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Synthesis of the first α-mercaptoketal and an antifungal ketodisulfide

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An improved synthesis of phenacyl methyl disulfide is described. It led to conditions that efficiently furnish the ketal of phenacyl mercaptan. The ketal of phenacyl mercaptan appears to be the first known α-mercapto ketal. Phenacyl mercaptan is smoothly prepared from its ketal under standard conditions.

Keywords: antifungal disulfides; α-mercapto ketone; α-mercapto ketal

1. Introduction

A recent review (*1*) provides an overview of our ongoing efforts to produce new, biologically-active disulfides. The construction and testing of α-sulfone disulfides has been prominently featured in our earlier reports (*2–4*). As work progressed, the possibility arose that α-keto disulfides might also have interesting/useful biological activities. To that end, we have produced the α-keto disulfide **1** (Figure 1) (*5*).

Compound **1** showed some interest as an antileukemic agent (*5*) and as an inhibitor of phagocytosis (*6*).

An obvious retrosynthetic analysis for **1** would go through the α-mercapto ketone **2** (Figure 2).

The α-keto thiolacetate **3** was readily prepared from phenacyl chloride (*5*). Although the α-mercaptoketone **2** can be prepared from the thiolacetate **3** (*7*), our attempts at one-pot deprotection (strong bases)/sulfenylation to obtain the corresponding methyl disulfide **1** were all unsuccessful. Once prepared, **1** served as an effective precursor for **2** (*6*). Our published synthesis of **1** (*5*) is presented in Scheme 1.

The very low yield of diphenacyl disulfide (Scheme 1) was due to the difficulty in purifying it. The next phase of this synthetic work (described herein) applied ketal intermediates in an attempt to avoid problems with thiolacetate deprotection and difficulty in the purification of intermediates.

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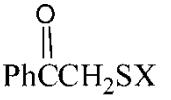
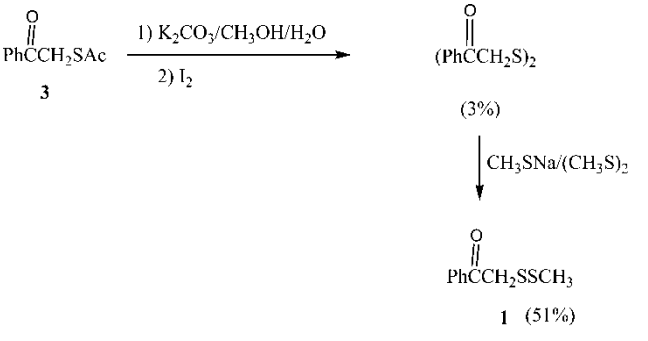
1

Figure 1. Phenacyl methyl disulfide.



2 (X = H)
3 (X = Ac)

Figure 2. Alpha-Thiophenacyl systems.



Scheme 1.

2. Results and discussion

2.1. *Chemistry*

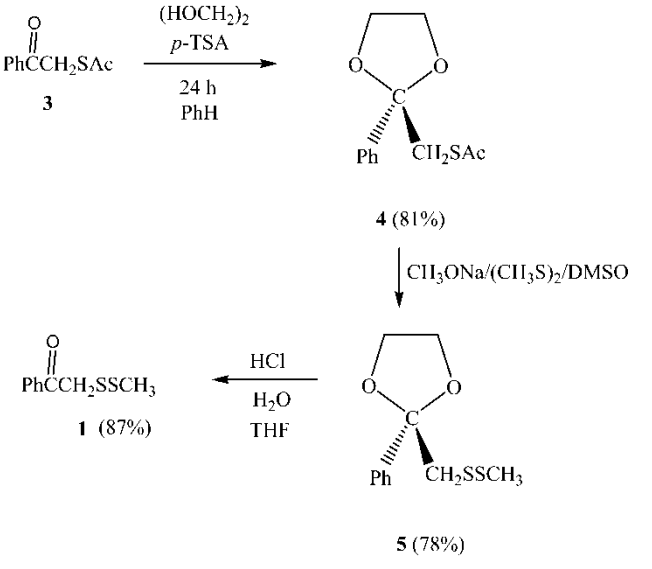
The conversion of the ketone thiolacetate **3** into the corresponding ketal thiolacetate **4** proceeded without complication. The application of our conditions for one-pot conversion of a thiolacetate into the corresponding methyl disulfide (*8*) provided the ketal methyl disulfide **5** from **4**. Deketalization of **5** gave **1** (Scheme 2).

The application of ketal intermediates to the synthesis of **1** (Scheme 2) gave an overall yield of **1** (55%) in contrast to the Scheme 1 preparation of **1** (<2%).

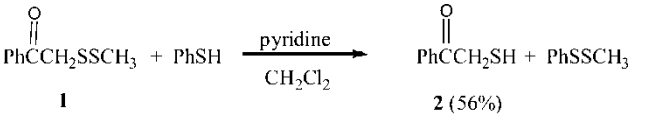
As part of our earlier work on the chemistry of α-sulfone disulfides, we developed conditions that smoothly convert the methyl disulfides into α-mercapto sulfones (*2, 9*). Those same conditions converted **1** into **2** (*6*) (Scheme 3).

However, the ketal disulfide **5** failed to react under Scheme 3 conditions (Scheme 4), establishing that the α-keto group significantly enhances electrophilicity at the remote sulfenyl sulfur of the disulfide linkage (Scheme 4).

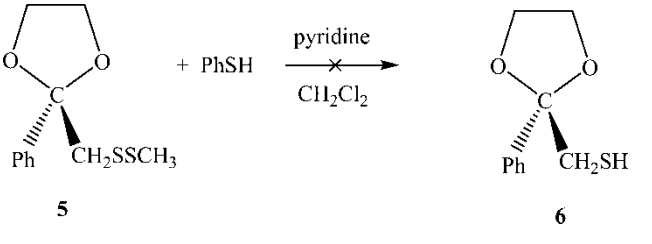
Given the dramatically diminished reactivity of ketals, relative to the corresponding ketones, the preparation of **6** appeared to be a worthwhile goal, since it could materially simplify the preparation of phenones bearing α-sulfenyl sulfur atoms. The failure of the Scheme 4 reaction led



Scheme 2.



Scheme 3.



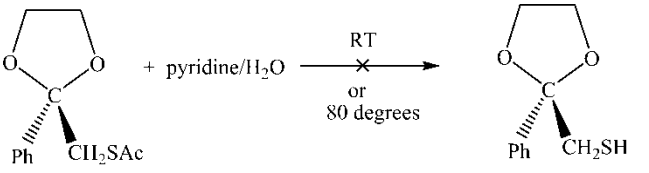
Scheme 4.

us to revisit the possible base-catalyzed deprotection of **4**. Attempts to hydrolyze the thiolacetate in aqueous pyridine, both at ambient temperature and at 80 °C, were unsuccessful (Scheme 5).

In view of our repeated failures to accomplish the controlled deprotection/sulfenylation of **3** and the deprotection of **4** with base/nucleophiles, both strong and weak, we next turned to the possibility that **4** could be deprotected by transesterification using ethylene glycol/benzene with *p*-toluenesulfonic acid catalysis (Scheme 6).

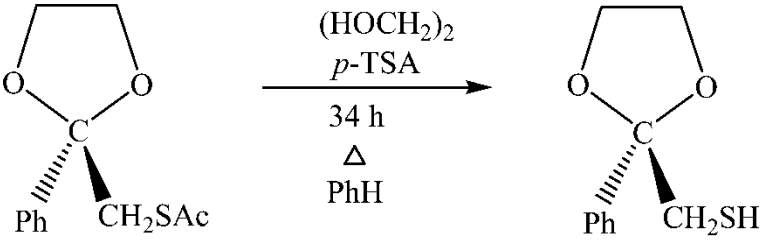
Taken together, the results in Schemes 2 (first step) and 6 open up the possibility that the α-mercapto ketal **6** might be available from a one-pot transformation beginning with the keto thiolacetate **3** (Scheme 7).

Although α-mercapto ketones have been prepared and used, particularly for heterocycle construction (*10–12*), **6** appears to be the first known α-mercapto ketal. Hence, a preliminary exploration of the chemistry of **6** was undertaken. First, the corresponding mercaptide anion was generated and alkylated in a straightforward substitution reaction (Scheme 8).



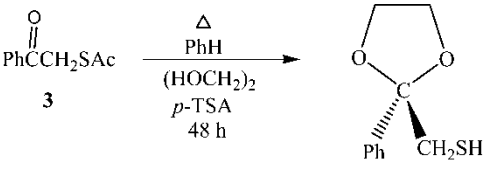
4 **6**

Scheme 5.



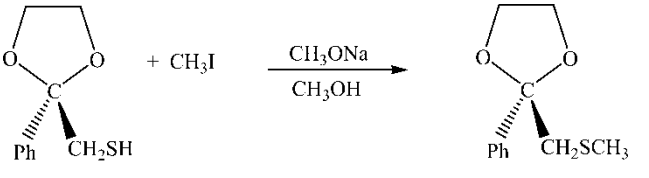
4 **6** (30%)

Scheme 6.



6 (52%)

Scheme 7.



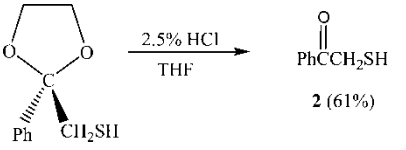
6 **7** (43%)

Scheme 8.

Second, the mercapto ketal **6** was smoothly deketalized under standard reaction conditions (Scheme 9).

2.2. *Biological testing*

In addition to the previously reported examinations of **1** and **2** as possible inhibitors of phagocytosis (*6*), the keto disulfide **1** and the ketal disulfide **5** were subjected to antifungal testing. We have examined a broad array of disulfides by means of screens for fungitoxicity with the result that



6

Scheme 9.

Table 1. Antifungal activities for selected disulfides.

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		Aspergillus niger	*A. flavus*
$PhC(O)CH_2SSCH_3$ **1**	25	10.4	11.4
$PhC(OCH_2CH_2O)CH_2SSCH_3$ **5**	100	0	0
$PhSO_2CH_2SSCH_3$*	25	5.5	4.2

Each compound was introduced onto a small paper disk that was placed in a culture medium. The diameter of the clear zone (the area where fungus – *A. niger* or *A. flavus* – did not grow) around each disk quantified antifungal activity.
*Antifungal test results previously revealed (*2*).

biological test results were nicely rationalized in terms of expected electrophilicity at sulfenyl sulfur (*1*). The solution-phase results given in Schemes 3 and 4 suggest that the keto disulfide **1** should be an effective antifungal agent, whereas the ketal disulfide **5** should not. Table 1 provides the results for antifungal testing of **1** and **5** along with the closest α-sulfone disulfide relative available for comparison.

This is the first time that we have obtained solution-phase results, which permitted us to forecast biological test results.

3. Experimental

3.1. *Synthesis*

3.1.1. *General*

Infrared spectra were recorded on a Thermo Nicolet 2000 spectrophotometer. ^{1}H NMR (270 MHz) and ^{13}C NMR spectra were obtained on a JEOL JNM-GSX270 Fourier-transform NMR system. Unless otherwise specified, all NMR spectra were obtained in deuterated chloroform using tetramethyl silane as an internal standard. Mass spectra were obtained on a Hewlett-Packard 5988A gas–liquid chromatography mass spectrometer system.

3.1.2. *Preparation of phenacyl thiolacetate 3*

The preparation and properties of the keto thiolacetate **3** have been described earlier (*5*).

3.1.3. *Preparation of the phenacyl thiolacetate ketal 4*

The ketone thiolacetate **3** (2.00 g, 10.3 mmol) was dissolved in benzene (60 mL). Ethylene glycol (1.92 g) and *p*-toluenesulfonic acid (0.2 g) were added. A Dean–Stark trap was affixed to the

reaction flask and the reaction mixture refluxed for 24 h. Chloroform (400 mL) was added and the resultant mixture extracted with 1% W/V sodium hydroxide (100 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated. The crude product was distilled affording ketal thiolacetate **4** (2.0 g, 8.4 mmol, 81%, 142–146 °C/1.5 Torr). **4** had IR 1691 cm^{-1}. ^1H NMR (270 MHz) δ 2.32 (s, 3H), 3.47 (s, 2H), 3.81 (m, 2H), 4.07 (m, 2H), 7.35 (m, 3H), 7.50 (d, 2H). ^{13}C NMR δ 30.4, 38.4, 65.5, 108.3, 125.8, 128.2, 128.5, 141.0, 194.6. MS: 149 ($M^{+\cdot}$ −89, 100%), 105 (62%), 77 (28%).

3.1.4. *Preparation of the phenacyl methyl disulfide ketal 5*

Sodium metal (0.19 g, 8.4 mmol) was dissolved in methanol (20 mL) and the solvent evaporated. Dimethyl Sulfoxide (DMSO) (9 mL) was added and the resultant mixture stirred vigorously (mechanical stirrer) and opened to the air, for 5 h. Dimethyl disulfide (18 mL) and the ketal thiolacetate **4** (1.98 g, 8.4 mmol) were added. The flask was stoppered and the reaction mixture stirred at ambient temperature for 76 h. Hydrochloric acid (2.5%, 200 mL) was added and the resultant mixture extracted with diethyl ether (three 200 mL aliquots). The combined organic layers were concentrated and the extraction procedure repeated. The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated. The residue was rectified at reduced pressure affording **5** (1.59 g, b.p. 142–150 °C/1.35 Torr, 77%). A small amount was further purified by column chromatography (1:1 chloroform/petroleum ether), was redistilled, and fully characterized. **5** has no ν_{CO} in the IR. ^1H NMR (270 MHz) δ 2.36 (s, 3H), 3.33 (s, 2H), 3.84 (m, 2H), 4.12 (m, 2H), 7.35 (m, 3H), 7.48 (d, 2H). ^{13}C NMR δ 23.4, 51.6, 65.4, 108.6, 125.9, 128.2, 128.4, 141.3. MS: 149 ($M^{+\cdot}$ −93, 100%), 105 (60%), 77 (20%).

3.1.5. *Preparation of phenacyl methyl disulfide 1*

The ketal disulfide **5** (1.01 g, 4.2 mmol) was dissolved in Tetrahydrofuran (THF) (50 mL). Hydrochloric acid (2.5%, 19 mL) was added and the reaction mixture stirred at ambient temperature for 24 h. Chloroform (250 mL) was added and the resultant mixture washed with 2.5% W/V sodium hydroxide (100 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated. The residue was rectified at reduced pressure affording clean phenacyl methyl disulfide (0.72 g, 3.6 mmol, b.p. 140–142 °C/1.5 Torr, 87%). The distilled keto disulfide **1** was identical to a previously described material (*5*).

3.1.6. *Conversion of ketal thiolacetate 4 into* **α***-mercapto ketal 6*

p-Toluenesulfonic acid (0.2 g) was dissolved in benzene (40 mL). Ethylene glycol (1.9 g) and the ketal thiolacetate **4** (0.96 g, 4.04 mmol) were added. A Dean–Stark trap was affixed to the reaction flask and the reaction mixture refluxed for 34 h. Chloroform (200 mL) was added and the resultant mixture washed with water (three 100 mL aliquots). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The crude product was chromatographed on silica gel (100 g) employing 2:1 chloroform/petroleum ether (100 mL fractions) for elution. Fractions 4 and 5 were combined and concentrated furnishing colorless, crystalline α-mercapto ketal **6** (0.241 g, 1.23 mmol, 30%). Fractions 7–10 were concentrated and combined giving unchanged **4** (0.429 g). Chromatographed α-mercapto ketal **6** was recrystallized from methanol (m.p. 33–35 °C). $C_{10}H_{12}O_2S$ requires C, 61.2; H, 6.2. Found: C, 61.3, H, 5.9. **6** had IR 2360 cm^{-1}. ^1H NMR (270 MHz) δ 1.54 (t, $J = 8.6$ Hz, 1H), 2.95 (d, $J = 8.6$ Hz, 2H), 3.86 (m, 2H), 4.12 (m, 2H), 7.35 (m, 3H), 7.49 (d, 2H). ^{13}C NMR δ 34.6, 65.5, 108.7, 125.8, 128.2, 128.3, 141.2. MS(EI): 149 ($M^{+\cdot}$ −47, 100%), 105 (53%), 77 (24%). MS(CI): 197 ($M^{+\cdot}$ +1, 100%).

3.1.7. *Preparation of phenacyl mercaptan ketal 6*

The ketone thiolacetate **3** (4.0 g, 16.8 mmol) was dissolved in benzene (120 mL). Ethylene glycol (10 mL) and *p*-toluenesulfonic acid (1.0 g) were added and the reaction flask fitted with a Dean–Stark trap. The reaction mixture was refluxed for 48 h and benzene (70 mL) distilled off. Chloroform (100 mL) was added and the resultant mixture washed with water (three 50 mL aliquots), dried ($MgSO_4$), filtered, and the solvent evaporated. Chloroform (50 mL) was added and the resultant solution extracted with 0.2% W/V sodium hydroxide (12 25 mL aliquots). The aqueous layers were split into four separate sets (75 mL each) and the original organic layer set aside.

Glacial acetic acid (6 mL) was added to each aqueous base solution. Each acidified aqueous solution was immediately extracted with chloroform (two 100 mL aliquots). Each organic solution (200 mL of chloroform) was washed with saturated sodium bicarbonate (four 50 mL aliquots). The combined organic layers (800 mL) were dried ($MgSO_4$), filtered, and the solvent evaporated to give clean, solid mercapto ketal **6** (1.25 g).

The entire procedure was repeated three additional times. In each case, the original organic layers were dried ($MgSO_4$), filtered, and finally all were combined to give base-washed organic material. From this material, a portion (10 g) was taken for column chromatography. The sample was chromatographed on silica gel (1000 g) employing 1:1 petroleum ether/methylene chloride (100 mL fractions) for elution. Fractions 41–75 were combined and concentrated affording clean mercapto ketal **6** (1.87 g).

Hence, one reaction on **3** (4 g) produced mercapto ketal **6** (1.72 g, 8.7 mmol, 52%). The mercapto ketal **6** was identical to the material described in Section 3.1.6.

3.1.8. *Conversion of mercapto ketal 6 into the ketal sulfide 7*

Sodium metal (16.9 mg, 0.73 mmol) was dissolved in methanol (6 mL), and the mercapto ketal **6** (145 mg, 0.74 mmol) was added. Methyl iodide (106 mg, 0.75 mmol) was added and the reaction mixture stirred at ambient temperature for 18 h. Water (50 mL) was added and the resultant mixture extracted with chloroform (three 50 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent evaportaed affording ketal sulfide **7** (68.2 mg, 0.32 mmol, 43%). The sulfide was characterized after bulb-to-bulb distillation. The IR of **7** showed no ν_{CO}. ^{1}H NMR (270 MHz) δ 2.06 (s, 3H), 2.96 (s, 2H), 3.82 (m, 2H), 4.11 (m. 2H), 7.34 (m, 3H), 7.47 (d, 2H). ^{13}C NMR δ 17.5, 44.5, 65.2, 110.0, 125.9, 128.2, 128.3, 141.6. MS: 149 ($M^{+\cdot}$ −61, 100%), 105 (59%), 77 (21%).

3.1.9. *Conversion of mercapto ketal 6 into mercapto ketone 2*

Mercapto ketal **6** (1.50 g, 7.6 mmol) was dissolved in THF (90 mL). Hydrochloric acid (2.5%, 33 mL) was added and the reaction mixture stirred at ambient temperature for 3 days. Chloroform (600 mL) was added and the resultant mixture washed with water (two 300 mL aliquots). The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated.

The residue was rectified at reduced pressure affording mercapto ketone **2** (0.71 g, 4.6 mmol, 61%), which had the properties described previously (*6*).

3.2. *Biological testing*

Details have been provided earlier (*13*).

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