Tuning Selectivity in Terpene Chemistry: Selective Hydrogenation *versus* Cascade Reactions over Copper Catalysts

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Abstract: The selectivity of Cu/Al_2O_3 under very mild catalytic hydrogenation conditions can be tuned only by switching the solvent. Geraniol can be converted in a one-pot one-step process into a mixture of citronellol and menthol in hydrocarbon solvents or reduced to citronellol with 98% selectivity in 2-propanol without any additive. Both reactions can be applied to essential oils or synthetic mixtures containing geraniol, citronellal and nerol.

Keywords: copper catalysts; essential oils; geraniol; menthol; selective hydrogenation; trifunctional catalysis

Introduction

Terpenes are very cheap precursors to fragrances, flavours, drugs and agrochemicals but their high reactivity often makes it difficult to achieve a selective transformation.[1] However, the target is worth pursuing as almost all their derivatives can be useful. We have long been involved in catalytic transformations of terpenes and terpenoids[2] studying acid-catalyzed rearrangements of terpenic epoxides over different amorphous silica-aluminas, hydrogenation reactions over supported copper catalysts, selective epoxidation of terpenic alcohols over titanium silicates. In particular, we have successfully set up several bifunctional processes by exploiting acidic and hydrogenation sites[3] or acidic and epoxidation sites[4] present on the catalyst surface.

Following our continued interest in catalytic transformations of renewable starting materials we began to study the behaviour of the terpenic allylic alcohol geraniol over copper systems under catalytic hydrogenation conditions.

The selective catalytic homogeneous hydrogenation of geraniol (**1**) to citronellol (**2**) has been widely investigated, focussing in particular on chiral catalysts. Rh- and Ru-based catalysts have been predominately utilized, Noyori's BINAP ligand being the most frequently used.[5] As far as heterogeneous catalysts are concerned, the earliest literature for the preparation of citronellol from geraniol reported the use of Pt black or Pt oxide and Ni,[6] while more recent papers report on the use of more complex catalytic systems such as platinum-containing zeolite,[7] Pt/Al_2O_3 modified with carboxylic acids,[8] Ni/diatomaceous earth and alkali hydroxides or carbonates[9] or Raney Ni and alkali or alkaline earth metal hydroxides.[10] In these studies yields never exceeded 85%. Thus, this reaction is complicated not only by undesired saturation of the isolated C=C bond, but also by hydrogenolysis and other reactions taking place on the catalyst surface.

Here we report that Cu/Al_2O_3 catalysts allow both the specific reduction of geraniol to citronellol and its one-step transformation into valuable mixtures of citronellol and menthol. The selectivity towards one reaction or the other can be switched simply by changing the solvent. Results obtained with citronellal under the same experimental conditions are also reported for the sake of comparison.

Results and Discussion

Multifunctional Processes

During our studies on catalytic hydrogenation over Cu/SiO_2 we found that hydrocarbon solvents are best suited to enhance the reaction rate; however, they also favour acid-catalyzed reactions. When the hydrogenation of geraniol (**1**) was carried out over Cu/SiO_2 these side-reactions could not be controlled and very complex mixtures were obtained including dehydration, cyclisation and rearrangement products. On the contrary by using a Cu/Al_2O_3 catalyst the reaction could be addressed to-

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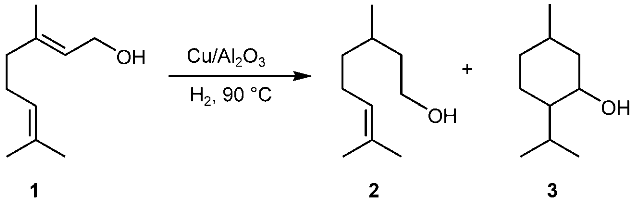
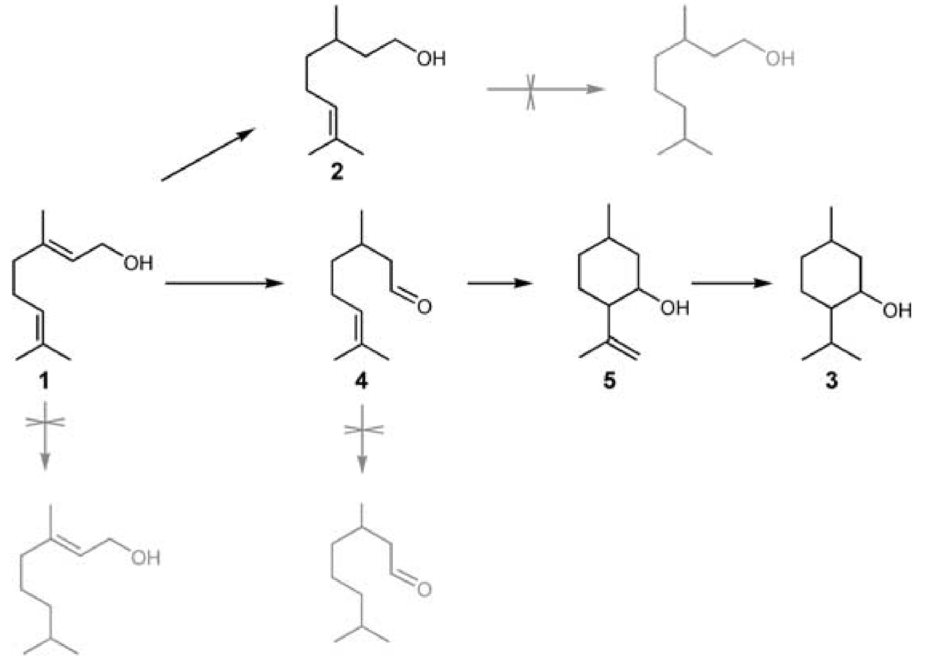


Scheme 1.

ward the formation of two main products, citronellol (**2**) and menthol (**3**) (Scheme 1).

Citronellol (**2**) is formed through selective hydrogenation of the C=C bond activated by the presence of the OH group, whereas menthol (**3**) is likely the product of a *three-functional* process involving isomerisation of the allylic alcohol **1** to citronellal (**4**), acid-catalyzed *ene* reaction to isopulegol (**5**) and final hydrogenation to menthol (**3**) (Scheme 2). The direct transformation of citronellal (**4**) into menthol (**3**) has already been studied over Cu/SiO_2,[3a] Ru-based catalysts[11] and Ir-beta-zeolite[12] and recently also the synthesis of menthols from citral over Ni-Al-MCM-41 has been reported.[13] To the best of our knowledge this is the first report of a process starting from geraniol (**1**).

The results are summed up in Table 1. When the reaction is carried out over the 8% catalyst citronellol (**2**) and isopulegol (**5**) are soon formed and in 2 hours also the hydrogenation of isopulegol (**5**) to menthol (**3**) is complete, thus giving a 56% yield in citronellol (**2**) and about 30% in menthol (**3**). The geometric isomer of geraniol (**1**), nerol (entry 2), reacts in a very similar way. It should be underlined that none of the products deriving from the hydrogenation of the C6/C7 double bond could be detected in the reaction mixtures, the only by-products, almost exclusively 3,7-dimethyl-1,6-octadiene, coming from dehydration of citronellol (**2**).



Scheme 2.

Table 1. Polyfunctional transformation of geraniol, nerol and citronellal over different catalysts under hydrogenation conditions.

Entry	Substrate	Experimental Conditions	*t* [h]	**2** [% mol]	**5** [% mol]	**3** [% mol]	Stereoselectivity[a] [%]	Others[b] [%]
1	geraniol	8% Cu/Al_2O_3, H_2	2	56	3	30	81	11
2	nerol	8% Cu/Al_2O_3, H_2	4	58	4	23	81	15
3	geraniol	5% Cu/Al_2O_3, H_2	7	46	1	41	80	12
4	geraniol	8% Cu/Al_2O_3, N_2	5	21	59	–	73	2
5	geraniol	Al_2O_3, H_2	24	–	–	–	–	15
6	citronellal	8% Cu/Al_2O_3, H_2	8	27	7	66	75	–
7	citronellal	Al_2O_3, H_2	1	–	95	–	71	–

[a] Amount of (±)-menthol.

[b] Amount of dehydration products (mainly 3,7-dimethyl-1,6-octadiene).

In order to increase the yield in menthol (**3**), we carried out the reaction over a catalyst with a lower Cu loading (5%) to reduce its hydrogenation activity. In this case the reaction is much slower, the intermediate formation of citronellal (**4**) can be observed (Figure 1) and an almost equimolar mixture of citronellol (**2**) and menthol (**3**), very easy to separate the one from the other, can be obtained at the end of the transformation.

A similar switching effect between the hydrogenation activity and the acidic features of the catalyst was reported for the reduction of citronellal (**4**) with 2-propanol over alkali metal-exchanged X-zeolite. This reaction gave mainly citronellol (**2**) or mainly isopulegol (**5**) depending on the compensating cation used[14] the bulkier ones favouring the hydrogen transfer reaction. The effect of Cu content on product distribution is reported in Figure 2.

In order to verify if citronellol (**2**) is produced through hydrogenation of geraniol (**1**) or citronellal (**4**) we carried out the reaction starting from **4** (entry 6). This gave the same products but the mixture was richer in menthol (**3**) thus showing that citronellol (**2**) is produced from both geraniol (**1**) and its isomerization product citronellal (**4**).

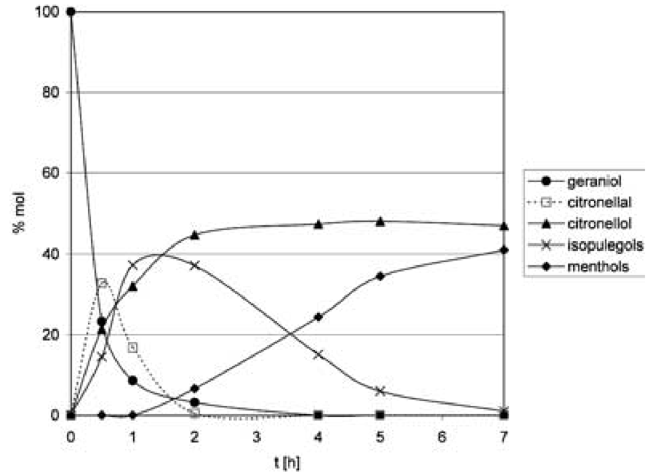


Figure 1. Hydrogenation of geraniol over 5% Cu/Al_2O_3 in *n*-heptane.

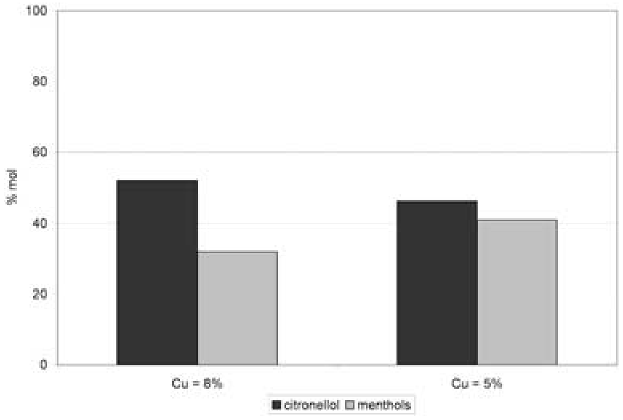


Figure 2. Effect of Cu loading on the product distribution.

The selective one-pot transformation of citronellal (**4**) into menthol (**3**) over Cu/Al_2O_3 is not possible under these conditions as the hydrogenation and cyclisation rates are comparable. On the contrary the acid-catalyzed *ene* reaction is much faster than the hydrogenation of citronellal (**4**) over Cu/SiO_2,[3a] thus allowing very fast and complete conversion of **4** into isopulegol (**5**) before the hydrogenation reaction begins and giving menthol (**3**) with a 90% chemical yield [based on starting citronellal (**4**)]. It is worth noting that also in the present case a small but definite improvement in stereoselectivity towards the all-equatorial isomer was observed when the reaction was carried out under H_2 (entry 1 *vs.* 4).

The chance of obtaining selectively isopulegol (**5**) from geraniol (**1**) by working in the absence of H_2 was also tested, but this reaction is not quantitative as it gives also citronellol (**2**) (entry 4).

This can be due to dehydrogenation of geraniol (**1**) to citral making some amount of hydrogen available. Thus, this same catalyst is able to dehydrogenate secondary and allylic alcohols under the experimental conditions used.[15] When a hydrogen acceptor is present the reaction of secondary alcohols can reach complete conversion and total selectivity, whereas in the particular case of geraniol (**1**) competition with other reactions does not allow the selective oxidation.

From Figure 3 it is apparent that citral produced through the dehydrogenation reaction is not reduced under these conditions, therefore citronellal (**4**) does not form in this way. On the contrary, all the hydrogen formed is used to produce citronellol (**2**). The presence of citronellal (**4**) and of its cyclization product isopulegol (**5**) thus shows the existence of a direct isomerization of the allylic alcohol to the aldehyde. The isomerization of

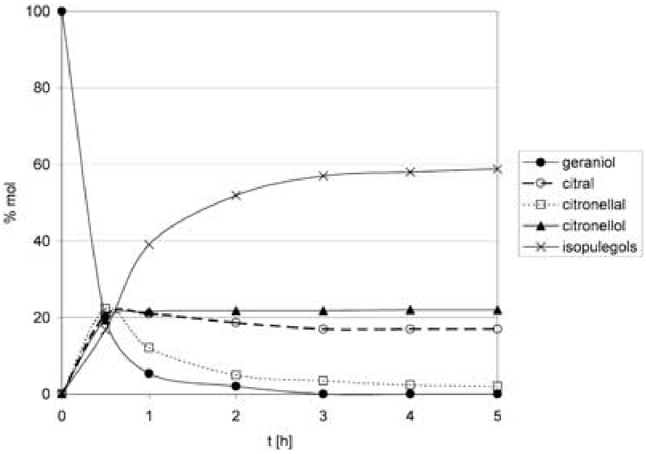


Figure 3. Reaction of geraniol over 8% Cu/Al_2O_3 under an inert atmosphere.

allylic alcohols into carbonyl compounds is catalyzed by a variety of transition metal complexes.[16] However, the case of geraniol (**1**) represents a challenging one. Although the isomerisation of geraniol to γ-geraniol under catalytic hydrogenation conditions in the presence of a Ru chiral complex has been reported[5b] achiral Ru phosphine complexes failed to isomerise geraniol (**1**) to citronellal (**4**).[17] Good yields in this particular isomerisation could be obtained only with tetrapropylammonium perruthenate and 2-undecanol.[18]

In our case, experiments carried out under H_2 over the bare support, activated as the metal catalyst, show that in fact Al_2O_3 is an effective promoter of the *ene*-reaction converting quantitatively citronellal (**4**) into isopulegol (**5**) as already reported,[19] whereas no reaction could be observed starting from geraniol (**1**) apart from some dehydration.

This unambiguously shows that the isomerisation of geraniol (**1**) to citronellal (**4**) is to be ascribed to the presence of reduced copper on the catalyst. Therefore at least two steps in the multifunctional process leading from geraniol to menthol depend on the presence of the metal.

Selective Hydrogenations

Solvents are very effective tools to tune the selectivity of copper catalysts in hydrogenation reactions. Thus, we already reported that unsaturated ketones prone to undergo secondary reactions under catalytic hydrogenation conditions can be selectively reduced to unsaturated alcohols by using a solvent that poisons the catalyst acidic sites.[20] Data reported in Table 2 show how the yield in citronellol (**2**) can be increased only by tuning the solvent basicity.

As already mentioned, the use of hydrocarbon solvents allows the acidic properties of the catalyst to show. Therefore, even though the reaction is fast, yields in citronellol (**2**) are quite low in these solvents (entries 1 and 2).

By using oxygenated solvents both menthol (**3**) and dehydration products formation are suppressed and the yield in citronellol (**2**) increases. In particular by using 2-propanol as solvent a quantitative yield can be achieved starting from both geraniol (**1**) and nerol. In this way also citronellal (**4**) can be selectively reduced, as all acid-catalyzed reactions are inhibited. Such high selectivities are unprecedented over heterogeneous catalysts. As already mentioned, yields in citronellol (**2**) during the hydrogenation of geraniol (**1**) in the heterogeneous phase never exceed 85% even when alkali is added to suppress hydrogenolysis.[6–10]

Table 2. [a] Solvent effect in the hydrogenation of geraniol and citronellal over 8% Cu/Al_2O_3.

Entry	Substrate	Solvent	t [h]	2 [% mol]
1	geraniol	*n*-heptane	2	56
2	geraniol	toluene	5	61
3	geraniol	dioxane	6	79
4	geraniol	2-propanol	12	>98
5	nerol	2-propanol	12	>98
5	citronellal	2-propanol	0.75	100
6	citronellal[b]	2-propanol	1	96

[a] Complete conversion.

[b] Catalyst activated at 180 °C.

As far as the hydrogenation of citronellal (**4**) is concerned, recently a 91% yield in citronellol (**2**) has been reported over an Ru/Fe/C catalyst when working in methanol/trimethylamine solution.[21] Cu/Al_2O_3 in 2-propanol represents a very simple and clean alternative to these systems as it works under very mild conditions and does not require the presence of any additive. Although under the experimental conditions here reported only 1 g of product per g of catalyst can be obtained in a single run, a productivity of 8.7 $mmols_{product}/g_{catalyst}/h$ can be computed for the hydrogenation of citronellal (**4**). Although reduction of the catalyst loading results in a slower reaction, the catalyst can be effectively recycled without significant losses in activity or in selectivity, as already reported for the dehydrogenation reaction[15] and for hydrogenation ones on Cu/SiO_2.[22]

It should be underlined that under these conditions the hydrogenation of citronellal (**4**) is very much faster than that of geraniol (**1**). Moreover, no citronellal formation could be observed during the hydrogenation of geraniol (**1**) in the oxygenated solvent. This suggests that the isomerisation of geraniol (**1**) to citronellal (**4**) requires the presence of both Cu, as shown in the previous subheading, and acidic sites. Also the isomerisation of allylic alcohols catalyzed by nickel in the homogeneous phase requires the presence of protic acids[23] and in the case of geraniol (**1**) gives mixture of citronellal (**4**) and isopulegol (**5**). This feature represents the peculiarity of our catalytic system. Thus, all the one-pot transformations of citronellal (**4**) into menthols (**3**) reported up to now[3a,11,12] rely on the presence of two functions on the catalyst surface, one active in the cyclisation step and the other in the hydrogenation one. The proper choice of the metal and of the support should then always result in a bifunctional system effective for this reaction.

We herein describe a unique, single-pot transformation of geraniol (**1**) into menthol (**3**) by a trifunctional catalyst. The diverse multifunctional activities are characteristic features of a synergic action between the metal centres and the support's active site.

The two reactions reported here can be also applied to complex mixtures of terpenes such as essential oils. There has recently been an increasing search for new catalytic processes for fine chemical production based on renewable resources[24] but up to now papers dealing with the transformation of essential oils are very rare.[25] Moreover, recently a selective hydrogenation process

Table 3. Hydrogenation of essential oils at 90 °C and 1 atm H_2 under different conditions.

	Experimental Conditions	*t* [h]	**1** [% mol]	**4** [% mol]	**2** [% mol]	**3** [% mol]
Citronella oil		0	18	52	12	
	8% Cu/Al_2O_3, 2-PrOH	1	16	2	64	
		16			80	
	5% Cu/Al_2O_3, *n*-heptane	11			37	32
Palmarosa oil		0	81			
	8% Cu/Al_2O_3, 2-PrOH	20			75	
	5% Cu/Al_2O_3, *n*-heptane	13			38	31

has been proposed to increase the value of distillation residues from terpene syntheses.[26] Reactions promoted by Cu/Al_2O_3 allow one to convert complex mixtures of products that are very difficult to separate into two valuable products with very different physical properties or to selectively reduce them to a single product.

Table 3 sums up the results obtained by using the readily available *Citronella oil* containing citronellal (**4**) and geraniol (**1**) and *Palmarosa oil* containing mainly geraniol (**1**) as starting materials. Both oils gave very similar mixtures of citronellol (**2**) and menthol (**3**) when hydrogenated in *n*-heptane and good yields in citronellol (**2**) when hydrogenated in 2-propanol, showing once more that over this catalyst geraniol (**1**) and citronellal (**4**) behave very similarly. In particular, the hydrogenation of *Citronella oil* (Figure 4) represents more evidence that in the presence of 2-propanol the reactions of citronellal and geraniol are completely independent from each other.

The results reported in this paper show once more the high versatility of these materials. Thus, copper catalysts prepared with this technique exhibited remarkable performances in different kind of transformations, varying from hydrogenation to acid-catalysed reactions under anaerobic oxidation, always showing excellent selectivity and good productivity – the basic features for the application of heterogeneous catalysts to fine chemicals synthesis. In particular, the use of Cu/Al_2O_3 under transfer dehydrogenation conditions shows that this simple system constitutes a rare example of selective oxidation of secondary alcohols in the presence of primary ones.[15] The catalyst works under very mild conditions and not only on pure substrates but also on natural mixtures such as vegetable[27] and essential oils. Moreover the catalyst preparation is not onerous or expensive and the material obtained is not pyrophoric or pyrogenic even in the reduced form. Therefore, in all these reactions these catalysts allow the setting-up of a simple, safe and clean protocol.

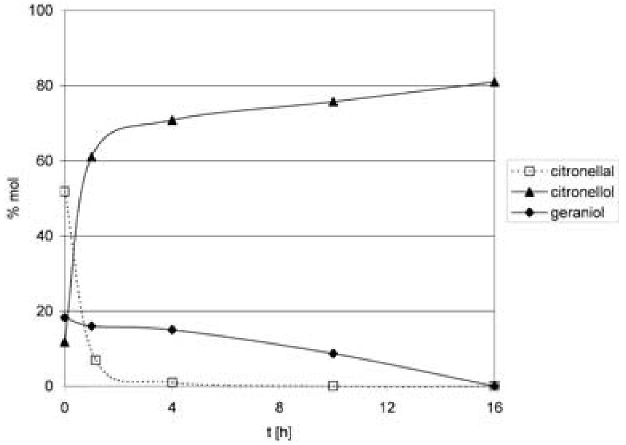


Figure 4. Hydrogenation of *Citronella oil* over 8% Cu/Al_2O_3.

Conclusion

Cu/Al_2O_3 is an effective catalyst for the transformation of geraniol, nerol and citronellal or mixtures of them into mixtures of two valuable products, citronellol and menthol. Moreover, merely by changing the solvent, it allows the specific hydrogenation of geraniol, nerol and citronellal to citronellol. This would allow one to obtain these two products from one or the other starting material, or from a mixture of them, both from synthetic or from renewable sources, depending on their availability.

Experimental Section

General Remarks

Al_2O_3 (BET = 300 m^2/g, PV = 1,0 mL/g) was kindly supplied by GRACE Davison (Worms, Germany). Geraniol (98%), nerol (97%) and *Citronella oil* (Java 85/35%) were purchased from Aldrich; citronellal (>80–90%) and *Palmarosa oil* were from Fluka.

Catalysts used, with metal loadings of 5% and 8% were prepared as already reported[28] with a non-conventional chemisorption-hydrolysis technique starting from a $[Cu(NH_3)_4]^{2+}$ aqueous solution.

Before reaction, catalysts (100 mg) were treated for 20 min in air at 270 °C, for 20 min under reduced pressure and thereafter reduced at the same temperature in H_2. The substrates (100 mg) were dissolved in *n*-heptane (8 mL) and the solution transferred under N_2 into the reaction vessel containing the pretreated catalyst. Catalytic tests were carried out at 90 °C with magnetic stirring. After the reaction, the catalyst was separated by filtration, washed with acetone, dried and reactivated by hydrogenation before recycling.

Reaction mixtures were analysed by GC (non-bonded biscyanopropyl-polysiloxane capillary column, 100 m) and GC-MS (HP-5MS cross-linked 5% phenyl methyl silicone, 30 m) analysis and by ^{1}H NMR (Bruker, 300 MHz) spectroscopy. Stereoselectivity given in Table 1, expressed as % (±)-menthol/% all (±) stereoisomers, was evaluated through both GC and ^{1}H NMR analysis.

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