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Green synthesis of (−)-isopulegol from (+)-citronellal: application to essential oil of citronella

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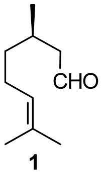
Abstract—A simple green and efficient method has been developed for the synthesis of (−)-isopulegol from (+)-citronellal in the presence of a solid supported catalyst ($SiO_2/ZnCl_2$), under solvent-free conditions and MW irradiation. It was also found that the same technology is applicable to the direct preparation of (−)-isopulegol from the essential oil of citronella (*Cymbopogon nardus*, growing in southern Brazil) in excellent yield. © 2003 Elsevier Science Ltd. All rights reserved.

The ene-cyclisation of the monoterpene (+)-citronellal (**1**) affording (−)-isopulegol (**2**) is the best industrial process for the preparation of (−)-menthol (**3**),[1,2] a fine chemical widely employed in pharmaceuticals, agrochemicals, cosmetics, toothpastes, chewing gum and other toilet goods. This methodology has also been extended to the preparation of several natural compounds with biological activities.[3–5]

The (+)-citronellal, employed in the industrial process for (−)-menthol preparation (Takasago process), is obtained from myrcene through a three steps sequence, being the isomerisation of geranyl diethylamine to (*R*)-citronellal enamine, using a chiral Rh(I)–BINAP catalyst as the key step. This reaction is performed at 100°C in THF for 12 h, furnishing this enamine in 98% yield and 98.5% *ee*.



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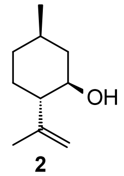

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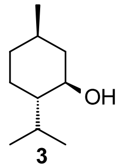

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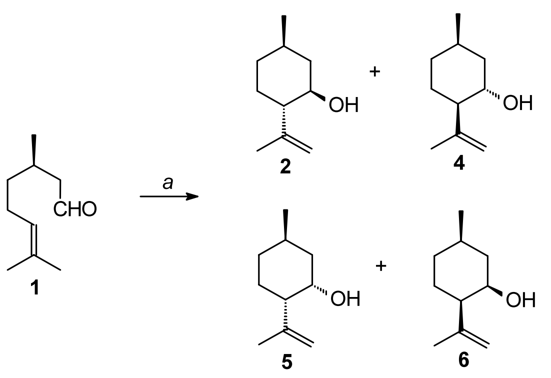
In the Takasago process aqueous $ZnBr_2$ is used to perform the ene-cyclisation in very good yield and excellent selectivity.[1] More recently, the Takasago Co. have patented the use of tris(2,6-diarylphenoxy)aluminum as a better catalyst for this cyclisation.[6] In fact, among the methods for the conversion of **1** into **2**, Lewis acids have shown the best catalytic activity, especially concerning the selectivity aspects, since (−)-isopulegol (**2**) was predominantly obtained among the three other possible isomers **4**–**6**[7–13] (Scheme 1). Aiming to improve the reaction's stereoselectivity to (−)-isopulegol (**2**), several heterogeneous catalysts have been studied and excellent results have been achieved by using silica- and clay-supported catalysts.[8–14]

Despite the heterogeneous catalytic system advantages of performing the cyclisation of (+)-citronellal (**1**), the methods described involve the use of hazardous solvents, heating, high molar ratio of the catalyst/substrate, expensive catalyst or the necessity for special treatment for its activation and are also not time efficient. These aspects are in disagreement with clean chemistry, especially with respect to the green chemistry



Scheme 1. a: $SiO_2/ZnCl_2$ (10%), MW (488 W).

Keywords: microwave; solvent-free reaction; isopulegol.

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principles #5 and #6, that refer to the elimination of the hazardous solvents and energy efficiency.[15]

During recent years a large number of papers have been advocating the advantages of 'MORE Chemistry' (microwave oven-induced reaction enhancement) as an effective green technique in organic synthesis.[16,17] When used with an energy-efficient heating method, several reactions under MW showed a dramatic increase in yield, rate and purity of products. Of particular interest are the MW dry reaction techniques or solvent-free procedures using supported reagents.[17] This technology provides enhanced reaction rates, safety, ease of manipulation and greater selectivity.

The clay-catalysed ring closure of (+)-citronellal (**1**) to (−)-isopulegol (**2**) under MW was studied, but no effect of the MW heating was observed.[18] A solvent-free variant protocol, involving the irradiation of **1** adsorbed on Na-Y-zeolites, showed good results.[19] (−)-Isopulegol (**2**) was obtained in 89% yield, together with (+)-neoiso-isopulegol (**6**) (6%) and some dehydration products of **2** and **6** (5%). However, this methodology requires high molar ratio solid catalyst: **1** (8:1, wt/wt) and its preparation demands a long time and the use of organic solvents.

As a part of our efforts in exploring the utility of citronellal in organic synthesis, we report here the optimal conditions for the synthesis of (−)-isopulegol (**2**) on solid supported Lewis acid under microwave irradiation. It was found that $SiO_2/ZnCl_2$ (10%)[20] under MW (1.5 min; 488 W, 58°C)[21] promotes the selective cyclisation of **1** in excellent yield (Scheme 1, Table 1). As a control experiment, the same reaction mixture was heated at 58°C using an oil bath. The reaction progress was followed by TLC and GC; after heating for 1 h, all the citronellal was consumed. However, the cyclisation products were obtained in only 72% yield, together with byproducts and with loss of selectivity in comparison with the experiment with MW (Table 1, entry 10). This fact shows a clear advantage of microwave irradiation over conventional heating techniques.

In order to evaluate the synergy between the solvent-free medium and microwave irradiation in this reaction, several experiments were carried out, as shown in Table 1. Silica gel and acidic alumina were used as inorganic support to several Lewis acids (HCl, $ZnCl_2$ and $FeSO_4$). When (+)-citronellal (**1**) was submitted to acidic cyclisation under MW in the absence of solid support or only using SiO_2 or acidic Al_2O_3, no reaction took place in all conditions tested and **1** was recovered unchanged. By using SiO_2/HCl catalyst, (+)-citronellal reacted smoothly to afford **2** as the predominant isomer, but with poor selectivity (entry 1, Table 1). When $ZnCl_2$ (10%) was supported on silica gel a higher selectivity was achieved at reduced MW power and lower reaction time (entry 4).

Irradiation time and ratio of reactants were investigated in order to make this microwave technology applicable on a commercial scale (entries 2–11). As shown in Table 1, increasing reaction time and ratio of the reactants lead to higher yields and selectivity. Although

Table 1. Solvent-free solid supported cyclisation of (+)-citronellal (**1**) to (−)-isopulegol (**2**) under MW

Entry	Solid supported catalyst	Solid catalyst: citronellal; mmol (ratio wt/wt)	Reaction time (min)	Conversion[b] (%)	Isomeric ratio[c] (%)			
					2	**4**	**5**	**6**
1	SiO_2/HCl	2:1 (1:1.3)	30[a]	100	51	22	27	–
2	$SiO_2/ZnCl_2$ (10%)	2:1 (1:1.2)	7	98	33	11	56	[d]
3	$SiO_2/ZnCl_2$ (10%)	2:1 (1:1.2)	8	98	44	20	34	2
4	$SiO_2/ZnCl_2$ (10%)	2:1 (1:1.2)	10	98	59	24	12	5
5	$SiO_2/ZnCl_2$ (10%)	10:5 (1:1.2)	10	90	56	26	18	[d]
6	$SiO_2/ZnCl_2$ (10%)	4:1 (1.6:1)	5	90	55	23	20	2
7	$SiO_2/ZnCl_2$ (10%)	4:1 (1.6:1)	10	98	60	35	–	5
8	$SiO_2/ZnCl_2$ (10%)	20:5 (1.6:1)	10	98	68	28	–	4
9	$SiO_2/ZnCl_2$ (10%)	40:10 (1.6:1)	10	100	77	23	[d]	–
10	$SiO_2/ZnCl_2$ (10%)	80:20 (1.6:1)	1.5	100	76	24	[d]	–
11	$SiO_2/ZnCl_2$ (10%)	400:100 (1.6:1)	1.5	100	74	26	[d]	–
12	$SiO_2/FeSO_4$ (4%)	2:1 (1:1.3)	4	98	48	38	14	–
13	$SiO_2/FeSO_4$ (4%)	2:1 (1:1.3)	10	80	60	36	–	4
14	$SiO_2/FeSO_4$ (4%)	4:1 (1.6:1)	5	80	57	43	–	–
15	Al_2O_3/HCl	4:1 (1.3:1)	15	70	40	30	28	2
16	$Al_2O_3/ZnCl_2$ (7%)	2:1 (1.3:1)	15	80	63	25	6	6
17	$Al_2O_3/FeSO_4$ (1.2%)	4:1 (2.7:1)	15	80	40	26	32	2

[a] The power of the MW oven was calibrated at 662 W; all the others experiments were performed at 488 W.[24]

[b] Determined by GC.

[c] Determined by GC and ^1H NMR of the crude reaction mixture and compared after purification.

[d] Traces of this isomer was detected by GC.

most experiments were performed on a 1.0 mmol scale, we have also explored scaling-up these reactions (10–100 mmol) and comparable yields were achieved (entries 7–11). Interestingly, when the reactions were performed with 20 and 100 mmol of **1** and a solid supported catalyst: **1** ratio = 1.6:1 (wt/wt), (–)-isopulegol (**2**) was obtained in excellent yield with 76–74% selectivity, together with (+)-neo-isopulegol (**7**) and traces the isomer **5**, after irradiation for 1.5 min (entries 10 and 11, Table 1).

When $SiO_2/FeSO_4$ (4%) was used in place of $SiO_2/ZnCl_2$ (10%), both yield and stereoselectivity of the cyclisation reaction were lowered (entries 12–14). Similarly, the use of the acidic alumina as support was studied. However, MW irradiation for 5–15 min failed to provide satisfactory yields and selectivity of (–)-isopulegol (entries 15–17). Attempts to directly reuse the solid supported catalysts in a new cyclisation reaction were unsuccessful, there was a loss of catalytic activity. However, the solid supports were regenerated by new treatment with $ZnCl_2$.[20] The $SiO_2/ZnCl_2$ (10%) prepared with used SiO_2 showed the same catalytic activity, affording **2** in almost identical yield.

To extend the scope of the reaction, our best catalytic system ($SiO_2/ZnCl_2$, 10%) was submitted to the essential oil of citronella (*Cymbopogon nardus* (L) Rendle). The major component of the essential oil of citronella, extracted from the plant grown in southern Brazil (Três Passos, RS), was found to be (+)-*R*-citronellal (40–51%).[22] Thus, selective cyclisation of citronellal to isopulegol was observed in excellent yield (100% of conversion) and comparable stereoselectivity,[23] when the essential oil of citronella was submitted to MW irradiation for 1 min under 427 W[24] in the presence of $SiO_2/ZnCl_2$ (10%). (–)-Isopulegol (**2**) was obtained in 75% yield, together with **4** (15%) and **5** (10%). Unreacted geraniol, citronellol, geranyl acetate, and other minor constituents of the starting oil were recovered.

In conclusion, (–)-isopulegol was prepared directly from the treatment of essential oil of citronella under solid supported acid catalysis and solvent-free MW assisted ene-cyclisation. This environmentally benign method involves a low consumption of solvent, simple work-up, short reaction time, mild reaction conditions, excellent yields and high selectivity. The elimination of hazardous and expensive solvents and auxiliaries, together with the low energy consumption, make this method potentially useful for the green production of (–)-isopulegol on a commercial scale, starting from citronella oil.

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20. The solid supported catalysts were prepared by the following procedures: **SiO_2/HCl catalyst**: To a 250 mL beaker was added silica gel (10.0g of silica gel 60, 230–240 mesh, Merck) and 5% HCl (100 mL). The suspension was stirred at room temperature for 30 min and the resulting mixture was filtered under reduced pressure, dried at 150°C for 15 h in an oven and then cooled in a desiccator. The same procedure was used for Al_2O_3/HCl (10.0g of Al_2O_3 90, 0.063–0.200 mm, Merck). **$SiO_2/ZnCl_2$ (10%)**: To a 100 mL beaker was added silica gel 60 (9.0g), $ZnCl_2$ (1.0g) and water (3.0 mL). The suspension was stirred for 15 min at room temperature, dried at 80°C for 3 h and for an additional 15 h at 150°C in an oven and then cooled in a desiccator. The aforementioned procedure was used for $SiO_2/FeSO_4$ (4%; 9.6:0.4 g), $Al_2O_3/ZnCl_2$ (7%; 9.3:0.7 g) and $Al_2O_3/FeSO_4$ (1.2%; 9.88:0.12 g) by varying the Lewis acid and its amount.
21. **(–)-Isopulegol (2) from (+)-citronellal (1)**: To a 250 mL reaction flask equipped with a septum port and containing $SiO_2/ZnCl_2$ (10%) (2.54 g; 40 mmol), (+)-citronellal **1** (1.54 g; 10 mmol) was added dropwise. The reaction

mixture was irradiated in an unmodified household MW oven (Brastemp model VIP-38 Sensor Crisp operating at 2.45 GHz) at 488 W.[24] The reaction progress was followed by GC. After 1.5 min, the reaction vessel was cooled, and the product was extracted from the silica gel with ethyl acetate (20 mL) and filtered. The solvent was evaporated under reduced pressure to afford a mixture of **2** and **4** (1.54 g; 100% yield, ratio **2**:**4** = 76:24), together with traces of **5**, as a colorless oil. The isomers were identified by ^{1}H NMR, in particular from the proton C*H*O signals, and the isomers ratio were determined by GC analysis. The spectral data of **2** and **4** were in perfect agreement with those reported in the literature.[7,9] IR (film, cm^{-1}): 3389, br (OH). ^{1}H NMR (200 MHz, $CDCl_3$) δ (**2**): 4.87 (m, 1H); 4.83 (s br, 1H); 3.43 (dt, $J=10.4$ and 4.3 Hz, 1H); 2.03 (m, 1H); 1.86 (m, 1H); 1.69 (d, $J=0.5$ Hz, 3H); 1.65 (m, 2H); 1.49 (m, 2H); 1.32 (m, 1H); 0.97 (m, 2H); 0.92 (d, $J=6.5$ Hz, 3H). (**4**): 3.67 (dt, $J=10.4$ and 4.2 Hz, 1H).

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23. **(−)-Isopulegol (2) from essential oil of citronella**: To a 250 mL reaction flask equipped with a septum port and containing $SiO_2/ZnCl_2$ (10%) (2.54 g; 40 mmol), essential oil of citronella (1.54 g; 40% of citronellal, determined by GC analysis) was added dropwise. The reaction mixture was irradiated at 427 W for 1.0 min, the reaction vessel was cooled at room temperature and the product was extracted from the silica gel with ethyl acetate (20 mL) and filtered. The solvent was evaporated under reduced pressure yielding a mixture of **2**, **4** and **5** (ratio **2**:**4**:**5** = 75:15:10) and other unreacted oil constituents.
24. The oven powers were determined according to: Kingston, H. M. In *Introduction to Microwave Sample Preparation, Theory and Practice*; Jassie, L. B., Ed.; American Chemical Society: Washington DC, 1988.