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The Reaction of Nitriles with Phosgene. VII.[1] Synthesis of α,β-Unsaturated Isocyanates

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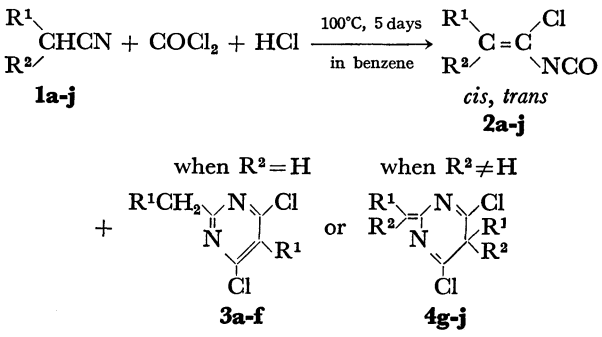
The reaction of nitriles with phosgene in the presence of hydrogen chloride was carried out for synthesizing α,β-unsaturated isocyanates. 3-Chloropropionitrile, 2,3-dichloropropionitrile, isobutyronirtile, and 2-chloromethylpropionitrile gave the corresponding α-chloro-α,β-unsaturated isocyanates in moderate yields (27—50%). Propionitrile, *n*-butyronitrile, and 3-phenylpropionitrile gave the corresponding pyrimidines as the major product. 3-Phenylpropionitrile, however, gave the isocyanate as the major product when the amount of benzene as a solvent increased. Reaction pathways to isocyanates and pyrimidines were discussed.

In a previous paper,[1] we reported a new synthesis of styryl isocyanates from arylacetonitriles with phosgene in the presence of hydrogen chloride. We have extended this isocyanate synthesis to variously substituted nitriles to determine its scope and utility for synthesizing α,β-unsaturated isocyanates.

Results and Discussion

Reactions were carried out at 100°C for 5 days in a 80 ml pyrex tube using benzene as a solvent.[2] A mixture of *cis*- and *trans*-α,β-unsaturated isocyanate **2** was formed along with pyrimidine derivative **3** or **4** (Scheme 1). Results are summarized in Table 1.



Scheme 1.

1,3-Dichloropropenyl isocyanate (**2e**) and 1,2,3-trichloropropenyl isocyanate (**2g**) were isolated by preparative glpc and were characterized by IR, NMR, and mass spectra and elemental analyses. Other isocyanates were characterized, without isolation, by IR and NMR spectra (Table 2). Their IR spectra showed an isocyanate band at 2255—2260 and a C=C stretching band at 1643—1675 cm^{-1}. Since the isocyanates were usually obtained as a mixture of the starting nitriles and benzene, it was difficult to isolate them by simple distillation. Thus, their yields were determined by NMR spectroscopic methods.

Pyrimidine derivatives **3** and **4** were identified by comparison with authentic samples except for **3c**,[3,4] which was identified by IR, NMR, and mass spectra. We reported that most of these pyrimidines were ob-

1) Part VI: M. Ohoka, S. Yanagida, and S. Komori, *J. Org. Chem.*, **36**, 3542 (1971).

2) Although other aromatic solvents such as toluene and chlorobenzene are preferable for the preparation of isocyanates with high boiling points, such high-boiling solvents are not advantageous for the reaction of a low-boiling nitrile, *e.g.* propionitrile. Thus, benzene was used as the solvent in this investigation.

3) S. Yanagida, T. Fujita, M. Ohoka, R. Kumagai, and S. Komori, This Bulletin, **46**, 299 (1973).

4) Since pyrimidine **4h** is very sensitive to moisture and an analytically pure sample was not obtained,[3] it was identified by its IR spectrum.

Table 1. Synthesis of unsaturated isocyanates[a]

Run	Nitriles			Yield,[b] %				Recov.[b] of nitriles, %
	No	R^1	R^2	Isocyanate		Pyrimidine		
1	**1a**	CH_3	H	13	(**2a**)	50	(**3a**)	12
2	**1b**	C_2H_5	H	8	(**2b**)	38	(**3b**)	
3[c]	**1c**	i-C_3H_7	H	11	(**2c**)	7	(**3c**)	
4	**1d**	t-C_4H_9	H	trace	(**2d**)	0	(**3d**)	92
5	**1e**	$ClCH_2$	H	40	(**2e**)	5	(**3e**)	40
6	**1f**	$C_6H_5CH_2$	H	18	(**2f**)	60	(**3f**)	21
7	**1g**	$ClCH_2$	Cl	27	(**2g**)	5	(**4g**)	52
8	**1h**	CH_3	CH_3	50	(**2h**)	12	(**4h**)	25
9	**1i**	C_2H_5	C_2H_5	14	(**2i**)	trace	(**4i**)	81
10	**1j**	$ClCH_2$	CH_3	39	(**2j**)	trace	(**4j**)	53
11[d]	**1f**			31	(**2f**)	14	(**3f**)	51
12[e]	**1f**			26	(**2f**)	5	(**3f**)	64

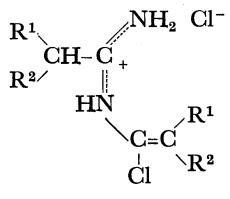
a) Reaction conditions are as follows unless otherwise noted. Temperature 100°C, time 5 days, nitrile 35 mmol, HCl 0.5 g (14 mmol), $COCl_2$ 9.5 g (96 mmol), benzene 5 ml.
b) Yields of isocyanates and recoveries of nitriles were determined by NMR.
c) Reaction temperature 150—160 °C, HCl 0.7 g (19 mmol).
d) Benzene 10 ml.
e) Benzene 15 ml.

Table 2. NMR spectra of isocyanates **2**[a]

Compd	Chemical shift, δ ppm
2a	1.35 (d, 6.8 Hz) and 1.39 (d, 6.8 Hz) (CH_3), 4.93 (q) and 5.11 (q) (H–C=)
2b	4.95 (t, 7.5 Hz) and 5.12 (t, 7.5 Hz) (H–C=)
2c	5.02 (d, 9.9 Hz) and 5.20 (d, 9.0 Hz) (H–C=)
2e	4.08 (d, 8.3 Hz) and 4.12 (d, 8.3 Hz) (total 2 H) (CH_2), 5.46 (t) and 5.66 (t) (total 1 H) (H–C=)
2f	3.55 (d, 7.5 Hz) and 3.38 (d, 7.5 Hz) (total 2 H) (CH_2), 5.33 (t) and 5.53 (t) (total 1 H) (H–C=)
2g	4.35 (s) and 4.38 (s) (CH_2)
2h	1.76 (s) (CH_3)
2j	1.90 (s, 3 H) (CH_3), 4.14 (s, 2 H) (CH_2)
2k	3.55 (d, 2 H, 7.5 Hz) (CH_2), 5.42 (t, 7.5 Hz) and 5.65 (t, 7.5 Hz) (total 1 H) (H–C=)

a) Solvent: **2a**—**c**, benzene; **2e**—**h** and **2j**, CCl_4; **2k**, $CDCl_3$.

tainable in good yields from the reaction of nitrile-HCl 2:2 adducts **5** with phosgene.[3]



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3-Chloropropionitrile (**1e**), 2,3-dichloropropionitrile (**1g**), isobutyronitrile (**1h**), and 2-chloromethylpropionitrile (**1j**) gave expected isocyanates in moderate yields (27→50%). However, propionitrile (**1a**), *n*-butyronitrile (**1b**), and 3-phenylpropionitrile (**1f**, run 6) gave expected isocyanates in low yields together with moderate yields (38—60%) of the corresponding pyrimidines. On the other hand, 3-methylbutyronitrile (**1c**), 3,3-dimethylbutyronitrile (**1d**), and 2-ethylbutyronitrile (**1i**) afforded both isocyanates and pyrimidines in very low yields under most recovery of the starting nitriles.

The effect of reaction time and temperature on the yield of isocyanate **2e** was studied (Figs. 1 and 2). As shown in Fig. 1, the yield of **2e** reached a maximum value (*ca.* 40%) after around 5 days, then it gradually decreased and the amount of a resinous substance increased as the reaction time was prolonged. This indicates the existence of equilibria between isocyanate **2e** and starting materials (Scheme 2). The yield of **2e** increased nearly proportionally to temperature giving a maximum value (*ca.* 40%) at around 100°C and then gradually decreased (Fig. 2). Thus, the reaction is optimum at 100°C and for 5 days.

The possible reaction pathways to isocyanates are shown in Scheme 2. The existence of an equilibrium between imidoyl chloride **6** and α-chloroenamine **7** has been proposed by Simchen.[5,6] In addition, he and his co-workers postulate that the α-chloroenamine rather

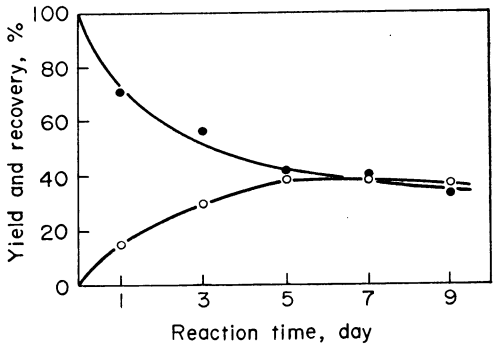

Fig. 1. Effect of reaction time on the yield of isocyanate **2e** and recovery of **1e**: yield of **2e**, ○; recovery of **1e**, ●. Reaction was carried out in 74 ml glass tube. Temperature 100 °C. Amounts of reactants: nitrile **2e** 3.1 g (35 mmol), HCl 0.5 g (14 mmol), $COCl_2$ 9.5 g (96 mmol), benzene 5 ml.

5) G. Simchen and W. Krämer, *Chem. Ber.*, **102**, 3656 (1969).
6) G. Simchen, *ibid.*, **103**, 407 (1970).

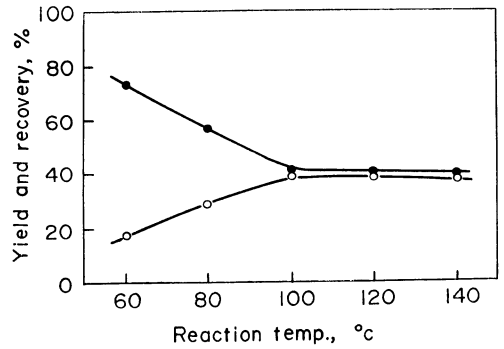

Fig. 2. Effect of reaction temperature on the yield of **2e** and recovery of **1e**: yield of **2e**, ○; recovery of **1e**, ●. Reaction was carried out in 75 ml glass tube. Amounts of reactants are the same as those shown in Fig. 1. Reaction time 5 days.

than the imidoyl chloride is acylated in the intramolecular cyclization of nitriles in the presence of hydrogen chloride.[5-7] However, the phosgenation of benzonitrile *via* imidoyl chloride to *N*-(α-chlorobenzylidene)-carbamoyl chloride **10** was found in our laboratory.[8] Therefore, in our case the phosgenation of both **6** and **7** probably takes place to give carbamoyl chlorides **8** and **9** as intermediates.

$$\mathrm{PhCN + COCl_2 \xrightarrow{HCl} PhC(Cl)=NC(=O)Cl}$$

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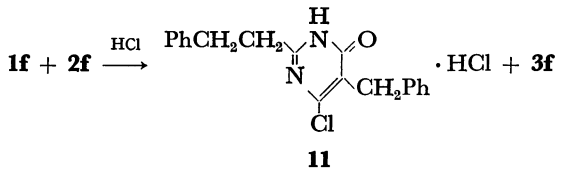
The following two paths (a and b) are possible routes to pyrimidines: path a involves a nitrile-HCl 2:2 adduct **5** as an intermediate and path b involves the secondary reactions of isocyanates. The pyrimidine formation *via* path b has been found in the reaction of α-chloro-*p*-nitrostyryl isocyanate with acetonitrile at 60°C in the presence of hydrogen chloride.[1] To clarify the possibility of path b, reactions of isocyanates **2e** and **2f** with some nitriles were carried out.

When **2f** was treated with **1f** in benzene at 100°C for 84 hr in the presence of hydrogen chloride, pyrimidone hydrochloride **11** was obtained in 39% yield along with pyrimidine **3f** (13%). The latter was apparently produced by chlorination of **11** with phosgene formed by the reverse reaction from **2f** (Scheme 2). This clearly indicates that pyrimidines can be formed *via* path b.



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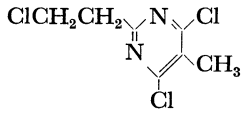
On the other hand, the reaction of **2e** with **1e** under similar conditions afforded only pyrimidine **3e** in 13% yield and a trace amount of **2e** was recovered. In addition, the reaction of **2e** with **1a** at 100°C for 3 days in the presence of phosgene and hydrogen chloride did not give **12**, but gave a mixture of **3a** and **3e** (mole ratio 88:12) and 34% of **2e** was recovered. These facts suggest that the reactivity of isocyanate **2e** toward a nitrile in the presence of hydrogen chloride is lower than that of **2f**.



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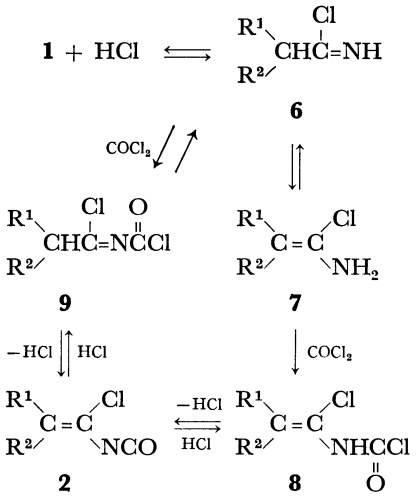
Nitrile-HCl 2:2 adducts **5** have been prepared by the reaction of nitriles with hydrogen chloride at 30—60°C using no solvents.[9] To examine whether **5** can also be formed under the reaction conditions or not, the reaction of **1a** with hydrogen chloride was carried out. The reaction at 100°C for 5 days resulted in the recovery of the starting materials. From these facts, pyrimidines are assumed to be formed mainly *via* path b. Since **5** might be formed as a labile intermediate even at 100°C, the pyrimidine formation *via* path a can not be neglected.



Scheme 2

The yields of isocyanates decreased as the number of β-hydrogens of nitriles decreased by methyl or chlorine substitution (run 3→4, 8→9, 8→10), especially 3,3-dimethylbutyronitrile (**1d**) having no β-hydrogens gave only a trace amount of isocyanate **2d**. This suggests that β-hydrogens stabilize the isocyanates by the hyperconjugation with the C=C bond of the isocyanates and shift the equilibria (Scheme 2) to the side of isocyanates. The stabilization of unsaturated isocyanates by the conjugation with aromatic rings has been observed in the synthesis of styryl isocyanates.[1] Since 2-ethylbutyronitrile (**1i**) has four β-hydrogens, it is expected to give good yield of isocyanate **2i**. However, the yield of **2i** as well as **4i** were low (run 9), indicating that the equilibria shifted to the side of the imidoyl chloride or the starting nitrile. The reason for this shift of the equilibria is not clear at present.

Whereas **1e** gave the isocyanate in good yield, **1a**, **1b**, and **1f** (run 6) gave the corresponding isocyanates in low

7) G. Simchen, *ibid.*, **103**, 389 (1970).

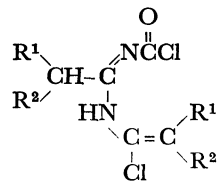
8) S. Yanagida, H. Hayama, M. Yokoe, and S. Komori, *J. Org. Chem.*, **34**, 4125 (1969).

9) S. Yanagida, T. Fujita, M. Ohoka, I. Katagiri, and S. Komori, This Bulletin, **46**, 292 (1973).

yields together with pyrimidines as the major products; this is explained by considering the difference in the reactivity of isocyanates toward nitriles. In the former case only a small amount of **2e** is consumed for the pyrimidine formation *via* path b because of its low reactivity and in the latter cases a considerable amount of the isocyanates is consumed for the pyrimidine formation.

When the amount of benzene as a solvent was increased (run 6→11→12), the yield of pyrimidine **3f** decreased dramatically and that of isocyanate **2f** increased as a result of suppression of path a or b by dilution.

The low yields of pyrimidines in run 7, 8, and 10 are reasonably ascribed to steric hindrance in the formation of **5** (path a) and **13** (path b).



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As a conclusion, it is essential for obtaining isocyanates exclusively to substitute the nitriles by such substituents that not only stabilize the C=C bond of isocyanates but also suppress both the further reactions of once formed isocyanates and the dimerization of nitriles to **5**, or to dilute the reaction system by a solvent.

Experimental

NMR spectra were obtained using a JNM-G-60 spectrometer (Japan Electron Optics Laboratory Co.) with tetramethylsilane as an internal reference. IR spectra were recorded on a Japan Electronic IR-E spectrophotometer. Mass spectra were recorded on a Hitachi RMU-6E spectrometer. Preparative glpc was carried out with a Yanagimoto G-8 gas chromatograph.

General Procedure. In a 80 ml Pyrex tube was placed 35 mmol of a nitrile and 0.5 g (14 mmol) of anhydrous HCl was dissolved in it; then a solution of 9.5 g (96 mmol) of $COCl_2$ in 5 ml of benzene was added to the mixture. The tube was stoppered, chilled in dry ice–acetone and sealed carefully. It was placed in a 300 ml stainless autoclave containing 70 ml of *n*-hexane and heated at 100°C in an oil bath; *n*-hexane was added to avoid burst of the tube by exerting external pressure. After 5 days the tube was chilled in dry ice–acetone and opened carefully. After $COCl_2$ and HCl were purged, the reaction mixture was distilled at ordinary or under reduced pressure to give a mixture of the objective isocyanate, the starting nitrile, and benzene. The yield of isocyanate and the recovery of nitriles were determined by NMR. Pyrimidines were obtained by distillation or by extraction of the distillation residue of isocyanates with CCl_4.

Isolation of Pure Isocyanate 2e and 2g by Preparative glpc. Isolation of **2e** and **2g** was carried out using a column (14 mmϕ×150 cm) packed with dioctyl sebacate (7%) on Diasolid L (60—80 mesh) (column temp. 80°C, carrier gas H_2) and a column (14 mmϕ×75 cm) packed with dioctyl sebacate (7%) on Diasolid L (60—80 mesh) (column temp. 100°C, carrier gas H_2), respectively. 1,3-Dichloropropenyl isocyanate (**2e**), IR (liquid film), 2260 (NCO) and 1655 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel. intensity), 151 (17, M^+), 116 (100, M^+–Cl), 88 (8), 63 (38), and 52 (24). (Found: C, 31.62; H, 1.93; N, 9.05%. Calcd for $C_4H_3Cl_2NO$: C, 31.61; H, 1.99; N, 9.23%). 1,2,3-Trichloropropenyl isocyanate (**2g**), IR (liquid film), 2260 (NCO) and 1643 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel. intensity), 185 (23, M^+), 150 (100), 63 (56), and 49 (100). (Found: C, 25.86; H, 1.03; N, 7.79%. Calcd for $C_4H_2Cl_3NO$: C, 25.77; H, 1.03; N, 7.51%).

4,6-Dichloro-1-isobutyl-5-isopropylpyrimidine (3c). The distillation residue of run 3 was chromatographed on silica gel; *n*-hexane eluted **3c** (colorless liquid), IR (liquid film), 1548, 1500, 1408, 1297, and 800 cm^{-1}; NMR (CCl_4), δ 1.00 (d, 6H, J=6.4 Hz), 1.44 (d, 6H, J=6.8 Hz), 2.05—2.78 (m, 3H), and 3.47 (sep, 1H, J=6.8 Hz); mass spectrum (70 eV) *m/e* (rel. intensity), 246 (15, M^+), 231 (36), 204 (100), and 189 (48).

Reaction of 2f with 1f in the Presence of HCl. In a 30 ml glass tube was placed a mixture of **2f** (1.1 g, 5.7 mmol) and **1f** (1.4 g, 11 mmol), then anhydrous HCl (0.4 g, 11 mmol) was dissolved in it followed by addition of 2 ml of benzene. The tube was sealed and heated at 100°C for 84 hr. After HCl was purged, the precipitate formed was filtered, washed with a small amount of benzene, and dried *in vacuo* to give tan powder of pyrimid one hydrochloride **11** (0.78 g, 39%), IR (Nujol), 1710 and 1630 cm^{-1}. Its crystallization from EtOH gave colorless fine needles of the free base [6-chloro-5-benzyl-2(2-phenylethyl)-4(3*H*)-pyrimidone], mp 224—225°C, IR (Nujol), 1672 and 1595 cm^{-1}; NMR (CF_3COOH), δ 3.32 (complex, 6H), 4.03 (s, 2H), and 7.24 (m, 10H); mass spectrum (70 eV) *m/e* (rel. intensity), 326 (33, M^++2), 324 (100, M^+), 233 (69), and 91 (71). (Found: C, 70.31; H, 5.31; N, 8.46%. Calcd for $C_{19}H_{17}ClN_2O$: C, 70.26; H, 5.28; N, 8.62%).

The solvent was removed from the filtrate, the residual liquid being distilled under reduced pressure to give 1.1 g of **1f** (contained a trace amount of **2f**). The distillation residue was extracted with CCl_4, the solvent being removed to give **3f** (0.25 g, 13%).

The Reaction of 2e with 1e in the Presence of HCl. A mixture of **2e** (0.9 g, 5.9 mmol), **1e** (1.1 g, 12 mmol), HCl (0.4 g, 11 mmol), and benzene (2 ml) in a 30 ml glass tube was heated at 100°C for 84 hr. After HCl was purged, the resulting dark precipitate (intractable solid) was filtered off. The solvent was removed from the filtrate and the residual liquid was distilled under reduced pressure to give 0.9 g of **1e** (contained a trace amount of **2e**). The distillation residue was extracted with CCl_4, the solvent being removed under reduced pressure to give a yellow liquid of **3e** (0.2 g, 13%).

Reaction of 2e with 1a in the Presence of $COCl_2$ and HCl. In a 80 ml Pyrex tube were placed 2.0 g of a mixture of **2e** and **1e** [content of **2e**, 1.8 g (12 mmol)] and 1.3 g (24 mmol) of **1a**, then anhydrous HCl (0.8 g, 23 mmol) was allowed to be absorbed in it followed by addition of a solution of $COCl_2$ (7.2 g, 73 mmol) in 5 ml of benzene. The tube was sealed and heated at 100°C in an oil bath. After 3 days the tube was opened and $COCl_2$ and HCl were purged. The reaction mixture was distilled initially at ordinary pressure to give a mixture of **1a**, **2a**, and benzene, then under reduced pressure to give a mixture of **1e** (0.43 g) and **2e** (0.62 g, 34% recovery). The distillation residue contained 0.98 g of **3a** and 0.17 g of **3e**.