Microreactor Networks

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Multistep Continuous-Flow Microchemical Synthesis Involving Multiple Reactions and Separations**

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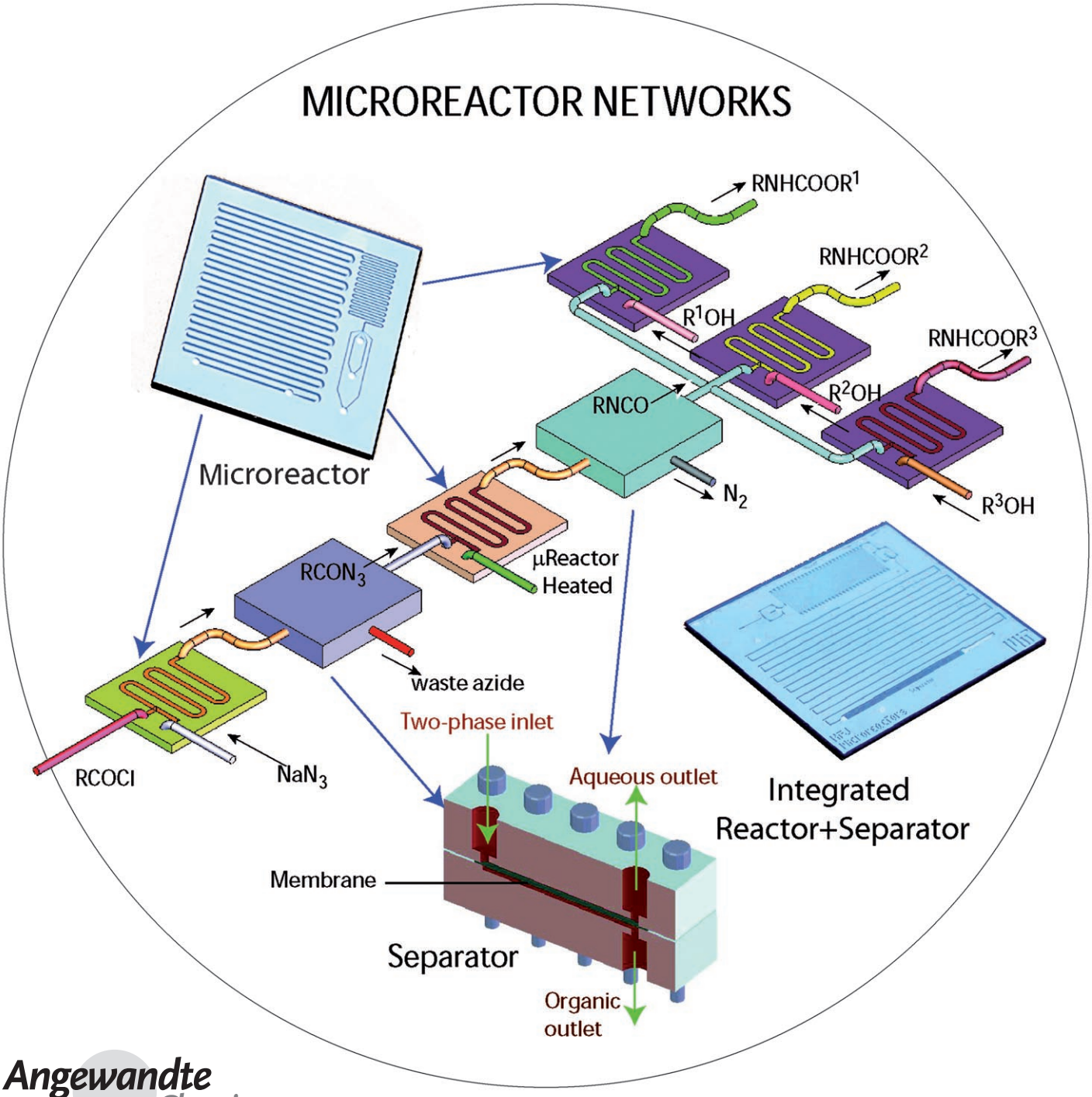


Microreactors enhance chemical synthesis through advantages offered by continuous operation at small-length scales in closed systems such as reduced reaction volumes, enhanced heat and mass transfer, and protection from air and moisture.[1–10] A typical chemical synthesis involves multiple reaction steps with separations (workup) between two successive reaction steps. However, the majority of microchemical demonstrations have been limited to a single reaction step,[1–10] multiple reaction steps without intermediate separations,[11,12] or multiple steps with solid-phase capture and off-line workup.[13,14] As an example of the latter, the first demonstration of the complete synthesis of the natural product oxomaritidine used solid-phase reactants and capture agents as well as an off-line manual solvent switch.[13] The total synthesis of ^{18}F-labeled fluorodeoxyglucose in an integrated microfluidic chip built in poly(dimethylsiloxane) (PDMS) combined five sequential steps: ^{18}F ion concentration on a solid capture agent, water evaporation through PDMS, radiofluorination, solvent exchange by evaporation through PDMS and replacement, and hydrolytic deprotection in sequential submicroliter batch quantities.[15] These studies elegantly demonstrate the potential of microreactors in multistep synthesis, however, the need remains for integration of continuous workup procedures with reactions. Solvent compatible microreactor systems combined with separation units would allow continuous multistep synthesis ranging from nanoliter to milliliter quantities with the potential to scale up to larger amounts through parallel operation. Moreover, avoiding the use of solid-phase capture agents reduces costs and the need for replacing/regenerating the solid phase.

The dominance of surface-tension forces over gravity in microfluidic devices[16] means that microfluidic extraction is typically based on immiscible fluid contacting.[17,18] By exploiting the laminar flow characteristics of microfluidic devices, extraction can be realized by side-by-side contacting of immiscible fluids in cocurrent and countercurrent flow arrangements.[17] Such devices offer the potential for more than one equilibrium extraction stage, but often have relatively low ratios of interfacial surface area to microchannel volume with a corresponding modest separation capacity (throughput) and in the case of countercurrent flow, a modest operating range.[17,19–25] Phase separation in these systems is usually achieved by having a small interfacial area to preserve sufficient capillary pressure to counter balance the imposed driving pressure or by modifying wetting characteristics to stabilize interfaces. The life time of the later approach can be limited by degradation of the surface modification over time either through gradual dissolution of the coating into the solvent flowing through the device or through susceptibility to chemical attack. We have recently developed efficient (mL min^{-1}), surface-tension-based continuous microfluidic techniques for separating immiscible fluids such as gas–liquid[26] and organic–aqueous phases.[18] In this contribution, we integrated these microfluidic extraction systems with microreactors[27,28] in a continuous multistep synthesis system (Figure 1) that enables sequential reactions without leaving the microreactor environment and creates the potential for the synthesis of varying amounts of analogous structures.

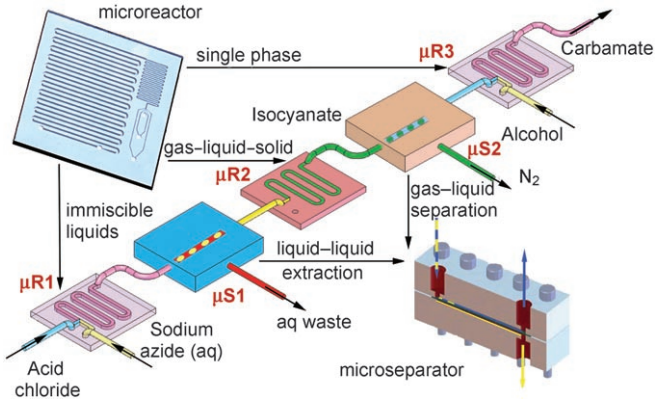
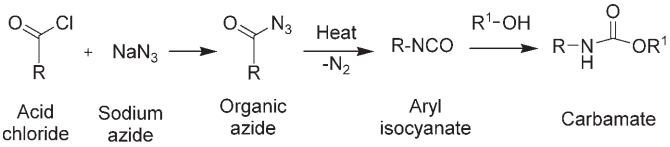


Figure 1. The experimental setup for carbamate synthesis. μR_1, microreactor for conversion of acid chloride to organic azide; μS_1, quantitative separation of organic and aqueous streams; μR_2, microreactor loaded with solid acid catalyst for conversion of organic azide to isocyanate; μS_2, quantitative separation of gaseous N_2 from the liquid stream; μR_3, microreactor for reaction of isocyanate and alcohol to carbamate.

The synthesis of carbamates by using the Curtius rearrangement of isocyanates[29] serves as the model chemical technique (Scheme 1) for demonstrating the multistep microchemical synthesis. Carbamates are useful products and building blocks and they show biological activity.[30,31] Moreover, isocyanates and organic azides are important intermediates that serve as a starting material for a variety of reactions in synthetic chemistry.[32,33] This choice of the model chemical reaction is further motivated by the intermediates azide and isocyanate being potentially hazardous and difficult to scale up in conventional batch chemistry. Continuous-flow synthesis offers generation and consumption of the inter-



Scheme 1. Carbamate synthesis as a case study.

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mediates in situ, which eliminates the need to store intermediates and thus makes the synthesis scheme safer. Furthermore, the use of glass-coated silicon-based microreactors provides the chemical inertness of glass with the excellent heat-transfer characteristics of silicon.[9]

The first step, the phase-transfer reaction between aqueous azide and acid chloride to produce the organic azide, was performed in a silicon-based microreactor (μR_1; Figure 1) previously described.[27,28] The subsequent continuous separation of the aqueous and organic mixture is realized in a microseparator (μS_1) based on preferential wetting characteristics.[18] The device has a thin porous fluoropolymer membrane that is selectively wetted by the organic solvent. The membrane has pore sizes in the 0.1–1-μm range (giving high capillary pressures) and a high pore density, which provides high throughput. The wetting by the organic phase prevents the aqueous phase from passing through the membrane while an imposed pressure drives the organic phase through the membrane holes resulting in quantitative separation of the two phases. The throughput increases with the imposed pressure difference across the membrane, and the maximum pressure limited by the capillary pressure. The first reaction and separation steps were also combined into a single device[18] (Figure 2), which integrates contact of the organic and aqueous reactants and subsequent phase separation of the reaction products.

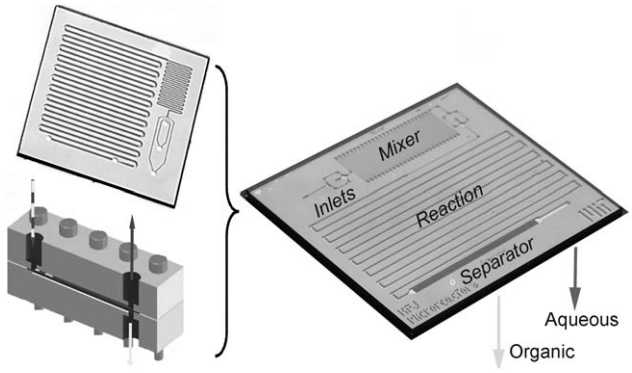

Figure 2. Combined reaction and workup procedures in a single device.

The formation of isocyanates in the second reaction step was first performed by heating the organic azide in a standard microreactor (μR_2) and then by packing this reactor with a solid acid catalyst (H-mordenite solid acid catalyst, HS-690, Wako Chemicals) to achieve high conversions at lower temperatures. Subsequent removal of the generated nitrogen was achieved in the separator unit (μS_2) by the liquid wetting and flowing through the membrane while preventing gas penetration.[26]

Carbamate was formed in the third step by contacting the generated isocyanate with alcohol in the third microreactor (μR_3). As a demonstration of using potentially hazardous intermediates generated in situ in subsequent parallel reactions, a small vial replaced the second gas–liquid separator and served as a liquid supply for three concurrent carbamate reactions (Figure 3). In this case, gas–liquid separation was driven by the differences in gas and liquid density as in conventional separation schemes. This branching method, which could also be applied to the organic azide stream, allowed simultaneous synthesis of multiple compounds in the same run. By using this scheme, we performed a parallel synthesis of methyl phenyl carbamate, ethyl phenyl carbamate, and benzyl phenyl carbamate.

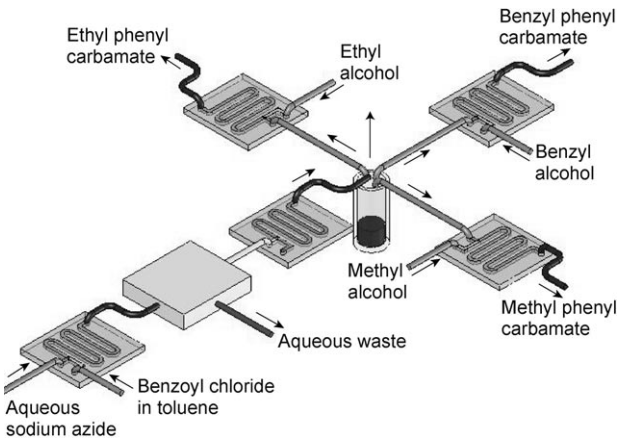

Figure 3. Reaction scheme for parallel synthesis of three analogous carbamates.

Two different pressure-driven flow schemes were used to flow liquid out of the vial: 1) The vial was pressurized with an inert gas (helium) while allowing a small leak for the generated nitrogen to escape. Tube diameters and lengths were adjusted to control the flow rates in the three systems. 2) The vial was kept open and three syringe pumps were connected independently to the three final microreactors. The syringe pumps were operated in withdrawal mode. The latter was the easier of the two methods as it did not pressurize the upstream devices and no adjustment of tubing lengths/diameters was needed. However, this method required the use of three additional syringe pumps, making the experimental setup bulkier and more expensive than the active pressure-driven scheme.

We observed uniform liquid–liquid segmented flow in the first microreactor when contacting benzoyl chloride in toluene (0.36 M) with a basic (pH 9) solution of sodium azide (0.4 M). The conversion of benzoyl chloride to benzoyl azide was a function of the residence time, 65% conversion at a residence time of 90 min and 98% conversion after 200 minutes. To facilitate better two-phase contact, a T mixer (Upchurch) was added upstream of the first reactor and tubing (1/16″ OD, 0.01″ ID Teflon, Upchurch) was provided for additional residence time before the first reactor. Liquid recirculation within the liquid segments enhanced mass transfer[16] beyond diffusive rates, and the increased surface to volume ratio at the microscale eliminated the need for a phase-transfer catalyst. As a result, we obtained the final carbamate without having to remove any contaminants such

as phase-transfer catalysts. The liquid–liquid separator (μS_1) provided complete separation of the organic and aqueous phases. The conversion of benzoyl azide to phenyl isocyanate in the second reactor was a function of the heating temperature (Table 1) and was seen to be consistent with reported kinetic data.[34,35] The decomposition temperature of benzoyl azide is reported to be between 50–80 °C.[33] In batch operation, the azide is typically heated gently to a temperature not much beyond the decomposition temperature to prevent uncontrolled release of energy. The microreactor enables higher temperatures, reducing the time needed to achieve complete conversion.

Table 1: Conversion as a function of temperature for the decomposition reaction $PhCON_3 \rightarrow PhNCO$.

T [°C]	Residence time [min]	Average Conversion $\pm$ s.d. [%][a]
60	60	7.0 ± 0.8
90	60	91.2 ± 1.4
105	60	99.0 ± 1.3

[a] s.d. = standard deviation for three samples.

The conversion of the azide to isocyanate in the second reactor proved to be the limiting step in increasing the overall system productivity. This limitation can be mitigated by adding a second heated reactor and operating at double the flow rate while keeping the same overall residence time. Another approach would be to use higher temperatures by 1) pressurizing the system and using the same solvent[28] or 2) by replacing toluene with a higher-boiling solvent, such as xylene. Yet another possibility is to speed up the decomposition by using acid catalysis.[36] We demonstrated the latter approach by loading the microreactor with 12.13 mg of H-mordenite solid acid catalyst (HS-690, Wako Chemicals) and operating at the same flow rate. At 90 °C, we obtained 99.9 % conversion of the azide into the isocyanate, as compared with the 91.2 % conversion obtained in the noncatalyzed case.

The higher boiling point (167 °C) of phenyl isocyanate compared with toluene (108 °C) should also make it possible to remove the toluene by a "solvent-stripping" operation. This process could be done by heating the gas–liquid separator vial (Figure 3) above the boiling point of toluene to obtain neat phenyl isocyanate and to remove toluene vapors along with nitrogen in the gas phase.

The gas–liquid separators operated as designed and removed all of the evolved gas. The final reaction between an alcohol and phenyl isocyanate was fast,[37] yielding 96–99 % of the carbamate. With a flowrate of 1 $\mu L\,min^{-1}$ for each of the aqueous (0.4 M) and organic reagents (0.36 M), the productivity ranged from 80–120 mg per day depending on the type of carbamate synthesized. Achieving high productivity was not the target of this investigation. Productivity can be increased by optimization of the microreactor design and the operating conditions.

In a typical run, we operated the continuous multistep synthesis setup for 6–7 days without any interruption until all the reagents were used. There was no change in system performance over the long-term continuous operation of the microreactors and separators. It was also feasible to use only the first two reactors and the corresponding phase separator to produce isocyanate on demand.

The Curtius rearrangement served as a case study with reactive and potentially hazardous intermediates (azide and isocyanate). However, the technique of combining microreactors and separators applies broadly to continuous multistep synthesis. When needed, the general microreactors can be replaced by specialized devices such as packed-bed catalytic microreactors,[38,39] as illustrated by introducing solid acid catalyst in the second transformation. Monitoring and optimization of the reaction yields become feasible when combining the microreaction system with analytic techniques as already demonstrated for individual microreactors.[10] Introducing branching after the formation of an intermediate provides for continuous synthesis of multiple, analogous compounds as demonstrated with the addition of multiple alcohols to the phenyl isocyanate to form different carbamates. Moreover, different reagent solutions could be run in succession to further expand the number of compounds synthesized. The continuous operation implies that the amounts of particular interesting products could be scaled up by increasing the run time or the number of systems.

In conclusion, we have performed a continuous multistep microchemical synthesis consisting of three transformations with separation steps in between by using the Curtius rearrangement as a model system. The work demonstrated the simultaneous use of a network of microreactors and separators for parallel synthesis of a family of compounds, in situ generation and consumption of hazardous intermediates such as isocyanates, safe operation of microreactor systems for reactive compounds such as azides, and small-scale synthesis of chemicals for screening and optimization purposes.

Experimental Section

The organic and aqueous phases were loaded in separate 10-mL syringes (GasTight, Hamilton) and connected to the inlets of the first reactor (Figure 1). The outlet from the third reactor was used directly for analysis without any further treatment. The flow rates used ranged from 1 to 5 $\mu L\,min^{-1}$ with a 1:1 ratio of reagents. The second reactor was heated by using a hotplate that was directly in contact with the reactor. A 5 % w/v aqueous sodium azide solution (VWR) was diluted with a NaOH solution to give a 0.4 M sodium azide solution with pH 9. Use of 0.36 M benzoyl chloride (Sigma Aldrich) in toluene resulted in the azide being in 11 % molar excess.

Sample analysis: NMR spectroscopy was used to identify the final product. GC–MS was used to quantify the concentration of benzoyl chloride, phenyl isocyanate, and the final carbamate, while HPLC was used to quantify the aqueous-phase concentration of azide in the feed stream to the first reactor as well as in the aqueous waste from the first separator.

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