# Unusual Head-to-Tail Coupling of Alkyl Benzoates by Electroreduction

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The electroreduction of alkyl benzoates in an alcoholic solvent gave unusual head-to-tail coupled products. Usual head-to-head coupled products derived from acyloin condensation could not be detected. The best result (73% yield) was obtained from methyl benzoate using an undivided cell with an Sn cathode in *i*-PrOH containing tetraalkylammonium salt as a supporting electrolyte. Using an undivided cell, the products cross-coupled with a solvent molecule were obtained as byproducts. The substitution at the para position of methyl benzoate considerably decreased the yields of the head-to-tail coupled products and increased those of the cross-coupled products. The possible mechanism of the head-to-tail coupling is the attack of anion radical, generated from methyl benzoate by one-electron transfer, to another methyl benzoate. The cross-coupled products were formed by the reaction with carbonyl compound anodically produced from a solvent molecule. The cross-coupling between methyl benzoate and aromatic aldehydes was also effected by the mixed electroreduction under the same conditions.

#### Introduction

We have already reported the electroreductive crosscoupling of ketones with aromatic rings,<sup>1</sup> nitriles,<sup>2</sup> and O-methyl oximes<sup>3</sup> using an Sn cathode in *i*-PrOH containing tetraalkylammonium salt as a supporting electrolyte. Next, we have planed to realize the electroreductive cross-coupling of ketones with esters. In the course of the study, we found the unusual head-to-tail homo-coupling of alkyl benzoates under these conditions. The reductive homo-coupling of esters with alkali metals has been well-known as acyloin condensation.<sup>4</sup> The electroreduction of aromatic esters using a consumable Mg anode in the presence<sup>5</sup> or absence<sup>6</sup> of SmCl<sub>3</sub> has been found to yield 1,2-diketones. The head-to-tail coupling of aromatic esters is hitherto unknown, although it has been reported that the electroreduction of acetophenone in the presence of  $\beta$ -cyclodextrin promoted the head-to-tail coupling.7 Recently, the reaction of aromatic ketones and

benzaldehyde with  $SmI_2$ -HMPA<sup>8</sup> or Li(Hg)-U(IV)<sup>9</sup> has also been reported to give the similar head-to-tail coupled products. In this paper, we report the results of the unusual head-to-tail coupling of alkyl benzoates in detail.<sup>10</sup> We propose the reaction mechanism of the headto-tail coupling promoted by electroreduction.

# **Results and Discussion**

At first, the electroreduction of methyl benzoate in 0.3 M Et<sub>4</sub>NOTs/*i*-PrOH using an undivided cell and an Sn cathode was carried out at a constant current of 0.2 A. As shown in Scheme 1, head-to-tail coupled product **1a** was obtained in 73% yield with a small amount of benzyl alcohol (12%) and the product cross-coupled with *i*-PrOH (**2a**', 7%). The same reaction using a divided cell gave the head-to-tail coupled product as an isopropyl ester **1b** in 29% yield with benzyl alcohol (15%), whereas no cross-coupled product was formed. The homo-coupled products, **1a** and **1b**, were formed as mixtures of two diastereomers. Under these conditions, bezoin and its related products such as benzil and 1,2-diphenylethane-1,2-diol could not be detected.

The results of the electroreduction of methyl benzoate under the different conditions using an undivided cell are summarized in Table 1. The other cathode materials Zn, Pb, Ag, and Cd gave **1a** (runs 2-5), although the yields decreased to some extent. However, methyl benzoate was recovered completely with Pt cathode due to exclusive hydrogen evolution (run 6). As a supporting electrolyte, tetraalkylammonium salts were crucial to promote the

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Using a divided cell



Table 1. Electroreduction of Methyl Benzoate Using an<br/>Undivided Cell $^a$ 

run	cathode	solvent	% yield <sup>b</sup> of <b>1</b>	% yield <sup>b</sup> of BnOH
1	Sn	<i>i</i> -PrOH	73	12
2	Pb	<i>i</i> -PrOH	52	8
3	Zn	<i>i</i> -PrOH	68	16
4	Ag	<i>i</i> -PrOH	53	5
5	Cď	<i>i</i> -PrOH	47	9
6	Pt	<i>i</i> -PrOH	0	0
7	Sn	<i>i</i> -PrOH <sup>c</sup>	70	10
8	Sn	<i>i</i> -PrOH <sup>d</sup>	0	0
9	Sn	<i>i</i> -PrOH <sup>e</sup>	0	4
10	Sn	t-BuOH	52	4
11	Sn	EtOH	$35^{f}$	13
12	Sn	<i>n</i> -PrOH	$40^{f}$	8
13	Sn	MeOH	0	0
14	Sn	DMF	13	3
15	Sn	CH <sub>3</sub> CN	20	2
16	Sn	THF <sup>c</sup>	0	0

<sup>*a*</sup> The electroreduction was carried out at 0.2 A with Et<sub>4</sub>NOTs as an electrolyte. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> With Bu<sub>4</sub>NClO<sub>4</sub> as an electrolyte. <sup>*d*</sup> With LiClO<sub>4</sub> as an electrolyte. <sup>*e*</sup> With NaClO<sub>4</sub> as an electrolyte. <sup>*f*</sup> See text.

head-to-tail coupling. Use of Bu<sub>4</sub>NClO<sub>4</sub> leaded the result similar to that in run 1 (run 7). On the other hand, use of LiClO<sub>4</sub> caused deposition of Li metal on the cathode surface and resulted in complete recovery of methyl benzoate (run 8). Almost all of methyl benzoate was recovered with a small amount of benzyl alcohol using NaClO<sub>4</sub> (run 9). The other alcoholic solvents *t*-BuOH, n-PrOH, and EtOH also promoted the head-to-tail coupling (runs 10-12). The electroreductions in EtOH and n-PrOH gave the homo-coupled product (1a') and considerable amounts of the products reacted with a solvent molecule at the para position (3' and 4') as depicted in Schemes 2 and 3. These products (X') were obtained as mixtures of saturated and unsaturated products. In the case of EtOH solvent, the products coupled with EtOH at the carbonyl carbon, 1-phenyl-1,2-propanediol (7%) and 1-phenyl-1-propanol (8%), were also formed (Scheme 2). Using a divided cell in EtOH, the head-to-tail coupled product was obtained as an ethyl ester 1c in 58% yield together with benzyl alcohol (10%), and no cross-coupled



product was detected (Scheme 2). Since hydrogen evolution occurred exclusively in MeOH, methyl benzoate was unchanged (run 13). Aprotic solvents such as DMF, acetonitrile, and THF brought about poor results (runs 14-16).

The mixtures of saturated and unsaturated products **1a**', **2a**', **3**', and **4**' were transformed to diastereomeric mixtures of saturated products **1a**, **2a**, **3**, and **4**, respectively, by hydrogenation (Scheme 4). The structures of the saturated products were determined by spectroscopic analysis and also supported by the conversion of **1a**', **2a**', **3**', and **4**' to the corresponding methyl 4-alkylbenzoates and comparison with authentic samples (Scheme 4). At the stage of methyl alkylbenzoates, the formation of the regioisomers such as 2- or 3-alkylbenzoates could not be detected by <sup>1</sup>H NMR and GLC analyses. The other products were confirmed by their spectroscopic data or comparison with authentic samples.

Next, we investigated the substituent effect in the electroreductive coupling of alkyl benzoates. First, ethyl and isopropyl benzoates also gave the corresponding head-to-tail coupled products 1c (50%) and 1b' (20%), though the yields of 1 were lower than that obtained from methyl benzoate (Scheme 5). This result shows that large alkoxy groups in alkyl benzoates hindered the head-to-tail coupling. The decrease of the yield of 1 under the conditions using a divided cell (Schemes 1 and 2) can be explained by transesterification of the starting methyl benzoate to ethyl or isopropyl one.

Second, the effect of para substituents on the aromatic ring was examined. The electroreduction of methyl 4-





methylbenzoate gave the head-to-tail coupled product **5** in a low yield (13%) (Scheme 6). In this case, considerable amounts of the products formed from reaction with *i*-PrOH at the carbonyl carbon, diol **7** and alcohol **8**, were produced along with the product cross-coupled with *i*-PrOH at the para position (**6**). In the electroreductions of methyl 4-*tert*-butylbenzoate and methyl 4-methoxybenzoate, the coupled product at the para position was no longer detectable and only the cross-coupled products at the carbonyl carbon, **9**–**12**, were obtained (Scheme 7). It should be emphasized that the formation of the both head-to-head (acyloin type) and tail-to-tail homo-coupled products could not be detected throughout all the experiments described above.

The electroreduction of the other aromatic carbonyl compounds other than alkyl benzoates was also explored.



As shown in Scheme 8, benzaldehyde and acetophenone afforded the simply reduced alcohols as main products together with pinacols under the same conditions as above. The reduction of *N*,*N*-dimethylbenzamide yielded only benzyl alcohol. These results imply that the elec-

Table 2. DFT (UB3LYP/6-311++G\*\*) Calculations of A<sup>a</sup>



	Mulliken charges <sup>b,c</sup>		natural charges <sup>b,d</sup>		MKS charges <sup>b,e</sup>		Mulliken spin densities <sup>c</sup>	
	gas phase	PCM (EtOH) <sup>f</sup>	gas phase	PCM (EtOH) <sup>f</sup>	gas phase	PCM (EtOH) <sup>f</sup>	gas phase	PCM (EtOH) <sup>f</sup>
C1	1.189	0.640	-0.241	-0.274	-0.012	-0.130	0.098	0.019
C2	-0.695(-0.562)	-0.540(-0.389)	-0.224(-0.022)	-0.276 (-0.077)	-0.178 (-0.117)	-0.226(-0.163)	0.199	0.254
C3	-0.017 (0.091)	-0.191 (0.010)	-0.239 (-0.065)	-0.228 (0.020)	-0.097 (-0.037)	-0.093 (0.018)	-0.048	-0.093
C4	-0.573 (-0.492)	-0.571 (-0.351)	-0.347 (-0.172)	-0.310 (-0.085)	-0.318 (-0.239)	-0.287 (-0.141)	0.347	0.338
C5	0.023 (0.132)	-0.091 (0.113)	-0.239 (-0.066)	-0.227 (0.054)	-0.072 (-0.013)	-0.053 (0.054)	-0.062	-0.097
C6	-0.712 (-0.569)	-0.598 (-0.402)	-0.233 (-0.035)	-0.259 (-0.017)	-0.229 (-0.179)	-0.254 (-0.174)	0.210	0.251
C7	-0.358	-0.094	0.674	0.628	0.473	0.446	0.132	0.201
08	-0.416	-0.528	-0.740	-0.799	-0.641	-0.721	0.148	0.143
09	-0.172	-0.256	-0.614	-0.626	-0.344	-0.381	0.018	0.025
C10	-0.229 (0.156)	-0.235 (0.258)	-0.197 (0.281)	-0.214 (0.317)	0.030 (0.110)	-0.026 (0.191)	-0.003	-0.003

<sup>*a*</sup> Structure of A was optimized by UB3LYP/6-311++G<sup>\*\*</sup> and confirmed by vibration analysis. <sup>*b*</sup> The values in parentheses were the atomic charges with hydrogens summed into heavy atoms. <sup>*c*</sup> Calculated by the Mulliken population analysis. <sup>*d*</sup> Calculated by the natural population analysis. Reference 14. <sup>*e*</sup> Calculated by the Melz–Kollman–Singh method. <sup>*f*</sup> Single point calculation with the Tomasi solvent model in EtOH ( $\epsilon = 24.55$ ).

troreductive head-to-tail coupling is limited to alkyl benzoates.

**Reaction Mechanism.** It has generally been accepted that the key step of usual acyloin condensation involves homolytic coupling of anion radicals induced by oneelectron transfer to esters. In the unusual head-to-tail coupling, it is likely that the active intermediate is an anion radical species. Actually, when the electroreduction of a 1:1 mixture of methyl benzoate and a methyl alkanoate such as methyl formate, acetate, and pivalate was carried out under the same condition as run 1 in Table 1, no cross-coupled product was formed and 1a was obtained in 65-70% yield with complete recovery of the methyl alkanoate. This result suggests that the key step of the head-to-tail coupling is not the nucleophilic attack of an anionic species, but it is the reaction of anion radical species. In the first step of the electroreduction, it is undoubted that the anion radical species A is generated by one-electron transfer to methyl benzoate, and the countercation of A is a tetraalkylammonium salt in contrast to usual acyloin condensation, in which the countercation is a alkali metal cation. It is reasonable that A is present as a naked anion, since the interaction between A and the countercation is much less than in the case of usual acyloin condensation. The DFT calculations (UB3LYP/6- $311++G^{**}$ ) of atomic charges in the naked anion radical A (Table 2) show that para (C4) carbon is negatively charged. Even if carbonyl (C7) carbon is positively charged, this carbon atom is surrounded by highly negative oxygen atoms (O8 and O9). These results suggest that the homolytic coupling of negatively charged A is strongly inhibited by the electronic repulsion between them. Therefore, the head-totail coupling proceeds via attack of A to another methyl benzoate. The calculations of atomic spin densities in A reveal that high spin density exists at the ortho (C2 and C6), para (C4), and carbonyl (C7) carbons (Table 2). There are two possible mechanisms for the head-totail coupling, that is, attack of A at the carbonyl carbon (C7) to the para position of methyl benzoate (path a) and attack of A at the para position (C4) to the carbonyl carbon of methyl benzoate (path b). It seems that path b is more favorable than path a from the result of the cross-coupling reaction of methyl benzoate with



acetone described below. In addition, path b is consistent with the calculated results that C4 carbon has the highest spin density in **A**. Consequently, the overall reaction mechanism can be illustrated as Scheme 9. The headto-tail coupled product **B** is formed through path b and then converted to unsaturated ketoester **C**. The carbonyl group and conjugated olefins of **C** were electrochemically reduced to saturated hydroxy ester **1a**.

The products coupled with a solvent molecule were formed only when the electroreduction was carried out using an undivided cell. This fact suggests that the anodic oxidation of a solvent alcohol to the corresponding carbonyl compound plays an important role in the crosscoupling. In fact, the addition of acetone to the reaction mixture increased the yield of cross-coupled product **2a**' as shown in Scheme 10. This result shows that methyl benzoate is more susceptible to reduction than acetone. The reported half-wave polarographic potentials of methyl benzoate (-2.14 V VS SCE) and acetone (-2.46 V VS SCE) in 0.05 M Et<sub>4</sub>NI/75% dioxane also



support it.<sup>11,12</sup> Therefore, a possible mechanism is proposed in Scheme 11. Carbonyl compound is anodically produced from a solvent. Similarly to the homo-coupling, the anion radical **A** attacks the carbonyl compound at the carbonyl carbon (path c) or the para position (path d) to produce **D** or **F**, respectively. The cross-coupled product **F** is further reduced to saturated hydroxy ester such as **2**, while **D** is transformed to hydroxy ketone **E** which is subsequently reduced to 1,2-diol. The 1,2-diol undergoes dehydration to aromatic ketone followed by reduction to alcohol.

**Cross-Coupling with Aromatic Aldehydes.** The results of cross-coupling with a solvent molecule de-



scribed above imply the possibility of cross-coupling between aromatic esters and other carbonyl compounds. For example, the mixed electroreduction of methyl benzoate and aromatic aldehydes gave cross-coupled products **13'** and **14'**, although the major products were pinacols (Scheme 12). In these reactions, the anion radical generated by one-electron transfer to aromatic aldehyde attacks the para position of methyl benzoate (like path a) to give the cross-coupled product.

# Conclusion

The electroreduction of alkyl benzoates in an alcoholic solvent containing a tetraalkylammonium salt gave unusual head-to-tail homo-coupled products. Head-tohead coupled products such as benzoin and its related compounds were not formed at all under the conditions. This result is attributed to the nature of the anion radical generated from alkyl benzoate electrochemically. Since the countercation of the anion radical is a tetraalkylammonium salt, the anion radical cannot couple each other due to the electronic repulsion and attack the carbonyl carbon of another alkyl benzoate. Using an undivided cell, cross-coupled products of alkyl benzoates with a solvent molecule were also obtained. The crosscoupled products were brought about by the reaction with the carbonyl compound anodically produced from a solvent alcohol. The electroreduction of a mixture of methyl benzoate and an aromatic aldehyde afforded the similar cross-coupled product.

# **Experimental Section**

**Typical Procedure for Electroreduction.** A solution of methyl benzoate (0.41 g, 3.0 mmol) and Et<sub>4</sub>NOTs (3.6 g, 12 mmol) in *i*-PrOH (40 mL) was put into an undivided cell (50 mL beaker) equipped with an Sn cathode ( $5 \times 10 \text{ cm}^2$ ) and a Pt anode ( $2 \times 2 \text{ cm}^2$ ). The electricity was passed with a constant current of 0.2 A until almost all of the esters were consumed (1740 C). The electrolyte was poured into water and extracted with Et<sub>2</sub>O. The products were isolated by column chromatography on silica gel (hexane–AcOEt).

**Typical Procedure for Aromatization of Unsaturated Products.** A solution of **1a**' (0.1 g) and *p*-TsOH·H<sub>2</sub>O (10 mg) in benzene (10 mL) was refluxed for 2 h with continuous removal of water using a Dean–Stark apparatus. After the

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usual workup, the crude product (94 mg) and DDQ (0.23 g) were dissolved in benzene (5 mL) and the mixture was refluxed for 12 h. After the usual workup, methyl 4-benzylbenzoate (31 mg) was isolated by column chromatography on silica gel. By the same method, **2a**', **3**' and **4**' were transformed to methyl 4-isopropyl benzoate, methyl 4-ethylbenzoate, and methyl 4-propylbenzoate, respectively. The products were confirmed by their comparison with authentic samples.

**Typical Procedure for Hydrogenation of Unsaturated Products.** A solution of **1a**' (0.2 g) and 10% Pd/C (0.1 g) in MeOH (5 mL) was stirred under H<sub>2</sub> (1 atm) at room temperature for 12 h. After the usual workup, the product **1a** was obtained quantitatively by column chromatography on silica gel. By the same method, **2a**-c', **3'**, **4'**, **13'** and **14'**, were transformed to the corresponding saturated products **2a**-c, **3**, **4**, **13**, and **14**.

**Synthesis of Authentic Samples.** Methyl 4-benzylbenzoate was prepared from commercially available 4-benzoylbenzoic acid by its hydrogenolysis and subsequent esterification. Methyl 4-alkylbenzoates were accessible from the corresponding 4-alkylbenzoic acids. 1-Phenyl-1,2-propanediol was derived from commercially available 1-phenyl-1,2propanedione by treatment with NaBH<sub>4</sub>. Alcohols **8**, **10**, and **12** were prepared by usual reaction of *i*-PrMgBr with the corresponding aromatic aldehydes. **DFT Calculations.** The DFT calculations were carried out using the Gaussian  $98W^{13}$  program at the unrestricted B3LYP/6-311++G\*\* level.

**Supporting Information Available:** Compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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