A Convenient Synthesis of Highly Substituted Benzonitriles and Benzenepolynitriles[1]

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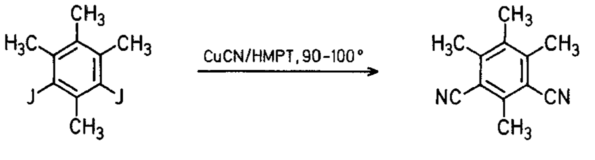
The conventional procedures of introducing multiple cyano groups into a benzene nucleus are the dehydration of benzenepolycarboxamides and the Sandmeyer reaction of appropriate aminocyano compounds. However, these direct methods often suffer from poor availability of the starting materials and low yields due to extensive side-reaction. Multiple replacement by cyano groups of aryl halogen atoms on nonadjacent carbon atoms can be effected in some cases by the action of alkali metal cyanide or copper(I) cyanide upon aryl polyhalides in aprotic solvents, preferably at elevated temperatures[2]. Solvents employed include dimethylformamide, pyridine, hexamethylphosphoric triamide and diglyme.

We have found that heating of polyiodobenzenes with copper(I) cyanide in hexamethylphosphoric triamide at around 80–100° for 1–2 hr leads to the smooth and complete replacement of iodine atoms by cyano groups. Dilution of the reaction mixture with water, followed by the decomposition of copper(I) halide complex with aqueous iron(III) chloride and recrystallization from ethanol gave a high yield of benzenepolynitriles as good-crystallized, colorless plates or needles. Great advantages in the use of hexamethylphosphoric triamide as solvent are the shortened reaction time and lowered temperature needed[3]. The reaction was clean and mild, and little amorphous substance was formed. Catalysts were unnecessary. As can be seen from the results summarized in the Table, other ring functional groups present in addition to iodine atoms remain unaffected. Ring substituents include various alkyl, halo, carboxy, and nitro groups. This method is especially attractive for the laboratory preparation of acid and/or alkali-sensitive, or thermally unstable benzenepolynitriles. The use of bromo compounds led to less satisfactory preparative results.

Application of this method to highly crowded iodobenzenes and mixed haloiodobenzenes similarly afforded the corresponding aryl cyanides in high yields. Thus, 3-iodo-1,2,4,5-tetraisopropylbenzene and 4-iodo-1,2,3-trimethyl-5-*t*-butylbenzene readily gave 2,3,5,6-tetraisopropylbenzonitrile and 2,3,4-trimethyl-6-*t*-butylbenzonitrile in 88% and 83% yields, respectively. Taking advantage of the different reactivities of two dissimilar halogen atoms, 1-iodo-2,4,6-trichlorobenzene (**3**) was converted to 2,4,6-trichlorobenzonitrile (**4**) in 82% yield.

Since various polyiodobenzene derivatives are readily obtained by the direct iodination of arenes with iodine/periodic acid[4], or by the Jacobsen reaction of simpler iodo compounds[5], the present procedure should provide an easy access to a variety of the titled compounds. Physical properties and yields of some benzonitriles and benzenepolynitriles obtained are shown in the Table.



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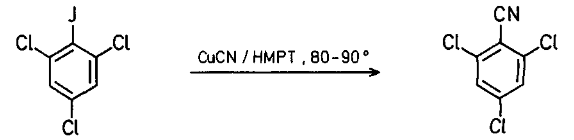


3 **4**

All melting points are uncorrected. ^{1}H-N.M.R. spectra were determined in deuteriochloroform solutions on a Varian T-60 spectrometer at probe temperatures against internal TMS. I.R. spectra were recorded in Nujol with a Jasco DS-402G spectrophotometer.

The procedures are illustrated by the representative preparations of some benzonitriles and benzenepolynitriles. Although no attempts were made to optimize the reaction, the use of somewhat excess copper(I) cyanide seems to give better results.

4,6-Dicyano-1,2,3,5-tetramethylbenzene (2):

A mixture of 4,6-diiodo-1,2,3,5-tetramethylbenzene (**1**: 6.6 g)[6], copper(I) cyanide (4.0 g), and hexamethylphosphoric triamide (10 g) was heated with stirring at 90–100° for 2 hr, and then poured into excess of aqueous iron(III) chloride solution to decompose the complex. The finely-divided light tan solid was collected by filtration and washed successively with water, aqueous sodium hydrogen sulfite, and water. It was sucked as dry as possible and then placed in a filter thimble and extracted with light petroleum using a Soxhlet extractor. The extract was evaporated and the residue was crystallized from ethanol to give fine needles; yield: 2.3 g, 73%; m.p. 178–180°.

$C_{12}H_{12}N_2$	calc.	C 78.23	H 6.57	N 15.20
	found	78.40	6.61	15.06

I.R. (Nujol): $\nu_{max}=2222$ cm^{-1} (CN).

N.M.R. (CDCl$_3$): $\delta=2.26$ (CH$_3$), 2.56 (2 CH$_3$), 2.71 ppm (CH$_3$).

2,4,6-Trichlorobenzonitrile (4):

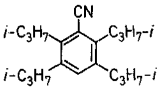
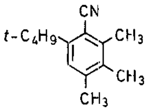
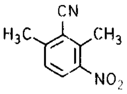
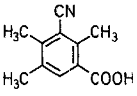
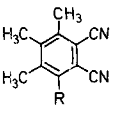
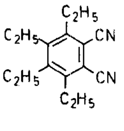
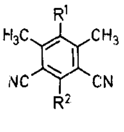
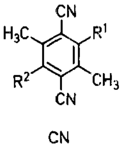
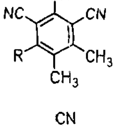
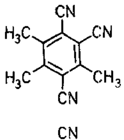
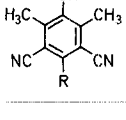
A mixture of 1-iodo-2,4,6-trichlorobenzene (**3**; 6.2 g)[7], copper(I) cyanide (1.9 g), and hexamethylphosphoric triamide (6 g) was heated slowly with stirring at 80–90°, and after 2 to 3 hr was poured into excess aqueous iron(III) chloride solution. The precipitate was filtered off, washed with dilute aqueous sodium hydrogen sulfite and water, and extracted with hot ligroin. A light brown crystalline solid recovered from the extract was recrystallized from ethanol to give nitrile **4** as slightly yellowish plates; yield: 3.3 g, 82%; m.p. 76–78°.

$C_7H_2NCl_3$	calc.	C 40.72	H 0.98	N 6.79
	found	40.56	0.96	6.90

I.R. (Nujol): $\nu_{max}=2238$ cm^{-1} (CN).

N.M.R. (CDCl$_3$): $\delta=7.47$ ppm (2 H).

Table. Benzonitriles and Benzenepolynitriles Obtained from the Reaction of Iodobenzene with Copper(I) Cyanide in Hexamethylphosphoric Triamide

Nitrile		m.p.	Yield (%)	^{1}H-N.M.R. δ (60 MHz)
		189–190°	88	1.23 (d, 12H), 1.47 (d, 12H), 3.9–3.0 (m, 4H) 7.35 ppm (s, H).
		90–91°	83	1.50 (s, 9H), 2.17 (s, 3H), 2.31 (s, 3H), 2.49 (s, 3H) 7.04 ppm (s, H).
		78–79°	75	2.65 (s, 3H), 2.78 (s, 3H), 7.30 (d, H), 7.99 ppm (s, H).
		227–228°	77	2.37 (s, 3H), 2.58 (s, 3H), 2.87 (s, 3H), 7.06 ppm (s, H).
	$R=CH_3$:	230–231°	48	2.54 (s, 6H), 2.35 ppm (s, 6H).
	$R=H$:	140–142°	58	2.37 (s, 3H), 2.45 (s, 3H), 2.60 (s, 3H) 7.44 ppm (s, H).
		155–156°	76	1.19 (t, 6H), 1.27 (t, 6H), 2.75 (q, 4H), 2.91 ppm (q, 4H).
	$R^1=CH_3$, $R^2=C_2H_5$:	116–117°	90	1.33 (t, 3H), 2.27 (s, 3H), 2.58 (s, 6H), 3.08 ppm (q, 2H).
	$R^1=C_2H_5$, $R^2=CH_3$:	121–122°	81	1.13 (t, 3H), 2.60 (s, 6H), 2.70 (s, 3H), 2.74 ppm (q, 2H).
	$R^1=CH_3$, $R^2=H$:	198–202°	66	2.32 (s, 3H), 2.57 (s, 6H), 7.73 ppm (s, H).
	$R^1=R^2=CH_3$:	208–210°	59	2.52 ppm (s, 12H).
	$R^1=CH_3$; $R^2=C_2H_5$:	95–96°	78	1.22 (t, 3H), 2.51 (s, 6H), 2.54 (s, 3H), 2.92 ppm (q, 2H).
	$R^1=R^2=H$:	213–215°	–	2.57 (s, 6H), 7.58 ppm (s, 2H).
	$R=CH_3$:	188–190°	40	2.40 (s, 3H), 2.65 ppm (s, 6H).
	$R=H$:	156–157°	38	2.65 (s, 3H), 7.90 ppm (s, H).
		183–184°	46	2.59 (s, 3H), 2.65 (s, 3H), 2.78 ppm (s, 3H).
	$R=CH_3$:	182–183°	–	2.83 ppm (s, 9H).
	$R=H$:	141–142°	47	2.86 (s, 6H), 8.03 ppm (s, H).

Unfortunately, the present method was found unsuitable for the conversion of 1-iodo-2,4,6-tribromobenzene to 2,4,6-tribromobenzonitrile; the product was contaminated by some impurity difficult to remove completely.

3,5-Dicyano-2,4,6-trimethylbenzoic Acid:

A stirred mixture of 3,5-diiodo-2,4,6-trimethylbenzoic acid (1.0 g)[8] copper(I) cyanide (1.0 g), and hexamethylphosphoric triamide (4 g) was heated at 110–120° for 3 hr. The resulting mixture was poured into aqueous solution of iron(III) chloride and hydrochloric acid to decompose the complex. The precipitate was collected, washed with water, and extracted with methanol. Evaporation of the solution to dryness, followed by crystallization of the residue from aqueous methanol gave acid monohydrate; yield: 0.3 g; 53%; as fine needles; m.p. 211–212°.

$C_{12}H_{10}N_2O_2 \cdot H_2O$	calc.	C 61.53	H 6.02	N 11.96
	found	61.75	6.01	11.34

N.M.R. ($CDCl_3$): δ = 2.67 (2 CH_3), 2.78 (CH_3), 6.65 ppm (OH).

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