Preparation of Chiral N-Vinyl Oxazolidinones by a Simple General Procedure

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Received 22 May 2003; revised 3 July 2003

Abstract: A high yielding, general, and practical procedure for the N-vinylation of 2-oxazolidinones via TMSOTf-promoted dehydroalkoxylation of N,O-acetals is described.

Key words: oxazolidinone, N-vinylation, TMSOTf, N,O-acetal

Scheme 1

N-Vinyl-2-oxazolidinones derived from enantiopure β-aminoalcohols have attracted much interest in asymmetric Pd-promoted carboacylations and alkylations,1,[2+2]-photocycloadditions2 and cyclopropanations.3a,b In connection with our ongoing studies concerning the dienophilicity and dipolarophilicity of such chiral N-vinyl carbamates, we were interested in developing a general and reliable preparation of these compounds. Direct N-vinylation of 2-oxazolidinones has already been described by using an excess of low-boiling vinyl ether catalyzed by mercuric salts, with low yields (35–55%).4 Hegedus and co-workers reported a one-pot method starting from the corresponding β-aminoalcohol based on the formation of an aminocarbene complex and its subsequent base-mediated treatment with diphenyl carbonate.16 This original procedure proved to give high yields but is somewhat complicated. More recently, an efficient route to aryl N-vinyl-2-oxazolidinones was proposed by Akiba and co-workers3 and was based on the acid-catalyzed trans-acetalization of acetaldehyde dimethylacetal with 2-oxazolidinones, producing an N,O-acetal which in turn underwent thermal elimination of methanol.5 Although practical, this method required appropriate elimination conditions for each compound and proceeded with moderate to good yields. For this dehydroalkoxylation step, we searched for a general method, which could be applied to a range of N,O-acetals under non-thermal conditions. Bach and Brummerhop demonstrated the efficiency of TMSOTf in combination with Hünig base to promote the dehydromethoxylation of 2-methoxy-N-carbomethoxy-pyrrolidines into the corresponding dihydropyrrols.6 On this basis, we recently described7 an efficient access to N-vinyl-2-oxazolidinone from the corresponding N,O-acetal by using such Gassman-type conditions (TMSOTf/Et₃N).5 We now report the high-yielding preparation of representative chiral N-vinyl-2-oxazolidinones by such a two-step, mercury-free, general procedure.

As in the achiral series, the N,O-acetals 2a–e were quantitatively prepared from the corresponding 2-oxazolidinones 1a–e by treatment with acetaldehyde diethyl acetal using camphorsulfonic acid9 as the catalyst (Scheme 1). Minor improvements were made to Akiba’s procedure concerning the catalyst ratio (reduced to 5%) and the reaction time (reduced to 3 h).

In order to prepare the chiral N-vinylloxazolidinones 3a–e, we successfully applied the eliminative conditions that proved efficient to generate chiral vinyl ethers from mixed O,O-acetals to the N,O-acetals 2a–e.10 Treatment of the N,O-acetal in solution in dichloromethane with triethylamine (1.5 equiv) and then trimethylsilyl trifluoromethanesulfonate (1.3 equiv) led in each case to a highly regiocontrolled elimination reaction, no N-silyl oxazolidinone that could result from the other elimination pathway was detected in the crude product. Another point of interest was the optimal rate of dehydroalkoxylation observed in these reactions. Because of the completion of such reactions, the purified N-vinyl oxazolidinones were obtained in high yields and free from the starting N,O-acetal 2. Such contamination can be a serious drawback,11 since compounds 2 and 3 proved to be difficult to separate from each other in most cases.
The level of enantiopurity of N-vinylloxazolidinones 3 was accurately determined by chiral GC, the ee values were found to be higher than 99% in all cases (Table 1).

<table>
<thead>
<tr>
<th>3</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Overall Yield (%)</th>
<th>ee (%)</th>
<th>YLD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>73</td>
<td>99.5</td>
<td>46^4</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
<td>i-Bu</td>
<td>H</td>
<td>78</td>
<td>&gt;99.5</td>
<td>55^4</td>
</tr>
<tr>
<td>3c</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>80</td>
<td>&gt;99.5</td>
<td>55^4</td>
</tr>
<tr>
<td>3d</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>90</td>
<td>n.d.</td>
<td>66^2</td>
</tr>
<tr>
<td>3e</td>
<td>H</td>
<td>Me</td>
<td>Ph</td>
<td>90</td>
<td>99.3</td>
<td>77^1,b</td>
</tr>
</tbody>
</table>

The percentages in parentheses are for the major isomers.

To conclude, we describe here a general procedure for the preparation of various enantiopure N-vinyl oxazolidino-

tes. This two-steps method requires only one purification at the final step and can be performed from millimol to multigram scale. Yields obtained by this easy-made procedure compares well with those reported in the literature.

All solvents were dried using standard procedures. Commercial acetaldehyde diethyl acetal can be employed without prior distillation. Chromatography was performed with 40–60 μm Merck Si60 silica gel under medium pressure (1 bar). All melting points are un-

corrected. Infrared spectra were performed on a FT Genesis (Matt-

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N-0-Acetals 2; General Procedure

A mixture of oxazolidinone 1 (10 mmol), acetaldehyde diethyl acetal (100 mmol) and (d)-camphorsulfonic acid (0.5 mmol) was heated for 3 h at 55 °C. After cooling and dilution with Et2O (40 mL), NaHCO3 solution (10 mL) was added and the organic phase was washed with brine (10 mL) and dried over MgSO4. Removal of solvent yielded a crude diastereoisomeric mixture of N-0-acetal 2 used without further purification.

(4R)-3-(1-Ethoxyethyl)-4-isobutyl-oxazolidin-2-one (2b)

From 1b (1.5 g, 10.5 mmol), 2b (2.26 g, quantitative yield) was obtained as an orange oil; Rf 0.35 (cyclohexane–EtOAc, 7:3).

IR (film): 1757 (C=O), 1415, 1377, 1254, 1223, 1100, 1052 (C–O), 941, 847, 764 cm–1.

To a cooled solution (0 °C) of crude N-O-acetal 2 (10 mmol) in anhydrous CH2Cl2 (10 mL) was added under nitrogen distilled Et3N (15 mmol), then dropwise, TMSOTf (13 mmol). After slowly warming to r.t. and stirring for 15 h, the mixture was treated with basic alumina to remove the excess of TMSOTf. After removal of the solvent, the residue was filtered on silica gel (Et2O) to remove the ammonium triflate salts and was purified by chromatography.

N-Vinylloxazolidinones 3; General Procedure

To a cooled solution (0 °C) of crude N,O-acetal 2 (10 mmol) in anhydrous CH2Cl2 (10 mL) was added under nitrogen distilled Et3N (15 mmol), then dropwise, TMSOTf (13 mmol). After slowly warming to r.t. and stirring for 15 h, the mixture was treated with basic alumina to remove the excess of TMSOTf. After removal of the solvent, the residue was filtered on silica gel (Et2O) to remove the ammonium triflate salts and was purified by chromatography.
(4R)-4-Ethyl-3-vinyl-oxazolidin-2-one (3a)

From 2a (2.69 g, 14.4 mmol), chromatographic purification (silica gel; cyclohexane–EtOAc; 8:2 → 7:3) afforded 3a (1.47 g, 73%) as a colorless oil; Rf 0.47 (cyclohexane–EtOAc, 1:1); tR 3a = 70.2 (c 1.6, CH2Cl2); ee 99.5%; tδ 3a (4R)-3a 14.5 min (0.2%), tδ 4R-3a 14.9 min (99.7%); bp 120–180 °C, 3 °C/min.

IR (film): 1755 (C=O), 1638 (C=C), 1469, 1430, 1356, 1270, 1229, 1089, 1040, 972, 854, 765 cm–1.

1H NMR (400 MHz, CDCl3): δ = 0.86 (d, 3 H, CH3), 1.14, 1.44 and 1.84 (2 m, 2 H, CH2CH3), 1.66 (1 H, CH=CH2), 4.06 (1 m, 1 H, H–4), 4.12 (1 d, 1 H, J2,3 = 3.0 Hz, J2,5 = 8.5 Hz, H–5), 4.35 (1 dd, 1 H, J1,2 = 16.3 Hz, J1,4 = 1.0 Hz, H–4), 4.20 (2 t, 1 H, J1,5 = 9.0 Hz, J1,4 = 1.0 Hz, H–4), 6.74 (1 d, 1 H, J1,2 = 16.3 Hz, H–2), 9.4 Hz, H–1).

13C NMR (50 MHz, CDCl3): δ = 19.4 and 23.3 (2 × CH2); 24.6 (CH3); 39.1 (CH); 52.0 (C–4); 68.0 (C–5); 93.5 (C–2’); 128.4 (C–1’); 154.9 (C–2’).

HRMS (EI): m/z calced for C8H10NO: 169.0128; found: 169.1105.

Anal. Calcd for C8H10NO: C, 63.88; H, 8.93; N, 8.28. Found C, 63.51; H, 9.06; N, 8.35.

(4R)-4-Phenyl-3-vinyl-oxazolidin-2-one (3b)¹

From 2b (1.4 g, 6.46 mmol), chromatographic purification (silica gel; cyclohexane–EtOAc; 8:2 → 7:3) afforded 3b (1.18 g, 90%) as a white solid; Rf 0.29 (cyclohexane–EtOAc, 1:2); mp 39.0–41 °C; [α]D25 = 162.5 – 164.3 °C (c 1.1, CH2Cl2); ee 99.2%; tδ 3b (4R)-3b 23.2 min (100%) (130 °C, 3 °C/min).

IR (film): 1764 (C=O), 1638 (C=C), 1452, 1420, 1358, 1315, 1290, 1112, 854, 756 cm–1.

1H NMR (400 MHz, CDCl3, CD3OD): δ = 0.86 (d, 3 H, CH3), 1.14, 1.44 and 1.84 (2 m, 2 H, CH2CH3), 1.66 (1 H, CH=CH2), 4.06 (1 m, 1 H, H–4), 4.12 (1 d, 1 H, J2,3 = 3.0 Hz, J2,5 = 8.5 Hz, H–5), 4.35 (1 dd, 1 H, J1,2 = 16.3 Hz, J1,4 = 1.0 Hz, H–4), 4.20 (2 t, 1 H, J1,5 = 9.0 Hz, J1,4 = 1.0 Hz, H–4), 6.74 (1 d, 1 H, J1,2 = 16.3 Hz, H–2), 9.4 Hz, H–1).

13C NMR (50 MHz, CDCl3): δ = 19.4 and 23.3 (2 × CH2); 24.6 (CH3); 39.1 (CH); 52.0 (C–4); 68.0 (C–5); 93.5 (C–2’); 128.4 (C–1’); 154.9 (C–2’).

HRMS (EI): m/z calced for C13H12NO: 199.0901; found: 199.0906.

Anal. Calcd for C13H12NO: C, 78.69; H, 7.53; N, 8.27. Found C, 78.73; H, 7.15; N, 8.21.

References


Acknowledgment

We thank Teddy Chapin for his helpful contribution.


(9) Camphorsulfonic acid can be conveniently replaced by *p*-toluenesulfonic acid.


(11) In our hands the *N*-vinyl oxazolidinones obtained via Hg(II)-catalyzed exchange contained typically (even after distillation or SiO₂ chromatography) 10–20% starting material.