A New Two-Step Preparation of Pyrroles from β-Amino Ketones Utilizing Trimethylsilyldiazomethane

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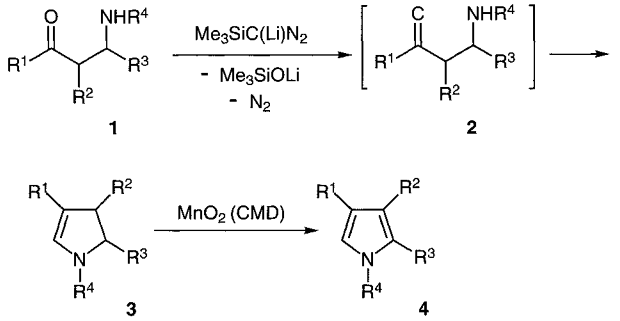
Abstract: Lithium trimethylsilyldiazomethane smoothly reacted with *N*-substituted β-amino ketones to give 2-pyrrolines which were easily converted to the corresponding pyrroles by treatment with MnO_2 (CMD, chemical manganese dioxide). The reaction with *N,N*-disubstituted β-amino ketones followed by oxidation with CMD also afforded pyrroles.

We have already revealed that the reaction of lithium trimethylsilyldiazomethane ($TMSC(Li)N_2$) with carbonyl compounds smoothly proceeds to generate alkylidene carbenes[1] which undergo various types of reactions to give the homologous alkynes,[1a] aldehydes,[1b] and heterocycles such as 1,2-dihydrofurans,[1c] cyclohepta[b]pyrrol-2-ones,[1d] and 3-pyrrolines[1e] depending upon substrates used. Our continued interest in the use of $TMSC(Li)N_2$ as an alkylidene carbene generator in organic synthesis led us to investigate the reaction of $TMSC(Li)N_2$ with β-amino ketones.

First, we investigated the reaction of $TMSC(Li)N_2$ with *N*-substituted β-amino ketones **1** and found that $TMSC(Li)N_2$ smoothly reacted with **1** in tetrahydrofuran to give the 2-pyrrolines **3**, the intramolecular N-H insertion product,[2] via the alkylidene carbene intermediates **2**, as shown in Scheme 1.



Scheme 1

The results are summarized in Table 1. Various *N*-substituted β-amino ketones **1** including acyclic and cyclic ones were smoothly converted to the corresponding 2-pyrrolines **3** in high to moderate yields. The carbamate **1i** also underwent the reaction to afford **3i**. Tetrahydrofuran seems to be the solvent of choice. The use of diethyl ether showed a remarkable decrease in the yield. Both n-butyllithium and lithium diisopropylamide could be used as a base. The 2-pyrrolines **3** thus obtained were easily converted to the pyrroles **4** by treatment with MnO_2 (CMD, chemical manganese dioxide),[3] as shown in Scheme 1 and Table 1.

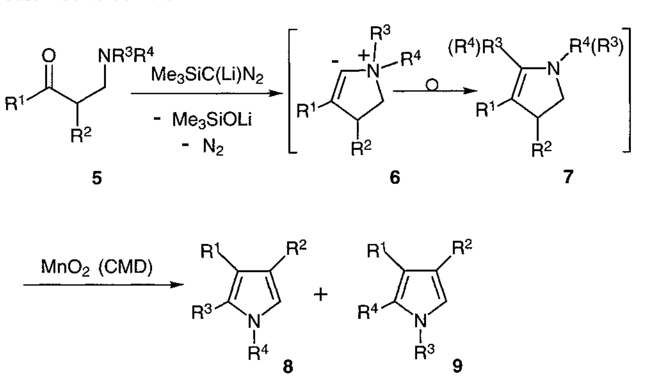
In a previous paper, we reported that $TMSC(Li)N_2$ smoothly reacted with β-trimethylsiloxyketones to give the 5-trimethylsilyl-2,3-dihydrofurans via the oxonium ylide intermediates.[1c] This results suggested that 2-pyrrolines **7** would be formed via ammonium ylide intermediates **6** if *N,N*-disubstituted β-amino ketones **5** were used as substrates, as shown in Scheme 2.

In fact, the reaction of $TMSC(Li)N_2$ with **5a** proceeded under similar reaction conditions as described for the preparation of **3**, but the products were an inseparable mixture. However, a mixture of the pyrrole **8a** (9%) and its regioisomer **9a** (6%) resulting from **7a** could be obtained when the reaction products were directly treated with CMD. As shown in Table 2, other β-amino ketones **5b~d** also afforded the corresponding pyrroles **8b~d** though in low yields. Interestingly, in the cases of reaction with **5b** and **5c**, the regioisomers (**9b** and **9c**) of **8** could not be detected.

Table 1.[a] Preparation of 2-Pyrrolines **3** and Pyrroles **4**

Compd. No.	R^1	R^2	R^3	R^4	Yield (%) **3**	Yield (%) **4**
a	Me	Me	H	$PhCH_2$	81	59
b	Et	Me	H	$PhCH_2$	83	68
c	*n*-Pr	Et	H	$PhCH_2$	79	55
d	*t*-Bu	H	H	$PhCH_2$	66	42
e	- $(CH_2)_4$-		H	$PhCH_2$	56	23
f	- $(CH_2)_5$-		H	$PhCH_2$	54	40
g	Et	H	Me	$PhCH_2$	66	71
h	Et	H	Me	Et	53	38
i	*n*-Pr	Et	H	COOEt	36	60

a) All products gave satisfactory spectral data and elemental analysis (or HR Mass spectra).



Scheme 2

In conclusion, the present method using commercially available $TMSCHN_2$ will provide a new and convenient two-step preparation of pyrroles from *N*-substituted β-amino ketones.

General procedure for the preparation of **3** : n-Butyllithium (1.69 M in hexane, 0.71 ml, 1.2 mmol) was added dropwise to a solution of $TMSCHN_2$[4] (1.65 M in hexane, 0.73 ml, 1.2 mmol) in THF (8 ml) at -78 °C under argon and the mixture was stirred for 30 min. A solution of **1** (1 mmol) in THF (2 ml) was then added dropwise. The mixture was stirred at -78 °C for 3 h, then heated under reflux for 3 h. After being quenched with water, the mixture was extracted with AcOEt. The

Table 2.[a] Formation of Pyrroles **8** and **9** from *N,N*-Disubstituted β-Amino Ketones **5**.

Compd. No.	R^1	R^2	R^3	R^4	Yield (%) **8**	**9**
a	Me	H	Me	$PhCH_2$	9^b	6^b
b	Et	Me	Me	$PhCH_2$	7	—[c]
c	- $(CH_2)_4$-		Me	$PhCH_2$	8	—[c]
d	Me	H	$PhCH_2$	$PhCH_2$	8	

a) All products gave satisfactory spectral data and elemental analysis (or HR Mass spectra). b) Determined by ^1H NMR. c) Not detected.

extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Fuji Davison BW-820 MH, hexane: AcOEt = 10:1) to give **3**.

Oxidation of **3** with CMD : A mixture of **3** (1 mmol) and CMD (10 mmol) in dichloromethane (10 ml) was heated under reflux for 12 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (Fuji Davison BW-820 MH, hexane: AcOEt = 40~100:1) to give **4**.

Reaction of $TMSC(Li)N_2$ with **5** : The reaction of $TMSC(Li)N_2$ (1.2 mmol) with **5** (1 mmol) was carried out under similar reaction conditions (at -78 °C for 2 h, then under reflux for 2 h) as described for the preparation of **3**. After the reaction, the solvent was evaporated and the residue was treated with CMD (10 mmol) in dichloromethane (10 ml), as described above, to give a mixture of **8** and **9**.

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References and Notes

1. a) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett*, **1994**, 107. b) *Idem*, *ibid.*, **1994**, 109. c) *Idem*, *ibid.*, **1994**, 461. d) Ogawa, H.; Aoyama, T.; Shioiri, T. *ibid.*, **1994**, 757. e) Ogawa, H.; Aoyama, T.; Shioiri, T. *Heterocycles*, **1996**, *42*, 75. f) For a review, see Shioiri, T.; Aoyama, T. *J. Synth. Org. Chem. Japan*, **1996**, *54*, 918.
2. We have already reported that the alkylidene carbenes generated from $TMSC(Li)N_2$ and aliphatic ketones inserted intermolecularlly to the N-H bond of a secondary amine to give enamines, see ref. 1b.
3. a) Ref. 1e and references cited therein. b) For a review, see Shioiri, T.; Aoyama, T.; Hamada, Y. *Wakojunyakujiho*, **1997**, *56*, 12.
4. Shioiri, T.; Aoyama, T.; Mori, S. *Org. Synth.*, Coll. Vol. 8, **1993**, 612.