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Mild and Efficient Photochemical and Thermal Deprotection of Thioacetals and Ketals Using DDQ

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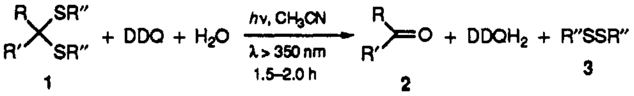
Thioacetals and ketals are often used as carbonyl protecting groups, as well as masked acyl anions in organic synthesis.[1] Hence, the deprotection of thioacetals and ketals to regenerate the carbonyl compound is an important synthetic transformation. Thioacetals and ketals are resistant to conventional acid-catalyzed hydrolytic cleavage. Among the various available methods for deprotection, the transition metal-induced hydrolysis, as well as oxidative and alkylative procedures are widely used.[1,2] Deprotection under neutral conditions is effected by reagents such as DMSO/I_2[3] or DMSO/*tert*-butyl chloride,[4] or simply heating in DMSO.[5] In view of the importance of thioacetals and ketals in organic synthesis, the search for newer and milder reagents to effect the deprotection is worthwhile. There is currently no photochemical method available for the deprotection of thioacetals and ketals. Our interest in the photochemistry of charge-transfer (CT) complexes led to the investigation of thioacetals and ketals as donors and quinones as acceptors.

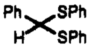
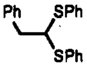
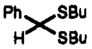
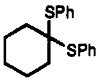
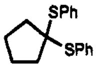
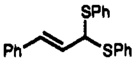
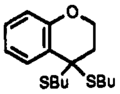
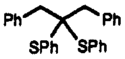
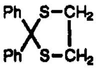
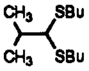
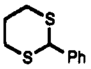
2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) has been used for the deprotection of the methoxybenzyl protecting group for alcohols,[6] acetals and ketals,[7] and silyl ethers.[8] DDQ is a well-known electron acceptor and forms CT complexes with a variety of donors.[9]

The addition of thioacetals and thioketals (1) (Table I) to a solution of DDQ in CH_3CN led to a dark red coloration due to the formation of the CT complexes.[10] The mixtures, when protected from room light, were stable, and no thermal reaction was observed over 12 h, in sharp contrast to the behavior of acetals and ketals which undergo hydrolysis within minutes at ambient temperature under these conditions.[7] Photolysis of the mixtures above 350 nm (both DDQ and the CT complexes absorb this wavelength of light) led to very clean deprotection according to the stoichiometry in Table I, and the carbonyl compounds were isolated in nearly quantitative yields. The course of the reaction is easily followed by the bleaching of the initial dark red color of the solution to pale yellow.

Table I[a]



$$R_2C(SR'')_2 + DDQ + H_2O \xrightarrow[\lambda > 350\text{ nm},\ 1.5\text{–}2.0\text{ h}]{h\nu,\ CH_3CN} RR'C{=}O + DDQH_2 + R''SSR''$$

compd no.	starting material	yield of 2 (%)	compd no.	starting material	yield of 2 (%)
1a		98 (90)	**1g**		95
1b		98 (95)	**1h**		98 (90)
1c		93	**1i**		98
1d		90	**1j**		90
1e		98	**1k**		93
1f		96	**1l**		90

[a] Numbers in parentheses indicate percentage yield of **2** in the thermal reaction.

The method is applicable to acyclic and cyclic thioacetals and thioketals of aromatic, heterocyclic, and aliphatic systems. Although the mixture of thioacetal and DDQ was stable at ambient temperature in the dark, we examined the thermal stability in the case of **1a**, **1b**, and **1h** in refluxing CH_3CN in the presence of DDQ. In the case of **1a**, after refluxing for 2 h, 40% hydrolysis to benzaldehyde was observed and complete hydrolysis was observed after 5 h. Similarly, in the case of **1b** and **1h** complete hydrolysis to **2b** and **2h**, respectively, was observed after 5 h.

In conclusion, we have found very mild and efficient photochemical and thermal methods for the deprotection of thioacetals and ketals using DDQ. Further studies on the role of water and other nucleophiles in the reaction and the use of other quinones are in progress.

Experimental Section

The thioacetals and thioketals **1a–l** were prepared from the corresponding carbonyl compound and the thiol using anhyd $AlCl_3$ or $BF_3{\cdot}Et_2O$ following reported procedures.[11,12] The compounds were purified by column chromatography on silica gel (60–120 mesh) and characterized by physical and spectroscopic (IR, ^{1}H-NMR, and MS) data. DDQ (Fluka) was used as received. Reagent grade CH_3CN was distilled.

Representative Procedure for Deprotection by the Photochemical Method. A mixture of thioacetal **1a** (0.20 g, 0.65 mmol) and DDQ (0.150 g, 0.66 mmol) in CH_3CN (20 mL) was photolyzed in a Pyrex tube that was immersed in a water bath

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(1) Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075, 1077. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 639. Grobel, B.-T.; Seebach, D. *Synthesis*, **1977**, 357.

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(10) In the case of **1a** and DDQ the λ_{max} (CT) = 550 nm.

(11) Ong, B. S. *Tetrahedron Lett.* **1980**, *21*, 4225.

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(20–25 °C) in a Dewar flask with quartz windows. A focused beam from a 200-W mercury arc lamp passing through a blue filter (cutoff wavelength $\lambda < 350$ nm) was used to photolyze the sample. During the photolysis the initial dark red color of the solution faded to give a pale yellow photolysate after 2 h. After removal of the solvent, CCl_4 was added to the reaction mixture upon which a pale yellow solid separated which was identified as 2,3-dichloro-5,6-dicyanohydroquinone ($DDQH_2$) by comparison with an authentic sample. After the removal of CCl_4 from the filtrate, the crude product was chromatographed on silica gel. Elution with hexane yielded diphenyl disulfide (85%) followed by benzaldehyde (98%). The products were characterized by comparison of TLC and spectral data with authentic samples.[13]

Representative Procedure for the Thermal Deprotection. A mixture of thioketal **1b** (0.20 g, 0.52 mmol) and DDQ (0.12 g, 0.53 mmol) in CH_3CN (20 mL) was refluxed for 5 h, after which the products were isolated as described in the photochemical method.

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(12) Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945.

(13) The cyclic disulfide **3k** could not be isolated. The disulfide **3l** was isolated by sublimation of the crude product and identified by mp and MS.