Synthesis of Novel 4-Functionalised Oxazolidin-2-ones

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This paper is dedicated to Prof. Dr. D. Geffken.

Abstract: The synthesis of O-substituted and O-unsubstituted 3-hydroxy-4-thioxo-oxazolidin-2-ones, functionalised 4-imino-oxazolidin-2-ones and 4-phenoxo-imino-oxazolidin-2-one starting from O-substituted and O-unsubstituted 3-hydroxy-4-imino-oxazolidin-2-ones is described. A one-pot protocol for the preparation of 4-methoxyimino-, 4-aralkoxyimino- and 4-phenoxoimino-oxazolidin-2-ones has been developed.

Key words: heterocycles, oxazolidin-2-ones, Dimroth rearrangement, thionation, ring closure

Oxazolidin-2,4-diones and their 4-imino(thioxo) analogues have attracted much attention in medicinal and agricultural chemistry. Famoxadone (Figure 1), a 3-phenylamino-oxazolidin-2,4-dione, is a broad spectrum fungicide, which is particularly active against grape downy mildew and potato and tomato late and early blights.1 Vinclozolin represents a well known dicarboximide fungicide used for the control of Botrytis and Sclerotinia spp.2 Trimethadione is an anticonvulsant for the treatment of epilepsy.3 Geffken reported the synthesis and fungicidal activity of 4-hydroxyimino-oxazolidin-2-ones, which have been obtained by treatment of 4-alkoxy-3-oxazolin-2-ones with hydroxylamine.4 Furthermore, in 1992 DuPont described 3-phenylamino-4-imino(thioxo)-oxazolidin-2-ones as novel classes of fungicides.5 Surprisingly, the corresponding O-substituted and O-unsubstituted 3-hydroxy-4-imino(thioxo)-oxazolidin-2-ones have not been reported so far.

Recently, we reported the first synthesis of O-substituted and O-unsubstituted 3-hydroxy-4-imino-oxazolidin-2-ones and their sodium methoxide-mediated conversion into the corresponding α-hydroxamidoximes.6 We now describe the synthetic potential of 1 as precursors in the preparation of novel 4-functionalised oxazolidin-2-one derivatives (Scheme 1).

Thionation of substrates 1a–l by hydrogen sulfide in anhydrous CH₂Cl₂ in the presence of pyridine afforded previously unreported O-substituted and O-unsubstituted 3-hydroxy-4-thioxo-oxazolidin-2-ones (2a–l) in good yields of 75–85% (Scheme 1, Table 1).5

Reactions of 1b with phenyl isocyanate, 4-fluorophenyl isothiocyanate, p-toluenesulfonyl chloride and 4-fluorobenzoyl chloride furnished the derivatised 4-imino-oxazolidin-2-ones 3a–d in 68–80% yield (Scheme 1).

Treatment of 1c with Et₃N in CH₂Cl₂ provided, in accordance with previous studies, the Dimroth rearrangement product 4c in 93% yield (Scheme 1).7,8

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The smooth conversion of 1c into 4c prompted us to develop the first one-pot protocol for the synthesis of 4-methoxyimino-, 4-aralkoxyimino- and 4-phenoxyimino-oxazolidin-2-ones (4a–e) (Scheme 2). Successive treatment of cyanohydrins with 1,1′-carbonyldiimidazole (CDI) and O-substituted hydroxylamines furnished intermediates 1, which upon treatment with Et₃N underwent Dimroth rearrangement to give 4a–e in good yields of 70–80% (Table 2). Discrimination between the structures of compounds 1 and 4 was accomplished by IR, ¹H and ¹³C NMR spectroscopy.

The structures of all compounds (2–4) were elucidated by IR, ¹H, ¹³C NMR spectroscopy and elemental analysis. In conclusion, we have synthesised a variety of novel 4-functionalised oxazolidin-2-one derivatives as analogues of existing biologically active oxazolidin-2-ones. Furthermore, we have developed a new and operationally simple one-pot protocol for the synthesis of 4-alkoxyimino-, 4-aralkoxyimino- and 4-phenoxyimino-oxazolidin-2-ones. This method complements Geffken’s multi-step synthesis of 4-hydroxyimino-oxazolidin-2-ones and offers advantages in convenience and yields.

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300 spectrometer. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using TMS as an internal standard and DMSO-d₆ as solvent.

### Table 1 3-Alkoxy-, 3-Aralkoxy-, 3-Phenoxy- and 3-Hydroxy-4-thioxo-oxazolidin-2-ones 2a–l

<table>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>a</td>
<td>Ph₂CH</td>
<td>Me</td>
<td>78</td>
</tr>
<tr>
<td>b</td>
<td>Ph₂CH</td>
<td>Bn</td>
<td>85</td>
</tr>
<tr>
<td>c</td>
<td>Ph₂CH</td>
<td>Ph</td>
<td>80</td>
</tr>
<tr>
<td>d</td>
<td>Ph₂CH</td>
<td>t-Bu</td>
<td>75</td>
</tr>
<tr>
<td>e</td>
<td>Ph₂CH</td>
<td>Ph(CH₂)₂</td>
<td>83</td>
</tr>
<tr>
<td>f</td>
<td>Ph₂CH</td>
<td>H</td>
<td>80</td>
</tr>
<tr>
<td>g</td>
<td>t-Bu</td>
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<tr>
<td>h</td>
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<td>Bn</td>
<td>84</td>
</tr>
<tr>
<td>i</td>
<td>t-Bu</td>
<td>Ph</td>
<td>75</td>
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<tr>
<td>j</td>
<td>t-Bu</td>
<td>t-Bu</td>
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</tr>
<tr>
<td>k</td>
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</tr>
<tr>
<td>l</td>
<td>t-Bu</td>
<td>H</td>
<td>75</td>
</tr>
</tbody>
</table>

### Table 2 4-Methoxyimino-, 4-Aralkoxyimino- and 4-Phenoxyimino-oxazolidin-2-ones (4a–e)

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>Bn</td>
<td>75</td>
</tr>
<tr>
<td>c</td>
<td>Ph</td>
<td>73</td>
</tr>
<tr>
<td>d</td>
<td>Ph(CH₂)₂</td>
<td>80</td>
</tr>
<tr>
<td>e</td>
<td>Ph(CH₃)₂</td>
<td>72</td>
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</tbody>
</table>

Preparation of 2a–l: General Procedure

H₂S gas was introduced for 30 min to a solution of 1a–l (3 mmol) in anhyd CH₂Cl₂ (20 mL) and anhyd pyridine (12 mL). After stirring at r.t. for 3 h the reaction mixture was diluted with Et₂O (50 mL) and washed thrice with 20% HCl (15 mL). The organic layer was dried over MgSO₄ and the solvent was evaporated to afford 2a–l as yellow solids, which were recrystallised from Et₂O–hexane.

5-Benzhydryl-3-methoxy-4-thioxo-oxazolidin-2-one (2a)
Yield: 0.73 g (78%); yellow solid; mp 75 °C.
IR (KBr): 1280, 1809 cm⁻¹.
¹H NMR (DMSO-d₆): δ = 3.45 (s, 3 H), 4.76 (d, J = 2.80 Hz, 1 H), 5.84 (d, J = 2.54 Hz, 1 H), 7.21–7.43 (m, 10 H).
¹³C NMR (DMSO-d₆): δ = 54.3, 64.2, 88.1, 127.2, 127.7, 128.4, 128.8, 129.0, 130.1, 137.8, 140.8, 151.2, 192.5.
Anal. Calcd for C₁₇H₁₅NO₃S: C, 65.16; H, 4.82; N, 4.47. Found: C, 65.01; H, 5.01; N, 4.35.

5-Benzhydryl-3-benzyloxy-4-thioxo-oxazolidin-2-one (2b)
Yield: 0.99 g (85%); yellow solid; mp 112 °C.
IR (KBr): 1275, 1810 cm⁻¹.
¹H NMR (DMSO-d₆): δ = 4.66 (q, J = 9.76 Hz, 2 H), 4.95 (d, J = 2.80 Hz, 1 H), 5.84 (d, J = 2.54 Hz, 1 H), 7.21–7.43 (m, 10 H).
¹³C NMR (DMSO-d₆): δ = 53.6, 64.2, 88.1, 127.2, 127.7, 128.4, 128.8, 129.0, 130.1, 137.8, 140.8, 151.2, 192.5.
Anal. Calcd for C₂₃H₁₉NO₃S: C, 70.93; H, 4.92; N, 3.60. Found: C, 70.80; H, 5.03; N, 3.49.

5-Benzhydryl-3-phenoxy-4-thioxo-oxazolidin-2-one (2c)
Yield: 0.90 g (80%); yellow solid; mp 120 °C.
IR (KBr): 1280, 1809 cm⁻¹.
¹H NMR (DMSO-d₆): δ = 3.46 (q, J = 9.76 Hz, 2 H), 4.95 (d, J = 2.80 Hz, 1 H), 5.61 (d, J = 2.54 Hz, 1 H), 7.21–7.44 (m, 10 H).
¹³C NMR (DMSO-d₆): δ = 53.6, 78.3, 88.2, 126.8, 127.5, 128.2, 128.6, 128.9, 129.02, 129.9, 130.9, 130.11, 132.9, 136.6, 140.0, 151.4, 194.4.
Anal. Calcd for C₁₇H₁₅NO₃S: C, 70.93; H, 4.92; N, 3.60. Found: C, 70.80; H, 5.03; N, 3.49.

5-Benzhydryl-3-benzylxoy-4-thioxo-oxazolidin-2-one (2b)
Yield: 0.99 g (85%); yellow solid; mp 112 °C.
IR (KBr): 1275, 1810 cm⁻¹.
¹H NMR (DMSO-d₆): δ = 3.46 (q, J = 9.76 Hz, 2 H), 4.95 (d, J = 2.80 Hz, 1 H), 5.61 (d, J = 2.54 Hz, 1 H), 7.21–7.44 (m, 15 H).
¹³C NMR (DMSO-d₆): δ = 53.6, 78.3, 88.2, 126.8, 127.5, 128.2, 128.6, 128.9, 129.02, 129.9, 130.9, 130.11, 132.9, 136.6, 140.0, 151.4, 194.4.
Anal. Calcd for C₂₅H₂₁NO₃S: C, 70.93; H, 4.92; N, 3.60. Found: C, 70.80; H, 5.03; N, 3.49.

5-Benzhydryl-3-phenoxo-4-thioxo-oxazolidin-2-one (2c)
Yield: 0.90 g (80%); yellow solid; mp 120 °C.
IR (KBr): 1276, 1815 cm⁻¹.
¹H NMR (DMSO-d₆): δ = 3.46 (q, J = 9.76 Hz, 2 H), 4.95 (d, J = 2.80 Hz, 1 H), 5.61 (d, J = 2.54 Hz, 1 H), 7.11–7.45 (m, 15 H).

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5-Benzhydryl-3-tert-butoxy-4-thioxo-oxazolidin-2-one (2d)
Yield: 0.80 g (75%); yellow solid; mp 73 °C.

IR (KBr): 1273, 1815 cm⁻¹.

1H NMR (DMSO-d₆): δ = 0.94 (s, 9 H), 2.95 (t, J = 6.87 Hz, 2 H), 4.71 (s, 1 H), 4.73 (s, 1 H), 4.87 (s, 1 H), 7.20–7.55 (m, 5 H).

Anal. Calcd for C₁₅H₁₇NO₃S: C, 60.19; H, 6.13; N, 3.94. Found: C, 60.05; H, 6.18; N, 3.92.

5-Benzhydryl-3-phenylethoxy-4-thioxo-oxazolidin-2-one (2e)
Yield: 0.60 g (75%); yellow solid; mp 67 °C.

IR (KBr): 1275, 1810 cm⁻¹.

1H NMR (DMSO-d₆): δ = 0.92 (s, 9 H), 1.00 (d, J = 6.87 Hz, 3 H), 4.70 (s, 1 H), 4.71 (s, 1 H), 4.73 (s, 1 H), 7.20–7.55 (m, 10 H).


5-Benzhydryl-3-hydroxy-4-thioxo-oxazolidin-2-one (2f)
Yield: 1.00 g (83%); yellow solid; mp 101 °C.

IR (KBr): 1270, 1815 cm⁻¹.

1H NMR (DMSO-d₆): δ = 0.95 (t, J = 6.87 Hz, 3 H), 4.71 (s, 1 H), 4.73 (s, 1 H), 7.20–7.55 (m, 20 H), 7.66 (d, J = 10.18 Hz, 2 H), 4.75 (d, J = 2.60 Hz, 1 H), 7.20–7.55 (m, 20 H), 7.66 (s, 1 H).

Anal. Calcd for C₁₉H₁₈NO₃S: C, 63.08; H, 5.95; N, 3.94. Found: C, 63.06; H, 5.93; N, 3.92.

5-Benzhydryl-3-phenyloxy-4-thioxo-oxazolidin-2-one (2g)
Yield: 0.80 g (80%); yellow solid; mp 93 °C.

IR (KBr): 1270, 1801 cm⁻¹.

1H NMR (DMSO-d₆): δ = 0.98 (s, 9 H), 2.96 (t, J = 6.87 Hz, 2 H), 4.68 (t, J = 7.12 Hz, 2 H), 4.73 (s, 1 H), 7.20–7.43 (m, 5 H).

Anal. Calcd for C₁₄H₁₅NO₃S: C, 58.85; H, 5.45; N, 4.70. Found: C, 58.70; H, 5.45; N, 4.68.

5-Benzhydryl-3-(5-Benzhydryl-3-benzyloxy-2-oxo-oxazolidin-4-ylidene)-3-butoxy-5-tert-butyl-4-thioxo-oxazolidin-2-one (2h)
Yield: 0.70 g (84%); yellow solid; mp 60 °C.

IR (KBr): 1273, 1815 cm⁻¹.

1H NMR (DMSO-d₆): δ = 0.91 (s, 9 H), 4.74 (s, 1 H), 5.07 (q, J = 10.68 Hz, 2 H), 7.88–7.55 (m, 5 H).

13C NMR (DMSO-d₆): δ = 24.5, 34.8, 78.5, 84.0, 126.9, 129.7, 120.5, 134.1, 151.8, 193.4.

Anal. Calcd for C₂₉H₂₅N₃O₄S: C, 73.31; H, 5.13; N, 8.55. Found: C, 73.20; H, 5.00; N, 8.41.

5-Benzhydryl-3-phenyloxy-4-thioxo-oxazolidin-2-one (2i)
Yield: 0.50 g (75%); yellow solid; mp 87 °C.

IR (KBr): 1270, 1801 cm⁻¹.

1H NMR (DMSO-d₆): δ = 0.94 (s, 9 H), 4.71 (s, 1 H), 7.20–7.55 (m, 20 H), 7.66 (d, J = 10.18 Hz, 2 H), 4.75 (d, J = 2.60 Hz, 1 H), 7.20–7.55 (m, 20 H), 7.66 (s, 1 H).

Anal. Calcd for C₁₉H₁₈NO₃S: C, 63.08; H, 5.95; N, 3.94. Found: C, 63.06; H, 5.93; N, 3.92.

5-Benzhydryl-3-phenyl-4-thioxo-oxazolidin-2-one (2j)
Yield: 0.43 g (75%); colourless solid; mp 175 °C.

IR (KBr): 1270, 1801 cm⁻¹.

1H NMR (DMSO-d₆): δ = 0.98 (s, 9 H), 2.96 (t, J = 6.87 Hz, 2 H), 4.73 (s, 1 H), 7.20–7.43 (m, 5 H).

13C NMR (DMSO-d₆): δ = 24.6, 34.2, 64.4, 88.6, 126.9, 129.7, 130.5, 134.1, 153.9, 194.0.

Anal. Calcd for C₁₄H₁₃NO₃S: C, 58.70; H, 5.45; N, 4.68. Found: C, 58.70; H, 5.40; N, 4.59.

5-Benzhydryl-3-phenylethoxy-4-thioxo-oxazolidin-2-one (2k)
Yield: 0.60 g (80%); yellow solid; mp 120 °C.

IR (KBr): 1695, 1720, 1810 cm⁻¹.

1H NMR (DMSO-d₆): δ = 0.94 (s, 9 H), 2.96 (t, J = 6.87 Hz, 2 H), 4.75 (d, J = 2.60 Hz, 1 H), 7.20–7.55 (m, 20 H), 7.66 (s, 1 H).

13C NMR (DMSO-d₆): δ = 53.6, 78.4, 88.2, 126.8, 127.5, 128.5, 128.6, 128.8, 129.9, 130.0, 130.2, 132.9, 136.6, 140.0, 151.4, 154.0, 167.0.

Anal. Calcd for C₁₉H₁₈NO₃S: C, 73.31; H, 5.13; N, 8.55. Found: C, 73.20; H, 5.00; N, 8.41.

with Et₂O, washed with brine and water. The organic layer was crystallised from Et₂O–hexane.

Preparation of 3c:d; General Procedure
p-Toluenesulfonyl chloride or 4-fluorobenzoyl chloride (3 mmol) was added to a solution of 1b (1.11 g, 3 mmol) and Et₃N (3 mmol) in anhyd THF (5 mL) under ice cooling. The reaction mixture was stirred at r.t. for 3 h and the solvent was evaporated under reduced pressure. The remaining oil was dissolved in EtOAc (20 mL) and the solution was washed with water (5 mL). The organic layer was dried over MgSO₄, the solvent evaporated and the resulting oil was crystallised from EtOAc–hexane.

**N-(5-Benzhydryl-3-benzyloxy-2-oxo-oxazolidin-4-ylidene)-4-methylbenzenesulphonamide (3c)**
Yield: 1.11 g (70%); colourless solid; mp 160 °C.
IR (KBr): 1695, 1795 cm⁻¹.

**N-(5-Benzhydryl-3-benzyloxy-2-oxo-oxazolidin-4-ylidene)-4-fluorobenzamidine (3d)**
Yield: 1.16 g (78%); colourless solid; mp 173 °C.
IR (KBr): 1670, 1690, 1790 cm⁻¹.

Preparation of 4a–e; General Procedure
A solution of cyanohydrine (5 mmol) in anhyd CH₂Cl₂ (5 mL) was added dropwise over a period of 10 min to a suspension of 1,1'-carbonyldimidazole (0.89 g, 5.5 mmol) in CH₂Cl₂ (5 mL) under ice cooling. After stirring at r.t. for 10 min a solution of the appropriate O-substituted hydroxylamine (5 mmol) in anhyd CH₂Cl₂ (5 mL) was added and the reaction mixture was stirred at r.t. for 1 h. The reaction mixture was concentrated under reduced pressure, Et₃N (3 mL) was added and the mixture was heated to 60–70 °C until two sharp bands in the IR spectrum appeared at 1745–1760 and 1650–1770 cm⁻¹. After cooling to r.t., the reaction mixture was diluted with EtO, washed with brine and water. The organic layer was dried over MgSO₄, filtered, concentrated and the remaining oil was crystallised from EtO–hexane.

5-Benzhydryl-4-methoxymino-oxazolidin-2-one (4a)
Yield: 1.04 g (70%); colourless solid; mp 101 °C.
IR (KBr): 1755, 1660 cm⁻¹.

5-Benzhydryl-4-benzyloxymino-oxazolidin-2-one (4b)
Yield: 1.40 g (75%); colourless solid; mp 130 °C.
IR (KBr): 1760, 1665 cm⁻¹.

5-Benzhydryl-4-phenoxymino-oxazolidin-2-one (4c)
Yield: 1.31 g (73%); colourless solid; mp 189 °C.
IR (KBr): 1760, 1670 cm⁻¹.

5-Benzhydryl-4-phenethylxoymino-oxazolidin-2-one (4d)
Yield: 1.55 g (80%); colourless solid; mp 110 °C.
IR (KBr): 1758, 1667 cm⁻¹.

5-Benzhydryl-4-phenylpropyloxymino-oxazolidin-2-one (4e)
Yield: 1.44 g (72%); colourless solid; mp 107 °C.
IR (KBr): 1760, 1672 cm⁻¹.

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