Heterocycles

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Nucleophilic Aromatic Substitution Reactions of 1,2-Dihydro-1,2-Azaborine**

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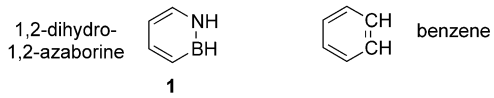
1,2-Dihydro-1,2-azaborine (**1**) is a benzene isostere in which a C=C unit of benzene is replaced with an isoelectronic B−N unit.[1,2] As part of our program to develop the basic science



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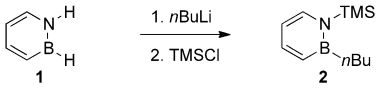
and applications of 1,2-azaborine heterocycles,[3–6] we have focused on expanding the scope of synthetically accessible 1,2-azaborines and investigating the aromatic character of this family of heterocycles.

Among the four commonly investigated criteria for aromaticity (structure, magnetism, energy, and reactivity), we have determined that 1,2-azaborines exhibit delocalized bonding,[7] have appropriate predicted NICS (−7.27 ppm; nucleus-independent chemical shift) values,[8] and have an experimentally determined resonance stabilization energy of 16.6 kcal mol^{-1},[9] which is consistent with significant aromatic character. With regard to the reactivity criterion, Ashe and co-workers have demonstrated that substituted 1,2-azaborines undergo electrophilic aromatic substitution reactions.[10] The parent 1,2-dihydro-1,2-azaborine (**1**) has recently been isolated.[8] However, there have been no reactivity studies performed on **1** to date. We are particularly interested in investigating the reactivity of parent **1** for two reasons: 1) to explore the fundamental reactivity differences between **1** and benzene, and 2) to develop new synthetic methods to access novel 1,2-azaborine derivatives. Herein we report that **1** readily undergoes nucleophilic aromatic substitution (SNAr) reactions to furnish new 1,2-azaborine compounds. We also present evidence that the substitution involves an addition-elimination mechanism consistent with SNAr.

In our initial investigation, we discovered that when **1** was treated with 1 equivalent of *n*BuLi in Et_2O followed by 4 equivalents of trimethylsilyl chloride, the substituted heterocycle **2** was formed in 17% yield (Table 1, entry 1). A dramatic increase in product yield was observed when 2 equivalents of the nucleophile were used (entry 2). However, an additional increase in the amount of nucleophile used led to a substantial decrease in product yield (entry 3). A survey of solvents revealed that Et_2O is the solvent of choice among etheral and hydrocarbon solvents (entries 4–7 versus entry 2). We also determined that the optimal temperature for performing this substitution reaction is −30 °C; increasing or lowering the reaction temperature resulted in diminished yield of **2** (entries 8 and 9 versus entry 2).

Table 1: Optimization survey of SNAr reaction.[a]



1 **2**

Entry	Solvent	Equiv of *n*BuLi	*T* [°C]	Yield [%][b]
1	Et_2O	1	−30	17
2	Et_2O	2	−30	94
3	Et_2O	3	−30	71
4	THF	2	−30	67
5	pentanes	2	−30	11
6	toluene	2	−30	53
7	DME	2	−30	86
8	Et_2O	2	25	46
9	Et_2O	2	−78	77

[a] For reaction conditions see the Supporting Information. [b] Yields determined by GC analysis of the reaction mixture versus pentadecane as a calibrated internal standard. Yields are average of two runs. DME = dimethoxy ether, THF = tetrahydrofuran, TMS = trimethlsilyl.

The formation of compound **2** is consistent with a nucleophilic aromatic substitution in which the hydride on boron is serving as a leaving group. The ease with which this substitution occurs (i.e., at −30 °C) is distinct from the reactivity of benzene. The corresponding substitution reaction with benzene typically requires a stronger nucleophile (e.g., *t*BuLi) and much harsher conditions (e.g., reflux in decalin at 165 °C for 20 h).[11,12]

Having established the optimal reaction conditions for this new substitution reaction, we then sought to expand its substrate scope. As can be seen from Table 2, oxygen-based nucleophiles are suitable for this reaction, including sodium

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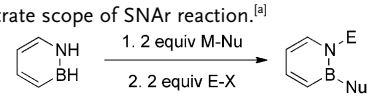
Table 2: Substrate scope of SNAr reaction.[a]

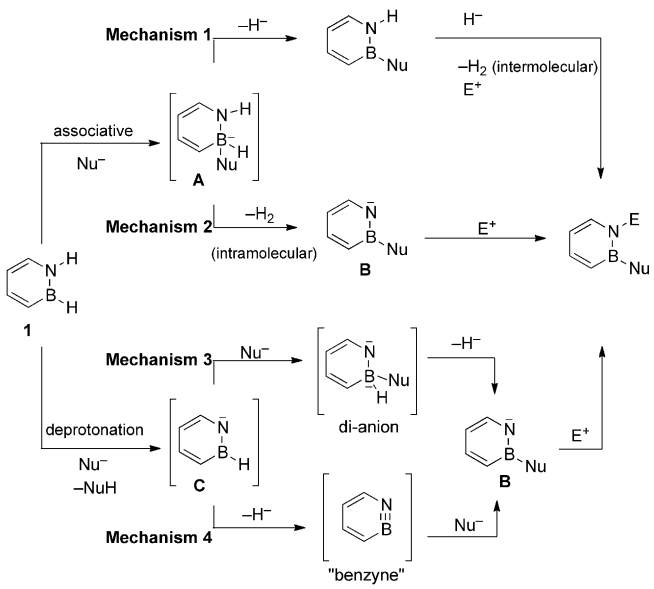


Entry	M–Nu	E–X	Yield [%][b]
1	Na–O*t*Bu	H–Cl	63
2	K–Oallyl	H–Cl	79
3	Li–*t*Bu	H–Cl	81
4	Li–*n*Bu	H–Cl	80
5	Li–Ph	H–Cl	98
6	BrMg–vinyl	H–Cl	59
7	BrMg–≡–Ph	H–Cl	71
8	Li–*n*Bu	TMS–Cl	89
9	Li–*n*Bu	Me–I	67
10	Li–*n*Bu	H–Cl	60

[a] For reaction conditions see the Supporting Information. [b] Yield of isolated product. Average of two runs.

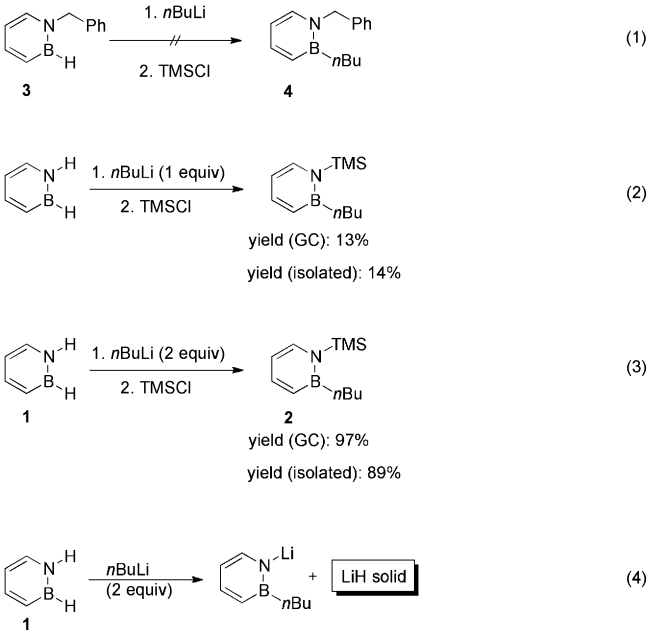
tert-butyloxide (entry 1) and potassium allyloxide (entry 2). Carbon nucleophiles are very effective reaction partners. Hindered branched (entry 3), less-hindered linear (entry 4) sp^3-hybridized organolithium reagents, as well as sp^2-hybridized phenyllithium (entry 5) furnish the desired substituted products in high yield. Grignard reagents also give the corresponding products in moderate to good yield (entries 6 and 7). Noteworthy is the synthesis of B–N styrene[13] (entry 6) and a novel B–N tolan derivative (entry 7). The scope with respect to the electrophile at the nitrogen position includes H, TMS, Me, and Bn (entries 4, 8–10).

Scheme 1 illustrates four possible mechanistic scenarios for the observed substitution reaction. Mechanism 1 involves a simple displacement of the B–H bond with the nucleophile (via intermediate **A**) with subsequent intermolecular deprotonation by the released metal hydride and quenching with the electrophile. In Mechanism 2, intermediate **A** releases H_2 in an intramolecular fashion to generate intermediate **B**, which is then quenched with the electrophile. In Mechanisms 3 and 4, 1 equivalent of the nucleophile serves first as a base to remove the N–H proton to produce **C**. Subsequently in Mechanism 3, the second equivalent of the nucleophile displaces the B–H bond (via a "di-anion") to produce intermediate **B**. Alternatively, intermediate **C** can eliminate a hydride to yield a "benzyne"-type 1,2-azaborine[14] which then reacts with the nucleophile to produce **B** (Mechanism 4).



Scheme 1. Possible reaction pathways of the substitution reaction.

In our mechanistic studies we initially focused on the reaction of **1** with *n*BuLi and TMSCl. To test the role of the NH group, we synthesized the N-benzyl-protected 1,2-azaborine **3** [Eq. (1)], which was then subjected to the SNAr reaction conditions (1 and 2 equivalents of *n*BuLi and subsequent quenching with TMSCl). Interestingly, the substituted product **4** was not formed [Eq. (1)].[15] This experimental observation is inconsistent with Mechanism 1, which should be largely independent of the nature of the N substituent. We determined that 2 equivalents of nucleophile are necessary to achieve a high yield of **2** [Eq. (2) versus (3)]. This result is incompatible with Mechanism 2, which requires only 1 equivalent of the nucleophile. Furthermore, when **1** was treated with 2 equivalents of *n*BuLi, a fine white powder precipitated out of solution [Eq. (4)]. IR analysis of this powder indicates formation of LiH.[16,17] The observation of LiH is again inconsistent with Mechanism 2.



Whereas the experiments illustrated in equations (1)–(4) are inconsistent with the proposed Mechanisms 1 and 2, they are in agreement with Mechanisms 3 and 4. We were not successful in trapping the "benzyne"-type 1,2-azaborine intermediate using a number of trapping agents.[18] Therefore, we used calculations to help determine the most likely mechanism for the SNAr reaction. The computationally determined energy diagram (Figure 1) at the G3MP2[19] plus COSMO[20] level indicates that the formation of the "benzyne"-type 1,2-azaborine is a high-energy process. In contrast, the formation of the "di-anion" intermediate is energetically very favorable. Based on all of the available data, we believe

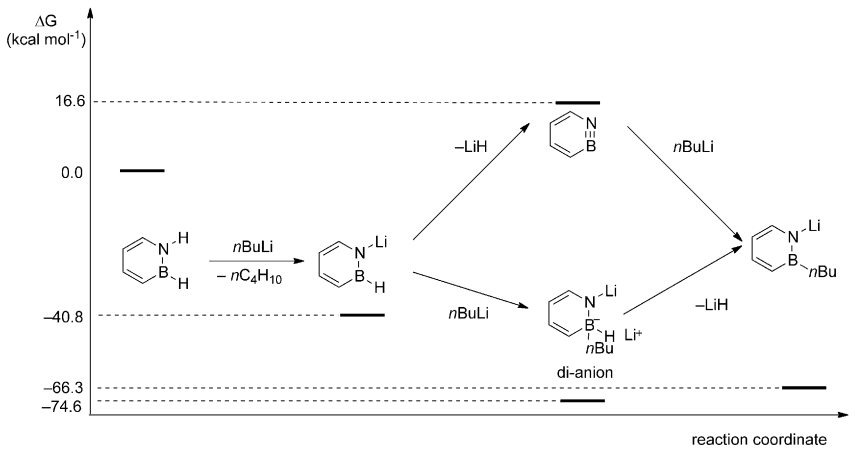
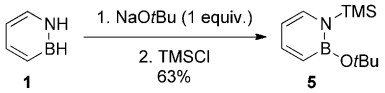


Figure 1. Calculated free energies in Et_2O (G3 MP2 + COSMO solvation model at the B3LYP-DZVP2 level of theory, see the Supporting Information) of the proposed intermediates in the SNAr reaction at 298 K.

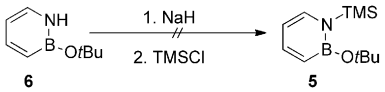
that Mechanism 3 is the most likely mechanism for the conversion of **1** into **2**.

The pK_a value of the N–H proton in 1,2-azaborines has been determined to be approximately 26.[21] Alkoxide nucleophiles are not basic enough to deprotonate the N–H of **1**. Consequently, Mechanisms 3 and 4 cannot be used to explain the SNAr reactivity with alkoxide nucleophiles (Table 2, entries 1 and 2). To investigate the mechanism for oxygen-based nucleophiles, we focused on the reaction of **1** with NaO*t*Bu and TMSCl. In this case, we determined that 1 equivalent of nucleophile is sufficient to furnish the substituted product **5** in comparable yield as when 2 equivalents of nucleophile were used [Eq. (5) versus Table 2,



(5)

entry 1]. Furthermore, the addition of NaO*t*Bu to **1** results in release of significant amount of gas consistent with H_2 formation. Mechanisms 1 and 2 are both consistent with these observations, the difference being whether H_2 is released in an intramolecular fashion (Mechanism 2) or intermolecularly through the formation of NaH (Mechanism 1). To address this, we added NaH to compound **6** and then addition of TMSCl [Eq. (6)]; the starting material **6** was



(6)

the only observed species of this reaction by NMR spectroscopy. If Mechanism 1 were operating, we would expect formation of **5**. Based on these observations, we conclude that substitution reactions of **1** with alkoxide nucleophiles are most consistent with Mechanism 2.

In summary, we have presented the first reactivity study of 1,2-dihydro-1,2-azaborine (**1**). We demonstrated that **1** can readily undergo nucleophilic aromatic substitution reactions under mild reaction conditions, a reactivity pattern that is distinct from its isostere benzene. This new reactivity allows access to novel 1,2-azaborine structures, including a B–N tolan derivative. By using a combined experimental and computational approach, we determined the most likely substitution mechanisms of **1** with both carbon- and oxygen-based nucleophiles. Current efforts are directed at utilizing this reactivity for incorporating 1,2-azaborines into biologically relevant and materials related molecules.

Experimental Section

Synthesis of compound **2**: In a glove box, a 4 mL vial was charged with a solution of **1** (0.020, 0.26 mmol), and ether (1.0 mL). *n*BuLi (1.6 M in Et_2O, 0.320 mL, 0.510 mmol) was added to the solution at −30 °C, and the mixture was allowed to stand at −30 °C for 3 h. Subsequently, a cold solution of trimethylsilyl chloride (0.111 g, 1.02 mmol in 0.5 mL Et_2O) was slowly added to the reaction mixture. The resulting mixture was allowed to stand for 1 h at −30 °C, and then warmed to room temperature and stirred for an additional hour. At the conclusion of the reaction, the mixture was concentrated under reduced pressure, and the crude material was subjected to silica gel chromatography using pentanes as the eluent, thus yielding **2** (0.047 g, 89 %) as a clear colorless oil.

^{1}H NMR (500 MHz, C_6D_6): $\delta = 7.59$ (dd, $^3J_{HH} = 6.3$, 4.8 Hz, 1H), 7.14 (d, $^3J_{HH} = 6.5$ Hz, 1H), 7.03 (d, $^3J_{HH} = 11.1$ Hz, 1H), 6.22 (d t, $^3J_{HH} = 1.18$, 5.23 Hz, 1H), 1.71(m, 2H), 1.48 (m, 2H), 1.38 (t, $^3J_{HH} = 8.3$ Hz, 2H), 0.99 (t, $^3J_{HH} = 7.4$ Hz, 3H), 0.17 ppm (s, 9H). ^{13}C NMR (125 MHz, C_6D_6): $\delta = 143.2$, 136.8, 130 (br), 111.3, 30.1, 26.4, 21 (br), 14.4, 1.5 ppm. ^{11}B NMR (96.3 MHz, C_6D_6): $\delta = 41.4$ ppm. FTIR (thin film) 2958, 2872, 1608, 1508, 1448, 1401, 1286, 1253, 1216, 1149, 1105, 1007, 991, 845, 765, 736, 685 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{22}BNSi$ [M^+] 207.16146, found 207.16073.

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