Tetrahedron Letters 53 (2012) 1319–1322

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

High yielding allylation of a chiral secondary alcohol containing base sensitive functional groups

James M. Kraus, Hunter C. Gits, Richard B. Silverman *

Department of Chemistry, Chemistry of Life Processes Institute, and Center for Molecular Innovation and Drug Discovery, Northwestern University, Evanston, IL 60208-3113, USA

ARTICLE INFO

Article history:
Received 29 November 2011
Revised 23 December 2011
Accepted 28 December 2011
Available online 14 January 2012

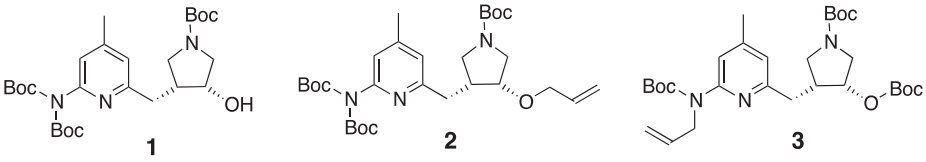
Keywords:
Decarboxylative allylation
Tetrakis(triphenylphosphine)palladium(0)
Neutral O-allylation

ABSTRACT

Inhibitors of neuronal nitric oxide synthase, based on a chiral pyrrolidine scaffold, show promise for the treatment of certain neurodegenerative diseases. We recently reported the synthesis of a series of selective inhibitors, but the method was limited at a key step of forming an allyl ether intermediate. Yields for this step were very inconsistent, and the presence of base sensitive functional groups limited the range of available methods for forming this ether bond. This work describes a novel application of palladium catalyzed decarboxylative allylation, consistently resulting in a 90% isolated yield, which is crucial for the synthesis of this critical late stage intermediate. We also report a new quantitative yielding and straightforward synthesis of the allyl-*t*-butylcarbonate precursor.

Introduction

In our ongoing research to develop potential chemotherapeutic agents to prevent neurodegeneration, we identified a series of compounds, based on a chiral pyrrolidine core that selectively inhibited neuronal nitric oxide synthase (nNOS) with respect to the other two enzyme isoforms, inducible (iNOS) and endothelial nitric oxide synthase (eNOS).[1] A key intermediate in the synthesis of these compounds from (3*R*,4*R*)-**1** is (3*R*,4*R*)-allyloxypyrrolidine **2**. Earlier work showed that the 2-amino nitrogen on the pyridine requires bulky



protecting groups to prevent a side reaction, and for various reasons, we decided to employ a diBoc strategy.[2] We discovered that an unexpected rearrangement takes place when Williamson conditions are used to convert precursor alcohol **1** into allyl ether **2**. Formally, the mechanism is N- to O transfer of a *tert*-butylcarbonyl (Boc) group and allylation of the 2-amino group at the pyridine ring, forming *N*-allyl **3** in a 95% yield. Recently, we reported an improved synthesis of intermediate **2**.[3] By using a method for allylation that proceeds under neutral conditions, we were successful in avoiding the formation of **3** via the aforementioned rearrangement; however, the yields were very inconsistent, often as low as 20%. There is considerable effort associated with obtaining this late stage intermediate in enantiomerically pure form, so we were interested in the identification of a more reliable and high yielding methodology for O-allylation of **1**.

Allylation strategies and their outcomes

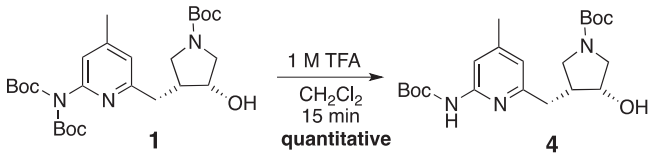
Several general methods were explored to identify a method for forming **2**. Based on the observation that the second Boc group is labile under basic and acidic conditions, we explored ether formation reactions that take place under neutral, or nearly neutral, conditions.

Des-Boc alcohol precursor

As mentioned above, we require the second Boc group on the 2-aminopyridine to prevent a side reaction at an earlier step in the synthesis, and having already served its purpose, we speculated that it might be possible to remove it at this stage, generating **4**, which might be relatively easier to allylate, compared to **1.** We screened various different conditions to find optimum parameters

* Corresponding author. Tel.: +1 847 491 5653.
E-mail address: Agman@chem.northwestern.edu (R.B. Silverman).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.12.120



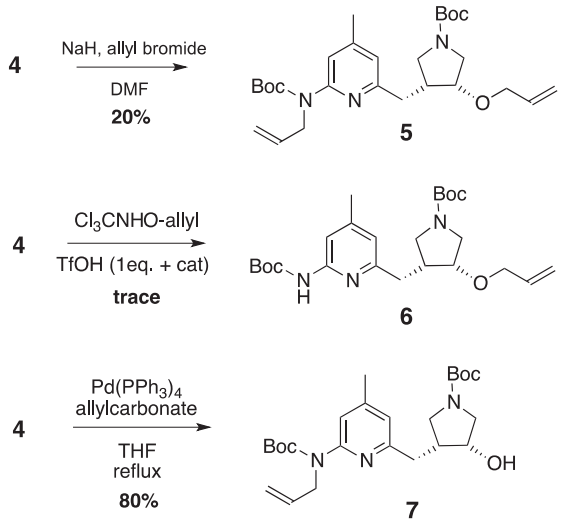
Scheme 1. Generation of **4** by mono deprotection of precursor **1**.

for quantitative removal of just one of the three Boc groups of **1**. When **1** was treated with 1 M TFA in methylene chloride, the Boc group was removed selectively in a near quantitative yield in only 15 min, yielding **4** (Scheme 1).

We predicted a priori that the alkoxide would be a better nucleophile than the carbamate nitrogen anion and hypothesized that **4** could be subjected to >2 equiv of sodium hydride in the presence of a stoichiometric amount of allyl bromide to afford the *O*-allyl product under Williamson conditions. Subsequent aqueous workup would neutralize the carbamate nitrogen anion. Surprisingly, the only major product that was isolated was the *N*,*O*-diallyl species in a 20% yield. There is precedence for using trichloroalkylimidates along with an acid catalyst for the allylation of hindered alcohols, such as carbohydrate secondary hydroxyl groups.[4] We tried the trichloroacetimidate methodology on des-Boc **4**, but only obtained a trace amount of product along with the loss of starting material. This seems to indicate that the substrate is not stable under the conditions of the reaction. Interestingly, treating **4** with palladium and allyl carbonate gave the *N*-allyl product in a high yield, but did not lead to any significant O-allylation, confirming the difficulty in forming the allyl ether of this substrate (Scheme 2).

Sterically hindered carbonate precursor

Next we revisited palladium^0 catalyzed decarboxylative allylation; an advantage of this reaction is that it takes place under nearly neutral conditions, since the amount of alkoxide that is present is never greater than the amount of catalyst. A disadvantage of Pd-catalyzed decarboxylative allylations, in general, is that water competes as a nucleophile twice,[5] first to attack the Pd π-allyl complex, then again, when the newly formed alcohol attacks another Pd π-allyl complex. We had limited success with allyl methyl carbonate, but inspection of the mechanism suggests that the reason may be because the pyrrolidine hydroxyl group is a secondary alcohol. The overall reaction can be viewed as proceeding

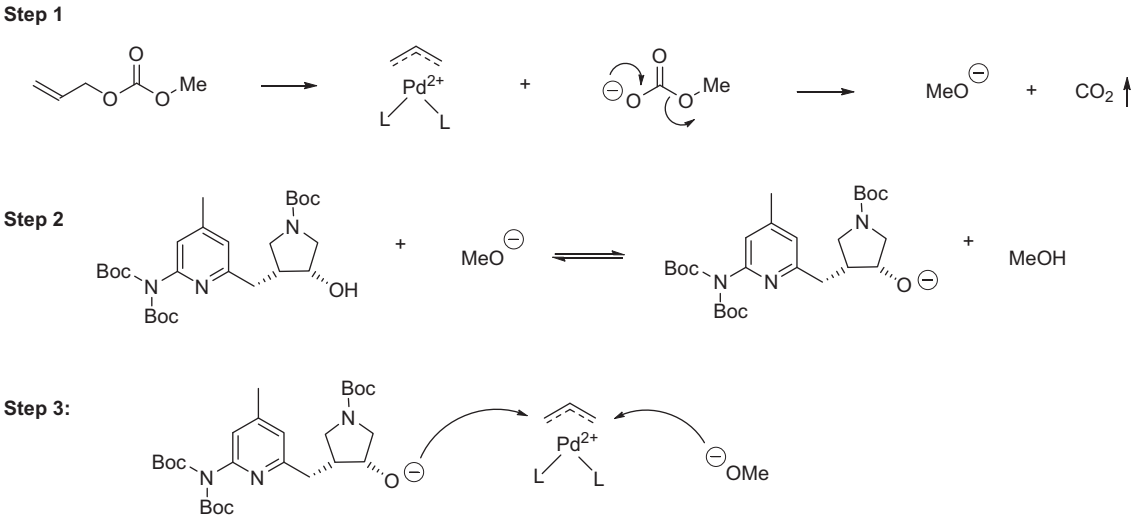


Scheme 2. Attempted O-allylation of **4** using various conditions.

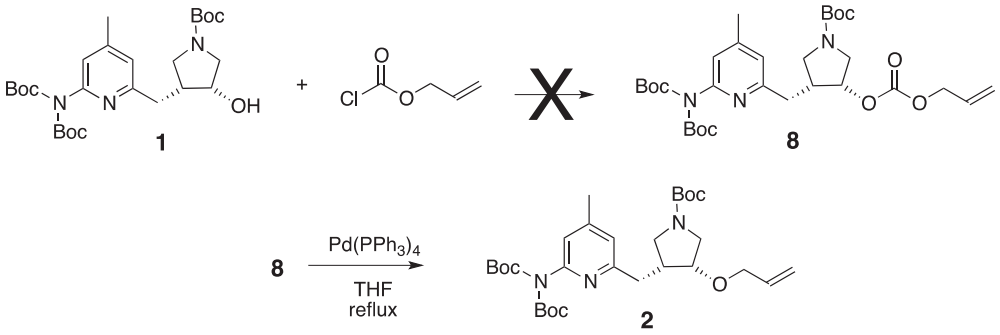
in three steps (Scheme 3): In step 1, methoxide is generated by decarboxylation. In step 2, the pyrrolidine alkoxide is generated from an acid-base reaction with methoxide, but the equilibrium is expected to lie to the left side (favoring the secondary alcohol), which should have a slightly higher pK_a. In step 3, both alkoxide species compete for the allyl cation; however, the nucleophilicity of the secondary pyrrolidine oxide is not expected to exceed that of the methoxide ion.

Therefore, when allyl methyl carbonate is used, we are penalized twice, first in the acid-base reaction, then again in the nucleophilic attack on the π-allyl complex. In general, this hypothesis is attributed to Sinou and coworkers, who used allyl *ethyl* carbonate with Pd^0 to form the allyl ether of carbohydrate substrates,[6] but there are also other variations. In one example, an allyl carbonate precursor was formed from the alcohol substrate,[7] which was then treated with the palladium catalyst. Under strictly anhydrous conditions, this implies that only one nucleophile (the alkoxide of the substrate) would be present to trap the allyl species, and the rate limiting step in the reaction would be the attack of the π-allyl complex by the alkoxide, since the acid-base equilibrium shown in step 2 of Scheme 3 would not be present in the mechanism. Similarly, forming allyl carbonate **8** from alcohol **1**, then subjecting it to palladium catalyzed decarboxylation conditions seemed promising. The requisite allyl chloroformate is commercially available, but we were unsuccessful in forming **8**. These results suggest that formation of the carbonate precursor might be of comparable difficulty to forming the ether product (**2**) from this sterically hindered alcohol, so we did not pursue this method further (Scheme 4).

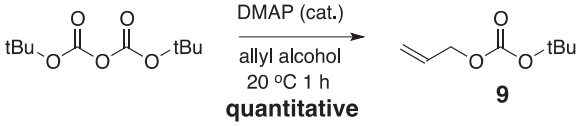
It has been reported that using a less nucleophilic alkoxide, such as *tert*-butoxide (generated from decarboxylation of allyl-*t*-butylcarbonate) should minimize the formation of side products.[8] In that work, they were able to obtain selective allylation of a hindered tertiary hydroxyl group on a carbohydrate substrate, in the presence of two unmasked secondary alcohols, while using only a slight excess (1.2 equiv) of allyl-*t*-butylcarbonate (**9**). The required allyl *tert*-butylcarbonate precursor is not commercially available. It has previously been synthesized from allyl alcohol and di-*tert*-butyl-dicarbonate (Boc_2O) in dichloromethane, using phase transfer catalysis and sodium hydroxide as base.[8] In our hands, the reaction is very sluggish and, even after 48 h, it does not go to completion. It is difficult to separate the carbonate product from the unreacted Boc_2O using silica gel chromatography because the difference in the R_f values is very small. With these factors in mind, we set out to optimize the reaction conditions. It seems likely that the reaction is sluggish because the generation of the alkoxide is not very efficient. Enhancing the activity of the *tert*-butylcarbonyl group would be expected to facilitate the reaction with neutral allyl alcohol. 4-(*N*,*N*-Dimethyl)aminopyridine, DMAP, seemed promising based on the known mechanism involved in DMAP catalysis of acylations using acetic anhydride. It was speculated that running the reaction neat (Boc_2O in allyl alcohol) would allow kinetics that are limited by diffusion rather than phase transfer. The hypothesis turned out to be correct; using DMAP catalysis enabled facile production of the required carbonate. The optimized conditions are as follows: Di-*tert*-butyl-dicarbonate (10 g) was dissolved in 20 mL of anhydrous allyl alcohol. DMAP (275 mg, 5 mol %) was added all at once, and a reflux condenser was attached. Immediate evolution of CO_2 occurred, which proceeded at a constant rate for about 1 h, at which time the reaction was complete, and Boc_2O was undetectable in the crude mixture by TLC. The crude product was a solution in allyl alcohol, which was used in excess. It would be desirable to remove the excess unreacted allyl alcohol before attempting the chromatographic purification of the carbonate, but when the crude reaction mixture was placed on the rotary evaporator, both the carbonate product and allyl alcohol were removed. Fractional distillation



Scheme 3. Three-step mechanism for palladium catalyzed decarboxylative allylation reaction.



Scheme 4. Attempted formation of **2** by direct decarboxylative allylation of **8**.



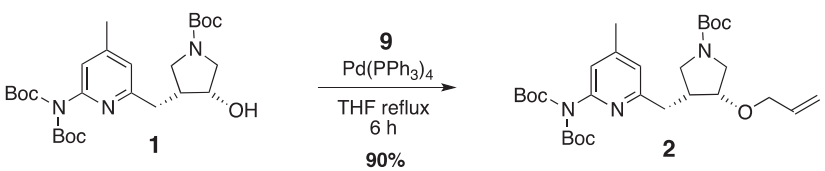
Scheme 5. Synthesis of allyl-*t*-butylcarbonate (**9**).

was not practical because the boiling points of the two compounds are very similar. Ultimately, the purification of the product was achieved by loading the crude reaction mixture directly onto silica gel. A mobile phase consisting of 5% ethyl acetate in hexanes eluted the product with an R_f of 0.5, while the DMAP catalyst and allyl alcohol were not eluted from the silica gel under these conditions. Potassium permanganate was used to visualize the olefin product by TLC. In this way, 7.3 g of **9** was produced from 10 g of di-*tert*-butyl-dicarbonate (Scheme 5).

On the basis of our previous work, we expected the second Boc group to be very labile under basic conditions. We predicted that we could use a very low catalyst loading to minimize the concentration of alkoxide, and utilize *tert*-butylcarbonate precursor to prevent side reactions. Using 2.5% palladium catalyst and 5 equiv of **9** led to the formation of the desired product in a 90% isolated yield in 6 h (Scheme 6). Further optimization could include using a lower stoichiometric ratio of carbonate, but will also require more rigorous exclusion of water, and **9** is easily synthesized in one step from inexpensive starting materials.

Conclusions

A simple protocol for the allylation of a complex substrate alcohol is reported. This robust method should be a useful addition to the synthetic tool kit for researchers interested in the allylation of sterically-hindered alcohols in key pharmacophoric scaffolds containing base-sensitive functional groups. By using commercially



Scheme 6. Decarboxylative allylation of **1** to form **2** in high yields.

available tetrakis(triphenylphosphine)palladium catalyst and a new simplified method for the synthesis of allyl-*t*-butylcarbonate (**9**), selective allylation of hindered alcohols proceeds in greater than 90% isolated yield.

Experimental

Allyl *tert*-butylcarbonate (9)

A flame-dried flask containing a stir bar was charged with di-*tert*-butyl-dicarbonate (10.0 g, 45.8 mmol), and anhydrous allyl alcohol (10.0 mL, 147 mmol) was added. A water-cooled condenser was attached and fitted with a calcium chloride drying tube. When the solids had dissolved, 4-(dimethylamino)-pyridine (275 mg, 2.25 mmol, 5%) was added all at once. Gas was evolved immediately, and continued at a steady rate for approximately 1 h. At this time, TLC indicated that the di-*tert*-butyl-dicarbonate starting material had been completely consumed, as visualized with I_2. The product was purified by flash chromatography using a 5.5 cm (od) column. The crude mixture was loaded directly onto the silica gel and eluted using a mobile phase consisting of 5% ethyl acetate/95% hexanes, producing 7.3 g (quantitative) of **9**. The product was visualized with potassium permanganate staining, R_f 0.4. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.94 (m, 1H), 5.35 (ddd, J = 1.5, 3, 17.5 Hz, 1H), 5.26 (dd, J = 1.5, 10.5 Hz, 1H), 4.56 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 153.31, 131.96, 118.60, 82.21, 67.62, 27.77.

(3*R*,4*R*)-*tert*-Butyl-3-(allyloxy)-4-((6-(bis(tert-butoxycarbonyl)-amino)-4-methylpyridin-2-yl)methyl)pyrrolidine-1-carboxylate (2)

A flame-dried flask containing a stir bar was fitted with a water-cooled condenser under an argon atmosphere. (3*R*,4*R*)-*tert*-Butyl 3-((6-(bis(tert-butoxycarbonyl)amino)-4-methylpyridin-2-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (1, 175 mg, 0.35 mmol) was dissolved in 20 mL of anhydrous THF and added to the flask, followed by $Pd(PPh_3)_4$ (12 mg, 2.5%) as a solution in anhydrous THF (5 mL). The mixture was degassed by bubbling in argon for 20 min (the volume of solvent was reduced slightly). A shift in the color of the solution was observed from bright yellow to dark yellow. The mixture was heated to reflux for several minutes. A solution of **9** (320 mg, 1.74 mmol) in 5 mL anhydrous THF was injected into the preheated, refluxing THF solution over approximately 1 min. The reaction was allowed to stir under reflux for 6 h, at which time, complete consumption of starting material was indicated by TLC, and a new spot was observed R_f = 0.8, 25% ethyl acetate/75% hexanes. Silica gel chromatography gave 2 as a white solid (172 mg, 90%) ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.91 (d, J = 8.5 Hz, 1H), 6.90 (s, 1H), 5.88 (m, 1H), 5.27 (m, 1H), 5.16 (d, J = 10.5 Hz, 1H), 4.03 (dt, J = 5.5, 13 Hz, 1H), 3.78 (m, 2H), 3.52 (m, 2H), 3.27 (dd, J = 3.5, 12.5 Hz, 1H), 3.16 (m, 1H), 3.01 (m, 1H), 2.81 (m, 1H), 2.69 (m, 1H), 2.33 (m, 3H), 1.44 (s, 18H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 159.25, 159.19, 154.78, 154.48, 151.81, 151.48, 151.43, 149.50, 134.67, 134.62, 122.94, 119.55, 116.87, 116.67, 82.82, 79.21, 79.13, 78.61, 77.78, 70.26, 70.18, 51.00, 50.43, 49.20, 48.87, 43.32, 42.67, 34.76, 34.66, 28.51, 27.92, 20.90. HR ESI-MS: m/z = 548.3325 (mono-isotopic mass = 547.3258).

Acknowledgments

The authors are grateful for financial support from the National Institutes of Health (GM049725). J.M.K. thanks the Center for Molecular Innovation and Drug Discovery at Northwestern University for a postdoctoral fellowship from the NIH training grant, Drug Discovery in Age Related Disorders (T32 AG000260).

References and notes

1. Ji, H.; Delker, S. L.; Li, H.; Martasek, P.; Roman, L. J.; Poulos, T. L.; Silverman, R. B. *J. Med. Chem.* **2010**, *53*, 7804.
2. Xue, F.; Silverman, R. B. *Tetrahedron Lett.* **2010**, *51*, 2536.
3. Xue, F.; Kraus, J. M.; Labby, K. J.; Ji, H.; Mataka, J.; Xia, G.; Li, H.; Delker, S. L.; Roman, L. J.; Martasek, P.; Poulos, T. L.; Silverman, R. B. *J. Med. Chem.* **2011**, *54*, 6399.
4. Wessel, H.-P.; Iverson, T.; Bundle, D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.
5. Stoner, E. J.; Peterson, M. J.; Allen, M. S.; DeMattei, J. A.; Haight, A. R.; Leanna, M. R.; Patel, S. R.; Plata, D. J.; Premchandran, R. H.; Rasmussen, M. *J. Org. Chem.* **2003**, *68*, 8847.
6. Lakhmiri, R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1989**, *30*, 4669.
7. Oltvoort, J. J.; Kloosterman, M.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 501.
8. Houlihan, F.; Bouchard, F.; Frechet, J. M. J. *Can. J. Chem.* **1985**, *63*, 153.