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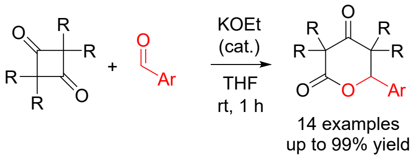

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Alkoxide-catalyzed ring expansion of 1,3-cyclobutanediones with aldehydes

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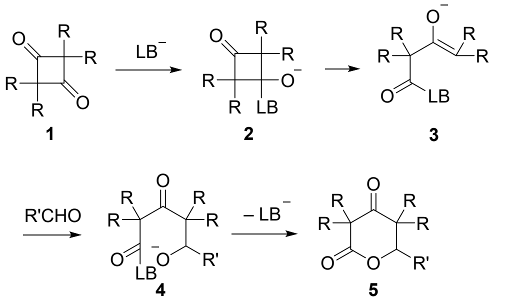
ABSTRACT

1,3-Cyclobutanediones (dialkyl ketene dimer) reacted with various aromatic aldehydes to give six-membered cyclic β-keto esters by using a catalytic amount of potassium ethoxide. Effects of alkoxide catalysts and spiro cyclic groups at the 2,4-positions of 1,3-cyclobutanediones were investigated.

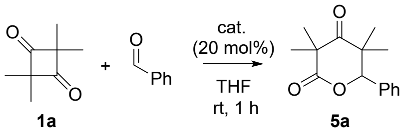
Cyclobutane derivatives are important synthetic blocks and they show unique reactivities by cleaving their strained four-membered rings.[1] Tetraalkyl 1,3-cyclobutanediones have been prepared by dimerization of dialkyl ketene, and their ring-cleavage reactions have been studied by using alcohols,[2] amines,[3] phosphites,[4] and phosphorus amides.[5] Ring expansions of the four-membered ring of 1,3-cyclobutanediones to a five-membered compounds were reported in syntheses of γ-lactams,[6] a γ-lactone,[7] and a cyclopentanone derivative.[8] However, there has been no report about ring expansion to six-membered compounds from 1,3-cyclobutanediones except formation of 1,3,5-cyclohexanetriones.[9] We report here a new ring expansion reaction of tetraalkyl 1,3-cyclobutanediones **1** to six-membered cyclic β-keto esters **5** by reactions with aldehydes (Scheme 1). We envisioned that a Lewis base catalyst would react with 1,3-cyclobutanedione **1** to form **2** and that ring cleavage of cyclobutanone **2** would give an enolate **3**. Aldol reaction of **3** with an aldehyde would afford **4**, and its intramolecular cyclization would give **5** with regeneration of the catalyst. Highly substituted β-keto δ-lactones **5**, which are seen in some bioactive natural products such as lankacidine C[10] and magromicins,[11] have been prepared by Reformatsky reactions of halo β-keto esters[12] and Claisen-aldol tandem reactions.[13]



Scheme 1. Lewis base-catalyzed ring expansion of 1,3-cyclobutanediones **1** with aldehydes to β-keto esters **5**.

A suitable Lewis base catalyst for the ring expansion reaction was explored in the reaction of 1.5 equivalents of tetramethyl-1,3-cyclobutanedione (**1a**) with benzaldehyde (Table 1). It was found that potassium alkoxides catalyzed the expected reaction and potassium ethoxide was the most effective one (entry 2).[14] Potassium ethoxide in THF solution was freshly prepared by the reaction of KH and ethanol in THF and the solution was stirred at room temperature for 1-2 h.[15] Gram-scale synthesis of **5a** was performed by using KOEt as a catalyst and 1.2 g (97%) of **5a** was obtained. Sodium ethoxide did not catalyze the present reaction (entry 7), and other Lewis bases including DABCO and Bu_3P did not catalyze the reaction even in refluxing THF (entries 8 and 9). The use of an equimolar amount of **1a** resulted in lowering the yield of **5a** (entry 10).

Table 1. Screening of catalysts.[a]



entry	cat.	conditions	yield (%)
1	KOMe	rt, 1 h	35
2	KOEt	rt, 1 h	95 (97)[b]
3	KOPr	rt, 1 h	21
4	KO*i*Pr	rt, 1 h	10
5	KO*t*Bu	rt, 1 h	23
6	KOPh	rt, 1 h	0
7	NaOEt	rt, 1 h	0
8[c]	DABCO	reflux, 6 h	0
9[c]	Bu_3P	reflux, 4 h	0
10[c]	KOEt	rt, 12 h	55

[a] Reaction conditions: 1,3-cyclobutanedione **1a** (1.5 equiv), benzaldehyde (1.0 equiv, 0.2 mmol), catalyst (20 mol%), THF, rt, 1 h.

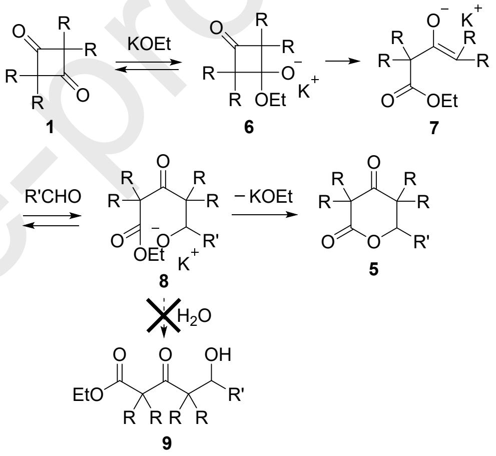
[b] Benzaldehyde (5.0 mmol) was used.

[c] 1,3-Cyclobutanedione **1a** (1.0 equiv) was used.

The scope and limitations of the present reaction were studied by using various aldehydes and cyclobutanediones (Table 2). Various benzaldehyde derivatives having electron-withdrawing groups or electron-donating groups smoothly reacted with 1,3-cyclobutanedione **1a** to give corresponding six-membered β-keto esters **5b**-**f** in high yields (94-99%). It was noted that the carbomethoxy group of **5c** was not affected under the present reaction conditions. 1-Naphthylaldehyde and 2-naphthylaldehyde also reacted effectively with **1a** to afford **5g** and **5h** in 98% and 97% yields, respectively. The reaction of cinnamaldehyde, an α,β-unsaturated aldehyde, proceeded incompletely even in refluxing THF and **5i** was obtained in 44% yield. The reaction of 3-thiophenecarboxaldehyde proceeded smoothly at room temperature to give **5j** in 99% yield, but the reaction of 2-furfural proceeded slowly at room temperature. Addition of a catalytic amount of 18-crown-6 in refluxing THF slightly improved the yield of the product **5k** from 2-furfural. However, the reaction with aliphatic aldehydes and ketones did not give the desired products. The reaction with 3-phenylpropanal afforded complex mixtures, and the reactions with isobutyraldehyde, pivalaldehyde, benzophenone, and cyclohexanone did not proceed. In the reactions of spirocyclobutanediones, it was found that the yields of products **5l-n** were lower as the ring sizes of spiro rings were larger. In these cases, the starting materials were detected even after a prolonged reaction time, and raising the reaction temperature to refluxing THF did not improve the yields of the desired products **5l-n**.[16]

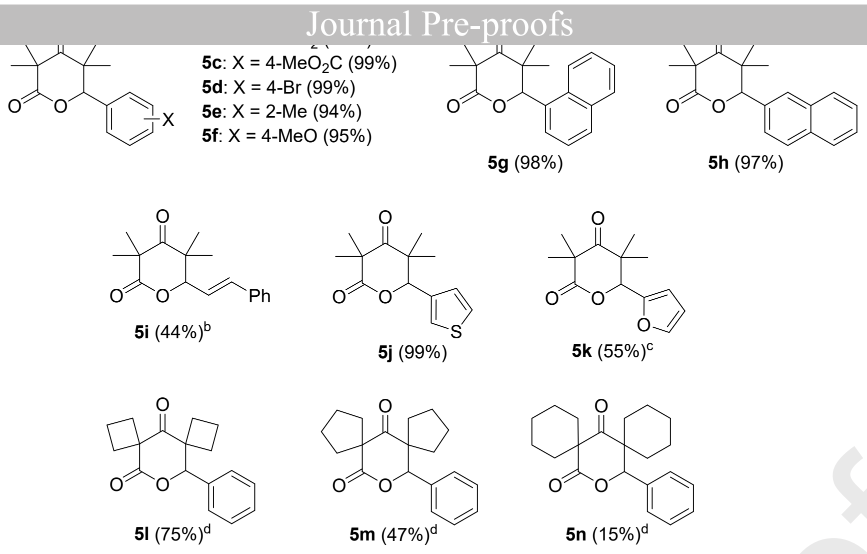
Table 2. Scope and limitations.[a]

A proposed mechanism for the present ring-enlargement of 1,3-cyclobutanediones **1** with aldehydes to six-membered β-keto esters **5** is shown in Scheme 2. Nucleophilic addition of potassium ethoxide to the 1,3-butanedione **1** forms **6** and a retro-Claisen reaction which is accelerated by cleaving a four-membered ring gives an enolate **7**. As the steric hindrance of alkoxides increases, the nucleophilic addition of alkoxides is thought to proceed more sluggishly (Table 1, entries 2-5). The excellent activity of an ethoxide ion might be explained by relative nucleophilicity of alkoxides.[14b] A weak nucleophile such as potassium phenoxide can not attack to the 1,3-butanedione **1** to form **2** (Table 1, entries 6-9). Aldol reaction of **7** with an aldehyde gives **8** and its intramolecular cyclization affords **5**. In the experiments described above, a linear aldol product **9** was not obtained even in the cases which gave low yields of desired products **5**. Therefore, the intramolecular cyclization of **8** proceeds smoothly and a reverse reaction of **5** with potassium ethoxide to **8** is suppressed by the presence of a more electrophilic compound **1** toward potassium ethoxide.



Scheme 2. Potassium ethoxide-catalyzed ring expansion of 1,3-cyclobutanediones **1** with aldehydes to six-membered β-keto esters **5**.

In conclusion, we have developed a KOEt-catalyzed ring-enlargement reaction of 1,3-cyclobutanediones with aldehydes to six-membered β-keto esters. Aromatic aldehydes including acid-labile ones reacted to give the desired products. Potassium ethoxide showed outstanding catalytic activity in the present ring enlargement reaction.



5c: X = 4-MeO$_2$C (99%)
5d: X = 4-Br (99%)
5e: X = 2-Me (94%)
5f: X = 4-MeO (95%)

5g (98%)

5h (97%)

5i (44%)[b]

5j (99%)

5k (55%)[c]

5l (75%)[d]

5m (47%)[d]

5n (15%)[d]

[a] Reaction conditions: 1,3-cyclobutanedione **1** (1.5 equiv), aldehyde (1.0 equiv), KOEt (20 mol%), THF, rt, 1 h. Numbers in parentheses are isolated yields.

[b] Reaction conditions: rt to reflux, 6 h.

[c] Reaction conditions: KOEt (20 mol%) and 18-crown-6 (20 mol%) , reflux, 22 h.

[d] Reaction conditions: rt, 3 h.

Acknowledgments

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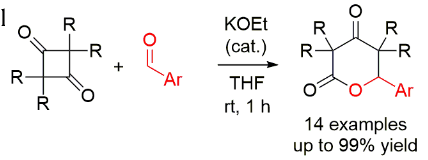
References and notes

1. (a) Marek, I.; Masarwa, A.; Delaye, P.-O.; Leibeling, M., *Angew. Chem., Int. Ed.* **2015**, *54*, 414-429; (b) Matsuo, J., *Tetrahedron Lett.* **2014**, *55*, 2589-2595; (c) Reissig, H.-U.; Zimmer, R., *Angew. Chem., Int. Ed.* **2015**, *54*, 5009-5011; (d) Vemula, N.; Pagenkopf, B. L., *Org. Chem. Front.* **2016**, *3*, 1205-1212.
2. Hasek, R. H.; Elam, E. U.; Martin, J. C.; Nations, R. G., *J. Org. Chem.* **1961**, *26*, 700-704.
3. (a) Hasek, R. H.; Elam, E. U.; Martin, J. C., *J. Org. Chem.* **1961**, *26*, 4340-4344; (b) Hansen, G. R.; DeMarco, R. A., *J. Heterocyclic Chem.* **1969**, *6*, 291-295.
4. Bentrude, W. G.; Johnson, W. D.; Khan, W. A.; Witt, E. R., *J. Org. Chem.* **1972**, *37*, 631-642.
5. Bentrude, W. G.; Johnson, W. D.; Khan, W. A., *J. Org. Chem.* **1972**, *37*, 642-649.
6. Orlando, C. M., Jr.; Gianni, M. H., *J. Org. Chem.* **1969**, *34*, 1154-1156.
7. Johnson, P. Y.; Yee, J., *J. Org. Chem.* **1972**, *37*, 1058-1059.
8. Venneri, P. C.; Warkentin, J., *Can. J. Chem.* **2000**, *78*, 1194-1203.
9. (a) Erickson, J. L. E.; Kitchens, G. C., *J. Org. Chem.* **1962**, *27*, 460-463; (b) Pregaglia, G. F.; Binaghi, M., *J. Org. Chem.* **1963**, *28*, 1152-1154; (c) Saaidi, P.-L.; Doridot, G.; Jeanneau, E.; Hasserodt, J., *Monatsh. Chem.* **2007**, *138*, 1011-1018.
10. Yao, Y.; Cai, L.; Seiple, I. B., *Angew. Chem., Int. Ed.* **2018**, *57*, 13551-13554.
11. (a) Nakashima, T.; Iwatsuki, M.; Ochiai, J.; Kamiya, Y.; Nagai, K.; Matsumoto, A.; Ishiyama, A.; Otoguro, K.; Shiomi, K.; Takahashi, Y.; Omura, S., *J. Antibiot.* **2014**, *67*, 253-260; (b) Nakashima, T.; Kamiya, Y.; Iwatsuki, M.; Sato, N.; Takahashi, Y.; Omura, S., *J. Antibiot.* **2015**, *68*, 220-222; (c) Nakashima, T.; Kamiya, Y.; Iwatsuki, M.; Takahashi, Y.; Omura, S., *J. Antibiot.* **2014**, *67*, 533-539.
12. (a) Shchepin, V. V.; Korzun, A. E.; Nedugov, A. N.; Sazhneva, Y. K.; Shurov, S. N., *Russ. J. Org. Chem.* **2002**, *38*, 248-250; (b) Shchepin, V. V.; Korzun, A. E.; Sazhneva, Y. K., *Russ. J. Org. Chem.* **2004**, *40*, 1500-1502; (c) Shchepin, V. V.; Korzun, A. E.; Sazhneva, Y. K.; Nedugov, A. N., *Chem. Heterocycl. Compd.* **2001**, *37*, 374-375; (d) Shchepin, V. V.; Sazhneva, Y. K.; Litvinov, D. N., *Russ. J. Gen. Chem.* **2003**, *73*, 596-602.
13. Tanabe, Y.; Hamasaki, R.; Funakoshi, S., *Chem. Comm.* **2001**, 1674-1675.
14. (a) Phan, T. B.; Mayr, H., *Can. J. Chem.* **2005**, *83*, 1554-1560; (b) Reeve, W.; Erikson, C. M.; Aluotto, P. F., *Can. J. Chem.* **1979**, *57*, 2747-2754.
15. Agitation of KOEt solution in THF at room temperature for 5 min did not give satisfactory results (**5a** 15%).
16. The use of KOMe instead of KOEt did not improve the yield of **5n** (11%).

Supplementary Material

Supplementary data associated this article can be found in the onl



- Formal [4+2] cycloaddition of 1,3-cyclobutanediones and aldehydes
- Effects of nucleophilic catalysts for activation of 1,3-cyclobutanediones
- Mechanism of the ring enlargement of 1,3-cyclobutanediones to six-membered β-keto esters