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Thiyl Radical and Mercuric Ion Induced Cyclizations of Dimethyl Dipropargylmalonate and Dimethyl Propargyl-3-thiylallylmalonates

M. E. Kuehne* and W. H. Parsons

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

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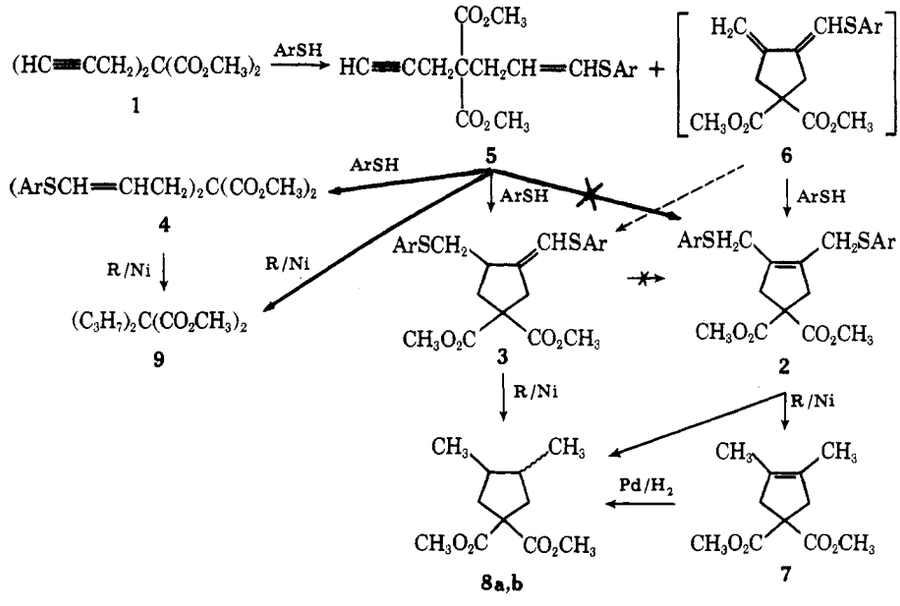
The first examples of radical-initiated cyclizations of a 1,6-diyne were found in the photochemical reactions of dimethyl dipropargylmalonate with thiophenols. The reactions are accompanied by formation of acyclic monothioenol ethers, which also undergo cyclization on reaction with thiophenols or with mercuric chloride. Cyclopentane products are formed in all of these reactions. Alternatively, the dipropargyl compound on direct reaction with aqueous mercuric chloride yields a diketone which can be cyclized to 5,5-dicarbomethoxy-3-methylcyclohex-2-enone.

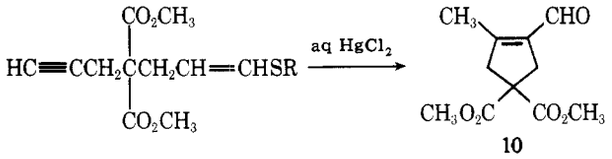
Geminal diallyl compounds undergo cyclization to cyclopentyl products in high yields on reaction with thiyl and other radicals.[1] However, 1,6-heptadiyne was reported to yield no radical induced cyclization but only an acyclic radical addition product.[2] While we also found that dimethyl dipropargylmalonate (1) gave only traces of cyclized material on photochemically initiated reaction with ethanethiol or butanethiol, a 2:1 mixture of the cyclized to uncyclized diadducts (**2, 3, 4**) and the uncyclized monoadduct **5** were formed in photochemical reactions with benzenethiol or *p*-toluenethiol.

A reaction of the monoadduct **5** with benzenethiol in the dark did not lead to any cyclization products, but on irradiation a mixture of the acyclic adduct **4** and the cyclization product **3** was formed. None of the encocyclic double bond isomer **2** could be detected in this reaction mixture, in contrast to the above thiol addition to the dipropargylmalonate, where as much endocyclic double bond isomer **2** as exocyclic double bond isomer **3** was obtained. Thus it was found that the cyclization product **2** does not arise from the acyclic adduct **5**, but that it is generated from the diacetylene **1** by direct cyclization to a presumed dimethylenecyclopentane intermediate **6**, which in turn can undergo 1,4 radical addition of benzenethiol to give **2** and probably 1,2 addition to give product **3**. The reactive intermediate **6** could not be isolated. While cyclizations of a cyanomalonyl radical with a terminal acetylenic group[3] and of a vinyl radical with a terminal vinyl group[4] have been shown to yield methylenecyclopentane products, the present result seems to be the first cyclization reaction of a vinyl radical with a terminal acetylene (i.e., the first example of a direct radical-initiated cyclization of a diacetylene).

Reductive desulfurization of the cyclization product mixture of **2** and **3** yielded the dimethylcyclopentene **7** and an epimeric mixture of the dimethylcyclopentanes **8a,b**. Hydrogenation of the olefin **7** also led to a cis/trans mixture of the dimethylcyclopentanes **8a,b**. Reductive desulfurization of the acyclic diadduct **4** and of the monoadduct **5** gave dimethyl di-*n*-propylmalonate (**9**). Since irradiation (a radical process) was required for the cyclization of the thioenol ether **5** with thiophenol, it was of interest to explore alternative ionic



cyclizations of this acetylenic thioenol ether. Its reaction with aqueous mercuric chloride gave the cyclopentenal **10** in 80% yield.



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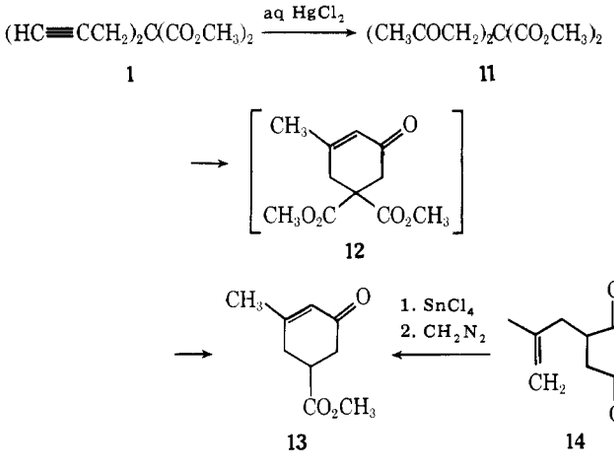
Under the same reaction conditions dimethyl dipropargylmalonate (**1**) was converted to the acyclic diketone **11**. The latter could be cyclized by sodium methoxide to the cyclohexenone **12**, which underwent monodecarbomethoxylation to the monoester **13**. The structures of these cyclohexenones are consistent with their spectroscopic data and could be confirmed by an alternative synthesis. Thus alkylation of maleic anhydride with isobutene and rearrangement of the olefinic anhydride **14** with stannic chloride followed by esterification also provided the enone ester **13**[5,6] obtained from the above reaction sequence.



Experimental Section

Photochemical Reactions of Dimethyl Dipropargylmalonate (1) with Thiols. Dimethyl dipropargylmalonate (**1**) [bp 75–80 °C (0.01 mm), 87–88 °C, *m/e* 208], prepared by the procedure for the diethyl ester[7] in 82% yield, and 1 or 2 equiv of *p*-toluenethiol, or 2 equiv of thiophenol, or an excess of *n*-butanethiol or ethanethiol, were subjected to identical reaction conditions represented by the following procedure. Corresponding results are shown in Table I.

A solution of 0.80 g (3.8 mmol) of the dipropargyl compound **1**, 0.50 g (4.0 mmol) of p-toluenthiol, and 10 mg of diphenyl disulfide in 5 mL of dry benzene was sealed under a nitrogen atmosphere in a Pyrex tube and irradiated for 6 h with a 450-W high-pressure Hg lamp. Distillation of the reaction mixture gave 0.34 g of recovered dipropargyl compound **1**, 0.28 g of the acyclic monoadduct **5** [bp 120 °C (0.01 mm); IR ν_{max} 3300 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (q, 4 H), 6.3 (m, 1 H), 5.6 (m, 1 H), 3.7 (s, 6 H), 2.8–3.1 (m, 4 H), 2.3 (s, 3 H), 2.05 (s, 1 H)], followed by a mixture of 0.40 g of the acyclic diadduct **4** and the cyclic diadducts **2** and **3** [bp 210–220 °C (0.01 mm); IR ν_{max} no acetylenic absorption at 3300 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (m, 8 H), 5.2–6.2 (m, $\simeq$2 H), 3.75 (s, 6 H), 2.7–3.2 (m, 6 H), 2.3 (s, 6 H).

An analogous diadduct mixture, bp 210–220 °C (0.02 mm), was obtained from reaction with 2 equiv of benzenethiol and separated by medium-pressure liquid chromatography on silica gel, eluting with chloroform at 80-lb pressure. Three fractions were collected. On reductive desulfurization (see below) the most rapidly eluted one (**4**) yielded dimethyl di-*n*-propylmalonate, while the other two gave only cyclopentyl products. The second eluate showed spectra corresponding to the thiomethylene structure **3**: *m/e* 428; NMR ($CDCl_3$) δ 7.2 (s, 10 H), 6.1 (s, 1 H), 3.7 (s, 6 H), 3.2 (s, 2 H), 3.1–2.6 (m, 5 H). The last fraction contained the cyclopentene **2**: *m/e* 428; NMR ($CDCl_3$) δ 7.2 (s, 10 H), 3.7 (s, 4 H), 3.1 (s, 4 H).

Comparison of the characteristic NMR signal at δ 6.1 for the exocyclic double bond of **3** with signals at δ 3.1–3.2 for **2** and **3** showed a 1:10 signal ratio in the initial mixture of diadducts, indicating approximately equal amounts of the isomers **2** and **3**.

Table I

Thiol	Registry no.	Wt % products: Recovered 1	Monoadducts 5	Diadducts 2, 3, 4
Thiophenol, 2 equiv	108-98-5	14	37	49
p-Toluenethiol, 1 equiv	106-45-6	33	27	40
p-Toluenethiol, 2 equiv		32	11	57
n-Butanethiol, excess	109-79-5	Trace	15	85
Ethanethiol, excess	75-08-1	46	31	23

Table II. Raney Nickel Reduction Products (%)

Mixture of thiol diadducts 2, 3, 4 from reaction of 1 with:	9	8a	8b
Thiophenol (2 equiv)	37	26	37
p-Toluenethiol (1 equiv)	49	28	23
p-toluenethiol (2 equiv)	49	28	23
n-Butanethiol (excess)	95	Trace	Trace
Ethanethiol (excess)	100		
From reaction of thiol monoadduct **5** with *p*-toluenethiol	22	50	28

Reaction of Dimethyl (3-*p*-toluenethiylallyl)propargylmalonate (5) with *p*-Toluenethiol. A solution of 100 mg (0.30 mmol) of the acyclic monoadduct **5**, 40 mg (0.32 mmol) of *p*-toluenethiol, and 10 mg of diphenyl disulfide in 5 mL of benzene was irradiated for 8 h as described above and distilled. The crude reaction product lacked the characteristic 1:1 pair of NMR singlets at δ 3.1 and 3.2 of the cyclopentene **2**, which was found in the reaction products of dimethyl dipropargylmalonate, but showed spectral characteristics of **3** and **4** at δ 6.1 and 2.6–3.1. Reductive desulfurization of the total reaction product gave dimethyl dipropylmalonate (**9**) and *trans*- and *cis*-1,1-dicarbomethoxydimethylcyclopentanes **8a,b** in ratios of 22:50:28, respectively. A corresponding reaction mixture stored without irradiation and diphenyl disulfide gave only dimethyl dirpopylmalonate (**9**) on subsequent reductive desulfurization.

Reductive Desulfurization of Reaction Products. The distilled thiol addition products (about 0.4 g) were heated at reflux in 10 mL of ethanol with about 3 g of W-6 Raney nickel for 10 h. Filtration and evaporation yielded desulfurized products sometimes showing allylic methyl singlets in NMR spectra due to the dimethylcyclopentene **7**. In those cases the reaction mixtures were hydrogenated further over 5% Pd/C catalyst in ethanol to the dimethylcyclopentane products **8a,b**. The mixtures of these products and dimethyl di-*n*-propylmalonate (**9**) were analyzed by GLC on a 6¼ ft column of 20% Carbowax on Firebrick at 145 °C. Under these conditions the reduction products had the following retention times: dimethyl di-*n*-propylmalonate (**9**), 8.2 min; 1,1-dicarbomethoxy-*trans*-3,4-dimethylcyclopentane[1] (**8a**), 10.4 min; 1,1-dicarbomethoxy-*cis*-3,4-dimethylcyclopentane[1] (**8b**) and 1,1-dicarbomethoxy-3,4-dimethylcyclopent-3-ene (**7**), 13 min. Hydrogenation of the cyclopentene **7** in the reaction mixture, by stirring under hydrogen over 5% Pd/C in ethanol, increased the amount of the *trans*-dimethylcyclopentane **8a** in accord with the hydrogenation of 1,2-dimethylcyclopentene, which gave a 4:1 *trans/cis*-1,2-dimethylcyclopentane ratio.[2] The composition of typical reduction product mixtures is shown in Table II. Products **8a,b** and **9** were identified by GLC enrichment with authentic samples[1] and matching of NMR spectra and mass fragmentation patterns.

4,4-Dicarbomethoxy-2-methylcyclopentenecarboxaldehyde (10). Irradiation of a solution of 1.8 g (8.6 mmol) of dimethyl dipropargylmalonate (**1**) 2.6 mL (35 mmol) of ethanethiol, and 12 mg of diphenyl disulfide in 3 mL of benzene for 6 h with a high-pressure 450-W Hg lamp and distillation of the mixture gave 1.1 g of recovered starting malonate (**1**), 0.75 g of monothiol adduct **5**, bp 120 °C (0.03 mm), and 0.55 g of diadduct **4**, bp 190 °C (0.01 mm). The lower boiling point product showed acetylenic absorption: IR ν_{max} 3300 cm^{-1}; NMR ($CDCl_3$) δ 6.2 (m, 1 H), 5.4 (m, 1 H), 3.75 (s, 6 H), 2.4–3.0 (m, 6 H), 2.1 (s, 1 H), 1.3 (t, 3 H); *m/e* 270. The higher boiling point product showed: no acetylenic IR absorption; NMR ($CDCl_3$) δ 6.0 (m, 2 H), 5.4 (m, 2 H), 3.7 (s, 6 H), 2.2–3.0 (m, 8 H), 1.2 (t, 6 H); *m/e* 332. On reductive desulfurization of either component only dimethyl di-*n*-propylmalonate (**9**) was obtained.

A solution of 0.20 g (0.74 mmol) of the lower boiling point fraction (5) and 0.65 g (2.4 mmol) of mercuric chloride in 7 mL of 4:1 acetonitrile/water was heated at reflux for 15 h, filtered, and distilled to 130 °C (0.05 mm) to give 0.14 g (80% yield) of the cyclopentyl aldehyde **10**: IR ν_{max} 1735, 1665 cm^{-1}; NMR ($CDCl_3$) δ 10.0 (d, 1 H), 3.8 (s, 6 H), 3.3 (s, 4 H), 2.2 (s, 3 H); *m/e* 226. The product showed a single peak in GLC on a 10-ft methylsilicone column at 200 °C. DNP derivative mp 201–202 °C.

Anal. Calcd for $C_{17}H_{18}N_4O_8$: C, 50.24; H, 4.47; N, 13.79. Found: C, 49.03; H, 4.40; N, 13.93.

4,4-Dicarbomethoxy-2,6-heptanedione (11). A solution of 4.0 g (19 mmol) of dimethyl dipropargylmalonate (1) in 60 mL of acetonitrile and 15 mL of water and 15.6 g (58 mmol) of mercuric chloride was heated at reflux for 12 h. Concentration under vacuum, extraction of the aqueous mixture with ether, washing of the extract with aqueous sodium sulfide, concentration, and distillation gave 4.2 g (90% yield) of the diketone **11**: bp 130 °C (0.5 mm); mp 54–55 °C; IR ν_{max} 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (s, 6 H), 3.3 (s, 4 H), 2.2 (s, 3 H); *m/e* 244.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.10; H, 6.56. Found: C, 54.31; H, 6.69.

5-Carbomethoxy-3-methyl-2-cyclohexenone (13). A. A solution of 2.6 g (11 mmol) of 4,4-dicarbomethoxy-2,6-heptanedione (11) and 0.58 g (11 mmol) of sodium methoxide in 50 mL of methanol was heated at reflux for 15 h. The reaction mixture was acidified with dilute aqueous HCl, concentrated, and partitioned between water and dichloromethane. Distillation of the organic extract at 110 °C (0.05 mm) gave 1.5 g (85% yield) of a single product: IR ν_{max} 1730, 1665, 1620 cm^{-1}; UV λ_{max} 245 nm; NMR ($CDCl_3$) δ 5.9 (s, 1 H), 3.7 (s, 3 H), 3.4–3.7 (m, 5 H), 2.0 (s, 3 H); *m/e* 168; and one peak in GLC at 16.5 min on a 10-ft methylsilicone column at 200 °. DNP derivative mp 126–127 °C (reported[5,6] 149–150 °C).

Anal. Calcd for $C_{15}H_{16}N_4O_6$: C, 51.87; H, 4.32; N, 16.14. Found: C, 51.79; H, 4.55; N, 16.04.

B. A solution of 3.0 g of methallylsuccinic anhydride (14) and 5.0 g of stannic chloride in 25 mL of dichloromethane was stirred at 0 °C for 1 h and at 20 °C for 20 h. Addition of water and dilute aqueous HCl, extraction with dichloromethane, and concentration gave a crude product which was dissolved in aqueous HCl, extraction with dichloromethane, and concentration gave a crude product which was dissolved in aqueous sodium bicarbonate, washed with ether, and recovered by acidification and extraction with dichloromethane, yielding 2.8 of gummy product. Recrystallization from ether–ligroin gave 1.4 g of the acid corresponding to ester **13** with mp 88–90 °C (reported[5,6] mp 92–94 °C). A solution of this compound in ether on reaction with diazomethane gave the ester **13**, identical in all spectroscopic properties with the product obtained above. The mixture melting point of corresponding DNP derivatives was not depressed.

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Registry No.—**1**, 63104-44-9; **2**(Ar = *p*-tolyl), 63104-45-0; **2** (Ar = Ph), 63133-61-9; **3** (Ar = *p*-tolyl), 63104-46-1; **3** (Ar = Ph), 63104-47-2; **4** (Ar = *p*-tolyl), 63104-48-3; **5** (Ar = *p*-tolyl), 63104-49-4; **5** (Ar = Ph), 63104-50-7; **10**, 63104-51-8; **10** DNP, 63104-42-7; **11**, 63104-52-9; **13**, 63104-53-0; **13** DNP, 63104-43-8; **14**, 18908-20-8; mercuric chloride, 7487-94-7.

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1,9,10-Anthyridines

Paul Caluwe* and Thomas G. Majewicz

Department of Chemistry, State University of New York, College of Environmental Science and Forestry, Syracuse, New York 13210

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The Friedländer condensation of 2,6-diaminopyridine-3,5-dicarboxaldehyde and ketones was investigated as a possible synthetic route to substituted and fused 1,9,10-anthyridines. Condensation of this bis-*o*-amino aldehyde with acenaphthenone gave the fused, fully aromatic diacenaphtho[1,2-*b*:1′,2′-*i*]1,9,10-anthyridine in 65% yield. Condensations with deoxybenzoin, α-tetralone, and acetophenone, on the other hand, resulted in the formation of the 5,10-dihydro-1,9,10-anthyridine moiety, rather than the expected fully aromatic 1,9,10-anthyridine nucleus. It was demonstrated that base-catalyzed hydride transfer from the solvent on the anthyridine initially formed in the reaction medium resulted in the overall reduction of this heterocyclic system. Oxidation of the dihydroanthyridines with nitrobenzene or nitric acid gave the fully aromatic anthyridines in moderate yield. Prolonged oxidation of 2,8-diphenyl-5,10-dihydro-1,9,10-anthyridine with hot nitric acid gave mainly 2,8-diphenyl-5(10*H*)-1,9,10-anthyridone. Friedländer condensation of 2-amino-5,6-diphenylpyridine-3-carboxaldehyde and deoxybenzoin gave 2,3,6,7-tetraphenyl-1,8-naphthyridine in excellent yield.

The linear fusion of benzene rings leads to the well documented "acene" homologous series.[1] Very little information on the analogous series, containing the pyridine ring as building unit, is available. Contrary to the linear carbocyclic series, introduction of heteroatoms in such polycondensed systems gives rise to an increasing number of isomeric ring structures. The fusion of pyridine rings through their 2,3 bonds is of special interest because such condensed systems have been proposed for the structural unit of pyrolyzed poly(acrylonitrile).[2] In earlier work we have described a new and facile approach to the 1,8-naphthyridine heterocyclic system.[3] We now wish to report a new synthetic method for its next higher homolog, containing three linearly annelated pyridine rings: 1,9,10-anthyridine. Very few compounds containing this fundamental heterocyclic system have been reported.[4] The parent compound was only recently synthesized in a six-step sequence starting from 2,6-diaminopyridine.[5] Our familiarity with the synthetic opportunities present in the *o*-amino aldehyde functional group prompted us to approach the anthyridine skeleton via Friedländer condensation of appropriate *o*-amino aldehydes with ketones.

This synthetic strategy required either 2,6-diaminopyridine-3,5-dicarboxaldehyde **2** or 2-amino-1,8-naphthyridine-3-carboxaldehyde. Hydrogenolysis of *o*-aminonitriles seemed a most promising synthetic method for the elaboration of the *o*-amino aldehyde functional group. Hydrogenation of the readily available[6] 2,6-diamino-3,5-dicyanopyridine **1** suspended in 2 N HCl produced the desired bis-*o*-amino aldehyde