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INTRODUCTION OF FUNCTIONAL GROUPS INTO THE α-POSITION OF N-ALKOXYCARBONYLPYRROLIDINES[1]

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Abstract — The reactions for the introduction of O-, S-, N-, and C-functional groups into the α-position of N-alkoxycarbonylpyrrolidines using N-alkoxycarbonyl-α-ethoxypyrrolidines are described.

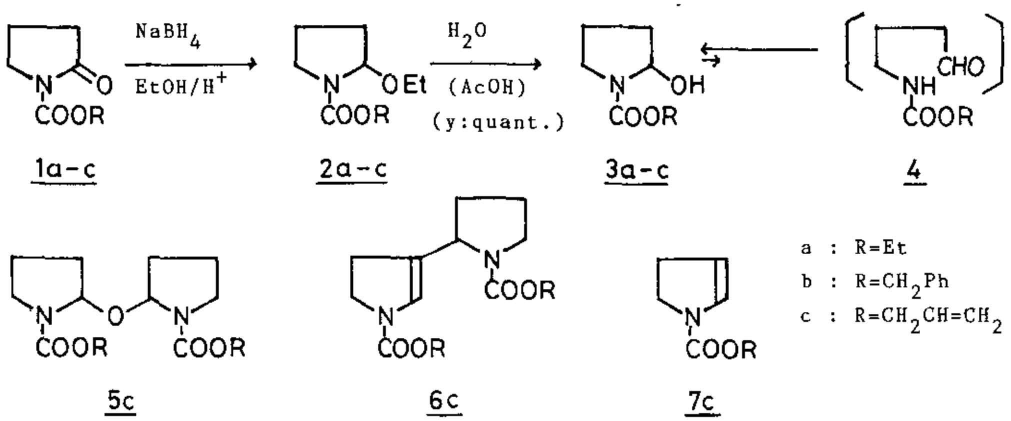
There are many well-known alkaloids, antibiotics and synthetic medicines with cyclic amine structures having various substituents (including fused rings) at the α-position of nitrogen. Thus, reactions by which functional groups can be introduced into the α-position of amines are presently of great interest.[2]

In the preceding paper,[3] we reported a convenient synthesis for α-ethoxycarbamates (2) by the reduction of N-alkoxycarbonyllactams (1) with $NaBH_4/H^+$ in ethanol. In the present research, the conversion of the ethoxy group of 2 into other functional groups is described.

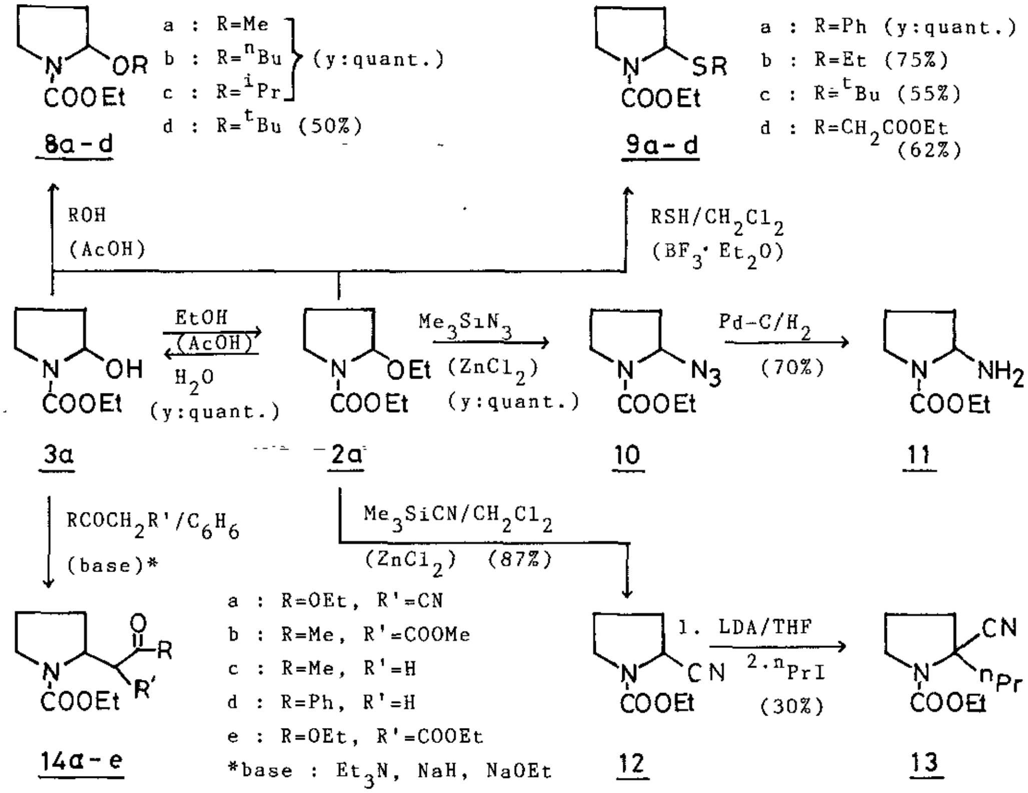
An investigation was first made of the synthesis of 2-hydroxycarbamate (3), which appears more reactive toward nucleophiles than 2-ethoxycarbamate (2), on the basis of a general idea of its equivalent isomer (4). Although the direct reduction of 1 to 3 could not be carried out successfully,[4] Hydrolysis of 2 in aqueous acetic acid gave 3 in nearly a quantitative yield. Other conditions (5%HCl, $AlCl_3/CH_2Cl_2$, $ZnCl_2/CH_2Cl_2$) for the hydrolysis of 2 caused contamination of 3 with the production of dimers 5 and 6 and enamine 7.[5]

Oxygen-functional Group: The refluxing of 2a or 3a in alcohols such as MeOH, n-BuOH, and iso-PrOH in the presence of a small amount of acetic acid gave the expected 2-alkoxycarbamates (8a-c) in quantitative yield. But the yield of 2-

Scheme 1



Scheme 2



tert-butoxy-carbamate (8d) using tert-butanol did not exceed 50%.

Sulfur-functionl Group: The substitution of 2-ethoxy and 2-hydroxy groups with sulfur groups was carried out by stirring 2a or 3a at room temperature with mercaptanes in dichloromethane in the presence of a catalytic amount of trifluoroborane-etherate. The reaction proceeded very quickly with good yield. Without the catalyst, the starting materials could be recovered even though they melted at 100°C.

Nitrogen-functionl Group: We have already reported the reaction for introducing amines, amides and carbamates into the α-position of the pyrrolidine ring using 5-ethoxy- and 5-acetoxy-2-pyrrolidinones.[6] However, these conditions were not found adequate in the case of 2a in spite of much effort. Finally, the reaction of 2a with trimethylsilyl azide in the presence of a catalytic amount of zinc chloride in dichloromethane gave azidocarbamate (10) in quantitative yield. The catalytic hydrogenation of 10 with 5% palladium-carbon gave rather unstable aminocarbamate (11).

Carbon-functional Group: Asher[7] and Shono[8] reported the reaction of α-methoxyamide or α-methoxycarbamate with trimethylsilyl cyanide in the presence of a Lewis acid to give α-cyanoamide or α-cyanocarbamate, respectively, in high yield. α-Cyanocarbamate (12), obtained from 2a in 87% yield by this method, was lithiated with lithium diisopropylamide in tetrahydrofuran and alkylated to give 2-cyano-2-n-propylcarbamate (13) in 30% yield. This reaction holds promise as a general method for introducing various carbon functional groups into the α-position of cyclic amines.[9]

The reaction of 2-hydroxycarbamates (3) with several carbonyl compounds including a simple ketone such as acetone in the presence of a base was examined[10] and the results are shown in Table I. Although the reaction of 3 with cyanoacetate or acetoacetate proceeded in the presence of triethylamine, its reaction with acetone, acetophenone, and malonate required sodium ethoxide or sodium hydride. Sodium hydride in benzene was a suitable condition for this reaction to proceed.

The infrared and proton nuclear magnetic resonance spectra of the 2-substituted N-alkoxycarbonylpyrrolidine derivatives[11] described in the present paper are listed in Table II.

The synthesis of alkaloids from these α-ethoxycarbamates is presently being investigated and the results will be published in the near future.

Table I. Reactions of α-Hydroxycarbamates (3) with Active Methylene Compounds

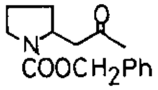
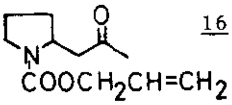
Run	Carbamate	Active Methylene Compound	Base/Solvent	Reflux Time (h)	Product	Yield (%)
1	3a	$NCCH_2CO_2Et$	$Et_3N/EtOH$	42	14a	80
2	3a	$NCCH_2CO_2Et$	Et_3N/C_6H_6	19	14a	88
3	3a	$MeCOCH_2CO_2Me$	Et_3N/C_6H_6	22	14b	73
4	3a	MeCOMe	NaOEt/EtOH	44	14c	31
5	3a	MeCOMe	NaH/C_6H_6	44	14c	71
6	3a	PhCOMe	NaOEt/EtOH	16	14d	33
7	3a	PhCOMe	NaH/C_6H_6	16	14d	60
8	3a	$CH_2(CO_2Et)_2$	NaH/C_6H_6	17	14e	40
9	3b	MeCOMe	NaH/C_6H_6	12	 15	40
10	3c	MeCOMe	NaH/C_6H_6	9	 16	70

Table II. IR and ^1H-NMR Spectra of 2-Substituted $\underline{N}$-Alkoxycarbonylpyrrolidine Derivatives

Compound*	IR ν (cm^{-1})	^1H-NMR δ (ppm) ($CDCl_3$)
3a	($CHCl_3$) 3575, 3425, 1690	1.27 (3H, t, $\underline{J}$=7Hz, $OCH_2C\underline{H}_3$), 1.67-2.17 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.13-3.67 (3H, m, $C\underline{H}_2N$, $O\underline{H}$), 4.17 (2H, q, $\underline{J}$=7Hz, $OC\underline{H}_2CH_3$), 5.50 (1H, m, $OC\underline{H}N$)
3b	($CHCl_3$) 3575, 3430, 1680	1.80-2.12 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.31-3.80 (3H, m, $C\underline{H}_2N$, $O\underline{H}$), 5.18 (2H, s, $OC\underline{H}_2Ph$), 5.55 (1H, m, $OC\underline{H}N$), 7.42 (5H, s, Ph)
3c	($CHCl_3$) 3575, 3450 1690	1.70-2.31 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.20-3.78 (2H, m, $C\underline{H}_2N$), 4.03 (1H, br, $O\underline{H}$), 4.67 (2H, m, $OC\underline{H}_2$), 5.16-5.47 (2H, m, $CH=C\underline{H}_2$), 5.47-5.70 (1H, m, $OC\underline{H}N$), 5.79-6.22 (1H, m, $C\underline{H}=CH_2$)
5c	(neat) 1700, 1100	1.70-2.29 (8H, m, $C\underline{H}_2C\underline{H}_2$ x 2), 3.21-3.70 (4H, m, $C\underline{H}_2N$ x 2), 4.65 (4H, m, $OC\underline{H}_2$ x 2), 5.15-5.46 (4H, m, $CH=C\underline{H}_2$ x 2), 5.46-5.70 (2H, m, $C\underline{H}N$ x 2), 5.78-6.20 (2H, m, $C\underline{H}=CH_2$ x 2)
6c	($CHCl_3$) 1680, 1650	1.58-2.19 (4H, m, $C\underline{H}_2C\underline{H}_2$), 2.37-2.76 (2H, m, $CH_2C\underline{H}_2C=CH$), 3.20-3.65 (2H, m, $C\underline{H}_2N$), 3.72 (2H, t, $\underline{J}$=9Hz, $C\underline{H}_2N$), 4.57 (5H, m, $OC\underline{H}_2$ x 2, $C=CC\underline{H}N$), 5.07-5.50 (4H, m, $CH=C\underline{H}_2$ x 2), 5.72-6.20 (2H, m, $C\underline{H}=CH_2$ x 2), 6.42 (1H, m, $NC\underline{H}=C$)
7c	(neat) 1710, 1620	2.46-2.83 (2H, m, $C\underline{H}_2CH_2N$), 3.77 (3H, t, $\underline{J}$=9Hz, $C\underline{H}_2N$), 4.60 (2H, m, $OC\underline{H}_2$), 5.20 (1H, m, $NCH=C\underline{H}$), 5.0-5.48 (2H, m, $CH=C\underline{H}_2$), 5.72-6.30 (1H, m, $C\underline{H}=CH_2$), 6.60 (1H, br s, $NC\underline{H}=CH$)
8a	(neat) 1700, 1080	1.25 (3H, t, $\underline{J}$=7Hz, $CH_2C\underline{H}_3$), 1.50-2.30 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.22-3.64 (2H, m, $C\underline{H}_2N$), 3.33 (3H, s, $OC\underline{H}_3$), 4.18 (2H, q, $\underline{J}$=7Hz, $OC\underline{H}_2CH_3$), 5.20 (1H, m, $OC\underline{H}N$)
8b	(neat) 1700, 1090	0.89 (3H, m, $CH_2CH_2C\underline{H}_3$), 1.00-2.10 (8H, m, $C\underline{H}_2C\underline{H}_2$ x 2), 1.24 (3H, t, $\underline{J}$=7Hz, $OCH_2C\underline{H}_3$), 3.12-3.63 (4H, m, $C\underline{H}_2N$, $OC\underline{H}_2CH_2$), 4.17 (2H, q, $\underline{J}$=7Hz, $OC\underline{H}_2CH_3$), 5.26 (1H, m, $OC\underline{H}N$)

(Continued)

8c	(neat)	1700, 1090	1.15 (3H, d, $\underline{J}$=7Hz, $\mathrm{CHC\underline{H}_3}$), 1.17 (3H, d, $\underline{J}$=7Hz, $\mathrm{CHC\underline{H}_3}$), 1.29 (3H, t, $\underline{J}$=7Hz, $\mathrm{CH_2C\underline{H}_3}$), 1.51-2.19 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 3.49 (2H, m, $\mathrm{C\underline{H}_2N}$), 4.18 (2H, q, $\underline{J}$=7Hz, $\mathrm{OC\underline{H}_2CH_3}$), 5.32 (1H, m, $\mathrm{OC\underline{H}N}$)
8d	(neat)	1700, 1100	1.20 (3H, t, $\underline{J}$=7Hz, $\mathrm{CH_2C\underline{H}_3}$), 1.23 (9H, s, $^t\mathrm{Bu}$), 1.55-2.20 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 3.09-3.58 (2H, m, $\mathrm{C\underline{H}_2N}$), 4.12 (2H, q, $\underline{J}$=7Hz, $\mathrm{OC\underline{H}_2CH_3}$), 5.32 (1H, m, $\mathrm{OC\underline{H}N}$)
9a	(neat)	1700	1.18 (3H, m, $\mathrm{CH_2C\underline{H}_3}$), 1.66-2.42 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 3.42 (2H, m, $\mathrm{C\underline{H}_2N}$), 4.10 (2H, m, $\mathrm{OC\underline{H}_2CH_3}$), 5.42 (1H, m, $\mathrm{SC\underline{H}N}$), 7.30-7.83 (5H, m, Ph)
9b	(neat)	1700	1.25 (6H, t, $\underline{J}$=7Hz, $\mathrm{CH_2C\underline{H}_3}$ x 2), 1.8-2.3 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 2.5-2.9 (2H, m, $\mathrm{SC\underline{H}_2CH_3}$), 3.3-3.6 (2H, m, $\mathrm{C\underline{H}_2N}$), 4.15 (2H, q, $\underline{J}$=7Hz, $\mathrm{OC\underline{H}_2CH_3}$), 5.25 (1H, m, $\mathrm{NC\underline{H}S}$)
9c	(neat)	1700	1.25 (3H, t, $\underline{J}$=7Hz, $\mathrm{CH_2C\underline{H}_3}$), 1.36 (9H, s, $^t\mathrm{Bu}$), 1.60-2.41 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 3.21-3.36 (2H, m, $\mathrm{C\underline{H}_2N}$), 4.18 (2H, q, $\underline{J}$=7Hz, $\mathrm{OC\underline{H}_2CH_3}$), 5.20 (1H, m, $\mathrm{SC\underline{H}N}$)
9d	(neat)	1730, 1690	1.20 (3H, t, $\underline{J}$=7.5Hz, $\mathrm{OCH_2C\underline{H}_3}$), 1.22 (3H, t, $\underline{J}$=7.5Hz, $\mathrm{OCH_2C\underline{H}_3}$), 1.7-2.3 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 3.2-3.7 (4H, m, $\mathrm{C\underline{H}_2N}$, $\mathrm{SC\underline{H}_2}$), 3.95-4.30 (4H, m, $\mathrm{OC\underline{H}_2CH_3}$ x 2), 5.40 (1H, d, $\underline{J}$=6Hz, $\mathrm{NC\underline{H}S}$)
10	(neat)	2110, 1710	1.30 (3H, t, $\underline{J}$=7Hz, $\mathrm{CH_2C\underline{H}_3}$), 1.90 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 3.10-3.75 (2H, m, $\mathrm{C\underline{H}_2N}$), 4.23 (2H, q, $\underline{J}$=7Hz, $\mathrm{OC\underline{H}_2CH_3}$), 5.61 (1H, m, $\mathrm{NC\underline{H}N}$)
11	(neat)	3400, 3300, 1700	1.28 (3H, t, $\underline{J}$=7.5Hz, $\mathrm{CH_2C\underline{H}_3}$), 1.5-2.5 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 3.42 (2H, t, $\underline{J}$=6Hz, $\mathrm{C\underline{H}_2N}$), 4.15 (2H, q, $\underline{J}$=7.5Hz, $\mathrm{C\underline{H}_2CH_3}$), 4.78 (1H, m, $\mathrm{NC\underline{H}N}$)
12	(neat)	2240, 1700	1.30 (3H, t, $\underline{J}$=7Hz, $\mathrm{CH_2C\underline{H}_3}$), 1.98-2.41 (4H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$), 3.22-3.64 (2H, m, $\mathrm{C\underline{H}_2N}$), 4.23 (2H, q, $\underline{J}$=7Hz, $\mathrm{OC\underline{H}_2CH_3}$), 4.59 (1H, m, $\mathrm{NC\underline{H}CN}$)
13	(neat)	2240, 1700	0.95 (3H, t, $\underline{J}$=6Hz, $\mathrm{CH_2C\underline{H}_3}$), 1.25 (3H, t, $\underline{J}$=7Hz, $\mathrm{OCH_2C\underline{H}_3}$), 1.3-2.6 (8H, m, $\mathrm{C\underline{H}_2C\underline{H}_2}$ x 2), 3.2-3.8 (2H, m, $\mathrm{C\underline{H}_2N}$), 4.17 (2H, q, $\underline{J}$=7Hz, $\mathrm{OC\underline{H}_2CH_3}$)

(Continued)

14a**	(neat)	2250, 1750, 1690	1.21 (3H, t, $\underline{J}$=7Hz, $CH_2C\underline{H}_3$), 1.25 (3H, t, $\underline{J}$=7Hz, $CH_2C\underline{H}_3$), 1.73-2.33 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.47 (1H, m, $C\underline{H}CN$), 3.50 (2H, t, $\underline{J}$=7Hz, $C\underline{H}_2N$), 4.07-4.43 (4H, m, $OC\underline{H}_2CH_3$ x 2), 4.70-4.80 (1H, m, $C\underline{H}N$)
14b**	($CHCl_3$)	1740, 1710, 1690	1.23 (3H, t, $\underline{J}$=7Hz, $CH_2C\underline{H}_3$), 1.67-2.03 (4H, m, $C\underline{H}_2C\underline{H}_2$), 2.13 (3H, s, $COC\underline{H}_3$), 3.13-3.57 (2H, m, $C\underline{H}_2N$), 3.73 (3H, s, $OC\underline{H}_3$), 4.11 (2H, q, $\underline{J}$=7Hz, $OC\underline{H}_2CH_3$), 4.15 (1H, m, $COC\underline{H}CO$), 4.33-4.47 (1H, m, $C\underline{H}N$)
14c	($CHCl_3$)	1710, 1680	1.27 (3H, t, $\underline{J}$=7Hz, $CH_2C\underline{H}_3$), 1.57-2.60 (6H, m, $C\underline{H}_2C\underline{H}_2$, $C\underline{H}_2CO$), 2.17 (3H, s, $COC\underline{H}_3$), 3.40 (2H, t, $\underline{J}$=7Hz, $C\underline{H}_2N$), 4.13 (2H, q, $\underline{J}$=7Hz, $OC\underline{H}_2CH_3$), 4.15 (1H, m, $C\underline{H}N$)
14d	($CHCl_3$)	1690, 1670	1.27 (3H, t, $\underline{J}$=7Hz, $CH_2C\underline{H}_3$), 1.73-2.00 (5H, m, $C\underline{H}_2C\underline{H}_2$, $HC\underline{H}CO$), 2.53-2.97 (1H, m, $\underline{H}CHCO$), 3.33-3.50 (2H, m, $C\underline{H}_2N$), 4.13 (2H, q, $\underline{J}$=7Hz, $OC\underline{H}_2CH_3$), 4.30-4.43 (1H, m, $C\underline{H}N$), 7.43-7.60, 7.97-8.07 (5H, m, Ph)
14e	(neat)	1740, 1700	1.25 (9H, t, $\underline{J}$=7Hz, $CH_2C\underline{H}_3$ x 3), 1.60-2.30 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.30 (2H, m, $C\underline{H}_2N$), 3.60 (1H, m, $C\underline{H}(COOEt)_2$), 4.15 (2H, q, $\underline{J}$=7Hz, $OC\underline{H}_2CH_3$), 4.20 (4H, q, $\underline{J}$=7Hz, $OC\underline{H}_2CH_3$ x 2), 4.38 (1H, m, $C\underline{H}N$)
15	(neat)	1740, 1700	1.40-2.17 (4H, m, $C\underline{H}_2C\underline{H}_2$), 2.12 (3H, br s, $COC\underline{H}_3$), 2.22-3.20 (2H, m, $C\underline{H}_2CO$), 3.30-3.54 (2H, m, $C\underline{H}_2N$), 4.07-4.38 (1H, m, $C\underline{H}N$), 5.20 (2H, s, $PhCH_2$), 7.41 (5H, s, Ph)
16	(neat)	1740, 1700	1.60-2.09 (4H, m, $C\underline{H}_2C\underline{H}_2$), 2.17 (3H, s, $COC\underline{H}_3$), 2.29-3.28 (2H, m, $C\underline{H}_2CO$), 3.42 (2H, t, $\underline{J}$=7Hz, $C\underline{H}_2N$), 4.09-4.39 (1H, m, $C\underline{H}N$), 4.60 (2H, m, $OC\underline{H}_2CH=C$), 5.12-5.45 (2H, m, $CH=C\underline{H}_2$), 5.77-6.21 (1H, m, $C\underline{H}=CH_2$)

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* All synthesized compounds were oils, which gave satisfactory elemental analyses and/or mass spectra.

** This compound appears a single product judging from its NMR spectrum and TLC spot.

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4 Mainly the ring-opened ω-hydroxycarbamate was obtained.

5 This reaction was examined in detail in the case of **2c**. The yields of dimers **5c** and **6c**, formed using HCl and a Lewis acid, respectively, increased with the scale-up of the reactions. Similar results were obeserved for both **2a** and **2b**.

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9 Further studies concerning this method are in progress.

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11 To form the carbon-carbon bond at the α-position of amines, the reaction of acyliminium ions with various enol ethers[11a] and propargyl- and allylsilanes[11b] appears also ideal. a) T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.*, 1981, **103**, 1172. b) H. Hiemstra, W. J. Klaver, and W. N. Speckamp, *J. Org. Chem.*, 1984, **49**, 1149; H. Hiemstra, M. H. A. M. Sno, R. J. Vijn, and W. N. Speckamp, *J. Org. Chem.*, 1985, **50**, 4014.

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