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Pd/C-Catalyzed Cyanation of Aryl Halides in Aqueous PEG

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An environmentally friendly Pd/C–PEG–H_2O system was developed for the cyanation of aryl halides under microwave irradiation. A wide range of aryl bromides, iodides, and some activated chlorides were demonstrated to be cyanated smoothly by using nontoxic $K_4[Fe(CN)_6]\cdot 3H_2O$ as the cyanide source. There is no phosphorus- or nitrogen-containing ligand or solvent involved. Moreover, this reaction can be carried out without the protection of inert atmosphere.

Introduction

Aryl nitriles are important building blocks of numerous pharmaceuticals, herbicides, natural products, and dyes.[1] In addition, nitriles are very useful intermediates in organic synthesis, because they can be easily converted into other functional groups.[2] For these reasons, much attention has been given to the development of efficient and practical methods for the synthesis of aryl nitriles. Of these transformations, transition-metal-mediated cyanation of aryl halides represents one of the most convenient approaches.[3] Typical procedures utilized toxic inorganic or organic cyanide sources, such as alkali cyanides,[4] $Zn(CN)_2$,[5] CuCN,[6] TMSCN,[7] and acetone cyanohydrin.[8] In most cases, various ligands were developed to maintain or improve the activity of the metal catalysts. However, the ligands are often toxic, expensive, and hard to be removed from the product.

Recently, an attractive improvement was made by Beller and coworkers.[9] Nontoxic, inexpensive, and easily handled $K_4[Fe(CN)_6]$ was, for the first time, introduced as a cyanide source to the cyanation reaction,[10] although a phosphane ligand was still necessary. Further modifications of the original protocol led to ligand-free versions soon after.[11] To ensure that the transformations were carried out smoothly, however, dehydrating or grinding the $K_4[Fe(CN)_6]\cdot 3H_2O$ into fine particles was a prerequisite. In addition, some electron-rich aryl bromides, for example, 4-bromoanisole, often encountered problematic and incomplete conversion.[11b,11c] It is noteworthy that the solvent showed a significant influence on the reaction. To the best of our knowledge, palladium-catalyzed cyanation reactions with the use of $K_4[Fe(CN)_6]$ as a cyanide source were almost always carried out in a highly polar amide solvent such as DMF, NMP, or DMAC under an inert gas atmosphere.[9,11,12] The utilization of $K_4[Fe(CN)_6]$ in copper-catalyzed cyanation reactions of aryl halides has also been realized. However, amine ligands as well as long reaction times were required in these copper-catalyzed protocols.[13]

Being the solvent of life, water is necessarily a nontoxic and economic solvent. As such, it has frequently been promoted as an alternative solvent in academic and industrial labs. In addition, the utilization of water as a solvent in transition-metal-catalyzed coupling reactions often greatly facilitates the workup procedure and avoids drying solvents and starting materials.[14] Although some experiments showed that small amounts of water or hydrate in the cyanide source was tolerated by the catalytic system in cyanation reactions,[5c–5f,11b,12a] only two papers described the transition-metal-catalyzed cyanation reaction in water in the absence of an amide cosolvent. One of these reported procedures involved the utilization of toxic NaCN as a cyanide source, water–heptane as a biphasic solvent, and sulfonated phosphane as a palladium ligand to accomplish the cyanation of aryl iodides and activated aryl bromides.[15] The other paper also used toxic NaCN or CuCN as a cyanide source, whereas the substrate scope was limited to aryl iodides.[16] Thus, the development of an efficient and environmentally friendly catalytic system for transition-metal-catalyzed cyanation reactions in water is still attractive.

As part of our ongoing research interest in aqueous cross-coupling reactions,[17] we herein wish to report our investigation on Pd/C-catalyzed cyanation of aryl halides with the use of nontoxic and commercially available $K_4[Fe(CN)_6]\cdot 3H_2O$ directly as the cyanide source in aqueous polyethylene glycols (PEGs) under microwave irradiation without protection of an inert atmosphere.

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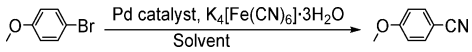
Results and Discussion

Cyanation of 4-bromoanisole was chosen as a model reaction to optimize the reaction conditions. The results are summarized in Table 1. Initially, the cyanation reaction was carried out in pure water under microwave irradiation at 140 °C for 30 min in the presence of Pd/C (10 mol-%), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.33 equiv.), Na_2CO_3 (20 mol-%), and KI (1 equiv.). Unfortunately, no desired product was detected (Table 1, Entry 1). This might be caused by the poor solubility of 4-bromoanisole in water and should be circumvented by the addition of surfactant. Polyethylene glycols (PEGs) are known to be nontoxic, recyclable, thermally stable, and inexpensive media for the use as phase-transfer catalysts (PTCs), and they may even be applicable in biomedical protocols.[18] In view of green chemistry, utilization of PEGs as PTCs was one of the best options. Hence, a variety of PEGs with different chain lengths were investigated both as cosolvents and PTCs under the same reaction conditions (Table 1, Entries 2–7). As shown in Table 1, PEG4000 was the most efficient in promoting the reaction (Table 1, Entry 5). Other PEGs with longer chain lengths, such as PEG2000, PEG6000, and PEG10000, also improved the conversion of the starting material remarkably, but they were less efficient than PEG4000. PEGs with shorter chain lengths, such as PEG600 and PEG1000, had lower activity. The influence of the ratio between PEG and water on the reaction was then further studied (Table 1, Entries 8–13). The results indicated that the appropriate quantity of water was crucial for success of the reaction. Utilization of pure PEG4000 as the solvent only gave trace amounts of product (Table 1, Entry 13), and the addition of small amounts of water was also not effective (Table 1, Entry 12). However, when the mass ratio between water and PEG4000 was 1:2, the yield dramatically increased to 55% (Table 1, Entry 9). Nevertheless, a lower amount of PEG4000 had a detrimental effect on the reaction (Table 1, Entries 5, 8). As mentioned above, in the absence of PEG, the transformation was completely halted (Table 1, Entry 1).

It should be noted that KI was beneficial to some extent for the cyanation reaction of aryl bromides (Table 1, Entry 17), because it could convert the aryl bromide into the more reactive aryl iodide by a palladium-catalyzed halide-exchange reaction.[19] However, when KI was used as an additive here, incomplete conversion of the starting material still remained a problem and even the reaction time was prolonged to 2 h under microwave irradiation (Table 1, Entry 19); the yield of the dehalogenation product also increased at the same time. Finally, a weaker base gave some advantages over strong bases in the conversion to the desired products. As shown in Table 1, the conversion of 4-bromoanisole increased to 99% when Na_2CO_3 was replaced with NaF, and the byproducts were suppressed to less than 1% as well (Table 1, Entry 23).

It is well documented that PEGs can serve as PTCs, as the poly(ethylene oxide) chains in PEGs can form complexes with the metal ions in a manner similar to that of crown ethers.[18] Probably, the PEG and K^+ from $K_4[Fe(CN)_6]$ formed complexes and brought the $[Fe(CN)_6]^{4-}$ fragment to the organic substrate. In addition, $K_4[Fe(CN)_6]\cdot 3H_2O$ has a good solubility in water. Furthermore, water is a good placeholder ligand for palladium and is particularly effective in ligand-free reactions. Because of the high concentration in aqueous solvents (giving a huge excess over the palladium catalyst), water is able to displace other labile

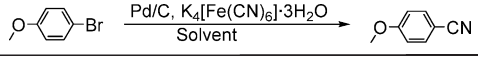
Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent [b]	Catalyst	Base	Time [min]	Conv. [%][c]	Yield [%][c]
1	Pure water	Pd/C	Na_2CO_3	30	3	trace
2	PEG600/H_2O (1:1)	Pd/C	Na_2CO_3	30	11	<5
3	PEG1000/H_2O (1:1)	Pd/C	Na_2CO_3	30	14	9
4	PEG2000/H_2O (1:1)	Pd/C	Na_2CO_3	30	52	37
5	PEG4000/H_2O (1:1)	Pd/C	Na_2CO_3	30	57	51
6	PEG6000/H_2O (1:1)	Pd/C	Na_2CO_3	30	40	37
7	PEG10000/H_2O (1:1)	Pd/C	Na_2CO_3	30	43	39
8	PEG4000/H_2O (1:2)	Pd/C	Na_2CO_3	30	17	15
9	PEG4000/H_2O (2:1)	Pd/C	Na_2CO_3	30	57	55
10	PEG4000/H_2O (4:1)	Pd/C	Na_2CO_3	30	40	36
11	PEG4000/H_2O (7:1)	Pd/C	Na_2CO_3	30	41	40
12[d]	PEG4000	Pd/C	Na_2CO_3	30	4	3
13	Pure PEG4000	Pd/C	Na_2CO	30	4	3
14	PEG4000/H_2O (7:1)	$PdCl_2$	Na_2CO_3	30	33	32
15	PEG4000/H_2O (7:1)	$Pd(OAc)_2$	Na_2CO_3	30	16	15
16	PEG4000/H_2O (7:1)	CuI	Na_2CO_3	30	0	0
17[e]	PEG4000/H_2O (2:1)	Pd/C	Na_2CO_3	30	31	28
18	PEG4000/H_2O (2:1)	Pd/C	No base	30	41	40
19	PEG4000/H_2O (2:1)	Pd/C	Na_2CO_3	120	67	61
20	PEG4000/H_2O (2:1)	Pd/C	K_3PO_4	120	70	62
21	PEG4000/H_2O (2:1)	Pd/C	KOH	120	66	40
22	PEG4000/H_2O (2:1)	Pd/C	NaF	120	89	88
23[f]	PEG4000/H_2O (2:1)	Pd/C	NaF	120	99	98

[a] Reaction conditions: 4-bromoanisole (0.5 mmol, 1 equiv.), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.33 equiv.), Pd/C (10 wt.-%, 10 mol-%), KI (1 equiv.), base (20 mol-%), solvent (1.5 g), 140 °C, microwave irradiation. [b] Mass ratio in parentheses. [c] GC yield. [d] H_2O (3 equiv.) was added. [e] No KI was added. [f] NaF (1 equiv.) was used.

Table 2. Cyanation reaction in various solvent.[a]



Entry	Solvent[b]	Conv. [%][c]	Yield [%][c]
1	NMP/H_2O (2:1)	7	6
2	DMF/H_2O (2:1)	5	4
3	DMAc/H_2O (2/1)	10	10
4	Toluene/H_2O (2:1)	3	2
5	Dioxane/H_2O (2:1)	2	1
6	CH_3CN/H_2O (2:1)	6	6
7	H_2O[d]	55	52
8	H_2O[e]	2	1
9	PEG4000/H_2O (2:1)	99	98

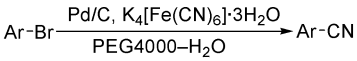
[a] Reaction conditions: 4-bromoanisole (0.5 mmol, 1 equiv.), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.33 equiv.), Pd/C (10 wt.-%, 10 mol-%), KI (1 equiv.), NaF (1 equiv.), solvent (1.5 g), 140 °C, 2 h, microwave irradiation. [b] Mass ratio in parentheses. [c] GC yield. [d] TBAB (1 equiv.) was added. [e] SDS (1 equiv.) was added.

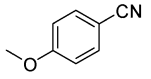
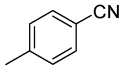
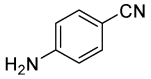
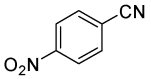
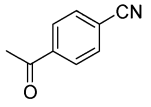
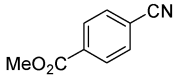
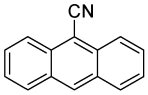
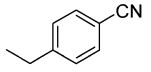
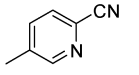
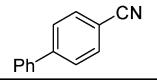
ligands from the coordination shell of palladium,[20] particularly cyanide, which poisons the catalyst and blocks the cationic path. Thus, it was no surprise to us that the combination of water and PEGs as the solvent led to a very smooth cyanation transformation.

Because most of the palladium-catalyzed cyanation reactions using $K_4[Fe(CN)_6]$ as the cyanide source were carried out in highly polar solvents such as DMF, NMP, and DMAc, we examined various aqueous solvents to compare with the PEG–water system. As shown in Table 2, the use of other organic cosolvents, including NMP, DMF, DMAc, dioxane, toluene, and CH_3CN, in place of PEG4000 had a dramatic detrimental effect on the reaction (Table 2, Entries 1–6). This proved that the PEGs in this reaction not only served as polar cosolvents but also as PTCs. Inspired by this result, we then tested two other representative surfactants including sodium dodecyl sulfate (SDS, anionic surfactant) and tetrabutylammonium bromide (TBAB, cationic surfactant). As shown in Table 2, TBAB also showed a beneficial effect on the reaction, but this might be due to the fact that the ammonium cation has the ability to extract the cyanide anion (Table 2, Entry 7).[21] However, SDS was almost inefficient (Table 2, Entry 8).

Encouraged by these results, the cyanation reactions of various aryl halides were performed under microwave irradiation to investigate the scope and limitation of the optimum conditions. The cyanation of various aryl bromides was first examined. As summarized in Table 3, both electron-rich and electron-deficient aryl bromides were converted into the corresponding aryl cyanides smoothly within 3 h in good-to-excellent yields. The cyanation of hin-

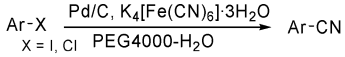
Table 3. Pd/C-catalyzed cyanation of aryl bromides in aqueous PEG.[a]

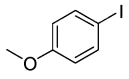
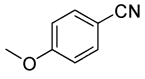
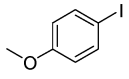
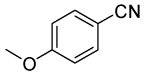
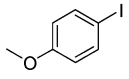
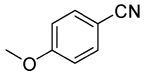
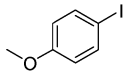
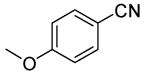
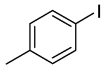
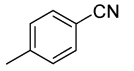
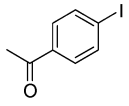
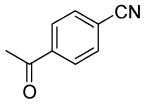
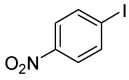
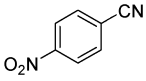
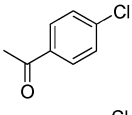
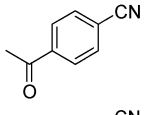
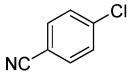
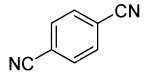
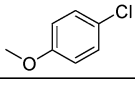
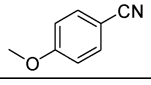


Entry	Products	Temp. [°C]	Time [h]	Yield [%][b]
1		140	2	95
2		140	2	80
3		140	2	81
4		140	2	75
5		140	2	87
6		140	2	82
7		140	3	90
8		160	2	85
9		160	2	76
10		160	2	73
11		160	2	70[c]
12		140	3	95

[a] Reaction conditions: aryl bromide (0.5 mmol, 1 equiv.), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.33 equiv.), Pd/C (10 wt.-%, 10 mol-%), KI (1 equiv.), NaF (1 equiv.), water (0.5 g), PEG4000 (1 g), 140 °C, microwave irradiation. [b] Isolated yield. [c] GC yield was 97%; the product is volatile.

Table 4. Pd/C-catalyzed cyanation of aryl halides in aqueous PEG.[a]



Entry	Aryl halides	Products	Temp. [°C]	Yield [%][b]
1			140	93
2			130	92
3			120	81
4			100	60
5			130	85
6			130	97
7			130	85
8[c]			160	48
9[c,d]			160	0
10[c]			160	0

[a] Reaction conditions: aryl bromide (0.5 mmol, 1 equiv.), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.33 equiv.), Pd/C (10 wt.-%, 10 mol-%), NaF (1 equiv.), water (0.5 g), PEG4000 (1 g), 2 h, microwave irradiation. [b] Isolated yield. [c] KI (1 equiv.) was used. [d] 4-Cyanobenzamide was isolated in 52%.

dered *o*-bromotoluene (Table 3, Entry 8) and other heteroaryl bromides only needed a slightly higher reaction temperature (Table 3, Entries 10, 11).

4-Iodoanisole was also cyanated smoothly under the optimum conditions to give the corresponding aryl nitrile (Table 4, Entry 1). We then tempted to carry out this reaction under milder conditions, because aryl iodides often showed to be more reactive than aryl bromides in transition-metal-catalyzed coupling reactions. As demonstrated in Table 4, the cyanation reaction temperature of 4-iodoanisole could be slightly lowered down to 130 °C. Lower temperatures led to lower yields of the target products as a result of the incomplete consumption of the starting material (Table 4, Entries 3, 4). Cyanation of other aryl iodides also proceeded smoothly at 130 °C in good-to-excellent yields within 2 h (Table 4, Entries 5–7).

Cyanation of aryl chlorides proved to be more difficult than that of aryl bromides and iodides. Some activated aryl chlorides, for example, 4-choroacetophone, can be partly cyanated (Table 4, Entry 8). 4-Chlorobenzenitrile was also able to react with $K_4[Fe(CN)_6]$. Nevertheless, only 4-cyanobenzamide was isolated due to the hydrolysis of the desired terephthalonitrile product (Table 4, Entry 9). Almost no cyanation reaction occurred by using electron-rich aryl chlorides like 4-chloroanisole as the starting material (Table 4, Entry 10).

The reusability of the Pd/C catalyst was also examined by using the cyanation of 4-bromoanisole as a model. The Pd/C catalyst was filtered and used in the second cycle. Unfortunately, the yield decreased to 15%, because of the incomplete consumption of 4-bromoanisole.

Conclusions

An environmentally friendly Pd/C–PEG–H_2O system was developed for the cyanation of aryl halides under microwave irradiation without the protection of an inert atmosphere. A variety of aryl bromides and iodides were cyanated smoothly with a wide range of substrate scope in good-to-excellent yields. It is noteworthy that nontoxic, commercially available $K_4[Fe(CN)_6]\cdot 3H_2O$ was used directly as the cyanide source without pretreatment. In addition, there is no phosphorus- or nitrogen-containing ligand or solvent involved. Therefore, our preliminary success was the cue to establish a more convenient and environmental Pd-catalyzed cyanation methodology, although the cyanation of aryl chlorides and the reuse of the catalytic system still remain troublesome.

Experimental Section

General Methods: All reactions were carried out with the CEM Discover in glass vessels (capacity 10 mL) sealed with a septum with a stirring option. Column chromatography was performed with silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. Thin-layer chromatography was carried out with Merck silica gel GF254 plates. All products were characterized by MS (EI) and ^1H NMR spectroscopic data, which were also verified by the literature data. ^1H NMR spectra were recorded at room temperature with a Varian Mercury-Plus 300 instrument with TMS as an internal reference. Gas chromatography–mass spectra were recorded with a Finnegan Voyager GC–MS instrument with an electron impact mass selective detector.

General Procedure for the Cyanation of Aryl Bromides under Microwave Irradiation: A 10-mL glass tube was charged with Pd/C (10 wt.-%, 53 mg, 10 mol-%), KI (83 mg, 0.5 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (70 mg, 33 mol-%), NaF (20 mg, 0.5 mmol), and water (0.5 g). The mixture was stirred for 3 min at room temperature. Then, 4-bromoanisole (94 mg, 0.5 mmol) and PEG4000 (1 g) were added. The vessel was sealed with a septum and placed into the microwave cavity. The temperature of the mixture was ramped from room temperature to 140 °C under microwave irradiation, which took 40–60 s. Once 140 °C was reached, the reaction mixture was held for 120 min. After allowing the mixture to cool to room temperature, it was extracted with diethyl ether (3×10 mL), and the combined organic layer was dried with Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by chromatography on silica gel to give the target product 4-methoxybenzonitrile (62 mg, yield 95%) as a white solid; the purity of the compound was confirmed by ^1H NMR and MS (EI) (see Tables 3 and 4).

All the compounds in this paper have been reported previously and characterized by comparison with their reported data.

Supporting Information (see footnote on the first page of this article): General procedure and spectroscopic data for the compounds listed in Table 3.

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