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Zn-Promoted Regioselective and Sequence-Selective One-Pot Joining Reaction of Three Components: Alkyl Iodides, α,*β*-Unsaturated Esters (or Nitriles), and Acylating Agents

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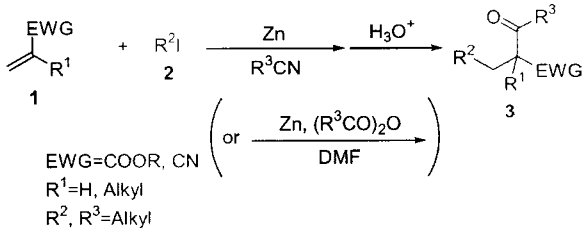
ABSTRACT



One-pot treatment of alkyl iodides, α,*β*-unsaturated esters (or nitriles), and acylating agents such as nitriles or acid anhydrides in the presence of Zn metal at room temperature in the same reaction system brought about a regioselective and sequence-selective three-component joining reaction involving first C-alkylation at the *β*-position and second C-acylation at the α-position of α,*β*-unsaturated esters (or nitriles) to afford the corresponding α,α-dialkylketoesters (or α,α-dialkylketonitriles) in moderate to good yields.

Conjugate addition of organozinc or organocopper reagents has been recognized as a versatile tool for introducing an alkyl group into the *β*-position of α,*β*-unsaturated carbonyl compounds and has been extensively studied from both synthetic and mechanistic aspects.[1] The subsequent trapping of the anionic intermediates formed by the conjugate addition of lithium dialkylcuprates, lithium vinyldimethylzincates, or dialkyl zinc to α,*β*-unsaturated carbonyl compounds has been reported to successfully proceed using alkyl halides,[2] acid chlorides,[3] aldehydes,[4] and phenylselenenyl halides.[5] However, the preparation and the handling of these organometallic reagents are troublesome and not necessarily simple, and these one-pot reactions, in principle, require two steps at low temperatures such as −78 °C. On the other hand, electrochemical one-pot vicinal double addition of two of the same functional groups such as acyl,[6] formyl,[7] carboxyl,[8] and alkyl groups[9] to activated olefins has been reported by us and other groups. Although one-pot three-component joining reaction

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[3] Tanaka, T.; Kurozumi, S.; Toru, T.; Kobayashi, M.; Miura, S.; Ishimoto, S. *Tetrahedron* **1977**, *33*, 1105.

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[6] Yamamoto, Y.; Maekawa, H.; Goda, S.; Nishiguchi, I. *Org. Lett.* **2003**, *5*, 2755.

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of electron-deficient olefins, alkyl iodides, and carbonyl compounds under solvent-reflux conditions has also been reported by our group[10] and Takai's group,[11] the use of nitriles as the acylating agent at room temperature has not yet been demonstrated to the best of our knowledge.

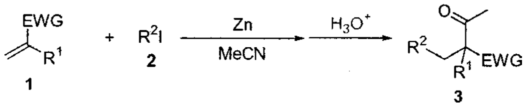
In this study, we wish to report a novel Zn-promoted one-pot three-component joining reaction of α,*β*-unsaturated esters (or nitriles), alkyl iodides, and nitriles (or acid anhydrides) involving first C-alkylation at the *β*-position and second C-acylation at the α-position of α,*β*-unsaturated esters (or nitriles) to give the corresponding α,α-dialkylketoesters (or α,α-dialkylketonitriles) in regioselective and sequence-selective manners in moderate to good yields. Zn metal usually possesses features such as friendliness to the environment, harmlessness, safety, and simplicity of treatment, easy availability, and inexpensiveness since it is one of the necessary elements involved in a human body.

A typical procedure is as follows. Into an acetonitrile (20 mL) solution containing small pieces of commercially available Zn plate[12] (60 mmol) was added dropwise an acetonitrile (40 mL) solution of benzyl methacrylate (**1a**, 10 mmol) and ethyl iodide (**2b**, 100 mmol) at 20−25 °C with magnetic stirring under a nitrogen atmosphere over a period of 45 min in a water bath. After the addition, the mixture was stirred at 20−25 °C for an additional 15 h. After the reaction, the reaction mixture was poured into 300 mL of aqueous 1% HCl solution to hydrolyze the formed imine to the corresponding ketone. After the usual workup, benzyl α,α-dialkylacetoacetate (**3b**) was isolated by column chromatography in 82% yield.

Similar treatment of benzyl methacrylate (**1a**) and a variety of alkyl iodides (**2a**−**f**) in the presence of Zn plate in acetonitrile at room temperature brought about regioselective and sequence-selective introduction of various alkyl groups at the *β*-carbon atom and an acetyl group at the α-carbon atom of **1a** to give the corresponding α,α-dialkylketoesters (**3a**−**f**) in moderate to good yields (Table 1, entries 1−8).

Increase of the concentration of benzyl methacrylate (**1a**) with ethyl iodide (**2b**) in acetonitrile resulted in some decrease in the yield of **3b**, as well as formation of dialkylated product (**4**) and *β*-monoalkylated product (**5**) as the byproducts in 5 and 2% yields, respectively (entry 3). Addition of trimethylsilyl chloride (TMSCl) as the activating agent of Zn metal also gave **3b** in a similar yield (entry 4).

Table 1. Zn-Promoted Three-Component Joining Reaction of α,*β*-Unsaturated Esters (or Nitriles), Alkyl Iodides, and Nitriles[a]



entry	EWG in **1**	R^1 in **1**	R^2 in **2**	yield of **3** (%)[b]
1[c]	COOBn	Me (**1a**)	Me (**2a**)	42 (66)[d] (**3a**)
2	COOBn	Me (**1a**)	Et (**2b**)	82 (82)[e] (**3b**)
3[f]	COOBn	Me (**1a**)	Et (**2b**)	70 (**3b**)
4[g]	COOBn	Me (**1a**)	Et (**2b**)	78 (**3b**)
5[h]	COOBn	Me (**1a**)	*n*-Pr (**2c**)	55 (**3c**)
6	COOBn	Me (**1a**)	*iso*-Pr (**2d**)	64 (**3d**)
7[i]	COOBn	Me (**1a**)	*n*-Bu (**2e**)	60 (**3e**)
8	COOBn	Me (**1a**)	cyclo-Hex (**2f**)	75 (**3f**)
9	COOBn	Et (**1b**)	Et (**2b**)	60 (**3g**)
10	COOBn	*n*-Pr (**1c**)	Et (**2b**)	58 (**3h**)
11	COOBn	H (**1d**)	Et (**2b**)	46 (**3i**)
12	CN	Me (**1e**)	Et (**2b**)	75 (**3j**)
13[g]	CN	Me (**1e**)	*n*-Pr (**2c**)	66 (**3k**)
14	CN	Me (**1e**)	*iso*-Pr (**2d**)	86 (**3l**)

[a] Substrate (10 mmol), alkyl iodides (10 equiv), Zn (6 equiv), MeCN (60 mL), 20−25 °C, 16 h, under N_2 atmosphere. [b] GC Yield. [c] Conversion = 64%. [d] Yield based on the consumed starting compound. [e] Isolated yield. [f] MeCN (30 mL). [g] Reaction was carried out in the presence of TMSCl (0.3 equiv). [h] Reaction time = 40 h. [i] Reaction time = 20 h.

The reaction of acrylate derivatives (**1b**−**d**)[13] with ethyl iodide (**2b**) and that of methacrylonitrile (**1e**) with various alkyl iodides (**2**) also led to three-component joining reaction to afford the corresponding α,α-dialkylketoesters (**3g**−**i**) or α,α-dialkylketonitriles (**3j**−**l**), respectively (entries 9−14). In the case of entry 13, the reaction was carried out in the presence of 0.3 equiv of TMSCl in order to accelerate the slow progress of the reaction.

The present three-component joining reaction of benzyl methacrylate (**1a**), ethyl iodide (**2b**), and various acid anhydrides (**6**) in *N*,*N*-dimethylformamide (DMF) also brought about successful regioselective introduction of various acyl groups to the α-position of **1a** in addition to the *β*-ethylation (Table 2, entries 1−3). Besides the α,α-dialkylketoesters (**3**), small amounts of the dialkylated product (**4**) and *β*-monoalkylated product (**5**) were obtained as byproducts.

It is quite noteworthy that α-monoalkylated product was not detected at all in this reaction. Furthermore, use of propionitrile and butyronitrile as the solvent instead of DMF without acid anhydrides (**6**) in the reaction also led to the formation of the similar corresponding products of three-component joining reaction in 60 and 65% yields, respectively (entries 4, 5).

The present reaction in the absence of any acid anhydrides (**6**) in DMF provided dialkylated product (**4**) as the main

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(9) Satoh, S.; Taguchi, T.; Itoh, M.; Tokuda, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 951.

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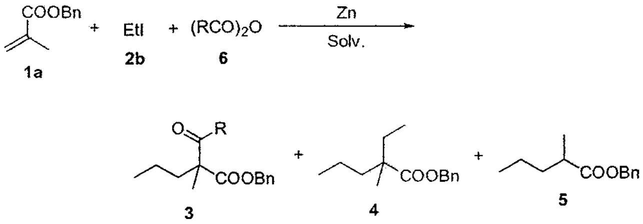
(11) Takai, K.; Ueda, T.; Ikeda, N.; Moriwaki, T. *J. Org. Chem.* **1996**, *61*, 7990.

(12) The present reaction took place smoothly using small pieces with 1 cm^2 of 99% Zn plate, purchased from Nacalai Tesque, Ltd., and used without any activation. The use of Zn dust or powder did not smoothly provide the corresponding α,α-dialkylketoesters (**3**). However, in the three-component joining reaction of benzyl methacrylate (**1a**) with ethyl iodide (**2b**) in acetonitrile, addition of a catalytic amount of $FeCl_3$ or $CoBr_2$ (0.02 mol % vs Zn) into 95% zinc powder, purchased from Merck, Ltd., led to formation of benzyl 2-acetyl-2-methylpentanoate (**3b**) in 46% yield. Furthermore, the use of Le Goff's Zn−Cu couple also gave **3b** in 37% yield. Although detailed studies on these phenomena have not been accomplished as yet at the present stage, trace amounts of metals such as iron, cobalt, or copper, which may be contained as the impurities in the Zn plate, may act as the catalyst for the activation of zinc. Le Goff's Zn−Cu couple was prepared by the reported method. See: Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1.

(13) 2-Benzyloxycarbonyl-1-butene (**1b**) and 2-benzyloxycarbonyl-1-pentene (**1c**) were prepared by the reported method. See: Ueno, Y.; Setoi, H.; Okawara, M. *Tetrahedron Lett.* **1978**, *39*, 3753.

Table 2. Zn-Promoted Three-Component Joining Reaction of Benzyl Methacrylate, Ethyl Iodide, and Acid Anhydrides[a]



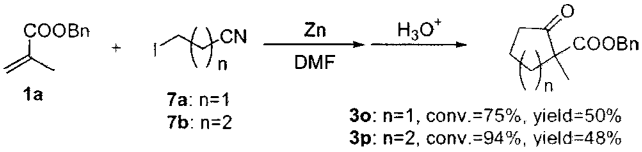
entry	R in **6**	solvent	conversion (%)	yield (%)[b] **3**	**4**	**5**
1	Me (**6a**)	DMF	92	62 (**3b**)	4	5
2	Et (**6b**)	DMF	86	55 (**3m**)	4	5
3	*n*-Pr (**6c**)	DMF	84	57 (**3n**)	4	10
4[c]		EtCN	100	60 (**3m**)	trace	trace
5[d]		*n*-PrCN	100	65 (**3n**)	trace	12
6[e]		DMF	100		36	17

[a] Substrate (10 mmol), ethyl iodide (5 equiv), acid anhydrides (5 equiv), Zn (6 equiv), solvent (60 mL), 20−25 °C, 16 h, under N_2 atmosphere. [b] GC Yield. [c] Ethyl iodide (10 equiv), 40 h. [d] Reaction was carried out in the presence of TMSCl (0.3 equiv) and ethyl iodide (10 equiv). [e] Ethyl iodide (10 equiv).

product (entry 6). In contrast with this result, the reaction in the absence of any alkyl iodide resulted in quantitative recovery of the substrate (**1a**). These facts and regioselective formation of only the *β*-monoalkylated product (**5**) may indicate that the present reaction may be initiated by C-alkylation at the *β*-carbon atom followed by C-acylation at the α-carbon of α,*β*-unsaturated esters (**1**) in a sequence-selective manner.

As one of applications of these reactions, the reaction of benzyl methacrylate (**1a**) with 3-iodopropionitrile (**7a**) or 4-iodobutylonitrile (**7b**) in the presence of zinc in DMF gave the corresponding cyclopentanone (**3o**) and cyclohexanone derivatives (**3p**) in moderate yields through the intermolecular tandem cycloaddition at the olefinic position of benzyl methacrylate (**1a**) (Scheme 1).[14]

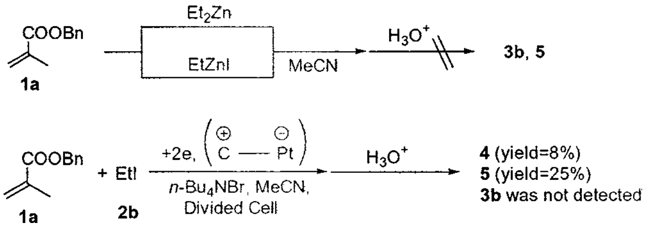
Scheme 1. Zn-Promoted Cycloaddition of Benzyl Methacrylate[a]



[a] Substrate (5 mmol), iodonitriles (10 equiv), Zn (10 equiv), DMF (60 mL), 20−25 °C, 16 h., under N_2 atmosphere.

To obtain some information on the for reaction mechanism of the present reaction, the reaction of benzyl methacrylate (**1a**) with organozinc reagents such as diethyl zinc or ethyl zinc iodide[15] was carried out in acetonitrile (Scheme 2).

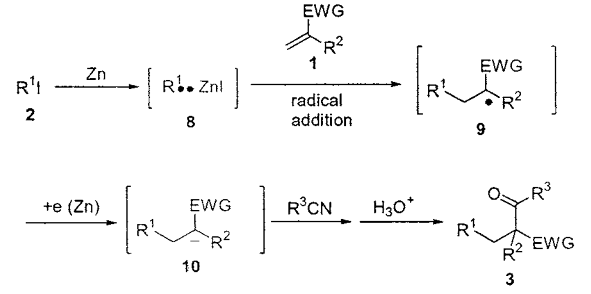
Scheme 2. Three-Component Joining Reaction by Electroreduction or Organozinc Compounds



However, most of **1a** was recovered and the expected α,α-dialkylketoesters (**3b**) and *β*-monoalkylated product (**5**) were not detected at all. This may indicate that the present three-component joining reaction was not initiated through Michael addition of organozinc reagents.

On the other hand, electroreduction of **1a** in the presence of ethyl iodide (**2b**) using a divided cell equipped with a carbon anode and a platinum cathode gave the dialkylated product (**4**) and *β*-monoalkylated product (**5**) in 8 and 25% yields, respectively, although the expected α,α-dialkylketoesters (**3b**) was not detected at all. It has been known that the alkyl radical species generated by one-electron transfer from the cathode to alkyl iodides possessing relatively positive reduction potential reacts with activated alkenes to form the carbon−carbon bond.[9]

Scheme 3. Proposed Reaction Mechanism for the Three-Component Joining Reaction



From these experimental results, the following reaction (Scheme 3) may be proposed as the most plausible mechanism, although the detailed mechanistic studies have not been conducted as yet. The reaction may be initiated through radical addition of the alkyl radical species generated by the radical pair (**8**) consisting of alkyl iodides (**2**) and zinc metal or by one-electron transfer from zinc metal to alkyl iodides (**2**) to form the C-alkylation at the *β*-position of α,*β*-unsaturated esters (**1**) giving the corresponding new radical species (**9**), which may be subjected to fast one-electron

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[14] Zn-promoted intramolecular conjugated addition of iodo enones has been previously reported. See: Bronk, B. S.; Lippard, S. J.; Danheiser, R. L. *Organometallics* **1993**, *12*, 3340.

[15] Ethyl zinc iodide was prepared by the reported method. See: Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79.

transfer from zinc metal, giving the corresponding carbanions (**10**). Subsequently, the electrophilic attack of nitriles (or acid anhydrides) to the carbanions (**10**) generated followed by hydrolysis may afford the corresponding α,α-dialkylketoesters (**3**) (Scheme 3).

In conclusion, the present Zn-promoted three-component joining reaction of α,*β*-unsaturated esters (or nitriles), alkyl iodides, and acylating agents brought about unique regioselective and sequence-selective C-alkylation at the *β*-position followed by C-acylation at the α-position of α,*β*-unsaturated esters or nitriles to give the corresponding α,α-dialkylketoesters or α,α-dialkylketonitriles in moderate to good yields. The present method may be characterized by its high regioselectivity and sequence-selectivity, simple procedure, unique reaction pattern, easy availability of reagents (commercial Zn plate can be used without any activation), and mild conditions (room temperature and ordinary pressure) and may provide usefulness and significance in organic synthesis.

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Supporting Information Available: Experimental procedures and full characterization (^{1}H NMR,^{13}C NMR, IR, and mass spectra and elemental analysis) for structures of the compounds **1b**, **1c**, and **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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