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

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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.

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

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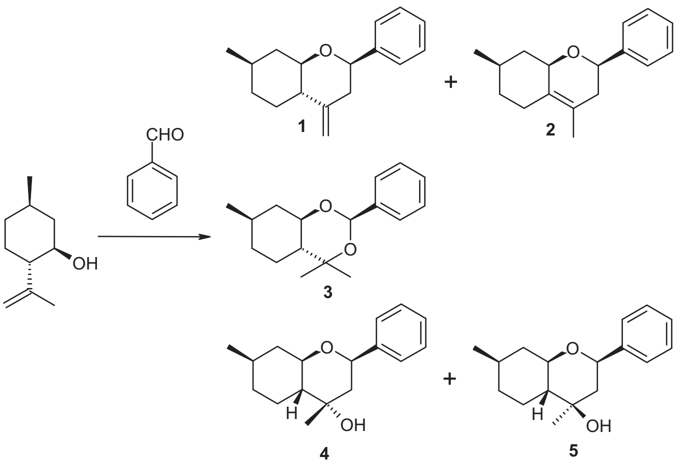

Fig. 1. Reaction scheme of Prins cyclization of isopulegol and benzaldehyde. The formed products are dehydration product (**1**) of tetrahydropyran (**4**, **5**), dioxinol (**3**) and product (**2**).

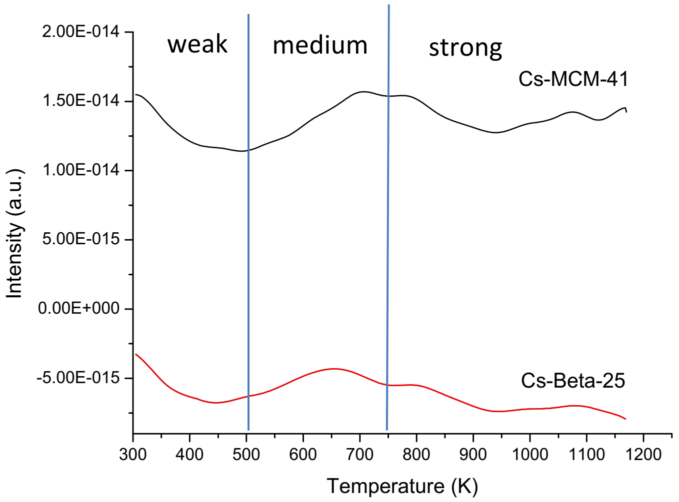

Fig. 2. TPD of CO_2 from Cs-MCM-41 mesoporous catalyst and Cs-Beta-25 zeolite catalyst determined by mass spectrometry.

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 Al_2O_3, (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 NH_4-Beta-25 and NH_4-Beta-300 zeolites (25 and 300 = SiO_2/Al_2O_3 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.

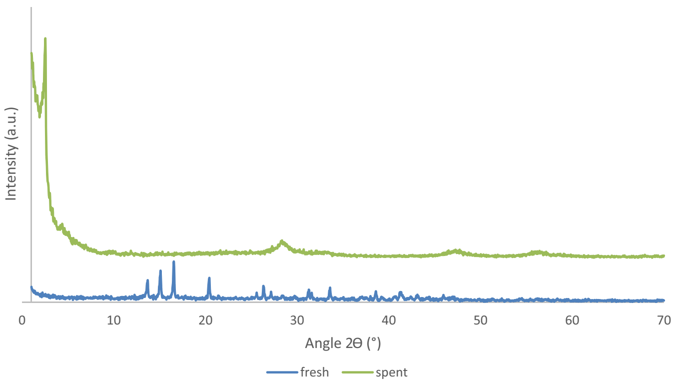

Fig. 3. X-ray powder diffraction patterns of fresh and spent mesoporous Ce composite.

2.2. Catalysts preparation

The NH_4^+ form of zeolites were transformed to proton forms at 500 °C in a muffle oven using a step calcination procedure.

MCM-41 (SiO_2/Al_2O_3 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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Table 1
Main textural characteristics of the prepared H-Beta-25, Fe-Beta-300, Cs-Beta-25, Cs-MCM-41, fresh and spent mesoporous Ce composite catalysts.

Catalyst/support	Nominal metal content (wt%)	Specific surface area (m^2/g)
H-Beta-25 [11]	–	807
Fe-Beta-300 [11]	2	587
Cs-Beta-25	2	229
Cs-MCM-41	10	642
Fresh mesoporous Ce composite	32	384
Spent mesoporous Ce composite	32	666

Table 2
Brønsted and Lewis acidities of the H-Beta-25, Fe-Beta-300, Cs-MCM-41, fresh mesoporous Ce composite and spent mesoporous Ce composite catalyst determined by FTIR using pyridine as a probe molecule.[a]

Catalysts	Brønsted acidity (μmol/g)			Lewis acidity (μmol/g)		
	250 °C	350 °C	450 °C	250 °C	350 °C	450 °C
H-Beta-25 [11]	269	207	120	162	128	113
Fe-Beta-300 [11]	90	57	0	67	16	0
Cs-MCM-41	0	0	0	11	10	0
Fresh mesoporous Ce composite	80	49	10	67	12	9
Spent mesoporous Ce composite	105	6	0	12	2	0

[a] Acidity of Cs-Beta-25 was not measured.

divergence slit and a fixed 15 mm mask. A 0.18 parallel plate collimator was used in the diffracted beam side prior to the proportional counter. The measured 2θ angle range was 1.0–70.0, with a step size of 0.04 and measurement time of 2.0 s per step. The samples were measured in Cu sample holders.

TPD of CO_2 was performed with the following procedure using Autochem 2910 apparatus. The catalyst, 250 mg was dried in helium flow by heating it with the rate of 30 °C/min up to 300 °C for 10 min. Thereafter the temperature was decreased to room temperature. The adsorption of CO_2 (AGA, 99.99%) was carried out at room temperature for 60 min followed by flushing the catalyst for 30 min with helium flow (AGA, 99.996%). Thereafter the TPD was performed under helium flow using the following temperature programme: 25 °C–20 °C/min–900 °C. The mass of CO_2, 44 was recorded with a mass spectrometry (Balzers Instruments).

2.4. Catalytic tests

Addition reactions of isopulegol and benzaldehyde over heterogeneous catalysts were carried out in liquid phase using a batch-wise glass reactor. In a typical experiment the initial amounts of isopulegol and the catalyst mass were 0.3 g each resulting in isopulegol concentration 0.04 mol/l. The kinetic experiments were performed in order to avoid internal and external mass transfer limitations using catalysts particle size <90 μm and the stirring speed of 390 rpm, respectively. The catalyst was activated in the reactor at 250 °C in an inert atmosphere for 30 min before the reaction. Benzaldehyde was used in excess ($V_L = 50$ mL) and no other solvent was applied. The reaction temperature was 70 °C. The samples were taken at different time intervals and analyzed by GC with a capillary column HP-5 (30 m x 320 μm x 0.5 μm) using the following temperature program: initial temperature 100 °C (held for 5 min), increased at 20 °C/min to 280 °C and held at the final temperature for 3 min. The products were confirmed by GC–MS and NMR spectroscopy.

The catalyst after the first reaction step was filtered and obtained reaction mixture was used in the second step of the synthesis. 0.3 g of catalyst was activated in the reactor at 250 °C in an inert atmosphere for 30 min before the reaction and tested in the rearrangement reaction. Reactions were carried out at different reaction temperatures without addition of any solvent. In some cases, sequential reactions were carried out for the second reaction step. The catalyst was filtered from the reaction mixture and another catalyst was tested with the same reaction mixture. The samples were taken at different time intervals and analyzed by GC using the same method as for samples from the addition reactions.

3. Results and discussion

3.1. Catalysts characterization

Specific surface areas of supports and metal modified catalysts are given in Table 1. The acidic pristine H-Beta-25 zeolite is characterized by very high specific surface area >800 m^2/g. The specific surface areas of the catalytic materials after the metal introduction are lower due to partial pore blocking. Significantly lower specific surface area was measured for Cs-Beta-25 and mesoporous Ce composite catalysts. A large decrease in specific surface area in the case of mesoporous Ce composite was caused by high loading of ceria (32 wt.%) and by partial distortion of the mesoporous hexagonal phase [8]. The spent mesoporous Ce composite catalyst showed higher specific surface area than the fresh Ce-composite catalyst (Table 1),

Loaded amounts of metals on the supports are given in Table 1. In most cases, supports were modified by small amounts of metals in the range 1–10 wt.%. An exception was Ce-composite derived from MCM-41 in order to achieve 32 wt.% loading of ceria. The nominal loading of Cs- in Cs-Beta-25 was 2 wt%.

The concentrations of acid sites in the studied materials are given in Table 2. The acidic pristine zeolite H-Beta-25 is characterized by the presence of highest Lewis and Brønsted acidity. Comparably mild Lewis and Brønsted acidity was determined for Fe-Beta-300 and Ce-MCM-41 based composite.

The pristine H-MCM-41 mesoporous catalyst is characterized by very mild Lewis and Brønsted acidity being 40 and 26 $\mu mol/g_{cat}$, respectively [12]. In case of cesium modification of this material, the Lewis acidity decreased and Brønsted acidity totally disappeared. The complete disappearance of the Brønsted acid sites from the Cs-MCM-41 mesoporous catalyst can be explained on the basis of the substitution of protons present in the H-MCM-41 by basic Cs sites (Table 2).

As can be seen from the comparison of concentrations of acid sites of the fresh and the spent Ce-MCM-41 composite catalyst (Table 2), Lewis acidity was decreased during the reaction. On the other hand, the total concentration of Brønsted acid sites increased and medium and strong acid sites at the same time decreased.

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Table 3
The relative amounts of CO_2 from the supported Cs catalysts determined by CO_2 TPD.

Catalyst	Weak	Medium	Strong	Total
Cs-MCM-41	0.20	0.50	0.11	0.81
Cs-Beta-25	0.34	0.32	0.34	1

Relative amounts of basic sites for Cs-MCM-41 were determined with mass spectrometry using the CO_2 signal and normalizing the results by assigning the value of 1 to Cs-Beta-25. The results presented in Table 3. It is noteworthy to mention here that although the Cs-MCM-41 mesoporous catalyst contained 10 wt% of Cs, the total relative amount of basic sites (0.81) was less than that of Cs-Beta-25, with only 2 wt% of Cs. The result clearly shows the inability of a larger amount of 10 wt% Cs to be transferred to the total active basic sites (Table 3). The basic sites in Cs-Beta-25 were determined by CO_2 desorption between 300 – 450 °C analogously to Ref. [13].

Comparison between the basicity data for 32 wt.% mesoporous Ce composite catalyst reported in [8] and the values for Cs containing materials is not straightforward because in the former case TCD detector was used and heating was done up to 600 °C, while in the current work TPD spectra were measured up to 900 °C. Moreover, different temperature domains were used in assignment of weak, medium and strong sites (Fig. 2).

The phase purity and structure of the fresh and the spent mesoporous Ce composite material were studied with X-ray powder diffraction (Fig. 3). As has been published previously [8], neither the major peaks which are characteristic for the MCM-41 mesoporous material (in the 2Θ; value of 0.2–11°) nor the peaks which are present in a cubic fluorite structure of CeO_2 were visible in the diffraction pattern of the fresh mesoporous Ce composite. This fact was most likely caused by partial distortion of the MCM-41 mesoporous structure [8]. However, the main CeO_2 peaks are shown at 2Θ; values of about 28.6, 33.1, 48 and 57 for the spent mesoporous Ce composite catalyst (Fig. 3).

The main contribution to the creation of mesoporous, an increase of the surface area and acidity should come from MCM-41 rather than ceria having a relatively low surface area. The peaks, shown in the X-ray powder diffraction patterns for 32 wt% Ce-MCM-41 spent mesoporous catalyst (Fig. 3) are, however, related not to MCM-41 mesoporous material, but CeO_2. The appearance of the peaks at 2θ values of 28–57° in the 32 wt% Ce-MCM-41 spent mesoporous material are attributed to CeO_2 cubic fluorite structure, while most of the peaks of MCM-41 mesoporous material appear before the 2θ value of 11°. Thus, while leaching of ceria might be present, resulting in lower intensity of XRD peaks, it cannot as such explain the creation of mesopores. MCM-41 mesoporous material studied in the current work has SiO_2/Al_2O_3 ratio of 35, hence, a substantial increase of Brønsted acidity can be tentatively attributed to rearrangement of the extra-framework aluminum species, situated at octahedral positions to the tetrahedral position, leading to an increase in the number of Brønsted acid sites from 80 μmol/g in the fresh catalyst to 105 μmol/g in the spent one.

This assumption relies on a concept that in general rearrangement of the extra framework octahedral Al species to the tetrahedral framework in aluminosilicate type of zeolites and mesoporous materials or re-insertion of Al in the framework may take place not only during well-documented *ex-situ* catalyst pretreatment [14–18], but during the reaction depending upon nature of reaction media and reaction conditions. This hypothesis requires further elaboration, being outside of the scope of the present work.

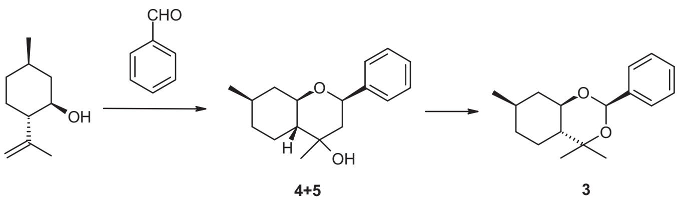

Fig. 4. Reaction scheme for the two-step synthesis of dioxinol **3** starting from isopulegol and benzaldehyde forming tetrahydropyran **4**, **5** in the first step.

3.2. *Catalytic results*

Two step synthesis of the desired dioxinol (Fig. 4, compound **3**), including Prins cyclization of isopulegol and benzaldehyde in the first step and the subsequent ring-rearrangement of formed tetrahydropyrans (Fig. 4, compounds **4** + **5**), was investigated in the current study. Besides ring-rearrangements also undesired dehydration of tetrahydropyrans was detected in the previous work [6].

3.2.1. *Prins cyclization*

Prins cyclization of isopulegol and benzaldehyde to synthesize tetrahydropyran moiety, was the main task of our previous research [6]. Different pristine proton (H-) zeolites as well as their metal modified forms (iron, cerium, gold) and MCM-41 mesoporous materials have been used as catalysts in the comparative investigation. The highest activity and selectivity towards tetrahydropyran moiety has been achieved using the mesoporous Ce composite catalyst. Therefore, the Prins cyclization was performed using this catalyst in the current study giving the results which are depicted in Table 4. Complete conversion (100%) of isopulegol at 70 °C was achieved within 1 h from the beginning of the reaction and the selectivity to tetrahydropyrans (compounds **4** + **5**) was 93%. The selectivity to dioxinol (compound **3**) was at the same time only 3%.

3.2.2. *Ring-rearrangement*

Two types of products in addition to tetrahydropyran **4** have been formed in the reaction of isopulegol with aldehyde, namely dehydration product of tetrahydropyran, **1** and its ring-rearrangement product, dioxinol, **3**. We suppose that the ring-rearrangement in tetrahydropyran compounds **4** and **5** leading to dioxinol compound **3** is possible. The reaction may start from the protonation of hydroxy-group in **4** and **5** followed by dehydration with formation of a tertiary cation which may turn into the corresponding benzylic cation (Fig. 5). It should be noted that these cations may be also formed by protonation of dehydration products **1** and **2**. Further interaction of benzylic cation with water and deprotonation leads to formation of an intermediate alcohol. Compound **3** may be formed by protonation of the double bond of the

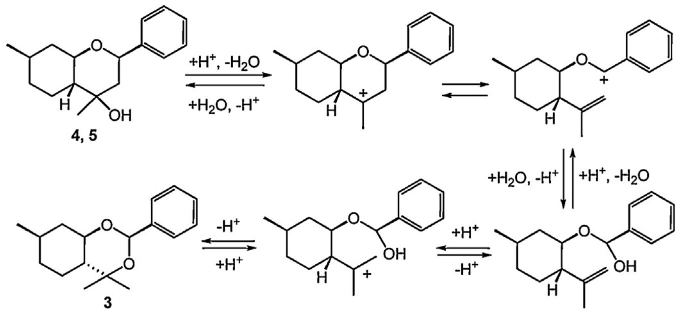

Fig. 5. Reaction mechanism of the ring-rearrangement of tetrahydropyran, **5** to dioxinol **3**.

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Table 4
Conversion of isopulegol, initial reaction rate and selectivities to different products at 100% conversion of isopulegol. The reaction temperature was 70 °C.

Catalyst	Conversion after 60 min (%)	Initial reaction rate (mol/(l min g_{cat}))	Selectivity at total conversion (%)			
			1	**3**	Unidentified products	**4 + 5**
mesoporous Ce composite	100	33.5	3	3	1	93

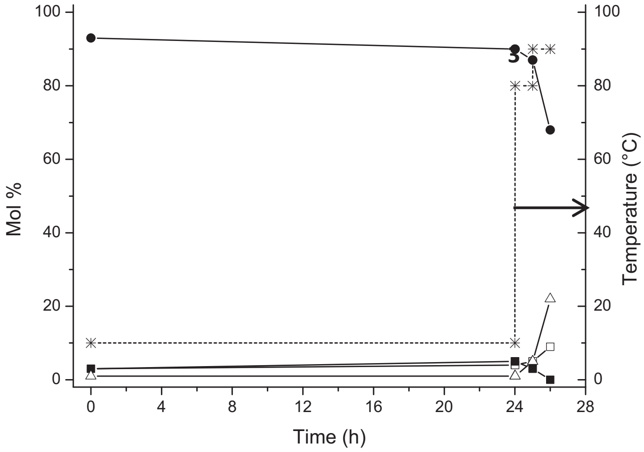

Fig. 6. Transformation of tetrahydropyran over H-Beta-25 zeolite catalyst. Symbols: tetrahydropyran (●), dioxinol (■), dehydration product **1** (open square), unknown products (open triangle) and temperature (*).

alcohol and subsequent heterocyclization. All these stages in principle may be reversible.

Since dehydration and hydration reactions can be catalyzed by acid and base catalysts [19], several different acidic, basic and metal modified (Cs-, Fe-, Ce-) catalysts were tested in the ring-rearrangement reaction of tetrahydropyran changes in the product distribution are given in Table 5. The main focus of the investigation was to study the role of Brønsted and Lewis acid sites, influence of basic sites and metal (Cs, Fe-, Ce) functions on the ring-rearrangement reaction of tetrahydropyran and selectivities to the products of dioxinol, dehydrated and other products.

Transformation of tetrahydropyrans over highly acidic H-Beta-25 containing Brønsted and Lewis acidity is depicted in Fig. 6. Interestingly, no transformation was observed over H-Beta-25 up to 60 °C. When the reaction temperature was elevated formation of unknown products was detected over this catalyst.

Nearly no transformation of tetrahydropyrans (compounds **4 + 5**) was observed with only Brønsted acidic Amberlite 120H (Fig. 7, Table 5, entry 2) at lower reaction temperature (10 °C) while enhanced formation of the undesired dehydration product **1** and unidentified products was observed at the higher temperatures. Similarly to Amberlite 120H, tetrahydropyran transformation was also quite minor (Table 5, entry 3) with Smopex 101 at 50 °C. Undesired transformation of tetrahydropyrans to unidentified products was, however, already observed at 50 °C over Smopex-101 (Table 5, Entry 3) and at 60 °C over Amberlite 120H (Table 5, Entry 2). In addition, highly Brønsted and Lewis acidic H-Beta-25 gave at 90 °C mostly unidentified products (Table 5, Entry 1) indicating that strongly acidic catalysts are not suitable for transformation of tetrahydropyran to dioxinol.

The results from the transformation of tetrahydropyran in a sequential experiment, where Cs-Beta-25 in the step 1 and Fe-Beta-300 in step 2 were used, are depicted in Fig. 8. Very slow transformation of **4 + 5** to the desired **3** was observed over Cs-Beta-25 without any improvement after elevation the temperature to 80 °C. It should be mentioned here that the step change in the concentration of reaction compounds was caused by long storage of the reaction mixture in the fridge (Fig. 8, before starting step 2). No transformations of tetrahydropyrans were also observed over a mildly acidic Fe-Beta-300 when the reaction temperature was in the range of 50–90 °C.

Lewis acidic alumina, did not catalyze any transformation of tetrahydropyrans despite temperature increase to 80 °C (Fig. 9, step 1), indicating that Lewis acidity does not catalyze the rearrangement of tetrahydropyrans to dioxinol (Table 5, Entry 5a, Fig. 9). The obtained results with Fe-Beta-300 and Al_2O_3 at relatively high temperatures with minor conversion of tetrahydropyran are also in line with the calculated total energies of tetrahydropyrans and dioxinol, being 95.7 kJ/mol and 118.6 kJ/mol, respectively, showing that the

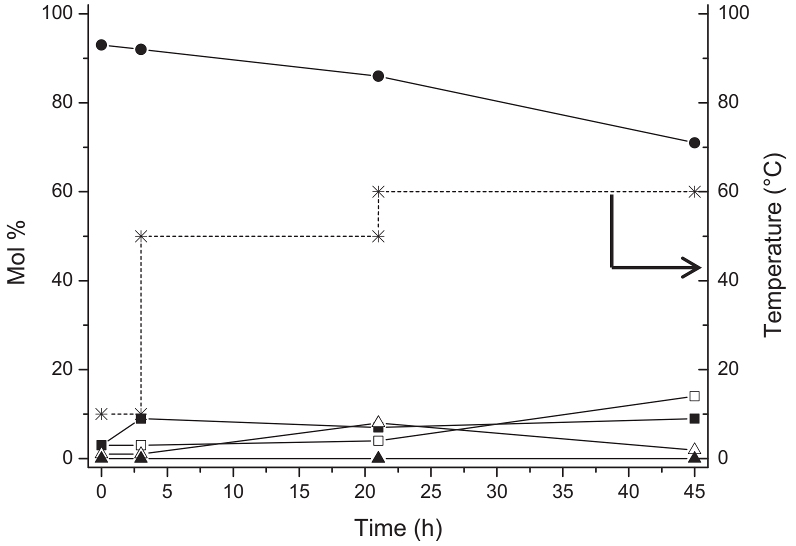

Fig. 7. Transformation of tetrahydropyran over Amberlite 120H. Symbols: tetrahydropyran (●), dioxinol (■), dehydration product **1** (□), unknown 1 (open triangle), unknown 2 (solid triangle) and temperature (*).

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Table 5
The change in molar fractions in percentage (consumed—negative values, formed—positive value) with solid acidic catalysts H-Beta-25, Amberlite 120H, Smopex 101, Fe-Beta-300, Lewis acidic Al_2O_3, basic Cs-Beta-25, MgO, and mesoporous catalysts Cs-MCM-41 and Ce-MCM-41.

Entry	Catalyst	Temperature (°C)	Time (h)	Tetrahydropyran (mol%) **4, 5**	Dehydrated product **1** (mol%)	Dioxinol **3** (mol%)	Other products (mol%)
1	H-Beta-25	90	1	−16	1	−1	16
2	Amberlite 120H	60	24	−15	10	−2	7
3	Smopex-101	50	20	−3	1	−2	4
4a	Cs-Beta-25	55	2	−3	1	2	0
4b	Fe-Beta-300	50–90	29	0	0	<−1	<1
5a	Al_2O_3	80	3	No reaction			
5b	MgO	50	3.5	7	2	−11	2
5c	Cs-MCM-41	100	15	−16	13	−2	5
6	mesoporous Ce composite	70	0.5	−9	1	9	−1

Table 6
Selectivities to different products after ring-rearrangement over Ce-MCM-41 mesoporous catalyst.

Catalyst	Temperature (°C)	Time (h)	Mol-% of different compounds			
			1	**3**	Unidentified products	**4 + 5**
Initial reaction mixture	–	–	3	3	1	93
mesoporous Ce composite (0.3 g)	70	2	3	3	5	89
+ fresh mesoporous Ce composite (0.1 g)	90	1	11	30	6	54
	90	24	11	21	8	59
+fresh mesoporous Ce composite (0.1 g)	90	0.5	10	36	8	46
	90	3	10	29	10	50
+fresh mesoporous Ce composite (0.1 g)	90	1	9	34	12	45

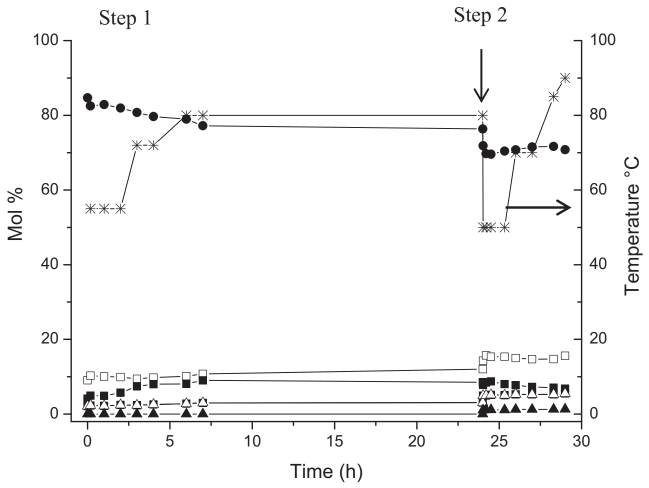

Fig. 8. Transformation of tetrahydropyran over Cs-Beta-25 (step 1) and Fe-Beta-300 (step 2). Symbols: tetrahydropyran (●), dioxinol (■), dehydration product 1 (□), unknown 1 (open triangle), unknown 2 (solid triangle) and temperature (*).

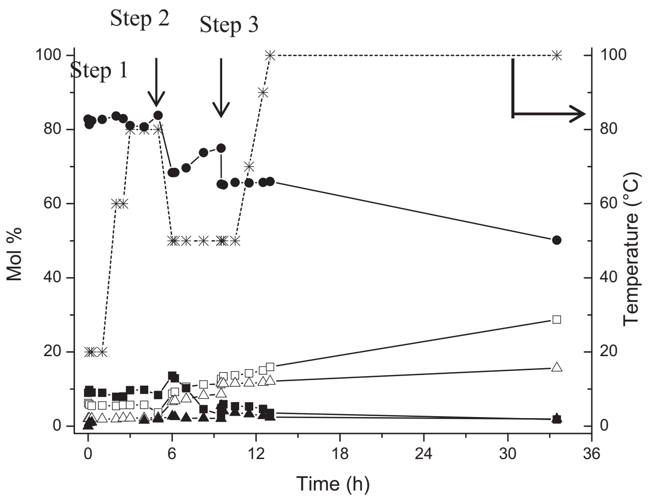

Fig. 9. Transformation of tetrahydropyran over Al_2O_3 (step 1), MgO (step 2) and Cs-MCM-41 mesoporous catalyst (step 3). Symbols: tetrahydropyran (●), dioxinol (■), dehydration product **1** (□), unknown 1 (open triangle), unknown 2 (solid triangle) and temperature (*).

tetrahydropyrans are more stable compounds. An important observation was the backward transformation of dioxinol (compound **3**) to tetrahydropyrans (compounds **4 + 5**) catalyzed by a purely basic catalyst, magnesium oxide (Table 5, entry 5b, Fig. 9, step 2).

The most significant dehydration of tetrahydropyrans to product **1** was observed in the case of testing of Cs-MCM-41 mesoporous catalyst at 100 °C (Table 5, Entry 5c, Fig. 9, step 3) while no transformations of tetrahydropyrans were seen using this catalyst at a lower temperature, 50 °C (Fig. 9, step 3).

Significant formation of the desired dioxinol **3** was observed over mesoporous Ce composite (Table 5, entry 6), which contains mild Brønsted and Lewis acid sites (Table 2) and also mild basic sites (see Section 3.1). On the other hand, only dioxinol **3** was formed from tetrahydropyrans over mesoporous Ce composite catalyst at 70 °C (Table 5, Entry 6) similarly to our previous results [6]. As it can be seen from Table 6 addition of the fresh mesoporous Ce composite catalyst caused initially a fast transformation of products **4 + 5** to the desired product **3**. After some time, the desired dioxinol **3**, however, was transformed back to tetrahydropyrans **4 + 5** and unidentified products.

This is also a reason for seemingly apparent contradiction between data in Table 5 (entry 6) after 30 min and the second entry from Table 6, where after 2 h, the dioxinol 3 selectivity remained at 3%.

An analogous formation of dioxinol from tetrahydropyran and the reverse reaction was repeated when another portion of the fresh ceria catalyst was added. This effect may be explained by fast deactivation of catalytic centers responsible for formation of dioxinol while centers leading to formation of tetrahydropyran compounds remain to be active. The highest achieved selectivity to the desired product with dioxinol framework (calculated based on initial isopulegol conversion) was 36% using mesoporous Ce composite catalyst.

The currently presented results are in line with those already published [6], where it was shown that pyran products **4 + 5** were

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transformed to dehydration product **1** over a catalyst containing high concentration of Brønsted acid sites, such as proton forms of Beta zeolites, Au-Beta-25 and Fe-Beta-150, and ring-rearrangement of **4 + 5** to **3** occurred in the case of using mildly acidic catalysts and mainly in the reaction catalyzed by mesoporous Ce composite mesoporous catalyst [6]. When starting the reaction from isopulegol and benzaldehyde using mesoporous Ce composite as a catalyst at 70 °C, it was observed [6] that the maximum amount of tetrahydropyran, 92 mol%, was formed with isopulegol conversion of 96%. Thereafter the conversion of tetrahydropyran was 24% within 120 min, out of which about 8 mol% was converted to dioxinol in addition to the formation of other products, such as dehydration product [6]. In the two-step synthesis method, the addition of 0.1 g of fresh mesoporous Ce composite facilitated a rapid transformation of tetrahydropyran and its conversion in 30 min was 23% corresponding to the formation of dioxinol about 15 mol%. In the current study, highly acidic catalysts, such as H-Beta-25, Amberlite 120H and Smopex-101, did not catalyze the desired ring-rearrangement of tetrahydropyran to dioxinol. Moreover, formation of unidentified products and dehydration of tetrahydropyrans were observed using these catalysts at higher reaction temperatures.

4. Conclusions

Synthesis of dioxinol exhibiting analgesic activity was investigated in this work via a two-step synthesis protocol including Prins cyclization of isopulegol with benzaldehyde and subsequent ring-rearrangement. The first step, selective synthesis of tetrahydropyran was performed over mesoporous Ce composite catalyst. Total conversion of isopulegol was achieved within 1 h and the selectivity toward tetrahydropyrans and dioxinol was 93% and 3%, respectively. The second step, transformation of tetrahydropyran over different acidic and basic catalysts was then studied. Different types of acidic catalysts, such as a proton form of zeolite Beta-25, a strongly acidic cation exchange resin Amberlite-120H, sulphonated Smopex-101 catalyst, Lewis acidic γ-alumina and a basic catalyst, e.g. magnesium oxide, were tested. In addition, experiments were also performed with bifunctional, metal modified mesoporous Ce composite and Cs-Beta-25 and Cs-MCM-41 catalysts.

Brønsted acidic catalysts, Amberlite 120H and Smopex 101 did not result in any transformation of tetrahydropyrans at lower reaction temperature, while formation of the undesired dehydration products and some unidentified products were observed at higher temperatures. Lewis acidic alumina catalyst was inactive in the transformation of tetrahydropyrans. Backward transformation of the desired dioxinol to tetrahydropyrans was observed over a basic magnesium oxide.

The desired ring-rearrangement, transforming tetrahydropyran to dioxinol was observed in the reaction catalyzed by mesoporous Ce composite catalyst, which exhibited both, mild acidic and basic properties. Dioxinol formation was also observed after addition of the fresh ceria catalyst even if after some time, dioxinol was transformed back to tetrahydropyran and to unidentified products. The highest achieved selectivity to the desired dioxinol was 36% over mesoporous Ce composite catalyst significantly improving the previously reported values for direct synthesis of dioxinol from isopulegol and benzaldehyde.

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References

[1] S.Yu. Kubrakova, I.V. Il'ina, A. Pavlova, D. Korchagina, O. Yarovaya, T. Tolstikova, K.P. Volcho, N.F. Salakhutdinov, Med. Chem. Res. 23 (2014) 1709–1717.
[2] I.V. Il'ina, D.V. Korchagina, K.P. Volcho, N.F. Salakhutdinov, Russ. J. Org. Chem. 46 (2010) 1002–1005.
[3] A. Torozova, P. Mäki-Arvela, A. Aho, N. Kumar, A. Smeds, M. Peurla, R. Sjöholm, I. Heinmaa, D.V. Korchagina, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, J. Mol. Catal. A: Chem. 397 (2015) 48–55.
[4] B.R. Rajeswara Rao, P.N. Kaul, K. Syamasundar, S. Ramesh, Flavour Fragr. J. 18 (2003) 133–135.
[5] M. Fuentes, J. Magraner, C. De Las Pozas, R. Roque-Malherbe, J. Pérez Pariente, A. Corma, Appl. Catal. 47 (1989) 367–374.
[6] M. Stekrova, P. Mäki-Arvela, N. Kumar, E. Behravesh, A. Aho, Q. Balme, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, J. Mol. Catal. 410 (2015) 260–270.
[7] K.M. Reddy, C. Song, Catal. Lett. 36 (1996) 103–109.
[8] N. Kumar, E. Leino, P. Mäki-Arvela, A. Aho, M. Käldström, M. Tuominen, P. Laukkanen, K. Eränen, J.-P. Mikkola, T. Salmi, D.Yu. Murzin, Microporous Mesoporous Mater. 152 (2012) 71–77.
[9] D. Kubicka, N. Kumar, P. Mäki-Arvela, M. Tiitta, V. Niemi, T. Salmi, D.Yu. Murzin, J. Catal. 222 (2004) 65–79.
[10] C.A. Emeis, J. Catal. 141 (1993) 347–354.
[11] M. Stekrova, N. Kumar, S.F. Diáz, P. Mäki-Arvela, D. Yu. Murzin, Catal. Today 241 (2015) 237–245.
[12] M. Stekrova, N. Kumar, A. Aho, I. Sinev, W. Gruenert, J. Dahl, J. Roine, S.S. Arzumanov, P. Mäki-Arvela, D. Yu Murzin, Appl. Catal. A: Gen. 470 (2014) 162–176.
[13] K.M. Wong, N. Hadi, T.Y. Abdul, R. Zainab, Phys. J. Ind. Phys. Soc. A7 (2004) 0211-1–0211-5.
[14] E. Bourgeat-Lami, P. Massiani, F. Di Renzo, P. Espiau, F. Fajula, T. Des Courières, Appl. Catal. 72 (1991) 139–152.
[15] T. Sano, Y. Uno, Z.B. Wang, C.-H. Ahn, K. Soga, Microporous Mesoporus Mater. 31 (1999) 89–95.
[16] R. Mokaya, Chem. Commun. (2000) 1891–1892.
[17] Y. Oumi, R. Mizuno, K. Azuma, S. Nawata, T. Fukushima, T. Uozumi, T. Sano, Microporous Mesoporus Mater. 49 (2001) 103–109.
[18] Y. Oumi, S. Nemoto, S. Nawata, T. Fukushima, T. Teranishi, T. Sano, Mater. Chem. Phys. 78 (2003) 551–557.
[19] D.Yu. Murzin, Chemical Reaction Technology, De Gruyter, Berlin, 2015, pp. 428.

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