Platinum-Catalyzed Selective Hydration of Hindered Nitriles and Nitriles with Acid- or Base-Sensitive Groups

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Hindered tertiary nitriles can be hydrolyzed under neutral and mild conditions to the corresponding amides using platinum(II) catalysts with dimethylphosphine oxide or other secondary phosphine oxides (SPOs, phosphinous acids) as ligands. We have found that this procedure also works well for nitriles with acid- or base-sensitive groups, which is unprecedented in terms of yield and selectivity. The catalyst loading can be as low as 0.5 mol %. Amides are isolated as the only product in high yield, and no further hydrolysis to the corresponding acids takes place. Reactions are carried out at 80 °C but take place even at room temperature. When enantiopure secondary phosphine oxide ligands are used in the hydrolysis of racemic nitriles, no kinetic resolution is observed, presumably due to racemization of the ligand during the reaction.

Introduction

The hydrolysis of nitriles to amides and carboxylic acids is an important transformation in organic chemistry. Many industrial examples are known, such as the hydrolysis of amino nitriles to amino acids, acrylonitrile to acrylamide and acetone cyanhydrin to the corresponding amide, en route to methyl methacrylate. Using specific conditions, it is possible to stop at the amide stage. Frequently used methods for nitrile hydrolysis to amides are strong acid (96% H₂SO₄) or base (50% KOH/t-BuOH). A simple and versatile method has been reported by Katritzky and co-workers who used a combination of 30% H₂O₂/K₂CO₃/DMSO at 0 °C for 5–10 min to obtain high yields of pure amides. However, in general, selective hydrolysis of nitriles to amides is troublesome and yields are reasonable at best for two reasons:

1. It is difficult to stop the hydrolysis at the amide stage and further hydrolysis to the carboxylic acid often takes place, as the rate constant of amide hydrolysis is usually larger than that for nitrile hydrolysis, especially under basic conditions (Scheme 1).

2. Since the nitrile group is not very reactive, harsh conditions using strong acids or bases are required, which precludes the presence of acid- or base-sensitive functional groups.

Tertiary nitriles are a special class as they are particularly resistant toward hydrolysis. There are only a few successful examples known in the literature. Use of 96% H₂SO₄ at 140 °C for 3 h yields tertiary amides with yields ranging from 10% to 90% depending on the substrate. Strong basic conditions have also been used, but this leads to much lower yields. For instance, tributylacetonitrile could be converted into tributylacetamide in 15% yield after 100 h of reflux with 50% KOH in tert-butyl alcohol. Due to these difficulties, tertiary amides are generally prepared from the corresponding acid chloride and NH₃. Furthermore, the method of...
SCHEME 1. Nitrile Hydrolysis

R- CN + H2O \rightleftharpoons R- COOH + NH3

Katritzky and co-workers mentioned above does not work for tertiary nitriles.11 No efficient method for the hydrolysis of tertiary nitriles has been reported so far.

To reduce salt formation in industrial nitrile hydrolysis, a number of methods based on the use of enzymes and transition-metal catalysts have been developed. Enzymatic hydrolysis takes place under exceptionally mild conditions. A number of examples have been reported, with some of them showing good enantioselectivity in the kinetic resolution of racemic nitriles or in the conversion of meso-dinitriles.13 A restriction, however, is the low reactivity of the enzymes, although DeSantis and co-workers have reported very high rates of hydrolysis with less hindered nitriles, such as mandelonitrile.14

Transition-metal catalysts have also been successful in the hydrolysis of nitriles to amides. Several classes of heterogeneous catalysts15 have been used, such as supported metals (Cu, Ni, Ag, Pd),16 metal oxides17 (MnO2, TiO2, SiO2, Al2O3), and zeolites18 (NaY,18a Zn2+ exchanged zeolites18b). Yields and selectivities generally are poor. Homogeneous catalysts have been used, based on complexes of Pd(II),19 Pt(II),20 Pt(0),21 Co(III),22 Cu(II),23,24a Re(III),29 or Mo(I)30 and others.31 Limitations of these catalysts are as follows:


(11) We were unable to hydrolyze nitrile 4a using Katritzky’s conditions.


(21) We were unable to hydrolyze nitrile 4a using Katritzky’s conditions.

(22) For a recent review on enzymatic hydrolysis of nitriles, see: Kobayashi, M.; Shimizu, S. Curr. Opin. Chem. Biol. 2000, 4, 95–102.


reported the preparation of enantiopure SPOs and their application as ligands in the Ir(I)-catalyzed asymmetric
imine hydrogenation.35 The ligands are prepared by the addition of a Grignard reagent to a solution of RPCl2 in
THF at −20 °C, followed by hydrolysis with water. They are readily obtained enantiopure by preparative chiral
HPLC. In particular, t-BuPHO L1 (Figure 2) is easy to separate by preparative chiral HPLC with a 4.3 min
retention time difference between the two enantiomers.35 Classical resolution has also been used to obtain enan-
tiopure SPOs.36
More recently, this ligand has also been used by Dai and co-workers in palladium-catalyzed allylic alkylation
reactions.37
In view of the above, we decided to further investigate the hydrolysis of nitriles that are not easy to hydrolyze
by other means, such as tertiary nitriles and nitriles containing acid- or base-sensitive groups. In addition, the
availability of the enantiopure L1 prompted us to investigate the possibility of kinetic resolution of racemic
nitriles.

Results and Discussion

Catalyst 1 has been prepared from Pt(PPh3)4 and 5 equiv of Me2PHO in toluene.20c,d The same procedure
could be used with Ph2PHO to form 3. Unfortunately, with L1, this procedure failed to give the analogous
complex. For this reason, we explored the preparation of complexes starting from PtCl2 instead of Pt(PPh3)4.
Gratifyingly, reaction of PtCl2 with 5 equiv of Me2PHO in toluene gave a white solid, the structure of which was
determined by X-ray analysis after crystallization from DCM/Et2O (Figure 2).

The structure of this complex (2), [PtCl (PMe2OH)-
(PMe2OH)OPh], is comparable to the structure of 1 (Figure 3). In particular, it shares with 1 the depo-
ration of one of the hydroxyl groups of the Me2POH ligands.38 The P–O is hydrogen-bonded to the adjacent

Me2PHO. Thus, a neutral Pt(II) complex is the net result. Again, no well-defined complex could be obtained using
L1. It turned out, however, that in situ preparation of the catalyst by using PtCl2 in combination with 3–4 equiv of racemic or enantiopure L1 gave comparable results in the hydrolysis reactions.

Initially, acetonitrile and α-methylbenzyl cyanide 4k (Scheme 3) were applied as model substrates in the
hydrolysis reactions. Catalysts 1–3 all gave full convergence to the corresponding amide as the sole product, 1
being the most active catalyst. Their catalytic activities decrease as follows: 1 > 3 > 2. With 0.5 mol % of 1, the
reaction took 3 h at 80 °C in EtOH/H2O (TOF 67 h−1), whereas using 3, a reaction time of 20 h (TOF 10 h−1)
was required. With 2 mol % of catalyst 2, 18 h was needed for complete conversion (TOF 3 h−1). When 4k was used
as substrate, similar trends were found. The somewhat reduced rate of 2 is due to the presence of chloride anion,
which can still compete with the nitrile for the binding site. This can be remedied by the addition of AgBF4, as shown by Parkins.20d This presumably creates the same cationic complex as the one obtained by hydrolysis of 1.

To expand the scope of this reaction, a number of sterically hindered tertiary nitriles and nitriles with acid
or base sensitive groups were hydrolyzed with the catalysts mentioned above (Figures 4 and 5).

Using catalyst 1, all substrates were smoothly converted to the corresponding amides in over 95% isolated
yield except for trimethylacetonitrile 4f. (Scheme 2, Table 1).

Catalyst 1 is more active than 2 and the in situ complexes made from PtCl2 and ligand L1, especially with
the sterically hindered tertiary nitriles. With unhindered nitriles, the difference is less pronounced. All nitriles
(4a–j) except 4c were completely converted to

Figure 1. Structure of L1.

Figure 2. Perspective PLUTO drawing of catalyst 2.

Figure 3. Structures of preformed catalysts.
the corresponding amides (5a–j) using only 0.5 mol % of catalyst 1 in EtOH/H₂O mixtures at 80 °C (Table 1). The hydrolysis of unhindered nitriles (4g–j) is completed in 3–4 h but the sterically hindered tertiary nitriles (4a b, 4d–f) need reaction time up to 41 h to give full conversion under these conditions. Increasing the catalyst loading to 2 mol % reduced the reaction time to 5–18 h.

Nitrile 4c remained unchanged with 0.5 mol % of 1 even after prolonged reaction time. Increasing the catalyst loading to 3.5 mol %, however, did result in its hydrolysis to amide 5c (entry 3). This sluggish reaction might be due to the conformation of the substrate in which the cyano group occupies an axial position. Its suffers severe steric hindrance (e.g., 1,3-diaxial interaction).

The nitriles possessing acid- or base-sensitive groups (4g–j) were all smoothly converted to the corresponding amides without any side reactions (entries 7–10, 20, and 21). Even the sensitive (S)-amygdalin (4j) was converted to the amide without racemization of any of the stereogenic centers in the sugar moieties in 98% yield. The stereochemical integrity of the product was confirmed by COSY and NOESY NMR experiments. All substrates could even be hydrolyzed at room temperature, although a long reaction time was needed (entries 13 and 21).

Because of the poor solubility of the catalysts in most organic solvents, the products can be extracted with THF or DCM after evaporation of the ethanol/water mixture. The recycled catalysts could be used at least one more time in subsequent reactions and were found to largely retain their activity.

There are very few reported examples of enantioselective hydration of nitriles, other than those catalyzed by enzymes. With the enantiopure ligand L1, we attempted a kinetic resolution of racemic nitriles. Using the in situ formed complex of (R)-(+) t-BuPhPHO (L1) and PtCl₂, nitrile 4k and sterically hindered tertiary nitriles 4d,e were hydrolyzed under the standard conditions. The hydrolysis of 4d,e did not go to completion (55% conversion determined by GC). The ee's of both the remaining substrate and the product were determined during the reaction by HPLC. However, in all cases (4k, 4d,e) both the nitrile and the product amide were found to be racemic. To exclude the possibility of racemization of the nitriles or amides an experiment was performed using D₂O instead of H₂O. Upon D-NMR analysis only a signal due to the ND₂ group was observed and no α-deuteriation was found neither in the nitrile nor in the amide (Scheme 3). These findings exclude racemization of the substrates or products.

After careful chiral HPLC–MS analysis of the hydrolysis samples, we discovered that the ligand L1 had largely racemized during the reaction. This explains the disappointing results in the kinetic resolution experiments.

**Conclusion**

By broadening the scope of the nitrile hydrolysis reaction reported by Parkins and co-workers, a catalytic
method has been developed for the hydrolysis of tertiary nitriles and nitriles containing sensitive groups to their corresponding amides. To the best of our knowledge, the excellent yields and chemoselectivity of these hydrolysis reactions are unprecedented in the literature. An attempted kinetic resolution failed and the ligand was found to racemize during the reaction.

Experimental Section

For general methods and details of experimental procedures, see the Supporting Information.

General Procedure for Catalytic Nitrile Hydrolysis Reaction. To a 25 mL round-bottom flask equipped with magnetic stirrer were added preformed catalyst (0.011 g, 0.0256 mmol, 0.5 mol %), nitrile (5 mmol), EtOH (4 mL), and the solution was heated to 80 °C (in air). After the required reaction time (conversion was checked by TLC and GC), the reaction was allowed to come to room temperature and the solvent was removed under vacuum. After redissolution in DCM or THF, the solution was filtered, the solvent was removed, and the solid product was dried overnight under vacuum to yield the corresponding amides, generally pure enough for analysis. If further purification is needed, the products were recrystallized from THF or DCM.

1-(4-Methylphenyl)cyclopropanecarboxamide (5a) was isolated as a white crystalline compound: yield 99%; mp 76–77.5 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.05 (t, J = 3.4 Hz, 2H), 1.58 (t, J = 3.7 Hz, 2H), 2.34 (s, 3H), 5.35 (br, 1H), 5.92 (br, 1H), 7.16 (d, J = 7.3 Hz, 2H), 7.30 (d, J = 7.6 Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 175.5, 136.2, 135.4, 129.2, 128.1, 28.1, 19.6, 14.5; HRMS (EI $^+$) m/z 215.0104, calcld for C$_{12}$H$_{11}$NO 215.0997. Anal. Calcld for C$_{12}$H$_{11}$NO: C, 76.81; H, 8.43; N, 6.89. Found: C, 75.71; H, 7.66; N, 7.96.

2-(Methyl-2,3-diphenylpropanamido)heterocycliccarboxamide (5c) was isolated as a white crystalline compound: yield 99%; mp 101–102 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.09–1.19 (m, 2H), 1.75–1.81 (m, 2H), 1.92–2.12 (m, 2H), 2.33 (s, 3H), 2.36–2.52 (m, 5H), 2.53 (br, 1H), 5.48 (br, 1H), 7.15 (d, J = 6.6 Hz, 2H), 7.26 (d, J = 6.4 Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 177.7, 138.8, 134.9, 128.0, 124.9, 48.9, 32.9, 24.3, 23.1, 19.4; HRMS (EI $^+$) m/z 217.1456, calcld for C$_{12}$H$_{11}$NO 217.1354.

2-Phenyl-2-(3,4,5-trihydroxy-6-(2H)tetrahydro-2H-pyran-2-yl)oxy)methyl(tetrahydro-2H-pyran-2-yl)oxycetamide (5j) was isolated as a white crystalline compound: yield 99% mp 57–59 °C; [d]$_D$ = −125 (c = 0.625, H$_2$O); $^1$H NMR (D$_2$O) $\delta$ 3.19–3.24 (m, 2H), 3.26–3.40 (m, 6H), 5.38 (dd, J = 5.4, 12.2 Hz, 1H), 3.73 (dd, J = 5.4, 12.2 Hz, 1H), 3.78 (d, J = 11.2 Hz, 1H), 4.06 (d, J = 11.2 Hz, 1H), 4.15 (d, J = 7.8 Hz, 1H), 4.39 (d, J = 7.8 Hz, 1H), 5.25 (s, 1H), 7.32–7.36 (m, 5H); $^{13}$C NMR (D$_2$O) $\delta$ 174.0, 133.3, 128.0, 127.5, 126.6, 101.3, 97.4, 77.0, 74.3, 74.1, 73.7, 73.4, 71.5, 71.2, 68.0, 67.7, 66.7, 59.1; MS (electrospray) 498 (M + Na$^+$, 100). Anal. Calcld for C$_{20}$H$_{23}$NO$_3$H$_2$O$_2$: C, 48.68; H, 6.33; N, 2.84. Found: C, 48.69; H, 6.63; N, 2.83.

2,4-Furandicarboxylic acid (6a) was isolated as off-white solid: yield 95%; mp 140–142 °C (lit. $^{30}$ mp 141–142 °C).

2-Formylbenzamide (5h) was isolated as a white solid: yield 97%; mp 165–167 °C; $^1$H NMR (DMSO-d$_6$) $\delta$ 7.61 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.3 Hz, 2H), 8.20 (s, 1H), 10.04 (s, 1H); $^{13}$C NMR (DMSO-d$_6$) $\delta$ 191.8, 166.0, 138.2, 136.7, 128.3, 127.1, MS (EI $^+$) 149 (M, 100).

3,3-Dimethylcyclohexylamine (5d) was isolated as an off-white solid: yield 96%; mp 176–178 °C (lit. $^{30}$ mp 169–171 °C).