Facile Desulfurization of Cyclic Thioureas by Hydrogen Peroxide in Acetic Acid

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A simple, mild and synthetically useful method for the desulfurization of cyclic thioureas and related compounds, existing as thiol–thione tautomeric mixtures, by hydrogen peroxide in acetic acid is proposed. The effect of substituting different solvents for the acetic acid was investigated.

In a recent alternative synthesis of the carcinogenic 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline,[1] we prepared 3-methyl-3H-imidazo[4,5-f]quinoline-2-sulfonic acid (1a) by alkaline hydrogen peroxide treatment of 1,3-dihydro-3-methylimidazo[4,5-f]quinoline-2-thione (2a).[2] However, the use of hydrogen peroxide in acetic acid as solvent resulted in desulfurization of 2a to the imidazole 3a (Scheme 1).
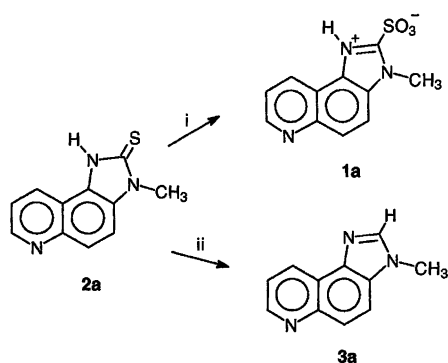
Scheme 1. (i) 30% aq. H_2O_2 in aq. 1 M KOH, 25 °C, 1 min. (ii) 30% aq. H_2O_2 in AcOH, 25 °C, 1 min.

Desulfurization of sulfur-containing compounds, including thioureas, has been achieved by use of a number of different reagents, Raney nickel being the most often employed.[3] Other methods involve the use of nickel–sodium hydride complexes[4] and other transition-metal compounds,[5] alkali bromates and iodates,[6] nitric acid,[7] potassium superoxide,[8] oxygen and potassium *tert*-butoxide,[9] ozone,[10] 3,3-dimethyldioxirane,[11] and photochemical reactions involving singlet oxygen.[12,13]

As early as in 1896, 1,2,4-triazole was obtained on treatment of the corresponding 3-thione with hydrogen peroxide.[14] However, a literature search revealed no systematic study on the desulfurization of cyclic thioureas by hydrogen peroxide. A few isolated papers deal with the hypochlorite or hydrogen peroxide mediated oxidations of 2-imidazolidinethione, a toxic breakdown product of fungicides, or its analogues.[15–17] Alkaline hydrogen peroxide has been used for the oxidation of pyrimidine-2-thiones to the corresponding sulfinic acids. Subsequent reflux of the isolated sulfinic acids with sulfuric acid afforded the desulfinated pyrimidines.[18] Alkaline hydrogen peroxide and sodium peroxide have also been used for the conversion of thioureas into ureas: $(R_2N)_2C = S \rightarrow (R_2N)_2C = O$.[19]

Apparently, the preparative value of the readily available and inexpensive hydrogen peroxide has not been considered as a convenient desulfurization agent for cyclic thioureas. This paper describes the desulfurization of cyclic thioureas and some related compounds by hydrogen peroxide in acetic acid.

Results and discussion

Seventeen compounds (2a–2p and 6q) were tested, first on a micro scale (20 μmol) in an NMR tube. This was done in order to reveal any by-products or intermediates and to obtain a general view of the reaction course. Then, all compounds were tested on a preparative scale (1 mmol) in order to determine isolated yields and thus evaluate the synthetic utility of the method (Table 1).

Thioureas 2a–2c were all desulfurized in good yield to form 3a–3c within one minute. To investigate whether the methyl group in 2a had any influence on the desulfurization, compounds 2d–2f were also tested and appeared to be desulfurized with the same ease, forming 3d–3f. The

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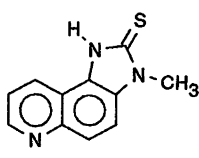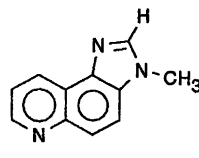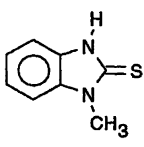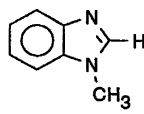*Table 1.* Desulfurization with 30% hydrogen peroxide in acetic acid at 25 °C.
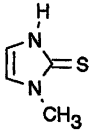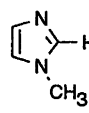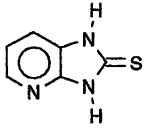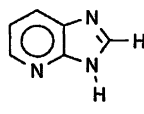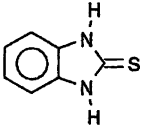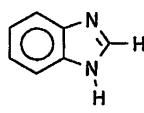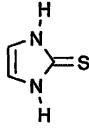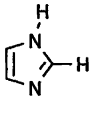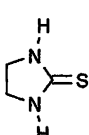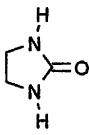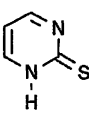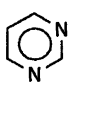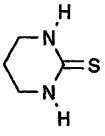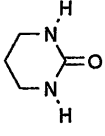
Substrate		Reaction time	Isolated yield (%)	Product		Purification method
2a		1 min	92	**3a**		A
2b		1 min	90	**3b**		A
2c		1 min	85	**3c**		B
2d		1 min	87	**3d**		A
2e		1 min	93	**3e**		A
2f		1 min	90	**3f**		B
2g		1 min	73	**4g**		F
2h		5 min	85	**3h**		C
2i		5 min	64	**4i**		G

Table 1. (Continued).

2j		5 min	35	4j		F
2k	PhHN⌇NHPh	5 min	—		> 10 products	D
2l		5 min	35	3l		H
2m		5 min	20	3m		C
2n		5 days	—		No reaction	D
2o		4 days	75	5o		E
2p	COOH	20 min	66	4p	COOH	A
6q	COOH	5 days	—		No reaction	D

related benzothiazole- and benzoxazole-thiones **2l** and **2m** gave only 35% and 20% desulfurization, respectively. In addition to **3l** and **3m**, compound **2l** gave the corresponding disulfide (**5l**, 43%), and **2m** gave 2-benzoxazolone and 2-aminophenol as by-products (5–10%). 2(1*H*)-Pyrimidinethione (**2h**) was desulfurized to afford **3h** in good yield within 5 min, but the pyridine analogue **2o** gave the disulfide **5o** while the acid **2p** gave the corresponding hydrolysis product **4p**. 2-Mercaptobenzoic acid (**6q**, with negligible content of the thione tautomer **2q**) failed to react. 2-Thiobarbituric acid (**2j**) was converted into barbituric acid (**4j**). The saturated thioureas **2g** and **2i** afforded the ureas **4g** and **4i** as the main products. Hydrogen peroxide treatment of the acyclic thiocarbanilide (**2k**) in acetic acid led to extensive decomposition even at low temperature (– 15°C); the initially formed amidine probably reacted further. 1,3,4-Thiadiazolidine-2,5-dithione (**2n**) failed to react.

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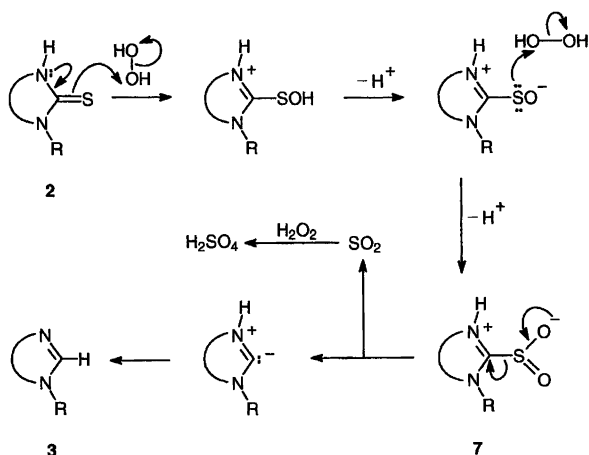
Scheme 2. One possible mechanism for the desulfurization of cyclic thioureas with hydrogen peroxide.

Table 2. Conversion of **2e** into benzimidazole (**3e**) and/or benzimidazole-2-sulfonic acid (**1e**). Conditions: 1 mmol **2e**, 4 mmol 30% H_2O_2 in 5 ml solvent, 25 °C, 1–30 min.

Solvent	Yield of **3e** (%)	Yield of **1e** (%)
Acetic acid	>95	—
Formic acid	78	15
1 M HCl, aq.	67	9
1 M KOH, aq.	—	>95
Dimethyl sulfoxide	95	3
N,N-Dimethylformamide	67	13
25% Ammonia aq.	36	61
95% Ethanol	75	8
Pyridine	>95	—
Tetrahydrofuran	>95	—
0.1 M Phosphate buffer, pH 7.0	82	16

Desulfurization of **2e** by singlet oxygen has led to the formation of the disulfide, benzimidazole and benzimidazol-2-one. The disulfide was suggested to be an intermediate.[12] The singlet oxygen desulfurization of **2e** has also been suggested to go via the sulfinic acid.[13] Also, a sulfinic acid was suggested as intermediate when acyclic thioureas are desulfurized by superoxide.[8] Further, desulfurization of 2-thiouracils and **2h** by ozone or dimethyldioxirane has led to the corresponding ureas and disulfides via a sulfinic acid.[11]

In our experiments, the use of a 3:1 molar ratio of hydrogen peroxide to the starting material was necessary for complete desulfurization. One possible mechanism (Scheme 2) involves first the oxidation of thiourea **2**, which consumes two out of three moles of the peroxide, to a sulfinic acid **7**. Next, sulfur dioxide is expelled and an intermediate ylide is formed. Finally, the desulfurized product **3** is formed by hydrogen migration.[20] The third mole of hydrogen peroxide is consumed when the sulfur dioxide is oxidized to sulfuric acid. The possibility that the thiourea is first oxidized to the sulfonic acid, and that sulfur trioxide is then the leaving group is excluded, because when we treated sulfonic acids such as **1a** with hydrogen peroxide in acetic acid, no reaction occurred. However, this possibility has been discussed for the 1,3-dimethyl derivative of **2g**.[17]

In order to investigate the influence of the solvent, thiourea **2e** was treated with hydrogen peroxide, as described below in the *typical preparative procedure for desulfurization*, but with ten solvents other than acetic acid (Table 2).

The choice of the reaction medium turned out to be critical. In most solvents, the desulfurization product **3e** was formed as the main product with some contamination by the corresponding sulfonic acid. It should be noted that in pyridine, **3e** was formed in >95% yield, whereas in 1 M KOH or 25% aqueous ammonia benzimidazole-2-sulfonic acid (**1e**) was the main product. One possible explanation is that deprotonation in the inter-

mediate sulfinate ion (**7**) prevents the expulsion of sulfur dioxide, since the negative charge left at the carbon would then be less stabilized.

In conclusion, hydrogen peroxide in acetic acid as solvent is proposed for the desulfurization of cyclic thioureas and related heterocycles. The method is inexpensive, mild, and highly efficient.

Experimental

General methods. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian VXR-400 spectrometer at 25 °C. The IR spectra were obtained on a Perkin-Elmer FT-IR 1760 X instrument. The mass spectra were obtained on a JEOL JMS-SX/SX102A instrument with direct insertion, 70 eV electron impact ionization and an ion source temperature of 200 °C. Flash liquid chromatography (FC) was performed on silica gel (230–400 mesh ASTM, Merck). All reactions and purifications were monitored by TLC, with UV detection, on aluminium sheets coated with silica gel 60 F_{254} (Merck). The compositions of the TLC or FC solvent systems refer to volumes. All evaporations were performed under reduced pressure below 40 °C.

Materials. All organic solvents were either freshly distilled or of *p.a.* quality. Petrol refers to petroleum ether boiling at 30–50 °C. Compound **2a** was prepared as described in Ref. 2. Compounds **2b** and **2d** were prepared as **2a** from *o*-methoxynitrobenzene and pyridine-2,3-diamine, respectively. Compounds **3a**,[21] **3b**,[22] and **5l**[23] have been reported in the references indicated. All other compounds are commercial.

NMR study of the reaction. The thiourea **2** (20 µmol) and *p*-dichlorobenzene (2.94 mg, 20 µmol), used as an internal standard, were dissolved in acetic acid-d_4 (0.7 ml) in a 5 mm NMR tube. An initial NMR spectrum was recorded. Then 30% hydrogen peroxide (8.2 µl, 80 µmol) was added. A new NMR spectrum was recorded every

three minutes for the first 15 min and then at increasing intervals.

Typical preparative desulfurization procedure. When possible, the thiourea **2** (1.00 mmol) was dissolved in glacial acetic acid (5 ml). Otherwise, it was sonicated to a homogeneous suspension. 30% Hydrogen peroxide (410 μl, 4.00 mmol) was added to the solution in one portion. When TLC showed complete reaction the products were purified according to Table 1.

Methods of purification. In methods (A–F) the reaction mixture was evaporated to dryness. The residue was suspended in water (10 ml), adjusted to pH 7 with sodium carbonate, evaporated to dryness, and finally purified as below. (A) The solid residue was crystallized from dilute ethanol. When necessary, the mother liquor was evaporated to dryness and the residue crystallized again to increase the yield. (B) The solid residue was extracted with hot ethyl acetate (5 × 10 ml). The extract was evaporated onto silica gel and purified by FC ($CHCl_3$–EtOAc 1:1). (C) As (B) but purification by FC (petrol–EtOAc 10:1). (D) The crude product was analysed by ^1H NMR spectroscopy and TLC to ascertain either that no reaction at all had occurred, or that extensive formation of by-products made the desulfurization useless as a synthetic method. (E) The oily residue was dissolved in 95% ethanol (10 ml). The solution was filtered and diluted with water, until the product precipitated. The precipitate was collected and crystallized from dilute ethanol. (F) As (B) but purification by FC ($CHCl_3$–MeOH 3:1). (G) Half of the reaction mixture was evaporated until the sulfate salt of **4i** started to precipitate. After cooling the salt was collected, crystallized from methanol, and **4i** was liberated by treatment with sodium carbonate. (H) The disulfide **5l** precipitated directly in the reaction mixture. It was collected and crystallized from acetic acid. The filtrate, containing **3l** was purified according to method (C).

The products obtained were characterized spectroscopically (^1H and ^{13}C NMR, MS and FTIR).

Investigation of different solvents (Table 2). The thiourea **2e** (150 mg, 1.00 mmol) and nicotinic acid, used as an internal standard, (123 mg, 1.00 mmol) were dissolved or suspended in 5 ml of the different solvents shown in Table 2. To the solution was added 30% hydrogen peroxide (410 μl, 4.00 mmol). After 1–30 min, or when the reaction was complete according to TLC, the reaction mixture was evaporated to dryness. Where the solvent was water or a high-boiling solvent, such as pyridine or dimethyl sulfoxide, toluene (10 ml) was added and evaporated as an azeotrope with the residual solvent. This was repeated until the solid residue was completely dry and homogeneous. The ^1H NMR spectrum of the residue in dimethyl sulfoxide-d_6 was then recorded. A drop of sulfuric acid-d_2 was added to the NMR tube to ensure the same acidity in all samples. To ensure complete relaxation in all hydrogen nuclei after each pulse, the pulse

width was decreased to 45°, and the repetition time was increased to 13.3 s. To obtain reliable integrals, 25.6 data points per Hz were recorded. The yields of the products **3e** and **1e** were then calculated by comparing the integrals of the 4,7- and 5,6-multiplets in the products with the integral of the 5-multiplet in nicotinic acid. The ^1H NMR yields were accurate to within ± 5% of those given in the Table 2, as found by recording mixtures of known composition.

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