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An alkoxide anion-triggered *tert*-butyloxycarbonyl group migration. Mechanism and application

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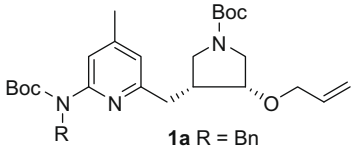
ABSTRACT

We report a fast N→O *tert*-butyloxycarbonyl (Boc) migration of the imide (3*R*,4*R*)-*tert*-butyl 3-((6-(bis-(*tert*-butoxycarbonyl)amino)-4-methylpyridin-2-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (**2**) via a base-generated alkoxide. The mechanism of the migration is intramolecular, involving an unusual nine-membered cyclic transition state.

In the course of research on the development of chiral pyrrolidine-based inhibitors for neuronal nitric oxide synthase (nNOS), we evaluated various methods for the synthesis of compounds **1a** and **1b**, the key intermediates to prepare drug candidates for different kinds of neurodegenerative diseases.[1–3] Given the poor efficiency of benzyl deprotection during the reported synthetic route to **1a**,[2] we attempted to use bis-Boc protection of the amino group on the pyridine ring (**1b**); these groups could be removed in one step during the late stage deprotection of the synthesis in excellent yields, providing a much more practical preparation of the final products on a multi-gram scale.[4]



1a R = Bn
1b R = Boc

To generate **1b**, allylation of alcohol **2** was attempted by treating a solution of **2** in DMF with NaH (2 equiv) at room temperature, followed by the addition of allyl bromide (2 equiv). The reaction was quenched with H_2O to form the product with 93% isolated yield (Scheme 1). To our surprise, mass spectrum and ^1H NMR data of this product did not match with those of the anticipated product (**1b**). The isolated product has only an ($M+H^+$) peak at 448, which is 100 less than the calculated molecular weight of **1b** (**M + H⁺ = 548**), implying a possible loss of one Boc group from the desired product. This was further confirmed by the fact that there were two distinctive singlets at 1.46 and 1.52 ppm (each integrating to nine protons) in the ^1H NMR spectrum (in $CDCl_3$) of the product. The instability of the Boc-protecting group under strong basic conditions has been documented.[5,6] Interestingly, however, one broad singlet in the ^1H NMR spectrum was found from 2.30 to 2.40 ppm, indicating the presence of a hydroxyl group in the product. Further NOSEY NMR data showed that the allyl group was connected through the nitrogen atom of the amino functionality to the pyridine ring.[7] On the basis of these results, we assigned the product as (3*R*,4*R*)-*tert*-butyl 3-((6-(allyl(*tert*-butoxycarbonyl)amino)-4-methylpyridin-2-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (**3**).[8] It was also noted that (1) compound **2** showed significant stability in aqueous NaOH even at accelerated temperature[9] and (2) no O-allylation product was detected in the reaction process.

To elucidate the origin of *N*-allyl alcohol **3**, the reaction was repeated and monitored closely by thin layer chromatography (TLC) and LC/MS analysis. Time course studies clearly showed the disappearance of the starting material (**2**) and the buildup of a new compound with significantly less polarity when **2** was treated with NaH in DMF. After the addition of H_2O, the product (**3**), with similar polarity to that of **2**, was formed quickly (Scheme 1). Accordingly, we speculated that the basic environment generated during the quenching step catalyzed a hydrolysis reaction of the initial product, leading to the formation of alcohol **3**. To test this hypothesis,

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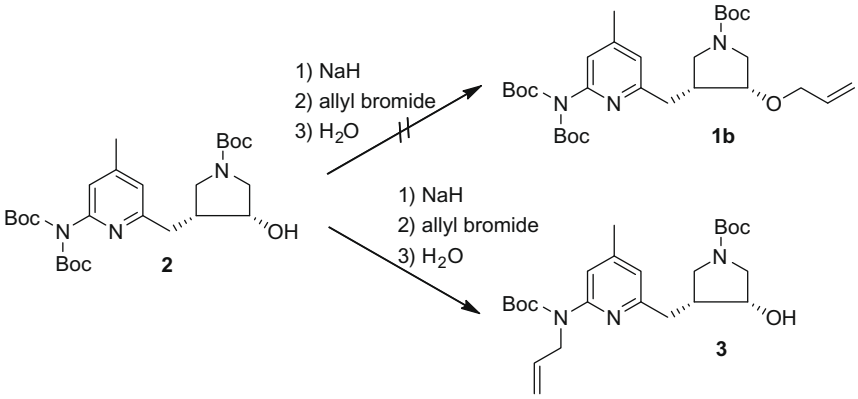
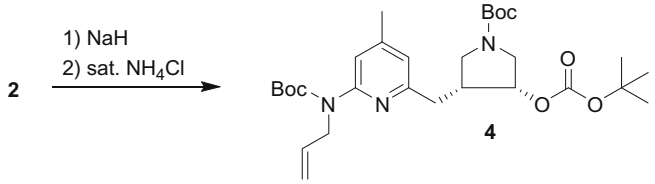


Scheme 1. Formation of **3** from **2**.



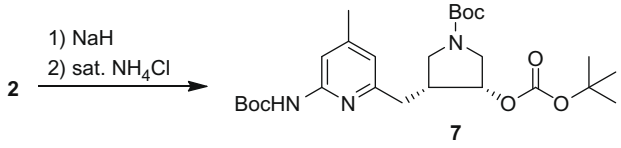
Scheme 2. Formation of **4** from **2**.

the same reaction was repeated and quenched with saturated aqueous NH_4Cl to avoid the potential base-catalyzed hydrolysis step. As a result, compound **4** was isolated in a 96% yield (Scheme 2).[10] This result implies that a carbonate derivative was an intermediate involved in the reaction course, which explains why there was no O-allylation product formed from the reaction.

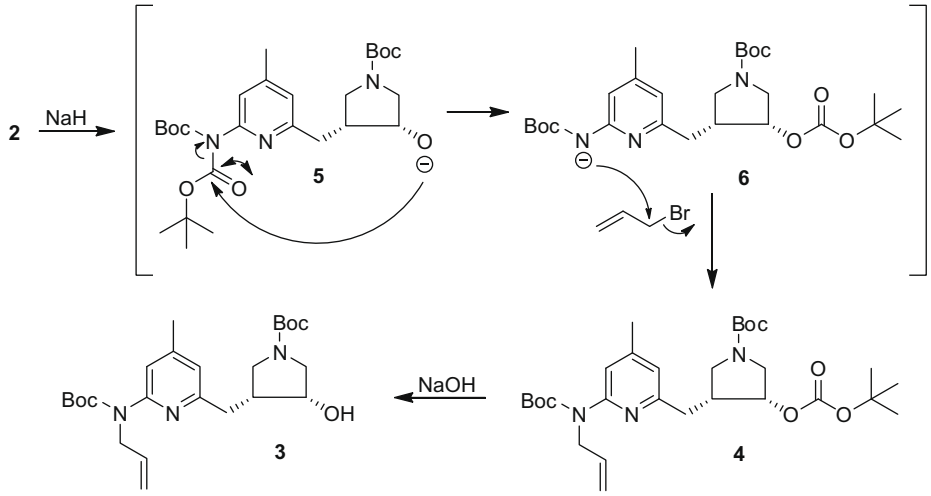
On the basis of this collected evidence, we propose that deprotonation of **2** by treatment with NaH forms **5** at the beginning of the reaction (Scheme 3). Alkoxide **5** initiates the migration of one of the two Boc groups on the aminopyridine through a nine-membered ring transition state to generate amide anion (**6**), which reacts with allyl bromide to generate **4**. Several examples of anion-triggered migration reactions have been described in the literature.[11–15] The carbonate linkage of **4** is unstable to the strong basic environment (e.g., aqueous NaOH, generated during the quenching step) and is hydrolyzed quickly to give alcohol **3** as the only product. To prove the presence of **6**, the reaction was quenched with saturated aqueous NH_4Cl before the addition of allyl bromide. As seen in Scheme 4, compound **7** was isolated in quantitative yields and characterized.[16]

To further investigate the reaction mechanism, we carried out a cross-over experiment using a mixture of compounds **2** and **8** as starting material. The mixture was treated with NaH, and after 5 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction did not give any cross-over product (i.e., *O*-Boc-**8**) as shown in Scheme 5: compound **7** was isolated in almost quantitative yield, and compound **8** was fully recovered from the reaction mixture. These results clearly indicate that the Boc migration reaction takes place by an intramolecular pathway.

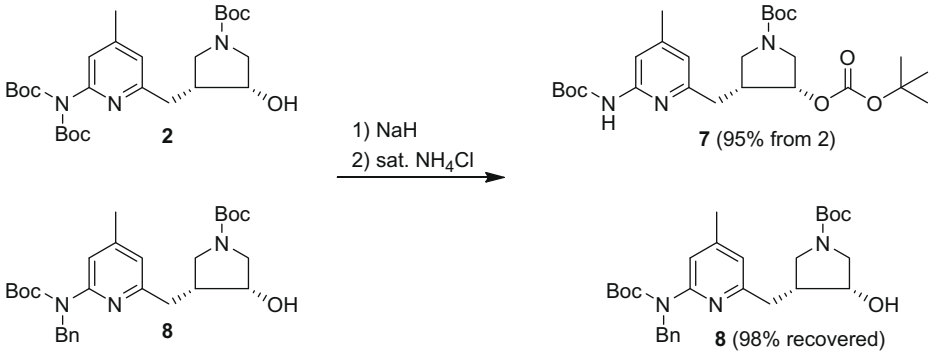
The unusual Boc-protecting group migration also provides a facile approach to selectively add an allyl or a benzyl group onto the amide N atom without hydroxyl group protection. The previous method for this reaction suffered from competition of O-allylation or O-benzylation reactions, leading to unsatisfactory yields of products unless the hydroxyl group was protected (Scheme 6).[2] Using di-Boc-protected **2** as the starting material, however, the



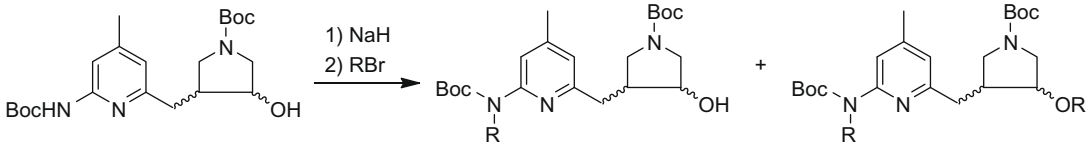
Scheme 4. Formation of **7** from **2**.



Scheme 3. Proposed mechanism for the formation of **3**.



Scheme 5. Cross-over experiment for Boc migration.



Scheme 6. Alkylation of the aminopyridine without hydroxyl protection.

reaction (e.g., allylation or benzylation) produces the desired compound as the only product in excellent yields without interference of side reactions at the hydroxyl group.

In summary, we demonstrated a novel alkoxide anion-triggered N→O Boc migration involving an unusually large nine-membered ring transition state. The Boc migration process provides a new high yield method to perform selective amide allylation/benzylation over hydroxyl allylation/benzylation reactions.

Acknowledgment

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9. Compound **2** was allowed to stir in a mixture of 1 N NaOH and MeOH (1:1) at room temperature. After 30 min, only 15% of the hydrolyzed product (3*R*,4*R*)-*tert*-butyl 3-((6-(*tert*-butoxycarbonylamino)-4-methylpyridin-2-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate was generated: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45–1.46 (m, 9H), 1.52 (s, 9H), 2.33 (s, 3H), 2.33–2.35 (br s, 1H), 2.70–2.80 (dt, *J* = 6.0, 9.5 Hz, 1H), 2.80–2.85 (m, 1H), 3.15–3.20 (dt, *J* = 5.5, 10.5 Hz, 1H), 3.40–3.55 (m, 2H), 3.58–3.62 (dd, *J* = 8.5, 10.0 Hz, 0.5H), 3.63–3.67 (dd, *J* = 8.5, 10.0 Hz, 0.5H), 4.09 (s, 1H), 4.75 (br s, 1H), 6.68–6.69 (d, *J* = 7.0 Hz, 1H), 7.19 (s, 1H), 7.68 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.4, 28.2, 28.52, 28.54, 35.16, 35.24, 44.5, 45.2, 49.0, 49.5, 53.2, 53.6, 60.4, 70.3, 71.3, 79.2, 81.2, 110.6, 119.1, 119.2, 151.0, 151.1, 151.2, 152.2, 154.4, 157.4, 157.5; LC-TOF (M+H$^+$) calcd for $C_{21}H_{34}N_3O_5$ 408.2498, found 408.2499.
10. Synthesis and characterization of (3*R*,4*R*)-*tert*-butyl 3-(allyloxy)-4-((6-(bis(*tert*-butoxycarbonyl)amino)-4-methylpyridin-2-yl)methyl)pyrrolidine-1-carboxylate (**4**). To a solution of **2** (505 mg, 1.0 mmol) in DMF (15 mL) was added NaH (60% in mineral oil, 80 mg, 2.0 mmol) at room temperature. After 5 min, allyl bromide (240 μL, 2.0 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 30 min, then the reaction was quenched with ice cold saturated NH_4Cl (5.0 mL). The solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to yield **4** as a colorless oil (525 mg, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.47–1.49 (m, 18H), 2.25–2.27 (m, 3H), 2.70–2.85 (m, 2H), 2.89–2.93 (dd, *J* = 5.5, 13.0 Hz, 1H), 3.14–3.21 (dd, *J* = 11.0, 21.5 Hz, 1H), 3.46–3.59 (m, 3H), 4.40–4.60 (m, 2H), 5.03–5.12 (m, 3H), 5.86–5.92 (ddd, *J* = 5.5, 12.0, 17.5 Hz, 1H), 6.64 (s, 1H), 7.32 (s, 0.5H), 7.36 (s, 0.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.11, 21.13, 27.8, 28.3, 28.47, 28.50, 34.7, 41.8, 42.3, 48.8, 49.06, 49.10, 49.2, 52.4, 52.8, 76.7, 76.8, 79.4, 80.9, 81.0, 82.4, 82.5, 115.8, 117.3, 117.4, 119.8, 134.91, 134.93, 148.5, 148.6, 153.1, 153.2, 153.9, 154.0, 154.1, 154.2, 154.4, 156.8; LC-TOF (M+H$^+$) calcd for $C_{29}H_{46}N_3O_7$ 548.3336, found 548.3339.
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