Palladium-catalyzed cyanation reaction of aryl halides using K$_4$[Fe(CN)$_6$] as non-toxic source of cyanide under microwave irradiation

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An efficient method for preparation of aryl nitriles – using [Pd{C$_6$H$_2$(CH$_2$CH$_2$ NH$_2$)-(OMe)$_2$,3,4} (μ-Br)]$_2$ complex as an efficient catalyst and K$_4$[Fe(CN)$_6$] as a green cyanide source – from aryl bromides, aryl iodides and aryl chlorides under microwave irradiation has been reported. This complex has been demonstrated to be an active and efficient catalyst for this reaction. Using a catalytic amount of this synthesized palladium complex in DMF at 130 °C led to production of the cyanoarenes in excellent yields in short reaction times. Copyright © 2010 John Wiley & Sons, Ltd.

Introduction

The substituted benzonitriles represent important materials for the preparation of different commercial compounds, including dyes, herbicides, pesticides, natural products and pigments.[1–7] The cyanide functional group may be converted to other functional groups such as carboxylic acids, amides, amines, aldehydes and ketones;[8,9] therefore these compounds play significant roles in modern organic synthesis. Furthermore in medical chemistry, nitriles are very valuable, since they can be transformed to various biologically active molecules such as terazoles, oxazoles and triazoles.[10] Most often aryl nitriles are prepared from aryl halides using stoichiometric amounts of CuCN by Rosenmund–Von Braun reaction.[11] These compounds have been produced industrially via amoxidation of the corresponding toluene derivatives[12] or from aniline via diazotization followed by Sandmeyer reaction.[13,14]

The harsh reaction conditions and the use of stoichiometric amounts of copper (I) cyanide leads to the production of equimolar amounts of heavy metal wastes, especially in the case of industrial large-scale synthesis, which is a major drawback of these methods.[4,15] Since the mid 1970s the synthesis of aryl nitriles through the cyanation of aryl halides, using transition metal catalysts and employing inexpensive cyanide salts such as KCN,[16,17] NaCN,[18,19] Me$_3$SiCN[20–22] and Zn(CN)$_2$, has become more popular.[23–27]

The toxicity of KCN and NaCN, the sensitivity of Me$_3$SiCN to moisture, the release of HCN and production of heavy metal waste, in the case of Zn(CN)$_2$, significantly limit the applications of these reagents. These difficulties have been overcome using inexpensive and non-toxic potassium hexacyanoferrate (II), K$_4$[Fe(CN)$_6$], as an efficient source of cyanide.[28–31]

In comparison to traditional Rosenmud–Von Braun nitrile synthesis, nickel[32]- and palladium[33]-catalyzed methods have been considered milder procedures; however these transition metal-catalyzed reactions require several hours.[16] The use of microwave irradiation in transition metal-catalyzed reactions, which are usually time consuming, has assumed great importance due to the reduction of the reaction times to minutes and the decrease of unwanted byproducts from thermal side-reactions.[34] Microwave-mediated chemistry is often carried out in microwave-active polar solvents such as N-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO) and N,N-dimethylformamide (DMF). The high dipole moment of these solvents means that they can be heated very quickly using microwave irradiation. Alterman and Hallberg have shown a pattern for using microwave heating to raise the rate of cyanation of different bromides with the previously utilized palladium–tetrakistriphenylphosphine.[35]

In continuation of our investigation of the new methods in organic reactions,[36–40] herein we have employed orthopalladate complex [Pd{C$_6$H$_2$(CH$_2$CH$_2$ NH$_2$)-(OMe)$_2$,3,4} (μ-Br)]$_2$ for cyanation reactions of various aryl halides under microwave irradiation using K$_4$[Fe(CN)$_6$] as a cyanide source.

Results and Discussion

In the previous work,[36] we synthesized complex **A** and reported its application in the Heck reaction successfully. The main advantage of this method is using microwave irradiation as a reaction accelerator by investigating the synergy of microwave heating with microwave active solvents and K$_4$[Fe(CN)$_6$] for cyanation of several aryl halides (Scheme 1).

The application of complex **A** as a catalyst for the cyanation reaction was examined by optimizing both base and solvent under microwave conditions [Table 1]. We treated 1-bromonaphtalene with K$_4$[Fe(CN)$_6$] in the presence of different bases and solvents (Table 1) and we found that K$_2$CO$_3$ is the best base for this

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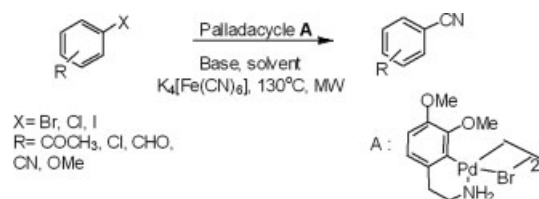
Scheme 1. Cyanation of aryl halides using $K_4[Fe(CN)_6]$ under microwave irradiation.

Table 1. Optimization of reaction condition in cyanation reaction of bromonaphtalene with $K_4[Fe(CN)_6]$

Entry	Base	Catalyst, mol%	Solvent	Temperature (°C)	Time (min)	Conversion (%)
1	Et$_3$N	0.4	NMP	130	20	0
2	Et$_3$N	1	NMP	130	20	Trace
3	Na$_2$CO$_3$	0.4	NMP	130	20	40
4	Na$_2$CO$_3$	1	NMP	130	20	50
5	K$_2$CO$_3$	0.4	NMP	130	20	50
6	K$_2$CO$_3$	1	NMP	130	30	80
7	K$_2$CO$_3$	0.4	DMF	130	11	60
8	K$_2$CO$_3$	1	DMF	130	11	90
9	K$_2$CO$_3$	0.4	DMAC	120	25	50
10	K$_2$CO$_3$	0.4	CH$_3$CN	80	30	0
11	K$_2$CO$_3$	0.4	Toluene	110	30	0

Table 2. Optimization of catalyst concentration in cyanation reaction of bromonaphtalene with $K_4[Fe(CN)_6]$

Entry	Base	Catalyst, mol%	Solvent	Time (min)	Temprature (°C)	Conversion (%)
1	K$_2$CO$_3$	0	DMF	20	130	0
2	K$_2$CO$_3$	0.1	DMF	20	130	20
3	K$_2$CO$_3$	0.2	DMF	20	130	40
4	K$_2$CO$_3$	0.5	DMF	11	130	90
5	K$_2$CO$_3$	0.8	DMF	13	130	90

reaction, while Et$_3$N is not efficient and Na$_2$CO$_3$ produced only 50% aryl cyanide. The microwave-inactive solvents such as toluene and acetonitrile were not suitable (Table 1, entries 10 and 11). Therefore we tried high boiling point and microwave-active polar solvents (Table 1, entries 1–9) and found that inexpensive and readily available DMF showed the best results (Table 1, entries 7 and 8). Also, we optimized the catalyst concentration (Table 2) and 0.5 mol% gave the best yields.

Using 0.5% palladacycle and a 1:1 molar ratio of 1-bromo-naphtalene to $K_4[Fe(CN)_6]$ conversion to the corresponding cyanide occurred in 90% yield. As each mol of $K_4[Fe(CN)_6]$ contains six-fold cyanide ions, decreasing the ratio of $K_4[Fe(CN)_6]$ to aryl halide to 0.2 : 1 did not decrease the reaction conversion.

We employed the optimal reaction conditions (aryl halide, 1 mmol; $K_4[Fe(CN)_6]$, 0.2 mmol; K_2CO_3, 1 mmol; and DMF as the best reaction media) for cyanation of different aryl halides and the results are demonstrated in Table 3. We found that different aryl halides such as aryl bromides (Table 3, entries 3–9), aryl iodides (Table 3, entries 1 and 2), were converted to the corresponding aryl cyanide under these conditions. The

Table 3. Cyanation reaction of aryl halides with $K_4[Fe(CN)_6]$ using catalyst A[a]

Entry	Ar−X	Product	Time (min)	Yield (%)[b]
1			16	93
2			20	68
3			8	90
4			11	85
5			25	73
6			20	94
7			10	95
8			16	93
9			20	57
10			20	Trace
11			20	0
12			15	50
13			25	24
14			20	58

[a] Reaction conditions: aryl bromide; 1 mmol, $K_4[Fe(CN)_6]\cdot 3H_2O$; 0.22 mmol, K_2CO_3; 1 mmol, catalyst A; 0.005 mmol, temperature; 130 °C.
[b] Isolated yield.

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aryl bromides with electron-withdrawing groups (Table 3, entries 6–8) were cyanated efficiently. However, 3-bromoacetophenone transformed to cyano derivative in moderated yield (Table 3, entry 9) and 2-bromoacetophenone remained unchanged after 20 min (Table 3, entry 10); also, electron neutral aryl bromides (Table 3, entries 3–5) were changed to desired cyanoarenes, but 2-bromopyridine was not converted to 2-cyanopyridine (Table 3, entry 11). The chemoselectivity of this method was examined by cyanation of 1-bromo-3-chlorobenzene to 1-chloro-3-cyanobenzene (Table 3, entry 12); however the aryl chlorides were converted to the cyanoarenes in low to moderate yields (Table 3, entries 13 and 14).

Conclusion

In this investigation, we have developed a fast and efficient method for the conversion of aryl halides to cyanoarenes using non-toxic potassium hexacyanoferrate(II) instead of toxic alkali cyanides as a green chemistry method using microwave irradiation with high yields and short reaction times. Employing a catalytic amount of palladacycle complex converted different aryl bromides and iodides to the corresponding benzonitriles in high yields, but aryl chlorides were changed to benzonitriles with moderate yields. In comparison to conventional thermal conditions, these reactions were completed in shorter reaction times (8–25 min).

Experimental

General

All melting points were taken on a Gallenkamp melting apparatus and are uncorrected. ^{1}H-NMR spectra were recorded using 500 and 400 MHz in CDCl$_3$ solutions at room temperature (TMS was used as an internal standard) on a Bruker, Avance 500 instrument (Rheinstetten, Germany) and Varian 400 NMR. FT-IR spectra were recorded on a spectrophotometer (Jasco-680, Japan). We used a Milestone microwave (Microwave Labstation for synthesis). Homoveratrylamine, palladium acetate, all of the aryl halides and K$_4$[Fe(CN)$_6$] were purchased from Merck and Aldrich and used as received.

Typical Procedure for the Cyanation Reaction of Aryl Halides with K$_4$[Fe(CN)$_6$]

In a 10 ml round-bottomed flask were placed aryl halide (1.0 mmol), potassium hexacyanoferrate(II) (0.2 mmol), potassium carbonate (1.0 mmol) and palladacycle **A** (which was synthesized as in a previous work[36]), 0.5 mol%. After adding DMF (2 ml), the round-bottomed flask was equipped with a condenser and placed into the Milestone microwave. Initial microwave irradiation of 500 W was used, the temperature being ramped from room temperature to the desired temperature of 130 °C with stirring. The reaction mixture was held at this temperature until the reaction was completed (TLC, EtOAc : cyclohexane, 25 : 75) and then cooled to room temperature. The mixture was diluted with water (30 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over MgSO$_4$ and the solvents were evaporated using rotary evaporator to produce crude product. The residue was purified by silica gel column chromatography to provide the pure products (Table 3).

Naphthalene-1-carbonitrile (entry 2, Table 3)

M.p 36–38 °C;[25] found 36–39 °C. ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.19$ (d, 1H, $J = 8.5$ Hz), 8.03 (d, $J = 8.8$ Hz, 1H), 7.87 (t, $J = 8.8$ Hz, 2H), 7.55–7.68 (m, 2H), 7.47 (t, $J = 8.8$ Hz, 1H). ^{13}C NMR (400 MHz, ppm, CDCl$_3$): $\delta = 132.2, 131.8, 131.5, 131.2, 127.6, 127.5, 126.5, 124.0, 123.8, 109.2$. IR (KBr, cm^{-1}): ν 2222.

3-Chlorobenzonitrile (entry 3, Table 3)

M.p. 136–140 °C; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.96$–7.97 (m, 1H), 7.89–7.92 (m, 1H), 7.63–7.68 (m, 1H), 7.58–7.59 (m, 1H); ^{13}C NMR (400 MHz, ppm, CDCl$_3$): $\delta = 136.2, 135.6, 132.0, 130.6, 117.8, 117.4, 102.1$. IR (KBr, cm^{-1}): ν 2215.

4-Acetylbenzonitrile (entry 4, Table 3)

M.p. 57–58 °C;[25] found 59–60 °C. ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.06$ (d, 2H, $J = 8.0$ Hz), 7.79 (d, 2H, $J = 8.4$ Hz). IR (KBr, cm^{-1}): ν 2229, 1687.

4-Methoxybenzonitrile (entry 7, Table 3)

M.p. 59–60 °C;[25] found 58–60 °C; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.57$–7.60 (m, 2H), 6.94–6.97 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (400 MHz, ppm, CDCl$_3$): $\delta = 163.1, 134.2, 127.9, 115.0, 114.4, 55.8$. IR (KBr, cm^{-1}): ν 2218.

Phenantrene-9-carbonitrile (entry 9, Table 3)

M.p. 88–92 °C. ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.73$ (t, 2H, $J = 8.4$ Hz), 8.33 (d, 1H, $J = 8.4$ Hz), 8.28 (s, 1H), 7.96 (d, 1H, $J = 8$ Hz), 7.76–7.85 (m, 3H), 7.70 (t, 1H, $J = 7.6$ Hz). ^{13}C NMR (400 MHz, ppm, CDCl$_3$): $\delta = 135.9, 130.1, 129.9, 129.7, 129.4, 128.6, 128.4, 127.9, 126.2, 123.1, 123.4, 101.5$. IR (KBr, cm^{-1}): ν 2219.

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