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Fast preparation of dihydrocyclocitral from citronellal under solventless microwave irradiation

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Abstract—Dihydrocyclocitral, a useful reagent in organic synthesis, has been synthesized in high yield and with high stereoselectivity from citronellal under microwave irradiation in two steps, involving acetic anhydride under base catalysis, then *p*-toluenesulfonic acid adsorbed on silica gel under solventless conditions (80% yield, reaction time 22 min).

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1. Introduction

Dihydrocyclocitral, 2,2,6-trimethylcyclohexanecarboxaldehyde **1**, is a useful starting material, for example, for the preparation of many products of interest in the flavour and pharmaceutical industries.[1–4]

Several synthetic pathways to dihydrocyclocitral from different starting materials have been described. Corey and Marcus synthesized **1** from 2,2,6-trimethylcyclohexanone by reaction with 1-diphenylphosphonio-1-methoxymethyllithium.[5] Marcel prepared **1**, also starting from 2,2,6-trimethylcyclohexanone, via 1-ethoxymethyl-2,2,6-trimethylcyclohexanol.[6] Simmons used 3,7-dimethyloct-7-enal, hydroxycitronellal as well as citronellal as starting materials to prepare **1** by two steps via an intermediate enol ester and using various acids to promote the ring-closure reaction. After purification by vacuum distillation, the product was obtained in about 60–65% yield (trans/cis isomers = 87/13).[1] Yamamoto used this procedure to prepare **1** with high purity in 51% yield from methoxycitronellal, the ratio of trans/cis isomers being 90/10.[2] However, all these preparations required long reaction times at high temperature, for example, the preparation of the enol ester required 7 h at 140 °C, and the subsequent cyclisation reaction required reflux for about 1.5–3.0 h with strong acids such as H_3PO_4 and H_2SO_4. The authors also used reagents like $TiCl_4$, CF_3COOH, CH_3SO_3H, $BF_3O(C_2H_5)_2$, but obtained lower yields.[1,2]

Microwave heating can be very useful for otherwise relatively slow reactions. Since the first publications on the application of microwave-assisted organic synthesis in the mid-1980s,[7] this technology has been developing rapidly.[8] Organic synthesis under solventless conditions is encouraged for environmental protection reasons.[9]

In this letter, we present a dihydrocyclocitral synthesis following a Simmons-like procedure from citronellal **2**, however using a microwave (MW) oven instead of conventional heating. The cyclisation reaction was carried out under mild conditions by using *p*-toluenesulfonic acid (PTSA) adsorbed on silica as catalyst in dry media. The sequence is shown in Scheme 1.

2. Results and discussion

Enol ester **3** was prepared from citronellal **2** by reaction with acetic anhydride in the presence of base under microwave irradiation (see Scheme 1). We investigated the significance of the molar ratio between **2** and Ac_2O, the reaction time and the base in order to optimize the reaction conditions (Table 1).

Keywords: Dihydrocyclocitral; Citronellal; Microwave irradiation; Solventless synthesis; Solid support; Isomeric selectivity.

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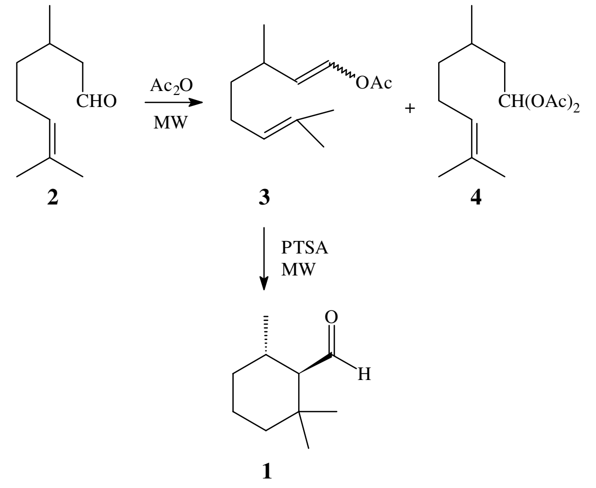

Scheme 1. Synthesis of dihydrocyclocitral from citronellal.

Table 1. Preparation of enol ester **3** from citronellal **2** using MW irradiation

Entry	**2**:Ac$_2$O (molar ratio)	Time (min)	Base	Yield of **3** (%)
1	1:4	20	K_2CO_3	87
2	1:3	20	K_2CO_3	87
3	1:2	20	K_2CO_3	72
4	1:3	25	K_2CO_3	86
5	1:3	15	K_2CO_3	74
6	1:4	15	K_2CO_3	80
7	1:3	420	K_2CO_3	86[a]
8	1:3	420	Et_3N	86[a]
9	1:3	25	Et_3N	85
10	1:3	20	Et_3N	86
11	1:3	15	Et_3N	70

[a] The reactions were refluxed by heating with stirring.

The results in Table 1 show that the yield of **3** was highest (87%) when the reaction was carried out under microwave irradiation for 20 min with a molar ratio of 1:3 between citronellal and acetic anhydride.[‡] Potassium carbonate and triethylamine were equally suitable as bases.

In order to investigate the cyclisation reaction, we purified **3** by vacuum distillation. The enol ester **3** was obtained as a mixture of the (*E*) and (*Z*) isomers with a purity of 97% (GC, $E/Z = 64{:}36$). The two geometrically isomeric enol esters were identified by their ^{1}H NMR signals at $\delta = 7.06$ ppm (dd, $J = 12.3$, 0.6 Hz; =**CH**–OCOCH$_3$, (*E*)-form) and $\delta = 6.99$ ppm (dd, $J = 6.6$, 1.2 Hz; =**CH**–OCOCH$_3$, (*Z*)-form).

The next step was the preparation of dihydrocyclocitral by treatment of **3** with an acid.[§] With strong acids such as phosphoric or sulfuric acid, the reaction was very difficult to control under microwave conditions. Therefore, we used PTSA as catalyst for cyclisation both with and without silica gel (Table 2).

As shown in Table 2, dihydrocyclocitral was prepared in an excellent yield (97%) with high isomeric selectivity (trans/cis isomers = 97:3) within a few minutes under solventless microwave irradiation using *p*-toluenesulfonic acid adsorbed on silica gel as catalyst. The trans and cis isomers of dihydrocyclocitral showed in the ^{1}H NMR spectrum the expected two high frequency resonances at $\delta = 9.65$ ppm (d, $J = 5.1$ Hz, –CHO, trans form) and $\delta = 9.89$ ppm (d, $J = 6.6$ Hz, –CHO, cis form).[5] The results proved that this catalyst promoted the reaction under mild conditions. In the absence of silica, the reaction occurred, but did not give a good yield owing to the formation of unexpected by-products (*p*-cymene and dimeric materials).

We also prepared **1** without purification (distillation) of **3**, which gave dihydrocyclocitral in 80% total yield with a purity of 98%.[¶]

Our investigation demonstrates that dihydrocyclocitral **1** can be synthesized from citronellal, following a Simmons-like procedure,[1] in an enhanced yield with an enhanced isomeric selectivity and within a short time by carrying out the two-step synthesis under solventless conditions assisted by microwave irradiation.

Spectral data of the enol ester **3**, (*E*)-isomer (CDCl$_3$): ^{1}H NMR (300 MHz) δ 7.06 (dd, $J = 12.3$, 0.6 Hz; 1H), 5.29 (dd, $J = 12.3$, 8.7, 1H), 5.04–5.14 (m, 1H), 2.09–2.19 (m, 1H), 2.10 (s, 3H), 1.90–2.00 (m, 2H), 1.68 (d, $J = 0.9$,

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[‡] 3,7-Dimethylocta-1,6-dien-1-yl acetate **3**: A mixture of citronellal (4.9 g, 30 mmol), acetic anhydride (see Table 1 for amounts), potassium carbonate (4.1 g, 30 mmol) or triethylamine (5.6 g + 0.2 g sodium acetate) was placed in the reaction vessel. The reactions were carried out in a professional microwave oven, Maxidigest MX350, Prolabo with reflux condenser. The temperature of the mixture was 142 °C. After adding diethyl ether (30 mL), the cooled reaction mixture was washed (with water, aqueous NaHCO$_3$ and brine) and dried (Na$_2$SO$_4$). The solvent was removed by evaporation at reduced pressure, and the residue was distilled at low pressure (67–75 °C/1 mbar) to give 97% of **3** with an *E*/*Z* isomeric ratio of 64/36. The pure isomers were obtained by a further fractional distillation followed by column chromatography separation (eluent: *n*-hexane/ethyl acetate = 95:5). A minor amount of diester **4** (5–8%) accompanied **3** in the mixture and was isolated by continued fractional distillation (98–100 °C/1 mbar).[1]

[§] Dihydrocyclocitral catalysed by *p*-toluenesulfonic acid on silica: *p*-Toluenesulfonic acid (monohydrate, 99%, Aldrich, amounts see Table 2) was dissolved in water followed by the addition of silica (silica gel 60, Merck) in the ratio 1/6 (w/w). From this slurry, water was removed completely by evaporation under reduced pressure at 60 °C to give the desired catalyst. A mixture of the distilled enol ester **3** (97%, 6.0 g) and catalyst was treated in the microwave oven, MDS-2000, CEM in a short time (see Table 2). The mixture was extracted with diethyl ether, washed with water and dried (Na$_2$SO$_4$). After removal of the solvent, the crude product was obtained according to Table 2.

[¶] Direct preparation of dihydrocyclocitral from citronellal: Citronellal (26.4 g, 0.17 mol) was treated with acetic anhydride as described above to give the crude enol ester **3**. This material was used directly for the preparation of **1**. Vacuum distillation of the crude **1** (74–75 °C/6 mbar), gave 20.2 g (total yield: 80%) of dihydrocyclocitral with a purity of 98% (according to GC).

Table 2. MW induced cyclisation of enol ester **3** into dihydrocyclocitral **1**

Entry	**3**:PTSA (molar ratio)	Supports	Time (min)	Yield of **1** (%)
1	10:3	SiO_2	1.5	97
2	10:2	SiO_2	1.5	94
3	10:2	SiO_2	1.0	91
4	10:2	SiO_2	2.0	93
5	10:1	SiO_2	1.5	48
6	10:2	Al_2O_3[a]	2.0	—
7	10:2	0	1.5	50
8	10:2	0	2.0	62
9	10:2	0	3.0	74
10	10:3	0	2.0	82
11	10:3	0	1.5	72

[a] Basic Al_2O_3.

3H), 1.59 (s, 3H), 1.23–1.41 (m, 2H), 1.02 (d, $J = 6.9$, 3H). ^{13}C NMR (75 MHz) 17.7, 20.7, 20.9, 25.7, 25.8, 32.0, 37.2, 120.6, 124.3, 131.5, 134.6, 168.2; (*Z*)-isomer: ^{1}H NMR (300 MHz) δ 6.99 (dd, $J = 6.6$, 1.2, 1H), 5.04–5.14 (m, 1H), 4.67 (dd, $J = 9.6$, 6.6, 1H), 2.61–2.75 (m, 1H), 2.13 (s, 3H), 1.90–2.00 (m, 2H), 1.68 (d, $J = 0.9$, 3H), 1.59 (s, 3H), 1.20–1.43 (m, 2H), 0.99 (d, $J = 6.9$, 3H). ^{13}C NMR (75 MHz) 17.6, 20.7, 22.7, 25.9, 29.3, 31.6, 37.4, 120.2, 124.5, 131.3, 133.2, 168.1.

Spectral data of dihydrocyclocitral **1** ($CDCl_3$): ^{1}H NMR (300 MHz) δ 9.89 (d, $J = 6.6$ Hz, –CHO, cis), 9.65 (d, $J = 5.1$ Hz, –CHO, trans), several resonances were observed in the range from 0.8 to 2.0 ppm. ^{13}C NMR (75 MHz) 20.8, 21.0, 21.7, 27.8, 31.0, 33.8, 34.3, 41.5, 66.2, 207.3. MS (*m*/*e*): 154 (M^+, 28), 139 (14), 121 (31), 111 (39), 95 (28), 83 (64), 69 (100), 55 (57), 41 (50).

Spectral data of the diester **4** ($CDCl_3$): ^{1}H NMR (300 MHz) δ 6.87 (dd, $J = 6.6$, 4.8 Hz; 1H), 5.05–5.10 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.93–2.03 (m, 2H), 1.74–1.83 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.52–1.59 (m, 2H), 1.19–1.41 (m, 2H), 0.96 (d, $J = 6.0$, 3H). ^{13}C NMR (75 MHz) 17.7, 19.6, 20.8, 20.9, 25.2, 25.7, 28.1, 37.0, 40.1, 89.7, 124.4, 131.5, 168.9, 169.0.

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