Synthesis of Alkylidenecyclopropanes via Thermal Cycloreversion of α-Spirocyclopropyl-β-Lactones

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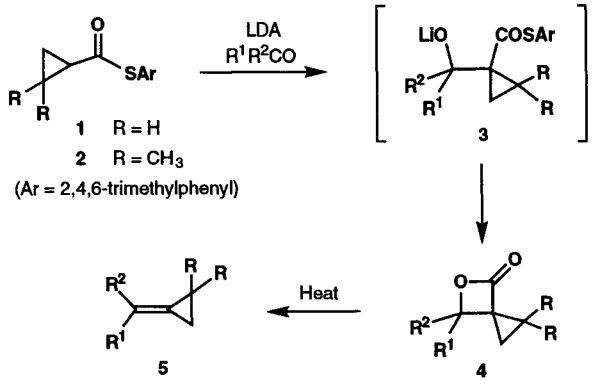
Dedicated to Professor E. J. Corey, an inspiring teacher and mentor whose contributions have greatly enriched the art and science of synthetic organic chemistry

Abstract: An efficient two-step synthesis of alkylidenecyclopropanes is reported based on the addition of metallated cyclopropyl thiol esters to carbonyl compounds. Thermolysis of the resulting α-spirocyclopropyl-β-lactones at 105-150 °C induces thermal [2+2] cycloreversion to furnish alkylidenecyclopropanes in good yield.

The chemistry of highly strained carbocycles is an area of longstanding interest to researchers concerned with the relationship of structure and reactivity in organic chemistry. Recently, strained ring compounds also have emerged as valuable building blocks in synthetic organic chemistry. Alkylidenecyclopropanes, for example, serve as useful synthons for the preparation of five-membered carbocyclic compounds.[3] Particularly noteworthy in this regard is the application of alkylidenecyclopropanes as TMM (trimethylenemethane) equivalents in the Ni and Pd catalyzed annulations investigated by Binger[3,4] and the thermal [3+2] cycloadditions developed in the laboratory of Nakamura.[5]

In this Communication we report a new strategy for the synthesis of alkylidenecyclopropanes from carbonyl compounds.[6] Scheme 1 outlines our approach, which involves an extension of our recent studies in the area of β-lactone chemistry.[7-9] In this earlier work, we showed that the addition of thiol ester enolates to carbonyl compounds provides the basis for a very convenient one-step synthesis of β-lactones. Under the proper conditions, the intermediate aldolates formed in this reaction undergo spontaneous cyclization to generate β-lactones in good to excellent yield. In conjunction with the well established stereospecific decarboxylation of β-lactones,[9] this chemistry also provides an attractive strategy for the stereocontrolled synthesis of substituted alkenes. Here we demonstrate the further extension of this methodology to the formation of highly strained olefins.

Pivotal to the success of our strategy was the identification of a thiol ester derivative that would participate in the desired metallation and aldol processes despite the considerable ring strain associated with the requisite enolate intermediate. Previous studies on small-ring ester and thiol ester enolates have revealed that these exceptionally reactive species prefer pyramidal rather than planar structures and display unusual reactivity including a propensity for self condensation.[10] In fact, reaction of the enolate derivative of *S*-phenyl cyclopropanethiocarboxylate with cyclohexanone affforded only 11% of the desired β-lactone (**6**) in addition to trimeric self-condensation products and other uncharacterizable materials. Similar unsatisfactory results were obtained from reactions of the corresponding 2-pyridyl thiol ester.

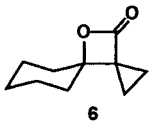
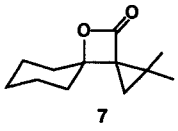
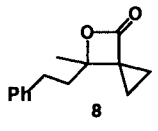
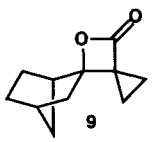
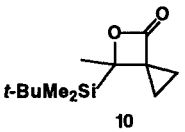


Scheme 1

Realization of the desired β-lactone synthesis was ultimately achieved by deployment of a hindered thiol ester derivative to suppress self-condensation.[10d] Excellent results were obtained by using the *S*-mesityl thiol ester **1**,[11] conveniently prepared in 81-88% yield by the reaction of commercially available cyclopropanecarbonyl chloride with mesitylenethiol[12,13] in CH_2Cl_2 containing 1 equiv of pyridine (0 to 25 °C, 2 h). Preparation of the substituted cyclopropyl thiol ester **2** was accomplished in 98% yield by the carbonyldiimidazole-mediated coupling of the corresponding carboxylic acid with mesitylenethiol according to the general procedure of Ohta.[14]

As illustrated in Table 1, a variety of ketones and acylsilanes combine with cyclopropyl thiol esters **1** and **2** to furnish α-spirocyclopropyl-β-lactones in good yield. In a typical procedure, the thiol ester is added dropwise to 1.05 equiv of LiN*i*-Pr_2 in THF at -78 °C, and after 40 min the ketone is added rapidly dropwise. The resulting mixture is stirred at -78 °C for 30 min and then allowed to warm to 0 °C over 2 h before being quenched by the addition of half-saturated NH_4Cl solution.[15] In the case of thiol ester **2**, the reaction mixture must be stirred at -40 °C for 40 min to complete metallation prior to recooling to -78 °C for addition of the ketone.

Table I. Synthesis of α-Spirocyclopropyl-β-lactones

entry	carbonyl compound	thiol ester	β-lactone	yield,[a] %
1	cyclohexanone	1	 **6**	77-81
2	cyclohexanone	2	 **7**	74
3	4-phenyl-2-butanone	1	 **8**	66-73
4	2-norbornanone	1	 **9**	45-55
5	CH_3COSi-*t*-$BuMe_2$	1	 **10**	62-65 (78-86)[b]

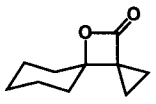
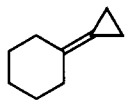
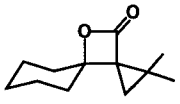
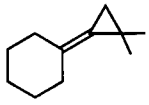
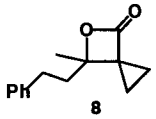
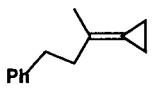
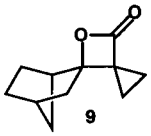
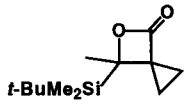
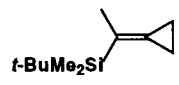
[a]Isolated yields of products purified by column chromatography on silica gel
[b]Yield corrected for unreacted thiol ester

In our earlier studies, we found that aldehydes react smoothly with a variety of thiol ester derivatives of *acyclic* carboxylic acids to provide β-lactones in good yield. Surprisingly, we have thus far been unable to obtain α-spirocyclopropyl-β-lactones from the addition of thiol ester **1** to aldehydes. Although the expected aldol addition

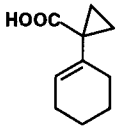
products can be isolated in 65-75% yield from reactions with benzaldehyde, cyclohexanecarboxaldehyde, and hydrocinnamaldehyde, thus far we have not been able to identify conditions for the efficient in situ cyclization of the aldolate intermediates. Other carbonyl compounds that fail to participate in the reaction include dicyclopropyl ketone and the conjugated alkynyl ketone 3-decyn-2-one. Also unsuccessful have been our attempts to employ phenyl or 2,4,6-trimethylphenyl esters in place of thiol esters for these reactions.[8a] For example, under various conditions, **6** is obtained in only 10-30% yield from the reaction of cyclohexanone with cyclopropyl aryl esters.

With efficient access to α-spirocyclopropyl-β-lactones in hand, we turned our attention to the key thermal [2+2] cycloreversion step. In most cases, decarboxylation is best achieved by heating a degassed solution of lactone in THF (threaded pyrex tube with teflon cap) at 105-120 °C for 64 to 70 h. However, in the case of lactone **7**, optimal conditions for decarboxylation involve heating at 150 °C for 18 h in acetonitrile. As noted previously, silica gel accelerates the cycloreversion process,[7,16] but interestingly, in the case of α-spirocyclopropyl-β-lactones significant quantities of elimination products (e. g. **16**) are produced under these conditions.

Table 2. Conversion of β-Lactones to Alkylidenecyclopropanes

entry	β-lactone	alkene	yield, %[a]
1	 **6**	 **11**	63
2	 **7**	 **12**	71
3	 **8**	 **13**	82 (91)[b]
4	 **9**	 **14**	70
5	 **10**	 **15**	78

[a]Isolated yields of products purified by column chromatography on silica gel.
[b]Yield corrected for unreacted β-lactone


16

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(2) Research Fellow of the Japan Society for the Promotion of Science.
(3) For a review on the chemistry of alkylidenecyclopropanes, see Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77.
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(11) For **1**: mp 28-30 °C; IR (CCl_4) 3005, 2960, 2910, 2850, and 1685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 2 H), 2.25 (s, 6H), 2.31 (s, 3 H), 2.16 (tt, *J*= 7.5, 5.6 Hz, 1 H), 1.19 (m, 2H), and 0.98 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 196.9, 142.5, 139.7, 129.1, 123.9, 21.9, 21.5, 21.0, and 10.5. Anal. Calcd for $C_{10}H_{14}O_2$: C, 70.87; H, 7.32. Found C, 70.72; H, 7.31.
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(15) Data for **6**: mp 82-84 °C; IR (CCl_4) 2930, 2855, and 1825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (m, 2 H), 1.2-1.8 (m, 8 H), 1.21 (dd, *J*= 7.1, 6.4 Hz, 2 H), and 1.04 (dd, *J*= 7.1, 6.4 Hz, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.1, 83.0, 39.2, 34.1, 24.6, 22.4, and 8.0. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found C, 72.13; H, 8.43.
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