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Mild and Selective Heterogeneous Catalytic Hydration of Nitriles to Amides by Flowing through Manganese Dioxide

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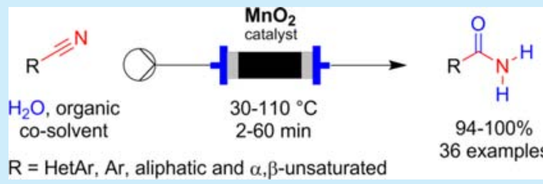
Supporting Information

ABSTRACT: A sustainable flow chemistry process for the hydration of nitriles, whereby an aqueous solution of the nitrile is passed through a column containing commercially available amorphous manganese dioxide, has been developed. The product is obtained simply by concentration of the output stream without any other workup steps. The protocol described is rapid, robust, reliable, and scalable, and it has been applied to a broad range of substrates, showing a high level of chemical tolerance.



Although the methods used for the preparation of primary amides[1,2] are generally considered to be straightforward (Figure 1), practical access to this key functionality can still be problematic.[3] Among the range of reported protocols, the hydration of nitriles represents the most atom-economical and industrially relevant process.

Indeed, nitrile hydration is a classic transformation but one which is still difficult to achieve, even with the range of available reagents. Traditional methods of hydration using acid or base catalysis can cause overhydrolysis or byproduct formation due to functional group incompatibility.[1,4,5] Homogeneous metal catalysis is frequently used in an industrial setting.[6] Intimate catalyst−substrate interaction, mild reaction conditions, and an understanding of the catalytic process are recognized as main advantages of this approach. Nevertheless, there are some disadvantages, such as a relatively short catalyst lifetime, a low tolerance for harsh conditions (high pressure and temperature), issues with catalyst−product separation and the cost of the catalyst itself. On the other hand, hydrolysis with a heterogeneous catalyst is a valid alternative with the important advantage that the catalyst can be easily separated. The surface of heterogeneous materials can provide an ideal framework for the disposition of catalytically active functionality in order to achieve selectivity, especially with base metal oxides which can have both Lewis acidic and Brönsted basic sites. Heterogeneous catalysts[7] have been successfully applied to the hydration of nitriles, although they are not widely used.

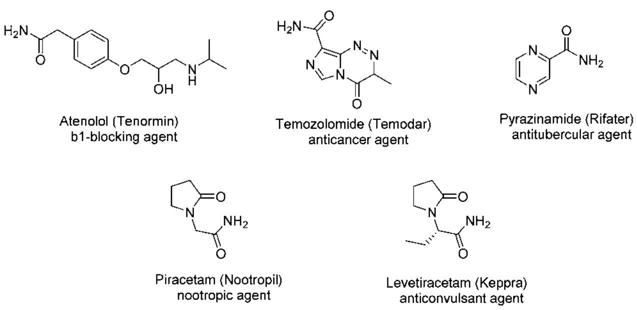
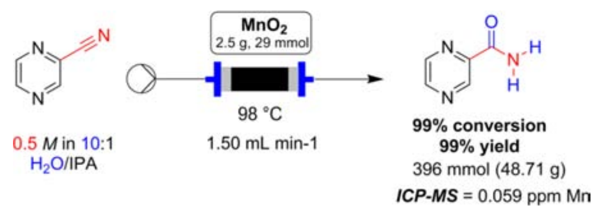


Figure 1. Examples of pharmaceuticals containing a primary amide functionality.

Scheme 1. Flow Synthesis of Pyrazinamide *via* Hydration of the Precursor Nitrile by Flowing through MnO_2



Metal catalysts such as Ag, Au, Ru, Ni, and Pd are expensive, and leaching of the catalyst into the product presents a serious problem. Catalysts such as Raney copper,[7a] gold-supported on titania (Au/TiO_2),[7b] ruthenium hydroxide loaded on alumina ($(Ru(OH)_x/Al_2O_3)$),[7c] and hydroxyapatite-supported silver nanoclusters (Ag/HAP)[7d] often require inconvenient inert atmospheres before they are effective. As high temperatures are generally needed (>140 °C),[7] the substrate compatibility can be limited and isolation of the product challenging. Although heterogeneous catalysis is usually associated with fast, easy product collection and catalyst recovery, in practice, extraction of the product with an organic solvent is often necessary with most of the procedures mentioned above. To the best of our knowledge therefore, a truly efficient, sustainable, widely applicable and recyclable system for the simple hydration of nitriles is still unknown, despite its inherent importance during the preparation of molecules of biological interest.

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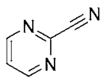
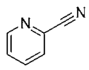
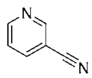
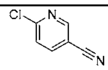
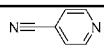
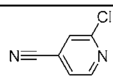
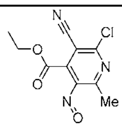
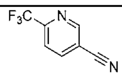
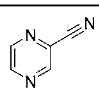
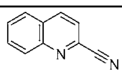
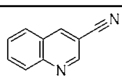
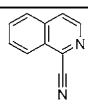
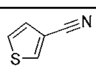
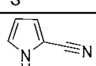
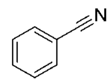
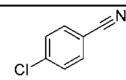
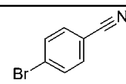
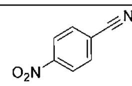
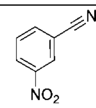
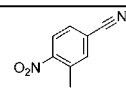
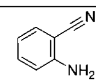
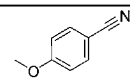
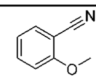
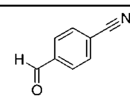
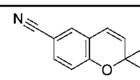
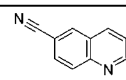
Table 1. Flow Hydration of Heteroaromatic Nitriles[a]

entry	Substrate	residence time (min)/temp (°C)	yield
1		20/40	94%
		15/50	98%
		15/60	99%
		3/100	99%[b]
2		10/50	99%[b,c]
		3/100	99%
3		12/60	99%
		5/100	99%[b]
4		10/50	99%
5		15/60	99%
6		12/60	98%
7		15/60	94%
8		15/70	98%
9		6/50	99%
		2/98	99%[d]
10		15/60	98%
11		15/70	99%
12		15/70	98%
13		20/70	98%
14		20/80	99%

[a]General procedure for the hydration of heteroaromatic nitriles: 5 mmol of nitrile in H_2O/acetone (20 mL, 5:1 v/v) were passed through a reactor column (Omnifit, 10.0 mm i.d. × 100.0 mm length) packed with amorphous MnO_2 (2.5 g) with both ends packed with Celite. A 100 psi bpr was placed after the reactor. For entries 4−8 and 10−14 the solution fed into the system was H_2O/IPA (1:1, v/v, 20 mL). [b]Reaction was scaled to 200 mmol. [c]Comparative microwave reaction showed 98% conversion after 3 h. [d]Reaction was scaled to 400 mmol.

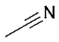
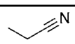
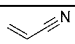
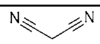
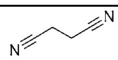
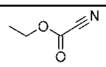
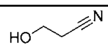
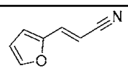
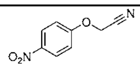
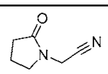
Table 2. Flow Hydration of Aromatic Nitriles[a]

entry	substrate	residence time (min)/temp (°C)	yield
15		15/100	99%
		15/100	98%[b]
16		12/100	99%
17		10/100	99%
18		8/100	99%
19		15/100	98%
20		20/100	99%
21		40/100	96%
22		50/110	97%
23		60/110	98%
24		20/100	99%
25		60/100	99%
26		30/100 °C	98%

[a]General procedure for the hydration of aromatic nitriles: 2 mmol of nitrile in H_2O/IPA (20 mL, 1:1 v/v) were passed through a reactor column (Omnifit, 10.0 mm i.d. × 100.0 mm length) packed with amorphous MnO_2 (2.5 g) with ends packed with Celite. A 100 psi bpr was placed after the reactor. For entries 22−26 the solution fed into the system was 1 mmol of substrate in H_2O/IPA (1:2, v/v, 20 mL). [b]Reaction was scaled to 100 mmol.

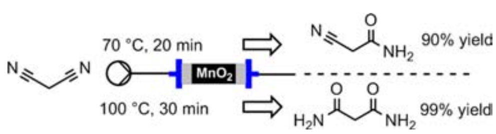
Manganese(IV) dioxide (MnO_2) is a cheap and useful reagent, known especially for its oxidative properties.[8] However, in practice, the use of this oxide for nitrile hydrolysis in batch-mode reactors is considered problematic and not without good reason. MnO_2 is a heavy powder that readily adheres to surfaces and causes blockages, making cleaning a challenging process. Despite these problems, MnO_2 has been described as an active catalyst for the hydration of nitriles under batch conditions for a number of substrates.[9] In particular, Mizuno and co-workers recently reported the hydration of a limited class of nitriles using amorphous manganese dioxide under batch conditions.[9f] In their manuscript, hydration of

Table 3. Flow Hydration of Aliphatic Nitriles[a]

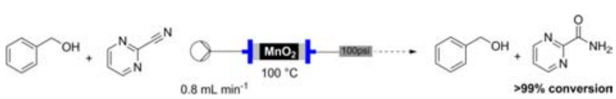
entry	substrate	residence time (min)/temp (°C)	yield
27		15/70	99%
28		15/70	99%
29		20/70	99%
30		30/100	98%
31		30/100	99%
32		15/30	96%
33		50/100	98%
34		15/80	98%
35		15/70	99%
36		15/100	97%

[a]General procedure for the hydration of aromatic nitriles: 5 mmol of nitrile in H_2O (20 mL) were passed through a reactor column (Omnifit, 10.0 mm i.d. × 100.0 mm length) packed with amorphous MnO_2 (2.5 g) with either ends packed with Celite. A 100 psi bpr was placed after the reactor. For 34 the solution fed into the system was 5 mmol of substrate in H_2O/IPA (1:2, v/v, 20 mL). For 35 the solution fed into the system was 1 mmol of substrate in H2O/IPA (1:2, v/v, 20 mL).

Scheme 2. Flow Hydration of Aliphatic Nitriles



Scheme 3. Selective Hydration of Nitrile 1 in the Presence of Benzyl Alcohol



nitriles was achieved in good conversions at high temperatures (>140 °C) with yields being determined by GC analysis. In our hands, this hydration of nitriles under microwave conditions, using MnO_2, was troublesome and products were difficult to isolate, especially on scale. However, since flow chemistry methods using heterogeneous catalysts packed into flow tubes can streamline chemical reactions by avoiding many down-stream processing problems,[10,11] we were attracted to the use of MnO_2 in a flow device for the mild and scalable hydration of nitriles.

Initial investigations using MnO_2 as a hydrating medium were promising and therefore we began by optimizing a flow setup using a commercially available source of MnO_2.[12] The catalyst (2.5 g) was simply packed inside an Omnifit column (100 mm length ×10 mm i.d.) and Celite plugs were placed at each end of the glass column in order to avoid contamination of the flow system. The applicability of the system for the hydration of heteroaromatic nitriles was evaluated first (Table 1). An aqueous solution of the nitrile (**1**) (H_2O/acetone 10:1 v/v) was pumped (0.1 mL min^{-1}) through an Omnifit glass column containing 2.5 g of the MnO_2 catalyst heated at 40 °C to provide clean conversion to the primary amide product (94% conversion determined by ^1H NMR). Quantitative hydration of heteroaromatic nitriles was achieved typically within a few minutes and at relatively low temperatures (40−70 °C), with no requirement for further purification (Table 1), simply by collection and concentration of the output stream. The products cleanly eluted from the MnO_2 column and were not strongly retained. Using this protocol, we were able to scale up the process over 9 h for the preparation of 396 mmol (48.71 g) of the simple antitubercular agent pyrazinamide (Table 1, entry 9 and Scheme 1).

Under these conditions, a reactor throughput equating to 45 mmol h^{-1} was achieved, giving 2.21 g h^{-1} of product output, per g of catalyst, as space−time yield. Notably, in these examples inductively coupled plasma mass spectrometry (ICP-MS) analyses of the product showed negligible leaching of Mn over several hours, with the residual concentration being less than 0.06 ppm. Halogen, nitroxyl, and ester substituents as well as low valent sulfur were all tolerated within the substrate scope (Table 1). Importantly, directing heteroatoms adjacent to the nitrile are not required. This is an advantage over other known procedures.[7d]

We observed similar results for aromatic nitriles (Table 2), and the procedure was successfully applied to the hydration of both electron-rich and -poor substrates. *Para-*, *meta-*, and *ortho-*substituted compounds were all processed smoothly. No byproducts were detected in any of the reactions investigated, and again the functional group tolerance was excellent.

Remarkably, we also found that the same column of catalyst could be reused for approximately 100 cycles without any detectable reduction of the catalytic activity of the system. In particular, we were able to use 2.5 g of MnO_2 to process 1.1 mol of overall material, generating more than 200 g of products in different runs.

We next investigated the hydration of aliphatic nitriles and found that the new flow procedure worked well with excellent conversions and yields achieved within 15−30 min at relatively mild temperatures (30−100 °C) (Table 3). The hydrolysis of acrylonitrile to acrylamide **29** without polymerizattion attests to the mildness of these conditions.

Interestingly dinitriles could be hydrated over longer reaction times, and the degree of hydration could be tuned by adjusting the temperature and residence time within the flow reactor (Scheme 2).

Importantly, hydration of the nitrile group in the presence of readily oxidized hydroxyl groups was achieved smoothly without oxidation or *β*-elimination occurring (entry 33). Similarly, when we examined the hydration of nitriles in the presence of a benzyl hydroxyl group, full hydration of 2-pyrimidinecarbonitrile occurred and no oxidation of the alcohol was observed (Scheme 3).

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In cases where compounds were poorly soluble in H_2O, we used a cosolvent to achieve the flow hydrolysis process, including 1° and 2° alcohols, THF, Me−THF, DME, acetone, and cyclohexanone. These water-miscible solvents can be used without affecting the reaction.

In conclusion we have reported a sustainable, mild, and efficient flow process for the hydration of nitriles, whereby the solution passed through the heterogeneous catalyst is concentrated to give the amide product without further workup or chromatographic purification. Remarkably negligible leaching of the manganese catalyst was detected. The method can be applied to heteroaromatic, aromatic, and aliphatic nitriles and tolerated the presence of a wide range of functional groups, including esters, aldehydes, Michael acceptors, and benzylic alcohols. Additionally, the protocol is scalable to molar quantities of material.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization of compounds, data related to the catalyst and the flow setup. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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