The Endocyclic Restriction Test: An Investigation of the Geometries of Thiophilic Additions of Aryl Radicals and Aryllithium Reagents to Dithioesters

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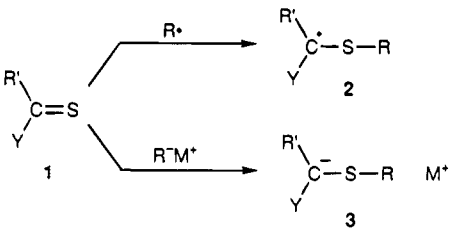
Prospective thiophilic additions of aryl radicals and aryllithium reagents in four-, six-, eight-, and 15-membered endocyclic rings have been investigated for the radical and organolithium intermediates generated from the dithioesters **8**–**11**. These reactions, selected to provide information about the geometries of endocyclic thiophilic reactions, show radical addition to be the major pathway for all but the four-membered ring whereas endocyclic thiophilic carbanionic addition is favorable only for the eight-membered ring. The implications of these results are discussed in terms of the possible reaction mechanisms.

Introduction

Thiophilic reactions are illustrated for additions to the thiocarbonyl group of **1** by a carbon radical to give **2** or by a carbanion of an organometallic reagent to give **3**.[1,2] Our interest in the mechanism of thiophilic additions has led us to determine if these reactions are subject to geometrical constraints as evaluated by the endocyclic restriction test.

For the radical reaction direct coupling between the sulfur of the thiocarbonyl group and the radical is the accepted mechanism.[1] Reports by Thuiller and by Bowman have shown endocyclic thiophilic additions of radicals can proceed in five- and six-membered rings.[3] In studies which addressed the mechanism of the carbanionic addition, Ohno suggested the formation of a charge transfer complex between **1** and the organometallic reagent.[4] Subsequent electron transfer and in-cage radical recombination afford **3**. We have reported that additions of configurationally defined vinylorganolithium and Grignard reagents to thiobenzophenone proceed with retention of configuration.[5] We noted those results require a mechanism which involves an in-cage radical recombination or an ionic process. The detection of radicals in organometallic reactions of thiocarbonyl compounds has been reported, often with the provision that the radicals may not lead to the thiophilic addition products.[2,6]



The endocyclic restriction test allows evaluation of the geometrical requirements for substitutions at nonstereogenic heteroatoms.[7] The relationship of the length of the tether between the reactive groups and the intra- or intermolecularity of the reaction provides information about the geometrical requirements of the substitution.[7] Application of this approach to a multiply bonded heteroatom is illustrated for endocyclic radical and carbanionic thiophilic additions in the conversions of **4** to **5**.[8] Alternative reaction pathways for **4** include exocyclic carbophilic reaction to give **6** or reaction with a proton or hydrogen source to provide **7**. A geometric requirement for a thiophillic addition would be expected to be

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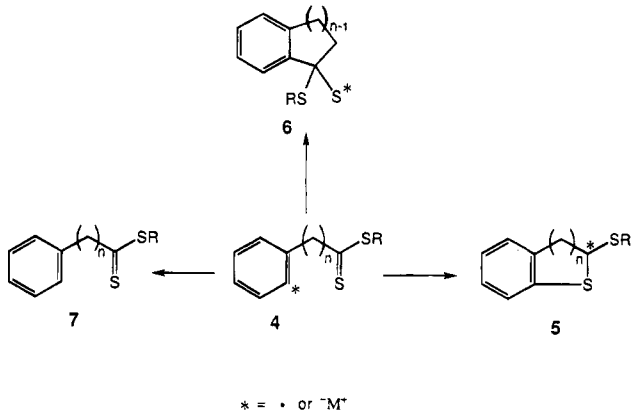
reflected in a change in the extent of formation of **5** as a function of the number of methylene groups linking the radical or carbanion to the thioesther group.

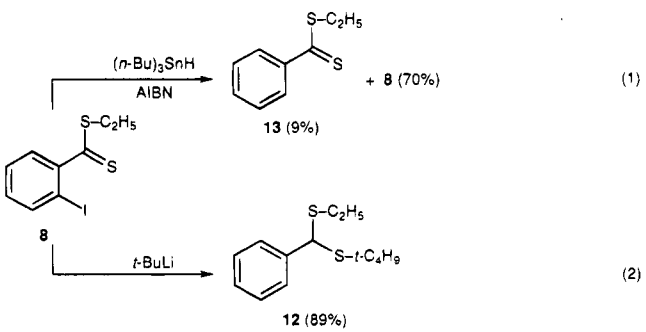


Results and Discussion

The dithioester aryl iodides **8-11** were prepared by standard methodology. For **9**, **10**, and **11**, sequences of chain elongations to thioesters, which were subsequently methylated and converted to dithioesters, were used. The *gem*-dimethyl substitutions in **9**, **10**, and **11** were found to be necessary to prevent competitive enolizations of the thioesters for the carbanionic reactions (*vide infra*). Synthetic schemes and experimental data are provided as supplementary material.

The carbon iodine bonds in **8-11** are the precursors to the radical or carbanionic centers for reactions in which endocyclic thiophilic additions would involve four-, six-, eight-, and 15-membered rings respectively. In order to determine if the suggested reaction sequence would be followed for the organolithium reaction, iodobenzene and methyl dithiobenzoate were treated with *t*-butyl lithium (*t*-BuLi) and found to provide the expected product of thiophilic addition, thiomethylphenylthiophenylmethane, in 41% yield. Efforts to carry out a similar model reaction with iodobenzene, methyl dithiobenzoate and tri-*n*-butyl tin hydride ((*n*-Bu)$_3$SnH) and azobisisobutyronitrole (AIBN) were not successful. However, the products of the reactions with **9**−**11** with (*n*-Bu)$_3$SnH and AIBN did provide thiophillic products (*vide infra*).

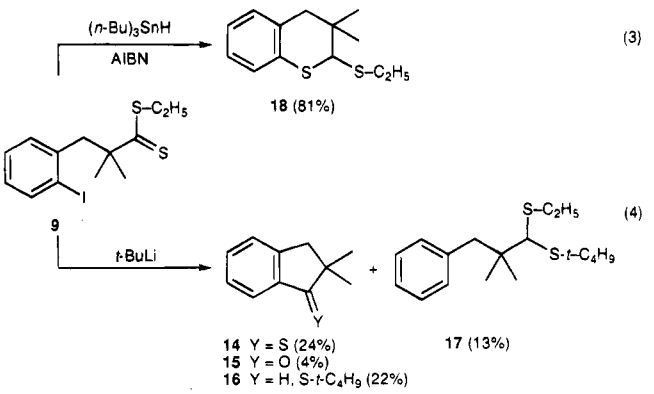
Each dithioester, **8, 9, 10,** and **11**, was allowed to react with (*n*-Bu)$_3$SnH/AIBN in benzene at reflux to generate the intermediate radical and with *t*-BuLi in THF at −78 °C to generate the organolithium intermediate. The major products under each reaction protocol and for each case are shown in eqs 1−8. The structures of the



(1)

(2)

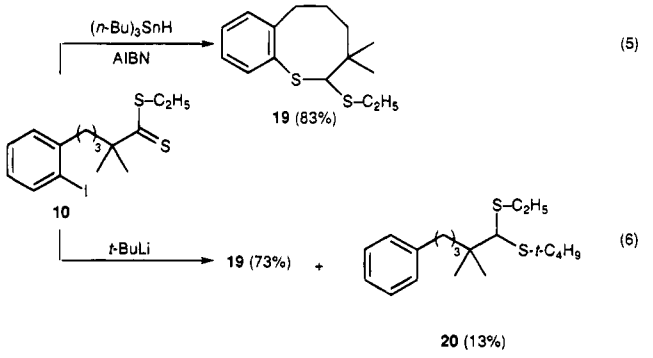
products **12**−**22** were assigned by the usual spectral and analytical criteria except for **16,** which was assigned only by GC/MS.



(3)

(4)

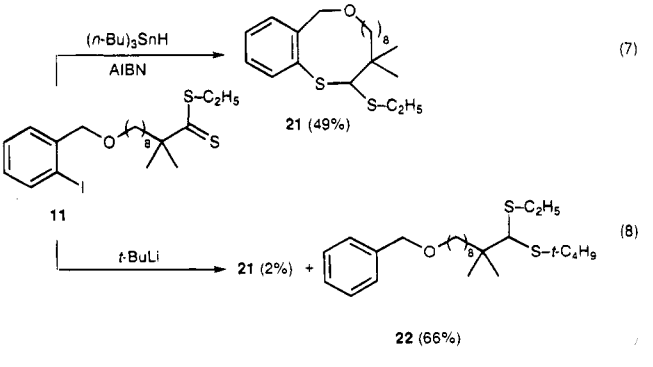
Analysis of the structural relationship between the reactants **8-11** and the products **12-22** reveals different geometrical dependencies for the reactions of radical and organolithium intermediates. For the prospective endo-



(5)

(6)

cyclic ring closures of the intermediates from **8**, neither the radical nor the organolithium reagent affords the putative four-membered ring. Endocyclic six-membered ring closure of the radical from **9** gives the radical precursor of **18** as the major reaction pathway. On the other hand, the organolithium reagent from **9** gives **14**, **15**, and **16** which arise from exocyclic carbophilic additions and less than 5% endocyclic ring closure.[9] In the case of **10**, both the radical and the organolithium intermediates undergo endocyclic eight-membered ring closures leading to **19**. For the 15-membered ring from **11**, the radical gives substantial endocyclic thiophilic addition to provide **21** whereas the organolithium intermediate affords only a small amount of the cyclized product.



(7)

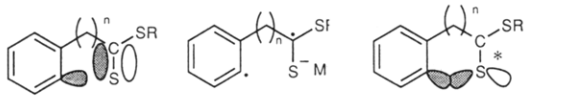
(8)

For the radical series, the major products for six-, eight-, and fifteen-membered rings result from endocyclic thiophilic ring closures. Thus, thiophilic radical reactions

(9) The thioketone **14** is presumed to be the precursor of **15** and **16**.

may prove useful for a variety of ring closures. For the carbanionic series, thiophilic addition follows an endocyclic pathway as a major pathway only for the eight membered ring from **10**. Direct comparison of radical and carbanionic patterns of reaction for a single precursor could be misleading because of the very different reaction conditions. Different temperatures, solvents, and competing reactions are known to affect significantly the products of organometallic thiophilic additions.[2,10] Nonetheless, we suggest that comparisons within the series of radical and carbanionic reactions is informative.

In the simplest frontier orbital terms, the radical reaction can be envisioned as an interaction of the radical SOMO and the thiocarbonyl HOMO as illustrated in **23**.



23 24 25 * = • or −

Endocyclic addition should have a wide range of allowed trajectories and proceed easily for the radicals from **9**, **10** and **11**. In the latter case, the well-known constraints on macrocyclic ring closure do appear to lower the yield. In the reaction of **8**, formation of the putative radical appears to be inhibited, since significant amounts of **8** are recovered under conditions in which **9**, **10**, and **11** are reactive.[11] Prohibitive strain for endocyclic ring closure of the radical to a four-membered ring is suggested by the formation of **13.**

In a frontier orbital picture for thiophilic addition of the organometallic carbanions, a concerted two electron process would involve a HOMO−LUMO interaction which could have a geometric restriction, albeit as a six-*endo-trig* process.[8] The alternative two-step reaction *via* a biradical **24** would involve frontier orbitals, SOMO−SOMO shown in **25** or SOMO−LUMO, which would have restrictive geometry also. The possibility of a geometrical requirement for formation or reaction of a charge transfer species could also be reflected in these results and is difficult to evaluate.

The present results can be taken to suggest that the patterns of thiophilic additions of radicals and organometallics to thiocarbonyl groups have different trajectorial requirements with respect to alternative reactions. The radical additions appear to have less geometric restrictions than do the carbanionic additions, although differences in the reaction conditions and a lack of quantitative information about the alternative reactions make that conclusion provisional.

Experimental Section

General. GC/EIMS was performed on a Hewlett-Packard 5890 gas chromatograph coupled to a Hewlett-Packard 5970 mass selective detector. Field ionization mass spectrometry (FIMS) utilizing a Finnigan-MAT 731 mass spectrometor was obtained by the University of Illinois Mass Spectrometry Center. Analytical capillary gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph with a flame ionization detector; the injector temperature was 250 °C, the detector temperature was 300 °C. The yields of reactions were based on relative GLC peak area, corrected for the sensitivity of the detector, using dodecane as an internal standard. Proton and carbon NMR spectra were obtained on either a Varian XL-200 spectrometer or a General Electric QE 300 spectrometer. Spectra were referenced as ppm downfield from TMS or the residual $CHCl_3$ signal, and chemical shifts are reported as ppm downfield from TMS. Infrared spectra were recorded on an IBM IR/32 FTIR spectrometer. Elemental analysis were performed by the University of Illinois Microanalytical Service Laboratory. All reactions were performed under a dry nitrogen atmosphere in oven-dried glassware. Reaction mixtures were stirred magnetically unless otherwise indicated. TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished by UV light (254 nm). Column chromatography was performed by using silica gel (0.05−0.2 mm, Merck) with hexane−ethyl acetate mixture as eluent.

Materials. All reagents and solvents were obtained from commercial sources and used without further purification, unless mentioned otherwise. THF and benzene were distilled from sodium and benzophenone under nitrogen atmosphere. Commercial solutions of *t*-BuLi in pentane were titrated using *N*-pivaloyl-*o*-toluidine as the indicator.[12]

General Procedure for the Reaction of Dithio Ester with *t*-BuLi. To a solution of a dithio ester in THF (*ca.* 5 mM) at −78 °C was added dropwise a 1.7 M solution of *t*-BuLi (2.2 equiv). The solution was stirred at −78 °C for 15 min and then quenched with HOAc and allowed to warm to room temperature. An internal standard and water were added and the solution was extracted three times with ether. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. This material was purified and seperated by silica flash chromatography followed by prep. TLC.

Reaction of *S*-Ethyl 2-Iododithiobenzoate (8). From 30 mg of **8**, **12** was obtained as 16 mg of a yellow oil in 70% yield (89% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 4.94 (s, 1H), 2.52 (m, 2H), 1.30 (s, 9H), 1.23 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 129.1, 128.6, 127.8, 127.6, 50.1, 45.4, 31.4, 27.2, 14.4; EIMS (70 eV) m/z (relative intensity) 240 (8, M^+), 179 (100), 151 (93), 123 (99), 77 (11), 57 (25) .

Reaction of *S*-Ethyl 2,2-Dimethyl-3-(2′-iodophenyl)-dithiopropanate (9). From 23 mg of **9**, **14** was obtained as 2.7 mg of a yellow oil in 24% yield (24% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, J = 7.8 Hz, 1H), 7.59 (m, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.30 (m, 1H), 3.11 (s, 2H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 254.6, 152.2, 145.1, 134.8, 127.6, 126.1, 125.0, 56.6, 46.5, 29.6; EIMS (70 eV) m/z (relative intensity) 176 (68, M^+), 162 (12), 161 (97), 143 (53), 141 (12), 134 (11), 129 (14), 128 (100), 127 (12), 115 (31). IR (film) 3065, 2961, 2923, 2861, 1599, 1465, 1431, 1321, 1293, 1266, 1121, 774, 718 cm^{-1}. Anal. Calcd for $C_{11}H_{12}S$ (176.3): C, 74.95; H, 6.86. Found: C, 74.69; H, 6.80.

15 as 0.7 mg of a yellow oil in 7% yield (4% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, J = 7.7 Hz, 1H), 7.58 (m, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.36 (m, 1H), 2.99 (s, 2H), 1.23 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.2, 152.0, 135.1, 134.7, 127.2, 126.5, 124.2, 45.3, 42.6, 25.1; EIMS (70 eV) m/z (relative intensity) 160 (48, M^+), 145 (100), 142 (15), 117 (28), 115 (32), 91 (21), 89 (13), 63 (13). IR (neat) 3034, 2963, 2926, 2867, 1717, 1609, 1466, 1437, 1379, 1325, 1287, 1204, 992, 737 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O$ (160.2): C, 82.46; H, 7.55. Found: C, 82.63; H, 7.31.

16 in 22% yield by GLC EIMS (70 eV) m/z (relative intensity): 234 (12, M^+), 177 (3, M^+ − *t*-Bu), 145 (100, M^+ − S-*t*-Bu), 129 (9), 128 (9), 117 (8), 91 (6), 57 (5).

17 as 1.7 mg of a yellow oil in 9% yield (13% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (m, 5H), 3.62(s, 1H), 3.00 (d, J

(10) Although thiophilic reactions of organolithium and Grignard reagents can give a single product, products of carbophilic addition, reduction, enolization, and double addition often are observed.[2] The multiplicity of products suggests branching, and/or access to more than one reaction pathway. For example, Ohno *et al.* have shown that thiophilic and carbophilic additions of organometallic differ substantially in enthalpies and entropies of activation with the latter favored at higher temperatures.[3]

(11) It should be noted that the proximity of the functional groups in **8** could interfere with the initial formation of the aryl radical and aryl lithium intermediates.

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= 12.8 Hz, 1H), 2.79 (m, 2H), 2.67 (d, J = 12.8 Hz, 1H), 1.37 (s, 9H), 1.28 (t, J = 7.5 Hz, 3H), 1.02 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75-MHz) δ 138.9, 130.8, 127.6, 125.9, 61.7, 45.5, 44.1, 42.2, 31.5, 28.1, 25.4, 25.3, 14.5; EIMS (70eV) m/z (relative intensity) 296 (12, M^+), 235 (52), 207 (21), 179 (22), 163 (10), 145 (100), 107 (28), 91 (77), 57 (22).

Reaction of *S*-Ethyl 2,2-Dimethyl-5-(2′-iodophenyl)-dithiopentanoate (10). From 73 mg of **10**, **19** was obtained as 24 mg of a yellow oil in 32% yield (73% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 4H), 4.13 (s, 1H), 3.05 (t, J = 6.6 Hz, 2H), 2.88 (m, 2H), 1.79 (m, 2H), 1.51 (m, 2H), 1.32 (t, J = 7.4 Hz, 3H), 1.24 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.9, 137.4, 133.1, 129.7, 128.1, 126.2, 67.5, 41.7, 36.5, 34.3, 29.2, 27.4, 26.7, 24.5, 14.4; EIMS (70 eV) m/z (relative intensity) 266 (71, M^+), 237 (11), 205 (91), 191 (42), 177 (39), 149 (53), 135 (100), 123 (29), 103 (43), 91 (27), 7 (10), 69 (14) Anal. Calcd for $C_{15}H_{22}S_2$: C, 67.62; H, 8.32; S, 24.06. Found: C, 67.67; H, 8.35; S, 23.90.

20 as 4 mg of a yellow oil in 5% yield (13% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (m, 5H), 3.60 (s, 1H), 2.72 (m, 2H), 2.59 (t, J = 7.2 Hz, 2H), 1.57 (m, 4H), 1.37 (s, 9H), 1.23 (t, J = 7.5 Hz, 3H), 1.02 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.8, 128.4, 128.3, 125.7, 61.2, 43.9, 41.0, 40.1, 36.8, 31.6, 27.9, 26.5, 25.7, 25.5, 14.5; EIMS (70 eV) m/z (relative intensity) 324 (8, M^+), 263 (35), 235 (47), 207 (75), 173 (36), 163 (27), 131 (18), 117 (100), 107 (64), 91 (70), 77 (5), 69 (21), 57 (50).

Reaction of *S*-Ethyl 2,2-Dimethyl-10-(2′-iodobenyloxyl)dithiononanoate (11). From 40 mg of **11**, **21** was obtained in 2% yield by GC: EIMS (70 eV) m/z (relative intensity) 366 (5, M^+), 337 (18), 305 (72), 243 (12), 199 (10), 181 (10), 149 (22), 139 (55), 135 (18), 123 (19), 97 (29), 91 (100), 77 (13), 69 (57), 57 (33).

23 as 9 mg of a yellow oil in 30% yield (66% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (m, 5H), 4.50 (s, 2H), 3.61 (s, 1H), 3.46 (t, J = 6.6 Hz, 2H), 2.74 (m, 2H), 1.42 (m, 15H), 1.38 (s, 9H), 1.04 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 61.4, 43.8, 40.9, 40.2, 31.6, 30.4, 29.8, 29.6, 29.5, 27.9, 26.2, 25.7, 25.5, 24.1, 14.5; EIMS (70 eV) m/z (relative intensity) 424 (12, M^+), 363 (76), 335 (100), 307 (100), 273 (28), 217 (32), 201 (81), 163 (100), 107 (100), 91 (100), 57 (100).

General Procedure for the Reaction of a Dithio Ester with (n-Bu)$_3$SnH and AIBN. To a solution of a dithio ester and AIBN (1 mg) in dry benzene (*ca.* 40 mM) heated to reflux under nitrogen was added a solution of tri-*n*-butyltin hydride (1.2 equiv) in dry benzene (*ca.* 50 mM) over a period of 2.5 h by syringe pump. The resulting solution was heated at the same temperature for an additional 0.5 h, and an internal standard was added. The solvent was removed *in vacuo* to give a yellow oil and this material was purified and seperated by silica flash chromatography followed by prep. TLC.

Reaction of *S*-Ethyl 2-Iododithiobenzoate (8). From 63 mg of **8**, **13** was obtained as 3 mg of a yellow oil in 5% yield (9% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (m, 5H), 3.38 (q, J = 7.5 Hz, 3H), 1.42 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 228.6, 145.2, 132.2, 128.3, 126.8, 31.5, 12.3; EIMS (70 eV) m/z (relative intensity) 182 (29, M^+), 121 (100), 77 (26).

Reaction of *S*-Ethyl 2,2-Dimethyl-3-(2′-iodophenyl)-dithiopropanate (9). From 45 mg of **9**, **18** was obtained as 29 mg as a yellow oil in 54% yield (81% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (m, 4H), 4.10 (s, 1H), 2.80 (d, J = 16.5 Hz, 1H), 2.76 (q, J = 7.4 Hz, 2H), 2.67 (d, J = 16.5 Hz, 1H), 1.31 (t, J = 7.4 Hz, 3H), 1.26 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.1, 132.2, 130.4, 126.3, 125.2, 124.2, 57.8, 43.4, 33.6, 28.9, 23.8, 14.7; EIMS (70 eV) m/z (relative intensity) 238 (41, M^+), 209 (1), 177 (100), 161 (26), 149 (25), 135 (81), 129 (10), 123 (2), 121 (6), 91 (9), 77 (7), 69 (3). Anal. Calcd for $C_{13}H_{18}S_2$: C, 65.49; H, 7.61; S, 26.89. Found : C, 65.45; H, 7.65; S, 26.76.

Reaction of *S*-Ethyl 2,2-Dimethyl-5-(2′-iodophenyl)-dithiopentanoate (10). From 50 mg of **10**, **19** was obtained as 20 mg as a yellow oil in 38% yield (83% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 4H), 4.13 (s, 1H), 3.05 (t, J = 6.6 Hz, 2H), 2.87 (m, 2H), 1.79 (m, 2H), 1.51 (m, 2H), 1.32 (t, J = 7.4 Hz, 3H), 1.24 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.9, 137.4, 133.1, 129.7, 128.1, 126.2, 67.6, 41.8, 36.5, 34.3, 29.2, 27.4, 26.7, 24.5, 14.4; EIMS (70 eV) m/z (relative intensity) 266 (100, M^+), 237 (13), 205 (80), 191 (35), 177 (31), 149 (37), 135 (69), 123 (19), 103 (25), 91 (20), 77 (6), 69 (8). Anal. Calcd for $C_{15}H_{22}S_2$: C, 67.62; H, 8.32; S, 24.06. Found: C, 67.71; H, 8.42; S, 23.92.

Reaction of *S*-Ethyl 2,2-Dimethyl-10-((2′-iodobenzyl)-oxy)dithiononanoate (11). From 70 mg of **11**, **21** was obtained as 11 mg of a yellow oil in 21% yield (49% by GLC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (m, 4H), 4.85 (d, J = 11.5 Hz, 1H), 4.52 (d, J = 11.5 Hz, 1H), 4.12 (s, 1H), 3.61 (m, 2H), 2.46 (m, 2H), 1.36 (m, 14H), 1.12 (s, 6H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.9, 136.0, 132.1, 129.7, 128.1, 126.7, 71.2, 69.3, 66.9, 40.9, 39.8, 29.7, 28.8, 28.1, 27.4, 27.3, 26.3, 25.4, 24.5, 21.3, 14.4; EIMS (70 eV) m/z (relative intensity) 366 (9, M^+), 337 (7), 305 (100), 243 (14), 199 (6), 181 (10), 149 (21), 139 (82), 135 (22), 123 (24), 97 (27), 91 (53), 77 (13), 69 (57), 57 (12). Anal. Calcd for $C_{13}H_{18}S_2$: C, 68.80; H, 9.35; S, 17.49. Found : C, 68.84; H, 9.42; S, 17.61.

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Supplementary Material Available: The syntheses of **8**, **9**, **10**, and **11** and ^{13}C spectra for **8**, **11**, **12**, **13**, **17**, **20**, **23**, and synthetic intermediates are provided (17 pages). This material is contained in libraries on microfiche, immediately follows this artible in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.