A Safer Route to Organic Azides Using Segmented Flow

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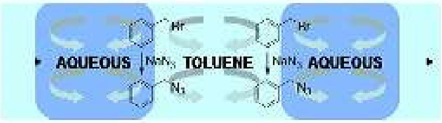
INTRODUCTION

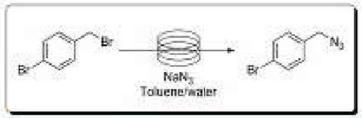
Flow techniques offer more precise control over reaction conditions, reproducibility, scalability, safety and ease of optimisation compared to traditional batch methods. We were interested in reducing the risk involved in the preparation and handling of organoazides. These are valuable intermediates in copper(I)-catalysed azide-alkyne cyclo-additions with the product triazoles required for one of our in-house projects. In batch, solubilisation of the inorganic azide component of the reaction might require the use of a solvent such as DMF or DMSO leading to toxic, readily absorbed solutions of azide. A safer alternative is to use phase transfer conditions which also simplifies work-up procedures.



Segmented flow (above) provides a means of simultaneously introducing aqueous and organic solutions into the reactor. Reactions occur at the interface of the solvent segments (below). The output can be used directly in cycloaddition reactions minimising the handling of these intermediates and leading to triazole formation in high yields and purities.

ORGANOAZIDE FORMATION

Initial studies used 0.5M NaN_3(aq) and a 0.4M toluene solution of 4-bromobenzyl bromide. By varying the temperatures, residence times and volumes of the two reagents, we aimed to optimise the reaction conditions. All reactions were performed in a 2.8 mL PFA coil.



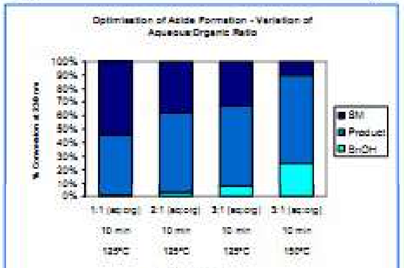


Figure 1

Figure 1 shows that increasing the volume and hence stoichiometry of dilute aqueous azide leads to a significant percentage of hydrolysis product (BnOH). Studies including more concentrated solutions of azide are shown in Figure 2.

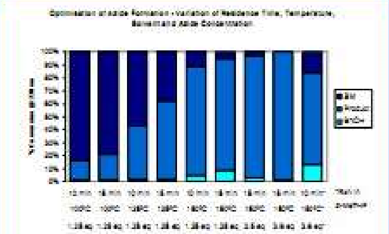


Figure 2

With 3.6 eq of azide, (150°C, 15 min res. time) quantitative conversion was achieved. The use of 2-methyl THF as an alternative to toluene was also investigated but was found to coalesce with the aqueous phase above 130°C, leading to a higher percentage of hydrolysis product.

Further azide displacement reactions on a range of benzyl bromides were investigated, guided by the results shown above. Optimal conditions in each case are shown in Table 1.

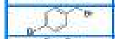
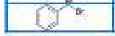
Bromide	Residence Time	Temp	Comments
	15 min	150°C	Scaled out to multigram quantities
	10 min	150°C	5 eq. azide Scaled-out to multigram quantities
	10 min	150°C	
	8 min	150°C	Scaled-out to multigram quantities
	30 min	120°C	Higher temperatures lead to by-product
	15 min	150°C	
	10 min	150°C	

Table 1

TRIAZOLE FORMATION

The outputs from these reactions were used directly (in batch) in copper (I)-catalysed azide-alkyne cycloadditions to afford a variety of triazoles. A selection is shown below (Figure 3); yields are following filtration through a short silica plug.

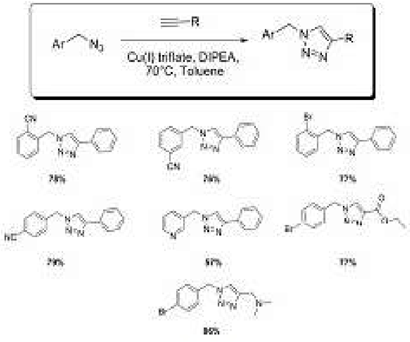


Figure 3

SUMMARY

We have demonstrated the pragmatic use of segmented flow for the synthesis of a range of organoazides. The reactions were simple to optimise and scaleable in the Uniqsis FlowSyn Reactor. The outputs were used directly in subsequent reactions to afford the desired products in high yields and purities, minimising the handling of the toxic and hazardous intermediates.