Silicon-Assisted Synthesis of Thiocarbonyl Derivatives and Reactivity of Dienophilic Thioaldehydes

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Treatment of bis(trimethylsilyl) sulfide with $CoCl_2 \cdot 6H_2O$ in the presence of aldehydes affords the corresponding thiocarbonyl analogues which can be trapped to avoid polymerization. The sulfurization reaction also takes place in the presence of $TfOSiMe_3$, in which case, besides thioaldehydes, thioketones may be obtained in satisfactory yields. When thioaldehydes are generated with the $CoCl_2 \cdot 6H_2O$ method the Diels–Alder reaction with cyclohexadiene occurs with very high selectivity in favor of the endo isomer, whereas when the $TfOSiMe_3$-based method is employed, the stereochemistry of the cycloadduct can be conveniently selected toward endo or exo by varying the molar ratio of the sulfurating agent.

Direct conversion of carbonyl units into their corresponding thiocarbonyl analogues has received considerable attention over the last few decades[1] due to the importance of thioxo derivatives in organic chemistry as useful intermediates for the synthesis of complex natural products.[2]

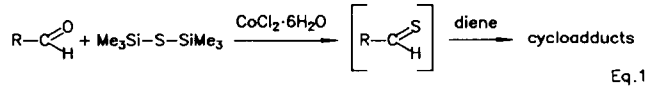
Several methods have been reported for the synthesis of thioketones, and their chemistry has been extensively studied.[1] In contrast, simple thioaldehydes have historically been considered to be elusive compounds until very recently, when Vedejs,[3] through the photochemical cleavage of phenacyl sulfides and Krafft,[4] through the fluoride-induced elimination of α-silyl disulfides, developed synthetically useful methods for their preparation and disclosed their participation in efficient and synthetically useful chemical reactions.[5]

Several other groups have also described Diels–Alder reactions of thioaldehydes generated thermally or by a variety of elimination reactions,[6] and, more recently, other methods for their preparation have been reported, such as the butyllithium-catalyzed conversion of aldehydes with bis(trimethylsilyl) sulfide[7] or the fragmentation of dithiolane *S*-oxides.[8]

Our long interest in acylsilane chemistry[9] led us to consider transformation of these carbonyl compounds into thioxo derivatives. Recent reports from this laboratory[10] detailed the synthesis of a wide series of thioacylsilanes[11] employing a mild general method which proved to be efficient for the "in situ" formation of thioaldehydes in their monomeric form.

We now report that the above thionation reaction using $Me_3Si–S–SiMe_3$ is of general value for the synthesis of a wide series of monomeric thioaldehydes, which can be trapped "in situ" by suitable reagents, and that the efficiency of the thionation, as well as the stereochemistry of the reaction products, are strongly affected by the nature of the catalyst employed.

When aldehydes are treated with $Me_3Si–S–SiMe_3$ in acetonitrile at room temperature in the presence of catalytic quantities of $CoCl_2 \cdot 6H_2O$ (eq 1), thioaldehydes are formed efficiently, as demonstrated by the high yields of the corresponding cycloadducts obtained by diene trapping, isolated from the reaction mixtures.



Eq. 1

This reaction was unsuccessful with ketones, even under more stringent reaction conditions (i.e., higher tempera-

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tures, 1:1 molar ratio with the catalyst, and higher concentrations).

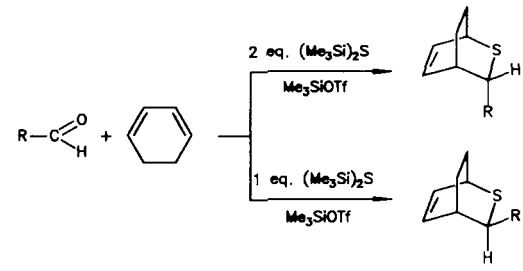
The mild conditions used in the present method minimize deleterious processes, thus permitting thioaldehydes, which are known to be rather prone to polymerization, to exist long enough in the monomeric form to undergo further reactions "in situ". Thus, on performing the thionation in the presence of dienes such as 2,3-dimethylbutadiene or 1,3-cyclohexadiene, which are known to be good trapping reagents for thioaldehydes, a variety of functionalized dihydrothiopyran systems are obtained in good to excellent yields starting from a wide range of thioaldehydes. Aromatic aldehydes and aldehydes bearing an electron-withdrawing substituent afford the adducts in excellent yields (Table I), making the bis(trimethylsilyl) sulfide method of thioaldehyde generation comparable to previously reported procedures. On the contrary, most of the trapping reagents employed proved, as expected, to be relatively unreactive with alkanethials, which then participated in alternative undesired reactions, leading to low yields of adducts together with large amount of oligomeric material.

One interesting aspect of the reaction in eq 1 is its high chemoselectivity which allows selective thionation of aldehydes in the presence of other carbonyl groups. This turns out to be particularly useful when further derivatization of the thiopyrans obtained is required and is of general interest in the thionation of polyfunctionalized aldehydes. Moreover, the reaction is equally efficient with compounds like glyoxal, methylglyoxal, and phenylglyoxal, (entries 16–20 in Table I) which were used as their hydrates or as commercial 40% solutions in water. This further extends the versatility of the proposed method for obtaining thioaldehydes directly even from materials which are commercially available as aqueous solutions.

Even more interesting for exploiting synthetic applications of the thioaldehyde Diels–Alder additions is the stereochemical control of the cyclization step. The reaction of thioaldehydes, generated by the $Me_3Si–S–SiMe_3$ method, with cyclohexadiene occurs with a very high preference for the formation of the endo adduct, with an endo/exo ratio usually greater than 95:5 (see Table I). Stereochemical assignments were based on NOE experiments, on the related findings of Kirby,[6a] Krafft,[4] and Vedejs,[3a] and on highly consistent chemical shifts and coupling correlations in all the adducts.

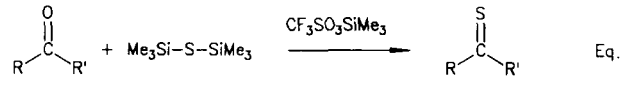
Besides $CoCl_2·6H_2O$, the activity of a large array of metal salts has been tested,[12] with unsatisfactory results. However, following the idea that in the thionation step a suitable activation of the carbonyl function might favor subsequent attack by nucleophiles such as $Me_3Si–S–SiMe_3$, the highly oxophilic agent[13] $CF_3SO_3SiMe_3$ was also tried as catalyst for inducing the thionation process. This compound turned out to be effective in promoting the thionation of the carbonyl compounds, the subsequent Diels–Alder reaction of the "in situ" generated thioaldehydes with cyclohexadiene leading to sizeable amounts of the corresponding cycloadducts (Table I). Several reactants could be converted to the corresponding thioxo derivatives, although only under anhydrous conditions and in somewhat lower yields.

Scheme I



A unique feature of the use of $TfOSiMe_3$ as catalyst is the stereochemical outcome of the reactions: the Diels–Alder adduct stereochemistry may, in fact, be effectively selected so that the endo or the exo adduct can be obtained as the predominant diastereoisomers by simply varying the molar ratio of the sulfurating agent (see Scheme I). When, in fact, a 2:1 ratio of $(Me_3Si)_2S$:aldehyde is used, the endo isomer is obtained selectively, while on using a 1:1 ratio of the same reagents the exo isomer is obtained.

The greater efficiency of $TfOSiMe_3$ in promoting thionation processes with respect to $CoCl_2·6H_2O$ is shown by its ability to induce even the thionation of carbonyl derivatives differing from simple aldehydes (eq 2) such as,



Eq. 2

for instance, ketones, leading to their sulfur analogues (Table II), whereas the ability of $TfOSiMe_3$ to induce the thionation of particularly sensitive reactants, such as diphenylketene (Table II, entry 7), in satisfactory yields is also particularly interesting.

The highly efficient and very mild method of thiocarbonyl generation under ambient conditions allows great flexibility in the choice of other carbonyl derivatives which can be thionated, whereas successful control of diastereoselectivity suggests applications of the thioaldehyde Diels–Alder reactions for remote stereocontrol in complex syntheses. These issues will be addressed in future work.

Experimental Section

NMR spectra were recorded at 200, 300, and 600 MHz and were measured as $CDCl_3$ solutions.

CH_3CN was purchased from Carlo Erba (RPE Grade) and stored under nitrogen. Column chromatography was carried out with the flash chromatography technique on Merck Kieselgel 60 (230–400 mesh ASTM). Preparative TLC was performed by using Merck Kieselgel 60 plates. All the reactions were run under a dry nitrogen atmosphere, and all manipulations regarding thioketones were performed under an inert atmosphere.

Organic solutions were dried over Na_2SO_4. Unless otherwise mentioned, starting materials were obtained from commercial sources and used without further purification.

Synthesis of Thioaldehydes. General Procedure A. A solution of the aldehyde (1 mmol), diene (1.5 mmol), and bis(trimethylsilyl) sulfide (2 mmol) in CH_3CN (0.5 mL) was treated at room temperature with a solution of $CoCl_2·6H_2O$ (0.2 mmol) in 2.5 mL of CH_3CN. Progress of the reaction was monitored by GC/MS analysis. The reaction mixture was quenched with saturated NH_4Cl, extracted with ether, and dried over Na_2SO_4,

(11) For alternative syntheses of thioacylsilanes see: (a) Bonini, B. F.; Mazzanti, G.; Zani, P.; Maccagnani, G. *J. Chem. Soc., Chem. Commun.* **1988**, 365. (b) Carisi, P.; Mazzanti, G.; Zani, P.; Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2647. (c) Bonini, B. F.; Lenzi, A.; Maccagnani, G.; Barbaro, G.; Giorgianni, P.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2643. (d) Barbaro, G.; Battaglia, A.; Giorgianni, P.; Maccagnani, G.; Macciantelli, D.; Bonini, B. F.; Mazzanti, G.; Zani, P. *J. Chem. Soc., Perkin Trans. 1* **1986**, 381. (e) Ricci, A.; Degl'Innocenti, A.; Seconi, G.; Dembech, P.; Ramadan, N.; Walton, D. R. M. *Tetrahedron Lett.* **1985**, *26*, 1091. (f) Bonini, B. F.; Mazzanti, G.; Sarti, S.; Zanirato, P.; Maccagnani, G. *J. Chem. Soc., Chem. Commun.* **1981**, 822.

(12) Several other catalysts, including Co(II), Ni(II), Fe(III), Rh(III) salts and Co(0) complexes were tested in the thionation reaction of PhCHO in presence of cyclohexadiene, but only $Co(Ac)_2·4H_2O$ and $RhCl_3·3H_2O$ proved partially effective in promoting the reaction (65% and 57% yield, respectively).

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and the solvent was removed under vacuum. The crude reaction product was then purified by column chromatography or TLC on silica gel.

General Procedure B. A stirred solution of aldehyde (1 mmol), diene (1.5 mmol), and bis(trimethylsilyl) sulfide (1 or 2 mmol, according to the ratios reported in Table I) in 4 mL of CH_3CN was treated at room temperature with $CF_3SO_3SiMe_3$ (0.1 mmol). The reaction mixture was stirred overnight, quenched with saturated $NaHCO_3$, extracted with ether, and dried with Na_2SO_4, and the solvent was removed in vacuo. Chromatography of the crude material thus obtained afforded the pure adducts.

General Procedure for the Synthesis of Thioketones. A stirred solution of the ketone (1 mmol) and bis(trimethylsilyl) sulfide (2 mmol) in 4 mL of CH_3CN was treated under nitrogen at room temperature with $CF_3SO_3SiMe_3$ (0.2 mmol). The reaction mixture was stirred at room temperature, and completion of the reaction was followed by GC/MS. The reaction mixture was then quenched with saturated $NaHCO_3$, extracted with diethyl ether, and dried, and the solvent was removed in vacuo to obtain a crude product, which was purified following literature procedures (see Table II).

Compound 2, major isomer (procedures A and B): ^1H NMR (600 MHz, $CDCl_3$) δ 1.77 (3 H, bs), 2.35–2.46 (1 H, m), 2.50–2.64 (1 H, m), 3.00–3.10 (1 H, m), 3.43–3.58 (1 H, m), 4.02 (1 H, dd, J = 9.9, 4.2 Hz), 5.67–5.75 (1 H, m), 7.27–7.65 (5 H, m); MS m/z (relative intensity) 190 (M^+, 56), 129 (12), 128 (10), 122 (100), 121 (55), 115 (12), 91 (14), 78 (11), 77 (14).

Compound 2, minor isomer (procedures A and B): ^1H NMR (600 MHz, $CDCl_3$) δ 1.80 (3 H, bs), 2.50–2.64 (2 H, m), 2.86–2.96 (1 H, m), 3.43–3.58 (1 H, m), 3.97 (1 H, dd, J = 12.6, 4.8 Hz), 5.67–5.75 (1 H, m), 7.27–7.65 (5 H, m); MS m/z (relative intensity) 190 (M^+, 56), 129 (12), 128 (10), 122 (100), 121 (55), 115 (12), 91 (14), 78 (11), 77 (14).

***endo*-3-Phenyl-2-thiabicyclo[2.2.2]oct-5-ene (3) (procedures A and B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.49–1.58 (1 H, m), 1.66–1.78 (1 H, m), 1.82–1.93 (1 H, m), 2.10–2.19 (1 H, m), 3.03–3.10 (1 H, m), 3.57–3.63 (1 H, m), 4.48 (1 H, d, J = 3.0 Hz), 5.95 (1 H, ap t), 6.72 (1 H, ap t), 7.18–7.45 (5 H, m); MS m/z (relative intensity) 202 (M^+, 34), 125 (12), 124 (100), 123 (49), 122 (15), 121 (36), 91 (60), 80 (98), 79 (69), 77 (28). Anal. Calcd for $C_{13}H_{14}S$: C, 77.20; H, 6.98. Found: C, 77.27; H, 6.91.

***exo*-3-Phenyl-2-thiabicyclo[2.2.2]oct-5-ene (3) (procedure B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.10–2.15 (4 H, m), 2.74–2.79 (1 H, m), 3.55–3.59 (1 H, m), 4.26 (1 H, bs), 6.50 (1 H, ap t), 6.61 (1 H, ap t), 7.28–7.42 (5 H, m); MS m/z (relative intensity) 204 (3), 202 (M^+, 14), 124 (78), 123 (39), 122 (12), 121 (30), 115 (12), 91 (53), 80 (100), 79 (66), 77 (31), 51 (14), 45 (16). Anal. Calcd for $C_{13}H_{14}S$: C, 77.20; H, 6.98. Found: C, 77.39; H, 7.04.

***endo*-3-*p*-Tolyl-2-thiabicyclo[2.2.2]oct-5-ene (4) (procedures A and B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.47–1.60 (1 H, m), 1.65–1.75 (1 H, m), 1.82–1.94 (1 H, m), 2.10–2.17 (1 H, m), 2.25 (3 H, s), 2.99–3.08 (1 H, m), 3.57–3.62 (1 H, m), 4.45 (1 H, d, J = 2.9 Hz), 6.01 (1 H, ap t), 6.70 (1 H, ap t), 7.05–7.43 (4 H, m); MS m/z (relative intensity) 216 (M^+, 10), 138 (58), 137 (100), 136 (27), 135 (37), 105 (35), 91 (19), 80 (55), 79 (41), 77 (18). Anal. Calcd for $C_{14}H_{16}S$: C, 77.75; H, 7.46. Found: C, 77.89; H, 7.38.

***exo*-3-*p*-Tolyl-2-thiabicyclo[2.2.2]oct-5-ene (4) (procedure B)**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.68–2.15 (4 H, m), 2.17 (3 H, s), 2.71–2.75 (1 H, m), 3.54–3.58 (1 H, m), 4.22 (1 H, bs), 6.49 (1 H, ap t), 6.60 (1 H, ap t), 7.16 (2 H, bd), 7.48 (2 H, bd); MS m/z (relative intensity) 216 (M^+, 10), 138 (58), 137 (100), 136 (26), 135 (37), 105 (35), 91 (19), 80 (55), 79 (41), 77 (18).

***endo*-3-(*p*-Chlorophenyl)-2-thiabicyclo[2.2.2]oct-5-ene (5) (procedures A and B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.45–1.55 (1 H, m), 1.63–1.77 (1 H, m), 1.81–1.91 (1 H, m), 2.10–2.18 (1 H, m), 2.97–3.03 (1 H, m), 3.58–3.61 (1 H, m), 4.41 (1 H, d, J = 2.8 Hz), 5.92 (1 H, ap t), 6.70 (1 H, ap t), 7.23 (4 H, s); MS m/z (relative intensity) 236 (M^+, 4), 160 (13), 158 (34), 157 (20), 155 (16), 125 (16), 80 (100), 79 (62), 77 (17).

***exo*-3-(*p*-Chlorophenyl)-2-thiabicyclo[2.2.2]oct-5-ene (5) (procedure B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.32–2.18 (4 H, m), 2.93–3.08 (1 H, m), 4.02–4.08 (1 H, m), 4.26 (1 H, bs), 6.27 (1 H, ap t), 6.67 (1 H, ap t), 7.28–7.47 (4 H, m); MS m/z (relative intensity) 236 (M^+, 4), 160 (13), 158 (34), 157 (20), 155 (16), 125 (16), 80 (100), 79 (62), 77 (17). Anal. Calcd for $C_{13}H_{13}ClS$: C, 65.97; H, 5.54. Found: C, 66.08; H, 5.59.

***endo*-3-(*o*-Chlorophenyl)-2-thiabicyclo[2.2.2]oct-5-ene (6) (procedure B)**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.47–1.58 (1 H, m), 1.63–1.78 (1 H, m), 1.84–2.00 (1 H, m), 2.11–2.21 (1 H, m), 3.12–3.19 (1 H, m), 3.59–3.66 (1 H, m), 4.99 (1 H, d, J = 2.8 Hz), 5.85 (1 H, ap t), 6.69 (1 H, ap t), 7.10–7.46 (4 H, m); MS m/z (relative intensity) 236 (M^+, 4), 160 (14), 158 (46), 157 (23), 156 (20), 155 (28), 127 (11), 125 (29), 123 (16), 80 (100), 79 (98), 78 (15), 77 (73), 75 (18), 63 (22), 53 (14), 51 (46). Anal. Calcd for $C_{13}H_{13}ClS$: C, 65.97; H, 5.54. Found: C, 65.80; H, 5.48.

***exo*-3-(*o*-Chlorophenyl)-2-thiabicyclo[2.2.2]oct-5-ene (6) (procedure B)**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.26–2.17 (4 H, m), 2.82–2.94 (1 H, m), 3.57–3.63 (1 H, m), 4.71–4.76 (1 H, m), 6.59–6.73 (2 H, m); MS m/z (relative intensity) 236 (M^+, 2), 158 (20), 156 (10), 155 (14), 125 (12), 80 (100), 79 (80), 77 (31), 51 (20). Anal. Calcd for $C_{13}H_{13}ClS$: C, 65.97; H, 5.54. Found: C, 66.12; H, 5.60.

***endo*-3-(*p*-Bromophenyl)-2-thiabicyclo[2.2.2]oct-5-ene (7) (procedures A and B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.41–1.57 (1 H, m), 1.68–1.77 (1 H, m), 1.82–1.92 (1 H, m), 2.11–2.19 (1 H, m), 2.98–3.02 (1 H, m), 3.56–3.61 (1 H, m), 4.40 (1 H, d, J = 2.8 Hz), 5.91 (1 H, ap t), 6.69 (1 H, ap t), 7.16 (2 H, d, J = 8.3 Hz), 7.35 (2 H, d, J = 8.3 Hz); MS m/z (relative intensity) 280 (M^+, 2), 204 (21), 202 (25), 201 (20), 171 (11), 123 (12), 80 (100), 79 (62), 77 (21).

1,4-Bis(3,6-dihydro-4,5-dimethyl-2*H*-thiopyranyl)benzene (8) (procedure A): ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (6 H, s), 1.77 (6 H, s), 2.44–2.67 (4 H, m), 2.90 (2 H, bd, J = 17 Hz), 3.45 (2 H, bd, J = 17 Hz), 3.95 (2 H, dd, J = 9.9, 4.5 Hz), 7.30 (4 H, s); MS m/z (relative intensity) 330 (M^+, 53), 249 (19), 248 (100), 215 (45), 166 (93), 136 (36), 91 (14), 82 (26), 67 (18). Anal. Calcd for $C_{20}H_{26}S_2$: C, 72.70; H, 7.93. Found: C, 72.79; H, 7.95.

2-(3,4,5-Trimethoxyphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran (9) (procedures A and B): ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (3 H, s), 1.77 (3 H, s), 2.42 (2 H, m), 2.92 (1 H, bd), 3.51 (1 H, bd), 3.83–3.88 (1 H, m), 3.86 (9 H, s), 6.59 (2 H, s); MS m/z (relative intensity) 294 (M^+, 14), 213 (11), 212 (100), 197 (25). Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.29; H, 7.53. Found: C, 65.15; H, 7.49.

2-(2-Furyl)-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran (10) (procedure A): ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (3 H, s), 1.74 (3 H, s), 2.54–2.56 (2 H, m), 2.93 (1 H, bd, J = 16.7 Hz), 3.26 (1 H, bd, J = 16.7 Hz), 4.11 (1 H, ap t), 6.13–6.15 (1 H, m), 6.30–6.32 (1 H, m), 7.34–7.36 (1 H, m); MS m/z (relative intensity) 194 (M^+, 68), 161 (10), 112 (100), 67 (11). Anal. Calcd for $C_{11}H_{14}OS$: C, 68.02; H, 7.27. Found: C, 67.90; H, 7.30.

Compound 11, major isomer (procedure A): ^1H NMR (600 MHz, $CDCl_3$) δ 1.78 (3 H, s), 2.50–2.67 (2 H, m), 3.00–3.11 (1 H, m), 3.34–3.39 (1 H, bs), 4.17 (1 H, ap t), 5.63–5.69 (1 H, m), 6.16–6.20 (1 H, m), 6.30–6.35 (1 H, m), 7.34–7.38 (1 H, m); MS m/z (relative intensity) 180 (M^+, 40), 113 (10), 112 (100), 84 (14), 53 (10).

Compound 11, minor isomer (procedure A): ^1H NMR (600 MHz, $CDCl_3$) δ 1.78 (3 H, bs), 2.50–2.67 (2 H, m), 2.89–2.98 (1 H, m), 3.21–3.33 (1 H, m), 4.09 (1 H, ap t), 5.56–5.62 (1 H, m), 6.16–6.20 (1 H, m), 6.30–6.35 (1 H, m), 7.34–7.38 (1 H, m); MS m/z (relative intensity) 180 (M^+, 40), 113 (10), 112 (100), 84 (14), 53 (10).

***endo*-3-(2-Furyl)-2-thiabicyclo[2.2.2]oct-5-ene (12) (procedures A and B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.47–1.86 (3 H, m), 2.11–2.12 (1 H, m), 3.27–3.29 (1 H, m), 3.49–3.66 (1 H, m), 4.48 (1 H, d, J = 2.9 Hz), 6.01–6.06 (2 H, m), 6.23–6.25 (1 H, m), 6.64 (1 H, ap t), 7.38–7.40 (1 H, m); MS m/z (relative intensity) 192 (M^+, 24), 115 (15), 114 (77), 113 (72), 112 (22), 111 (12), 91 (12), 81 (58), 80 (89), 79 (100), 77 (34). Anal. Calcd for $C_{11}H_{12}OS$: C, 68.74; H, 6.29. Found: C, 68.82; H, 6.23.

2-(2-Thienyl)-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran (13) (procedure A): ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (3 H, s), 1.75 (3 H, s), 2.59–2.61 (2 H, bs), 2.95 (1 H, bd, J = 17.0 Hz), 3.38 (1 H, bd, J = 17.0 Hz), 4.3 (1 H, ap t), 6.92–6.98 (2 H, m), 7.20–7.23 (1 H, m); MS m/z (relative intensity) 210 (M^+, 47), 128 (100), 127 (30), 126 (14). Anal. Calcd for $C_{11}H_{14}S_2$: C, 62.85; H, 6.71. Found: C, 63.04; H, 6.70.

Compound 14, major isomer (procedure A): ^1H NMR (600 MHz, $CDCl_3$) δ 1.78 (3 H, bs), 2.55–2.69 (2 H, m), 3.04–3.12 (1 H, m), 3.43–3.48 (1 H, m), 4.33 (1 H, dd, J = 13.0, 5.7 Hz), 5.63–5.70 (1 H, m), 6.92–7.02 (2 H, m), 7.19–7.24 (1 H, m); MS m/z (relative

Table I. Synthesis of Thioaldehydes and Their Trapping in Situ by a Diene

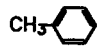
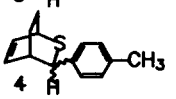
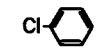
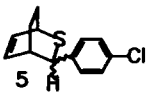
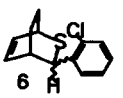
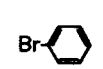
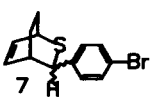
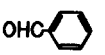
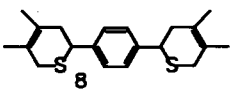
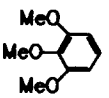
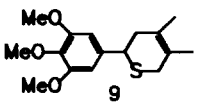
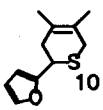
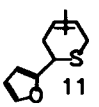
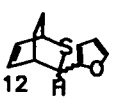
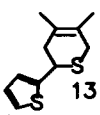
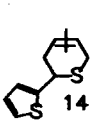
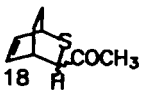
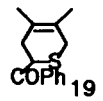
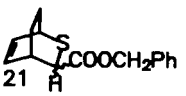
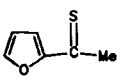
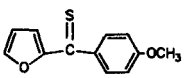
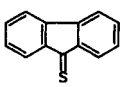
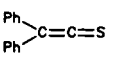
				$CoCl_2 \cdot 6H_2O$		TfOTMS		
							endo/exo[b]	
entry	R	diene	adduct	yield[a] (%)	endo/exo[b]	yield[a] (%)	1:2[c]	1:1[c]
1	Ph			90		88		
2	Ph			81[d]		79[d]		
3	Ph			94	95:5	85	97:3	4:96
4				78	95:5	48	94:6	5:95
5				89	97:3	87	95:5	30:70
6						72	94:6	8:92
7				85	96:4	52	90:10	–
8				62[e]				
9				60		78		
10				85				
11				75[d]				
12				85	96:4	45	95:5	–
13				85				
14				70[d]				
15				87	97:3	57	96:4	30:70
16	-CHO			88				
17	CH_3CO			70				

Table I (Continued)

				$CoCl_2 \cdot 6H_2O$		TfOTMS		
							endo/exo[b]	
entry	R	diene	adduct	yield[a] (%)	endo/exo[b]	yield[a] (%)	1:2[c]	1:1[c]
18	CH_3CO		 18	85	97:3			
19	PhCO		 19	85				
20	PhCO		 20	89	96:4			
21	$PhCH_2OCO$		 21	60	97:3			

[a] Yields of isolated products. [b] As determined by integration of the vinyl protons in the ^1H NMR spectra of the crude mixture. [c] RCHO:$(TMS)_2S$ molar ratio. [d] A 2:1 mixture of the two regioisomers was obtained. [e] 10% of the mono adduct was detected by GC/MS. [f] See ref 6f.

Table II. Synthesis of Thioketones

entry	product	reaction time	yield[a,b] (%)	ref
1		6 days	51	*c*
2		2 days	60[d]	*e*
3		2 days	68[d]	*f*
4		3 days	72	
5		3 days	49	*g*
6		30 min	85[h]	*i*
7		1 day	61[l]	*m*

[a] Unless otherwise stated, yields are of isolated products. [b] All compounds gave satisfactory spectroscopic data (^1H, ^{13}C NMR, MS) in agreement with those reported in the literature. [c] Kimura, K.; Niwa, H.; Motoki, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2751. [d] Determined by GLC. [e] Karakasa, T.; Motoki, S. *J. Org. Chem.* **1978**, *43*, 4147. [f] Dimukhamedov, A. I.; Sadimenko, A. P.; Sheinker, V. N.; Osipov, O. A. *Izv. Sev.-Kavk. Nauchn. Tsentra Vyssh. Shk. Estest. Nauki* **1984**, No. 3, 50. [g] Scheibye, S.; Lawesson, S.-O.; Romming, C. *Tetrahedron* **1982**, *38*, 993. [h] Isolated as a trimer. [i] Paquer, D.; Morin, L.; Vazeux, M.; Andrieu, C. G. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 52. [l] Isolated as a dimer. Reaction may be carried out even in the presence of $CoCl_2 \cdot 6H_2O$. [m] Seybold, G.; Heibl, C. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 248.

intensity) 196 (M^+, 53), 163 (12), 129 (21), 128 (100), 127 (40), 112 (17), 97 (11).

Compound 14, minor isomer (procedure A): ^1H NMR (600 MHz, $CDCl_3$) δ 1.78 (3 H, bs), 2.55–2.69 (2 H, m), 2.91–2.97 (1 H, m), 3.35–3.43 (1 H, m), 4.27 (1 H, dd, J = 8.5, 4.5 Hz), 5.60–5.63 (1 H, m), 6.92–7.02 (2 H, m), 7.19–7.24 (1 H, m); MS m/z (relative intensity) 196 (M^+, 53), 163 (12), 129 (21), 128 (100), 127 (40), 112 (17), 97 (11).

***endo*-3-(2-Thienyl)-2-thiabicyclo[2.2.2]oct-5-ene (15) (procedures A and B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.49–1.58 (1 H, m), 1.64–1.75 (1 H, m), 1.79–1.85 (1 H, m), 2.08–2.15 (1 H, m), 3.15–3.19 (1 H, m), 3.56–3.59 (1 H, m), 4.73 (1 H, d, J = 2.9 Hz), 6.09 (1 H, ap t), 6.73 (1 H, ap t), 6.86–6.90 (2 H, m), 7.13 (1 H, dd, J = 4.5, 1.5 Hz); MS m/z (relative intensity) 208 (M^+, 32), 130 (100), 129 (97), 128 (29), 127 (33), 97 (45), 80 (61), 79 (61), 77 (18). Anal. Calcd for $C_{11}H_{12}S_2$: C, 63.45; H, 5.81. Found: C, 63.52; H, 5.85.

***exo*-3-(2-Thienyl)-2-thiabicyclo[2.2.2]oct-5-ene (15) (procedure B)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.64–2.15 (4 H, m), 2.86–2.95 (1 H, m), 3.32–3.46 (1 H, m), 4.44 (1 H, bs), 6.47 (1 H, ap t), 6.61 (1 H, ap t), 6.98–7.00 (1 H, m), 7.11–7.17 (1 H, m), 7.20–7.23 (1 H, m). Anal. Calcd for $C_{11}H_{12}S_2$: C, 63.45; H, 5.81. Found: C, 63.53; H, 5.86.

2-Formyl-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran (16) (procedure A): ^1H NMR (200 MHz, $CDCl_3$) δ 2.02 (6 H, s), 2.28–2.39 (2 H, m), 3.03–3.13 (2 H, m), 3.55 (1 H, bs), 8.70 (1 H, s); MS m/z (relative intensity) 156 (M^+, 63), 141 (14), 138 (13), 127 (68), 123 (24), 112 (22), 99 (51), 94 (32), 93 (100), 91 (38), 79 (32), 77 (45), 67 (32), 65 (24), 59 (59), 41 (60).

2-Acetyl-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran (17) (procedure A): ^1H NMR (200 MHz, $CDCl_3$) δ 1.74 (6 H, s), 2.32 (3 H, s), 2.30–2.39 (2 H, m), 2.95 (2 H, bs), 3.59 (1 H, t); MS m/z (relative intensity) 170 (M^+, 32), 127 (100), 112 (11), 111 (12), 99 (48), 94 (13), 91 (30), 79 (14), 77 (33), 67 (12), 65 (14), 59 (50), 45 (33), 43 (99), 41 (40).

***endo*-3-Acetyl-2-thiabicyclo[2.2.2]oct-5-ene (18) (procedure A)**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.45–1.47 (2 H, m), 1.62–1.76 (2 H, m), 2.10 (3 H, s), 3.27–3.32 (1 H, m), 3.50–3.54 (1 H, m), 3.95 (1 H, d, J = 2.8 Hz), 6.22 (1 H, ap t), 6.55 (1 H, ap t); MS m/z (relative intensity) 168 (M^+, 4), 125 (42), 97 (100), 91 (30), 90 (40), 79 (26), 77 (14), 43 (33).

2-Benzoyl-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran (19) (procedure A): ^1H NMR (200 MHz, $CDCl_3$) δ 1.76 (6 H, s), 2.5 (2 H, m), 3.0 (2 H, bs), 4.5 (1 H, ap t), 7.43–7.56 (3 H, m), 7.98–8.02 (2 H, m); MS m/z (relative intensity) 232 (M^+, 23), 128 (11), 127 (100), 120 (24), 105 (77), 98 (24), 93 (54), 77 (63).

***endo*-3-Benzoyl-2-thiabicyclo[2.2.2]oct-5-ene (20) (procedure A)**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.53–1.87 (2 H, m), 2.11–2.23 (2 H, m), 3.36–3.43 (1 H, m), 3.46–3.52 (1 H, m), 4.72 (1 H, d, J = 2.6 Hz), 6.46–6.51 (2 H, m), 7.40–7.58 (3 H, m), 7.86–7.91 (2 H, m); MS m/z (relative intensity) 230 (M^+, 3), 152 (58), 125 (23), 105 (74), 97 (100), 91 (30), 80 (15), 79 (43), 77 (96). Anal. Calcd for $C_{14}H_{14}OS$: C, 73.03; H, 6.13. Found: C, 72.94; H, 6.09.

***endo*-2-Thiabicyclo[2.2.2]oct-5-ene-3-carboxylic acid benzyl ester (21) (procedure A)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.45–2.20 (6 H, m), 3.23–3.41 (1 H, m), 3.47–3.54 (1 H, m), 4.07 (1 H, d, J = 3.7 Hz), 6.21 (1 H, ap t), 6.64 (1 H, ap t), 7.32–7.40 (5 H, m); MS m/z (relative intensity) 260 (M^+, 6), 148 (17), 125 (21), 97 (56), 91 (100), 80 (14), 79 (18), 77 (11). Anal. Calcd for $C_{15}H_{16}O_2S$: C, 69.22; H, 6.20. Found: C, 68.99; H, 6.12.

2-((4-Methoxyphenyl)thiocarbonyl)furan: ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.70 (C=S), 162.87, 160.07, 149.05, 139.32, 131.27, 118.57, 113.48, 113.35, 55.52; MS m/z (relative intensity) 220 (6), 219 (19), 218 (M^+, 100), 217 (72), 203 (22), 187 (83), 175 (39), 147 (47), 111 (26), 108 (39), 103 (22), 89 (31), 87 (25), 82 (31), 77 (53), 64 (25), 63 (87), 62 (40), 51 (55), 50 (47), 45 (78). Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.05; H, 4.62. Found: C, 65.92; H, 4.55.

Registry No. 1, 84040-18-6; 2 (regioisomer 1), 87362-82-1; 2 (regioisomer 2), 136912-20-4; *endo*-3, 136912-21-5; *exo*-3, 136984-03-7; *endo*-4, 136912-22-6; *exo*-4, 136984-04-8; *endo*-5, 136912-23-7; *exo*-5, 136984-05-9; *endo*-6, 136912-24-8; *exo*-6, 136984-06-0; *endo*-7, 136912-25-9; 8, 136912-26-0; 9, 136912-27-1; 10, 117775-55-0; 11 (regioisomer 1), 136912-28-2; 11 (regioisomer 2), 136912-29-3; *endo*-12, 136912-30-6; 13, 117775-54-9; 14 (regioisomer 1), 136912-31-7; 14 (regioisomer 2), 136912-32-8; *endo*-15, 136912-33-9; *exo*-15, 136984-07-1; 16, 126019-26-9; 17, 80738-11-0; *endo*-18, 100946-74-5; 19, 80738-10-9; *endo*-20, 136912-34-0; *endo*-21, 136912-35-1; PhCHO, 100-52-7; *p*-MeC_6H_4CHO, 104-87-0; *p*-ClC_6H_4CHO, 104-88-1; *o*-ClC_6H_4CHO, 89-98-5; *p*-BrC_6H_4CHO, 1122-91-4; *p*-OHC_6H_4CHO, 623-27-8; CH_3COCHO, 78-98-8; PhCOCHO, 1074-12-0; $PhCH_2OCOCHO$, 52709-42-9; $H_2C{=}C(CH_3)C(CH_3){=}CH_2$, 513-81-5; $H_2C{=}C(CH_3)CH{=}CH_2$, 78-79-5; PhC(=S)Ph, 1450-31-3; $PhC(=S)CH_3$, 16696-68-7; $(Ph)_2C{=}C{=}S$, 136912-37-3; $MeSiSSiMe_3$, 3385-94-2; $CF_3SO_3SiMe_3$, 27607-77-8; $CoCl_2$, 7646-79-9; PhCOPh, 119-61-9; PhCOMe, 98-86-2; $Ph_2C{=}C{=}O$, 103006-94-6; 3,4,5-trimethoxybenzaldehyde, 86-81-7; 2-furaldehyde, 98-01-1; 2-thiophenecarboxaldehyde, 98-03-3; ethanediol, 107-22-2; 1,3-cyclohexadiene, 592-57-4; 2-(methylthiocarbonyl)furan, 97564-64-2; 2-[(4-methoxyphenyl)thiocarbonyl]furan, 136912-36-2; 9-thiofluorene, 830-72-8; thiocyclohexane, 57715-16-9; 2-acetylfuran, 1192-62-7; 2-[(methoxyphenyl)carbonyl]furan, 15970-74-8; 9-oxofluorene, 486-25-9; cyclohexanone, 108-94-1.

Supplementary Material Available: ^1H NMR spectra for compounds 2, 4, 5, 7, 11, and 14-19 (11 pages). Ordering information is given on any current masthead page.

meso-2,5-Dimercapto-*N*,*N*,*N*′,*N*′-tetramethyladipamide: A Readily Available, Kinetically Rapid Reagent for the Reduction of Disulfides in Aqueous Solution[1]

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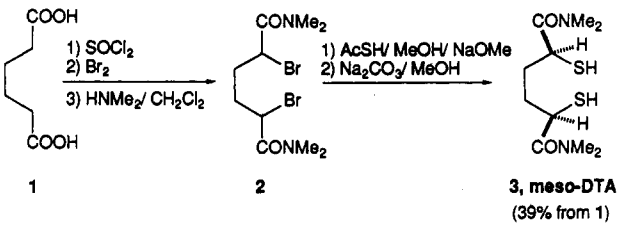
meso-2,5-Dimercapto-*N*,*N*,*N*′,*N*′-tetramethyladipamide (*meso*-DTA) reduces disulfide bonds up to 8 times faster (kinetic) than does dithiothreitol (DTT) in aqueous solution at pH 7.0. *meso*-DTA is easily synthesized in five steps (39% overall yield) from adipic acid. *meso*-DTA, which forms a cyclic disulfide, is less reducing than DTT by approximately 56 mV, but is much more reducing than mercaptoethanol.

Introduction

This paper reports the reduction of small organic disulfides and protein disulfides in water at pH 7.0 using a new reagent, *meso*-2,5-dimercapto-*N*,*N*,*N*′,*N*′-tetramethyladipamide (*meso*-DTA). Disulfide-reducing reagents are used in biochemistry to inhibit the oxidation of thiol groups and to reduce disulfide groups in proteins.[3-5] A useful thiol reducing reagent for disulfides should have $pK_a \sim 7.0$ for the SH group, a high reduction potential, ready availability, an unobjectionable odor, high solubility in water, kinetic stability at room temperature, and low toxicity.[6,7]

We have previously examined *N*,*N*′-dimethyl-*N*,*N*′-bis(mercaptoacetyl)hydrazine (DMH),[8] a reagent that reduces disulfides faster than dithiothreitol (DTT), but is more expensive to synthesize. Mercaptoethanol (ME) and dithiothreitol (DTT)[6] are the most commonly used disulfide-reducing reagents in biochemistry.[3] The principal advantage of ME is its low cost. ME has, however, the disadvantage of a low reduction potential and a relatively high pK_a, 9.6. The primary advantage of DTT is that it is strongly reducing. DTT also has several disadvantages: oxidation of DTT by O_2 in the presence of transition-metal ions can generate hydrogen peroxide;[9] it is a strong chelating agent and can sequester essential ions (especially transition metals); it is not a fast reductant (the lower pK_a of the thiol groups in DTT is 9.2;[10] thus only about 1% of DTT exists as the thiolate at pH 7.0); it is expensive.[11] (For nomenclature, we indicate the oxidized form of a thiol, the disulfide, by the superscript "ox" and leave the reduced

Scheme I



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(11) The present price of DTT is $870/mol from Aldrich.

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