

Formal [4+2] Cycloaddition of di-*tert*-Butyl 2-Ethoxycyclobutane-1,1-dicarboxylate with Ketones or Aldehydes and Tandem Lactonization

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A catalytic amount of tin(IV) chloride catalyzed formal [4+2] cycloaddition reaction of di-*tert*-butyl 2-ethoxycyclobutane-1,1-dicarboxylate with ketones or aldehydes to give diethyl 6-ethoxydihydro-2*H*-pyran-3,3(4*H*)-dicarboxylates, whereas two equivalents of trimethylsilyl triflate promoted tandem [4+2] cycloaddition and lactonization to afford 3-oxo-2,6-dioxabicyclo[2.2.2]octane-4-carboxylate esters.

Key words donor-acceptor cyclobutane; [4+2] cycloaddition; tandem lactonization

Donor-acceptor (DA) cyclobutanes have been studied extensively¹⁾ in recent years as well as DA cyclopropanes.^{2–4)} DA cyclobutanes reacted with aldehydes,^{5–7)} imines,⁸⁾ or nitrones⁹⁾ to form [4+2] or [4+3] cycloadducts. As donor substituents of DA cyclobutane, aryl⁶⁾ and cobalt-alkyne complex⁵⁾ were studied before we started this study. We found that 3-ethoxycyclobutanones were activated by Lewis acid to form a 1,4-zwitter ionic intermediate which reacted with various aldehydes and ketones.¹⁰⁾ It was then expected that 2-ethoxycyclobutane-1,1-dicarboxylate ester **1** bearing an ethoxy group as a donor substituent would be a useful DA cyclobutane for formal [4+2] cycloaddition reaction. That is, it was thought that zwitter ionic intermediate **2** would be formed from **1** by treatment with Lewis acid, and **2** would react with carbonyl compounds (Chart 1). Pagenkopf recently reported a similar [4+2] cycloaddition of **1** only with aldehydes.⁷⁾ We report here a more widely applicable [4+2] cycloaddition reaction of DA cyclobutane **1** with ketones and also tandem lactonization reaction.

DA cyclobutane **5** was readily prepared in 85% yield by the reaction between di-*t*-butyl methylenemalonate **4**¹¹⁾ and ethyl vinyl ether in the presence of zinc bromide (Eq. 1).

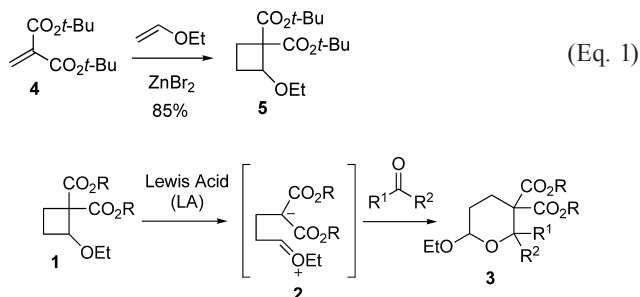


Chart 1. Formal [4+2] Cycloaddition between DA Cyclobutane **1** and Ketones or Aldehyde

Reaction conditions were screened by the reaction between DA cyclobutane **5** and cyclohexanone. Pagenkopf reported that Yb(OTf)₃ catalyzed [4+2] cycloaddition reaction of diethyl 2-ethoxycyclobutane-1,1-dicarboxylate with aldehydes.⁷⁾ However, the use of a catalytic amount (15 mol%) of Yb(OTf)₃ did not catalyze the reaction of **5** with cyclohexanone (Table 1, entry 1). The use of catalytic amounts of BF₃·OEt₂, Me₃SiOTf, and TiCl₄ was found to catalyze this reaction to afford the desired product **6** in 64%, 35%, and 4% yields, respectively (entries 2–4). A catalytic amount (0.2 eq) of SnCl₄ catalyzed the reaction most efficiently to afford the cycloadduct **6** in 90% yield (entry 5). Interestingly, it was found that lactone **7** was isolated in low yields when BF₃·OEt₂ or Me₃SiOTf was employed. After optimization of reaction conditions, lactone **7** was directly obtained from **5** in 62% yield by using two equivalents of Me₃SiOTf (entry 6).

A plausible reaction mechanism for formation of lactone **7** is shown in Chart 2. The initially formed tetrahydropyran **6** was activated with Me₃SiOTf to give oxocarbenium ion **8** *in situ*. Intramolecular attack of the *t*-butyl ester group to the part of oxocarbenium ion afforded lactone **7**.

Next, scope and limitations of the present [4+2] cycloaddition of **5** and tandem lactonization were investigated by using various ketones and aldehydes (Table 2). Two methods were employed for obtaining tetrahydropyran **9** or lactone **10**: tetrahydropyran **9** was obtained by using a catalytic amount (0.2 eq) of SnCl₄ at –78°C for 10 min (Method A), whereas lactone **10** was obtained as the major product by using two equivalents of Me₃SiOTf at –78°C for 10 min (Method B). Various ketones and aldehydes reacted with **5** to form tetrahydropyran **9** in good to high yields (entries 1, 3, 5, 7, 9, 11). Lactones **10a–c** were formed directly from ketones in 35–42% yields (entries 2, 4, 6), while aldehydes reacted with **5** to afford lactones **10d–f** in 56–66% yields with moderate *trans*-selectivity (entries 8, 10, 12). The structure of **10** was unambiguously determined by X-ray crystallography of *trans*-**10d**.¹²⁾

In summary, di-*tert*-butyl 2-ethoxycyclobutane-1,1-dicarboxylate **5** reacted with ketones and aldehydes to give formal [4+2] cycloadducts, tetrahydropyran derivatives, by the catalytic use of SnCl₄. Also, treatment of **5** with two equivalents of Me₃SiOTf directly gave 3-oxo-2,6-dioxabicyclo[2.2.2]octane-4-carboxylate ester by tandem lactonization reaction.

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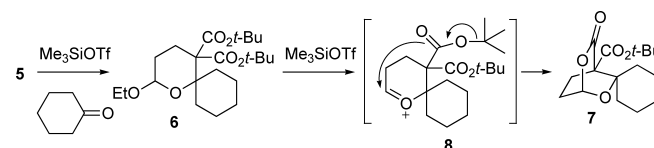
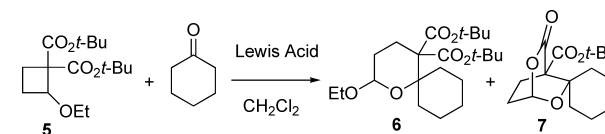


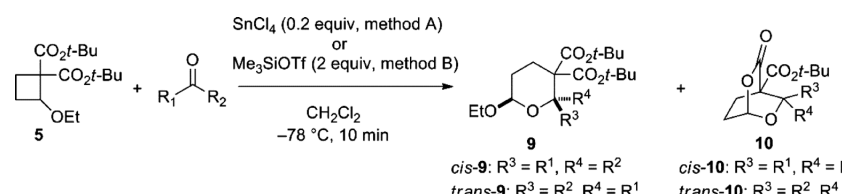
Chart 2. Mechanism for Tandem Formation of Bicyclic Lactone **7** from **5**

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Table 1. Effect of Lewis Acid on Selective Formation of **6** or **7**


Entry	Lewis acid (eq)	Conditions	6 ^{b)}	7 ^{b)}
1	Yb(OTf) ₃ (0.15)	0°C, 15 min	Trace	0
2	BF ₃ ·OEt ₂ (0.5)	−78°C, 27 h	64	8
3	Me ₃ SiOTf (0.1)	−78°C, 10 min	35	10
4	TiCl ₄ (0.5)	−78 to −45°C, 4 h	4	0
5	SnCl ₄ (0.2)	−78°C, 10 min	96	Trace
6	Me ₃ SiOTf (2)	−78°C, 10 min	14	62

a) Cyclobutane **5** (1.5 eq) and cyclohexanone (1.0 eq) were used. b) Isolated yield (%).

Table 2. Formal [4+2] Cyclization between DA Cyclobutane **5** and Ketones or Aldehydes to Give Tetrahydropyran **9** or Lactone **10**^{a)}


Entry	R ¹	R ²	Method ^{b)}	9 (% yield) ^{c)}	10 (% yield) ^{c)}
1	(CH ₂) ₃		A	9a (93)	10a (nd ^{d)})
2			B	9a (12)	10a (40)
3	(CH ₂) ₄		A	9b (72)	10b (2)
4			B	9b (trace)	10b (42)
5	Me	Me	A ^{e)}	9c (70)	10c (trace)
6			B ^{f)}	9c (nd)	10c (35)
7	Ph	H	A	9d (93), 43:57	10d (nd)
8			B	9d (14), 29:71	10d (62), 11:89
9	<i>n</i> -C ₇ H ₁₅	H	A	9e (93), 33:67	10e (nd)
10			B	9e (11), 31:69	10e (51), 9:91
11	<i>i</i> -Pr	H	A	9f (79), 24:76	10f (nd)
12			B	9f (nd)	10f (66), 17:83

a) Cyclobutane **5** (1.5 eq) and ketone or aldehyde (1.0 eq) were used. b) Method A: SnCl₄ (0.2 eq). Method B: Me₃SiOTf (2 eq). c) Isolated yield and cis/trans ratio.

d) Not detected. e) Cyclobutane **5** (1.0 eq), acetone (1.3 eq), and SnCl₄ (0.13 eq) were used. f) Cyclobutane **5** (1.0 eq), acetone (1.3 eq), and Me₃SiOTf (1.3 eq) were used.

References and Notes

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- Cell length a: 12.818(3), b: 6.381(2), c: 19.484(5), cell angle α: 90, β: 106.356(7), γ: 90, cell volume: 1529.2(7), space group: *P*2₁/*c*, *Z* value: 4, *R*-factor: 0.0653.