = 1.5), 6.45 (t, 1H, J = 1.5), 7.5–8.0 (m, 7H)	71.1, 113.2, 163.7, 173.9	123.2, 126.4, 127.0, 127.2, 127.9, 128.1, 128.7, 129.2, 132.8, 134.6
3l	166 (100)	1795, 1720, 1600	5.17 (d, 2H, J = 1.8), 6.15 (t, 1H, J = 1.8), 7.15 (dd, 1H, J = 5.1, 3.7), 7.27 (dd, 1H, J = 3.7, 1.1), 7.57 (dd, 1H, J = 5.1, 1.1)	70.8, 111.2, 157.2, 173.5	128.4, 128.5, 130.5, 132.7
3m	140 (6), 41 (100)	1780, 1750, 1630	1.24 (s, 9H), 4.85 (d, 2H, J = 1.8), 5.79 (t, 1H, J = 1.8)	70.7, 112.9, 174.0, 179.3	28.8, 67.3
3n	98 (21), 41 (100)	1785, 1750, 1725, 1650	2.13 (s, 3H), 4.74 (brs, 2H), 5.83 (brs, 1H), 7.4 (brs, 2H)	73.7, 115.9, 166.2, 173.9	13.8
3o	138 (48), 109 (100)	1790, 1740, 1640	1.2–3.1 (m, 8H), 4.7 (m, 1H), 5.72 (m, 1H)	81.4, 112.3, 172.1, 173.5	22.5, 26.6, 28.1, 34.4

[a] NMR data were obtained in DMSO-d_6.

The unsaturated lactones are expected to possess some physiological activity. For example **3h** exhibited herbicidal activity against broad-leaf weeds.

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-GX270 (270 MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were obtained at 70 eV with Shimadzu QP1000 mass spectometer. IR spectra were obtained using JASCO A-100 spectrophotometer. $HClO_4$ (0.1 mol/L in AcOH), SeO_2 and trimethylphosphonoacetate, triethylphosphonoacetate, 4-phenoxyacetophenone and methyl β,β-dimethylacrylate (**2n**) were purchased from Wako Chemicals Co.

The ethyl esters **1a**,[8] **1b–d**,[14] **1e**,[15] **1f**,[16] **1i**,[17] **1k**,[18] **1l**,[19] **1m**,[20] and **1o**[8] were prepared according to literature. These were converted to the known corresponding methyl esters **2a–f, i, k–m, o** by the general procedure given below.

Methyl Esters 2a–f, i, k–m, o; General Procedure:

A solution of the appropriate ethyl ester **1** (0.1 mol) and NaOH (40 mg, 0.001 mol) in MeOH (150 mL) was stirred at reflux for 6–24 h. Most of the solvent was evaporated at 50 °C under reduced pressure. The methyl ester was extracted with benzene (100 mL) and the extract was washed with water (2 × 50 mL) and dried (Na_2SO_4). Evaporation of the solvent and subsequent distillation of the residue in vacuum afforded **2** in 60–90% yield contaminated with 3–5% of the ethyl ester. This crude product was used without further purification (Table 2).

The new compounds **2g,h,j** were prepared from 1-acetylnaphthalene, 4-phenoxyacetophenone and 4-(2,4-dichlorophenoxy)acetophenone, respectively following the general procedure. The starting material needed for the preparation of **2h**, 4-(2,4-dichlorophenoxy)acetophenone is unknown in the literature. It was prepared following the new procedure for the synthesis of diphenyl ethers by Yeager and Schissel.[22]

4-(2,4-Dichlorophenoxy)acetophenone: To a solution of 2,4-dichlorophenol (16.2 g, 0.10 mol) and 4-fluoroacetophenone (13.8 g, 0.10 mol) in dimethylacetamide was added finely powdered anhydrous K_2CO_3 (14.9 g, 0.12 mol). The mixture was refluxed for 11 h, then allowed to cool to r.t. and diluted with H_2O (100 mL). The solid product was filtered and dried. The crude product was washed with hexane (10 mL) and can be used as such for further reactions. For analysis a small portion was sublimated at 170 °C/18 Torr; yield: 16.8 g (59 %); mp 57–58 °C.

$C_{14}H_{10}Cl_2O_2$	calc.	C 59.81	H 3.59
(281.1)	found	59.90	3.48

IR (KBr): ν = 1665 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 2.57 (s, 3 H), 6.94 (d, 2 H, J = 8.8 Hz), 7.05 (d, 1 H, J = 8.9 Hz), 7.28 (dd, 1 H, J = 8.9, J = 2.0 Hz), 7.51 (d, 1 H, J = 2.0 Hz), 7.95 (d, 2 H, J = 8.8 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 26.5, 116.5, 120.6, 123.2, 126.8, 127.7, 128.5, 130.7, 130.8, 132.5, 149.7, 161.0, 196.6

Methyl 3-(α-Naphthyl)crotonate (2j); Typical Procedure:
Trimethylphosphonoacetate (21.0 g, 0.1 mol) was added to a solution of NaOMe (5.4 g, 0.1 mol) in MeOH (100 mL). After stirring for 10 min 1-acetylnaphthalene (8.5 g, 0.05 mol) was added dropwise at r.t. The mixture was refluxed for 20 h. Most of the solvent was distilled off under reduced pressure. The residue was extracted with benzene (200 mL), washed with water (2 × 100 mL) and dried. The benzene was evaporated, and the residual liquid distilled to afford **2j**; yield: 8.5 g (75 %), bp 169–173 °C/0.1 Torr.

$C_{15}H_{14}O_2$ Exact Mass:	calc.	226.099
(226.1)	found	226.010

IR (KBr): ν = 1718, 1638 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 2.62 (d, 3 H, J = 1.5 Hz), 3.77 (3 H, s), 5.99 (q, 1 H, J = 1.5 Hz), 7.26 (dd, 1 H, J = 7.0, J = 1.1 Hz), 7.38–7.52 (3 H, m), 7.75–7.92 (3 H, m).

^{13}C NMR ($CDCl_3$/TMS): δ = 21.7, 51.5, 120.2, 124.2, 125.2, 125.3, 126.0, 126.3, 128.1, 128.2, 128.5, 130.0, 133.7, 157.4, 167.0.

2g: yield; 63 %, bp 185–191 °C/0.1 Torr (Lit.[21] 161–165/0.02 Torr).

2h: yield; 52 %, bp 183–190 °C/0.01 Torr.

$C_{17}H_{14}Cl_2O_3$ Exact Mass:	calc.	337.205
(337.2)	found	337.208

^1H NMR ($CDCl_3$/TMS): δ = 2.58 (d, 3 H, J = 1.5 Hz), 3.74 (3 H, s), 6.11 (q, 1 H, J = 1.5 Hz), 6.85–7.0 (m, 3 H), 7.20 (dd, 1 H, J = 9.1, J = 2.0 Hz), 7.35–7.50 (3 H, m).

^{13}C NMR ($CDCl_3$/TMS): δ = 17.7, 51.0, 116.0, 117.3, 122.1, 127.1, 127.9, 128.2, 128.3, 129.8, 130,6, 150.6, 154.6, 157.8, 167.1.

IR (KBr): ν = 1710, 1625, 1600 cm^{-1}.

4-Aryl- and 4-*tert*-butyl-2(5*H*)-furanones 3a–m, 4-*p*-Tolyl-2(5*H*)-furanone (3d); Typical Procedure:
Method A: A solution of methyl β-*p*-tolylcrotonate (**2d**; 1.90 g, 0.01 mol), SeO_2 (1.11 g, 0.01 mol and $HClO_4$ (1 mL of 0.1 mol/L in AcOH) in glacial AcOH (10 mL) was stirred at 100 °C for 12 h. The mixture was cooled, diluted with Et_2O (30 mL), and the precipitated elemental Se was filtered. Most of the AcOH was removed by distillation. The residue was diluted with benzene (40 mL) and washed with 5 % aqueous $NaHCO_3$ (2 × 20 mL) and water (2 × 20 mL), and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from Et_2O/hexane (1 : 2) to give **3d**.

5,6,7,7a-Tetrahydro-2(4*H*)-benzofuranone (3o); Typical Procedure:
Method B: A solution of methyl cyclohexylideneacetate (**1o**; 1.54 g, 0.01 mol), SeO_2 (1.11 g, 0.01 mol) in Ac_2O (2.04 g, 0.02 mol), glacial AcOH (2.40 g, 0.04 mol) and $HClO_4$ (1 mL of 0.1 mol/L in AcOH) was stirred at 40 °C for 4 h. The mixture was cooled and the precipitated Se was removed by filtration. The filtrate was diluted with Et_2O (50 mL) and washed successively with water (50 mL), 10 % aq $NaHCO_3$ (20 mL) and brine. The Et_2O layer was dried and freed from solvent, and the residue fractionally distilled.

Compound **3n** was prepared from **1n** adapting the above procedure (Method B).

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