A Synthesis of Phenylglycine and α-Methylphenylglycine by Electroreductive Carboxylation of Schiff Bases

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The electroreductive carboxylation of the Schiff bases (**1a–c**) derived from benzaldehyde and benzylamine or α-alkylbenzylamines followed by hydrogenolysis of the electrolyzed solution afforded phenyglycine in good yields. The reduction of the Schiff bases (**1d, e**) led to the formation of α-methylphenylglycine. The method was further extended to the transformation of benzalazine into phenyl-glycine. The mechanism of the electroreductive carboxylation is also discussed.

KEY WORDS: Electroreductive Carboxylation/ Cathodic Reduction/ Schiff Base/ Carbon Dioxide/ Benzalazine/ Phenyl-glycine/ α-Methylphenylglycine/

The recent revival of interest in the synthesis of phenylglycine and the derivatives is due to an increased demand as indispensable intermediates for the synthesis of semisynthetic β-lactam antibiotics.[1] These amino acids have been synthesized usually by the classical methods including Strecker or Bucherer synthesis. Although the potential versatility of these methods has been recognized in the laboratory scale preparation, rising demands with respect to protecting the environment in the industrial scale production enforce the use of a very stringent economic pathway to construct the amino acids. In the last decade, the utilization of carbon dioxide as a source of a carboxylic acid group has gained considerable preparative significance in amino acid chemistry. The prominent method is exemplified[2] by the synthesis of phenyl-glycine, based on the efficacy of carboxylation of the carbanion generated from benzyl isonitrile which involves isonitrile group-assisted lithiation. On the other hand, electroorganic reactions have provided a powerful tool for generation of the carbanions of organic substrates.[3] Several reports in the copious literature have dealt with the use of carbon dioxide as a trapping agent in order to probe both the existence of the reducing anionic intermediates of organic substrates and their synthetic utility; the electrochemical behavior of olefins[4] and alkyl halides[5] in a nonaqueous solvent, and of benzalaniline[6] in molten salt at 150°C has been studied in the presence of carbon dioxide. In the present paper,[7] we herein report a synthesis of phenylglycine and α-methylphenylglycine by exploiting cathodic reduction of several Schiff bases (**1a–e, 3**) under conditions favoring carboxylation.

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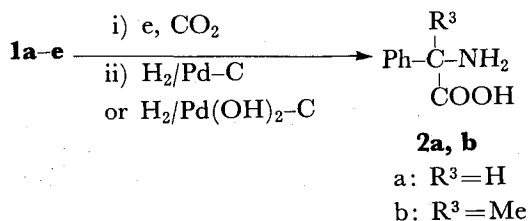
$$R^1 \qquad R^2$$
$$Ph\text{--}\overset{|}{C}=N\text{--}\overset{|}{C}HPh$$

1
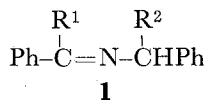
a: $R^1=R^2=H$
b: $R^1=H$; $R^2=Me$
c: $R^1=H$; $R^2=Et$
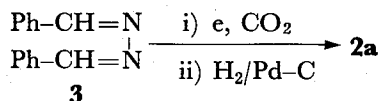d: $R^1=Me$; $R^2=H$
e: $R^1=Me$; $R^2=Me$

Formula

A series of macroelectrolyses was carried out using a mercury pool cathode in a nondivided cell in a nonaqueous catholyte into which carbon dioxide was bubbled continuously. The cathodic reduction of the Schiff base (**1a**) derived from benzaldehyde and benzylamine in dimethylformamide-tetraethylammonium chloride followed by hydrogenolysis of the electrolyzed solution (Run 1) afforded phenylglycine in 84% yield (Scheme 1). The use of acetonitrile as the cathodic solvent resulted in a rather low yield (Run 2). The Schiff bases (**1b, c**) derived from α-alkylbenzyl-amines instead of benzylamine gave phenylglycine in 53–56% yields (Run 4, 5). The electroreductive carboxylation is also applicable to a preparation of α-methyl-phenylglycine. When the cathodic reduction of the Schiff bases (**2d, e**) derived from acetophenone was carried out under reaction conditions similar to those described above, α-methylphenylglycine was obtained in 44–52% yields (Run 6, 7).

$$
\textbf{1a--e} \quad \xrightarrow[\substack{\text{ii) } H_2/Pd\text{--}C \\ \text{or } H_2/Pd(OH)_2\text{--}C}]{\text{i) } e,\ CO_2} \quad Ph\text{--}\overset{\overset{\displaystyle R^3}{|}}{\underset{\underset{\displaystyle COOH}{|}}{C}}\text{--}NH_2
$$

2a, b

a: $R^3=H$
b: $R^3=Me$

Scheme 1

The electroreductive carboxylation was further extended to the transformation of benzalazine into phenylglycine. The cathodic reduction of benzalazine in an aqueous solution has been reported[8] to form benzylamine by protonation of the initially formed radical anion[9] followed by cleavage of the nitrogen-nitrogen bond. We anticipated that the nonaqueous cathodic reduction of the azine using carbon dioxide as a trapping agent of the anionic intermediates gives directly phenylglycine through carboxylation and subsequent nitrogen-nitrogen bond cleavage. Thus, electro-reductive carboxylation of benzalazine was carried out in the nonaqueous catholyte as described above by passing 1.5 times the theoretical amount of electricity (six-electron transfer). Under the reaction conditions, however, phenylglycine was formed only in 19% yield. On the other hand, the hydrogenolysis of the electrolyzed solution over palladium on charcoal gave phenylglycine in 43% yield (Run 8) (Scheme 2).

$$\begin{array}{c} \text{Ph–CH=N} \\ \;\;\;\;\; | \\ \text{Ph–CH=N} \\ \mathbf{3} \end{array} \quad \xrightarrow[\text{ii) } H_2/Pd\text{–}C]{\text{i) e, } CO_2} \quad \mathbf{2a}$$

Scheme 2

In Table are summarized the reaction conditions and the yields of the electroreductive carboxylations.

Table   Electroreductive Carboxylation of the Schiff Bases[1]

Run	Substrate (mmol)	Solvent (ml)	Initial (Final) Current Density (mA/cm^2)	Cathodic Potential $(V_{vs}SCE)$	Reaction Time (hr)	Product	Yield (%)
1	1a (10)	50	2.9 (2.3)		6	2a	84
2	1a (10)	50[2]	5.8 (0.6)		12	2a	61
3	1a (1)	40		−2.10	23	2a	88
4	1b (5)[4]	50	2.6 (0.6)		8	2a	53
5	1c (5)[4]	50	2.6 (0.6)		8	2a	56
6[3]	1d (2.5)	40		−2.20	0.9	2b	52
7[3]	1e (2.5)[5]	40		−2.20	3	2b[6]	44
8	3 (1)	25	7.0 (1.4)		5	2a	43

1) The reactions were carried out at 15–25°C in dimethylformamide-tetraethylammonium chloride (10 mmol).   2) Acetonitrile was used as the cathodic solvent.   3) The reaction was carried out at 0°C using tetraethylammonium bromide as an electrolyte.   4) The Schiff bases derived from racemic α-alkylbenzylamines were used.   5) The Schiff base derived from $R(+)$-α-methylbenzylamine $[[\alpha]_D^{25}+40.4(benzene)]$ was used.   6) The optical purity of the product $[R(-)$-α-methylphenylglycine] is 10.0%.

For the electroreductive carboxylations of the Schiff bases described above, the following two electron-transfer reactions are possible; the one involves the generation of the activated species of the Schiff bases followed by their reaction with carbon dioxide, while the other does the addition of carbon dioxide radical anion onto the double bonds of the Schiff bases.   In order to clarify the mechanism of the electroreductive carboxylations, the polarographic behavior and the controlled potential electrolysis of the Schiff bases were investigated.   The Schiff bases (1a) and (1d) showed a single well-defined wave representing an irreversible two-electron transfer at the half-wave potentials of −2.08 and −2.20 V vs S.C.E., respectively, in dimethylformamide-tetrabutylammonium iodide.   On the other hand, carbon dioxide has been documented[10] to be reduced at the half-wave potential of −2.3 V vs S.C.E. which is more negative than those of the Schiff bases.   The controlled potential electrolysis of the Schiff base (1a) where only the Schiff base is reduced was carried out in dimethyl-formamide-tetraethylammonium chloride system in the presence of carbon dioxide. The electrolysis of the Schiff base (1a) at the cathodic potential of −2.02 V vs S.C.E. followed by hydrogenolysis of the electrolyzed solution afforded phenylglycine in 88% yield (Run 3).   The results indicate unequivocally that the radical anion of the Schiff bases is involved in the primary species of the electroreductive carboxylation.   Thus,

the mechanistic scheme can be conceived of in the following ECEC[11] pathways. Pathway 1 involves the transformation into the dicarboxylate (**6**) in which the radical anion (**4**) reacts with carbon dioxide followed by subsequent reduction to form the carbanion and further carboxylation. On the other hand, the basicity of the radical
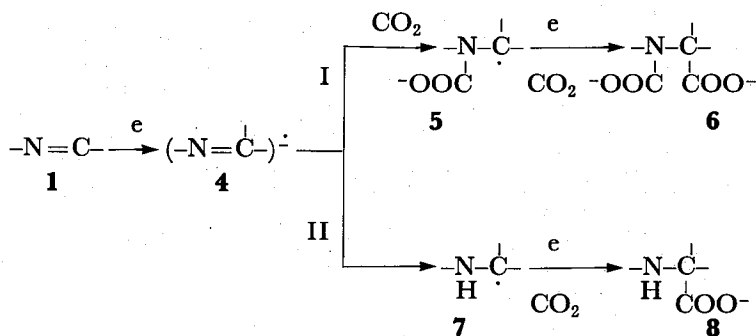
$$\text{Scheme 3}$$

Scheme 3

anion (**4**) of this type of Schiff base has been reported[12] to be high enough to subtract a proton from the surroundings in a nonaqueous solution on a polarographic time scale. Thus, pathway II involving the protonated intermediate (**7**) is also plausible in the carboxylations. The life time of the radical anion and the concentration of carbon dioxide near the cathode probably govern whether pathway I or II is taken. However, in the case of benzalazine, pathway I is most probably favorable over pathway II; the life time of the radical anion is long enough to be susceptible to the attack of alkyl halides[9] which are less electrophilic than carbon dioxide.

EXPERIMENTAL

Equipment

The Kepco JQE 36–3ME was used as a DC-power source. The Hokuto Potentiostat/Galvanostat Model 101 was used for controlled potential electrolysis and for constant current electrolysis. The polarograms were measured by a Sargent Model XV. Analyses of amino acids were carried out by the Phoenix K 5000. An ordinary beaker with a 69 mm diameter was used as an electrolysis cell. A cylindrical tube with a 23 mm diameter and a fine-porosity glass frit at the bottom was used as the anodic compartment. In some experiments, a cylindrical anodic compartment with a 34 mm diameter was also used. Mercury was used as a cathode with a 34 cm² area and a platinum foil was used as the anode. The gas inlet, thermometer, and anode compartment were tightly fixed in the cathode compartment. The salt bridge of a saturated calomel electrode used as a reference electrode was fixed about 1 mm above the mercury cathode.

Reagents and starting materials

The mercury was purified in the usual way and was distilled under reduced

perssure. Dimethylformamide was dried over sodium sulfate for 3 days and was distilled (b.p. 152–153°C). Acetonitrile was refluxed with phosphorous pentoxide for 6 hrs and then distilled. Other compounds were used immediately after fresh distillation. The boiling points of the reagents are as follows: acetophenone, b.p. 53°C (2 mm Hg); benzaldehyde, b.p. 42°C (3 mm Hg); $R(+)$-α-methylbenzylamine, b.p. 57°C (4 mm Hg); racemic α-ethylbenzylamine, b.p. 98–99°C (36 mm Hg).

Hydrazine (95%), which was purchased from Eastman Organic Chemicals, was used without purification. Supporting electrolytes were purified as follows. Tetraethylammonium chloride was dried over phosphorous pentoxide under reduced pressure for two days. Tetraethylammonium bromide was recrystallized from ethanol and dried. Tetrabutylammonium iodide was recrystallized twice from benzene and dried.

The Schiff bases used as starting materials were prepared according to the method described in the literature.[13,14] The peak corresponding to benzaldehyde or acetophenone was not observed in the polarograms of the Schiff bases $(2 \times 10^{-3}\text{M})$ in dimethylformamide-tetrabutylammonium iodide.

Benzalazine was prepared as follows. Benzaldehyde (535 mg) and 95% hydrazine (85 mg) were dissolved in 30 ml of absolute ethanol and the solution were kept at room temperature for 2 hrs. The solution was evaporated under reduced pressure below 30°C. The residue was dissolved in benzene and the solution was dried with sodium sulfate for 2 hrs. The sodium sulfate was separated by filtration and the benzene solution was evaporated under reduced pressure. The syrupy residue was used for further carboxylation reactions without purification.

The DL-phenylglycine used as the standard compound was purchased from Nutritional Biochemicals. DL-α-Methylphenylglycine was prepared from acetophenone, ammonium chloride, and sodium cyanide by the Strecker synthesis.

Electrolysis procedure

All parts of the electrolysis equipment were oven dried and assembled under a carbon dioxide atmosphere. The assembled equipment was put in a water bath.

A catholyte (see Table) was charged in the cathodic compartment. An anolyte was used in the same solvent-salt system as the catholyte, and the liquid level of the anolyte was adjusted to equal to that of the catholyte. Prior to the electrolysis reaction, dried carbon dioxide was introduced to the catholyte. Then, electrolysis was carried out under the conditions described in Table with continuous introduction of carbon dioxide. The applied voltage between the cathode and the anode was 38 to 60 V. To prevent the dispersion of the anolyte to the cathodic compartment, the anolyte was continuously replaced with fresh solution.

During the controlled potential electrolysis, the starting material was added slowly to the anolyte to maintain not to exceed applied voltage of 38 V between the anode and the cathode.

After the electrolysis was over, the catholyte was separated from mercury and was treated as described below.

Procedure after electrolysis

After electrolysis, the catholyte was evaporated to dryness under reduced pressure at 40°C. The residue was dissolved in a mixture of methanol (30 ml), acetic acid (10 ml), and water (5 ml). To this solution was added 0.8 g of 5% Pd–C and hydrogenolysis was carried out at 40 psi for 12 hrs. In run 4, 5 and 7, 0.80 g of Pd(OH)$_2$–C was used instead of 5% Pd–C. After hydrogenolysis, the catalyst was removed by filtration and washed with 5% aqueous ammonia. A portion of the combined filtrate was diluted appropriately and the yields were determined by the amino acid analyzer using authentic phenylglycine or α-methylphenylglycine as a standard.

Isolation of the products

After hydrogenolysis, the combined filtrate described above was evaporated to dryness under reduced pressure. A small amount of water was added. The pH of the solution was adjusted at 7 by addition of 4N HCl. To the solution was added 20 ml of ethanol. The mixture was kept at 4°C overnight. The precipitated crystals were filtered and washed with cold water. The obtained phenylglycine and α-methylphenylglycine had the same elution volumes as authentic ones. Phenylglycine was recrystallized from water. Anal. Calcd. for C$_8$H$_9$O$_2$N: C, 63.56; H, 6.00; N, 9.27%. Found: C, 63.40; H, 6.26; N, 9.33%. α-Methylphenylglycine was recrystallized from water-acetone. Anal. Calcd. for C$_9$H$_{11}$O$_2$N: C, 65.44; H, 6.71; N, 8.48%. Found: C, 65.41; H, 6.67; N, 8.40%.

Determination of optical purity (Run 7)

After the electrolysis was over, the catholyte was evaporated to dryness *in vacuo* below 40°C. The residue was dissolved in acetic acid (30 ml), methanol (10 ml) and water (5 ml) and hydrogenolysis was carried out using 1.0 g of Pd(OH)$_2$–C. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water and the solution was washed with ethyl acetate. The aqueous layer was treated with Dowex 50×8 (H$^+$ form, 3 cm × 40 cm) and non-amino acid acidic components were eluted with water, then amino acid was eluted with 5% ammonia. The solution was evaporated to dryness *in vacuo* to give colorless crystals. The cochromatography with an authentic α-methylphenylglycine showed a single spot. The crude crystals were not recrystallized to prevent fractionation during crystallization. The optical purity was determined by measuring the optical rotation of the crude crystals.

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