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One-pot synthesis of a new potential analgesic over bifunctional palladium/amberlyst catalysts

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Abstract

(−)-(2*S*,3*S*)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride was directly dehydroxylated to the new opioidic (−)-(2*R*,3*R*)-[3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethyl-amin hydrochloride over Pd containing Amberlyst-15. The obtained product exhibits pronounced analgesic efficiency. Two reaction steps are involved in this one-pot synthesis: dehydration of the starting tertiary alcohol followed by hydrogenation of the obtained olefin (*Z* + *E*)-(*S*)-[3-(3-methoxy-phenyl)-2-methyl-pent-3-enyl]-dimethyl-amine hydrochloride. The dehydration of the alcohol occurs only in the presence of an Amberlyst resin as solid acid catalyst, which also serves as support for the hydrogenation component Pd. Surprisingly, only such a relatively simple well known Pd/Amberlyst system provides excellent results for this complicated one-pot conversion. Other acidic heterogeneous catalysts did not show catalytic performance for this kind of reaction. The various reaction parameters of this one-pot dehydroxylation reaction were optimized using a statistical test design program.

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1. Introduction

Highly efficient analgesic compounds derived from morphine, the so called opioids, have been used for many years as analgesics for the treatment of pain, although they give rise to a series of side effects, for example addiction and dependency, respiratory depression, gastrointestinal inhibition and obstipation [1]. They can therefore be used over an extended period of time or in higher dosages only as a subject of special precautions [2]. The main objective of the opioid-research exists in development of substances having an analgesic effect which are suitable for the treatment of severe pain without causing substantial side effects. For example the drug Tramadol, the (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol (**1**) (Scheme 1) possesses a special position amongst centrally acting analgesics, since this active ingredient gives rise to a pronounced inhibition of pain without the side effects which are known from other opioids [3]. Tramadol is a racemate and consists of identical amounts of the (+)- and (−)-enantiomers. Investigations have shown that both enantiomers contribute to the analgesic effect [4].

Certain derivatives of tramadol such as dimethyl-(3-aryl-butyl)-amines (**2**) (Scheme 2) exhibit enhanced analgesic effects compared to the original compound. The increase of the analgesic potency was obtained by the removal of a tertiary hydroxy group as illustrated in Scheme 3. The (+)-enantiomer **2** is at least equipotent to morphine, whereas the (−)-enantiomer **2**, having a dual mechanism of action like tramadol, has an analgesic potency between morphine and tramadol [4].

Scheme 3 shows two important reaction steps involved in the synthesis of (−) or (+)-dimethyl-(3-aryl-butyl)-amines **2**, i.e. the dehydration of the tertiary alcohol **3** and the hydrogenation of the formed alkene **4**. Both steps require the use of catalysts. Starting from (−)-(2*S*,3*S*) or (−)-(2*S*,3*R*)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, denoted by **3-HCl**, with a protected hydroxyl function and in form of a physiologically compatible hydrochloride salt, the (−)-(*R*,*R*)-enantiomer **2-HCl** can be produced. However, using (+)-(2*R*, 3*R*)- or (−)-(2*R*,3*S*)-**3-HCl** as starting stereoisomers, the (+)-(*S*,*S*)-**2-HCl** can be obtained.

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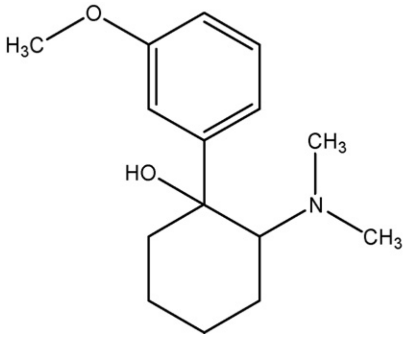
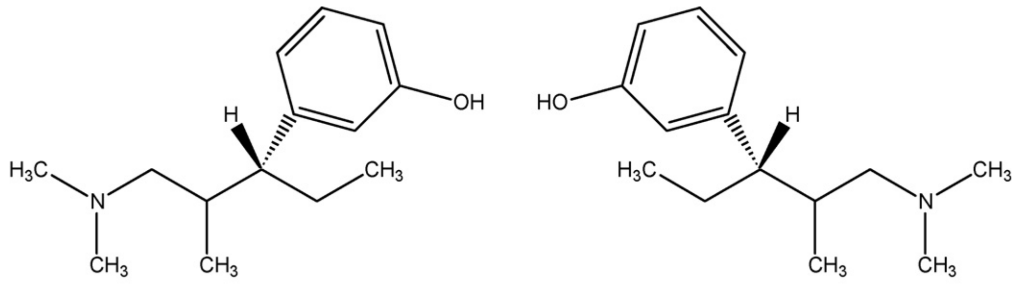


Scheme 1. Tramadol.

From former investigations of Grünenthal GmbH it was know that the dehydration occurs between the C3 and C4 carbon atoms and not between the C2 and C3 carbon atoms. In the presence of homogeneous concentrated hydrochloric acid, the dehydration of the tertiary alcohol **3-HCl** takes place at 60 °C [5]. The yield of the resulting dehydrated intermediate **4-HCl** is only in the range of 40%. As hydrogenation catalysts for the second reaction step, classical, homogeneous palladium-chloride-solutions, as well as palladium on charcoal can be applied. This homogeneously catalyzed process causes corrosion problems and produces large volumes of chemically reactive waste streams. Therefore, a pure heterogeneously catalyzed procedure is desirable to overcome those drawbacks.

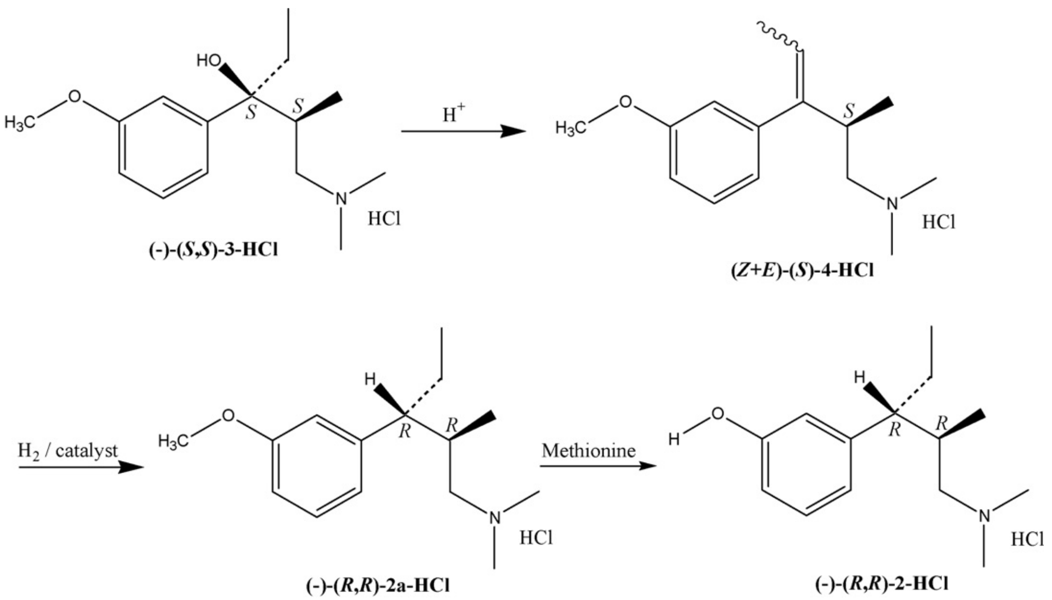
Due to the importance of these new analgesic substances **2**, a strongly evolving production demand is expected. Hence, a simple economical and ecological procedure for their synthesis is desirable. From economical, ecological and technical point of view, heterogeneously catalyzed processes are favored over the homogeneously catalyzed reaction routes due to the ease of separation, the reusability and the prevention of salt formation due to the neutralization step. The requirement for using non-toxic, polar solvents like ethanol or acetone, in which the hydrochlorides are soluble, needs a highly demanding catalyst.

Brønsted acidic heterogeneous catalysts such as Nafion and Nafion resin/silica nanocomposite materials [6–8], Amberlyst [9], zeolites, metal phosphates or ZrO_2/WO_3 and/or ZrO_2/SO_4^{2-} [10–13] could be considered as alternatives to hydrochloric acid, in the dehydration step of **3-HCl**. Besides palladium on charcoal, other noble metal supported heterogeneous catalysts might be applied for the hydrogenation of the intermediate **4-HCl**.



(-)-(*R*,*R*)-2 **(+)-(*S*,*S*)-2**

Scheme 2. (−)- and (+)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenole (**2**).



Scheme 3. Reaction steps involved in the synthesis of the new analgesic **2**.

The present investigation is devoted to the direct, heterogeneously catalyzed dehydroxylation of **3-HCl** combining both reaction steps, i.e. dehydration and hydrogenation eventually in a one-pot reaction. For this purpose, bifunctional heterogeneous catalysts possessing appropriate Brønsted acidic sites as well as precious metal active centers have been developed. Catalysts of various acidic strength have been tested for the dehydration reaction, and afterwards the selected material has been doped by palladium. Finally, the reaction parameters of this one-pot synthesis have been optimized to maximize the yield of **2a-HCl**.

2. Experimental

2.1. Catalysts preparation and analyses

The acid ion-exchange resin Amberlyst-15 was purchased from Fluka (No. 06423) Prior to use, the resin was dried at 120 °C in vacuum for 4 h. The impregnation of Amberlyst-15 with palladium was carried out by means of suspending 2 g of carrier in 20 g of water, followed by adding the required amounts of $[Pd(NH_3)_4](NO_3)_2$. The suspension was heated to 80 °C and stirred for 24 h, then the catalyst was filtered off, washed and dried at 110 °C under air. A part of the material obtained in this manner was subsequently reduced at 140 °C (heating rate 1 °C/min) by a 10 vol.% hydrogen/argon mixture. The concentrations of Pd in the bifunctional catalysts were determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES), using a Spectroflame D (Spectro Analytic) instrument.

The other heterogeneous catalysts applied for this reaction have been provided by various companies, purchased from catalyst providers, or synthesized by well-known production procedures.

The chromatographic analysis was performed in a HP 6890 gas chromatograph equipped with a flame ionization detector using a FS-SE54 capillary column (60 m × 0.25 μm). Nitrogen was used as carrier gas, the detector temperature was at 250 °C and a volume of 1 μl sample was injected. The temperature program was defined as a heating between 50 °C and 270 °C with a ramp of 5 °C/min followed by 10 min isotherm. Samples were analyzed using methyl undecanoate as internal standard. The enantiomeric purity of the compounds was determined in the laboratory of Grünenthal GmbH using capillary electrophoresis.

2.2. Reaction procedure

The reactor, a 75-ml stainless steel autoclave, equipped with a pressure indicator and a magnetic stirrer, was heated by an oil bath. Typically, 0.5 g (1.7 mmol) (−)-(2*S*,3*S*)-**3-HCl** and 0.25 g Pd-Amberlyst-15 were charged into the autoclave. After careful evacuation, 10 ml of ethanol and 4 bar H_2 were added under argon atmosphere. The three-phase reaction mixture was maintained at 150 °C for 4 h while stirring. The total pressure of the system at 150 °C amounted to ca. 10–12 bar. Subsequently, the reactor was cooled down to room temperature.

With respect to the deactivation of the catalyst by leaching, the product mixture was checked for Pd by means of ICP analysis after the reactions. No Pd was detected at all. That means the catalyst is stable and does not show any leaching.

3. Results and discussion

For the dehydration of the tertiary alcohol **3-HCl** in ethanol under reflux conditions, various heterogeneous Brønsted acid catalysts were examined. Crosslinked, vinylaromatic polymers functionalized with strongly acidic functional groups, known as Amberlyst-resins, were found to be able to dehydrate the alcohol **3-HCl**. Surprisingly, other catalyst types such as strong acidic Nafion resin or Nafion silica/resin nanocomposite materials, clays (K-10, KP-10, KSF), zeolites (H-BEA, H-Y, MCM-41), silica-supported heteropolyacids (i.e. $H_3PW_{12}O_{40}\cdot nH_2O$ on silica) or acidic oxides (SO_4^{2-}/ZrO_2, WO_3/ZrO_2) did not show any catalytic activity in this dehydration reaction. It seems that the catalysis of the reaction requires an appropriate Brønsted acidity as provided by the Amberlyst-resins.

Alcohol dehydration reactions occur generally by heating the alcohol in the presence of a strongly acidic compound. The necessary conditions are usually drastic for primary alcohol, milder for secondary and even more for tertiary alcohol [14]. It is also known that Amberlyst-15 is weaker acidic than the perfluorinated resin sulfonic acid Nafion, the value of the Hammett acidity function (H_0) ranges from −11 to −13 for Nafion while it amounts to about −2.2 for Amberlyst 15 [8]. Silica supported heteropolyacids, which are efficient catalysts for the dehydration of secondary alcohols, e.g. cholesterol [15], possess greater acidity than that of *p*-toluenesulfonic acid [16]. Zeolites did not show any catalytic performance in this reaction, which might be explained by the bulkiness of the alcohol **3-HCl** which cannot reach the active sites inside the zeolitic pore system.

3.1. Study of the reaction parameters

Applying Amberlyst-15 (AM-15), which was found to be the only suitable solid acid catalyst for this dehydration reaction, only 54% conversion of tertiary alcohol **3-HCl** was achieved when the reaction was carried out in refluxing ethanol during a long reaction time of 24 h and using a mass ratio of alcohol to catalyst of 2 to 1.

Table 1 illustrates that high conversion values (>95%) were obtained under slightly elevated pressure (4 bar) at 150 °C after 4 h contact time. The selectivity to the alkene **4-HCl** depicted in Table 1 refers to a mixture of the formed *Z*- and *E*-isomers. The ratio of *Z*- to *E*-isomer (70:30) could not be influenced by any reaction parameter. Moreover, the amount of the solvent ethanol did not influence significantly the obtained results, i.e. the same selectivity to *Z*- + *E*-**4-HCl** of 96% was obtained either in 10–20 ml or in 40–50 ml ethanol. Slightly lower initial **3-HCl** conversion was observed by using a more diluted solution. However, the activity of the reused catalyst decreases more rapidly in concentrated than under diluted reaction

Table 1
Dehydration of **3-HCl** over Amberlyst-15

Ethanol (ml) ($V_{autoclave}$ = 75 ml)	Run	Conversion (%) (**3-HCl**)	Selectivity (%) (*Z*- + *E*-**4-HCl**)
10–20	1	99	96
10–20	2	42	88
40–50	1	95	96
40–50	2	76	96

Reaction conditions: 1.0 g (3.4 mmol) **3-HCl**; 0.5 g Amberlyst-15, $T = 150$ °C, $t = 4$ h; **1** = first reaction cycle; **2** = second reaction cycle after washing of the catalyst with ethanol, $p_{max} = 4$ bar.

conditions. Using concentrated solutions (10 or 20 ml) in a second reaction cycle, the conversion drops from 99 to 42%, while in the case of a more diluted solution (40 or 50 ml) the decline was only from 95 to 76%.

Nevertheless, the target of the present work was the development of an one-pot process for the dehydroxylation of **3-HCl** to the desired analgesic **2a-HCl**. According to our preliminary studies of the first reaction step, i.e. the dehydration of the tertiary alcohol **3-HCl**, only Amberlyst-15 was selected as support. This material has to be impregnated with a precious metal in order to obtain a bifunctional catalyst, which is also able to hydrogenate the intermediate **4-HCl**. In the field of fine chemicals, palladium is arguably the most versatile and the most widely applied catalytic metal [17]. Besides, palladium is the most active metal for the saturation double bonds in conjugation with an aromatic ring as it is the case for **4-HCl**. Furthermore, under certain reaction conditions palladium is inactive for the hydrogenation of most aromatic rings.

The impregnation of Amberlyst-15 was carried out by using $[Pd(NH_3)](NO_3)_2$ solution in water, as described elsewhere [18–20]. The resulting Pd/Amberlyst-15 catalysts were found to be very efficient for the hydrogenation of the intermediate **4-HCl** to **2-HCl**. For example, using an Amberlyst-15 catalyst loaded with 1% of Pd at 150 °C, the hydrogenation of *Z*-**4-HCl** in the presence of ethanol and a three fold molar excess of hydrogen leads to very high conversion with >98%, while the selectivity to the desired enantiomer (−)-(*R*,*R*)-**2a-HCl** amounts 76%. According to the analytical studies by means of capillary electrophoreses the researchers of Grünenthal GmbH found only the (−)-(*R*,*R*)-**2a-HCl** isomer. The only by-product is the diastereomer (2*R*,3*S*)-**2a-HCl** which does not have any analgesic potential. The 2*S*-**2a-HCl** stereoisomer was not observed in the reaction mixture. Furthermore, formation of diethyl ether could not be observed.

In the following, the results obtained in this one-pot dehydroxylation of the starting alcohol **2a-HCl** will be presented. The influence of the noble metal loading, the temperature as well as the hydrogen pressure on the reaction will be discussed, followed by the final optimization of the reaction parameters.

Fig. 1 depicts the dependence of the catalytic activity upon the Pd-amount on Amberlyst-15. The hydrogenation of the *in situ* produced isomers *Z*- + *E*-**4-HCl** does not occur over a catalyst with low palladium loading of e.g. 0.1 wt%.

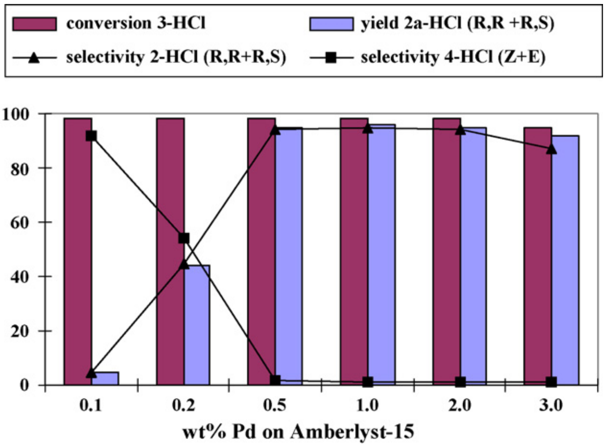


Fig. 1. Influence of Pd-loading on the one-pot reaction (reaction conditions: 0.5 g (1.7 mmol) (*S*,*S*)-**3-HCl**, 10 ml ethanol, 0.25 g Pd/AM-15, 4 bar H_2, $T = 150$ °C, $t = 4$ h).

Increasing the palladium loading between 0.1 and 0.5% increases the yield of **2a-HCl** (*R*,*R* + *R*,*S*) whereas the selectivity to the intermediate **4-HCl** (*Z* + *E*) decreases. Thereby we focused on the activity of the catalyst and less on the selectivity of the single stereoisomers. Between 0.5 and 2 wt% loading, the catalytic activity hardly changes, while beyond 2 wt% both conversion and selectivity to **2a-HCl** product starts to decrease. This drop can be explained by the decreasing number of the acid sides in the ion exchanger Amberlyst-15 due to the substitution of the protons by Pd^{2+}. One can therefore conclude that the bifunctional nature of the catalyst is necessary for the desired catalytic performance, i.e. the availability of both acidic and noble metal sites in an appropriate ratio is required. For the final optimization of the reaction parameters, a catalyst loaded by 1% Pd will be taken since this is the lowest loading level, which can safely ensure high conversion and selectivity to the desired products.

The reduction of the catalysts prior to the reaction, in the view to decompose the Pd-tetramine complexes, did not have any influence on the catalytic activity. The same results were obtained over Pd/Amberlyst-15, which was reduced under a 10 vol.% H_2 in Ar atmosphere at 140 °C as over the unreduced catalyst. In the course of the reaction, the catalyst is reduced by the reactant, hydrogen, which seems to yield similar active sites, which are formed during the pre-reduction step.

After the reduction at 140 °C in hydrogen atmosphere, Pd must be mostly present as completely reduced, but could also be partially present as unreduced Pd(II), bonded to the HSO_3 groups of the Amberlyst. The presence of unreduced Pd species in similar catalyst systems was explained earlier [20] by a relatively low reaction temperature (higher reduction could not be used because of the temperature sensitivity of the resin), resulting in an incomplete decomposition of the tetramine complex. The acidic strength of the catalyst after impregnation could not be determined by TPD. Nevertheless, while the exact content of acid groups is unknown, during impregnation the remaining acid groups are not affected.

The reaction temperature had a tremendous impact on the direct dehydroxylation of **3-HCl**. Fig. 2 shows that higher

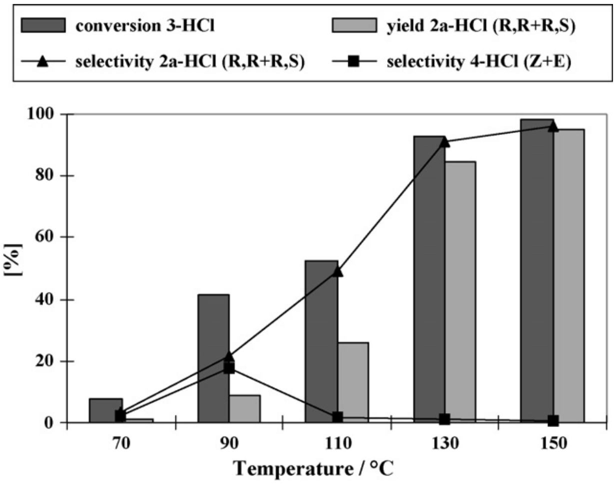


Fig. 2. Influence of temperature on the one-pot reaction (reaction conditions: 0.5 g (1.7 mmol) (*S*,*S*)-**3-HCl**, 0.25 g Pd/AM-15 with 1% Pd, 10 ml ethanol, 4 bar H_2, $T = 150$ °C, $t = 4$ h).

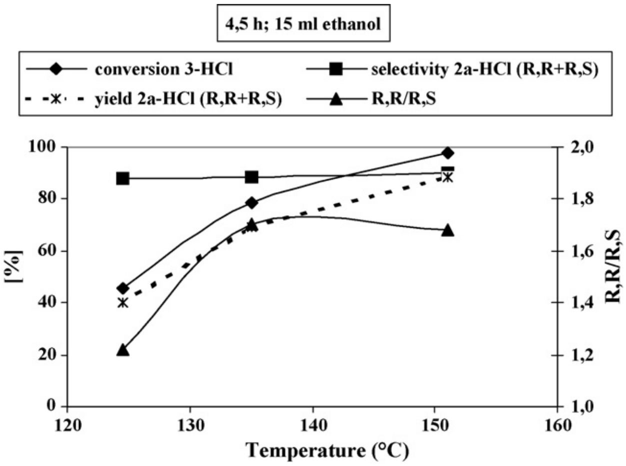


Fig. 4. Influence of reaction temperature (reaction conditions: 0.5 g (1.7 mmol) **3-HCl**, 0.25 g catalyst (1% Pd/AM-15), 2 bar H_2).

temperatures favor the one-pot process; high conversion was achieved at temperatures above 130 °C.

It has to be noted here that the temperature resistance of the Amberlyst-15 support limited the maximum reaction temperature. Between 110 °C and 150 °C, the conversion of **3-HCl** increased along with the selectivity to the mixture of stereoisomers **2a-HCl**. The obtained reaction mixture contains only a small amount of non-hydrogenated alkene *Z*- + *E*-**4-HCl**. At temperatures below 90 °C the hydrogenation is not favored at all.

Moreover, it has been found that hydrogen pressure does not affect the reaction when molar excess is more than two fold compared with the initial **3-HCl** concentration.

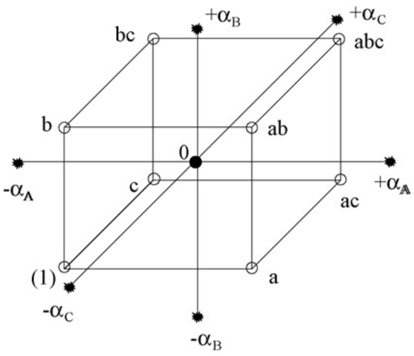
3.2. Optimization of the reaction conditions

Statistical optimization of the operating conditions was carried out in order to maximize the yield of the **2a-HCl** products. Based on the preliminary results described above, a 1 wt% Pd content of the catalyst was chosen and the initial pressure of hydrogen was fixed at 2 bar. In addition to the temperature, which prevailed to affect significantly the reaction, the reaction time and the quantity of the solvent, were varied according to a statistical experimental design pattern, called Central Composite Design [21]. Each parameter, denoted by A, B and C for temperature, time and solvent amount respectively, was varied at five levels according to the design pattern depicted in Fig. 3. The design involves a center point (0), two extreme values for each variable, denoted by $-\alpha$ and $+\alpha$, while the middle of the experimental field is covered by eight experimental points forming a cube, of which the edges represent the combination of levels marked by -1 and $+1$ in the table. Thus altogether 15 experiments were carried out.

The structure of the experimental design allows comparing the experimental results obtained at the extreme values of each variable with that of the center point. The investigated responses, viz. conversion of **3-HCl**, selectivity and yield to **2a-HCl** products, including both *R*,*R* and *R*,*S* enantiomers, as well as the ratio of *R*,*R* over *R*,*S* are depicted against the experimental variables, i.e. temperature, reaction time and solvent volume in Figs. 4–6, respectively.

The temperature increase results in strongly increasing conversion of **3-HCl** in the investigated range (Fig. 4) whereas the selectivity to **2a-HCl** maintains. The ratio of *R*,*R* over *R*,*S* enantiomers increases sharply between 125 °C and 135 °C, while at higher temperature a slight drop could be observed.

The reaction time hardly influences the conversion and selectivity as well as consequently the yield, while the *R*,*R* over *R*,*S* ratio drops significantly above 4.5 h (Fig. 5).



Levels / Variables	- α	- 1	0	+1	+ α
Temperature (A), °C	119	125	135	145	151
Time (B), h	3	3.6	4.5	5.1	6
Solvent (C), ml	5	9	15	21	25

Fig. 3. Central composite design [21] for the optimization of the operating variables.

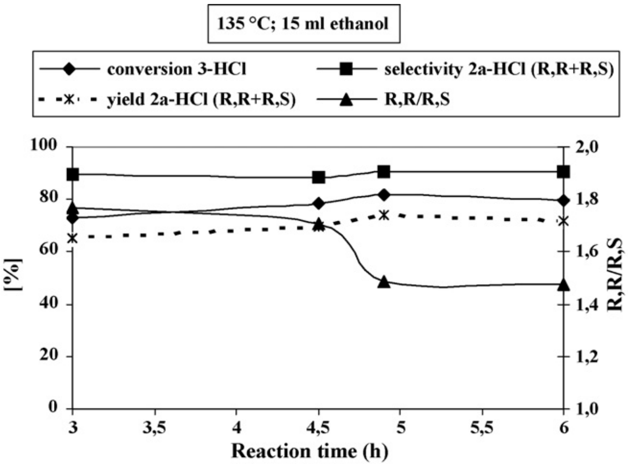


Fig. 5. Influence of reaction time (reaction conditions: 0.5 g (1.7 mmol) **3-HCl**, 0.25 g catalyst (1% Pd/AM-15), 2 bar H_2).

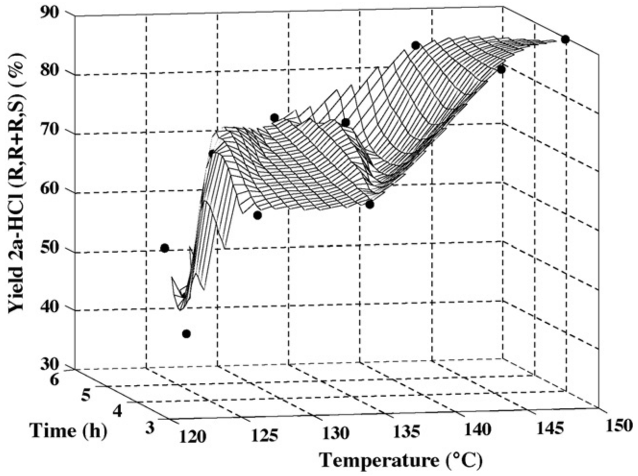


Fig. 7. Dependence of **2a-HCl** yield from reaction temperature and time (reaction conditions: 0.5 g (1.7 mmol) **3-HCl**, 0.25 g catalyst (1% Pd/AM-15), 2 bar H_2).

Fig. 6 shows that a solvent volume of more than 9 ml does not have a significant effect on the major reaction characteristics. The *R*,*R* to *R*,*S* ratio reaches a maximum at 15 ml, therefore the ratio of 15 ml of ethanol to 0.5 g **3-HCl** is considered to be optimal.

The yield of the **2a-HCl** enantiomers is represented as a function of time and reaction temperature on a 3D chart (Fig. 7) for all the experimental results that were taken at a solvent volume higher than 9 ml, i.e. including also the experimental points located at the cube of the design. One might observe in Fig. 7 that the reaction temperature is the most influencing variable and that the yield monotonously increases with the temperature.

Unfortunately, the stability of Amberlyst-15 sets the constraint for maximum temperature around 160 °C. There seems to be a slight additional effect brought in by the reaction time i.e. slight maxima arise in the middle of the investigated time range around 4 h.

Therefore, in order to maximize the yield of *R*,*R* **2a-HCl** enantiomers, the following experimental conditions are proposed: temperature 150 °C, reaction time 4 h, whereas the solvent to reactant ratio being 15 ml for 0.5 g. The results of the direct dehydroxylation obtained under those optimized reaction conditions are as follows: 98% conversion of **3-HCl** 91% yield of **2a-HCl** (*R*,*R* + *R*,*S*) and 64% selectivity to the desired *R*,*R* enantiomer.

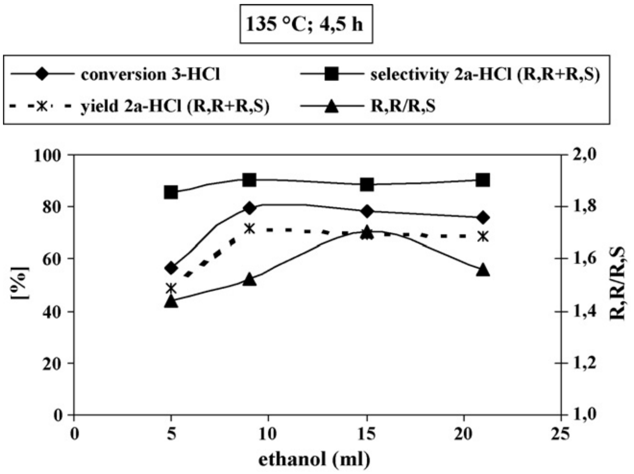


Fig. 6. Influence of solvent quantity (reaction conditions: 0.5 g (1.7 mmol) **3-HCl**, 0.25 g catalyst (1% Pd/AM-15), 2 bar H_2).

Unfortunately, the catalyst was found to deactivate. After the first recycle of the catalyst, the yield of **2a-HCl** (*R*,*R* + *R*,*S*) decreased from 91% to ca. 50%. The deactivation of the catalyst cannot be explained by the instability of the resin at the reaction temperature of 150 °C in ethanol. As described in literature [9] for macroreticular resins, operation at temperatures higher then 150 °C may cause desulfonation leading to a release of sulfonic acid as well as a drop in the activity. According to the ICP measurements of the used Pd/Amberlyst-15, the catalyst did not shown any loss of sulfur. Consequently, there is no deactivation of the catalyst by desulfonation under the optimized reaction conditions in ethanol as solvent. The Pd content of the catalyst was also found to remain constant after the reaction. Therefore, leaching of Pd from the support could also be excluded. The deactivation of the catalyst probably arises from the formation of coke on the resin. Subsequently, the dehydration of **3-HCl** is mainly affected. Some preliminary experiments on the regeneration behaviour of the Pd/Amberlyst-15 catalysts were carried out. After recovery, the catalyst was washed with acetone, stirred in a 0.1N aqueous HCl solution at 80 °C for 2 h, washed again with distillated water and dried at 120 °C in vacuum for 4 h. Unfortunately, the original activity could not yet be restored completely, i.e. the yield of the **2a-HCl** in the second reaction cycle dropped from 91% to 80%. But there was already a tremendous improvement and there is a good chance to achieve the original activity by optimization of the regeneration conditions.

4. Conclusions

(−)-(2*S*,3*S*)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride was directly dehydroxylated in the presence of hydrogen to the analgesic (−)-(2*R*,3*R*)-[3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethyl-amin hydrochloride over a Pd/Amberlyst-15 catalyst using ethanol as solvent. The dehydration of the alcohol occurs only in the presence of Amberlyst resins as solid acid catalysts. The direct dehydroxylation could be carried out over a bifunctional catalyst, i.e. Amberlyst-15 loaded with palladium. It was found that the temperature significantly affects the conversion of the starting material. The optimized metal loading and reaction conditions are as follows: 1.0 wt% Pd (0.25 g), 150 °C, 0.5 g reactant dissolved in 15 ml ethanol and 4 h contact time.

Besides the possibility to carry out the dehydroxylation in a "one-pot" manner, the Pd/Amberlyst-15 catalyst brings another advantage compared to hydrochloric acid, namely its the heterogeneous nature. It prevents problems associated to the homogeneous systems such as neutralization and handling of the resulting salt formation. Although the catalyst could be reactivated with diluted hydrochloric acid and recycled, the original activity could not be restored completely at the present time.

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