Heterocyclic Ring-Closure Reactions. IV.[1] The Reaction of *S,S'*-Dialkyl Dithiooxaldiimidates with Thiocyanic Acid[2]

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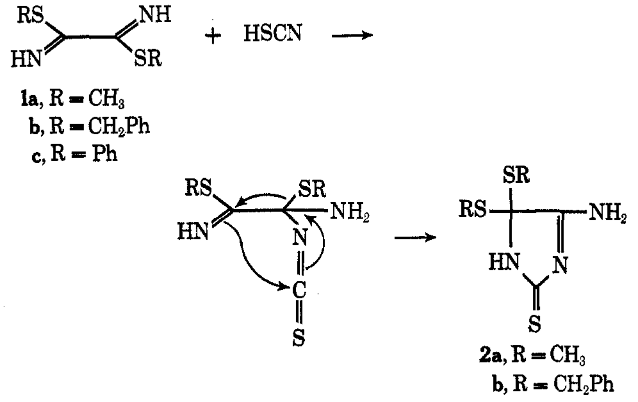
Reaction of *S,S'*-dimethyl dithiooxaldiimidate (1a) with thiocyanic acid gives the 1:1 addition product, 4-amino-2-thioimidazole-2,5-dione 5-(dimethyl mercaptole), as determined by an X-ray crystallographic study. An intramolecular reaction mechanism is proposed for migration of the *S*-methyl substituent. A similar product is obtained with *S,S'*-dibenzyl dithiooxaldiimidate. *S,S'*-Diphenyl dithiooxaldiimidate does not yield a similar product.

We have investigated the reaction of S,S'-disubstituted dithiooxaldiimidates (1) with thiocyanic acid[3] as part of our study of heterocyclic ring-closure reactions. There appeared to be a variety of reaction modes open to these reactants, leading to both five- and six-membered ring systems.

When *S,S'*-dimethyl dithiooxaldiimidate (**1a**) was treated with 1 mol of thiocyanic acid or ammonium thiocyanate, the only isolated product was shown by elemental analysis and mass spectrometry to be a 1:1 adduct, disclosed by an X-ray crystallographic study (see below) to be 4-amino-2-thioimidazole-2,5-dione 5-(dimethyl mercaptole) (**2a**). This product did not provide spectral data in complete agreement with any of the possible products resulting from simple addition reactions.[4] Interpretation of the apparently contradictory spectral data was hampered by lack of appropriate model compounds. The nmr spectrum in deuterated DMSO showed three proton peaks in the ratio of 1:2:6 at δ 11.5, 8.83, and 1.95, respectively, thereby indicating that the two SMe groups are equivalent. The signal integrating for one proton at δ 11.5 is assigned to an NH rather than an SH (δ 1.5–3.5) proton, thereby indicating that the thioamide form of **2a** exists in solution as well as in the crystal. The high resolution mass spectrum at *m/e* 47 showed the presence of both HNS and CH_3S ions, but studies at *m/e* 46 do not show the presence of SN^+ ion. There was no evidence for elimination of SH from the adduct. It appeared that a somewhat more involved reaction had occurred, so we turned to the X-ray crystallographic study to elucidate the structure of this substance. It was found to be 4-amino-2-thioimidazole-2,5-dione 5-(dimethyl mercaptole) (**2a**), obtained apparently by migration of an alkylmercapto group[5] (Scheme I).

SCHEME I



1a, R = CH_3
b, R = CH_2Ph
c, R = Ph

2a, R = CH_3
b, R = CH_2Ph

The ir spectra of **2a** shows a strong doublet at 1670 and 1640 cm^{-1} which can be attributed to C=S and C=N, and the marked enhancement in the uv spectrum from **1a** [λ_{max} 262 nm (ϵ 5200)] to **2a** [λ_{max} 292 nm (ϵ 33,100)] is in agreement with the extended chromophore which contains a C=S bond.

In order to investigate the possibility that the SR group might rearrange by an addition–elimination process, we carried out the reaction of the dimethyl diimidate **1a** in the presence of benzyl mercaptan and of the dibenzyl diimidate **1b** in the presence of methyl mercaptan. In neither case was a cross product obtained, indicating the rearrangement to be intramolecular as suggested in the mechanistic scheme. It is interesting to note that at no stage has the normally more nucleophilic sulfur atom of the thiocyanate acted as a nucleophile.[7]

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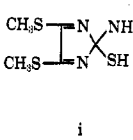
[1] Paper III: S. C. Mutha and R. Ketcham, *J. Org. Chem.*, **34**, 3661 (1969).

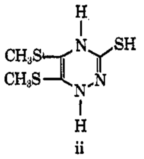
[2] Supported, in part, by Grant MH 08787, from the U. S. Public Health Service.

[3] G. M. Varshal and M. M. Senyavin, *Zh. Anal. Khim.*, **17**, 903 (1962).

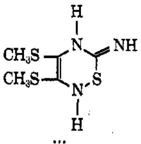
[4] Addition of the NH substituents of **1a** to the nitrile group of HSCN would give i, which could account for the equivalence of the SMe groups in the nmr. However, this structure should not be stable and does not agree with the mass spectrum (no loss of SH). The imidate might act as a heterodiene and the thiocyanate as a dienophile, in which case ii or iii or tautomers thereof would be obtained. However, among other objections, neither of these products have equivalent *S*-methyl substituents.



i



ii



iii

[5] In response to a suggestion that we were not dealing with **1a**,[6] but with an isomer, $N{\equiv}CC(SMe)_2NH_2$, we reinvestigated its ir spectrum and found no evidence for either a nitrile or an amino function. A compound isomeric with **1a** would not be expected to show any uv absorption. The fact that the diimidate shows a uv absorption, λ_{max} 262 nm (ϵ 5200), further supports structure **1a**.

[6] (a) H. M. Woodburn and C. E. Sroog, *J. Org. Chem.*, **17**, 371 (1952); (b) A. R. Martin and R. Ketcham, *ibid.*, **31**, 3612 (1966).

[7] In displacement reactions at saturated carbon the S atom is normally the nucleophile, whereas in displacement reactions in carboxylic acid derivatives the nitrogen atom is the nucleophile. See, *e.g.*, M. Bögemann, S. Petersen, O. E. Schultz, and H. Soll, "Methoden der Organischen Chemie (Houben–Weyl)," Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, p 773.

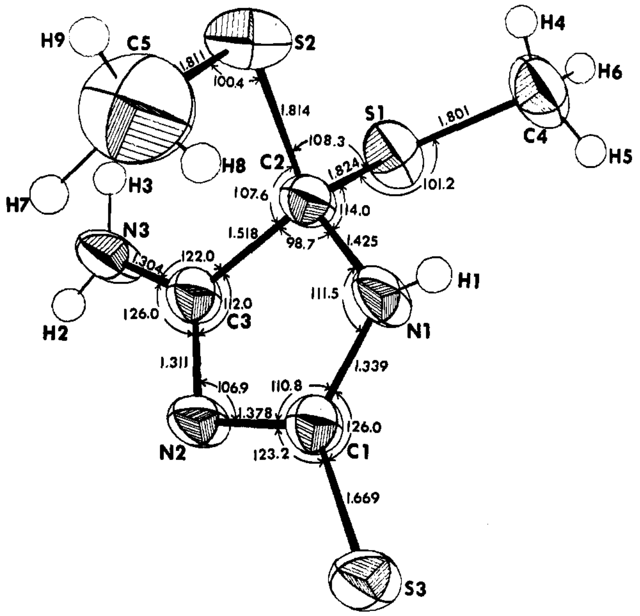


Figure 1.—The atom numbering system used in the crystallographic part of the paper and the bond distances and bond angles between nonhydrogen atoms are shown. The angles S-2–C-2–N-1 and C-3–C-2–S-1 could not be conveniently illustrated; they are 114.0 and 107.6°, respectively.

As further representative reactants we selected *S,S′*-dibenzyl (**1b**) and *S,S′*-diphenyl dithiooxaldiimidates (**1c**). The former provided an analogous product using either ammonium thiocyanate or the free acid. With thiocyanic acid, **1c** gave a deeply colored substance of apparently different structure which has so far resisted purification. With ammonium thiocyanate, **1c** gave only diphenyl disulfide,[8,9] even when the reaction was carried out under nitrogen.

X-Ray Crystallographic Study.—The crystal structure determination proves that the molecule under investigation has a five-membered ring composed of three carbon and two nitrogen atoms. The two $-SCH_3$ groups are definitely bonded to the same ring carbon atom. The second ring carbon atom has a sulfur atom side chain while the third ring carbon atom has a $-NH_2$ side chain.

An Ortep[10] drawing of the molecule is shown in Figure 1. This figure also gives the atom numbering system used[11] and the interatomic distances and angles for all atoms except hydrogen. The estimated standard deviations are 0.004 Å for the distances, 0.3° for the angles between heavy atoms, and 3° for angles involving the hydrogen atom.

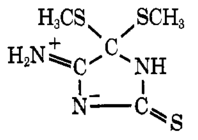
The stereoscopic view of the molecule, shown in Figure 2, illustrates the spatial arrangement of the atoms. In the crystal, each molecule forms four hydrogen bonds. Two of them, S-3–N-1, are to the same molecule and are related by a center of symmetry; the other two hydrogen bonds occur between the N-2 and N-3 atoms.[12] These bonds are related by a *c* glide plane and involve two other molecules. Each molecule is thus hydrogen bonded to three of its neighbors. The hydrogen bond distances and angles are listed in Table I. The primes differentiate the symmetry-related molecules which are hydrogen bonded to the unprimed molecule.

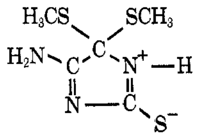
Table I

Hydrogen Bond Distances and Angles

	Heavy atom distance, Å	Angle, deg
N-1-H-1---S′-3	3.326	175
S-3---H′-1-N′-1	3.326	175
N-3-H-3---N″-2	2.860	161
N-2---H‴-3-N‴-3	2.860	161

The C-1–S-3 bond distance of 1.67 Å falls between the single bond value of 1.81 Å and the double bond value of 1.61 Å.[13,14] This is in agreement with recent results[15,16] obtained on molecules which also contain the group >NCSN<. The C-2–N-1 and C-2–C-3 bond lengths rule out delocalized aromatic bonds for the ring system. The bond lengths and angles given in Figure 1 clearly indicate that structures such as **3a** and **3b** are important contributors to the resonance hybrid.


3a


3b

Experimental Section

Melting points are corrected and were measured on a Thomas-Hoover melting point apparatus. Ir spectra were taken on a Beckman IR 8 or a Perkin Elmer 457 spectrophotometer. Uv spectra were taken in 95% or 50% EtOH using a Cary Model 11 spectrophotometer. Nmr spectra were taken on a Varian A-60A or JEOLCO 100-H using TMS as an internal standard. Mass spectra were measured with an AEI MS9 high resolution mass spectrometer. Apparent pK_a values were determined in 50% EtOH using a Metrohm Herisau Potentiograph E 336. Elemental analyses were carried out by the Microanalytical Laboratory of the University of California at Berkeley, Calif.

S,S′-Disubstituted dithiooxaldiimidates were prepared by previously described procedures.[6]

4-Amino-2-thioimidazole-2,5-dione 5-(Dimethyl mercaptole) (2a). A. Ammonium Thiocyanate.—To 5 g (0.034 mol) of *S,S′*-dimethyl dithiooxaldiimidate (1a) dissolved in 30 ml of acetone, by warming, was added 2.6 g (0.034 mol) of ammonium thiocyanate. A blue color developed which disappeared on shaking. After 2 hr white crystals of the adduct precipitated

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(8) "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1965, p 1279.

(9) The Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, Pa., Spectrum No. 7389.

(10) C. K. Johnson, Oak Ridge National Laboratory, Report No. 3794.

(11) The numbering in the X-ray crystallographic portion of the paper conforms to the practice of such studies in giving each type of atom in the molecule sequential numbers. They are not related to the numbers in the system of chemical nomenclature.

(12) Tables of the final positional and thermal parameters and calculated and observed *F* values and a figure showing the projection of the structure on the (100) plane, which illustrates the intermolecular hydrogen bonds, will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-2155. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(13) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960.

(14) B. Krebs and P. F. Koenig, *Acta Crystallogr.*, **25**, 1022 (1965).

(15) G. B. Ansell, D. M. Forkey, and D. W. Moore, *Chem. Commun.*, 56 (1970).

(16) N. W. Isaacs and C. H. L. Kennard, *ibid.*, 631 (1970).

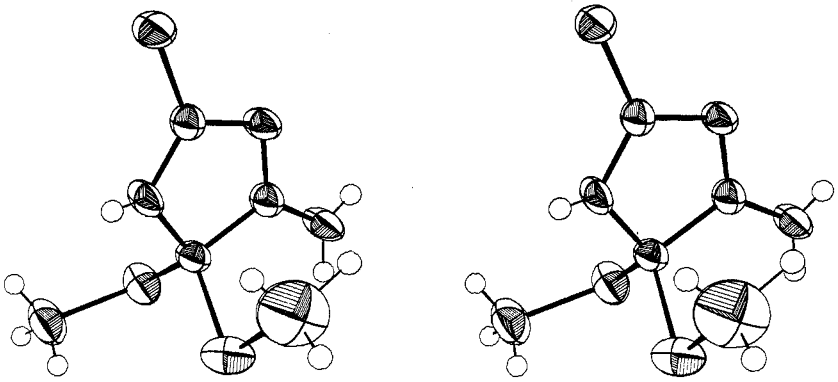

Figure 2.—A stereoscopic view of the molecule, with 50% probability ellipsoids.

and the maximum yield was obtained in about 3 hr. The product was collected and washed with acetone to give 2.5 g (36%) of white crystals, mp 136–145° dec. It was crystallized from ethanol, mp 165° dec.

The pK_a's of the compound were determined by titration in 50% aqueous alcohol, first with 1 *N* HCl and then with 1 *N* NaOH. The pK_a's were found to be 5.9 and 8.0. The uv measurements at different pH's showed two isosbestic points, thus confirming the pK_a studies: uv$_{max}$ 292 nm (ϵ 33,100); acidic λ_{max} 242 nm (ϵ 19,900), λ_{max} 296 (21,700); alkaline λ_{max} 290 nm (ϵ 20,900); nmr (CDCl$_3$) δ 1.67; nmr (DMSO-d_6) δ 11.5 (1 H), 8.83 (2 H), 1.95 (6 H).

Anal. Calcd for $C_5H_9N_3S_3$: C, 28.97; H, 4.37; N, 20.26; S, 46.40. Found: C, 28.97; H, 4.25; N, 20.09; S, 46.20.

To 200 mg (1.35 mmol) of *S,S'*-dimethyl dithiooxaldiimidate dissolved in 10 ml of acetone was added 100 mg of ammonium thiocyanate and 400 mg of benzyl mercaptan. After 2.5 hr white crystals, mp 138° dec, precipitated, which were crystallized from EtOH, mp 165° dec. Its ir spectrum was identical with that of the product obtained from ammonium thiocyanate and the dimethyl diimidate **1a** alone.

B. Thiocyanic Acid.—Thiocyanic acid was generated from ammonium thiocyanate using a cation exchange resin by the procedure of Varshal and Senyavin.[8] The resin was first washed with 5 *N* HCl, and then with water. Ammonium thiocyanate (15 g) was dissolved in 300 ml of acetone and passed through the resin on a column. The column was further eluted with 200 ml of acetone. A total of 500 ml of the thiocyanic acid solution in acetone (*ca.* 0.1 *M*) was collected and stored in a refrigerator.

Dimethyl diimidate (**1a**, 2.5 g, 0.017 mol) was dissolved in 170 ml of acetone containing 0.017 mol of thiocyanic acid in acetone and allowed to stand at room temperature. In 2 hr white crystals separated in 40% yield which were identical with those obtained with ammonium thiocyanate. No addition product was isolated with potassium thiocyanate.

4-Amino-2-thioimidazole-2,5-dione 5-(Dibenzyl mercaptole) (2b).—Dibenzyl dithiooxaldiimidate (**1b**, 4 g, 0.013 mol) and 1 g (0.013 mol) of ammonium thiocyanate in acetone were allowed to stand for 17 hr at 25° and then poured over ice. The product was collected and crystallized from ethanol to give 2 g (40%) of white crystals, mp 164–165°.

Anal. Calcd for $C_{17}H_{17}N_3S_3$: C, 56.08; H, 4.77; N, 11.68; S, 26.76. Found: C, 56.23; H, 4.77; N, 11.49; S, 26.92.

When the above reaction was repeated using a solution of thiocyanic acid in acetone and dibenzyl diimidate **1b**, an identical product was isolated in 40% yield.

To 400 mg (1.35 mmol) of dibenzyl diimidate **1b** in 20 ml of acetone were added 100 mg of ammonium thiocyanate and 200 mg (1.35 mmol) of methyl mercaptan. The reaction mixture was allowed to stand for 17 hr at 25° and poured over ice. The product was collected and crystallized from ethanol. White crystals, mp 164–165°, with an ir spectrum identical with that of **2b**, were obtained.

Reaction of *S,S'*-Diphenyl Dithiooxaldiimidate. A. With Ammonium Thiocyanate.—To 5.44 g (0.02 mol) of diphenyl diimidate **1c** in 30 ml of acetone was added 1.52 g (0.02 mol) of ammonium thiocyanate. The reaction mixture turned dark red in 1 hr at 25°. The mixture was poured over ice, and the precipitate was collected by filtration and recrystallized from hexane, mp 60–62°.[8] Its ir spectrum was identical with that of diphenyl disulfide.[9]

When the above reaction was carried out at 5 or 25° under N_2 only diphenyl disulfide was identified besides starting material, as evidenced from tlc, melting point, and ir spectra.

B. With Thiocyanic Acid.—Diphenyl diimidate **1c** (500 mg, 1.85 mmol) was added to 1.85 mmol of thiocyanic acid in 18.5 ml of acetone. The reaction mixture was kept at 15° for 1 hr and poured on ice. The brown precipitate was collected by filtration, mp 135° dec. It showed an ir spectrum different from that of the starting material. It was insoluble in petroleum ether, ether, and benzene and was soluble in acetone, chloroform, ethanol, and tetrahydrofuran. All attempts to purify this material, including column chromatography, have been unsuccessful.

X-Ray Determination of Structure.—Crystals suitable for X-ray diffraction analysis were crystallized from hot ethyl alcohol. The density of the crystals was measured by suspension in a mixture of xylene and ethylene bromide and found to be 1.429 g cm^{-3}. There are eight molecules in the unit cell, each occupying a general position. Weissenberg and precession photographs established the space group as *Pccn*. The lattice constants were obtained from high angle θ–2θ scans with the diffractometer set at a take-off angle of 1°. The crystal data are summarized in Table II.

TABLE II

CRYSTAL DATA

$C_5N_3S_3H_9$	Fw 207.34
Orthorhombic	Space group *Pccn*
$a = 11.150\ (5)$ Å	$Z = 8$
$b = 19.90\ (1)$ Å	$F(000) = 864$
$c = 8.734\ (4)$ Å	$\rho_m = 1.429$ g cm^{-3}
λCu Kα_1 = 1.54051 Å	$\rho_c = 1.425$ g cm^{-3}

Intensity data were obtained from a small crystal, about 0.1 mm on a side, mounted on a computer-controlled four-circle diffractometer equipped with a full-circle goniostat. The Ni-filtered Cu radiation was detected by a scintillation counter coupled with a single-channel pulse height analyzer. Data were recorded for angles up to $2\theta = 125°$ using the θ–2θ scanning technique. The scan rate was 1°/min (in 2θ). Background was measured 0.5° on each side of the scan limits. Each background was counted for 20 sec. A total of 3804 reflections were measured, of which 1540 were independent; 42 of these were measured as zero.

Two reflections designated as standards were measured every 48 reflections. The intensity of these two standard reflections decreased with irradiation time, and these data were used to correct the observed intensities in a step-wise fashion.

A full-matrix least-squares program[17] was used to minimize the function $\Sigma w(\Delta F)^2/\Sigma wF_o^2$; $\Delta F = |F_o| - |F_c|$, where F_o and F_c are the observed and calculated structure factors, and w is a weighting factor taken equal to $1/\sigma^2(F)$. The value of $\sigma(F)$ was calculated by the expression $\sigma(F) = F_o - [F_o^2 - \sigma(F_o^2)]^{1/2}$ when $I > \sigma(I)$; w was set equal to zero when $I \leq \sigma(I)$.

Normalized structure factors $|E|$ were calculated by Wilson's

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[17] The least-squares program was furnished by Dr. A. Zalkin, Lawrence Radiation Laboratory, Berkeley, Calif. 94720.

method by means of a computer program written by Maddox and Maddox.[18] These values were used to calculate phases by the symbolic addition procedure.[19] Origin determining signs were chosen for (058), (173), and (871) as all positive. Their E values are 3.38, 3.20, and 2.66, respectively. The 16 possible combinations of signs of four additional reflections were used to calculate probable phases for the remaining 110 reflections whose $|E|$ values were equal to or greater than 1.50. One combination of signs was clearly superior to the others. The four reflections chosen for iteration, their E values and correct phases are as follows (51 phases are plus and 66 are negative).

3	12	1	+2.72
3	2	1	−2.25
1	3	3	−2.46
1	6	1	−2.33

An E Fourier synthesis revealed the position of the heavy atoms. The positional parameters and an isotropic temperature factor for each of the 11 atoms were least-squares refined and resulted in an R index of 0.16, where R is defined as $\Sigma||F_o| - |F_c||/\Sigma|F_o|$. With anisotropic temperature factors, R was reduced to 0.060. A Fourier difference calculation revealed the approximate position of the nine hydrogen atoms. Three additional cycles of least-squares refinement, with anisotropic temperature factors for the heavy atoms, and isotropic temperature factors for the hydrogen atoms, gave a final R index of 0.046.[12]

Registry No.—**1c**, 34454-53-0; **2a**, 34454-54-1; **2b**, 34454-55-2; HSCN, 463-56-9.

Acknowledgment.—The authors wish to thank Miss Leila Wing for technical assistance and Dr. Alan Zalkin for use of his computer programs.

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[18] H. S. Maddox and M. L. Maddox, private communication, 1965.

[19] J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

1-Acyl-2,4,5-triphenyl-3-imidazolines[1]

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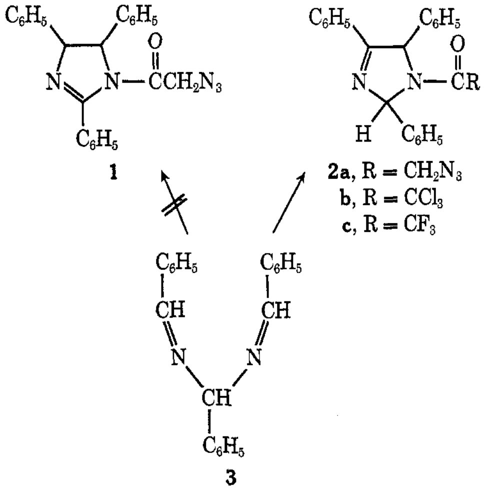
Condensation of hydrobenzamide with acid chlorides in the presence of triethylamine is shown to give 1-acyl-2,4,5-triphenyl-3-imidazolines. Synthesis of the isomeric 1-acyl-2-imidazolines and the hydrolysis of 1-acyl-2- and -3-imidazolines is also discussed.

A recent publication from these laboratories[2] reported the isolation of a compound postulated to be 1-azidoacetyl-2,4,5-triphenyl-2-imidazoline (**1**). We now wish to report further work which indicates that this compound is instead a mixture of *cis*- and *trans*-azidoacetyl-2,4,5-triphenyl-3-imidazoline (**2a**). We have also expanded the cyclization to other acid chlorides and trifluoroacetic anhydride.

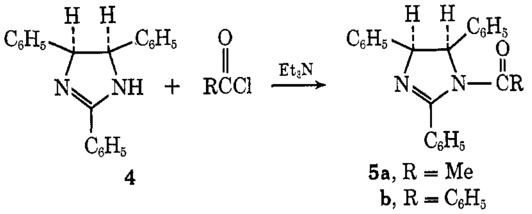
The imidazoline **2a** was produced by the reaction of hydrobenzamide (**3**) and azidoacetyl chloride in the presence of triethylamine. Although other imines have been treated with acid chlorides or ketenes to give cycloaddition products,[3-5] there seem to have been no reports of related electrophilic substitutions of hydrobenzamide in the literature. It was reported that the order of addition of the reactants played an important role in the course of this reaction. When **3** and triethylamine were combined and a solution of azidoacetyl chloride was added dropwise, 3-azido-4-phenyl-2-azetidinone was produced. If the order of addition was reversed, *i.e.*, if **3** and azidoacetyl chloride were combined and triethylamine was added, the imidazoline was obtained. Although **3** cyclizes on heating to 2-*cis*-4,5-triphenyl-2-imidazoline (**4**),[6] no reaction was observed with **3** and triethylamine in methylene chloride solution in the absence of acid chloride.


1

2a, R = CH_2N_3
b, R = CCl_3
c, R = CF_3

3

The two geometrical isomers of **1** have been prepared by an alternate method. 2-*cis*-4,5-Triphenyl-2-imidazoline (**4**) with acetyl chloride and trichloroacetyl chloride gave the corresponding 1-acyl-2-*cis*-4,5-triphenyl-2-imidazolines (**5**). Acylation with benzoyl chloride gave a compound whose physical data agreed with those of authentic 1-benzoyl-2-*cis*-4,5-triphenyl-2-imidazoline (**5b**).[7] Reaction with azidoacetyl chloride gave 1-azidoacetyl-2-*cis*-4,5-triphenyl-2-imidazoline (**5d**).


4

5a, R = Me
b, R = C_6H_5
c, R = CCl_3
d, R = CH_2N_3

Conversion of **4** to 2-*trans*-4,5-triphenyl-2-imidazoline (**6**) occurs on heating to 170° in the presence of metallic

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[1] Abstracted from the Ph.D. Thesis of O. Reed Tarwater, Purdue University, Aug 1970.

[2] J. N. Wells and R. E. Lee, *J. Org. Chem.*, **34**, 1477 (1969).

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[5] J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, Jr., *J. Org. Chem.*, **36**, 2211 (1971).

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[7] A. Claus and L. Scherbel, *Ber.*, **18**, 3077 (1885).