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Copper-catalyzed cyanation of benzyl chlorides with non-toxic $K_4[Fe(CN)_6]$

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ABSTRACT

Copper-based catalysts were firstly introduced into the cyanation of benzyl chlorides with non-toxic $K_4[Fe(CN)_6]$. The presented method avoids the use of extremely poisonous alkali cyanides and precious palladium catalysts. No other reagent apart from CuI, $K_4[Fe(CN)_6]$ and toluene was used in the cyanation, showing that the presented protocol is simple and practical. A series of benzyl chlorides were smoothly cyanated in up to 85% yield under the optimal conditions.

Cyanation of alkyl halides is an important synthetic transformation as the resulting products are extremely useful synthetic intermediates that have widely been used in the construction of a variety of compounds such as amines, nitrogen-containing heterocycles, carboxylic acids, and carboxylic acid derivatives.[1] NaCN and KCN are generally used as the cyanating agents for cyanation of alkyl halides.[2] However, an extremely poisonous character of these cyanide salts seriously restricts their application from environmental perspectives. Recently, several methods for cyanation of alkyl halides with lower poisonous trimethylsilyl cyanide (Me_3SiCN) as the cyanating agent have been developed.[3] Unfortunately, the use of Me_3SiCN has some inconvenience, it is expensive, sensitive to moisture, and easily liberates highly poisonous hydrogen cyanide.

More recently, we introduced non-toxic and inexpensive $K_4[Fe(CN)_6]$[4–6] as the cyanating agent for the cyanation of alkyl halides catalyzed by palladium compounds.[7] Considering the fact that copper salts are less expensive than palladium compounds, our attention was drawn to developing a copper-catalyzed procedure. Here, we report a simple and practical copper-catalyzed method for the cyanation of benzyl chlorides with $K_4[Fe(CN)_6]$ as the cyanating agent.

At the start of our investigations, the cyanation of benzyl chloride was chosen as a model reaction to demonstrate the catalytic effectiveness of various copper compounds. As shown in Table 1, the cyanation using CuI in combination with DMEDA, a typical and effective catalyst system for the cyanation of aryl halides,[8] afforded the desired product in 6% yield (Table 1, entry 1). Changing DMEDA to other N-ligands such as ethylenediamine, 1,2-diaminobenzene, triphenylphosphine, 2,2′-bipyridine, and 1,10-phenanthroline did not result in satisfactory results (Table 1, entries 2–7). However, it was delight that the desired product was obtained in a high yield in the absence of ligand (Table 1, entry 8). Surprisingly, an addition of 1.5 mmol Na_2CO_3 led to a significant decrease in yield (Table 1, entry 9), while our previous investigations revealed that the cyanations with Pd catalysts were highly dependent on the amount and type of inorganic base.[7] The cyanation reactions proceeded efficiently with as low as 20 mol % ligand-free CuI catalyst. We tried to reduce the catalyst loading to 10 mol %, but found that this was not possible without sacrificing the product yield even if the reaction time was prolonged to 30 h. The same was true when we tried to decrease the reaction temperature or the ratio of $K_4[Fe(CN)_6]$ to benzyl chloride. Our experimental results indicated that the presence of oxygen badly prevented benzyl chloride from being cyanated, which possibly resulted from the oxidation destruction of catalytically active Cu(I) species by oxygen.[8b] Thus the reactions were required to be performed in an inert ambiance to avoid or suppress the deactivation of the catalysts.

Subsequently, various ligand-free copper salts were examined to understand the effect of the metal precursors on the reaction. Among the screened copper salts, CuI turned out to be the most effective one (Table 1, entries 8–19). CuCN had comparable catalytic effectiveness with CuI, while most of the tested Cu(II) salts were less effective. A considerable amount of 1,2-diphenylethane and benzylacetate products were respectively observed in the case of using $CuBr_2$ and $Cu(OAc)_2{\cdot}H_2O$ as the catalysts (Table 1, entries 14, 15). According to the literatures related to $K_4[Fe(CN)_6]$ as the cyanating agents[8,9] as well as our previous investigations on Pd-catalyzed cyanation of benzyl chloride,[7] high-boiling, and polar solvents were preferred in order to ensure sufficient solubility.

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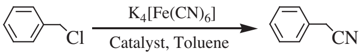
Table 1
Copper-catalyzed cyanation of benzyl chloride[a]



Entry	Ligand	Copper salt	Conv.[b] (%)	Yield[b] (%)
1	DMEDA	CuI	~100	6
2	Ethylenediamine	CuI	~100	0
3	1,2-Diaminobenzene	CuI	~100	0
4	Triphenylphosphine[d]	CuI	100	30
5	2,2′-Bipyridine	CuI	~100	59
6	1,10-Phenanthroline	CuI	~100	50
7[c]	1,10-Phenanthroline	CuI	100	47
8	–	CuI	~100	78
9[c]	–	CuI	~100	69
10	–	CuCl	93	57
11	–	CuBr	99	39
12	–	CuCN	100	70
13	–	Cu_2O	100	22
14	–	$CuBr_2$	100	0
15	–	$Cu(OAc)_2{\cdot}H_2O$	90	28
16	–	$CuSO_4{\cdot}5H_2O$	100	41
17	–	$Cu(NO_3)_2{\cdot}3H_2O$	70	0
18	–	$CuCl_2{\cdot}2H_2O$	100	44
19	–	CuO	29	8

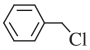
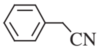
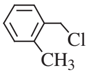
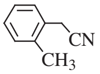
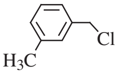
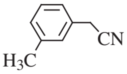
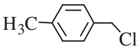
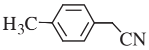
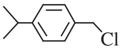
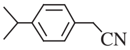
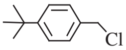
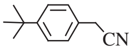
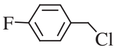
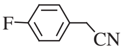
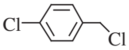
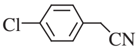
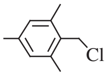
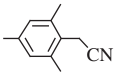
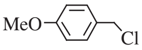
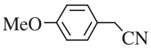
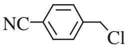
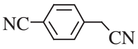
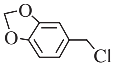
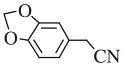
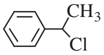
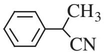
[a] Reaction conditions: benzyl chloride (1 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), ligand (0.5 mmol), copper salts (0.3 mmol), toluene (1 mL), N_2, 180 °C, 20 h.
[b] Determined by GC.
[c] Additional 1.5 mmol Na_2CO_3 was used.
[d] 0.6 mmol PPh_3 was used.

However, the cyanations with polar solvents such as NMP (*N*-methyl-2-pyrrolidone) and DMF afforded benzyl cyanide in low yields, while toluene as solvent was optimal in terms of the yield and selectivity.[10]

In some cases, the formation of a small amount of benzyl alcohol by-product was observed, resulting from the reaction between benzyl chloride and trace amounts of H_2O in the solvent. Thus, several experiments were conducted where different amounts of H_2O were added into the reaction systems to investigate the effect of H_2O concentration on the reactions.[11] The experimental results suggested that less than 4.8 vol% H_2O did not remarkably restrain the cyanation. Attempts to developing a procedure for the cyanation with environmentally benign water as the solvent were not successful. For instance, only 30% yield of benzyl cyanide, accompanied by a considerable amount of benzyl alcohol was obtained under the condition of H_2O as the solvent, CuI as the catalyst, 180 °C, and 20 h.

Based on these results we chose the following conditions for further exploration of substrates: 20–50 mol % CuI, 0.5 equiv $K_4[Fe(CN)_6]$, 1 mL toluene, 180 °C, and 20 h. As shown in Table 2, the reactions were able to tolerate several functional groups such as fluoro, chloro, and methoxy groups. Several benzyl chlorides with alkyl substituents in the benzene ring were converted into the desired products in high yields. The cyanations of 4-, 3-, and 2-methylbenzyl chlorides gave similar yields (Table 2, entries 2–7). However, two methyl substituents in ortho-position lowered the yield considerably (Table 2, entry 16). 4-Fluorobenzyl chlorides performed reasonably well (85% yield), whereas 4-chlorobenzyl chlorides were converted in lower yield to 4-chlorobenzyl cyanide (Table 2, entries 12, 14). By the way, the side coupling reaction did not occur on the aromatic chloride in the case of using 4-chlorobenzyl chloride. Conversions of 4-methoxylbenzyl chloride, 4-cyanobenzyl chloride, 1-naphthylacetonitrile, and α-chloroethylbenzene were of poor selectivity under our reaction conditions. We had tried the reaction with allylic chlorides, but no cyanation product was observed.

Table 2
Cyanations of various benzyl chlorides catalyzed by CuI[a]

Entry	Substrate	Product[b]	CuI (mol %)	Yield[c] (%)
1			30	78
2			30	82
3			20	70
4			30	76
5			20	63
6			30	82
7			20	77
8			30	60
9			20	57
10			30	58
11			20	68
12			30	85
13			20	60
14			30	43
15			20	48
16			30	64
17			50	66
18			30	33
19			30	27
20			50	42
21			30	8

[a] Reaction conditions: benzyl chloride (1 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), CuI, toluene (1 mL), N_2, 180 °C, 20 h. For the detailed experimental procedure see reference.[14]
[b] Identified by GC–MS data.
[c] Determined by GC.

Upon the basis of previous literatures,[12] a plausible mechanism is proposed and presented in Scheme 1, omitting some details such as ancillary ligands, etc. The catalytic cycle starts with the oxidative addition of benzyl chloride to the catalytically active Cu(I) species. The resulting benzyl copper species, which is possibly η^1-benzyl or η^3-benzyl copper intermediate,[13] undergoes a transmetallation to afford benzyl copper cyanide intermediate, followed by a reductive elimination to give the expected nitrile and regenerate the catalytically active Cu(I) species. The ordering of oxidative addition and transmetallation steps in such a catalytic cycle is unknown, so another possibility that the transmetallation step precedes oxidative addition can take place (Scheme 1b).[12]

In conclusion, copper-based catalysts were firstly demonstrated to be effective in the cyanation of benzyl chlorides with non-toxic $K_4[Fe(CN)_6]$, meanwhile presenting a simple and practical method that is ligand-, base-free and avoids the use of extremely poisonous alkali cyanides and precious palladium catalysts.[7] A series of benzyl chlorides were smoothly cyanated in up to 85% yield applying only CuI as catalyst, $K_4[Fe(CN)_6]$ as the cyanating agent, and toluene as the solvent.

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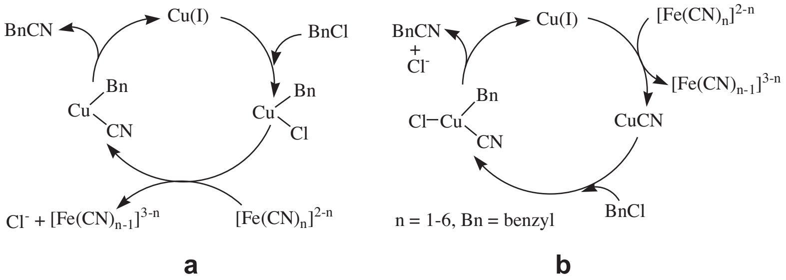

Scheme 1. Proposed mechanism, omitting some details such as ancillary ligands, etc.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.109.

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10. For the detailed experimental data, see Table S3 in the Supplementary data.
11. For the detailed experimental data, see Table S4 in the Supplementary data.
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14. *General experimental procedure for cyanation of benzyl chlorides*: 0.3 mmol CuI and 0.3 mL toluene were added into a dried 40 mL tube under a dry nitrogen atmosphere. After the mixture was stirred at room temperature for about 1 min, 0.5 mmol $K_4[Fe(CN)_6]$, 1 mmol benzyl chloride, and 0.7 mL toluene were added under a dry nitrogen atmosphere. The reaction tube was sealed with a septum and placed in a constant-temperature oil bath set at 180(±5) °C to perform the reaction for 20 h. Once the reaction time was reached, the mixture was cooled to room temperature, then 1 mL solution of acetophenone (0.8 mmol/mL in dichloromethane) was added as an internal standard into the reaction tube. Subsequently, GC analysis of the mixture provided the yield of the product (note: in order to decrease the analysis error, the mixture after the reaction was not purified or concentrated). The cyanation product was identified by GC–MS data.