A Two-Step Conversion of Carbonyl Compounds into Functionalized Five- and Six-Membered Ring Thioethers via Intramolecular Cycloaddition[1]

Alfred Hassner* and Wim Dehaen

Department of Chemistry, Bar-Ilan University, Ramat-Gan 52100, Israel

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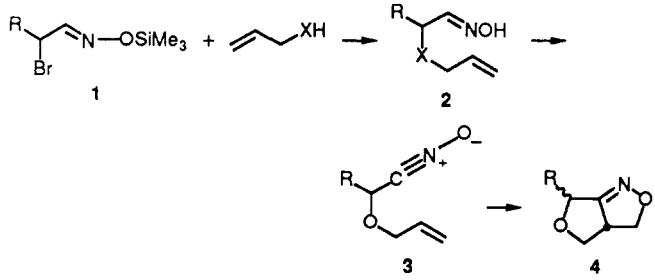
Reaction of aldehydes or ketones with nitromethane in the presence of unsaturated thiols led directly to unsaturated nitro sulfides **7**, **12**, **14**, or **19**. These compounds were converted by intramolecular nitrile oxide–olefin cycloaddition to tetrahydrothiopheno[3,4-*c*]isoxazoles **9**, **10**, **13**, and **20** or to homologous thiopyrans **15** and **16** in some cases with a fair degree of stereoselectivity. Reduction of **9** or **13** led to tetrahydrothiophenes possessing stereoselectively placed amino alcohol functions, while desulfurization provided open-chain keto alcohol **24**.

Introduction

Intramolecular nitrile oxide–olefin cycloadditions (INOC) have been of considerable synthetic and mechanistic interest, especially since the resulting isoxazoline ring can serve as a precursor to hydroxy ketones or to other functional groups.[2] We have recently shown that the α-bromo aldoxime synthon **1** can be converted into α-allylamino or α-allyloxy aldoximes by reaction with an allyl amine or alcohol.[3] Oxidation of aldoximes **2** (X = O) to nitrile oxides **3** provided a stereoselective route to functionalized cyclic ethers **4** via an INOC reaction.[4]



When we tried to apply this route to the thio analogues of **2** with a view to learning about the scope and stereoselectivity of these intramolecular cycloadditions, we found that although formation of unsaturated oximes **2** (thioether instead of ether) can be achieved, the second step, namely, oxidation to the nitrile oxide and subsequent cycloaddition, proceeded poorly because of the sensitivity of the sulfide function to the reagents employed (NaOCl or chloramine-T).[5] We now report an alternate pathway to isoxazolinothiophenes such as **9**, **10**, and **13** by two simple steps starting from aldehydes or ketones via nitro compounds.

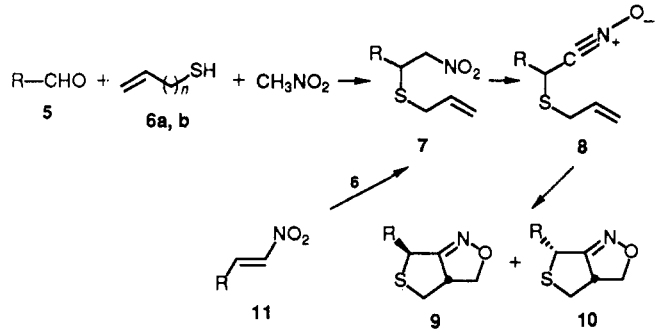
Results and Discussion

When isobutyraldehyde (**5c**) was allowed to react with nitromethane in the presence of allyl mercaptan (**6a**) in the presence of piperidine at room temperature, the unsaturated sulfide **7c**, bearing a nitro group, was isolated in 83% yield. Reaction of the nitroolefin **7c** with PhNCO–Et_3N at room temperature provided the stereoisomeric cyclic sulfides **9** and **10** in 90% yield. We found that both aliphatic and aromatic aldehydes **5** are suitable for the formation of **7**, though better yields (80–95%) were obtained with aliphatic (except *tert*-butyl) than with aromatic aldehydes (63–75%) (see Table I). A possible explanation may be our observation that β-nitrostyrenes tend to polymerize under the reaction conditions.

Table I. Yields of β-Nitro Sulfide 7 and of Fused Tetrahydrothiophenes 9 and 10

	R	yield of 7 (%) Method A[a]	Method B	yield of 9 + 10 (%)	ratio of 9:10
a	Me	71	*b*	84	1:1
b	Et	77	*b*	87	1:1
c	iPr	83	*b*	90	1:1
d	tBu	14	92	74	2:1
e	Ph	68	93	80	3:2
f	4-$MeOC_6H_4$	54	89	83	3:2
g	3,4-$(MeO)_2C_6H_3$	32	85	75	3:2
h	3,4,5-$(MeO)_3C_6H_2$	72	92	67	3:2
i	3,4-$(CH_2O_2)C_6H_3$	*b*	96	70	3:2
j	4-ClC_6H_4	63	92	62	3:2
k	2,4,6-$Me_3C_6H_2$	*b*	87	87	5:2

[a] Method A, one-pot procedure from aldehyde **5**; method B, starting from nitroalkene **11**. [b] Not attempted.



In the first step, formation of the unsaturated nitro sulfide **7** apparently results from 1,4-addition of mercaptan **6a** to an in situ generated unsaturated nitro compound (method A). In fact, **7a** was also obtained in high yield when **6a** was added to preformed nitroalkene **11** (method B). Parham et al.[6] had shown that this approach can be used for a nitro alkyl sulfide synthesis.

In the second step, the nitro sulfides **7a–k** were converted on treatment with phenyl isocyanate–triethylamine[7]

(1) Cycloadditions. 44. For paper 43, see: Hassner, A.; Maurya, R. *Tetrahedron Lett.* **1989**, *30*, 5803.

(2) See, for instance: (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. (c) Jager, V.; Buss, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3133. (d) Jager, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199. (e) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024. (f) Curran, D. P., Kim, B. H. *Synthesis* **1986**, 312. (g) Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; J. Wiley and Sons: New York, 1984; Vol. 1, Chapter 3, p 337 and references cited. (h) Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1986**, *27*, 1407.

(3) (a) Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1987**, *28*, 683; (b) *Tetrahedron Lett.* **1987** *28*, 4097. (c) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Bullock, W. H.; Stull, P. D. *J. Org. Chem.* **1988**, *53*, 5063.

(4) (a) Padwa, A.; Chiacchio, Y.; Dean, D. C.; Schoffstall, A. M.; Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1988**, *29*, 4169. (b) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, Y.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277.

(5) Hassner, A.; Rai, K. M. L. *Synthesis* **1989**, 57.

(6) Parham, W. E.; Ramp, F. L. *J. Am. Chem. Soc.* **1951**, *73*, 1293.

(7) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

0022-3263/90/1955-5505$02.50/0

Table II. Calculated Ground-State Energy Differences[9] (E) (between Trans and Cis INOC Cycloadducts) and Experimentally Determined Trans/Cis Ratios

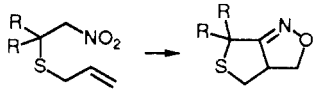
	trans-cis adduct	calcd E, kcal	exptl trans/cis
S cmpd	**9e–10e**	0.5	3:2
O cmpd	**4** (R = Ph)	0.96[4]	4:1
N cmpd	**9e–10e**, where S = NPh	3.5	99:1

to the unsaturated nitrile oxides **8**, which without isolation underwent spontaneous cycloaddition to the fused isoxazolines **9a–k** and **10a–k**.[8]

The cyclizations of **7** led to a trans–cis mixture of diastereomers **9** and **10** and proceeded with a low degree of stereoselectivity, depending on the nature of the R group derived from the aldehyde component. Apparently, a steric factor plays a role during the cycloaddition, since an equal mixture of stereoisomers **9** and **10** was generated from the alkyl-substituted systems **7a–c** (R = Me, Et, iPr), while when R = tBu or aromatic, the trans isomer **9** predominated 2:1 or 3:2, respectively. From the extremely hindered β-nitro sulfide, **7k** or a 5:2 trans/cis mixture was formed. Electronic effects in the aromatic ring (R = Ar) apparently do not influence the isomer ratio (see Table I). Separation of the aryl-substituted tetrahydrothiophenes **9e–j** and **10e–j** was achieved by chromatography. The structure of the two isomers **9** and **10** was assigned unambiguously by NOE experiments, the major isomer (**9**) possessing the trans stereochemistry.

By comparison, cyclization of the analogous ethers **2** had been found to be more stereoselective and somewhat more sensitive to steric factors. For instance, the trans/cis product ratio in **4** was 2.4:1 when R = Me, 6:1 when R = isopropyl, and 4:1 when R = Ph.[4] This may be attributable to the longer bond length of C–S vs C–O, leading to a less constrained transition state during the INOC cyclization in the sulfide cases. Indeed MM2 calculations[9] (see Table II) indicate a lower energy difference between trans and cis isomers **9** and **10** in the cyclic sulfides series (0.5 kcal for R = Ph, still in favor of the trans isomer) than in the ether series **4** (ca. 1 kcal),[4] with the largest energy difference in the formation of pyrrolidines (**9** and **10**, with N-Ph in place of S).

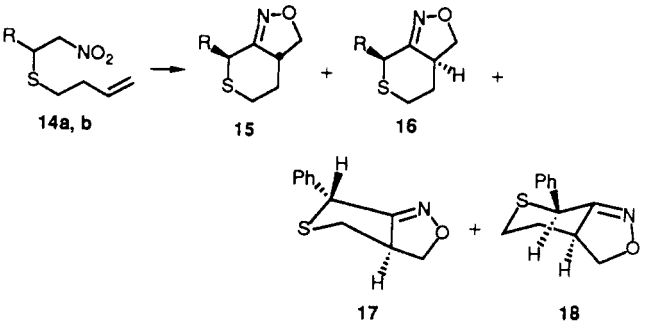
This method was also applied successfully to ketones. Thus, β-nitro sulfides **12a,b** were prepared in satisfactory yields from the corresponding ketone, nitromethane, and mercaptan **6a**. Subsequent cyclization under standard conditions gave tetrahydrothiophenes **13a,b**.



12a, b **13a, b**

a, R = Me; **b**, R, R = $(CH_2)_5$

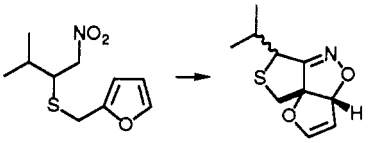
With 3-butenethiol (**6b**) as a substrate, isobutyraldehyde and benzaldehyde were converted into the unsaturated nitro sulfides **14a** and **14b**, which were cyclized in the same way as **7** to a mixture of the six-membered ring sulfides **15** and **16** in 84% and 72% yields, respectively. The ratio of **15**:**16**, as determined by NMR and indicating a preference for formation of the cis (**15**) over the trans isomer (**16**), was 7:2 for R = iPr and 3:2 for R = Ph. ^{13}C NMR spectra (the γ effect) were particularly useful in the stereochemical assignments of **15** and **16**. The difference in stereochemical preference in the INOC ring closure leading to trans five- vs cis six-membered ring sulfides can be explained in terms of a preference for conformations **17** and **18**, respectively.



14a, b **15** **16**

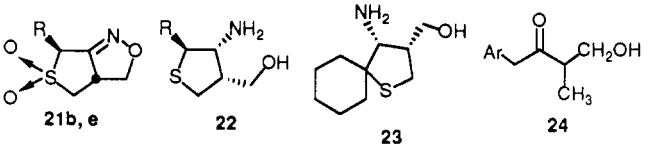
17 **18**

Cycloaddition to seven-membered ring sulfides by the above method required heating and proceeded in poor yield. An interesting example of the INOC reaction leading to functionalized cyclic sulfides, e.g., **20** as a 1:1 mixture of stereoisomers, is the cyclization of the nitro furan **19**, prepared from 2-furylmethanethiol, isobutyraldehyde, and nitromethane by the method described above.



19 **20**

Reaction of **9b** with *m*-chloroperbenzoic acid led to an unstable thiophene oxide, which epimerized and partially decomposed on chromatography. However, oxidation of **9b,e** with SeO_2/H_2O_2[10] at room temperature produced crystalline thiophene dioxides **21b,e**. Lithium aluminum hydride reduction of **9f** and **13b** led to stereospecifically substituted 3-amino-4-(hydroxymethyl)tetrahydrothiophenes **22** and **23**, respectively. In this manner, three adjacent stereocenters were introduced into amino alcohol **22**. The potential for utilizing the cyclic sulfides **9**, **10**, **13**, and **22** in the synthesis of desulfurized molecules is illustrated by the catalytic reduction of **9f** in the presence of Raney nickel to produce the β-hydroxy ketone **24** in good yield.



21b, e **22** **23** **24**

Extensions of synthetic potential of these cyclizations are being investigated.

Experimental Section

General. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured, using $CDCl_3$ as the internal standard. J values are given only in the general procedures for compounds **7a**, **9a**, and **10a**. Similar coupling constants apply for all analogues. Mass spectra were obtained at an ionization energy of 35 eV and are recorded as m/e (peak, rel intensity). Melting points are uncorrected. Microanalyses were performed at the Hebrew University, Jerusalem. All reactions were run on the same scale as

(8) For recent analogies, see: (a) Annunziata, R.; Cinquini, M.; Cozzi, F., Dandio, G., Raimondi, L. *Tetrahedron* **1987**, *43*, 2369. (b) Lee, M. H.; Baggiolini, E. G.; Uskokovic, M. R. *Ibid.* **1987**, *43*, 4887.

(9) We are indebted to Prof. A. Padwa for MM2 calculations on these systems.

(10) Drabowicz, I.; Lyzwa, P.; Mikolajczyk, M. *Phosphorus Sulfur* **1983**, *17*, 169.

(11) (a) Irradiation at the frequency of the benzylic singlet increased the intensity of the bridgehead signal by 3% (NOE). (b) Irradiation at the frequency of the 2,6-methyl singlet increased the intensity of the bridgehead signal by 2.5% (NOE).

in the general procedures. Working with the unsaturated mercaptans requires a good hood. The purified β-nitro sulfides and cyclized thioethers are practically odorless.

General Procedure for the Preparation of β-Nitroalkyl Sulfides. 2-(Allylthio)-1-nitropropane (7a). A stirred mixture of 2.01 g (33 mmol) of nitromethane, 0.26 g (3 mmol) of piperidine, and 2.22 g (30 mmol) of allyl mercaptan was treated with 1.45 g (33 mmol) of acetaldehyde. Heat evolved and the mixture was refluxed for 2 h (80 °C, oil bath). Ether was added and the resulting solution was washed with dilute hydrochloric acid, water, and brine and dried ($MgSO_4$). After evaporation of the solvent in vacuo, the oily residue was chromatographed on silica gel (eluent petroleum ether/ether 10:1). The yield of **7a** was 71% (oil): ^{1}H NMR δ 1.38 (d, J = 7.5 Hz, 3 H, CH_3), 3.21 (dt, J = 7, 1 Hz, 2 H, CH_2S), 3.42 (ddq, J = 9, 7.5, 6 Hz, 1 H, $CHCH_2NO_2$), 4.37 (dd, J = 13, 9 Hz, 1 H, CH_2NO_2), 4.56 (dd, J = 13, 6 Hz, 1 H, CH_2NO_2), 5.18 (dq, J = 10, 1 Hz, 1 H, vinyl), 5.20 (dq, J = 17, 1 Hz, 1 H, vinyl), 5.82 (ddt, J = 17, 10, 7 Hz, 1 H, vinyl); ^{13}C NMR δ 18.81 (q, CH_3), 34.35 (t, CH_2S), 36.39 (d, $CHCH_2NO_2$), 80.48 (t, CH_2NO_2), 117.98 (t, vinyl), 133.77 (d, vinyl); MS (m/z, rel intensity, EI) 162 (MH^+, 15), 161 ($M^{\bullet+}$, 4), 160 ($M^{\bullet+}$ – H, 14), 131 ($M^{\bullet+}$ – NO, 35), 115 ($M^{\bullet+}$ – NO_2, 100), 101 ($M^{\bullet+}$ – CH_2NO_2, 22), 89 ($M^{\bullet+}$ – C_3H_7SH, 19), 73 ($C_3H_7S^+$, 76).

2-(Allylthio)-1-nitrobutane (7b) was prepared from propionaldehyde in 77% yield (oil): ^{1}H NMR δ 1.05 (t, 3 H), 1.57 (ddq, 1 H), 1.73 (ddd, 1 H), 3.19 (dt, 2 H), 3.22 (ddt, 1 H), 4.46 (dd, 1 H), 4.52 (dd, 1 H), 5.15 (dq, 1 H), 5.18 (dq, 1 H), 5.80 (ddt, 1 H); ^{13}C NMR δ 10.82 (q), 25.50 (t), 34.57 (t), 43.43 (d), 79.19 (t), 117.86 (t), 133.97 (d); MS (m/z, relative intensity, EI) 175 ($M^{\bullet+}$, 70), 129 ($M^{\bullet+}$ – NO_2, 100).

2-(Allylthio)-3-methyl-1-nitrobutane (7c) was prepared from isobutyraldehyde in 83% yield (oil): ^{1}H NMR δ 0.95 and 1.04 (d, 3 H), 1.96 (d septet, 1 H), 3.16 (ddd, 2 H), 3.22 (dt, 1 H), 4.48 and 4.57 (dd, 1 H), 5.10 (dq, 1 H), 5.17 (dq, 1 H), 5.76 (ddt, 1 H); ^{13}C NMR δ 17.88 and 20.07 (q), 30.23 (d), 35.55 (t), 48.73 (d), 78.37 (t), 117.99 (t), 133.86 (d); MS (m/z, relative intensity, EI) 190 (MH^+, 24), 189 ($M^{\bullet+}$, 11), 143 ($M^{\bullet+}$ – NO_2, 100).

2-(Allylthio)-3,3-dimethyl-1-nitrobutane (7d) was isolated in 14% yield from the reaction of trimethylacetaldehyde. The major product (43% yield) was the known 3,3-dimethyl-1-nitrobutan-2-ol.

Alternative Procedure for the Preparation of 7d from a Nitroalkene. A mixture of 1 mmol of 3,3 dimethyl-1-nitro-1-butene, 1.1 mmol of allyl mercaptan, and 0.1 mol of piperidine in 10 mL of ether was stirred for 1 h at 20 °C and worked up as described for **7a**. The yield of **7d** (oil) was 92%: ^{1}H NMR δ0.95 (s, 9 H), 3.05 and 3.12 (ddt, 1 H), 3.06 (dd, 1 H), 4.37 and 4.67 (dd, 1 H), 5.07 and 5.08 (dq, 1 H), 5.68 (ddt, 1 H); ^{13}C NMR δ 27.53 (q), 34.94 (s), 36.95 (t), 53.05 (d), 76.49 (t), 118.08 (t), 133.77 (d); MS (m/z, relative intensity, EI) 204 (MH^+, 18), 157 (M^+ – NO_2, 100). Anal. Calcd for $C_9H_{17}NO_2S$: C, 53.20; H, 8.37; N, 6.90. Found: C, 53.46; H, 8.56; N, 6.66.

2-(Allylthio)-1-nitro-2-phenylethane (7e) was prepared from benzaldehyde in 68% yield or from β-nitrostyrene in 93% yield (oil): ^{1}H NMR δ 3.03 and 3.13 (ddt, 1 H), 4.52 (t, 1 H), 4.75 (d, 2 H), 5.13 (dq, 1 H), 5.18 (dq, 1 H), 5.78 (ddt, 1 H), and 7.30–7.38 (m, 5 H); ^{13}C NMR δ 34.55 (t), 45.31 (d), 79.17 (t), 118.31 (t), 127.81 (d), 128.45 (d), 129.00 (d), 133.40 (d), 137.31 (s); MS (m/z, relative intensity, EI) 223 ($M^{\bullet+}$, 11) 104 ($PhC{\equiv}CH^{\bullet+}$, 100).

2-(Allylthio)-2-(4-methoxyphenyl)-1-nitroethane (7f) was prepared from 4-methoxybenzaldehyde in 54% yield or from 4-methoxy-β-nitrostyrene in 89% yield (oil): ^{1}H NMR δ 3.01 (ddt, 1 H), 3.12 (ddt, 1 H), 3.80 (s, 3 H), 4.49 (t, 1 H), 4.68 and 4.73 (dd, 1 H), 5.12 and 5.18 (dq, 1 H), 5.78 (dddd, 1 H), 6.88 (dt, 2 H), 7.25 (dt, 2 H); ^{13}C NMR δ 34.48 (t), 44.83 (d), 55.26 (q), 79.33 (t), 114.38 (1d), 118.17 (t), 128.98 (s + d), 159.56 (s); MS (m/z, relative intensity, EI) 253 ($M^{\bullet+}$, 26), 180 ($M^{\bullet+}$ – C_3H_5S, 100). Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.92; H, 5.93; N, 5.53. Found: C, 56.59; H, 6.18; N, 5.43.

2-(Allylthio)-2-(3,4-dimethoxyphenyl)-1-nitroethane (7g) was obtained from 3,4-dimethoxybenzaldehyde in 32% yield or from 3,4-dimethoxy-β-nitrostyrene in 85% yield (oil): ^{1}H NMR δ 3.02 and 3.12 (ddt, 1 H), 3.80 and 3.86 (s, 3 H), 4.48 (t, 1 H), 4.72 (d, 2 H), 5.13 and 5.18 (dq, 1 H), 5.79 (dddd, 1 H), 6.79–6.89 (m, 3 H); ^{13}C NMR δ 34.53 (t), 45.30 (d), 55.89 and 55.96 (q), 79.38 (t), 110.67 (d), 111.24 (d), 118.21 (t), 120.27 (d), 129.36 (s), 133.51 (d), 149.13 and 149.39 (s); MS (m/z, relative intensity, EI) 283 ($M^{\bullet+}$, 25), 223 ($M^{\bullet+}$ – CH_2NO_2, 100).

2-(Allylthio)-1-nitro-2-(3,4,5-trimethoxyphenyl)ethane (7h) was prepared from 3,4,5-trimethoxybenzaldehyde in 72% yield or from 3,4,5-trimethoxy-β-nitrostyrene in 92% yield: crystals from ethanol, mp 57–58 °C; ^{1}H NMR δ 3.06 and 3.17 (ddt, 1 H), 3.84 (s, 3 H), 3.86 (s, 6 H), 4.46 (t, 1 H), 4.72 (d, 2 H), 5.14 and 5.20 (dq, 1 H), 5.80 (ddt, 1 H), 6.45 (s, 2 H); ^{13}C NMR δ 34.73 (t), 45.86 (d), 56.23 (q), 60.83 (q), 79.38 (t), 104.91 (d), 118.47 (t), 132.66 (s), 133.47 (d), 138.10 (s), 153.60 (s); MS (m/z, relative intensity, CI (MH_3)) 314 (MH^+, 76), 194 ($ArC{\equiv}CH^{\bullet+}$, 100). Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.67; H, 6.07; N, 4.47. Found: C, 53.38; H, 6.11; N, 4.32.

2-(Allylthio)-2-(3,4-(methylenedioxy)phenyl)-1-nitroethane (7i) was prepared from 3,4-(methylenedioxy)-β-nitrostyrene in 96% yield (oil): ^{1}H NMR δ 3.03 and 3.12 (ddt, 1 H), 4.44 (t, 1 H), 4.67 and 4.70 (dd, 1 H), 5.12 and 5.18 (dq, 1 H), 5.77 (dddd, 1 H), 5.95 (s, 2 H), 6.75 (m, 2 H), 6.84 (m, 1 H); ^{13}C NMR δ 34.54 (t), 45.38 (d), 79.33 (t), 101.35 (t), 107.84 (d), 108.38 (d), 118.21 (t), 121.51 (d), 130.84 (s), 133.39 (d), 147.70 and 148.21 (s); MS (m/z, relative intensity, CI (methane)) 267 ($M^{\bullet+}$, 37), 148 ($M^{\bullet+}$ – aryl, 100).

2-(Allylthio)-2-(4-chlorophenyl)-1-nitroethane (7j) was prepared from 4-chlorobenzaldehyde (63%) or 4-chloro-β-nitrostyrene (92% yield, oil): ^{1}H NMR δ 3.01 and 3.13 (ddt, 1 H), 4.49 (dd, 1 H), 4.69 and 4.74 (dd, 1 H), 5.12 and 5.19 (dq, 1 H), 5.77 (dddd, 1 H), 7.27 and 7.33 (dt, 2 H); ^{13}C NMR δ 34.61 (t), 44.63 (d), 78.97 (t), 118.52 (t), 129.18 (d), 129.22 (d), 133.18 (d), 134.32 (s), 135.75 (s); MS, (m/z, relative intensity, EI) 257 ($M^{\bullet+}$, 3), 138 ($M^{\bullet+}$ – C_3H_5 – NO_2, 100) accompanied by the ^{37}Cl peaks at 259 and 140.

2-(Allylthio)-1-nitro-2-(2,4,6-trimethylphenyl)ethane (7k) was prepared from 2,4,6-trimethyl-β-nitrostyrene in 87% yield (oil): ^{1}H NMR δ 2.23, 2.37, and 2.48 (s, 3 H), 3.22 (dt, 2 H), 4.77–5.04 (m, 3 H), 5.22 and 5.26 (dq, 1 H), 5.83 (ddt, 1 H), 6.81 (s, 2 H); ^{13}C NMR δ 20.76, 21.03 and 21.16 (q), 36.20 (t), 40.80 (d), 78.63 (t), 118.50 (t), 129.57 (d), 130.93 (s), 131.30 (d), 133.91 (d), 136.33 (s), 136.64 (s), 139.91 (d); MS (m/z, relative intensity, CI, methane) 265 ($M^{\bullet+}$, 10), 192 ($M^{\bullet+}$ – C_3H_5S, 100).

2-(3-Butenylthio)-2-methyl-1-nitrobutane (14a) was prepared from isobutyraldehyde and 3-butenethiol in 59% yield or from 3-methyl-1-nitro-1-butene in 96% yield (oil): ^{1}H NMR δ 0.96 and 1.08 (d, 3 H), 1.98 (d, septet, 1 H), 2.34 (tdt, 2 H), 2.63 (t, 2 H), 3.25 (td, 1 H), 4.47 and 4.58 (dd, 1 H), 5.05 and 5.10 (dq, 1 H), 5.84 (ddt, 1 H); ^{13}C NMR δ 17.82 and 20.18 (q), 30.47 (d), 32.26 (t), 33.96 (t), 50.47 (d), 78.53 (t), 116.38 (t), 136.19 (d); MS (m/z, relative intensity, EI) 203 ($M^{\bullet+}$, <1), 101 ($CH_2{=}S^+$ – C_4H_9, 99), 69 ($C_5H_9^+$, 100).

2-(3-Butenylthio)-1-nitro-2-phenylethane (14b) was prepared from benzaldehyde in 46% or from β-nitrostyrene in 91% yield (oil): ^{1}H NMR δ 2.27 (tdt, 2 H), 2.51 (t, 2 H), 4.58 (dd, 1 H), 4.75 (2d, 2 H), 5.01 and 5.03 (dq, 1 H), 5.73 (ddt, 1 H), 7.30–7.36 (m, 5 H); ^{13}C NMR 30.98 (t), 33.98 (t), 46.61 (d), 79.26 (t), 116.47 (t), 127.60 (d), 128.44 (d), 128.99 (d), 135.68 (d), 137.29 (s); MS (m/z, relative intensity, EI) 237 ($M^{\bullet+}$, 10), 191 ($M^{\bullet+}$ – NO_2, 100).

2-((2-Furylmethyl)thio)-3-methyl-1-nitrobutane (19) was obtained from isobutyraldehyde and furfuryl mercaptan in 84% yield (oil): ^{1}H NMR δ 0.89 and 0.93 (d, 3 H), 1.91 (d septet, 1 H), 3.24 (td, 1 H), 3.76 (s, 2 H), 4.37 and 4.53 (dd, 1 H), 6.24 (dd, 1 H), 6.32 (dd, 1 H), 7.38 (dd, 1 H); ^{13}C NMR δ 17.68 and 19.94 (q), 29.17 (t), 30.27 (d), 49.90 (d), 78.34 (t), 108.31 (d), 110.57 (d), 142.64 (d), 150.80 (s); MS (m/z, relative intensity, CI, methane) 229 ($M^{\bullet+}$, 2), 81 (furyl CH_2^+, 100).

2-(Allylthio)-1-nitro-2-methylpropane (12a) was prepared from acetone in 77% yield (8 h, 80 °C) as an oil: ^{1}H NMR δ 1.50 (s, 6 H), 3.28 (dt, 2 H), 4.52 (s, 2 H), 5.13 (dq, 1 H), 5.25 (dq, 1 H), 5.84 (ddt, 1 H); ^{13}C NMR δ 26.53 (q), 32.17 (t), 44.16 (s), 85.02 (t), 117.87 (t), 134.32 (d); MS (m/z, relative intensity, EI) 175 ($M^{\bullet+}$, 11), 129 ($M^{\bullet+}$ – NO_2, 100).

1-(Allylthio)-1-nitromethylcyclohexane (12b) was prepared from cyclohexanone in 76% yield (8 h, 80 °C) as an oil: ^{1}H NMR δ 1.26 (m, 1 H), 1.55–1.87 (m, 9 H), 3.15 (dt, 2 H), 4.54 (s, 2 H), 5.12 (dq, 1 H), 5.23 (dq, 1 H), 5.85 (ddt, 1 H); ^{13}C NMR 21.37 (t), 25.22 (t), 30.92 (t), 33.34 (t), 49.34 (s), 84.74 (t), 117.81 (t), 134.03 (d); MS (m/z, relative intensity, EI), 215 ($M^{\bullet+}$, 60), 95 ($M^{\bullet+}$ – C_3H_7SH – NO_2, 100).

General Procedure for the Cycloaddition of 7, 12, 14, and 19. 6-Methyl-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10a). To a solution of 0.322 g (2 mmol) of **7a** in 10 mL of dry benzene, containing a few drops of triethylamine, was added 0.714 g (6 mmol) of phenyl isocyanate. The solution was allowed to stand at room temperature for 3 days. Diphenylurea was filtered, benzene was removed in vacuo, and the residue was chromatographed over silica (eluent petroleum ether/ether 2:1) to yield 240 mg (84%) of 1:1 mixture of **9a/10a**.

9a (trans isomer): ^{1}H NMR δ 1.51 (d, J = 7 Hz, 3 H, CH_3), 2.77 (t, J = 10 Hz, 1 H, CH_2S), 3.07 (dd, J = 10, 8 Hz, 1 H, CH_2S), 4.03 (dd, J = 10, 8 Hz, 1 H, CH_2O), 4.07 (qd, J = 7, 1 Hz, 1 H, $CHCH_3$), 4.25 (qdd, J = 10, 8, 1 Hz, 1 H, CH_2CHCH_2), 4.53 (dd, J = 10, 8 Hz, 1 H, CH_2O); ^{13}C NMR δ 23.14 (q, CH_3), 31.63 (t, CH_2S), 34.32 (d, CHMe), 54.65 (d, CH_2CHCH_2), 74.36 (t, CH_2O), 169.87 (s, C=N); MS (m/z relative intensity, mixture of isomers, EI) 144 (MH^+, 100) 143 ($M^{\cdot+}$, 85); 128 ($M^{\cdot+}$ – CH_3, 26), 113 ($M^{\cdot+}$ – CH_2O, 16).

10a (cis isomer): ^{1}H NMR δ 1.59 (d, J = 7 Hz, 3 H, CH_3), 2.81 (dd, J = 10, 9.5 Hz, 1 H, CH_2S), 2.99 (dd, J = 10, 8.5 Hz, 1 H, CH_2S), 4.07 (dd, J = 10, 8 Hz, 1 H, CH_2O), 4.08 (qd, J = 7, 1 Hz, 1 H, CH-Me), 4.20 (tddd, J = 10, 9.5, 8.5, 1 Hz, 1 H, CH_2CHCH_2), 4.53 (dd, J = 10, 8 Hz, 1 H, CH_2O); ^{13}C NMR δ 18.50 (q, CH_3), 30.59 (t, CH_2S), 34.83 (d, *C*HMe), 56.70 (d, CH_2CH CH_2), 75.01 (t, CH_2O), 169.06 (s, C=N).

6-Ethyl-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10b). A 1:1 mixture of **9b/10b** was obtained from nitro sulfide **7b** in 87% yield.

9b (trans isomer): ^{1}H NMR δ 1.03 (t, 3 H), 1.74 and 1.83 (d quintet, 1 H), 2.77 (t, 1 H), 3.03 (dd, 1 H), 3.87 (td, 1 H), 4.02 (dd, 1 H), 4.22 (qdd, 1 H), 4.53 (dd, 1 H); ^{13}C NMR δ 11.74 (q), 30.25 (t), 31.23 (t), 41.40 (d), 55.08 (d), 74.26 (t), 168.80 (s); MS (m/z, relative intensity, mixture of isomers, EI) 158 (M^+, 35), 157 ($M^{\cdot+}$, 99), 128 ($M^{\cdot+}$ – HCO, 100).

10b (cis isomer): ^{1}H NMR δ 1.09 (t, 3 H), 1.83 and 2.13 (ddq, 1 H), 2.75 (t, 1 H), 2.98 (dd, 1 H), 3.96 (ddd, 1 H), 4.02 (dd, 1 H), 4.24 (qdd, 1 H), 4.51 (dd, 1 H); ^{13}C NMR δ 11.40 (q), 26.91 (t), 30.50 (t), 42.12 (d), 57.57 (d), 74.20 (t), 168.56 (s).

6-(1-Methylethyl)-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10c). A 1:1 mixture of **9c/10c** was obtained from nitro sulfide **7c** in 90% yield.

9c (trans isomer): ^{1}H NMR δ 1.04 and 1.06 (d, 3 H), 1.85 (d septet, 1 H), 2.72 (t, 1 H), 3.00 (dd, 1 H), 3.72 (dd, 1 H), 4.03 (dd, 1 H), 4.16 (qdd, 1 H), 4.52 (dd, 1 H); ^{13}C NMR δ 20.00 and 20.13 (q), 31.23 (t), 34.07 (d), 47.48 (d), 55.94 (d), 74.38 (t), 168.40 (s); MS (m/z, relative intensity, mixture of isomers, EI) 171 ($M^{\cdot+}$, 100).

10c (cis isomer): ^{1}H NMR δ 1.02 and 1.08 (d, 3 H), 2.28 (d septet, 1 H), 2.69 (t, 1 H), 2.91 (dd, 1 H), 3.95 (dd, 1 H), 3.96 (dd, 1 H), 4.21 (qdd, 1 H), 4.47 (dd, 1 H); ^{13}C NMR δ 18.66 and 21.43 (q), 30.73 (t), 34.07 (d), 47.88 (d), 58.63 (d), 73.76 (t), 168.18 (s).

6-(1,1-Dimethylethyl)-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10d). A 2:1 mixture of **9d/10d** was formed from nitro sulfide **7c** in 74% yield.

9d (trans isomer): ^{1}H NMR δ 1.04 (s, 9 H), 2.72 (t, 1 H), 2.96 (dd, 1 H) 3.87 (d, 1 H), 3.98 (dd, 1 H), 4.12 (qdd, 1 H), 4.51 (dd, 1 H); ^{13}C NMR δ 27.06 (q), 31.31 (t), 35.00 (s), 52.18 (d), 57.43 (d), 74.54 (t), 168.74 (s); MS (m/z, relative intensity, mixture of isomers, CI, NH_3) 203 ($M^{\cdot+}$, 89), 186 (M^+ – CH_4 – H, 100).

10d (cis isomer) ^{1}H NMR δ 1.14 (s, 9 H), 2.70 (t, 1 H), 2.89 (dd, 1 H), 3.91 (d, 1 H), 4.24 (qdd, 1 H), 4.44 (dd, 1 H); ^{13}C NMR δ 27.35 (q), 30.50 (t), 34.95 (s), 52.52 (d), 59.83 (d), 73.16 (t), 166.96 (s).

6-Phenyl-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10e). A 3:2 mixture of **9e/10e** was obtained from nitro sulfide **7e** in 80% yield. The mixture was separated by careful chromatography over SiO_2 with dichloromethane as the eluent.

9e (trans isomer): ^{1}H NMR δ 2.87 (dd, 1 H), 3.18 (dd, 1 H), 4.11 (dd, 1 H), 4.28 (tddd, 1 H), 4.57 (dd, 1 H), 5.22 (br s, 1 H), 7.27–7.52 (m, 5 H); ^{13}C NMR δ 31.68 (t), 43.33 (d), 55.12 (d), 74.70 (t), 127.19, 127.85 and 128.74 (d), 138.86 (s), 168.03 (s); MS (m/z, relative intensity, CI, NH_3) 223 (MNH_4^+, 53), 206 (MH^+, 100.

10e (cis isomer): ^{1}H NMR δ 3.02 (t, 1 H), 3.13 (dd, 1 H), 4.14 (dd, 1 H), 4.33 (tddd, 1 H),[11a] 4.57 (dd, 1 H), 5.14 (br s, 1 H), 7.25–7.48 (m, 5 H); ^{13}C NMR δ 31.47 (t), 44.24 (d), 56.95 (d), 75.04 (t), 128.16, 128.56 and 128.66 (d), 136.92 (s), 168.22 (s); MS (m/z, relative intensity, CI, NH_3) 223 (MNH_4^+, 100), 206 (M^+, 59).

6-(4-Methoxyphenyl)-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10f). A 3:2 mixture of **9f/10f** was obtained from nitro sulfide **7f** in 83% yield. Careful chromatography over SiO_2 with CCl_4/EtOAc (4:1) separated the isomers.

9f (trans isomer): crystals from chloroform/petroleum ether, mp 112–113 °C; ^{1}H NMR δ 2.90 (dd, 1 H), 3.18 (dd, 1 H), 3.80 (s, 3 H), 4.10 (dd, 1 H), 4.28 (tddd, 1 H), 4.56 (dd, 1 H), 5.19 (s, 1 H), 6.88 and 7.38 (dt, 2 H); ^{13}C NMR δ 31.64 (t), 42.85 (d), 55.19 (d), 55.33 (q), 74.68 (t), 114.13 and 128.39 (d), 130.90 (s), 159.24 (s), 168.36 (s); MS (m/z, relative intensity, CI, NH_3) 253 (MNH_4^+, 68), 236 (M^+, 100). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.28; H, 5.53; N, 5.96. Found: C, 61.40; H, 5.42; N, 5.60.

10f (cis isomer): crystals from methanol, mp 103 °C; ^{1}H NMR δ 2.99 (dd, 1 H), 3.11 (dd, 1 H), 3.78 (s, 3 H), 4.19 (dd, 1 H), 4.29 (tddd, 1 H),[11a] 4.56 (dd, 1 H), 5.12 (s, 1 H), 6.87 and 7.37 (dt, 2 H); ^{13}C NMR δ 31.35 (t), 43.85 (d), 55.29 (q), 56.67 (d), 75.18 (t), 114.05 and 129.89 (d), 128.69 (s), 159.47 (s), 168.33 (s); MS (m/z, relative intensity, CI, NH_3) 253 (MNH_4^+, 70), 236 (MH^+, 100).

6-(3,4-Dimethoxyphenyl)-3,3a,4,6-tetrahydrothiopheno-[3,4-*c*]isoxazole (9–10g). A 3:2 mixture of **9g/10g** was prepared from nitro sulfide **7g** in 75% yield. The mixture was separated chromatographically over SiO_2 with 10:1 CH_2Cl_2/EtOAc as the eluent.

9g (trans isomer): crystals from methanol; mp 99 °C ^{1}H NMR δ 2.86 (dd, 1 H), 3.18 (dd, 1 H), 3.88 and 3.90 (s, 3 H), 4.11 (dd, 1 H), 4.26 (tddd, 1 H), 4.56 (dd, 1 H), 5.18 (br s, 1 H), 6.84 (d, 1 H), 6.97 (d, 1 H), 7.04 (dd, 1 H); ^{13}C NMR δ 31.59 (t), 43.17 (d), 55.05 (d), 55.97 (q), 74.71 (t), 110.62, 111.22 and 119.37 (d), 131.19 (s), 148.77 and 149.15 (s), 168.27 (s); MS (m/z, relative intensity, CI, NH_3) 283 (MNH_4^+, 54), 266 (MH^+, 100). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.87; H, 5.66; N, 5.28. Found: C, 59.01; H, 5.72; N, 5.12.

10g (cis isomer): crystals from methanol, mp 115–116 °C; ^{1}H NMR δ 3.01 (t, 1 H), 3.14 (dd, 1 H), 3.85 and 3.88 (s, 3 H), 4.17 (dd, 1 H), 4.32 (tddd, 1 H), 4.59 (dd, 1 H), 5.14 (br s, 1 H), 6.81 (d, 1 H), 7.00 (m, 2 H); ^{13}C NMR δ 31.26 (t), 44.24(d), 55.93 (q), 56.59 (d), 75.12 (t), 111.05 and 128.79 (d), 128.79 (s), 149.01 (s), 167.99 (s); MS (m/z, relative intensity, CI, NH_3) 283 (MNH_4^+, 100), 266 (MH^+, 97).

6-(3,4,5-Trimethoxyphenyl)-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10h). A 3:2 mixture of **9h/10h** was prepared from nitro sulfide **7h** in 67% yield. The mixture was separated chromatographically over SiO_2 with 3:1 CH_2Cl_2/EtOAc as the eluent.

9h (trans isomer): crystals from methanol, mp 159–60 °C; ^{1}H NMR δ 2.86 (dd, 1 H), 3.18 (dd, 1 H), 3.82 (s, 3 H), 3.88 (s, 6 H), 4.12 (dd, 1 H), 4.24 (tddd, 1 H), 4.57 (dd, 1 H), 5.17 (br s, 1 H), 6.72 (s, 2 H); ^{13}C NMR δ 31.63 (t), 43.67 (d), 54.90 (d), 56.26 (q), 60.82 (q), 74.76 (t), 104.49 (d), 134.00, 137.73 and 153.39 (s), 168.00 (s); MS (m/z, relative intensity, CI, NH_3) 313 (MNH_4^+, 72), 296 (MH^+, 100). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.95; H, 5.76; N, 4.75. Found: C, 57.01; H, 5.82; N, 4.57.

10h (cis isomer): crystals from methanol, mp 89–90 °C; ^{1}H NMR δ 3.03 (t, 1 H), 3.17 (dd, 1 H), 3.83 (s, 3 H), 3.87 (s, 6 H), 4.18 (dd, 1 H), 4.35 (tddd, 1 H), 4.61 (dd, 1 H), 5.12 (br s, 1 H), 6.72 (s, 2 H); ^{13}C NMR δ 31.33 (t), 44.73 (d), 56.16 (q), 56.76 (d), 60.75 (q), 105.88 (d), 128.72, 131.73 and 153.19 (s), 167.62 (s); MS (m/z, relative intensity, CI, NH_3), 313 (MNH_4^+, 77), 296 (MH^+, 100).

6-(3,4-(Methylenedioxy)phenyl)-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10i). A 3:2 mixture of **9i/10i** was prepared from nitro sulfide **7i** in 70% yield. The mixture was separated chromatographically over SiO_2 with CH_2Cl_2 as the eluent.

9i (trans isomer): crystals from methanol, mp 90–91 °C; ^{1}H NMR δ 2.80 (t, 1 H), 3.13 (dd, 1 H), 4.04 (dd, 1 H), 4.26 (qdd, 1 H), 4.51 (dd, 1 H), 5.11 (br s, 1 H), 5.93 (s, 2 H), 6.74 (d, 1 H), 6.88 (dd, 1 H), 6.93 (d, 1 H); ^{13}C NMR δ 31.62 (t), 43.19 (d), 55.11 (d), 74.66 (t), 101.27 (t), 107.72, 108.16 and 120.48 (d), 132.73, 147.24, 147.98 (s), 168.18 (s); MS (m/z, relative intensity, CI, NH_3) 267 (MNH_4^+, 71), 250 (MH^+, 100). Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.83; H, 4.42; N, 5.62. Found: C, 57.88; H, 4.43; N, 5.36.

10i (cis isomer): crystals from methanol, mp 118–119 °C; ^{1}H NMR δ 2.96 (t, 1 H), 3.08 (dd, 1 H), 4.12 (dd, 1 H), 4.25 (qdd, 1 H), 4.52 (dd, 1 H), 5.07 (s, 1 H), 5.92 (s, 2 H)8 6.73 (d, 1 H),

6.87 (dd, 1 H), 6.98 (d, 1 H); ^{13}C NMR δ 31.31 (t), 44.19 (d), 56.59 (d), 75.08 (t), 101.21 (t), 107.84, 108.84 and 122.23 (d), 130.47, 147.52, and 147.84 (s), 168.12 (s); MS (*m/z*, relative intensity, CI, NH_3) 267 (MNH_4^+, 37), 250 (MH^+, 100).

6-(4-Chlorophenyl)-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (9–10j). A 3:2 mixture of **9j/10j** was prepared from nitro sulfide **7j** in 62% yield. The mixture was separated chromatographically over SiO_2 with CH_2Cl_2 as the eluent.

9j (trans isomer): crystals from methanol, mp 68 °C; ^{1}H NMR δ 2.87 (dd, 1 H), 3.18 (dd, 1 H), 4.12 (dd, 1 H), 4.24 (qdd, 1 H), 4.58 (dd, 1 H), 5.18 (br s, 1 H), 7.33 and 7.41 (dt, 2 H); ^{13}C NMR δ 31.71 (t), 42.86 (d), 54.98 (d), 74.76 (t), 128.65 and 128.88 (d), 135.46 and 137.37 (s), 167.86 (s); MS (*m/z*, relkative intensity, CI, NH_3) 257 (MNH_4^+, 47), 240 (MH^+, 100). Anal. Calcd for $C_{11}H_{10}ClNOS$: C, 55.11; H, 4.18. Found: C, 55.39; N, 4.48.

10j (cis isomer): crystal from methanol, mp 110–112 °C; ^{1}H NMR δ 3.03 (t, 1 H), 3.16 (dd, 1 H), 4.19 (dd, 1 H), 4.29 (qdd, 1 H),[11a] 4.61 (dd, 1 H), 5.12 (br s, 1 H), 7.32 and 7.41 (dt, 2 H); ^{13}C NMR δ 31.48 (t), 43.55 (d), 56.71 (d), 75.11 (t), 128.74 and 130.08 (d), 133.79 and 133.99 (s), 167.78 (s) MS (*m/z*, relative intensity, EI) 239 ($M^{\bullet+}$, 92), 155 ($ArC{\equiv}S^+$, 100).

6-(2,4,6-Trimethylphenyl)-3,3a,4,6-tetrahydrothiopheno-[3,4-*c*]isoxazole (9–10k). A 5:2 mixture of **9k/10k** was obtained from nitro sulfides **7k** in 87% yield.

9k (trans isomer): ^{1}H NMR δ 2.23 (s, 3 H), 2.43 (s, 6 H), 3.01 (m, 2 H), 3.96 (dd, 1 H), 4.57 (dd, 1 H), 4.66 (m, 1 H),[11b] 5.62 (d, 1 H), 6.82 (s, 2 H); ^{13}C NMR δ 20.77 and 21.06 (q), 32.96 (t), 40.43 (d), 60.04 (d), 74.40 (dd), 130.01 (d), 130.11, 136.91 and 137.68 (s), 173.53 (s); MS (*m/z*, relative intensity, mixture of isomers, CI, CH_4) 248 (MH^+, 100), 128 (M^+ – Ar, 27). Anal. (mixture) Calcd $C_{14}H_{17}NOS$: $C_{14}H_{17}NO_s$: C, 68.02; H, 6.88. Found: C, 67.75; H, 7.13.

10k (cis isomer): ^{1}H NMR δ 2.23 (s, 3 H), 2.42 (s, 6 H), 3.12 (m, 2 H), 4.15 (dd, 1 H), 4.39 (m, 1 H),[11a] 4.59 (dd, 1 H), 5.76 (br s, 1 H), 6.82 (s, 2H) ^{13}C NMR 20.77 and 21.06 (q), 31.67 (t), 38.43 (d), 58.07 (d), 74.83 (t), 130.01 (d), 130.11, 136.91 and 137.68 (s), 166.76 (s).

6,6-Dimethyl-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (13a). Compound **13a** was obtained, starting from nitro sulfide **12a**, as an oil in 65% yield after chromatography (silica gel, petroleum ether/ether 2:1): ^{1}H NMR δ 1.64 and 1.70 (s, 6 H), 2.82 (dd, 1 H), 3.08 (dd, 1 H), 4.07 (dd, 1 H), 4.37 (tdd, 1 H), 4.57 (dd, 1 H); ^{13}C NMR δ 27.57 and 31.25 (q), 30.62 (t), 45.63 (s), 55.44 (d), 76.26 (t), 171.92 (s); MS (*m/z*, relative intensity, EI) 158 (MH^+, 100), 157 ($M^{\bullet+}$, 47).

6,6-Pentamethylene-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazole (13b). Compound **13b** was obtained from nitro sulfide **12b** in 71% yield after crystallization from chloroform/hexane, mp 88–89 °C: ^{1}H NMR δ 1.30–1.70 (m, 5 H), 1.80–200 (m, 4 H), 2.06–2.17 (m, 1 H), 2.76 (dd, 1 H), 2.99 (dd, 1 H), 4.02 (dd, 1 H), 4.35 (tdd, 1 H), 4.51 (dd, 1 H); ^{13}C NMR δ 23.18, 24.57, 25.12, 30.27, 36.81 and 39.77 (t), 52.10 (s), 56.06 (d), 74.26 (t), 171.78 (s); MS (*m/z*, relative intensity, EI) 198 (MH^+, 100), 197 ($M^{\bullet+}$, 41). Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.91; H, 7.61. Found: C, 61.19; H, 7.79.

7-Isopropyl-3,3a,4,5-tetrahydro-2*H*-thiopyrano[3,4-*c*]isoxazole (15–16a). A 7:2 mixture of **15a/16a** was obtained as an oil in 84% yield, starting from nitro sulfide **14a**.

15a (cis isomer): ^{1}H NMR δ 1.11 and 1.16 (d, 3 H), 1.91 (qd, 1 H), 2.38–2.48 (m, 2 H), 2.49 (d septet, 1 H), 2.73 (dt, 1 H), 2.89 (td, 1 H), 3.07–3.19 (m, 1 H), 3.52 (dd, 1 H), 3.90 (dd, 1 H), 4.48 (dd, 1 H); ^{13}C NMR δ 19.38 and 21.30 (q), 28.42 (t), 28.86 (d), 36.05 (t), 48.48 (d), 49.56 (d), 73.37 (t), 157.05 (s); MS (*m/z*, relative intensity, mixture of isomers, EI) 185 ($M^{\bullet+}$, 35), 142 ($M^{\bullet+}$ – C_3H_7, 100).

16a (trans isomer): ^{1}H NMR δ 1.04 and 1.19 (d, 3 H), 2.05 (m, 1 H), 2.38–2.54 (m, 2 H), 2.70–2.92 (m, 2 H), 3.14–3.26 (m, 1 H), 3.26 (d, 1 H), 3.95 (t, 1 H), 4.47 (dd, 1 H); ^{13}C NMR δ 20.66 and 21.07 (q), 23.61 (t) 29.06 (d), 36.30 (t), 45.00 (d), 45.29 (d), 73.63 (t), 157.63 (s).

7-Phenyl-3,3a,4,5-tetrahydro-2*H*-thiopyrano[3,4-*c*]isoxazole (15b, 16b). A 3:2 mixture of **15b:16b** was obtained in 71% yield from nitro sulfide **14b**. The two isomers were separated upon rechromatography over silica gel with dichloromethane as the eluent.

15b (cis isomer): crystals from methanol, mp 119 °C; ^{1}H NMR δ 2.01 (dddd, 1 H), 2.52 (dddd, 1 H), 2.80 (dddd, 1 H), 3.03 (ddd, 1 H), 3.30 (dddd, 1 H), 4.00 (dd, 1 H), 4.59 (s, 1 H), 7.30–7.50 (m, 5 H); ^{13}C NMR δ 29.91 (t), 35.49 (t), 45.68 (d), 49.03 (d), 74.08 (t), 128.38, 128.46 (d), 136.35 (s), 156.37 (s, C=N); MS (*m/z*, relative intensity, CI, NH_3) 237 (MNH_4^+, 9), 220 (MH^+, 100). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.75; H, 5.94; N, 6.3. Found: C, 65.48; H, 5.98; N, 6.77.

16b (trans isomer): crystals from methanol, mp 99 °C; ^{1}H NMR δ 2.01 (dtd, 1 H), 2.35 (ddt, 1 H), 2.51 (ddd, 1 H), 2.73 (ddd, 1 H), 3.17 (dddd, 1 H), 3.98 (dd, 1 H), 4.52 (dd, 1 H), 5.08 (s, 1 H), 7.28–7.62 (m, 5 H); ^{13}C NMR δ 24.38 (t), 35.96 (t), 40.96 (d), 44.55 (d), 74.02 (t), 127.50, 127.57 and 128.83 (d), 136.15 (s), 156.60 (s); MS (*m/z*, relative intensity, CI, NH_3) 237 (MNH_4^+, 9), 220 (MH^+, 100).

6-Isopropyl-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]furano-[2,3-*d*]isoxazole (20). A 1:1 mixture of *cis*- and *trans*-**20** was obtained from nitro sulfide **19** in 90% yield after chromatography over silica gel, with 3:2 petroleum ether/ether as the eluent.

***trans*-20**: ^{1}H NMR δ 1.02 and 1.07 (d, 3 H), 2.02 (d septet, 1 H), 3.15 (d, 2 H), 3.73 (d, 1 H), 5.36 (t, 1 H), 5.64 (dd, 1 H), 6.67 (dd, 1 H); ^{13}C NMR δ 20.65 and 20.79 (q), 33.90 (d), 34.64 (t), 48.72 (d), 90.28 (d), 101.22 (d), 106.58 (s), 149.33 (d), 161.93 (s); MS (*m/z*, relative intensity, mixture of isomers, CI, NH_3) 229 (MNH_4^+, 23), 212 (MH^+, 100).

***cis*-20**: ^{1}H NMR δ 1.10 and 1.16 (d, 3 H), 2.34 (d septet, 1 H), 3.08 (s, 2 H), 4.04 (d, 1 H), 5.34 (t, 1 H), 5.58 (dd, 1 H), 6.65 (dd, 1 H); ^{13}C NMR δ 19.57 and 21.44 (q, CH_3), 30.62 (d), 33.47 (t), 47.99 (d), 88.92 (d), 101.42 (d), 107.70 (s), 149.30 (d), 161.28 (s).

Thiophene Dioxide 21b.[10] To a stirred solution of 157 mg (1 mmol) of cyclic sulfide **9b** and 111 mg (1 mmol) of SeO_2 in 10 mL of CH_3OH at 0 °C was added 1 mL (10 mmol) of 30% hydrogen peroxide solution. After 1 h, the ice bath was removed and the mixture was left overnight. Water was added and the aqueous phase was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with water, dried over $MgSO_4$, and evaporated to give the crude sulfone as a white solid. Recrystallization from benzene/hexane gave **21b** in 63% yield, mp 107 °C. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.44; H, 5.82; N, 7.41. Found: C, 44.07; H, 5.75; N, 7.09.

Thiophene dioxide 21e was prepared analogously from **9e** in 67% yield after recrystallization from methanol, mp 201 °C. Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.67; H, 4.64; N, 5.91. Found: C, 55.41; H, 4.75; N, 5.68.

***cis*-3-Amino-4-(hydroxymethyl)-*trans*-2-(4-methoxyphenyl)tetrahydrothiophene (22).** A solution of 0.47 g (2 mmol) of **9e** in 10 mL of anhydrous ether was added dropwise at room temperature to 0.16 g (4 mmol) of $LiAlH_4$ suspended in 10 mL of anhydrous ether. The mixture was refluxed for 6 h, cooled, and quenched by dropwise addition of 10 mL of concentrated Na_2SO_4 solution. The reaction mixture was extracted with ether. The organic extracts were combined, dried over $MgSO_4$, and evaporated, giving crude amino alcohol which was recrystallized from ethanol in 85% yield, mp 122–123 °C: ^{1}H NMR δ 2.57 (m, 1 H), 2.65 (br, 3 H), 2.85 (dd, 1 H), 3.15 (dd, 1 H), 3.64 (dd, 1 H), 3.80 (s, 3 H), 3.83 (dd, 1 H), 4.00 (dd, 1 H), 4.20 (d, 1 H), 6.87 (dt, 2 H), 7.37 (dt, 2 H); ^{13}C NMR δ 30.16 (t), 44.98 (d), 55.30 (q), 58.00 (d), 62.73 (t), 66.14 (d), 113.97 (d), 129.01 (d), 132.23 (s), 159.00 (s); MS (*m/z*, relative intensity, CI, NH_3) 240 (MH^+, 100). Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.25; H, 7.11; N, 5.86. Found: C, 60.42; H, 7.31; N, 5.71.

4-Amino-*cis*-3-(hydroxymethyl)thiaspiro[4.5]decane (23) was prepared analogously from **13b** in 77% yield after recrystallization from methanol, mp 103 °C: ^{1}H NMR δ 1.20–1.90 (m, 10 H), 2.59 (m, 1 H), 2.75 (br, 3 H), 2.79 (dd, 1 H), 3.07 (t, 1 H)8 3.18 (dd, 1 H), 4.06 (dd, 1 H); ^{13}C NMR δ 23.30 (t), 24.84 (t), 25.68 (t), 28.66 (t), 34.18 (t), 40.15 (t), 44.99 (d), 45.99 (s), 62.69 (t), 65.78 (d); MS (*m/z*, relative intensity, CI, NH_3) 202 (MH^+, 63), 184 ($M^{\bullet+}$ – OH, 100). Anal. Calcd for $C_{10}H_{19}NOS$: C, 59.70; H, 9.45. Found: C, 59.46; H, 9.08.

3-(Hydroxymethyl)-1-(4-methoxyphenyl)-2-butanone (24). A mixture of 50 mg (0.21 mmol) of **9e**, 100 mg of Raney nickel, and 100 mg of boric acid in 10 mL of methanol was stirred overnight at room temperature under a hydrogen atmosphere. The reaction mixture was filtered, and the filter cake was washed with MeOH. The combined filtrates were concentrated, and the residue was partitioned between ether and water. The organic phase was dried with $MgSO_4$ and concentrated. The resulting crude oil was

chromatographed over SiO_2 with 20:1 CH_2Cl_2/MeOH to yield 66% of **24** as an oil: ^1H NMR δ 1.13 (d, 3 H), 2.87 (quintet of d, 1 H), 3.64 (dd, 1 H), 3.72 (s, 2 H), 3.73 (dd, 1 H), 3.79 (s, 3 H), 6.87 (dt, 2 H), 7.11 (dt, 2 H; ^{13}C NMR δ 13.32 (q), 47.15 (t), 48.05 (d), 55.27 (q), 64.50 (t), 114.22 (d), 125.80 (s), 130.47 (d), 158.74 (s); MS (*m/z*, relative intensity, EI) 208 ($M^{\bullet+}$, 27), 122 ($ArCH_2^+$, 100).

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Supplementary Material Available: ^{13}C NMR (δ) spectra for compounds **7a–c,e,g,i–k**, **9 + 10 (a–d)**, **9e**, **10e–g,i,j**, **12a,b**, **13a,b**, **14b**, **15a + 16a**, **15b**, **16b**, **19**, **20**, and **24** (30 pages). Ordering information is given on any current masthead page.

Structure–Reactivity Aspects of Nitroalkyl Acetate Hydrolysis[1a]

David E. Gallis,[1b] Bruce J. Acken, James A. Warshaw, A. Lee Richardson, and DeLanson R. Crist*

Department of Chemistry, Georgetown University, Washington, D.C. 20057

Dorothy A. Cichra

Energetic Materials Division, Naval Surface Warfare Center, Silver Spring, Maryland 20903-5000

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In the first systematic study of hydrolysis of nitroalkyl esters, it was found that hydrolysis of seven dinitro- and trinitroalkyl acetates follow first-order kinetics in the presence of either strong acid ($HClO_4$) or acetate (A^-) buffers. The observed rate constant is given by

$$k_{obs} = k_o + k_H[H^+] + k_{OH}[OH^-] + k_A[A^-]$$

in water at 60 °C at constant (0.2 M) ionic strength. Values of k_H correlate with σ^* and various spectral parameters of the esters taken as measures of the electronic effects of the alkyl group. The value of ρ^* of -0.33 ± 0.03 is consistent with a prior protonation step which is more sensitive to these structural changes than later steps. In contrast, k_{OH} does not correlate with σ^*, $\delta_{^{13}C=O}$ $\delta_{O^{13}CH_2}$, δ_{OCH_2}, or $\nu_{C=O}$. The most likely explanation at the present time for noncorrelation is an enhanced reactivity caused by trinitro substitution.

Although the subject of some of the earliest kinetic studies, the mechanism of ester hydrolysis[2,3] is by no means completely understood. While most authors consider transition states for alkaline hydrolysis similar in structure to tetrahedral intermediates,[4] deuterium[5] and heavy atom[6] isotope effects favor more sp^2-hybridized species mostly due to the desolvation energy of OH^-.[5,7] Also, while OH^- is usually considered a nucleophile, it may function as a

Table I. Nitroalkyl Acetates and σ^* Values[a]

symbol	ester	σ^*
1	CY_3CH_2OAc	1.62[b,c]
2	$CH_3CY_2CH_2OAc$	0.99[b,d]
3	$CY_3CH_2CH_2OAc$	0.579[b,e]
4	$CH_3CY_2CH_2CH_2OAc$	0.352[e]
5	$CY_3CH_2CH_2CH_2OAc$	0.207[b]
6	CFY_2CH_2OAc	1.57[b,f]
7	$CFY_2CH(CH_3)OAc$	1.55[g]

[a] In formulas of esters, Y represents NO_2. σ^* is the value for the entire nitroalkyl group (relative to 0.00 for methyl) determined experimentally, either directly or on a homologue, except for the value for ester **7** which was calculated. [b] A damping factor of 2.8 for inserted CH_2[9d] was used with a σ^* determined for an analogue. [c] Reference 36. [d] Reference 42a. [e] Hine, J.; Bailey, W. C., Jr. *J. Org. Chem.* **1961**, *26*, 2098–2099. [f] Kaplan, L. A.; Pickard, H. B. *J. Org. Chem.* **1970**, *35*, 2044–2045. [g] Calculated from σ^* for **6** according to Perrin, D. D.; Dempsy, B.; Serjeant, E. P. *pK_a Prediction for Organic Acids and Bases*; Chapman and Hall: New York, 1981.

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