Cyanide Substitution in Aryl Halides by Copper(I) Complexes Derived from Formamide and from Formaldehyde Oxime

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The copper complexes $[Cu_3(CN)_4L_4]$ [L = MeCN, pyridine (pyr)], $[Cu(CN)(pyr)_2]$ and $[Cu_2(O_2CMe)-(CN)]$ derived from formamide, and $[Cu_3(O_2CMe)_5(MeCONH_2)(CH_2NOH)_2]$ and $[Cu(O_2CMe)-(CH_2NOH)_2]$ derived from formaldehyde oxime (formaldoxime) react with 2'-acetamido-6-bromo-4'-diethylamino-2,4-dinitroazobenzene, ArBr, to form the corresponding aryl cyanide, ArCN, and the products ArH and Ar_2 of reductive substitution and biaryl coupling. Copper(I) bromide complexes are also formed. Kinetic studies of these reactions in acetonitrile solution show that the cyanation reactions are equal concentration, second-order processes in each case. The effect of a radical scavenger on the reaction suggests the involvement of radicals in the formation of Ar_2, but not in the formation of ArCN. A mechanism involving concerted nucleophilic substitution within the co-ordination sphere of copper(I) is proposed.

Copper metal, its salts and co-ordination complexes have been used to effect various interesting transformations in synthetic organic chemistry.[1] The discovery, just over a century ago by Sandmeyer[2] that copper(I) cyanide reacts with aryldiazonium compounds to form aryl cyanides has been developed, as have many other copper-assisted and -catalysed reactions.[3] The mode of action of the metal atom in many of these transformations remains rather poorly understood in many instances, particularly in terms of the processes which may be presumed to occur within the co-ordination sphere of the metal ion.

The use of copper(I) cyanide to substitute halogen in aryl halides by cyanide is widespread.[4] Polar donor solvents are known to assist the reaction,[5] but little is known about either the copper species which effects the substitution or the mechanism of the reaction. The patent literature describes[6] mild and efficient cyanation processes in which copper salts, a dehydrating agent and either formamide or formaldoxime are used in the synthesis of aryl cyanides. There reactions could have significant environmental and economic advantages.

We have shown[7] that copper(I) acetate reacts with acetic anhydride–formamide (1:1) in acetonitrile to give $[Cu_2-(O_2CMe)(CN)]$ (1). Anhydrous copper(II) acetate with the same reagent gives the mixed valence complex $[Cu(NCMe)_4]-[Cu_2(CN)_4]$ (2) which reacts with pyridine (pyr) to form $[Cu(pyr)_4][Cu_2(CN)_4]$ (3). Anydrous copper(II) acetate reacts with acetic anhydride–formamide (1:1) in pyridine solution to form $[Cu(CN)(pyr)_2]$ (4). We have also shown[8] that copper(II) acetate reacts with formaldoxime in acetonitrile to form the mixed-valence complex $[Cu_3(O_2CMe)_5(NH_2COMe)-(CH_2NOH)_2]$ (5). Complex (5) is degraded by pyridine and the copper(I)–formaldoxime complex $[Cu(O_2CMe)(CH_2NOH)_2]$ (6) is formed together with $[Cu_2(O_2CMe)_4(pyr)_2]$.

$[Cu_2(O_2CMe)(CN)]$	(1)
$[Cu(NCMe)_4][Cu_2(CN)_4]$	(2)
$[Cu(pyr)_4][Cu_2(CN)_4]$	(3)
$[Cu(CN)(pyr)_2]$	(4)
$[Cu_3(O_2CMe)_5(MeCONH_2)(CH_2NOH)_2]$	(5)
$[Cu(O_2CMe)(CH_2NOH)_2]$	(6)

We describe studies of the reactions in acetonitrile solution between the copper complexes (1)—(6) and a representative aryl halide substrate, 2'-acetamido-6-bromo-4'-diethylamino-2,4-dinitroazobenzene (7), which we had used in similar studies
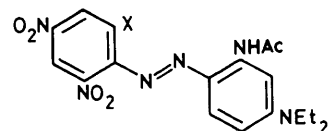
(7) X = Br
(8) X = CN
(9) X = H
(10) Dimer

of phosphonation reactions,[9] and we shown that each of these complexes will effect cyanide substitution for bromide at *room temperature* in solution in the absence of any added cyanide ion. We have established that the acetonitrile solvent does not act as a source of cyanide ion in these reactions. Extensive use has been made of high performance liquid chromatography (h.p.l.c.), particularly in kinetic studies of these reactions.

Results

The aryl bromide (7) reacts with copper(II) acetate and either formamide–acetic anhydride (1:1) or formaldoxime in a boiling polar solvent such as acetonitrile to form the aryl cyanide (8), together with small quantities (<5%) of the reductive substitution product (9) and the dimer (10). At room temperature *no* reaction was detected in a similar mixture during a comparable period of time (1 h). The copper complexes (2)—(6) react with the bromide (7) in dry, deoxygenated acetonitrile at room temperature to give the cyanide (8) as the principal product, together with very small quantities (<0.5%) of compound (9); the biaryl coupling product (10) is not formed. The copper(I) complex $[Cu_2(O_2CMe)(CN)]$ (1) reacts with the bromide (7) at room temperature to give the dimer (10) as the major (70%) product together with compounds (8) and (9). Careful analysis of the product mixture from reaction between the complex (2) and the bromide (7), after isolation of the azobenzene compounds (7)—(10) showed that the bromide which is displaced becomes attached to copper(I) in the ion $[Cu_2(CN)_3Br]^{2-}$. As in earlier work,[9] we find that formation of the reductive substitution product is complete in the early stages of the reaction and does not increase thereafter, although the cyanation reaction continues to produce the cyanide (8). A typical example of the results obtained is shown in Table 1.

Table 1. Evolution of products (8) and (9) from the cyanation of the aryl bromide (7) (0.5 mmol) by the copper complexes (4) and (6) (0.5 mmol) in acetonitrile solution (50 cm^3) at 293 K, determined by h.p.l.c.

Time	Composition (% mol fraction) of sample analysed at time t		
t (min)	(7)	(8)	(9)
A (6)			
11	90.3	9.7	0.0
19	85.3	14.7	0.1
72	58.3	41.4	0.3
112	45.9	53.6	0.5
187	3.2	95.9	0.8
199	0.8	98.8	0.4
B (4) + pyridine (5 cm^3)			
10	82.1	10.6	0.3
20	73.8	25.9	0.3
50	66.3	33.4	0.3
60	63.9	35.8	0.3
85	57.7	42.1	0.1
108	36.2	63.3	0.6
143	8.4	91.3	0.3
219	8.2	91.6	0.2
303	6.7	92.9	0.4

Table 2. Second-order rate constants, k_{obs} (l mol^{-1} s^{-1}) for aryl cyanide (8) production in acetonitrile solution from reaction of copper complexes with the aryl bromide (7) at 293 K

Copper complex	k_{obs}/l mol^{-1} s^{-1}
(1)	4.6×10^{-4}
(2)	1.3×10^{-5}
(3)	4.2×10^{-5}
(4)	1.6×10^{-4}
(5)	1.1×10^{-3}
(6)	2.0×10^{-4}

Kinetic and Mechanistic Studies.—Kinetic measurements of the cyanation of the aryl bromide (7) to give the cyanide (8) in acetonitrile solution were made by h.p.l.c. In each case, the cyanation reaction at room temperature is an equal concentration second-order process (Table 2). In the case of complex (1), production of the biaryl coupling product (10) is very strongly inhibited by the addition of a radical scavenger, 1,1-diphenyl-2-picrylhydrazyl (dpph) (0.1 mmol) to the reaction (293 K) between the complex (0.2 mmol) and the aryl bromide (7). There is a slight acceleration of the cyanation reaction in the presence of the radical scavenger, and a small amount of the reductive substitution product (9) is also formed in the presence of dpph (Table 3). The role of the solvent is significant. The copper(I) complex, [Cu$_2$(O$_2$CMe)(CN)] (1), reacts rapidly with the bromide (7) in acetonitrile, but only slowly in acetone. This suggests that in acetone solution, complex (1) dissociates to give [Cu(O$_2$CMe)] and CuCN to a significant extent. We have shown that CuCN will effect the conversion of the bromide (7) to the cyanide (8) only very slowly at room temperature in acetonitrile. The presence of the acetate ligand in complex (1) serves to activate the cyanide ion. The structure[10] of CuCN suggests that it is polymeric with cyanide bridges. The structure of complex (1) is not known. Comparison of the i.r. spectra of complex (1) and CuCN in the CN stretching absorption region[7] provides no evidence of a marked difference. We suggest that in acetonitrile solution the cyanide bridges in complex (1) are

Table 3. Evolution of products (8)—(10) from the cyanation of the aryl bromide (7) (0.5 mmol) by the copper complex (1) (0.5 mmol) in acetonitrile (50 cm^3) solution at 293 K determined by h.p.l.c.

Time	Composition (% mol fraction) of sample analysed at time t			
t (min)	(7)	(8)	(9)	(10)
A Daylight				
7	61.0	7.0		32.0
17	37.0	29.2		33.8
40	11.1	33.2		55.7
50	3.5	32.8		63.8
60		31.1	1.0	68.0
B Daylight; dpph (0.26 mmol) added				
4	87.9	12.2		
7	84.5	14.5		1.1
14	72.1	27.3		0.6
19	64.9	34.2		0.9
35	59.6	39.3	0.5	0.6
52	32.2	66.6	1.0	0.2

broken, thereby creating a terminal cyanide ligand of increased nucleophilicity.

Two of the complexes derived from formamide, [CuL$_4$]-[Cu$_2$(CN)$_4$] [L = MeCN (2), pyr (3)] are rather insoluble in acetonitrile. Cyanation of the bromide (7) by these complexes proceeds in a heterogeneous mixture at room temperature, and the conversion of (7) into the cyanide (8) is incomplete even after 72 h. When the temperature is increased to reflux (ca. 355 K), the cyanation proceeds much more rapidly and is complete within 5 h for complex (2) and 3 h for (3), respectively. The rate of the heterogeneous reaction at room temperature is faster for complex (3) than for (2), which is consistent with the known[5] ability of pyridine to promote cyanide substitution of aryl halides. The structures of complexes (2) and (3) differ in that the cation in (2) is a distorted octahedron as a result of co-ordination of the copper(II) by two nitrogen atoms in the polymeric [Cu$_2$(CN)$_4$]$^{2-}$ ion, whereas complex (3) contains discrete [Cu(pyr)$_4$]$^{2+}$ ion within the [Cu$_2$(CN)$_4$]$^{2-}$ framework.

Cyanation of the bromide (7) by the soluble formaldoxime complex [Cu$_3$(O$_2$CMe)$_5$(MeCONH$_2$)(H$_2$CNOH)$_2$] (5) is rapid at room temperature. The complex [Cu(O$_2$CMe)(H$_2$CNOH)$_2$] (6), which is derived from (5) is much less soluble even in polar solvents and reacts with the bromide (7) more slowly than complex (5), but in this case the cyanation goes to completion.

Discussion

In contrast to copper(I) cyanide, which effects cyanation of the bromide (7) very slowly at ambient temperature to give the cyanide (8), the cyanide complexes (1)—(4) all react much more rapidly with (7) under the same conditions. The rates of these reactions seem to depend on the accessibility of the cyanide group for nucleophilic substitution of the bromine atom in compound (7); thus, the more soluble complexes (1) and (4) effect cyanation at a much faster rate than the less soluble, mixed-valence complexes (2) and (3). The presence of other ligands attached to copper(I) causes activation of the cyanide.

The formaldoxime complexes (5) and (6) are particularly interesting because they not only cause cyanation of the bromine compound (7) as a result of dehydration of the formaldoxime ligand under mild conditions, but also because they bear a formal similarity to the phosphite complexes [Cu$_3$-

[Cu$_3$(O$_2$CMe)$_5$\{P(OEt)$_3$\}$_2$] (11)
[Cu(O$_2$CMe)\{P(OEt)$_3$\}$_2$] (12)
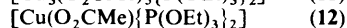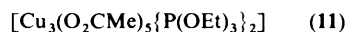
(O$_2$CMe)$_5$\{P(OEt)$_3$\}$_2$] (11) and [Cu(O$_2$CMe)\{P(OEt)$_3$\}$_2$] (12) which were investigated previously.[9] There is an important difference in the solvents used for the two systems: the cyanation reaction was studied in acetonitrile, whereas the phosphonation reactions were carried out in ethanol solution. The most interesting distinction between the two systems is that the biaryl coupling product (10) is not formed in the cyanation reactions, but it is formed in the phosphonation reactions. The reductive substitution product (9) is much less abundant in the presence of the formaldoxime complexes (5), and (6) than in the presence of the phosphite complexes (11) and (12). We have not been able to determine the reason(s) for this difference between the two systems, but we suspect that the role of the solvent[11] may be significant. Nevertheless, the rates of substitution by the copper(I) complexes (6) and (12) are both slower than those for the mixed-valence complexes (5) and (11).

The observation of second-order kinetics in the reaction between the bromide (7) and both complexes (5) and (6), suggests that both H$_2$O and H$^+$ are lost from formaldoxime (to form cyanide) in concert with the displacement of bromide ion from the bromide (7) to give the cyanide (8).

The structure of the aryl halide substrate in these reactions is important. Removal of the acetamido-function from the bromide (7), gives a substrate (6-bromo-4'-diethylamino-2,4-dinitroazobenzene) which does not react with complex (1) at room temperature in acetonitrile and will react only slowly with (1) in refluxing acetonitrile to produce 6-cyano-4'-diethyl-amino-2,4-dinitroazobenzene. We conclude that, as with complexes (11) and (12), the presence of two donor atoms in the substrate greatly facilitates the exchange of cyanide for bromide on a copper(I) site. The nature of the interaction between the metal and the aryl halide substrate in these cyanation reactions has been investigated and we will report the results separately.[12] A concerted exchange[11] between the bromine atom and the cyanide group via a four-centre transition state appears most probable in the room temperature reactions, just as was suggested for phosphonation reaction of complexes (11) and (12).

Experimental

The preparations of the copper complexes (1)—(6), the aryl halide (7), the aryl cyanide (8) and the products of reductive substitution (9) and biaryl coupling (10) have been described.[7,8,13] All solvents were purified by distillation, dried and purged with deoxygenated, dry dinitrogen before use. Reagents were of the highest available purity. Reactions, which were carried out in Schlenk-type glassware under anaerobic conditions, were commonly monitored by thin layer chromatography on Polygram Sil G/u.v. 254 pre-coated plastic sheets using toluene–nitromethane (4:1) and ethyl acetate–light petroleum (b.p. 40—60 °C) (3:2) as eluants. H.p.l.c. was undertaken using Hewlett–Packard 1080B instrument with Spherisorb 50DS columns. Samples for h.p.l.c. were prepared by eluting an aliquot (1 cm^3) of the reaction mixture through a short (4 cm) column of alumina (Grade 0) with acetonitrile to remove any active copper species.

Acknowledgements

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