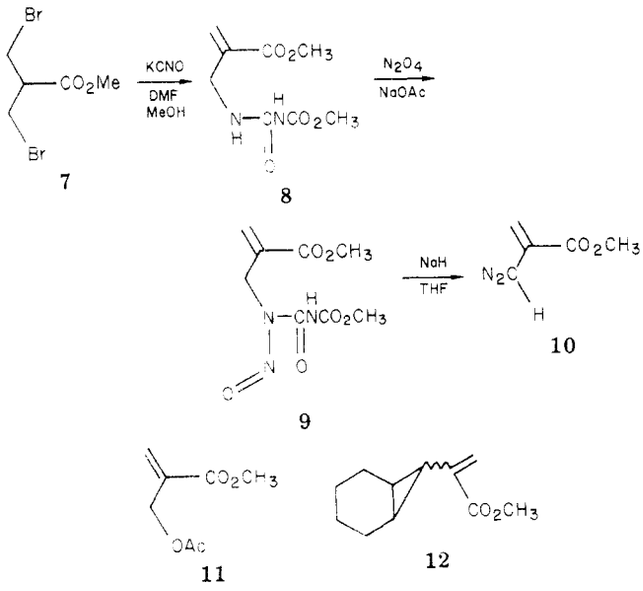

methyl 4-[2-(carbomethoxy)propen-3-yl]allophanate (**8**), mp 151–153 °C, and 47% 1,3,5-tris[2-(carbomethoxy)-propen-3-yl]-2,4,6-trioxo-5-triazine, mp 91–93 °C, which are easily separated by crystallization from benzene. Reaction of allophonate **8** with dinitrogen tetroxide in CCl_4 with NaOAc buffer at −15 °C afforded the 4-nitroso compound **9** in 98% yield (mp 81–83 °C). Treatment of this nitrosoallophanate **9** with sodium hydride in THF at 0 °C afforded orange-red solutions of **10** as evidenced by strong infrared bonds at 2075 (CHN_2), 1740, and 1660 cm^{-1} and by the observation that quenching portions of these solutions with acetic acid resulted in vigorous gas evolution and the formation of methyl 2-(acetoxymethyl)acrylate (**11**) (69%). Direct treatment of **9** with acetic acid yielded no **11**.

Copper trifluoroacetate catalyzed[12] decomposition of THF solutions of **10** in the presence of cyclohexene produced, among many other substances, a 2:1 ratio of the *exo*- and *endo*-methyl 2-(bicyclo[4.1.0]hepten-7-yl)-propenoates (*exo*-**12** and *endo*-**12**) (6% yield). Other components identified in the mixture were dimethyl terphthalate, dimethyl 1,3-cyclohexadiene-1,4-dicarboxylate,[13] and *cis*- and *trans*-1,3,5-cyclohexatriene-3,4-dicarboxylate;[14] these materials were apparently derived from the dimerization of **10** and electrocyclic closure. Compound *exo*-**12** was identified by synthesis of an authentic sample through Wittig condensation[9] with the cyclopropyl glyoxalate derived from methyl diazopyruvate (**5b**) and cyclohexene.[7] Studies of the addition of **10** to dienes and efforts to improve the yields of products such as **12** by this pathway are continuing.

The synthesis of the lower homologue, *tert*-butyl 2-(bicyclo[3.1.0]hex-6-enyl)propenoate, from cyclopentadiene and **5a** has also been accomplished and its rearrangement is under examination. Both the generation of cations (**2**) from alternative functional groups and the application of these procedures to the synthesis of natural products are being studied. We are particularly interested in using this approach for the synthesis of model structures necessary for the detailed study of the chemical interaction of *trans*-α-methylene γ-lactone functions with proteins.[15]

Acknowledgment. Fellowship support from the American Foundation for Pharmaceutical Education is sincerely acknowledged. The work was supported in part by funds from the National Institute of Health (1R01-GM 23679-01A2).

Registry No. **1**, 71901-62-7; **3**, 60916-78-1; **4a**, 39061-59-1; **5a**, 71901-63-8; **6**, 71901-64-9; **7**, 22262-60-8; **8**, 71901-65-0; **9**, 71901-66-1; **10**, 71901-67-2; **11**, 30982-08-2; *exo*-**12**, 71901-68-3; *endo*-**12**, 71901-69-4; anilide, 71901-70-7; 1,3,5-tris[2-(carbomethoxy)propen-3-yl]-2,4,6-trioxo-5-triazine, 71901-71-8; *tert*-butyl *exo*-2-(bicyclo[3.1.0]-hex-6-enyl)propenoate, 71928-57-9; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4.

(12) R. G. Salomon, M. F. Salomon, and T. R. Heyne, *J. Org. Chem.*, **40**, 756 (1975).

(13) A sample of dimethyl 1,3-cyclohexadiene-1,4-dicarboxylate prepared according to a literature procedure was generously provided by Jeff Vanderbilt. See N. B. Chapman, S. Sotheeswaran, and K. J. Toyne, *J. Org. Chem.*, **35**, 917 (1970).

(14) Identified by mass spectral analysis only.

(15) S. Mitra and R. G. Lawton, *J. Am. Chem. Soc.*, **101**, 3097 (1979).

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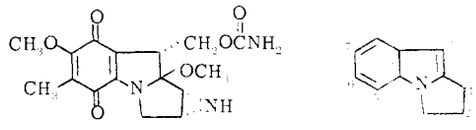
New Synthesis of Ethyl 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates via Apparent 1-Aza-1′-oxa [3,3]Sigmatropic Rearrangement

Summary: The reaction of *N*-arylhydroxylamines (**3a–f**) with ethyl 6-oxo-2-hexynoate (**4**) and sodium cyanoborohydride affords a series of tricyclic ethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates (**5a–g**) in 25–68% yield via apparent 1-aza-1′-oxa [3,3]sigmatropic rearrangements of *N*-aryl-*O*-vinylhydroxylamine intermediates (e.g., **7**).

Sir: The mitomycins (e.g., mitomycin A, **1**) constitute a small group of pyrroloindole quinones which are isolated from various *Streptomyces* cultures and exhibit both antibacterial and antitumor activities.[1] The novel structure and biological activities of these compounds have stimulated considerable interest in the synthesis of the parent 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles (**2**) as well as the



1 **2**

natural products themselves.[2–4] Since we have developed

(1) For references on the earlier literature, see Sundberg, R. J. "The Chemistry of the Indoles"; Academic Press: New York, 1970; pp 431–434.

(2) References to research on the synthesis of pyrroloindoles and mitomycin analogues prior to spring, 1977, are given in the following: (a) Siuta, G. J.; Franck, R. W.; Kempton, R. J. *J. Org. Chem.* **1974**, *39*, 3739–3744. (b) Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835–4836.

(3) For recent total syntheses of the mitomycins, see Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115–8116. Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295–4298.

(4) Other recent synthetic work in the mitomycin field includes the following: Rebek, J., Jr.; Gehret, J.-C. E. *Tetrahedron Lett.* **1977**, 3027–3028. Danishefsky, S.; Doehner, R. *Ibid.* **1977**, 3029–3030; *Ibid.* **1977**, 3031–3034. Akiba, M.; Kosugi, Y.; Takada, T. *J. Org. Chem.* **1978**, *43*, 4472–4475. Kametani, T.; Kigawa, Y.; Takahashi, K.; Nemoto, H.; Fukumoto, K. *Chem. Pharm. Bull.* **1978**, *26*, 1918–1922. Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 662–666. Parker, K. A.; Kang, S.-K. *J. Org. Chem.* **1979**, *44*, 1536–1540. For a review on the synthesis of pyrrolo[1,2-*a*]indoles, see Kametani, T.; Takahashi, K. *Heterocycles* **1978**, *9*, 293–351.

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Table I
Ethyl 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates (5) Prepared by Reductive Cyclization of Aromatic Hydroxylamines (3) and Ethyl 6-Oxo-2-hexynoate (4)

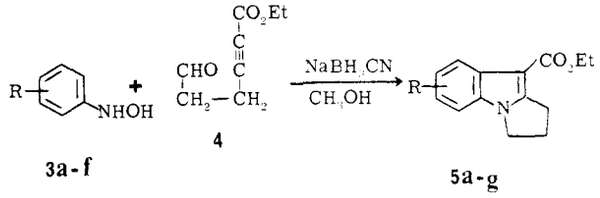
hydroxylamine, R =	pyrroloindole substituent, no.	R =	mp, °C	% yield
H (3a)	5a	H	96-98.5[a]	37
p-CH_3 (3b)	5b	7-CH_3	90-91.5	68
p-Cl (3c)	5c	7-Cl	149-151	33
p-OCH_3 (3d)	5d	7-OCH_3	125.5-127	25
o-OCH_3 (3e)	5e	5-OCH_3	143-144	45
m-CH_3 (3f)	5f	6-CH_3	98-101	52[b]
	5g	8-CH_3	109-111	

[a] Lit.[16] mp 95.5-96 °C; mmp 95.5-96.5 °C. [b] The ratio of isomers 5f/5g was 1:1.24.

new procedures for effecting alkylation ortho to nitrogen on benzene rings and for the synthesis of indoles via 1-aza-1′-oxa [3,3]sigmatropic rearrangements of *N*-aryl-*O*-vinylhydroxylamine derivatives,[5] it was natural to inquire whether this approach might be applied to the preparation of pyrroloindoles. We wish to report a novel synthesis of ethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates (**5**) from aromatic hydroxylamines (**3**) in which the two five-membered heterocycles are assembled in a single operation.

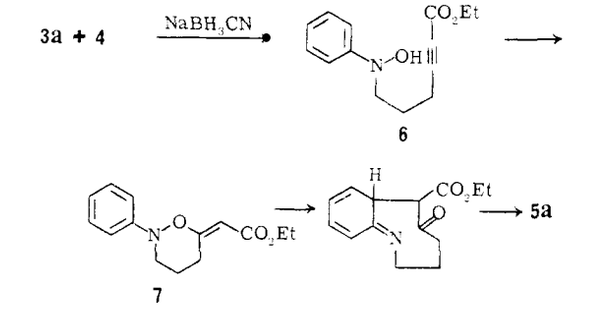
Ethyl 6-oxo-2-hexynoate (**4**) was prepared from 4-pentyn-1-ol by the following sequence of reactions: (1) oxidation with pyridinium chlorochromate (CH_2Cl_2, 25 °C; 47%)[6] or dimethyl sulfoxide–dicyclohexylcarbodimide (H_3PO_4, ether, reflux; 55%);[7,8] (2) acetalization with ethylene glycol (TsOH, C_6H_6, reflux; bp 66–68 °C (23 mm), 62%);[9] (3) metalation with butyllithium (THF, -78 °C) followed by acylation with ethyl chloroformate (THF, -78 to 25 °C; bp 96–100 °C (0.1 mm), 64%);[10] (4) hydrolysis of the acetal (TsOH, 2:1 acetone–water, reflux, 24 h; 59%).[9] Condensation of aromatic hydroxylamines **3**[11] with aldehyde ester **4** afforded more polar products (TLC on silica gel) presumed to be the corresponding nitrones,[12] which were reduced in situ with sodium cyanoborohydride.[13,14]

The products of the reactions proved to be the ethyl pyrroloindole-9-carboxylates **5a–g**[9] which were isolated as crystalline solids by extraction and, in some cases, column chromatography on silica gel (see Table I).



The pyrroloindole structures for the products are based upon satisfactory elemental analyses and appropriate IR, NMR, UV, and mass spectral characteristics.[15] Moreover, the parent compound, the only previously known member of this series, was identical with an authentic sample of **5a** according to melting point, mixture melting point, TLC, IR, and NMR comparisons.[16] A 1:1.24 mixture of the 6-methyl- and 8-methylpyrroloindole isomers (**5f** and **5g**) was obtained from *N*-(3-methylphenyl)hydroxylamine (**3f**) and was separated by LC. The appearance of the characteristic low-field absorption for the proton at C-8 (doublet at δ 7.85) in the NMR spectrum of the minor isomer and its absence in the spectrum of the major isomer serves to distinguish the two compounds.

The mechanism of this cyclization reaction presumably involves reduction of the nitrone to the hydroxylamine (**6**), intramolecular Michael addition of the hydroxyl group to the acetylenic ester,[17] rearrangement of the resulting *N*-aryl-*O*-vinylhydroxylamine (**7**), aromatization of the benzene ring, and finally dehydration to form the pyrroloindole.[18] Whether the crucial ortho alkylation step

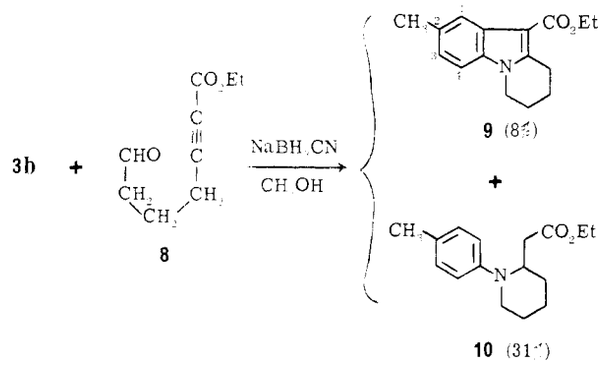


occurs by a concerted [3,3]sigmatropic rearrangement or homolysis to a diradical and recombination cannot be stated with certainty. However, if a free diradical had been formed, one might have expected rebonding to have occurred between carbon and nitrogen (formally a [1,3]sig-

(5) Coates, R. M.; Said, I. Md. *J. Am. Chem. Soc.* **1977**, *99*, 2355-2357. Coates, R. M.; Hutchins, C. W., unpublished results.
(6) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647-2650.
(7) Bohlmann, F.; Miethe, R. *Chem. Ber.* **1967**, *100*, 3861-3868.
(8) IR, ^{1}H NMR, and, in certain cases, mass spectra were recorded for the compounds reported in this paper and found fully consistent with the structures shown or implied.
(9) A satisfactory elemental analysis was obtained on this compound(s).
(10) Brandsma, L. "Preparative Acetylenic Chemistry"; Elsevier: Amsterdam, 1971; pp 80-81.
(11) Zeeh, B.; Metzger, H. *Methoden Org. Chem.* (*Houben-Weyl*) **1971**, *10/1*, 1140-1148.
(12) The nitrone intermediate from the reaction of **3b** with **4** was isolated. The NMR spectrum exhibits a one-proton triplet at δ 7.26, characteristic of the nitrone hydrogen (RC**H**=N$^+$(O$^-$)Ar). Reduction of the isolated nitrone with sodium cyanoborohydride in methanol as described in the text gave the pyrroloindole **5b** in 45% yield.
(13) Morgan, P. H.; Beckett, A. H. *Tetrahedron* **1975**, *31*, 2595-2601.
(14) A typical procedure is as follows. A solution of 1.05 g (7.55 mmol) of **3e** in 15 mL of methanol was stirred under nitrogen at room temperature as 1.22 g (7.92 mmol) of **4** in 2 mL of methanol was added quickly. After 10 min 0.52 g (8.25 mmol) of sodium cyanoborohydride was added in one portion, and the electrode from a pH meter was inserted into the solution. The pH, which was initially ~8.5, was lowered to 5 by rapid dropwise addition of 10% hydrogen chloride in methanol, causing evolution of gas and a rise in temperature to near the boiling pint of the methanol solvent. After the initial vigorous reaction subsided, additional 10% hydrogen chloride in methanol was added dropwise as needed (ca. once every 3–5 min) to maintain the pH between 5 and 6.5 for 1 h. Saturated aqueous sodium chloride was added, the aqueous mixture was extracted three times with ethyl ether, and the combined ethereal extracts were dried with anhydrous sodium sulfate. Evaporation and recrystallization from ethyl acetate–hexane afforded 0.89 g (45%) of pyrroloindole **5e**, mp 143-144 °C.
(15) The spectral properties of **5b** are given as a typical representative of the series: IR (CCl_4) 1680 cm^{-1} (C=O); NMR (CCl_4) δ 1.35 (t, 3 H, J = 7 Hz, OCH_2CH_3), 2.42 (s, 3 H, CH_3), 2.47 (quintet, 2 H, J = 7 Hz, $NCH_2CH_2CH_2$), 3.05 (t, 2 H, J = 7 Hz, $NCH_2CH_2CH_2$), 3.93 (t, 2 H, J = 7 Hz, NCH_2), 4.23 (q, 2 H, J = 7 Hz, OCH_2CH_3), 6.82 (s, 2 H, aryl H at C-5 and C-6), 7.76 (s, 1 H, aryl H at C-8); UV (EtOH) λ_{max} (log ϵ) 214 (4.45), 234 (4.23), 283 (4.02), 291 (4.01); mass spectrum (70 eV) *m/e* (rel intensity): 243 (M$^+$, 100), 215 (19), 214 (65), 199 (10), 198 (72), 171 (22), 170 (25), 154 (12).
(16) Franck, R. W.; Bernardy, K. F. *J. Org. Chem.* **1968**, *33*, 3050-3055. We are grateful to Professor Franck for providing a sample of **5a**.
(17) The intermolecular Michael addition of *N*-aryl-*N*-acylhydroxylamines to dimethyl acetylenedicarboxylate and subsequent sigmatropic rearrangement has been reported recently: Sheradsky, T.; Nov, E.; Segal, S.; Frank, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1827-1831.
(18) The possibility that the conjugate addition of the aryl hydroxylamine to the acetylenic ester occurs first by an intermolecular pathway is unlikely for two reasons. The initial reactions between **3** and **4** to give the corresponding nitrones[12] are rapid and complete. No reaction was observed between *N*-ethyl-*N*-phenylhydroxylamine and methyl 2-butynoate in methanol at room temperature for 1.5 h under conditions similar to those used to prepare the pyrroloindoles.

matropic rearrangement), thus forming an *N*-phenylpiperidine derivative.

The reductive cyclization of two *N*-arylhydroxylamines (**3b** and **3e**) with the homologue, ethyl 7-oxo-2-heptynoate (**8**), has also been studied briefly for comparison. Aldehyde ester **8**, prepared from 5-hexyn-1-ol as described above for **4**, was condensed with **3b** and **3e**, and the nitrone so formed was reduced with sodium cyanoborohydride in the same manner. Ethyl 2-methyl-6,7,8,9-tetrahydropyrido-[1,2-*a*]indole-10-carboxylate (**9**, mp 55.5–57 °C) was isolated from the former reaction in 8% yield. The major product (31%) was an unstable liquid identified as ethyl 1-(4-methylphenyl)piperidine-2-acetate (**10**).[19] The (*o*-



methoxyphenyl)hydroxylamine (**3e**) afforded the corresponding 4-methoxytetrahydropyridoindole (mp 117–118 °C)[9,20] in 12% yield.

The pyridoindole **9** and the piperidine acetate **10** very likely arise from competitive intramolecular Michael addition of the hydroxylamine intermediate (homologue of **6**) at oxygen and nitrogen, respectively. The piperidine *N*-oxide formed in the latter cyclization may undergo Polonovski-type rearrangement and twofold reduction with cyanoborohydride to give **10**. This pathway also competes to some extent in the reductive cyclizations with **4**, since the corresponding ethyl 1-arylpyrrolidine-2-acetates were isolated in small amounts from some of the preceding reactions (e.g., 10–20% of ethyl 1-(3-methylphenyl)-pyrrolidine-2-acetate from **3f** + **4**).

The reductive condensation of aromatic hydroxylamines with ethyl 6-oxo-2-hexynoate offers a short synthetic route to a variety of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates which may be of value in the preparation of mitomycin analogues. This reaction serves to illustrate the utility of the 1-aza-1′-oxa [3,3]sigmatropic rearrangement as a synthetic method for ortho alkylation and the rapid construction of complex heterocyclic ring systems.[5]

Acknowledgment. This investigation was supported in part by a research grant from the National Cancer Institute (CA 20436).

Registry No. 3a, 100-65-2; **3b**, 623-10-9; **3c**, 823-86-9; **3d**, 4546-20-7; **3e**, 35758-76-0; **3f**, 620-25-7; **4**, 71948-59-9; **5a**, 16916-14-6; **5b**, 71948-60-2; **5c**, 71948-61-3; **5d**, 71948-62-4; **5e**, 71948-63-5; **5f**, 71948-64-6; **5g**, 71948-65-7; **8**, 71948-66-8; **9**, 71948-67-9; **10**, 71948-68-0; 4-pentyn-1-ol, 5390-04-5; 4-pentynal, 18498-59-4; 4-pentynal ethylene acetal, 71948-69-1; ethyl 6-oxo-2-hexynoate ethylene acetal, 71974-88-4; 5-hexyn-1-ol, 928-90-5; 4-methoxytetrahydropyridoindole, 71948-70-4.

(19) IR (neat) 1725 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 1.13 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.62 (br s, 6 H, three CH_2), 2.20 (s, 3 H, $ArCH_3$), 2.28 (d, 2 H, J = 7 Hz, CH_2CO_2Et), 2.8–3.3 (br m, 2 H, NCH_2), 3.92 (br q, 3 H, J = 7 Hz, NCH and OCH_2CH_3), 6.65 (d, 2 H, J = 8 Hz, aryl H), 6.85 (d, 2 H, J = 8 Hz, aryl H); mass spectrum (70 eV) m/e (rel intensity) 261 (M^+, 10), 175 (15), 174 (100), 91 (10).

(20) ^1H NMR ($CDCl_3$) δ 1.39 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.65–2.20 (m, 4 H, $NCH_2CH_2CH_2$), 3.27 (t, 2 H, J = 7 Hz, CH_2), 3.87 (s, 3 H, OCH_3), 4.31 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.48 (t, 2 H, J = 7 Hz, NCH_2), 6.55 (d, 1 H, J = 8 Hz, H at C-3), 7.02 (t, 1 H, J = 8 Hz, H at C-2), 7.68 (d, 1 H, J = 8 Hz, H at C-1); mass spectrum (70 eV) m/e (rel intensity) 273 (M^+, 100), 245 (13), 244 (59), 228 (31), 201 (13), 200 (22), 185 (11), 184 (12).

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One-Step Synthesis of Complex Cyclopropanone Phenylthioketals by the Reaction of Sulfur-Stabilized Anions with Ketene Bis(phenylthio)acetal

Summary: Organolithium compounds which are stabilized by a phenylthio group lose the latter and form cyclopropanone phenylthioketals upon reaction with 1,1-bis(phenylthio)ethene; the latter is prepared by copper(I)-induced elimination of thiophenol from 1,1,1-tris(phenylthio)ethane, which is in turn generated by the reaction of acetic acid with a reagent formed by the reaction of trimethylaluminum with thiophenol.

Sir: We have recently revealed a remarkably efficient 1,3-elimination of thiophenol from 1,1,3-tris(phenylthio)-alkanes (**1**) induced by methyllithium in the presence of tetramethylethylenediamine (TMEDA) to produce cyclopropanone thioketals (**3**) in excellent yield (Scheme I);[1a] one important use of the products is their facile reduction to sulfur-stabilized cyclopropyl anions by lithium naphthalenide.[1b] We are now pleased to report that the presumed anionic intermediate (**2**)[1c] of the ring closure reaction can be produced in a connective manner by the reaction[2] of sulfur-stabilized anions (**4**) with ketene bis(phenylthio)acetal (**5**), a material which is now readily available (see below).[3] Examples are provided in eq 1–4.[4]

The lithio derivative[5] of **6** decolorized at 25 °C in the presence of **5**; we had previously prepared the product **7** by the nonconnective version of this ring closure.[1a] As hoped, the lithio derivative[6] of **8** reacted predominantly at the sulfur-bearing carbon atom to produce **9**; the mobility on TLC of the only other product leads us to believe that it possesses three phenylthio groups and it probably arises by attack of **5** on the γ position of the anion. It was gratifying to observe that the anions[7] of 1,3-bis(phenylthio)alkenes readily attack the ketene thioacetal even though the starting anion must be more highly stabilized than the intermediate **2**; substrate **10** was produced by the reaction of cyclohex-2-en-1-one with boron thiophenoxide

(1) (a) T. Cohen and W. M. Daniewski, *Tetrahedron Lett.*, 2991 (1978); (b) T. Cohen, W. M. Daniewski, and R. B. Weisenfeld, *ibid.*, 4465 (1978); (c) T. Cohen and J. R. Matz, *J. Org. Chem.*, in press.

(2) The addition of alkyllithiums to 2-methylene-1,3-dithiane has been known for some years: R. M. Carlson and P. M. Helquist, *Tetrahedron Lett.*, 173 (1969); D. Seebach, *Synthesis*, 17 (1969); D. Seebach, R. Bürstinghaus, B.-T. Gröbel, and M. Kolb, *Justus Liebigs Ann. Chem.*, 830 (1977). See also N. H. Andersen, P. F. Duffy, A. D. Denniston, and D. B. Grotjahn, *Tetrahedron Lett.*, 4315 (1978).

(3) T. Cohen, G. Herman, J. R. Falck, and A. J. Mura, Jr., *J. Org. Chem.*, **40**, 812 (1975).

(4) New compounds were characterized by ^1H NMR, IR, and mass spectroscopy and by their exact masses as determined by high-resolution mass spectroscopy. These data are in the supplementary material.

(5) T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972).

(6) J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 5629 (1968); P. M. Atlani, J. F. Biellmann, S. Dube, and J. J. Vicens, *ibid.*, 2665 (1974).

(7) T. Cohen, D. A. Bennett, and A. J. Mura, Jr., *J. Org. Chem.*, **41**, 2506 (1976).

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