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Preparation of chiral isobenzofurans from 3-carene in the presence of modified clays

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ABSTRACT

Isomerization of 3-carene to the reaction mixture, containing 2-carene and its further utilization in the synthesis of chiral isobenzofurans, was investigated in the presence of acid-modified clays at 140 °C. The catalysts were characterized by XRF, FTIR with pyridine and nitrogen adsorption. Quantification of the effect of the type and concentration of acid sites in different clays comprising commercial montmorillonite and natural illite on the yield of 2-carene as well as by-products was obtained for the first time. It was established that selectivity to 2-carene decreased with an increase of the Lewis to Brønsted acid sites ratio. The largest amount of 2-carene in the mixture (15.0 wt.%) with the highest ratio of 2-carene to menthadienes (0.63) was observed at 50% 3-carene conversion over a commercial montmorillonite K-30 clay, which has a moderate (100 μmol/g) acidity. It was demonstrated for the first time that the mixture containing 2-carene can be effectively used as a starting material in the reaction with vanillin resulting in chiral isobenzofurans. The products obtained in this reaction exhibit neuroprotective activity in an animal Parkinson's disease model. It was established that isobenzofurans yield decreased with an increase in the Lewis to Brønsted acid sites ratio. The largest yield of these products was obtained in the presence of a commercial K-10 clay (59.8%), which is higher than using 2-carene per se. Catalytic synthesis of isobenzofurans based on a readily available monoterpene 3-carene instead of expensive 2-carene was thus developed.

1. Introduction

The main components of turpentine areterpene hydrocarbons – α-pinene and 3-carene. Processing of α-pinene can give several valuable products, for example, camphene, limonene, verbenone, campholenic aldehydes, carveol, which are used in the synthesis of fragrances and physiologically active compounds [1–5]. For example a diol with the *p*-menthane structure synthesized from α-pinene showed a high activity with respect to the Parkinson disease symptoms [5], while its derivatives have analgesic and antiviral activities [6,7]. There are fewer examples of 3-carene utilization in preparation of physiologically active compounds and thus this area remains almost unexplored [8,9]. Note that this hydrocarbon is present in nature exclusively as an (+)-enantiomer, which makes its use in the synthesis of optically pure compounds very promising [8,9]. One of the possible ways to involve 3-carene in fine organic synthesis is its conversion to a more labile 2-carene [10–16].

It is known that in the presence of bases, 3-carene can undergo isomerization with formation of an equilibrium mixture of 2- and 3-carene with the 2:3 ratio [10]. On strongly basic NaX and NaY zeolites at 250 °C selectivity to 2-carene was 36.3% at 3-carene conversion of 78.4%, [11]. In the presence of a sodium/o-chlorotoluene catalytic system, selectivity to the target product was 83.3% after 48 h at 27.7% conversion of 3-carene [12]. At the same time, the gas phase reaction of 3-carene at 350 °C on decationated zeolites X, Y and ZSM-5 led to formation of cymenes with a yield up to 30% [13]. Selectivity to these products increased to 61–70% in the presence of alumina-chromia catalysts at 360–425 °C [14], whereas 2-carene formation was not observed [13,14].

Recently it has been shown that transformations of 3-carene to 2-carene are also possible by acid catalysis at relatively mild conditions [15,16]. The liquid-phase isomerization of 3-carene at 140 °C was

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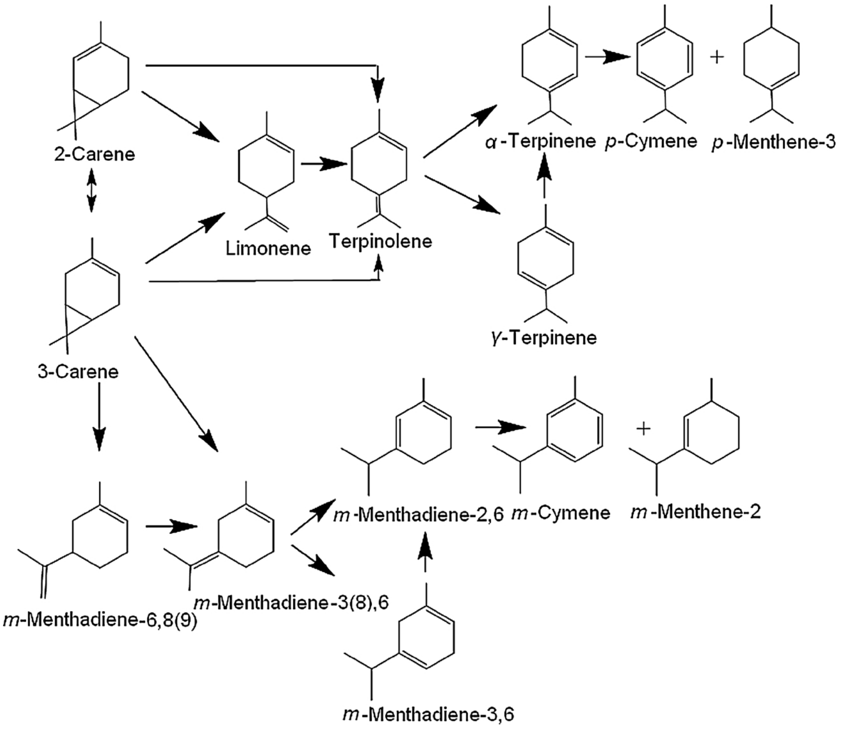

Fig. 1. A reaction network for 3-carene isomerization [16].

studied in the presence of acid-modified clays from Belarus (illite, glauconite) and Mongolia (montmorillonite, kaolinite) [15,16]. Formation of monoterpenes with different structures (menthadienes, menthenes, cymenes and 2-carene) was observed (Fig. 1). On a weakly acidic illite clay, the main products were menthadienes (48.5 wt.%), while the largest content of 2-carene in the reaction mixture (15.0 wt.%) was obtained in the presence of Mongolian montmorillonite [16]. The reaction network of 3-carene isomerization (Fig. 1) was confirmed by kinetic modelling [16].

Although (+)-2-carene is widely available in nature, its content in natural sources is extremely small, and isolation from essential oils or reaction mixtures is a very difficult task [9]. Therefore, 2-carene is considered as not a readily available and expensive reagent, which hinders its wide use in organic synthesis [9].

It is known that reactions of terpenes with aldehydes in the presence of catalysts lead to formation of chiral heterocyclic compounds with different structures [17–20]. Thus, in the condensation of 2-carene (I) or a mixture of 2- and 3-carenes (2:3) with vanillin (3-methoxy-4-hydroxybenzaldehyde, II) in the presence of commercial montmorillonite K-10, chiral hexahydroisobenzofurans (III) are formed as two (IIIa,b) diastereomers (Fig. 2). The yield of the desired product III increased from 33 to 52% when 2-carene was replaced with a mixture of 2- and 3-carene (2:3), which may be explained less prominent 2-carene transformations to by-products [17]. Note that formation of compounds with the structure III was also observed in the reaction of trans-4-hydroxymethyl-2-carene with salicylic aldehyde in the presence of a bentonite clay [18]. Opening of the cyclopropane ring in I led to formation of by-products with 3-oxabicyclo[3.1.1]nonane structure (IV) [17]. These compounds are also formed by the interaction of aldehydes with menthadienes and 3-carene in the presence of clays or heteropolyacids [17–20].

It is known that isobenzofurans derivatives can exhibit different biological activity [21–26]. In particular, it has been found that the product III, synthesized from 2-carene I and vanillin II, exhibits a high neuroprotective activity in a Parkinson disease model *in vivo* [27]. Therefore, synthesis of novel substituted isobenzofurans and a study of their physiological activity are important tasks. However, 2-carene is too expensive for a practical use as a starting molecule for such syntheses.

A mixture of 3- and 2-carenes used in [17] for reactions with aldehydes was made by mixing pure monoterpenes. At the same time, the reaction mixtures that are formed during isomerization of 3-carene in the presence of clays also contain significant amounts of 2-carene [16] and theoretically may be used as a feedstock in synthesis of chiral isobenzofurans. It should be noted that these mixtures contain many other monoterpenes besides carenes, which influence the catalyst performance.

Acid-modified montmorillonites (*e.g.* K-10 and K-30) currently produced in industry, have not been investigated in 3-carene isomerization. Moreover, the effect of the catalyst type and its acidity on the yield and stereoselectivity to the desired isobenzofurans remains unexplored. The aim of the present work is to develop a method of the catalytic synthesis of chiral hexahydroisobenzofurans based on readily available and inexpensive monoterpene 3-carene through its preliminary isomerization into a 2-carene containing mixture followed by a subsequent condensation with aldehydes.

2. Experimental

2.1. Characterization of catalysts

Commercial montmorillonite clays K-10 and K-30 (Sigma-Aldrich), Belarusian illite clay from Lukoml-1 mine (L-1) and synthetic aluminosilicate AS-36 (Russia) were used as catalysts for isomerization of 3-carene and synthesis of hexahydroisobenzofuran from 2-carene containing mixture. The particle size of the catalysts was below 100 μm in all experiments.

The samples of K-10, K-30 and AS-36 were used without any chemical treatment. An acid modification of L-1 clay was carried out by stirring it with 5 ml per g 10% HCl (5 ml/g) for 3 h at 90 °C [4]. The resulting precipitate was washed with distilled water until Cl^- ions were completely absent in the washing waters (test with $AgNO_3$) and dried at 105 °C.

The chemical composition of the catalysts was determined by X-ray

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