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ADVANCED SYNTHESIS & CATALYSIS

Synthesis of Dibenzoxasilepine Using Ring Expansion Reaction of a Pentacoordinate Silicon Intermediate

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Abstract: Dibenzoxasilepine is an important skeleton in both synthetic organic and medicinal chemistry. Here, we have succeeded in obtaining it in higher yield than the conventional method, elucidating for the first time the rearrangement tendency of the two aromatic rings during the ring expansion reaction on the cyclic pentacoordinate silicon intermediate.

Keywords: Silicon; Heterocycles; Ring expansion; Medium-ring compounds

Introduction

Silicon belongs to the same group 14 elements as carbon. However, silicon differs from carbon in several characteristics. Due to these characteristics, silicon switches are known to replace carbon in bioactive compounds with silicon.[1,2] From these studies, it is widely recognised that the introduction of silicon into a compound improves its liposolubility. This is expected to lead to changes in physical properties such as solubility and membrane permeability. In addition, since the increase in bond length of the carbon-silicon (C–Si) bonds affects the molecular shape, changes in biological activity are expected.[3] Therefore, research on the reactivity of silicon-containing compounds and the development of synthetic methods are still important issues in synthetic organic chemistry and medicinal chemistry.

Tricyclic compounds containing a heteroatom and a 7-membered ring are partial structures of biologically active substances (Figure 1).[4,5,6] We are interested in the synthesis of dibenzoxasilepine (**1a**), a compound in which the methylene carbon of dibenzoxapine is replaced by silicon. In reviewing previous papers on the synthesis of **1a**, Corey *et al.* reported one synthesis (Scheme 1a).[7] A six-membered silicon ring compound is synthesised by double ortho lithiation of biphenyl

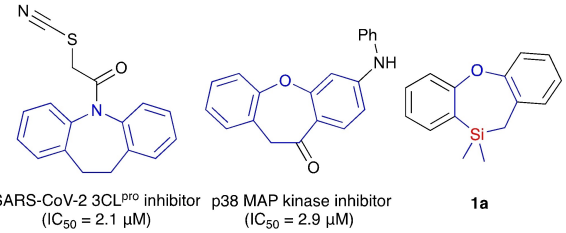
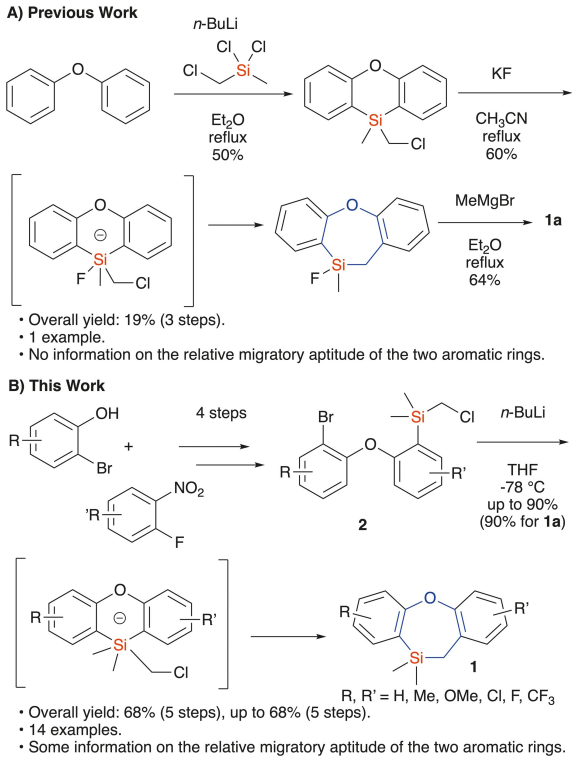


Figure 1. Biologically active tricyclic compounds containing a heteroatom and a 7-membered ring and a structure of dibenzoxasilepine **1a**.



Scheme 1. Synthesis of dibenzoxasilepine **1**.

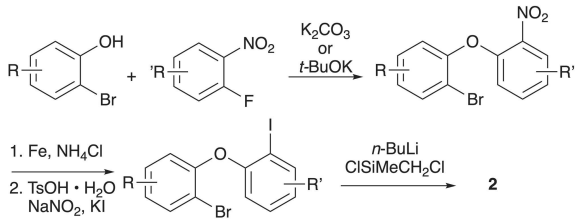
ether. Treatment of this 6-membered ring silicon compound with KF leads to a ring expansion reaction via a pentacoordinate silicon intermediate to construct a dibenzoxasilepine ring. Finally, the fluorine group is methylated using MeMgBr to give **1a** in 19% overall yield. However, this synthetic method has the problem that the overall yield of **1a** from biphenyl ether, a commercial product, is low at 19%. In addition, the relative migratory aptitude of the two aromatic rings during ring expansion is unknown.

With this background, we would like to report that we developed a new synthetic route to obtain the desired dibenzoxasilepine (**1**) in high yield by utilising the ring expansion reaction of the pentacoordinate silicon intermediate generated from substrate **2**, synthesised from 2-bromophenol and 1-fluoro-2-nitrobenzene in four steps, and *n*-BuLi (Scheme 1B).

Many reactions utilising pentacoordinate silicon intermediates have been reported.[8] Examples of reactions in which cyclic silicon pentacoordinate intermediates are prepared by lithium reagents and used for synthesis can be classified into two types. The first is the S_N–Si-type reaction, in which a nucleophile attacks silicon to form a cyclic silicon pentacoordinate intermediate, and then the C–Si bond of the leaving group attached to the silicon is cleaved, and the leaving group is desorbed.[9,10,11] The second is a rearrangement reaction in which a nucleophile attacks silicon to form a cyclic pentacoordinate silicon intermediate, then the C–Si bond possessed by one of the substituents attached to the silicon nucleophilically attacks the carbon atom of the chloromethyl group attached to the silicon, causing the chlorine atom to desorb.[12,13]

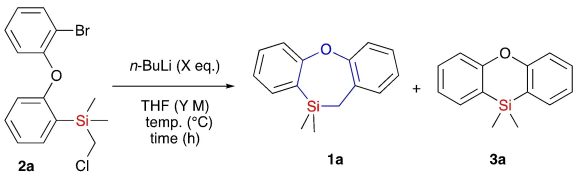
Results and Discussion

Substrate **2** can be synthesised in good yield from commercially available compounds in four steps: aromatic nucleophilic substitution, reduction of the nitro group to an amino group, conversion of the amino group to an iodine group via the Sandmeyer reaction, and silylation followed by lithium iodine exchange reaction (Scheme 2, See SI for details). The conversion of compound **2a** to **1a** was examined. First, the temperature, reaction time, and equivalent amount of *n*-BuLi were examined (Table 1). Treatment of substrate **2a** with *n*-BuLi at −40 °C gave the 7-membered ring compound **1a** and 6-membered ring compound **3a** in 54% and 19% yields, respectively (run 1). Compound **3a** was formed by the cleavage of the C(sp^3)–Si bond in a progressive S_N–Si-type reaction. The same reaction was examined at a lower temperature of −78 °C, and the yield of **1a** was improved significantly to 77% (run 2). Next, the concentration of the substrate in the reaction solution



Scheme 2. Synthesis of substrate **2**.

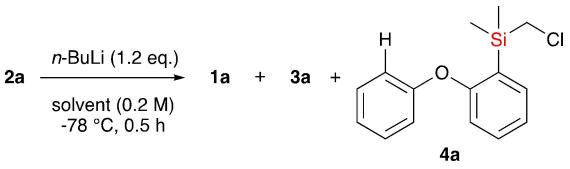
Table 1. Effect of temperature, reaction time, and equivalent amount of *n*-BuLi on product yield.



run	X (eq.)	Y (M)	temp. (°C)	time (h)	yield (%)[a] 1a	3a
1	1.1	0.2	−40	1	54	19
2	1.1	0.2	−78	1	77	13
3	1.1	0.1	−78	1	78	10
4	1.1	0.5	−78	1	80	9
5	1.2	0.2	−78	0.5	85	9

[a] NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

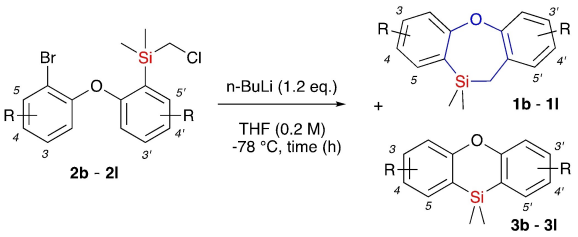
Table 2. Effect of solvents on product yield.



run	solvent	yield (%)[a] 1 a	3 a	4 a
1	Et_2O	trace	5	83
2	CPME	trace	10	79
3	MTBE	0	0	quant.
4	THF	85(77)[b]	9(9) [b]	trace
5	2-MeTHF	69	trace	27

[a] NMR yields using 1,3,5-trimethoxybenzene as an internal standard.
[b] Isolated yields.

Table 3. Effect of substituents on benzene rings on product yield.

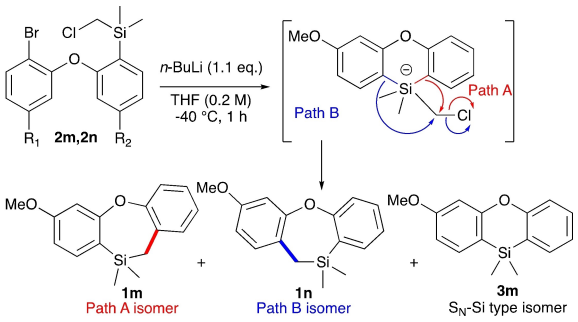


run	substrate R=[b]		time (h)	yield (%)[a] 1	3	ratio 1 / 3
1	**2 b**	3-Me, 3′-Me	0.5	53	28	1.9
2	**2 c**	3-OMe, 3′-OMe	0.5	51	43	1.2
3	**2 d**	4-Me, 4′-Me	0.5	72	9	8.0
4	**2 e**	4-OMe, 4′-OMe	0.5	34	9	3.8
5	**2 f**	5-Me, 5′-Me	0.5	nd	15	–
6	**2 f**	5-Me, 5′-Me	17	18	61	0.3
7	**2 g**	3-Cl, 3′-Cl	17	79	nd	–
8	**2 h**	3-F, 3′-F	17	40	nd	–
9	**2 i**	3-CF_3, 3′-CF_3	17	47	nd	–
10	**2 j**	4-Cl, 4′-Cl	17	96	nd	–
11	**2 k**	4-F, 4′-F	17	58	nd	–
12	**2 l**	4-CF_3, 4′-CF_3	17	56	nd	–

[a] Isolated yields.
[b] Substituent position numbers for convenience.

was examined (runs 3 and 4). The results showed that the concentrations did not significantly affect the yield

Table 4. Experiments to elucidate the reaction mechanism.



run	substrate	R^1	R^2	yield (%)[a] 1 m	1 n	3 m
1	**2 m**	OMe	H	23	11	23
2	**2 n**	H	OMe	24	12	35

[a] Isolated yields.

of 7-membered ring compound **1 a** or the ratio of **1 a** to **3 a**. Furthermore, reaction time and the equivalent amount of *n*-BuLi was also examined (SI, Table S1). The reaction was carried out under reaction conditions reflecting these results, i. e., 1.2 equivalents of *n*-BuLi was added to a 0.2 M THF solution of substrate **2 a** at −78 °C and the reaction was stirred for 0.5 h (run 5). As a result, the yield of 7-membered ring compound **1 a** and the ratio of **1 a** to **3 a** were both favourable, making run 5 the final optimal conditions.

The organometallic reactants used in the halogen-lithium exchange (See Table S1) and the reaction solvents (Table 2) were then examined. First, acyclic ether solvents were used, resulting in more of the reduced product **4 a** (runs 1–3).

Next, cyclic ether solvents (tetrahydrofuran and 2-methyltetrahydrofuran) were used. As a result, we succeeded in obtaining the 7-membered ring compound **1 a** in 69% to 85% yields in both solvents (runs 4 and 5). The same reaction was also carried out using hydrocarbon solvents such as hexane, benzene, and toluene, resulting in the recovery of the raw material, substrate **2 a**. This recovery occurred because the halogen-lithium exchange did not proceed. These results indicate that cyclic ether solvents are the best solvents for this reaction. Of these solvents, the THF solvent (run 4) showed the highest yield of **1 a** and was selected as the optimal solvent. Furthermore, the solvent was fixed to THF, and additives were examined. TMEDA,[14] HMPA,[15] and DMPU[16] were used as specific additives (see SI Table S3).

In the reaction using **2 a** as the substrate, the chloro group is released during the progress of the ring expansion reaction. Therefore, to investigate the leaving group that gives 7-membered ring compound **1 a** in the highest yield, derivatives (**5**–**8**) were synthesised by replacing the chlorine atom of the

chloromethyl group attached to the silicon with another leaving group and subjected to this reaction (See SI, Table S4). However, the chlorine atom was found to be the optimal leaving group.

To investigate the effect of electron density on the aromatic ring in this reaction, substrates (**2b**–**2f**) with electron-donating groups and (**2g**–**2l**) with electron-withdrawing groups were synthesised, and these substrates were subjected to the optimal reaction conditions (Table 2, run 4).

Both 7-membered ring compounds (**1b**–**1f**) and 6-membered ring compounds (**3b**–**3f**) were obtained from substrates with electron-donating groups (**2b**–**2f**). The selectivity of **1b**–**1e** for **3b**–**3e** was higher for methyl groups than for methoxy groups as substituents on the aromatic ring, indicating that the electron density of the aromatic ring affects product selectivity, and that the lower the electron density of the aromatic ring, the higher the percentage of 7-membered ring compounds formed (runs 1–4).[17]

As for the position of the substituent attached, the substrate with a substituent at the 4-position gave a higher percentage of 7-membered ring compounds than the substrate with a substituent at the 3-position, indicating that the lower electron density on the pentacoordinate silicon intermediate to be formed is more likely to give a 7-membered ring compound. Furthermore, a substrate with a methyl group attached to the 5-position was subjected to the reaction conditions (run 5). As a result, **1f** was not obtained, and only **3f** was obtained in low yield. Therefore, the reaction time was extended to 17 h (run 6), and **1f** and **3f** were obtained in 18% and 61% yields, respectively. These results suggest that the steric environment of the pentacoordinate silicon intermediate also has a significant effect on the formation of the 7-membered ring compound.

When the substrate with electron withdrawing groups (**2g**–**2l**) was subjected to the reaction conditions (Table 2, run 4), the optimum reaction time of 0.5 h gave a large amount of bromine reductants. Therefore, the reaction time was extended to 17 h. This result may be attributed to the fact that the reactivity of the substrate decreased due to the introduction of electron-withdrawing groups. From the substrate with electron-withdrawing groups (**2g**–**2l**), no 6-membered ring product **3** was observed and only the desired 7-membered ring compounds (**1g**–**1l**) were successfully obtained in 40% to 96% yields.

Is the 7-membered ring compound really formed via the pentacoordinate silicon intermediate ring expansion reaction?[12,13] Another possible reaction mechanism is the S_N2 reaction on the carbon atom on the chloromethyl group.[18] To verify which reaction mechanism is responsible for this reaction, we synthesised the substrates (**2m**, **2n**) with substituents on only one aromatic ring. If the reaction proceeds via a cyclic pentacoordinate silicon intermediate, the ratio of the two regioselective isomeric products obtained should be the same regardless of whether the substituent is attached to R^1 or R^2, due to the electronic effect of the aromatic ring.

In fact, when **2m** or **2n** was subjected to this reaction, regardless of whether the methoxy group was substituted at R^1 or R^2, the product Path A isomer **1m**, in which the aromatic ring to which the methoxy group is not attached is rearranged, was obtained in about twice the yield of Path B isomer **1n**, where the aromatic ring to which the methoxy group is attached is rearranged (Table 4). From these experimental results, it is expected that the two substrates proceed through the same intermediate. Therefore, the possibility that this reaction proceeds via S_N2 reaction to the carbon atom on the chloromethyl group has not been completely ruled out, but it is suggested that most of the reaction proceeds via the pentacoordinate silicon intermediate, followed by a rearrangement, followed by the elimination of the chloro group.[19,7] The structures of Path A isomer **1m** and Path B isomer **1n** were determined by X-ray crystallography and the crystal sponge method, respectively (Figure S1). The results in Table 4 also allow us to discuss the rearrangement tendency of two aromatic rings on a cyclic pentacoordinate silicon intermediate. We found that rearrangements involving the cleavage of the C(sp^2)–Si bond are more likely to occur in the absence of a methoxy group.[20,21]

Conclusion

We have developed a new synthetic method for dibenzoxasilepine (**1**) in good yields. Specifically, we discovered a new synthetic method to prepare the corresponding cyclic pentacoordinate silicon intermediate from biaryl ether **2** and a lithium reagent, followed by a ring expansion reaction to give **1** in up to 96% yield. Our method is applicable to a wide range of substrates, and we successfully synthesised 14 dibenzoxasilepines.

We also found that substituents on the aromatic ring affect the formation of 7-membered ring compounds after the formation of cyclic pentacoordinate silicon intermediates (electronic and steric effects). Furthermore, we verified whether this reaction is an S_N2 reaction to the carbon atom on the chloromethyl group or a rearrangement followed by the elimination of the chloro group via a silicon pentacoordination intermediate. Our findings indicate that this reaction mechanism proceeded via a pentacoordinate silicon intermediate. Furthermore, the rearrangement tendency of the two aromatic rings during the ring expansion reaction on a pentacoordinate silicon intermediate was also clarified for the first time.

Experimental Section

General procedure, Cyclisation of compounds 2, 5, 6, 7 and 8, to give 1: To a solution of **2 a** (71 mg, 0.2 mmol) in THF (0.2 M) was added dropwise 1.6 M solution of *n*-BuLi (0.14 mL, 0.24 mmol) at –78 °C. After the mixture was stirred at –78 °C for 0.5 h, to the mixture was added H_2O and organic compounds were extracted with Et_2O and washed with brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified by pTLC with *n*-hexane as eluent to give **1 a** (77%, 37.1 mg, 0.15 mmol) as a colourless oil and **3 a** (9%, 4.2 mg, 0.019 mmol) as a colourless oil. **4 a** was observed in crude NMR, but not isolated. **4 a** was isolated by Table 3**, run 3** conditions. (0.2 mmol, **2 a** was used and 55.3 mg, 0.200 mmol, quant., **4 a** was isolated).

1 a: Analytical data corresponds with literature data.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.01 (m, 8H), 2.49 (s, 2H), 0.21 (s, 6H) **3 a**: Analytical data corresponds with literature data.[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.3, 1.8 Hz, 2H), 7.43–7.39 (ddd, J = 8.6, 7.0, 1.8 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 7.13 (ddd, J = 7.3, 7.3, 0.9 Hz, 2H), 0.47 (s, 6H) **4 a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.3, 1.8 Hz, 1H), 7.38-7.32 (m, 3H), 7.12 (t, J = 7.3 Hz, 2H), 7.00 (dd, J = 8.5, 1.1 Hz, 2H), 6.79 (d, J = 8.2 Hz, 1H), 3.08 (s, 2H), 0.43 (s, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 162.2, 156.9, 135.8, 131.5, 129.9, 126.5, 123.5, 123.0, 119.0, 117.1, 30.5, −4.2. HRMS (ESI) calcd for $C_{15}H_{17}ClOSi$: 299.0629 ($[M+Na]^+$), found 299.0623 ($[M+Na]^+$)

The supporting information contains all the necessary experimental information, including details of experimental procedures and NMR spectra.

Acknowledgements

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[20] When the cyclic pentacoordinate silicon intermediate is formed, the C(sp^2)-silicon bond is strengthened through the electron donating property of the methoxy group, which makes it easier for the chloromethyl group to be removed. Conversely, if an electron-withdrawing group is attached during the formation of the intermediate, the C(sp^2)-silicon bond is weakened, making it more likely that the C(sp^2)-silicon bond will break rather than the chloromethyl group being removed. We tried to verify this with DFT calculations; however, we were unable to do so at present. The experimental results and discussion show the same tendency as reported by François *et al.* (ref. 13).

[21] The different ratios of **3 m** may suggest the existence of a third pathway that does not involve the bracketed intermediate; however, further experiments are required to elucidate this.

RESEARCH ARTICLE

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