

(70% ethyl acetate in hexane) showed no alcohol left, a 25% ammonium acetate, ethyl acetate extractive workup was performed. Flash chromatography (70% ethyl acetate in hexane) gave the mesylate compound (580 mg, 78%), which was stored at  $-78^{\circ}\text{C}$  until used:  $^1\text{H NMR}$  (250 MHz, acetone- $d_6$ )  $\delta$  3.23 (3 H,  $\text{OSO}_2\text{Me}$ ), 5.33 (s, 2 H,  $\text{OCH}_2$ ), 7.66, 7.83, 8.05, 8.06, 8.43, and 9.00 (6 H, aromatic); high-resolution mass spectrum,  $m/z$  calculated for  $\text{C}_{11}\text{H}_{12}\text{NO}_3\text{S}$  ( $\text{M} + \text{H}$ ) $^+$  238.0538, found 238.0538.

4-(((Methylsulfonyl)oxy)methyl)quinoline:  $^1\text{H NMR}$  (250 MHz, acetone- $d_6$ )  $\delta$  3.23 (s, 3 H,  $\text{SO}_2\text{Me}$ ), 5.83 (s, 2 H,  $\text{OCH}_2$ ), 7.63, 7.70, 7.83, 8.12, and 8.96 (6 H, aromatic); high-resolution mass spectrum,  $m/z$  calculated for  $\text{C}_{11}\text{H}_{12}\text{NO}_3\text{S}$  ( $\text{M} + \text{H}$ ) $^+$  238.0538, found 238.0538.

1,2:3,4-Bis-*O*-(1-methylethylidene)-6-*O*-(3-quinolinylmethyl)- $\alpha$ -D-galactopyranose (10). To a suspension of KH (35% in oil) (40 mg, 0.350 mmol) in THF (350 mL) at  $0^{\circ}\text{C}$  was added to a solution of diacetone. To this mixture was added a solution of 3-(((methylsulfonyl)oxy)methyl)quinoline (100 mg, 0.40 mmol) in THF (250  $\mu\text{L}$ ). The temperature was then raised to room temperature to give a dark solution after few hours. A 25% ammonium acetate-ethyl acetate extractive workup was performed. Flash chromatography (50% ethyl acetate in hexane) of the crude mixture afforded the desired ether 10 (90 mg, 80%) as an oil:  $[\alpha]_D^{22}$   $-61.8^{\circ}$  ( $c$  1.6, acetone);  $^1\text{H NMR}$  (250 MHz, acetone- $d_6$ )  $\delta$  1.30, 1.31, 1.36, and 1.48 (4 s, 12 H, 2 ( $\text{CH}_3$ ) $_2\text{C}$ ), 4.60 and 4.75 (2 m, 2 H, H-6 and H-6'), 4.06 (5, 1 H,  $J = 5.4$  Hz, H-5), 4.31 (m, 2 H, H-2 and H-4), 4.63 (dd, 1 H,  $J_{3,2} = 8.0$  Hz,  $J_{2,3} = 2.3$  Hz, H-3), 4.78 (AB, 2 H,  $J = 12.4$  Hz,  $\text{OCH}_2$ ), 5.50 (d, 1 H,  $J_{1,2} = 6.0$  Hz), 7.58, 7.63, 7.95, 8.03, 8.23, and 8.91 (6 H, aromatic); high-resolution mass spectrum,  $m/z$  calculated for  $\text{C}_{22}\text{H}_{28}\text{NO}_6$  ( $\text{M} + \text{H}$ ) $^+$  402.1917, found 402.1917.

1,2:3,4-Bis-*O*-(1-methylethylidene)-6-*O*-(4-quinolinylmethyl)- $\alpha$ -D-galactopyranose (11):  $[\alpha]_D^{22}$   $-65.6^{\circ}$  ( $c$  1, acetone);

$^1\text{H NMR}$  (250 MHz, acetone- $d_6$ )  $\delta$  1.32, 1.33, 1.38, and 1.48 (4 s, 12 H, 2 ( $\text{CH}_3$ ) $_2\text{C}$ ), 3.80 (AB, 2 H,  $J_{6,6} = 10.4$  Hz, H-6 and H-6'), 4.11 (5, 1 H,  $J = 8.3$  Hz, H-5) 4.28-4.38 (m, 2 H, H-2 and H-4), 4.63 (dd, 1 H,  $J = 3.1$  and 8.2 Hz, H-3), 5.11 (AB, 2 H,  $J = 12.8$  Hz,  $\text{CH}_2$ ), 7.55, 7.60, 7.71, 8.05, 8.13, and 8.85 (6 H, aromatic); high-resolution mass spectrum,  $m/z$  calculated for  $\text{C}_{22}\text{H}_{28}\text{NO}_6$  ( $\text{M} + \text{H}$ ) $^+$  402.1917, found 402.1917.

**Typical Procedure for the Cleavage of 2-Quinolinylmethyl Ethers by  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ . Regeneration of 1,2:3,4-Di-*O*-isopropylidene-D-galactopyranose (20) from the Ether 9.** To the ether 9 (3.5 g, 8.7 mmol) in DMF (22.0 mL) was added water (5.4 mL). To the resulting homogeneous mixture was then added  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (2.24 g, 13.0 mmol), and the resulting dark green solution was stirred at  $65^{\circ}\text{C}$  in a flask closed by a septum through which a gauge no. 20 needle was introduced. After 18 h, the brown mixture was then poured in an aqueous solution of 25% ammonium acetate (100 mL), and then ethyl acetate (100 mL) was added. The organic phase was washed three times with aqueous 25% ammonium acetate (50 mL). The colored organic phase was then dried with  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure. Flash chromatography (30% to 50% ethyl acetate in hexane) of the residue afforded the desired alcohol 20 (1.7 g, 75%) showing a light brown coloration. To the alcohol dissolved in MeOH (40 mL) was added charcoal until a colorless solution was obtained, and after filtration on Celite, 1.5 g (70%) of pure alcohol 20 was isolated.

**Acknowledgment.** We wish to thank Marc Labelle for helpful suggestions in the preparation of this manuscript.

**Supplementary Material Available:**  $^1\text{NMR}$  spectra for 6, 7, 9-13, 3- and 4-(((methylsulfonyl)oxy)methyl)quinoline (9 pages). Ordering information given on any current masthead page.

## Regiochemical Effects Associated with Nucleophilic Aromatic Substitutions by Bidentate Sulfur Nucleophiles

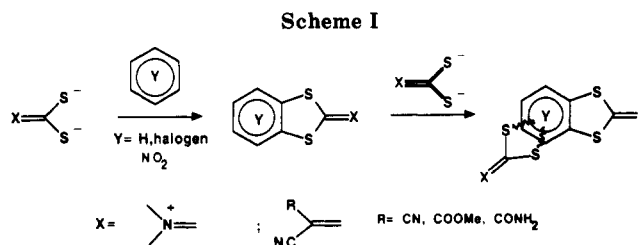
Yves Gimbert,<sup>†</sup> Alec Moradpour,<sup>\*,†</sup> and Claude Merienne<sup>†</sup>

Laboratoire de Physique des Solides (UA2 of CNRS) and Laboratoire de Chimie et Physicochimie des Milieux Structurés (UA1384 of CNRS), Université Paris-Sud, 91405 Orsay, France

Received March 12, 1990

Aromatic nucleophilic substitutions using 2,2-bis(methylthio)ethene 1,1-dithiolate 1 have been investigated. A possible control of the regiochemistry of the compounds resulting from the multiple substitution reactions by this ambident nucleophile have been examined. Starting from hexafluorobenzene, 2a, containing two para fluorines, is obtained. When 2,3,4-trichloro-1,5-dinitrobenzene is reacted with 1, leading to 8, the observed regiochemistry of the two bidentate entering groups is completely modified. The regiochemical aspects of these processes are discussed.

The scope, mechanism, and synthetic utility of the nucleophilic aromatic substitution by thiolate anions  $\text{RS}^-$  have been extensively studied.<sup>1-3</sup> With rings containing more than one leaving group, an important well-documented<sup>4</sup> aspect concerns the orientations of these reactions. These effects determine the regiochemistry of (i) the compounds from multiple substitutions by a given thiolate anion and (ii) the isomeric thioethers from different thiolates used in consecutive substitutions. Several studies concerning these regiochemical problems have been reported;<sup>5-7</sup> they include the modifications of (i) the nature and the ring arrangements of the leaving groups<sup>5,6</sup> and (ii)

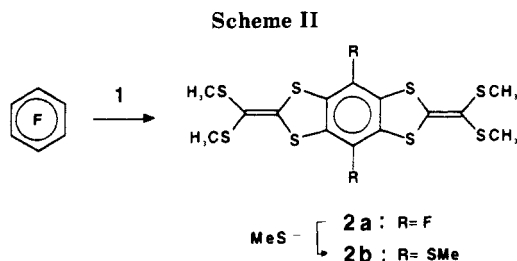


the reactivity of the attacking nucleophile and/or the mechanism of the reaction.<sup>7</sup>

<sup>†</sup>Laboratoire de Physique des Solides.

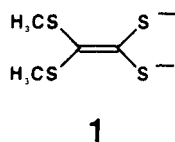
<sup>\*</sup>Laboratoire de Chimie et Physicochimie des Milieux Structurés.

(1) Peach, M. E. In *The Chemistry of the Thiol Group*; Patai, S., Ed. J. Wiley: New York, 1974.



If the substitutions by gem-bidentate sulfur nucleophiles are now considered, additional orientation effects—specific to the forced proximity of two nucleophilic reacting centers—might be involved. Few studies have been devoted to aromatic substitutions by ambident sulfur nucleophiles.<sup>8–10</sup> None of them have examined the possibility of introducing more than one such nucleophile on an aromatic ring; therefore, the regiochemistries involved in such processes (Scheme I) have never been investigated.

We have recently published<sup>11</sup> the preparation of the 2,2-bis(methylthio)-1,1-ethenedithiol dilithium salt **1** as an intermediate to the syntheses of tetrakis(alkylthio)-ethylenes and 1,3-dithioles derivatives. We now have



carried out aromatic nucleophilic substitutions using this dianion **1**, and we report here the results of our studies about the regiochemical problems associated with the multiple substitutions by this reagent, as an example of bidentate sulfur nucleophiles; we also report one possible line of investigation toward the modifications and the control of the regiochemistry of these processes.

### Results

The dianion **1** was first reacted with hexafluorobenzene in DMF at 0 °C. The compound **2a**, containing two para fluorine atoms, was obtained (41% yield). The remaining fluorines were further reacted with excess  $\text{CH}_3\text{S}^-$ , leading to the fully sulfur-substituted compound **2b** (Scheme II). Other less reactive fluoroaromatic compounds (1,2-difluoro- or 1,2,4,5-tetrafluorobenzene) did not react with **1**, even at higher temperatures (DMF, 80 °C).

The substitution reactions of **1** were investigated with a number of halonitro aromatic substrates and the most significant results are summarized in Table I. When 2-chloro-1,3-dinitrobenzene (**3**) was allowed to react with excess dianion **1** the product **4** was obtained with a modest (11%) yield. Similar treatment of **5** gave **6** (65%) and a small amount (5%) of the previous nitro-containing com-

**Table I. Substitution Reactions of Halonitro Aromatics by**

starting compound	product	% yields
		11
		65 + 5
		65
		6
		0

ound **4**, resulting here from the alternate substitution of the two chlorines. The same process with 2,3,4-trichloro-1,5-dinitrobenzene gave the interesting derivative **8** (65%). The latter was also obtained from **9** (6%).

When hexasubstituted compounds were used as starting materials, the course of the reactions were very different. Thus, 1,3,4,5-tetrachloro-2,6-dinitrobenzene (**10**) gave no isolable substitution products; similarly, 1,3,5-trihalo-2,4,6-trinitrobenzenes led only to unidentified mixtures, excluding any substitution compound. A number of other halonitro aromatics usually reacted with **1** under the present conditions, but these reactions led also to complex mixtures and the separations were not attempted.

### Discussion

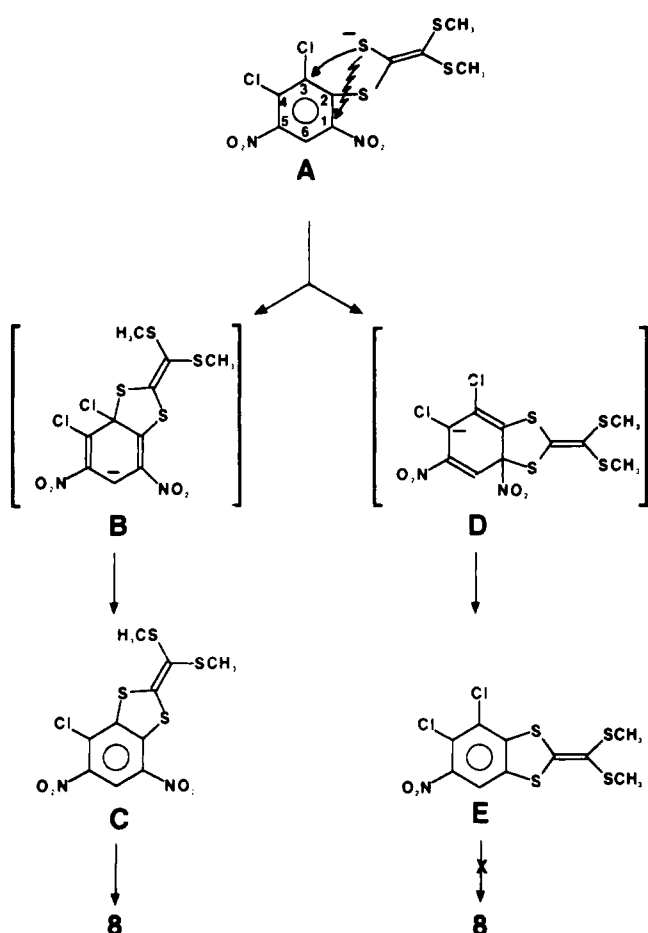
Assuming the oldest and most important  $\text{S}_{\text{N}}\text{Ar}$  mechanism<sup>2</sup> to be operating in the substitutions of polyhalobenzenes by thiolates, rationalizations of the orientations of these reactions have been worked out.<sup>4</sup> If the first addition step is rate-determining, the position of attack of the nucleophile is determined by the relative stabilities of the various possible  $\sigma$ -complex intermediates. A similar argument and the known ability of sulfur to stabilize a negative charge next to it, due to favorable overlap interactions with available d orbitals,<sup>12</sup> rationalize the observed predominantly para-directing orientation of an SR group on the ring. Thus, if  $\text{C}_6\text{F}_6$  multiple substitutions are considered, after the first product  $\text{C}_6\text{F}_5\text{SR}$  is formed, the subsequent substitution gave 1,4- $\text{C}_6\text{F}_4(\text{SR})_2$ , and further substitutions led to  $\text{C}_6\text{F}_2(\text{SR})_4$ , with the two remaining fluorines being para to each other.<sup>13</sup>

As a matter of fact, with the substitutions of hexafluorobenzene by the present bidentate nucleophile **1**, the same structure was obtained for compound **2**, after two

(2) Bernasconi, C. F. *Chimia* 1980, 34, 1.  
 (3) Pastor, S. D. *Helv. Chim. Acta* 1988, 71, 859 and references cited therein.  
 (4) Burdon, J. *Tetrahedron* 1965, 21, 3373. See also: Burdon, J.; Parsons, I. W. *J. Am. Chem. Soc.* 1977, 99, 7445.  
 (5) Cogolli, P.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* 1979, 44, 2636.  
 (6) Beck, J. R.; Yahner, J. A. *J. Org. Chem.* 1978, 43, 2048.  
 (7) Stack, T. D. P.; Holm, R. H. *J. Am. Chem. Soc.* 1988, 110, 2484 and references cited therein.  
 (8) Yokoyama, M. *J. Org. Chem.* 1970, 35, 283.  
 (9) D'Amico, J. J.; Tung, C. C.; Dahl, W. E.; Dahm, D. J. *J. Org. Chem.* 1976, 41, 3564.  
 (10) Rasheed, K.; Walkentin, J. D. *J. Org. Chem.* 1980, 45, 4041.  
 (11) Moradpour, A.; Bittner, S. *Synthesis* 1988, 346.

(12) Kobrina, L. S. In *Fluorine Chemistry Reviews*; Tarrault, P., Ed.; M. Dekker: New York, 1974; Vol. 7, and references cited.  
 (13) Peach, M. E.; Langille, K. R. *J. Fluorine Chem.* 1971/72, 1, 407. Peach, M. E.; Smith, A. M. *J. Fluorine Chem.* 1974, 4, 341.

Scheme III



such subunits had been introduced on the ring. Is it possible to circumvent this considerable sulfur para-orienting effect and to modify these reaction regiochemistries? One such possibility is offered by a proper choice of the leaving groups. This approach involves additional directing effects—if nucleofugic groups other than halogen are considered—which in combination with the possible intramolecular effects due to the present ambident nucleophile might modify the course of these reactions. The nitro group, as an activating function or as a nucleofuge, with sometimes enhanced reactivity as compared to even fluorine,<sup>14</sup> is a valuable candidate.

Considering the substitution of 2,3-dichloro-1-nitrobenzene (5) by the dianion 1, the mobility of the substituents, already determined<sup>6</sup> by stepwise substitutions by  $\text{CH}_3\text{S}^-$ , are reflected in the structure of the main resulting compound 6. When halonitro aromatics with higher levels of substitutions, such as 7, were reacted with an excess of nucleophile 1, the very interesting “angularly” disubstituted compound 8 is formed (65%). The latter was also prepared likewise from 9, although with a poorer yield (6%).

The formation of compound 8 can be reasonably rationalized within the frame of existing theories.<sup>4,12</sup> The key intermediate A (Scheme III), formed by the combined ortho and para directing effects of the two nitro groups, determines the ring closure to C. This preferential formation of C, as compared to E, is explained when the corresponding  $\sigma$ -complex intermediates B and D are taken into account. The relative stabilities of the latter are determined by the  $I_r$  repulsive effects: this effect is larger

for chlorine (addition on carbon (1) leading to D) than for hydrogen (addition on carbon (3) leading to B), and it promotes the formation of C through the more stable precursor B. The set up of the second nucleophile leading from C to 8 is straight forward, while the same regiochemistry is not expected from E, due to the high para-orienting effect of the two sulfurs (see 1  $\rightarrow$  2a). A similar argument can also be easily applied to the preparation of 8 from its precursor 9.

When hexasubstituted aromatics were reacted with 1, in the present conditions, no substitution products were, unfortunately, any more detected. This failure is possibly related to competing redox reactions involving oxidation of the highly sensitive dianion 1 and reduction of the nitro groups; the occurrence of such side reactions might also account for the low yields observed for the syntheses of 4 and 8.

Our main interest, in this study, concerned the modification of the substitution regiochemistry, leading to the formation of the compound 8. The latter is, in principle, a possible precursor to the 3-fold symmetry fully substituted ring, if another adequate leaving group is substituted on the remaining free carbon of the ring. Efforts toward this direction, as well as other possible lines of investigations to monitor these nucleophilic substitutions, will be subjects of future communications.

### Experimental Section

NMR spectra were obtained with a Bruker AM 250 MHz spectrometer operating at 62.86 MHz for the  $^{13}\text{C}$  resonances. The chemical shifts expressed in ppm are reported in  $\delta$  relative to tetramethylsilane (TMS) as an internal reference for  $^1\text{H}$  spectra, and to the deuterated solvent signal for  $^{13}\text{C}$  spectra. In this latter case long relaxation delays (>10 s), short flip angle pulses ( $30^\circ$ ), and a relaxation reagent for compound 2b [chromium(III) 2,4-pentanedionate] have been used in order to allow a convenient observation of quaternary carbons. The melting points were determined on a Kofler Heizback apparatus and were not corrected. The mass spectra (CI mode) were obtained with a Nermag R10 spectrometer. The microanalytical results are obtained from the CNRS Laboratory at Gif sur Yvette.

**2,2-Bis(methylthio)-1,1-ethenedithiol Dilithium Salt (1).** This air-sensitive salt was prepared according to previous results<sup>11</sup> in oxygen-free dry THF and filtered under argon, washed with a small amount of dry oxygen-free ether, and used as such in subsequent reactions.

**Substitution Reactions: General Procedure.** A known amount of 1 is dissolved in dry DMF, under argon. The substrate to be substituted is then added to this, stirred, and cooled in an ice bath solution. The stirred solution is kept overnight at room temperature. The precipitate formed (2a, 2b) was collected by filtration, or, alternatively, the reaction mixture was poured in water and extracted with ether or  $\text{CH}_2\text{Cl}_2$  and the organic layer was dried on  $\text{Na}_2\text{SO}_4$ . Crude reaction mixtures were flash chromatographed with mixtures of toluene in cyclohexane as eluant; the isolated products were recrystallized.

**2,6-Bis(bis(methylthio)methylene)-4,8-difluorobenzo[1,2-d:4,5-d']bis[1,3]dithiole (2a):** from 2.56 g ( $13 \times 10^{-3}$  mol) of 1 and 0.242 g ( $1.3 \times 10^{-3}$  mol) of hexafluorobenzene in 50 mL of DMF; recrystallized from toluene as a white solid melting at  $203.5^\circ\text{C}$ , 260 mg (41% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.3 (s, 12 H,  $\text{SCH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 17.35 ( $\text{SCH}_3$ ), 112.55 and 145.70 (tetrathioethylene carbons), 143.16 and 147.07 (dd,  $^1J_{\text{CF}} = 246$  Hz,  $^4J_{\text{CCCCF}} = 3.7$  Hz, C(4) and C(8)), 122.90 (t,  $^2J_{\text{CCF}} = 13$  Hz,  $^3J_{\text{CCCF}} = 13$  Hz, C(3a), C(4a), C(7a), C(8a)). Anal. Calcd for  $\text{C}_{14}\text{H}_{12}\text{F}_2\text{S}_8$ : C, 35.4; H, 2.54; F, 8.1; S, 54.0. Found: C, 35.6; H, 2.5; F, 7.6; S, 53.8. MS  $m/z$ : 475 ( $\text{MH}^+$ ).

**4,8-Bis(methylthio)-2,6-bis(bis(methylthio)methylene)benzo[1,2-d:4,5-d']bis[1,3]dithiole (2b):** from 0.35 g ( $0.6 \times 10^{-3}$  mol) of 2a in 6 mL of DMF containing 0.7 g ( $14.5 \times 10^{-3}$  mol) of MeSH to which 0.9 g ( $14.5 \times 10^{-3}$  mol) of LiOH was added in small portions. The immediately formed yellow precipitate is recrystallized from toluene: 270 mg (80% yield) melting at  $260^\circ\text{C}$

(14) Beck, R. J. *Tetrahedron* 1978, 34, 2057.

(Differential Scanning Calorimeter DSC4 Perkin-Elmer).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.3 (s, 12 H), 2.4 (s, 6 H).  $^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ ): 16.6 ( $\text{SCH}_3$ ), 18.0 (ring  $\text{SCH}_3$ ), 110.95, 144.5 (tetrathioethylene carbons), 120.9, 141.3 (ring carbons). Anal. Calcd for  $\text{C}_{16}\text{H}_{18}\text{S}_{10}$ : C, 36.2; H, 3.4; S, 60.4. Found: C, 36.17; H, 3.3; S, 60.51. MS  $m/z$ : 531 ( $\text{MH}^+$ ).

**2-(Bis(methylthio)methylene)-4-nitro-1,3-benzodithiole (4):** from 0.33 g ( $1.68 \times 10^{-3}$  mol) of 1 and 0.17 g ( $0.86 \times 10^{-3}$ ) of 2-chloro-1,3-dinitrobenzene (3) in 2.5 mL of DMF; eluant, toluene/cyclohexane, 30/70 (v/v); 31 mg (11%) of a red solid was isolated.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.35 (s, 6 H), 7.21-7.24 and 7.27 (t, 1 H), 7.38-7.41 (d, 1 H), 8.04-8.08 (d, 1 H). Anal. Calcd for  $\text{C}_{10}\text{H}_9\text{NO}_2\text{S}_4$ : C, 39.6; H, 2.9; N, 4.6; S, 42.2. Found: C, 39.36; H, 2.71; N, 4.50; S, 42.01.

**2-(Bis(methylthio)methylene)-4-chloro-1,3-benzodithiole (6):** from 2.5 g ( $12.7 \times 10^{-3}$  mol) of 1 and 1.62 g ( $8.4 \times 10^{-3}$ ) of 2,3-dichloro-1-nitrobenzene (5) in 10 mL of DMF; eluant, toluene/cyclohexane, 30/70 (v/v); 0.13 g (5%) of 4 and 1.58 g (65%) of 6 as a white solid recrystallized from ethanol and melting

at 58.5 °C are obtained.  $^1\text{H}$  NMR: 2.35 (s, 6 H), 7.0-7.2 (m, 3 H). Anal. Calcd for  $\text{C}_{10}\text{H}_9\text{ClS}_4$ : C, 41.0; H, 3.2; Cl, 12.1; S, 43.7. Found: C, 40.98; H, 3.37; Cl, 12.8; S, 42.8.

**2,5-Bis(bis(methylthio)methylene)-7-nitrobenzo[1,2-d:3,4-d']bis[1,3]dithiole (8):** from 2 g ( $10.2 \times 10^{-3}$  mol) of 2,3,4-trichloro-1,5-dinitrobenzene<sup>15</sup> in 20 mL of DMF; eluant, toluene/cyclohexane, 20/80 (v/v); 0.87 g (65%) of a red compound melting at 133 °C is obtained.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ ): 2.35 (s, 12 H), 7.8 (s, 1 H).  $^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ ): 16.67 ( $\text{SCH}_3$ ), 113.93-114.23, 135.32-135.59 (tetrathioethylene carbons), 113.32, 130.93, 133.96, 139.21, 192.11, 144.42 (ring carbons). Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{NO}_2\text{S}_8$ : C, 34.7; H, 2.69; N, 2.89; O, 6.62; S, 53.0. Found: C, 35.11; H, 3.01; N, 2.86; O, 6.3; S, 52.72. MS  $m/z$ : 485 ( $\text{MH}^+$ ).

**Acknowledgment.** We acknowledge generous financial support of this work by the CNET.

(15) Joshi, S. S.; Gupta, R. S. *J. Ind. Chem. Soc.* 1953, 30, 548.

## Regiospecific Preparation of Cyclobutenedione Monoacetals

Lanny S. Liebeskind\*<sup>1</sup> and Kevin R. Wirtz

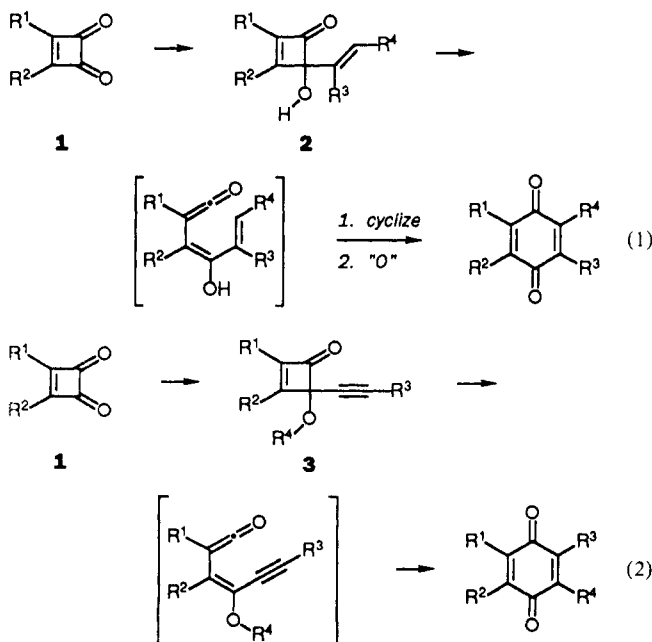
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received January 25, 1990

Treatment of 2,3-diisopropoxy-4-hydroxy-4-organyl-2-cyclobuten-1-ones, prepared by addition of nucleophiles ( $\text{H}^-$ ,  $\text{C-sp}^3$ ,  $\text{C-sp}^2$ ,  $\text{C-sp}$ ) to diisopropyl squarate, with  $\text{Me}_3\text{SiOCH}_2\text{CH}_2\text{OSiMe}_3$  and catalytic trimethylsilyl triflate in THF induces a regiospecific monoacetalization, providing the 3-isopropoxy-4-organyl-3-cyclobutene-1,2-dione 2-(ethylene acetal) in high yield. These compounds react with a wide range of nucleophiles to give 1,2-adducts that can be converted into 3,4-disubstituted-3-cyclobutene-1,2-dione-2-ethylene acetals under mild conditions. By changing the order of introduction of substituents, this sequence of reactions provides access to a variety of isomeric cyclobutenedione monoacetals in a regiodefined fashion.

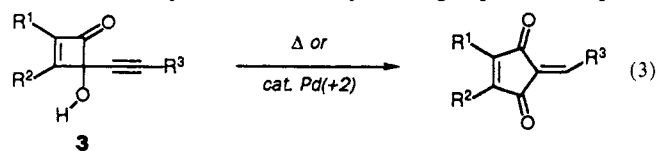
### Introduction

Two powerful new methods for the synthesis of highly substituted quinones based on the thermolysis of 4-hydroxycyclobutenones bearing  $\text{sp}^2$ - and  $\text{sp}$ -hybridized substituents at the 4-position were uncovered within the last few years (eqs 1 and 2).<sup>2</sup> The 4-alkynyl-4-hydroxy-



(1) Camille and Henry Dreyfus Teacher-Scholar, 1985-1990.

cyclobutenones also serve as precursors to alkylidene-cyclopentenone derivatives, either via thermolysis<sup>2a,j</sup> or more efficiently via metal-catalyzed ring expansion (eq 3).<sup>3</sup>



The thermal processes are presumed to proceed via ring opening of the cyclobutenone to an unsaturated vinylketene intermediate. Unsymmetrically substituted quinones and alkylidene-cyclopentenones can be prepared by these methods, but because the placement of substituents in the products is established in the initial addition of the unsaturated nucleophile to the cyclobutenedione (1  $\rightarrow$  2, 1  $\rightarrow$  3), regiochemical control in the quinone synthesis and stereochemical control in the alkylidene-cyclopentenone

(2) (a) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* 1985, 107, 3392. (b) Moore, H. W.; Decker, O. H. *W. Chem. Rev.* 1986, 86, 821. (c) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* 1986, 51, 3065. (d) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* 1986, 51, 3067. (e) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* 1987, 52, 1174. (f) Reed, H. W.; Chow, K.; Nguyen, N. W. *J. Org. Chem.* 1987, 52, 3491. Perri, S.; Moore, H. W. *Tetrahedron Lett.* 1987, 4507. (g) Perri, S.; Moore, H. W. *J. Org. Chem.* 1988, 53, 996. (h) Reed, M. W.; Moore, H. W. *J. Org. Chem.* 1988, 53, 4166. (i) Selwood, D. L.; Jandu, K. S. *Heterocycles* 1988, 27, 1191. (j) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* 1989, 111, 975. (k) Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* 1989, 111, 989. (l) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* 1989, 54, 2032. (3) (a) Liebeskind, L. S.; Mitchell, D.; Foster, B. *J. Am. Chem. Soc.* 1987, 109, 7908. (b) Liebeskind, L. S. *Tetrahedron* 1989, 45, 3053. (c) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* 1990, 112, 291.