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SYNTHESIS OF ARYLBORONIC ACIDS VIA THE REACTION OF BORANE WITH ARYLMAGNESIUM HALIDES

GEORGE W. KABALKA*, USHA SASTRY, and K.A.R. SASTRY,
Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996-1600 (U.S.A.)

FURN F. KNAPP Jr. and PREM C. SRIVASTAVA
Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830 (U.S.A.)

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Summary

The reaction of borane complexes with arylmagnesium halides produces the corresponding arylborohydrides in high yield. The arylborohydrides are readily hydrolyzed to the arylboronic acids. The syntheses are conveniently carried out in one pot. The reaction mechanism was clarified via a boron-11 NMR study.

Introduction

Arylboronic acids are useful synthetic intermediates. They are generally prepared via the reaction of organometallic reagents with boron halides or boron esters [1–3]. The yields, however, are generally modest (~ 50%) [4].

$$ArM + BX_3 \rightarrow ArBX_2 + MX$$

$$ArBX_2 \xrightarrow{H_2O} ArB(OH)_2$$

In an effort to produce higher yields, studies have been carried out in which various organometallic reagents were treated with borane complexes to yield the arylborohydrides which were then hydrolyzed to the corresponding arylboronic acids. (In most cases the intermediate organoborane products were also oxidized to the phenols.) Organometallic derivatives of Li [5], Na [5], K [5], Ca [5], Hg [6], Tl [7], Sn [8], Pb [8], Cu [9] and Cd [9] have been utilized to synthesize arylboronic acids with varying degrees of success. Again, the yields of the arylboronic acids were generally less than 50%. Furthermore, the yields of phenols (in the instances in which the reaction mixtures were oxidized) always exceeded the yields of the arylboronic acids which indicates that diarylborohydride and triarylborohydride were formed along with the monoarylborohydride.

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We are utilizing arylboronic acids and vinylboronic acids as precursors in the syntheses of radiohalogenated reagents for use in nuclear medicine [10,11,12]. We decided to investigate the synthesis of arylboronic acids via the reaction of arylmagnesium halides with borane complexes.

$$\mathrm{ArMgX} + \mathrm{BH_3} \rightarrow \mathrm{ArBH_3MgX}$$

$$\mathrm{ArBH_3MgX} \xrightarrow{\mathrm{H_2O}} \mathrm{ArB(OH)_2}$$

Results

The reaction of borane complexes with Grignard reagents has been utilized to prepare trialkylboranes [13], biaryls [14], and phenols [15]. The intermediacy of monoaryl-, diaryl- and triaryl-borohydrides in these reactions was assumed but no arylborohydrides or arylboronic acids were isolated or characterized.

In our preliminary studies, we investigated the use of the iodo, bromo, and chloro substituted benzene. We eliminated the aryl iodides because the yields of the corresponding arylmagnesium iodides were erratic. Generally, significant quantities of biaryl byproducts were obtained with the concomitant loss of the arylmagnesium derivative. The aryl chlorides were also abandoned as starting reagents since the corresponding Grignard reagents were difficult to prepare. Fortunately, the aryl bromides were readily available and formed Grignard reagents in good yield.

We then investigated the preparation of arylmagnesium borohydride via the addition of an arylmagnesium bromide to tetrahydrofuran solutions of borane. We ran duplicate experiments in which the Grignard reagent was prepared in the presence of the borane. The in-situ preparations of Grignard reagents produced the arylborohydrides in yields identical to those obtained using externally prepared Grignard reagents.

$$\mathrm{ArBr} \xrightarrow[\mathrm{BH_3}]{\mathrm{Mg}} \mathrm{ArBH_3MgBr} \xrightarrow{\mathrm{H_2O}} \mathrm{ArB(OH)_2}$$

During these initial studies, it became clear that the desired products were formed in highest yield when the borane was kept in excess. Representative results are presented in Table 1.

The role of the excess borane became apparent when we examined the boron-11 NMR of a series of reactions. The NMR data clearly demonstrate that the reaction

TABLE 1

EFFECT OF THE BORANE CONCENTRATION ON THE YIELD OF ARYLBORONIC ACID

PhBr(mmol) [a]	$\mathrm{BH_3 \cdot THF}$(mmol)	Isolated yield (%)
10	10	19
10	30	56
10	40	71
10	60	74
10	100	71

[a] The bromobenzene was added to a mixture of magnesium (20% excess) and borane. The reaction was stirred at 25°C until most of the magnesium reacted. The product was hydrolyzed with 10% HCl.

is a complex one in which arylmagnesium borohydrides readily transfer a hydride to the more acidic borane molecule. The following equilibria apparently occur readily.

$$\mathrm{ArMgBr} + \mathrm{BH_3} \rightleftarrows \mathrm{ArBH_3MgBr}$$

$$\mathrm{ArBH_3MgBr} + \mathrm{BH_3} \rightleftarrows \mathrm{ArBH_2} + \mathrm{BH_4MgBr}$$

$$\mathrm{ArBH_2} + \mathrm{ArMgBr} \rightleftarrows \mathrm{Ar_2BH_2MgBr}$$

$$\mathrm{Ar_2BH_2MgBr} + \mathrm{BH_3} \rightleftarrows \mathrm{Ar_2BH} + \mathrm{BH_4MgBr}$$

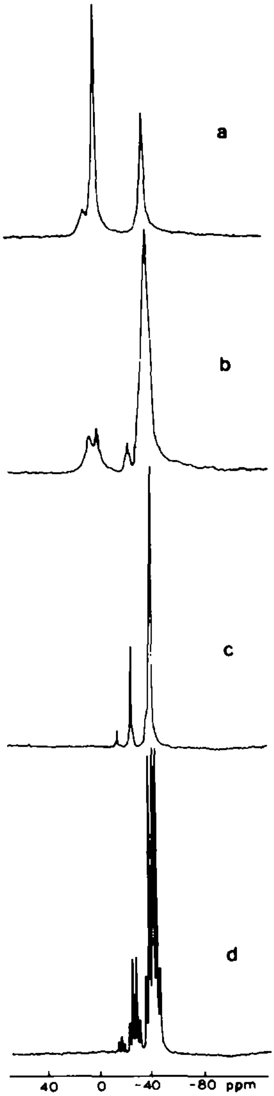


Fig. 1. Boron-11 NMR spectra of typical reaction mixtures: (a) ^{1}H-decoupled spectrum of reaction mixture; (b) ^{1}H-decoupled spectrum of reaction (a) with one equivalent of hydride added (as $LiAlH_4$); (c) ^{1}H-decoupled spectrum of reaction (a) with excess hydride added (as $LiAlH_4$); (d) ^{1}H-coupled spectrum of reaction (a) with excess hydride added (as $LiAlH_4$).

$$Ar_2BH + ArMgBr \rightleftarrows Ar_3BHMgBr$$

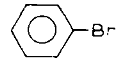
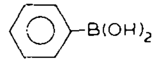
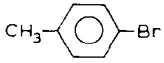
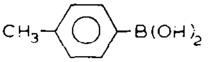
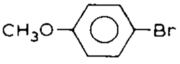
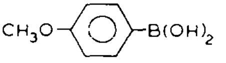
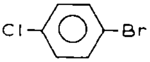
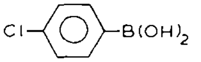
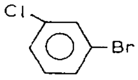
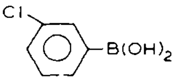
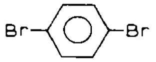
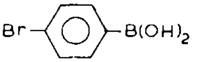
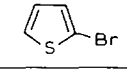
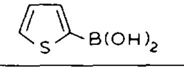
$$Ar_3BHMgBr + BH_3 \rightleftarrows Ar_3B + BH_4MgBr$$

$$Ar_3B + ArMgBr \rightleftarrows Ar_4BMgBr$$

In the absence of excess BH_3, the monoaryl borohydride is quickly converted to diaryl-, triaryl-, and tetraaryl-boron derivatives. The formation of the multiarylated boron derivatives presumably occurs in reactions involving other organometallic reagents and readily explains the fact that the yields of phenols (after oxidation) were consistently greater than the yields of arylboronic acids in these earlier studies [5,6,8,9]. The use of a four-fold excess of borane minimizes the formation of multiarylated boron derivatives by insuring that borane is present in sufficient quantities to react with the arylmagnesium bromide as it is formed. The proton decoupled, ^{11}B-NMR spectrum of a typical reaction is presented in Fig. 1(a). The borohydride peak at -39.3 ppm (relative to $BF_3 \cdot O(CH_2CH_3)_2$) is clearly visible as well as the borane peak at 0 ppm. The peak at 7 ppm is due to the monoarylborane derivative. The more diffuse monoarylborane signal is clearly visible in spectrum (b) in which nearly an equivalent of hydride (as $LiAlH_4$) has been added to convert the

TABLE 2

SYNTHESIS OF ARYLBORONIC ACIDS FROM ARYL BROMIDES VIA GRIGNARD REACTIONS WITH BORANE

Aryl bromide[a]	Product[b]	Yield (%)[c]	M p (°C)[d]	δ (ppm)[e]
		75	214-216	28.8
		71	242-243	29.2
		73	202-204	29.5
		81	268-272	28.8
		82	177-178	28.5
		75	277-278	28.8
		68	132-133	26.7

[a] Converted to the corresponding Grignard reagent prior to reaction with borane. Nearly identical yields are obtained when the Grignard is formed in-situ. [b] All products exhibited physical and spectral properties in accord with published values [16,17]. [c] Isolated yields based on aryl bromides. [d] Melting points are those of the corresponding acid anhydride [16]. [e] Boron-11 NMR chemical shifts relative to boron trifluoride etherate (solvent: THF).

borane to the borohydride ion. The peak at −26.2 ppm is due to the monoarylborohydride ion. If excess hydride is added, the spectrum in Fig. 1(c) is produced. The peak at −15.2 ppm corresponds to the diarylborohydride ion. Figure 1(d) is the non-proton decoupled spectrum of the reaction mixture with excess hydride added. The splitting pattern confirms the analysis of the reaction products.

The addition of excess hydride simplifies analysis of the reaction mixtures and aids in product identification. When this procedure was used on a reaction mixture in which the arylmagnesium bromide was treated with only one equivalent of borane, all of the equilibrium products were observed: tetraarylborate (a singlet at −6.8 ppm), diarylborohydride (a triplet at −15.2 ppm), monoarylborohydride (a quartet at −26.2 ppm) and borohydride (a pentuplet at −39.3 ppm). Interestingly, we do not observe a peak for triarylborohydride which would, presumably, appear as a doublet at −20 ppm in the proton coupled spectrum; instead, we observed a singlet at +52.4 ppm which corresponds to triphenylborane (even though excess hydride is present.)

Utilizing the Grignard method, good yields of arylboronic acids are obtained. Our results are summarized in Table 2. The yields are based on the aryl bromide and are minimum yields because it is assumed that the Grignard is formed in 100% yield. Presumably the yields would increase if the Grignard reagent were preformed and the yields of boronic acids were based on measured quantities of the Grignard reagents.

Experimental

Melting points are uncorrected. All boron-11 chemical shifts are reported in parts per million downfield from $BF_3 \cdot O(CH_2CH_3)_2$. ^{11}B NMR spectra were run on a JEOL-FX 90Q spectrometer. Commercially available samples (Aldrich) of the aryl bromides were used as received.

General Procedure

Magnesium turnings (12 mmol) were placed in a round-bottomed flask and then flame-dried under a nitrogen atomosphere. After cooling to 0°C, borane (40 mmol, 20.0 ml of a 2.0 *M* solution in THF) was added to the flask followed by the slow addition of the aryl bromide in THF (10 mmol, 5 ml of a 2.0 *M* solution). The reaction mixture was stirred at room temperature until most of the magnesium disappeared (normally 12–16 h). The mixture was then poured into ice-water (250 g) and then acidified with 10% HCl (~ 5 ml). The product was extracted into ether (3 × 75 ml). The ethereal extracts were dried over anhydrous sodium sulfate, the solvent removed under reduced pressure, and the products precipitated by trituration with petroleum ether. The products were recrystallized from water. (For reactions involving externally prepared Grignard reagents, 10 mmol of the Grignard reagent is slowly added to a stirred solution of borane in THF (40 mmol). The workup is identical to that described earlier.)

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