Supplementary Material Available: Full color, NMR, IR, UV, and mass spectral data for compounds **3** (Table I); NMR, IR, and mass spectral data for compounds **4** (Table II); IR, UV, and mass spectral data for compounds **14** (Table III) (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) M. Ohta and H. Kato, "Non Benzenoid Aromatics", J. P. Snyder, Ed., Academic Press, New York, N.Y., 1969.
(2) W. D. Ollis and C. A. Ramsden, "Advances in Heterocyclic Chemistry", A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N.Y., 1976.
(3) M. Begtrup and C. Roussel, "Thiazoles and Derivatives", A. Weissberger, Ed., Interscience, New York, N.Y., in press.
(4) J. Sandstrom, *Ark. Kemi*, **9**, 127 (1955).
(5) G. Isaksson and J. Sandstrom, *Acta Chem. Scand.*, **21**, 442 (1967).
(6) D. H. R. Barton, E. Buschmann, J. Hausler, C. W. Holzapfel, T. Sheradsky, and D. A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1107, (1977).
(7) M. Ohta, H. Chosho, C. Shin, and K. Ichimura, *Nippon Kagaku Zasshi*, **85**, 440 (1964); *Chem. Abstr.*, **61**, 14657 (1964).
(8) M. Ohta, and S. Sato, *Nippon Kagaku Zasshi*, **89**, 199 (1968); *Chem. Abstr.*, **69**, 4383 (1968).
(9) K. T. Potts, E. Hougton, and U. P. Shing, *J. Org. Chem.*, **39**, 3627 (1974).
(10) K. T. Potts, S. J. Chen, J. Kane, and J. L. Marshall, *J. Org. Chem.*, **42**, 1633 (1977).
(11) M. Baudy and A. Robert, *J. Chem. Soc., Chem. Commun.*, 23 (1976).
(12) K. T. Potts, R. Armbruster, E. Houghton, and J. Kane, *Org. Mass Spectrom.* **7**, 203 (1973).
(13) Supplementary material available.
(14) H. Sander, *Chem. Rev.*, **66**, 297 (1966).
(15) A. Le Marechal, *Thèse 3ème Cycle*, Rennes, 1977.
(16) J. J. Pommeret and A. Robert, *Tetrahedron*, **27**, 2977 (1971).
(17) H. Rivier and J. Zeltner, *Helv. Chem. Acta*, **20**, 691 (1937).
(18) R. Boudet, *Bull. Soc. Chim. Fr.*, 172 (1949).
(19) A. Ono and N. Kito, Japan Kokai, 72 25 144 (1972); *Chem. Abstr.*, **78**, 15849 (1973).
(20) N. Yamazaki, T. Tomioka, and F. Higashi, *Synthesis*, 384 (1975).
(21) C. Larsen and P. Jakobsen, *Acta Chem. Scand.*, **27**, 2001 (1973).
(22) M. H. Rivier, *Bull. Soc. Chim. Fr.*, **35**, 837 (1906).

Cycloaddition Reactions of Nitrile Sulfides with Acetylenic Esters. Synthesis of Isothiazolecarboxylates

Robert K. Howe,* Terry A. Gruner, Linda G. Carter, Linda L. Black, and John E. Franz

Research Department, Monsanto Agricultural Products Company, St. Louis, Missouri 63166

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Evidence is reported for production of nitrile sulfides as reactive intermediates in the thermolysis of 1,3,4-oxathiazol-2-ones. The nitrile sulfides were trapped with dimethyl acetylenedicarboxylate to give good yields of dimethyl 3-substituted-4,5-isothiazoledicarboxylates **6a–t.** The diacids **7a–r** were readily converted to 3-substituted-4-isothiazolecarboxylic acids **8a–r** by thermal decarboxylation. 3-Aryl-4-isothiazolecarboxylates **9a,j,u–w** and 3-aryl-5-isothiazolecarboxylates **10a,j, u–w** were obtained in nearly equivalent amounts from nitrile sulfides and ethyl propiolate. Thermolysis of 5-methyl- and 5-phenyl-1,3,4-oxathiazol-2-ones in excess ethyl 2-butynoate and of 5-methyl-1,3,4-oxathiazol-2-one in excess ethyl phenylpropiolate resulted in excessive byproduct formation and low yields of isothiazoles. Thermolysis of 5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxathiazol-2-one (**5u**) in the presence of excess ethyl phenylpropiolate gave a product mixture which contained ethyl 3-(α,α,α-trifluoro-*m*-tolyl)-5-phenyl-4-isothiazolecarboxylate (**18**) (47% yield by GC) and ethyl 3-(α,α,α-trifluoro-*m*-tolyl)-4-phenyl-5-isothiazolecarboxylate (**19**) (9.5% yield by GC).

Nitrile ylides (**1**), nitrile imines (**2**), and nitrile oxides (**3**) all have been utilized in 1,3-dipolar cycloaddition reactions to form heterocycles.[1] Until very recently,[2–6] nitrile sulfides (**4**) were conspicuously missing from this series of 1,3-dipoles.

$RC{\equiv}N^+{-}C^-R'R''$ (**1**) $\quad RC{\equiv}N^+{-}N^-R'$ (**2**)

$RC{\equiv}N{\rightarrow}O$ (**3**) $\quad RC{\equiv}N{\rightarrow}S$ (**4**)

We report here evidence for the production of nitrile sulfides as reactive intermediates in the thermolysis of 1,3,4-oxathiazol-2-ones and reaction of the nitrile sulfides with acetylenic esters to form isothiazolecarboxylates in preparatively significant reactions.[7]

A report[8] that thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one (**5a**) produced benzonitrile and sulfur suggested to us that benzonitrile sulfide **4a** was a possible intermediate in this reaction. Thermolysis of **5a** in the presence of dimethyl acetylenedicarboxylate (DMAD), in an experiment designed to trap the nitrile sulfide, resulted in isothiazoledicarboxylate **6a** (>90% yield); similarly, thermolysis of **5a** in the presence of ethyl propiolate gave isothiazolecarboxylates **9a** and **10a.**[2] These reactions now have been extended to a large variety of 5-substituted-1,3,4-oxathiazol-2-ones to produce the products outlined in Scheme I.

Formation of nearly equivalent amounts of **9** and **10** from ethyl propiolate and the various oxathiazolones is consistent only with a 1,3-dipolar cycloaddition reaction[9] (e.g., path A or path B, Scheme II). An alternative mechanism, path C, involving heterolysis of a bond of **5** to produce an ionic species **12,** followed by Michael addition of **12** to ethyl propiolate to give **13** and eventually **9,** is contrary to the observed formation of both **9** and **10.** Path C, as well as a similar homolytic mechanism, should produce **9** exclusively.[10]

A choice between path A and path B, which involves adduct (**11**) formation prior to loss of carbon dioxide, was made possible by the kinetic studies summarized in Table I. These studies, performed with varied concentrations of DMAD as the trapping agent, show that the rate of disappearance of **5a** is independent of the concentration of DMAD and is first order. Furthermore, the rate constants for formation of isothiazole and benzonitrile are both first order and equal to the rate constant for disappearance of **5a.** In the absence of DMAD, **5a** gave benzonitrile in 100% yield. These results rule out path B as a possible reaction mechanism and thus provide support for path A and benzonitrile sulfide as the reactive intermediate.

The order of rates of thermolysis of several 5-substituted-1,3,4-oxathiazol-2-ones is 5-CH_3 ≫ 5-$ClCH_2$ > 5-EtO_2C and 5-*o*-$CH_3C_6H_4$, 5-*m*-$CH_3C_6H_4$, 5-*p*-$CH_3C_6H_4$ > 5-C_6H_5 > 5-*m*-ClC_6H_4 > 5-*m*-$CF_3C_6H_4$ > 5-[3,5-$(CF_3)_2C_6H_3$], 5-*p*-NCC_6H_4, 5-*p*-$O_2NC_6H_4$, indicative of development of a partial positive charge at the 5 position in the transition state for

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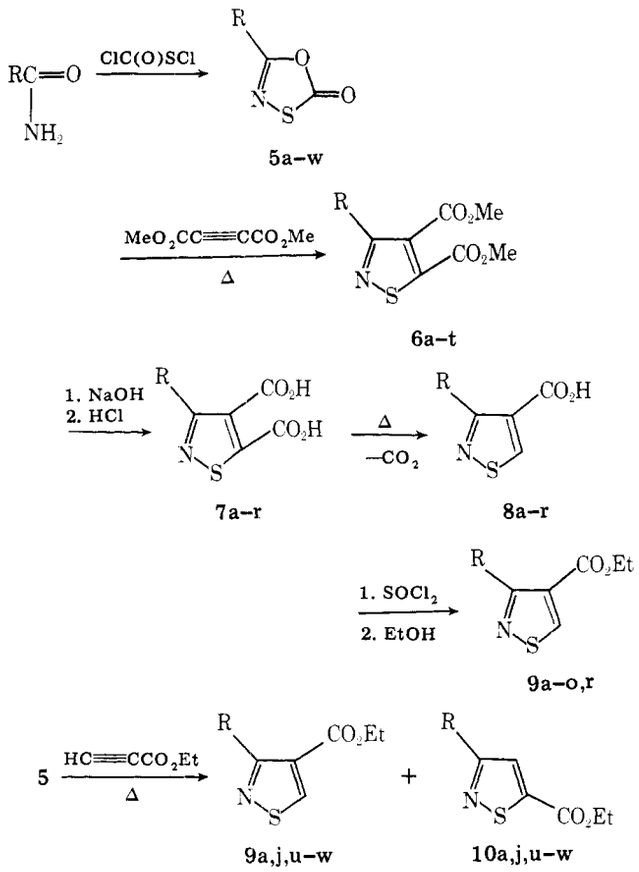
Scheme I



a, R = C_6H_5
b, R = 2-FC_6H_4
c, R = 2-$CH_3C_6H_4$
d, R = 2-$CF_3C_6H_4$
e, R = 2,6-$Cl_2C_6H_3$
f, R = 3-$CH_3C_6H_4$
g, R = 3-ClC_6H_4
h, R = 3-$O_2NC_6H_4$
i, R = 4-$CH_3C_6H_4$
j, R = 4-ClC_6H_4
k, R = 4-$O_2NC_6H_4$
l, R = 3,4-$(MeO)_2C_6H_3$
m, R = 3,4-$(CH_2O_2)C_6H_3$
n, R = 3,4-$Cl_2C_6H_3$
o, R = 3,5-$(CF_3)_2C_6H_3$
p, R = CH_3
q, R = t-C_4H_9
r, R = cyclohexyl
s, R = $ClCH_2$
t, R = EtO_2C
u, R = 3-$CF_3C_6H_4$
v, R = 4-NCC_6H_4
w, R = 3,5-$(CH_3O)_2C_6H_3$

decarboxylation. Also, 5-(2,6-dichlorophenyl)-1,3,4-oxathiazol-2-one thermolyzes slightly faster than 5-phenyl-1,3,4-oxathiazol-2-one, indicative of relief of steric strain in the decarboxylation and consistent with a transition state for the thermolysis that approaches the structure of the nitrile sulfide. The decarboxylation proceeds by a thermally allowed $_\sigma2_s + _\sigma2_s + _\pi2_s$ process.

Decarboxylation could also occur by a photochemically allowed $_\sigma2_s + _\sigma2_s + _\pi2_a$ process. Irradiation of **5a** and 1 equiv of DMAD in ethyl acetate solution at 253.7 nm produced benzonitrile and sulfur but no isothiazoledicarboxylate. Irradiation of the reactants at 300 or 360 nm (in the presence or absence of the triplet sensitizer benzophenone) did not result in an appreciable rate of decomposition of **5a**. Holm et al., however, reported that photolysis through Pyrex of **5a** in neat DMAD for 88 h gave isothiazole **6a** in 22% yield (based on the amount of starting material consumed).[11] In any event, photolysis of **5a** does not lead to preparatively significant yields of isothiazoles.

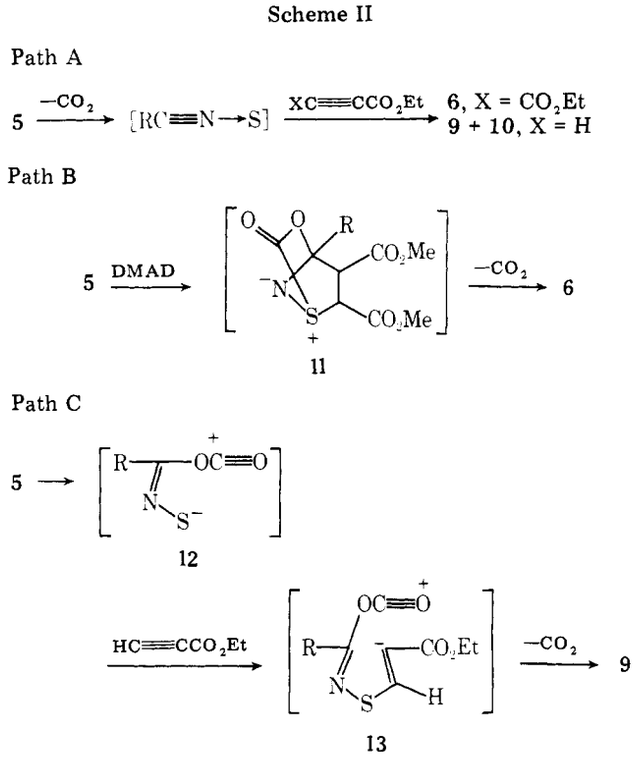
In addition to thermolysis and photolysis of 5-phenyl-1,3,4-oxathiazol-3-one, benzonitrile sulfide appears to have been generated by four other routes. Photolysis at 404–408 nm of 4-phenyl-1,3,2-oxathiazolium-5-olate (**14**) in a large excess of dimethyl acetylenedicarboxylate gave **6a** in 10% yield;[5]

Table I. First-Order Rate Constants[a] for Thermolysis of 0.103 M 5a in Chlorobenzene at 125.0 ± 0.1 °C

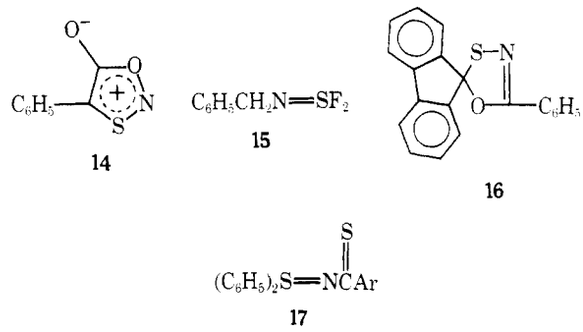
[DMAD], M[b]	k_5, 10^5 s^{-1}	k_{BN}, 10^5 s^{-1}	k_6, 10^5 s^{-1}
0	2.77 ± 0.1	2.48 ± 0.1[c]	
0.103	2.61 ± 0.12		2.63 ± 0.04[d]
0.515	2.84 ± 0.08		2.62 ± 0.09[e]

[a] Determined by gas chromatography, using least-squares method. k_5 = rate constant for disappearance of **5a**; k_{BN} = rate constant for appearance of benzonitrile; k_6 = rate constant for appearance of **6a**. [b] Initial concentration. [c] 100% yield of benzonitrile. [d] 90.5% yield of **6a**. [e] 94.7% yield of **6a**.

Scheme II



photolysis of **14** at 420 nm at 85 °K resulted in new UV absorption bands attributed to benzonitrile sulfide.[11] Thermolysis of (*N*-benzylimino)sulfur difluoride (**15**) in the presence of DMAD and sodium fluoride gave HF and **6a** in 65% yield.[6] Decomposition of **16** at room temperature gave



fluorenone, benzonitrile, and sulfur,[12] possibly via benzonitrile sulfide. Thermolysis of *N*-thiocarbonylsulfimides **17** at 50 °C in the presence of DMAD gave 3-arylisothiazoledicarboxylates in 27–34% yields, apparently via nitrile sulfide intermediates.[13]

Aliphatic nitrile sulfides also may be generated and trapped in synthetically useful reactions, as shown by thermolysis of 5-methyl- (**5p**), 5-*tert*-butyl- (**5q**), and 5-cyclohexyl-1,3,4-oxathiazol-2-one (**5r**) in 2 equiv of DMAD to give **6p**, **6q**, and

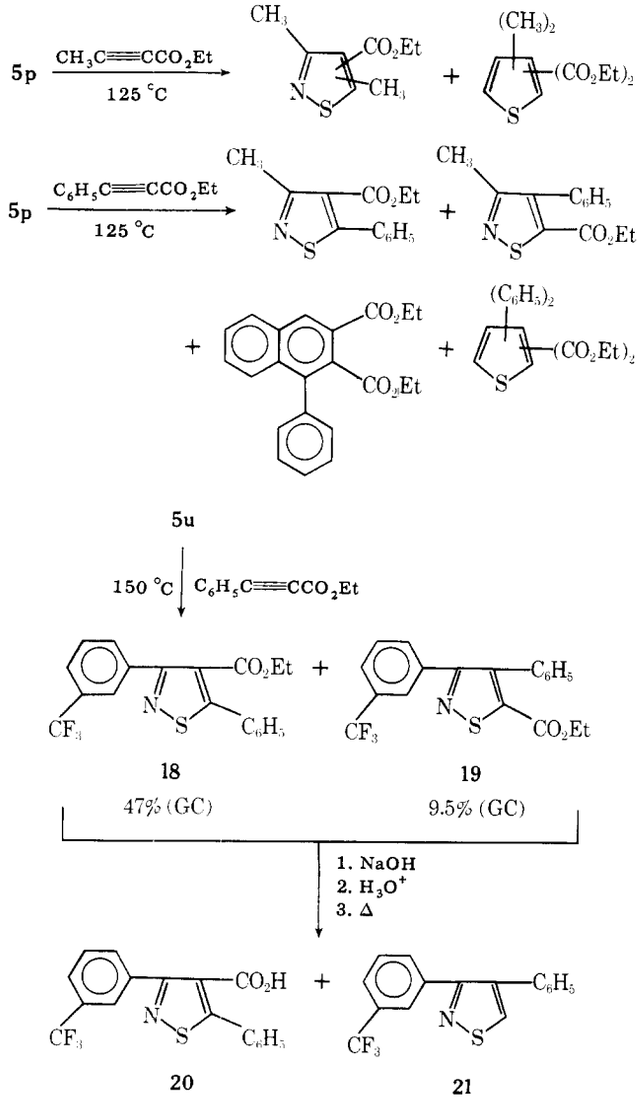
Table II. Thermolysis of Oxathiazolones in the Presence of 4 Equiv of Ethyl Propiolate in *o*-Dichlorobenzene at 150 °C

5	registry no.	9, % yield[a]	registry no.	10, % yield[a]	registry no.
a, R = C_6H_5	5852-49-3	40 (29)	67049-00-7	43 (31)[b]	27545-57-9
j, R = 4-ClC_6H_4	17452-79-8	44 (18)	67048-37-7	45 (26)	67048-96-8
u, R = 3-$CF_3C_6H_4$	57459-15-1	46 (34)	67048-99-1	39 (29)	67048-95-7
v, R = 4-NCC_6H_4	67048-87-7	44 (32)	67048-98-0	46 (10)	67048-94-6
w, R = 3,5-$(CH_3O)_2C_6H_3$	67048-85-5	35 (25)	67048-97-9	37 (32)	67048-93-5

[a] Yields determined by GC. Yields in parentheses are for pure isolated products. [b] Isolated as the acid.

6r in 58, 39, and 59% yields (GC analyses), respectively (Scheme I). Thermolysis of 5-aryloxathiazolones in 2 equiv of DMAD gave, with few exceptions, isothiazoledicarboxylates in >90% yields (GC analyses). The requisite oxathiazolones **5** are readily prepared from amides and chlorocarbonylsulfenyl chloride.[14] This route provides a particularly convenient synthesis of a wide range of 3-substituted-4,5-isothiazoledicarboxylates and thus the 3-substituted-4-isothiazolecarboxylates.

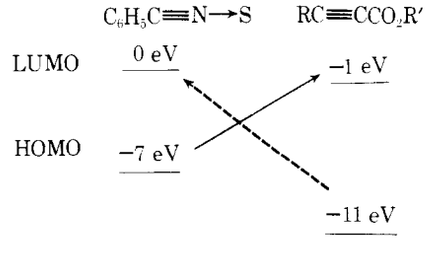
Thermolysis of the oxathiazolones in the presence of ethyl propiolate provides a quick route to samples of 3-substituted-5-isothiazolecarboxylates, as well as 3-substituted-4-isothiazolecarboxylates. Table II gives yield data for reactions in which 4 equiv of ethyl propiolate were employed. The isomers generally are readily separable by column chromatography. The 4-carboxylates are easily distinguished from the 5-carboxylates by NMR spectroscopy;[15] the 5-H of 3-aryl-4-isothiazolecarboxylates appears at δ 9.2–9.4, whereas the 4-H of 3-aryl-5-isothiazolecarboxylates appears at δ 8.0–8.2. Generally, the 5-carboxylates have longer retention times upon GC on SE-30 columns, elute faster on silica gel with benzene, have higher melting points, and are less soluble in ethanol than the corresponding 4-carboxylates.



Thermolysis of 5-methyl-1,3,4-oxathiazol-2-one at 125 °C in 10 equiv of ethyl 2-butynoate gave, based on GC–MS analyses, a complex mixture that contained a very small amount of a dimethylisothiazolecarboxylate (*m/e* 185) and larger amounts of thiophenedicarboxylates (*m/e* 256). The latter apparently arise from reaction of sulfur (from decomposition of the nitrile sulfide) with the acetylenic ester. Thermolysis of 5-methyl-1,3,4-oxathiazol-2-one at 125 °C in 10 equiv of ethyl phenylpropiolate gave a mixture of ethyl 3-methyl-5-phenyl-4-isothiazolecarboxylate and ethyl 3-methyl-4-phenyl-5-isothiazolecarboxylate, as well as ethyl phenylpropiolate dimer (*m/e* 348) and a mixture of diphenylthiophenedicarboxylates (*m/e* 380). The yield of isothiazoles appeared to be greater in the reaction with the phenylpropiolate than with the butynoate. Thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one in 10 equiv of ethyl 2-butynoate gave an exceedingly complex mixture in which the isothiazolecarboxylates were minor components (GC–MS analyses).

Thermolysis of 5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxathiazol-2-one in 10 equiv of ethyl phenylpropiolate gave reasonable yields of isothiazolecarboxylates **18** and **19** (47 and 9.5%, respectively, GC and MS analyses), but isolation of these materials in pure form was extremely difficult due to problems in separation from large amounts of side products that included ethyl phenylpropiolate dimer and diphenylthiophenedicarboxylates; separation of a mixture of **18** and **19** was also difficult. Pure **20** (14%) was isolated by hydrolysis of the mixture of **18** and **19**, followed by selective decarboxylation of the 5-carboxylic acid and separation of **20** from **21** by crystallization.

Frontier orbital theory has been employed extensively recently to explain a wide variety of 1,3-dipolar cycloaddition data.[16–18] Since sulfur is only slightly more electronegative than carbon, nitrile sulfides should have LUMO and HOMO energy levels just slightly lower than those of nitrile ylides. From the reported[16] LUMO, HOMO energy levels for phenylnitrile ylide (0.6, −6.4 eV) and 1,3-diphenylnitrile imine (−0.5, −7.5 eV), LUMO and HOMO values of ~0 and −7 eV are to be expected for benzonitrile sulfide. Acetylenic esters should have LUMO and HOMO levels at ~−1 and −11 eV, respectively.[16] Based on these estimates and experimental results with nitrile ylides,[16] nitrile sulfides should react readily



with the electron-deficient, conjugated acetylenic esters in dipole HOMO-controlled reactions, and the reaction rate should increase as the dipolarophile LUMO energy level is decreased. Qualitatively, the acetylenic ester LUMO levels should lie in the order ethyl 2-butynoate > ethyl propiolate > ethyl phenylpropiolate > dimethyl acetylenedicarboxylate. The observed order of reactivity of the acetylenic esters with nitrile sulfides, dimethyl acetylenedicarboxylate > ethyl propiolate > ethyl phenylpropiolate > ethyl 2-butynoate, is consistent with the LUMO energy level order with a superimposed rate-retarding steric effect in the case of ethyl phenylpropiolate.

The yields of isothiazoles from nitrile sulfides depend on the relative rates of decomposition and cycloaddition of the nitrile sulfides. Alkanecarbonitrile sulfides have higher HOMO levels than arenecarbonitrile sulfides and should react faster in cycloaddition reactions with acetylenes. The lower yields of isothiazoles from alkanecarbonitrile sulfides thus indicates that they decompose more rapidly than arenecarbonitrile sulfides. The regioselectivity found for cycloaddition of benzonitrile sulfide to ethyl propiolate is less than that observed[9] for the corresponding cycloaddition of benzonitrile oxide, due undoubtedly in part to the higher reaction temperature used for the nitrile sulfide reaction.

The substituent effects observed on yields of 1,2,4-thiadiazoles formed by cycloaddition of nitrile sulfides with nitriles[4] can similarly be explained on the basis of frontier orbital theory with reinforcement by coulombic effects. This reaction also should be dipole HOMO controlled,[16] so that lowering of the nitrile LUMO level by electronegative substituents should result in a faster rate of cycloaddition and higher yield of thiadiazole, as observed.[4] The yield of thiadiazole also depends on the competition between cycloaddition of the nitrile sulfide to nitrile and decomposition of the nitrile sulfide; electronegative substituents in the nitrile sulfide should lower the dipole LUMO and HOMO levels, slowing a dipole HOMO-controlled cycloaddition. Since electronegative substituents in the nitrile sulfide were observed to increase the yield,[4a] it appears that such substituents slow the nitrile sulfide decomposition to a greater extent.

Experimental Section

Melting points were taken in open capillaries in a Mel-Temp apparatus and are corrected. Boiling points are uncorrected.

Chlorocarbonylsulfenyl chloride was prepared according to a literature procedure[14] and was employed without purification. Amides, when not available commercially, were prepared by addition of acid halides to cold solutions of ammonia in THF.

General Procedure for 1,3,4-Oxathiazol-2-ones (5). The amide and 1.25–1.50 equiv of chlorocarbonylsulfenyl chloride in toluene were stirred at 100 °C until gas evolution had nearly ceased and/or until IR spectra revealed the absence of residual amide. Up to 5.0 equiv of chlorocarbonylsulfenyl chloride were employed for the less reactive amides, such as *p*-cyanobenzamide, 3,5-bis(trifluoromethyl)benzamide, and ethyl oxamate. The reaction mixture was concentrated under vacuum, and the residue was crystallized from an appropriate solvent.

1,2-Dichloroethane at reflux was employed as the solvent in the preparation of 5-methyl- and 5-*tert*-butyl-1,3,4-oxathiazol-2-one.

5a: mp 69–71 °C (EtOAc) (lit.[8] mp 68.5–70 °C); 83% yield.

5b: mp 52–53.5 °C (MeOH) (lit.[19] mp 47.5–50 °C); 47%.

5c: mp 30.5–32 °C (cold hexane) (lit.[19] mp ~15 °C); 59%. Anal. Calcd for $C_9H_7NO_2S$: C, 55.94; H, 3.65. Found: C, 56.06; H, 3.66.

5d: mp 49–51 °C (methylcyclohexane); 32%. Anal. Calcd for $C_9H_4F_3NO_2S$: C, 43.73; H, 1.63. Found: C, 43.90; H, 1.63.

5e: mp 81–82.5 °C (methylcyclohexane); 54%. Anal. Calcd for $C_8H_3Cl_2NO_2S$: C, 38.72; H, 1.22. Found: C, 38.60; H, 1.06.

5f: mp 82.5–84 °C (methylcyclohexane) (lit.[20] mp 80 °C); 46%.

5g: mp 83–84.5 °C (EtOAc) (lit.[8] mp 81.5–83 °C); 66%.

5h: mp 95–96.5 °C (THF) (lit.[8] mp 96.5–98.5 °C); 63%.

5i: mp 91–92 °C (methylcyclohexane) (lit.[14a] mp 89 °C); 66%.

5j: mp 129–131 °C (methylcyclohexane) (lit.[8] mp 127–130 °C); 48%.

5k: mp 168–169 °C dec (THF) (lit.[14a] mp 163–164 °C); 39%.

5l: mp 143–144.5 °C (EtOAc); 68%. Anal. Calcd for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79. Found: C, 49.97; H, 3.68.

5m: mp 123–124.5 °C (EtOAc); 81%. Anal. Calcd for $C_9H_5NO_4S$: C, 48.43; H, 2.26. Found: C, 48.29; H, 2.22.

5n: mp 130.5–131.5 °C (EtOAc) (lit.[8] mp 128–130 °C); 86%.

5o: mp 61–62.5 °C (methanol); 30%. Anal. Calcd for $C_{10}H_3F_6NO_2S$: C, 38.11; H, 0.96. Found: C, 38.22; H, 0.90).

5p: bp 75–76 °C (30 Torr) [lit.[14a] bp 60 °C (12 Torr)]; mp 16–17 °C; 56%.

5q: bp 35–36 °C (1.2 Torr); 33%. Anal. Calcd for $C_6H_9NO_2S$: C, 45.26; H, 5.70. Found: C, 44.99; H, 5.87.

5r was not obtained in pure form.

5s: bp 85–86 °C (4 Torr) [lit.[14a] bp 78 °C (4.5 Torr)]; 56%; NMR ($CDCl_3$) δ 4.47 (s, $ClCH_2$).

5t: mp 49–50.5 °C (methylcyclohexane); 64%. Anal. Calcd for $C_5H_5NO_4S$: C, 34.29; H, 2.88. Found: C, 34.28; H, 2.81.

5u: mp 85–86.5 °C (cold EtOAc); 86%. Anal. Calcd for $C_9H_4F_3NO_2S$: C, 43.73; H, 1.63. Found: C, 43.66; H, 1.58.

5v: mp 173 °C dec (EtOAc); 75%. Anal. Calcd for $C_9H_4N_2O_2S$: C, 52.93; H, 1.97. Found: C, 53.25; H, 2.02.

5w: mp 176–178 °C dec ($ClCH_2CH_2Cl$); 70%. Anal. Calcd for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79. Found: C, 50.14; H, 3.69.

General Procedure for Dimethyl 4,5-Isothiazoledicarboxylates (6). A solution of 0.10 mol of oxathiazolone and 0.20 mol of dimethyl acetylenedicarboxylate in 60 mL of chlorobenzene was stirred at reflux until CO_2 evolution had ceased and GC analyses revealed that no residual oxathiazolone remained (5–56 h). The solvent and excess dimethyl acetylenedicarboxylate were removed under vacuum. The residue was crystallized from cold methanol and then recrystallized from an appropriate solvent.

6a: mp 72–73 °C (cold MeOH); 73%; IR (mineral oil mull) 5.8 μm; NMR ($CDCl_3$) δ 7.65 (m, 5, ArH), 4.02 (s, 3, OCH_3), 3.99 (s, 3, OCH_3); mass spectrum *m/e* 277, 262, 246, 215, 187, 159, 135, 103, 77. Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56. Found: C, 56.47; H, 4.02; N, 4.93; S, 11.69.

6b: mp 73.5–75 °C (MeOH); 67%. Anal. Calcd for $C_{13}H_{10}FNO_4S$: C, 52.88; H, 3.41. Found: C, 53.08; H, 3.54.

6c: mp −33 to −31 °C (chromatographed on silicic acid with benzene–hexane); 66%. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50. Found: C, 57.44; H, 4.64.

6d: bp 160 °C (0.015 Torr) (molecular distillation); 96%. Anal. Calcd for $C_{14}H_{10}F_3NO_4S$: C, 48.70; H, 2.92. Found: C, 48.66; H, 3.24.

6e: mp 93–94.5 °C (chromatographed on silica gel and crystallized from methylcyclohexane); 30%. Anal. Calcd for $C_{13}H_9Cl_2NO_4S$: C, 45.70; H, 2.62. Found: 45.71; H, 2.81.

6f: mp 53–54.5 °C (ether–petroleum ether); 52%. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50. Found: C, 57.79; H, 4.20.

6g: mp 69–70 °C (ether–petroleum ether); 52%. Anal. Calcd for $C_{13}H_{10}ClNO_4S$: C, 50.09; H, 3.23. Found: C, 50.24; H, 3.42.

6h: mp 120.5–122 °C (cold MeOH); 54%. Anal. Calcd for $C_{13}H_{10}N_2O_6S$: C, 48.45; H, 3.13. Found: C, 48.51; H, 3.14.

6i: mp 92.5–93.5 °C (cold ether) (lit.[5] mp 90–91 °C); 74%. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50. Found: C, 57.78; H, 4.67.

6j: mp 108.5–109.5 °C (cold ether); 58%. Anal. Calcd for $C_{13}H_{10}ClNO_4S$: C, 50.09; H, 3.23. Found: C, 50.23; H, 3.12.

6k: mp 142–143 °C (EtOAc); 25%; the reactants were heated in *o*-dichlorobenzene at reflux for 15 h. Anal. Calcd for $C_{13}H_{10}N_2O_6S$: C, 48.45; H, 3.13. Found: C, 48.76; H, 3.18.

6l: mp 113.5–114.5 °C (MeOH, then EtOAc); 73%. Anal. Calcd for $C_{15}H_{15}NO_6S$: C, 53.41; H, 4.48. Found: C, 53.03; H, 4.46.

6m: mp 104–105 °C (MeOH); 51%. Anal. Calcd for $C_{14}H_{11}NO_6S$: C, 52.33; H, 3.45. Found: C, 52.09; H, 3.28.

6n: mp 105–107 °C (MeOH); 71%. Anal. Calcd for $C_{13}H_9Cl_2NO_4S$: C, 45.10; H, 2.62. Found: C, 45.12; H, 2.48.

6o: mp 73–75 °C (MeOH); 53%; the reactants were heated in *o*-dichlorobenzene at reflux for 10 h. Anal. Calcd for $C_{15}H_9F_6NO_4S$: C, 43.59; H, 2.19. Found: C, 43.77; H, 2.13.

6p: Distillation of the reaction mixture, which contained **6p** in 58% yield (GC assay), gave the desired product at bp 81–83 °C (0.3 Torr) in 50% yield. The oil crystallized upon standing and was recrystallized from petroleum ether to give solid of mp 34.5–35.5 °C. Anal. Calcd for $C_8H_9NO_4S$: C, 44.64; H, 4.21; N, 6.51; S, 14.90. Found: C, 44.73; H, 4.30; N, 6.62; S, 15.08.

6q: Distillation of the reaction mixture, which contained **6q** in 39% yield (GC assay), gave the desired product at bp 95 °C (0.15 Torr), in 24% yield. Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 47.15; H, 4.84. Found: C, 47.09; H, 4.82.

6r: Distillation of the reaction mixture gave **6r** contaminated with sulfur at bp 150–165 °C (0.7 Torr), in ~59% yield. Three crystalliza-

tions of the material from methanol and once from hexane gave pure product: mp 38.5–40.5 °C; 18%. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05. Found: C, 55.12; H, 6.02.

6s: The reactants were heated in chlorobenzene at 130–135 °C for 170 h, at which time there still was some residual oxathiazolone. Distillation of the reaction mixture gave 95.5% pure **6s**; bp 116 °C (0.1 Torr); 38% yield. Redistillation of this material gave 99% pure **6s**: bp 98 °C (0.08 Torr); 32% yield; IR (film) 5.78 μm; NMR ($CDCl_3$) δ 4.93 (s, 2, CH_2Cl), 4.00 (s, 6, OCH_3). Anal. Calcd for $C_8H_8ClNO_4S$: C, 38.49; H, 3.23. Found: C, 38.33; H, 3.23.

6t: A mixture of 8.76 g (0.050 mol) of ethyl 2-oxo-1,3,4-oxathiazole-5-carboxylate and 14.21 g (0.10 mol) of dimethyl acetylenedicarboxylate was heated at reflux for 43 min, at which time GC analysis revealed that most of the acetylenedicarboxylate was gone but much oxathiazolone was left. Another 14.2 g of dimethyl acetylenedicarboxylate was added, and the mixture was heated another 50 min at reflux. At this point, GC analysis revealed that most, but not all, of the oxathiazolone was gone, and that several oligomers of the acetylenedicarboxylate had formed in addition to the desired product. The viscous, black reaction mixture was extracted with 200 mL of 50:50 ether–hexane, and the supernatant was decanted from the black insoluble residue. The insoluble residue was dissolved in 100 mL of ethyl acetate, and 300 mL of ether and then 400 mL of hexane was added. The black, viscous gum that came out of solution contained only a trace of the desired product (GC assay). The two supernatants were combined and concentrated under vacuum to an oil. This oil was chromatographed on silica gel (Woelm material, for dry column chromatography); use of 60% ether in cyclohexane to elute the column gave 1.6 g (11.7%) of pure product as a viscous oil; IR (film) 5.83 μm; NMR ($CDCl_3$) δ 4.50 (q, 2, J = 7 Hz, OCH_2), 4.06 (s, 3, OCH_3), 4.01 (s, 3, OCH_3), 1.44 (t, 3, J = 7 Hz, CH_3). Anal. Calcd for $C_{10}H_{11}NO_6S$: C, 43.95; H, 4.06. Found: C, 43.86; H, 4.04.

General Procedure for 4,5-Isothiazoledicarboxylic Acids (7). A mixture of 0.10 mol of **6** and 0.50 mol of NaOH in 125 mL of water was held at reflux for 2 h (for very insoluble esters, a little dioxane was added to the reaction mixture). The resultant solution was acidified to pH <1 with a large excess of concentrated HCl and was extracted several times with ether. The ether layers were combined, dried ($CaSO_4$), and concentrated under vacuum. Generally, only a small sample of the crude diacid was purified for analysis. The remainder of the product was converted directly to the monoacid.

7a: mp 184–185 °C dec (CH_3CN); 90% yield. Anal. Calcd for $C_{11}H_7NO_4S$: C, 53.01; H, 2.83; N, 5.62. Found: C, 53.16; H, 2.80; N, 5.64.

7b: mp 144.5–145.5 °C dec ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_6FNO_4S$: C, 49.44; H, 2.26. Found: C, 49.35; H, 2.53.

7c and **7d** were not obtained in analytically pure form.

7e: mp 159–160 °C dec (ether–methylcyclohexone). Anal. Calcd for $C_{11}H_5Cl_2NO_4S$: C, 41.53; H, 1.58. Found: C, 41.55; H, 1.61.

7f: mp 166.5–167 °C dec ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{12}H_9NO_4S$: C, 54.75; H, 3.45. Found: C, 54.54; H, 3.63.

7g: mp 185–186 °C dec (rapid heating rate) ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_6ClNO_4S$: C, 46.57; H, 2.13. Found: C, 46.50; H, 2.17.

7h and **7i** were not obtained analytically pure.

7j: mp 177–177.5 °C dec ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_6ClNO_4S$: C, 46.57; H, 2.13. Found: C, 46.22; H, 2.26.

7k was not obtained analytically pure.

7l was obtained as a partial hydrate, mp 190.5–191.5 °C dec (rapid heating rate) (aqueous EtOH). Anal. Calcd for $C_{13}H_{11}NO_6S \cdot 0.7H_2O$: C, 48.50; H, 3.88. Found: C, 48.73; H, 4.10.

7m: mp 181.5–182.5 °C dec (rapid heating rate) (CH_3CN). Anal. Calcd for $C_{12}H_7NO_6S$: C, 49.15; H, 2.41. Found: C, 49.32; H, 2.50.

7n: mp 187.5–188.5 °C dec (rapid heating rate) (ether–$ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_5Cl_2NO_4S$: C, 41.53; H, 1.58. Found: C, 41.56; H, 1.60.

7o; mp 193–193.5 °C dec; 93% yield. Anal. Calcd for $C_{13}H_5F_6NO_4S$: C, 40.53; H, 1.31. Found: C, 40.31; H, 1.18.

7p: mp 163 °C dec (lit.[21] mp 160 °C dec); 90%.

7q: mp 173 °C dec (ether–hexane). Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.15; H, 4.84. Found: C, 47.09; H, 4.82.

7r: mp 146–147 °C dec ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.79; H, 5.13. Found: C, 51.67; H, 5.20.

General Procedure for 4-Isothiazolecarboxylic Acids (8). The 4,5-isothiazoledicarboxylates were heated in *o*-dichlorobenzene at reflux for 15 min to effect monodecarboxylation. The solution was allowed to cool, and the solid product was collected, washed with hexane, and recrystallized. With the more soluble acids, the chlorobenzene solvent was removed under vacuum, and the residue was crystallized.

8a: mp 167–168.5 °C (50% aqueous ethanol) (lit.[15] mp 165–166 °C); 73%.

8b: mp 163.5–165 °C ($ClCH_2CH_2Cl$); 87%, Anal. Calcd for $C_{10}H_6FNO_2S$: C, 53.81; H, 2.71. Found: C, 53.50; H, 2.73.

8c: mp 157–158.5 °C ($ClCH_2CH_2Cl$); 83%. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14. Found: C, 59.95; H, 4.10.

8d: mp 148–150 °C (benzene–heptane); 58%. Anal. Calcd for $C_{11}H_6F_3NO_2S$: C, 48.35; H, 2.21. Found: C, 48.34; H, 2.32.

8e: mp 183–185 °C (benzene) (lit.[22] mp 182–183 °C); 65%.

8f: mp 144.5–146 °C ($ClCH_2CH_2Cl$); 83%. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14. Found: C, 60.21; H, 4.04.

8g: mp 215–216 °C ($ClCH_2CH_2Cl$–CH_3CN); 87%. Anal. Calcd for $C_{10}H_6ClNO_2S$: C, 50.11; H, 2.52. Found: C, 50.32; H, 2.47.

8h: mp 234–235.5 °C (THF–CH_3CN); 48%. Anal. Calcd for $C_{10}H_6N_2O_4S$: C, 48.00; H, 2.42; N, 11.20. Found: C, 48.08; H, 2.38; N, 11.06.

8i: mp 179.5–181 °C ($ClCH_2CH_2Cl$); 82%. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14. Found: C, 60.49; H, 4.10.

8j: mp 177–179 °C (75% aqueous EtOH) (lit.[15] mp 172–174 °C); 89%.

8k: mp 264.5–265.5 °C dec (dioxane); 62%; did not give a satisfactory C,H analysis.

8l: mp 215.5–216 °C dec (EtOAc); 90%. Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18. Found: C, 54.32; H, 4.24.

8m: mp 232.5–233.5 °C dec (aqueous EtOH); 79%. Anal. Calcd for $C_{11}H_7NO_4S$: C, 53.01; H, 2.83. Found: C, 52.98; H, 2.82.

8n: mp 247–247.5 °C dec (ether–toluene). Anal. Calcd for $C_{10}H_5Cl_2NO_2S$: 43.82; H, 1.84. Found: C, 43.84; H, 1.87.

8o: mp 152–154 °C (heptane); 84%. Anal. Calcd for $C_{12}H_5F_6NO_2S$: C, 42.24; H, 1.48. Found: C, 42.13; H, 1.34.

8p: mp 235.5–237.5 °C; 99% (lit.[21] mp 236–238 °C).

8q: mp 128–130 °C; 90%. Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99. Found: C, 51.77; H, 6.04.

8r: mp 155–156 °C (heptane); 68%. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20. Found: C, 57.06; H, 6.15).

General Procedure for Ethyl 4-Isothiazolecarboxylates. Pure carboxylic acid was heated with excess thionyl chloride at reflux on a steam bath for 30 min. The resultant solution was concentrated under aspirator vacuum, and the residue was heated in excess ethanol at reflux for 30 min. The solution was concentrated under vacuum to give pure ester. In cases of solid esters, the solid was recrystallized.

9a: oil, 86%; IR (film) 5.8 μm; NMR ($CDCl_3$) δ 9.4 (s, 1, 5-H), 7.5 (m, 5, ArH), 4.3 (q, 2, OCH_2), 1.3 (t, 3, CH_3); mass spectrum *m/e* 233, 204, 188, 161, 133, 116, 104, 85, 77, 63, 57, 51. Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.64; H, 4.93; N, 6.20.

9b: mp 29.5–31 °C (EtOH at −78 °C); 93%. Anal. Calcd for $C_{12}H_{10}FNO_2S$: C, 57.36; H, 4.01. Found: C, 57.58; H, 4.00.

9c: $n^{25}D$ 1.5722; 93%. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 63.15; H, 5.23.

9d: mp 57.5–59 °C (hexane); 51%. Anal. Calcd for $C_{13}H_{10}F_3NO_2S$: C, 51.82; H, 3.35; N, 4.65. Found: C, 52.07; H, 3.33; N, 4.56.

9e: mp 87.5–89.5 °C (EtOH); 86%. Anal. Calcd for $C_{12}H_9Cl_2NO_2S$: C, 47.70; H, 3.00. Found: C, 47.74; H, 3.04.

9f: $n^{25}D$ 1.5823; 98%. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 63.27; H, 5.38.

9g: mp 66.5–68 °C (EtOH); 95%. Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76. Found: C, 53.86; H, 3.73.

9h: mp 136.5–138 °C (EtOH); 72%. Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07. Found: C, 51.85; H, 3.38; N, 10.07.

9i: $n^{25}D$ 1.5671; 90%. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 62.95; H, 5.52.

9j: mp 70.5–71.5 °C (aqueous EtOH); 66%. Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76. Found: C, 54.01; H, 3.90. **9j** was obtained also in a crystal form with mp 55.5–56.5 °C.

9k: mp 152–154 °C (EtOH); 63%. Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62. Found: C, 51.82; H, 3.63.

9l: mp 74–75.5 °C (EtOH–hexane); 98%. Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15. Found: C, 57.36; H, 5.14.

9m: mp 119.5–120.5 °C (EtOH–EtOAc); 94%. Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05. Found: C, 56.28; H, 3.91; N, 5.04.

9n: mp 111.5–112 °C (EtOH); 88%. Anal. Calcd for $C_{12}H_9Cl_2NO_2S$: C, 47.70; H, 3.00. Found: C, 47.61; H, 3.02.

9o: mp 61.5–63 °C (96%). Anal. Calcd for $C_{14}H_9F_6NO_2S$: C, 45.53; H, 2.46. Found: C, 45.31; H, 2.51.

9r: $n^{25}D$ 1.5263; 88%. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 59.98; H, 5.83.

Ethyl 3-Phenyl-5-isothiazolecarboxylate (10a). A solution of 8.96 g (0.050 mol) of 5-phenyl-1,3,4-oxathiazol-2-one and 19.62 g (0.20 mol) of ethyl propiolate in 75 g of *o*-dichlorobenzene was held at reflux (150 °C) for 3.5 h. GC analysis (2 ft 10% SE-30 column) of the reaction mixture revealed that all the oxathiazolone had reacted and that ethyl 3-phenyl-4-isothiazolecarboxylate (**9a**) and ethyl 3-phenyl-5-isothi-

azolecarboxylate (**10a**) had formed in 40 and 43% yields, respectively. The reaction mixture was concentrated under vacuum to 12.2 g of black oil. Dry column chromatography of the oil on 800 g of Woelm silica gel (for dry column chromatography) with benzene gave 4.7 g of 98% pure **10a**, mp 63–65 °C, and 6.0 g of crude **9a**. Two crystallizations of the **10a** from ethanol gave 3.4 g (29%) of pure **10a**: mp 66–67 °C; IR (mineral oil mull) 5.82 μm; NMR ($CDCl_3$) δ 8.07 (s, 1, 4-H), 7.9 (m, 2, ArH), 7.4 (m, 3, ArH), 4.43 (q, 2, OCH_2), 1.37 (t, 3, CH_3). Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.97; H, 4.71; N, 6.06.

Hydrolysis of a sample of the 5-carboxylic ester gave 3-phenyl-5-isothiazolecarboxylic acid, mp 184–185 °C (lit[23] 184–186 °C).

The 6.0 g of crude **9a** was hydrolyzed with 3.6 g (0.090 mol) of NaOH in aqueous ethanol at reflux for 1 h. The solution was cooled in ice and acidified with concentrated HCl to give 4.01 g of tan solid, mp 150–165 °C. The solid was crystallized from aqueous EtOH to give 3.45 g of tan solid, mp 162–167 °C. This material was heated in 40 mL of *o*-dichlorobenzene at reflux for 8 min. The solution was cooled, and the resultant solid was collected and washed with *o*-dichlorobenzene and then hexane to give 3.13 g (31%) of solid, mp 167–168.5°; the IR spectra of this material and of authentic 3-phenyl-4-isothiazolecarboxylic acid were identical.

Ethyl 3-(*p*-Chlorophenyl)-5-isothiazolecarboxylate (10j). A solution of 10.68 g (0.050 mol) of 5-(*p*-chlorophenyl)-1,3,4-oxathiazol-2-one and 19.62 g (0.20 mol) of ethyl propiolate in 75 g of *o*-dichlorobenzene was held at reflux (150 °C) under N_2 for 10 h and was concentrated under vacuum at 90 °C (0.2 Torr) to give 16.0 g of black oil. Dry column chromatography of the oil on silica gel with benzene and crystallizations of the fractions rich in 5-carboxylate gave 3.50 g (26% yield) of pure ethyl 3-(*p*-chlorophenyl)-5-isothiazolecarboxylate: mp 87.5–89 °C (from ethanol); NMR ($CDCl_3$) δ 8.13 (s, 1, 4-H), 7.7 (m, 4, ClC_6H_4), 4.47 (q, 2, OCH_2), 1.43 (t, 3, CH_3). Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76. Found: C, 53.84; H, 3.64.

Crystallization of the fractions rich in 4-carboxylate from aqueous ethanol gave 2.45 g (18% yield) of pure ethyl 3-(*p*-chlorophenyl)-4-isothiazolecarboxylate, mp 70.5–71.5 °C.

Ethyl 3-(α,α,α-Trifluoro-*m*-tolyl)-4-isothiazolecarboxylate (9u) and Ethyl 3-(α,α,α-Trifluoro-*m*-tolyl)-5-isothiazolecarboxylate (10u). A solution of 12.36 g (0.050 mol) of 5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxathiazol-2-one and 19.62 g (0.20 mol) of ethyl propiolate in 75.0 g of *o*-dichlorobenzene was held at reflux under N_2 for 20 h, at which time analysis by GC revealed that the reaction was complete and that the 4-carboxylate and the 5-carboyxlate had formed in 46 and 39% yields, respectively. Concentration of the solution under vacuum gave 16.4 g of dark oil. Crystallization of the oil from 35 mL of ethanol at −20 °C gave 5.05 g (34%) of tan solid, mp 77–79 °C, that was ~98% pure 5-carboxylate (GC assay). Concentration of the filtrate gave 10.8 g of oil. Chromatography of the oil on 550 g of silicic acid with benzene gave 5.2 g (35%) of 4-carboxylate that was 97% pure (3% low boilers, no 5-carboxylate present; GC analysis): IR ($CHCl_3$) 5.83 μm; NMR ($CDCl_3$) δ 9.43 (s, 1, 5-H), 8.03–7.43 (m, 4, ArH), 4.30 (q, 2, OCH_2), 1.23 (t, 3, CH_3). Anal. Calcd for $C_{13}H_{10}F_3NO_2S$: C, 51.82; H, 3.35. Found: C, 52.09; H, 3.50.

The chromatography also gave 0.31 g (2%) of pure 5-carboxylate, mp 80–81.5 °C. Recrystallization of the 5.05 g of 5-carboxylate from ethanol gave 4.05 g (27%) of colorless crystals: mp 80–81.5 °C; IR ($CHCl_3$) 5.81 μm; NMR ($CDCl_3$) δ 8.20 (s, 1, 4-H), 8.30–7.47 (m, 4, ArH), 4.47 (q, 2, OCH_2), 1.43 (t, 3, CH_3). Anal. Calcd for $C_{13}H_{10}F_3NO_2S$: C, 51.82; H, 3.35. Found: C, 51.98; H, 3.39.

Ethyl 3-(*p*-Cyanophenyl)-4-isothiazolecarboxylate (9v) and Ethyl 3-(*p*-Cyanophenyl)-5-isothiazolecarboxylate (10v). A solution of 10.2 g (0.050 mol) of 5-(*p*-cyanophenyl)-1,3,4-oxathiazol-2-one and 19.62 g (0.20 mol) of ethyl propiolate in 75.0 g of *o*-dichlorobenzene was held at reflux under N_2 for 20 h, at which time GC analysis indicated that the 4-carboxylate and the 5-carboxylate had formed in 44 and 46% yields, respectively. Concentration of the reaction mixture under vacuum gave 20.3 g of brown solid. Crystallization of this material from ethanol gave 5.54 g (43%) of 5-carboxylate as a beige solid, mp 175–179 °C. Crystallization of the solid from ethanol gave 0.1 g of unidentified, fairly insoluble white solid: mp 236–237 °C; IR ($CHCl_3$) 4.50, 5.81 μm. The residue from the filtrate was chromatographed on silica gel with benzene, and the purest fractions were crystallized from ethanol to give 1.27 g (10%) of 5-carboxylate as a white solid: mp 183–184.5 °C; IR ($CHCl_3$) 4.50, 5.81 μm; NMR ($CDCl_3$) δ 8.17 (s, 1, 4-H), 7.93 (AA′BB′ m, 4, ArH), 4.43 (q, 2, J = 7 Hz, OCH_2CH_3), 1.40 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90. Found: C, 60.49; H, 3.98.

The filtrate from the crystallization of the 20.3 g of brown solid was concentrated under vacuum, and the residue was chromatographed on silica gel with benzene. The 4-carboxylate thus obtained was crystallized from heptane to give 4.06 g (32%) of white solid: mp 109–110 °C; IR ($CHCl_3$) 4.50, 5.81 μm; NMR ($CDCl_3$) δ 9.40 (s, 1, 5-H), 7.73 (s, 4, ArH), 4.30 (q, 2, J = 7 Hz, OCH_2CH_3), 1.27 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90. Found: C, 60.48; H, 3.96.

Ethyl 3-(3,5-Dimethoxyphenyl)-4-isothiazolecarboxylate (9w) and Ethyl 3-(3,5-Dimethoxyphenyl)-5-isothiazolecarboxylate (10w). By a procedure similar to that employed for **9j** and **10j**, ethyl 3-(3,5-dimethoxyphenyl)-4-isothiazolecarboxylate was obtained in 25% yield as a white solid: mp 71.5–73 °C (from ethanol); NMR ($CDCl_3$) δ 9.23 (s, 1, 5-H), 6.72 (d, 2, J = 2 Hz, ArH), 6.48 (t, 1, J = 2 Hz, ArH), 4.23 (q, 2, J = 7 Hz, OCH_2CH_3), 3.78 (s, 6, OCH_3), 1.23 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15. Found: C, 57.40; H, 5.21.

Ethyl 3-(3-dimethoxyphenyl)-5-isothiazolecarboxylate was obtained in 32% yield as a white solid: mp 101–103 °C (from ethanol); NMR ($CDCl_3$) δ 7.98 (s, 1, 4-H), 7.03 (d, 2, J = 2 Hz, ArH), 6.47 (t, 1, J = 2 Hz, ArH), 4.37 (q, 2, J = 7 Hz, OCH_2CH_3), 3.82 (s, 6, OCH_3), 1.40 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15. Found: C, 57.50; H, 5.17.

5-Phenyl-2-(α,α,α-trifluoro-*m*-tolyl)-4-isothiazolecarboxylic Acid 20. A solution of 5.44 g (0.022 mol) of 5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxathiazol-2-one, 38.15 g (0.22 mol) of ethyl phenylpropiolate, and 38.15 g of *o*-dichlorobenzene was held at 150 °C under N_2 for 20 h, at which time GC analysis revealed the isothiazole-4-carboxylate and isothiazole-5-carboxylate had formed in 47 and 9.5% yields, respectively. The reaction mixture was concentrated under vacuum (0.15 Torr and 180 °C bath temperature) to 12.7 g of residue (products and high-boiling side products). The residue was chromatographed on 1154 g of silica gel (Woelm, for dry column chromatography) with benzene to give 2.72 g of 91% pure 4- and 5-isothiazolecarboxylate mixture. A 2.5-g sample of the mixture was heated with 2.8 g of sodium hydroxide in 50% aqueous ethanol at reflux for 2 h. The solution was concentrated under vacuum. The residue was acidified with dilute HCl. The mixture was extracted with three 150-mL portions of ether. The ether extracts were dried ($CaSO_4$) and concentrated under vacuum to 2.1 g of solid. The solid was heated in 20 mL of *o*-dichlorobenzene at reflux for 20 min, at which time gas evolution had ceased. Concentration of the solution under vacuum gave 1.8 g of solid. Crystallization of the solid from benzene gave 1.1 g (14% yield from oxathiazolone) of solid 5-phenyl-3-(α,α,α-trifluoro-*m*-tolyl)-4-isothiazolecarboxylic acid, mp 192.5–194 °C. Recrystallization of the solid from 1,2-dichloroethane gave 0.97 g of solid: mp 194–195 °C; IR (mineral oil mull) 3.0–4.2 (m), 5.84 μm (s); mass spectrum m/e 349 (M^+). Anal. Calcd for $C_{17}H_{10}F_3NO_2S$: C, 58.45; H, 2.98. Found: C, 58.52; H, 3.04.

Ethyl 5-Phenyl-3-(α,α,α-trifluoro-*m*-tolyl)-4-isothiazolecarboxylate (18). A solution of 0.97 g (0.00278 mol) of 5-phenyl-3-(α,α,α-trifluoro-*m*-tolyl)-4-isothiazolecarboxylic acid and 1.58 g (5 equiv) of thionyl chloride was heated on a steam bath for 0.5 h. The reaction mixture was concentrated under vacuum. The residue in 5 cm^3 of ethanol was heated on a steam bath for 1 h. The mixture was concentrated under vacuum to give 0.65 g of oil. The oil was crystallized from hexane to give 0.13 g of solid, mp 41–45 °C. The residue from the filtrate was crystallized three times from pentane to give 0.05 g of solid: mp 44–46 °C; IR (mineral oil mull) 5.82 μm (C=O); NMR ($CDCl_3$) δ 7.99 (m, 9, ArH), 4.16 (q, 2, J = Hz, OCH_2CH_3), 1.03 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{19}H_{14}F_3NO_2S$: C, 60.47; H, 3.74; N, 3.71. Found: C, 60.32; H, 3.71; N, 3.75.

Registry No.—**5b,** 52059-63-9; **5c,** 52059-70-8; **5d,** 67048-92-4; **5e,** 67048-91-3; **5f,** 23589-68-6; **5g,** 23589-73-3; **5h,** 23589-77-7; **5i,** 17452-78-7; **5k,** 17452-80-1; **5l,** 67048-90-2; **5m,** 67048-89-9; **5n,** 67048-88-8; **5o,** 67048-86-6; **5p,** 17452-74-3; **5q,** 67049-04-1; **5r,** 67049-12-1; **5s,** 17452-75-4; **5t,** 61689-40-5; **6a,** 27545-53-5; **6b,** 67048-77-5; **6c,** 67048-73-1; **6d,** 67048-71-9; **6e,** 67048-68-4; **6f,** 67048-65-1; **6g,** 67048-62-8; **6h,** 67048-59-3; **6i,** 35550-01-7; **6j,** 67048-54-8; **6k,** 59291-74-6; **6l,** 67113-95-5; **6m,** 67048-50-4; **6n,** 59291-75-7; **6o,** 67113-94-4; **6p,** 49570-33-4; **6q,** 67049-17-6; **6r,** 67049-14-3; **6s,** 67049-11-0; **6t,** 67049-09-6; **7a,** 27545-54-6; **7b,** 67049-02-9; **7c,** 67049-10-9; **7d,** 67049-07-4; **7e,** 67048-84-4; **7f,** 67048-82-2; **7g,** 67048-79-7; **7h,** 67049-05-2; **7i,** 67049-01-8; **7j,** 67048-76-4; **7k,** 67048-83-3; **7l,** 67113-96-6; **7m,** 67048-70-8; **7n,** 67048-66-2; **7o,** 67048-64-0; **7p,** 67048-61-7; **7q,** 67048-58-2; **7r,** 67048-56-0; **8a,** 18160-82-2; **8b,** 67048-52-6; **8c,** 67048-49-1; **8d,** 67048-47-9; **8e,** 19547-33-2; **8f,** 67113-93-3; **8g,** 67049-19-8; **8h,** 67049-16-5; **8i,** 67049-13-2; **8j,** 19762-93-7; **8k,** 67049-08-5; **8l,** 67049-06-3; **8m,** 67049-03-0; **8n,** 67113-97-7; **8o,** 67048-81-1; **8p,** 15903-66-9; **8q,** 67048-75-3; **8r,** 67049-72-0; **9b,** 67048-69-5; **9c,** 67048-67-3; **9d,** 67048-63-9; **9e,** 67048-60-6; **9f,** 67048-57-1; **9g,** 67048-55-9; **9h,** 67048-53-7; **9i,** 67048-51-5; **9k,** 67048-48-0; **9l,** 67048-46-8; **9m,** 67049-21-2; **9n,** 67049-20-1; **9o,** 67049-18-7; **9r,**

67049-15-4; **18**, 67048-80-0; **19**, 67048-74-2; **20**, 67048-78-6; benzamide, 55-21-0; *o*-fluorobenzamide, 445-28-3; *o*-toluamide, 527-85-5; α,α,α-trifluoro-*o*-toluamide, 360-64-5; 2,6-dichlorobenzamide, 2008-58-4; *m*-toluamide, 618-47-3; *m*-chlorobenzamide, 618-48-4; *m*-nitrobenzamide, 645-09-0; *p*-toluamide, 619-55-6; *p*-chlorobenzamide, 619-56-7; *p*-nitrobenzamide, 619-80-7; 3,4-dimethoxybenzamide, 1521-41-1; 3,4-methylenedioxybenzamide, 4847-94-3; 3,4-dichlorobenzmaide, 2670-38-4; 3,5-bis(trifluoromethyl)benzamide, 22227-26-5; acetamide, 60-35-5; 2,2-dimethylpropanamide, 754-10-9; cyclohexanecarboxamide, 1122-56-1; 2-chloroacetamide, 79-07-2; ethyl oxamate, 617-36-7; α,α,α-trifluoro-*m*-toluamide, 1801-10-1; *p*-cyanobenzamide, 3034-34-2; 3,5-dimethoxybenzamide, 17213-58-0; ClCl(O)5CL, 2757-23-5; dimethyl acetylenedicarboxylate, 762-42-5; ethyl phenylpropiolate, 2216-94-6.

References and Notes

(1) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
(2) J. E. Franz and L. L. Black, *Tetrahedron Lett.*, 1381 (1970).
(3) R. K. Howe and J. E. Franz, *J. Chem. Soc., Chem. Commun.*, 524 (1973).
(4) (a) R. K. Howe and J. E. Franz, *J. Org. Chem.*, **39**, 962 (1974); (b) R. K. Howe, T. A. Gruner, and J. E. Franz, *ibid.*, **42**, 1813 (1977); (c) J. E. Franz, R. K. Howe, and H. K. Pearl, *ibid.*, **41**, 620 (1976).
(5) (a) H. Gotthardt, *Tetrahedron Lett.*, 1277 (1971); (b) H. Gotthardt, *Chem. Ber.*, **105**, 188 (1972).
(6) J. R. Grunwell and S. L. Dye, *Tetrahedron Lett.*, 1739 (1975).
(7) Preliminary accounts of some of this work were reported in ref 2 and 3.
(8) A. Senning and P. Kelly, *Acta Chem. Scand.* **21**, 1871 (1967).
(9) Benzonitrile oxide adds to methyl propiolate to give a 72:28 mixture of methyl 3-phenyl-5-isoxazolecarboxylate and methyl 3-phenyl-4-isoxazolecarboxylate [M. Christl and R. Huisgen, *Tetrahedron Lett.*, 5209 (1968)].
(10) Addition of mercaptides and thiol radicals to acetylenic esters occurs exclusively at the β-carbon atom: (a) W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, **37**, 2391 (1972); (b) F. Bohlmann and E. Bresinsky, *Chem. Ber.*, **97**, 2109 (1964); (c) *Chem. Abstr.*, **61**, 11865 g (1964).
(11) (a) A. Holm, N. Harrit, and N. Toubro, *J. Am. Chem. Soc.*, **97**, 6197 (1975); (b) A. Holm, N. Harrit, K. Bechgaard, O. Buchardt, and S. E. Harnung, *J. Chem. Soc., Chem. Commun.*, 1125 (1972).
(12) (a) E. M. Burgess and H. R. Penton, Jr., *J. Am. Chem. Soc.*, **95**, 279 (1973); (b) E. M. Burgess and H. R. Penton, Jr., *J. Org. Chem.*, **39**, 2885 (1974).
(13) H. Yoshida, H. Taketani, T. Ogata, and S. Inokawa, *Bull. Chem. Soc. Jpn.*, **49**, 3124 (1976).
(14) (a) British Patent 1 079 348 (1966); (b) E. Kühle, *Synthesis*, 617 (1971).
(15) T. Naito, S. Nakagawa, and K. Takahashi, *Chem. Pharm. Bull.*, **16**, 148 (1968).
(16) (a) K. N. Houk, et al., *J. Am. Chem. Soc.*, **95**, 7287 (1973); (b) *ibid.*, **95**, 7301 (1973).
(17) J. Bastide and O. Henri-Rousseau, *Bull. Soc. Chim. Fr.*, 1037 (1974), and references quoted therein.
(18) G. Klopman, "Chemical Reactivity and Reaction Paths", Wiley, New York, N.Y., 1974, pp 55–165.
(19) A. Senning and J. S. Rasmussen, *Acta Chem. Scand.*, **27**, 2161 (1973).
(20) Belgian Patent 710 988 (1968).
(21) M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 446 (1964).
(22) T. Naito et al., *Bull. Chem. Soc. Jpn.*, **41**, 965 (1968).
(23) M. Beringer, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **49**, 2466 (1966).

Cycloaddition Reactions of Nitrile Sulfides with Olefins

Robert K. Howe* and John E. Franz

Research Department, Monsanto Agricultural Products Company, St. Louis, Missouri 63166

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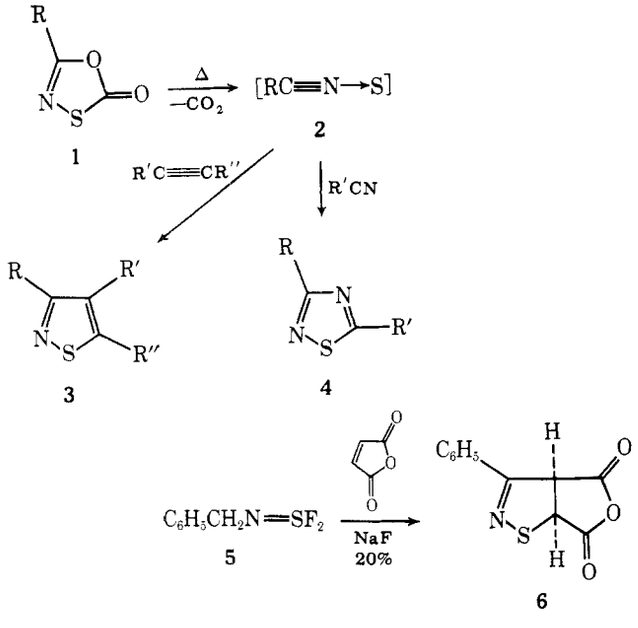
Dipolar cycloadditions of arenecarbonitrile sulfides to various olefins are described. Isothiazolines were obtained in fair to good yields from diethyl fumarate, phenyl acrylate, a norbornene derivative, and maleimides. Isothiazolecarboxylates were formed (via intermediate isothiazolines) from ethyl 2-chloroacrylate and ethyl β-pyrrolidinylacrylate. Significant amounts of adducts were not obtained from tetraethyl ethenetetracarboxylate, β-nitrostyrene, and 3-nitrostyrene.

We have reported previously cycloaddition reactions of nitrile sulfides (**2**), generated by thermolysis of 5-substituted-1,3,4-oxthiazol-2-ones (**1**), with acetylenic esters to give isothiazoles[1-3] (**3**) and with nitriles to give 1,2,4-thiadiazoles[4-6] (**4**) (Scheme I). We report here our studies of cycloadditions of nitrile sulfides with olefins. Subsequent to the completion of our work but prior to this account, Grunwell and Dye[7] reported cycloaddition of benzonitrile sulfide, generated from *N*-benzyliminosulfur difluoride (**5**), to maleic anhydride to give 3-phenyl-2-isothiazoline-*cis*-4,5-dicarboxylic acid anhydride (**6**) in 20% yield.

Scheme I



Thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one (**1a**) at 190 °C in 4 equiv of dimethyl fumarate under nitrogen gave dimethyl 3-phenyl-2-isothiazoline-*trans*-4,5-dicarboxylate (**7**) in 55% yield (GC analysis) (Scheme II); the pure product was isolated in 45% yield. The coupling constant J = 4 Hz between H_4 and H_5 in the proton NMR spectrum of **7** reveals that H_4 and H_5 are trans. The corresponding coupling constant in dimethyl 3-phenyl-2-isoxazolin-*trans*-4,5-dicarboxylate is 4.9 Hz and in dimethyl 3-phenyl-2-isoxazolin-*cis*-4,5-dicarboxylate is 11.5 Hz.[8] Dehydrogenation of **7** with dichlorodicyanobenzoquinone (DDQ) gave dimethyl 3-phenyl-4,5-isothiazoledicarboxylate (**3a**), which we had prepared earlier[1-3] from **1a** and dimethyl acetylenedicarboxylate.

Thermolysis of **1a** in 4 equiv of tetraethyl ethenetetracarboxylate at 190 °C gave benzonitrile (from decomposition of benzonitrile sulfide)[1,2] in 91% yield and an unidentified high-boiling material (~6%, GC analysis). Because of steric

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