Nitrile Hydration

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Rh^{I}-Catalyzed Hydration of Organonitriles under Ambient Conditions**

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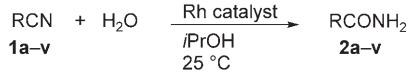
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

The hydration of organonitriles is a reaction of great synthetic significance for the preparation of organoamides (e.g., acrylamide and nicotinamide) in view of its broad industrial and pharmacological applications.[1] For example, hydration of acrylonitrile is used to produce more than 2×10^5 tons of acrylamide per year.[2] Classically the reaction proceeds in a sequence of distinct steps upon treatment with strong inorganic acid or base, but these methods are frequently unable to control overhydrolysis.[1f] Although several pioneering precedents involving molecular[3] and heterogeneous[4] catalysts have been reported, in many cases, drastic conditions including high temperatures (80–180 °C) or high pressure (e.g., 80 psi) are required. As an exception, Co^{III} [3a,d] and Pt^{II} [3e,h–j,o] complexes mediate hydration under milder conditions; however, the substrate range applicable under standard or ambient conditions remains unclarified. We report here a notable advance towards expanding the substrate scope, by demonstrating an easier to conduct and milder hydration of organonitriles using a low-valent Rh^{I}-(OMe) species as the molecular catalyst (Scheme 1).

The Rh^{I} catalyst was prepared by treatment of commercially available [{Rh(OMe)(cod)}$_2$] (0.01 equiv) with PCy_3 (0.04 equiv) in anhydrous THF at 25 °C for 15 min under argon (cod = cyclooctadiene, Cy = cyclohexyl). After the solvent THF and residual cod had been removed by evaporation in vacuo, oxygen-free, Ar-saturated *i*PrOH was added. The *i*PrOH solution of the Rh^{I}OMe/2 PCy_3 catalyst (Rh: 0.04 M) was treated sequentially with benzonitrile (**1a**) (1 equiv) and H_2O (5 equiv) at 25 °C under argon, and the reaction mixture was stirred at 25 °C for 17 h. Subsequent purification by column chromatography on silica gel provided benzamide (**2a**) in 90 % yield. The reaction mixture was not contaminated by further hydration and/or alcoholysis products; in contrast, the formation of benzoic acid and/or the ester was frequently the side reaction in several methods previously described.[1f] Use of [{Rh(OH)(cod)}$_2$] in place of [{Rh(OMe)(cod)}$_2$] resulted in a slightly lower yield (74 %). Scant reactivity was observed with other Rh^{I} complexes including [{RhCl(cod)}$_2$] and [Rh(acac)(cod)] (acac = acetylacetonate) under otherwise identical conditions, suggesting that the OR (R = H, Me) component is the critical functional group in facilitating the reaction. When we screened the solvents, we found that protic solvents (MeOH, EtOH, *i*PrOH, and *t*BuOH) led to rate enhancement (**2a**, 60–99 %: 25 °C, 24 h), whereas aprotic solvents (dimethylacetamide (DMA), dimethyl sulfoxide, and *N*-methylpyrrolidinone (NMP)) resulted in low conversion (< 10 %). Additional experiments revealed that the yield of benzamide (**2a**) depends least on the concentration of the Rh catalyst when the hydration is carried out in *i*PrOH, so that we chose this solvent for further screening. Two equivalents of PCy_3 per equivalent of Rh ([{Rh(OMe)(cod)}$_2$]/PCy_3 1:4) was sufficient to give reasonable yields of **2a**. In contrast, the use of a 1:1 ratio slightly decreased the yield, whereas using a three- or fourfold excess of PCy_3 did not improve the results. Other monodentate phosphines and phosphites including Ph_3P, tBu_3P, 2-(2′-methyl-1,1′-biphenyl)PCy_2, and $P(OPh)_3$ were completely unsatisfactory (Rh/P = 1:2; **2a**: < 10 %). This is in stark contrast to the [{RhCl(cod)}$_2$]/P(*m*-$C_6H_4SO_3Na$)/NaOH (1:3:10) system, where the PPh_3 derivative facilitated the hydration under high pressure (80 psi) and in aqueous media.[3g] In comparison, 2-(1,1′-biphenyl)PCy_2 and 2,2′-(1,1′-biphenyl)$(PCy_2)_2$ gave the product in poor yields (Rh/P = 1:2; **2a**: < 26 %).

Finally we succeeded in reducing the loading of [{Rh(OMe)(cod)}$_2$] and PCy_3 to 0.005 and 0.02 equiv, respectively, after increasing the amount of H_2O to 20–40 equiv (with respect to nitrile) and by running the reaction at higher dilution (Rh: 0.01–0.02 M). Since the optimal conditions



Scheme 1. Catalytic hydration of organonitriles.

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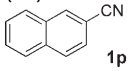
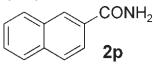
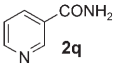
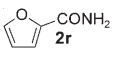
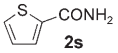
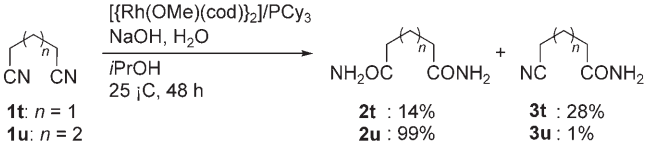
provided benzamide (**2a**) in 99% yield, this hydration catalysis was applied to other representative organonitriles (Table 1). The hydration showed substrate generality with respect to aliphatic, aromatic, heteroaromatic, and α,β-unsaturated nitriles **1b–s** (entries 1–19, Table 1). Benzonitriles **1k–n** with electron-donating and -withdrawing groups at the *para* or *meta* positions are equally hydrated (entries 11–14, Table 1). Without any solvent, the expected amide formed quantitatively from the reasonably water-soluble substrate propionitrile (**1b**) (entry 1, Table 1). In contrast, bulkier or solid organonitriles **1c–s** need organic solvents such as *i*PrOH to remain in homogeneous solution, thus ensuring smooth conversion (entries 2–19, Table 1). Nicotinamide (**2q**) was produced without any problems (entry 17, Table 1), and potentially polymerizable methacrylonitrile (**1i**) was compatible with this protocol, generating methacrylamide **2i** in quantitative yield (entry 8, Table 1). Formyl and olefinic groups were tolerated and remained completely unreacted (entries 7–9 and 14, Table 1). A difficulty in hydration was seen with slightly bulkier organonitriles **1g** and **1o** (entries 6 and 15, Table 1), and the amides **2g** and **2o** were obtained in fair yields under the optimized conditions but in excellent yields when the loading of the Rh dimer was increased by a factor of four and a catalytic amount of Na_2CO_3 was added (0.1 equiv). Increasing the reaction temperature to 50 °C resulted in a black precipitate and did not improve the conversion of **1g** and **1o**. Unfortunately, 2-cyanopyridine and 5-hexynenitrile were totally unreactive under similar conditions.

Table 1: Catalytic hydration of organonitriles by the Rh^I catalyst.[a]

Entry	Nitrile	*t* [h]	Product	Yield [%][b]
1	CH_3CH_2CN (**1b**)	24	$CH_3CH_2CONH_2$ (**2b**)	94(93)[c]
2	$CH_3(CH_2)_4CN$ (**1c**)	72	$CH_3(CH_2)_4CONH_2$ (**2c**)	99
3	CH_3OCH_2CN (**1d**)	24	$CH_3OCH_2CONH_2$ (**2d**)	99
4	$(CH_3)_2CHCN$(**1e**)	24	$(CH_3)_2CHCONH_2$ (**2e**)	93
5	CyCN (**1f**)	72	$CyCONH_2$ (**2f**)	96
6	*t*BuCN (**1g**)	24	*t*$BuCONH_2$ (**2g**)	17(99)[d]
7	$CH_2{=}CH(CH_2)_3CN$ (**1h**)	72	$CH_2{=}CH(CH_2)_3CONH_2$ (**2h**)	92(99)[e]
8	$CH_2{=}C(CH_3)CN$ (**1i**)	24	$CH_2{=}C(CH_3)CONH_2$ (**2i**)	58(96)[f]
9	$(C_6H_5)CH{=}CHCN$ (**1j**)	72	$(C_6H_5)CH{=}CHCONH_2$ (**2j**)	92(99)[f]
10	C_6H_5CN (**1a**)	24	$C_6H_5CONH_2$ (**2a**)	99
11	*m*-$CH_3(C_6H_4)CN$ (**1k**)	72	*m*-$CH_3(C_6H_4)CONH_2$ (**2k**)	96
12	*p*-$CH_3(C_6H_4)CN$ (**1l**)	24	*p*-$CH_3(C_6H_4)CONH_2$ (**2l**)	99
13	*p*-$Cl(C_6H_4)CN$ (**1m**)	24	*p*-$Cl(C_6H_4)CONH_2$ (**2m**)	99
14	*p*-$(OHC)(C_6H_4)CN$ (**1n**)	24	*p*-$(OHC)(C_6H_4)CONH_2$ (**2n**)	97
15	*o*-$CH_3(C_6H_4)CN$ (**1o**)	24	*o*-$CH_3(C_6H_4)CONH_2$ (**2o**)	16(96)[d]
16	 **1p**	24	 **2p**	99
17	 **1q**	24	 **2q**	94
18	 **1r**	48	 **2r**	99
19	 **1s**	24	 **2s**	99

[a] [{Rh(OMe)(cod)}$_2$]/PCy_3/nitrile/H_2O = 0.005:0.02:1:20–40. Conditions: 25 °C, 24–72 h in *i*PrOH (Rh: 0.01–0.02 M). [b] Yield of isolated, purified products. [c] 2 equiv of H_2O was used without *i*PrOH solvent. [d] [{Rh(OMe)(cod)}$_2$]/PCy_3/nitrile/Na_2CO_3/H_2O = 0.02:0.08:1:0.1:80; 24 h. [e] [{Rh(OMe)(cod)}$_2$]/PCy_3/nitrile/H_2O = 0.01:0.04:1:20; 24 h. [f] [{Rh(OMe)(cod)}$_2$]/PCy_3/nitrile/H_2O = 0.01:0.04:1:30–40; 24 h.

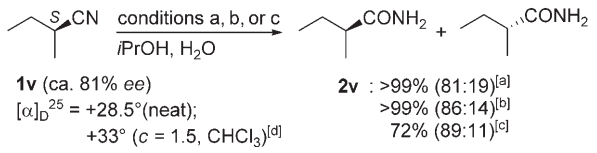
One of the significant challenges in this area is the double hydration of 1,*n*-dicyanoalkane, since, for example, dicyanoalkanes represented by **1t** are susceptible to side reactions such as monohydration[5] and cyclization of the diamide intermediate to give the six-membered carbocyclic imide derivative.[6] An enzymatic biotransformation of **1u** resulted in merely monohydration to give **3u**,[7] and other side processes have also been described.[8] Only Pt phosphinito[3h] and Ru hydride[3c] complexes afforded the diamide **2u** in excellent yields at 95 °C and 120 °C, respectively. We changed the reaction conditions slightly to expedite the double hydration. Finally the following conditions, through the aid of a catalytic amount of NaOH (0.1 equiv), were more promising (Scheme 2). This modified procedure is potentially capable of hydrating poly(acrylonitrile), which is composed of the repeating units of 1,3-dicyanopropane. This could generate partially or fully hydrated poly(acrylonitrile), the latter corresponding to poly(acrylamide), which has significant technological applications.[6,9]



Scheme 2. Catalytic hydration of dicyanoalkanes. [{Rh(OMe)(cod)}$_2$]/PCy_3/NaOH/H_2O/**1t** (or **1u**) = 0.02:0.08:0.1:80:1 (equiv).

Under our conditions the reaction is run at essentially neutral pH, as proven by the following experiments (Scheme 3). When the optically active nitrile **1v**[10,11] was subjected to slightly modified conditions, the chirality at the α-carbon was well preserved to give hydrate **2v**[12] with retention of configuration (Scheme 3). The best result was obtained when the reaction was performed at 4 °C with an increased amount of H_2O (160 equiv); this demonstrates the mildness of the Rh catalysis.

In summary, we have introduced a new catalyst system for the hydration of organonitriles under very mild conditions using a Rh^I species. This reaction was demonstrated to tolerate various functional groups as well as a stereogenic center and could produce several industrially and pharmaceutically important substances in a straightforward fashion. The present system is complementary to the many practical methods that use microorganisms for emzymatic hydration of nitriles under ambient and/or nearly neutral conditions involving the higher valent metals Fe^{III} and Co^{III}.[1g,h] We envision that the functionalization of nitrile-containing poly-



Scheme 3. Catalytic hydration of optically active nitrile **1v**. Conditions: [a] [{Rh(OMe)(cod)}$_2$]/4 PCy_3 (Rh/H_2O/**1v** = 0.04:80:1), Rh: 0.016 M, 25 °C, 24 h. [b] [{Rh(OMe)(cod)}$_2$]/4 PCy_3 (Rh/H_2O/**1v** = 0.04:160:1), Rh: 0.01 M, 25 °C, 24 h. [c] Conditions are the same as those in [b], except that the reaction was conducted at 4 °C for 72 h. The enantiomeric excess (*ee*) of **2v** was determined by GC analysis using the chiral stationary phase β-CP (Astec, Ltd.) [d] 99% *ee* (*S*) of **1v**: $[\alpha]_D^{25} = +36.3$ deg cm^3 g^{-1} dm^{-1} (neat): Ref. [10]; +39° deg cm^3 g^{-1} dm^{-1} (c = 1.5 g cm^{-3}, $CHCl_3$): Ref. [11].

mer may be realized using the present hydration strategy, which otherwise might be difficult to achieve. In addition, the search for the improvement of the catalyst efficiency and substrate generality is now underway in our laboratory.

Experimental Section

A degassed and argon-aerated solution of [{Rh(OMe)(cod)}$_2$] (0.01 mmol, 4.8 mg) in anhydrous THF (0.5 mL) at 25 °C was treated quickly with a 1.0 M toluene solution of PCy_3 (0.04 mmol, 40 μL; commercially available from Aldrich), and the mixture was stirred at this temperature for 15 min. After any volatile compounds had been evaporated in vacuo (1–3 Torr), degassed and argon-saturated *i*PrOH (2.0 mL) was added to the resulting slurry, followed by sequential addition of **1a** (2.0 mmol, 205 μL) and distilled H_2O (40 mmol, 0.72 mL). The reaction mixture was stirred at 25 °C for 24 h and was diluted with MeOH to dissolve all the precipitate. The entire mixture was transferred into a 50 mL round-bottom flask, evaporated in vacuo, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc only) to give benzamide (**2a**) (241 mg, 99% yield), which is a commercially available compound. Products **2b**–**2v** are all known compounds, and their spectral and analytical data matched the results reported elsewhere.

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