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Research Note

# Highly selective synthesis of menthols from citral in a one-step process

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## Abstract

We report for the first time the selective synthesis of menthols from citral in a one-step process. Bifunctional metal/acid catalysts active and selective for menthol synthesis were developed by studying the individual steps involved in the reaction pathway leading to menthols from citral. The metallic component was selected by testing silica-supported metals for citral hydrogenation to citronellal. Acid site requirements to efficiently isomerize citronellal to isopulegols were investigated on different solid acids. Potential bifunctional metal/acid catalysts were then prepared and tested for citral conversion to menthols. The best catalyst was Ni/Al-MCM-41, which yielded about 90% menthols and gave 70–75% of racemic (±)-menthol in the menthol mixture.

*Keywords:* Menthol synthesis; Citral conversion; Fine chemistry; Sustainable processes

## 1. Introduction

Menthol is used extensively in pharmaceuticals, cosmetics, toothpastes, and chewing gum, as well as in cigarettes. The menthol molecule comprises four pair of optical isomers: (±)-menthol, (±)-isomenthol, (±)-neomenthol, and (±)-neo-isomenthol. Of the eight optically active isomers, only (−)-menthol possesses the characteristic peppermint odor and exerts a unique cooling sensation on the skin and mucous membranes. Most (−)-menthol is obtained by freezing peppermint and cornmint oils, but it is also produced synthetically. In 1998, production of synthetic menthol was 2500 metric tons, which represented about 20% of the world production of menthol [1]. Synthetic menthol is currently produced in the world by two companies: Haarmann & Reimer and Takasago International Corporation. In the Haarmann & Reimer process [2] racemic (±)-menthols are obtained by hydrogenation of thymol, which is, in turn, produced by propylation of *m*-cresol, a non-stereospecific feedstock. (−)-Menthol is obtained by further treating the racemic menthol via a separation crystallization process. This is the first commercial synthetic route to (−)-menthol. In the early 1980s, Takasago developed an asymmetric synthesis technology for producing (−)-menthol from myrcene [3]. The key to the Takasago process was the use of a chiral Rh BINAP catalyst for transforming diethylgeranylamine obtained from myrcene to the chiral 3*R*-citronellal enamine, with more than 95% enantiomeric excess.

Considerable effort has been devoted to the production of (−)-menthol by synthetic or semisynthetic means from other more readily reliable raw materials. We report here for the first time the selective synthesis of menthols from citral in a one-step process, which involves the initial hydrogenation of citral to citronellal, followed by the isomerization of citronellal to isopulegols, and the final hydrogenation of isopulegols to menthols. Menthols from citral is an attractive synthetic route because citral is a renewable raw material that is obtained mainly by distillation of essential oils, such as lemongrass oil, which contains ca. 70–80% citral. Reactions involved in the citral-to-menthols pathway have been studied separately. For example, the selective hydrogenation of citral was widely investigated on different metal-supported catalysts for producing either nerol/geraniol or citronellal and citronelol [4,5]. The citronellal cyclization to isopulegol has been carried out by using liquid [6,7] and solid [8–10] acid catalysts, while the direct synthesis of menthols from citronellal was recently investigated on ruthenium-based catalysts [11]. In this note we report the development of bifunctional metal–acid catalysts that promote selectively the direct conversion of citral to menthols.

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The best catalyst was Ni supported on Al-MCM-41, which yields about 90% menthols from citral and gives 70–75% racemic (±)-menthol in the menthol mixture.

## 2. Experimental

Six catalysts were prepared by supporting metals [Pt(0.3%), Pd(0.7%), Ir(1%), Ni(12%), Co(12%), Cu(12%)] on a $SiO_2$ powder (Grace G62, 99.7%). The silica has a BET surface area ($S_g$) of 230 $m^2/g$ and pore volume of 0.49 $cm^3/g$. $Pt/SiO_2$ catalyst was made by incipient-wetness impregnation at 303 K with an aqueous solution of tetraamine platinum nitrate, $Pt(NH_3)_4(NO_3)_2$ (Alfa). The impregnated silica was dried overnight at 363 K, then heated in $N_2$ to 673 K at 2 K/min, and finally reduced for 2 h at 673 K in pure hydrogen. The other five metal/$SiO_2$ catalysts were prepared following the same preparation procedure of $Pt/SiO_2$. Metal nitrate solutions were used for impregnating Pd, Co, Ni, and Cu, whereas $Ir/SiO_2$ was prepared by using $H_2IrCl_6$ precursor.

Al-MCM-41 ($Si/Al = 10$) was synthesized by the sol–gel method. Sodium silicate solution (14% NaOH and 27% $SiO_2$, Aldrich), cetyltrimethylammonium bromide (Aldrich), aluminum isopropoxide, and deionized water were used as the reagents. The composition of the synthesis gel was $7SiO_2–xAl_2O_3–2.7Na_2O–3.7CTMABr–1000H_2O$. The pH was adjusted to 10 using a 1 M $H_2SO_4$ solution, then the gel was transferred to a Teflon-lined stainless-steel autoclave and heated to 373 K in an oven for 96 h. After crystallization, the solid was washed with deionized water, dried at 373 K, and finally calcined at 773 K for 4 h. Al-MCM-41 has a BET surface area of 690 $m^2/g$, and mean pore diameter of 30 Å. Zeolite Beta (Zeocat PB, $Si/Al = 25$, $S_g = 630\ m^2/g$) was calcined in air at 773 K for 4 h. ZnO(25%)/$SiO_2$ was made by incipient-wetness impregnation at 303 K of Grace G62 $SiO_2$ with an aqueous solution of $ZnCl_2$ (Riedel de Haën, 98.5%). Cs-HPA ($Cs_{0.5}H_{2.5}PW_{12}O_{40}$, $S_g = 130\ m^2/g$) was prepared using $H_3PW_{12}O_{40} \cdot 6H_2O$ (HPA, Merck p.a.) and $CsCO_3$ (Sigma). Cs-HPA was obtained by precipitation, by adding dropwise a solution of $CsCO_3$ to an aqueous solution of HPA. Nickel supported on zeolite Beta (3% Ni/Beta) and nickel supported on Al-MCM-41 (3% Ni/Al-MCM-41) were obtained by incipient-wetness impregnation at 303 K, using $Ni(NO_3)_2$ (Alfa). The impregnated samples were dried overnight at 363 K, then treated in air at 673 K for 6 h and reduced in $H_2$ for 2 h at 723 K.

Acid site densities were determined by temperature programmed desorption (TPD) of $NH_3$ preadsorbed at 373 K. Samples (0.200 g) were treated in He (60 ml/min) at 773 K for 0.5 h and then exposed to a 1% $NH_3$/He stream for 40 min at 373 K. Weakly adsorbed $NH_3$ was removed by flowing He at 373 K during 2 h. Temperature was then increased at 10 K/min, and the $NH_3$ concentration in the effluent was measured by mass spectrometry in a Baltzers Omnistar unit.

The nature of surface acid sites was determined by infrared spectroscopy (IR) using pyridine as probe molecule. Data were obtained using a Shimadzu FTIR-8101M spectrophotometer after admission of pyridine, adsorption at room temperature, and sequential evacuation at 298, 423, 573, and 723 K. Spectra were taken at room temperature. The crystalline structure of the samples was determined by X-ray diffraction (XRD) using a Shimadzu XD-D1 diffractometer. BET surface areas ($S_g$) were measured by $N_2$ physisorption at its boiling point in a Quantochrome Corporation NOVA-1000 sorptometer.

The liquid phase hydrogenation of citral (Aldrich, 98%, isomer mixture of 42% *cis* and 58% *trans*) was studied in a Parr 4843 reactor at 343 and 393 K, using isopropanol or toluene (Cicarelli, p.a.) as solvent. The autoclave was loaded with 150 ml of solvent, 10 ml of citral, and 0.2–1 g of catalyst. Prior to catalytic tests, samples were activated ex situ in flowing hydrogen (30 ml/min) at 473 K for 1 h. The reaction system was heated to the reaction temperature of 2 K/min, and the pressure was then rapidly increased to 506.5 or 1013 kPa with $H_2$. The liquid phase conversion of citronellal (Sigma, 95%) was carried out in the same reactor used for citral hydrogenation. The reactor was loaded with 150 ml of toluene, 2 ml of citronellal, and 0.200 g of catalyst. The reaction was performed at 343 K and 506.5 kPa of nitrogen. Product concentrations were followed during the reaction by ex situ gas chromatography using an Agilent 6850 GC chromatograph equipped with flame ionization detector, temperature programmer, and a 30-m Innowax (Agilent) column coupled with a 30-m Supelco $\alpha$-DEX capillary column. Data were collected every 15–30 min for about 500 min. Selectivities ($S_j$, moles of product $j$/moles of citral reacted) were calculated as $S_j(\%) = C_j \times 100/\sum C_j$, where $C_j$ is the concentration of product $j$. Product yields ($\eta_j$, moles of product $j$/moles of citral fed) were calculated as $\eta_j = S_j X_{\mathrm{Cit}}$.

## 3. Results and discussion

Fig. 1 shows the citral conversion reaction network. The reaction pathway leading from citral to menthols involves three consecutive steps: (i) hydrogenation of citral to citronellal; (ii) isomerization/cyclization of citronellal to isopulegol; (iii) hydrogenation of isopulegol to menthols. Fig. 1 shows that the selective transformation of citral to menthols requires bifunctional catalysts with the ability not only of promoting coupled hydrogenation/isomerization reactions of the citral-to-menthols pathway but also of minimizing the parallel hydrogenation reactions of citral to nerol/geraniol or 3,7-dimethyl-2,3-octenal and of citronellal to citronelol or 3,7-dimethyloctanal. In other words, from a kinetic point of view the selective formation of menthols from citral requires that $k_1 \gg (k_4 + k_5)$ and $k_2 \gg (k_6 + k_7)$ (Fig. 1).

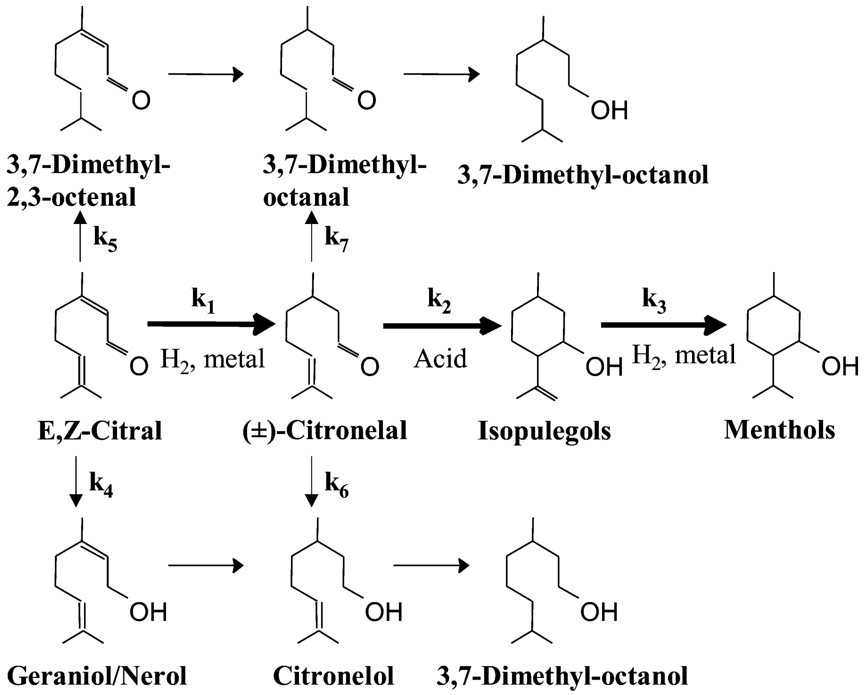

Fig. 1. Reaction network for citral conversion reactions.

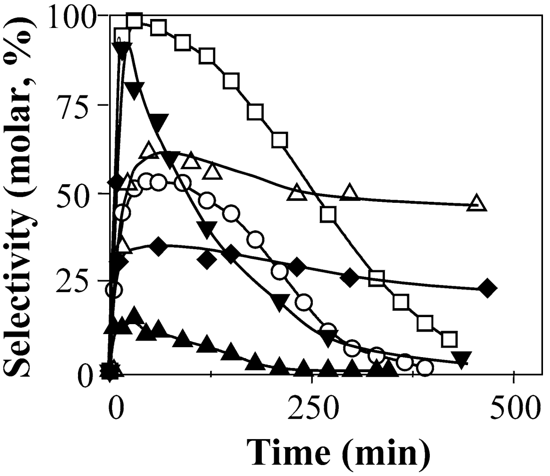

Fig. 2. Hydrogenation of citral: selectivities toward citronellal as a function of time. Ni/$SiO_2$ (□), Pd/$SiO_2$ (▼), Pt/$SiO_2$ (△), Cu/$SiO_2$ (○), Ir/$SiO_2$ (◆), Co/$SiO_2$ (▲) [393 K, 1013 kPa hydrogen, $W = 1$ g, citral:isopropanol = 2:150 (ml)].

We first investigated the initial hydrogenation of citral by comparing the catalytic performance of different silica-supported metals. Samples were tested at 393 K using as solvent isopropanol, a polar compound. Only products formed via citral hydrogenation reactions were observed; isopulegol was never detected, reflecting the absence of surface acid sites on the support. In Fig. 2 we have plotted citronellal selectivity ($S_j$, moles of product $j$/moles of citral reacted) as a function of reaction time. Pd/$SiO_2$ and Ni/$SiO_2$ selectively hydrogenated the conjugated C=C bond of the citral molecule, forming initially citronellal in about 100% selectivity. The citronellal selectivity decreases then with reaction time because citronellal is in turn hydrogenated to citronelol or 3,7-dimethyloctanal. But it should be noted that on Pd and Ni metals, it is verified that $k_1 \gg (k_4 + k_5)$. In contrast, Co/$SiO_2$ and, to a lesser degree, Ir/$SiO_2$ preferentially promoted the initial hydrogenation of citral to nerol/geraniol isomers, and thus citronellal was a minor product. On Co/$SiO_2$ the maximum citronellal selectivity was lower than 20%. Finally, on Cu/$SiO_2$ and Pt/$SiO_2$ the citral conversion rates to citronellal and to geraniol/nerol were similar, and thereby the initial citronellal selectivity was about 50–60% on both catalysts. Overall, our results are consistent with previous works on citral hydrogenation showing that Ni and Pd favor C=C bond hydrogenation [4] while Co and Ir are more selective for C=O hydrogenation [5].

In a second part, we studied the isomerization of citronellal to isopulegols. Cyclization of citronellal has been investigated on different solid acids, but the exact nature of the surface active sites required for efficiently catalyzing the cyclization of citronellal to isopulegols is still debated. While several authors [9] reported that the reaction is readily catalyzed on Lewis acids, others [8] correlated the cyclization activity on acid zeolites with accessible Brønsted acid sites. Chuah et al. [10] found that catalytic materials containing strong Lewis and weak Brønsted acidity show good activity and selectivity for cyclization of citronellal to isopulegol. They proposed then a cyclization mechanism based on the coordination of the citronellal to a strong Lewis site, followed by protonation from a Brønsted acid site. In this work we used two solid acids containing either Lewis

($ZnO/SiO_2$) or Brønsted (Cs-HPA) sites and two catalysts containing weak (Al-MCM-41) and strong (zeolite Beta) Lewis and Brønsted acid sites. In all the cases, isopulegol isomers were the only products detected. We found that the citronellal cyclization rate is clearly lower on $ZnO/SiO_2$ and Cs-HPA samples as compared with both zeolite Beta and Al-MCM-41. The superior activity shown by zeolite Beta and Al-MCM-41 samples are consistent with the assumption that strong Lewis/weak Brønsted dual sites are required to efficiently catalyze the citronellal cyclization. We therefore performed a detailed characterization of the surface acid site nature and strength on zeolite Beta and Al-MCM-41 samples.

The $NH_3$ TPD profiles showed that on Al-MCM-41, $NH_3$ desorbs in a band between 425 and 550 K while on zeolite Beta $NH_3$ desorbs in two broad bands, from 425 to 800 K. The $NH_3$ surface densities for acid sites on both samples were obtained by deconvolution and integration of TPD traces. It was determined that the total adsorbed $NH_3$ surface density on zeolite Beta (0.92 $\mu mol/m^2$) was significantly higher compared with that on Al-MCM-41 (0.20 $\mu mol/m^2$). On the other hand, from the IR spectra of adsorbed pyridine at 373 K we measured the areal densities of Lewis and Brønsted acid sites and found that the Lewis/Brønsted site ratios were about 1 and 2.5 on zeolite Beta and Al-MCM-41, respectively. The Brønsted and Lewis site densities per square meter on zeolite Beta were about seven and two times higher, respectively, than on Al-MCM-41. In summary, sample acidity characterization revealed that zeolite Beta contains a higher density of stronger acid sites compared with Al-MCM-41.

Based on the above results, we prepared three bifunctional catalysts containing one of the metals most selective for hydrogenating citral to citronellal (Pd or Ni) and one of the solid acids more active for converting citronellal to isopulegols (zeolite Beta or Al-MCM-41). Specifically, we prepared Pd (1%) supported on zeolite Beta (Pd/Beta) and Ni (3%) supported on zeolite Beta (Ni/Beta) and on Al-MCM-41 (Ni/Al-MCM-41). These bifunctional catalysts were tested for the conversion of citral to menthols at 343 K and $P_{H_2} = 506.5$ kPa, using 1 g of sample and toluene as solvent. Catalytic results are given in Table 1. In all the cases, citral and citronellal were totally converted after 5 h of reaction. Pd/Beta produced a considerable amount of 3,7-dimethyl-octanal, thereby showing that Pd is significantly active for hydrogenating the C=C bond of citronellal. Thus, it seems that the second requirement for selectively obtaining menthols from citral [i.e., $k_2 \gg (k_6 + k_7)$] (Fig. 1) is not fulfilled using Pd as the metal component of the bifunctional catalyst because of the high value of rate constant $k_7$ on Pd. As shown in Table 1, the yield of menthols was only about 20% on Pd/Beta catalyst. Ni/Beta was clearly more selective to menthols than Pd/Beta, essentially because formation of 3,7-dimethyl-octanal was negligible on Ni/Beta. Actually, none of the by-products formed from hydrogenation of citral or citronellal (Fig. 1) were detected using Ni/Beta, suggesting that this bifunctional catalyst satisfactorily combines the hydrogenation and isomerization functions needed to selectively promote the reaction pathway leading from citral to menthols. However, formation of secondary compounds formed probably via decarbonylation and cracking reactions on the strong acid sites of zeolite Beta was significant, and the by-product yield on Ni/Beta was about 20%. The best catalyst was Ni/Al-MCM-41, which yielded ca. 90% menthols. The observed menthol yield improvement on Ni/Al-MCM-41 is probably explained by considering that the moderate acid sites of Al-MCM-41 do not promote the formation of by-products via side cracking reactions. In contrast, Al-MCM-41 rapidly isomerizes citronellal to isopulegols, and menthols are then formed at high rates. Regarding the distribution of menthol isomers, it is noted that (±)-neo-isomenthol was never detected in the products. On Ni-based catalysts, the menthol mixture was composed of 70–75% (±)-menthols, 15–20% (±)-neo-menthol, and 5–10% (±)-isomenthol. On Pd/Beta the racemic (±)-menthol mixture represented only about 50% of total menthols.

The evolution of product yields and citral conversion as a function of time on Ni/Al-MCM-41 (not shown here) indicated that citral was totally converted to citronellal on metallic Ni crystallites in about 80 min, but the concentration of citronellal remained very low (maximum citronellal yield was about 10% at 25 min) because it was readily converted to isopulegols on acid sites of mesoporous Al-MCM-41 support. Isopulegols were then totally hydrogenated to menthols on metal Ni surface sites.

In summary, Ni(3%)/Al-MCM-41 yields 90% menthols directly from citral and produces 70–75% racemic (±)-menthol in the menthol mixture. Further improvement in catalytic performance is certainly expected by optimizing both the catalyst formulation (Ni loading, Si/Al ratio) and the reactor operation (hydrogen pressure).

Table 1
Product yields and menthol isomer distribution[a]

| Catalyst | Yield (%)[b] | | | | Menthol isomer distribution (%)[b] | | |
|---|---|---|---|---|---|---|---|
| | Menthols | 3,7-DMAL | Isopulegols | Others | (±)-Menthols | (±)-Neomenthol | (±)-Isomenthol |
| Pd/Beta | 22.0 | 25.8 | 18.5 | 33.7 | 47.2 | 15.6 | 37.2 |
| Ni(3%)/Beta | 81.0 | 0 | 0 | 19.0 | 72.0 | 21.3 | 6.7 |
| Ni(3%)/Al-MCM-41 | 89.2 | 0 | 0 | 10.8 | 72.3 | 20.2 | 7.5 |

[a] $T = 343$ K, $P_{H_2} = 506.5$ kPa, $W = 1$ g, citral:toluene = 2:150 (ml).

[b] Values determined at 300 min reaction; $X_{cit} = 100\%$ on all catalysts.

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