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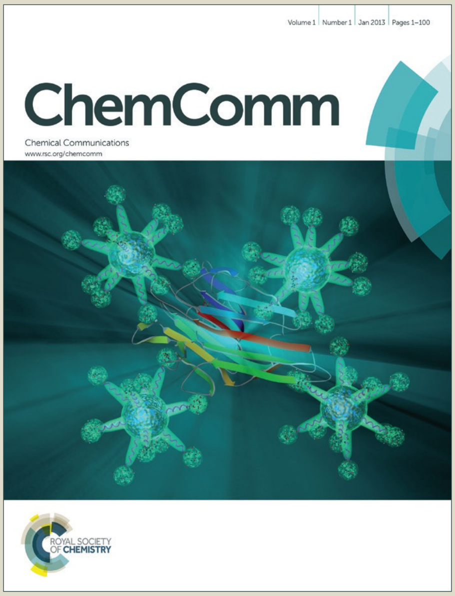

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A Mild Hydration of Nitriles Catalysed by Copper(II) Acetate

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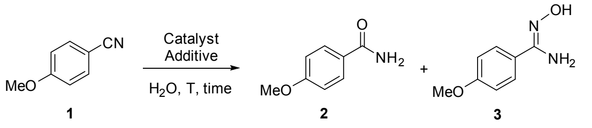
A simple, mild and general procedure for the hydration of nitriles to amides using copper as catalyst and promoted by *N*,*N*-diethylhydroxylamine is described. The reaction can be conducted in water at low temperature in short reaction times. This new procedure allows amides to be obtained from a wide range of substrates in excellent yields.

The availability of efficient processes to obtain amides is of great interest due to their many applications in organic chemistry. Amides can be found in a large variety of drugs, fabrics, fertilizers, plastics and lubricants. Additionally, amides are key intermediates in organic synthesis. Among all the methods reported for the synthesis of amides,[1,2] hydration of nitriles has become one of the most widely used methods to obtain primary amides in both, academia and industry.[3] Conventional procedures involve the use of strong acids and bases which can cause the formation of by-products in sensitive substrates along with the formation of carboxylic acids.[4] In the last decade an important advance/progress of this transformation has been achieved. In that sense, the use of metal catalysts such as Ru,[5] Au,[6] Rh,[7] Mn[8] have been crucial for the development of milder and more efficient transformations.[9] Recent work has reported the use of metal nanoparticles for the hydration of nitriles.[10] Despite all the efforts, most of the methods reported to date require high temperatures, long reaction times, large excess of reagents or the use of expensive catalysts. We therefore decided to explore a new methodology to obtain amides from nitriles which would require milder conditions than those previously reported.

Mechanistic studies carried out in the transformation of aldoximes to amides have shown that the first step involves the *in situ* formation of a nitrile by dehydration of the aldoxime. In a second step this nitrile is transformed into an amide by reaction with another molecule of aldoxime.[1b,2,11,12] Based on these results and our earlier work using hydroxylamine hydrochloride to catalyse transamidation,[2] as well as the conversion of nitriles into secondary amides using hydroxylamine,[13] we decided to explore this reactivity for the synthesis of primary amides.

Table 1 Optimization of the Hydration of Nitriles



Entry	Additive	Catalyst	T (°C)	Time (h)	Conv (%)[a]
1	NH_2OH (16 equiv.)	--	r.t.	24	100 **2**:**3** 1:1
2	NH_2OH (16 equiv.)	$[Ir\ Cp^*I_2]_2$ (1 mol%)	r.t.	24	100 **2**:**3** 1:1
3	NH_2OH (16 equiv.)	$Cu(OAc)_2$ (2 mol%)	r.t.	24	100 **2**:**3** 1:1
4	NH_2OH (16 equiv.)	$Zn(OAc)_2$ (5 mol%)	r.t.	24	100 **2**:**3** 1:1
5	NEt_2OH (10 equiv.)	--	25	24	82
6	NEt_2OH (10 equiv.)	--	35	24	100
7	NEt_2OH (3 equiv.)	--	35	24	100
8	NEt_2OH (3 equiv.)	$[Ir\ Cp^*I_2]_2$ (2 mol%)	35	3	100
9	NEt_2OH (3 equiv.)	$Cu(OAc)_2$ (2 mol%)	35	3	100

[a] Conversions were determined by analysis of the ^{1}H-NMR of the reaction mixture

In a first approach, *p*-methoxybenzonitrile (**1**) was treated with 16 equivalents of hydroxylamine. The reaction proceeded at room temperature and no starting material was observed after 24 h. Analysis of the reaction crude by ^{1}H-NMR showed the

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formation of two products in the same ratio which were assigned to the desired amide (**2**) and the amidoxime (**3**) (table 1, entry 1).[14] In order to reduce the amount of amidoxime different catalysts were tested but none of them seemed to play any role in the formation of the by-product (table 1, entries 2 - 4, see ESI).

Several reaction conditions were tested to transform the amidoxime (**3**) into the desired amide (**2**). Treatment of the reaction mixture with HCl and NaOH provided different ratios of products (see ESI). The addition of NaOH after 24 h to the reaction mixture led to the formation of **2** as the sole product. Although the hydrolysis of the amidoxime could be accomplished, the use of NaOH increased the harshness and the number of steps of the reaction making this approach impractical for synthetic purposes. In order to overcome this problem, the use of other additives was further investigated.

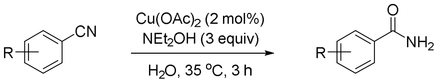
The synthesis and the mechanistic study of the formation of amidoximes suggests that it would be possible to regulate the formation of amidoxime by using *N*,*N*-disubstituted hydroxylamine.[14] Indeed the treatment of **1** with 10 equivalents of NEt_2OH at room temperature provided the desired amide **2** in 82% conversion (table 1, entry 5). Increasing the temperature to 35 ^{o}C afforded the amide in 100% conversion (table 1, entry 6). Further optimisation of the reaction conditions allowed us to reduce the amount of NEt_2OH to three equivalents. The introduction of a Lewis acid such as $[IrCp^*I_2]_2$ permitted the decrease in reaction times to 3 h (see ESI). Interestingly, the replacement of $[IrCp^*I_2]_2$ with $Cu(OAc)_2$ did not show any drop in the reaction conversions. The use of $Cu(OAc)_2$ makes this reaction more sustainable and economical. To the best of our knowledge these are the mildest reactions conditions reported until now for the hydrolysis of nitriles.[15,16,17]

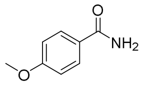
With the optimal conditions in hand the scope of the reaction was subjected to study. We were pleased to find that a broad range of nitriles could be hydrolysed under these reaction conditions (table 2).

Electron-withdrawing and electron-donating groups in the *ortho*, *meta* and *para* positions are very well tolerated as well as the use of aliphatic nitriles. Vinylic nitriles and nitriles containing heteroaromatic groups such as 2-furonitriles and 2-thiophenecarbonitriles as well as the use of ethylphenylcyanoacetate gave the corresponding amides in excellent isolated yields. The general applicability of our hydrolysis conditions was proved in a variety of substrates affording the corresponding amides in excellent yields, showing the potential of this reaction.

The most accepted mechanism for the hydration of nitriles involves the coordination of the nitrile to the metal centre. Through this coordination, the CN group increases its electrophilicity being more susceptible to nucleophilic attack by water.[18] The subsequent rearrangement of the corresponding iminolate species leads to the formation of the desired amide (scheme 2).

Table 2. Scope of the hydration of nitriles[a]

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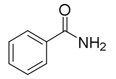
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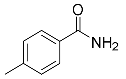
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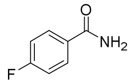
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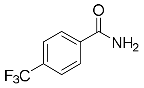
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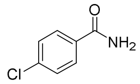
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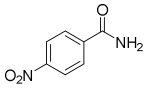
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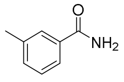
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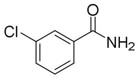
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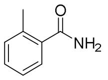
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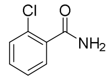
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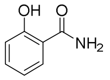
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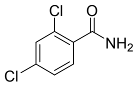
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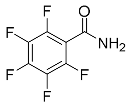
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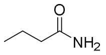
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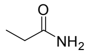
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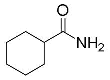
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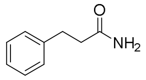
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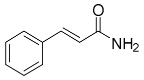
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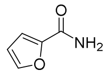
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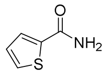
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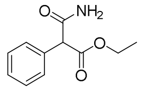
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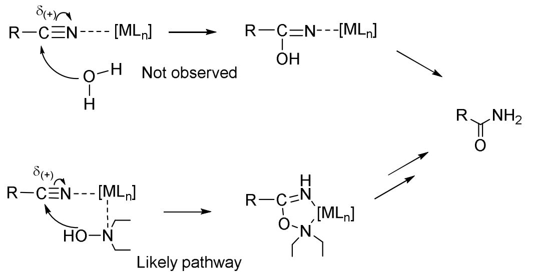
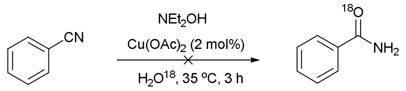
[a] Isolated yields



Scheme 2 Plausible mechanisms for the hydration of nitriles

When NEt_2OH is employed, the oxygen could act as nucleophile and in subsequent steps the reaction could follow a radical pathway[15,16] or a rearrangement facilitated by the metal (scheme 2).[2]

Intrigued by the nature of this transformation NMR experiments were carried out to attempt to detect intermediates which could give some information about the mechanism. Unfortunately, only the rapid appearance of the final amide was observed (see ESI). In order to study if water was indeed acting as nucleophile, the reaction was performed in the presence of H_2O^{18} (scheme 3).



Scheme 3 Hydration of benzonitrile using H_2O^{18}

The analysis of the reaction crude by mass spectrometry did not show the incorporation of ^{18}O into the final amide (see ESI). This evidence indicates that in the hydration pathway water is not acting as nucleophile. These results will support the nucleophilic attack of the NEt_2OH followed by a radical[11,12] or rearrangement pathway facilitated by the Lewis acid.[2,14] Further studies to uncover the more plausible pathway are still undergoing.

Conclusions

In summary, we report a new methodology for the hydration of nitriles. The use of copper as Lewis acid allows the synthesis of amides in water as a solvent at low temperatures and short reaction times. The amides were obtained in excellent yields for a broad range of nitriles making this methodology very efficient and general, solving the main problems associated to the methods reported until now.

Acknowledgements

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