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The Cyanation of Aromatic Halides Catalyzed by Nickel(0) Complexes Generated in Situ. II.[1)] The Cyanation of Heteroaromatic Halides[2)]

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Synopsis. The cyanation of 3-bromopyridine catalyzed by in situ generated $Ni(PPh_3)_n$ was examined with various MCN (M=K, Na)-dipolar aprotic solvent systems by four procedures. Under certain reaction conditions, 3-bromopyridine and several heteroaromatic halides were cyanated to give the corresponding nitriles in fair to good yields. Noticeable differences in reactivity among 3-bromopyridine, 3-bromofuran, 3-bromothiophene, and bromobenzene were observed.

Previously, the authors investigated the cyanation of aromatic (benzenoid) halides catalyzed by $Ni(PPh_3)_n$ which was generated in situ from $NiBr_2(PPh_3)_2$–Zn–PPh_3.[1)] As a noteworthy result, it was found that the cyanation proceeds smoothly by a simple procedure of mixing the reactants with the catalyst system without pretreatment when certain MCN (M=K, Na)-dipolar aprotic solvent systems with low cyanide solubilities are used. However, 3-bromopyridine, examined as a representative heteroaromatic halide, gave the nitrile in a low yield by the simple procedure described.[1)] Concerning such a catalytic reaction of heteroaromatic halides with MCN, the cyanation of bromothiophenes catalyzed by $NiClAr(PPh_3)_2$ has been recently reported,[3)] besides that of chloropyrazines by $Pd(PPh_3)_4$.[4,5)] In this paper, we investigate the cyanation of heteroaromatic halides catalyzed by Ni(0) phosphine complexes, which are generated in situ from $NiBr_2(PPh_3)_2$–Zn–PPh_3, to extend the scope of the cyanation of aromatic halides by this method (Chart 1).

Experimental

Materials. All the solvents were purified by the ordinary methods. Dibromobis(triphenylphosphine)nickel[6)] and the two halides, 3-bromothiophene[7)] and 2-chloropyrimidine,[8)] were prepared according to the literature methods. The other chemicals were commercially available and were used without further purification.

Procedures. Four procedures were examined for the cyanation of 3-bromopyridine and compared. A typical example of each is described below.

Procedure A: A 30 cm^3 flask was charged with $NiBr_2(PPh_3)_2$ (740 mg, 1.0 mmol), Zn powder (196 mg, 3.0 mmol), PPh_3 (520 mg, 2.0 mmol), and KCN (2.15 g, 33 mmol; fine powder). This mixture was degassed by evacuation and flushed with nitrogen, and a solution of 3-bromopyridine (4.74 g, 30 mmol) and 2-methylnaphthalene (about 0.2 g, GC internal standard) in HMPA (8 cm^3) was added by syringe while stirring. The reaction mixture was kept at 60 °C for 16 h. Small aliquots of the mixture were withdrawn, diluted with a small amount of CH_2Cl_2, and, after bubbling air, subjected to GC analysis.

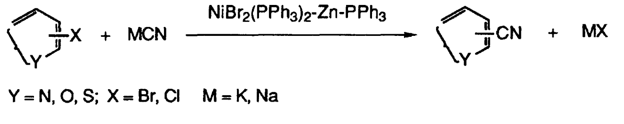

Chart 1.

Procedure A′: The catalyst components and KCN were placed in a flask. After replacing the air with nitrogen, HMPA was added by syringe while stirring. The mixture was heated at 60 °C for 30 min, and then 3-bromopyridine was added. The reaction mixture was further heated at 60 °C for 16 h.

Procedure B: Only the catalyst components were placed in a flask whose side arm was connected, by means of ground-glass joint, to a KCN container. After replacing the air with nitrogen, HMPA was added by syringe. The mixture was heated at 60 °C for 30 min with stirring, and then 3-bromopyridine was added. After continued heating for 30 min, KCN was added from the KCN container, and the reaction mixture was further heated at 60 °C for 16 h.

Procedure C: This procedure was the same as Procedure B except that the order of the addition of 3-bromopyridine and KCN was reversed.

Analysis. The gas chromatographic analyses were made with He carrier gas using a 3-m 20% PEG-20M+5% KOH column. All products, except 3-cyanofuran, were identified by comparison with authentic samples.

Isolation of Nitriles. The isolation of two nitriles will be exemplified.

3-Cyanopyridine: The resulting mixture of Run 17 (Table 1) was centrifuged after bubbling air. The solution was concentrated and distilled under reduced pressure to give 5.31 g (85%) of 3-cyanopyridine: Bp 66—68 °C/5 mmHg (1 mmHg=133.322 Pa); mp 50—51 °C; MS *m*/*z* 104 (M^+).

3-Cyanofuran: The reaction mixture from 3-bromofuran (Table 2) was centrifuged after bubbling air. The solution was distilled under reduced pressure to give 2.23 g (80%) of 3-cyanofuran:[9)] Bp 63—65 °C/35 mmHg; mp 24—26 °C; IR (neat) 2230 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ=6.64 (1H, m), 7.51 (1H, m), 7.96 (1H, m).

Results and Discussion

Cyanation of 3-Bromopyridine. The cyanation with MCN (M=K, Na) of 3-bromopyridine catalyzed by $Ni(PPh_3)_n$ which was generated in situ from $NiBr_2(PPh_3)_2$–Zn–PPh_3 (Ni : Zn : P=1 : 3 : 2 molar ratio), was examined at 60 °C with various MCN-dipolar aprotic solvent systems by means of four procedures:

Table 1. Cyanation of 3-Bromopyridine

Run	Solvent	MCN (Solubility /mmol dm^{-3})b)		Procedurea)	Conversion %	Yield %
1	HMPA	KCN	(1.5)	A	74	68
2	HMPA	KCN	(1.5)	B	100	92
3	HMPA	KCN	(1.5)	A′	100	93(88)g)
4	MeCN	KCN	(1.9)	A	97	69
5	MeCN	KCN	(1.9)	A′	100	88
6	Acetone	NaCN	(0.9)	A′c)	100	90
7	TMUd)	KCN	(2.1)	A′	100	94
8	THF	KCN	(2.4)	A′	19	11
9	MeCN	NaCN	(4.4)	A′	100	86
10	Sulfolane	KCN	(8.1)	A′	73	61
11	DMACe)	KCN	(10.8)	A′	100	90
12	Sulfolane	NaCN	(15.0)	A′	100	90
13	DMF	KCN	(15.0)	A′	3	1
14	DMF	KCN	(15.0)	C	100	87
15	DMACe)	NaCN	(123)	A′	4	0
16	HMPA	NaCN	(461)	B	5	3
17	MeCN	KCN	(1.9)	Cf)	100	92(85)g)

a) See Experimental section. NiBr$_2$(PPh$_3$)$_2$, 1 mmol (Ni : Zn : P=1 : 3 : 2); KCN, 33 mmol; 3-Bromopyridine, 30 mmol; Solvent, 8 cm^3; Temp, 60 °C; Time, 16 h. b) Values at 60 °C except for acetone (50 °C). c) Carried out at 50 °C. d) *N,N,N′,N′*-Tetramethylurea. e) *N,N*-Dimethylacetamide. f) Carried out for 48 h at 50 °C with 60 mmol 3-bromopyridine and 66 mmol KCN in 9 cm^3 MeCN. g) Isolated yield of 3-cyanopyridine.

A (catalyst–reactant mixing without pretreatment), A′ (catalyst reduction in the presence of MCN–halide addition), B (catalyst reduction–halide addition–cyanide addition), and C (catalyst reduction–cyanide addition–halide addition) (see Experimental section for further details). The results are shown, together with the solubilities of MCN, in Table 1.

Our attention is first focused on the results obtained by the three procedures A, A′, and B using the KCN–HMPA and KCN–MeCN systems with desirable low cyanide solubilities (Runs 1—5). By Procedure A, which is the most convenient of the four procedures, 3-bromopyridine was cyanated slowly compared with chlorobenzene and bromobenzene and gave 3-cyanopyridine in lower yields of ca. 69% than expected (Runs 1 and 4). In contrast with Procedure A, Procedure B, though being the most tedious of the procedures attempted, gave a good yields of 92% (Run 2). Judging from the results by both procedures, it may be presumed that 3-bromopyridine have an inhibitory action on the reduction of Ni(II) to Ni(0). So, Procedure A′, in which 3-bromopyridine only was added later, was tested because it is more convenient than Procedure B. Consequently, good yields of 93% with KCN–HMPA (Run 3) and 88% with KCN–MeCN (Run 5) were obtained. Thus, the results of Runs 1—5 reveal that with the above two systems, Procedure A′ is not only preferable to Procedure A, but comparable to Procedure B. As to the by-product of reaction, 3,3′-bipyridyl and pyridine were generally observed in appreciable amounts, for example, 7 and 1% yields respectively for Run 5.

Next, the versatility of Procedure A′ will be appreciated by reference to the results obtained by the use of other MCN–solvent systems (below Run 6). By the procedure, most of the systems with lower cyanide solubilities than about 15 mmol dm^{-3} gave fair to good results (61—94%), in contrast to the ones with higher solubilities which scarcely allowed the cyanation to proceed. In the case of the systems with high solubilities, the bromine atom of NiBr$_2$(PPh$_3$)$_2$ would be preferentially replaced by a cyano group to give no reducible cyanonickel(II) complexes, NiBr$_{2-n}$(CN)$_n$(PPh$_3$)$_2$, as discussed in our previous paper.1) THF, which has a comparatively low dipole moment, was a poor solvent, as illustrated by KCN–THF system with a low cyanide solubility (Run 8). With the KCN–DMF system, which was unfavorable for Procedure A′ (Run 13), the cyanation proceeded fairly smoothly when Procedure C was applied (Run 14). With the NaCN–HMPA system, however, 3-bromopyridine was not cyanated also by Procedure B (Run 16) in contrast with chlorobenzene.1) By the way, the cyanation was completed also at a high halide/Ni ratio of 60 when the reaction was carried out for 48 h at 50 °C by Procedure C with the KCN–MeCN system (Run 17).

Cyanation of Various Heteroaromatic Halides. The cyanation of various heteroaromatic halides was examined by Procedure A′ using the MCN–solvent systems with low cyanide solubilities (Table 2). 3-Chloropyridine was less reactive than 3-bromopyridine, but was cyanated to give a 78% yield of 3-cyanopyridine. However, 2-bromopyridine, although known to be

Table 2. Cyanation of Various Heteroaromatic Halides[a)]

Halide	Solvent	Conversion %	Yield %
3-Bromopyridine	HMPA	100	93
3-Bromopyridine	TMU	100	94
3-Chloropyridine	TMU	88	78
2-Bromopyridine	HMPA	7	0
3-Bromoquinoline	TMU	100	99
2-Chloropyrimidine	TMU	11	0
3-Bromofuran	HMPA	100	88(80)[b)]
3-Bromothiophene	HMPA	100	89
2-Bromothiophene	HMPA	64	42
2-Chlorothiophene	TMU	81	69

a) Carried out by Procedure A′. $NiBr_2(PPh_3)_2$, 1 mmol (Ni : Zn : P=1 : 3 : 2); Halide, 30 mmol; KCN, 33 mmol; Solvent, 8 cm^3; Temp, 60 °C; Time, 16 h. b) Isolated yield of 3-cyanofuran.

more reactive than does 3-bromopyridine in usual nucleophilic substitution,[10,11)] hardly reacted in contrast with 3-bromopyridine. This may be due to the fact that a 2-pyridylnickel(II) complex, which is formed by oxidative addition of 2-chloropyridine to $Ni(PPh_3)_4$, are stable compared to the corresponding 3-pyridylnickel(II) complex.[12)] With 3-bromoquinoline, 3-cyanoquinoline was obtained in a high yield of 99%. 2-Chloropyrimidine hardly reacted similarly to 2-bromopyridine. Both 3-bromofuran and 3-bromothiophene gave the corresponding nitriles in good yields of 88 and 89% respectively. In contrast with 2-bromopyridine, 2-bromo- and 2-chlorothiophene underwent the cyanation fairly.

Relative Reactivity of Several Heteroaromatic Halides. The cyanation of 3-bromopyridine, 3-bromofuran, 3-bromothiophene, and bromobenzene was carried out at 60 °C with the KCN–HMPA system by Procedure A′ to determine their relative reactivity. The decreasing order of reactivity was as follows: 3-bromofuran (nitrile yield at 2 h, 88%)>3-bromobenzene (55%)>3-bromothiophene (27%)>3-bromopyridine (13%). On the other hand, equimolar amounts (each 15 mmol) of two halides were mixed and allowed to react to compare their reactivity in competitive reaction. As the results, a different order: 3-bromopyridine>3-bromothiophene>3-bromofuran>bromobenzene was observed. With the competitive reaction of 3-bromopyridine and bromobenzene, bromobenzene began to react when about half the amount of 3-bromopyridine was consumed. In view of the above results, it can be presumed that with the individual reaction, 3-bromopyridine strongly coordinates to a reaction intermediate, bromo(3-pyridyl)nickel(II) complex, to retard the replacement of its bromine atom by cyano group and that with the competitive reaction, 3-bromopyridine preferentially coordinates to $Ni(PPh_3)_n$ to inhibit the oxidative addition of the other halide to the nickel(0) complex.

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