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Ibuprofenamide: a convenient method of synthesis by catalytic hydration of 2-(4-isobutylphenyl)propionitrile in pure aqueous medium

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ABSTRACT

An efficient and practical synthesis of the non-steroidal anti-inflammatory drug (NSAID) ibuprofenamide by catalytic hydration of 2-(4-isobutylphenyl)propionitrile is described. The readily accessible arene-ruthenium(II) complex [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] is used as the catalyst, pure water as the solvent, and microwave irradiation as the heating source.

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Non-steroidal anti-inflammatory drugs (NSAIDs) are the first choice of drugs in the treatment of pain, degenerative joint diseases and rheumatic disorders. The clinical effects of NSAIDs are based on the inhibition of the enzyme cyclooxygenase (COX), which catalyzes the formation of prostaglandins (PGs).[1] Production of PGs is induced at sites of inflammation, where they are involved in the propagation of inflammation, pain, and fever. Inhibition of PGs production alleviates these pathologic effects, but it also interferes with the normal physiologic role of these molecules, that is, cytoprotection of gastric mucosa, hemostasis, renal function, gestation, and parturition.[2] Consequently, long-term therapy with NSAIDs is frequently limited by their adverse effects, particularly those caused by gastrointestinal bleeding, ulceration and perforation.[3]

Ibuprofen, chemically 2-(4-isobutylphenyl)propionic acid (**1**), is a well-known NSAID widely prescribed for the treatment of musculoskeletal disorders, inflammation, fever, primary dysmenorrhea and also in the management of mild pain.[1–3] Similar to other prototypical NSAIDs (aspirin, indomethacin, etc.), ibuprofen suffers from the limitation of gastrointestinal toxicity caused by the presence of a carboxylic acid moiety in its structure.[3]

A common strategy in pharmaceutical research is the use of well-established drugs as lead compounds to design new drug candidates with improved therapeutic properties (the 'prodrug approach'). Accordingly, in order to minimize its negative effects, considerable synthetic efforts have been made to mask the carboxylic acid group of ibuprofen. In this sense, a large number of amides able to *in vivo* deliver its parent acid **1** in a controlled manner by hydrolysis of the $-C(=O)NR^1R^2$ function have been developed, some of them showing improved analgesic activity and lower ulcerogenic effects.[4,5] The simplest member of this family, that is, ibuprofenamide (**3**), presents by itself a very good anti-inflammatory activity,[4a,j] and it has been used as an advanced intermediate in the preparation of several N-substituted derivatives with reduced ulcerogenic action.[4e–g,k,m] Repertaxin, a non-competitive allosteric blocker of interleukin-8 (CXCL8/IL-8) receptors (CXCR1/R2) belonging to the class of 2-phenylpropionyl methanesulfonamides, is also produced starting from **3**.[6]

The conventional method to prepare ibuprofenamide (**3**) involves a two-step sequence consisting in the conversion of ibuprofen (**1**) to the acid chloride **2**, by action of harmful thionyl chloride, followed by treatment with aqueous or gaseous ammonia (Scheme 1).[4a,e–g,j,k,m] Herein, an alternative, efficient, and practical synthetic approach to this valuable intermediate, via catalytic hydration of 2-(4-isobutylphenyl)propionitrile (**4**), is presented (Scheme 2).[7]

Hydration of nitriles is one of the most appealing and greener routes presently available for the large-scale production of amides. Traditionally, these hydration processes have been catalyzed by strong acids and bases under harsh conditions, methods which are not compatible with many sensitive functional groups and usually cause over-hydrolysis of the amides into the corresponding carboxylic acids.[8] It is now well-established that all these limitations can be circumvented by using enzymes[9] and metal

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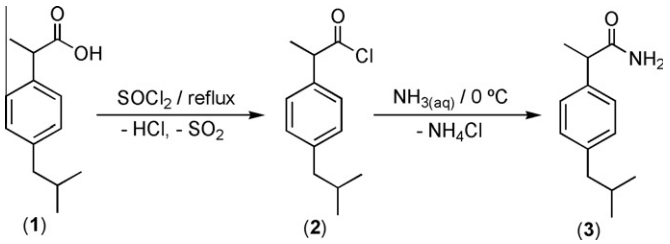
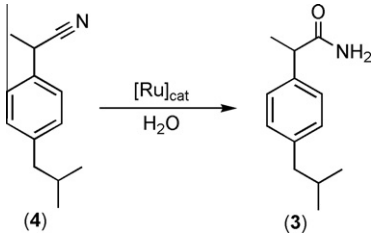


Scheme 1. Classical synthesis of ibuprofenamide (**3**).



Scheme 2. Catalytic hydration of 2-(4-isobutylphenyl)propionitrile (**4**).

catalysts,[10] several protocols for the selective formation of the amides being presently available for practical applications. However, despite these recent advances, no efficient preparations of **3** by catalytic hydration of **4** have been reported to date.[11,12]

In the course of our recent studies on metal-catalyzed nitrile hydration reactions,[13] we have found that the arene-ruthenium(II) complex **5** and the bis(allyl)-ruthenium(IV) derivatives **6**–**7** are extremely efficient and selective catalysts for this transformation (Fig. 1), the presence of hydrosoluble P-donor ligands in these complexes allows us to run the catalytic reactions in pure aqueous medium at neutral pH.[13a,b] With all these precedents in mind, the ability of complexes **5**–**7** to promote the hydration of 2-(4-isobutylphenyl)propionitrile (**4**) into ibuprofenamide (**3**) under these challenging reaction conditions has been explored as an alternative method of synthesis of this relevant compound.

In a typical experiment, the corresponding ruthenium precursor **5**–**7** (5 mol % of Ru) was added to a 0.33 M aqueous solution of 2-(4-isobutylphenyl)propionitrile (**4**) and the mixture heated in an oil-bath at 100 °C. The course of the reaction was monitored by regular sampling and analysis by gas chromatography (GC). The results obtained are summarized in Table 1.

As expected from our previous works,[13a,b] complexes **5**–**7** were able to provide ibuprofenamide **3** as the unique reaction product after 24 h of heating (ibuprofen was not detected by GC/MSD in the crude reaction mixtures). However, only a good conversion (91% GC yield) could be attained with the mononuclear Ru(II) complex **5** (entry 1), the ruthenium(IV) species **6** and **7** being poorly effective under the reaction conditions employed (22–64% GC yield; entries 2–3). With the aim of finding a more efficient catalyst for this relevant transformation other mononuclear [$RuCl_2(\eta^6$-$C_6Me_6)(PR_3)$] derivatives were checked,[14] and to our delight we discovered that the readily accessible tris(dimethylamino)phosphine-based complex [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**8**)[15] (5 mol %) is able to generate the desired amide **3** in a remarkable 97% GC yield after only 7 h of heating at 100 °C (entry 4 in Table 1). [16a] Subsequent purification by column chromatography on silica gel provided analytically pure ibuprofenamide in 87% isolated yield (copies of the ^1H and $^{13}C\{^1H\}$ NMR and GC/MSD spectra of this sample are given as Supplementary material).

The combined use of microwaves (MWs), as a nonclassical low-energy-consuming heating source, and water, as an environmentally friendly solvent, to perform organic reactions has recently

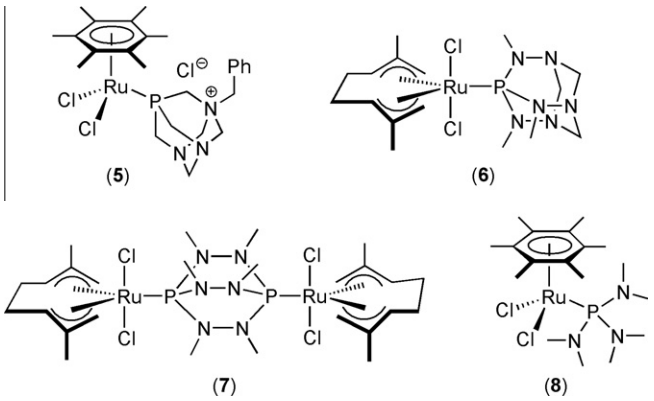


Figure 1. Structure of the ruthenium catalysts employed in this work.

Table 1
Ru-catalyzed hydration of 2-(4-isobutylphenyl)propionitrile (**4**) under thermal conditions[a]

Entry	Catalyst	Time (h)	Yield (%)[b]	TOF (h^{-1})[c]
1	**5**	24	91 (80)	0.8
2	**6**	24	22	0.2
3	**7**	24	64	0.5
4	**8**	7	97 (87)	2.8

[a] Reactions performed under N_2 atmosphere at 100 °C using 1 mmol of **4** (0.33 M in water). Substrate/Ru ratio:100/5.
[b] Yield of ibuprofenamide (**3**) determined by GC. Isolated yields after appropriate chromatographic work-up are given in brackets.
[c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the indicated time.

Table 2
Hydration of 2-(4-isobutylphenyl)propionitrile (**4**) catalyzed by complex [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**8**) under MW irradiation[a]

Entry	Ru (mol %)	Time (h)	Yield (%)[b]	TOF (h^{-1})[c]
1	5	0.33	>99	60.0
2	2.5	1	>99 (91)	39.6

[a] Reactions were performed under N_2 atmosphere using 1 mmol of **4** (0.33 M in water). A CEM Discover® S-Class microwave was used (150 W, 150 °C).
[b] Yield of ibuprofenamide (**3**) determined by GC. Isolated yield after appropriate chromatographic work-up is given in brackets.
[c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the indicated time.

emerged as a promising new field of research within the 'Green Chemistry' context.[17] In this sense, as shown in Table 2, the catalytic hydration of **4** by means of complex [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**8**) can be conveniently performed in pure water under MW-irradiation, the working conditions employed (150 W/150 °C) allowing to reduce drastically the reaction time. Thus, in the presence of 5 mol % of **8**, quantitative formation of ibuprofenamide was observed after only 20 min of irradiation (entry 1). More interestingly, the use of MWs also allowed the reduction of the catalyst loading without compromising the efficiency of the hydration process. Thus, using only 2.5 mol % of **8**, ibuprofenamide was generated in >99% GC yield after 1 h and could be isolated in analytically pure form with an excellent 91% yield (entry 2). [16b] However, we must note that all attempts made to recycle **8** by selective extraction of ibuprofenamide from the aqueous phase failed.

In summary, an effective and practical synthesis of ibuprofenamide, a very valuable raw material for the design of novel NSAIDs, has been developed by catalytic hydration of 2-(4-isobutylphenyl)propionitrile using the readily accessible arene-ruthenium(II) complex [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**8**). To the best

of our knowledge this is the first efficient and selective protocol described in the literature for this transformation.[11,12] Moreover, the process is truly sustainable since, in addition to its atom-economy, it proceeds in a pure aqueous medium and is compatible with the use of low-energy-consuming MW-irradiation as the heating source. Further investigations into the application of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**) to the catalytic hydration of other challenging organonitriles are now in progress in our laboratories, and will be the subject of future contributions.

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Supplementary data

Supplementary data (Copies of the $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectra of complex **8**. Copies of the ^1H and $^{13}C\{^1H\}$ NMR and GC/MSD spectra of ibuprofenamide (**3**) isolated from entry 4 in Table 1. GC conditions employed and GC profiles of the catalytic reactions) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.026.

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15. Preparation of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**): A solution of dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ (0.130 g, 0.194 mmol) in dichloromethane (20 mL) was treated with $P(NMe_2)_3$ (0.352 mL, 1.94 mmol) at room temperature for 3 h. The solution was then evaporated to dryness and the resulting oily residue washed with a 1:2 mixture of diethyl ether/hexane (4 × 10 mL), thus yielding an orange solid which was vacuum-dried. Yield: 0.133 g, 71% (Found: C, 43.33; H, 7.40; N, 8.60%. $C_{18}H_{36}N_3Cl_2PRu$ requires C, 43.46; H, 7.29; N, 8.45%). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162.1 MHz) δ 114.9 (s) ppm. ^1H NMR ($CDCl_3$, 400.5 MHz) δ 2.68 (d, 18H, $^3J_{PH}$ = 8.0 Hz, NMe), 1.96 (s, 18H, C_6Me_6) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 100.6 MHz) δ 90.1 (s, C_6Me_6), 35.2 (br, NMe), 16.0 (s, C_6Me_6) ppm. Copies of the spectra can be found in the Supplementary material.
16. (a) Catalytic hydration of 2-(4-isobutylphenyl)propionitrile (4) using complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**) under classical thermal conditions: Under nitrogen atmosphere, 2-(4-isobutylphenyl)propionitrile (0.187 g, 1 mmol), water (3 mL), and $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (24.8 mg, 0.05 mmol; 5 mol % of Ru) were introduced into a sealed tube and the reaction mixture stirred at 100 °C for 7 h. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by flash chromatography over silica gel using diethyl ether as eluent to afford 0.178 g of analytically pure ibuprofenamide (**3**) as a white solid (87% yield). The identity of **3** was assessed by comparison of its ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MSD;
(b) Catalytic hydration of 2-(4-isobutylphenyl)propionitrile (**4**) using complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**) under MW-irradiation: Under nitrogen atmosphere, a pressure-resistant septum-sealed glass microwave reactor vial was charged with 2-(4-isobutylphenyl)propionitrile (0.187 g, 1 mmol), water (3 mL), $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (12.4 mg, 0.025 mmol; 2.5 mol % of Ru) and a magnetic stirring bar. The vial was then placed inside the cavity of a CEM Discover® S-Class microwave synthesizer and power was held at 150 W until the desired temperature was reached (150 °C). Microwave power was automatically regulated for the remainder of the experiment to maintain the temperature (monitored by a built-in infrared sensor; P_{max} = 25 psi). Work-up as described above led to 0.187 g of analytically pure ibuprofenamide (91% yield).
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