

# **K<sub>4</sub>[Fe(CN)<sub>6</sub>] as non-toxic source of cyanide for the cyanation of aryl halides using Pd-Beta zeolite as a heterogeneous catalyst**

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**Abstract:** A new method for the synthesis of aryl nitriles has been developed by the reaction of aryl halides with K<sub>4</sub>Fe(CN)<sub>6</sub> in the presence of Pd-Beta zeolite as efficient and recyclable catalyst.

**Keywords:** Aryl nitriles, aryl halide, K<sub>4</sub>Fe(CN)<sub>6</sub>, cyanation, palladium, zeolite

## **Introduction**

They are also versatile intermediates in organic synthesis, since they not only constitute key components of a range of pharmaceuticals, agrochemicals, dyes, etc,<sup>1</sup> but can also easily be converted into other functional groups such as nitrogen-containing heterocycles, aldehydes, acids and acid derivatives.<sup>2,3</sup>

Nitriles are conventionally synthesized by reaction of aryl halides with stoichiometric amounts of CuCN,<sup>4,5</sup> the diazotization of anilines and subsequent Sandmeyer reaction,<sup>6,7</sup> the transition metal-catalyzed cyanation of aryl halides using KCN, NaCN, Me<sub>3</sub>SiCN and Zn(CN)<sub>2</sub> as cyanating agents.<sup>8-13</sup>

However, most of these synthetic methods suffer from different drawbacks such as employing expensive, moisture sensitive, toxic and hazardous reagents, use of expensive catalyst or reagents, several-step methods, long reaction times, low yields of the products that restrict their usage in practical applications. Also, CuCN and Zn(CN)<sub>2</sub> lead to heavy metal waste.

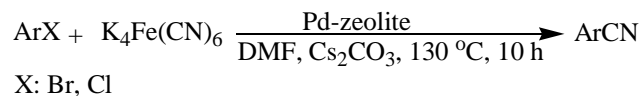
Due to safety considerations, we required a method that did not use of toxic reagents. Therefore, it is desirable to develop a more efficient and convenient method for the synthesis of aryl nitriles without the application of expensive, moisture sensitive and toxic reagents. To resolve this problem, Beller and co-workers have described a convenient synthesis of nitriles by potassium hexacyanoferrate (II),  $K_4Fe(CN)_6$ , as a non-toxic cyanide source.<sup>14,15</sup> This reagent is commercially available on ton scale and cheaper than KCN and NaCN and even used in food industry for metal precipitation.

Among various catalysts for the transition metal-catalyzed cyanation of aryl halides with  $K_4Fe(CN)_6$ , homogeneous catalysts have been widely investigated,<sup>16-19</sup> while less expensive heterogeneous catalysts received scant attention. Thus, the development of a *catalytic* synthetic method for the synthesis of nitriles still remains an active research area.

In recent years there has been a tremendous upsurge of interest in various chemical transformations performed under the heterogeneous catalysis.<sup>20-28</sup> Moreover, using inexpensive and non corrosive heterogeneous catalysts, chemical transformations occur with better efficiency, higher purity of the products, and easier workup, with evident economic and ecological advantages especially for the industrial processes. Zeolites are crystalline hydrated aluminosilicates of the earth alkalines. The application of inorganic solid acids, especially zeolites, as effective heterogeneous catalysts for organic synthesis has received considerable attention in the recent decades due to their microporosity, large surface area, thermal and chemical stability zeolites.<sup>29-32</sup> We recently published synthesis of formamides in high yields using HEU Zeolite as a natural and heterogeneous catalyst.<sup>32</sup> In spite of these interesting properties of zeolites, there are no reports on the synthesis of aryl nitriles via cyanation of aryl halides using Pd-zeolite. Among zeolites, Beta zeolite has been reported to be an efficient catalyst in a number of chemical transformations including alkylation and acylation.<sup>33,34</sup> Its activity owes to its large pore size, high Si/Al ratio, high acid strength, and thermal stability.

In continuation of our recent studies on application of nitriles, zeolites and other natural products,<sup>32,35,36</sup> we hereby report a new protocol for the preparation of aryl nitriles via

cyanation aryl halides with  $K_4Fe(CN)_6$  in the presence of Pd-Beta zeolite<sup>37</sup> as a heterogeneous catalyst.



**Scheme 1**

## Results and Discussion

In order to examine the feasibility of our rationale and find optimum conditions, we carried out the reaction of bromobenzene with  $K_4Fe(CN)_6$  in the presence of various solvents and bases using Pd-Beta zeolite (0.025 mmol Pd) under various temperature conditions. Several organic solvents such as toluene, methanol, DMF, NMP and acetonitrile were examined. According to data given in Table 1, DMF was the most efficient solvent for this reaction (Table 1, entry 5). After choosing DMF as the solvent, we examined several different bases. Our experiments showed that the base was necessary for the cyanation reaction (Table 1, entry 11). Among the selected bases,  $Cs_2CO_3$  acted as the most effective one (Table 1, entry 5). Moreover, as each mol of  $K_4Fe(CN)_6$  contains six-fold cyanide ions, the ratio of  $K_4Fe(CN)_6$  to aryl halide was chosen 0.22:1. We then used the optimal reaction conditions (aryl halide (1.0 mmol),  $K_4Fe(CN)_6$  (0.22 mmol),  $Cs_2CO_3$  (1.0 mmol) and DMF as solvent) for cyanation of different aryl halides under thermal conditions and the results are shown in Table 2.

**Table 1** Optimization of reaction conditions in cyanation reaction of bromobenzene with  $K_4Fe(CN)_6$

Entry	Base	Solvent	Temperature ( °C)	Time (h)	Yield <sup>a</sup> (%)
1	$Cs_2CO_3$	Toluene	Reflux	20	0
2	$Cs_2CO_3$	$CH_3CN$	Reflux	20	0
3	$Cs_2CO_3$	MeOH	Reflux	20	0
4	$Cs_2CO_3$	NMP	130	10	80
5	$Cs_2CO_3$	DMF	130	10	91
6	$Et_3N$	DMF	130	12	21
7	NaF	DMF	130	12	27
8	$K_2CO_3$	DMF	130	10	85
9	KOAc	DMF	130	11	79
10	$Na_2CO_3$	DMF	130	11	61
11	-	DMF	130	20	0

<sup>a</sup> Yields are after work-up.

**Table 2** Cyanation reaction of various aryl halides using  $K_4Fe(CN)_6$  in the presence of Pd-zeolite at 130 °C<sup>a</sup>

Entry	Substrate	Product	Yield <sup>b</sup> (%)	M.p. (°C)	Lit. m.p. (°C) <sup>Ref.</sup>
1	$C_6H_5I$	$C_6H_5CN$	85	Oil	Oil <sup>7</sup>
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> I	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CN	80	Oil	Oil <sup>7</sup>
3	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub> I	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub> CN	83	Oil	Oil <sup>38</sup>
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> I	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CN	84	59-61	58-60 <sup>7</sup>
5	<i>p</i> -COMeC <sub>6</sub> H <sub>4</sub> I	<i>p</i> -COMeC <sub>6</sub> H <sub>4</sub> CN	87	57-59	56-59 <sup>39</sup>
6	<i>p</i> -COOMeC <sub>6</sub> H <sub>4</sub> I	<i>p</i> -COOMeC <sub>6</sub> H <sub>4</sub> CN	87	64-66	65-67 <sup>39</sup>
7	<i>m</i> -OMe- <i>p</i> -OHC <sub>6</sub> H <sub>3</sub> I	<i>p</i> -OH- <i>m</i> -OMeC <sub>6</sub> H <sub>3</sub> CN	86	84-86	85-87 <sup>39</sup>
8	4-IC <sub>5</sub> H <sub>4</sub> N	4-CNC <sub>5</sub> H <sub>4</sub> N	79	76-78	76-79 <sup>39</sup>
9	$C_6H_5Br$	$C_6H_5CN$	85	Oil	Oil <sup>7</sup>
10	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> Br	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CN	83	59-61	58-60 <sup>7</sup>
11	<i>p</i> -COMeC <sub>6</sub> H <sub>4</sub> Br	<i>p</i> -COMeC <sub>6</sub> H <sub>4</sub> CN	82	56-58	56-59 <sup>39</sup>
12	<i>p</i> -COOMeC <sub>6</sub> H <sub>4</sub> Br	<i>p</i> -COOMeC <sub>6</sub> H <sub>4</sub> CN	89	65-67	65-67 <sup>39</sup>
13	<i>p</i> -CNC <sub>6</sub> H <sub>4</sub> Br	<i>p</i> -CNC <sub>6</sub> H <sub>4</sub> CN	90	221-225	221-225 <sup>7</sup>
14	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> I	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CN	91	110-115	110-115 <sup>38</sup>
15	1-C <sub>10</sub> H <sub>7</sub> Br	1-C <sub>10</sub> H <sub>7</sub> CN	87	36-38	36-38 <sup>38</sup>

<sup>a</sup> Reaction conditions: Pd-zeolite (0.025 mmol Pd), aryl halide (1 mmol),  $K_4Fe(CN)_6$  (0.22 mmol),  $Cs_2CO_3$  (1.0 mmol), DMF (5 mL), 130 °C, 10 h.

<sup>b</sup> Yields are after work-up.

To study the effects of the nature of the substituents on the benzene ring of the aryl halide, various aryl nitriles were synthesized from different aryl halides containing both electron-releasing and electron-withdrawing groups with  $K_4Fe(CN)_6$  in DMF in excellent yields under thermal conditions. In addition, the reactions were able to tolerate a wide range of functional groups such as ketone carbonyl, ester, methoxy, nitrile and hydroxy groups. The reactions appeared to be insensitive to the steric hindrance around the reaction site. For instance, 4-iodotoluene gave a yield of 80%, while 2-iodotoluene with a bigger steric hindrance around the reaction site also gave a high yield (Table 2, entries 2 and 3). As an example for an electron-poor nitrogen heterocycle 4-iodopyridine was cyanated in good yield (Table 2, entry 8). High selectivity was observed for 1-bromo-4-iodobenzene (Table 2, entry 14).

The products were characterized by melting points, elemental analysis (CHN), IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR. The IR spectra of the products showed one sharp absorption band in the range of 2225-2360 cm<sup>-1</sup> (CN stretching band).

In conclusion, we have developed an efficient procedure for the ligand-free cyanation of aryl iodides and aryl bromides using non-toxic  $K_4Fe(CN)_6$  as the cyanide source and Pd-Beta

zeolite as a reusable heterogeneous catalyst under thermal conditions in DMF. However, the reactions occurred on the external surface of the zeolite. This method has the advantages of high yields, elimination of toxic reagents, simple methodology and easy work-up in which the chromatographic separation is not necessary to get the pure compounds.

## Experimental

### *General*

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Products were characterized by comparison of their physical and spectral data with authentic samples. The NMR spectra were recorded in DMSO.  $^1\text{H}$  NMR spectra were recorded on a Bruker Avance DRX 250 MHz instruments. The chemical shifts ( $\delta$ ) are reported in ppm relative to the TMS as an internal standard and  $J$  values are given in Hz.  $^{13}\text{C}$  NMR spectra were recorded at 62.5 Hz. FT-IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. The elemental analysis was performed using Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel polygram SIL G/UV 254 plates. The catalyst was prepared according to the literature.<sup>37</sup>

### *Preparation of catalyst*

The catalyst was prepared according to the literature.<sup>37</sup> Zeolite-supported palladium catalyst was prepared by ion exchange of Beta zeolite (2 g) using a 0.1 M aqueous solution of  $[\text{Pd}(\text{NH}_3)_4]^{2+}$ . The solution mixture was stirred for 24 h at room temperature, filtered and washed with water until no  $\text{Cl}^-$  ion was detectable within the filtrate. Calcination at 500 °C under pure  $\text{O}_2$  (180 mL/min) of the exchanged palladium zeolite gave the pd-Beta zeolite. The palladium content was determined by the inductively coupled plasma (ICP) method, using a Perkin-Elmer 3300 DV spectroscope, after calcinations of the sample at 450 °C for 100 min in flowing oxygen. The catalyst was characterized using the powder XRD, TEM and BET.

### *General procedure for the cyanation of aryl halides with $K_4Fe(CN)_6$*

To a mixture of aryl halide (1.0 mmol),  $K_4Fe(CN)_6$  (0.22 mmol),  $Cs_2CO_3$  (1.0 mmol), Pd-zeolite (0.025 mmol Pd) and 5 mL of solvent (DMF) was placed in a Schlenk tube (25 mL), and the mixture was vigorously stirred under for 10 h at 130 °C. Upon completion, the mixture was cooled to room temperature, and diluted with ether and water. Organic layer was washed with brine, dried over  $MgSO_4$ , filtered and evaporated under reduced pressure using rotary evaporator to give the crude product. The residue was purified by recrystallization using ethanol and water. The purity of the compounds was checked by  $^1H$  NMR and yields are based on aryl halide. All the products are known and the spectroscopic data (FT-IR and NMR) and melting points were consistent with those reported in the literature.<sup>4-19,38,39</sup>

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