[Letter]

Synthesis of 2-Oxazolidinone from β -Aminoalcohol Using Supercritical Carbon dioxide

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The synthesis of 2-oxazolidinone from β -amino alcohol by chemical fixation of carbon dioxide under supercritical conditions using *N,N'*-dicyclohexylcarbodiimide (DCC) was developed. Even though in non-solvent conditions, 2-oxazolidinone was synthesized with a maximum yield of 96.7% at the critical pressure.

Keywords

2-Oxazolidinone, Amino alcohol, Carbon dioxide, Supercritical condition, Chemical fixation

From the standpoint of the development of safe and environmental friendly processes, carbon dioxide has been drawing much interest as an alternative C1 source to toxic phosgene in industrial chemistry and pharmaceutical engineering. Chemical fixation of carbon dioxide for the production of urethane derivatives such as 2-oxazolidinones from β -aminoalcohols is of great importance in the chemical industry and pharmacy as a chiral auxiliary or useful building block for a variety of bioactive compounds¹⁾, because there are a lot of possibilities that carbon dioxide can be used as a cheap and obtainable C1 component from air to produce useful organic compounds. These oxazolidinone syntheses have been conventionally achieved in organic solvents²⁾⁻⁵⁾ using various halide substrates such as tetrachloromethane with triphenylphosphines⁴⁾, or using an organo-tin compound as a catalyst⁵⁾. As an alternative to these organic solvents, it is noteworthy that supercritical carbon dioxide (scCO₂) itself has been employed as a substrate as well as a medium to synthesize the urethanes⁶⁾. Organic reactions under supercritical carbon dioxide conditions are expected to be promoted even under rather milder conditions due to enhanced diffusivity and disappearance of a gas-liquid phase boundary peculiar to the supercritical state. The urethane

“超臨界二酸化炭素を用いた β -アミノアルコールから 2-オキサゾリジノンの合成”

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synthesis has thus been attempted by the chemical fixation of carbon dioxide under supercritical conditions using halide substrates^{7), 8)}. However, the chemical fixation suffers the disadvantage of taking place only at temperatures higher than 100°C, because carbamic acid, which is generated by the reaction of amines with carbon dioxide⁹⁾, scarcely has activity at lower temperatures.

To achieve the synthesis of 2-oxazolidinone **4** from β -aminoalcohol **1** under milder conditions without halide substrates and organic solvents, we attempted to use *N,N'*-dicyclohexylcarbodiimide (DCC) in scCO₂ (Scheme), which has some advantages such as good solubility in scCO₂¹⁰⁾, as well as being an effective dehydration reagent. In this work, we successfully synthesized 2-oxazolidinone **4** in a maximum yield of 96.7% without organic solvents at 40°C. A recent example of the synthesis of dimethyl carbonate with DCC under high pressure carbon dioxide (at 12 MPa) has been reported by N. S. Isaacs *et al.*¹¹⁾, but the pressure dependence of the yield is still not clear at all. So, we also investigated and found the pressure dependence in the reaction of β -aminoalcohol **1** with carbon dioxide under scCO₂ using DCC.

The synthesis of 2-oxazolidinone **4** from β -aminoalcohol **1** was conducted batch-wise under various conditions as shown in Table 1¹²⁾. By the use of DCC (run 2), the yield of 5-phenyl-2-oxazolidinone **4a** was almost the same as that under the condition of using phosphine and halide substrates (run 1)⁴⁾. Furthermore, in the presence of acetonitrile at the critical pressure of 8.6 MPa (run 4), 96.5% of 2-oxazolidinone **4a** was obtained. Besides, in the absence of a co-solvent which is an environmentally friendly condition, β -aminoalcohol **1a** was also converted at ambient pressure, and 58.1% of a better yield was obtained at 8.6 MPa (run 6) which is supercritical condition. This enhancement of the yield in scCO₂ can be ascribed to the improvement in mass transfer of reactants. So this method under supercritical condition using DCC can be available for the synthesis of 2-oxazolidinone **4**.

Figure 1 shows the pressure dependences of the yield of 5-phenyl-2-oxazolidinone **4a** without acetonitrile as a co-solvent in scCO₂ at 40°C (black circles)¹³⁾. One can see an interesting pressure dependence in which the yield increases with increasing pressure, reaching a maximum yield of 2-oxazolidinone **4a** at 8.6 MPa near the critical pressure of carbon dioxide, and then significantly decreases. To clarify this pressure dependence, visual observation was carried out using a high-pressure view-cell attached with quartz glass windows. Below 8.6 MPa, gas-liquid-solid ternary phase, which

Table 1 2-Oxazolidinone **4** Synthesis from β -Aminoalcohol **1** in Various Conditions ^{a)}

Run	Substrate 1	Product 4	Pressure [MPa]	Co-solv.	Temperature [°C]	Dehydrate reagent	Yield of 4a [%]
1	1a	4a	0.1	MeCN	r.t.	Ph ₃ P, Et ₃ N and CCl ₄	67 ^{b)}
2			0.1	MeCN	r.t.	DCC	67.8 ^{c)}
3			0.1	MeCN	40	DCC	80.3 ^{c)}
4			8.6	MeCN	40	DCC	96.5 ^{c)}
5			0.1	None	40	DCC	24.8
6			8.6	None	40	DCC	58.1
7			8.6	None	40	None	0

^{a)} Reaction condition: 2-amino-1-phenylethanol; 3 mmol, DCC; 3.1 mmol, reaction time 12 h.

^{b)} Reference 4. Reaction time; 20 h.

^{c)} MeCN: 1.0 mL.

The mole fraction was calculated using PROPATH.
Reaction conditions: time, 30 min; temperature, 40°C.

Fig. 1 The Pressure Dependence of the Yield of 5-Phenyl-2-oxazolidinone **4a** in Carbon Dioxide in the Absence (black circles) of Acetonitrile, and the Mole Fraction of DCC (triangles)

contains carbon dioxide, DCC and carbamic acid **2**, was seen. Therefore, in this reaction, increasing the content of carbon dioxide by increasing pressure can contribute to the increasing solubility of 2-oxazolidinone **4a**. On the other hand, above 8.6 MPa, gas-liquid phase disappeared to form a supercritical fluid but solid remained, because DCC can easily dissolve in scCO₂ but carbamic acid **2** cannot completely dissolve. To explain the decrease in yield with increasing pressure above 8.6 MPa, we introduce the mole fraction of DCC in supercritical fluid as shown in Fig. 1 (triangles)¹⁴. It can be found that the decrease of the mole fraction of DCC with increasing pressure shows close agreement with the decrease of the yield of 2-oxazolidinone **4a**. Since the second step of the reaction in scheme is taken place

Table 2 Variety of 2-Oxazolidinone **4** Synthesis at 8.6 MPa from β -Aminoalcohol **1**^{a)}

Run	Substrate 1	Product 4	Yield
1		Ph	86 ^{b)}
2			85.7 ^{c)}
3	1b	4b	96.7
4			91.4
	1c	4c	
5			27.1
	1d	4d	
6			69.1
	1e	4e	

^{a)} Reaction conditions: β -aminoalcohol **1**; 3 mmol, DCC; 3.1 mmol, reaction temp.; 40°C, Pressure; 8.6 MPa, reaction time; 12 h.

^{b)} Reference 3.

^{c)} MeCN; 1.0 mL.

in scCO₂, DCC must come in contact with carbamic acid **2** to form the intermediate **3**. However, the decrease of the mole fraction of DCC in scCO₂ would affect the reaction rate of formation of the intermediate **3**^{14),15)}.

Using this condition of 8.6 MPa at 40°C without co-solvent, we have further attempted the reaction of other β-aminoalcohols **1**, and the results are shown in Table 2. All 2-oxazolidinones **4b-4e** were obtained in good yields, and especially, even in the absence of co-solvent, the yield of 4-phenyl-2-oxazolidinone **4b** from 2-phenyl-2-aminoethanol **1b** (run 3) is superior to the yield under the supercritical condition with co-solvent (run 2) and the yield of the previous paper (run 1)³⁾. Furthermore, *N*-aromatic-substituted β-aminoalcohol **1d**, which has low nucleophilicity in regard to carbon dioxide (run 5), can also react with scCO₂ to give *N*-aromatic-substituted 2-oxazolidinone **4d**. So this reaction with DCC using scCO₂ is available for the synthesis of 2-oxazolidinone **4** from β-aminoalcohol **1**.

In conclusion, our synthetic method of 2-oxazolidinone without using halo- or phosphorous-reagents can be developed at supercritical conditions, and the maximum yields were given under scCO₂ at 8.6 MPa as not only reaction media but also as substrates, despite the addition of organic co-solvent.

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- 10) Dissolution of DCC in scCO₂ was confirmed by visual observation.
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- 12) Typical experimental procedure is as follows: 2-amino-1-phenylethanol (3 mmol), *N,N'*-dicyclohexyl carbodiimide (DCC, 3 mmol) were charged into a 50 cm³ reactor at 40°C, and carbon dioxide was introduced into the reactor. The reactions were started by stirring the mixture and continued for 30 min or 12 h. After reaction, the reactor was cooled with ice and the pressure was released. The crude products were purified by distillation, and analysed GC-MS and NMR. The yield of products were determined by GC-MS.
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