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Chloroalkylation of aryl aldehydes using alkylboron dichlorides in the presence of oxygen

George W. Kabalka,* Zhongzhi Wu and Yuhong Ju

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, TN 37996-1600, USA

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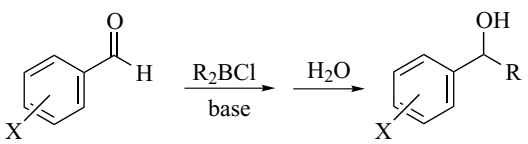
Abstract—Reactions of aryl aldehydes with alkylboron dichlorides in the presence of oxygen at room temperature produces arylalkyl chlorides in good to excellent yields. © 2001 Published by Elsevier Science Ltd.

The direct 1,2-migration of an organic group from an organometallic reagent to a carbonyl carbon is an important method for assembling a variety of useful carbon skeletons. Generally, only reactive alkylmetals such as the organomagnesium,[1] organolithium,[2] organozinc[3] and organotransition metal reagents[4–9] can be utilized to achieve this transformation. Although borane reagents have been used in many reactions involving the formation of new carbon–carbon bonds, saturated organoborane derivatives are typically unreactive toward carbonyl compounds.[10–15] Early attempts at achieving a Grignard-like reaction using alkylboranes resulted in the reduction of the aldehyde via a β-hydrogen elimination.[16] Although the direct 1,2-addition of a trialkylborane to a carbonyl carbon is difficult to achieve, certain modifications in either the carbonyl compound or the trialkylborane have led to a few successful alkylation reactions.[17,18] Nevertheless, a Grignard-like reaction involving organoborane reagents would possess a number of synthetic advantages including mild reaction conditions, potential stereochemical control and the fact that a large number of functional substituents are unaffected in most organoborane transformations.[19]

Alkylboron halide derivatives have been extensively used for the reduction of carbonyl compounds[20] and as enolate reagents for aldol reactions, a methodology that has become one of the most important procedures for diastereoselective and enantioselective C–C bond formation.[21] We recently reported a successful alkylation of aryl aldehydes using dialkylboron chlorides in the presence of base (Scheme 1).[22] Since only one alkyl group in the dialkylboron chloride transfers to the carbonyl carbon, the reaction does not lead to efficient utilization of the alkyl groups. Unfortunately, alkylboron dichloride failed to react under the conditions reported.

Organoboranes readily undergo autoxidation in the presence of oxygen. This reaction has been used to prepare alcohols and alkyl hydroperoxides and to mediate free radical reactions.[23,24] In addition, organoboranes can be used to alkylate α,β-unsaturated carbonyl compounds through a radical 1,4-addition reaction in the presence of air,[25] but they do not normally react with saturated carbonyl compounds except for the reaction of formaldehyde with trialkylboranes in the presence of air.[26] We have discovered that oxygen induces the reaction of alkylboron dichlorides with aryl aldehydes to produce alkylation products in good to excellent yields (Scheme 2).

We first examined the reaction of alkylboron dichlorides with aryl aldehydes in hexane under a nitrogen atmosphere at room temperature, no alkylation was observed. However, when oxygen or dry air was introduced into the reaction mixtures, an alkylation reaction occurred. Interestingly, the reaction produced arylalkyl



Scheme 1.

Keywords: boron and compounds; aldehydes; alkylation; alkyl halides.

* Corresponding author. Tel.: (865) 974-3260; fax: (865) 974-2997; e-mail: kabalka@utk.edu

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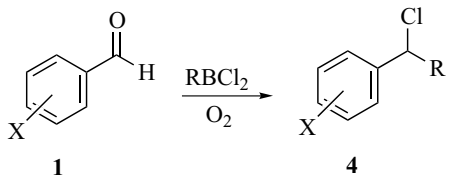
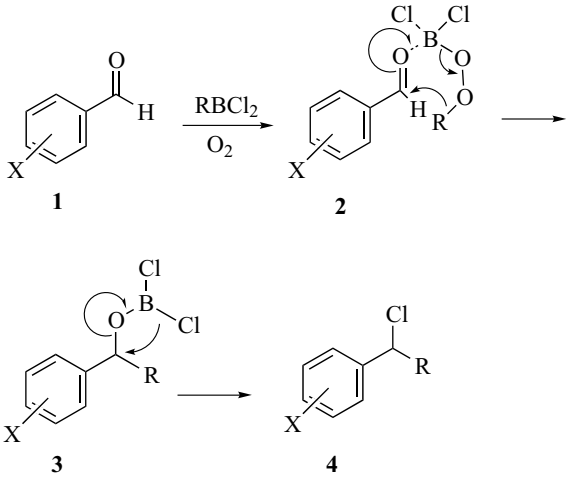


Scheme 2.

chloride products instead of arylalkyl alcohols (Scheme 2). We noted that a small quantity of benzyl chloride formed along with the desired alkylation product, as had been noted in our earlier reports.[22,27] α,α-Dichlorotoluenes were also formed in small quantities if reactions were carried out at the higher temperature.[28] If reactions were carried out at −20°C, no alkylation occurred and alkyl peroxides were isolated upon hydrolysis of the reaction mixture.

In an effort to elucidate the reaction mechanism, a mixture of benzaldehyde and *n*-butylboron dichloride was monitored by NMR spectroscopy. Benzaldehyde was mixed with one equivalent of *n*-butylboron dichloride in benzene-d_6 in a argon flushed NMR tube. The ^{1}H and ^{13}C spectra revealed no resonances related to a carbonyl group. Eventually, reductive chlorination of the aldehyde occurred which led to the formation of benzyl chloride. In a separate experiment, oxygen was introduced into the mixture of benzaldehyde and *n*-butylboron dichloride. The NMR spectra revealed resonances due to the chloroalkylation product (1-chloropentyl)benzene. In a third experiment, the addition of a radical scavenger, galvinoxyl, did not inhibit the chloroalkylation reaction in the presence of oxygen, indicating that a chain reaction is probably not involved. Thus, the reaction presumably proceeds through oxidation of the borane reagent to form an alkyl peroxide intermediate which then undergoes alkyl transfer through transition state **2** to give borinate ester **3**, followed by migration of chloride to afford the final product **4** (Scheme 3). Further mechanistic studies are planned.



Scheme 3.

A series of aryl aldehydes were subjected to the alkylation reaction. Essentially all aldehydes examined were successfully converted to the corresponding arylalkyl chlorides (Table 1). Both primary and secondary alkylboron dichlorides were successfully utilized in the reactions to produce products in good yields.

The synthesis of cyclohexyl-(4-fluorobenzyl)chloride (**4k**) is representative. 4-Fluorobenzaldehyde (4.3 mmol, 0.53 g) was dissolved in hexane (10 ml) contained in a dry argon-flushed, 50 ml round-bottomed flask. Cyclohexylboron dichloride (4.3 mmol, 0.71 g) was added via a syringe and the solution was allowed to stir for 30 min at room temperature. Oxygen was introduced over the reaction mixture via a needle attached to an oxygen filled balloon. The reaction solution gradually turned cloudy. After stirring at room temperature for 1 h, the mixture was filtered. The filtrate was then hydrolyzed with water, the organic layer separated, dried over anhydrous $MgSO_4$, the solvent evaporated, and the residue subjected to column chromatography to yield 0.90 g (92% yield) of the desired product **4k** as a colorless liquid: ^{1}H NMR δ 7.32–7.24 (m, 2H), 7.06–6.96 (m, 2H), 4.58 (d, 1H, $J=8.4$ Hz), 2.20–0.84 (m,

Table 1. Synthesis of arylalkyl chlorides

Entry	X	R	Time (h)	Product	Yield %[a,b]
1a	H	*n*-Butyl	2	**4a**	52
1b	4-F	*n*-Butyl	1	**4b**	85
1c	4-Cl	*n*-Butyl	1	**4c**	75
1d	2-Cl	*n*-Butyl	3	**4d**	50
1e	3-Cl	*n*-Butyl	2	**4e**	51
1f	4-Br	*n*-Butyl	1	**4f**	63
1g	4-Me	*n*-Butyl	2	**4g**	55
1h	4-(CHO)	*n*-Butyl	2	**4h**	73
1i	H	Cyclohexyl	2	**4i**	81
1j	4-Br	Cyclohexyl	1	**4j**	86
1k	4-F	Cyclohexyl	1	**4k**	92
1l	4-Cl	*sec*-Butyl	1	**4l**	67
1m	4-F	*sec*-Butyl	1	**4m**	74

[a] Isolated yield based on aldehyde.
[b] All compounds were characterized by elemental analysis and NMR spectroscopy.

11H); ^{13}C NMR δ 164.2, 160.3, 136.8, 129.3, 129.1, 115.4, 115.0, 68.9, 45.8, 30.2, 26.1, 25.0. Anal. calcd for $C_{13}H_{16}ClF$: C, 68.87; H, 7.11. Found: C, 68.66; H, 7.14.

In summary, the new alkylation reaction provides a potentially useful alternative to traditional alkylation reactions. The reaction occurs under mild conditions and affords arylalkyl chlorides in good yields. The reaction is limited to aldehydes which do not possess α-hydrogens due to the well-known enolization reactions that occur with boron halides.

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