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Ruthenium-Catalyzed Dimerization of Propiolates: A Simple Route to α-Pyrones

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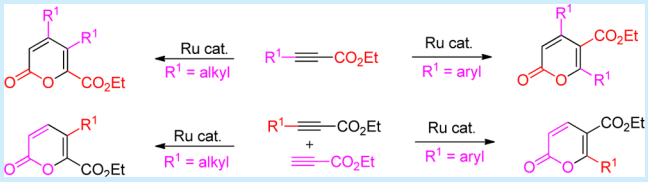
Supporting Information

ABSTRACT: A ruthenium-catalyzed regioselective intermolecular multistep homo- and heterodimerization of substituted propiolates providing α-pyrone-5-carboxylates and α-pyrone-6-carboxylates is described. The synthetic utilities of α-pyrone derivatives are shown. The proposed mechanism is strongly supported by experimental evidence.

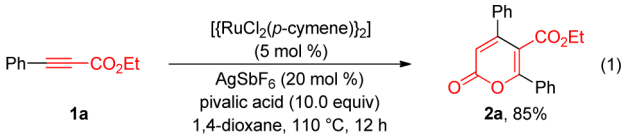


α-Pyrones are naturally occurring six-membered unsaturated lactones. This core is found in various natural products, and it shows a wide range of biological activities.[1] In addition, α-pyrone is a highly useful building block for synthesizing more complex organic molecules.[2] Particularly, 5- or 6-carboxylate-substituted α-pyrones show various biological activities and tremendous applications in organic synthesis.[3] Substituted α-pyrones are traditionally prepared by lactonization of substituted α,β-unsaturated enones or intramolecular cyclization of 3,5-diketo carboxylic acids.[4] However, the preparation of the corresponding α,β-unsaturated enones or 3,5-diketo carboxylic acids needs a number of steps, and the overall observed yields are much less. Alternatively, α-pyrones are efficiently prepared by metal-catalyzed organic transformations.[5] Metal-catalyzed cyclization of halogen-substituted α,β-unsaturated esters with alkynes[5a] or allenylstannanes,[5b] cyclization of β-ketoesters with alkynes,[5c] cyclization of α,β-unsaturated acids with alkynes,[5d,e] intramolecular cycloisomerization of carbon−carbon π-components,[5f−i] and cycloaddition of π-components[5j] are widely used to synthesize α-pyrones. However, the control of regioselectivity and observation of competitive side products are practical problems in the reaction.

Transition-metal-catalyzed cyclization of π-components via a five-membered metallacycle intermediate is a unique method to synthesize heterocyclic compounds from easily available starting materials in a highly regioselective manner.[6] Various π-component combinations such as alkyne/alkyne, alkyne/alkene, allene/alkene, alkene/alkene, and C−C π-components/heteroatom presented π-components are known in the reaction. Among these combinations, oxidative cyclization of unsymmetrical alkyne/alkyne is quite difficult and very challenging due to the possibility of formation of several side products.[7] Thus, dimerization of alkynes/alkynes has not been well-explored in the literature.

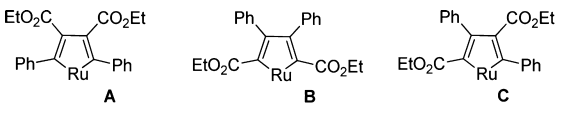
Herein, we report an unprecedented, highly regioselective synthesis of α-pyrone derivatives via alkyne/alkyne intermolecular homocyclization of substituted propiolates and hetero-cross-cyclization of substituted propiolates in the presence of a ruthenium catalyst. By employing this method, various aromatic and alkyl-substituted 5- or 6-carboxylate α-pyrone derivatives are prepared in a highly regioselective manner. In the present method, four different types of reactions are involved in one pot. Later, various synthetic utilities of α-pyrone derivatives in organic synthesis are shown. A possible reaction mechanism is proposed, and the mechanism is supported by experimental evidence.

The intermolecular dimerization of ethyl phenylpropiolate (**1a**) proceeded smoothly in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %), and pivalic acid (10.0 equiv) in 1,4-dioxane at 110 °C for 12 h, yielding 5-ester-substituted α-pyrone derivative **2a** in 85% yield (eq 1) (for



(1)

detailed optimization studies, see Tables S1−S3 in the Supporting Information). The catalytic reaction is highly regioselective; only compound **2a** is observed, and the other competitive side products are not observed. The structure and regioselectivity of product **2a** was confirmed by a single-crystal X-ray diffraction (see Supporting Information). The present catalytic reaction proceeds via a five-membered metallacycle intermediate. In substrate **1a**, two coordinating groups such as Ph and CO_2Me are there. Thus, three different types of metallacycle intermediates **A**, **B**, and **C** are expected (eq 2). It is



(2)

expected that the Ph group might coordinate with ruthenium better than the ester group. Thus, intermediate **A** is expected

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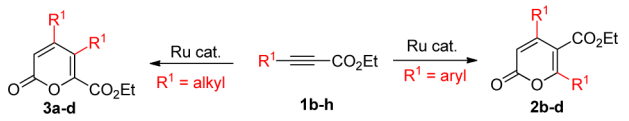
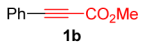
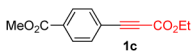
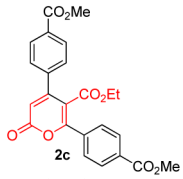
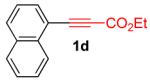
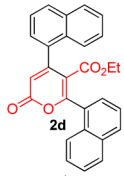
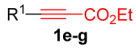
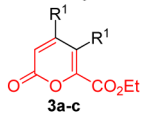
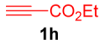
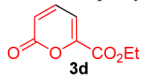
for the reaction. Surprisingly, intermediate **C** was observed in the reaction.

Under the optimized reaction conditions, the homocyclization of substituted propiolates **1b–h** was examined (Table 1). Thus, methyl phenylpropiolate (**1b**) and the

Table 1. Scope of the Homocyclization of Propiolates[a]

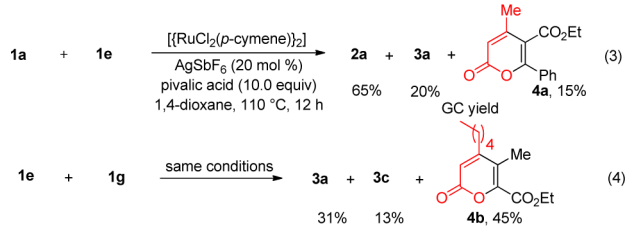


entry	1	2 or 3	yield (%)[b]
1	 **1b**	 **2b**	85
2	 **1c**	 **2c**	81
3	 **1d**	 **2d**	71
	 **1e-g**	 **3a-c**	
4	**1e**: R^1 = Me	**3a**: R^1 = Me	75
5	**1f**: R^1 = *n*-propyl	**3b**: R^1 = *n*-propyl	72
6	**1g**: R^1 = *n*-pentyl	**3c**: R^1 = *n*-pentyl	70
7	 **1h**	 **3d**	45

[a]All reactions were carried out using **1b–h** (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %), and pivalic acid (10.0 equiv) in 1,4-dioxane (3.0 mL) at 110 °C for 12 h. [b]Isolated yield.

electron-deficient phenylpropiolate **1c** underwent cyclization efficiently to yield 5-ester-substituted α-pyrone derivatives **2b** and **2c** in 85 and 81% yields, respectively (entries 1 and 2). Interestingly, sterically hindered ethyl naphthylpropiolate **1d** also underwent oxidative cyclization, smoothly affording α-pyrone derivative **2d** in 71% yield (entry 3). In products **2b–d**, aromatic and ester groups are adjacent to each other as in **2a**. In contrast, alkyl-substituted propiolates **1e–g** such as ethyl but-2-ynoate (**1e**), methyl hex-2-ynoate (**1f**), and methyl oct-2-ynoate (**1g**) underwent cyclization effectively, yielding 6-ester-substituted α-pyrone derivatives **3a–d** in 75, 72, and 70% yields, respectively (entries 4–7). In products **3a–d**, two alkyl groups are adjacent to each other, which is the reverse regiochemistry of that of products **2a–d**. In these reactions, products consistent with the involvement of intermediate **B** were observed exclusively in which both alkyne ester moieties coordinate with ruthenium (eq 2). The catalytic reaction was also compatible with terminal alkyne **1h**. Thus, ethyl propiolate (**1h**) underwent intermolecular cyclization to provide 6-ester α-pyrone **3d** in 45% yield as with **3a** regiochemistry (entry 7).

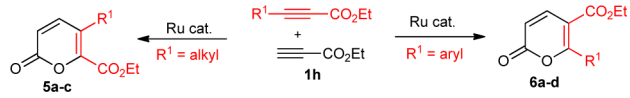
The scope of the cyclization reaction was tested with two different propiolates **1**. Initially, the hetero-cross-oxidative cyclization of **1a** with **1e** was examined. In the reaction, three different types of α-pyrone derivatives such as homocyclization of **1a**, homocyclization of **1e**, and heterocyclization of **1a** and **1e** are observed (eq 3). Next, the hetero-cross-cyclization of **1e**

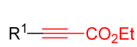
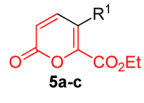
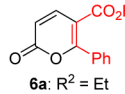
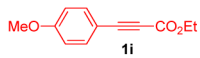
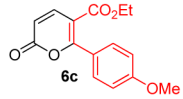
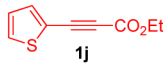
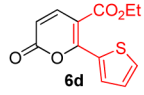


was tested with a less reactive methyl oct-2-ynoate (**1g**). In the reaction, the heterocyclization product **4b** was observed in 45% yield (eq 4). Still, the homocyclization of **1e** and **1g** is formed. On the basis of these results, we have concluded that internal alkynes favor homocyclization, and the cyclization of internal alkyne and terminal alkyne combination could be the better choice for the reaction.

Hence, the cyclization of terminal alkyne, ethyl propiolate (**1h**), and internal alkyne, ethyl but-2-ynoate (**1e**) was examined (Table 2). As we expected, the corresponding

Table 2. Scope of the Hetero-Cross-Cyclization of Two Different Substituted Propiolates[a]



entry	1	5 or 6	yield (%)[b]
	 **1e-g**	 **5a-c**	
1	**1e**: R^1 = Me	**5a**: R^1 = Me	68
2	**1f**: R^1 = *n*-propyl	**5b**: R^1 = *n*-propyl	65
3	**1g**: R^1 = *n*-pentyl	**5c**: R^1 = *n*-pentyl	63
4	**1a**	 **6a**: R^2 = Et **6b**: R^2 = Me	79
5	**1b**		76
6	 **1i**	 **6c**	77
7	 **1j**	 **6d**	71

[a]All reactions were carried out using **1h** (1.0–1.5 mmol), **1b–j** (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), and $AgSbF_6$ (20 mol %) in acetic acid (3.0 mL) at 110 °C for 12 h. [b]Isolated yield.

heterocyclization product **5a** was observed in 55% yield (entry 1). However, the homocyclization of **1e** and **1h** products **3a** and **3d** was also observed in 10 and 5% yields, respectively. To avoid the homocyclization products, the reaction was examined with various solvents. Very interestingly, in acetic acid solvent, no homocyclization products were observed, and the hetero-cyclization product **5a** was observed in 68% yield (entry 1). It is very interesting to note that only the ester group of methyl

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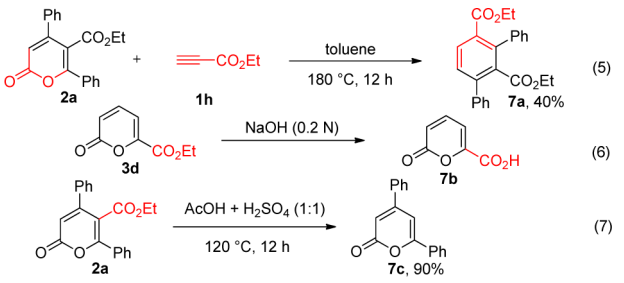
propiolate (**1h**) underwent selective C−O bond formation with **1e**, and the ester moiety of **1e** was intact in the reaction. The catalytic reaction is highly regioselective; the ester moiety of **5a** was placed in the C-6 position, and the alkyl group was placed in the C-5 position of the α-pyrone. Encouraged by this result, we examined the cyclization reaction of **1h** with other alkyl-group-substituted propiolates **1f** and **1g** in acetic acid solvent. In the reaction, 5,6-substituted α-pyrone derivatives **5b** and **5c** were observed in 65 and 63% yields, respectively (entries 2 and 3). However, in the reaction, only homocyclization of **1h** was observed in only 2−3% yield. Next, the cyclization reactions of **1h** with aromatic-group-substituted propiolates **1a** and **1b** and methoxy-substituted **1i** were examined. In the reaction, cyclization products **6a−c** were observed in 79, 76, and 77% yields, respectively (entries 4−6). In the reaction, only homocyclization of **1a**, **1b**, and **1i** was observed in 2−3% yield. The structure and regioselectivity of product **6c** was confirmed by a single-crystal X-ray diffraction (see Supporting Information). Heteroaromatic-group-substituted ethyl 2-thienyl propiolate **1j** also efficiently participated in the reaction with **1h** to yield cyclization product **6d** in 71% yield (entry 7). Interestingly, no homocyclization products were observed in the reaction. These reactions are highly regioselective; the ester moiety of **6a−d** was attached at the C-5 position and the aryl or 2-thienyl group was attached at the C-6 position of the α-pyrone. The cyclization reaction was also tested with diphenylacetylene, 1-phenyl-1-propyne, and 3-phenylprop-2-yn-1-ol with propiolate **1e** or **1h**. However, in the reaction, no expected α-pyrone derivatives were observed.

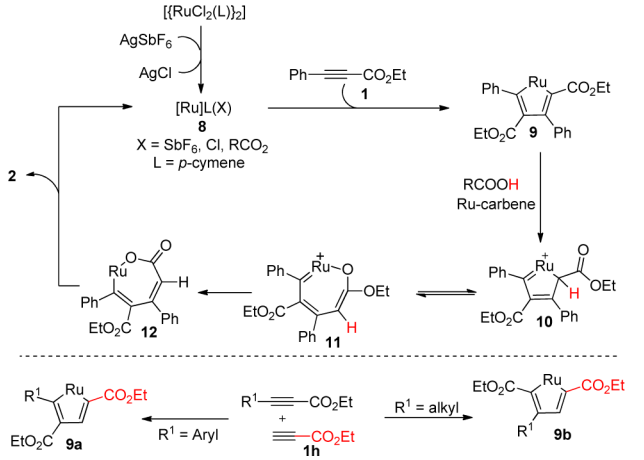
By employing the present method, 5-carboxylate pyrones **2a−d** and **6a−d** and 6-carboxylate α-pyrones **3a−d** and **5a−c** were prepared (Tables 1 and 2). Pyrone-5-carboxylates are called coumalates, which have been widely used as a key synthetic precursor for various organic transformations.[3] To show the utility of coumalates, the cycloaddition of **2a** with ethyl propiolate (**1h**) in xylene at 180 °C for 12 h was carried out.[3b] In the reaction, a synthetically useful polymer precursor, phenyl-substituted isopthalate **7a**, was observed in 40% yield (eq 5). It is also known that pyrone-6-carboxylic acid **7b** shows



tumor growth inhibition activity (eq 6).[3a] It can be prepared by base-mediated de-esterification at the ester group of **3d** (eq 6).[8] Further, decarboxylation of the α-pyrone derivative of **2a** in the presence of a 1:1 mixture of AcOH and H_2SO_4 at 120 °C yielded decarboxylated α-pyrone derivative **7c** in 90% yield (eq 7).[8]

A possible reaction mechanism for the present dimerization of propiolates is proposed in Scheme 1. Silver salt $AgSbF_6$ likely removes the chlorine ligand from the $[\{RuCl_2(p\text{-cymene})\}_2]$ complex, forming a cationic ruthenium complex **8**. Highly regioselective coordination of propiolates **1** to the complex **8** followed by oxidative cyclometalation leads to intermediate **9**.[7] Selective protonation at the ester attached to the carbon next to

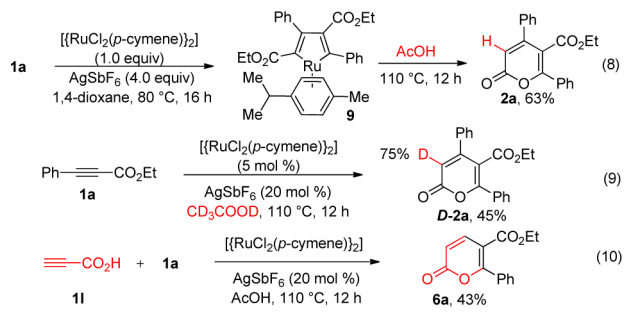
Scheme 1. Proposed Mechanism



ruthenium of intermediate **9** by the organic acid via a Ru-carbene intermediate **10** or O-bound enolate formation gives intermediate **11**.[6,7] Nucleophilic attack of the carbonyl oxygen of the ester moiety to the ruthenium in intermediate **11** yields intermediate **12**.[5a] Reductive elimination of intermediate **12** yields cyclic product **2** and regenerates the ruthenium species **8**. In the selective protonation in intermediate **9**, it seems likely that an O-bound enolate could be involved, which would favor protonation on the carbon of the ester. In the cross-cyclization reaction, only the ester moiety of terminal alkyne **1h** was involved in the C−O bond formation. The internal alkyne ester moiety was not involved. It could be possible that steric hindrance at the ester group of terminal alkyne is less compared with internal alkyne in intermediates **9a,b**.

The substituent present on the propiolates decides the regioselectivity of the reaction. In the aryl- or 2-thienyl-substituted propiolates **1a−d** and **1j**, 5-carboxylate pyrones **2a−d** and **6a−d**, alkyl-substituted propiolates **1e−h**, and 6-carboxylate α-pyrones **3a−d** and **5a−c** were observed. We strongly believe that aryl or 2-thienyl or ester groups in intermediate **9** coordinate with Ru better than alkyls. In the alkynes **1a−d**, two coordinating groups such as Ph and ester are there. Thus, intermediates **C** and **9a** are favorable. In the alkynes **1e−h**, only an ester coordinating group is there. Thus, intermediates type **B** and **9b** are favorable (eq 2, Scheme 1).

The proposed mechanism in Scheme 1 was strongly supported by the following experimental evidence. Initially, we have tried to isolate the key intermediate **9** in the reaction of **1a** with a stoichiometric amount of ruthenium and silver salt. In the reaction, a Ru species was obtained in impure form, which was tentatively identified as structure **9** (eq 8). Further, the



intermediate was treated with acetic acid at 110 °C for 12 h. In the reaction, the expected product **2a** was observed. Further,

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the cyclization of **1a** was examined in CD_3COOD solvent (eq 9). In the reaction, deuterated α-pyrone derivative **D-2a** was observed in 45% yield in 75% deuterium incorporation at the C-3 carbon of α-pyrone. These results clearly revealed that the catalytic reaction proceeds via a five-membered metallacycle intermediate and only organic acid protonates the metallacycle intermediate. Further, the treatment of **1a** with propiolic acid (**1l**) gave α-pyrone derivative **6a** in 43% yield (eq 10). This result clearly reveals that the acid group of propiolic acid was involved in the C−O bond formation of product **5** or **6**.

In conclusion, we have shown a ruthenium-catalyzed dimerization of substituted propiolates. In these reactions, substituted α-pyrone-5-carboxylates and α-pyrone-6-carboxylates were prepared. Further extension of cyclization of other π-components is in progress.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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