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A scalable approach to diaminopyrazoles using flow chemistry

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ABSTRACT

This Letter reports on how the combination of microwave and continuous flow chemistry facilitated the convenient preparation of aminopyrazoles from commercial aryl halides. The method was applied to a variety of substrates with good to excellent yields and further extended toward the complete flow synthesis of 5,7-dimethyl-3-phenylpyrazolo[1,5-*a*]pyrimidin-2-amine.

The scale-up of single mode microwave reactions typically involves the use of batch reactors and continuous flow systems.[1,2] While useful, the use of large batch reactors for this purpose involves the transfer of optimized chemistry from smaller single-mode systems,[3] and may result in the need for re-optimization.[2] Continuous flow reactors offer many benefits including eliminating the need for re-optimization of time and temperature that is typically required for scale-up.[4] Further, their increased safety benefits (e.g. small amounts of reagents in the reactor, reaction scalability, and precise control of reaction variables)[5] attracted our interest. Several groups have demonstrated the utility of accelerating organic reactions in a continuous flow reactor with microwave irradiation;[6] however, our in-house observations have shown that these systems are limited in their heating capabilities due to the short resonance times when using small single mode microwaves.[7] To overcome this inadequate heating capability, lower flow rates can be employed to maximize resonance time in the microwave; however, this limits the overall throughput of the system. More recently, it has been reported that microwave processes can be scaled using continuous flow systems equipped with conventional heating modules.[8]

In our need to efficiently prepare multi-gram quantities of a variety of aminopyrazole and pyrazolopyrimidine derivatives we sought to develop a scalable process utilizing conventional chemistry methods and/or microwave. Our initial efforts were accompanied by undesired longer reaction protocols and the lack of scalability with single-mode microwave technology. To this end we initiated our own internal investigation into scaling up single-mode microwave processes using commercial meso-flow systems.

Fused heterocyclic derivatives such as pyrazolo[1,5-*a*]pyrimidin-2-amine **1** continue to play a major role in many 'small molecule' drug discovery programs and as a result pyrazolo[1,5-*a*]pyrimidine derivatives have recently been identified as kinase inhibitors and as CNS therapeutic agents.[9,10] Synthetic methodology for the generation of these scaffolds has been described previously.[11] In one approach, the diamino-pyrazole **3** was reacted with diketones **4** (or a corresponding equivalent such as **5)** under microwave irradiation to afford pyrazolo[1,5-*a*]pyrimidin-2-amines. Although the transformation of **3** to **1** proceeded with good yields, the microwave approach has limitations when larger quantities of material are required to prosecute structural–activity relationships (SAR) and in vivo evaluation of desirable analogs. We describe herein a convenient and scalable approach to substituted diamin-

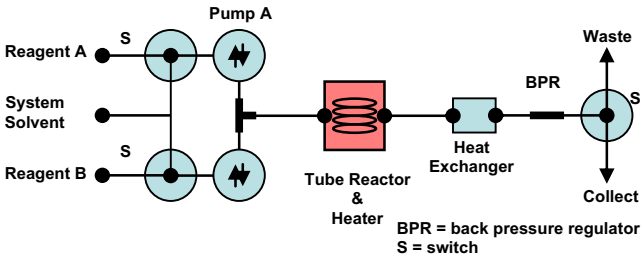

Figure 1. Schematic representation of the flow apparatus.

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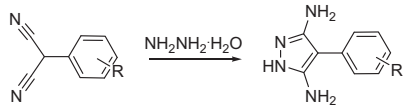
Table 1
Optimization of flow reaction conditions for the formation of diaminopyrazoles



Entry	Method	Solvent	R_t (min)	Temp (°C)	Equiv hydrazine hydrate	Conversion (%)
1	Microwave	EtOH	15	140	5	<20
2	Microwave	*n*BuOH	15	140	5	60
3	Flow	EtOH	14	140	5	100
4	Flow	EtOH	10	140	5	100
5	Flow	EtOH	5	140	5	99
6	Flow	EtOH	1	140	5	95
7	Flow	EtOH	5	140	2	96
8	Flow	EtOH	5	140	1	93
9	Flow	EtOH	10	140	1	97
10	Flow	EtOH	10	120	1	92
11	Flow	EtOH	10	100	1	84

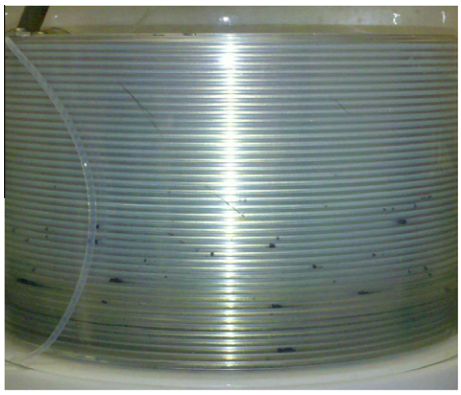
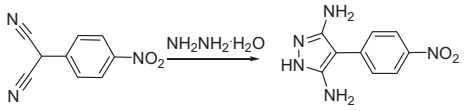


Figure 2. Dark precipitate observed in coils when 2-(4-nitrophenyl)malononitrile is treated with 1 equiv of hydrazine hydrate in ethanol as solvent.

Table 2
Optimization of solvent conditions for the formation of diaminopyrazoles using 2-(4-nitrophenyl)malononitrile and 1 equiv of hydrazine hydrate under microwave irradiation at 140 °C for 10 min and continuous flow at 140 °C for 10 min



Entry	Method	Solvent	Conversion (%)
1	Microwave	EtOH	50
2	Microwave	MeOH	24
3	Microwave	Dioxane	80
4	Microwave	1:0.5 MeOH/Dioxane	28
5	Microwave	1:1 MeOH/Dioxane	81
6	Microwave	0.75:1 MeOH/Dioxane	91
7	Microwave	0.5:1 MeOH/Dioxane	100
8	Flow	0.5:1 MeOH/Dioxane	100

opyrazoles and extensions toward the development of a continuous flow process of 5,7-dimethyl-3-phenylpyrazolo[1,5-*a*]pyridin-2-amine.

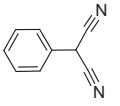
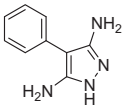
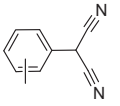
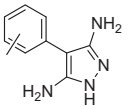
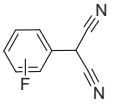
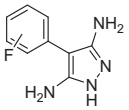
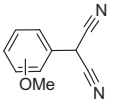
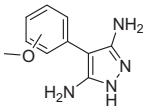
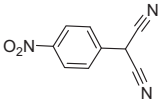
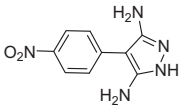
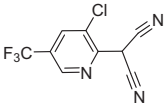
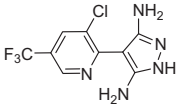
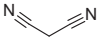
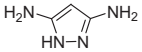
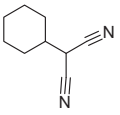
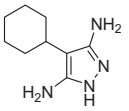
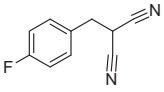
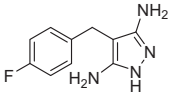
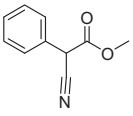
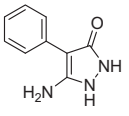
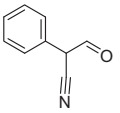
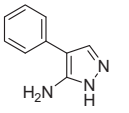
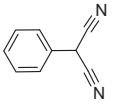
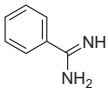
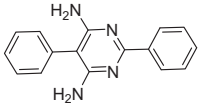
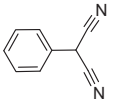
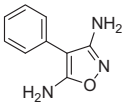
A commercially available continuous-flow unit, the Unqisis Flowsyn,[12] was used for all flow reactions. The reagents were pre-dissolved, pumped through a static T-mixer, and heated in a PTFE coil reactor (14 mL) or stainless steel coil reactor (20 mL) via an aluminum heating block. The exiting reaction mixture was passed through a heat exchanger followed by a 100 psi rated back-pressure regulator and collected. The configuration is depicted in Figure 1.

Our preliminary results when transferring optimized, single-mode batch microwave conditions to a continuous flow unit were comparable with only solvent manipulation (Table 1, entries 2 and 3). However, superior yields were obtained using continuous flow versus irradiation with a single-mode microwave (Table 1, entry 3). The equivalents of hydrazine hydrate were reduced without compromising the overall % conversion to product by increasing the overall resonance time to 10 min (Table 1, entries 5 and 9). When 2-(4-nitrophenyl)malononitrile was treated with 1 equiv of hydrazine hydrate in ethanol a dark precipitate was observed in coils (Fig. 2). A single-mode microwave was used to quickly scan solvents for reactivity and solubility (Table 2). We found that a 2:1 mixture of dioxane/methanol was the optimum solvent for conversion of 2-(4-nitrophenyl)malononitrile to the corresponding aminopyrazole (Table 2, entries 7 and 8).

We have found that a variety of aryl malononitriles in a 2:1 mixture of dioxane/methanol, are easily converted into their corresponding aminopyrazoles in good to excellent yield by treatment with 1 equiv of hydrazine hydrate in flow at 140 °C and a residence time of 10 min (Table 3). Interestingly aliphatic and benzyl malononitriles did not undergo cyclization and only starting material was obtained. However increasing the equivalents of hydrazine hydrate to five did provide the corresponding benzylpyrazole, albeit in 16% conversion (Table 3, entry 9). The continuous flow methodology can be extended to synthesize other heterocyclic compounds. Cyclization of methyl 2-cyano-2-phenylacetate and 3-oxo-2-phenylpropanenitrile with 1 equiv of hydrazine hydrate successfully afforded 5-amino-4-phenyl-1*H*-pyrazol-3(2*H*)-one and 4-phenyl-1*H*-pyrazol-5-amine, respectively (Table 3, entries 10 and 11). Furthermore, additional structural diversity can be achieved by reacting phenyl malononitrile with other nucleophiles, such as benzamidine (Table 3, entry 12). To our surprise, reacting hydroxylamine with 2-phenylmalononitrile did not yield the desired cyclized product (Table 3, entry 13).

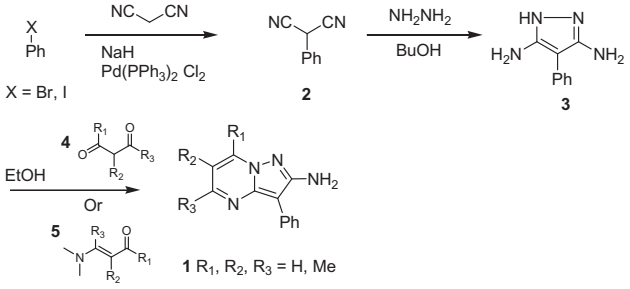
Additionally, we have expanded the scope of the flow process for the generation of a pyrazolo[1,5-*a*]pyrimidin-2-amine derivative (Scheme 1**)**. Our goal was to develop a two step continuous flow process that does not require a work-up step after formation of the aminopyrazole. To this end, the aminopyrazole along with excess acetylacetone were pumped into a second flow reactor to perform the next synthetic transformation. Our initial results indicated that this sequential flow process is amenable to the forma-

Table 3
Results from reacting various malononitriles with 1 equiv of nucleophile under continuous flow

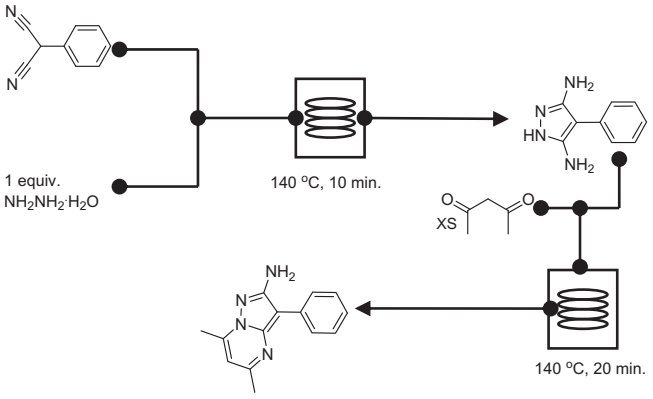
Entry	Starting material	Nucleophile	Product	Conversion (%) (isolated yield)
1		$NH_2NH_2{\cdot}H_2O$		100(94)
2		$NH_2NH_2{\cdot}H_2O$		*ortho*—97 (42) *meta*—100 (95) *para*—100 (94)
3		$NH_2NH_2{\cdot}H_2O$		*ortho*—100 (81) *meta*—100 (88) *para*—100 (97)
4		$NH_2NH_2{\cdot}H_2O$		*ortho*—89 (26) *meta*—100 (99) *para*—100 (92)
5		$NH_2NH_2{\cdot}H_2O$		100 (99)
6		$NH_2NH_2{\cdot}H_2O$		93 (33)
7		$NH_2NH_2{\cdot}H_2O$		0
8		$NH_2NH_2{\cdot}H_2O$		0
9		$NH_2NH_2{\cdot}H_2O$		0 16[a]
10		$NH_2NH_2{\cdot}H_2O$		96 (83)
11		$NH_2NH_2{\cdot}H_2O$		100 (85)
12				70 (62)
13		NH_2OH		0

[a] 5.0 equiv of hydrazine hydrate were used.

tion of both the aminopyrazole as well as 5,7-dimethyl-3-phenylpyrazolo[1,5-*a*]pyridin-2-amine (Scheme 2). The scope and limitations of these reactions are currently under detailed investigation and will be reported in due course.



Scheme 1. Methodology for the generation of diaminopyrazole and pyrazolo[1,5-*a*]pyrimidine derivatives.



Scheme 2. Flow synthesis of 5,7-dimethyl-3-phenylpyrazolo[1,5-*a*]pyrimidin-2-amine.

In summary, we have developed a process that allows the controlled continuous flow synthesis of aminopyrazoles in good to excellent yields. The versatility of this flow process can be further extended to the complete flow synthesis of 5,7-dimethyl-3-phenylpyrazolo[1,5-*a*]pyridin-2-amine.

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