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Practical Synthesis of Diethyl Phenylsuccinate by Mg-promoted Carboxylation of Ethyl Cinnamate

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Mg-promoted reduction of ethyl cinnamate (**1a**) in the presence of carbon dioxide gave a mixture of β-carboxylated compound **2a** and α,β-dicarboxylated compound **3a**. Similar reductive carboxylation of **1a** followed by acidic decarboxylation of one of the two geminal carboxyl groups of the generated **3a** and esterification afforded selective formation of diethyl phenylsuccinate (**2a**) in good yield.

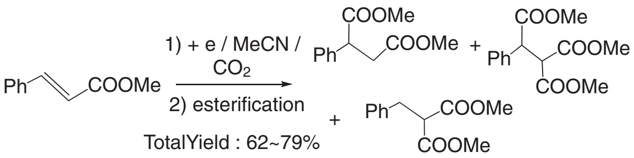
Effective utilization of carbon dioxide has been an important theme for a long time because of concern about global warming gasses and securing carbon resources against exhaustion of petroleum and coal. Many studies on reactions of carbon dioxide have been reported and most of them are related to synthesis of carbonate.[1,2] Transition-metal-catalyzed carbon fixation, with the exception of nickel[3–7] has generally treated not carbon dioxide[8] but carbon monoxide. Electrophilic attack of anionic species like Grignard reagents[9] may be one of the most promising synthetic routes to make use of carbon dioxide.

Tokuda and Senboku revealed electrochemical fixation of carbon dioxide in the presence of halogenated compounds, vinyl triflate, and alkenes and the application to synthesis of organic fine-chemicals and pharmaceuticals.[10–12] Electrochemical carboxylation of benzylideneacetone,[13] acetophenone,[14] styrene,[15,16] and phenylacetylene[17] has been also reported to give selective formation of α-carboxylated or α,β-dicarboxylated compounds in high yields. Lamy,[18] Inesi,[19] and Lu[20,21] reported electrochemical carboxylation of cinnamic acid derivatives, however their methods are not practical because of few reaction examples, considerable recovery of starting material, or formation of three different products as shown in Scheme 1.[20]

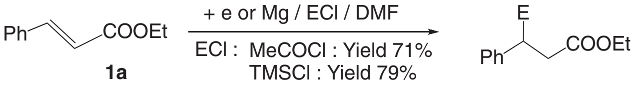
We have already reported generation and reactions of radical anion species by electron transfer, especially electrochemical and Mg-promoted reduction of aromatic carbonyl compounds and their selective cross-coupling reactions.[22,23] In our previous work, Mg-promoted acylation or electrochemical silylation of ethyl cinnamate in *N*,*N*-dimethylformamide[22,23] brought about selective formation of β-acylated or β-silylated compound shown in Scheme 2 in high yield, however this carboxylation gave different products from the reported acylation, silylation, and electrochemical carboxylation due to the difference of electrophilicity or reaction conditions.[18–20,22,23]

In this study, Mg-promoted reduction of ethyl cinnamate in the presence of carbon dioxide followed by esterification gave a mixture of β-carboxylated compound **2** and α,β-dicarboxylated compound **3**, which were easily transformed to diethyl phenylsuccinate after decarboxylation and esterification.

Ethyl cinnamate and its derivatives were also carboxylated to give a mixture of **2** and **3**, which were directly transformed into the corresponding esters by ethyl iodide and sodium hydrogen carbonate as shown in Table 1. The products, α,β-dicarboxylated compounds, are expected to result in selective decarboxylation under heating to afford β-carboxylated compounds, while β-carboxylated compounds formed in this Mg-promoted reduction may be still alive under the same conditions.

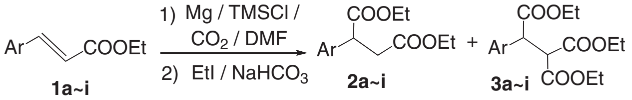


Scheme 1.



Scheme 2.

Table 1. Mg-promoted carboxylation of ethyl cinnamate derivatives[a]



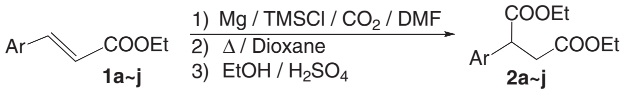
Entry		Ar	GC yield/%		
			2	**3**	Total
1	**1a**	C_6H_5	32	38	70
2	**1d**	$2\text{-}ClC_6H_4$	54	27	81
3	**1f**	$4\text{-}MeOC_6H_4$	9	36	45
4	**1g**	$4\text{-}CF_3C_6H_4$	33	39	72
5	**1h**	2-Furyl	30	18	48
6	**1i**	2-Thienyl	44	14	58

[a] Reaction conditions: 1) Substrate (2 mmol), Mg (3 mol equiv), TMSCl (2 mol equiv), DMF (10 mL), −15 °C, CO_2 bubbling; 2) EtI (9.5 mol equiv), $NaHCO_3$ (4.5 mol equiv), 50 °C.

The results of Mg-promoted carboxylation followed by decarboxylation and esterification are summarized in Table 2. In all the examples, phenylsuccinic acid derivatives **2** were obtained in good yield and no remarkable electron-withdrawing effect was observed (Table 2, Entries 2–4 and 7) although yield of the products with a methoxy or methyl group at the 4-position might decrease because of the electron-donating effect to make generated anionic species unstable (Table 2, Entries 5 and 6).

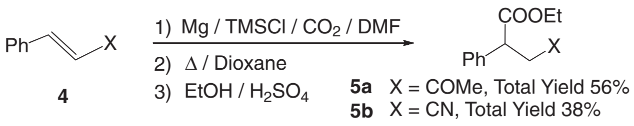
Derivatives with naphthalene or heteroaromatic rings such as furan and thiophene instead of phenyl rings can be transformed to give the corresponding carboxylated compounds (Table 2, Entries 8–10). Benzylideneacetone (**4a**) and cinnamonitrile (**4b**) were also applicable to this reaction to give the corresponding ethyl 4-oxo-2-phenylpentanoate (**5a**) and ethyl 3-

Table 2. Synthesis of succinic acid derivatives[a]

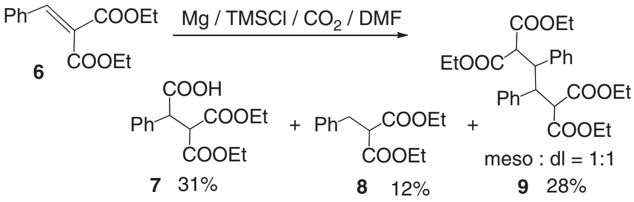


Entry	Ar		Isolated yield/%
1	C_6H_5	**2a**	61
2	$4\text{-}ClC_6H_4$	**2b**	62
3	$3\text{-}ClC_6H_4$	**2c**	64
4	$2\text{-}ClC_6H_4$	**2d**	71
5	$4\text{-}MeC_6H_4$	**2e**	42
6	$4\text{-}MeOC_6H_4$	**2f**	42
7	$4\text{-}CF_3C_6H_4$	**2g**	65
8	2-Furyl	**2h**	43
9	2-Thienyl	**2i**	51
10	1-Naphthyl	**2j**	55

[a] Reaction conditions: 1) Substrate (2 mmol), Mg (3 mol equiv), TMSCl (2 mol equiv), DMF (10 mL), −15 °C, CO_2 bubbling; 2) Dioxane (10 mL), reflux 36 h; 3) EtOH (10 mL), H_2SO_4 (0.4 mL).



Scheme 3.



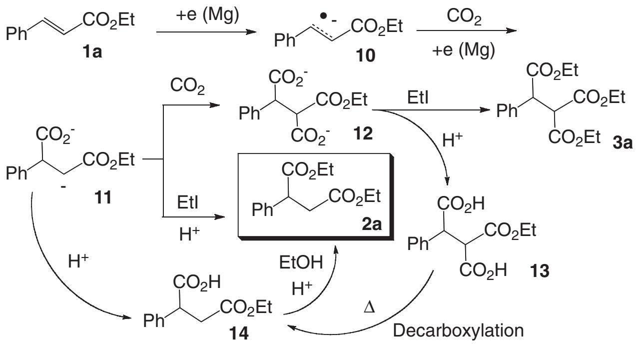
Scheme 4.

cyano-2-phenylpropionate (**5b**) in 56 and 38% yield respectively (Scheme 3).

Similar reactions of α,β-unsaturated ester **6** with two ester groups at the same α-carbon obtained from benzaldehyde and diethyl malonate gave a mixture of β-carboxylated compound **7**, simply reduced compound **8**, and dimeric compound **9** (Scheme 4).

To clarify the reaction mechanism for this Mg-promoted carboxylation of ethyl cinnamate, the reduction potential of starting materials was measured by cyclic voltammetry. Ethyl cinnamate showed a reduction peak at −1.88 V versus Ag/AgCl although carbon dioxide and chlorotrimethylsilane did not show a reduction peak under the same reduction conditions. Since carbon dioxide shows more negative reduction potential according to the literature,[16] this reaction may start by single electron transfer from magnesium to ethyl cinnamate.

A proposed reaction mechanism is shown in Scheme 5. A radical anion species **10** generated from ethyl cinnamate reacts with carbon dioxide at the β-position of the ester group to give an enolate anion **11** after a second electron transfer from magnesium. The possibility of the second carboxylation depends on the reactivity of the enolate anion **11**, which is stable and has low reactivity in DMF. A mixture of β-carboxylated compound **2a** and α,β-dicarboxylated compound **3a** was isolated after esterification at lower temperature. On the other hand **12** is transformed into **14** through decarboxylation by heating the reaction mixture in dioxane and finally typical esterification conditions in ethanol gave diethyl phenylsuccinate (**2a**) as a sole product.



Scheme 5.

In conclusion, Mg-promoted reduction of ethyl cinnamate in the presence of carbon dioxide gave a mixture of β-carboxylated and α,β-dicarboxylated compounds, which was converted into diethyl phenylsuccinate as a single product after decarboxylation and esterification.[24] This Mg-promoted carboxylation is in contrast to our β-selective acylation and silylation from the same anion radical species of ethyl cinnamate and to the electrochemical carboxylation showing different selectivity of the products.

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