(m, 2 H), 3.19 (d, 0.8 H, $J$ = 12.2 Hz), 2.69 (m, 0.2 H), 2.42 (dt, 0.8 H, $J$ = 12.9, 4.9 Hz), 1.90–1.46 (complex, 11 H), 1.31 and 1.29 (2 t, 3 H, $J$ = 7.2 Hz), 1.07 and 1.01 (2 d, 3 H, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 208.8, 178.3, 170.2, 121.3, 102.1, 62.4, 60.8, 60.1, 55.8, 38.5, 38.4, 38.0, 36.7, 36.5, 34.0, 30.2, 27.3, 26.9, 25.8, 25.4, 24.9, 21.0, 14.2; HRMS $m/e$ for $C_{14}H_{22}O_3$ calcd 238.1569, found 238.1577.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.82; H, 9.39.

**Representative Procedure for Methylation of the 6-Membered Cyclic $\beta$-Keto Ester Derivatives. (1*R**,6*R**)-Ethyl 1,6-Dimethyl-2-oxocyclohexanecarboxylate (11).** Ethanolic sodium ethoxide was prepared by dissolving 0.104 g (4.50 g-atom) of sodium metal in 5 mL of absolute EtOH. The solution was cooled to 20 °C, a 2-mL absolute EtOH solution of 0.55 g (3.00 mmol) of **6** was added dropwise, and the mixture was stirred for 30 min. To the resulting yellow solution was added 2.13 g (15.0 mmol) of methyl iodide, and the reaction was stirred at 20 °C for 12 h. The crude reaction mixture was concentrated in vacuo, diluted with 0.5 M HCl, and extracted (2×) with ether. The combined ether extracts were washed with water, $Na_2S_2O_3$, water, and NaCl, dried ($MgSO_4$), and concentrated under vacuum. The crude product, containing a 93:7 mixture of trans–cis alkylation products (GC analysis), was separated on one 20-cm × 20-cm PTLC plate eluted with increasing concentrations of ether in hexane to give the pure trans isomer: 0.42 g (2.10 mmol, 70%); IR, $^1$H NMR, $^{13}$C NMR, and HRMS matched those reported[18e] previously.

**(1*R**,6*R**)-Ethyl 6-ethyl-1-methyl-2-oxocyclohexanecarboxylate (12)**: isolated from a 93:7 trans–cis mixture; 0.43 g (2.04 mmol, 68%); IR (thin film) 1740, 1718, 1380 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.14 (q, 2 H, $J$ = 7.1 Hz), 2.75 (dt, 1 H, $J$ = 14.0, 7.4 Hz), 2.45 (dm, 1 H, $J$ = 14.0 Hz), 2.07 (m, 1 H), 1.92 (m, 1 H), 1.80–1.50 (complex, 2 H), 1.50–1.20 (complex, 2 H), 1.35 (s, 3 H), 1.25 (t, 3 H, $J$ = 7.1 Hz), 0.94 (t, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 208.5, 171.3, 61.0, 60.9, 51.0, 40.0, 26.2, 25.3, 23.8, 18.7, 14.1, 13.2; HRMS $m/e$ for $C_{12}H_{20}O_3$ calcd 212.1412, found 212.1415.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 68.18; H, 9.61.

**(1*R**,6*R**)-Ethyl 6-butyl-1-methyl-2-oxocyclohexanecarboxylate (13)**: isolated from a 95:5 trans–cis mixture; 0.50 g (2.07 mmol, 69%); IR (thin film) 1741, 1720, 1380 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.13 (q, 2 H, $J$ = 7.2 Hz), 2.71 (dt, 1 H, $J$ = 14.1, 7.3 Hz), 2.42 (dm, 1 H, $J$ = 14.1 Hz), 2.04 (m, 1 H), 1.88 (m, 1 H), 1.80–1.50 (complex, 3 H), 1.45–1.08 (complex, 6 H), 1.33 (s, 3 H), 1.24 (t, 3 H, $J$ = 7.2 Hz), 0.89 (t, 3 H, $J$ = 7.3 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 208.5, 171.4, 61.0, 60.9, 49.1, 40.1, 30.9, 30.7, 27.0, 25.4, 22.8, 18.8, 14.1, 14.0; HRMS $m/e$ for $C_{14}H_{24}O_3$ calcd 240.1725, found 240.1724.

Anal. Calcd for $C_{14}H_{24}O_3$: C, 70.00; H, 10.00. Found: C, 69.95; H, 10.13.

**(1*R**,6*S**)-Ethyl 1-methyl-2-oxo-6-phenylcyclohexanecarboxylate (14)**: isolated from a 99:1 trans–cis mixture; 0.55 g (2.10 mmol, 70%); mp 51–52 °C; IR (thin film) 3090, 3070, 3035, 1741, 1715, 1602, 1498, 1380 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.36–7.16 (complex, 5 H), 4.04 (m, 2 H), 3.07 (dt, 1 H, $J$ = 14.1, 7.5 Hz), 2.73 (m, 2 H), 2.54 (dm, 1 H, $J$ = 14.1 Hz), 2.19 (m, 1 H), 1.94–1.68 (complex, 2 H), 1.24 (s, 3 H), 1.12 (t, 3 H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 207.9, 170.6, 140.4, 128.9, 128.0, 127.2, 61.7, 61.1, 55.3, 39.8, 28.0, 25.4, 19.1, 13.9; HRMS $m/e$ for $C_{16}H_{20}O_3$ calcd 260.1412, found 260.1410.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69. Found: C, 73.85; H, 7.66.

**(1*R**,6*S**)-Ethyl 6-ethenyl-1-methyl-2-oxocyclohexanecarboxylate (15)**: isolated from a 93:7 trans–cis mixture; 0.43 g (2.04 mmol, 68%); IR (thin film) 3060, 1730, 1709, 1632, 1368, 995, 911 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.09 (m, 1 H), 5.07 (d, 1 H, $J$ = 10.1 Hz), 5.03 (d, 1 H, $J$ = 16.1 Hz), 4.16 (q, 2 H, $J$ = 7.1 Hz), 2.68 (dt, 1 H, $J$ = 13.7, 6.1 Hz), 2.45 (dm, 1 H, $J$ = 13.7 Hz), 2.09 (m, 3 H), 1.70 (m, 2 H), 1.29 (s, 3 H), 1.28 (t, 3 H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 207.2, 171.2, 137.8, 116.6, 61.0, 60.0, 54.0, 39.9, 28.4, 25.5, 19.1, 14.0; HRMS $m/e$ for $C_{12}H_{18}O_3$ calcd 210.1256, found 210.1257.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.48; H, 8.59.

**(1*R**,6*R**)-Ethyl 1,3,3,6-tetramethyl-2-oxocyclohexanecarboxylate (18)**: isolated from a 90:10 trans–cis mixture; 0.23 g (1.00 mmol, 33%); IR (thin film) 1738, 1705, 1380, 1370 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.03 (m, 2 H), 2.00 (m, 1 H), 1.70 (m, 1 H), 1.54 (m, 3 H), 1.28 (s, 3 H), 1.16 (t, 3 H, $J$ = 7.1 Hz), 1.11 (d, 3 H, $J$ = 6.8 Hz), 1.06 (s, 3 H), 1.04 (s, 3 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 212.4, 171.5, 60.6, 58.8, 45.0, 41.6, 38.5, 27.8, 26.6 (2), 21.3, 16.8, 14.0; HRMS $m/e$ for $C_{13}H_{22}O_3$ calcd 226.1569, found 226.1576.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.02; H, 9.73. Found: C, 68.92; H, 9.88.

**(7*R**,8*R**)-Ethyl 7,8-dimethyl-6-oxospiro[4.5]decane-7-carboxylate (19)**: isolated from a 91:9 trans–cis mixture; 0.47 g (1.86 mmol, 62%); IR (thin film) 1740, 1705, 1372 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.09 (m, 2 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.83 (m, 1 H), 1.79–1.55 (complex, 10 H), 1.36 (s, 3 H), 1.23 (t, 3 H, $J$ = 7.1 Hz), 1.15 (d, 3 H, $J$ = 6.7 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 212.1, 171.4, 60.6, 59.2, 56.3, 41.0, 37.8, 37.7, 36.1, 27.3, 25.2, 24.8, 21.2, 16.8, 14.0; HRMS $m/e$ for $C_{15}H_{24}O_3$ calcd 252.1725, found 252.1716.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.43; H, 9.52. Found: C, 71.45; H, 9.69.

**Acknowledgment.** The authors thank the Oklahoma Center for the Advancement of Science and Technology (HR1-035) for support of this work. Finally, partial support by NSF grant DMB-8603864 and OCAST grant 1506 for the upgrade of our 300-MHz NMR and NSF grant BSS-8704089 for our mass spectrometry facility is acknowledged with gratitude.

**Registry No.** 1, 126761-20-4; (*Z*)-1, 144192-19-8; 2, 144192-20-1; (*Z*)-2, 144192-21-2; 3, 103621-29-0; (*Z*)-3, 103621-30-3; 4, 144192-22-3; (*Z*)-4, 144192-23-4; 5, 144192-24-5; (*Z*)-5, 144192-25-6; 6, 58019-68-4; 6 enol, 144192-26-7; 7, 144192-27-8; 7 enol, 144192-28-9; 8, 144192-29-0; 8 enol, 144192-30-3; 9, 144192-31-4; 9 enol, 144192-32-5; 10, 73392-80-0; 10 enol, 144192-33-6; 11, 144192-34-7; *cis*-11, 144192-35-8; 12, 144192-36-9; *cis*-12, 144192-37-0; 13, 144192-38-1; *cis*-13, 144192-40-5; 14, 144192-39-2; 15, 144192-41-6; *cis*-15, 144192-42-7; 16, 144192-43-8; 16 enol, 144192-44-9; 17, 144192-45-0; 17 enol, 144192-46-1; 18, 144192-47-2; *trans*-18, 144192-48-3; 19, 144192-49-4; *trans*-19, 144192-50-7; $EtO_2C(CH_2)_3CH{=}CH_2$, 54653-25-7; $EtO_2C(CH_2)_3CHO$, 22668-36-6; $Ph_3P{=}CHCO_2Et$, 1099-45-2; $Ph_3P{=}C(Me)CO_2Et$, 5717-37-3; $EtO_2C(CH_2)_3COCH_3$, 13984-57-1; $EtO_2CCH_2P(O)(OEt)_2$, 867-13-0; $EtO_2CCH(CH_3)_2$, 97-62-1; $Br(CH_2)_3CH{=}CH_2$, 5162-44-7; MeMgCl, 676-58-4; EtMgCl, 2386-64-3; *n*-BuMgCl, 693-04-9; PhMgCl, 100-59-4; $CH_2{=}CHMgCl$, 3536-96-7; $CH_2{=}CHMgBr$, 1826-67-1; *n*-BuLi, 109-72-8; *n*-BuMgBr, 693-03-8; CuCl, 7758-89-6; CuI, 7681-65-4; CuCN, 544-92-3; ethyl cyclopentanecarboxylate, 5453-85-0.

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## Synthesis of Thiiranecarboxylic Esters from Cysteine and Cystine Esters

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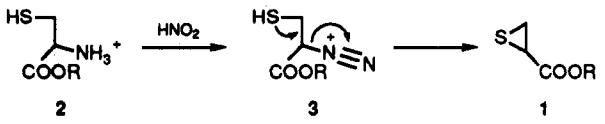
*Received July 14, 1992*

For many years it was thought that thiiranecarboxylic esters (thioglycidic esters, $\alpha,\beta$-epithioesters, **1**) were unstable. Attempts to prepare them[1] had produced instead a variety of isomeric mercaptoacrylates, dithianes, low polymers, and desulfurization products. In 1967 it was

(1) (a) Culvenor, C. C. J.; Davies, W.; Heath, N. S. *J. Chem. Soc.* **1949**, 278. (b) Culvenor, C. C. J.; Davies, W.; Maclaren, J. A.; Nelson, P. F.; Savige, W. E. *J. Chem. Soc.* **1949**, 2573. (c) Owen, T. C.; Gladys, C. L.; Field, L. *J. Chem. Soc.* **1962**, 501. (d) Owen, T. C.; Gladys, C. L.; Field, L. *J. Chem. Soc.* **1962**, 656. (e) Tung, C. C.; Speziale, A. J. *J. Org. Chem.* **1964**, *29*, 1577. Mueller, W. H. *J. Org. Chem.* **1969**, *34*, 2955.

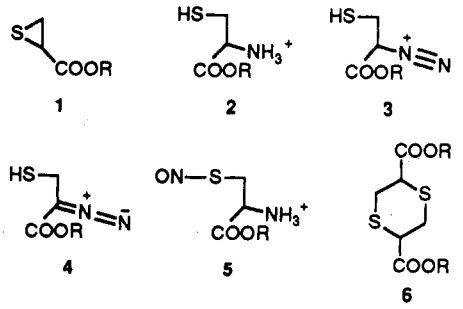
0022-3263/92/1957-6985$03.00/0 

Scheme I



2 3 1

reported that the corresponding amides could be obtained by treating α-chloro-β-thiolactones with ammonia or amines.[2] Extension of the work soon provided the related esters and the free thioglycidic acids.[3] A few years later, optically active forms of these compounds were reported to be produced in a state of high optical purity upon treating cysteine esters 2 with nitrous acid.[4]



1 2 3 4 5 6

We have had occasion to repeat certain of these conversions. The preparations do proceed as described and the compounds are reasonably stable. However, the preparations from cysteine esters exhibit a number of unexpected characteristics. These constitute the subject of the work reported here.

The conversion in question might appear to be merely a matter of diazotization of the amine followed by $S_Ni$ expulsion of nitrogen (Scheme I) from the diazonium thiol 3.[4,5] Pathways involving a diazoacetic ester (4) are excluded by the optical purity of the products as well as by the nonincorporation of deuterium into products from reactions carried out in deuterium oxide. But the use of 3 mol of nitrite per mol of amino thiol is repeatedly specified; the simple diazonium displacement pathway requires no more than 1 mol. It is specified also that the nitrite is added in one portion, all at once, and, it seems, as the solid salt. No explanation is offered for the use of the 3-fold excess or for the addition in one portion. Further, despite repeated descriptions of deep red and deep green colorations in the reactions of cysteine and penicillamine derivatives, respectively, thionitrites, of which such colors are characteristic,[6,7] are not mentioned. It is comprehensively documented[7] that thiols react with nitrous acid and other nitrosating agents much faster than amines do. A particularly careful study[8] reported near-quantitative yields of cystine from cysteine upon reaction with limited amounts (0.5 mol) of nitrous acid. It would seem, therefore, that any reaction of a cysteine ester with a large excess of nitrite could not give diazonium thiol 3. Additionally, while the synthesis provides chiral epithioesters of very high optical purity, the chemical yields are poor and variable (5–50%). It became our purpose to explore and account for all of these matters.[9]

## Results

Upon adding solid sodium nitrite (3 mol) to ice-cold cysteine ethyl ester hydrochloride in hydrochloric acid, a deep red color characteristic of thionitrite developed and faded. Solvent extraction afforded a pale yellow oil out of which was volatilized the thioglycidate 1 (R = Et) (40%) as a colorless mobile liquid. These observations are as previously reported.[4] The bulb residue (44%), a viscous yellow oil, exhibited an NMR spectrum consistent with its being a low polymer or a cyclic dimer such as dithiane 6 (R = Et). Smaller proportions of nitrite gave lower yields of solvent-extractable products. Two moles, for example, gave 10% 1 and 15% polymer while 1 mol gave even less. Additional solvent-extractable products, mainly polymer, formed when the reaction mixtures were allowed to stand exposed to air. A large number of experiments in which the nitrite was added portionwise (solid) or dropwise (solution), and others in which acid was added to solutions containing nitrite and cysteine, produced much less satisfactory results and revealed exasperatingly irrational variability and irreproducibility. Diluting the reaction mixtures or reducing the proportion of acid brought about no useful change. Concentrating them, as by conducting reactions in 3 M acid, led to temperature control problems and to significantly lowered yields of thioglycidate.

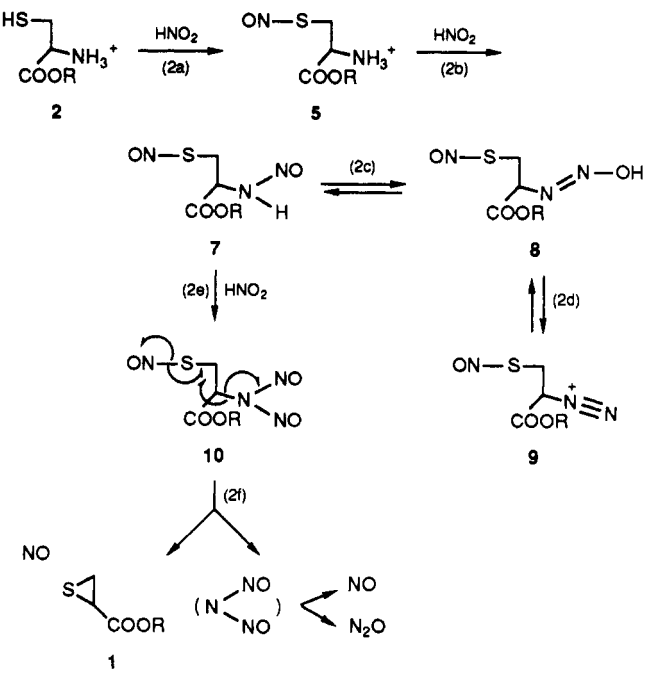
Recognizing that thionitrite 5 must surely be intermediate in the reactions described above, and reasoning that other S-substituted cysteine derivatives might also serve as precursors to the thioglycidate, we treated a solution of cystine dimethyl ester hydrochloride in hydrochloric acid with nitrite in the usual way. As expected, no thionitrite color developed. Nevertheless, solvent extraction gave a yellow oil similar to that obtained from the thiol, and methyl thioglycidate (1, R = Me) was isolated from it. This finding does not prove the intermediacy of the disulfide, of course, nor was it meant to; but it does demonstrate the capability of the disulfide as starting material, it suggests similar capability for the thionitrite, and it demonstrates conclusively that thiol is not essential as starting material.

The conversion of cysteine into cystine by nitrite is improved by carrying out the reaction anaerobically.[8] Suspecting that radical processes might be involved, and that oxygen might well interfere in the thionitrite → episulfide conversion much as it interferes in the thionitrite → disulfide process, we treated cysteine ethyl ester in *deaerated* hydrochloric acid with nitrite under a nitrogen atmosphere. The product, isolated in the usual way, proved to be much better material than any previously obtained, and an 80% yield of thioglycidate was volatilized out of it. This is a much better yield than any reported heretofore.

Thioglycidate 1 (R = Et), kept for 3 months under air in ordinary light at room temperature, decomposed some 10% to elemental sulfur and ethyl acrylate. There was no evidence of polymerization. In contrast, a trace of nitrogen dioxide (from NO + $O_2$) caused discoloration and polymer formation within hours. Polymerization and desulfurization also occurred at temperatures above 80 °C, rapidly

(2) Orlov, A. M.; Kuleschova, N. D.; Knunyants, I. L. *Izvest. Akad. Nauk S.S.S.R., Ser. Khim.* **1967**, 1400.
(3) (a) Lin'kova, M. G.; Orlov, A. M.; Kil'desheva, O. V.; Knunyants, I. L. *Izvest. Akad. Nauk S.S.S.R., Ser. Khim.* **1969**, 1148. (b) Parshina, L. P.; Lin'kova, M. G.; Kil'desheva, O. V.; Knunyants, I. L. *Izvest. Akad. Nauk S.S.S.R., Ser. Khim.* **1970**, 931.
(4) (a) Maycock, C. D.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1976**, 234. (b) Maycock, C. D.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. I* **1979**, 1852.
(5) *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Furniss, B. S., Hannaford, A. J., Smith, P. W. G., Tatchell, A. R., Eds.; Longman, U. K., Wiley, New York, 1989; pp 1128–30.
(6) Oae, S.; Shinhama, K. *Org. Prep. Proc. Int.* **1983**, *15*, 165.
(7) Williams, D. L. H. *Chem. Soc. Rev.* **1985**, *2*, 171.
(8) Schulz, U.; McCalla, D. R. *Can. J. Chem.* **1969**, *47*, 2021.
(9) Maycock and Stoodley's 1979 paper is entitled "Part 1". No further work seems to have been published, however.

**Scheme II**



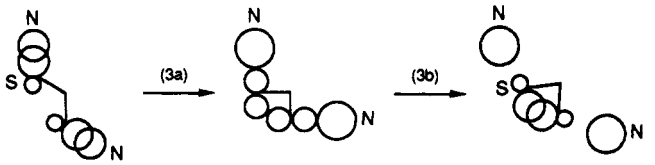
above 120 °C, so that attempts to determine an atmospheric-pressure boiling point were unsuccessful.

## Discussion

Scheme I, the reaction pathway involving $S_Ni$ displacement of the diazonium group, is not in accord with the experimental observations. It does not consider the initial formation of thionitrite, it cannot accommodate the formation of epithioester from disulfide, it does not account for the relative amounts of products with the several proportions of nitrite used, and it does not relate to the effect of anaerobic reaction conditions. No pathway involving disulfide as intermediate is tenable either, for the formation of this, though near quantitative under the right conditions, is much too slow.[8] Nevertheless, the bizarre and often irrational characteristics of the episulfide-forming reaction suggested that it might proceed also through one-electron homolytic processes paralleling those involved in the formation of disulfide and nitric oxide from thionitrite 5. With an excess rather than a deficiency of nitrite, nitrosation at sulfur would be followed by nitrosation at nitrogen, and homolysis of the S–NO bond might now be concerted with homolysis of the C–N bond of the nitrosated amine.

We propose the sequence delineated in Scheme II as being able to accommodate all of the observations. Thionitrite formation (step 2a) is followed by nitrosation of the amino group to nitrosamine 7 (step 2b). This reaction is well authenticated for secondary amines, where the nitrosamine is the stable product of the reaction. In the ordinary way, with the usual carefully limited proportion of nitrite, a primary nitrosamine undergoes prototropic tautomerization to a diazo hydroxide (8, step 2c), and this, to an extent governed by the acidity of the medium, loses hydroxide (step 2d) to give a diazonium cation (9). In the presence of yet a third mole of nitrous acid, however, we propose that a further nitrosation takes place yielding the dinitrosamine 10 (step 2e). A nitrosamine such as 7, one observes, is no more than an amide (a nitrosamide) of the amine and should be just as susceptible to nitrosation as is *N*-methylacetamide or *N*-methyl-*p*-toluenesulfonamide. There is no reason that an *N*-nitroso

**Scheme III**



nitrosamide such as 10 should be in any way less prone to form than any other *N*-nitroso amide.

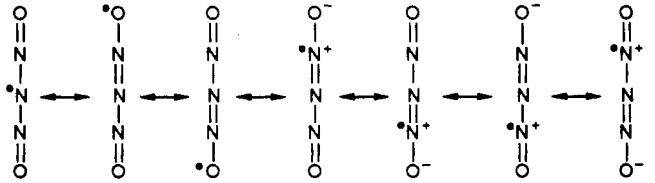
The dinitrosamine group should be a superb one-electron leaving group. Its departure may occur concomitantly with homolysis into nitric oxide and nitrous oxide, or $N_3O_2$ may be stable enough[10] to depart as such and dissociate subsequently. In any event, the dinitrosamine thionitrite 10 assembled from a cysteine ester is ideally constructed for electrocyclic collapse by intramolecular single-electron pairing (step 2f), with formation of episulfide 1 and expulsion of two molecules of nitric oxide and one of nitrous oxide.

Episulfide is stable to nitric oxide, to atmospheric oxygen, and to nitrous oxide. It is polymerized rapidly, however, by nitrogen dioxide, a radical which is reactive toward electron-paired substrates generally. Access to dissolved oxygen during reaction in which nitric oxide is being liberated thus results in the formation of much polymer. Slow addition of nitrite produces even more polymer. In contrast, as we now report, anaerobic reaction conditions raise the yield of monomer dramatically.

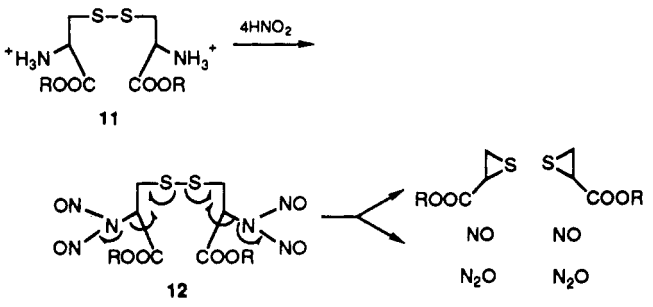
Analogy with the behavior of simple alkylammonium ions and alkylamides makes it reasonable to suggest that nitrosations 2b and 2e will proceed at fairly similar rates. Accordingly, if more than 1 but less than 3 mol of nitrite is used, once any nitrosamine 7 is generated it will compete for nitrite with amine 5. To the extent that it so competes and produces dinitrosamine 10, rapid formation of episulfide still occurs, albeit in amounts which decrease markedly as the excess of nitrite is decreased. Nitrosamine 7 not captured as dinitrosamine now has opportunity to equilibrate with diazonium salt 9, which will not be extracted into solvent any more than will remaining cysteine thionitrite 5. Extraction within a few minutes, just as the thionitrite color is fading, thus affords episulfide in considerably lower yield but of as good quality as that which results with excess nitrite. Subsequently, with access to air, interaction of liberated nitric oxide with atmospheric oxygen generates nitrogen dioxide, a known nitrosating agent ("nitrous fumes"), resulting in further nitrosation of amine 5 and, possibly, of nitrosamine 7 in equilibrium with diazonium salt 9. Accordingly, with 2 mol of nitrite the eventual yield of episulfide plus polymer approaches that obtained rapidly with 3 mol, but there is much more polymer. With 1 mol, on the other hand, the total eventual yield of solvent-soluble material is small.

Inversion of configuration is accounted for, as is the marked absence of racemization (Scheme III). The antibonding lobes of the $sp^3$ orbitals of the bonds from sulfur and carbon to nitrogen expand as the NO and $N_3O_2$ rad-

(10) Seven canonical forms which distribute the odd electron over the five atomic centers of the $N_3O_2$ hybrid are



Scheme IV



icals begin to depart (step 3a). The hybridization approaches $sp^2$ p. The expanding lobes eventually overlap to form the new S–C bond as the leaving groups separate completely (step 3b) and $sp^3$ hybridization is established anew. Inversion is mandated by the endergonic nature of the homolyses and the need for the energy of formation of the new bond to compensate in a concerted process.

The reaction of cystine ester 11 follows a similar course (Scheme IV). The bis dinitrosamine 12 formed by reaction with excess nitrite can undergo electrocyclic collapse producing 2 mol of episulfide per mol, nitric and nitrous oxides again being produced. Alternatively, one of the half-cystine residues may depart as thiyl radical, to be trapped by nitric oxide or in other side reactions. In either case, formation of episulfide is well accounted for.

## Experimental Section

$^1$H NMR spectra were obtained in $CDCl_3$/TMS. Dichloromethane was stripped at ~25 °C, 30–40 mmHg. Epithioesters were volatilized at 40–45 °C and trapped at –60 °C. Microanalyses were by Atlantic Microlab, Norcross, GA. Methyl and ethyl thioglycidates (1, R = Me and R = Et) were identified by NMR spectra and optical activities which were as previously reported[4] and gave satisfactory elemental analyses (CHNS). The NMR spectra of polymers were similar to those of monomers except that the $SCH_2$ and SCH multiplets were displaced downfield to $\delta$ 3.2 and 3.85, respectively.

**Reaction of L-Cysteine Ethyl Ester Hydrochloride with Nitrous Acid. (a) Anaerobic Reaction with 3 Equiv of Nitrite (Optimum Conditions).** Solid $NaNO_2$ (2.07 g, 30 mmol) was added in one portion to stirred, ice-chilled L-cysteine ethyl ester·HCl (1.85 g, 10 mmol) in deaerated HCl (50 mL, 1 M) under nitrogen. A deep red color developed and faded. Extraction ($CH_2Cl_2$) after 5 min gave a pale yellow oil (1.34 g) from which ethyl thiiranecarboxylate (1.05 g, 80%) was volatilized at 3 mmHg. The residue after 24 h (0.25 g), a viscous yellow oil, contained no monomer.

**(b) Aerobic Reaction with 3 Equiv of Nitrite (Literature Procedure[4]).** Procedure a was carried out in ordinary (air-saturated) hydrochloric acid. The red color faded and a red-brown coloration was observed in the air space above the mixture. Extraction after 5 min gave 1.18 g of oil from which 0.53 g (40%) of epithioester and 0.58 g of polymer were obtained. Further extraction after 2 h gave additional material (0.14 g) which contained about 30% of monomer (NMR).

**(c) Aerobic Reaction with Less Than 3 Equiv of Nitrite.** When procedure b was carried out with 2 equiv (0.14 g) of sodium nitrite, the red color faded more slowly (10–15 min). Extraction after 5 min gave oil (0.33 g) from which epithioester (0.13 g, 10%) was volatilized. Extraction after 2 h gave further oil (0.9 g) which contained additional epithioester (0.22 g, 17%). With 1 equiv of nitrite (0.7 g), the red color did not fade noticeably during 2 h. Extraction after 5 min gave an oil (0.1 g) which contained (NMR) about 0.07 g (5%) of epithioester. Extraction after 2 h gave further oil (0.45 g) containing 0.13 g (10%) of volatile product.

**Reaction of L-Cystine Dimethyl Ester Hydrochloride with Nitrous Acid.** $NaNO_2$ (0.6 g, 9 mmol) was added to a solution of L-cystine dimethyl ester·HCl (1.0 g, 3 mmol) in HCl (15 mL, 0.2 M) as in procedure b. No color developed. Extraction afforded an oil (0.40 g) from which volatization at 10 mmHg gave methyl thiiranecarboxylate (1, R = Me) (0.18 g, 52% or 26%).

**Acknowledgment.** Support for this research was provided in part from the Petroleum Research Fund administered by the American Chemical Society.

# $\alpha$-Selective Coupling Reactions of Allylic Alcohols with Aldehydes Using $Me_3SiCl/NaI/H_2O$–Sn

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*Received April 20, 1992*

It is well established that additions of allylic organometallic reagents to aldehydes lead to branched homoallylic alcohols ($\gamma$-adducts).[1] However, despite the synthetic importance of linear homoallylic alcohols ($\alpha$-adduct), obtaining them from regioinverted additions of allylic metals to aldehydes has remained an unsolved problem in organic synthesis.

During the last decade, some $\alpha$-selective coupling reactions using allylic tin compounds have been reported.[2] For instance, 1-buten-3-yldibutyltin chloride, which was generated from 2-butenyltributyltin and $Bu_2SnCl_2$, reacts with propanal to give only the (*Z*)-linear alcohol.[3] Treatment of tributylcrotyltin with aldehydes in the presence of $AlCl_3$–$^i$PrOH affords $\alpha$-adducts, but the nature of the aldehydes significantly influences the selectivity in the adducts produced.[4] More recently, a highly $\alpha$-selective allylation has been achieved by the reaction of allylic barium[5] and allylic cerium reagents[6] with aldehydes.

Previously, we showed that a $Me_3SiCl/NaI/H_2O$ system was a useful method for in situ generation of hydrogen iodide.[7,8] In a continuation of our study on the utilization of $Me_3SiCl/NaI/H_2O$ in synthetic reactions, we have found that $\alpha$-selective coupling reactions of allylic alcohols with aldehydes are efficiently mediated by the $Me_3SiCl/NaI/H_2O$–Sn system.[9]

Metallic tin was treated with $Me_3SiCl/NaI/H_2O$ in acetonitrile at room temperature. (E)-2-Hexen-1-ol (1) was added, and, 1 h later, butanal (2) was added. The resulting solution was stirred at ambient temperature to produce homoallylic alcohols 3 and 4 in a combined yield of 76% with remarkably high $\alpha$-selectivity with an $\alpha$:$\beta$ ratio of 98:2 (eq 1).[10] Most coupling reactions of allylic organometals with aldehydes take place at the $\gamma$-carbon rather than the $\alpha$-carbon of the allylic metals to afford branched homoallylic alcohols ($\gamma$-adducts).[1] Therefore, it is interesting

(1) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.
(2) (a) Pereyre, M.; Quintard, J-P.; Rahm, A. *Tin in Organic Synthesis*: Butterworth: London, 1987. (b) Yamamoto, Y. *Aldrichimica Acta* **1987**, *20*, 45.
(3) Gambaro, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1982**, *231*, 307.
(4) Yamamoto, Y.; Maeda, N.; Maruyama, K. *J. Chem. Soc., Commun.* **1983**, 742.
(5) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955.
(6) Guo, B.-S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710.
(7) Kanai, T.; Kanagawa, Y.; Ishii, Y. *J. Org. Chem.* **1990**, *55*, 3274.
(8) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.
(9) Recently, allylation of carbonyl compounds with allylic compounds using metallic tin has been reported. (a) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 1527. (b) Nokami, J.; Otera, T.; Sudo, T.; Okawara, R. *Organometallic* **1983**, *2*, 191. (c) Petrier, C.; Einnhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 1449.
(10) The coupling constants of the vic-vinyl protons for (*E*)- and (*Z*)-3 were 14.8 and 10.0 Hz, respectively.
(11) In our previous paper, we showed that the reactions of 1, 12, and 13 with the $Me_3SiCl/NaI/H_2O$ reagent forms the same iodide, 1-iodo-2-hexene.[12]

0022-3263/92/1957-6988$03.00/0 