Organic Process Research & Development **2002**, *6*, 416–418

An Efficient Scalable Process for the Synthesis of *N*-Boc-2-*tert*-butyldimethylsiloxypyrrole

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Abstract:

A safe, reliable and scalable process for the preparation of *N*-Boc-2-*tert*-butyldimethylsiloxy-pyrrole (TBSOP) is described. In a three-step, one-pot sequence (±)-4-amino-3-hydroxybutyric acid was converted to *N*-Boc-4-hydroxy-2-pyrrolidinone. This stable crystalline product was isolated by filtration directly from the reaction mixture. Dehydration followed by enolization and silylation produced the target compound without the need for chromatographic purification. The process was demonstrated in the pilot plant to make multikilogram quantities of material in 85% overall yield.

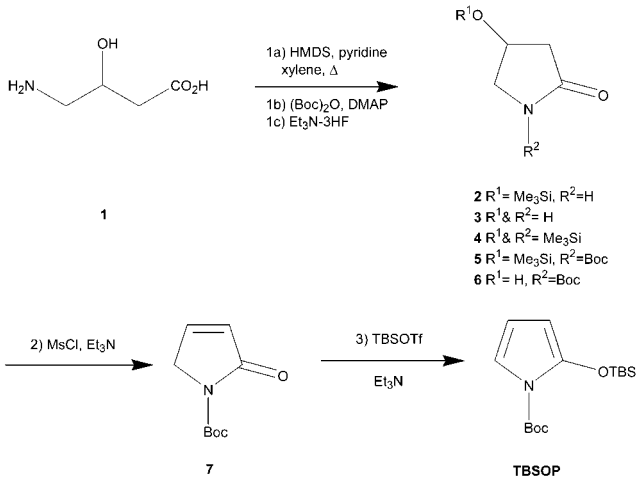
Introduction

N-Boc-2-*tert*-butyldimethylsiloxypyrrole (TBSOP) was introduced nearly a decade ago for the synthesis of homochiral α,β-unsaturated γ-lactams.[1] This building block has been used extensively in the context of vinylogous aldol reactions,[2,3] including an example of a condensation with an *N*-acyliminium ion.[4] We required multikilogram quantities of this compound to support the development of a clinical candidate. The method cited in the literature[1] for the preparation of TBSOP involved the oxidation of pyrrole with hydrogen peroxide,[5] a reaction that raised safety concerns if done on large scale. Several chromatographic purifications seemed to be necessary to produce good-quality material. In this work, we describe an alternate preparation that is safe, reliable, and amendable to multikilogram-scale production.

Results and Discussion

We were prompted by a paper from the Pifferi group regarding the dehydrative cyclization of (±)-4-amino-3-hydroxybutyric acid **1** with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and chlorotrimethylsilane in refluxing xylene.[6] The reaction proceeded with in situ protection of the hydroxyl group, to yield (±)-4-(trimethylsiloxy)-2-pyrrolidinone **2**. In our hands the yields of **2** were variable (60−95%). The remainder of the material being the des-silyl derivative **3** (Scheme 1) that was thought to be caused by ammonium chloride mediated desilylation under the reaction conditions. Buffering the reaction with pyridine (0.05−0.40 equiv) tightened the yield range to some extent (80−96%). However, our desire to minimize manipulations and run as many transformations as possible without isolation led us to explore conducting the reaction under basic conditions. Exposure of **1** to HMDS and pyridine in refluxing xylene led to a high yield of **2**[7] (91−98%) and some bis-silylation product **4** (2−7%). The exclusion of chlorotrimethylsilane from the reaction allowed for the work up to be simplified to merely concentration under reduced pressure to remove volatile reaction byproducts. The residue was dissolved in THF or isopropyl acetate (iPAc) and treated with di-*tert*-butyl dicarbonate and DMAP to introduce the Boc group and give (±)-*N*-Boc-4-(trimethylsiloxy)-2-pyrrolidinone **5**.[8] When this reaction was judged to be complete shown by HPLC analysis of starting material of less than 1%, triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$)[9] was added to the reaction mixture to remove the trimethylsilyl moiety. As the deprotection

Scheme 1



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(6) Pellegata, R.; Pinza, M.; Pifferi, G. *Synthesis* **1978**, 614.

(7) (±)-4-(trimethylsiloxy)-2-pyrrolidinone (**2**) was prepared and characterized: mp 106.5−107.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (br s, 1H), 4.45−4.36 (m, 1H), 3.46 (dd, 1H, *J* = 10.1, 5.9 Hz), 3.11 (dd, 1H, *J* = 9.9, 3.7 Hz), 2.42 (dd, 1H, *J* = 16.9, 6.6 Hz), 2.13 (dd, 1H, *J* = 16.9, 4.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 67.4, 51.5, −0.3; MS (DCI/NH_3): *m*/*z* 174 $[M + H]^+$, 191 $[M+NH_4]^+$, 208 $[M + NH_3{\cdot}NH_4]^+$, 347 $[2M + H]^+$; FAB-HRMS: Calcd *m*/*z* for $[M + H]^+$ $C_7H_{16}NO_2Si$: 174.0950, found: 174.0948; Anal. Calcd for $C_7H_{15}NO_2Si$: C, 48.52; H, 8.72; N, 8.08; found: C, 48.51; H, 8.55; N, 8.07.

Published on Web 05/17/2002
10.1021/op025532+ CCC: $22.00

proceeded, the product (±)-*N*-Boc-4-hydroxy-2-pyrrolidinone **6** crystallized from the reaction mixture. Heptane was charged to the suspension to maximize product recovery. This one-pot three-step sequence provided **6** in 97% overall yield in the laboratory and in 89% yield on 15-kg scale in the pilot plant. After our work was completed, a communication[10] describing the synthesis of (S)-(+)-*N*-Boc-4-hydroxy-2-pyrrolidinone from *N*-Boc-2-pyrrolidinone by resting cells of *Sphingomonas* sp. HNX-200 was published. This biocatalytic process can generate the desired product in 46% yield and 92% ee.

The stable crystalline **6** was a convenient intermediate to stockpile for ready access to TBSOP. To convert **6** to TBSOP, the intermediate was dissolved in THF and the dehydration was accomplished by treatment with methanesulfonyl chloride and triethylamine to give the *N*-Boc-Δ^3-pyrrolidinone **7**. After the reaction was complete shown by HPLC analysis of starting material of less than 1%, it was diluted with ethyl acetate (to precipitate byproduct triethylammonium hydrochloride) and filtered. The filtrate was washed with brine solution and dried by azeotropic distillation with heptane. To the mixture of **7** and heptane was added triethylamine and a filter agent.[11] The mixture was chilled to 0 °C and treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate. The triethylammonium trifluoromethanesulfonate formed as a byproduct was absorbed onto the filter agent as the reaction progressed. At the end of reaction, the darkened filter agent was removed by filtration. All other reaction byproducts were volatile and were removed by concentration of the filtrate. For use in our process, the residue was reconstituted in heptane and held for next step. The HPLC assayed yield of TBSOP was 95−98%.

Advantages of this process are the high overall yield and the operational efficiency that avoids any chromatographic purification. There is only one isolation step, and the intermediate **6** is a stable crystalline solid that can be stored prior to facile conversion to TBSOP. The process is very robust and has been demonstrated on different scales.

Experimental Section

General Procedure. Starting materials, reagents, and solvents were purchased from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded at 300 or 500 MHz and ^{13}C NMR spectra were recorded at 75 MHz with chemical shifts (δ ppm) reported relative to tetramethylsilane (TMS) as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories. Column chromatography was carried out on silica gel 60 (230−400 mesh). Thin-layer chromatography (TLC) was performed using 250 mm silica gel 60 glass-backed plates with F254 as indicator. Visualization of TLC was done by UV light, $KMnO_4$ or phosphomolybdic acid spray reagent.

Preparation of (±)-*N*-Boc-4-hydroxy-2-pyrrolidinone (6). To a jacketed reactor were charged (±)-4-amino-3-hydroxy-*n*-butyric acid **1** (10.0 kg), pyridine (48.9 kg), 1,1,1,3,3,3-hexamethyldisilazane (21.9 kg) and xylenes (86.4 kg). The reaction mixture was stirred and heated to reflux (118 °C) for 14 h (jacket temperature was set at 140 °C). In-process analysis showed that the reaction was complete. The reaction mixture was cooled and volatile solvents were distilled under reduced pressure. The reaction mixture was cooled to ≤+10 °C and a solution of DMAP (0.494 kg) in isopropyl acetate (18.3 kg) was charged to the reaction mixture, followed by another solution of di-*tert*-butyl dicarbonate (21.5 kg) in isopropyl acetate (27.9 kg). The reaction mixture was stirred for 30 min at +15 °C and for 17 h at +20 °C. When the in-process sample showed that the reaction was complete, triethylamine trihydrofluoride (5.9 kg) was charged to the reaction mixture over a period of 15 min. The reaction mixture was stirred for 1 h when analysis showed that the TMS cleavage was complete. The stirring speed was slowly increased while heptane (111.2 kg) was charged over a period of 2 h. Reaction mixture was cooled to 0 °C and stirred for 2.5 h. The product **6** was collected by filtration and washed with heptane (51 kg) that was first used to rinse the reactor. **6** was initially dried in the filter pot with nitrogen for 3 h, and then dried under vacuum at 40 °C for 8 h; yield 15 kg (89% yield), mp 150.4−151.4 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50−4.46 (m, 1H), 3.90 (dd, 1H, J = 12.1, 5.1 Hz), 3.78 (ddd, 1H, J = 12.4, 2.03, 1.1 Hz), 2.79 (dd, 1H, J = 17.8, 5.9 Hz), 2.54 (ddd, 1H, J = 17.8, 2.4, 1.1 Hz), 2.21 (br. s, 1H), 1.53 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.4, 149.8, 81.6, 61.9, 55.2, 42.5, 27.7. MS (DCI/NH_3): m/z 202 $[M+H]^+$, 219 $[M + NH_4]^+$; FAB-HRMS: Calcd m/z for $[M + H]^+$, 202.1079, found: 202.1079, Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96; found: C, 53.84; H, 7.74; N, 7.12.

Preparation of *N*-Boc-2-*tert*-butyldimethylsiloxypyrrole (TBSOP). To a 100-L reactor equipped with an addition funnel, a nitrogen inlet, and a temperature probe was charged **6** (3.20 kg, 15.6 mole). THF (31.3 kg) and triethylamine (4.425 kg) were added. The reaction mixture was cooled to 0 °C. Methanesulfonyl chloride (2.319 kg) was charged to the reaction mixture over a period of 2 h while maintaining the temperature of reaction mixture below 5 °C. The reaction mixture was stirred at 5 °C for 30 min and at ambient temperature for 2 h. Analysis of an in-process sample showed that the reaction was complete. Ethyl acetate (40 L) was charged and the reaction mixture was stirred for 30 min. Triethylammonium chloride was removed by filtration and

(8) (±)-*N*-*tert*-Butyloxycarbonyl-4-(trimethylsiloxy)-2-pyrrolidinone (**5**) was prepared and characterized: mp 65.5−66.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40−4.35 (m, 1H), 3.87 (dd, 1H, J = 11.6, 5.7 Hz), 3.63 (ddd, 1H, J = 11.6, 2.9, 0.9 Hz), 2.72 (dd, 1H, J = 17.3, 6.3 Hz), 2.46 (ddd, 1H, J = 17.3, 2.9, 0.9 Hz), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 149.8, 82.7, 63.3, 55.2, 42.9, 27.8, −0.3; MS [ESI (+) ion]: m/z 274 $[M + H]^+$, 291 $[M + NH_4]^+$, 296 $[M + Na]^+$, 564 $[2M + NH_4]^+$, 564 $[2M+ NH_4]^+$, 569 $[2M + Na]^+$; FAB-HRMS: Calcd m/z for $[M + H]^+$ $C_{12}H_{24}NO_4Si$: 274.1475, found: 274.1468; Anal. Calcd for $C_{12}H_{23}NO_4Si$: C, 52.72; H, 8.48; N, 5.12; found: C, 52.45; H, 8.33; N, 5.12.

(9) We do not have quantitative data of triethylamine trihydrofluoride ($Et_3N\cdot 3HF$) on glass etching, but we did take the precaution of using a stainless steel reactor rather than a glass-lined reactor for this step of the reaction. Triethylamine trihydrofluoride ($Et_3N\cdot 3HF$) is a liquid and easy to handle in operation. Its high concentration of fluoride ion makes the reaction volume small, which benefits process scale-up.

(10) Chang, D.; Witholt, B.; Li, Z. *Org. Lett.* **2000**, *2*, 3949.

(11) A filter agent such as Celite or diatomaceous earth is suitable.

washed with isopropyl acetate (2 × 13.3 L). The filtrate was washed with 15 wt % NaCl solution (2 × 13 L). The combined aqueous washes (15 wt % NaCl) were back-extracted with the isopropyl acetate (26.6 L) obtained from washes of the triethylammonium chloride cake. All organic layers and extracts containing **7** were combined and concentrated to about 20 L. Heptane (20 L) was charged to the concentrate and distilled under reduced pressure. This process was repeated four times to remove water, ethyl acetate, and isopropyl acetate, and finally a slurry of **7** in heptane (30 L) was obtained. Dichloromethane (37 L) was charged to the slurry to dissolve **7**, followed by filter agent (3.3 kg), heptane (25.8 kg), and triethylamine (4.5 kg). The reaction mixture was cooled to ca. 0 °C. *tert*-Butyldimethylsilyl trifluoromethane-sulfonate (TBSOTf) (4.705 kg) was added over a period of 1 h while maintaining the internal temperature below +4 °C. The reaction mixture was stirred at 0 °C for 1 h, when analysis of an in-process sample showed that the conversion was complete. Methanol (1.0 L) was added to the reaction mixture over a period of 10 min to quench the reaction. The reaction mixture was stirred at 0 °C for 20 min, then was concentrated under reduced pressure to about 20 L. Heptane (20 L) was charged to the suspension and concentrated under reduced pressure to replace dichloromethane. This process was repeated four times and finally a suspension in heptane (30 L) was obtained. The mixture was cooled to ca. 0 °C and stirred for 1 h. The solid filter agent was removed by filtration under nitrogen, and washed with heptane (20 L). The TBSOP product solution was distilled to the desired concentration (39.3 wt %) and held for next step, yield by assay 4.486 kg (95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (dd, 1H, J = 3.9, 2.1 Hz), 5.90 (t, 1H, J = 3.7 Hz), 5.23 (dd, 1H, J = 3.5, 2.1 Hz), 1.57 (s, 9H), 0.99 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 143.5, 113.0, 108.0, 92.3, 82.7, 28.0, 25.7, 18.4, −4.86.

Acknowledgment

The authors thank the Structural Chemistry Department of Abbott Laboratories for spectroscopic determinations and Drs. David Barnes, Paul Nichols, and John DeMattei for useful discussions.

Received for review March 20, 2002.

OP025532+