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Synthesis of Furan Derivatives. LXXXIII.[1] Kinetics of Acyl Azide Formation of Carboxylic Acids with Diphenyl Phosphorazidate[2]

HARUO SAIKACHI and TOKUJIRO KITAGAWA

Faculty of Pharmaceutical Sciences, Kobe Gakuin University[3]

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5-Substituted 2-furoyl azides (**7a**, **7b** and **7c**), 5-substituted 2-thenoyl azides (**7d**, **7e** and **7f**), 2-, 3- and 4-pyridinemonocarbonyl azides (**7j**, **7k** and **7l**) and *p*-substituted benzoyl azides (**7g**, **7h** and **7i**) were prepared from the corresponding carboxylic acids with DPPA (**4**) in one step and in good yields, respectively. It was found through the kinetic studies that an electron-withdrowing group substituted at 5-position (furan and thiophene ring) or *p*-position (benzene ring) decreases the rate of the reaction, and reversely, an electron-donating substituted at 5- or *p*-position increases it. In addition, it looks to be reasonable that the most probable pathway is to form the above acyl azides *via* the activated six-membered cyclic complex (**9**) as an intermediacy and then to proceed in the concerted reaction, based on the activation energies (ΔE^*) and entropies (ΔS^*) obtained.

Keywords——kinetics; heteroaroyl azide; diphenyl phosphorazidate; infrared spectroscopic analysis; activated six-membered cyclic intermediacy; concerted mechanism; compensation effect; structur-nucleophilicity relationship; substituent effect

We have been interested in the direct synthesis of 2-aminofuran derivatives in anticipation of any biological activity. For this object, however, it is attended with much difficulty to utilize one of the simplest amino derivative of furan, 2-aminofuran as a starting material, because it is highly unstable.[4a] Hence, Singleton and his co-worker[4b] were successful in the indirect preparation of 2-aminofurans from the reaction of 2-furyl isocyanate obtained from 2-furoyl azide by means of the Curtius reaction, with the alcohols and the Grignard reagents, respectively. Saikachi and his co-worker[5] have also reported that 5-nitro-2-furyl isocyanate *via* 5-nitro-2-furoyl azide reacts with the amines, the alcohols and the thiols to give the corresponding carbamoylamines, carbamates and thiocarbamates, respectively.

In connection with our great interest in that 2-furoyl azide(**7b**) and its related compounds (**7a** and **7c**) as starting materials of the Curtius reaction are readily prepared in excellent yields, Yamada and his co-workers[6] have opportunely announced diphenyl phosphorazidate (abbrivated to DPPA) (**4**), as a characteristic reagent, which converts smoothly carboxylic acid (**1**) into acyl azide (**7**) in the presence of equivalent triethylamine, and also have suggested several possible mechanisms with respect to the formation of **7** in this case as shown in Chart 1.

As a consequence of the foregoing, the above announcements[6] promoted us to examine the reaction of aryl or heteroaryl carboxylic acids such as 5-substituted 2-furoic acids (**1a**, **1b**, and **1c**), 5-substituted 2-thenoic acids (**1d**, **1e**, and **1f**), 2-, 3-, and 4-pyridinemonocarboxylic

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[1] Part LXXXII: H. Saikachi and T. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **25**, 809 (1977).

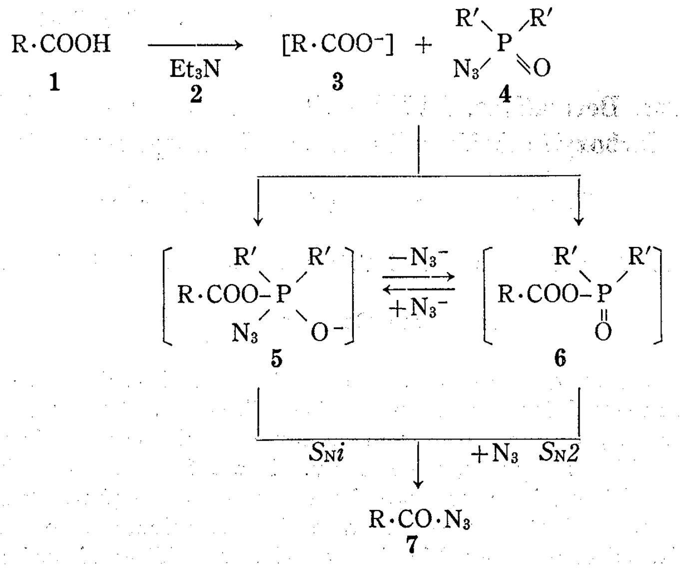
[2] Some parts of this work presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan at Nagoya, April 1976.

[3] Location: *Ikawadani, Tarumi-ku, Kobe, 673, Japan.*

[4] *a*) P. Bosshard and C.H. Eugster, "Advances in Heterocyclic Chemistry, Vol. 17," ed. A.R. Katritzky and A.J. Boulton, Academic Press, N.Y., U.S.A., 1966, p. 468; *b*) H.M. Singleton and W.R. Edwards, Jr. *J. Am. Chem. Soc.*, **60**, 540 (1938).

[5] *a*) H. Saikachi and K. Takai, *Yakugaku Zasshi*, **89**, 34 (1969); *b*) *Idem, ibid.*, **89**, 304 (1969).

[6] *a*) T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1973); *b*) T. Shioiri and S. Yamada, *Yuki Gosei Kagaku Kyokai Shi*, **31**, 666 (1973); *c*) T. Shioiri and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 849 (1974); *d*) T. Shioiri and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 855 (1974).



R=aryl or heteroaryl group
R'=phenoxy group

Chart 1

acids (**1j**, **1k**, and **1l**), and *p*-substituted benzoic acids (**1g**, **1h**, and **1i**) with DPPA (**4**) in order to prepare the corresponding acyl azides (**7a**—**l**), respectively.

In this work, we have two objects. The first is to find out an optimum reaction condition in order to obtain the desired acyl azides (**7a**—**l**) as starting materials of our kinetic study of the Curtius reaction, and the second is to decide the most probable pathway in this reaction (see Chart 1). In connection with the two objects, first of all, the kinetic study of acyl azide formation with DPPA (**4**) was executed by means of quantitative analysis of infrared (IR) spectroscopic method with time (see Fig. 1 and experimental section).

In the course of this reaction, at least, the determination of the rate of each elementary reaction (see Chart 1) is too difficult to do it, because both of the intermediacies, (**5**) and (**6**) seem likely to be almost impossible to isolate from the reaction system as shown in Chart 1. Therefore, the measurement of the overall reaction rates [from carboxylate anion (**3**) to acyl

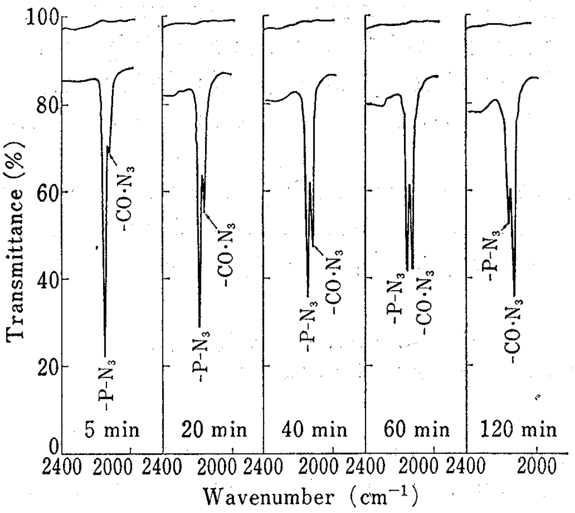


Fig. 1. IR Spectra of the Reaction of 2-Furoic Acid (**1b**) with DPPA (**4**) in the Presence of Triethylamine in Toluene

Temperature, 60°.

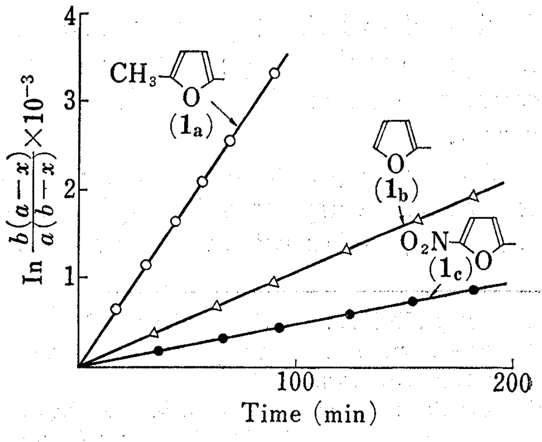


Fig. 2. Second Order Rate Plots for 5-Substituted 2-Furoic Acids (**1a**, **1b** and **1c**) with DPPA(**4**) in Toluene at 70°

a = initial concn. (mole/liter) of acid;
b = initial concn. (mole/liter) of DPPA (**4**);
x = decreasing concn. (mole/litre) of DPPA (**4**) at time t(min).

azide (**7**)] of each carboxylic acids (**1a**—**l**) with DPPA (**4**) was forced to undertake in our laboratory (see Chart 1).

As listed in Table I and II, the rate constants and other thermodynamical functions were evaluated from the above experimental results. Further, on the basis of these data, a close relationship between the nucleophilicity of carboxylate anion (**3**) to DPPA (**4**) and kinetics effected by the structural changes in the carboxylic acids (**1a**—**l**) is also discussed.

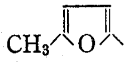
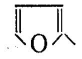
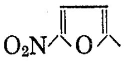
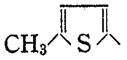
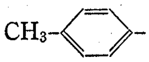
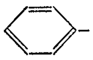
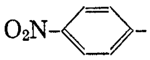
Results and Discussion

The pseudo rate constants were calculated from the customary second order rate expression (Eq. 1),[7]

$$k = \frac{1}{t(a-b)} \ln \frac{b(a-x)}{a(b-x)} \qquad \text{(Eq. 1)}$$

where a is equal to the initial concentration of the carboxylic acids (**1a**—**l**) (mole/liter), b to the initial concentration of DPPA (**4**) (mole/liter), and x is the number of mole per liter of **4** consumed with time t. The second rate order plots were obtained by plotting $\ln[b(a-x)/a(b-x)]$ against time t. As shown in Fig. 2, typical plots indicate three straight lines obtained from

Table I. Kinetic Results of the Reaction of Aryl and Heteroaryl Carboxylic Acids with DPPA in Toluene

Compd. (**1**)	R·COOH	Rate constant, k(l/mole·min) 50°	60°	70°	80°	ΔE kcal/mole	log A
a		0.63	0.96	1.37	1.95	8.53	5.57
b		0.45	0.66	0.93	1.29	7.91	5.01
c		0.09	0.15	0.24	0.39	11.55	6.75
d		1.00	1.43	1.93	2.65	7.26	4.91
e		0.97	1.38	1.90	2.51	7.19	4.85
f		0.08	0.14	0.24	0.39	12.00	7.02
g		0.86	1.21	1.65	2.26	7.34	4.90
h		0.81	1.07	1.32	1.61	4.78	3.17
i		0.50	0.82	1.16	1.73	9.61	6.19
j		0.87	1.15	1.45	2.25	5.56	3.70
k		1.26	1.31	1.93	2.77	5.81	3.99
l		1.07	1.58	2.25	3.15	8.23	5.60

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[7] K.J. Laidler, "Chemical Kinetics," McGraw-Hill, London, 1965, p. 9.

the reaction of 5-methyl-2-furoic acid (**1a**), 2-furoic acid (**1b**) and 5-nitro-2-furoic acid (**1c**), respectively, with DPPA (**4**) in the presence of triethylamine at 70°.

The second order plots for the each reaction result in a straight line to about 70% in every cases. The pseudo second order rate constants are listed in Table I. Using the method of least squares, the activation energies (ΔE^*) and the frequency factors (A) were obtained from the Arrhenius equation, as listed in Table I. The activation entropies (ΔS^*) were obtained from equation (Eq. 2),[8]

$$\Delta S^* = 2.303 \cdot R \cdot \left(\log A - 1 - \log \frac{k_b T}{h}\right) \qquad \text{(Eq. 2)}$$

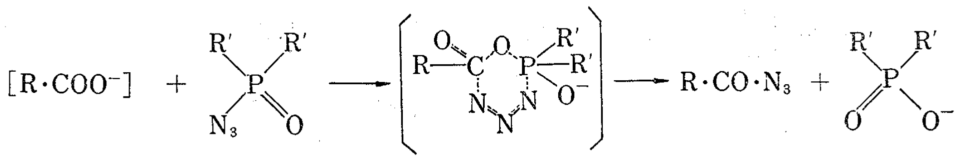
where k_b is Boltzmann's constant and h is Planck's constant. These activation entropies (ΔS^*) are listed in Table II.

Table II. Activation Entropies for the Reaction of Aryl and Heteroaryl Carboxylic Acids with DPPA in Toluene

Compd. (**1**)	R·COOH	ΔS^* e.u. (70°)
a	5-Methyl-2-furyl	−37.9
b	2-Furyl	−40.5
c	5-Nitro-2-furyl	−32.5
d	5-Methyl-2-thienyl	−40.9
e	2-Thienyl	−41.2
f	5-Nitro-2-thienyl	−31.3
g	*p*-Tolyl	−41.0
h	Phenyl	−48.9
i	*p*-Nitrophenyl	−35.1
j	2-Pyridyl	−46.5
k	3-Pyridyl	−45.1
l	4-Pyridyl	−37.8

Kinetic Studies

It is apparent in Table I that the activation energies (ΔE^*) in the reaction of each one of the carboxylic acid-(**1a**—**l**) with DPPA (**4**) range from 4 kcal/mole to 12 kcal/mole, and these all values are smaller than the mean values (20—21 kcal/mole) of the activation energies of other ion-dipole reactions,[9] which are similar to the reaction of carboxylic acid (**3**) with DPPA (**4**) in the presence of equivalent triethylamine (see Chart 1). Also, the entropy changes (ΔS^*) in the passage from initial state to the activation state give the all large negative values (−31—−49 e.u. at 70.°) as shown in Table II.



3 **4** **9** **7** **8**

R =aryl or heteroaryl group
R' =phenoxy group

Chart 2

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[8] M.S. Newman, S.H. Lee, Jr. and A.B. Garrett, *J. Am. Chem. Soc.*, **69**, 113 (1949).

[9] E.A. Moelwyn-Hughes, "The Kinetics of Reactions in Solution," 2nd ed., Oxford Univ. Press, London, 1947, p. 70.

The findings of the large negative values for (ΔS^*) suggest that an activated six-membered cyclic complex (**9**) to be an intermediacy may be formulated in the course of this reaction as shown in Chart 2. The assumption of the forming of such a possible activated complex (**9**) in this reaction system is much helpful for us to understand a logical sequence regarding the formation of acyl azide (**7**) from carboxylic acid (**1**) with DPPA (**4**) (see Chart 2). Namely, it appears to be most reasonable that the nucleophilic attack of carboxylate anion (**3**) on the phosphorus atom of **4** and the internal nucleophilic substitution reaction (*SNi*) of the azide group of **4** on the carbon atom (carbonium) of carboxylate anion (**3**) take place in a concerted process to form the activated complex (**9**) as mentioned above (see Chart 2). Finally, (**9**) was led to acyl azide (**7**) and diphenyl phosphate anion (**8**) (in practice, as a salt with triethylamine[6b)]).

Furthermore, in order to learn of the relationship between the rate of this reaction and the nucleophilicity of carboxylate anion ($R \cdot COO^-$) (**3**) to DPPA (**4**) (see Chart 2), the structural dependency of the carboxylic acids (**1a**—**l**) on kinetic effects in the formation of the corresponding acyl azides (**7a**—**l**) was investigated. As shown in Table I, there is no difference among the rate constants of 2-furonic acid (**1b**), 2-thenoic acid (**1e**) and benzoic acid (**1h**). However, an electron-withdrowing 5-(or *p*-)substituent such as 5-(or *p*-)nitro compounds (**1c**, **1f**, and **1i**) indicates a tendency to decrease the rate constants in comparison with the unsubstituted parents (**1b**, **1e**, and **1h**). For example, in the case of 5-nitro-2-furoic acid (**1c**), it looks likely to be reasonable that the nucleophilicity of 5-nitro-2-furoate anion (**3c**) toward the active phosphorus center atom in DPPA (**4**) is responsible for the rate constant of (**1c**). Namely, a decrease in electron density on the oxygen atom of 5-nitro-2-furoate anion (**3c**) under the influence of the electron-withdrowing nitro group at 5-position of furan ring leads to difficulty of the nucleophilic attack of this anion (**3c**) against the phosphorus atom of DPPA (**4**). Therefore, it appears to be uneasy to form a six-membered ring as an intermediacy (see Chart 2) derived from 5-nitro-2-furoic acid (**1b**). Decisively, our experiment indicated clearly that the rate constant of the former (**1c**) is smaller than that of the latter (**1b**) (see Table I).

Reversely, it is interesting to note that the rate constants of an electron-donating 5-(or *p*-)substituted compounds (**1a**, **1d**, and **1g**) gave larger values than that of the unsubstituted parents (**1b**, **1e**, and **1h**). This result suggests us that the nucleophilicity of carboxylate anions (**3a**, **3d**, and **3g**) derived from 5-(or *p*-)methyl compounds (**1a**, **1d**, and **1g**) increases under the influence of methyl group at 5-(or *p*-)-position of the parent rings, and thereby this reactive nucleophilicity is more favalable for the formation of the six-membered ring (**9**) (see Chart 2).

Incidentally, in Fig. 3, the plots of (ΔE^*) against the logarithms of A about the twelve carboxylic acids (**1a**—**l**) listed in Table I are found to be an over-all linear function. The finding of this linear relationship indicates that all the reactions of these carboxylic acids (**1a**—**l**) with DPPA (**4**) proceed through the same sequence as explained above (see Chart 2).

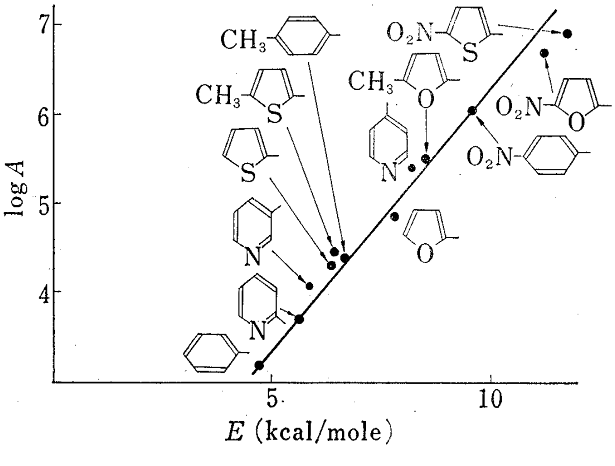


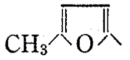
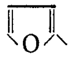
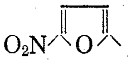
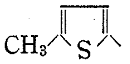
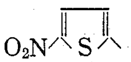
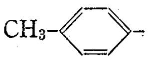
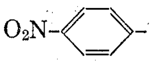
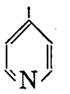
Fig. 3. The Compensation Effect for the Reaction of Aryl and Heteroaryl Carboxylic Acids (**1a**–**l**) with DPPA (**4**) in Toluene

Product Studies

In connection with dimethylformamide (DMF) as a solvent using DPPA (**4**), it has been showed that some dipolar aprotic solvents ,as DMF and tetrahydrofuran (THF), are convenient for the peptide synthesis using DPPA.[6c)]

In our laboratory, the use of a dipolar aprotic solvent DMF instead of toluene gave expectedly the desired acyl azides (**7a**—**l**) in good yields as listed in Table III. The results suggest that the solvent DMF may be favorable for increasing of the concentration of free carboxylate anion (**3**) (see Chart 3) to accelate the formation of the six-membered cyclic intermediacy (**9**) in the course of this reaction.

TABLE III. Aroyl and Heteroaroyl Azides $R \cdot CO \cdot N_3$

Compd. (**7**)	R	Reaction[a] time (hr)	Yield[b] (%)	mp (°C)	Appearance	IR cm^{-1} (KBr)	Lit.
a		1	72	35—36	Colorless[c] needles	2170	19*a*)
b		1	80	62—63	Colorless[c] needles	2130	4*b*)
c		6	71	67—68	Pale yellow[d] needles	2140	5*a*)
d		1	76	54—55	Colorless[c] needles	2180	
e		1	82	32—33	Colorless[c] needles	2140	19*b*)
f		6	70	61—62	Pale yellow[d] prisms	2160	
g		2	69	35—36	Colorless[c] plates	2160	19*b*)
h		1	75	27—28	Colorless[c] plates	2150	19*b*)
i		2	72	65—67	Pale yellow[d] needles	2150	19*b*)
j		1	68	49—50	Pale yellow[c] needles	2160	19*c*)
k		1	89	47—48	Colorless[c] needles	2160	19*c*)
l		1	74	50—51	Colorless[c] needles	2140	19*c*)

[a] At 35°.
[b] Calcd. on the basis of the acids (**1a**—**l**), respectively.
[c] Recrystallized from pet. ether (bp 45—50°)-ether.
[d] Recrystallized from pet. ether (bp 45—50°)-cyclohexane.

$$\underset{\mathbf{1}}{R \cdot COOH} + \underset{\mathbf{2}}{Et_3N} \rightleftarrows \underset{\substack{\mathbf{10}\\ \text{salt}}}{[R \cdot COO^-] \cdot [Et_3NH^+]} \rightleftarrows \underset{\substack{\mathbf{3}\\ \text{free anion}}}{R \cdot COO^-} + \underset{\substack{\mathbf{11}\\ \text{free cation}}}{Et_3NH^+}$$

R=aryl or heteroaryl group

Chart 3

Especially, it is worthy to note that 5-nitro-2-furoyl azide (**7c**) was obtained from the corresponding carboxylic acid (**1c**) with DPPA (**4**) in one step and in good yield (71%).

Finally, it looks likely to be logical to consider that the one of the most probable pathways (see Chart 1) is to form the acyl azides (**7a**—**l**) by way of the activated six-membered cyclic complex (**9**) as an intermediacy (see Chart 2) and to proceed in the concerted reaction.

Experimental

Materials——*p*-Toluic acid (**1g**), benzoic acid (**1h**), *p*-nitrobenzoic acid (**1i**), 2-, 3- and 4-pyridinemonocarboxylic acids (**1j**, **1k** and **1l**) were obtained from the Wako Pure Chemical Industries, Ltd. and were used without purification. 5-Methyl-2-furoic acid (**1a**),[10] 2-furoic acid (**1b**),[11] 5-nitro-2-furoic acid (**1c**),[12] 5-methyl-2-thenoic acid (**1d**),[13] 2-thenoic acid (**1e**)[14] and 5-nitro-2-thenoic acid (**1f**),[15] were prepared by known procedures. DPPA (**4**) was obtained from the Daiichi Pure Chemicals Co., Ltd. and purified by distillation, bp 149—152°/0.2 mmHg (lit. 157/0.17 mmHg).[6c] Toluene was spectroscopic grade[16] and stored over Linde Molecular Sieves (Type 4A 1/16) to prevent it from moisture.

Kinetic Procedure——IR measurements were made in a 0.5 mm sodium chloride micro cell using the Shimazu Model IR-400 double-beam recording spectrophotometer.

In a 50 ml four-necked round-bottomed flask which was fitted calcium chloride drying tube and a thermometer, were placed carboxylic acids (**1a**—**l**) (0.016 mol), triethylamine (0.016 mol) and toluene (20 ml). The flask and its contents were placed in a constant temperature oil-bath (50°, 60°, 70° and $80° \pm 0.01°$)[17] and the temperature in the contents was equilibrated at the prescribed temperature. The time of addition of toluene solution (5 ml) of DPPA (**4**) (0.015) into the reaction flask at the above prescribed temperature was taken as zero time. About 0.3 ml of samples from the reaction mixture were quickly withdrawn at regular intervals, and quenched in a mixture of acetone and dry ice. The samples were immediately examined in the IR spectrum from 2500 to 2000 cm^{-1} *vs.* pure solvent (toluene). The amount of unchanged DPPA (**4**) was obtained from the intensity of the $-N_3$ asymmetric streching frequency of (**4**) at 2200 cm^{-1}. There was no interference of this band with that of acyl azides (**7a**—**l**). The typical IR spectra of the reaction of 2-furoic acid (**1a**) with **4** in the presence of triethylamine at 60° are shown in Fig. 1.

The Preparative Scale Experiments of Acyl Azides (7a—l)[18]——To a DMF solution (30 ml) of carboxylic acids (**1a**—**l**) (0.04 mol) and triethylamine (0.04 mol), was added a DMF solution (5 ml) of DPPA (**4**) (0.04 mol) with stirring and cooling. After all **4** had been added (10 min), the each mixture was stirred at 35° and treated in the each duration as listed in Table III, and immediately poured into a mixture of ether and ice to quench the reaction. The requisite products (**7a**—**l**) were extracted with ether, and the organic layers were washed with a 10% solution of sodium bicarbonate and with water, and then dried over anhydrous sodium sulfate. The ether layers were removed under reduced pressure at room temperature. The residues were recrystallized respectively from the solvents in Table III. The products (**7a**—**l**) were identified as acyl azide in comparison of their IR spectra [IR cm^{-1}: ν_{N_3} 2130—2180 (KBr)] with that of the authentic samples[19] (see Table III). The yield, mp and appearance for (**7a**—**l**) are also given in Table III.

5-Methyl-2-thenoyl Azide (7d)——**7d** was prepared by the above-mentioned general procedure using 6 g (0.04 mol) of 5-methyl-2-thenoic acid (**1d**) and recrystallized from pet. ether (bp 45—50°)-ether (1:1); colorless needles, yield, 5.1 g (76%), mp 54—55°. *Anal.* Calcd. for $C_6H_5N_3OS$: C, 42.12; H, 3.02; N, 25.15. Found: C, 42.05; H, 2.90; N, 25.10. IR cm^{-1}: ν_{N_3} 2180 (KBr).

5-Nitro-2-thenoyl Azide (7f)——**7f** was also prepared by the usual method as mentioned above using 6.9 g (0.04 mol) of 5-nitro-2-thenoic acid (**1f**) and recrystallized from pet. ether (bp 45—50°)-cyclohexane (1:1); pale yellow prisms, yield, 5.5 g (70%), mp 61—62°. *Anal.* Calcd. for $C_5H_2N_4O_3S$: C, 30.31; H, 1.02; N, 28.28. Found: C, 30.47; H, 1.21; N, 28.15. IR cm^{-1}: ν_{N_3} 2160 (KBr).

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