

## Synthesis via ultrasound: A short and convenient synthesis of 9-oxo-2(*E*)-decanoic acid

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**Abstract.** A simple synthesis of 9-oxo-2(*E*)-decanoic acid (I), queen substance of honeybee *Apis mellifera* is reported using ultrasonic waves.

**Keywords.** Sonochemistry; modified Wittig reaction.

### 1. Introduction

Butler *et al* (1950, 1954) isolated 9-oxo-2(*E*)-decanoic acid as the queen substance of the honeybee *Apis mellifera*. The biologically active compound (I) inhibits development of ovaries in worker bees and also queen rearing within the colony. Literature reports multistep synthesis (Sato *et al* 1989; Mori 1992) of I though in low yields. We report herein a simple, elegant and straightforward synthesis of I via the use of ultrasonic waves (Luche and Allavena 1988) and modified Wittig reaction (Villieras 1983).

### 2. Reaction strategy

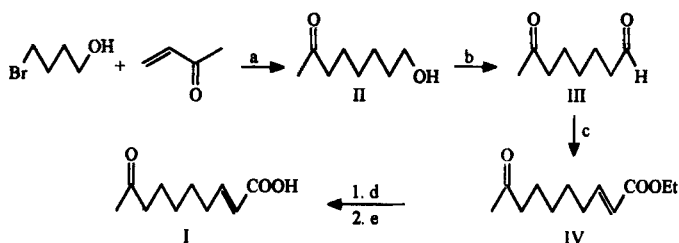
The sequence of reactions followed has been outlined in scheme 1.

Zinc–copper couple catalysed conjugate addition of 3-buten-2-one with 4-bromo-1-butanol under sonochemical aqueous conditions afforded 7-oxo-octanol (II) (Ogura *et al* 1982) which on PCC oxidation gave 7-oxo-octanal (III) (Villieras 1983). Compound III was subjected to modified Wittig reaction with ethyl- $\alpha$ -dimethylphosphonoacetate using  $K_2CO_3/H_2O$  as a base at reflux temperature to give  $\alpha,\beta$ -unsaturated ester (IV) which on alkaline hydrolysis furnished the title compound (I). The spectral data of (I) were found to be consistent with the values reported in the literature.

### 3. Experimental

$^1H$ NMR spectra were recorded in  $CDCl_3$  or  $CCl_4$  on a Varian EM-390 (90 MHz) spectrometer utilising tetramethylsilane as internal standard, chemical shifts in ppm ( $\delta$ -scale), coupling constants ( $J$ ) in Hz. IR spectra of thin films were recorded on a Perkin–Elmer 337 spectrophotometer ( $\nu_{max}$  in  $cm^{-1}$ ). The instrument used for sonication is a probe sonicator model XL 2015 whose working frequency is 20 kHz and output power is 475 watts. Unless otherwise stated, all organic extracts were dried over

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### Reagents

a) Zn(Cu), EtOH:H<sub>2</sub>O(9:1)

b) PCC, anhyd. CH<sub>2</sub>Cl<sub>2</sub>

c) (H<sub>3</sub>CO)<sub>2</sub>PCH<sub>2</sub>COOEt, K<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, 1 hour, Δ

d) NaOH

e) H<sub>3</sub>O<sup>+</sup>

### Scheme 1.

anhydrous sodium sulphate. Silica gel (ASC, Bombay) impregnated with calcium sulphate was used for TLC.

#### 3.1 7-Oxo-octanol (II)

To the zinc-copper couple, prepared under nitrogen from zinc (1.56 g, 24.0 mmol) and copper (I) iodide (0.96 g, 5.0 mmol), in an ethanol-water mixture (9:1, 30 ml) in a 100 ml reaction vessel and using the probe sonicator, was added 3-buten-2-one (0.70 g, 10.0 mmol) and 4-bromo-1-butanol (2.29 g, 15.0 mmol). The reaction mixture was sonicated for 1 hour. The product obtained was quenched with saturated brine and filtered. Ethanol was evaporated under reduced pressure and the residue extracted with ether. The ether extract was washed twice with water and then with brine to obtain the crude material which was chromatographed over silica gel using pet ether: ethyl acetate (9:1) as eluant to furnish pure compound (II); yield 1.05 g (73.0%). IR: 3400, 2880, 1720, 970, 720 and 660 cm<sup>-1</sup>. NMR (CCl<sub>4</sub>), δ 1.2 (m, 8H, (-CH<sub>2</sub>-)<sub>4</sub>); 2.1 (s, 3H, CH<sub>3</sub>CO-); 2.3 (t, 2H, J = 7, -CH<sub>2</sub>CO-); 3.1 (bs, 1H, -OH, D<sub>2</sub>O exchangeable); 3.7 (t, 2H, J = 7, -CH<sub>2</sub>OH). Analysis - Found C, 66.4%, H, 11.3%; C<sub>8</sub>H<sub>16</sub>O<sub>2</sub> requires C, 66.6%, H, 11.2%.

#### 3.2 7-Oxo-octanal (III)

To a well-stirred solution of PCC (1.54 g, 7.0 mmol) and a pinch of fused sodium acetate in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added the keto-alcohol (II, 0.58 g, 4.0 mmol) in one portion. The reaction mixture was stirred for 5 hours and then diluted with anhydrous diethyl ether (120 ml). The supernatant layer was decanted from the gummy residue and passed through a column of neutral alumina. Solvent evaporation afforded pure keto-aldehyde (III), yield 0.34 g (60.0%). IR: 2900, 2720, 1710, 1690, 970 and 780 cm<sup>-1</sup>. NMR (CCl<sub>4</sub>) δ 1.16 (m, 6H, (-CH<sub>2</sub>-)<sub>3</sub>); 2.1 (s, 3H, CH<sub>3</sub>CO-); 2.2-2.3 (t, 2H, J = 7, -CH<sub>2</sub>CO-); 2.4 (t, 2H, J = 7, -CH<sub>2</sub>CHO-); 9.5 (s, 1H, -CHO). Analysis - Found C, 67.8%, H, 10.0%; C<sub>8</sub>H<sub>14</sub>O<sub>2</sub> requires C, 67.6%, H, 9.9%.

### 3.3 Ethyl-9-oxo-2(E)-decenoate (IV)

Potassium carbonate (1.38 g, 10.0 mmol), ethyl  $\alpha$ -dimethyl-phosphonoacetate (1.18 g, 6.0 mmol), compound III (0.711 g, 5.0 mmol) and water (6 ml) were heated under reflux along with stirring for 1 hour. Water (10 ml) was then added. The mixture was extracted with hexane (4  $\times$  25 ml) and dried. Solvent evaporation followed by purification of the crude product by column chromatography over silica gel using pet. ether:ether (4:1) as eluant provided IV, yield 0.77 g (72.4%). IR: 2880, 1715, 1695, 1660, 1080 and 660  $\text{cm}^{-1}$ . NMR( $\text{CCl}_4$ ):  $\delta$  0.9(t, 3H,  $J = 6$ ,  $-\text{CH}_3$ ); 1.1–1.3(m, 6H,  $(-\text{CH}_2-)_3$ ); 1.9(m, 2H,  $-\text{CH}_2-\text{CH}=\text{CH}-$ ); 2.1(s, 3H,  $\text{CH}_3\text{CO}-$ ); 2.25(t, 2H,  $J = 7$ ,  $-\text{CH}_2\text{CO}-$ ); 4.0(q, 2H,  $-\text{COOCH}_2\text{CH}_3$ ); 5.5(d, 1H,  $J = 16$ ,  $-\text{CH}=\text{CH}-\text{COOEt}$ ); 6.7–6.9(m, 1H,  $-\text{CH}=\text{CH}-\text{COOEt}$ ). Analysis – Found C, 67.7%, H, 9.3%;  $\text{C}_{12}\text{H}_{20}\text{O}_3$  requires C, 67.9%; H, 9.3%.

### 3.4 9-Oxo-2 (E)-decenoic acid (I)

A solution of unsaturated keto-ester (IV, 0.42 g, 1.98 mmol), NaOH (0.14 g, 3.37 mmol) in water (1 ml) and methanol (4 ml) was refluxed for 5 hours on a water bath. Methanol was evaporated under reduced pressure and the resultant product diluted with water. The unreacted material was extracted with ether. The aqueous phase was neutralized with dilute HCl, extracted with ether (3  $\times$  25 ml) and dried. Evaporation of the solvent gave crude material which upon recrystallization in methanol afforded pure acid (I), yield 0.24 g (65.6%) m.p. 52–54° (lit. m.p. 51–52°, Bestmann *et al* 1988). IR: 3500–2950, 1710, 1690, 1650, 1310, 1280 and 990  $\text{cm}^{-1}$ . NMR ( $\text{CCl}_4$ ):  $\delta$  1.1–1.3(m, 6H,  $(-\text{CH}_2-)_3$ ); 1.85(m, 2H,  $-\text{CH}_2-\text{CH}=\text{CH}-$ ); 2.1(s, 3H,  $\text{CH}_3\text{CO}-$ ); 2.25(t, 2H,  $J = 7$ ,  $-\text{CH}_2\text{CO}-$ ); 5.6(d, 1H,  $J = 16$ ,  $-\text{CH}=\text{CH}-\text{COOH}$ ); 6.5–6.7(m, 1H,  $-\text{CH}=\text{CH}-\text{COOH}$ ); 10.8(bs, 1H,  $-\text{COOH}$ ,  $\text{D}_2\text{O}$  exchangeable). Analysis – Found C, 65.0%; H, 8.9%;  $\text{C}_{10}\text{H}_{16}\text{O}_3$  requires C, 65.2%; H, 8.8%.

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