

AgI–PEG400–KI Catalyzed Environmentally Benign Synthesis of Aroyl Cyanides Using Potassium Hexacyanoferrate(II) as the Cyanating Agent

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Abstract: A practical cyanation of aroyl chlorides with 0.2 equivalent of non-toxic cyanide source, $K_4[Fe(CN)_6]$, 3 mol% AgI, 4 mol% PEG-400, and 3 mol% KI as the catalyst system is described. The reactions were performed in DMF at room temperature and provided the corresponding aroyl cyanides in 64–89% yield, typically in less than ten hours.

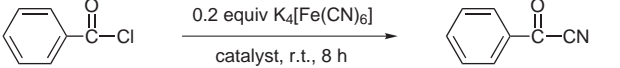
Key words: green chemistry, catalysis, synthesis, phase-transfer catalysis, cyanation

Acyl cyanides are important intermediates for organic synthesis. They have been used for the synthesis of 1,2-diketones,¹ β,γ -unsaturated ketones,² α -cyano ketones,³ diaryl ketones,⁴ allenic and propargylic ketones,⁵ β -enamino diketones,⁶ β -enamino keto esters,⁶ β -enamino diesters,⁶ β -ketoesters,⁷ cyanohydrin esters,⁸ *O*-benzoyl cyanohydrin adducts,⁹ cyanohydrin benzoates,¹⁰ alkenylated malonic diamide,¹¹ polysubstituted cyclopentadienes,¹² azazirconacyclopentenes,¹³ 5-acyltetrazoles,¹⁴ 5-substituted uracil derivatives,¹⁵ naphthols,¹⁶ isoquinolones,¹⁶ isocoumarins,¹⁶ and cyano-substituted 1,2,4-trioxolanes,¹⁷ etc. The early development of the chemistry of acyl cyanides was also reviewed.¹⁸ The general synthetic methods for acyl cyanides include using mercuric cyanide,¹⁹ silver cyanide,²⁰ cuprous cyanide,²⁰ potassium cyanide,²¹ tributyltin cyanide,²² and trimethylsilyl cyanide²³ as cyanide sources. However, all metal cyanides are highly poisonous, and trimethylsilyl cyanide is sensitive to moisture and can easily liberate toxic hydrogen cyanide. Choudary²⁴ reported an indirect method to prepare aroyl cyanides by peroxovanadium complex catalyzed selective oxidation of methylene of benzyl cyanides, which also required the above-mentioned toxic reagents as original cyanide sources.

Potassium hexacyanoferrate(II), $K_4[Fe(CN)_6]$, is non-toxic and is even used in the food industry for metal precipitation. In addition, it has been described as an anti-agglutinating auxiliary for table salt (NaCl). $K_4[Fe(CN)_6]$ is commercially available on a ton scale and is even cheaper than KCN. Recently, $K_4[Fe(CN)_6]$ has been used as a cyanide source in the synthesis of benzonitriles.²⁵ In this study, we report an efficient method to aroyl cyanides

using non-toxic $K_4[Fe(CN)_6]$ as the cyanide source. This is the first example that the intensely toxic metal cyanides are avoided in cyanation of aroyl chlorides.

Initially, benzoyl chloride was used as a substrate to examine the feasibility of cyanation using $K_4[Fe(CN)_6]$ under different conditions. It was found that the suitable ratio of benzoyl chloride to $K_4[Fe(CN)_6]$ was 5:1 for the synthesis of benzoyl cyanide. That indicated all cyanide ions bound to Fe in $K_4[Fe(CN)_6]$ were transferred to benzoyl cyanide. It was also observed that the presence of water resulted in the hydrolysis of benzoyl chloride and benzoyl cyanide, which then led to the formation of $[PhCOOC(CN)_2Ph]$ and a polymer; this also explained the low yield of the reaction. Therefore, it is necessary to carry out the reaction under anhydrous conditions in the presence of a catalyst. In order to select the appropriate catalyst, the reaction was performed using different catalytic systems. Although no reaction occurred in the absence of catalyst (Table 1, entry 1) or in the presence of ZnI_2 (Table 1, entry 2), a combined ZnI_2 –PEG400–KI system gave 34% yield of benzoyl cyanide at room temperature (Table 1, entry 3). The CuX –PEG400–KI systems also gave low yields (Table 1, entries 4–6). Meanwhile, NiX_2 –PEG400–KI systems produced the desired product in moderate yield (Table 1, entries 7 and 8). Fortunately, it was found that silver compounds could efficiently catalyze cyanation of benzoyl chloride with $K_4[Fe(CN)_6]$ (Table 1, entries 9–17). Among them, the AgI–PEG400–KI system produced the benzoyl cyanide in the highest yield (Table 1, entries 12). Furthermore, the appropriate amount of AgI, PEG400, and KI was 3 mol%, 4 mol%, and 3 mol%, respectively. A catalytic amount of AgI could remarkably enhance the reaction rate because the silver cation could promote $K_4[Fe(CN)_6]$ to release the cyanide ion. The role of PEG400 was as a phase-transfer catalyst, which could form the stable complex $(K-PEG400)^+$ and $(Fe-PEG400)^{2+}$ with $K_4[Fe(CN)_6]$ to liberate more free CN^- . KI could improve the solubility of AgI and increase the concentration of iodide ion in the solution. The iodide anion in solution acting as a good leaving group could efficiently exchange with the chloride of benzoyl chloride to facilitate the nucleophilic substitution reaction. In addition, quaternary ammonium salts were also tested as phase-transfer catalysts, but lower yields were obtained than with PEG400 (Table 1, entries 15–17). In order to ensure sufficient solubility of reactants, the reaction required polar aprotic solvents. Thus, *N,N*-dimethyl

Table 1 Cyanation of Benzoyl Chloride with $K_4[Fe(CN)_6]$


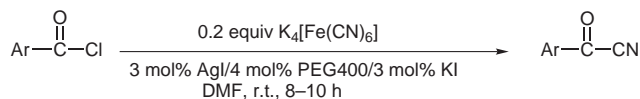
Entry	Catalytic system ^a	Solvent	Yield (%) ^b
1	None	DMF	0
2	ZnI ₂	DMF	0
3	ZnI ₂ -PEG400-KI	DMF	34
4	CuCl-PEG400-KI	DMF	10
5	CuI-PEG400-KI	DMF	32
6	Cu(BF ₄) ₂ -PEG400-KI	DMF	20
7	NiCl ₂ -PEG400-KI	DMF	40
8	NiI ₂ -PEG400-KI	DMF	51
9	AgNO ₃ -PEG400	DMF	53
10	AgCl-PEG400-KI	DMF	61
11	AgI	DMF	37
12	AgI-PEG400-KI	DMF	78
13	AgI-PEG400-KI	DMAc	70
14	AgI-PEG400-KI	NMP	71
15	AgI-(CH ₃) ₄ NI-KI	DMF	60
16	AgI-(C ₂ H ₅) ₄ NI-KI	DMF	61
17	AgI-(<i>n</i> -C ₄ H ₉) ₄ NI-KI	DMF	69



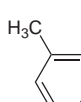



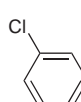




^a The general catalytic systems utilize metal compounds (3 mol%), phase-transfer catalyst (4 mol%), and (or) KI (3 mol%).

^b Isolated yields.

acetamide (DMAc), NMP, and DMF were attempted, and the cheap and readily available DMF gave the best result (Table 1, entries 12–14).

To explore the generality and scope of the cyanation of aroyl chlorides with $K_4[Fe(CN)_6]$ catalyzed by AgI-PEG400-KI, representative aroyl chlorides as substrates were examined in DMF at room temperature (Scheme 1, Table 2).²⁶ All aroyl chlorides, including those with electron-withdrawing or electron-donating substituents on aromatic rings reacted well under these conditions. Both TLC and GC analyses indicated that almost no dimers or polymers were produced for the substrates in all cases except for Table 2, entries 8 and 9, where a small amount of dimer was observed. This might be due to the electron-withdrawing effect of the halogen groups on the phenyl ring, which rendered the carbonyl groups more active to react with two or more cyanides to form dimers or polymers. It is worth mentioning that heteroaroyl chlorides, such as 2-furoyl chloride and 2-thiophenecarbonyl chloride, also performed well under these conditions (Table 2, entries 10 and 11). All reactions were complete within eight to ten hours at room temperature.

**Scheme 1****Table 2** Cyanation of Aroyl Chlorides to the Corresponding Aroyl Cyanides with $K_4[Fe(CN)_6]$ ^a

Entry	Ar	Time (h)	Yield (%) ^b	Mp (°C) or bp (°C/mmHg) (Lit. ^{21b})
1		8	78	31.5–33 (31–32)
2		10	89	130–132/30 (130–131/30)
3		10	80	27–28.5 (26–27.5)
4		10	84	49–50 (48–49)
5		10	88	56–58 (56.5–57.5)
6		8	79	75.5–77
7		8	83	79–81.5
8		8	64	41–42.5 (41–42)
9		8	65	66–67 (66–67)
10		9	86	144–145/25 (145–146/25)
11		9	84	54–56 (53.5–54.5)

^a All products were characterized by comparison of their mps or bps, IR, and ¹H NMR spectra with those of authentic samples.

^b Yields refer to isolated products.

In conclusion, we have developed an environmentally benign method for cyanation of aroyl chlorides to synthesize aroyl cyanides by using non-toxic potassium hexacyanoferrate(II) instead of strongly toxic metal cyanides. The reactions could be efficiently catalyzed by the AgI-PEG400-KI system under mild conditions in good yield. This protocol is suitable for the preparation of both (un)substituted benzoyl cyanides and heteroaroyl cyanides.

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- (26) **General Procedure:** A mixture of AgI (0.1 g, 0.45 mmol), PEG400 (0.24 g, 0.6 mmol), KI (0.08 g, 0.45 mmol), and $K_4[Fe(CN)_6]$ (1.15 g, 3 mmol) (dried at 80 °C under vacuum for 24 h and finely powdered prior to use) in anhyd DMF (10 mL) was first stirred for 10 min, then aroyl chloride (15 mmol) was added. The mixture was stirred for the appropriate time indicated in Table 2 at r.t. The progress of the reaction was monitored by TLC (PE–EtOAc, 5:1). Then CH_2Cl_2 (20 mL) was added. The suspension was filtered to remove the solid, the filtrate was washed with cold H_2O (3 × 30 mL), and dried over anhyd $MgSO_4$. Then the solvent was removed by distillation and the residue was crystallized from hexane to give the product. 2-Chlorobenzoyl cyanide: IR (KBr): 2089 (C≡N), 1776 cm^{-1} (C=O). 1H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.81 (m, 4 H, Ph). Anal. Calcd for C_8H_4ClNO : C, 58.03; H, 2.44; N, 8.46. Found: C, 57.91; H, 2.50; N, 8.39. 3-Chlorobenzoyl cyanide: IR (KBr): 1964 (C≡N), 1793 cm^{-1} (C=O). 1H NMR ($CDCl_3$, 400 MHz): δ = 7.22–7.78 (m, 4 H, Ph). Anal. Calcd for C_8H_4ClNO : C, 58.03; H, 2.44; N, 8.46. Found: C, 58.11; H, 2.49; N, 8.53. 2-Furoyl cyanide: IR (KBr): 2067 (C≡N), 1758 cm^{-1} (C=O). 1H NMR ($CDCl_3$, 400 MHz): δ = 6.70–7.69 (m, 3 H, Furan). Anal. Calcd. for $C_6H_3NO_2$: C, 59.51; H, 2.50; N, 11.57. Found: C, 59.70; H, 2.43; N, 11.49. 2-Thiophenecarbonyl cyanide: IR (KBr): 2052 (C≡N), 1766 (C=O). 1H NMR ($CDCl_3$, 400 MHz): δ = 7.10–7.71 (m, 3 H, Thiophene). Anal. Calcd for C_6H_3NOS : C, 52.54; H, 2.20; N, 11.66. Found: C, 52.42; H, 2.30; N, 11.72.