



A practical experiment to teach students continuous flow and physico-chemical methods: acetylation of ethylene diamine in liquid bi-phase

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Abstract

Despite growing applications being reported both in academia and industry, continuous flow chemistry remains a relatively untaught field across most chemistry undergraduate courses. This is particularly true in laboratory practical classes, where it is often deemed simpler to carry out synthetic reactions in traditional batch mode using round-bottomed flasks. Herein, we report the development of an undergraduate project that utilises cheap and readily available materials to construct continuous flow reactors. The students compare the performance of different types of reactors and conditions in a biphasic selective acetylation of a symmetrical diamine. Throughout the investigation, the students can vary multiple parameters as they optimise the reaction, thus actively learning and readjusting them based on their improved understanding. The experiments give the students an appreciation of continuous flow techniques in comparison to batch.

Keywords Undergraduate laboratory practical · Continuous flow methodology · Multiphase flow reactor · Diamine acetylation

Introduction

Conventionally, undergraduate laboratory organic chemistry experiments focus upon batch reactions whereby the full quantity of reagents to be reacted are added to the reaction vessel. Flow chemistry offers an alternative approach to synthesis, with a variety of different reactors allowing more rapid exploration and precise control of reaction parameters, and improved safety and handling of reagents and products [1–5]. There are a number of reports on the use of continuous flow methodology for the synthesis of important pharmaceutical products, highlighting the applicability of flow chemistry

and its importance as a modern synthetic technique [6–9]. However, this methodology is not often taught within undergraduate curriculums, although there are reports of the use of flow experiments for undergraduate teaching in the literature [10–12], they are still few and limited.

With the advantages in productivity, sustainability and safety offered by continuous synthesis, such methodology is being increasingly utilized within both industrial and academic environments. Therefore, it is important that this technique is addressed within chemical education. Using the experimental procedure detailed herein, students gain both theoretical and practical experience in planning and carrying out a continuous chemical reaction. The reaction chosen for study is sufficiently fast, allowing several parameters to be tested and a large wealth of data to be obtained. Students gain experience of the whole process: reactor design, optimisation of reaction conditions and interpretation of data obtained. This use of continuous flow chemistry demonstrates to students the power of the technique for rapid, efficient screening of reaction conditions, and can represent a sample process to be readily adopted by undergraduate laboratories.

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Experimental details

Reaction

The reaction chosen for this study was the monoacetylation of a symmetrical diamine (Scheme 1), representing a commonly utilised reaction within published chemical research [13–15]. The reaction complements existing teachings within the undergraduate curriculum including practical synthetic techniques, S_N2 reactions, protecting group theory and analytical techniques. It also provides a good example of the industrial relevance of undergraduate teachings, with the ability to functionalize amines being an important process within the pharmaceutical, agrochemical and materials industry. One relevant example showing this is the Eli Lilly report of the continuous acylation of sulfonamides during formation of Tasituslam, an anticancer agent [16]. The reaction also allows the introduction of new concepts to students including the nature of biphasic reactions and the partitioning of compounds in different phases [17], as well as flow chemistry and the importance of interphase mass transfer and residence time for maximizing product formation. We have also found the experiment to be a good opportunity for students to gain and develop experience in experimental design and planning, with the option of allowing students to decide which reaction parameters to investigate and the ranges for each parameter. Examples of these parameters are shown in Table 1.

Reactor setup

The reactor shown in Fig. 1 comprises of commercial, widely available equipment: 2 syringe pumps, 1/8" PTFE tubing,

Table 1 Reaction parameters investigated during undergraduate experiments

Parameter	Ranges investigated
Residence time ^a (by changing total flow rate)	0.5–15 min.
Temperature	0–30 °C
pH of aqueous amine solution	5.5–12
Stoichiometry (diamine:Ac ₂ O)	1:2–2:1

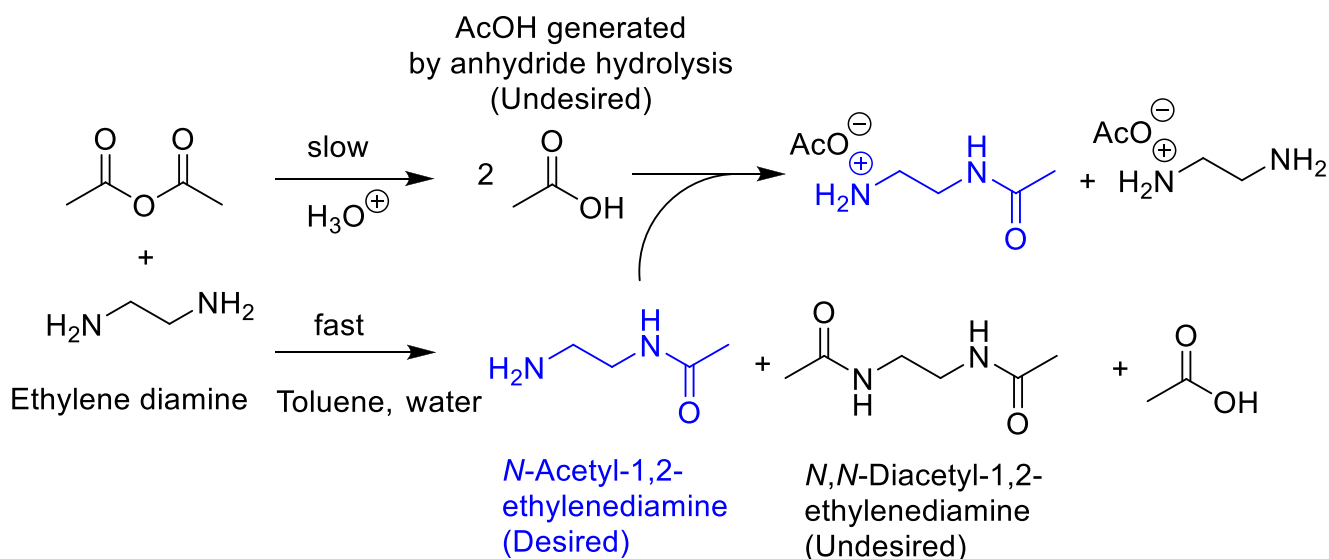
a. Residence time = volume (cm³) / flow rate (cm³/min). This is known as the average time the reaction medium spends in the reactor tubing.

1/8" PTFE Tee-piece, fReactor [18–20], and accessible reagents: diamine, acetylating agent (e.g. Ac₂O), toluene, water and standard buffer solutions. The reaction products were analysed by ¹H NMR, but other analytical techniques such as HPLC or GC could also be used. Although not quantitative, IR analysis could also be carried out to confirm the presence of the carbonyl functionality in the product.

Results

Example results obtained by 3rd year undergraduate students carrying out the reaction are summarized in Table 2. Students used a tubular reactor with volume 3.8 mL (192 cm length of 1/16th inch internal diameter PTFE tubing). A qualitative scan of the parameters was performed by the students to understand the important effects present that lead to varying conversions and selectivity.

The results shown in Table 2 indicate the effect of the various reaction parameters on product formation. The overall conversion of starting material ranges from 60 to 82% and selectivity for the mono-acetylated product from 63 to 80%



Scheme 1 Reaction studied: mono-acylation of symmetric diamines.

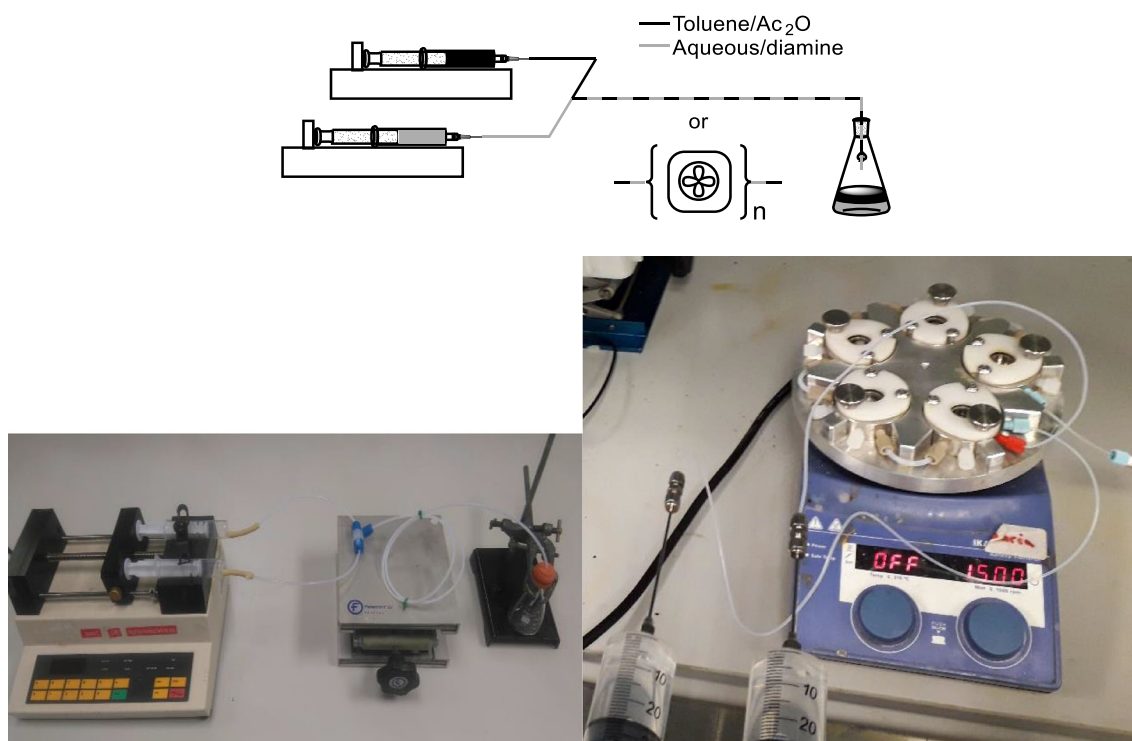


Fig. 1 Continuous tube reactor and CSTR

for the parameter range investigated. It is important to note that, when using a tubular coil reactor, changing the residence time by changing the overall flow rate will impact on the interphase mass transfer; while changes in solution's ratio will affect the slug's size ratio, which can also affect the result. Although experimentally no effort was made to control those factors, they can be used to further expand the discussion about how changes in one parameter can have further implications in the reaction outcome.

Residence time As residence time increases, conversion also increases, but selectivity for the mono-substituted product decreases. With longer residence times the starting material has a longer time to react with the acetic anhydride, increasing overall conversion. However, it also means that once formed, the mono-acetylated product has time to react a second time forming the di-acetylated product. The kinetics of each step can be discussed with the students.

Table 2 Results obtained by undergraduate students

Residence time (min.)	Ambient Temp. (°C)	pH of amine solution	Conc. Diamine (Mol.dm ⁻³)	Conc. Ac ₂ O (Mol.dm ⁻³)	Conversion (%)	Selectivity for mono-acetylated product (%)
0.5	20	~12 (unbuffered)	1.6	1.6	74	73
0.8	20	~12 (unbuffered)	1.6	1.6	74	73
1.6	20	~12 (unbuffered)	1.6	1.6	73	74
3.8	20	~12 (unbuffered)	1.6	1.6	71	75
15.2	20	~12 (unbuffered)	1.6	1.6	80	69
3.8	0	~12 (unbuffered)	1.6	1.6	65	63
3.8	28 ^a	~12 (unbuffered)	1.6	1.6	71	67
3.8	20	7 (buffered)	1.6	1.6	80	74
3.8	20	5.5 (buffered)	1.6	1.6	82	78
3.8	20	~12 (unbuffered)	3.2	1.6	61	70
3.8	20	~12 (unbuffered)	1.6	3.2	60	80

Shaded regions indicate where parameters are being varied. Conversion and selectivity determined by ¹H NMR analysis. ^a tubing placed in a temperature-controlled water bath.

Temperature Ambient temperature was used as the default, and higher temperatures are achieved by immersing the tubing in a controlled water bath. The CSTRs sit on a hotplate-stirrer and a thermocouple can be inserted into one of the ports if required. With increasing temperature, a slight increase in conversion is seen, however, there is little change to the selectivity of the reaction. The temperature range investigated by students during this experiment is narrow (0, 20 and 28 °C) and we would recommend increasing the temperature further to observe more significant effects on product formation. We might expect an increase in conversion and decrease in selectivity for the mono-acetylated product to be observed at higher temperatures, due to increased reactivity of the starting diamine and more mono-acetylated product present, however the rate of acetic anhydride hydrolysis may compete in affecting the conversion.

pH As pH decreases, conversion and selectivity for the mono-substituted product increase. The increase in selectivity may be due to changes in the partitioning of reagents at different pH. Under acidic conditions, the diamine and indeed mono-acetylated product, once formed, would be protonated and would hence partition into the aqueous phase, leaving the organic phase containing acetic anhydride. This minimises over-reaction to the di-acetylated product. A model involving protonation of species and partitioning between each liquid phase can be discussed with the students. (Scheme 2).

Stoichiometry Excess diamine is undesirable as it complicates the purification process due to the need to remove large quantities of starting material. A 1:1 ratio of diamine:acetic anhydride gave the highest conversion, and high selectivity for the mono-substituted product. Different stoichiometries can be used to access the order of the reaction.

Reactor & mixing The extent of mixing within a reactor can have a significant effect on the conversion and

selectivity of a reaction. For biphasic systems, the rate of mass transfer is limited by the interfacial area between the phases, which is low in conventional batch and tubular flow reactors. To overcome these limitations, a “plug-and-play” miniature CSTR cascade was utilised, which maximises the interfacial area by utilising a magnetic coupling design to provide active mixing within the reaction chamber.⁷

As the mixing speed (RPM) of the CSTRs increases, both the conversion and mono-selectivity increases (Fig. 2). Similarly, the CSTRs provide a higher conversion and mono-selectivity compared to both the batch and tubular reactors (Table 3). These results indicate that the active mixing provided by the CSTRs increases the rate of mass transfer and hence the rate of formation of the product.

Summary

It has been shown that using simple flow equipment and a method of quantitative analysis, previously untrained students can perform continuous flow experiments to determine the yield and selectivity for a diamine acetylation reaction. Although the factors were only qualitatively assessed, as a mean to practice flow experimentation, it would also be possible to teach statistical-based methods that can quantify these effects. Further teaching and experimentation can also be applied to explore concepts of kinetics or experimental design (DoE).

Other options may also be implemented for teaching flow chemistry for example considerations of mass/heat transfer and reaction kinetics are also important, where students can critically analyse the differences between different conditions and reactors to draw conclusions and promote further chemical understanding.

Scheme 2 Partition of starting materials, products and by-products between the aqueous and organic phases

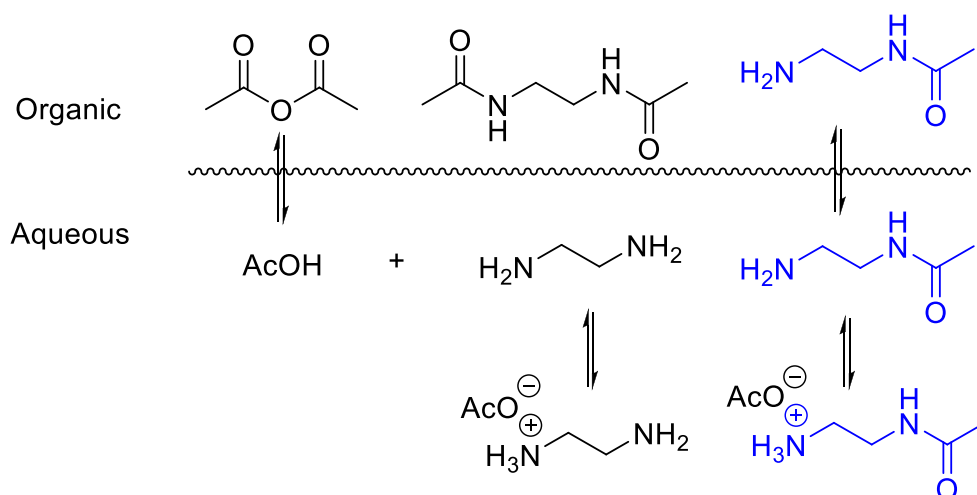
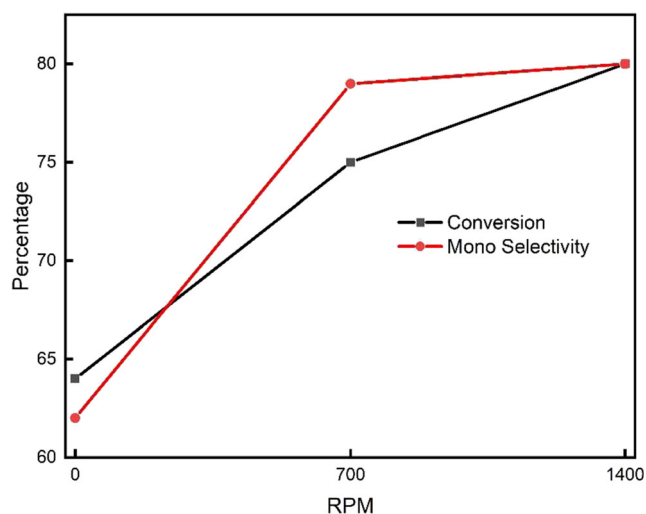


Table 3 Comparison of conversion and mono selectivity in different reactors. Conditions: 10 min, 25 °C, 1:1 stoichiometry, 1400 rpm

Reactor	Conversion (%)	Selectivity for mono-acetylated product (%)
Batch	63	54
Tubular	71	70
CSTR	81	79

**Fig. 2** Comparison of conversion and mono selectivity and different mixing speeds in the miniature CSTR cascade ($N=2$). Conditions: 15 min, 25 °C, 1:1 stoichiometry

The herein reported diamine acetylation experiment has been utilized in undergraduate laboratories for years at the University of Leeds. Further experimentation can continue to expand the skillsets of the students by broadening their understanding of continuous processing, but this experimentation can serve as a basic framework for their introduction to flow chemistry development.

Experimental

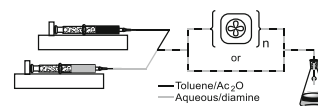
Batch procedure

To a round bottom flask is added ethylene diamine (481 mg, 8 mmol) and water (5 mL). The solution is stirred and cooled to 0 °C with an ice bath. To the cooled solution is slowly added a solution of acetic anhydride (817 mg, 8 mmol) in toluene (5 mL). The solution is stirred at 0 °C for 20 min. The phases of the reaction solution are separated. The water is removed from the aqueous phase under reduced pressure to leave the crude product as an oil. The composition of the crude product is determined by NMR analysis in D_2O . The organic phase may also be dried under

reduced pressure and analysed by NMR using $CDCl_3$, however this phase should not contain any product. Data compares with that previously reported for the compounds.⁸

δ_H ppm (300 MHz, D_2O) *N*-Acetyl-1,2-ethylenediamine: 3.24 (2H, t $J=5.9$ Hz, CH_2COCH_3), 2.89 (2H, t $J=5.9$ Hz, CH_2NH_2), 1.88 (3H, s, CH_3). *N,N*-Diacetyl-1,2-ethylenediamine: 3.00 (4H, s, 2 x CH_2), 1.77 (6H, s, 2 x CH_3).

Flow procedure



Two syringe pumps are each connected to 1/8th inch PTFE tubing (1/8th inch OD, 1/16th inch ID). The tubing from each pump is connected with a PTFE Tee-piece to the reactor tubing (also 1/8" PTFE) or fReactor of the required length to give the required reactor volume.

The first syringe pump is loaded with a 1.6 M solution of ethylene diamine in water and the second with a 1.6 M solution of acetylating agent (acetic anhydride in our case, but acetyl chloride or Boc-anhydride could be used instead) in toluene. Enough solution should be prepared to give at least 3 reactor volumes of solution in total. The solutions are flowed through the reactor at a rate to give the desired residence time. The solution is collected from the reactor and the phases separated. The water is removed from the aqueous phase by rotary evaporation to leave the crude product mixture as an oil. The composition of the crude product was determined by 1H NMR analysis (D_2O) as in the batch procedure above.

In order to reduce the pH of the reaction solution, a pH 5 aqueous NaOAc/AcOH aq. Buffer is used in place of the water for the ethylene diamine solution. The aqueous NaOAc/AcOH solution is prepared by dissolving sodium acetate (3.7 g, 45 mmol) in the minimum amount of deionised water. To this is then added AcOH (4.1 g, 68 mmol). The total volume of the solution is diluted to 50 cm^3 by the addition of deionised water. Additional NaOAc or AcOH is added to the diamine/buffer solution if necessary until pH 5 or 7 is reached. In order to heat the reaction, the reactor tube was coiled and secured in a beaker of water which was pre-heated to the required reaction temperature.

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