Microreactors

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Continuous In Situ Generation, Separation, and Reaction of Diazomethane in a Dual-Channel Microreactor**

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Performing organic transformations with toxic, sensitive, and explosive volatile chemicals or gaseous intermediates has always been challenging both in academia and industry. Although the experience of various ill-effects or accidents is not uncommon among those working with these chemicals, most of the events remain unpublished unless large disasters occur.[1] It is, therefore, not surprising that recently much attention has been focused on developing safe or sustainable routes to produce such invaluable reagents as ozone, hydrazoic acid, diazomethane, and hydrogen cyanide.[2]

Diazomethane, an extremely toxic, carcinogenic, odorless, and explosive yellow gas,[3] is one of those most versatile reagents available to the organic chemists for the preparation of carbon–carbon and carbon–heteroatom bonds.[4] Despite its interesting and versatile chemistry, use of diazomethane on laboratory or pilot-plant scale is considered quite problematic owing to the well-known safety concerns associated with its preparation, separation, purification, transportation, and decomposition.[3,4] Even when diazomethane can conveniently be generated under mild conditions by treating a suitable precursor with an alkaline base, efficient separation and proper purification of the prepared diazomethane for the subsequent reaction is required owing to the chemical vulnerability in the presence of alkaline bases and water or alcohol impurities. Routine separation processes, such as distillation, are certainly inappropriate for toxic gases. Furthermore, the extraction and transportation of highly reactive gaseous substances even using an inert gas (such as N_2) are also very risky, with possible leakage or detonation. Ideally, it would be highly desirable to have a total reaction system that self-contains a toxic and explosive material, and in which the reagent is self-generated and then separated within, and in turn consumed for the formation of the desired product, all within the reaction system.

Microfluidic chemical systems are the most promising tools to miniaturize the inventory of such toxic and explosive substances owing to their extremely small internal volume and continuous consumption capability.[5] Herein, we present a concept and method in the form of a microchemical chip based on a dual-channel microreactor[6] that enables self-generation of the toxic and explosive reagent within, its efficient separation, and subsequent reaction to yield desired products, all within the same closed flow system (Figure 1). The reaction system is validated with reactions involving diazomethane. The unprecedented triple role of generation/separation/reaction that is played by the reaction system is all the more attractive in that the toxic and explosive reagent is not only contained solely within the system but also is not accumulated within, thus leaving no trace of the toxic material after the desired product is obtained.

Recently, we presented a poly(dimethylsiloxane) (PDMS) microreactor for oxidative Heck reactions in which two parallel channels were separated by a thin PDMS membrane.[6] PDMS membranes have also been utilized in various separation devices, site isolation, and cascade reactions because most small organic molecules have high flux rate through the membrane whereas water and ionic salts are blocked completely.[7] It is anticipated, therefore, that diazomethane could be selectively transported through the PDMS membrane from the aqueous saline channel containing water and KOH and other salts, where it is generated, to the other channel above the membrane for subsequent organic reaction. Thus, a proper microfluidic design of two parallel channels separated by a membrane layer could be employed for simultaneous generation, separation, and reaction of diazomethane. This concept of a PDMS dual-channel microchemical system is shown in Figure 1. Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) quickly reacts with KOH to generate diazomethane in the bottom channel, the Diazomethane readily diffuses out to the upper channel where it reacts with main reactant. The PDMS membrane, which is extremely hydrophobic, prevents the diffusion of KOH, water, and potassium *p*-toluenesulfonate from the bottom channel to the upper channel. Similarly, the organic reactants or the products from the reaction with diazomethane in the upper channel have little tendency to diffuse into the aqueous saline phase in the lower channel.

To test the selective and efficient separation of thus-generated diazomethane through a thin PDMS membrane, a bulk reaction was firstly conducted (Supporting Information, Figure S2, S3). The results were generally dependent on the solvents used for the interior and exterior of the membrane

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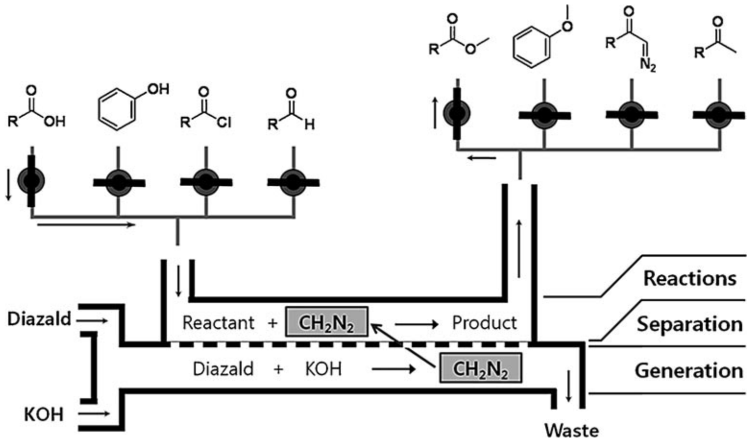


Figure 1. Illustration of the microchemical system for in-situ generation, separation, and reactions of diazomethane.

cylinder: polar solvents were quite suitable for yielding a high conversion of benzoic acid with no swelling of the membrane.[8] However, it still raises a safety concern owing to accumulation of hazardous diazomethane caused by the relatively large reaction volume. Furthermore, the batch system is not suitable for continuous production and does not allow repeated use owing to its insufficient stability. For continuous production and repeated use of the reaction system involving toxic materials, a continuous-flow microfluidic system that offers a small internal volume would be needed. For this purpose, the original dual-channel microreactor[6] was modified and retooled for simultaneous in-situ generation, separation, and reaction. The PDMS membrane layer separating the two channels was 45 μm thick. To obtain quick reaction of KOH with diazald by enhanced mixing, the channel entrance that was a few centimeters long was made curved (For details of fabrication and an optical image and SEM image of the dual-channel reactor, see the Supporting Information). Although diazomethane should preferentially diffuse through the membrane as it is continuously consumed on other side of membrane, its diffusion through the remaining three walls of channel (Figure 2a) cannot be ignored when handling hazardous diazomethane. Therefore, it became necessary to come up with a way of preventing diffusion through the exterior walls.

We have shown that a monolithic type of solvent-resistant microfluidic system could be fabricated from poly(vinyl silazane) (PVSZ, KION VL-20, Clarient).[9] We therefore thought that PVSZ coating on the plain PDMS channel in a selective manner may prevent the undesired toxic diazomethane from diffusing into the walls of the dual-channel (Figure 2b). Briefly, PVSZ was first spin-coated onto two PDMS blocks with channel structure and then the coated polymer on the PDMS slab was gently wiped out with a glass slide. After solidifying the PVSZ coating through a series of UV and thermal curing steps, both PVSZ-coated channels and the PDMS membrane were bound together in a sandwich manner with the aid of plasma treatment and the bound dual channel was kept at 110 °C in an oven overnight to strengthen the bonding (Figure 2c; for details, see the Supporting Information, Figure S6). The fabricated PVSZ-coated PDMS dual-channel microreactor was 75 cm long, and 60 μL in volume with the 45 μm thick membrane. The bottom channel with two inlets and one outlet was used for continuous generation of diazomethane. The generated diazomethane was diffused into the top channel through the PDMS membrane. The reactions of diazomethane with various organic substrates were performed in the top channel.

Methylation of benzoic acid was taken as a model reaction to illustrate the concept of in-situ generation, efficient separation, and reaction of diazomethane in the continuous-flow dual-channel microreactor. The connections of the dual channel with syringes and product collector were made by PFA capillaries (id = 500 μm). It was crucial to efficiently generate a high concentration of diazomethane in the bottom channel without any clogging or precipitation so that it could diffuse into the top channel. Therefore, a series of experiments were performed to optimize the reaction conditions (for details, see the Supporting Information, Table S2). After extensive studies, it was found that flowing solutions of diazald (1.0 M in DMF) and KOH (2.0 M in water containing 0.01 % aliquat 336) with an identical flow rate were the optimal conditions for efficient generation of diazomethane without any precipitation or clogging of the channel. In the top channel, a solution of benzoic acid (0.5 M in DMF) was flown simultaneously. Blank experiments revealed that neither benzoic acid nor the product methyl benzoate diffused from the top channel to the aqueous saline bottom channel.[10]

As the reaction of diazald with KOH is quite fast, the residence time of diazomethane in the bottom channel would be almost equal to that of KOH and diazald. Diazomethane is continuously consumed in the top channel; thus a steady diffusion of diazomethane from the bottom to the top channel

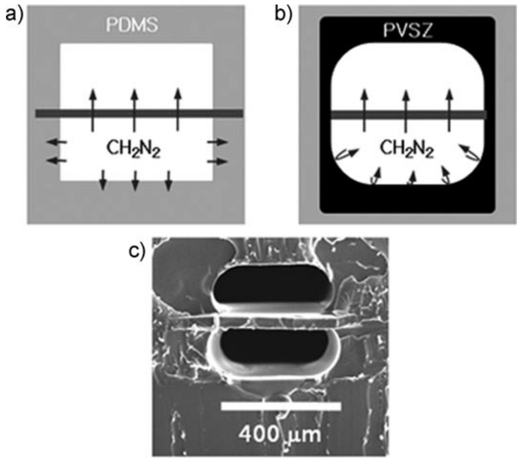


Figure 2. Restricted diffusion of CH_2N_2 into the walls of a PDMS dual-channel reactor by PVSZ coating. a) Normal PDMS dual-channel reactor (unrestricted diffusion of CH_2N_2); b) PVSZ-coated PDMS dual-channel (restricted diffusion of CH_2N_2); c) cross-sectional SEM image of a typical PVSZ-coated PDMS dual-channel reactor.

can be achieved. The reaction of benzoic acid with diazomethane is known to be quantitative and instantaneous. Thus when enough benzoic acid is present in the top channel, all diffused diazomethane is consumed instantaneously. Under the same concentrations and flow rates of diazomethane and benzoic acid, the conversion represents the separation efficiency of the dual channel (Table 1). The separation efficiency can be defined as the fraction of diazomethane that is diffused across the membrane out of total diazomethane generated in the bottom channel. It depends on several parameters, such as temperature, concentration, and residence time. With other parameters fixed, the diffusion of diazomethane across the membrane would be higher at longer retention time. Theoretically, it is not possible to obtain 100 % separation efficiency, yet by controlling the flow rate or residence time we can obtain higher separation efficiency (45 % at flow rate of 10 μL min^{-1} and 63 % at a flow rate of 4 μL min^{-1}). Eventually, the complete reactions of the diffused diazomethane were accomplished by controlling the feeding rate of benzoic acid. It is particularly notable that the PVSZ-coated dual-channel reactor provided better separation efficiency than the non-coated dual-channel reactor. This result indicates that PVSZ protective coating on the walls of the dual channel prevents diazomethane from diffusing into the walls, thus little diazomethane is accumulated in the channels (Figure 2 a,b). Additionally, since the outlet of the bottom channel is immersed in acetic acid, any diazomethane transported out along with waste is instantaneously quenched. Thus, extremely toxic diazomethane can be handled with safety and efficiency in the dual-channel microreactors.

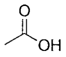
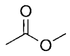
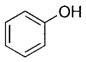
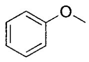
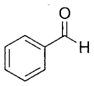
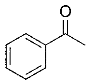
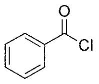
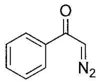
Table 1: Continuous in-situ generation, separation, and reaction of diazomethane with benzoic acid in a dual-channel microreactor.[a]

Entry	Flow rate [μL min^{-1}] diazomethane (KOH+diazald)	Flow rate [μL min^{-1}] benzoic acid	Conversion [%][b]
1	4	4	63 (34)[c]
2	4	2	100 (77)[c]
3	4	1.3	100 (100)[c]
4	10	10	45 (26)[c]
5	10	5	92 (50)[c]
6	10	3.3	100 (78)[c]

[a] All experiments were performed at room temperature. [b] Conversions were determined by GC/MS analysis using anisole as an internal standard. Results are the average of three independent experiments; standard deviation ± 5 %. [c] Results in parentheses are from non-coated PDMS dual channels.

The wide applicability of the microfluidic system with PVSZ coated dual-channel could be demonstrated by various organic transformations using diazomethane (Table 2). In all of the cases, diazomethane was generated in the bottom channel as aforementioned, and reactants were introduced to the top channel (0.5 M in DMF). Various methylation reactions showed complete reaction of the diffused diazomethane under controlled flow rates (Table 2, entries 1–3). In particular, it is worth noting that even the Arndt–Eistert reaction (entry 4),[11] which is highly sensitive to water, could be performed without any problem. In classical flask reactions, the synthesized diazomethane has to be dried over KOH before using in the Arndt–Eistert reaction. The complete conversion of benzoyl chloride to 2-diazo-1-phenylethanone indicates that the PDMS membrane allows only selective diffusion of diazomethane from the bottom to the top channel, leaving water and other ionic salts behind. Thus, a thin PDMS membrane-separated PVSZ coated dual-channel reactor can generate and separate anhydrous diazomethane in a continuous-flow system at room temperature, thereby avoiding risky distillation of diazomethane and an additional drying process, which means full handling of hazardous diazomethane in completely shielded microfluidic system without accumulation of hazardous diazomethane.

Table 2: In situ generation, separation, and reactions of diazomethane in a PVSZ-coated dual-channel microreactor at room temperature.[a]

Entry	Substrate	Flow rate [μL min^{-1}]	KOH + Diazald flow rate [μL min^{-1}]	Product	Yield [%][b]	Daily output [mmol]
1		4	10		> 99	2.88
2		1	4		> 99	0.72
3		1	4		81	0.58
4[c]		1	4		90	0.65

[a] Diazomethane was generated in the bottom channel by flowing solutions of diazald (1.0 M in DMF) and KOH (2.0 M in water containing 0.01 % aliquat 336) with the same flow rate. Substrates were introduced to the top channel in DMF (0.5 M solution). [b] Yields were determined by GC/MS analysis using an internal standard. [c] Arndt–Eistert synthesis.

In conclusion, the concept and method that we devised for continuous in-situ generation on demand, separation, and reaction of toxic and/or explosive reagent(s) has been shown to be quite effective when it was applied to reactions involving diazomethane. The significance of the microchemical device as exemplified by the application lies in its room temperature generation and separation of toxic anhydrous diazomethane from aqueous saline phase without dangerous distillation. The separated diazomethane is subsequently reacted to obtain desired final products. Once the products are obtained, there is no trace of the toxic substance remaining, in this case diazomethane, in the continuous microchemical system nor in its surroundings. The new handling technique of toxic substance such as diazomethane and the unique dual-channel microreactor could be potentially useful not only for laboratory-scale or large-scale production of diazo pharmaceutical intermediates but also for other toxic and explosive substances in a safe and continuous way.

Experimental Section

Continuous in-situ generation, separation, and reaction of diazomethane in the PVSZ-coated dual-channel microreactor: The connections of the dual channel were formed of PFA capillaries (inside diameter 500 μm) and the device was immersed in 25 % aqueous acetic acid. Diazomethane was generated in the bottom channel by flowing solutions of diazald (1.0 M in DMF) and KOH (2.0 M in water containing 0.01 % aliquat 336). In a model reaction, a solution of benzoic acid (0.5 M in DMF) was flown simultaneously in the top channel. The product methyl benzoate was collected and analyzed by GC/MS.

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