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Rapid microwave assisted synthesis of 3-substituted 4-thioxo-oxazolidin-2-ones

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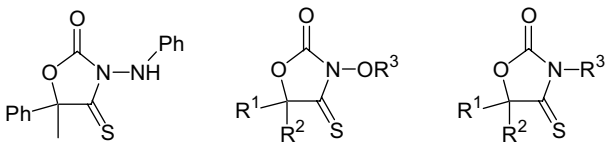
Abstract—The microwave assisted thionation of 3-substituted 4-imino-oxazolidin-2-ones with hydrogen sulfide in dichloromethane–pyridine afforded 3-substituted 4-thioxo-oxazolidin-2-ones.

1. Introduction

4-Functionalized oxazolidin-2-ones have found applications as drugs and agrochemicals.[1,2] While 3-arylamino-4-thioxo-oxazolidin-2-ones (**I**) display potent fungicidal activity, the corresponding 3-alkoxy(arylalkloxy) derivatives (**II**) are inactive.[1,2] In the course of our research directed to the synthesis and biological activity of 4-functionalized oxazolidin-2-ones, we became interested in the microwave assisted synthesis of 3-aryl(arylalkyl)-4-thioxo-oxazolidin-2-ones.[2,3] Interestingly, an intensive literature research revealed that the title compounds (**III**) have not been prepared till now (Fig. 1). Although a Beilstein search refers to two patents containing 3-aryl(arylalkyl)-4-thioxo-oxazolidin-2-ones (**III**), the isomeric 2-thioxo-oxazolidin-4-ones are in fact described.[4,5] Compounds **I** and **II** are commonly prepared by treatment of 3-substituted 4-imino-oxazolidin-2-ones with hydrogen sulfide in the presence of pyridine in dichloromethane or THF.[1,2]



I II III

Figure 1. 3-Substituted 4-thioxo-oxazolidin-2-ones.

Microwave assisted syntheses have become an important tool in organic and medicinal chemistry. Due to higher yields, clean reactions and short reaction times, microwave assisted reactions often offer a considerable advantage over conventional heating.[6] We herein report the rapid microwave assisted synthesis of previously unreported 3-substituted 4-thioxo-oxazolidin-2-ones (**5a**–**k**) starting from 3-substituted 4-imino-oxazolidin-2-ones (**4a**–**k**).

2. Results and discussion

Substrates **4a**–**k** have been prepared by reacting cyanohydrins (**1**) subsequently with 1,1′-carbonyl-diimidazole or 1,1′-carbonyl-di-(1,2,4-triazole) and primary amines via carbamates (**3**) in 51–72% yields (Scheme 1, Table 1).[7,8]

Microwave assisted thionation of **4a**–**k** was accomplished within only 1.5–6 min by reacting substrates **4a**–**k** with a saturated solution of hydrogen sulfide in dry dichloromethane/pyridine. A simple aqueous workup procedure followed by filtration through a short silica gel column and recrystallization from an appropriate solvent afforded the target compounds **5a**–**k** in 54–70% yield (Scheme 2, Table 2).[9]

In all cases, the completion of the reaction was monitored by IR spectroscopy. While the IR spectra of the starting materials **4a**–**k** showed two characteristic

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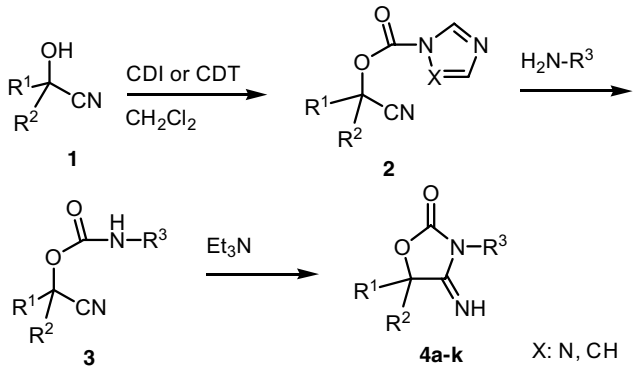
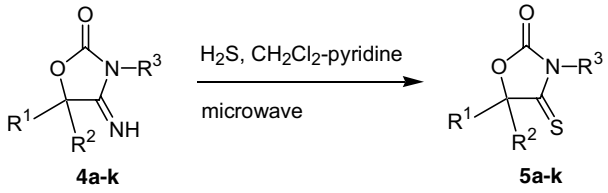


Scheme 1. Synthesis of 4-imino-oxazolidin-2-ones (**4a**–**k**).

Table 1. 3-Substituted 4-imino-oxazolidin-2-ones (**4a**–**k**)

4	R^1	R^2	R^3	Yield [%]
a	1-Naphthyl	H	3-F–Ph	64
b	CH_3	H	4-CH_3–Bn	72
c	CH_3	H	4-F–Bn	69
d	Ph	H	2-Cl–Bn	51
e	Ph	H	2-F–Bn	65
f	Ph	H	3-Cl–Bn	66
g	4-CH_3–Ph	H	2-CH_3–Bn	67
h	4-CH_3O–Ph	H	4-Cl–Bn	58
i	2,4-Cl–Ph	H	CH_3	59
j	4-Cl–Ph	CH_3	2-Cl–Bn	62
k	CH_3	CH_3	4-CH_3–Ph	61



Scheme 2. Thionation of 4-imino-oxazolidin-2-ones.

Table 2. 3-Substituted 4-thioxo-oxazolidin-2-ones (**5a**–**k**)

5	R^1	R^2	R^3	Yield [%]	Hold time (min)
a	1-Naphthyl	H	3-F–Ph	54	1[a]
b	CH_3	H	4-CH_3–Bn	65	3[a]
c	CH_3	H	4-F–Bn	70	5.5[a]
d	Ph	H	2-Cl–Bn	62	2[a]
e	Ph	H	2-F–Bn	68	2[a]
f	Ph	H	3-Cl–Bn	61	2[a]
g	4-CH_3–Ph	H	2-CH_3–Bn	70	2.5[a]
h	4-CH_3O–Ph	H	4-Cl–Bn	68	2.5[a]
i	2,4-Cl–Ph	H	CH_3	68	5[a]
j	4-Cl–Ph	CH_3	2-Cl–Bn	55	5.5[a]
k	CH_3	CH_3	4-CH_3–Ph	54	5[a]

[a] See Ref. 9 for more detailed conditions.

absorption bands at 1760–1795 cm^{-1} (C=O) and 1664–1686 cm^{-1} (C=N), the IR spectra of 4-thioxo-oxazolidin-2-ones (**5a**–**k**) showed two new absorption bands at 1789–1811 cm^{-1} (C=O) and 1215–1230 cm^{-1} (C=S).

In summary, we have developed a practical and rapid method for the microwave assisted thionation of 3-substituted 4-imino-oxazolidin-2-ones using hydrogen sulfide in dichloromethane/pyridine to obtain previously unreported 3-aryl-, 3-alkyl-, and 3-arylalkyl-substituted 4-thioxo-oxazolidin-2-ones.

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8. The novel analogs **4e**–**k** have been purified by column chromatography using EtOAc–hexane (3:7) as an eluent. Analytically pure products have been obtained after recrystallization from EtOAc/hexane. For the synthesis of 5,5-disubstituted 4-imino-oxazolidin-2-ones (**4j**,**k**) 1,1′-carbonyl-di-(1,2,4-triazole) and catalytic amounts of DMAP have been used for the activation of cyanohydrines **1**.
   Experimental data for compound **4e**. 3-(2-Fluorobenzyl)-4-imino-5-phenyl-oxazolidin-2-one: Colorless solid (65%). Mp 82.6°C; IR (KBr): $\nu = 1781$, 1667 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 4.74–4.83 (m, 2H), 6.14 (s, 1H), 7.16–7.23 (m, 2H), 7.32–7.38 (m, 2H), 7.40–7.47 (m, 5H); ^{13}C NMR (DMSO-d_6) δ (ppm): 37.55, 79.75, 115.81, 124.82, 127.66, 129.36, 129.72, 129.77, 129.90, 129.98, 134.30, 134.92, 155.96, 161.65; Anal. Calcd for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.46; H, 4.93; N, 9.91.
9. General procedure for the microwave-assisted synthesis of **5a**–**k**. 0.5 mmol of **4a**–**k** and 5 mL of a saturated solution of hydrogen sulfide in dry dichloromethane–pyridine were added into a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for the indicated time using parameters *a* or *b* (Table 2). The reaction mixture was allowed to cool to room temperature and was transferred to a round bottomed flask. The solvent was evaporated, diethylether (20 mL) was added and the mixture was washed with 1 M hydrochloric acid (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated. The remaining residues were purified by filtration through a short silica gel column (3 cm) with CH_2Cl_2–hexane (3:1) as an eluent. Crystallization from Et_2O–hexane provided **5a**–**k** as pure pale yellow solids. Microwave assisted reactions were carried out using a CEM microwave reactor model Discover. Parameters *a*; for compounds **5a**,**d**–**h**: Discover mode; power: 250 W; ramp time: 30 s; hold time as indicated in Table 2; temperature: 40 °C; pressure: 2 bar; PowerMax-cooling mode. Parameters *b*; for compound **5b**,**c**,**i**–**k**: Discover mode, power: 300 W; ramp time: 30 s hold time as indicated in Table 2; temperature: 50 °C; pressure: 2 bar; PowerMax-cooling mode.

Experimental data for compounds **5a**–**k**. 3-(3-Fluorophenyl)-5-naphth-1-yl-4-thioxo-oxazolidin-2-one (**5a**): Pale yellow solid (54%). Mp 138 °C; IR (KBr): $\nu = 1811$, 1223 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 7.24 (s, 1H), 7.43–7.51 (m, 2H), 7.59–7.74 (m, 5H), 7.83–7.85 (m, 1H), 8.05–8.16 (m, 3H); ^{13}C NMR (DMSO-d_6) δ (ppm): 87.35, 115.73, 115.97, 117.40, 123.40, 124.66, 125.86, 126.74, 127.73, 129.27, 130.23, 131.01, 131.41, 133.81, 134.87, 154.93, 161.19, 203.41; Anal. Calcd for $C_{19}H_{12}FNO_2S$: C, 67.64; H, 3.59; N, 4.15. Found: C, 67.41; H, 3.66; N, 4.13.

5-Methyl-3-(4-methylbenzyl)-4-thioxo-oxazolidin-2-one (**5b**): Colorless solid (65%). Mp 54 °C; IR (KBr): $\nu = 1810$, 1221 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.58–1.60 (d, $J = 7.03$ Hz, 3H), 2.27 (s, 3H), 4.91 (s, 2H), 5.41–5.46 (q, $J = 6.78$ Hz, 1H), 7.14–7.24 (m, 4H); ^{13}C NMR (DMSO-d_6) δ (ppm): 19.71, 21.03, 46.39, 85.88, 128.15, 129.48, 131.76, 137.54, 155.87, 206.14; Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.37; H, 5.76; N, 5.96.

3-(4-Fluorobenzyl)-5-methyl-4-thioxo-oxazolidin-2-one (**5c**): Colorless solid (70%). Mp 57 °C; IR (KBr): $\nu = 1790$, 1226 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.59–1.61 (d, $J = 7.02$ Hz, 3H), 4.91–4.99 (m, 2H), 5.41–5.46 (q, $J = 7.02$ Hz, 1H), 7.15–7.21 (m, 2H), 7.38–7.43 (m, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm): 19.62, 45.93, 85.98, 115.63, 115.85, 130.39, 130.47, 155.84, 160.87, 206.22; Anal. Calcd for $C_{11}H_{10}FNO_2S$: C, 55.22; H, 4.21; N, 5.85. Found: C, 55.32; H, 4.39; N, 5.82.

3-(2-Chlorobenzyl)-5-phenyl-4-thioxo-oxazolidin-2-one (**5d**): Pale yellow solid (62%). Mp 110 °C; IR (KBr): $\nu = 1798$, 1231 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 5.08–5.17 (m, 2H), 6.50 (s, 1H), 7.29–7.38 (m, 3H), 7.46–7.53 (m, 6H); ^{13}C NMR (DMSO-d_6) δ (ppm): 45.00, 89.76, 127.79, 128.21, 128.59, 129.25, 129.88, 129.96, 130.23, 131.49, 132.20, 134.58, 155.76, 203.38; Anal. Calcd for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81; N, 4.41. Found: C, 60.20; H, 3.95; N, 4.42.

3-(2-Fluorobenzyl)-5-phenyl-4-thioxo-oxazolidin-2-one (**5e**): Pale yellow solid (68%). Mp 102 °C; IR (KBr): $\nu = 1789$, 1227 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 5.07–5.15 (m, 2H), 6.44 (s, 1H), 7.18–7.26 (m, 2H), 7.36–7.46 (m, 7H); ^{13}C NMR (DMSO-d_6) δ (ppm): 41.35, 89.55, 124.94, 128.05, 129.25, 130.12, 130.20, 130.41, 130.49, 134.62, 134.67, 155.71, 159.16, 203.10; Anal. Calcd for $C_{16}H_{12}FNO_2S$: C, 63.77; H, 4.01; N, 4.65. Found: C, 63.65; H, 4.30; N, 4.62.

3-(3-Chlorobenzyl)-5-phenyl-4-thioxo-oxazolidin-2-one (**5f**): Pale yellow solid (61%). Mp 81 °C; IR (KBr): $\nu = 1801$, 1230 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 5.07 (s, 2H), 6.46 (s, 1H), 7.33–7.47 (m, 9H); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.30, 89.70, 126.75, 128.06, 128.33, 129.24, 130.21, 130.94, 133.57, 134.60, 137.09, 155.91, 203.33; Anal. Calcd for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81; N, 4.41. Found: C, 60.55; H, 4.02; N, 4.36.

3-(2-Methylbenzyl)-4-thioxo-5-p-tolyl-oxazolidin-2-one (**5g**): Pale yellow solid (70%). Mp 120 °C; IR (KBr): $\nu = 1792$, 1230 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.33 (s, 3H), 2.38 (s, 3H), 4.98–5.08 (m, 2H), 6.46 (s,1H), 7.07–7.09 (m, 1H), 7.15–7.24 (m, 3H), 7.26–7.34 (m, 4H); ^{13}C NMR (DMSO-d_6) δ (ppm): 19.32, 21.17, 44.70, 89.65, 126.27, 126.41, 127.93, 127.99, 129.82, 130.71, 131.82, 132.48, 135.94, 139.85, 156.02, 203.69; Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.36; H, 5.71; N, 4.36.

3-(4-Chlorobenzyl)-5-(4-methoxyphenyl)-4-thioxo-oxazolidin-2-one (**5h**): Pale yellow solid (68%). Mp 120 °C; IR (KBr): $\nu = 1784$, 1225 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 3.77 (s, 3H), 5.00–5.08 (m, 2H), 6.37 (s, 1H), 6.97–7.00 (m, 2H), 7.30–7.34 (m, 2H), 7.40–7.46 (m, 4H); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.26, 55.63, 89.64, 114.68, 129.01, 129.80, 130.20, 129.04, 133.01, 133.79, 155.81, 160.72, 203.61; Anal. Calcd for $C_{17}H_{14}ClNO_3S$: C, 58.71; H, 4.06; N, 4.03. Found: C, 58.36; H, 4.06; N 3.66.

5-(2,4-Dichlorophenyl)-3-methyl-4-thioxo-oxazolidin-2-one (**5i**): Pale yellow solid (68%). Mp 88 °C; IR (KBr): $\nu = 1802$ cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 3.30 (s, 3H), 6.51 (s, 1H), 7.54–7.71 (m, 2H), 7.76–7.77 (d, $J = 2.26$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 30.00, 86.33, 127.96, 129.85, 130.44, 133.44, 134.26, 135.81, 155.65, 201.50; Anal. Calcd for $C_{10}H_7Cl_2NO_2S$: C, 43.50; H, 2.56; N, 5.07. Found: C, 43.41; H, 2.60; N, 5.02.

3-(2-Chlorobenzyl)-5-(4-chlorophenyl)-5-methyl-4-thioxo-oxazolidin-2-one (**5j**): Pale yellow solid (55%). Mp 90 °C; IR (KBr): $\nu = 1793$, 1215 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.09 (s, 3H), 5.04–5.13 (m, 2H), 7.11–7.13 (m, 1H), 7.29–7.37 (m, 2H), 7.48–7.60 (m, 5H); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.15, 45.03, 93.65, 127.47, 128.12, 128.70, 129.52, 129.60, 130.97, 131.84, 134.07, 136.48, 154.42, 206.23; Anal. Calcd for $C_{17}H_{13}Cl_2NO_2S$: C, 55.75; H, 3.58; N, 3.82. Found: C, 55.57; H, 3.61; N, 3.79.

5,5-Dimethyl-4-thioxo-3-p-tolyl-oxazolidin-2-one (**5k**): Pale yellow solid (54%). Mp 122 °C; IR (KBr): $\nu = 1804$, 1217 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.73 (s, 6H), 2.37 (s, 3H), 7.33–7.38 (m, 4H); ^{13}C NMR (DMSO-d_6) δ (ppm): 20.75, 23.04, 26.53, 92.81, 127.51, 129.60, 131.12, 139.15, 153.96, 209.74; Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.15; H, 5.61; N, 5.86.