

Novel Tunable CuX₂-Mediated Cyclization Reaction of Cyclopropylideneacetic Acids and Esters for the Facile Synthesis of 4-Halomethyl-2(5*H*)-furanones and 4-Halo-5,6-dihydro-2*H*-pyran-2-ones

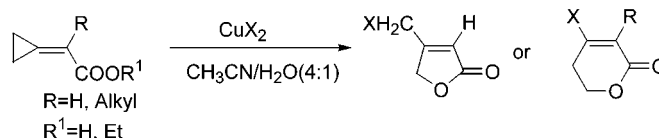
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ABSTRACT

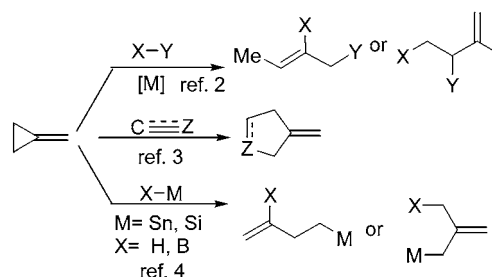


A mixture of cyclopropylideneacetic acids (or esters) and CuBr₂ (or CuI₂) in aqueous acetonitrile afforded 4-substituted 2(5*H*)-furanones or 3,4-substituted 5,6-dihydro-2*H*-pyran-2-ones in moderate to good yields. The selectivity of the reaction greatly depended on the reaction temperature.

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.¹ An attractive feature of MCPs is the multiform reactive possibilities of the three δ -bonds (two proximal and one distal bonds) in the cyclopropane ring. Recently, increasing attention has been paid to the transition metal-catalyzed reactions of MCPs (Scheme 1), which have been usually employed for the construction of complex and interesting organic molecules by intermolecular reaction.^{2–4}

For intramolecular reactions, usually a phenolic hydroxyl group^{2b} or a C \equiv C or C=C bond³ is employed. In this paper,

Scheme 1



we report the realization of a new concept in which the proximal and distal C–C bonds were selectively cleaved with

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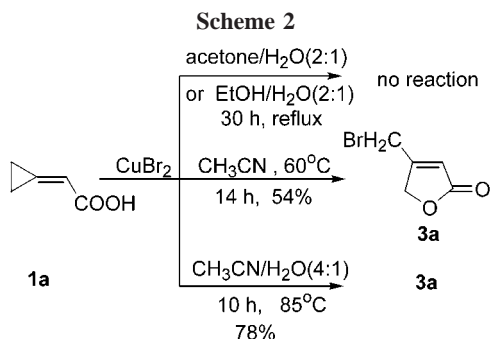
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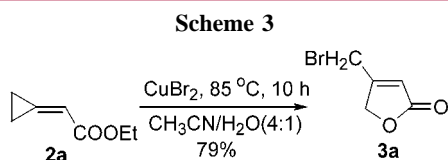
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CuX₂⁵ followed by applying an COOH or COOEt group as the intramolecular nucleophile to trap the in situ-generated organometallic intermediate.

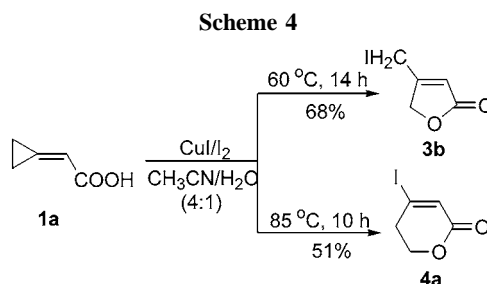
As a first attempt, we used cyclopropylideneacetic acid (**1a**) as the starting point. When the reaction of **1a** with CuBr₂ was conducted in 2:1 EtOH/H₂O or 2:1 acetone/H₂O, no product was obtained; interestingly, 4-bromomethyl-2(5*H*)-furanone (**3a**) was isolated in 54% for the reaction in CH₃CN at 60 °C. Further screening demonstrated that 4:1 CH₃CN/H₂O was the more suitable reaction medium, and the reaction at the higher reaction temperature (85 °C) afforded a good yield of **3a** (Scheme 2).



Because the synthesis of 2-substituted cyclopropylideneacetic acids was not well documented and we obtained them from the corresponding esters,⁶ we managed to directly use ethyl cyclopropylideneacetate (**2a**) as the starting material. The result showed that a similar reaction occurred, and the yield was satisfactory (Scheme 3).



It is interesting to note that the reaction of **1a** with CuI/I₂ in 4:1 CH₃CN/H₂O afforded 4-iodomethyl-2(5*H*)-furanone (**3b**) and/or 4-iodo-5,6-dihydro-2*H*-pyran-2-one (**4a**) at various temperatures (Scheme 4).



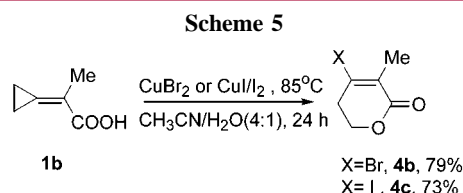
We chose ester **2a** to examine the temperature effect. The ¹H NMR spectra of the reaction mixture showed that the reaction was sensitive to the reaction temperature. The reaction afforded **3b** and **4a** in different ratios at the temperature range from 60 to 85 °C (Table 1).

Table 1. Temperature Effect of the Reaction of **1b** with CuI/I₂^a

entry	temp (°C)	time (h)	product	yield (%)
1	60	14	3b	63
2	65	14	3b/4a	53 (10:1)
3	70	14	3b/4a	50 (2.6:1)
4	78	12	3b/4a	52 (1:2)
5	85	10	4a	49

^a CH₃CN/H₂O (4:1) was the reaction medium.

Then we examined the effect of the α-substituent by studying the reaction of α-methyl-substituted cyclopropylidenepropanoic acid (**1b**) with CuBr₂ or CuI/I₂; to our surprise, no reaction was observed at 60 °C, while at 85 °C, only six-membered lactones, i.e., 3-methyl-4-bromo-5,6-dihydro-2*H*-pyran-2-one (**4b**) and 3-methyl-4-iodo-5,6-dihydro-2*H*-pyran-2-one (**4c**), were formed using CuBr₂ or CuI/I₂, respectively (Scheme 5).



A series of ethyl 2-alkyl-substituted cyclopropylideneacetates were chosen as substrates, and 4-halo-5,6-dihydro-2*H*-pyran-2-ones were obtained highly selectively (Table 2).

The reaction of ethyl 2-allyl-cyclopropylideneacetate (**2f**) with CuX₂ afforded 6-bromo-4,5,6,7-tetrahydro-3*H*-cyclo-

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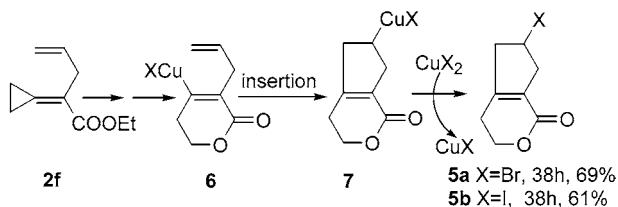
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Table 2. Synthesis of 4-Halo-5,6-dihydro-2*H*-pyran-2-ones^a

entry	R	X	time (h)	product (yield %)
1	Me (2b)	Br	30	4b (81)
2	Me (2b)	I	30	4c (71)
3	Et (2c)	Br	31	4d (83)
4	Et (2c)	I	31	4e (77)
5	<i>n</i> -Pr (2d)	Br	30	4f (80)
6	<i>n</i> -Pr (2d)	I	30	4g (76)
7	Bn (2e)	Br	35	4h (76)
8	Bn (2e)	I	35	4i (70)

^a Reaction temperature = 85 °C; CuBr₂ (4 equiv), I₂ (4 equiv), CuI (0.1 equiv).

penta[c]-pyran-1-one (**5a**) and 6-iodo-4,5,6,7-tetrahydro-3*H*-cyclopenta[c]-pyran-1-one (**5b**) indicating the possibility of intermediate **6**.⁷ Intermediate **6** gave bicyclic copper intermediate **7**, which upon intramolecular insertion afforded 6-halo-4,5,6,7-tetrahydro-3*H*-cyclopenta[c]-pyran-1-one (**5**) via oxidative cleavage with CuX₂ (Scheme 6).

Scheme 6

Furthermore, the reaction of aryl-substituted methylenecyclopropanes with CuX₂ afforded 2,4-dihalo-1-alkenes (**9**) and 2,2-dihalomethyl-1-alkenes (**10**), indicating the possibility of two ways to cleave the cyclopropane ring (Scheme 7). Further screening showed that benzylenecyclopropane (**8c**) has similar whereas weaker temperature effect compared to **1b** (Table 3).

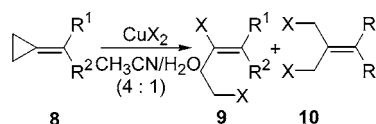
Ito has proposed a metallocyclic intermediate mechanism to explain the selective distal or proximal C–C bond cleavage of MCPs via Pd- and Pt-catalyzed silaboration,^{4a} and Ma has proposed a coordination copper-complex mechanism for the CuX₂-mediated cyclization reaction of 2,3-allenoic acids.⁸ Considering the similarity of the cyclopropane ring with the C=C bond, we suggest the possibility of a coppercyclic intermediate mechanism for the reaction. Due to the fact that **3b** could not be transformed to **4a** under the same conditions, it is concluded that **3b** and **4a** were formed by parallel reaction routes. The coordination of CuX₂ to

Table 3. Distal and Proximal Cleavages of Aryl-Substituted Methylenecyclopropanes and the Temperature Effect

substrate	temp (°C)	time (h)	X	yield (%)	
				9	10
8a	85	8	Br	87	0
8b	85	14	Br	72	17
8c	85	10	I	88	0
8c	75	15	I	81	0
8c	65	22	I	84	0
8c	55	30	I	78	4
8c^a	45	48	I	52	9

^a Recovery of **8c** = 25%.

cyclopropylideneacetic acid **1a** provides two possible ways to cleave cyclopropane ring and may form two organocopper coordination complexes **11** and **13**.^{8,4a} In complex **11**, the

Scheme 7

8a R¹=Ph, R²=Ph

8b R¹=*p*-Me₂N-Ph, R²=H

8c R¹=Ph, R²=H

hydroxy oxygen atom acting as an intramolecular nucleophile attacks the γ-position of complex **11** to undergo lactonization to give **12** and a molecule of HX. Oxidative cleavage of **12** with CuX₂ affords 4-halomethyl-2(5*H*)-furanone **3**.⁸ In complex **13**, the hydroxy oxygen atom attacks the δ-position instead, to form vinylic copper intermediate **14**, and gives a molecule of HX. Intermediate **14** leads to 4-halo-5,6-dihydro-2*H*-pyran-2-one after oxidative cleavage by CuX₂ (Scheme 8). For the reaction of carboxylates, the carbonyl oxygen may act as the nucleophile.⁹

Although the Nickel(0)-catalyzed intermolecular dimerization and Michael reaction of ethyl cyclopropylideneacetates were reported,¹⁰ to the best of our knowledge, no similar intramolecular cyclization has been documented. In conclusion, we have developed a novel, convenient, and efficient method for the synthesis of 4-substituted 2(5*H*)-furanones and 3,4-substituted-5,6-dihydro-2*H*-pyran-2-ones. Both furanones and pyranones are important classes of

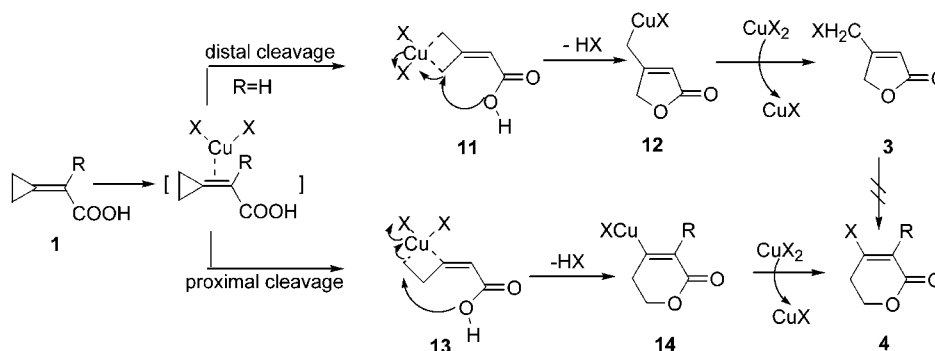
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Scheme 8



compounds because they are pivotal skeletons in many natural products with an unusual range of biological activities¹¹ and can be obtained from moderate to good yields by the reaction of cyclopropylideneacetic acids (or esters) and CuBr_2 (or CuI/I_2) in aqueous acetonitrile. The reaction mechanism, influence of temperature on selectivity, and synthetic application of this methodology are being investigated in our laboratory.

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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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