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Potassium haloalkyltrifluoroborate salts: synthesis, application, and reversible ligand replacement with MIDA

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ABSTRACT

Increased interest in boron-containing pharmaceuticals has created a need for efficient syntheses of organoboron compounds. This article describes one- and two-pot syntheses of potassium haloalkyltrifluoroborate salts, important building blocks for the incorporation of boron into complex molecules. The sequential, high-yielding procedures (65% to 92%) involve hydroboration of commercially available haloalkenes with dichloroborane (prepared in situ from triethylsilane and boron trichloride), followed by treatment of the crude hydroboration products with potassium hydrogen difluoride. A hexaethyldisiloxane byproduct that hinders the isolation of the desired boronic acids and esters was identified and easily removed via this procedure. The value of the potassium haloalkyltrifluoroborate salts is subsequently demonstrated in example substitution reactions, which were followed by a reversible ligand replacement with *N*-methyliminodiacetic acid (MIDA). Reversibly switching these orthogonal boron protecting groups enables full exploitation of their favorable chemical properties, effectively bridging these platforms and further expanding their scope and utility.

Introduction

Boronic acids and their derivatives have recently emerged as biologically interesting moieties due to their increasing use as pharmaceutical agents.[1] To date the FDA has approved two drugs containing boron atoms: Velcade®, a peptidyl boronic acid treatment for multiple myeloma,[2] and Kerydin™, an oxaborole-containing antifungal.[3] The approval of these drugs and other studies[4] address years of toxicity concerns associated with boron.[1a,2] In fact, the primary boron-containing metabolite of Velcade® was identified as boric acid,[5] which exhibits similar toxicity to common table salt (oral LD_{50} in rats is 2660 mg/kg for boric acid while it is 3000 mg/kg for table salt).[2] The incorporation of boron in pharmaceutical agents has been motivated by its intriguing properties, the most interesting of which is the boron atom's Lewis acidic character. Under physiologically relevant conditions, a neutral, trigonal planar boron center contains a vacant p-orbital that may interact with Lewis bases. Boron's vacant p-orbital has been shown to engage in reversible, dative bonding with Lewis basic amino acids in the active sites of enzymes to form anionic, tetrahedral boron–enzyme complexes.[1]

While investigating nucleophilic substitution reactions with boron-containing electrophiles as a methodology for synthesizing new boron-containing pharmaceutical agents, it was found that this chemistry presented several difficulties. MIDA boronates[6] and potassium organotrifluoroborate salts[7] have been developed to mask one of these difficulties, the susceptibility of boron's empty p-orbital to nucleophilic attack.[6d,8] Yet both have limitations that are problematic in multistep organic syntheses: potassium organotrifluoroborate salts are incompatible with silica gel chromatography and MIDA boronates are incompatible with hard nucleophiles. Initial experiments determined that haloalkyl MIDA boronates were not compatible with the basic conditions required for many substitution reactions; therefore, potassium haloalkyltrifluoroborate salts were examined more closely. Obtaining these reagents presented yet another difficulty because they are not commercially available and their corresponding boronic acids are relatively expensive. Consequently, their synthesis was envisioned via hydroboration of commercially available haloalkenes (Scheme 1, bottom). Reports of the hydroboration of haloalkenes have been related by others,[4b,8a,b,9] but the drawbacks of these reactions include the use of large boronate esters (i.e., pinacol) which lack atom economy, low yields and/or irreproducibility, expensive reagents, inadequate experimental details, or unpurified reaction products. We herein communicate an addition to the dearth of suitable haloalkene hydroboration reactions: a *sequential* synthesis of potassium haloalkyltrifluoroborate salts via hydroboration of haloalkenes **1a–c** with dichloroborane and exposure of the

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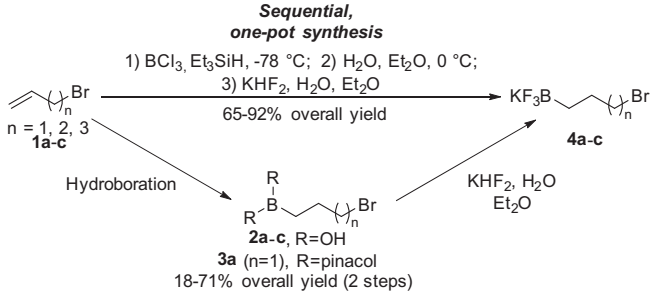


Scheme 1. The reported high yielding, *sequential* synthesis of potassium haloalkyltrifluoroborate salts (top) compared to a lower yielding, two-step procedure where the boron intermediates are isolated (bottom).

unpurified products to potassium hydrogen difluoride (Scheme 1, top). To illustrate their synthetic utility as boron building blocks, we present example substitution reactions with potassium haloalkyltrifluoroborate salts **4a–c**. Additionally, we report a reversible, one-step conversion of the substitution products to MIDA boronates (Tables 3 and 4), overcoming the purification limitations of the potassium organotrifluoroborate salts.

Results and discussion

Initial synthetic studies explored various hydroboration procedures with commercially available haloalkenes (allyl bromide, 4-bromo-1-butene, and 5-bromo-1-pentene, **1a–c**, respectively). Reactions with Wilkinson's catalyst and pinacolborane[10] resulted in decomposition, likely caused by poor catalyst chemoselectivity. Success was realized with $[Ir(cod)Cl]_2$ and pinacolborane,[9h] but high cost and modest yields discouraged further consideration. Additionally, use of catecholborane as the hydroboration reagent[4b] afforded good yields of the hydroboration product. However, hydrolysis or transesterification with pinacol presented catechol and benzoquinone contamination, which have been widely reported in the literature. Finally, use of commercially available dichloroborane dioxane[11] and dibromoborane dimethyl sulfide[12] complexes resulted in low yields and mixtures of products. Both the desired boronic acid and a borinic acid byproduct were observed. As previously discussed by Brown,[11a] the borinic acid byproducts are caused by disproportionation of the dihaloborane complexes.

Due to the difficulties encountered using standard hydroboration protocols with haloalkenes **1a–c**, dichloroborane was next examined as the hydroboration reagent. To avoid the disproportionation problems previously observed, dichloroborane was prepared in situ from BCl_3 and Et_3SiH (dichloroborane is also more reactive than the commercially available dihaloborane complexes).[9b] This reagent provided moderate to low yields of boronic acids **2a–c** or pinacol ester **3a** (Table 1) after aqueous work-up and purification via partitioning, recrystallization, or column chromatography. Low yields were caused by a rarely mentioned hydroboration byproduct: 1,1,1,3,3,3-hexaethyldisiloxane, or $(Et_3Si)_2O$. It was observed that the boronic acid and ester products were soluble in this byproduct, making purification challenging. In only one case was an acceptable yield of the hydroboration product obtained, boronic acid **2c** (Table 1). Here the crude mixture of the boronic acid and the $(Et_3Si)_2O$ byproduct was dissolved in water with heat, and the boronic acid was recrystallized to obtain significantly higher yields than were achieved with **2a** and **2b**. The longer alkyl chain ($n = 3$) may have resulted in decreased solubility of **2c** in water compared to **2a** and **2b**, allowing the recrystallization to occur. As expected, treatment of **2a–c** and **3a** with potassium hydrogen difluoride as previously related by Vedejs[13] and Molander[7a] (Scheme 1) proceeded without difficulty in moderate to high yields (Table 1).

The hydroboration complications using in situ prepared dichloroborane led to the examination of a *sequential* two-pot procedure that carried the crude hydroboration products forward through the potassium haloalkyltrifluoroborate salt synthesis (Table 2). The $(Et_3Si)_2O$ byproduct was expected to be inert under the subsequent reaction conditions of potassium hydrogen difluoride in ether and water. Additionally, $(Et_3Si)_2O$ would be easily removed from the reaction product via trituration due to its high ether solubility, contrary to the potassium haloalkyltrifluoroborate salts. The *sequential* haloalkyltrifluoroborate salt synthesis worked better than expected for boronic acids **2a** and **2b** (Table 2), with the overall yield being notably higher than when the boronic acid was first purified (Table 1). Unfortunately this two-step *sequential* procedure gave a relatively unimpressive yield of **4c**, 60%. While a modest yield was obtained with unpurified pinacol ester **3a** as the intermediate (65% for the two steps), further studies on the pinacol ester were not attempted due to the lower atom economy of this process. Note that a similar procedure to synthesize haloalkyl MIDA boronates was not fruitful.

With the success achieved carrying the crude hydroboration materials forward, it was postulated that a one-pot synthesis might be feasible. Here the hydroboration reaction was performed as previously described, but instead of an aqueous workup, the

Table 2
Comparison of potassium haloalkyltrifluoroborate salt syntheses via a two-pot *sequential* procedure versus one-pot *sequential* procedure

Compound $Br(CH_2)_{2+n}BF_3K$	n	Two-pot *sequential* procedure yield[a] (%)	One-pot *sequential* procedure yield[a] (%)
4a	1	74	65
4b	2	80	70
4c	3	60	92

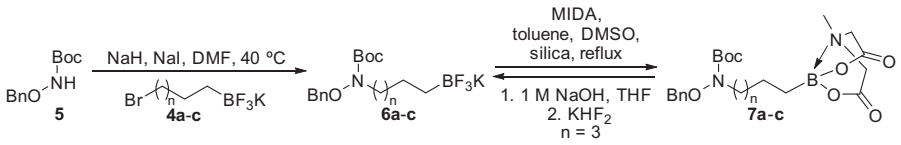
[a] Hydroboration was conducted with dichloroborane, prepared in situ from triethylsilane and boron trichloride. The *sequential* procedures take the unpurified hydroboration product immediately forward to the potassium haloalkyltrifluoroborate salt synthesis.

Table 1
Dichloroborane hydroboration of haloalkenes **1a–c** (with purification of the resulting boronic acids **2a–c** and ester **3a**) and subsequent synthesis of potassium haloalkyltrifluoroborate salts **4a–c**

Compound	n	R	$Br(CH_2)_{2+n}BR_2$ yield[a] (%)	Compound	$Br(CH_2)_{2+n}BF_3K$ yield[b] (%)	Overall yield[c] (%)
2a	1	OH	27	**4a**	65	18
2b	2	OH	22	**4b**	62	14
2c	3	OH	79	**4c**	90	71
3a	1	Pinacol	51	**4a**	66	34

[a] Hydroboration was performed with dichloroborane, prepared in situ from triethylsilane and boron trichloride. Quenching was conducted with water or pinacol, and the products were purified.
[b] Reaction was conducted on the purified boronic acid or ester.
[c] Overall yield of the two-step sequence.

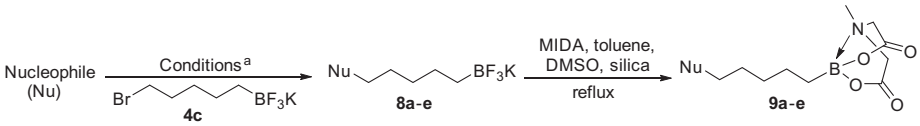
Table 3
Substitution reaction with potassium haloalkyltrifluoroborate **4a–c** followed by a ligand replacement to synthesize the corresponding MIDA boronate

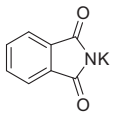
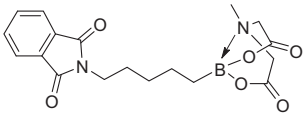
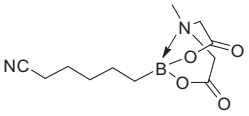
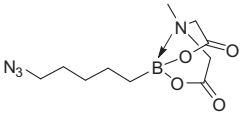
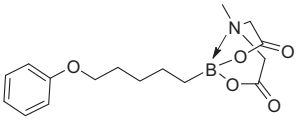
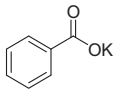
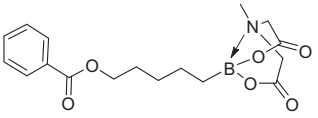


Compound	*n*	Overall yield[a] (%)
7a	1	76
7b	2	81
7c	3	60

[a] Overall yield for the two-step process: substitution and ligand replacement with MIDA.

Table 4
Substitution reactions with potassium haloalkyltrifluoroborate **4c** followed by a ligand replacement to synthesize the corresponding MIDA boronate



Nucleophile	Compound	Product	Overall yield[b] (%)
	**9a**		73
KCN	**9b**		82
NaN_3	**9c**		59
	**9d**		81
	**9e**		72

[a] See Supporting information for full experimental details.
[b] Overall yield for the two-step process: substitution and ligand replacement with MIDA. Yields were not optimized.

reaction pot was concentrated to dryness and immediately subjected to potassium hydrogen difluoride. This *sequential*, one-pot procedure provided good yields (65% to 92%) of the desired potassium haloalkyltrifluoroborate salts **4a–c** (Table 2), all significantly higher than the overall yields described in Table 1. These results provide strong evidence that the described sequential procedure provides a more consistent and effective method for the production of potassium haloalkyltrifluoroborate salts than those previously related.

To illustrate the synthetic utility of the potassium haloalkyltrifluoroborate salts, **4a–c** were successfully employed in substitution reactions with carbamate **5** (Table 3), used as an example of a highly functionalized nucleophile.[14] Due to the instability of trifluoroborate salts to silica gel chromatography, the substitution products **6a–c** were not purified. Instead, crude organotrifluoroborate salts **6a–c** were immediately carried through a ligand replacement reaction with MIDA to form **7a–c**,[6a] which were successfully purified on a silica gel column. The overall yield for the two-step reaction sequence ranged from 60% to 81% (Table 3). This sequence exploits the orthogonal functionality of the trifluoroborate and MIDA boronate protecting groups in a transformation that would have otherwise been difficult to accomplish. Here the MIDA boronates were unstable to the hard nucleophiles required for the reaction. But to purify the substitution product, column chromatography was required. Therefore, the chemical stability of the trifluoroborate salts and the silica stability of the MIDA boronates were each employed in different phases of the transformation, the reaction itself and the product purification. The described procedure will also be useful if subsequent steps in a reaction sequence require silica gel

chromatography. Finally, we demonstrated that this ligand replacement is reversible by subjecting MIDA boronate **7c** to hydrolysis followed by potassium hydrogen difluoride in one-pot. This provided the original potassium organotrifluoroborate salt **6c** in 98% yield.

Additional examples illustrating the breadth of the potassium haloalkyltrifluoroborate salt substitution and MIDA ligand replacement reactions are shown in Table 4. Substitution reactions were conducted with bromide **4c**, and a variety of nucleophiles/functional groups were well tolerated, such as amide (**9a**), cyano (**9b**), azide (**9c**), phenolate/phenyl ether (**9d**), and carboxylate anion/ester (**9e**). For the two-step process, yields ranged from 59% to 82%.

Conclusion

We have accomplished convenient, one- and two-pot *sequential* syntheses[15] of potassium haloalkyltrifluoroborate salts through hydroboration with dichloroborane followed by treatment of the crude hydroboration products with potassium hydrogen difluoride. The *sequential* sequences provided high yields and easy separation from $(Et_3Si)_2O$, a rarely mentioned hydroboration byproduct. This technique improves upon those that have been reported in terms of yield, reproducibility, atom economy, convenience, and cost, and ultimately generates synthetically useful intermediates. Several example substitution reactions with the potassium haloalkyltrifluoroborate salts were also reported, illustrating their value as potential boron building blocks, along with a reversible ligand replacement with MIDA. These ligand replacement reactions allow two of the most robust boron protecting groups to be used interchangeably, so the most advantageous properties of each may be readily exploited.

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Supplementary data

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, and ^{19}F NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.012.

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14. Banks, J. C.; Moody, C. J. *Tetrahedron Lett.* **2009**, *50*, 3371–3373.
15. *One-pot procedure for the synthesis of potassium haloalkyltrifluoroborate salts* **4a–c**: An Ar-flushed, flame-dried round bottom flask was charged with alkene (1.0 equiv) and Et_3SiH (1.06 equiv). This was cooled to −78 °C, followed by the addition of a 1.0 M solution of BCl_3 in hexane (1.13 equiv). The mixture was stirred at this temperature for 40 min, and then was allowed to warm to room temperature over the course of 2–4 h. Next, the reaction was cooled to 0 °C and ether and water were added. After 30 min the reaction mixture was concentrated to dryness. The resulting residue was taken up in ether, and KHF_2 (4.2 equiv) was added, followed by the addition of 1 mL water over the course of 1 h. Next Na_2SO_4 was then added to the reaction to absorb any excess water, and the mixture was filtered while rinsing with acetone. The filtrate was concentrated, and then purified by dissolving in a minimum amount of acetone and precipitating the potassium organotrifluoroborate salt with ether. Filtration provided the potassium organotrifluoroborate salt.