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A Stereoselective Synthetic Route to 1,6-Dioxaspiro[4.4]non-3-en-2-ones from Cyclopropyl Alkyl Ketones and α-Ketoesters

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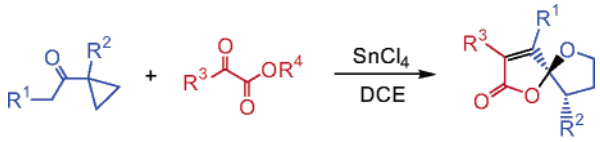
ABSTRACT

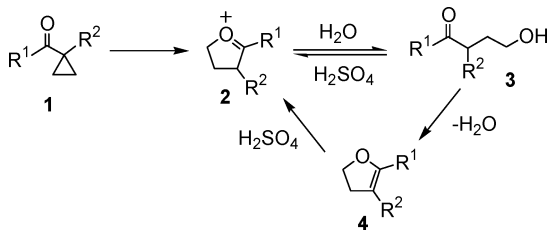


R^1, R^2, R^3 = aromatic, aliphatic group or H;
R^4 = methyl, ethyl or H.

The $SnCl_4$-mediated reactions of cyclopropyl alkyl ketones with α-ketoesters afford a novel method for the synthesis of 1,6-dioxaspiro[4.4]-non-3-en-2-ones with high stereoselectivities in moderate to good yields. This process is a sequential reaction involving a nucleophilic ring-opening reaction of the cyclopropane by H_2O, an aldol-type reaction, and a cyclic transesterification mediated by Lewis acid.

Cyclopropane-containing compounds, as versatile building blocks in organic synthesis, have been well understood.[1] The ring-opening reactions of cyclopropyl ketones are synthetically useful reactions that have been studied extensively. Previously, Ranfaing and Pittman independently reported the rearrangement reactions of simple cyclopropyl ketones **1** in concentrated sulfuric acid to produce oxolan-2-ylium ions **2**, γ-hydroxyketones **3**, and 2,3-dihydrofurans **4** as hydrolyzed products (Scheme 1).[2] Later, Nakai reported a convenient synthetic route to 1,4-dicarbonyl compounds based on the rearrangement of protonated cyclopropyl ketones.[3] Recently, we found that this promising rearrangement reaction could also be promoted by Lewis acids and subsequently developed mild synthetic methods for the preparation of 2-(2-hydroxyethyl)-1,3-diarylpropenones and 5,6-dihydropyran-2-ones from the reaction of cyclopropyl aryl ketones with arylaldehydes and α-ketoesters, respectively.[4] We envisioned that these two processes involve formation of γ-hydroxyketone **3** as a ring-opened product of the corresponding cyclopropane via nucleophilic attack by ambient H_2O in the

Scheme 1. Rearrangement of Cyclopropyl Ketones in Concentrated Sulfuric Acid



(1) (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733. (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (d) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20. (e) Kulinkovich, O. G. *Russ. Chem. Rev.* **1993**, *62*, 839. (f) Kulinkovich, O. G. *Polish J. Chem.* **1997**, 849. (g) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. (h) Wenkert, E. *Heterocycles* **1980**, *14*, 1703. (i) Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (j) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.

(2) (a) Ranfaing, P. J.; Combaut, G.; Giral, L. *Bull. Soc. Chim. Fr.* **1974**, 1048. (b) Pittman, C. U., Jr.; McManus, S. P. *J. Am. Chem. Soc.* **1969**, *91*, 5915.

(3) Nakai, T.; Wada, E.; Okawara, M. *Tetrahedron Lett.* **1975**, *16*, 1531.

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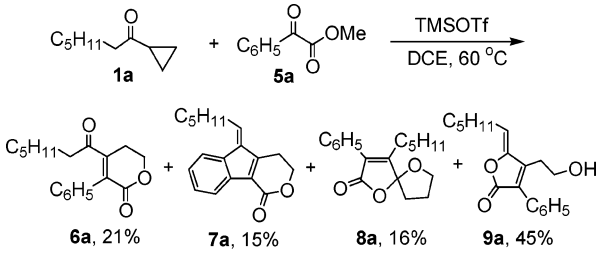
presence of a Lewis acid. During our ongoing investigations of this Lewis acid mediated reaction, we found that when using cyclopropyl alkyl ketones (R^1 = alkyl group, R^2 = H) as the substrate, the reaction produced an interesting spiro-γ-lactone along with other products. Herein, we report a novel method for the synthesis of 1,6-dioxaspiro[4.4]non-3-en-2-ones with high stereoselectivities by reaction of cyclopropyl alkyl ketones with α-ketoesters in the presence of the Lewis acid $SnCl_4$.

Initially we attempted to examine the reaction of cyclopropyl hexyl ketone with methyl benzoylformate (**5a**) in the presence of the Lewis acid TMSOTf (1.0 equiv). Surprisingly the reaction not only afforded the expected product 5,6-dihydropyran-2-one **6a** in 21% yield, but also gave the three additional products 9-hexylidene-1,9-dihydro-2*H*-3-oxafluoren-4-one (**7a**), 5-hexylidene-4-(2-hydroxyethyl)-3-phenyl-5*H*-furan-2-one (**9a**), and spiro-γ-lactone compound **8a** in 15%, 45%, and 16% yields, respectively (Scheme 2).[5]

Scheme 2. Reaction of Cyclopropyl Hexyl Ketone **1a** with α-Ketoester **5a** in the Presence of TMSOTf (1.0 equiv)



Spiro-γ-lactones constitute an important class of oxygen-containing heterocyclic compounds, and such groups can be found in many biologically active natural products. For example, the most widely studied spiro-γ-lactone compound, (+)-*Pyrenolide D*, exhibits significant cytotoxic activity toward HL-60 cells,[6] and *Massarinoline A* shows biological activity against *Bacillus subtilis* (ATCC 6051) and *Staphylococcus aureus* (ATCC 29213), affording zones of inhibition of 17 and 10 mm, respectively (Figure 1). The biological profiles of these compounds, in combination with their special structure have spawned many efforts to develop synthetic methods for the synthesis of spiro-γ-lactones. Therefore, our above findings encouraged us to explore a selective synthetic method for the spiro-γ-lactone from readily available cyclopropyl alkyl ketone and α-ketoester.

During our previous studies on the reaction of cyclopropyl aryl ketones with α-ketoesters,[4b] it was determined that all four of the products are formed via the same intermediate **3a**, which is a hydrolyzed product produced from cyclopropyl hexyl ketone and ambient H_2O in the presence of Lewis acid.

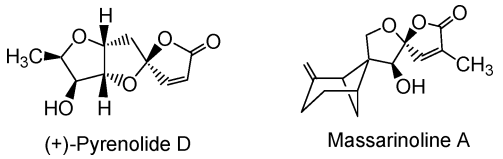
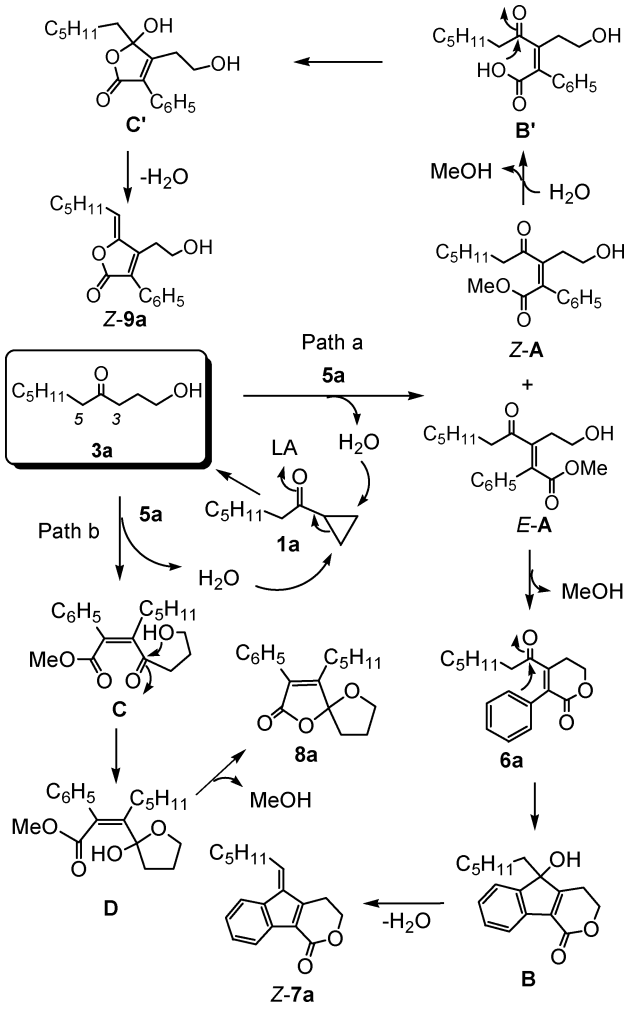


Figure 1. Important compounds bearing a spiro-γ-lactone moiety.

Scheme 3. Proposed Mechanism for the Reaction of Cyclopropyl Hexyl Ketone **1a** with α-Ketoester **5a**



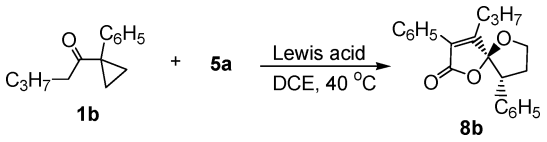
As shown in Scheme 3, if an aldol-type reaction occurs at the C-3 position (Path a), intermediate **A** could be formed as a mixture of *E*- and *Z*-isomers. Thus, product **6a** can be formed after an intramolecular transesterification process via intermediate *E*-**A**.[4b] The highly conjugated product *Z*-**7a** can be formed by dehydration of intermediate **B**, which itself can be derived from a Bradsher-type cyclization reaction (or

(4) (a) Shi, M.; Yang, Y.-H.; Xu, B. *Tetrahedron* **2005**, *61*, 1893. (b) Yang, Y.-H.; Shi, M. *J. Org. Chem.* **2005**, *70*, 10082−10085.

(5) The structures of all the products were determined by NMR spectroscopic data, microanalyses, and HRMS. The geometrical configuration of **7a** and **9a** was determined by NOESY (see the Supporting Information).

(6) (a) Nukina, M.; Hirota, H. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1158. (b) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 843. (3) Engstrom, K. M.; Mendoza, M. R.; Navarro-Villalobos, M.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1128.

Table 1. Optimization of the Reaction Conditions of Cyclopropyl Alkyl Ketone **1b** with Methyl Benzoylformate **5a**[a]



entry	Lewis acid (equiv)	time/h	yield/%[b] **8b**
1	TMSOTf (1.0)	10	60
2	TfOH (1.0)	10	66
3	$TiCl_4$ (1.0)	24	trace
4	$Sn(OTf)_2$ (1.0)	24	trace
5	$SnCl_4$ (1.0)	10	72
6	$SnCl_4$ (0.5)	24	34

[a] Reactions were carried out in parallel with 0.4 mmol of **1b** and 0.2 mmol of **5a** at 40 °C in DCE, please see the Supporting Information for details. [b] Isolated yields.

a Friedel−Crafts reaction) of **6a**. On the other hand, product *Z*-**9a** can be formed from Z-**A** via dehydration of intermediate **C′**, which itself can be produced via an intramolecular cyclization of intermediate **B′** derived from hydrolysis of Z-**A**. Alternatively, if the aldol-type reaction takes place at the C-5 position in γ-hydroxyketone **3a**, another intermediate, **C**, would be formed along with regeneration of an equivalent of H_2O, which can react with **1a** to initiate the next reaction cycle. Intramolecular nucleophilic attack by the terminal hydroxyl group at the ketone group can take place, leading to the corresponding cyclic intermediate **D** containing a hemiacetal hydroxyl group. From intermediate **D**, the corresponding product 1,6-dioxaspiro[4.4]non-3-en-2-one **8a** can be formed via an intramolecular transesterification. Overall, the formation of spiro-γ-lactone product **8a** is a cascade reaction involving a nucleophilic ring-opening reaction of the cyclopropane group by H_2O, an aldol type reaction, and an intramolecular transesterification. Moreover, ambient water is only required to initiate the process since the following necessary H_2O in the reaction is regenerated in situ during the aldol-type reaction.

On the basis of the above mechanistic analysis, we envisioned that the spiro-γ-lactone product **8** would be the predominant product obtained if a substituent is introduced at the position of cyclopropane adjacent to the carbonyl group in substrate **1** because it could give the corresponding intermediate **3** containing a substituent at C-3 position. This would prevent the reaction shown in Path a because the release of H_2O is prohibited. Therefore, we chose substrate **1b**, with a substituent phenyl group at the α-position of the carbonyl group, for study. As expected, the compound 3,9-diphenyl-4-propyl-1,6-dioxaspiro[4.4]non-3-en-2-one (**8b**) was obtained as a sole product with trans-configuration in 60% yield in the presence of 1.0 equiv of TMSOTf (Table 1, entry 1). The structure and the configuration of the **8b** were confirmed by X-ray crystallographic analysis (Figure 2).[7] Moreover, we also examined the effect of Brønsted acid and other Lewis acids on the reaction. As can be seen from

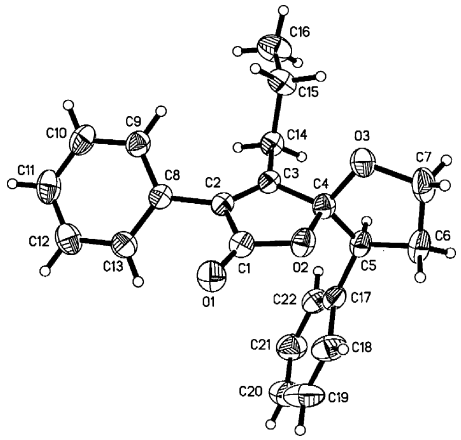


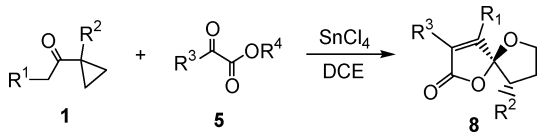
Figure 2. ORTEP drawing of **8b**.[7]

Table 1, the corresponding spiro-γ-lactone compound can be obtained in 60% yield in the presence of 1.0 equiv of TfOH in 1,2-dichloroethane (DCE) at 40 °C (Table 1, entry 2). On the other hand, $TiCl_4$ and $Sn(OTf)_2$ showed low catalytic abilities in this reaction and led to the recovery of most starting materials (Table 1, entries 3 and 4). Other metal triflates, such as $Zn(OTf)_2$, $Cu(OTf)_2$, $Ln(OTf)_2$, and $Yb(OTf)_3$, did not promote this reaction under the standard conditions. However, $SnCl_4$ showed high catalytic ability for the reaction and afforded **8b** in 72% within 10 h (Table 1, entrie 5). When the amount of $SnCl_4$ employed was decreased to 0.5 equiv, the yield of **8b** decreased to 34% yield (Table 1, entry 6). Therefore, 1.0 equiv of $SnCl_4$ is necessary for this reaction to give **8b** in good yield.

Next, the scope of this new and efficient synthetic protocol for the construction of 1,6-dioxaspiro[4.4]non-3-en-2-ones was investigated by employing a variety of cyclopropyl alkyl ketones and α-ketoesters under the optimized reaction conditions. As shown in Table 2, starting from 1-(1-phenylcyclopropyl)pentan-1-one **1b** and various α-ketoesters, the corresponding 1,6-dioxaspiro[4.4]non-3-en-2-ones **8a**−**g** were obtained in moderate to good yields (Table 2, entries 1−6). In the reactions of **1b** with various aryl α-ketoesters, an electronic effect was clearly observed. In general, aryl α-ketoesters having an electron-withdrawing group on the aromatic ring were more reactive and afforded the corresponding products **8** in higher yields (Table 2, entries 2 and 3). For aryl α-ketoesters **5d** and **5e** bearing an electron-donating substituent (methyl or methoxyl group) on the aromatic ring, the corresponding products **8e** and **8f** were obtained in lower yields under the standard conditions (Table 2, entries 4 and 5). This reactivity of α-ketoesters is also consistent with the role of the aldol acceptors in the reactions.

(7) The crystal data of **8b** have been deposited in the CCDC, number 287396. Empirical formula $C_{22}H_{22}O_3$; formula weight 334.40; crystal size 0.503 × 0.361 × 0.160; crystal color colorless; habit prismatic; crystal system monoclinic; lattice type primitive; lattice parameters a = 15.4115(17) Å, b = 15.2733(17) Å, c = 15.5755(18) Å, α = 90°, β = 101.178(2)°, γ = 90°, V = 3596.7(7) Å^3; space group $C2/c$; Z = 8; D_{calc} = 1.235 g/cm^3; F_{000} = 1424; R1 = 0.0526, wR2 = 0.1355; diffractometer Rigaku AFC7R.

Table 2. Reactions of Cyclopropyl Ketones **1b**−**e** with Various α-Ketoesters under These Optimized Conditions



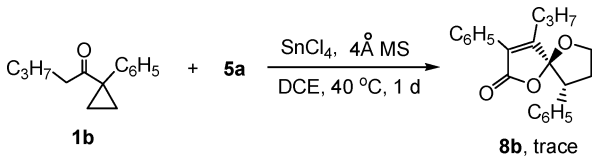
entry	R^1/R^2	R^3/R^4	yield/%[a] 8
1	**1b**, C_3H_7/C_6H_5	**5a**, C_6H_5/Me	**8b**, 72
2	**1b**, C_3H_7/C_6H_5	**5b**, *p*-ClC_6H_4/Et	**8c**, 85
3	**1b**, C_3H_7/C_6H_5	**5c**, *p*-FC_6H_4/Et	**8d**, 77
4	**1b**, C_3H_7/C_6H_5	**5d**, *p*-MeC_6H_4/Me	**8e**, 66
5	**1b**, C_3H_7/C_6H_5	**5e**, *p*-$MeOC_6H_4$/Et	**8f**, 41
6	**1b**, C_3H_7/C_6H_5	**5f**, EtOOC/Et	**8g**, 74
7	**1b**, C_3H_7/C_6H_5	**5g**, Me/Et	**8h**, trace
8	**1b**, C_3H_7/C_6H_5	**10**, Me/H	**8h**, 55
9	**1b**, C_3H_7/C_6H_5	**11**, C_6H_5/H	**8b**, 55
10	**1c**, $C_{3H}7/CH_3$	**5a**, C_6H_5/Me	**8i**, 63
11	**1d**, H/C_6H_5	**5a**, C_6H_5/Me	**8j**, 67
12	**1e**, C_6H_5/C_6H_5	**5a**, C_6H_5/Me	**8k**, 72

[a] Isolated yields.

On the other hand, diethyl ketomalonate **5f** showed high reactivity in this reaction and afforded the product **8g** in 74% yield due to the high electrophilicity of the carbonyl group in **5f** (Table 2, entry 6). As for aliphatic α-ketoesters, the reaction of ethyl pyruvate **5g**, an enolizable compound, with **1a** only afforded a trace amount of product **8h** (Table 2, entry 7). However, when pyrivic acid (**10**) was subjected to the reaction instead of **5g**, the yield of the product **8h** increased to 55% (Table 3, entrie 8). The reaction of oxophenylacetic acid **(11**) with **1b** also afforded the product **8b** in moderate yield (Table 2, entry 9). Furthermore, we examined the reaction of a variety of cyclopropyl alkyl ketones with methyl benzoylformate **5a** using the standard conditions (Table 2, entries 10−12). A series of 3-phenyl-1,6-dioxaspiro[4.4]non-3-en-2-ones **8i**−**k** were prepared in moderate to good yields. In summary, the reaction was found to be quite general for a variety of substrate with trans-configuration selectivity in which R^1, R^2, and R^3 could be aromatic and aliphatic groups.

To further understand the role of H_2O in the reaction, the control experiment shown in Scheme 4 was performed, where 60 mg of 4 Å molecular sieves was introduced to a 0.2 mmol scale reaction. As a consequence, the reaction became sluggish and gave only a trace amount of product **8b** after 1 day at 40 °C, indicating that H_2O does indeed play a key role in the initiation step of the reaction. On the other hand, we also examined the effect of the amount of H_2O on the reaction by addition of 1.0 equiv of H_2O into the reaction system. The result showed that the yield of the corresponding

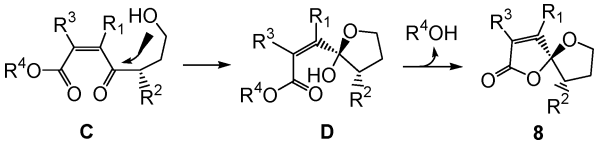
Scheme 4. Reaction of **1b** with **5a** Mediated by $SnCl_4$ in the Presence of 4 Å MS (60 mg)



product **8b** abruptly decreased to 39% under identical conditions. Therefore we believe that additional H_2O in this system does not favor the reaction. The best result was obtained with commercially available DCE solvent without any additional water.

Exclusive formation of products **8** with trans-configuration in the reaction can be rationalized by the proposed mechanism shown in Scheme 2. Because the terminal hydroxyl group in intermediate **C** would presumably prefer to attack from the opposite side of the R^2 functional group to avoid the steric interactions, this would lead exclusively to trans-configuration in the cyclization process (Scheme 5).

Scheme 5. Configuration in the Formation of Spiro-γ-lactone Moiety



In conclusion, we have found a reaction process involving the sequential ring-opening reaction of cyclopropyl alkyl ketones by H_2O, followed by an aldol-type reaction, and finally a transesterification reaction mediated by Lewis acids, which affords an efficient synthetic protocol for the preparation of 1,6-dioxaspiro[4.4]non-3-en-2-ones. Further work directed at elucidation of the detailed mechanisms of this process and the application of it to the synthesis of spiro-γ-lactone containing natural products is currently in progress.

Acknowledgment. We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (20472096, 203900502, and 20272069).

Supporting Information Available: The spectroscopic and analytic data, X-ray crystal data for **8b**, and a detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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