[Chem. Pharm. Bull. 27(10)2398—2404(1979)]

UDC 547.786.1.04 : 546.264.131-31.04

Studies on Isoxazoles. VIII.[1] Versatile Syntheses and Chemical Properties of 3-Chloroisoxazolium Chlorides[2]

Kazuo Tomita, Soji Sugai, Tomiko Kobayashi, and Tadashi Murakami

Agricultural Chemicals Research Laboratory, Sankyo Co., Ltd.[3]

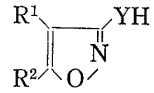
(Received April 10, 1979)

The reaction of 4-isoxazolin-3-ones with phosgene or trichloromethyl chloroformate gave various 3-chloroisoxazolium chlorides in good yields, and these were converted to 4-isoxazolin-3-thiones on treatment with sodium hydrosulfide. Pyrolysis of 3-chloro-2-methylisoxazolium chlorides afforded 3-chloroisoxazoles. In the presence of tri-*n*-butylamine, 3-chloro-2-methyl-5-phenylisoxazolium chloride condensed carboxylic acids with alcohols or amines to give the corresponding esters or amides in high yields, together with 2-methyl-5-phenyl-4-isoxazolin-3-one.

Keywords——3-chloroisoxazolium chlorides; quaternization; nucleophilic substitution; pyrolysis; condensation reaction

Various 3-hydroxyisoxazoles (I)[4] and their derivatives[5] have been synthesized. Among them, 3-hydroxy-5-methylisoxazole[6] and diethyl 5-phenyl-3-isoxazolyl phosphorothioate[7] have been marketed as pesticides. Various 3-aminoisoxazoles (II) have also been synthesiz-

1) Part VII: K. Tomita, H. Oka, T. Murakami, H. Tsuji, and K. Matsumoto, *Ann. Rep. Sankyo Res. Lab.*, **30**, 193 (1978).
2) A part of this work was presented at the 11th Congress of Heterocyclic Chemistry, Kanazawa, Japan, October 1978.
3) Location: *2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo, 140, Japan.*
4) *a*) P. Bravo, G. Gaudiano, A. Quilico, and A. Ricca, *Gazz. Chim. Ital.*, **91**, 47 (1961); *b*) H.D. Stachel, *Chem. Ber.*, **96**, 1088 (1963); *c*) A.J. Boulton, A.R. Katritzky, A. Malid Hamid, and S. Øksne, *Tetrahedron*, **20**, 2835 (1964); *d*) K. Sirakawa, O. Aki, S. Tsushima, and K. Konishi, *Chem. Pharm. Bull.* (Tokyo), **14**, 89 (1966); *e*) I. Iwai and N. Nakamura, *ibid.* **14**, 1277 (1966); *f*) R. Jacquier, C. Petrus, F. Petrus, and J. Verducci, *Bull. Soc. Chim. Fr.*, **1967**, 3003; *g*) K. Bowden, G. Crank, and W.J. Ross, *J. Chem. Soc. C*, **1968**, 172; *h*) M. Frater-Schroeder, R. Good, and C.H. Eugster, *Helv. Chim. Acta*, **52**, 720 (1969); *i*) T. Yokobe and T. Kakemoto, *Yakugaku Zasshi*, **89**, 1236 (1969); *j*) R. Jacquier, C. Petrus, F. Petrus, and J. Verducci, *Bull. Soc. Chim. Fr.*, **1970**, 1978; *k*) B. Loer, J.W. Wilson, and M.M. Goodman, *J. Med. Chem.*, **13**, 738 (1970); *l*) R. Jacquier, C. Petrus, F. Petrus, and J. Verducci, *Bull. Soc. Chim. Fr.*, **1970**, 2685; *m*) K. Tomita, M. Nagano, T. Yanai, H. Oka, T. Murakami, and N. Sampei, *Ann. Rep. Sankyo Res. Lab.*, **22**, 215 (1970); *n*) N. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **19**, 46 (1971); *o*) T. Kato, N. Katagiri, and N. Minami, *ibid.*, **20**, 1368 (1972).
5) Ethers: *a*) S. Cabiddu, G. Gaudiano, and A. Quilico, *Gazz. Chim. Ital.*, **92**, 501 (1962); *b*) T. Yokobe, *Yakugaku Zasshi*, **89**, 1254 (1969); *c*) N. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **15**, 1025 (1967); *d*) H. Saeki, Y. Shimada, and T. Murakami, *Ann. Rep. Sankyo Res. Lab.*, **25**, 131 (1973). Carboxylic esters; *e*) L. Bauer, C.N.V. Nambury, and C.L. Bell, *Tetrahedron*, **20**, 165 (1964); *f*) H. Goth, A.R. Gagneux, C.H. Eugster, and H. Schmid, *Helv. Chim. Acta*, **50**, 137 (1967); *g*) H. Böshagen, *Chem. Ber.*, **100**, 954 (1967); *h*) H. Böshagen and W. Geiger, *ibid.*, **102**, 3775 (1969); *i*) H. Oka and K. Tomita, *Ann. Rep. Sankyo Res. Lab.*, **29**, 99 (1977). Carbamates: *cf.* 1); *j*) N. Sampei, K. Tomita, H. Tsuji, and T. Yanai, *Ann. Rep. Sankyo Res. Lab.*, **22**, 230 (1970). Phosphates; *k*) N. Sampei, K. Tomita, H. Tsuji, T. Yanai, H. Oka, and T. Yamamoto, *ibid.*, **22**, 221 (1970).
6) This compound is a soil fungicide and also a plant growth regulating agent: K. Tomita, Y. Takahi, R. Ishizuka, S. Kamimura, M. Nakagawa, M. Ando, T. Nakamura, and H. Okudaira, *Ann. Rep. Sankyo Res. Lab.*, **25**, 1 (1973).
7) This compound is an insecticide: K. Ando, K. Tomita, H. Tsuji, T. Asawa, M. Ando, M. Nakagawa, T. Nakamura, H. Okudaira, and M. Ishida, *Ann. Rep. Sankyo Res. Lab.*, **29**, 1 (1977).

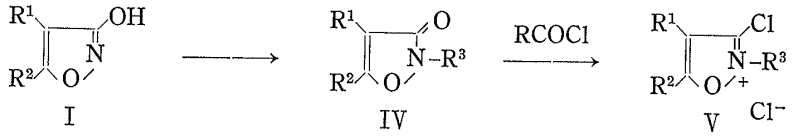


Y=O (I), Y=NH (II)
Y=S (III)

Chart 1

ed[4b,e,8] and sulfamethoxazole[9] (derived from 3-amino-5-methylisoxazole) is widely used as an antibacterial agent. On the other hand, no 3-mercaptoisoxazoles (III) are known. We have therefore sought to synthesize them in view of their potential biological activity. During the course of studies on the synthesis of III, 3-chloroisoxazolium chlorides (V) have been found to be key intermediates. The present paper deals with improved synthetic procedures and some chemical properties of the salts (V).

Faust[10] has prepared two 3-haloisoxazolium salts, 3-bromo-2-ethyl-5-phenylisoxazolium fluoroborate (VIII) and 3-chloro-2-ethyl-5-phenylisoxazolium chloride (Vp). The former was synthesized by quaternization of 3-bromo-5-phenylisoxazole (IX) with triethyloxonium fluoroborate, and the latter by heating 2-ethyl-5-phenyl-4-isoxazolin-3-one (IVp) and oxalyl chloride. The 3-bromoisoxazole (IX) was obtained by the Grignard reaction of dibromoformaldoxime with phenylethynylmagnesium bromide,[11] whereas the 4-isoxazolin-3-ones (IV) were easily prepared by alkylation[12] of 3-hydroxyisoxazoles (I). The latter method seemed preferable.



R=ClCO, Cl, Cl_3CO

Chart 2

According to Faust's method, 3-isoxazolones (IVa, d, e, h, j, k, p, s) were treated with oxalyl chloride in boiling carbon tetrachloride. This procedure resulted in polymerization, except in the cases of IVk and IVp, which afforded 3-chloro-2-methyl-5-phenylisoxazolium chloride (Vk) and Vp, respectively, in good yields (Table I). When the reactions were carried out at room temperature, the corresponding onium salts (Va, d, e, h, k, p, s) were isolated in low yields, except in the case of 2,4,5-trimethyl-4-isoxazolin-3-one (IVj). The use of phosgene in place of oxalyl chloride gave the salts, including, Vj in higher yields. Their structures were confirmed by the spectral data. Some did not give satisfactory elemental analyses due to their hygroscopic character, and were therefore analyzed as the hexachloroantimonates (X) or the tetrafluoroborate (XI). Trichloromethyl chloroformate (TCF) gave the salts in lower yields than phosgene, but the yields were improved by increasing the reaction time (Table I).

The formation of various 3-chloroisoxazolium chlorides (V) by these methods appears to be affected by the electronic and steric properties of the substituents on the isoxazole ring. In fact, the introduction of a bulky or an electro-withdrawing group at the 4-position of 2-methyl-5-phenyl-4-isoxazolin-3-ones prevented the synthesis of V (Table I).

The reaction of VIII with sodium sulfide or aniline has been reported to afford 2-ethyl-5-phenyl-4-isoxazolin-3-thione (VIp) or 3-anilino-2-ethyl-5-phenylisoxazolium fluoroborate, respectively.[10] Generally speaking, the chlorine at the 3-position of the salts (V) might also be displaced by the attack of suitable nucleophiles. The chloride (Vk) was spontaneously hydrolyzed with alkali to IVk, whereas no change was observed under acidic conditions. Treatment of Vk with sodium hydrosulfide or sodium thiosulfate gave 2-methyl-5-phenyl-

8) *cf.* 4*b*); *a*) A. Obregia, *Ann.*, **266**, 324 (1891); *b*) D.E. Worrall, *J. Am. Chem. Soc.*, **59**, 933 (1937); *c*) J.T. Plati and W. Wenner, Fr. Patent 1363643 (1964) [*C.A.*, **61**, 14678*h* (1964)].
9) N^1-(5-Methyl-3-isoxazolyl)sulfanilamide: H. Kano and K. Ogata, *Ann. Rep. Shionogi Res. Lab.*, **7**, 1 (1957) [*C.A.*, **51**, 17889 (1957)].
10) J. Faust, D. Arndt, and R. Mayer, *Z. Chem.*, **8**, 19 (1968).
11) S. Cabiddu and V. Sobinas, *Gazz. Chim. Ital.*, **99**, 1107 (1969).
12) *cf.* 5*a*); *a*) A.J. Boulton, Tetrahedron, **20**, 2835 (1964); *b*) T. Yokobe, *Yakugaku Zasshi*, **89**, 1245 (1969).

Table I. Isolation Yields (%) of 3-Chloroisoxazolium Chlorides (V) by the Reaction[a] of IV with RCOCl

V	R^1	R^2	R^3	mp (°C)	RCOCl			
					$(COCl)_2$[b]	$COCl_2$[b]	TCF[c]	
a	H	H	Me	152—154	58.1	96.8	72.1	
b	H	H	Allyl	92— 94	—	74.7	—	
c	H	H	Benzyl	88— 90	—	82.8	—	
d	H	Me	Me	122—123	45.0[e]	94.2	87.3,	97.0[f]
e	H	Me	Et	105—109	24.6[e]	94.9	85.8,	95.3[f]
f	H	Me	iso-Pr	97— 99	—	93.5	—	
g	H	Me	Allyl	75— 77	—	89.3	67.6	
h	H	Me	Benzyl	76— 80	37.2	93.0	79.8	
i	H	Me	Ph	89— 93	—	86.2	—	91.1[f]
j	Me	Me	Me	78— 79	Resin	92.0	89.5	
k	H	Ph	Me	122—125	31.5,	89.3[d] 97.8	74.8	
l	Me	Ph	Me	96— 98	—	—	53.5	
m	Et	Ph	Me	95— 97	—	—	28.0	
n	iso-Pr	Ph	Me	88— 90	—	—	5.7	
o	Cl	Ph	Me	—	—	—	0	
p	H	Ph	Et	111—115[g]	20.0,	97.8[d] 89.5	68.2	
q	H	Ph	iso-Pr	133—134	—	89.1	—	
r	H	Ph	Allyl	86— 88	—	86.6	—	
s	H	Ph	Benzyl	82— 90	18.0	62.1	44.3	
t			Allyl	66— 69	—	47.0	—	

a) In dry benzene at room temperature for 2 hr.
b) Two-fold molar excess used.
c) Equimolar amount used.
d) In CCl_4 at 70° for 2 hr.[10]
e) Isolation as the hexachloroantimonate.
f) For 6 hr.
g) Lit.[10] mp 129—132°.

Table II. 3-Chloroisoxazolium Chlorides (V)

V	Formula	Analyses (%) Calcd. C ; H ; Cl ; N	Found C ; H ; Cl ; N	NMR δ_{ppm} solv.[a]	4-H
a	$C_4H_5Cl_2NO$	31.20; 3.27; 46.04; 9.10	30.84; 3.46; 45.69; 8.69	M	7.83
b	$C_6H_7Cl_2NO$	40.03; 3.92; 39.38; 7.78	39.98; 3.91; 37.85; 7.39	M	7.85
c	$C_{10}H_9Cl_2NO$	52.20; 3.94; 30.82; 6.09	51.53; 3.98; 30.44;10.85	—	—
d	$C_5H_7Cl_2NO$	35.72; 4.20; 42.18; 8.33	34.50; 4.39; 42.36; 7.76	M	7.53
e	$C_6H_9Cl_2NO$	39.59; 4.98; 38.95; 7.69	37.84; 5.14; 38.82; 7.19	C	7.82
f	$C_7H_{11}Cl_2NO+HCl$	36.16; 5.20; 45.74; 6.02	35.43; 5.44; 44.21; 5.63	C	7.53
g	$C_7H_9Cl_2NO$	43.33; 4.67; 36.54; 7.22	41.23; 4.34; 36.11; 6.87	C	8.07
h	$C_{11}H_{11}Cl_2NO$	54.12; 4.54; 29.05; 5.74	54.00; 4.58; 28.53; 5.39	M	7.60
i	$C_{10}H_9Cl_2NO$	52.20; 3.94; 30.82; 6.09	53.27; 4.13; 26.53; 6.46	C	7.6—8.2
j	$C_6H_9Cl_2NO+1/2HCl$	35.98; 4.78; 41.25; 6.99	34.25; 5.15; 42.20; 6.76	N	2.23[b]
k	$C_{10}H_9Cl_2NO$	52.21; 3.94; 30.82; 6.09	52.61; 4.06; 30.77; 5.96	M	8.13
l	$C_{11}H_{11}Cl_2NO$	54.10; 4.51; 29.10; 5.75	53.43; 4.70; 29.22; 5.22	C	2.47[b]
m	$C_{12}H_{13}Cl_2NO+1/2H_2O$	53.93; 5.24; 26.59; 5.34	54.55; 5.26; 23.50; 5.39	C	2.83[c]
n	$C_{13}H_{15}Cl_2NO+1/2HCl$	53.79; 5.34; 30.60; 4.83	53.11; 5.67; 29.82; 4.72	C	3.30[d]
p	$C_{11}H_{11}Cl_2NO$	54.12; 4.54; 29.05; 5.74	52.76; 4.83; 29.30; 5.64	M	8.18
q	$C_{12}H_{13}Cl_2NO$	55.83; 5.08; 27.47; 5.43	54.31; 5.35; 28.08; 5.28	M	8.30
r	$C_{12}H_{11}Cl_2NO$	56.27; 4.33; 27.68; 5.47	55.74; 4.29; 27.44; 5.59	M	8.20
s	$C_{16}H_{13}Cl_2NO$	62.76; 4.28; 23.16; 4.57	63.15; 4.34; 22.66; 3.89	M	8.20
t	$C_{10}H_9Cl_2NO$	52.20; 3.94; 30.82; 6.09	52.25; 3.37; 31.16; 6.13	—	—

a) C ($CDCl_3$); M (CD_3OD); N (CD_3CN).
b) CH_3. *c*) CH_2. *d*) CH.

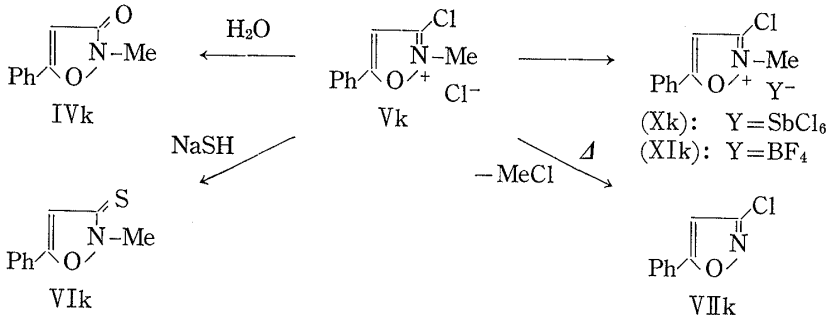


Chart 3

TABLE III. 4-Isoxazolin-3-thiones (VI)

VI	Yield (%)	mp (°C) (n_D)	Formula	Analyses (%) Calcd. C ; H ; N ; S	Analyses (%) Found C ; H ; N ; S	NMR δ_{ppm} solv.	NMR δ_{ppm} 4-H
a	82.4	76— 77	C_4H_5NOS	41.72; 4.38;12.16; 27.84	41.72; 4.25;11.87; 27.95	C	6.45
b	98.6	(n_D^{19} 1.5889)	C_6H_7NOS	51.04; 5.00; 9.92; 22.71	50.70; 5.02; 9.98; 22.59	C	6.47
c	72.6	82— 83	$C_{10}H_9NOS$	62.80; 4.74; 7.32; 16.77	63.31; 4.77; 7.31; 16.89	T	6.30
d	91.6	94	C_5H_7NOS	46.49; 5.46;10.84; 24.82	46.58; 5.54;10.68; 25.09	T	6.05
e	87.4	43— 44	C_6H_9NOS	50.32; 6.33; 9.78; 22.39	49.46; 6.02; 9.70; 22.16	C	6.13
f	86.8	(n_D^{27} 1.5582)	$C_7H_{11}NOS$	53.47; 7.05; 8.91; 20.39	53.67; 7.18; 8.99; 20.22	C	6.13
g	73.7	(n_D^{18} 1.5825)	C_7H_9NOS	54.17; 5.84; 9.02; 20.66	54.30; 5.83; 9.26; 20.25	C	6.13
h	86.6	91— 92	$C_{11}H_{11}NOS$	64.36; 5.40; 6.82; 15.62	64.69; 5.39; 7.03; 15.63	T	6.06
j	82.4	101—103	C_6H_9NOS	50.32; 6.33; 9.78; 22.39	50.13; 6.38; 9.61; 22.40	C	1.94
k	84.2	120—121	$C_{10}H_9NOS$	62.80; 4.74; 7.32; 16.77	62.74; 4.73; 7.26; 17.01	C	6.63
l	91.1	80— 81	$C_{11}H_{11}NOS$	64.39; 5.37; 6.83; 15.61	64.68; 5.38; 6.82; 15.80	C	2.30[c]
m	83.3	69— 71	$C_{12}H_{13}NOS$	65.75; 5.94; 6.39; 14.61	65.66; 5.92; 6.22; 14.76	C	2.78[d]
n	87.0	85— 86	$C_{13}H_{15}NOS$	66.92; 6.48; 6.00; 13.74	66.66; 6.40; 5.98; 13.62	C	3.23[e]
p	89.6	96— 98[b]	$C_{11}H_{11}NOS$	64.36; 5.40; 6.82; 15.62	64.09; 5.34; 6.54; 15.84	C	6.64
q	89.8	77— 78	$C_{12}H_{13}NOS$	65.72; 5.98; 6.39; 14.62	66.06; 6.35; 6.44; 14.56	C	6.65
r	92.6	80— 81	$C_{12}H_{11}NOS$	66.33; 5.10; 6.45; 14.76	66.31; 4.98; 6.25; 14.99	C	6.67
s	68.6	121—122	$C_{16}H_{13}NOS$	71.88; 4.90; 5.24; 11.99	72.17; 4.78; 5.12; 12.03	C	6.66
t	50.5	(n_D^{21} 1.6460)	$C_{10}H_9NOS$	62.80; 4.74; 7.32; 16.77	61.64; 4.79; 7.30; 16.59	—	—

a) C ($CDCl_3$); T (CCl_4).
b) Lit.[10] mp 62°. *c*) CH_3. *d*) CH_2. *e*) CH.

4-isoxazolin-3-thione (VIk), and treatment with thiourea also gave VIk, together with thiodiformamidine. The thione (VIk) could not be obtained directly by the reaction of IVk with phosphorus pentasulfide. The other 4-isoxazolin-3-thiones (VI) listed in Table III were also prepared by treatment of the corresponding onium salts (V) with sodium hydrosulfide. In the case of 3-chloro-5-methyl-2-phenylisoxazolium chloride (Vi), a complex mixture was obtained; details of the reaction will be reported in another paper of this series.

The reaction of 2,4,5-trimethyl-4-isoxazolin-3-one (VIj) with oxalyl chloride in boiling carbon tetrachloride has been reported[10] to give 3-chloro-4,5-dimethylisoxazole (VIIj). This suggests the formation of 3-chloro-2,4,5-trimethylisoxazolium chloride (Vj), followed by pyrolysis. In fact, heating of the isolated 3-chloro-2,4,5-trimethylisoxazolium chloride (Vj) gave VIIj together with methyl chloride. The other onium chlorides (Va, d, k, n) were also pyrolyzed to give the corresponding 3-chloroisoxazoles (VIIa, d, k, n) (Table IV). The low yields of VIIa and VIIj may be a result of their high volatility.

Recently, much attention has been focused on heteroaromatic onium salts such as 2-chloro-1-methylpyridinium iodide (XII)[13] and 2-chloro-3-ethylbenzothiazolium fluoroborate

13) T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, **1975**, 1045.

Table IV. 3-Chloroisoxazolium Chlorides (VII)

VII	From V	Isolation yield (%)	Physical constant
a	a	29.9	n_D^{25} 1.4553[a]
d	d	74.7	n_D^{26} 1.4510[b]
j	j	35.7	bp 85°/30 mm Hg[c] n_D^{24} 1.4460
k	k	82.0	mp 36—37°[d]
n	n	85.6	mp 62—63°

a) Lit.[4a] n_D^{25} 1.4560. *b*) Lit.[16] n_D^{20} 1.4610.
c) Lit.[10] bp 93°/45 mmHg. *d*) Lit.[4a] mp 37—38°.

Table V. Isolation Yields of Condensation Products from Carboxylic Acids (R^4COOH) and Nucleophiles in the Presence of Vk

Carboxylic acids (R^4)	Nucleophiles	Reaction temp. (°C)	Yield (%)
Ph	$PhCH_2OH$	−10	69.8[a]
PhCH=CH	$PhCH_2OH$	15	80.7[a]
4-ClC_6H_4	PhCH(Me)OH	−25	76.8
Me	$PhCH_2OH$	20	84.7
$NCCH_2SCH_2$	2,6-$(Et)_2C_6H_3NH_2$	−40	87.5
$NCCH_2SCH_2$	$PhCH_2NHMe$	−50	77.6
PhCH=CH	$PhCH_2NH_2$	−40	88.8
Ph	$PhCH_2NH_2$	−50	83.2
HC≡C	$PhNH_2$	−30	68.1

a) A small amount of acid anhydride was isolated as a by-product.

(XIII)[14] as potentially useful coupling reagents. Since the 3-chloroisoxazolium chlorides (V) have chloroiminium structures similar to those of the pyridinium (XII) and the benzothiazolium (XIII) salts, they should be efficient condensing reagents. The equimolar reaction of carboxylic acids and alcohols or amines with Vk in the presence of a 2-fold molar excess of tri-*n*-butylamine afforded the corresponding esters or amides in good yields, together with 3-isoxazolone (IVk) (Table V). This reagent is superior to the known onium salts (XII, XIII) in forming Vk from the 3-isoxazolone (IVk) generated by the methods described above.

Experimental

Melting points are not corrected. Infrared (IR) spectra were recorded with a Hitachi G_3 spectrometer. NMR spectra were taken with a Varian A-60 spectrometer using tetramethylsilane as an internal standrad. The abbreviations are as follows: s (singlet), d (doublet), t (triplet) and m (multiplet).

4-Isoxazolin-3-ones (IV)——These compounds were prepared by alkylation of the corresponding 3-hydroxyisoxazoles (I) as reported in the literature,[12] except that 5-methyl-2-phenyl-4-isoxazolin-3-one (IVi) was obtained according to Matter's method.[15] The physical data for the new compounds are listed in Table VI.

3-Chloro-2-methyl-5-phenylisoxazolium Chloride (Vk)——A mixture of 2-methyl-5-phenyl-4-isoxazolin-3-one (IVk) (3.5 g) and phosgene (3.96 g), TCF (3.96 g) or oxalyl chloride (5.08 g) in dry benzene (150 ml) was stirred at room temperature for 2 hr. The precipitated crystals were collected, washed successively with dry benzene (30 ml) and *n*-hexane (20 ml), and then dried *in vacuo* to yield Vk (4.5 g, 97.8%: phosgene;

14) T. Mukaiyama and K. Hojo, *Chem. Lett.*, **1976**, 1267.
15) M. Matter, C. Vogel, and R. Bosshard, Ger, Patent 1146494 (1963) [*C.A.*, **59**, 10058*g* (1963)].
16) R. Fusco and S. Rossi, *Rend. Ist. Lombardo Sci. Pt. I. Classe Sci. Mat. e Nat.*, **94A**, 729 (1960) [*C.A.*, **57**, 16583*d* (1961)].

Table VI. 4-Isoxazolin-3-ones (IV)

IV	mp (°C) (n_D)	Formula	Analyses (%) Calcd. C ; H ; N	Found C ; H ; N	NMR ($CDCl_3$) δ_{ppm} 4-H	IR (Liquid) ν_{max} cm^{-1} C=O
b	(n_D^{23} 1.4934)	$C_6H_7NO_2$	57.59; 5.64;11.19	57.37; 5.82;11.42	5.85	1670
c	($n_D^{25.5}$ 1.5550)	$C_{10}H_9NO_2$	68.56; 5.18; 8.00	68.43; 5.29; 8.16	—	1665
f	(n_D^{23} 1.4640)	$C_7H_{11}NO_2$	59.56; 7.85; 9.92	59.61; 8.03; 9.86	5.48	1670
g	(n_D^{20} 1.4830)	$C_7H_9NO_2$	60.42; 6.52;10.07	60.22; 6.55; 9.98	5.52	1660
h	54—55	$C_{11}H_{11}NO_2$	69.80; 5.86; 7.44	69.50; 5.96; 7.47	5.38	1670
l	85—86	$C_{11}H_{11}NO_2$	69.84; 5.82; 7.41	69.67; 8.87; 7.66	2.13(CH_3)	1660[a]
m	(n_D^{24} 1.5730)	$C_{12}H_{13}NO_2$	70.94; 6.40; 6.90	70.34; 6.69; 6.66	2.55(CH_2)	1660
n	($n_D^{29.5}$ 1.5546)	$C_{13}H_{15}NO_2$	71.87; 6.96; 6.45	70.70; 7.09; 6.42	2.97(CH)	1660
o	80—81	$C_{10}H_8ClNO_2$	57.28; 3.82; 6.68	57.32; 3.80; 6.54	—	1695[a]
q	($n_D^{25.5}$ 1.5606)	$C_{12}H_{13}NO_2$	70.92; 6.45; 6.89	70.57; 6.37; 6.74	6.02	1690
r	54—55	$C_{12}H_{11}NO_2$	71.63; 5.51; 6.96	71.62; 5.44; 6.91	6.08	1660[a]
t	($n_D^{25.5}$ 1.5838)	$C_{10}H_9NO_2$	68.56; 5.18; 7.99	67.49; 5.57; 7.59	—	1690

a) Phase (Nujol).

3.32 g, 72.1%: TCF; 1.45 g, 31.5%: Oxalyl chloride), mp 122—125°. NMR (CD_3OD) δ: 4.52 (3H, s, CH_3), 7.5—8.3 (5H, m, C_6H_5), 8.13 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1605 (C=N).

The other 3-chloroisoxazolium chlorides (V) were prepared by the procedure used for Vk. The physical data are listed in Table II.

3-Chloro-2-methyl-5-phenylisoxazolium Hexachloroantimonate (Xk)——Pentachloroantimonate (1.5 g) was added dropwise to a solution of Vk (1.15 g) in $CHCl_3$ (50 ml) under ice-cooling, and the mixture was stirred for 1 hr. After removal of the solvent, the crude product was purified by precipitation in CH_3CN with $CHCl_3$ to give 2.35 g (88.8%) of Xk, mp 290—292°. *Anal.* Calcd. for $C_{10}H_9Cl_7NOSb$: C, 22.70; H, 1.72; Cl, 46.90; N, 2.65. Found: C, 22.78; H, 1.74; Cl, 46.82; N, 2.88. IR ν_{max}^{Nujol} cm^{-1}: 3120 (=CH–), 1590 (C=N).

3-Chloro-2-isopropyl-5-methylisoxazolium Hexachloroantimonate (Xf)——mp 195—197°. *Anal.* Calcd. for $C_7H_{11}Cl_7NOSb$: C, 16.98; H, 2.24; Cl, 50.13; N, 2.83. Found: C, 16.49; H, 1.82; Cl, 49.31; N, 2.64.

3-Chloro-2,4,5-trimethylisoxazolium Hexachloroantimonate (Xj)——mp 226—229°. *Anal.* Calcd. for $C_6H_9Cl_7NOSb$: C, 14.98; H, 1.85; Cl, 51.59; N, 2.91. Found: C, 15.34; H, 2.34; Cl, 51.24; N, 3.17.

3-Chloro-2-methyl-5-phenylisoxazolium Fluoroborate (XIk)——Sodium tetrafluoroborate (0.49 g) in CH_3CN (100 ml) was added to a cold solution of Vk (1.0 g) in CH_3CN (60 ml) and $CHCl_3$ (20 ml). The mixture was stirred at room temperature for 2 hr. After filtration, the filtrate was concentrated to one-fifth of its original volume. Ether (30 ml) was added to the resulting solution, and the precipitated crystals were collected and washed with $CHCl_3$ (20 ml) to give 0.90 g (73.8%) of XIk, mp 157—159°. *Anal.* Calcd. for $C_{10}H_9BClF_4NO$: C, 42.68; H, 3.22; Cl, 12.60; F, 27.00; N, 4.98. Found: C, 42.84; H, 2.88; Cl, 12.89; F, 23.88; N, 4.91. IR ν_{max}^{Nujol} cm^{-1}: 3130 (=CH–), 1610 (C=N), 1060 (BF_4^-).

2-Methyl-5-phenyl-4-isoxazolin-3-thione (VIk)——a) NaSH (1.12 g) was added dropwise to a stirred aq. solution of Vk (2.3 g) under ice-cooling. The resulting mixture was stirred at room temperature for 1 hr and extracted with CH_2Cl_2 (50 ml). After removal of the solvent, the crude product was recrystallized from isopropylether to afford VIk (1.60 g, 84.2%) as white needles, mp 120—121°. NMR ($CDCl_3$) δ: 3.98 (3H, s, CH_3); 6.63 (1H, s, 4-H); 7.4—7.8 (5H, m, C_6H_5). IR ν_{max}^{Nujol} cm^{-1}: 3150 (=CH–).

b) A mixture of Vk (2.0 g) and thiourea (1.4 g) in acetone (40 ml) was heated under reflux for 4 hr. After cooling, the precipitated crystals were collected, washed with acetone (40 ml), and dried to give thiodiformamidine dihydrochloride (1.4 g, 84.8%), mp 174—176° (lit.[17] mp 182°). The filtrate and the washing were combined and the solvent was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography, eluting with *n*-hexane–acetone (10:1) to give VIk (1.26 g, 76.0%).

The other 4-isoxazolin-3-thiones (VI) were prepared according to method (a). The yields, physical constants and elemental analyses are listed in Table III.

3-Chloro-4,5-dimethylisoxazole (VIIj)——3-Chloro-2,4,5-trimethylisoxazolium chloride (Vj) (700 mg) was heated at 130° for 10 min in a flask equipped with a dry ice-acetone condenser. The resulting oil was distilled to give methyl chloride (35 mg, 19.6%) and VIIj (200 mg, 35.7%, bp 85°/30 mmHg: lit.[10] 93°/45 mmHg).

17) B.H. Chase and J. Walker, *J. Chem. Soc.*, **1955**, 4443.

The physical constants for the other 3-chloroisoxazoles prepared in the same way are listed in Table IV.

3-Chloro-4-isopropyl-5-phenylisoxazole (VIIn)——*Anal.* Calcd. for $C_{12}H_{12}ClNO$: C, 65.02; H, 5.46; Cl, 15.99; N, 6.32. Found: C, 65.08; H, 5.43; Cl, 16.15; N, 6.34. NMR ($CDCl_3$) δ: 1.33 (6H, d, J=7 Hz, 2×CH_3), 3.30 (1H, septet, J=7 Hz, CH), 7.3—7.5 (5H, m, C_6H_5). IR ν_{max}^{Nujol} cm^{-1}: 1620 (C=N).

Benzyl Cinnamate——A mixture of benzyl alcohol (108 mg), cinnamic acid (148 mg) and tri-*n*-butylamine (445 mg) in CH_2Cl_2 (2 ml) was added to a suspension of Vk (276 mg) in CH_2Cl_2 (2 ml) at −10° under an argon atmosphere, and the resulting mixture was stirred at 10° for 2 hr. After removal of the solvent under reduced pressure, the residue was separated by silica gel preparative TLC using benzene as a developing solvent to give benzyl cinnamate (192 mg, 80.7%), cinnamic anhydride (21 mg, 15.1%) and IVk (183 mg, 87.3%). These compounds gave spectral data in full accord with the assigned structures.

N-Benzyl-N-methyl(cyanomethylthio)acetamide——A mixture of (cyanomethylthio)acetic acid[18] (262 mg), N-methylbenzylamine (242 mg) and tri-*n*-butylamine (890 mg) in CH_2Cl_2 (6 ml) was added to a suspension of Vk (552 mg) in CH_2Cl_2 (7 ml) at −50°. After stirring for 2 hr at the same temperature under an argon atmosphere, ether (20 ml) was added to the reaction mixture, and the resulting mixture was washed with 5% aq. HCl solution (20 ml×3) and H_2O (20 ml×2). After removal of the solvent, the residue was subjected to silica gel preparative TLC, developing with *n*-hexane–acetone (1: 1), to afford IVk and N-benzyl-N-methyl(cyanomethylthio)acetamide (364 mg, 77.6%), n_D^{19} 1.5619. *Anal.* Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.95; S, 13.68. Found: C, 60.74; H, 6.08; N, 11.85; S, 13.29. IR $\nu_{max}^{Liq.}$ cm^{-1}: 2250 (CN), 1645 (CO).

The other equimolar reactions of carboxylic acids and alcohols or amines with Vk in the presence of a 2-fold molar excess of tri-*n*-butylamine were conducted as described above; the condensation products (Table V) gave IR and NMR spectral data in accord with the assigned structures.

Acknowledgement The authors are grateful to Miss K. Tachibana and Miss Y. Iwasaki for technical assistance.

18) (Cyanomethylthio)acetyl chloride is unstable, and should be used immediately or stored at very low temperature: H. Nakao, H. Yanagisawa, B. Shimizu, M. Kaneko, M. Nagano, and S. Sugawara, *J. Antibiot.* (Tokyo). Ser. A, **29**, 554 (1976).