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Note

(2-Halogeno-5-pyridyl)dimethyl(oxiran-2-ylmethyl)silanes: New potential building blocks for the synthesis of silicon-containing drugs

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ABSTRACT

(2-Fluoro-5-pyridyl)dimethyl(oxiran-2-ylmethyl)silane (**1a**) and (2-chloro-5-pyridyl)dimethyl(oxiran-2-ylmethyl)silane (**1b**) were prepared in two-step syntheses, starting from allylchlorodimethylsilane. Compounds **1a** and **1b** were characterized by elemental analyses and NMR studies. With the synthesis of **1a** and **1b**, new potential building blocks for the synthesis of silicon-containing drugs have been made accessible.

1. Introduction

Epoxides exhibit a synthetically very useful balance between stability and reactivity, and they are often employed as versatile intermediates in organic synthesis [1]. Their ability to be attacked by various nucleophiles to undergo stereospecific ring-opening reactions and the formation of bifunctional compounds emphasizes the role of epoxides as important chiral building blocks. Furthermore, the treatment of epoxides with a base/nucleophile may lead to a removal of an α-proton to generate α-metallated epoxides which are useful reactive intermediates in organic synthesis [2]. Not least, epoxides are of importance as precursors for the synthesis of polymers [3] and as valuable intermediates [1] in medicinal chemistry.

Silicon-containing epoxides, with the silicon atom in the β-position [(oxiran-2-ylmethyl)silanes], show a special reactivity profile because the silicon atom influences the reactivity of the epoxide moiety: the stabilization of positive charge in the β-position of hydrocarbons by silyl substituents (referred to as the silicon β-effect) [4] is a very important property of silicon which controls a large variety of ring-opening reactions [5]. For this reason, silicon-containing epoxides of the (oxiran-2-ylmethyl)silane type can be generally regarded as very useful chiral reagents for the stereocontrolled synthesis of novel organosilicon compounds.

In context with our systematic studies on silicon-based drugs [6], we have recently reported on the synthesis of (2-halogeno-5-pyridyl)silyl substituted phenylboronic acids as useful reagents in Suzuki-Miyaura cross coupling reactions [7]. In continuation of these studies, we have now succeeded in synthesizing the (2-halogeno-5-pyridyl)dimethyl(oxiran-2-ylmethyl)silanes **1a** and **1b**. As halogenopyridyl substituents are generally of great importance as functional groups in medicinal chemistry [8] and as the epoxide moiety in (oxiran-2-ylmethyl)silanes is characterized by a special reactivity profile for stereocontrolled ring-opening reactions, compounds **1a** and **1b** are expected to be very useful building blocks for the synthesis of novel biologically active silicon compounds (for selected examples referring to the reactivity and the synthetic potential of (oxiran-2-ylmethyl)silanes, see Refs. [5] and [9]). We report here on the synthesis and characterization of **1a** and **1b**.

2. Results and discussion

Compounds **1a** and **1b** were prepared according to Scheme 1 in two-step syntheses, starting from allylchlorodimethylsilane. The respective 5-bromo-2-halogenopyridines were transferred into the corresponding lithiated derivatives [7] and were then treated *in situ* with allylchlorodimethylsilane to give the respective allyl(2-halogeno-5-pyridyl)dimethylsilanes **2a** and **2b** (yields: **2a**, 80%; **2b**, 84%). The epoxidation of the allyl group of **2a** and **2b** with *m*-chloroperbenzoic acid [10] failed due to the sensitivity of the resulting epoxides against acids (upon protonation of the epoxide oxygen atom ring-opening occurs to give a β-silyl stabilized carbocation). However, the target compounds **1a** and **1b** could be synthesized by using an alternative, very mild and efficient epoxidation method: thus, treatment of the allylsilanes **2a** and

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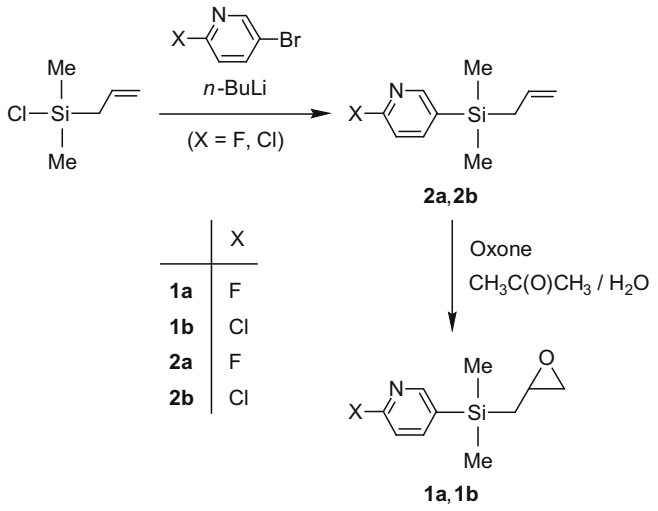


Scheme 1.

2b with dimethyldioxirane, generated *in situ* from Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) and acetone at high pH [11], yielded the corresponding (oxiran-2-ylmethyl)silanes **1a** and **1b**, respectively. A certain sensitivity of these compounds against moisture and acids, resulting in a ring-opening of the epoxide moiety (which is favored by the silicon β-effect), complicated their purification and resulted in moderate yields. After purification by column chromatography on silica gel (with an eluent containing 3% of triethylamine to ensure basic conditions), compounds **1a** and **1b** were isolated as colorless liquids in 50% (**1a**) and 56% (**1b**) yield.

The identities of **1a**, **1b**, **2a**, and **2b** were established by elemental analyses (C, H, N) and multinuclear NMR-spectroscopic studies (^1H, ^{13}C, ^{19}F, ^{29}Si, solvent $CDCl_3$). Compounds **1a** and **1b** were found to undergo a slow decomposition under ambient conditions (humid atmosphere) but can be stored without decomposition (GC control) under an atmosphere of dry nitrogen at room temperature over a period of at least one month.

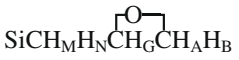
3. Conclusions

With the synthesis of the (2-halogeno-5-pyridyl)dimethyl(oxiran-2-ylmethyl)silanes **1a** and **1b**, two new functionalized silicon-containing epoxides have been made accessible. The syntheses of the allyl(2-halogeno-5-pyridyl)dimethylsilanes **2a** and **2b** are further examples of the high synthetic potential of the coupling reaction between chlorosilanes and (2-halogeno-5-pyridyl)lithium reagents, generated *in situ* from the corresponding 5-bromo-2-halogenopyridines and *n*-butyllithium in diethyl ether. The epoxidation of the allylsilanes **2a** and **2b** by using *in situ* generated dimethyldioxirane has been proven to be a mild and efficient method for the synthesis of the corresponding (oxiran-2-ylmethyl)silanes **1a** and **1b**. These functionalized organosilicon compounds, with their 2-halogeno-5-pyridyl and oxiran-2-ylmethyl groups, can be regarded as synthetically useful potential building blocks for the synthesis of new silicon-based drugs.

4. Experimental

4.1. General procedures

All syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. A Büchi GKR-51 apparatus was used for the bulb-to-bulb distillations. The ^1H, ^{13}C, ^{19}F, and ^{29}Si NMR spectra were recorded at 23 °C on a Bruker Avance 400 (^1H, 400.1 MHz; ^{13}C, 100.6 MHz; ^{19}F, 376.5 MHz) or Bruker Avance 500 NMR spectrometer (^1H, 500.1 MHz; ^{13}C, 125.8 MHz; ^{29}Si, 99.4 MHz). $CDCl_3$ was used as the solvent. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^1H, δ 7.24), internal $CDCl_3$ (^{13}C, δ 77.0), external $CFCl_3$ (^{19}F, δ 0), or external TMS (^{29}Si, δ 0). Analysis and assignment of the ^1H NMR data were supported by ^1H,^1H COSY, ^{13}C,^1H HMQC, and ^{13}C,^1H HMBC experiments, and the spin systems were analyzed by using the WIN-DAISY software package (version 4.05, Bruker) [12]. Assignment of the ^{13}C NMR data was supported by DEPT135 and the aforementioned ^{13}C,^1H correlation experiments. The $H_AH_BH_GH_MH_N$ spin systems of **1a** and **1b** refer to the oxiran-2-ylmethyl group:



4.2. Allylchlorodimethylsilane

This compound was commercially available (ACROS Organics) and was used without further purification.

4.3. Preparation of (2-fluoro-5-pyridyl)dimethyl(oxiran-2-ylmethyl)silane (*1a*)

A solution of Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$; 11.3 g, 18.4 mmol) in an aqueous EDTA solution (4×10^{-4} M, 49 mL) and a solution of potassium carbonate (11.3 g, 81.8 mmol) in water (49 mL) were added simultaneously dropwise at 20 °C within 2 h to a stirred mixture consisting of **2a** (1.20 g, 6.14 mmol), tetrabutylammonium iodide (125 mg, 338 μmol), acetone (10.7 g, 184 mmol), acetonitrile (32 mL), 1,2-dimethoxyethane (16 mL), and an aqueous potassium carbonate solution (0.1 M, 12 mL). After the addition was complete, the mixture was stirred at 20 °C for 15 h, dichloromethane (150 mL) was added, the organic layer was separated, and the aqueous phase was extracted with dichloromethane (2×150 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was rapidly purified by column chromatography on silica gel (silica gel (32–63 μm, ICN 02826); eluent, *n*-hexane/ethyl acetate/triethylamine (90:10:3 (v/v))). The relevant fractions (GC control) were combined, and the solvent was removed under reduced pressure to give **1a** in 50% yield as a colorless liquid (655 mg, 3.10 mmol) [13]. *Anal.* Calc. ($C_{10}H_{14}FNOSi$): C, 56.84; H, 6.68; N, 6.63; *M*, 211.31. Found: C, 57.03; H, 6.53; N, 7.03%. ^1H NMR (400.1 MHz, $CDCl_3$): δ 0.366 (3H, s, $SiCH_3$), 0.368 (3H, s, $SiCH_3$), 0.92 (δ_M), 1.28 (δ_N), 2.33 (δ_A), 2.71 (δ_B), and 2.92 (δ_G) (5H, $^2J_{AB}$ = 5.0 Hz, $^3J_{AG,trans}$ = 2.7 Hz, $^4J_{AM}$ = −0.2 Hz, $^4J_{AN}$ = −0.4 Hz, $^3J_{BG,cis}$ = 3.9 Hz, $^4J_{BM}$ = 0.0 Hz, $^4J_{BN}$ = 0.8 Hz, $^3J_{GM}$ = 7.4 Hz, $^3J_{GN}$ = 5.8 Hz, $^2J_{MN}$ = 14.5 Hz, $H_AH_BH_GH_MH_N$ spin system (see Section 4.1)) [12], 6.89–6.92 (1H, m, *H*-3, C_5H_3N), 7.85–7.90 (1H, m, *H*-4, C_5H_3N), 8.26–8.27 (1H, m, *H*-6, C_5H_3N). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −2.69 ($SiCH_3$), −2.65 ($SiCH_3$), 20.0 ($SiCH_2C$), 48.5 (CCH_2O), 49.7 ($SiCH_2CO$), 109.3 (d, $^2J_{CF}$ = 34.9 Hz, *C*-3, C_5H_3N), 130.4 (d, $^4J_{CF}$ = 4.7 Hz, *C*-5, C_5H_3N), 146.3 (d, $^3J_{CF}$ = 7.3 Hz, *C*-4, C_5H_3N), 152.4 (d, $^3J_{CF}$ = 13.4 Hz, *C*-6, C_5H_3N), 164.6 (d, $^1J_{CF}$ = 240.7 Hz, *C*-2, C_5H_3N). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −66.8. ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ −4.1 (d, $^5J_{SiF}$ = 1.8 Hz).

4.4. Preparation of (2-chloro-5-pyridyl)dimethyl(oxiran-2-ylmethyl)silane (*1b*)

A solution of Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$; 8.67 g, 14.1 mmol) in an aqueous EDTA solution (4×10^{-4} M, 38 mL) and a solution

of potassium carbonate (8.64 g, 62.5 mmol) in water (38 mL) were added simultaneously dropwise at 20 °C within 4 h to a stirred mixture consisting of **2b** (995 mg, 4.70 mmol), tetrabutylammonium iodide (69.0 mg, 187 μmol), acetone (8.19 g, 141 mmol), acetonitrile (25 mL), 1,2-dimethoxyethane (13 mL), and an aqueous potassium carbonate solution (0.1 M, 10 mL). After the addition was complete, the mixture was stirred at 20 °C for 15 h, dichloromethane (100 mL) was added, the organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was rapidly purified by column chromatography on silica gel (silica gel (32–63 μm, ICN 02826); eluent, *n*-hexane/ethyl acetate/triethylamine (90:10:3 (v/v/v))). The relevant fractions (GC control) were combined, and the solvent was removed under reduced pressure to give **1b** in 56% yield as a colorless liquid (594 mg, 2.61 mmol) [13]. *Anal.* Calc. ($C_{10}H_{14}ClNOSi$): C, 52.73; H, 6.20; N, 6.15; *M*, 227.77. Found: C, 52.69; H, 5.99; N, 6.55%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.355 (3H, s, SiC*H*$_3$), 0.358 (3H, s, SiC*H*$_3$), 0.92 (δ_M), 1.27 (δ_N), 2.33 (δ_A), 2.70 (δ_B), and 2.91 (δ_G) (5H, $^2J_{AB}$ = 5.0 Hz, $^3J_{AG,trans}$ = 2.7 Hz, $^4J_{AM}$ = −0.3 Hz, $^4J_{AN}$ = −0.5 Hz, $^3J_{BG,cis}$ = 3.9 Hz, $^4J_{BM}$ = 0.2 Hz, $^4J_{BN}$ = 0.8 Hz, $^3J_{GM}$ = 7.3 Hz, $^3J_{GN}$ = 5.8 Hz, $^2J_{MN}$ = 14.5 Hz, $H_AH_BH_GH_MH_N$ spin system (see Section 4.1)) [12], 7.28 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^5J_{HH}$ = 0.9 Hz, *H*-3, C_5H_3N), 7.72 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.1 Hz, *H*-4, C_5H_3N), 8.41 (1H, dd, $^4J_{HH}$ = 2.1 Hz, $^5J_{HH}$ = 0.9 Hz, *H*-6, C_5H_3N). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ −2.84 (SiC*H*$_3$), −2.79 (SiC*H*$_3$), 19.9 (SiC*H*$_2$C), 48.5 (CC*H*$_2$O), 49.6 (SiCH$_2$C*O*), 123.9 (*C*-3, C_5H_3N), 131.7 (*C*-5, C_5H_3N), 143.8 (*C*-4, C_5H_3N), 152.7 (*C*-2, C_5H_3N), 154.0 (*C*-6, C_5H_3N). ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ −3.8.

4.5. Preparation of allyl(2-fluoro-5-pyridyl)dimethylsilane (**2a**)

A 2.5 M solution of *n*-butyllithium in hexanes (4.9 mL, 12.3 mmol of *n*-BuLi) was added dropwise at −75 °C (±3 °C, temperature measurement within the flask) within 90 min to a stirred mixture of allylchlorodimethylsilane (1.54 g, 11.4 mmol), 5-bromo-2-fluoropyridine (2.16 g, 12.3 mmol), and diethyl ether (60 mL). After the addition was complete, the mixture was stirred at −75 °C for 90 min and then warmed to 20 °C within 18 h. Water (50 mL) and diethyl ether (25 mL) were added, the organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (55–65 °C/0.1 mbar) to give **2a** in 80% yield as a colorless liquid (1.79 g, 9.16 mmol). *Anal.* Calc. ($C_{10}H_{14}FNSi$): C, 61.50; H, 7.22; N, 7.17; *M*, 195.31. Found: C, 61.15; H, 7.23; N, 7.47%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.28 (6H, s, SiC*H*$_3$), 1.72 (δ_M), 4.82 (δ_B), 4.84 (δ_A), and 5.69 (δ_G) (5H, $^2J_{AB}$ = 2.0 Hz, $^3J_{AG,cis}$ = 10.1 Hz, $^4J_{AM}$ = 1.0 Hz, $^3J_{BG,trans}$ = 17.0 Hz, $^4J_{BM}$ = 1.4 Hz, $^3J_{GM}$ = 8.1 Hz, $SiC(H_M)_2CH_G{=}CH_AH_B$) [12], 6.87–6.89 (1H, m, *H*-3, C_5H_3N), 7.81–7.85 (1H, m, *H*-4, C_5H_3N), 8.237–8.241 (1H, m, *H*-6, C_5H_3N). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ −3.6 (SiC*H*$_3$), 23.3 (SiC*H*$_2$CH=CH$_2$), 109.1 (d, $^2J_{CF}$ = 34.5 Hz, *C*-3, C_5H_3N), 114.2 (SiCH$_2$CH=C*H*$_2$), 130.7 (d, $^4J_{CF}$ = 4.6 Hz, *C*-5, C_5H_3N), 133.4 (SiCH$_2$C*H*=CH$_2$), 146.4 (d, $^3J_{CF}$ = 7.3 Hz, *C*-4, C_5H_3N), 152.5 (d, $^3J_{CF}$ = 13.2 Hz, *C*-6, C_5H_3N), 164.5 (d, $^1J_{CF}$ = 240.4 Hz, *C*-2, C_5H_3N). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −67.2. ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ −4.7 (d, $^5J_{SiF}$ = 1.8 Hz).

4.6. Preparation of allyl(2-chloro-5-pyridyl)dimethylsilane (**2b**)

A 2.5 M solution of *n*-butyllithium in hexanes (4.9 mL, 12.3 mmol of *n*-BuLi) was added dropwise at −75 °C (±3 °C, temperature measurement within the flask) within 90 min to a stirred mixture of allylchlorodimethylsilane (1.57 g, 11.7 mmol), 5-bromo-2-chloropyridine (2.36 g, 12.3 mmol), and diethyl ether (50 mL). After the addition was complete, the mixture was stirred at −75 °C for 90 min and then warmed to 20 °C within 18 h. Water (50 mL) and diethyl ether (25 mL) were added, the organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (70–85 °C/0.03 mbar) to give **2b** in 84% yield as a colorless liquid (2.08 g, 9.82 mmol). *Anal.* Calc. ($C_{10}H_{14}ClNSi$): C, 56.72; H, 6.66; N, 6.61; *M*, 211.77. Found: C, 56.35; H, 6.77; N, 7.01%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.28 (6H, s, SiC*H*$_3$), 1.72 (δ_M), 4.82 (δ_B), 4.83 (δ_A), and 5.68 (δ_G) (5H, $^2J_{AB}$ = 2.0 Hz, $^3J_{AG,cis}$ = 10.1 Hz, $^4J_{AM}$ = 1.2 Hz, $^3J_{BG,trans}$ = 17.0 Hz, $^4J_{BM}$ = 1.4 Hz, $^3J_{GM}$ = 8.0 Hz, $SiC(H_M)_2CH_G{=}CH_AH_B$) [12], 7.27 (1H, dd, $^3J_{HH}$ = 7.9 Hz, $^5J_{HH}$ = 0.8 Hz, *H*-3, C_5H_3N), 7.69 (1H, dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 2.1 Hz, *H*-4, C_5H_3N), 8.39 (1H, dd, $^4J_{HH}$ = 2.1 Hz, $^5J_{HH}$ = 0.8 Hz, *H*-6, C_5H_3N). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ −3.7 (SiC*H*$_3$), 23.1 (SiC*H*$_2$CH=CH$_2$), 114.4 (SiCH$_2$CH=C*H*$_2$), 123.8 (*C*-3, C_5H_3N), 132.0 (*C*-5, C_5H_3N), 133.3 (SiCH$_2$C*H*=CH$_2$), 144.0 (*C*-4, C_5H_3N), 152.4 (*C*-2, C_5H_3N), 154.0 (*C*-6, C_5H_3N). ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ −4.4.

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[13] Further purification of compounds **1a** and **1b** by distillation was not performed due to their thermal instability. The products isolated by column chromatography on silica gel were NMR-spectroscopically and gas-chromatographically pure.