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Facile and Effective Copper-Mediated Cyclization Reaction of Cyclopropylideneacetic Acids (or Esters) and Cyclopropylideneacetonitriles

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The full details of the copper-mediated cyclization reaction of cyclopropylideneacetic acids (or esters) and cyclopropylidenenitriles, the synthetic application of this reaction, and the study of the reaction mechanism are reported.

Introduction

In the past decades, methylenecyclopropanes (MCPs), which are highly strained but readily available and stable molecules, have been studied. They are of synthetic interest due to the attractive feature that MCPs have multiple possibilities for reaction of the three strained bonds (two proximal and one distal bonds) in the cyclopropane ring.[1] Especially, increasing attention has been paid to the transition-metal-mediated reactions of MCPs, which have been usually employed for the construction of complex and interesting organic molecules.[2] The reactivities of MCPs toward various transition metals, including Pd,[3] Ni,[4] Pt,[5] and Rh,[6] have been studied, and various reaction pathways, including oxidative addition of the distal or proximal C−C bond[7] and regioselective hydrometalation[8] or carbometalation[9] of the C=C bond, have been observed. In addition, attention has being focused on their intermolecular and intramolecular reactions. Usually a phenolic hydroxyl group[3a] or a C≡C or C=C bond[3b−d] was employed for intramolecular reactions.

In a preliminary communication, we have reported a new concept in which the proximal and distal C−C bond was selectively cleaved with CuX_2. The in situ generated organometallic intermediates were trapped by a COOH or COOEt group acting as the intramolecular nucleophile, leading to a CuX_2-mediated cyclization reaction of cyclopropylideneacetic acids and esters.[10]

In this paper, we wish to report the full details of the copper-mediated cyclization reactions of cyclopropylideneacetic acids (or esters) and cyclopropylidenenitriles, the synthetic application of this reaction, and the study of the reaction mechanism.

Results and Discussion

CuX_2-Mediated Cyclization Reaction of Cyclopropylidenecarboxylic Acids and Esters. The reactions of cyclopropylideneacetic acid (**1a**) and $CuBr_2$ in different solvents and at various temperatures were first investigated. 4-Bromomethyl-2(5*H*)-furanone (**3a**) was obtained in 54% yield when **1a** was treated with $CuBr_2$ (4 equiv) in acetonitrile at 60 °C. Further optimization of conditions demonstrated the solvent system CH_3CN/H_2O (4:1) at 85°C was more favorable, and **3a** was isolated in 78% yield.

Interestingly, 4-iodo-5,6-dihydro-2*H*-pyran-2-one (**4a**) instead of 4-iodomethyl-2(5*H*)-furanone (**3b**) was isolated when **1a** was treated with CuI/I_2 (4 equiv) in CH_3CN/H_2O (4:1) and at 85 °C. Furthermore, a dramatic temperature effect was observed in the further screening: 4-iodomethyl-2(5*H*)-furanone (**3b**) was obtained in aque-

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SCHEME 1

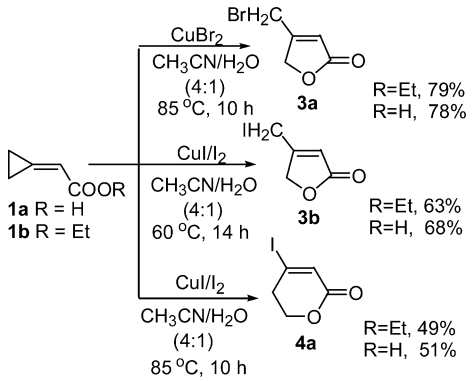
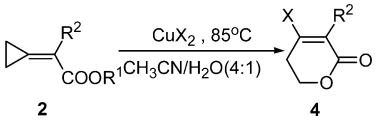


TABLE 1. Synthesis of 4-Halo-5,6-dihydro-2*H*-pyran-2-ones[a]



2 4

R^1=H, Et
R^2=Alkyl

entry	R^1	R^2	X	time (h)	product (yield %)
1	H	Me (**2a**)	Br	24	**4b** (79)
2	H	Me (**2a**)	I	24	**4c** (73)
3	Et	Me (**2b**)	Br	30	**4b** (81)
4	Et	Me (**2b**)	I	30	**4c** (71)
5	Et	Et (**2c**)	Br	31	**4d** (83)
6	Et	Et (**2c**)	I	31	**4e** (77)
7	Et	*n*-Pr (**2d**)	Br	30	**4f** (80)
8	Et	*n*-Pr (**2d**)	I	30	**4g** (76)
9	Et	Bn (**2e**)	Br	35	**4h** (76)
10	Et	Bn (**2e**)	I	35	**4i** (70)

[a] Reaction temperature = 85 °C; $CuBr_2$ (4 equiv), I_2 (4 equiv), CuI (0.1 equiv).

ous acetonitrile in 68% yield by treating **1a** with CuI/I_2 in aqueous acetonitrile at a lower temperature (60 °C) for 14 h. When the more available ethyl cyclopropylideneacetate (**2a**)[11] was used as the substrate, similar results were also obtained (Scheme 1).

The reactions of cyclopropylidenepropanoic acid (**2a**) and ethyl cyclopropylidenepropanate (**2b**) with $CuCl_2$ were also investigated. No reaction was observed when these reactions were carried out at either 85 or 60 °C in aqueous acetonitrle.

A series of ethyl 2-alkyl-substitued cyclopropylideneacetates (**2**) were chosen as substrates, and 4-halo-5,6-dihydro-2*H*-pyran-2-ones were obtained highly selectively; the results are summarized in Table 1.

Cyclization of Cyclopropylidenenitriles. 4-Halo-5,6-dihydro-2(1*H*)-pyridinones, as well as pyranones and furanones, are important classes of compounds because they are pivotal skeletons in many natural products with an unusual range of biological activities.[12] It can be envisioned that pyridinones could be obtained if the reaction described above could be extended to cyclopropylideneacetonitriles in which the CN group is the potential intramolecular nucleophile.

SCHEME 2

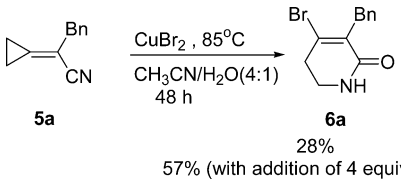
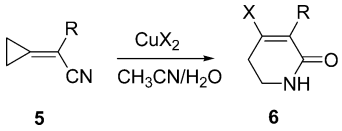


TABLE 2. Synthesis of 4-Halo-5,6-dihydro-2(1*H*)-pyridinones



5 6

entry	R	X	time (h)	product (yield %)
1	Bn (**5a**)	Br	48	**6a** (57)
2	Bn (**5a**)	I	56	**6b** (54)
3	Me (**5b**)	Br	44	**6c** (52)
4	Me (**5b**)	I	50	**6d** (50)
5	Et (**5c**)	Br	44	**6e** (60)
6	Et (**5c**)	I	48	**6f** (55)

[a] Reaction temperature = 85 °C; $CuBr_2$ (4 equiv), I_2 (4 equiv), CuI (0.1 equiv); 4 equiv of LiBr or LiI was added

2-Benzyl-cyclopropylideneacetonitrile[14] (**5a**) was chosen as starting material. The cyclization reaction proceeded slowly and 4-bromo-5,6-dihydro-2(1*H*)-pyridinone (**6a**) was obtained in only 28% yield when **5a** was treated with $CuBr_2$ (4 equiv) in aqueous acetonitrile at 85 °C, even after heating for **3d**. Fortunately, we found that addition of 4 equiv of LiBr accelerated the reaction,[13] and **6a** was obtained in 57% yield (Scheme 2).

Similarly, in the presence of 4 equiv of LiI, the corresponding 4-iodo-5,6-dihydro-2(1*H*)-pyridinone (**6b**) was isolated in 54% yield by treating **5a** with CuI/I_2 at 85 °C for 56 h. The reaction can be extended to other 2-alkyl-cyclopropylideneacetonitriles, and the results were summarized in Table 2.

Pd(0)/CuI-Catalyzed Cross-Coupling Reaction of 4-Halo-5,6-dihydro-2*H*-pyran-2-ones or 4-Halo-5,6-dihydro-2(1*H*)-pyridinones with Terminal Alkynes. Because of the potential biological activities of 4-ynyl-pyranones or 4-ynyl-pyridinones,[15] a facile and efficient synthetic method for prepation of these compounds is valuable. Transition-metal-catalyzed coupling reactions of terminal alkynes with organohalides is a very useful method for the formation of C−C single bonds. Therefore, 4-halo-5, 6-dihydro-2*H*-pyran-2-ones or 4-halo-5,6-dihydro-2(1*H*)-pyridinones might be an important class of building blocks for the synthesis of 4-ynyl-pyranones or 4-ynyl-pyridinones by coupling reactions with alkynes.

Thus, the Pd (0)/CuI-catalyzed cross-coupling reaction of 4-halo-5,6-dihydro-2*H*-pyran-2-ones or 4-halo-5,6-di-

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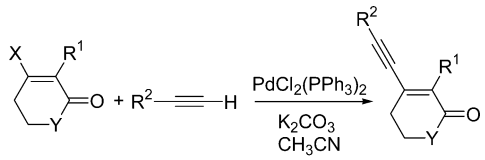
TABLE 3. Pd(0)/CuI-Catalyzed Cross-Coupling Reaction of 4-Halo-5,6-dihydro-2*H*-pyran-2-ones or 4-Halo-5,6-dihydro-2(1*H*)-pyridinones with Terminal Alkynes[a]



entry	R^1	R^2	X	Y	time (h)	product (yield %)
1	H (**4a**)	*n*-C_5H_9	I	O	12	**7a** (92)
2	H (**4a**)	Ph	I	O	12	**7b** (95)
3	Me (**4c**)	*n*-C_4H_9	I	O	12	**7c** (90)
4	Me (**4c**)	Ph	I	O	10	**7d** (88)
5	Me (**4c**)	*n*-C_5H_{11}	I	O	10	**7e** (87)
6	Me (**4c**)	*t*-Bu	I	O	10	**7f** (89)
7	Me (**4c**)	CH_3OCH_2	I	O	14	**7g** (80)
8	Et (**4e**)	*n*-C_4H_9	I	O	12	**7h** (95)
9	Et (**4e**)	Ph	I	O	12	**7i** (92)
10	Me (**6c**)	Ph	I	NH	15	**7j** (83)
11[b]	Et (**4d**)	Ph	Br	O	20	**7i** (45)

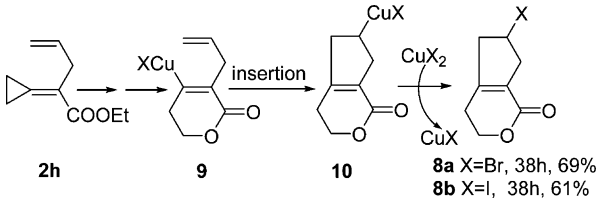
[a] The reaction was carried out in CH_3CN at 50 °C; substrate was $PdCl_2(PPh_3)_2$/CuI/K_2CO_3/alkyne 1:0.02:0.02:2:1.2. [b] The recovery of **4d** = 39%.

hydro-2(1*H*)-pyridinones was studied. Usually the coupling reaction was carried out in the presence of Et_3N.[16] However, reaction of **4a** with 1-hexyne in Et_3N catalyzed by $PdCl_2(PPh_3)_2$ and CuI afforded an unidentified mixture. Fortunately, 4-(1′-hexynyl-)-5,6-dihydro-2*H*-pyran-2-one was obtained in 92% yield by using CH_3CN as the solvent and K_2CO_3 as the base. Further studies showed that the reaction is general for a number of substituted terminal alkynes and pyranones or pyridinones (Table 3): R^1 can be H (entries 1 and 2, Table 3) or an alkyl group (entries 3−11, Table 3); R^2 can be an alkyl (entries 1, 3, 5−8, Table 3) or phenyl group (entries 2, 4, 9−11, Table 3); X can be Br (entry 11, Table 3) or I (entries 1−10, Table 3); Y can be O (entries 1−9, 11, Table 3) or NH (entry 12, Table 3). When 4-bromo-5,6-dihydro-2*H*-pyran-2-one was chosen as substrate, the yield of product was lower (entry 11, Table 3).

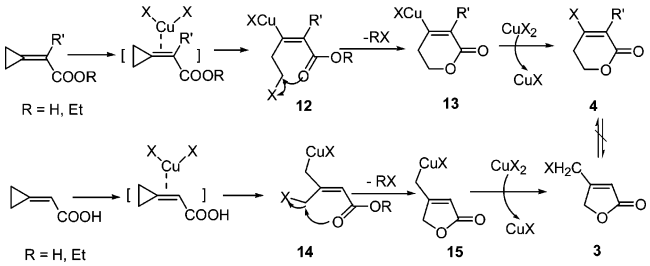
Plausible Mechanism. The reaction of ethyl 2-allylcyclopropylideneacetate (**2h**) with CuX_2 afforded 6-bromo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*c*]-pyran-1-one (**8a**) and 6-iodo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*c*]-pyran-1-one (**8b**), indicating the possibility of intermediate **9**.[17] Intermediate **9**, upon intramolecular insertion, would give the bicyclic organocopper intermediate **10**, which would lead to 6-halo-4,5,6,7-tetrahydro-3*H*-cyclopenta[*c*]-pyran-1-one (**8**) via oxidative cleavage with CuX_2 (Scheme 3).

Ma has proposed an acyclic copper-complex mechanism for the CuX_2-mediated cyclization reaction of 2,3-allenoic acids,[13] and Ito has proposed a metallocyclic intermediate in the mechanism of the Pd- and Pt-catalyzed silaboration of MCPs.[5] However, considering that Cu(II) is an oxidizing agent and difficult to be oxidized to Cu(IV), we suggest the possibility of an acyclic organocopper intermediate in the mechanism for the reaction. Because **3** could not be transformed to **4** under the same conditions,

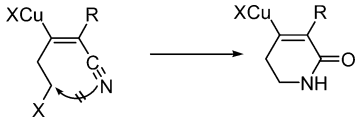
SCHEME 3



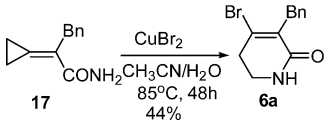
SCHEME 4



SCHEME 5



SCHEME 6



it is concluded that **3** and **4** were formed by parallel reaction routes. The coordination of CuX_2 to 2-alkyl-substitued cyclopropylideneacetic acid (or ester) may form an organocopper coordination complex **11** (or **13**).[5,10] The carbonyl oxygen atom attacks the *δ*-position of complex **11** (or **13**) to form vinylic copper intermediate **12** (or **14**). Oxidative cleavage of **12** (or **14**) with CuX_2 affords **4** (or **3**)[10] (Scheme 4).

However, in the case of cyclopropylideneacetonitriles it is improbable that the intramolecular nucleophile attack occurs on the *δ*-position owing to the lineal structure of nitriles (Scheme 5).

Thus, we suggest the possibility that the nitrogen atom of amide, formed in situ by hydrolysis of nitriles, acts as the nucleophile.[18b] 2-Benzyl-cyclopropylideneacetamide (**17**) was prepared and treated with $CuBr_2$ in aqueous acetonitrile at 85 °C. As expected, **6a** was obtained in 44% yield after 48 h (Scheme 6).

On the other hand, we examined the reaction of 2-benzyl-cyclopropylideneacetonitrile with $CuBr_2$ in anhydrous acetonitrile. Surprisingly, 2-benzyl-3,5-dibromopentenitrile instead of **6a** was obtained, which further

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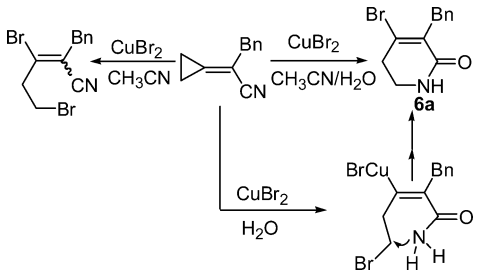
SCHEME 7



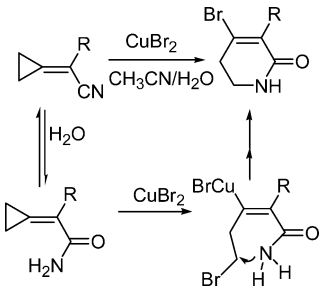
supported the idea that the in situ formed amide intermediate is crucial for the cyclization of cyclopropylidenenitriles (Scheme 7).

Considering the difficulty of hydrolysis of nitriles, we propose an equilibrium between nitrile and amide and that the interception of the copper intermediate involved in the equilibrium allows the cyclization reaction to be successful (Scheme 8).

Conclusion

In conclusion, we have developed a facile and effective copper-mediated cyclization reaction of cyclopropylideneacetic acids (or esters) and cyclopropylideneacetonitriles for the synthesis of 4-halomethyl-2(5*H*)-furanones, 4-halo-5,6-dihydro-2*H*-pyran-2-ones, and 4-halo-5,6-dihydro-2(1*H*)-pyridinones. The synthetic utility of this reaction and a preliminary study of the reaction mechanism were carried out. As a result of the ready availability of starting materials and the simple and convenient operation, the reaction has potential utility in organic synthesis.

SCHEME 8



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Supporting Information Available: Experimental procedures and spectral data for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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