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Intramolecular Sila-Matteson Rearrangement: A General Access to Silylated Heterocycles

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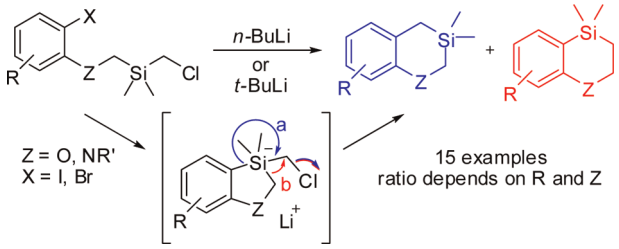
ABSTRACT



A series of new silylated heterocycles has been efficiently prepared using an intramolecular silicon version of the Matteson rearrangement, providing two isomers of binuclear heterocycles. This method applies to a large variety of substrates, a direct relationship between the Hammett constants of the aromatic substituents and the isomer ratio being observed. Complementary experiments suggest that a common penta-organosilicate species is involved.

Replacing a carbon atom with a silicon can be regarded as a way to develop innovative new drugs.[1] Despite the large similarities between these elements, significant advantages can be returned.[2] Thus, the effect of a C/Si swap on the physiological and biological properties of known drug skeletons has been widely investigated in the past two decades,[3] and several bioactive silacycles have been synthesized. For example, sila-haloperidol **1**, a dopamine receptor antagonist, displays higher subtype selectivity and a different metabolism pattern compared to its carbon analogue.[4] The tetrahydrosilaisoquinoline **2**[5] showed psychotropic activity, while the disila-bexarotene **3**[6] was studied for its retinoid agonist potency (Figure 1). If several compounds contain a heteroatom−silicon bond, heterocyclic molecules bearing a tetraorganosilicon moiety incorporated in a cycle are much less described.[7]

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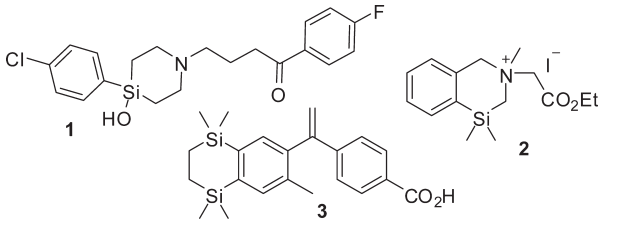
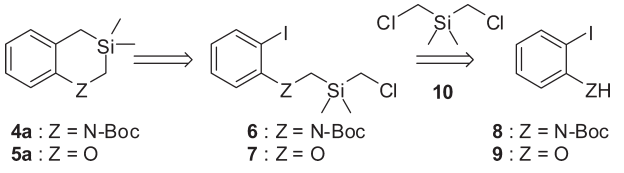


Figure 1. Examples of bioactive silacycles.

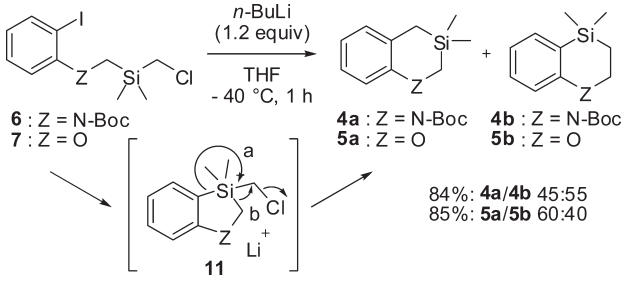
Increasing interest in silylated derivatives and a lack of general synthetic procedures prompted us to focus on the preparation of the hydrosilaquinoline **4a** (Z = *N*-Boc) and silachroman **5a** (Z = O) moieties, obtained previously in moderate yields and under drastic conditions.[8] Our initial retrosynthetic route is outlined in Scheme 1: the expected products **4a** and **5a** could be formed by an intramolecular cyclization of the precursors **6** and **7**, respectively. These substrates would in turn be prepared from aniline and phenol derivatives **8** and **9** in the presence of bis-(chloromethyl)dimethylsilane **10**.

Scheme 1. Initial Synthetic Route for the Preparation of Hydrosilaquinoline **4a** and Silachroman **5a**



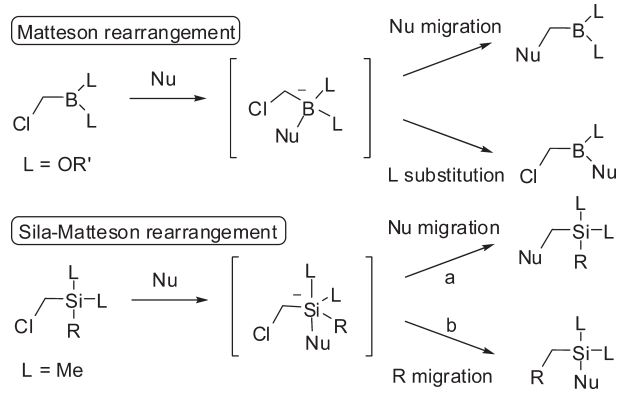
The precursors **6** and **7** were prepared in good yields from **8** and **9** (72% and 82% yields, respectively). Then, the halogen−lithium exchange and subsequent nucleophilic substitution were performed at −40 °C using *n*-butyllithium in tetrahydrofuran. Surprisingly, the intramolecular cyclization furnished not only the desired products **4a** and **5a** but also their regioisomers **4b** and **5b**.[8a,9] In both series, the cyclization proceeds in good yield (about 85%) and low selectivity (**4a**/**4b** = 45:55 and **5a**/**5b** = 60:40, Scheme 2).

Scheme 2. First Cyclization Attempts and Proposed Pentavalent Silicate Species



We hypothesized that a common pentaorganosilicate species **11** could explain this result. The latter would evolve by either migration of the aromatic ring (path a, Scheme 2) or the CH_2−Si bond (path b). Such a mechanism parallels the reactivity of the α-halosilanes with that of the α-haloboronic esters, classically employed in the Matteson rearrangement (Scheme 3).[10]

Scheme 3. Matteson and Sila-Matteson Rearrangements



This reactivity has been previously proposed for silicon in the case of the nucleophilic addition of halide or alkoxide[11] and was briefly evoked for a carbon nucleophile.[12]

Next, various experimental conditions were screened.[13] In tetrahydrofuran, none of the following parameters seemed to exert a significant influence on the ratio of the

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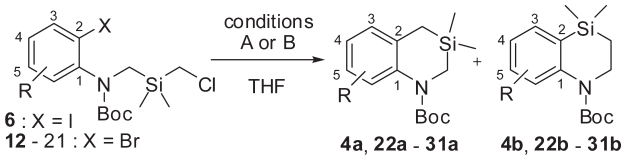
(13) Comparative results are detailled in the Supporting Information.

isomers: (i) temperature; (ii) structure of the organometallic (*n*-BuLi, *t*-BuLi, MeLi, *i*-PrMgCl); (iii) halogen on the aromatic ring (iodine or bromine); (iv) leaving group on the silicon side chain (chlorine, iodine, mesylate, or tosylate). These observations suggested that the isomer ratio is mainly governed by the intrinsic reactivity of the pentaorganosilicate species **11** and, more precisely, by the respective stabilities of the Ar−Si and CH_2−Si bonds.[14]

Table 1. Aromatic Substituents Effect



entry	R	starting material	cond.[a]	prod. (**a**/**b**)[b]	yields [%][c]
1	H	**6**	A	**4a/4b** 45:55	84
2	5-CF_3	**12**	A	**22a/22b** 86:14	52
3	–	–	B	**22a/22b** 90:10	72
4	5-Cl	**13**	A	**23a/23b** 83:17	74
5	–	–	B	**23a/23b** 83:17	81
6	5-F	**14**	A	**24a/24b** 57:43	74
7	4-CF_3	**15**	B	**25a/25b** 89:11	76
8	4-F	**16**	A	**26a/26b** 78:22	47
9	–	–	B	**26a/26b** 82:18	82
10	4-MeO	**17**	B	**27a/27b** 61:39	79
11	5-MeO	**18**	B	**28a/28b** 25:75	73
12	5-Me_2N	**19**	B	**29a/29b** 10:90	92
13	4-CH_3	**20**	B	**30a/30b** 43:57	89
14	5-CH_3	**21**	B	**31a/31b** 37:63	93

[a] Condition A: *n*-BuLi (1.2 equiv), −40 °C. Condition B: *t*-BuLi (2.4 equiv), −78 °C. [b] Ratio **a**/**b** determined from the crude ^{1}H NMR spectra. [c] Isolated yields.

To evaluate the influence of the aromatic substituents on the ratio of the two isomers, the intramolecular cyclization was applied to substrates incorporating electron-rich or -deficient aromatics (Table 1).

For all substituents, the silylated heterocycles were obtained in good chemoselectivities and yields, as long as *n*-BuLi (Condition A) was replaced by *t*-BuLi (Condition B).[15]

We first noted that the electron-withdrawing effect of the trifluoromethyl or of the halogen substituents favors the heterolytic cleavage of the Ar−Si bond in the pentaorganosilicate species, increasing the amount of the **a**-isomer (entries 2−9). The delicate balance between inductive and mesomer effects probably explains that similar ratios were obtained with the 5-CF_3 (**12**) and 5-Cl (**13**) substituents (entries 2 to 4), as well as 4-CF_3 (**15**) and 4-F (**16**) (entries 7 to 9). Similarly, the 5-F (**14**) affords modest selectivity because of the contradictory resonance donor and inductive attractor effects it generates (entry 6).[16a]

In contrast, the pure electron-donating character of substituents in the *para* position activates the aromatic ring and disfavors the Ar−Si bond heterolytic cleavage, leading to **b**-isomers predominantly (entries 11, 12, and 14). The low donating effect of a methyl substituent in the *meta* position leads to a negligible influence on the isomer ratio. Finally, and as pointed out by Schlosser et al.,[16b] the competition between the attractor inductive and donor resonance effects associated to the *meta* methoxy group could explain that the **a**-isomer is favored in this case (entry 10). Such results suggest that the limiting step is the C−Si bond heterolytic cleavage rather than the displacement of the leaving group by the nucleophile. A similar observation was published before by Allen et al.[11g]

It was tempting at this stage to correlate these results to the σ Hammett constants.[17] Gratifyingly, the plot of the log(ratio **b**/**a**) against σ led to a satisfying linearity (correlation coefficient = 0.940) on a relatively large scale of σ values (−0.83 to +0.54) and for substituents in the *meta* as well as the *para* position (Figure 2).

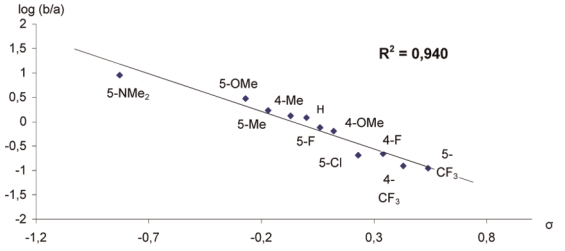


Figure 2. Plot of log(**b**/**a**) against Hammett σ constants.

Next, a study on the influence of the protecting group borne by the nitrogen atom was undertaken (Table 2). If both carbamates **6** and **32** led to disappointing selectivities (entries 1−2), the mesyl and tosyl protected iodoanilines **33**

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(15) Most of the time, *n*-BuLi (−40 °C, 1.2 equiv) was replaced by *t*-BuLi (−78 °C, 2.4 equiv) to avoid the Wurtz−Fittig type addition of the aryllithium on the cogenerated butyl halide: (a) Bailey, W. F.; Longstaff, S. C. *Chimica Oggi (Chemistry Today)* **2001**, *19*, 28–32. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, U.K., 2002; pp 111−142.

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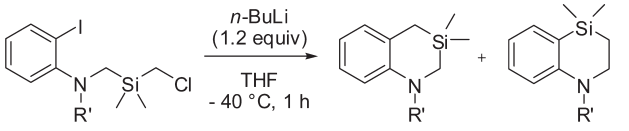
and **34** afforded almost exclusively the **b**-isomer (entries 3–4). This striking effect can be understood in light of the recent results by Chataigner et al. suggesting that the efficient π-delocalization of the nitrogen lone pair occurring toward the carbonyl group of the carbamate fully deactivates the donor character of the nitrogen and therefore the aromatic ring.[18] Note that, in the case of the mesyl protected substrate **34** (entry 4), a competitive deprotonation and subsequent intramolecular nucleophilic substitution of the chlorine afford a cyclic sila-sulfonamide,[19] decreasing the yield in **37**. Thus, the nitrogen substituent can also be used as a lever to control the selectivity.

Table 2. Electron-Withdrawing Protecting Group Effect



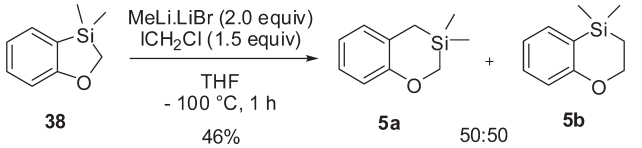
6, **32** - **34** **4a**, **35a** - **37a** **4b**, **35b** - **37b**

entry	R′	starting material	prod (**a**/**b**)[a]	yields [%][b]
1	Boc	**6**	**4a/4b** 45:55	84
2	Alloc	**32**	**35a/35b** 48:52	70
3	Ts	**33**	**36a/36b** 0:100	63
4	Ms	**34**	**37a/37b** 26:74	28

[a] Ratio **a**/**b** determined from the crude ^{1}H NMR spectra. [b] Isolated yields.

In further attempts to evaluate the mechanism of this reaction and in particular the likelihood of a pentaorganosilicate species such as **11**, the siladihydrobenzofuran **38**[20] was reacted with the lithium carbenoid generated from chloroiodomethane and MeLi·LiBr at −100 °C (Scheme 4).[12b]

Scheme 4. Evidence for a Hypervalent Silicon Pathway



38 46% **5a** 50:50 **5b**

Both isomers **5a** and **5b** were obtained in a ratio comparable to that of Scheme 2 (50:50 vs 60:40), hinting at the formation of a similar hypervalent species. However, it remains unclear at this stage whether **11** is a transition state or an intermediate in this transformation. Calculations are in progress to answer this question and to evaluate to which extent the Berry pseudorotation[21] can influence the selectivity.

In summary, we have developed a general and efficient access to silylated heterocycles through an original "sila-Matteson" type rearrangement. The influence of both the aromatic ring substituents and nitrogen protecting group on the ratio of the isomers was established, as well as the verisimilitude of a mechanism involving a hypervalent-silicon species. In addition, a good correlation between the isomer ratio and the Hammett constants of the aromatic substituents could be established. We hope these observations will promote the application of this new reaction to little known families of silaheterocycles.

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Supporting Information Available. Experimental methods for the preparation of compounds **4**–**7** and **12**–**38** and their characterization. Copies of ^{1}H and ^{13}C NMR spectra of the new compounds (**4**–**7** and **12**–**38**). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.