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]

	a	b	c	d	e	f	g	h	i	j
P_1	Boc	Boc	Boc	Boc	CO_2Et	Ts	Boc	Boc	Bn	Bn
P_2	Boc	CO_2Et	Cbz	Ts	CO_2Et	Ts	Boc	Bn	Bn	Boc
EWG	SO_2Ph	SO_2Ph	SO_2Ph	SO_2Ph	SO_2Ph	SO_2Ph	CO_2Et	SO_2Ph	CO_2Et	CO_2Et

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_2Ph	69
b	Boc	CO_2Et	SO_2Ph	39
c	Boc	Cbz	SO_2Ph	23
d	Boc	Ts	SO_2Ph	0[b]
e	CO_2Et	CO_2Et	SO_2Ph	26
f	Ts	Ts	SO_2Ph	0[b]
g	Boc	Boc	CO_2Et	10
h	Boc	Bn	SO_2Ph	0[b]
i	Boc	Bn	CO_2Et	0[b]
j	Bn	Boc	CO_2Et	0[b]

[a] Isolated yield from flash column chromatography but not optimized. [b] The cyclization reaction did not proceed or gave decomposed products.
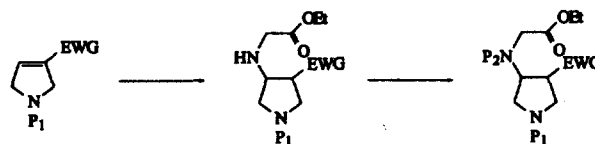
The cyclization of compound 1 was performed using *t*-BuOK in THF to obtain compound 2. However, any compound except 2a ($P_1=P_2=$Boc, EWG=SO_2Ph) could not be isolated from the cyclization reaction. From this cyclization step, the following results were obtained. In the case of 1h and 1j the cyclization 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_2Ph, 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

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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 MgSO₄ and concentrated. The residue was chromatographed on silica gel eluting Et₂O : *n*-Hex (1 : 2) as an eluent to give 333 mg (74%) of **2a**. ^1H NMR (CDCl₃) 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 MgSO₄ 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 (CDCl₃) 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 (CDCl₃) 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 (CDCl₃) 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 (CDCl₃) 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 (CDCl₃) 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).

References

1. (a) Massiot, G.; Delaude, C. in *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1986, Vol. 27, Chapter 3. (b) Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801, and references therein.
2. Oppolzer, W.; Sniecheus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 376.
3. Kimpe, N. D.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* **1994**, *35*, 1925.
4. Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.
5. Trost, B. M. *Pure Appl. Chem.* **1981**, *105*, 2357.
6. Begue, J.-P.; Bonnet-Delpon, D.; Lequeux, T. *Tetrahedron Lett.* **1993**, *34*, 3279.
7. Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276.
8. (a) Barco, A.; Benetti, S.; Risi, C. D.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, *35*, 9293. (b) Sasaki, N. A.; Pauly, R.; Fontaine, C.; Chiaroni, A.; Riche, C.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 241.
9. (a) Lee, J. W.; Son, H. J.; Choi, M. J. *Korean J. Med. Chem.* **1994**, *4*, 119. (b) Lee, J. W.; Son, H. J.; Lee, K. S.; Park, M. H.; Kim, B. H. *Korean J. Med. Chem.* **1994**, *4*, 126.
10. (a) Lee, J. W.; Son, H. J.; Lee, J. H.; Jung, Y. E.; Yoon, G. H.; Park, M. H. *Synthetic Commun.* in press. (b) Lee, J. W.; Son, H. J.; Jung, Y. E.; Lee, J. H. *Heterocycle* Submitted.
11. In general, 3-pyrroline derivatives were prepared by the dehydration of N-protected 3-hydroxy-4-ethoxycarbonyl (or phenylsulfonyl) pyrrolidine.
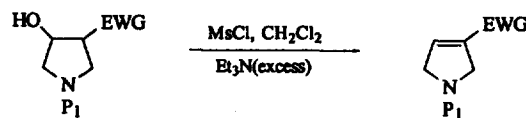
(a) Dupre, B.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 3197. (b) Macdonald, T. L.; Narayanan, B. A. *J. Org. Chem.* **1983**, *48*, 1129. (c) Jaeger, E.; Biel, J. H. *J. Org. Chem.* **1965**, *30*, 740. (d) Lee, J. W.; Son, H. J.; Jung, Y. E. *Bull. Korean Chem. Soc.* in press.
12. Greene, T. W.; Wuts, P. G. M. 2nd Ed., *Protective Groups in Organic Synthesis*; John Wiley and Sons, Inc., 1991.