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A green bromination method for the synthesis of benzylic dibromides

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\textbf{ARTICLE INFO}

\textbf{ABSTRACT}

Reported herein is the identification of 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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1. Introduction

The 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, and commercial disinfectant.17 It has also been used as a bromination reagent for aromatic C-H bonds,18 alkenes,19 and alkynes.20 These literature precedents prompted our investigation into the use of this reagent as a less toxic bromination reagent to achieve efficient benzylic bromination.

2. Results

Initial investigations focused on the synthesis of dibromide 3a, driven by ongoing research in the synthesis of electronically-differentiated macrocycles (Scheme 1).21 A screen of various reaction conditions quickly led to the identification of optimal conditions (Table 1, entry 6): tetrahydrofuran (THF) solvent, 2.2 equivalents of DBDMH and triphenylphosphine, 2 hour reaction time, and a reaction temperature of 0 °C to room temperature. Under these optimized conditions, compound 1a was converted to its dibrominated 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.

![Scheme 1. Synthesis of 3a](image)

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 1. Optimization of Reaction Conditions](image)

<table>
<thead>
<tr>
<th>solvent</th>
<th>eq.</th>
<th>time</th>
<th>temp.</th>
<th>yield</th>
<th>yield 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CN</td>
<td>1.1</td>
<td>1 hr</td>
<td>0 °C</td>
<td>30%</td>
<td>15%</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>1.5</td>
<td>1.5 hr</td>
<td>RT</td>
<td>39%</td>
<td>19%</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>2.5</td>
<td>3 hr</td>
<td>0 °C-RT</td>
<td>0%</td>
<td>53%</td>
</tr>
<tr>
<td>EtOAc</td>
<td>2.2</td>
<td>2 hr</td>
<td>RT</td>
<td>0%</td>
<td>17%</td>
</tr>
<tr>
<td>THF</td>
<td>2.2</td>
<td>2 hr</td>
<td>0 °C-RT</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>THF</td>
<td>2.2</td>
<td>2 hr</td>
<td>0 °C-RT</td>
<td>0%</td>
<td>54%</td>
</tr>
</tbody>
</table>

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

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-diols 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 literature precedent (see ESI for detailed structural elucidation). 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, directs para-bromination to form 3kk, but has sufficient steric bulk to shut down the ortho-bromination pathway. The bromination reaction also proceeded well for a heteroaromatic diol to yield the desired dibromide in moderate yield (compound 3n).

Scheme 3. Proposed Mechanism for the Dibromination of Benzylic Diols with DBDMH

Scheme 4. Application of DBDMH Bromination in the Synthesis of an Omeprazole Precursor

A direct comparison of the yields obtained using DBDMH and CBr₄ in THF are shown in Table 2, and indicate that the DBDMH bromination yields were equal to or higher than yields obtained using CBr₄ for all substrates investigated. Whereas CBr₄ worked well for electron-deficient substrates 1a-e, it was much less efficient for electron-rich substrates. DBDMH, by contrast, led to...

71% yield over 2 steps

oomprazole "Prilosec"
moderate to good bromination yields in all cases, and has the added advantage of being substantially less toxic to both the environment and to human health. Although higher yields for CBr₄-promoted reactions could likely be found in chlorinated solvents, our focus on green chemistry led us away from pursuing that direction of research.

3. Discussion

The proposed mechanism of this reaction is shown in Scheme 3, and involves the initial formation of a phosphonium bromide salt 5 and highly resonance-stabilized anion 6, which deprotonates one of the benzylic diols to form anion 8. Nucleophilic attack of compound 8 on phosphonium 5 leads to the formation of intermediate 9, which undergoes nucleophilic attack by a bromide ion to form the monobrominated product. Repeating this mechanistic sequence then leads to the formation of the desired dibromide product. In support of this mechanistic proposal, both DBDMH and triphenylphosphine were shown to be essential for achieving the desired reactivity.

Table 2. Percent Yield Comparison Using DBDMH and CBr₄ as Brominating Agents

<table>
<thead>
<tr>
<th>substrate</th>
<th>DBDMHᵇ</th>
<th>CBr₄ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>53%</td>
<td>55%</td>
</tr>
<tr>
<td>1b</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>1c</td>
<td>51%</td>
<td>20%</td>
</tr>
<tr>
<td>1d</td>
<td>40%</td>
<td>35%</td>
</tr>
<tr>
<td>1e</td>
<td>58%</td>
<td>25%</td>
</tr>
<tr>
<td>1g</td>
<td>58%</td>
<td>33%</td>
</tr>
<tr>
<td>1h</td>
<td>43%</td>
<td>11%</td>
</tr>
<tr>
<td>1i</td>
<td>67%</td>
<td>14%</td>
</tr>
<tr>
<td>1m</td>
<td>63%</td>
<td>28%</td>
</tr>
</tbody>
</table>

a DBDMH, PPh₃, THF, 0 °C to room temp., 2 hours
b CBr₄, PPh₃, THF, 0 °C to room temp., 16 hours

Finally, the practical utility of this benzylic bromination methodology was demonstrated through a one-pot synthesis of a key precursor for omeprazole 17, a commercially available antisecretory agent (Prilosec) (Scheme 4). The monobromination of compound 13 occurred using DBDMH in THF, and was followed by removal of the solvent and introduction of sulfide 15 under basic conditions to generate compound 16 in 71% yield over two steps. Compound 16 is remarkably close to the structure of Prilosec (compound 17), requiring only an oxidation of the sulfur to complete the synthetic sequence.

A direct comparison of several common brominating reagents (DBDMH, CBr₄, N-bromosuccinimide, and bromine in acetic acid) indicates that DBDMH has several operational advantages. It is substantially cheaper than both CBr₄ and bromine in acetic acid,25 it is stable at room temperature (unlike both N-bromosuccinimide and bromine in acetic acid, which require cold temperature storage), and it is purchased as an easy-to-handle white solid. Additional advantages were found when the reactions of substrates 1h and 1i were scaled to 4 and 8 times the standard scale. Under these scaled-up conditions, compound 3h was formed in 70% yield for both a 2.9 mmol and 5.8 mmol scale reaction, compared to the 43% yield observed under standard conditions. Compound 3i was formed in 65% isolated yield on a 2.4 mmol and 4.8 mmol scale, highlighting the practical utility of this methodology for larger scale reactions.

4. Conclusion

In conclusion, a new methodology for benzylic bromination using an environmentally friendly solvent and reagent is reported herein. This methodology has a number of advantages compared with traditional bromination reactions, including the ability to achieve good yields for a wide range of electron-rich, electron-deficient, and electron-neutral substrates, the substantially reduced reagent toxicity, and the ability to conduct these reactions in environmentally benign tetrahydrofuran rather than more toxic chlorinated solvents. The applications of this methodology in the synthesis of more complex molecules, as well as detailed mechanistic investigations, are currently underway in our group, and results will be reported in due course.

5. Supplementary Material

Syntheses of all starting materials, synthetic procedures for DBDMH bromination reactions, full spectral characterization of all new compounds. This material is available free of charge via the Internet.

6. Acknowledgements

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7. Bibliography


25. DBDMH: $0.08/gram; CBr_4: $0.39/gram; NBS: $0.10/gram; Br_2 in AcOH: $0.37/gram