

# Alkylation of Aromatic Aldehydes with Boron Halide Derivatives

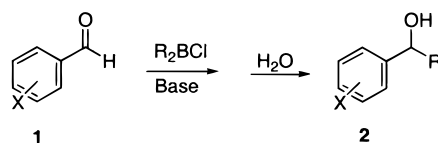
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## ABSTRACT



Aryl aldehydes react with alkylboron chloride derivatives in the presence of base to generate the corresponding arylalkylmethanols in good yields. A variety of alkylboron chlorides can be utilized in the new alkylation reaction.

The alkylation of aldehydes and ketones by organometallic reagents is one of the most important reactions in synthetic organic chemistry. Generally, only reactive alkylmetals can be utilized to achieve this transformation.<sup>1</sup> Organoborane reagents do not normally react with carbonyl compounds in a Grignard-like fashion with the exception of allylborane and vinylborane reagents.<sup>2</sup> The few known alkylborane alkylation reactions require reactive organoboranes, free radical conditions, or activation of the carbonyl groups.<sup>3</sup> Nevertheless, a Grignard-like reaction involving organoborane reagents would possess a number of synthetic advantages including stereochemical control and the fact that a large number of functional substituents are unaffected by the mild reaction conditions found in most organoborane transformations.

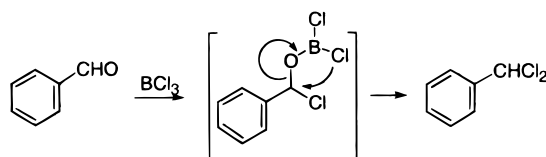
(1) (a) Wakefield, B. J. *Organolithium Methods*; Academic Press: New York, 1988. (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989. (c) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall: New York, 1954. (d) Sweeney, J. B. *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Ley, S. V., Eds.; Pergamon: Cambridge, 1995; Vol. 2, p 37.

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We recently reported a new method for converting arylaldehydes into dichloroarylmethanes using boron trichloride.<sup>4</sup> The reaction appears to proceed via an alkoxyboron chloride intermediate, Scheme 1. It occurred to us that the

**Scheme 1.** Formation of Dichloromethylbenzene

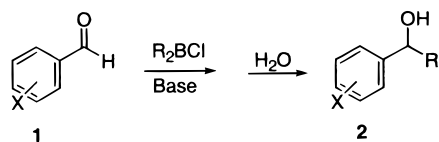


use of an alkylboron derivative in place of boron trichloride could lead to a new alkylation reaction which would provide a Grignard-like addition reaction.

We wish to report the initial results of this new reaction, Scheme 2.

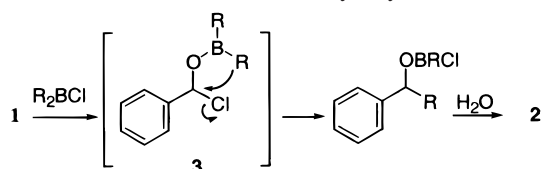
We first examined the use of alkylboron dichloride reagents and found that no reaction occurred in the absence of base. Upon addition of bases such as triethylamine, quinuclidine, and lutidine, a small amount of the desired product was formed but significant quantities of the dichloromethane derivatives were also obtained. We then examined

(4) Kabalka, G. W.; Wu, Z. *Tetrahedron Lett.*, in press

**Scheme 2.** Alkylation of Aryl Aldehydes

reactions involving dialkylboron chlorides. Again, no reaction occurred in the absence of base but good yields of the desired arylalkylmethanol derivatives were obtained in the presence of bases such as lutidine.

Although a detailed mechanistic study has not yet been undertaken, the reaction appears to proceed via a borinate ester intermediate such as **3**, which then undergoes replacement of the chloride by an alkyl group, Scheme 3.

**Scheme 3.** Formation of Arylalkylmethanols

Evidence for the intermediacy of **3** includes the fact that, in the reaction of dihexylboron chloride with benzaldehyde, the characteristic  $^1\text{H}$  and  $^{13}\text{C}$  resonances for the aldehyde group gradually disappear over a period of hours and new resonances appear at 5 ppm in the  $^1\text{H}$  and 70 ppm in the  $^{13}\text{C}$  NMR spectra. Furthermore, upon addition of water (instead of an amine), benzaldehyde is regenerated.

A series of aromatic aldehydes were subjected to the reaction sequence. Essentially all aldehydes examined were successfully converted to the corresponding arylalkylmethanols, Table 1.

**Table 1.** Preparation of Arylalkylmethanol Derivatives via the Reaction of Aryl Aldehydes with Dialkylboron Chlorides, Scheme 2

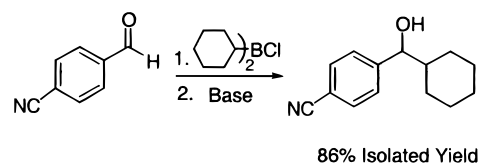
<b>1</b>	X	R	yield of <b>2</b> (%) <sup>a,b</sup>
<b>1a</b>	H	cyclohexyl	75
<b>1b</b>	H	<i>s</i> -butyl	60
<b>1c</b>	H	<i>n</i> -hexyl	35 <sup>c</sup>
<b>1d</b>	<i>p</i> -Cl	cyclohexyl	78
<b>1e</b>	<i>o</i> -Cl	cyclohexyl	49 <sup>d</sup>
<b>1f</b>	<i>p</i> -F	cyclohexyl	90 <sup>d</sup>
<b>1g</b>	<i>p</i> -OCH <sub>3</sub>	cyclohexyl	83
<b>1h</b>	<i>p</i> -CH <sub>3</sub>	cyclohexyl	78
<b>1i</b>	<i>o</i> -CH <sub>3</sub>	cyclohexyl	65

<sup>a</sup> Isolated yields. <sup>b</sup> All products exhibited physical and spectral characteristics in accord with literature values. <sup>c</sup> A significant quantity of the secondary alkyl isomer was also formed. <sup>d</sup> Satisfactory elemental analysis was obtained.

The synthesis of cyclohexylphenylmethanol is representative. Benzaldehyde (3.0 mmol, 0.32 g) was dissolved in

hexane (10 mL) contained in a dry, nitrogen-flushed, 50 mL round-bottomed flask. Dicyclohexylboron chloride<sup>5</sup> (3.0 mmol, 3.0 mL of a 1.0 M hexane solution) was added via syringe, and the solution was allowed to stir for 30 min at room temperature. 2,6-Lutidine (3.0 mmol, 0.32 g) was then added and the mixture stirred for 5 h.<sup>6</sup> A precipitate formed which contained boron. Hydrolysis, as well as oxidation, of the remaining alkylboron group was accomplished by addition of hydrogen peroxide (0.5 mL of a 30% aqueous solution) and sodium hydroxide (3.0 mmol, 1.0 mL of a 3.0 M aqueous solution). [Alternatively, water could be added and the product isolated from the organic phase.] After separation of the organic layer, 0.43 g of the desired product was isolated (75% yield) by column chromatography (dichloromethane, silica gel):  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  7.36–7.23 (m, 5H), 4.35 (d, 1H), 2.01–0.94 (m, 12H);  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>)  $\delta$  143.6, 128.2, 127.4, 126.6, 79.4, 44.9, 29.3, 28.8, 26.4, 26.1, 25.9.

The new alkylation reaction provides a potentially useful alternative to traditional Grignard and organolithium reactions. It is limited to aldehydes which do not possess  $\alpha$ -hydrogens due to the well-known enolization reactions that occur with dialkylboron chlorides and triflates.<sup>7</sup> Benzyl alcohols are also formed in small quantities along with the desired alkylated products; this reaction predominates if the more reactive diisopinocampheylboron chloride reagent is utilized.<sup>8</sup> The reaction can also be carried out using the corresponding dialkylboron triflates but the yields are modest. We are currently attempting to optimize the new alkylation reaction while evaluating its application to functionally substituted derivatives. As an example we have found that nitrile substituents do not interfere with the reaction, Scheme 4.

**Scheme 4.** Synthesis of Cyclohexyl(4-cyanophenyl)methanol

**Acknowledgment.** We thank the U.S. Department of Energy for research support.

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(5) Dicyclohexylboron chloride was used as received (Aldrich Chemical Co.). Other dialkylboron chlorides were prepared according to literature procedures. See: Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499.

(6) The reaction times vary. Primary alkyl groups react more slowly than secondary alkyl groups. We have observed reaction times as long as 10 h for the formation of the intermediate as well as the alkyl rearrangement reaction.

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