



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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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-phenylethanol 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

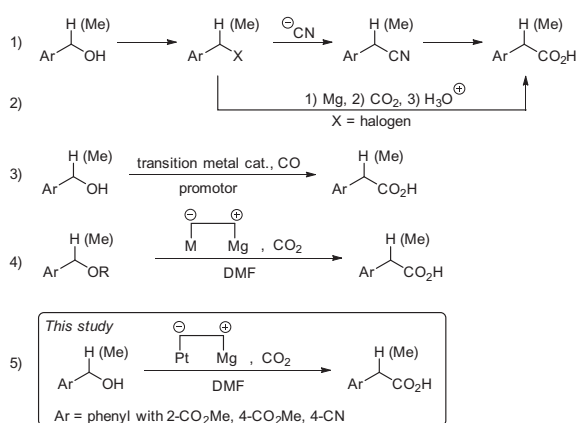
achieved in one step. This has been accomplished using transition metal catalysts such as palladium, rhodium, and nickel with hazardous carbon monoxide as a homologation carbon source⁴ (Eq. 3). However, the use of pressurized carbon monoxide and a high reaction temperature with strong acids and/or halide 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

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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 yields (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

containing 0.1 M Bu₄NBF₄ using a test tube-like undivided cell equipped with a Pt plate cathode (2 × 2 cm²) and an Mg rod anode (3 mmϕ, ca. 20 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 yield (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 electron-withdrawing 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

Table 1
Screening of reaction conditions



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-dinitrobenzene as an internal standard.

^b Isolated yield.

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