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SHORT COMMUNICATIONS

Cyclization of Citronellal in a Supercritical Solvent in a Flow Reactor in the Presence of Al_2O_3

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Abstract—The reactivity of citronellal under supercritical solvent conditions in a flow reactor in the presence of Al_2O_3 is examined. It is shown that at 160°C, the main transformation product of citronellal is isopulegol, and when the temperature is increased to 190°C, they are monoterpenes with a *para*-menthane framework and myrcene.

Keywords: citronellal, isopulegol, cyclization, supercritical solvent, alumina.

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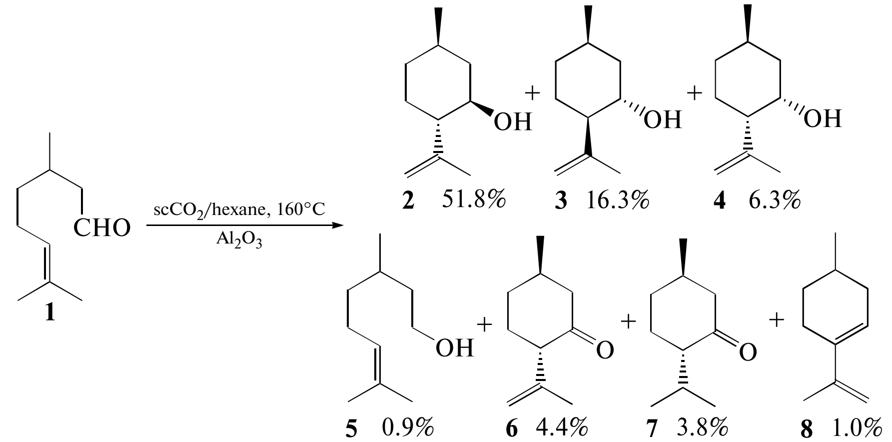
The use of flow reactors for the reactions in fine organic synthesis has a number of indisputable advantages over traditional periodic processes [1–4]. The first of these is accurate control of the contact time, rapid and reproducible alteration of parameters such as temperature and pressure, effective mixing of reagents, easy scaling, and so on. The application of supercritical solvents in flow reactors considerably expands the possibilities for their employment [5]. For example, it is known [6–10] that the use of supercritical solvents for the transformations of terpenoids provides not only a substantial increase in their transformation rate, relative to those in gas or liquid phases, but also can remarkably affect their selectivity.

We showed recently [11, 12] that adding a heterogeneous catalyst to a supercritical solvent/flow reactor system enables us to effectively perform different transformations of natural compounds: isomerization, Meerwein–Ponndorf–Verley reduction [12], and oxidation by atmospheric oxygen [11].

(-)-Menthol is an important substances that finds wide application in the pharmaceutical, perfume, and food industries. A key stage in the production of synthetic menthol is the acid-catalyzed cyclization of citronellal **1** into isopulegol **2** [13]. It should be noted that cyclization is usually accompanied by the formation of other stereoisomers of **2**, primarily *iso*-isopulegol **3** and *neo*-isopulegol **4** (Scheme 1).



Scheme 1. Transformation of citronellal **1** at 160°C (mixture component concentration in %; gas-liquid chromatography and mass spectrometry data).

Mixture component concentration, %, according to the GLC-MS data (selectivity). Transformation of citronellal **1** occurred at 190°C

Flow, mixture/CO_2, ml/min	**1**	**2**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	*P*
2/5	–	–	–	30.8	5.2	11.9	4.9	15.8	6.2	25.2
3/7.5	31.0	3.2 (4.6)	6.6 (9.6)	21.4 (31.0)	2.3 (3.3)	8.2 (11.9)	6.3 (9.1)	6.9 (10.0)	1.6 (2.3)	12.5 (18.1)

Note: *V* is flow, and *P* is other products.

The aim of this work was to study the possibility of cyclizing **1** into **2** in a supercritical solvent in a flow reactor.

EXPERIMENTAL

To conduct our studies, we used citronellal **1** (Fluka), Al_2O_3 (Macherey-Nagel, pH 7 ± 0.5, 50–200 μm, BET free surface ~130 m^2/g).

The experimental investigation of reactions under supercritical conditions was performed on the laboratory setup described in detail in [14] with the use of a tube reactor containing 22.1 cm^3 (20.6 g) of Al_2O_3.

The reaction mixture was fed into the reactor in two flows. The first flow (supercritical CO_2) was syringe-pumped into a mixer at the reactor inlet through a heat-exchanger, where it was heated to the reaction temperature. The second flow (1% solution of **1** in hexane) was piston-pumped into the same mixer.

The reaction mixture was cooled at the reactor outlet and transferred for analysis. The composition of liquid reaction products was analyzed by chromato-mass spectrometry on a gas Agilent 6890N chromatograph with a quadruple Agilent 5973N mass analyzer used as a detector. A quartz HP-5MS column (5%-diphenyl-95%-dimethylsiloxane copolymer) with a length of 30 m, internal diameter of 0.25 mm, and a stationary phase film thickness of 0.25 μm was used for analysis. The scan range was from m/z 29 to m/z 500. Quality analysis was performed by comparing the retention times of components and their total mass spectra with NIST (190825 compounds) and Wiley7 (375000 mass spectra) data. The percentage composition of mixtures was calculated from the peak areas in chromatograms without correcting coefficients.

The contact time of the reaction mixture (τ) was calculated as a ratio between the catalyst volume in the reactor V_C (cm^3) and the total consumption of the mixture at the reactor inlet Q (cm^3/s); it was ~3.2 min at a flow of 7 ml/min. The transformation was performed in the temperature range $T = 160–190°C$ at pressure $p = 190$ atm.

The temperature and pressure in the reactor that provided supercritical conditions for the reaction mixture were chosen on the basis of thermodynamic calculations and phase diagrams.

RESULTS AND DISCUSSION

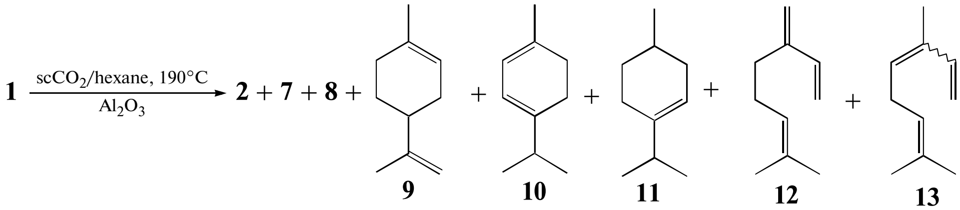
To perform the transformations of **1**, an $scCO_2$/hexane mixture was chosen as the solvent. The use of sc CO_2 as a component of the complex solvent considerably reduced the critical temperature, thus avoiding undesirable secondary transformations of products formed in the course of the reaction.

We used neutral Al_2O_3 without any preliminary activation as a catalyst in this reaction. We successfully used this catalyst earlier for the isomerization of pinane epoxides in supercritical fluids [12]. Note that attempts to use nonactivated Al_2O_3 for the cyclization of **1** (16 h, 25°C) had also been made earlier, but citronellol **5** was obtained as the main reaction product, while **2** was not found in the reaction mixture [15]. It seems that **5** was formed as a result of the disproportionation of aldehyde **1** into alcohol **5** and the corresponding acid by the Cannizzaro reaction.

Our first experiment on the cyclization of **1** in a flow reactor in complex supercritical solvent was performed at 160°C and flow rates of the solution of **1** in hexane and CO_2 of 2 and 5 mL/min, respectively, and a contact time of 3.2 min. The obtained product distribution is shown in Scheme 1. The conversion of aldehydes **1** was quantitative under these conditions, and the main products were targeted isopulegols **2**–**4** whose fraction in the reaction mixture was 74.4%. The selectivity with respect to compound **2** among all of the formed isopulegols was ~70%. Citronellol **5**, pulegone **6**, menthone **7**, and *para*-mentha-3,8-diene **8** were detected as minor products. Compound **8** evidently forms as a result of the dehydration of isopulegols under reaction conditions.

Our attention was focused on obtaining compounds that can formally be related to the reduction (**5**) or oxidation (**6**) products. It is not improbable that these compounds can be formed from **1** and **2** by the Meerwein–Ponndorf–Verley reaction, which (as we showed in [12]) can proceed under these conditions. The nonequivalent amount of **5** and **6** observed in the reaction mixture can be explained by the different stability of these compounds under reaction conditions

As the reaction temperature rose to 190°C, isopulegols completely disappeared from the reaction mixture (table) and the main product turned out to be diene **8**. Other *para*-menthadienes (limonene **9** and α-terpinene **10**) were identified in noticeable amounts along with *para*-menth-3-ene **11** (Scheme 2). The formation of acyclic trienes (myrcene **12** and β-ocimene **13**) in appreciable amounts was quite unexpected. We found no examples in the literature where compounds **12** and **13** were obtained from **1**, isopulegols, or menthadienes with a *para*-menthane framework.



Scheme 2. Transformation of citronellal **1** at 190°C.

In order to reduce the contribution of secondary transformation products, we shortened the contact time and raised the flow rates of the citronellal solution **1** in hexane and CO_2 by a factor of 1.5. As was expected, the reaction mixture contained a considerable amount of unreacted compound **1** along with **2**, but the concentration of the latter proved to be minor (table). At 190°C, the rate of secondary transformations of isopulegols evidently exceeds the rate of their formation considerably. Menthone **7**, which was absent from the reaction mixture at a longer periods of contact, was detected in large amounts. The reduced contact time had virtually no effect on the selectivity of the formation of *para*-menthadienes **8**–**10**, but resulted in a noticeable drop in the concentration of acyclic trienes **12** and **13**.

It should be noted that the authors were the first to study the reactivity of citronellal **1** under supercritical conditions in a flow reactor in the presence of Al_2O_3. It was shown that at 160°C, the main product is isopulegol **2** and when the temperature is elevated to 190°C, the main products are myrcene and monoterpenes with *para*-menthane framework.

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