

Novel One-Pot Vicinal Double C-Acylation of Styrenes and Methacrylates by Electroreduction

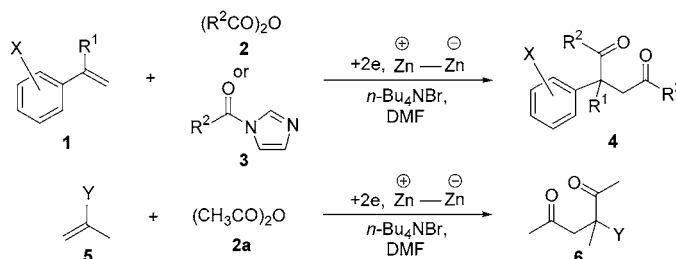
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ABSTRACT



Electroreduction of styrenes or alkyl methacrylates in the presence of aliphatic acid anhydrides or *N*-acylimidazoles with an undivided cell equipped with zinc electrodes as the anode and the cathode brought about novel one-pot vicinal double C-acylation to afford the corresponding 1,4-diketones in satisfactory yields.

Many studies have concentrated upon the synthesis of 1,4-dicarbonyl compounds, particularly 1,4-diketones. These substances are important as synthetic intermediates of many biologically active substrates and useful heterocyclic compounds such as pharmaceutical drugs, insecticides, and perfume materials containing the ring systems of cyclopentenones,¹ furans,² pyrroles,³ and thiophenes.⁴

We have already reported electrochemical or Mg-promoted regioselective C-acylation⁵ of α,β -unsaturated carbonyl compounds to give the corresponding C-acylated 1,4-dicarbonyl compounds which may be obtained by electrophilic attack of acylating agents to the β -carbons of the anion radicals generated by electron transfer from cathode or Mg metal, as shown in Scheme 1. The α -carbanions generated by the subsequent second electron transfer are subjected to protonation. These products formally possess the same structures as the ones which would be obtained by the Michael-type of nucleophilic attack of difficult-to-generate acyl anion to the electron-deficient olefinic bonds.

In this study, we report novel one-pot vicinal double C-acylation of styrene derivatives and methacrylates by electroreduction using an undivided cell to afford the corresponding 1,4-diketones in good yields (Scheme 2).

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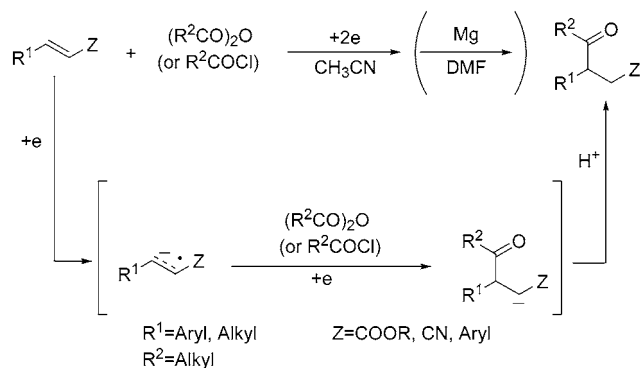
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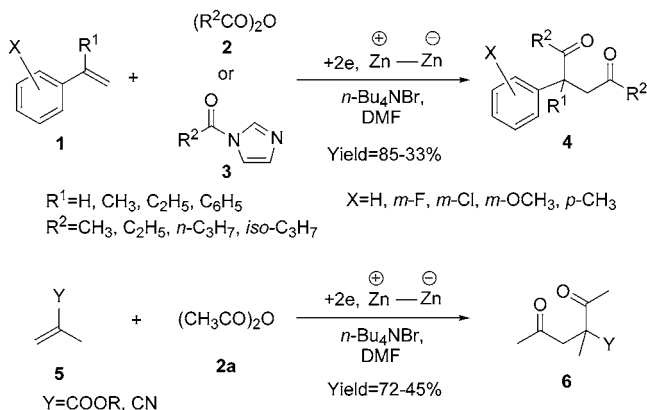
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Scheme 1. Mono C-Acylation of Activated Olefins by Electron Transfer



Scheme 2. Electroreductive Vicinal Double C-Acylation of Activated Olefins



Although electrochemical vicinal double C-carboxylation⁶ and C-formylation⁷ of styrene derivatives in the presence of carbon dioxide and *N,N*-dimethylformamide (DMF), respectively, has been reported, vicinal double C-acylation has not been known as yet to our best knowledge.

The corresponding 1,4-diketones (**4a–f**) were obtained in satisfactory yields, as shown in Table 1. It is interesting that the addition of 1.0 equiv per mol of H₂O to the medium in the reaction of styrene (**1a**) with acetic anhydride (**2a**) brought about the formation of a small amount of the β -monoacylated product (entry 2), which was also obtained from the reaction of **1a** with a less electrophilic acylating agent, *N*-acetylimidazole (**3a**),⁸ as the byproduct (entry 6), indicating that the first C-acylation took place at the β -carbon atom of **1a**.

Use of *N*-carboalkoxyimidazoles (**3e,f**) also led to successful introduction of two carboalkoxy groups to the vicinal

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(7) In the electroreductive vicinal double C-formylation of styrene, the double C-formylated products were not isolated, but were characterized as the corresponding *O*-methyloxime derivatives. See: Engels, Y.; Schäfer, H. J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 460.

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Table 1. Electroreductive Vicinal Double C-Acylation of Styrene^a

entry	R ¹ in 1	X in 1	R ² in 2 , 3	yield of 4 (%) ^b
1	H	H (1a)	Me (2a)	82 (4a)
2	H	H (1a)	Me (2a)	73 (4a)
3	H	H (1a)	Et (2b)	81 (4b)
4	H	H (1a)	<i>n</i> -Pr (2c)	85 (4c)
5	H	H (1a)	<i>iso</i> -Pr (2d)	73 (4d)
6 ^d	H	H (1a)	Me (3a)	73 (4a)
7	H	H (1a)	Et (3b)	63 (4b)
8	H	H (1a)	<i>n</i> -Pr (3c)	75 (4c)
9 ^e	H	H (1a)	MeO (3e)	82 (4e)
10 ^e	H	H (1a)	EtO (3f)	72 (4f)

^a Reaction conditions: substrate (10 mmol), acylating agent (10 equiv per mol), *n*-Bu₄NBr (1.66 equiv per mol), current density (7 mA/cm²), supplied electricity (6 F/mol), DMF (60 mL), –5 to 5 °C, under N₂ atmosphere. ^b GC yield. ^c The presence of 1.0 equiv per mol of H₂O gave 4-phenyl-2-butanone as the byproduct in 9% yield. ^d 4-Phenyl-2-butanone was obtained as the byproduct in 17% yield. ^e *n*-Bu₄NBr (3 equiv per mol)

nal α - and β -carbon atoms of **1a** to give corresponding phenylsuccinic acid esters (**4e,f**) as the main products in good yields (entries 9 and 10).

Introduction of a variety of substituents to the benzene ring or to the α -carbon of styrenes (**1b–i**)⁹ in this reaction with acetic anhydride (**2a**) also brought about similar vicinal double C-acylation, and the results are summarized in Table 2. It may be a general tendency that the presence of electron-

Table 2. Electroreductive Vicinal Double C-Acylation of Styrene Derivatives^a

entry	X in 1	R ¹ in 1	R ² in 2	conv (%)	yield of 4 (%) ^b
1	H	H (1a)	Me (2a)	100	82 (4a)
2	<i>m</i> -F	H (1b)	Me (2a)	100	72 (4g)
3	<i>m</i> -Cl	H (1c)	Me (2a)	100	54 (4h) ^c
4	<i>m</i> -MeO	H (1d)	Me (2a)	100	77 (4i)
5	<i>p</i> -Me	H (1e)	Me (2a)	84	40 (4j)
6	<i>p</i> -MeO	H (1f)	Me (2a)	0	<i>d</i>
7	H	Me (1g)	Me (2a)	80	56 (4k)
8	H	Et (1h)	Me (2a)	67	33 (4l)
9	H	Ph (1i)	Me (2a)	100	46 (4m)

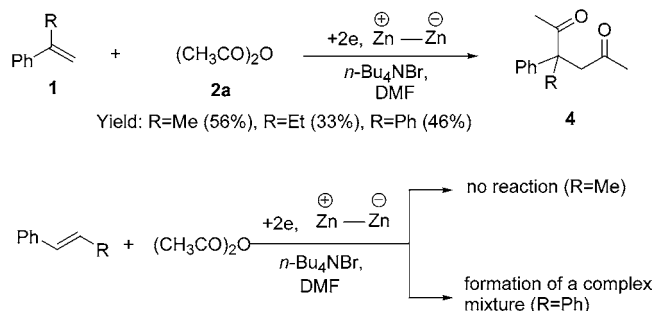
^a Reaction conditions: substrate (10 mmol), acetic anhydride (10 equiv per mol), *n*-Bu₄NBr (1.66 equiv per mol), current density (7 mA/cm²), supplied electricity (6 F/mol), DMF (60 mL), –5 to 5 °C, under N₂ atmosphere. ^b GC yield. ^c Dehalogenated product, 3-phenyl-2,5-hexanedione, was obtained in 14% yield. ^d Not detected.

withdrawing groups on the phenyl ring of styrene gave the 1,4-diketones **4g–i** in satisfactory yield (Table 2, entries 2–4), whereas that of electron-donating groups on the phenyl ring resulted in much decrease in product yield (entry 5) or quantitative recovery of the starting material (entry 6).

(9) The styrenes, **1d–f,h**, were prepared by Wittig reaction, and **1b** and **1c** were prepared by the reported method. See: Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2669.

It is also noteworthy that the presence of alkyl or phenyl groups at the α -carbon of styrene led to only some decrease in the yield of the diacylated products possibly by steric and/or electronic effects (entries 7–9) while that at the β -carbon resulted in quantitative recovery of the starting compounds or formation of a complex mixture (Scheme 3).

Scheme 3. Electroreduction of Substituted Styrenes in the Presence of Acetic Anhydride



Furthermore, electroreduction of alkyl methacrylates **5a–c** and methacrylonitrile (**5d**) in the presence of acetic anhydride (**2a**) under similar conditions provided the corresponding vicinal double acylated products **6a–d** in good to moderate yields. In contrast, only β -monoacylated products **7e,f** were obtained from the reaction of ethyl cinnamate (**7e**) and crotonate (**7f**) under the same conditions, as shown in Table 3.¹⁰

Table 3. Electroreductive C-Acylation of Activated Olefins^a

entry	R ¹ in 5	R ² in 5	Y in 5	yield (%) ^b	
				6	7
1	H	Me	COOBn (5a)	72 (6a)	11 (7a)
2	H	Me	COOMe (5b)	61 (6b)	<i>c</i>
3	H	Me	COOEt (5c)	59 (6c)	<i>c</i>
4	H	Me	CN (5d)	45 (6d)	<i>c</i>
5	Ph	H	COOEt (5e)	<i>c</i>	68 (7e)
6	Me	H	COOEt (5f)	<i>c</i>	50 (7f)

^a Reaction conditions: substrate (10 mmol), acetic anhydride (15 equiv per mol), *n*-Bu₄NBr (1.66 equiv per mol), current density (7 mA/cm²), supplied electricity (6 F/mol), DMF (60 mL), 15–25 °C, under N₂ atmosphere. ^b GC yield. ^c Not detected.

On the other hand, reduction potentials measured by cyclic voltammetry as shown in Table 4 indicate that acetic anhydride (**2a**: no reduction peak up to –3.0V vs Ag/AgCl) and β -methylstyrene (**1j**: E_p = –2.96 V) are quite difficult to reduce electrochemically while styrene (**1a**), α -methylstyrene (**1g**), alkyl methacrylates (**5a–c**), ethyl cinnamate (**5e**), and crotonate (**5f**) (E_p = –1.88 to –2.88 V) are accessible to electrochemical reduction.

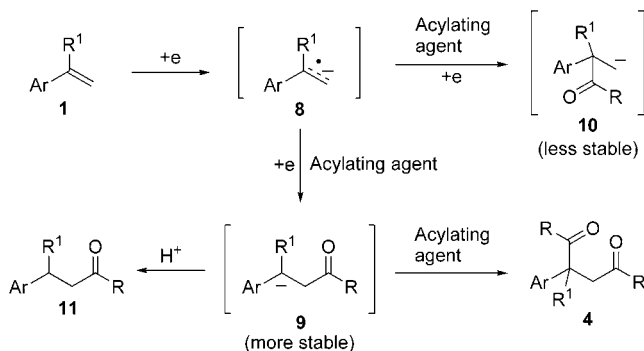
Table 4. Reduction Potentials of Activated Olefins^a

entry	R ¹	Y	reduction potential (V vs Ag/AgCl)	product type
1	H	Ph (1a)	–2.81	diacylation
2	H	Ph (1g)	–2.88	diacylation
3	H	COOBn (5a)	–2.38	diacylation
4	H	COOEt (5c)	–2.50	diacylation
5	Ph	COOEt (5e)	–1.88	monoacylation
6	Me	COOEt (5f)	–2.68	monoacylation
7	Me	Ph (1j)	–2.96	no reaction

^a Counter electrode, Pt; working electrode, Pt; reference electrode, Ag/AgCl; solvent, DMF; supporting electrolyte, *n*-Bu₄NClO₄; scan rate 200 mV/s

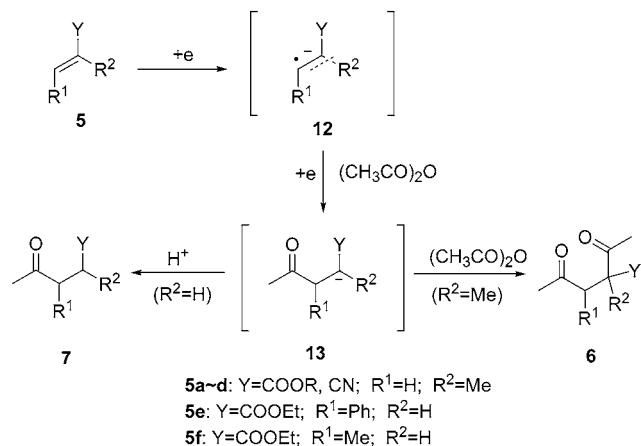
From these experimental results, the following reaction scheme may be proposed although the detailed mechanistic studies have not been conducted as yet. Thus, the first electron transfer from the cathode to styrene derivatives (**1**) generates anion radicals (**8**) which may be subjected to the first electrophilic attack by the acylating agent at the β -carbon of **1** followed by the fast second electron transfer, giving more stable benzylic anions (**9**) preferentially rather than less stable methylene anions (**10**). Subsequently the second electrophilic acylation and protonation take place toward benzylic anions (**9**) to give vicinal double C-acylation products (**4**) and monoacylation products (**11**), respectively (Scheme 4).

Scheme 4. Proposed Reaction Mechanism for C-Acylation of Styrenes



In the case of alkyl methacrylates (**5a–c**), methacrylonitrile (**5d**), ethyl cinnamate (**5e**), and crotonate (**5f**), anion radicals (**12**) generated by the first electron transfer undergo β -acylation followed by a second fast electron transfer giving enolate anions (**13**). The tertiary enolate anions (**13**) derived from **5a–d** (R¹ = H, R² = Me) are presumably less stable but more reactive to the second acylation than the secondary enolates derived from **5e** (R¹ = Ph, R² = H) and **5f** (R¹ = Me, R² = H), which are preferentially subjected to proto-

Scheme 5. Proposed Reaction Mechanism for C-Acylation of Alkyl Methacrylate, Ethyl Cinnamate, and Crotonate



nation. Thereby this hypothesis may account for the sharp contrast between one-pot vicinal α,β -diacylation for **5a–d** and β -monoacylation for **5e** and **5f** (Scheme 5).¹¹

In conclusion, novel one-pot vicinal double C-acylation of styrene derivatives and alkyl methacrylate was successfully accomplished to give useful 1,4-diketones or their precursors. The reaction is characterized by a simple procedure, mild conditions, high selectivity, and a unique reaction pattern. In addition, the products are useful, the starting materials are readily available, and the yields are good.

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Supporting Information Available: Spectral (¹H NMR, ¹³C NMR, IR, and mass) data for all the products **4a–m**, **6a–d**, **7a**, **7e**, and **7f**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) In a 100-mL beaker-type undivided cell equipped with Zn plates (40 × 70 × 0.5 mm³, nacalai tesque, 99%) as the cathode and the anode were introduced 60 mL of anhydrous DMF as a solvent, *n*-Bu₄NBr (16.6 mmol) as a supporting electrolyte, acid anhydrides or *N*-acylimidazoles (100 mmol) and styrenes or alkyl methacrylates (10 mmol). The electrolysis was carried out under constant current conditions (current density: 7 mA/cm²) at –5 to 5 °C with magnetic stirring until 6 F/mol of electricity was passed. After the electrolysis, the reaction mixture was poured into saturated NaHCO₃ solution when acid anhydrides were used as the acylating agents. When *N*-acylimidazoles were used, the reaction mixture was poured into 1% HCl solution after the electrolysis. Organic materials were extracted with three 100-mL portions of ether. The combined ethereal solution was washed with saturated NaCl solution and dried over anhydrous MgSO₄. After removal of MgSO₄ by filtration and evaporation of the solvent, the isolation by column chromatography gave diacylated compounds in satisfactory yields.

(11) This hypothesis is consistent with the phenomenon obtained in Mg-promoted silylation of aromatic active olefins. Simply hydrogenated products are easier to form than the corresponding silylated products in the reaction of the starting substrates possessing less negative reduction potentials, giving more stable anion species through electron transfer from Mg-metal. See: Kyoda, M.; Yokoyama, T.; Kuwahara, T.; Maekawa, H.; Nishiguchi, I. *Chem. Lett.* **2002**, 228.