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One carbon homologation of halides to benzyl ethers

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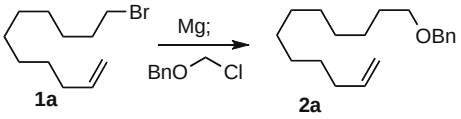
ABSTRACT

The preparation of one carbon homologated benzyl ethers from alkyl and aromatic halides is reported. The coupling reaction is rapid and efficient at room temperature.

1. Introduction

Often in organic synthesis, removing unwanted steps in a synthetic route is convenient from both a time and material standpoint. Adding a step for protection of an alcohol after homologation can be circumvented by the approach presented here. This reduces both the time and the solvent costs needed to purify products, minimizing waste.

As the starting point for a total synthesis, we needed the benzyl ether **2a**. Although a multi-step preparation had been reported,[1] we thought (Eq. 1) that a one-step assembly might be possible, by coupling the Grignard reagent derived from the commercial bromide **1a** with commercial benzyl chloromethyl ether (BOM-Cl).[2–5] We were pleased to observe that the homologation proceeded in good yield (Table 1, entry 1). We have expanded upon this observation to prepare an array of products derived from commercial bromides and Grignard reagents (Table 1, entries 2–6).



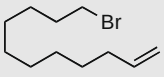
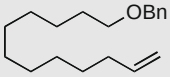
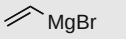
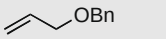
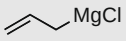
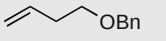
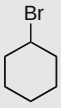
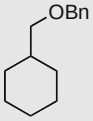
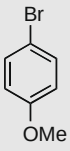
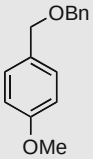
(1)

This coupling shows a good range of scope. Both sp^3 (entries 1, 3, 4, and 6) and sp^2-hybridized Grignard reagents (entries 2 and 5) participated efficiently. The work-up was easy, and the products were readily purified. The yields in Table 1 are for products purified by silica gel chromatography, but on scale distillation worked as well.

We anticipate many uses for the products from this facile homologation. For example, **2c** has been used in a range of useful transformations, inter alia for epoxidation,[8a] as the starting material for the synthesis of 3,5-dihydroxypentyl nucleoside analogues,[8b] and as a metathesis substrate.[8c]

In conclusion, we have developed a rapid and efficient procedure for the one-carbon homologation of halides to benzyl ethers. We anticipate that this coupling will be useful in a wide range of applications.

Table 1
Homologation of halides to benzyl ethers

Entry	Substrate		Product		Yield[a] (%)
1		**1a**[b]		**2a**[c]	90
2		**1b**[d]		**2b**[e]	84
3		**1c**[b]		**2c**[f]	73
4		**1d**[d]		**2d**[g]	64
5		**1e**[b]		**2e**[e]	98
6		**1f**[b]		**2f**[b]	98

[a] Yields are reported for pure products.
[b] The Grignard was prepared from the bromide.
[c] Product had previously been prepared by alternate route: Ref. 1.
[d] Commercial Grignard reagent was used.
[e] Products are commercially available.
[f] Product had previously been prepared by an alternate route: Ref. 6.
[g] Product had previously been prepared by an alternate route: Ref. 7.

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2. Experimental

2.1. Procedure for the preparation of 2c

To a solution of commercial allyl magnesium chloride (4.0 mmol) in THF (8 mL) at 0 °C was added all at once a solution of benzyl chloromethylether (3.8 mmol) in 2 mL of THF. The reaction mixture was held at 0 °C for 30 min, and then was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed. Yields are based on benzyl chloromethyl ether charged. **2c**: Clear oil (73% yield), TLC $R_f = 0.64$ (MTBE/petroleum ether 1:10); ^1H NMR (400 MHz, $CDCl_3$) δ 2.4 (m, 2H), 4.07 (t, $J = 6.8$ Hz, 2H), 4.54 (s, 2H), 5.04 (d, $J = 12.3$ Hz, 1H), 5.14 (d, $J = 17.2$ Hz, 1H), 5.84 (m, 1H), 7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d[9] 135.2, 128.3, 127.6, 127.5 u 138.2, 116.3, 72.9, 69.6, 34.2.

Acknowledgments

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Supplementary data

General experimental procedures, experimental procedures and spectra for all products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.010.

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9. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as 'd' and for methylene and quaternary carbons as 'u'.