

3-Aryl-3-hydroxy-2,2,4,4-tetramethylcyclobutanones and related compounds[†]

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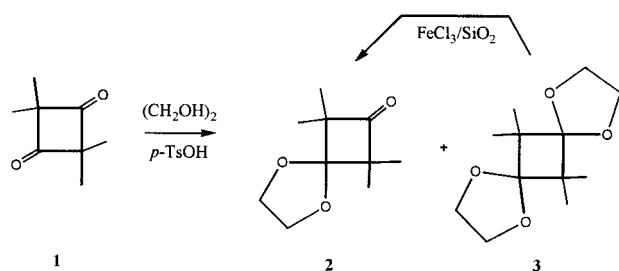
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3-aryl-3-hydroxy-2,2,4,4-tetramethylcyclobutanones and 1-aryl-2,2,4-trimethyl-1,3-pentadiones were prepared from arylation of 1,1,3,3-tetramethyl-5,8-dioxaspiro [3,4]octan-2-one followed by hydrolysis using THF and HCl respectively.

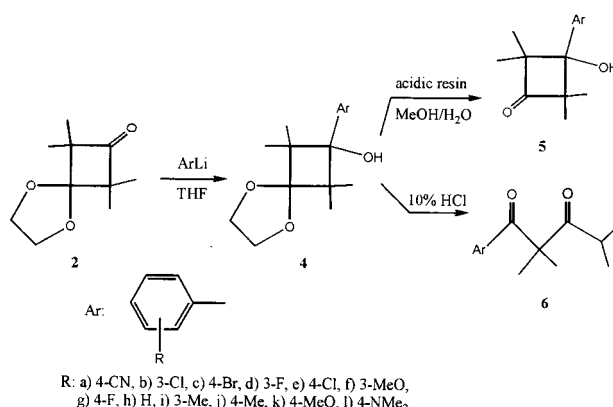
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Because of their small size, rigid geometry, and strain energy, cyclobutanes have been a fascinating topic for theoretical investigations.^{1–3} 2,2,4,4-Tetramethyl-1,3-cyclobutanedione (**1**) undergoes ring cleavage reactions in the presence of bases such as Grignard reagents, organolithium and Wittig reagents.^{4,5} These ring-opening reactions indicated that it would be necessary to protect one of the carbonyl groups during the course of any derivatization. Direct conversion of just one of the carbonyl groups to the ketal by reaction of compound **1** with ethylene glycol occurs, but the yield of isolated monoketal (**2**) was always low.⁶ On the other hand, good yields of monoketal **2** can be obtained from the conversion of both carbonyl groups and subsequent modification. This is done by reaction of ethylene glycol and cyclobutanedione **1** in 2:1 molar ratio in benzene using *p*-toluenesulfonic acid (*p*-TsOH) to form diketal **3** followed by treatment with silica gel containing ferric chloride in solid form.⁷ We now report on some synthetically useful transformation of monoketal **2**.

Thus we prepared 2-aryl-2-hydroxy-1,1,3,3-tetramethyl-5,8-dioxaspiro[3.4]octanes (**4a–4l**) by the reaction of substituted bromobenzenes and *n*-BuLi followed by the addition of monoketal **2**. The mass spectra of compounds **4** contain a common fragment of *m/z* 114 as a base peak and *m/z* 99 as a second intense signal with the absence of the molecular ion. Treatment with Dowex-50 X 4-400 led to a simple and direct hydrolysis to yield 3-aryl-3-hydroxy-2,2,4,4-tetramethylcyclobutanones (**5a–5l**).



Consistent with the presence of the strained ring ketone, the IR absorption of the carbonyl group for compounds **5a–5l** appeared at 1760–1770 cm^{-1} ,⁸ and the chemical shifts for the carbon of the carbonyl appeared at δ_c 220–222. 1-Aryl-2,2,4-trimethyl-1,3-pentadiones (**6a–6l**) were readily prepared by treating compounds **5** with 2*N* HCl aqueous solution under



reflux. The absorption of the two carbonyl groups in this series of compounds appeared at 1707–1715 and 1655–1678 cm^{-1} .

Experimental

¹H NMR spectra were recorded at 250 MHz on a Bruker AC-250 spectrometer at ambient temperature with deuteriochloroform as the solvent and tetramethylsilane as an internal standard. IR spectra were obtained either by placing the sample between KBr plates (for liquid) or KBr pellets (solid) on a Perkin-Elmer 883 grating spectrophotometer. GC-MS analyses were performed on a gas chromatography (Fisons GC-8000) coupled with a mass detector (Fisons MD-800). A capillary column coated with Carbowax (30 m × 0.53 mm, thickness 1.2 μm) was used for separations under the following conditions: injector temperature, 230°C; column temperature: initial, 100°C for 5.0 min, rate 25°C/min to 200°C, 200°C for 10 min, rate 20°C/min until final temperature at 230°C, kept at that temperature for 20 min. Elemental Analyses were performed at the Instrumental Analytic Center at National Chung Hsien University.

1,1,3,3-Tetramethyl-5,8-dioxaspiro[3,4]octan-2-one (2): (a) Partial protection of tetra-methyl-1,3-cyclobutanedione (**1**) was achieved by reaction of the diketone compound, ethylene glycol and *p*-TsOH in benzene solution as described in the literature,⁶ except for the isolation of compound **2**, which was performed by sublimation at 50°C under ambient pressure.

(b) Partial deprotection of diketal **3** was prepared with silica gel containing ferric chloride in the solid state at room temperature.⁷ The resultant **2** was further purified by sublimation.

Preparation of 1-aryl-1-hydroxyl-1,1,3,3-tetramethyl-5,8-dioxaspiro[3,4]octane (4). *Typical procedure:* To a solution of compound **2** (1.84 g, 10.0 mmol) in THF (24.0 ml) was added phenyllithium prepared from *n*-butyllithium (10.0 mmol, 4.0 ml of 0.2 M hexane solution), bromobenzene (10.0 mmol), and THF (25.0 ml) at –80.0°C for 5.0 h. The reaction mixture was allowed to stand overnight at room temperature; then it was hydrolyzed with NH₄Cl (0.1 M, 100 ml), and the aqueous layer were extracted with ethyl acetate (50 ml × 3). The combined organic layers was dried (MgSO₄), concentrated, and puri-

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[†] This is a Short Paper, there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Physical data of 2-aryl-2-hydroxy-1,1,3,3-tetramethyl-5,8-dioxaspiro[3.4]octanes (**2**)

R	Yield %	M.P. °C	Elemental Anal. (Found)		MS ^a (m/e)	IR ^b cm ⁻¹	¹ H NMR δ CDCl ₃
			C	H			
H	79	46/2.0 ^d	73.25 (73.14)	8.45 (8.39)	262(--), 114	3554	1.25(s, 6H), 1.31(5, 6H), 3.90(m, 4H), 7.31(m, 5H).
4-CN	22	167.0– 167.3	71.05 (70.85)	7.36 (7.40)	287(--), 114	3462, 2237 ^c	1.17(5, 6H), 1.24(s, 6H), 3.92 (m, 4H), 7.57(d, 2H, J 8.6 Hz), 7.62(d, 2H, J 8.6 Hz).
3-Cl	58	Liq.	64.75 (64.64)	7.13 (7.22)	296(--), 114	3504	1.24(s, 6H), 1.27 (s, 6H), 3.94 (m, 4H), 7.30 (m, 4H)
3-F	76	Liq.	68.55 (68.41)	7.55 (7.44)	280(--) 114	3503	1.22 (s, 6H), 1.25 (s, 6H), 3.94 (m, 4H), 7.11 (m, 4H).
4-Br	63	55/2.0 ^d	65.64 (65.58)	6.20 (6.29)	340(--), 114	3545	1.17 (s, 12H), 3.86 (m,4H), 7.22 (d, 2H, J 8.6 Hz), 7.39 (d, 2H, J 8.6 Hz).
4-Cl	60	76.5~77.0	64.68 (64.75)	7.02 (7.13)	296(--), 114	3522	1.22 (s, 6H), 1.24 (s, 6H), 3.92 (m, 4H), 7.28 (d, 2H, J 8.5 Hz), 7.32 (d, 2H, J 8.5 Hz).
3-OMe	84	88.1~88.3	69.84 (69.75)	8.27 (8.16)	292(--), 114	3525	1.24 (s, 6H), 1.35 (s, 6H), 3.80 (s, 3H), 3.93 (m, 4H), 7.03 (m, 4H).
4-F	84	59.0~60.5	68.55 (68.70)	7.55 (7.45)	280(--), 114	3546	1.27 (s, 6H), 1.31 (s, 6H), 3.93 (m, 4H), 6.98 (t, 2H, J 8.7 Hz), 7.32 (dd, 2H, J 8.7, 5.5 Hz).
3-Me	88	Liq.	73.88 (73.92)	8.75 (8.65)	276(--), 114	3548	1.28 (s, 6H), 1.34 (s, 6H), 2.36 (s, 3H), 3.90 (m, 4H), 7.12 (m, 4H).
4-Me	89	88.5~89.5	73.88 (73.88)	8.75 (8.65)	276(--), 114	3548	1.25 (s, 6H), 1.29 (s, 6H), 2.32 (s, 3H), 3.89 (m, 4H), 7.12 (d, 2H, J 8.1 Hz), 7.25 (d, 2H, J 8.1 Hz)
4-OMe	79	69.8~70.1	69.84 (69.75)	8.27 (8.31)	292(--), 114	3545	1.22 (s, 6H), 1.27 (s, 6H), 3.76 (s, 3H), 6.83 (d, 2H, J 8.9 Hz), 7.27 (d, 2H, J 8.9 Hz).
4-NMe	71	71.6~72.8	73.88 (73.98)	8.75 (8.71)	305(--), 114	3539	1.26 (s, 6H), 1.37 (s, 6H), 2.93 (s, 6H), 3.90 (m, 4H), 6.68 (d, 2H, J 8.7 Hz), 7.22 (d, 2H, J 8.7 Hz).

^a Molecular ion (–, not observed) and base peak (mass 114); ^b ν OH; ^c ν CN; ^dbp. °C/torr.

Table 2 Physical data of 3-aryl-3-hydroxy-2,2,4,4-tetramethylcyclobutanones (**5**)

R	Yield %	M.P. °C	Elemental Anal. (found)		MS ^a (m/e)	IR ^b cm ⁻¹	¹ H NMR δ CDCl ₃
			C	H			
H	76	134.6~ 136.1 (135) ^d	77.03 (77.31)	8.31 (8.05)	218(8), 148	3408, 1760	1.39 (3, 6H), 1.42 (s, 6H), 142 (s 1H), 7.20 (m, 5H).
4-CN	35	151.0~ 152.5	74.05 (74.30)	7.04 (7.09)	243(13), 173.	3415, 2237, ^c 1763	1.38 (s, 6H), 1.40 (s, 6H), 2.25 (s, 1H), 7.47 (d, 2H, J 8.4 Hz), 7.68 (d, 2H, J 8.4 Hz).
3-Cl	77	131.0~ 133.5	66.53 (66.49)	6.78 (6.81)	252(4), 182.	3422, 1762	1.36 (s, 6H), 1.40 (s, 6H), 2.03 (s, 1H), 7.28 (m, 4H).
3-F	90	97.0~ 98.2.	71.16 (71.17)	7.25 (7.20)	236 (12), 166.	3439, 1764	1.35 (s, 6H), 1.38 (s, 6H), 2.07 (s, 1H), 7.19 (m, 4H).
4-Br	63	107.3~ 108.7	56.58 (56.60)	5.77 (5.82)	296(8), 226.	3487, 1769	1.29 (s,12H), 1.30 (m, 4H), 2.46 (s, 1H), 7.17 (d, 2H, J 8.5 Hz), 7.46 (d, 2H, J 8.5 Hz).
4-Cl	75	100.2~ 102.7	66.53 (66.36)	6.78 (6.85)	252(4), 182	3483, 1769	1.35 (s, 6H), 1.38 (s, 6H), 2.21 (s, 1H), 7.26 (d, 2H, J 8.6 Hz), 7.36 (d, 2H, J 8.6 Hz).
3-OMe	84	105.5~ 106.3	72.55 (72.58)	8.12 (8.09)	248(26), 178.	3446, 1760	1.32 (s, 6H), 1.78 (s, 6H), 2.18 (s, 1H), 3.78 (s, 3H), 7.56 (m, 4H).
4-F	73	122.5~ 125.0	71.16 (71.34)	7.25 (7.15)	236(6), 166.	3484, 1762	1.35 (s, 6H), 1.38 (s, 6H), 1.96 (s, 1H), 7.07 (t, 2H, J 8.6 Hz), 7.32 (t, 2H, J 8.6, 5.4 Hz).
3-Me	78	121.0~ 122.4	77.55 (77.41)	8.68 (8.81)	232(11), 162.	3443~ 1759	1.36 (s, 6H), 1.40 (s, 6H), 1.97 (s, 1H), 2.37 (s, 3H), 7.20 (m, 4H).
4-Me	87	120.4~ 121.5	77.55 (77.59)	8.68 (8.62)	232(6), 162.	3447, 1760	1.35 (s, 6H), 1.39 (s, 6H), 2.07 (s, 1H), 2.35 (s, 3H), 7.19 (m, 4H).
4-OMe	92	123.0~ 124.5	72.55 (72.73)	8.12 (8.16)	248(20), 135.	3502, 1769	1.32 (s, 6H), 1.36 (s, 6H), 2.31 (s, 1H), 3.78 (s, 3H), 6.86 (d, 2H, J 8.6 Hz), 7.22 (d, 2H, J 8.6 Hz).
4-NMe	92	114.0~ 115.5	73.53 (73.59)	8.87 (8.94)	261(55), 148.	3513, 1770	1.34 (s, 6H), 1.39 (s, 6H), 2.95 (s, 6H), 2.20 (s, 1H), 6.70 (d, 2H, J 8.8 Hz), 7.19 (d, 2H, J 8.8 Hz).

^a Molecular ion with its relative intensity and base peak; ^b ν OH and ν CO; ^c ν CN; ^dref. 10.

Table 3 Physical data of 1-aryl-2,2,4-trimethyl-1,3-pentadione (**6**)

R	Yield %	M.P. °C	Elemental Anal. (Found)		MS ^a (m/e)	IR ^b cm ⁻¹	¹ H NMR δ CDCl ₃
			C	H			
4-CN	78	80.0~81.5	74.05 (74.24)	7.04 (7.21)	243(1), 43	2232, ^c 1707, 1678.	1.00 (d, 6H, <i>J</i> 6.6 Hz), 1.50 (s, 6H), 2.85 (h, 1H, <i>J</i> 6.6Hz), 7.71 (d, 2H, <i>J</i> 8.2 Hz), 7.86 (d, 2H, <i>J</i> 8.2 Hz).
3-Cl	59	Liq.	66.53 (66.67)	6.78 (6.93)	252(1), 43	1713, 1678	0.94 (d, <i>J</i> 6.7 Hz, 6H), 1.46 (s, 6H), 2.78 (h, 1H, <i>J</i> 6.6 Hz), 7.53 (m, 4H).
3-F	70	Liq.	71.16 (71.09)	7.25 (7.22)	236(1), 43	1715, 1678	0.95 (d, 6H, <i>J</i> 6.6 Hz), 1.49 (s, 6H), 2.79 (h, 1H, <i>J</i> 6.6 Hz), 7.38 (m, 4H).
4-Br	79	Liq.	56.58 (56.48)	5.89 (5.89)	296(1), 43.	1713, 1674	0.93 (d, 6H, <i>J</i> 6.7 Hz), 1.47 (s, 6H), 2.78 (h, 1H, <i>J</i> 6.6 Hz), 7.53 (d, 2H, <i>J</i> 8.6 Hz), 7.67 (d, 2H, <i>J</i> 8.6 Hz).
4-Cl	75	12.7~13.6	66.53 (66.61)	6.78 (6.83)	252(1), 43	1713, 1674	0.98 (d, 6H, <i>J</i> 6.7 Hz), 1.48 (s, 6H), 2.80 (h, 1H, <i>J</i> 6.7 Hz), 7.38 (d, 2H, <i>J</i> 8.5 Hz), 7.74 (d, 2H, <i>J</i> 8.5 Hz).
3-OMe	83	-13.5~-12.8	72.55 (72.54)	8.12 (8.10)	248(3), 43.	1713, 1674	0.89 (d, 6H, <i>J</i> 6.6Hz), 1.46 (s, 6H), 2.74 (h, 1H, <i>J</i> 6.6 Hz), 3.78 (s, 3H), 7.15 (m, 4H).
4-F	76	-16.7~-15.8	71.16 (70.99)	7.25 (7.32)	280(--), 114	3546	0.85 (d, 6H, <i>J</i> 6.6 Hz), 1.41 (s, 6H), 2.70 (h, 1H, <i>J</i> 6.6 Hz), 7.00 (t, 2H, <i>J</i> 8.9 Hz), 7.78 (dd, 2H, <i>J</i> 8.9, 5.4 Hz).
3-Me	82	-1.6~-1.3	77.55 (77.37)	8.68 (8.69)	232(1), 119.	1713, 1674	0.86 (d, 6H, <i>J</i> 6.6 Hz), 1.42 (s, 6H), 2.28 (s, 3H), 2.71 (h, 1H, <i>J</i> 6.6 Hz), 7.38 (m, 4H).
4-Me	85	-15.5~-12.5	77.55 (77.43)	8.68 (8.73)	232(1), 119.	1712, 1673	0.89 (d, 6H, <i>J</i> 6.6 Hz), 1.45 (s, 6H), 2.34 (s, 3H), 2.75 (h, 1H, <i>J</i> 6.6 Hz), 7.16 (d, 2H, <i>J</i> 8.2 Hz), 7.68 (d, 2H, <i>J</i> 8.2 Hz).
4-OMe	85	-2.4~-1.7	72.55 (72.50)	8.12 (8.12)	248(2), 135.	1711, 1666.	0.91 (d, 6H, <i>J</i> 6.6 Hz), 1.47 (s, 6H), 2.75 (h, 1H, <i>J</i> 6.6 Hz), 3.83 (s, 3H), 6.86 (d, 2H, <i>J</i> 8.9 Hz), 7.80 (d, 2H, <i>J</i> 8.9 (HJz)).
4-NMe	76	Liq.	73.53 (73.41)	8.87 (8.92)	261(11), 148.	1707, 1655.	0.84 (d, 6H, <i>J</i> 6.6 Hz), 130 (s, 6H), 2.86 (h, 1H, <i>J</i> 6.6 Hz), 2.95 (s, 6H), 6.50 (d, 2H, <i>J</i> 9.1 Hz), 7.67 (d, 2H, <i>J</i> 9.1 Hz).

^a Molecular ion with relative intensity and base peak; ^bν_{CO}; ^cν_{CN}.

fied by chromatography through silica gel with a mixture of ethyl acetate and hexane (1:5) as an eluent. The physical and spectral data for the new compounds are summarised in Table 1.

Preparation of 3-aryl-3-hydroxy-2,2,4,4-tetramethylcyclobutanone (5). Typical procedure: A mixture of compound **4h** (2.0 g, 8.3 mmol) and Dowex 50 × 4-400 ion exchanger (strong acidic resin, 10.0 g) in water (50 ml) was stirred at 25°C for 5 h. After filtration to remove resin, water (100 ml) was added to the filtrate and then extracted with ethyl acetate (10 ml × 3). The combined organic layer was dried (MgSO₄), filtered, and evaporated to dryness under reduced pressure. The pure product was obtained after chromatographic separation on silica gel (with EtOAc: *n*-hexane = 1:5) as an eluent. The physical and spectral data of the new compounds are summarized in Table 2.

Preparation of 1-aryl-2,2,4-trimethyl-1,3-pentadiones (6). Typical procedure: Compound **4h** (2.0 g, 8.3 mmol) in a mixture of THF (50 ml) and HCl (2*N*, 40 ml) was refluxed for 1h. After the mixture was cooled to room temperature, the mixture was extracted with ethyl acetate (60 ml × 3) and then the combined organic layer was washed (H₂O, 30 ml × 3), dried (MgSO₄), filtered and dried under vacuum. The product was obtained via column chromatographic separation by using silica gel as a stationary phase and EtOAc : *n*-hexane = 1:5 as an eluent. The physical and spectral data are summarised in Table 3.

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