Comparing and taming the reactivity of HWE and Wittig reagents with cyclic hemiacetals

Jokin Carrillo, Anna M. Costa *, Mireia Sidera, Jaume Vilarrasa *
Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, Diagonal 647, 08028 Barcelona, Catalonia, Spain

ARTICLE INFO

Article history:
Received .......... Revised .......... Accepted .......... Available online .....

KEYWORDS:
Lactols
Wittig and HWE reactions
Oxa-Michael cyclisation

A practical solution to the formation of mixtures of E/Z and open/cyclic isomers in the reaction of (2R,4S)-4-hydroxy-2-methylpentanal (as its hemiacetal, a lactol) with conjugated phosphoranes (stabilised Wittig reagents) and Horner–Wadsworth–Emmons reagents is disclosed. The HWE reaction has a strong bias to give oxolanes. On the other hand, stabilised Wittig reagents give unsaturated carboxyl derivatives of configuration E (major) and oxolanes (minor); the latter can be avoided by addition of CF3CH2OH or using morpholineamide phosphorane.

© 2011 Elsevier Ltd. All rights reserved

In a total synthesis of amphidinolides B/D/H/G under way (see the plans for B1 in Scheme 1)1 we obtained erratic results in a Wittig-like double bond formation. Whereas we had no trouble in preparing fragment C1–C6 and a precursor of fragment C7–C13, fragment C20–C25 posed technical difficulties. We envisaged synthesising it from enantiopure 4-hydroxy-2-methylpentanal (1) via a double-bond formation (to obtain 2) followed by Sharpless asymmetric dihydroxylation. However, we knew2 that heating 1, which exists in its cyclic hemiacetal forms (1'/1'', 60:40), with the stabilised Wittig reagent Ph3P=CHCOOEt would give the (E)-unsaturated ester impurified by 7% of its Z isomer (which could not be separated by flash chromatography).2 We needed to avoid stereoisomeric mixtures, as we required stereopure C20–C25 fragments. We synthesised 1/1'/1'' in four steps, in 50% overall yield, from O-protected (S)-2-hydroxypropanal3 and treated the equilibrium mixture (Scheme 2) with Ph3P=CHCOOEt in toluene at room temperature (rt) up to the consumption of the starting material. The crude product contained the desired compound, 2a (70%), ca. 5% of its Z isomer and 20% of a cyclic product (oxolane/oxolan 3a, impurified by 3a', ca. 2%), arising from the addition in situ of the hydroxy group of 2a to the conjugated double bond. Moreover, heating 1/1'' with Ph3P=CHCOOEt or with Ph3P=CHCOOMe in toluene at 80 °C for a few hours gave 2a and 2b, respectively, as the major products (ca. 60%), but with percentages of cyclic

Scheme 1. Retrosynthesis of fragment C20–C25 of amphidinolide B1.

Scheme 2. Reaction of 1 with a standard stabilised phosphorane.
products 3a and 3b around 30% (again, 3a and 3b contained minor amounts of 3a’ and 3b’, respectively).

Many similar ring openings of 5- and 6-membered lactols can be found in the literature. The base-catalysed, oxo-Michael cyclisation of the resulting α-hydroxy and α,β-unsaturated esters is a common procedure to prepare furan6 and pyran derivatives, respectively. Often the oxolane-containing moieties of other amphidinolides are constructed in such a way,2,6,8 but in our case we were not interested in the second step. We report how to avoid the “undesired cyclic by-products”, in a case in which, possibly owing to the spatial relationship of the methyl groups,6 the α-hydroxy unsaturated substrates, 2a and 2b, are quite prone to cyclisation.

First, we examined the reactions of 1’/1” with phosphonates (Table 1) with the expectation of shortening the reaction times, as the anions of HWE reagents are more basic7 and nucleophilic than stabilised phosphoranes. As shown in Table 1, oxolanes 3 always predominated:8 oxolane 3a in entries 1–3, under standard conditions; oxolane 3d from diethoxymethylphosphonate (entry 4); even with a defect of base (entries 5–7). Quenching the reactions at shorter reaction times did not provide a solution, since the oxo-Michael or cyclisation step was more rapid than the phosphonate attack at the hidden CHO and the loss of (EtO)2P(=O)O– (see Scheme 3 for a simplified explanation).

Table 1.
Screening of the reactivity of 1 with HWE reagents.9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>m</th>
<th>Base</th>
<th>n</th>
<th>Solv.</th>
<th>Temp. (ºC)</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>2/3 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OEt</td>
<td>1.3</td>
<td>DBU</td>
<td>1</td>
<td>toluene</td>
<td>80</td>
<td>16</td>
<td>100</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>OEt</td>
<td>1.3</td>
<td>NaH</td>
<td>1</td>
<td>THF</td>
<td>65</td>
<td>1</td>
<td>100</td>
<td>0:100</td>
</tr>
<tr>
<td>3</td>
<td>OEt</td>
<td>1.2</td>
<td>DBU</td>
<td>1</td>
<td>CH3CN</td>
<td>rt</td>
<td>16</td>
<td>100</td>
<td>0:100</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>1.2</td>
<td>DBU</td>
<td>0.8</td>
<td>CH3CN</td>
<td>rt</td>
<td>16</td>
<td>68</td>
<td>10:90</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>1.0</td>
<td>DBU</td>
<td>0.8</td>
<td>CH3CN</td>
<td>rt</td>
<td>16</td>
<td>68</td>
<td>10:90</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>1.2</td>
<td>Cs2CO3</td>
<td>0.9</td>
<td>PrOH</td>
<td>rt</td>
<td>16</td>
<td>100</td>
<td>0:100</td>
</tr>
<tr>
<td>7</td>
<td>OEt</td>
<td>1.2</td>
<td>KHMDSi</td>
<td>1.1</td>
<td>THF</td>
<td>–78ºC</td>
<td>1</td>
<td>77</td>
<td>20:80</td>
</tr>
</tbody>
</table>

* From 0.5–0.8 mmol of 1’/1” in 5 mL of solvent (0.10–0.16 M).

The morpholine amide derivative of the phosphonate, (EtO)2POCH2CON(CH2CH2)O,12 i.e. with Y = morpholin-4-yl in Table 1 and Scheme 3, was also examined, without success. In polar and basic media (as in entry 3 of Table 1) oxolane 3e predominated. With Ba(OH)2 in moist THF, the attack of that phosphonate did not occur even on heating. With DBU in less polar media, such as toluene, there was no attack at rt, whereas on heating the cyclisation to oxolane 3e again turned out to be more rapid than the previous steps.

In sharp contrast, this is not the case for simple lactol 4; the internal hemiacetal of 4-hydroxybutanal (4),13 for which both the open and cyclic forms are clearly observed by NMR. We re-examined its reaction with the standard HWE reagent and DBU in CH3CN (Scheme 4). Only the open unsaturated ester (5a)14 was obtained (under conditions in which 2a completely or largely cyclised to 3a). The corresponding morpholine amide (5c) was obtained similarly, in excellent yield.
In view of the disappointing results with 1′′/1′′′ and HWE reagents, we returned to the stabilised Wittig (sw) reagents. At least, in our preliminary experiments the oxolanes had been the minor compounds. Assuming that the “premature” or unwanted cyclisation of 2a is catalysed by any base present, even the excess of a very moderate base like phosphorane Ph₃P=CH-COOEt should be avoided. We changed the reagent ratio, adding dropwise 0.9 equiv of phosphorane to 1′′/1′′′ in toluene at 80 ºC. Only (E)-2a was formed, but it had to be separated from the remaining starting material.

Bearing in mind that 1′′/1′′′ is more expensive than the phosphorane, we developed a better “trick”. We used 1.3 equiv of phosphorane Ph₃P=CHCOOEt but added 2,2,2-trifluoroethanol (CF₃CH₂OH, pKₐ = 12.2 in water) to the reaction mixture. In practice, 200 mol % was enough. The moderate acidity of the hydroxy group of trifluoroethanol disturbed or blocked the base-catalysed conjugate addition (however, the cyclisation of 2c at rt; unsaturated ester with a more polar solvent CH₃CN by addition of NaH). By heating this morpholine compound, but, to our knowledge, never used in synthesis. By contrast, the corresponding Weinreb amide was commercially available and has been utilised in over 50 papers (SciFinder search). By heating this morpholine amide-containing phosphorane Ph₃P=CHCON(CH₃)₂O, a known compound, but, to our knowledge, never used in synthesis. By contrast, the corresponding Weinreb amide is commercially available and has been utilised in over 50 papers (SciFinder search). By heating this morpholine amide-containing phosphorane and 1′′/1′′′, without any precautions and without any additive, the desired 2c was obtained quantitatively (Scheme 5, bottom). We attributed the lack of oxolane formation to the poorer EW character of the amide group with regard to an ester group. In fact, in an independent experiment, a mixture of 2a and 2c was treated in an NMR tube, in CDCl₃, with DBU at rt; unsaturated ester 2c fully cyclised in 2–3 days, whereas unsaturated amide 2e remained unaltered (however, the cyclisation of 2e to 3e took place in the more polar solvent CH₃CN by addition of NaH).

These two synthetic tricks can be instrumental in lactols that are very stable and may give rise to ε- or ζ-hydroxy α,β-unsaturated esters in which the respective formation of 5- or 6-membered rings is very favoured. In summary, lactol 1′′/1′′′ is a model of very stable cyclic hemiacetalic forms of hydroxy-aldehydes. Their derivatives, with CH=CH–EWG instead of CH=O, show a similar strong tendency to form stable oxolanes (THF derivatives as very major products). If these are required, as happens in many cases, even in the total synthesis of several oxolane-containing amphidinolides other than those we are dealing with, this is an advantage. In fact, the HWE reactions, without base other than the phosphonate anion, are spontaneously followed by an oxa-Michael cyclisation (which cannot be tamed). In the light of Table 1, the title of this paper could have been “one-pot conditions for obtaining oxolanes of type 3 from lactols in excellent yieds (impurified only by small amounts of 3′′′)”. However, our goal was not 3 but 2.

When ε-hydroxy α,β-unsaturated carboxyl derivatives (open compounds 2) are desired, we have disclosed two useful tricks to tame the weaker tendency of sw reagents to give rise to oxolanes as by-products: (i) to carry them in the presence of CH₃CN or (ii) to use the morpholine amide of the phosphonium ylide.

Acknowledgments

This study was started with funds from grant CTQ-2006-15393 (Spanish Government, Madrid) and continued with grant CTQ2009-13590 and with a gift of the AGAUR (2009SGR-825, GRC Stereoselective Synthesis of Antitumour and Antiviral Agents). M.S. deeply thanks the AGAUR, Generalitat de Catalunya, Barcelona, for a doctorate studentship (2007–2010). J.C. has had a CTQ2009-linked studentship since mid-2010. Thanks are due to Prof. M. F. Semmelhack (Princeton University) for exchange of NMR information (Ref. 8a).

Supplementary data

Supplementary data (copies of ¹H and ¹³C NMR spectra, ¹H NMR spectra of the reaction of 2a and 2e with DBU) associated with this article can be found, in the online version, at doi:.................. References and notes


The relative reactivity of PhPO₃–CICO₂Et is weak, since its conjugate acid is relatively strong (pKa = 8.5 in DMSO, several units lower in water). In sharp contrast, the methylene protons of (EtO)₂POCH₂COOEt have an estimated pKa value in DMSO of 18.6. It means that the basicity of the HWE reagent (the carboxyl derivative, see: (b) Mas, G.; Gonzàlez, L.; Vilarrasa, J. J. Org. Chem. 2003, 68, 863–927) is ca. 10 units stronger than that of the SWE reagent.


11. An alternative approach may be suggested, based on a suitable opening of lactol 1′′, followed by the protection of the hydroxy group.
Comparing and taming the reactivity of HWE and Wittig reagents with cyclic hemiacetals
Jokin Carrillo, Anna M. Costa*, Mireia Sidera, Jaume Vilarrasa*

Graphical abstract