A CONVENIENT METHOD FOR THE SYNTHESIS OF 2-OXAZOLIDINONES FROM ETHYLENE CARBONATE AND PRIMARY ARYL AMINES

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Abstract – One-step procedure for the synthesis of 2-oxazolidinones from ethylene carbonate and primary aryl amines in the presence of amine catalysts was described. Various reaction parameters including catalyst, temperature, reaction time, solvent and the amount of catalyst were investigated. Excellent results were obtained using DBU as catalyst at 100 °C within 2 h free of solvent.

2-Oxazolidinones have been extensively used in organic synthesis. They are, in fact, employed as protecting groups in organic synthesis, chiral auxiliaries (Evans’ chiral auxiliaries) in asymmetric synthesis and as biologically active pharmaceutical agents and so on. Conventionally 2-oxazolidinones are synthesized by reactions of β-aminoalcohols or other β-amino compounds with toxic phosgene or its derivative, which may cause serious environmental pollution and equipment corrosion. Therefore, a number of non-toxic procedures have been suggested: (1) oxidative carbonylation using CO/O2 and β-aminoalcohols, (2) they are prepared by dialkyl carbonates and β-aminoalcohols, (3) direct synthesis of 2-oxazolidinones from carbon dioxide and β-aminoalcohols or aziridines. The intramolecular oxidative cyclocarbonylation of β-aminoalcohols catalyzed by transition metals is a way to produce these heterocyclic compounds, but the oxidative carbonylation is expensive in using carbon monoxide and it has potential explosion hazards. As an alternative, dialkyl carbonates were used for the synthesis of 2-oxazolidinones. It should be noted that dimethyl carbonate is currently produced by phosgenation and oxidative carbonylation routes. There are several reports on the direct synthesis of 2-oxazolidinones by carbon dioxide and β-aminoalcohols or aziridines, however, toxic catalysts and high pressure and/or high temperature are required in most of those work. Development of a...
simple, highly efficient and environmentally benign method for synthesis of 2-oxazolidinone derivatives is still highly desired.

Recently, the synthesis of 2-oxazolidinones from ethylene carbonate (EC) and \( \beta \)-aminoalcohols in the presence of homogenous base catalyst\(^{20} \) or heterogeneous base catalyst\(^{21} \) was reported. The reaction could be considered as a carbon dioxide fixation reaction, since EC is synthesized via reaction of ethylene oxide with carbon dioxide.\(^{22,23,24,25,26,27} \)

However, there are very few reports on the direct conversion of simple primary amine into 2-oxazolidinones. S. Tanimori and M. Kirihata reported that the reaction of dimethyl (Z)-2-butenylene dicarbonate with primary amines in the presence of \([\text{Pd}(\eta^3-C_3H_5)\text{Cl}]_2\) and 1,1’-bis(diphenylphosphino) ferrocene (dppf) produced vinyl-oxazolidone compounds in 70% yield\(^{28} \) (Scheme 1).

\[
\text{MeO}_2\text{CO}^\circledast \text{OCO}_2\text{Me} + \text{RNH}_2 \xrightarrow{[\text{Pd}(\eta^3-C_3H_5)\text{Cl}]_2, \text{dppf}} \text{CH}_2\text{Cl}_2 \rightarrow \text{HN} \xrightarrow{\text{O}}
\]

**Scheme 1.** The reaction of dimethyl (Z)-2-butenylene dicarbonate with primary amines in the presence of \([\text{Pd}(\eta^3-C_3H_5)\text{Cl}]_2\) and dppf.

Herein, we report a novel method for synthesis of 2-oxazolidinones from five-membered cyclic carbonates EC and primary aryl amines under mild conditions (Scheme 2). This synthetic method has several advantages: (1) the reaction can be considered as a carbon dioxide fixation reaction, since five-membered cyclic carbonates are synthesized via reaction of ethylene oxide with carbon dioxide; (2) the 2-oxazolidinones were obtained under mild conditions that are neither dangerous nor noxious; (3) this reaction was wasteless and pollution-free, water was the sole co-product; (4) the readily available aryl amines was used as substrate. So, this reaction process was environmentally benign and high atom economic.

\[
\begin{array}{c}
\text{NH}_2 \quad + \quad \text{O} \quad \text{O} \quad \xrightarrow{\text{DBU}} \quad \text{R} \quad \text{O} \\
\quad \text{R} \quad \text{H}_2\text{O}
\end{array}
\]

**Scheme 2.** Synthesis of oxazolidinones from EC and aryl amine in the presence of DBU.

The reaction of aniline and ethylene carbonate was investigated as a model. And the results are summarized in Tabel 1. The reaction could not occurred if the catalyst was absent (Table 1, entry 1). In this reaction, the yield of 2-oxazolidinone was greatly affected by basic catalyst (Table 1, entries 2–7). When DBU was used as catalyst, the excellent yield (91%) of 2-oxazolidinone was obtained (Table 1,
It is due to the stability of quaternary ammonium salt through conjugation, which increases its equilibrium concentration (Scheme 3). In order to establish the optimized reaction conditions, we examined the effect of temperature, reaction time, the amount of the catalyst and different catalysts. Slightly high temperature was necessary for this reaction. If the temperature was too low, the reaction does not proceed normally. The preferred temperature was 100 °C in our experiments (Table 1, entries 7-8). The yield was affected by the reaction time, and increasing reaction time was propitious to improve the yield of 2-oxazolidinone, yet the reaction almost completed within 2 h (Table 1, entries 7, 12–13). A higher yield was obtained by increasing the amount of the catalyst (Table 1, entries 7, 9-11). The yield of 2-oxazolidinone was affected by the scale of the substrates, the excessive of ethylene carbonate was required, perhaps it is caused by the decomposability of ethylene carbonate in the presence of the catalyst (Table 1, entries 7, 14-16). Another problem need to point out is that the reaction should proceed under the inert atmosphere, such as argon, to avoid the oxidation of aniline.

**Table 1.** Effects of reaction conditions on the synthesis of 2-oxazolidinone from aniline and EC

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Aniline:EC:Cat.</th>
<th>Temperature(°C)</th>
<th>Time (h)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>1:5:1</td>
<td>100</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(n-C(_3)H(_7))(_3)N</td>
<td>1:5:1</td>
<td>100</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PPh(_3)</td>
<td>1:5:1</td>
<td>100</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>urotropine</td>
<td>1:5:1</td>
<td>100</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>DABCO</td>
<td>1:5:1</td>
<td>100</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>DMAP</td>
<td>1:5:1</td>
<td>100</td>
<td>2</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>DBU</td>
<td>1:5:1</td>
<td>100</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>DBU</td>
<td>1:5:1</td>
<td>80</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>DBU</td>
<td>1:5:0.2</td>
<td>100</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>DBU</td>
<td>1:5:0.5</td>
<td>100</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>11</td>
<td>DBU</td>
<td>1:5:2</td>
<td>100</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>12</td>
<td>DBU</td>
<td>1:5:1</td>
<td>100</td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td>13</td>
<td>DBU</td>
<td>1:5:1</td>
<td>100</td>
<td>4</td>
<td>92</td>
</tr>
<tr>
<td>14</td>
<td>DBU</td>
<td>1:2:1</td>
<td>100</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>15</td>
<td>DBU</td>
<td>1:3:1</td>
<td>100</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>16</td>
<td>DBU</td>
<td>1:4:1</td>
<td>100</td>
<td>2</td>
<td>79</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: aniline 1.0 mmol; free of solvent; under argon;

\(^b\) Isolated yield.
Under the optimized reaction conditions (the molar ratio of substrates and catalyst, aniline:EC:DBU = 1:5:1; temperature, 100 °C, reaction time, 2 h), it was found that this method was applicable to the synthesis of corresponding 2-oxazolidinones from different aryl amines and ethylene carbonate. The results are summarized in Table 2. It was found that the aryl amines bearing electron-withdrawing groups or none-substituent at the para- or meta-position on the benzene rings gave the corresponding 2-oxazolidinones with high yields (Table 2, entries 1-2, 4-5). Other aryl amines with electron-donating substituents at the para- or meta-position on the benzene rings provide middle to good yields (Table 2, entries 8-10). Especially, if there is a substituent at the ortho-position of the benzene ring of the aryl amine, the reaction yields will be much lower (Table 2, entries 3, 6-7, 11). Perhaps it is caused by the steric effect of the ortho-substituent. Yet the 2,4,6-trichloroaniline gives a middle yield. Maybe it is caused by the steric effect and electronic effect (Table 2, entry 12).

Table 2. Results for the reaction of EC with aryl amines in the presence of DBU

<table>
<thead>
<tr>
<th>Entry</th>
<th>RArNH2 (R)</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1a</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>p-NO2</td>
<td>2a</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>o-NO2</td>
<td>3a</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>m-NO2</td>
<td>4a</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>p-Br</td>
<td>5a</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>o-Br</td>
<td>6a</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>o-Cl</td>
<td>7a</td>
<td>57</td>
</tr>
<tr>
<td>8</td>
<td>p-MeO</td>
<td>8a</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>m-MeO</td>
<td>9a</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>p-Me</td>
<td>10a</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>o-Me</td>
<td>11a</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>2,4,6-trichloro</td>
<td>12a</td>
<td>66</td>
</tr>
<tr>
<td>13b</td>
<td>n-C4H9NH2</td>
<td>13a</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction conditions: amine, 1 mmol; amine:EC:DBU=1:5:1; temperature, 100 °C; reaction time 2 h.

b No product was found under this condition when aliphatic amine used as reagent.

Proposed mechanism for the reaction of ethylene carbonate with aniline catalyzed by amine catalyst displays in Scheme 3, which is similar to the the indole benzylation catalyzed by the amine catalyst. On the Cycle I, the amine catalyst acts as nucleophilic catalyst, which acts as a base on the Cycle II.
Scheme 3. Proposed mechanism for the synthesis of 2-oxazolidinones.

In summary, we have found that the synthesis of 2-oxazolidinones from ethylene carbonate and corresponding primary aryl amines could be performed with excellent yields by using DBU as catalyst under mild conditions. This atom economical methodology represents a valuable and environmentally benign non-phosgene alternative to the use of toxic phosgene or expensive dimethyl carbonate. Since ethylene carbonate was prepared from epoxide and carbon dioxide, the title reactions will be chemical fixation of carbon dioxide to important chemicals indirectly.

EXPERIMENTAL
General remarks
All glassware was dried in oven and cooled in a desiccator (silica gel desiccant) prior to use. Liquid amine were distilled and stored under a nitrogen atmosphere before being used. Other commercially supplied reagents were used without further purification. All the products were characterized by $^1$H NMR, $^{13}$C NMR and elemental analysis.

General procedure for the synthesis of 2-oxazolidinones (Table 2)
For each reaction, aryl amine (1 mmol), EC (5 mmol) and DBU (1 mmol) were charged into a 5 mL round-bottomed flask equipped with a magnetic stirrer in argon atmosphere at 100 °C for 2 h. At the end of the reaction, after the mixture was cooled back to rt, the mixture was diluted by 10 mL water. Then solid or oil was found in the mixture. The solid was filtered in vacuo and washed with water (5 mL×2), then dried in vacuo to obtain the purified product. In the circumstance of oil, the reaction mixture was extracted with CH$_2$Cl$_2$ (5 mL×3) and the crude product was obtained after evaporation of solvent. The crude product was purified by preparative TLC (silica gel, CH$_2$Cl$_2$) to give the fine product. All the products were characterized by $^1$H NMR, $^{13}$C NMR and elemental analyses.
Characterization of the oxazolidinone derivatives

Compound 1a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 4.08 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 4.50 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 7.15 (1H, $t$, $J = 7.4$ Hz, Ar), 7.39 (2H, $dd$, $J = 7.8$, 8.1 Hz, Ar), 7.55 (2H, $d$, $J = 8.0$ Hz, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): δ 45.23, 61.31, 118.30, 124.10, 129.07, 138.32, 155.30; Anal. Calcd for C$_9$H$_9$NO$_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.16; H, 5.56; N, 8.75.

Compound 2a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 4.15 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 4.57 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 7.74 (2H, $d$, $J = 9.3$ Hz, Ar), 8.26 (2H, $d$, $J = 9.3$ Hz, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): δ: 44.95, 61.37, 117.48, 125.00, 143.45, 143.80, 154.54; Anal. Calcd for C$_9$H$_8$N$_2$O$_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.03; H, 3.81; N, 13.40.

Compound 3a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 4.10 (2H, $t$, $J = 7.8$ Hz, -CH$_2$-), 4.59 (2H, $t$, $J = 7.8$ Hz, -CH$_2$-), 7.44-7.49 (2H, $m$, Ar), 7.67 (1H, $dd$, $J = 7.8$, 7.8 Hz, Ar), 7.67 (1H, $d$, $J = 8.2$ Hz, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): δ: 47.43, 62.83, 125.96, 128.00, 128.12, 131.53, 133.93, 145.64, 156.21; Anal. Calcd for C$_9$H$_8$N$_2$O$_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.80; H, 3.75; N, 13.66.

Compound 4a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 4.15 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 4.57 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 7.57 (1H, $dd$, $J = 8.2$, 8.2 Hz, Ar), 8.00 (1H, $d$, $J = 8.0$ Hz, Ar), 8.16 (1H, $d$, $J = 8.5$ Hz, Ar), 8.22 (1H, $s$, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): δ 45.01, 61.40, 112.32, 118.59, 123.90, 130.05, 139.53, 148.74, 154.84; Anal. Calcd for C$_9$H$_8$BrNO$_2$: C, 44.66; H, 3.33; N, 5.79. Found: C, 44.87; H, 3.28; N, 5.80.

Compound 5a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 4.04 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 4.50 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 7.44-7.49 (2H, $m$, Ar), 7.67 (1H, $dd$, $J = 9.1$ Hz, Ar), 7.67 (1H, $d$, $J = 9.6$ Hz, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): δ 29.69, 61.28, 116.88, 119.70, 132.00, 137.43, 155.04; Anal. Calcd for C$_9$H$_8$BrNO$_2$: C, 44.66; H, 3.33; N, 5.79. Found: C, 44.87; H, 3.28; N, 5.80.

Compound 6a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 4.02 (2H, $t$, $J = 7.9$ Hz, -CH$_2$-), 4.55 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 7.22-7.25 (1H, $m$, Ar), 7.38-7.40 (2H, $m$, Ar), 7.65 (1H, $d$, $J = 8.5$ Hz, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): δ 47.27, 62.60, 122.51, 128.73, 129.73, 129.85, 133.77, 136.48, 156.75; Anal. Calcd for C$_9$H$_8$BrNO$_2$: C, 44.66; H, 3.33; N, 5.79. Found: C, 44.87; H, 3.28; N, 5.80.

Compound 7a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 4.02 (2H, $t$, $J = 7.9$ Hz, -CH$_2$-), 4.54 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 7.30-7.34 (2H, $m$, Ar), 7.40 (1H, $d$, $J = 1.8$ Hz, Ar), 7.46 (1H, $d$, $J = 1.8$ Hz, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): δ 47.13, 62.61, 127.99, 129.42(two carbon), 130.61, 132.34, 134.99, 156.85; Anal. Calcd for C$_9$H$_8$ClNO$_2$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.26; H, 4.11; N, 6.98.

Compound 8a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 3.80 (3H, $s$, Me), 4.03 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 4.47 (2H, $t$, $J = 8.0$ Hz, -CH$_2$-), 6.91 (2H, $d$, $J = 9.0$ Hz, Ar), 7.43 (2H, $d$, $J = 9.0$ Hz, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): δ 45.79, 55.54, 61.27, 114.38, 120.38, 131.52, 155.61, 156.50; Anal. Calcd for C$_{10}$H$_{11}$NO$_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.10; H, 5.80; N, 7.20.
Compound 9a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): $\delta$ 3.83 (3H, s, Me), 4.04 (2H, $t$, $J$ = 8.0 Hz, -CH$_2$-), 4.48 (2H, $t$, $J$ = 8.0 Hz, -CH$_2$-), 6.70 (1H, $d$, $J$ = 8.3 Hz, Ar), 7.04 (1H, $d$, $J$ = 8.6 Hz, Ar), 7.26-7.30 (2H, $m$, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): $\delta$ 45.36, 55.40, 61.27, 104.59, 109.65, 110.38, 129.78, 139.58, 155.17, 160.28; Anal. Calcd for C$_{10}$H$_{11}$NO$_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.42; H, 5.77; N, 7.30.

Compound 10a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): $\delta$ 2.34 (3H, s, Me), 4.05 (2H, $t$, $J$ = 8.0 Hz, -CH$_2$-), 4.48 (2H, $t$, $J$ = 8.0 Hz, -CH$_2$-), 7.19 (2H, $d$, $J$ = 8.3 Hz, Ar), 7.43 (2H, $d$, $J$ = 8.5 Hz, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): $\delta$ 20.75, 45.40, 61.28, 118.43, 129.60, 133.80, 135.82, 155.38; Anal. Calcd for C$_{10}$H$_{11}$NO$_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.91; H, 6.31; N, 7.87.

Compound 11a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): $\delta$ 2.31 (3H, s, Me), 3.94 (2H, $t$, $J$ = 8.0 Hz, -CH$_2$-), 4.48 (2H, $t$, $J$ = 8.0 Hz, -CH$_2$-), 7.23-7.28 (4H, $m$, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): $\delta$ 17.83, 47.88, 62.42, 126.51, 127.00, 128.17, 131.38, 135.92, 136.17, 156.80; Anal. Calcd for C$_{10}$H$_{11}$NO$_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.71; H, 6.24; N, 7.78.

Compound 12a $^1$H NMR (CDCl$_3$, 400 MHz, TMS): $\delta$ 3.93 (2H, $t$, $J$ = 8.0 Hz, -CH$_2$-), 4.60 (2H, $t$, $J$ = 8.0 Hz, -CH$_2$-), 7.44 (2H, $s$, Ar); $^{13}$C NMR (CDCl$_3$, 60 MHz, TMS): $\delta$ 45.30, 63.07, 128.98, 131.31, 135.58, 136.36, 155.73; Anal. Calcd for C$_3$H$_6$Cl$_3$NO$_2$: C, 40.56; H, 2.27; N, 5.26. Found: C, 40.45; H, 2.20; N, 5.12.

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