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Nucleophilic Aromatic Substitution of Heterocycles Using a High-Temperature and High-Pressure Flow Reactor

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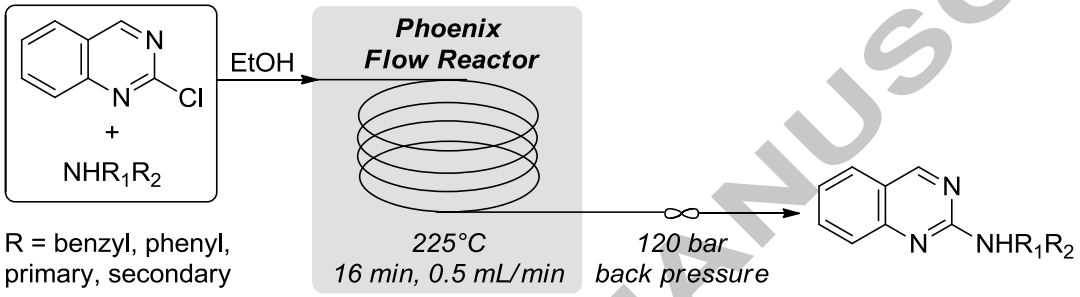


Abstract

We report herein a high-temperature and high-pressure continuous-flow protocol to carry out nucleophilic aromatic substitution (S_NAr) of heterocycles with nitrogen nucleophiles. Utilizing the Phoenix Flow Reactor™ in parallel with Design-of-Experiment software enabled rapid optimization of the S_NAr protocol. This protocol facilitated efficient synthesis of a broad range of 2-aminoquinazolines, and was extended to 2-aminoquinoxalines and 2-aminobenzimidazoles.

Introduction

Innovations in continuous-flow technology have stimulated both industrial and academic laboratories to approach organic chemistry with a new level of efficiency.[1] Technologies in continuous-flow synthesis offer opportunities to accelerate chemical transformations, maximize product outcome, automate synthesis, and scale-up with minimal optimization. Performing reactions under continuous-flow conditions offer many advantages over batch processes including increased safety, efficient heat transfer due to high surface-to-volume ratio in microchannels, and good control of reaction variables such as temperature and residence time. A particularly impactful feature of continuous-flow chemistry is process intensification, which is the ability to obtain higher product quality (purity, selectivity, and/or yield) of desired product rapidly by enhancing reaction parameters such as temperature and pressure.[1d]

The nucleophilic aromatic substitution (S_NAr) of heterocycles is a high-value, synthetically versatile reaction used widely in both the medicinal and process chemistry communities. Examples of S_NAr being run in flow exist in the literature using activated aryl halides under both traditional and microwave heating.[2] As a starting point towards a general approach for the direct amination of heterocycles in continuous-flow, we chose to investigate the S_NAr reaction of 2-

chloroquinazoline with nitrogen nucleophiles.[3] The resulting 2-aminopyrimidine-like structure is commonly found in pharmaceutical reagents, such as Rosuvastatin and Imatinib. Traditionally, amination of 2-chloroquinazoline requires conditions such as refluxing in 1-pentanol, isoamyl alcohol, or isopropyl alcohol between 3-20 hours,[4] heating ethanol or isopropyl alcohol in sealed tubes to 150 ˚C until reaction completion,[5]heating in *N*-methyl-2-pyrrolidine (NMP) to 110 ˚C for 24 hours,[6] or microwave-assisted heating in acetonitrile in the range of 120-180 ˚C or neat within 5-60 minutes.[3b, 7] For example, Henriksen and Sørensen reported a microwave-assisted synthesis of 2-benzylaminoquinazoline by heating a mixture of 2-chloroquinazoline, benzylamine, and potassium carbonate in acetonitrile to 170 ˚C for 50 minutes to obtain a 50% yield. Previous examples using flow reactors in S_NAr reactions of heterocycles with nitrogen nucleophiles include the preparation of 2-aminopyridines.[8] In this protocol, 2-chloropyridine and piperidine were optimized in NMP heated to 260 ˚C to afford the desired product in 20 minutes.[8a] Compared to conventional and microwave-assisted heating, high-temperature and high-pressure flow reactors significantly extend the spectrum of reaction conditions. It should be noted that most commercially-available microwave reactors have a temperature maximum of 250˚C, a pressure maximum of 2 MPa, and have scale-up limitations. Unlike microwave reactors, high-temperature and high-pressure flow reactors can execute synthesis in low-boiling solvents at temperatures above their boiling points without pressure and solvent limitations.[1c, 8b, 9] Adopting this technology into synthesis may minimize reaction time, enhance substrate scope, maxmize yield, and more importantly, provide a practical platform for reaction telescoping and automation.

In our investigations, we used a commercially available high-temperature and high-pressure Phoenix Flow Reactor™ from ThalesNano (Figure 1). This flow reactor was designed to achieve a temperature maximum of 450 ˚C, and a pressure maximum of 14 MPa when equipped with a proper back-pressure regulator. The reactor coil consists of a stainless steel tubing (1.0 mm diameter) of 8 mL volume, which is wrapped around a metallic housing tube and placed inside the Phoenix. Our flow platform consisted of four components: a JASCO PU-2085 plus HPLC pump, a JASCO BP-2080 Plus back pressure regulator, a manual injection loop, and the Phoenix Flow Reactor™. The HPLC pump allowed for a range of flow rates from 0.01 to 4.0 mL/min, and along with the variable back pressure regulator, a wide array of residence times, pressures and temperatures could readily be assessed.

In this report, we disclose a rapid optimization of the S_NAr reaction of 2-chloroquinazoline with benzylamine using the Phoenix Flow Reactor™ and statistical Design-of-Experiment (DoE) software. A comprehensive optimization of three parameters—temperature, pressure, and flow rate was executed to achieve a general protocol for the S_NAr reaction of 2-chloroquinazoline with benzylamine in continuous-flow. The optimal conditions were applied to a variety of nucleophiles such as primary and secondary amines, as well as anilines. Additional electrophilic heterocycles, such as 2-chloroquinoxaline and benzimidazole, were also investigated.

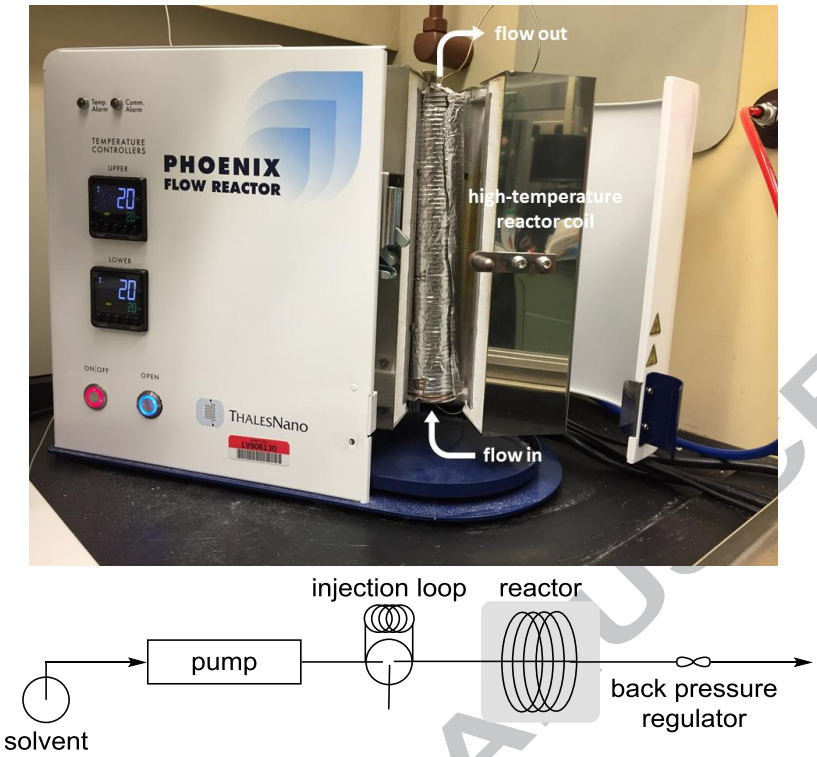
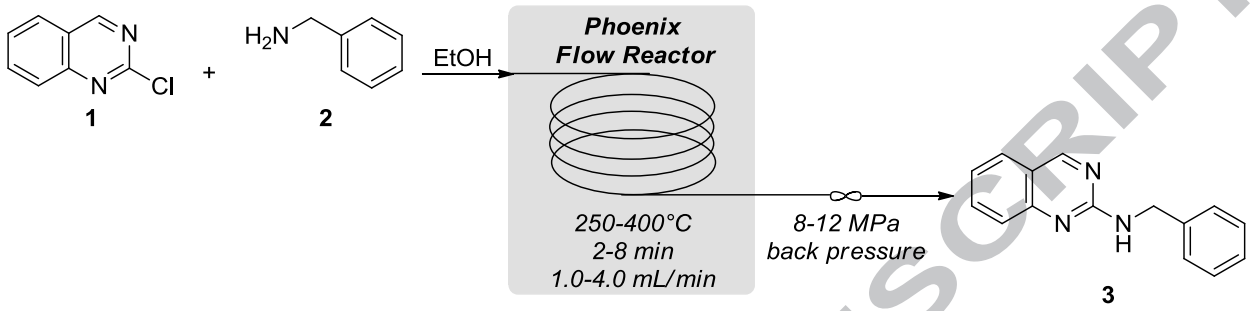


Figure 1. Schematic of the Phoenix Flow Reactor™ and flow platform.

Results and Discussion

A continuous-flow S_NAr of 2-chloroquinazoline with benzylamine was investigated using DoE (Table 1). Using Stat-Ease Design Expert 7, a series of reactions were designed and subsequently carried out using the Phoenix. All reactions were analyzed using HPLC/MS, and the resulting data was input in the DoE software. In this investigation, three parameters were optimized, which included a range of temperatures, pressures, and flow rates. Ethanol was chosen as the solvent of choice due to its green chemistry nature and its wide use in S_NAr chemistry. Contour plots were generated using the Design Expert software from the acquired data. These plots allowed the relationship between temperature, pressure, and flow rate on reaction outcome could be visualized (Figure 2). In Figure 2a, the results indicated that lower temperatures and higher pressures gave a higher percent of desired product **3**. While conversions were high in all cases, significant decomposition and side-reactions were observed at temperatures of 325 ˚C and above. More evident in Table 1, decomposition was observed by LC at 400 ˚C, giving a lower percentage of product. In comparison, reactions performed at 250 ˚C afforded clean conversions from **1** to **3**.

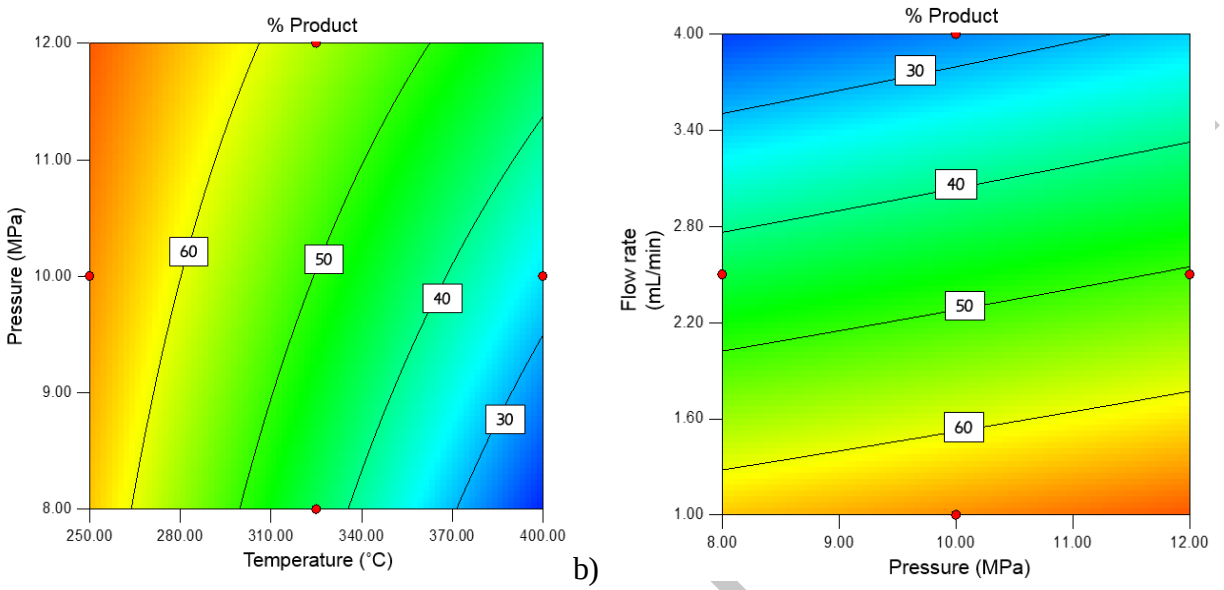
Table 1. DoE optimization of continuous-flow S_NAr between 2-chloroquinazoline and benzylamine.



temperature (˚C)	pressure (MPa)	flow rate (mL/min)	product (%UV)[a]
250	8	2.5	46
250	10	4.0	29
250	10	1.0	75
250	12	2.5	42
325	8	1.0	37
325	8	4.0	20
325	10	2.5	34[b]
325	12	1.0	62
325	12	4.0	47
400	8	2.5	25
400	10	1.0	37
400	10	4.0	27
400	12	2.5	37

[a] Percent product by analytical HPLC.
[b] Center point, average of 4 runs.

Figure 2. DoE contour plots for a) the relationship between temperature and pressure at 1.0 mL/min and b) the relationship between flow rate and pressure at 250 ˚C.



Reaction temperatures less than 250 ˚C were deemed optimal for the S_NAr. In Figure 2b, the results depicted higher conversions of **3** when a slower flow rate was employed. Accordingly, increasing the residence time of the reaction mixture in the flow reactor increased product yield. Based on data, optimal conditions were predicted to require flow reactor temperature of 225 ˚C or lower, pressure of 12 MPa, and flow rate of 0.5 mL/min (equivalent to a 16 minute residence time) as shown in Figure 3. The suggested conditions were used, and a complete conversion from **1** to **3** was observed by analytical HPLC that led to an isolated yield of 97%. Under these optimized conditions, a range of nucleophiles was screened to demonstrate the scope of S_NAr (Table 2). The S_NAr of 2-chloroquinazoline with primary amines gave desired products in excellent yields (example **4-8**, Table 2), while secondary amines gave desired products in modest to high yields (examples **10-14**). Lower yielding examples such as example **9** are presumably due to that fact the hydrochloride salt was used as the monomer. Additionally, low molecular weight amines such as methylamine could readily be used in flow to afford the methylamine adduct **4** in high yield (Table 2). Monomers such as imidazole and benzyl amines could also be used, giving the resultant product in modest yields (examples 15-18). We examined several anilines including both electron-poor and electron-rich substituted anilines and heterocycles, and unfortunately, only observed modest yield (example **19-21**, Table 2). Further optimization using DoE of weak nucleophiles, as in the case of anilines would be required to increase the yield and scope. Next, S_NAr of related heterocycles such as 2-chloroquinoxaline and benzimidazole were investigated. In Table 3, S_NAr reactions of either 2-chloroquinoxaline or benzimidazole with primary and secondary amines afforded the desired products in modest yields. Further optimization could be carried out on these substrates to increase their isolated yields. It is also worth noting that no ethanol adducts were observed while running these reactions.

Figure 3. DoE-suggested optimal reaction condition and isolated yield of **3**.

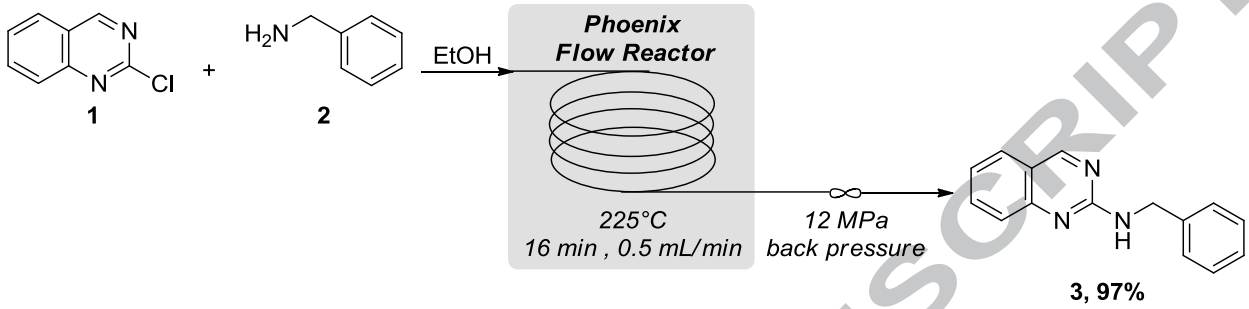
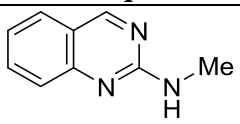
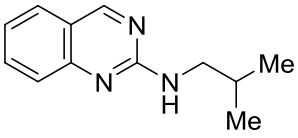
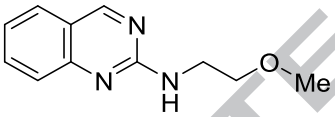
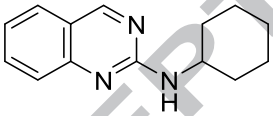
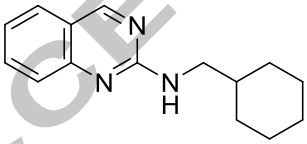
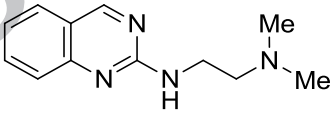
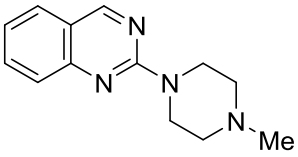
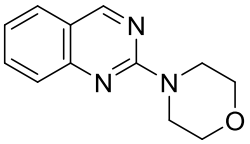
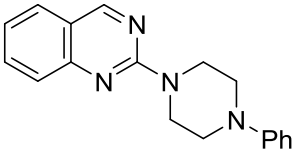
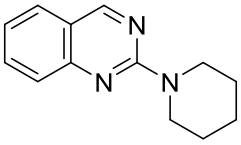
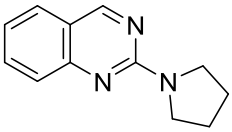
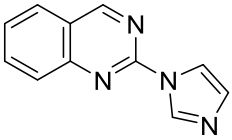
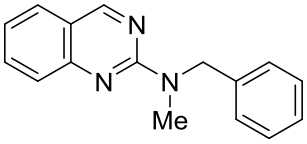
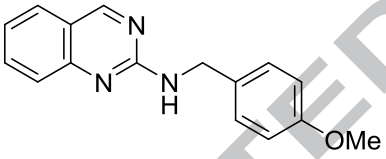
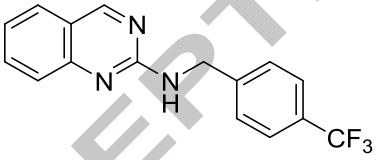
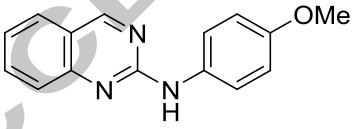
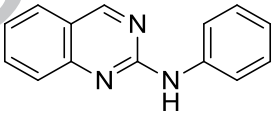
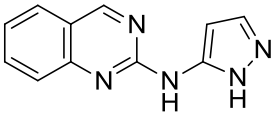


Table 2. Scope for the continuous-flow S_NAr of **1** with nitrogen nucleophiles.[a-c]

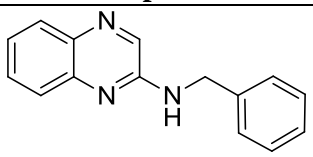
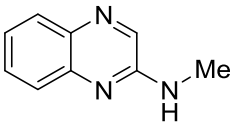
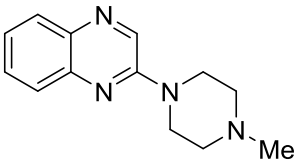
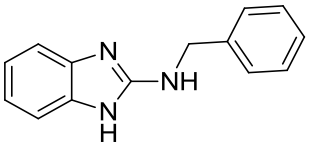
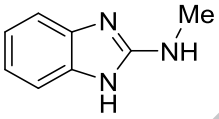
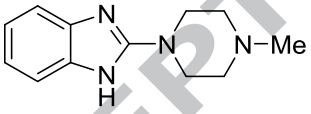
	2-aminoquinazoline product	isolated yield (%)
4		73
5		92
6		92
7		82
8		90
9		38
10		71

11		79
12		66
13		64
14		73
15		50
16		68
17		66
18		60
19		63
20		39
21		27

[a]All reactions were carried out in ethanol. The reaction stoichiometry was 0.063 mmol of 2-chloroquinazoline and 0.125 mmol of amines, which were used as 0.25 M solutions. In a 1-dram

vial, 0.25 mL of 2-chloroquinazoline and 0.5 mL of amine were premixed. The reaction mixture was introduced into the Phoenix Flow Reactor™ via a 1mL injection loop.
[b]Flow rate of 0.5 mL/min, residence time of 16 min, 225 ˚C, and 12 MPa.
[c]Compounds were purified by a mass triggered, reverse phase HPLC method.

Table 3. Additional evaluation of reaction scope using 2-chloroquinoxaline and 2-chlorobenzimidazole.[a-c]

	product	isolated yield (%)
22		42
23		59
24		60
25		78
26		73
27		65

[a]All reactions were carried out in ethanol. The reaction stoichiometry was 0.063 mmol of 2-chloroquinoxaline or benzimidazole and 0.125 mmol of amines, which were used as 0.25 M solutions. In a 1-dram vial, 0.25 mL of 2-chloroquinoxaline and 0.5 mL of amine were premixed. The reaction mixture was introduced into the Phoenix Flow Reactor™ via a 1mL injection loop.
[b]Flow rate of 0.5 mL/min, residence time of 16 min, 225 ˚C, and 12 MPa.
[c]Compounds were purified by a mass triggered, reverse phase HPLC method.

Conclusion

In summary, we have demonstrated the use of a simple high-temperature and high-pressure flow reactor to carry out S_NAr reactions of heterocycles with a broad range of nitrogen nucleophiles. This flow platform was used alongside with DoE analysis to establish an optimized synthesis of amino-substituted heterocycles in an efficient manner. We find that this straightforward and easily assembled flow platform is amenable for the preparation of libraries, automation, and the scale-up of compound synthesis. More importantly, this protocol is not only an alternative

method to microwave-assisted heating, but offers the advantages of using green solvents at elevated temperatures, shortened reaction times, as well as the prospect of continuous-flow scale-up. Additionally, we are continuing to investigate high-temperature chemistry with the hope of discovering new, fast and clean methodologies that are enabled by running reactions close to their transition state temperature.

Disclosures

All authors are employees or former employees of AbbVie. This study was sponsored by AbbVie. AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the manuscript.

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Graphical Abstract