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

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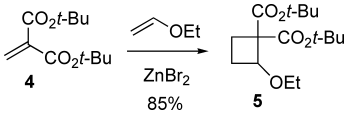
A catalytic amount of tin(IV) chloride catalyzed formal [4+2] cycloaddition reaction of di-*tert*-butyl 2-ethoxycyclobutane-1,1-carboxylate with ketones or aldehydes to give diethyl 6-ethoxydihydro-2*H*-pyran-3,3(4*H*)-dicarboxylates, whereas two equivalents of trimethylsilyl triflate promoted tandem [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 extensively[1] in recent years as well as DA cyclopropanes.[2—4] DA cyclobutanes reacted with aldehydes,[5—7] imines,[8] or nitrones[9] to form [4+2] or [4+3] cycloadducts. As donor substituents of DA cyclobutane, aryl[6] and cobalt-alkyne complex[5] 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).



(Eq. 1)

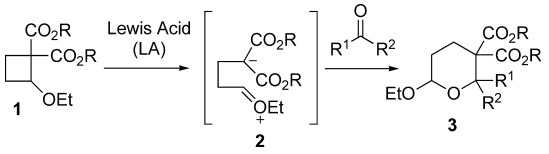


Chart 1. Formal [4+2] Cycloaddition between DA Cyclobutane **1** and Ketones or Aldehyde

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 $BF_3{\cdot}OEt_2$, Me_3SiOTf, and $TiCl_4$ 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 $SnCl_4$ 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 BF_3-OEt_2 or Me_3SiOTf was employed. After optimization of reaction conditions, lactone **7** was directly obtained from **5** in 62% yield by using two equivalents of Me_3SiOTf (entry 6).

A plausible reaction mechanism for formation of lactone **7** is shown in Chart 2. The initially formed tetrahydropyrane **6** was activated with Me_3SiOTf 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 $SnCl_4$ at −78°C for 10 min (Method A), whereas lactone **10** was obtained as the major product by using two equivalents of Me_3SiOTf 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-ethoxycylobutane-1,1-dicarboxylate **5** reacted with ketones and aldehydes to give formal [4+2] cycloadducts, tetrahydropyran derivatives, by the catalytic use of $SnCl_4$. Also, treatment of **5** with two equivalents of Me_3SiOTf directly gave 3-oxo-2,6-dioxabicyclo[2.2.2]-octane-4-carboxylate ester by tandem lactonization reaction.

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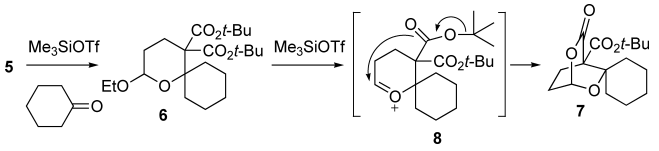

Chart 2. Mechanism for Tandem Formation of Bicyclic Lactone **7** from **5**

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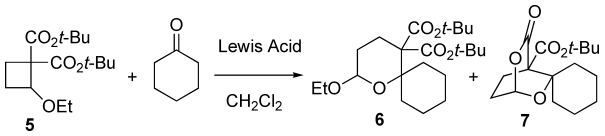
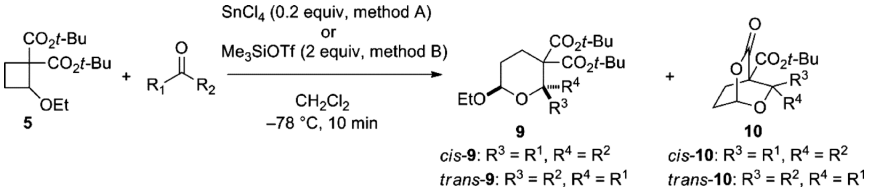
Table 1. Effect of Lewis Acid on Selective Formation of **6** or **7**



Entry	Lewis acid (eq)	Conditions	**6**[b]	**7**[b]
1	$Yb(OTf)_3$ (0.15)	0°C, 15 min	Trace	0
2	$BF_3{\cdot}OEt_2$ (0.5)	−78°C, 27 h	64	8
3	Me_3SiOTf (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_3SiOTf (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	n-C_7H_{15}	H	A	**9e** (93), 33 : 67	**10e** (nd)
10			B	**9e** (11), 31 : 69	**10e** (51), 9 : 91
11	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: $SnCl_4$ (0.2 eq). Method B: Me_3SiOTf (2 eq). *c*) Isolated yield and cis/trans ratio. *d*) Not detected. *e*) Cyclobutane **5** (1.0 eq), acetone (1.3 eq), and $SnCl_4$ (0.13 eq) were used. *f*) Cyclobutane **5** (1.0 eq), acetone (1.3 eq), and Me_3SiOTf (1.3 eq) were used.

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12) 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: $P2_1/c$, Z value: 4, R-factor: 0.0653.