Synthesis of Amino-acids by Electroreductive Coupling of Alkyl Halides with Schiff's Bases [1]

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α-Methyl-α-amino-acids and phenylalanine have been synthesized in 36—86% yield by a route involving controlled potential cathodic reduction of alkyl halides in the presence of Schiff's bases in a non-aqueous catholyte.

INTERMOLECULAR electroreductive coupling has received increasing attention as a potential method for preparation of polyfunctional organic compounds.[2] Of the various types of coupling reaction reported, the reaction between activated olefins and reactive intermediates such as anions or anion radicals generated by cathodic reduction has figured prominently. However, only recently has the synthetic potential of the dehalo-

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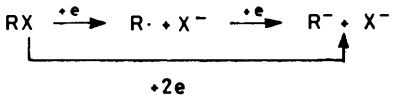
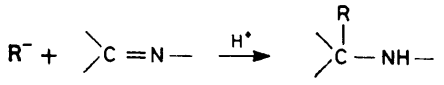
genated fragments formed by cathodic reduction of alkyl halides been exploited.[3]

Macroelectrolytic and polarographic reductions of alkyl halides have been studied extensively.[4] The products of cathodic reduction of the monohalides are the



SCHEME 1

corresponding hydrocarbons, organometallic compounds, and dimers. The cathode process is thought to involve radical and/or anionic species as intermediates (Scheme 1). Anionic intermediates have been suggested in early



SCHEME 2

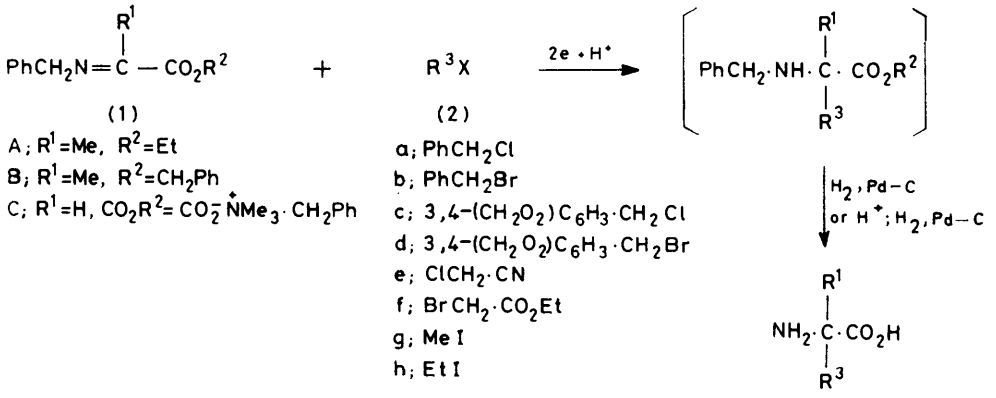
papers [5,6] and in recent stereochemical studies of the reduction of cyclopropyl [7] and aliphatic [8,9] monohalides. If a Schiff's base is present in the reduction system, as shown in Scheme 1, the anionic intermediate would be expected to attack the polarized azomethine linkage to afford a secondary amine (Scheme 2).

We report here a synthesis of α-methyl-α-amino-acids by coupling the anionic species generated by cathodic reduction of a variety of alkyl halides (2a—h) with Schiff's bases (1A—C).The Schiff's bases were prepared by the reactions of benzylamine with pyruvate esters or with benzyltrimethylammonium glyoxylate. The reduction potentials of the Schiff's bases in dimethylformamide–tetrabutylammonium iodide are −2.28, −2.28, and −2.25 V *vs.* s.c.e., respectively.[1] The alkyl halides show more anodic reduction potentials. Electroreductive couplings were carried out in non-aqueous catholyte at cathodic potentials where only the alkyl halides were reduced.

With Benzyl Halides.—Benzoyl chloride and bromide are polarographically reduced at −2.25 and −1.22 V *vs.* s.c.e., respectively, in dimethylformamide–tetrabutylammonium bromide. Macroelectrolytic reduction of these halides gives toluene, bibenzyl, and dibenzylmercury compounds.[10a,b] Recently, reductions of these halides in the presence of carbon dioxide in non-aqueous catholyte have been reported to afford benzyl phenylacetate.[3,11] This indicates that the reaction proceeds *via* an anionic rather than a radical intermediate.

The electroreductive couplings were carried out in dimethylformamide–tetrabutylammonium halides * by using a mercury pool cathode. When the Schiff's base (1B) was coupled with benzyl chloride at the cathodic potentials −1.90 and −1.80 V *vs.* s.c.e., α-methylphenylalanine was obtained in 86 and 60% yield, respectively, after hydrogenolysis of the electrolysed solutions over palladium–charcoal. Use of benzyl bromide afforded the same amino-acid in lower yield (52%). Coupling of the Schiff's base (1C) with benzyl bromide gave phenylalanine in 24% yield after hydrogenolysis.

This method was extended to the preparation of α-methyl-β-(3,4-dihydroxyphenyl)alanine, a well known



SCHEME 3

* In these coupling reactions, a proton may be donated from the dimethylformamide and/or the tetra-alkylammonium salt.[9,12]

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anti-hypertensive agent. 3,4-Methylenedioxybenzyl chloride and the Schiff's base (1B) gave α-methyl-β-(3,4-methylenedioxyphenyl)alanine in 36% yield after hydrogenolysis, and 3,4-methylenedioxybenzyl bromide gave the same amino-acid in 27% yield. This amino acid was hydrolysed to α-methyl-β-(3,4-dihydroxyphenyl)-alanine with 6N-hydrochloric acid.

Detailed electrolysis conditions are summarized in the Table.

With Chloroacetonitrile and Ethyl Bromoacetate.—Chloroacetonitrile and ethyl bromoacetate are polarographically reduced at −1.45 and −0.88 V *vs.* s.c.e., respectively.[3,11a] Cathodic reduction of these compounds in dimethylformamide containing a small amount of water is reported to afford the corresponding hydrocarbons, dimeric products, and cyclopropane derivatives.[3] The reaction course has been shown to be similar to that of reduction with a metal dissolving in liquid ammonia.[13] An initially formed anionic species in this electrode reaction would be the dehalogenated carbanion.

The conditions for the couplings with the Schiff's base (1A) are given in the Table. α-Methylaspartic acid was obtained in 70% yield from electrolysis of chloroacetonitrile at −1.6 V *vs.* s.c.e., followed by hydrolysis of the cathodic solution and subsequent hydrogenolysis over palladium–charcoal. When the potential was set at a more cathodic value, however, the yield was markedly decreased to 36%; this may be due to a change of mechanism of the coupling reaction.*

Ethyl bromoacetate and the Schiff base (1A) gave α-methylaspartic acid in 30—40% yield. Change in cathodic potential produced no appreciable change in product yield.

* A similar dependence of the yield on potential was observed in the electroreductive coupling between chloroacetonitrile and *N*-benzylidenebenzylamine.[14] The yield of β-amino-β-phenylpropionic acid, maximum at −1.45 V *vs.* s.c.e., gradually decreased as the potential was made more negative.

$$PhCH_2{\cdot}N{=}CHPh + ClCH_2CN \xrightarrow{2e} \xrightarrow[H_2,Pd\text{–}C]{H^+} NH_2{\cdot}CHPh{\cdot}CH_2{\cdot}CO_2H$$

With Methyl Iodide and Ethyl Iodide.—The half-wave potentials of methyl iodide and ethyl iodide in dimethylformamide–tetrabutylammonium iodide are −2.08 and −2.12 V *vs.* s.c.e. respectively. Controlled potential electrolyses affords methane and ethane respectively, *via* anionic intermediates.[5] Coupling reactions with the Schiff's base (2B), under the conditions listed in the Table, gave α-methylalanine (32% after hydrogenolysis) and α-ethylalanine (15%), respectively.

EXPERIMENTAL

A Hokuto 101 potentiostat–galvanostat was used for controlled potential electrolyses. The polarograms were measured with a Sargent XV instrument. Analyses of amino-acids were carried out with a Phoenix K 5000 analyser. A beaker (52 mm diam.) was used as an electrolysis cell. A cylindrical tube (23 mm diam.) with a fine porosity glass sinter at the bottom was used as the anodic compartment, a mercury pool (21 cm^2) as the cathode, platinum foil as the anode, and a saturated calomel electrode (s.c.e.) as a reference.

Dimethylformamide was dried over sodium sulphate for 3 days and distilled (b.p. 152—153 °C). 3,4-Methylenedioxybenzyl chloride and bromide were prepared [15] from 3,4-methylenedioxybenzyl alcohol. Tetrabutylammonium bromide was recrystallized twice from hot ethyl acetate and stored under dry nitrogen. Tetraethylammonium chloride was dried over phosphorus pentaoxide for at least 3 days. Tetraethylammonium toluene-*p*-sulphonate was recrystallized from tetrahydrofuran. The Schiff's bases (1) were prepared as follows.[16] Ethyl pyruvate (0.01 mol) and benzylamine (0.01 mol) were dissolved in benzene (30 ml) and the mixture was dried (Na_2SO_4) for 2 h at room temperature. The solvent was removed under reduced pressure below 40 °C, and the residue (1A) was used immediately for electrolyses. The Schiff's base (1B) was prepared from benzyl pyruvate and benzylamine by the same procedure. For the Schiff's base (1C), benzylamine (0.01 mol) in methanol (30 ml) was added to methanolic 40% benzyltrimethylammon-

Electrolysis conditions [a]

Run	Schiff's base (mmol)	Halide (mmol)	Electrolyte (mmol)	Solvent [b] (ml)	Cath. pot. (V *vs.* s.c.e.)	Product	Yield (%)
1	(1B) 10	(2a) (4)	TBABr [d] (4)	20	−1.80	Me–Phe [e]	64
2	(1B) (10)	(2a) (5)	TBABr (4)	20	−1.90	Me–Phe	86
3	(1B) (10)	(2a) (3)	TBABr (5)	20	−1.80	Me–Phe	60
4	(1B) (5)	(2b) (3)	TBABr (20)	20	−1.30	Me–Phe	52
5	(1C) (10)	(2b) (2)	TBABr (5)	20	−1.90	Phe [f]	24
6	(1B) (20)	(2c) (10)	TBABr (10)	30	−1.70	Me–MhPhe [g]	36 [h]
7	(1B) (20)	(2d) (10)	TBABr (10)	30	−1.20	Me–MhPhe	27 [h]
8	(1A) (10)	(2e) (4)	TEACl [i] (5)	10	−1.60	Me–Asp [j]	70
9	(1A) (10)	(2e) (4)	TEAPTS [k]	10	−1.65	Me–Asp	36
10	(1A) (10)	(2f) (2.5)	TBABr (5)	15	−1.70	Me–Asp	33
11	(1A) (10)	(2f) (2.5)	TBABr (5)	15	−1.30	Me–Asp	33
12	(1A) (10)	(2f) (2.5)	TBABr (5)	15	−0.95	Me–Asp	38
13	(1B) (10)	(2g) (2)	TBABr (5)	30	−1.70	Me–Ala [l]	32
14	(1B) (10)	(2h) (4)	TBABr (10)	15	−1.70	Et–Ala [m]	15

[a] Carried out at 15—20 °C with a mercury pool cathode. [b] Dimethylformamide. [c] Yields (determined by automatic amine-acid analysis) based on alkyl halide used. [d] Tetrabutylammonium bromide. [e] α-Methylphenylalanine. [f] Phenylalanine. [g] α-Methyl-β-(3,4-methylenedioxyphenyl)alanine. [h] Yield of isolated product. [i] Tetraethylammonium chloride. [j] α-Methylaspartic acid. [k] Tetraethylammonium toluene-*p*-sulphonate. [l] α-Methylalanine. [m] α-Ethylalanine.

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ium hydroxide (0.01 mol) at 0 °C. The mixture was stirred for 2 h at room temperature and set aside overnight at 4 °C. Benzene (100 ml) was added and the solution was evaporated to dryness *in vacuo*. The residual oil was used for electrolyses without further purification. The Schiff's bases thus prepared were polarographically pure.

General Electrolysis Procedure.—The electrolysis cell, thermometer, stirrer, *etc.*, were fixed in the water-bath under nitrogen. The Schiff's base and supporting electrolyte dissolved in dimethylformamide were put in the cathode compartment. The anolyte, which consisted of the same solvent–electrolyte system as the catholyte, was placed in the anode compartment so as to make the height of the anolyte identical with that of the catholyte. Nitrogen was bubbled through the catholyte for at least 15 min before electrolysis. Pre-electrolysis was carried out at −1.2 to −1.6 V *vs.* s.c.e. to remove impurities in the catholyte. Then, the alkyl halide was added dropwise to the catholyte under the conditions shown in the Table, while an electrolysis current of 150—300 mA was maintained. The reaction was discontinued when the current had fallen to 30—60 mA.

Work-up of Catholyte.—The catholyte, separated from the mercury, was evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate, and the solution was shaken with water. The ethyl acetate layer was separated, dried (Na_2SO_4), then evaporated to dryness *in vacuo*. The residue was treated by one of the following two methods. In runs 1—7, 13, and 14 (Table) it was hydrogenolysed in methanol (30 ml), acetic acid (10 ml), and water (5 ml) at 40 lb in^{-2} for 10 h over palladium–charcoal (0.8 g). The catalyst was filtered off and the filtrate was analysed (amino-acid analyser). In runs 8—12 the residue was hydrolysed in 6N-hydrochloric acid at 110 °C for 5 h. The mixture was evaporated to dryness *in vacuo* and the residue was dissolved in methanol (30 ml), acetic acid (10 ml), and water (5 ml). To this solution was added 5% palladium–charcoal (0.8 g), and hydrogenolysis was carried out at 40 lb m^{-1} for 10 h. The catalyst was filtered off, and the filtrate was analysed (amino-acid analyser).

Identification of Products.—Amino-acid analyses were carried out automatically on a column (60 cm) of Aminex A-6 (particle size 17.5 ± 2). Flow rates of buffer solution (pH 3.25) and of ninhydrin solution were 60 and 30 ml h^{-1}, respectively. Components were identified by comparison of R_f values with those of authentic samples under identical conditions (peak enhancement), and by comparison of ratios of absorbances at 570 and 440 nm.

Isolation of Products.—*α-Methylphenylalanine* (*run* 2). After the catholyte had been hydrogenolysed, the catalyst was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in distilled water and passed through Dowex 50 × 8 resin (H^+ form; 3 × 40 cm). Non-amino-acid components were eluted with water, then amino-acids with 5% ammonia. The eluate was evaporated to dryness *in vacuo* and the residue was crystallized from water and recrystallized twice from water–ethanol to give α-methylphenylalanine, m.p. >260 °C [17] (C, 66.7; H, 7.25; N, 7.7. Calc. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8%).

Preparation of α-methyl-β-(3,4-methylenedioxyphenyl)-alanine (*run* 6). After hydrogenolysis of the catholyte, the catalyst was filtered off and the filtrate passed through Dowex 50 × 8 resin (H^+ form). The column was further washed with distilled water and amino-acids were eluted with 5% ammonia. The eluate was evaporated to dryness *in vacuo* and the residual *amino-acid* recrystallized from water–acetic acid; m.p. 260—268 °C; δ (CF_3·CO_2D) 6.81 (3 H, s), 5.98 (2 H, s), 3.22 and 3.58 (2 H, ABq, *J* 16 Hz), and 1.93 (3 H, s) (Found: C, 59.2; H, 5.95; N, 6.15. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.85; N, 6.3%).

This amino acid was converted into α-methyl-β-(3,4-dihydroxyphenyl)alanine; [15] the physical properties of the product agreed with those reported.[18]

Preparation of α-methylaspartic acid (*run* 8). After the hydrogenolysis, the catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in distilled water, and the solution was washed with ethyl acetate. The separated aqueous layer was treated with Dowex 50 × 8 resin (H^+ form; 3 × 40 cm), non-amino-acid acidic components were eluted with water, then amino-acids were eluted with 5% ammonia. The eluate was evaporated to dryness *in vacuo* and the residue was dissolved in distilled water. The solution was further treated with Dowex 1 resin (HCO_2^- form; 2 × 30 cm), neutral and basic amino-acids were eluted with water, then acidic amino-acids were eluted with 5% formic acid. The eluate was evaporated to dryness *in vacuo*. The resulting crystals ran concurrently on t.l.c. with authentic α-methylaspartic acid, and had the same elution volume. It was recrystallized from water-acetone; m.p. 228—230 °C,[19] (Found: C, 36.1; H, 6.7; N, 8.4. Calc. for $C_5H_9NO_4$,H_2O: C, 36.35; H, 6.75; N, 8.5%).

This work was supported by a grant from the National Aeronautics and Space Administration, U.S.A.

[6/2308 *Received*, 20*th December*, 1976]

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