Mono- and N^1,N^7-Dialkylation of 1,4,7,10-Tetraazacyclododecane *via* Silicon Protection

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The protection of 1,4,7,10-tetraazacyclododecane by a methylsilyl group leads selectively to *N*-mono- and N^1,N^7-symmetrically or dissymmetrically alkylated compounds.

Selective *N*-substitution of tetraazamacrocycles, particularly of cyclen (1,4,7,10-tetraazacyclododecane), remains an interesting challenge owing to their many applications in imaging and radioimmunotherapy.[1] In most derivatives, the macrocycle has four identical pendant arms and only a few reports of compounds carrying side chains of different natures on the nitrogen atoms have appeared.[2]

In previous papers, boron, phosphoryl and group 6 metal carbonyls have shown their ability to coordinate three nitrogen atoms of cyclic tetramines to give complexes in which the free nitrogen is available for a first substitution.[3] We report here some results obtained with a novel triprotection of cyclen by silicon which affords N^1,N^7-dissymmetrically disubstituted-1,4,7,10-tetraazacyclododecane in high yield.

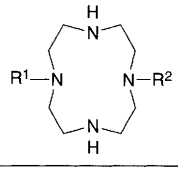
When methyltrichlorosilane (1 mmol) is allowed to react with 1,4,7,10-tetraazacyclododecane (1 mmol) in the presence of diisopropylethylamine in THF, a moisture-sensitive precipitate appears instantaneously. The study of the stoichiometry of the reaction has shown that only 2 mmol of base are required. After filtration and washing of the precipitate with THF, 2 mmol of base hydrochloride are isolated in the filtrate. The yield (>95%) and the nature of the precipitate are not modified when adding an excess of base. The ^{13}C NMR spectrum of the precipitate exhibits a signal at δ 2.10 for the methylsilyl group and only two sharp signals at δ 43.40 and 45.05 for the carbon atoms of the macrocycle. The ^1H NMR spectrum indicates a very symmetrical species: so, in addition to the sharp signal at δ 0.48 due to the methylsilyl group and two ammonium hydrogens at δ 6.84 (broad quintuplet, J = 5.5 Hz), four signals (multiplets, 4 H) are located at δ 2.65, 2.80, 3.08 and 3.26, each one corresponding to the four anisochronous hydrogens localized on the two different carbon atoms of the macrocycle. In addition, the ^{29}Si NMR chemical shift at δ −71.34 is consistent with a hypervalent silicon as reported for tetraazasilatranes.[4]

These results suggest the averaged structure **1** for the precipitate which can be described by two mesomeric forms (Scheme 1).

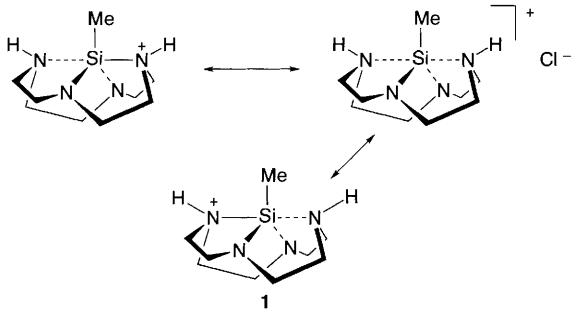
When a suspension of **1** in THF is treated with 1 or 2 equiv. of butyllithium, and then with an electrophile (methyliodide or benzylbromide), various amounts of mono-*N*-alkylation and N^1,N^7-dialkylation adducts are produced after hydrolysis. We observe that the mono-: di-alkylation proportion is essentially temperature and butyllithium addition rate dependent. Very versatile results are obtained when 3 equiv. of butyllithium are added to the suspension of **1** in THF at −30 °C. According to the amount of alkylating reagent (1 or 2 equiv.), mono- and N^1,N^7-dialkylated 1,4,7,10-tetraazacyclododecane derivatives, respectively, are isolated in good yields after hydrolysis (Table 1, entries 2, 3, 4, 5). The mass spectrum of adducts before hydrolysis indicates unambiguously a butyl group incorporation on the atom of silicon. Furthermore, the addition of 1 equiv. of benzylbromide followed 1 h later by the addition of another equivalent of methyliodide leads selectively to the N^1,N^7-dissymmetrically dialkylated cyclen (Table 1, entry 6); the reverse addition of the reagents yields to the same product. These results lead us to propose the following mechanism (Scheme 2).

After addition of 3 equiv. of butyllithium, a dianionic species is obtained. One butyllithium reacts with the silicon atom and cleaves an Si–N bond, while the others deprotonate the nitrogen atoms. According to the experiment with 2 equiv. of butyllithium we can assume that silylalkylation is as fast as complete deprotonation. This dianionic species possesses two nitrogen atoms having different reactivities. Two processes may account for this behaviour: (a) one of these nitrogen atom might interact with a *d* orbital of the silicon atom and becomes thus less reactive; (b) the presence of a butyl group on the silicon atom generates a steric hindrance on one side of the dianion leading

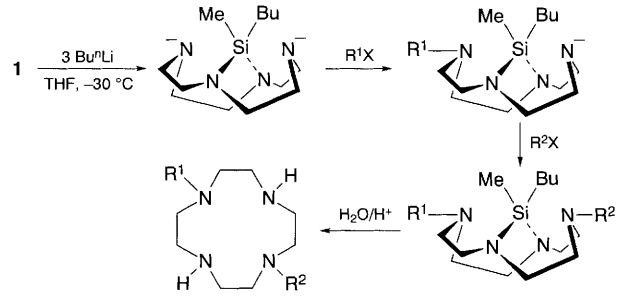
Table 1 Mono- and N^1,N^7-disubstitution of 1,4,7,10-tetraazacyclododecane†

Alkylating agent	Stoichiometry	End product	Yield (%)	Entry
				
MeI	1	R^1 = H R^2 = Me	60	**2**
MeI	2	R^1 = R^2 = Me[a]	85	**3**
$PhCH_2Br$	1	R^1 = H R^2 = CH_2Ph	80	**4**
$PhCH_2Br$	2	R^1 = R^2 = CH_2Ph[a]	70	**5**
$PhCH_2Br$	1			
MeI[b]	1	R^1 = CH_2Ph, R^2 = Me	80	**6**

[a] Previously reported.[3a,5] [b] Added 1 h later.



Scheme 1



Scheme 2

to different reactivities. So, when methyllithium is used in place of butyllithium, under the conditions of the mono *N*-alkylation, a mixture of mono- and di-alkylated adducts is obtained in the ratio 2:1. The dissymmetry introduced by the addition of a butyl group on the atom of silicon seems therefore to be the most important feature governing the selectivity of the reaction.

In conclusion, compared to other triprotected derivatives, silicon-complexed 1,4,7,10-tetraazacyclododecane is of particular interest in *N*-alkylation reactions. Easily prepared, the intermediate exhibits an unexpected and singular behaviour since the protecting group is involved in the reaction. Under experimental conditions, the selective cleavage of an Si–N bond allows the one-pot synthesis of N^1,N^7-dissymmetrically dialkylated cyclen, which provides a convenient entry to tetrasubstituted tetraazacyclododecane derivatives having three different pendant arms.

The extension to other macrocycles and electrophile agents is in progress.

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Footnote

† All compounds were characterized by ^1H and ^{13}C NMR.

Selected spectroscopic data for **2**: ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 53.78, 46.79, 46.26, 44.80 ($CH_{2\alpha}$–N) and 43.35 (CH_3). For **3**: ^{13}C NMR δ 53.95, 44.86 ($CH_{2\alpha}$–N), 43.92 (CH_3–N). For **4**: ^{13}C NMR δ 138.47, 128.57, 127.91, 126.66 (C_6H_5), 58.99, 50.79, 46.87, 45.79 and 44.84 ($CH_{2\alpha}$–N). For **5**: ^{13}C NMR δ 138.93, 128.77, 128.14, 126.98 (C_6H_5), 59.80, 51.55 and 45.09 ($CH_{2\alpha}$–N). For **6**: ^{13}C NMR δ 138.54, 128.69, 127.91, 126.72 (C_6H_5), 59.45, 54.07, 51.60, 44.93, 44.85 ($CH_{2\alpha}$–N) and 43.70 (CH_3).

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