# Notes

## Synthesis of 4,5-Disubstituted-2,7-diazabicyclo[3.3.0.]octane Derivatives by Intramolecular Cyclization Reaction

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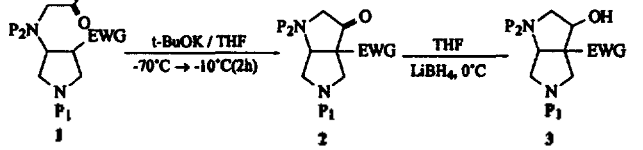
Biologically and synthetically important polysubstituted pyrrolidines have received extensive attention from synthetic chemists in recent years.[1] Particularly useful general approaches to pyrrolidines are intramolecular ene strategy,[2] electrophilic promoted cyclization of unsaturated amine derivatives,[3] tandem cationic aza-cope-mannich cyclization,[4] transition metal catalyzed cyclization of unsaturated amines,[5] 1,3-dipolar cycloaddition reaction,[6] and intramolecular anionic cyclization.[7] The elaboration of pyrrolidines using intramolecular anionic cyclization strategy has attracted a great deal of attention due to its brevity and efficiency.[8] In connection with our ongoing synthetic program to develop new methods for pyrrolidine synthesis[9] and diazabicyclic compounds,[10] we wish to report a method for the synthesis of polysubstituted pyrrolidine ring systems and the influence of N-protecting groups on cyclization reactions.

As summarized in the Scheme 1, the strategy entails on the intramolecular anionic cyclization and subsequent reduction.

The bifunctional starting materials **1** required for the construction of pyrrolidine derivatives were prepared easily by standard chemistry, involving the Michael-type addition of glycine ethyl ester to 3-pyrroline derivatives[11] followed by nitrogen-protection using an appropriate protecting group.[12]



**1** **2** **3**

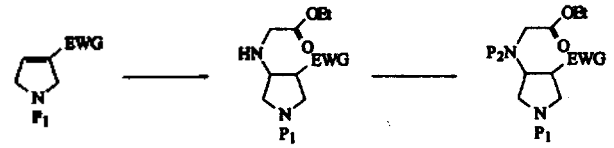
| | a | b | c | d | e | f | g | h | i | j |
|---|---|---|---|---|---|---|---|---|---|---|
| P$_1$ | Boc | Boc | Boc | Boc | CO$_2$Et | Ts | Boc | Boc | Bn | Bn |
| P$_2$ | Boc | CO$_2$Et | Cbz | Ts | CO$_2$Et | Ts | Boc | Bn | Bn | Boc |
| EWG | SO$_2$Ph | SO$_2$Ph | SO$_2$Ph | SO$_2$Ph | SO$_2$Ph | SO$_2$Ph | CO$_2$Et | SO$_2$Ph | CO$_2$Et | CO$_2$Et |

**Scheme 1.**

**Table 1.** Synthesis of 2,7-diazabicyclo[3.3.0]derivatives 3 *via* cyclization of 1 and subsequent reduction

| entry | P$_1$ | P$_2$ | EWG | Yield (%)[a] |
|---|---|---|---|---|
| a | Boc | Boc | SO$_2$Ph | 69 |
| b | Boc | CO$_2$Et | SO$_2$Ph | 39 |
| c | Boc | Cbz | SO$_2$Ph | 23 |
| d | Boc | Ts | SO$_2$Ph | 0[b] |
| e | CO$_2$Et | CO$_2$Et | SO$_2$Ph | 26 |
| f | Ts | Ts | SO$_2$Ph | 0[b] |
| g | Boc | Boc | CO$_2$Et | 10 |
| h | Boc | Bn | SO$_2$Ph | 0[b] |
| i | Boc | Bn | CO$_2$Et | 0[b] |
| j | Bn | Boc | CO$_2$Et | 0[b] |

[a] Isolated yield from flash column chromatography but not optimized. [b] The cyclization reaction did not proceed or gave decomposed products.



The cyclization of compound **1** was performed using *t*-BuOK in THF to obtain compound **2**. However, any compound except **2a** (P$_1$=P$_2$=Boc, EWG=SO$_2$Ph) could not be isolated from the cyclization reaction. From this cyclization step, the following results were obtained. In the case of **1h** and **1j** the cyclization reaction was not proceeded. In the case of **1d** and **1f** the cyclization reaction was not proceeded but gave unidentified product. The cyclization reaction was not proceeded or gave decomposed products at the reaction condition in the case of **1i**. In the case of **1b**, **1c**, **1e**, and **1g** the cyclization reaction was proceeded but the cyclized products **2** could not be isolated in pure form after flash chromatography. These results could be the caused by the unstability of the cyclized compound.[11c] From the above results, it was thought that the class of N-protecting group (P$_1$ and P$_2$) and activating group (EWG) had influenced on the reactivity of cyclization reaction and the stability of the cyclized compound.

Therefore, it was decided to investigate the cyclization and subsequent reduction to obtain the stable compound. The desired hydroxy compound **3** was successfully obtained from the cyclization of compound **1** and subsequent reduction. The results were summarized in Table 1. As shown in Table 1, the success of this sequential strategy relies on the protecting groups of nitrogen and the electron withdrawing group. The best result is derived from *t*-butoxycarbonyl (Boc) group as N-protecting group (P$_1$, P$_2$) and benzenesulfonyl moiety as the electron withdrawing group (entry a in Table 1). When P$_1$ and EWG were Boc and SO$_2$Ph, respectively, the desired products were obtained in different yield by the class of P$_2$ (entries a, b, c, d, and h in Table 1). The influence of the protecting group seems to be important in the reaction and the reason is not clear at this moment. When $P_1$ and EWG were Boc and $CO_2Et$, respectively, the desired product was obtained only one case ($P_2$=Boc, entry *g* in Table 1). Other substrates except those explained above did not give the desired product. It corresponds with the result of the cyclization study.

In summary, we have developed the method for the synthesis of polysubstituted pyrrolidine ring systems and found that the choice of N-protecting group and activating group influenced on the reactivity of cyclization reaction and also the stability of the cyclized compounds. The application of **3** for the synthesis of biologically active compound is under investigating in these laboratories and will be reported in the future.

## Experimental Section

All reactions were performed under nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. $^1H$ NMR spectra were measured in chloroform-*d* containing 0.03% tetramethylsilane as an internal standard on a Bruker AC200 (200 MHz) spectrometer. Chemical shifts are reported in ppm (δ) downfield from the tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 681 apparatus. Melting points were taken on a Gallenkemp melting point apparatus and uncorrected. Column chromatography was performed on 230-400 mesh silica gel.

**N,N'-di-tert-Butoxycarbonyl-5-phenylsulfonyl-2,7-diazabicyclo[3.3.0.]octan-4-one (2a).** To a stirred solution of **1a** (512 mg, 1 mmol) in THF (10 mL) was added dropwise 1.32 mL (1.2 mmol) of *t*-BuOK (1.0 M in THF) at −70 ℃. The reaction mixture was allowed to warm at −10 ℃ for 2 h, quenched with saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (20 mL× 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was chromatographed on silica gel eluting $Et_2O$ : *n*-Hex (1 : 2) as an eluent to give 333 mg (74%) of **2a**. $^1H$ NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.50 (s, 9H), 3.41-4.01 (m, 6H), 5.31-5.44 (m, 1H), 7.46-7.90 (m, 5H).

**General Procedure for Preparation of 3.** The synthesis of **3a** is representative. To a stirred solution of **1a** (512 mg, 1 mmol) in THF (10 mL) was added dropwise 1.32 mL (1.2 mmol) of *t*-BuOK (1.0 M in THF) at −70 ℃. The reaction mixture was allowed to warm at −10 ℃ for 2 h, quenched with saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (20 mL×3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in THF (10 mL) and cooled to 0 ℃. Lithium borohydride (33 mg, 1.5 mmol) was added to reaction mixture. The resulting mixture was stirred for 1 h at 0 ℃, quenched with saturated ammonium chloride solution (30 mL) and extracted with methylene chloride (20 mL×3). The extracts was dried, concentrated and conducted flash column chromatography using ethyl acetate : *n*-hexane (1 : 2) as eluent to afford 323 mg (69%) of desired product **3a** as a solid : mp 174-176 ℃; $^1H$ NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.48 (s, 9H), 3.12-4.22 (m, 7H), 4.94 (m, 1H), 7.53-7.75 (m, 3H), 7.98-8.10 (m, 2H); IR (KBr) 3399, 1697, 1680, 1408, 1368, 1308, 1251, 1169, 1149 $cm^{-1}$.

**3b** : $^1H$ NMR ($CDCl_3$) δ 1.21-1.34 (m, 3H), 1.42 (s, 9H), 3.19-4.18 (m, 10H), 4.90-5.10 (m, 1H), 7.58-7.74 (m, 3H), 8.01-8.05 (m, 2H).

**3c** : $^1H$ NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.17-4.20 (m, 8H), 5.06-5.20 (m, 3H), 7.36 (s, 5H), 7.58-7.74 (m, 3H), 8.00-8.04 (m, 2H).

**3e** : $^1H$ NMR ($CDCl_3$) δ 1.18-1.35 (m, 6H), 3.21-4.23 (m, 12H), 4.98-5.08 (m, 1H), 7.59-7.79 (m, 3H), 8.02-8.05 (m, 2H).

**3g** : $^1H$ NMR ($CDCl_3$) δ 1.24-1.30 (m, 3H), 1.44 (s, 9H), 1.49 (s, 9H), 3.46-4.28 (m, 10H), 4.85-4.93 (m, 1H).

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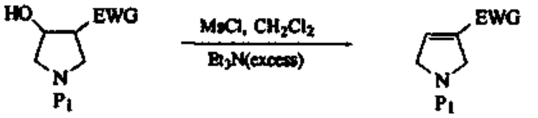
11. In general, 3-pyrroline derivatives were prepared by the dehydration of N-protected 3-hydroxy-4-ethoxycarbonyl (or phenylsulfonyl) pyrrolidine.



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