Synthesis of Piperidines from Z-α,β-Unsaturated Diazoketones

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INTRODUCTION

Piperidine systems are highly widespread in many natural products of great pharmaceutical interest.1 These systems have many interesting biological activities, such as anticancer and anti-HIV.2 In this work, we describe the stereoselective preparation of Z-α,β-unsaturated diazoketones from aldehydes and their conversion to substituted dihydropyridin-3-ones like 3 in just one step after an intramolecular N-H insertion reaction. The application of this chemistry in the direct synthesis of the natural 3,4,5-trihydroxypiperidine 4 is also described (Fig 1).

RESULTS AND DISCUSSION

Three new Ando-type phosphonates, containing a diazo group, were synthesized (Fig. 2) and employed in the HWE reaction (Tab 1), aiming the preparation of the Z-unsaturated diazoketones.

First, we studied the preparation of the Z-α,β-unsaturated diazoketones, using benzaldehyde as a model in the HWE reaction.

Table 1. Optimization of HWE reaction to Z-α,β-unsaturated diazoketones synthesis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield (%)</th>
<th>Z:E ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>63</td>
<td>2:3</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>97</td>
<td>7:3</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA</td>
<td>11</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td>t-BuLi</td>
<td>41</td>
<td>6:4</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOK</td>
<td>92</td>
<td>9:1</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOK</td>
<td>80</td>
<td>8:2</td>
</tr>
</tbody>
</table>

*Measured by 1H NMR – 2 equiv. of the phosphonate anion was employed. 1 equiv. of 18-crown-6 ether was used as additive.

Next, to show the scope of the methodology, new Z-α,β-unsaturated diazoketones with aliphatic, aryl and amino groups were prepared in good yields and selectivity (Fig. 3). These diazoketones were converted to substituted dihydropyridin-3-ones after an intramolecular N-H insertion reaction and applied to the synthesis of (+/-)-(3R,5R)-piperidine-3,4,5-triol 4, an α-glycosidase and β-galactosidase inhibitor isolated from Eupatorium fortunei TURZ2 (Fig. 4).

CONCLUSION

We have developed a two-step method for the easy access to highly functionalized piperidine systems, such as dihydropyridin-3-ones, from aldehydes4. The sequence is direct and permits the synthesis of several types of hydroxylated piperidines.

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REFERENCES