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HCN on Tap: On-Demand Continuous Production of Anhydrous HCN for Organic Synthesis

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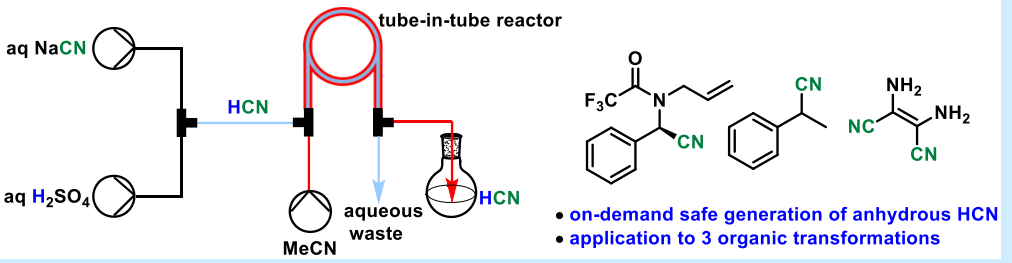
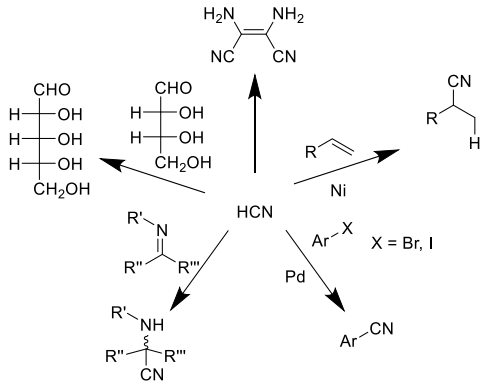
Supporting Information



ABSTRACT: A continuous process for the on-demand generation, separation, and reaction of hydrogen cyanide (HCN) using membrane separation technology was developed. The inner tube of the reactor is manufactured from a gas-permeable, hydrophobic fluoropolymer (Teflon AF-2400) membrane. HCN is formed from aqueous reagents within the inner tube and then diffuses through the membrane into an outer tubing containing organic solvent. This technique enabled the safe handling of HCN for three different organic transformations without the need for distillation.

Hydrogen cyanide (HCN) is a highly useful and atom-efficient reagent for organic synthesis.[1] HCN is used in a plethora of synthetic transformations, including the Strecker reaction for amino acid synthesis,[2] transition-metal-catalyzed cyanation of aryl bromides,[3] chain elongation of sugars,[4] and diaminomalonitrile synthesis (Scheme 1).[5] The industrial manufacture of HCN is achieved by the Andrussow process,[6] the Degussa process,[7] or the Sohio acrylonitrile process, where HCN forms as a byproduct.[8] HCN is a bulk chemical produced in about 1.3 million tonnes per annum (t/a).[1] In contrast with the industrial large-scale production of pure HCN, its use on the laboratory scale is considered problematic and dangerous.[9] In 1927, Ziegler developed a laboratory scale method for the isolation of anhydrous HCN from an aqueous solution of sodium cyanide (NaCN) or potassium cyanide (KCN) and mineral acid by distillation.[10] The method is still the main approach applied today for preparing anhydrous HCN on the laboratory scale. Given its potential synthetic utility, HCN is arguably significantly underutilized in organic synthesis, which can be attributed to its method of preparation, high toxicity (LC_{human} = 150 ppm for 30 min),[11] low boiling point (26 °C), and the possibility of spontaneous exothermic polymerization.[9]

Scheme 1. Reactions of Hydrogen Cyanide



Consequently, many HCN surrogates have been developed,[12] most notably trimethylsilylcyanide (TMSCN)[13] and acetone cyanohydrin.[14] These reagents are easier and safer to handle than HCN due to their higher boiling point but suffer from poor atom economy, high cost per mol, high toxicity, and potentially different reactivity than HCN.[15] Another solution is to liberate HCN in situ from liquid reagents.[16] Very recently, Grundke and Opatz reported a biphasic procedure for the use of hexacyanoferrates as a nontoxic cyanide source for conducting Strecker reactions.[17] Nonetheless, some reactions utilizing HCN are highly sensitive to the presence of water; therefore, the use of an anhydrous HCN source is required. In addition, there are often compatibility issues between the HCN-producing and HCN-consuming reactions, thus preventing a one-pot protocol.

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Recently, the Skrydstrup group reported the ex situ generation of anhydrous HCN from KCN and acetic acid (AcOH) in ethylene glycol within a two-chamber batch system for use in organic reactions.[18] However, the precise control and range of reaction conditions (temperature, pressure, and reaction time) are limited compared with conditions that could be achieved by using continuous-flow technologies.[19]

The utilization of continuous-flow technology eliminates the need to store highly reactive and hazardous reagents and enables them to be prepared on-site and on-demand inside a closed system with only small quantities generated at any one time.[20] Stevens and coworker reported the in situ formation of HCN in flow; however, the HCN is generated within the same tubing as the organic reaction, and thus this protocol relies on the fact that the organic transformation is compatible with AcOH and KCN.[21] Ley and coworkers pioneered the tube-in-tube reactor gas-loading concept to enable the safer introduction of gases into the liquid phase.[22] The tube-in-tube reactor consists of an outer tubing manufactured from polytetrafluoroethylene (PTFE) and a smaller inner tubing manufactured from a gas-permeable and hydrophobic fluoropolymer, Teflon AF-2400. The device has been successfully applied in organic transformations using gases such as H_2, CO, CO_2, O_3, NH_3, and CHF_3.[22,23] Our group previously reported the on-demand continuous generation of diazomethane within the inner tube of the tube-in-tube device by combining a liquid stream of a Diazald solution with a stream of strong base, which diffuses through the membrane to be consumed by the substrate in the outer tube.[24] On the basis of our previous experience with diazomethane, we hypothesized that membrane technology could also be utilized for the on-demand generation of anhydrous HCN from aqueous reagents.[25] The continuous generation, separation, and reaction of anhydrous HCN in a controlled manner without the need for distillation would significantly improve safety. Herein we describe the development of a safe protocol for the production of anhydrous HCN and demonstrate the protocol on a number of important organic transformations.

We commenced our investigation by evaluating the hydrocyanation of diphenylmethaneimine (**1a**) as a model reaction within a tube-in-flask setup (Figure 1 and Figure S1). The tube-in-flask configuration is particularly appropriate for organic transformations with long reaction times. Within the tube-in-flask configuration, the gas-permeable tubing carrying the aqueous phase for the formation of dissolved gas is coiled within the flask, and the liquid phase for the organic transformation is stirred within the flask.[26] For the in situ on-demand generation of HCN, aqueous solutions of 4 M NaCN and 4 M H_2SO_4 were continuously pumped into a T-mixer, and the combined mixture passed through a short PFA coil before entering the gas-permeable Teflon AF-2400 membrane coil (1.75 mL internal volume). HCN is generated on the mixing of the two feeds. A back pressure of 2 bar was applied to the aqueous stream to ensure that generated HCN remained in solution. The AF-2400 membrane coil was contained in a 10 mmol stirred solution of **1a** (0.2 M in acetonitrile (MeCN)) within a sealed flask (fill volume = 50 mL and total volume = 100 mL). The outlet aqueous stream was then neutralized with a saturated solution of sodium hydroxide (NaOH), which was subsequently quenched with H_2O_2. The conversion of **1a** was measured by high-performance liquid chromatography (HPLC) and corroborated by proton nuclear magnetic resonance (^{1}H NMR) at

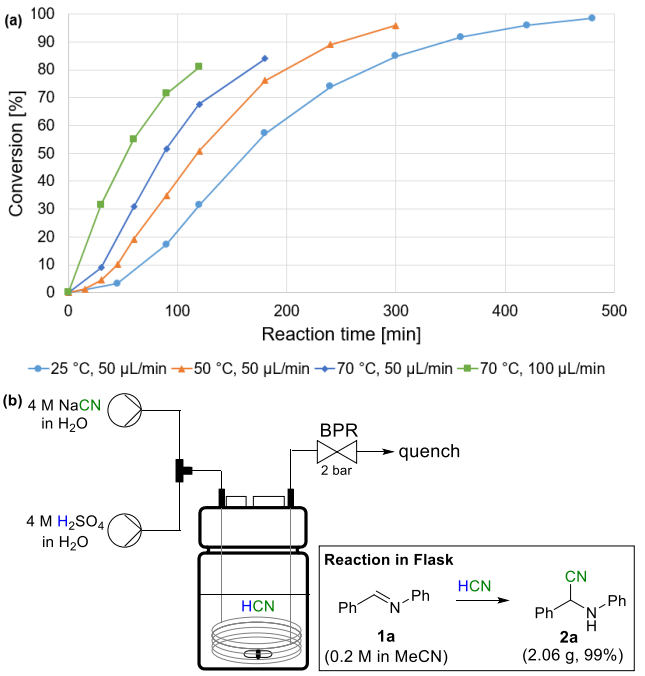

Figure 1. (a) Influence of temperature and flow rate on conversion in the tube-in-flask. (b) Tube-in-flask setup for the hydrocyanation of diphenylmethanimine (**1**).

different reaction temperatures and flow rates. The reaction rate was accelerated at higher temperatures and by using faster flow rates (Figure 1a). The results clearly demonstrate that HCN successfully diffuses through the membrane; however, the relatively slow reaction rate of hydrocyanation resulted in the accumulation of HCN within the headspace of the flask (as measured by an HCN detector), particularly at 50 and 70 °C. By using a 50 μL/min flow rate for each of the aqueous streams to generate HCN throughout the experiment, corresponding to ~10 equiv of HCN, 8.5 h reaction time for the batch transformation at room temperature provided **2a** in 99% isolated yield (2.06 g) after the evaporation of the solvent (Figure 1b).

We were interested in measuring the HCN yield in the organic phase within the tube-in-flask system. There is no established method for determining HCN concentrations within organic solvents, so we selected to compare ^{1}H NMR integrals of HCN against 1,2-dichloro-4-nitrobenzene as an internal standard in MeCN. NMR measurements were conducted at 10 °C to slow proton-exchange rates. To our delight, a sharp signal was observed at 4.20 ppm for HCN. By operating at a combined aqueous flow rate of 200 μL/min, 50 °C reaction temperature, and a residence time of ~9 min for the aqueous stream, an HCN yield of 21% was achieved. This yield corresponds to a throughput of 5 mmol/h. The HCN yield was decreased to 14% by increasing the combined aqueous flow rate to 400 μL/min, but throughput was increased to 6.6 mmol/h.

After the initial proof-of-concept, we turned our attention to the commercially available tube-in-tube reactor (Scheme 2).[27] The utilization of the tube-in-tube reactor ensured that all HCN remained in solution, with no gas present within the system. Within this configuration, HCN diffuses from the aqueous stream within the inner tube through the membrane into the outer tube containing a stream of the imine derivative

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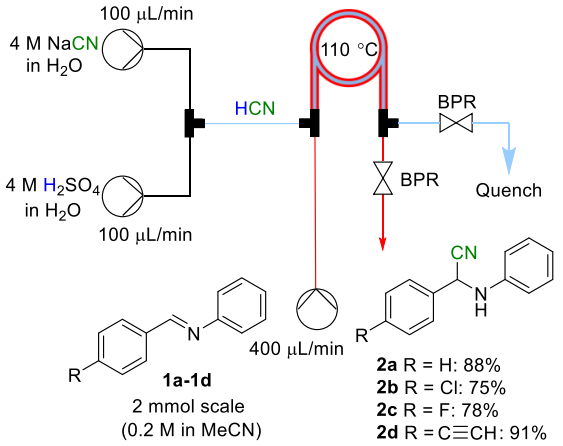
Scheme 2. Continuous Hydrocyanation of Diphenylmethanimine Derivatives 1a−1d Using a Tube-in-Tube Reactor



dissolved in MeCN. The streams were successfully heated above the solvent boiling point by using 2 and 2.7 bar back-pressure regulators for the inner tube and outer tube, respectively. The approach prevents potential operator exposure to HCN during sampling. After the optimization of reaction parameters, the full conversion of the starting materials **1a−1d** on a 2 mmol scale to the hydrocyanated analogues **2a−2d** was achieved at 110 °C within 15 min of residence time. This residence time is a significant decrease in tube-in-flask protocol because higher temperatures can be applied safely and HCN is not lost to the headspace. Under the conditions used, 5 equiv of HCN, in theory, could be generated for each reaction, which could be reduced further to minimize the amount of HCN and improve the inherent safety. However, a reduction in HCN equivalents would increase the residence time and therefore reduce throughput. Thus we selected 5 equiv as a compromise, a sufficient concentration to provide a reasonable reaction rate, and a relatively low amount of HCN formed at any one time to minimize the accumulation of hazardous HCN. An increase in the impurity formation was observed at higher temperatures. The derivatives were isolated with excellent yields (75−91%) after recrystallization from ethanol (EtOH).

Subsequently, we determined the amount of HCN that passed through the membrane in relation to the residence time of the aqueous stream through the tube-in-tube reactor. The organic stream (MeCN or toluene) was maintained at 15 min of residence time. NMR measurements were conducted in a similar manner to the method described above. The internal standard used was 1,2-dichloro-4-nitrobenzene for MeCN, and MeCN was the internal standard in the case of toluene as an organic feed. A positive correlation between the residence time of the aqueous phase within the inner tube and the HCN yield in the organic phase was observed (Figure 2a). The yield of HCN drops from near-quantitative yield within 40 min of residence time to 47% yield in the case of 10 min of residence time in MeCN. This HCN yield is a significant improvement when compared with the tube-in-flask results. In addition, higher HCN concentrations within the organic phase, albeit at lower HCN yields, were obtained by applying higher flow rates for the aqueous streams (Figure 2b). Higher concentrations of HCN have greater synthetic utility, and thus we decided on a compromise and used 10 min of residence time for the

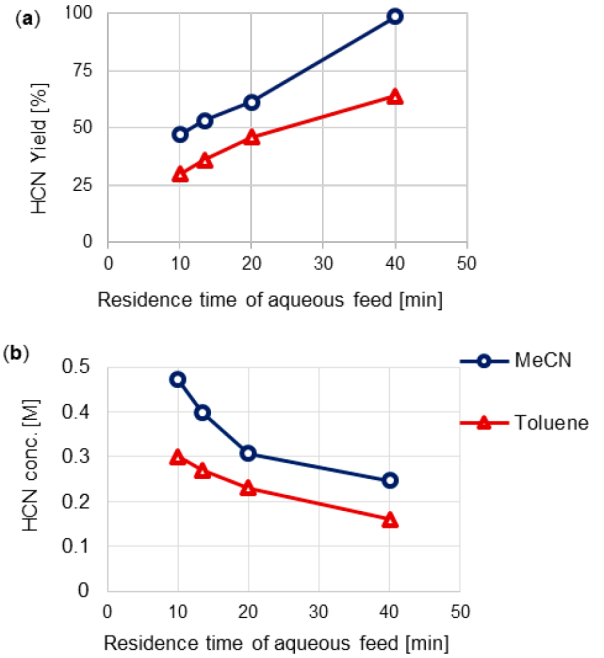


Figure 2. Achievable (a) HCN yield and (b) HCN concentration within organic feed at 50 °C at different aqueous stream residence times. Residence time of organic feed was 15 min.

aqueous feed for all subsequent reactions (200 μL/min flow rate of aqueous stream). HCN yields were lower in toluene than in MeCN. Some organic reactions involving HCN are sensitive to water; therefore, we assessed the water content within the organic phase by Fourier-transform infrared spectroscopy (FTIR) (Figure S6). The level of water detected in MeCN was <1000 ppm (<0.1 wt %), and the water content in toluene (PhMe) was below the levels possible for quantification, thus showing that the organic phase in both cases can be considered as anhydrous.

The use of the outer tube for performing the organic transformation in the tube-in-tube reactor has limitations in terms of feasible reaction times (<1 h) and the fact that the handling of solids can be challenging (e.g., blockage of the system from solid formation). Additionally, the inability to operate the reactor system at low temperatures due to the freezing of the aqueous stream at 0 °C limits its application, particularly when considering asymmetric transformations. To address these challenges, the continuous generation of an HCN stream within a tube-in-tube reactor to provide "HCN on tap" to a batch flask, where the HCN was subsequently consumed in an organic transformation, was envisioned. Within the tube-in-flask protocol, the HCN is generated inside the membrane, and the HCN continuously passes through the membrane into the solution for the duration of the batch reaction. In contrast, within the "HCN on tap" protocol, the HCN is generated within a tube-in-tube reactor and passes through the membrane to a carrier solvent, which is then added in a semibatch manner to the reaction. The "HCN on tap" configuration enables the HCN to be introduced in a controlled manner and at a known HCN concentration. The versatility of this configuration was demonstrated through its application to three well-known model transformations that require the use of anhydrous HCN (Scheme 3).

The enantioselective Strecker reaction catalyzed by chiral (salen)Al(III) complex **8** requires the use of low temper-

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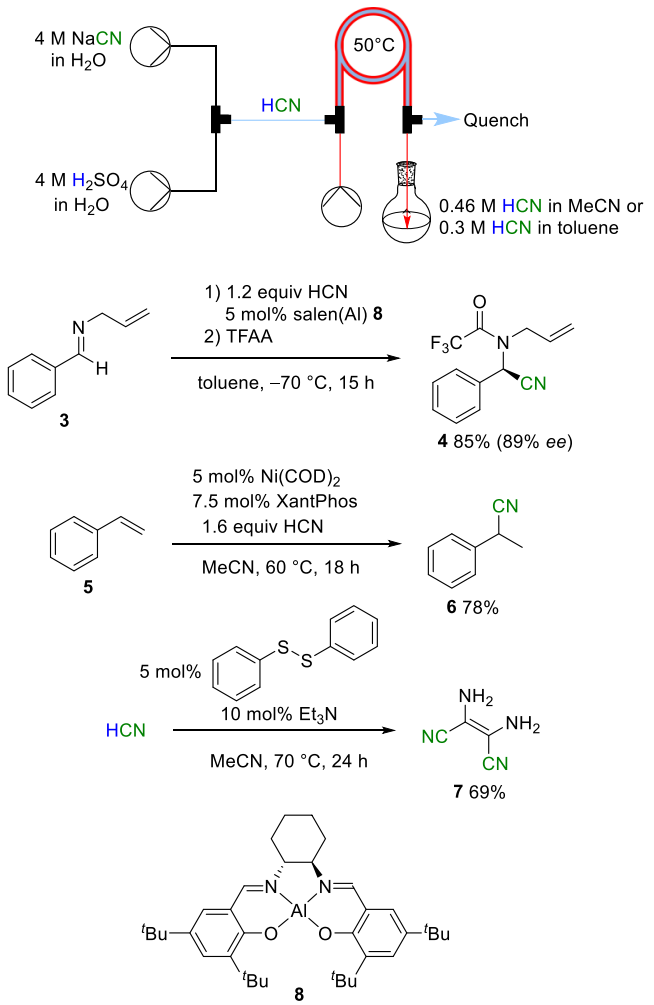
Scheme 3. On-Demand "HCN on Tap" for Synthetically Important Reactions



atures.[28] The stream from the outer tube containing dissolved HCN (0.3 M in PhMe) was fed directly over 10 min into a batch flask cooled to −70 °C containing phenylmethanimine derivative **3** and catalyst. The protocol provided product **4** in 85% yield and 89% *ee*. This result is similar to the reported literature yield for the batch protocol from Sigman and Jacobsen, where product **4** was obtained in 91% yield and 95% *ee*.[28a] The result demonstrates that the "HCN on tap" approach can be used for the safe preparation of enantiomerically enriched *R*-amino-acid derivatives.

The Ni-catalyzed hydrocyanation of olefins is a well-established transformation and is generally known to require anhydrous conditions;[3] however, the $Ni(COD)_2$ and Xantphos catalytic system, which was previously developed in the two-chamber batch system,[18] forms a suspension in toluene and MeCN. Thus this catalytic system cannot be readily performed within the tube-in-tube system. By using our "HCN on tap" generator, the hydrocyanation of styrene (**5**) afforded product **6** in 78% isolated yield.

Finally, the tetramerization of HCN to the industrially relevant building block diaminomaleonitrile (DAMN, **7**) was investigated. DAMN is a possible precursor to molecules involved in prebiotic chemistry and the origin of life.[29] The polymerization of HCN to give tetramer **7** was achieved in MeCN by using 10 mol % triethylamine as a basic catalyst and 5 mol % diphenyl sulfide as a cocatalyst. DAMN (**7**) was isolated in 69% yield, which was comparable to the reported yield using HCN directly.[30]

In summary, we have developed a protocol for the safe generation of anhydrous HCN by using membrane technology. HCN is generated in the inner tube of the tube-in-tube reactor containing an aqueous stream carrying NaCN and H_2SO_4. HCN subsequently diffuses through a gas-permeable membrane into an organic solvent in the outer tube. HCN is a powerful reagent for organic synthesis, but it has been severely underutilized in the past due to its low boiling point, toxicity, and explosiveness. The on-demand generation, separation, and consumption of this valuable reagent in a commercially available membrane reactor described herein drastically improves safety and circumvents the need for distillation. The described approach avoids the storage, transportation, and handling of this volatile and toxic compound in large amounts. The application to useful synthetic transformations for academic and industrial chemists has been shown. Therefore, this new approach may allow new synthetic reactions using HCN to be explored and expand the interest in reactions utilizing HCN in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01941.

Description and images of the experimental setups, optimization data, and ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra of all isolated products (PDF)

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Notes

The authors declare no competing financial interest.

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