by the dienolate under these conditions is not consistent with the enhanced cis/trans ratio observed, because the enhanced deprotonation process is expected to decrease the cis/trans ratio.

The possible extension of this oxidative cyclization to longer chain diesters has also been studied (Table III). The same procedures which were most successful for dimethyl glutarate ($CuBr_2$ and $CuCl_2$) were used, especially the same concentration of the dienolate to be cyclized. Earlier experiments with dimethyl glutarate indicated that concentrations lower than 0.06 M reduced the amount of cyclization. Only dimethyl suberate ($n = 6$) has been found to cyclize in high yield to dimethyl *cis*- and *trans*-1,2-cyclohexanedicarboxylate.[14] It is interesting that formation of the trans isomer is favored over the cis isomer in this case. It is presumably because of the fact that the complexation between Cu^{2+} and the dicarboxylate favors the conformation (diequatorial-like) which leads to the trans isomer over the conformation (axial–equatorial-like) leading to the cis isomer.

The attempted oxidative cyclizations of dimethyl adipate ($n = 4$) and dimethyl pimelate ($n = 5$) led to quantitative yields of Dieckmann cyclization products **3** and **4**.[15] Evidently, the Dieckmann cyclization of their monoenolates is much faster than a second deprotonation to form their dienolates. The use of 10% TMEDA/THF as a solvent at −22 °C sufficiently increased the rate of deprotonation in both cases to completely suppress the Dieckmann cyclization, but subsequent treatment of the respective dienolates with excess $CuBr_2$ or $CuCl_2$ failed to produce any oxidative cyclization. It remains unexplained why neither the oxidative cyclization nor the Dieckmann cyclization could be observed for the diesters with $n = 7$, 8, and 10 under the standard conditions successfully used for the diesters with $n = 3$ and 6.

In summary, the oxidative cyclization of dicarboxylate dianion appears to be quite effective in preparation of the three and six-membered-ring systems, although its generality to other ring sizes is lacking.

Experimental Section

General Information. Dimethyl glutarate and dimethyl adipate were obtained from Aldrich Chemical Co. Other diesters were prepared from their respective diacids (Aldrich) by Fisher esterification. All solvents used were distilled from the appropriate drying agent prior to use: THF (soldium–benzophenone), diisopropylamine (CaH_2), TMEDA (CaH_2), HMPA (CaH_2), and DMF (CaH_2). Transition-metal salts (anhydrous) were dried at 130 °C immediately before use. All reactions were done in flame-dried glassware under N_2 by using standard syringe techniques for all liquid transfers. ^1H NMR spectra were obtained on a Varian EM-390 or Varian FT-80 spectrometer in $CDCl_3$ containing Me_4Si as an internal reference. IR spectra were obtained on a Pye-Unicam 2-300 or a Perkin-Elmer 297 spectrometer. Mass spectra were obtained on a Hewlett-Packard 5980A spectrometer. Gas chromatographic analyses were performed on an Antek Model 300 GC equipped with a flame ionization detector and a Hewlett-Packard 3390A integrator.

Oxidative Cyclization of Dimethyl Glutarate (Representative Procedure). A solution of dimethyl glutarate (338 mg, 2.11 mmol) in THF (30 mL) was added dropwise to a THF (6 mL) solution of LDA (2.2 equiv), prepared from diisopropylamine (491 mg, 4.85 mmol) and *n*-BuLi (3.00 mL of a 1.55 M solution in hexane, 4.64 mmol) at −78 °C over 30 min, to give a viscous, cloudy solution. After an additional 15 min at −78 °C, $CuBr_2$ (943 mg, 4.22 mmol) was added in one portion. The resulting dark brown reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by pouring the mixture into 3 M HCl, and this mixture was extracted with ether. The combined organic extract was washed with brine until neutral, dried over $MgSO_4$, and evaporated. The crude product was purified on a silica gel column (ether/hexane eluent) to give a total of 313 mg (94% yield) of **1a** and **1b**. The same procedure was used for $CuCl_2$. Dimethyl suberate could also be cyclized with both $CuBr_2$ and $CuCl_2$ by the same procedure. Pure isomers could be obtained by using a longer silica gel column (ether/hexane eluent) or by silica gel preparative thin-layer chromatography (10% ether/hexane).

Acknowledgment. We thank the Robert A. Welch Foundation (Grant A-752) for the financial support of the research.

Registry No. **1a**, 826-34-6; **1b**, 826-35-7; **2a**, 1687-29-2; **2b**, 3205-35-4; **3**, 10472-24-9; **4**, 41302-34-5; dimethyl glutarate, 1119-40-0; dimethyl adipate, 627-93-0; dimethyl pimelate, 1732-08-7; dimethyl suberate, 1732-09-8.

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(15) Identified by comparison with the authentic samples.

Formation of Ethers by the Reductive Desulfurization of Thiono Esters

Jerald S. Bradshaw,* Brian A. Jones, and James S. Gebhard

Department of Chemistry and the Institute for Thermochemical Studies,† Brigham Young University, Provo, Utah 84602

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We have recently reported the conversion of esters to ethers via a thionation–reductive desulfurization process (Scheme I.)[1] The thionation step was that used by Lawesson and his co-workers.[2] The desulfurization process was carried out with Raney nickel under very mild conditions in aprotic solvents.[1] We now report additional ester compounds that have been reduced by using this thionation–desulfurization procedure. The conversion of two dithiono esters to the diethers by the Raney nickel desulfurization process and results of metal hydride reductions of the thiono esters are also reported.

Table I shows the results of the reductive desulfurization of several thiono esters. The thiono esters of runs 1–5 were prepared by using Lawesson's reagent (**1**, see Scheme I). These thiono esters were not isolated but were immediately treated with Raney nickel to form the corresponding ethers. The desulfurization process was also carried out on *O,O'*-dimethyl 2,6-pyridinedicarbothioate (**2**)[3] and *O,O'*-diethyl dithiooxalate (**3**),[4] which were prepared by a different synthetic route. The product ethers were analyzed by VPC using an internal standard. The NMR and/or IR spectra of the isolated ethers were identical with those of authentic samples.

The thionation step appears to be a limiting factor in the overall reduction process. β-Methoxyethyl benzoate did not form the thiono ester when treated with reagent **1**.[1] β-Phenoxyethyl benzoate, on the other hand, readily reacted with **1** and was reduced to the ether in an overall yield of 70% (run 1, Table I). Apparently the phenyl group is deactivating the ether oxygen toward the electrophilic phosphorus atoms of compound **1**. Ethyl γ-chlorobutyrate failed to form a thiono ester because it polymerized in the presence of reagent **1** (run 2).

Methyl picolinate also failed to react with reagent **1**.[1] Compound **2**, a dithiono ester analogue of methyl picolinate was prepared by a different synthetic route.[3] This

† Contribution No. 288.

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Scheme I

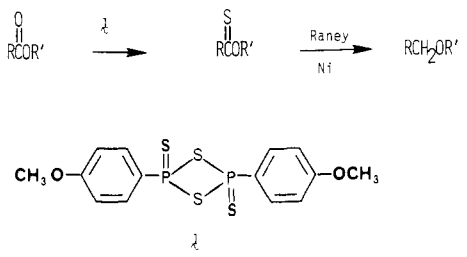

Table I. Reductive Desulfurization of Thiono Esters by Raney Nickel

run	thiono ester (RC(S)OR') R	R'	percent ether (RCH_2OR')[a]
1	Ph	CH_2CH_2OPh	70
2	$Cl(CH_2)_3$	Et	0[c]
3	PhCH=CH	Et	20[b]
4	coumarin		43[b]
5	2-cumaranone		6
6	*O,O'*-dimethyl 2,6-pyridinedicarbothioate (2)		18
7	*O,O'*-diethyl dithiooxalate (3)		23

[a] Yields were determined by VPC analyses using an internal standard. Yields for runs 1-5 are based on the amount of starting ester as shown in Scheme I, while yields for runs 6 and 7 are for the Raney nickel reduction of the dithiono esters that were prepared by a different route. [b] The product was the saturated ether. [c] The starting chloroester polymerized when treated with the thionating reagent.

compound was reductively desulfurized in an 18% yield (run 6).

Unsaturated esters, ethyl cinnamate, and coumarin were also subjected to the thionation–desulfurization process. The thiono esters gave saturated ethers during the desulfurization procedure (runs 3 and 4).

Other reducing agents were tried in the reduction of the thiono esters. When treated with lithium aluminum hydride (LAH), methyl thionobenzoate was converted to at least four products: toluene (6%), benzyl mercaptan (14%), 1,2-diphenylethane (trace), and stilbene (13%). Similar results were obtained for desulfurizations with sodium borohydride and LAH–boron trifluoride except the mercaptan was not observed. None of the desired benzyl methyl ether was obtained in any of these reduction reactions. Mayer and his co-workers found similar results in the Clemmensen reduction of methyl thionobenzoate and methyl dithiobenzoate, which gave stilbene and toluene as well as other products.[5]

Experimental Section

All infrared (IR) spectra were obtained on a Beckman Acculab 2 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on a JOEL FX-90Q spectrometer using deuteriochloroform as the solvent. A Hewlett-Packard 5710A vapor-phase chromatograph (VPC) equipped with a thermal conductivity detector and a 4 ft × $^1/_8$ in. column packed with either 10% SE-30 on Chromosorb G or 10% OV-17 on Chromosorb W-HP was used for all separations.

Starting Materials. The starting ester compounds were either purchased or prepared from the corresponding acids or acid chlorides and alcohols. In either event, the starting esters were freshly distilled or recrystallized prior to their use. The 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson reagent, 1) was prepared according to the method of Lawesson and coworkers,[6] although it can now be purchased from Aldrich. The preparation of *O,O'*-dimethyl 2,6-pyridinedicarbothioate (2) will be reported at a later date.[3] *O,O'*-Diethyl dithiooxalate (3) was prepared as reported.[4] Raney nickel was prepared according to the procedure of Fieser and Fieser[7] and stored under absolute ethanol until used.

Sulfurization Procedure (Runs 1–5). A mixture of 0.5 g of the ester, 2.0 g of thionation reagent 1, and 4 mL of anhydrous toluene was refluxed in a nitrogen atmosphere until a TLC or VPC analysis showed that the ester had reacted. The crude reaction product was adsorbed onto 2–3 g of silica gel. The adsorbed gel was added to the top of a column of 35–50 g of silica gel, and the column was eluted with hexane. When the orange thiono ester band started to elute, the solvent was changed to ether/hexane (2:98). After the solvent was removed, the crude product was diluted with 5 mL of anhydrous ether and the resulting orange solution was dried over molecular sieves for at least 1 h. The thiono esters were not further purified or characterized.

Desulfurization. About 10 g of wet Raney nickel was placed in a centrifuge tube and then washed 10 times with anhydrous ethanol followed by 10 washings with anhydrous ether. The Raney nickel was then stored under 5 mL of anhydrous ether, and the mixture was dried with molecular sieves for at least 1 h. The thiono ester–ether solution and the Raney nickel–ether mixture were each cooled to −15 °C and then mixed together. The resulting mixture was shaken while the temperature was kept below about −10 °C until the orange color disappeared (usually less than 2 min). The temperature was particularly critical for benzoate esters, which were converted to toluene at higher temperatures. The mixture was then centrifuged and decanted. The Raney nickel was washed with five portions of anhydrous ether. **Caution**: The Raney nickel must be kept under solvent at all times since it becomes pyrophoric when exposed to air. The combined ether solutions were evaporated to a 5-mL volume and analyzed by VPC using an internal standard. The product ethers were collected from the VPC for analysis. IR and NMR spectra of the products were identical with those of authentic samples. The results of these reductions are given in Table I.

Metal Hydride Reductions of Methyl Thionobenzoate. A solution of 0.5 g of methyl thionobenzoate was added to 0.15 g of lithium aluminum hydride (LAH) in 25 mL of anhydrous ether. The orange thiono ester color disappeared within 1 min. Ethyl acetate and then dilute aqueous hydrochloric acid were added to the solution. The resulting mixture was separated, and the aqueous layer was washed once with 50 mL of ether. The combined ether extracts were dried, and the ether was removed under vacuum. The resulting mixture was analyzed by VPC using tetralin as an internal standard. The products were isolated and analyzed by IR and NMR as toluene (6%), benzyl mercaptan (14%), 1,2-diphenylethane (>1%), and stilbene (13%).

The above reaction was repeated with LAH–boron trifluoride etherate as the reducing agent in ether. The reaction mixture was stirred at 0 °C for 45 min and then refluxed for 3 h. The mixture was then worked up as above to give toluene (<1%), 1,2-diphenylethane (<1%), and stilbene (18%).

Methyl thionobenzoate was reduced with sodium borohydride in anhydrous diglyme at room temperature. The orange thiono ester color disappeared after about 20 min. The reaction mixture was worked up as above to give toluene, 1,2-diphenylethane, and stilbene.

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Students of the Brigham Young University are gratefully acknowledged.

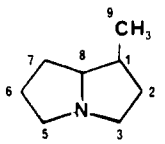
Registry No. 1, 19172-47-5; 2, 84877-69-0; 3, 54129-84-9; $PhC(O)OCH_2CH_2OPh$, 4173-59-5; $Cl(CH_2)_3C(O)OEt$, 3153-36-4; PhCH=CHC(O)OEt, 103-36-6; $PhC(S)OCH_2CH_2OPh$, 52772-15-3; PhCH=CHC(S)OEt, 73818-80-1; $PhCH_2OCH_2CH_2OPh$, 84877-70-3; $PhCH_2CH_2CH_2OEt$, 5848-56-6; $EtOCH_2CH_2OEt$, 629-14-1; methyl thionobenzoate, 5873-86-9; toluene, 108-88-3; benzyl mercaptan, 100-53-8; 1,2-diphenylethane, 103-29-7; stilbene, 588-59-0; coumarin, 91-64-5; 2-cumaranone, 553-86-6; 2-thiocoumarin, 3986-98-9; 2(3*H*)-benzofuranthione, 84877-71-4; chroman, 493-08-3; 2,3-dihydrobenzofuran, 496-16-2; 2,6-bis(methoxymethyl)pyridine, 64726-18-7.

Communications

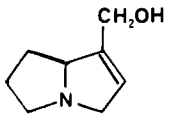
Pyrrolizidine Alkaloid Synthesis. (±)-Supinidine

Summary: Synthesis of the $\Delta^{1,2}$-unsaturated pyrrolizidine alkaloid supinidine proceeding via regioselective N1–C2 vicinal annulation of a 1,3-dihaloalkane onto a 3-(hydroxymethyl)-3-pyrroline system is described.

Sir: The pyrrolizidine alkaloids have a broad distribution within the plant kingdom.[1] The over 100 constituents of this alkaloid class, which possesses the 1-azabicyclo[3.3.0]bicyclooctane skeleton 1 often functionalized by



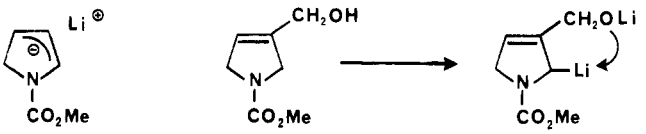
1



2

hydroxyl or carboxylic ester moieties at a variety of structural sites, demonstrate a broad range of pharmacological activities. The $\Delta^{1,2}$-unsaturated subgroup of the pyrrolizidine alkaloids has been associated with severe pneumovascular- and hepatotoxicities and with carcinogenic, mutagenic, and teratogenic activities at sublethal doses.[1,2] In addition, $\Delta^{1,2}$-unsaturated pyrrolizidine alkaloids have been examined by the National Cancer Institute as potential agents against neoplastic diseases.[3] Due to their intriguing chemical structures and their pharmacological activities, the pyrrolizidine alkaloids have witnessed considerable synthetic attention.[4,5] Our laboratory has been engaged in developing synthetic entries into the pyrrolizidine and the structurally homologous indolizidine ring systems, which proceed via 1,2-vicinal annulation of an appropriate three-carbon (pyrrolizidine) or four-carbon (indolizidine) unit onto a suitably substituted five-membered 1-azaheterocyclic ring.[6] We describe here the utility of this strategy in a direct entry into the $\Delta^{1,2}$-unsaturated pyrrolizidine alkaloids as illustrated by the synthesis of supinidine **2**.[5]

Our initial studies on the viability of this strategy in the synthesis of fused pyrrolidine systems employed α-alkylation of the dipole-stabilized pyrroline anion **3** in the



3 4 5

central carbon–carbon bond-forming step of a synthesis of the indolizidine gephyrotoxin 223AB.[6] Adaptation of this strategy to the synthesis of the eight carbon-containing $\Delta^{1,2}$-unsaturated pyrrolizidine alkaloid skeleton required the use of an unsymmetrical 3-alkyl-substituted pyrroline anion precursor. 3-(Hydroxymethyl)-3-pyrroline (**4**) was selected as the pyrroline synthon because of the common presence of a C-1 hydroxymethyl substituent or a derived carboxylate ester in these alkaloids and the capability of the hydroxyl function to assist in regioselective pyrroline deprotonation. In an unsymmetrical 3-pyrroline system, pyrroline anion formation might be anticipated to occur a priori at either or both the C-2 and C-5 positions. We envisioned that regiospecific 2-pyrroline anion formation would occur in pyrroline **4** as a consequence of two possible and nonexclusive factors, which are a function of complexation with the proximate pro-C-9 hydroxyl (or alkoxide) function. Thus, complexation of the pro-C-9 alkoxide moiety with the metalation base prior to ring-proton removal might act to direct pyrroline deprotonation to the proximate C-2 position via a seven-membered transition state (e.g., primarily an entropic effect). An additional feature of pyrroline **4** that might act to reinforce regioselective pyrroline deprotonation was postulated to be alkoxide complexation of the incipient C-2 organolithio derivative via a five-membered internal chelate as illustrated in **5** (e.g., primarily an enthalpic effect). Regioselective alkylation of the derived allylic organometallic (e.g., **5**) at the C-2 (rather than the C-4) position was anticipated on the basis of our and Lapierre Armande and Pandit's[7]

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