



Heterogeneous catalysis for transformation of biomass derived compounds beyond fuels: Synthesis of monoterpenoid dioxinols with analgesic activity



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ABSTRACT

Catalytic synthesis of a dioxinol compound, (2*S*,4*aR*,8*R*,8*aR*)-4,4,7-trimethyl-2-phenyl-4*a*,5,8,8*a*-tetrahydro-4*H*-benzo[*d*][1,3]dioxin-8-ol, exhibiting analgesic activity was demonstrated over Fe-modified beta zeolite. During interactions between *cis*-verbenol oxide and benzaldehyde, two main reactions occurred. In the first reaction, namely isomerization of verbenol oxide both cyclopentenic hydroxyketone, oxetane as well as a cyclohexyl compound, (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol were formed. In the second parallel reaction the target compound was generated. The highest yield of the target compound was achieved in the reaction between verbenol oxide and benzaldehyde at their molar ratio of 1:133 with the bifunctional iron modified Fe-H-Beta-150 catalyst at 70 °C giving a much higher yield than reported earlier in the literature, being 46 mol-% at complete conversion of verbenol oxide.

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1. Introduction

New biologically active substances are synthesized from a variety of compounds isolated from natural sources or from side products of softwood industry [1], for example from α -pinene and verbenone found in coniferous trees [2]. α -Pinene belongs to the largest group of natural compounds, terpenes. Oxidation or rearrangement leads to formation of terpenoids, such as verbenone. α -Pinene can be easily obtained by fractional distillation of commercial natural terpenes, in which it is a major constituent [3]. The process for obtaining verbenone from α -pinene in the presence of biocatalysts (e.g. liquid cultures of *Saccharomyces cerevisiae*, or *Rauwolfia Sellowii* or *Psychotria Brachyceras* cells) leads to 80% yield during transformation in 5–10 days [4]. Catalytic oxidation of α -pinene in the presence of Co(II) and Cu(II) polyphthalocyanines exhibits the yield of 70% of the aimed product at 70 °C and 4 days

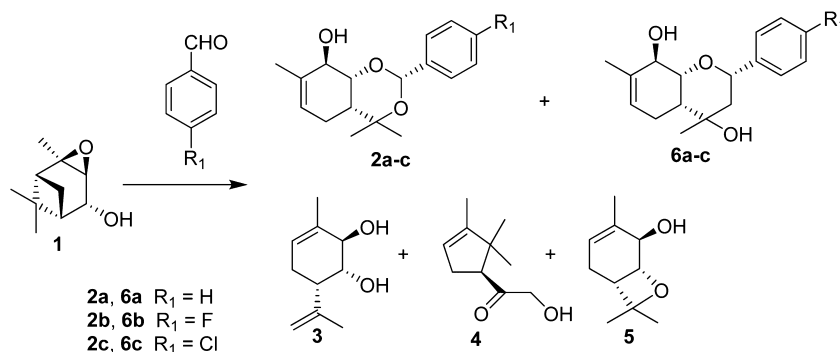
of the reaction time [5]. Further epoxidation with hydrogen peroxide in the presence of NaOH and reduction using LiAlH₄ allow to synthesize *cis*-verbenol oxide [6], a starting monoterpenoid for synthesis of chiral compounds with various types of framework [7].

For example, verbenol oxide **1** may be isomerized [8] or react with aromatic aldehydes [9] to form compounds with anti-Parkinsonian [10] or analgesic activity [9,11] of new structural types, respectively. It should be noted that traditional analgesic and anti-inflammatory agents, such as opiates, steroids, and non-steroidal anti-inflammatory drugs all have serious side effects, and the development of highly effective, low-toxic analgesics thus remains a challenge in pharmacology and medicinal chemistry [12].

Compounds with benzodioxin framework which possess promising analgesic activity were synthesized early by the reaction between *cis*-verbenol oxide **1** and aromatic aldehydes in the presence of an excess of montmorillonite clay (mass ratio between clay and aldehyde was 5.7 [13] or 5 [9]). The reactions were carried out in dichloromethane at room temperature using an equimolar ratio of aldehyde and verbenol oxide. The isolated yields of the desired dioxinols **2** exhibiting benzodioxin framework, separated

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Scheme 1. Products of reaction of verbenol oxide **1** with aldehydes (compounds **2** and **6**), and isomerization products **3–5**.

by column chromatography, and formed using either fluorobenzaldehyde or chlorobenzaldehyde as a reactant were 10% and 29%, respectively, based on aldehyde consumption with complete conversion of terpenoid [9] (Scheme 1). A moderate yield of the target products can be explained by a number of competitive reactions including isomerization of verbenol oxide to diol **3** with cyclohexene framework, hydroxyketone **4** with cyclopentyl skeleton and oxetane **5**, as well as formation of heterocyclic compounds of type **6** with chromene framework (Scheme 1) [9]. Furthermore, the exact nature of the catalyst is not known and the role of iron oxide present in montmorillonite clay K10 remained unclear [14].

Due to importance of the target compound, low selectivity towards it and a very limited amount of experimental data available only for one type of clay [9,13], there is a need to investigate the reaction between verbenol oxide and benzaldehyde for synthesis of compounds with promising biological activity. The aim of this work was to find for the first time an effective catalyst for synthesis of dioxinols starting from verbenol oxide and benzaldehyde. The main parameters were the reaction conditions and a type of heterogeneous catalysts, namely proton and bifunctional, metal modified zeolites. H-Beta-300 catalyst was selected due to its high selectivity towards isomerization of verbenol oxide to diol [8]. H-Beta zeolite was also used earlier in transformations of monoterpenoids [15], although the first attempts to use this type of catalyst in the reaction of verbenol oxide with aldehydes (in CH_2Cl_2 at room temperature) were unsuccessful [6].

2. Experimental

2.1. Catalyst synthesis and characterization methods

NH_4 -Beta-25 ($SiO_2/Al_2O_3 = 25$), NH_4 -Beta-150 ($SiO_2/Al_2O_3 = 150$) and NH_4 -Beta-300 ($SiO_2/Al_2O_3 = 300$) zeolites were purchased from Zeolyst International. The ammonium forms of these zeolites were transformed to proton forms using step calcination procedure at $500^\circ C$ for 4 h. 5 wt% Fe-H-Beta-150 zeolite catalyst was prepared using an aqueous solution of ferric nitrate. H-Beta-150 zeolite and the aqueous solution of ferric nitrate was subjected to ultrasound irradiation for 4 h. Thereafter a round bottom flask containing the above mentioned solution was rotated in a rotavapor for 24 h followed by evaporation of water, drying of Fe-H-Beta-150 zeolite catalyst at $100^\circ C$ and calcination in a muffle oven [16].

Nitrogen physisorption measurements were performed using Sorptomatic 1900. The sample preparation was carried out by outgassing at $150^\circ C$ for 3 hours. Specific surface area (m^2/g) and micropore volume (cm^3/g) were calculated with Dubinin's method.

The morphology of some catalysts was studied with scanning and transmission electron microscopy. Zeiss Leo Gemini 1530 microscope was equipped with SE (secondary electron) and BSE (backscattered electron) detectors. The equipment for TEM was

JEM 1400 plus with acceleration voltage of 120 kV and resolution of 0.98 nm using Quems II MPix bottom mounted digital camera.

The phase purity and structure of zeolites were investigated by XRD using X'Pert Pro MPD instrument using monochromated $CuK\alpha$ radiation at 40 kV/50 mA. The collimation of X-ray beam was performed with a fixed 0.25° divergence slit with a fixed 20 mm mask. The measurements were performed in a range of $1.15^\circ - 90^\circ$ with a scanning speed of $0.04^\circ/2s$. The diffractograms were analyzed by Philips High Score and Maud programmes [17] and the crystal structures were confirmed with those presented in IZA web site [18].

The acidity of the catalysts was determined with ATI Mattson FTIR of adsorbed pyridine (Sigma–Aldrich, $\geq 99.5\%$, a.r.) as a probe molecule. Infrared transmission spectra were recorded on the thin pressed tablets with mass about 10–20 mg. The pretreatment of the pellets was made at temperature of $450^\circ C$ for 1 hour at 7 Pa before the measurement. At first pyridine was adsorbed for 30 min at temperature of $100^\circ C$. To get the distribution of weak, medium and strong Brønsted and Lewis acid sites desorption of pyridine was made at the range of temperatures: $250^\circ C$, $350^\circ C$ and $450^\circ C$.

Brønsted and Lewis acid site concentrations were calculated by the integration of the infrared bands at 1545 cm^{-1} ($1.67\text{ cm}^2/\text{mmol}$ as a molar absorption coefficient) and at 1455 cm^{-1} ($2.22\text{ cm}^2/\text{mmol}$ as a molar absorption coefficient), respectively. The molar extinction coefficients were taken from the work of Emeis [19].

MAS-NMR of the proton forms of Beta zeolites was performed. Single pulse excitation spectra were obtained with Bruker AVANCE-III-800 spectrometer in 18.8 T magnetic field, where ^{27}Al resonance frequency was 208.4 MHz, Bruker MAS probe for 3.2 mm outer diameter zirconia rotors was used. The spinning speed of the samples was 22.0 kHz in all experiments. To keep quantitative intensities 10° short excitation pulses at RF field strength 50 kHz and 0.1 s relaxation delay between the accumulations were used. Intensity was normalized dividing the absolute intensity with the mass of the sample and with the number of scans. The spectra were referenced to the resonance frequency of $KAl(SiO_4)_2 \times 12H_2O$.

^{29}Si MAS-NMR spectra of the H-Beta samples were recorded with Bruker AVANCE-II-360 spectrometer at 8.5 T magnetic field (^{29}Si resonance at 71.45 MHz) using home built MAS probe for 10 mm outer diameter zirconia rotors. The spinning speed of the samples was 5 kHz, 90° excitation pulse was 7 μs , relaxation delay between the pulses was 100 s. About 800 scans were accumulated for each spectrum. The intensities were normalized by dividing the absolute intensity with the sample weight and with the number of scans.

2.2. Experimental set-up for evaluation of catalytic activity

The reactor set-up for the reaction between verbenol oxide and aldehydes at atmospheric pressure consisted of a four necked glass

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