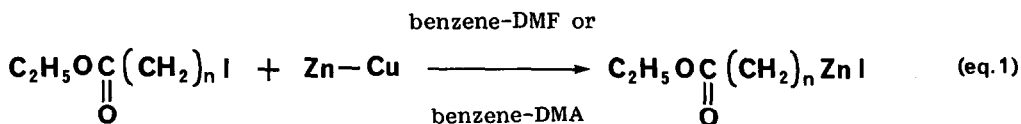Generation of 2-Carboethoxyethylzinc Iodide and 3-Carboethoxypropylzinc Iodide and Their
Application to the Synthesis of γ- and δ-Keto Esters

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Summary: 2-Carboethoxyethylzinc iodide and 3-carboethoxypropylzinc iodide are generated by
the reaction of the corresponding iodoesters with Zn-Cu couple and utilized for the palladium
catalyzed coupling reaction with acid chloride to quantitatively provide gamma- and delta- keto
esters, respectively.

The generation and use of β-metalloketones and esters (homoenolates) are a current
interest of great concerns of organic chemists.[1]   Typically, these species may be formed by
(1) cyclopropane ring opening,[2] (2) 1,2-addition of acyltransition metals to olefins,[3] (3)
Michael type addition of metalhydride to enones,[4] or (4) selective deprotonation of the
β-hydrogen of some γ,δ-unsaturated amides.[5]   Allylic metals with hetero atom substituents at
the olefinic terminus may also be used as a synthetic equivalent of homoenolate.[6]

$$\underset{O}{C_2H_5O\overset{\|}{C}}(CH_2)_n I \ + \ Zn-Cu \ \xrightarrow[\text{benzene-DMA}]{\text{benzene-DMF or}} \ \underset{O}{C_2H_5O\overset{\|}{C}}(CH_2)_n Zn I \qquad \text{(eq.1)}$$

Homoenolate   **1**: n = 2
Bishomoenolate **2**: n = 3

In this communication, we describe the fifth and straightfoward synthesis of zinc
homoenolate (equation 1, n = 2) and zinc bishomoenolate (equation 1, n = 3), which is
reminiscent of the Reformatsky type zinc enolate formation (equation 1, n = 1).[7] The
homoenolate (2-carboethoxyethylzinc iodide 1) was prepared by the direct reaction of ethyl
3-iodopropionate with Zn-Cu couple in dry benzene containing a small amount of
N,N-dimethylformamide (DMF) or N,N-dimethylacetamide (DMA).   The formation of 1 was
indicated by the formation of ethyl propionate and the concomitant disappearance of the
iodide, as judged from vpc analyses of the reaction aliquots after acid hydrolysis.   DMF or
DMA is indispensable for the formation of 1.   In the absence of DMF or DMA, no formation
of enolate 1 was discernible.

Table I. Palladium Catalyzed Coupling Reaction of Acid Chlorides with $\underset{\sim}{1}$ or $\underset{\sim}{2}$[a]

entry	$\underset{\sim}{1}$ or $\underset{\sim}{2}$	acid chloride	product	% isolated yield[b]	
				DMF	DMA
1	$\underset{\sim}{1}$	C_2H_5COCl	$C_2H_5CO-(CH_2)_2CO_2Et$	72	84
2	$\underset{\sim}{1}$	$n-C_7H_{15}COCl$	$n-C_7H_{15}CO-(CH_2)_2CO_2Et$	79	100
3	$\underset{\sim}{1}$	$PhCOCl$	$PhCO-(CH_2)_2CO_2Et$	72[c]	100
4	$\underset{\sim}{1}$	$4-MeOC_6H_4COCl$	$4-MeOC_6H_4CO-(CH_2)_2CO_2Et$	69	94
5	$\underset{\sim}{1}$	$4-ClC_6H_4COCl$	$4-ClC_6H_4CO-(CH_2)_2CO_2Et$	74	100
6	$\underset{\sim}{1}$	$2-MeOC_6H_4COCl$	$2-MeOC_6H_4CO-(CH_2)_2CO_2Et$	54	81
7	$\underset{\sim}{1}$	$PhCH{=}CHCOCl$	$PhCH{=}CHCO-(CH_2)_2CO_2Et$	66	92
8	$\underset{\sim}{1}$	$CH_2{=}\underset{\underset{Me}{\mid}}{C}COCl$	$CH_2{=}\underset{\underset{Me}{\mid}}{C}CO-(CH_2)_2CO_2Et$	--	90
9	$\underset{\sim}{2}$	$n-C_7H_{15}COCl$	$n-C_7H_{15}CO-(CH_2)_3CO_2Et$	60	94
10	$\underset{\sim}{2}$	$MeO_2C(CH_2)_4COCl$	$MeO_2C(CH_2)_4\underset{\underset{O}{\|}}{C}-(CH_2)_3CO_2Et$	66	90
11	$\underset{\sim}{2}$	$MeO_2C(CH_2)_7COCl$	$MeO_2C(CH_2)_7\underset{\underset{O}{\|}}{C}-(CH_2)_3CO_2Et$	63	89
12	$\underset{\sim}{2}$	$EtO_2C(CH_2)_8COCl$	$EtO_2C(CH_2)_8\underset{\underset{O}{\|}}{C}-(CH_2)_3CO_2Et$	58	72

a) For the reaction conditions, see text.
b) Yields refer to the isolated ones by means of column chromatography and based on acid chloride.
c) Benzoic anhydride was isolated in 25% yield (based on benzoyl chloride) in addition to the expected ketone.

In connection with the preceding communication and owing to the synthetic importance of γ-keto esters, we examined the palladium catalyzed coupling reaction of $\underset{\sim}{1}$ with acid chloride (equation 2).[8] By applying exactly the same procedure as the reaction of acid chloride and alkylzinc iodide,[9] i. e., addition of a benzene solution of tetrakis(triphenylphosphine)-palladium(0) and acid chloride into a solution of $\underset{\sim}{1}$ (at room temperature or at 60°C bath temperature, generated in the presence of DMF), was obtained the expected γ- keto esters in rather low yields (e.g., $n\text{-}C_7H_{15}COCH_2CH_2CO_2CH_2CH_3$ in 50 - 60% yield).   Sequential addition of tetrakis(triphenylphosphine)palladium(0) in bezene at 60°C followed by removal of a heating bath and prompt addition of a benzene solution of acid chloride gave slightly improved results (e.g., entry 2, DMF column in Table I).   Despite of our considerable experimentations, however, the yield never exceeded over 80%, irrespective of the kinds of acid chlorides.   In the reaction of benzoyl chloride with $\underset{\sim}{1}$, benzoic anhydride was isolated in 25% yield (based on benzoyl chloride) in addition to the expected γ-keto ester (72%, based on benzoyl chloride, entry 3, DMF column in Table I).   The formation of benzoic anhydride may be attributed to a concomitant formation of Vilsmeier reagent (N,N-dimethylchloroformiminium chloride)[10] from DMF and 2 moles of benzoyl chloride.   In order to minimize this side reaction, we replaced DMA for DMF as a co-solvent and obtained quite satisfactory results. *Dramatic effect of DMA for the improvements in yields is apparent by comparison of the columns of DMA and DMF in Table I.*   The coupling reaction of the homoenolate $\underset{\sim}{1}$ with acid chloride is generally applicable to a wide structural variety of acid chlorides, including aromatic and saturated acid chlorides as well as unsaturated ones.

$$\underset{\sim}{1} \text{ or } \mathbf{2} \quad + \quad RCOCl \quad \longrightarrow \quad RCO\text{-}(CH_2)_n CO_2Et \qquad \text{(equation 2)}$$
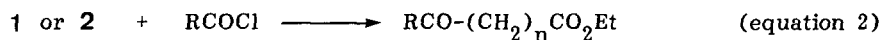
$$n = 2 \text{ or } 3$$

Zinc bishomoenolate (3-carboethoxypropylzinc iodide $\underset{\sim}{2}$) was also found to be smoothly generated by the reaction of ethyl 4-iodobutyrate and Zn-Cu couple *according to the similar procedure (equation 1, n = 3).*   The bishomoenolate $\underset{\sim}{2}$ showed the similar reactivity to $\underset{\sim}{1}$ toward the palladium catalyzed coupling reaction with acid chlorides.   Here again, DMA showed the better and more satisfactory results than DMF.   In the entries 9 - 12 in Table I are summarized the results, where the synthetic utility of $\underset{\sim}{2}$ was exemplified by the synthesis of *synthetically important unsymmetrical keto 1,ω-diesters.*

All the reactions listed in Table I were performed in the same procedure typified by the reaction of α-methacryloyl chloride and $\underset{\sim}{1}$: Into a nitrogen purged flask containing Zn-Cu couple (150 mg, 2.3 mmol)[11] was added a solution of ethyl 3-iodopropionate (329 mg, 1.5 mmol) in dry benzene-DMA (3 mL - 0.2 mL).   The mixture was stirred at an ambient temperature for 1 h and then at 60°C (bath temperature) for 3 - 4 h.   A suspension of tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol) in dry benzene (1 mL) was added and stirred at the same temperature for 5 min.   After removal of a heating bath, a solution of α-methacryloyl chloride (105 mg, 1 mmol) in a small amount of dry benzene was promptly added in one portion.   After a highly exothermic reaction had subsided, the reacton was

continued for ca. 30 min. Addition of the reaction mixture into ethyl acetate (50 mL), sequential washing with 1N-HCl, sat. $NaHCO_3$, and then with sat. NaCl, drying over $MgSO_4$ and evaporation of the solvent left a colorless liquid, which was chromatographed over silica-gel (hexane-ethyl acetate gradient).[12] Ethyl 4-oxo-5-methyl-5-hexenoate: 90% isolated yield; colorless oil; ^{1}H NMR (δ, $CDCl_3$) 1.25 (t, J = 7.3 Hz, 3 H), 1.89 (s, 3 H), 2.61 (t, J = 5.6 Hz, 2 H), 3.02 (t, J = 5.6 Hz, 2 H), 4.14 (q, J = 7.3 Hz, 2 H), 5.79 (s, 1 H), and 6.01 (s, 1 H); IR (neat film, cm^{-1}) 1725, 1670, 940, and 860; mass (m/z, relative intensity) 170 (M^+, 9), 125 (34), 101 (19), and 69 (100).

The homoenolate 1 and bishomoenolate 2 are promissing synthetic intermediates and we are now under extensive study on their reactions with many kinds of electrophiles as well as their structural elucidation.

References and Notes

(1) I. Ryu and N. Sonoda, J. Synthetic Organic Chemistry, Japan, 43, 112 (1985).

(2) (a) E. Nakamura and I. Kuwajima, J. Am. Chem. Soc., 106, 3368 (1984); (b) I. Ryu, M. Ando, A. Ogawa, S. Murai, and N. Sonoda, J. Am. Chem. Soc., 105, 7192 (1983).

(3) (a) R. F. Heck, "Organotransition Metal Chemistry", Academic Press, 1974. (b) B. L. Booth, S. Casey, R. P. Critchley, and R. N. Haszeldine, J. Organomet. Chem., 226, 301 (1982). (c) P. DeShong and G. A. Slough, Organometall., 3, 634 (1984).

(4) R. A. Howie, E. S. Paterson, J. L. Wardell, and J. W. Barley, J. Organomet. Chem., 259, 71 (1983).

(5) P. Beak, J. E. Hunter, and Y. M. Jun, J. Am. Chem. Soc., 105, 6350 (1983).

(6) D. Hoppe, Angew. Chem. Int. Ed. Engl., 23, 932 (1984).

(7) M. W. Rathke, In "Organic Reactions", W. G. Dauben, Ed.; Wiley, New York, 1975; Col. Vol. 22, p. 423.

(8) For copper-catalyzed coupling reaction of zinc homoenolate and acid chloride, see E. Nakamura and I. Kuwajima, J. Am. Chem. Soc., 106, 3368 (1984).

(9) See, preceding communication.

(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, 1968; Col. Vol. 1, p. 286.

(11) R. D. Smith and H. E. Simmons, In "Organic Syntheses", H. E. Baumgarten, Ed.; Wiley: New York, 1973; Col. Vol. V, p. 855.

(12) All the products listed in Table I are properly characterized by comparison of the spectral data (^{1}H, ^{13}C NMR, and IR) with those of authentic samples and partly by means of high resolution mass spectra or elemental analysis.

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