Investigation of copper(II) tetrafluoroborate catalysed epoxide opening

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A R T I C L E  I N F O

Article history:
Received 12 August 2011
Revised 30 September 2011
Accepted 17 October 2011
Available online 21 October 2011

Keywords:
Epoxide
Copper(II) tetrafluoroborate
Lewis acid
Alcohols

Abstract

We report the extension of the copper(II) tetrafluoroborate catalysed opening of epoxides with alcohols to include a wider variety of alcohols, a range of solvents and a method to purify the products from the reaction.

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Scheme 1. General reaction for copper(II) tetrafluoroborate catalysed epoxide opening.

The reaction has previously been reported using common alcohols, such as methanol, isopropanol, tert-butanol, allyl alcohol and benzyl alcohol, which do not provide much opportunity for further synthesis. It was decided to expand the scope of the reaction, both in terms of what substrates are suitable, and synthetic utility. We present further synthetically useful substrates for this reaction, a new method for separating the products from excess alcohol and a study of alternative solvents.

Initially, work focused around opening the epoxides with mono-protected diols and N-protected alkyl amino alcohols (entries 1–4); these gave the desired products in reasonable yields (Table 1). These protected alcohols can be further functionalised in a wider synthesis. The O-protected amino alcohol (entry 5) did not react, possibly because the primary amine coordinated to the copper catalyst; the copper(II) tetrafluoroborate catalysed amine epoxide opening has only been reported in solvent-free versions of this reaction.25 A number of other functionalised alcohols were investigated (Table 1). For some of them the reaction worked well, however in other cases the yields were poor. The poor solubility of some of the substrates in CH₂Cl₂ is likely to have contributed to the failure of the reaction in at least some cases (entries 7, 8, 12 and 13).

The only solvent recorded in the literature for this procedure is CH₂Cl₂, therefore the effect of solvent on the reaction was investigated. The ring-opening reaction with TBDPS-protected...
butane-1,4-diol was used because this was one of the few examples where the product could be purified directly (Scheme 2). In addition, the alcohol is also readily soluble in all the solvents used in the study.

The CH$_2$Cl$_2$ control reaction worked with TBDPS-protected butane-1,4-diol (Table 2, entry 2) to give a yield comparable to previous reactions ($\approx$60%), indicating that the results under these conditions can be usefully compared to previous findings. The three chlorinated solvents tested showed similar yields, with chloroform and CH$_2$Cl$_2$ giving slightly higher yields than DCE. Solvents containing a carbonyl group (EtOAc, DMF, NMP) generally gave poor yields, with only EtOAc giving a minimal amount of product. Similarly MeCN only gave a low yield. The solvents containing an ether functionality gave yields that were generally lower than the chlorinated solvents, although diethyl ether performed almost as well as CH$_2$Cl$_2$. However, CMPE and THF were low yielding and 1,4-dioxane gave no reaction at all. Toluene gave the highest yield of all the solvents tested.

There are several possible reasons for nonpolar solvents increasing the rate of reaction. Firstly, polar solvents with readily available lone pairs, such as DMF, NMP and 1,4-dioxane, could potentially compete with the epoxide in coordinating to the copper catalyst, leading to a reduced rate of reaction. In contrast, solvents with no lone pairs, such as the chlorinated solvents and toluene do not complex strongly to the copper and do not prevent the epoxide binding. Secondly, if the rate determining step is the attack of alcohol on the copper catalyst epoxide complex via an SN2 mechanism, then the transition state complex will have a more distributed charge relative to the reactants and hence is more stabilised by a nonpolar solvent (Scheme 3). In addition, both reactants would have a higher degree of solvation in a polar solvent.

### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol/amine</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Alcohol/amine</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BocHN $\sim$ OH</td>
<td>66</td>
<td>8</td>
<td>HO $\sim$ OH</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>BocHN $\sim$ OH</td>
<td>53</td>
<td>9</td>
<td>HO $\sim$ OH</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>TBDPSO $\sim$ OH</td>
<td>78</td>
<td>10</td>
<td>TBDPSO $\sim$ OH</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>TBDPSO $\sim$ OH</td>
<td>63</td>
<td>11</td>
<td>TBDPSO $\sim$ NH$_2$</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>TBDPSO $\sim$ NH$_2$</td>
<td>0</td>
<td>12</td>
<td>HO $\sim$ OH</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>HO $\sim$ OTr $\sim$ Boc</td>
<td>53</td>
<td>13</td>
<td>HO $\sim$ OH</td>
<td>0</td>
</tr>
</tbody>
</table>

* Reactions carried out using 1% catalyst and 4 equiv alcohol at room temperature for 24 h in CH$_2$Cl$_2$.

* Unidentified product.

### Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Snyder polarity index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl$_3$</td>
<td>62</td>
<td>4.1</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>58</td>
<td>3.1</td>
</tr>
<tr>
<td>3</td>
<td>DCE</td>
<td>46</td>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>16</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>0</td>
<td>6.4</td>
</tr>
<tr>
<td>6</td>
<td>NMP</td>
<td>0</td>
<td>6.7</td>
</tr>
<tr>
<td>7</td>
<td>MeCN</td>
<td>10</td>
<td>5.8</td>
</tr>
<tr>
<td>8</td>
<td>Et$_2$O</td>
<td>54</td>
<td>2.8</td>
</tr>
<tr>
<td>9</td>
<td>CPME$^c$</td>
<td>38</td>
<td>Not available</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>21</td>
<td>4.0</td>
</tr>
<tr>
<td>11</td>
<td>1,4-Dioxane</td>
<td>0</td>
<td>4.8</td>
</tr>
<tr>
<td>12</td>
<td>Toluene</td>
<td>66</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* Monitored by TLC, product isolated by radial-band chromatography and the structure confirmed by NMR spectroscopy.

* Polarity is indicated by the Snyder Polarity Index.$^{26}$

* CMPE-cyclopentyl methyl ether.

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**Scheme 2.** Copper(II) tetrafluoroborate catalysed epoxide opening solvent study.

**Scheme 3.** Transition state for the copper(II) tetrafluoroborate catalysed opening of cyclohexene oxide.
and therefore the nucleophile would be less available to attack the epoxide.  

Although the solvent must allow some of the copper catalyst to dissolve, it was observed that the negative effects of a polar solvent far outweighed the benefit of having more catalyst in solution. However, some of the more polar but lower yielding solvents may be useful where substrate solubility is an issue. These results show that there are several other solvents that are suitable for this reaction, which may extend the type of substrates that can be used. There is certainly more scope for exploring solvents for this reaction.

A further complication arises because the reaction works best with four equivalents of alcohol. In a number of instances, the product and the alcohol reagent had similar polarity, which made separation of the product and the alcohol problematic. Previously, this problem has been overcome either by using volatile alcohols which could be removed in vacuo, by washing with water, or by acetylation the reaction mixture before performing column chromatography, and then deacetylating the purified material.

The first two options were not available because none of the alcohols used in this study are volatile or water soluble, and the third option is laborious because it adds two steps to a synthesis. There are several other solvents that are suitable for this reaction, even some of the more polar but lower yielding solvents may be used where substrate solubility is an issue. These results show that the nucleophile would be less available to attack the epoxide.

General ring-opening method, as exemplified by trans-2-[3-[(tert-butyldiphenylsilyl)oxy]propan-1-ol (1.980 mg, 6.296 mmol, 4 equiv) and Cu(BF₄)₂(4 mg, 0.016 mmol, 0.01 equiv) were dissolved in CH₂Cl₂ (10 mL) using sonication (1 min). The mixture was stirred under argon overnight at room temperature. The mixture was diluted with H₂O (20 mL), extracted with CH₂Cl₂ (3 × 15 mL) and then the combined organic extracts were washed with brine (50 mL) and filtered through cotton wool. The solvent was removed to leave a residue.

General tritylation method as exemplified by trans-2-[3-[(tert-butyldiphenylsilyl)oxy]propan-1-ol (1.980 mg, 6.296 mmol, 4 equiv) and Cu(BF₄)₂(4 mg, 0.016 mmol, 0.01 equiv) were dissolved in CH₂Cl₂ (10 mL) using sonication (1 min). The mixture was stirred under argon overnight at room temperature. The mixture was diluted with H₂O (20 mL), extracted with CH₂Cl₂ (3 × 15 mL) and then the combined organic extracts were washed with brine (50 mL) and filtered through cotton wool. The solvent was removed to leave a residue.

Scheme 4. Example of the trityl chloride method for removing excess alcohol.

Cyclohexene oxide (0.159 mL, 1.574 mmol, 1 equiv), 3-[(tert-butyldiphenylsilyl)oxy]propan-1-ol (1.980 mg, 6.296 mmol, 4 equiv) and Cu(BF₄)₂(4 mg, 0.016 mmol, 0.01 equiv) were dissolved in CH₂Cl₂ (10 mL) using sonication (1 min). The mixture was stirred under argon overnight at room temperature. The mixture was diluted with H₂O (20 mL), extracted with CH₂Cl₂ (3 × 15 mL) and then the combined organic extracts were washed with brine (50 mL) and filtered through cotton wool. The solvent was removed to leave a residue.

Acknowledgements

We would like to acknowledge the MRC for a PhD studentship (A.S.C.) and the Wellcome Trust (grants 085622 and 083481) for funding.

References and notes