Electroreductive Coupling of Schiff Bases with Alkyl Halides. Synthesis of Amino Acids

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Summary Electroreductive coupling of Schiff bases with alkyl halides to form amino acids was carried out using constant potential electrolysis.

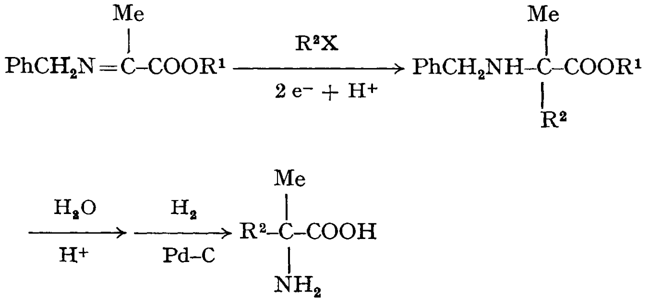
ELECTROREDUCTIVE coupling has been discussed by several authors as a possible synthetic tool.[1] Two types of coupling reaction have been studied in aqueous and nonaqueous

TABLE

	R^1 (mmol)	R_2X (mmol)	Electrolyte (mmol)	Solvent (ml)	Cathodic potential V *vs.* SCE	Temp. °C	Product	Yield[d] %
1	$PhCH_2$ (10)	$PhCH_2Cl$ (5)	TBA·Br[a] (4)	20	−1·9[c]	20	α-Me-Ph-Ala	86[e]
2	Et (5)	$PhCH_2Br$ (3)	TBA·Br (20)	20	−1·3	20	α-Me-Ph-Ala	52[f]
3	Et (10)	$ClCH_2CN$ (4)	TEA·Cl[b] (5)	10	−1·6	20	α-Me-Asp	70[f]
4	Et (10)	$BrCH_2COOEt$ (2·5)	TBA·Br (5)	15	−1·3	15—20	α-Me-Asp	38[f]

[a] Tetrabutylammonium bromide. [b] Tetraethylammonium chloride. [c] See ref. 5. [d] The yields were determined by an automatic amino acid analyzer using authentic DL-α-methylphenylalanine and DL-α-methylaspartic acid based on alkylhalides used. [e] Analysis after hydrolysis with 6N HCl. [f] Analysis after hydrolysis with 6N HCl and subsequent hydrogenolysis in MeOH–AcOH–H_2O (20:10:5) with 5% Pd–C.

solutions; the coupling of activated olefins and the coupling of compounds containing leaving groups with activated olefins. The electroreductive coupling between Schiff bases and electrochemically active compounds has not been studied systematically.[2]



$$PhCH_2N{=}\overset{\displaystyle Me}{\overset{|}{C}}\text{–}COOR^1 \xrightarrow[2\,e^- + H^+]{R^2X} PhCH_2NH\text{–}\underset{\displaystyle R^2}{\underset{|}{\overset{\displaystyle Me}{\overset{|}{C}}}}\text{–}COOR^1$$

$$\xrightarrow[H^+]{H_2O}\xrightarrow[Pd\text{–}C]{H_2} R^2\text{–}\underset{\displaystyle NH_2}{\underset{|}{\overset{\displaystyle Me}{\overset{|}{C}}}}\text{–}COOH$$

The Schiff bases used as acceptors were benzylamine with ethyl pyruvate and benzyl pyruvate. Each Schiff base is reduced at −2·28 V *vs.* S.C.E.† The alkyl halides used were benzyl chloride (−2·25 V *vs.* S.C.E.),[3] benzyl bromide (−1·22 V *vs.* S.C.E.),[4] and chloroacetonitrile (−1·45 V *vs.* S.C.E.).[3] The reactions were carried out in a DMF–tetra-alkylammonium halide system at the cathode, where the alkyl halides were reduced, but not the Schiff bases. A mercury pool cathode (21 cm^2) and a platinum foil anode were used. The cathode and anode compartments were separated by a fine-porosity glass frit. A pre-electrolysis procedure was performed in each case to remove impurities, at the operated potentials listed in the Table. The alkyl halide which was dissolved in 3 ml of DMF was then added dropwise to the catholyte in the course of the electrolysis (with bubbling of N_2 gas through the catholyte) to maintain a current of 200—300 mA. The quantity of electricity passed through the solutions was one and a half times the theoretical amount, based on the molarity of alkyl halides used. The yield of amino acids produced was 38—86%. The results are summarised in the Table.

(*Received*, 4*th February* 1974; *Com.* 153.)

† The value shows $E_{1/4}$ determined in DHF–tetrabutylammonium iodide by chronopotentiometry.

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[1] For reviews in this area, see: (a) M. M. Baizer and J. P. Petrovich, in 'Progress in Physical Organic Chemistry'; eds., A. Streitwieser and R. W. Taft, vol. 7, p. 189, Wiley Interscience, New York, 1970; (b) L. Eberson and H. Schafer, in 'Fortschritte der Chemischen Forschung,' eds. A. Davison *et al.*, vol. 21, p. 113, Springer-Verlag, Berlin, 1971; (c) M. M. Baizer, in 'Organic Electrochemistry,' ed. M. M. Baizer, p. 679, Marcel Dekker Inc., New York, 1973.

[2] Electrolysis of benzalaniline in the presence of excess of acrylonitrile has been reported, but the yield was not described. M. M. Baizer, J. D. Anderson, J. H. Wagenknett, M. R. Ort, and J. P. Petrovich, *Electrochim. Acta*, 1967, **12**, 1377.

[3] M. M. Baizer and J. L. Chruma, *J. Org. Chem.*, 1972, **37**, 1951.

[4] F. H. Covitz, *J. Amer. Chem. Soc.*, 1967, **89**, 5403.

[5] Benzyl chloride was reduced at −1·90 V *vs.* S.C.E. under the conditions employed here. The relationship between micro- and macro-phenomena has been reported. See P. Zuman, in 'Organic Electrochemistry,' ed. M. M. Baizer, p. 155, Marcel Dekker Inc., NewYork, 1973.