

K₄[Fe(CN)₆] as non-toxic source of cyanide for the cyanation of aryl halides using Pd-Beta zeolite as a heterogeneous catalyst

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A new method for the synthesis of aryl nitriles has been developed by the reaction of aryl halides with K₄Fe(CN)₆ in the presence of Pd-Beta zeolite as efficient and recyclable catalyst.

Keywords: aryl nitriles, aryl halide, K₄Fe(CN)₆, cyanation, palladium, zeolite

Nitriles are versatile intermediates in organic synthesis, since they not only constitute key components of a range of pharmaceuticals, agrochemicals, dyes,¹ but can also easily be converted into other functional groups such as nitrogen-containing heterocycles, aldehydes, acids and acid derivatives.^{2,3} Nitriles are conventionally synthesised by reaction of aryl halides with stoichiometric amounts of CuCN,^{4,5} the diazotisation of anilines and subsequent Sandmeyer reaction,^{6,7} the transition metal-catalysed cyanation of aryl halides using KCN, NaCN, Me₃SiCN and Zn(CN)₂ as cyanating agents.^{8–13} 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. Furthermore, CuCN and Zn(CN)₂ lead to heavy metal waste.

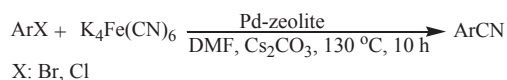
Due to safety considerations, we required a method that did not use of toxic reagents. Therefore, it is desirable to develop a more efficient and convenient method for the synthesis of aryl nitriles without the application of expensive, moisture sensitive and toxic reagents. To resolve this problem, Beller and co-workers have described a convenient synthesis of nitriles by potassium hexacyanoferrate (II), K₄Fe(CN)₆, as a non-toxic cyanide source.^{14,15} This reagent is commercially available on ton scale and cheaper than KCN and NaCN and it is even used in food industry for metal precipitation.

Homogeneous catalysts have been widely investigated, among various catalysts for the transition metal-catalysed cyanation of aryl halides with K₄Fe(CN)₆.^{16–19} Less expensive heterogeneous catalysts have received scant attention. Thus, the development of a catalytic synthetic method for the synthesis of nitriles still remains an active research area.

Recent studies of catalysis^{20–28} have shown that by using inexpensive and non-corrosive heterogeneous catalysts, chemical transformations occur with better efficiency, providing 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.^{29–32} We recently published a synthesis of formamides in high yields using HEU Zeolite as a natural and heterogeneous catalyst.³² In spite of these interesting properties of zeolites, there are no reports of

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.^{33,34} Its activity arises from its large pore size, high Si/Al ratio, high acid strength, and thermal stability.

In continuation of our recent studies on the application of nitriles, zeolites and other natural products,^{32,35,36} we report a new method for the preparation of aryl nitriles *via* cyanation aryl halides with K₄Fe(CN)₆ in the presence of Pd-Beta zeolite³⁷ as a heterogeneous catalyst.



Scheme 1

Results and discussion

In order to find the optimum conditions, we carried out the reaction of bromobenzene with K₄Fe(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. The data shown in Table 1, revealed that 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, Cs₂CO₃ acted as the most effective (Table 1, entry 5). Moreover, as each mol of K₄Fe(CN)₆ contains six cyanide ions, the ratio of K₄Fe(CN)₆ to aryl halide was chosen 0.22:1. We then used the optimum reaction conditions (aryl halide (1.0 mmol), K₄Fe(CN)₆ (0.22 mmol), Cs₂CO₃ (1.0 mmol) and DMF as solvent) for the cyanation of different aryl halides under thermal conditions. The results are shown in Table 2.

Table 1 Optimisation of reaction conditions in cyanation reaction of bromobenzene with K₄Fe(CN)₆

Entry	Base	Solvent	Temperature/°C	Time/h	Yield/% ^a
1	Cs ₂ CO ₃	Toluene	Reflux	20	0
2	Cs ₂ CO ₃	CH ₃ CN	Reflux	20	0
3	Cs ₂ CO ₃	MeOH	Reflux	20	0
4	Cs ₂ CO ₃	NMP	130	10	80
5	Cs ₂ CO ₃	DMF	130	10	91
6	Et ₃ N	DMF	130	12	21
7	NaF	DMF	130	12	27
8	K ₂ CO ₃	DMF	130	10	85
9	KOAc	DMF	130	11	79
10	Na ₂ CO ₃	DMF	130	11	61
11	–	DMF	130	20	0

^aYields are after work-up.

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

Entry	Substrate	Product	Yield/% ^b	M.p./°C	Lit.m.p./°C ^{Ref}
1	C_6H_5I	C_6H_5CN	85	Oil	Oil ⁷
2	$p\text{-MeC}_6\text{H}_4I$	$p\text{-MeC}_6\text{H}_4CN$	80	Oil	Oil ⁷
3	$o\text{-MeC}_6\text{H}_4I$	$o\text{-MeC}_6\text{H}_4CN$	83	Oil	Oil ³⁸
4	$p\text{-MeOC}_6\text{H}_4I$	$p\text{-MeOC}_6\text{H}_4CN$	84	59–61	58–60 ⁷
5	$p\text{-COMeC}_6\text{H}_4I$	$p\text{-COMeC}_6\text{H}_4CN$	87	57–59	56–59 ³⁹
6	$p\text{-COOMeC}_6\text{H}_4I$	$p\text{-COOMeC}_6\text{H}_4CN$	87	64–66	65–67 ³⁹
7	$m\text{-OMe-}p\text{-OHC}_6\text{H}_3I$	$p\text{-OH-}m\text{-OMeC}_6\text{H}_3CN$	86	84–86	85–87 ³⁹
8	$4\text{-IC}_5\text{H}_4N$	$4\text{-CNC}_5\text{H}_4N$	79	76–78	76–79 ³⁹
9	C_6H_5Br	C_6H_5CN	85	Oil	Oil ⁷
10	$p\text{-MeOC}_6\text{H}_4Br$	$p\text{-MeOC}_6\text{H}_4CN$	83	59–61	58–60 ⁷
11	$p\text{-COMeC}_6\text{H}_4Br$	$p\text{-COMeC}_6\text{H}_4CN$	82	56–58	56–59 ³⁹
12	$p\text{-COOMeC}_6\text{H}_4Br$	$p\text{-COOMeC}_6\text{H}_4CN$	89	65–67	65–67 ³⁹
13	$p\text{-CNC}_6\text{H}_4Br$	$p\text{-CNC}_6\text{H}_4CN$	90	221–225	221–225 ⁷
14	$p\text{-BrC}_6\text{H}_4I$	$p\text{-BrC}_6\text{H}_4CN$	91	110–115	110–115 ³⁸
15	$1\text{-C}_{10}\text{H}_7Br$	$1\text{-C}_{10}\text{H}_7CN$	87	36–38	36–38 ³⁸

^aReaction 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.

^bYields are after work-up.

Various aryl nitriles were synthesised 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 characterised by melting points, elemental analysis (CHN), IR, 1H NMR and ^{13}C NMR. The IR spectra of the products showed one sharp absorption band in the range of 2225–2360 cm^{-1} (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. 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. Chromatographic separation was not required to obtain the pure compounds.

Experimental

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Products were characterised by comparison of their physical and spectroscopic data with authentic samples. The NMR spectra were recorded in DMSO. 1H NMR spectra were recorded on a Bruker Avance DRX 250 MHz instruments. The chemical shifts (δ) are reported in ppm relative to the TMS as an internal standard and J values are given in Hz. ^{13}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 analyser. TLC was performed on silica gel polygram SIL G/UV 254 plates.

Preparation of catalyst

The catalyst was prepared according to the literature.³⁷ Zeolite-supported palladium catalyst was prepared by ion exchange of Beta zeolite (2 g) using a 0.1 M aqueous solution of $[Pd(NH_3)_4]^{2+}$. The

solution mixture was stirred for 24 h at room temperature, filtered and washed with water until no Cl^- ion was detectable within the filtrate. Calcination at 500 °C under pure O_2 (180 mL min^{-1}) 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 characterised using the powder XRD, TEM and BET.

Cyanation of aryl halides with $K_4Fe(CN)_6$: general procedure

A mixture of the 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 was vigorously stirred 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 recrystallisation 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.^{4–19,38,39}

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