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Dehydrative synthesis of chiral oxazolidinones catalyzed by alkali metal carbonates under low pressure of CO_2

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ABSTRACT

Dehydrative synthesis of oxazolidinones from amino alcohols and CO_2 was achieved in the presence of alkali metal carbonates such as Cs_2CO_3 as catalyst. It is noteworthy that 1 atm of CO_2 is enough for the reaction to proceed and no special dehydrating agent is required in this system. A mechanstic study showed that the OH of amino alcohol acts as nucleophile and the OH in the carbamic acid moiety is liberated during the cyclization process.

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In recent years, the expected depletion of petroleum has impelled us to seek other carbon resources. Carbon dioxide (CO_2) is one of the potential candidates as it is the most abundant carbon source in the Earth's atmosphere—with around 300 billion tons.[1] Increasing exploitation of CO_2 as starting material in the chemical industry is thus highly desirable. It is an abundant, cheap, and nontoxic source of C_1.[2] In recent years, studies in CO_2 transformation have extended to the synthesis of polymers,[3] carbonates,[4] carbamates,[5] formate,[6] methanol,[7] carbon monoxide,[8] etc.

Oxazolidinones are in the family of carbamates, and are among the most widely used chiral auxiliaries in asymmetric natural product synthesis.[9] Oxazolidinones are mainly manufactured by phosgenation of β-amino alcohols.[10,11] However, the use of phosgene ($Cl_2C{=}O$) precludes widespread application in laboratory and industry due to phosgene's toxicity and adverse environmental impact.[5b,11] Replacement of phosgene with CO_2 is an ideal alternative. In fact, research on the synthesis of oxazolidinones starting from β-amino alcohol[5b,11,12] and CO_2 has been an important subject for many years.[13–16] Nevertheless, simple and salt-free approach in oxazolidinone synthesis starting from β-amino alcohol has yet to be established. This might be due to thermodynamic reasons (vide infra) and catalyst deactivation caused by the coproduced water.[5b,11] In order to overcome these drawbacks, many attempts have been made to shift the equilibrium to the product side. The most straightforward way is to use a dehydrating agent to trap the coproduced water[14a,b,15]; other attempts include the use of aziridine[17] (a predehydrated form of β-amino alcohol) and phosphorylating agents (similar to Mitsunobu's reaction).[16i–m] Carbon monoxide (CO)[5b,11,18] and supercritical CO_2 are additional popular alternatives for combating the thermodynamic issues in oxazolidinone synthesis.[13,15] Although several groups have reported catalytic synthesis of oxazolidinone using cyclic carbonate as 'carbonyl source', it rarely attracted much attention because the use of cyclic carbonate incurred higher production cost and complexity in the reaction.[19] Recently, CeO_2 nanoparticles were used as catalyst in the reaction of N-substituted-β-amino alcohols or other ω-amino alcohols with CO_2 (7 bar) at 160 °C but the conversion was unsatisfactory.[20] Therefore, simply dehydrative methods are rarely employed in the general synthesis of chiral auxiliaries. We report here a chiral oxazolidinone synthesis via the incorporation of CO_2 under atmospheric pressure (1 atm) into β-amino alcohols, with merely H_2O as byproduct and without using any special dehydrating agents (Scheme 1).

In order to assess a possibility of simple dehydrative method of oxazolidinone synthesis from CO_2, we started our considerations with fundamentals, that is, the Gibbs free energy and enthalpy calculations. The reaction with ethanolamine ($R^1 = H$) is endergonic and endothermic [$\Delta G = +3.1$ kcal/mol and $\Delta H = +1.6$ kcal/mol (B3LYP/6–31+G**) and $\Delta G = +2.63$ kcal/mol and $\Delta H = +1.33$ kcal/mol (M062X/6–311++G**)]. Nonetheless, the thermodynamics are

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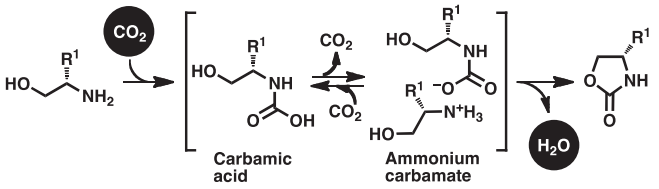
more favorable when ethanolamine is replaced with L-valinol ($R^1 = {}^iPr$) [$\Delta G = +0.35$ kcal/mol and $\Delta H = -0.84$ kcal/mol (B3LYP/6–31+G**) and $\Delta G = +0.01$ kcal/mol and $\Delta H = -0.80$ kcal/mol (M062X/6–311++G**)]. For this reason, amino alcohols derived from natural amino acids were selected ($R^1 \neq H$) (Scheme 1).

Based on the results obtained in the synthesis of dialkyl carbamates[21a,b] and of dialkyl carbonates[21c,d] from CH_2Cl_2 and CO_2 at a low pressure,[21d] we found, to our surprise, that an alkali metal salt sufficed to promote the dehydration, when L-valinol ((*S*)-**1a**: $[\mathbf{1a}]_0 = 0.90$ M) and Cs_2CO_3 (10 mol %: $[Cs_2CO_3]_0 = 0.09$ M) in DMSO-d_6 were exposed to a 1 atm of CO_2 (purity = 99.9%) at 150 °C for 24 h; (*S*)-**2a** was obtained in 90% (isolated yield: 80%,[22] Table 1, entry 10).

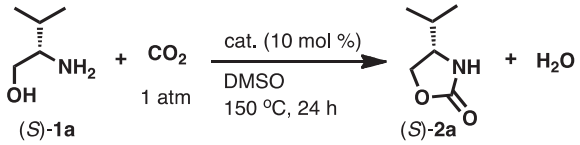
The yield was only 6% when Cs_2CO_3 was replaced with ammonium carbonate (entry 1). Among the alkali metal (bi)carbonates (e.g., Li_2CO_3, Na_2CO_3, K_2CO_3, Rb_2CO_3, $KHCO_3$, and $CsHCO_3$) that promoted this reaction (entries 2–7 and 10), Cs_2CO_3 was the most effective. The catalytic activity decreased in the order $Cs^+ \approx Rb^+ > K^+ > Na^+ > Li^+$ (entries 2–5 and 10). Based on this observed trend, dissociation of the alkali metal cation from the carbonate anion appeared to be playing an important role in the reactivity. Hence, in the case of K_2CO_3, 18-crown-6 was used as an additive (10 mol %), and in fact the product yield was improved to 64% (compared to entry 4). Equivalent amount of $CsHCO_3$ (10 mol %) gave a less encouraging result (entries 7 and 10). Other Cs sources, for example, CsOAc or Cs_2SO_4 (**2a**: 4% and 6%, respectively), were ineffective compared to Cs_2CO_3 (entry 10). Different solvents such as DMF (4%), NMP (8%), DMI (55%), DMA (9%), and MeCN (<1%) did not provide a satisfying yield of **2a**. No significant difference in reactivity was observed between a commercial DMSO directly used and anhydrous DMSO-d_6 distilled over CaH_2 (**2a**: 91% and 90%, respectively). Thus, the moisture present in a commercial DMSO did not interfere with the action of Cs_2CO_3. A $\geqslant$1 mL of DMSO per 1 mmol of **1a** was needed to obtain satisfactory results (entry 8). When dimethyl sulfone was used as solvent or no catalyst was present (entry 11), only a trace amount of the desired product was obtained (**2a**: <1%).

With the optimized conditions in hand, various amino alcohols have been screened (Table 2). Oxazolidinones, especially those widely used as Evans auxiliaries,[9] were obtained in satisfactory yields (entries 4, 5, and 7). Regardless of whether the substituent (R^1) on the amino-alcohol skeleton was a primary, secondary, or tertiary carbon, trapping of CO_2 proceeded smoothly. Albeit some of them needed slightly higher CO_2 pressure (3–5 atm) compared to the optimized conditions, moderate to good yields were obtained. When R^1 was the methyl group, the product yield was not as good as when it was a larger substituent (entries 1–8). The larger the R^1, the better the yield of **2**. This observation can be rationalized by the Thorpe–Ingold effect.[23] According to the initial calculations, the reaction with ethanolamine ($R^1 = H$) faces a thermodynamic disadvantage, and the experimental observation is in accordance with the calculations (vide supra). Indeed, when ethanolamine was used, only 7% of the desired product was obtained under the optimized conditions. A higher catalyst load (20 mol %) or an increased CO_2 pressure (9 atm) failed to increase the product yield. The retention of the absolute configuration at the β-positions of amino alcohols **1a**–**h** was consistently observed, giving products **2a**–**h** as single enantiomers (see Supplementary data).



Scheme 1. Synthesis of oxazolidinone from CO_2 under atmospheric pressure.

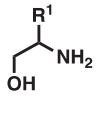
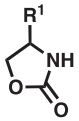
Table 1
Synthesis of oxazolidinone (*S*)-**2a** from (*S*)-**1a**[a]



Entry	Cat.	Yield[b] (%)
1	$(NH_4)_2CO_3$	6
2	Li_2CO_3	3
3	Na_2CO_3	22
4	K_2CO_3	49
5	Rb_2CO_3	88
6	$KHCO_3$	56
7	$CsHCO_3$	48
8	Cs_2CO_3	34[c,d]
9	Cs_2CO_3	62[c]
10	Cs_2CO_3	90[e] (80)
11	None	<1

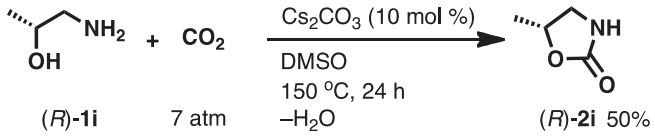
[a] The reaction was performed using (*S*)-**1a** (1 mmol) in DMSO (1 mL) with an initial CO_2 pressure of 1 atm at 25 °C.
[b] Determined by ^1H NMR (DMF as internal standard); the number in parentheses is the isolated yield.
[c] 5 mol % of Cs_2CO_3.
[d] 0.5 mL of DMSO.
[e] Anhydrous DMSO-d_6 was used.

Table 2
Substrate scope[a]

Entry	Amino alcohol **1**	Oxazolidinone **2**	Yield[b,c] (%)
			
1[d]	(*S*)-**1b** (R = Me)	(*S*)-**2b** (R = Me)	42 (36)
2[d]	(*S*)-**1c** (R = Et)	(*S*)-**2c** (R = Et)	63 (51)
3[d]	(*S*)-**1d** (R = ^{i}Bu)	(*S*)-**2d** (R = ^{i}Bu)	57 (49)
4[d]	(*S*)-**1e** (R = Bn)	(*S*)-**2e** (R = Bn)	88 (90)
5	(*R*)-**1a** (R = ^{i}Pr)	(*R*)-**2a** (R = ^{i}Pr)	89 (70)
6	(*S*)-**1f** (R = ^{s}Bu)	(*S*)-**2f** (R = ^{s}Bu)	81 (78)
7	(*S*)-**1g** (R = ^{t}Bu)	(*S*)-**2g** (R = ^{t}Bu)	— (80)
8[e]	(*R*)-**1h** (R = Ph)	(*R*)-**2h** (R = Ph)	61 (69)

[a] Unless otherwise specified, the reaction conditions were: **1** (1 mmol), Cs_2CO_3 (10 mol %), CO_2 (P_{CO2} = 1 atm; CO_2 balloon) in anhydrous DMSO or DMSO-d_6 (1 mL), at 150 °C for 24 h.
[b] Determined by ^1H NMR (DMF as internal standard); the number in parentheses is the isolated yield.
[c] Conversion of **1**:>99%. Other products: carbamic acid ($RNHCO_2H$, major) and carbamate $(RNHCO_2)^-(RNH_3)^+$ or ammonium bicarbonate $RNH_3^+HCO_3^-$ were detected by ^1H NMR (DMSO-d_6) in a crude mixture (R = –(R^1)$CHCH_2OH$). See Refs. 24a,b for the assignment.
[d] P_{CO2} = 3 atm, adjusted using autoclave.
[e] P_{CO2} = 5 atm, adjusted using autoclave.

Carbamic acid (Scheme 1) can be formed from amino alcohol when exposed to 1 atm of CO_2 and was detected in DMSO-d_6 as a more favorable structure than the ammonium carbamate.[24] Carbamic acid has two hydroxyl groups (the alcohol OH and the acid OH). One acts as nucleophile and the other is liberated, as will be shown in Scheme 3. Generally, the alcohol OH acts as a nucleophile in the C–O bond formation.[25] Nonetheless, selectivity of the leaving OH can be altered by steric control.[26,27] Thus, control experiments

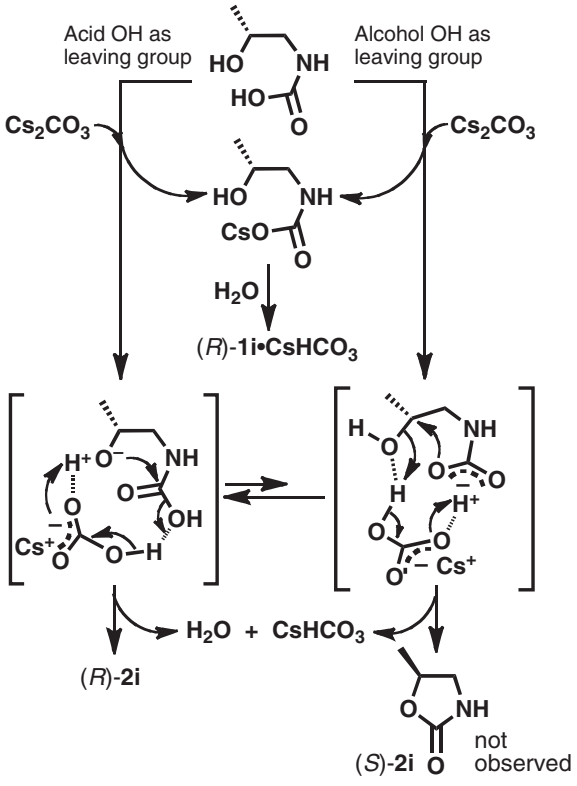


Scheme 2. Reaction with (*R*)-1-aminopropan-2-ol ((*R*)-**1i**).

were carried out to clarify which OH is liberated as water (Scheme 2).

In contrast to the absolute retention at the β-carbon of β-amino alcohols, the chirality at the α-position can provide useful information on which OH group (the alcohol OH or the acid OH) in the carbamic acid is liberated (Scheme 3). In this case, (*R*)-1-aminopropan-2-ol ((*R*)-**1i**) was used under similar reaction conditions (Scheme 2). The chiral GC analysis of the product showed complete retention of the parent chiral center bearing the methyl substituent, demonstrating the exclusive formation of (*R*)-**2i** (see Supplementary data). In addition, when $C^{18}O_2$ was used upon reaction with **1a**, one ^{18}O was incorporated predominantly into **2a**.[21a,28] These results suggest that the alcohol OH acts as a nucleophile and the acid OH is a leaving group. The HCO_3^- anion seems one of the most critical species involved in the reaction.[29]

In summary, oxazolidinones were synthesized from amino alcohols and CO_2 (1–5 atm) with the aid of catalytic alkali metal (bi)carbonates represented by Cs_2CO_3. Special dehydrating agents were not needed in this system. The reaction protocol reported herein is very simple, straightforward, and can be replicated in any laboratory. The preliminary mechanistic study revealed that the OH of amino alcohol acts as nucleophile and the OH at carbamic acid moiety is liberated during the cyclization process.[30]



Scheme 3. Possible pathways in the reaction of (*R*)-**1i**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.100.

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29. A carbamic acid ($RNHCO_2H$) derived from beta-amino alcohol **1** and CO_2 has an acid proton more susceptible to deprotonation by Cs_2CO_3 than that of the alcohol OH. However, the reaction system is weakly acidic rather than basic, since carbamic acid remains consistently in an excess quantity during the course of the reaction (at least from the beginning to the later stage), compared with the amount of Cs_2CO_3, $CsHCO_3$ (<10 mol %), or $RNHCO_2Cs$ (<10 mol %) that may not react as substrate. In fact, the yield of **2** has so far never exceeded 90% (Tables 1 and 2). In addition, when a similar oxazolidinone synthesis was carried out using a 2:1 molar ratio of **1a** and Cs_2CO_3 or **1a** and $CsHCO_3$ except that CO_2 was absence, only more acidic $CsHCO_3$ gave **2a** but in a low yield (15% based on **1a**; 30% based on $CsHCO_3$). The HCO_3^{2-}, rather than a more basic CO_3^{2-}, is capable of promoting the reaction. This suggests that a weak acid–weak base cooperative catalysis as shown in Scheme 3 would be responsible.
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