Improved Syntheses of 2-Hydroxymethylenecyclopentanone (2-Formylcyclopentanone) and Spiro[4.5]dec-6-en-1,8-dione

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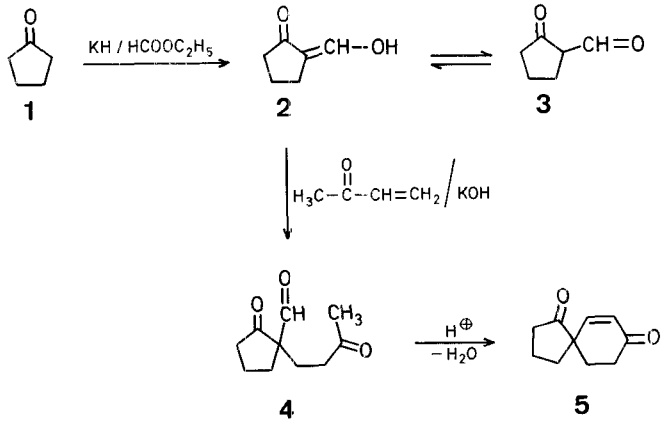
2-Hydroxymethylenecyclopentanone **(2)** is an important and exceedingly useful building block. There are numerous methods reported for its synthesis[1-10]. Unfortunately, none of these is really very good. Indeed, the compound has been noted to be the least accessible of the simple 2-hydroxymethylenecycloalkanones[2]. In all previous procedures the yields are low (less than 20%) and undependable, varying greatly with chance changes in experimental conditions. The crude product is always contaminated with many condensation products and purification is difficult because of its instability.

We have now overcome these problems. The key to our procedure is the use of potassium hydride as the base in an otherwise classical formylation of cyclopentanone **(1)** with ethyl formate. The reaction of potassium hydride with cyclopentanone **(1)** to give the ketone enolate is exceedingly rapid[11]. Thus, when cyclopentanone is added to potassium hydride suspensions the concentration of free cyclopentanone in the basic medium is kept low, mitigating unwanted condensation and proton transfer reactions which caused the problems in previous attempts. Multigram quantities of 2-hydroxymethylenecyclopentanone **(2)** sufficiently pure for further synthetic elaboration can now be prepared easily and reproducibly in yields of 60–65%. We note that, in deuteriochloroform at room temperature, the equilibrium between the hydroxymethylene compound **(2)** and the tautomeric aldehyde **(3)** favors the former by approximately 12 : 1.

In using 2-hydroxymethylenecyclopentanone **(2)** for the synthesis of the spiro compound **5**, we found that the base-catalyzed addition to methyl vinyl ketone goes well, as described[2]. However, we had difficulty, particularly with larger scale



1 2 3 4 5

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runs, in bringing about the cyclization by slow distillation of the adduct **4** from potassium hydroxide following the reported prescription. We found, however, that this conversion could be done smoothly and reproducibly under acidic conditions. Specifically, azeotropic removal of water from **4** in refluxing benzene containing a catalytic amount of methanesulfonic acid gives an excellent yield of the spiro-enone **5** without difficulty. We have used this material successfully in the non-photochemical synthesis of propellanes[12].

2-Hydroxymethylenecyclopentanone (2-Formylcyclopentanone) (2, 3):
A mixture of cyclopentanone (**1**; 50 g, 0.59 mol) and ethyl formate (49 g, 0.66 mol) is added dropwise over 30 min at −5° to 5°C to a stirred suspension of potassium hydride (120 g of 32% KH in oil, 0.96 mol) in dry diethyl ether (500 ml) under nitrogen. Use of a larger amount of KH does not improve the final yield. The mixture is stirred for 1 h, while the temperature is maintained at −5 to 5°C by the use of an ice/methanol bath. The suspension is poured carefully into stirred ice/water (880 g) in a large beaker, and the layers are separated. The aqueous phase is extracted with ether (2 × 250 ml) and the extract discarded. The aqueous layer is placed in a 2 l Erlenmeyer flask immersed in an ice bath, stirred vigorously, and acidified with solid sodium dihydrogen phosphate ($NaH_2PO_4 \cdot H_2O$; 100 g) followed by concentrated hydrochloric acid (100 g). The resulting pale yellow solution is thoroughly extracted with ether (7 × 200 ml). The extracts are combined, washed once with saturated aqueous ammonium chloride (100 ml), and dried with magnesium sulfate. A light yellow solid (70 g, m.p. 66–72°C) is obtained by removal of the solvent in vacuo. This crude product is ground to a coarse powder and then triturated with boiling pentane (4 × 500 ml). The pale supernatant is decanted from the residual red oil (discarded). Removal of the pentane in vacuo gives 2-hydroxymethylenecyclopentanone as a white solid; yield: 42 g (63%); m.p. 74–76°C. This material is pure enough (>95%) to be used without further purification. A small analytical sample is prepared by crystallization from hexane followed by sublimation at 40°C/0.01 torr; m.p. 74.5–75°C (Lit.[1-10] m.p. values vary).

$C_6H_8O_2$	calc.	C 74.97	H 8.39
(96.1)	found	75.24	8.62

I.R. (CCl_4): ν = 1674, 1609, 1395, 1189, 1074 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$, 500 MHz): hydroxymethylene form **2**: δ = 1.97 (d, 2 H, J = 8 Hz); 2.40 (t, 2 H, J = 8 Hz); 2.53 (td, 2 H, J = 7 Hz, 1 Hz); 7.22 (t, 1 H, J = 1 Hz); 9.70 ppm (s, 1 H); aldehyde form **3**: δ = 3.35 (t, 1 H, J = 8 Hz); 9.73 ppm (br. s, 1 H).

2-Formyl-2-(3-oxobutyl)-cyclopentanone (4):
2-Hydroxymethylenecyclopentanone (**2**; 11.0 g, 96 mmol) and powdered potassium hydroxide (250 mg) are suspended in methyl vinyl ketone (20 ml) under nitrogen at room temperature. The mixture becomes homogeneous in about 1 h. The reaction is allowed to continue for an additional 3 h after which excess methyl vinyl ketone is removed in vacuo. The brown residue is taken up in dichloromethane (100 ml) and washed with buffer solution (2 × 40 ml, 1 molar aqueous potassium dihydrogen phosphate) and brine, and dried with magnesium sulfate. The solvent is removed in vacuo. The residue is distilled to give the 1:1 adduct **4** as a clear oil; yield: 13.4 g (75%); b.p. 64°C/0.002 torr.

M.S.: m/e = 182.0946 (M^+; $C_{10}H_{14}O_3$ requires 182.0942).

I.R. (CCl_4): ν = 1730–1695 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$, 500 MHz): δ = 1.76 (dt, 1 H, J = 13 Hz, 7 Hz); 1.85–2.05 (m, 3 H); 2.13 (s, 3 H); 2.17–2.28 (m, 1 H); 2.33 (t, 2 H, J = 8 Hz); 2.40–2.55 (m, 3 H); 9.40 ppm (s, 1 H).

Spiro[4.5]dec-6-en-1,8-dione (5):
A solution of compound **4** (12.1 g, 66 mmol) and methanesulfonic acid (200 mg) in benzene (200 ml) is stirred under reflux for 8 h under nitrogen. Water is removed using a Dean-Stark trap. The mixture is cooled to room temperature; sodium acetate (2 g) is added, and the solvent is removed in vacuo. The dark brown residue is taken up in dichloromethane (100 ml); the solution is washed once with aqueous sodium hydrogen carbonate, water, and brine, and dried with magnesium sulfate. Distillation gives the spiro-enone **5** as a viscous oil; yield: 8.6 g (79%); b.p. 82°C/0.04 torr (Ref.[1], b.p. 60°C/0.01 torr).

M.S.: m/e = 164.0831 (M^+; $C_{10}H_{12}O_2$ requires 164.0837).

I.R. (CS_2): ν = 1745, 1690 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$, 350 MHz): δ = 1.90–2.20 (m, 5 H); 2.30–2.43 (m, 2 H); 2.43–2.55 (m, 1 H); 2.67 (ddd, 2 H, J = 17 Hz, 10 Hz, 5 Hz); 6.08 (d, 1 H, J = 10 Hz); 6.56 ppm (dd, 1 H, J = 10 Hz, 2 Hz).

^{13}C-N.M.R. ($CDCl_3$, 22.63 MHz): δ = 18.6 (t, J = 135 Hz); 29.5 (t, J = 135 Hz); 33.0 (t, J = 129 Hz); 35.8 (t, J = 133 Hz); 36.7 (t, J = 129 Hz); 50.9 (s); 129.7 (d, J = 162 Hz); 149.7 (br. d, J = 159 Hz); 197.9 (s); 216.4 ppm (s).

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