



Two-step synthesis of monoterpenoid dioxinols exhibiting analgesic activity from isopulegol and benzaldehyde over heterogeneous catalysts



Martina Stekrova^a, Päivi Mäki-Arvela^a, Ewelina Leino^a, Karolina M. Valkaj^a, Kari Eränen^a, Atte Aho^a, Annika Smeds^a, Narendra Kumar^a, Konstantin P. Volcho^{b,c}, Nariman F. Salakhutdinov^{b,c}, Dmitry Yu. Murzin^{a,*}

^a Laboratory of Industrial Chemistry and Reaction Engineering, Åbo Akademi University, FI-20500 Turku, Finland

^b N. N. Vorozhtsov Institute of Organic Chemistry, Russian Academy of Sciences, Novosibirsk 630090, Russia

^c Novosibirsk State University, Novosibirsk 630090, Russia

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ABSTRACT

Benzodioxinols, compounds with 6-membered heterocycles containing two oxygen atoms, exhibit promising analgesic activity. In the current study, synthesis of dioxinol via two-step approach including Prins cyclization of isopulegol with benzaldehyde to tetrahydropyran and its ring-rearrangement to dioxinol was investigated. Different acidic and basic catalysts were studied in the second step and the highest selectivity toward dioxinol was achieved using mesoporous Ce-composite material.

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1. Introduction

Interesting biologically active substances are synthesized from a variety of compounds isolated from natural sources. It has been recently reported that compounds with benzodioxin framework can possess promising analgesic activity [1]. The compounds with the mentioned structure were synthesized by the reaction between *cis*-verbenol oxide and aromatic aldehydes in the presence of an excess of montmorillonite clay [1,2] or later Fe-modified Beta zeolite [3]. Due to importance of the target compound, low selectivity towards it and a very limited amount of experimental data available, there is a need to further investigate synthesis of dioxinols with promising biological activity.

In the current research, synthesis of the desired dioxinol (Fig. 1, compound 3) was investigated by the reaction between isopulegol and benzaldehyde. Monoterpenic alcohol, isopulegol (Fig. 1)

belongs to a group of natural compounds which can be isolated from a variety of essential oils [4] or can be synthetically prepared by catalytic cyclization of citronellal [5].

Synthesis of tetrahydropyran (Fig. 1, compounds 4+5) by Prins cyclization reaction of isopulegol and benzaldehyde was recently demonstrated by our group [6]. Different parent zeolites as well as their metal modified forms and mesoporous materials have also been used in the comparative investigation focused on Prins cyclization of isopulegol and 3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (*diol*) with benzaldehyde. It has been discovered, that dioxinol (Fig. 1, compound 3) is formed only in minor amounts in the above-mentioned Prins cyclization reaction, and acidic catalysts favor the formation of tetrahydropyrans (Fig. 1, compound 4 and 5) [6]. The highest selectivity (over 90%) toward tetrahydropyrans was achieved using mesoporous Ce composite material derived from MCM-41.

The aim of the current work was to synthesize dioxinol over different heterogeneous catalysts applying a two-step synthesis route for the desired dioxinol, including Prins cyclization of isopulegol and benzaldehyde for producing mainly tetrahydropyran, 4 in the

* Corresponding author.

E-mail address: dmurzin@abo.fi (D.Yu. Murzin).

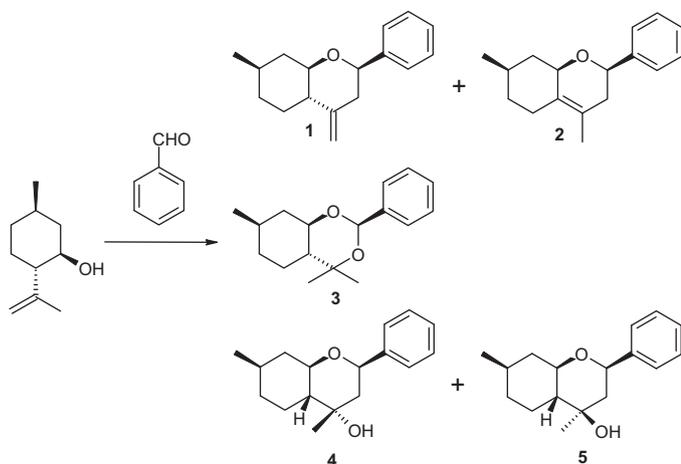


Fig. 1. Reaction scheme of Prins cyclization of isopulegol and benzaldehyde. The formed products are dehydration product (1) of tetrahydropyran (4, 5), dioxinol (3) and product (2).

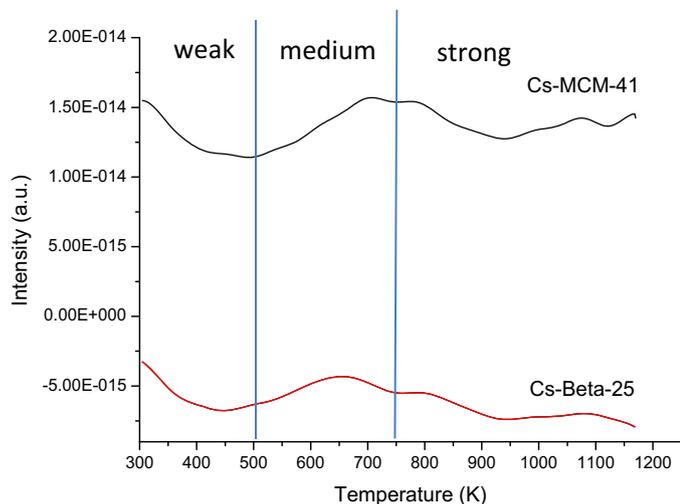


Fig. 2. TPD of CO₂ from Cs-MCM-41 mesoporous catalyst and Cs-Beta-25 zeolite catalyst determined by mass spectrometry.

first step followed by its ring-rearrangement to dioxinol, **3**. Since the transformation of tetrahydropyran to dioxinol has been very scarcely investigated [6], several types of catalysts, exhibiting only Brønsted acidity, such as (1) ion-exchange resin Amberlite 120-H and (2) Smopex-101, a fibrous, non-porous catalyst containing sulfonic groups, (3) only Lewis acidic Al₂O₃, (4), a basic MgO as well as (5) both Brønsted and Lewis acidic sites containing metal modified H-Beta zeolites and mesoporous materials derived from H-MCM-41 were used.

2. Experimental/methodology

2.1. Materials

The NH₄-Beta-25 and NH₄-Beta-300 zeolites (25 and 300 = SiO₂/Al₂O₃ molar ratios, Zeolyst International), Aluminum oxide (UOP Inc.) and Smopex-101 (Smoptech, Johnson Matthew).

Ferric, cerium and cesium nitrates (Fluka) used as the metal precursors, magnesium oxide, Amberlite IR-120H, benzaldehyde (Fluka, 99.0%), (–)-isopulegol (Aldrich, 98.9%) and toluene (anhydrous, 99.8%) were supplied by Sigma-Aldrich (Germany) and used as received.

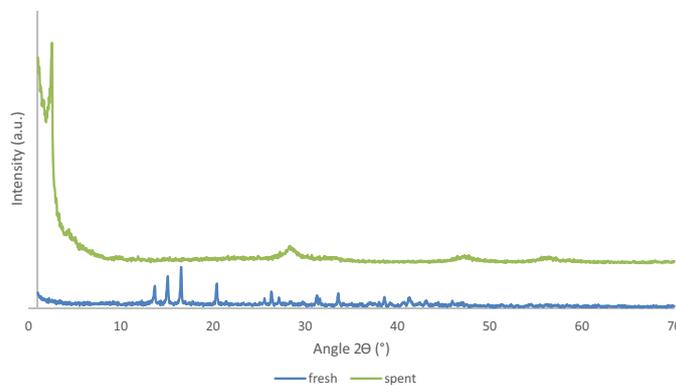


Fig. 3. X-ray powder diffraction patterns of fresh and spent mesoporous Ce composite.

2.2. Catalysts preparation

The NH₄⁺ form of zeolites were transformed to proton forms at 500 °C in a muffle oven using a step calcination procedure.

MCM-41 (SiO₂/Al₂O₃ ratio of 35) was synthesized in the sodium form (Na-MCM-41) using a Parr autoclave (300 mL) according to Ref. [7] with a few modifications [8]. After synthesis of MCM-41, it was filtered, washed with distilled water, dried overnight at 100 °C and calcined at 450 °C.

Cerium, iron and cesium modified catalysts were prepared using conventional evaporation impregnation method. Cerium, ferric and cesium nitrates were used as metal precursors. The mixtures containing the support material and an aqueous solution of metal precursor were stirred for 24 h at 60 °C. The other steps of the synthesis were evaporation, drying at 100 °C overnight and calcination at 450 °C for 4 h (the cesium catalyst calcination temperature was 400 °C).

2.3. Catalysts characterization

The specific surface areas of supports and of metal modified catalysts were determined by nitrogen adsorption using Sorptometer 1900 (Carlo Erba instruments). The samples were outgassed at 150 °C for 3 h before each measurement. The BET equation was used for calculation of the specific surface area of mesoporous materials, silica and alumina and the Dubinin equation was used for calculation of the specific surface area of microporous zeolites.

The acidity of the proton and metal modified catalysts was measured by infrared spectroscopy (ATI Mattson FTIR) using pyridine (≥99.5%) as a probe molecule for qualitative and quantitative determination of both Brønsted and Lewis acid sites. The samples were pressed into thin pellets (10–25 mg), which were pretreated at 450 °C before the measurements. Pyridine was first adsorbed for 30 min at 100 °C and then desorbed by evacuation at different temperatures. Three different temperatures were used for desorption of pyridine. Desorption at 250–350 °C corresponds to all (weak, medium and strong) sites, while 350–450 °C interval reflects medium and strong sites. Pyridine stays adsorbed after desorption at 450 °C only on strong sites [9]. The amount of Brønsted and Lewis acid sites was calculated from the intensities of the corresponding spectral bands, 1545 cm⁻¹ and 1450 cm⁻¹ respectively, using the molar extinction parameters previously reported by Emeis [10]. The catalyst weights were taken into account in the calculations.

A Philips X'Pert Pro MPD X-ray powder diffractometer was used in the XRD measurements. The diffractometer was operated in Bragg-Brentano diffraction mode, and the monochromatized Cu-Kα radiation was generated with a voltage of 40 kV and a current of 50 mA. The primary X-ray beam was collimated with a fixed 0.25

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