ABSTRACT

An effective reagent system was developed for the p-methoxybenzylolation of alcohols, giving p-methoxybenzyl (PMB) ethers in moderate to good yields. 5-(p-methoxybenzylthio)-1-phenyl-1H-tetrazole (PMB-tetrazole) was used in conjunction with thiophilic activator silver triflate (AgOTf) and non-nucleophilic base 2,6-di-tert-butyl-4-methylpyridine (DTBMP) to execute the PMB protection of alcohols under mild conditions. Solvent optimisation studies were performed with cyclohexanol. Studies were also made to explore other methods of synthesizing the PMB-tetrazole reagent. The optimized protection protocol was applied to various substrates bearing sensitive functionalities giving PMB ethers in good yields without undesired reactions. The ease of preparation of PMB-tetrazole and the mild conditions accompanying this reagent system makes it a promising protocol for PMB protection of multifunctional molecules.

INTRODUCTION

Protecting groups play an important role in the synthesis of organic molecules. As chemists aspire to synthesize increasing complex multifunctional organic molecules, there is a need for the use of increasingly mild protection and deprotection protocols, which do not affect sensitive functionalities of the molecules.

PMB ethers are useful hydroxyl protecting groups in the synthesis of complex organic molecules, especially in oligosaccharide synthesis, peptide coupling, and nucleoside chemistry. The PMB group has the advantage of being cleaved under mild oxidative conditions using either 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or ceric (IV) ammonium nitrate (CAN) which do not affect benzyl ethers or silyl ethers. The orthogonality offered makes it useful in the synthesis of complex molecules where extensive selective protection-deprotection protocols are required.

In 2005, the Lear group developed a new reagent, 5-(p-methoxybenzylthio)-1-phenyl-1H-tetrazole (PMB-tetrazole), which was shown to be capable of converting alcohols to PMB ethers under mild conditions. The p-methoxybenzylolation reactions were optimized using both silver hexafluorophosphate (AgPF₆) and silver triflate (AgOTf) as thiophilic activator in conjunction with 2,6-di-tert-butyl-4-methylpyridine (DTBMP) as additive (Scheme 1).
Scheme 1: p-methoxybenzylolation of alcohols using PMB-tetrazole

Moderate to good yields were obtained from the two optimization studies carried out previously\textsuperscript{7,8}. In this project, we expand on the work done previously by proposing other methods of preparing the PMB-tetrazole reagent as well as to optimise the solvent used in this reagent system. Lastly, the optimised protocol would be applied to protect a variety of substrates bearing sensitive or labile functionalities to investigate the mildness of the reagent system.

MATERIALS AND METHODS

Optimisation of solvent for p-methoxybenzylolation of cyclohexanol (Table 2, Entries 1-4).

A solution of 2,6-di-tert-butyl-4-methylpyridine (0.0513g, 0.25mmol) and 5-(p-methoxybenzylthio)-1-phenyl-1H-tetrazole (0.0955g, 0.32mmol) in 1 ml of anhydrous solvent (2ml) was transferred into a 1ml ice cooled solution mixture of cyclohexanol (0.0200g, 0.2mmol) and silver triflate (0.0822g, 0.32mmol). The reaction mixture was allowed to warm up to room temperature and left to stir overnight. The solvent was evaporated. Ethyl acetate was added and the suspension obtained was filtered through celite. The filtrate was evaporated to dryness in vacuo and the crude product was purified by silica gel chromatography using n-hexane: ethyl acetate (98: 2) to obtain the p-methoxybenzyl-cyclohexylether.

General procedure for p-methoxybenzylolation of various substrates (Table 3, Entries 1-8).

A solution of 2,6-di-tert-butyl-4-methylpyridine (0.0513g, 0.25mmol) and 5-(p-methoxybenzylthio)-1-phenyl-1H-tetrazole (0.0955g, 0.32mmol) in anhydrous dichloromethane (1ml) was transferred into an ice cooled solution mixture of substrate (0.2mmol) and silver triflate (0.0822g, 0.32mmol) in anhydrous dichloromethane (1ml). The reaction mixture was allowed to warm up to room temperature and left to stir overnight. The solvent was evaporated. Ethyl acetate was added and the suspension obtained was filtered through Celite. The filtrate was evaporated to dryness in vacuo and the crude product was purified by silica gel chromatography using n-hexane: ethyl acetate.

RESULTS AND DISCUSSION

Synthesis of PMB-tetrazole

The various syntheses of PMB-tetrazole, their durations and the cost per gram of reagent for each synthesis are shown below (Table 1).
Table 1: Cost of synthesizing PMB-tetrazole

<table>
<thead>
<tr>
<th>Method</th>
<th>Yield</th>
<th>Duration</th>
<th>Cost per gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Synthesis</td>
<td>93%</td>
<td>Over 2 nights</td>
<td>$1.90</td>
</tr>
<tr>
<td>Mitsunobu Reaction</td>
<td>95%</td>
<td>1h</td>
<td>$3.09</td>
</tr>
<tr>
<td>Williamson Ether Synthesis</td>
<td>92%</td>
<td>Overnight</td>
<td>$3.10</td>
</tr>
</tbody>
</table>

Optimization of solvent

Previous optimization studies carried out by Tan\textsuperscript{5} have shown dichloromethane was the most ideal solvent for this reagent system giving yields of up to 89\% with cyclohexanol.

\[
\text{AgOTf (1.60eq), 4A MS DTBMP (1.25eq)}
\]

\[
\text{Solvent (2ml), RT, overnight}
\]

Table 2: Variation of solvent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CICH\textsubscript{2}CH\textsubscript{2}Cl</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>CH\textsubscript{3}CN</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>C\textsubscript{6}H\textsubscript{5}CF\textsubscript{3}</td>
<td>38%</td>
</tr>
</tbody>
</table>

Dichloromethane remains the most ideal solvent for this reagent system

p-Methoxybenzylolation of Alcohols bearing Sensitive Functionalities

Table 3: p-Methoxybenzylolation of various alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate\textsuperscript{a}</th>
<th>Yield/ %\textsuperscript{b}</th>
</tr>
</thead>
</table>
| 1     | \begin{align*}
\text{TESO} & + \text{OH} \\
11 & \end{align*}                      | 85                          |
| 2\textsuperscript{c} | \begin{align*}
\text{Si} & + \text{OH} \\
12 & \end{align*}                      | 23                          |
a 0.2 mmol of substrate was used unless otherwise stated. b All reported yields are isolated yields unless otherwise stated.

Unreacted substrate was recovered. c Substrate was not purified prior to protection. Unreacted substrate was not recovered due to instability in column. d Separation of protected alcohol was difficult due to proximity of product band to side product and PMB tetrazole. e Deprotection of the 1,2-dithiane occurred upon work up. f 0.032 mmol of substrate was used. g 0.17 mmol of substrate was used. h No deprotection was observed and substrate was recovered quantitatively.

With the exception of the 1,2-dithane protection of levulinic ester (Table 3, Entry 4), the p-methoxybenzylolation of alcohols bearing labile groups such as trimethylsilyl (Table 3, Entry 5), triethylsilyl (Table 3, Entry 6), dichloroacetate (Table 3, Entries 6 and 7) and tosylates (Table 3, Entry 8) gave no undesired reactions, giving PMB ethers in moderate to good yields. Selective monoprotection of diols also gave moderate to good yields (see full report).

CONCLUSION

PMB-tetrazole is an effective reagent for the p-methoxybenzylolation of alcohols giving PMB ethers in moderate to good yields. The conditions for reaction are mild, making this reagent system suitable for use on sensitive multi-functional molecules.

REFERENCES