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Solvent-free *N*-Boc deprotection by *ex situ* generation of hydrogen chloride gas†

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An efficient, scalable and sustainable method for the quantitative deprotection of the *tert*-butyl carbamate (*N*-Boc) protecting group is described, using down to near-stoichiometric amounts of hydrogen chloride gas in solvent-free conditions. We demonstrate the *ex situ* generation of hydrogen chloride gas from sodium chloride and sulfuric acid in a two-chamber reactor, introducing a straightforward method for controlled and stoichiometric release of HCl gas. The solvent-free conditions allow deprotection of a wide variety of *N*-Boc derivatives to obtain the hydrochloride salts in quantitative yields. The procedure obviates the need for any work-up or purification steps providing an uncomplicated green alternative to standard methods. Due to the solvent-free, anhydrous conditions, this method shows high tolerance towards acid sensitive functional groups and furnishes expanded functional group orthogonality.

Introduction

Protecting groups are principal elements in organic synthesis considering that complex intermediates and products typically contain a wide variety of functional groups.[1,2] To prevent the formation of undesired bonds and side reactions, synthetic chemists make strategic use of their ability to mask and, at a later stage in the synthesis, liberate functional groups to unlock their desired reactivity.[3] The *tert*-butyloxycarbonyl protecting group (Boc group) is one of the most important amino protecting groups and has contributed substantially to the achievements in present organic synthesis.[4] Its applicability comes from the ability to be introduced into the molecule under mild conditions in a selective and high-yielding manner. The same requirements are to be expected for the cleavage, while keeping other protecting groups and unprotected functionalities unaffected by the deprotection conditions. This concept of orthogonally stable protecting groups is key in the synthesis of complex molecules.[5] Due to its acid lability, the most commonly used Boc-deprotection procedures use solutions of 25–50% trifluoroacetic acid in DCM or HCl solutions.[2] Consequently, other acid labile protecting groups are typically not tolerated in these procedures, imposing restrictions on orthogonal strategies. In recent years, progress has been made using alternatives such as solid supported catalysis,[6,7] high-temperature water[8–11] and ionic liquid mediated deprotections.[12,13] However, the *N*-Boc-deprotection toolbox still suffers from chemoselectivity limitations. Furthermore, practically all deprotection strategies require several post-cleavage manipulations such as quenching, removal of solvents and purification steps. It is estimated that in typical fine chemical and pharmaceutical batch syntheses, solvents account for 80 to 90% of mass utilization.[14] Efforts have been made to improve on sustainability, but in reality, even the solvent-recycling and solvent-free *N*-Boc deprotections still require post-synthesis manipulations and purification steps, inviting further improvement.[12,15,16]

To solve these current problems, we confided in our previous experience with gas chemistry. Herein, we present an *N*-Boc deprotection method with high functional group tolerance and expanded orthogonality while also being a green alternative to standard methods. Despite the fact that gases are commonly avoided and undervalued in a laboratory setting for practical and safety reasons, they can be convenient reagents with great potential for high atom economy.[17–20] Moreover, gas-solid reactions have achieved unsurpassed atom economy due to their solvent-free nature and elimination of any purifying work-up upon full conversion.[21,22] A literature survey reveals that hydrogen chloride gas has the potential to cleave *tert*-butyl carbamates.[23–25] However, it has never been extensively studied, and no general protocol has been described. The few mentions that do exist typically use a pressurized gas cylinder to pass HCl gas through the solid substrate for several hours or even overnight. Though effective, lecture bottles are associated with high cost and risk of leakage or even explosion. Moreover, excessive amounts of a

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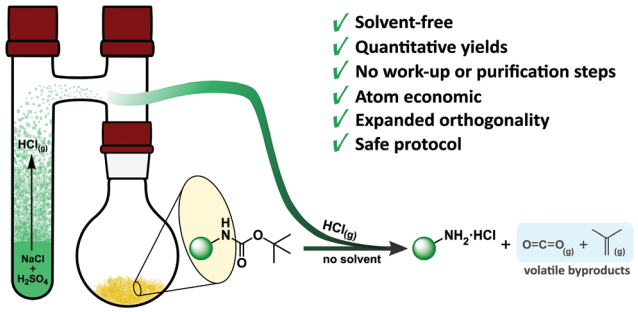


Scheme 1 Solvent-free deprotection of *N*-Boc compounds by *ex situ* generation of HCl gas using a two-chamber reactor with a detachable product chamber.

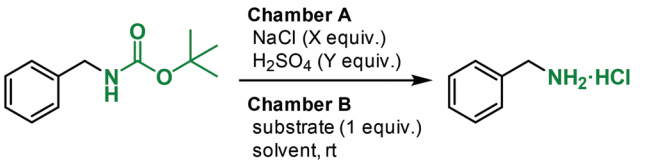
constant stream of the harmful, corrosive gas in open air are required to drive the reaction to decent conversion. This set-up and the lack of precautionary measures to safely evacuate the excess gas make it impractical and exposes the operator to severe risks. Furthermore, the continuous supply of gas needed, adds up to excessive quantities hampering the potential towards a sustainable methodology. In recent years, *ex situ* gas generation has proven to be an enabling technology with an improved safety profile allowing precise control over stoichiometry.[19,20] Using a two-chamber reactor, we envisioned the liberation of HCl gas from cheap and readily available precursor molecules (NaCl and H_2SO_4)[26] in one chamber, which subsequently diffuses to the adjacent chamber where it participates in the deprotection reaction (Scheme 1). The byproducts of the reaction, CO_2 and isobutene, are both gaseous. As a consequence, upon quantitative conversion it eliminates the need for any work-up or purification steps. Thereby, a truly solvent-free procedure is achieved where the whole process from substrate to pure product does not consume any solvent. These types of gas–solid and gas–liquid reactions are able to achieve remarkable waste minimization.[27,28] Finally, the anhydrous nature of this procedure has shown the potential to eliminate unwanted hydrolysis of other acid sensitive functional groups, thus increasing functional group tolerance and orthogonality.

Results and discussion

Optimization

The solvent-free *N*-Boc deprotection strategy was first evaluated by generating an excess of HCl gas (5 equiv. NaCl and 5 equiv. H_2SO_4) in chamber A of a two-chamber reactor, which then diffuses to chamber B to deprotect *N*-Boc benzylamine. To our surprise, after reacting for 1 hour under solvent-free conditions 38% of the substrate had been deprotected and converted towards the hydrochloride salt (Table 1, entry 2). We realize that in the domain of gas-solid chemistry, the kinetic challenges are often of physical rather than chemical nature. Therefore, we hypothesize that the macroscopic size of the substrate crystals prevents the HCl gas from interacting with the substrate molecules in the core of the crystals. To solve this, we grinded our

Table 1 Optimization of *N*-Boc deprotection of *N*-Boc benzylamine by *ex situ* generation of HCl gas[a]



Entry	NaCl (equiv.)	H_2SO_4 (equiv.)	Solvent	Time	Yield[b]
1	0	5	—	1 h	0%
2[c]	5	5	—	1 h	38%
3	5	5	—	1 h	63%
4	**3**	**0.5 mL**	**—**	**1 h**	**>99%**
5[c]	3	0.5 mL	—	1 h	70%
6	3	3	—	1 h	20%
7	1.3	0.5 mL	—	20 h	>99%
8	1.2	0.5 mL	—	20 h	85%
9[d]	3	0.5 mL	DCM	1 h	7%
10[d]	3	0.5 mL	Ethanol	1 h	16%
11[d]	3	0.5 mL	Dioxane	1 h	26%

[a] Reaction conditions: chamber A: NaCl, H_2SO_4 at rt. Chamber B: *N*-Boc benzylamine (0.5 mmol) at rt. [b] Determined by ^{1}H NMR. [c] Unground, crystalline substrate. [d] 0.5 mL of solvent in chamber B.

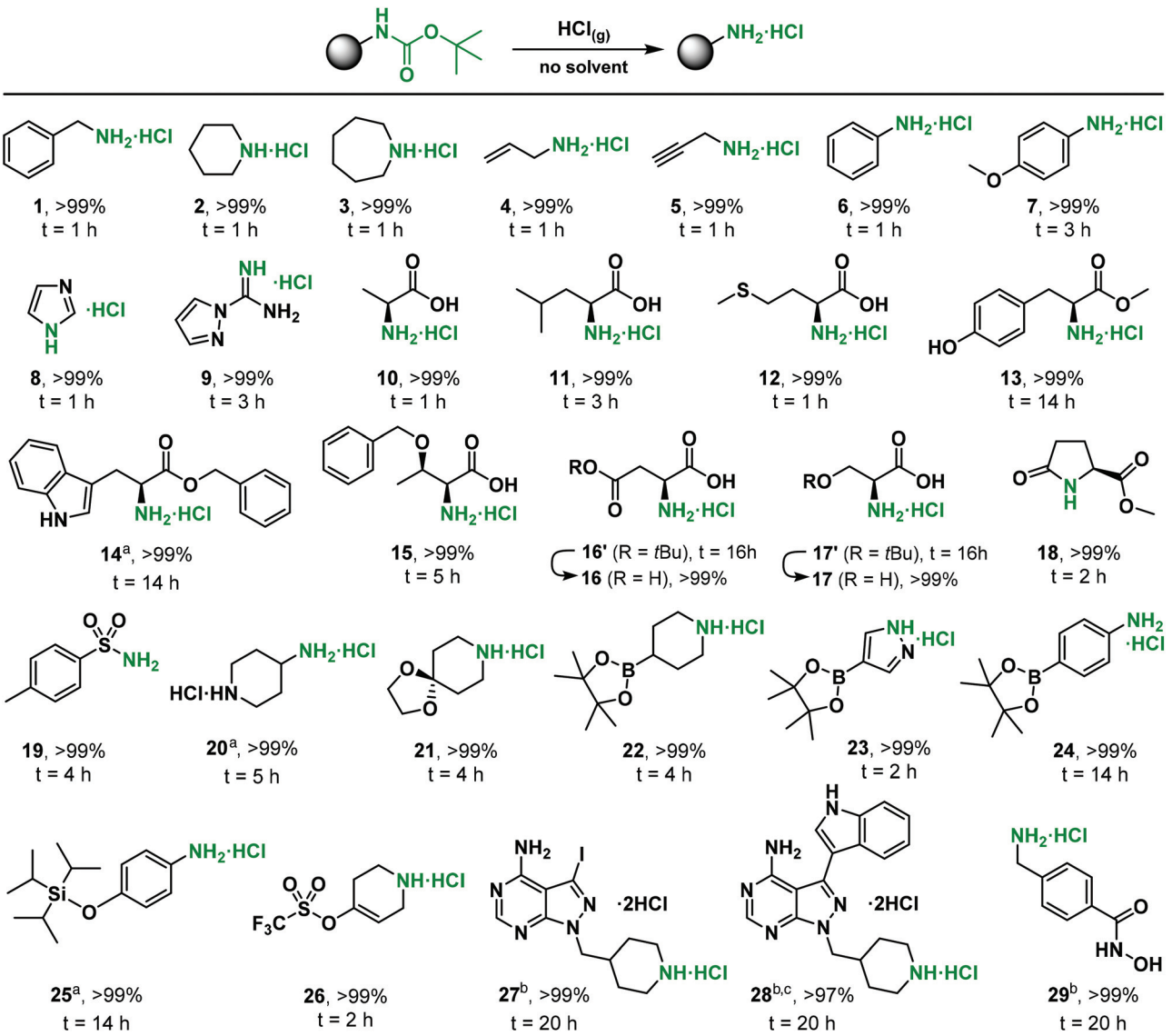
substrate with pestle and mortar to increase the surface to volume ratio. Under otherwise identical conditions, the conversion towards the hydrochloride salt increased to 63% using the powdered substrate (entry 3). Further screening of reaction conditions was carried out to minimize reagent use while maintaining fast reaction completion. The optimization table summarizes the results (Table 1). By using a 1 : 1 ratio of NaCl/H_2SO_4, apart from gas generation in chamber A, a sticky paste also developed in that same chamber. We rationalize that as a result of inefficient mixing, not all NaCl is converted into HCl gas. This was addressed by using an excess of H_2SO_4 (0.5 mL) as it dissolves NaCl well and thereby ensures better conversion towards HCl gas. Using only 3 equivalents of NaCl and 0.5 mL of sulfuric acid, we are able to achieve quantitative NMR conversion after only 1 hour (entry 4). Remarkably, it was established that the reaction can be driven to completion by generating near-stoichiometric amounts of HCl gas (entries 7 and 8). However, it was decided to proceed by generating 3 equivalents of HCl gas to ensure full conversion in short reaction times (<1 hour). Undoubtedly, it is an advantage to carry out this transformation under solvent-free conditions. Nonetheless, for comparison, we carried out the same reaction procedure with the exception of dissolving the substrate in different solvents (DCM, EtOH and dioxane). None of these systems performed better than the solvent-free procedure, displaying an apparent kinetic advantage (entries 9–11).

After achieving full conversion at fast reaction times and low stoichiometry, we considered the possibility to isolate our products quantitatively. To minimize the handlings, we devised a new type of two-chamber reactor with a detachable chamber designed as a round-bottom flask (see Scheme 1 and ESI†). Due to the solvent-free procedure and gaseous nature of the byproducts (CO_2 and isobutene), chamber B can simply be

detached after reaction completion to isolate the corresponding product in quantitative yield without any further handling.[29] Besides decreasing the overall labor intensity of this deprotection method, this allows consecutive product manipulation without transferring the compound. With the increased interest in *ex situ* gas generation, we believe this new reactor design will also prove useful in other chemical transformations using gaseous reagents.

Substrate scope

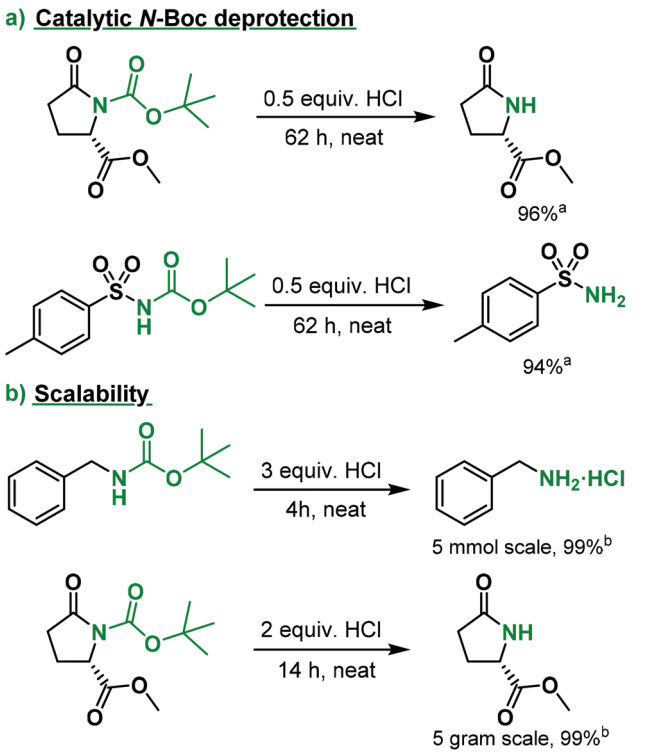
Next, we applied this efficient and green deprotection procedure to more complex amines and other nitrogen-protected substrates. The generality of this procedure is shown in Scheme 2, demonstrating efficient deprotection of various classes of nitrogen-containing functional groups (primary and secondary amines, anilines, (sulfon)amides, carboximidamides, amino acids and heteroaryls). Depending on the ease of deprotection of the substrate, more equivalents of HCl gas were generated. All substrates display quantitative isolated yields after reaction times varying from 1 hour to 20 hours. We started with several simple primary, secondary and benzylic protected amines, which could be fully deprotected within 1 hour (**1**–**5**). Noteworthy are the liquid substrates that were converted to the solid hydrochloride products in quantitative yields under solvent-free conditions (**2**, **3**, **26**). Some other solid substrates went through a viscous liquid state during the transformation to also end up as the solid hydrochloride product. However, most substrates in this study remain in the solid



Scheme 2 Solvent-free deprotection of *N*-Boc protected amino groups by *ex situ* generation of HCl gas using a two-chamber reactor with detachable chamber. Reaction conditions: at room temperature under argon atmosphere; chamber A: NaCl (1.5 mmol, 3 equiv.); chamber B: substrate (0.5 mmol, 1.0 equiv.); finally, 0.5 mL H_2SO_4 was added by injection through the septum in chamber A. See ESI and Instructional Video.† [a] NaCl (2.5 mmol, 5.0 equiv.). [b] NaCl (5 mmol, 10.0 equiv.). [c] 10 mg scale.

state during the whole deprotection procedure. Interestingly, unactivated alkenes and alkynes are unaffected in this method (**4**, **5**). Aminoaryls were readily deprotected in short reaction times to yield **6** and **7**. *N*-Boc protected heteroaryls such as imidazoles and pyrazoles were no exception (**8**, **23**). Furthermore, *N*-Boc-1*H*-pyrazole-1-carboxamidine was isolated in quantitative yield as **9**. Considering the great value of amino acids to medicinal chemists, we investigated the deprotection of several amino acid derivatives. Simple amino acids could be deprotected after reaction times varying from 1 to 3 hours (**10**, **11**, **12**). *N*-Boc-L-tryptophan benzyl ester required 5 equivalents of HCl to fully deprotect and **14** was quantitatively isolated after 14 hours of reaction time. The reaction displayed perfect chemoselectivity as the benzylic ester protecting group was unaffected. Similarly, the benzyl ether protecting group of *N*-Boc-*O*-benzyl-L-threonine also remained intact to yield **15**. Gratifyingly, unlike many alternative methods, no *tert*-butylation of the tyrosine phenol and tryptophan indole were observed (**13**, **14**). This problem occurs when *tert*-butyl cations are formed during Boc-deprotection and unwantedly react with a nucleophile.[30–32] Due to the solvent-free nature of this procedure, there is no possibility for a solvated *tert*-butyl cation to exist and cause complications. This also obviates the need of adding scavengers.[33–35] *tert*-Butyl ester **16** and *tert*-butyl ether **17** are also deprotected using this method. The simultaneous deprotection of the *N*-Boc group and *tert*-butyl ester/ether was possible using only 3 equivalents of HCl gas. Moreover, these examples further emphasize the labor-, waste- and cost-effectiveness of this procedure. To verify the enantiomeric purity of the amino acid products, they were submitted to chiral HPLC and compared to commercially available racemic mixtures. Single peaks were observed at the corresponding retention times whereas the racemic mixtures gave two. The specific optical rotations also confirmed no detectable racemization. Boc-L-pyroglutamic acid methyl ester was isolated quantitatively as free base **18** rather than the hydrochloride salt. This led us to conclude that nitrogen-protected substrates with low basicity do not consume the HCl gas after deprotection. The deprotection of *N*-Boc tosylamide towards free base **19** further supported this hypothesis. Consequently, these particular substrate classes have the potential to be catalytically deprotected. This was confirmed by deprotection of Boc-L-pyroglutamic acid methyl ester and *N*-Boc tosylamide using only 0.5 equivalents of HCl gas. Over the period of two days, both substrates were deprotected in >94% yield (Scheme 3a). In contrast, substrates containing additional basic functional groups are converted to dihydrochloride salts as demonstrated in compound **20**.

Substrates bearing acid-labile functional groups were subjected to our method to investigate the functional group compatibility. To our delight, methyl and benzyl esters and ethers remained stable under these conditions (**13**, **14**, **15**, **18**). Furthermore, due to the anhydrous and neat conditions, the presence of an acetal group is well tolerated and **21** was quantitatively obtained with perfect chemoselectivity. Similarly, boronate esters are also known to undergo decomposition using other *N*-Boc deprotection methods while under our conditions



Scheme 3 (a) Conceptual examples of the catalytic *N*-Boc deprotection. (b) Scale-up of the solvent-free *N*-Boc deprotection. [a] NMR yields. [b] Isolated yields.

aliphatic, aryl as well as heteroaryl pinacol boronate esters **22**, **23**, **24** behaved well.[11,36,37] The mild nature of this procedure is further highlighted by the chemoselective deprotection in the presence of acid sensitive silyl ethers (**25**). The same was true in the presence of an enol triflate (**26**). Within our lab, this procedure has already proven extremely useful. During the synthesis of a pyrazolo[3,4-*d*]pyrimidine-based protein kinase D inhibitor (**28**), *N*-Boc was initially selected as the protecting group in order to install a piperidine moiety. At the time, multiple efforts to cleave the *N*-Boc-group under acidic conditions failed to yield pure **28** due to side reactions.[38] Upon developing this procedure, we discovered that the solvent-free conditions eliminated these side reactions. Hereby, we enabled the *N*-Boc deprotection of these scaffolds (**27**, **28**) in quantitative yields without requiring any purifying work-up. Given the importance of hydroxamic acids as strong metal ion chelators,[39] we investigated the chemoselectivity of the *N*-Boc deprotection of a benzohydroxamic acid. Attempting several standard deprotection methods for 4-(boc-aminomethyl)-*N*-hydroxybenzamide always led to an arduous task due to side product formation. Employing the procedure described in this work, we were able to deprotect this substrate without affecting the hydroxamic acid moiety to obtain **29** in quantitative yield.

All substrates containing acid labile functionalities are deprotected under dry conditions (flame-dried glassware, argon atmosphere, sulfuric acid acting as a desiccant[40]). If not, minor side products were observed for some substrates (*e.g.* in

the presence of water, acid catalysed hydrolysis can occur.). Therefore, when handled under the proposed dry and solvent-free conditions, the presence of these protecting groups and functionalities becomes inconsequential. However, we did observe that epoxides, activated olefins and the *N*-Cbz group were not stable under these conditions and reacted with HCl.

Finally, this procedure is easily scalable by simply using a larger two-chamber reactor. This was illustrated by deprotection of *N*-Boc benzylamine on a 5 mmol scale and Boc-L-pyroglutamic acid methyl ester on a 5 gram scale resulting in quantitative isolated yields of **1** and **18** (Scheme 3b).[41] This procedure was shown to be scalable on a laboratory scale and can be used as an enabling framework towards kilogram scale gas-solid *N*-Boc deprotections.[27]

Conclusions

In summary, a procedure has been developed for the clean removal of *N*-Boc protecting groups and isolation of products in quantitative yields without the need for purification or work-up. The reaction proceeds under solvent-free conditions at room temperature, using down to near-stoichiometric amounts of *ex situ* generated HCl gas. We devised an operationally simple two-chamber reactor with a detachable chamber allowing transfer-free product isolation and follow-up reactions. Besides being a labor-, waste- and cost-effective *N*-Boc deprotection method, it displays a broad scope with respect to the *N*-Boc groups that can be deprotected and functional groups that are tolerated. The high tolerance towards otherwise acid sensitive functional groups and expanded functional group orthogonality will likely render it a useful tool in protecting group strategies for complex organic syntheses. Moreover, this solvent-free procedure and new reactor design are promising for further sustainable synthetic purposes.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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41 It should be noted that we are under the impression that larger molecules and larger scale deprotections require longer reaction times or increased HCl stoichiometry. This could be a consequence of the gas-solid interactions required to drive the reaction, where the kinetics are subject to the physical availability of the carbamates.