Synthesis of (3S, 4aS, 8aS)-*N*-(*t*-butyl)decahydro-3-isoquinolinecarboxamide by diastereoselective hydrogenation over supported metal catalysts

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The heterogeneous catalytic hydrogenation of (S)-*N*-(*t*-butyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide was carried out over supported metal catalysts. Except for Pt, all the catalysts were very selective toward the formation of (3S, 4aS, 8aS)-*N*-(*t*-butyl)decahydro-3-isoquinolinecarboxamide. However, Pd and Ni catalysts deactivated fairly quickly, while Ru and Rh did not deactivate at all for more than 100 h. Among these catalysts, Ru showed the best performance. The high diastereoselectivity was assumed to be the result of the rigidity of the appended chiral group which helps the preferential adsorption of the reactant in one direction.

KEY WORDS: hydrogenation; diastereoselective; (3S, 4aS, 8aS)-*N*-(*t*-butyl)decahydro-3-isoquinolinecarboxamide; supported metal catalysts.

1. Introduction

(3S, 4aS, 8aS)-*N*-(*t*-butyl)decahydro-3-isoquinolinecarboxamide (DHIQ) is a key intermediate for the synthesis of HIV-protease inhibitors [1,2] and antagonists of the excitatory amino acid receptors [3]. This chemical can be made by various multistep synthesis methods [4–6]. One of the important steps for the preparation of DHIQ is the hydrogenation of (S)-*N*-(*t*-butyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (THIQ) as depicted in figure 1. As eight isomers can be formed from THIQ by racemization followed by hydrogenation or vice versa, highly diastereoselective hydrogenation of THIQ is a challenging task. For hydrogenation, supported Pd [4], Rh [5] or Ru [6] was used as a catalyst. Although harsh reaction conditions, *e.g.*, batch reaction times of 10 to 45 h, were employed, the (isolation) yield of DHIQ did not exceed 73%. Other details such as catalyst preparation method and reaction yield are not described explicitly.

The induction of asymmetry by heterogeneous catalytic hydrogenation of molecules containing appended chiral auxiliaries is a useful tool for the synthesis of optically active compounds [7,8]. Various functional groups, *e.g.*, C=N [7], olefinic C=C [9], aromatic C=C [10–14] and C=O [15,16] bonds, can be hydrogenated to prepare valuable compounds. Among these, the diastereoselective hydrogenation of substituted aromatics using supported metal catalysts is of special interest as findings by other investigators might be applied to our target reaction. Unfortunately, the studies of this category are limited to the molecules modified by (S)-proline [10,12–14] and its derivative, pyroglutamic acid [11,14], except for two articles by researchers at Hoffmann-La Roche [15,16], who studied the hydrogenation of TICC to DHIQ. From the studies of (S)-proline and its derivatives, it is revealed that the diastereoselectivity to a specific compound depends on the chiral auxiliary, metal and reaction conditions. Especially the orientation and functional groups attached to the chiral modifier strongly affect the diastereoselectivity. In the case of our target reaction, these researchers [15,16] either mentioned the total synthesis of DHIQ from an amino acid in a very general manner or did not made a detailed description of the hydrogenation, although their selectivity was claimed to be higher than patent data [4–6].

In this paper, we report the results of highly diastereoselective heterogeneous hydrogenation of an aromatic compound which has a chiral carboxamide group in more detail.

2. Experimental

As a support material, SA3177 (alumina, surface area 100 m^2/g), kindly supplied by Norton, was used after crushing and sieving. A fraction with mesh sizes between 16 and 25 was taken and impregnated with an appropriate metal solution to make the final metal loading of *ca.* 2 wt% by the incipient wetness method. Ruthenium chloride hydrate ($RuCl_3 \cdot xH_2O$, Johnson Matthey), chloroplatinic acid (H_2PtCl_6, Heraus), nickel nitrate hydrate ($Ni(NO_3)_2 \cdot 6H_2O$, Junsei), palladium nitrate ($Pd(NO_3)_2$, Han-Gyeul Gold), or rhodium chloride

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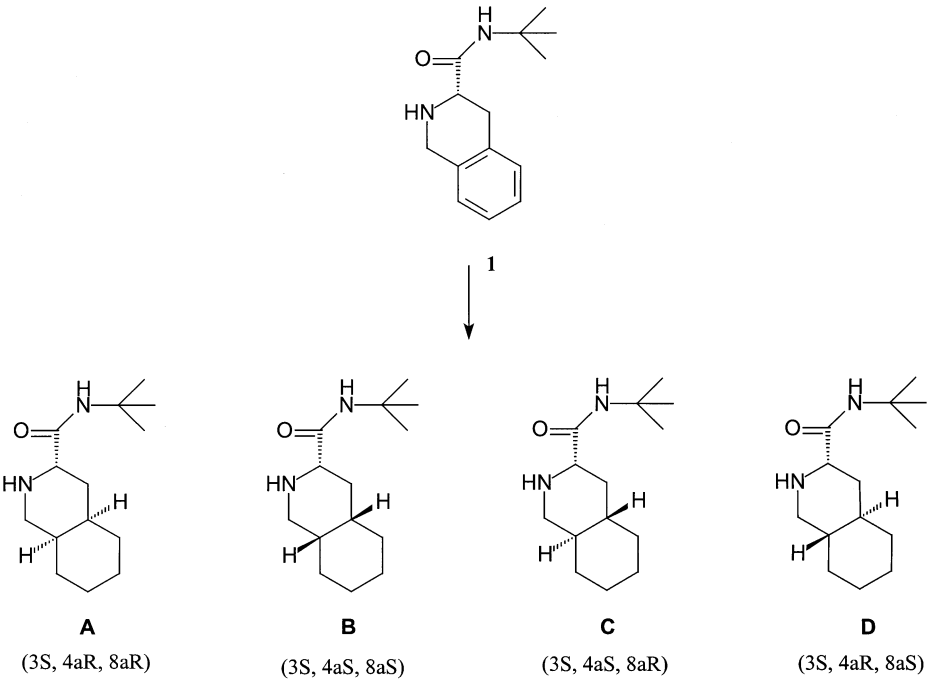

Figure 1. Hydrogenation of (S)-*N*-(*t*-butyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide.

hydrate ($RhCl_3 \cdot xH_2O$, Aldrich) was used as a metal precursor. After impregnation, the sample was dried at 200 °C for 2.5 h and calcined at 500 °C for 3 h in air.

Catalytic tests were carried out using a fully automatic continuous reaction system (AMI-1, Altamira). A solution containing 5 wt% of TICC (homemade (commercial product, 99+% purity)) in *n*-butyl acetate was pumped to the reactor at a LHSV (liquid hourly space velocity, h^{-1}) of 2, a temperature of 130 °C and a pressure of 92 bar. Before tests, the catalyst (3 g) was reduced with flowing hydrogen (50 cm^3/min). Products and reactant were periodically analyzed with gas chromatography (Hewlett-Packard 5890 equipped with a flame ionization detector and a BetaDEX 120 column (60 m × 0.25 mm × 0.25 μm)) using an analytical method kindly provided by Agouron Pharmaceuticals who commercially produces an HIV-protease inhibitor, Nelfinavir, from DHIQ. The retention time of DHIQ was doubly checked using a commercial product (Aldrich). The dispersion of metal was measured using CO at room temperature (Micromeritics ASAP 2010C) while the metal content was analyzed with inductively coupled plasma spectroscopy (GBC Model 1250).

3. Results and discussion

The hydrogenation of THIQ was shown to depend on the solvent used, the catalyst support, the method of catalyst preparation, and the reaction conditions from our extensive preliminary tests. Therefore, here we only report some of the prescreened results from these studies using best solvent, metal precursors and support under optimized reaction conditions. The hydrogenation over a heterogeneous catalyst gave four (3S)-isomers as major products, four (3R)-isomers as byproducts by racemization, and small amounts of decomposed products. Besides DHIQ (isomer B (3S, 4aS, 8aS)), isomers A (3S, 4aR, 8aR) and D (3S, 4aR, 8aS) were predominant. Here we define diastereomeric excess (d.e.) as follows:

$$\text{d.e.} = 100 \times [(3S,4aS,8aS) - (3S,4aR,8aR)]/[(3S,4aS,8aS) + (3S,4aR,8aR)].$$

Table 1 shows reaction results for alumina-supported catalysts. The result with 2% Pt/alumina was not listed as the activity of this catalyst was very low (conversion <0.3%). Among the four catalysts, 2% Ru/alumina was the most active. The activity of 2% Rh/alumina was comparable with that of the Ru catalyst followed

Table 1
The results of hydrogenation over four alumina supported catalysts. [a]

Catalyst	Conversion (%)	Selectivity to DHIQ (%)	d.e.
Ru	99.8	96.7	98.4
Ni	23.8	48.3	92.7
Pd	89.6	68.8	86.9
Rh	99.6	85.6	94.3

[a] All the data were taken at 10 h on stream.

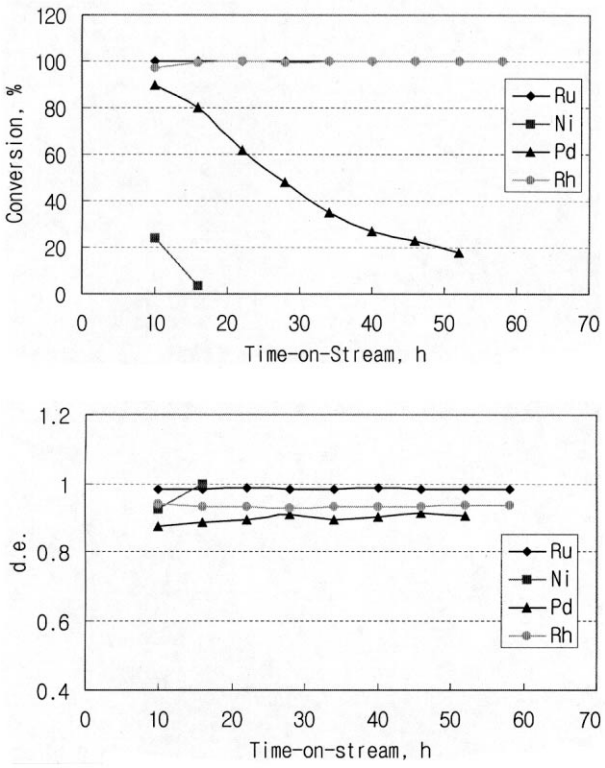

Figure 2. Hydrogenation of (S)-*N*-(*t*-butyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide as a function of time-on-stream: (a) conversion; (b) d.e.

by 2% Pd/alumina. However, the activity of 2% Ni/alumina was the lowest. As shown in figure 2, the activity of the Pd and Ni catalysts decreased very quickly with time. Only the Ru and Rh samples survived more than 100 h. In the case of the selectivity to DHIQ, all the catalysts but 2% Ni/alumina showed relatively high values. Among these, the selectivity was the highest on 2% Ru/alumina, followed by Ni, Rh and Pd. On the other hand the d.e. value followed a different order:

$$\mathrm{Ru} > \mathrm{Rh} > \mathrm{Ni} > \mathrm{Pd}.$$

Note that the initial d.e. value was retained with time for almost all the catalysts tested, although the conversion decreased for some catalysts. The molecular modeling study of THIQ with a molecular modeling program Cerius[2] indicates that DHIQ is a preferred diastereomer in the hydrogenation, as it is difficult for THIQ to adsorb on the surface of a catalyst in such a way as the benzene ring having the same direction as the chiral carboxamide group to sit on the metal crystallites due to steric hindrance of the bulky *tert*-butyl group. Unlike other chiral auxiliaries, *e.g.*, (S)-proline, the chiral carboxamide group is shown to be attached to the ring very rigidly from dynamics simulation modeling. Therefore, only one conformer is present. This might be why the diastereoselectivity to DHIQ is particularly high for all metals tested, unlike other reactions [10,12,17,18]. In other words, the high rigidity of the chiral group appended to the ring is conjectured to drive the reactant molecule to adsorb in one direction, thus predominantly forming the *cis*-diastereomer. On the other hand, it is not clear why Ru is better than other metals, especially Rh. When a reactant molecule is coupled with (S)-proline or its derivative, Rh is invariably found to be better than Ru in activity and d.e. in the hydrogenation of aromatic compounds [10–13]. One possible explanation is the higher bonding strength of the aromatic substrate on Ru than on other metals [10]. However, other factors such as metal dispersion and metal precursor might have affected the catalytic performance. To investigate the effect of dispersion, chemisorption studies were done after reducing the samples at 350 °C under flowing H_2 for 2 h followed by evacuation at the same temperature for 1 h with a turbo-molecular pump. As shown in table 2, the dispersion value was lowest for the Ru catalyst, although all the samples were prepared under the same pretreatment condition. When we varied the dispersion of Ru catalysts (data not shown in this paper), the d.e. value decreased with the increase of the dispersion. Therefore, it is manifest that large crystallites are beneficial for the diastereoselective hydrogenation of TICC. This may be one of the reasons the Ru catalyst is better than the Rh catalyst. The Ni catalyst, on the other hand, is poorer in activity and d.e. despite its lowest dispersion, presumably owing to the lower adsorption strength of aromatic compounds on Ni. In this respect further studies are needed to investigate this reaction in more detail. We are currently working on the factors affecting the activity and selectivity and will report the results in subsequent papers.

Table 2
CO chemisorption results for alumina supported catalysts.

Catalyst	Metal content (wt%)	Dispersion (%)[a]
Ru	1.97	1.50
Ni	2.01	0.39
Pd	1.90	14.75
Rh	1.95	144.65

[a] Dispersion = 100 × (moles of CO chemisorbed)/(atoms of metal).

In summary, we have shown another example of highly diastereoselective hydrogenation of (S)-*N*-(*t*-butyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide to (3S, 4aS, 8aS)-*N*-(*t*-butyl)decahydro-3-isoquinolinecarboxamide. The rigidity of the carboxamide group appended to the ring is believed to induce high diastereoselectivity.

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