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Open-Flask Synthesis of Amine–Boranes via Tandem Amine–Ammonium Salt Equilibration–Metathesis

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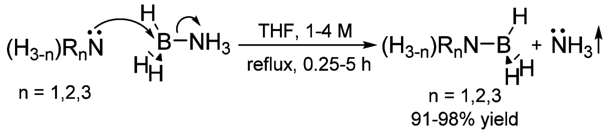
Ⓢ *Supporting Information*

ABSTRACT: An amine–ammonium salt equilibration–metathesis sequence provides high-purity amine–boranes in excellent yields from sodium borohydride in refluxing reagent-grade tetrahydrofuran in an open flask.

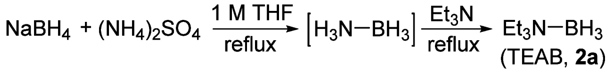
The past decade has seen amine–boranes receive considerable attention because of their potential as safe carriers of hydrogen for energy storage.[1] In addition to their traditional use as borane carriers for exchange reactions,[2] applications as precursors to high-performance polymers via catalytic dehydrocoupling[3] and as reagents for novel organic transformations[4] have made them even more relevant. They have also gained significance as reagents of choice for the syntheses of metal nanoparticles[5] and nucleic acid analogues[6] and electroless plating.[7] Furthermore, amine–boranes and their derivatives display a wide range of biological properties, such as antiviral, antineoplastic, antiinflammatory activities, etc.[8] Recently, we reported on the prospect of amine–boranes as hypergolic bipropellants with consistently low ignition delays.[9] This finding led us to the decades-old quest to replace toxic hydrazine and its derivatives as hypergolic fuels for space and missile applications.[10] To expand our study, the preparation of large quantities of a variety of amine–boranes became a necessity.

Scheme 1. Transamination of AB[12]



The repeated large-scale preparation of ammonia borane (AB)[11] to obtain multigram quantities of the corresponding amine–boranes via transamination[12] (Scheme 1) hampered progress. This prompted us to adopt or develop either a more efficient AB synthesis or a direct synthesis of amine–boranes. We opted for the latter approach. Unfortunately, the reported metathesis of ammonium salts with sodium borohydride (SBH)[13] lacks generality because of the poor solubility of SBH and alkylammonium salts in common ether solvents, such as diethyl ether (Et_2O) and tetrahydrofuran (THF).[14] This is circumvented by using either more reactive, but flammable lithium borohydride[15] or SBH in dimethoxyethane,[16] adding to the cost of the product. Also, the lack of commercial availability of the necessary amine salts restricts its wide applicability. Additives such as 18-crown-6 have been used to catalyze the reaction in Et_2O.[17] Another reported modification involves addition of organic acids to prepare specific amine–boranes.[18]

Scheme 2. Proposed in Situ AB Synthesis–Transamination Sequence



$$NaBH_4 + (NH_4)_2SO_4 \xrightarrow[\text{reflux}]{\text{1 M THF}} [H_3N–BH_3] \xrightarrow[\text{reflux}]{Et_3N} \underset{\text{(TEAB, \textbf{2a})}}{Et_3N–BH_3}$$

Table 1. Effect of the Temperature on the TEAB Synthesis[a]

entry	time (h)	temperature (°C)	TEAB–AB ratio[b]
1	1	reflux	99:1
2	4	reflux	100:0
3	1	rt	85:15
4	4	rt	85:15
5	24	rt	86:14
6	1	40	88:12
7	4	40	88:12
8	24	40	91:9

[a]Reactions were performed using 5 mmol each of SBH, $(NH_4)_2SO_4$, and TEA in 5 mL of THF, open to air. [b]On the basis of the ^{11}B NMR spectra of reaction aliquots.

With in situ AB synthesis, followed by transamination (Scheme 2), being envisioned, 1 equiv each of SBH, ammonium sulfate, and *N,N,N*-triethylamine (TEA, **1a**) were refluxed in 1 M THF.[19] All of SBH was consumed within 1 h, and we were delighted to observe, by ^{11}B NMR spectroscopy, the formation of 99% TEA–borane (TEAB, **2a**) and 1% AB (Table 1, entry 1). Continued refluxing for an additional 3 h converted the traces of AB to TEAB (Table 1, entry 2). Filtering off the solids and removing the solvent provided 90% yield of pure **2a** (^{11}B, ^{1}H, and ^{13}C NMR and hydride analysis). Notably, no dehydrogenation byproducts were observed even in the presence of mildly acidic $(NH_4)_2SO_4$.[20]

Unexpectedly, when the reaction was carried out in THF at room temperature (rt; Scheme 3), all of SBH was consumed within 1 h, with the concurrent evolution of 1 equiv of H_2. Spectroscopic analysis revealed the formation of a mixture of TEAB and AB in a 17:3 ratio, which remained essentially unchanged over the next 3 h (Table 1, entries 3 and 4),

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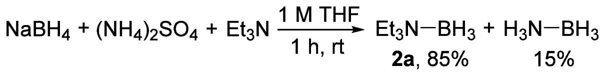
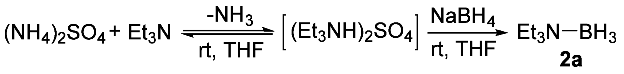
Scheme 3. Room Temperature Formation of a TEAB−AB Mixture



$$NaBH_4 + (NH_4)_2SO_4 + Et_3N \xrightarrow[1\ h,\ rt]{1\ M\ THF} \underset{\mathbf{2a},\ 85\%}{Et_3N{-}BH_3} + \underset{15\%}{H_3N{-}BH_3}$$

suggesting that *the reaction could not have proceeded via the formation of AB as envisioned in Scheme 2*. The extremely slow transamination of AB with TEA even after 24 h at rt (Table 1, entry 5)[21] formed the basis for this assumption. Monitoring the reaction temperature inside the flask revealed negligible change, thus negating its role in the reaction progress. The formation of TEAB at rt (Scheme 3) can only be rationalized by invoking an amine−ammonium salt equilibrium,[22] followed by salt metathesis of triethylammonium sulfate with SBH (Scheme 4). Under reflux conditions, either the amine−salt exchange is facilitated or any AB formed undergoes facile transamination[12] with the remaining TEA. Refluxing is essential because maintaining the temperature at 40 °C[23] resulted only in a 91:9 mixture of TEAB and AB in 24 h (Table 1, entry 8). Extended refluxing does not deteriorate TEAB (^{11}B NMR spectroscopy).[24]

Scheme 4. Tandem Amine−Ammonium Salt Equilibration−Metathesis



$$(NH_4)_2SO_4 + Et_3N \underset{rt,\ THF}{\overset{-NH_3}{\rightleftharpoons}} \left[(Et_3NH)_2SO_4\right] \xrightarrow[rt,\ THF]{NaBH_4} \underset{\mathbf{2a}}{Et_3N{-}BH_3}$$

Several ammonium salts, such as ammonium chloride, fluoride, formate, and carbonate, were then scanned for the salt-exchange reaction under varying conditions. The results, summarized in Table 2, show that ammonium chloride and sulfate provide the best outcomes (entries 1 and 9), with the reaction with the latter being faster. Significantly, the reaction stoichiometry revealed that, *unlike for the AB synthesis where 2 equiv of ammonium ion were necessary,*[11a,b] *herein 1 equiv is sufficient to achieve optimal yields*, thus decreasing the overall cost of the process. The reaction is extremely slow in refluxing Et$_2$O, requiring 4 days for completion (entry 13). The optimal concentration for best yields and fast reaction (entry 10, highlighted in boldface) is 1 M THF.

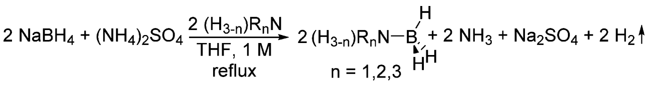
Table 2. Optimization of Conditions for the Preparation of TEAB from SBH[a]

entry	NH$_4$X	SBH−NH$_4$X ratio	time (h)	yield[b] (%)
1	NH$_4$Cl	1:2	8	87
2	NH$_4$Cl	1:1	20[c]	67
3	NH$_4$F	1:2	4	97[d]
4	NH$_4$F	1:1	2	74[d]
5	NH$_4$OCOH	1:2	4	110[e]
6	NH$_4$OCOH	1:1	3	71[e]
7	(NH$_4$)$_2$CO$_3$	1:1	6	78
8	(NH$_4$)$_2$CO$_3$	2:1	20[c]	53
9	(NH$_4$)$_2$SO$_4$	1:1	4	90
10	**(NH$_4$)$_2$SO$_4$**	**2:1**	**6**	**90**
11	(NH$_4$)$_2$SO$_4$	2:1	4[f]	85
12	(NH$_4$)$_2$SO$_4$	2:1	16[g]	92
13	(NH$_4$)$_2$SO$_4$	2:1	96[h]	88

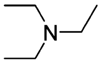
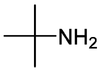
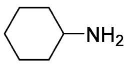
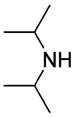
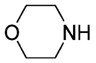
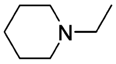
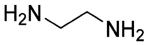
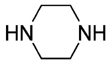
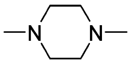
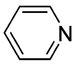
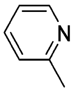
[a] Reactions were performed using 5 mmol each of SBH and TEA in 5 mL of THF under reflux, open to air. [b] Isolated yield. [c] Peaks corresponding to trace quantities of SBH were present in the ^{11}B NMR spectrum. [d] 96% purity (^{11}B NMR). [e] Product contains a triethylammonium formate impurity. [f] 2 M reaction. [g] 4 M reaction. [h] Reaction in Et$_2$O.

Having standardized the conditions for TEAB synthesis, the protocol was applied to a variety of 1°, 2°, and 3° alkylamines to demonstrate its generality as well as to prepare all of the amine−boranes necessary for our project.[9] As can be seen from Table 3, most alkylamines gave excellent yields of the corresponding amine−boranes (**2a**−**2f**, entries 1−6). Because of the distinct advantages of diamine−bisboranes as potential hybrid rocket fuels,[25] 1°, 2°, and 3° diamines were included in our study and the corresponding bisboranes were isolated in high yields (**2g**−**2i**, entries 7−9). Extensive application for reductive amination[4j] prompted the inclusion of heteroarylamines, such as pyridine (**1j**) and 2-picoline (**1k**), yielding the corresponding borane adducts (**2j** and **2k**, respectively, entries 10 and 11) in near-quantitative yields.

Table 3. Synthesis of Amine−Boranes from SBH[a]



$$2\,NaBH_4 + (NH_4)_2SO_4 \xrightarrow[\substack{THF,\ 1\ M\\ reflux}]{2\,(H_{3-n})R_nN} 2\,(H_{3-n})R_nN{-}BH_3 + 2\,NH_3 + Na_2SO_4 + 2\,H_2\uparrow \quad n = 1,2,3$$

entry	amine		time (h)	amine-borane	
	no	amine		no	yield[b] (%)
1	**1a**		6	**2a**	90
2	**1b**	 	6	**2b**	93
3	**1c**	 	6	**2c**	98
4	**1d**	 	6	**2d**	80
5	**1e**	 	6	**2e**	98
6	**1f**	 	6	**2f**	87
7	**1g**	 	8	**2g**	83[c]
8	**1h**	 	8	**2h**	82
9	**1i**	 	8	**2i**	97[d]
10	**1j**	 	8	**2j**	99
11	**1k**	 	8	**2k**	93

[a] Reactions were performed using 5 mmol of SBH, 2.5 mmol of (NH$_4$)$_2$SO$_4$, and 5 mmol of amine/2.5 mmol of diamine in 5 mL of THF under reflux, open to air. [b] Isolated yield. [c] See the Supporting Information. [d] A mixture of diastereomers.

In conclusion, we have developed an economical protocol to prepare a variety of aliphatic and heteroarylamine−boranes in excellent yields directly from SBH and the corresponding amines. In addition to the wide substrate scope, the described amine−ammonium salt equilibrium−metathesis protocol has several significant benefits: (i) open-flask conditions; (ii) atom-economical use of stoichiometric ammonium sulfate; (iii) use of reagent-grade THF; (iv) no tedious purification required beyond filtration; (v) recovery and recycling of the solvent over multiple runs. The viability of this convenient preparation of amine−boranes, demonstrated with a mole-scale synthesis of TEAB (**2a**),[26] should make them readily available and aid the advancement of hydrogen energy and propellant research. In addition, this could also find applications in the potential synthesis of 1° amineborane-derived borazines.[27]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Representative procedures and characterization data for amine−boranes. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.5b00572.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Ei-ichi Negishi on the occasion of his 80th birthday.

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(26) ***Caution!*** *Adequate safety precautions should be taken while carrying out these experiments. Because of the toxic and corrosive nature of ammonia and the liberation of large quantities of highly flammable hydrogen, the reactions were carried out in a well-ventilated hood, with the reaction vessel outlet directly leading into the hood exhaust.*

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