Chinese Chemical Letters Vol. 12, No. 12, pp 1061 – 1064, 2001
http://www.imm.ac.cn/journal/ccl.html

One-Pot Synthesis of *N*-Boc-2, 5-bis(trimethylsilyl)pyrrolidine

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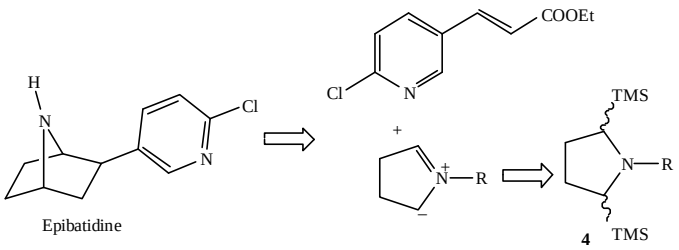
Abstract: *N*-Boc-2, 5-bis(trimethylsilyl)pyrrolidine **4** was synthesized from the reaction of *N*-Boc-pyrrolidine **1** with trimethylsilyl chloride (TMSCl) at optional temperature in one-pot in good yield.

Keywords: *N*-Boc-2, 5-bis(trimethylsilyl)pyrrolidine, trimethylsilylation, one-pot.

Since Daly reported the structure of epibatidine and its potent analgesic activity in 1992[1], study on the synthesis of epibatidine and its derivatives and relationships between the structure and activity of epibatidine has received much attention[2].

During the course of our research for the synthesis of epibatidine derivatives, *N*-boc-2, 5-bis(trimethylsilyl)pyrrolidine **4** was used as the key intermediate to construct the skeleton of epibatidine *via* the 1, 3-dipolar cycloaddition (**Scheme 1**). According to the report of Pandey *et al.*[3], **4** was obtained by two steps. The intermediate **2** was required to separate and then to introduce the second trimethylsilyl group at 5-position.

Scheme 1



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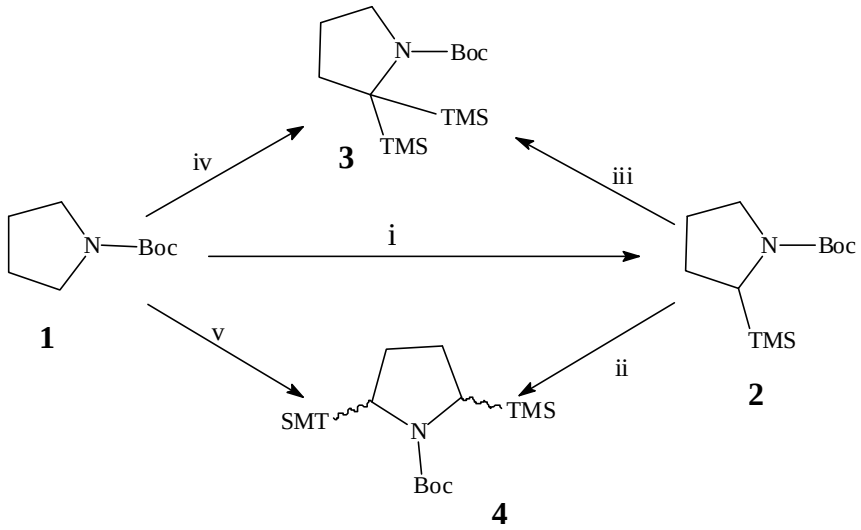
Scheme 2



i) TMEDA, sec-BuLi (1.1 eq), ether, -78°C, 2h, TMSCl; ii) TMEDA, sec-BuLi (1.1 eq), ether, -30°C, 0.5h, TMSCl; iii) TMEDA, sec-BuLi (1.1eq), ether, -78°C, 2h, TMSCl; iv) TMEDA, sec-BuLi (2.2 eq), ether, -78°C, 2h, TMSCl; v) TMEDA, sec-BuLi (1.1 eq), ether, -78°C, 2h, TMSCl, then TMEDA, sec-BuLi (1.1 eq), ether, -30°C, 0.5h, TMSCl.

Table Synthesis of Substituted N-boc-pyrrolidines

Compound	Starting Material	*s*-BuLi (eq.)	Temp. (°C)	Time (h)	Ratio (**4:3**)	Yield (%)
3	**1**	2.2	-78	2	1:6.5	65
2	**1**	1.1	-78	2	-	93
3	**2**	1.1	-78	2	1:6.2	74
4	**2**	1.1	-45	1	1.1:1	41
4	**2**	1.1	-30	1.5	2.4:1	61
4	**2**	1.1	-30	0.5	6.3:1	75
4	**2**	1.1	-20	0.5	4.8:1	78
4	**1**	1.1+1.1	-78, then -30	2+0.5	5.8:1	71

In order to simplify its tedious work-up, we attempted to obtain **4** by the reaction of *N*-Boc-pyrrolidine **1** with TMSCl in one-pot. However, when carrying out the lithiation of **1** in ethyl ether using 2.2 eq. mol of *sec*-BuLi at -78°C for 2 h, and then trimethylsilation with 2.2 eq. mol of TMSCl at once, only 2, 2-bis(trimethylsilyl)-pyrrolidine **3** was isolated as major product in 65% yield (**Table**, entry 1). Because compound **2** could be obtained in 93% yield from **1**(**Table**, entry 2), the main problem is in the second step.

After investigating the conditions of second trimethylsilylation carefully, we found the temperature affected on the position of the second trimethylsilylation significantly. Elevating temperature was obviously helpful to increase the ratio of **4** to **3** (**Table**, entry 2~7). As shown in the **Table**, when the reaction was performed at -30°C, the ratio of **4** to **3** increased to 6.3:1 and the yield of **4** is 75%.

Based on the above results, the *N*-Boc-2, 5-bis(trimethylsilyl)pyrrolidine **4** was prepared by the following one-pot method. Firstly, **2** was obtained under the condition of entry 2, and then second trimethylsilyl group was introduced under the condition of entry 6 without separation of **2**. The ratio of **4** to **3** was 5.8:1 and yield of **4** is 71% (lit[3]: 70% from **2**).

In summary, *N*-Boc-2, 5-*bis*(trimethylsilyl)pyrrolidine as 1, 3-dipole precursor can be easily obtained by one-pot method in good yield.

Preparation of N-boc-2, 5-bis(trimethylsilyl)pyrrolidine 4

A solution of **1** (5.21 g, 21.4 mmol) in anhydrous ether (40 mL) was cooled to -78°C under nitrogen and treated with TMEDA (23.5 mmol), then *sec*-BuLi (1.9 mol/L, 12.4 mL, 23.5 mmol) was added dropwise. The solution was stirred for 2 h at -78°C and then treated with trimethylsilyl chloride (2.54 g, 23.5 mmol). The temperature of the mixture was allowed to rise to room temperature and continued to stir for 30 mim. The reaction system was then recooled to -50°C and another portion of TMEDA (23.5 mmol) and *sec*-BuLi (1.9 mol/L, 12.4 mL, 23.5 mmol) were added dropwise. After stirred for 30 min at -30°C, the mixture was treated with equal portion of TMSCl (2.54 g, 23.5 mmol) and warmed up to room temperature. Then the reaction was quenched with saturated NH_4Cl solution (25 mL). The organic layer was separated and the water phase was extracted with ether (50 mL×3). The combined extract was dried over Na_2SO_4, filtered and then concentrated to give a crude product. The product was purified by column chromatography on silica gel with petroleum/ethyl acetate (60:1) as an eluent to give 4.79 g of **4** as colorless oil: ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm): 0.05 (s, 18H), 1.46 (s, 9H), 1.75~1.79 (m, 2H), 1.88~1.90 (m, 2H), 3.00~3.30 (bs, 2H). ^{13}CNMR ($CDCl_3$, 300MHz, δ ppm): -0.89, -0.03, 29.43, 29.51, 49.24, 50.33, 79.49, 155.41. Mass (*m/z*, relative intensity): 315 (M^+, 10), 258 (100), 243 (35), 228(72), 214(84), 186 (67), 157 (58), 142 (87), 73 (72).

Acknowledgments

This work is supported by the National Natural Science Foundation of China (No 29772004).

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Received 20 April, 2001

Erratum:

The δ values of Compound **1** in ^{1}HNMR 5.95, 5.81 should be corrected to 5.81, 5.95 respectively, (**Table 1**, line 10, 13), in CCL Vol. 12, No. 7, p.612.