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Direct Preparation of Nitriles from Carboxylic Acids in Continuous Flow

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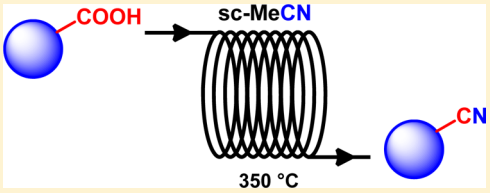
Supporting Information

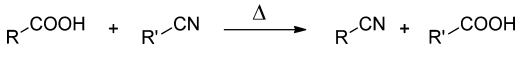
ABSTRACT: A continuous-flow protocol for the preparation of organic nitriles from carboxylic acids has been developed. The method is based on the acid−nitrile exchange reaction with acetonitrile, used as the solvent, and takes place without any catalyst or additives under the high-temperature/high-pressure conditions employed. At 350 °C and 65 bar, where acetonitrile is in its supercritical state, the transformation of benzoic acid to benzonitrile requires 25 min. The protocol has been tested for a variety of nitriles, including aromatic and aliphatic substrates.



Organic nitriles are an important class of compounds in organic synthesis, having widespread application as intermediates in the preparation of several other functional groups[1] or heterocycles such as tetrazoles.[2] Apart from the Kolbe nitrile synthesis,[3] which refers to the reaction of alkyl halides with a metal cyanide, the preparation of nitriles from aldehydes,[4] amides,[5] or alcohols[6] has been described. Usually these synthetic procedures require two or more reaction steps, use hazardous reagents, and generate significant amounts of waste.[3−6] Several methods for the synthesis of nitriles from carboxylic acids have also been reported.[7−14] These generally consist of an amidation process followed by dehydration using different dehydrating agents such as thionyl chloride[7] or phosphorus compounds.[8] Other methods generate the acyl chloride[9] (or fluoride),[10] which is treated with a sulfonamide or azide and subsequently transformed into the nitrile under thermal conditions.

The acid−nitrile exchange reaction[11] (Scheme 1) is a simple method for the direct generation of nitriles from carboxylic acids that consists of heating the carboxylic acid substrate in the presence of an organic nitrile (such as acetonitrile) using an inorganic acid as a catalyst. However, this straightforward procedure has found little application because of the very high temperatures required. For example, the preparation of aliphatic nitriles such as dodecanedinitrile and adiponitrile by heating the corresponding acids in acetonitrile in an autoclave at ca. 300 °C have been described.[11,12] In both cases, H_3PO_4 was used as the catalyst although the reaction was observed to proceed slowly also in the absence of a catalyst. More recently, the synthesis of several nitriles from carboxylic acids and acetonitrile at lower temperatures (ca. 95 °C) has been reported.[13] However, this method employed very high amounts (20 equiv) of sulfuric acid as an additive and heating for 4−18 h, providing low yields and product mixtures. Aromatic nitriles decorated with electron-withdrawing groups have also been prepared by heating the corresponding acid in acetonitrile at 300 °C, without catalyst, in a silver-coated autoclave.[14]

Scheme 1



The above-mentioned drastic conditions required for the acid−nitrile exchange reaction make this method of little practical use, especially on a large scale. Scale-up of a reaction that requires heating of acetonitrile at about 300 °C is inherently hazardous because of the high vapor pressures generated by the solvent. Microreactor technology could potentially overcome this problem, allowing the process to be performed at very high temperatures and pressures in a safe and controllable manner,[15] even under conditions where acetonitrile is in its supercritical state (T_c = 275 °C, P_c = 48 bar).[16] In principle, when an organic solvent in its supercritical state is used under continuous-flow conditions, improved mass transfer due to the high diffusivity and improved hydrodynamic properties due to the very low viscosity of the reaction system can be expected.[17] Moreover, an additional attractive feature of microreaction technology is the ease with which the reaction conditions can be scaled through the operation of multiple systems in parallel (numbering-up, scaling-out), thereby readily achieving production-scale capabilities.[15] In this paper, we present a continuous-flow synthesis of organic nitriles from carboxylic acids based on the acid−nitrile exchange reaction with acetonitrile, which is used as the solvent under supercritical conditions. No catalyst or other additives are employed in this high-temperature/pressure (high-T/p) process, thus simplifying the workup procedure, which simply consists of evaporation of the solvent and extraction with aqueous $NaHCO_3$ in cases where not all of the carboxylic acid is consumed.

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We initiated our investigation by performing some batch experiments in a sealed microwave vessel using the reaction of benzoic acid in acetonitrile to generate benzonitrile as a model. Thus, 2 mL of a 0.5 M solution of benzoic acid in acetonitrile was heated at 250 °C for 1 h in a single-mode microwave reactor.[18] The pressure generated by the solvent at this temperature was ca. 31 bar, the limit of the instrument, and therefore, batch experiments at higher temperatures could not be performed. HPLC analysis of the resulting mixture revealed that only ca. 10% of the starting benzoic acid was converted to benzonitrile. Small amounts of benzamide and *N*-acetylbenzamide, intermediates in the proposed reaction mechanism (see below), were also detected (1% and 7% yield for benzamide and *N*-acetylbenzamide, respectively).

The relatively low pressure limit of most commercially available microwave reactors (20−30 bar) makes genuine high-T/p processing prohibitive.[19] However, stainless steel microtubular continuous-flow reactors are capable of readily achieving temperatures of 350 °C and pressures of 200 bar (and beyond),[20] where acetonitrile is in its supercritical state. Thus, we decided to move forward with a high-T/p continuous-flow protocol for the transformation of carboxylic acids to nitriles using the acid−nitrile exchange reaction with acetonitrile. Our flow setup (Figure 1 and Figure S1 in the Supporting Information) consisted of a 60 mL stainless steel coil (1/8 in. inner diameter) heated in a conventional GC oven (max. 350 °C). The reaction mixture was pumped through the reactor with an HPLC pump (0.1−10 mL min^{-1}), and the pressure of the system was controlled with an adjustable backpressure regulator set to 65 bar (see Figure S1 in the Supporting Information).

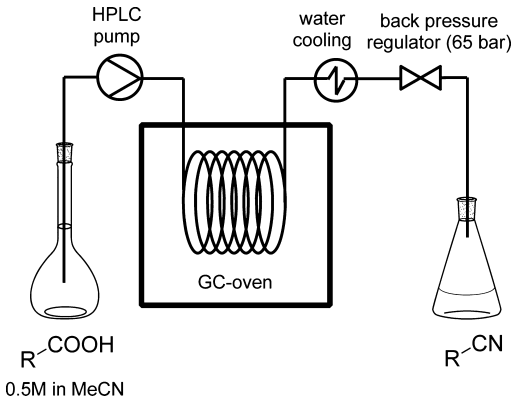


Figure 1. Schematic diagram of the continuous-flow setup employed for the preparation of organic nitriles from carboxylic acids.

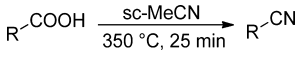
Conversion of benzoic acid to benzonitrile was again chosen as the model reaction for the flow optimization. To avoid problems derived from the high rate of diffusion of the reaction mixture through the coil in the superheated solvent, we decided to continuously pump the solution of the substrate in acetonitrile, collecting samples for analysis when steady-state conversion was reached. Our first attempts in continuous flow indicated that very low conversions, comparable to those in the above-mentioned batch experiments, were achieved at temperatures ranging from 250 to 300 °C (see Figure S2 in the Supporting Information). As the temperature was increased (keeping the residence time constant), higher conversions were achieved, and notably, no side products were detected even when the reaction mixture was heated at 350 °C. Thus, we decided to further optimize the reaction parameters at this temperature. Increasing the residence time from 10 to 25 min (flow rate = 0.4 mL min^{-1})[21] led to 94% conversion of benzoic acid to benzonitrile (Figure S3a in the Supporting Information). Further increases in the residence time did not significantly improve the conversion. Because of the acidic character of the substrate, a bimolecular process where the carboxylic acid group catalyzes the acid−nitrile exchange reaction of another benzoic acid molecule could be expected. In this case, the reactivity would be considerably dependent on the substrate concentration. However, experiments performed with variable concentration, keeping all other parameters constant, revealed that the conversion is independent of the substrate concentration (Figure S3b).

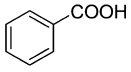
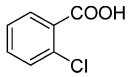
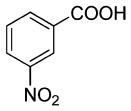
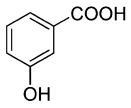
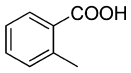
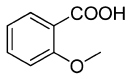
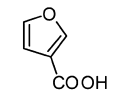
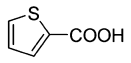
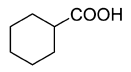
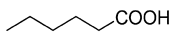
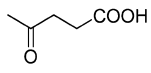
To demonstrate the general applicability of this continuous-flow protocol, a series of aromatic and aliphatic carboxylic acids containing different functionalities, including electron-withdrawing and electron-donating groups, were transformed into the corresponding nitriles (Table 1). In all cases, identical conditions as optimized for benzoic acid (350 °C, 25 min) were applied. Despite the high temperature employed, the method displayed a very good compatibility with common functional groups such as halogen, nitro, alcohol, and ester (Table 1, entries 2−6). Heteroaromatic compounds such as furan-3-carboxylic acid (entry 7) and thiophene-2-carboxylic acid (entry 8) as well as several aliphatic carboxylic acids (entries 9−11) were also successfully converted into the corresponding nitriles. In most instances, small amounts of unconsumed starting material were identified after the reaction (Table 1), but gratifyingly, no other side products or impurities were detected. The workup procedure thus simply consisted of evaporation of the acetonitrile under reduced pressure, dilution of the crude mixture in ethyl acetate or diethyl ether, and extraction of the unreacted acid with aqueous $NaHCO_3$ (see the Experimental Section for details). Evaporation of the organic phase under reduced pressure then furnished the nitrile in good to excellent yield (Table 1).

A mechanism for the acid−nitrile exchange reaction was proposed by Becke et al.[14] on the basis of experiments with isotopically labeled acetonitrile. The authors could demonstrate that during the reaction the carbon atoms of the carboxylic acid and nitrile moieties are not interchanged, and they proposed a pathway involving *N*-acetylbenzamide (**B**) as an intermediate (Scheme 2). Hydrolysis of **B** would generate benzamide **C** and release acetic acid as a side product. In the last step, dehydration of benzamide leads to the nitrile.

To shed further light on the mechanistic proposal and demonstrate that, as expected, formation of **B** is the rate-determining step of the reaction, we decided to perform a series of microwave batch experiments involving each of the intermediates. As mentioned above, heating of benzoic acid in acetonitrile at 250 °C for 1 h gave a mixture containing small amounts of benzonitrile (10%), *N*-acetylbenzamide (7%), and benzamide (1%), while after only 30 min the conversion to benzonitrile was reduced to ca. 5% (Figure 4 in the Supporting Information). Notably, heating of *N*-acylbenzamide **B** (Scheme 2) in acetonitrile under the same conditions (250 °C, 30 min) produced a much faster reaction that provided higher amounts of benzonitrile (53%) and benzamide (10%). Thus, under the high-T/p reaction conditions used in our protocol, when benzoic acid reacts with acetonitrile, the *N*-acetylbenzamide rapidly evolves to ultimately form benzonitrile. This explains why no intermediates were observed in the continuous-flow

Table 1. Preparation of Organic Nitriles from Carboxylic Acids and Acetonitrile in Continuous Flow[a]



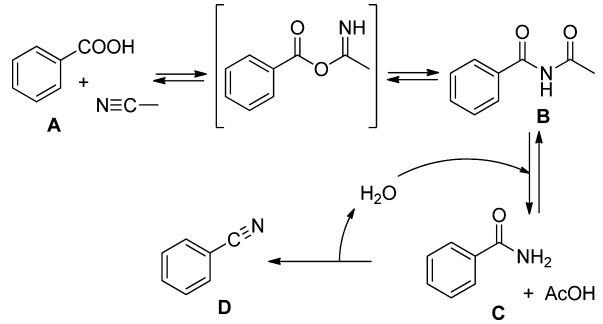
Entry	Substrate	Conversion (%)[b]	Yield (%)[c]
1		95	89
2		99	97
3		94	90
4		92	78
5		92	90
6		98	92
7		91	86
8		88	82
9		--[d]	72
10		--[d]	78
11		--[d]	85

[a]Conditions: 0.5 M acid in acetonitrile, 350 °C, 0.4 mL min^{-1} (25 min residence time). [b]HPLC conversion (215 nm). [c]Isolated yields from 10 mL (5 mmol) of the crude reaction mixture (see the Experimental Section for details). [d]Not determined.

reactions performed at 350 °C. Formation of benzonitrile from benzamide (**C**) involves dehydration of the amide group, which requires the presence of a compound that can scavenge water. In our mechanistic proposal (Scheme 2) the *N*-acetylbenzamide intermediate acts as water scavenger. Indeed, pure benzamide in acetonitrile at 250 °C was completely unreactive, while when it was mixed with *N*-acetylbenzamide, both evolved to give benzonitrile (see Figure S4).

In summary, we have developed an efficient, catalyst-free continuous-flow procedure for the direct preparation of organic nitriles from carboxylic acids and acetonitrile. The capabilities of the capillary microreactor approach allowed us to work at

Scheme 2. Proposed Mechanism for the Acid−Nitrile Exchange Reaction, Using as a Model the Reaction of Benzoic Acid with Acetonitrile



very high temperatures and pressures not accessible by conventional sealed-vessel batch reactors and therefore to minimize the reaction time for a transformation that would otherwise take exceedingly long periods. At 350 °C, acetonitrile in its supercritical state reacted with benzoic acid to yield benzonitrile after only 25 min in a clean reaction. The protocol was tested for a number of aromatic and aliphatic acids. In all cases, good to excellent yields were obtained. Moreover, a series of batch experiments including all of the intermediates involved in the proposed mechanism for the reaction were performed, and the results demonstrated the intermediacy of *N*-acetylbenzamide and benzamide during the exchange process, with the initial formation of *N*-acetylbenzamide being the rate-determining step.

EXPERIMENTAL SECTION

General Experimental Details. ^{1}H NMR spectra were recorded on a 300 MHz instrument. Chemical shifts (δ) are expressed in parts per million downfield from TMS as an internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 mm × 4.6 mm, particle size 5 mm) at 25 °C using mobile phases A [water/acetonitrile 90:10 (v/v) + 0.1% TFA] and B (MeCN + 0.1% TFA) at a flow rate of 1.0 mL min^{-1}. The following gradient was applied: linear increase from 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. GC/MS monitoring was based on electron impact ionization (70 eV) using an HP/5MS column (30 m × 0.250 mm × 0.025 μm). After 1 min at 50 °C, the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL min^{-1} in constant-flow mode. HPLC-grade acetonitrile was used in all of the experiments. Chemicals were obtained from standard commercial vendors and were used without any further purification.

All of the compounds synthesized herein are known in the literature. Proof of purity and identity was obtained by ^{1}H NMR and MS analysis.

General Procedure for the Preparation of Nitriles from Carboxylic Acids in Continuous Flow. Flow experiments were performed using a GC oven equipped with a 60 mL stainless steel coil (1.6 mm inner diameter) and standard HPLC pumps.[22] Before use, the stainless steel coil was subjected to a cleaning and repassivation procedure (see the Supporting Information). The adjustable back-pressure regulator (Swagelok) was set to 65 bar. Initially pure acetonitrile was pumped through the reactor, and after the desired reaction parameters were achieved (350 °C, 65 bar), the inlet was switched to a 0.5 M solution of the corresponding substrate in acetonitrile. Because of the significant solvent expansion produced under supercritical conditions, careful control of the residence time was required.[21] The residence time was estimated by observing the total residence time in the reactor (visual inspection) and taking into

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account the volume of the "cold" zones of the reactor (pumps, tubing, etc.) and the flow rate. After steady state was achieved (ca. 45 min), 10 mL of the crude reaction mixture was collected at the reaction outlet, and the solvent was gently evaporated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and extracted with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL). The organic phase was then dried over magnesium sulfate and evaporated under vacuum, yielding the pure nitrile.

Benzonitrile (Table 1, Entry 1). (459 mg, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.60 (m, 3H), 7.49 (t, J = 12.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8, 132.2, 129.1, 118.9, 112.4; MS-EI m/z 103 (100%), 76 (45%).

2-Chlorobenzonitrile (Table 1, Entry 2). (667 mg, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 12.0 Hz, 2H), 7.56 (dd, J = 12.0 Hz, J = 8.0 Hz, 2H), 7.40 (t, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 134.0, 133.9, 130.1, 127.1, 116.0, 113.4; MS-EI m/z 139 (30%), 137 (100%), 102 (40%), 75 (30%).

3-Nitrobenzonitrile (Table 1, Entry 3). (668 mg, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.50 (d, J = 12.0 Hz, 1H), 8.02 (d, J = 12.0 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 137.6, 130.7, 127.5, 127.2, 116.5, 114.1; MS-EI m/z 148 (35%), 102 (100%), 90 (15%), 75 (40%).

3-Hydroxybenzonitrile (Table 1, Entry 4). (465 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, J = 12.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.17−7.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 130.6, 124.5, 120.8, 118.7, 118.6, 112.8; MS-EI m/z 119 (100%), 91 (40%), 64 (30%).

2-Methylbenzonitrile (Table 1, Entry 5). (527 mg, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 12.0 Hz, 1H), 7.49 (t, J = 12.0 Hz, 1H), 7.34−7.26 (m, 2H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 132.6, 132.5, 130.2, 126.2, 118.2, 112.7, 20.5; MS-EI m/z 117 (100%), 116 (60%), 90 (70%), 89 (45%), 63 (30%).

2-Methoxybenzonitrile (Table 1, Entry 6). (612 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (t, J = 12.0 Hz, 1H), 7.04−6.97 (m, 2H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 134.4, 133.8, 120.8, 116.5, 111.3, 101.8, 56.0; MS-EI m/z 133 (80%), 104 (100%), 90 (65%), 76 (25%), 63 (45%).

3-Furonitrile (Table 1, Entry 7). (400 mg, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.52 (d, J = 4.0 Hz, 1H), 6.65 (d, J = 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 144.1, 113.1, 111.1, 97.9; MS-EI m/z 93 (100%), 65 (45%), 64 (40%).

2-Thiophenecarbonitrile (Table 1, Entry 8). (447 mg, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.0 Hz, J = 4.0 Hz, 2H), 7.15 (t, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 132.6, 127.7, 114.3, 109.9; MS-EI m/z 109 (100%), 82 (10%), 70 (12%), 58 (40%).

Cyclohexanecarbonitrile (Table 1, Entry 9). (392 mg, 72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67−2.59 (m, 1H), 1.91−1.65 (m, 6H), 1.53−1.42 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 122.6, 29.5, 28.0, 25.2, 24.0; MS-EI m/z 108 (20%), 94 (30%), 81 (25%), 67 (35%), 56 (100%).

Hexanenitrile (Table 1, Entry 10). (378 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (t, J = 12.0 Hz, 2H), 1.72−1.62 (m, 2H), 1.49−1.32 (m, 4H), 0.93 (t, J = 12.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.9, 30.7, 25.1, 21.9, 17.1, 13.7; MS-EI m/z 96 (15%), 82 (30%), 68 (40%), 54 (100%).

4-Oxopentanenitrile (Table 1, Entry 11). (413 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (t, J = 12.0 Hz, 2H), 2.57 (t, J = 12.0 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 119.0, 38.6, 29.5, 11.4; MS-EI m/z 97 (25%), 54 (100%).

■ ASSOCIATED CONTENT

Supporting Information

Supporting figures and copies of ^{1}H NMR spectra of all prepared compounds. 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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