

A New Oxazole Ligand for the Copper-catalyzed Cyanation of Aryl halides with $K_4[Fe(CN)_6]$

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Abstract: An efficient and new method for the copper-catalyzed cyanation of aryl halides is reported using a new oxazole ligand and $K_4Fe(CN)_6$ as a non-toxic source of cyanide.

Keywords: Cyanation, Aryl halide, Oxazole, Copper, $K_4Fe(CN)_6$, Aryl nitriles

INTRODUCTION

Nitriles are an important intermediate in synthetic organic chemistry, since they not only constitute key components of a range of pharmaceuticals, agrochemicals and dyes [1], but can also easily be transformed into various classes of compounds such as nitrogen-containing heterocycles, aldehydes, acids and acid derivatives [2].

The classical approaches to nitriles are based on the reaction of aryl halides with stoichiometric amounts of $CuCN$ [3], Sandmeyer reaction via the diazotization of anilines [4] or the transition metal-catalyzed cyanation of aryl halides using KCN , $NaCN$, Me_3SiCN and $Zn(CN)_2$ as cyanating agents [5].

However, each of these methods suffers from different drawbacks such as employing expensive, toxic, hazardous and moisture sensitive reagents, harsh reaction conditions, tedious work-ups, long reaction times, low yields, several-step methods, environmental pollution caused by formation of heavy metal waste and formation of side products. Thus, due to safety considerations, it is desirable to develop a more efficient and convenient method for the synthesis of nitriles that reduce or eliminate the use and generation of hazardous compounds is essential.

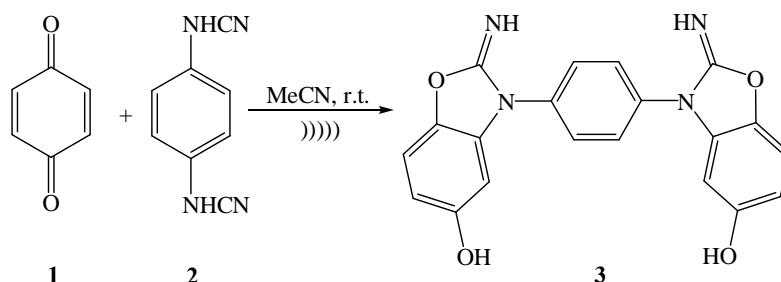
Among cyanation agents in the synthesis of nitriles, $K_4Fe(CN)_6$ is commercially available on ton scale and cheaper than KCN and $NaCN$ and even used in food industry for metal precipitation. Also, it is a nonexplosive, non-flammable, nonexpensive and non-toxic cyanide source and can be easily stored and is neither moisture sensitive and nor very volatile [6].

Among various methods for the cyanation of aryl halides with $K_4Fe(CN)_6$, very expensive palladium catalysts have been widely investigated [7], while less expensive copper catalysts received scant attention. The high cost of palladium salts restricts their applications, especially in large-scale process. Thus, it is desirable to develop a convenient and simple method for the copper-catalyzed cyanation of aryl halides.

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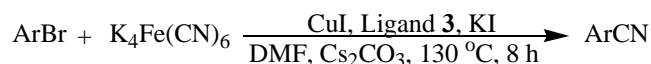
Among various methods for the transition copper-catalyzed cyanation of aryl halides with $\text{K}_4\text{Fe}(\text{CN})_6$, diamines and 1-alkylimidazoles as effective ligand have been investigated [8a-8c]. Recently, Ren and coworkers reported copper-catalyzed cyanation of aryl halides and benzyl halides with $\text{K}_4[\text{Fe}(\text{CN})_6]$ under microwave irradiation and thermal conditions. In spite of these methods, there are no reports on the synthesis of aryl nitriles via cyanation of aryl halides using efficient heterocycles such as oxazoles.

Nasrollahzadeh and coworkers recently published synthesis of 3,3'-(1,4-phenylene)bis-(2-imino-2,3-dihydrobenzo[*d*]-oxazol-5-ol) (**3**) in high yields (Scheme 1) [9]. We believe that ligand **3** can play an important role in this reaction for the synthesis of aryl nitriles.



Scheme 1

As part of our ongoing interest in heterocyclic chemistry [10], we now wish to report the copper-catalyzed cyanation of aryl halides with $\text{K}_4\text{Fe}(\text{CN})_6$ as the cyanating agent and 3,3'-(1,4-phenylene)bis-(2-imino-2,3-dihydrobenzo[*d*]-oxazol-5-ol) (**3**) as a new ligand under thermal conditions (Scheme 2).



Scheme 2

RESULTS AND DISCUSSION

For optimization of the reaction conditions, we chose the reaction of 2-bromotoluene (1 mmol) with $\text{K}_4\text{Fe}(\text{CN})_6$ (0.22 mmol) in the presence of 0.3 mmol of CuI and 0.8 mmol of ligand **3** as the model reaction, and the effects of the base and solvents were examined. First, several solvents were screened for the reaction. 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. As shown in Table 1, the reaction was influenced significantly by the base employed and the best result obtained in the case of cesium carbonate (Table 1, entry 5). In our study, the optimal stoichiometry of $\text{K}_4\text{Fe}(\text{CN})_6$ was found to be 0.2 mmol. Moreover, as each mol of $\text{K}_4\text{Fe}(\text{CN})_6$ contains six-fold cyanide ions, the ratio of $\text{K}_4\text{Fe}(\text{CN})_6$ to aryl halide was chosen 0.2:1.0. The reaction was also not very effective in absence of KI (Table 1, entry 11). Thus, KI was added to improve the reaction yield. According to a related report [8b,8d], the KI-acceleration effect resulted possibly from a conversion of the aryl bromide into the more reactive aryl iodide followed by the cyanation of the resulting aryl iodide (Scheme 3). The optimum conditions were found to be 1.0 mmol of aryl bromide, 0.3 mmol of CuI, 0.8 mmol of ligand **3**, 50 mol% of KI, 25 mol% of Cs_2CO_3 and 0.2 mmol of $\text{K}_4\text{Fe}(\text{CN})_6$ in DMF (5.0 mL). The results are shown in Table 1 and 2-

bromotoluene with a bigger steric hindrance around the reaction site gave a high yield. Thus, the reactions appeared to be insensitive to the steric hindrance around the reaction site (Table 1, entry 5). Increasing the amount of ligand **3** from 0.8 mmol to 1.0 mmol and copper salt from 0.3 mmol to 0.5 mmol showed no substantial improvement in the yield.

Table 1. The model reaction in the synthesis of 2-bromobenzonitrile under thermal conditions

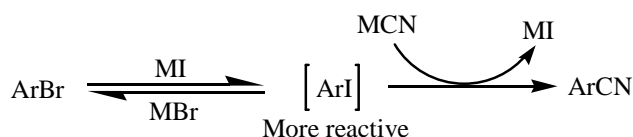
Entry	Base	KI (mol%)	Solvent	Temperature (°C)	Time (h)	Yield ^b (%)
1	CS ₂ CO ₃	50	Toluene	Reflux	12	77
2	CS ₂ CO ₃	50	MeCN	Reflux	12	73
3	CS ₂ CO ₃	50	MeOH	Reflux	12	75
4	CS ₂ CO ₃	50	NMP	130	10	82
5	CS ₂ CO ₃	50	DMF	130	8	93
6	Et ₃ N	50	DMF	130	8	23
7	NaF	50	DMF	130	8	31
8	K ₂ CO ₃	50	DMF	130	8	86
9	KOAc	50	DMF	130	8	48
10	Na ₂ CO ₃	50	DMF	130	8	88
11	CS ₂ CO ₃	-	DMF	130	8	7

^a Reaction conditions: CuI (0.3 mmol), 2-bromotoluene (1 mmol), K₄Fe(CN)₆ (0.2 mmol), KI (50 mol%), base (25 mol%), Ligand **3** (0.8 mmol), DMF (5 mL), pressure tube, N₂ atm, 130 °C.

^b Isolated yields.

Next, using the optimized procedure, a variety of aryl halides possessing both electron-donating and electron-withdrawing groups were employed (Table 2). According to the table, the nature of the substituent on the benzene ring did not affect the reaction time and the yields were excellent. This method is also suitable for the cyanation of activated and non-activated aryl halides.

As indicated in Table 2, it is evident that our method is reasonably general and can be applied to several kinds of aryl iodides (Entry 13-18). In all cases the reaction gives the corresponding aryl nitriles in good to excellent yields under the reaction conditions.



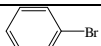
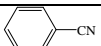
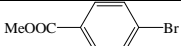
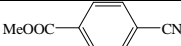
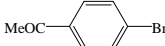
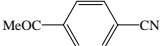
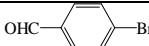
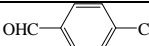
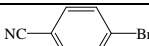

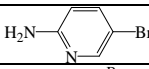
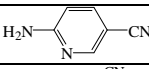
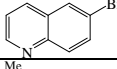
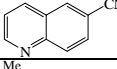




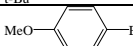
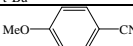


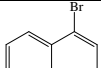
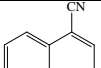

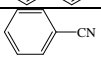
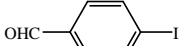
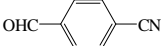
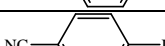


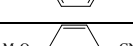
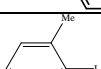

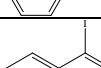
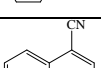
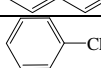
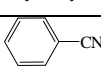
Scheme 3.

In contrast with previous reports for the copper-catalyzed cyanation of aryl halides, a more remarkable KI-accelerating effect was observed, the catalyst and the ligand **3** are inexpensive and the use of stoichiometric amounts of Cu and more KI is avoided. We believe that ligand **3** can play an important role in the transition metal reactions for the organic compounds synthesis.

Several similar mechanisms have been reported for the palladium or copper-catalyzed cyanation of aryl halides using various ligands. We believe that ligand **2** can have ability to coordinate with copper either through oxygen atoms of the phenol ring or nitrogen atoms of the oxazole ring. Although we have not yet fully characterized the oxazole complexes, the ligand, in combination with CuI, has been shown to catalyze the coupling reactions of aryl halides with K₄[Fe(CN)₆] efficiently.

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

Table 2. Formation of aryl nitriles via copper-catalyzed cyanation of various aryl halides with $K_4Fe(CN)_6$ at 130 °C^a

Entry	Substrate	Product	Yield ^b (%)
1			92
2			90
3			91
4			88
5			89
6			86
7			93
8			88
9			94
10			95
11			94
12			87
13			94 ^c
14			91 ^c
15			92 ^c
16			95 ^c
17			96 ^c
18			91 ^c
19			0

^a Reaction conditions: CuI (0.3 mmol), aryl halide (1 mmol), $K_4Fe(CN)_6$ (0.2 mmol), KI (50 mol%), Cs_2CO_3 (25 mol%), Ligand **2** (0.8 mmol), DMF (5 mL), pressure tube, N_2 atm, 8 h, 130 °C.

^b Yields are after work-up.

^c In the absence of KI.

CONCLUSION

In summary, a new and simple method has been developed for the copper-catalyzed cyanation of aryl halides using non-toxic $K_4Fe(CN)_6$ as the cyanide source and 3,3'-(1,4-phenylene)bis-(2-imino-2,3-dihydrobenzo[*d*]-oxazol-5-ol) as an efficient ligand under

thermal conditions. The significant advantages of this methodology are high yields, elimination of dangerous and toxic reagents and a simple work-up procedure.

EXPERIMENTAL

General procedure for the synthesis of 3,3'-(1,4-phenylene)bis-(2-imino-2,3-dihydrobenzo[d]-oxazol-5-ol) (**3**)

A mixture of *p*-benzoquinone (2.0 mmol) and 1,4-phenylenecyanamide (1 mmol) in MeCN (10 mL) was irradiated with ultrasound for 45 min at room temperature. After completion (as monitored by TLC), the solid residue was filtered from the reaction mixture and then was washed with acetone to afford the pure product **3** [9].

General procedure for the copper-catalyzed cyanation of aryl halides with $K_4Fe(CN)_6$

To a mixture of copper salt (0.3 mmol) and ligand **3** (0.8 mmol) in DMF (2.5 mL), aryl halide (1.0 mmol), base (0.25 mmol), KI (0.5 mmol), $K_4Fe(CN)_6$ (0.2 mmol) and DMF (2.5 mL) was added and the mixture was vigorously stirred at 130 °C for 8 h under a dry nitrogen atmosphere. After completion (as monitored by TLC with EtOAc and n-hexane), H_2O was added and the organic layer was extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography. The purity of the compounds was checked by 1H NMR and yields are based on aryl bromide. All the products are known and the spectroscopic data (FT-IR and NMR) and melting points were consistent with those reported in the literature [3-8].

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REFERENCES

- [1] Larock, R.C. *In Comprehensive Organic Transformations*, VCH: New York, **1989**.
- [2] (a) Rappoport, Z. *In Chemistry of the Cyano Group*, John Wiley & Sons: London, **1970**. (b) Nasrollahzadeh, M.; Bayat, Y.; Habibi, D.; Moshaei, S. $FeCl_3-SiO_2$ as a reusable heterogeneous catalyst for the synthesis of 5-substituted 1*H*-tetrazoles via [2+3] cycloaddition of nitriles and sodium azide. *Tetrahedron Lett.*, **2009**, *50*, 4435-4438. (c) Modarresi-Alam, A.R.; Khamooshi, F.; Rostamizadeh, M.; Keykha, H.; Nasrollahzadeh, M.; Bijanzadeh, H.R.; Kleinpeter, E. Dynamic 1H NMR spectroscopic study of the restricted S-N rotation in aryl-*N*-(arylsulfonyl)-*N*-(triphenylphosphoranylidene) imidocarbamates. *J. Mol. Struct.*, **2007**, *841*, 61-66. (d) Modarresi-Alam, A.R.; Nasrollahzadeh, M. Synthesis of 5-Arylamino-1*H*(2*H*)-tetrazoles and 5-Amino-1-aryl-1*H*-tetrazoles from Secondary Arylcyanamides in Glacial Acetic Acid: A Simple and Efficient Method. *Turk. J. Chem.*, **2009**, *33*, 267-280. (e) Habibi, D.; Nasrollahzadeh, M. Faraji, A.R.; Bayat, Y. Efficient synthesis of arylaminotetrazoles in water. *Tetrahedron*, **2010**, *66*, 3866-3870. (f) Habibi, D.; Nasrollahzadeh, M. ZnO as an Effective and Reusable Heterogeneous Catalyst for the Synthesis of Arylaminotetrazoles. *Synth. Commun.* **2012**, *42*, 2023-2032. (g) Habibi, D.; Nasrollahzadeh, M. Bayat, Y. $AlCl_3$ as an Effective Lewis Acid for the Synthesis of Arylaminotetrazoles. *Synth. Commun.*, **2011**, *41*, 2135-2145. (h) Shahroosvand, H.; Najafi, L.; Mohajerani, E.; Janghouri, M.; Nasrollahzadeh, M. Unusual electroluminescence in ruthenium(II) tetrazole complexes. *RSC Adv.*, **2013**, *3*, 6323-6326. (i) Shahroosvand, H.; Najafi, L.; Mohajerani, E.; Khabbazi, A.; Nasrollahzadeh, M. Green, near-infrared electroluminescence of novel yttrium tetrazole complexes. *J. Mater Chem. C*, **2013**, *1*, 1337-1344. (j) Habibi, D.; Nasrollahzadeh, M. Synthesis of arylaminotetrazoles by

ZnCl₂/AlCl₃/silica as an efficient heterogeneous catalyst. *Monatsh. Chem.*, **2012**, *143*, 925-930. (k) Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. A general synthetic method for the formation of arylaminotetrazoles using natural natrolite zeolite as a new and reusable heterogeneous catalyst. *Tetrahedron*, **2009**, *65*, 10715-10719. (l) Habibi, D.; Nasrollahzadeh, M. Silica-Supported Ferric Chloride (FeCl₃-SiO₂): An Efficient and Recyclable Heterogeneous Catalyst for the Preparation of Arylaminotetrazoles. *Synth. Commun.*, **2010**, *40*, 3159-3167. (m) Habibi, D.; Nasrollahzadeh, M.; Kamali, T.A. Green synthesis of the 1-substituted 1*H*-1,2,3,4-tetrazoles by application of the Natrolite zeolite as a new and reusable heterogeneous catalyst. *Green Chem.*, **2011**, *13*, 3499-3504. (n) Habibi, D.; Nasrollahzadeh, M. Green synthesis of formamides using the Natrolite zeolite as a natural, efficient and recyclable catalyst *J. Mol. Catal. A: Chem.*, **2013**, *378*, 148-155. (o) Nasrollahzadeh, M.; Ehsani, A.; Rostami-Vartouni, A. Ultrasound-promoted green approach for the synthesis of sulfonamides using natural, stable and reusable Natrolite nanozeolite catalyst at room temperature. *Ultrason. Sonochem.*, **2013**, DOI: 10.1016/j.ultsonch.2013.07.012. (p) Habibi, D.; Nasrollahzadeh, M. An ultrasound-promoted green approach for the *N*-formylation of amines under solvent- and catalyst-free conditions at room temperature. *C. R. Chim.*, **2013**, DOI: 10.1016/j.crci.2013.02.020. (q) Habibi, D.; Sahebkhari, H.; Nasrollahzadeh, M. and Taghipour, A. A very simple, highly efficient and catalyst-free procedure for the *N*-formylation of amines using triethyl orthoformate in water under ultrasound-irradiation. *Lett. Org. Chem.*, **2013**, *10*, 209-212.

[3] (a) Mowry, D.T. The preparation of nitriles. *Chem. Rev.* **1948**, *42*, 189-283. (b) Ellis, G.P.; Romney-Alexander, T.M. Cyanation of aromatic halides. *Chem. Rev.*, **1987**, *87*, 779-794.

[4] (a) Sandmeyer, T. Ueber die Ersetzung der Amid-gruppe durch Chlor, Brom und Cyan in den aromatischen Substanzen. *Berichte der Deutschen Chemischen Gesellschaft*, **1884**, *17*, 2650-2653. (b) Habibi, D.; Heydari, S. and Nasrollahzadeh, M. Synthesis of aryl nitriles using the stable aryl diazonium silica sulfates. *J. Chem. Res.*, **2012**, *36*, 573-574.

[5] (a) Chatani, N.; Hanafusa, T. Transition-metal-catalyzed reactions of trimethylsilyl cyanide. 4. Palladium-catalyzed cyanation of aryl halides by trimethylsilyl cyanide. *J. Org. Chem.*, **1986**, *51*, 4714-4716. (b) Zieger, H.E.; Wo, S. Titanium(IV) chloride-catalyzed cyanation of benzylic halides with trimethylsilyl cyanide. *J. Org. Chem.*, **1994**, *59*, 3838-3840. (c) Chobanian, H.R.; Fors, B.P.; Lin, L.S. A facile microwave-assisted palladium-catalyzed cyanation of aryl chlorides. *Tetrahedron Lett.*, **2006**, *47*, 3303-3305. (d) Jensen, R.S.; Gajare, A.S.; Toyota, K.; Yoshifujia, M.; Ozawab, F. A convenient procedure for palladium catalyzed cyanation using a unique bidentate phosphorus ligand. *Tetrahedron Lett.*, **2005**, *46*, 8645-8647. (e) Hatsuda, M.; Seki, M. A practical synthesis of highly functionalized aryl nitriles through cyanation of aryl bromides employing heterogeneous Pd/C: in quest of an industrially viable process. *Tetrahedron*, **2005**, *61*, 9908-9917.

[6] Schareina, T.; Zapf, A.; Beller, M. potassium hexacyanoferrate(II)-A new cyanating agent for the palladium-catalyzed cyanation of aryl halides. *Chem. Commun.*, **2004**, 1388-1389.

[7] (a) Schareina, A.; Zapf, A.; Beller, M. Improving palladium-catalyzed cyanation of aryl halides: development of a state-of-the-art methodology using potassium hexacyanoferrate(II) as cyanating agent. *J. Organomet. Chem.*, **2004**, *689*, 4576-4583. (b) Schareina, T.; Zapf, A.; Cotte, A.; Muller, N.; Beller, M. A bio-inspired copper catalyst system for practical catalytic cyanation of aryl bromides. *Synthesis*, **2008**, 3351-3355. (c) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. Copper-catalyzed cyanation of hetero-aryl halides: A new, simple and versatile biomimetic Catalyst System. *Synlett*, **2007**, 555-558. (d) Cheng, Y.-N.;

Duan, Z.; Li, T.; Wu, Y. Cyanation of Aryl Chlorides with Potassium Hexacyanoferrate(II) Catalyzed by Cyclopalladated Ferrocenylimine Tricyclohexylphosphine Complexes. *Synlett*, **2007**, 543-546.

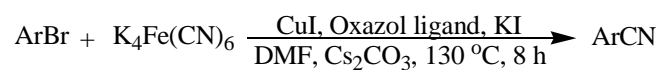
[8] (a) Zanon, J.; Klapars, A.; Buchwald, S.L. Copper-Catalyzed Domino Halide Exchange-Cyanation of Aryl Bromides. *J. Am. Chem. Soc.*, **2003**, *125*, 2890-2891. (b) Ren, Y.L.; Liu, Z.F.; Zhao, S.A.; Tian, X.Z.; Wang, J.J.; Yin, W.P.; He, S.B. Ethylenediamine/Cu(OAc)₂ H₂O-catalyzed cyanation of aryl halides with K₄[Fe(CN)₆]. *Catal. Commun.*, **2009**, *10*, 768-771. (c) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. A State-of-the-Art Cyanation of Aryl Bromides: A Novel and Versatile Copper Catalyst System Inspired by Nature. *Chem. Eur. J.*, **2007**, *13*, 6249-6254. (d) Ren, Y.; Wang, W.; Zhao, S.; Tian, X.; Wang, J.; Yin, W.; Cheng, L. Microwave-enhanced and ligand-free copper-catalyzed cyanation of aryl halides with K₄[Fe(CN)₆] in water. *Tetrahedron Lett.*, **2009**, *50*, 4595-4597. (e) Ren, Y.; Dong, C.; Zhao, S.; Sun, Y.; Wang, J.; Ma, J. Hou, C. Copper-catalyzed cyanation of benzyl chlorides with non-toxic K₄[Fe(CN)₆]. *Tetrahedron Lett.*, **2012**, *53*, 2825-2827.

[9] Habibi, D.; Nasrollahzadeh, M.; Sahebkhitiari, H. and Parish, R.V. Ultrasound-promoted synthesis of novel 2-imino-3-aryl-2,3-dihydrobenzo[d]oxazol-5-ol 2-iminooxazolidines derivatives. *Tetrahedron*, **2013**, *69*, 3082-3087.

[10] (a) Habibi, D.; Nasrollahzadeh, M.; Sahebkhitiari, H.; Sajadi, S.M. Ultrasound-Promoted Regioselective Synthesis of 1-Aryl-5-amino-1*H*-tetrazoles. *Synlett*, **2012**, *23*, 2795-2798. (b) Nasrollahzadeh, M.; Sajadi, S. M.; Maham, M.; Salaryan, P.; Enayati, A.; Sajjadi, S.A.; Naderi, K. Optimal extraction method of phenolics from the root of *Euphorbia condylocarpa*. *Chem. Nat. Comp.*, **2011**, *47*, 434-435.

A New Oxazole Ligand for the Copper-catalyzed Cyanation of Aryl halides with $\text{K}_4[\text{Fe}(\text{CN})_6]$

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Cyanation of aryl halides