Diastereoselective synthesis of dihydroquinolines and tetrahydroquinolines from Morita Baylis-Hillman adducts

Manoel T. Rodrigues Jr., Andre Capretz Agy, Danilo Machado Lustosa and Fernando Coelho*

Laboratório de Síntese de Produtos Naturais e Fármacos, Instituto de Química, Universidade Estadual de Campinas-UNICAMP, Caixa Postal 6154, 13083-970, Campinas-SP-Brazil
*coelho@iqm.unicamp.br

Keywords: Morita-Baylis-Hillman Reaction, dihydroquinolines and tetrahydroquinolines.

INTRODUCTION

The quinolone, dihydroquinolines and tetrahydroquinolines unities are present in many natural and synthetic compounds. These nuclei exhibit a wide spectrum of medicinal properties, such as antimalarial, antitumor, antibacterial, anti-inflammatory, and many others.1 Due to this biological profile several synthetic approaches have been known for the preparation of these heterocycles.2 In this work we disclosed a facile method to prepare quinolines derivatives through a Morita-Baylis-Hillman adduct. Our approach is based on a tandem sequence involving a Michael addition reaction and a \( \text{S}_{\text{E}}\text{Ar} \) reaction.

RESULTS AND DISCUSSION

2-Bromo-3-nitrobenzaldehyde (3) was prepared according to a procedure described in literature. Acid 1 was reduced in the presence of \( \text{BH}_3\text{SMe}_2 \) to afford alcohol 2 (Scheme 1). Oxidation of the alcohol 2 to aldehyde was accomplished using PCC, in 91% overall yield (2 steps). MBH adduct 4 was prepared using a protocol developed by our group.3 In brief, aldehydes were treated with methyl acrylate to provide the corresponding MBH adduct in 98% yield. Compound 4 was therefore silylated in the presence of TBSOTf to give silylated derivative 5, in 95% yield (Scheme 1).

Scheme 1. Preparation of aldehyde 3 and MBH adduct 4 and silylation of the MBH adduct. a) \( \text{BH}_3\text{SMe}_2 \), rt, 12h; b) PCC, \( \text{CH}_2\text{Cl}_2 \), rt, 12h (91% - 2 steps); c) Methyl acrylate, DABCO, rt, 24h, 98%; d) TBSOTf, \( \text{CH}_2\text{Cl}_2 \), rt, 2h, 95%.

A solution of the silylated MBH adduct 5 in methanol was treated, under reflux, with amine (1.2 eq.) in the presence of triethylamine (acting as a base) to give the substituted quinolines derivatives in good syn diastereoselectivity (syn/anti) and yields (Table 1).

Table 1. Synthesis of dihydro- and tetrahydroquinolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R )</th>
<th>6a-e Yield(^*)</th>
<th>7a-e Yield (%) (syn/anti)(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{CH}_2\text{Ph} )</td>
<td>6a, 35</td>
<td>7a, 60 (11:1)</td>
</tr>
<tr>
<td>2</td>
<td>(( \text{CH}_3 ))indolyl</td>
<td>6b, 42</td>
<td>7b, 53 (13:1)</td>
</tr>
<tr>
<td>3</td>
<td>(( \text{CH}_2 ))( \text{CH}_2\text{OMe} )</td>
<td>6c, 43</td>
<td>7c, 53 (12:1)</td>
</tr>
<tr>
<td>4(^*)</td>
<td>( \text{CH}_2\text{Ph}(\text{OMe})_2 )</td>
<td>6d, 48</td>
<td>7d, 35 (11:1)</td>
</tr>
<tr>
<td>5</td>
<td>( \text{CH}_2\text{CH}=\text{CH}_2 )</td>
<td>6e, 43</td>
<td>7e, 52 (13:1)</td>
</tr>
</tbody>
</table>

\(^*\)Yields refer to isolated purified products. \(^*\)Diastereoselectivity was determined by \( ^1\text{H} \) NMR, by measuring the coupling constant of the carbinolic proton.6 Entry 4: we observe a product degradation.

The formation of compounds 6a-e can be explained by a \( \text{S}_{\text{E}}\text{Ar} \) displacement reaction of silylated MBH 5 with amine followed by cyclization. Otherwise, the high diastereoselectivity attained in the preparation of compounds 7a-e can be explained by the control exerted by the voluminous silyl group. Previous results described by our group support this proposition. Unfortunately all chromatographic attempts to separate the diastereoisomers failed.6

CONCLUSION

In summary, we have demonstrated that dihydro- and tetrahydroquinolines can be easily prepared in good yields and diastereoselectivity from MBH adducts.

ACKNOWLEDGEMENTS

We thank FAPESP, CNPq and CAPES for financial support.

REFERENCES