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Photoreduction of aliphatic and aromatic thioketals: new access to the reduction of carbonyl groups by a desulfurization chain process

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ABSTRACT

Aromatic and aliphatic ketones can be converted to methylene groups by desulfurization of the corresponding dithioketals in moderate to good yields. The reaction proceeds by photoinduced electron transfer from *tert*-BuOK in the presence of 1,4-dicyclohexadiene as hydrogen atom donor. The diene is able to trigger and keep a chain process by hydrogen transfer–proton transfer reactions.

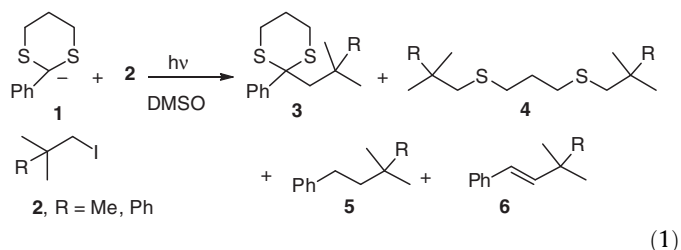
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Introduction

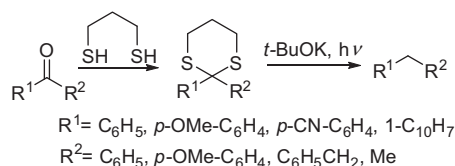
Carbonyl reduction is a very well described and useful reaction in organic chemistry.¹ A carbonyl group can be reduced to the alcohol, or the oxygen atom can be removed altogether in a process called deoxygenation. The methodologies most commonly applied to reduce a ketone carbonyl group to a methylene include Clemmensen and Wolff–Kishner reductions,² the former being more extensively employed (zinc amalgam and concentrated HCl). However, the substrate must be stable in the strongly acidic conditions. Acid sensitive substrates should be reduced by the latter methodology, which requires treatment of aldehyde and ketone hydrazones with strong base (NH₂–NH₂/KOH, 200 °C). A further, milder method is the Mozingo reduction.² In this reaction a thioketal is first produced by the reaction of the ketone with an appropriate thiol. The product is then hydrogenolyzed to the alkane, using Raney Nickel.

Recently we have reported a comprehensive study of the reactions of 2-aryl-1,3-dithiane anion (**1**) with neopentyl and neophyl iodides (**2**), under a variety of conditions in DMSO at 20 °C. The substitution proceeds by a S_{RN}1 mechanism with radicals and radical anions as intermediates. This mechanism was suggested mainly from observation of the products from the C–S bond fragmentation of the radical anion of the substitution product (products **5** and **6** in (Eq. 1)).³

These results encouraged us to develop a novel photoinduced reductive process for an aromatic and aliphatic ketone to methylene transformation by desulfurization of the corresponding dithioketals. This protocol represents an environmentally friendly alternative that avoids the use of transition metals and toxic/explosive reagents such as mercury, hydrazine, and molecular hydrogen.



In this Letter, the reduction of a family of 1,3-dithianes and 1,3-dithiolanes in the presence of *tert*-BuOK/1,4-cyclohexadiene under photostimulation is reported (Scheme 1). The synthetic outcome as well as a detailed mechanistic exploration is discussed on the basis of quantitative photochemical measurements.



Scheme 1.

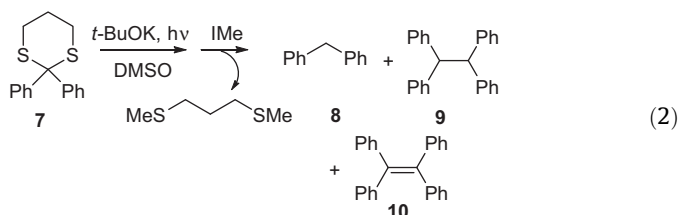
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Results and discussion

Photoinduced reductive process of dithioketals

We began exploring the photoinduced ET reduction of dithiane derivatives as an alternative for the de-oxygenation of carbonyl groups. 2,2-Diphenyl-1,3-dithiane (**7**) was selected as a model compound for optimization of the reductive conditions.⁴ Although different electron donors, such as cyclohexanone enolate anion, 2-naphthoxide ion, *tert*-BuOK, DABCO, *N,N*-dimethylaniline, and *N,N,N',N'*-tetramethyl-benzene-1,4-diamine were evaluated in DMSO under a nitrogen atmosphere and irradiation at $\lambda_{\max} > 350$ nm, only *tert*-BuOK was effective. Thus, the photoinduced reduction of **7** with 3 equiv of this base gave diphenylmethane (**8**) in 72% yield together with 1,1,2,2-tetraphenylethane (**9**) and 1,1,2,2-tetraphenylethane (**10**) in 17% and 11% yields, respectively (Table 1, entry 1) (Eq. 2).



When this reductive process was performed in the presence of 3 equiv of a good hydrogen atom donor such as 1,4-cyclohexadiene, the yield of **8** increased up to 92% and only 8% of **9** was obtained (Table 1, entry 2). The yield of diphenylmethane drops to 37% in the presence of a good electron acceptor such as *p*-DNB (Table 1, entry 3). The dark reaction gave 52% yield of reduction, and this reaction was also inhibited by *p*-DNB (Table 1, entries 4 and 5). The acceleration by light together with the inhibition in the presence of a strong electron acceptor (*p*-DNB) suggests a photoinduced electron-transfer reaction between the dithiane and the base. In order to gain more information on the intermediates, the reaction was quenched by IMe after 2 h irradiation. The product analysis reveals the presence of 3-(methylthio)propyl diphenylmethyl sulfide (**11**)⁵ (Eq. 3), which at a longer irradiation time is further reduced to diphenylmethane (Table 1, entry 6).

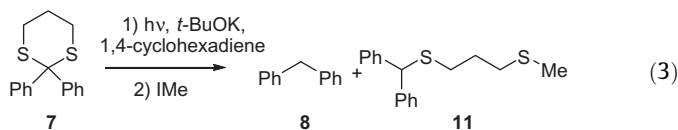


Table 1
Photoinduced reduction of 2,2-diphenyl-1,3-dithiane (**7**) with *tert*-BuOK in DMSO^a

Entry	Conditions	Product yields (%)		
		8	9	10
1 ^b	hv/	72	17	11
2 ^c	hv/1,4-cyclohexadiene	92	8	—
3 ^{c,d}	hv/1,4-cyclohexadiene/ <i>p</i> -DNB	37	—	—
4 ^e	Dark/1,4-cyclohexadiene	52	—	—
5 ^{c,d}	Dark/1,4-cyclohexadiene/ <i>p</i> -DNB	35	—	—
6 ^{c,e}	hv/1,4-cyclohexadiene/IMe	24 ^f	—	—

^a Irradiation at $\lambda_{\max} > 350$ nm for 3 h under nitrogen atmosphere, at room temperature; [**7**] = 0.1 M; *tert*-BuOK = 0.3 M. Reaction quenched with IMe. Product yield determined by CG using the internal method, error <5%.

^b This reaction was quenched with NH_4NO_3 .

^c 1,4-Cyclohexadiene = 0.3 M.

^d *p*-DNB = 0.3 M.

^e Irradiated for 2 h.

^f Together with 30% yield of 3-(methylthio)propyl diphenylmethyl sulfide (**11**) (Eq. 3).

This reaction proceeded with the formation of a CTC between **7** and *tert*-BuOK prior to the ET, as confirmed by UV-vis absorption spectroscopy. Neither dithiane **7** nor *tert*-BuOK shows absorption to red at 350 nm. However, when increasing the amount of the base relative to **7**, a new absorption band at a maximum of 467 nm is observed (Fig. 1). Therefore, this new absorption band can be ascribed to an interaction between **7** and the *tert*-BuOK, that is, the formation of a CTC between both species.⁶

In the absence of 1,4-cyclohexadiene, upon photoinduced electron transfer (PET), the radical anion of dithiane **7** is formed, fragmentation of the C-S bond yields distonic radical anion **12** that gives intermediate **13** after hydrogen abstraction (Eqs. (4)–(7)). The mediation of **13** was confirmed by the presence of its methylated derivative **11** found at a shorter irradiation time (Eq. 3) and Scheme 2). Further reduction of **13** generates diphenylmethane (**8**) and methylated 1,3-propyldisulfide when quenched by methyl iodide (Scheme 2).



1,4-Cyclohexadiene improves the selectivity of the reaction by decreasing the yield of dimer **9**; it also seems to accelerate the overall process. Thus, we gain greater reactivity and more selectivity by the addition of this particular hydrogen donor. After hydrogen donation, a cyclohexadienyl radical is formed; we wondered whether this intermediate could trigger a chain reaction since it is well accepted, the key step in the hydrogen atom substitution reactions (HAS) is the addition of an aryl radical to an arene to afford cyclohexadienyl-type radicals. In basic media, re-aromatization of these intermediates can occur by deprotonation to render the radical anion of the substitution product, which is a strong

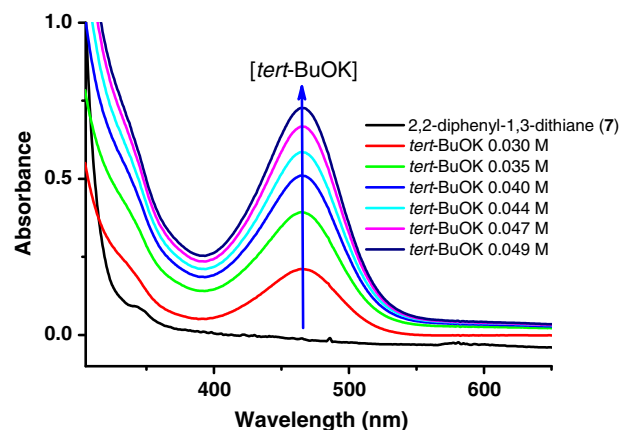
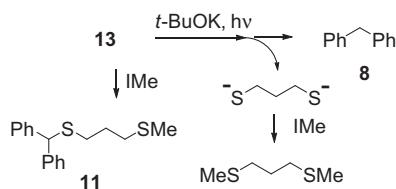
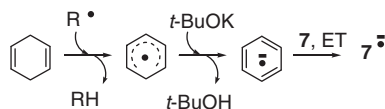


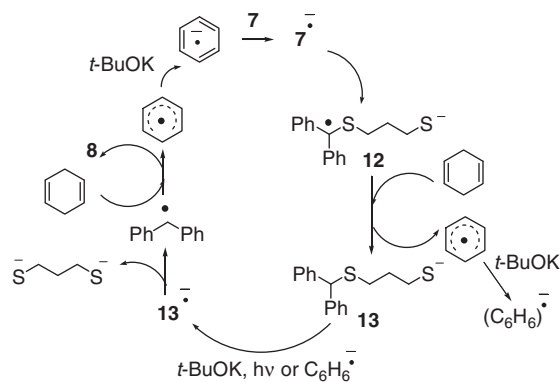
Figure 1. UV-vis spectra of 2,2-diphenyl-1,3-dithiane (**7**) 1.2×10^{-4} M and CTC formation with increasing concentrations of *tert*-BuOK.



Scheme 2.



Scheme 3.



Scheme 4.

reducing agent, and transfers its odd electron to the substrate.⁷ For this reason, the role of the hydrogen donor as a chain reaction initiator was further explored.

To measure efficiency and chain length in a photochemical reaction, it is necessary to know the quantum yield for product formation (Φ_p), and also information on the quantum yield for the initiation step (Φ_i). Thus, it is possible to obtain a good approximation of the propagation efficiency (i.e., chain length, c.l.) from the ratio of the overall quantum yield and the quantum yield of the initiation step (c.l. = Φ_p/Φ_i).⁸ By using our model compound **7**, quantitative information was measured by chemical actinometry.⁹ In the absence of hydrogen donor and at the concentration indicated in Table 1, the quantum yield for the reduction of **7** by *tert*-BuOK is 0.007. The addition of 3 equiv of 1,4-cyclohexadiene enhanced the quantum yield up to 0.03. This result indicates that the reaction is faster when 1,4-cyclohexadiene is present. The acceleration in the photoreduction of **7** can be explained considering that 1,4-cyclohexadiene not only donates a hydrogen atom but also triggers a chain reaction by deprotonation of cyclohexadienyl radical by *tert*-BuOK to render a benzene radical anion, which transfers its odd electron to the dithiane **7**, propagating a chain (Scheme 3). Moreover, if we consider the quantum yield of the reaction in the absence of hydrogen donor as the initiation quantum yield, an approximate value of four can be obtained for the chain length when the diene is added.

Once the dithiane radical anion is formed (Eqs. 4 and 5), it follows the proposed mechanism (Scheme 4). A chain reaction is included to account for the increase in photonic efficiency in the presence of 1,4-cyclohexadiene as hydrogen donor.

The observed reactivity of the system *tert*-BuOK/1,4-cyclohexadiene toward 2,2-diphenyl-1,3-dithiane encouraged us to further explore the potential of this procedure. Quite a few examples of the use of commercially available ketones are included. The selection of ketones was based on the inclusion of electron-donating and electron-withdrawing groups and the use of aliphatic ketones. Dithioketals were synthesized according to reported procedure. Thus, using these optimized reaction conditions, we evaluated the scope of this methodology for the reduction of several dithioketals (Table 2).

This procedure is compatible with both electron-donor and electron-acceptor groups on aromatic dithianes. As expected good yields are obtained for the CN derivative;¹⁰ however, for the dithiane bearing OMe substituents, the yield of the reduction product was moderate requiring a higher temperature (Table 2, entries 1–3). This is particularly relevant since desulfurization of dithianes by Raney nickel or Na in liquid ammonia is not possible for ketones bearing a CN group. Dithiane **16** is stable at 350 nm and its reduction was efficient at 300 nm affording a good yield of the hydrocar-

Table 2

Photochemical reduction of dithianes and dithiolanes with *tert*-BuOK in DMSO.^a

Entry	Dithiane	Product yield (%)
1		Ph-Ph 92 ^b
2		MeO-C ₆ H ₄ -CH ₂ -C ₆ H ₄ -OMe 7
3 ^c		34
4		NC-C ₆ H ₄ -CH ₂ -Ph 83
5 ^d		Ph-CH ₂ -C(CH ₃) ₃ 77 ^e
6		54
7 ^f		40
8 ^f		44

^a Irradiation at $\lambda_{max} > 350$ nm for 3 h under nitrogen atmosphere, at room temperature; [dithiane] = 0.1 M; *tert*-BuOK = 0.3 M; 1,4-cyclohexadiene = 0.3 M. Reaction quenched with NH_4NO_3 . Product yield determined by CG using the internal method, error <5%.

^b Together with **9** in 8% yield.

^c In DMF at 70 °C with 4 equiv *tert*-BuOK (*tert*-BuOK = 0.4 M).

^d Irradiation at $\lambda_{max} = 300$ nm.

^e Together with alkene **6** in 23% yield.

^f In DMF at 70 °C with 8 equiv *tert*-BuOK (*tert*-BuOK = 0.8 M) for 6 h.

bon **5** with a low amount of **6**. Finally, this methodology can also be extended to aliphatic ketones (Table 2, entries 7 and 8). For this purpose, benzene-1,2-dithiol was employed as a protecting group and chromophore in dithianes **18**¹¹ and **19**;¹² longer irradiation time and 8 equiv of *tert*-BuOK were required to obtain moderate yields (40–44%).

In conclusion, we have developed photoinduced reductive methodology to convert the carbonyl group in aromatic and ali-

phatic ketones to CH₂ groups by desulfurization of the corresponding dithioketals. This protocol is an environmentally friendly alternative to the current reduction methodologies.

Acknowledgments

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Supplementary data

NMR and ¹³C NMR of compounds **11**, **15**, **18** and **19** COSY 45 and HSQC or HMBC spectra to support the assignments.

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.12.118>.

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- Representative experimental procedure for the reduction process*: these reactions were carried out in a 10 mL three-necked Schlenk tube, equipped with a nitrogen gas inlet and a magnetic stirrer. The tube was dried under vacuum, filled with nitrogen and then with dried DMSO (10 mL). *tert*-BuOK (336.7 mg, 3.0 mmol), dithiane **7** (272.0 mg, 1.0 mmol) and 1,4-cyclohexadiene (284 μL, 3.0 mmol) were added to the degassed solvent under nitrogen. After irradiation as indicated in Table 1, the reaction was quenched by the addition of excess ammonium nitrate and 10 mL of water, and the mixture was extracted with methylene chloride (3 × 20 mL). The organic extract was washed twice with water and dried over anhydrous MgSO₄, and the products were quantified by GC using the internal standard method, or isolated by radial chromatography from the crude product reaction mixture.
- 3-(Methylthio)propyl diphenylmethyl sulfide (**11**) liquid. ¹H NMR: δ = 1.78–1.85 (q, 2H); 2.04 (s, 3H); 2.47–2.55 (m, 4H); 5.15 (s, 1H); 7.20–7.24 (m, 2H); 7.28–7.32 (m, 4H); 7.41–7.43 (m, 4H). ¹³C NMR: δ = 15.5; 31.2; 33.1; 54.2; 127.2; 128.3; 128.6; 141.4 ppm. MS (EI⁺), *m/z* (relative intensity), 167 (62); 165 (50); 152 (25); 121 (100); 73(28). HRMS (MNa⁺), calcd for C₁₇H₂₀NaS₂ 311.0899, found 311.0793.
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- 4-(2-Benzyl-1,3-dithian-2-yl) benzonitrile (**15**). Solid mp: 98.3–98.5 °C ¹H NMR: δ = 1.94–1.97 (m, 2H); 2.52–2.60 (m, 2H); 2.64–2.70 (m, 2H); 3.25 (s, 2H); 6.70–6.71 (d, *J* = 7 Hz, 2H); 7.09–7.20 (m, 3H); 7.58–7.60 (d, *J* = 8.7 Hz, 2H); 7.84–7.86 (d, *J* = 8.7 Hz, 2H). ¹³C NMR: δ = 24.7; 27.5; 51.3; 59.2; 110.9; 118.8; 127.3; 127.6; 130.4; 130.8; 132.1; 133.5; 146.7 ppm. MS (EI⁺), *m/z* (relative intensity), 220 (100); 204 (8); 190 (5); 146 (54); 91 (14). HRMS (MH⁺), calcd for C₁₈H₁₈NS₂ 312.0881, found 312.0885.
- 2,2-(2-Adamantyl)benzo[d][1,3]dithiole (**18**). Solid mp: 103.0–103.1 °C. ¹H NMR: δ = 1.75–1.78 (m, 6H); 1.88 (m, 2H); 2.19–2.22 (m, 4H); 2.48 (m, 2H); 6.96–6.98 (dd, *J*_{ortho} = 6, *J*_{meta} = 3, 2H); 7.15–7.17 (dd, *J*_{ortho} = 6, *J*_{meta} = 3, 2H) ppm. ¹³C NMR: δ = 26.6; 35.3; 37.6; 39.8; 122.1; 125.0; 138.1 ppm. MS (EI⁺), *m/z* (relative intensity), 274 (M⁺, 64); 231 (8); 179 (11); 153 (100); 91 (12); 77 (11). HRMS (M⁺), calcd for C₁₆H₁₈S₂ 274.0850, found 274.0861.
- 2-Adamantyl-2-methylbenzo[d][1,3]dithiole (**19**). Solid mp: 122.9–123 °C. ¹H NMR: δ = 1.62–1.71 (m, 6H); 1.84–1.85 (m, 6H); 1.91 (s, 3H); 2.06 (m, 3H); 6.95–6.97 (dd, *J*_{ortho} = 6, *J*_{meta} = 3, 2H); 7.13–7.15 (dd, *J*_{ortho} = 6, *J*_{meta} = 3, 2H) ppm. ¹³C NMR: δ = 26.9; 28.7; 36.6; 38.6; 40.7; 80.02; 122.1; 124.9; 137.9 ppm. MS (EI⁺), *m/z* (relative intensity), 302 (M⁺, 6); 268 (7); 209 (9); 167 (100); 134 (10). HRMS (MH⁺), calcd for C₁₈H₂₃S₂ 303.1236, found 303.1195.