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Towards a selective Boc deprotection on acid cleavable Wang resin

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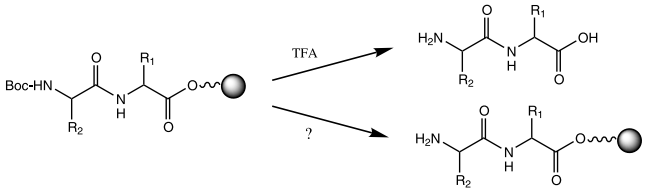
Abstract—Deprotection of the Boc group of an amino acid attached to the Wang resin has been investigated. Several conditions, including bases, solvents and reaction time, were studied. Quantitative yield of Boc deprotection was achieved with less than 10% loss of resin loading with trimethylsilyltriflate. This reagent allows the replacement of *tert*-butyl to TMS group, leading to a new temporary urethane protection readily hydrolyzed. © 2003 Elsevier Science Ltd. All rights reserved.

The Wang resin is one of the most commonly used solid polymer in SPPS. A Fmoc strategy for the lengthening of the peptide chain is commonly used due to its compatibility with the final acid cleavage of the peptide-resin bond. To enlarge the existing tactic possibilities on this resin type, we investigated the use of Boc protection as a new potential combination. Classical acid conditions (TFA 30–90% in DCM) for Boc removal also cleave the peptide from the Wang resin. Therefore, we investigated new conditions for the removal of the Boc group which would preserve the peptide-resin bond (Scheme 1).

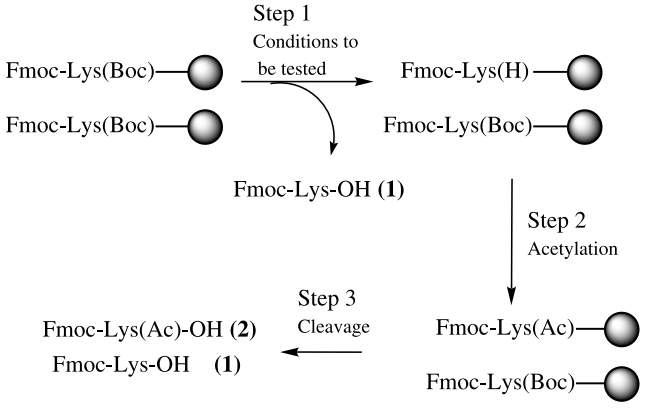
Although several efforts have been dedicated to achieve selective Boc deprotection in the presence of acidolabile *tert*-butyl esters,[1–5] to the best of our knowledge, no study has been related to the Wang resin.

We studied numerous conditions on a model substrate, Fmoc-Lys(Boc) attached to the Wang resin. The chromophoric Fmoc group was left unaffected, which allowed us to evaluate by HLPC the amount of both cleaved and supported amino acid. In order to compare the efficacy of several conditions, Fmoc-Lys(Boc)-Wang resin was subjected to the three consecutive steps described in Scheme 2.

Deprotection of the Boc group in the screened conditions (step 1) may also cleave the aminoacid derivative from the support, leading to Fmoc-Lys-OH (**1**) in solution. HPLC analysis of the cleavage solution allowed us to evaluate this unwanted loss of loading.[6] On the other hand, these deprotection conditions may also prevent the completion of the reaction, forcing both species, Fmoc-Lys(H) and Fmoc-Lys(Boc), to co-exist on the resin. The relative proportion of these two compounds was determined by HPLC analysis of the filtrate col-



Scheme 1.



Scheme 2.

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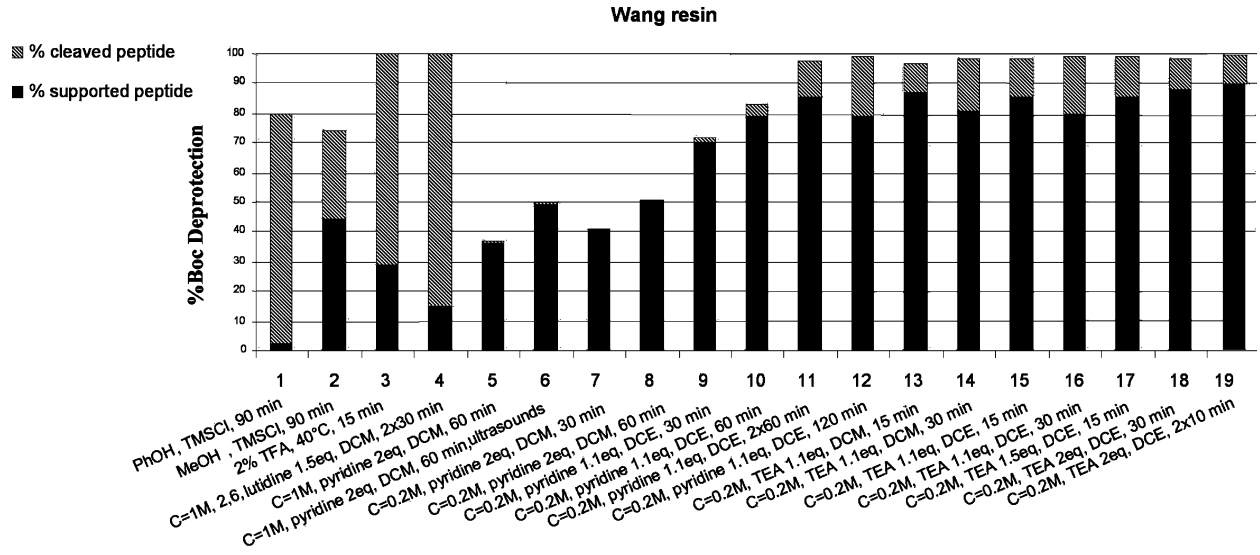


Figure 1. Boc cleavage conditions on Wang resin.

lected after acetylation (step 2) and cleavage (step 3).[6] The calculated amount of compound (**2**) depends on the Boc deprotection rate of step 1 and corresponds to the deprotected lysine remaining grafted on the resin. The results from the conditions screened in step 1 are gathered in Figure 1.

We initially applied acidic conditions, using in situ generated HCl with phenol and chlorosilane[7,8] (entry 1), methanol and chlorosilane[9] (entry 2) or diluted TFA (entry 3) but without any success, since these conditions induced the loss of peptide from the support. A method for the removal of N-Boc groups on Rink's amide resin was described using a combination of TMSOTf and 2,6-lutidine.[10] In our hands, these conditions led to a high percentage of peptide cleavage on the Wang resin (entry 4). We then tried pyridine with TMSOTf. While the Boc group could be removed with little cleavage of the peptide from the resin, the yield was not satisfactory (entry 5). We therefore retained these reagents and modified reaction time, solvent and concentration of TMSOTf (entries 6–12). We also tested TEA as another base in several conditions (entries 13–19), since TEA is commonly used with trialkylsilyltriflate reagents.[11] The comparison of entries 11 and 15 highlights the need for a shorter reaction time with TEA (15 min), while 60 min were necessary to obtain a similar deprotection rate with pyridine. Increasing the amount of TEA favored Boc deprotection with regard to peptide cleavage (entries 15 and 17 and entries 16 and 18). The best conditions involved 2 equivalents of TEA (entries 18 and 19).

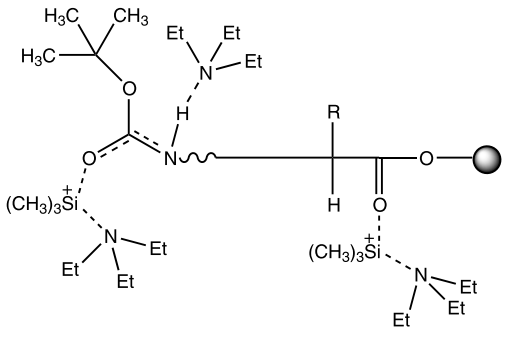
Several solvents were also tested. Attempts in DMF did not lead to any deprotection reaction. This imposed the use of chlorinated solvents. DCE seems to accelerate the reaction in comparison with DCM (entries 14 and 16).

Greater efficiency was observed by repeating deprotection step for short periods of time with freshly prepared solution (entries 11 and 12 and entries 18 and 19) since the unwanted cleavage was minimized for the same deprotection rate.

In summary, kinetic of the reaction showed that a short reaction time was preferable, DCE was a better solvent than DCM and TEA was eligible. Conditions 19 were defined as the most satisfactory.[12]

Replacing the *t*Bu group of the Boc protection with a TMS group enlarges the choice of other protections. Indeed this TMS urethane is compatible with a larger range of chemical protecting groups since cleavage merely occurred by hydrolysis or methanolysis. This type of transitory protecting group gave rise to many studies in solution phase.[13–15]

The competition between Boc deprotection and cleavage from the resin can be explained by a double complexation of the silyl derivative with the oxygen atoms on the urethane and ester functions (Scheme 3). However, since urethane reacts quicker than ester, and



Scheme 3.

probably because of steric hindrance related to the resin, deprotection occurred in preference.

In conclusion, we found that avoiding acidic conditions by using a trimethylsilyl urethane transitory protection allowed Boc removal on the resin in a quantitative yield with a relatively small percentage (10%) of peptide cleavage from the support. The deprotection procedure presented here may not be recommended for repetitive cycles for peptide lengthening in Boc strategy. However, it can be very useful as a unique deprotection step in a complex synthesis involving a triple orthogonality. For example, it might represent a useful alternative for the preparation of cyclic peptides in which a side chain to side chain ring is formed while the peptide is still attached to the solid support, and where the sequence might be subjected to further reactions such as peptide elongation following this step.

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6. Measure of deprotection and cleavage percentages: the combined deprotection mixture and washing layers (5×2 ml of DCM) were concentrated under vacuum. The residue was completely dissolved in 9 ml of acetonitrile and a fraction of 5 μl was injected in HPLC (analysis at 263 nm). On the resin, acetylation was carried out with 40 equiv. of Ac_2O (1 mmol, 94.4 μl) and 40 equiv. of TEA (1 mmol, 139.1 μl) in 5 ml of DCM overnight. Then the cleavage was effected with TFA 95% (1.5 ml) for 3 h. The resin was then filtered and washed three times with DCM. The combined filtrates were concentrated and the residue was dissolved in 9 ml of acetonitrile, of which 5 μl were injected in HPLC (analysis at 263 nm).
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12. Deprotection protocol: To a reaction vessel containing 35 mg of resin (22 μmol, according to the loading), were added 2.4 ml of deprotection mixture, freshly prepared from 133.5 μl of TEA, 76.5 μl of TMSOTf and 2.2 ml of DCM. The resin was shaken for 10 min then filtered and washed with 5×2 ml of DCM, 2×2 ml of DIEA 10% in DCM, 3×2 ml of DCE. Deprotection was carried out for another 10 min with a fresh deprotection mixture. The resin was filtered then washed with 5×2 ml of DCM, 2×2 ml of DIEA 10% in DCM, 2×2 ml of DCM and 2×2 ml of DMF. Then 3 ml of methanol were added to the resin and the reaction mixture was sonicated for 30 min. After filtration, the resin was washed with 5×2 ml of DMF and 3×2 ml of DCM.
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