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Communication

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Process Development and Pilot-Plant Synthesis of (*S*)-*tert*-Butyl 1-Oxo-1-(1-(pyridin-2-yl)cyclopropylamino)propan-2-ylcarbamate: Studies on the Scale-Up of Kulinkovich–Szymoniak Cyclopropanation

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Supporting Information

ABSTRACT: A practical and scalable synthesis of (*S*)-*tert*-butyl 1-oxo-1-(1-(pyridin-2-yl)cyclopropylamino)-propan-2-ylcarbamate, an intermediate in the manufacture of a lymphocyte function-associated antigen 1 inhibitor, is described. The titled compound is prepared via an efficient one-pot, two-step telescoped sequence starting from readily available materials. A modified Kulinkovich–Szymoniak cyclopropanation of a nitrile followed by in situ amide formation with an activated carboxylic acid derivative afforded the target product in about 50% overall isolated yield and >97% purity.

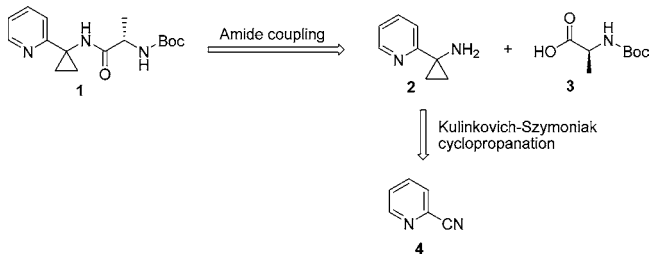
INTRODUCTION

Recently our development program required a large-scale synthesis of cyclopropylaminopyridine-(L)-alanine dipeptide (**1**), a key intermediate for lymphocyte function-associated antigen (LFA-1) antagonist as a potential treatment of immune disorders. Although the synthetic route is relatively straightforward, extensive development and optimization efforts were required to implement a practical and scalable process for the multikilogram production of this seemingly simple molecule. Our strategy involved a modified protocol of Kulinkovich–Szymoniak cyclopropanation of 2-cyanopyridine to afford 2-cyclopropylaminopyridine (**2**). The reaction mixture of the cyclopropanation was directly subjected to an amide coupling with activated Boc-(L)-alanine without purification or isolation. This one-pot, two-step sequence enabled the multikilogram preparation of the dipeptide (**1**) in pilot-plant without column purification (Scheme 1).

RESULTS AND DISCUSSION

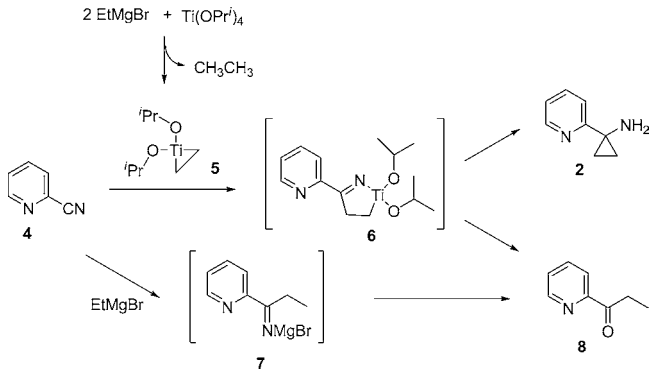
Szymoniak and Bertus have reported that treatment of nitriles with ethyl Grignard reagents and titanium tetraisopropoxide followed by a Lewis acid (such as $BF_3{\cdot}OEt_2$) afforded cyclopropylamines.[1−4] This is a variation of the commonly known Kulinkovich reaction,[5−13] which involves the synthesis of cyclopropanols from esters using ethylmagnesium bromide and titanium tetraisopropoxide. Following the reaction conditions described by Szymoniak, our synthesis started from readily available 2-cyanopyridine, which was treated

Scheme 1. Retrosynthesis of 1



with 2 equiv of ethylmagnesium bromide in the presence of 1 equiv of $Ti(OPr^i)_4$. The reaction proceeded to give the desired cyclopropylamine in a modest 55% yield, consistent with the reported results. The major byproduct of this reaction was identified as pyridyl ethyl ketone (**8**), and its formation can be explained in the mechanism of Kulinkovich–Szymoniak reaction. As outlined in Scheme 2, reaction between ethyl

Scheme 2. Reaction mechanism for the formation of 2 and 8



magnesium bromide and titanium tetraisopropoxide gives titanacyclopropane **5**, which undergoes addition to the nitrile group to form azatitanacyclopentane **6** as intermediate. Contraction of **6** leads to the desired cyclopropylamine (**2**). If the contraction of **6** is slow, ethyl ketone **8** could be obtained

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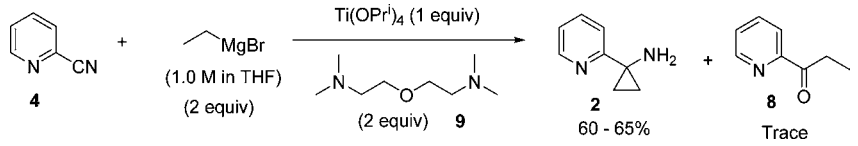
Scheme 3. Addition of the diamine ligand 9 to improve the yield of 2



after workup. Another possibility for the formation of **8** is that ethyl Grignard reagent undergoes direct addition to the nitrile to give **7** instead of forming the titanacyclopropane species **5**.

It has been discovered by this department that the organic ligand bis[2-(*N*,*N*-dimethylaminoethyl)]ether (**9**) can modulate the reactivity of the organomagnesium reagents.[14−16] Therefore, it was envisioned that bis[2-(*N*,*N*-dimethylaminoethyl)]ether (**9**) could form a complex with ethyl Grignard reagent and moderate its reactivity, thereby suppressing the addition of ethyl Grignard reagent to the nitrile group. Indeed, addition of this ligand to the reaction mixture gave a cleaner reaction profile with less formation of **8**[17] (see Scheme 3). Due to the decreased reactivity, the reaction needs to be run at high temperature (over 60 °C). As a result, the contraction of intermediate **6** is also accelerated, and therefore less **8** is formed.[18]

Our initial procedure for the cyclopropanation involved addition of ethyl Grignard reagent to the mixture of 2-cyanopyridine, Ti(OPr^i)$_4$, and diamine ligand (**9**) in 2-methyl THF. Although the reaction profiles were cleaner than those without the diamine ligand, several low-level byproducts were detected (Figure 1). LC/MS analysis revealed they were

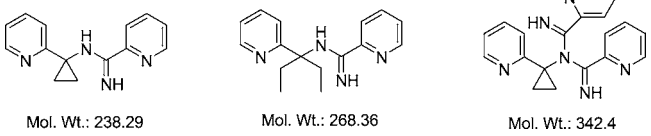


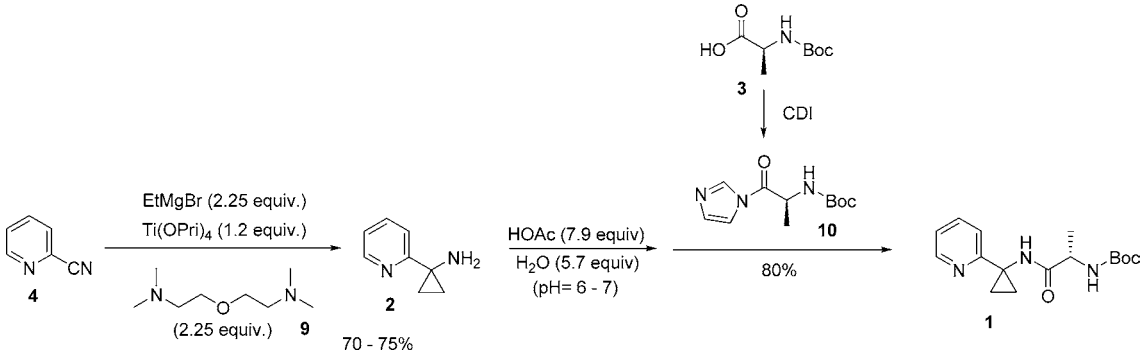
Figure 1. Byproducts detected in the cyclopropanation.

dimeric species, possibly due to further reaction between the product (**2**) and starting material (**4**).

We rationalized that in order to prevent the formation of these dimeric byproducts, we needed to reduce the time of contact between 2-cyanopyridine (**4**) and the product **2**. To this purpose, a revised procedure was applied in which 2-cyanopyridine (**4**) and ethyl Grignard reagent were added simultaneously at the same rate to a heated solution of diamine ligand and Ti(OPr^i)$_4$. Using this process, the concentration of 2-cyanopyridine (**4**) in the reaction mixture remained at low level because it was quickly consumed by the reagents while being added.[19] As a result, the reaction gave a much cleaner profile as byproduct formation was minimized. The yield of the product **2** was increased to 70−75% by HPLC assay.

Although the yield for cyclopropanation had been significantly improved, serious challenges remained for running the reaction at large scale. The reaction produced a large amount of titanium and magnesium salt, and their removal was tedious and difficult. More importantly, the isolation and purification of product cyclopropylamine (**2**) was problematic because it had high solubility in water. Any extractive workup, which is often needed to remove inorganic salt, would result in significant loss of product in the aqueous layer. One way to address this issue is to derivatize the amine (**2**), making it less soluble in aqueous media. We soon realized that the most convenient derivative for the amine was the desired product **1**. The ideal condition would be the one that allowed the amide to be formed in situ after the cyclopropanation without isolating amine **2**. To this end we chose to use carbonyldiimidazole (CDI) as the activating agent, and developed a one-pot procedure for the in situ formation of the amide. As illustrated in Scheme 4, after the cyclopropanation reaction was complete, the right amount of acetic acid (7.88 equiv) and water (1 vol) were added to the reaction mixture to adjust the pH between 6 and 7. In a separate reactor, *N*-Boc-alanine imidazole derivative (**10**) was prepared by mixing *N*-Boc-alanine (**3**) with CDI. The solution containing **10** was then transferred to the reaction mixture of **2**. The reaction proceeded smoothly to provide the desired coupling product **1**. At this point, most of the inorganic salts (titanium and magnesium) were precipitated out of the reaction mixture and could be easily filtered off. The filtrate was washed with sodium potassium tartrate (Rochelle salt) aqueous solution to remove residual inorganic salt. Finally, the product was isolated by crystallization from methyl *tert*-butyl ether and heptane. The overall yield for the entire sequence was 60−65% by solution assay (5−8% lost to filtrate), and the isolated yield was consistently at 48−50% at multikilo scale. The process was streamlined and scaled up smoothly in pilot plant, and the product **1** was isolated in high quality.

Scheme 4. One-pot process for the cyclopropanation and amide coupling to synthesize 1



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In summary, we have overcome many challenges related to scale-up and developed a streamlined, reproducible, and scalable process for the pilot-plant production of Boc-protected (*S*)-2-amino-*N*-(1-(pyridin-2-yl)cyclopropyl)propanamide. The Kulinkovich–Szymoniak cyclopropanation reaction was improved by modulating the reactivity of ethyl Grignard reagent using bis[2-(*N*,*N*-dimethylaminoethyl)]ether (**9**) and simultaneous addition of the two reacting agents. The product 2-cyclopropylaminopyridine (**2**) was directly subjected to amide formation without isolation. This one-pot process has been run successfully in the kilo lab and pilot-plant to produce multikilogram quantities of the desired compound **1** with >97% quality. These results provided the required drug substance to meet the needs of the development program.

EXPERIMENTAL SECTION

General. Bis[2-(*N*,*N*-dimethylaminoethyl)]ether and 2-methyl THF were tested by Karl Fischer for water content prior to use. The concentration of ethylmagnesium bromide in THF solution was taken from supplier COA without titration.

HPLC analyses were performed on Hewlett-Packard 1200 system. **Method 1** (for reaction monitor and product purity): Halo C-18 column (4.6 mm × 150 mm, 2.7 μm); elution: 0.1% $HClO_4$ in H_2O with 40 mM NH_4PF_6/HPLC grade acetonitrile = 99.5:0.5 up to 0.7 min to 80:20 at 1.3 min to 65:35 at 6 min to 50:50 at 6.5 min.; flow rate 1.5 mL/min.; 30 °C; UV detection at 215 nm. **Method 2** (for chiral purity): Regiscell column (4.6 mm × 250 mm, 5 μm); elution: HPLC grade heptane/ethanol = 97:3 up to 10 min.; flow rate 2.0 mL/min.; 25 °C; UV detection at 254 nm.

GC analyses were performed on a HP 6890 GC or equivalent equipped with MSD detector. J&W 122-0731 DB1701 column (30 m × 0.25 mm, 0.15 μm); inlet mode: split; split ratio = 75:1; temperature 150 °C; carrier gas: helium; 1.3 mL/min constant flow; syringe: 10 μL; injection volume: 1.0 μL; temperature program: 100 to 270 °C at a rate of 25 °C/min, hold at 270 °C for 4.0 min; run time: 10.8 min.

Pilot-Plant Process for the One-Pot Synthesis of (*S*)-*tert*-Butyl 1-Oxo-1-(1-(pyridin-2-yl)cyclopropylamino)-propan-2-ylcarbamate (1). *Part 1. 1-(Pyridin-2-yl)-cyclopropanamine (2).* To a 400-L reactor (Reactor 1) was charged titanium(IV) isopropoxide (26.48 kg, 93.17 mol), bis[2-(*N*,*N*-dimethylamino)ethyl]ether (27.76 kg, 173.22 mol, K_f = 1000 ppm), and 2-methyl THF (41 kg, K_f = 147 ppm). The solution was heated to 50 °C. Ethylmagnesium bromide (1.0 M in THF, 174.56 kg, 172.89 mol) and 2-cyanopyridine (8.0 kg, 76.84 mol) in 2-methyl-THF (13.76 kg) solution were charged simultaneously over 45–60 min (the batch temperature rose to 66 °C and started refluxing). The batch was aged at 60 °C for 30 min to 1 h. A sample was taken for HPLC analysis (method 1). Once reaction reached completion (determined by the area % of 2-cyanopyridine **4** below 2%), it was cooled to 25 °C. Acetic acid (36.32 kg, 605.52 mol) was charged slowly (the batch temperature rise to 45 °C, pH between 6 and 7 after addition), followed by water (7.9 kg, 440.32 mol) to quench the reaction.

Part 2. (S)-tert-Butyl 1-Oxo-1-(1-(pyridin-2-yl)-cyclopropylamino)propan-2-ylcarbamate (1). To reactor 2 was charged 1,1′-carbonyldiimidazole (12.48 kg, 76.84 mol) and 2-methyl THF (6.8 kg). A solution of Boc-L-alanine (14.56 kg, 76.84 mol) in 2-methyl THF (34.1 kg) was charged slowly. The solution was stirred at 25 °C for 30 min. A sample was taken for GC analysis. Once completion was reached (determined by the area % of Boc-(L)-alanine **3** below 0.5%), it was transferred to reactor 1. The reaction mixture was stirred at 50 °C for 30 min to 1 h. A sample was taken for HPLC analysis (method 1). Once reaction reached completion (determined by the area % of 1-(pyridin-2-yl)-cyclopropanamine **2** below 5%), the batch was filtered through a pad of Celite, and the solid cake was rinsed with 2-methyl THF (68.2 kg). HPLC analysis of the solid cake showed no product present. The filtrate was transferred to the reactor and distilled to ∼1/2 volume. An aqueous solution of sodium potassium tartrate (25 wt %, 152 kg) was charged. The phases were separated after the mixture was agitated for 15–30 min. The organic layer was distilled under vacuum. Heptane (80 kg) was charged, and the batch was concentrated under vacuum. Heptane (54.6 kg), methyl *tert*-butyl ether (29.6 kg), and water (12.8 kg) were charged to the reactor. The mixture was heated to 60 °C for 30 min and cooled to 20 °C. The solid was collected by filtration, washed with MTBE/heptane (1:2) and water, and dried to obtain 11.505 kg of **1** with 97.9% purity (48.0% isolated yield) and 97.4% ee.[20] mp 151.2–151.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 2H, J = 4 Hz), 1.32 (d, 3H, J = 8 Hz), 1.41 (s, 9H), 1.50 − 1.57 (m, 2H), 4.27 (t, 1H, J = 8 Hz), 5.63 (d, 1H, J = 8 Hz), 6.94 (t, 1H, J = 8 Hz), 7.27 (d, 1H, J = 8 Hz), 7.44 (t, 1H, J = 8 Hz), 7.65 (s, 1H), 8.36 (d, 1H, J = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.29, 19.12, 28.33, 35.97, 50.17, 79.91, 119.19, 120.49, 135.95, 148.99, 155.76, 160.71, 174.05; HRMS (m/z) $[M + H]^+$ calcd for $C_{16}H_{24}N_3O_3$, 306.1812, found, 306.1804.

ASSOCIATED CONTENT

Supporting Information

NMR spectra of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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(17) Other diamine ligands (such as TMEDA) were also tried and found to be less effective than **9**.
(18) It was found that raising temperature without adding ligand **9** did not improve the reaction yield.
(19) A control experiment was conducted without the diamine ligand **9**, and it indicated that the presence of the ligand **9** was beneficial even with the simultaneous addition protocol.
(20) The optical purity of **1** exceeded the specifications at this point. If higher ee % is desired, the compound can be slurried in MTBE/heptane (1:1, 10× volume) at rt for 1 h. After filtration, the chiral purity of the isolated material is 99.5% with 2% loss in the filtrate.