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Dimethylformamide as a Useful Solvent in Preparing Nitriles from Aryl Halides and Cuprous Cyanide; Improved Isolation Techniques[1a]

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Reaction of aryl bromides and activated aryl chlorides with cuprous cyanide occurs advantageously in dimethylformamide to give the corresponding nitriles. Effective methods have been developed for efficient decomposition of complexes of nitriles and cuprous halides and subsequent isolation of products.

Cuprous cyanide reacts with aryl halides to yield the corresponding nitriles (Equations 1 and 2); the general value of this reaction is demonstrated

$$2\ Ar\text{—}X + CuCN \longrightarrow [Ar\text{—}CN]_2CuX + CuX \quad (1)$$

$$[Ar\text{—}CN]_2CuX \longrightarrow 2\ Ar\text{—}CN + CuX \quad (2)$$

by the frequency in which it has been used (*vide infra*). The displacement is usually effected in excellent yield (> 85%) by heating a mixture of the aryl halide with cuprous cyanide in the presence of pyridine or quinoline as a promoter or solvent.[2] Aryl chlorides, unless especially activated require more severe reaction conditions (eighteen to twenty-four hours; 190–240°) than do aryl bromides (two to eight hours; 130–200°). The general disadvantages of these reactions are the media (pyridine and quinoline, etc., are expensive and malodorous), the necessary temperatures, and the equipment required for stirring a relatively immobile mixture.

Reactions of cuprous cyanide with aryl bromides have also been effected at 220–300° (sealed tubes; metal baths with stirring) in the absence of basic solvents.[3] Without such solvents these reactions are autocatalytic; small amounts of copper sulfate and nitriles or basic compounds such as pyridine, quinoline or cyclohexylamine have marked accelerative effects and overcome the usual induction periods.[4] It thus appears that the original methods[2] are often superior to some of the subsequent modifications.[3]

The isolation of nitriles from such reaction mixtures is usually difficult and laborious. The methods used involve direct distillation,[3] extraction,[5] or decomposition of the nitrile–copper halide and nitrile–cuprous cyanide complexes with aqueous ammonia and/or aqueous hydrochloric acid.[2] Direct distillation is seldomly used and is only readily applicable when the reaction is effected in the absence of solvents. Extraction has been used but the difficulties involved led to the use of distillation or treatment with ammonia and acid. The most practical method, even though arduous and lengthy, has been the latter.

In the present research it has been found that reactions of aryl bromides and suitably active aryl chlorides with cuprous cyanide proceed rapidly (two to six hours) and efficiently in refluxing dimethylformamide. The reactions are mildly exothermic[6a] and catalysts[6b,c] are usually unnecessary.[6d] As a reaction proceeds, the mixture becomes dark brown. The complex formed from the nitrile and cuprous halide is soluble, and copper, uncomplexed copper halides, and excess cuprous cyanide remain as precipitates. Technical dimethylformamide and cuprous cyanide are satisfactory reagents.

Preparative examples using dimethylformamide are summarized in Table I. There were no substituents found which prevent displacement reactions of aryl bromides and cuprous cyanide from occurring. The yields are comparable if not slightly better than when pyridine is used. Use of dimethylformamide as a reaction medium is superior to that of previous methods with respect to equip-

(1) (a) Abstracted in part from the Ph.D. dissertation of L. Friedman, The Ohio State University, 1959. (b) Present address: Department of Chemistry, Case Institute, Cleveland, Ohio.

(2) (a) For a complete literature survey using this method, see Ref. 1a. (b) Principal references are: Ger. Patent, **271,790** (1914); Ger. Patent, **275,517** (1914); Ger. Patent, **293,094** (1919); H. de Diesbach and E. von der Weid, *Helv. Chim. Acta*, **10**, 886 (1927); M. S. Newman, *J. Am. Chem. Soc.*, **59**, 2472 (1937); W. Braun and K. Koberle, U. S. Patent, **2,195,076** (1940); W. Braun, O.T.S.P.B. Report 626 (1946); R. C. Fuson, J. W. Kneisly, N. Rabjohn and M. L. Ward, *J. Am. Chem. Soc.*, **68**, 533 (1946), and D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1108 (1946).

(3) Principal references[1a] are: J. v. Braun and G. Manz, *Ann.*, **488**, 116 (1931); C. K. Bradsher, *J. Am. Chem. Soc.*, **62**, 486 (1940); M. A. Goldberg, E. P. Ordas, and G. Carsh, *J. Am. Chem. Soc.*, **69**, 260 (1947); J. E. Callen, C. A. Dornfeld, and G. H. Coleman, *Org. Syntheses*, Coll. Vol. III, 212 (1955); and R. G. Haber, A. Ebnather, and H. Schmid, *Helv. Chim. Acta*, **39**, 1536 (1956).

(4) C. F. Koelsch and A. G. Whitney, *J. Org. Chem.*, **6**, 795 (1941).

(5) E. Mosettig and J. van de Kamp, *J. Am. Chem. Soc.*, **54**, 3334 (1932).

(6) (a) In large scale reactions, the mixtures may reflux vigorously as a result of the exotherms. (b) *o*-Bromo-*t*-butylbenzene was unreactive under these conditions unless catalyzed with a little pyridine; L. Friedman and M. E. D. Hillman, private communication. (c) The presence of cupric ion at the beginning of reaction is indicated by the green color the dimethylformamide mixture assumes and by the precipitation of copper. (d) The method does not effect conversion of *o*- and *p*-chlorotoluenes and 1-chloronaphthalene to their corresponding nitriles.

TABLE I

REACTION OF AROMATIC HALIDES AND CUPROUS CYANIDE IN DIMETHYLFORMAMIDE

Halide	Moles	Cuprous Cyanide, Moles	Reaction Time, Hr.	Isolation Method	M.P.[c]	Yield, %
5-Bromoacenaphthene	0.26	0.30	4	B[a]	111–112	91
4-Bromoacetophenone	0.25	0.30	3	A[b]	54–56[d]	88
4-Bromoaniline	0.50	0.50	4	C[a]	85–86	83
m-Bromobenzaldehyde	0.20	0.24	6	A[a]	76–77	92
4-Bromobiphenyl	0.50	0.58	4	A[b]	85–86[e]	92
4-Bromofluoranthene	0.25	0.30	5	C[a]	114–115[f]	75
2-Bromofluorene	0.50	0.58	4	A[b]	88–89[g]	92
1-Bromonaphthalene	1.00	1.15	4	A, B, C[b]	33–34[h]	94
9-Bromophenanthrene	0.50	0.58	4	A[b]	107–108[i]	95
o-Bromotoluene	3.35	3.80	4	A, B, C[b]	—[j]	93
p-Bromotoluene	2.00	3.40	6	A[b]	27–28[k]	91
2-Bromo-*p*-xylene	1.30	1.58	6	A[b]	9–10[l]	88
4-Bromo-*m*-xylene	1.48	1.72	4	B[b]	20–22[m]	91
4-Bromo-*o*-xylene	0.20	0.24	6	A[b]	65–66[n]	87
o-Bromoethylbenzene	0.20	0.24	4	A[b]	—[o]	90
p-Dibromobenzene	1.00	2.30	4	B, C[a]	221–222[p]	100
4,4′-Dibromobiphenyl	0.50	1.16	4	B, C[a]	242–244[p]	100
Methyl 3-bromobenzoate	0.20	0.24	3	A[a]	64–65	95
Methyl 4-chlorobenzoate	0.20	0.24	5	A[a]	61–63	87

[a] The product was purified by distillation. [b] The product was purified by recrystallization. [c] The physical constants of the products compare favorably with those reported previously.[2a] [d] B.p. 110–112° (1 mm.). [e] B.p. 162–163° (10 mm.). [f] Fluoranthene-3-carboxamide, m.p. 277–279°, was also obtained in 10% yield. [g] B.p. 200–205° (1 mm.). [h] B.p. 160–161° (14 mm.) [i] B.p. 170–175° (1 mm.). [j] B.p. 88–89° (14 mm.), n_D^{20} 1.5251. [k] B.p. 74–75° (8 mm.). [l] B.p. 62–63° (1 mm.). [m] B.p. 102–103° (10 mm.). [n] B.p. 102–103° (10 mm.). [o] B.p. 100–102° (10 mm.). Hydrolyzed to *o*-ethylbenzoic acid, m.p. 67–68°. [p] The product obtained is the dinitrile.

TABLE II

REACTION OF AROMATIC CHLORIDES AND CUPROUS CYANIDE IN PYRIDINE

Halide	Moles	Cuprous Cyanide, Moles	Reaction Time, Hr.	Temp., °	Isolation Method	Yield, %
1-Chloronaphthalene	1.00	1.15	24	220–250	A[a]	94[b]
o-Chlorotoluene	1.00	1.20	72[c]	190–210	A[a]	85[d]
p-Dichlorobenzene	1.00	2.30	24	210–220	C[e]	92[f]
2,4-Dichlorotoluene	1.52	3.77	24	200–220	B[e]	93[g]

[a] The product was purified by distillation. [b] M.p. 33–34°. [c] Reaction was effected by adding the halide to a stirred melt of cuprous cyanide-pyridine at such a rate that the temperature was maintained above 190°. [d] B.p. 88–89° (14 mm.). [e] The product (dinitrile) was purified by recrystallization. [f] M.p. 221–223°. [g] M.p. 142–144°.

ment, reaction conditions, odor, convenience and expense.[7]

The previous methods for preparing nitriles from aryl halides and cuprous cyanide have been greatly improved in the present study by developing more effective procedures for decomposing the complexes of the nitriles and cuprous halides. Aqueous ferric chloride has been found to be an excellent general reagent for destroying the reaction complexes formed in dimethylformamide (Table I) or in pyridine (Table II)[8] and subsequent isolation of the nitriles (Method A). Ferric chloride rapidly oxidizes the adduct of cuprous halide and a nitrile to cupric ion[9]; the nitrile does not complex with cupric ion and separates from the aqueous solution. Aqueous ethylenediamine is also an effective reagent (Method B) because it complexes efficiently with cupric and cuprous ions and allows efficient isolation of a nitrile.[10] In use of

(7) After the present study was completed it was found in this laboratory (M. S. Newman and D. K. Phillips, *J. Am. Chem. Soc.*, **81**, 3667 (1959); H. Boden, Ph.D. dissertation, The Ohio State University, 1960) that *N*-methylpyrrolidone is also a satisfactory solvent for reaction of aryl halides and cuprous cyanide. Cuprous cyanide is soluble in *N*-methylpyrrolidone at temperatures above 90° and reactions in such homogeneous mixtures occur relatively rapidly. The yields of nitriles on using dimethylformamide and *N*-methylpyrrolidone are essentially identical; dimethylformamide is of advantage with respect to expense.

(8) Typical examples are included using pyridine since this solvent is often of advantage for reaction of aryl chlorides with cuprous cyanide.

(9) C. Rabaut, *Bull. Soc. Chim., France*, (3), **19**, 785 (1898) reports that complexes of nitriles and cuprous halides are decomposed by air, ferric chloride, aqueous ammonia and hydrogen sulfide, respectively.

(10) The cupric ethylenediamine complex is apparently more stable than that of cuprous ion and ethylenediamine since additional copper is formed in the workup; see H. A. Laitinen, E. I. Onstatt, J. C. Bailar, Jr., and S. Swann, Jr., *J. Am. Chem. Soc.*, **71**, 1550 (1949).

this method it is often advantageous to extract the crude nitrile with aqueous sodium cyanide; the sodium cyanide dissolves suspended copper derivatives and removes residual traces of copper ions. Excess aqueous sodium cyanide (Method C) is also a satisfactory reagent in that it rapidly destroys the complexes of cuprous halides by formation of soluble sodium cuprocyanide with liberation of the nitrile.

The isolation methods are often comparable and usually quantitative; there are virtues in their differences however. Method A is recommended for isolation of cyano acids, esters, ketones, and aldehydes, and other relatively non-basic nitriles. Methods B and C are of advantage in isolating basic nitriles such as *p*-aminobenzonitrile and 2-cyanopyridine, etc.[11] The use of dimethylformamide (or pyridine) as a solvent medium[7] and any of the above isolation techniques thus makes the reaction of aryl halides and cuprous cyanide a convenient, efficient, and general synthetic method.

EXPERIMENTAL

General techniques. The reactions of bromoaromatic compounds (1 mole) and cuprous cyanide (1.15 to 1.2 moles; 15–20% excess) to give nitriles are effected in refluxing dimethylformamide (150 ml., 3–6 hr.). In preparations on a large scale the quantity of dimethylformamide was decreased (125 ml./mole). When the reaction is completed, the nitrile can be isolated by one of several routes: (1) isolation of the complex of the aromatic nitrile and cuprous halide by pouring the reaction mixture into water and then decomposing the complex by Methods A, B, or C; or (2) working up the preparative mixture directly by Methods A, B, or C. The properties of the nitrile and scale of operation determine which route is the most desirable. As the techniques vary little from compound to compound, only representative procedures will be described and the remaining experimental data are contained in Table I and II. Pertinent details to the tables appear as footnotes.

1-Naphthonitrile. Method A. A stirred mixture of 1-bromonaphthalene (207 g., 1 mole), cuprous cyanide (103 g., 1.15 moles; 15% excess) and dimethylformamide (150 ml.; DuPont, technical) was refluxed for 4 hr. The reaction was mildly exothermic. The resulting brown mixture was poured (residues are conveniently transferred with hot dimethylformamide) into a solution of hydrated ferric chloride (400 g.) and concd. hydrochloric acid (100 ml.) in water (600 ml.). After the reaction mixture had been maintained at 60–70° for 20 min. to decompose the complex, the layers were separated.

Separation of the layers was difficult since the interface is obscured by dark colors. However, light reflected off the separatory funnel helps, or differences in fluidity of the two layers may be discerned as the liquid leaves the separatory funnel. The hot aqueous layer was extracted with toluene (2 × 250 ml.); the extracts were combined with the organic layer, washed with dilute hydrochloric acid (1:1, 250 ml.), water, and 10% aqueous sodium hydroxide. The organic layer was filtered to remove the dark insoluble matter (copper, etc.), dried and vacuum distilled. After the solvent was separated, colorless 1-naphthonitrile (144 g., 0.94 mole; 94%), b.p. 160–161° (14 mm.), m.p. 33–334°, was collected (pot residue 3–4 g.).

Method B. The hot, dark reaction mixture from 1-bromonaphthalene (1 mole), cuprous cyanide (1.15 moles), and dimethylformamide (150 ml.) was poured into a solution of ethylenediamine (200 ml.) in water (600 ml.) and gave a dark blue aqueous lower layer, a small interface containing copper and the copper chloride complex of 1-naphthonitrile and a light brown organic layer. After vigorous shaking the blue aqueous layer was separated and extracted with benzene; the benzene extract was added to the organic layer and washed with 10% aqueous sodium cyanide (150 ml.) and water and then filtered through sodium sulfate. After removal of solvent, 1-naphthonitrile (142 g.), b.p. 152–153° (8 mm.), m.p. 33–34°, was obtained in 93% yield.

Method C. The hot, dark reaction mixture, obtained as described in Method A, was poured into a warm solution of sodium cyanide (200 g.) in water (600 ml.). After the mixture had been vigorously shaken, the lower aqueous layer was separated, extracted once with benzene (250 ml.) and discarded. The extract was combined with the organic layer and washed with 10% aqueous sodium cyanide (200 ml.) and water, and then dried over sodium sulfate. After removal of solvent, 1-naphthonitrile (143 g.), b.p. 152–155° (8 mm.), m.p. 33–34°, was obtained in 94% yield.

The yields *via* the various work-up methods are similar. Although another step is involved, isolation of the crude nitrile–cuprous bromide complex (pouring the reaction mixture into water and filtering) prior to cleavage is desirable in large scale reactions as large volumes of dimethylformamide can thus be discarded conveniently. This operation does not affect the yield.

2,4-Dimethylbenzonitrile. Method B. 1-Bromo-2,4-dimethylbenzene (274 g., 1.48 moles), cuprous cyanide (154 g., 1.72 moles, 15% excess), and dimethylformamide (225 ml.) were refluxed for 4 hr. while being stirred; the hot reaction mixture was poured, while stirring, into cold water (1:1). The near white-tan precipitate was collected, washed thoroughly with water, and then shaken with a warm (50°) solution of ethylenediamine (300 ml.) in water (700 ml.). Benzene was added, the mixture was shaken thoroughly, and the lower aqueous layer was discarded. The benzene extract was washed with 10% aqueous sodium cyanide (150 ml.), water, and dried over sodium sulfate. After removal of solvent, the residue was rectified *in vacuo*. A 91% yield of 2,4-dimethylbenzonitrile (176 g., 1.34 moles), b.p. 102–103° (10 mm.), n_D^{25} 1.5279–1.5281, was obtained.

Reactions in pyridine. 1-Naphthonitrile. Method A. 1-Chloronaphthalene (163 g., 1 mole), cuprous cyanide (103 g., 1.15 moles; 15% excess) and pyridine (65 ml.) were heated at 220–250° for 24 hr. The resulting brown mixture was poured into a solution of hydrated ferric chloride (400 g.) and hydrochloric acid (150 ml.) in water (650 ml.). The nitrile was isolated using techniques described previously for ferric chloride and hydrochloric acid; 143 g. (0.94 mole, 94%).

4-Methylisophthalonitrile. Method B. 2,4-Dichlorotoluene (245 g., 1.52 moles), cuprous cyanide (337 g., 3.75 moles; 25% excess) and pyridine (250 ml.) were heated at 200–220° for 24 hr. The dark reaction mixture was poured into a warm solution of ethylenediamine (500 ml.) in water (1500 ml.) and heated to break up the complex and precipitate 4-methylisophthalonitrile. The finely-divided solid was collected and washed successively with aqueous ethylenediamine (25%, 300 ml.), water, warm aqueous sodium cyanide (10%, 200 ml.) and water. 4-Methylisophthalonitrile was obtained as a buff-colored powder, 200 g. (1.41 moles, 93%), m.p. 142–144°, lit.[12] m.p. 144–150°. Hydrolysis with sodium hydroxide-triethylene glycol gave 4-methylisophthalic acid, m.p. 330–332°, lit.[13] m.p. 332°.

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(11) Hot strong alkali can be used to decompose the complexes and hydrolyze a nitrile to its carboxylic acid. Though the hydrolysis is quantitative, the difficulty in filtering the copper oxide precipitates from the alkaline solution seriously limits the usefulness of this method.

(12) W. Borsche, *Ann.*, **386**, 308 (1912).

(13) A. Claus, *J. prakt. Chem.*, (2), **42**, 510 (1890).