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A Remarkable Tendency of *o*-Lithio-*N*-(2-lithiooxyethyl)-*N*-methyl-aniline to Form Heterocyclic Derivatives by its Reaction with Dichlorodialkylsilanes or Silicon Tetrachloride. Synthesis of 2,5,1-Benzoxazasilepines and of the Silaspiro Analogue

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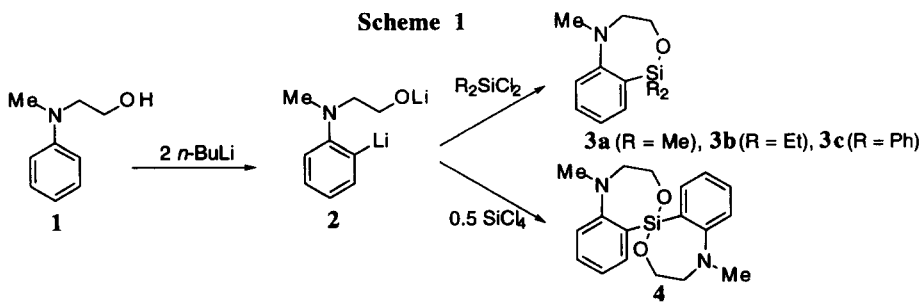
Abstract: The synthesis of 2,5,1-benzoxazasilepines **3** or the benzoxazasilaspiro compound **4**, has been achieved by the reaction of *o*-lithio-*N*-(2-lithiooxyethyl)-*N*-methyl-aniline (**2**) with R_2SiCl_2 (R = Me, Et, Ph) or $SiCl_4$, respectively. The reaction led to the formation of cyclic products, even under conditions favorable for the formation of polymeric materials. © 1997 Elsevier Science Ltd.

Reaction between a bifunctional nucleophilic reagent, such as **2**, and a bifunctional electrophile, e.g. R_2SiCl_2, can take two competing courses; namely, to form a polymeric or oligomeric material, or to produce a cyclic structure. Here we report on the remarkable tendency of the lithiooxyaryllithium **2** to form seven-membered heterocyclic rings containing N, O, and Si, by reaction with dichlorodialkylsilanes or silicon tetrachloride. As compounds with heterocyclic rings containing N, O, and Si exhibit biological activity[1,2] or are useful as chemical modifiers,[3] the above mentioned reaction can provide a facile route to bioactive or other useful compounds of this type. Various syntheses of compounds with a 4-, 5-, 6- and 7-membered heterocyclic ring containing N, O, and Si have previously been reported.[2-4] However, specific information concerning the syntheses of benzoxazasilepines, compounds with a 7-membered heterocyclic ring, is rather scarce.[5]

Specifically, we report a very simple preparation of 2,5,1-benzoxazasilepines **3** and the silaspiro analogue **4** by a ring closure reaction of *o*-lithio-*N*-(2-lithiooxyethyl)-*N*-methyl-aniline **2** with R_2SiCl_2 (R = Me, Et, Ph) or $SiCl_4$, respectively (Scheme 1). Even when we carried out the reaction under conditions favorable for the formation of polymeric materials, we still obtained cyclic products.

Scheme 1



1 **2** **3a** (R = Me), **3b** (R = Et), **3c** (R = Ph) **4**

The lithiooxyaryllithium **2** was made by *ortho*-lithiation[6] of **1** by *n*-BuLi in ether/methylcyclohexane. The reaction of **2** with 1 molar equivalent of R_2SiCl_2 (R = Me, Et, Ph) or 0.5 molar equivalents of $SiCl_4$ at -78 °C to room temperature afforded the corresponding benzoxazasilepines **3** in yields between 53-62 %, or the silaspiro compound **4** in 44 % yield.[7] To the best of our knowledge, analogues of benzoxazasilaspiro compounds have not previously been reported. The reaction of **2** with Me_2SiCl_2 was carried out also under conditions favorable for the formation of polymeric material, by means a dropwise addition of a solution of Me_2SiCl_2 in methylcyclohexane to the solution of **2** at room temperature. Even under these conditions, the cyclic product **3a** was produced in a yield of 32 % together with other compounds of higher molecular weight which were not further investigated. It is of importance also to mention that the organolithium **2** shows a higher tendency to form cyclic products than the corresponding organomagnesium reagent. An overnight reaction of **2** with an equivalent amount of magnesium bromide at room temperature and subsequent addition of Me_2SiCl_2 under identical conditions as in the reaction of the organolithium **2** with Me_2SiCl_2, yielded the cyclic product **3a** in 22 % yield.

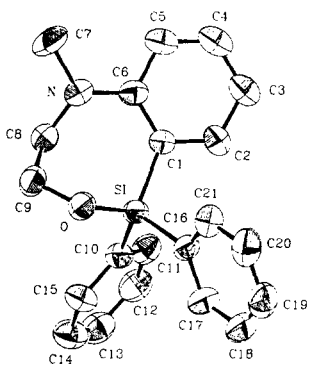


Fig 1. ORTEP drawing of 3c at 50% probability level.

Metal alkoxides are known to form complexes with organolithium reagents[8] and to affect their reactivity,[9] and so one is tempted to attribute the pronounced tendency of **2** to form cyclic products with the aforementioned electrophiles to an intramolecular Li···OLi interaction.[10]

The crystal structure of **3c** was of interest as a representative compound of these new benzoxazasilepines. Suitable crystals for an X-ray crystal structure determination were obtained after recrystallization of **3c** from isopropanol. The crystal structure of **3c** is shown in Figure 1.[11] The coordination sphere around the silicon atom is tetrahedral and the Si-C bond distances have normal values. The silicon atom is almost coplanar with the planes of the aromatic rings A (C1-C6), B (C10-C15), and C (C16-C21); the distances of the silicon atom from the planes A, B, and C are 0.26, 0.12, and 0.02 Å, respectively.

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7. Preparation of **3** and **4:** To a solution of **1** (usually 6 mmol) in ether (15 mL) under argon, 2.17 molar equivalents of *n*-butyllithium (1.87 M in methylcyclohexane) was added at -78 °C, after which it was stirred at room temperature for 24 h and then refluxed for 2.5 h, yielding the organolithium **2**. Then the solution of **2** was cooled to -78 °C and 0.94 molar equivalents of R_2SiCl_2 (R = Me, Et, Ph) or 0.46 molar equivalents of $SiCl_4$ (0.82 M in methylcyclohexane) was added, after which it was warmed slowly to room temperature and stirred overnight. The volatile materials were removed by evaporation, cold water and dichloromethane were added, the organic layer was dried over Mg_2SO_4, filtered and evaporated to dryness, yielding the crude product. Isolation of pure product was carried out by distillation (**3a**, yield 53%; **3b**, yield 54%) or recrystallization (**3c**, yield 62%; **4**, yield 44%). Data for **3** and **4**. **3a:** bp 75 °C (0.5 mm Hg). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.31 - 7.26 (m, 2H, H_{arom}), 6.93 - 6.88 (m, 2H, H_{arom}), 3.96 (t, ^3J = 4.6 Hz, 2H, CH_2O), 3.27 (t, ^3J = 4.6 Hz, 2H, CH_2N), 2.96 (s, 3H, NCH_3), 0.35 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 157.52, 134.21, 130.12, 129.12, 119.99 and 114.65 (arom), 64.69 (CH_2O), 60.53 (CH_2N), 40.65 (NCH_3), -0.44 ($Si(CH_3)_2$). GC-MS (EI): *m/z* (relative intensity) 207 (M^+, $C_{11}H_{17}NOSi$, 100). Anal. Calcd for $C_{11}H_{17}NOSi$: C, 63.72; H, 8.26; N, 6.76. Found: C, 63.40; H, 8.39; N, 6.86. **3b:** bp 101-104 °C (0.6 mm Hg). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.29 - 7.26 (m, 2H, H_{arom}), 6.91 - 6.86 (m, 2H, H_{arom}), 3.97 (t, ^3J = 4.6 Hz, 2H, CH_2O), 3.26 (t, ^3J = 4.6 Hz, 2H, CH_2N), 2.95 (s, 3H, NCH_3), 1.00-0.95 (m, 6H, $Si(CH_2CH_3)_2$), 0.86-0.79 (m, 4H, $Si(CH_2CH_3)_2$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 157.87, 134.56, 130.00, 126.84, 119.71 and 114.56 (arom), 64.88 (CH_2O), 60.65 (CH_2N), 40.65 (NCH_3), 6.91 ($Si(CH_2CH_3)_2$), 6.33 ($Si(CH_2CH_3)_2$). GC-MS (EI): *m/z* (relative intensity) 235 (M^+, $C_{13}H_{21}NOSi$, 36). Anal. Calcd for $C_{13}H_{21}NOSi$: C, 66.33; H, 8.99; N, 5.95. Found: C, 65.25; H, 9.38; N, 6.27. **3c:** mp 120-123 °C (*i*-PrOH). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.53 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 4H, H_{arom}), 7.43 -7.31 (m, 7H, H_{arom}), 7.19 (dd, ^3J = 7.3 Hz, ^4J = 1.6 Hz, 1H, H_{arom}), 6.94 (d, ^3J = 8.2 Hz, 1H, H_{arom}), 6.83 (t, ^3J = 7.3 Hz, 1H, H_{arom}), 4.10 (t, ^3J = 4.6 Hz, 2H, CH_2O), 3.37 (t, ^3J = 4.6 Hz, 2H, CH_2N), 2.93 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 158.37, 137.08, 135.45, 135.109, 130.71, 129.72, 127.70, 123.55, 119.33 and 114.53 (arom), 65.58 (CH_2O), 60.26 (CH_2N), 40.38 (NCH_3). GC-MS (EI): *m/z* (relative intensity) 331 (M^+, $C_{21}H_{21}NOSi$, 100). Anal. Calcd for $C_{21}H_{21}NOSi$: C, 76.09; H, 6.39; N, 4.23. Found: C, 75.96; H, 6.47; N, 4.52. **4:** mp 122-124 °C (*i*-PrOH). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.33 - 7.28 (m, 4H, H_{arom}), 6.88 (d, ^3J = 8.2 Hz, 2H, H_{arom}), 6.78 (t, ^3J = 7.2 Hz, 2H, H_{arom}), 4.13-4.09 (m, 4H, CH_2O), 3.65-3.56, 3.40-3.32 (m, m, 4H, CH_2N), 3.02 (s, 6H,

NCH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 157.27, 137.15, 130.74, 122.88, 119.21 and 114.12 (arom), 64.97 (CH_2O), 59.84 (CH_2N), 40.37 (NCH_3). GC-MS (EI): *m/z* (relative intensity) 326 (M^+, $C_{18}H_{22}N_2O_2Si$, 100). Anal. Calcd for $C_{18}H_{22}N_2O_2Si$: C, 66.22; H, 6.79; N, 8.58. Found: C, 65.82; H, 6.91; N, 8.55.

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11. X-ray structural analysis for **3c**: $C_{21}H_{21}NOSi$, 0.20 × 0.30 × 0.55 mm, monoclinic, space group $P2_1/c$, a = 11.489(2), b = 14.122(2), c = 11.564(2) Å, β = 108.104(6)°, V = 1783.3(5) $Å^3$, Z = 4, d_{calcd} = 1.235 gcm^{-3}, 2θmax =50°, Mo Ka radiation (λ = 0.710730 Å), T = 298 K, θ-2θ scan, 3347 measured reflections, 3138 independent reflections (Rint = 0.0143) all included in the refinement, Lorentz, polarization and ψ-scan absorption corrections were made, μ = 0.138 mm^{-1}, $[\Delta/\sigma]_{max}$ = 0.022, 301 parameters refined, R1 = 0.0363 (for 2421 reflections with $I > 2\sigma(I)$), wR2 = 0.0933 (on F^2). Max./min. residual peaks in the final difference map 0.255/-0.207 $eÅ^3$. A crystal of **3c** was mounted in air and covered with epoxy glue. The structure was solved by direct methods with SHELXS-86 and refined by full-matrix least-squares techniques on F^2 by using SHELXL-93. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located by diference maps and their positions were refined isotropically. Crystallographic data (exluding stucture factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre.

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