



A green bromination method for the synthesis of benzylic dibromides



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ABSTRACT

Reported herein is the identification of a new methodology for the dibromination of benzylic diols. This method proceeds in moderate to good yields for a wide variety of electron-deficient, electron-neutral, and electron-rich aromatic substrates. Moreover, the reagent, 1,3-dibromo-5,5-dimethylhydantoin, and the solvent, tetrahydrofuran, are substantially more environmentally benign than traditional solvents and reagents used for bromination. The utility of this methodology was demonstrated in the high-yielding synthesis of a key intermediate in the synthesis of omeprazole.

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Introduction

Bromination of benzylic alcohols to yield benzylic bromides is a widely used transformation in synthetic organic chemistry,¹ with applications in the synthesis of key drug intermediates,² natural products,³ highly functionalized materials,⁴ and multiple dyes and pigments.⁵ Conventional reagents for the bromination of benzylic alcohols include molecular bromine,⁶ hydrobromic acid,⁷ carbon tetrabromide,⁸ and *N*-bromosuccinimide (NBS).⁹ Conventional solvents for this transformation include chloroform, dichloromethane, and carbon tetrachloride.

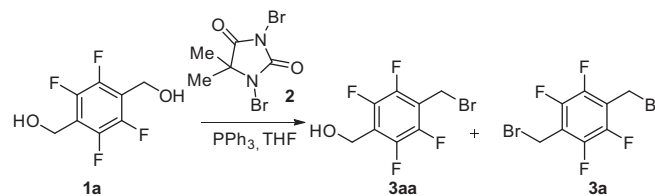
All of the reagents and solvents listed above have been shown to be harmful to the environment,¹⁰ toxic to a wide variety of organisms,¹¹ and expensive to use and dispose of safely.¹² More environmentally benign reagents and solvents that efficiently brominate a wide variety of substrates would provide significant operational advantages in accomplishing such synthetic transformations while limiting the potential environmental damage.

Some examples of environmentally benign bromination methods include the use of solvent-free conditions,¹³ ionic liquids,¹⁴ and aqueous solvents¹⁵ to promote the reactions of organic substrates with bromine-containing salts. The substrates for these reactions include both alkenes and aromatic compounds; however, bromination of benzylic alcohols using environmentally benign reagents has not been reported to date.

1,3-Dibromo-5,5-dimethylhydantoin (DBDMH, compound **2**) has been well-studied in the literature as a catalyst,¹⁶ oxidant,¹⁷ and commercial disinfectant.¹⁸ It has also been used as a bromination reagent for aromatic C–H bonds,¹⁹ alkenes,²⁰ and alkynes.²¹ These literature precedents prompted our investigation into the use of this reagent as a less toxic bromination reagent to achieve efficient benzylic bromination.

Results

Initial investigations focused on the synthesis of dibromide **3a**, driven by ongoing research in the synthesis of electronically-differentiated macrocycles (Scheme 1).²² A screen of various reaction conditions quickly led to the identification of optimal conditions (Table 1, entry 6): tetrahydrofuran (THF) solvent, 2.2 equiv of DBDMH and triphenylphosphine, 2 h reaction time, and a reaction temperature of 0 °C to room temperature. Under these optimized conditions, compound **1a** was converted to its dibrominated



Scheme 1. Synthesis of **3a**.

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Table 1
Optimization of reaction conditions

	Solvent	Eq. 2	Time (h)	Temp	Yield 3aa (%)	Yield 3a (%)
1	CH ₃ CN	1.1	1	0 °C	30	15
2	CH ₃ CN	1.5	1.5	rt	39	19
3	CH ₃ CN	2.5	3	0 °C–rt	0	53
4	EtOAc	2.2	2	rt	0	17
5	THF	2.2	2	0 °C	0	50
6	THF	2.2	2	0 °C–rt	0	54

product **3a** in 54% yield (with no detectable amounts of monobrominated compound **3aa**), compared to the 64% yield observed when the same substrate was treated with carbon tetrabromide in dichloromethane.²² Both the DBDMH reagent and THF solvent are substantially less environmentally harmful than the previously used bromination reagent and solvent,²³ and led to a mild reduction in the product yield.

Under these optimized conditions, a wide variety of electron-deficient benzylic diols were converted to their corresponding dibromides in moderate to good yields (Scheme 2, compounds **3a–3g**). Multiple substitution patterns were well-tolerated (both 1,4-diols and 1,3-diols worked well), as were a wide variety of electron-deficient substituents. Interestingly, whereas one bromine substituent was well-tolerated (compound **3c**), the introduction of two bromine substituents completely shut down the bromination to form compound **3f**. Rather, a mixture of mono- and dialdehydes was formed under these conditions. DBDMH is a well-known oxidant;¹⁷ however, it is interesting that this is the only substrate for which such reactivity was observed.

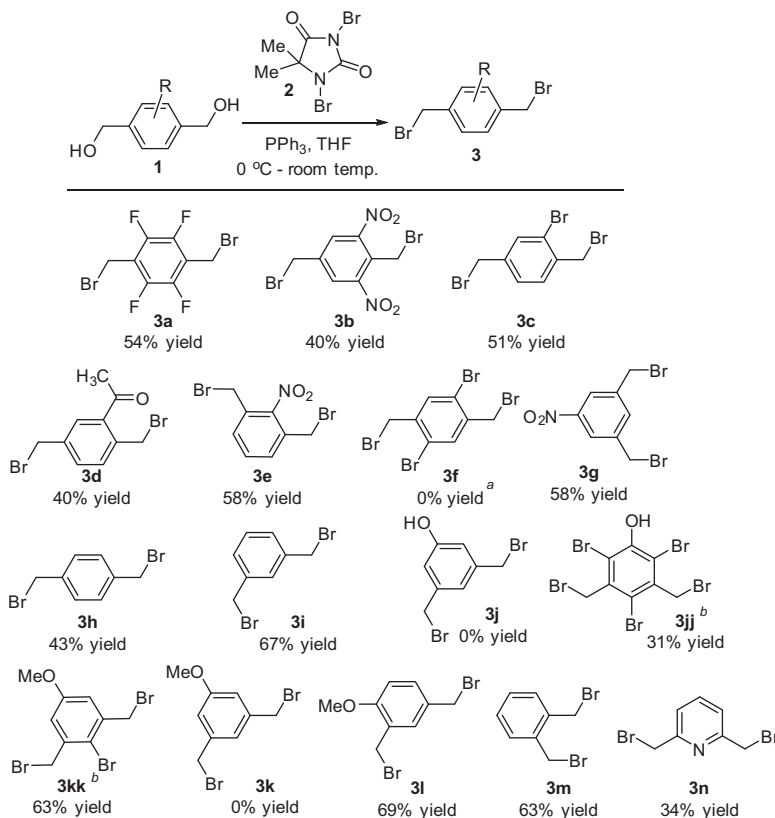
Table 2
Percent yield comparison using DBDMH and CBr₄ as brominating agents

Substrate	DBDMH ^a (%)	CBr ₄ ^b (%)
1a	53	55
1b	40	40
1c	51	20
1d	40	35
1e	58	25
1g	58	33
1h	43	11
1i	67	14
1m	63	28

^a DBDMH, PPh₃, THF, 0 °C to rt, 2 h.

^b CBr₄, PPh₃, THF, 0 °C to rt, 16 h.

These reaction conditions also worked well for a variety of electron-neutral and electron-rich benzylic diols (compounds **3h–3n**), which formed the benzylic dibromide products. Again, multiple substitution patterns were well-tolerated, with 1,2-, 1,3- and 1,4-diol substrates proceeding in high yields. The only limitation observed for these substrates is that the presence of a hydroxyl group or methoxy group at the *meta* position led to a 0% yield of compounds **3j** and **3k**. Instead, substrates **1j** and **1k** underwent both benzylic bromination as well as aromatic bromination to form compounds **3jj** and **3kk**, in accordance with the literature precedent (see ESI for a detailed structural elucidation).²⁴ The strongly activating nature of the hydroxyl group, combined with its small steric size, leads to the bromination of all available *ortho*- and *para*-positions to form **3jj**. The methoxy substituent, by contrast,



^a The reaction of diol **1f** led to the formation of a mixture of aldehydes rather than the desired dibromide **3f**.

^b The reactions of **1j** and **1k** led to the formation of **3jj** and **3kk** rather than **3j** and **3k**.

Scheme 2. Synthesis of benzylic dibromides.

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