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

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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, 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 thio ketal 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_{SRN1} 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.
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. 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 \( \lambda_{\text{max}} >350\) 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-tetraphenylethene (9) and 1,1,2,2-tetraphenylethenyl (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 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 with IMe after 2 h irradiation. The product analysis reveals the presence of 3-(methylthio)propyl diphenylmethyl sulfide (11) (Eq. 3), which at a longer irradiation time is further reduced to diphenylmethane (Table 1, entry 6).

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.

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 with methyl iodide (Scheme 2).

![Figure 1.](http://example.com/figure1.png)

**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.

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>1b</td>
<td>hv</td>
<td>72</td>
</tr>
<tr>
<td>2c</td>
<td>hv/1,4-cyclohexadiene</td>
<td>92</td>
</tr>
<tr>
<td>3d</td>
<td>hv/1,4-cyclohexadiene/p-DNB</td>
<td>37</td>
</tr>
<tr>
<td>4c</td>
<td>Dark/1,4-cyclohexadiene</td>
<td>52</td>
</tr>
<tr>
<td>5d</td>
<td>Dark/1,4-cyclohexadiene/p-DNB</td>
<td>35</td>
</tr>
<tr>
<td>6e</td>
<td>hv/1,4-cyclohexadiene/IMe</td>
<td>24*</td>
</tr>
</tbody>
</table>

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

b This reaction was quenched with NH₄NO₃.
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 diphenylmethane sulfide (11) (Eq. 3).

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reducing agent, and transfers its odd electron to the substrate. 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 (\(\Phi_p\)), and also information on the quantum yield for the initiation step (\(\Phi_i\)). 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. = \(\Phi_i/\Phi_p\)). By using our model compound 7, quantitative information was measured by chemical actinometry. 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; 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 hydrocarbon 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 and 19; 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 aliphatic ketones to hydrocarbons with good efficiency and chain length.
phatic ketones to CH₂ groups by desulfurization of the corresponding dithioketals. This protocol is an environmentally friendly alternative to the current reduction methodologies.

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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.

References and notes

4. 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).
5. 3-(Methylthio)propl diphenylmethyl sulfide (11) liquid. 1H NMR: δ = 1.78–1.85 (q, 2H); 2.04 (s, 3H); 2.47–2.53 (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; 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.
10. 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); 2.90–2.98 (d, J = 8.7 Hz, 2H); 7.31–7.32 (m, 2H); 7.38–7.40 (d, J = 8.7 Hz, 2H); 7.44–7.49 (m, 2H); 7.51–7.54 (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; 118.3; 127.3; 127.6; 130.8; 131.2; 133.5; 146.7 ppm. MS (EI+), m/z (relative intensity), 220 (100); 204 (8); 190 (5); 146 (54); 91 (14). HRMS (M+H+), calcd for C18H18NS2 312.0881, found 312.0885.
11. 2,2-(2-Adamantyl)benzo[d][1,3]dithiole (11). 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, Jorto = 6, Jmeta = 3, 2H); 7.15–7.17 (dd, Jmeta = 6, Jorto = 3, 2H); 7.24 (s, 2H); 7.30–7.34 (m, 2H); 7.39–7.41 (m, 2H); 7.41–7.43 (m, 2H); 7.44–7.48 (m, 2H); 7.56–7.60 (d, J = 8.7 Hz, 2H). 13C NMR: δ = 17.1; 26.8; 35.3; 37.6 ppm. MS (EI+), m/z (relative intensity), 274 (M+, 64); 231 (8); 179 (11); 153 (100); 91 (12); 77 (11). HRMS (M+), calcd for C19H18S2 314.0860, found 314.0856.
12. 2-Adamantyl-2-methylbenzyl(d)[1,3]dithiole (19). Solid mp: 122.9–123.3 °C 1H NMR: δ = 1.62–1.71 (m, 6H); 1.74–1.85 (m, 4H); 1.91 (s, 3H); 2.06 (m, 3H); 6.95–6.97 (dd, Jorto = 6, Jmeta = 3, 2H); 7.13–7.15 (dd, Jmeta = 6, Jorto = 3, 2H) ppm. 13C NMR: δ = 26.9; 28.7; 36.6; 38.6; 40.7; 40.8; 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 (M+H+), calcd for C24H22S2 330.1236, found 330.1195.