A NEW METHOD FOR INTRODUCING ACETYLENE GROUPS AT THE α-POSITION OF THE PYRROLIDINE RING

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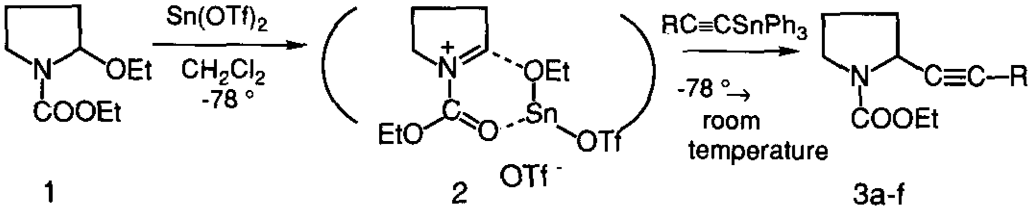
Abstract-A new method has been established for introducing acetylene groups at the α-position of pyrrolidine ring, in which 2-ethoxy-*N*-ethoxycarbonylpyrrolidine reacts with tin(IV) acetylides in the presence of tin(II) triflate.

Reactions for introducing functional groups at the α-position of cyclic amines are of particular interest due to potential application to the preparation of many important alkaloids, antibiotics and medicines possessing cyclic amines (including fused rings).[1]

The preceding paper[2] presented a convenient method for introducing various functional groups at the α-position of pyrrolidine derivatives, starting from 2-pyrrolidinone. By that method, several alkaloids and metabolites[3] could be easily synthesized. In the present study, a new method was developed for introducing acetylene groups at the α-position of *N*-alkoxycarbonylpyrrolidines.

Table. Synthesis of 2-(1-Alkynyl)-*N*-ethoxycarbonylpyrrolidine Derivatives[a]



3a-f	R	Yield of 3 (%)	Bp of 3 (°C)[b]
3 a	C_6H_5	63	145 (3 mmHg)
3 b	$Me(CH_2)_3$	85	138 (5 mmHg)
3 c	$Me(CH_2)_5$	72	152 (5 mmHg)
3 d	$Me(CH_2)_6$	67	152 (5 mmHg)
3 e	$Me(CH_2)_7$	65	160 (3 mmHg)
3 f	$C_6H_5(CH_2)_2$	78	156 (3 mmHg)

a Molar ratio; **1** : $Sn(OTf)_2$: $Ph_3SnC{\equiv}CR$ = 1 : 1.5 : 1.5

b Other data are shown in reference 8.

The reactions of 2-ethoxy-*N*-ethoxycarbonylpyrrolidine (**1**), *via* acyl-iminium ion (**2**), with carbanions such as Grignard or lithium reagents were reported by Shono *et al.*[4] However the reaction conditions they used (combinations of carbanions and Lewis acids such as BF_3-etherate, $TiCl_4$) are not ideal since carbanions may be quenched with Lewis acids prior to the occurrence of the desired reactions with acyl iminium ions (**2**). Indeed the authors observed that such conditions led to poor results in several attempts. If the nucleophile is not deactivated with a Lewis acid for converting **1** to **2** in the same vessel, the desired reaction occurs without difficulty. In consideration of this, numerous experiments were carried out to determine appropriate combination of a Lews acid and a nucleophile.[5] Tin(II) triflate [tin(II) trifluoromethanesulfonate][6] and triphenyltin acetylides were found ideal as a Lewis acid and nucleophiles, respectively. Combining **1** with tin(II) triflate followed by treatment with triphenyltin acetylides was found to be a new means for introducing acetylene groups[7] at the α-position of pyrrolidine ring, as shown in the Table. It appears that tin(IV) acetylides are not deactivated with tin(II) triflate.

Our new method was typically conducted as follows:

A solution of tin(II) triflate (862 mg, 2.1 mmol) in dry CH_2Cl_2 (30 ml) was cooled at -78°C under an Ar atmosphere. To this solution was added **1** (260 mg, 1.4 mmol) followed by stirring for 2 h. A solution of 1-triphenylstannyl-1-hexyne[9] (901 mg, 2.1 mmol) in CH_2Cl_2 (2 ml) was added dropwise to the stirred mixture, followed by additional stirring at -78°C for 3 h and then warming to room temperature by removing the cooling bath. The reaction mixture was quenched with 10% NH_4Cl solution and extracted with ether. The ether extract was washed with brine, dried over $MgSO_4$ and evaporated to give a white solid (862 mg). Chromatographic separation of the solid on silica gel by elution with hexane-acetone (2:1) gave the desired product which was purified by distillation to give a colorless oil (263 mg, 85%), bp 138°C/5 mmHg.

In summary, a combination of tin(II) triflate and tin(IV) acetylides was found to be a new means for introducing acetylene groups at the α-position of the pyrrolidine ring. The scope of possible applications and limitations of this method is presently being clarified.

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REFERENCES AND NOTES

1. D. Seebach and D.Enders, *Angew. Chem., Int. Ed. Engl.*, 1974, **14**, 15; A. I. Meyers and W. T. House, *J. Am. Chem. Soc.*, 1980, **102**, 7175; J. C. Hobert, J. B. P. A. Wijnberg, and W. N. Speckamp, *Tetrahedron*, 1975, **31**, 1437; T. Shono, H. Hamaguchi, and Y. Matsumura, *J. Am. Chem. Soc.*, 1975, **97**, 4264; Y. Nagao, W-M. Doi, M. Ochiai, S. Tsukagoshi, and E. Fujita, *J.Am. Chem. Soc.*, 1988, **110**, 289.
2. T. Nagasaka, H. Tamano, T. Maekawa, and F. Hamaguchi, *Heterocyles*, 1987, **26**, 617.
3. T. Nagasaka, H. Hayashi, and F. Hamaguchi, *Heterocycles*, 1988, **27**, 1685; T. Nagasaka, H. Yamamoto, A. Sugiyama, and F. Hamaguchi, *Heterocycles*, 1988, **27**, 2219; T. Nagasaka, H. Yamamoto, H. Hayashi, M. Watanabe, and F.Hamaguchi, *Heterocycles*, 1989, **29**, 155; T. Nagasaka, Y. Koseki and F. Hamaguchi, *Tetrehedron Lett.*, 1989, **30**, 1871; T. Nagasaka, H. Yamamoto, H. Hayashi, H. Kato, M. Kawaida, K. Yamaguchi, and F. Hamaguchi, *Heterocycles*, 1989, **29**, 1209; T. Nagasaka, H. Hayashi, M. Kumakawa, M. Sakamoto, M. Mizuno, and F. Hamaguchi, *Heterocycles*, 1989, **29**, 2157; T. Nagasaka, H. Kato, H. Hayashi, M. Shioda, H. Hikasa, and F. Hamaguchi, *Heterocycles*, 1990, **30**, 561.
4 T. Shono, Y. Matsumura, and K. Tsubata, 43rd Annual Meeting of Japan Chem. Soc., 1981, Abstract p.1085; T. Shono, *Tetrahedron*, 1984, **40**, 811.
5. Lithium-, magnesium-, borane-[7] or tin acetylide without Lewis acid and tin acetylide with BF_3-etherate, $SnCl_4$, Bu_3SnOMe or Me_3Al failed to provide the desired product (**3**). The results of reactions of **1** with other carbon-nucleophiles using tin(II) triflate will be reported in the future.

6. Tin(II) triflate must be handled under an Ar atmosphere. Excellent works using tin(II) triflate by the Mukaiyama group and the Nagao group have been reported: e. g., T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, *Tetrahedron*, 1984, **40**, 1381; Y. Nagao, W.-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, *J. Am. Chem. Soc.*, 1988, **110**, 289.
7. The reaction[4] of **1** (methyl ester) with lithium phenylacetylide in the presence of $BF_3{\cdot}Et_2O$ has been reported, without experimental details, leading to **3a** in 95% yield; The synthesis of 1-methyl-2-phenylethynylpyrrolidine from 1-methyl-2-pyrrolidinone has been reported; M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 1719.
8. **3a**: Ir ($CHCl_3$) 1690 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ 1.27 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.80-2.40 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.20-3.75 (2H, m, $C\underline{H}_2N$), 4.18 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 4.60-4.90 (1H, m, $C\underline{H}N$), 7.20-7.82 (5H, m, Ph), Ms *m/z* 243 (M^+). High ms calcd for $C_{13}H_{12}NO_2$ (M^+-Et): 214.0866. Found: 214.0866.

   3b: Ir ($CHCl_3$) 1680 cm^{-1}. ^{1}-H-Nmr ($CDCl_3$) δ 0.90 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.27 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 1.10-2.31 (10H, m, $C\underline{H}_2C\underline{H}_2$, $\equiv CC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.08-3.72 (2H, m, $C\underline{H}_2N$), 4.17 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 4.40-4.60 (1H, br, $C\underline{H}N$). Ms *m/z* 223 (M^+). High ms calcd for $C_{11}H_{16}NO_2$ (M^+-Et): 194.1179. Found: 194.1155.

   3c: Ir ($CHCl_3$) 1680 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ 0.72-1.10 (3H, m, $CH_2C\underline{H}_3$), 1.26 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 1.15-1.72 (8H, m, $(C\underline{H}_2)_4CH_3$), 1.74-2.38 (6H, m, $C\underline{H}_2C\underline{H}_2$, $\equiv CC\underline{H}_2$), 3.19-3.69 (2H, m, $C\underline{H}_2N$), 4.18 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 4.43-4.70 (1H, m, $C\underline{H}N$). Ms *m/z* 251 (M^+). High ms calcd for $C_{15}H_{25}NO_2$ (M^+): 251.1883. Found: 251.1878.

   3d: Ir ($CHCl_3$) 1680 cm^{-1}. ^{1}-H-Nmr ($CDCl_3$) δ 0.65-1.08 (3H, m, $C\underline{H}_3$), 1.30 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 1.10-1.72 (10 Hz, m, $(C\underline{H}_2)_5$), 1.74-2.34 (6H, m, ≡CC$\underline{H}_2$, C$\underline{H}_2$C$\underline{H}_2$), 3.13-3.78 (2H, m, C$\underline{H}_2$N), 4.18 (2H, q, *J*=7 Hz, OC$\underline{H}_2$CH$_3$), 4.40-4.80 (1H, m, C$\underline{H}$N). Ms *m/z* 265 (M$^+$). High ms calcd for $C_{14}H_{22}NO_2$ (M$^+$-Et): 236.1648. Found: 236.1648.

3e: Ir (CHCl$_3$) 1680 cm^{-1}. ^{1}H-Nmr (CDCl$_3$) δ 0.86-1.10 (3H, m, C$\underline{H}_3$), 1.10-1.80 (15H, m, OCH$_2$C$\underline{H}_3$, (C$\underline{H}_2$)$_6$), 1.70-2.56 (6H, m, C$\underline{H}_2$C$\underline{H}_2$, ≡CC$\underline{H}_2$), 3.14-3.60 (2H, m, C$\underline{H}_2$N), 4.17 (2H, q, *J*=7 Hz, OC$\underline{H}_2$CH$_3$), 4.35-4.62 (1H, m, C$\underline{H}$N). High ms calcd for $C_{17}H_{29}NO_2$ (M$^+$): 279.2196. Found: 279.2186.

3f: Ir (CHCl$_3$) 1680 cm^{-1}. ^{1}-H-Nmr (CDCl$_3$) δ 1.25 (3H, t, *J*=8 Hz, C$\underline{H}_3$), 1.80-2.20 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 2.34-2.60 (2H, m, ≡CC$\underline{H}_2$), 2.70-2.98 (2H, m, C$\underline{H}_2$Ph), 3.25-3.58 (2H, m, C$\underline{H}_2$N), 4.17 (2H, q, *J*=8 Hz, OC$\underline{H}_2$), 4.53 (1H, br s, C$\underline{H}$N), 7.20-7.50 (5H, br, Ph). High ms calcd for $C_{17}H_{21}NO_2$ (M$^+$): 271.1570. Found: 271.1544.

9. Triphenyltin acetylides were prepared in 60-90% yields by reactions of the corresponding acetylenes with n-BuLi followed by treatment with triphenyltin chloride.

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