

Electrochemical Synthesis of some Heterocyclic Molecules in Aqueous Media (1) Large Scale Preparative Electrolysis on Mercury Pool Electrode

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Summary: Practical hints for preparative electrolysis in aqueous media are reported together with the detailed experimental procedure for synthesis of some new heterocyclic molecules.

Introduction

Electrochemical synthesis, initiator of any large scale chemical industrialisation, is considered to be one of the most up-to-date aspects of applied electroorganic chemistry [1-5]. Recently, the number of related comprehensive articles and reports increased remarkably in literature [1-3]. On the other hand, heterocyclic compounds occur extensively in nature and appear to play a variety of roles in the life cycles of living organisms. Thus, a basic interest in the biological role and function of these compounds has stimulated a significant amount of electrochemical research into their properties and behaviour [6-9].

Although recent techniques such as cyclic voltammetry are now used for the elucidation of electrode processes, nevertheless, the basic foundation of this field of interest remains controlled potential electrolysis (CPE) [10]. A circuit as the one illustrated in Fig. 1 is fairly sufficient for performing such CPE experiments together with the help of a classical DC polarograph, a must for finding out the optimum experimental conditions through routine analyses of the compound to be electrolysed. The circuit consists in its simple form of a potentiostat (used for controlling the applied potential), galvanometer (used as current measurement device) and a valve voltmeter to check from time to time the accuracy of the applied potential and to detect any resistance in the cell during the course of electrolysis. A 250 ml conical or flat bottom flask (Fig. 2), in which the reference (RE) and auxiliary (AE) electrodes have been inserted by means of cork or teflon stopper, is a practical cell for this purpose. The working electrode (WE) in electroreduction processes is usually mercury which has been previously purified by classical methods

[11]. Finally, a magnetic stirrer is used for agitation of mercury with the help of a stream of purified N₂ or H₂ gas which is continuously bubbled through the mixture. This stream prevents also contamination of the solution with atmospheric O₂. The num-

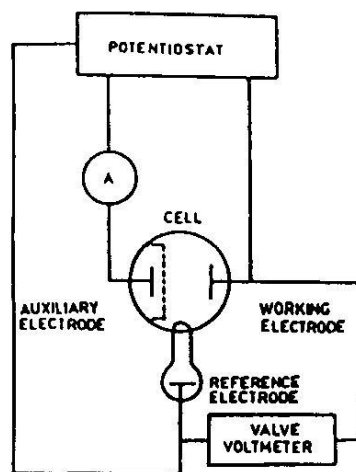


Fig. 1: Circuit used in controlled potential electrolysis.

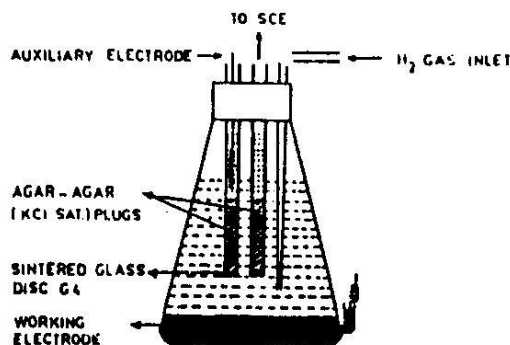


Fig. 2: Controlled potential electrolysis cell.

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ber of electrons consumed in the electrochemical reaction is usually calculated either directly by inserting an electronic integrator into the circuit or simply by recording the decay in current with time using Lingane's method of analysis [12] as illustrated in Fig. (3 a & b) for N-(3'-pyridyl)2,3-dioxobutanamide-2- arylhydrazone [13], taken as representative example.

Representative Procedure

i-t curves were studied on solution containing 50 ml of 10^{-4} M of N-(3'-pyridyl-2,3-dioxobutanamide)-2-arylhydrazone in 50% ethanol 50% 0.1 N HCl

showed that 4 electrons were consumed per molecule according to Lingane calculations [12] as revealed from a typical representative calculation (Data 1 and 2). Fig. (3a) $\log i_t = \log i_0 - (K)/2.303 \times t$

$$i_0 = 4.76 \text{ mA} = 4.76 \times 10^{-3} \text{ A}$$

$$K = 1.56/11.4 \times 60 = 2.281 \times 10^{-3} = \text{slope}$$

$$Q = n \times F \times C \times V$$

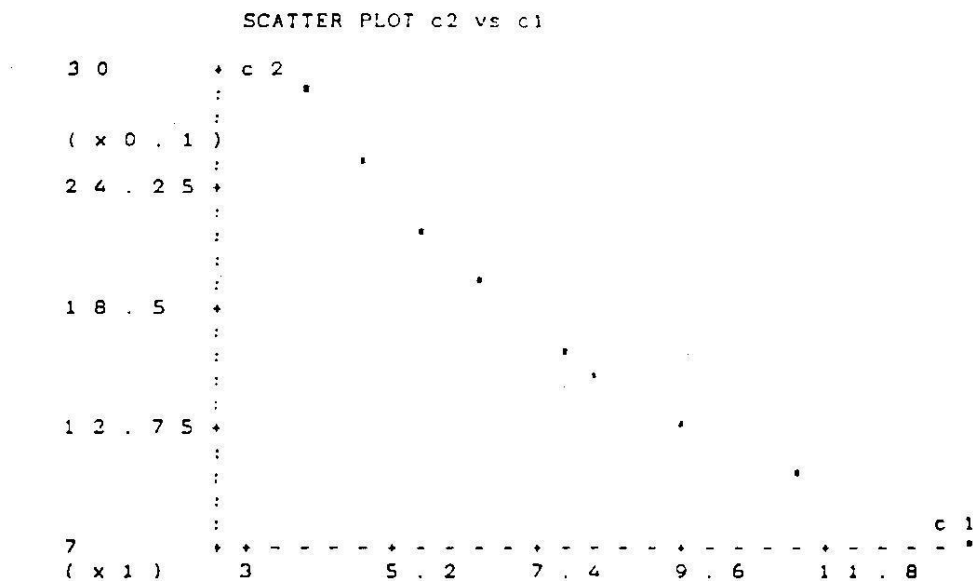
$$Q = 4.76 \times 10^{-3} / 2.281 \times 10^{-3} = 2.0868 \text{ (1)}$$

$$Q = n \times 96500 \times 10^{-4} \times 50/1000$$

$$Q = n \times 0.4825 \text{ (2)}$$

From (1) and (2)

$$n = 4.325$$



DATA

row	col. 1	col. 2
1	3.49	3
2	23.88	2.84
3	34.84	2.5
4	45.82	2.229
5	56.4	2
6	67.76	1.657
7	78.33	1.5
8	89.7	1.24
10	13.95	0.75

FIG. 3 a

Data 1: Variation of electrolysis current i (mA) with time t (min). (Plotted with a Sinclair ZX Spectrum Computer using Unistat statistical package software, published by Unisoft Ltd, London, 1984)

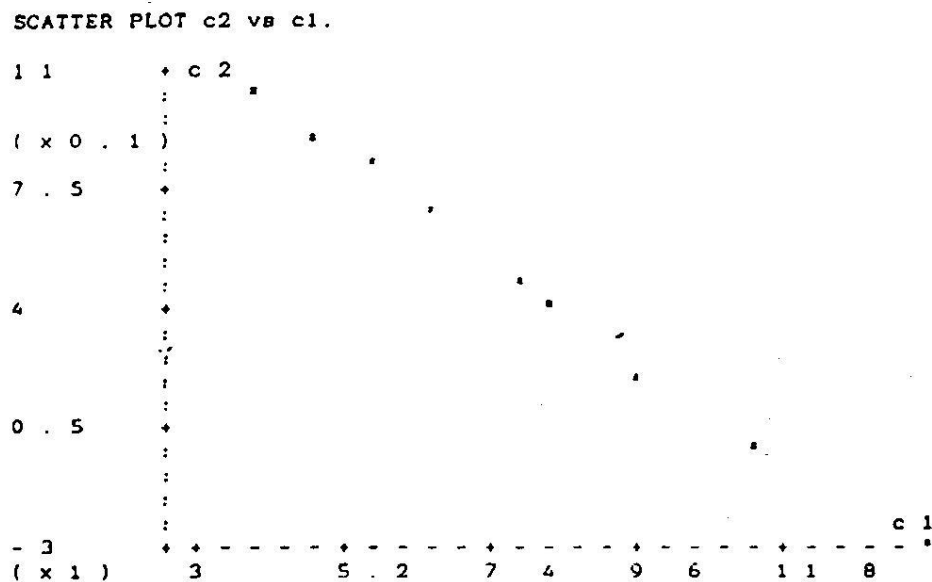


FIG.3b

DATA		Results of Regression
rowcoli.1	col. 2	c2 on, c1
1 3.49	1.1	Est. Coeff. t-stat.std.err.
2 3.88	1.0452	Const. 1.568 83.78 .0187
3 4.84	0.9	c1:v1:-0.1365 -59.85 .0023
4 5.82	0.802	(R2) = 0.9978
5 6.4	0.7	corrected (R2) = 0.9975
6 7.76	0.505	F(1,8) = 3581.8911
7 8.33	0.4	std.er.of. reg = 0.231
8 9.7	0.215	D-W stat. = 1.2709
9 11.4	0	
10 13.95	-0.3	

Data 2: Ln i_1 vs t plot

(Plotted with Sinclair ZX Spectrum Computer using Unistat statistical package software, published by Unisoft Ltd, London 1984).

$C_2 = \text{Ln } i_1$, $C_1 = t$ in min, Const = $\text{long } i_0$, corrected R_2 = correlation coefficient and std. er. of. reg = Standard deviation.

Optimum Conditions for Practical CPE Experiment

For this purpose a complete detailed study of the half-wave potential ($E_{1/2}$) and limiting current (i_1) versus pH dependence of the compound to be electrolysed must be undertaken using different solvent compositions. A plot i_1 versus time t curve, from which a knowledge about the stability of a cer-

tain compound towards a certain medium, is also of great value. In the following are summarized some important hints for carrying out large scale laboratory preparative electrolysis:

(1) The choice of electrolysis potential must be taken in the medium where i_1 is practically pH and time independent.

(2) In molecules displaying well defined polarographic waves the potential of electrolysis must be chosen in a way that it covers the beginning of the limiting current i.e. $-0.2 \text{ V} > E_{1/2}$ value. On the other hand if the wave is located at very negative potential i.e. near hydrogen evolution in acid media or near the limiting wall of supporting electrolyte, the potential must be fixed at the $E_{1/2}$ value or at the beginning of the rising portion of the wave in question.

(3) Calculated amounts, not exceeding 100 mg, of starting material are practical in CPE experiments to decrease as much as possible electrolysis time and in turn side chemical (CR) and electrochemical reactions (ECR). In addition, the use of calculated amounts help controlling the efficiency of experiment.

(4) It is preferable to use a medium in which the compound to be electrolysed is completely soluble. However, if the products of electrolysis are soluble in the medium, suspensions of the starting materials may be used. Preferable to use acid medium or faintly acidified medium to minimize as much as possible conductance problems.

(5) pH-control is mandatory since, in some processes molecules of basic character are obtained as main products of electrolysis and thus will change the pH of solution in the course of electrolysis. A typical examples are the products obtained *via* the electroreduction of azo hydrazono compounds [14].

(6) Room temperature is suitable for most CPE experiments if not otherwise specified for a certain reaction.

Finally, before carrying out a large scale electrolysis it is wise to perform an experiment on a small scale say 10^{-4} M depolariser, in which the electrolysis products can be identified via spot tests or any other simple analytical tool in the purpose to get information about the resulting products and to estimate the average time of electrolysis. In the following we report a typical representative procedure for CPE, experimental, isolation and identification of the electrolysis product.

Representative Procedure for CPE

50 mg of N-(3'-pyridyl)-2,3-dioxobutanamide-2-phenylhydrazono were dissolved in 50 ml absolute

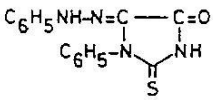
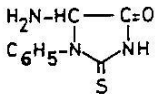
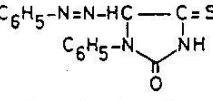
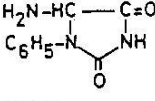
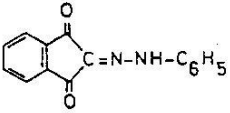
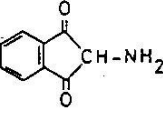
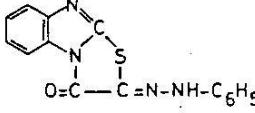
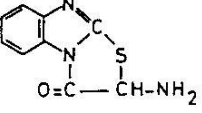
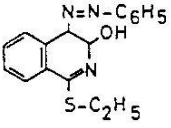
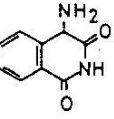
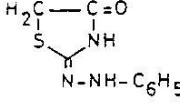
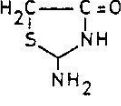
ethanol and 30 ml of 0.1 N HCl, the potential was controlled at -0.74 V vs SCE, the solution was deaerated with a stream of pure hydrogen gas which was present throughout the period of electrolysis, after approximately 3 h the colour changed from yellow to colourless and a polarogram was taken which showed no wave indicating that the starting compound was completely reduced. The electrolysis was then stopped and the solution was separated from the mercury and evaporated to 1/4 of its original volume. The remaining solution was neutralized with a concentrated NaOH solution to pH 8 and evaporated till dryness on a water bath. The obtained residue was then washed carefully with petroleum ether (60-80) to get rid of aniline and the mixture was decanted, the remaining ether was evaporated. Finally, the residue was treated with distilled water to dissolve the sodium chloride present, the brown precipitate was collected through filtration and washed several times with distilled water, the obtained product (56% yield) was collected and identified as 2,5-dimethyl-3,6-di[N-(3'-pyridyl)amide]-1,4-dihydro-pyrazine. M.p. 300°C . Elem. anal; found (Calcd.) for $\text{C}_9\text{H}_9\text{N}_3\text{O}$: C, 61.2 (24); H, 5.1 (5.1); N, 26.1. IR in KBr cm^{-1} 3550-3000 broad band (NH), 1660 (CONH), 1600 (C=C). NMR δ ppm NH (anilide) singlet at 12.9, aromatic and NH multiplet at 7.3-8.9, CH_3 singlet at 2.1. The disappearance of CH absorbance indicates that the amino compound was condensed with each other. Aniline was tested for by a standard spot test and azo dye which gave positive results. On the other hand ammonia was tested for by Nessler's reagent which gave negative test.

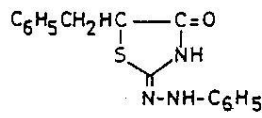
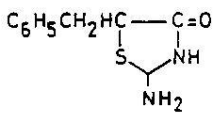
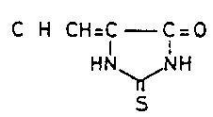
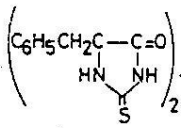
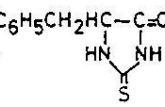
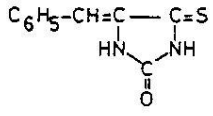
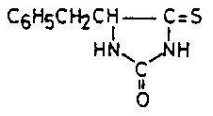
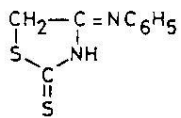
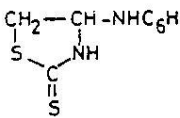
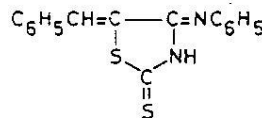
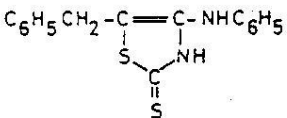
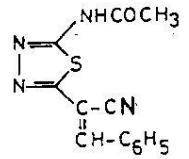
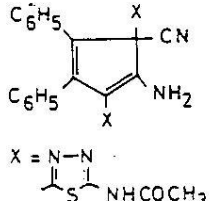
The electrosynthesis of some new organic heterocyclic systems included in some scattered articles from our laboratory will be treated under the following headings.

(A) Electrolysis of substituted heterocyclic compounds in which the hetero ring is unattacked

These side chains, where the electroreduction takes place, are divided into three types: azo and/or hydrazono moieties, activated olefines and carbonyl compounds. In the following Table-1 are compiled the starting and final products of electrolysis together with the experimental conditions of the electrode process. The medium is usually 10^{-2} M HCl or otherwise stated.

Table 1

Compound No	Starting compound	Main electrolytic product	Experimental conditions	Reference
I	 5-Phenylhydrazono-1-phenyl-2-thiohydantoin	 5-Amino-1-phenyl-2-thiohydantoin (30% yield)	-0.7 V vs SCE 4e ⁻ , 4H ⁺	15
II	 5-Phenylazo-1-phenyl-4-thiohydantoin	 5-Amino-1-phenylhydantoin (40% yield)	-0.8 V vs SCE 4e ⁻ , 4H ⁺ acid hydrolysis	16
III	 2-Phenylhydrazono-1,3-indandione	 2-Amino-1,3-indandione	-0.4 V vs SCE 4e ⁻ , 4H ⁺	17
IV	 2-Phenylhydrazonothiazolo [3,2-a] benzimidazol-3 (2H)-one	 2-Aminothiazolo [3,2-a] benzimidazol-3 (2H)-one	-0.65 V vs SCE 4e ⁻ , 4H ⁺	18
V	 4-Phenylazo-1-ethylmercapto-3(4H)-isoquinolone	 4-Aminomophthalimide	-0.3 V vs SCE 4e ⁻ , 4H ⁺ acid hydrolysis	19
VI	 2-Phenylhydrazono-thiazolidin-4-one	 2-Aminothiazolidin-4-one	-1.0 V vs SCE 4e ⁻ , 4H ⁺	20

Compound No	Starting compound	Main electrolytic product	Experimental conditions	Reference	
VII	 5-Phenyl(methylene)-2-phenylhydrazonothiazolidin-4-one	 5-Benzyl-2-aminothiazolidin-4-one	-1.0 V vs SCE 6e ⁻ , 6H ⁺	20	
VIII	 5-Benzyliden-2-thiohydantoin	 5-Benzyl-2-thiohydantoin dimer	 5-Benzyl-2-thiohydantoin (35% yield)	-1.15 V vs SCE pH 3.5 (B.R. Buffer) 2e ⁻ , 2H ⁺	21
IX	 5-Benzyliden-4-thiohydantoin	 5-Benzyl-4-thiohydantoin (70% yield)	-0.95 V vs SCE 2e ⁻ , 2H ⁺	22	
X	 4-Phenyliminorhodanine	 4-Anilinorhodanine	-0.6 V vs SCE 2e ⁻ , 2H ⁺	23	
XI	 5-Benzylidene-4-phenyliminorhodanine	 5-Benzyl-4-anilino-4-thiazolidine-2-thione	-0.6 V vs SCE 2e ⁻ , 2H ⁺	23	
XII	 2-Benzyliden-1-(2-acetylamino-1,3,4-thiadiazol-5-yl)propionitrile	 X = N-N	-0.8 V vs SCE 2e ⁻ , 2H ⁺	24	

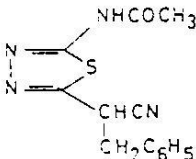
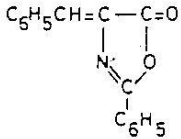
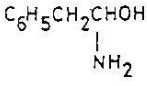
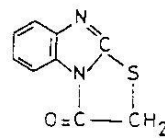
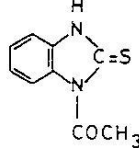
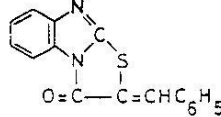
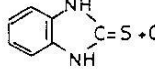
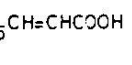
Compound No	Starting compound	Main electrolytic product	Experimental conditions	Reference
XII			-1.3 V vs SCE 2e, 2H ⁺ pH 8.6 (B.R.Buffer)	24

Table 2

Compound No	Starting Compound	Main Electrolytic Product	Experimental Conditions	References	
I	 4-Benzylidene-2-phenyl-2-oxazolin-5-one	 2-Amino-3-phenylpropanol	-0.9V vs SCE 6e, 6H ⁺ acid hydrolysis	25	
II	 Thiazolo [3,2-a] benzimidazol-3(2H)-one	 1-Acetyl-2,3-dihydrobenzimidazole-2-thione	-1.0 V vs SCE 2e, 2H ⁺	28	
III	 2-Benzyliden-2,3-dihydrothiazolo (3,2-a) benzimidazol-3-one	 2-Mercapto benzimidazole	 Cinnamic acid	-0.95 V vs SCE 2e, 2H ⁺ (acid hydrolysis)	26

(B) Electrolysis of substituted heterocycles in which the reaction takes place on the nucleus.

The electrode reactions of heterocyclic compounds where a cleavage of the hetero ring takes place are discussed in Table 2.

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