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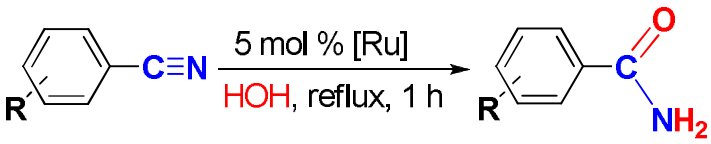

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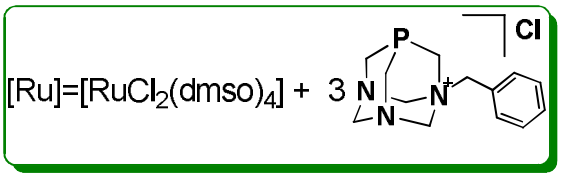

Tetrahedron Letters
journal homepage: www.elsevier.com

Efficient selective hydration of nitriles to amides in aqueous systems with Ru(II)-phosphaurotropine catalysts.

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Nitrile hydration
Ruthenium
Phosphine
Dimethylsulfoxide
Amides

ABSTRACT

A simple and efficient synthesis of amides by selective hydration of aromatic and aliphatic nitriles is described. The catalysts are prepared „in situ" from easily available Ru-precursors and ligands using water as a solvent. The most active catalyst, is obtained from $[RuCl_2(dmso)_4]$ and benzylated 1,3,5-triaza-7-phosphaadamantane. Of 16 substrates examined, 92-99% conversions of 14 nitriles was achieved in 1 h at reflux temperature.

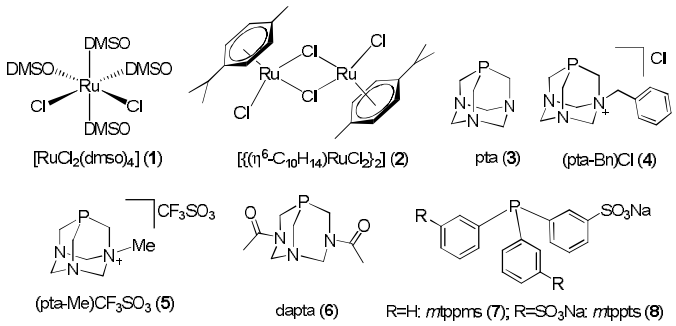
Selective hydration of nitriles to amides is an important reaction applied for –among others– synthesis of pharmaceuticals, detergents, polymers and their stabilizers, and rubber products.[1] Traditionally this process employs strongly acidic or basic solutions and obviously these cannot be used in case of acid- or base-sensitive compounds. In several cases the obtained amides are overhydrolysed to carboxylic acids. In addition, the acid or base component of the reaction mixture has to be neutralized at the end of the reaction what leads to formation of large quantities of unwanted salts.

Catalysis by transition metal complexes may allow selective synthesis of amides under neutral conditions.[2] Water is a straightforward choice as solvent for hydration reactions, however, so far only a few water-soluble catalysts are known for such transformations which lead to high yields under mild conditions. There are examples of catalytic hydrations in water with Pd(II)[3] and Rh(I)[4] complexes, however, the field is dominated by the use of ruthenium-based catalysts.[2,5] Several of these catalysts have the general formula of $[(\eta^6\text{-arene})RuCl_2(L)]$ with arene= η^6 -*p*-cymene (η^6-$C_{10}H_{14}$)[6,7] or η^6-C_6Me_6,[8,9] and L= PPh_2CH_2NHR (R=^{i}Pr, ^{t}Bu)[6,7] *m*tppms-Na (sodium salt of *meta*-monosulfonated triphenylphosphine),[6,7] pta (1,3,5-triaza-7-phosphaadamantane),[6,7] $P(NMe_2)_3$,[8,9] *tris*-(5-(2-aminothiazolyl)phosphine,[11] pyrazole,[12] or 2-(3-pyrazolyl)pyridine.[12] In some cases Ru-complexes of benzylated pta (pta-Bn) were used as catalysts.[6-8] The water-soluble bis(allyl)ruthenium(IV) complexes, $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(P)]$ (P=*m*tppms, pta, pta-Bn and dapta=**6**, Scheme 1) were found to be less effective than the corresponding $[(arene)RuCl_2(P)]$ complexes. In contrast, reactions of caged hexaaza-phosphines with $[RuCl(\mu\text{-}Cl)(\eta^3{:}\eta^3\text{-}C_{10}H_{16})]_2$ afforded active catalysts.[10] Heterogenized Ru(II)-arene-pta (RAPTA) complexes were shown active in hydration of nitriles both under conventional (thermal) conditions and with microwave irradiation.[15] Catalytic hydration of a variety of aliphatic and aromatic nitriles (with benzonitrile as a common substrate) proceeded at room to reflux temperatures with the complexes discussed above. In general, the catalysts were applied in 1-5 mol% and their typical catalytic activity was characterized by turnover frequencies TOF $\leq$20 h^{-1} (TOF=mol reacted substrate/mol catalyst×h).

Frost et al. applied $[RuCl_2(pta)_4]$ for catalysis of hydration of various nitriles. In hydration of benzonitrile the catalytic activity of this complex (TOF=2.9 h^{-1}) was inferior to the efficiency of the half-sandwich catalysts mentioned above, however, it was found that most of the product amides precipitated from the aqueous reaction mixture. Consequently, for isolation of the products in these systems there was no need to use extraction with organic solvents. The catalyst was very stable and could be recycled seven times with no significant loss of activity.[13] The half-sandwich complexes of β-aminophosphines derived from pta were also found to be active in the hydration of benzonitrile (TOF =1.5 - 2.7 h^{-1}). Interestingly, the turnover frequencies increased with decreasing concentrations of the catalyst and reached 285 h^{-1} at 0.001 mol%.[14]

This short summary of prior results on nitrile hydration shows that although several catalytic procedures are known for selective syntheses of amides from nitriles there is still a considerable need for improvement in catalysts' activity. In the following we report on a new and facile synthetic method based on the use of easily available catalyst precursors. These Ru(II)-catalysed aqueous-phase hydrations proceed with unequalled rate and lead to high conversion of nitriles to amides, furthermore several of the products can be isolated in high purity by simple filtration of the aqueous reaction mixtures.

In this study the catalysts for nitrile hydration were obtained „in situ" from $[RuCl_2(dmso)_4]$ (**1**) or $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (**2**) and the various water-soluble phosphines (**3**-**8**) shown on Scheme 1. These Ru(II)-complexes[16,17] as well as the ligands[18-23] are readily available, some of them (e.g. **2**, **3**, **6**, **7**, **8)** can be obtained from commercial sources.

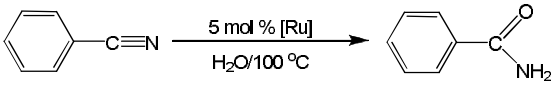


Scheme 1. Ru(II)-sources and water-soluble phosphines used in this study.

Hydration of benzonitrile was chosen as a model reaction. The „in situ" catalysts were prepared by mixing an aqueous solution of $[RuCl_2(dmso)_4]$ (**1**) or $RuCl_3\times3H_2O$ and the appropriate phosphine ligand **3**-**8** at room temperature. After addition of a given amount (1 mmol in most cases) of benzonitrile the reaction mixture was stirred at reflux temperature on air. Samples were withdrawn regularly and the conversions were determined by gas chromatography.[24] Conversions of benzonitrile to benzamide are shown in Table 1. No formation of byproducts (e.g. benzoic acid) was observed. The results obtained with the use of the isolated $[RuCl_2(dmso)_2(pta)_2]$,[25] $[RuCl_2(dmso)_2(pta\text{-}Bn)_2]Cl_2$[25] and *trans*-$[RuCl_2(pta)_4]$ catalysts are also shown for comparison.

Table 1.

Conversions of benzonitrile in hydration to benzamide catalyzed by various water-soluble Ru(II)-phosphine catalysts



Entry	catalyst	conversion* (%)		
		1 h	2 h	3 h
1	**1** + 3 *m*tppms-Na	0	0	0
2	**1** + 3 *m*tppts-Na_3	0	0	0
3	**1** + 2 pta	20	43	62
4	**1** + 3 pta	45	78	93
5	**1** + 2 (pta-Bn)Cl	75	90	95
6	**1** + 3 (pta-Bn)Cl	99	99	100
7	**1** + 3 (pta-Me)CF_3SO_3	16	36	78
8	**1** + 3 dapta	51	69	91
9	$[RuCl_2(dmso)_2(pta)_2]$	0	13	46
10	$[RuCl_2(dmso)_2(pta\text{-}Bn)_2]Cl_2$	15	34	62
11	*trans*-$[RuCl_2(pta)_4]$	35	70	87
12	$RuCl_3\times3H_2O$ + 3 pta	0	0	0
13	$RuCl_3\times3H_2O$ + 5 pta	21	46	55
14	$RuCl_3\times3H_2O$ + 5 (pta-Bn)Cl	4	14	24

Reaction conditions: 5 mol% Ru, 1 mmol benzonitrile, 3 mL water, reflux, *determined by GC

$[RuCl_2(dmso)_4]$ (**1**) or its mixtures with sulfonated triphenylphosphines (**7** or **8**) did not catalyze the hydration of benzonitrile (entries 1 and 2). In contrast, use of phosphaurotropines **3**-**8** allowed hydrations to proceed with good or excellent conversions in 3 h (entries 3-8) and the catalytic activities were higher (entries 4-6, 8) than or close to (entry 7) that of *trans*-$[RuCl_2(pta)_4]$ (entry 11). Hydrated $RuCl_3$ could also be used as a source of ruthenium, however conversions of benzonitrile were low compared to those with $[RuCl_2(dmso)_4]$ (entries 12-14). The most active catalyst was obtained in the reaction of **1** + 3 (pta-Bn)Cl (entry 6) which led to complete conversion of benzonitrile in 1 h (but see also Figure S1). Interestingly, the isolated complexes $[RuCl_2(dmso)_2(pta)_2]$ and $[RuCl_2(dmso)_2(pta\text{-}Bn)_2]Cl_2$ showed lower reactivity (entries 9, 10) than the „in situ" prepared catalysts.

Reaction of $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (**2**) and (pta-Bn)Cl in a [(pta-Bn)Cl]/[Ru]=3 ratio also gave a very active catalyst for benzonitrile hydration with 99% conversion in 1 h (Table S1). However, time course of the conversion showed an induction period and complete conversion was achieved only in 60 min (Figure S1). In contrast, the reaction catalyzed by $[RuCl_2(dmso)_4]$ + 3 (pta-Bn)Cl started with no induction period and arrived at 98% conversion already in 20 min. From this conversion a TOF=58.8 h^{-1} can be calculated. (The initial turnover frequency of the latter catalyst is 90 h^{-1}.) This reactivity compares very favorably to the activities of *trans*-$[RuCl_2(pta)_4]$ (TOF=2.9 h^{-1}),[13] $[(\eta^6\text{-}p\text{-cymene})RuCl_2(pta\text{-}Bn)]Cl$ (TOF=5 h^{-1}),[7] $[(\eta^6\text{-cymene})RuCl_2\{P(NMe_2)_3\}]$ (TOF=4 h^{-1}),[11] and to Romero's catalyst (TOF=26.7 h^{-1})[12]. (Catalytic activities at 80°C and 90°C are shown in Table S5.)

The isolated $[(\eta^6\text{-}p\text{-cymene})RuCl_2(pta\text{-}Bn)]Cl$ was less active than the „in situ" $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ + 6 (pta-Bn)Cl catalyst and afforded only 23% conversion in 1 h hydration of benzonitrile (Table S1). However, addition of further 1 or 2 equivalents of (pta-Bn)Cl increased the catalytic activity substantially, leading 86% and 98% conversions, respectively.

The scope of hydrations with the most active new catalysts **1**+3 (pta-Bn)Cl and **2**+6 (pta-Bn)Cl was studied with 16 aromatic and aliphatic nitriles. Table 2 shows the conversions determined by gas chromatography together with isolated yields by ethereal extraction (in round brackets), and isolated yields by simple filtration and aqueous washing (in curly brackets).

Table 2.

Hydration of various nitriles to amides catalyzed by the „in situ" catalysts $[RuCl_2(dmso)_4]$ (**1**) + 3 (pta-Bn)Cl and $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (**2**) + 6 (pta-Bn)Cl.

Entry	Substrate	**1** + 3 (pta-Bn)Cl [Ru]:[P]= 1 : 3	**2** + 6 (pta-Bn)Cl [Ru]:[P]= 1 : 3
1	Benzonitrile	99 (90) {42}	99 (80) {18}
2	4-Tolunitrile	99 (65) {64}	98 (91) {49}
3	4-Chlorophenyl-acetonitrile	98 {56}	96 {51}
4	4-Chloro-benzonitrile	98 (86) {59}	98 (68) {60}
5	4-(Trifluoromethyl)-benzonitrile	95 (72) {47}	90 (47) {43}
6	3-Phenyl-propionitrile	97 (90) {16}	98 (93) {27}
7	1,3-Dicyanobenzene	99 (91)	99 (99)
8	1,4-Dicyanobenzene	99 (99)	99 (99)
9	4-Nitrobenzonitrile	98 {77}	98 {49}
10	3-Pyridinecarbonitrile	99	95{86}
11	4-Pyridinecarbonitrile	99	97{66}
12	2-Pyridinecarbonitrile*	10	20
13	Propionitrile*	95	85
14	Butyronitrile	92{32}	82{25}
15	i-Butyronitrile	97{47}	92{89}
16	Acetonitrile	0	0

Reaction conditions: 5 mol% Ru, 1 mmol substrate, 3 mL water, reflux, 1h. *No solid product separated.

With the exception of acetonitrile the substrates are poorly soluble in water and the reactions take place in aqueous-organic biphasic media. A very advantageous feature of aqueous systems is in that upon cooling several of the products precipitate or crystallize from the reaction mixtures.[13] In some cases, however, partial dissolution or incomplete crystallization of the product may lead to lower isolated yields compared to the conversion of the substrate nitrile and one may have to resort to extraction by a suitable solvent as a more efficient method of workup.

From the data in Table 2 it can be seen that most of the nitriles were efficiently hydrated in a short reaction time with both catalysts. With **1** + 3 (pta-Bn)Cl all but two of the substrates reacted with conversions higher than 90% and in 11 cases the conversions were in the 97-99% range. (This catalyst led to high conversions already in 30 min; Table S2). The use of **2** + 6 (pta-Bn)Cl gave approximately the same results with the exception of propionitrile and butyronitrile (entries 13,14) which gave slightly lower conversions with this catalyst in 1 hr. Both „in situ" catalysts showed low catalytic activity in case of 2-pyridinecarbonitrile (entry 12) while acetonitrile was not hydrated at all (entry 16). Strong coordination of both substrates[5,13] to Ru(II) may be the reason for the poor or no conversion. The products of hydration of both 1,3- and 1,4-dicyanobenzene (entries 7,8) are so much insoluble in water that they precipitate already at reflux temperature and only traces of unreacted dinitriles could be observed by gas chromatography after 1 hr. ^{1}H and ^{13}C NMR characteristics of the products (Supporting Material) showed exclusive formation of diamides.

In this short reaction time **2** + 6 (pta-Bn)Cl catalyzed the hydration of several substrates with greater conversions than [(η^6-*p*-cymene)$RuCl_2$(pta-Bn)]Cl (Table S3).

Recovery and recycling of the catalyst was studied with **1** + 3 (pta-Bn)Cl in hydration of benzonitrile under the standard conditions of Table 2. After 1 hr reaction time, the conversion was determined by gas chromatography. The reaction mixtures were kept at ice water temperatures for a few hours and then the precipitated benzamide was filtered out. A new batch of benzonitrile was added and the procedure was repeated. In the 6th cycle the conversion was 95% (compared to 99% in the 1st cycle) and the yield of the isolated amide was 48% (57% in the 1st cyle). It can be concluded that the catalyst can be efficiently recovered in the aqueous phase, shows high stability, and retains its activity through several repeated cycles (detailed data are reported in Table S3).

In summary, we have developed a simple and efficient catalytic method for selective hydration of aliphatic and aromatic nitriles to the corresponding amides. The catalysts are prepared „in situ" from easily available Ru-precursors and ligands. The most active catalyst is obtained from [$RuCl_2(dmso)_4$] and benzylated 1,3,5-triaza-7-phosphaadamantane (pta-Bn)Cl. The reactions take place in aqueous reaction mixtures on air at reflux temperatures in short reaction times and are characterized with excellent conversions and isolated yields. In several cases the product amides precipitate or crystallize from the aqueous mixture upon cooling and can be isolated by filtration and aqueous washing in high purity. This latter feature makes the procedure operationally simple and largely eliminates contamination of the environment.

Acknowledgments

This work was supported by the European Union and Hungary and co-financed by the European Social Fund through the grant TÁMOP-4.2.2.A-11/1/KONV-2012-0043 (ENVIKUT) and the TÁMOP 4.2.4.A/2-11-1-2012-0001 priority project (Program of National Excellence: Establishing and operating a national system providing personal support for students and researchers). The authors are grateful for the support of the National Research Fund of Hungary (OTKA 101372).

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