10b, 114362-56-0; **11**, 115437-27-9; **12a**, 114362-57-1; **12b**, 114362-58-2; **13**, 115437-28-0; **14a**, 114362-61-7; **14b**, 115437-29-1; **14c**, 115437-30-4; **14d**, 114362-59-3; **14e**, 114362-60-6; **14f**, 114362-63-9; **14g**, 115437-31-5; **14h**, 115437-32-6; **14i**, 114362-62-8; **15a**, 115437-33-7; **15b**, 115437-34-8; **15c**, 115437-35-9; **16** (R_1 = Ph), 115437-71-3; **16** (R_1 = H_3C-*p*-C_6H_4), 115437-72-4; **17a**, 114362-64-0; **17b**, 114362-65-1; **19a**, 115437-36-0; **19b**, 115437-37-1; **19c**, 115437-38-2; **19d**, 115437-39-3; **20a**, 115437-41-7; **20b**, 115437-43-9; **20c**, 115437-45-1; **20d**, 115437-47-3; **20e**, 115437-49-5; **20f**, 115437-51-9; **20g**, 115437-53-1; **21**, 97326-47-1; **22**, 115437-25-7; **23a**, 115437-54-2; **23b**, 115437-55-3; **24a**, 115437-56-4; **24b**, 114362-66-2; **25a**, 115462-12-9; **25b**, 114362-67-3; **25c**, 114362-68-4; **27**, 115437-57-5; **29a**, 115462-13-0; **29b**, 115462-14-1; **29c**, 115462-15-2; **29d**, 115462-16-3; **30**, 108263-77-0; **31**, 115437-26-8; **32a**, 115437-58-6; **32b**, 115437-59-7; **33a**, 115437-60-0; **33b**, 115437-61-1; **35a**, 115437-63-3; **35b**, 115437-64-4; **35c**, 115437-65-5; **36d**, 115437-66-6; **36a**, 115437-67-7; **36b**, 115437-68-8; **37**, 115437-62-2; **38** (Ar^2= Ph), 115437-73-5; **38** (Ar^2 = H_3C-*p*-C_6H_4), 115437-74-6; **38** (Ar^2 = H_3CO-*p*-C_6H_4), 115437-75-7; **39a**, 115437-69-9; **39b**, 115437-70-2; **39c**, 115462-17-4; $PhNH_2$, 62-53-3; H_3C-*p*-$C_6H_4NH_2$, 106-49-0; C_2H_5NCO, 109-90-0; H_2C=$CHCH_2$-NCO, 1476-23-9; Cl-*m*-C_6H_4NCO, 2909-38-8; Cl-*p*-C_6H_4NCO, 104-12-1; H_3CO-*p*-C_6H_4NCO, 5416-93-3; PhNCO, 103-71-9; C_2H_5COCl, 79-03-8; H_3C-*p*-C_6H_4COCl, 874-60-2; H_3CO-*p*-C_6H_4COCl, 100-07-2; Cl-*p*-C_6H_4COCl, 122-01-0; H_3C-*p*-C_6H_4NCO, 622-58-2; (*p*-nitrophenyl)hydrazine, 100-16-3.

Reaction of Thioaldehydes with 5-Alkoxyoxazoles: A Route to 3-Thiazolines

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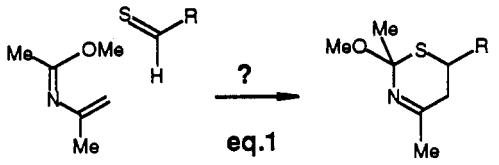
Generation of thioaldehydes **4** by photolysis of **15** or by thermolysis of **9** in the presence of oxazoles **2** or **3** affords **7** or **8**, respectively. Thermally generated thioacetone reacts similarly to give **16** and **17**. A mechanism involving an unstable Diels–Alder adduct **5** is most likely.

As part of our investigation of thioaldehyde chemistry,[1] we were interested to know whether Diels–Alder addition of these highly reactive dienophiles might take place with 2-aza-1,3-dienes.[2] The resulting adducts (eq 1) would be of interest due to their relationship to the cephalosporins. Attempts to trap thermally[1b] or photochemically[1a] generated RCH=S (R = CO_2Et, Ph, CH_2CH_2Ph) according to eq 1 did not result in detectable thioaldehyde adducts. In



an attempt to increase trapping efficiency by constraining the diene to the cisoid conformation, we next examined several oxazoles as potentially reactive 2-azadienes. The oxazole **1** proved too unreactive to intercept the thioaldehydes **4** prior to thioaldehyde decomposition, but the exceptionally activated 5-alkoxyoxazoles[3] **2** and **3** did afford 1:1 adducts in good yield. Spectroscopic evidence and chemical derivatization experiments established that the major product has the 3-thiazoline structure **7** (from **2**) or **8** (from **3**). The Diels–Alder adducts **5** or **6** were not detected.[4]

Table I

entry	RCHS	oxazole	precursor/ method[a]	yield,[b] %	product
1	**4a**	2	**15a**/B	0	
2	**4a**	2	**9a**/A1	81	**7a**
3	**4a**	3	**15a**/B	55	**8a**
4	**4a**	3	**9a**/A1	25	**8a**
5	**4b**	2	**15b**/B	0	
6	**4b**	2	**9b**/A1	59	**7b** (1:1)[c]
7	**4b**	3	**15b**/B	85	**8b** (2.5:1)
8	**4b**	3	**9b**/A1	85–95	**8b** (2.5:1)
9	**4c**	2	**15c**/B	0	
10	**4c**	2	**9c**/A2	95	**7c** (1:1)[c]
11	**4c**	3	**15c**/B	67	**8c** (2.5:1)
12	**4c**	3	**9c**/A2	92	**8c** (1:1)
13	**4d**	2	**15d**/B	0	
14	**4d**	2	**9d**/A2	70	**7d** (2:1)
15	**4d**	3	**15d**/B	35–50[e]	**8d** (>95:5)
16	**4d**	3	**9d**/A2	93	**8d** (>10:1)
17	**4e**	2	**15e**/B	0	
18	**4e**	2	**9e**/A2	29–34	**7e** (1:1)[c,d]
19	**4e**	3	**15e**/B	76	**8e** (2:1)[c]
20	**4e**	3	**9e**/A2	46[f]	**8e** (3:1)[c]

[a] See the Experimental Section: A1, 135–145 °C; A2, 105–115 °C; B, $h\nu$, 25 °C. [b] Isolated yields. [c] Diastereomers not completely separable. [d] Product aromatizes readily to thiazole. [e] Product unstable to $h\nu$ conditions. [f] 42% (1:1 ratio) of ester exchanged (R = CO_2Me) products **8f**.

In a representative example, the cyclopentadiene adduct **9b** of the photochemically generated thioacetaldehyde[1a] was heated with **3** at 140 °C. The product contains characteristic methyl ester signals in the NMR spectrum and therefore cannot be **5** or **6**. Among the remaining structural possibilities, **8b** and **10** are not easily distinguished by spectroscopic evidence. However, reduction of **8b** with sodium cyanoborohydride and trifluoroacetic acid gave a thiazolidine **11**, characterized by typical vicinal coupling in the NMR spectrum (major diastereomer, $J_{4,5}$ = 9.7 Hz). Similar coupling was observed in the product

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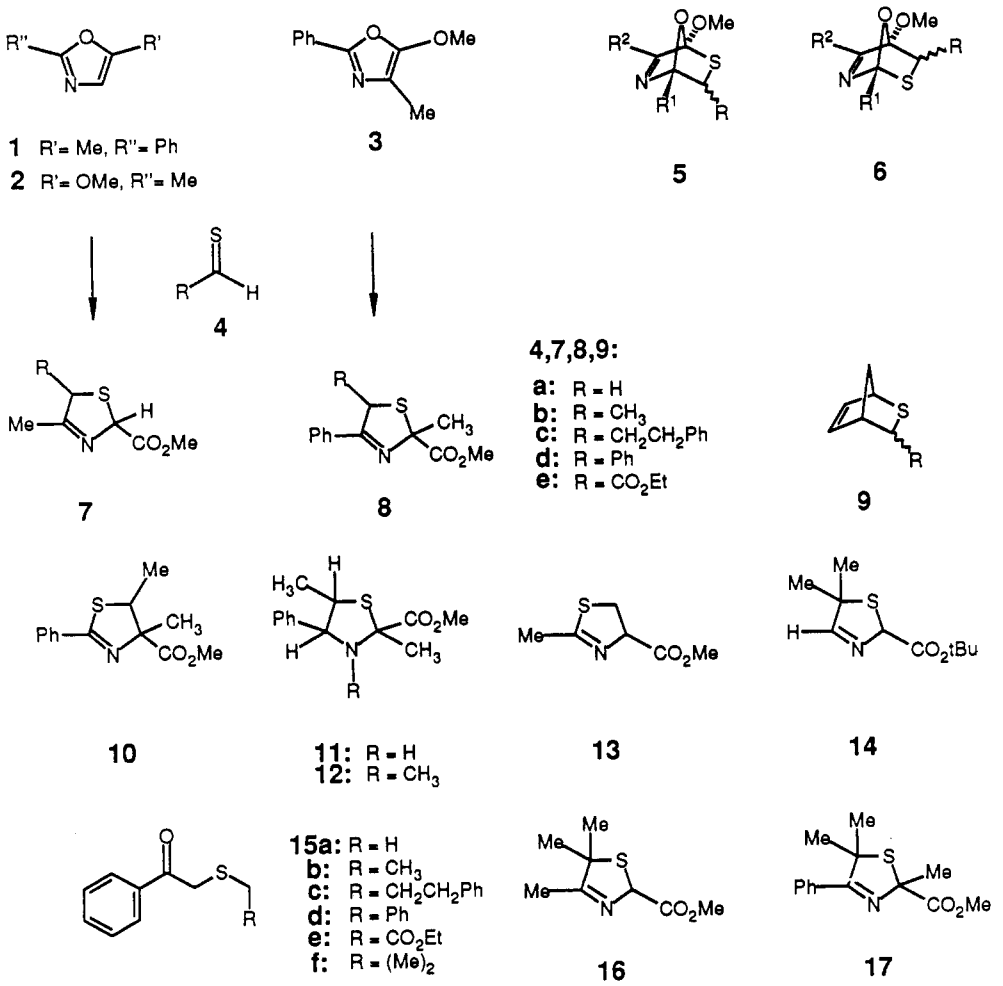
(3) (a) Turchii, I. J. In *The Chemistry of Heterocyclic Compounds*, Turchii, I. J., Ed.; Wiley: New York, 1986; Vol. 45, pp 127–134. (b) For a review of oxazole Diels–Alder reactions, see: Turchii, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.

(4) The absence (<5%) of these potentially unstable products was established by NMR analysis of sealed reaction tubes.

0022-3263/88/1953-4663$01.50/0

Scheme I



12 from N-methylation of 11 with $CH_3OSO_2CH_3$. These results rule out the 2-thiazoline structure 10 and support the connectivity in 8.

Further evidence for the structural assignments is available for the less highly substituted adduct series 7. The parent compound 7a was prepared by independent synthesis from α-mercaptoacetone,[5] ammonia, and methyl glyoxylate by using a known method[6a] and was identical with the product derived from 2 and thioformaldehyde. The regioisomeric 2-thiazoline 13 has already been described in the literature and is clearly different.[7] Furthermore, there is one previous report of a 3-thiazoline-2-carboxylate 14,[8] and its infrared as well as NMR data are closely analogous to the spectra of 7.

Since the only previous general method for synthesis of 3-thiazolines is restricted by the availability of α-mercapto carbonyl compounds,[6] we have briefly investigated the preparative aspects of the reaction of thioaldehydes with 2 and 3. As summarized in Table I, the thermal method from 9 (method A) is successful with both of the 5-alkoxyoxazole substrates and affords 3-thiazoline-2-carboxylates in good yield. Photochemical generation of thioaldehydes (method B, Table I) from the phenacyl sulfides 15[1a] is less effective with 3 as the trapping agent and fails completely in the case of 2. Analogous behavior has been noted using relatively unreactive 1,3-dienes in other thioaldehyde trapping experiments.[9] Generation of thioaldehydes from 9 has the advantage that the cycloreversion process is reversible and the thioaldehyde does not easily decompose to intractable polymers because cyclopentadiene recaptures it efficiently. Eventually, the equilibrium between 9 and the thioaldehyde and cyclopentadiene fragments is drained off by reaction with the oxazole. However, in the photochemical method, there is no analogous safety valve. The thioaldehyde undergoes competing self-condensation if the trapping agent is relatively inefficient.

Similar results were obtained in the only example studied of thioketone trapping. Photochemical generation of thioacetone from the phenacyl sulfide 15f[9b] gave no trapping products in the presence of either 2 or 3. However, thermolysis of 9f produced the 3-thiazolines 16 and 17, respectively.

The mechanism for the formation of 3-thiazoline products in the above experiments has not been established, but the most likely pathway involves the Diels–Alder reaction as the first step. Thus, 5 would be expected to readily undergo C–S bond cleavage as shown in Scheme II (eq 2) and there are several possibilities for subsequent conversion into the 3-thiazoline. If this pathway accounts

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(6) (a) Thiel, M.; Asinger, F.; Schmiedel, K. *Justus Liebigs Ann. Chem.* **1958**, *611*, 121. (b) Dubief, R.; Robe, Y.; Fernendez, J. P.; Subra, G.; Terol, A.; Chapat, J. P.; Sentenac-Roumanov, H.; Fatome, M. *Eur. J. Med. Chem.-Chim. Ther.* **1986**, *21*, 461. (c) Badr, M. Z. A.; Aly, M. M.; Fahmy, A. M.; Mansour, M. E. Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1844. (d) Martens, J.; Offermanns, H.; Scherberich, P. *Angew. Chem.* **1981**, *93*, 680.
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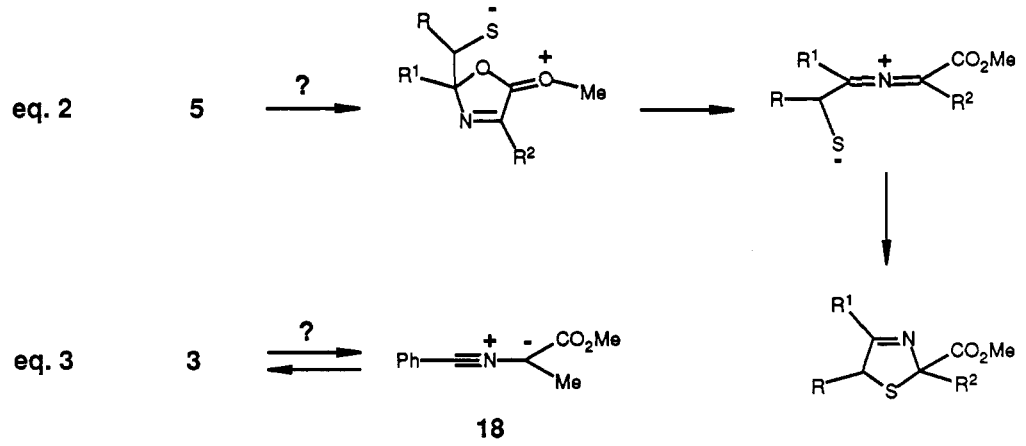
Scheme II



for the formation of all of the 3-thiazolines, then it would require (1) the formation of **5** as the major Diels–Alder adduct for all of the examples in Table I or (2) the facile retro-Diels–Alder interconversion of regioisomers **5** and **6**. Other Diels–Alder reactions of thioaldehydes occur with a strong regiochemical dependence on the thioaldehyde substituent. Thus **4a–c** with R = alkyl reacts with the opposite regiochemistry compared to **4e** with R = $CO_2C_2H_5$.[10] In apparent contradiction, **4e** (Table I, entries 17–20) reacts with oxazoles to give the same 3-thiazoline regiochemistry as do the simple alkane thials.

Since neither **5** nor **6** has been detected in any of the experiments, we cannot evaluate the possibility that **6e** is formed kinetically and equilibrates with **5e** under the reaction conditions. This process could occur by the retro-Diels–Alder reaction of **6e**, a reaction that is analogous to the generation of thioaldehyde from **9** under the thermal conditions. However, such equilibration is suspect in the room temperature photochemical generation of thioaldehydes. One alternative is to assume that regiochemistry in the 2 + 4 cycloaddition of **4** with the 2-aza diene subunit is not dominated by LUMO polarization of the thioaldehyde, in contrast to the all-carbon diene case.[10] However, there are several other mechanistic possibilities that we cannot rule out. These involve stepwise variations of the above rationale via diradical or dipolar intermediates.[11]

Formally, **8** is the 2 + 3 cycloadduct of **4** with a nitrile ylide **18** (eq 3). Under the thermal conditions (method A), it is conceivable that **18** might be involved because thermal electrocyclic ring opening of related oxazoles having additional carbonyl substituents is well known.[12] However, there is no precedent for the formation of **18** under the conditions of photochemical thioaldehyde generation, an alternative which would require either the formation of two different transient species, or a synergistic photochemical process involving both substrates. This rationale is also difficult to reconcile with the failure of oxazole **1** to give adducts under the thermal conditions at 135 °C. Overall, the results are most consistent with the Diels–Alder interpretation and reversible adduct formation, but the regiochemical issue is not fully understood.

The 5-alkoxyoxazoles are known for their exceptional Diels–Alder reactivity compared to 5-alkyl or 5-unsubstituted oxazoles.[3] Their ability to trap thioaldehydes or thioacetone is therefore not surprising. The result is a simple and versatile method for synthesis of the relatively rare 3-thiazolines.[7]

Experimental Section

General Procedure for 3-Thiazoline Generation. Preparation of 2-Carbomethoxy-2,5-dimethyl-4-phenyl-3-thiazoline (8b). Method A: Thermal. In a representative case, the thioacetaldehyde–cyclopentadiene (thioaldehyde–Cp) adduct **9b**[1a] (36 mg of a 60 mol % solution in CH_2Cl_2, 0.197 mmol) was dissolved in benzene-d_6 (0.2 mL, distilled from P_2O_5) and transferred via syringe to a thick-walled NMR tube containing a ground-glass joint with a septum under nitrogen. To this solution was added a solution of 1.7 equiv of 5-methoxy-4-methyl-2-phenyloxazole[13] **3** (64 mg, 0.340 mmol) in benzene-d_6 (0.2 mL) via syringe. The septum was removed and replaced with a stopcock fitted with a ground-glass joint. The other end of the stopcock was attached to a vacuum pump via thick-walled rubber tubing. After the aparatus was purged with nitrogen, the temperature of the vessel was lowered to −78 °C. The stopcock was then opened, and the flask exposed to high vacuum for several minutes. The stopcock was then closed and the contents of the vessel were allowed to warm to room temperature while still under vacuum. This constitutes one cycle of the freeze–pump degas process. The process was repeated three times. After the third warming cycle, the benzene solution (with stopcock closed) was frozen again, and the tube was sealed with the contents under vacuum. The tube was then heated to 135–140 °C (method A2) for 48 h, after which an NMR spectrum showed the appearance of cyclopentadiene monomer (6.5, 6.3 ppm) and none of the starting thioaldehyde–Cp adduct left. The presence of Cp dimer (5.95, 5.45 ppm) was also apparent by NMR.

After the tube was cracked, the mxiture was passed through a short plug of silica gel (1 g) with hexane/EtOAc (10:1), and the eluent was evaporated (aspirator). The residue was purified by HPLC (10:1 hexane/EtOAc) to give 11.7 mg (24%) of the minor diastereomer of **8b** (isomer 1) and 30.0 mg (61%) of the major diastereomer of **8b** (isomer 2) for a combined 85% yield of cycloadducts (1:2.6 diastereomer ratio).

Method B: Photolytic. Phenacyl ethyl sulfide **15b**[1] (400 mg, 2.22 mmol) and 1.4 equivalents of a 5-methoxy-2-methyloxazole[13] **3** (600 mg, 3.17 mmol) were dissolved in benzene (40 mL, distilled from P_2O_5) in a 100-mL round-bottom flask. The flask was then fitted with a condenser and connected to a stopcock via a ground-glass joint. The other end of the stopcock was connected to a vacuum pump. The solution was freeze–pump degassed as described for method A. After the third warming cycle, the flask was filled with nitrogen. The contents were then distributed equally via cannula to four 25-mL oven-dried round-bottom flasks. The solution was photolyzed for 12 h with a GE sun lamp with use of a 324-nm cutoff (5% aqueous solution of copper sulfate in a 150 × 75-mm Pyrex crystallizing dish). The temperature was maintained by <28 °C with a cooling coil, and all vessels were

(10) Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1983**, *105*, 6999.
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stirred with magnetic stir bars during photolysis. After the 12-h photolysis, no phenacyl sulfide was detectable by TLC.

The solvent was removed (aspirator), and the residue was purified by HPLC (12:1 hexane/EtOAc) to give 136 mg (25%) of the minor diastereomer (**8b**, isomer 1) and 328 mg (59%) of the major diastereomer of **8b** (isomer 2) for a combined purified yield of 84% (1:2.4 diastereomer ratio). Characterization of these and related adducts is tabulated below.

7a: oil; analytical TLC (silica gel F254), 1:1 hexane/EtOAc, R_f 0.40; m/e exact mass calcd for $C_6H_9O_2N_1S_1$ 159.0352, found 159.0355, error 2 ppm; IR ($CHCl_3$, cm^{-1}) 1735 (C=O), 1620 (C=N); 200-MHz NMR (C_6D_6, ppm) 6.09–6.01 (1 H, m), 3.4–3.0 (2 H, m), 3.25 (3 H, s), 1.6 (3 H, s).

8a: solid; mp 73.5–74 °C (crystallized from hexane); m/e exact mass calcd for $C_{12}H_{13}O_2N_1S_1$ 235.0664 found, 235.0635, error 12.2 ppm; IR ($CHCl_3$, cm^{-1}): 1735 (C=O), 1638 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.75–7.65 (3 H, m), 7.10–6.95 (2 H, m), 3.96 (2 H, AB quartet, J = 15 Hz), 3.30 (3 H, s), 2.10 (3 H, s).

7b, isomer 1: oil; analytical TLC (silica gel F254), 1:1 hexane/EtOAc, R_f 0.27; m/e no peak match for parent, 171.0347 (M − 2, calcd 171.0354, error 4.1 ppm, formula $C_7H_{11}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}) 1730 (C=O), 1665 (C=N); 200-MHz NMR (C_6D_6, ppm) 6.03 (1 H, qd, J = 1.4, 4.1 Hz), 3.94 (1 H, dq, J = 4.1, 7.05 Hz), 3.28 (3 H, s), 1.60 (3 H, d, J = 1.4 Hz), 0.92 (3 H, d, J = 7.05 Hz).

7b, isomer 2: oil; analytical TLC (silica gel F254), 1:1 hexane/EtOAc, R_f 0.30; m/e exact mass calcd for $C_7H_{11}O_2N_1S_1$ 173.0508, found 173.0522, error 8 ppm; IR ($CHCl_3$, cm^{-1}) 1735 (C=O), 1635 (C=N); 200-MHz NMR (C_6D_6, ppm) 5.96 (1 H, q, J = 1.46 Hz), 3.67 (1 H, q, J = 6.9 Hz), 3.25 (3 H, s), 1.61 (3 H, d, J = 1.46 Hz), 1.12 (3 H, d, J = 7.0 Hz).

8b, isomer 1: oil; analytical TLC (silica gel F254), 4:1 hexane/EtOAc, R_f 0.37; m/e exact mass calcd for $C_{13}H_{15}O_2N_1S_1$ 249.082, found 249.0823, error 1.2 ppm; IR ($CHCl_3$, cm^{-1}) 1735 (C=O), 1630 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.7–7.6 (3 H, m), 7.1–7.0 (2 H, m), 4.74 (1 H, q, J = 7.0 Hz), 3.39 (3 H, s), 2.10 (3 H, s), 1.21 (3 H, d, J = 7.0 Hz).

8b, isomer 2: oil; analytical TLC (silica gel F254), 4:1 hexane/EtOAc, R_f 0.45; m/e exact mass calcd for $C_{13}H_{15}O_2N_1S_1$ 249.082, found 249.0823, error 1.2 ppm; IR ($CHCl_3$, cm^{-1}) 1735 (C=O), 1665 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.85–7.7 (2 H, m), 7.1–7.0 (3 H, m), 4.70 (1 H, q, J = 7.06 Hz), 3.32 (3 H, s), 2.11 (3 H, s), 1.40 (3 H, d, J = 7.06 Hz).

7c, isomer 1: oil; analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.14; m/e of an enriched HPLC fraction: no peak match for parent, 261.0829 (M − 2, calcd 261.0823, error 2.3 ppm, formula $C_{14}H_{17}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}) 1745 (C=O), 1670 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.15–6.75 (5 H, m), 6.03 (1 H, qd, J = 1.6, 4.3 Hz), 4.02 (1 H, ddd, J = 3.5, 3.8, 9.8 Hz), 3.30 (3 H, s), 2.7–2.4 (2 H, m), 1.9–1.7 (2 H, m), 1.62 (3 H, d, J = 1.6 Hz); ^{13}C NMR (C_6D_6, ppm) 176, 170.5, 141, 77.5, 62.8, 52, 37, 35, 17.5.

7c, isomer 2: oil; analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.16; IR ($CHCl_3$, cm^{-1}) 1745 (C=O), 1670 (C=N); 200-MHz NMR (ppm) 7.15–6.75 (5 H, m), 5.99 (1 H, qd, J = 1.6, 1.6 Hz), 3.78 (1 H, dt, J = 1.6, 7.5 Hz), 3.27 (3 H, s), 2.7–2.4 (2 H, m), 1.9–1.7 (2 H, m), 1.60 (3 H, d, J = 1.6 Hz); ^{13}C NMR (C_6D_6, ppm) 176, 170.5, 141, 77.5, 62.8, 52, 37, 35, 10.

8c, isomer 1: oil; analytical TLC (silica gel F254), 4:1 hexane/EtOAc, R_f 0.41; m/e no peak match for parent, 340.1400 (M + 1, calcd 340.1371, error 8.5 ppm, formula $C_{20}H_{21}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}) 1740 (C=O), 1635 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.75–7.65 (4 H, m), 7.1–6.8 (6 H, m), 4.78 (1 H, dd, J = 4.7, 9.1 Hz), 3.34 (3 H, s), 2.8–2.5 (2 H, m), 2.12 (3 H, s), 1.9–1.5 (2 H, m).

8c, isomer 2: oil; analytical TLC (silica gel F254), 4:1 hexane/EtOAc, R_f 0.35; m/e exact mass calcd for $C_{20}H_{21}O_2N_1S_1$ 339.1288, found 339.1302, error 4 ppm; IR ($CHCl_3$, cm^{-1}) 1740 (C=O), 1620 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.65–7.55 (4 H, m), 7.05–6.80 (6 H, m), 4.85 (1 H, dd, J = 2.7, 10.0 Hz), 3.32 (3 H, s), 2.57 (2 H, dd, J = 7.2, 8.0 Hz), 2.13 (3 H, s), 1.8–1.6 (2 H, m).

7d: oil; analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.21; m/e no peak match for parent; 233.0515 (M − 2, calcd 233.0510, error 2.5 ppm, formula $C_{12}H_{13}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}) 1740 (C=O), 1660 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.40–6.80 (5 H, m), 6.25 (0.67 H, qd, J = 1.8, 4.7 Hz), 6.12 (0.33 H, qd, J = 2.0, 2.3 Hz), 5.08 (0.67 H, d, J = 4.7 Hz), 4.85 (0.33 H, d, J = 2.3 Hz), 3.3 (2 H, s), 3.29 (1 H, s), 1.62 (2 H, d, J = 1.8 Hz), 1.61 (1 H, d, J = 2.0 Hz).

8d: solid; MP 121.5–123 °C (recrystallized from hexane); m/e exact mass calcd for $C_{18}H_{17}O_2N_1S_1$ 311.0976, found 311.0984, error 2.5 ppm; IR ($CHCl_3$, cm^{-1}): 1735 (C=O), 1635 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.80–7.70 (2 H, m), 7.05–6.80 (8 H, m), 5.98 (1 H, s), 3.38 (3 H, s), 2.23 (3 H, s); ^{13}C NMR (C_6D_6 (DEPT), ppm) 171.6, 170.4, 141.1, 133.2, 130.8, 129.9, 129.2, 128.4, 128.3, 128.3, 127.7, 65.5, 52.5, 28.6.

7e: oil; analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.45; m/e no peak match for parent, 229.0398 (M − 2, calcd 229.0409, error 4.8, formula $C_9H_{13}O_4N_1S_1$); IR ($CHCl_3$, cm^{-1}) 1725 (C=O), 1620 (C=N); 200-MHz NMR (C_6D_6, ppm) 6.15–6.10 (0.5 H, m), 6.00–5.95 (0.5 H, m), 4.83 (0.5 H, s), 4.59 (0.5 H, d, J = 5.0 Hz), 3.97 (1 H, dq, J = 2.5, 7.1 Hz), 3.81 (1 H, dq, J = 1.0, 7.1 Hz), 3.34 (1.5 H, s), 3.22 (1.5 H, s), 1.96 (1.5 H, s), 1.83 (1.5 H, d, J = 1.5 Hz), 0.92 (1.5 H, t, J = 7.1 Hz), 0.79 (1.5 H, t, J = 7.1 Hz).

8e, isomer 1: oil; analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.56; m/e of an enriched HPLC fraction, no peak match for parent; 308.0954 (M + 1, calcd 308.0956, error 0.9 ppm, formula $C_{15}H_{17}O_4N_1S_1$); IR ($CHCl_3$, cm^{-1}) 1730 (C=O), 1665 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.95–7.80 (2 H, m), 5.36 (1 H, s), 3.70 (2 H, q, J = 10 Hz), 3.33 (3 H, s), 2.22 (3 H, s), 0.69 (3 H, t, J = 10 Hz); ^{13}C NMR (C_6D_6 (DEPT, 2D), ppm) 171.6, 169.5, 166.3, 131.2, 128.8, 128.4, 91.3, 61.9, 61.4, 52.5, 28.5, 13.6.

8e, isomer 2 (not separated): analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.52; IR ($CHCl_3$, cm^{-1}) 1735 (C=O), 1637 (C=N); 200-MHz NMR deduced from the mixture (C_6D_6, ppm) 7.95–7.80 (2 H, m), 7.05–6.95 (3 H, m), 5.34 (1 H, s), 3.73 (2 H, q, J = 10 Hz), 3.37 (3 H, s), 2.05 (3 H, s), 0.72 (3 H, t, J = 10 Hz); ^{13}C NMR (C_6D_6 (DEPT, 2D), ppm) 171.4, 168.6, 166.2, 131.1, 129.0, 128.3, 89.8, 61.7, 61.5, 52.5, 28.7, 13.6.

8f, isomer 1: oil; analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.45; m/e exact mass calcd for $C_{14}H_{15}O_4N_1S_1$ 293.0718, found 293.0751, error 11.2 ppm; IR ($CHCl_3$, cm^{-1}) 1735 (C=O), 1645 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.90–7.80 (2 H, m), 7.05–6.90 (3 H, m), 5.40 (1 H, s), 3.33 (3 H, s), 3.10 (3 H, s), 2.19 (3 H, s).

8f, isomer 2: oil; analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.40; m/e exact mass calcd for $C_{14}H_{15}O_4N_1S_1$ 293.0718, found 293.0701, error 5.8 ppm; IR ($CHCl_3$, cm^{-1}) 1735 (C=O), 1640 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.95–7.85 (2 H, m), 7.05–6.95 (3 H, m), 5.40 (1 H, s), 3.38 (3 H, s), 3.12 (3 H, s), 2.05 (3 H, s).

16: oil; analytical TLC (silica gel F254), 2:1 hexane/EtOAc, R_f 0.27; m/e exact mass calcd for $C_8H_{13}O_2N_1S_1$ 187.0664, found 187.0668, error 2.1 ppm; IR ($CHCl_3$, cm^{-1}) 1740 (C=O), 1655 (C=N); 200-MHz NMR (C_6D_6, ppm) 5.90 (1 H, q, J = 1.0 Hz), 3.28 (3 H, s), 1.70 (3 H, d, J = 1.0 Hz), 1.38 (3 H, s), 1.15 (3 H, s); ^{13}C NMR (C_6D_6 (2D, long range C–H correlation), ppm) 179.40, 170.60, 74.95, 66.77, 51.88, 29.89, 28.84, 14.68.

17, oil; analytical TLC (silica gel F254), 10:1 hexane/EtOAc, R_f 0.21; m/e exact mass calcd for $C_{14}H_{17}O_2N_1S_1$ 263.0976, found 263.098, error 1.5 ppm; IR ($CHCl_3$, cm^{-1}) 1730 (C=O), 1625 (C=N); 200-MHz NMR (C_6D_6, ppm) 7.75–7.65 (2 H, m), 7.10–7.00 (3 H, m), 3.33 (3 H, s), 2.10 (3 H, s), 1.64 (3 H, s), 1.49 (3 H, s).

Sodium Cyanoborohydride Reduction of 8b. Preparation of 2-Carbomethoxy-2,5-dimethyl-4-phenylthiazolidine (11). To the mixture of diastereomers **8b** (42.5 mg, 0.170 mmol) dissolved in anhydrous methanol (3 mL, distilled from metallic sodium) was added $NaCNBH_3$ (24 mg, 0.2 mmol). Bromocresol green (3 drops) was added, and the resulting blue color was titrated with a freshly prepared 2 N solution of CF_3CO_2H in methanol until the solution was a pale yellow color (pH 4). The yellow color was maintained by periodic additions of the acidic methanol solution for a period of 1 h, at which point no further change in the indicator color was seen. Complete conversion of the 3-thiazoline diastereomers to four products was apparent by TLC (4:1 hexane/EtOAc).

The reaction mixture was poured into a separatory funnel containing $CHCl_3$ (10 mL) and washed with 1 N KOH (10 mL). The aqueous layer was separated and extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and

concentrated in vacuo to yield 26.6 mg of a crude oil, which was subsequently purified by HPLC (4:1 hexane/EtOAc). The purified yield was 62% of a mixture of diastereomers **11a** (8.1 mg), **11b** (4.0 mg), **11c** (11.4 mg), and **11d** (3.1 mg) in a 2:1:3:1 ratio.

11a: solid; mp 64–66 °C (crystallized from hexane); *m/e* no peak match for parent, 252.1053 (M + 1, calcd 252.1058, error 1.9 ppm, formula $C_{13}H_{17}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}) 3330 (N—H), 1735 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 7.40–7.25 (5 H, m), 3.85–3.80 (1 H, m), 3.83 (3 H, s), 3.66 (1 H, br s), 3.51 (1 H, dq, J = 9.7, 6.3 Hz), 1.80 (3 H, s), 1.22 (3 H, d, J = 6.3 Hz).

11b: solid, mp 88–88.5 °C (crystallized from hexane); *m/e* no peak match for parent, 252.1067 (M + 1, calcd 252.1058, error 3.5 ppm, formula, $C_{13}H_{17}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}) 3330 (N—H), 1730 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 7.35–7.25 (5 H, m), 4.83 (1 H, d, J = 5.1 Hz), 3.76 (3 H, s), 3.69 (1 H, dq, J = 5.1, 6.8 Hz), 2.72 (1 H, br s), 1.91 (3 H, s), 0.89 (3 H, d, J = 6.8 Hz).

11c: solid; mp 94–96 °C (crystallized from hexane); *m/e* no peak match for parent 252.1067 (M + 1, calcd 252.1058, error 3.6 ppm, formula $C_{13}H_{17}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}): 3300 (N—H), 1730 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 7.42–7.25 (5 H, m), 4.63 (1 H, dd, J = 4.7, 14.5 Hz), 3.87 (1 H, br d, J = 14.5 Hz), 3.85 (3 H, s), 3.80 (1 H, dq, J = 4.7, 7.0 Hz), 1.77 (3 H, s), 0.82 (3 H, d, J = 7.0 Hz).

11d: solid; mp 74–75 °C (crystallized from hexane); *m/e* no peak match for parent; 252.1071 (M + 1, calcd 252.1058, error 5.2 ppm, formula $C_{13}H_{17}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}) 3300 (N—H), 1730 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 7.45–7.30 (5 H, m), 4.14 (1 H, d, J = 9.25 Hz), 3.79 (3 H, s), 3.55 (1 H, qd, J = 6.4, 9.25 Hz), 2.72 (1 H, br s), 1.82 (3 H, s), 1.20 (3 H, d, J = 6.4 Hz).

Methylation of 11. Preparation of 2-Carbomethoxy-4-phenyl-2,3,5-trimethylthiazolidine (12). To the purified diastereomer **11d** (5.7 mg, 0.029 mmol) dissolved in acetonitrile (3 mL, distilled from CaH_2) was added 1.1 equiv of methyl triflate (MeOTf) (0.003 mL, 0.03 mmol) at room temperature. After 30 min, excess MeOTf (1 equiv) was added to the reaction mixture, and the reaction was followed by TLC until no starting thiazolidine **11d** remained. A crude NMR spectrum indicated the N-protonated ammonium salt of **12**. Filtration through a plug of silica gel (5 g, 10:1 hexane/EtOAc eluent) afforded the single diastereomeric product **12** in quantitative yield (5.8 mg).

12: oil; analytical TLC (silica gel F254), 4:1 hexane/EtOAc, R_f 0.65; *m/e* no peak match for parent, 264.1067 (M − 1, calcd 264.1058, error 3.4 ppm, formula $C_{14}H_{19}O_2N_1S_1$); IR ($CHCl_3$, cm^{-1}) 1723 (C=O); 200-MHz NMR (C_6D_6, ppm) 7.40–7.30 (5 H, m), 4.08 (1 H, d, J = 8.6 Hz), 3.75 (3 H, s), 3.40 (1 H, dd, J = 6.6, 8.6 Hz), 2.11 (3 H, s), 1.76 (3 H, s), 1.20 (3 H, d, J = 6.6 Hz).

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Endocyclic Nucleophilic Substitution at Tetracoordinate Sulfur(VI)[1]

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A search for endocyclic nucleophilic substitution at tetracoordinate sulfur(VI), usually sulfonyl sulfur, was carried out through the use of molecules so constructed that any intramolecular substitution process was forced to proceed through four-, five-, or six-membered cyclic transition states or intermediates with each ring incorporating both the nucleophile, sulfur atom, and leaving group. Three compounds [*N*-methyl-*N*-phenyl-4-toluenesulfonamide (**5**), 2′-(methylamino)phenyl 4-toluenesulfonate (**30**), and 2′-[(*N*-methylamino)methyl]phenyl 4-toluenesulfonate (**38**)] that underwent apparent endocyclic substitution when treated with strong base were synthesized—one for each ring size. Crossover reactions were carried out with mixtures of deuteriated and undeuteriated substrates. These reactions showed that **5** and **30** rearranged intramolecularly to give 2′-(methylamino)phenyl 4-methylphenyl sulfone (**7**) and *N*-(2′-hydroxyphenyl)-4-toluenesulfonamide (**14**), respectively. Although **5** may have rearranged via an endocyclic process, it seems, on the basis of other evidence, that **30** did not. Sulfonate **38** upon treatment with LDA reacted intermolecularly to give *N*-(2′-hydroxybenzyl)-*N*-methyl-4-toluenesulfonamide.

This paper reports the results of a study of nucleophilic substitution at tetracoordinate sulfur(VI) with molecules so constructed that the nucleophile (Nu), leaving group (L), and sulfur atom need not be colinear in the transition state or intermediate.[3] Several earlier studies found that nucleophilic substitution at tetracoordinate sulfur(VI) proceeded with inversion of configuration.[4–7] Usually, a trigonally bipyramidal intermediate or transition state with the sulfur atom at its center and the nucleophile and leaving group at the apical positions was postulated to account for such stereochemistry.[8,9] That is, Nu, the sulfur atom, and L are colinear, or at least closely so, an arrangement analogous to that in an S_N2 transition state. Even though a stable anion that is a model for such an intermediate has been synthesized, it is conceivable that an atom (A), sulfur or otherwise, could undergo substitution via a transition state or intermediate in which Nu, A, and L are far removed from colinearity.[10] A trigonal bipyramidal intermediate (a lone electron pair on sulfur is counted as a ligand) with Nu and L in an apical–equatorial arrangement with respect to one another has been postulated to account for examples of retention of configuration observed in nucleophilic substitution at tricoordinate S(IV).[8] Recently, an analogous intermediate has been postulated involving sulfonyl sulfur.[11]

One approach to test for nonlinearity is to construct a molecule potentially capable of undergoing the desired substitution reaction intramolecularly by having Nu connected to L by a sequence of atoms as depicted below. Nu

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