



Odorless Isocyanide Chemistry: An Integrated Microfluidic System for a Multistep Reaction Sequence**

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Isocyanides have a long history in organic chemistry and have been used in all areas, from academia to industry.^[1] It is one of the most versatile and extensively examined stable divalent carbon nucleophiles, and has the interesting ability to form multiple bonds on the terminal carbon. It has drawn enduring attention because of its ubiquitous applications in organometallics, where isocyanides are a well-studied family of ligands,^[2] and in combinatorial syntheses, where new desired products can be found by isocyanide-based multi-component processes, such as Passerini and Ugi reactions.^[3] These intrinsic qualities of isocyanides, in combination with the avalanche of research on their use in the synthesis of drug-like molecules, make them a privileged group for synthetic chemists.^[4]

Despite the huge potential of the isocyanide chemistry, some lack of academic interest toward this field is yet evident. This reluctance is undoubtedly related to the extremely distressing odor of isocyanides, which has also led to their proposed use as non-lethal weapons.^[5] The foul odor makes their purification especially difficult, as exposure to them, even at very low levels, is extremely agonizing. It is believed that this characteristic foul odor of volatile isocyanides is the reason for the underdevelopment of isocyanide chemistry for so many years, as the foul smell turned away many potential workers in this field. Therefore, a system that removes the odor problem should enable the expansion of the scope of isocyanide chemistry to new, unexplored dimensions. In this report, we present an automated continuous microfluidic system that performs a serial synthesis, purification, and in situ consumption of isocyanides into final products with little exposure to the surroundings.

Establishing safe and efficient procedures for conducting chemical reaction has been greatly aided by technological

advances. Among these, continuous-flow synthesis based on microfluidics has emerged as a welcome development in organic synthesis. In addition to enhanced process safety, this technology offers important advantages, such as increased surface-to-volume ratio and rapid mass and heat transfer, which results in highly accelerated reaction rates, as well as a reduction in reaction time.^[6] Nowadays, this technique is considered as an important approach towards green and sustainable chemistry because it minimizes exposure to reagents and products under reaction conditions when using toxic materials.^[7] Over the last few years, many important efforts have been made to avoid exposure to toxic and hazardous material through the microfluidic approach.^[8] Nonetheless, efficient separation of initially produced toxic compounds from the reaction mixtures for subsequent downstream utilization in a continuous reaction is still an enormous challenge.^[9]

One way of accomplishing the task is to purify the generated reagent by selective removal of unwanted chemicals and then to separate the reagent stream. Droplet microfluidics could be used for purification by liquid-liquid extraction.^[10] A convenient medium for the extraction is water, because the water phase containing the unwanted chemicals can be separated from the organic-solvent phase containing the reagent with the aid of a suitable thin membrane. These requirements dictate the selection of the synthesis method for the reagent.

The first synthesis of isocyanide goes back to 1859, and involved allyl iodide and silver cyanide.^[11] For our purpose, however, dehydration of *N*-substituted formamides was selected as a model reaction for in situ generation of isocyanides, not only because of its quantitative yield and wide substrate compatibility,^[12] but, more importantly, because of the compatibility of the synthesis method with the aforementioned requirements for self-purification and separation. In situ generation of isocyanides could be carried out in a capillary microreactor. The reaction mixture would then be combined with water for subsequent extraction. The resulting biphasic fluid should self-separate into a water phase and an organic phase in the microseparator. The purified isocyanide would then be consumed in the capillary microreactor to deliver the desired products, as shown in the Figure 1.

For the in situ generation of isocyanide, a solution of *N*-cyclohexylformamide in *N,N*-diisopropylethylamine (DIPEA; 1.0 M) and a solution of POCl₃ in toluene (2.0 M) were introduced into the capillary microreactor with a T-mixer using two separate syringe pumps. The flow rate of the DIPEA solution was kept at twice the rate of POCl₃, in

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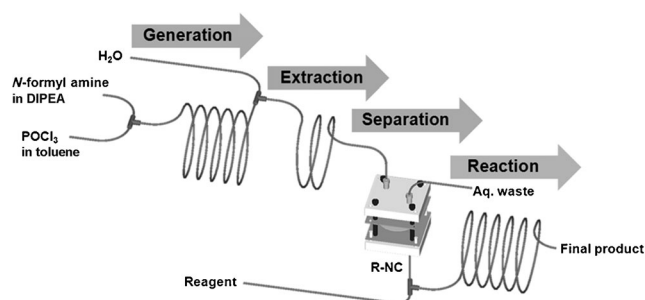


Figure 1. A continuous four-step in-line process (in situ generation, extraction, separation, and reaction of isocyanides) in an integrated microfluidic system.

accordance with the stoichiometry of reagent and substrates. However, right after mixing of the two solutions (substrate–DIPEA and POCl_3), a tube-plugging problem was encountered, presumably due to formation of an insoluble DIPEA hydrochloride precipitate in toluene. To solve the problem, the micromixer and the tubing were kept in an ultrasonic bath (power = 330 W, frequency = 40 kHz) which eventually resolved the clogging problem of the tubing caused by the $\text{DIPEA} \cdot \text{HCl}$.^[13] The resulting reaction mixture then smoothly passed through perfluoroalkoxy (PFA) tubing (inner diameter (id) = 500 μm , length = 3 m, volume = 589 μL) for the reaction to occur. A residence time of 6 min was found to be enough for the dehydration of the cyclohexylformamide to form a nearly stoichiometric yield of cyclohexyl isocyanide (Table 1, entry 2). The identical method in the continuous

Table 1: Optimization and synthesis of isocyanides by POCl_3 -mediated dehydration of N-substituted formamides in a capillary microreactor.^[a]

Entry	RNHCHO	Formamide flow rate [$\mu\text{L min}^{-1}$]	POCl_3 flow rate [$\mu\text{L min}^{-1}$]	Residence time [min]	Yield [%] ^[b]
1	cyclohexyl (1a)	32	16	12	99
2	cyclohexyl (1a)	64	32	6	99
3	cyclohexyl (1a)	128	64	3	83
4	<i>tert</i> -butyl (1b)	64	32	6	99
5	benzyl (1c)	64	32	6	99
6	4-MeOC ₆ H ₄ (1d)	64	32	6	99
7	phenyl (1e)	64	32	6	97
8 ^[c]	cyclohexyl (1a)	64	32	6	99

[a] Reaction conditions: RNHCHO (1.0 M) in DIPEA, POCl_3 (2.0 M) in toluene, sonication, room temperature. [b] Determined by GC-MS using anisole as an internal standard. [c] CH_2Cl_2 was used as the reaction solvent.

flow system was applied to several other N-substituted formamides, and the formation of isocyanides was mostly complete within 6 min (Table 1, entry 4–7). Owing to the efficient heat and mass transfer of the microreactor, both the exothermic reaction and the mixing of POCl_3 and substrate solutions could be successfully performed at room temperature, whereas a typical batch reaction generally requires cooling with an ice bath.

As indicated earlier, droplet microfluidics can be quite efficient for the selective removal of unwanted chemicals by

extraction because of their very large surface area per unit volume. For the extraction of reaction wastes (containing DIPEA and/or its hydrochloride and phosphate salts) into the aqueous stream, a simple microfluidic system composed of a capillary and a T-junction was used to merge the toluene solution of the reaction mixture with water (Figure 1), for the formation of an organic–aqueous droplet, and real time extraction through a PFA capillary (id = 500 μm , length = 1 m, vol. = 196.3 μL). Key factors for the extraction efficiency are the flow-rate ratio of water to toluene and the contact time, as determined by the capillary length for a given flow rate. A 2:1 ratio (192 $\mu\text{L min}^{-1}$ for water and 96 $\mu\text{L min}^{-1}$ for toluene) and a length of 1 m (0.6 min, vol. = 196.3 μL) were sufficient for the selective purification of isocyanide.

As shown in Figure 1, the biphasic stream leaving the extraction stage was separated into aqueous and organic streams with a microseparator. A polyimide (PI)-based microseparator was constructed with a PTFE film membrane placed in the middle of the separator. The salient features of the PI microseparator are its easy fabrication and its excellent mechanical, thermal, and chemical stability (see the Supporting Information). In contrast, a metal-based microseparator is not only difficult to fabricate, but also could be subject to possible corrosion. Only the isocyanide-containing organic phase wets the thin fluoropolymer membrane (pore size = 0.45 μm) and is allowed to pass through the holes to the bottom of the separator, thereby completing the toluene–water separation. Complete separation can be achieved by regulating the back pressures (Supporting Information, Movie S1), thereby allowing transfer of the purified isocyanides in toluene to the microreactor (Figure 1) for in situ synthesis.

Now that the basic concepts, the procedures, and the corresponding apparatus have been established for isocyanide generation and its self-purification in situ, the integrated microfluidic system can now be used for an in situ synthesis involving the isocyanide. One major area of isocyanide chemistry is isocyanide-based multicomponent reactions (MCRs) in which multiple bonds form in one pot. These MCRs are known to be particularly suited for drug discovery.^[1,3] Therefore, cascade reactions of isocyanides to form pharmaceutically important chemicals were examined in the integrated continuous flow microreactor.

Ugi and Passerini MCRs have been considered as a forefront of isocyanide chemistry since their discovery.^[14] Initially, the Passerini three-component reaction was chosen because of its lesser complexity relative to the Ugi reaction. A solution of benzaldehyde (4.0 M in DMF; DMF = dimethylformamide) and benzoic acid (4.0 M in DMF) was allowed to mix with the obtained isocyanide solution (2.0 M in toluene) from the PI microseparator using an X-mixer (Figure 2). The reaction mixture was then introduced into a PFA capillary (id = 500 μm , length = 9 m, vol. = 1767.14 μL) for the reactions to proceed. As seen in Table 2, it was observed that a residence time of 27.6 min at room temperature gave a 53 % yield of **4a**, and that ultrasonic irradiation at the same residence time significantly improved the yield of **4a** to 85 % (Table 2, entry 2). Furthermore, it was found that a reduction in the reaction time down to ca. 13 min under sonication did not

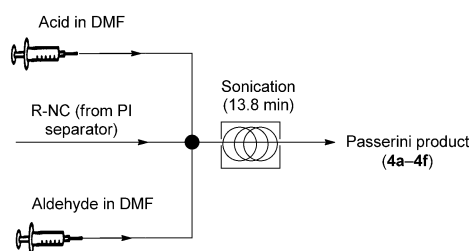


Figure 2. Continuous-flow Passerini reactions using isocyanides generated in situ.

Table 2: Optimization and synthesis of Passerini products in an integrated microfluidic system.^[a]

Entry	R ¹ NHCHO	R ² CHO	Residence time [min] ^[b]	Product	Yield [%] ^[c]
1 ^[d]	cyclohexyl (1a)	Ph (3a)	27.6	4a	53
2	cyclohexyl (1a)	Ph (3a)	27.6	4a	85
3	cyclohexyl (1a)	Ph (3a)	13.8	4a	86
4	cyclohexyl (1a)	Ph (3a)	6.9	4a	52
5	<i>tert</i> -butyl (1b)	Ph (3a)	13.8	4b	83
6	benzyl (1c)	Ph (3a)	13.8	4c	77
7	4-MeOC ₆ H ₄ (1d)	Ph (3a)	13.8	4d	80
8	<i>tert</i> -butyl (1b)	4-FC ₆ H ₄ (3b)	13.8	4e	80
9	<i>tert</i> -butyl (1b)	CH ₂ OBz	13.8	4f	81

[a] Reaction conditions: Isocyanide was generated using the optimized procedure in Table 1, aldehyde (4.0 M) and benzoic acid (4.0 M) were taken and sonicated at room temperature. [b] Flow rates for 27.6 min residence time: 32 $\mu\text{L min}^{-1}$ (isocyanide), 16 $\mu\text{L min}^{-1}$ (acid), and 16 $\mu\text{L min}^{-1}$ (aldehyde); flow rates for 13.8 min residence time: 64 $\mu\text{L min}^{-1}$ (isocyanide), 32 $\mu\text{L min}^{-1}$ (acid), and 32 $\mu\text{L min}^{-1}$ (aldehyde); flow rates for 6.9 min residence time: 128 $\mu\text{L min}^{-1}$ (isocyanide), 64 $\mu\text{L min}^{-1}$ (acid), and 64 $\mu\text{L min}^{-1}$ (aldehyde). [c] Yield of isolated product on a 5 mmol scale. [d] No sonication. Bz = benzyl.

affect the yield (Table 2, entry 3), but that a further reduction (Table 2, entry 4) significantly lowered the yield of **4a**. With these results, the method for a serial four-step process (generation, extraction, separation, and reaction of isocyanides) for the Passerini reaction was optimized as follows: room temperature, ultrasonication, and 13 min of reaction time. Various Passerini products were also synthesized with yields of 77–83 % from different types of isocyanides (Table 2, entry 5–9). When the same Passerini MCRs were carried out in a conventional batch process, a reaction time of 18 h was needed (Supporting Information, method S4), which took only 13 min in the integrated microfluidic system, and yields were comparable to the conventional batch process. Such a striking contrast highlights the additional power of the microfluidic system that results when it is combined with MCRs.

Encouraged by this initial success, we next focused our attention on the Ugi four-component reaction, which involves the condensation of a carbonyl, an amine, an isocyanide, and a carboxylic acid to form bis(amide)s. As aldehydes and amines are prone to form Schiff bases, we did not premix the

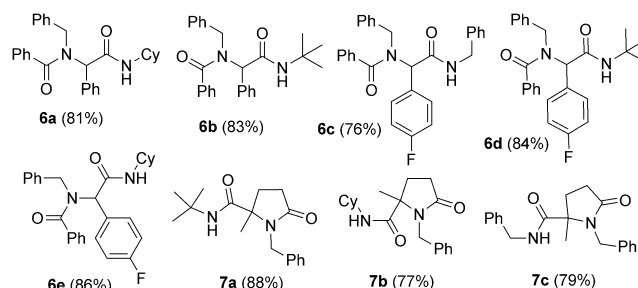
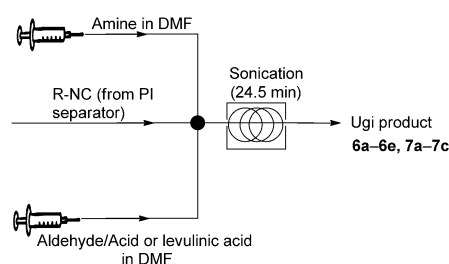


Figure 3. Continuous-flow Ugi multi-component reactions using isocyanides generated in situ to synthesize bis(amide) products **6a–e** and heterocycle products **7a–c** from levulinic acid.

amine and aldehyde solutions. Instead, we mixed acid and aldehyde (2.0 M in DMF), and the amine in another syringe (4.0 M in DMF) so that all four components (acid, aldehyde, amine, and isocyanide) could mix together at an X-junction (Figure 3). A residence time of 24.5 min under ultrasonic irradiation at room temperature was found to be the best conditions for performing the continuous Ugi reaction (For optimization details, see Table S1). Bis(amide)s **6a–e** (Figure 3) were synthesized using the optimized reaction conditions (room temperature, ultrasonication, 24.5 min). All of the Ugi products were obtained in good to excellent yields (76–86 %). This result is particularly promising, as the Ugi reaction was complete in a very short time (24.5 min.) compared to the batch reactions, which generally required hours to reach completion. Moreover, several interesting heterocycles, **7a–c**, were also synthesized using levulinic acid (a biomass-derived natural product) as a substitute for carbonyl and acid components under the same optimized setup for the Ugi reaction (Figure 3) in excellent yields (up to 88 %), further demonstrating the wide range of application of our method. An isocyanide-based four-component reaction that allows convenient synthesis of substituted amidines (**8a–g**) was also carried out. Yields of up to 90 % were achieved (Table S2, Figure S2, and method S7).

Besides the distressing odor, some *ortho*-functionalized aromatic isocyanides generally have long-term storage problems because of ring–chain tautomerization.^[15] It is also difficult to obtain the product in high purity, as it readily decomposes during purification by column chromatography (Method S8). Therefore, a serial approach to synthesis, purification, and in situ consumption of these isocyanides into stable products is a plausible means to overcome this problem. We applied our developed method for the oxidative coupling of in situ synthesized 2-isocyanobenzamide (**9**) and amines using a palladium catalyst and O₂ gas as a green

oxidant for the synthesis of 2-amino quinazolinone derivatives^[16] by gas–liquid biphasic reaction in a tube-in-tube microreactor.^[6g,17]

Prior to a continuous-flow synthesis, we optimized the reaction conditions in batch experiments (Table S3 and Method S8). A solution of palladium catalyst (in DMF) and amine (in DMF) was allowed to mix with the isocyanide solution obtained from the PI microseparator at an X-junction (Figure 4). The reaction mixture was then introduced

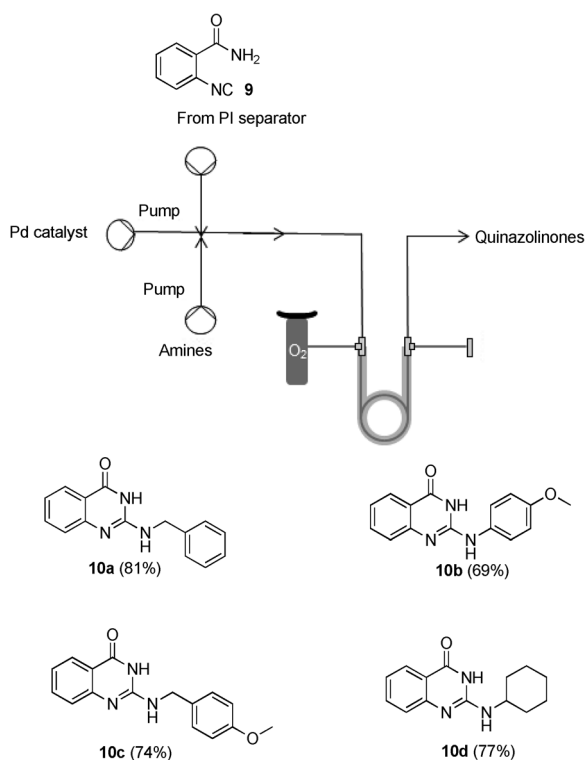


Figure 4. Metal-catalyzed continuous-flow oxidative isocyanide insertion into amines for the synthesis of quinazolinones.

into a tube-in-tube microfluidic system, which was submerged in an oil bath at 100 °C for 7.1 min. This gas–liquid biphasic microreactor was assembled by positioning a gas-permeable inner teflon tube (outer diameter (od) = 750 μ m, id = 500 μ m, length = 200 cm) into the outer PTFE tube (id = 1.0 mm, length = 200 cm) for the timely supply of oxygen. After fraction collection under optimized conditions on a 1 mmol scale, 2-amino substituted quinazolinones (**10a–d**) were isolated in 69 to 81 % yield, which is superior to the overall yield (53 % of **10a** over 2 steps) of the batch reaction process (Figure S3 and Method S9). Finally, we further extended our horizons from organic chemistry to organometallics by the insertion of isocyanides into palladium–carbon bonds in good yield (Figure S4 and Method S10).^[18,19]

The ability of the system to arrive at the desired conversion in minutes rather than the hours that are usually needed in a conventional batch system, and its capability to deliver much higher yields in spite of these short reaction times, illustrate the power of the microfluidic system when it is combined with multicomponent reactions. Enhanced mass

and heat transfer in the microreactor allowed a reduction in reaction time while avoiding the formation of side products, which is one of the drawbacks with a wide range of multi-component reactions. Thus, the reaction system afforded by the microfluidic system that is free of distressing odors also results in short reaction times and high yields, and provides an approach that should enable full exploration of the potential of isocyanide chemistry, including isocyanide-based MCRs and carbon–metal bonds.

In conclusion, the transformation to an odor-free reaction system was made possible by introducing an autonomous self-purification and separation system that does not require any outside input, such as heating. In light of numerous important organic and organometallic syntheses involving explosive, toxic, or noxious reagents, this method and the integrated microfluidic system have broader implications for use in those syntheses where the byproducts of the in situ generated reagent can be extracted with water, including isocyanide-based developments in drug discovery, natural products, and biology.

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