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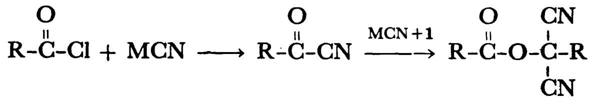
Reaction of Aromatic Acyl Chlorides with Potassium or Sodium Cyanide Impregnated onto Amberlite XAD Resins. Efficient Synthesis of Aromatic Acyl Cyanides

Kazuaki SUKATA
Nihon Tokushu Kagaku Kogyo Co., Ltd., 1, Takijiri-aza-hashimoto,
Izumi-cho, Iwaki, Fukushima 970-04
(Received October 16, 1986)

The effects of alkali metal cyanide impregnated on Amberlite XAD resins (KCN/XAD, NaCN/XAD) have been examined using the cyanation of benzoyl chloride. In benzene, benzoyl cyanide was obtained in a very high yield with high selectivity under mild conditions. It is proposed that the reaction occurs on the surface of the resin. On the basis of the result obtained in the absence of any solvent, the reactivity of KCN/XAD toward dimerization of benzoyl cyanide has been found to be much poorer than that of KCN in solution. Although the reaction of acyl chlorides with KCN/XAD or NaCN/XAD in benzene gave various acyl cyanides in good to excellent yields, no aliphatic acyl cyanide could be obtained.

Acyl cyanides are versatile and important synthetic intermediates and have classically been prepared by the reaction of acyl chloride (**1**) with mercury(II) cyanide, silver cyanide, or copper(I) cyanide.[1] Subsequently, improved methods have been developed using thallium(I) cyanide,[2] trimethylsilyl cyanide,[3] tributyltin cyanide,[4] or acyl iodide.[5] Although these procedures give good results, the use of them are limited in view of the availability and cost of cyanating agents. Also the liquid–liquid two phase reaction of **1** with NaCN has been reported.[6] This reaction, however, gives substantial quantities of the acyl cyanide dimer (**3**) as well as the acyl cyanide (**2**).



$$R-\overset{O}{\overset{\|}{C}}-Cl + MCN \longrightarrow R-\overset{O}{\overset{\|}{C}}-CN \xrightarrow{MCN+1} R-\overset{O}{\overset{\|}{C}}-O-\underset{CN}{\underset{|}{\overset{CN}{\overset{|}{C}}}}-R$$

M: Na, K

1 **2** **3**

Recently, it has been reported that the reaction of **1** with KCN is remarkably promoted by the addition of a trace amount of water[7] and irradiation with ultrasound[8] giving **2** in good yields. However, the former requires a high reaction temperature and the addition of a crown ether in the case of less reactive *p*-methoxybenzoyl chloride. In the latter, the yield of **3** is still high.

On the other hand, in a previous paper,[9] it has been reported that substitution reactions are accelerated by a simple impregnation of reagents on macroporous polymer resins such as Amberlite XAD-2, XAD-4, and XAD-7. These polymer resins have no ion-exchange capabilities and no phase-transfer catalysis functions. This paper reports that the reaction of aromatic acyl chloride with NaCN or KCN impregnated on XAD-2 or XAD-4 (NaCN/XAD-2,4 or KCN/XAD-2,4) gives **2** in good yields with high selectivities under mild conditions.

Results and Discussion

In order to ascertain the effect of solvents, the reaction of benzoyl chloride (**4**) with KCN/XAD-2 was carried out in various solvents. Table 1 shows the results. The coversion rate of **4** was in the order of acetonitrile ≫ benzene>CH_2Cl_2, hexane, tetrahydrofuran (THF), dioxane≈no solvent. Although the reaction was extremely fast in acetonitrile, the benzoyl cyanide dimer (**5**) was obtained in very high yield (24%) even for the molar ratio KCN/**4**=1.0. For the molar ratio KCN/**4**=4.0, a large amount of unidentified product was produced. This result contrasts with that of the reaction of **1** with KCN using a trace amount of water or ultrasound in which acetonitrile was effective.[7,8] The yields of benzoyl cyanide (**6**) and **5** in acetonitrile were very similar to those obtained by phase-transfer catalysis.[6] Surprisingly, in the absence of any solvent, the yield of dimer (**5**) was extremely low. This fact indicates that the reactivity of the KCN impregnated on XAD-2 toward the dimerization of **6** is much poorer than that in solution. The yields of **5** in other solvents were very low and quite similar to that in the absence of any solvent. These facts indicate that in acetonitrile the reaction occurs substantially in the bulk organic phase, while in the other solvents, it occurs predominantly on the surface of the resin. Contrary to expectations, the reaction rates in THF and dioxane were similar to those in CH_2Cl_2 and hexane or in the absence of any solvent. Interestingly, when benzene was used as a solvent, **6** was produced in substantial quantities with high selectivity. Also, the reaction rate with benzene was faster than those in other solvents with the exception of acetonitrile.

On the other hand, the importance of a trace amount of water to attack the crystal lattice of the solid in solid-liquid two phase systems is well-known.[7,9,10,11] The same effect was also observed in the present reaction. In the case of THF, CH_2Cl_2, benzene, and hexane, the effect was examined. It was observed that the addition of a trace amount of water substantially completed the conversion of **4** in 1—2 h. In THF or CH_2Cl_2, however, substantial quantities of benzoic anhydride (**7**) were produced along with **5** as by-products, and in hexane, **5** was produced in a substantial yield as a by-product. On the contrary, in benzene, the yield of by-products such as **5** and **7** was extremely low and was similar to that obtained in the absence of water.

Mass transfer strongly influences the reaction rate in heterogeneous systems.[12] In the present reaction, the mass transfer of substrate **4** from the bulk organic phase to the surface of the resin and the mass transfer of product **6** from the surface of the resin to the bulk organic phase will strongly affect the reaction rate. In the reaction without water, the rates of reaction in the solvents, except benzene and acetonitrile, were quite similar to that in the absence of any solvent. This fact indicates that the mass transfer of **4** from the bulk organic phase to the surface of the resin minimally affects the reaction rate.

At present, although I have no explanation why benzene is the best solvent, I suggest the following interpretation for the specific solvent effect of benzene: It is well-known that XAD-2 and XAD-4 resins can efficiently extract most organic compounds from

Table 1. Reaction of PhCOCl (**4**) with KCN/XAD-2 in Several Solvents[a)]

Solvent	H_2O / μl	Time / h	Yield/%[b)]			
			4	PhCOCN(**6**),	Dimer(**5**),	$(PhCO)_2O$(**7**)
None	—	2	34	51	1	≈0
Acetonitrile	—	2[c)]	10	58	24	≈1
	—	0.5	0	18	0	0
THF	—	2	27	51	≈1	≈1
	10	2	5	67	1	12
Dioxane	—	2	35	45	≈1	≈1
CH_2Cl_2	—	2	26	59	≈1	<1
	10	2	≈0	83	≈2	7
Benzene	—	2	5	85	≈1	0
	10	1	0	89	2	<1
Hexane	—	2	21	54	1	0
	10	2	≈0	68	9	≈0

a) Unless otherwise noted, reactions were carried out with KCN(30 mmol)/XAD-2 (7.5 g), **4** (7.5 mmol), and a solvent (40 ml) at 30 °C. b) Yields were determined by GLC using dodecane for **4** and **6**, and dibenzyl ether for **5** and **7** as internal standards. c) KCN (10 mmol)/XAD-2 (2.5 g) and **4** (10 mmol) were used.

Table 2. Reaction of **4** Using Several Supports in Benzene[a)]

Support	H_2O / μl	Temp / °C	Time / h	Yield/%[b)]			
				4,	**6**,	**5**,	**7**
Alumina[c)]	10	30	3	0	15	0	0
c, d)	10	30	0.5	0	0	0	0
e)	5	30	2	74	3	0	11
e)	—	30	2	77	3	0	6
Silica gel	10	30	2	0	<1	0	0
f)	5	30	2	19	2	0	31
f)	—	30	2	24	2	0	31
Activated C[g)]	10	60	2	≈95	0	0	≈0
	—	60	2	≈95	0	0	0
XAD-2	10	30	2	≈0	89	2	<1
h)	10	30	2	≈0	86	2	<1
XAD-4	10	30	2	≈0	90	3	<1
h)	10	30	2	≈0	86	3	<1

a) Unless otherwise noted, reactions were carried out with KCN (30 mmol)/support (7.5 g), **4** (7.5 mmol), and benzene (40 ml). b) Yields were determined by GLC using internal standards. c) KCN (30 mmol)/Al_2O_3 (12.0 g) was used. d) No solvent was used. e) KCN (10 mmol)/Al_2O_3 (4.0 g), **4** (10 mmol), and benzene (20 ml) were used. f) KCN (10 mmol)/silica gel (2.5 g), **4** (10 mmol), and benzene (20 ml) were used. g) Granular activated charcoal was ground in a mortar. KCN (30 mmol)/activated C (12.0 g) was used. h) NaCN was used.

water.[13] Nonpolar compounds are more strongly adsorbed on these resins than polar compounds, and furthermore, aromatic compounds are much more strongly adsorbed on the resin than low-molecular-weight aliphatic compounds.[13] Similarly, in the present system, the XAD resin has such properties as previously described. Since product **6** is an aromatic and relatively polar compound, it must have a stronger affinity to the XAD resin than the solvent with the exception of benzene. Therefore, only in benzene, the cyanide (**6**) produced on the surface migrates much more effectively from the surface of the resin to the bulk organic phase. Consequently, the reaction of **4** with KCN is accelerated and the formation of by-products such as **5** and **7** is suppressed.

Table 2 summarizes the results of cyanation of **4** using several other supports. In the case of alumina, which is effective in the cyanation of alkyl halides,[14] for the molar ratio KCN/**4**=4.0, the conversion of **4** was very fast in the presence of a trace amount of water. The yield of **6**, however, was very poor and a large amount of tarry material was obtained. For the molar ratio KCN/**4**=1.0, the coversion was slow, and the main product was benzoic anhydride (**7**) in both the presence and absence of water. When silica gel was used, for the molar ratio KCN/**4**=1.0, the reaction was faster than that using alumina and gave mainly **7**. A substantial amount of water appeared to remain after drying. For the molar ratio KCN/4=4.0, although the conversion of **4** was fast, almost no product was isolated. In the impregnation of KCN onto the silica gel, the evolution of a substantial amount of HCN gas was observed when silica gel was added to an aqueous KCN solution. This HCN must be produced through the reaction of KCN with acidic silica ≡Si–OH.[15]

$$\mathrm{KCN} + \equiv\mathrm{Si\text{-}OH} \longrightarrow \equiv\mathrm{Si\text{-}OK} + \mathrm{HCN}$$

For the molar ratio KCN/**4**=4.0, most of **4** would react with ≡SiOK, being trapped on the silica-gel surface as ≡SiOCOPh. When activated charcoal was used as a support, almost all of **4** was recovered. The effect of XAD-4 was similar to that of XAD-2. The reaction using KCN/XAD was slightly faster than that using NaCN/XAD.

Table 3 summarizes the results of the cyanation of the other acyl chlorides using KCN/XAD in benzene. XAD-4 was superior to XAD-2 in reaction rate. This fact may be due to the difference in the surface area.[16] When R in **1** was a strong electron-attracting group such as *p*-chloro- or *p*-bromophenyl, the addition of water increased the yield of by-products such as the acyl cyanide dimer (**3**) and the acid anhydride. In the reaction of **4** in benzene, the increase in the reaction rate by the addition of water was small, though substantially no increase in the yield of by-products was observed (Table 1). These findings suggest that the merit of the addition of water is small with respect to the yield and selectivity.

Table 3. Preparation of Acyl Cyanides Using KCN/XAD in Benzene[a)]

Acyl chloride	H_2O / μl	Resin[b)]	Time / h	Yield[c)] / %	Mp or Bp θ_m/°C (mmHg)	Lit. Mp or Bp θ_b/°C (mmHg)
PhCOCl	10	A	2	81 (89)	30—32	30—32[6)]
	10	B	2	83 (90)		
p-MeC_6H_4COCl	10	A	5 (3)	92 (90)[d)]	50—51	49.5—50[7)]
	10	B	3	95 (98)		
o-MeC_6H_4COCl	0	B	2	82 (91)	76—77	75—76[8)]
					(4)	(4)
p-$MeOC_6H_4COCl$	10	A	6	(80)[d)]	57—58	57—58[8)]
	10	B	3	87		
p-ClC_6H_4COCl	10	A	6	(58)	40.0—41.5	41.4—42.1[8)]
	10	B	3	60 (68)		
	0	B	4	75 (85)		
p-BrC_6H_4COCl	10	B	2	70 (80)	61.5—62.5	62.5—64.0[7)]
	0	B	4	84		
PhCH=CHCOCl	10	B	3	(36)	111—113	114.5—115.2[7)]
	0	B	4	41		
	10	B	2	58 (80)	86—87	86—88[8)]
	0	B	2	73 (89)	(15)	(15)
	0	A	4	(75)[d)]		

a) All reactions were carried out with KCN (30 mmol)/XAD (7.5 g), acyl chloride (7.5 mmol) at 30 °C in benzene (40 ml). b) A: XAD-2; B: XAD-4. c) Isolated yields. Values in parentheses are the yields determined by GLC. d) Conversion percentage of acyl chloride determined by GLC.

Experimental

Materials. Acetonitrile, benzene, and hexane were dried with molecular sieves 3A or 4A. THF and dioxane were passed through an alumina column, distilled, and then dried with molecular sieves 4A. Dichloromethane was washed with aqueous Na_2CO_3, distilled, and then dried with molecular sieves 3A. Benzoyl chloride (**4**) was distilled prior to use. The other acyl chlorides were used as obtained (Tokyo Kasei Kogyo Co.). Authentic samples (benzoyl cyanide (**6**) and benzoyl cyanide dimer (**5**)) were prepared by the literature method,[6] and benzoic anhydride (**7**) was purchased from Wako Chemicals Co. Amberlite XAD resins were purchased from Organo Co., thoroughly washed with methanol, benzene–methanol (1:2 vol), and methanol, and then dried under vacuum. Alumina (Merck 90, neutral, 70—230 mesh, activity I, Art 1077) and silica gel (Merck 60, 70—230 mesh, Art 7734) were used as obtained. Activated charcoal was pulverized in a mortar. KCN/XAD and NaCN/XAD were prepared according to the method previously reported,[9] dried at 90 °C and 0.1 mmHg (1 mmHg=133.322 Pa).

Typical Procedure for the Reaction of Acyl Chloride (1) with KCN or NaCN/Support. In all reactions, **1** was directly added to the flask in which the KCN or NaCN/Support was made and dried. All the products were known compounds.

The Reaction of Benzoyl Chloride (4) with KCN/XAD-2 in Various Solvents. A mixture of KCN/XAD-2 made from KCN (1.95 g, 30 mmol) and XAD-2 (7.5 g) and a solvent (30 ml) with or without water (10 μl) was stirred for 1—2 min. To the mixture was added **4** (1.05 g, 7.5 mmol) in benzene (10 ml) and the resulting mixture was stirred for 2 h at 30 °C. The solid material was filtered off and eluted with benzene (70 ml) and CH_2Cl_2 (30 ml). After removal of most of the solvent under reduced pressure at room temperature, the yields of **4**, **5**, **6**, and **7** were determined by GLC (Silicone OV-17, 10%, 3 m×3 mm, 140 °C for **4** and **6**: Silicone OV-17, 3%, 0.5 m×3 mm, 200 °C for **5** and **7**). Internal standards for **4** and **6**, and **5** and **7** were dodecane and dibenzyl ether, respectively.

Benzoyl Cyanide (6): A solution of **4** (1.05 g, 7.5 mmol) in benzene (10 ml) was added to a mixture of KCN/XAD-4 made from KCN (1.95 g, 30 mmol) and XAD-4 (7.5 g), benzene (30 ml), and water (10 μl). The mixture was stirred for 2 h at 30 °C. The solid material was filtered through Celite and eluted with benzene (70 ml) and CH_2Cl_2 (30 ml). After removal of the solvent, the residue, which solidified immediately at room temperature, was recrystallized from hexane to give 0.81 g (83%) of **6**, mp 30—32 °C (lit,[6] mp 30—32 °C).

***p*-Methylbenzoyl Cyanide:** The reaction was performed with KCN (30 mmol)/XAD-4 (7.5 g), *p*-methylbenzoyl chloride (1.16 g, 7.5 mmol), water (10 μl), and benzene (40 ml) as a solvent for 3 h at 30 °C according to the same method as **6**. Removing the solvent gave 1.04 g (95%) of the cyanide, mp 49—51 °C (lit,[7] mp 49.5—50.0 °C) which was recrystallized from CH_2Cl_2–hexane to give pure *p*-methylbenzoyl cyanide, mp 50—51 °C.

***p*-Chlorobenzoyl Cyanide:** The reaction was performed with KCN (1.95 g, 30 mmol)/XAD-4 (7.5 g), *p*-chlorobenzoyl chloride (1.31 g, 7.5 mmol), and benzene (40 ml) as a solvent for 4 h at 30 °C according to the same method as **6**. Removal of the solvent gave 1.13 g of the crude product. To this product was added CH_2Cl_2 (1 ml) and the insoluble solid was filtered off. The filtrate was passed through a silica-gel column (10 cm) with CH_2Cl_2–hexane (1:4) as an eluent. Removing the solvent gave 0.93 g (75%) of *p*-chlorobenzoyl cyanide, mp 40.0—41.5 °C (lit,[8] mp 41.4—42.1 °C).

***p*-Bromobenzoyl Cyanide:** The reaction was performed with KCN (1.95 g, 30 mmol)/XAD-4 (7.5 g), *p*-bromobenzoyl chloride (1.65 g, 7.5 mmol) and benzene (40 ml) as a solvent for 4 h at 30 °C according to the same method as **6**. Removal of the solvent gave 1.32 g (84%) of *p*-bromobenzoyl cyanide, mp 60.5—62.0 °C (lit,[7] mp 62.5—64.0 °C), recrystallization of which from CH_2Cl_2–hexane gave the pure compound, mp 61.5—62.5 °C.

Cinnamoyl Cyanide: The reaction was performed with KCN (1.95 g, 30 mmol)/XAD-4 (7.5 g), cinnamoyl chloride (1.25 g, 7.5 mmol), and benzene (40 ml) as a solvent at 30 °C for 4 h according to the same method as **6**. Removal of the solvent gave 1.15 g of the residue, which was purified by silica-gel column chromatography (CH_2Cl_2–hexane, 1:3) to give 0.48 g (41%) of cinnamoyl cyanide, mp 111—113 °C (lit,[7] 114.5—115.2 °C).

2-Furoyl Cyanide: The reaction was performed with KCN (1.95 g, 30 mmol)/XAD-4 (7.5 g), 2-furoyl chloride (0.98 g, 7.5 mmol), and benzene (40 ml) as a solvent at 30 °C for 2 h according to the same method as **6**. Removal of the solvent gave 0.81 g (89% yield, 96% purity GLC) of the product, distillation of which gave 0.66 g (73%) of 2-furoyl cyanide, bp 86—87 °C/15 mmHg (lit,[8] bp 86—88 °C/15 mmHg).

I thank Nihon Tokushu Kagaku Kogyo Co., Ltd. for permission to publish this article.

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16) XAD-2: Surface area, 300 m^2/g; Av. pore diameter, 90 Å. XAD-4: Surface area, 780 m^2/g; Av. pore diameter, 50 Å.