Zinc-Mediated Conversion of β-Keto Esters to γ-Keto Esters

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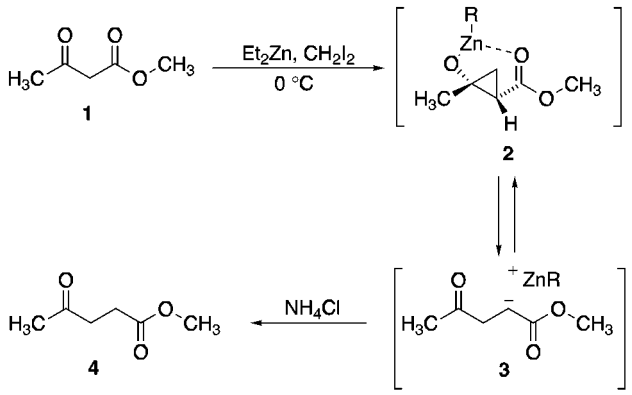
The efficient preparation of γ-keto esters has been the goal of numerous research efforts. Although methods have been developed in which the ketone and ester functionalities are brought together from different sources,[1] reactions which promote the insertion of a single methylene unit between the carbonyl functionalities of a readily accessible β-keto ester have dominated these efforts. The formation and fragmentation of 2-carboxycyclopropyl alcohols have been central to this methodological development.[2]

Three complementary disconnective strategies have been implemented for the formation of these functionalized cyclopropyl alcohols. The most common strategy has involved exposure of a enol ether to metal carbenoids generated from diazo esters.[3] Cleavage of the ether linkage in a second separate step and fragmentation of the mixture of cyclopropanol stereoisomers provided the corresponding γ-keto ester. A complementary method utilized Simmons−Smith methodology to generate a cyclopropane from protected β-keto esters.[4] Opening of the functionalized cyclopropanes was initiated by treatment with aqueous acid or fluoride. A more recently reported chain extension method involved treatment of an α-substituted β-keto ester enolate with methylene bromide followed by exposure to tin hydride.[5] Addition of the primary radical to the carbonyl followed by fragmentation of the intermediate cyclopropanol radical provided the ester-stabilized radical. Quenching of the radical with tri-*n*-butyltin hydride continued the chain process and provided the γ-keto ester.

We have recently developed a mild and efficient one-step method for the formation of γ-keto esters from β-keto esters which appears to proceed through a similar cyclopropyl alcohol intermediate **2** (Scheme 1). Exposure of an α-unsubstituted β-keto ester to a 1:1 mixture of diethylzinc and methylene iodide results in its clean and rapid conversion to the chain-extended keto ester. This zinc-mediated process holds two distinct advantages over the previously reported chain extension methods. The most obvious advantage is that no additional steps are required for the formation of the intermediate enol ether or for the cleavage of the protected cyclopropyl alcohol. Second, utilization of diethylzinc is operationally much more simple than preparation and application of the zinc

Scheme 1



amalgam reported by Saigo.[4b] Since α-unsubstituted β-keto esters react cleanly under these reaction conditions, this new reaction nicely complements the radical-based methodology which requires an α-substituent to prevent elimination.[5]

The reaction is remarkably efficient with respect to the substitution pattern about the β-keto ester. Unsubstituted β-keto esters were efficiently converted into the corresponding γ-keto esters in yields which ranged from 58% to 81% (Table 1). Chromatographic analysis of the reactions listed in Table 1 indicated that the only product formed upon consumption of the starting material was the γ-keto ester.[6] Chain extension proceeded cleanly with as few as 2.0 equiv of the presumed ethyl(iodomethyl)zinc reagent, although unreacted starting material was occasionally observed at this stoichiometry. Therefore, typical reaction conditions consisted of adding the β-keto ester to a 0 °C solution of methylene chloride which contained 5 equiv of both methylene iodide and diethylzinc.

The β-keto esters which contained olefin functionality (Table 2) were susceptible to concomitant cyclopropane formation. Substrates which possessed either electron-rich or electron-poor olefins underwent selective chain extension of the alkene in preference to cyclopropane formation. Nevertheless, extended reaction times and excess ethyl(iodomethyl)zinc provided an appropriate environment for tandem chain extension and cyclopropanation which culminated in the preparation of **20**.

Although the chain extension reaction worked very well for simple β-keto esters, variation from the acyclic α-unsubstituted β-keto ester series resulted in diminished efficiency (Table 3). Treatment of acetylacetone **21** for 40 min at room temperature resulted in no observable reaction, even though addition of methyl acetoacetate (**1**) to the reaction mixture and its conversion to methyl levulinate (**4**) demonstrated that the active chain extension reagent was present. Exposure of 1,3-cyclohexanedione (**22**) to the standard reaction conditions generated in low yield a compound which possessed a cyclopropyl group. The structure of product **23** was firmly established by H,H-COSY[7] and was shown to be the result of the expected ring expansion followed by the rapid addition of a second methylene group.

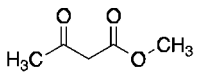
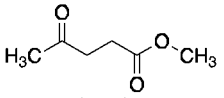
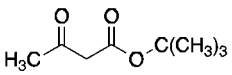
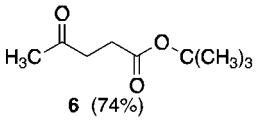
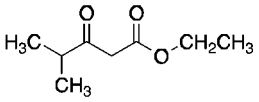
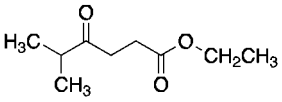
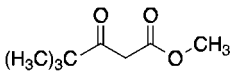
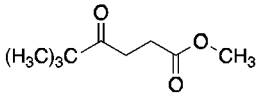
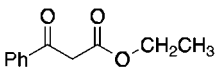
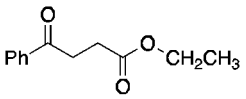
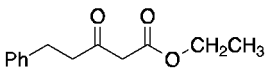
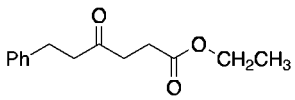
The regioselective incorporation of the methylene unit was addressed through the exposure of α-substituted

(1) (a) Miyakoshi, T. *Org. Prep. Proc. Int.* **1989**, *21*, 659. (b) Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 255.
(2) (2) Reissig, H.-H. *Top. Curr. Chem.* **1988**, *144*, 73.
(3) (a) Wenkert, E.; McPherson, C. A.; Sanchez, E. L.; Webb, R. L. *Synth. Commun.* **1973**, *3*, 255. (b) Reichelt, I.; Reissig, H.-U. *Chem. Ber.* **1983**, *116*, 3895. (c) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Leibigs Ann. Chem.* **1984**, 512. (d) Reichelt, I.; Reissig, H.-U. *Leibigs Ann. Chem.* **1984**, 531. (e) Saigo, K.; Kurihara, H.; Miura, H.; Hongu, A.; Kubota, N.; Nohira, H. *Synth. Commun.* **1984**, 787. (f) Reissig, H.-U.; Grimm, E. L. *J. Org. Chem.* **1985**, *50*, 242.
(4) (a) Bieraugel, H.; Akkerman, J. M.; Lapierre Armond, J. C.; Pandit, U. K. *Tetrahedron Lett.* **1974**, 2817. (b) Saigo, K.; Yamashita, T.; Hongu, A.; Hasegawa, M. *Synth. Commun.* **1985**, 715.
(5) (a) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493. (b) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 6548. (c) Dowd, P.; Choi, S.-C. *Tetrahedron*. **1989**, *45*, 77. (d) Dowd, P.; Choi, S.-C. *Tetrahedron Lett.* **1989**, *30*, 6129.

(6) All reported reactions were performed on a 1 mmol scale. The modest yields of the compound in Table 1 apparently reflect the efficiency of chromatographic purification.
(7) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542.

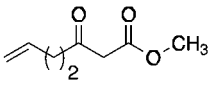
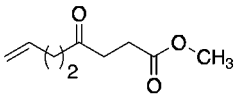
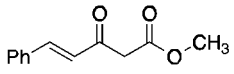
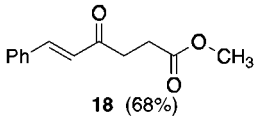
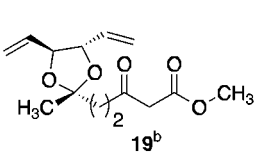
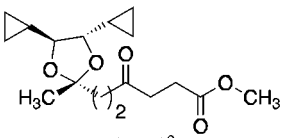
S0022-3263(97)00868-2 CCC: $14.00

Table 1. Chain Extension of Simple β-Keto Esters

Substrate	Product (Yield)[a]
 **1**	 **4** (81%)
 **5**	 **6** (74%)
 **7**	 **8** (68%)
 **9**	 **10** (71%)
 **11**	 **12** (58%)
 **13**[b]	 **14** (73%)

(a) isolated yield of purified product. (b) The starting β-ketoester was prepared by the method of Roskamp (ref 11).

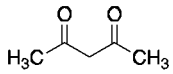
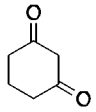
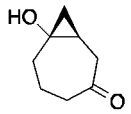
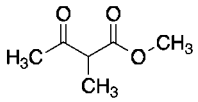
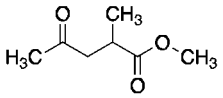
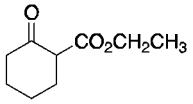
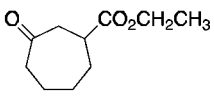
Table 2. Chain Extension of Olefin-Containing Substrates

Substrate	Product (%)[a]
 **15**[b]	 **16** (74%)
 **17**[b]	 **18** (68%)
 **19**[b]	 **20** (40%)[c]

(a) isolated yield of purified product. (b) The starting β-ketoester was prepared by the method of Masamune (ref 14). (c) Additional ethyl(iodomethyl)zinc (12 equiv) was necessary to convert all starting material to bis-cyclopropanated product.

β-keto esters to the standard reaction conditions. Conversion of acyclic β-keto ester **24** into **25** indicated that, in a fashion similar to the previously reported methodologies,[3–5] the new methylene was incorporated adjacent to the ketone functionality. This conclusion was reinforced through the identification of **27** as the major product generated from α-carboethyloxycyclohexanone (**26**).

Table 3. Chain Extension of β-Diketones and α-Substituted β-keto Esters

Substrate	Product (%)[a]
 **21**	No Reaction
 **22**	 **23** (25%)
 **24**	 **25** (26%)
 **26**	 **27** (20%)[b]

(a) isolated yield of purified material. (b) Isolated yield based on reacted starting material was 33%.

The precise zinc species responsible for initiating the chain extension process is not known at the present time, although it has been demonstrated that an equimolar combination of diethylzinc and methylene iodide generates the moderately stable cyclopropanation reagent ethyl(iodomethyl)zinc.[8] It has yet to be clarified whether the reactive zinc species performs a direct cyclopropanation of the enolate, a direct cyclopropanation of the enol, or a stepwise procedure which involves an α-alkylation of the β-keto ester followed by nucleophilic attack on the ketone carbonyl. Nevertheless, the similarity of this reaction to the transformations reported by Dowd and Saigo suggests that a cyclopropyl alcohol intermediate is involved.[9] At this time there is no direct evidence for the formation of an intermediate cyclopropane in the simple chain extension procedure; however, the isolation of the secondary compound **23** supports its proposed existence.

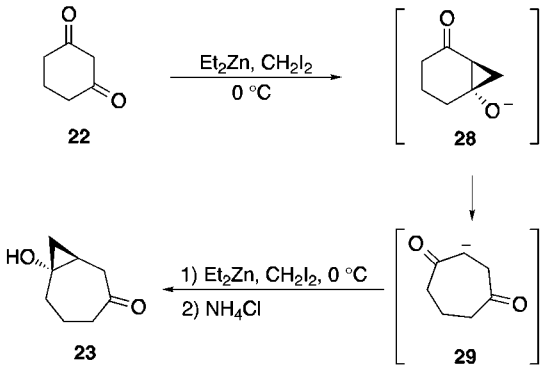
It is not entirely clear why the addition of the second methylene unit is so rapid with the cyclic and/or α-substituted substrates **22**, **24**, and **26**. Disruption of an equilibrium between, for example, cyclopropanoxide **28** and its isomeric and very reactive ester enolate **29** (Scheme 2) may play a role. The extremely rapid conversion of **29** into **23** would appear to lend support to a mechanism in which cyclopropanation events occur through an enolate intermediate. If the reaction proceeded through cyclopropanation of the enol, it is unlikely that rapid addition of a second methylene unit would be observed.

In summary, we have identified a simple and efficient procedure for the conversion of β-keto esters to γ-keto

(8) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53. (c) Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539.

(9) Lenhert, E.; Sawyer, J. S.; McDonald, T. L. *Tetrahedron Lett.* **1989**, *30*, 5215.

Scheme 2



esters which has distinct advantages when compared to existing methodology. The reaction works remarkably well for α-unsubstituted *β*-keto esters. Substrates in which the ketone is incorporated into a small ring or which possess α-substitution of the *β*-keto ester react with diminished efficiency, although these limitations can most likely be overcome through prior formation of the trimethylsilyl enol ether in a fashion similar to that reported by Saigo. The intermediacy of a cyclopropyl alcohol has been implicated by product formation, although details of its formation are still under investigation. Efforts are underway to optimize the reaction conditions and to define more clearly the scope and synthetic utility of this chain extension reaction.

Experimental Section

Methylene chloride was distilled from calcium hydride. Column chromatography was performed on Baker 40 *μ*m silica gel. The reactions were monitored by thin layer chromatography (TLC) on EM Science F254 glass plates which were visualized by short wavelength UV and anisaldehyde stain. All reactions were run in oven-dried glassware under a nitrogen atmosphere. Starting materials **1**, **5**, **7**, **9**, **11**, **21**, **22**, **24**, and **26** were purchased from commercial sources and used as received. Compound **13**[10] was prepared according to the procedure of Roskamp,[11] and compounds **15**[12] and **17**[13] were prepared through application of the procedure of Masamune.[14] Compound **19** was prepared in a multistep sequence from levulinic acid.[15] Characterization data of the purified products **4**,[16] **6**,[17] **8**,[18] **10**,[19] **12**,[20] **14**,[21] **16**,[22] **18**,[23] **25**,[24] and **27**[25] were shown to be consistant to the literature values.

Typical Experiment. A 50 mL round-bottom flask was equipped with a stir bar and charged with methylene chloride (15 mL) and diethylzinc (1.0 M in hexanes, 5 mL, 5 mmol). Methylene iodide (0.4 mL, 5 mmol) in 2.5 mL of CH_2Cl_2 was added dropwise with stirring. The resulting suspension was stirred for 10 min, and methyl acetoacetate (**1**) (116 mg, 1.0 mmol) was added rapidly by syringe. The mixture was stirred for 30 min, quenched with saturated aqueous NH_4Cl, and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography on silica (20% EtOAc in hexanes) and yielded methyl levulinate (**4**) (106 mg, 81%).

***trans*-4,5-Dicyclopropyl-2-(5-(carboxymethyl)-3-oxopentyl)-2-methyl-1,3-dioxolane (20).** A large excess (12 equiv) of the proposed ethyl(iodomethyl)zinc reagent was necessary to form this product cleanly, 40%: ^{1}H NMR ($CDCl_3$) *δ* 3.7 (s, 3H), 3.1 (t, 1H, J = 8.3 Hz), 2.9 (t, 1H, J = 8.3 Hz), 2.7 (t, 1H, J = 6.7 Hz), 2.55 (m, 4H), 2.0 (m, 2H), 1.35 (s, 3H), 0.7−0.9 (m, 4H), 0.2−0.5 (m, 4H); ^{13}C NMR ($CDCl_3$) *δ* 208.4, 173.3, 108.2, 86.7, 86.0, 51.7, 36.4, 36.9, 33.9, 27.7, 25.6, 12.6, 11.9, 2.9, 2.8, 1.6; IR (film) 3000−2900, 1741, 1718 cm^{-1}; MS (CI, NH_3) 328, 311, 293, 279, 204, 187, 167, 155, 125; HRMS (CI, CH_4) ([M + H]$^+$) calcd for $C_{17}H_{27}O_5$ 311.1858, found 311.1865.

7-Hydroxybicyclo[5.1.0]octan-3-one (23): 25%; ^{1}H NMR ($CDCl_3$) *δ* 3.1 (br s, 1H), 2.8 (ddd, 1H, J = 14.5, 6.7, 1.3 Hz), 2.7 (apparent pentet, 1H, J = 6.4 Hz), 2.4 (dt, 1H, J = 15.1, 4.0 Hz), 2.3 (ddd, 1H, J = 12.2, 8.7, 5.7 Hz), 2.0 (m, 1H), 1.88 (dd, 1H, J = 14.3, 9.3 Hz), 1.75 (m, 1H), 1.45 (ddd, 1H, J = 15.2, 12.2, 3.1 Hz); ^{13}C NMR ($CDCl_3$) *δ* 212.0, 58.1, 44.7, 44.0, 34.5, 24.0, 21.2, 18.8; IR (film) 3418, 2945, 1700, 1450 cm^{-1}; MS (CI, NH_3) 174, 158, 144, 134, 127; HRMS (CI, NH_3) (MNH_4^+) calcd for $C_4H_{18}NO_2$ 158.1180, found 158.1186.

Acknowledgment. We express our appreciation to the National Institutes of Health (R15 GM51064) and the University of New Hampshire for financial support. We appreciate an informative conversation with Professor Paul Helquist.

Supporting Information Available: Characterization data, including ^{1}H and ^{13}C NMR, for all products and noncommercially available starting *β*-keto esters. ^{1}H and ^{13}C NMR spectra for **20** and **23**, including an H−H COSY for compound **23** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970868G

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(12) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
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(14) Brooks, D. W.; Lu, L. D-D.; Masamune, S., *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.
(15) Brogan, J. B.; Bauer, C.; Rogers, R. D.; Zercher, C. K. *J. Org. Chem.* In press.
(16) Schmid, G. H.; Weiler, L. S. J., *Can J. Chem.* **1965**, *43*, 1242.
(17) Widmer, U. *Synthesis* **1983**, 136. (b) Chem. Abstr. **1965**, *62*, 16197.
(18) Parker, K. A.; Petraitis, J. J.; Kosley, Jr., R. W.; Buchwald, S. L. *J. Org. Chem.* **1982**, *47*, 389.
(19) Marks, M. J.; Walborsky, H. M. *J. Org. Chem.* **1981**, *46*, 5405.
(20) Meijer, L. H. P.; Pandit, U. K. *Tetrahedron* **1985**, *41*, 467.
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