ORGANIC
LETTERS

2010
Vol. 12, No. 4
700−703

Chemoselective Bromodeboronation of Organotrifluoroborates Using Tetrabutylammonium Tribromide: Application in (*Z*)-Dibromoalkene Syntheses

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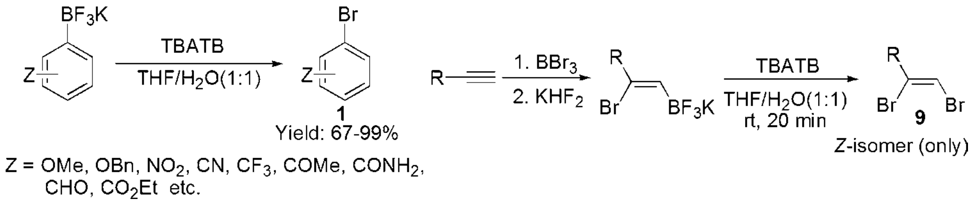
Received November 24, 2009

ABSTRACT



Tetrabutylammonium tribromide (TBATB) has been found to be a unique bromodeboronation reagent for organotrifluoroborates. When compared to previously reported bromodeboronation methods, the mild and metal-free reaction conditions tolerate a wider range of functional groups. High regio- and chemoselectivity are observed in the presence of both unsaturated carbon−carbon bonds and aldehyde functional groups. An efficient synthetic route to (*Z*)-dibromoalkenes from terminal alkynes has been developed using the TBATB-mediated bromodeboronation as a key step.

Aryl halides are important synthetic intermediates that are used extensively in carbon−carbon and carbon−heteroatom bond-forming reactions.[1] The most common method for preparing aryl halides is the electrophilic halogenation of arenes, but the regiochemistry of this process is determined by the electronic nature of the arene's substituents. As a consequence, until recently,[2] multistep syntheses have been required to obtain isomers that are not predicted by theory. Furthermore, in some cases, the electrophilic reactions generate mixtures of mono- and dihalogenated products that are difficult to separate.[3] To overcome these limitations, alternative halogenation methods have been developed that include the conversion of anilines to aryl halides *via* diazonium salts (Sandmeyer reaction)[4] and the halodemetalation of organometallic species (Zn,[5] Li,[6] Sn,[7] Hg,[8] Si,[9] B,[10] etc.).

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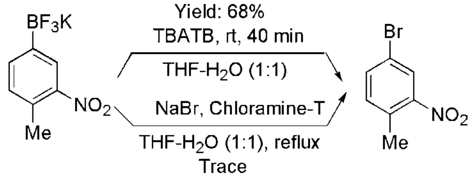
10.1021/ol9027144

Among the organometallic reagents investigated, organoboron derivatives have drawn much attention because they are generally nontoxic and stable under atmospheric conditions. With the development of palladium-catalyzed borylations of aryl triflates (as well as tosylates and halides),[11] iridium-catalyzed direct borylations of arenes via C−H bond activation,[12] and the syntheses of functionalized organotrifluoroborates through a variety of organic transformations,[13] the ready availability of numerous organoboron derivatives enhances the significance of modern organoboron-based chemistry. Prompted by our long-term interest in efficient radiohalogenation reactions based on organoboron chemistry,[10a−d,14] we have developed halodeboronations of electron-rich arylboronic esters and potassium aryltrifluoroborates using a chloramine-T/halide system. In collaboration with Huffman, we also developed a $CuBr_2$-mediated bromodeboronation method[10f] that successfully bromodeboronates arylboronic esters bearing both electron-donating and electron-withdrawing groups. The method has been successfully applied in the synthesis of *meta*-halogenated 1,3-disubstituted arenes.[10g] The bromodeboronation of arylboronic acids using dibromodimethylhydantoin and a catalytic amount of NaOMe in acetonitrile was also reported.[10e] Although this method has been used successfully in a scaleable synthesis of 2-bromo-3-fluorobenzonitrile, the use of NaOMe is problematic in the synthesis of compounds containing base-sensitive functional groups.[15]

In a continuation of our halogenation studies, we discovered that commercially available tetrabutylammonium tribromide (TBATB) is a powerful bromodeboronation reagent for converting potassium aryltrifluoroborates to aryl bromides. For example, at room temperature, a potassium aryltrifluoroborate bearing a nitro group readily undergoes bromodeboronation to produce the corresponding aryl bromide in good yield within 40 min (Scheme 1). In contrast, under previously reported bromodeboronation conditions (chloramine-T/NaBr), only a trace amount of product was formed after 24 h at reflux. To the best of our knowledge, this is the first report of TBATB being used to convert a carbon−metal bond to a carbon−bromine bond.

Scheme 1. Efficiency of Bromodeboration Using TBATB Compared to That of Previous Method



Although the interconversion between arylboronic acids, boronic esters, and organotrifluoroborates is known,[16] the use of organotrifluoroborate precursors for bromodeboronation offers several advantages over the other organoboron derivatives. These advantages include (i) simple preparation,[13,16b] (ii) straightforward purification,[17] and (iii) easy isolation of the brominated product due to the large polarity difference between precursors and products.

The scope of the new bromination reaction is highlighted in Table 1. As shown in Table 1, a variety of functional groups, including methoxy, aldehyde, ester, amide, phenol, cyano, and nitro groups, survive the new bromodeboronation reaction. The tolerance of the aldehyde group is remarkable since TBATB has been reported to convert aldehydes to acids.[18] As distinguished from the previously reported $CuBr_2$-mediated bromodeboronation, the new copper-free reaction permits the presence of phenol and amide groups by

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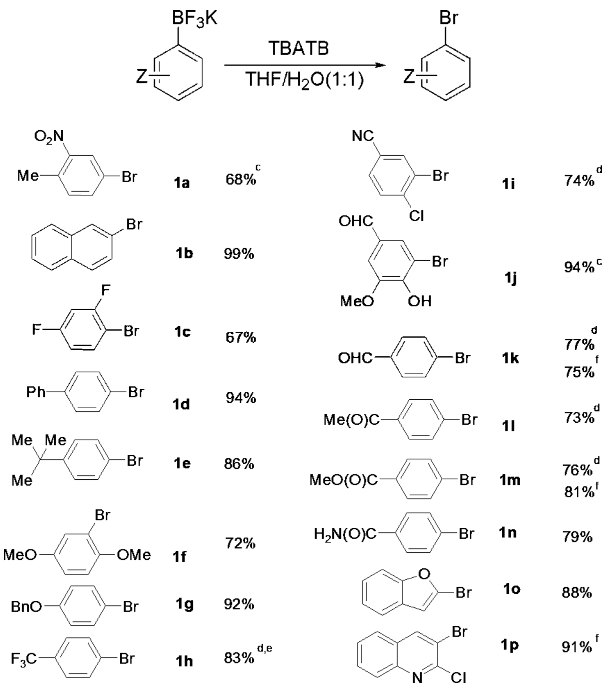
obviating undesired copper-catalyzed side reactions.[19] For an aryltrifluoroborate bearing an activated methyl group (product **1l**), no bromination of the methyl group is detected. Generally speaking, aryltrifluoroborates bearing electron-donating groups are converted to the corresponding bromoarenes in good to excellent yields at room temperature within 20 min. Aryltrifluoroborates bearing electron-withdrawing groups require slightly longer reaction times. However, simply elevating the reaction temperature greatly facilitates the reaction without inducing undesirable side reactions.

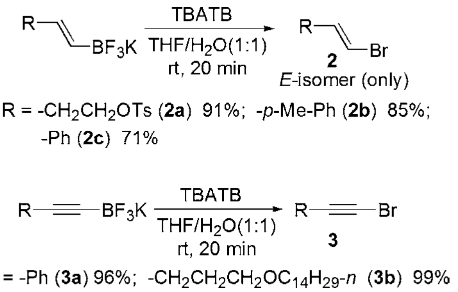
Table 1. Conversion of Potassium Aryl Trifluoroborates to Aryl Bromides[a]



[a] Reaction carried at room temperature for 20 min unless otherwise noted. [b] Isolated yield. [c] Reaction runs for 40 min. [d] Reaction runs at 60 °C for 2 h. [e] GC yield. [f] Reaction runs at room temperature for 12 h.

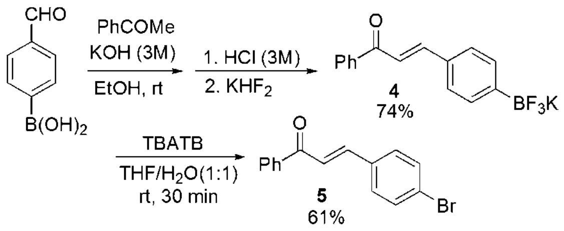
The bromodeboronation of alkenyl- and alkynyltrifluoroborates was also examined (Scheme 2). These reactions proceed smoothly at room temperature to produce alkenyl and alkynyl bromides, respectively, in good to excellent yields. The retention of stereochemistry of the alkenyl group is attractive because stereoselective halodemetalation of the corresponding vinylsilanes can be challenging.[20] Chemoselective bromodeboronation in the presence of unsaturated carbon−carbon bonds is notable since TBATB is considered to be an environmentally benign brominating reagent for alkenes and alkynes.[21]

Scheme 2. Bromodeboronation of Alkenyl- and Alkynyltrifluoroborates



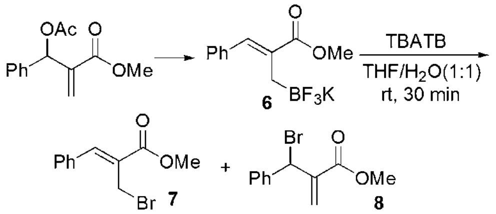
It has also been reported that the alkenyl group in enones undergoes bromination at a higher rate than a simple alkene using TBATB.[21] However, aryltrifluoroborate **4** was found to be chemoselectively bromodeboronated to give **5** in 61% yield (Scheme 3).

Scheme 3. Chemoselectively Bromodeboronation in the Presence of Enone



We were also able to brominate allyltrifluoroborate **6**, a trifluoroborate whose precursor allylboronic ester has been found to be unstable (Scheme 4).[17b] Unfortunately, the reaction gives a mixture of allyl bromide products (**7**:**8** = ~3:2). Attempts to bromodeboronate alkyltrifluoroborates using TBATB were unsuccessful.

Scheme 4. Bromodeboronation of Allyltrifluoroborate



The synthesis of thermodynamically disfavored (*Z*)-dibromoalkenes has long been a challenge in organic

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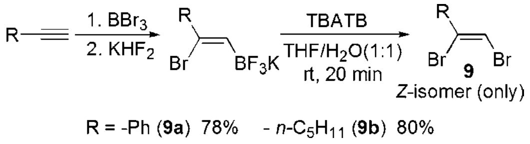
synthesis.[22] Synthetic methods available in the literature generally require either long reaction times or elevated reaction temperatures. As a result of the thermal instability of (*Z*)-dibromoalkene, the reported methods normally give poor isolated yields and the products are often contaminated by the (*E*)-isomer.[22] Encouraged by the retention of configuration in the bromodeboronation of alkenyltrifluoroborates noted earlier, we examined the feasibility of a two-step synthetic route to (*Z*)-dibromoalkenes, such as **9**, from terminal alkynes (Scheme 5). Pure (*Z*)-isomers were isolated in good yields from readily prepared, stereodefined (*Z*)-2-bromovinyltrifluoroborates.[23]

Scheme 5. Two-Step Synthetic Route to (*Z*)-Dibromoalkenes



At present, little is known concerning the mechanism of the new bromination reaction. The slow bromodeboronation of potassium 2-naphthalenyltrifluoroborate in the presence of tetrabutylammonium bromide (which leads to water-soluble tetrabutylammonium trifluoroborate salt) in the presence of chloramine-T appears to rule out simple solubility effects.[24] However, it is clear that the tetrabutylammonium counterion does influence the bromodeboronation reaction since bromodeboronation reactions using pyridinium tribromide produces a mixture of protodeboronation and bromodeboronation products. Although previous reports[25] have demonstrated that TBATB is a substitute for both Br_2 and anhydrous HBr, it has never been considered as a potential source of "Br^+". Notably, Br_2, either commercially available or generated *in situ*, has proven to be ineffective for bromodeboronation reactions in the absence of strong bases.[10e,g] Bromodeboronation reactions of boronic acids and boronic esters using TBATB are much slower at room temperature when compared to the potassium aryltrifluoroborates.

In conclusion, we have discovered that commercially available TBATB is a powerful bromodeboronation reagent for organotrifluoroborates. Under mild reaction conditions, aryl, alkenyl, and alkynyl trifluoroborates bearing a wide range of functional groups can be converted to the corresponding bromo derivatives in good to excellent yields. High regio- and chemoselectivity are observed in the presence of unsaturated carbon−carbon bonds and aldehyde functional groups. In addition, an efficient synthetic route to (*Z*)-dibromoalkenes from terminal alkynes has been developed using the TBATB mediated bromodeboronation as a key step. Mechanistic studies are currently underway.

Acknowledgment. Financial support from the U.S. Department of Energy and the Robert H. Cole Foundation is acknowledged. I.W. is grateful for a University of Tennessee Summer Undergraduate Research Fellowship. We also thank Frontier Scientific for providing organoboronic acids and organotrifluoroborate precursors.

Supporting Information Available: Procedures for synthesis and characterization of products (^{1}H and ^{13}C NMR data). This material is available free of charge via the Internet at http://pubs.acs.org.

OL9027144

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