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Practical One-Pot and Large-Scale Synthesis of *N*-(*tert*-Butyloxycarbonyl)-3-pyrroline

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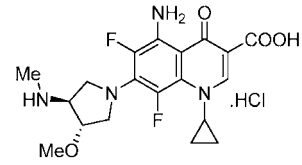
Abstract:

***N*-(*tert*-Butyloxycarbonyl)-3-pyrroline was prepared with high purity in large scale starting from *cis*-1,4-dichloro-2-butene via delepine reaction and subsequent cyclization in the presence of potassium carbonate followed by *N*-Boc protection in methanol. Judicious selection of base and solvent led to the use of a single solvent, i.e., methanol, for cyclization as well as for *N*-Boc protection to render the one-pot process from compound 2 more practical and greener than the stepwise version.**

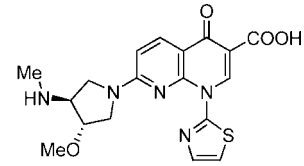
Introduction

N-Substituted 3-pyrrolines are an important class of compounds which exhibit biological activity[1,2] and serve as useful synthetic intermediates.[3−8] The alkene moiety of 3-pyrroline serves as an handle for various organic functional group transformations. *N*-(*tert*-Butyloxycarbonyl)-3-pyrroline has been used to synthesize various β-aryl-GABA analogues by Heck arylation with arenediazonium salts,[9] and it is also used to synthesize aryl pyrrolizidines.[10]

N-(*tert*-Butyloxycarbonyl)-3-pyrroline is a key starting material for the preparation of 3,4-disubstituted pyrrolines,[11] piperazines,[12] *N*-substituted pyrroles,[13] bicyclic aziridines,[14] and polysubstituted pyrroles.[15] 3-Pyrroline is an important constituent of various biologically important molecules such as riddelliine, retronecine, and heliotridine. One of the pyrroline derivatives, (3*S*,4*S*)-3-methoxy-4-methylamino-pyrroline, is an important subunit linked at the C-7 position of quinolone carboxylic acid, a derivative of potent anti-tumor agents such as **I** and **II** and are prepared from 3-pyrroline.[16]



I



II

Recent studies reveal that bovine plasma amine oxidase (BPAO), working as a mechanism-based inactivator, metabolizes 3-pyrroline.[17] 3-Pyrroline derivatives are important to a huge extent in both biologically active molecules as well as new classes of therapeutics.

Our need for large quantities of *N*-(*tert*-butyloxycarbonyl)-3-pyrroline led us to develop a scalable synthesis for this compound. It is possible to purchase this compound (96%) from Sigma-Aldrich (~$166/g). 3-Pyrroline is commercially available as a 3:1 mixture of 3-pyrroline (Figure 1a) and pyrrolidine (Figure 1b), the mixture being obtained by reduction of pyrrole with zinc and acetic acid or hydrochloric acid[18] (one of the research publications[19] reports about 15% of the content is pyrrolidine). 3-Pyrroline can be separated from pyrrolidine by crystallizing its hydrochloride or urethane, but with significant losses.[19,20] Since the difference in boiling points is 1.5 °C only, separation of 3-pyrroline from pyrrolidine by distillation is difficult[19] and may not be applicable for large-scale laboratory preparations.

The literature reveals a method for the preparation of 3-pyrroline through 5-*endo-trig* mode cycloisomerization of α-amino allenes[21] and ring-closing metathesis (RCM) of *N*-protected diallyl amines,[16,22] but this method may not be applicable for industrial scale because of its cost and remaining metallic impurities at ppm levels. Hayes, C. J. et al. used a two-step alkylation/alkylidene carbene 1,5-CH insertion reaction for the synthesis of a range of 3-pyrrolines.[22c] Various other methods are also described that synthesize 3-pyrroline.[23−26]

The pyrroline ring system is formed in the reaction of *cis*-1,4-dichloro-2-butene with primary amines. Aromatic amines give higher yields (61−81%)[26,27] of *N*-substituted 3-pyrrolines than the aliphatic amine (35−60%).[27,29] A widely adopted

a **b**

Figure 1. **Structures of (a) 3-pyrroline and (b) pyrrolidine.**

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method for the preparation of *N*-*tert*-Boc-3-pyrroline involves the treatment of *cis*-1,4-dichloro-2-butene with ammonia followed by *N*-Boc protection. However, poor yield in the first step (amination) is the main hurdle of this method for huge scale.[26,30] The corresponding dichloride **1** is commercially available and is easily prepared from the corresponding diol, which is a bulk chemical.[26] We therefore sought an improved route to 3-pyrroline starting from the dichloride **1**.

Results and Discussion

Earlier, Brandänge[31] et.al. reported a convenient route for the preparation of 3-pyrroline, and it appeared to have the potential to produce multigram quantities of material. However, upon attempting to repeat the procedure, we encountered some difficulties. While preparing the title compound by the reported method,[31] we observed the tedious isolation of every intermediate, the instability of the isolated intermediates, and the formation of 4−5% of an oxidative impurity, *N*-(*tert*-butyloxycarbonyl)pyrrole (Figure 2b). Also we obtained a low yield due to the volatile nature of the 3-pyrroline intermediate. Formation of multiple impurities was observed on prolonged storage of the intermediates at ambient conditions based on HPLC, whereas on prolonged storage of the title compound, the enrichment of the oxidized impurity was observed.

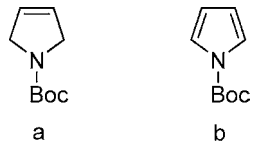
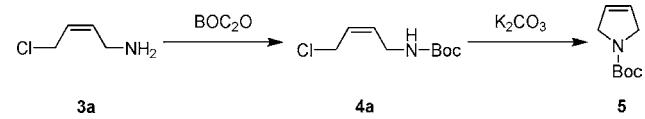


Figure 2. **Structures of (a) *N*-(*tert*-butyloxycarbonyl)-3-pyrroline and (b) *N*-(*tert*-butyloxycarbonyl)pyrrole.**

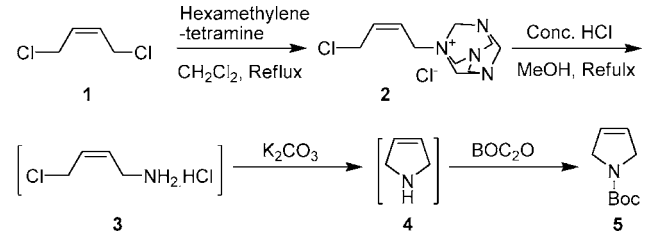
To avoid the isolation of intermediates and to improve the yield of the title compound, we tried to prepare the *cis*-*tert*-butyl-4-chlorobut-2-enylcarbamate **4a** by reaction of *cis*-1-amino-4-chloro-2-butene, **3a** with di-*tert*-butyldicarbonate followed by cyclization to get **5** (Scheme 1). Our attempts failed to obtain the required *cis*-*tert*-butyl-4-chlorobut-2-enylcarbamate, **4a**. Instead of **4a**, the formation of **5** was observed exclusively in low yield (45%). Finally, we have made a conclusion to prepare the title compound, **5**, without isolation of intermediates **3** and **4** (Scheme 2).

Substitution of one of the chlorides of *cis*-1,4-dichloro-2-butene, **1**, with hexamethylenetetramine proceeded in quantitative yield. The crude salt **2** was converted to **3** by reaction with

Scheme 1. **Preparation of *N*-(*tert*-butyloxycarbonyl)-3-pyrroline**



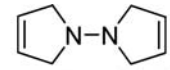
Scheme 2. **Efficient preparation of *N*-(*tert*-butyloxycarbonyl)-3-pyrroline**



concd HCl using Delepine reaction conditions. Without isolation, the crude salt **3** was cyclized under basic conditions (pH > 9) followed by in situ *N*-*tert*-Boc protection of **4** with di-*tert*-butyldicarbonate to give the final compound **5** with high purity (99.05% by HPLC) and 85% overall yield (Scheme 2).

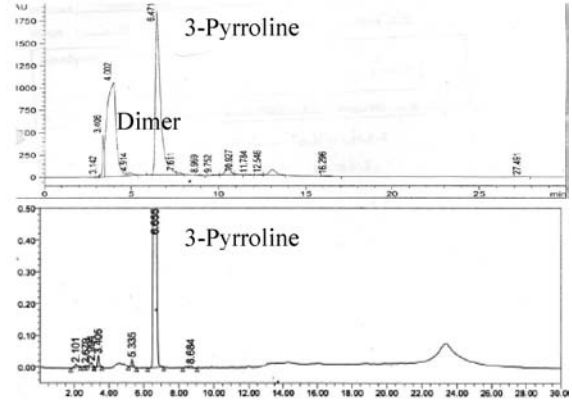
Surprisingly, in cyclization of **3** by using potassium carbonate, the formation of two products was observed in the HPLC. Among both, one product corresponded to the standard 3-pyrroline, but after the addition of di-*tert*-butyldicarbonate, the absence of both the products and the formation of **5** was observed.

Moreover, the unknown product in the cyclization reaction was isolated using preparative HPLC and characterized. From the analytical data it has been identified as 2,2′,5,5′-tetrahydro-1,1′-bipyrrole (dimer of 3-pyrroline), **4b**. It was found to be unstable at room temperature conditions.



2,2',5,5'-tetrahydro-1,1'-bipyrrole, 4b
(Dimer of 3-pyrroline)

HPLC Chromatograms of the cyclisation step:



HPLC Method. A Waters model Alliance 2690-separation module equipped with a Waters 996-photo diode array detector was used. The analysis was carried out on Inertsil-ODS-3V, 250 mm × 4.6 mm, 5 μ with a buffer consisting of 10 mL of ammonium hydroxide in 1000 mL water and pH adjusted to 7.0 with orthophosphoric acid. The mobile phase consisted of buffer and methanol in the ratio of 70:30 (filtered and degassed

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through 0.45 μ membrane filter paper). Program isocratic elution was used with UV detection at 210 nm at a flow rate of 1.0 mL/min. The column temperature was maintained at 35 °C. The data was recorded using waters millennium software [run time - 30 min].

In conclusion, we developed an efficient and commercial viable preparative method for *N*-(*tert*-butyloxycarbonyl)-3-pyrroline with high purity on 50 kg scale with an over all yield of ~85%. By considering both operational efficiency as well as reduction of effluent, this process is greener than the stepwise version.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Perkin-Elmer FT-IR Instrument. ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6, $CDCl_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turbo-ion spray interface at 375 °C.

1-[(*Z*)-4-Chloro-2-buteny1]-l-azonia-3,5,7-triaza- tricyclo-[3.3.l.l]decane Chloride (2). Five hundred liters of methylene dichloride and hexamethylenetetramine (56.07 kg, 400.00 mol) were introduced in a 1 kL reactor. To this was added *cis*-1,4-dichloro-2-butene (50 kg, 400.00 mol), and the mixture was heated to reflux for 5 h. After completion of the reaction by HPLC, reaction mass was cooled to 25 °C, filtered, and washed with excess methylenedichloride. The obtained white solid was dried under vacuum (1 mm) at 25 °C to afford 106 kg (HPLC purity 98%, yield 100%); ^{1}H NMR (D_2O): δ 3.5 (d, 2 H), 4.1 (d, 2H), 4.4−4.6 (m, 6H), 4.7 (s, 6H), 5.6 (q, 1H), 6.2 (q, 1H).

***N*-(*tert*-Butyloxycarbonyl)-3-pyrroline (5).** Five hundred liters of methanol and 1-[(*Z*)-4-chloro-2-buteny1]-l-azonia-3,5,7-triaza-tricyclo[3.3.l.l]decane chloride, **2**, were introduced in a 2 kL reactor. To this solution was added 146.5 L of concd hydrochloric acid, and the mixture was heated to reflux for 1 h. Once, after the completion of **2** was monitored by HPLC, reaction mass was cooled to 35 °C and concentrated to half of its volume under vacuum. Precipitated solids were filtered off, and the filtrate was cooled to 0 °C. To the reaction mixture was added potassium carbonate (138 kg, 1000.00 mol) in portions at 0−5 °C, and the reaction mass was heated to reflux for 2 h. Once the completion of **3** was observed by HPLC, reaction mass was cooled to 25 °C. To this was slowly added, for 1 h, a solution of 50 L of methanol and di-*tert*-butyldicarbonate (83 kg, 380.37 mol). Reaction mass was stirred at 25 °C for 24 h. After the disappearance of two peaks in HPLC, the reaction mass was filtered to remove excess potassium carbonate. The solid was washed with *n*-hexane. The filtrate was concentrated to remove the solvent and diluted with 500 L water; the title compound was extracted with *n*-hexane (5 × 250 L). Combined organic layers were washed with water (2 × 250 L). The organic layer was distilled completely to get the crude **5** (HPLC purity 96.0%). The obtained crude was purified by distillation under vacuum (reactor jacket temp 120−140 °C/0.4 mbar) to get 57.5 kg of **5** (HPLC purity 99.05%, yield 84.94%); ^{1}H NMR ($CDCl_3$): δ 1.4 (s, 9 H), 4.0 (d, 4 H), 5.8 (d, 2 H).

2,2′,5,5′-Tetrahydro-1,1′-bipyrrole (4b): ^{1}H NMR (DMSO-d_6): δ 3.8 (s, 4 H), 5.7 (s, 2 H).

Acknowledgment

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Supporting Information Available

^{1}H NMR spectra of **2**, **3**, **4**, and **5**, HPLC chromatogram and IR of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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