A Facile, Efficient Synthesis of 2-substituted-4-Hydroxy-2-cyclopenten-1-ones

P.G. Baraldi, G.P. Pollini*, D. Simoni, V. Zanirato

Dipartimento di Scienze Farmaceutiche, Via Scandiana 21, I-44100 Ferrara, Italy

A. Barco, S. Benetti

Dipartimento Chimico, Via L. Borsari 46, I-44100 Ferrara, Italy

A simple procedure for the transformation of 2-substituted 4-bromo-2-cyclopenten-1-ones into the title compounds as well as into the corresponding 4-methoxy derivatives is described.

4-Hydroxy-2-cyclopenten-1-ones (**2**) are highly versatile intermediates in natural product synthesis, and their value is reflected in the myriad of methods for their preparation described in the literature[1].

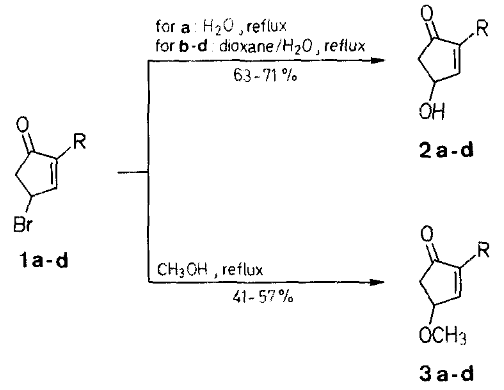
We describe in this paper a mild and effective procedure for the preparation of 2-substituted 4-hydroxy-2-cyclopenten-1-ones (**2**), which we have developed in connection with our recent interest[2] in the chemistry of 4-bromo-2-cyclopenten-1-ones (**1**). The latter compounds are known to be extremely prone to *β*-elimination, even if only slightly basic conditions are used. Direct substitution of the bromine by a hydroxy group has been previously achieved under solvolytic conditions in the presence of silver perchlorate in aqueous acetone[3], in which silver acetate replaces the bromine with an acetate group, which was subsequently hydrolyzed to the desired hydroxy-enone[4].

More recently, as the result of a careful investigation[5] aimed to improve silver-salt-promoted, solvolytic procedures, silver oxide in aqueous acetone was determined to be the reagent of choice for effecting this type of solvolysis "when price is no object".

Surprisingly no reports can be found in the literature dealing with attempts to achieve direct hydrolysis of 4-bromo-2-cyclopentenones **1** simply by boiling with water, although since 1913[4] it has been reported that α-haloketones are hydrolyzed to the corresponding α-hydroxyketones under these conditions. For instance 2-chlorocyclopentanone has been transformed, albeit in moderate yield (28%), into 2-hydroxycyclopentanone. Taking into account the vinylogous relationship between α-haloketones and γ-bromo-enones, we were confident that boiling in plain water may well do the trick. We are pleased to report that this is the case.

When the readily available 4-bromo-2-cyclopentenones **1a–d**[7] were exposed to these neutral reaction conditions, hydrolysis proceeded smoothly, producing excellent yields of the corresponding 4-hydroxy-2-cyclopentenones **2a–d**, through an easy substitution of bromine by a hydroxy group. Thus the simplest member of the family **2a**, which has been already prepared both in racemic form (usually starting from cyclopentadiene) or as the pure *R* and *S* enantiomers (either *via* resolution or starting from chiral materials[8]) can be obtained in 63% yield. Similarly compounds **2b–d** were prepared in 65, 71 and 70% yield, respectively, starting from **1b–d**.

The three compounds **2a**, **2c** and **2d** are important intermediates for convergent approaches to prostaglandins, namely consecutive introduction of the two side chains in the case of **2a** and conjugated addition in the other cases[9].



1–3	R
a	H
b	CH_3
c	$CH_2CO_2CH_3$
d	$(CH_2)_6CO_2CH_3$

Although this method affords **2a–d** in racemic form, the sequence is so short and simple as to make resolution a viable alternative.

We have also found that substitution occurred when methanol[10] was substituted for water, giving the corresponding derivatives **3a–d**, although in less satisfactory yields[11]. This behaviour parallels that of 2-bromocyclopentanone, which reacts with refluxing methanol to afford 2-methoxycyclopentanone in good yields[12].

In conclusion we have developed a practical and useful route to 4-hydroxy-2-cyclopenten-1-ones **2**, which features several advantages over the existing ones, including simplicity, employment of readily available starting materials, use of inexpensive and non hazardous reagents, and high overall yields.

4-Hydroxy-2-cyclopenten-1-one (2a):

A mixture of 4-bromo-2-cyclopenten-1-one (**1a**; 16.1 g, 0.1 mol) and water (200 ml) is heated for 5 h under reflux. The cooled mixture is extracted with chloroform (2 × 25 ml) to remove some cyclopentadienone dimer formed as by-product, then saturated with sodium chloride and extracted with ethyl acetate (6 × 25 ml). The organic extracts are dried with magnesium sulfate, evaporated *in vacuo*, and the residue distilled to give **2a** as a colorless liquid; yield: 6.1 g (63%); b.p. 63–64°C/2 torr (Lit.[13] b.p. 100–103°C/4 torr).

$C_5H_6O_2$	calc.	C 61.21	H 6.17
(98.1)	found	61.38	6.12

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.25$ (dd, 1 H, $J = 18.4$ Hz, 2.3 Hz); 2.77 (dd, 1 H, $J = 18.4$ Hz, 5.9 Hz); 3.5 (bs, 1 H); 5.0 (m, 1 H); 6.20 (d, 1 H, $J = 6.0$ Hz); 7.60 ppm (dd, 1 H, $J = 6.0$ Hz, 2.0 Hz).

IR (film): $\nu = 3350, 1710, 1660, 1585$ cm^{-1}.

2-Substituted 4-Hydroxy-2-cyclopenten-1-ones (2b–d); General procedure:

A solution of 2-substituted 4-bromo-2-cyclopenten-1-one (**1b–d**; 0.1 mol) in a 1 : 1 mixture of dioxane/water (200 ml) is heated for 3 h at reflux. After removal of the solvent *in vacuo* (20 torr), the aqueous solution is extracted with chloroform (6 × 25 ml). After drying with magnesium sulfate, the organic extract is concentrated *in vacuo*, and the residual oil is flash chromatographed on silica gel (eluent ether) to afford pure hydroxy derivatives **2b–d**.

2-Methyl-4-hydroxy-2-cyclopenten-1-one (**2b**); yield: 7.28 g (65%); oil (Lit.[1c]).

$C_6H_8O_2$	calc.	C 64.27	H 7.19
(112.1)	found	64.02	7.13

^{1}H-NMR (CDCl$_3$/TMS): δ = 1.83 (d, 3 H, J = 1 Hz); 2.24 (dd, 1 H, J = 18 Hz, 2 Hz); 2.82 (dd, 1 H, J = 18 Hz, 6 Hz); 3.40 (bs, 1 H); 4.90 (m, 1 H); 7.72 ppm (m, 1 H).

IR (film): ν = 3400, 1710, 1640 cm^{-1}.

2-(Methoxycarbonylmethyl)-4-hydroxy-2-cyclopenten-1-one (**2c**); yield: 12.0 g (71 %); oil.

$C_8H_{10}O_4$ calc. C 56.46 H 5.92
(170.2) found 56.38 6.07

^{1}H-NMR (CDCl$_3$/TMS): δ = 2.35 (dd, 1 H, J = 18.5 Hz, 2.5 Hz); 2.85 (dd, 1 H, J = 18.5 Hz, 7 Hz); 3.25 (s, 2 H); 3.7 (s, 3 H); 3.40 (bs, 1 H); 4.95 (m, 1 H); 7.45 ppm (m, 1 H).

IR (film): ν = 3400, 1740, 1710, 1640 cm^{-1}.

2-(6-Methoxycarbonylhexyl)-4-hydroxy-2-cyclopenten-1-one (**2d**); yield: 16.6 g (69 %); m.p. 48–49 °C (Lit.[4] m.p. 48–49.5 °C).

$C_{13}H_{20}O_4$ calc. C 64.98 H 8.39
(240.3) found 64.77 8.27

^{1}H-NMR (CDCl$_3$/TMS): δ = 2.30 (dd, 1 H, J = 18.5 Hz, 2.5 Hz); 2.80 (dd, 1 H, J = 18.7 Hz, 7 Hz); 3.70 (s, 3 H); 4.90 (m, 1 H); 7.23 ppm (m, 1 H).

IR (nujol): ν = 3415, 1735, 1685, 1630 cm^{-1}.

4-Methoxy-2-cyclopenten-1-ones (3a–d); General Procedure:
A mixture of the crude bromo derivative (**1a–d**; 0.1 mol) and methanol (150 ml) is heated under reflux for 3 h. Most of the solvent is removed *in vacuo*, then water (40 ml) and ether (200 ml) are added. The ether layer is separated, dried with magnesium sulfate, and concentrated. The crude product is purified by column chromatography (silica gel, ether).

4-Methoxy-2-cyclopenten-1-one (**3a**); yield: 4.6 g (41 %); oil.

$C_6H_8O_2$ calc. C 64.27 H 7.19
(112.1) found 64.13 7.09

^{1}H-NMR (CDCl$_3$/TMS): δ = 2.25 (dd, 1 H, J = 18 Hz, 2.4 Hz); 2.7 (dd, 1 H, J = 18 Hz, 6.0 Hz); 3.45 (s, 3 H); 4.6 (m, 1 H); 6.25 (d, 1 H, J = 6 Hz), 7.62 ppm (dd, 1 H, J = 6 Hz, 2.0 Hz).

2-Methyl-4-methoxy-2-cyclopenten-1-one (**3b**): yield: 5.4 g (43 %); oil.

$C_7H_{10}O_2$ calc. C 66.64 H 7.99
(126.2) found 66.31 7.78

^{1}H-NMR (CDCl$_3$/TMS): δ = 1.85 (d, 1 H, J = 1 Hz); 2.25 (dd, 1 H, J = 18 Hz, 2 Hz); 2.8 (dd, 1 H, J = 18 Hz, 6 Hz); 3.4 (s, 3 H); 4.55 (m, 1 H); 7.5 ppm (m, 1 H).

2-Methoxycarbonylmethyl-4-methoxy-2-cyclopenten-1-one (**3c**); yield: 10.5 g (57 %); oil.

$C_9H_{12}O_4$ calc. C 58.69 H 6.57
(184.2) found 58.88 6.67

^{1}H-NMR (CDCl$_3$/TMS): δ = 2.3 (dd, 1 H, J = 18 Hz, 2.5 Hz); 2.78 (dd, 1 H, J = 18 Hz, 6 Hz); 3.25 (s, 2 H); 3.42 (s, 3 H); 3.7 (s, 3 H); 4.55 (m, 1 H); 7.55 ppm (m, 1 H).

2-(6-Methoxycarbonylhexyl)-4-methoxy-2-cyclopenten-1-one (**3d**); yield: 13 g (51 %); oil.

$C_{14}H_{22}O_4$ calc. C 66.11 H 8.72
(254.3) found 66.28 8.59

^{1}H-NMR (CDCl$_3$/TMS): δ = 1.1–1.8 (m, 10 H); 2.0–2.8 (m, 6 H); 3.4 (s, 3 H); 3.68 (s, 3 H); 4.4 (m, 1 H); 7.34 ppm (m, 1 H).

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