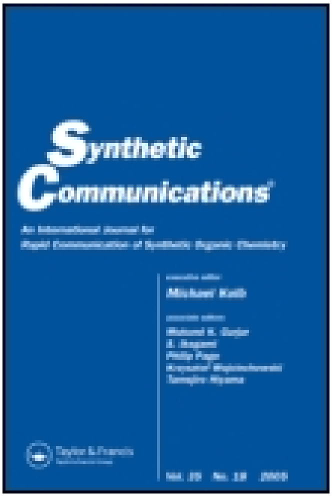

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Yu-Qing Cao [a], Yun-Fei Du [a], Bao-Hua Chen [a] & Ji-Tai Li [a]

[a] College of Chemistry and Environmental Science, Hebei University, Baoding, 071002, P.R. China

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A Novel Heterogeneous Synthesis of Acyl Cyanides Catalyzed by PEG400 and Zinc Iodide

Yu-Qing Cao,*[*] Yun-Fei Du, Bao-Hua Chen, and Ji-Tai Li

College of Chemistry and Environmental Science, Hebei University,
Baoding, P.R. China

ABSTRACT

Aroyl cyanides were readily synthesized in moderate yields by the cyanation of aroyl chlorides with dry powdered potassium cyanide under the catalysis of PEG400 and zinc iodide in dichloromethane at room temperature. A preliminary study on the one-pot preparation of acetyl cyanide was also reported.

Key Words: Aroyl cyanides; Aroyl chlorides; KCN; PEG400.

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[*] Correspondence: Yu-Qing Cao, College of Chemistry and Environmental Science, Hebei University, Baoding 071002, P.R. China; E-mail: pharm_hbu@yahoo.com.

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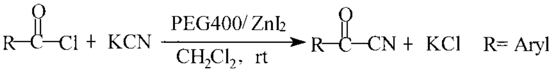
INTRODUCTION

Acyl cyanides have played important roles in organic synthesis which allow numerous transformations to such compounds as α-ketoacids, 1-amino-2-ethanol derivatives, and a wide range of heterocyclic compounds, furthermore, some of them even show significant biological activity in agricultural use and are useful as mild and selective acylating agents.[1] Literature survey indicates that only a small number of methods have been reported for the preparation of this useful class of compounds, and seldom of them can be regarded as fairly satisfactory. Benzoyl cyanide was first prepared in 1832 by the reaction of benzoyl chloride with mercuric cyanide.[2] Later on, silver cyanide and cuprous cyanide[3] were used as cyanogen sources in the cyanating reaction of acyl chlorides, which only afforded moderate yields. It was not until trimethylsilyl cyanide (TMSCN),[4] acyl iodide,[5] and tributyltin cyanide[1] were used that the satisfactory yields were obtained. However, none of those reagents is readily available and some of them even pose potential danger to the health and generate severe pollution to the environment. In this respect, some other cheaper or more available cyanogen sources, such as hydrogen cyanide, sodium cyanide, and potassium cyanide should be preferable.

The cyanation of aroyl chlorides with potassium cyanide was ever performed in acetonitrile, catalyzed either by small amount of water[6] or ultrasonic radiation.[7] However, the presence of water or the ultrasound will lead to the formation of more aroyl cyanide dimers [R–CO–OC(CN)$_2$–R] and colorful polymers, which are the main reasons for the low yields. On the other hand, the catalytic water will be partially consumed by the aroyl chlorides at the reflux temperature in acetonitrile, which will greatly decrease the catalytic efficiency of the water as well as the overall yields of the aroyl cyanides. Tetrabutyl ammonium bromide has been used as phase transfer catalyst (PTC) in the two-phase reaction of aroyl chlorides with aqueous potassium cyanide. However, lower temperature was needed to reduce the hydrolysis of the aroyl chlorides and aroyl cyanides, both of which are sensitive to water. In addition, a larger amount of dimers were formed in the presence of water.[2]

Polyethylene glycols (PEGs) can be regarded as the acyclic crown-ether and have been used as PTC in many organic reactions owing to their stability, low cost, poisonlessness, and easy availability.[8–10] In our previous work, PEG400 has been used as PTC for the synthesis of primary aliphatic and aromatic nitriles.[11] In the continuation of our investigation on the research of using PEGs as PTC, we herein report an alternative and an efficient method for the preparation of aroyl cyanides by the cyanation of aroyl chlorides with KCN catalyzed by PEG400 (Sch. 1). We also introduced catalytic



Scheme 1.

amount of zinc iodide to increase the reaction rate based on the fact that iodide anion, as both a strong nucleophilic reagent and a good leaving group, had been extensively used in the S_N2 substitution reactions. The experimental results were listed in Table 1.

Benzoyl chloride was used as substrate to study the catalytic efficiency. It was found that lower dosage of PEG400 could not catalyze the reaction effectively, and higher dosage would undoubtedly lead to more loss of products during the washing procedure. Compared with the case without the participation of ZnI_2, the reaction rate was greatly enhanced with the introduction of ZnI_2. Based on the results of the comparative experiments, we suggest an amount of 4 mol% PEG400 and 1.6 mol% ZnI_2 to be used and an excess (20%) of dried and fine powdered potassium cyanide was necessary for ensuring the complete conversion of the acyl chlorides.

Both TLC and GC showed that only a negligible amount of colorful dimers was found for the substrates in all cases except for the ones in entries **6** and **7**. Generally, it supported the idea that potassium cyanide was a close ion pair in the reaction system, which greatly decreased the formation of the dimers.[10] However, when it came to the entries **6** and **7**, the formation of dimers could not be neglected, which was found to be the major reason that

Table 1. Cyanation of aroyl chlorides to the corresponding aroyl cyanides.

Entry	R	Time (hr)	Yield[a] (%)	M.p. (°C) or b.p. (°C/mmHg) Found	Lit.[7]
1	C_6H_5	4.5	76	31–32	31.5–32.5
2	$4\text{-}CH_3C_6H_4$	6	82	48–49	48.9–49.7
3	$2\text{-}CH_3C_6H_4$	6	86	130–131/30	75–76/4
4	$3\text{-}CH_3C_6H_4$	6	78	26–27.5	27–28[2]
5	$4\text{-}MeOC_6H_4$	7	88	56.5–57.5	57–58
6	$4\text{-}ClC_6H_4$	4	60	41–42	41.4–42.1
7	$4\text{-}BrC_6H_4$	4	64	66–67	66–67[4]
8	2-Furyl	5	86	145–146/25	86–88/15
9	2-Thienyl	5	83	53.5–54.5	54–55[6]

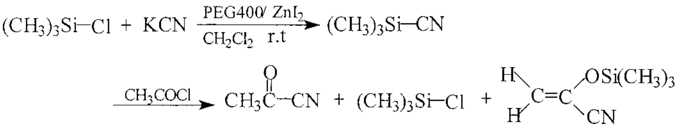
[a] Yield of isolated product calculated according to total aroyl chlorides.

led to their lower yields. We proposed that this might due to the electron-withdrawing effect of the halogen groups on the benzene ring, which made the carbonyl group highly active to react with two cyanides to form dimers or polymers. While for the substrate in entry **5**, because of the electron-donating effect of the methoxy group, less dimer was formed. However, the less reactivity of the substrate required longer reaction time.

It was shown by GC and TLC that nearly 30% of PEG400 was acylated by aroyl chloride to form esters in the comparative experiment concerning the reaction of PEG400 with benzoyl chloride catalyzed by zinc iodide performed at room temperature covering a period of time of 12 hr. However, the experiment indicated that the acylated PEG400 still possesses certain ability of phase transfer catalysis, since its structure also resembles that of the acyclic crown-ether.

However, the experimental results concerning acetyl chloride, propionyl chloride, and chloroacetyl chloride show that no acyl cyanides were obtained and nearly 90% of acyl chloride was recovered after the reactions were performed under reflux covering a period of time as long as 24 hr, which might indicate that the method might not be suitable for the preparation of aliphatic acyl cyanides.

It has been reported by the previous literature that aliphatic acyl cyanides may be prepared by reaction of aliphatic acyl chlorides with TMSCN.[12] Based on this and our reported method for the preparation of TMSCN catalyzed by PEG400,[13] we launched an investigation on a one-pot synthesis of aliphatic acyl cyanide using TMSCl as catalyst, since it was easily conceived that the formed TMSCN in the first step could be converted back into TMSCl in the second step, which could be used circularly (Sch. 2). The readily available acetyl chloride was used as substrate in our preliminary study. However, it was found that catalytic amount of TMSCl could not afford acetyl cyanide at all. In the case, the majority of acetyl chloride (85%) was recovered, similar to the case without the participation of TMSCl discussed above. Equal molar ratio of TMSCN and acetyl chloride (1 : 1) was finally proposed to participate in the second-step conversion. With the formation of TMSCN completed, acetyl chloride was added dropwise and kept the mixture refluxing for 2 hr. After the removal of the inorganic salts by filtration



Scheme 2.

and dichloromethane by distillation, 70% of TMSCl was recovered and 55% of acetyl cyanide was obtained. Surprisingly, α-[(trimethylsilyl)oxy] acrylonitrile was further separated by distillation under reduced pressure, and the structure was confirmed by comparing its IR and H NMR with that of the pure sample prepared according to the previous literature.[14] The mechanism concerning its formation is under investigation.

The experimental results indicated that the present procedure for the preparation of aroyl cyanide compared favorably well with the previous methods for its high yield, mild reaction condition, and availability of the starting materials. The method described for the preparation of acetyl cyanide should also be applicable to the preparation of other aliphatic acyl cyanides, the results as well as the mechanism will be discussed in due course.

EXPERIMENTAL

GC-17A is a column packed with SE30 on Chromsorb using *o*-terphenyl as an internal standard. TLC was GF_{254} thin layer chromatography with petroleum ether/ethyl acetate (10/1) as eluent. Melting points were determined on microscopy apparatus and were uncorrected. Potassium cyanide was dried at 120°C under vacuum for 24 hr and finely powdered. All the glass apparatus were oven-dried before use and all the reactions were performed in a hood with good ventilation.

Typical Procedure for the Preparation of Benzoyl Cyanide

A 100 mL three-necked, round-bottomed flask equipped with a magnetic bar and nitrogen inlet tube was charged with 0.5 g (0.0016 mol) ZnI_2, 30 mL of CH_2Cl_2, 1.5 g (0.004 mol) of PEG400, and 7.8 g (0.12 mol) of KCN, after stirring for 20 min, 14 g (0.100 mol) of benzoyl chloride was added. Then the mixture was vigorously stirred under nitrogen at room temperature. The process of the reaction was monitored by TLC. When the spot of the benzoyl chloride on the TLC was completely disappeared, the stirring was continued for half-an-hour. The solid residue was filtered off and washed with dichloromethane, and the filtrate was washed with cold water (2 × 30 mL). The dichloromethane layer was separated, dried over magnesium sulfate, filtered and distilled to give the crude benzoyl cyanide which was further purified by recrystallization from hexane, 11.2 g of colorless crystal was obtained. Yield, 76%, m.p. 31–32°C.

Typical Procedure for the Preparation of Acetyl Cyanide and α-[(Trimethylsilyl)oxy] Acrylonitrile

A 0.5 g of ZnI_2, 30 mL of CH_2Cl_2, 2 g (0.005 mol) of PEG400, 7.8 g (0.12 mol) of potassium cyanide, and 12 g (0.11 mol) of TMSCl were added to a 100 mL three-necked, round-bottomed flask equipped with a magnetic bar and nitrogen inlet tube. The mixture was stirred under nitrogen at room temperature for 20 hr. With the filtering off the inorganic salts, the liquid filtrate was fed back to the original flask, and 7.9 g (0.10 mol) of acetyl chloride was added dropwise under nitrogen atmosphere. The mixture was kept reflux for 2 hr. After the removal of CH_2Cl_2, 8.4 g of TMSCl was recycled (70%) and 3.8 g of acetyl cyanide was obtained. Yield, 55%, b.p. 91–93°C (Lit.[15] 93°C). A 2.1 g of α-[(trimethylsilyl)oxy] acrylonitrile was further collected by distillation at reduced pressure. Yield, 15%, calculated based on acetyl chloride. B.p. 80–82°C/50 mmHg (Lit.[14] 58–59°C/40 mmHg). Identification was based on IR and H NMR spectroscopies. $\nu_{\max}$ IR (KBr): 2950, 2230, 1600, 1210, 1050, 800, 750. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.29 (s, 9 H), 5.03 (s, 1 H), 5.09 (s, 1 H).

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