Anodic Oxidations. III.[1] Controlled Potential Cyanomethoxylation of 2,5-Dimethylfuran

KUNIHISA YOSHIDA* AND TAKAYUKI FUENO

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, Japan

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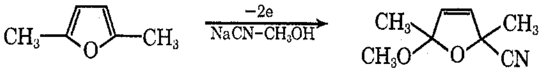
The anodic oxidation of 2,5-dimethylfuran in methanolic solution of sodium cyanide at 1.0–1.3 V gave a 2:1 isomeric mixture of *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofurans. The current efficiency ranged from 61 to 95% in the potential region studied. Small amounts of *cis*- and *trans*-2,5-dimethoxy-2,5-dimethyldihydrofurans and traces of 2-methoxymethyl-5-methylfuran and 2,5-bis(methoxymethyl)furan were also formed as by-products. Coulometric data showed that on an average two electrons were lost per 2,5-dimethylfuran molecule. It was concluded that the overall reaction involves the initial oxidation of 2,5-dimethylfuran and proceeds nonstereospecifically.

There are already several reports available concerning anodic cyanation of aromatic compounds.[2] In most of these published examples, however, the reactions were conducted in methanol, thus leading to the competitive formation of methoxylated products which were often predominant in quantity over the cyanation products. An improved method of cyanation has recently been proposed by Andreades and Zahnow,[3] who electrolyzed various aromatic compounds in the presence of tetraethylammonium cyanide in acetonitrile.

In a previous communication of this series,[4] we have briefly described that a methanolic sodium cyanide solution containing 2,5-dimethylfuran provides a cis–trans isomeric mixture of 2-cyano-5-methoxy-2,5-dimethyldihydrofuran in high current efficiency, when electrolyzed under a controlled anode potential.



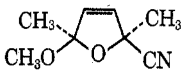
The purpose of the present paper is to examine the nature of the above reaction in more detail under various experimental conditions. It has been found that the reaction involves an initial oxidation of the furan and that the overall reaction is nonstereospecific.

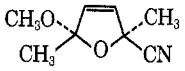
Results

Controlled Potential Electrolysis.—First of all, current–potential measurements were carried out on an 0.8 *M* sodium cyanide solution in methanol at 25°, both in the presence and absence of 2,5-dimethylfuran. The measurements are not only useful for selecting the potentiostat setting at which the controlled potential electrolysis may efficiently be conducted but also provide a preliminary knowledge of the mechanistic features of the overall reactions. The current–potential curves observed are graphically shown in Figure 1.[5]

As can be seen in Figure 1, a methanolic solution of sodium cyanide alone is not discharged unless the anode potential exceeds 1.4 V, whereas a solution containing 2,5-dimethylfuran allows current to pass through it at a potential as low as 1.0 V. Clearly, 2,5-dimethylfuran is oxidizable at a relatively low anode potential.[6]

Electrolytic oxidation of 2,5-dimethylfuran was conducted at anode potentials controlled to within 0.01 V at a voltage between 1.0 and 1.3 V. Coulometric data showed an average of two electrons lost per 2,5-dimethylfuran molecule. The oxidation products comprized mainly *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofuran (I_c and I_t).[4] Small amounts of *cis*- and *trans*-2,5-dimethoxy-2,5-dimethyldihydrofuran (II_c and II_t) with traces of 2-methoxymethyl-5-methylfuran (III) and 2,5-bis(methoxymethyl)furan (IV) were also formed as minor products. Identifications of these products will be the subject of the next subsection.


I_c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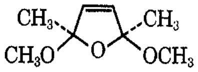
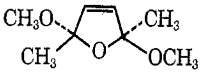
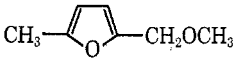

II_c


II_t


III

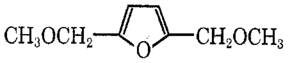

IV

Table I summarizes the results of electrolysis conducted at various anode potentials. The initial concentrations of sodium cyanide and 2,5-dimethylfuran were both fixed at 0.8 *M*.

TABLE I
ANODIC OXIDATIONS CONDUCTED AT VARIOUS POTENTIALS AT 25° [a]

Anode potential, V	Conversion, %	Current efficiency for I, %	Molar ratios II/I	Molar ratios I_c/I_t
1.0	3	95	0.05	2.1
1.1	5	87	0.08	2.2
1.2	17	70	0.09	1.9
1.3	31	61	0.09	2.0
35[b]	~60	49	0.10	2.0

[a] [NaCN] = [2,5-dimethylfuran] = 0.8 *M*; reaction time, 6 hr. [b] Nonpotentiostatic oxidation at an overall voltage of 35 V. See the Experimental Section.

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(1) Part II: K. Yoshida and T. Fueno, *Chem. Commun.*, 711 (1970).

(2) (a) K. Koyama, T. Susuki, and S. Tsutsumi, *Tetrahedron Lett.*, 627 (1965); (b) V. D. Parker and B. E. Burgert, *ibid.*, 4065 (1965); (c) K. Koyama, T. Susuki, and S. Tsutsumi, *Tetrahedron*, **23**, 2675 (1967); (d) T. Susuki, K. Koyama, A. Omori, and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **41**, 2663 (1968); (e) L. Eberson and S. Nilsson, *Discuss. Faraday Soc.*, **45**, 242 (1968); (f) S. Tsutsumi and K. Koyama, *ibid.*, **45**, 247 (1968); (g) V. D. Parker and B. E. Burgert, *Tetrahedron Lett.*, 2415 (1968).

(3) S. Andreades and E. W. Zahnow, *J. Amer. Chem. Soc.*, **91**, 4181 (1969).

(4) K. Yoshida and T. Fueno, *Bull. Chem. Soc. Jap.*, **42**, 2411 (1969).

(5) All potentials were measured against sce.

(6) It has been known that the half-wave potential of 2,5-dimethylfuran in acetic acid is 1.20 V: L. Eberson and K. Nyberg, *J. Amer. Chem. Soc.*, **88**, 1686 (1966).

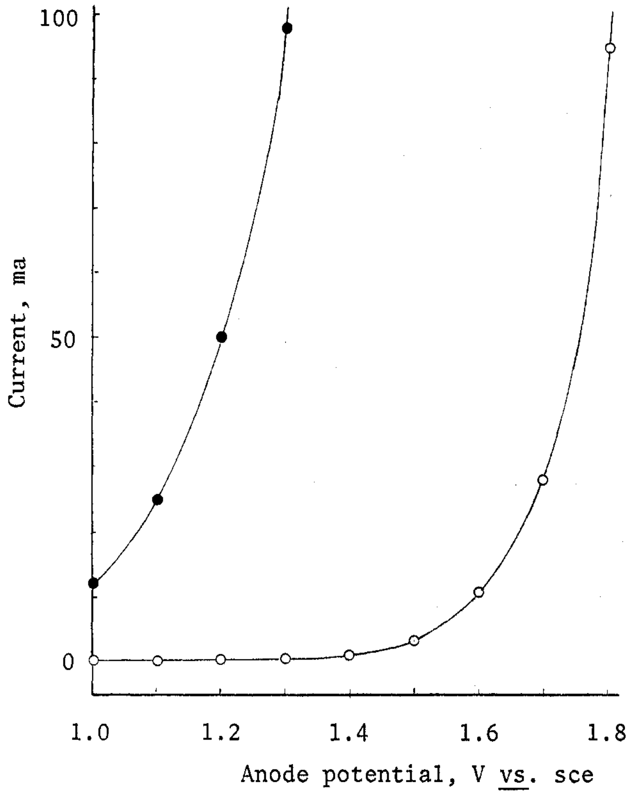

Figure 1.—Plots of current *vs.* anode potential for electrolyses of solutions containing 0.8 *M* sodium cyanide in methanol at 25°: ○, without 2,5-dimethylfuran; ●, with 0.8 *M* 2,5-dimethylfuran.

It may be seen from Table I that, although the conversion of 2,5-dimethylfuran tended to decrease with the lowering in anode potential, the current efficiency for the formation of I steadily increased with the lowering potential until it reached a value as great as 95% (based on a 2e process) at 1.0 V. In contrast, there was no significant variation in distribution of the products I_c, I_t, and II ($II_c + II_t$). The trend remained the same in the nonpotentiostatic experiment (at 35 V). It thus appears that the anode potential plays no essential role in determining the product distribution.

Comparative experiments were also carried out with different initial concentrations of reactants at a given anode potential of 1.3 V. The results are shown in Table II.

TABLE II

ANODIC OXIDATIONS CONDUCTED WITH VARIOUS INITIAL CONCENTRATIONS OF SODIUM CYANIDE[a]

[NaCN]	Conversion, %	Current efficiency for I, %	Molar ratios II/I	Molar ratios I_c/I_t
0.1[b]	4	80	0.05	2.2
0.1	5	70	0.09	1.9
0.2	10	65	0.07	2.0
0.8	31	61	0.09	2.0

[a] [2,5-Dimethylfuran] = 0.8 *M;* anode potential, 1.3 V; reaction time, 6 hr; temperature, 25°. [b] [2,5-Dimethylfuran] = 2.0 *M*.

The data listed in Table II clearly show that the conversion increased with the increasing concentration of the cyanide used but that the current efficiency for the formation of I again ran antiparallel to the conversion. Here also, the product distribution was practically unaltered.

Identification of the Products.—Each product was isolated by fractional distillation or preparative vpc and identified by the infrared, mass, and nmr spectroscopies.

The structural assignments for the two isomers, I_c and I_t, were based on their nmr spectra.[7] The methoxy protons of I_c (τ 6.81) resonated at a magnetic field a little lower than did those of I_t (τ 6.92). It is apparent from molecular models that the methoxy protons in the cis isomer are located closer to the cyano group than those in the trans isomer, indicative of the lower-field shift[8] of the methoxy protons in the former compound. This implies that a cis configuration is assignable to the product I_c. Extensive nmr spectral data[9-11] of geometrical isomer pairs of 2,5-disubstituted furans lend support to the present structural assignments.

It was confirmed that neither of the isomers I_c and I_t undergoes interconversion under the present experimental conditions. Both of them also remained intact on vpc. The isomeric compositions determined from nmr spectroscopy and analytical vpc always agreed with each other, the ratio of I_c to I_t being 2.0 as has been shown in Tables II and III. However, a trace of sulfuric acid instantaneously converted either isomer into an equilibrium mixture of the two isomers ($I_c/I_t = 2.0$). When heated in carbon tetrachloride, the individual isomers suffered slow isomerization, eventually attaining equilibrium.

The minor products II_c, II_t, III, and IV were identified by comparisons with the authentic samples prepared by other routes. The ratio of II_c to II_t was *ca.* 1, a value which was essentially equal to the ratio already reported for the anodic methoxylation of 2,5-dimethylfuran.[12]

Discussion

As has already been described, a methanolic solution of sodium cyanide is not discharged at an anode potential between 1.0 and 1.3 V.[13] Because in the same potential range the solution containing 2,5-dimethylfuran is oxidizable, the primary electrode process in this latter case must be the oxidation of 2,5-dimethylfuran to a cationic species. By analogy with anodic aromatic substitution reactions,[14] a mechanism involving a cation radical intermediate as in Scheme I is conceivable. Probably, the anodically generated cation radical **1** is attacked by the cyanide ion (or methanol) to produce the radical **2** (or **4**), followed by further anodic oxidation and successive nucleophilic attack by

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[7] The proton peaks of both these isomeric products were of the $ABM_3P_3X_3$ type (see Table III).

[8] This arises mainly from the local magnetic anisotropy effect of the cyano group. In addition, since the methoxy protons are more or less positively charged, a weak interaction may be expected between the methoxy protons and the electron-rich cyano group at a closer distance. The interaction is expected to be a kind of weak hydrogen bonding. Such an interaction is considered to cause a lower-field shift of the resonance signal of the proton involved in the interaction.[9]

[9] A. Aito, T. Matsuo, and C. Aso, *Bull. Chem. Soc. Jap.*, **40**, 130 (1967).

[10] D. Gagnaire and P. Vottero, *Bull. Soc. Chim. Fr.*, **12**, 2779 (1963).

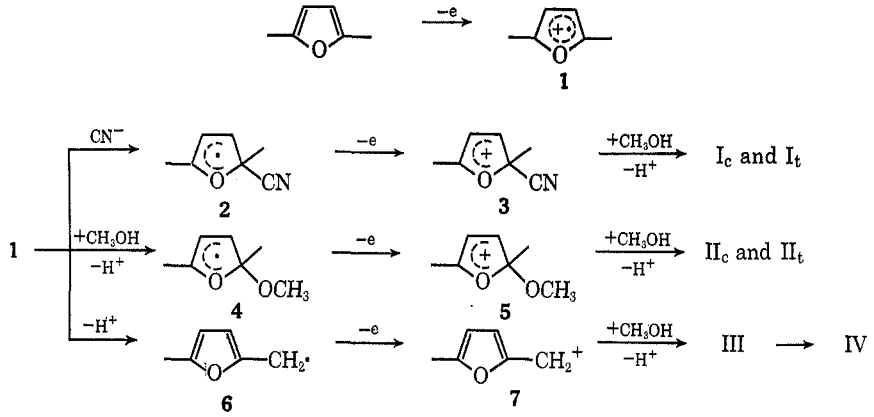
[11] T. Hiraoka, T. Iwashige, and I. Iwai, *Chem. Pharm. Bull.*, **13**, 285 (1965).

[12] S. D. Ross, M. Finkelstein, and J. J. Uebel, *J. Org. Chem.*, **34**, 1018 (1969).

[13] Andreades and Zahnow reported that the cyanide ion dissolved in acetonitrile is oxidized at *ca.* 0.6 V.[3] In methanol, however, the cyanide ion (or, more strictly, the ion pair of sodium cyanide) is apparently stabilized by strong solvation, thus surviving under the anode potential of even 1.3 V.

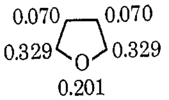
[14] (a) R. N. Adams, *Accounts Chem. Res.*, **2**, 175 (1969); (b) G. Manning, V. D. Parker, and R. N. Adams, *J. Amer. Chem. Soc.*, **91**, 4584 (1969).

SCHEME I



solvent, leading to the formations of I and II. Part of 1 should also undergo deprotonation to afford the 5-methyl-2-furylmethyl radical 6, which should finally give rise to III and IV.

It is to be expected that the carbon atoms of a higher positive charge in the cationic species 1 and 3 would



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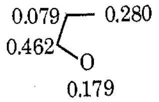

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react more readily with a nucleophile. Net charge distributions calculated for these cationic species by the ω technique[15] as used in π-electron approximation indicated that in both these species the greatest positive charge is imparted on the 2 (and 5) position, in accord with the products obtained.

Stereochemical phase of the reactions leading to the formation of geometrical isomers deserves comment. We at first anticipated operation of some factor that might control the stereochemistry, assuming that the attack of nucleophiles on the cations 3 and 5 take place primarily on the electrode surface. In reality, however, the products were in all cases equilibrium mixtures of the cis and trans isomers. It must be concluded, therefore, that the intermediates 3 and 5 suffer the attack by solvent primarily in a homogeneous environment. Analogous results have recently been obtained in both the chemical and electrochemical methoxylation of 2,5-dimethylfuran.[12]

In conclusion, the cyanomethoxylation of 2,5-dimethylfuran proceeds *via* a polar mechanism involving initial oxidation of the furan ring to give an intermediate cation radical. The overall reaction proceeds nonstereospecifically.

Experimental Section

Materials.—Methanol used in the current–potential measurements was of optical pure grade. For the preparative runs, methanol was purified by fractional distillation from magnesium activated with iodine. Reagent grade sodium cyanide was used with no purification other than drying. 2,5-Dimethylfuran was prepared according to a known procedure[16] and the purity checked by vpc.

Authentic samples of *cis*- and *trans*-2,5-dimethoxy-2,5-dimethyldihydrofurans were prepared by anodic methoxylation of 2,5-dimethylfuran.[12,17] 2,5-Bis(methoxymethyl)furan was prepared by the bromination of 2,5-dimethylfuran with *N*-bromosuccinimide, followed by treatment with sodium methoxide.[12] 2-Methoxymethyl-5-methylfuran was obtained according to the same method as above except that 1 equiv of *N*-bromosuccinimide was used.

Analytical Method.—Reaction products and the furan recovered were determined by vpc (column, PEG 6000; column temperature, 120°; internal standard, tetralin). Infrared spectra of the products were recorded on a JASCO Model IR-E infrared spectrophotometer. Nmr spectra were obtained with a JEOCO Model JNM-4H-100 spectrometer. Mass spectra were measured with a Hitachi Model RMS-4 instrument.

Current–Potential Measurements.—Current–potential curves (uncorrected for the internal resistance drop in the cell) were taken at 25° by using a two-compartment cell with a platinum wire electrode in the cathode compartment and the saturated calomel reference electrode, a platinum plate electrode having an area of 8 cm^2, and a magnetic stirrer bar in the anode compartment. Prior to use the electrodes were cleaned with a dichromate cleaning solution, rinsed with water, and dried. Nitrogen was bubbled through the cell before measurements. Anode potential was controlled by means of a YANACO Model VE-3 potentiostat.

Current was measured as a function of anode reference potential in the range of 1.0–1.8 V, using 0.8 *M* furan concentrations. The time required for the current and potential to reach steady-state values varied from solution to solution and depended on current. Most measurements took from 10 to 20 min per point, and during that time interval the current fell only slightly.

To examine the influence of cell resistance, measurements were also carried out by using an undivided cell. However, no significant difference was found between the two results.

Potentiostatic Oxidations.—Controlled potential electrolyses were performed by using the same cell that was used for current–potential measurements. The total electrolysis current was determined in two ways; one was by the gain in weight of the copper cathode while the other by a graphic current–time integration method. Replicate determinations of the total current by the two methods agreed to within 5%.

The electrolyses were carried out under an atmosphere of nitrogen pressure at 25°. In a typical experiment a methanolic solution (50 ml) of 2,5-dimethylfuran (3.85 g, 0.04 mol) and sodium cyanide (1.96 g, 0.04 mol) was electrolyzed for 6 hr, using an anode potential of 1.3 V. The catholyte was methanol, 0.8 *M* in sodium cyanide. The total electricity used amounted to 2430 C.

The electrolyzed mixture was treated with 150 ml of water and the organic material extracted with two 50-ml portions of ether. The combined ether extract was washed thoroughly with water, dried over anhydrous magnesium sulfate, and filtered. Vpc analysis showed that 1.27 g of 2,5-dimethylfuran had been consumed, corresponding to 1.9 electrons lost per 2,5-dimethylfuran molecule. The furan remaining unchanged as well as ether was then evaporated off under reduced pressure. Vacuum distillation of the residual liquid gave the following fractions:

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(15) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 115, 135. The parameters used were $h_O = 2$, $k_{C-O} = 0.8$, $h_C = -0.5$ (inductive model for the methyl group), $\delta = 0.1$, $\omega = 1.4$, Other reasonable choices of the parameter set did not alter the results materially.

(16) R. Gaertner and R. G. Tonkyn, *J. Amer. Chem. Soc.*, **73**, 5872 (1951).

(17) A. J. Baggaley and R. Brettle, *J. Chem. Soc. C*, 969 (1968).

fraction 1, bp 60–70° (14 mm), 0.2 g; fraction 2, bp 85–89° (14 mm), 1.1 g; fraction 3, bp 120–150° (14 mm), 0.4 g.

The infrared spectrum of the main fraction (fraction 2) showed absorption bands at 3115 (=CH), 2860 (OCH_3), 2260 (CN), 1635 (C=C), 1175, 1145, 1100, 1060, and 1045 cm^{-1} (COCOC); mol wt (mass spectrum), 153. *Anal.* Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.78; H, 7.30; N, 9.06. The nmr spectrum of this fraction (100 MHz, 10% in CCl_4) suggested that this material was a 2:1 isomeric mixture of *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofuran (I_c and I_t). The yield was 20% (based on 2,5-dimethylfuran used; current efficiency, 61%). Each isomer was then separated in pure form by preparative vpc, the column packing being PEG 6000. The cis isomer had a shorter retention time. The melting points were 31.5–32.5°, cis, and 49.5–50.5°, trans. The proton chemical shifts τ of these isomers are listed in Table III.

Fraction 1 was mainly a 1:1 mixture of 2-cyano-5-methoxy-2,5-dimethyldihydrofuran (I_c and I_t) and 2,5-dimethoxy-2,5-dimethyldihydrofuran (II_c and II_t), with trace quantities of 2-methoxymethyl-5-methylfuran (III) and 2,5-bis(methoxymethyl)furan (IV). Fraction 3 was a clear, viscous liquid. No attempt was made to identify it.

Nonpotentiostatic Oxidations.—Preparative-scale electrolysis was carried out in a two-compartment H-type cell with glass frit separating the compartments fitted with platinum foil electrodes (20 × 30 mm^2). The anolyte was made up of 15.4 g (0.16 mol) of 2,5-dimethylfuran, 7.8 g (0.16 mol) of sodium cyanide, and 200 ml of methanol. The catholyte was a methanolic solution of sodium cyanide. The electrolysis was carried out under a nitrogen atmosphere for 18 hr at 35 V until 18,900 C had passed through the electrolyte. During the electrolysis, the solution was kept stirred magnetically and cooled externally with ice (2–5°).

The electrolyzed mixture was treated as usual. Vacuum distillation afforded 7.4 g of I (30% yield based on 2,5-dimethylfuran used; current efficiency, 49%; cis/trans = 2.0) and 0.8 g of II (3% yield; current efficiency, 5%; cis/trans $\simeq$ 1), with traces of III and IV. When the electrolysis was conducted in a undivided cell, the yield of I decreased considerably.

TABLE III

PROTON CHEMICAL SHIFTS (τ VALUES) IN *cis*- AND *trans*-2-CYANO-5-METHOXY-2,5-DIMETHYLDIHYDROFURAN[a,b]

Compd	Vinyl proton	Methoxy proton	Methyl proton
I_c	3.92 (1 H, d, J = 5.6 cps)	6.81 (3 H, s)	8.38 (3 H, s)
	4.18 (1 H, d, J = 5.6 cps)		8.55 (3 H, s)
I_t	3.99 (1 H, d, J = 5.8 cps)	6.92 (3 H, s)	8.34 (3 H, s)
	4.13 (1 H, d, J = 5.8 cps)		8.49 (3 H, s)

[a] Measured at 100 MHz in CCl_4. [b] Abbreviations: d, doublet; s, singlet.

Registry No.—I_c, 28463-58-3; I_t, 28463-59-4; 2,5-dimethylfuran, 625-86-5.

Homolytic Arylation of Pyridine and Pyridine *N*-Oxide and the Effect of Localization Energy and Temperature on Arylation Patterns

R. M. ELOFSON,* F. F. GADALLAH, AND K. F. SCHULZ

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Pyridine and pyridine *N*-oxide have been phenylated by electrolytic reduction of benzenediazonium tetrafluoroborate in aprotic media giving high yields of phenylated products. Nonelectrolytic reduction systems were also investigated, leading to a new mechanism for diazonium salt–pyridine reactions. Partial rate factors and total rate ratios for pyridine *N*-oxide are reported for the first time. Experimental results are related to theoretical values calculated from molecular orbital theory by Brown and Barnes.

Previously this laboratory reported the polarographic reduction in aprotic solvents of substituted benzenediazonium tetrafluoroborates in which the most positive wave is produced by a reversible one-electron step.[1a] The phenyl radical formed in this system has been used to phenylate benzene, toluene, anisole, benzonitrile, nitrobenzene, bromobenzene, and naphthalene with most encouraging results.[1b]

Therefore, it seemed of interest to examine the electrochemical arylation of heteroaromatic nitrogen compounds. Pyridine was chosen because the abundant available data concerning the homolytic arylation of pyridine would provide a way to evaluate our method. Pyridine *N*-oxide was chosen for precisely the opposite reason: the few and conflicting data might be elucidated by our study.

Homolytic arylation of pyridine has been achieved using benzoyl peroxide, lead tetrabenzoate, phenyl iodobenzoate, and electrolysis of benzoic acid as sources of the free radical.[2-6] Abramovitch and coworkers,[7,8] using an equimolar mixture of pyridine and benzenediazonium tetrafluoroborate, reported production of phenyl radicals, but no results for the phenylation of pyridine were given.

Data on homolytic phenylation of pyridine *N*-oxide are scarce. Dyall and Pausaker[9] treated pyridine *N*-oxide with phenyl radical generated from diazoaminobenzene and succeeded in separating the three phenylpyridine *N*-oxides. The isomer ratio they observed agrees qualitatively with ratios predicted by Barnes[10] from molecular orbital theory. The actual ratios differed from one run to the next and no total rate ratio was measured. On the other hand, Abramovitch and Koleoso,[8] phenylating pyridine *N*-oxide at room temperature to 60°, with an equimolar mixture of benzenediazonium tetrafluoroborate and pyridine, obtained 0.9% of isomeric phenylated oxides and 6% of phenylated pyridines with isomer ratios qualitatively similar to theory, but no attempt was made to obtain the total rate ratio ${}^{\mathrm{N-O}}_{\mathrm{C-H}}K$ or partial rate factors. Since the total rate ratio we obtained is high, we have pursued

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(1) (a) R. M. Elofson and F. F. Gadallah, *J. Org. Chem.*, **34**, 854 (1969); (b) F. F. Gadallah and R. M. Elofson, *ibid.*, **34**, 3335 (1969).

(2) R. O. C. Norman and G. K. Radda, *Advan. Heterocycl. Chem.*, **2**, 131 (1963).

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(4) G. H. Williams, "Homolytic Aromatic Substitution," Pergammon Press, London, 1960.

(5) D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.*, 3963 (1955).

(6) P. J. Bunyan and D. H. Hey, *ibid.*, 3787 (1960).

(7) R. A. Abramovitch and J. G. Saha, *Tetrahedron*, **21**, 3297 (1965).

(8) R. A. Abramovitch and O. A. Koleoso, *J. Chem. Soc. B*, 1292 (1968).

(9) L. K. Dyall and K. H. Pausaker, *ibid.*, 18 (1961).

(10) R. A. Barnes, *J. Amer. Chem. Soc.*, **81**, 1935 (1959).