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A mild Boc deprotection and the importance of a free carboxylate

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ABSTRACT

We report a facile and rapid removal of Boc protecting groups using microwave heating in H_2O, with deprotection only requiring a free carboxylic acid group in the starting material. Unlike previous approaches, no additional reagents are required.

The protection–deprotection cycle associated with the synthesis of modified amino acids and peptides has been crucial to yield improvement and ease of synthesis. With Boc-protection, of amino acids and amines in general, the installation of the protecting group is typically by addition of Boc-anhydride; and deprotection via acidic means such as TFA and HCl.[1–3] Whilst from a green chemistry perspective, the addition of two additional steps is contrary to the '12 principles of green chemistry', it does facilitate rapid access to materials that would otherwise be generated in a significantly less efficient, and hence in a less green manner.[4] However, the use of acidic deprotection strategies means that such approaches are not suited to acid-sensitive substrates and alternative protecting groups are required. Notwithstanding this, our group has had a long held interest in rapid access to focused libraries of biologically active molecules, in particular, protein phosphatase 1 and 2A[5–10] and dynamin GTPase inhibitors,[11–13] and it is this access rather than the synthetic elegance that has typically been our focus. In our most recent effort, we wished to examine the effect of the 5,6-ethyl bridge and oxygen atom of the THF ring associated with cantharidin (**1**) and norcantharidin (**2**) to determine their roles, if any, in the inhibition of protein phosphatases 1 and 2A and their potential role in the associated anticancer effects for this class of compounds. In the synthesis of these Δ-5,6-ethyl analogues, such as (3*R*,6*S*)-tetrahydrofuro[3,4-*c*]furan-1,3-dione (**3**), we investigated the possibility of conducting key steps using rapid microwave heating, especially for the preparation of a focused library of amino acid substituted imides (**4**).

Microwave heating has added to the organic and medicinal chemists repertoire of techniques to impart the energy necessary to effect a synthetic transformation.[14–17] Microwaves heat reactants much more quickly than conventional means and many syntheses that usually take hours are now conducted in minutes. Microwave quick heating is significantly beneficial in accelerating a number of conventional heated chemistries with enhanced selectivity, improved reaction rates, milder and solvent-free reaction conditions and formation of cleaner products with associated ease of manipulation. These are facets of green chemistry.

In this work, we report our observations of an extremely mild, TFA- and HCl-free method for the rapid and highly efficient Boc-deprotection of amino acids, dipeptides and of related compounds.

The syntheses of **4** with various amino acids were conducted under standard thermal conditions, however as analogues of **3** had been prepared in good to high yield under microwave conditions (data not shown, using a *Smith Synthesiser* from *Personal Chemistry*), we attempted to apply microwave heating to the synthesis of **4** via a Boc-protected pyrrole diacid. Interestingly, we observed, in those examples where a Boc protecting group was required, that in H_2O and under microwave conditions, recovery of only the free amino substituted analogue, with quantitative Boc group removal in as little as 2–3 min. Intrigued by this observation, and given the typical use of harsher conditions with TFA and HCl, we sought to explore the utility of microwave heating in H_2O as a mild and green approach to removing a Boc group. The outcome of a systematic evaluation of several Boc-protected amino acids is shown in Table 1.

The data in the Table clearly show that the Boc-deprotection in H_2O is a remarkably facile process, but only in those instances in which the starting protected amino acids possessed a free carboxylate moiety (entries 1–7). Disappointingly, the deprotection of Boc-L-Glu (entry 8) proceeded predominately with cyclisation to the corresponding β-lactam. This is likely due to the favourable length of the amino side chain, and whilst an unwanted outcome, knowing the limitation of this technology is also crucial for determining its widespread utility. Also of note is that esterification of the free carboxylate (entry 9) followed by microwave irradiation in H_2O, under the same conditions as those used in entries 1-7, resulted in recovery of starting material only, suggesting that the free carboxylic acid is important in the removal of the Boc group (this

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Table 1
MAOS (170 °C) in H_2O deprotection of Boc amino acids

Entry	Amino acid	Yield (%)
1	Boc-L-Ala	100[a]
2	Boc-D-Ala	95
3	Boc-β-Ala	100
4	Boc-L-Pro	100
5	Boc-L-Leu	100
6	Boc-L-Met	98[b]
7	Boc-L-Tyr	100[c]
8	Boc-L-Glu	29[d,e]
8	Boc-L-Phe-OMe	0
9	Boc-D-Asp-OBn	100
10	Boc-L-Arg-NTos	100
11	Cbz-L-Asp	61[e]

[a] $[\alpha]_D^{22}$ +14.5 (*c* 10, 6 N HCl), authentic sample $[\alpha]_D^{20}$ +14.5 (*c* 10, 6 N HCl).
[b] $[\alpha]_D^{22}$ +22.0 (*c* 2, 6 N HCl), authentic sample $[\alpha]_D^{20}$ +21.3 (*c* 2, 6 N HCl).
[c] $[\alpha]_D^{20}$ −11.0 (*c* 4, 1 N HCl), authentic sample $[\alpha]_D^{20}$ −10.6 (*c* 4, 1 N HCl).
[d] Cyclisation to β-lactam observed.
[e] Conversion based on ^1H NMR analysis.

was also observed with a model dipeptide below). It is also of note that microwave irradiation in H_2O had no effect on the removal of a benzyl ester (entry 10) or a tosyl group (entry 11), but was applied, with moderate success, in removal of the CBz group (entry 12). Importantly, when the optical rotation values of selected deprotected amino acids were examined, no evidence of racemisation was detected (entries 1, 6 and 7) (see Fig. 1).

Similar approaches have been reported by Vasanthakumar[18] and Vaquero,[19] however, both procedures require the addition of *p*-TsOH and silica gel, respectively, and are hence less green than our current report (see Scheme 1).

In an effort to ensure that this process was applicable in the proposed development of focused libraries of biologically active molecules, we first synthesised the model dipeptide Val-Val,[20–22] as shown in Scheme 2, and explored the orthogonal deprotection of the final product.

N-Boc-Val-Val-OBn **7** is readily accessed as shown in Scheme 2. As anticipated, our attempts at the MAOS Boc-deprotection of the parent **7** in H_2O failed, with only starting material being recovered. To ensure that this lack of deprotection was not an artefact of the dipeptide, **7** was debenzylated under standard hydrogenation conditions smoothly to *N*-Boc-Val-Val **9** which was readily Boc deprotected after 3 minutes microwave treatment with H_2O, to afford the free Val-Val dipeptide in quantitative yield from **9**.

We next turned our attention to analogues more closely related to the imide library **4**. Via the orthogonally protected **12**, we were able to access both the dicarboxylate **13**, and subsequently *cis*-5-*tert*-butoxycarbonyltetrahydro-3a*H*-furo[3,4-*c*]pyrrole-1,3-dione **15** in excellent yields. The MAOS removal of the Boc group in H_2O proceeded smoothly to afford the amine **14** (Scheme 3).

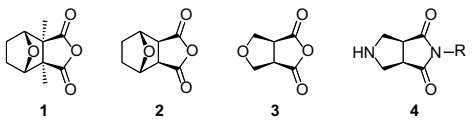
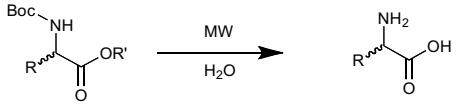
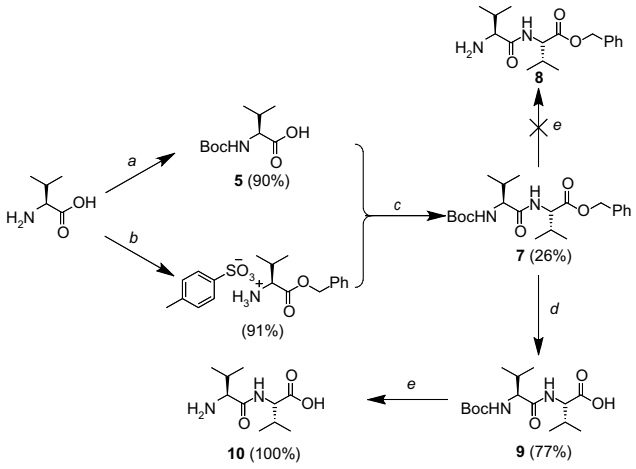


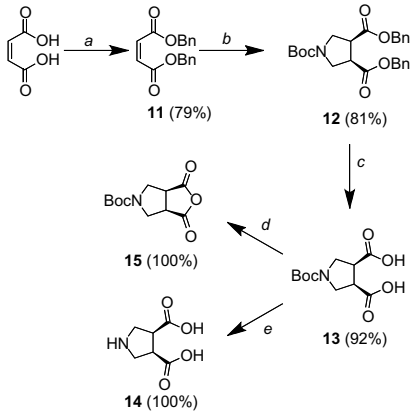
Figure 1. Chemical structures of cantharidin (**1**), norcantharidin (**2**) and the Δ-5,6-ethyl analogues, (3*R*,6*S*)-tetrahydrofuro[3,4-*c*]furan-1,3-dione (**3**) and generic amino acid imide substituted analogues (**4**).



Scheme 1. Microwave assisted Boc-deprotection in H_2O at 170 °C.



Scheme 2. Reagents and conditions: (a) $(Boc)_2O$-anhydride, dioxane, NaOH, rt, 20 h; (b) BnOH, *p*-TsOH, $PhCH_3$, reflux, 5 h; (c) DCC, Et_3N, DMF, rt, 5 h; (d) H_2 (1 atm), 10% Pd–C, rt, 43 h; (e) Microwave, H_2O, 3 min.



Scheme 3. Reagents and conditions: (a) K_2CO_3, BnBr, DMA, 0 °C, rt, 48 h; (b) (i) Gly, $(CH_2O)_n$, (ii) $(Boc)_2O$, rt, 24 h; (c) H_2 (1 atm), 10% Pd–C, rt, 48 h; (d) Ac_2O, AcOH, reflux, 35 min; (e) Microwave, H_2O, 2 min.

In this work, thus far, we have shown that *N*-Boc-Phe-OMe and *N*-Boc-Val-Val-OBn are resistant to Boc-de-protection under microwave heating conditions in H_2O. However, in an effort to further confirm the importance of the free carboxylic acid group in the deprotection step, we examined the deprotection of an *N*-Boc-pyrrolidine, a system known to undergo a very facile TFA or HCl-mediated Boc removal. In all our efforts at Boc removal with H_2O, we only recovered unreacted *N*-Boc-pyrrolidine.

Thus microwave heating with water removal of the Boc protecting group is a facile, and green process, but relies on the presence of a free carboxylic acid group in the substrate. In the absence of this carboxylate, typically only starting material is recovered.

Acknowledgements

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Supplementary data

Supplementary data (full experimental detail is provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.027.

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