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Synthesis of amines, carbamates and amides via multi-step continuous flow synthesis

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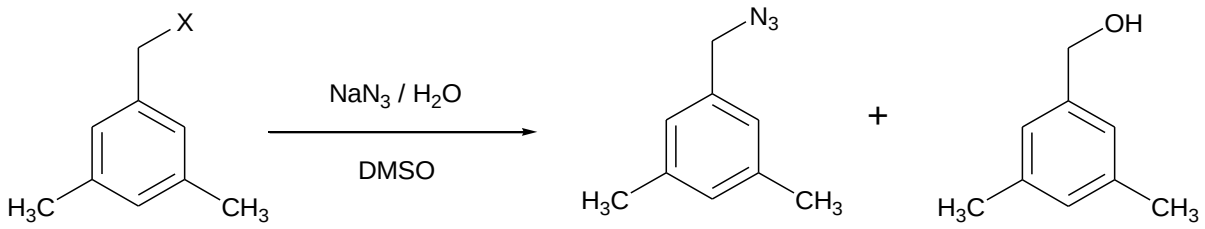
Abstract

We report the continuous flow synthesis of acyl azides in various continuous flow systems and demonstrate that liquid-liquid separation may be incorporated to prepare anhydrous solutions of the acyl azide, which may be subsequently reacted with appropriate nucleophiles to prepare amines, carbamates and amides within a fully integrated multi-step process in high yields (>80%). Interesting effects were also observed when preparing carbamates with long chain alcohols, whereby as the chain length of the alcohol increased the products could be made in high yield even without incorporation of the liquid-liquid separation module.

Introduction

Reactions involving azides represent an important but hazardous process. These reactions are extremely exothermic and it is hence difficult to control the temperature of such reactions when performed on a large scale. In addition, some azides are explosive which adds future complexity to their synthesis. Flow reactors have a considerable attraction for exothermic reactions because the high surface to volume ratio of the reactor enables excellent temperature control of the process.[1–3]

Regarding alkyl azides, Kopach *et al.*[4] illustrated the synthesis of benzyl azide derivative **2** in a continuous flow system by an efficient nucleophilic substitution reaction between the corresponding benzyl chloride **1** and sodium azide (Scheme 1).[4] The reactor system was a 316-stainless steel system with tubing measuring 0.64 mm (I.D.) and 63.1 mm long, having an internal volume of 20 ml. The GC oven containing the reactor was maintained at 90 °C and 200 psi of N_2 was applied to the outlet of the reaction system. The two reagents were pumped into a T-shaped fitting just outside the oven and mixed, before they flowed through the reactor. A residence time of 20 min in the reactor afforded 97 % conversion at 90 °C. The product solution was collected for a batch work-up, to give the product in 94% isolated yield.

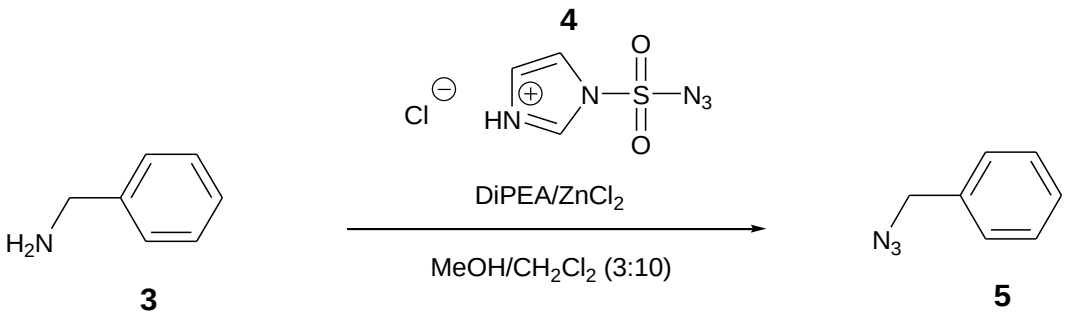


1 **2**

Scheme 1. Reaction of sodium azide and 3,5-bis-(trifluoromethyl)benzyl halides.

In comparison, Delville *et al.*[5] synthesised benzyl azide **5** from benzylamine **3** using imidazole-1-sulfonyl azide hydrochloride **4** as the diazo transfer reagent (Scheme 2) in a 92 µL internal volume glass reactor. It had two mixing units of the folding flow type incorporated and the reactor temperature was controlled by Peltier elements. In case of short reaction times, a 7.0 µL internal volume glass reactor was used. This reactor did not have mixing units because of the inherent short diffusion distances which led to efficient mixing. The optimal reaction conditions

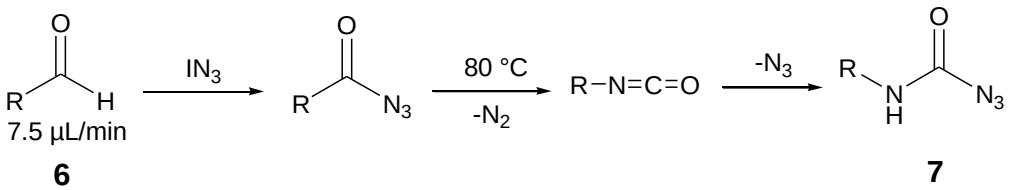
were found to be room temperature, 600 s residence time and imidazole-1-sulfonyl azide hydrochloride/benzylamine stoichiometric ratio of 3:4. A GC yield of 97 % was obtained and after batch work-up a yield of 73 % of was obtained.



Scheme 2. Diazotransfer reaction on benzylamine.

The first multi-step continuous flow synthesis was reported by Ley and co-workers[6] through the preparation of a natural product oxomaritidine. Product isolation at all the intermediate stages was not necessary unlike in the batch process which was time consuming and wasteful as a result of the laborious laboratory manipulations involved.[6]

Acyl azides are also of significant application in synthesis. Johan *et al.*[3] illustrated the synthesis of carbamoyl azides **7** *via* Curtius rearrangement from corresponding aromatic aldehydes **6** using iodine azide (Scheme 3) as the key reagent. The authors used tetrabutylammonium azide for the *in situ* generation of iodine azide. The reactor had a capillary volume of 192 µL and optimum conditions were found to be 26 min residence time and a temperature of 80 °C. The product yields were found to be in the range of 21-44 %.[3]



R = Ph (Substituted or unsubstituted)

Scheme 3. Carbomyl azides synthetic route.

Ley and co-workers[7] used an azide-containing monolith in a flow system for conducting Curtius rearrangement reactions *via* acid chloride inputs. They prepared azide functionalised monolithic columns to facilitate Curtius rearrangement reactions within flow systems. Azide ions were immobilised onto ion exchange resins to increase its safety profile, as these polymers supported azide systems can handle shock, impact and exposure hazards which are posed by azides themselves. The isocyanate formed as a result of Curtius rearrangement reaction was then subsequently trapped with various nucleophiles resulting in the respective products, however it needs to be emphasised that this approach of using immobilised azides is not suitable for the large scale synthesis of such compounds.[7] Baumann *et al.*[8] used mesofluidic flow reactors to perform Curtius rearrangement reactions of carboxylic acids in the presence of diphenylphosphoryl azide (DPPA) and trapped the intermediate isocyanate with various nucleophiles. Figure 1 shows the general setup for the Curtius rearrangement of carboxylic acids under continuous flow condition. A mixture of triethylamine, appropriate nucleophile and carboxylic acid was pumped into the system through channel 1 and DPPA into channel 2. Both solutions were prepared in acetonitrile and a temperature of 120 °C and a residence time between 20-50 min was used to ensure complete conversion. Amberlyst 21 (A-21) and Amberlyst 15 (A-15) were used as in-line scavengers for this process. The authors used a Biotage V10 solvent evaporator that enabled direct isolation of a wide range of products in both high yield (>75 %) and excellent purity.[8] Although the scavenger systems allow easy synthesis on a small scale, again the methodology is not suitable for the synthesis of larger quantities of product.

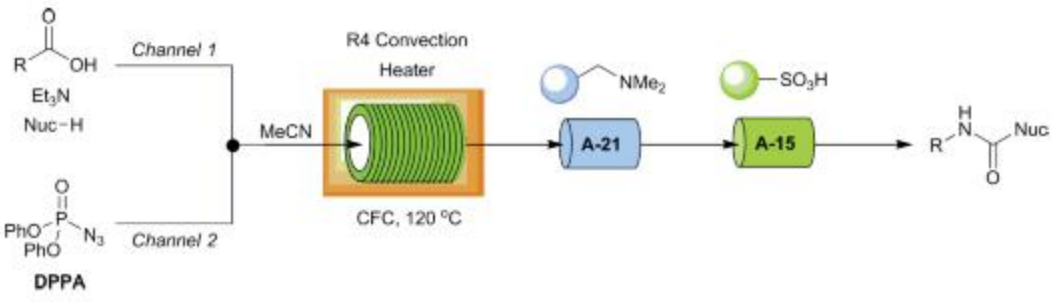
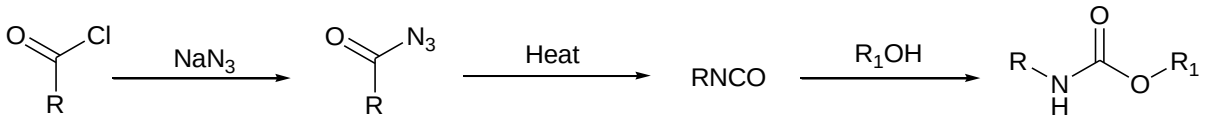


Figure 1. General scheme for Curtius rearrangement of carboxylic acids.

A pioneering example, where an acyl azide was prepared and consumed *in situ* in a potentially scalable fashion, was reported by Jensen *et al.*,[9] where an acyl chloride **8** was reacted with

sodium azide to give the organic azide **9**, which was then heated to form an isocyanate **10** in the Curtius reaction followed by alcohol addition to yield carbamate **11** (Scheme 4). The phase-transfer reaction between aqueous azide and acid chloride to produce the organic azide was performed in a silicon microreactor. An inline micro-separator with a selectively wetted porous membrane was used for the subsequent continuous separation of the aqueous and organic mixture. The membrane is exclusively wetted by the organic phase, preventing the aqueous phase from passing through resulting in quantitative separation of the two phases.[12,51] Organic azides from the first step in the microreactor were subsequently heated giving isocyanates *via* Curtius rearrangement. The generated nitrogen was subsequently removed out of the system using a gas/liquid separator.[9] They formed carbamates in the third step by contacting the generated isocyanate with different alcohols in the third microreactor.



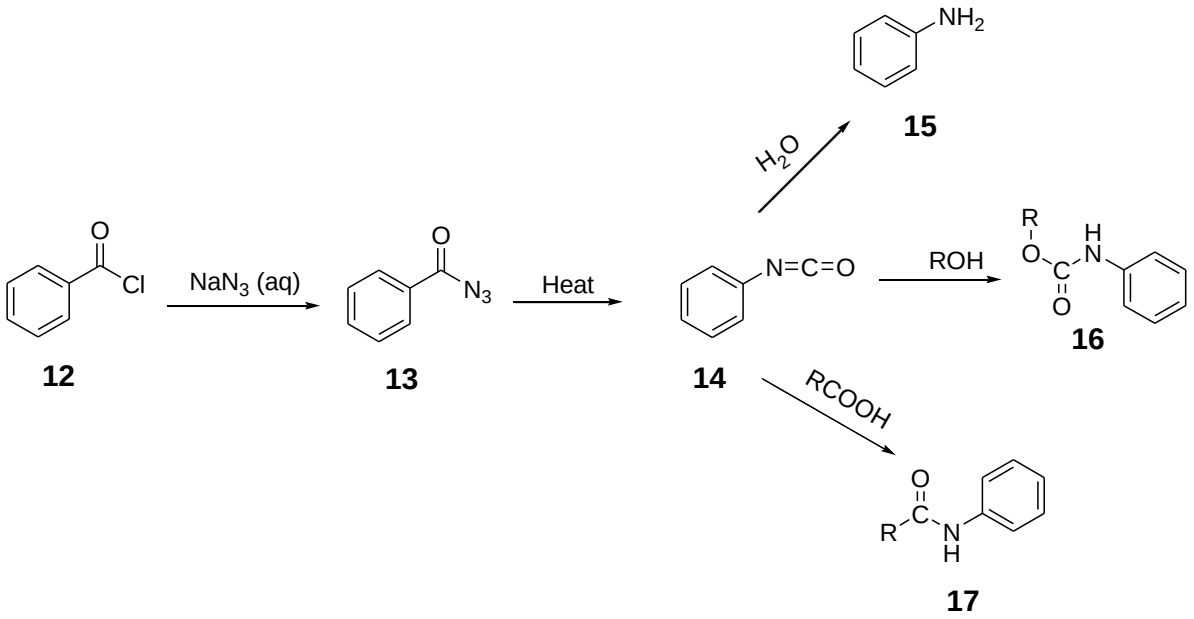
8 **9** **10** **11**

R = Ph and R_1 = Alkyl group

Scheme 4. Multi-step synthetic process of carbamate.

When contacting benzoyl chloride in toluene (0.36 M) with a solution of sodium azide (0.4 M) they observed that the conversion of benzoyl chloride to benzoyl azide was a function of residence time (65 % conversion at 90 min residence time and 98 % conversion at 200 min residence time). A T-mixer was added upstream of the first reactor to improve mixing. Residence time was increase by adding tubing before the first reactor. The Curtius rearrangement step proved to be the limiting step in increasing productivity of the overall system. However, adding a second reactor while operating at double the flow rate can mitigate this limitation. The authors achieved 99 % conversion at 90 °C using 12 mg of H-mordenite solid acid catalyst at, compared to the uncatalysed conversion 91.2 % at the same residence time (60 min) and temperature.[9] The reaction between an alcohol and isocyanate was rapid and 96-99 % of carbamate was obtained. Productivity range of 80-120 mg was achieved per day depending the type of the carbamate synthesised working at a flow rate of 1 µL/min for each of the aqueous (0.4 M) and organic (0.36 M) reagents. Although this system was very elegant, clearly the throughput was small.[9]

As part of our ongoing program into local drug manufacture, we were interested in further studying the *in situ* synthesis of acyl azide chemistry in continuous flow systems with a view to conducting multistep synthesis of amines **15**, carbamates **16** and amides **17** *via* Curtius rearrangement and subsequent reaction (Scheme 5). In order to ensure that all processes were scalable, we wished to only use solution phase synthesis methodology.



Scheme 5. In situ acyl azide synthesis and consumption.

Results and Discussion

Optimisation of benzoyl azide synthesis. As a model, the reaction between benzoyl chloride **12** and sodium azide **18** to afford benzoyl azide **13** was used (Figure 2) to optimise the reaction conditions. In our preliminary experiments, benzoyl chloride (0.1 M) in acetone was reacted with aqueous sodium azide (0.1 M) in a 19.5 µl Labtrix SOR-mixer glass reactor (Chemtrix) at 25 °C and a flow rate of 10 µl/min for each reagent was used. As anticipated the benzoyl azide **13** successfully reacted in good conversions (96 %); the extent of the reaction was confirmed by GC and HPLC against a characterised synthetic benzoyl azide standard.

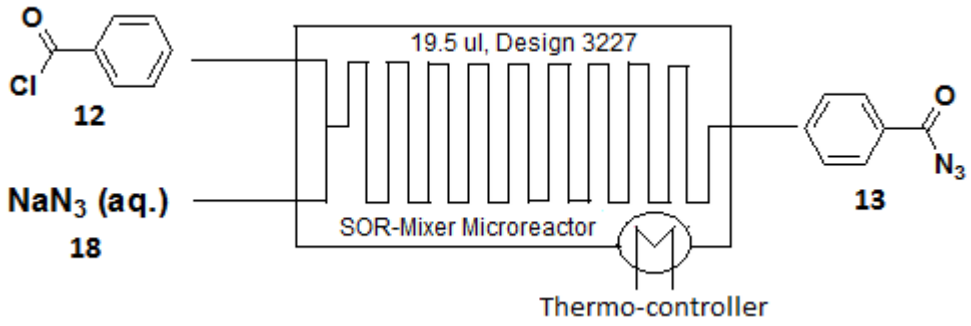


Figure 2. Schematic manifold used for benzoyl azide synthesis and optimisation studies.

A comprehensive study on the effects of different solvents, temperature, molar ratios and residence time was conducted to optimise the reaction. Table 1 summarises the screening results (Figure 2).

Table 1. Condition screening and optimisation of model reaction in flow.

Run	**12**/**18**[a]	Solvent for **12**	**12**/M[b]	*T*/°C	R_t/s	Conv.[c]
1	1/1.1	Acetone	0.05	25	117	100
2	1/1.1	Acetonitrile	0.05	25	117	100
3	1/1.1	Toluene	0.05	25	117	25
4	1/1.1	Acetonitrile	0.05	80	117	97
6	1/1.1	Acetonitrile	0.1	25	117	100

7	1/1.1	Acetonitrile	0.05	50	117	100
8	1/1.1	Acetonitrile	0.025	25	117	100
9	1/1	Acetonitrile	0.05	25	117	97
10	1/1.1	Toluene	0.05	50	117	45
11	1/1.1	Acetonitrile	0.05	25	11.7	100
12	1/1.1	Toluene	0.05	25	11.7	7
13	1/1.1	Acetone	0.05	25	11.7	100
14	1/1.1	Toluene	0.05	25	200	38

[a] Molar equivalent

[b] Feed concentration of **12**

[c] Conversion towards benzoyl azide

0.11 M aqueous sodium azide stock solution was prepared to achieve 1:1.1 reacting ratio

In initial studies, acetone and acetonitrile were found to be good solvents for benzoyl chloride as they all afforded full conversions whilst toluene afforded a conversion of only 25 % using a molar ratio of 1/1.1 of **12**/**18**, at 25 °C and a residence time of 117 s (Table 1: entries 1, 2 and 3). Full conversion was also achieved using both acetone and acetonitrile when the residence time was reduced by a factor of ten to 11.7 s; however as expected in toluene a lower conversion of only 7 % was obtained (entries 11, 12 and 13). The poor conversions in toluene may be attributed to the fact that it is immiscible in water, which is the solvent for the sodium azide, consequently meaning that the reagents did not have enough contact in the reactor for the reaction to proceed successfully unlike when water miscible solvents were used as the mixing efficiency provided by the Chemtrix SOR-mixer reactor 3227 was good enough to successfully achieve full conversions. An increase in temperature from 25 to 50 °C, while maintaining the same molar ratio, concentration and residence time resulted in an increase in conversion from 25 % to 45 % for the reaction in toluene (entries 3 and 10).

Full conversion was still achieved at elevated temperatures of 50 °C in acetonitrile (entry 7) and conversely the conversion decreased to 97 % when the temperature was elevated to 80 °C while maintaining the same reagents molar ratio, concentrations and residence time (entry 4). The drop

in conversion is as a result of decomposition of benzoyl azide to form benzoyl isocyanate, which is also known as the Curtius rearrangement. Zabalov and Tiger[10] reported an onset temperature for thermal decomposition of acyl azides of around 70-80 °C, which was also echoed by Baumann *et al.*[11] Further experiments showed that an increase in residence time from 117 s to 200 s in toluene, while maintaining the same reagents molar ratio, concentrations and temperature resulted in an increase in conversion from 25 % to 38% (entry 3 and 14). A small excess of sodium azide (1.1 equiv.) was necessary to ensure full conversions in acetonitrile (entry 2).

Equimolar ratios of the reagents afforded 97 % conversion (entry 9). Varying benzoyl azide concentration between 0.025M and 0.1 M while maintaining the same reagents molar ratio, temperature and residence time did not have any notable effect on conversions (entries 2, 6 and 8). It should be mentioned that some precipitates were observed when carrying out the reaction in acetone starting at 0.05 M concentration of the benzoyl chloride and became more evident at 0.1 M. This eventually resulted in the system blockage, however it allowed us to collect enough sample for analysis before complete blockage. We concluded that the precipitation was as a result of incompatibility between aqueous sodium azide and acetone.

In summary, the reaction proceeded smoothly and in a very clean manner affording full conversions when acetonitrile was the solvent of choice for benzoyl chloride **12**. The reaction was successful at 25 °C, molar ratio of 1:1.1 where sodium azide **18** was slightly in excess. 11.7 s was the residence time of choice for this reaction as it was the shortest time investigated. From an industry perspective it is ideal to use short residence time (high reagents flow rates) as it enhances the throughput of the process. Concentrations higher than 0.1 M were investigated however they were characterised by eventual system blockages.

Other continuous flow systems for benzoyl azide synthesis. Having successfully prepared benzoyl azide in a continuous flow system using acetonitrile as the solvent for benzoyl chloride **12** at the aforementioned conditions, the next step was to develop a simpler continuous flow system that can efficiently synthesise benzoyl azide **13**. Taking advantage of the fact that the reaction

proceeded well at 25 °C and short residence time, we investigated the reaction using a T-mixer only at room temperature (Figure 3).

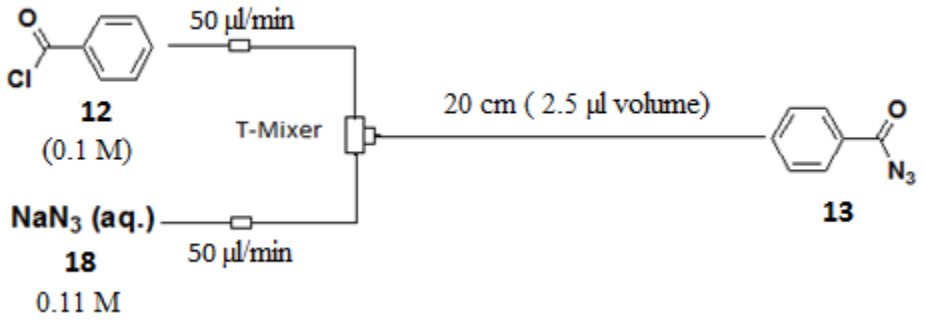


Figure 3. Schematic diagram of a simple continuous flow system for benzoyl azide.

Benzoyl chloride **12** (0.1 M) in acetonitrile and sodium azide **18** (0.11 M) in water were each pumped at 50 µl/min flow rate through the continuous flow system at room temperature affording benzoyl azide **13** in full conversions. A T-mixer and a 20 cm tube (125 µm ID) was enough for the reaction to proceed successfully, meaning that there was no need for the SOR-mixer glass reactor for this reaction. Investigations of the synthesis of benzoyl azide **13** in a simple continuous flow system were motivated by the fact that we wanted to carry out subsequent reactions after *in situ* preparation of the azide. So there was always a need of simplifying the system at each step if possible in order to avoid a complicated and clumsy continuous flow system for multistep synthesis.

Curtius rearrangement: Acyl azides to isocyanates. Thermal decomposition of acyl azides, commonly known as the Curtius rearrangement, is one of the classic reactions in organic chemistry. The Curtius rearrangement can be carried out with or without a catalyst; however in the absence of a catalyst the reaction is known to be predominantly dependent on temperature.[9,10,12] Lewis acids are usually used to catalyse this reaction to reduce residence/reaction time.[10,13,14] Catalyst free Curtius rearrangement will be investigated in this project in order to simplify the system; however we are aware that this may require higher temperatures.

Benzoyl azide Curtius rearrangement in acetonitrile. After successfully carrying out benzoyl azide synthesis using just a T-mixer and tube (Figure 3) we added a glass reactor downstream which was meant to be heated for the Curtius rearrangement; the system was then fitted with a 10 Bar back pressure regulator (Figure 4). Benzoyl chloride **12** (0.1 M) in acetonitrile and sodium azide **18** (0.11 M) in water were pumped at various flow rates (to effect residence times of 11.7 s, 23.4 s and 117 s) through the continuous flow system to determine the effects of residence time on the Curtius rearrangement in the heated microreactor. Benzoyl azide **13**, which was formed after the T-mixer in full conversions (based on our previous results described earlier), was subsequently pumped into a heated (30-190°C) glass micro reactor, forming phenyl isocyanate **14** and an amine (Aniline) **15**.

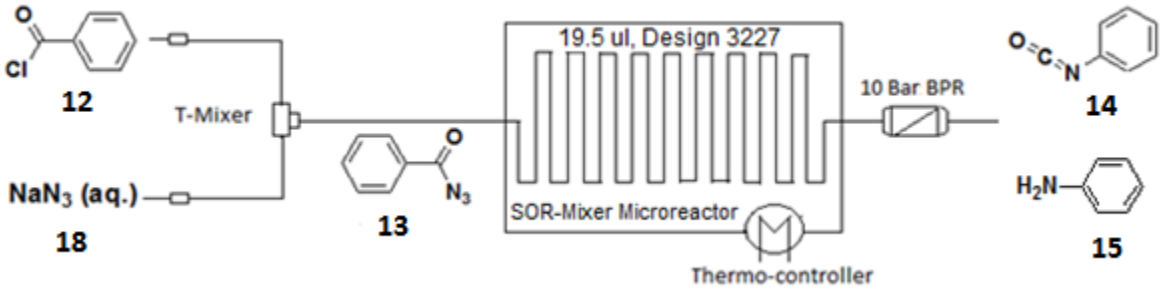


Figure 4. Proposed schematic diagram for multistep phenyl isocyanate synthesis in a continuous flow system.

In our attempt to synthesise phenyl isocyanate **14** *via* the Curtius rearrangement of benzoyl azide **13** formed *in situ* upon heating, we however observed that aniline **15** was the main product formed in the reaction. We realised that the reaction did not stop at the phenyl isocyanate formation as we desired; since there was water in the system it acted as a nucleophile thereby reacting with phenyl isocyanate **14** affording aniline **15**, which was confirmed by a characterised synthetic standard. The effects of temperature and residence time on aniline synthesis are shown in Figure 5; which illustrates that both temperature and residence time have a direct relationship with aniline formation in this reaction. Generally, an increase in temperature and residence time resulted in an increase in the amount of the aniline **15** formed. 11.7 s residence time (Curtius rearrangement and subsequent aniline synthesis) afforded a maximum conversion of 55 % at 190

°C and a ten times longer residence time (117 s) afforded a maximum conversion of 94 % at the same temperature 190 °C.

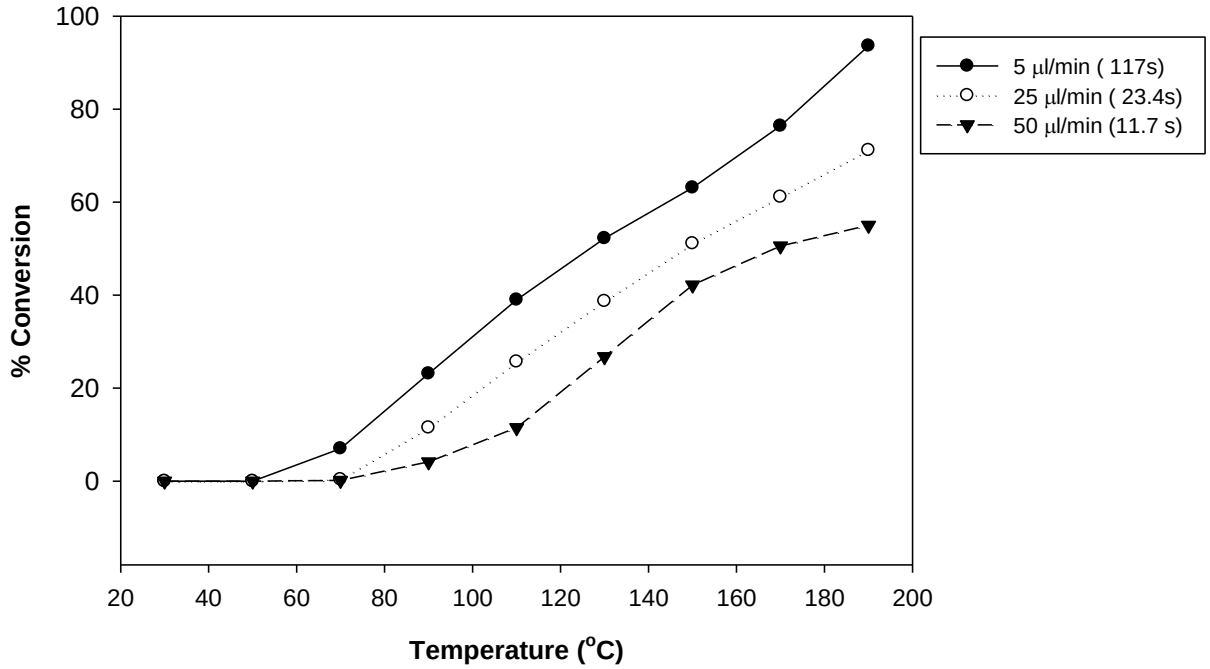


Figure 5. Effect of temperature and residence time on aniline formation.

The Curtius rearrangement was found to be the limiting step for the whole multistep process as it determined the residence time in the system and also the temperature for second reactor. The first step (benzoyl azide synthesis from benzoyl chloride) in acetonitrile afforded full conversion at 11.7 s residence time however to achieve good conversion towards aniline *via* the Curtius rearrangement of benzoyl azide, we had to settle for a 50 times longer residence time (585 s, 9.75 min, 1 µl/min for each reagent) and a temperature of 150 °C for the Curtius rearrangement in the multistep aniline synthesis. The phenyl isocyanate reacted with water affording aniline **15** at 98 % conversion over all steps.

Given the inherent dangers in the handling of organic azides, one of our aims was to prepare benzoyl azide **13** *in situ* and without isolation, to conduct subsequent reactions to give more complex products such as amines **15**, carbamates **16** and amides **17** (Scheme 5). The formation of aniline in our attempt to just do the Curtius rearrangement towards phenyl isocyanate **14** was

an apparent misfortune, which led to some interesting observations since amines (aniline) **15** were one of our target compounds. However, this development to an extent was not welcomed since it would always push the reaction towards aniline **15** formation as long as water is present in the system, consequently meaning that other compounds such as carbamates **16** and amides **17** would not be achieved. This therefore meant that water had to be eliminated from the system just after benzoyl azide **13** formation before the Curtius rearrangement, or replace water with a solvent which will not react with phenyl isocyanate **14**. In an effort to eliminate water from the system, we incorporated a Zaiput[15] liquid-liquid separator after forming benzoyl azide **13** at the T-mixer, before it entered the heated glass reactor for the Curtius rearrangement (Figure 6).

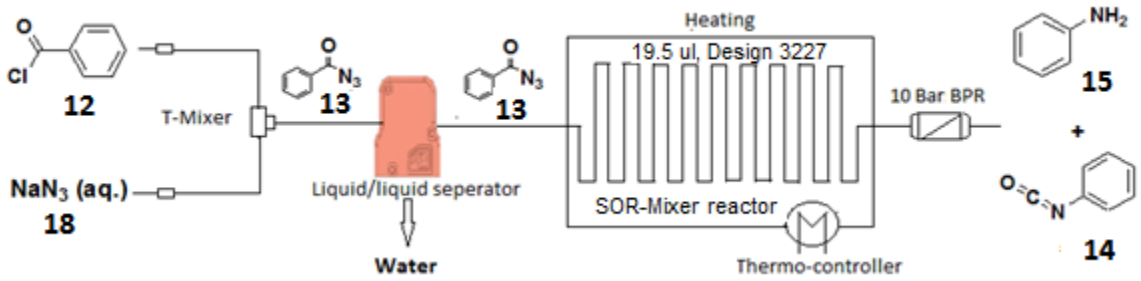


Figure 6. Water removal from the system attempt using a Zaiput liquid/liquid separator.

Benzoyl chloride **12** (0.1 M) in acetonitrile and sodium azide **18** (0.11 M) in water were pumped at 1 µl/min into the system affording 9.75 min residence time in the glass microreactor. The micro reactor was heated at 150 °C for the Curtius rearrangement reaction to take place after benzoyl azide **13** was formed in full conversion at the T-mixer and water elimination by a liquid/liquid separator. The separator did not work for our system as aniline **15** was still formed (98 %). This meant that water went through the membrane and reacted with phenyl isocyanate **14** hence it failed to separate the aqueous phase from the organic phase effectively. We elucidated that the miscibility of acetonitrile and water was the root cause of this failure.

Acetonitrile can be replaced with toluene as a solvent for benzoyl chloride as it is immiscible in water. This may enhance the chances of success in elimination of water using a Zaiput liquid/liquid separator from the system; however results of preliminary reactions of benzoyl azide synthesis in a toluene/water solvent system showed very poor conversions compared to

acetonitrile/water solvent system (Table 1). These observations had initially made us choose acetonitrile as benzoyl chloride solvent over toluene only until we faced the aforementioned challenges upon performing the Curtius rearrangement reaction. However, using a continuous flow system in Figure 7, a catalytic amount sodium dodecylbenzenesulfonate (SDS) (0.05%) was used to achieve full conversions towards benzoyl azide **13** using toluene as benzoyl chloride **12** (0.1 M) solvent and NaN_3 **18** in water (0.11 M) at 25 °C and 117 s residence time compared to 25 % conversion of the uncatalysed reaction (Table 1) using the same glass microreactor as above (Design 3227).

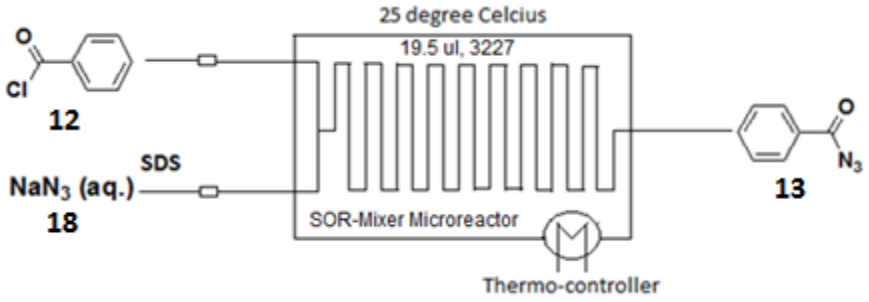


Figure 7. Schematic manifold used for benzoyl azide synthesis in toluene using SDS as a catalyst in Labtrix flow system.

SDS was used as a phase transfer catalyst (PTC) to successfully promote the formation of benzoyl azide **13**. However, in the presence of SDS the Zaiput liquid/liquid separator failed to efficiently remove water probably because the SDS lowers the interfacial tension[16] in the toluene/water solvent system thus making it difficult to separate the phases. Consequently, the benzoyl azide synthesis using toluene as a solvent in the absence of a catalyst was hence further optimised in a continuous flow system.

Benzoyl azide optimisation in toluene. Preliminary experiments had shown that benzoyl azide synthesis in toluene required longer residence times than reactions performed in acetonitrile. We therefore switched using a FlowSyn 2 ml internal volume glass reactor (0.5 mm channel diameter). The larger channel diameter allowed us to optimise the reaction at higher concentrations (0.5 M) without encountering blockages (Figure 8). Benzoyl chloride **12** (0.5 M) in toluene and sodium azide **18** (0.55 M) in water were prepared in separate FlowSyn reagent

delivery bottles. An experimental domain (Table 2) was established after numerous reactions were performed in the continuous flow system at various residence times and temperatures**.**

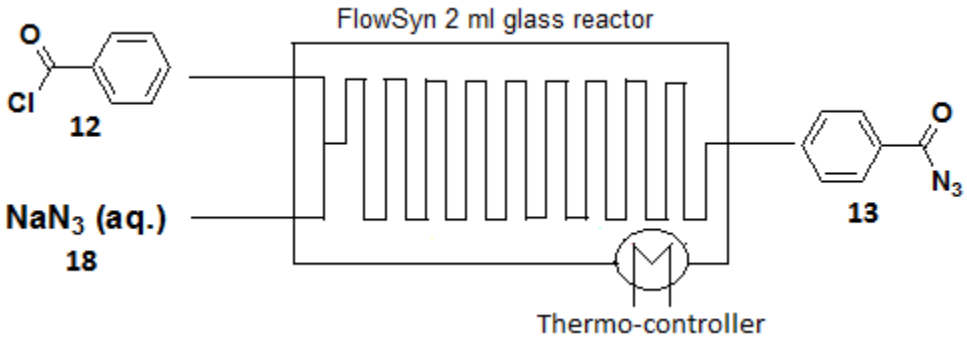


Figure 8. Schematic manifold for benzoyl azide synthesis optimisation in toluene.

Table 2. Experimental domain.

Variable	Minimum	Maximum
Temperature (° C)	25	95
Residence Time (Min)	5	20

Observations (Table 1) demonstrated that benzoyl azide synthesis in toluene was dependant on flow rate and temperature. Benzoyl azide is known to start decomposing from 70-80 °C,[11–13] however we were still keen to investigate the conversion effects above these temperatures. The experimental domain was further used to create a central composite design (CCD) to systematically execute the experiments. A total of 12 experiments were created from the CCD and all these experiments were performed as triplicates. The CCD was generated from the experimental domain (Table 2) to carry out benzoyl azide optimisation studies in a continuous flow system. Optimisation studies were carried out by varying temperature and residence time; the results are shown in Table 3. The data was analysed using Statistica software obtaining a 3-D surface response (Figure 9).

Table 3. CCD experimental output and observations.

Run	Temp.	Res. Time	Exp.1 Conversion	Exp.2	Exp.3

	(° C)	(Min)	(%)	Conversion (%)	Conversion (%)
1	35	14.3	22	20	20
2	35	5.6	10	8	10
3	85	14.3	89	88	89
4	85	5.6	59	59	59
5	60	20.0	71	72	71
6	60	5.0	25	21	24
7	25	7.7	12	14	13
8	95	7.7	95	97	96
9	60	7.7	32	32	32
10	60	7.7	32	32	32
11	60	7.7	32	32	32
12	60	7.7	32	32	33

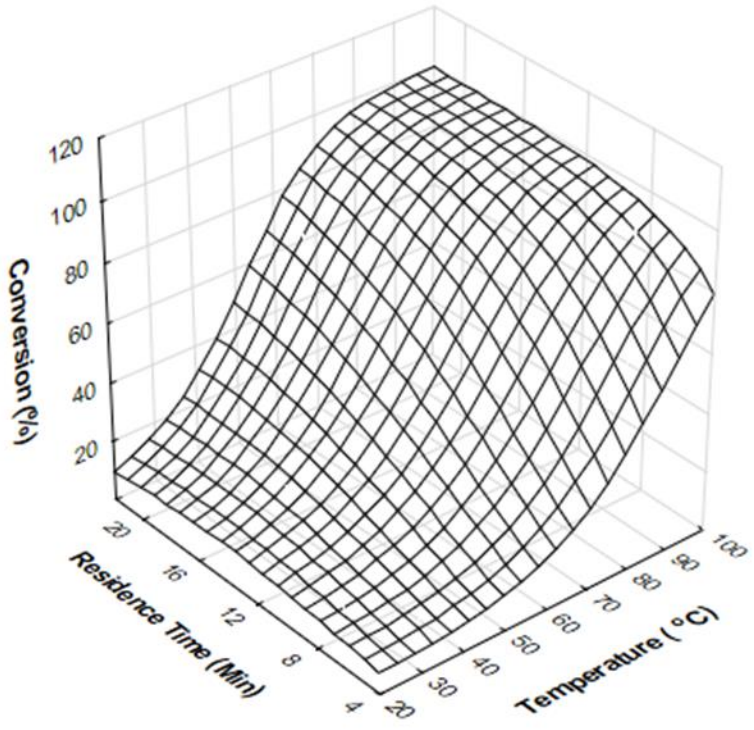


Figure 9. 3-D surface plot for benzoyl azide synthesis in toluene.

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From the 3-D surface plot, it can be deduced that both temperature and residence time have influence on conversion towards benzoyl azide **13**. Generally higher temperatures and longer residence times afforded better conversions. The 3-D plot can be illustrated by means of profile plots (2-D) where the effect that temperature and residence time have on conversion towards benzoyl azide **13** can be easily visualised and explained. Profile plots are used to investigate the effect of one given variable over its complete range while the other variable is kept constant. Below are the temperature and residence time profile plots (Figure 10 and 11) respectively.

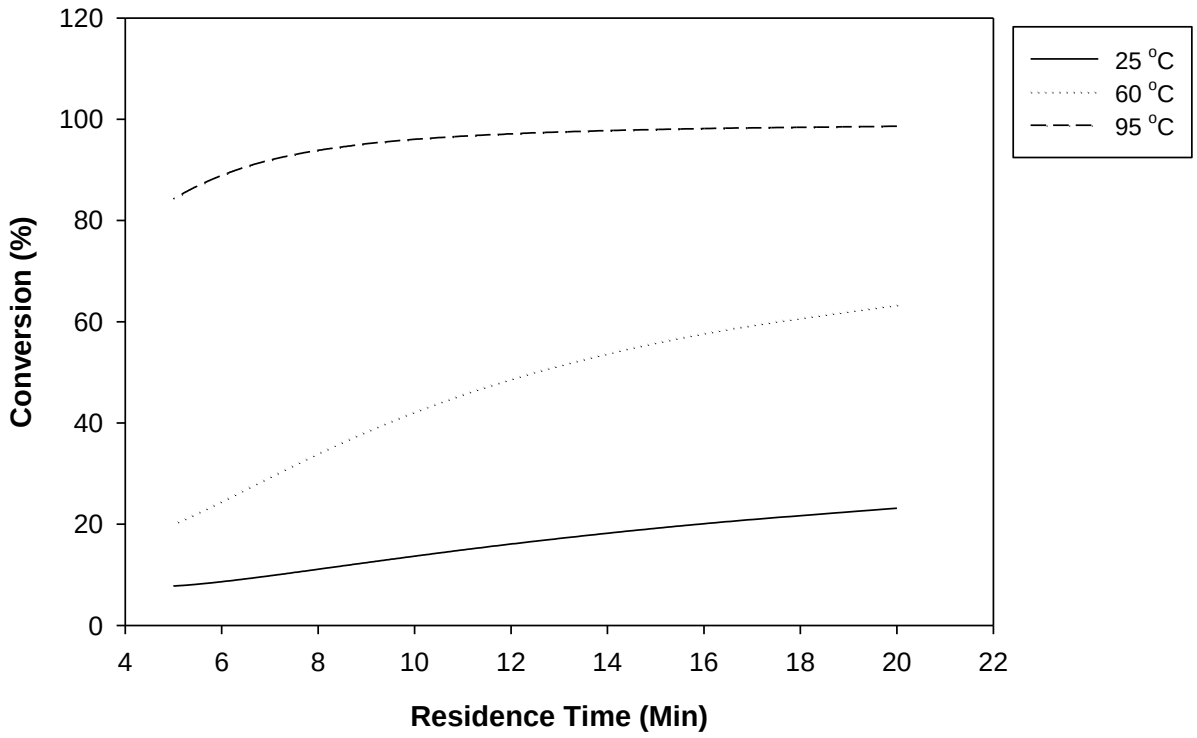


Figure 10. Residence time effect on % conversion profile plot.

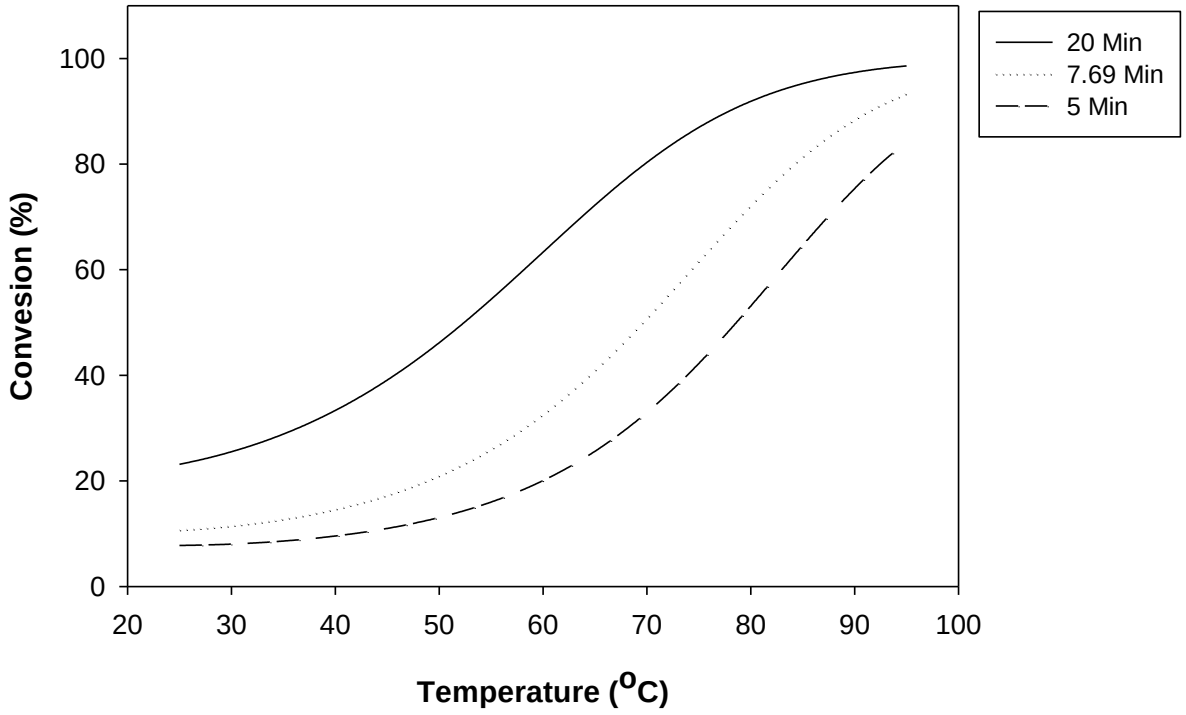


Figure 11. Temperature effect on % conversion profile plot.

In general conversion towards benzoyl azide 13 increases as residence time increases (Figure 10) and also with an increase in temperature following a sigmoidal curve (Figure 11). As shown by sigmoid shaped curves in Figure 11, there is a slow increase in conversion initially as temperature increases from 25-40 °C followed by a sharp increase in conversion from temperatures beyond 40 °C to 70 °C where an almost linear relationship was displayed between temperature and conversion. Beyond 70 °C, conversion increased slowly as temperature increased until it reached a constant optimum point. This observation can be explained by the fact that benzoyl azide decomposition is reported to start around 70-80 °C meaning that beyond 70 °C, benzoyl azide decomposition may be occurring as indicated by the slow increase in conversions towards benzoyl azide **13**. Conversion increases as residence time increases at any given temperature; for example, at 95 °C, the conversion is 99 % at 20 min, 93 % at 7.69 min and 84 % at 5 min residence time.

Reaction optimisation was our aim of these investigations. The 3-D surface plot and profile plots show that the predicated optimum conversion towards benzoyl azide **13** is 99 % at 95 °C using a 20 min residence time. However, for further studies we selected the 'optimum conditions' to be 95 °C and 7.69 min residence time (0.13 ml/min flow rate for each reagent) which affords conversion of 93 %. Our motivation behind this was from an industrial perspective, as doing this reaction at a residence time which is 2.6 times shorter has only a tiny effect of reaction efficiency. Jensen *et al.*[9] achieved 65 % conversion towards benzoyl azide at room temperature at 90 min residence time, of which our approach had much shorter residence time and produced better conversions.

Continuous flow synthesis of various acyl azides. Using the abovementioned conditions (95 °C and 7.69 min residence time) and the same continuous flow system, various acyl azides were synthesised to investigate the chemical reaction behaviour of different acyl chlorides **19** with sodium azide **18** towards their respective acyl azides **20**. These investigations were done using the 2 ml FlowSyn system (Figure 12) where an acyl chloride **19** (0.5 M) in toluene and sodium azide **18** (0.55 M) in water were prepared into separate FlowSyn reagent bottles. Using the continuous flow system, various acyl azides were synthesised (Table 4).

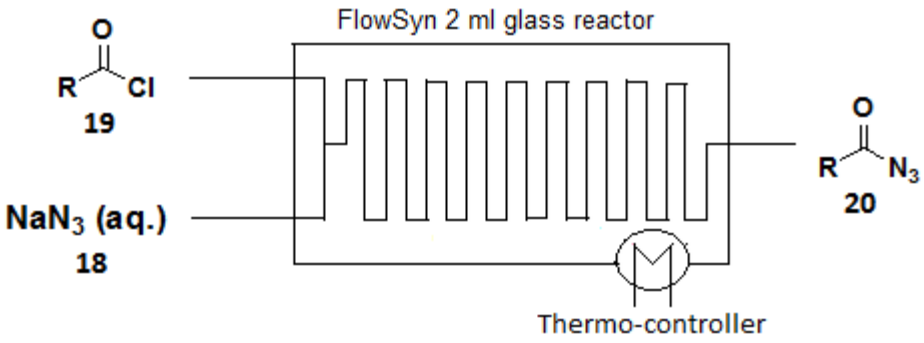
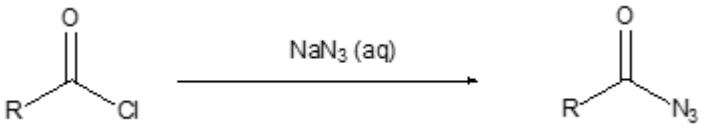
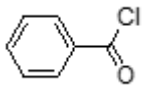
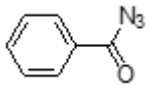
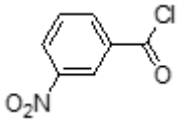
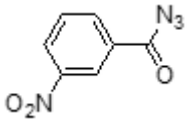
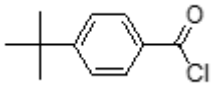
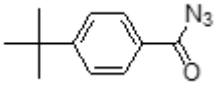
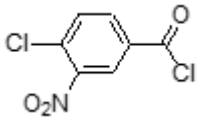
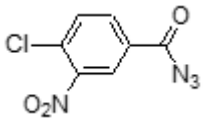
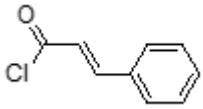
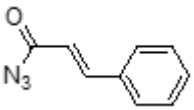
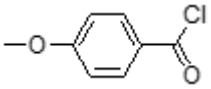
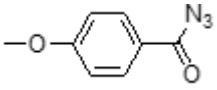
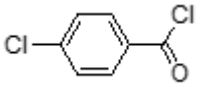
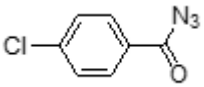


Figure 12. Continuous flow system for acyl azide synthesis.

Table 4. Various acyl azides synthesis in continuous flow using the previous condition.



Entry	Substrate	[a] Product	[c] Conversion %
1			92
2			96
3			48 (65)
4			96
5			90
6			34 (51) [b]
7			94

[a] All reactions used 1 equiv. acyl chloride in toluene (0.5M) and 1.1 equiv. NaN_3 in water (0.55 M)
[b] % Conversion at 20 min residence time and 95 °C
[c] Conversion determined by GC-FID and HPLC (UV-Vis)

According to the results in Table 4, aromatic acyl chlorides with electron withdrawing groups (EWG) afforded higher conversions to the corresponding acyl azides compared with electron

donating groups (EDG) (Compare entry 1, 2 and 3) as expected. Comparing entry 1 and entry 5, cinnamoyl chloride afforded better conversions than benzoyl chloride because of the *α, β*-unsaturated double bond attached to the carbonyl carbon of cinnamoyl chloride. To investigate whether the substrate conversion in entry 3 and 6 was limited by the reaction conditions or not, we performed the reaction at a lower flow rate (0,05 ml/min, 20 min residence time), keeping the rest of the variables constant. Hence, we effectively increased residence time by a factor of 2.6 and conversion increased to 65 % and 51 % respectively. These observations showed that it possible to get higher conversions even when EDG are involved although at a longer residence time than when EWD groups are attached to the phenyl moiety.

Incorporating a liquid-liquid separator into multi-step syntheses. The benzoyl chloride **12** solvent was changed from acetonitrile to toluene in benzoyl azide **13** synthesis to enable the use of a liquid/liquid separator, in order to facilitate water elimination from the system prior to Curtius rearrangement. The use of toluene rather than acetonitrile however significantly increased the residence time needed for benzoyl azide synthesis. As clearly illustrated water removal in the system after benzoyl azide **13** synthesis was very important for the success of subsequent reactions in the multistep synthesis towards compounds such as carbamates and amides *via* Curtius rearrangement (phenyl isocyanate **14**) otherwise an amine (aniline) will be afforded. A FlowSyn continuous flow system with a glass mixer block and a 10 ml stainless steel coil reactor was utilised (Figure 13).

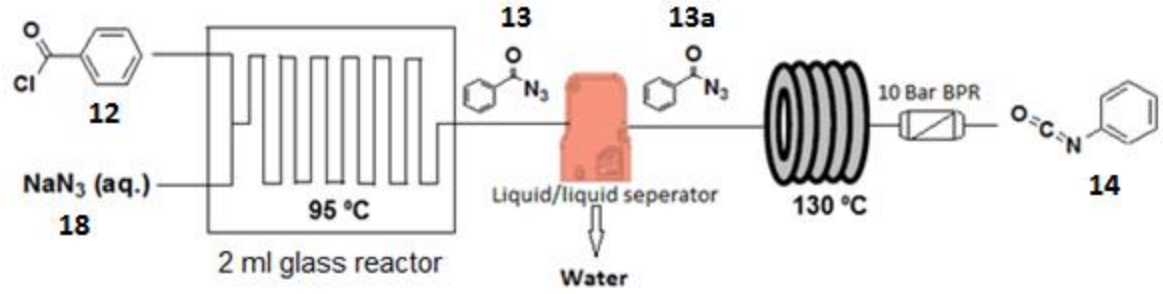


Figure 13 Use of Liquid/liquid separator towards Curtius rearrangement reaction.

Benzoyl chloride **12** (0.5 M) in toluene and sodium azide **18** (0.55 M) in water were prepared in separate FlowSyn reagent bottles. Each reagent was pumped at 0.13 ml/min and the reactor

temperature was kept at 95 °C for the first reactor (7.69 min residence time) to allow benzoyl azide **13** synthesis. A Zaiput liquid/liquid separator was used to remove the aqueous phase in the system beforeanhydrous benzoyl azide **13a** underwent Curtius rearrangement in the 10 ml stainless steel coil reactor (38.5 min residence time) held at temperatures in the range of 70-150 °C, to afford phenyl isocyanate **14**. The system was used under 10 Bar pressure to allow superheating to prevent the solvent boiling. The effect of temperature on the conversion of benzoyl chloride to phenyl isocyanate *via* the Curtius rearrangement of benzoyl azide **13a** formed *in situ* is shown in Figure 14 below.

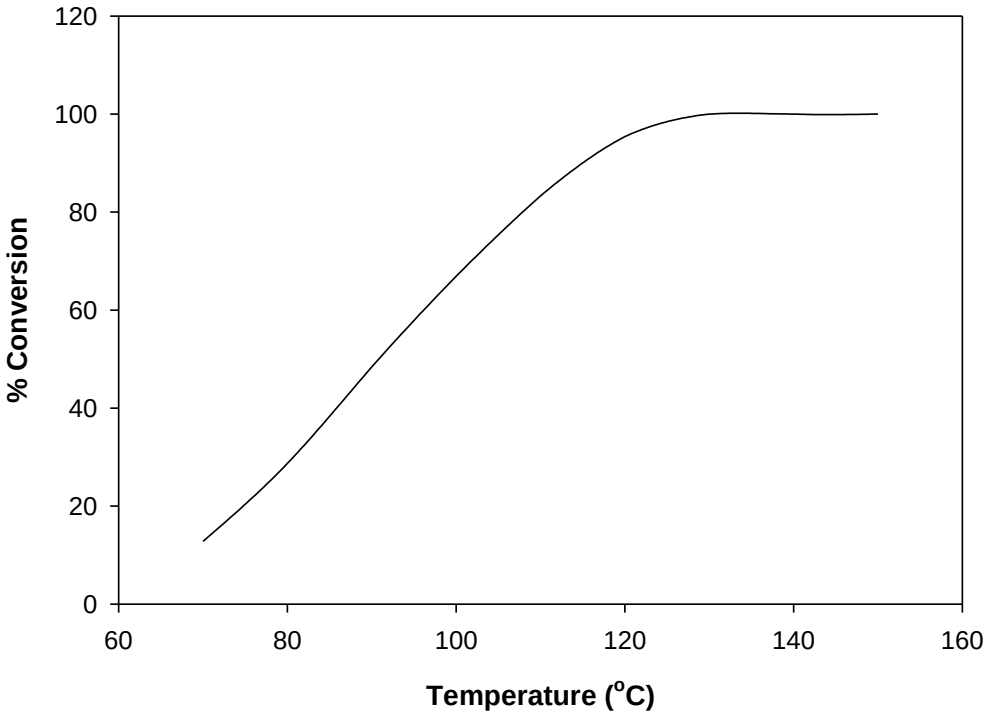


Figure 14. Temperature effect on Curtius rearrangement reaction in a continuous flow system at 38.5 min residence time in the heated coil reactor.

As illustrated in Figure 14, conversion of benzoyl chloride **13** towards phenyl isocyanate **14** in the stainless steel coil reactor was a function of temperature at 38.5 min residence time. Conversion increased with increase in temperature reaching full conversion at 130 °C. This observation was as expected since the Curtius rearrangement only occurs in the presence of heat above 70 °C.[9,13] Jensen *et al.*[9] reported 99 % benzoyl azide conversion towards phenyl isocyanate at 60 min residence time (105 °C). We managed to obtain full conversion at a lower

residence time (38.5 min, 130 °C) than Jensen *et al*,[9] (60 min, 105 °C) by pressuring the system which allowed us to superheat the reaction to higher temperatures. The liquid/liquid separator successfully removed the aqueous phase after the first step which leads to the successful Curtius rearrangement. These developments made it possible to react the phenyl isocyanate with different nucleophiles of our choice in a continuous flow system, affording compounds such as carbamates and amides as discussed below.

Multi-step continuous flow synthesis of amines, carbamates and amides. As above-mentioned, given the inherent dangers in the handling of organic azides, one of our aims was to prepare benzoyl azide **13** *in situ* and without isolation conduct subsequent reactions to give more complex products such as amines **15**, carbamates **16** and amides **17** *via* Curtius rearrangement of benzoyl azide **13** into phenyl isocyanate **14** (Scheme 5). The amine (aniline **15**) was the only product when acetonitrile was used as solvent for benzoyl chloride **12** as the liquid/liquid separator failed to eliminate water from the system. However, solvent change to toluene enabled effective use of the liquid/liquid separator making it possible to trap the phenyl isocyanate **14** with nucleophiles such as alcohols and carboxylic acids yielding carbamates **16** and amides **17** respectively in good conversions (Figure 15).

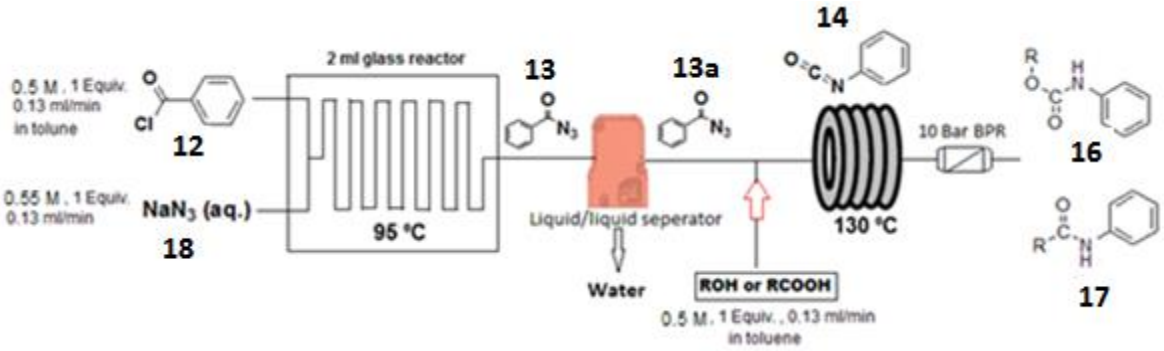


Figure 15 General continuous flow system used in multi-step synthesis of carbamates and amides via Curtius rearrangement.

Benzoyl chloride **12** (0.5 M) in toluene and sodium azide **18** (0.55 M) in water were prepared in FlowSyn reagent bottles and each reagent was pumped at 0.13 ml/min and the reactor temperature was kept at 95 °C for the first reactor (7.69 min residence time) to allow benzoyl

azide synthesis **13**. A liquid/liquid separator was used to remove the aqueous phase from the system before either an alcohol or carboxylic acid (0.5 M) in toluene was pumped into the system at 0.13 ml/min flow rate. This mixture entered the 130 °C coil reactor at a total flow rate of 0.39 ml/min (25.6 residence time) for the Curtius rearrangement reaction and subsequent trapping of the resultant phenyl isocyanate **14** with the pre-introduced nucleophiles (alcohols and carboxylic acids) affording carbamates **16** and amides **17** respectively. Figure 16 is a summary of carbamates synthesised *via* Curtius rearrangement using respective alcohols (ethanol, propanol, butanol, hexanol and octanol) using the aforementioned conditions. Good conversions and good isolated yield were afforded in the multistep synthesis of carbamates **21** - **25** (94 %), for example the isolated yield for the carbamate **21** was 92 %.

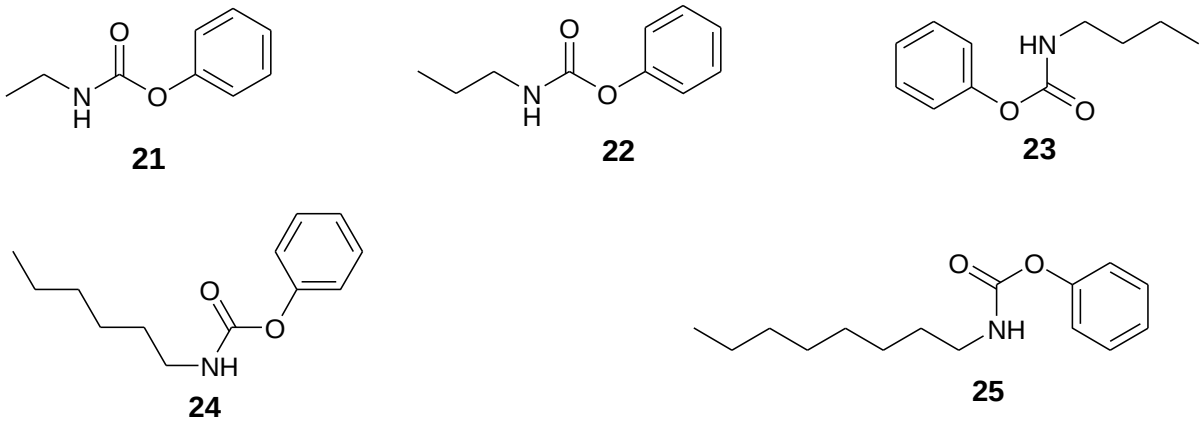


Figure 16 Various carbamates and their respective % conversions synthesised in a continuous flow system via Curtius rearrangement.

It was interesting to note that some carbamates were successfully synthesised in good conversions without incorporating a liquid/liquid separator in the continuous flow system (Figure 17) when toluene was used as a solvent.

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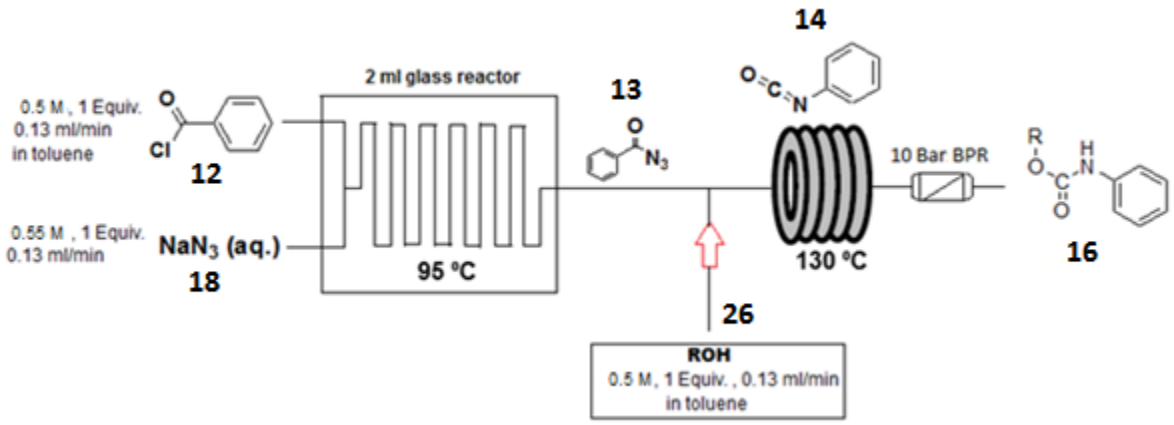


Figure 17 Carbamate synthesis in the absence of a liquid/liquid separator.

Benzoyl chloride **12** (0.5 M) in toluene and sodium azide **13** (0.55 M) in water were each pumped through the system at 0.13 ml/min flow rate and the reactor temperature was kept at 95 °C for the first reactor (7.69 min residence time) to allow benzoyl azide **13** synthesis. An alcohol **26** (0.5 M) in toluene was pumped into the system at 0.13 ml/min flow rate. This mixture entered the 130 °C coil reactor at a total flow rate of 0.39 ml/min (25.6 residence time) for the Curtius rearrangement reaction and subsequent trapping of the resultant phenyl isocyanate with appropriate alcohols giving carbamates **16**. Figure 18 shows the conversions afforded from various alcohols without the use of a liquid/liquid separator to remove water in the system.

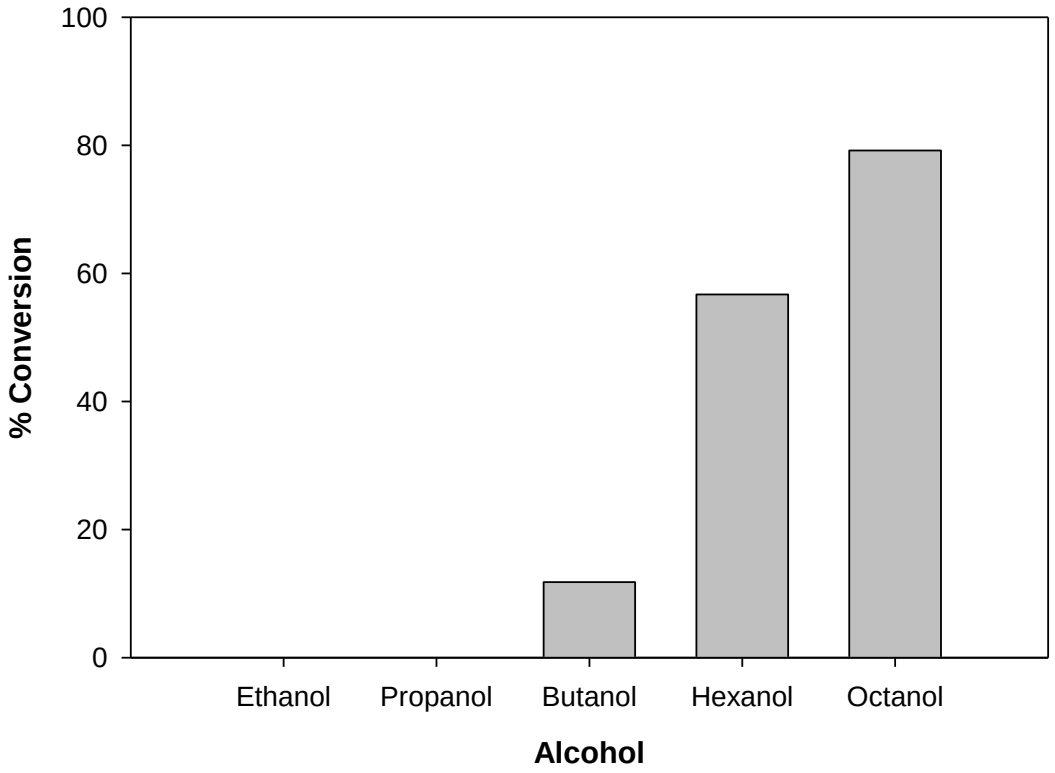
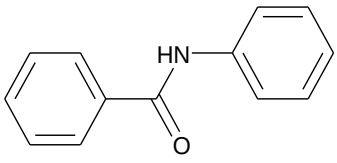


Figure 18 Carbamate synthesis in a continuous flow system without a liquid/liquid separator.

It shows that conversion of alcohols towards respective carbamates using a continuous flow system generally increases with increase in the hydrocarbon chain length of the alcohol. Using ethanol and propanol, no respective carbamates were synthesised, instead aniline was produced via reaction of the phenyl isocyanate with water in the system. However, some considerable conversions towards respective carbamates were achieved using butanol (12 %), hexanol (57 %) and octanol (79 %). Hydrophobicity of alcohols increases with an increase in hydrocarbon chains. Ethanol and propanol are miscible in water where miscibility decreases with hydrocarbon chain length. Therefore, the contact between the organic phase and aqueous phase in the system is diminished as the hydrocarbon chain length of the added alcohol increases which has a positive impact on reaction towards carbamates. The reaction will occur in the organic phase as phenyl isocyanate contact with water will be minimal thus favouring carbamates synthesis. We noted that the formation of the unwanted aniline decreased as the hydrocarbon chain length increased. However, this continuous flow system (Figure 17) produced carbamates at lower

conversion at higher temperatures compared to the one in Figure 15 where a liquid/liquid separator was used as no aniline was formed at all. This might be because solubility of toluene increased with temperature therefore inciting miscibility between the organic phase and aqueous phase resulting in some water to react with phenyl isocyanate. Hence conversion towards the target carbamates is decreased in this case.

Multi-step continuous flow synthesis of amides. Under the conditions used in the continuous flow system (Figure 15), the phenyl isocyanate formed *in situ via* Curtius rearrangement of benzoyl azide was trapped with an appropriate carboxylic acid to produce amides **17**. Figure 19 summarises the amides **27**-**30** prepared in good conversions (80 - 85 %) and the isolated yield for amide 28 was 83%, demonstrating minimum loss on work-up.



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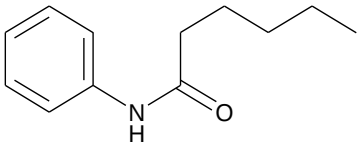

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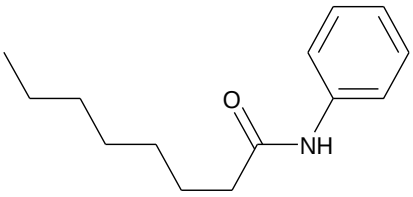

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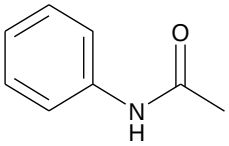

30

Figure 19. Various amides and their respective % conversions synthesised in a continuous flow system via Curtius rearrangement.

Optimising the last step (phenyl isocyanate reaction with carboxylic acid) was not a target in this research. However, conversion towards amides can be enhanced by using bases such as triethylamine as these bases deprotonate carboxylic acids, forming more reactive carboxylate ions, which are better nucleophiles. Hence better conversions will be obtained in the presence of a base in the last step of the multistep synthesis.

Conclusion

Given the inherent dangers in the handling of organic azides, we managed to perform continuous multistep synthesis of amines, amides and carbamates *via* Curtius rearrangement of benzoyl azide formed *in situ*. Continuous multistep synthesis of aniline in acetonitrile was successfully performed in the absence of a liquid/liquid separator where benzoyl azide synthesis was effected from benzoyl chloride and aqueous sodium azide at room temperature using a T-mixer followed by Curtius rearrangement and subsequent trapping of the resultant phenyl isocyanate with water in a glass micro reactor at 150 °C and 9.75 min residence time yielding 98 % conversion towards aniline. We successfully achieved continuous multistep synthesis of carbamates and amides in toluene at 94 % and 80 - 85 % conversion respectively. Compared to literature Our approach was effective as we achieved benzoyl azide synthesis in toluene (92 % conversion) at a much shorter residence time (7.69 min) than literature precedent (98 % conversion, room temperature and 200 min residence time)[9] by increasing the reaction temperature and ensuring efficient mixing throughout the system. Curtius rearrangement in the absence of a catalyst was successfully achieved in full conversion at shorter residence time 25.6 min by pressurizing the system allowing superheating without solvent boiling. Jensen *et al* [9] achieved 91 % conversion at 90 °C and 60 min residence time, however full conversion was only attained in the presence of a catalyst under these conditions. The preparation of carbamates with long chain alcohols was achieved in high yield even without the incorporation of the liquid-liquid separation module. Therefore, our work demonstrated the use of a simple network of micro reactors, inline separation and *in situ* generation and consumption of hazardous intermediates such as isocyanates. Multivariate optimisation of benzoyl azide synthesis in continuous flow systems was successfully performed.

Experimental procedures

General experimental methods

All reagents were obtained from commercial sources and used as supplied without further purification. All solvents were analytical or HPLC grade and were used as supplied. Nuclear magnetic resonance (NMR) spectra were recorded at room temperature as solutions in deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6). A Bruker spectrometer was used to record the spectra and the chemical shifts are reported in parts per million (ppm) with coupling constants in Hertz (Hz). Infra-red spectra were recorded from 4000-500 cm^{-1} using a Bruker spectrometer and peaks (V_{max}) reported in wavenumbers (cm^{-1}). Agilent gas chromatography (7820A) fitted with a HP-1 (Crosslinked Methyl Siloxane 30m x 0.32mm x 0.25 µm) column using nitrogen as carrier gas was used to record GC data. High performance liquid chromatography (HPLC) data was obtained using Agilent 1100 with a UV/Vis detector and a Zorbax C18, 10µm, 4,6mm x 250mm column. Continuous flow reactions were performed on a Labtrix® Start system and a Uniquis FlowSyn system and reactions were monitored by HPLC-UV/Vis and GC.

Flow systems

The Labtrix Start system equipped with glass microreactor (Model 3227, 3223, 3023 and 3022), reactor holder, standard syringe pump, 1 mL SGE gastight syringes, polyetheretherketone (PEEK) tubing (1/32" OD x 125 µm ID), an IDEX 10 bar backpressure regulator. The Uniqsis FlowSyn system with a 2mL borosilicate glass reactor, aluminum coil reactor, polytetrafluoroethylene (PTFE) tubing (1 mm OD x 0.7 mm ID) and 20 Bar Upchurch back pressure reactor.

Benzoyl azide synthesis in the The Labtrix ® Start system

Sodium azide **18** was dissolved in water and benzoyl chloride **12** dissolved in appropriate solvents to be screened (acetone, toluene or acetonitrile). The molar ratios and concentration of these solutions varied as described. The sodium azide solution and benzoyl chloride solutions were pumped through the Labtrix flow system (Figure 2). The product **13** sample was extracted

by ethyl acetate for HPLC and GC analysis. Prepared benzoyl azide and characterised benzoyl azide standard was used to confirm the benzoyl azide peak from the continuous flow reaction.

Benzoyl azide synthesis optimization in continuous flow: Uniqsis FlowSyn system

Benzoyl azide **13** synthesis and optimisation was done in FlowSyn reactor system (Figure 8) using a FlowSyn 2 ml glass reactor. Benzoyl chloride (0.5 M) in toluene and sodium azide (0.55 M) in water were prepared into two separate FlowSyn reagent bottles. Approximately 1.1 ml solution of each reagent was used for each experiment as the system required a total of 2 ml of solution to equilibrate before collecting a sample for analysis. Central composite experimental design (CCD) was used for optimisation. Each experimental run was done in triplicate for reproducibility purposes.

Continuous flow synthesis of various acyl azides

Various acyl chlorides were synthesised at the optimum conditions found for the model reaction (7.69 min residence time and 95 °C), benzoyl azide synthesis. After optimising the model reaction, the same system and optimum conditions were used to synthesise different acyl azides. Various acyl chlorides **19** (1 equiv.) were treated with sodium azide **18** (1.1 equiv.) to afford respective acyl azide **20** in continuous flow system (Figure 12). HPLC and GC were used to analyse the product and prepared synthetic standards were used to identify the product peaks.

Multistep synthesis carbamates and amides *via* Curtius rearrangement

Benzoyl chloride (0.5 M) in toluene and sodium azide (0.55 M) in water were pumped through continuous flow system at 0.13 ml/min flow rate for the first reaction to occur in the 2 ml glass reactor at 95 °C (9.75 min residence time). Water was removed from the system by the Zaiput liquid/liquid separator and nucleophile (0.5M, 1 equiv, alcohol or carboxylic acid) in toluene was then introduced into the system. This reaction mixture was pumped through the 10 ml coil reactor at 130 °C (25.6 min residence time) to allow for Curtius rearrangement and subsequent trapping of the resulting phenyl isocyanate **14** with an appropriate nucleophile (alcohol or carboxylic acid). A 10 bar back pressure regulator was fitted downstream after the coil reactor to allow super-heating (Figure 15). The product and waste samples were extracted by ethyl acetate for GC and HPLC analysis.

Multistep synthesis of carbamates *via* Curtius rearrangement without a liquid/liquid seperator

Benzoyl chloride **12** (0.5 M) in toluene and sodium azide **13** (0.55 M) in water were pumped through the continuous flow system for the first reaction to occur in the 2 ml glass reactor at 95 °C. The nucleophile (0.5 M) in toluene was then introduced into the system. This reaction mixture was pumped through the 10 ml coil reactor at 150 °C (25.6 min residence time) to allow for Curtius rearrangement and subsequent trapping of the resulting phenyl isocyanate **14** with an appropriate nucleophile (alcohol) towards compound **16**. A 10 bar back pressure regulator was fitted downstream after the coil reactor to allow super-heating (Figure 17). The product and waste samples were extracted into ethyl acetate for GC and HPLC analysis.

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Keywords

Acyl azides, amines, carbamates, amides, multi-step

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