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Article

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Deprotection of *N*-Boc Groups Under Continuous Flow High Temperature Conditions

Bryan Li,* Ruizhi Li,* Peter Dorff, J. Christopher McWilliams, Robert M. Guinn, Steven M. Guinness, Lu Han, Ke Wang, and Shu Yu

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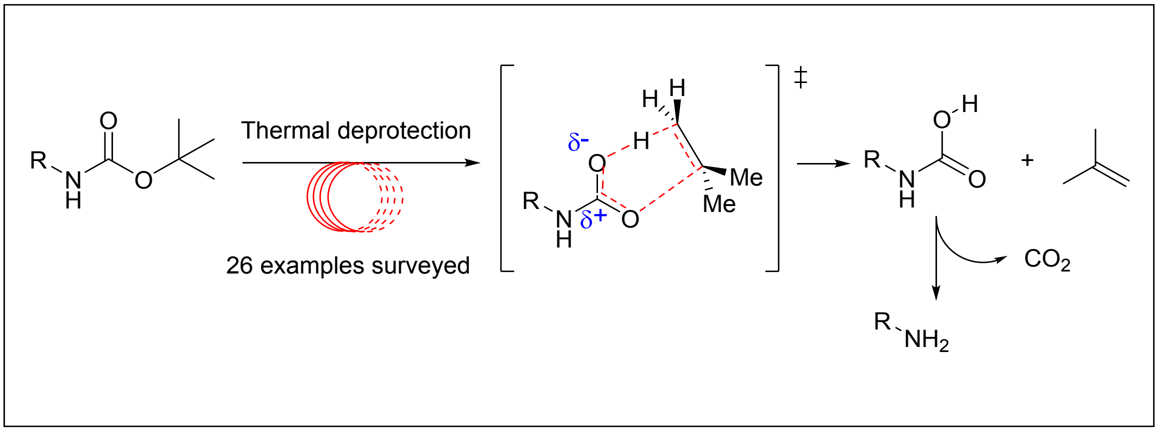
Abstract: The scope of the thermolytic, *N*-Boc deprotection was studied on twenty six compounds from the Pfizer compound library, representing a diverse set of structural moieties. Among these compounds, 12 substrates resulted in clean (≥ 95% product) deprotection, and an additional 3 compounds gave ≥ 90% product. The thermal de-Boc conditions were found to be compatible with large number of functional groups. A combination of computational modeling, statistical analysis, and kinetic model fitting, was used to support an initial, slow and concerted proton transfer with release of isobutylene, followed by a rapid decarboxylation. A strong correlation was found to exist between the electrophilicity of the *N*-Boc carbonyl group and the reaction rate.

Keywords: Green chemistry, amine, carbamate, de-Boc, continuous flow, and modeling.

Table of Contents Graphic



1. Introduction

Deprotection of *N*-Boc groups (de-Boc) is one of the most often encountered reactions in pharmaceutical research and development.[1] Deprotection thermally with no added reagents is advantageous over traditional acid-catalyzed techniques for compounds that have functional group incompatibilities or workup complications, as the products from the thermal deprotection are free amines that can be directly carried into the next reaction step reaction without salt breaks, extractions or isolations (e.g. amidation or S_NAr).[2] Recently published literature indicated continuous flow thermal conditions are compatible with a variety of functional groups,[3] and a kilogram scale continuous de-Boc process at 270 °C demonstrated by Eli Lilly researchers marked a milestone for its application in the pharmaceutical industry.[4] In a survey of reactions executed in the Pfizer Groton scale up facility in the past 30 months, we found *N*-Boc deprotections and amidations ranked among the most often executed reactions. The results coincided with Brown and Boström's findings[5] in which the top three most frequently occurring reactions were amide bond formation, S_NAr reactions, and *N*-Boc protection/deprotection. As acid-mediated de-Boc typically follows either an extractive aqueous workup and isolation or a salt break before the amidation step, it becomes evident that continuous thermal deprotection conditions can enhance speed and productivity by eliminating several unit operations in a large scale, production setting. Thus, we set out to investigate continuous thermolytic deprotections of *N*-Boc over a broad range of intermediates in our past and current portfolio projects.

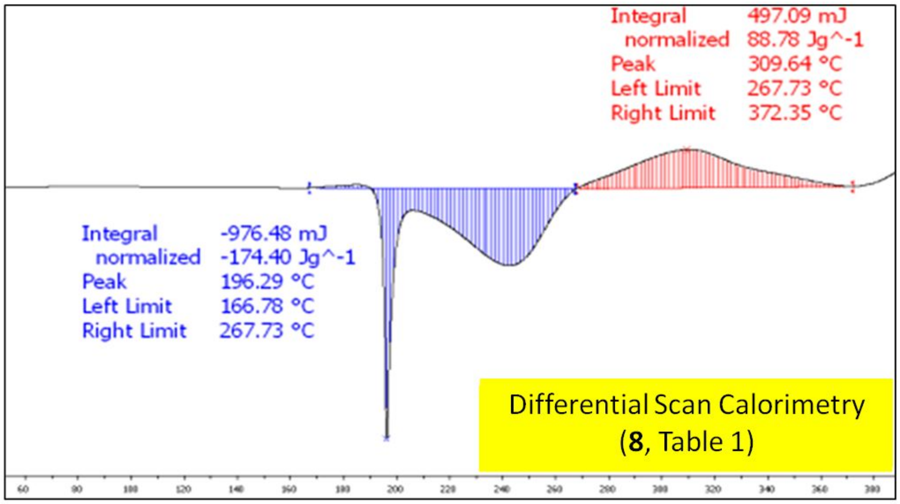
2. Results and Discussion

Since the thermal de-Boc reaction involves high temperature and pressure, a PFR design was an obvious choice as it can readily handle high temperature and pressure.[4,6] Several PFR reaction screen instruments are commercially available. As stable and homogenous feed and effluent streams are critical for the development of continuous processes in plug flow reactors (PFR),[7] solubility screening was the first step for this study. In considering the selection of solvents,[8] alcohols were excluded as preliminary studies indicated formation of carbamate impurities, RNHC(O)OR$_1$ (R$_1$ = Me, Et, or *i*Pr from the alcoholic solvents), under high temperature conditions. Lilly researchers found the use of methanol led to significant impurity formation in thermal de-Boc under 270 °C. By changing the solvent system to THF/MeOH mixture, the impurity was suppressed.[4] In our hands, we had also observed the use of t-amyl alcohol as solvent could lead a t-amyl carbamate impurity Likewise, acetate esters (EtOAc, *i*PrOAc) were not suitable as they would react with amine products to give acetamide byproducts.[9] Acetonitrile is not preferred as it is known to have high vapor pressure; acetonitrile has a vapor pressure of 4455 kPa (646 psi) at 540 K (266.8 °C), and its thermal decomposition begins at ~536 K (262.6 °C).[10] While the high vapor pressure of acetonitrile can be handled in a flow reactor, the potential thermal decomposition under the high temperature presents a process safety hazard. Toluene did not offer good solubility for many substrates. Thus, the list of solvents was narrowed down to tetrahydrofuran, anisole, and 2,2,2-trifluoroethanol (TFE[11]); TFE is known to facilitate de-Boc reactions[12] and also displayed unique solubilizing ability for many of the substrates studied. Water was commonly used as an additive to increase the solubility and accelerate the reaction.[13] The substrates we selected encompassed both early and late stage research portfolio intermediates in API syntheses. Thus, they were representative of broad spectra of structural complexity and diversity.

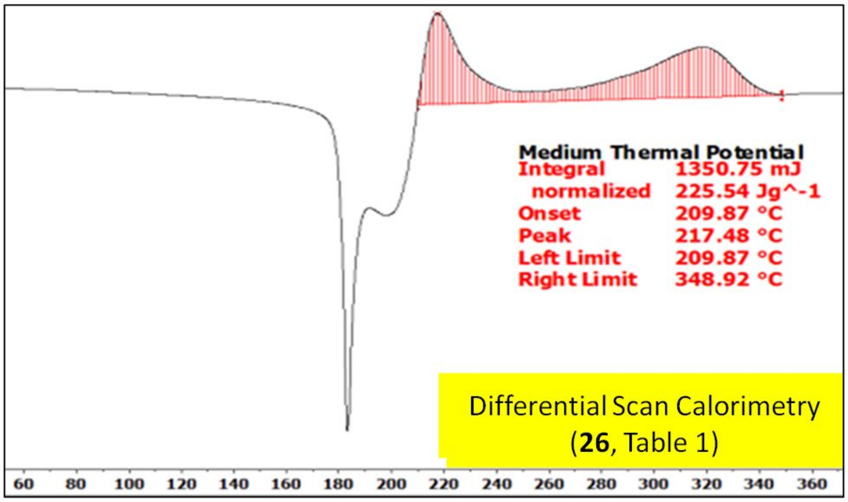
2.1 Residence time vs. temperature.

In the next phase, we sought to identify the temperature range of thermal de-Boc with an objective of limiting the nominal residence time (τ, herein defined as reaction coil volume/feed flow rate) to ≤60 min.[14]. We were hopeful that common tools used to profile exotherms and endotherms when compounds are subjected to progressively increasing heat, Differential Scan Calorimetry (DSC) and Thermal Screening Unit (TSU), could be used as efficient predictive tools for thermolytic de-Boc, as one would anticipate an exothermic event at the temperature where de-Boc begins. While exotherms were typically observed at the DSC onset temperatures, as exemplified by **26 (Figure 1**), wherein the DSC onset at 209.9 °C appeared to suggest the thermal de-Boc event, the data did not offer a clear indication for many of the substrates. For example, the DSC onset for **8** was at 267.7 °C, but the thermal de-Boc was observed at the lower temperature of 225 °C (coinciding with an endotherm event spanning from 166.8 °C to 267.7 °C). It was also a surprise that Thermal Screening Unit did not detect a significant exotherm for any of the compounds studied. Our initial screen in the Uniqsis reactor suggested that thermolysis started to occur at 200 ~ 230 °C for most of the substrates (except for two substrates *vide infra*), this temperature range is substantially lower than in previous reports under continuous flow,[2,4] and is considered operationally more achievable in our current scale-up PFR platform.[15]

Figure 1. Differential Scan Calorimetry (DSC) for **8** and **26** (Table 1)



Differential Scan Calorimetry (**8**, Table 1)



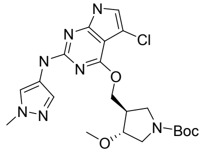
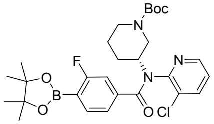
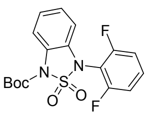
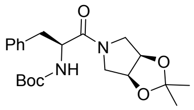
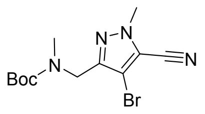
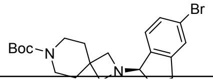
Differential Scan Calorimetry (**26**, Table 1)

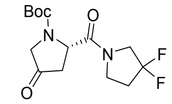
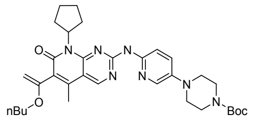
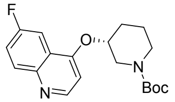
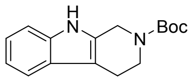
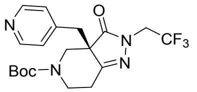
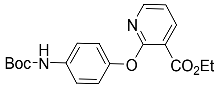
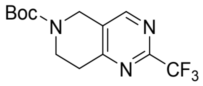
The selected compounds were subjected to thermal de-Boc screens and the results are summarized in **Table 1**. A nominal residence time of 10 min at 225 °C was initially tested for thermal de-Boc feasibility assessment.[16] Five compounds (entries 1, 2, 3, 17 and 19, **Table 1**) were immediately found not suitable for thermolytic de-Boc as decomposition occurred at the temperature required to effect de-Boc. Those showing reasonably clean reaction profiles but with incomplete conversion (≤ 98%) were further examined after a 60 min residence time at 225 °C. Out of 26 compounds studied, 12 of them gave reasonably clean (≥ 95% product) deprotection, and an additional three substrates gave ≥ 90% product. While some compounds gave fairly clean conversion at shorter residence times, longer reaction times led to formation of impurities. For instance, compound **19** gave 44% conversion under 225 °C for 10 min, it gave a UPLC area percent reaction profile of 97% product (excluding the starting material). However, when the reaction was carried out for 60 min at the same temperature, the conversion increased to 97%, but the reaction profile dropped to 85% product with multiple impurities. This degradation was more pronounced for compounds **6, 9,** and **17** with longer residence times. Increased reaction temperatures did not seem to improve the reaction profiles for at least two of the substrates (**4** and **26**) investigated. This was particularly obvious for **26**, a very clean reaction was observed under 200 °C in 10 min, though only with 15% conversion. As the reaction temperature was increased, the conversion rate grew accordingly to 100%, however, undesired reactions started to dominate and the product was fully decomposed at 265 °C. After a further reaction screen, it was determined that the optimal temperature was 210 °C at a longer residence time (80 min). These observations suggest that a simple temperature vs. residence time screen is insufficient to determine the optimal reaction conditions for thermal de-Boc reactions.

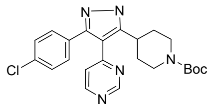
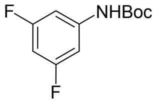
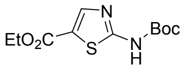
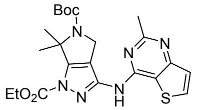
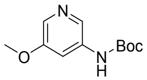
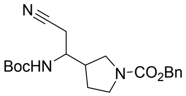
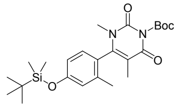
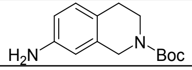
2.2 Functional group compatibility

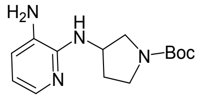
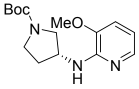
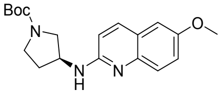
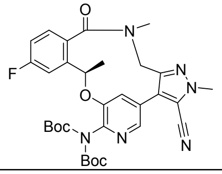
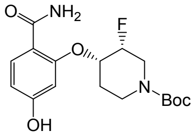
A number of functionalities were found to be compatible under thermal de-Boc conditions, including ketones, amides, esters, enol ethers, ketals, nitriles, alkyl halides, aryl halides, aryl- and akyl trifluoromethyl, benzyl carbamate and phenol. The results are summarized in **Table 2.** Aryl and heteroaryl systems were well-tolerated, including pyridines, pyrimidines, pyrazoles, pyrazolones, imidazoles, thiazoles, and pyrroles. Pinacol boronate esters and the thiadiazole (**3**) gave complete decomposition. While aryl fluorides and chlorides are well-tolerated, aryl bromides gave partial dehalogenation byproducts (5 ~ 20%). We hypothesized that this might be related to the formation of aryl metallic bromides in the metallic reaction coil under the high temperature.[17] This was subsequently confirmed by heating substrates in glass capillary tubes (solid state without any solvent) using a melting point device (Buchi Model B-545). In both cases (**5** and **6, Table 1)**, the solid state thermal deprotection in the glass capillary tubes was fairly clean with no detection of the dehalogenated byproduct.[18] The results suggest that *N*-Boc compounds containing aryl bromide moieties can be thermally deprotected under continuous flow conditions in a PFR with proper construction of material.[19] Ethers are expected to survive thermal conditions; nevertheless, some aryl alkyl ethers were observed to give ether cleavage byproducts. This seemed to be correlated with the leaving group (ArO) stability; 6-fluoroquinoline (**9**, **Table 1**) gave the highest level of ether cleavage byproduct, which suggested the aryl alkyl ether cleavage proceeded via a S_NAr solvolysis[20] mechanism with the ArO being a leaving group.

Table 1. Thermal de-Boc screen results of 26 substrates

Entry/ compound	Structure	Computational Indices of C=O			Solvent$^{\varphi}$	225 °C 10 min τ (unless noted otherwise)		225 °C 60 min τ (unless noted otherwise)		Reaction Profile
		Nucleophilicity (O)	Charge (O)	Electrophilicity(C=O)		Conversion (%)	Product (%)$^{\yen}$	Conversion (%)	Product (%)§	
1[21]		0.0315	-0.579	0.0069	THF	7.61%	17%	N/A	N/A	Dehalogenation as the major impurity
2[22]		0.2809	-0.535	0.014	anisole	0.48% (200 °C)	2%	N/A	N/A	Pinacol boronate ester hydrolysis as the major byproduct
3[23]		0.0868	-0.488	0.0379	anisole (20 mL/g)	0% (150 °C)	0%	N/A	N/A	Multiple impurities; major impurity loss of SO_2
4[24]		0.1681	-0.552	0.013	anisole	33%	97%	88%	97%	Water as additive to suppress urea formation
						90% (240 °C 30 min)	97%	92% (240 °C)	95%	
					THF(1% water)	27%	90%	N/A		
					TFE	91%	94%	N/A		
5[25]		0.3297	-0.540	0.0136	anisole	44%	95%	93%	93%	Single impurity (~5% dehalogenated)
					THF	37%	95%	N/A		
					None	54% (225 °C 10 min)	100%	N/A		Clean de-Boc (borosilicate glass capillary tube, solid without solvent)
6[26]		0.1	-0.551	0.00	TFE	78%	94%	80%	80%	dehalogenated as major impurity

					anisole	33%	83%	N/A		
					None	11% (225 °C 10 min)	99%	N/A		Clean de-Boc (borosilicate glass capillary tube, solid without solvent)
7[27]		0.21	-0.509	0.06	anisole (15 mL/g)	24% (200 °C)	95%	50%	50%	Multiple impurities
8[28]		0.04	-0.548	0.01	anisole	44%	93%	95%	95%	~2% methyl ketone
					THF	39%	94%			
					TFE	75%	83%			~50% methyl ketone
9[29]		0.13	-0.533	0.01	anisole	44%	91%	65%	65%	aryl ether cleavage as major impurity
10[30]		0.17	-0.553	0.00	anisole	51%	97%	88%	88%	clean
11[31]		0.13	-0.512	0.04	anisole	77%	100%	100%	99%	clean
					THF	56%	100%			
					THF (1% H2O)	70%	97%			
12[32]		0.15	-0.548	0.02	anisole	48%	89%	96%	96%	clean
13[33]		0.31	-0.553	0.04	anisole	72%	95%	99%	98%	clean
					THF	64%	95%	N/A		

					THF (1% H_2O)	68%	97%	N/A		
					TFE	93%	98%	N/A		
14[34]		0.17	-0.541	0.01	TFE	69% (200°C)	98%	94%	94%	Clean
15[35]		0.15	-0.529	0.2	anisole	84%	100%	98%	98%	Clean
16[36]		0.1	-0.534	0.18	anisole	94%	98%	96%	96%	Clean
17[37]		0.09	-0.540	0.02	anisole	17%	24%	N/A		Multiple impurities
18[38]		0.11	-0.523	0.1	TFE	93%	95%	N/A		Single impurity, ~5% demethylated
					THF(1% H_2O)	56% (20 min)	98%	N/A		
					anisole	13%	82%	N/A		
19[39]		0.05	-0.539	0	anisole	44%	97%	85%	85%	Multiple impurities
20[40]		0.04	-0.47	0.03	THF (15 mL/g)	70% (200 °C)	100%	100%	95%	clean
21[41]		0.06	-0.540	0.02	TFE	N/A		100% (220 °C)	100%	Clean; Solvent must be degassed to avoid N-

					THF	N/A		45% (220 °C)	55%	oxidation
22[42]		0.05	-0.57	0.01	TFE	N/A	N/A	100% (220 °C)	100%	clean
					THF			45%	45%	
23[43]		0.08	-0.57	0.01	TFE	98% (220 °C , 15 min)	100%	100%	100%	clean
					toluene	20% (220 °C, 22 min)	100%	N/A		
					THF	N/A		45%	45%	
24[44]		0.04	-0.57	0.01	TFE	100% (210 °C)	100%	N/A	N/A	
					THF	5% (220 °C, 22 min)	90%			
25[45]		0.14/0.14	-0.48/-0.46	0.03/0. 03	THF (13 mL/g)	99%	99%	N/A	N/A	Clean
26[46]		0.08	-0.55	0.01	THF	15% (200 °C, 10 min)	99%$^{¥}$	57% (200 °C, 80 min)	92%$^{¥}$	Ether cleavage was predominant byproduct at higher temperature.
						27% (210°C /10mi)	97%$^{¥}$	74% (210 °C, 80 min)	90%$^{¥}$	
						40% (220°C /10min)	95%$^{¥}$	89% (220 °C, 60 min)	87%$^{¥}$	
						58% (235°C /10min)	86%$^{¥}$			
						96% (250°C /10min)	6%$^{¥}$			
						99% (265°C /10min)	0%			

[φ] 10 ml per gram of substrate was used unless otherwise noted.

[¥] Defined as product area% in the reaction mixture *excluding* the unconverted starting material.[47]

[§] Defined as product area% in the reaction mixture *including* the unconverted starting material.[47]

Table 2. Functional group compatibility under thermal de-Boc conditions

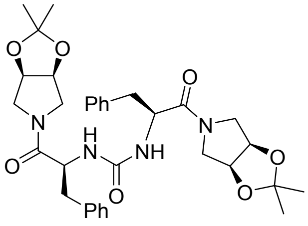
Functionalities	**Entries in Table 1**	**Compatibility (Y/N)**	**Comments**
ketone	7	Y	
amide	4, 7, 25, 26	Y	Including primary amide
enol ether	8	Y	methyl ketone formed as a minor impurity presumably due to inadvertent presence of water
ketal	4	Y	
nitrile	5, 20, 25	Y	
Ar-F	9, 15, 25	Y	
Ar-CF_3	13	Y	
Alk-CF_3	11	Y	
Alk-F	7, 26	Y	Limited to 2^o examples
Ar-Cl	1,14	See Comments	Dehalogenation impurity was observed for Entry 1 substrate.
Ar-Br	5, 6	See comments	Up to 90% desired product observed, dehalogenation was observed as an impurity
TBDMS ether	20	Y	
Boronate ester	2	N	
ArNH-SO_2-NHAr	3	N	Loss of SO_2 as the major byproduct

$ArCO_2Et$	12, 16	Y	
Ar-O-Alk ether	9, 18, 23, 24, 25	See comments	Mostly tolerated, desired products were observed as the major product, but some aryl alkyl ethers were partially cleaved
Ar-O-Ar ether	12	Y	
$ArNH_2$	21, 22, 23, 24, 27	Y	
CBz	19	Y	The impurity formation for the substrate was unrelated to CBZ.
Phenol	26	Y	

2.3 Solvent effects

Among the solvents (TFE, THF, anisole, and toluene) studied, TFE was observed to have the highest rate of reaction. This was clearly illustrated with results from entry 4 (Table 1), the conversion rates at 10 min under 225 °C were 91% in TFE, 33% in anisole and 27% in THF (1 wt% water). In entry 8 (Table 1) the conversion rates were 75% in TFE, 44% in anisole and 39% in THF; and entry 23 (Table 1) the conversion rate were 100% in TFE and 20% in toluene. The reaction rates in THF (with or without 1 wt% water as an additive)[48] and anisole were comparable as shown in entries 11 and 13. We attempted to add catalytic amounts of acids[49] (aq HCl or TsOH), and hexafluoroisopropanol (HFIPA), but did not observe accelerated reaction rates. In general, solvents were not dried or degassed before use, and were expected to contain adventitious amount of water, especially for TFE, a highly polar protic solvent. However, for one particular substrate (**21**, Table 1), the solvent (THF or TFE) needed to be nitrogen-sparged thoroughly to avoid the formation of an N-oxide impurity. Urea (**27**, **Figure 2**) was observed as a major byproduct in the thermal de-Boc of the compound **4**. With the addition of 1 wt% water, the impurity was completely suppressed. The rate of the thermal de-Boc reaction appeared to have no correlation with the substrate concentration (*vide infra*).

Figure 2 Byproduct from deprotection of 4

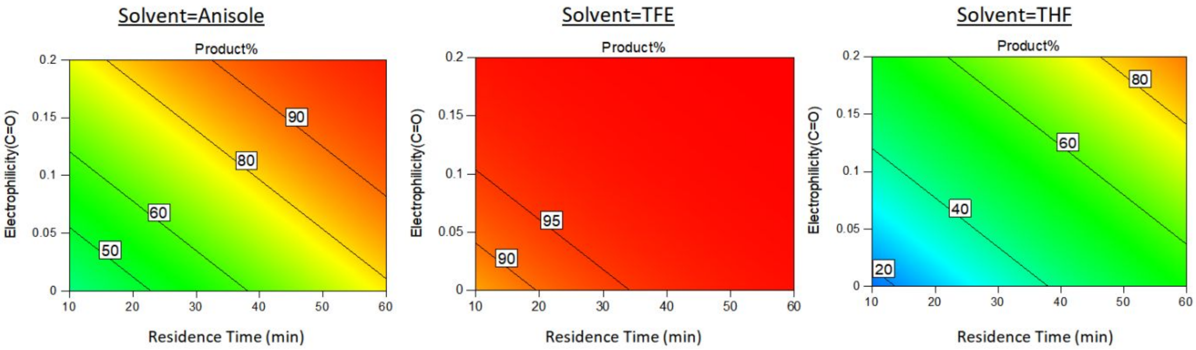


27

2.4 **Statistical analysis**

Reactive indices of substrates were calculated using an internally development computational model.[50] The carbonyl electrophilicity, oxygen nucleophilicity and charge (of C=O) in *N*-Boc carbonyl groups of each substrate were tabulated in **Table 1** with the hope that *in silico* data can help predict the proclivity towards thermal de-Boc. Linear regression was used to explore the functional relationship between de-Boc conversion and reaction parameters, including reaction time, temperature, solvent, concentration and reactive indices. As displayed in **Figure 3**, reaction time, solvent and electrophilicity (C=O) were significantly associated with the product conversion. TFE offers faster rate of reaction compared to anisole and THF, and higher C=O electrophilicity leads to more facile thermal de-Boc. The observed parameter effects become less evident as the reaction time is extended.

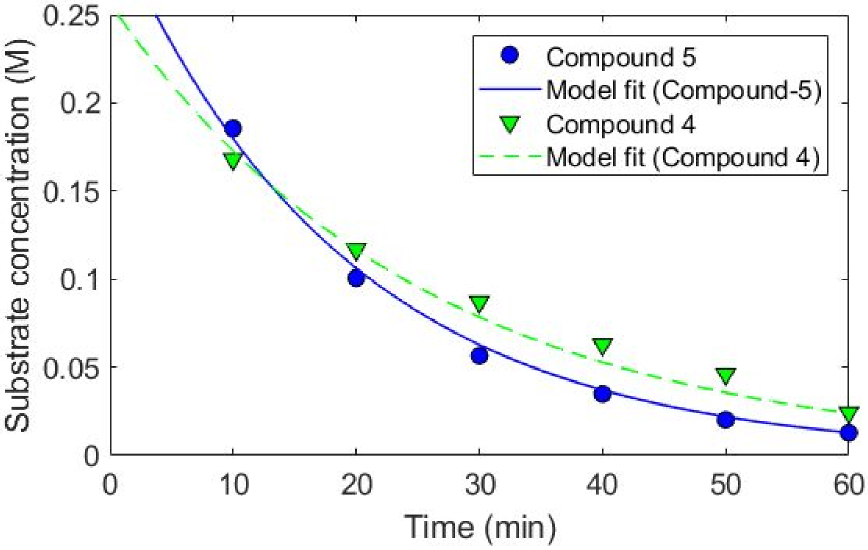
Figure 3. Contour plots of predicted conversion to product vs electrophilicity (C=O)



2.5 Computational modeling and Kinetics

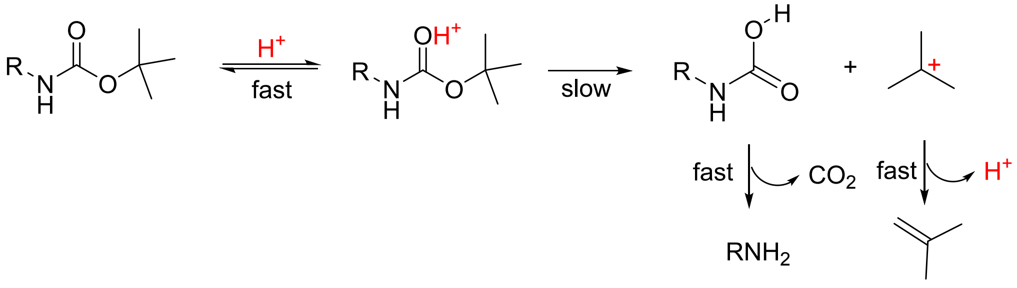
Acid catalyzed *N*-Boc deprotection has been well studied,[3b] the reaction typically proceeds at ambient temperature when strong acids are employed. The reaction rate exhibited a second-order kinetics with a dependency on the acid concentration[51] (Scheme 1). Water mediated *N*-Boc deprotections were also reported at 100 °C or higher temperature (under pressure). It was attributed to increased self-ionization of water, *i.e* more abundant H^+ and OH^- at higher temperature ($-\log K_w = 12$ at 100 °C *vs* 14 at ambient temperature), and appeared to follow a second order reaction kinetics (Scheme 2).[52] For the study of thermal de-Boc reaction kinetics, two substrates (**4** and **5, Table 1**) were chosen as they both offered clean deprotections and displayed distinctively different electronics. The experiments were performed with a range of residence times (10-60 min), while the temperature and initial substrate concentration were fixed at 225 °C and 10 mL of solvent/g of substrate. As a first-level approximation, the de-Boc reaction was postulated to follow first order kinetics. The kinetic rate constant for each substrate was fitted to the experimentally-derived conversions from UPLC results. The model was implemented in Matlab (R2017b) and solver *lsqnonlin* was applied to perform the parameter estimation. The results from the model fitting are presented in **Figure 4** and the estimated rate constants are shown in the figure caption. Based on the good agreement between model and experimental data, this result suggests that thermal de-Boc reactions follow a first order kinetics (Scheme 3), with the rate determination step being the formation of the carbamic acid. As adventitious amount of water was always present in the thermal deBoc reactions (and at times purposely introduced), it is possible the reaction may follow both mechanisms shown in Schemes 2 and 3, with the latter being the predominant one. This is supported by computational modeling using a *Gaussian 09*[53] as it seems to proceed initially through a concerted mechanism.[54] When TFE is employed in thermal de-Boc, the reaction could possible follow a hybrid of all three mechanisms as it is a weakly acidic solvent (pK_a 12.5 at 25 °C). The acidity of TFE is expected to be further increased at higher temperature.[55] For most acids, disassociation is an endothermic process. Hence according to Le Chatelier's Principle, adding heat to an endothermic process means a shift in equilibrium to the right. A similar phenomena is also exhibited with water.[56] Thermal de-Boc without added catalysis has a considerably higher activation energy as illustrated in **Figure 5**. The activation energy for the thermal de-Boc of **16** and **13** was calculated to be ~34.0 and ~34.8 kcal/mol, respectively, which was consistent with the experimental results. The conversion rate for **16** and **13** in 10 min (nominal τ) at 225 °C was 94% and 72%, respectively (Table 1).

Figure 4. Thermal de-Boc reaction kinetics (4 and 5) at 225 °C in Anisole or THF[a]

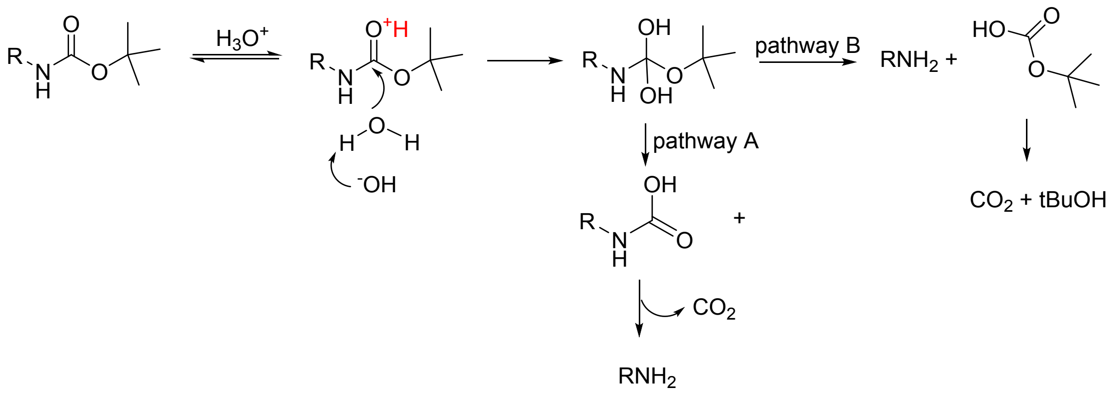


[a] The estimated kinetic rates are the following: 0.0394 min^{-1} for **4** and 0.0525 min^{-1} for **5**.

Scheme 1. Acid catalyzed de-Boc reaction mechanism



Scheme 2 Water participation in thermal de-Boc reactions



Scheme 3. Thermally driven, concerted release of isobutylene, followed by decarboxylation

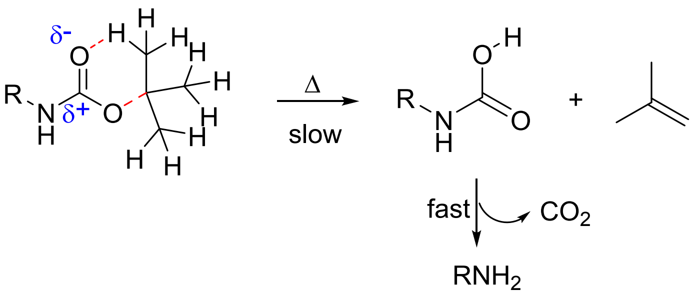
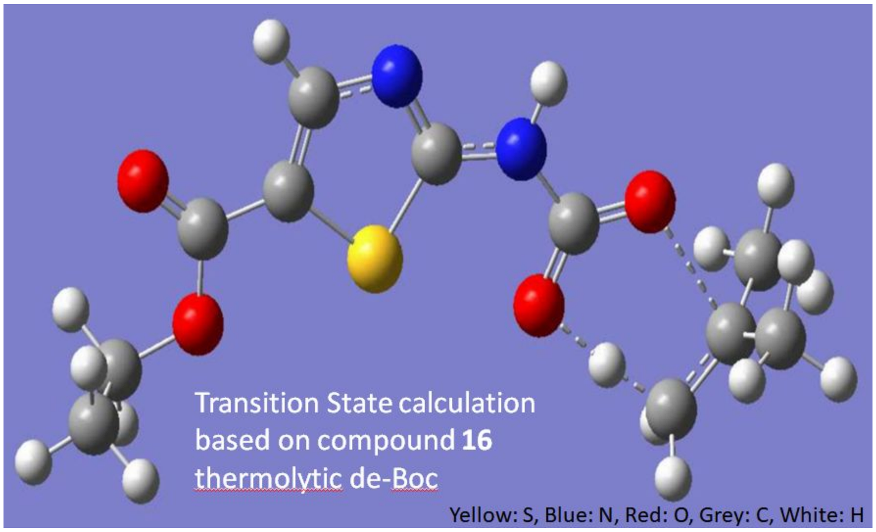
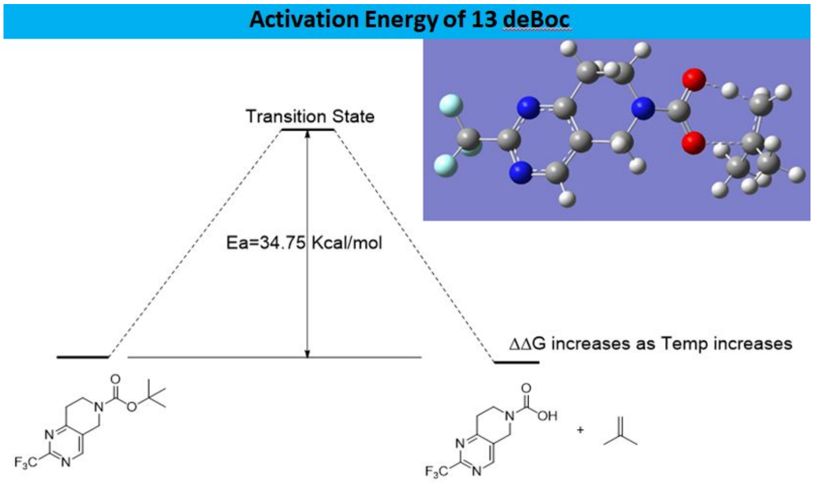
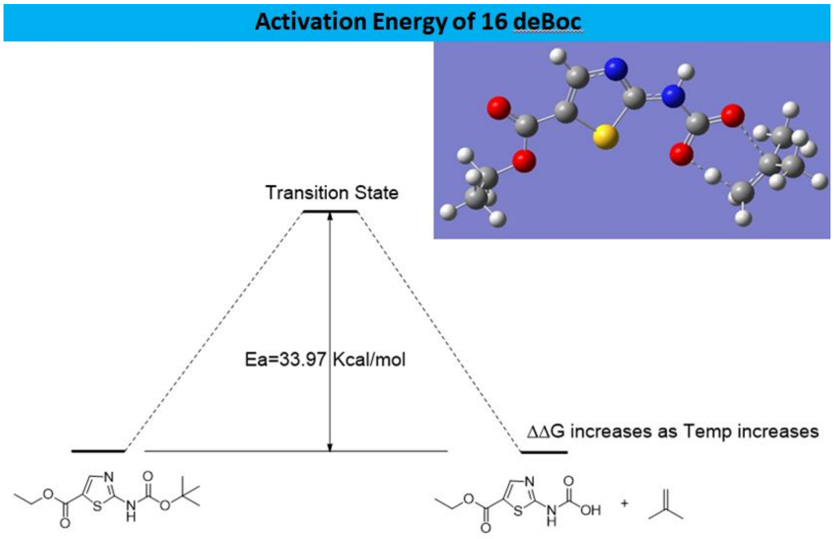


Figure 5. Thermolytic de-Boc Transition State and Activation Energy






Activation Energy of 16 deBoc
Transition State
Ea=33.97 Kcal/mol
ΔΔG increases as Temp increases
N
S
O
H
OH
+

2.6 Scale up considerations

From the thermal de-Boc studies, it appears there is not a simple protocol that fits all N-Boc substrates, especially pharmaceutical intermediates of high complexity. A thorough reaction screening of solvents, additives (water/TFE), temperature, and residence time will be needed to determine the optimal conditions. As TFE offers great solubities for almost all substrates we have surveyed, it can be used a good starting point to use a TFE solution of the substrate by performing a constant temperature (225 °C) screen with various residence time (10 – 60 min) and a constant time (30 min) screen with various temperature (180 – 250 °C). Other solvent systems, such as water/THF or water/THF/TFE mixtures, may be studied thereafter for scale up considerations to address both cost and low level impurities that may arise from the use of TFE. (TFE solvolysis was noted for some amide substrates to give $RC(O)OCH_2CF_3$ impurities).

While the focus of this study was on reaction screening in lab-based flow chemistry equipment, here we provide a brief primer on process engineering and scale-up considerations. Special attention should be paid to the change in density from both thermal expansion of solvents below their critical temperature (T_c) and supercritical fluid behavior beyond T_c.[4] The actual residence time can be significantly shorter than the nominal residence time in a PFR system when solvent density changes are significant within the system. The volume expansion (%)[57] of common solvents at elevated temperatures can be found in the Supplemental Information.

Furthermore, hydrodynamics and heat transfer phenomena should be considered when scaling from laboratory PFRs (10-40 ml) to manufacturing scale PFRs (>1000 ml). In brief, ideal plug flow conditions have perfect mixing in the radial direction but no mixing in the axial direction. In practice, the degree of axial dispersion will depend on the flow regime (laminar *vs*. turbulent) and in the case of thermal deprotection also the temperature.[4] Axial dispersion will determine the true residence time distribution of the substrate in the PFR. This directly impacts product quality as substrate exposed to reaction conditions shorter or longer than deemed necessary may result in incomplete reaction, impurity formation, or thermal degradation inside the PFR. Furthermore, heat transfer in the radial direction as a function of flow rate should also be considered as the

PFR coil diameter increases. Overall, the thermal expansion of the solvent, axial dispersion and its associated residence time distribution, and heat transfer are important factors to be aware of when scaling-up a thermal deprotection reaction. May and colleagues from Eli Lilly have elegantly covered deprotection of an *N*-Boc-protected imidazole, its scale-up, and the associated engineering principles.[4]

3. Conclusion

Out of 26 compounds surveyed, 12 gave clean (≥ 95% product) deprotection, and a broad functional group compatibility. This suggests the thermal de-Boc can be a viable method in developing a continuous end to end process, in particular, when the immediate next step is on the resulting amine. Among the compounds giving clean reactions, 3 compounds (**11**, **12**, and **13**) were chosen for multi-gram scale up, and all gave > 92% isolated yields. In addition, the conversion of **25** to lorlatinib on 10 g scale proceeded in essentially quantitative yield. Kinetic analysis and computational modeling suggests the thermolytic de-Boc follows an initial concerted fragmentation as the predominant mechanism, releasing isobutylene, followed by rapid decarboxylation.

Statistical analysis shows a strong correlation of thermal de-Boc reaction rate with a computationally determined electrophilicity coefficient of the *N*-Boc carbonyl group.

Experimental Section

General Methods. Flow experiments were performed using a Uniqsis FlowSyn reactor equipped with a 22 ml stainless steel coil and a 750 psi back pressure regulator. The Uniqsis FlowSyn reactor was flushed with the solvent the tested substrate was dissolved in at 1 ml/min at room temperature. The flow reactor was then set to the desired temperature and allowed to equilibrate for 15 mins with the said solvent being continuously perfused through the reactor. One gram of each substrate was dissolved in the specified solvents (anisole, THF, and/or TFE) at a desired volume (ml/g) in two dram vials with pressure relief caps (Chemglass Life Sciences). Samples were then loaded into an injection loop. The flow rate was set to achieve the intended nominal residence time, and samples were injected into the Uniqsis Flow Syn reactor. Reaction screening for compound **25** was carried out using Propel, a segmented flow reactor system.[58] For the multi-gram scale demo on compound **25**, Vapourtec was used instead, and the procedures were followed analogously. Samples were collected at the outlet of the reactor and characterized without any further purification, unless otherwise noted. Reaction segments were collected neat and analyzed via UPLC. Reaction progress and chemical purity were evaluated by UPLC analysis using a Waters HSS T3 column (2.1 x 50 mm) with mobile phases A (0.05% TFA in water) and B (acetonitrile); wavelength 210 nm, flow rate 0.65 mL/min. 0 – 2.90 min, 5% B; 2.90 – 3.40 min, ramp to 100% B; 3.40 – 3.50 min, ramp to 5% B; 3.50 – 4.00 min, 5% B. Column temperature: 45 °C.

Representative Examples:

***N*-Boc deprotection of tert-butyl (S)-3-oxo-3a-(pyridin-4-ylmethyl)-2-(2,2,2-trifluoroethyl)-2,3,3a,4,6,7-hexahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (11):** **11** (2.92 g, 7.08 mmol) was dissolved in THF (29 mL) to give a complete solution. Flow was started with THF solvent bottle until the flow reactor pressure reading (set by back pressure regulator) was stablized at ~750 psi. The reaction coil was then heated until the internal coil temperature reached 225 °C. A three-way valve on the Uniqsis was then used to switch from solvent bottle to the substrate in solvent bottle and continuously perfused at 0.37 mL/min in a 22 ml stainless steel reactor coil for a planned nominal residence time of 60 min. Just prior to the substrate in solvent bottle running dry the three-way valve was switched back to the solvent feed bottle and effluent was continuously collected for an additional 60 min. The product containing effluent solution was concentrated by rotorvap under reduced pressure to dryness to give the desired product as a white solid (2.11 g, 95.4%). Spectroscopic data were consistent to those reported in the literature.[31]

***N*-Boc deprotection of ethyl 2-(4-((tert-butoxycarbonyl)amino)phenoxy)nicotinate (12):**

12 (5.00 g, 14.0 mmol) was dissolved in anisole (50 mL) to give a complete solution. A second 50 mL Pyrex bottle containing pure anisole was used as the solvent feed. A similar procedure to the multi gram demo of compound **11** was followed. The product was isolated as an oil (3.71 g, > 95%). Spectroscopic data were consistent to those of an authentic commercial sample.[32]

***N*-Boc deprotection of tert-butyl 2-(trifluoromethyl)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (13):** 13 (5.00 g, 16.5 mmol) was dissolved in anisole (50 mL) to give a completion. The same procedure as outlined above was followed. The product was isolated as a white solid (3.11g, 92.9%). Spectroscopic data were consistent to those reported in the literature.[33]

Imidodicarbonic acid, 2-[(10*R*)-3-cyano-12-fluoro-10,15,16,17-tetrahydro-2,10,16-trimethyl-15-oxo-2*H*-4,8-methenopyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-7-yl]-, 1,3-bis(1,1-dimethylethyl) ester (25): **25** as the EtOAc solvate (10.0 g, $MW_{(EtOAc\ solvate)}$ = 694.8 g/mol, 14.4 mmol) was dissolved in THF (99.5 mL) and H_2O (0.5 mL) and pumped through a PFR (Vapourtec; 10 mL coil, flow rate 0.5 mL/min, 20 min nominal residence time), the effluent was collected until no more product was detected in the output stream. The *in situ* reaction yield (5.83 g, 99.6%) and area percent purity (99.3%) was determined by UPLC with an authentic reference standard of the product. Spectroscopic data were consistent to those reported in the literature.[46]

ASSOCIATED CONTENTS

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

(1) Calculation method of electrophilicity reactivity indexes;

(2) Calculation method and results of transition state;

(3) Volume Expansion (%) of Common Solvents at Elevated Temperatures, and

(4) Multi-gram thermal de-Boc examples and product characterizations by UPLC and NMR.

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Notes

The authors declare no competing financial interest.

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14. This residence time was picked arbitrarily, but was deemed a reasonable upper limit for good productivity in our scale up PFR unit.

15. We were mindful of the Abbvie work (reference 2 above) was carried out in Phoenix flow reactor under 300 °C that is not deemed for scale up operations. Our production facility uses jacketed coil using fluid for heat exchange that has a temperature upper limit of ~ 270 °C

16. Different τ and temperature were selected for several substrates.

17. Copper flow reactor was employed in the click chemistry. See Bogdan, A. R.; Sach, N. W. The Use of Copper Flow Reactor Technology for the Continuous Synthesis of 1,4-Disubstituted 1,2,3-Triazoles. *Adv. Synth. Catal.* **2009**, *351*, 849 – 854.

18. The reactions did not reach full conversion even with prolonged heating. This was due to that gas evolution pushed some material in the capillary to the upper non-

heated region. With further development, this method could potentially be a simple, practical method to test thermal de-Boc feasibility with 1 – 2 mg of substrate.

19. One approach is to use Teflon coated metallic coil.

20. Adventitious of water or TFE in the solvent system may act as the nucleophile.

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predominantly contributed from aromatic groups, and the *N*-Boc carbonyl had a very weak UV response even at 210 nm wavelength. Comparisons were also made at 230 or 254 nm where the N-Boc group had no response. Additionally, the N-Boc group UV response was not relevant where ¥ was defined as product area% in the reaction mixture e*xcluding* the unconverted starting material. Where § was defined as product area% in the reaction mixture *including* the unconverted starting material, the reaction was often at near reaction completion, *i.e*. starting material at low levels, therefore, the UV response from the N-Boc group had little impact on the overall *in situ* yield reported.

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