

# Enolate Addition to a 2-Alkylidene[1,3]dithiane-Derived Bissulfoxide. A New $\alpha^2$ -Acceptor

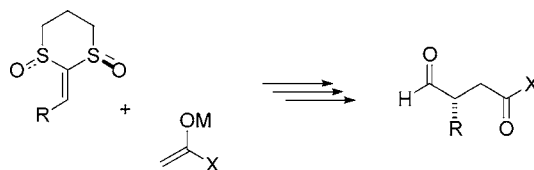
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Received July 15, 2005

## ABSTRACT



Reaction of enolates derived from esters and ketones to an easily prepared alkylidene[1,3]dithiane-1,3-dioxide afforded the respective adducts with good yields and selectivities generally exceeding 85:15. The base used for enolate addition played no significant role for the reaction outcome, and addition of a silyl enole ether gave similar results. The thus formed oxygenated *S,S*-acetals were transformed into the corresponding 1,4-dicarbonyls by a reduction/oxidation sequence with 84% yield.

1,3-Dioxygenated and 1,5-dioxygenated carbon chains are common motifs in natural products. A plethora of methods for their synthesis is known, among them the addition of enolates to carbonyl compounds and their  $\alpha,\beta$ -unsaturated derivatives, respectively. Though significantly less abundant, 1,4-dioxygenated carbon chains are similarly important, with prominent representatives in nature being  $\gamma$ -butyrolactones.<sup>1</sup> Nevertheless, methods for their synthesis are scarce.<sup>2</sup>

In this communication we report on enolate additions to dioxygenated ketene *S,S*-acetal **1**,<sup>3</sup> which after hydrolysis of the acetal moiety yields 1,4-dicarbonyls.

Unsymmetrically substituted sulfoxides are chiral and show a high optical stability.<sup>4</sup> Because they are favorably prepared by enantioselective oxidation of the respective sulfides, both enantiomers are usually accessible. Nucleophilic addition to chiral vinyl sulfoxides has been occasionally reported,<sup>5</sup> and Fensterbank et al. published additions of amines, cuprates, and malonate anions to alkylidene bis-(tolylsulfoxides).<sup>6</sup> Nevertheless, most of these methods have in common that the preparation of the substrates is rather cumbersome or the sulfoxide is hardly transferable into useful functionalities. We used alkylidene-[1,3]dithiane-1,3-diones as Michael-type acceptors, which are easily prepared via published procedures by Peterson olefination and stereoselective oxidation of the dithiane moiety. The respective alkylidene-dithianes are thus synthesized in high yields (Scheme 1).<sup>7</sup>

The yield of the sulfoxides was significantly improved by slightly changing the workup procedure (entries **1** and **2** in

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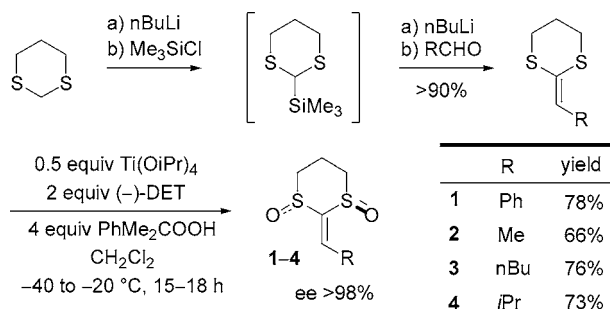
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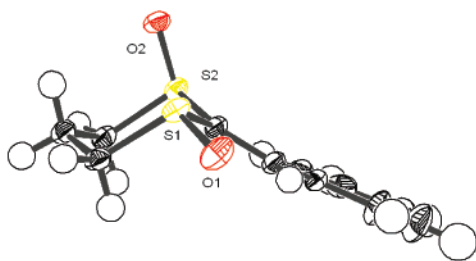
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**Scheme 1.** Synthesis of 2-Alkylidene-[1,3]dithiane-1,3-diones



Scheme 1). The titanate slurry was additionally treated by ultrasonication for about 3 h, resulting in an easily filterable precipitate.

The products were highly crystalline, and a crystal structure was obtained for the phenyl-substituted product **1**. The exocyclic moiety turned out to be perfectly planar, the less hindering vinylic hydrogen reaching toward the equatorial S=O oxygen (O1 in Figure 1).<sup>8</sup>



**Figure 1.** Crystal structure<sup>9</sup> of bisulfide **1**.

Addition of an enolate prepared by deprotonation of acetophenone with sodium hexamethyldisilazide yielded the corresponding adduct with 82% yield and 96:4 selectivity (Table 1, entry 1). No changes in the reaction outcome were observed when deprotonation was performed with lithium diisopropylamide (LDA). However, best results were only achieved at low temperatures (−78 °C). Astonishingly, adduct formation was reached even with catalytic amounts of the base, though the reaction was much more sluggish. The diastereoisomers were easily separated by either chromatography or crystallization. Yields in Table 1 are given for the isolated and purified major isomers.

The enolate prepared from cyclohexanone could be added to the phenyl-substituted bisulfide **1** with high yield

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(8) A crystal structure of racemic **2** has been published. Its structure is very similar to the herein presented compound **1**: Newlands, M. J.; Bo, L.; Fallis, A. G.; Gabe, E. J.; Le Page, Y. *Acta Crystallogr.* **1988**, C44, 503.

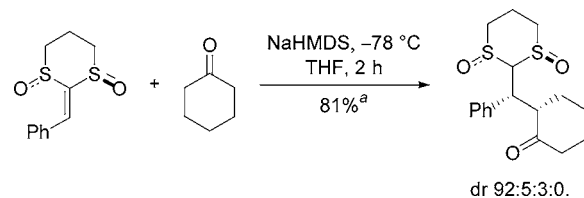
**Table 1.** Enolate Addition to a Dioxxygenated Ketene S,S-Acetal

entry	X	product	yield <sup>a</sup> (%)	dr
1	Ph	<b>5</b>	82	96:4
2	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>6</b>	76	92:8
3	Me	<b>7</b>	68	86:14
4	OEt	<b>8</b>	75	89:11

<sup>a</sup> Yields are given for the isolated and purified major isomers.

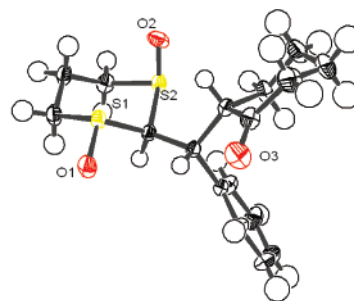
(Scheme 2). Though two new stereogenic centers were formed during this reaction, only three isomers were detected where one is predominantly produced (92:5:3:0).

**Scheme 2.** Addition of a Cyclohexanone-Derived Enolate



<sup>a</sup> Yield given for the isolated and purified major isomer.

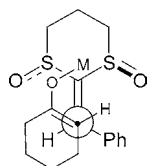
The major product **9a** could be crystallized, and its structure was unambiguously determined by X-ray crystallography (Figure 2). Obviously the enolate attacked from the top side (orientation of the alkylidene substrate as depicted in Figure 1) where less steric hindrance through hydrogen atoms of the dithiane moiety was present.



**Figure 2.** Crystal structure<sup>9</sup> of adduct **9a**.

Though the role of the counterion or an eventually added Lewis acid is hardly investigated in additions to vinyl

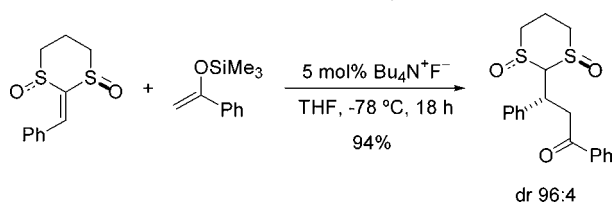
sulfoxides<sup>10</sup> we assume that a complexation of both the enolate and the sulfoxide by the metal (here sodium) occurs in the transition state, which is best rationalized by a Newman projection as depicted in Figure 3.



**Figure 3.** Proposed rational for the formation of adduct **9a**.

Because the utilized base for deprotonation and thus the counterion of the enolate played no significant role, we tested an independently prepared silyl enole ether as nucleophile (Scheme 3).<sup>11</sup> Again we got an identical reaction outcome, which led us to the conclusion that an open-chain mechanism might apply here. Nevertheless, further information seems to be necessary to support this theory.

**Scheme 3.** Addition of a Silyl Enole Ether



Protocols for a cleavage of the dioxygenated *S,S*-acetal via a Pummerer-type rearrangement (leading to carboxylic acid derivatives)<sup>3</sup> were frequently applied to similar bissul-

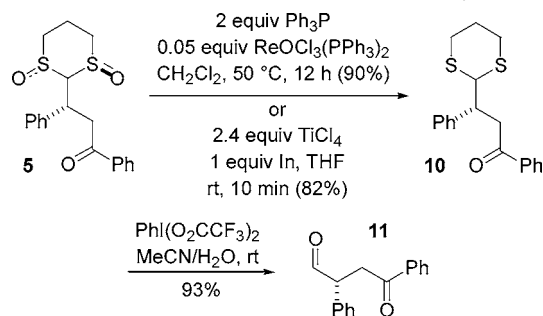
(9) Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-250402. Data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. [fax: +44 (0) 1223-336-033. E-mail: deposit@ccdc.cam.ac.uk]

(10) A survey on how the counterion is influencing reactions with bissulfoxides is given in ref 3.

(11) Mukaiyama, T. *Org. React.* **1982**, 28, 203. Carreira, E. M. In *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, p 997.

foxides. We further performed a two-step procedure leading to the respective carbaldehyde **11** (Scheme 4). Here, the

**Scheme 4.** Liberation of 1,4-Dicarbonyls



sulfoxides were reduced with either rhenium catalysis<sup>12</sup> or with titanium tetrachloride/indium<sup>13</sup> and subsequent *S,S*-acetal cleavage by oxidation (here with a hypervalent iodine compound<sup>14</sup>). Unfortunately we could not establish a suitable method for the determination of the optical purity. With no chromatographic method (HPLC or GC) could baseline separation of the enantiomers be achieved, and application of a chiral shift reagents [Eu(hfc)<sub>3</sub>] led to partial racemization during ee determination (er = 91:9). Nevertheless, the specific rotation of **11** ([α] = −133.4) is even higher than reported for putative enantiomerically pure material in the literature ([α] = −55.6).<sup>2c</sup>

Investigations on the scope of this reaction and studies on the mechanism of this reaction are currently ongoing in our laboratories.

**Acknowledgment.** We are deeply indebted to Dr. Wolfgang U. Frey (University of Stuttgart) for the X-ray crystal structure analyses. We thank Prof. Dr. T. Ziegler (University of Tübingen) and Prof. Dr. W. Kloppe (University of Karlsruhe) for helpful discussions.

**Supporting Information Available:** Experimental procedures, spectroscopic data and spectra of all new compounds, and details of the X-ray analyses in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL051670I

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