

Studies of Organic Catalytic Reactions. VI.¹⁾ The Function of Pyridine and Copper in the Rosenmund-von Braun Reaction

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The Rosenmund-von Braun reaction with aryl halide, with its $\text{Ar-X} + \text{CuCN-Base} \rightarrow \text{Ar-CN} + \text{CuX-Base}$, has been studied in nitrobenzene in place of an organic base at 160–180°C. The free nitriles formed during the reaction were determined exactly by gas chromatography. In the use of bases with suitable coordination forces to CuCN, the reactivity of the base for the substitution was found to be in the order: $\text{prim.} > \text{sec.} > \text{tert.}$ A steric hindrance of the base was observed, and the reactivity of the pyridine homologue followed the order: $\text{pyridine} > \text{quinoline} > \alpha\text{-picoline} > 2, 6\text{-lutidine}$. Ortho-substituted groups in the halobenzene seem to manifest no steric hindrance on the reaction. From the results of the kinetic study, it can be said that CuCN participates in the reaction essentially in the form of a Base(1 mol)-CuCN complex. The overall reaction is second-order, $dc/dt = k[\text{Complex}][\text{Ar-X}]$. The rate-determining step may be in the halogen exchange stage in the intervening complex, Base-CuCN-Ar-X , where the plane including CN-Cu-X and that of the benzene ring may be nearly perpendicular to each other. When an excess of CuCN over the base is used, the base is liberated from the Base-CuX complex, after the displacement, and then coordinates to the unreacted CuCN again.

It has previously been reported²⁾ that the Rosenmund-von Braun reaction in which nitriles are obtained from aryl bromides and cuprous cyanide is generally useful for the preparation of aromatic nitriles. In that study, the aryl halides were converted to the nitriles in a good yield by refluxing them in pyridine. The succeeding study with four sorts of halobenzene established that the ease of the displacement of halogen is in the order: $\text{I} > \text{Br} > \text{Cl} > \text{F}$. Representative examples are shown in Table I.

Improvements of this reaction have been reported by Newman and his co-workers,^{3,4)} who used *N*-methylpyridone or dimethylformamide as the solvent. Bacon and his co-workers⁵⁾ studied the reaction, $\text{Ar-hal} + \text{Cu-X} \rightarrow \text{Ar-X} + \text{Cu-hal}$ ($\text{X} = \text{Cl, Br, CN, SCN}$), in various polar solvents and explained that the reaction proceeds as a bimolecular type between Ar-hal and Cu-X . In the studies mentioned above, however, the reactions were carried out through the dissolution of the complex (solvent-CuCN) in the same solvent

(organic base); therefore, the quantity of the base that participated in the reaction could not be elucidated. Further, in the experimental procedure, the separation of the nitrile from the reaction mixture was very troublesome because the reaction mixture containing the nitrile was obtained as a solid complex at room temperature; it then had to be decomposed with ammonia or concentrated hydrochloric acid to get the free nitrile.

This paper will deal with studies of the Rosenmund-von Braun reaction in a nitrobenzene solution attempting to overcome the disadvantages mentioned above. In this way, the ratio of the organic base to CuCN can be calculated, and the nitrile formed during the reaction is liberated as a free form in a nitrobenzene solution. Therefore, the behavior of the organic base, aryl halide, and cuprous cyanide can be examined, and the formation of the nitrile can be determined exactly. The mechanism of this reaction is presented here.

In this study, bromobenzene and pyridine were mainly used; they were heated with cuprous cyanide at 180°C in nitrobenzene. It did not matter whether the reaction was carried out in the air or in an oxygen-free nitrogen atmosphere. Cuprous cyanide and cuprous chloride were hardly ever soluble in nitrobenzene and did not react with bromobenzene without the addition of pyridine or other organic bases. When the organic base was added to the copper salt in nitrobenzene, both of them were dissolved by the mild heating forming the complex. As far as our tests were concerned, nitrobenzene was the best solvent for this reaction.

1) Paper V: K. Sakai, T. Ito and K. Watanabe, *This Bulletin*, **40**, 1660 (1967).

2) N. Akanuma, H. Amemiya, T. Hayashi, K. Watanabe and K. Hata, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **81**, 333 (1960); *Chem. Abstr.*, **56**, 406 (1962).

3) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).

4) M. S. Newman and H. Boden, *ibid.*, **26**, 2535 (1961).

5) R. G. R. Bacon and H. O. Hill, *J. Chem. Soc.*, **1964**, 1097.

TABLE 1. ROSENMUND-VON BRAUN REACTION IN PYRIDINE¹⁾

Exp. No.	Aryl halide	g	CuCN g	Pyridine g	Reaction temp. °C	Reaction time hr	Yield of nitrile %
1	Iodobenzene	20	10.8	15	170—190	6	80
2	Bromobenzene	20	12.0	15	140—155	9	85
3	<i>o</i> -Bromonitrobenzene	10	5.0	10	140—155	2	91
4	<i>p</i> -Bromonitrobenzene	20	9.9	20	140—155	9	80
5	Bromomesitylene	20	9.9	10	165—175	8	80
6	<i>o</i> -Bromoacetophenone	25	12.5	75	120	1.5	70
7	β -Bromonaphthalene	5	6	10 ²⁾	260—280	3	78
8 ³⁾	Chlorobenzene	22.6	20	15	140—150	14	trace
9	<i>o</i> -Chloronitrobenzene	10	12.5	15	160—180	3	80
10	Fluorobenzene	5.8	14.4	10	140—160	3	—

1) The reaction method by Newman was employed; M. S. Newman, "Organic Syntheses," Coll. Vol. III, p. 631 (1955).

2) Quinoline was used as solvent instead of pyridine.

3) By the reaction in an autoclave at 250°C for 9 hr, the yield of the nitrile was 34%.

Decalin, benzyl alcohol, or cyclohexanone was unfavorable, and the reaction proceeded under heterogeneous conditions.

After the reaction was started, the heterogeneous reaction mixture turned into a brownish homogeneous solution at *ca.* 120°C. When the reaction was completed, the reaction mixture was cooled to room temperature; a brownish mass was then obtained by filtration. When the mass was extracted enough with ether, very small quantities of nitrile and unreacted bromobenzene were ob-

tained. Both the ether fraction and the nitrobenzene solution were analyzed by gas chromatography; the ratios of nitrile to bromobenzene were almost the same in both fractions. By the IR spectrum analysis of the crystals after the ether extraction, only the pyridine used for the reaction was detected. Thus, the tests revealed that the quantities of halide and nitrile can be determined by the gas chromatographic analysis of the reaction mixture in the course of the reaction*¹ (Fig. 1).

TABLE 2.²⁾ THE REACTION OF BROMOBENZENE WITH CUPROUS CYANIDE IN NITROBENZENE

Bromobenzene 4 ml, CuCN 3 g, Nitrobenzene 20 ml, React. temp. 180°C

Exp. No.	Base	ml	Reaction time hr	Benzonitrile %
1	Pyridine	0.2	6	49
2	Pyridine	0.5	6	86
3	Pyridine	1.0	6	79
4	Pyridine	5.0	6	82
5	Pyridine ²⁾	1.0	3	73
6	γ -Picoline	1.0	3	83
7	Quinoline	1.0	3	59
8	α -Picoline	1.0	3	28
9	2,6-Lutidine	1.2	3	26
10	Aniline	4.0	5	68
11	Diethylamine	1.0	3	24
12	Dimethylaniline	1.0	3	—
13	Ethylenediamine	3.0	6	25 ³⁾
14	Picolinic acid	1.0	3	22

1) The yield was calculated by gas chromatographic analysis based on the amount of bromobenzene.

2) The yield of the product rised to 78% when 0.5 g of hydroquinone was added.

3) Unknown 35%.

*¹ In the results of the gas chromatographic analysis, no other product was detected.

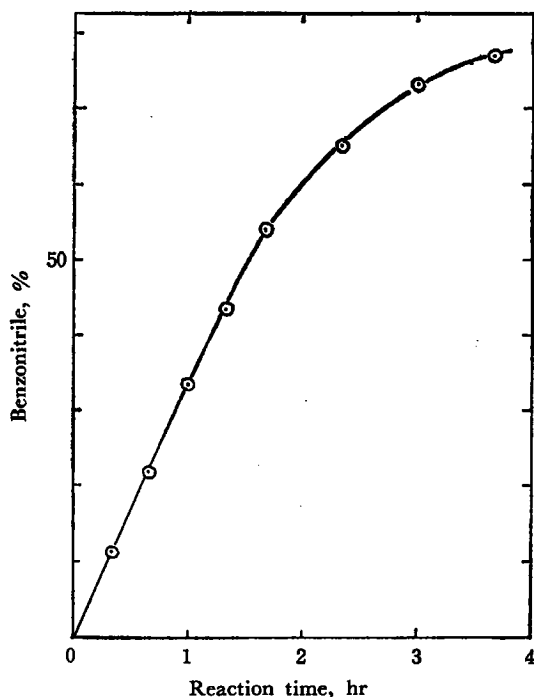


Fig. 1. The formation of benzonitrile. Bromobenzene 1.0 ml, cuprous cyanide 1.0 g, pyridine 1.0 ml, nitrobenzene 20 ml, reaction temp. 177°C.

When a complex of CuCN with pyridine was prepared^{*2} beforehand and was used for the reaction with bromobenzene, the reaction proceeded as well as in the case of the ordinary method. In order to examine whether the free nitrile formed would participate in the reaction or not, benzonitrile was used in place of pyridine, but no change in bromobenzene was observed.

The results of the reactions with various kinds of bases in nitrobenzene are shown in Table 2.^{*3} The reactions were carried out at 180°C ; no reaction occurred below 130°C . The organic bases used in the reaction should coordinate moderately to the copper atom of the cuprous cyanide.^{*4} In the use of bases with suitable coordination forces, the reactivity of the substitution depended on their basicity: prim. > sec. > tert. No reaction occurred with dimethylaniline. The steric hindrance of the

substituents of bases had an influence upon the reactivity of the complexes of the pyridine homologues; the reactivity was found to be in the order: pyridine > quinoline > α -picoline > 2, 6-lutidine. Bacon⁵⁾ pointed out this problem as a solvent effect. The methyl group of the γ -picoline seemed to enhance the coordination ability of the base by means of its 1-effect (Exp. 6, Table 2). It is assumed that the activity of the complex is dependent upon both the character and the molecular structure of the base.

In order to investigate the mechanism of this reaction, simple kinetic studies were done. Some were carried out in a bromobenzene solution, the mole ratio of Py/CuCN was set up as 1, 2, or 3.

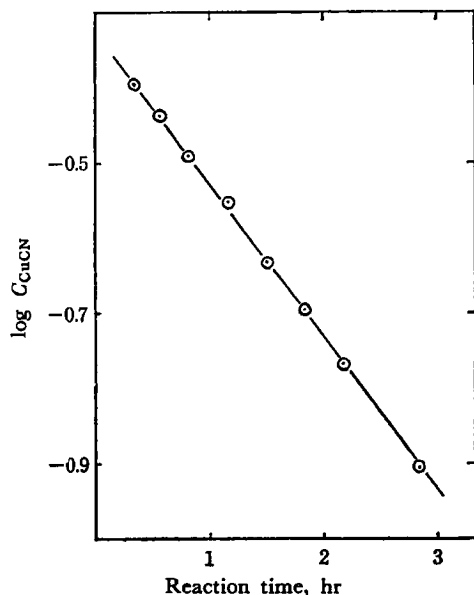


Fig. 2. The correlation of C_{CuCN} vs. reaction time.

Bromobenzene 25 ml, cuprous cyanide 4.0 g, pyridine 2.0 ml, reaction temp. 152°C .

^{*2} Pyridine and cuprous cyanide were heated at 120°C for about 30 min and then cooled. The yellow material thus obtained was used directly in the reaction.

^{*3} All the reactions except Exp. 4 proceeded heterogeneously, for the amount of the bases used was less than that of the cuprous cyanide, so a part of the cyanide remained insoluble in the solvent. On the other hand, the amount of the cyanide used was less than that of the bromobenzene; therefore, the conversion of the bromobenzene into benzonitrile could not reach 100% even if all of the cyanide did react with the bromobenzene.

^{*4} Ethylenediamine afforded a stable copper complex, the process being accompanied by a side reaction, and the yield of the nitrile was very low (Exp. 13, Table 2). No reaction occurred when dimethylglyoxime or acetyl acetone was used as the base. When 8-oxyquinoline or picolinic acid was used, the reaction proceeded extremely slowly.

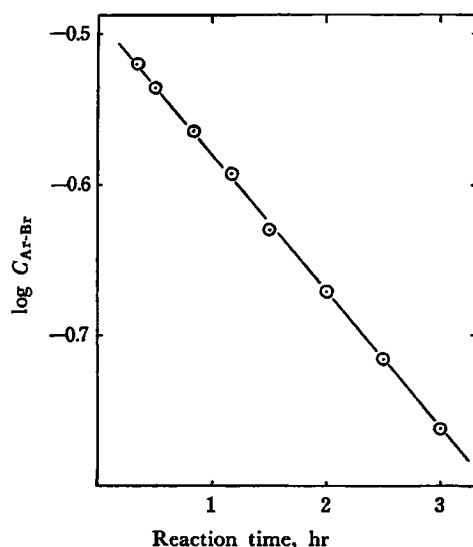


Fig. 3. The correlation of $C_{\text{Ar-Br}}$ vs. reaction time.

Bromobenzene 1.0 ml, cuprous cyanide 4.0 g, pyridine 2.0 ml, nitrobenzene 30 ml, reaction temp. 159°C

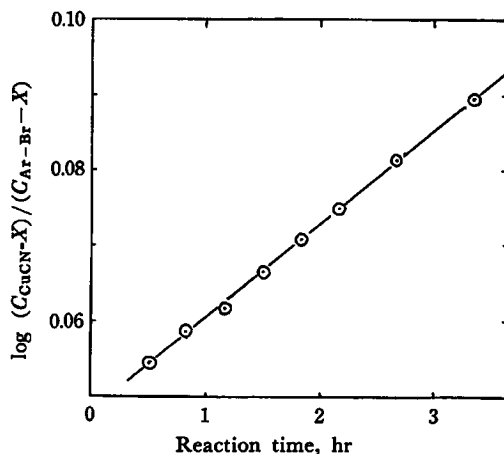


Fig. 4. Ar-Br (1.0 ml) + CuCN (1.0 g) + pyridine (1.0 ml) in nitrobenzene (20 ml) at 160°C .

TABLE 3.

A. CYANIZATION

Bromobenzene 1.0 ml, Nitrobenzene 20.0 ml, React. temp. $159 \pm 0.5^\circ\text{C}$

Base	ml	CuCN g	Base/CuCN	Initial rate mol/min $\times 10^3$	Reaction rate ratio
Pyridine	1.0	2.0	0.62	3.06	0.59
Pyridine	1.0	1.0	1.24	5.18	1.0
Pyridine	2.0	1.0	2.48	5.17	1.0

B. CHLORINATION

Bromobenzene 1.0 ml, CuCl 1.0 g, Nitrobenzene 40 ml, React. temp. $180 \pm 0.5^\circ\text{C}$,
in an oxygen free nitrogen

Base	ml	Base/CuCl	Initial rate mol/min $\times 10^3$	Reaction rate ratio
α -Picoline	0.5	0.5	9.0×10^{-1}	0.5
α -Picoline	1.0	1.0	1.77	1.0
α -Picoline	2.0	2.0	1.75	1.0
α -Picoline	4.0	4.0	1.7	1.0
2,6-Lutidine*	1.0	0.85	1.6	0.86
2,6-Lutidine*	2.0	1.7	1.87	1.0

* 1.0 ml of *o*-bromotoluene was used instead of bromobenzene.

TABLE 4. EFFECT OF METHYL GROUP IN BROMOBENZENE

CuCl 1.0 g, Base/CuCl 1.8–2.2, Nitrobenzene 40 ml (solvent), React. temp. $181 \pm 0.5^\circ\text{C}$,
in an atmosphere of oxygen-free nitrogen

Aryl halide (1.0 ml)	Base (2.0 ml)	Rate const. l/mol $\cdot$ min $^{-1}$	k_{ortho}/k_{para}
Bromobenzene	2,6-Lutidine	1.78×10^{-2}	
<i>o</i> -Bromotoluene	2,6-Lutidine	4.27×10^{-2}	2.07
<i>p</i> -Bromotoluene	2,6-Lutidine	2.05×10^{-2}	
<i>o</i> -Bromotoluene	Pyridine	3.82×10^{-1}	2.08
<i>p</i> -Bromotoluene	Pyridine	1.84×10^{-1}	
Bromobenzene	α -Picoline	3.29×10^{-2}	

Some representative results of the reactions are shown in Fig. 2, in which the reactions are first-order with regard to the CuCN. When an excess of CuCN over pyridine was used, the relation between the quantity of nitrile formed and the reaction time was linear. These facts indicate that the CuCN participates in the form of the CuCN-pyridine complex and that the concentration of the complex is approximately constant during the initial period of the reaction. On the other hand, other reactions were carried out in a nitrobenzene solution with an excess of CuCN over pyridine, these reactions were found to be first-order with regard to the bromobenzene (Fig. 3). As a result, the overall reaction is shown as a second-order reaction, $dc/dt = k[\text{Complex}][\text{Ar-Br}]$, in Fig. 4.

To elucidate the correlation of the reaction rate with the number of base molecules coordinated to the copper atom, some kinetic studies were done in

a nitrobenzene solution with bromobenzene. Pyridine, α -picoline, and 2,6-lutidine were used as the bases, while CuCN and CuCl were used as the copper salt. The results of the experiments are shown in Table 3. The reaction rate was set at 1 when the mole ratio of the base to the Cu-salt was equal to 1 (Base/Cu-salt=1). When Base/Cu-salt > 1, the ratio of the reaction rate was also equal to 1. On the other hand, when Base/Cu-salt < 1, the ratio was equal to that of Base/Cu-salt. Accordingly, it could be inferred that the reaction may occur by the coordination of bromobenzene to the complex of one mole of the base with one mole of the Cu-salt. This is independent of the kinds of base and Cu-salt present. Even though more than one mole of the base coordinate to the copper, it still may not be capable of affecting the reaction essentially.

In order to study the steric hindrance of the halide coordinated to the copper salt, reactions

with bromobenzene, *o*-, and *p*-bromotoluene were examined. Pyridine, α -picoline, and 2,6-lutidine were used as the bases, while nitrobenzene was used as the solvent. The rate constant is presented in Table 4. It is apparent that the methyl group in the ortho position of the halobenzene does not exert any steric hindrance on the reaction, but that, rather, the reaction is accelerated.*⁵ The ratio of the reaction rate of *o*- to *p*-bromotoluene is approximately equal to 2, independent of the kind of base. The promoting effect of the *o*-substituted group in the halobenzene might be explained by the effect of expelling the halogen from the ortho position (Table 4 and Table 1). On the other hand, the steric effect of the methyl group in the pyridine nucleus can be accurately observed (Table 4). It seems most reasonable to say that, in the coordination of base-CuCN-halide, the plane including CN-Cu-X and that of the benzene ring are nearly perpendicular to each other (Fig. 5).

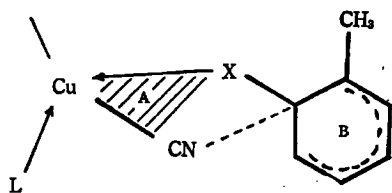
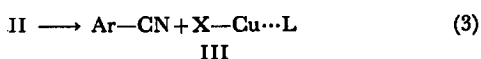
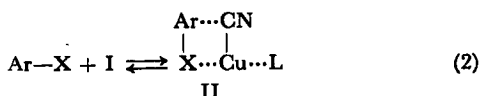
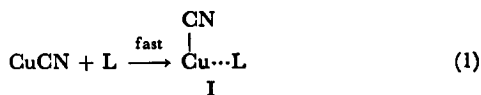


Fig. 5. The model of intervened complex Base-CuCN-Ar·X, L=Base, A $\perp$ B.

From these discussions, it seems that the Rosenmund-von Braun reaction proceeds as follows:



L: Ligand (Base) X: Halogen

When I which had been prepared beforehand was used in the reaction (2), no difference was observed in the kinetic study. Thus, it is conceivable that the rate-determining step is not in the reaction (1) but in the halogen-CN exchange stage in the intervening complex II, the reaction (3). The

order of the reactivity, $\text{I} > \text{Br} > \text{Cl} \gg \text{F}$, supports this assumption. When an excess of the CuCN over the base is used, a ligand is liberated from III (4); it coordinates to the unreacted CuCN to form I again (1).^{*6} That is, the base may act as a catalyst.

Experimental

Materials. The cuprous chloride and cupric chloride, obtained from the Wako Pure Chemical Industry Co., Ltd., Tokyo, were used without further treatment. The cyanide was prepared from copper sulfate and sodium cyanide.⁹⁾ Commercial pyridine, picoline, 2,6-lutidine, and nitrobenzene were dried and distilled under reduced pressure. All of the liquid reagents used in the studies was checked by gas chromatographic analysis.

Reaction Procedure in Table 2 (Exp. 4). In a 100-ml, three-necked, round flask fitted with a sealed stirrer, a thermometer, and a reflux condenser, were placed 4.0 ml of bromobenzene, 3.0 g of cuprous cyanide, 5.0 ml of pyridine (in the case of Exp. 4), and 20 ml of nitrobenzene. The contents were then heated to 180°C in 15 min while being stirred well; then the contents were maintained for 6 hr at 180°C. After the required time, the contents were cooled to room temperature, and a brownish complex of the CuBr-Base was precipitated from the solution. A part of the solution containing benzonitrile and bromobenzene was analyzed by gas chromatography; benzonitrile 82%; bromobenzene 18%. The other experiments in Table 2 were carried out using the same procedure.

Kinetic Measurements (Fig. 4). In a 100-ml, three-necked, round flask fitted with a sealed stirrer, a thermometer, and a reflux condenser, were placed 20.0 ml of nitrobenzene, 1.0 g of cuprous cyanide, and 1.0 ml of pyridine. The contents were then heated to 160°C on an oil bath. When the temperature became constant ($160 \pm 0.5^\circ\text{C}$), 1.0 ml of bromobenzene was added to the mixture. A tiny quantity of the reaction mixture (nitrobenzene solution) was extracted every 20 min and analyzed by gas chromatography. From these measurements the reaction rate was calculated.

Gas Chromatography. Apparatus: Yanagimoto-GCG 220 Type. Yanagimoto Mfg. Co., Ltd., Kyoto, Japan. Column, 10% Cyanosilicone XF-1150 on Chromosorb 60-80 mesh; length, 2 m; temp., 160°C; flow rate, 35-40 ml/min; carrier gas, H_2 . Relative retention time, $\text{ArBr} : \text{ArCN} : \text{ArNO}_2 = 1 : 3 : 5.2$. Column, 5% Carbowax 1500 on Chromosorb 60-80 mesh; length, 2 m; temp., 130°C; flow rate, 40 ml/min; carrier gas, H_2 . Relative retention time, $\text{ArCl} : \text{ArBr} : \text{ArNO}_2 = 1 : 1.4 : 5.7$.

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*⁵ No steric hindrance of the aryl halides in the reaction with CuCN is observed either as is roughly shown in Table 1.

*⁶ See Exps. 1-4, Table 2.

9) H. J. Barben, *J. Chem. Soc.*, 1943, 79.