Palladium catalyzed cyanation of *o*-dichloroarenes with potassium hexacyanoferrate(II)

E. A. Savicheva and V. P. Boyarskiy*

Department of Chemistry, Saint Petersburg State University, 26 Universitetsky prosp., 198504 Staryi Petergof, Russian Federation. Fax: +7 (812) 428 6939. E-mail: vadimpb@yahoo.com

Cyanation of *o*-dichloroarenes with potassium hexacyanoferrate(II) catalyzed by $Pd(OAc)_2/PPh_3$ system gave the corresponding phthalodinitriles in moderate yields. The method of competitive reactions revealed that activation rate of chloroarenes by Pd-catalyst increased in the presence of the electron-withdrawing groups in the arene core.

Key words: catalysis, Pd-complexes, cyanation, phthalodinitriles, the method of competitive reactions.

Arvl cvanides (benzonitriles) are widely used in drug manufacturing, agrochemical industry, and as dyes and their precursors.¹ These compounds are also important building blocks in organic chemistry and can easily be transformed into diverse functionally substituted arenes.² Numerous synthetic strategies to access aryl nitriles from arenecarboxylic acid derivatives,³ aromatic aldehydes⁴ and amines,^{5,6} alkyl arenes,⁷ aryl sulfonic acids,^{8,9} and aryl halides^{10–13} have been developed. Aryl halides are apparently the most versatile and affordable starting materials for aryl cyanides allowing direct displacement of the halogen atom by the nitrile group. It is known that the $C(sp^2)$ —Hal bond is low reactive, therefore fairly harsh conditions are required for the activation of these substrates by common methods. Palladium-catalyzed cyanation of aryl halides^{14,15} introduced in the 1970s makes this approach promising. Cyanation of aryl chlorides,^{15–17} which are the most easy available compounds, is particularly attractive and at the same time particularly difficult to accomplish.

One of the severe drawbacks of cyanation is the use of highly poisonous metal cyanides as the cyanide ion sources. Therefore, palladium catalyzed cyanation of aryl halides employing cheap and non-toxic potassium hexa-cyanoferrate(II), which was first developed in 2004,¹⁸ immediately attracted great attention. In less than 10 years, approximately a dozen papers devoted to the synthetic application of this approach for the cyanation of aryl chlorides were published.^{19–27} Some of these papers^{19–22} described microwave-accelerated reactions; the other publications are concentrated on the use of expensive and complicated ligands.^{23–26}

The data on the application of this method for cyanation of polychloroarenes are virtually absent.²⁸ Cyanation of *ortho*-dichloro-substituted arenes to give *o*-arenedicarbonitriles (phthalodinitriles) is of considerable interest. The latter, for instance, are important intermediates for the synthesis of phthalocyanines²⁹ and organic light-emitting materials.^{30,31}

The present work presents the study of palladium-catalyzed cyanation of dichloroarenes using potassium hexacyanoferrate(II) as a source of the nitrile group with the aim to access phthalodinitriles.

Results and Discussion

For cyanation of 1,2-dichlorobenzene (1a), 2,3-dichlorobiphenyl (1b), and 3,4-dichlorobiphenyl (1c), we employed conditions used previously for Pd-catalyzed cyanation of monochlorobenzenes.²⁷ These conditions (*e.g.*, atmospheric pressure and the use of triphenylphosphine as cheap and affordable phosphine ligand) were chosen taking in account potent practical application. The results obtained are summarized in Table 1.

These data indicated that cyanation of dichloroarenes (similar to cyanation of monochloroarenes²⁷) requires relatively severe conditions. The attempts to use the milder reaction conditions (lower reaction temperature, various solvents, and different reaction times) failed. Hence, in contrary to our expectations, introduction of an additional chlorine atom in the molecule does not increase considerably the reaction rate. Regardless of this issue, complete conversion of aryl halide was achieved after prolonged reaction time (Scheme 1).

It is of note that preparative yields of dinitrile were significantly lower in all cases. Gas chromatography/ mass spectrometry revealed the presence of side products resulting from reduction, which were formed upon cyana-

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Substrate	Solvent	<i>T</i> /°C	τ/h	Conver-	Y (%) ^a
				sion $(\%)^{b}$	
1a	DMF	140	6	30	17 ^b
1a	DMF	140	24	62	38 ^b
1a	DMF	140	72	>98	55^{b}
1b	DMF	140	24	46	25 ^c
1c	DMF	140	6	27	15 ^c
1c	DMF	140	24	>98	60 ^c
					$(0^{d,e})$
1c	DMF	100	24	0	0
1c	Acetonitrile	85	24	0	0
1c	Ethanol	80	24	0	0
1c	Dioxane : water (1 : 1)	100	24	0	0

Table 1. Cyanation of *o*-dichloroarenes with potassium hexacyanoferrate(II) catalyzed by $Pd(OAc)_2 - PPh_3$

^{*a*} Y is the yield of dinitrile.

^b Based on GC analysis.

^c Preparative yield.

^{*d*} Without $Pd(OAc)_2$.

^e Without PPh₃.

Scheme 1



R = H(a), 3-Ph(b), 4-Ph(c)

1c

tion of **1c** at complete conversion (Scheme 2). Amounts of the side products were determined by gas chromato-graphy.

It should be emphasized that in all cases, products of bis-cyanation of the corresponding dichloroarenes were formed. Therefore, even on the initial stage of the reaction (at conversions lower 50%), dinitrile was a major reaction product, *i.e.*, the cyanation involved both the chlorine atoms at once.

This fact can be explained by the noticeably higher reactivity of the intermediate *o*-chlorobenzonitrile towards

activation by Pd-complex in respect of the starting dichloroarene. However, at the first glance, this explanation contradicts our observation that the reaction rate of di- and monochlorides are nearly equal. To approach this question, we studied the effect of the substituent on the activation rate for a series of substituted chlorobenzenes. Since we were interested in the reactivity of aryl chloride towards the catalyst, the method of competitive reactions was used and the relative rate constants were calculated from a decrease in the content of the starting substrates. The data obtained are given in Table 2.

It is obvious that the presence of electron-withdrawing substituents accelerates the reaction. Estimation of a reaction parameter value $\rho = 2.3\pm0.06$ indicated that the aryl halide activation is significantly sensitive to the electronic effect of the substituents. This fact apparently explains why intermediate *o*-chlorobenzonitriles were not detected in cyanation of *o*-dichloroarenes, *viz.*, the nitrile group in the *ortho* position being the strong electron-with-drawing substituent accelerates cyanation of the half-product by several times with respect to the starting *o*-dichloroarene (see Table 2). It is worth of noticing that the small size of the nitrile group introduced should also facilitate the second cyanation.

1,2-Dichlorobenzene (1a) is turned to be 6 times more reactive than chlorobenzene (8) (see Table 2, based on the number of reactive centers in a molecule). At the same time, the cyanation conditions for compounds bearing the second chlorine atom are not much milder. This suggest-

Table 2. Relative reactivity of substituted chloroarenes in cyanation with potassium hexacyanoferrate(π) catalyzed by Pd(OAc)₂—PPh₃

Substrate	k _{rel}
4-Chloroanisole (6)	0.23
4-Chlorotoluene (7)	0.44
Chlorobenzene (8)	1.0
1,4-Dichlorobenzene (9)	2.9*
1,3-Dichlorobenzene (10)	7.6*
4-Chlorobenzonitrile (11)	35
1,2-Dichlorobenzene (1a)	3.2*
2-Chlorobenzonitrile (12)	43

4 (12%)*

* Statistically corrected.

Scheme 2

3 (15%)*

i. K₄[Fe(CN)₆], [Pd], PPh₃, Na₂CO₃, DMF, 140 °C, 24 h. * Mixture of isomers in a 1 : 1 ratio.

2c (60%)

Scheme 3



ed that the harsh cyanation conditions is due to the transmetalation stage but not to the aryl halide activation stage as for the majority of cross-coupling reactions (Scheme 3).³² The transmetalation is involved destruction of a very stable hexacyanoferrate(II) anion, which obviously required severe conditions.

In summary, we found that the electron-withdrawing substituents in the aromatic ring accelerate the aryl halide activation in Pd-catalyzed cyanation ($\rho = 2.3 \pm 0.06$). It was shown that phthalodinitriles can be synthesized in moderate yields from *o*-dichloroarenes using non-toxic potassium hexacyanoferrate(II) as the source of the nitrile group. This approach is promising for practical application.

Experimental

¹H and ¹³C NMR spectra were run on a Bruker DPX 300 instrument at working frequencies of 300.13 (1H) and 75.03 MHz (¹³C) in CDCl₃. Gas chromatography/mass spectrometry (GC/MS) was performed on a Shimadzu QP-5000 instrument (EI (70 eV), SPB-5 column, length of 6 m, diameter of 0.25 mm, film of 0.25 µm). IR spectra were obtained on a Shimadzu FTIR-8400S instrument in KBr pellets in the range of 400-4000 cm⁻¹. Gas chromatography was performed on a Chrom-5 chromatograph (flame ionization detector, glass column 3 mm in diameter and 2500 mm in length, stationary phase either SE-30 (10%) or OV-225 (5%) on Chromaton N-Super (80-100 mesh)). Inorganic reagents (pure for analysis grade) were used as purchased. The solvents were purified by standard procedures. Substituted chlorobenzenes, triphenylphosphine, 1,2,4,5-tetramethylbenzene, naphthalene, and acenaphthene (pure for analysis grade) were used as purchased. Dichlorobiphenyls were synthesized by the known procedures, ^{33,34} purity of the products were monitored by GC and NMR¹H.

Cyanation of *o*-dichloroarenes (general procedure). The Schlenk flask was charged with dichloroarene (2 mmol), potassium hexacyanoferrate(11) trihydrate (1.8 g, 4.2 mmol), acenaphthene (0.077 g, 0.5 mmol; the GC internal standard), sodium carbonate (1.1 g, 10 mmol), and DMF (10 mL). The mixture was magnetically stirred and flushed with argon for 0.5 h. Then the flushed with argon solution of palladium acetate (0.020 g, 0.09 mmol) and triphenylphosphine (0.080 g, 0.3 mmol) in DMF (2 mL) was added. The mixture was heated at 140 ± 2 °C (bath temperature) for specified time (see Table 1) under argon. After completion of the reaction, the mixture was cooled to ambient temperature and poured into a mixture of hexane—dichloromethane (9 : 1, 20 mL) and water (20 mL). The organic layer was washed with water, brine, and dried with Na_2SO_4 . The aliquot of the organic phase was analyzed by GC. The solvent was removed *in vacuo*, the resulted residue was analyzed by NMR ¹H.

The products were purified by column chromatography (silica gel (Merck, 0.04-0.063 mm), elution with hexane—ethyl acetate, 7 : 1).

In the case of cyanation of 1,2-dichlorobenzene (1a), the reaction products were identified by GC (by comparing the retention times of the analytes with that of 2-chlorobenzonitrile and phthalodinitrile) and NMR spectroscopy. Dinitriles 2b and 2c were identified by melting points, IR spectra, and ¹H and ¹³C NMR spectra. The side products formed in cyanation of compound 1c were identified by GC/MS and, in several cases, by GC (by comparing the retention times of the analytes with that of biphenyl (5), 3-chlorobiphenyl (4a), and 4-chlorobiphenyl (4b)).

Biphenyl-2,3-dicarbonitrile (2b)^{28,35}. Yield 103 mg (25%). M.p. 136–137 °C (*cf.* Ref. 34: 137 °C). IR, v/cm⁻¹: 3064, 2926, 2854 (C_{Ar} –H); 2232 (C=N); 1730, 1581, 1452 (C_{arom} – C_{arom}); 808, 761, 699 (C_{arom} – C_{arom} –H). ¹H NMR (CDCl₃), δ : 7.53–7.57 (m, 5 H, Ph); 7.78–7.82 (m, 3 H, C(4)H, C(5)H, C(6)H). ¹³C NMR (CDCl₃), δ : 114.9; 115.5; 116.2; 117.5; 129.1; 129.8; 130.3; 132.5; 133.3; 134.8; 136.9; 147.9.

Biphenyl-3,4-dicarbonitrile (2c)^{28,36}. Yield 244 mg (60%). M.p. 158–159 °C (*cf.* Ref. 35: 158 °C). IR, v/cm⁻¹: 3070, 2924, 2848 (C_{arom} -H); 2233 (C=N); 1714, 1595, 1481, 1391 (C_{arom} - C_{arom}); 1273, 913, 850, 766, 701 (C_{arom} - C_{arom} -H). ¹H NMR (CDCl₃), &: 7.53–7.63 (m, 5 H, Ph); 7.88–7.96 (m, 2 H, C(5)H, C(6)H); 8.03 (s, 1 H, C(2)H). ¹³C NMR (CDCl₃), &: 114.4; 115.8; 115.9; 116.9; 127.6; 129.9; 130.2; 131.8; 132.4; 134.4; 137.4; 146.9. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 204 [M]⁺ (100), 176 [M – HCN]⁺ (11), 102 (8), 88 (10), 75 (9).

Biphenyl-3-carbonitrile and biphenyl-4-carbonitrile (3). The GC chromatogram contains two neighboring peaks, which were not attributed to a particular product. MS of compound with lower retention time (EI, 70 eV), m/z (I_{rel} (%)): 179 [M]⁺ (100), 151 [M - HCN - H]⁺ (15), 89 (10), 76 (30). MS of compound with higher retention time (EI, 70 eV), m/z (I_{rel} (%)): 179 [M]⁺ (100), 151 [M - HCN - H]⁺ (13), 89 (12), 76 (25).

3-Chlorobiphenhyl and 4-chlorobiphenyl (4). The GC chromatogram contains two neighboring peaks, which were not attributed to a particular product. MS of compound with lower retention time (EI, 70 eV), m/z (I_{rel} (%)): 188 [M]⁺ (100), 152 [M - HCl]⁺ (50), 76 (35). MS of compound with higher retention time (EI, 70 eV), m/z (I_{rel} (%)): 188 [M]⁺ (100), 152 [M - HCl]⁺ (52), 76 (40). Characteristic molecular ion isotope pattern revealed the presence of one chlorine atom in the molecules of both compounds.

Biphenyl (5). MS (EI, 70 eV), m/z (I_{rel} (%)): 154 [M]⁺ (15), 153 [M - H]⁺ (100), 76 (53).

Gas chromatography (with calibration coefficients) was used for quantitative analysis of the reaction mixtures. The relative reactivity was determined by the method of competitive reactions; calculations were based on the consumption of the starting substrates.

Determination of relative rates of cyanation (general procedure). The 25 mL Schlenk flask was charged with a pair of studied aryl halides (2 mmol of each), the GC internal standard (1,2,4,5-tetramethylbenzene or naphthalene), potassium hexacyanoferrate(II) trihydrate (1.8 g, 4.2 mmol), sodium carbonate (1.1 g, 10 mmol), and DMF (10 mL). The mixture was stirred and aliquot for the GC analysis was taken. Then the mixture was magnetically stirred and flushed with argon for 0.5 h. To the mixture, the flushed with argon solution of palladium acetate (0.020 g, 0.09 mmol) and triphenylphosphine (0.080 g, 0.3 mmol)in DMF (2 mL) was added. The mixture was heated at 140 ± 2 °C (bath temperature) for 10–12 h (conversion of the starting material was 30-70%) with stirring. After completion of the reaction, an aliquot (0.5 mL) was taken, diluted with water (2 mL), and unreacted starting compounds and internal standard were extracted with hexane (2×2 mL). The organic layer was separated, washed with brine (2 mL), and analyzed by GC.

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