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Selective NaOH–catalysed hydration of aromatic nitriles to amides†‡

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The selective synthesis of aromatic and heteroaromatic amides through base–catalysed hydration of nitriles was achieved using inexpensive and commercially available NaOH as the only catalyst. A wide range of nitriles was selectively converted to their corresponding amides. Kinetic studies show that the double hydration of nitriles towards undesirable carboxylic acids is negligible under our reaction conditions.

The selective hydration of nitriles leading to the formation of amides is of great interest to both academia and industry.[1] Due to an increasing demand for amides as versatile building blocks,[2] the hydration of nitriles has emerged as a straightforward and atom-economical methodology for the preparation of such compounds. Typically, hydration reactions have been carried out in the presence of acids,[3] although a strict control of the reaction time, temperature, concentration and other parameters is required for optimal results (in particular to avoid over-hydrolysis to the related carboxylic acids). In addition, an excess of the acid is usually required, which leads to difficult amide purification and substantial waste generation. Recently, base-catalysed procedures have attracted considerable attention.[4]

The use of peroxides under basic conditions has been widely reported as an efficient and selective variation for the base-promoted synthesis of amides.[5] Nevertheless, the special handling required for peroxides[6] and the low functional group tolerance of these protocols have progressively decreased the overall interest in this approach, particularly for industrial applications. Similar inconveniences have been found with other reported hydration systems, such as the use of sodium superoxide,[7] despite its good performance under mild conditions. In order to overcome these significant drawbacks, enzymatic systems[8] and transition-metal catalysts[9–11] have been developed, and these protocols are nowadays extensively used in this reaction due to their excellent

performance and suitability for a large variety of synthetic needs. In spite of these remarkable advances, the simpler acid- or base-catalysed hydration of nitriles still remains the most desirable approach, due to its simplicity and low operational costs. Alami and co-workers have reported the synthesis of a variety of aromatic and heteroaromatic amides in good to excellent yields using Cs_2CO_3 (1.5 equivalents) in pyrrolidinone.[4c] In the same year, Tu and co-workers reported a microwave-assisted process using 5 to 50 mol% of K_2CO_3 in water,[4d] with a wider scope of substrates. Recently, the catalytic use of a NHC (N-heterocyclic carbene) precursor, the 1,3-dimethylimidazolium bicarbonate (IMe·HCO₃), in an EtOH/H_2O mixture[4e] and CsOH in a DMSO/water mixture[4f] has been described as efficient promoter of this reaction. Despite these latest breakthroughs, there is still a need to further improve this process.

As part of our work on mixed N-heterocyclic carbene/phosphine palladium systems for the aqueous Suzuki–Miyaura reaction,[12] and in the course of testing some nitrile-containing aromatic substrates, surprising results were obtained. The isolated cross-coupling products using such substrates were found to bear an amide group rather than the initial nitrile functionality. After some background experiments supporting the non-involvement of a catalytic Pd species in such a transformation, the role of NaOH as a selective hydrolysis promoter of aromatic nitriles was identified as the culprit for the observed transformation. To validate this hypothesis, the hydrolysis of benzonitrile using hydroxide bases (M = Li, Na, K, Cs) as catalysts was first investigated (Table 1).

Several solvents were tested using 1 mol% of NaOH (Table 1, entries 1–6) at 110 °C. EtOH and MeOH were shown to perform optimally in 1:1 mixtures with H_2O (27% and 35% conversion, respectively). EtOH was selected for further optimisation due to its lower toxicity and environmental impact. Next, the ratio of the EtOH/H_2O mixture was varied (Table 1, entries 7–11), and an optimal value of 7:3 was

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Table 1   Optimisation of benzonitrile hydration catalysed by MOH[a]

Entry	Solvent	Base	Loading (mol%)	Conversion (%)[b]
1	EtOH/H$_2$O (1:1)	NaOH	1	27
2	CH$_3$CN/H$_2$O (1:1)	NaOH	1	15
3	1,4-Dioxane/H$_2$O (1:1)	NaOH	1	3
4	MeOH/H$_2$O (1:1)	NaOH	1	35
5	THF/H$_2$O (1:1)	NaOH	1	15
6	H$_2$O	NaOH	1	4
7	EtOH/H$_2$O (8:2)	NaOH	1	28
8	EtOH/H$_2$O (7:3)	NaOH	1	45
9	EtOH/H$_2$O (6:4)	NaOH	1	42
10	EtOH/H$_2$O (3:7)	NaOH	1	15
11	EtOH/H$_2$O (2:8)	NaOH	1	8
12	EtOH/H$_2$O (7:3)	LiOH	1	25
13	EtOH/H$_2$O (7:3)	KOH	1	33
14	EtOH/H$_2$O (7:3)	CsOH	1	52
15	EtOH/H$_2$O (7:3)	NaOH	5	80
16	EtOH/H$_2$O (7:3)	NaOH	10	>99 (82)[c]
17	EtOH/H$_2$O (7:3)	NaOH[d]	10	>99
18	EtOH/H$_2$O (7:3)	NaOH	10	>99 (81)[c,e]

[a] Reaction conditions: benzonitrile (1 mmol), base (1 M stock solution), solvent (0.5 mL), 110 °C (external temperature), 17 h. [b] Conversion determined by GC based on benzonitrile, average of two reactions. [c] Isolated yield. [d] Semiconductor grade NaOH used. [e] 90 °C (external temperature).

determined. The role of the cation associated with the hydroxide base was also examined (Table 1, entries 12–14).

While CsOH led to the best result (52% conversion) compared to NaOH (45% conversion), NaOH was selected for further optimisation due to its lower cost and ease of handling. Increasing the catalyst loading to 10 mol% (Table 1, entry 16) gave full conversion of benzonitrile to the desired benzamide, with 82% isolated yield. In order to rule out any catalytic species other than NaOH being operative in this process (such as metal traces contaminating low grade NaOH), the same reaction was repeated using semiconductor grade NaOH (Table 1, entry 17).[13] Moreover, decreasing the reaction temperature to 90 °C afforded the amide product with no significant decrease in the isolated yield (Table 1, entry 18).
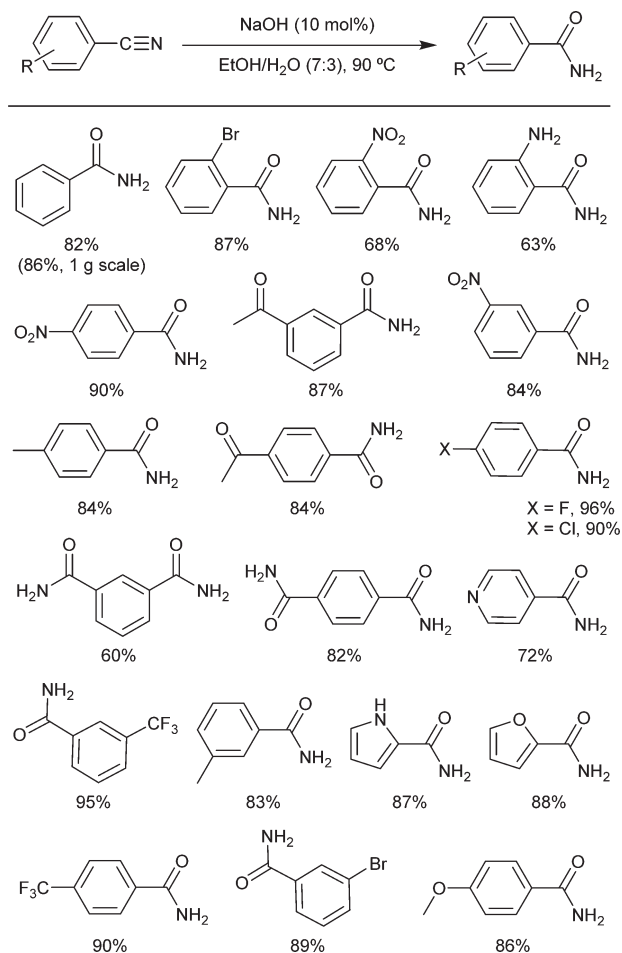
In order to demonstrate the versatility of the method, a reaction scope was explored. The optimised conditions were tested on a wide range of substituted aromatic nitriles, bearing either electron-donating or electron-withdrawing substituents. Some heteroaromatic nitriles were also tested. These results are summarised in Scheme 1. *Ortho*-, *meta*- and *para*-substituted amides were all obtained in high yields. The transformation of some challenging heteroaromatic nitriles also proceeded with good yields. To our delight, the reaction with benzonitrile was reproduced on a 1 g scale with no apparent loss in efficiency or selectivity (86% isolated yield, no chromatographic separation needed). All reactions were carried out in air using distilled water and reagent grade ethanol.[14]

Kinetic studies were conducted in order to understand the selectivity of this catalytic system. The catalytic hydration of benzonitrile using 10 mol% of NaOH in EtOH/H$_2$O (7:3) at 90 °C was monitored *in situ* using IR (see ESI‡). Results showed that benzamide was the major species present, along with trace amounts of sodium benzoate (*ca.* 2%). Benzoic acid was not observed. Using sodium benzoate instead of NaOH as the reaction catalyst, under our optimal conditions, did not allow for any reactivity. Thus, these results suggest that the hydrolysis of benzamide is a negligible side-reaction, under our reaction conditions. Experimental data were successfully fitted to a pseudo-first order rate equation (Fig. 1), with a rate constant k_1 of 1.1×10^{-2} M^{-1} s^{-1} and $t_{1/2} \approx 39$ min. A similar approach was followed to study the second hydrolysis step, by monitoring the hydration of benzamide under the optimal reaction conditions. Results confirmed that this second hydration reaction was significantly slower than the first hydration process (see ESI‡).

To test whether the methodology could be further extended, the reactivity of aliphatic nitriles was next examined. Acetonitrile was selected as a model substrate, and after conducting IR-monitored tests, under our optimal reaction conditions, very low concentrations of an acetamide/acetate mixture were detected. The low catalytic efficiency of the system was explained by the complete consumption of OH$^-$ in the second hydration step, as the amide species were over-hydrolysed to their carboxylate derivatives. The hydration of isobutyronitrile, pivalonitrile and hexanenitrile, under the same conditions, also led to very low isolated yields of their related amides (5%, 8% and 13%, respectively). Based on these findings, we conclude that aliphatic nitriles are not suitable substrates for the synthesis of amides using the present system.

To understand the difference in reactivity between aromatic and aliphatic nitriles, an analysis of the well described base-catalysed nitrile hydration mechanism has to be considered. As the base only acts catalytically in the first hydration

Scheme 1 Scope of the NaOH-catalysed hydration of nitriles. Reaction conditions: nitrile (1 mmol), NaOH (0.1 mmol), EtOH/H$_2$O (7:3, 0.5 mL), 90 °C (external temperature), 17 h. Isolated yields, average of 2 reactions.
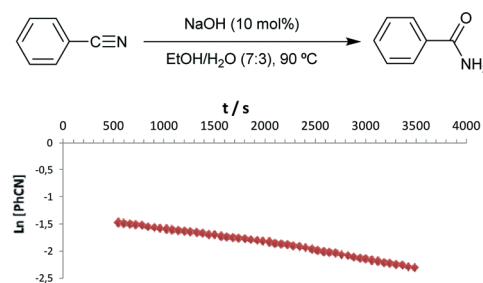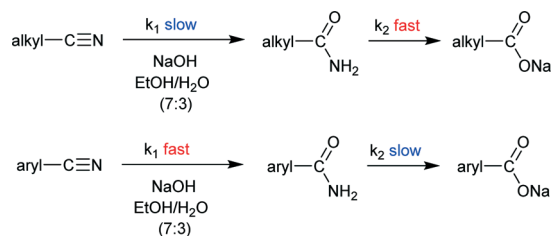
Fig. 1 IR monitoring data for the hydration of benzonitrile. Reaction conditions: benzonitrile (24 mmol), base (2.4 mmol), EtOH/H$_2$O (7:3, 12 mL), 90 °C (external temperature).

Scheme 2 Base-catalysed hydration of aromatic and aliphatic nitriles under the described reaction conditions.

Conclusions

In conclusion, we have demonstrated the efficiency of a simple base-catalysed hydration of aromatic nitriles leading to the selective synthesis of the corresponding amides. A wide range of aromatic nitriles bearing a variety of electron-donating and electron-withdrawing substituents, as well as challenging heteroaromatic nitriles, were successfully converted to their corresponding amides in good to excellent yields, using 10 mol% of NaOH as catalyst and a EtOH/H$_2$O (7:3) solvent mixture. This methodology represents a highly practical, economical and straightforward protocol for the preparation of aromatic amides.

Notes and references

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step, a rapid second hydration to the corresponding carboxylates would consume this species, thus decreasing the rate of the amide synthesis. A slower second hydration step would afford more available base for the conversion of nitriles to amides, and also a better selectivity towards the latter. These conclusions are supported by our experimental data (see ESI‡). The proposed kinetics of the hydration of aromatic and aliphatic nitriles are thus presented in Scheme 2.

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