Organic Letters

Letter

pubs.acs.org/OrgLett

Ruthenium-Catalyzed Synthesis of β-Hydroxyamides from β-Ketonitriles in Water

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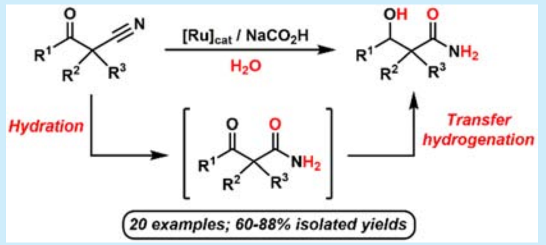
Supporting Information

ABSTRACT: An unprecedented hydration/transfer hydrogenation tandem process for the catalytic conversion of β-ketonitriles into synthetically useful β-hydroxyamides in water has been developed, making use of the ruthenium(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ in combination with sodium formate.

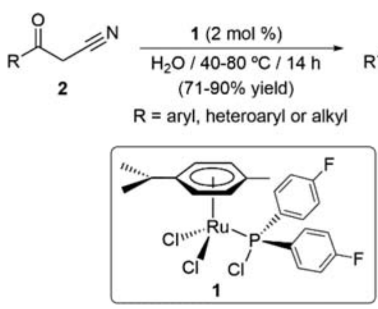


β-Hydroxyamides form a pivotal class of compounds in organic synthesis, particularly useful for the preparation of diverse types of heterocycles like β-lactams, azetidines, oxazolidinones, or 1,4-diazepanes, among others.[1] Involvement of β-hydroxyamides as advanced intermediates in the synthesis of pharmaceutically relevant molecules, such as levamisole,[1d] GABOB (γ-amino-β-hydroxybutyric acid),[1f] L-alanosine,[2] loracarbef,[3] and fluoxetine,[4] has also been described. Accordingly, the search for efficient approaches to such derivatives has attracted considerable attention. In this regard, the amidation of β-hydroxy esters/acids,[5] the aldol reaction between amide enolates and carbonyl compounds (aldehydes, ketones, acyl silanes, etc.),[6] and the catalytic hydrogenation of β-ketoamides[7] are currently the most common methods employed in the literature to synthesize β-hydroxyamides. However, many of them are inappropriate for the preparation of N-unsubstituted derivatives. Access to this particular class of compounds is usually achieved by hydration of the C≡N bond of β-hydroxynitriles.[8,9]

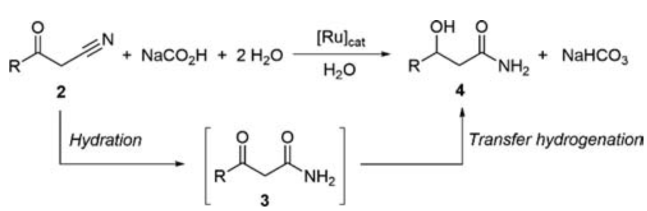
In the context of our studies on metal-catalyzed nitrile hydration reactions,[10] we recently described the first nonenzymatic catalyst, i.e., the arene−ruthenium(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**), capable of converting selectively β-ketonitriles **2** into β-ketoamides **3** (Scheme 1).[11−13] The hydration reactions proceeded cleanly in pure water without the need of any organic cosolvent or the assistance of acidic or basic additives. Based on these results, and the known ability of ruthenium(II) complexes to promote the transfer hydrogenation (TH) of carbonyl compounds by sodium formate in water,[14] we report herein an unprecedented procedure for the direct conversion of β-ketonitriles **2** into synthetically useful β-hydroxyamides **4** through a *one-pot* tandem process combining both catalytic reactions (Scheme 2).

Initial experiments were performed using commercially available 3-(4-fluorophenyl)-3-oxopropanenitrile (**2a**) as a model substrate, and the most relevant results obtained are shown in Table 1.

Scheme 1. Hydration of β-Ketonitriles Using Complex 1



Scheme 2. Catalytic Transformation of β-Ketonitriles into β-Hydroxyamides in Water through a Hydration/TH Tandem Process

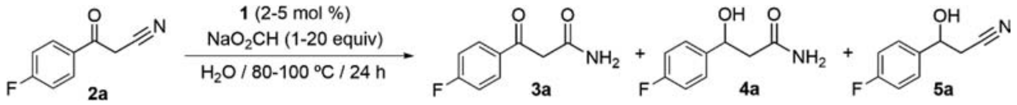


Thus, we found that the treatment of **2a** with 1 equiv of $NaCO_2H$ and 2 mol % of **1**, in water at 80 °C for 24 h, leads to the formation of the desired β-hydroxyamide **4a** in only 5% yield (determined by $^{19}F\{^1H\}$ NMR spectroscopy).[15] Under these conditions, the β-ketoamide **3a** is the major reaction product (entry 1). Fortunately, the transfer hydrogenation of

Received: October 23, 2016
Published: November 21, 2016

DOI: 10.1021/acs.orglett.6b03172
Org. Lett. 2016, 18, 6164−6167

Table 1. Ruthenium-Catalyzed Hydration/TH of 3-(4-Fluorophenyl)-3-oxopropanenitrile (2a): Optimization of the Reaction Conditions[a]



entry	catalyst	Ru (mol %)	$NaCO_2H$ (equiv)	T (°C)	conv[b] (%)	yield[b] (%)		
						3a	4a	5a
1	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (1)	2	1	80	>99	91	5	0
2	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (1)	2	5	80	>99	67	27	0
3	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (1)	2	10	80	>99	44	52	0
4	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (1)	2	20	80	>99	24	71	0
5	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (1)	2	20	100	>99	15	76	0
6	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (1)	5	20	100	>99	0	92	0
7	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2OH\}]$ (6)	5	20	100	>99	0	91	0
8	$[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$	5	20	100	>99	0	0	62
9	$[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_3)]$	5	20	100	>99	4	0	22
10	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_3\}]$	5	20	100	98	18	1	18
11	$[RuCl_2(PPh_3)_3]$	5	20	100	>99	3	0	24
12	$[RuCl_2(DMSO)_4]$	5	20	100	>99	2	1	34
13	$[RuCl(\eta^5\text{-}C_5Me_5)(PPh_3)_2]$	5	20	100	>99	1	0	24
14	$[RuCl(\eta^5\text{-indenyl})(PPh_3)_2]$	5	20	100	95	1	0	75
15	$RuCl_3{\cdot}nH_2O$	5	20	100	>99	7	5	44

[a]Reactions were performed under Ar atmosphere starting from 1 mmol of the β-ketonitrile **2a** (0.33 M in water). [b]Determined by $^{19}F\{^1H\}$ NMR spectroscopy.

intermediate **3a** could be facilitated by increasing the amount of sodium formate (entries 2–4). In particular, when the reaction was performed with 20 equiv of $NaCO_2H$, the yield of **4a** increased to 71% (entry 4). Further improvements in the yield of **4a** were achieved by increasing the working temperature (entry 5) and the loading of catalyst **1** (entry 6). In particular, when the reaction was performed at 100 °C with 5 mol % of **1** and 20 equiv of $NaCO_2H$, β-hydroxyamide **4a** could be generated in 92% yield (by $^{19}F\{^1H\}$ NMR) after 24 h (entry 6). Under these conditions, the $^{19}F\{^1H\}$ NMR spectrum of the crude reaction mixture indicated the complete consumption of the starting material **2a**, along with the formation of minor amounts of some unidentified products (the characteristic signals of the intermediate β-ketoamide **3a** and the β-hydroxynitrile **5a** were not observed). Solvent removal and subsequent chromatographic workup allowed the isolation of pure **4a** in 74% yield. Overall, the results collected in entries 1–6 clearly indicate that the TH step is the rate-limiting one of the present tandem process catalyzed by $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**). This statement was confirmed by studying separately the formation of **4a** through the transfer TH of the β-ketoamide **3a** and through the hydration of the β-hydroxynitrile **5a**. Thus, under identical experimental conditions (i.e., with 5 mol % of complex **1** and 20 equiv of sodium formate at 100 °C), the hydration of **5a** proceeded much faster than the TH of **3a** (4 vs 24 h).

On the other hand, in our previous work with the chlorophosphine complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**) we demonstrated that, when dissolved in water, **1** readily evolves into the corresponding phosphinous acid derivative $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2OH\}]$ (**6**), via hydrolysis of the P–Cl bond, which is the active species responsible for the C≡N bond hydration.[11,16] Accordingly, when the same reaction was performed employing the isolated complex **6** as the catalyst, comparable results were achieved (entry 7). The key role played by the cooperative phosphine ligand in the process is clearly evidenced by the results collected in entries 8–10. Neither the dimeric precursor $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ nor the related phosphine derivatives $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_3)]$ and $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_3\}]$ were able to generate **4a** in significant amounts. Although the starting nitrile **2a** was completely consumed with these three complexes, a mixture of products was formed, among which the β-hydroxynitrile **5a** resulting from the TH of **2a** could be identified. Similar observations were also made employing other classical ruthenium sources (entries 11–15).[17]

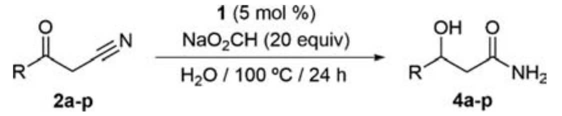
With the optimized reaction conditions in hand, we next explored the scope of the process (Table 2).[18] To our delight, we found that, as observed for **2a** (entry 1), other commercially available α-unsubstituted β-ketonitriles **2b–p** can be conveniently converted into the corresponding β-hydroxyamide **4b–p** using complex **1** (70–88% isolated yields). Aromatic substrates with different substitution patterns and electronic properties (entries 1–13), as well as heteroaromatic (entries 14–15) and aliphatic systems (entry 16), were employed without significant differences in reactivity. Only in the case of **2o**, containing the potentially coordinating thienyl group, did we have to extend the reaction time to 48 h to obtain the β-hydroxyamide product **4o** in high yield (entry 15). The only byproducts detected by ^1H NMR spectroscopy in the crudes of all these reactions were the corresponding β-ketoamide intermediates (ca. 3–7% yield).

Further evidence of the generality of the process was gained when the α-substituted β-ketonitriles **2q–t** were employed as substrates. As shown in Scheme 3, when identical reaction conditions were employed, the corresponding β-hydroxyamides **4q–t** could be synthesized in 60–75% yield.

In summary, a general procedure for the catalytic conversion of β-ketonitriles into synthetically useful β-hydroxyamides has been developed. The process involves an unprecedented *one-pot* tandem reaction combining the hydration the C≡N unit and the transfer hydrogenation of the carbonyl group of the substrates, being both promoted by a single metal source,

DOI: 10.1021/acs.orglett.6b03172
Org. Lett. 2016, 18, 6164–6167

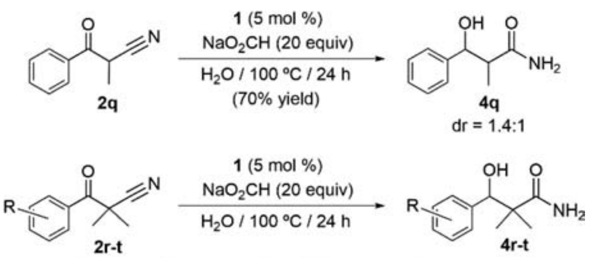
Table 2. Synthesis of β-Hydroxyamides 4a–p from β-Ketonitriles 2a–q Catalyzed by Complex 1[a]



entry	β-ketonitrile 2	yield of 4[b] (%)
1	R = 4-C_6H_4F (**2a**)	**4a**, 74
2	R = Ph (**2b**)	**4b**, 82
3	R = 4-C_6H_4Cl (**2c**)	**4c**, 88
4	R = 3-C_6H_4Cl (**2d**)	**4d**, 70
5	R = 2-C_6H_4Cl (**2e**)	**4e**, 70
6	R = 3,4-$C_6H_3Cl_2$ (**2f**)	**4f**, 73
7	R = 4-C_6H_4Br (**2g**)	**4g**, 85
8	R = 3-$C_6H_4CF_3$ (**2h**)	**4h**, 77
9	R = 4-C_6H_4Me (**2i**)	**4i**, 84
10	R = 3-C_6H_4Me (**2j**)	**4j**, 82
11	R = 4-C_6H_4OMe (**2k**)	**4k**, 85
12	R = 3,5-$C_6H_3(OMe)_2$ (**2l**)	**4l**, 86
13	R = 1,2,3,4-tetrahydro-6-naphthyl (**2m**)	**4m**, 76
14	R = 2-furyl (**2n**)	**4n**, 80
15[c]	R = 2-thienyl (**2o**)	**4o**, 70
16	R = ^{t}Bu (**2p**)	**4p**, 81

[a]Reactions were performed under Ar atmosphere starting from 1 mmol of the corresponding β-ketonitrile (0.33 M in water). [b]Isolated yield after chromatographic workup. [c]Reaction time 48 h.

Scheme 3. Catalytic Synthesis of the α-Substituted β-Hydroxyamides 4q–t



R = H (**r**; 60% yield); 4-Cl (**s**; 74% yield); 3-Cl (**t**; 75% yield)

i.e., the easily accessible ruthenium(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$.[19] Further studies aimed at exploiting this aqueous protocol for the preparation of related α- and γ-hydroxyamides, molecules also of high synthetic value in organic chemistry, from the corresponding ketonitriles are now in progress in our laboratory and will be the subject of a future contribution.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03172.

Experimental details, characterization data, and NMR spectra of β-hydroxyamides **4a–t** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Spanish MINECO (Projects CTQ2013-40591-P, CTQ2016-75986-P, and CTQ2014-51912-REDC) and the Gobierno del Principado de Asturias (Project GRUPIN14-006).

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(13) Ketoamides **3** exist in solution as a tautomeric mixture of their keto and enol forms. For clarity, only the keto form is drawn all along the manuscript.
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(15) Unfortunately, the reaction progress could not be monitored by GC. That is why we decided to use $^{19}F\{^1H\}$ NMR spectroscopy, in which the signals of the starting material and products appear suitably separated to be integrated. Chemical shifts in CD_3OD are as follows: **2a** (δ_F = −105.7 ppm), **3a** (δ_F = −106.9 and −112.1 ppm; keto and enol form, respectively), **4a** (δ_F = −117.6 ppm) and **5a** (δ_F = −116.7 ppm).
(16) The phosphinous acid ligands are known to cooperate with the metal in the nitrile hydration reactions. As recently discussed in ref 10e, the hydration process involves the initial addition of the OH group of the ligand on the coordinated nitrile and subsequent hydrolysis of the resulting five-membered metallacycle.
(17) The unidentified products generated in these reactions seem to be related to the instability of **2a** in basic aqueous medium since, in an independent experiment, we observed the extensive decomposition of **2a** upon treatment with $NaCO_2H$ (20 equiv) in refluxing water for 24 h.
(18) **General Procedure for the Catalytic Reactions.** The corresponding β-ketonitrile **2** (1 mmol), water (3 mL), the ruthenium(II) complex **1** (0.028 g, 0.05 mmol; 5 mol %), and NaO_2CH (1.360 g, 20 mmol) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 100 °C for 24 h (48 h in the case of **2o**). After removal of the solvent under vacuum, flash chromatography (silica gel) of the residue using a mixture MeOH/EtOAc (1:10) as eluent afforded the desired β-hydroxy amides **4** in pure form.
(19) Complex **1** is readily synthesized from the reaction of two commercially available reagents, the dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$, and the chlorophosphine $P(4\text{-}C_6H_4F)_2Cl$ (see ref 11).

DOI: 10.1021/acs.orglett.6b03172
Org. Lett. 2016, 18, 6164−6167