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A Novel Synthesis of 1,3-Oxazine-2,4-diones via a Simple and Efficient Reaction of CO_2 with 2,3-Allenamides

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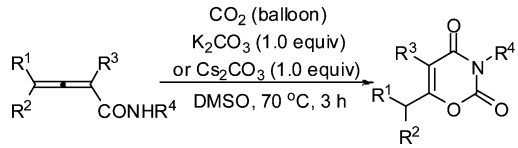
ABSTRACT



A simple and efficient reaction of CO_2 with 2,3-allenamides under mild conditions (CO_2 balloon without any metal catalyst in the presence of K_2CO_3 or Cs_2CO_3) leads to an efficient synthesis of 1,3-oxazine-2,4-diones. The high reactivity of the allene moiety is crucial for the success of this transformation since the corresponding reaction of α,β-unsaturated alkenamides or alkynamides does not occur.

Carbon dioxide is one of the most attractive carbon resources in organic synthesis as it is highly functionalized, abundant, economical, and nontoxic; thus, the chemical fixation of CO_2 for the synthesis of useful organic chemicals has attracted more and more attention of scientists from different areas.[1] However, due to the thermodynamic and kinetic stability of CO_2, reports on the reaction of CO_2 to afford useful organic products are still limited. Some reactions of nucleophilic reagents such as alcohols[2] and amines[3] with CO_2 require high pressure and/or high temperature to afford carbonates and ureas. Stoichiometric organometallic reagents such as RMgX,[4] RLi,[5] RBX_2 (with Rh or Cu catalyst),[6] and R_2Zn (with Ni catalyst)[7] have been used to generate corresponding

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carboxylic acids. Recently it was reported that the reaction of alkynes, alkenes, or allenes with CO_2 under the catalysis of metallic complexes[1,8−11] afforded esters or lactones. Thus, the efficient chemical fixation of CO_2 under mild conditions is still of high interest. On the other hand, 1,3-oxazine-2,4-diones are not only an important class of organic intermediates in organic synthesis[12] but also exhibit some biological activities, for which they are considered as antiulcer agents, anticonvulsant drugs, herbicides, and plant growth regulators (Figure 1).[13]

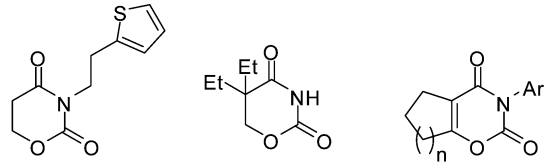
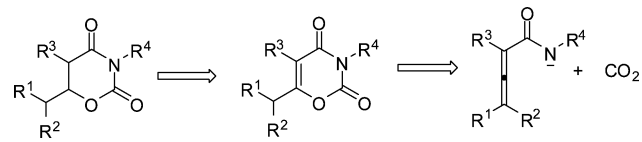


Figure 1. Some biologically active 1,3-oxazine-2,4-diones.

According to the structure of 1,3-oxazine-2,4-diones, we envisioned that 2,3-allenamides may be used to react with CO_2 to synthesize such products in just one step (Scheme 1).[14] However, although there are a few reports on the reaction of amides with carbon dioxide, electrochemical methods[15] or stoichiometric strong bases LDA or *n*-BuLi[16] have to be used. Herein, we report a simple and efficient reaction of CO_2 with 2,3-allenamides under mild conditions (1 atm of CO_2 without metal catalyst), which provides a novel and efficient synthesis of the potentially useful 1,3-oxazine-2,4-diones.

Scheme 1



Initially, we used *N*-benzyl 4-methyl-2,3-pentadienamide **1a** as the substrate to try the reaction. The CO_2 gas from a CO_2 balloon was dried by passing through a gas washing bottle containing concd H_2SO_4 and released through a relief needle to the reaction vessel with an outlet. After many attempts, we were happy to find that 6-isopropyl-1,3-oxazine-2,4-dione **2a** was formed in 73% NMR yield in the presence of 1.0 equiv of K_2CO_3 in DMSO at 70 °C for 3 h (entry 3, Table 1). Some other typical results under different conditions are summarized in Table 1. Among the most commonly used solvents, DMSO is the best (entries 1−3, Table 1). The carbonate used is also very important: From Li_2CO_3 to Na_2CO_3 to K_2CO_3, the reaction rate was accelerated (entries 3, 5, and 6, Table 1). However, the yield of **2a** cannot be improved further by using Cs_2CO_3 or increasing the dosage of K_2CO_3 (entries 4 and 8, Table 1). When K_2CO_3 was reduced to 0.5 equiv or the temperature lowered to 60 °C, the reaction was slower with recovery of **1a** within 3 h (entries 7 and 9, Table 1). Finally, it is fortunate to note that **2a** can also be formed in 75% NMR yield by using a CO_2 balloon with the relief needle in DMSO to direct CO_2 to the reaction mixture with 1.0 equiv of K_2CO_3 at 70 °C for 3 h, which was defined to be our standard reaction conditions for further study (entry 10, Table 1). Here an outlet is not necessary, avoiding the continuous release of CO_2 to air. Other bases such as $KHCO_3$, KOH, Et_3N, and $(i\text{-Pr})_2NH$ were also tested; however, no better result was afforded (entries 11−14, Table 1). It is noted that when the reaction was carried out in the presence of K_2CO_3 under N_2 atmosphere, no product was afforded with 90% recovery of the starting

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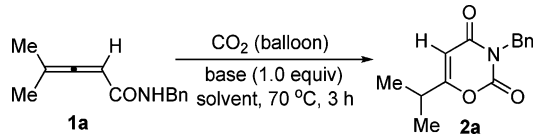
Table 1. Optimization of Reaction Conditions for the Reaction of *N*-Benzyl-4-methyl-2,3-pentadienamide **1a** with Carbon Dioxide[a]



entry	base	solvent	NMR yield of **2a** (%)	recovery of **1a** (%)
1	K_2CO_3	DMF	4	90
2	K_2CO_3	DMA	17	77
3	**K_2CO_3**	**DMSO**	73	0
4	Cs_2CO_3	DMSO	69	0
5	Na_2CO_3	DMSO	32	56
6	Li_2CO_3	DMSO	13	83
7[b]	K_2CO_3	DMSO	72	6
8[c]	K_2CO_3	DMSO	70	0
9[d]	K_2CO_3	DMSO	55	34
10[e]	**K_2CO_3**	**DMSO**	75	0
11[e]	$KHCO_3$	DMSO	25	21
12[e]	KOH	DMSO	16	20
13[e]	Et_3N	DMSO	5	50
14[e]	$(i\text{-Pr})_2NH$	DMSO	3	70
15[e,f]	K_2CO_3	DMSO	0	90

[a] The reaction was carried out using 0.2 mmol of **1a**, and the yields were determined by ^1H NMR analysis with mesitylene as the internal standard. [b] K_2CO_3 (0.5 equiv) was used. [c] K_2CO_3 (2.0 equiv) was used. [d] The reaction was conducted at 60 °C. [e] The reaction was conducted in a closed vessel without an outlet. [f] The reaction was carried out under N_2 atmosphere.

material **1a**, which indicated that the CO_2 unit in the product **2a** was from the CO_2 gas, not the carbonate base (entry 15, Table 1). The structure of **2a** was further confirmed by the X-ray diffraction study (Figure 2).[17]

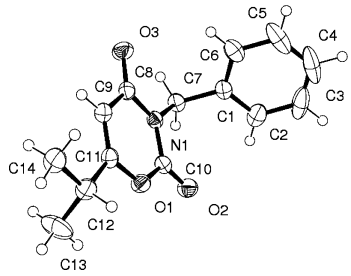
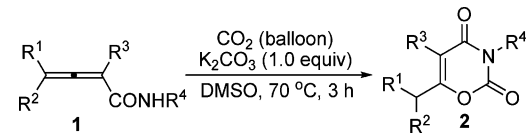


Figure 2. ORTEP representation of **2a**.

Some typical results of different 2,3-allenamides under the optimized conditions are listed in Table 2. The substituent

(17) Crystal data for compound **2a**: $C_{112}H_{120}N_8O_{24}$, MW = 1962.16, monoclinic, space group *P*2(1)/*c*, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0355, wR2 = 0.0876; *R* indices (all data), R1 = 0.0389, wR2 = 0.0903; a = 6.2715(2) Å, b = 11.4983(4) Å, c = 34.2480(11) Å, α = 90°, β = 90.7310(10)°, γ = 90°, V = 2469.48(14) Å^3, T = 173(2) K, Z = 1, reflections collected/unique 27845/4366 (R_{int} = 0.0195), number of observations [$I > 2\sigma(I)$] 4005, parameters: 329. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 722623.

Table 2. Reaction of Different 2,3-Allenamides with Carbon Dioxide[a]



	1				isolated yield
entry	R^1	R^2	R^3	R^4	of **2** (%)
1	Me	Me	H	Bn (**1a**)	75 (**2a**)
2[b]	Me	Me	H	Bn (**1a**)	70 (**2a**)
3[c]	Me	Me	H	Bn (**1a**)	64 (**2a**)
4	Et	Me	H	Bn (**1b**)	80 (**2b**)
5	*i*-Bu	Me	H	Bn (**1c**)	64 (**2c**)
6	Ph	Me	H	Bn (**1d**)	49 (**2d**)
7	Me	Me	H	allyl (**1e**)	47 (**2e**)
8	Me	Me	H	propargyl (**1f**)	58 (**2f**)
9	Me	Me	H	*n*-Bu (**1g**)	48 (**2g**)
10	Me	Me	H	Ph (**1h**)	0[d]
11	Me	Me	H	H (**1i**)	33 (**2i**)
12[e]	Me	Me	H	H (**1i**)	55 (**2i**)
13	$n\text{-}C_5H_{11}$	H	H	Bn (**1j**)	59 (**2j**)
14	Me	H	Et	Bn (**1k**)	76 (**2k**)
15	Me	H	$n\text{-}C_7H_{15}$	Bn (**1l**)	70 (**2l**)
16	Me	Me	Me	Bn (**1m**)	92 (**2m**)
17[f]	Me	Me	Et	Bn (**1n**)	94 (**2n**)
18[f]	$-(CH_2)_5-$		Me	Bn (**1o**)	78 (**2o**)

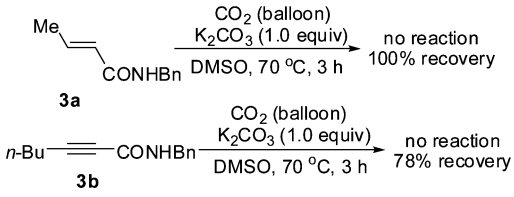
[a] The reaction was carried out using 0.2−0.4 mmol of **1** and 1.0 equiv of K_2CO_3 in DMSO with a CO_2 balloon at 70 °C for 3 h unless otherwise stated. [b] The reaction was conducted in the presence of 10 mol % of K_2CO_3 with a reaction time of 12 h. [c] The reaction was conducted using 5.0 mmol of **1a** and a glass pipe instead of the relief needle. [d] Compound **1h** was recovered in 74% yield. [e] The reaction was conducted at 60 °C. [f] Cs_2CO_3 (1.0 equiv) was used.

R^1 or R^2 can be an alkyl and phenyl group. Allenamides with bulkier substituents such as isobutyl and phenyl groups gave the corresponding products **2c** and **2d** in relatively lower yields (entries 5 and 6, Table 2). The substituent R^4 on the nitrogen atom of 2,3-allenamides may be allyl, propargyl, alkyl, or hydrogen (entries 7−9 and 11−12, Table 2). However, when *N*-phenyl-substituted 2,3-allenamide **1h** was applied, no reaction occurred with 74% recovery of the starting material (entry 10, Table 2). The reaction of **1i** should be conducted at 60 °C since the reaction at 70 °C afforded **2i** in only 33% yield (entries 11 and 12, Table 2). 4-Monosubstituted and 2,4-disubstitued 2,3-allenamides can form the corresponding products in moderate to good yields (entries 13−15, Table 2). 2,4,4-Trisubstituted 2,3-allenamides **1m**, **1n**, and **1o** gave **2m**, **2n**, and **2o** in good to excellent yields. It is noted that 1.0 equiv of Cs_2CO_3 was required in the reaction of 2,3-allenamides **1n** and **1o** since the starting materials were not consumed completely under the standard reaction conditions (entries 17 and 18, Table 2). When we conducted the reaction with a catalytic amount of K_2CO_3 (10 mol %), the product **2a** could also be formed in 70% yield with a much longer reaction time (12 h) (entry 2, Table 2). Using a glass pipe instead of the relief needle, the reaction can also be conducted using 5.0 mmol (1.0 g) of **1a** to form **2a** in 64% yield (entry 3, Table 2).

It should be noted that the reaction of *N*-benzyl but-2(*E*)-enamide **3a** and *N*-benzyl hept-2-ynamide **3b** under the same

reaction conditions did not occur with 100% and 78% recovery of the starting materials, respectively, which shows the importance of the high reactivity of the allene moiety for this transformation (Scheme 2).

Scheme 2



Based on these facts, a rationale for this reaction is depicted in Scheme 3. The 2,3-allenamide **1** would lose a proton under the basic conditions to form intermediate **M1**, which to some extent may attack the carbon atom in carbon dioxide to form the intermediate **M2**. Subsequently, the oxygen anion in the intermediate **M2** would attack the central carbon atom in the allene moiety to drive the equilibrium between **1**, **M1**, and **M2** to generate the delocalized allylic intermediate **M3**,[18] which undergoes protonolysis to form product **2** with the C=C bond in the six-membered ring.

In conclusion, we have developed a very mild protocol for chemical transformation of carbon dioxide by conducting its reaction with the readily available 2,3-allenamides[19] in

(18) For a review on the nucleophilic hydrohalogenation of electron-deficient allenes, see: Ma, S.; Li, L. *Synlett* **2001**, 1206.

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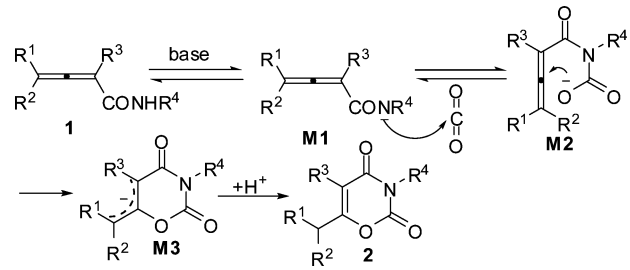
Scheme 3



DMSO at 70 °C for 3 h using a CO_2 balloon in the presence of K_2CO_3 or Cs_2CO_3, which leads to an efficient synthesis of 1,3-oxazine-2,4-diones. As a result of usefulness of the products[12,13] and the efficient reaction of carbon dioxide, the reaction may have potentials in organic and medicinal chemistry. Further studies in this area are being pursued in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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