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An environmentally benign procedure for the Cu-catalyzed cyanation of aryl bromides

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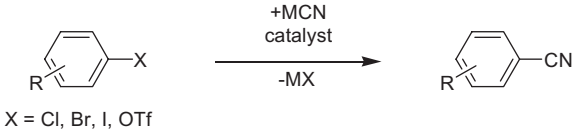
Abstract—The development of a general Cu-catalyzed synthesis of (hetero)aromatic nitriles from the corresponding aryl bromides and potassium hexacyanoferrate(II) is described. This novel protocol avoids the use of highly toxic alkali cyanides and precious palladium catalysts. Best results were achieved applying $Cu(BF_4)_2 \cdot 6H_2O$ (0.1 equiv) and *N*,*N*′-dimethyl ethylenediamine (DMEDA; 1.0 equiv) in *N*,*N*-dimethyl acetamide (DMAc).

Benzonitriles are of considerable interest for organic synthesis as integral part of dyes, herbicides, agrochemicals, pharmaceuticals and natural products.[1] In addition, the nitrile group serves as an important intermediate for a multitude of transformations into other functional groups.

Traditional methods for the preparation of benzonitriles on laboratory as well as on industrial scale are the Rosenmund-von Braun reaction[2] of aryl halides and the diazotization of anilines and subsequent Sandmeyer reaction.[3] For multi-ton-scale productions of less complex benzonitriles toluenes are directly oxidized in the presence of ammonia (ammoxidation).[4] General problems of these procedures are the limited substrate scope and the often drastic reaction conditions.

More recently, useful alternative procedures for the preparation of higher substituted benzonitriles were developed. Here, especially the transition metal-catalyzed cyanations of aryl–X compounds (X = Cl, Br, I, OTf) with cheap and readily available cyanation agents like sodium or potassium cyanide are noteworthy (Scheme 1).[5]

Catalysts applied for the coupling of aryl halides or triflates with cyanide have been often palladium complexes.[6] Until very recently, the main problem of these catalysts was productivity due to deactivation by excess



Scheme 1. Transition metal-catalyzed cyanation of Ar–X derivatives.

of cyanide ions.[7,8] Hence, the use of less expensive catalysts is of continuing interest. In this regard it is interesting to note that the addition of copper salts has been proven beneficial in some palladium-catalyzed cyanation reactions.[9] Nevertheless it was a significant progress when Buchwald and co-workers reported the development of a cyanation reaction for aryl bromides that is based on the use of substoichiometric amounts of copper (10 mol % copper(I) iodide) and no additional metal catalyst.[10]

Apart from the catalyst the cyanide source plays an important role for the applicability of a given cyanation reaction. Recently, we introduced potassium hexacyanoferrate(II) for palladium-catalyzed cyanations of aryl halides.[11] This reagent has significant advantages compared to other cyanide sources known for benzonitrile synthesis. While alkali cyanides are highly poisonous (e.g., KCN LD_{Lo} (oral, human) = 2.86 mg/kg), zinc cyanide leads to stoichiometric waste of heavy metal salts, and trimethylsilyl cyanide is sensitive to moisture and can easily liberate hydrogen cyanide, which is also true for acetone cyanohydrin. On the other hand $K_4[Fe(CN)_6]$ is non-toxic (the LD_{Lo} of $K_4[Fe(CN)_6]$ is

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comparable to NaCl!) and even used in food industry for metal precipitation. In addition, it has been described as anti-agglutinating auxiliary for table salt (NaCl). Hence, for the first time in cyanations of aryl halides the use of toxic cyanides can be avoided. Interestingly, $K_4[Fe(CN)_6]$ is commercially available on ton scale and even cheaper than KCN.[12]

To further improve and expand the tools for cyanation of aryl halides, we set out to combine the advantages of non-expensive copper catalysts with the non-toxic cyanide source, potassium hexacyanoferrate(II). Here, we describe the successful development of such a novel procedure.

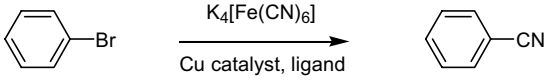
As a starting point of our investigations, we applied a catalyst system according to Buchwald (10 mol % CuI, 100 mol % *N*,*N*′-dimethyl ethylenediamine (DMEDA), 20 mol % KI) together with $K_4[Fe(CN)_6]$ as cyanide source (20 mol %, i.e., 1.2 equiv cyanide).[13] In order to ensure sufficient solubility we used dipolar aprotic solvents, for example, *N*,*N*-dimethyl acetamide (DMAc) and NMP.

The influence of different copper precursors, ligands, temperature, solvents and additives was studied for the cyanation of bromobenzene to benzonitrile. Selected results of the variation of reaction parameters on this model reaction are shown in Table 1. When using CuI at 120 °C, a moderate yield of 62% of benzonitrile was obtained. $Cu(BF_4)_2{\cdot}6H_2O$ led to some improvement, but the corresponding water-free catalyst did not prove beneficial (Table 1, entries 1–3).[14] Interestingly, it is not necessary to use an excess of $K_4[Fe(CN)_6]$. Hence, basically all the cyanide ions bound to Fe are transferred to the aryl group. As a result KBr and iron bromide salts are formed.

At 100 °C only low yields of benzonitrile are obtained, however, increasing the temperature to 140 °C led to benzonitrile in up to 89% yield (Table 1, entry 4). Attempts to vary the copper pre-catalyst or to reduce the amount of copper salt and KI decreased the product yield significantly (Table 1, entries 5, 7–9). Changing the solvent to *N*-methylpyrrolidinone (NMP) made basically no difference (Table 1, entry 6). Although no detailed study of the ligand influence has been made the use of DMEDA seems to be crucial (Table 1, entries 4, 10 and 11). On the other hand the addition of a catalytic amount of an inorganic base is less important (Table 1, entries 4, 12–14). The fact that $Cu(BF_4)_2{\cdot}6H_2O$ is—so far—the best copper catalyst for use with $K_4[Fe(CN)_6]$ as cyanide source seems to be unexpected, but is understandable. This precursor is well soluble in DMAc, its anion is rather inert, and the inherent crystal water[15] presumably helps to solvate the highly charged $[Fe(CN)_6]^{4-}$ anion in the organic solvent. Although the resulting copper hexacyanoferrate complexes are hardly soluble in aqueous solution and therefore used for the precipitation of copper impurities in wine, the catalytically active metal and the nucleophile are in close contact to each other and may provide a well-suited reaction environment for the cyanation reaction.

Next, a number of aryl and heteroaryl bromides were tested applying the optimized conditions (similar to Table 1, entry 4). The results are described in Table 2. Both electron-poor and electron-rich bromoarenes react well under these conditions. Hence, 1-bromonaphthalene,

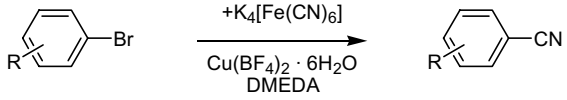
Table 1. Cyanation of bromobenzene

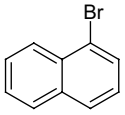
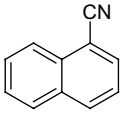
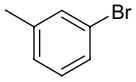
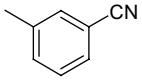


Entry	Cu pre-catalyst (mol %)	Ligand[a]	Temp (°C)	Conv. (%)	Yield (%)
1	CuI (10)	DMEDA	120	85	62
2	$Cu(BF_4)_2{\cdot}6H_2O$ (10)	DMEDA	120	84	68
3	$Cu(BF_4)_2$ (10)	DMEDA	120	73	59
4	**$Cu(BF_4)_2{\cdot}6H_2O$ (10)**	**DMEDA**	**140**	**100**	**89**
5	CuI (10)	DMEDA	140	86	74
6[b]	CuI (10)	DMEDA	140	84	75
7	$Cu(OAc)_2$ (10)	DMEDA	140	74	58
8[c]	$Cu(BF_4)_2{\cdot}6H_2O$ (5)	DMEDA	140	56	44
9[d]	$Cu(BF_4)_2{\cdot}6H_2O$ (10)	DMEDA	140	40	33
10	$Cu(BF_4)_2{\cdot}6H_2O$ (10)	TMEDA	140	8	0
11	$Cu(BF_4)_2{\cdot}6H_2O$ (10)	EDA	140	66	31
12[e]	$Cu(BF_4)_2{\cdot}6H_2O$ (10)	DMEDA	140	89	80
13[f]	$Cu(BF_4)_2{\cdot}6H_2O$ (10)	DMEDA	140	90	74
14[g]	$Cu(BF_4)_2{\cdot}6H_2O$ (10)	DMEDA	140	99	88

Reaction conditions: 2.0 mmol bromobenzene, 20 mol % dry $K_4[Fe(CN)_6]$, 2 mL DMAc, 20 mol % KI, 20 mol % Na_2CO_3.
[a] 100 mol %; DMEDA = *N*,*N*′-dimethyl ethylenediamine, TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine, EDA = ethylene diamine.
[b] Solvent = NMP.
[c] 10 mol % KI.
[d] No KI.
[e] No Na_2CO_3.
[f] 20 mol % Et_3N instead of Na_2CO_3.
[g] 20 mol % K_3PO_4 instead of Na_2CO_3.

Table 2. Cyanation of various aryl and heteroaryl halides



Entry	Ar–X	Ar–CN	Conv. (%)	Yield (%)
1			97	80
2			94	90
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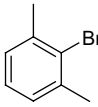
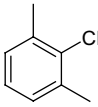
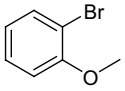
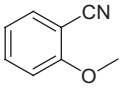
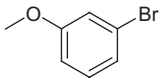
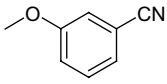
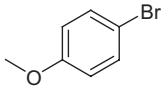
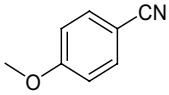
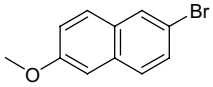
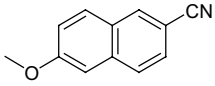
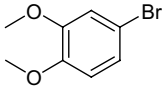
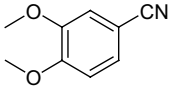
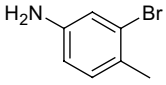
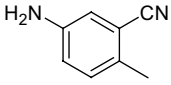
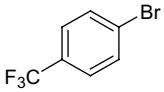
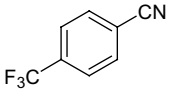
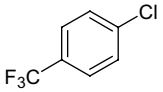
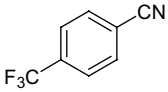
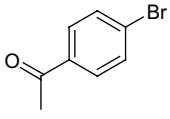
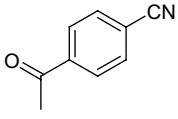
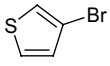
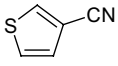
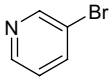
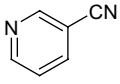
4			54	29
5			92	54
6			100	91
7			96	85
8			100	96
9			94	59
10			81	70
11			100	73
12			25	12
13[a]			100	61
14			100	90
15			100	67

Reaction conditions: 2.0 mmol aryl halide, 20 mol % dry $K_4[Fe(CN)_6]$, 2 mL DMAc, 20 mol % KI, 20 mol % Na_2CO_3, 100 mol % DMEDA.
[a] In case of 4-bromoacetophenone a side product is also formed in ca. 20% yield, which gave upon hydrolysis with water the desired product.

2- and 3-bromotoluene, 3- and 4-bromoanisole, 6-methoxy-2-bromonaphthalene and 3-bromothiophene gave the corresponding benzonitriles in 80–96% yield. Highly electron-rich substrates like 4-bromoveratrol[16] and 3-bromo-4-methylaniline are more difficult to transform. Nevertheless, they led to the products in moderate to good yield (59–70%) (Table 2, entries 9 and 10). However, two substituents in *ortho*-position lowered the yield considerably (Table 2, entry 4).

The difference between C–Br and C–Cl activation is demonstrated in case of 4-halobenzotrifluoride (Table 2, entries 11 and 12). While 4-bromobenzotrifluoride performs reasonably well (73% yield), the corresponding chloride is only slightly converted under these conditions (12% yield).

In conclusion, we have shown for the first time, that it is possible to perform copper-catalyzed cyanations of aryl halides using potassium hexacyanoferrate(II).[17] A variety of different aryl and heteroaryl bromides gave the corresponding benzonitriles in good yield. This novel procedure represents a more environmentally benign and less hazardous protocol by using the non-toxic potassium hexacyanoferrate(II) instead of the highly toxic alkali cyanides.

Acknowledgements

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12. The price per mol CN^- is 2.7€ for $K_4[Fe(CN)_6]$ and 7.9€ for KCN; source Aldrich Chemicals Catalogue 2003.
13. General procedure: under inert conditions 0.4 mmol Na_2CO_3, 0.4 mmol $K_4[Fe(CN)_6]$ ($K_4[Fe(CN)_6]\cdot 3H_2O$ is ground to a fine powder and dried in vacuum (ca. 2 mbar) at 80 °C over night), 0.2 mmol copper precursor and 0.4 mmol KI are placed in a pressure tube. An argon needle is inserted into the pressure tube and the solids are flushed with argon for at least 1 min. Then 2 mmol aryl halide, 2 mmol amine and 2 mL of a 0.1 M stock solution of $Cu(BF_4)_2\cdot 6H_2O$ in the corresponding solvent are added. The pressure tube is sealed and heated for 16 h at the temperature specified in the table. After cooling to room temperature 3 mL dichloromethane and 400 μL diethyleneglycol di-*n*-butylether (internal standard) are added and the mixture is analyzed by GC. The conversion and yield are calculated as the average of two parallel runs. For isolating the products the reaction mixture is washed with water and the organic phase is dried over Na_2SO_4. After evaporation of the solvents the residue is subjected to column chromatography (silica, hexane/ethyl acetate). All prepared benzonitriles are known compounds and identified by comparison with commercially available materials.
14. $Cu(BF_4)_2\cdot 6H_2O$ was dried overnight in a desiccator over sicapent (Merck KGaA, Darmstadt) in vacuum, then at 80 °C (melt) in vacuum.
15. Water (60 mol %) relative to the substrate are introduced into the reaction mixture with the catalyst precursor.
16. In case of 4-bromoveratrol the reaction mixture developed a deep purple colour. This may indicate the formation of copper complexes from which the product is not fully liberated.
17. After submission of this manuscript Weissman et al. reported also on the use of $K_4Fe(CN)_6$ with palladium catalysts: Weissman, S. A.; Zwerge, D.; Chen, C. *Org. Chem.* **2004**, *70*, 1508–1510.