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Synthesis of 2-oxazolidones by sulfur-assisted thiocarboxylation with carbon monoxide and oxidative cyclization with molecular oxygen under mild conditions

Takumi Mizuno,[a,*] Junko Takahashi[b] and Akiya Ogawa[b]

[a]*Osaka Municipal Technical Research Institute, 1-6-50, Morinomiya, Joto-ku, Osaka 536-8553, Japan*
[b]*Department of Chemistry, Faculty of Science, Nara Women's University, Kitauoyanishi-machi, Nara 630-8506, Japan*

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Abstract—Simple synthetic method on 2-oxazolidone derivatives was established. 2-Aminoethanols were easily subjected to the thiocarboxylation with carbon monoxide promoted by elemental sulfur, followed by the oxidative cyclization with molecular oxygen to give corresponding 2-oxazolidones in good yields under mild conditions (1 atm, rt). Furthermore, 2-imidazolidones and 2-thiazolidone were also prepared in good yields similarly.

1. Introduction

The importance of 2-oxazolidones **1** has been addressed in both pharmaceutical and synthetic organic chemistry. Especially, some substituted **1** are focused on a new class of antibiotics. Linezolid (ZYVOX®), developed by Pharmacia & Upjohn, is the first member of the class. The drug is active against Gram-positive bacteria, including those that are resistant to other drugs (Fig. 1).[1,2]

A variety of conventional syntheses of 2-oxazolidones (**1**) have been developed from 2-aminoethanols (**2**) as starting materials. Syntheses of **1** were carried out by cyclization of alkyl or aryl carbamates under either acidic[3] or basic[4,5] conditions, cyclization of triphenylphosphonium salts[6] or *N*-nitroso compounds,[7] and carbonylation of 2-aminoethanols (**2**) with phosgene,[8,9] diphosgene,[10,11] triphosgene,[12,13] urea,[14] or cyanates.[9,15] Most of these preparative methods need drastic conditions (high temperature or, strong acid or base), or toxic compounds such as phosgene or phosgene derivatives.

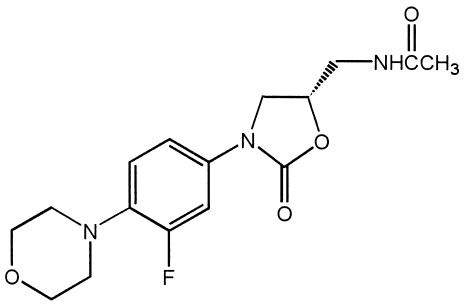
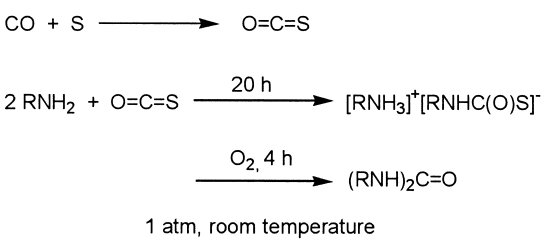


Figure 1. Linezolid (ZYVOX®).

Among them, the carbonylation of 2-aminoethanols (**2**) with carbon monoxide in the presence of selenium catalyst[16] is an excellent method, using cheap and easily available carbon monoxide, catalytic amount of selenium, and mild reaction conditions (1 atm, rt). However, because of toxicity of elemental selenium, use of this preparative method is considerably limited for industrial large-scale production of 2-oxazolidones (**1**).

Recently, we developed the synthesis of urea derivatives from amines or aromatic diamines, coupled the thiocarboxylation with carbon monoxide using non-toxic elemental sulfur compared with selenium, with the oxidation using molecular oxygen under mild conditions (1 atm, rt) (Scheme 1).[17,18]

Our plan was the exploration of a synthetic method for 2-oxazolidones by the thiocarboxylation of 2-aminoethanols



Scheme 1.

Keywords: oxazolidone; carbon monoxide; sulfur; thiocarboxylation; cyclization.

* Corresponding author. Tel.: +81-6-6963-8051; fax: +81-6-6963-8049; e-mail: tmizuno@omtri.city.osaka.jp

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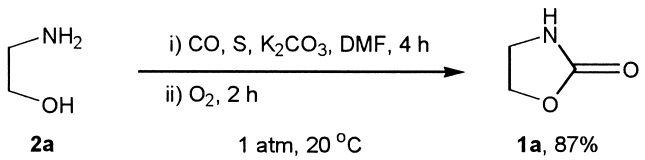


Scheme 2.

with carbon monoxide and sulfur, followed by the oxidative cyclization with molecular oxygen under very mild reaction conditions (1 atm, rt).

2. Results and discussion

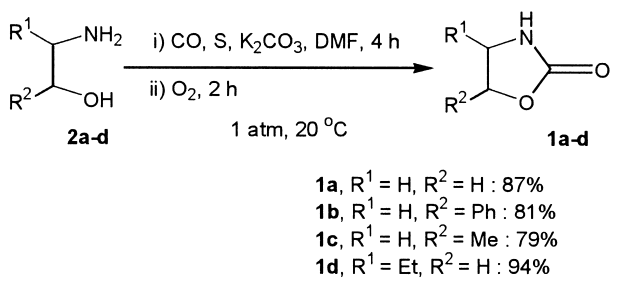
Our initial studies showed that successful synthesis of 2-oxazolidinone (**1a**) from 2-aminoethanol (**2a**) using the sulfur-assisted thiocarboxylation with carbon monoxide, and the oxidative cyclization with molecular oxygen in the presence of base. 2-Aminoethanol (**2a**) smoothly reacted with carbon monoxide and sulfur at 1 atm, 20°C for 4 h in the presence of K_2CO_3 in DMF. Resulting thiocarbamate salt in DMF solution was easily oxidized by molecular oxygen under 1 atm, 20°C for 2 h. Finally, 2-oxazolidone (**1a**) was given in an 87% yield (Scheme 2).

Various bases (1.0 equiv.) and solvents were investigated for this sulfur-assisted thiocarboxylation (4 h) and oxidative cyclization with molecular oxygen (2 h) under similar mild conditions (Table 1). Best results of synthesis of 2-oxazolidone (**1a**) (85–87%) were given using K_2CO_3, Na_2CO_3, NaOH, or KOH as base (entries 1, 4–6). DME and THF as solvents, having low polarity lowered the yields (entries 2, 3). Using of an organic base, such as Et_3N resulted in no formation of the product (**1a**) (entry 7). Weak base ($NaHCO_3$) and none of base only gave the complex mixture of products (entries 8, 9).

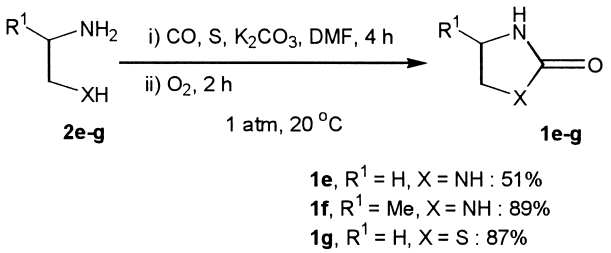
Table 1. Effect of bases and solvents for synthesis of 2-oxazolidone (**1a**)

Entry	Base	Solvent	Yield (%)[a]
1	K_2CO_3	DMF	87
2	K_2CO_3	DME	29
3	K_2CO_3	THF	17
4	Na_2CO_3	DMF	87
5	NaOH	DMF	85
6	KOH	DMF	86
7	Et_3N	DMF	0
8	$NaHCO_3$	DMF	Mixture
9	None	DMF	Mixture

[a] Isolated yields based on 2-aminoethanol (**2a**) used.



Scheme 3.



Scheme 4.

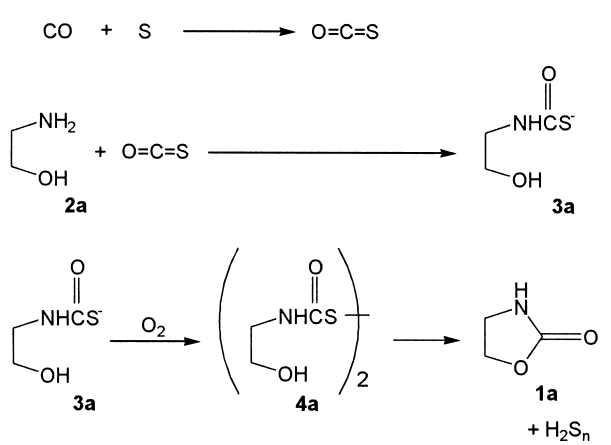
Several 2-oxazolidones (**1b–d**) were synthesized similarly in excellent yields, by the thiocarboxylation of corresponding 2-aminoethanols (**2b–d**), substituted by alkyl or aryl groups with carbon monoxide and sulfur in the presence of K_2CO_3 (4 h) and the oxidative cyclization with molecular oxygen (2 h) under mild conditions (1 atm, 20°C) (Scheme 3).

Furthermore, synthesis of 2-imidazolidones (**1e**,**f**) from ethylenediamines (**2e**,**f**) was successfully performed in the same manner (Scheme 4). 4-Methyl-2-imidazolidones (**1f**) was obtained in good yields. However, isolated yield of 2-imidazolidones (**1e**) was slightly lowered, because of low solubility of **1e** for organic solvents.

Also, 2-thiazolidone (**1g**) was similarly prepared from 2-aminoethanethiol (**2g**) in good yield, under mild conditions (1 atm, 20°C) (Scheme 4).

Scheme 5 shows a plausible pathway for the formation of 2-oxazolidone (**1a**) from 2-aminoethanol (**2a**) by the sulfur-assisted thiocarboxylation and oxidative cyclization with molecular oxygen. At first, carbonyl sulfide is formed in situ from carbon monoxide and sulfur in the presence of base. The thiocarboxylation of **2a** with carbonyl sulfide generates a thiocarbamate salt (**3a**) in the presence of K_2CO_3. Then, oxidation with molecular oxygen of **3a** gives disulfide type intermediate (**4a**). Finally, nucleophilic cyclization of **4a** affords 2-oxazolidone (**1a**) as a final product. Sulfur was recovered as potassium salts of hydrogen sulfide.[19]

In this sulfur-assisted thiocarboxylation using carbon monoxide and oxidative cyclization with molecular oxygen which proceeds, even if under 1 atm, 20°C, the formation of



Scheme 5.

isocyanate as an intermediate by the elimination of hydrogen sulfide from the carbamate salt (**3a**) might be impossible. Reported urea derivative synthesis from primary aliphatic amines with carbon monoxide and sulfur, in which an isocyanate is a key intermediate was performed under pressurized carbon monoxide and high temperature.[20,21]

3. Conclusion

A useful synthetic method for 2-oxazolidinones (**1**) by the thiocarboxylation of 2-aminoethanols (**2**) with carbon monoxide using elemental sulfur, followed by the oxidative cyclization with molecular oxygen was developed. From the viewpoint of application to actual industrial production of 2-oxazolidinone (**1**) as intermediates of medicines or agricultural chemicals, the present preparative method is very significant, using cheap and easily available carbon monoxide, sulfur, and oxygen, and mild reaction conditions (1 atm, rt).

4. Experimental

4.1. General

Melting points were determined on a Mettler FP 5 instrument and were uncorrected. FT-IR spectra were recorded on a Nicolet Magna-IR 550 instrument. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL JNM-AL300 (300, 75 MHz) instrument. Chemical shifts were reported in ppm relative to tetramethylsilane (δ-units). Mass and exact mass spectra were recorded on a JEOL JMS-600 spectrometer. 2-Aminoethanols (**2a**–**d**), ethylene-diamines (**2e**,**f**), 2-aminoethanethiol (**2g**), DMF, DME, THF, bases, sulfur (99.5%), carbon monoxide (99.9%), and oxygen (99.5%) were used as purchased.

4.2. Typical procedure for synthesis of oxazolidinone (1a)

A DMF solution (20 mL) containing powdered sulfur (641 mg, 20 mmol), 2-aminoethanol (**2a**) (1.21 mL, 20 mmol) and K_2CO_3 (2.76 g, 20 mmol) was vigorously stirred under carbon monoxide (1 atm) at 20°C for 4 h. After the carbonylation, carbon monoxide was purged and molecular oxygen was charged. The reaction mixture was stirred vigorously for additional 2 h under 1 atm of oxygen, 20°C. Than, evaporation of solvent, followed by purification by short column-chromatography (AcOEt/MeOH, 1:1), gave 2-oxazolidone (**1a**) (1.52 g, 87%) as a pure form.

4.2.1. 2-Oxazolidone (1a). Mp 87.9°C (88–89°C[22]); IR (KBr) 3270, 1735, 1255 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.43 (t, J=8 Hz, 2H), 4.27 (t, J=8 Hz, 2H), 7.42 (brs, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 40.0, 64.2, 159.6; MS (*m*/*z*, %) 87 (M$^+$, 100), 59 (79).

4.2.2. 5-Phenyl-2-oxazolidone (1b). Mp 83.6°C; IR (KBr) 3280, 1715, 1240 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.39 (dd, J=9, 7 Hz, 1H), 3.93 (t, J=9 Hz, 2H), 5.64 (t, J=8 Hz, 2H), 7.39–7.49 (m, 5H), 7.73 (brs, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 47.4, 76.3, 125.8, 128.4, 128.7, 139.5, 158.7; MS (*m*/*z*, %) 163 (M$^+$, 92), 107 (100), 79 (64); Exact MS calcd for $C_9H_9NO_2$: 163.0633. Found: 163.0614.

4.2.3. 5-Methyl-2-oxazolidone (1c). Oil; IR (neat) 3300, 1745, 1245 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.28 (d, J=6 Hz, 3H), 3.01 (t, J=8 Hz, 1H), 3.54 (t, J=8 Hz, 1H), 4.59–4.66 (m, 1H), 7.37 (brs, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 20.3, 46.5, 72.2, 158.9; MS (*m*/*z*, %) 101 (M$^+$, 100), 86 (26), 73 (13), 56 (27); Exact MS calcd for $C_4H_7NO_2$: 101.0477. Found: 101.0462.

4.2.4. 4-Ethyl-2-oxazolidone (1d). Oil; IR (neat) 3275, 1750 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 0.79–0.89 (m, 3H), 1.38–1.47 (m, 2H), 3.62–3.71 (m, 1H), 3.83–3.91 (m, 1H), 4.29–4.37 (m, 1H), 7.73 (brs, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 9.0, 27.7, 52.9, 68.8, 158.9; MS (*m*/*z*, %) 115 (M$^+$, 22), 86 (100), 85 (24), 58 (20); Exact MS calcd for $C_5H_9NO_2$: 115.0633. Found: 115.0609.

4.2.5. 2-Imidazolidone (1e). Mp 129.1°C (131°C[23]); IR (KBr) 3305, 1670, 1275 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.26 (s, 4H), 6.11 (brs, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 40.2, 164.4; MS (*m*/*z*, %) 86 (M$^+$, 100), 85 (12), 58 (4).

4.2.6. 4-Methyl-2-imidazolidone (1f). Mp 118.2°C (120–122°C[24]); IR (KBr) 3215, 1695, 1260 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.08 (d, J=6 Hz, 3H), 2.72–2.88 (m, 1H), 3.34–3.40 (m, 1H), 3.63–3.69 (m, 1H), 6.06 (brs, 1H), 6.26 (brs, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 21.2, 47.4, 47.5, 163.3; MS (*m*/*z*, %) 100 (M$^+$, 84), 85 (100).

4.2.7. 2-Thiazolidone (1g). Oil; IR (neat) 3255, 1675 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.36 (t, J=7 Hz, 2H), 3.46 (t, J=7 Hz, 2H), 7.94 (brs, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 29.4, 42.8, 173.7; MS (*m*/*z*, %) 103 (M$^+$, 100), 60 (84), 59 (40); Exact MS calcd for C_3H_5NOS: 103.0092. Found: 103.0064.

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