

## Photosensitized Cleavage of the Dithio Protecting Group by Visible Light

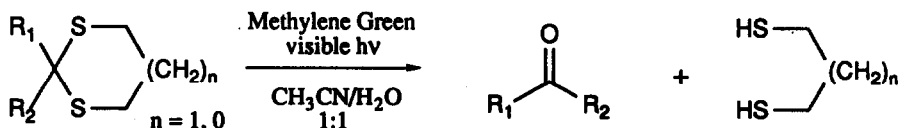
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**Abstract:** Dithio derivatives of aldehydes and ketones have been deprotected under neutral conditions using visible light provided by a 120 Watt spotlight and methylene green as a sensitizer. The key step in the deprotection is apparently an electron transfer from the dithio derivative to the electronically excited visible dye. The resulting dithio radical cation undergoes fragmentation, and the corresponding aldehydes and ketones are isolated in excellent yields.

Dithio acetals and ketals are useful protecting groups which are widely used in organic synthesis.<sup>1</sup> However, their deprotection is sometimes difficult, and there is a continuing need for new methods which proceed under mild conditions. Chemical deprotection most often involves the use of toxic heavy metals such as Hg<sup>+2</sup>, Ag<sup>+</sup>, or Tl<sup>+3</sup>); alternatives have been suggested—cleavage by photolysis<sup>2,3</sup> or electrolysis.<sup>4-7</sup> These alternatives suffer from the necessity of expensive equipment, are only appropriate for small-scale reactions, and routinely provide only modest yields. Photochemically induced electron transfer reaction of the dithio group using triphenylpyrylium salts has been recently explored,<sup>8,9</sup> but Kamata reported this cleavage to proceed only in the presence of oxygen. Dye-sensitized irradiations under oxygen would be expected to lead to singlet oxygen formation. Subsequent singlet oxygen reactions would likely lead to extensive byproduct formation with complex substrates. Indeed, dye-sensitized oxidation of dithiolanes to dithiolane oxides *via* singlet oxygen has been reported by Pandey<sup>10</sup> to proceed in “synthetically useful yields.” 1,4- and 1,5-Dithia compounds have been similarly reported to mainly undergo photooxidation with other dyes.<sup>11,12</sup> Accordingly, we have worked for the development of a method which could proceed efficiently with *visible* light in an *inert* atmosphere. We report that acetonitrile–water solutions of dithio derivatives *are* efficiently hydrolyzed under nitrogen when an ordinary tungsten spotlight is used as the light source and methylene green used as the photocatalyst. Our simple experimental procedure can be readily scaled up to multigram quantities; 3 to 15 g quantities of dithio compounds have been utilized in the examples reported in this communication.



We routinely obtained isolated yields of purified aldehydes or ketones (Table 1) in excess of 90% yield. Our usual procedure involved irradiating a solution of 3.0 g (ca 15 mmol) of dithio compound, 182 mg (0.50 mmol) methylene green, and 1.1 g (5.0 mmol) magnesium perchlorate in a 500 mL round-bottomed flask equipped with a reflux condenser. The solution was purged with nitrogen throughout the reaction (ca. 3–4 hr),

which was induced by irradiation with a GE Miser 120 W spotlight. Products were isolated by chloroform extraction and flash chromatography. Our starting dithianes and dithiolanes were prepared by minor modifications of published methods.<sup>13,14</sup> The identity and purity of the isolated products of photocleavage were confirmed by high field NMR and GC/MS.

Table 1. Isolated Yields of Deprotected Dithio Aldehydes and Ketones

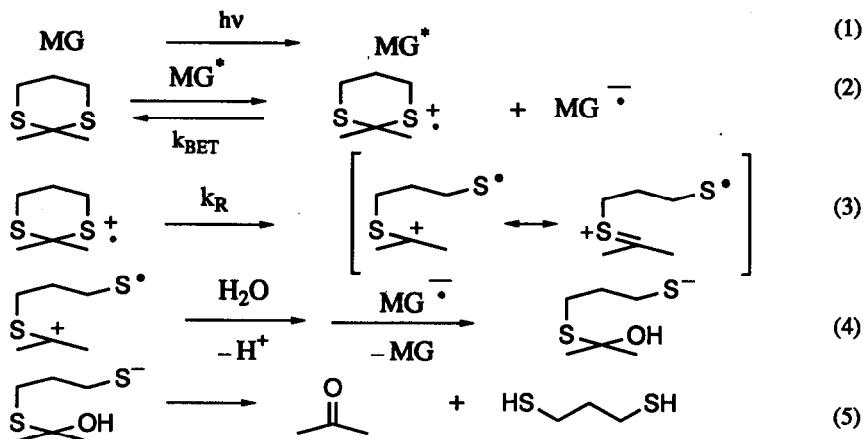
Compound #	Starting Material	Product	Isolated Yield, %
1			91
2			95
3			94
4			90
5			91
6			90

We believe the mechanism of deprotection involves the major steps shown in Scheme 1. Several experimental observations support such a pathway:

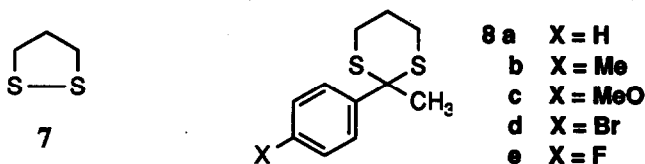
- (1) Irradiation of a dithiane under the same conditions except *without* methylene green ("MG") led to *no* detectable reaction of the dithiane.
- (2) Stirring the dithiane under the same conditions (with MG present) but *in the dark* led to no detectable reaction of the dithiane.
- (3) The role of the MG is catalytic. Reaction of a 30 to 100-fold molar excess of the dithiane occurred without any observable reaction of the MG.
- (4) The formation of the carbonyl product is accompanied by the formation of either 1,2-ethanedithiol or 1,3-propanedithiol (from dithiolanes or dithianes, respectively).
- (5) The deprotection reaction proceeded faster in the presence of inorganic salts, e.g. Mg(ClO<sub>4</sub>).
- (6) The cleavage of dithiolanes (5-membered ring) was faster than that of a dithiane (6-membered ring). For example, cleavage of dithiolane 1 proceeded twice as fast as that of the corresponding dithiane.

(7) Substituents on the carbon bearing the dithio group affect the cleavage rate in a manner consistent with formation of a partial positive charge on the carbon in the rate-determining step.

Scheme 1.



Step 2 and 3 of Scheme 1 are similar to the pathway proposed by Steckhan to explain the electrocatalytic cleavage of dithianes.<sup>6</sup> Other elements differ in our attempt to explain other experimental observations. First, the role of the MG is catalytic, being temporarily reduced in step 2 to the radical anion, but regenerated by back electron transfer to the ring opened intermediate (step 4). Any mechanistic scheme must explain the overall *hydrolytic* nature of the cleavage; neither catalyst nor any part of the dithiane is oxidized or reduced. This feature distinguishes our route from the previously reported photooxidative path<sup>8</sup> or the electrochemical<sup>5</sup> cleavage, as these methods lead to the formation of the oxidized disulfide, 7. The faster reaction of dithiolanes may be from the more favorable cleavage of a 5-membered ring than a 6- (step 3). The formation of the hemithioacetal is plausible since the intermediate can be hydrolyzed readily by acid or base catalysis to the



carbonyl products.<sup>15,16</sup> The effect of salts is illustrated in Figure 1, and is probably due to enhanced efficiency of formation of charge separated ions from an initial exciplex between MG and dithiane. The effect of varying substituents on the aromatic ring is consistent with the formation of an intermediate bearing a partial positive charge on the benzylic carbon. Applying a linear free energy treatment to the initial rate of product formation (Figure 2) led to a slope corresponding to a  $\rho$  value of  $-0.59$ . This treatment is mechanistically defensible if several assumptions regarding the mechanism are valid. First, the light intensity and MG concentration are held constant, so the rate of formation of  $MG^*$  is constant. Substituents have only a minor effect on the oxidation potential of dithianes.<sup>17</sup> Thus, the rate of exciplex formation and separated ions will be virtually identical at the same substrate concentrations for this exothermic reaction. (The overall rate becomes diffusion controlled once electron transfer is exothermic by a few kilocalories.<sup>18</sup>) The overall *quantum efficiency* of the transformation (which directly affects the measured rate of formation of product under these "constant" conditions) will be affected by the ratio between  $k_R$  and the sum of  $k_R$  and  $k_{BET}$ . Essentially, ring cleavage must compete with back electron transfer, and the rate of ring cleavage will depend upon stabilization of the

developing positive charge in step 3. The small value of  $\rho$  suggests that ring cleavage does not completely occur before nucleophile attack (step 4) begins, and the bracketed intermediate of step 3 may not be formed as a discrete intermediate. We believe that steps 3 and 4 do not actually occur as discretely, but have shown this possibility to emphasize electron transfer introduces weakness to the carbon-sulfur bond. Scheme 1 does not use oxygen or singlet oxygen because our transformation occurs in an inert atmosphere. The reaction also proceeded under oxygen, but the yields were lower and photooxidized products were then detected.

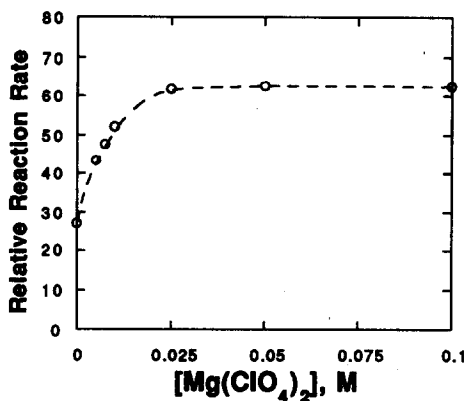


Figure 1. Effect of Salt Concentration on Rate of Product Formation from Compound 8b

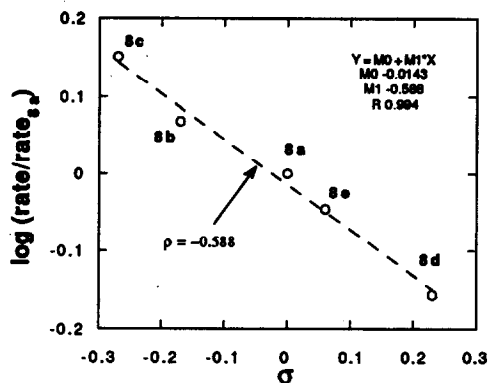


Figure 2. Effect of Substituents on Rate of Product Formation from Compound 8

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