Cyanation of Aromatic Halides

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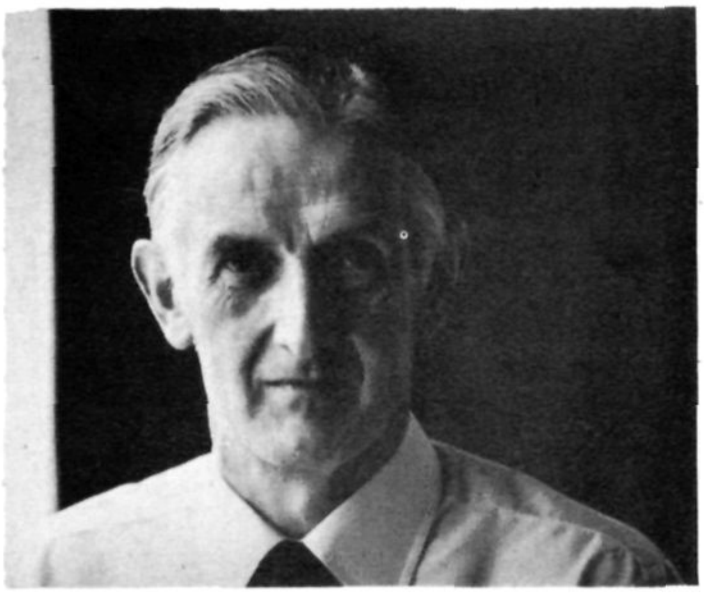

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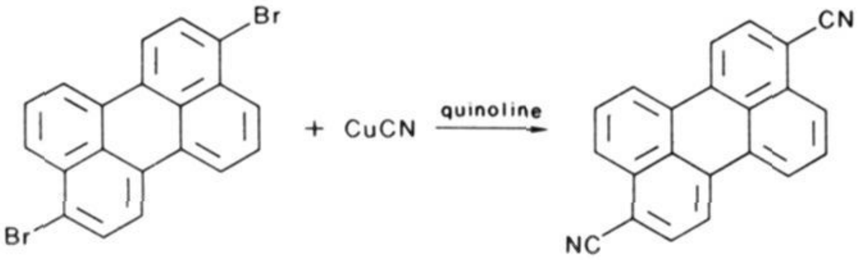
I. Introduction

When a benzenoid or heterocyclic halide (ArX) is treated with copper(I) cyanide, the corresponding nitrile is formed. This type of reaction was first described in

$$\mathrm{ArX} + \mathrm{CuCN} \xrightarrow{\text{heat}} \mathrm{ArCN} + \mathrm{CuX}$$

1927 by Pongratz.[1] He synthesized perylene-3,9-dicarbonitrile (**2**) in 95% yield by heating the dibromide (**1**) with copper(I) cyanide in quinoline. He subsequently[2] repeated the reaction as the first stage of a synthesis of perylene-3,9-dicarboxylic acid from either 3,9-dibromo- or 3,9-dichloroperylene. In 1931, von Braun and Manz[3] in a paper devoted to various derivatives of fluoranthene, converted the 4-bromo derivative (**3**) into the 4-carbonitrile (**4**) in 80% yield by heating with copper(I) cyanide (in the absence of a solvent) at 260 °C for 6 h.



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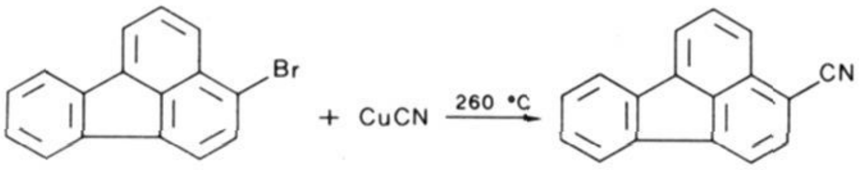

(3) (4)

Although this type of conversion has been known as the *Rosenmund–von Braun reaction*,[4-9] Rosenmund's contribution was to show[10] that an aryl halide reacts with potassium cyanide, potassium hydroxide, and water under pressure at temperatures between 180 °C and 200 °C in a reaction which is promoted by copper(I) cyanide; the only product isolated from these reactions was the carboxylic acid. Neither Pongratz[1,2] nor von Braun and Manz,[3] refer to Rosenmund and Struck's work.[10] The two papers in which von Braun,[3,11] used the nitrile synthesis were largely devoted to other reactions and no attempt was made to study this important reaction or to extend its scope.[12] In this review,

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conversion of an aromatic halide into the corresponding nitrile is called cyanation but it has also been referred to as nitrilation and cyanodehalogenation.

Although the early investigators of this reaction were unable to demonstrate the displacement of aryl halides by metal cyanides other than that of copper(I),[13] more recent workers have found that alkali metal cyanides in the presence of certain ligands give high yields of aryl nitriles under relatively mild conditions. Some cyanations of the latter type require anaerobic conditions.

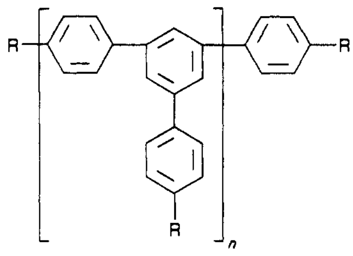
This review attempts to cover the main developments in the study of this reaction so that the scope and limitations may be appreciated. The tables list a wide variety of examples but they are illustrative rather than comprehensive. In addition to the original conversion of an aryl halide into the corresponding nitrile by the action of copper(I) cyanide, more recent modifications in which organometallic compounds containing other transition metals are discussed.

II. Scope of the Reaction

Aromatic (benzenoid and heterocyclic) iodides, bromides, chlorides, and fluorides are converted by copper(I) cyanide into the nitriles, the iodides being the most reactive. The difference in reactivity between iodide and chloride is sufficient to permit preferential cyanation of the iodide in the presence of both halogens, for example, in the synthesis of 2,4,6-trichlorobenzonitrile from 1-iodo-2,4,6-trichlorobenzene.[14] Similarly, the reactivities of bromides and fluorides differ greatly.[15] Further discussion of this topic is to be found in section IVA.

The presence of some substituents on the aromatic ring has an effect on the progress of the reaction. Electronic activation of the 2-halogen in 2,3-dichloro-1-nitrobenzene[16] (and similar compounds)[17-19] renders it more labile towards nucleophiles (see also section IIIA). Nitro and carboxy groups in the 2- or 4-positions increase the reaction rate.[20,21] Aryl halides carrying the following substituents have been converted into the corresponding nitriles: alkyl, alkoxy, alkylthio, hydroxy, acyl, formyl, carboxyl, carboxyl ester, nitro, primary amino, and tertiary amino. A substituent such as a primary amino may exert a pronounced effect on the reaction; for example, 4-bromoaniline gives a good yield of nitrile when treated with copper(I) cyanide in pyridine[22] but 4-iodoaniline fails to react with potassium cyanide–palladium(II) acetate–hexamethylphosphoramide (hexamethylphosphoric triamide, HMPT)—conditions which give high yields of other benzonitriles.[23]

Substrates containing more than one halogen usually react to give a polycarbonitrile, for example, 1,3,5-tribromo-2,4,6-trimethylbenzene yields the tricarbonitrile in high yield[24] but one halogen may remain unaltered[25] or may be lost.[26] Polymers (**5**, R = CN) of high thermal stability have been prepared by treating the poly(bromophenylenes) (**5**, R = Br) with copper(I) cyanide in quinoline at 237 °C for 52 h.[27]



(**5**)

During the last decade or two, cyanation of aryl halides in the presence of other transition metals has been investigated. In most of these methods, copper(I) cyanide has been replaced by an alkali metal cyanide or a complex of copper(I) cyanide and a transition-metal salt. Sodium dicyanocuprate, $NaCu(CN)_2$, does not fall into either of these categories but it was shown by House and Fischer[28] to have the advantage of being soluble in *N,N*-dimethylformamide (DMF) and to give a high yield of 1-naphthonitrile from the iodonaphthalene. However, 1-chloronaphthalene was almost unaffected by this reagent and its rate of reaction with the aryl halides mentioned was about 25% of that of copper(I) cyanide.

One of the early examples which demonstrated the usefulness of palladium salts was the preparation of 4-methoxybenzonitrile from the iodide, potassium cyanide, and palladium(II) cyanide,[29] but a prolonged reaction time (≈16 h) in boiling DMF was necessary. Subsequently, a development of this reaction by replacement of palladium cyanide by palladium(II) acetate enabled reaction times to be reduced and very high yields to be obtained from iodobenzene and several nuclear substituted iodobenzenes.[23]

Impregnating alumina with sodium cyanide and heating this with iodobenzene and tetrakis(triphenylphosphine)palladium in toluene is another new and promising method.[30-32] The same palladium complex gave high yields of benzonitriles from bromobenzenes and potassium cyanide in the presence of a crown ether.[33,34] Complexes containing nickel or cobalt are also capable of converting aryl halides into the benzonitriles (see section IIIB).

III. Mechanism of Cyanation

Halogen atoms attached to aromatic rings are usually resistant to nucleophilic displacement unless electron-withdrawing substituent(s) are present or the ring contains one or more double-bonded nitrogen atoms as in pyridine. Copper(I) cyanide has been known for many years to be an exception to this rule in that it reacts on heating with bromobenzene, for example, to give benzonitrile. The use of other transition-metal complexes in recent years has enabled aryl halides to be converted into the nitriles often under anaerobic conditions using potassium or sodium cyanide.

A. Cyanation with Copper(I) Cyanide

Many of the early workers[3,11,35] heated the halide and copper(I) cyanide to a temperature of about 260 °C, sometimes in a sealed vessel,[24,36,37] while others[1,2] added a solvent such as quinoline[1,2] or pyridine.[38-41] Good results have also been obtained by heating the reactants until a melt was formed and then reducing the pressure so that the nitrile distilled out of flask.[42,43] The mechanism of the reaction in a sealed tube and in the absence of a solvent was studied by Koelsch and Whitney[44] who found that under these conditions there was an induction period which was shortened by addition of a copper(II) salt and lengthened by the presence of an antioxidant such as quinol. The reaction was accelerated by addition of a trace of a nitrile such as the expected product. They demonstrated that a shortened reaction time of about 10–30 min could be achieved by using their conclusions and that copper(I) bromide forms a crystalline complex with the benzonitrile. From their study, the authors proposed the mechanism shown in Scheme I which depends on the presence of copper(II) ions and which assumes that the halide forms a stable complex with copper(II) but not with copper(I) ions.

SCHEME I

$$\mathrm{ArX} + \mathrm{Cu}^{2+} \rightleftharpoons [\mathrm{ArX}{\rightarrow}\mathrm{Cu}]^{2+} \xrightarrow{\mathrm{Cu}^+}$$

$$[\mathrm{ArX}{\rightarrow}\mathrm{Cu}]^{+} + \mathrm{Cu}^{2+} \rightarrow \mathrm{Ar}^+ + \mathrm{CuX} \xrightarrow{\mathrm{CN}^-} \mathrm{ArCN}$$

The reaction is now rarely conducted under pressure and various solvents are employed, for example, quinoline or pyridine. These solvents enable a certain degree of homogeneity to be achieved and they thus shorten reaction time and lower reaction temperature. The course of the reaction at these lower temperatures probably involves a complex formed by interaction of the halide with copper(I) cyanide; this complex (**6**) then decomposes into the benzonitrile and copper(I) halide (Scheme II).[22]

SCHEME II

$$2\mathrm{ArX} + 2\mathrm{CuCN} \rightarrow \underset{(\mathbf{6})}{[\mathrm{ArCN}]_2\mathrm{CuX}} + \mathrm{CuX} \rightarrow$$

$$2\mathrm{ArCN} + \mathrm{CuX}$$

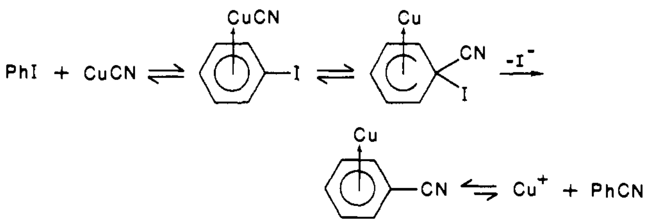
The reaction in refluxing pyridine was studied as one of a number of nucleophilic substitutions of 1-halogenonaphthalene under uniform reaction conditions.[45] This demonstrated the greater reactivity of iodine over bromine as shown by the yield of nitrile obtained after 24 h of heating: 24% from the bromide, 100% from the iodide. Kinetic measurements in boiling dimethyl sulfoxide ($\mathrm{Me_2SO}$) showed that the reaction was complicated, the second-order constants increasing as the reaction progressed but tending to become constant later. When copper(I) cyanide was replaced by either silver or nickel(II) cyanide, no naphthonitrile was formed in $\mathrm{Me_2SO}$ at 144 °C. The ability of the aryl nitrile to act as a strong ligand[39] may explain the unusual kinetics of this displacement compared with those of copper(I) halides. The relative rate of cyanation (as measured by the yield of product over a fixed time) of several bromobenzenes with copper(I) cyanide showed that the reaction was faster in DMF or $\mathrm{Me_2SO}$ than in HMPT.[33] The yield was almost unaffected by electron-donating or electron-withdrawing substituents at the 3- or 4-positions.

Recently, a thorough kinetic study[20] of the cyanation of iodoarenes in dimethylacetamide confirmed that the second-order constant increased with time, especially when stoichiometric proportions of halide and copper salt were used. A large excess of copper(I) cyanide produced an almost pseudo-first-order plot, thus confirming Ito and Watanabe's observation.[17] Several attempts were made to find a kinetic model which fitted the results; of these, two were satisfactory:

$$\nu = k_{3/2}[\mathrm{CuCN}]^{1/2}[\mathrm{PhI}] \qquad (1)$$

$$\nu = k_2[\mathrm{CuCN}][\mathrm{PhI}] + k_3[\mathrm{CuCN}][\mathrm{PhI}][\mathrm{CuI}] \qquad (2)$$

SCHEME III



The $^3/_2$ order of eq 1 is better at describing the initial rate while the third-order term of eq 2 is justified by the observation that addition of copper(I) iodide (one of the products) causes a slight acceleration of rate (cf. Koelsch and Whitney's conclusion[44] that their reactions were catalyzed by the aryl nitrile). A similar autocatalytic effect was noted in the cyanation of 2-bromobenzoic acid.

Under the conditions used in this study, Ullmann coupling was nonexistent although in earlier work, using other solvents, this was a competing reaction in some solvents.[23] Nucleophilic substitution of aryl halides is not affected by radical traps and so this eliminates mechanisms which involves radicals. Addition of an excess of $\mathrm{CN^-}$ (as potassium cyanide) or $\mathrm{I^-}$ (as potassium salt) decreases the reaction rate and makes it unlikely that a dissociative mechanism is involved.

The effect of substituents placed ortho to the iodine is significant. *o*-Methyl, *o*-*tert*-butyl, or *o*-iodo group has little effect but a carboxyl greatly increases the reactivity of the halide.[20] This effect is further enhanced by a factor of about 10^2 for the sodium salt of the *o*-carboxyl group; a *p*-carboxylic salt has no effect. From a plot of activation parameters, Couture and Paine[20] conclude that a difference in activation entropy accounts for the marked effect of the *o*-carboxylate group. They also observed that *o*- and *p*-diiodobenzene react in a stepwise process (as had been deduced by earlier workers with polybromoarenes),[24] the monocyano product being formed to the extent of 40–60% before reacting again to yield the dinitrile.

Couture and Paine[20] suggest two possible mechanisms which explain most of their observations and calculations. In one, rapid electron transfer from CuCN to halogenoarene, which does not permit the escape of radical ions from the immediate vicinity of the reaction, is postulated. This involves the formation of a complex such as ArCu(X)CN which may possibly and momentarily yield an arene radical and $\mathrm{XCu^{\bullet}Nu}$, (Cu being copper(II)), or an arene ion radical and $\mathrm{XCu^{-}Nu}$ (this Cu being copper(I)). The second possibility requires an 18-electron π-complexed organocuprate being formed from the copper(I) cyanide and the π-electrons of the halogenoarene. Intramolecular attack of the $\mathrm{CN^-}$ ion to give a tetrahedral intermediate is followed by a rate-determining step of loss of halide and rapid formation of aryl nitrile (Scheme III). This mechanism explains the retarding effect of both potassium cyanide and iodide and is supported by similar $\mathrm{S_N}$ reactions with stable transition-metal arene carbonyl complexes, some of which have been isolated and characterized. The accelerating effect of an *o*-carboxylate group is difficult to explain in terms of anchimeric assistance and the increased entropy of activation observed. Whether cyanation of aryl halides by copper(I) cyanide proceeds through halogen complexation or π-electron-type com-

TABLE I. Cyanation of Aryl Bromides[a]

formula	product	reagent[b]	solv[c]	temp,[d] °C	reaction time, h	yield,[e] %	ref
C_7F_5N	C_6F_5CN	CuCN	A	147–158	13	82	15
$C_7H_4N_2O_2$	2-$NO_2C_6H_4CN$	CuCN	B	140–155	2	91	17
			B	140–155	2	91	18
	4-$NO_2C_6H_4CN$		B	140–155	9	80	17
			B	140–155	9	91	18
C_7H_5N	PhCN	a	A	153	11.5	80	23
		c	A	100	0.3	93	23
		b	C	90	2.3	94	23
		e	D	100	65	93	33
		CuCN	B	140–155	9	85	17
		f, p		80	19	99	30
		CuSCN	B	180	8.5	23	82
		f	E	reflux		12	48
		g, i, m	D, H	55	9	88 (98)	51
		g, h, j, m,	D, H	55	8	85 (94)	51
		g, h, l, m	D, H	55	9	81 (90)	51
		g, h, i, m	D, H	45	9	89 (99)	51
		g, h, m, w	D, H	45	14	88 (98)	51
		d, k	S	55	1	(97)	49
		g, h, t, u	A	55	1	90	49
		g, h, t, u	S	55	1	(<2)	49
		g, h, t, u	R	50	0.4	(98)	49
		g, h, t, u	R	35	2	(80)	49
		g, h, t	B, R	50	1	(<1)	49
		d, k	S	55–60	3–12	(90)	49
		g, h, t, u	D	55	3	(95)	49
		g, h, t, u	R	30	0.6	(98)	49
		CuCN, x	Q	180	6	(79)	17
		CuCN, y	Q	180	3	(28)	17
C_7H_5NO	4-HOC_6H_4CN	CuCN	F			68	71
		CuCN	G			72	71
$C_7H_6N_2$	2-$NH_2C_6H_4CN$	CuCN	B	145–155	9	83	18
	4-$NH_2C_6H_4CN$		B	160–200	5	72	18
			A	reflux	4	83	22
		o	H	55	24	25	52
$C_8F_4N_2$	C_6F_4-1,2-$(CN)_2$	CuCN	A	147–158	13	62	15
	C_6F_4-1,4-$(CN)_2$		A	147–158	13	61	15
$C_8H_4N_2$	C_6H_4-1,4-$(CN)_2$	CuCN	B	reflux	5	50	18
			A	reflux	4	100	22
C_8H_5NO	3-CNC_6H_4CHO	CuCN	A	reflux	6	92	22
$C_8H_5NO_2$	4-$CNC_6H_4CO_2H$	CuCN	B	140–155	8	82	18
$C_8H_5NO_3$	5-CN-2-$HOC_6H_3CO_2H$	CuCN	A	reflux	3	67	92
C_8H_7N	2-MeC_6H_4CN	CuSCN	B	200	10	22	84
		CuCN	A	reflux	4	93	22
		d, k	A	50	1	(90)	49
	3-MeC_6H_4CN	CuCN	A	150	-	85	33
			F	150	-	82	33
			C	150	40	35	33
		d, k	S	55–60	3	(84)	49
	4-MeC_6H_4CN		A	150	-	89	33
			F	150	-	90	33
			C	150	40	36	33
			A	reflux	6	91	22
		f	E	reflux		88	48
		CuSCN	B	220–250	12	-	82
C_8H_7NO	2-$MeOC_6H_4CN$	d, k	A	20	16	(90)	49
	3-$MeOC_6H_4CN$	CuCN	A	150	-	78	33
			F	150	-	82	33
			C	150	70	51	33
	4-$MeOC_6H_5CN$		A	150	-	65	33
			F	150	-	68	33
			C	150	70	45	33
			B	210	8	60	18
		o				4	52
		d, k	S	55	2	(97)	49
	2-HO-6-MeC_6H_3CN	CuCN	A	reflux	4	94	74
C_8H_7NS	3-$MeSC_6H_4CN$	CuCN	A	150	-	95	33
			F	150	-	87	33
	4-$MeSC_6H_4CN$		A	150	-	96	33
			F	150	-	92	33
$C_9H_4N_2O_2$	3,4-$(CN)_2C_6H_3CO_2H$	CuCN	A	reflux	4	45	93

TABLE I (Continued)

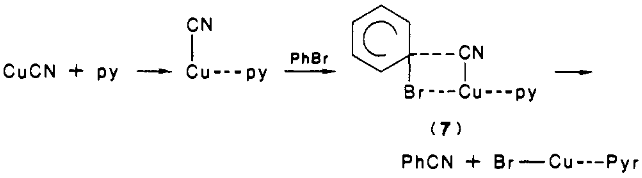
formula	product	reagent[b]	solv[c]	temp,[d] °C	reaction time, h	yield,[e] %	ref
C_9H_7NO	2-AcC_6H_4CN	CuCN	B	120	1.5	70	18
			B	120	1.5	70	17
			I	reflux		80	41
	4-AcC_6H_4CN	CuCN	B	reflux	20	70	40
			A	reflux	3	88	22
			B	reflux	6	74	94
$C_9H_7NO_2$	4-Ac-3-HOC_6H_3CN	CuCN	A	reflux	3	26	26
	3-CN$C_6H_4CO_2$Me	CuCN	A	reflux	3	95	22
			A	150	-	66	33
			F	150	-	57	33
	4-CN$C_6H_4CO_2$Me	CuCN	A	150	-	80	33
			F	150	-	73	33
C_9H_9N	2,4-$Me_2C_6H_3$CN	CuCN	A	reflux	4	91	22
	3,4-$Me_2C_6H_3$CN	CuCN	A	reflux	6	87	22
	2,5-$Me_2C_6H_3$CN	CuCN	A	reflux	6	88	22
	2-EtC_6H_4CN	CuCN	A	reflux	4	90	22
C_9H_9NO	4-[MeCH(OH)]C_6H_4CN	CuCN	B	reflux	15	36	94
	3-EtOC_6H_4CN	$Cu^{14}CN$	-	210	1.5	68	95
$C_9H_{10}N_2$	4-$Me_2NC_6H_4$CN	d, k	S	55–60	3	(5)	49
$C_{10}H_6N_2O_2$	5-AcC_6H_3-1,3-$(CN)_2$	CuCN	A	reflux	3	44	26
$C_{10}H_8N_2$	4,5-$Me_2C_6H_2$-1,2-$(CN)_2$	CuCN	A	reflux		68	93
$C_{10}H_9N_3$	4-$NMe_2C_6H_3$-1,2-$(CN)_2$	CuCN	A	reflux	5	60	93
$C_{10}H_{11}N$	2,4,6-$Me_3C_6H_2$CN	CuCN	B	165–175	8	80	18
			B	165–175	8	80	17
		d, k	S	55–60	3	(5)	49
		g, h, t, u	R	50	2	(<1)	49
$C_{11}H_7N$	1-$C_{10}H_7$CN	CuCN	A	reflux	4	94	22
		CuCN	J	reflux	3	60	68
		CuCN	K	reflux	3	89	68
		CuCN	B	reflux	24	24	45
		CuCN	F	-	2	99	45
		CuCN	B	115	24	100	45
		CuCN	B	220	15	86–93	78, 96
		f	-	100	40	90	30
		o	H	55	24	64	52
$C_{11}H_7N$	2-$C_{10}H_7$CN	CuCN	K	reflux	3	90	68
		o				7	52
		CuCN	B	260–280	3	78	17
$C_{11}H_9N_2O_2$	3,4-$(CN)_2C_6H_3CO_2$Et	CuCN	A	reflux	4	40	93
$C_{11}H_9BrN_2$	3-Br-2,4,5-Me_3C_6-1,5-$(CN)_2$	CuCN, r	B	190	0.75	31	24
$C_{11}H_{13}N$	3,5-$Et_2C_6H_3$CN	CuCN	-	235–240	16	67	97
	4-*sec*-BuC_9H_4CN	CuCN	-	-	12	84	98
$C_{12}H_8N_2O_4$	2,5-$(CN)_2$-C_6H_2-1,4-$(CO_2Me)_2$	CuCN	A	reflux	1	29	82
$C_{12}H_9NO_2$	4-hydroxy-5-methoxynaphthalene-2-carbonitrile	CuCN	-	245	1.25	72	99
$C_{12}H_9N_3$	2,4,6-Me_3-C_6-1,3,5-$(CN)_3$	CuCN	B	205	1.3	56	24
			A	reflux	-	70	100
$C_{12}H_{11}NO_4$	3-Ac-5-CN-4-HO$C_6H_2CO_2$Et	CuCN	A	reflux	3	43	26
$C_{12}H_{12}N_2$	4-*t*-BuC_6H_3-1,2-$(CN)_2$	CuCN	A	reflux	5	72	93
$C_{13}H_6BrN$	2-bromoacenaphthylene-1-carbonitrile	CuCN	K	170	2	28	101
$C_{13}H_9N$	4-$C_6H_5C_6H_4$CN	CuCN	A	reflux	4	92	22
	acenaphthene-5-carbonitrile	CuCN	A	reflux	4	91	22
$C_{13}H_{17}N$	2,4,6-$Et_3C_6H_2$CN	CuCN	B	reflux	11	64	102
$C_{14}H_6N_2$	acenaphthylene-1,2-dicarbonitrile	CuCN	K	160	2	60	101
$C_{14}H_8N$	fluorene-2-carbonitrile	CuCN	A	reflux	4	92	22
$C_{14}H_9N_2$	$C_6H_4C_6H_4$-4,4′-$(CN)_2$	CuCN	A	reflux	4	100	22
$C_{14}H_{10}F_6N_2O_2$	4,5-$(CF_3CH_2OCH_2)_2$-C_6H_2-1,2-$(CN)_2$	CuCN	A	reflux	5	62	103
$C_{14}H_{10}N_2O_2$	3-(2-MeC_6H_4)-2-$NO_2C_6H_3$CN	$Cu^{14}CN$	B	reflux	5	68	104
$C_{14}H_{12}N_2O_2$	2-acetamido-6-methoxynaphthalene-2-carbonitrile	CuCN	B	reflux	3	57	105
$C_{14}H_{16}N_2O_2$	4,5-$(EtOCH_2)_2C_6H_2$-1,2-$(CN)_2$	CuCN	A	reflux	5	65	103
$C_{15}H_9N$	phenanthrene-9-carbonitrile	CuCN	A	reflux	4	95	22
		CuCN	-	260	6	93	106
		CuCN	-	360		87	107
		CuCN	B	220	18	81	108
		CuCN	B	220	9	87	109
		CuCN, r		260	6	92–95	36
$C_{15}H_{14}N$	1,2,3,4-tetrahydrophenanthrene-9-carbonitrile	CuCN	B	220	18	81	109
$C_{15}H_{15}N_3$	2,4,6-Et_3C_6-1,3,5-$(CN)_3$	CuCN, r	-	205	1.2	81	24
$C_{16}H_8N_2$	anthracene-9,10-dicarbonitrile	CuCN+ $CuSO_4$	L	240	2	45	110
$C_{17}H_9N$	fluoranthene-4-carbonitrile	CuCN	A	reflux	5		22
			-	260	6	80	3
$C_{17}H_{11}N$	1-phenylnaphthalene-4-carbonitrile	CuCN	-	270	5	-	11
$C_{18}H_{24}N_2O_4$	4,5-$[EtO(CH_2)_2OCH_2]_2C_6H_2$-1,2-$(CN)_2$	CuCN	A	reflux	5	60	103
$C_{19}H_{11}N$	benzo[*c*]phenanthrene-1-carbonitrile	CuCN	K	reflux	1	71	66
			K	reflux	1	71	67
$C_{19}H_{12}N_2O$	4-methoxy-1-phenylnaphthalene-2,3-dicarbonitrile	CuCN	M	155	3–6	70	25

TABLE I (Continued)

formula	product	reagent[b]	solv[c]	temp,[d] °C	reaction time, h	yield,[e] %	ref
$C_{19}H_{29}N$	2,4,6-(*t*-Bu)$_3C_6H_2CN$	CuCN	J	137	108	60	20
$C_{21}H_{16}N_2O$	4-methoxy-6-methyl-1-(4-methylphenyl)naphthalene-2,3-dicarbonitrile	CuCN	M	155	3–6	35	25
$C_{22}H_{10}N_2$	perylene-3,9-dicarbonitrile	CuCN	L	reflux	2	95	1, 2
$C_{22}H_{13}NO$	3-(4-cyanophenyl)-2-phenyl-1*H*-inden-1-one	CuCN	-	250	4	-	35
	6-cyano-2,3-diphenyl-1*H*-inden-1-one	CuCN	-	250	4	-	35
$C_{22}H_{18}N_2O$	6-ethyl-1-(4-ethylphenyl)-4-hydroxynaphthalene-2,3-dicarbonitrile	CuCN	M	155	3–6	32	25
$C_{22}H_{21}NO$	6-ethyl-1-(4-ethylphenyl)-4-methoxynaphthalene-2(or 3)-carbonitrile	CuCN	L	200	5	14	25
$C_{23}H_{20}N_2O$	6-ethyl-4-methoxy-1-(4-ethylphenyl)naphthalene-2,3-dicarbonitrile	CuCN		155	3–6	68	25
$C_{24}H_{20}N_2O_2$	4-acetoxy-6-ethyl-1-(4-ethylphenyl)naphthalene-2,3-dicarbonitrile	CuCN	M	155	3–6	18	25

[a] A hyphen in any of columns 5–7 shows that the data are not recorded in the original reference. A blank space in columns 4–7 shows that the information is not available to us. [b] Code for reagents: a, $Pd(OAc)_2$, KCN; b, $Pd(OAc)_2$, KCN, KOH (or NaOEt), KI; c, $Pd(OAc)_2$, KCN, PPh_3, $Ca(OH)_2$; d, NaCN; e, $Pd(PPh_3)_4$, KCN, 18-crown-6 ether; f, $Pd(PPh_3)_4$, NaCN or KCN; g, *trans*-chloro(1-naphthyl)bis(triphenylphosphine)nickel; h, PPh_3; i, Aliquat 336; j, Et_3PhCH_2NCl; k, $(Ph_3P)_3Ni$; l, dicyclohexyl-18-crown-6 ether; m, NaCN, H_2O; n, KCN; o, $K_3[Co(CN)_4]$; p, Al_2O_3–NaCN; q, $NaCu(CN)_2$; r, under pressure; s, Me_4NCN; t, $Me_2C(OH)CN$; u, Et_3N; v, $Pd(OAc)_2$, KCN, H_2O; w, aq NaOH; x, pyridine; y, 2-methylpyridine; z, Me_3SiCN, $Pd(PPh_3)_4$. [c] Code for solvents: A, DMF; B, pyridine; C, hexamethylphosphoric triamide; D, benzene; E, THF; F, Me_2SO; G, dimethyl sulfone; H, water; I, pyridine and quinoline; J, *N,N*-dimethylacetamide; K, *N*-methylpyrrolidin-2-one; L, quinoline; M, tetramethylurea; N, toluene or *p*-xylene; O, reagents heated without solvent; reaction time and temperature not stated; P, 4-methylpyridine; Q, nitrobenzene; R, acetone; S, ethanol. [d] Some of the temperatures are bath temperatures. [e] Yields determined by GLC are shown in parentheses.

SCHEME IV

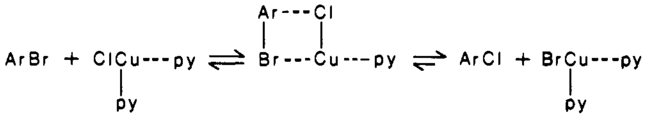


plexation or a mixture of both is still not finally resolved in spite of a great deal of detailed investigation.

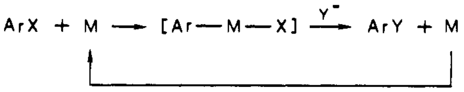
In order to separate the role of pyridine as a base from that of possible catalyst, Ito and Watanabe[17] studied kinetically the reaction of bromobenzene with copper(I) cyanide at 160–180 °C in nitrobenzene to which a known amount of pyridine was added. This method also avoided the precipitation of the product as an insoluble complex with the copper halide which then had to be decomposed with ammonia or mineral acid in order to release the free nitrile. Moreover, the effect of changing the base could be studied. Ito and Watanabe found that, in contrast to cyanation in a sealed tube,[44] oxidizing conditions had no effect. Since copper(I) cyanide and chloride were usually insoluble in the quantities of solvent used, there was no interaction with bromobenzene unless pyridine was added. When the temperature reached 120 °C, a homogeneous mixture was obtained and on cooling, the product remained in solution and was determined by gas chromatography. Replacement of pyridine by 2-methyl- or 2,6-dimethylpyridine lowered the yield of benzonitrile appreciably, and this was ascribed to steric hindrance to coordination of the base with copper(I) cyanide.

These kinetic studies showed that the rate of reaction was first order with regard to bromobenzene and copper(I) cyanide. A copper(I) cyanide–pyridine complex was formed and, provided the ratio of these two reagents was at least equimolar, the amount of nitrile formed increased with reaction time. Bromobenzene coordinates to the complex which then yields the nitrile by exchanging nitrile for halogen and this appears to be the rate-determining step of the reaction (Scheme IV). Ito and Watanabe concluded that the bromine, copper, and nitrile carbon atoms group of the complex (7) were in a plane which was almost perpendicular to that of the benzene ring.

SCHEME V



SCHEME VI



Further support for these conclusions were obtained by Sato, Motoyama, and Hata[46] who studied the halogen exchange of bromobenzene with the copper(I) chloride–pyridine complex in nitrobenzene at 155–175 °C. Activation enthalpy and activation entropy were determined. Comparison of these with those of similar reactions showed that the results supported the four-center (or double-bridge transition state of Ito and Watanabe).[17] Strong coordination of pyridine to the copper atom of the complex accelerates the reaction; its course is governed by the relative ease of formation of the C–Cl compared with the Br–Cu bond (Scheme V).

B. Cyanation with Other Reagents

Complexes of sodium or potassium cyanide with transition metals or with metal–triphenylphosphine have been investigated recently as sources of cyanide ion. The reactions of some of these with aryl halides are believed to be oxidative one-electron transfer reactions,[21] and the transition complex (Ar–M–X, where M is the transition-metal catalyst) formed may react with a nucleophile to give a new product,[23] for example, ArY in Scheme VI.

The metals which have been successfully used in this way are palladium,[23,30,31,33,34,47,48] nickel,[49–51] and cobalt.[52]

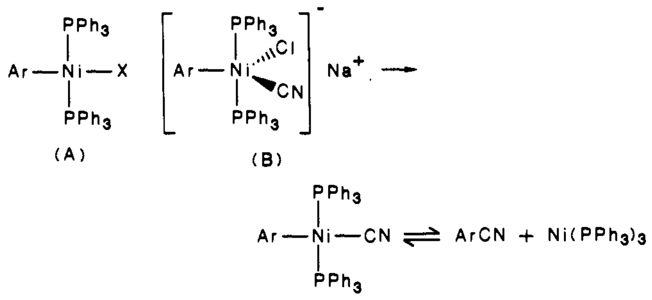
Cassar and his co-workers have made a thorough study of the use of nickel complexes as catalysts for the cyanation of benzenoid halides by alkali metal cyanides. Tris(triphenylphosphine)nickel, $(Ph_3P)_3Ni$, used in the absence of oxygen, was found to be a more effective catalyst than its 4-tolyl homologue whereas replacing the phenyl by cyclohexyl or cyclooctadienyl gave inef-

TABLE II. Cyanation of Aryl Chlorides and Fluorides[a]

formula	product	reagent[b]	solv[c]	temp,[d] °C	reaction time, h	yield, %	ref
$C_7H_3ClN_2O_2$	2-Cl-6-$NO_2C_6H_3CN$	CuCN	A	reflux	15	85	16
			F	153	18	30	16
$C_7H_3N_3O_4$	2,6-$(NO_2)_2C_6H_3CN$	CuCN	F	153	18	52	16
C_7H_4ClN	2-ClC_6H_4CN	d, k	A	80	5	(<2)	49
		d, k	S	55	12	(<2)	49
	3-ClC_6H_4CN	g, h, i, m	D	55	4.5	(16)	51
C_7H_4FN	2-FC_6H_4CN	d, k	S	55–60	3–12	(<3)	49
		d, k	A	55	4	(5)	49
	3-FC_6H_4CN	d, k	S	55–60	3–12	(84)	49
$C_7H_4N_2O_2$	2-$NO_2C_6H_4CN$	CuCN	B	160–180	3	80	17
C_7H_5N	PhCN	b	C	90	1.5	2	23
		h, k, l, n		45	17	81 (90)	51
		f		110	16	0.2	30
		CuCN	B	140–150	14	trace	17
		d, k	S	55–60	3–12	(95)	49
C_7H_5N	PhCN (from the fluoride)	CuCN	B	140–150	3	-	17
C_7H_5NO	4-HOC_6H_4CN	CuCN	J			51	71
		CuCN	K			24	71
$C_8H_4N_2$	C_6H_4-1,3-$(CN)_2$	g, h, i, m	D	55	4.5	(50)	51
	C_6H_4-1,4-$(CN)_2$	CuCN, r	-	420	-	70	58
			B	210–220	24	92	22
$C_7H_6N_2$	4-$NH_2C_6H_4CN$	d, k	S	55–60	6	(30)	49
$C_8H_4N_2$	C_6H_4-1,2-$(CN)_2$	d, k	A	80	5	(<2)	49
	C_6H_4-1,3-$(CN)_2$	d, k	S	55–60	3–12	(86)	49
	C_6H_4-1,4-$(CN)_2$	d, k	S	55–60	3–12	(80)[f]	49
		d, k	S	55–60	3–12	(91)[g]	49
C_8H_7N	2-MeC_6H_4CN	CuCN+KCN, r	B	190–210	72	85	22
	4-MeC_6H_4CN	h, k, l, n	D	55	25	77	51
$C_9H_6N_2$	4-MeC_6H_3-1,3-$(CN)_2$	CuCN	B	200–220	24	93	22
C_9H_7NO	2-AcC_6H_4CN	CuCN	I	reflux	-	39	41
	4-AcC_6H_4CN	g, h, i, m	D, H	55	14	(96)	51
		d, g	S	55	1	(93)	49
		d, k	S	55–60	3–12	(80)	49
$C_9H_7NO_2$	4-$CNC_6H_4CO_2Me$	CuCN	A	reflux	5	87	22
$C_{11}H_7N$	naphthalene-1-carbonitrile	CuCN	A	220–250	24	94	22
			K	205	24	87	68
			B	245–250	24	92	78
			B	220–250	6	70	96
			B	reflux	24	92	96
		o				18	52
		g, h, t, u	R	50	2	(90)	49
		d, g	S	55	0.75	(98)	49
		d, k	S	55–60	7	90	49
$C_{11}H_7N$	naphthalene-2-carbonitrile	CuCN	C	230–240	3	85	28
		g, h, i, m	D, H	55	16	(90)	51
$C_{12}N_6$	$C_6(CN)_6$ (from the 1,3,5-trifluoride)	$Ca(CN)_2$	A	25	33	50	63
$C_{12}H_{13}NO_2$	2-CN-3,5,6-$Me_3C_6HCO_2Me$	CuCN	K	205	3	82	68
$C_{13}H_9N$	3-PhC_6H_4CN	d, k	S	55–60	3–12	(85)	49
	4-PhC_6H_4CN	d, g	S	55	0.75	(94)	49
$C_{13}H_9NO$	3-$PhOC_6H_4CN$	d, g	S	55	6	(98)	49
$C_{14}H_9NO$	4-$PhCOC_6H_4CN$	d, k	S	55–60	3–12	(83)	49
$C_{14}H_{11}N$	2-$PhCH_2C_6H_4CN$	CuCN	-	250	23	54	111
$C_{22}H_{10}N_2$	perylene-3,9-dicarbonitrile	CuCN	G	reflux	2	-	1, 2

[a–e] See Table I. [f] From 4-ClC_6H_4CN. [g] From 1,4-$Cl_2C_6H_4$.

SCHEME VII



fective complexes.[49] Some of the nickel complexes may be prepared in situ, for example, *trans*-chloro(aryl)bis(triphenylphosphine)nickel (A, Scheme VII) may be prepared from an aryl halide and tris(triphenylphosphine)nickel. One of the advantages of using these complexes is the low temperatures which may be used to prepare nitriles; for example, temperatures of 50–60 °C usually suffice for good yields of many nitriles to be obtained. In a few experiments, even lower temperatures have been successfully employed.[49] The need to exclude oxygen from such reactions and the additional cost of the reactants detract somewhat from the convenience of this method. It appears that cyanation in this way involves two steps: oxidative reaction between the aryl halide and tris(triphenylphosphine)nickel followed by displacement of the halide complex (A, Scheme VII) by the cyanide ion. The nature and position of a substituent on the aromatic ring has an effect on the rate of reaction; a *m*- or *p*-methoxy or -methyl increases reactivity of the aryl halide while an *o*-cyano

TABLE III. Cyanation of Aryl Iodides[a]

formula	product	reagent[b]	solv[c]	temp,[d] °C	reaction time, h	yield,[e] %	ref
$C_7H_2Cl_3N$	2,4,6-$Cl_3C_6H_2CN$	CuCN	C	80–90	2–3	82	14
C_7H_4BrN	4-BrC_6H_4CN	u, z	-	90	0.5	56	52a
C_7H_4ClN	3-ClC_6H_4CN	a	C	100	5.5	70	23
	4-ClC_6H_4CN	u, z	-	90	0.5	70	52a
$C_7H_4N_2O_2$	4-$NO_2C_6H_4CN$	a	C	100	10	70	23
$C_7H_4N_4O_4$	2-NH_2-3,5-$(NO_2)_2C_6H_2CN$	CuCN	A	130	2	33	112
C_7H_5N	PhCN	CuCN	B	170–190	6	80	17
		f, p	N	80	2	98	30
		f	E	reflux	9	83	48
		a	C	100	4.5	97	23
		a	A	140	0.2	84	23
		b	C	60	9	99	23
		v	A	140	1	0	23
		a	C	102	0.5	86	55
		d, k	S	55–60	3–12	(75)	49
		u, z	-	90	0.5	88	52a
C_7H_5NO	4-HOC_6H_4CN	CuCN	F			72	71
		CuCN	A	reflux	1.75	84	113
$C_7H_6N_2$	4-$NH_2C_6H_4CN$	a	C	100	10	0	23
$C_8H_4N_2$	C_6H_4-1,3-$(CN)_2$	a	C	100	5.5	21	23
	C_6H_4-1,4-$(CN)_2$	u, z	-	90	0.5	53	52a
C_8H_7N	2-MeC_6H_4CN	a	C	100	2	96	23
	3-MeC_6H_4CN	f, p		80	3	95	30
	4-MeC_6H_4CN	f	E	reflux	9	91	48
		a	C	100	5.5	93	23
		u, z	-	90	0.5	76	52a
C_5H_7NO	4-$MeOC_6H_4CN$	CuCN	A	reflux	16	75	29
		u, z	-	90	0.5	89	52a
$C_9H_7NO_2$	4-Ac-3-HOC_6H_3CN	CuCN	C	90	3	94	26
	4-$MeOOCC_6H_4CN$	u, z	-	90	0.5	68	52a
	4-$CNC_6H_4CH_2CO_2H$	CuCN	A	reflux	3	60	26
$C_9H_7NO_3$	5-Ac-2,4-$(HO)_2C_6H_2CN$	CuCN	C	100	3	74	26
$C_9H_8N_2O_2$	2,6-Me_2-3-$NO_2C_6H_2CN$	CuCN	C	90		75	14
$C_{10}H_9NO_3$	4-Ac-2-HO-6-$MeOC_6H_2CN$	CuCN	-	165–170	0.17	57	114
	5-Ac-4-HO-2-$MeOC_6H_2CN$	CuCN	-	185–190	0.17	67	114
$C_{11}H_7N$	1-$C_{10}H_7CN$	CuCN	B	115	24	100	45
		CuCN	A	150–155	4	97	28
		q	A	150–155	4	98	28
		o				24	52
$C_{11}H_7N_3$	4,5-Me_2C_6H-1,2,3-$(CN)_3$	CuCN	C	90	2	38	14
	2,6-Me_2C_6H-1,3,5-$(CN)_3$	CuCN	C	90	2	47	14
$C_{11}H_{10}N_2$	3,4,5-Me_3C_6H-1,2-$(CN)_2$	CuCN	C	90	2	58	14
$C_{11}H_{11}NO_2$	3-CN-2,4,5-$Me_3C_6HCO_2H$	CuCN	C	90	2	77	14
$C_{12}H_9NO$	6-$MeOC_{10}H_6$-1-CN	CuCN	-	200–230	8	82	64
$C_{12}H_9N_3$	3,5,6-Me_3-C_6-1,2,4-$(CN)_3$	CuCN	C	90	2	46	14
	4,5,6-Me_3-C_6-1,2,3-$(CN)_3$	CuCN	C	90	2	40	14
$C_{12}H_{11}NO_4$	3-Ac-5-$CNC_6H_3CO_2Et$	CuCN	C	100–130	3	40	26
$C_{12}H_{12}N_2$	1,2,3,5-Me_4C_6-4,6-$(CN)_2$	CuCN	C	90–100	2	73	14
$C_{13}H_7N$	biphenylene-1-carbonitrile	CuCN	A	reflux	4	58	75
	biphenylene-2-carbonitrile	CuCN	B	140–150	10	61	115
$C_{14}H_{11}NO$	4-$PhCH_2OC_6H_4CN$	$Cu^{14}CN$	A	reflux	3	96	116
$C_{14}H_{19}N$	2,3,4-Me_3-6-*t*-BuC_6HCN	CuCN	C	90	2	83	14
$C_{19}H_{29}N$	2,3,5,6-(*i*-Pr)$_4C_6HCN$	CuCN	C	90	2	88	14
$C_{22}H_{13}NO$	2-(4-cyanophenyl)-3-phenyl-1*H*-inden-1-one	CuCN	-	240	3	100	35

[a–e] See Table I.

or -chloro reduces it. For example, 4-methoxybenzonitrile has been prepared in 97% yield whereas only traces of 2-chlorobenzonitrile were obtainable. Another limitation is that halonitrobenzenes cannot be thus cyanated because of interaction between the nitro group and the catalyst. The nickel complexes can catalyze about 110 molar quantities of halide but can also react stoichiometrically to give the same product.[49] A phase-transfer catalyst (either a crown ether or a quaternary ammonium salt) in the presence of a nickel catalyst can give a high yield of nitrile.[51] Since some of these reactions proceed in alkaline conditions, it is likely that the cyanide ion (rather than hydrocyanic acid) reacts with the aryl–nickel complex at the water–organic solvent interface. From observations on kinetic and other studies, Cassar, Ferrara, and Foà[49] conclude that a coordinated complex (B, Scheme VII) is an intermediate in the cyanation of the nickel halide (A, Scheme VII). Substitution of other square-planar complexes is known to involve a five-coordinated intermediate similar to B (Scheme VII); this undergoes reductive elimination during which nickel(0) is formed and the aryl nitrile is generated by aryl migration.

Replacement of sodium cyanide in this type of reaction by acetone cyanohydrin has been described for three aryl halides, namely, bromobenzene, bromomesitylene, and 1-chloronaphthalene.[49] By varying the solvent, base, temperature, and reaction time, this method promises to be a mild and effective variant of classical cyanation; for example, bromobenzene is cyanated in 98% yield in acetone under nitrogen at 50 °C for 0.6 h in the presence of *trans*-chloro(1-naphthyl)-

bis(triphenylphosphine)nickel–triphenylphosphine–triethylamine but bromomesitylene gave a negligible amount of nitrile under very similar conditions. The method thus shares with that using sodium cyanide the inability to displace some *o*-substituted halides.

Cassar et al.[51] obtained high yields of nitriles by heating the aryl bromide or chloride with sodium or potassium cyanide, tris(triphenylphosphine)nickel, and a phase-transfer catalyst (a quaternary ammonium salt or 18-crown-6 ether).

Tetrakis(triphenylphosphine)palladium, $(Ph_3P)_4Pd$, and potassium cyanide similarly converted iodobenzene into benzonitrile in tetrahydrofuran without a phase-transfer catalyst.[48] The same ligand has been used recently in the cyanation of iodobenzenes with trimethylsilylcyanide.[52a] Anaerobic conditions were necessary and the most effective solvent was anhydrous triethylamine. Bromo- and chlorobenzenes were unaffected while 4-bromoiodobenzene gave a moderate yield of the bromo nitrile; the dinitrile was a minor byproduct. Extending the reaction time from 30 min to 24 h and increasing the molar ratio of silyl cyanide made little difference to these yields of mono- and dinitrile. Good yields were obtained whether electron-releasing or electron-withdrawing substituents were present.[52a]

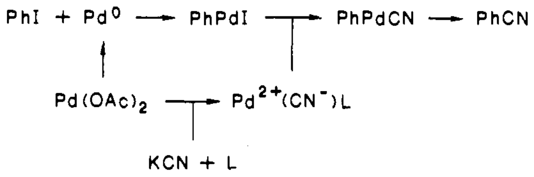
Catalysis of aryl iodide displacement by palladium(II) salts, especially palladium(II) acetate, gives high yields of nitriles at temperatures of 100–120 °C in the presence of HMPT but small amounts of bases (such as potassium hydroxide or sodium ethoxide) as cocatalysts enable the reaction to proceed at lower temperatures.[23] Aryl bromides need longer reaction times and/or higher temperatures but, by careful choice of conditions and reagents, high yields can still be obtained; for example, bromobenzene, palladium(II) acetate, potassium cyanide, triphenylphosphine, and calcium hydroxide in DMF at 100 °C for 20 min gave a 93% yield of benzonitrile.[23] The use of bases as cocatalysts to induce a reduction in the valency of transition-metal ions[53] and the inertness of some palladium salts (for example, palladium(II) cyanide and potassium tetracyanopalladate) which are known to be difficult to reduce, support the theory that zero-valent palladium plays a vital role in these reactions. Further support for this comes from the finding[54] that application of a reducing potential increases the lifetimes of homogeneous nickel and palladium catalysts of this kind by intercepting catalytically inactive metal species and converting them into the active state. The process requires few electrons and is therefore commercially attractive.

In another paper,[55] the Japanese authors studied the palladium catalysis in HMPT and determined the rate of reaction of iodobenzene with potassium cyanide, palladium(II) acetate, and HMPT at 102 °C. Their results suggest that cyanation obeys the rate law required by eq 3 where $[Pd(OAc)_2]_0$ is the initial concentration of palladium(II) acetate and M_{KCN} is the amount of reagent in the reaction mixture.

$$d[PhCN]/dt = k[Pd(OAc)_2]_0(M_{KCN})^{2/3} \qquad (3)$$

Under these experimental conditions, potassium cyanide dissolves within about 20 min in HMPT and the CN^- ion is trapped by palladium(II) acetate to form a salt $[Pd^{2+}(CN^-)L$, (L = ligand such as acetate ion or solvent)] which does not initiate the cyanation. Therefore, an excess of palladium(II) acetate over potassium cyanide must be present for the reaction to proceed. Comparison of the rate of dissolution of potassium cyanide in HMPT with that of the formation of benzonitrile shows that most if not all of the cyanide ion comes directly from the solid potassium cyanide. The authors propose that palladium acetate reacts with iodobenzene to give an oxidative-addition complex, PhPdI, as shown in Scheme VIII (which is a simplified version of that in the paper). They draw an analogy between this sequence and the known conversion[56] (which they repeated) in 99% yield of an aryl mercury halide into an aryl cyanide by reaction with potassium cyanide and palladium(II) chloride in DMF.

SCHEME VIII



Prochazka and Siroky[33] optimized the results of several of the above-mentioned procedures by using tetrakis(triphenylphosphine)palladium, potassium cyanide, and 18-crown-6 ether in boiling benzene. High yields of the aryl nitriles were thus obtained and similar conclusions to those mentioned above were reached regarding the mechanism of the reaction, namely, oxidative addition of aryl halide to metal to form a transition complex which reacts with cyanide to form aryl nitrile.

The overall reaction rate is independent of the concentration of halobenzene; abstraction of cyanide ion from the surface of the solid palladium complex is the rate-determining step.[55] Palladium appears to have two roles in the overall reaction: first, as Pd^0 it activates the halobenzene and as Pd^{2+} it promotes the dissolution of potassium cyanide. Oxidative addition of aryl halides to the tetracyanocobaltate ion (formed by reaction of cobalt(II) chloride with potassium cyanide in aqueous potassium hydroxide) gave the complex $K_3^+[ArCo(CN)_4X]^{3-}$ which on displacement of the halogen by another cyanide ion gives the pentacyanocobaltate.[52] This breaks down to give a benzonitrile and the regenerated tetracyanobaltate ion (Scheme IX), which is in accordance with the catalytic nature of the reaction. Spectral evidence was obtained for the presence of the aryl pentacyanocobaltate ion, $[ArCo(CN)_5]^{3-}$, but elemental analysis of one such complex which was isolated did not fully support this structure.

SCHEME IX

$$[Co(CN)_4]^{3-} + ArX \rightarrow [ArX^{-}Co(CN)^{2-}] \rightarrow [ArCo(CN)_4X]^{3-} \xrightarrow{CN^-} [ArCo(CN)_5]^{3-} + X^- \rightarrow [Co(CN)_4]^{3-} + ArCN$$

By the application of electrochemical kinetic measurements, it has recently been shown that cyanation of some aryl halides with potassium cyanide may be induced electrochemically by using a cell containing aqueous potassium bromide and a hanging mercury drop as electrode; a silver reference electrode in liquid ammonia was employed.[46a] The reaction is maintained at −38 °C and is complete when the wave for ArH

TABLE IV. Cyanation of Heterocyclic Halides[a]

formula	product (halide in substrate)	reagent[b]	solv[c]	temp,[d] °C	reaction time, h	yield, %	ref
$C_5H_2N_2O_2S$	5-nitrothiophene-2-carbonitrile (I)	CuCN	B	reflux			117
$C_5H_3N_3$	pyrazine-2-carbonitrile (F)	NaCN	F	80	0.6	83	62
$C_6F_4N_2$	2,3,5,6-tetrafluoropyridine-4-carbonitrile (F)	CuCN	A	0	1	33	61
$C_6H_3N_2O_2$	3-nitropyridine-2-carbonitrile (Br)	CuCN	-	150	0.01	60	118
$C_6H_4N_2$	pyridine-2-carbonitrile (Br)	CuCN	-	reflux	-	74	42
	pyridine-3-carbonitrile (Br)	CuCN	-	165–170	1	50	119
$C_6H_4N_2O$	2-hydroxypyridine-2-carbonitrile (I)	CuCN	N	120–125	15	62	72
$C_7H_3N_2$	pyridine-2,6-dicarbonitrile (Br)	CuCN	A	reflux	3.5	44	120
$C_7H_3N_3O$	3-hydroxypyridine-3,6-dicarbonitrile (I)	CuCN	B	reflux	6	-	38
$C_7H_5N_2$	indole-5-carbonitrile (Br)	CuCN	L	reflux	10	57	121
	indole-5-carbonitrile (I)	CuCN	L	reflux	10	38	121
	indole-5-carbonitrile (Br)	CuCN	K	reflux	4	73	122
$C_7H_6N_2$	3-methylpyridine-2-carbonitrile (Br)	CuCN	O	-	-	71	123
	4-methylpyridine-2-carbonitrile (Br)	CuCN	O	-	-	10	123
		CuCN	O	-	-	28	124
	5-methylpyridine-2-carbonitrile (Br)	CuCN	O	-	-	52	123
	6-methylpyridine-2-carbonitrile (Br)	CuCN	O	-	-	66	123
$C_7H_7N_3$	3,5-dimethylpyrazine-2-carbonitrile (Br)	CuCN	P	reflux		95	69
	3,5-dimethylpyrazine-2-carbonitrile (Cl)	f	A	reflux	2.5	80	47
$C_8H_2N_4S$	2,1,3-benzothiadiazole-6,7-dicarbonitrile (Br)	CuCN	A	reflux	3–10	50–87	19
	2,1,3-benzothiadiazole-5,7-dicarbonitrile (Br)	CuCN	A	reflux	3.5–4	40–52	19
$C_8H_5N_3S$	6-methyl-2,1,3-benzothiadiazole-7-carbonitrile (Br)	CuCN	A	reflux	5	63	19
$C_8H_8N_2$	4-ethylpyridine-2-carbonitrile (Br)	CuCN	O	-	-	61	124
$C_9H_5N_3$	quinazoline-4-carbonitrile (Cl)	CuCN	-	reflux	-	2	125
$C_9H_6N_2$	indole-4-carbonitrile (Cl)	CuCN	L	237	20	51	65
	indole-5-carbonitrile (Br)	CuCN+KI	L	reflux	12	34	66
	indole-7-carbonitrile (Cl)	CuCN+KI	L	reflux	12	29	77
$C_9H_{10}N_2$	4-propylpyridine-2-carbonitrile (Br)	CuCN	O	120	-	-	126
$C_{10}H_4N_4$	quinoxaline-2,3-dicarbonitrile (Cl)	s	F	25	3	67	86
$C_{10}H_5NO_2$	4-oxochromene-6-carbonitrile (Br)	CuCN	A	reflux	4	67	92
	4-oxochromene-7-carbonitrile (Br)	CuCN	K	reflux	6	20	26
$C_{10}H_5NO_3$	7-hydroxy-4-oxochromene-8-carbonitrile (Br)	CuCN	K	reflux	6	28	26
$C_{10}H_6N_2$	quinoline-2-carbonitrile (Cl)	CuCN	K	205	4.5	93	68
	quinoline-2-carbonitrile (Br)	CuCN	-	-	-	63	80
	quinoline-3-carbonitrile (Br)	CuCN	O	-	-	92	43
	quinoline-3-carbonitrile (Br)	CuCN	-	-	-	60	80
	quinoline-2-carbonitrile (Br)	CuCN	-	-	0.5	80–92	43
	quinoline-8-carbonitrile (Cl)	CuCN–MeCN, r	B	200	18	67	37
	isoquinoline-4-carbonitrile (Br)	CuCN	-	250	0.75	88	127
	isoquinoline-5-carbonitrile (Br)	CuCN	-		0.75	81	127
	isoquinoline-6-carbonitrile (Br)	CuCN	-		0.75	25	127
	isoquinoline-8-carbonitrile (Br)	CuCN	-		0.75	53	127
$C_{10}H_6N_4S$	5,6-dimethyl-2,1,3-benzothiadiazole-4,7-dicarbonitrile (Br)	CuCN	A	reflux	6.5	50	19
$C_{10}H_7N_3$	3-methylquinoxaline-2-carbonitrile (Cl)	s	F	60	6	33	86
$C_{10}H_8N_2$	1-methylindole-5-carbonitrile (Br)	CuCN+KI	L	reflux	20	39	81
$C_{11}H_5N_3OS$	5-oxothiazolo[2,3-*b*]quinazoline-7-carbonitrile (Br)	CuCN	A	reflux	16	-	76
$C_{11}H_7NO_2$	5-methyl-4-oxochromene-8-carbonitrile (Br)	CuCN	K	reflux	6	39	26
$C_{11}H_9N_3$	1-benzylpyrazole-4-carbonitrile (Br)	CuCN	-	-	-	76	128
$C_{11}H_9N_3O$	3-ethoxyquinoxaline-2-carbonitrile (Cl)	s	F	50	2	70	86
$C_{11}H_{10}N_2O$	1-acetylindoline-5-carbonitrile (Br)	CuCN	K	reflux	4	73	122
$C_{11}H_{15}N_3$	3,5-diisopropylpyrazine-2-carbonitrile (Cl)	f	A	reflux	2.5	47	47
$C_{12}H_7NO_2$	2-oxo-6-phenylpyran-3-carbonitrile (I)	CuCN	A	reflux	2	55	129
$C_{12}H_7N_3OS$	2-methyl-5-oxothiazolo[2,3-*b*]quinazoline-7-carbonitrile (Br)	CuCN	A	reflux	16	-	76
$C_{12}H_8N_2$	4-phenylpyridine-2-carbonitrile (Br)	CuCN	O	-	-	60	124
	6-phenylpyridine-2-carbonitrile (Br)	CuCN	O	-	-	67	124
$C_{12}H_9NO_2$	7-methoxy-2-methyl-4-oxochromene-6-carbonitrile (I)	CuCN	-	245–250	0.17	58	114
	7-methoxy-2-methyl-4-oxochromene-8-carbonitrile (I)	CuCN	-	235–240	0.17	63	114
$C_{12}H_9N_3$	3-methyl-5-phenylpyrazine-2-carbonitrile (Cl)	f	A	reflux	2.5	58	47
	5-phenyl-6-methylpyrazine-2-carbonitrile (Cl)	f	A	reflux	2.5	66	47
$C_{12}H_9N_3O_2$	2-cyanoquinoxaline-3-CO_2Et (Cl)	s	F	45	2	44	86
$C_{13}H_7NS$	dibenzothiophene-2-carbonitrile (Br)	CuCN	-	240–270	6	36	130
$C_{13}H_9NO_2$	2-oxo-6-(4-methylphenyl)pyran-3-carbonitrile (I)	CuCN	A	reflux	2	55	129
$C_{13}H_9NO_3$	2-oxo-6-(4-methoxyphenyl)pyran-3-carbonitrile (I)	CuCN	A	reflux	2	55	129
$C_{13}H_9NO_4$	6-cyano-4-oxochromene-2-CO_2Et(Br)	CuCN	K	reflux	6	82	131
	7-cyano-4-oxochromene-2-CO_2Et(Br)	CuCN	A	reflux	3	68	26
	8-cyano-4-oxochromene-2-CO_2Et (I)	CuCN	C	120	3	67	26
$C_{13}H_9NO_5$	8-cyano-7-hydroxy-4-oxochromene-2-CO_2Et(I)	CuCN	C	120	3	66	26
$C_{13}H_{19}N_3$	3,5-diisobutylpyrazine-2-carbonitrile (Cl)	f	A	reflux	2.5	77	47
$C_{14}H_{11}NO_4$	6-cyano-3-methyl-4-oxochromene-2-CO_2Et(Br)	CuCN	A	reflux	4	43	26
	8-cyano-6-methyl-4-oxochromene-2-CO_2Et(Br)	CuCN	E	reflux	6	52	131
$C_{14}H_{11}N_3OS$	2-isopropyl-5-oxothiazolo[2,3-*b*]quinazoline-7-carbonitrile (Br)	CuCN	reflux	A	16	70	76
$C_{14}H_{18}N_4$	3,6-diisobutylpyrazine-2,5-dicarbonitrile (Cl)	f	A	reflux	2.5	76	47
$C_{15}H_9N_3$	2-phenylquinazoline-4-carbonitrile (Br)	CuCN	Q	reflux	8	87	70
$C_{15}H_{10}N_4$	1,4-diphenyl-1,2,3-triazole-5-carbonitrile (Cl)	NaCN	F	140	4	75	60
$C_{15}H_{11}N_3O_2$	9-cyanopyrrolo[1,2-*c*]quinazoline-2-CO_2Et(Br)	CuCN	A	reflux	16	14	132

TABLE IV (Continued)

formula	product (halide in substrate)	reagent[b]	solv[c]	temp,[d] °C	reaction time, h	yield, %	ref
$C_{16}H_9NO_2$	flavone-3-carbonitrile (Cl)	CuCN	K	205	-	-	133
	isoflavone-6-carbonitrile (Br)	CuCN	K	reflux	4	22	26
$C_{16}H_{12}N_2O$	5-benzyloxyindole-4-carbonitrile (Cl)	CuCN	L	220	12	10	134
$C_{17}H_{11}NO_3$	6-methoxyisoflavone-5-carbonitrile (I)	CuCN		220	0.5		135
	7-methoxyisoflavone-8-carbonitrile (I)	CuCN	-	220–225	0.17	54	114
$C_{17}H_{11}N_3$	5,6-diphenylpyrazine-2-carbonitrile (Cl)	f	A	reflux	2.5	81	47
	3,6-diphenylpyrazine-2-carbonitrile (Cl)	f	A	reflux	2.5	31	47
	3,5-diphenylpyrazine-2-carbonitrile (Cl)	f	A	reflux	2.5	98	47
$C_{17}H_{12}N_2O$	5-acetyl-5H-dibenz[*b,f*]azepine-10-carbonitrile (Br)	CuCN		reflux	2	79	136
$C_{17}H_{13}Cl_2N_3O_2$	3-(4,5-dichlorothiazol-2-yl)-7-diethylaminocoumarin-4-carbonitrile (Cl)	CuCN+KI	A	reflux	1	98	58
$C_{18}H_{10}N_4$	3,5-diphenylpyrazine-2,6-dicarbonitrile (Cl)	f	A	reflux	2.5	68	47
	5,6-diphenylpyrazine-2,3-dicarbonitrile (Cl)	f	A	reflux	2.5	16	47
$C_{19}H_{13}NO_4$	6-cyanoisoflavone-2-CO_2Et(Br)	CuCN	A	reflux	4	47	26

[a–e] See Table I.

disappears. Cyanation of 4-bromobenzophenone was studied and was shown to involve the formation of the following species:

$$[4\text{-PhCOC}_6\text{H}_4\text{Br}]^{\bullet-} \rightarrow 4\text{-PhCOC}_6\text{H}_4^{\bullet} + \text{Br}^- \rightarrow [4\text{-PhCOC}_6\text{H}_4\text{CN}]^{\bullet-}$$

In conclusion, it is apparent that the copper(I) cyanide reaction involves either an electron-transfer process or a π-complex formed from copper(I) cyanide and the aryl halide but the dependence of this reaction on the dissolving properties of the solvent requires further work to explore the generality of these conclusions. Cyanation by the use of nickel or palladium complexes (and probably those of cobalt, although little work has been done on this aspect), on the other hand, requires that a zero-valent form of the metal be generated. This requirement is met by triarylphosphine–nickel, palladium(II) acetate, or a (triphenylphosphine)palladium complex which is then cyanated by alkali metal cyanide.

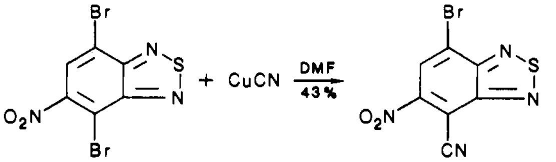
IV. Practical Aspects of Cyanation

A. Reactivity of Aromatic Halides

The reactivity of halogens toward nucleophiles,[57] namely, decreasing in the order: I > Br > Cl > F, applies to cyanation of aryl halides; aryl iodides react with copper(I) cyanide in *N,N*-dimethylacetamide about 40–100 times more readily than do bromides.[20] Nitriles are, therefore, in general obtained more readily at low temperature and with shorter reaction time from iodides than from the other halides under similar conditions.[23] Since bromides are more readily available and are quite reactive, they are frequently used as precursors. Other factors, such as the choice of solvent, ratio of reactants, and method of isolation of product, play a part and no direct and valid comparisons have been made of the reactivity of different halides under identical conditions. Examination of the data given in Tables I–IV will give an indication but the original papers will have to be consulted for the ratio of reactants and other details which may affect the rate and extent of reaction.

An example of the different reactivities of iodide and chloride atoms toward copper(I) cyanide was given in section I.[14] A parallel difference was demonstrated by Takagi et al.[23] toward palladium-catalyzed cyanation with potassium cyanide of 3-chloroiodobenzene in HMPT with sodium ethoxide as cocatalyst. At 100 °C for 5.5 h, the product was a mixture of 70% of 3-chlorobenzonitrile and 21% of benzene-1,3-dicarbonitrile. A similar selectivity was demonstrated for trimethylsilyl cyanide toward 4-bromochlorobenzene.[52a]

Polyiodides,[14] polybromides,[18,22,24] and dichlorides[22,58] usually give the corresponding polycarbonitriles but selectivity between two (or more) bromine or chlorine atoms is sometimes possible, for example, when 4,7-dibromo-5-nitro-2,1,3-benzothiadiazole is treated with copper(I) cyanide in DMF at 75 °C, 7-bromo-5-nitro-2,1,3-benzothiadiazole-4-carbonitrile (8) was the sole product.[19] 2,3-Dichloronitrobenzene is converted into 2-chloro-6-nitrobenzonitrile (9),[16] and the chlorine on the pyran ring of the thiazolylcoumarin (10) is more reactive than those on the thiazole.[59]



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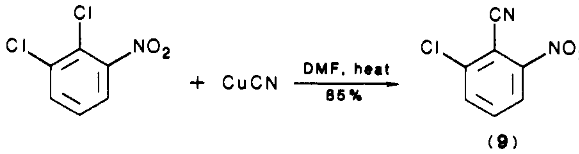

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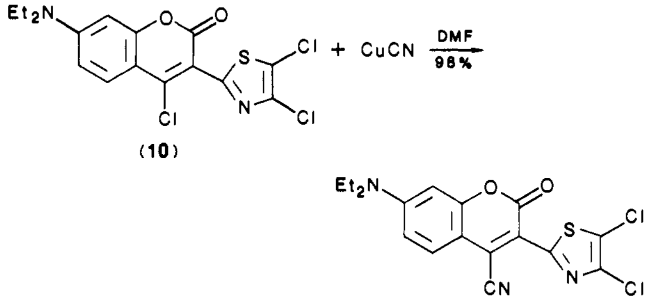
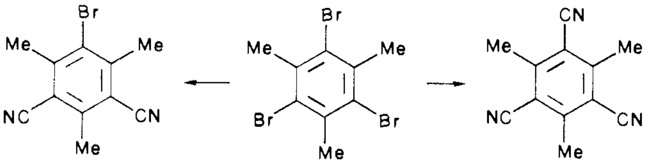


(10)

Replacement of either two or three of the bromine atoms of 1,3,5-tribromo-2,4,6-trimethylbenzene (11) by cyano groups is possible under pressure; at 190 °C for 0.75 h, one bromine remains but at 205 °C for 1.3 h all three are displaced to give the trinitrile (Scheme X).[24]

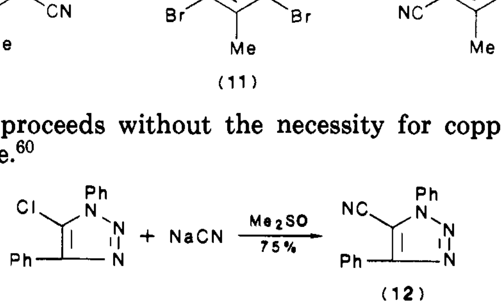
The effect of a pair of pyridine-type nitrogens in a 1,2,3-triazole ring more than compensates for the comparatively unreactive nature of chlorine in the preparation of 1,4-diphenyl-1,2,3-triazole-5-carbonitrile (12)

SCHEME X



(11)

which proceeds without the necessity for copper(I) cyanide.[60]



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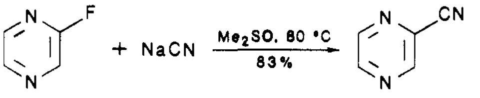

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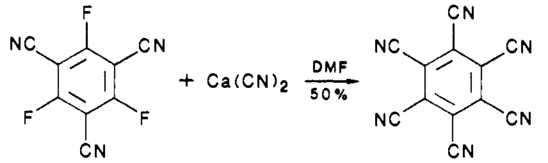


(14)

Examples of a fluorine atom being displaced by cyanide are rare but pentafluoropyridine reacts readily with copper(I) cyanide at 0 °C in DMF to give a 33% yield of 2,3,5,6-tetrafluoropyridine-4-carbonitrile.[61] A recent patent[62] describes the conversion of 2-fluoropyrazine into the corresponding nitrile (13) and claims that the 2-chloropyrazine gave only a trace of the nitrile. Activation by functional groups attached to the ring accounts for the lability of the fluorine atoms of 2,4,6-trifluorobenzene-1,3,5-tricarbonitrile (14) which are cyanated under remarkably mild conditions.[63]

B. Choice of Solvent

Although some of the early examples of the cyanations were effected by heating the halide and copper(I) cyanide without a solvent,[35,42,64] the use of pyridine[38-41] or quinoline[1,2,65,66] was soon recognized to have beneficial effects.[44,45] Many solvents have been tried in an attempt to find one which enables the reaction mixture to be and to remain homogeneous. This would require a solvent which would dissolve the aryl halide and copper(I) cyanide and any complexes formed between the reagents and bases (for example, pyridine) and between the products. The ideal solvent would prevent the formation of the last named and thus enable the free nitrile to be easily isolated.

N-Methylpyrrolidin-2-one (NMP) is a good solvent for copper(I) cyanide[66,67] and DMF dissolves the nitrile–copper(I) halide complex.[22] These two solvents shorten reaction times and simplify isolation of the product and are frequently used as will be seen from Tables I–IV.

Many other solvents have been used, for example, Me_2SO,[16,25,33,45] 4-methylpyridine,[69] nitrobenzene,[17,70] dimethyl sulfone,[71] acetonitrile,[33] *p*-xylene,[72] toluene,[72] isopentyl alcohol,[72] tetrahydrothiophene dioxide,[71] *N*,*N*-dimethylacetamide,[20,68,71] tetrahydrofuran (THF),[33] and tetramethylurea (TMU).[25] Pyridine may have been chosen originally for its good solvent properties but was later found to form a complex with copper(I) cyanide and this has occasionally been preformed and used as a reactant.[19]

Suzuki and Hanafusa[14] demonstrated that for the replacement of one or more iodine atoms, HMPT acts as an efficient solvent (which may also have other roles) and this has been confirmed by other workers,[26,33] although it is not invariably the best solvent.[25] However, in view of its suspected carcinogenic effect,[73] it should be used with care (see also section II). Tetramethylurea gave better results than heating without solvent, or with HMPT or Me_2SO for a 2,3-dibromonaphthalene.[25]

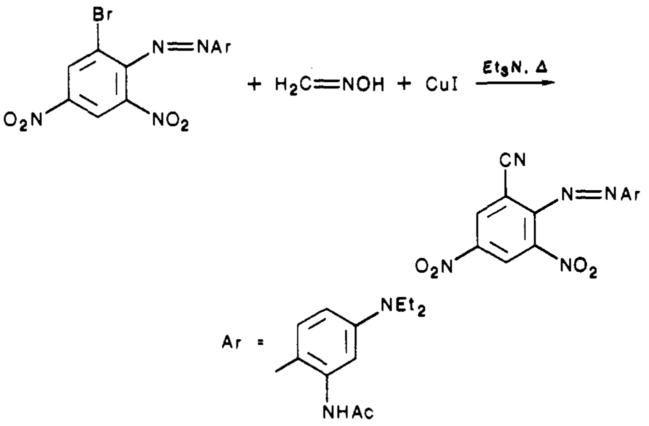
The rate of a particular cyanation may vary according to the solvent used. For example, cyanation of the trifluoride (14) proceeded much more slowly and needed a higher temperature in diethylene glycol bis(methyl ether) than in DMF.[62]

The basicity and structure of some compounds which are used as solvents was shown to affect the yield of nitrile formed when the reaction was conducted in nitrobenzene at 180 °C. At the end of this reaction, the nitrile was not complexed with the copper halide as is usually the case; its isolation was therefore easier. Varying amounts of the bases were added to bromobenzene, copper(I) cyanide, and nitrobenzene, and heated for 3 or 6 h. When the yield was used as a measure of efficiency of the base, it appeared that steric hindrance played a part: for example, the yield decreased in the order: pyridine $\approx$ 4-methylpyridine $>$ 2-methylpyridine $>$ 2,6-dimethylpyridine. Aniline was almost as good as pyridine and rather better than quinoline while *N*,*N*-dimethylaniline was useless. The basicities of these compounds do not appear to have been considered in this study.[17]

Since the aromatic nitrile often forms an insoluble complex, the ease of isolation of the nitrile is partly dependent on the solvent used. The advantage of DMF in this respect is mentioned in a previous paragraph. The nitrile may be obtained from the complex by one of several methods: (a) warming with iron(III) chloride–hydrochloric acid to oxidize copper(I) to copper(II), followed by extraction of the nitrile with toluene;[22,74,75] (b) complexation of copper(I) and copper(II) ions with aqueous ethylenediamine and extraction of the nitrile with benzene;[22,76] (c) addition of an excess of aqueous sodium cyanide (which converts the copper(I) complex into the soluble sodium cuprocyanide) and removal of the nitrile by extraction with benzene;[22] (d) acidification of the reaction mixture (which contained pyridine) and extraction with benzene[19,66] or a similar solvent;[65,77] (e) for reactions in DMF or pyridine, a mixture of dilute aqueous ammonia and benzene may be added,[18,19,78] sometimes after distilling off some of the solvent;[35] (f) the mixture in DMF is oxidized with hydrogen peroxide in acid solution and then extracted with benzene;[19] (g) distillation of the product at reduced pressure; this is most convenient in the absence of a solvent;[42,43,60,75] (h) the product is extracted in a Soxhlet apparatus with acetone[35] or with methylene chloride;[20] (i) reaction mixture is poured into water and the precipitate is extracted with 1,2-dichloroethane.[16]

When a thermolabile function is present in the aryl halide, a high-boiling solvent is disadvantageous. Although it is possible to maintain the temperature below the boiling point of such solvents, it is often more

SCHEME XI



convenient to use a lower boiling material. Among the commonly used solvents, quinoline (bp 237 °C) and NMP (bp 202 °C) are higher boiling than DMF (bp 153 °C) and pyridine (bp 115 °C). The advantage of using these last two is illustrated in section IVC.

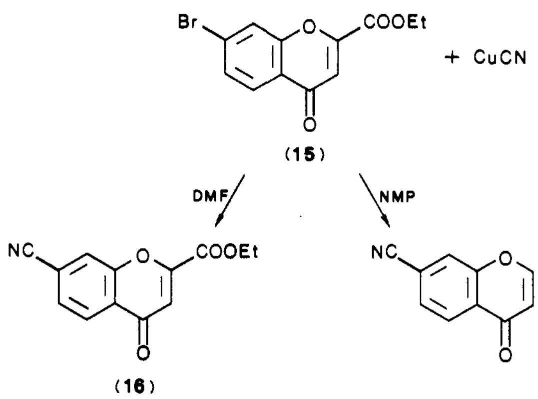
The course of the reaction of 2-bromoacetophenone with copper(I) cyanide depends to some extent on the solvent chosen. In boiling pyridine, the expected 2-acetylbenzonitrile was formed in high yield[18] but in quinoline at about 215 °C the copper complex of tetrabenzomonoazaporphine was produced.[79] Another abnormal product (carbostyril) was obtained when 2-bromoquinoline was heated with a mixture of potassium cyanide and copper(I) cyanide in aqueous ethanol.[80]

A variety of solvents has been used in the reactions of aryl halides with alkali metal cyanides in the presence of catalysts other than copper salts. Palladium-catalyzed reactions proceed well at about 140–150 °C in HMPT, tetramethylurea, *N*,*N*-dimethylacetamide, NMP, propylene carbonate, and DMF,[23,33] but rather poorly in dimethyl sulfoxide, sulfolane, acetic acid, 1-butanol, diethylene glycol bis(ethyl ether), acetonitrile, and propionitrile.[23,33,63] Some of these solvents, for example, HMPT and tetramethylurea, gave good results even when the reaction temperature was lowered to 90 °C.[23] However, the presence of other additives and the molar proportion of reactants can affect the success of the reaction, as was shown by Takagi et al.[23] It appears that a large excess of dissolved CN^- ion reduces the yield, possibly by forming an inert palladium–cyanide bond. This may explain also why sodium cyanide (which has a greater solubility in most solvents) cannot replace the potassium salt successfully. In the palladium-catalyzed cyanation with trimethylsilyl cyanide, anhydrous triethylamine was much superior to DMF, acetonitrile, dioxane, or pyridine.[52a]

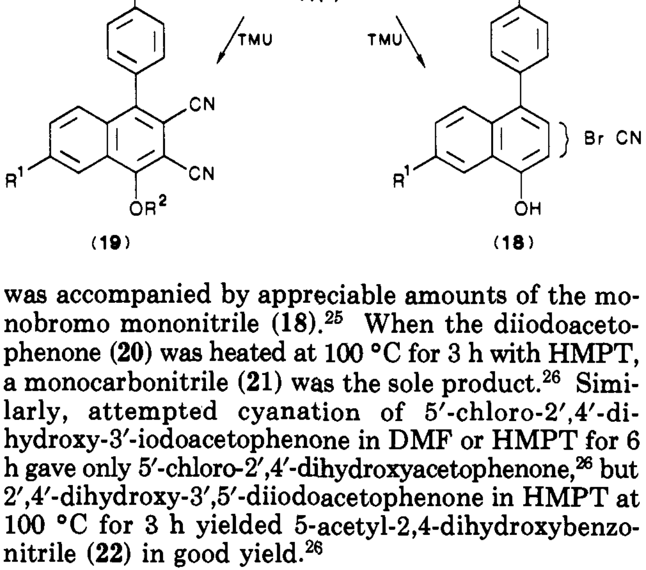
A phase-transfer catalyst (such as a crown ether) is sensitive to the choice of solvent. In water and benzene, sodium cyanide catalyzed by tris(triphenylphosphine)nickel gives good yields of nitrile[51] but potassium cyanide gave equally good results in dry benzene containing tetrakis(triphenylphosphine)palladium but required a reaction time of 65 h.[33] Other solvents which have been used with nickel–phosphine complexes are ethanol and DMF.[49]

C. Unexpected Reactions

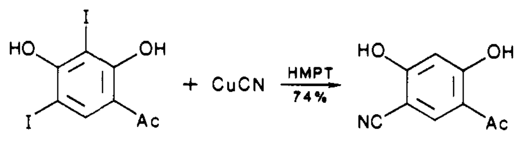
It has already been mentioned that the presence of another substituent in the aryl halide sometimes had a deleterious effect on cyanation (see section II). However, a simultaneous chemical change at another site in the molecule occasionally gives rise to an unexpected product. Decarboxylation occurred simultaneously when 5- or 7-halogenoindole-2-carboxylic acid or its 1-methyl derivative was refluxed with copper(I) cyanide in quinoline (bp 237 °C).[66,77,81] Deethoxycarbonylation and cyanation were observed when ethyl 7-bromo-4-oxochromene-2-carboxylate (**15**) (and others) was heated in NMP (bp 202 °C) but when the lower boiling DMF (bp 153 °C) was used, the expected cyano ester (**16**) was obtained in 68% yield.[26]



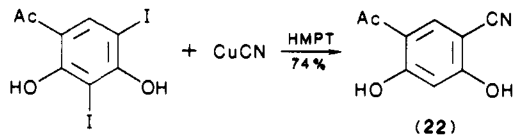
Attempted dicyanation of the dibromonaphthalene (**17**, R^2 = Me) with copper(I) cyanide in quinoline at 200 °C gave a low yield of a mononitrile of uncertain structure but in tetramethylurea, the major product from both ether (**17**, R^1 = H, Me, Et, R^2 = Me) and ester (**17**, R^1 = Et, R^2 = Ac) was the dinitrile (**19**). This was accompanied by appreciable amounts of the monobromo mononitrile (**18**).[25] When the diiodoacetophenone (**20**) was heated at 100 °C for 3 h with HMPT, a monocarbonitrile (**21**) was the sole product.[26] Similarly, attempted cyanation of 5′-chloro-2′,4′-dihydroxy-3′-iodoacetophenone in DMF or HMPT for 6 h gave only 5′-chloro-2′,4′-dihydroxyacetophenone,[26] but 2′,4′-dihydroxy-3′,5′-diiodoacetophenone in HMPT at 100 °C for 3 h yielded 5-acetyl-2,4-dihydroxybenzonitrile (**22**) in good yield.[26]



Reaction of the newly introduced nitrile group with an adjacent carboxyl can lead to the formation of an imide; thus, 2,5-dibromoterephthalic acid gave a high

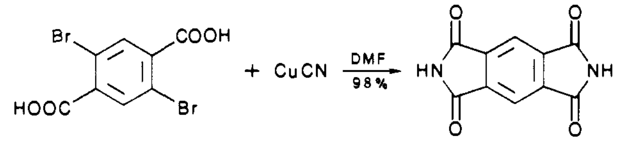


(20) (21)

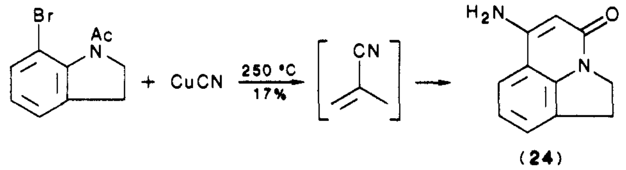


(22)

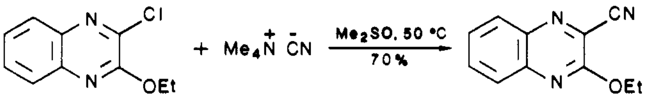
yield of the diimide (23) on heating with copper(I) cyanide in DMF.[82] Similarly, a nitrile and a nearby reactive methyl group yielded the pyrrolo[3,2,1-*ij*]-quinolin-3-one (24) instead of the expected 7-carbonitrile.[83]



(23)



(24)



(25)

Finally, it is of interest to mention some little-used methods of bringing about cyanation of aryl halides. Copper(I) thiocyanate in pyridine converts bromobenzene and its 2- and 4-methyl homologues into the nitriles but many other aryl halides yield only the diaryl sulfide.[84] A patent[85] describes the cyanation of halobenzene by treatment with sodium or potassium cyanate and carbon monoxide in the presence of a nickel or platinum catalyst.

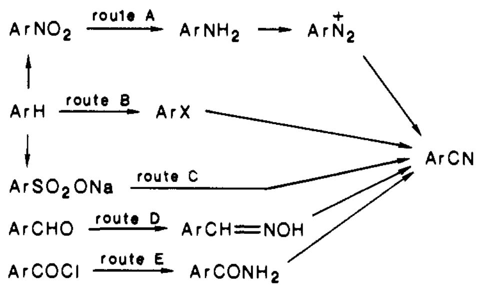
Reactive halides are displaced when treated at ambient or slightly higher temperature with tetramethylammonium cyanide to give moderate to good yields of the nitrile, for example, 3-ethoxyquinoxaline-2-carbonitrile (25).[86]

Formaldoxime is a source of nitrile group when warmed with an aryl halide at 60 °C in the presence of copper(I) iodide and a base (Scheme XI).[87]

V. Conclusion

There are five commonly used methods of preparing aryl nitriles (Scheme XII). The method of choice for a particular nitrile depends mainly on (a) the availability of a suitable precursor, (b) the stability of other functional groups and/or a heterocyclic ring system present in the precursor to various reaction conditions which are characteristic of each route, and (c) the prospective overall yield of each route. Consideration of these factors would probably eliminate (i) route A when Ar already contains an easily reducible function, (ii) route C when the intermediate is thermally unstable at 400 °C, and (iii) routes D and E when a function capable of being dehydrated is present.

SCHEME XII



There are several methods of introducing an iodine[88,89] or bromine[89–91] atom into an aromatic ring and this review shows that there is a variety of effective and convenient methods of converting such halides into the carbonitriles in acceptable yields.

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