A NEW SUPPORTED RHODIUM CATALYST FOR SELECTIVE HYDROGENATION OF NITRILES TO PRIMARY AMINES

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Received December 27, 2006
Accepted March 13, 2007

Dedicated to Dr Karel Mach on the occasion of his 70th birthday in recognition of his outstanding contributions to the area of organometallic synthesis and catalysis.

Nitriles are converted to primary amines with high selectivity using a newly developed alumina-supported rhodium catalyst. The high selectivity is obtained without any additives, which are often used to prevent the formation of higher amines. The catalyst is active under mild conditions in various solvents, which makes it specifically suitable for use in pharmaceutical applications or for other substrates that can react with additives like strong acids or bases.

Keywords: Selective hydrogenation; Reductions; Nitriles; Amines; Heterogeneous catalysis; Rhodium.

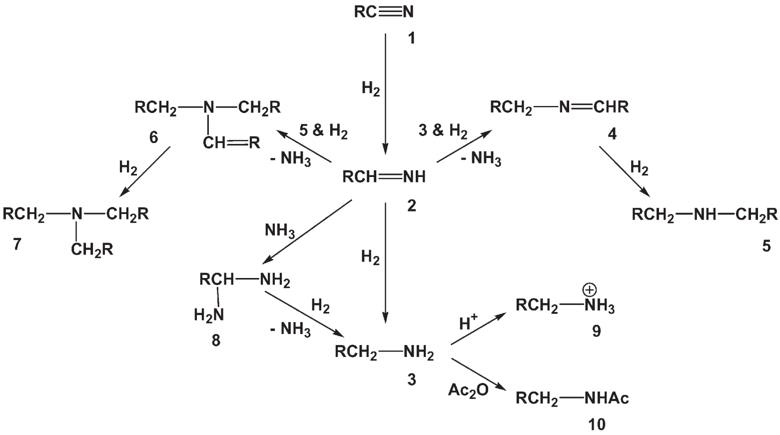
Hydrogenation of nitriles is an important tool for organic chemists to prepare compounds containing amine groups[1]. Catalytic hydrogenation is preferred to stoichiometric reductions (e.g. using hydridoaluminates or -borates), since much less waste is formed in catalytic reactions. The mechanism of catalytic nitrile hydrogenation and coupling to higher amines is depicted in Scheme 1 [2]. The nitrile **1** is hydrogenated to an intermediate imine **2**, and subsequently to primary amine **3**. Reaction of imine **2** with amine **3** can lead to the formation of secondary amine **5**, and further coupling can lead to tertiary amine **7**.

In order to obtain high selectivity for primary amines, large amounts of additives are often used to suppress the formation of higher amines. The most commonly used additive is ammonia[3], which can react with imine **2** to intermediate **8**, thereby preventing coupling of **2** with **3** [2b]. However, in order to remove **2** completely from the reaction mixture, large amounts of ammonia are necessary[4]. Coupling of **2** and **3** can also be prevented by protonation[5] or acylation[6] of amine **3**, yielding **9** and **10**, respectively.

Collect. Czech. Chem. Commun. 2007, Vol. 72, No. 4, pp. 468–474

doi:10.1135/cccc20070468

However, this requires at least a stoichiometric amount of acid or acylating agent, and an additional deprotection step to obtain the desired primary amine. Aqueous solutions of an inorganic base have been used to prevent amine coupling to take place[7]. This effect cannot be explained by the reaction scheme in Scheme 1. An inorganic base can neutralize acid sites of the catalyst, which can easily bind basic amines, and are possibly responsible for coupling of imine **2** with amine **3**.



SCHEME 1
Reaction mechanism of nitrile hydrogenation to primary amines

Using additives to increase the selectivity creates a waste problem if the additives cannot be recycled, while recycling often requires special equipment. In either way, additives make the process more expensive, and less easy to implement on industrial scale. Doping of a catalyst can lead to an increase in selectivity for primary amines, without the need to use additives[8]. However, so far all examples of doped catalysts used high temperatures and pressures to obtain good activity of the catalyst, which makes the processes unsuitable for use in pharmaceutical industry. A selective nitrile hydrogenation catalyst that works under mild conditions is therefore desired.

EXPERIMENTAL

The catalysts were obtained from the Engelhard Co., Rome or were prepared by standard deposition-precipitation methods (homemade). Solvents and substrates were obtained from Sigma–Aldrich and used as received.

All hydrogenations were carried out in a 250 ml stainless steel reactor, containing baffles for optimum mixing. The reactor was charged with 1.2 g (dry weight) of catalyst, 100 ml 96% EtOH, and 10 ml butyronitrile. The reactor was pressurized with H_2 to 5×10^2 kPa, and subsequently vented. This step was repeated twice, after which stirring was started (1500 rpm) and the reaction mixture was heated to 50 °C. At this temperature the reactor was again pressurized with H_2 to 5×10^2 kPa, which was considered the start of the reaction. The reaction was stopped when 4.0 l of H_2 gas was consumed, which corresponds to a conversion of ca. 80%. After opening the reactor, the exact conversion and selectivity were calculated from the GC spectra[9] using 1-dodecanol as internal standard. All reactions showed a mass balance >95%. (Agilent 6850, HP-1 Methyl siloxane column, 30.0 m × 320 μm × 0.25 μm.)

RESULTS AND DISCUSSION

A first comparison of carbon-supported precious metal catalysts (Ru, Rh, or Pd on carbon powder, CP) shows that only with Rh/CP small amounts of primary amine are produced. Ru/CP is inactive under the used reaction conditions, while Pd/CP produces mainly tertiary amine with small

Table I

Hydrogenation of butyronitrile on Rh catalysts[a]

Entry	Support[b]	Catalyst	Reaction time min	Conversion %	Selectivity %
1	CP[c]	Escat 340	90	70	31
2	CP[c]	Rome 42753	37	73	30
3	CP[c]	Rome 43798	45	72	30
4	CP[c]	Rome 46617 egg shell	35	73	29
5	CP[c]	Rome 43951 uniform	38	74	30
6	CP[c]	Rome 43671 mixed	38	73	31
7	AP	Rome 4824	60	79	75
8	TSP	homemade[d]	50	76	46
9	AP	homemade[e]	85	86	93
10	TSP	homemade[e]	140	73	56
11	SP	homemade[e]	90	11[f]	50[g]
12	SAP1.5	homemade[e]	105	78	77
13	SAP20	homemade[e]	125	76	58
14	SAP40	homemade[e]	120	74	49

[a] All catalysts contain 5% Rh-loading. [b] CP, carbon powder; AP, alumina powder; TSP, titanium-silicate powder; SP, silica powder; SAP, silica-aluminate powder (the number indicates the amount of silica in wt.%). [c] For carbon-supported catalysts only 0.4 g (dry weight) of catalyst was used. [d] Preparation according to the Rome procedure. [e] Preparation according to an adapted procedure. [f] Extensive deactivation was observed. [g] Based on combined secondary amine and imine formation.

amounts of secondary amine. Table I shows the hydrogenation results for a series of Rh catalysts on various supports.

Rh catalysts supported on carbon were much more active, but less selective than Rh catalysts on mineral supports. Variations of carbon support (entries 1–3) or variations in metal location (entries 4–6) had little effect on the primary amine selectivity.

Rh catalysts on mineral supports were less active, but their selectivity for primary amines was higher. The alumina support yielded the most selective commercial catalyst (entry 7). Changes in the preparation method increased the selectivity even more to 93% at 86% conversion (entry 9). The selectivity did not decrease when the reaction was allowed to run to full conversion.

All reactions could be run to full conversion, except when silica was used as support (entry 11). In this case hydrogenation started with a comparable rate as in entry 9, but quickly slowed down. After 90 min H_2 consumption had almost completely stopped.

Table II shows hydrogenation results of the newly developed Rh on alumina powder catalyst under different reaction conditions. The hydrogenation selectivity is not dependent on the solvent polarity (entries 9, 15), although the catalyst is not equally active in all used solvents (entries 16, 17). The CH_2=CH double bond in allyl cyanide is preferably hydrogenated over the nitrile functionality (entry 18), while the phenyl group in 3-phenylpropionitrile is stable to hydrogenation (entry 19), even after prolonged reaction times. The selectivity in the hydrogenation of this sterically

TABLE II
Nitrile hydrogenations using homemade Rh/AP catalyst

Entry	Remark	Reaction time min	Conversion %	Selectivity %
9	Standard reaction[a,b]	85	86	93
15	Cyclohexane as solvent[a]	120	83	92
16	NMP as solvent[a]	90	0	–
17	Ethyl acetate as solvent[a]	60	12	87
18	Allyl cyanide as substrate[b]	95	28	–[c]
19	3-Phenylpropionitrile as substrate[b]	90	100	98[d]

[a] Butyronitrile as substrate. [b] 96% EtOH as solvent. [c] CH_2=CH bond completely hydrogenated. [d] C_6H_5 group not hydrogenated.

more hindered substrate is much higher (~98%) than for the linear-chain butyronitrile.

Our results of screening Rh, Ru, and Pd supported on carbon powder are in agreement with earlier publications. Without additives, Pd catalysts generally yield tertiary amines, while Rh can be used to prepare secondary amines[1a,10]. Our attempts to influence the selectivity of Rh/CP by changing the type of carbon support or location of the metal were unsuccessful. Ru/CP was inactive, which is also consistent with earlier results[10]. However, Ru has been reported to yield primary amines with a reasonable selectivity when supported on zeolite, while a lower selectivity was found when Ru was supported on AP [11].

The role of the support in nitrile hydrogenations has been investigated in several studies, but with contradictory results. Huang et al. investigated hydrogenation of nitriles using supported Ru catalysts, and did not observe any effect of the support acidity[11]. They claim that any acidity of the support is neutralized by the basic amines formed in the reaction. Verhaak et al. observed that catalysts with more basic supports were more selective, claiming that acid sites catalyze the coupling to higher amines[12]. Dallons et al. found that acid sites on the catalyst actually increase primary amine selectivity. They argue that these sites coordinate primary amines formed in the hydrogenation, keeping them away from hydrogenation sites that contain the imine intermediate and preventing coupling of the two compounds[13]. It is our belief that interaction of the support with the active metal determines the catalyst selectivity. This interaction is influenced by support properties (such as its acidity) as well as by the method used to prepare the catalyst. Indeed, our studies show that the catalyst selectivity depends not only on the type of support, but that the method of preparation of the catalyst also greatly affects its selectivity. Optimization of the catalyst preparation procedure for Rh/AP led to an increase in primary amine selectivity from 75 to 93% at ~80% conversion.

It is interesting to note that the silica-supported Rh catalyst (entry 11) started with a similar activity as the alumina-supported catalyst, but quickly deactivated. GC measurements of the reaction mixture showed a different composition of the reaction products (Fig. 1). For very fast hydrogenations catalyzed by Rh/CP (entries 1–6), only peaks belonging to amines **3**, **5** and **7** are observed. The slower but more selective hydrogenations catalyzed by Rh/AP (entries 7, 9) show peaks of amine **3**, **5** and of an unknown compound. The peak of the unknown compound lies close to the peak of **5**; when the reaction is allowed to run to completion the peak disappears. It was therefore ascribed to a hydrogenation intermediate, most probably imine **4**. In case of the Rh/SP catalyst (entry 11), the peak of **4** is significantly higher than in GC spectra of other hydrogenations. It seems that imine **4** is very difficult to hydrogenate with Rh/SP and may act as a poison. When a catalyst with a very low activity is used (Ru/AP), the peak of imine **4** is even higher than that of amine **5** and a small peak next to the peak of primary amine **3** is observed, which is tentatively ascribed to primary imine **2**. In their work on nitrile hydrogenation on supported Ru catalysts, Huang et al. observed the combination of secondary imine formation and catalyst deactivation[10]. They observed that performing the reaction in the gas phase gives much more deactivation than in the liquid phase. Their conclusion that the deactivation probably arises from "adsorbed molecules" is also consistent with our observations.

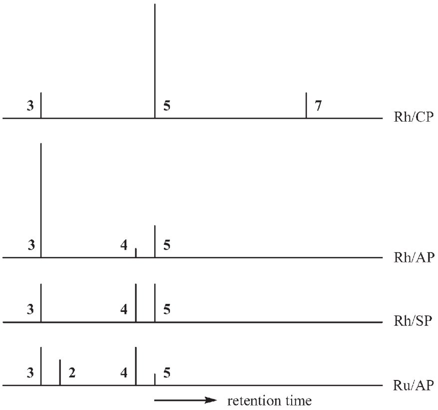


FIG. 1

Graphical representation of GC spectra for selected reactions (see Scheme 1 and Table I)

In conclusion, we have developed a Rh/AP catalyst that can selectively hydrogenate nitriles to primary amines (93% or higher yield) under mild conditions (50 °C, 5×10^2 kPa H_2) without using any additives.

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4. In ref.[3] the ratio ammonia/nitrile 2:1 was used, which may not seem to be a large excess. However, the intermediate imine **2**, which is the actual reactive species, is present only in very low concentrations. Therefore, the effective ratio ammonia/imine is much higher than 2:1.
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