

A Novel Synthesis of 1,3-Oxazine-2,4-diones via a Simple and Efficient Reaction of CO₂ with 2,3-Allenamides

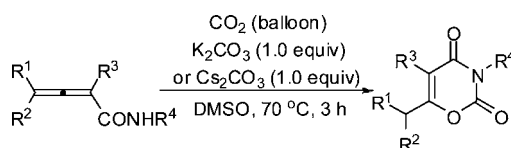
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ABSTRACT



A simple and efficient reaction of CO₂ with 2,3-allenamides under mild conditions (CO₂ balloon without any metal catalyst in the presence of K₂CO₃ or Cs₂CO₃) 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 alkenamides 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 CO₂ 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 CO₂, reports on the reaction of CO₂ to afford useful organic products are still limited. Some reactions of nucleophilic reagents such as alcohols² and amines³ with CO₂ require high pressure and/or high temperature to afford carbonates

and ureas. Stoichiometric organometallic reagents such as RMgX,⁴ RLi,⁵ RBX₂ (with Rh or Cu catalyst),⁶ and R₂Zn (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 CO₂ under the catalysis of metallic complexes^{1,8–11} afforded esters or lactones. Thus, the efficient chemical fixation of CO₂ 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 synthesis¹² but also exhibit some biological activities, for which they are considered as antiulcer agents, anticonvulsant drugs, herbicides, and plant growth regulators (Figure 1).¹³

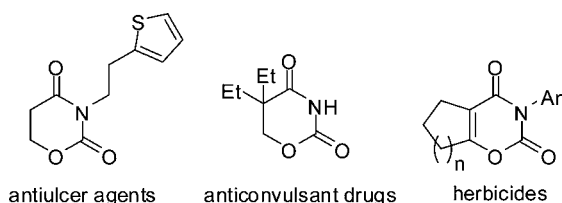


Figure 1. Some biologically active 1,3-oxazine-2,4-diones.

According to the structure of 1,3-oxazine-2,4-diones, we envisioned that 2,3-allenamides may be used to react with

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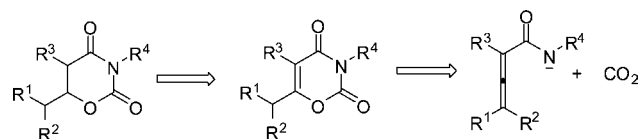
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CO₂ to synthesize such products in just one step (Scheme 1).¹⁴ However, although there are a few reports on the

Scheme 1



reaction of amides with carbon dioxide, electrochemical methods¹⁵ or stoichiometric strong bases LDA or *n*-BuLi¹⁶ have to be used. Herein, we report a simple and efficient reaction of CO₂ with 2,3-allenamides under mild conditions (1 atm of CO₂ without metal catalyst), which provides a novel and efficient synthesis of the potentially useful 1,3-oxazine-2,4-diones.

Initially, we used *N*-benzyl 4-methyl-2,3-pentadienamide **1a** as the substrate to try the reaction. The CO₂ gas from a CO₂ balloon was dried by passing through a gas washing bottle containing concd H₂SO₄ 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 K₂CO₃ 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 Li₂CO₃ to Na₂CO₃ to K₂CO₃, the reaction rate was accelerated (entries 3, 5, and 6, Table 1). However, the yield of **2a** cannot be improved further by using Cs₂CO₃ or increasing the dosage of K₂CO₃ (entries 4 and 8, Table 1). When K₂CO₃ 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 CO₂ balloon with the relief needle in DMSO to direct CO₂ to the reaction mixture with 1.0 equiv of K₂CO₃ 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 CO₂ to air. Other bases such as KHCO₃, KOH, Et₃N, and (*i*-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 K₂CO₃ under N₂ 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 ₂ CO ₃	DMF	4	90
2	K ₂ CO ₃	DMA	17	77
3	K ₂ CO ₃	DMSO	73	0
4	Cs ₂ CO ₃	DMSO	69	0
5	Na ₂ CO ₃	DMSO	32	56
6	Li ₂ CO ₃	DMSO	13	83
7 ^b	K ₂ CO ₃	DMSO	72	6
8 ^c	K ₂ CO ₃	DMSO	70	0
9 ^d	K ₂ CO ₃	DMSO	55	34
10 ^e	K ₂ CO ₃	DMSO	75	0
11 ^e	KHCO ₃	DMSO	25	21
12 ^e	KOH	DMSO	16	20
13 ^e	Et ₃ N	DMSO	5	50
14 ^e	(<i>i</i> -Pr) ₂ NH	DMSO	3	70
15 ^{e,f}	K ₂ CO 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 K₂CO₃ (0.5 equiv) was used. ^c K₂CO₃ (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 N₂ atmosphere.

material **1a**, which indicated that the CO₂ unit in the product **2a** was from the CO₂ 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

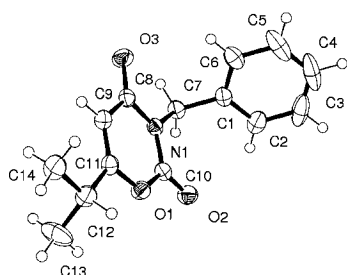


Figure 2. ORTEP representation of **2a**.

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**: C₁₁H₁₂N₂O₂, MW = 196.16, monoclinic, space group P2(1)/c, final *R* indices [*I* > 2σ(*I*)], *R*₁ = 0.0355, *wR*₂ = 0.0876; *R* indices (all data), *R*₁ = 0.0389, *wR*₂ = 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) Å³, *T* = 173(2) K, *Z* = 1, reflections collected/unique 27845/4366 (*R*_{int} = 0.0195), number of observations [*I* > 2σ(*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

entry	R ¹	R ²	R ³	R ⁴	isolated yield 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>i</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	<i>n</i> -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	<i>n</i> -C ₈ H ₁₇	H	H	Bn (1j)	59 (2j)
14	Me	H	Et	Bn (1k)	76 (2k)
15	Me	H	<i>n</i> -C ₇ H 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	Me	Bn (1o)	78 (2o)

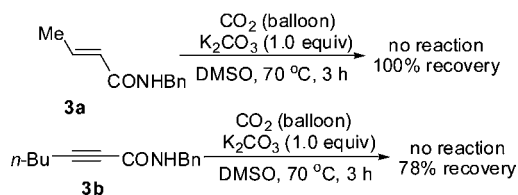
^a The reaction was carried out using 0.2–0.4 mmol of **1** and 1.0 equiv of K₂CO₃ in DMSO with a CO₂ balloon at 70 °C for 3 h unless otherwise stated. ^b The reaction was conducted in the presence of 10 mol % of K₂CO₃ with a reaction time of 12 h. ^c The reaction was conducted using 5.0 mmol of **1a** 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 Cs₂CO₃ (1.0 equiv) was used.

R¹ or R² 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 R⁴ 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-Mono-substituted and 2,4-disubstituted 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 Cs₂CO₃ 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 K₂CO₃ (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).

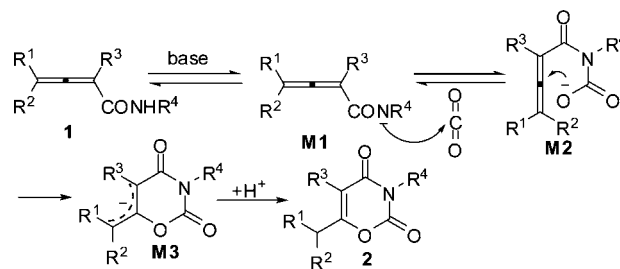
Scheme 2



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-allenamides¹⁹ in

Scheme 3



DMSO at 70 °C for 3 h using a CO₂ balloon in the presence of K₂CO₃ or Cs₂CO₃, 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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