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Loss of the *tert*-Butyloxycarbonyl (Boc) Protecting Group Under Basic Conditions

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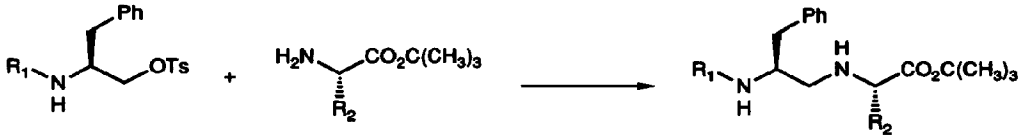
Abstract: Reaction of **3**, the N-Boc, O-tosyl derivative of phenylalaninol, with base leads to loss of the Boc and tosyl groups and formation of oxazolidinone **9**. Similar reactions have also been examined. A mechanism to explain loss of the Boc group under basic reaction conditions is proposed.

The *tert*-butyloxycarbonyl (Boc) group[1] has found widespread use in both organic and peptide synthesis as an amine protecting group[2] because it is readily removed under acidic conditions, but is generally stable under neutral or basic conditions.[3] In this paper we wish to report some examples where a Boc group is lost under basic conditions.

The loss of the Boc group under basic conditions was first observed during a project aimed at exploring methods for the synthesis of **8**, which contains a reduced amide (CH_2NH) bond.[4]

Scheme 1



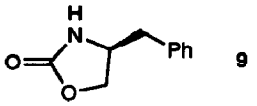
1 R_1=Tos
2 R_1=Cbz
3 R_1=Boc

4 R_2=CH_3
5 R_2=CH_2Ph

6 R_1=Tos, R_2=CH_3
7 R_1=Cbz, R_2=CH_3
8 R_1=Boc, R_2=CH_2Ph

Because they are not readily degraded *in vivo* by proteases,[4b,5] peptides having reduced amide bonds are common synthetic targets.[6] Consequently, the development of synthetic methods for preparing reduced amides has received some attention.[7] One conceptually simple approach for making reduced amide peptides involves nucleophilic attack of an amino acid ester on an N-protected, O-tosylaminoalcohol, as shown in Scheme 1. This approach has previously been explored by Ondetti and co-workers,[8] who found that the reduced amide could be prepared when the N-protecting group was tosyl.[9] For example, **1** and **4** will react to provide **6**. However, when the N-protecting group was Cbz, for example the reaction of **2** and **4**, the desired product **7** was not obtained. Because the Boc group was not examined in these experiments, we

investigated whether it can successfully be employed as the N-protecting group in these reactions. Accordingly, 3[10] and 5 were reacted in a $CHCl_3$ solution containing diisopropylethylamine (DIEA). At room temperature 3 was slow to react; however, when the solution was brought to reflux, 3 but not 5 was consumed and a new species was produced. Subsequent spectral analysis revealed that this new species derived from 3 was not the anticipated product 8; rather, it was the oxazolidone 9.[11] In previous work, 9 and other oxazolidones were reported as minor, unwanted side products in the formation of thiomethylene (CH_2S) amide bond surrogates from reaction of 3 and similar tosylates with the disodium salt of mercaptoacetic acid.[12] In the present case, 9 was the sole product of the reaction.

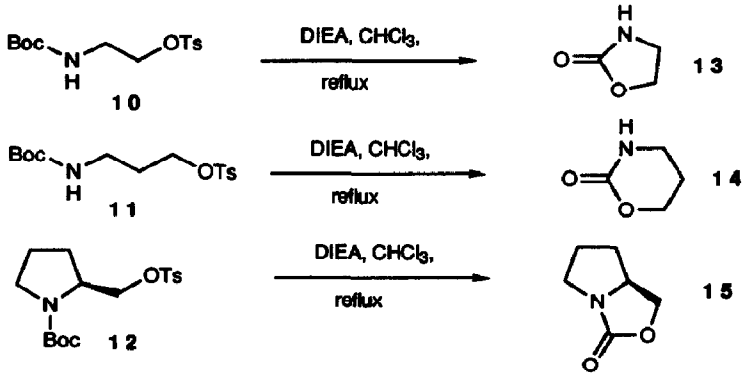


9

In order to further explore the rearrangement that leads to the formation of 9, 3 was subjected to base treatment under a variety of conditions. First, simply refluxing 3 in a DIEA/$CHCl_3$ solution quickly produced 9. Second, although it is formed slowly, 9 is formed from 3 in DIEA/$CHCl_3$ solutions at room temperature. Third, treatment of 3 with LDA at -78°C also leads to formation of 9.

To explore the generality of the rearrangement, several readily available structural relatives of 3 were reacted with DIEA in refluxing $CHCl_3$. Scheme 2 shows the molecules that were

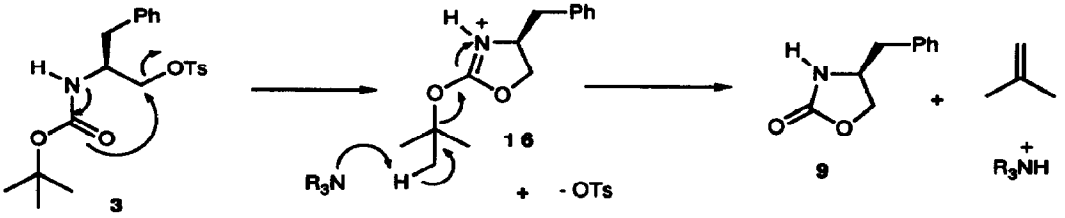
Scheme 2



examined. Both 5- (9, 13, 15) and 6-membered ring (14) urethane products were obtained.[13] In addition, both secondary (3, 10, 11) and tertiary (12) Boc urethanes undergo the rearrangement. In fact, 12 as a pure oil undergoes reaction simply on standing at room temperature for a week.[14]

Based on the reactions examined, a likely mechanism for rearrangement of 3 is given in Scheme 3. Initially, the urethane carbonyl displaces the tosylate yielding the cationic

Scheme 3



intermediate 16. Attack of a urethane carbonyl on an electrophilic carbon has been noted before. For example, the first step in the formation of α-amino acid-N-carboxyanhydrides from N-alkoxycarbonyl α-amino acid chlorides involves attack of the urethane carbonyl at the activated acyl carbon.[15] In addition, attack of a urethane carbonyl at an electrophilic alkyl carbon has been seen in a rearrangement that occurs when N-carbobenzyloxy-L-homoiodoalanine methyl ester is subjected to Arbuzov reaction conditions.[16] In the second step in Scheme 3, abstraction of a proton from one of the *t*-butyl methyls in 16 leads to elimination of isobutylene and formation of 9. This elimination step is similar to the base-catalyzed mechanism for removal of the Fmoc protecting group.[17] Alternatively, a mechanism in which deprotonation and cyclization occur simultaneously is also possible.

Previously, it has been observed that activation of N-Boc amino acids with dicyclohexylcarbodiimide (DCC) leads to loss of the Boc group and formation of ninhydrin-positive products, and a mechanism which initially involves formation of an oxonium intermediate by attack of the t-butyl oxygen of the Boc group on the activated carboxyl was proposed.[18] Based on our findings here, a more likely mechanism for the formation of ninhydrin-positive products would be analogous to the mechanism shown in Scheme 3: attack of the urethane carbonyl on the activated carboxyl followed by an elimination to form isobutylene and the amino acid-N-carboxyanhydride.

To conclude, the results presented here show that the Boc protecting group is not impervious to treatment with base. With suitably placed leaving groups, the Boc protecting group is readily lost under a variety of basic reaction conditions and rearranged products are obtained. Accordingly, care must be exercised when using the Boc group in a synthetic sequence requiring base treatment. Also, the results suggest that rearrangements like the ones detailed here are the probable reason why Boc- and Cbz-protected tosylates, like 2 and 3, fail to yield reduced amide dipeptides from nucleophilic attack by amino acid esters; intramolecular rearrangement proceeds much faster than the desired bimolecular displacement.

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11. **9**: a white, crystalline solid, m.p. 80-81°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (5H, m), 6.1 (1H, s), 4.40 (1H, m), 4.07 (2H, m), 2.84 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 136.1, 129.2, 129.1, 129.0, 128.8, 127.3, 69.7, 53.9, 41.5. TLC R_f 0.63 (EtOAc). Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.64; H, 6.22; N, 7.84.
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