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Rearrangement of 2,5-Bis(silylated)-*N*-Boc Pyrroles into the Corresponding 2,4-Species

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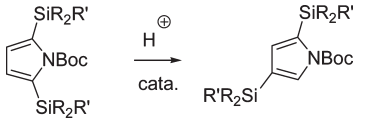
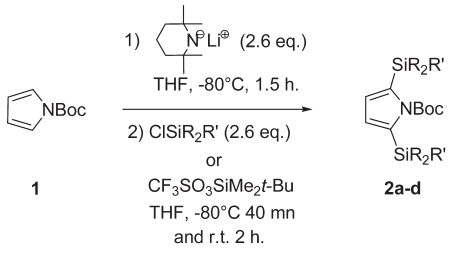


The rearrangement of 2,5-bis(silylated)-*N*-Boc pyrroles in their 2,4-isomers is shown to proceed under mild acidic conditions. A reasonable mechanism, based on literature as well as experiments, is proposed to rationalize this transformation.

Since the middle of the 1980s, there has been an interest in the 2,3-, 3,4-, and 2,4-regioisomers of the 2,5-bis(silylated) pyrroles. In 1985, Barton et al. studied the rearrangement of 2,5-bis(trimethylsilyl) pyrrole under irradiation[1] and showed that it led to a mixture of the corresponding 2,3- and 3,4-species. Recently, Wong et al. have reported an efficient synthesis of 3,4-bis(trimethylsilyl) pyrroles via a [2 + 3] cycloaddition of cyanoaziridines on the bis(trimethylsilyl) acetylene,[2] studied their reactivity,[3] and used them as precursors of an uncommon 3,4-didehydro-1*H*-pyrrole[4] and in an elegant synthesis of Lukianol A.[5] Concerning the 2,4-bis(silylated) pyrroles, they were only reported as byproducts in modest yields (24−55%) in this latter publication and in the electrophilic substitution of N-substituted pyrroles (10−18%).[6] Nevertheless, these 2,4-regioisomers could be particularly interesting as potential precursors of the corresponding 2,4-diaryl species[7] through palladium-catalyzed desilylative coupling reactions.[8] The access to 2,4-disubstituted pyrroles from the corresponding 2,5-compounds was reported via the acid-catalyzed α to β migration of acyl,[9] sulfinyl,[10] bromo or chloro,[11] and enol[12] substituents. Such a transformation involves, as mentioned in the latter publication, the formation of a transient β cation by protonation of the pyrrole ring at the α position prior to rearrangement. The well-known ability of silicon to stabilize carbocations at the β positions could favor such a rearrangement in the silylpyrrole series and open an access to the aforementioned 2,4-disilylated species. The present paper deals with our first investigations concerning this transformation.

In connection with our interest in the synthesis of pyrrolylrhenium complexes,[13] we reported the synthesis of a new monodimethylphenylsilyl-substituted pyrrole according to a procedure reported in the literature for the corresponding trimethylsilyl compound.[14] This procedure, modified by the addition of 2 equiv of lithium 2,2,6,6-tetramethylpiperidine (LTMP) and of the appropriate silylating agent (Scheme 1), gave the desired disilylated compounds **2a**−**d** in good yields (70−86%) from the commercialy available *N*-Boc pyrrole **1**.

SCHEME 1. Synthesis of 2,5-Bis(silylated)-*N*-Boc Pyrroles 2a−d



2a: R = R' = Me (85%) **2b**: R = R' = Et (70%)
2c: R = Me, R' = Ph (80%) **2d**: R = Me, R' = *t*-Bu (86%)

The yield obtained (85%) for compound **2a** is better than that previously reported (68%) following another route involving two steps.[15] While the ^{1}H NMR spectra of compounds **2** in C_6D_6 show characteristic singlets for the identical protons of the ring between 6.6 and 6.7 ppm, their ^{1}H NMR spectra in $CDCl_3$ point out the existence of mixtures of compounds **2** and the rearranged products **3** (Scheme 2) in

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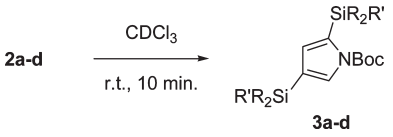
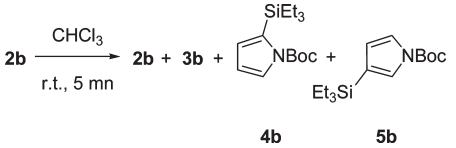
variable proportions according to the concentration used to prepare the analytical samples and the quality of the deuterated solvent. These latter compounds are characterized by two doublets at 6.44−6.47 and 7.26−7.44 ppm in $CDCl_3$ with a small coupling constant (^4J = 1.5 Hz).

SCHEME 2. Rearrangement of 2a−d in $CDCl_3$



Because deuterated chloroform frequently contains traces of hydrochloric acid, a solution of 2,5-bis(triethylsilyl)-*N*-Boc pyrrole **2b** in chloroform (0.04 M) was acidified with the same acid for the optimization process (Scheme 3 and Table 1). Hydrochloric acid (0.15−3.30 equiv) in chloroform was added to a solution of **2b** in chloroform and stirred for 5 min before quenching with water. The ^{1}H NMR spectra of the crude reaction mixture thus obtained showed the existence of two new products **4b** and **5b**, resulting from protodesilylation. Compound **4b** was independently synthesized as previously mentioned for the monophenyldimethylsilyl-*N*-Boc pyrrole (vide supra, see Supporting Information for the synthesis of **4b−d**) to confirm its structure, while the structure of its regioisomer **5b** was assigned on the basis of the ^{1}H NMR spectra of the crude reaction mixture obtained with an excess of hydrochloric acid (Table 1, entry 4). These two compounds differ by the nature of their chemical shifts as well as the coupling constants of the ring protons. The monosilylated pyrrole **4b** presents, as the result of the nitrogen influence, only one deshielded proton (7.43 ppm in C_6D_6) at the C5 position, while its analogue **5b** has two deshielded protons (7.59 and 7.40 ppm in C_6D_6) in positions 2 and 5. Furthermore, compound **4b** possesses three protons associated with a $^3J_{H-H}$ coupling constant ($^3J_{H3-H4}$ = $^3J_{H4-H5}$ = 3 Hz), while compound **5b** has only two protons involved with such a coupling constant ($^3J_{H4-H5}$ = 3 Hz). Increasing the number of equivalents of HCl relative to **2b** (Table 1, entries 1−4) progressively increased the byproduct formation at the expense of the desired product **3b**. Despite many attempts varying the reaction conditions (temperature, solvent, concentration) or the nature of the acid used (AcOH, PTSA), we were unable to direct the reaction toward the formation of the sole product **3b**. The best conditions (entry 2) led to the formation of **3b** in 80% yield along with an unseparable mixture of **4b** and **5b**.

SCHEME 3. Acid-Catalyzed Rearrangement of 2b



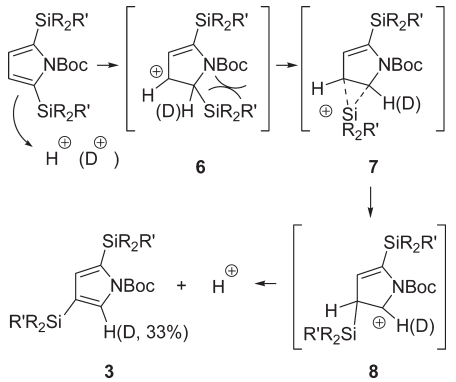
To illustrate the scope of this rearrangement, the current study was carried out with the compounds **2a**, **2c**, and **2d** in similar conditions (see Supporting Information). The rearranged products were thus obtained after purification by flash chromatography in good yields (74% for **3a**, 70% for **3c**, and 91% for **3d**). The ^{1}H NMR spectra of the crude reaction mixtures showed traces of the only monodesilylated product **4d** in the rearrangement of **2d**, while **3a** (respectively, **3c**) was obtained along with **4a** (9%) and **5a** (8%) (respectively, **4c** (12%) and **5c** (8%)). Compounds **4a**[14] and **5a**[3] were identified on the basis of the ^{1}H NMR data reported in the literature,[14] whereas **4c** and **4d** were synthesized as mentioned earlier in the text (vide supra). The ^{1}H NMR data of **5a** and **5c** were deduced from the crude reaction mixture spectra.

TABLE 1. Optimization Process for the Rearrangement of 2b (The Proportions of Compounds 2b, 3b, 4b, and 5b Are Determined on the Basis of the ^{1}H NMR Spectra of the Crude Reaction Mixtures)

entry	HCl (equiv)	2b	3b	4b	5b
1	0.15	2%	94%	3%	1%
2	0.33		96%	2%	2%
3	1.30		92%	4%	4%
4	3.30		67%	5%	28%

From a mechanistic standpoint, this rearrangement could be reasonably explained by the following steps (Scheme 4). The first carbocation intermediate **6**, which is favored by the well-known β effect,[16] could be the result of the protonation of compound **2** in the α position as previously advanced for other substituents.[9−12] The rearrangement of this entity, through a stabilized bridged form **7**,[17] could give the carbocation **8** and the isolated products **3** after deprotonation and aromatization. To validate the first step of this mechanism, deuterium chloride was added to a solution of **2b** in $CDCl_3$. After 5 min at room temperature, the ^{1}H NMR spectra showed the presence of the rearranged product **3b** (67%), unreacted compound **2b** (1%), and a new compound (32%, singlet at 6.84 ppm) resulting from the incorporation of deuterium at the C5 position. The formation of **3b** in that case can be explained both by the residual acidity of $CDCl_3$ as well as by the generation of H^+ during the process. This rearrangement is not reversible because compound **3b** gave no starting material in acidic conditions and the 3,4-bis-(silylated) species were never observed in our case.

SCHEME 4. A Reasonable Mechanism



By analogy with the phenylsulfinyl migration reported by Carmona et al.,[10] the present rearrangement might proceed

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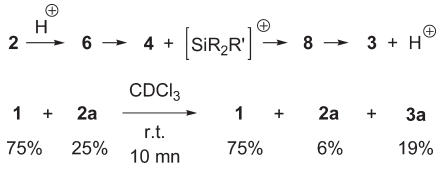
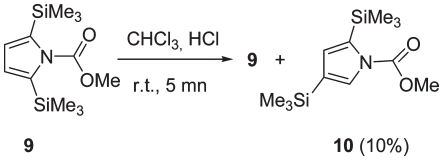
by dissociation of **6** to the silylium ion and pyrrole **4** followed by recombination into **8** (Scheme 5). This hypothesis was discarded by carrying out the rearrangement of **2a** in $CDCl_3$ in the presence of 3 equiv of *N*-Boc pyrrole **1**. This experiment showed no product resulting from a crossover process (monosilylated species), and only the rearranged product **3a** (19%), unreacted compound **1**, and **2a** (6%) were observed. Finally, the formation of the intermediate **7** would be favored by the release of the steric strain between the Boc substituent and the migrating silyl group (Scheme 4). This hypothesis was corroborated by the acid-catalyzed rearrangement of the methyl 2,5-bis(trimethylsilyl)-1*H*-pyrrole-1-carboxylate **9** incorporating a less hindered N-protecting group, which led, in the acidic reaction conditions used for **2a**, to only 10% conversion in the rearranged product **10**[5] (Scheme 6).

SCHEME 5. Crossover Experiment



SCHEME 6. Steric Hindrance Influence on the Rearrangement



In conclusion, the present work deals with a mild access to 2,4-bis(silylated)-*N*-Boc pyrroles via an acid-catalyzed rearrangement of the corresponding 2,5-species. Despite many attempts based on the work of Pierrat et al.[18] and using compound **3a** as a reagent, we were not able to perform the palladium-catalyzed process leading to the 2,4-bis(aryl) pyrroles. The pyrrole heterocycle is a rather π excessive system, and the absence of reaction under these conditions could be expected due to a probable too weak polarization of the C−Si bond. We are consequently working on the substitution of our silyl subtituents by silanolates which are more prone to such a transformation.[19]

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Experimental Section

General Procedure for the Synthesis of Compounds 2a−d: A solution of 2,2,6,6-tetramethylpiperidine (TMP) (7.9 mmol) in THF (15 mL) was cooled to −78 °C, and *n*-butyllithium (7.8 mmol, 1.6 M in hexane) was slowly added, keeping temperature under −65 °C. The resulting mixture was allowed to stir for 30 min at −78 °C. *N*-Boc pyrrole (*N*-acetyl pyrrole for **9**) (3 mmol) in THF (15 mL) was then slowly added. The resulting mixture was allowed to stir for 1.5 h at −78 °C, and the appropriate silyl chloride (silyl triflate in the *t*-Bu(Me)$_2$Si) (7.8 mmol) was slowly added. The crude reaction mixture was stirred for 30 min at −78 °C then for 2 h at room temperature. The reaction mixture was diluted with ether (50 mL) and poured into water (50 mL). The aqueous layer was extracted with ether (3 × 30 mL), and the resulting organic layers were dried over $MgSO_4$ and evaporated under vacuum. The crude mixture was purified by flash chromatography using pentane as eluent.

***tert*-Butyl 2,5-bis(triethylsilyl)-1*H*-pyrrole-1-carboxylate 2b:** 70% yield; colorless oil; ^{1}H NMR (300 MHz, C_6D_6) δ 6.69 (s, 2H), 1.44 (s, 9H), 1.1−0.9 (m, 30H) ppm; ^{13}C NMR (75 MHz, C_6D_6) δ 152.5, 137.0, 126.3, 85.1, 28.3, 8.1, 4.9 ppm; MS *m*/*z* $[M + H]^+$ 396, $[M - C_4H_8 + H]^+$ 340; IR (KBr) ν = 2954, 2874,1729, 1340, 1005, 729 cm^{-1}. Anal. Calcd for $C_{21}H_{41}NO_2Si_2$: C, 63.74; H, 10.44. Found: C, 63.75; H, 10.13.

General Procedure for the Synthesis of Compounds 3a−d: A solution of HCl (18 μL, 35% w/w for **2a** or **9**, 30 μL, 35% w/w for **2b** and **2d**, 45 μL, 35% w/w for **2c**) in $CHCl_3$ (15 mL) was added to compounds **2a−d** or **9** (1 mmoL) in $CHCl_3$ (10 mL). The resulting mixture was allowed to stir at room temperature for 5 min and diluted into ether (100 mL). Water (50 mL) was added to the crude reaction mixture. Aqueous layer was extracted with ether (3 × 25 mL). The organic layers were dried over $MgSO_4$ and evaporated under vacuum. The resulting oil was purified by flash chromatography using pentane as eluent to give **3a−d** and unseparable mixtures of the monosilylated products **4a−d** and **5a−d**.

***tert*-Butyl 2,4-bis(triethylsilyl)-1*H*-pyrrole-1-carboxylate 3b:** 80% yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 1.5 Hz, 1H), 6.46 (d, J = 1.5 Hz, 1H), 1.60 (s, 9H), 1.0−0.7 (m, 30H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 132.2, 130.5, 130.3, 118.4, 83.1, 28.2, 7.9, 7.7, 4.2, 3.9 ppm; IR (NaCl) ν = 2953, 2875, 1742, 1357, 1290, 1219, 1158, 1103, 1007, 732 cm^{-1}; MS *m*/*z* $[M + H]^+$ 396, $[M - C_4H_8 + H]^+$ 340; HRMS *m*/*z* calcd for $C_{21}H_{42}NO_2Si_2^+$ 396.2754, found 396.2751.

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Supporting Information Available: General procedures, characterization of compounds and ^{1}H NMR and ^{13}C NMR spectra of compounds **2a−d**, **3a−d**, **4b−d**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.