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Continuous flow thermolysis of azidoacrylates for the synthesis of heterocycles and pharmaceutical intermediates†

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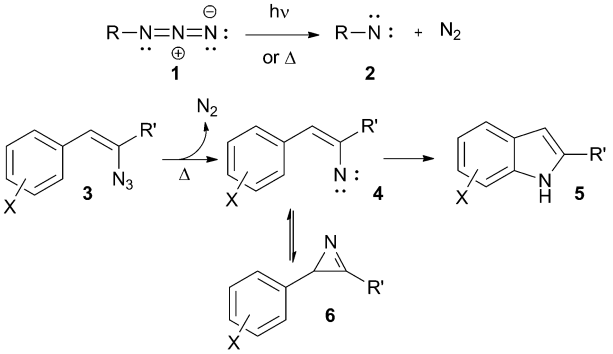
An efficient, safe and scalable procedure for the continuous flow thermolysis of azidoacrylates to yield indoles has been developed and was applied to the synthesis of related heterocycles. The scalability of the process was demonstrated in the continuous flow synthesis of a precursor to the DAAO inhibitor 4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid.

Flow reactor systems provide ideal conditions for detailed study of the formation and subsequent transformations of high-energy compounds.[1] High temperature and pressure conditions can be achieved with improved safety and efficiency compared to batch processes;[2] superheating of solvents is simple,[3] reactions are easily scalable, and hazardous reagents can be more safely handled by minimizing their concentration at the point of reaction.[4] Additionally, the short residence times accessible in micro- and meso-flow reactors[5] often reduce the potential for side reactions of highly reactive species, increasing yields and selectivities.[6] In particular, we are interested in reactions of organic azides,[7] a class of compounds for which safety concerns are well-documented, particularly when handled on large scale.[8] Thermolysis[9] or photolysis[10] of an organic azide **1** affords, *via* extrusion of dinitrogen, a reactive nitrene intermediate **2** (Scheme 1).[11] The generation of nitrenes from vinyl azides is well-studied[12] and this reaction forms the basis of the Hemetsberger–Knittel synthesis of indoles **5** where the nitrene **4** generated from 3-phenyl-2-azidoacrylates **3** formally undergoes a C–H insertion.[13] Nitrene **4** is in equilibrium with 2*H*-azirine intermediate **6**. Indeed, 2*H*-azirines prepared *via* other routes such as the Neber rearrangement[14] also undergo rearrangement to the corresponding indole.[15]

The reaction is a widely-used route to indole-2-carboxylates,[16] which has also been used in total synthesis.[17] The reaction is not limited to 3-phenyl substituents; heteroaryl substituents undergo the reaction,[18,22b] and the analogous dienes react to give the corresponding pyrrole.[19] High-boiling

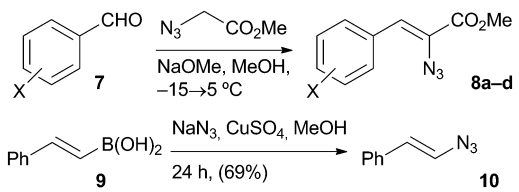


Scheme 1 The thermolysis of organic azides.

solvents such as mesitylene and xylenes under sealed-tube conditions are typically employed, and limit the potential of this process for large-scale synthesis. Otherwise, extended reaction times in refluxing toluene are required. While both microwave-mediated[20] and transition metal-catalysed[21] Hemetsberger–Knittel reactions have been reported, there remains scope for development of this reaction. Few reports discuss the scalability of the reaction. Here, we report the development of an efficient, scalable procedure for the Hemetsberger–Knittel synthesis of indoles, related heterocycles and finally pharmaceutical intermediates using continuous-flow reactors.

Our initial investigations concerned the reactions of 3-phenyl-2-azidoacrylates **8a–d**, which were prepared *via* Knoevenagel condensation.[22] We also studied the reaction of styryl azide **10**,[12a] obtained *via* Cu(I) catalysed Ullmann type coupling of styrylboronic acid **9** with sodium azide (Scheme 2).[23]

A commercially-available Vapourtec R series flow reactor was employed for the development of this reaction.[24] Toluene was selected due to the good general solubility of substrates in this solvent, its stability under the reaction conditions and ease of removal. The system was fitted with a 2 mL stainless steel



Scheme 2 Preparation of azide substrates.

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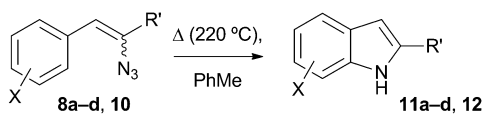
reaction loop, allowing for a minimum residence time of 6 s, when the instrument was run at its maximum flow rate (19.8 mL min^{-1}). All reactions were performed at 220 °C using a back-pressure of 25.5 bar with either 1.0 or 0.5 M solutions of **8a–d** or **10** as dictated by substrate solubility. The reactant entered the heating loop at half this concentration due to mixing with the second pump (run at the same rate). The internal temperature and pressure monitoring of the Vapourtec system was used. For this initial study, 0.4 mmol samples were injected using a sample loop, and the output stream was concentrated under reduced pressure (see ESI†). Under these conditions complete conversion to indoles **11a–d** in high yield was attained at remarkably high flow rates (Scheme 3, Table 1).

In all cases, performing the reaction at 180 °C resulted in complete consumption of the starting material, but incomplete conversion of the 2*H*-azirine intermediates to the indole products. For example, following reaction of **11a** at 180 °C, a singlet at 3.48 ppm was observed in the crude ^{1}H NMR spectrum accompanied by an additional methyl-ester singlet, in agreement with data for 2*H*-azirine **13a** reported by Knittel (Scheme 4).[25] The 2*H*-azirine intermediate was also observed at residence times shorter than those shown in Table 1. In the case of 3-substituted aryl groups (Table 1, entries c and d), although yields were good, performing the reaction under these conditions had no influence on the regioselectivity of the cyclisation.[26] Styryl azide **10**, which we expected to react and give 1*H*-indole **12** decomposed under the reaction conditions, even at 180 °C (Table 1, entry e). We found that purification of products **11a–d** was required to remove traces of side product **14** that formed *via* dimerisation of the 2*H*-azirine intermediate.[27] Disappearance of the singlet attributed to the NH proton of **14d**, when changing the NMR solvent

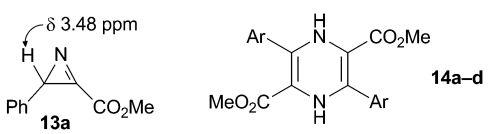


Scheme 3 Synthesis of indoles.

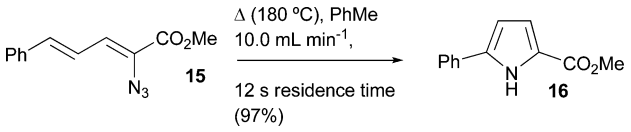
Table 1 Synthesis of indoles in a flow reactor

Entry	X	R	*E*/*Z*	[**8** or **10**][a]/ M	Flow rate[b]/ mL min^{-1}	Residence time/s	Yield (%)
a	H	CO_2Me	*Z*	0.50	4.0	30.0	80
b	2-Cl	CO_2Me	*Z*	0.50	4.0	30.0	80[c]
c	3-OMe	CO_2Me	*Z*	0.25	4.0	30.0	85[d]
d	3-OBn	CO_2Me	*Z*	0.25	4.0	30.0	75[d]
e	H	H	*E*	0.50	5.0	24.0	0

[a] Concentration at the point of reaction, following a two-fold dilution of the substrate solution. [b] Combined flow rate of both pumps. [c] Obtained in 94% purity by ^{1}H NMR comparison with MTBE as an internal standard. [d] Obtained as a 1 : 1 mixture of 5- and 7-regioisomers by ^{1}H NMR.



Scheme 4 Observed side products in the preparation of **11**.



Scheme 5 Synthesis of pyrrole **16**.

from d_1-chloroform to d_4-methanol, along with the 1 : 3 ratio of NH and methyl ester singlets, respectively, lends support to the structural assignment of this dimer.

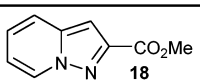
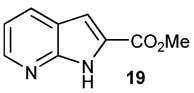
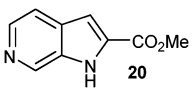
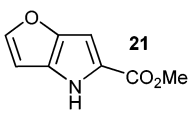
The synthesis of pyrrole **16** was easily achieved at lower temperature. Precursor **15** gave **16** in high yield with a residence time of only 12 s without the need for purification. This protocol represents a distinct improvement over metal catalysed procedures that often require extended reaction times (Scheme 5).[19b] Our attention then turned to the reactions of azidoacrylates bearing heteroaryl groups, which were also prepared *via* Knoevenagel condensation.[22b] The reaction conditions used for the synthesis of indoles **11a–d** were applied unaltered.

Pyrazolopyridine **18** was formed in quantitative yield without the need for purification (Table 2, entry a). Azaindole **19** precipitated in the collection flask and high purity material was obtained following recrystallisation, albeit in reduced yield (Table 2, entry b). Conversely, the reaction of the 4-substituted pyridine **17c** to give **20** failed as only decomposition of the starting material was observed. Lower temperatures and shorter residence time had no effect (Table 2, entry c). We found that the reaction of furan **17d** proceeded very efficiently (Scheme 6). Product **21** was isolated in quantitative yield and excellent purity, even at 12 s residence time and at a temperature of 180 °C (Table 2, entry d).

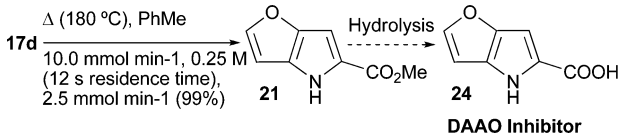
Taking into account the short residence times required to form indoles and related heterocycles, this process may

Scheme 6 Synthesis of heterocycles **18–21**.

Table 2 Synthesis of heterocycles **18–21** in a flow reactor

Entry	Substrate	Product	Flow rate[a]/ mL min^{-1}	*T*/°C	Residence time/s	Yield (%)
a	**17a**	 **18**	4.5	220	26.5	>99
b	**17b**	 **19**	4.0	220	30.0	57%
c	**17c**	 **20**	10.0	160	12.0	0
d	**17d**	 **21**	10.0	180	12.0	>99

[a] Combined flow rate of both pumps.



Scheme 7 Continuous flow synthesis of pharmaceutical intermediate **21**.

quickly generate large amounts of product. Compound **21** serves as a precursor to acid **24**: a recently reported D-amino acid oxidase (DAAO) inhibitor that can be used for the treatment of schizophrenia.[28,29] To study the cyclisation of **17d** in continuous flow and demonstrate the scalability of the reaction, the system was reconfigured to pump a solution of **17d** directly from a reservoir into the reactor. However, during reaction of a 1.0 M solution (reduced to 0.5 M by mixing) of **17d**, an exotherm was observed, resulting in reactor fouling. A two-fold dilution of the substrate solution alleviated this problem and an 8.5 g batch of **21** was prepared within 21 min in excellent purity and yield, corresponding to a throughput of 2.5 mmol min^{-1}.

In summary, we have demonstrated a practical procedure for the thermolysis of azidoacrylates in continuous flow, applicable to the synthesis of indoles and related heterocycles. Importantly, the scalability of this process has been shown in the synthesis of pharmaceutical intermediate **21** (Scheme 7).

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