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High-Temperature Boc Deprotection in Flow and Its Application in Multistep Reaction Sequences

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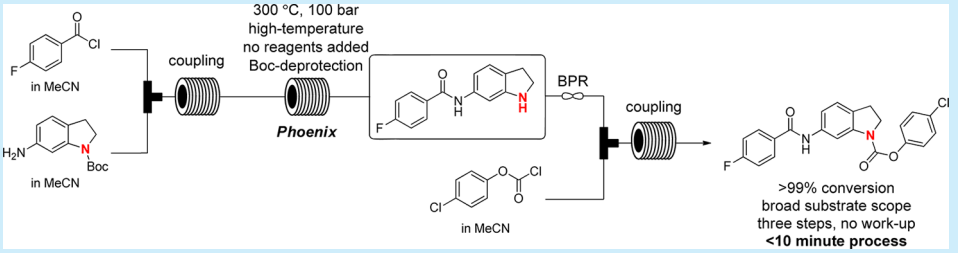
Supporting Information



ABSTRACT: A simplified Boc deprotection using a high-temperature flow reactor is described. The system afforded the qualitative yield of a wide variety of deprotected substrates within minutes using acetonitrile as the solvent and without the use of acidic conditions or additional workups. Highly efficient, multistep reaction sequences in flow are also demonstrated wherein no extraction or isolation was required between steps.

Over the past decade, an array of new technologies has been developed to enable novel chemical transformations within organic synthesis.[1] The major benefits of these technologies include increased speed, improved efficiency via simplified purification and workup, as well as enhanced safety profiles. Polymer-supported reagents/catalysts,[2] microwave technology,[3] continuous flow synthesis,[4,5] and flow photochemistry[6] are examples of these tools, which have been widely used in both academic and industrial settings to increase efficiency and to broaden the scope of chemistry. New flow reactors are constantly being developed due to their ability to perform safer, more efficient, and selective chemical transformations as well as their ability to couple multiple reaction steps into one continuous sequence. Many advantages associated with flow reactors are attributed to large surface area-to-volume ratios that allow rapid heat transfer and efficient mixing, enabling reactions to be performed in a manner that could not be readily obtained in batch. Forcing conditions, such as elevated temperatures and pressures, can also be readily accessed using various heat sources, such as gas chromatograph ovens and hot plates, and back-pressure regulators. This enables solvents to be used well beyond their boiling points, thus, opening up the possibility of using green solvents to replace traditional high-boiling solvents, such as diphenyl ether, xylenes, or diglyme.

Having used high-temperature flow chemistry in 1,2,4-oxadiazole and 1,2,4-triazole formations (175−225 °C),[7] as well as nucleophilic aromatic substitutions (225 °C),[8] we began to evaluate chemistry in a reaction space outside of what is typically run in a chemistry laboratory (i.e., >250 °C). The ability to access new analogues in an efficient manner is of utmost importance in the pharmaceutical industry. For this reason, we sought to accelerate reaction rates by considering the Arrhenius equation and running the reactions at temperatures that would allow a greater fraction of molecules to reach the activation energy necessary for the transformation. As commercially available microwaves have temperature, pressure, and solvent limitations, we sought to use a flow reactor that could handle more demanding conditions. Thus, we opted to evaluate the high-temperature and high-pressure Phoenix flow reactor from ThalesNano (Figure 1). This flow system is capable of reaching a maximum temperature of 450 °C and a pressure maximum of 140 bar when equipped with a variable back-pressure regulator (BPR).[9]

In medicinal chemistry, *tert*-butyloxycarbonyl (Boc) is by far the most commonly used protecting group for amines. Subsequently, the deprotection of Boc groups accounts for >50% of amine deprotections in the literature.[10] We chose to investigate the thermal deprotection of Boc groups as this could serve as an alternative to the widely used acidic methods. While a few thermolytic deprotections have been reported in the literature, these reactions are optimal when run on small scale due to the high temperature requirements and vigorous off-gassing of the reaction.[11] A thermal deprotection would have advantages over traditional techniques where there is functional group incompatibility or workup complications; it would also remove the need for expensive reagents or the use of materials in vast excess. Compounds also would be isolated as the free amine, not salts. Additionally, using a deprotection with no added

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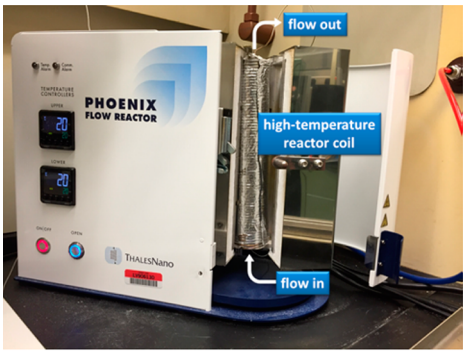
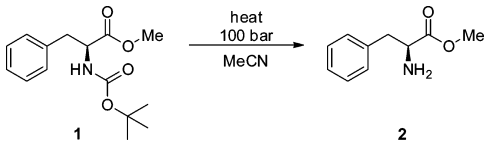


Figure 1. Schematic of the high-temperature Phoenix flow reactor.

Table 1. Thermal Deprotection of Boc-Phe-OMe 1



1 2

entry	temp (°C)	flow rate (mL/min)	residence time (min)	% conv (UV)	% product **2** (MS ion count)
1	200	1.0	8.0	0	
2	250	1.0	8.0	49	
3	300	1.0	8.0	>99	52
4	300	2.0	4.0	>99	68
5	300	3.0	2.7	>99	77
6	300	4.0	2.0	>99	80
7[a]	200		8.0	0	

[a]Sample run in Biotage microwave at 200 °C for 8 min.

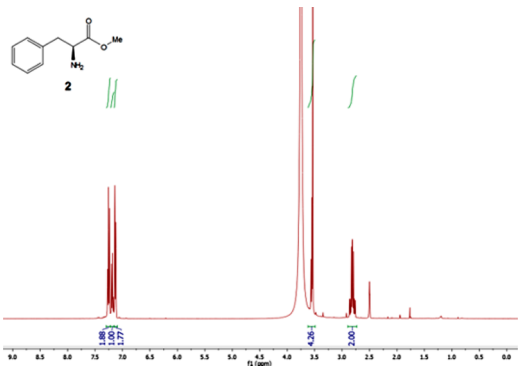
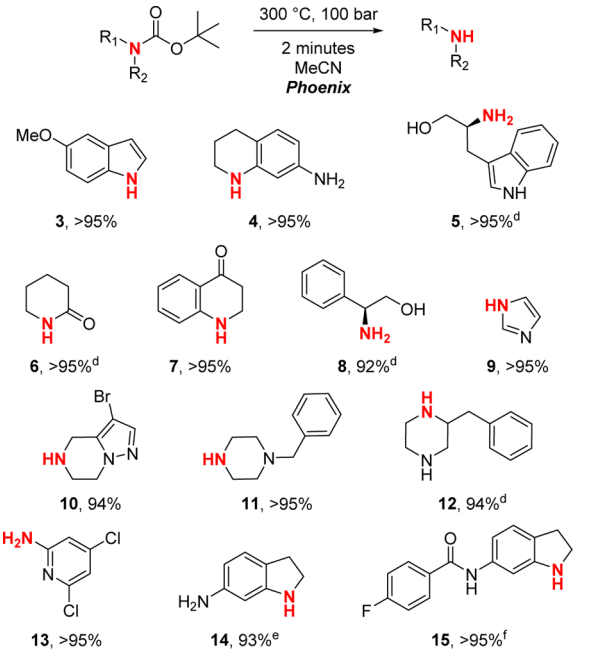


Figure 2. Crude ^{1}H NMR spectra of **2**.

reagents would enable multistep reaction sequences to be run in flow without any in-line extractions or workups.

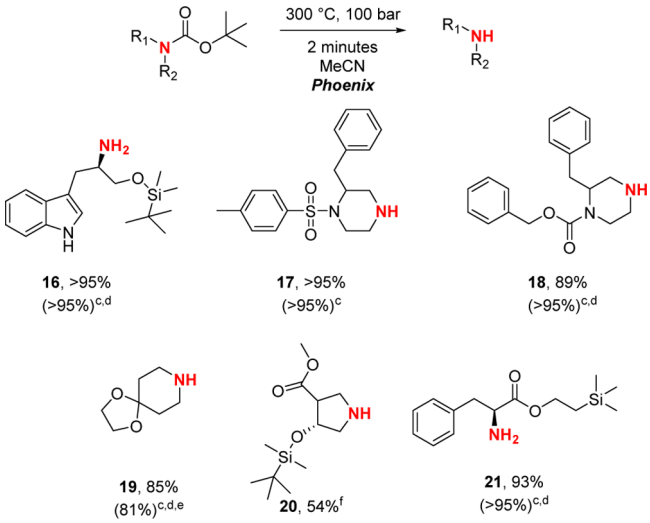
Initially, we screened a range of temperatures for the deprotection of Boc-Phe-OMe **1** using acetonitrile as the solvent (Table 1). Starting at 200 °C for 8 min (Table 1, entry 1) afforded no conversion to the desired product. However, increasing the temperature up to 300 °C gave a complete conversion to the deprotected amine (Table 1, entry 3). These reactions were

Scheme 1. Substrate Scope for the High-Temperature Boc Deprotection in Flow[a−c]



[a]Isolated yield after solvent removal. [b]The bold red nitrogen indicates the amine that has been deprotected. [c]Reactions run at 0.1 M substrate unless otherwise noted. [d]Reactions run at 0.2 M substrate. [e]Approximately 15% indole was observed after dry-down. [f]Approximately 10% indole was observed after dry-down.

Scheme 2. Substrate Scope for Bis-protected Compounds[a,b]



[a]Isolated yield after solvent removal. [b]The bold red nitrogen indicates the amine that has been deprotected. [c]Isolated yield after treatment with TFA. [d]A mixture of products was seen by ^{1}H NMR. [e]10% piperdin-4-one was seen by ^{1}H NMR. [f]Isolated yield after purification using normal-phase chromatography.

analyzed using HPLC/MS. While the UV trace showed a clean conversion to product at 300 °C, the mass trace showed significantly more peaks, indicating that there was some decomposition occurring when the reaction was exposed to high temperatures for an extended period of time. For this reason, the residence time was shortened by increasing the flow rate of the reactor (Table 1, entries 3−6). To our surprise, complete

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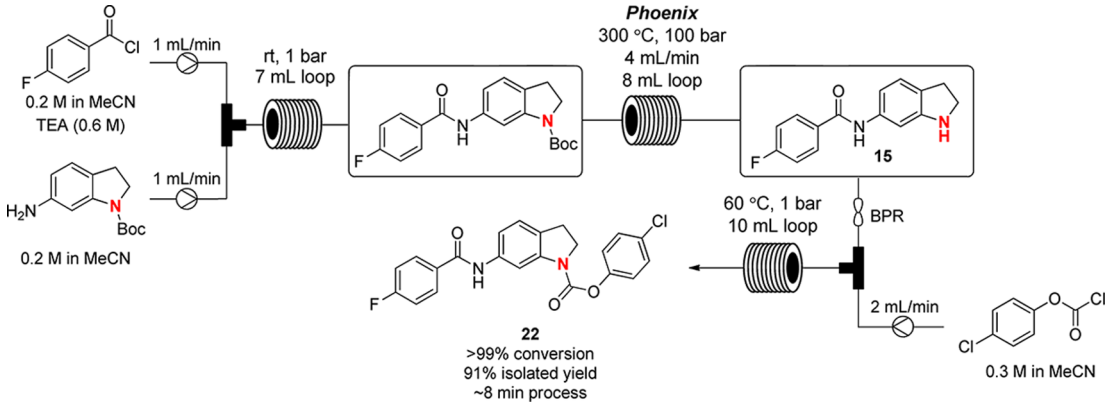
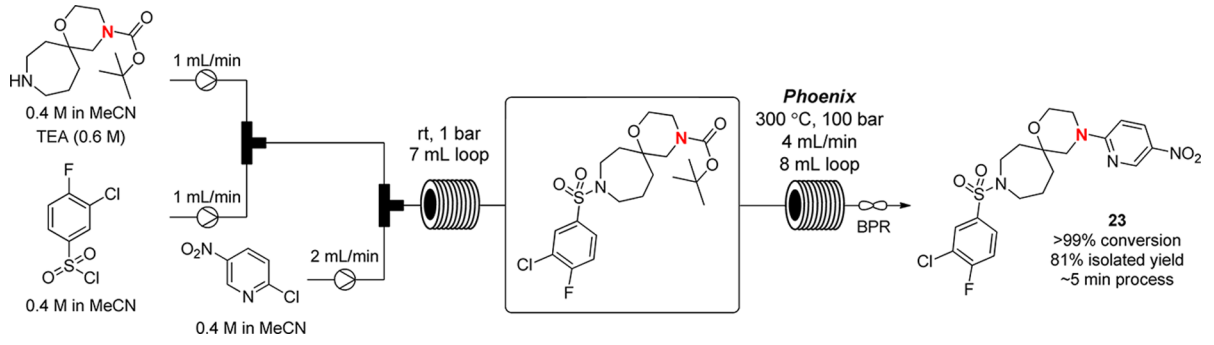
Scheme 3. Acylation−Deprotection−Carbamate Formation Sequence Using an in-Line High-Temperature Boc Deprotection



Scheme 4. Sulfonylation−Deprotection−S_NAr sequence Using an in-Line High-Temperature Boc Deprotection



conversion was still observed using the system's maximum flow rate of 4.0 mL/min (Table 1, entry 6), and the mass trace showed a much higher percentage of the desired product. It should also be noted that running the deprotection in the microwave at 200 °C (the maximum temperature for acetonitrile) gave no conversion to the amine **2** (Table 1, entry 7).

The reaction was concentrated, and a crude NMR was taken of **2** (Figure 2). The resulting ^{1}H and ^{13}C NMR spectra were >95% pure with very minor baseline peaks in the ^{1}H NMR spectrum. This indicates that subjecting the material to the high-temperature flow reactor was not causing an appreciable amount of decomposition and that no additional workup was required to obtain the final material. Chiral chromatography proved that the stereochemistry of the amine is retained during the process (see the Supporting Information). Additional green solvents, such as ethanol, methanol, tetrahydrofuran, and 2-methyltetrahydrofuran, were also screened but showed impure crude NMR spectra and LC/MS traces. In the case of ethanol, transesterification was observed. The byproducts formed when other solvents were tested were not characterized.

With the optimized conditions in hand, a series of Boc-protected amines were deprotected using the flow reactor (Scheme 1). From the substrate scope, it can be seen that this is a general methodology for deprotecting a variety of amines. To illustrate this, a series of primary and secondary amines were quantitatively deprotected. Indole **3** and anilines **4**, **7**, **14**, and **15** were also readily deprotected, as were lactam **6** and imidazole **9**. A number of functional groups were also tolerated, including alcohols, amides, esters, aryl halides, ketones, and diamines.[12] All reported substrates achieved complete conversion, and only concentration of the reaction solvent was required to obtain the product. Of note is the fact that all of the reactions were completed using only a 2 min residence time. In the case of amines **14** and **15**, oxidation to form the indole was observed after the reaction had been concentrated. As the crude LC/MS of the samples prior to drying indicated no trace of the indole, it was determined that this elimination was not due to the flow reaction but the stability of the products to oxidation.

Another set of substrates, which contained additional protecting groups, were synthesized and subjected to the high-temperature flow deprotection (Scheme 2). Protecting groups, such as TBS, tosyl, and CBz, were not affected during the deprotection and gave nearly qualitative yields of the desired amine. Acetal **19** was more sensitive to the conditions but still gave a good yield of the product. It is worth noting that the Boc groups can selectively be cleaved using this protocol in the presence of other acid-labile functional groups. When the substrates in Scheme 2 are treated with TFA, often a mixture of products are seen in the crude NMR as is seen in the case of compounds **16**, **18**, **19**, and **21**. While the Boc group has been completely cleaved, substrates deprotected under acidic conditions showed impure crude NMR spectra (see the Supporting Information). The ability to selectively cleave a Boc group using this acid-free, thermal method emphasizes its potential impact on synthesis.

The ability to functionalize scaffolds orthogonally to map out structure−activity relationship information efficiently is of crucial importance to medicinal chemistry projects. In this context, having validated the deprotection protocol on multiple substrates, we sought to use the Phoenix in a multistep reaction sequence in flow, in which one of the reaction steps is a Boc deprotection. The advantages of using the high-temperature deprotection include avoiding the use of in-line extractors to work up the reaction steps and/or the use of excess reagents, such as TFA or HCl. We first examined an acylation−deprotection−carbamate formation

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reaction sequence (Scheme 3). A stream of acid chloride was mixed with a protected diamine at room temperature and ambient pressure to form the amide. The reaction stream was flowed into an injection loop and injected into the Phoenix to deprotect the indoline to give intermediate **15**. After exiting the Phoenix, the reaction solution was mixed with a stream of 4-chlorophenyl chloroformate and heated to 60 °C for 100 s. The entire synthesis took ~8 min to complete, and following concentration of the collected solution and purification on normal-phase silica, **22** was obtained in 91% isolated yield. It is also worth noting that intermediate **15** could be immediately coupled in this sequence, which prevents the indole formation that was observed if the reaction mixture containing **15** was dried (Scheme 1, footnote f).

A sulfonylation−deprotection−SNAr reaction sequence was also carried out using the Phoenix (Scheme 4). In this sequence, a protected diamine was sulfonylated and mixed with an aryl halide at room temperature and ambient pressure. The reaction stream was once again flowed into an injection loop and loaded into the Phoenix reactor set to 300 °C and 100 bar. In this case, the deprotected amine was immediately coupled to the aryl halide via a high-temperature S_NAr to give **23** in 81% yield following purification by normal-phase flash chromatography.

Both processes shown in Schemes 3 and 4 are high-throughput methods, capable of generating grams of material in a matter of minutes. Coupling−deprotection−coupling reaction sequences are highly prevalent in the medicinal chemistry community, and the overall process is greatly telescoped using this methodology. In the cases described, where the concentration of the substrate was not optimized, the system generates 0.4 mmol of product per minute, indicating that these procedures are suitable for both small-scale medicinal chemistry efforts, as well as reaction scale-up.

The mechanism of the flow-mediated Boc deprotection appears to be thermolytic, as the outlet of the reactor is pH neutral when only acetonitrile is flushed through the system. As expected, the pH of the reaction solution is slightly basic (pH ~8) due to the pK_a of the products eluting from the system.

In conclusion, we have developed a general, high-temperature Boc deprotection in flow using the Phoenix flow reactor.[13] Removal of the solvent is the only workup required, and subsequent reactions can be carried out without purification or concentration. The protocol demonstrates a high functional group tolerance and can be readily used with substrates that have multiple protecting groups. We also demonstrate the utility of the Boc deprotection in two different multistep reaction sequences, showing how diverse molecular structures can rapidly be synthesized without any intermediate extractions or purifications within a matter of minutes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00378.

Experimental procedures and full characterization (^{1}H and ^{13}C NMR data and spectra, MS) (PDF)

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Notes

The authors declare no competing financial interest.

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(9) Our reaction coil consisted of an 8 mL stainless steel loop (1.0 mm diameter) wrapped around a metallic housing 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 has a range of flow rates from 0.01 to 4.0 mL/min, and the variable back pressure regulator has a maximum pressure of 140 bar.

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(12) Reactions were run at either 0.1 or 0.2 M in acetonitrile, but it was observed that higher concentrations could also be used without further optimization. Using a 1.0 M solution of Boc-Phe-OMe gave a complete conversion but resulted in far more vigorous off-gassing at the reactor outlet.

(13) When taking into account solvent recycling, no waste is generated during this process as no reagents or workups are required. For this reason, E-factors for this flow process would be much lower compared to traditional batch deprotection techniques.

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