Flow and batch mode focused microwave synthesis of 5-amino-4-cyanopyrazoles and their further conversion to 4-aminopyrazolopyrimidines†

Catherine J. Smith, Francisco Javier Iglesias-Sigüenza, Ian R. Baxendale and Steven V. Ley*

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A new approach to the synthesis of 5-amino-4-cyanopyrazoles has been developed, utilising a novel flow microwave device. These products are then converted by a batch mode microwave process to structurally more complex dimeric and 'mixed' pyrazolopyrimidine structures.

The use of focused microwave techniques[1] has become a routine component of modern organic synthesis programmes. The enhanced reaction rate for serial processing to generate chemical libraries or the ability to achieve reactions not previously possible, or at least difficult, by conventional heating are key factors in the success of this technology. Furthermore, the opportunities presented by continuous flow processing methods[2,3] for the efficient scale-up of chemical transformations are impacting the way we design, plan and execute molecule assembly, especially within the pharmaceutical context.[4] Nevertheless, these techniques need to constantly evolve in order to accommodate the developing trends and requirements that relate to cost, scale, sustainability and reproducibility of the methods.

Here we report a new protocol for the synthesis of 5-amino-4-cyanopyrazoles and their subsequent reaction to form 4-aminopyrazolopyrimidines. Our approach is based upon the use of simple chemical inputs such as hydrazines, ethoxymethylene malononitrile and nitriles to create more complex product architectures *via* the application of both continuous flow and batch mode focused microwave methods.[1,5,6] To facilitate this synthesis, we have developed a novel flow microwave device which permits reactions to be performed on scale, and in combination with supported reagent techniques, allows the isolation of clean products in high yield without recourse to chromatography.

We believe that this flow microwave device represents a useful addition to existing flow-based microwave technologies,[5,6] as it is readily adaptable to a variety of transformations at a low cost. The microwave flow device itself consists of fluorinated polymer tubing wound around a central Teflon core fitted with a dummy pressure cap typical of microwave reaction vessels (see Fig. 1a). The unit used for the work described below is wrapped with 11.5 m of 0.4 mm i.d. tubing, providing an internal volume in the microwave cavity of 1.45 mL (Fig. 1b). A major benefit of this new device over glass or metal microwave inserts previously described in the literature[6,7] is the versatility and low production cost of the polymer tubing. The Teflon spigots (also relatively low-cost) can be easily re-wrapped in the laboratory to replace blocked or damaged devices or to allow access to new configurations; for example, wrapping different lengths of tubing to provide reactors with varying internal volumes or wrapping multiple tubing to accommodate different reactions or flow rates within the same microwave device.

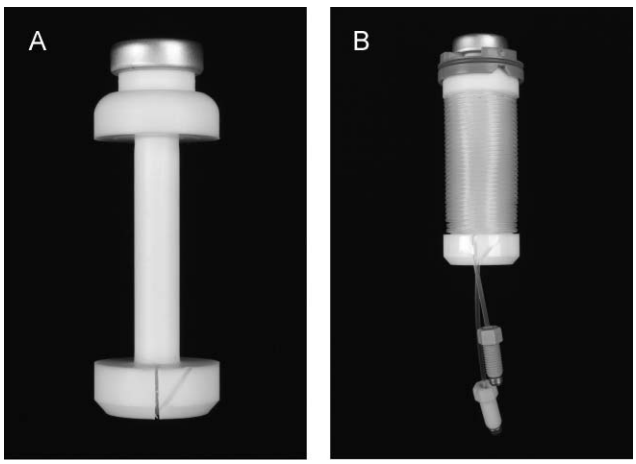


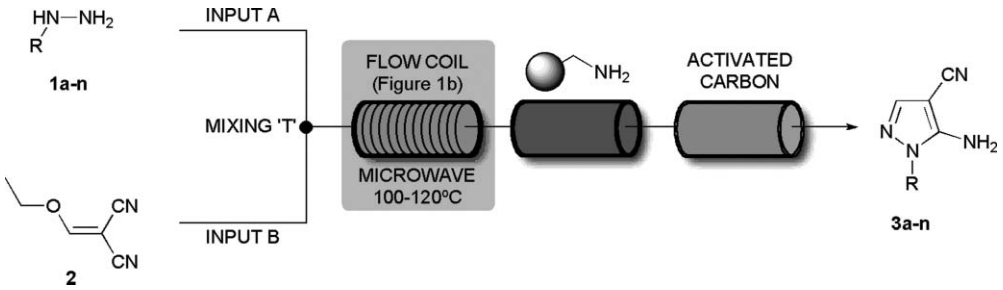
Fig. 1 A) Teflon core. B) Flow microwave coil.

The microwave flow device described above fits into the standard cavity of commercially available microwave equipment (Emrys Optimiser or Initiator[8]) with the input and exit tubes on the underside of the microwave unit. One or more HPLC pumps[9] were used to drive the overall system, which is kept under pressure by the use of a 100 psi back-pressure regulator at the exit. Finally, purification is achieved by passage of the exiting flow stream through columns packed with solid-supported reagents and scavengers.[3,10] These clean-up units can be varied depending upon the chemistry being conducted in the system and the scale of the process.

The choice of pyrazoles and pyrazolopyrimidines as products for the application of this new technology was based on the prevalence of these structures in pharmaceuticals and agrochemicals. In particular, the pyrazolopyrimidine core has been used as a scaffold for the design of anti-tumour agents[11] and inhibitors of kinases,[12a–c] adenosine receptors[12d] and adenosine deaminase.[12e] Our route to these important compounds involved two stages: the advanced pyrazolopyrimidine structures were prepared *via* batch mode elaborations of the corresponding 5-amino-4-cyanopyrazole intermediates, which were themselves easily generated on multigram scale under continuous flow conditions.

Innovative Technology Centre (ACS), Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK. E-mail: svl1000@cam.ac.uk; Fax: +44 1223 336442; Tel: +44 1223 336398

† The HTML version of this article has been enhanced with colour images.



Scheme 1 Flow microwave synthesis of 5-amino-4-cyanopyrazoles.

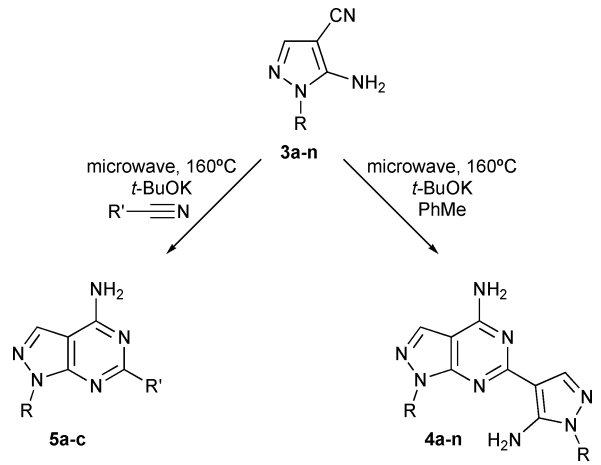
The flow synthesis of 5-amino-4-cyanopyrazoles **3a–n** (Scheme 1) was achieved through the reaction of a series of aryl hydrazines **1a–n** with ethoxymethylene malononitrile **2** in methanol by passage through the flow device described above (Fig. 1b).[11] This process involved exposure of the reaction mixture to focused microwave irradiation (temperatures of 100–120 °C [13]) for a short period of time, usually 0.8–4.0 min (corresponding to flow rates of 0.36–1.75 mL min^{-1}). The exiting flow stream was then processed in-line by passage through a column of benzyl amine resin (Quadrapure™ BZA)[14] acting as a scavenging agent for any unreacted starting material **2** or uncyclised intermediates, followed by a column packed with activated carbon to remove coloured or polymeric impurities. After exiting through a 100 psi back-pressure regulator, the product was obtained by direct evaporation using a Vapourtec V-10® apparatus[15] for smaller samples, or a rotary evaporator for larger samples to give high purity products (≥95%) in good to excellent isolated yields (62–96%, Table 1, **3a–n**).

The 5-amino-4-cyanopyrazole products **3a–n** can be considered as useful materials for other synthesis programmes; in this work we have chosen to investigate their further reaction with aryl nitriles, or dimerisation leading to 4-aminopyrazolopyrimidines under focused microwave heating at higher temperatures (Scheme 2). These reactions were first pioneered by Taylor *et al.* in the early 1960s using conventional heating and required long reaction times under harsh conditions.[16] Recent work by our laboratory[17] and others[12e,18] on the formation of substituted pyrimidine rings using similar synthetic strategies has shown that these reactions can be greatly accelerated by the application of focused microwave irradiation.

Table 1 Yields for flow microwave synthesis of 5-amino-4-cyanopyrazoles and their subsequent dimerisations

Entry	R =	Isolated yield of pyrazole **3** [a]	Isolated yield of dimer **4** [a]	Entry	R =	Isolated yield of pyrazole **3** [a]	Isolated yield of dimer **4** [a]
a	H	62%	—	**h**	Me	75%	68%
b	Ph	89%	64%	**i**	2-pyridyl	90%	76%
c	4-Cl-Ph	84%	42%	**j**	4-F-Ph	85%	82%
d	4-NO_2-Ph	82%	NR[b]	**k**	4-OMe-Ph	84%	60%
e	2-F_3C-Ph	91%	28%	**l**	4-COOH-Ph	96%[c]	NR[b]
f	2,4-Cl$_2$-Ph	81%	48%	**m**	2-Cl-4-F-Ph	62%	NR[b]
g	2,5-Cl$_2$-Ph	82%	53%	**n**	2-Cl-5-CF_3-Ph	90%	80%

[a] Yields reported for products of ≥95% purity as determined by ^{1}H NMR. [b] NR = no reaction. [c] BZA excluded; product isolated in 90% purity.



Scheme 2 Synthesis of dimeric and 'mixed' pyrazolopyrimidines.

By heating under microwave irradiation we have accessed a small collection of these structurally more complex dimeric pyrazolopyrimidines **4a–n** as shown in Scheme 2. These dimerisation reactions are performed in batch mode in toluene in the presence of sub-stoichiometric amounts of potassium *tert*-butoxide, allowing access to the dimeric pyrazolopyrimidines in drastically reduced reaction times (30 min to 3.5 h) compared to conventional heating (20 h at 200 °C in methanol–ammonia).[16] Not all of the substrates prepared showed equal propensity for dimerisation under the specified reaction conditions. Certain pyrazoles gave no observable transformation while others furnished the desired dimer albeit sometimes accompanied by additional side products. Establishing a general workup for these often extremely insoluble mixtures has proven challenging. However, an effective method has been developed employing a 'catch-and-release' protocol with solid-supported sulfonic acid (Amberlyst™ 15) in DMF. The crude reaction mixtures are taken up in DMF and the desired products trapped onto Amberlyst™ 15 as their salts, enabling side products to be eluted by washing with DMF. Subsequent release by treatment with triethylamine–DMF allows isolation of clean (≥95% purity) products in reasonable yields (see Table 1, **4a–n**) after evaporation of solvents.

We have also begun to investigate the reactivity of these 5-amino-4-cyanopyrazole products with various aryl nitriles to access 'mixed' 4-aminopyrazolopyrimidine structures (Scheme 2, **5a–c**) under microwave conditions. Pyrazolopyrimidines **5a–c** (Table 2) were prepared by cycled microwave heating of neat reagents to access the desired products in excellent yields (88–94%) and purities (≥95%), and again, in drastically reduced reaction times (3 × 15 min) compared to previous syntheses using conventional heating (20 h at 200 °C in methanol–ammonia).[16]

In summary, this work describes a low-cost, practical approach to flow microwave chemistry. Our novel flow microwave device renders pyrazole synthesis easily scalable by simply including larger purification columns or by column-switching; we have found the existing setup capable of delivering over 250 g of material (Table 1, entry **3l**). This flow system also allows isolation of a range of substituted pyrazoles in excellent purity (≥95%) without the requirement for any traditional work-up or purification procedures, especially chromatography. The products of this flow process can in turn be dimerised or reacted with various nitriles under batch-mode microwave conditions to access potentially useful 4-aminopyrazolopyrimidines.

Table 2 Yields for the synthesis of 'mixed' pyrazolopyrimidines

Entry	R =	R′ =	Isolated yield[a]
5a	H		94%
5b	H	N	88%
5c	H	Br	91%

[a] Yields reported for products of ≥95% purity as determined by ^{1}H NMR.

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