Application Note 10

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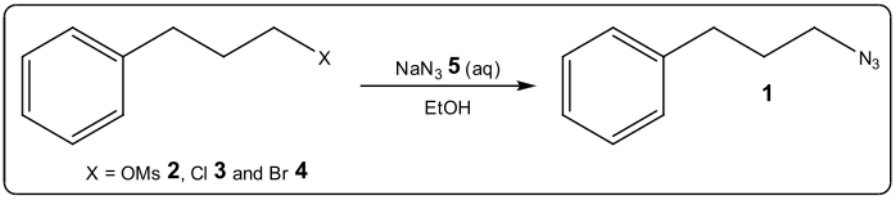
Application Note 10: A safe and efficient method for the preparation of organic azides under continuous flow



The azide functional group offers the researcher a facile route to the installation of a range of synthetically interesting motifs which include amines, aziridines, 1,4-substituted-1,2,3-triazoles and isocyanates. In particular, the [3+2] azide-alkyne cycloaddition (Click chemistry) [1], can be attributed with increasing the popularity of azides with medicinal chemists due to the ease with which biologically active molecules can be constructed with a high degree of structural diversity (Figure 1). The synthesis of organic azide precursors can however be problematic, owing to the fact that the products are thermally unstable materials which readily eliminate N_2 making them prone to detonation. In addition, the build-up of hydrazoic acid (HN_3) within the headspace of reactors and within the traps of rotary evaporators makes the preparation of this class of compound extremely hazardous, particularly when performed at scale.

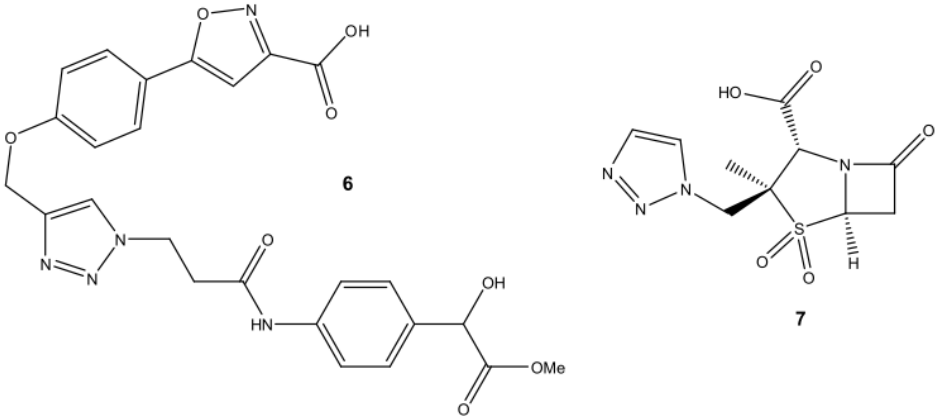


Figure 1. Examples of biologically active substituted-1,2,3-triazoles (PTP1B inhibitor **6** and Tazobactam **7**).

As a means of developing a safe and efficient technique for the preparation of organic azides, on both a R&D and production scale, the synthesis of an alkyl azide **1** from alkyl mesylates **2** and halides (Cl **3** and Br **4**) was investigated under continuous flow conditions using the inexpensive and readily available reagent NaN_3 **5**.

Reaction conditions: Reactions were performed using the Labtrix® S1 system (Figure 1) fitted with a glass micro reactor (Reactor type = 3123, Volume = 12.37 µl) containing an SOR-2 mixer [2]. Reactant solutions were introduced into the micro reactor using 1000 µl gas-tight syringes (SGE) and a 25 bar ULDV-BPR (Upchurch Scientific) was fitted to the system; in order to maintain reactants in the liquid phase over the temperature range evaluated (25 to 195 °C). In all cases, the substrate was prepared as a solution in EtOH (0.66 M), NaN_3 **5** in aq. EtOH (50 v/v %) (0.66 M) and the reactions quenched using aqueous MeOH (50:50); which was found to be necessary to solubilise the internal standard in the post reaction mixture and enable accurate quantification of the product **1** formed.

Figure 2. Illustration of the micro reactor development equipment, Labtrix® S1, supplied by Chemtrix BV.

Reaction products were collected in 25 µl aliquots and diluted with MeOH (75 µl) prior to offline analysis by HPLC-UV (Column = Prodigy 5µ ODS(2) (Phenomenex); Mobile phase = 70:30 MeCN:H_2O; Flow rate = 3.0 ml min^{-1}; Sample volume = 25 µl; Wavelength = 254 nm), with retention times compared with fully characterised synthetic standards and conversions determined using an internal standardisation method (Internal standard = Anisole). Where product isolation was performed, an aliquot of the flow reaction product was diluted with DI H_2O (15 ml) and washed with diethyl ether (3 x 15 ml), prior to drying over $MgSO_4$. The organic extracts were then concentrated *in vacuo* to afford (3-azidopropyl)benzene **1** as a colourless oil. Product purity was then confirmed by ^1H and ^{13}C NMR spectroscopy by dissolution in $CDCl_3$ and GC-MS (CP-Sil 8 column (30 m, Zebron ZB-5, (Phenomenex) and ultra high purity helium (99.999 %, Energas, UK) carrier gas) analysis.

Results and Discussion: Employing the reaction set-up illustrated in Figure 3, the effect of reactant residence time (15 s to 20 min) and reaction temperature (25 to 195 °C) was investigated for the synthesis of (3-azidopropyl)benzene **1** in the presence of one equivalent of NaN_3 **5**. The reactions employed a substrate concentration of 0.66 M, as this was found to be the maximum concentration that afforded a homogeneous solution of 3-phenylpropyl methanesulfonate in abs. EtOH.

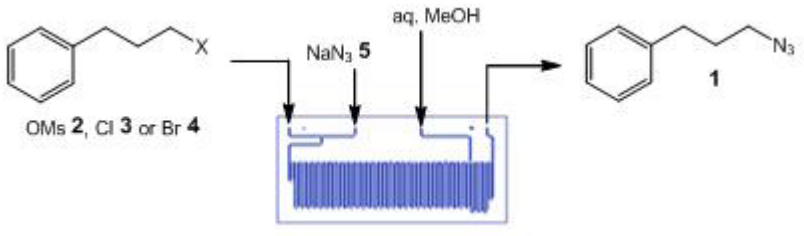


Figure 3. Schematic illustrating the reaction manifold used for the synthesis of (3-azidopropyl)benzene **1** under flow.

As Figure 4 illustrates, initial experiments were performed using a residence time of 30 s over the temperature range of 25 to 195 °C. From the results obtained, it was clear to see that the reaction was thermally activated, with no reaction observed at < 75 °C and quantitative conversion of the mesylate **2** to the target azide **1** achieved at 195 °C.

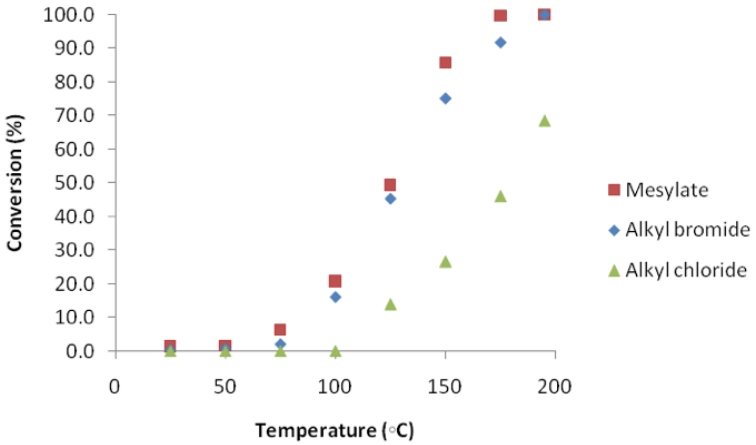


Figure 4. Illustration of the effect of reaction temperature on the azidation of 3-phenylpropyl methanesulfonate **2**, 1-chloro-3-propylbenzene **3** or 1-bromo-3-propylbenzene **4** using a Chemtrix BV micro reactor (Device 3123); residence time = 30 s and NaN_3 **5** 1.0 eq.).

To demonstrate the generality of the technique, the effect of leaving group was also investigated by substituting 3-phenylpropyl methanesulfonate **2** with 1-chloro-3-phenylpropane **3** and 1-bromo-3-phenylpropane **4** (Figure 3). Performing the same condition screen, we were able to demonstrate the azidation of both the chloro **3** and bromo **4** derivatives (Table 1). As expected, the mesylate **2** and bromo **4** precursors were observed to react similarly, affording a throughput of 79 mg h^{-1}, with complete conversion of the chloro **3** derivative only attainable when employing an extended reaction time of 20 min.

	Conversion (%)		
Reaction Time (s)	OMs **2**	Br **4**	Cl **3**
15	95.1	93.0	33.9 (58.4) [a]
30	100.0	100.0	68.5 (75.9) [a]
60	100.0	100.0	65.0 (100.0) [a]
90	100.0	100.0	75.0 (100.0) [a]
120	100.0	100.0	80.3 (100.0) [a]
150	100.0	100.0	85.0 (100.0) [a]
300	100.0	100.0	92.9 (100.0) [a]
600	100.0	100.0	93.0 (100.0) [a]

Table 1. Comparison of the effect of leaving group on the synthesis of (3-azidopropyl)benzene **1** under continuous flow conditions, employing a reactor temperature = 195 °C and [NaN_3 **5**] = 0.66 M (1.0 eq.), [a] [NaN_3 **5**] = 1.22 M (2.0 eq.).

In order to reduce the time taken to synthesise (3-azidopropyl)benzene **1**, from 1-chloro-3-propylbenzene **3**, two equivalents of NaN_3 **5** were employed. As Table 1 illustrates, this resulted in a reduction in the reaction time required to quantitatively convert 1-chloro-3-phenylpropane **3** (26 mg h^{-1}) to 60 s. In this case, the excess NaN_3 **5** was easily removed from the reaction product by aqueous extraction, with no product decomposition observed for any of the reaction conditions evaluated.

Employing the optimal reaction conditions for the mesylate **2**, 30 s at 195 °C, and performing the reaction in the absence of the internal standard (anisole), the methodology developed was capable of producing (3-azidopropyl)benzene **1** at a throughput of 79 mg h^{-1}. Pumping 0.5 ml of each reactant solution through the micro reactor and collecting the reaction products into a single vessel, we were able to isolate the azide **1** after extraction into diethyl ether as a colourless oil (53 mg, 99.6 %); δ_H (400 MHz, $CDCl_3$/TMS) 1.87-1.95 (2H, m, CH_2), 2.67-2.72 (2H, m, CH_2), 3.28-3.29 (2H, t, J 6.9, CH_2), 7.17-7.22 (3H, m, 3 x ArH) and 7.26-7.31 (2H, m, 2 x ArH); δ_C (100 MHz, $CDCl_3$/TMS) 30.4 (CH_2), 32.7 (CH_2), 50.6 (CH_2), 128.3 (CH), 128.4 (4 x CH) and 140.8 (C_0); *m/z* (EI) 162 (M^+ +1, 1 %), 161 (1), 133 (20), 132 (80), 119 (10), 117 (20), 105 (50), 104 (100), 91 (65), 77 (25) and 65 (20). Figure 4 illustrates the ^1H NMR spectra of the azide **1** synthesised under flow conditions after an aqueous extraction; no further purification steps were found to be necessary.

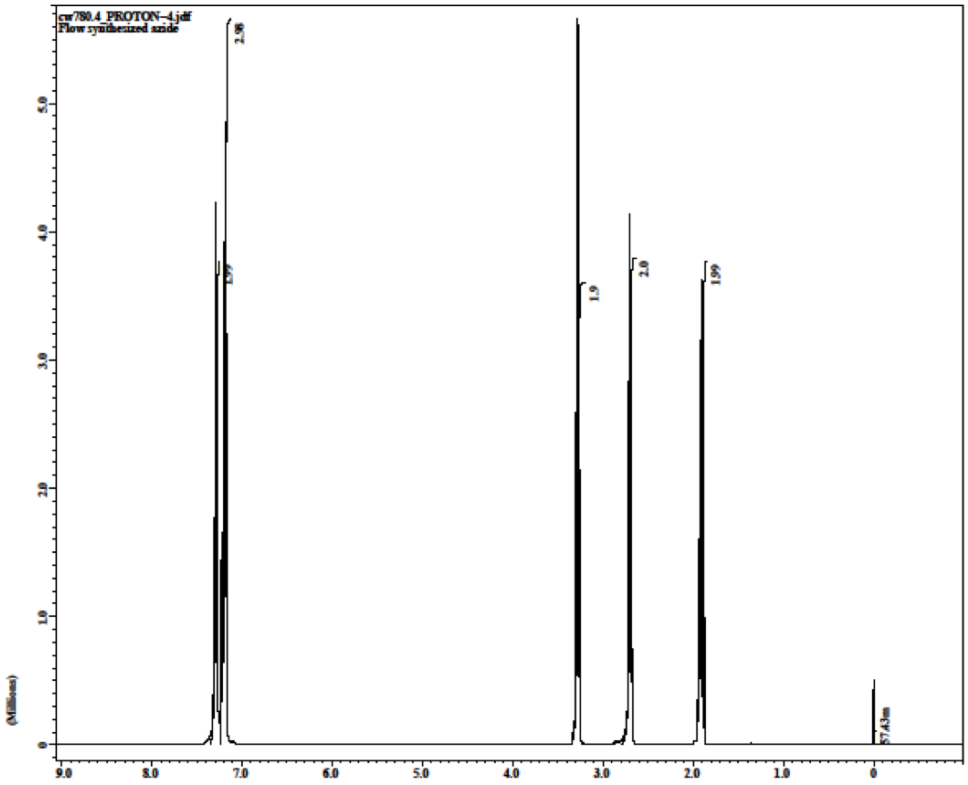


Figure 5. Illustration of the product purity obtained in the flow synthesis of (3-azidopropyl)benzene **1**.

Conclusions: From the investigation reported, it can be seen that by employing reaction temperatures in excess of those deemed safe at a batch scale, we were able to accelerate the azidation reaction to afford access to an analytically pure alkyl azide **1** with a reaction time of only 30 s. Whilst the synthesis of azides has been shown to be accelerated by the use of microwave irradiation [3], the technique is not easily scaled. In comparison, flow reactor methodology enables the larger scale production of azides to be achieved through the use of meso reactors, such those employed within the Plantrix® system [4]. Using the results of the study reported herein, transfer of the synthetic methodology from Labtrix® to Plantrix® would afford a theoretical throughput of 41.5 g **1** hr^{-1} $reactor^{-1}$.

From a medicinal chemist's perspective, the optimised protocol can be readily applied to additional substrates with the Labtrix® Start [4] personal synthesiser, affording rapid access to libraries of organic azides (10's to 100's mg scale) in a safe and reproducible manner.

CHEMTRIX
Scalable Flow Chemistry

References:
[1]. H. C. Kolb and K. Barry Sharpless, 'The Growing Impact of Click Chemistry on Drug Discovery', *Drug Disc. Today,* 2003, **8**(24), 1128-1137.
[2]. See Application Note 1, 'The use of Static Micro Mixers within Labtrix® Micro Reactors' www.chemtrix.com
[3]. S. H. Park, 'Acceleration of Azidation by Microwave Irradiation', *Bull. Korean Chem. Soc.,* 2003, **24**(2), 253-255.
[4]. See www.chemtrix.com for the latest product information.

Note: Chlorinated solvents should be avoided when preparing organic azides as they can lead to the formation of explosive by-products such as diazidomethane and triazidomethane. All azides synthesised should be stored in the dark and at -18 °C in order to avoid decomposition.