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Silver-catalyzed C–C bond formation with carbon dioxide: significant synthesis of dihydroisobenzofurans†

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The silver salt catalyzed the C–C bond forming reaction of *o*-alkynylacetophenone derivatives and carbon dioxide. In this reaction, a carbonyl group and a furan skeleton were successively constructed to afford the corresponding dihydroisobenzofuran derivatives.

Carbon dioxide has drawn much attention as a C1 resource due to its abundant supply from industries, low toxic properties and easy handling.[1] The Kolbe–Schmitt reaction, found in any organic chemistry textbook, has been employed for the commercial production of salicylic acid. On the other hand, the transition-metal-catalyzed carboxylation reactions of various carbon nucleophiles have been actively researched for the preparation of fine chemicals.[2] The synthesis of value-added chemicals, for example medicinal supplies, agrichemicals and functional materials, requires toxic C1 sources such as carbon monoxide and phosgene. In this paper, it was noted that instead of using these toxic reagents, safe and inexpensive carbon dioxide could be effectively employed to produce dihydroisobenzofuran derivatives which would be useful frameworks for synthesizing natural products and medicines.

Dihydroisobenzofuran(phthalan) is a class of characteristic structures used as a building block for natural product synthesis or a key mother nucleus of significant bioactive compounds (Fig. 1).[3] For example, Pestacin displays antioxidant activity and moderate antifungal properties.[3a] Escitalopram is known as an antidepressant of the selective serotonin reuptake inhibitor class.[3b] Compound **1** having a benzylidene structure shows a potential tyrosine-kinase inhibitory effect.[3c] Among the various synthetic reactions for the phthalan derivatives, the transition-metal-catalyzed cyclization reactions of *o*-alkynylbenzylalcohol[4] or *o*-alkynylbenzaldehyde[5] are particularly useful with respect to atom economy. In many cases, however, phthalan and isochromene were obtained through the 5-*exo*-dig and 6-*endo*-dig cyclizations, respectively. Though the selective synthesis of phthalan derivatives by the transition-metal-catalyzed cyclization has been achieved,[4a,e,f,h,5g] substituents of phthalans were limited and in some cases high temperature was required.

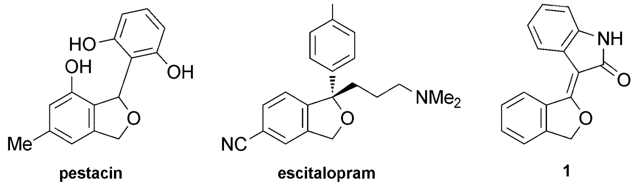

Fig. 1 Bioactive compounds bearing dihydroisobenzofuran structure.

Enolate has been a promising reagent for the C–C bond forming reactions. The reactions of carbon dioxide with an enolate to produce the corresponding β-ketocarboxylic acid have been examined.[6] Due to its thermodynamic instability, however, the product would easily return back to the starting material. Therefore, careful treatment or subsequent reduction of the product was required. A tandem reaction for the conversion of β-ketocarboxylic acid into a stable compound is one of the most reasonable methods for the reaction of an enolate and carbon dioxide.

Recently, we reported that the combination of a silver salt and base effectively promoted the incorporation of carbon dioxide into propargylic alcohols, propargylic amines and *o*-alkynylanilines.[7] In these reactions, the geometry of the *exo*-olefin in every product was confirmed as the *Z* isomer by X-ray analysis or an NOE experiment. These results and DFT calculations supported the fact that the alkyne activation by a silver catalyst should be essential.[7e] The silver-catalyzed C–C bond forming reaction of alkyne-containing ketones and carbon dioxide was also successfully developed to provide the corresponding 5-membered ring lactone derivatives.[8] Interestingly, during the reaction optimization of the alkyne-containing aliphatic ketones, not only the corresponding lactone derivatives, but also furan derivatives containing a carboxyl group were detected. Based on the structure of the furan, it was assumed that the ketone carbonyl of the β-ketocarboxylic acid was trapped on the C–C triple bond activated by the silver catalyst unlike in our previous studies.[9]

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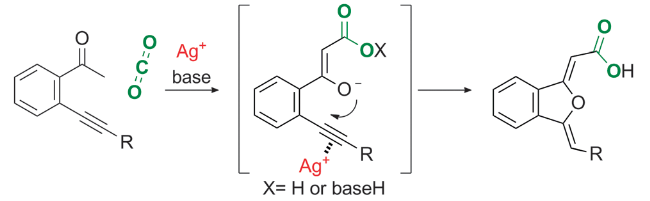
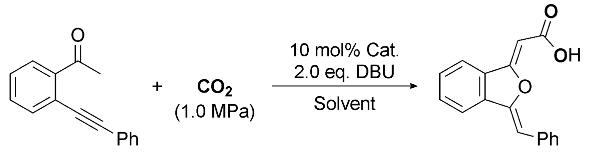


Scheme 1 Silver-catalyzed cyclization affords dihydroisobenzofuran derivatives.

This result inspired us to examine the C–C bond forming reaction with carbon dioxide to successively construct a carboxyl group and a furan skeleton. It was postulated that dihydroisobenzofuran derivatives bearing a carboxyl group could be obtained by the 5-*exo*-dig regioselective cyclization of *o*-alkynylacetophenone and carbon dioxide using the silver-catalytic system (Scheme 1). In the literature, these compounds were synthesized by the coupling–cyclization of 3-(2-iodophenyl)-3-oxopropanoic acid derivatives and terminal alkynes[10] or the functionalization of 1-alkylidene-1,3-dihydroisobenzofurans,[11] but the yields were unsatisfactory or the scope of the substrates was limited. We now report the silver-catalyzed C–C bond formation using carbon dioxide to afford dihydroisobenzofuran derivatives *via* the 5-*exo*-dig cyclization.

In an initial study, compound **2a** was employed as a model substrate and various metal salts were examined in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_3CN under a 1.0 MPa CO_2 atmosphere (Table 1). In the absence of a metal salt, a trace amount of the desired product **3a** was observed in the ^{1}H NMR spectrum (Table 1, entry 1). Although Au^I, Cu^I, and Pd^{II} were expected to activate the C–C triple bond to catalyze the cyclization reaction of *o*-alkynylbenzyl alcohol or *o*-alkynylbenzaldehyde, these metals did not effectively work in the present reaction (Table 1, entries 2–4). On the other hand, when a catalytic amount of a Ag^I salt was employed, the reaction smoothly proceeded to afford dihydroisobenzofuran **3a** in an excellent yield (Table 1, entry 5). When $AgNO_3$, AgBr and AgOAc were used, in every case, the dihydroisobenzofuran **3a** was exclusively produced *via* the 5-*exo*-dig cyclization (Table 1, entries 5–7). Under a 1 atm (balloon) CO_2 atmosphere, this reaction also proceeded but a longer reaction time was required (Table 1, entry 8). In DMF and DMSO, **3a** was obtained in 94% and 91% yields, respectively (Table 1, entries 9 and 10). Other bases were also examined, but DBU was found to be the most suitable base in this reaction.[9] Unfortunately, the purification of **3a** was not successful using the standard methods, such as back extraction and silica gel column chromatography, though **3a** could be isolated by recrystallization in 66% yield (Table 1, entry 7). In order to obtain the corresponding ester of **3a**, esterification was attempted. It was found that **3a** could be esterified with methyl iodide in a one-pot synthesis to give the corresponding methyl ester **4a** in 92% yield (Table 2).

Table 1 Investigation of several metal salts and solvents



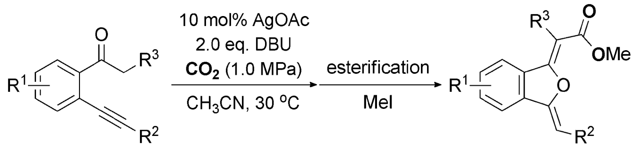
2a **3a**

Entry[a]	Catalyst	Solvent	Yield[b]/%
1	None	CH_3CN	<1
2	$(PPh_3)AuCl$	CH_3CN	0
3[c]	CuBr	CH_3CN	7
4	$Pd(OAc)_2$	CH_3CN	3
5	AgBr	CH_3CN	89
6	$AgNO_3$	CH_3CN	91
7	AgOAc	CH_3CN	99 (66)[d]
8[e]	AgOAc	CH_3CN	98
9	AgOAc	DMF	94
10	AgOAc	DMSO	91

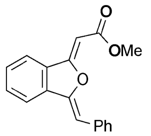
[a] The reaction was carried out with 0.15 mmol of the substrate, 30 °C, 1 h. [b] Yields were determined by ^{1}H NMR using trimethylphenylsilane as the internal standard. [c] 21 h. [d] Isolated yield. Purified by recrystallization. [e] Under a 1 atm (balloon) CO_2 atmosphere, 24 h.

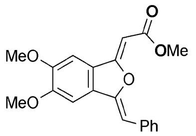
The substrate scope of the silver-catalyzed cyclization under the optimized reaction conditions was investigated (Table 2). Substituents on the phenyl ring in the R^1 group were evaluated. The reactions of substrates having 4,5-OMe (**2b**), 4-F (**2c**), or 5-Cl (**2d**) were efficiently catalyzed to give the corresponding products **4b–4d** in high yields. As for **2e** bearing 2-naphthylketone, the product **4e** was obtained in 69% yield. The reactions were

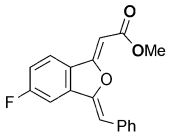
Table 2 Silver-catalyzed cyclization of various *o*-alkynylacetophenones[a]

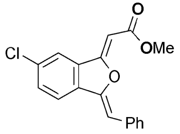


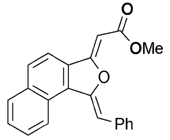
2 **4**

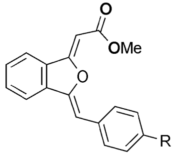

4a, 92% (3 h)

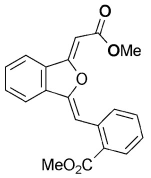

4b, 91% (6 h)

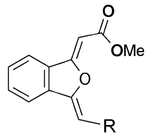

4c, 90% (6 h)

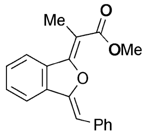

4d, 95% (6 h)

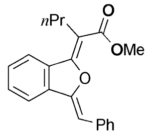

4e, 69% (24 h)

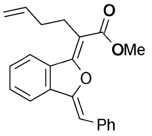

4f, R = Me, 87% (1 h)
4g, R = CF_3, 87% (1 h)
4h, R = COMe, 89% (6 h)
4i, R = CHO, 70% (6 h)


4j, 91% (4 h)


4k, R = *n*Bu, 95% (8 h), *Z*:*E* = 95:5[b]
4l, R = CH_2CH_2Ph, 97% (6 h), *Z*:*E* = 93:7[b]
4m, R = CH_2OMe, 94% (6 h), *Z*:*E* = 93:7[b]
4n, R = H, 62% (3 h), *Z*:*E* = 88:12[b]


4o, 51% (24 h)
71% (24 h, in DMF)
73% (24 h, in DMSO)


4p, 55% (24 h, in DMSO)


4q, 47% (24 h, in DMSO)

[a] Isolated yield. [b] The ratio of *Z* and *E* isomers about the C–C double bond adjacent to the carbonyl group. Determined by ^{1}H NMR.

suitable when the phenyl ring in the R^2 group was substituted with *p*-Me (**2f**), *p*-CF_3 (**2g**), *p*-COMe (**2h**), *p*-CHO (**2i**), and *o*-CO_2Me (**2j**) regardless of the electron-withdrawing or electron-donating groups. The alkyl-substituted alkynes were also good substrates, and the corresponding products **4k**, **4l**, and **4m** were obtained in 95%, 97%, and 94% yields, respectively. The reaction of the substrate **2n** bearing the terminal alkyne gave the corresponding product **4n** in 62% yield. The silver-catalyzed system was applied to α-substituted ketones. However, even if the reaction time was 24 h, substrate **2o** was not completely transformed and produced the product **4o** in only 51% yield. Aprotic polar solvents were examined expecting the effective solvation to promote the generation of the enolate. As a result, DMSO was found to be suitable as the solvent to afford the product **4o** in the highest yield. The reaction of substrates **2o–2q** in DMSO afforded the corresponding products **4o–4p** in 73%, 55% and 47% yields, respectively. For the purified products **4k–4n**, as for the geometry of the C–C double bond adjacent to the carbonyl group, *Z*/*E* isomers were observed based on the ^1H NMR spectrum (Table 2). Similar *Z*/*E* isomerization of 1-(alkoxycarbonyl)methylenephthalan derivatives was detected in a previous study[12] which suggested that the *Z*/*E* isomerization occurs in silica gel or under slightly acidic conditions. The products **4a–4j**, **4o–4q** were obtained as a single isomer. The geometries of the two C–C double bonds were suggested to be *Z* isomers based on NOE experiments.[13]

It is noted that the silver-catalyzed system effectively promoted the C–C bond forming reaction of the *o*-alkynylacetophenone derivatives and carbon dioxide to afford the dihydroisobenzofuran derivatives bearing a carboxyl group or a methoxycarbonyl group in high-to-excellent yields. Furan derivatives were selectively obtained *via* the 5-*exo*-dig cyclization. Further investigations are currently underway in our laboratory.

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