Accepted Manuscript

Reductive Carboxylation of Aromatic Esters by Electron Transfer from Magnesium Metal

Hirofumi Maekawa, Hikaru Okawara, Taro Murakami

PII: DOI: Reference:	S0040-4039(16)31627-6 http://dx.doi.org/10.1016/j.tetlet.2016.12.001 TETL 48413
To appear in:	Tetrahedron Letters
Received Date:	1 November 2016
Revised Date:	29 November 2016
Accepted Date:	2 December 2016



Please cite this article as: Maekawa, H., Okawara, H., Murakami, T., Reductive Carboxylation of Aromatic Esters by Electron Transfer from Magnesium Metal, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet. 2016.12.001

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Graphical Abstract

To create your abstract, type over the instructions in the template box below. Fonts or abstract dimensions should not be changed or altered.





Tetrahedron Letters

journal homepage: www.elsevier.com

Reductive Carboxylation of Aromatic Esters by Electron Transfer from Magnesium Metal

Hirofumi Maekawa*, Hikaru Okawara, and Taro Murakami

Department of Materials Science and Technology, Nagaoka University of Technology, 1603-1, Kamitomioka-cho, Nagaoka, Niigata 940-2188, Japan

ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online

Keywords: Ethyl benzoate Carboxylation Magnesium Umpolung Benzoyl formic acid Magnesium-promoted reductive carboxylation of ethyl benzoate in the presence of chlorotrimethylsilane in N,N-dimethylformamide brought about a new carbon-carbon bond formation between the carbonyl carbon atom and carbon dioxide to give the corresponding benzoylformic acid in good yield. It is noteworthy that only ethyl benzoates with substituents at the meta-position were converted into benzoylformic acid derivatives. Moreover, no mandelic acid was detected even under the reductive conditions. This result indicates that benzoylformic acid was obtained after hydrolysis of a carboxylated intermediate, which would be alive as a stabilized structure in the reaction media.

2009 Elsevier Ltd. All rights reserved.

1

Introduction

Carboxylation to form a new carbon- carbon bond has been one of the attractive topics in organic synthesis because it is a solution for both the global warming and the utilization of carbon dioxide as a carbon source. Carbon monoxide is a reactive and available carbon source and has been a star reagent in C1 chemistry. So many reactions related with carbon monoxide were reported especially in the field of the transition metal catalyzed synthesis. However, carbon dioxide had not been controlled by the transition metals in the carbon-carbon bond formation for a long time.^{1,2} Recently, the fixation of carbon dioxide has become one of the topics in the transition metal catalyzed reactions.³⁻⁶

On the other hand, the reactions between carbon dioxide and an anionic species are well known in organic synthesis and the most famous reaction would be the Grignard reaction of carbon dioxide.⁷ The electron transfer reactions, especially, the electrochemical reactions have targeted carbon dioxide as a reagent and there are many reports on the electrochemical carbon dioxide fixation reactions.⁸⁻¹⁸ These reactions suggested that a radical anion species might catch carbon dioxide to form a new carbon-carbon bond under the suitable reaction conditions.

We have also reported magnesium-promoted reduction of ethyl cinnamates in the presence of carbon dioxide to give the selective formation of succinic acid derivatives in good yields.¹⁹ Recently, Hirao and coworkers reported another type of the carbon dioxide fixation reaction by electron transfer from magnesium metal.²⁰ In this study, reductive coupling reaction of ethyl benzoate with carbon dioxide by magnesium brought about the selective carbon-carbon bond formation to give the corresponding benzoylformic acid in good yield. The typical synthetic routes to benzoylformic acids are Friedel-Crafts type acylation of benzene with chlorooxalic acid esters²¹⁻²² and oxidation of mandelic acids.²³ There are a few examples to synthesize benzoylformic acids from benzoic acid derivatives and the important one is the electrochemical carboxylation of benzoyl chlorides.²⁴⁻²⁶ However, no carboxylation of benzoic acid esters carboxylation of benzoic acid be found to our best knowledge.

Results and discussion

At first, supplying methods of carbon dioxide were investigated in N,N-dimethylformamide (DMF). The reduction under the carbon dioxide atmosphere gave the best results and the bubbling condition decreased the yield of the product (**2a**) because of the vaporization of chlorotrimethylsilane from the reaction media (Table 1). In our previous work,¹⁹ magnesium-promoted reduction in supercritical carbon dioxide only or supercritical carbon dioxide in the presence of DMF as the solvent did not proceed smoothly. Therefore, simple supply of carbon dioxide by a balloon was selected in this reaction as the best way.

Furthermore, the effects of temperature, solvent and reaction time were examined under the carbon dioxide atmosphere and reactions in DMF at room temperature proceeded smoothly to give benzoylformic acid (2a) as shown in Table 2. The coupling reaction at room temperature was essential (entries 1-5) and only aprotic polar solvents were suitable to consume the starting

^{*} Corresponding author. Tel.: +81-258-47-9320; fax: +81-258-47-9300; e-mail: maekawa@vos.nagaokaut.ac.jp

Tetrahedron Letters

material (1a). To simplify the reaction process, the reaction conditions in entry 2 were selected as the best procedure.

Table 1. Investigation of the CO₂ supply



Entry	Conditions	Isolated yield (%)
1	CO ₂ atmosphere	69
2	CO ₂ atmosphere ^a	67
3	CO ₂ bubbling	39
4	No CO ₂ supply	No Reaction

1a (5 mmol), Mg (4 equiv.), TMSCl (6 equiv.), DMF (30 mL), 0° C (5 h) and 20 °C (4.5 h). ^a The solvent after CO₂ bubbling was used.



reaction time



Entry	Temperature (°C)	Reaction time (h)	Solvent	Isolated Yield (%)
1^{a}	20	9.5	DMF	69
2	20	8.5	DMF	65
3	15	9.5	DMF	63
4	0	48	DMF	56
5	45	8	DMF	Complex mixture ^b
6	20	8.5	NMP	47
7	20	8.5	DMAc	39
8	20	8.5	THF	No reaction
9	20	8.5	CH₃CN	No reaction

1a (5 mmol), Mg (4 equiv.), TMSCl (6 equiv.), Solvent (30 mL), CO_2 atmosphere. ^a0°C (5 h) and 20°C (4.5 h). ^bMain products were benzoic acid and mandelic acid.

Table 3. Steric effect of the alkyl group of ester



1 (5 mmol), Mg (3 equiv.), TMSCl (4 equiv.), DMF (30 mL), 20 $^{\circ}\text{C},$ CO $_2$ atmosphere.

To investigate the effects of the alkyl group of ester, the carboxylation of several esters was carried out under the similar reaction conditions as shown in Table 3. Reactions of ethyl ester and methyl ester gave the desired compound in good yield, respectively, however, a low yield of the product was obtained

for isopropyl ester because of the steric effect of the isopropyl group.

The ratio of magnesium and chlorotrimethylsilane was also investigated and the combination of 3 equivalent of magnesium and 5 equivalent of chlorotrimethylsilane (entry 7) was found to be the optimized reaction conditions (Table 4).

Table 4. Optimization of carboxylation of ethyl benzoate



Entry	Mg (equiv. mol)	TMSCl (equiv. mol)	Isolated Yield (%) ^a		
1	2	2	31		
2	2	3	29		
3	2	4	66		
4	2	5	68		
5	2	6	55		
6	3	4	66		
7	3	5	75		
8	3	6	63		
9	4	5	65		
10	4	6	65		
11	4	7	69		
12	5	6	69		
13	5	7	67		
14	6	4	72		

1a (5 mmol), DMF (30 mL), 20°C, CO2 atmosphere.

^aBenzoic acid was detected as a byproduct.

Carboxylation of a variety of ethyl benzoate derivatives was carried out under the optimized reaction conditions (Table 5). As a result, most of meta-substituted derivatives were smoothly transformed into the corresponding carboxylated compounds (entries 1-6 and 9-12). Exceptionally, the substitution of a hydroxyl group or an acetoxy group on the benzene ring at the meta-position complicated the results probably because of the reaction between chlorotrimethylsilane and the hydroxyl group or the attack to the acetyl group by an anionic species (entries 7 and 8). On the contrary, ortho- and para-substituted derivatives gave no carboxylated product (entries 13-17).

Because an electron-donating group such as a methyl group and a methoxyl group caused the negative shift of the reduction potential and the instability of the radical anion species. Especially in entry 15, the reduction of **10** was impossible by magnesium metal. This result indicates that the critical limitation of the reduction potential in magnesium-promoted reduction in DMF may exist between -2.33 V and -2.54 V versus Ag/AgCl. A trifluoromethyl group may lead to the elimination of a fluorine atom by conjugated system of the anionic species generated from a single electron transfer to **1**, to give a complex mixture (entries 13 and 16). Application of a naphthyl group and a pyridyl group to this reductive carboxylation failed under our reaction conditions.

Ethyl benzoate labeled with ¹³C carbon on the carbonyl carbon atom (**1a**') was reduced by magnesium metal under the same reaction conditions to give the corresponding benzoylformic acid labeled on the carbonyl carbon atom of ketone (**2a**') (Scheme 1).

NUSCRIPT ED)

Table 5. Carboxylation of ethyl benzoate derivatives

11

Η

CF₃

Η



CF₃

12 Н F Н F 62 1m Н 13 н CF₃ н Complex mixture 1n -2.39 14 Н Н Me Н Trace 10 15 Η Η Н 2.54 OMe No reaction 16 CF₃ Н Н Н 1p Complex mixture 1a 17 Η Η -2.38 Trace Me Η

1 (5 mmol), Mg (3 equiv.), TMSCI (5 equiv.), DMF (30 mL), CO₂ atmosphere, 20°C. ^aWorking electrode Pt, counter electrode Pt, reference electrode Ag/AgCl, solvent DMF, supporting electrolyte 1% nBu₄NBF₄, scan rate 0.2 V s¹.

1k

11



This fact suggests that no rearrangement occurred in the course of the reduction and that carbon dioxide was introduced into the benzoylformic acid as a carboxylic acid group.

Furthermore, it was quite strange that benzoylformic acid (2a) was obtained instead of mandelic acid in this reductive coupling because 2a would be easily reduced under the reduction conditions. The reduction potential of 2a and commercially available ethyl benzoylformate was measured, however, 2a did not show a significant peak while the reduction peak of ethyl benzoylformate was observed at -1.35 V. Next, magnesiumpromoted reduction of 2a was investigated under the similar reaction conditions as our previous carboxylation to give the corresponding mandelic acid (3a) in 58 % yield (Scheme 2).



This result may suggest that benzoylformic acid will not generate as a free form in situ, but exist as a protected form,

although our trial to isolate a protected compound as the intermediate failed to give no evidence on the formation of the intermediate. On the basis of our investigation, a plausible reaction mechanism is shown in Scheme 3.

2k

21



A single electron transfer from magnesium metal to ethyl benzoate 1a produces a radical anion species 4a, which reacts first with chlorotrimethylsilane and receive a second electron

Isolated Yield (%)

75

65

50

Ğ1

53

Complex mixture

Complex mixture

60

40

65

4

ACCEPTED MANUSCRIPT

Tetrahedron

from magnesium at the same time to give an anionic species 5a. The intermediate 5a reacts with carbon dioxide at the benzylic position to afford 6a with reproduction of an aromatic ring. The anion 6a is stabilized by the coordination with magnesium cation and will not be reduced because of its anionic moiety and the protection of the carbonyl group as an acetal structure. Therefore, benzoylformic acid may survive in situ and generate after the hydrolysis.

Conclusion

Magnesium-promoted reductive coupling of aromatic esters **1** with carbon dioxide in the presence of chlorotrimethylsilane produced the corresponding benzoylformic acids in moderate to good yield, which might be controlled by the reduction potential and the substituent effect on the benzene ring. Formation of benzoylformic acids suggested that the products in the reaction media would survive as a protected structure.

Acknowledgments

This work was supported in part by JSPS KAKENHI Grant Number 22605003 and 25410110.

Supplementary Material

Supplementary data (copies of the ¹H and ¹³C NMR spectra of the derivatives that were produced by this procedure were supplied) associated with this article can be found, in the online version.

References

- 1. Cohen, C. T.; Chu, T.; Coate, G. W. J. Am. Chem. Soc. 2005, 127, 10869-10878.
- Yamada, W.; Sugawara, Y.; Cheng, H. M.; Ikeno, T.; Yamada, T. Eur. J. Org. Chem. 2007, 2604-2607.
- Williams, C. M.; Johnson, J. B.; Rovis, T. J. Am. Chem. Soc. 2008, 130, 14936-14937.

C

- 4. Takimoto, M.; Mizuno, T.; Mori, M.; Sato, Y. *Tetrahedron* 2006, 62, 7589-7597.
- Yeung, C. S.; Dong, V. M. J. Am. Chem. Soc. 2008, 130, 7826-7827.
- Takaya, J.; Sasano, K.; Iwasawa, N. Org. Lett. 2011, 13, 1698-1701.
- 7. Gilman, H.; Kirby, R. H. Org. Synth. **1925**, *5*, 75-78.
- Kamekawa, H.; Senboku, H.; Tokuda, M. *Electrochim. Acta* 1997, 42, 2117-2123.
- 9. Senboku, H.; Fujimura, Y.; Kamekawa, H.; Tokuda, M. *Electrochim. Acta* **2000**, *45*, 2995-3003.
- Kamekawa, H.; Senboku, H.; Tokuda, M. Tetrahedron Lett. 1998, 39, 1591-1594.
- 11. Chowdhury, M. A.; Senboku, H.; Tokuda, M.; *Tetrahedron* **2004**, *60*, 475-481.
- 12. Tokuda, M. J. Nat. Gas Chem. 2006, 15, 275-281.
- 13. Silvestri, G.; Gambino, S.; Filardo, G. *Tetrahedron Lett.* **1986**, *27*, 3429-3430.
- 14. Harada, J.; Sakakibara, Y.; Kunai, A.; Sasaki, K. Bull. Chem. Soc. Jpn. **1984**, *57*, 611-612.
- 15. Engels, R.; Schäfer, H. J. Angew. Chem. 1978, 90, 483.
- 16. Senboku, H.; Komatsu, H.; Fujimura, Y.; Tokuda, M. Synlett 2001, 418-420.
- 17. Yuan, G.-Q.; Jiang, H.-F.; Lin, C. *Tetrahedron* **2008**, *64*, 5866-5872.
- Ohkoshi, M.; Michinishi, J.; Hara, S.; Senboku, H. *Tetrahedron* 2010, 66, 7732–7737.
- Maekawa, H.; Murakami, T.; Miyazaki, T.; Nishiguchi, I. Chem. Lett. 2011, 40, 368-369.
- 20. Amaya, T.; Kurata, I.; Hirao, T. Org. Chem. Front. 2016, 3, 929-933.
- 21. Itoh, O.; Nagata, T.; Nomura, I.; Takanaga, T.; Sugita, T.;
- Ichikawa, K. Bull. Chem. Soc. Jpn. 1984, 57, 810-814.
 Chiba, S.; Zhang, L.; Lee, J.-Y. J. Am. Chem. Soc. 2010, 132,
- 7266-7267.
- Ma, Z.; Bobbitt, J. M. J. Org. Chem. 1991, 56, 6110-6114.
 Pokhodenko, V. D.; Koshechko, V. G.; Titov, V. E.;
- Lopushanskaja, V. A. *Tetrahedron Lett.* **1995**, *36*, 3277-3278. 25. Koshechko, V. G.; Titov, V. E.; Lopushanskaya, V. A. *Russ. J.*
- *Electrochem.* 2000, *36*, 149-154.
 Titov, V. E.; Lopushanskaya, V. A.; Koshechko, V. G. *Theor. Exp. Chem.* 2002, *38*, 289-294.

Click here to remove instruction text...

ACCEPTED MANUSCRIPT

Graphical Abstract

To create your abstract, type over the instructions in the template box below. Fonts or abstract dimensions should not be changed or altered.



CCEPTED MANUSCRIPT

Tetrahedron

The carbonyl carbon atoms of aromatic esters were reductively carboxylated by Mg.

Acceleration Under our reduction conditions, 1,2-dicarbonyl compounds can survive.

Non-substituted and meta-substituted aromatic esters can be applied.

4