

# GENERATION, SEPARATION, AND REACTIONS OF ETHYL DIAZOACETATE USING INTEGRATED MICROFLUIDIC SYSTEM

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## ABSTRACT

An integrated microfluidic system for multiple reactions and separations involving ethyl diazoacetate is presented. Combined for the integration are: droplet technique for liquid-liquid and/or gas-liquid separation and in-situ generation of toxic reagent, a polymeric microseparator for liquid-liquid separation, and capillary microreactor for cascade reactions in a sequential and continuous manner.

## KEYWORDS

Microreactor, flow chemistry, hazardous materials, diazo-chemicals.

## INTRODUCTION

Diazomethane and ethyl diazoacetate are amongst the most common diazo-compounds that have remarkably attracted a huge interest in the production of fine chemicals and pharmaceuticals.[1] Despite commercial availability, the storage, transportation, and reaction of diazo-chemicals have raised significant safety concerns due to their instability, high reactivity and explosive nature. Although in most of the cases the diazo reagents are freshly prepared prior to their use, the possibilities of detonation of the chemical reagent inventory cannot be fully ignored. Recently microreactors attracted much interest because they could resolve these safety concerns owing to their miniaturised reaction volume, continuous flow processing, and fast heat as well as mass transfer ability.[2]

In our earlier communication, we reported the generation of diazomethane and the successive processes in PDMS dual channels.[3] Despite controlling various parameters, only up to 63% of the total generated diazomethane could be separated and utilized for further reactions. Thus, it was disadvantageous that the safe manipulation of diazomethane was associated with significant amount of hazardous waste. Additionally, the durability and productivity of the microfluidic device (~1 mmol/day) were also quite low. We, therefore, realized to develop a robust microfluidic set-up for advanced production of fine chemicals and/or pharmaceuticals using toxic, explosive and hazardous reagents without compromising on safety and waste hazard concerns.

## EXPERIMENT

Presented in this letter is a microfluidic system that is integrated for multiple reactions and multiple separations involving hazardous materials. In the system, the toxic and explosive reactant is synthesized in-situ and then reacted to produce valuable intermediate for the synthesis of fine chemicals and pharmaceuticals. Complete separation of the product is made possible through the use of a droplet microreactor in the system in which the reactants and the toxic product separate by themselves, i.e., self-separation without any input from outside such as heating or polymer support, which in turn facilitates almost complete conversion to the product. The material of construction for subsequent separation and further reaction for the intermediate is such that the throughput of the final product is two order of magnitude higher than that obtained earlier in a one-pot, non-integrated system.[3] Ethyl diazoacetate (EDA) was taken as a model hazardous and explosive reagent to illustrate the concept. The integrated microfluidic system is shown in Figure 1.

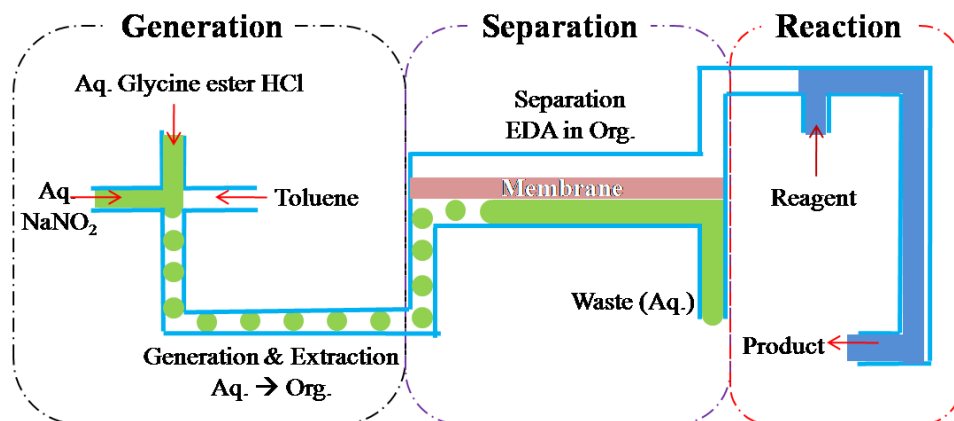


Figure 1. Schematic illustration of continuous generation, extraction, separation, and reaction of EDA in an integrated microfluidic system.

### Fabrication of polyimide (PI) film dual channel microseparator

Laser ablation on polyimide film was employed to fabricate the proposed dual channel device as illustrated in Figure 2. First of all, layers of 125  $\mu\text{m}$  thick polyimide films (Kapton HN film, Dupont, USA) were ablated by UV laser (355 nm, ESI, USA) to form linear microchannel (1000  $\mu\text{m}$  width, 80  $\mu\text{m}$  depth and 35 mm length) as previously reported.[4] The 4-corners of each film were holed (1 mm diameter) to align the film patterns. After laser ablation, the films were cleaned by washing with acetone under ultrasonic and dried. Polytetrafluoroethylene (PTFE) membrane (Whatman, 0.45  $\mu\text{m}$  pore, 37 mm dia) sandwiched by two sheets of polyimide film microchannels were placed between metal holder which align PI films by inserting metal pins through the holes at the film corners. Finally metal holders were tightly assembled by screw to connect tube. To test separation of immiscible organic/aqueous mixture, water with green ink and toluene were introduced into the separator as shown in Fig. 2b. Because PTFE membrane wets selectively non-aqueous solvents due to hydrophobic nature, water flow only into top channel while toluene phase are wetting on PTFE membrane and are shoved to bottom channel by flowing of water phase. Finally toluene phase were separated from inlet of top channel to outlet of bottom channel.

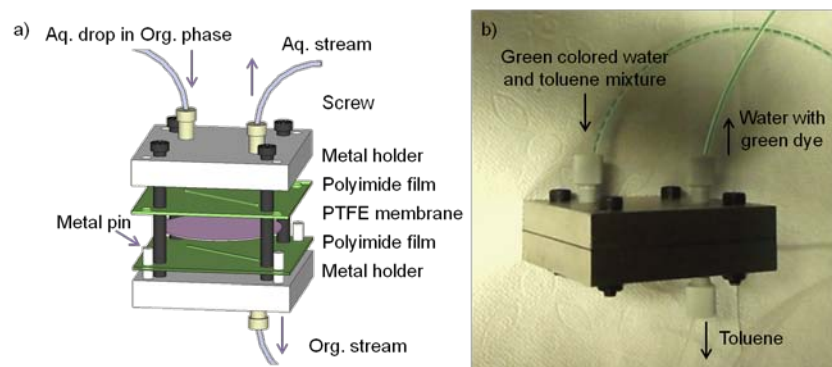


Figure 2. a) Illustration and b) photograph of polyimide film dual channel microseparator.

### In-situ synthesis, extraction, and separation of EDA

In-situ synthesis, extraction, and separation of EDA were carried out by introducing glycine ethyl ester hydrochloride in acetate buffer (pH = 3.5), aqueous  $\text{NaNO}_2$ , and extracting solvent to the microfluidic set-up. Initially we attempted to mix the aqueous solutions of glycine and  $\text{NaNO}_2$  and then dispersed that mixture into toluene using two T-junctions (Figure 3a). However, there was a significant loss of EDA when two T-junctions were used, although cooling of the reaction mixture in ice bath diminished the degradation. We, therefore, decided to use an X-junction (Figure 3b) for mixing the two aqueous solutions for instant dispersion of mixture into extracting solvent to minimize the decomposition of EDA in acidic medium. The results of EDA synthesis using two T-set and one X-junction are comparatively summarized in Table 1.

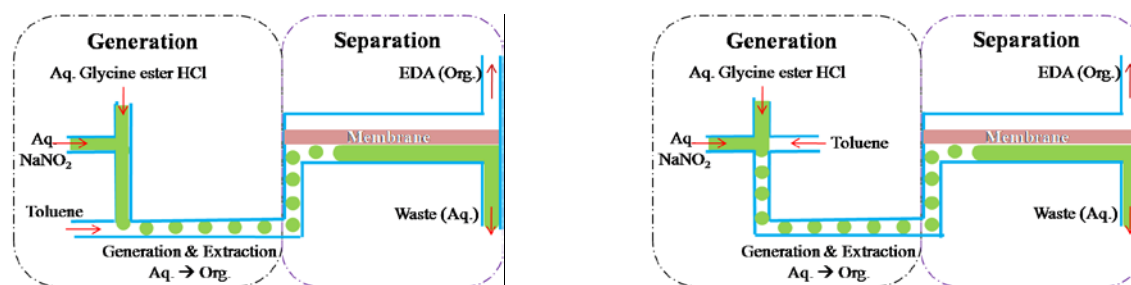
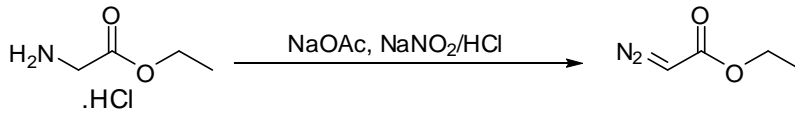


Figure 3. Illustration of microfluidic set-up with a) T-junction and b) X-junction.

### Cascade aldol reaction with aldehydes

1.50M solution of  $\text{EtOOCCH}_2\text{NH}_2\cdot\text{HCl}$  in acetate buffer (pH = 3.5), 1.51M solution of  $\text{NaNO}_2$  in DI water, and extracting solvent (toluene) were taken in three separate syringes and were introduced to X-junction at identical flow rates. The X-junction was connected to PI dual channel microseparator via PFA tube (id = 800  $\mu\text{m}$ ). The out-coming organic phase containing EDA (1.5 M) from PI dual channel separator was allowed to mix with the toluene solutions of DBU (1.2M) and aldehydes (6.0M) respectively through X-junctions (Figure 4). The final reaction mixture (EDA, DBU, and aldehyde) was then passed through ultrasonication (40  $^\circ\text{C}$ ) using a PFA capillary (id = 800  $\mu\text{m}$ , length = 5 m) and the reaction was quenched into aqueous  $\text{NaHCO}_3$ . Under the stable conditions, exactly 5 mmol of the product was collected (Run time 55.6 min). The temperature of ultrasonication bath was maintained constant by continuous water circulation. The organic phase was separated, dried, and evaporated to yield crude which was purified by silica-gel column chromatography.

Table 1. Results of EDA synthesis using two T-set (Figure 3a) and one X-junction (Figure 3b)

					
Entry <sup>a</sup>	Temp. (°C)	Mixing device	Extracting solvent	Res. Time <sup>[b]</sup>	Yield (%) <sup>[c]</sup>
1	rt	2 T-set	Toluene	2.0 min	60
2	0	2 T-set	Toluene	2.0 min	91
3	rt	X- junction	Toluene	2.0 min	99

[a] Composition of EDA precursors: 1.50M EtOOCCH<sub>2</sub>NH<sub>2</sub>.HCl in acetate buffer (pH=3.5), 1.51M NaNO<sub>2</sub> in water; flow rates of aq. solutions and extracting solution were in 1:1:1 ratio. [b] Residence time for droplet reaction and extraction in PFA capillary (id = 800 μm, length = 120 cm). [c] Determined by GC/MS using anisole as an internal standard.

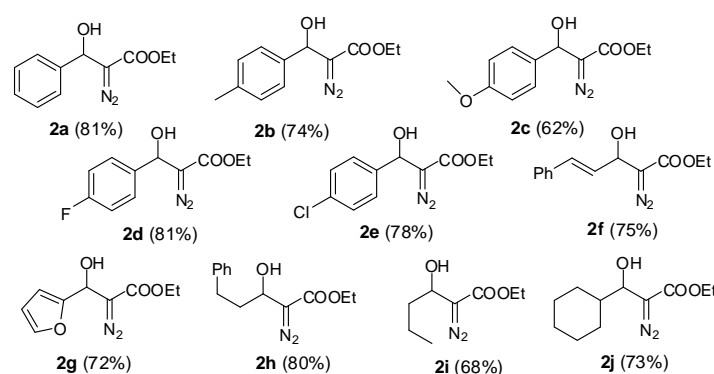


Figure 4. Cascade generation, separation, and reaction of EDA with various aldehydes (Yields in the parentheses are of isolated product on 5 mmol scale).

The integrated microfluidic system has been proven to be resilient and robust in handling hazardous reagents even when subjected to continuous operation of the system over long periods of time. The durability can readily be attributed to the chemical inertness of the materials (PFA, PTFE and PI). The integrated microfluidic system was repeatedly used for multiple optimization and reactions over several months without any noticeable change in the system performance.

## REFERENCES

- [1] (a) Y. Zhang, J. Wang, *Eur. J. Org. Chem.*, 2011, 1015; (b) G. Maas, *Angew. Chem. Int. Ed.*, 2009, 48, 8186; (c) M. P. Doyle, D. C. Forbes, *Chem. Rev.*, 1998, 98, 911; (d) D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stuppel, *Chem. Soc. Rev.*, 2001, 30, 50.
- [2] (a) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed.*, 2011, 50, 7502; (b) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.*, 2011, 47, 4583; (c) J.-i. Yoshida, H. Kim, A. Nagaki, *ChemSusChem*, 2011, 4, 331; (d) C. P. Park, R. A. Maurya, J. H. Lee, D.-P. Kim, *Lab Chip*, 2011, 11, 1941; (e) A. Odedra, K. Geyer, T. Gustafsson, R. Gilmour, P. H. Seeberger, *Chem. Commun.*, 2008, 3025; (f) R. A. Maurya, P. H. Hoang, D.-P. Kim, *Lab Chip*, 2012, 12, 65.
- [3] R. A. Maurya, C. P. Park, J. H. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.*, 2011, 50, 5952.

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