HETEROCYCLES, Vol. 80, No. 1, 2010, pp. 679 - 687. © The Japan Institute of Heterocyclic Chemistry
Received, 23rd July, 2009, Accepted, 25th August, 2009, Published online, 25th August, 2009
DOI: 10.3987/COM-09-S(S)70

SYNTHESIS OF 3-SUBSTITUTED 3-(TRIMETHYLSILOXY)PYRROLIDINES FROM β-AMINOKETONES AND LITHIUM TRIMETHYLSILYLDIAZOMETHANE

Yoshiyuki Hari,[a] Takuya Yokoyama,[b] and Toyohiko Aoyama[b]*

[a] Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

[b] Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabedori, Mizuho, Nagoya 467-8603, Japan

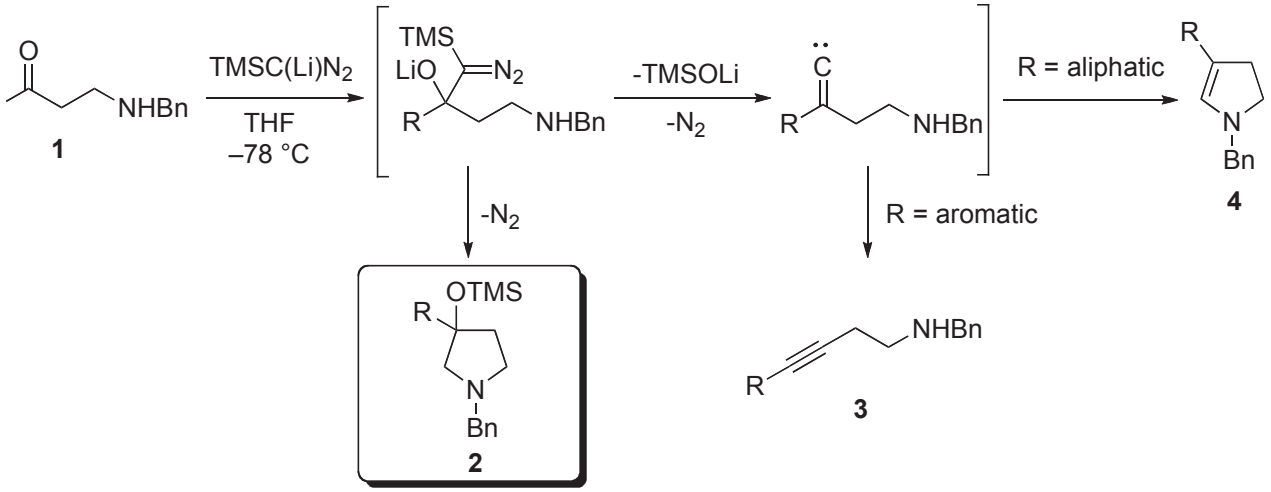
E-mail: aoyama@phar.nagoya-cu.ac.jp

Dedicated to Professor Dr. Akira Suzuki on the occasion of his 80th birthday

Abstract – Lithium trimethylsilyldiazomethane reacted with *N*-benzyl-β-aminoketones at -78 °C in THF to give 3-substituted 1-benzyl-3-(trimethylsiloxy)pyrrolidines in moderate to good yields.

INTRODUCTION

We have previously reported that lithium trimethylsilyldiazomethane [TMSC(Li)N_2] readily reacts with aliphatic β-aminoketones to give the corresponding 2-pyrrolines (intramolecular N-H insertion products)



Scheme 1

in moderate to good yields via alkylidenecarbene intermediates (Scheme 1).[1] Furthermore, we have demonstrated that the reaction of TMSC(Li)N_2 with aryl ketones efficiently produces the corresponding aryl acetylenes (1,2-aryl rearrangement products) also via alkylidenecarbene intermediates.[2] Due to our continued interest in the use of $TMSCHN_2$ in organic synthesis,[3] the reaction of TMSC(Li)N_2 with *N*-benzyl-β-aminoketones **1** was reexamined in detail. Interestingly, we found that when the reaction was carried out at low temperature, -78 °C, intramolecular *N*-alkylation via initially formed diazoalkoxides preferentially occurred and the 3-substituted 1-benzyl-3-(trimethylsiloxy)pyrrolidines **2** were obtained as major products (Scheme 1). In this paper, we describe the details of our results.

RESULTS AND DISCUSSION

All *N*-benzyl-β-aminoketones **1** used in this study were synthesized from the corresponding *N*-methoxy-*N*-methylamides, vinylmagnesium bromide and benzylamine according to the procedure reported by Gomtsyan and co-workers (Figure 1).[4] Initially, the *N*-benzyl-β-aminoketone **1a** was employed as a model substrate to optimize reaction conditions. The results are summarized in Table 1. In analogy with the reaction with aryl ketones,[2] the reaction of TMSC(Li)N_2 with **1a** at -78 °C for 2 h followed by reflux for 2 h smoothly proceeded to give the alkyne **3a** (50% yield) as a major product, but an unexpected product, the pyrrolidine **2a**, was also obtained in 29% yield (entry 1). Interestingly, lowering the reaction temperature remarkably affected the reaction mode and **2a** was obtained as a major product (entries 2, 3 and 6-8). The change of the reaction mode at low temperature is most likely due to suppression of the elimination of lithium trimethylsiloxide (TMSOLi) and N_2 gas, which generates an alkylidenecarbene intermediate, and consequently, intramolecular alkylation of the initially formed diazoalkoxide preferentially occurs with evolution of N_2 to give **2a** as shown in Scheme 1. THF was the reaction solvent of choice to efficiently produce **2a** (entries 3 and 4). Replacement of TMSC(Li)N_2 by the magnesium bromide salt [TMSC(MgBr)N_2][5] was less effective (entries 3 and 5). The reaction at -78 °C in THF for 12 h was found to give the best result (entry 7). The structure of **2a** was confirmed by alternative

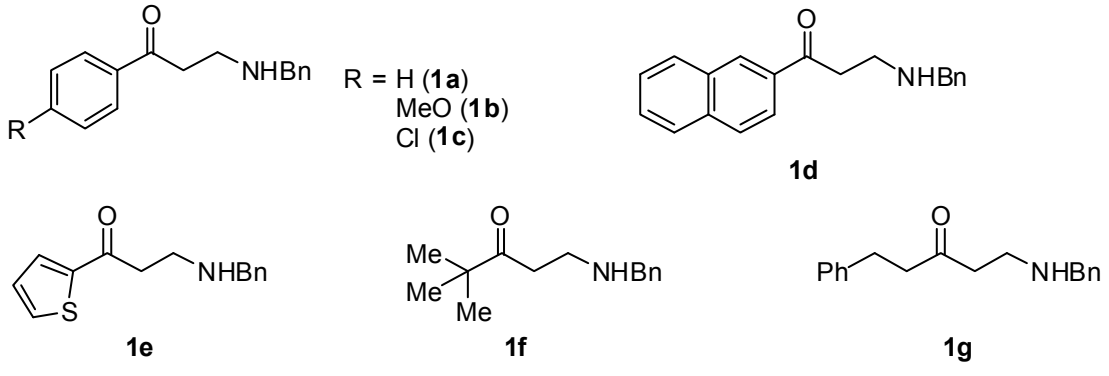
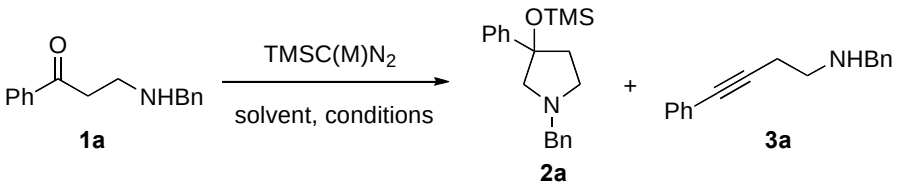


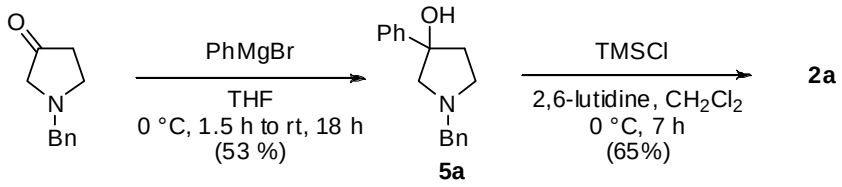
Figure 1. *N*-Benzyl-β-aminoketones **1** used in this study

Table 1. Reaction of TMSC(M)N_2 (M = Li or MgBr) with **1a**[a]



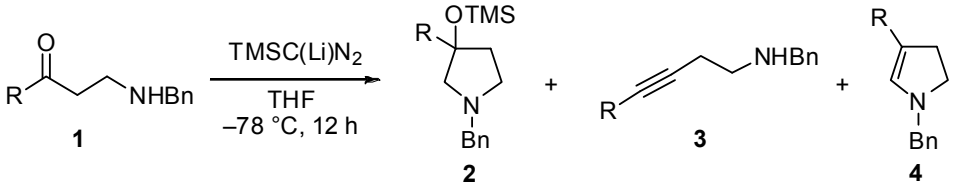
Entry	M	Solvent	Conditions	Yield (%)[b] of **2a**	Yield (%)[b] of **3a**
1	Li	THF	-78 °C, 2 h to reflux, 2 h	29	50
2	Li	THF	-78 °C, 2 h to rt, 2 h	45	33
3	Li	THF	-78 °C, 2 h to 0 °C, 2 h	49	26
4	Li	Et_2O	-78 °C, 2 h to 0 °C, 2 h	3	30
5	MgBr	THF	-78 °C, 2 h to 0 °C, 2 h	9	21
6	Li	THF	-78 °C, 6 h	52	28
7	Li	THF	-78 °C, 12 h	56	22
8	Li	THF	-78 °C, 24 h	56	22

a, TMSC(Li)N_2 was prepared from $TMSCHN_2$ and *n*-BuLi. TMSC(MgBr)N_2 was prepared from $TMSCHN_2$, *n*-BuLi and $MgBr_2$. b, Isolated yield.



Scheme 2

Table 2. The generality of substrates **1**



Entry	R	Yield (%)[b] of **2**	Yield (%)[b] of **3**	Yield (%)[b] of **4**
1[a]	Ph (**1a**)	56	22	-[c]
2	*p*-MeOPh (**1b**)	42	43	-[c]
3	*p*-ClPh (**1c**)	31	7	-[c]
4	Naphth-2-yl (**1d**)	47	33	-[c]
5	Thiophen-2-yl (**1e**)	36	19	-[c]
6	*tert*-Butyl (**1f**)	60	-[c]	23
7	$PhCH_2CH_2$ (**1g**)	72	-[c]	-[d]

a, Shown in entry 7 of Table 1. b, Isolated yield. c, Not obtained. d, An unseparable mixture of the corresponding 2-pyrroline **4g** and an unknown product was obtained.

synthesis from *N*-benzyl-3-pyrrolidinone, namely the reaction of *N*-benzyl-3-pyrrolidinone with phenylmagnesium bromide followed by trimethylsilylation by TMSCl (Scheme 2).

Next, the generality of the substrate was investigated (Table 2). When the substitutent on the benzene ring was an electron-donating group like a methoxy group (**1b**), the ratio of the alkyne **3b** to the pyrrolidine **2b** increased compared to that of **1a**. Conversely, an electron-withdrawing group such as a chloro group (**1c**)

preferentially furnished the desired pyrrolidine **2c** though the yields of **2c** and **3c** were somewhat low due to the inherent lability of **1c**.[6] In the case of the naphthyl derivative **1d**, the reaction proceeded smoothly to give **2d** in 47% yield with 33% yield of **3d** (entry 4). This reaction was also applicable to the substrate **1e** bearing heteroaromatics like thiophene for R and the desired **2e** was obtained in moderate yield (entry 5). The aliphatic β-aminoketone **1f** also underwent the reaction to give the desired **2f** in good yield (60%) though the pyrroline **4f** was formed as by-product (entry 6). Similarly, phenethyl derivative **1g** gave **2g** in 72% yield (entry 7).

CONCLUSION

We found that reaction of $TMSC(Li)N_2$ with β-aminoketones at -78 °C mainly proceeded in an intramolecular *N*-alkylation mode, and 3-substituted 3-(trimethylsiloxy)pyrrolidines were obtained in moderate to good yields. The present method is a new application of $TMSC(Li)N_2$ as a reagent in organic synthesis.

EXPERIMENTAL

All melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8400S spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX-270 spectrometer (^1H, 270 MHz; ^{13}C, 67.8 MHz). MS spectra were recorded on a JEOL JMS-SX-102A spectrometer. Silica gel used for column chromatography is Fuji Sylisia BW-820MH.

General procedure for the synthesis of *N*-benzyl-β-aminoketone (1).[4] Under an argon atmosphere, vinylmagnesium bromide (1.0 M in THF, 11 mL, 11 mmol) was added dropwise to a solution of *N*-methoxy-*N*-methylamide derivative (10 mmol) in THF (100 mL) at 0 °C and the mixture was stirred for 10 min, then stirred at room temperature for 1 h. A solution of $BnNH_2$ (1.0 M in water, 15 mL, 15 mmol) was added and the mixture was stirred at room temperature for 20 min-2 h. The mixture was extracted with EtOAc. The organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the following product.

3-(Benzylamino)-1-phenylpropan-1-one (1a).[4] Prepared from *N*-methoxy-*N*-methylbenzamide. EtOAc was used as eluent for column chromatography. 70% yield.

3-(Benzylamino)-1-(4-methoxyphenyl)propan-1-one (1b). Prepared from 4-methoxy-*N*-methoxy-*N*-methylbenzamide.[7] EtOAc was used as eluent for column chromatography. 88% yield. Yellow oil. IR (neat): 3319, 1672, 1258 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.72 (brs, 1H), 3.03 (t, J = 5.9 Hz, 2H), 3.16 (t, J = 5.9 Hz, 2H), 3.83 (s, 2H), 3.86 (s, 3H), 6.91-6.94 (d, J = 8.9 Hz, 2H), 7.31-7.33 (m, 5H), 7.91-7.95 (d, J =

8.9 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ: 38.43, 44.37, 54.15, 55.48, 113.66, 126.83, 126.96, 128.02, 128.31, 128.44, 130.18, 140.02, 197.94. EI-MS *m/z*: 269 (M^+), 135 (bp).

3-(Benzylamino)-1-(4-chlorophenyl)propan-1-one (1c). Prepared from 4-chloro-*N*-methoxy-*N*-methylbenzamide.[8] EtOAc was used as eluent for column chromatography. 41% yield. Yellow oil. IR (neat): 1682 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (brs, 1H), 3.03 (t, *J* = 5.9 Hz, 2H), 3.16 (t, *J* = 5.9 Hz, 2H), 3.83 (s, 2H), 7.23-7.33 (m, 5H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ: 38.92, 44.07, 54.15, 126.85, 127.97, 128.31, 128.81, 129.30, 135.09, 139.46, 140.01, 198.14. EI-MS *m/z*: 275 (M^+), 273 (M^+), 139 (bp). HR-MS calcd for $C_{16}H_{16}{}^{35}ClNO$: 273.0920, found: 273.0910. HR-MS calcd for $C_{16}H_{16}{}^{37}ClNO$: 275.0891, found: 275.0867.

3-(Benzylamino)-1-(naphthalen-2-yl)propan-1-one (1d). Prepared from *N*-methoxy-*N*-methyl-2-naphthamide [Yellow oil. IR (neat): 1643 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (s, 3H), 3.57 (s, 3H), 7.52-7.58 (m, 2H), 7.74-7.77 (m, 1H), 7.85-7.92 (m, 3H), 8.22 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 33.87, 61.06, 124.90, 126.31, 127.21, 127.45, 127.53, 128.51, 128.66, 131.25, 132.32, 134.05, 169.66. EI-MS *m/z*: 215 (M^+), 155 (bp). HR-MS calcd for $C_{13}H_{13}NO_2$: 215.0946, found: 215.0945.].[9] Hexane-EtOAc (2:1 to 0:1) was used as eluent for column chromatography. 55% yield. Yellow solid, mp 66-69 °C. IR (neat): 3303, 1672 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.91 (brs, 1H), 3.13 (t, *J* = 6.2 Hz, 2H), 3.38 (t, *J* = 6.2 Hz, 2H), 3.90 (s, 2H), 7.28-7.38 (m, 5H), 7.55-7.66 (m, 2H), 7.89-8.07 (m, 4H), 8.49 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 38.92, 44.28, 54.17, 123.57, 126.65, 126.81, 127.63, 127.99, 128.29, 128.33, 128.36, 129.44, 129.64, 132.31, 134.03, 135.44, 140.04, 199.35. EI-MS *m/z*: 289 (M^+), 155 (bp). HR-MS calcd for $C_{20}H_{19}NO$: 289.1467, found: 289.1462.

3-(Benzylamino)-1-(thiophen-2-yl)propan-1-one (1e). Prepared from *N*-methoxy-*N*-methylthiophene-2-carboxamide.[10] Hexane-EtOAc (2:1) was used as eluent for column chromatography. 55% yield. Yellow oil. IR (neat): 3315, 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (brs, 1H), 3.03 (t, *J* = 5.8 Hz, 2H), 3.15 (t, *J* = 5.8 Hz, 2H), 3.83 (s, 2H), 7.12 (m, 1H), 7.23-7.33 (m, 5H), 7.62-7.64 (m, 1H), 7.70-7.71 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ: 39.54, 44.30, 54.07, 126.84, 127.99, 128.02, 128.31, 131.90, 133.61, 139.96, 144.07, 192.29. EI-MS *m/z*: 245 (M^+), 111 (bp). HR-MS calcd for $C_{14}H_{15}NOS$: 245.0874, found: 245.0860.

1-(Benzylamino)-4,4-dimethylpentan-3-one (1f). Prepared from *N*-methoxy-*N*-methyl-2,2,2-trimethylacetamide.[11] Hexane-EtOAc (1:1) was used as eluent for column chromatography. 69% yield. Yellow oil. IR (neat): 2966, 1699 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (s, 9H), 1.77 (brs, 1H), 2.73 (t, *J* = 5.8 Hz, 2H), 2.84 (t, *J* = 5.8 Hz, 2H), 3.78 (s, 2H), 7.20-7.32 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ:26.37, 26.49, 36.84, 44.16, 54.21, 126.79, 127.97, 128.28, 140.10, 215.53. EI-MS *m/z*: 219 (M^+), 91 (bp).

1-(Benzylamino)-5-phenylpentan-3-one (1g). Prepared from *N*-methoxy-*N*-methyl-3-

phenylpropanamide.[12] Hexane-EtOAc (1:1) was used as eluent for column chromatography. 74% yield. Yellow oil. IR (neat): 3026, 1713 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.71 (s, 1H), 2.60 (t, *J* = 6.2 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 6.2 Hz, 2H), 2.88 (t, *J* = 7.2 Hz, 2H), 3.75 (s, 2H), 7.14-7.33 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ: 29.68, 43.11, 43.81, 44.49, 54.06, 125.99, 126.82, 127.95, 128.15, 128.27, 128.36, 140.00, 140.81. EI-MS *m/z*: 267 (M^+), 91 (bp). HR-MS calcd for $C_{18}H_{21}NO$: 267.1623, found: 267.1624.

General procedure of reaction between TMSC(Li)N_2 and *N*-benzyl-β-aminoketones (1). Under an argon atmosphere, a solution of **1** (1.0 mmol) in THF (3 mL) was added dropwise to a solution of TMSC(Li)N_2, prepared from $TMSCHN_2$ (2.17 M in hexane, 0.55 mL, 1.2 mmol) and *n*-BuLi (1.59 M in hexane, 0.75 mL, 1.2 mmol) in THF (10 mL), at -78 °C, and the mixture was stirred at -78 °C for 12 h. After being quenched with H_2O, the mixture was extracted with EtOAc. The organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the following products.

1-Benzyl-3-phenyl-3-(trimethylsilyloxy)pyrrolidine (2a) and *N*-benzyl-4-phenylbut-3-yn-1-amine (3a). Hexane-EtOAc (10:1 to 2:1) was used as eluent for column chromatography. **2a**: 56% yield. Yellow oil. IR (neat): 1250, 1109 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.15 (s, 9H), 2.33-2.41 (m, 2H), 2.76-2.84 (m, 1H), 2.95-3.09 (m, 3H), 3.71, 3.85 (ABq, *J* = 12.9 Hz, 2H), 7.26-7.57 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ: 2.14, 42.57, 53.70, 60.66, 69.23, 83.62, 125.34, 126.49, 126.80, 127.77, 128.09, 128.68, 139.01, 147.45. EI-MS *m/z*: 325 (M^+), 133 (bp). HR-MS calcd for $C_{20}H_{27}NOSi$: 325.1859, found: 325.1862. **3a**: 22% yield. Yellow oil. IR (neat): 3028, 2229 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (br, 1H), 2.65 (t, *J* = 6.6 Hz, 2H), 2.90 (t, *J* = 6.6 Hz, 2H), 3.87 (s, 2H), 7.27-7.43 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ: 20.63, 47.62, 53.39, 82.04, 87.86, 126.83, 127.57, 127.95, 128.05, 128.27, 128.39, 128.44, 131.45. EI-MS *m/z*: 235 (M^+), 91 (bp). HR-MS calcd for $C_{17}H_{17}N$: 235.1359, found: 235.1361.

1-Benzyl-3-(4-methoxyphenyl)-3-(trimethylsilyloxy)pyrrolidine (2b) and *N*-benzyl-4-(4-methoxyphenyl)but-3-yn-1-amine (3b). Hexane-EtOAc (5:1 to 2:1) was used as eluent for column chromatography. **2b**: 42% yield. Yellow oil. IR (neat): 1248, 1103 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (s, 9H), 2.19-2.26 (m, 2H), 2.65-2.73 (m, 1H), 2.83-2.96 (m, 3H), 3.67 (ABq, *J* = 12.4 Hz, 2H), 3.76 (s, 3H), 6.79-6.83 (m, 2H), 7.18-7.35 (m, 7H). ^{13}C-NMR ($CDCl_3$) δ: 2.11, 42.12, 53.26, 55.25, 60.77, 68.94, 83.29, 113.11, 126.61, 126.81, 128.09, 128.69, 130.92, 138.95, 158.17. EI-MS *m/z*: 355 (M^+), 263 (bp). HR-MS calcd for $C_{21}H_{29}O_2NSi$: 355.1968, found: 355.1959. **3b**: 43% yield. Yellow oil. IR (neat): 2928, 2046, 1246 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (br, 1H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 3.75 (s, 2H), 3.79 (s, 3H), 6.78-6.98 (m, 3H), 7.23-7.98 (m, 6H). ^{13}C-NMR ($CDCl_3$) δ: 20.68, 47.77, 53.46, 55.30, 81.54, 86.26, 113.78, 115.74, 126.86, 128.02, 128.33, 132.84, 140.13, 159.04. EI-MS *m/z*: 265 (M^+), 91 (bp). HR-MS calcd for $C_{18}H_{19}NO$: 265.1467, found: 265.1470.

1-Benzyl-3-(4-chlorophenyl)-3-(trimethylsilyloxy)pyrrolidine (2c) and *N*-benzyl-4-(4-chlorophenyl)but-3-yn-1-amine (3c). Hexane-EtOAc (20:1 to 2:1) was used as eluent for column chromatography. **2c**: 31% yield. Yellow oil. IR (neat): 1250, 1094 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 9H), 2.24 (t, *J* = 7.1 Hz, 2H), 2.72-2.75 (m, 1H), 2.84-2.90 (m, 3H), 3.61, 3.76 (ABq, *J* = 12.9 Hz, 2H), 7.24-7.42 (m, 9H). ^{13}C-NMR ($CDCl_3$) δ: 2.16, 42.68, 53.24, 60.50, 69.13, 83.14, 126.73, 126.89, 127.85, 128.14, 128.66, 132.15, 138.77, 146.43. EI-MS *m/z*: 361 (M^+), 359 (M^+), 133 (bp). HR-MS calcd for $C_{20}H_{26}{}^{35}ClNOSi$: 359.1472, found: 359.1466. HR-MS calcd for $C_{20}H_{26}{}^{37}ClNOSi$: 361.1443, found: 361.1434. **3c**: 7% yield. Yellow oil. IR (neat): 2924, 2228 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (brs, 1H), 2.63 (t, *J* = 6.6 Hz, 2H), 2.87 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 2H), 7.23-7.34 (m, 9H). ^{13}C-NMR ($CDCl_3$) δ: 20.61, 47.43, 53.35, 80.77, 88.91, 122.02, 126.99, 128.04, 128.37, 128.43, 132.73, 133.61, 139.78. EI-MS *m/z*: 271 (M^+), 269 (M^+), 91 (bp). HR-MS calcd for $C_{17}H_{16}{}^{35}ClN$: 269.0971, found: 269.0959.

1-Benzyl-3-(naphthalen-2-yl)-3-(trimethylsilyloxy)pyrrolidine (2d) and *N*-benzyl-4-(naphthalen-2-yl)but-3-yn-1-amine (3d). Hexane-EtOAc (15:1 to 1:1) was used as eluent for column chromatography. **2d**: 47% yield. Yellow oil. IR (neat): 1250, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 9H), 2.26-2.47 (m, 2H), 2.74-2.82 (m, 1H), 2.89-3.08 (m, 3H), 3.65, 3.81 (ABq, *J* = 13.0 Hz, 2H), 7.21-7.48 (m, 7H), 7.59-7.63 (m, 1H), 7.77-7.88 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 2.19, 42.51, 53.42, 60.63, 69.01, 83.67, 123.24, 124.52, 125.49, 125.80, 126.83, 127.32, 127.56, 128.05, 128.11, 128.67, 132.18, 132.78, 138.96, 144.80. EI-MS *m/z*: 375 (M^+), 91 (bp). HR-MS calcd for $C_{24}H_{29}ONSi$: 375.2019, found: 375.2018. **3d**: 33% yield. Yellow oil. IR (neat): 2945, 2230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (br, 1H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.90 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 2H), 7.21-7.46 (m, 8H), 7.72-7.91 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 20.64, 47.50, 53.31, 82.04, 88.21, 120.71, 126.18, 126.81, 127.39, 127.49, 127.66, 127.94, 128.25, 128.42, 131.01, 132.29, 132.74, 139.88. EI-MS *m/z*: 285 (M^+), 91 (bp). HR-MS calcd for $C_{21}H_{19}N$: 285.1518, found: 285.1521.

1-Benzyl-3-(thiophen-2-yl)-3-(trimethylsilyloxy)pyrrolidine (2e) and *N*-benzyl-4-(thiophen-2-yl)but-3-yn-1-amine (3e). Hexane-EtOAc (10:1 to 2:1) was used as eluent for column chromatography. **2e**: 36% yield. Yellow oil. IR (neat): 1250, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 9H), 2.30-2.37 (m, 2H), 2.68-2.73 (m, 1H), 2.71-3.03 (m, 3H), 3.63, 3.75 (ABq, *J* = 13.0 Hz, 2H), 6.91-6.93 (m, 2H), 7.14-7.33 (m, 6H). ^{13}C-NMR ($CDCl_3$) δ: 1.89, 43.02, 52.75, 60.43, 69.32, 81.68, 122.01, 123.63, 126.32, 126.83, 128.09, 128.64, 138.78, 153.03. EI-MS *m/z*: 331 (M^+), 133 (bp). HR-MS calcd for $C_{18}H_{25}NOSSi$: 331.1426, found: 331.1434. **3e**: 19% yield. Yellow oil. IR (neat): 3026, 2226 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (s, 1H), 2.65 (t, *J* = 6.6 Hz, 2H), 2.86 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 2H), 6.91-6.94 (m, 1H), 7.12-7.34 (m, 7H). ^{13}C-NMR ($CDCl_3$) δ: 20.81, 47.27, 53.29, 74.89, 91.90, 123.49, 126.07, 126.65, 126.88, 127.99, 128.30, 131.14, 139.75. EI-MS *m/z*: 241 (M^+), 91 (bp). HR-MS calcd for $C_{15}H_{15}NS$: 241.0925, found:

249.0916.

1-Benzyl-3-*tert*-butyl-3-(trimethylsilyloxy)pyrrolidine (2f) and 1-benzyl-4-*tert*-butyl-2,3-dihydro-1*H*-pyrrole (4f). Hexane-EtOAc (50:1 to 5:1) was used as eluent for column chromatography. **2f**: 60% yield. Yellow oil. IR (neat): 1248, 1036 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.11 (s, 9H), 0.89 (s, 9H), 1.65 (m, 1H), 2.08 (m, 2H), 2.43, 2.63 (ABq, *J* = 10.0 Hz, 2H), 2.82 (m, 1H), 3.34, 3.74 (ABq, *J* = 12.7 Hz, 2H), 7.26-7.32 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 2.26, 25.69, 35.25, 37.57, 53.57, 60.70, 62.67, 88.26, 126.72, 128.00, 128.80, 139.16. EI-MS *m/z*: 305 (M^+), 91 (bp). HR-MS calcd for $C_{18}H_{31}ONSi$: 305.2175, found: 305.2170. **4f**: 23% yield. Yellow oil. IR (neat): 1678 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.04 (s, 9H), 2.39 (td, *J* = 8.7, 1.5 Hz, 2H), 2.90 (t, *J* = 8.7 Hz, 2H), 3.77 (s, 2H), 5.61 (d, *J* = 1.5 Hz, 1H), 7.26-7.34 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 29.47, 29.77, 31.20, 54.43, 59.53, 126.90, 128.18, 128.44, 128.60, 132.27, 138.72. EI-MS *m/z*: 215 (M^+), 91 (bp). HR-MS calcd for $C_{15}H_{21}N$: 215.1674, found: 215.1684.

1-Benzyl-3-phenethyl-3-(trimethylsilyloxy)pyrrolidine (2g). Hexane-EtOAc (10:1) was used as eluent for column chromatography. 72% yield. Yellow oil. IR (neat): 1250, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.22 (s, 9H), 1.92-2.01 (m, 4H), 2.48-2.59 (m, 2H), 2.68-2.85 (m, 4H), 3.57, 3.74 (ABq, *J* = 12.9 Hz, 2H), 7.23-7.38 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ: 2.41, 30.94, 39.69, 44.61, 52.98, 60.52, 66.98, 82.60, 125.49, 126.76, 128.04, 128.20, 128.24, 128.65, 138.95, 142.73. EI-MS *m/z*: 353 (M^+), 91 (bp). HR-MS calcd for $C_{22}H_{31}NOSi$: 353.2175, found: 353.2168.

Alternative synthesis of 2a from 1-benzylpyrrolidin-3-one. Under an argon atmosphere, phenylmagnesium bromide (1.09 M THF solution, 1.0 mL, 1.1 mmol) was added dropwise to a solution of 1-benzylpyrrolidin-3-one (0.16 mL, 1.0 mmol) in THF (10 mL) at 0 °C and the mixture was stirred for 1.5 h, then stirred for 18 h at room temperature. The mixture was extracted with EtOAc. The organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using hexane-EtOAc (1:1) as eluent to give 1-benzyl-3-phenylpyrrolidin-3-ol (134 mg, 53 %) [Yellow oil. IR (neat): 3414 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18-2.26 (m, 1H), 2.32-2.43 (m, 1H), 2.51-2.66 (m, 2H), 2.97-3.00 (m, 1H), 3.12-3.20 (m, 1H), 3.74 (s, 2H), 7.21-7.36 (m, 8H), 7.48-7.51 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 41.86, 52.65, 59.89, 68.39, 80.65, 125.09, 126.90, 127.03, 128.06, 128.23, 128.66, 138.44, 143.92. EI-MS *m/z*: 253 (M^+), 91 (bp). HR-MS calcd for $C_{17}H_{19}NO$: 253.1467, found: 253.1464.]. Under an argon atmosphere, 2,6-lutidine (0.23 mL, 2.0 mmol) and TMSCl (0.10 mL, 0.75 mmol) were added to a solution of 1-benzyl-3-phenylpyrrolidin-3-ol (127 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) at 0 °C and the mixture was stirred for 7 h. After addition of brine, the mixture was extracted with EtOAc. The organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using hexane-EtOAc (10:1) to give **2a** (106 mg, 65%).

ACKNOWLEDGEMENTS

This work was financially supported by a Grant-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Science, and Special Coordination Funds for Promoting Science and Technology of the Ministry of Education, Culture, Sports, Science and Technology, Japan.

REFERENCES AND NOTES

1. T. Yagi, T. Aoyama, and T. Shioiri, *Synlett*, 1997, 1063.
2. K. Miwa, T. Aoyama, and T. Shioiri, *Synlett*, 1994, 107.
3. CAUTION: Two deaths were recently reported from use of $TMSCHN_2$ without proper ventilation. D. F. Taber, *Org. Chem. Highlights*, 2009, Jun 8, http://www.organic-chemistry.org.
4. A. Gomtsyan, R. J. Koenig, and C.-H. Lee, *J. Org. Chem.*, 2001, **66**, 3613.
5. Reactions using $TMSC(MgBr)N_2$. Y. Hari, S. Tsuchida, and T. Aoyama, *Tetrahedron Lett.*, 2006, **47**, 1977; Y. Hari, S. Tsuchida, R. Sone, and T. Aoyama, *Synthesis*, 2007, 3371; Y. Hari, K. Date, R. Kondo, and T. Aoyama, *Tetrahedron Lett.*, 2008, **49**, 4965; Y. Hari, R. Sone, and T. Aoyama, *Org. Biomol. Chem.*, 2009, **7**, 2804.
6. The inherent lability of **1c** might be due to bimolecular condensation which produces an enamine.
7. J. R. Martinelli, D. M. M. Freckmann, and S. L. Buchwald, *Org. Lett.*, 2006, **8**, 4843.
8. A. Leggio, A. Liguori, A. Napoli, C. Siciliano, and G. Sindona, *J. Org. Chem.*, 2001, **66**, 2246.
9. J. M. Kraus, C. L. M. J. Verlinde, M. Karimi, G. I. Lepesheva, M. H. Gelb, and F. S. Buckner, *J. Med. Chem.*, 2009, **52**, 1639.
10. J. M. White, A. R. Tunoori, B. J. Turunen, and G. I. Georg, *J. Org. Chem.*, 2004, **69**, 2573.
11. J. C. S. Woo, E. Fenster, and G. R. Dake, *J. Org. Chem.*, 2004, **69**, 8984.
12. J. A. Murphy, A. G. J. Commeureuc, T. N. Snaddon, T. M. McGuire, T. A. Khan, K. Hisler, M. L. Dewis, and R. Carling, *Org. Lett.*, 2005, **7**, 1427.