Domino-cyclisation and hydrogenation of citronellal to menthol over bifunctional Ni/Zr-Beta and Zr-beta/Ni-MCM-41 catalysts

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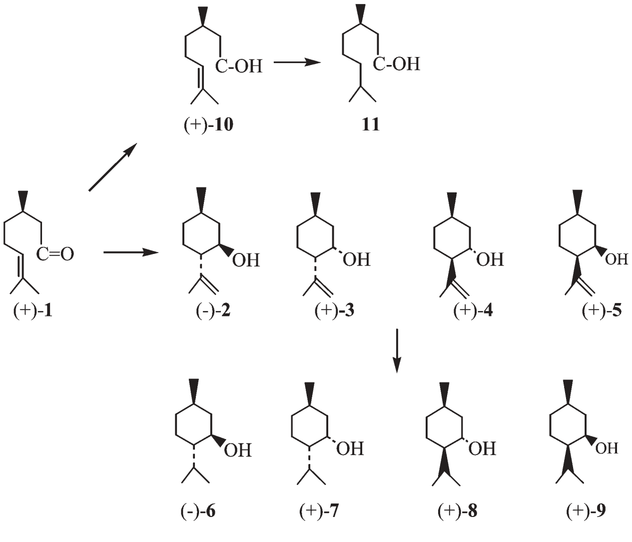
The one-pot conversion of (±)-citronellal to menthol can be selectively catalysed by either a bifunctional Ni/Zr-zeolite beta catalyst or a dual catalyst system of Zr-beta and Ni/MCM-41, giving a high diastereoselectivity to (±)-menthol of 90–94%.

Menthol is widely used in pharmaceuticals, cosmetics, toothpastes, chewing gum, cigarettes, *etc*. One of the routes to menthol involves the cyclisation of citronellal **1** to give four stereoisomers of isopulegol, each of which occurs as a pair of enantiomers–(±)-isopulegol **2**, (±)-neo-isopulegol **3**, (±)-iso-isopulegol **4** and (±)-neoiso-isopulegol **5** (Scheme 1).[1] Hydrogenation of these isopulegols leads to four pairs of enantiomeric menthols–(±)-menthol **6**, (±)-neomenthol **7**, (±)-isomenthol **8**, and (±)-neoisomenthol **9**. Of these, the most useful isomer is (−)-menthol which has a peppermint odour and also exerts a cooling effect. The latter property is peculiar to this isomer as none of the other isomers possesses this "refreshing" property.

The cyclisation of (+)-citronellal over $ZnBr_2$ catalyst gives (−)-isopulegol with a selectivity of 94%.[2] A recent patent by Takasago International Corporation[3] reports the use of another homogeneous catalyst, tris(2,6-triarylphenoxy)aluminium, which gives almost exclusively (−)-isopulegol, 99.3%, with only traces of the other isomers. However, the use of homogeneous catalysts requires extensive workup and hence, frequently the catalyst can not be recovered and reused. Heterogeneous catalysts such as zeolite beta, MCM-41, HY, mordenite, *etc.*, offer ease of recovery and reuse of catalyst but the reported diastereoselectivity to (−)-isopulegol **2** is relatively low at 52–76%.[4–8] As the ratio of the isopulegol isomers determines the diastereoselectivity to the desired (±)-menthol isomer **6**, one approach was to immobilize $ZnBr_2$ on SiO_2.[9] Depending on the pretreatment temperature, the selectivity to (−)-isopulegol varied from 72 to 86%. A related bifunctional catalyst, Ru-$ZnBr_2$/SiO_2, gave a yield of 85% for (−)-menthol **6** in a one-pot reaction. Ravasio *et al.*[10] reported that Cu/SiO_2 was similarly active although a surprising increase in the diastereoselectivity was observed upon hydrogenation of (−)-isopulegol **2** (69%) to (−)-menthol **6** (80%). A 3 wt% Ir/beta zeolite catalyst gave a high yield of menthols, 93–95%, of which 75% was (−)-menthol **6**.[11] The synthesis of menthols has also been carried out starting from citral instead of citronellal.[12] Nickel was found to effectively catalyse the hydrogenation of the conjugated C=C bond in citral to form citronellal. In contrast, metals such as Co and Ir preferentially catalysed the hydrogenation of C=O giving geraniol and nerol rather than citronellal. A menthol yield of 90% was reported for the direct hydrogenation of citral over a 3% Ni/Al-MCM-41 catalyst with (±)-menthol **6** forming 70–75% of the menthol mixture.



Scheme 1

Recently, Corma *et al.*[13] reported that the diastereoselectivity to (6)-isopulegol **2** could be increased to 85% over Sn-zeolite beta. We showed that Zr-zeolite beta was able to achieve an even higher diastereoselectivity of 93%.[14] This was attributed to a shape-selectivity effect brought about by the framework substitution of Al^{3+} by the bigger Zr^{4+} in the pore channels of zeolite beta. In this study, we have combined the high diastereoselectivity for the cyclisation reaction of Zr-zeolite beta with hydrogenation activity in order to form a bifunctional catalyst for the direct transformation of citronellal to menthol. Nickel was chosen as the metal for hydrogenation based on its low cost compared to other metals such as platinum, palladium, rhodium and iridium. A dual catalytic system based on Zr-zeolite beta and Ni/MCM-41 was also tested for the one-pot synthesis of menthol. The high surface area of MCM-41 makes it a good support for metal deposition. One-pot reactions are seen as environmentally friendly as chemical conversions consisting of a number of individual reaction can be achieved in a single reaction step by multifunctional catalysts.[15] This avoids side product formation and loss of starting material, in addition to reducing operational costs.

The surface area of Zr-beta was slightly reduced ($\leqslant$11%) following impregnation with Ni up to 15 wt%. The reduced micropore volume indicates that partial blockage of the micropores occurred. The Ni phase could be detected in the powder

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Table 1 Product distribution in hydrogenation of (±)-citronellal over bifunctional Ni/Zr-beta and dual catalysts Zr-beta&Ni/MCM-41

Entry	Catalyst	Time (h)	Conversion (%)	Selectivity (%)				Yield (%)	
				6–9	**10**	**11**	**2–5**	**6–9**	**6**
1	3%Ni/ZrBEA	22	95	90 (90)[a]	0	3	7	86	77
2	4%Ni/ZrBEA	22	96	96 (90)	0	3	1	92	83
3	5%Ni/ZrBEA	22	96	90 (90)	6	1	3	86	78
4	15%Ni/ZrBEA	10	96	74 (86)	8	14	4	71	61
5	ZrBEA-3%Ni[b]	22	97	95 (93)	0	5	0	92	86
6	ZrBEA-3%Ni	22	97	95 (93)	0	5	0	92	86
7	ZrBEA-5%Ni	22	100	95 (94)	0	5	0	95	89
8	ZrBEA-10%Ni	8	93	94 (93)	1	5	0	97	81
9	ZrBEA-15%Ni[b]	22	95	95 (93)	0	5	0	90	84
10	ZrBEA-15%Ni	8	93	95 (94)	0	4	1	88	83
11	ZrBEA-15%Ni[c]	7	92	84 (94)	3	12	1	77	73
12	ZrBEA-30%Ni	7	96	92 (93)	0	5	3	88	82
13	3%Ni/ZrBEA[d]	22	94	88 (89)	3	4	7	83	74
14	ZrBEA-3%Ni[d]	22	96	94 (92)	1	5	0	90	83

[a] In parentheses, diastereoselectivity to (±)-menthol **6**. [b] 75 mg each of Zr-beta and Ni/MCM-41; rest–150 mg each of Zr-beta and Ni/MCM-41. [c] H_2 introduced from start of reaction. [d] After 3 cycles.

X-ray diffractograms for loadings of 3–15 wt%. The metal particle size, estimated from the Scherrer equation, was between 22 and 33 nm. The rather large particle size could be due to poor spreading on the hydrophobic surface of Zr-zeolite beta, which had been prepared using HF as a mineralizer.

Racemic citronellal was rapidly converted over the bifunctional Ni/Zr-beta catalysts. The reaction was carried out in He for the first hour. This improves the selectivity to menthol as the cyclisation reaction can first proceed without any competing hydrogenation reactions. Subsequently, H_2 was introduced to the autoclave. Introduction of H_2 from the start of the reaction led to a lower menthol selectivity as more citronellol **10** and 3,7-dimethyloctanol **11** were formed (entry 11, Table 1).

The main products formed after 2 h were isopulegols (96%) with a small amount of menthols (Fig. 1). Only three isomeric isopulegols were detected: (±)-isopulegol **2**, (±)-neo-isopulegol **3** and (±)-iso-isopulegol **4** in the ratio 90 : 8 : 2. The subsequent hydrogenation of the isopulegols occurred with an induction period which depended on the Ni loading. The hydrogenation was highly selective for the formation of menthols rather than the hydrogenation of citronellal **1** to citronellol **10** or 3,7-dimethyloctanol **11**. At the onset of reaction, only menthols were formed while 3,7-dimethyloctanol **11** was detected at longer reaction times although its selectivity was low, 3%. The high diastereoselectivity observed for (±)-isopulegol **2** was retained during hydrogenation, so that the desired (±)-menthol **6** was the predominant isomer (90%). After 22 h, the yield of menthols was 92% with a citronellal conversion of 96%.

The highest selectivity to menthols was observed for Ni loadings ⩽5 wt% with a diastereoselectivity to the desired (±)-menthol **6** of 90% (Table 1). Increasing the Ni content to 15 wt% was not advantageous. Although the rate of hydrogenation increased, the initial rate of isopulegol formation decreased (Fig. 2). This, together with a lower diastereoselectivity to (±)-menthol **6** of 86%, suggests that access to the active Zr sites within the zeolitic pores was substantially blocked by the higher Ni content. As a consequence, more of the open-chain hydrogenated products, citronellol **10** and 3,7-dimethyloctanol **11**, were formed over 15% Ni/Zr-beta (entry 4, Table 1). The lower diastereoselectivity is not due to cyclisation of citronellal occurring over Ni crystallites. The

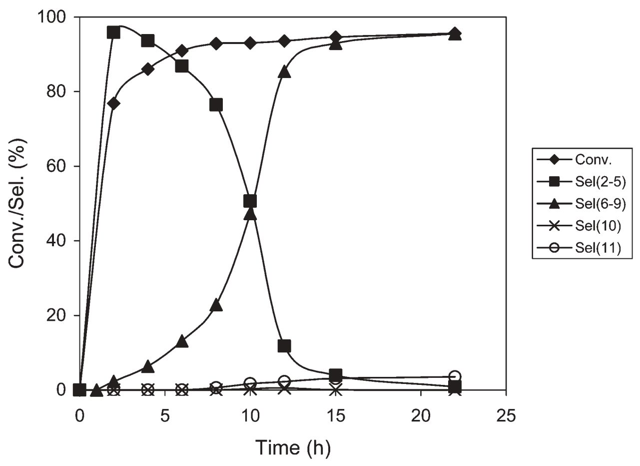

Fig. 1 Hydrogenation of (±)-citronellal over 4% Ni/Zr-beta. Reaction conditions: 9.5 mmol citronellal, 50 ml *tert*-butanol, 0.15 g catalyst, 80 °C, 2 MPa H_2.

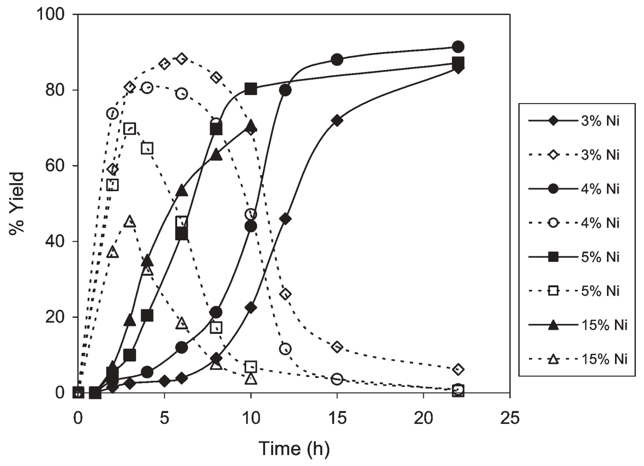

Fig. 2 Comparison of yields over bifunctional Ni/Zr-beta catalysts with different Ni loadings. Open symbols: isopulegols; closed symbols: menthols. Reaction conditions as in Fig. 1.

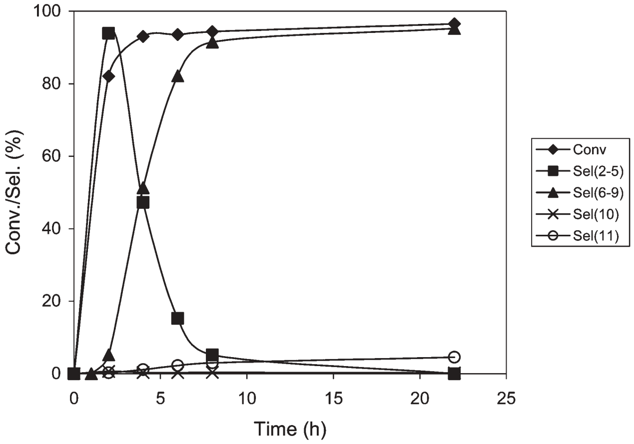

Fig. 3 Hydrogenation of (±)-citronellal over Zr-beta-3%Ni//MCM-41. Reaction conditions as in Fig. 1.

conversion of citronellal to isopulegols over the MCM-41 support and a 3% Ni/MCM-41 sample after 22 h was 1.6 and 2.6%, respectively. This indicates that cyclisation occurs predominantly over Zr-beta. Hence, the lower diastereoselectivity over Ni/Zr-beta can be attributed to pore blockage so that part of the cyclisation reaction occurred on the external surface without pore constraints. Comparing the catalysts, the highest yield to menthols was obtained over 4% Ni/Zr-beta. The yield of the (±)-menthol isomer **6** was 83%.

The one-pot synthesis of menthol was also carried out using a mixture of Zr-beta and Ni supported on MCM-41. The use of MCM-41 allows a high metal dispersion on the mesoporous support. The crystallite size, calculated from the Scherrer equation, was 8.1 and 11.3 nm for the 10 and 15% Ni sample, respectively. These crystallites are two to three times smaller than those formed on Zr-beta. The initial rate of cyclisation of citronellal over Zr-beta was about twice as fast as the rate of hydrogenation over Ni/MCM-41. This, together with the delayed introduction of H_2 for the first hour, ensured that the major products formed after 2 h were isopulegols (Fig. 3). The diastereoselectivity to (±)-isopulegol **2** was 93–94% which is higher than that observed over the bifunctional Ni/Zr-beta catalysts, 90% (Table 1). Increasing the Ni loading led to a faster rate of hydrogenation. The selectivity to menthols was >94% for all Ni loadings, of which 92–94% are the desired (±)-menthol **6**. Besides menthols, the other products detected were unreacted isopulegols **2–5**, 3,7-dimethyloctanol **11** and to a small extent, citronellol **10**. However, hydrogenation products of citronellal constitute only 6% of the products. Doubling the catalyst amount led to almost complete hydrogenation of the isopulegols after 8 h *vs.* 22 h for reaction systems with a smaller catalyst weight.

At the same Ni loading, Ni/MCM-41 catalysts catalysed the hydrogenation of isopulegols at a much faster rate than the bifunctional Ni/Zr-beta catalysts (*cf.* Fig. 3). The induction time was shortened from 1–5 h in the bifunctional catalysts to 0.5–2 h in the dual catalyst systems. The rate of formation of menthols increased with Ni loading up to a maximum at 15%Ni/MCM-41. Both bifunctional 3%Ni/ZrBEA catalyst and ZrBEA-3%MCM-41 were recycled by recalcining at 540 °C for 4 h and reduction in H_2 (entries 13 and 14, Table 1). No significant loss in activity or menthol selectivity was observed up to 3 cycles. The good tolerance to regeneration conditions of both catalytic systems makes them useful catalysts.

In conclusion, bifunctional Ni/Zr-beta or a physical mixture of Zr-beta with Ni/MCM-41 are effective catalysts for the one-pot synthesis of menthol from citronellal. The use of Zr-beta in combination with a Ni hydrogenation functionality enables a high diastereoselectivity to (±)-menthol **6** of 90–94% with a total menthol yield of 86–97%.†

Notes and references

† The preparation of Zr-beta has been reported in ref. 16. Siliceous MCM-41 was synthesized following ref. 17. The supported Ni catalysts were prepared by wet impregnation using $Ni(NO_3)_2$. The impregnated samples were dried overnight at 90 °C and calcined at 450 °C for 6 h. The Ni loading on Zr-beta was from 3 to 15 wt% and on MCM-41, from 3 to 30 wt%. The catalytic tests were performed at 80 °C under a H_2 pressure of 2 MPa in a 100 ml Teflon-lined stainless steel autoclave. The reaction mixture consisted of 1.7 ml (9.5 mmol) (±)-citronellal in 50 ml *tert*-butanol as solvent and 0.15 g catalyst. The volume of the solvent was rather large due to the need to flush the sample withdrawing line before sampling. For the dual catalyst system, a 1 : 1 mixture of Zr-beta and Ni/MCM-41 were used. The catalyst was pre-reduced in H_2 (50 ml min^{-1}) for 2 h at 450 °C before charging into the autoclave. The reaction was conducted in a He atmosphere for the first hour before introduction of H_2. Samples were removed at regular intervals and analyzed by gas chromatography. The products were identified by comparison with known standards and by GCMS.

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