Tetrahedron Letters 56 (2015) 6772-6776

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Electrochemical direct carboxylation of benzyl alcohols having an electron-withdrawing group on the phenyl ring: one-step formation of phenylacetic acids from benzyl alcohols under mild conditions

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ARTICLE INFO

Article history: Received 20 August 2015 Revised 15 October 2015 Accepted 20 October 2015 Available online 21 October 2015

Keywords: Electrochemical reduction Fixation of carbon dioxide Benzyl alcohols Phenylacetic acids One-step formation

ABSTRACT

Electrochemical direct carboxylation of benzyl alcohols having an electron-withdrawing group on the phenyl ring was successfully carried out by constant current electrolysis using an undivided cell equipped with a platinum plate cathode and a magnesium rod anode in DMF in the presence of carbon dioxide. Reductive cleavage of the C–O bond followed by fixation of carbon dioxide efficiently took place at the benzylic position without any additive to give the corresponding phenylacetic acids in good yields in one step under neutral and mild conditions.

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Oxidation of a primary alcohol is a straightforward approach to obtain a carboxylic acid.¹ However, when a primary alcohol yielding the desired carboxylic acid by oxidation is not readily available, one useful alternative approach is transformation of readily available primary and secondary alcohols to desired carboxylic acids with one-carbon homologation. For instance, transformation of benzyl alcohols including 1-phenylethanols to phenylacetic acids and phenylpropanoic acids, known as potential bioactive compounds including non-steroidal anti-inflammatory agents, demands one-carbon homologation and two or more steps are generally required. One conventional approach involves hydrolysis of benzyl cyanides, which are generally prepared by transformation of a hydroxyl group to an appropriate leaving group followed by reaction with hazardous cyanide ion as a homologation carbon source (Eq. 1).² Reaction of Grignard reagents prepared from the corresponding benzyl halides, derived from benzyl alcohols, with carbon dioxide as a carbon source can also provide carboxylic acids, although high reactivity of Grignard reagents limits acceptable functional groups in the substrates (Eq. 2).³ For one-step synthesis of carboxylic acids from alcohols, substitution of a hydroxyl group to a carboxyl group has to be

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metal catalysts such as palladium, rhodium, and nickel with hazardous carbon monoxide as a homologation carbon source⁴ (Eq. 3). However, the use of pressurized carbon monoxide and a high reaction temperature with strong acids and/or halide salts as promoters were necessary in most cases, and it seems to be hazardous and troublesome. Therefore, the development of milder and environmentally benign alternatives is desirable from the viewpoint of eco-friendly organic synthesis. Because of its abundance and non-toxicity, on the other hand, carbon dioxide (CO₂) is well known as a useful, important and environmentally benign C1 carbon source, and results of applications to organic synthesis have been widely reviewed.⁵ The electrochemical method⁶ has widely used for fixation of carbon dioxide in organic molecules with carbon-carbon bond formation yielding carboxylic acids.⁷ When a reactive metal, such as magnesium or aluminum, is used as an anode in the electrolysis,^{8,9} even under atmospheric pressure of carbon dioxide, fixation can be accomplished to give carboxylic acids in high yields under neutral and mild conditions. For instance, Troupel and co-workers reported synthesis of phenylacetic acids by electrochemical carboxylation of several benzyl alcohol derivatives in moderate to good yields.¹⁰ Recently, we successfully demonstrated two-step conversion of benzyl alcohols to phenylacetic acids using the electrochemical method. Constant current electrolysis of benzyl carbonates, readily prepared from the corresponding benzyl alcohols with appropriate

achieved in one step. This has been accomplished using transition





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chloroformates in one step, using a one-compartment cell equipped with a platinum cathode and a magnesium anode in acetonitrile in the presence of atmospheric carbon dioxide resulted in reductive carboxylation at the benzylic position of benzyl carbonates to give the corresponding phenylacetic acids and phenylpropanoic acids in good yields (Eq. 4).¹¹ In the course of our studies on electroorganic synthesis,¹² we recently found that direct one-step conversion of benzyl alcohols having an electron-withdrawing group on the phenyl ring to phenylacetic acids was possible using the electrochemical method with carbon dioxide as a carbon source under neutral and mild conditions. Constant current electrolysis of benzyl alcohols having an electron-withdrawing group on the phenyl ring using a one-compartment cell equipped with a platinum cathode and a magnesium anode in DMF in the presence of atmospheric carbon dioxide resulted in direct formation of the corresponding phenylacetic acid in one step in good vields (Eq. 5). To the best of our knowledge, there is no example of one-step transformation of benzyl alcohols to phenylacetic acids using carbon dioxide as a carbon source under neutral and mild conditions. Here, we report the results of electrochemical direct carboxylation of benzyl alcohols having an electron-withdrawing group on the phenyl ring: one-step formation of phenylacetic acids from benzyl alcohols under mild conditions.



Firstly, reaction condition screening was carried out using benzyl alcohol **1a** having an ester substituent at the *para* position as a substrate. The results are summarized in Table 1. Constant current electrolysis (20 mA/cm²) of **1a** was carried out in acetonitrile

Table 1

Screening of reaction conditions

containing 0.1 M Bu₄NBF₄ using a test tube-like undivided cell equipped with a Pt plate cathode $(2 \times 2 \text{ cm}^2)$ and an Mg rod anode $(3 \text{ mm}\phi, \text{ca. } 20 \text{ mm})$ in the presence of carbon dioxide at 0 °C with 4 F/mol of electricity. After the usual work-up, the corresponding phenylacetic acid 2a was obtained in 32% yield along with a simple reduction product, toluene derivative 3 in 25% yield with 57% conversion of 1a (entry 1 in Table 1). Switching the solvent from acetonitrile to DMF under the same conditions resulted in an improvement of the conversion of **1a** and the yield of **2a** with a reduction of the yield of **3** to 4% (entry 2). An increase or decrease in current density was not effective for improving the conversion of 1a and the yield of 2a (entries 3 and 4). When 6 F/mol of electricity was passed to a DMF solution of **1a** with 20 mA/cm² of current density, we could obtain 2a in 73% isolated yield with 83% conversion (entry 5). Effect of reaction temperature was also investigated. Electrolysis at -20 °C resulted in a slight decrease of the yield of **2a** and the conversion of **1a** (entry 6). Although the yield of **2a** and the conversion of 1a slightly increased in electrolysis at 20 °C, the product selectivity of 2a unfortunately decreased (entry 7).

The scope and limitation of the present direct electrochemical carboxylation of several benzylic alcohols were investigated, and the results are summarized in Table 2.13 Unsubstituted benzyl alcohol (1b) and mono-fluorobenzyl alcohols 1c and 1d were not applicable for this direct carboxylation (entries 2-4). 3.5-Difluorobenzyl alcohol (1e) and 4-phenylbenzyl alcohol (1f) were also ineffective (entries 5 and 6). In these cases, most of the starting alcohol 1 was unchanged and was recovered in 51-91% ¹H NMR yield. On the other hand, when para-cyanobenzyl alcohol (1g) was used as a substrate and was electrolyzed under the same conditions, carboxylation at the benzylic position occurred efficiently to give the corresponding phenylacetic acid 2g in 78% isolated yield (entry 7). These results indicate that a strong electron-withdrawing group is necessary on the phenyl ring of benzyl alcohol for the present direct carboxylation. Although a similar reaction of benzyl alcohol **1h**, having an ester group at the *ortho* position on the phenyl ring, provided the corresponding carboxylic acid **2h** in 55% isolated vield (entry 8), a similar reaction of alcohol **1i** having an ester group at the meta position gave only a trace amount of carboxylic acid (entry 9). These results indicated that the location of an electronwithdrawing group on the phenyl ring of benzyl alcohol is critical for the present direct carboxylation of benzyl alcohol. From the fact that an electron-withdrawing group at the ortho or para position is effective and one at the meta position is ineffective, it is thought that a resonance effect plays an important role.

The present direct carboxylation was also carried out by using pentafluorobenzyl alcohol (**1j**) and 4-trifluoromethylbenzyl

	$H_{3}CO_{2}C$ $1a$ $H_{3}CO_{2}C$ $1a$ $H_{3}CO_{2}C$ $H_{3}CO_{2}C$ $H_{3}CO_{2}C$ $H_{3}CO_{2}C$ $H_{3}CO_{2}C$ $2a$ $H_{3}CO_{2}C$ 3									
Entry	Solvent	Current density [mA/cm ²]	Electricity [F/mol]	Temperature [°C]	Conversion ^a [%]	Yield [%]				
						2a ^b	3 ^a			
1	CH ₃ CN	20	4	0	57	32	25			
2	DMF	20	4	0	74	59	4			
3	DMF	15	4	0	75	59	5			
4	DMF	30	4	0	65	55	4			
5	DMF	20	6	0	83	73	3			
6	DMF	20	6	-20	71	67	2			
7	DMF	20	6	20	99	79	10			

^a Determined by ¹H NMR using 1,4-dintrobenzene as an internal standard.

^b Isolated yield.

Table 2

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In parenthesis, the yield determined by $^1\mathrm{H}$ NMR using 1,4-dintrobenzene as an internal standard.

^a Determined by ¹H NMR using 1,4-dinitrobenzene as an internal standard.

alcohol (**1k**) as substrates, and the results are summarized in Scheme 1.¹⁴ Although a complex mixture was only obtained by electrolysis of **1j** under the same conditions as those shown in Table 2, we finally found that reductive cleavage of the C–F bond followed by carboxylation selectively occurred at the *para* position on the phenyl ring to give 4-hydroxymethyl-2,3,5,6-tetrafluo-robenzoic acid (**4**)^{12g} under milder electrolysis conditions as shown in Scheme 1.¹⁵ We also tested a trifluoromethyl group as an electron-withdrawing group for the direct carboxylation. When 4-trifluoromethylbenzyl alcohol (**1k**) was subjected to the present direct carboxylation under the same conditions as those shown in Table 1, reductive cleavage of the C–F bond followed by carboxylation selectively occurred at the benzylic position of the CF₃ group on the phenyl ring to give 2,2-difluoro-(4-hydroxymethylphenyl) acetic acid (**5**) in 74% yield (Scheme 1). Similar electrochemical carboxylation of benzotrifluoride (α,α,α -trifluorotoluene) has already

been reported by Troupel and Périchon's group¹⁶ and by us.¹⁷ These results indicate that fluorine atoms and a trifluoromethyl group are not suitable as electron-withdrawing groups for the present direct electrochemical carboxylation of benzyl alcohol.

We next investigated application of secondary and tertiary benzyl alcohols to the present direct carboxylation as substrates. Some of the results are shown in Scheme 2.¹⁸ When 1-phenylethanol 6a having an ester group at the para position of the phenyl ring was electrolyzed in the presence of carbon dioxide under the same conditions as those shown in Table 1, similar direct carboxylation of a secondary benzyl alcohol also took place to give the corresponding 2-arylpropanoic acid **7a** in 59% yield, and 40% recovery of **6a** was detected by ¹H NMR. In a similar manner, electrochemical direct carboxylation of secondary benzyl alcohol 6b having a cyano group, instead of an ester group, gave 2-(p-cyanophenyl)propanoic acid (**7b**) in 60% vield, and 25% recovery of **6b** was detected by 1 H NMR. The present direct carboxylation was also applicable to tertiary benzyl alcohol. It proceeded, however, less effectively than that of secondary benzyl alcohols. When tertiary benzyl alcohol 8 was electrolyzed under the same conditions, the corresponding carboxylic acid 9 was obtained only in 25% yield as shown in Scheme 2 and 62% recovery of 8 was detected by ¹H NMR. Although diphenylmethanol (benzhydrol) was, on the other hand, subjected to the present direct carboxylation under the same conditions, the starting material was recovered in 96% and only a trace amount of diphenylacetic acid was detected by ¹H NMR.

Although details are still unclear at this stage, one plausible reaction mechanism in the present electrochemical direct carboxylation of benzyl alcohol is shown in Scheme 3.¹⁹ At the cathode, one-electron reduction of the benzyl alcohol **1** results in hydrogen and alkoxide ion **A**. Evolution of hydrogen at the cathode can be easily observed by the naked eyes. The generated alkoxide ion **A** reacts with carbon dioxide to form benzyl carbonate ion **B**. Twoelectron reduction of the thus-generated benzyl carbonate ion **B** at the cathode generates benzylic anion **C**. Electrochemical reduction of benzyl carbonate **10** in the presence of carbon dioxide has been reported by Troupel¹⁰ and by us.¹¹ It is thought that reduction of benzyl carbonate ion **B** is more difficult than reduction of



Scheme 1. Electrochemical carboxylation of pentafluorobenzyl alcohol (1j) and 4-trifluoromethylbenzyl alcohol (1k).



Scheme 2. Electrochemical direct carboxylation of secondary and tertiary benzyl alcohols 6a, 6b and 8.

^b Isolated yield.

at the cathode



Scheme 3. Probable reaction mechanism of electrochemical direct carboxylation of benzyl alcohols.

electronically-neutral benzyl alkyl carbonate 10. It is likely that the electron-withdrawing group on the phenyl ring of 1 plays an important role in reduction of **B**. The generated benzyl anion **C** and carbon dioxide react with formation of a carbon-carbon bond to give the corresponding carboxylate ion **D**. At the anode, on the other hand, dissolution of magnesium metal takes place to generate magnesium cation. Carboxylate ion **D**, carbonate ion, and magnesium cation form magnesium salts. Acid treatment in the workup gives carboxylic acid 2. Competitively, electrochemical reduction of carbon dioxide would take place at the cathode, resulting in an excess amount of electricity for a high rate of conversion and high yield. The possibility of direct electrochemical reduction of benzyl alcohol 1 generating benzyl anion C cannot be excluded. When benzyl alcohol 1a was electrolyzed in the absence of carbon dioxide, methyl p-methylbenzoate, which would be produced by reductive cleavage of the benzylic C-O bond followed by protonation, was detected in 7% yield along with 61% of recovery of **1a** by ¹H NMR. Both reaction paths of reduction might be involved in the generation of benzyl anion **C**. Although detection of intermediate **B** by the reaction with iodomethane failed, these results indicate that carbon dioxide plays an important role in reductive cleavage of the C-O bond at the benzylic position.

In conclusion, electrochemical direct carboxylation of benzyl alcohols having an electron-withdrawing group was successfully carried out. The present method could provide the corresponding phenylacetic acids and phenylpropanoic acids from benzyl alcohols using atmospheric pressure of carbon dioxide in good yields under neutral and mild conditions. This is the first example of one-step transformation of benzyl alcohols into phenylacetic acids and phenylpropanoic acids using carbon dioxide as a carbon source without the use of pressurized carbon monoxide and any initiators such as strong acids or halide salts.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research (C), JSPS KAKENHI Grant Number 25410104.

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- 13. Benzyl alcohols **1a**–**g** are commercially available. Alcohol **1h**²⁰ was prepared from phthalide by the reaction with aq NaOH followed by iodomethane. Alcohol 1i²¹ was prepared from the corresponding commercially available aldehyde by the reaction with NaBH₄ in MeOH. Isolated and detected carboxylic acids 2a,¹¹ 2d,²² 2e,²³ 2f,^{22b,24} 2g¹¹ and 2h²⁵ are known compounds and their spectral data were good agreement with reported ones.
- 14. Benzyl alcohols 1j and 1k are commercially available. Selected spectral data of carboxylic acid **5**: *δ*_H (400 MHz, DMSO-d6) 2.50 (1H, s), 4.55 (2H, s), 7.46 (2H, d, J = 8.1 Hz), 7.52 (2H, d, J = 8.1 Hz); δ_C (100 MHz, DMSO-d6) 62.4, 113.7 (t, J = 248 Hz), 125.0 (t, J = 6 Hz), 126.7, 131.1 (t, J = 25 Hz), 146.0, 165.2 (t, = 34 Hz); δ_F (372.5 MHz, DMSO-d6) –101.8.
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 Alcohols **6a**,²⁶ **6b**²⁰ and **8**²⁷ were prepared from the corresponding commercially available ketones by the reaction with NaBH4 in MeOH or with methylmagnesium bromide in THF. Isolated carboxylic acids 7a and 7b are known compounds and their spectral data were good agreement with reported ones.¹¹ Selected spectral data of carboxylic acid **9**: $\delta_{\rm H}$ (400 MHz, CDCl₃) 1.63 (6H, s), 3.91 (3H, s), 7.47 (2H, d, J = 8.0 Hz), 8.01 (2H, d, J = 8.0 Hz); δ_{C} (100 MHz, CDCl₃) 26.0, 46.6, 52.1, 125.9, 128.7, 129.7, 148.9, 166.9, 182.4.
- 19. Cyclic voltammetry of several representative benzyl alcohols 1a, 1b, 1i, 1j, 1k, and 6a was carried out. While no reduction peaks were observed in CVs of 1b, 1j, and 1k at more positive potential than -3.0 V versus Ag/Ag⁺, reduction peaks were observed in CVs of 1a, 1i and 6a. Their reduction peaks appeared at about -2.8 V versus Ag/Ag⁺ in their CVs although the reaction of 1a and 6a gave carboxylic acids and the reaction of 1i did not. These results indicate that relationships between the yields and the reduction potentials are so complicated to explain clearly and reasonably at the present stage.
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