JOC*Note*

Zinc-Mediated Ring-Expansion and Chain-Extension Reactions of β-Keto Esters

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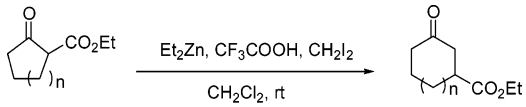

The reaction of cyclic β-keto esters with $CF_3CO_2ZnCH_2I$ provided the corresponding ring-expanded products in moderate to good yields. Although α-substituted acyclic β-keto esters reacted with much less efficient, chain-extension reaction of simple β-keto esters also proceeded effectively to generate γ-keto esters in high yields.

Medium size (8-, 9-, and 10-membered) rings are found to be the structural core of a number of biologically important natural products.[1] Ring-expansion reaction of cyclic β-keto esters is a useful method for synthesis of medium- and large-membered ring compounds.[2] An efficient ring expansion is the use of a free radical.[3] Treatment of α-halomethyl and α-(3-halopropyl) cyclic β-keto esters with tributyltin hydride and AIBN in refluxing benzene solution gave one- and three-carbon ring-expanded cyclic keto esters in good yields, respectively. A complementary method using indium-mediated Barbier-type reaction of cyclic β-keto esters in water provided two-carbon ring-expanded products.[4] Recently, it was reported that one-carbon ring-expansion and chain-extension reactions of β-keto esters proceeded smoothly with zinc powder in refluxing aqueous alcohol.[5] These methods are efficient for ring-expansion of the β-keto esters, and these reactions are very attractive for the advantage of ease of execution and specific radical reaction.

In 1997, Zercher reported an operationally simple and efficient approach to the chain extension of β-keto esters using the Furukawa reagent, ethyl(iodomethyl)zinc.[6] The reaction worked well for α-unsubstituted β-keto esters,[7] β-keto amides,[8] as well as β-keto phosphonates.[9] However, ring-expansion of cyclic β-keto esters reacted with diminished efficiency.[6] Our interest in CF_3COOH enhancing the reactivity of zinc reagent has led us to find that treatment of zinc species $CF_3CO_2ZnCH_2I$ with cyclic β-keto esters can afford the corresponding ring-expanded products in moderate to good yields (Table 1).[10]

The zinc species $CF_3CO_2ZnCH_2I$ can be readily prepared by stirring $ZnEt_2$ with CF_3CO_2H in CH_2Cl_2 at 0 °C for 30 min, followed by addition of CH_2I_2. Treatment of benzoclclic β-keto ester **1** with the in situ generated $CF_3CO_2ZnCH_2I$ (3.0 equiv) in CH_2Cl_2 at room temperature for 8 h afforded the desired ring-expansion product **2** in 83% yield. The reaction proceeded smoothly in 2.5 equiv of $CF_3CO_2ZnCH_2I$ for 5 h with a little low yield (69%). The choice of Et_2O and toluene as solvent afforded the product **2** in 25% and 14% yields, respectively.

Substrate **3** also gave the ring-expansion product **4** in a good yield. A considerable low yield was obtained in cyclic β-keto ester **5**, which was derived from 1-indanone. Lengthy reaction time gave no effect on yield. β-Keto ester **9** derived from cyclohexanone could afford the ring-expanded product **10** in 67% yield. Likewise, 7-, 8-, and 12-membered ring β-keto esters (**11**, **13**, and **15**) were expanded similarly with zinc species $CF_3CO_2ZnCH_2I$ to give 8-, 9-, and 13-membered ring products (**12**, **14**, and **16**) in good yields, respectively. However, β-keto ester **7** derived from cyclopentanone reacted with diminished efficiency, providing the corresponding ring-expanded product in only 20% yield. Low yields were found for substrates **5** and **7**, presumably due to the strain five-membered ring.

Chain extension of acyclic β-keto esters also proceeded effectively to generate γ-keto esters in good to high yields. These results were summarized in Table 2. Exposure of substrate **17** with 3 equiv of $CF_3CO_2ZnCH_2I$ at room temperature for 8 h gave the corresponding chain-extended product **18** in 90% yield. The efficiency of the reaction was not hampered by the presence of bulky tert butyl group or phenyl group. But it should be noted that the reaction of ethyl acetoacetate **25** with $CF_3CO_2ZnCH_2I$ at room temperature gave trance amount of the desired product **26**, and providing unidentified mixtures. Fortunately, the chain-extended product **26** was obtained in

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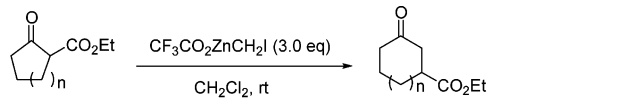
TABLE 1. Ring Expansion of β-Keto Esters Using $CF_3CO_2ZnCH_2I$



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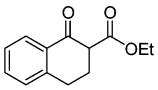
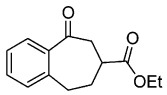
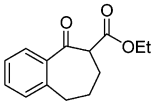
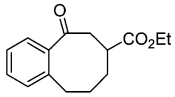
1		8		83
2		5		72
3[b]		5		69
4[c]	**1**	12	**2**	25
5[d]		11		14
6		8		75
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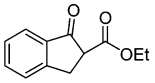
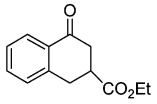
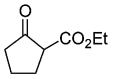
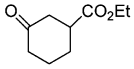
7		2		46
	5		**6**	
8		10		20
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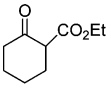
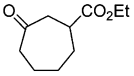
9		12		67
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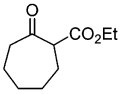
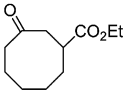
10		8		88
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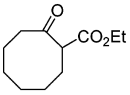
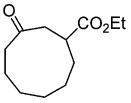
11		12		72
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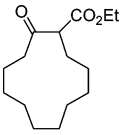
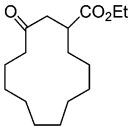
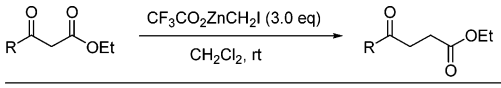
12		12		70
	15		**16**	

[a] Isolated yields. [b] 2.5 equiv of $CF_3CO_2ZnCH_2I$ was used. [c] Performed in Et_2O solvent. [d] Performed in toluene solvent.

good yield when the reaction was carried out at 0 °C. β-Keto esters which possessed olefin functionality were susceptible to concomitant cyclopropanation, since olefins could be converted into cyclopropanes efficiently by this zinc species $CF_3CO_2ZnCH_2I$.[11,12] Substrate **27**, which contained electron-poor olefin, underwent selective chain-extended reaction in preference to cyclopropanation of the olefin under our standard reaction conditions. However, β-keto ester **29** with terminal olefin functionality provided the chain-extension and cyclopropanation product **30** in 70% yield along with a small amount of chain-extended product under the same conditions. When 4 equiv of $CF_3CO_2ZnCH_2I$ was submitted to the reaction, the sole product **30** was obtained in 95% yield.

TABLE 2. Chain Extension of β-Keto Esters Using $CF_3CO_2ZnCH_2I$



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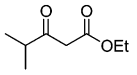
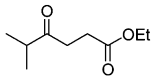
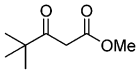
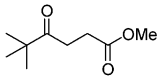
1		8		90
	17		**18**	
2		7		96
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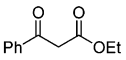
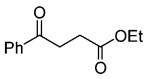
3		8		87
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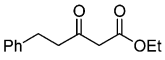
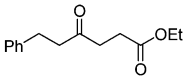
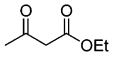
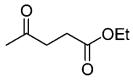
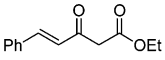
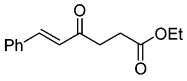
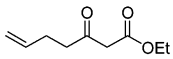
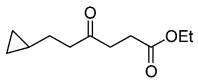
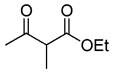
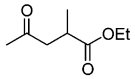
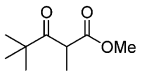
4		8		77
	23		**24**	
5[b]		4		81
	25		**26**	
6		5		71
	27		**28**	
7		8		70 (95)[c]
	29		**30**	
8		10		36
	31		**32**	
9		10	No Reaction	
	33			

[a] Isolated yields. [b] The reaction was performed at 0 °C. [c] Using 4 equiv of $CF_3CO_2ZnCH_2I$.

(11) (a) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621. (b) Lorenz, J. C.; Long, J.; Yang, Z. Q.; Xue, S.; Xie, Y. N.; Shi, Y. *J. Org. Chem.* **2004**, 69, 327.

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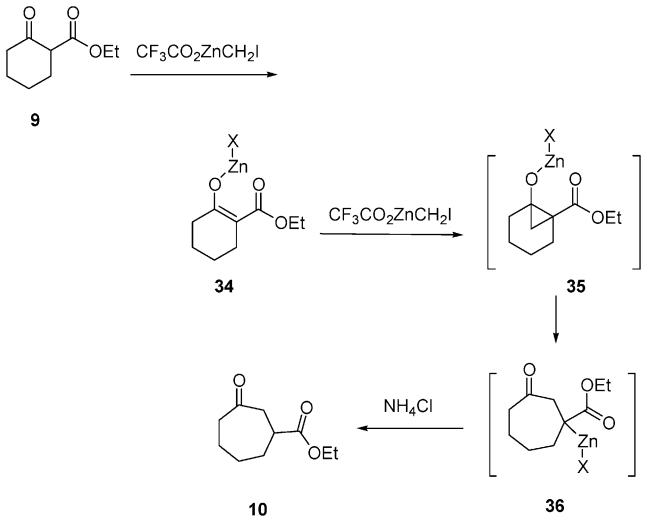
SCHEME 1. A Plausible Mechanism of the Ring-Expansion Reaction



The zinc species $CF_3CO_2ZnCH_2I$ worked well for ring-expansion reaction of cyclic β-keto esters; however, α-substituted β-keto esters resulted in diminished efficiency (Table 2). Reaction of **31** gave the chain-extended product **32** in 36% yield. Substrate **33** with a *tert*-butyl group was submitted to this reaction, no chain-extended product was formed and the starting material was recovered (>90%). These results suggest the steric hindrance between α-methyl group and γ-substituted group has obvious influence on the reaction.

Based on the work of Zercher,[6,7] a plausible mechanism of the reaction is shown in Scheme **1**. The first step of the reaction is formation of the enolate **34**, which consumes 1 equiv of $CF_3CO_2ZnCH_2I$. Enolate **34** then undergoes cyclopropanation with second equivalent of zinc species to give cyclopropyl intermediate **35**, followed by cleavage to give an intermediate **36**, then quenched by saturate aqueous NH_4Cl to provide the ring-expanded product. Compared to ethyl(iodomethyl)zinc, the $CF_3CO_2ZnCH_2I$ was found to afford the ring-expanded product in much higher yields. The reason may be that ionization of the electron deficient CF_3CO_2 group creates a vacant coordination site on the zinc permitting coordination of the iodine of a second $CF_3CO_2ZnCH_2I$ species that results in activation of the methylene group toward reaction with enolates resulting in formation of cyclopropanaes.[11] Here, CF_3CO_2H accelerated the cyclopropanation reaction of olefins dramatically, and the ring-expanded products were effectively formed. Unfortunately, the chain-extension of α-substituted β-keto esters reacted with much less efficient. The increased steric hindrance of the resultant enolate may be responsible.

In this paper, we have developed a simple and efficient procedure for the ring-expansion of cyclic β-keto esters and chain-extension of α-unsubstituted β-keto esters by using zinc reagent $CF_3CO_2ZnCH_2I$ (Scheme 1). The obvious advantage of the reaction is mild condition, and no preparation of α-halomethyl β-keto esters.

Experimental Section

General Procedure for Ring Expansion and Chain Extension of β-Keto Ester with $CF_3COOZnCH_2I$. To a solution of $ZnEt_2$ (90 μL, 0.9 mmol, 3 equiv) in 3 mL of CH_2Cl_2 at 0 °C was added dropwise CF_3COOH (70 μL, 0.9 mmol, 3 equiv) slowly via syringe under N_2. After the mixture was stirred for 30 min at 0 °C, methylene iodide (75 μL, 0.9 mmol, 3 equiv) was added dropwise with stirring. The suspension was stirred for 30 min, and then β-keto ester **1** (66 mg, 0.3 mmol) was added rapidly by syringe. The mixture was stirred at room temperature for 8 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (10 mL × 3). The combined organic extracts was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to an oil residue. The desired product 5-Ethoxycarbonyl-1,2-benzo-3-oxocycloheptenone **2** (58 mg, 83%)[13] as a colorless oil was isolated by flash silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (dd, 1H, J = 7.6, 1.5 Hz), 7.37 (td, 1H, J = 7.5, 1.5 Hz), 7.25 (td, 1H, J = 7.5, 1.2 Hz), 7.14 (d, 1H, J = 7.5 Hz), 4.15 (q, 2H, J = 7.2 Hz), 3.05−2.75 (m, 5H), 2.22 (m, 1H), 2.09 (m, 1H), 1.15 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 174.3, 140.8, 138.2, 132.6, 129.8, 128.8, 127.0, 61.0, 42.8, 38.3, 31.2, 28.6, 14.2.

Procedure for Synthesis of Ethyl 6-Cyclopropyl-4-oxohexanoate (30) Using $CF_3COOZnCH_2I$. To a solution of $ZnEt_2$ (120 μL, 1.2 mmol, 4 equiv) in 3 mL of CH_2Cl_2 at 0 °C was added dropwise CF_3COOH (93 μL, 1.2 mmol, 4 equiv) slowly via syringe under N_2. After the mixture was stirred for 30 min at 0 °C, methylene iodide (100 μL, 1.2 mmol, 4 equiv) was added dropwise with stirring. The suspension was stirred for 30 min, and then β-keto ester **29** (51 mg, 0.3 mmol) was added rapidly by syringe. The mixture was stirred at room temperature for 8 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (10 mL × 3). The combined organic extracts was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to an oil residue. The desired product **30** (56 mg, 95%) as a colorless oil was isolated by flash silica gel column chromatography. IR (neat, cm^{-1}): 3077, 2984, 2927, 1736, 1448, 1411, 1373, 1350, 1194, 1095, 1017. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.15 (q, 2H, J = 7.2 Hz), 2.75 (t, 2H, J = 6.5 Hz), 2.60−2.51 (m, 4H), 1.5 (q, 2H, J = 7.3 Hz), 1.2 (t, 3H, J = 7.2 Hz), 0.68 (m, 1H), 0.5−0.35 (m, 2H), 0.01 (dd, 2H, J = 10.2, 5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.2, 173.0, 60.7, 42.9, 4.3, 29.1, 28.1, 14.3, 10.6, 4.6. HRMS (EI)L calcd for $C_{11}H_{18}O_3$ 198.1257 [M$^+$], found 198.1256.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for products **2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **26**, **28**, **30**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Treatment of $CF_3CO_2ZnCH_2I$ (9 mmol) with 5-ethoxycarbonyl-1,2-benzo-2-oxocyclohexenone **1** (650 mg, 3 mmol) gave the desired product **2** in comparable yield (562 mg, 81%) under the same procedure. See the Supporting Information for details.