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Intramolecular Hydrogen Transfer Reaction: Menthon from Isopulegol

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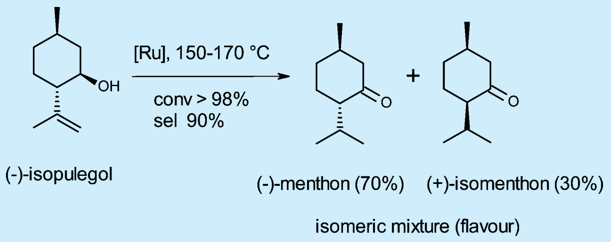
Supporting Information

ABSTRACT: The flavor menthon (isomeric mixture of (−)-menthon and (+)-isomenthon) was obtained in good yields and selectivities by a solventless ruthenium catalyzed isomerization of the homoallylic alcohol (−)-isopulegol. In contrast to most previous assumptions on such "isomerization" reactions, this reaction follows an intermolecular pathway, with menthol and pulegon being the central intermediates in this transformation.

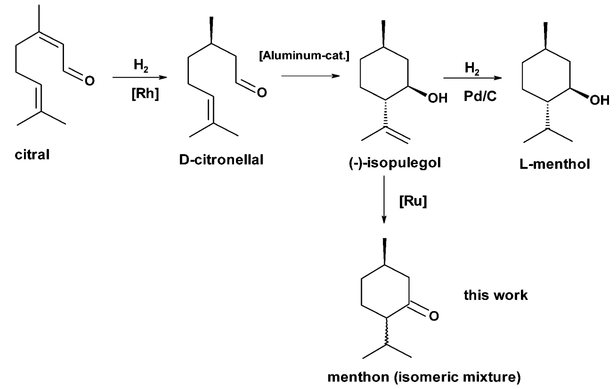


Menthon is a mint-like flavor and is currently available on the market as a mixture of isomers (70% (−)-menthon, 30% (+)-isomenthon). The main industrial production is based on distillation of *dementholized cornmint oil*, a side stream originating from the production of menthol from *Menthe arvensis*.[1] Hence, the supply and the quality of the natural menthon are dependent on menthol production capacities as well as on seasonal influences on crop yields. A merely synthetical production of menthon would be able to overcome these difficulties. From a retrosynthetical analysis, it is very obvious that either oxidation of the natural product (L)-menthol or hydrogenation of the aromatic precursor thymol is the most straightforward route to menthon. Nonetheless, these approaches impose several disadvantages. The oxidation suffers from the use of the valuable menthol and additional oxidizers. On the other hand, the hydrogenation of thymol with Pd/C as the catalyst leads to an unfavorable mixture of all isomers (mixture of *rac*-menthon and *rac*-isomenthon).[2] Therefore, isomerization of the homoallylic alcohol (−)-isopulegol would offer the most atom-efficient approach to menthon.[4] This isomerization is also of industrial attractivity as (−)-isopulegol is the central intermediate of the new BASF process for the production of (L)-menthol (see Scheme 1) and therefore available on a technical scale.[5] Surprisingly, only very little literature data are available on this reaction. To the best of our knowledge, the only reported method for the synthesis of menthon from isopulegol is a gas-phase reaction using a heterogeneous copper catalyst. Nonetheless, this procedure suffers from low selectivities due to the harsh reaction conditions required and more than 35% of the undesired side product thymol is formed.[4] Hence, a mild and efficient homogeneously catalyzed approach is highly attractive.

Different ruthenium complexes are known to be suitable homogeneous catalysts for the transfer hydrogenation of alkenes with alcohols as the hydrogenation source, whereby most of these reactions are intermolecular.[6]

In the case of formal intramolecular transfer hydrogenations, the transition metal catalyzed isomerization of allylic alcohols is well-known with iron and ruthenium complexes.[7] It is assumed that this redox isomerization follows an intramolecular rearrangement pathway via a 1,3-hydrogen transfer.[8] In the case of the iron catalyzed isomerization of higher unsaturated alcohols such as 9-decen-1-ol, first a double bond isomerization cascade is suggested, before the resulting enol tautomerizes to the aldehyde.[9,10] For the isomerization of homoallylic alcohols to ketones very little is known,[4,9a,10] and all reports refer to an intramolecular isomerization mechanism. We achieved the isomerization of the homoallylic alcohol (−)-isopulegol to menthon in more than 90% yield, using a simple ruthenium catalyst at temperatures of 130 to 170 °C (Table 1).

Scheme 1. New BASF Process for for the Production of Menthol from Citral



Only nonchiral phosphine ligands were used, as the natural flavor menthon consists of an equilibrium isomeric mixture of about 70% (−)-menthon and 30% (+)-isomenthon which reequilibrates rapidly at room temperature. The absolute configuration on the 5-position was retained, as demonstrated by GC and the flavor properties.

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Table 1. Isomerization of Isopulegol to Menthon Using Different Ruthenium Catalysts[a]

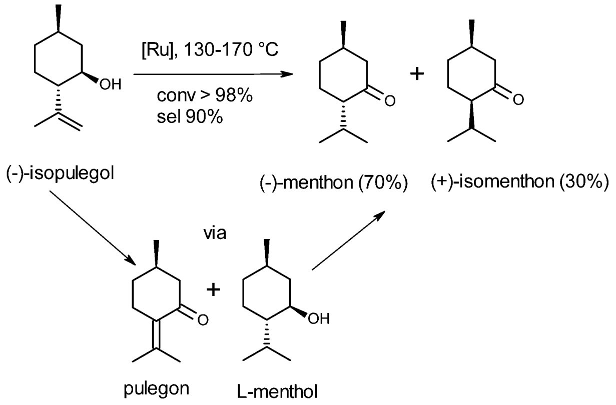
catalyst [mol %]	isopulegol [%]	temp [°C]	conversion [%]	yield menthon [%]
[Ru(P*n*Oct$_3$)$_4$(H)$_2$] (1)[b]	15	133	58.8	47.3
[Ru(P*n*Bu$_3$)$_4$(H)$_2$]/ dcpe (1)[b]	15	133	62.9	42.1
[Ru(PEt$_3$)$_4$(H)$_2$] (1)[b]	15	133	64.6	45.0
[Ru(P*n*Oct$_3$)$_4$(H)$_2$] (1)[c]	15	130	64.5	46.3
[Ru(P*n*Oct$_3$)$_4$(H)$_2$] (1)[c]	15	150	98.6	47.9
[Ru(P*n*Oct$_3$)$_4$(H)$_2$] (0.5)[d]	30	170	98.2	89.6

[a] All reactions carried out under argon using xylene as solvent with a reaction time of 20 h. Yields and selectivity were determined by GC. [b] Reaction under reflux in an open system using 10 mL of *o*-xylene and 1.8 g of isopulegol. [c] Reaction in a glass Autoclave under inherent pressure using 20 mL of *o*-xylene and 3.6 g of isopulegol. [d] Reaction in a glass Autoclave under inherent pressure using 20 mL of *o*-xylene and 8.6 g of isopulegol. dcpe = 1,2-bis(dicyclohexyl-phosphino)ethane was purchased by Sigma-Aldrich, and [Ru(PR$_3$)$_4$(H)$_2$]-complexes were prepared according to the literature.[11]

The experimental data also revealed some insights into the suggested reaction mechanism. At temperatures below 150 °C, the reaction was obviously too slow to go directly into complete conversion, giving ~50% selectivity of the desired product along with ~30% of L-menthol and pulegon in an approximately 1:1 ratio.

Consequently, these two compounds are formed in an intermolecular transfer hydrogenation, whereby one molecule of isopulegol acts as a hydrogen donor and another as a hydrogen acceptor, resulting in menthol and pulegon (Scheme 2). The pulegon is formed under these conditions instead of isopulegon due to the higher stability of the conjugated unsaturated carbonyl compound. If the reaction is carried out without an additional solvent and followed by GC, the amount of these two compounds rises at the beginning and then drops slowly whereas the amount of the desired menthon rises. This implies that menthol and pulegon are the intermediates in this reaction, which results in the formation of 2 equiv of the target molecule after a second transfer hydrogenation.

Scheme 2. Intermolecular Transfer Hydrogenation with Isopulegon and L-Menthol As Intermediates



This was proved independently by the reaction of pulegon with menthol using the [Ru(P*n*Oct$_3$)$_4$(H)$_2$] catalyst under the same conditions as in the isomerization of isopulegol. Within these experiments, menthon is formed from pulegon and menthol under solventless conditions.[12]

If the temperature is raised from 170 to 180 °C, the reaction is significantly faster with 90% conversion after 4 h compared to 20 h at the lower temperature (Figures 1 and 2). The selectivity to menthon at 180 °C is as high as that at 170 °C (90%), and the maximum of the two intermediates is reached after 2 h at 180 °C. The molar ratio of pulegon to menthol is approximately 1:1 over the observed period of time.

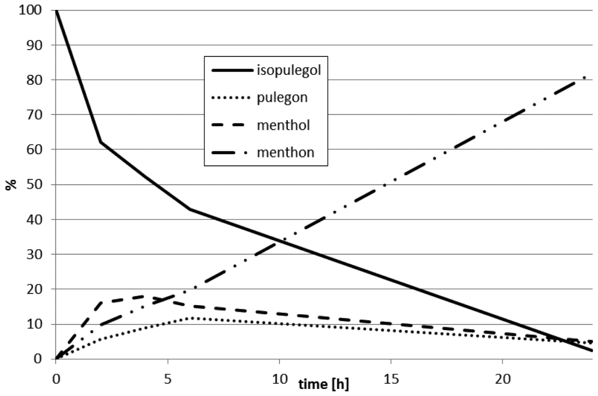


Figure 1. Isomerization of isopulegol at 170 °C. Conditions: 21 g of isopulegol, 0.3 mol % [Ru(P*n*Oct$_3$)$_4$(H)$_2$], no solvent, reaction in a glass reactor under inherent pressure at 170 °C.

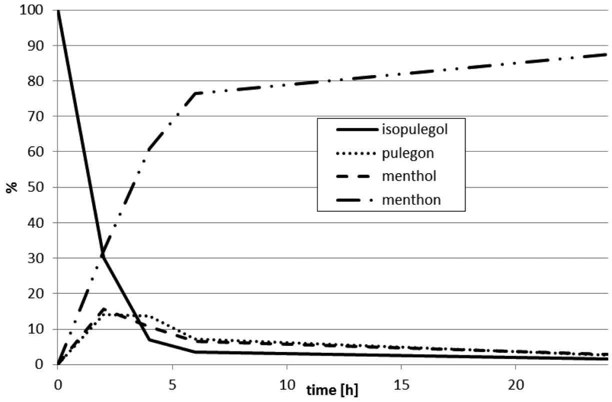


Figure 2. Isomerization of isopulegol at 180 °C. Conditions: 21 g of isopulegol, 0.3 mol % [Ru(P*n*Oct$_3$)$_4$(H)$_2$], no solvent, reaction in a glass reactor under inherent pressure at 180 °C.

A similar observation was made in the isomerization of the allylic alcohol geraniol in a current work by Wu et al. When using a ruthenium catalyst, apart from the isomerization product citronellal, also the products from an intermolecular hydrogen transfer, citronellol and citral, could be detected as byproducts.[13] In this work, they were not assumed as intermediates of the isomerization.

Based on our observations, we cannot exclude that parts of the isomerization are following an intramolecular mechanism, but most of the product is formed by an intermolecular transfer hydrogenation cascade.

The reaction can be carried out without any additional solvent in pure isolpulegol just by simple addition of the catalyst and heating in a glass reactor under a moderate pressure of 2–3 bar (Table 2). Due to the high conversion, excellent product concentrations in the reaction mixture can be

Table 2. Solventless Synthesis of Menthon and Catalyst Recycling[a]

run	isopulegol [g]	conversion [%]	menthon [%]	menthol [%]	isopulgeon [%]
1	44.0	92.6	86.5	4.9	8.0
2	17.4	95.1	74.3	5.7	14.4

[a]All reactions carried out under argon. Reaction in a 50 mL glass reactor in pure isopulegol (2 × 22 g) for 64 h at 170 °C. After distilling of the product, fresh isopulegol was added to the catalyst containing sump (~13 g containing 71.3% menthon, 2.7% isopulegol, 5.1% menthol, and 12.6% isopulegol) and the reaction was repeated for 72 h. Catalyst: 0.2 mol % $[Ru(PnOct_3)_4(H)_2]$.

achieved, resulting in a simple workup by distillation to obtain the highly valuable menthon as the isomeric mixture, which has the same properties as the flavor obtained from natural sources. The active ruthenium catalyst remains in the sump of the distillation and can simply be reused without any significant loss in selectivity by adding fresh isopulegol and running the reaction again.

In summary, we reported a new, simple, and highly atom-efficient protocol for the synthesis of the flavor menthon using the now readily available isopulegol. The isomeric mixture obtained has identical properties to the product isolated from natural sources. In contrast to most other reports on the isomerization of unsaturated alcohols to the corresponding carbonyl compound, this reaction follows an intermolecular pathway with a transfer hydrogenation cascade.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for the catalyst synthesis and the preparation of menthon according to this method are given. This material is available free of charge via the Internet at http://pubs.acs.org. Parts of these results were also disclosed in the patent applications WO 2014037264 and US 20140073817 from the same authors.[14]

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Notes

The authors declare no competing financial interest.

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(12) Experimental details: 8.0 g (50 mmol) of pulegon, 8.0 g (50 mmol) of menthol, and 0.36 g (0.16 mmol) of $[Ru(PnOct_3)_4(H)_2]$ were added to a 50 mL glass reactor under inert conditions and stirred for 15 h in the closed system. After the reaction, the mixture contains 78.0% menthon (35.4% (+)-menthon and 64.6%(−)-isomenthon), 9.2% pulegon, and 6.5% menthol as determined by GC.

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