Cleavage of 1,3-Dithianes via Acid-Catalyzed Hydrolysis of the Corresponding 1,3-Dithianemonooxides

Karsten Krohn,* Stephan Cludius-Brandt

Department Chemie, Universität Paderborn, Warburger Str. 100, 33098 Paderborn, Germany
Fax +49(5251)603245; E-mail: k.krohn@uni-paderborn.de

Received 30 January 2008; revised 23 April 2008

Abstract: The hydrolysis of 1,3-dithianes to their parent carbonyl compounds via their corresponding monosulfoxides was systematically investigated. The oxidation of the 1,3-dithianes was carried out in high yields using tert-butyl hydroperoxide. Acid-catalyzed hydrolysis of the monosulfoxides to the carbonyl compounds was then performed in excellent yields. The cleavage reactions were monitored by gas chromatography and kinetics were investigated on substrates varying in electron density and steric requirements. Neither effect prevented high overall yields in the cleavage reaction.

Key words: 1,3-dithianes, dithioacetals, 1,3-dithiane-1-oxides, cleavage, dethioacetalization

Dithioacetals are important protecting groups for carbonyl compounds due to their ease of formation and their stability under acidic and basic conditions.1 In addition, their well known umpolung reactivity makes them extremely useful reagents.2 Unfortunately, the regeneration of the carbonyl groups often leads to unexpected difficulties. In spite of the large number of deprotection methods,3 many of these procedures have considerable drawbacks such as the use of toxic reagents, long reaction times, harsh reaction conditions, expensive catalysts, or the occurrence of undesired side reactions. Therefore, there is still a need for generally applicable and mild methods for the cleavage of dithioacetals to their parent carbonyls.

In 1961, Kuhn et al. reported that the monosulfoxides of 1,3-dithianes undergo easy cleavage to the carbonyl compounds in acidic methanol.4 Later, Krohn and Behnke modified this method by transformation of photochemically generated 1,3-dithiane-1-oxides into the corresponding dimethyl acetals, which were subsequently cleaved to the carbonyl compound.5 However, neither of these very convenient methods found many applications and were not included in the latest review article on deprotecting methods for 1,3-dithianes.6a Therefore, we initiated a systematic investigation with a selected number of 1,3-dithianes varying in steric demand and electronic properties in order to probe the scope and limitations of the Kuhn dithiane cleavage methodology.

The straightforward hydrolysis of 1,3-dithianes 1, via their oxidation to the monosulfoxides 2 and subsequent cleavage to their parent carbonyl compounds 3 in acetonitrile, is shown in Scheme 1. In the first series of experiments, a number of 1,3-dithianes 1a–g were synthesized using known methods by reaction of the corresponding carbonyl compounds with 1,3-propanedithiol.5,6 As substrates, we selected aromatic, olefinic and aliphatic aldehydes and ketones 3a–g. Table 1 summarizes the synthesized dithianes and sulfoxides.

The subsequent oxidation to the corresponding monosulfoxides 2a–g was carried out using tert-butyl hydroperoxide (TBHP) in dichloromethane and catalytic amounts of camphorsulfonic acid (CSA).8 The yields in this transformation were nearly quantitative and the formation of undesired side products was not observed.

The acidic hydrolysis reactions (see Table 2) were performed in acetonitrile (1 mmol substrate in 10 mL acetonitrile to which 0.5 mL of 6 N HCl was added) and conducted overnight for reasons of convenience and in order for the reactions to reach completion. Alternatively,
complete conversion could also be observed by heating at 30 °C for 12 hours. The conversions were quantitative by TLC comparison and no side products were formed except the expected 1-(hydroxythio)-3-mercaptopropane (see Scheme 2). The isolated yields were in the range of 91–95%; some losses in the workup procedure occurred in the case of the volatile benzaldehyde 3a and ketone 3f. The polar 1-(hydroxythio)-3-mercaptopropane or the polymeric ethylenedisulfide were easily separated by filtration over a short silica gel column (see Experimental).

**Table 2** Acidic Cleavage of 1,3-Dithiane-1-oxides in Acetonitrile

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>38</td>
<td>3a</td>
<td>83</td>
</tr>
<tr>
<td>2b</td>
<td>12</td>
<td>3b</td>
<td>94</td>
</tr>
<tr>
<td>2e</td>
<td>12</td>
<td>3e</td>
<td>91</td>
</tr>
<tr>
<td>2d</td>
<td>12</td>
<td>3d</td>
<td>95</td>
</tr>
<tr>
<td>2e</td>
<td>12</td>
<td>3e</td>
<td>95</td>
</tr>
<tr>
<td>2f</td>
<td>12</td>
<td>3f</td>
<td>86</td>
</tr>
<tr>
<td>2g</td>
<td>8 min</td>
<td>3g</td>
<td>93</td>
</tr>
</tbody>
</table>

Scheme 2 shows the assumed mechanism for the cleavage reaction in acidic acetonitrile. In the first step, the addition of a proton to the oxygen atom of the sulfoxide leads to the formation of a sulfonium ion. Subsequent ring-cleavage gives an open-chain sulfur-stabilized carbenium ion, which is then transformed into the corresponding carbonyl compound by nucleophilic attack by water.

In order to gain insight into the kinetics of the cleavage reaction, the formation of the desired product was monitored by gas chromatography and the rate constants were determined. A typical graph obtained by monitoring the reactions by gas chromatography is shown in Figure 1. At the beginning, the concentration increases more or less exponentially and, after a short time, asymptotically when approaching the termination of the cleavage reaction. The formation of by-products was not observed in the GC. The very polar 1-(hydroxythio)-3-mercaptopropane was easily separated by filtration over a short silica gel column.

In summary, we have shown for a representative number of examples that the two-step Kuhn cleavage of 1,3-dithianes via the corresponding monosulfoxides is a straightforward and high-yielding process. The method does not seem to be restricted by electronic or steric effects and can be considered as an economic and environmentally friendly alternative to existing methods.

In order to gain insight into the kinetics of the cleavage reaction, the formation of the desired product was monitored by gas chromatography and the rate constants were determined. A typical graph obtained by monitoring the reactions by gas chromatography is shown in Figure 1. At the beginning, the concentration increases more or less exponentially and, after a short time, asymptotically when approaching the termination of the cleavage reaction. The formation of by-products was not observed in the GC. The very polar 1-(hydroxythio)-3-mercaptopropane was easily separated by filtration over a short silica gel column.

Table 3 shows the calculated rate constants for a range of substrates. For the kinetic investigation, the substrates were selected according to steric and electronic parameters. Thus, the steric effects on the reaction rate should be evaluated by comparison of compounds 2h and 2i in Table 2, whereas electronic effects are exemplified by compounds 2g and 2j. The results from the calculated rate constants showed that increased steric hindrance did not decrease the reaction rate. By contrast, the rate was even larger in a sterically more hindered substrate (compounds 2h and 2i). This is in accord with the putative reaction mechanism (Scheme 2) in which more stabilized carbenium ions should enhance the reaction rate. The destabilization of the carbenium ions by introduction of electron-withdrawing groups (compound 2j), causing a small decrease in the reaction rate as seen by comparison of compounds 2g and 2j, is in agreement with this assumption.

In summary, we have shown for a representative number of examples that the two-step Kuhn cleavage of 1,3-dithianes via the corresponding monosulfoxides is a straightforward and high-yielding process.

The method does not seem to be restricted by electronic or steric effects and can be considered as an economic and environmentally friendly alternative to existing methods.
However, the substrates have to be stable to the TBHP oxidation and the mild acidic cleavage conditions.

Column chromatography was performed on silica gel 60 (particle size 0.040–0.063 mm). Melting points were measured on a Büchi SMP-20 melting point apparatus using one-side-open capillary tubes, and are uncorrected. NMR spectra were recorded at r.t. on a Bruker ARX 200 or ARX 500 instrument. Chemical shift values (δ) are given in ppm relative to TMS. IR spectra were measured on a Nicolet 510 FT-IR Spectrometer. GC analyses were carried out on a Hewlett-Packard 5890 Series II instrument. Solvents were purified if necessary by standard methods.

**Oxidation of 1,3-Dithianes to 1,3-Dithiane-1-oxides; General Procedure**

A stirred solution of dithiane I (1 mmol) in CH₂Cl₂ (5 mL) was treated with a tert-butyl hydroperoxide (TBHP) solution in CH₂Cl₂ (1 mL, 2 mmol) and a catalytic amount of CSA (0.1 mmol). The reaction mixture was stirred at r.t. and monitored by TLC until complete (8–12 h). The mixture was then poured directly onto a short silica gel column (10 g) and eluted with CH₂Cl₂ (50 mL) to afford the pure sulfoxide from the nonpolar fraction after evaporation of the solvent.

**Table 3** Cleavage Reactions Monitored by Gas Chromatography

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time (min)</th>
<th>Rate constant (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>38 h</td>
<td>1.6 × 10⁻³</td>
</tr>
<tr>
<td>2h</td>
<td>12</td>
<td>0.07</td>
</tr>
<tr>
<td>2i</td>
<td>40 h</td>
<td>9.5 × 10⁻⁴</td>
</tr>
<tr>
<td>2g</td>
<td>8</td>
<td>0.25</td>
</tr>
<tr>
<td>2j</td>
<td>15</td>
<td>0.2</td>
</tr>
</tbody>
</table>

2,2-Bis(4-chlorophenyl)-1,3-dithiane (1j)

Yield: 98%; mp 97 °C.

IR (KBr): 2892, 1436, 1396, 1272, 1087, 794, 788 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 2.02–2.13 (m, 2 H), 2.77–2.83 (m, 4 H), 3.00–3.09 (m, 4 H), 6.70–6.76 (m, 4 H).

13C NMR (50 MHz, CDCl₃): δ = 24.9, 29.8, 63.5, 129.0, 131.1, 134.1, 141.2.

MS (EI): m/z (%) = 341 (58) [M]+, 265 (100), 230 (60), 199 (70), 154 (68), 110 (10), 75 (8), 44 (10).

HRMS: m/z calcd for C₂₂H₁₅S₂Cl₃: 341.3434; found: 340.9978.

2-Phenyl-1,3-dithiane-1-oxide (2a)

Yield: 76%; mp 138 °C (Lit.⁹ 137 °C).

2-Phenyl-1,3-dithiane-1-oxide (2b)

Yield: 70%; mp 152 °C.

2-Phenyl-1,3-dithiane-1-oxide (2c)

Yield: 75%; mp 88 °C.

2-(Naphthalene-6-yl)-1,3-dithiane-1-oxide (2d)

Yield: 79%; mp 144 °C.

2,2-Diphenylethylene-1,3-dithiane-1-oxide (2e)

Yield: 80%; mp 203 °C (Lit.⁴ 203 °C).

2,2-Diphenylethylene-1,3-dithiane-1-oxide (2f)

Yield: 90%; mp 119 °C.

IR (KBr): 2917, 2856, 1442, 1228, 1145, 1097, 1033, 941, 860, 738

Yield: 66%; mp 76 °C.

1,5-Dithiaspiro[5,5]undecane-1-oxide (2i)

IR (KBr): 2915, 1654, 1490, 1400, 1268, 1093, 1035, 991, 902, 759, 681 cm⁻¹.

Yield: 80%; mp 171 °C.

2,2-Bis(4-chlorophenyl)-1,3-dithiane-1-oxide (2j)

HRMS: m/z calcd for C₁₆H₁₄S₂Cl₂O: 357.3428; found: 356.9905.

2,2-Diphenyl-1,3-dithiane-1-oxide (2g)

HRMS: m/z calcd for C₁₅H₂₀S₂O: 280.0955.

-%Butyl-2-methyl-1,3-dithiane-1-oxide (2h)

Prior to measuring the reaction samples, the GC was calibrated by measuring a dilution series of the respective carbonyl compounds (3: 0.05 mg/mL, 0.07 mg/mL, 1 mg/mL, 3 mg/mL). For sample measurements, a volume of 1 μL was injected; each sample was measured three times.

Acknowledgment
We thank Dr Heinz Weber for professional help with the GC analysis and Mariola Zukowski for the MS measurements. Furthermore we thank Prof van Ree for checking the manuscript.

References