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Studies on Isoxazoles. X.[1] Syntheses of Acylketene S,N-Acetals from 3-Phenylthio- and 3-Alkylthioisoxazolium Salts[2]

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The reaction of 2-methyl-5-phenyl-3-phenylthioisoxazolium chloride (IIa) with a mixture of optimum amounts of thiophenol (2 eq.) and triethylamine (TEA) (1 eq.) gave benzoylketene S,N-acetal (IIIa) in maximum yield. To determine the reaction mechanism, IIa was treated with tri-*n*-butylphosphine in the presence of acetic acid (AcOH) to afford N-acetyl-N-methylbenzoylacetamide (VIII). The isolation of VIII provides evidence for the involvement of an intermediate, benzoylketene N-methylimine (VII), in the transformation of IIa to IIIa. Various acylketene S,N-acetals (III) were synthesized by the reaction of 3-chloroisoxazolium chlorides (I) with mixtures of optimum amounts of thiols (3 eq.) and TEA (2 eq.).

On the other hand, the S,N-acetal (IIIj) was also prepared by the reduction of 3-ethylthio-2,5-dimethylisoxazolium iodide (XIII) with zinc in AcOH. Cyclization of IIIj with hydroxylamine or hydrazine afforded 3-methylaminoisoxazole (XIV) or 3-methylaminopyrazole (XV) in good yield.

Keywords——3-phenylthioisoxazolium salts; 3-alkylthioisoxazolium salts; acylketene S,N-acetals; thiol-catalyzed ring cleavage; radical-induced bond fission; benzoylketene N-methylimine; cyclization reaction

In the preceding paper,[1] the reaction of 3-chloroisoxazolium chlorides with thiophenol in the presence of sodium methoxide was reported to give 3-phenylthioisoxazolium chlorides. In place of sodium methoxide, however, treatment with triethylamine (TEA) led to cleavage of the isoxazole ring. In this paper, we describe the application of this reaction to the synthesis of acylketene S,N-acetals.

When 3-chloro-2-methyl-5-phenylisoxazolium chloride (Ia) was treated with a mixture of thiophenol and TEA in benzene, an unexpected product with cleavage of the N–O bond was obtained. The structure of this compound was determined on the basis of the physicochemical data. Microanalysis and the molecular peak (*m/e* 269) in the mass spectrum (MS) gave a molecular formula of $C_{16}H_{15}NOS$. Two fragment peaks in MS were assigned as phenylthio (*m/e* 109) and benzoyl (*m/e* 105) groups. The nuclear magnetic resonance (NMR) spectrum showed a broad peak (1H) at δ 11.7, a doublet (3H, J=5.0 Hz) at δ 3.14, a vinyl and aromatic proton peaks. On addition of deuterium oxide, the broad peak disappeared and the doublet changed to a singlet, indicating a methylamino group ($NHCH_3$). The very low chemical shift of NH suggests an intramolecular hydrogen bond.[4] The absorption of 1585 cm^{-1} in the infrared (IR) spectrum was assigned to a carbonyl group conjugated with strong electron releasing functions. Based on these results, this compound was assigned as 1-methylamino-3-phenyl-1-phenylthio-1-propen-3-one (IIIa), possessing a characteristic acylketene S,N-acetal moiety as shown in Chart 1.

Several benzoylketene S,N-acetals (III, R^1=phenyl) are known to be useful intermediates in syntheses of heterocycles such as isoxazoles and pyrazoles.[5] These acetals have been

1) Part IX: K. Tomita, S. Sugai, and M. Saito (neé Masuda), *Chem. Pharm. Bull.* (Tokyo), **27**, 2415 (1979).
2) A part of this work was presented at the 11th Congress of Heterocyclic Chemistry, Kanazawa. October 1978.
3) Location; *2–58, Hiromachi 1-chome, Shinagawa-ku, Tokyo, 140, Japan.*
4) G.O. Dudek and E.P. Dudek, *J. Am. Chem. Soc.*, **88**, 2407 (1966).
5) *a*) R. Gompper and R.R. Schmidt, *Chem. Ber.*, **98**, 1385 (1965); *b*) A. Dornow and K. Dehmer, *ibid.*, **100**, 2577 (1967).

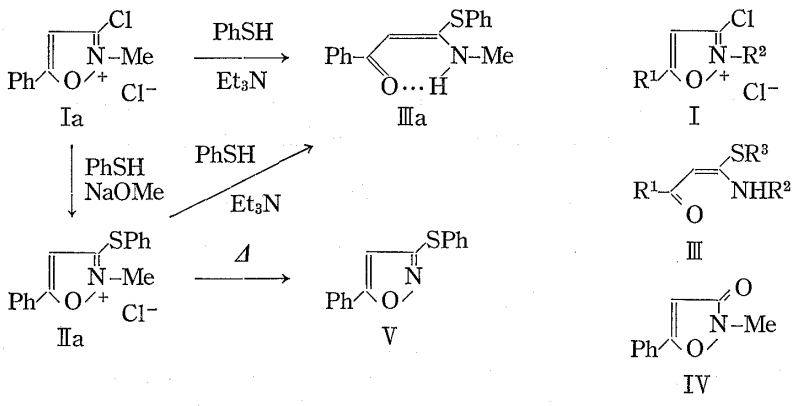


Chart 1

synthesized by the substitution reaction of the corresponding dithioacetals with amines.[6] For the development of the general reaction of I to III, it was important to elucidate the mechanism of the reaction of Ia to IIIa. The reaction of Ia with thiophenol in benzene containing TEA proceeded heterogeneously to give diphenyl disulfide and triethylamine hydrochloride (TEA·HCl) in addition to the main product, IIIa, and the hydrolyzed compound, 2-methyl-5-phenyl-4-isoxazolin-3-one (IV). On the other hand, only the substitution reaction occurred in the homogeneous system (sodium methoxide in methanol), affording 2-methyl-5-phenyl-3-phenylthioisoxazolium chloride (IIa)[1] (Chart 1). This suggests that in the former case a possible intermediate, IIa, is more susceptible to N–O bond cleavage by TEA, thiophenol or their complex than the starting material (Ia), yielding IIIa because of the greater solubility of IIa than of Ia in benzene.

Generally speaking, the N–O bond fission of isoxazolium salts is initiated by base-catalyzed abstraction of the proton at the 3-[7] or 5-position[8] on the ring or at the α-position with respect to the 2-substituent.[9] The reaction of IIa with TEA at room temperature did not occur, but at higher temperature a polymerized reaction mixture was obtained. Treatment of IIa with thiophenol at room temperature resulted in recovery of IIa, but treatment in boiling benzene gave 5-phenyl-3-phenylthioisoxazole (V)[1] (48%) and IIIa (17%) (Chart 1). On employing a mixture of these reagents, however, the ring opening reaction occurred at room temperature. With increase in the amount of thiophenol, the yield of IIIa improved and that of 3-isoxazolone (IV) decreased (Entries 1—5 in Table I). The maximum yield of IIIa was obtained by the use of the optimum ratio of thiophenol (2 eq.) and TEA (1 eq.) (Entry 4).

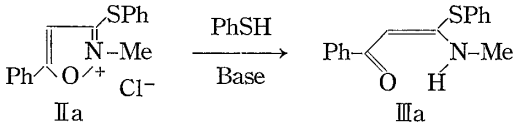
Reaction of IIa with thiophenol and a primary or a secondary amine also gave IIIa (Entries 6—8), but in the case of aniline, no reaction was observed (Entry 9). The basicity of aniline might be too weak to initiate the reaction. Amines were assumed to play an important role in the ionization of thiophenol at the first stage of the reaction. In fact, the reaction of IIa with a completely ionized species, sodium thiophenolate, in dimethylformamide gave an excellent yield of IIIa (Entry 10). On the basis of these results, the mechanism of the reaction of IIa to IIIa was proposed to be as given in Chart 2.

TEA could ionize thiophenol to produce thiophenolate, which would attack the sulfur atom at the 3-position to afford diphenyl disulfide, TEA·HCl and a kind of nitrogen ylid

6) *a*) Y. Kuwayama and S. Kataoka, *Yakugaku Zasshi*, **85**, 387 (1965); *b*) R. Gompper and W. Töpfl, *Chem. Ber.*, **95**, 2871 (1962).
7) *a*) R.B. Woodward and R.A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961); *b*) *Idem*, *Tetrahedron*, **22**, Suppl. No. 7, 415 (1966).
8) *a*) I. Adachi and H. Kanō, *Chem. Pharm. Bull.* (Tokyo), **17**, 2201 (1969); *b*) I. Adachi, *ibid.*, **17**, 2209 (1969); *c*) R.H. Good, G. Jones, and J.R. Phipps, *Tetrahedron Lett.*, **1972**, 609.
9) J.F. King and T. Durst, *Can. J. Chem.*, **40**, 882 (1962).

(VI). The ylid was assumed to be identical with the intermediate in the reaction initiated by proton abstraction from the 3-position.[7] The ylid would be isomerized to benzoylketene N-methylimine (VII), which might be attacked by another thiophenol molecule to give the acetal (IIIa) (Chart 2). There is a close analogy between this reaction and some ring cleavage

Table I. Reaction[a] of 2-Methyl-5-phenyl-3-phenylthioisoxazolium Chloride (IIa) with Thiophenol in the Presence of Base



IIa IIIa

Entry	PhSH mmol	Base (mmol)	Reaction time (hr)	Yield (%) of IIIa	Yield (%) of IV[c]
1	0.5	TEA[b] (1.1)	15	37.9	26.9
2	1.0	TEA[b] (1.1)	15	56.5	13.1
3	1.5	TEA[b] (1.1)	15	76.2	6.9
4	2.0	TEA[b] (1.1)	15	93.7	2.0
5	2.5	TEA[b] (1.1)	15	91.8	—
6	2.0	^{n}BuNH$_2$ (1.1)	1.5	61.0	—
7	2.0	^{n}Bu$_2$NH (1.1)	1.5	86.6	—
8	2.0	^{n}Bu$_3$N (1.1)	1.5	57.2	—
9	2.0	PhNH$_2$ (1.1)	48	0	0
10[d]	2.1	NaH (1.1)	15	88.5	—

a) All reactions were carried out in benzene at room temperature.
b) TEA=triethylamine.
c) IV=2-methyl-5-phenyl-4-isoxazolin-3-one.
d) DMF was used as a solvent.

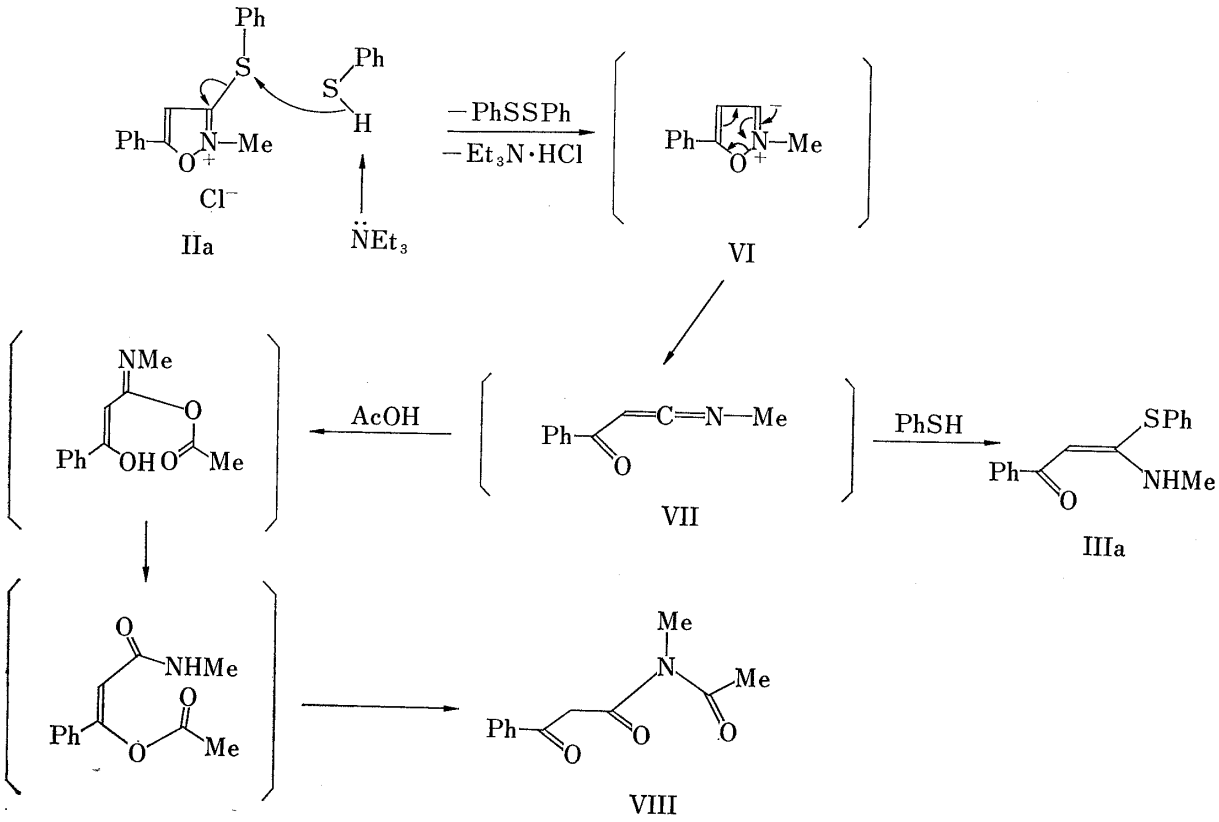
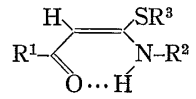


Chart 2

TABLE II. Acylketene S,N-Acetals (III)



III

III	R^1	R^2	R^3	Yield (%)	mp (°C) (n_D)	Formula	Analyses (%) Calcd. (Found) C : H : N : S	IR (Nujol) ν_{max} cm^{-1} C=O	NMR solvent[a]	δ_{ppm} N–C<u>H</u>$_3$	–C<u>H</u>=	N<u>H</u>
a	Ph	Me	Ph	98.9	127—129	$C_{16}H_{15}NOS$	71.34; 5.61; 5.20; 11.90 (71.01; 5.49; 5.20; 11.97)	1585	C	3.13	5.27	11.75
b	Ph	Me	4-MePh	92.5	83— 84	$C_{17}H_{17}NOS$	72.05; 6.05; 4.94; 11.31 (72.19; 6.03; 4.92; 11.38)	1590	T	3.11	5.28	11.90
c	Ph	Me	4-ClPh	90.6	107—108	$C_{16}H_{14}ClNOS$	63.26; 4.64; 4.61; 10.55 (63.19; 4.59; 4.68; 10.66)	1600	—	—	—	—
d	Ph	Me	CH_2Ph	88.7	105—106	$C_{17}H_{17}NOS$	72.05; 6.05; 4.94; 11.31 (71.81; 5.89; 4.88; 11.32)	1590	C	3.07	5.78	11.70
e	Ph	Me	Et	55.2	53— 54	$C_{12}H_{15}NOS$	65.12; 6.83; 6.33; 14.49 (65.47; 6.85; 6.20; 14.34)	1590	T	3.02	5.67	11.97
f	Me	Me	Ph	90.8	81.5— 83	$C_{11}H_{13}NOS$	63.74; 6.32; 6.76; 15.47 (63.88; 6.31; 6.96; 15.54)	1600	T	3.02	4.48	11.13
g	Me	Me	4-MePh	85.9	117—118	$C_{12}H_{15}NOS$	65.12; 6.83; 6.33; 14.49 (65.20; 6.84; 6.05; 14.67)	1585	C	3.06	4.55	11.33
h	Me	Me	4-ClPh	87.8	129—130	$C_{11}H_{12}ClNOS$	54.65; 5.00; 5.79; 13.26 (55.15; 5.00; 5.96; 13.41)	1585	T	3.04	4.50	11.13
i	Me	Me	CH_2Ph	84.5	76—78	$C_{12}H_{15}NOS$	65.12; 6.83; 6.33; 14.49 (65.44; 6.88; 6.70; 14.76)	1600	T	2.93	4.98	11.17
j	Me	Me	Et	65.4	48.5—50	$C_7H_{13}NOS$	52.80; 8.23; 8.80; 20.13 (52.53; 8.22; 8.80; 20.14)	1590	T	2.96	4.90	11.30
k	Me	Et	Ph	86.4	(n_D^{22} 1.5878)	$C_{12}H_{15}NOS$	65.12; 6.83; 6.33; 14.49 (64.98; 7.03; 6.46; 14.78)	1600[b]	T	3.40[c]	4.42	11.17

a) C($CDCl_3$); T(CCl_4).
b) As a liquid.
c) CH_3.

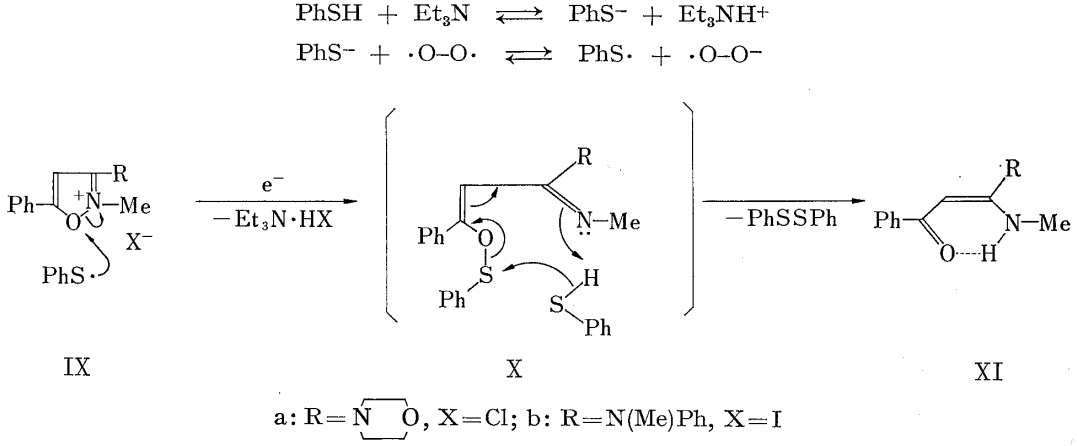
reactions of isoxazoles involving the formation of negative charge on the 3-position of the isoxazole ring.[10,11] From a mechanistic viewpoint, the reaction of 3-acetyl-5-methylisoxazoles with sodium ethoxide to yield acetoacetonitriles[11] is very similar. An analogous sulfur-sulfur interaction in the initial step (Chart 2) was also observed in the syntheses of disulfides from thiols and sulfenyl chlorides[12] or sulfenylamides.[13] In order to confirm the involvement of the intermediate ketenimine (VII), the salt (IIa) was treated with a thiophile,[14] tri-*n*-butylphosphine in the presence of acetic acid (AcOH). From the reaction mixture, IIIa, N-methylbenzoylacetamide and N-acetyl-N-methylbenzoylacetamide (VIII) were isolated. The reaction of VII with AcOH has been reported to give VIII[7] (Chart 2). Therefore, the isolation of VIII provides evidence for the involvement of the intermediate, VII.

From a stoichiometric point of view based on the above mechanism, the synthesis of acylketene S,N-acetals (III) from 3-chloroisxazolium chlorides (I) should require 3 mol of thiols and 2 mol of TEA. In fact, the reaction of Ia with thiophenol under such conditions gave IIIa in a yield of 99%. Various benzoylketene S,N-acetals (IIIb—e) (Table II) were synthesized by the reaction of Ia with various thiols in the presence of TEA.

There has been only one report[15] referring to aliphatic acylketene S,N-acetals (III, R^1 =alkyl). That is, 1-allylthio-1-anilino-1-buten-3-one was prepared by the reaction of *tert*-butyl acetoacetate with phenyl isothiocyanate in the presence of potassium *tert*-butoxide, followed by treatment with allyl bromide and then by acid-catalyzed development of the ester function.

The synthesis of aliphatic acylketene S,N-acetals (III, R^1=alkyl) should also be facile by the application of this ring opening reaction to 5-alkylisoxazolium salts (I, R^1=alkyl).[16] In fact, the reactions of 3-chloro-5-methylisoxazolium chlorides with various thiols afforded the corresponding acetylketene S,N-acetals (IIIf—k) in good yields (Table II).

The following isoxazolium salts, which have no sulfur atom at the 3-position, were also treated with a mixture of thiophenol and TEA. Nitrogen-substituted compounds at the 3-position, 3-morpholino- and 3-(N-methylanilino)isoxazolium salts (IXa, b), did not undergo the ring cleavage reaction in benzene, but in dichloromethane gave the corresponding N,N-ace-



a: R=morpholino, X=Cl; b: R=N(Me)Ph, X=I

Chart 3

10) *a*) L. Claisen, *Ber. Dtsch. Chem. Ges.*, **36**, 3672 (1903); *b*) W.S. Johnson. J.W. Petersen, and C.D. Gutsche, *J. Am. Chem. Soc.*, **69**, 2942 (1947).
11) *a*) A. Quilico, R. Fusco, and V. Roanati, *Gazz. Chim. Ital.*, **76**, 30 (1946); *b*) A. Quilico and M. Simonetta, *ibid.*, **77**, 586 (1947).
12) S. Kuwamura, T. Horii, and J. Tsurugi, *J. Org. Chem.*, **36**, 3677 (1971).
13) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, **1968**, 5907.
14) W. Kessler and B. Iselin, *Helv. Chim. Acta*, **49**, 1330 (1966).
15) F.C.V. Larsson and S.O. Lawesson, *Tetrahedron*, **30**, 1283 (1974).
16) K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, *Chem. Pharm. Bull.* (Tokyo), **27**, 2398 (1979).

tals (XIa, b) in poor yields. A carbon-substituted compound, 2,3,5-trimethylisoxazolium iodide,[17] however, was inert in these solvents.

The mechanism of the reaction of IX to XI was assumed to be as shown in Chart 3. The thiyl radical formed by air oxidation of thiophenol could attack the oxygen atom of the isoxazole ring of IX, resulting in N–O bond fission, and thiophenol might attack the sulfenate (X) to give XI. Alkylamines are known to catalyze the oxidation of thiols.[18] Therefore, the salt (IXa) was exposed to a radical species, zinc (Zn) in AcOH, which was reported to be ineffective against a neutral isoxazole nucleus,[19] to afford XIa in moderate yield.

Thus, we had discovered another synthetic method for S,N-acetals (III), which did not require thiol and TEA. This involved quaternization of 4-isoazolin-3-thiones[16] with alkyl halides, followed by bond fission with Zn in AcOH. For example, the S,N-acetal (IIIj) was prepared in 71% yield from 2,5-dimethyl-4-isoxazolin-3-thione (XII) *via* 3-ethylthio-2,5-dimethylisoxazolium iodide (XIII). Furthermore, the reaction of IIIj with hydroxylamine or hydrazine gave 3-methylaminoisoxazole (XIV) or 3-methylaminopyrazole (XV) in good yield (Chart 4).

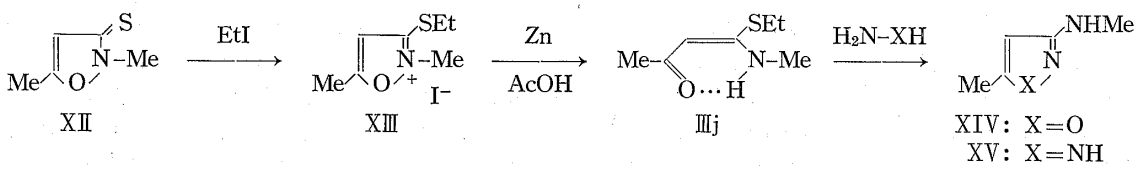


Chart 4

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi G_3 spectrometer, ultraviolet (UV) spectra on a Beckmann DB spectrophotometer and MS spectra on a JEOL JMS-01SG mass spectrometer. NMR spectra were taken on a Hitachi-Perkin Elmer R-24 at 60 MHz and on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b(broad). All solvents used were dry. The plates used for preparative TLC were Silica Gel $60F_{254}$ (E. Merck). Evaporations were carried out under reduced pressure with a rotatory evaporator.

1-Methylamino-3-phenyl-1-phenylthio-1-propen-3-one (IIIa)——a) A suspension of 3-chloro-2-methyl-5-phenylisoxazolium chloride (Ia)[16] (230 mg) in benzene (4 ml) was treated with a mixture of thiophenol (110 mg) and TEA (111 mg) in benzene (5 ml), and the mixture was stirred for 4.5 hr. After filtration, the solid was heated at 140° for 10 min to decompose the remaining Ia.[16] The resulting solid was washed with ether to give TEA·HCl (82 mg). The above filtrate was evaporated down to leave a residue, which was separated by preparative TLC. Development with *n*-hexane–acetone (3: 1) gave the following four products: diphenyl disulfide (68 mg); 3-chloro-5-phenylisoxazole[16] (2 mg); IIIa (57 mg, 21.2%), mp 127—129° (Table II); 2-methyl-5-phenyl-4-isoxazolin-3-one (IV) (3 mg), mp 115—116° (lit.[20] mp 114°).

b) A suspension of 2-methyl-5-phenyl-3-phenylthioisoxazolium chloride (IIa)[1] (1.0 g) and thiophenol (1.09 g) in benzene (15 ml) was heated under reflux for 3 hr. The solvent was removed, and the residue was chromatographed on silica gel. Elution with *n*-hexane gave diphenyl disulfide (0.89 g). Further elution with *n*-hexane–acetone (50: 1) afforded 5-phenyl-3-phenylthioisoxazole (V)[1] (0.41 g, 48.4%) and IIIa (0.15 g, 16.9%).

c) A suspension of IIa (1.0 mmol) in benzene (5 ml) was treated with a mixture of thiophenol (0.5—2.5 mmol) and TEA (1.1 mmol) in benzene (5 ml). The mixture was stirred for 15 hr, then filtered. The filtrate was evaporated down to leave an oil, which was separated by preparative TLC. The products and their yields are given in Table I (Entries 1—5).

17) W. Lampe and J. Smolińska, *Roczniki Chem.*, **28**, 163 (1954) [*C.A.*, **49**, 8922*b* (1955)].
18) A.A. Oswald and T.J. Wallace, "Anionic Oxidation of Thiols and Cooxidation of Thiols with Olefins," ed. by N. Kharasch C.Y. Meyers, "Organic Sulfur Compounds," Vol. II, Chap. 8, pp. 205—232 (1966).
19) *a*) N.K. Kochetkov and A. Ja. Kholin, *Zhur. Obschei, Khim.*, **28**, 1937 (1958); *b*) P. Grünanger and S. Mangiapan, *Gazz. Chim. Ital.*, **88**, 149 (1958).
20) S. Cabiddu, G. Gaudiano, and A. Quilico, *Gazz. Chim. Ital.*, **92**, 501 (1962).

d) A suspension of IIa (1.0 mmol) in benzene (5 ml) was treated with a mixture of thiophenol (2.0 mmol) and 1.1 mmol of *n*-butylamine, di-*n*-butylamine, tri-*n*-butylamine or aniline in benzene (5 ml). After stirring, the mixture was worked up as described in the case of (c). The crude product was purified by preparative TLC. The yisld of IIIa are listed in Table I (Entries 6—9).

e) A solution of thiophenol (231 mg) in DMF (3 ml) was treated with NaH (31 mg), followed by addition of IIa (304 mg). After stirring for 15 hr, the solution was poured into water (20 ml), and extracted with ether. The extract was concentrated, and the residue was separated by preparative TLC. Development with *n*-hexane–acetone (3: 1) gave diphenyl disulfide (242 mg) and IIIa (238 mg, 88.5%) (Entry 10).

Acylketene S,N-Acetals (III)——General Procedure: A mixture of thiols (3 eq.) and TEA (2 eq.) in benzene was added to a suspension of 3-chloroisoxazolium chlorides (I) (1 eq.) in benzene, and the mixture was stirred for 2—6 hr. After addition of water, the organic layer was separated. The solvent was evaporated off and the residue was purified by silica gel column chromatography to give III. The physical data for III are listed in Table II.

N-Acetyl-N-methylbenzoylacetamide (VIII)——A solution of IIa (152 mg) in CH_2Cl_2 (3 ml) and AcOH (300 mg) was treated with tri-*n*-butylphosphine (101 mg). After stirring for 16 hr, the mixture was poured into water, and extracted with ether. The solvent was removed, and the residue was separated by preparative TLC using *n*-hexane–acetone (2: 1) as a developing solvent to give N-methylbenzoylacetamide (8 mg, 9.0%) mp 104—106° (lit.[21] mp 101—102°), IIIa (7 mg, 5.2%) and VIII (9 mg, 8.2%), mp 98—100° (lit.[7b] 100—101°). The above aqueous layer was extracted with CH_2Cl_2. The extract was concentrated to leave a solid, which was washed with ether to give IIa (102 mg). N-Methylbenzoylacetamide: *Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.44; H, 6.24; N, 7.92. NMR ($CDCl_3$) δ: 2.83 (3H, d, J=5 Hz, C$\underline{H}_3$), 3.95 (2H, s, C$\underline{H}_2$), 7.1—8.2 (6H, m, N$\underline{H}$ and C$_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 3260, 3100 (NH), 1685, 1650 (CO). VIII: NMR ($CDCl_3$) δ: 2.30 (3H, s, COC$\underline{H}_3$), 3.31 (3H, s, N–C$\underline{H}_3$), 4.54 (2H, s, C$\underline{H}_2$), 7.3—8.2 (5H, m, C$_6\underline{H}_5$). MS *m/e*: 219 (M$^+$), 205 (M$^+$—CH_2), 177 (M$^+$—CH_2=C=O), 160, 147 (PhCOCH_2CO$^+$), 120 (PhCOCH_3), 105 (PhCO$^+$), 77 (Ph$^+$), 43 (CH_3CO^+). UV λ_{max}^{EtOH} nm: 312, 242 (lit.[7b] 314, 242). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1700, 1685 (CO). The IR spectrum of VIII was identical with that of an authentic sample.[7b]

2-Methyl-3-morpholino-5-phenylisoxazolium Chloride (IXa)——Morpholine (265 mg) and TEA (313 mg) were added to a suspension of Ia (690 mg) in benzene (5 ml), and the mixture was stirred for 4.5 hr. After filtration, the solid was dissolved in methanol (7 ml). Sodium methoxide (200 mg) was added to the solution, which was then stirred for 0.5 hr, and evaporated to dryness. After addition of CH_2Cl_2 (45 ml), insoluble solids were filtered off. The filtrate was condensed to the one-third of the original volume. Ether was added to the resulting solution to precipitate IXa (725 mg, 86.0%), mp 181—184°. *Anal.* Calcd. for $C_{14}H_{17}ClN_2O_2$+ $2H_2O$: C, 53.08; H, 6.68; Cl, 11.19; N, 8.84. Found: C, 52.89; H, 6.63; Cl, 11.18; N, 8.79. NMR ($CDCl_3$) δ: 3.98 (8H, almost s, 4×C$\underline{H}_2$), 4.30 (3H, s, C$\underline{H}_3$), 7.30—8.13 (5H, m, C$_6\underline{H}_5$), 8.60 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 3050 (–CH=), 1635 (C=N).

2-Methyl-3-(N-methylanilino)-5-phenylisoxazolium Iodide (IXb)——A solution of 2-methyl-5-phenyl-3-phenylimino-4-isoxazoline[22] (0.5 g) and methyl iodide (0.67 g) in acetone (5 ml) was stirred for 20 hr. The precipitated crystals were collected by filtration, and washed with ether to give IXb (0.69 g, 88.5%), mp 154—156°. *Anal.* Calcd. for $C_{17}H_{17}IN_2O$: C, 52.06; H, 4.37; I, 32.35; N, 7.14. Found: C, 52.27; H, 4.52; I, 32.09; N, 7.11. NMR ($CDCl_3$) δ: 3.55 [3H, s, N(C$\underline{H}_3$)Ph], 3.86 (3H, s, 2-C$\underline{H}_3$), 7.72 (1H, s, 4-H), 7.4—8.2 (10H, m, 2×C$_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 3050 (–C$\underline{H}$=), 1635 (C=N).

1-Methylamino-1-morpholino-3-phenyl-1-propen-3-one (XIa)——a) A mixture of thiophenol (231 mg) and TEA (111 mg) in CH_2Cl_2 (5 ml) was added to a solution of IXa (281 mg) in CH_2Cl_2 (5 ml). The mixture was stirred for 18 hr, and filtered. The filtrate was concentrated, and the residue was purified by preparative TLC, developing with *n*-hexane–acetone (3: 1), to yield XIa (31 mg, 12.6%), n_D^{21} 1.6266. *Anal.* Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.99; H, 7.33; N, 10.99. NMR ($CDCl_3$) δ: 2.90 (3H, d, J=3 Hz, C$\underline{H}_3$), 3.09 (4H, t, J=4.5 Hz, O$\langle$C$\underline{H}_2$ C$\underline{H}_2$), 3.72 (4H, t, J=4.5 Hz, N$\langle$C$\underline{H}_2$ C$\underline{H}_2$), 5.28 (1H, s, –C$\underline{H}$=), 7.3—8.0 (5H, m, C$_6\underline{H}_5$), 10.82 (1H, b, N$\underline{H}$). MS *m/e*: 246 (M$^+$), 160 (M$^+$— ), 105 (PhCO$^+$). IR $\nu_{max}^{Liq.}$ cm^{-1}: 1600 (CO).

b) A solution of IXa (83 mg) in CH_2Cl_2 (10 ml) was treated with Zn (23 mg), followed by addition of AcOH (44 mg). The resulting mixture was stirred for 18 hr, then poured into a mixture of water (10 ml) and ether (10 ml). The organic layer was separated, and concentrated to give XIa (39 mg, 53.4%).

1-Methylamino-1-(N-methylanilino)-3-phenyl-1-propen-3-one (XIb)——A mixture of thiophenol (177 mg) and TEA (85 mg) in CH_2Cl_2 (4 ml) was added to a solution of IXb (301 mg) in CH_2Cl_2 (4 ml), and the mixture was stirred for 18 hr. After concentration, the residue was extracted with isopropylether. The extract was evaporated down and the residual oil was purified by preparative TLC. Development with *n*-hexane-acetone (2: 1) gave XIb (7 mg, 4.2%), n_D^{25} 1.6150. NMR (CCl_4) δ: 2.58 (3H, d, J=5 Hz, NHC$\underline{H}_3$),

21) O. Mumm and G. Münchmeyer, *Chem. Ber.*, **43**, 3335 (1910).
22) The synthesis of this compound will be reported in a separate paper

3.30 [3H, s, N(C$\underline{H}_3$)Ph], 5.57 (1H, s, -C$\underline{H}$=), 6.9—8.0 (10H, m, 2×C$_6\underline{H}_5$), 11.30 (1H, b, N$\underline{H}$). MS *m/e*: 266 (M^+), 238 (M^+-CO), 160 [$M^+-N(CH_3)Ph$], 105 ($PhCO^+$), 77 (Ph^+). IR $\nu_{max}^{Liq.}$ cm^{-1}: 3050 (NH), 1610 (CO).

1-Ethylthio-1-methylamino-1-buten-3-one (IIIj)——A solution of 2,5-dimethyl-3-ethylthioisoxazolium iodide (570 mg) in CH_2Cl_2 (3 ml) was treated with Zn (143 mg), followed by AcOH (180 mg). The mixture was stirred for 1 hr, then poured into a mixture of ether (50 ml) and water (20 ml). The organic layer was separated, and concentrated. The residue was purified by preparative TLC using *n*-hexane–acetone (3: 1) as a developing solvent to afford IIIj (227 mg, 71.4%), mp 48.5—49°. NMR (CCl_4) δ: 1.37 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.90 (3H, s, $COC\underline{H}_3$), 2.84 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 2.96 (3H, d, J=7 Hz, $NHC\underline{H}_3$), 4.90 (1H, s, -C$\underline{H}$=), 11.28 (1H, b, N$\underline{H}$). IR ν_{max}^{Nujol} cm^{-1}: 3200—3000 (NH), 1590 (CO).

5-Methyl-3-methylaminoisoxazole (XIV)——An aqueous solution (3 ml) of free hydroxylamine prepared from hydroxylamine hydrochloride (0.65 g) and KOH (0.53 g) was added to a solution of IIIj (1.0 g) in methanol (10 ml). The mixture was stirred for 4 hr, then heated under reflux for 1 hr. After neutralization with 1 N HCl, the solution was extracted with CH_2Cl_2. The solvent was evaporated off to leave a residue, which was purified by preparative TLC. Development with benzene–ethanol (5: 1) gave XIV (0.7 g, 100%), mp 63—65°. (lit.[23] mp 57—59°). *Anal.* Calcd. for $C_5H_8N_2O$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.42; H, 7.12; N, 24.79. NMR (CCl_4) δ: 2.10 (3H, s, 5-C$\underline{H}_3$), 2.83 (3H, d, J=5 Hz, $NHC\underline{H}_3$), 4.70 (1H, s, 4-H), 5.32 (1H, b, N$\underline{H}$). IR ν_{max}^{Nujol} cm^{-1}: 3230 (NH), 3030 (-CH=), 1620 (C=N).

5-Methyl-3-methylaminopyrazole (XV)——A mixture of IIIj (0.8 g) and hydrazine hydrate (0.28 g) in ethanol (5 ml) was stirred for 12 hr. The solvent was removed, then the residue was purified by preparative TLC, developing with benzene–ethanol (5: 1), to give XV (0.37 g, 66.1%), n_D^{26} 1.5194. *Anal.* Calcd. for $C_5H_9N_3+2/5H_2O$: C, 50.74; H, 8.34; N, 35.50. Found: C, 50.98; H, 8.37; N, 35.01. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3200 (NH), 1590 (C=N).

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23) J.T. Plati and W. Wenner, Fr. Patent 1363643 (1964) [*C.A.*, **61**, P14678*h* (1964)].