CHEMTRIX
Scalable Flow Chemistry

Application Note 7

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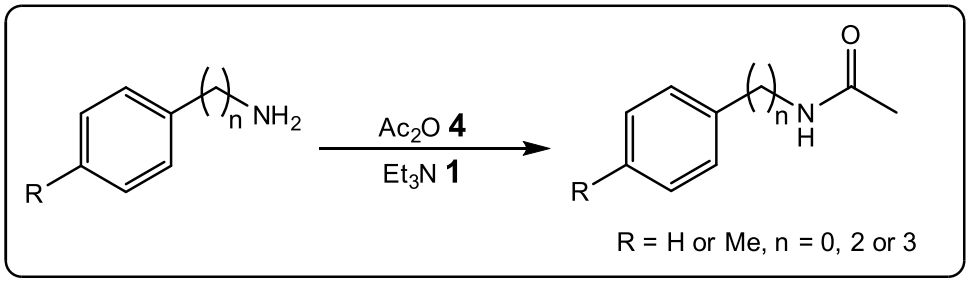
Chemtrix BV

Application Note 7: High-throughput Synthesis of Alkyl Amides within Labtrix® S1



Along with its prevalence within naturally occurring compounds, the amide functionality can also be found in many synthetic and semi-synthetic biologically active compounds such as Tamiflu® and lysergic acid diethylamide (LSD). In addition to finding use as synthetic products, amides are in themselves synthetically useful precursors which can be dehydrated to nitriles, be converted to imines, using Vilsmeier-Haack conditions, and afford primary amines, with a carbon atom removed, via the Hofmann degradation. With these factors in mind, the synthesis of amides was investigated using Labtrix® S1, the micro reactor development apparatus from Chemtrix BV, as a means of developing synthetic methodology suitable for the continuous flow production of amides [1].

Reaction Conditions: Reactions were performed using the Labtrix® S1 system (Figure 1a) fitted with a glass micro reactor (Reactor type = 3123, Volume = 10 µl) containing static mixing elements (SOR-2), selected to maximise mixing efficiency and increase the available reaction volume (Figure 1b) [2].

(a).

(b).

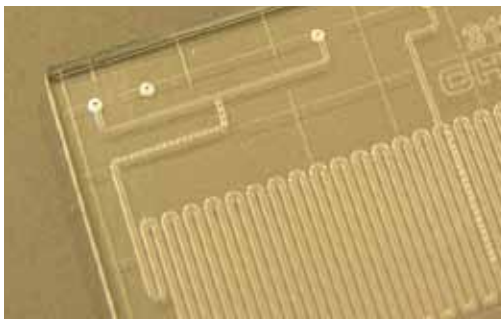


Figure 1. Illustration of (a). Labtrix® S1, the micro reactor development apparatus supplied by Chemtrix BV and (b). a close-up of a Labtrix® micro reactor containing SOR-2 micro mixing elements.

Reactant solutions were delivered to the micro reactor using three 1000 µl glass gas-tight syringes (SGE, UK) and a series of flow rates investigated (30 to 600 µl min^{-1}). Where reaction temperatures ranging from 10 to 125 °C were employed, a back-pressure regulator (25 bar) was fitted and a maximum reagent throughput of 50 µl min^{-1} utilised. Reaction products were collected in 20 µl aliquots (n = 3) and diluted to 1 ml with the proportion of product formed quantified offline using HPLC-UV analysis (Varian ProStar, Luna C18 column = 5 µm, 100 Å, 15 cm (Phenomenex, UK), Isocratic program = 90 % MeOH in DI H_2O at a flow rate of 1 ml min^{-1} and Injection volume = 10 µl) and biphenyl as an internal standard. Analyte retention times were compared with those obtained from fully characterised or commercially available synthetic standards and the system calibrated for the consumption of the 1° amine and formation of the amide.

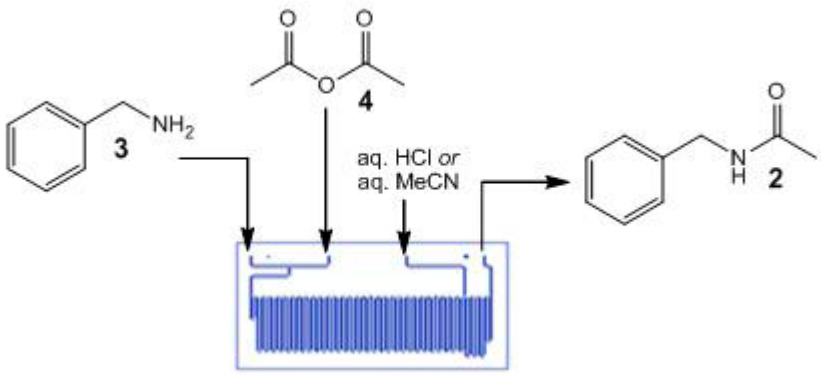


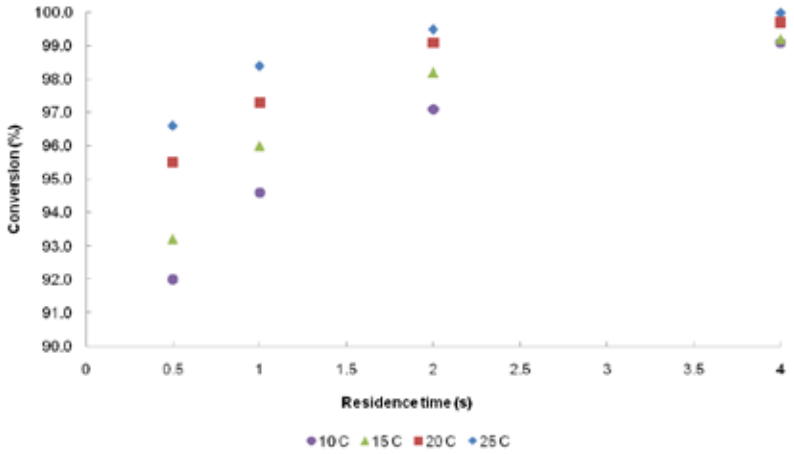
Figure 2. Schematic illustrating the order of reactant addition employed for the evaluation of benzylamine **3** amidation under continuous flow.

Results and Discussion: In order to optimise the synthesis of amides under continuous flow, a series of reaction conditions were investigated including the presence of an organic base (triethylamine **1**), the effect of reaction time (0.5 to 10 s) and temperature (10-25 °C) using the formation of *N*-benzylacetamide **2** as a model reaction (Figure 2).

Employing a series of stock solutions, the first containing benzylamine **3** (1.0 M) and biphenyl (3.0×10^{-3} M) in anhydrous THF, the second acetic anhydride **4** (1.1 M, 1.1 eq.) in anhydrous THF and aq. HCl (0.5 M) as the quench agent, the reaction was initially investigated in the absence of an organic base. As Figure 3a illustrates, at 10 °C conversions of 92.0 % were obtained with a reaction time of 0.5 s, which was observed to increase to 99.1 % at a residence time of 4.0 s. Increasing the reactor temperature to 25 °C enabled quantitative conversion of benzylamine **3** to be obtained at 4.0 s and afforded a system throughput of 0.67 g h^{-1}. Repeating the aforementioned investigation in the presence of triethylamine **1** (1 eq.), added to the benzylamine **3** stock solution, resulted in a four-fold increase in system throughput (2.68 g h^{-1}), affording quantitative conversion of the amine **3** to the amide **2** with a reaction time of 1.0 s; at temperatures ranging from 10 to 25 °C (Table 1 and Figure 3b).

Substrate Scope: In order to investigate the scope of the reaction, a series of reactions were performed using a range of aromatic and aliphatic amines. In all cases, a stock solution concentration of 1.0 M was maintained and unless otherwise stated a 1.1 eq. excess of acetic anhydride **4** was employed. As Table 2 illustrates, aliphatic amines such as 2-phenylethylamine and 3-phenyl-1-propylamine afforded high conversions at room temperature however aromatic amines such as aniline required extended reaction times and increased reactor temperatures to enable isolation of the target amides in quantitative conversion.

(a).



(b).

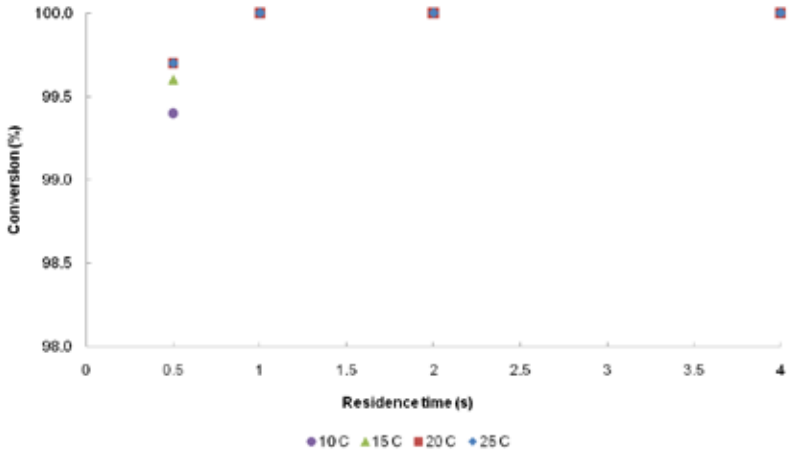
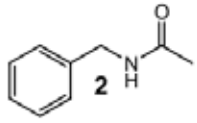
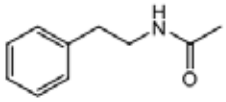
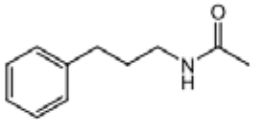
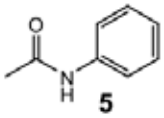
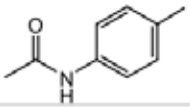


Figure 3. Effect of reactant flow rate on the synthesis of *N*-benzylacetamide **2** using micro reactor 3123 (a). in the absence of Et_3N **1** and (b). in the presence of Et_3N **1**.

Set Temperature (°C)	Residence Time (s)	Conversion (%)	
		No Base **1**	1 eq. Base **1**
10	0.5	92.0	99.4
	1.0	94.6	100.0
	2.0	97.1	100.0
	4.0	99.1	100.0
15	0.5	93.2	99.6
	1.0	96.0	100.0
	2.0	98.2	100.0
	4.0	99.2	100.0
20	0.5	95.5	99.7
	1.0	97.3	100.0
	2.0	99.1	100.0
	4.0	99.7	100.0
25	0.5	96.6	99.7
	1.0	98.4	100.0
	2.0	99.5	100.0
	4.0	100.0	100.0

Table 1. Summary of the effect of reactant residence time, temperature and base **1** on the synthesis of *N*-benzylacetamide **2** using a 10 µl Chemtrix BV glass micro reactor (3123).

Product	Reactor Temperature (°C)	Residence Time (s)	Conversion (%)	Throughput (g h^{-1})
 **2**	25	1.0	100.0	2.68
	25	2.0	93.1	1.47
	25	10.0	95.4	0.32
 **5**	100	20.0	100.0	0.12 [a]
	125	10.0	100.0	0.27

[a] 1.5 equivalents of acetic anhydride **4** was employed.

Table 2. Illustration of the optimal conditions identified for the acetylation of a series of 1° amines evaluated using Labtrix® S1.

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Summary: Through utilising static micro mixers, reaction times of 0.5 to 20.0 s were accessible within glass micro reactors, which enabled the efficient synthesis of amides such as *N*-benzylacetamide **2** with space-time-yields of 268 g ml^{-1} h^{-1} (calculated). In the case of aromatic derivatives, the use of a glass micro reactor was found to afford dramatic enhancements in reaction efficiency, affording *N*-phenylacetamide **5** in 100 % conversion with a 10 s residence time (100 °C), when compared to a previously reported tubular stainless steel device whereby residence time of 42 min were required to obtain the amide in 94 % yield [3].

References:

[1]. J. Hooper and P. Watts, *J. Label. Compd. Radiopharm*., 2007, **50**, 189-196.
[2]. See Application Note 1: The use of Static Micro Mixers within Labtrix® Micro Reactors.
[3]. T. Schwalbe, V. Autze and G. Wille, *Chimia*, 2002, **56**, 636-646.

Acknowledgements:

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Note:

Due to the use of high linear velocities, for reaction times of 10 s or less, it is imperative that reactions be performed in the absence of back-pressure regulation. Failure to do so may lead to the generation of system pressures in excess of those tolerated by the glass gas-tight syringes.