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Lewis Acid Mediated Reactions of Cyclopropyl Aryl Ketones with α-Ketoesters: Facile Preparation of 5,6-Dihydropyran-2-ones

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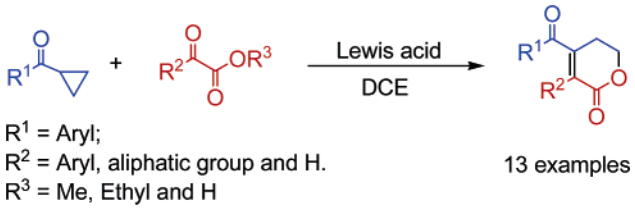
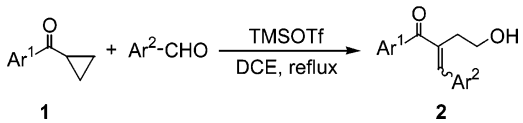


A new general method for the synthesis of 5,6-dihydropyran-2-ones from cyclopropyl aryl ketones (monoactivated cyclopropanes) and α-ketoesters in good to excellent yields has been developed. The process involves a cascade of reactions, including a nucleophilic ring-opening reaction of monoactivated cyclopropane by H_2O, Lewis acid mediated transesterification, and an aldol type reaction.

Introduction

Cyclopropane derivatives, as versatile building blocks, have been more than laboratory curiosities for quite some time.[1] Electron-donating or -accepting substituents are generally involved in the activation of strained three-membered rings, as they make polar processes more favorable. However, cyclopropanes involved in synthetically useful reactions frequently contain two activating groups.[2] Ring-opening reactions of monoactivated cyclopropane derivatives are generally sluggish because of their low reactivities. So far the only reported examples have required severe conditions assisted either by strong nucleophiles such as the iodide anion[3] and strong Lewis acids such as $TiCl_4$[4] or by the β-effect of the silicon atom of a trimethylsilyl group.[5] More recently, a Bu_3SnH-mediated free-radical process and a SmI_2-promoted electron-transfer process have been also reported with this transformation.[6] Therefore, it is desirable to develop methods for ring-opening reactions of simple monoactivated cyclopropane derivatives under mild conditions.

SCHEME 1. Reaction of Cyclopropyl Aryl Ketones with Arylaldehydes Promoted by the Lewis Acid TMSOTf.



1 **2**

Recently, we reported the ring-opening reaction of cyclopropyl aryl ketones **1** with arylaldehydes to afford 2-(2-hydroxyethyl)-1,3-diarylpropenones **2** in the presence of a Lewis acid (Scheme 1).[7] We envisioned that this

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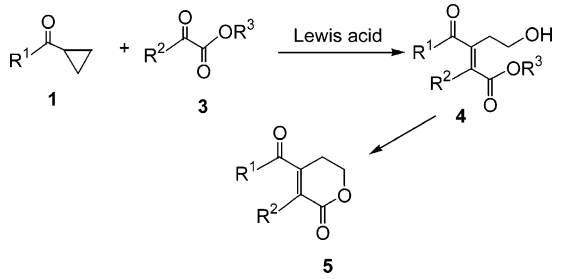
SCHEME 2. Design of a Cascade Process for the Preparation of 5,6-Dihydropyran-2-ones



process included a ring-opening reaction of the cyclopropane moiety by nucleophilic attack of ambient H_2O and a subsequent aldol type reaction in the presence of a Lewis acid.

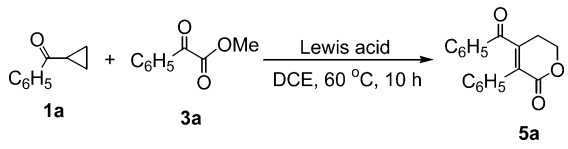
A natural extension of this work is to explore the possibility of replacing the arylaldehyde with other carbonyl-containing compounds. The primary hydroxyl group in product **2** inspired us to determine whether a tandem reaction process could be applied to the preparation of 5,6-dihydropyran-2-one compounds (**5**) if the subsequent transesterification reaction takes place. It is well-known that 5,6-dihydropyran-2-ones are an important class of compounds because they are skeletal motifs in many natural products that possess important biological activities.[8] Therefore, we selected α-ketoesters **3** for use in this reaction to replace the arylaldehyde on the basis of this hypothesis (Scheme 2).

Results and Discussion

To determine whether such a reaction cascade is possible, we examined the reaction of cyclopropyl phenyl ketone (**1a**) with methyl 2-oxo-phenylacetate (**3a**) mediated by a variety of Lewis acids. As can be seen from Table 1, 4-benzoyl-3-phenyl-5,6-dihydropyran-2-one (**5a**) was indeed obtained in the presence of 0.5 equiv of the Lewis acid $Zr(OTf)_4$ or TMSOTf, or the Brønsted acid TfOH in 66, 64, and 52% yields, respectively, in 1,2-dichloroethane (DCE) at 60 °C with some recovered starting materials within 10 h (Table 1, entries 1−3). The Lewis acids $BF_3{\cdot}OEt_2$, $TiCl_4$, and $SnCl_4$ and Brønsted acid *p*-toluenesulfonic acid exhibited comparatively much lower catalytic abilities in this reaction, with the recovery of most of the starting materials. Other metal triflates, such as $Zn(OTf)_2$ and $Yb(OTf)_3$, cannot mediate this reaction under the same reaction conditions. When the amount of the Lewis acid TMSOTf or $Zr(OTf)_4$, or the Brønsted acid TfOH used was increased to 1.0 equiv, the yields of **5a** were enhanced to 89, 66, and 72%, respectively (Table 1, entries 4−6), with Lewis acid TMSOTf being the best promoter for this reaction.

We also examined various solvents in this reaction using TMSOTf as the Lewis acid, and the results are summarized in Table 2. We found that DCE is the best solvent for this reaction. As for THF and MeCN, the reactions became sluggish, and most of starting materials were recovered, presumably because of the coordination of THF and MeCN to the silicon atom in Lewis acid TMSOTf (Table 2, entries 2 and 3). At a higher temperature in toluene (100 °C), the reaction solution was deep colored and only a trace amount of **5a** was formed, which indicated that high reaction temperatures do not favor the reaction (Table 2, entry 4).

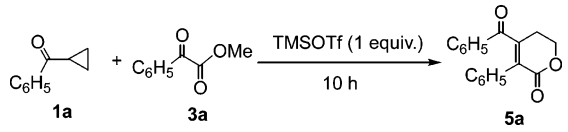
TABLE 1. Reactions of Cyclopropyl Phenyl Ketone 1a with α-Ketoester 3a Mediated by Various Acids in DCE[a]



entry	Lewis acid (equiv)	yield[b] of **5a** (%)
1	$Zr(OTf)_4$ (0.5)	66
2	TfOH (0.5)	64
3	TMSOTf (0.5)	52
4	$Zr(OTf)_4$ (1.0)	66
5	TfOH (1.0)	72
6	TMSOTf (1.0)	89

[a] All reactions were performed at 60 °C for 10 h on a 0.3 mmol scale with the use of **1a** and **3a**. See Supporting Information for details. [b] Isolated yields.

TABLE 2. Solvent Effects in the Reaction of Cyclopropyl Phenyl Ketone 1a with α-Ketoester 3a Mediated by TMSOTf (1.0 equiv)



entry	solvent	*T* (°C)	yield[a] of **5a** (%)
1	DCE	60	89
2	THF	60	22
3	MeCN	60	0
4	toluene	100	trace

[a] Isolated yields.

Next, the scope of this new and efficient synthetic protocol for the construction of 5,6-dihydropyran-2-ones was investigated by employing a variety of cyclopropyl aryl ketones and α-ketoesters under the optimized conditions. As shown in Table 3, starting from cyclopropyl phenyl ketone (**1a**) and various α-ketoesters, the corresponding 5,6-dihydropyran-2-ones **5a**−**h** were obtained in moderate to excellent yields (Table 3, entries 1−8). From the reactions of **1a** with various aryl α-ketoesters, electronic effects were clearly observed. In general, aryl α-ketoesters having no substituents or electron-withdrawing groups on the aromatic ring were more reactive, and afforded the corresponding products **5** in better yields (Table 3, entries 1 and 4). For aryl α-ketoesters **3b** and **3c**, which bear an electron-donating substituent (methyl or methoxyl group) on the aromatic ring, the corresponding products **5** were obtained in lower yields under the same conditions (Table 3, entries 2 and 3). On the other hand, ethyl glyoxalate (**3e**) showed a high reactivity in this reaction, and afforded the corresponding product **5e** in 94% yield because of the high electrophilicity of the aldehyde moiety in **3e** (Table 3, entry 5). As for aliphatic

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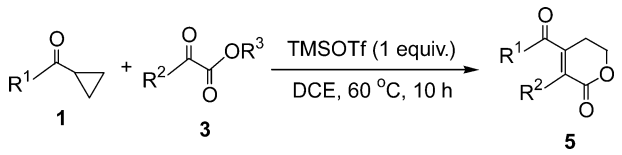
TABLE 3. Reactions of Cyclopropyl Aryl Ketones 1a−f with Various α-Ketoesters under Optimized Conditions



1 3 5

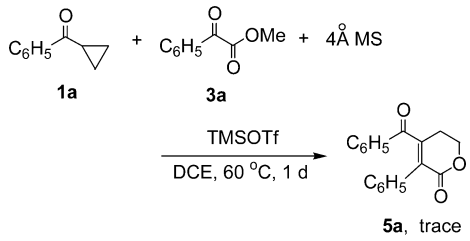
entry	R^1	R^2/R^3	yield[a] of **5** (%)
1	**1a**, C_6H_5	**3a**, C_6H_5/Me	**5a**, 89
2	**1a**, C_6H_5	**3b**, *p*-MeC_6H_4/Me	**5b**, 60
3	**1a**, C_6H_5	**3c**, *p*-$MeOC_6H_4$/Et	**5c**, 50
4	**1a**, C_6H_5	**3d**, *p*-ClC_6H_4/Et	**5d**, 87
5	**1a**, C_6H_5	**3e**, H/Et	**5e**, 94
6	**1a**, C_6H_5	**3f**, Me/Et	**5f**, 97
7	**1a**, C_6H_5	**3g**, hexyl/Et	**5g**, 40
8	**1a**, C_6H_5	**3h**, cyclohexyl/Et	**5h**, 35
9	**1b**, *p*-FC_6H_4	**3f**, Me/Et	
10	**1c**, *p*-MeC_6H_4	**3f**, Me/Et	**5j**, 97
11	**1d**, *o*,*o*-$Me_2C_6H_3$	**3f**, Me/Et	**5k**, 92
12	**1e**, *p*-$MeOC_6H_4$	**3f**, Me/Et	**5l**, 72[b]
13	**1f**, thiophen-2-yl	**3f**, Me/Et	**5m**, 80[b]

[a] Isolated yields. [b] The reaction time was prolonged to 2 days.

α-ketoesters, the reaction of ethyl pyruvate (**3f**) with **1a** proceeded smoothly to afford **5f** in 97% yield (Table 3, entry 6). However, when aliphatic α-ketoesters having a larger aliphatic group were utilized in this reaction, such as ethyl 2-oxo-octanoate (**3g**) and ethyl cyclohexyl-oxoacetate (**3h**), the yields of the corresponding products **5g** and **5h** abruptly decreased, presumably because of their steric bulkiness (Table 3, entries 7 and 8). Furthermore, we also examined the reactions of a variety of cyclopropyl aryl ketones with ethyl pyruvate **3f** under these optimized conditions (Table 3, entries 9−13). A series of 4-substituted 3-methyl-5,6-dihydropyran-2-ones were prepared in good to excellent yields. Similar electronic effects were also observed as illustrated in Table 3. For cyclopropyl aryl ketones bearing an electron-rich aryl group, such as cyclopropyl 4-methoxyphenyl ketone (**1e**) and thiophene-derived substrate **1f**, a prolonged reaction time (2 days) was required, and the corresponding products **5l** and **5m** were obtained in 72 and 80% yields, respectively (Table 3, entries 12 and 13). The structures of all products were determined by NMR spectroscopic data, microanalyses, and HRMS (see the Supporting Information).

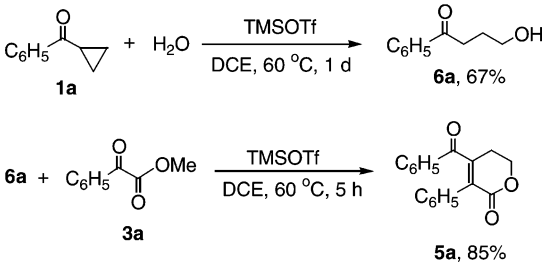
To understand the reaction mechanism for the formation of 5,6-dihydropyran-2-ones **5**, we introduced 4 Å molecular sieves (100 mg for 0.3 mmol of substrate) into the reaction system to eliminate the ambient moisture. As a consequence, the reaction became sluggish, and gave only a trace of the desired product **5a** after 1 day at 60 °C in the presence of TMSOTf (Scheme 3). This indicates that H_2O probably plays a key role in the reaction mechanism. Moreover, we examined the effect of the amount of H_2O on the reaction by adding of 1.0, 2.0, or 5.0 equiv of H_2O into the reaction system. These control experiments showed that 1.0 equiv of H_2O did not clearly affect the reaction, giving **5a** in 88% yield under identical conditions. When the amount of H_2O was increased to 2.0 or 5.0 equiv, the reaction turned out to be sluggish, giving **5a** in 60 and 37% yields, respectively, along with some recovered starting materials, when performed

SCHEME 3. Reaction of 1a with 3a Mediated by TMSOTf in the Presence of 4 Å MS (100 mg)



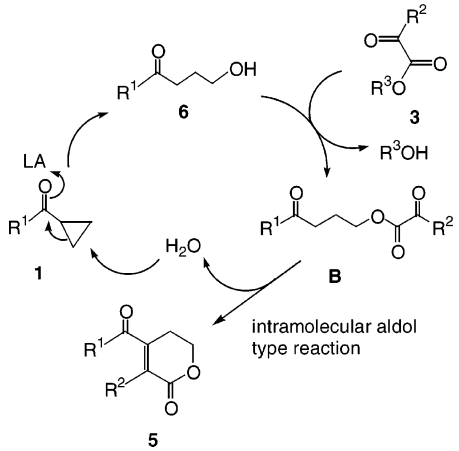
1a 3a **5a**, trace

SCHEME 4. Reaction of 6a with 3a in the Presence of TMSOTf



1a **6a**, 67% 3a **5a**, 85%

SCHEME 5. Proposed Mechanism of the Reaction of Cyclopropyl Aryl Ketone with α-Ketoester Mediated by Lewis Acid



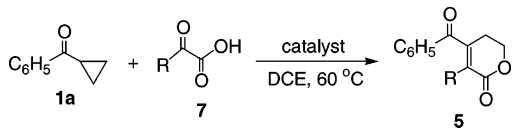
6 3 1 B 5

under identical conditions. Therefore, we believe that an excess of H_2O in the reaction system does not favor the reaction.

Additionally, we prepared 4-hydroxy-1-phenylbutan-1-one (**6a**) from the reaction of **1a** with H_2O in the presence of Lewis acid TMSOTf. We confirmed that **6a** can react with methyl oxo-phenylacetate (**3a**) smoothly to give **5a** in 85% yield within 5 h (Scheme 4).

On the basis of the above results, a plausible reaction mechanism is proposed in Scheme 5. In the presence of a Lewis acid, cyclopropyl aryl ketone **1** reacts with ambient H_2O to give the corresponding adduct 4-hydroxy-1-arylbutan-1-one **6**. This is consistent with the electronic effects observed in Table 3 (entries 6 and 9−13) because substrates **1**, which are electrophiles and bear an electron-withdrawing group on the benzene ring, showed higher reactivities than those of electron-rich substrates, and gave the corresponding products **5** in higher yields. Thus, formed **6** reacts with the α-ketoester to produce another α-ketoester intermediate **B** through an intermolecular transesterification reaction and the release of an alcohol

TABLE 4. Reaction of 1a with α-Ketoacetic Acid Catalyzed by TfOH



entry	catalyst	R	time (days)	yield[a] of **5** (%)
1	none	**7a**, Me	3	**5e**, trace
2	TfOH (20 mol %)	**7a**, Me	3	**5e**, 90
3	TfOH (20 mol %)	**7b**, C_6H_5	1	**5a**, 76

[a] Isolated yields.

molecule. The product 5,6-dihydropyran-2-one **5** is formed through an intramolecular aldol type reaction from intermediate **B** along with the regeneration of 1 equiv of H_2O (aldol type reaction), which can initiate the next reaction cycle. The mechanism is also consistent with the electronic effects observed in these reactions shown in Table 3 (entries 1−4) because α-ketoesters having electron-withdrawing groups on the benzene ring showed higher reactivities than those of α-ketoesters bearing electron-rich groups on the benzene ring in the aldol type reaction, and gave the corresponding products **5** in higher yields. Overall, this process is a cascade of a nucleophilic ring-opening reaction of the monoactivated cyclopropane by H_2O, a transesterification reaction, and an aldol type reaction in the presence of Lewis acid.

The Lewis and Brønsted acid-promoted reactions indicated that the construction of 5,6-dihydropyran-2-ones might proceed via a self-catalyzed process when an α-ketoacetic acid (**7**) was used instead of an α-ketoester. Unfortunately, only a trace amount of product was obtained from a reaction of **1a** with pyruvic acid (**7a**) kept at 60 °C for 3 days in DCE (Table 4, entry 1). However, when 20 mol % TfOH was added, the reaction proceeded smoothly to give 5,6-dihydropyran-2-ones **5a** and **5e** in good yields (Table 4, entries 2 and 3).

Conclusion

In conclusion, we have developed a cascade process involving the ring-opening reaction of monoactivated cyclopropanes by H_2O, followed by a transesterification reaction and an aldol type reaction mediated by a Lewis acid to provide an efficient synthetic protocol for the preparation of 5,6-dihydropyran-2-ones. When an α-ketoacetic acid was subjected to the reaction instead of an α-ketoester, the corresponding 5,6-dihydropyran-2-one could be obtained in good yield with 20 mol % TfOH. Further work directed at elucidation of the detailed reaction mechanism and application of this procedure to the synthesis of α,*β*-unsaturated *δ*-lactone-containing natural products is currently in progress.

Experimental Section

General Procedure for the Preparation of 5,6-Dihydropyran-2-one from Cyclopropyl Aryl Ketone with α-Ketoester. Under an argon atmosphere,the mixtures of cyclopropyl phenyl ketone **1a** (0.3 mmol), α-ketoester **3** (0.3 mmol), and TMSOTf (0.3 mmol) were dissolved in 1,2-dichloroethane (DCE, 3 mL), and the reaction mixtures were heated to 60 °C for the necessary time. The reaction solution was cooled to room temperature, and was then quenched by addition of aqueous $NaHCO_3$ solution. The reaction mixture was extracted by dichloromethane (3 × 15 mL), and dried over anhydrous $MgSO_4$. The solvent was then removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate as an eluent to give the corresponding 5,6-dihydropyran-2-one product **5a** as a white solid (yield: 89%, 74 mg).

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Supporting Information Available: The spectroscopic data of the compounds shown in Table 3 and the detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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