A Novel Highly Stereoselective Synthesis of Pyrrolidines and their Derivatives through Thermal Cyclization Reaction of *N*-[bis(trimethylsilyl)methyl]-1-aza-1,3-dienes

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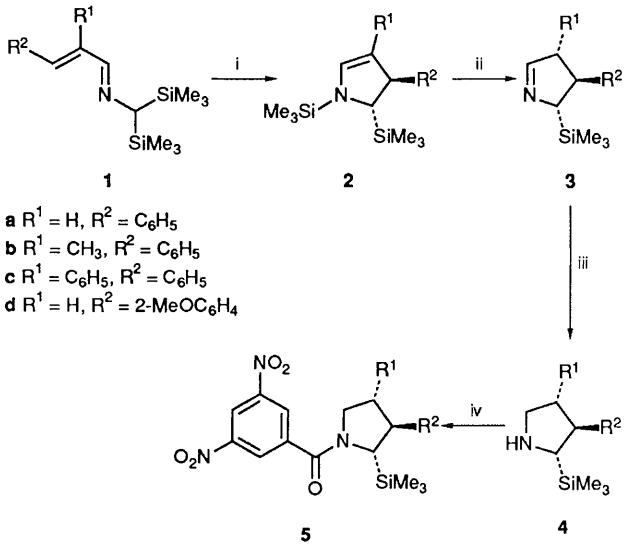
The first example of the thermal intramolecular cyclization of *N*-[bis(trimethylsilyl)methyl]-1-aza-1,3-dienes to give 5-trimethylsilyl-Δ^2-pyrrolines is reported; two straightforward and highly stereoselective routes to 3,4-disubstituted-5-trimethylsilyl-Δ^1-pyrrolines and 3,4-disubstituted-2-trimethylsilylpyrrolidines are also described.

Recently, we have described a highly stereoselective [2 + 2] cycloaddition reaction of ketenes or their equivalents to *N*-[bis(trimethylsilyl)methyl]-1-aza-1,3-dienes[1] and some heterocyclic applications of the resulting cycloadducts.[2] Herein we report a novel construction of the pyrrolidine ring system[3] through a highly stereoselective thermal cyclization of this new class of 1-aza-1,3-dienes,[4] easily available from α,β-unsaturated carbonyl compounds and C,C-bis(trimethylsilyl)methylamine.†

We found that *N*-[bis(trimethylsilyl)methyl]-1-aza-1,3-dienes **1**, under thermal conditions, cyclize by unusual C → N shift of trimethylsilyl group to the 5-trimethylsilyl-Δ^2-pyrrolines **2** in good to excellent yields (Scheme 1). To achieve this transformation, a minimum temperature (200–240 °C) was required, depending on the substitution pattern at the C-3 position in the starting 1-aza-1,3-diene **1**. Some representative examples are given in Table 1. The reaction always afforded exclusively the *trans*-*N*-trimethylsilyl enamines **2**, this high stereoselectivity being the principal feature of the reaction. Compounds **2a–d** when subjected to mild *N*-desilylation by use of methanol and trimethylchlorosilane as catalyst, afforded the corresponding 5-trimethylsilyl-Δ^1-pyrrolines **3**‡ in good to excellent yields. These new compounds showed remarkable thermal stability, especially when compared with their unsubstituted or unsilylated analogues.[5] The desilylative protonation step also proceeded with a high degree of stereoselectivity (Table 2), thus allowing the formation of a Δ^1-pyrroline skeleton bearing three contiguous chiral centres.



1 **2** **3**

a R^1 = H, R^2 = C_6H_5
b R^1 = CH_3, R^2 = C_6H_5
c R^1 = C_6H_5, R^2 = C_6H_5
d R^1 = H, R^2 = 2-$MeOC_6H_4$

5 **4**

Scheme 1 *Reagents and conditions*: i, 200–240 °C, neat; ii, MeOH, $ClSiMe_3$ cat., 0 °C, 60 min; iii, $LiAlH_4$, Et_2O, 20 °C, 1 h; iv, 3,5-$(NO_2)_2C_6H_3COCl$, CH_2Cl_2, NEt_3, room temp., 60 min

† *C,C*-bis(trimethylsilyl)methylamine was prepared in 76% overall yield by reaction of the bis(trimethylsilyl)chloromethane (Petrarch Systems) with sodium azide in hexamethyl phosphorus triamide (20 °C, 5 h) and reduction of the resulting bis(trimethylsilyl)methyl azide by means of lithium aluminium hydride (LAH) in diethyl ether (20 °C, 20 min).

‡ Characteristic imine peaks at δ_H 7.35–7.55, δ_C 161–166.

Table 1 Thermal cyclization of 1-aza-1,3-dienes **1**[a]

Product	T/°C	t/min	Yield (%)[b]	B.p./°C/Torr[c]	δ (=CH–N)	$J_{4,5}$/Hz
2a	200	60	70[d]	125–126/0.04	6.22	3.3
2b	240	70	74	120/0.03	5.71	3.1
2c	240	30	82	155/0.09	6.89	2.7
2d	200	30	77[d]	145–150/0.01	6.25	3.2

[a] All reactions were conducted on a 10 mmol scale, by heating under nitrogen the 1-aza-1,3-dienes in a Kügelrohr apparatus. Only *trans*-isomers at C-4–C-5, as established by ^{1}H NMR analysis of the crude reaction mixture. [b] Yields refer to pure isolated products. Purity determined by GLC. [c] Uncorrected boiling points, observed during distillation. [d] Product accompanied by 15–25% of *N*-desilylated imines **3a** and **3d**, respectively.

Table 2 Preparation of 5-trimethylsilyl-Δ^1-pyrrolines **3**[a] and 2-trimethylsilylpyrrolidines **4**[b]

			δ		J/Hz	
Compound	Yield (%)	B.p./°C/Torr	(C*H*=N)	(C*H*–SiMe$_3$)	(R_2C*H*–C*H*SiMe$_3$)	(R_1C*H*–C*H*R_2)
3a	93	85–87/0.2	7.55	3.71	4.2	4.1; 10.5
4a	84	110/0.005	—	2.42	10.2	—[e]
3b[d]	70	155/0.09	7.38	3.69	7.2	7.1
3c[c]	68	125/0.05	7.56	3.12	8.6	8.6
4c[c]	60	175/0.04	—	2.38	9.7	9.5
3d	86	155/0.02	7.54	3.68	4.5	4.5; 9.8
4d	82	155/0.005	—	2.41	10.1	—[e]

[a] Reactions were carried out at 0 °C (5 mmol scale) in a mixture of methanol (15 ml) and trimethylchlorosilane (0.05 ml), stirring for 1 h, and evaporating the solvent under reduced pressure (T < 15 °C). [b] Reduction of **3** (5 mmol) conducted in diethyl ether (12 ml) at 0 °C (1 h) by means of 1.2 equiv. of LAH. [c] Only *trans* stereochemistry observed around the R_2CH–CHSiMe$_3$ and R_1CH–CHR_2 bonds. [d] A mixture of *trans* and *cis* diastereoisomers at R_1CH–CHR_2 bond was obtained in a 85 : 15 ratio. [e] High complexity signal; not determined.

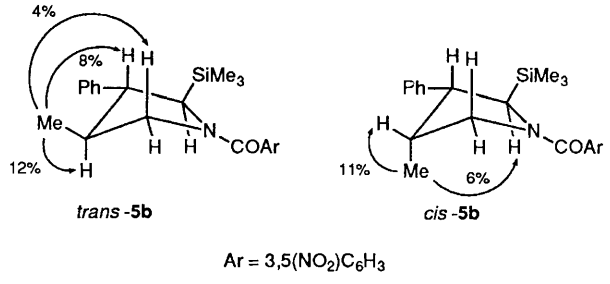


Fig. 1 Determination of the relative stereochemistry at C-2–C-3 and C-3–C-4 in compounds **5b** by NOE experiment. Only greater than 2% enhancements are indicated.

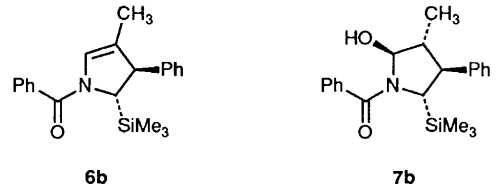


Fig. 2 Structures of **6b** and **7b**

For example, **2c**, upon treatment with methanol and a catalytic amount of trimethylchlorosilane, afforded the C-3–C-4 *trans* isomer **3c** as the sole reaction product. Under similar conditions, **2b** afforded its corresponding C-3–C-4 *trans*-pyrroline **3b** together with its epimer at C-3 in a ratio of 85 : 15, respectively. This ratio is sensitive to the methanolysis temperature, and when carried out at −78 °C, a 92 : 8 mixture of *trans*- and *cis*-isomers at C-3–C-4 was obtained. Reduction of **3** by use of LAH produced the corresponding 3,4-disubstituted 2-trimethylsilylpyrrolidines **4**, which were isolated as their 3,5-dinitritobenzamides **5**. The relative stereochemistry of pyrrolines **3** was established by use of the ^{1}H NMR spectra of their corresponding *N*-acyl-pyrrolidines **5**§ (Fig. 1). Presaturation of the methyl group in *trans*-**5b** (δ 0.89) under NOE conditions, resulted in an enhancement of the two axial protons at C-3 (δ 2.83) and C-5 (δ 3.28). Similar irradiation of the methyl group (δ 0.60) in the *cis*-**5b** isomer resulted only in the enhancement of the C-2 proton (δ 4.24).

Acylation of 5-trimethylsilyl-pyrroline **3b** with benzoyl chloride in the presence of diisopropylethylamine, at −78 °C in tetrahydrofuran (THF), leads to the enamide **6b** in 50% yield, which upon hydration of the double bond gave the corresponding hydroxy pyrrolidine (**7b**)¶ in 85% yield. The high degree of stereoselectivity in the hydration step is, once again, the principal feature of the reaction.

The above results demonstrate the potential offered by the present methodology in the chemistry of heterocyclic enamines.[6]

§ ^{1}H NMR ($CDCl_3$) *trans*-(**5b**): δ 9.12 (m, 1H, arom.), 8.75 (m, 2H, arom.), 7.2–7.4 (m, 5H, arom.), 4.11 (d, 1H, *J* 11.2 Hz, C*H*-SiMe$_3$), 3.72 (dd, 1H, *J* 10.8, 6.8 Hz, C_5H_{eq}), 3.28 (t, 1H, *J* 11.0, 10.8 Hz, C_5H_{ax}), 2.83 (t, 1H, *J* 11.2, 11.0 Hz, C*H*-Ph), 2.08 (m, 1H, *J* 11.0, 11.0, 6.8, 6.5 Hz, C*H*-CH$_3$), 0.89 (d, 3H, *J* 6.5 Hz, CH$_3$), 0.06 (s, 9H, SiMe$_3$). *cis*-(**5b**): 9.11 (m, 1H, arom.), 8.73 (m, 2H, arom.), 7.2–7.4 (m, 5H, ar), 4.14 (d, 1H, *J* 9.5 Hz, C*H*-SiMe$_3$), 3.69 (dd, 1H, *J* 10.2 Hz, *J* 5.9 Hz, C_5H_{ax}), 3.49 (dd, 1H, *J* 9.2, 5.9 Hz, C*H*-Ph), 3.18 (dd, 1H, *J* 10.2, 3.2 Hz, C_5H_{eq}), 2.49 (m, 1H, C*H*-CH$_3$), 0.60 (d, 3H, *J* 6.9 Hz, CH$_3$), 0.10 (s, 9H, SiMe$_3$).

¶ Representative data for **7b**: m.p.: 162–3 °C; ^{1}H NMR ($CDCl_3$), δ 7.75 (d, 2H, arom.), 7.2–7.5 (m, 8H, arom.), 5.16 (m, 1H, C*H*-OH), 4.04 (d, 1H, *J* 11.4 Hz, C*H*-SiMe$_3$), 3.13 (dd, 1H, *J* 11.4, *J'* 11.4 Hz, C*H*-Ph), 2.05 (m, 1H, C*H*-CH$_3$), 0.82 (d, 3H, *J* 6.6 Hz, CH$_3$), 0.05 (s, 9H, SiMe$_3$).

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References

1 J. Lasarte, C. Palomo, J. P. Picard, J. Dunogues and J. M. Aizpurua, *J. Chem. Soc., Chem. Commun.*, 1989, 72.

2 (*a*) C. Palomo, J. M. Aizpurua, J. M. García, I. Ganboa, F. P. Cossio, B. Lecea and C. Lopez, *J. Org. Chem.*, 1990, **55**, 2498; (*b*) C. Palomo, J. M. Aizpurua, J. M. García, J. P. Picard and J. Dunogues, *Tetrahedron Lett.*, 1990, **31**, 1921.

3 For some recent reviews, see: (*a*) R. J. Sundberg, *Comprehensive Heterocyclic Chemistry*, eds. C. W. Bird and G. W. H. Cheeseman, Pergamon: Oxford, vol. 4, 1984, p. 313; (*b*) Y. Nishimura, *Studies in Natural Products Chemistry*, ed. A.-ur Rahman, Elsevier: Amsterdam, vol. 1, 1988, p. 227; (*c*) W. H. Pearson, *Studies in Natural Products Chemistry*, ed. A.-ur Rahman, Elsevier: Amsterdam, vol. 1, 1988, p. 323; (*d*) R. Huisgen, *1,3-Dipolar Cycloaddition Introduction, Survey and Mechanism*, ed. A. Padwa, Wiley: New York, vol. 1, 1986, p. 1; (*e*) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon: Oxford, vol. 3, 1990, p. 269. For leading references, see: (*a*) A. G. H. Wee, *J. Chem. Soc.; Perkin Trans. 1*, 1989, 1363, (*b*) S. Kanemasa, O. Uchida and E. Wada, *J. Org. Chem.*, 1990, **55**, 4411.

4 For recent reviews on 1-aza-2,3-dienes, see: (*a*) D. L. Boger and S. N. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic, New York, 1987; (*b*) J. S. Sandhu and B. Sain, *Heterocycles*, 1987, **26**, 777.

5 G. A. Kraus and K. Neuenschwander, *J. Org. Chem.*, 1981, **46**, 4791.

6 O. Cervinka in *Enamines*, ed. A. G. Cook, Marcel Dekker, New York, 1988, p. 441.