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Towards the Synthesis of 3-Silapiperidines

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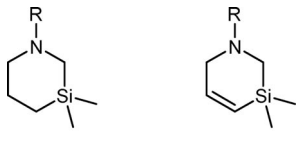
Dedicated to Professor Alain Krief

Keywords: Nucleophilic substitution / Silacycles / Diastereoselectivity / Isomerization / Dianions

A straightforward and unprecedented method towards the synthesis of 3-silapiperidines is described. The key step involves a formal double nucleophilic substitution reaction between the (bromomethyl)dimethylsilyl chloride and a *N*,*C*-sp^2-1,4-dianionic species generated from *N*-monoprotected allylamines. Subsequent functionalizations are also presented.

Introduction

Over the last two decades silacycles have received a particular attention.[1] Their preparation has often provided the occasion to study the reactivity and to prove the existence, even transient, of highly reactive and hardly characterizable species such as silenes ($R_2Si{=}CH_2$, alkene sila analogues) or silylenes (R_2Si, carbene sila analogues). Further motivation was the desire to obtain sila derivatives possessing interesting and possibly original chemical,[2] physical[3] or biological[4] properties, relative to their carbon analogues.[5] This synthetic effort provided a large variety of silacycles, but, quite surprisingly, only a limited number of 3-silapiperidines **I** and **II** (Scheme 1) have been reported in the literature over the last half-century.[6] Herein, we report a new first synthesis of a 3-silapiperidine of type **II** and its subsequent functionalization.



I II

Scheme 1.

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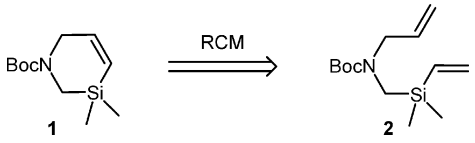
Results and Discussion

We first investigated the formation of 3-silapiperidine **1** from allyl–vinylsilane **2** using a ring closing metathesis (RCM) reaction as the key step (Scheme 2).



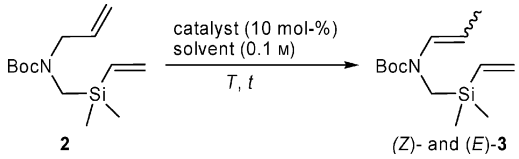
1 2

Scheme 2.

Allyl–vinylsilane **2** unfortunately did not undergo the expected RCM to any extent under any attempted conditions of catalyst, solvent or temperature. In the best case, the only generated products were diastereomeric enamines (*Z*)-**3** and (*E*)-**3**, along with unreacted precursor **2** (Table 1). The reported relative percentages calculated from the crude ^1H NMR spectra (Entries 1,2 and 4–6) correspond to the conversion of precursor **2** into enamines (*Z*)-**3** and (*E*)-**3** as well as to its unreacted form. Gratifyingly, both enamines could be isolated separately (Entry 3), and their respective configurations undoubtedly determined.

The generated enamines (*Z*)-**3** and (*E*)-**3** resulted from the isomerization of the allyl moiety of precursor **2**, its vinylsilane part remaining apparently untouched during the process. Interestingly, this isomerization process proved to be diastereoselective towards enamine (*Z*)-**3**, as shown by the characteristic double bond coupling constant (J_{cis} = 8.3 Hz) obtained for this major diastereomer [a J_{trans} coupling constant of 20.2 Hz was measured for the minor diastereomer (*E*)-**3**]. In all these reactions, it is believed that a ruthenium hydride species, generated from the catalyst and compound **2**, triggers the isomerization process with high

Table 1. Attempted RCM reactions.



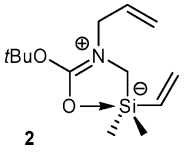
Entry	Catalyst	Solvent	*T*, *t* [h]	Relative% (*Z*)-**3** / (*E*)-**3** / **2**
1	Grubbs I	CH_2Cl_2	r.t., 22	18 / – / 82
2	Grubbs I	PhH	r.t., 24	3 / – / 97
3	Grubbs I	PhH	reflux, 1	75 / 10 / –[a]
4	Grubbs I	PhH	reflux, 18	25 / 75 / –
5	Grubbs II	CH_2Cl_2	reflux, 18	5 / 25 / 70
6	Schrock	PhH	r.t., 24	<1 / – / >99

[a] Isolated yields.

Z diastereoselectivity.[7–9] On the other hand, refluxing conditions and prolonged reactions times would promote the formation of the *E* isomer (Entries 3 and 4).

In order to explain the observed reactivity and to rationalize why the expected RCM did not or could not occur, we first hypothesized that the (dimethyl)vinylsilane moiety was too sterically demanding for the RCM to take place. Unfortunately, although (methyl)vinylsilanes have indeed been reported on several occasions to remain inert towards first generation Grubbs' catalyst,[10] they have also been shown to efficiently react through RCM with both second generation Grubbs'[10c] and Schrock's[10a,10b] catalysts under mild conditions.

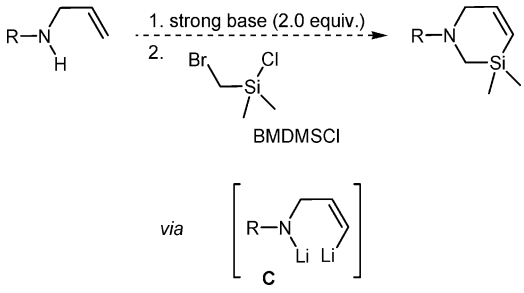
We then hypothesized that the inability of allyl–vinylsilane **2** to undergo RCM simply reflects the physical impossibility for the metathesis partners to interact, and we proposed the existence of intramolecular coordination phenomena occurring within precursor **2** (Scheme 3). These would be responsible for the formation of rigid conformations, in which both metathesis partners are too far apart to react together. As a consequence, the isomerization of the pendant allyl moiety would then become the beneficiary process.



Scheme 3.

The proposed intramolecular coordination phenomena involves the silicon and the carbonyl oxygen atoms (Scheme 3). This type of interaction has already been established by X-ray analyses.[11] This spatial disposition is indeed favoured since it simultaneously involves a five-membered chelate, a strong oxygen–silicon interaction[12] and a pentavalent silicon atom – a situation that is particularly favourable.[13]

At this point, we then decided to turn our attention to an alternative strategy. The latter was inspired by the dianionic chemistry[14] recently developed on *N*-monoprotected allylamines and by the reported reactivity of (bromomethyl)dimethylsilyl chloride (BMDMSCl) as a 1,2-dielectrophile (Scheme 4).[15]



Scheme 4.

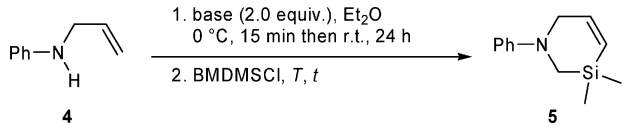
Indeed, under the action of 2 equiv. of a strong base,[16] *N*-monoprotected allylamines (*N*-alkyl, -silyl or -phenyl) have been shown to form dianionic species of type **C**.[17] While the first deprotonation occurs at the nitrogen (most acidic) site, the second one occurs regioselectively at the terminal position of the double bond.

More importantly, this second deprotonation has been shown by X-ray analysis[17] to be completely stereoselective since only the *Z*-terminal proton is abstracted.[16a,16d,17,18] Additionally, these dianionic species have proven to efficiently react with electrophiles to form a large variety of heterocycles.[16,18,19] BMDMSCl, on the other hand, has been shown to be an excellent 1,2-dielectrophilic partner for the formation of sila heterocycles, although reports in the literature remain sporadic[20,5a,5b] We therefore anticipated that combination of both the dianionic chemistry of *N*-monoprotected allylamines and the 1,2-dielectrophilic property of BMDMSCl would constitute a powerful synthetic tool for the preparation of 3-silapiperidines.

We initially tested our strategy on *N*-phenylallylamine (**4**). Gratifyingly, upon treatment with 2.0 equiv. of *n*BuLi at room temperature for 24 h[16] and after trapping of the generated dianion[21] with BMDMSCl at –78 °C, we were effectively able to isolate the targeted 3-silapiperidine **5** with an encouraging yield of 30% (Table 2, Entry 1). We also recovered 30% of the starting amine **4**. Interestingly, when BMDMSCl was added at 0 °C, the yield increased to 52%, and the recovery of the starting material was only 18% (Entry 2). Finally, addition of BMDSMCl at room temperature, with *t*Buli as a base, allowed us to even further improve the yield to 70% (Entry 3).[22] Unfortunately, no other tested *N*-monoprotected allylamine was as successful; either lower yields (*N*-*p*-methoxyphenyl) or side-products [*N*-TBDMS, *N*-(*S*)-α-methylbenzyl or *N*-tosyl] were obtained or they did not react (*N*-Me or *N*-trityl).

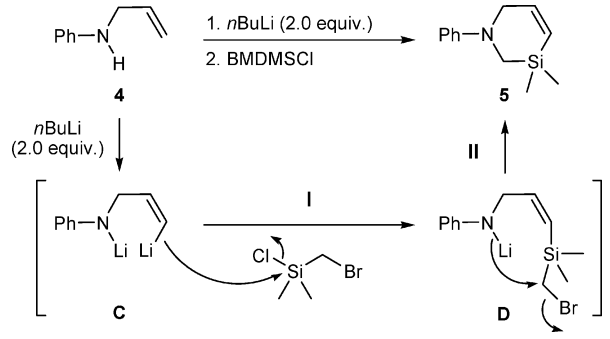
The proposed mechanism relies on a formal double nucleophilic substitution reaction (Scheme 5). In a first step (**I**), the vinylic anion, the most nucleophilic part of dianion **C**, reacts with the most electrophilic BMDMSCl site (the silicon atom[5]) to give intermediary **D**. Final intramolecular nucleophilic substitution (**II**) ultimately gives rise to **5**.

Table 2. Formation of 3-silapiperidine **5**.



4 **5**

Entry	Base	*T* [°C], *t* [h]	Yield in **5** [%]	Recovery of **4** [%]
1	*n*BuLi	–78 then r.t., 12	30	30
2	*n*BuLi	0 then r.t., 2	52	18
3	*t*BuLi	r.t., 0.5	70	–



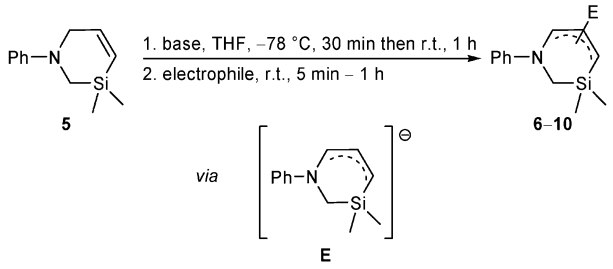
Scheme 5.

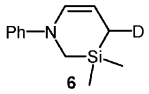
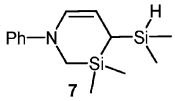
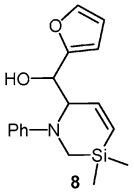
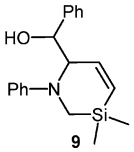
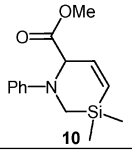
Finally, we turned our attention to the functionalization of 3-silapiperidine **5**. Besides preparing derivatives, we incidentally wanted to develop access to sila analogues of biological interest. Our strategy consisted of treating **5** with 1 equiv. of base and then intercepting the resulting expected delocalized anion **E**[23,24] with an electrophilic species (Table 3).

Upon treatment with 1 equiv. of *t*BuLi followed by hydrolysis with D_2O, 3-silapiperidine **5** regioselectively led to its 4-deuterated enamine derivative **6** (Entry 1). The same regioselectivity is observed for compound **7** when **5** is successively treated with *t*BuLi followed by chlorodimethylsilane (Entry 2). Furfuraldehyde and benzaldehyde also efficiently undergo reaction to provide β-aminoalcohols **8** and **9** in 60 and 75% yields and as 7:3 and 6:4 mixtures of diastereomers, respectively (Entries 3 and 4). In these cases, proximal regioselectivity (α to the nitrogen atom) was observed. Unfortunately, methyl chloroformate only afforded α-aminoester **10** in a low yield of 16% (Entry 5). Nevertheless, this compound constitutes an interesting candidate for the preparation of sila analogues of pipecolic acid, a molecule of biological interest.[26]

At this stage it is difficult to rationalize the observed regioselectivities, as well as to correlate them with the few closely reported studies. Indeed, studies on α-silyl anions suggest that the regioselectivity is dependent on the size of the silyl substituents, the size of the electrophile or its nature.[27] Moreover, the alkylation of 3-silyl enamines gives only α-silyl alkylated products.[28]

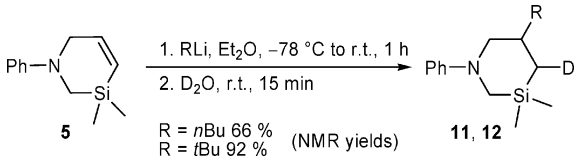
Table 3. Deprotonation/alkylation of **5**.



Entry	Base	Electrophile	Product	Yield [%]
1	*t*BuLi	D_2O	 **6**	88[a,b]
2	*t*BuLi	Me_2SiHCl	 **7**	79[b]
3	*t*BuLi		 **8**	60 *dr* 7:3[c]
4	*n*BuLi	PhCHO	 **9**	75 *dr* 6:4[c]
5	*n*BuLi	$ClCO_2Me$	 **10**	16[d]

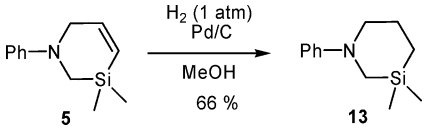
[a] Deuterium regioselective incorporation determined by NMR spectroscopy. [b] NMR yield. [c] Undetermined stereochemistries. [d] The reverse addition of anion **E** to $ClCO_2Me$ was necessary.[25]

Interestingly, when THF is replaced by ethyl ether for the anion formation step, *t*BuLi or *n*BuLi do not act as bases but as nucleophiles and give rise to alkylated products **11** and **12** (Scheme 6).



Scheme 6.

Finally, the saturated 3-silapiperidine **13** was generated upon hydrogenation of 3-silapiperidine **5** with palladium on charcoal (Scheme 7).



Scheme 7.

Conclusions

In conclusion, we have reported an interesting and straightforward method towards the synthesis of unprecedented 3-silapiperidines. Our strategy relies on a formal double nucleophilic substitution reaction involving a *N*,*C*-sp^2-1,4-dianionic species generated from *N*-monoprotected allylamines and takes advantage of the remarkable but yet underexploited 1,2-dielectrophilic properties of (bromomethyl)dimethylsilyl chloride. Subsequent functionalizations proved to be successful and, while providing a variety of new sila derivatives, also opens new and promising opportunities towards the synthesis of sila analogues of biological interest.

Acknowledgments

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[22] ***N*-Phenyl-3,3-dimethyl-1-aza-3-silacyclohex-4-ene (5):** To a stirred solution of *N*-phenylallylamine (**4**, 2.9 mL, 20 mmol, 1.0 equiv.) in freshly distilled Et_2O (50 mL) was added dropwise freshly titrated *t*BuLi (1.48 M, 27 mL, 40 mmol, 2.0 equiv.) at –78 °C. After the addition, the reaction mixture was slowly warmed to 0 °C, after which BMDMSCl (3.4 mL, 24 mmol, 1.2 equiv.) was added dropwise, and the reaction mixture was stirred for 1 h at room temperature. The resulting solution was then submitted to an Et_2O/H_2O extraction. The combined organic layers were washed with NaCl, dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification was achieved by flash column chromatography on silica gel (PE/Et_2O gradient). A pale yellow oil was obtained. Yield: 2.89 g (70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26 (m, 2 H, *m*-Ph), 6.97 (m, 2 H, *o*-Ph), 6.82 (m, 1 H, *p*-Ph), 6.74 (m, 1 H, CH_2–C*H*=CH–Si), 5.91 (m, 1 H, CH_2–CH=C*H*–Si), 3.80 (br. s, 2 H, C*H*$_2$–CH=CH–Si), 2.80 (s, 2 H, N–C*H*$_2$–Si), 0.17 (s, 6 H, Si*Me*$_2$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.7, 145.9, 129.1, 125.6, 118.9, 116.6, 53.3, 40.4, –2.4 ppm. IR (neat): $\tilde{\nu}$ = 3080, 3060, 3022, 1596, 1245, 1208, 845 cm^{-1}. MS (CI NH_3): *m*/*z* = 204 [MH^+]. $C_{12}H_{17}NSi$: C 70.88, H 8.43, N 6.89; found: C 70.82, H 8.53, N, 6.95.

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