BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49 (12), 3574—3577 (1976)

Acyl Cyanide. III. Thermal and Base-Catalyzed Reactions of Phenylcarbamoyl Cyanide

Akira Oku,* Takamasa Suzuki, Hajime Koura, and Fujio Mashio

Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606

(Received May 6, 1976)

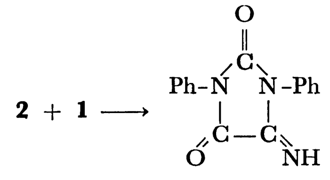
Phenylcarbamoyl cyanide (**1**), under thermal conditions or base-catalysis, behaves as a source of both phenyl isocyanate and hydrogen cyanide in the syntheses of carbamates, cyanohydrins, and iminohydantoins. The reaction mechanism of **1** with methanol in the presence of tertiary amine was investigated. The following observations (i—iii) led us to deduce that phenyl isocyanate was not involved as the intermediate and that the rate-determining step involves nucleophilic displacement of **1** by the alkoxyl group, reinforced by the base: (i) the N-H exchange was too fast to be rate-determining; (ii) *d*-labelling experiments showed $k_H/k_D = 1.8$—1.9 in any of the reactions, **1**-d_1+MeOH, **1**-d_0+MeOD, and **1**-d_1+MeOD, and (iii) diphenylcarbamoyl cyanide reacted only 7.2 times slower than did **1**.

Monosubstituted carbamoyl cyanides, RNHCOCN, have been known since 1905, when Dieckmann prepared 1,3-diphenyl-5-iminohydantoin from phenyl isocyanate. However, because of their low thermal stability, relatively few surveys of their chemical properties have appeared in the literature.[1,2] Through the synthesis of a series of thermostable poly(5-iminohydantoin)s from diisocyanates,[3,4] we previously found that the formation of iminohydantoins by the self-condensation of carbamoyl cyanides was facilitated by heating as well as by base catalysis. For this reaction, two mechanisms can be postulated: a) carbamoyl cyanide decomposes thermally or base-catalytically into hydrogen cyanide and isocyanate, after which the latter reacts with another cyanide to give the hydantoin, or b) carbamoyl cyanide self-condenses without forming isocyanate. Much as in the above reaction, carbamoyl cyanide was found to react easily with alcohols to give the corresponding carbamates, and two mechanisms analogous to the above can be postulated: a′) *via* isocyanate, or b′) *via* the nucleophilic displacement of carbamoyl cyanide by alcohol. In view of the paucity of information supporting either mechanism, we have now performed a kinetic study of the reaction of phenylcarbamoyl cyanide with alcohols. Also investigated in the present study is the utilization of phenylcarbamoyl cyanide as a source of isocyanate (masked isocyanate reagent) and hydrogen cyanide as well.

Results and Discussion

*Thermal Decomposition of Phenylcarbamoyl Cyanide (**1**).* Cyanide (**1**) gives 1,3-diphenyl-5-iminohydantoin (**4**) when heated in solutions or in molten states. The reaction was interpreted in terms of the thermal decomposition of **1** into hydrogen cyanide and phenyl isocyanate (**2**, not isolated); the latter then reacted further with the undecomposed **1** to give **4**. This assumption prompted the use of bifunctional carbamoyl cyanides as masked reagents of diisocyanates for the synthesis of poly(5-iminohydantoin)s.[3] Thus, we hope that monofunctional carbamoyl cyanides can be utilized as a stable source of isocyanates as well as of hydrogen cyanide in reactions requiring neutral or thermal conditions.

$$\underset{\mathbf{1}}{\text{PhNHCOCN}} \xrightarrow{\text{heat}} \underset{\mathbf{2}}{\text{Ph-NCO}} + \underset{\mathbf{3}}{\text{HCN}} \qquad (1)$$


4 (2)

The mass spectrum of phenylcarbamoyl cyanide (**1**), even when the ionization chamber voltage was varied from 80 to 15 eV and the chamber temperature was lowered from 250 to 160 °C by both direct and indirect in-letting methods, showed no P^+ peak (m/e 146 for $C_8H_6N_2O$), but only those peaks ascribable to phenyl isocyanate and hydrogen cyanide. Therefore, either the decomposition of the parent molecule into isocyanate prior to the electron bombardment or the fragmentation of the parent molecular ion after the bombardment must be too fast to allow the detection of the P^+ ion. Coupled with this measurement, the pyrolysis of **1** was carried out by the thermobalance method. Under reduced pressure (20 Torr) **1** started to lose weight appreciably at 85 °C. The decomposition gas trapped in a cold vessel was proved by IR (N=C=O 2270 cm^{-1}) to consist mainly of **2**, while treatment with aniline gave *N,N′*-diphenylurea. Above 110 °C, **1** became a liquid and its decomposition as well as sublimation were considerably accelerated.

The thermal reaction of **1** in solution was then investigated. When **1** alone was heated in boiling dioxane for 60 h, 1,3-diphenyl-5-(phenylcarbamoylimino)-hydantoin (**5**) or **4** was obtained, depending on the reaction conditions (concentration, solvent, and catalyst.)[5] The IR analysis of the solution did not detect **2** throughout the period. Similarly, when **1** was warmed with alcohols in dioxane, the corresponding phenylcarbamates were formed in high yields (Table 1) (as for the mechanism, see below). Consequently, **1** can be adopted as a *phenylcarbamoylating* reagent or, in other words, as a masking reagent of phenyl

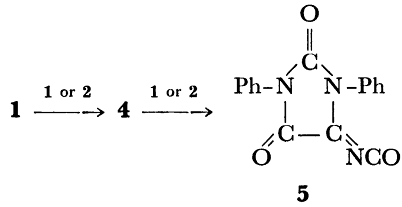

5 (3)

TABLE 1. REACTION OF PhNHCOCN (**1**) WITH ALCOHOLS

ROH	[ROH]/[**1**]	Solvent	[**1**]/Solvent mol/l	Temp °C	Time h	Urethane %
CH_3OH	2.5×10^5	CH_3OH	7.8×10^{-5}	30	8	45
CH_3OH	2.5×10^5	$CH_3OH^{b)}$	7.5×10^{-5}	30	4	56
CH_3OH	1×10^2	$CH_3OH^{c)}$	2.8×10^{-1}	30	0.1	*a*)
CH_3OH	2	Dioxane	7×10^{-2}	50	15	98
CH_3OH	1×10^2	c-C_6H_{12}	7×10^{-2}	50	25	3
C_2H_5OH	2	Dioxane	7×10^{-2}	100	68	95
$PhCH_2OH$	2	Dioxane	7×10^{-1}	100	25	65

a) Iminohydantoin 90%. b) Et_3N 7×10^{-7} mol/l added. c) Et_3N 2.8×10^{-3} mol/l added.

TABLE 2. REACTION OF PhNHCOCN (**1**) WITH CYCLOHEXANONE (**8**)

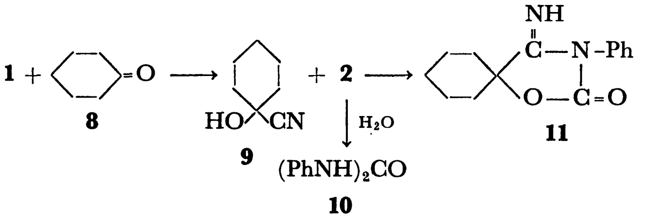
Run	[**1**]/[**8**] mol ratio	**8** (g)	Additive (g)$^{b)}$ H_2O	AcOH	NaCN	Temp (°C)	Time (h)	Cyano-hydrin (%)
1	0.12	14.1	—	—	—	150	2	—
2	0.12	13.5	0.6	—	—	80	24	—$^{a)}$
3	0.15	14.1	0.5	1.5	—	80	20	29
4	0.15	14.1	0.5	1.5	0.001	80	20	49
5	0.20	9.5	1.0	1.0	—	80	20	36
6	0.20	9.5	1.0	1.0	0.001	67	17	98
7	0.15	14.1	0.5	—	—$^{c)}$	25	1	—$^{d)}$

a) A trace amount. b) AcONa was added in Runs 5 and 6. c) Et_3N(0.1 g) was added instead of NaCN. d) The main product was 1,3-diphenyl-5-iminohydantoin.

$$\underset{}{\mathbf{1}} + \text{R-OH} \longrightarrow \underset{\mathbf{6}}{\text{PhNHCOOR}} + \underset{\mathbf{7}}{\text{HCN}} \qquad (4)$$

isocyanate in some thermal reactions (or in low-temperature reactions with the aid of bases). Analogously, though less effectively, compound **5** yielded a trace amount of benzyl phenylcarbamate (2%) when treated with benzyl alcohol in boiling dioxane for 30 h, whereas **4** did not.

Generally, investigators are nervous handling hydrogen cyanide in the laboratory. Carbamoyl cyanide, *e.g.*, **1**, can be handled in solid states, being soluble in many organic solvents, and is a safer HCN source. In order to estimate this utilizability, the reaction of **1** with cyclohexanone (**8**) was chosen as the model. The reaction was carried out in the presence of water in order to remove the simultaneously formed isocyanate, **2**, from the reaction system by forming diphenylurea (**10**), because **2** will react further with cyanohydrin,



9, to give cyclic urethane, **11**.[6] The results are shown in Table 2, in which the same salt effect as has been known for the general cyanohydrin synthesis[7] is indicated: *i.e.*, catalysis by a trace amount of the cyanide anion and a buffer effect of sodium acetate in acetic acid.[8] These basic additives also seem to facilitate the decomposition of **1** to generate HCN. Thus, the optimum yield of cyanohydrin **9** was attained almost quantitatively under the conditions of Run 6.

*Base-Catalyzed Reaction of Phenylcarbamoyl Cyanide (**1**) with Methanol.* The formation of carbamates as well as of 5-iminohydantoins from **1** has been known to be facilitated significantly by bases, such as tertiary amines and basic solvents.[3] In order not only to clarify the characteristics of this catalysis, but also to make a rational choice between the two reaction mechanisms, a′) and b′) (see the Introduction), the rate of the reaction of **1** with methanol was measured under various conditions of base-catalysts, solvents, and isotope-labelling.

Table 3, showing the rate constants as measured by a UV spectroscopic method, indicates that the catalysis of weak bases, such as pyridine or *N*,*N*-dimethylaniline, is not appreciable, while strong bases such as triethylamine exhibit an apparent rate enhancement even in diluted solutions (10^{-4}—10^{-6} mol/l for base). The

TABLE 3. RATES OF REACTION OF PhNHCOCN (**1**) WITH METHANOL (31±0.5 °C in MeOH)$^{a)}$

Base	[Base]/[**1**]$_0$	$k_1\times10^4$ s^{-1}
—	—	4.2
Me_2N-Ph	0.025	3.8
Pyridine	0.040	4.2
Pyridine	0.40	3.8
Et_3N	0.002	4.1
Et_3N	0.020	6.6
Et_3N	0.048	10.0
Et_3N	0.23	37.7
Imidazole	0.021	4.6

a) [**1**]$_0$: 8.7×10^{-5} mol/l.

Table 4. Rates of reaction of PhNHCOCN (**1**) with methanol in solvents other than methanol (at 31±0.5 °C)

Solvent	Substrate ratio (10^{-5} mol/l)			$k_2\times10$ (l/mol s)
	1	MeOH	Et_3N	
Dioxane	1	1	1	7.83
Dioxane	1	5	1	7.75
Dioxane	1	1	5	28
c-C_6H_{12}	1	1	1	$<10^{-1}$

Table 5. Rates of reaction of PhNDCOCN (**1**-d_1) with methanol-d_1 in dioxane (at 31±0.5 °C)

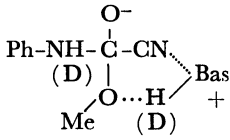
Run	Reactant[a,b]	$k_2\times10$ (l/mol s)	k_H/k_D[c]
1	**1**-d_0+MeOH	7.8	—
2	**1**-d_1(20%)+MeOH	7.0	1.11
3	**1**-d_1(85%)+MeOH	4.6	1.70
4	**1**-d_0+MeOD	4.2	1.85
5	**1**-d_1(85%)+MeOD	4.0	1.95

a) The d-content was roughly determined by IR and MS. b) Et_3N was added; substrate ratio [**1**]:[MeOH]:[Et_3N]=1:1:1. c) Uncorrected for **1**-d_1(100%)

solvent effect is also significant (see Table 4). For example, in dioxane the rate is only 9 times as slow as in methanol, while in cyclohexane it is more than 10^2 times as slow as in dioxane. From these results, we presumed that either of the following two transitions constitutes the rate-determining step: a″) proton abstraction from **1** by a base, or the elimination of cyanide anion from the conjugate base, or b″) the nucleophilic displacement of the cyano group by a base-reinforced methoxyl group.[9]

Mechanism b″) was preferred to a″) by characterizing the deuterium-labelling effect on the rate of the reaction system, Ph–ND (or H)–CO–CN+MeOD(or H) (Table 5). First of all, it was noted that, when **1**-d_1 was prepared by shaking a warm $CDCl_3$ solution of **1**-d_0 with D_2O, the H–D exchange was completed rapidly, without forming either diphenylurea (**10**) or phenyloxamide. This indicates that the N–H abstraction, followed by the rapid elimination of the cyanide anion to give **2**, does not constitute the rate-determining step. In addition, the observed isotope effect, $k_H/k_D=1.8$—1.95, though not large enough to be the primary kinetic isotope effect, indicates that the elimination of the CN^- group can not be the single step constituting the transition state. The almost equal isotope effects in Runs 3 and 4 (Table 5) may be attributed to the rapid H–D exchange between **1** and methanol prior to the substitution in both runs, and the same equilibrium mixture, in which deuterium incorporates largely into methanol, is formed. This assumption is supported by Run 5, where k_H/k_D is about the same as in Runs 3 and 4.

Consequently, the observed isotope effect can be most rationally interpreted by means of the following tentative model, **12**, for the transition state where the bond fission of MeO–H(D), but not of N–H(D), is involved and where the proton must be almost completely transferred to the base, as is indicated by the small value of the isotope effect. In this mechanism,



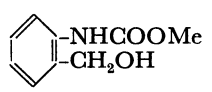
+ **12**

the presence of hydrogen on the amide nitrogen must be unimportant in effecting the rate.[10] In fact, the rate of the reaction of diphenylcarbamoyl cyanide (**13**)[11] with methanol, as measured under the same conditions as were set for **1** was only slightly slower than that of **1** ($k_{13}=6.5\times10^{-5}$ s^{-1}, $k_1/k_{13}=7.2$).[12]

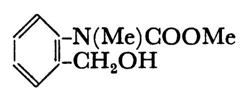
$$\underset{\mathbf{13}}{(Ph)_2NCOCN} + MeOH \longrightarrow \underset{\mathbf{14}}{(Ph)_2NCOOMe} \qquad (6)$$

A disproof of Mechanism a″) can also be deduced from the results of Hutchins and his co-workers,[13] who observed a 10^4-fold faster rate of the base-catalyzed intramolecular cyclization of **15** than that of **16**. They elucidated how the reaction of **15** proceeds *via* an isocyanate intermediate, followed by a fast addition of the benzyloxy group, whereas in **16** only a slow displacement by the benzyloxy group is possible. Although this interpretation seems quite similar to Mechanism a″), the k_1/k_{13} ratio of 7.2 seems too small to be accounted for analogously.[14]

In conclusion, though some ambiguity still remains with regard to its details, Mechanism b″), where the RO–H bond fission and the nucleophilic attack of the resulting alkoxyl group are simultaneously involved in the rate-determining transition state, seems most plausible for the reaction of carbamoyl cyanide with alcohols.



15



16

Experimental

Reagents. Phenylcarbamoyl cyanide (**1**) was synthesized from Ph–NCO and HCN according to the method reported for diisocyanates in our previous study.[3] Recrystallization from alcohol-free $CHCl_3$ or Et_2O yielded colorless flakes of **1** (>90%): mp 116—117 °C; $UV_{max}^{cyclohexane}$ 267 nm (ε 10050). Diphenylcarbamoyl cyanide (**13**) was prepared by the reaction of the corresponding chloride with NaCN in MeCN.[11] Recrystallization from a cyclohexane-benzene mixture afforded slightly yellow solids of **13** (65%): mp 130—132 °C; $UV_{max}^{dioxane}$ 262 nm (ε 5000).

Preparation of Phenylcarbamoyl Cyanide-d_1 *(1-*d_1*).* Deuterated cyanide was prepared by two methods: (i) the reaction of Ph–NCO with DCN, which had been generated from D_2SO_4–D_2O and anhydrous NaCN; (ii) shaking a warm $CDCl_3$ (99.8% d-content) solution of **1** with excess D_2O (99.8% d_2). For recrystallization, $CDCl_3$ was used; otherwise, D–H exchange took place. Also, care was taken not to heat the solution longer than 30 min.

Kinetics. S.P.-Reagent-grade methanol, dioxane, and cyclohexane, available from the Nakarai Chemicals Co., were used in all the measurements. The rates of the reactions of **1** and **13** with methanol were obtained by measuring the change in the absorbance in diluted dioxane solutions (*ca.*

6—8.8$\times 10^{-5}$ mol/l), where the validity of Beer's rule has preliminarily been confirmed. A Hitachi Model-124 spectrophotometer was used. The analyzing UV bands were: **1** 267 nm (ε 10050), **13** 262 (5000), **7** (R=Me) 236 (15070).

*Pyrolysis of **1**.* A 0.194-g portion of finely pulverized powder of **1** was placed in a platinum basket of a thermobalance (Shimadzu Thermobalance for 2000 mg), whose evacuating outlet was connected to a cold trap cooled at −78 °C. The apparatus was then evacuated to a reduced pressure (20 Torr), and the temperature was raised at a programming rate of 0.7 °C/min from 21 to 74 °C, at a rate of 0.5 °C/min from 74 to 94 °C, and at a rate of 0.2 °C/min from 94 to 103 °C; the weight loss *vs.* time was plotted. The weight loss was observed from 80 °C and was remarkable above 90 °C. Above 110 °C, however, a considerable amount of **1** was sublimed and deposited on the wall of the glass ware; the net loss by the pyrolysis was 46% of the gross loss after 2 h. The trapped liquid (*ca.* 40 mg) showed its ν(NCO) at 2270 cm^{-1} (taken by JASCO IRA-1). An ethereal solution of the trapped liquid gave diphenylurea (65 mg) upon treatment with a few drops of aniline. The remaining solid (88 mg) in the basket was analyzed by TLC (silica gel, $CHCl_3$). Two spots appeared; they were identified with 1,3-diphenyl-5-(phenylcarbamoylimino)hydantoin (**5**, mp 223—225 °C) and unreacted **1** by comparing the R_f values. The mass spectrum of **1** was taken by means of a Hitachi Model RMU-6L by both indirect and direct inletting methods. The spectrum taken at 160 °C and 30 eV showed ion peaks at (m/e) 119(Ph-NCO$^+$), 91(PhN$^+$), 64, and 27(HCN$^+$).

*Decomposition of **1** in Cyclohexanone.* To a mixture of **1** (2.6 g, 0.018 mol) and cyclohexanone (9.5 g), we added a solution (2 g) of AcONa saturated in a 1 : 1 mixture of H_2O and AcOH. A catalytic amount of aq NaCN (10 μl of 10% aq solution) was then added, and the total mixture was heated at 67 °C for 17 h. The reaction mixture, without working-up, was directly analyzed by GLC (Apiezon L, 10%, 3 mm×2 m) at 160 °C (below this temperature decomposition of the cyanohydrin was negligible) to find that it consisted of cyclohexanone cyanohydrin (**9**, 98%) and *N,N′*-diphenylurea (**10**). For other runs, see the details in Table 2.

*Thermal Reaction of **1** with Alcohols.* A dioxane solution of **1** and an alcohol were mixed, and the mixture was warmed under the conditions cited in Table 1. After removing the solvent *in vacuo*, the residue was chromatographed (silica gel, $CHCl_3$). The phenylcarbamates thus obtained were all identical with those synthesized independently from Ph–NCO and the corresponding alcohols as for mp and spectroscopic data.

*Reaction of Diphenylcarbamoyl Cyanide (**13**) with Methanol.* Methyl diphenylcarbamate (**14**) was obtained by heating a methanol solution of **13** with a trace amount of triethylamine over 18 h; 100%; mp 84—86 °C.

The authors wish to express their thanks to Mr. Shigeru Fukumori and Mr. Hiroyuki Ueda for their assistance in this study.

References

1) W. Dieckmann and H. Kammerer, *Ber.*, **38**, 2977 (1905).

2) a) W. Dieckmann and H. Kammerer, *Ber.*, **40**, 3737 (1907); b) Schulz, Rhode, and Herzog, *J. Prakt. Chem.* (2), **74**, 86.

3) A. Oku, M. Okano, and R. Oda, *Makromol. Chem.*, **78**, 186 (1964).

4) A. Oku, T. Shono, and R. Oda, *Makromol. Chem.*, **100**, 224 (1967).

5) W. Dieckmann and H. Kammerer, *Ber.*, **40**, 3742 (1907).

6) T. L. Patton, *J. Org. Chem.*, **32**, 383 (1967).

7) H. A. Piggott, *J. Chem. Soc.*, **1955**, 425.

8) a) R. L. Frank, R. E. Berry, and O. L. Shotwell, *J. Am. Chem. Soc.*, **71**, 3889 (1949); b) W. D. Emmons and J. P. Freeman, *ibid.*, **77**, 4387 (1955).

9) An analogous displacement has been reported for the hydrolysis of acyl cyanides: a) F. Hibbert and D. P. N. Satchell, *J. Chem. Soc., B*, **1967**, 653; b) A. Dornow and H. Theidel, *Angew. Chem.*, **66**, 605 (1954); c) J. Thesing and D. Witzel, *ibid.*, **68**, 432 (1956).

10) The hyperconjugative secondary isotope effect of the N–H(D) bond, if any, may be comparable to the k_H/k_D value of 1.2 that was observed for the C–H(D) bond: see A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2367 (1958).

11) R. G. Hisky and F. I. Carroll, *J. Am. Chem. Soc.*, **83**, 4644 (1961).

12) The small difference observed in the rates (k_1/k_{13}= 7.2) seems ascribable to the steric hindrance in **13** or to the difference in the carbonyl polarization, that might be greater in **1** ($\nu_{C=O}$ 1670 cm^{-1}) than in **13** (1680).

13) J. E. C. Hutchins and T. H. Tafe, *J. Am. Chem. Soc.*, **95**, 3786 (1973).

14) In other words, if Mechanism a″) is correct, the k_1/k_{13} ratio should have been more than 10^4 because the acidity of the N–H in **1** is greater than in **15** due to the conjugation in the conjugate base, Ph–N=C(–O$^-$)–C≡N.