

SPR16 Application Note

Highly Selective Preparation of *trans*-4-Aminocyclohexane Carboxylic Acid from *cis*-Isomer over Raney[®] Nickel Catalyst

Adapted from: Göbölös et al, *Catalysis of Organic Reactions*, CRC Press, 2003, 10

In recent years stereochemically pure drugs have increasingly dominated the global pharmaceutical industry. The need for single isomers has fuelled the development of stereochemical reactions with the aim to preferentially synthesise the desired isomer, rather than produce a mixture which must be separated later. Stereochemically pure amino acid derivatives containing N-terminal *trans*-4-alkylcyclohexanol fragment are reported as precursors of physiologically active agents in the treatment of various diseases such as cancer and osteoporosis. Hydrogenation of disubstituted aromatics, particularly amino benzoic acids to the corresponding cyclohexane carboxylic acids is therefore of particular interest, these compounds are used as key intermediates for the manufacture of pharmaceuticals. *Trans*-4-substituted cyclohexane carboxylic acids can be obtained by the hydrogenation of the corresponding benzoic acid compounds followed by the isomerisation of the resulting mixture of *trans*- and *cis*- isomers.

Using the SPR16 for catalytic tests, 4-amino-benzoic acid was hydrogenated to 4-aminocyclohexane over different alumina supported 5 wt.% Ru and Rh catalysts. In the hydrogenation of the aromatic ring the effect of catalyst, solvent and reaction temperature were investigated.

By carrying out sixteen reactions in parallel it could be found in a single run that 2% NaOH-H₂O was the only appropriate solvent for the hydrogenation of 4-aminobenzoic acid over alumina supported Ru and Rh catalysts. The poor activity of catalysts in organic solvents can be explained by the absence of salt formation and lower substrate solubility. As would be expected, Ru and Rh are highly active in the hydrogenation of the aromatic ring, conversion was almost complete at 80 and 100°C, *cis/trans* ratio estimated from TLC results was around 1:1.

In addition *cis* isomer of the acid isolated by a fractional crystallization was reacted over Raney[®] nickel (Metalyst, 35% nickel content) catalyst to prepare the desired *trans* isomer with high yield. The following parameters were varied:

- Mass of catalyst: 0, 50, 100, 150 mg
- Temperature: 100, 110, 120, 130°C
- Pressure: 10, 30, 70 bar

It was found that the yield of the *trans* isomer increases by:

- Increasing the reaction temperature (120-130°C) required to reach the 45-55% *trans* isomer yield
- H₂ pressure also had an influence on the *trans* isomer yield, however, the maximum yield was obtained at 10 bar and 120°C, suggesting that the hydrogen pressure should have an optimum value.

In another *single experimental run* the following conditions were investigated in the isomerisation reaction using the Metalyst Raney® nickel catalyst (B 113 W, 90% nickel content).

No	Mcat, mg	T (°C)	P (bar)	Trans-isomer (%)
1	150	100	10	45
2	150	120	10	70
3	150	140	10	70
4	150	100	20	45
5	150	120	20	50
6	150	140	20	60
7	150	100	40	40
8	150	120	40	50
9	150	140	40	60
10	100	100	10	40
11	100	140	10	70
12	100	100	40	30
13	100	140	40	50
14	200	100	20	45
15	200	120	20	55
16	200	140	20	60

The yield of the *trans* isomer significantly increased with temperature (e.g. from 45 to 70% from 100 to 140°C, 10 bar, 150 mg catalyst). The hydrogen pressure also had an effect, however, the highest yield of the *trans* isomer was reached at 10 bar pressure. Upon increasing catalyst mass the yield of the *trans* isomer slightly increased.

In conclusion, the 4-amino-benzoic acid can be hydrogenated to 4-aminocyclohexane carboxylic acid on 5 wt% Ru and Rh/alumina catalysts with 100% yield in 2 wt% NaOH-H₂O at 80-100°C, 100 bar H₂ in 5 hours. Raw reaction mixture can be processed in the presence of a commercial Raney® nickel catalyst at 130°C, 100bar H₂, and the *cis* isomer separated by fractional crystallization can be isomerised on Raney® nickel in 2% NaOH-H₂O at 120-140°C, 10 bar H₂ for 5h to obtain the *trans* isomer with a yield of around 70%. The two-step synthesis resulted in *trans*-4-aminocyclohexane carboxylic acid with a yield above 90%.

The SPR is highly usefeful for fast screening of liquid phase catalytic reactions, a large parameter space can be explored in a single run, the results above show how the system can be used to screen multiple parameters such as catalyst composition, solvents, temperatures and pressures in a short time.

Original Article:

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Catalysis of Organic Reactions, CRC Press, 2003, 10

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