[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE ROSENMUND-VON BRAUN NITRILE SYNTHESIS[1]

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The general value of the reaction between cuprous cyanide and aryl halides as a preparative method for nitriles is demonstrated by the number of recent investigations in which it has been used. But nothing is known of the mechanism of the transformation involved, and no systematic study has been made to determine the optimum conditions for carrying out the reaction. Usually a mixture of an aryl halide with cuprous cyanide is heated at 250° for six hours or more, sometimes with no added substance and sometimes with pyridine added as a promoter or solvent.

Since this synthesis is one involving replacement of an aromatically bound halogen, it was felt that a quantitative study of it might lead to useful data regarding the relative reactivities of aryl halides and in addition might lead to the development of a rational procedure for carrying out the reaction. This paper reports the results of such a study.

It was expected that a reaction taking place between two phases, solid and liquid, would not be as free from complications as the equation $Ar—X + CuCN \rightarrow Ar—CN + CuX$ would indicate. This was soon found to be the case. The reaction between *p*-bromotoluene and cuprous cyanide at 250° was only 15% completed after the first hour, but after the next thirty minutes the reaction was nearly 75% completed. Similar behavior was found to be characteristic of the reactions of all the aromatic halides studied (Figs. 1 to 9). In each case[2] there was an induction period during which little reaction took place, and this was followed by a period of rapid reaction.

Such behavior made it impossible to obtain reaction constants for use in comparing the reactivities of the various halides. But for practical purposes a comparison was made by considering the reactivity of an aryl halide to be inversely proportional to the length of time, including the

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[1] Abstracted from a thesis submitted to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree, August, 1940.

[2] Points corresponding to extent of reaction during probable induction periods were not determined for all the aryl halides. However when such points were established, the induction period was clearly shown, and therefore it was assumed in all the curves.

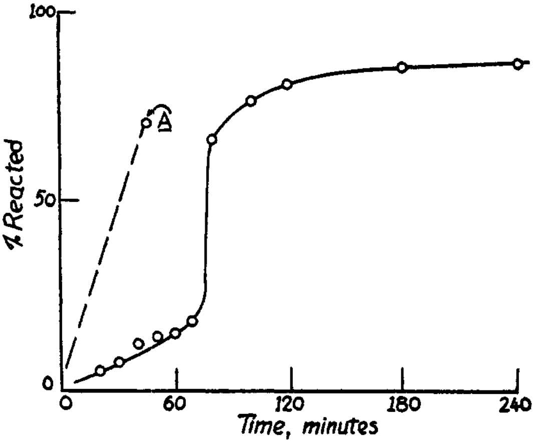

FIG. 1. p-C_7H_7Br
A, with p-C_7H_7CN

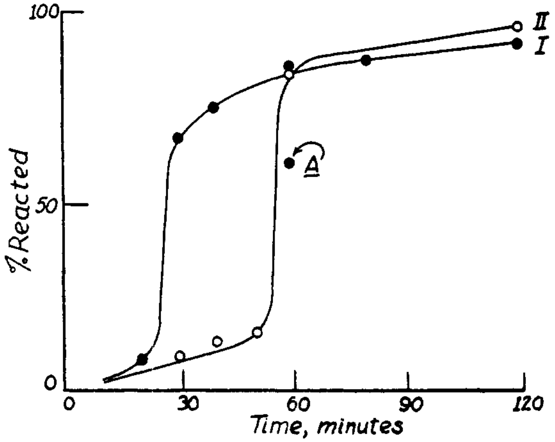

FIG. 2. I, C_6H_5Br; A, under CO_2. II, $C_6H_5Br + C_6H_4(OH)_2$

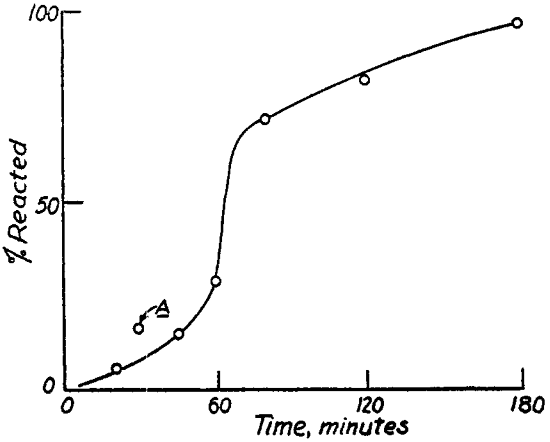

FIG. 3. m-C_7H_7Br
A, with 0.05 g. $CuSO_4$

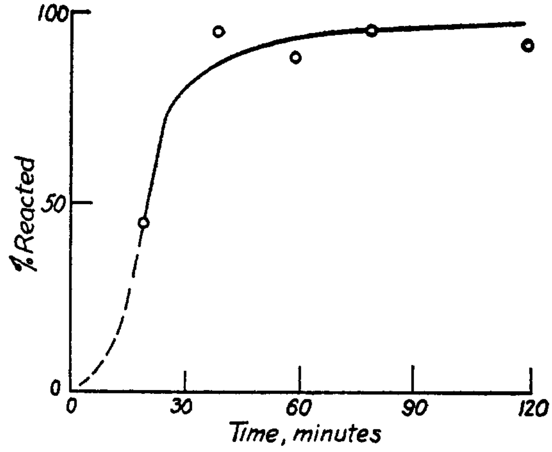

FIG. 4. s-$(CH_3)_3C_6H_2Br$

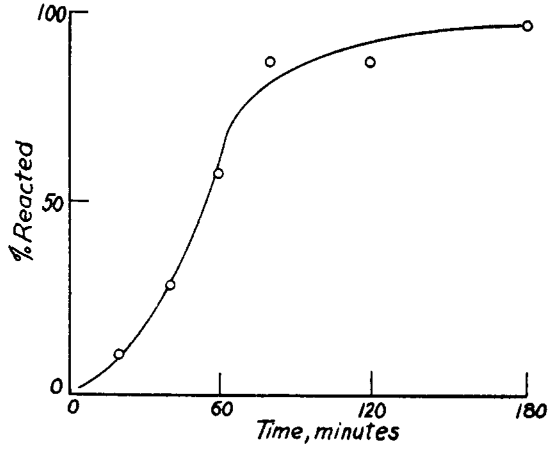

FIG. 5. p-$C_6H_5COC_6H_4Br$

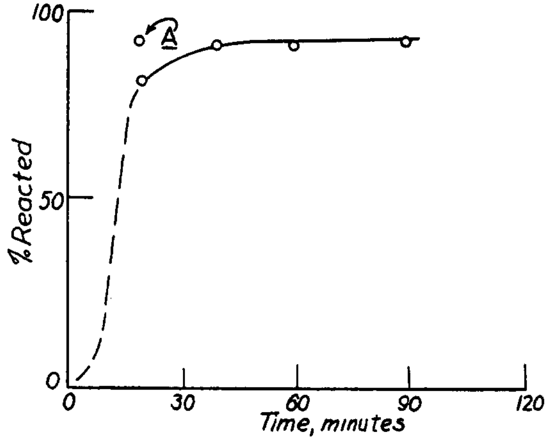

FIG. 6. α-$C_{10}H_7Br$
A, with 0.3 g. C_5H_5N

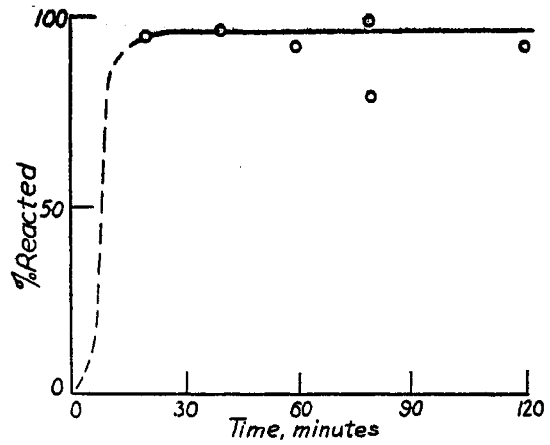

FIG. 7. p-BrC_6H_4COOH

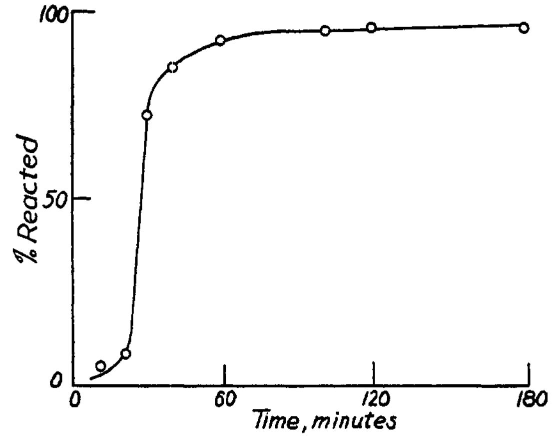

FIG. 8. o-C_7H_7Br

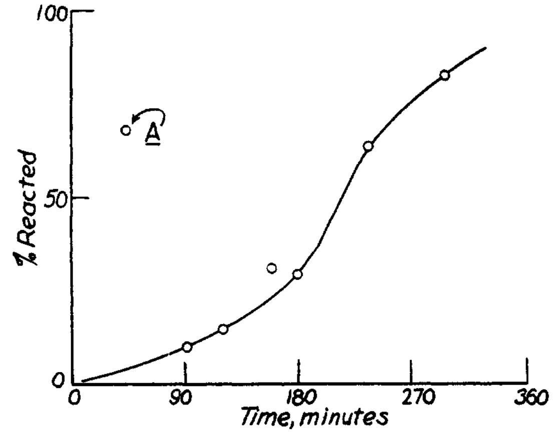

FIG. 9. p-$(C_6H_5)_2CHC_6H_4Br$
A, with p-C_7H_7CN

induction period, which was required for the substance to react with cuprous cyanide to the extent of 50%. On this basis the compounds studied were arranged in the following series of increasing reactivities: *p*-bromotriphenylmethane < *m*-bromotoluene < *p*-bromobenzophenone < *o*-bromotoluene < bromobenzene < bromomesitylene < α-bromonaphthalene < *p*-bromobenzoic acid. The curves describing the reactions indicate that the customary six hour heating period is usually too long, for with most aryl halides reaction is nearly complete after two hours.

An induction period indicated an autocatalytic reaction, and in the present case it was thought that the catalyst formed was probably the aromatic nitrile. This substance, through its ability to form a complex with cuprous cyanide, might dissolve the inorganic compound and thus accelerate the reaction by tending to make the mixture homogeneous. In agreement with this concept, it was found that when a small amount of *p*-tolunitrile was added to a mixture of *p*-bromotriphenylmethane and cuprous cyanide, the extent to which the reaction proceeded in a given time was greatly increased (Fig. 10, Curve I). When the amount of added nitrile was made larger, the extent of reaction fell off again, showing that the diluting effect of the nitrile finally outweighed its catalytic effect. Point A in Fig. 9, taken from Fig. 10, shows that the time required for 65% reaction between *p*-bromotriphenylmethane and cuprous cyanide was reduced by a factor of nearly six by the addition of the optimum amount of *p*-tolunitrile. The time for 71% completion of the comparatively fast reaction between *p*-bromotoluene and cuprous cyanide was almost halved (Fig. 1, point A) when *p*-tolunitrile was added to the reaction mixture.

But the line connecting point A (Fig. 1) with the origin had a slope representing a slower over-all reaction rate than the maximum rate of the uncatalyzed reaction. Since the uncatalyzed reaction curve had only begun to flatten out at 71% completion, this meant that not all of the induction period was eliminated by the addition of *p*-tolunitrile. Inhomogeneity of the reaction mixture at the start of the reaction therefore was not the only factor responsible for the induction period.

On the theory that peroxides, present originally and destroyed during the course of the reaction, might be acting as anticatalytic agents, the course of the reaction between bromobenzene and cuprous cyanide (Fig. 2, Curve I) was re-investigated using a series of reaction mixtures each containing 10–12 mg. of hydroquinone (Fig. 2, Curve II). The length of the induction period was almost doubled by the antioxidant; this indicated that an oxidizing agent might promote the reaction. Accordingly, the effect of adding varying amounts of cupric sulfate to reaction mixtures of *p*-bromotriphenylmethane and cuprous cyanide was investigated. The cupric salt was found to exert a marked promoting effect[3] (Fig. 10, Curve 2); so part of the induction period in the usual reaction mixtures can be ascribed to the necessity for some of the cuprous salt to become oxidized.

The following equations represent a mechanism which may account for the catalytic power specific to copper salts, and for the apparent necessity for the presence of both cuprous and cupric forms of these salts in reactions involving replacement of aromatically bound halogen.

$$\text{Ar—X} + \text{Cu}^{++} \rightleftarrows [\text{Ar—X} \rightarrow \text{Cu}]^{++} \xrightarrow{\text{Cu}^+} \text{Cu}^{++} + [\text{Ar—X} \rightarrow \text{Cu}]^+$$

$$[\text{Ar—X} \rightarrow \text{Cu}]^+ \rightarrow \text{CuX} + \text{Ar}^+$$

It is assumed that only Cu^{++} can form a stable complex with a halide through interaction with the halogen. In the absence of reducing agent (Cu^+) this complex can only revert to the substances from which it was formed. But a cuprous salt converts it into a new complex which can decompose to an aryl ion, which will then combine with any anion present.

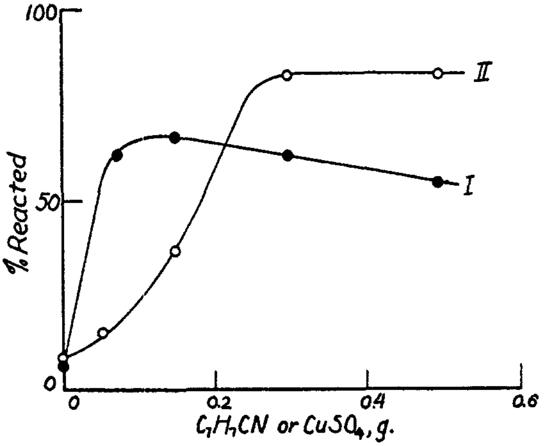

FIG. 10. 0.5 g. p-$(C_6H_5)_2CHC_6H_4Br$
With: I, p-C_7H_7CN, 45 min.; II, $CuSO_4$, 60 min.

The observations made in the present research have been of practical utility in a number of syntheses carried out in this laboratory. To a mixture of an aryl halide with cuprous cyanide is added a few drops of tolunitrile and a small spatulaful of cupric sulfate. The whole is then placed in a bath heated by boiling biphenyl (250°). Completion of reac-

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[3] Weston and Adkins [*J. Am. Chem. Soc.*, **50**, 859 (1928)] observed that the formation of a catalyst from copper for the reactions between bromobenzene and potassium phenoxide or bromotoluene and acet-toluidide took place only when air was present.

tion, indicated by a marked diminution in volume of the solid copper salts and the formation of a dark liquid phase, follows rapidly (10 to 30 minutes).

EXPERIMENTAL

A weighed amount of an aromatic bromide together with two equivalents of cuprous cyanide was sealed in a 10 x 80 mm. soft glass tube. The reaction mixture was then heated for the required length of time in a bath of diethyl phthalate kept at 250° by contact with the vapor of boiling biphenyl in an appropriately designed apparatus. After being heated, the tube was removed and broken in a 250 ml. round bottomed analytical flask, where its contents were crushed. Organic substances were extracted by boiling with two successive 100-ml. portions of acetone. The acetone was removed after each extraction by decantation through a Hirsch filter, any copper salts caught on the filter being returned to the analytical flask. The adhering acetone was evaporated on a steam-bath and an excess of potassium dichromate was added, followed by 10–15 ml. of water.

The flask was then attached by means of a ground glass joint to a still-head bearing a dropping-funnel and a condenser pointing downwards. The lower end of the condenser dipped into a mixture of 8 ml. of 4% sodium hydroxide and 5 to 8 drops of 30% hydrogen peroxide contained in a 250 ml. Erlenmeyer flask. Through the dropping-funnel was then added 15 ml. of 40% (wt.) sulfuric acid to the analytical flask containing the copper salts and dichromate. The mixture was heated until fumes of sulfur trioxide were given off (20 to 30 minutes), bromine, hydrogen cyanide, and cyanogen bromide being taken up by the sodium peroxide solution. This solution was then boiled for five minutes, cooled, acidified with sulfuric acid, and again boiled for five minutes in order to convert all bromine and cyanogen bromide to bromide (1) and to expel hydrogen cyanide. The solution was cooled, made slightly alkaline with sodium hydroxide, and finally neutralized (litmus) with acetic acid. Potassium chromate was added as an indicator and the bromide was titrated with 0.1 *N* silver nitrate.

Numerous control experiments, in which the bromine contents of synthetic mixtures of cuprous bromide and cuprous cyanide were determined, showed that the analytical method was never in error by more than 1% and that the usual error was less than 0.3%.

The data from which Fig. 1 was constructed, given in Table I, are typical of the data representing the behaviors of the other aryl halides. It will be noted that the few duplicate determinations check each other well and that most of the points lie close to the curve. Accordingly it was not considered necessary to run duplicate determinations for every point.

Miscellaneous experiments. Since some of the curves did not approach 100% reaction, a loss of bromine was indicated. Experiments in which *p*-tolunitrile was heated (250°) for five hours in a sealed tube filled with carbon dioxide or for thirty-six hours in a sealed tube filled with air showed that this loss was not caused by bromination of the nitrile.

C_7H_7CN, g.	Cu_2Br_2, g.	% Br
0.3435	0.4310	49.3 (air)
.3626	.4434	51.7 (air)
.3478	.3293	52.9 (CO_2)
.3085	.4525	52.9 (CO_2)
	Calcd.,	55.7

Increasing the concentration of cuprous bromide in a reaction mixture caused a greater loss; a mixture of 0.4968 g. of *p*-bromotoluene, 0.4484 g. of cuprous bromide, and two equivalents of cuprous cyanide was heated for three hours at 250°. The analytical titration required 54.37 ml. of 0.1 *N* silver nitrate but the cuprous bromide added would require 31.25 ml. The difference, 23.12 ml. representing cuprous bromide formed, corresponded to 79.5% reaction, while under the usual conditions (Fig. 1) 84.8% reaction would have taken place.

This pointed to the loss of cuprous bromide through the formation of a complex slightly soluble in acetone. It was then found that a complex of cuprous bromide and *p*-tolunitrile could be prepared. Cuprous bromide was dissolved by heating with an excess of the nitrile; on being cooled, the solution deposited a colorless crystalline substance which was then air dried on a suction filter.

TABLE I

REACTIONS OF *p*-BROMOTOLUENE WITH CUPROUS CYANIDE

Ar—Br, G.	ML. 0.1 *N* $AgNO_3$	TIME, MINS.	% REACTED
0.4417	1.65	20	6.4
.5090	2.35	30	7.9
.4829	3.38	40	12.0
.5272	4.30	50	13.9
.5128	4.42	60	14.7
.5316	4.52	60	14.5
.5182	5.32	70	17.6
.4764	18.28	80	65.6
.5058	22.68	100	76.6
.5090	23.87	120	80.2
.5125	25.42	180	84.8
.5164	25.17	180	83.3
.5051	25.40	240	86.0
.4928 (a)	24.47	180	84.9
.4976 (b)	21.42	60	73.6
.5050 (c)	2.57	300	8.7
.5030 (c)	2.98	420	10.1
.5599 (d)	23.42	45	71.5
.5077 (e)	21.22	45	71.5

(a) Contained 3 eq. of Cu_2Cy_2, (b) Plus 0.3 g. of $CuSO_4$, (c) at 210°, (d) Plus 0.4977 g. of C_7H_7CN, (e) Plus 0.5356 g. of C_7H_7CN.

Anal. Calc'd for $C_7H_7CN + Cu_2Br_2$, Br, 39.5. Found: Br, 39.2, 39.8.

The complex was at least partially dissociated into its components when it was dissolved in acetone, but it is possible that some of it escaped dissociation in the analytical method, and that its formation accounted for the failure of the analysis ever to show 100% reaction.

SUMMARY

It is shown that the reaction between aromatic bromides and cuprous cyanide is autocatalytic and that the time required for the reaction to

reach practical completion can be shortened materially if small amounts of cupric salts and of nitriles are included in the reaction mixtures. A mechanism is proposed to account for the catalytic effect of copper salts on reactions involving aromatic halogen compounds.

MINNEAPOLIS, MINN.

REFERENCE

(1) KUBIERSCHKY, *Z. angew. Chem.*, **40**, 1512 (1927).