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Heterogeneous diastereoselective hydrogenation of pyridine and corresponding enamine covalently bound to pantolactone

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Abstract

The diastereoselective hydrogenation of 2-methyl nicotinic acid covalently bound to pantolactone was studied over supported metallic catalysts. With this chiral auxiliary, a two-steps reaction was observed with formation of tetrahydropyridine intermediate. The influence of different reaction parameters on the diastereoselectivity of the hydrogenation of pyridine and enamine substrates was studied.

Keywords: Hydrogenation; Pyridine; Pantolactone; Nicotinic

1. Introduction

The applicability of diastereoselective hydrogenation catalyzed by heterogeneous metallic catalysts has been largely reported in the literature. C=C, C=O, C=N and aromatic rings were reduced using this route and moderate to excellent *de*'s were achieved [1–4]. Previous reports on the diastereoselective hydrogenation of methyl-2-nicotinic acid derivatives showed that with amino acids such as proline or pyroglutamic ester used as chiral auxiliaries, *de* up to 30% could be achieved [5,6]. Pantolactone has also been frequently used as chiral auxiliary for different asymmetric reactions [7–9]. Here, we report the results obtained with pantolactone as chiral auxiliary for the hydrogenation of methyl-2-nicotinic acid. The influence of the formation during the reaction of partially saturated species on the final diastereoselectivity was checked in more detail.

2. Experimental

NMR ^{1}H and ^{13}C spectra were recorded on AC 250 Bruker spectrometers using residual solvent as reference ($CDCl_3$: δH: 7.24 ppm, δC: 77 ppm). FT-IR spectra were recorded on a Bruker Vector 22 apparatus. Elemental analyses were performed at the "Service Central d'Analyse" of CNRS. The catalysts used for hydrogenation were 4.2% Rh/C (Aldrich, reference 20,616-4), 3.8% Rh/Al_2O_3 (Aldrich, reference 21,285-7), 4.6% Ru/C (Aldrich, reference 20,618-0), 2.3% Ru/Al_2O_3 (Aldrich, reference 22,853-2), 4.9% Pd/C (Aldrich, reference 20,568-0), 0.7% Rh–3.3% Pd/C (Hereaus, reference K-0234).

2.1. (R)-(2-Methylnicotinyl)pantolactone *1*

To a stirred solution of methyl-2-nicotinic acid chloride (5.7 g) in chloroform (15 ml) under argon at 0 °C were added successively, 4.75 g of pantolactone (1 equiv) in 15 ml of chloroform and 15.2 ml of triethylamine (3 equiv). The stirring was continued for 8 h at 80 °C. The organic layer was washed with water (3 × 30 ml), dried ($MgSO_4$) and concentrated to give a brown oil that crystallized. Recrystallization in ethanol gave 4.1 g of a white crystal (yield = 45%). ^{1}H RMN δ (ppm): 8.65 (dd, 4.8 and 1.8 Hz, 1H); 8.26 (dd, 7.9 and 1.8 Hz, 1H); 7.23 (dd, 7.9 and 4.8 Hz, 1H); 5.6 (s, 1H); 4.1 (s, 2H); 2.85 (s, 3H); 1.30 (s, 3H); 1.20 (s, 3H); ^{13}C RMN δ (ppm): 172.1; 165.2; 160.6; 152.6; 138.8; 124.1; 121.1; 76.3; 75.8; 40.5; 25.1 23.2; 20.2. GC–MS: *m*/*z* 65, 92, 120 (100%), 249 (M). IR (cm^{-1}): 3050; 2960; 2881; 1782; 1726; 1585; 1469; 1291; 1133. $[\alpha]_D^{20}$: +8 (c = 1, $CHCl_3$). Anal. Calcd. for $C_{13}H_{15}NO_4$: C 62.2%, H 6.0%, N 5.6%; Found: C 62.6%, H 6.0%, N 5.6%. mp: 100–101 °C.

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2.2. (R)-(2-Methyltetrahydronicotinyl)pantolactone 2

In a stainless steel autoclave, 1.42 g of **1** (5.7 mmol) in 50 ml ethanol and 350 mg of 4.2% Rh/C were introduced. Eighty milliliters of ethanol were added and the autoclave was pressurized to 50 bar. After 1 h stirring, the reaction was stopped. The composition of the solution determined by gas chromatography (GC) analysis was 1% of **1**, 75% of **2** and 24% of **3a** + **3b**. After purification on silica, 0.7 g of a white solid was obtained (GC analysis: 95% of **2** and 5% of **1**).

2.3. Hydrogenation reaction and analysis

Hydrogenation of the substrates was carried out in a 300 ml stainless steel autoclave equipped with a magnetically driven turbine stirrer under 50 bar and at room temperature. Standard experiments were carried out using the substrate dissolved in 130 ml ethanol in the presence of 10–12 mol% of metal as the catalyst. Sampling of the reaction mixture, to follow reaction progress, was possible and the conversion and selectivity were determined from gas chromatography analyses, which were performed using a J&W DB1701 column (errors = ±5%). The reaction products were identified by GC–MS analysis.

3. Results and discussion

1 was prepared by reaction of methyl-2-nicotinic acid chloride with pantolactone in 45% yield. The hydrogenation of the substrate in ethanol at room temperature and under 50 bar hydrogen gave partially hydrogenated intermediate **2** as well as the two *cis* isomers **3a** and **3b** (Fig. 1). Less than 5% of the corresponding *trans* isomers were detected.

Fig. 2 shows the product distribution as a function of time for hydrogenation of **1** over a 2.3 wt.% Ru/Al_2O_3 catalyst at 50 °C.

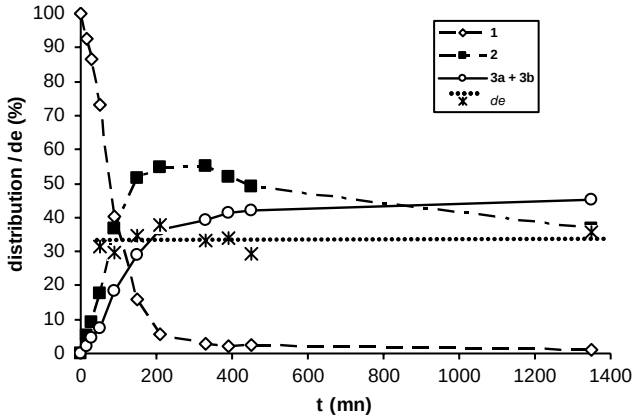

Fig. 2. Distribution of products vs. time of hydrogenation of **1** over Ru/Al_2O_3.

The piperidine derivatives **3a** and **3b**, which resulted from a *cis* hydrogenation of the heteroaromatic ring, were detected together with the enamine **2**. This intermediate was formed with a maximum yield of 55% and was progressively hydrogenated to the saturated ring, but 37% of partially hydrogenated compound **2** were still present after 24 h reaction. The *de* of the *cis* isomers was almost constant during the course of the reaction and reached 30% while the hydrogenation of the proline or the pyroglutamic derivatives yielded, respectively, 25 and 20% under the same conditions [5,6]. The initial reaction rate, amount of enamine **2** and diastereoisomeric excess obtained on Rh-, Ru- and Pd-based catalysts are given in Table 1.

Ruthenium catalysts supported on alumina or carbon as well as rhodium catalysts supported on alumina were little active (initial reaction rate lower than 4 mol h^{-1} mol_{met}^{-1}). The Pd/C and bimetallic Rh–Pd/C catalysts exhibited very high activity (11.7 and 17.2 mol h^{-1} mol_{met}^{-1}, respectively) while low reaction rates were observed in the hydrogenation of the proline derivative (0.5 and <0.1 mol h^{-1} mol_{met}^{-1},

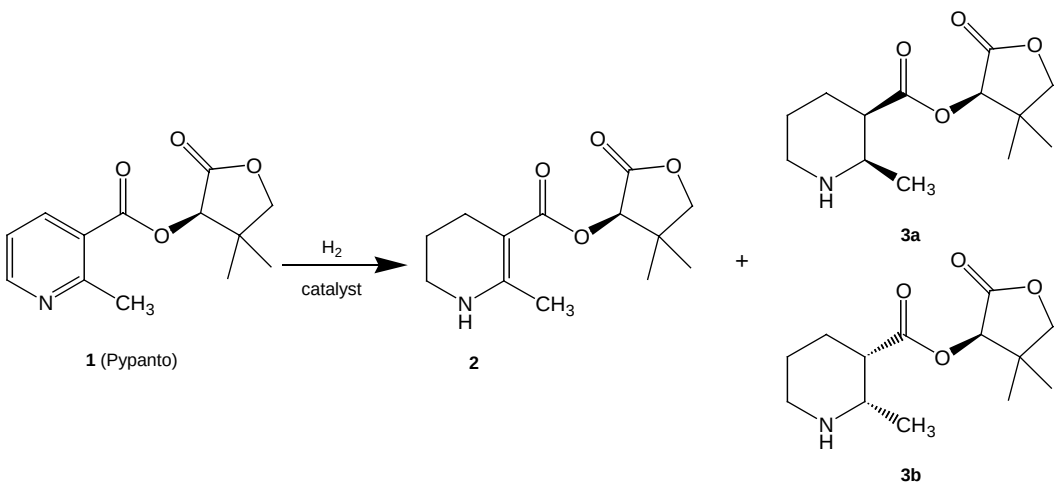

Fig. 1. Hydrogenation of (*R*)-(2-methylnicotinyl)pantolactone **1**.

Table 1
Hydrogenation of (*R*)-(2-methylnicotinyl)pantolactone **1**

Catalyst	Enamine **2** (%) (max → 24 h reaction)	r_i (mol h^{-1} mol_{met}^{-1})	*de* (%) (24 h)
4.2% Rh/C	70 → 30	19.2	30
3.8% Rh/Al_2O_3	87 → 60	4	17
4.6% Ru/C	65 → 20	3.2	30
2.3% Ru/Al_2O_3	55 → 37	3.5	30
4.9% Pd/C	69 → 6	11.7	32
0.7% Rh–3.2% Pd/C	72 → 7	17.2	30

Influence of the nature of metal catalyst on the intermediate **2**, the diastereoselectivity and the initial reaction rate of the hydrogenation (reaction conditions: 1.21 mmol of **1**, 0.168 mmol of the metal, 130 ml ethanol, 50 bar H_2, 50 °C).

respectively) [5]. The best activity was observed with carbon supported rhodium catalyst (19.2 mol h^{-1} mol_{met}^{-1}). Whatever the catalyst, a large amount of enamine was formed (65–87% at the maximum level) and this intermediate was then hydrogenated at different rates depending on the catalyst. Particularly, in the case of Pd-based catalysts, **2** reacted almost quantitatively while 30% were still present after 24 h on Rh/C. The diastereoselectivity decreased slightly during the reaction (about 5%) but surprisingly it was not affected by the nature of the metal or the support and it was in the same 30% range except with Rh/Al_2O_3 catalyst giving the highest amount of enamine (*de* = 17%).

The nature of the solvent had a significant influence on the initial reaction rate as shown in Table 2. In fact, using protic solvents that allowed the formation of hydrogen bonds between the solvent and the substrate, the reaction was faster (19.2 mol h^{-1} and 3 mol h^{-1} mol_{Rh}^{-1} in EtOH and CH_2Cl_2, respectively). The addition of a bulky amine (ethyl dicyclohexylamine (EDCA)) in alcoholic medium reduced the initial reaction rate. As previously observed for the proline modified substrate [5] and described for heterogeneous hydrogenation of pyridinium ring [10], the addition of acid increased the initial reaction rate. The diastereoselectivity was also slightly improved up to 40% by addition of 6.4 eq HCl/Rh.

The nature of the solvent affected also the formation of the tetrahydrogenated intermediate **2**. In ethanol, the enamine was formed up to 80% yield and after 24 h reaction time, 30% were still present. With addition of ethyldicyclohexylamine in the medium, 75% of **2** were obtained after only 40 min reaction time, and surprisingly, it was totally consumed after 24 h. In CH_2Cl_2 or with addition of a mineral acid in the medium, the maximum was 40% and 8%, respectively, and this intermediate was totally hydrogenated after only 2 h and 40 min, respectively.

Table 2
Hydrogenation of (*R*)-(2-methylnicotinyl)pantolactone **1**

Solvent	r_i (mol h^{-1} mol_{met}^{-1})	$\mathbf{2}_{max}$ (%) (*t*)[a]	*de* (%) (24 h)
EtOH	19.2	80 (40 min)	~30
CH_2Cl_2	3	8 (20)	~35
EtOH + 2.4 eq EDCA/Rh	14	75 (30)	~35
EtOH + 6.4 eq HCl/Rh	22	40 (35)	~40

Effect of the solvent on the initial reaction rate, the maximum amount of enamine and the final diastereoselectivity (reaction conditions: 1.21 mmol of **1**, 0.168 mmol of Rh, 130 ml ethanol, 50 bar H_2, 50 °C).

[a] Maximum amount of detected enamine, corresponding reaction time in parenthesis.

Table 3
Hydrogenation of (*S*)-nicotinyl prolinate

Catalyst	Max enamine (%)	*de* (%)
4.2% Rh/C Aldrich	20	35 → 13
9.8% Pd/C Selcat®	20	40 → 22

Effect of the catalyst on the intermediate and the diastereoselectivity (reaction conditions: 2.28 mmol of substrate, 0.315 mmol of metal, 130 ml MeOH, 50 bar H_2, RT).

Such partially hydrogenated species were also detected during the hydrogenation of nicotinic acid coupled with methyl prolinate. The diastereoselectivities obtained with Rh- and Pd-catalysts are reported in Table 3.

Whatever the metal catalyst, the enamine was detected up to 20% at maximum. At the beginning of the reaction, significant *de*'s (35–40%) were observed. Then, the enamine was hydrogenated to completion and simultaneously, the diastereoselectivity decreased considerably to modest *de* indicating a different mechanism of hydrogenation.

Since we observed fairly important amounts of partially hydrogenated intermediate with pantolactone as chiral auxiliary, we focussed on the hydrogenation of this enamine under different conditions (Fig. 3). **2** was prepared by hydrogenation of **1** over Rh/C catalyst for 1 h. After isolation and purification, the enamine was further hydrogenated over Pd/C catalyst that showed to be the most active (vide supra, Table 1). After 24 h in dichloromethane at 50 °C and under 50 bar H_2, the hydrogenation was complete but the diastereoisomeric excess did not exceed 15%. Moving to EtOH gave a lower reaction rate with slightly higher *de* (18%). Addition of HCl that should protonate the enamine, increased the reaction rate but yielded only the racemic compound.

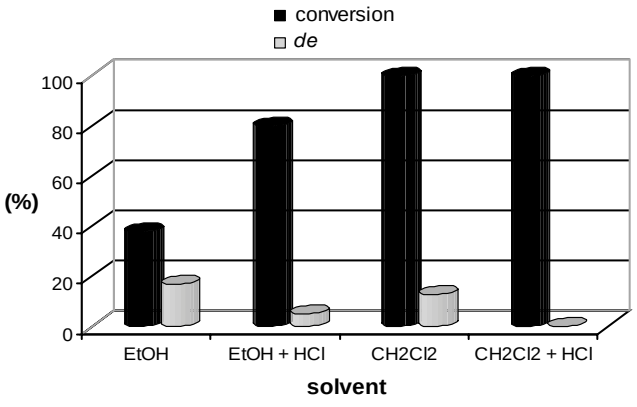

Fig. 3. Conversion and diastereoisomeric excess in the hydrogenation of enamine **2** in different solvents (24 h).

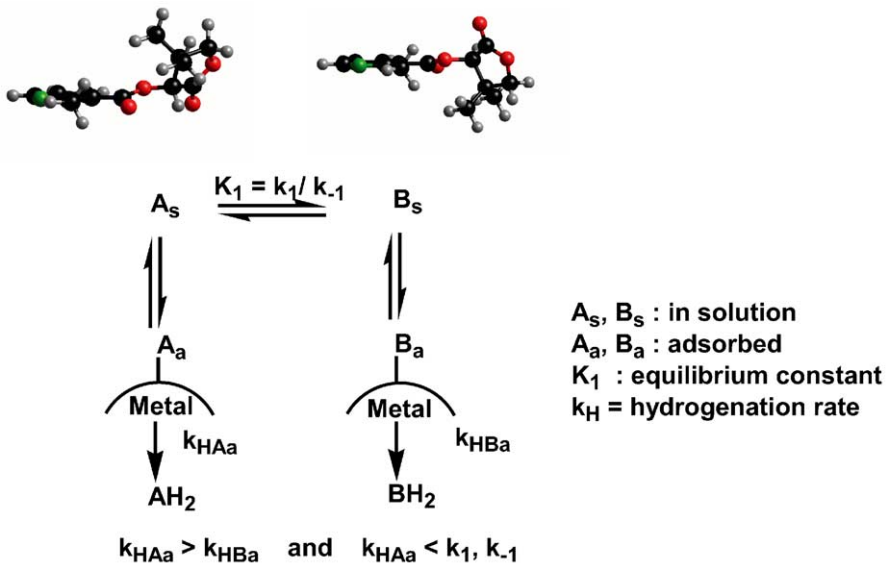

Fig. 4. Proposed mechanism for diastereoselective hydrogenation of **1**.

These results are in agreement with *de* obtained for the hydrogenation of **1**. As reported in Table 2, the higher the concentration of intermediate enamine, the lower the final *de* suggesting that the hydrogenation of the enamine over supported metal catalyst was less selective than the hydrogenation of the initial pyridine substrate. This hypothesis is corroborated by results achieved during the hydrogenation of methyl-(*S*)-nicotinyl prolinate: the *de* decreased while the intermediate disappeared (Table 3).

Adsorption of cyclic enamine derivatives over Rh(1 1 1) surface occurs mainly through the unshared pair of nitrogen atom as determined by DFT calculation [11]. This mode of adsorption lead to lower differentiation of the two faces of the ring because the molecule is almost vertical compared to the catalytic surface and this could explain the lower *de* observed for the hydrogenation of the enamine.

The low influence of reaction parameters on the *de* when pantolactone is used as chiral auxiliary implies that the mechanism is different to that proposed for the pyridinic substrates covalently bound to proline or pyroglutamic ester. Using the latter amino acid auxiliaries, blocked conformers were formed and the molecule was adsorbed on the metallic surface through the less hindered face of the heteroaromatic ring. In the case of pantolactone, a supplementary bond is present between the pyridine ring and the lactone. Moreover, the pyririne ring and the chiral auxiliary are connected via an ester bond which is more flexible than an amide bond. Two stable conformations were found by molecular modeling calculations, in which the pantolactone ring is almost perpendicular to the pyridine ring either above or below the aromatic plan (Fig. 4, **A** and **B**, respectively). The rotational barrier energy between these two conformers **A** and **B** is only 22 kJ/mol indicating that no blocked conformer exists and then no privileged adsorption on the metallic surface may occur. The following scheme (Fig. 4), inspired by the mechanism of homogeneous hydrogenation of dehydroamino acids by rhodium organometallic complexes described by Halpern [12], could explain the noteworthy diastereoselectivity.

In solution, the conformers **A** and **B** are in rapid equilibrium and they adsorb reversibly on the metallic surface through the heteroaromatic ring. At this stage, the metallic surface inhibits the free rotation of the auxiliary, thus differentiating the two conformers. Consequently the rate of hydrogenation of one of them may be higher compared to the rate of the second one, yielding different amounts of $\mathbf{AH_2}$ and $\mathbf{BH_2}$ hydrogenated compounds and so a diastereoisomeric excess.

In conclusion, several parameters have been studied which were shown to influence the diastereoselectivity of a designed reaction. Among them, the nature of the chiral auxiliary is one of the most important. It is not necessary to get the substrate with a blocked conformation to obtain differentiation of the two faces of the heteroaromatic ring. In the case of the methyl-2-nicotinic acid, the pantolactone auxiliary yielded efficient diastereoselectivity.

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