References and Notes

(1) T. H. James, in "The Theory of the Photographic Process", 3rd ed, C. E. K. Mees and T. H. James, Ed., Macmillan, New York, N.Y., 1966, pp 344–346.
(2) G. T. Eaton, in "The Theory of the Photographic Process", 3rd ed, C. E. K. Mees and T. H. James, Ed., Macmillan, New York, N.Y., 1966, pp 398–405.
(3) E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.*, **37**, 563 (1959).
(4) E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran, and R. D. Hites, *Can. J. Chem.*, **36**, 801 (1958).
(5) A. Meriljan and P. D. Gardner, *J. Org. Chem.*, **30**, 3965 (1965).
(6) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, **25**, 9 (1960).
(7) T. Zawadowski, *Rocz. Chem.*, **42**, 297 (1968).
(8) R. Grice and L. N. Owen, *J. Chem. Soc.*, 1947 (1963).
(9) N. P. Newreiter, *J. Org. Chem.*, **28**, 3486 (1963).
(10) J. M. Grasshoff and L. D. Taylor, U.S. Patent 3 698 898 (1972).
(11) J. M. Grasshoff and L. D. Taylor, U.S. Patent 3 674 478 (1972).
(12) J. M. Grasshoff and L. D. Taylor, U.S. Patent 3 685 991 (1972).
(13) J. M. Grasshoff and L. D. Taylor, U.S. Patent 3 932 480 (1976).
(14) J. P. Horwitz, B. Fisher, and A. Tomasewski, *J. Am. Chem. Soc.*, **81**, 3076 (1959).

Synthesis of γ- and δ-(1,3-Dithianyl) β-Keto Esters[1]

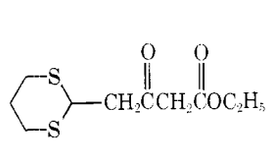
Edward C. Taylor* and John L. LaMattina[2]

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

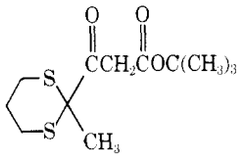
Received September 21, 1977

The preparations of ethyl γ-(1,3-dithian-2-yl)acetoacetate (**1**), *tert*-butyl 3-oxo-4-trimethylenedithiopentanoate (**2**), and ethyl 5-benzyloxy-3-oxopentanoate (**3**) are described. Some additional reactions relevant to the chemistry of dithiane are also discussed.

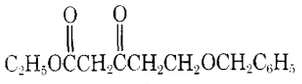
Previous papers from this laboratory have described an unambiguous approach to the synthesis of 6-substituted pteridines by guanidine cyclization of 2-amino-3-cyano (or alkoxycarbonyl) pyrazines suitably substituted at position 5. These latter critical intermediates were prepared in turn by cyclization of aminomalononitrile (or esters of α-aminocyanoacetic acid) with an α-ketoaldoxime, followed by deoxygenation of the resulting pyrazine 1-oxide (see Scheme I).[3] In this sequence, the group α to the carbonyl of the α-ketoaldoxime becomes the C-6 substituent on the final pteridine. Since the α-ketoaldoximes are themselves prepared from β-keto esters by hydrolysis, oximation, and subsequent decarboxylation, the preparation of a specific C-6 substituted pteridine requires an appropriately substituted β-keto ester. Our current interest in the preparation of certain 2,4-diaminopteridines carrying side chains at position 6 substituted with carbonyl groups thus necessitated the preparation of a variety of β-keto esters containing a (potential) carbonyl at either the γ or δ position. This paper describes our efforts to prepare β-keto esters **1**, **2**, and **3**.



1

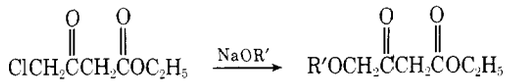


2



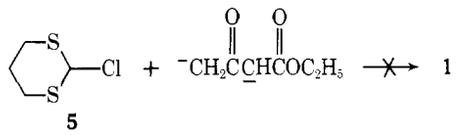
3

Initial approaches to **1** attempted to attach the dithiane moiety directly to the γ position of an appropriately substituted acetoacetic ester. A promising model was the successful conversion of ethyl γ-chloroacetoacetate (**4**) with excess alkoxide to yield γ-alkoxy derivatives in good yield.[4] Unfortunately, however, no reaction occurred between 2-lithio-1,3-dithiane and **4** (as its sodium salt). The dithiane anion is apparently not sufficiently nucleophilic to displace the γ-chloro substituent.[5] Attempts to carry out this reaction in the presence of 1 equiv of sodium iodide[6] resulted only in self-condensation of **4**.



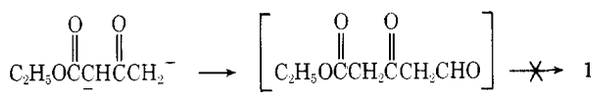
4

An alternative approach to **1** involves treatment of 2-chloro-1,3-dithiane (**5**)[7] with the dianion of ethyl acetoacetate.[8] No displacement of halide ion occurred; instead, the dianion was protonated by **5**, leading to the recovery of ethyl acetoacetate and to the decomposition of the dithiane moiety.



5

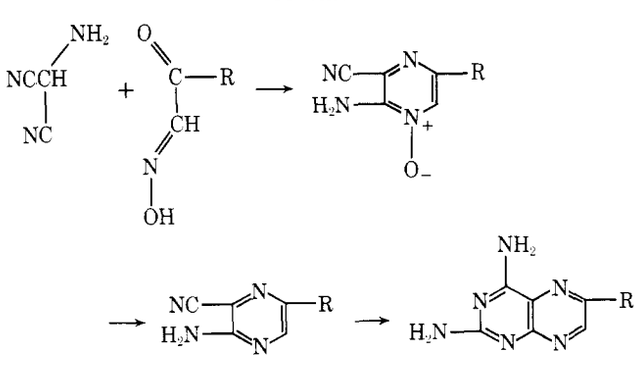
Since direct linkage of 1,3-dithiane with the γ position of ethyl acetoacetate did not seem feasible, an attempt was made to incorporate this moiety indirectly. Treatment of the dianion of ethyl acetoacetate with methyl formate gave the unstable aldehyde **6**,[9] but attempted reaction of this material with



6

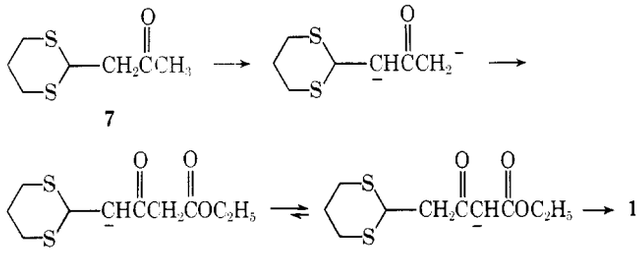
propane-1,3-dithiol resulted only in the formation of an intractable tar; no **1** could be isolated.

Scheme I



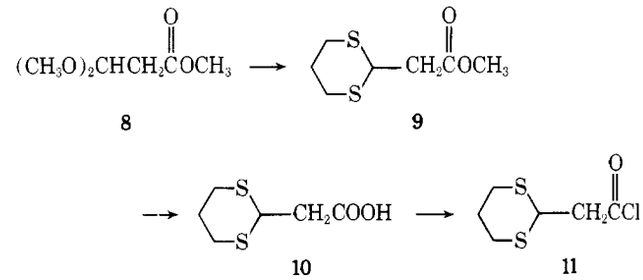
0022-3263/78/1943-1200$01.00/0

An alternative conceptual approach to **1** would utilize a 1,3-dithiane unit already possessing a carbon substituent at position 2 capable of elaboration to the desired β-keto ester. Thus, α-(1,3-dithian-2-yl)acetone (**7**), although an unsymmetrical ketone, would be expected to undergo selective functionalization on the methyl group (kinetically favored product).[10] Treatment of **7** with 2 equiv of lithium diethylamide, followed by quenching with ethyl chloroformate, indeed gave the desired β-keto ester **1** but only in 15% yield. All attempts to improve this reaction by the use of different solvents or alternate bases failed.

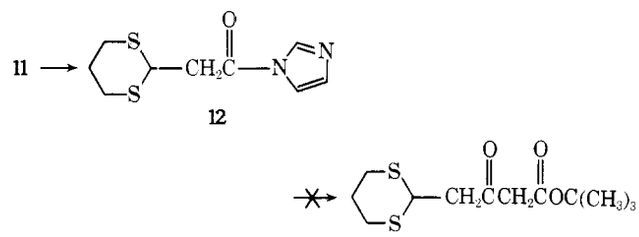


The use of diketene as a β-keto ester synthon was then briefly examined. It is known that diketene reacts with chlorine to give γ-chloroacetoacetyl chloride which, on treatment with alcohols, affords esters of γ-chloroacetoacetic acid.[11] It therefore seems reasonable to anticipate that treatment of diketene with 2-chloro-1,3-dithiane using titanium tetrachloride as catalyst, followed by addition of ethanol, might yield the desired β-keto ester **1**. Instead, ethyl acetoacetate was recovered from the reaction mixture, and it appears that 2-chloro-1,3-dithiane is completely unreactive toward diketene. Only tar formation was observed upon attempts to react diketene with triethyl orthoformate in the presence of boron trifluoride as catalyst.[12]

A stepwise approach to **1** was then considered. Treatment of methyl 3,3-dimethoxypropanoate (**8**)[13] with propane-1,3-dithiol gave methyl (1,3-dithian-2-yl)acetate (**9**) in 81% yield. Hydrolysis of **9** to the corresponding carboxylic acid **10**,

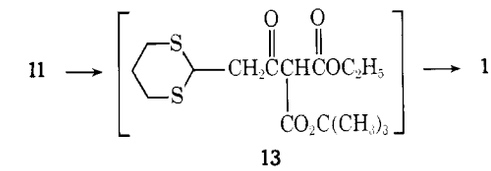


followed by treatment with oxalyl chloride, gave the corresponding acid chloride **11** in 93% overall yield. Surprisingly, however, attempts to convert **11** directly to the desired β-keto ester **1** were unsuccessful. For example, only decomposition was observed when **11** was treated with 1 equiv of lithio *tert*-butyl acetate in the presence of 1 equiv of lithium diethylamide.[14] Since this may have been the result of deprotonation of **11** by the strongly basic nucleophile, **11** was converted to the acyl imidazole **12**, which was then treated with lithio *tert*-butyl trimethylsilylacetate, a reagent developed by Rathke for the preparation of β-keto esters.[15] Unexpectedly,

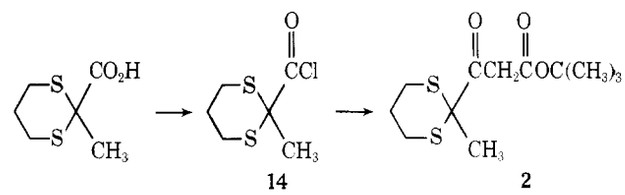


however, *tert*-butyl trimethylsilylacetate was obtained in quantitative yield from this reaction; no trace of acylation by **12** was observed.

In order to avoid the use of a nucleophilic reagent which was also strongly basic, **11** was treated with the magnesium ethoxide salt of *tert*-butyl ethyl malonate,[16] and the resulting adduct **13** was then heated under reflux in xylene in the presence of *p*-toluenesulfonic acid as catalyst. The desired β-keto ester **1** was thus finally obtained in 44% overall yield from **9**.

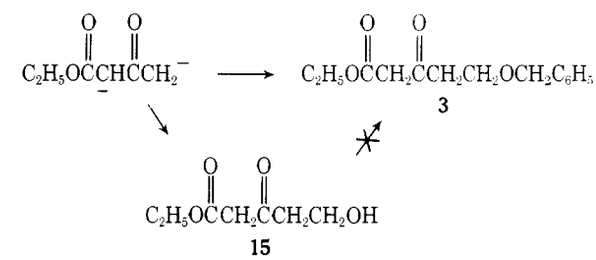


Preparation of the desired β-keto esters **2** and **3** proved to be more straightforward. Thus, **2** was obtained from 2-methyl-1,3-dithiane-2-carboxylic acid[5] by initial conversion with oxalyl chloride to its acid chloride **14**, followed by reaction



with lithio *tert*-butyl acetate (65% overall yield). The success of this reaction, in contrast to the failure of the corresponding attempted acylation of lithio *tert*-butyl acetate with the acid chloride **11**, is consistent with our assumption that monosubstituted dithiane substrates are incompatible with nucleophiles which are strong bases.

Finally, the desired β-keto ester **3** was prepared directly by alkylation of the dianion of ethyl acetoacetate with chloromethyl benzyl ether. This method proved to be superior to an alternative route which involved condensation of the dianion of ethyl acetoacetate with formaldehyde to give **15**, followed by attempted alkylation of the hydroxyl group with benzyl chloride; this latter step was complicated by competitive alkylation on the enol oxygen.

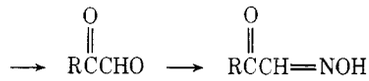


Although the preparation of **1**, **2**, and **3** completed this phase of the project, some additional reactions relevant to the chemistry of dithiane were carried out which are reported briefly below.

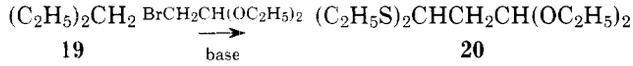
Since our purpose in preparing various γ-substituted β-keto esters was to convert them subsequently to α-ketoaldoximes, an alternative synthesis of these latter key intermediates for pteridine synthesis was explored in which the dithiane moiety was designed to serve as the potential α-keto functionality. Thus, it was envisioned that a 2-substituted dithiane might then, by selective trans-oximation with acetone oxime,[17] give the desired α-ketoaldoxime. Treatment of 2-lithio-1,3-dithiane with bromoacetaldehyde diethylacetal gave the known acetal **16**.[5] Formylation of **16** then gave the aldehyde **17** in good yield, but all attempts to deprotect this latter intermediate (NBS in aqueous acetone, NCS, $AgNO_3$ in aqueous ac-

etonitrile,[18] SO_2Cl_2, silica gel[19]) failed. Attempted conversion of the aldehyde functionality to its corresponding acetal led only to polymerization.

16, R = $CH_2CH(OC_2H_5)_2$ **17**, R = $CH_2CH(OC_2H_5)_2$

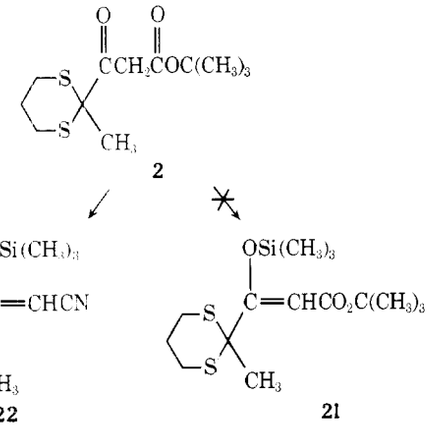


In view of this failure to convert the substituted dithiane **17** to the corresponding α-ketoaldehyde, we briefly explored the possible utilization in this reaction scheme of an alternative acyl anion equivalent, ethyl ethylthiomethyl sulfoxide, **18**.[20] We have found, as have others,[21] that **18** could not be prepared by $NaIO_4$ oxidation of bis(ethylthio)methane (**19**) as had been reported:[20] instead, **18** was prepared by peracid oxidation of **19**.[21] However, attempted reaction of the anion of **18** (under conditions identical to those successfully employed in the formation of **16**) with bromoacetaldehyde diethylacetal was unsuccessful, and only starting materials were recovered. It appears that bromoacetaldehyde diethyl acetal is an unpredictable electrophile; although no reaction took place with the dianion of ethyl acetoacetate, it did react successfully with the anion of bis(ethylthio)methane (**19**) to give the expected product **20**.

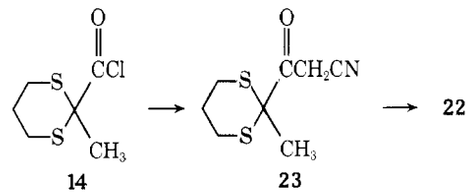


19 **20**

One curious reaction of the β-keto ester **2** merits comment at this time. We were interested in the conversion of **2** to its *O*-trimethylsilyl derivative **21**, which was to serve as a substrate for a subsequent oximation. A recent procedure[22] for the preparation of such derivatives from methyl β-keto esters uses hexamethyldisilazane and a catalytic amount of imidazole. Reaction of **2** under these conditions gave a product which, although it possessed the expected trimethylsilyl grouping, had lost the *tert*-butyl group and apparently possessed a nitrile substituent (IR band at 2210 cm^{-1}). The presence of nitrogen was confirmed by combustion analysis which indicated a molecular formula of $C_{11}H_{19}NOS_2Si$. It thus appeared that the product of this reaction was 1-cyano-2-trimethylsilyloxy-3-trimethylenedithio-1-butene (**22**), and this was confirmed by an independent synthesis from the acid chloride **14**. Thus, treatment of **14** with lithioacetonitrile[23] gave the β-ketonitrile **23**, which underwent normal O-trimethylsilation to give **22** upon treatment with hexamethyldisilazane in the presence of imidazole. The mechanism of this unusual transformation of **2** to **22** is unclear, but it may not represent a general reaction, since the ester moiety of *tert*-butyl acetoacetate remains intact under the same reaction conditions.



22 **21**



14 **23**

Experimental Section

Methyl (1,3-Dithian-2-yl)acetate (9). A mixture of 17.2 g (0.116 mol) of methyl 3,3-dimethoxypropanoate, 1.25 g (0.166 mol) of propane-1,3-dithiol, 0.2 g of *p*-toluenesulfonic acid, and 200 mL of benzene was heated at reflux for 25 h. The mixture was concentrated and the residue distilled under reduced pressure. After a small amount of forerun was collected, the product distilled at 108–109 °C (0.3 Torr); yield 18.0 g (81%). NMR ($CDCl_3$) δ 1.8–2.3 (m, 2), 2.8–3.1 (m, 6), 3.79 (s, 3), 4.49 (t, 1); IR (neat) 1735 (ester) cm^{-1}.

Anal. Calcd for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29; S, 33.35. Found: C, 43.67; H, 6.02; S, 33.42.

(1,3-Dithian-2-yl)acetic Acid (10). A mixture of 14.8 g (77 mmol) of **9**, 6.16 g (154 mmol) of sodium hydroxide, and 50 mL of water was heated at reflux for 0.5 h. The mixture was cooled to room temperature and then acidified with concentrated HCl. After cooling, the mixture was filtered, washed with cold water, and then dried in vacuo to afford 13.3 g (97%) of **10** as a white fluffy solid, mp 109–110 °C. This material was used without further purification, although it could be recrystallized from CCl_4: NMR ($CDCl_3$) δ 1.8–2.3 (m, 2), 2.8–3.1 (m, 4), 4.42 (t, 1), 9.90 (s, 1); IR (KBr) 3200–2800 (OH), 1690 (carbonyl) cm^{-1}.

Anal. Calcd for $C_6H_{10}O_2S_2$: C, 41.42; H, 5.65; S, 35.97. Found: C, 41.13; H, 5.19; S, 35.35.

(1,3-Dithian-2-yl)acetyl Chloride (11). A mixture of 1.78 g (10 mmol) of **10**, 0.40 g (10 mmol) of sodium hydroxide, and 10 mL of water was gently heated until homogeneous and then concentrated under reduced pressure. The resulting sodium salt was dried in vacuo [100 °C (0.5 Torr) for 2 h] and then added slowly to a stirred solution of 1.52 g (12 mmol) of oxalyl chloride in 40 mL of benzene at room temperature. After addition was complete, the mixture was heated at reflux for 2 h, cooled, filtered to remove NaCl, and concentrated under reduced pressure to give 1.9 g (100%) of **11** as a light brown liquid. This material was used without further purification: NMR ($CDCl_3$) δ 1.7–2.1 (m, 2), 2.7–3.1 (m, 4), 3.27 (d, 2), 4.30 (t, 1); IR (neat) 1790 (carbonyl) cm^{-1}.

(1,3-Dithian-2-yl)acetylimidazole (12). To a stirred solution of 2.45 g (36 mmol) of imidazole in 25 mL of dry THF at room temperature was added a solution of 3.5 g (18 mmol) of **11** in 10 mL of THF. The mixture was heated at reflux for 0.5 h, cooled, and filtered, and the filtrate was concentrated under reduced pressure to give an oil which solidified while being dried in vacuo overnight. Recrystallization from CCl_4 afforded 3.05 g of **12** as a white solid, mp 79–80 °C.

Anal. Calcd for $C_9H_{12}N_2OS_2$: C, 47.34; H, 5.30; N, 12.27; S, 28.09. Found: C, 47.44; H, 5.52; N, 12.08; S, 27.88.

Ethyl γ-(1,3-Dithian-2-yl)acetoacetate (1). Method A. Freshly prepared magnesium ethoxide (9.12 g, 80 mmol) was added to a 500-mL three-necked round-bottomed flask fitted with a gas-inlet tube, condenser, and magnetic stirrer, and containing 150 mL of sodium-dried ether. While stirring under nitrogen, 13.1 g (80 mmol) of *tert*-butyl ethyl malonate was added. The mixture was heated at reflux for 15 min, and then a solution of 15.7 g (80 mmol) of **11** in 50 mL of ether was cautiously added. The mixture was again heated at reflux for 3 h. After cooling, 100 mL of 10% H_2SO_4 was slowly added. The ether layer was separated and the aqueous solution was extracted twice with 20-mL portions of ether. The combined ether layers were dried (Na_2SO_4), filtered, and evaporated, leaving a light yellow oil. The oil was dissolved in 150 mL of xylene, 0.35 g of *p*-toluenesulfonic acid was added, and the mixture was heated at reflux for 3.5 h. The mixture was concentrated and the residual dark oil was scratched to induce crystallization. Recrystallization of this crude solid from cyclohexane (Norite) afforded 8.74 g (44%) of **1** as an off-white solid: mp 64–65 °C; NMR ($CDCl_3$) δ 1.32 (t, 3), 1.9–2.3 (m, 6), 3.58 (s, 2), 4.25 (q, 2), 4.54 (t, 1) (these last two sets of signals overlap); IR (KBr) 1740 (ester), 1715 (ketone) cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3S_2$: C, 48.36; H, 6.49; S, 25.82. Found: C, 48.59; H, 6.30; S, 25.68.

Method B. A solution of lithium diisopropylamide was prepared by adding, *via syringe*, 4.4 mL (10.5 mmol) of 2.4 M *n*-butyllithium

to a stirring solution of 1.06 g (10.5 mmol) of diisopropylamine in 15 mL of dry THF under nitrogen at −78 °C. This was stirred at −78 °C for 0.5 h. To the base solution was added dropwise a solution of 1.76 g (10.0 mmol) of α-(1,3-dithian-2-yl)acetone (7) in 15 mL of dry THF. After addition was complete, the mixture was stirred at −78 °C for 45 min. To the anion solution was added 1.14 g (10.5 mmol) of freshly distilled ethyl chloroformate. The mixture was stirred at −78 °C for 5 min and then allowed to warm to room temperature for 0.5 h. The mixture was poured into 100 mL of saturated NaCl, and the organic layer was separated from the basic aqueous solution. The aqueous solution was acidified with 10% HCl, and then extracted three times with a total of 100 mL of $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4), filtered, and evaporated, leaving 0.35 g (15%) of a light yellow oil which solidified on standing. Recrystallization from 2-propanol afforded a white fluffy solid, mp 64–65 °C, identical in all respects with the material prepared by method A. Attempts to improve the yield by using excess base (i.e., 2 equiv of LDA) led to lower yields.

α,α-Trimethylenedithiopropionyl Chloride (14). A mixture of 1.78 g (10 mmol) of 2-methyl-1,3-dithiane-2-carboxylic acid, 0.40 g (10 mmol) of sodium hydroxide, and 15 mL of water was gently heated until homogeneous and then concentrated under reduced pressure. The resulting sodium salt was dried in vacuo (100 °C, 0.5 Torr) for 2 h) and then added slowly to a solution of 1.52 g (12 mmol) of oxalyl chloride in 40 mL of benzene at room temperature. After addition was complete, the mixture was heated to reflux for 2 h, cooled, filtered to remove NaCl, and concentrated under reduced pressure to give 1.9 g (100%) of **14** as a light orange oil. This material was used without further purification: NMR ($CDCl_3$) δ 1.70 (s, 3), 1.8–3.3 (m, 6); IR (neat) 1755 (carbonyl) cm^{-1}.

***tert*-Butyl 3-Oxo-4-trimethylenedithiopentanoate (2).** A three-necked 250-mL round-bottomed flask fitted with a gas-inlet tube, addition funnel, and magnetic stirring bar was charged with 52 mL (0.126 mol) of 2.4 M *n*-butyllithium. While stirring under nitrogen, the flask was cooled (ice bath) and a solution of 12.7 g (0.126 mol) of diisopropylamine in 50 mL of dry THF was added over 15 min. This solution of LDA was cooled to −70 °C and 7.3 g (63 mmol) of *tert*-butyl acetate in 25 mL of dry THF was added. After stirring at −70 °C for 0.5 h, a solution of 63 mmol of **14** in 50 mL of dry THF was added dropwise to the anion solution. This mixture was stirred at −70 °C for 0.5 h, allowed to warm to room temperature over 0.5 h, and quenched with 100 mL of 10% HCl. The organic layer was separated and the aqueous solution extracted twice with 50-mL portions of ether. The combined organic layers were washed six times with saturated aqueous NaCl (to remove traces of acid), dried over Na_2SO_4, and filtered, and the filtrate was evaporated. The residual brown liquid was distilled under reduced pressure to give 11.2 g (64%) of **2** as a colorless liquid: bp 122–124 °C (0.01 Torr); NMR ($CDCl_3$) δ 1.38 (s, 9), 1.56 (s, 3), 1.8–3.3 (m, 6), 3.51 (s, 2); IR (neat) 1735 (ester), 1700 (ketone) cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_3S_2$: C, 52.14; H, 7.30. Found: C, 52.02; H, 7.17.

Ethyl 5-Hydroxy-3-oxopentanoate (15). A mixture of 2.6 g (0.11 mol) of sodium hydride (prepared by washing 5.2 g of 50% NaH/paraffin oil with pentane) and 75 mL of dry THF was stirred at 0 °C under nitrogen in a 250-mL round-bottomed flask fitted with an addition funnel, gas-inlet tube, and septum. To this was added dropwise a solution of 13.0 g (0.10 mol) of ethyl acetoacetate in 75 mL of dry THF. Stirring was continued at 0 °C for 0.5 h after addition was complete. To this anion solution was added 42 mL (0.10 mol) of a 2.4 M solution of *n*-butyllithium and the resulting dianion solution was stirred at 0 °C for 1 h. A side-armed flask containing 3.0 g (0.10 mol) of paraformaldehyde was inserted between the nitrogen source and the reaction vessel. The paraformaldehyde was vaporized by heating with a heat gun, and these vapors were carried into the reaction flask by the nitrogen stream. After 0.5 h, no paraformaldehyde remained. The reaction mixture was stirred at room temperature for 15 min, neutralized with 10% HCl, and extracted three times with a total of 100 mL of $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4), filtered, and evaporated to give a light brown liquid. Distillation under reduced pressure afforded 1.8 g (14%) of ethyl acetoacetate followed by 4.75 g (30%) of colorless **15:** bp 106–108 °C (0.3 Torr). The remaining material decomposed during distillation: NMR ($CDCl_3$) δ 1.17 (t, 3), 2.66 (t, 2), 3.40 (s, 2), 3.73 (t, 2), 4.07 (q, 2); IR (neat) 3200–3600 (OH), 1750 (ester), 1710 (ketone) cm^{-1}.

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.29; H, 7.74.

4,4-Diethoxy-2-trimethylenedithiobutanal (17). A solution of 29.7 g (0.126 mol) of 1,1-diethoxy-3,3-trimethylenedithiopropane (**16**)[4] in 200 mL of dry THF was stirred at −30 °C under nitrogen in a 500-mL round-bottomed flask fitted with an addition funnel with septum and a thermometer. To this solution was added dropwise 54 mL (0.13 mol) of 2.4 M *n*-butyllithium. After addition was complete, the light brown solution was stirred at −20 °C for 2 h and poured into a mixture of 36.6 g (0.50 mol) of DMF (distilled from CaH_2) and 100 mL of dry THF, and the resulting yellow solution was stirred at −15 °C for 18 h. It was then added to 400 mL of water, and the organic layer was separated. The aqueous solution was extracted with three 50-mL portions of ether, the combined organic layers were washed twice with water, once with aqueous 7% KOH solution, once more with water, and then dried over Na_2SO_4, filtered, and evaporated. Vacuum distillation of the residual brown oil afforded 25.2 g (78%) of **17** as a colorless oil: bp 109 °C (0.05 Torr); NMR ($CDCl_3$) δ 1.15 (t, 6), 1.8–3.8 (m, 12), 4.70 (t, 1), 8.88 (s, 1); IR (neat) 2700 (**CHO**), 1710 (carbonyl) cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_3S_2$: C, 49.97; H, 7.62; S, 24.25. Found: C, 50.17; H, 7.37; S, 24.31.

1,1-Diethoxy-3,3-diethylthiopropane (20). A solution of 6.8 g (50 mmol) of bis(ethylthio)methane in 50 mL of dry THF was stirred at −30 °C under nitrogen in a 250-mL three-necked round-bottomed flask fitted with a thermometer, gas-inlet tube, addition funnel, and magnetic stirring bar. *n*-Butyllithium (21.6 mL, 52 mmol, as a 2.4 M solution) was added dropwise, with the temperature maintained below −20 °C. After addition was complete, the mixture was stirred at −20 °C for 1.5 h, and bromoacetaldehyde diethyl acetal (10.8 g, 55 mmol) was added. The mixture was stirred at −15 °C for 46 h and poured into 200 mL of water, and the organic layer was separated. The aqueous phase was washed with three 30-mL portions of ether. The combined organic layers were washed with water, aqueous 7% KOH, and saturated NaCl solution, and then dried over Na_2SO_4, filtered, and evaporated. Vacuum distillation of the residual light brown oil afforded 3.9 g (31%) of **20** as a colorless oil: bp 108 °C (0.15 Torr); NMR (neat) δ 0.9–1.3 (m, 12), 1.92 (q, 2), 2.50 (m, 4), 3.2–3.9 (m, 5), 4.70 (t, 1).

Anal. Calcd for $C_{11}H_{24}O_2S_2$: C, 52.34; H, 9.58; S, 25.40. Found: C, 52.34; H, 9.71; S, 25.67.

Ethyl 5-Benzyloxy-3-oxopentanoate (3). Sodium hydride, as a 50% paraffin oil dispersion (1.3 g, 27.5 mmol), was washed with pentane and added to a three-necked 250-mL round-bottomed flask fitted with a gas inlet tube, addition funnel, magnetic stirring bar, and septum. Dry THF (20 mL) was added, the slurry was stirred under nitrogen at −5 °C, and a solution of ethyl acetoacetate (3.25 g, 25 mmol) in 20 mL of dry THF was added dropwise. After addition was complete, the mixture was stirred for 10 min, 11.2 mL (26 mmol) of a 2.4 M solution of *n*-butyllithium was added dropwise, and the dianion solution was stirred for 10 min at 0 °C. A solution of 3.91 g (25 mmol) of benzyl chloromethyl ether in 10 mL of dry THF was then added, and the mixture was stirred at 0 °C for 1 h and then poured into 50 mL of saturated NaCl solution. The mixture was acidified with 10% HCl and the organic layer separated. The aqueous solution was extracted twice with 25-mL portions of ether, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give 6.3 g of a light yellow oil. The material was purified by passing through a silica gel column (35 × 3.5 cm), with $CHCl_3$ as the eluent, to give 4.42 g (70%) of **3** as a colorless oil. The material could be further purified by distillation [bp 135 °C (0.01 Torr)].

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.00; H, 7.13.

3-Oxo-4-trimethylenedithiovaleronitrile (23). To a solution of 16.7 mL (40 mmol) of a 2.4 M solution of *n*-butyllithium in 10 mL of dry THF, stirred under nitrogen at −70 °C, was added dropwise a solution of 1.64 g (40 mmol) of dry acetonitrile in 10 mL of dry THF. After addition was complete, the mixture was stirred at −70 °C for 1 h, during which time a milky white suspension formed. To this was added a solution of 3.92 g (20 mmol) of acid chloride **14** in 10 mL of dry THF. After addition was complete, the mixture was stirred at −70 °C for 0.5 h, allowed to warm to room temperature over 0.5 h, and poured into 50 mL of 10% HCl. The organic layer was separated, and the aqueous phase was extracted twice with a total of 25 mL of ether. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated, leaving a brown oil. Distillation under reduced pressure afforded 3.46 g (86%) of a colorless oil, bp 148–150 °C (0.05 Torr), which solidified upon cooling; mp 50–53 °C. Recrystallization from benzene/cyclohexane afforded **23** as white needles, mp 59–60 °C.

Anal. Calcd for $C_8H_{11}NOS_2$: C, 47.73; H, 5.51; N, 6.96; S, 31.86. Found: C, 47.92; H, 5.53; N, 6.77; S, 31.90.

1-Cyano-2-trimethylsilyloxy-3-trimethylenedithio-1-butene (22). Method A. In a dry 50-mL three-necked flask, swept with dry nitrogen and equipped with a magnetic stirrer and condenser, was placed 2.01 g (10.0 mmol) of **23** and 0.04 g (0.6 mmol) of recrystallized

imidazole. Hexamethyldisilazane (10 mL, 43 mmol) was then added and the mixture was heated at reflux for 2 h. The mixture was concentrated and the residue distilled under reduced pressure, affording 2.29 g (84%) of a colorless oil, bp 124 °C (0.05 Torr), which solidified on scratching. Recrystallization from cyclohexane afforded **22** as a white solid: mp 57–58 °C; NMR ($CDCl_3$) δ 0.32 (s, 9), 1.52 (s, 3), 1.7–2.9 (m, 6), 5.50 (s, 1); IR (neat) 2210 (nitrile) cm^{-1}. Satisfactory microanalytical values could not be obtained for this compound, since it hydrolyzed back to **23** with extreme ease (Found: C, 47.63; H, 5.30; N, 6.96; S, 32.32; *m/e* 201).

Method B. In a dry 50-mL three-necked round-bottomed flask, swept with dry nitrogen and equipped with a magnetic stirrer and condenser, was placed 2.76 g (10.0 mmol) of keto ester **2** and 0.04 g (0.06 mmol) of recrystallized imidazole. Hexamethyldisilazane (10 mL, 43 mmol) was then added and the mixture was heated at reflux for 2 h. The mixture was concentrated and the residue was distilled at reduced pressure, affording 2.70 g of a colorless oil, bp 127 °C (0.08 Torr), which solidified on scratching. Recrystallization from cyclohexane afforded a white solid, mp 57–58 °C, identical in all respects with the material prepared by method A.

Registry No.—**1,** 64714-77-8; **2,** 64714-78-9; **3,** 64714-79-0; **7,** 18554-39-7; **8,** 7424-91-1; **9,** 64714-80-3; **10,** 64714-81-4; **11,** 64714-82-5; **12,** 65714-83-6; **14,** 64714-84-7; **15,** 64714-85-8; **16,** 5849-13-8; **17,** 64714-86-9; **20,** 64714,87-0; **22,** 64714-88-1; **23,** 64714-89-2; propane-1,3-dithiol, 109-80-8; imidazole, 288-32-4; *tert*-butyl ethyl malonate, 32864-38-3; ethyl chloroformate, 541-41-3; 2-methyl-1,3-dithiane-2-carboxylic acid, 4901-19-3; *tert*-butyl acetate, 540-88-5; ethyl acetoacetate, 141-97-9; bis(ethylthio)methane, 4396-19-4; bromoacetaldehyde diethyl acetal, 2032-35-1; benzyl chloromethyl ether, 3587-60-8; acetonitrile, 75-05-8; hexamethyldisilazane, 999-97-3.

References and Notes

(1) We are grateful to the National Cancer Institute, National Institutes of Health, Bethesda, Md. (Grant CA 12876), Eli Lilly and Co., Indianapolis, Ind., and Lonza AG for financial support of this work and for generous gifts of chemicals.
(2) NIH Postdoctoral Fellow (CA 05017-2), 1975–1977.
(3) (a) See: E. C. Taylor and J. V. Berrier, *Heterocycles,* **6,** 449 (1977) and preceding papers in this series; (b) E. C. Taylor, in "Chemistry and Biology of Pteridines", W. Pfleiderer, Ed., Walter de Gruyter, Berlin, 1975, pp 543–573.
(4) See: Lonza AG brochure on "γ-Alkoxyketoesters".
(5) E. J. Corey and D. Seebach, *J. Org. Chem.,* **40,** 231 (1975).
(6) R. Macomber, *J. Org. Chem.,* **40,** 1990 (1975).
(7) M. Oki and K. Arai, *Tetrahedron Lett.,* 2183 (1975).
(8) S. Huckin and L. Weiler, *J. Am. Chem. Soc.,* **96,** 1082 (1974).
(9) S. Huckin and L. Weiler, *Can. J. Chem.,* **52,** 1343 (1974).
(10) G. Stork, G. Kraus, and G. Garcia, *J. Org. Chem.,* **39,** 3459 (1974).
(11) E. Beriger, German Patent 2 048 470, May, 1971; *Chem Abstr.,* **75,** 19716h (1971).
(12) D. Crosby and R. Berthold, *J. Org. Chem.,* **27,** 3083 (1962).
(13) J. S. Walia and A. S. Walia, *J. Org. Chem.,* **41,** 3765 (1976).
(14) M. W. Rathke and J. Deitch, *Tetrahedron Lett.,* 2953 (1971).
(15) S. L. Hartzell and M. W. Rathke, *Tetrahedron Lett.,* 2757 (1976).
(16) E. C. Taylor and A. McKillop, *Tetrahedron,* **23,** 897 (1967).
(17) E. C. Taylor and P. A. Jacobi, *J. Am. Chem. Soc.,* **98,** 2301 (1976).
(18) E. J. Corey and B. W. Erickson, *J. Org. Chem.,* **36,** 3553 (1971).
(19) M. Hojo and R. Masuda, *Synthesis,* 678 (1976).
(20) J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.,* 3267 (1973).
(21) K. Ogura and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.,* **45,** 2203 (1972).
(22) S. Torkelson and C. Ainsworth, *Synthesis,* 722 (1976).
(23) E. Kaiser and C. Hauser, *J. Org. Chem.,* **33,** 3402 (1968).

A Convenient One-Flask Synthesis of Dialkyl Selenides and Diselenides via Lithium Triethylborohydride Reduction of Se_x

J. A. Gladysz,* John L. Hornby, and James E. Garbe

Contribution No. 3879 from the Department of Chemistry, University of California, Los Angeles, California 90024

Received August 22, 1977

Commercially available $Li(C_2H_5)_3BH$ rapidly and quantitatively cleaves gray elemental Se_x in THF to Li_2Se or Li_2Se_2, depending upon stoichiometry. Only volatile byproducts (H_2 and $(C_2H_5)_3B$) are formed. The heterogeneous Li_2Se and Li_2Se_2 preparations may be alkylated in 50–95% yield, optimally in the presence of *tert*-butyl alcohol cosolvent. This one-flask procedure constitutes a substantial improvement over conventional dialkyl selenide and dialkyl diselenide syntheses. $Li(C_2H_5)_3BH$ (2 equiv) also effects reduction of diselenides to selenolates, which may be alkylated to give unsymmetrical selenides.

During the last few years, organoselenium compounds[1] have emerged as important reagents and intermediates in organic synthesis.[2] Starting materials for their preparation are often symmetrical selenides (R_2Se) and diselenides (R_2Se_2). Hence, convenient high-yield syntheses of these key parent molecules are desirable. Current methodology,[3-14] however, suffers from various combinations of (a) low yields, (b) lack of demonstrated generality, (c) cumbersome manipulations, and (d) the use of toxic and malodorous H_2Se.

During the course of another research project underway in this laboratory, it was discovered that commercially available trialkylborohydrides such as $Li(C_2H_5)_3BH$ effect rapid reductive cleavage of several types of metal–metal bonds in THF at room temperature.[15] As a result, we were able to develop a preparation for metal carbonyl monoanions from the corresponding metal–metal dimers (eq 1)[15] which is substantially more convenient than existing procedures.[16]

$$L_n(CO)_xM\text{–}M(CO)_xL_n + 2Li(C_2H_5)_3BH \rightarrow 2Li[L_n(CO)_xM] + 2(C_2H_5)_3B + H_2 \quad (1)$$

Consequently, one objective of this study was to determine if trialkylborohydrides could be used in *metalloid* anion synthesis. Due to the independent need for several organoselenium compounds in our laboratory, we decided to investigate the feasibility of Li_2Se and Li_2Se_2 syntheses from gray elemental selenium. Dialkyl selenides and dialkyl diselenides would be available via the transformations depicted in eq 2–5.

$$Se + 2Li(C_2H_5)_3BH \rightarrow Li_2Se + 2(C_2H_5)_3B + H_2 \quad (2)$$

$$Li_2Se + 2RX \rightarrow R_2Se \quad (3)$$

$$2Se + 2Li(C_2H_5)_3BH \rightarrow Li_2Se_2 + 2(C_2H_5)_3B + H_2 \quad (4)$$

$$Li_2Se_2 + 2RX \rightarrow R_2Se_2 \quad (5)$$

We report in this paper that symmetrical dialkyl selenides and diselenides can be conveniently prepared in a one-flask operation in good to high yields via the simple sequences depicted above. Unsymmetrical dialkyl selenides are also easily

0022-3263/78/1943-1204$01.00/0