

Cite this: *Green Chem.*, 2012, **14**, 921

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## Efficient and practical transition metal-free catalytic hydration of organonitriles to amides†

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Received 21st December 2011, Accepted 14th February 2012

DOI: 10.1039/c2gc16637b

**K<sub>2</sub>CO<sub>3</sub> can act as an efficient catalyst for the hydration of organonitriles in aqueous conditions assisted by microwave irradiation, which represents an inexpensive, practical, atom-economical, and straightforward transition metal-free protocol to various amides.**

As versatile synthons in organic synthesis and essential intermediates in pharmaceutical and material sciences,<sup>1,2</sup> amides played significant roles and exhibited a wide range of applications in academia and industry.<sup>3</sup> In contrast with other methodologies, hydration of organonitriles constitutes a more atom-economical and straightforward protocol to access various amides, which has been applied as an important technology in industry to produce a wide number of profitable fine chemicals such as acrylamide and nicotinamide.<sup>4</sup> Moreover, industries generated enormous amounts of organonitrile chemical waste and directly disposed them into rivers, lakes and the sea, and they are now considered as a disastrous threat to the environment. Therefore, a practical and general protocol to convert organonitriles to amides is intriguing, especially in water media. Classic hydrations are traditionally carried out with strong acids or bases such as H<sub>2</sub>SO<sub>4</sub> or NaOH in aqueous condition, which frequently resulted in over-hydrolysis to form undesirable carboxylic acids.<sup>5</sup> Hence, the hydration precedents accelerated by transition metal homogeneous<sup>6</sup> and heterogeneous<sup>7</sup> catalysts as well as nanoparticles<sup>8</sup> were developed and some of them demonstrated higher selectivity to form amides, even tolerating substrates with sensitive functional groups. However, in many cases harsh reaction conditions, long reaction time and oxygen-free techniques are requested. In addition, expensive transition metal precursors (such as cobalt,<sup>9</sup> copper,<sup>10</sup> gold,<sup>11</sup> rhodium,<sup>12</sup> ruthenium,<sup>13</sup> palladium,<sup>14</sup> platinum,<sup>15</sup> etc.) or luxurious ligands (phosphines, NHC carbenes, etc.), high catalyst loading, toxic organic solvents or even oxidative reagents (DMSO, H<sub>2</sub>O<sub>2</sub>, etc.) as well as inconvenient catalyst/product separation procedures also hinder their application as practical protocols in industry. Therefore, the development of an efficient green catalytic hydration protocol in aqueous media, especially in water, is an important pursuit and challenge.

Although microbial enzymatic hydration of organonitriles offered a mild, highly selective and environmentally friendly option to produce amides,<sup>6c</sup> low reactivity, narrow substrate scope and special handling of microorganisms restrained it as a practical protocol. However, various amides widely exist in the nature and amino bonds play crucial roles to construct peptides, proteins and enzymes, which are vital to organisms and arouse us to explore how to generate the first amide in the nature without the aid of enzymes. The hypothesis of a mineral-mediated origin of life, which assumes minerals could catalyze the chemical reactions in prebiotic time, has inspired us. Therefore, we reported in this communication an efficient and practical hydration of organonitriles catalyzed by inorganic salts with broad substrates scope.

Initially, various inorganic salts, such as CaCO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, KOAc, K<sub>3</sub>PO<sub>4</sub>, etc., were involved to test their potential ability to accelerate hydration of organonitriles in water. To our delight, with a stoichiometric amount of Cs<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub>, when the hydration of *p*-chlorobenzonitrile **1a** in water was carried out under reflux conditions, *p*-chlorobenzamide **2a** was obtained in good isolated yield within 3 hours by simple filtration (Table 1, entries 1–2) and no corresponding acid was

**Table 1** Microwave-assisted hydration of *p*-chlorobenzonitrile accelerated by various inorganic bases<sup>a</sup>

Entry	Base	Mol%	Temp. (°C)	Time	Yield <sup>b</sup> (%)
1	K <sub>2</sub> CO <sub>3</sub>	100	100 <sup>c</sup>	3 h	92
2	Cs <sub>2</sub> CO <sub>3</sub>	100	100 <sup>c</sup>	3 h	97
3	K <sub>2</sub> CO <sub>3</sub>	100	100	5 min	94
4	K <sub>2</sub> CO <sub>3</sub>	5	100 <sup>c</sup>	8 h	29
5	K <sub>2</sub> CO <sub>3</sub>	5	100	15 min	14
6	K <sub>2</sub> CO <sub>3</sub>	5	140	15 min	44
7	K <sub>2</sub> CO <sub>3</sub>	5	150	15 min	91
8	K <sub>2</sub> CO <sub>3</sub>	5	150	5 min	50
9	K <sub>2</sub> CO <sub>3</sub>	3	150	15 min	44
10	Cs <sub>2</sub> CO <sub>3</sub>	5	150	15 min	98
11	Na <sub>2</sub> CO <sub>3</sub>	5	150	15 min	24
12	KOAc	5	150	15 min	11
13	K <sub>3</sub> PO <sub>4</sub>	5	150	15 min	82

<sup>a</sup> All reactions were carried out under air in 1 mmol scale in water.

<sup>b</sup> Isolated yield. <sup>c</sup> The reaction mixture was heated in an oil bath.

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† Electronic supplementary information (ESI) available: Experiment details. See DOI: 10.1039/c2gc16637b

detected. This process can dramatically be expedited by microwave irradiation,<sup>16</sup> and the hydration completed within 5 minutes (Table 1, entry 3). Furthermore, catalytic amounts still accelerated the hydration at 100 °C; however, with 5 mol% K<sub>2</sub>CO<sub>3</sub>, the yields of *p*-chlorobenzamide were relatively low even with microwave assistance (Table 1, entries 4–5). Further increasing the reaction temperatures, the yields of **2a** were enhanced (Table 1, entries 6–7); the best result was observed when the hydration was carried out at 150 °C. By shortening the reaction time to 5 minutes or slightly decreasing the catalyst loading to 3 mol%, unsatisfying results were obtained (50% and 44%, Table 1, entries 8–9). When 5 mol% Cs<sub>2</sub>CO<sub>3</sub> was applied, almost a quantitative yield was obtained (98%, Table 1, entry 10). The other inorganic salts such as Na<sub>2</sub>CO<sub>3</sub>, KOAc and K<sub>3</sub>PO<sub>4</sub> still resulted in lower yields (11–82%, Table 1, entries 11–13).

Under the optimal reaction conditions, inexpensive K<sub>2</sub>CO<sub>3</sub> was involved as a catalyst to test the scope of the protocol with

regard to various kinds of functionalized nitriles, although Cs<sub>2</sub>CO<sub>3</sub> resulted in a better yield in the model reactions (Table 1, entry 10). The results are summarized in Table 2, which indicated that K<sub>2</sub>CO<sub>3</sub> exhibited high catalytic activity for hydrations of active, inactive and heterocyclic nitriles to corresponding amides in aqueous media. A variety of benzonitriles were almost quantitatively hydrated in water (>99% conversions, determined by GC) and resulted in excellent isolated yields with 5–50 mol% K<sub>2</sub>CO<sub>3</sub> (Table 2, entries 1–23). In the case of water-insoluble amides, the analytically pure white products could be easily isolated by simple filtration after cooling to ambient conditions; therefore, the isolated yields also depended on nuances of the solubility of the benzoamides. The other water-soluble or liquid amides were isolated by extraction with EtOAc. The relative position of substituents in benzonitriles slightly affected the efficiency of the hydration; *m*-substituted benzonitriles resulted in the best isolated yields in contrast to the other two isomers (Table 2, entries 2–3 and 8–10). And *o*-substituted benzonitriles

**Table 2** Microwave-assisted hydration of various nitriles catalyzed by K<sub>2</sub>CO<sub>3</sub> in aqueous media<sup>a</sup>

		R-CN		K <sub>2</sub> CO <sub>3</sub> , Solvent		R-CONH <sub>2</sub>			
				Microwave, 150 °C					
Entry	Amide	K <sub>2</sub> CO <sub>3</sub> (mol%)	Time (min)	Yield <sup>b</sup> (%)	Entry	Amide	K <sub>2</sub> CO <sub>3</sub> (mol%)	Time (min)	Yield <sup>b</sup> (%)
1		5	15	90	14		50	15	99
2		5	15	97( <i>o</i> )	15		20	15	99
3		5	15	>99( <i>m</i> )	16		20	15	96
4		5	15	88	17		5	15	94
5		5	15	90	18		5	15	>99
6		5	15	97	19 <sup>c</sup>		5	15	76
7 <sup>c</sup>		5	15	99	20		20	15	72
8		20	15	91( <i>o</i> )	21 <sup>c</sup>		25	15	94
9		20	15	96( <i>m</i> )	22 <sup>d</sup>		15	15	92
10		5	15	88( <i>p</i> )	23 <sup>c</sup>		25	40	67
11		20	20	97					
12		20	30	>99( <i>o</i> )					
13		20	30	93( <i>p</i> )					

<sup>a</sup> Microwave-assisted hydration reactions were carried out with 1 mmol nitrile and a catalytic amount of K<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O at 150 °C. <sup>b</sup> Isolated yield.

<sup>c</sup> Reactions were carried out in aqueous media (*i*-PrOH–H<sub>2</sub>O = 1 : 2). <sup>d</sup> Reactions were carried out in aqueous media (EtOH–H<sub>2</sub>O = 1 : 20).

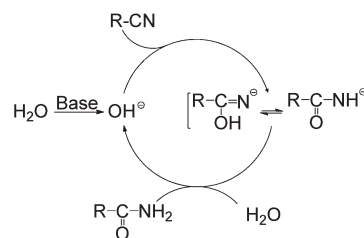
**Table 3** The catalytic behaviour of the recycling filtrates<sup>a</sup>

Entry	Nitrile	K <sub>2</sub> CO <sub>3</sub> (mol%)	Amide	Yield <sup>b</sup> (%) for each cycle		
				1st	2nd	3rd
1	<b>1a</b>	5	<b>2a</b>	85	84	82
2	<b>1o</b>	50	<b>2o</b>	89	90	83

<sup>a</sup> Microwave-assisted hydration with 1 mmol scale. <sup>b</sup> Isolated yield.

were usually less-active substrates than their *m*- and *p*-analogues, however, sterically more-demanding substrates like *o*-chlorobenzonitrile **1c** and *o*-tolunitrile **1i** afford better results than their *p*-analogues (**1a** and **1k**). The substrates bearing electron-withdrawing groups were more reactive than those with electron-donating groups; for most electron-donating substituted substrates, 20 mol% K<sub>2</sub>CO<sub>3</sub> was required to achieve satisfied conversions and yields (Table 2, entries 8–13). With 50 mol% K<sub>2</sub>CO<sub>3</sub>, sterically more demanding substrates like 1-naphthonitrile **1o** were also tolerated (Table 2, entry 14). To our delight, di-*ortho*-substituted benzonitriles converted to the corresponding amides **2p** and **2q** even with 20 mol% K<sub>2</sub>CO<sub>3</sub>, indicating a broad substrate scope of the protocol (Table 2, entries 15 and 16). In addition, our protocol tolerated heterocyclic substrates such as 3-thiophenecarbonitrile **1r** and 4-cyanopyridine **1s** (Table 2, entries 17 and 18). For less soluble organonitriles, additional organic solvents such as *i*-PrOH or EtOH have to be involved to increase their solubility in water. With the help of *i*-PrOH, double hydration of dinitrile underwent conversion to diamides **2t** within 15 minutes (76%, Table 2, entry 19). Under similar conditions, the protocol can successfully be extended for the hydration of 2-phenylacetoneitrile **1u** and 2-(naphthalen-1-yl) acetoneitrile **1v** to the corresponding amides **2u** and **2v** in 72% and 94% yields, respectively (Table 2, entries 20 and 21). Cinnamamide **2w** was readily obtained with similar procedure in a 92% isolated yield (Table 2, entry 22), and a small amount EtOH was required in this case. Furthermore, hydration of aliphatic nitriles like octanenitrile **1x** resulted in a 67% yield for **2x** with 25 mol% K<sub>2</sub>CO<sub>3</sub>, even when prolonging the reaction time to 40 minutes in the aqueous *i*-PrOH (Table 2, entry 23).

As a practical protocol with broad substrate scope, the possibility of catalyst recycling is considered as another important issue. With 5 mol% K<sub>2</sub>CO<sub>3</sub>, almost constant isolated yields for **2a** were obtained by the hydration with the first three recycling filtrates (82–85%, Table 3, entry 1). Only trace amide **2a** along with a big amount of starting material was obtained with the 4th filtrate. Similarly, the filtrate can also be recycled for another three times in the hydration of **1o** with 50 mol% K<sub>2</sub>CO<sub>3</sub>; 82–90% yields were observed (Table 3, entry 2). The pH value of the 3rd filtrate of hydration of **1a** is *ca.* 7.5, which is much lower than the pH value of solution of 5 mol% K<sub>2</sub>CO<sub>3</sub> in water (pH = 8.5) and suggests that OH<sup>−</sup> plays a crucial role in the hydration of organonitriles. Therefore, a possible weak base catalytic hydration mechanism is proposed in Fig. 1. However, if the catalytic route went along this mechanism, theoretically the filtrate should be recycled more than three times. By carefully acidification of the 3rd filtrate of the reaction mixture of **1a** and

**Fig. 1** A proposal mechanism for hydration of organonitriles in water.

extraction by EtOAc, less than 10% yield of *p*-chlorobenzoic acid was isolated, which suggested a part of *p*-chlorobenzamide **2a** was further converted to acid under the basic conditions after a long time of microwave irradiation. Due to only catalytic amount of K<sub>2</sub>CO<sub>3</sub> being applied and high solubility of the corresponding potassium benzoate in water, a satisfactory isolated yield of amides was still afforded by simply filtration even after the 3rd recycle, which further indicated the protocol practicability and efficiency. In addition, with this negative charge mechanism, it is easy for us to understand that the organonitriles with electron-withdrawing groups show better reactivity than the electron-donating analogues in Table 2.

In summary, K<sub>2</sub>CO<sub>3</sub> can act as an efficient catalyst for the hydration of organonitriles in aqueous conditions assisted by microwave irradiation, which represents an inexpensive, practical, atom-economical, and straightforward transition metal-free protocol to various amides. Besides various mono-, di- and even tri-substituted benzonitriles, heterocyclic and aliphatic substrates were also readily converted to the corresponding amides in high selectivity, which demonstrated the broad substrate scope of the newly developed catalytic hydration system. In addition, a simple product separation procedure and recyclability of the filtrate as the catalyst highlight the applicability of the protocol.

Financial support from National Science Foundation of China (No. 20902001 and 21172045) and Shanghai Leading Academic Discipline Project (B108) is gratefully acknowledged.

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