Intramolecular Wittig reactions with esters utilising triphenylphosphine and dimethyl acetylenedicarboxylate

Lyndsay A. Evans, Kimberley E. Griffiths, Holger Guthmann and Patrick J. Murphy*

Department of Chemistry, University of Wales, Bangor, Gwynedd LL57 2UW, UK

Received 9 August 2001; revised 17 October 2001; accepted 26 October 2001

Abstract—The intramolecular Wittig olefination of α-hydroxy- and α-amino esters has been effected in high yield using a combination of triphenylphosphine and dimethyl acetylenedicarboxylate. © 2002 Elsevier Science Ltd. All rights reserved.

We previously reported¹ that reaction of α-hydroxybutyrolactones, for example 1, with triphenylphosphine (TPP) and dimethyl acetylenedicarboxylate (DMAD) in dioxane at reflux led to the formation of two bicyclic products 3 and 4 in a 2:1 ratio via the ylide intermediate 2 (Scheme 1).

In order to test the generality of this reaction, we investigated the corresponding reaction of esters and thus treated ethyl glycolate 5a under similar conditions² and were pleased to observe the formation of the expected Wittig product 6a in 57% yield together with 8a, the product from the conjugate addition of ethyl glycolate to DMAD, in 26% yield (Table 1, entry 1). This was a particularly encouraging result as we had envisaged that more forcing conditions might have been required to effect the cyclisation, as is often the case with esters.³ We attempted to minimise the formation of the by-product 8a by increasing the relative amounts of TPP and DMAD and allowing the reaction to stir at room temperature for longer periods of time, however, this had little effect on the overall outcome of the process. Structural determination of the product 6a was aided by the characteristic 3JH-H coupling found in 2,5-dihydrofurans, which is of the order of 4–5 Hz for the cis-protons and 1–2 Hz for the corresponding trans-protons.⁴ In the case of 6/7a, these values were found to be J=4.6 and 1.8 Hz, respectively (Scheme 2).

When the reaction was repeated using ethyl lactate 5b (Table 1, entry 2) a similar result was observed with the cyclisation products 6/7b being isolated in 90% yield and in a 5:1 ratio, together with a smaller amount of 8b (8%). These again were identified on the basis of the magnitude of their 3JH-H values. The relative ratio of these two compounds remained constant (ca. 4.5–5:1) over several reactions indicating that the selectivity for the cis-product probably has its origins in the step leading to the formation of the intermediate ylide. This might also suggest that the products are stable to epimerisation under the reaction conditions. Finally, reaction of ethyl mandelate 5c (Table 1, entry 3) under identical conditions gave 6/7c in 78% yield and in a 25:1 ratio, together with the addition product 8c in 15% yield (Scheme 2).

We next turned our attention to the formation of the corresponding dihydropyrroles and initially looked at the series of Boc-protected amino acid esters 9a–c (Table 2, entries 1–3 and Scheme 3).⁵ We were encouraged to see that reaction of N-Boc glycine ethyl ester 9a under the standard conditions gave a respectable 46% yield of 10a.

Scheme 1. (a) PPh₃/DMAD/dioxane/10°C, 1 h, then reflux 3 h 84% (2:1).

Keywords: intramolecular Wittig reaction; 2,5-dihydrofurans; 2,5-dihydropyrroles.

* Corresponding author. E-mail: paddy@bangor.ac.uk
Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>5 R</th>
<th>6/7 (%)</th>
<th>6-7 (%)</th>
<th>8 (%)</th>
<th>$^5J_{H-H}^{cis}$ (Hz)</th>
<th>$^5J_{H-H}^{trans}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a H</td>
<td>57</td>
<td>–</td>
<td>26</td>
<td>$J=4.6$</td>
<td>$J=1.8$</td>
</tr>
<tr>
<td>2</td>
<td>b* Me</td>
<td>90</td>
<td>5:1b</td>
<td>8</td>
<td>$J=3.9$</td>
<td>$J=1.5$</td>
</tr>
<tr>
<td>3</td>
<td>c Ph</td>
<td>78</td>
<td>25:1b</td>
<td>15</td>
<td>$J=4.1$</td>
<td>$J=2.6$</td>
</tr>
</tbody>
</table>

* Ethyl (S)-(-)-lactate was used.
* Inseparable by column chromatography.

Scheme 2. (a) PPh$_3$/DMAD/dioxane/10°C, 1 h, then reflux 16 h.

yield of the expected 2,5-dihydropyrrole 10a, together with a considerable amount of recovered 9a which raised the yield, based on conversion, to 90%. Again, structural determination of 9a was aided by the characteristic $^5J_{H-H}$ coupling found in 2,5-dihydropyrroles. Following on from this, we attempted a similar reaction with N-Boc alanine ethyl ester 9b and were disappointed to achieve only a 13% yield of the desired products 10/11b in ca. 1:1 ratio. Again, based on recovered starting material this yield rose to 93%. We next investigated the reaction of ethyl thioglycolate 12 under these conditions and not surprisingly obtained only the addition product 13 in high yield. We attempted to prevent the formation of this product by firstly generating the vinyl phosphonium salt 14 in situ from DMAD and triphenylphosphonium hydrobromide. This was then reacted with 12 in the presence of pyridine or DBU to effect the formation of the intermediate ylide. Despite considerable effort, we were unable to isolate any of the required 2,5-dihydrothiophene, the only major product obtained being triphenylphosphine sulphide, suggesting that desulfurisation of the starting material and/or product is a competitive process (Scheme 3).

We felt that the low conversion of substrates 9a–c was probably due to a steric effect related to the Boc protecting group. We thus performed a series of reactions on the corresponding series of Z-protected amino acid esters 9d–f. We were pleased to find that these substrates were far more suitable for the reaction leading to the dihydropyrroles 10/11d–f in 75–96% overall yield (Table 2, entries 4–6), with only 9e (entry 5) being recovered in any appreciable amount (Scheme 3). As observed with the dihydronaphthalene examples, in all these reactions, there appeared to be a bias towards the formation of the cis-products 10, however, the effect was not as pronounced.

We next investigated the reaction of ethyl thioglycolate 12 under these conditions and not surprisingly obtained only the addition product 13 in high yield. We attempted to prevent the formation of this product by firstly generating the vinyl phosphonium salt 14 in situ from DMAD and triphenylphosphonium hydrobromide. This was then reacted with 12 in the presence of pyridine or DBU to effect the formation of the intermediate ylide. Despite considerable effort, we were unable to isolate any of the required 2,5-dihydrothiophene, the only major product obtained being triphenylphosphine sulphide, suggesting that desulfurisation of the starting material and/or product is a competitive process (Scheme 4).

Table 2. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>9 R</th>
<th>10/11 (%)</th>
<th>10/11</th>
<th>$^5J_{H-H}^{cis}$ (Hz)</th>
<th>$^5J_{H-H}^{trans}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a H</td>
<td>46 (90)</td>
<td>–</td>
<td>$J=4.4$</td>
<td>$J=1.7$</td>
</tr>
<tr>
<td>2</td>
<td>b Me</td>
<td>13 (93)b</td>
<td>ca. 1:1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>c Ph</td>
<td>46 (99)</td>
<td>1.4:1</td>
<td>$J=4.6$</td>
<td>$J=0$</td>
</tr>
<tr>
<td>4</td>
<td>d H</td>
<td>91</td>
<td>–</td>
<td>$J=4.2$</td>
<td>$J=1.3$</td>
</tr>
<tr>
<td>5</td>
<td>e Me</td>
<td>75 (96)b</td>
<td>ca. 1:1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>f Ph</td>
<td>96</td>
<td>1.2:1</td>
<td>$J=4.4$</td>
<td>$J=0$</td>
</tr>
</tbody>
</table>

a Yields in parentheses are based on recovered starting material.
* Inseparable by column chromatography.
* Signals obscured.

Scheme 3. (a) PPh$_3$/DMAD/dioxane/10°C, 1 h, then reflux 16 h.
In conclusion, we have demonstrated that the intramolecular Wittig reaction of the ylide generated from the reaction of α-hydroxy or Z-protected α-aminoesters leads to the formation of 2,5-dihydropyrroles or 2,5-dihydropyrrol-2-ones, respectively, in high yields. In addition, the preferential formation of the cis-heterocycles in these reactions and their apparent stability to epimerisation would suggest that this reaction could be utilised in an asymmetric manner. We intend to investigate this eventuality, as well as other transformations, for example preliminary results include the aromatisation of 10a to the pyrrole 15 and the deprotection of 10/11b to give 16a, both of which proceeded in high yield (Scheme 5).

Acknowledgements

Thanks are given to the ERASMUS/SOCRATES scheme (H.G.) and to the EPSRC Mass spectrometry centre at Swansea.

References

2. General procedure: The required α-hydroxy ester or protects α-amino acid ester (1 equiv., typically 10 mmol) was dissolved in dry dioxane (20 ml) together with triphenylphosphine (1.1–3.0 equiv.) and cooled in ice water (to ca. 10°C). DMAD (1.0–1.5 equiv.) was then added dropwise over 5 min and the reaction warmed to rt over 1 h. The reaction was refluxed overnight (16 h), cooled to rt which was followed by the addition of silica gel (8–10 g) and evaporation of the solvent. The resulting free flowing powder was applied to a silica gel column and the products eluted with a diethyl ether/petroleum ether mix. All compounds displayed satisfactory analytical data.

4,5-Dicarbomethoxy-3-ethoxy-2,5-dihydropyran 6a. 1H NMR: δ 5.25 (dd, 1H, J = 4.6, 1.8 Hz, CH), 4.88 (dd, 1H, J = 13.7, 4.6 Hz, CH3), 4.70 (dd, 1H, J = 13.7, 1.8 Hz, CH3), 4.15 (q, 2H, J = 7.0 Hz, CH2), 3.90 (s, 3H, CH3), 3.60 (s, 3H, CH3), 1.37 (t, 3H, J = 7.0 Hz, CH3). 13C NMR: δ = 171.52 (C), 166.06 (C), 162.31 (C), 99.51 (C), 83.33 (CH3), 71.96 (CH2), 68.64 (CH2), 52.31 (CH2), 51.28 (CH3), 15.37 (CH3). IR: νmax = 2984, 2953, 2911, 2860 (C-H), 1745, 1724 (C=O), 1650 (C=C). MS (CI): m/z = 171 (10%, [M–CO2Me]+), 231 (100%, [M+H]+), 248 (80%, [M+NH4]+). HRMS (CI): C10H15O6 ([M+H]+) requires 330.1553; found: 330.1556.

N-Boc-4,5-dicarbomethoxy-3-ethoxy-2,5-dihydropyrrole 10a. (The Boc and Z-protected derivatives were found to exist as atropisomers, figures in parentheses represent chemical shift values for the alternate isomer where given.) 1H NMR: δ 5.05 (5.09) (dd, 1H, J = 4.4, 1.7 Hz, CH), 4.52 (4.49) (dd, 1H, J = 16.0, 4.4 Hz, CH3), 4.40 (4.32) (dd, 1H, J = 16.0, 1.7 Hz, CH3), 4.18 (m, 2H, CH2), 3.74 (3.76) (s, 3H, CH3), 3.72 (3.73) (s, 3H, CH3), 1.44 (m, 12H, t-Bu+CH3). 13C NMR: δ = 171.92 (C), 164.59 (C), 162.52 (C), 152.98 (C), 100.44 (C), 81.17 (C), 67.95 (CH2), 63.72 (CH2), 52.37 (CH3), 51.24 (CH3), 50.33 (CH3), 28.28 (3× CH3), 15.27 (CH3). IR: νmax = 2979, 2951, 2868 (C-H), 1748, 1708 (C=O), 1639 (C=C). MS (CI): m/z = 230 (40%, [M+H-Boc]+), 291 (100%, [M+NH4]+), 347 (35%, [M+NH4]+). HRMS (CI): C10H15O6 ([M+H]+) requires 330.1553; found: 330.1556.