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# Dehydroxymethyl Bromination of Alkoxybenzyl Alcohols by Using a Hypervalent Iodine Reagent and Lithium Bromide

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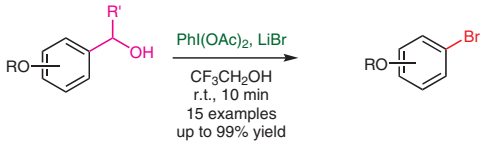


mild conversion of alkoxybenzyl alcohols to bromides

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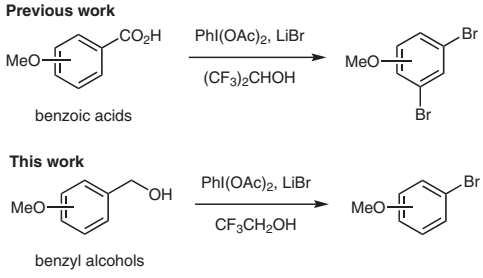
**Abstract** We describe the dehydroxymethylbromination of alkoxybenzyl alcohol by using a hypervalent iodine reagent and lithium bromide in $F_3CCH_2OH$ at room temperature. Selective monobromination or dibromination was possible by adjusting the molar ratios of hypervalent iodine reagent and lithium bromide.

**Key words** hypervalent iodine reagent, bromination, bromoarenes, benzylic alcohol, regioselectivity

Organic halides are an important class of compounds in organic synthesis, and they are widely used as synthons for nucleophilic substitution and transition-metal-catalyzed coupling reactions. Therefore, synthetic methods for organic halides remain important. Decarboxylative halogenation can be used to prepare organic halides by converting carboxylic acids into their corresponding halides by using oxidants.[1] The Hunsdiecker reaction is representative of decarboxylative halogenation but requires relatively harsh conditions or a transition metal.[1e] We have recently developed a mild process for decarboxylative halogenation of aromatic carboxylic acids by using a combination of hypervalent iodine reagents and alkali metal halides,[2] and we have also applied this method to total syntheses of natural compounds.[3] Hypervalent iodine reagents are mild oxidants with low toxicity that exhibit a unique reactivity similar to that of highly toxic heavy-metal oxidants. Therefore, many researchers have developed a number of useful reactions that use hypervalent iodine reagents.[4] Alkali-metal bromides are also used in aromatic brominations, but transition-metal catalysts[5] or inorganic salt[6] are required as oxidants for the reaction. This report describes a novel transformation of alkoxybenzyl alcohols into their corresponding aromatic bromides by using a combination of a hypervalent iodine reagent and lithium bromide under mild reaction conditions (Scheme 1).




**Scheme 1** Conversion of benzoic acids or benzylic alcohols into the corresponding halide

There are a few reports describing the conversion of benzylic alcohols into their corresponding halides.[7] Unfortunately, most of these studies focused on the oxidation of benzylic alcohols to aldehydes, in which halide production was treated as a side reaction. Therefore, a full substrate-scope analysis has not yet been performed, and hypervalent iodine reagents have never been used specifically to prepare halides from benzylic alcohols. Here, we chose 4-methoxybenzyl alcohol (**1a**) as a substrate and we conducted the reaction using 3.0 equivalents of $PhI(OAc)_2$ and 3.0 equivalents of LiBr in $F_3CCH_2OH$, on the basis our previous report. The reaction proceeded successfully, and the corre-

sponding dibrominated compound **3a** was obtained in 93% yield at room temperature within ten minutes (Table 1, entry 1). When other solvents were examined, the monobrominated compound **2a** was the main product (entries 2–5), with the aldehyde also being obtained when THF was used as the solvent (entry 4). Decreasing the proportions of both $PhI(OAc)_2$ and LiBr to one equivalent in $F_3CCH_2OH$ afforded the monobrominated product **2a** in 91% yield at room temperature in 10 min (Entry 7).

**Table 1** Conversion of 4-Methoxybenzyl Alcohol (**1a**) into the Corresponding Halide by Using $PhI(OAc)_2$ and LiBr

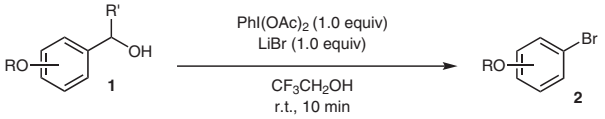

| Entry | $PhI(OAc)_2$ (equiv) | LiBr (equiv) | Solvent | Yield (%) | |
|---|---|---|---|---|---|
| | | | | **2a** | **3a** |
| 1 | 3.0 | 3.0 | $F_3CCH_2OH$ | – | 93 |
| 2 | 3.0 | 3.0 | $CH_3OH$ | – | – |
| 3 | 3.0 | 3.0 | $CH_3CN$ | 81 | – |
| 4 | 3.0 | 3.0 | THF | 68[a] | – |
| 5 | 3.0 | 3.0 | $CH_2Cl_2$ | 73 | – |
| 6 | 2.0 | 2.0 | $F_3CCH_2OH$ | 17 | 69 |
| 7 | 1.0 | 1.0 | $F_3CCH_2OH$ | 91 | – |

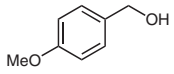
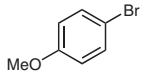
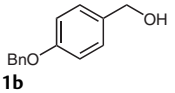
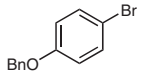
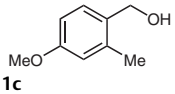
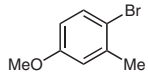
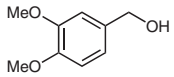
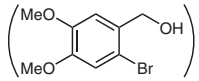
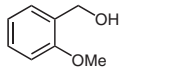
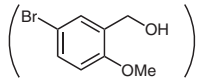
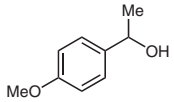
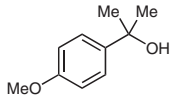
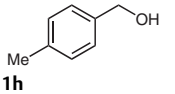
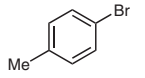
[a] A small amount of the aldehyde was also obtained.

We then investigated the substrate scope for the monobromination of various alkoxybenzyl alcohols by using 1.0 equivalent of $PhI(OAc)_2$ and 1.0 equivalents of LiBr in $F_3CCH_2OH$ at room temperature (Table 2): 4-(benzyloxy)benzyl alcohol (**1b**) was converted into the corresponding bromide **2b** in 80% yield without any oxidized product in the benzyl ether position (entry 2). A methyl substituent *ortho* to the hydroxymethyl group decreased the yield to 48% (entry 3). Electron-donating substituents caused direct bromination of the aromatic ring, and did not result in the desired dehydroxymethyl bromination (entry 4). The reaction of 2-methoxybenzyl alcohol (**1e**) also gave the aromatic bromination product **4e** (entry 5). The secondary benzylic alcohol **1f** gave the corresponding bromide **2a** in quantitative yield (entry 6), whereas the tertiary benzyl alcohol **1g** afforded the corresponding bromide **2a** but with a yield of only 25% (entry 7). No reaction occurred with 4-methylbenzyl alcohol under the aforementioned conditions (entry 8).

Next, we dibrominated the various alkoxybenzyl alcohols by using 3.0 equivalents of $PhI(OAc)_2$ and LiBr in $F_3CCH_2OH$ at room temperature (Table 3). The reaction of 4-(benzyloxy)benzyl alcohol (**1b**) proceeded in 90% yield to give the dibrominated compound **3b** for one hour (Table 3,

**Table 2** Monobromination of Various Substituted Benzyl Alcohols



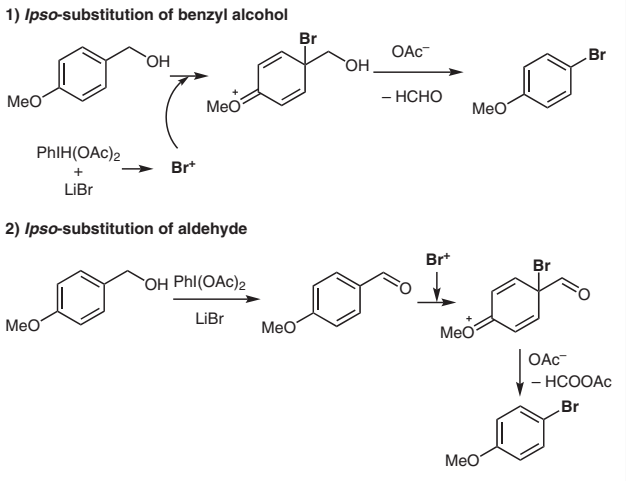

| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 91 |
| 2 |  **1b** |  **2b** | 80 |
| 3[a] |  **1c** |  **2c** | 48 |
| 4 |  **1d** |  **4d** | 0 (quant)[a] |
| 5 |  **1e** |  **4e** | 0 (98)[a] |
| 6 |  **1f** | **2a** | quant |
| 7 |  **1g** | **2a** | 25 |
| 8 |  **1h** |  **2h** | 0[b] |

[a] The aromatic ring-brominated compound **4** was obtained.
[b] The corresponding aldehyde was obtained.

entry 2). 4-Methoxy-2-methylbenzyl alcohol (**1c**) was converted into an inseparable mixture of dibrominated regioisomers **3c** and **3c′** in 66% and 16% yield, respectively (entry 3). Dibromination of 3,4-dimethoxybenzyl alcohol (**1d**) successfully gave the corresponding dibrominated product **3d** in 91% yield, whereas monobromination of **1d** was unsuccessful (entry 4 and Table 2, entry 4). These results demonstrate that dehydroxymethyl bromination of **1d** is possible. However, when using one equivalent of reagent, direct bromination of the aromatic ring is preferred due to the high

electron density of the aromatic ring as a result of the two methoxy substituents. Dibromination of **1e** proceeded to afford **3e**, but in low yield (13%), possibly due to steric hindrance (entry 5). In the monobromination reaction, the *ortho*-substituted substrate **1c** resulted in a significantly lower yield of product (48%) than with substrate **1a** (compare entry 3 and Table 1, entry 1). Therefore, whereas the presence of an *o*-methoxy group caused a low yield of **3e**, it was effective in allowing the reaction to proceed. The reactions of secondary and tertiary alkoxybenzyl alcohols **1f** and **1g**, respectively, gave the corresponding dibrominated product **3a** (entries 6 and 7, respectively).

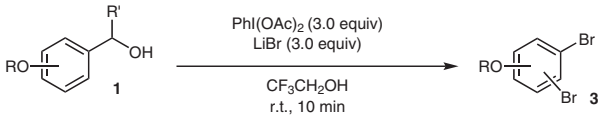
We initially hypothesized that the reaction proceeds through the oxidation of the alkoxybenzyl alcohol to the corresponding carboxylic acid in the presence of $PhI(OAc)_2$ and LiBr,[8] with subsequent conversion of the carboxylic acid into the corresponding bromide. However, because the reaction even proceeded when only 1.0 equivalent of each reagent was used, another reaction pathway was considered. Previous reports describe two reaction mechanisms. One is the *ipso*-substitution of benzyl alcohol by a bromonium species,[7a] and the other is the *ipso*- substitution of the aldehyde generated by oxidation of benzyl alcohol (Scheme 2).[7c] In our reaction, a bromonium species such as PhI(OAc)Br or BrOAc might be generated from the combination of $PhI(OAc)_2$ and LiBr.[8] In this case, *ipso*-substitution should occur at the benzylic alcohol and not the aldehyde. This is likely, because 1.0 equivalents of $PhI(OAc)_2$ and LiBr promoted the reaction, and the tertiary benzylic alcohol underwent dehydroxymethyl bromination under our reaction conditions (Table 2, entry 7 and Table 3, entry 7, respectively).

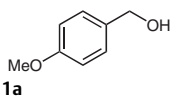
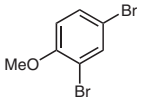
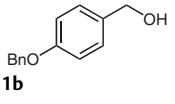
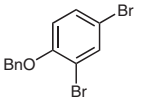
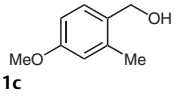
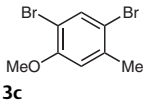
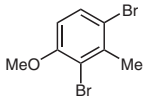
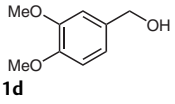
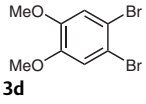
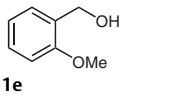
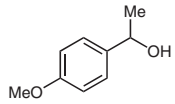
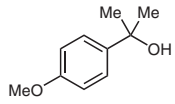



**Scheme 2** Plausible reaction mechanism

We also conducted the reaction with *p*-anisaldehyde under the same conditions but none of the desired product was obtained, and only aromatic bromination proceeded

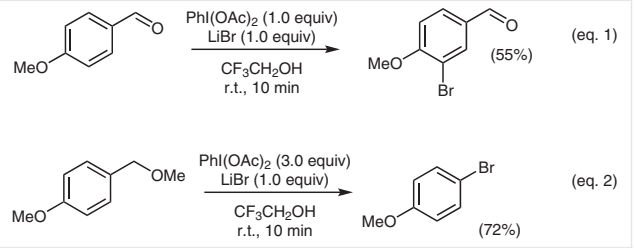
**Table 3** Dibromination of Various Alkoxybenzyl Alcohols




| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1[a] |  **1a** |  **3a** | 93 |
| 2[a] |  **1b** |  **3b** | 90 |
| 3[a] |  **1c** |  **3c**  **3c'** | 66[b] 16[b] |
| 4 |  **1d** |  **3d** | 91 |
| 5 |  **1e** | **3a** | 13 |
| 6 |  **1f** | **3a** | quant |
| 7 |  **1g** | **3a** | 55 |

[a] The reaction time was 1 h.
[b] These products were obtained as inseparable mixtures and the yields were determined by $^1H$ NMR.

(Scheme 3, equation 1). Moreover, the reaction of *p*-methoxybenzyl methyl ether afforded bromoarene **2a**, indicating that no oxidation of the benzyl alcohol occurred (Scheme 3, equation 2). These results strongly imply that the brominated product is formed by direct *ipso*-substitu-




**Scheme 3** The reactions of *p*-anisaldehyde and 4-methoxybenzyl methyl ether under the optimized conditions

tion of the benzylic alcohol followed by aromatization through dehydroxymethylation.

In conclusion, we describe a novel method for the dehydroxymethyl bromination of alkoxybenzyl alcohols by using a hypervalent iodine reagent and lithium bromide in $F_3CCH_2OH$ at room temperature.[9,10] This is the first study detailing the direct conversion of alkoxybenzyl alcohols to aryl bromides. This method affords the corresponding bromide regiospecifically, which might be more useful than the Friedel–Crafts-type bromination. Selective monobromination and dibromination were achieved by changing the proportions of reagents. This reaction is currently being applied to other halogenation processes and the elucidation of a detailed reaction mechanism is underway.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610980.

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(9) **1-Bromo-2-methoxybenzene (2a) (see Ref. 10); Typical Procedure**
$LiBr·H_2O$ (0.2 mmol) and $PhI(OAc)_2$ (0.2 mmol) were added to a solution of 4-methoxybenzyl alcohol (**1a**; 0.2 mmol) in $F_3CCH_2OH$ (1 mL) at r.t. When the reaction was complete (TLC), sat. aq $Na_2SO_3$ was added and the mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by column chromatography (silica gel) to give a yellow oil; yield: 34.1 mg (91%); $^1H$ NMR ($CDCl_3$): δ = 3.79 (s, 3 H), 6.79 (dd, *J* = 2.0, 8.6 Hz, 2 H), 7.38 (dd, *J* = 2.0, 8.6 Hz, 2 H).

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