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Carbon dioxide-mediated synthesis of 3(2*H*)-furanones from diyne alcohols

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ABSTRACT

A novel type of carbon dioxide-mediated reaction of diyne alcohols without any metal catalysts was reported. Carbon dioxide held the key to the success of this reaction, in which 3(2*H*)-furanones were selectively obtained in moderate to high yields.

Recently, it has been reported that the coupling reaction of propargyl alcohols with CO_2 could afford cyclic carbonates using various metal salts and organic compounds as the catalysts.[1] In addition, carbon dioxide could also promote the rearrangement of propargyl alcohols to afford α,β-unsaturated ketones.[2] Our investigations indicated that cuprous(I) well promoted the reaction of propargyl alcohols with CO_2 to form cyclic carbonates.[3] We further studied on the reaction of diyne alcohols with CO_2. To our surprise, the obtained product is 3(2*H*)-furanones instead of the desired cyclic carbonates. The interesting result inspires us to investigate the synthesis of 3(2*H*)-furanones from diyne alcohols.

The 3(2*H*)-furanones widely occur as key structural units in a variety of natural products (e.g., geiparvarin,[4] eremantholide A,[5] jatrophone,[4a,6] bullatenon,[7] and pseurotin A[8]), and many of the 3(2*H*)-furanones have shown pharmaceutical activities such as antitumor activity,[4a,7c,9] antiproliferative activity,[9a] inhibitory activity on COX-2,[10] inhibitory activity on MAO,[11] and several other pharmaceutical activities.[7b,12] Conventional approaches for the synthesis of these serviceable compounds mainly rest on base-catalyzed cyclization of γ-hydroxyalkynones[7a] and acid-catalyzed cyclocondensation of 1-hydroxy 1,3-diketones.[4a,13] There were also many alternative methods such as the hydrogenations and subsequent acidic hydrolysis of isoxazoles,[7b,9a,14] base-catalyzed cyclizations of 1-halo-2,4-diketones[15] or β-keto esters,[16] Lewis acid-catalyzed aldol reaction of 3-silyloxyfurans,[17] and the transition metal-catalyzed preparations of 3(2*H*)-furanones.[18] In this communication, we reported the first example of the preparation of 3(2*H*)-furanones from diyne alcohols under the promotion of CO_2 without any metal catalysts.

The reaction of the model substrate 2-methyl-6-phenylhexa-3,5-diyn-2-ol (**1a**) with CO_2 was first investigated. With CuI as the catalyst and MeCN/Et_3N (volume ratio 10:1) as the mix-solvent, 5-benzyl-2,2-dimethylfuran-3(2*H*)-one (**2a**) was obtained in 25% yield (Table 1, entry 1). However, **2a** was not obtained at all in the absence of carbon dioxide (entry 2). This means that CO_2 plays a key role in the formation of **2a**. The yield of **2a** increased when water was added into the reaction system (entry 3). In the absence of water, **2a** was almost not formed (entry 5), which indicated that the water was indispensable for this reaction. **1a** could be also converted into **2a** in a good yield without CuI, implying that it is a metal-free catalytic reaction (entry 4). In addition, the reaction did not proceed without Et_3N even in the presence of CO_2 and water or acetonitrile as the solvent (entries 6–7). In the present case, base Et_3N practically acts as the catalyst. With individual Et_3N as the solvent, **2a** was obtained only in a very low yield (entry 8), so extra solvent (such as MeCN) was also crucial for the reaction. Among the various mix-solvents examined (entries 9–14), MeCN/Et_3N (volume ratio 10:1) appears to be more favorable for the reaction. The effect of these solvents on the reaction may be related to their polarity. Also, the yield of **2a** varied obviously with the reaction temperature, and 90 °C seemed to be appropriate for the present reaction (entries 15–17).

Under the optimum reaction conditions (Table 1, entry 16), the scope and the utility of this method were examined in detail, as shown in Scheme 1. The reaction could tolerate various substrates with aryl and alkyl R^1 groups (**2a–2j**). It is worthy to note that the electron-deficient groups on the R^1 aromatic ring could give higher yields (**2f–2i**), while the electron-rich group was unfavorable for

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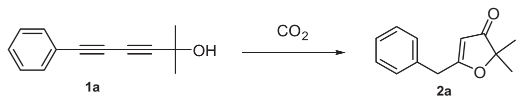
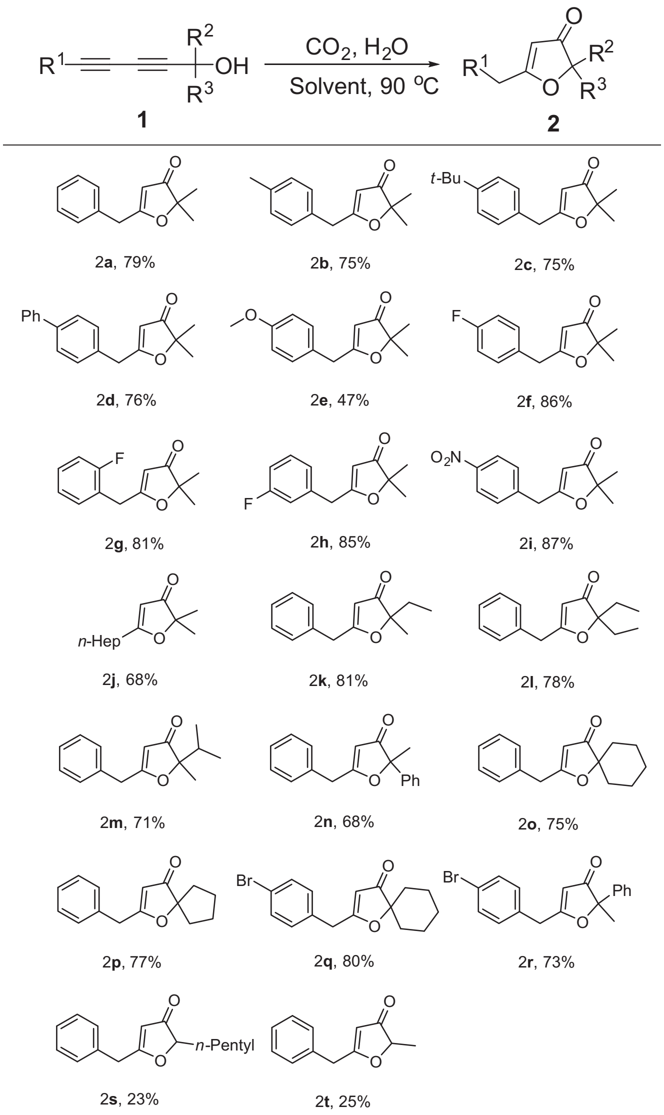
Table 1
Optimization of reaction conditions[a]



Entry	Solvent	Cat	H_2O (equiv)	Temp (°C)	CO_2 (MPa)	Yield (%)[b]
1	MeCN/Et_3N (10:1)	CuI	—	80	2	25
2	MeCN/Et_3N (10:1)	CuI	—	80	0	n.p
3	MeCN/Et_3N (10:1)	CuI	10	80	2	66
4[c]	MeCN/Et_3N (10:1)	CuI	—	80	2	Trace
5	MeCN/Et_3N (10:1)	—	10	80	2	71
6	H_2O	—	—	80	2	n.p
7	MeCN	—	10	80	2	n.p
8	Et_3N	—	10	80	2	11
9	DMF/Et_3N (10:1)	—	10	80	2	55
10	DMSO/Et_3N (10:1)	—	10	80	2	45
11	THF/Et_3N (10:1)	—	10	80	2	Trace
12	$MeNO_2$/Et_3N (10:1)	—	10	80	2	23
13	toluene/Et_3N (10:1)	—	10	80	2	Trace
14	dioxane/Et_3N (10:1)	—	10	80	2	Trace
15	MeCN/Et_3N (10:1)	—	10	100	2	82
16[d]	**MeCN/Et_3N (10:1)**	—	**10**	**90**	**2**	**83(79)**
17	MeCN/Et_3N (10:1)	—	10	rt	2	33

[a] Reaction conditions: substrates (0.25 mmol), MeCN/Et_3N (10:1) as the solvent (2 mL), 36 h.
[b] Determined by GC–MS. Number in parentheses is isolated yield.
[c] Distilled solvent.
[d] 83% of **1a** was converted.



Scheme 1. Carbon dioxide-mediated synthesis of 3(2*H*)-furanones. Reaction conditions: substrates (0.25 mmol), MeCN/Et_3N (10:1) as the solvent (2 mL), CO_2 (2 MPa), H_2O (10 equiv), 90 °C, 36 h. Isolated yield, unconverted substrates were recovered.

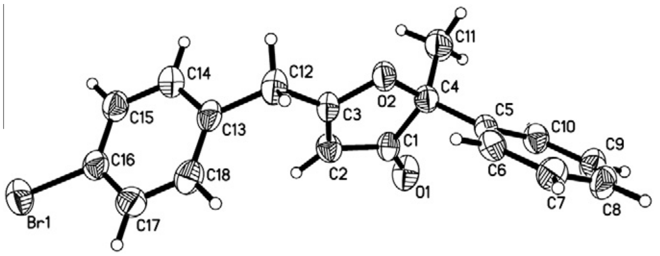


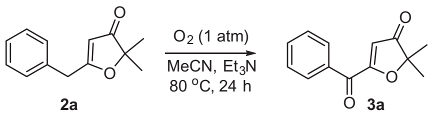
Figure 1. X-ray structure of **2r**.

the reaction (**2e**). In addition, the tertiary diyne alcohols with alkyl and aryl R^2 or R^3 groups, even with five- or six-membered ring substituents, could be smoothly converted into the corresponding product in good yields (**2k–2r**), whereas the reactions with secondary diyne alcohols gave fairly low yields (**2s**,**2t**). Obviously, the yield of the target product is influenced by the structure and property of diyne alcohols. The molecular structure of representative product **2r** is further confirmed by an X-ray diffraction study (Fig. 1).

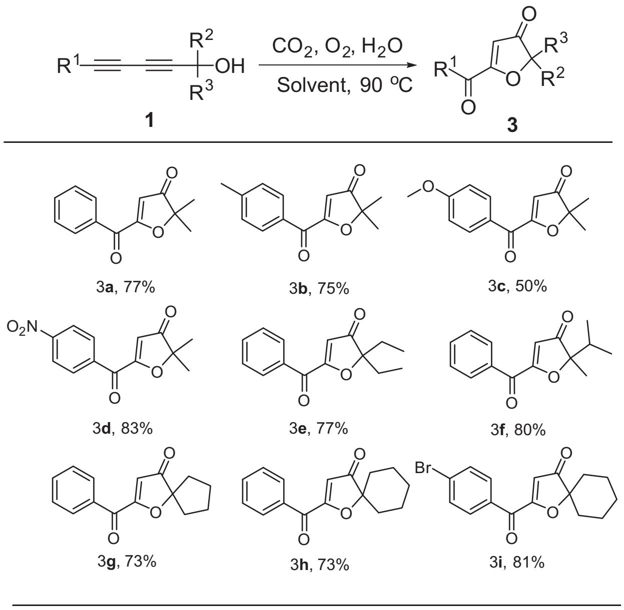
Benzylic oxidation is a fundamental transformation in organic chemistry because the product ketones can serve as valuable building blocks for the manufacture of speciality chemicals in pharmaceuticals and agrochemicals. Our studies showed that **2a** could be oxidized into 5-benzoyl-2,2-dimethylfuran-3(2*H*)-one (**3a**) in 98% yield with Et_3N as catalyst and O_2 as the sole oxidant (Scheme 2). Inspired by this result, we further investigated the one–pot synthesis of **3a** from **1a** in the presence of CO_2 and O_2.

As expected, **3a** could be obtained in a good yield at 90 °C in the mix-solvent MeCN/Et_3N for 48 h, under CO_2 (2 MPa) and O_2 (0.6 MPa).[19] The scope of the reaction with various diyne alcohols was further examined, as summarized in Scheme 3. The alkyl group on the benzene ring has a slight impact on the reaction. The electron-withdrawing group increased the reaction yield (**3d**), while the electron-donating group decreased the reaction yield **(3b,3c)**.The symmetric and asymmetric propargyl alcohols or the propargyl alcohols with a five-or six-membered ring could be smoothly converted into the corresponding products in high yields (**3e–3h**). The reaction was also feasible for the substrate with bromine substituted benzene ring (**3i**).

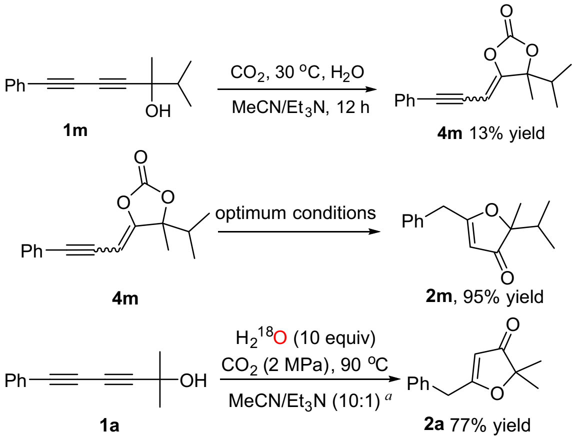
To understand the reaction mechanism, some control experiments were done (Scheme 4). With **1m** as a substrate, **4m** was obtained in 13% yield at 30 °C for 12 h under 2 MPa of CO_2. It was found that **4m** could be also converted into **2m** under the optimum



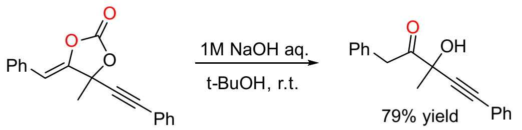
Scheme 2. Oxidation of 5-benzyl-2,2-dimethyl-3(2*H*) furanone (**2a**) into 5-benzoyl-2,2-dimethyl-3(2*H*)-furanone (**3a**). Reaction conditions: **2a** (0.25 mmol), MeCN (2 mL), Et$_3$N (1 equiv), O$_2$ (1 atm), 80 °C.



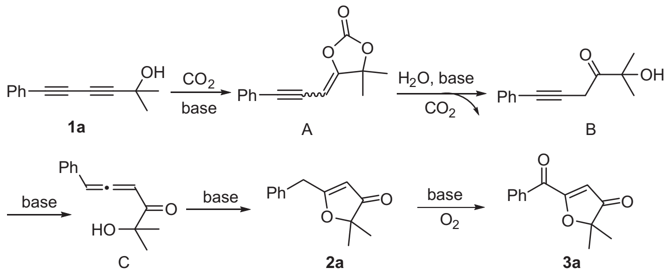
Scheme 3. One-pot synthesis of 5-benzoyl-3(2*H*)-furanones. Reaction conditions: (0.25 mmol), MeCN/Et$_3$N (10:1) as the solvent (2 mL), CO$_2$ (2 MPa), O$_2$ (0.6 MPa), H$_2$O (10 equiv), 90 °C, 48 h. Isolated yield, unconverted substrates were recovered.



Scheme 4. Control experiments. Reaction conditions: **1m** (0.25 mmol), **4m** (0.05 mmol), **1a** (0.25 mmol), MeCN/Et$_3$N (10:1) as the solvent (2 mL), CO$_2$ (2 MPa), H$_2$O (10 equiv), ^{a} distilled solvent.



Scheme 5. Yamada's work.



Scheme 6. A possible reaction mechanism.

conditions. These results indirectly indicated that the formation of **2a** might undergo the intermediates of cyclic carbonates. To further understand the role of water in this reaction, $H_2{}^{18}O$ as the isotope label was used to trace the reaction. It was observed that the product **2a** did not contain ^{18}O (Scheme 4). According to the experimental results and Yamada's work[1a] (Scheme 5), we deduce that the oxygen atom of the carbonyl group in **2a** results from carbon dioxide, and the other oxygen atom originates from diyne alcohol rather than water. Based on the above-mentioned experimental results and the literatures,[1a,20,21] a possible mechanism is proposed in Scheme 6. Carbon dioxide first reacts with **1a** to form A under the catalysis of base (Et$_3$N). The cyclic carbonate could get hydrolyzed in the presence of base and water giving rise to an alpha-hydroxy ketone (B),[1a] followed by the isomerization process of alpha-substituted alkyne to the allenylketone (C).[20] Finally, C is converted into **2a** through base-catalyzed endo-mode cyclization,[21] and **2a** could be oxidized to **3a** in the presence of a base and an oxidant. In fact, the exact mechanism of the reaction is still unclear and details are needed to study further.

In conclusion, in the mix-solvent MeCN/Et$_3$N various diyne alcohols are efficiently promoted by CO$_2$ to afford substituted 3(2*H*)-furanones without any metal catalysts in moderate to high yields. The present work provides an efficient and valuable route for the synthesis of 3(2*H*)-furanones derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.130.

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