

## SYNTHESIS OF UREA-HYDROGEN PEROXIDE AND ITS APPLICATION FOR PREPARING THIOSULFINATE

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### Abstract

The Urea-Hydrogen Peroxide complex (UHP) was synthesized from urea and hydrogen peroxide, characterized by FT-IR. This UHP complex could be employed as an oxidizing agent for metal-free oxidation reaction of disulfides to thiosulfinate compounds. This protocol was carried out under very mild conditions at 0°C in CH<sub>3</sub>CO<sub>2</sub>H solvent, was efficient and compatible with a range of alkyl, aryl or allyl disulfides to afford direct access to thiosulfinate compounds in very good yields up to 92% and high selectivities.

**Keywords:** Oxidation reaction; disulfide; thiosulfinate; urea hydrogen peroxide.

### 1. Introduction

Thiosulfinate **1** is a functional group consisting of the linkage R-S(O)-S-R (R are organic substituents). Thiolsulfinates are also named as alkanethiosulfinic (or arenethiosulfinic) acid esters. A variety of acyclic and cyclic thiosulfinates are found in plants or formed when the plants are cut or crushed. A well-known thiosulfinate is allicin **2**, R is an allyl group, one of the active ingredients formed when garlic is crushed [1] (Fig. 1).

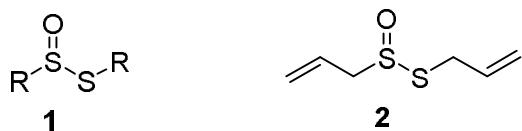


Fig. 1. Structure of thiosulfinate **1** and Allicin **2**

Thiosulfinates show radical-trapping antioxidant activity associated with a simple formation of sulfenic acids [2]. The acyclic thiosulfinates from *Allium* and *Brassica* species possess antimicrobial, antiparasitic, antitumor and cysteine protease inhibitory activity while the natural 1,2-dithiolane-1-oxides are growth inhibitors. The thiosulfinates from *Petiveria* also exhibit antimicrobial activity [3]. Besides, thiosulfinate with two group R of *tert*-butyl is one of the most important intermediate largely used in organic synthesis [4]. This thiosulfinate is stable and can be obtained by catalytic oxidation of di-*tert*-butyl disulfide with many of oxidizing agents such as hydrogen peroxide,

*meta*-chloroperoxybenzoic acid (*m*-CPBA), Oxone... [5]. But there are a lot of drawbacks to this oxidation involving low yield and low selectivity. In recent years, urea-hydrogen peroxide (UHP) is an inexpensive, stable, and easy to handle source of pure urea and 30% aqueous H<sub>2</sub>O<sub>2</sub> solution and UHP is a useful oxidizing agent for many organic reactions such as Baeyer-Villiger oxidations of ketones to lactones [6], oxidation of aromatic aldehydes [7]...

To the best of our knowledge, there have been no reports related to using UHP for synthesis of this di-*tert*-butyl disulfide for synthesis of thiosulfinate, to date. Thus, in this paper, we investigated the preparation of UHP and application as an oxidizing agent for the preparation of di-*tert*-butyl disulfide thiosulfinate, especially, the natural bioactive molecule such as allicin **2**.

## 2. Experimental

All reagents were obtained commercially and used without further purification. All reactions have been carried out under a nitrogen atmosphere and dry conditions. The reaction mixtures have been magnetically stirred with Teflon stirring bars, and the temperatures were measured externally. All the reactions have been monitored by thin-layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were mixtures of *n*-pentane and ethyl acetate (EtOAc), with detection by UV light, or a KMnO<sub>4</sub> staining solution. Across silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. Infrared spectrum has been recorded with Spectrum Two, Perkin Elmer at Le Quy Don Technical University. The nuclear magnetic resonance (NMR) spectra have been recorded with Brucker Avance 500 MHz spectrometers at Vietnam National University. <sup>1</sup>H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using δ (CDCl<sub>3</sub>) = 7.26 ppm as internal reference. <sup>13</sup>C NMR spectra: δ (C) are given in ppm relative to TMS, using δ (CDCl<sub>3</sub>) = 77.0 ppm as an internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), quintuplet (qt), multiplet (m) or br (broad).

**Synthesis of urea-hydrogen peroxide (UHP).** To a 100 ml glass becker containing urea (6.01g, 10.0 mmol) with a magnetic stir bar, was slowly added a solution of H<sub>2</sub>O<sub>2</sub> 30% (10.2 ml, 10.0 mmol) [8]. The reaction mixture was stirred and heated in 15 minutes at 60°C (keep the internal temperature always below 65°C), then cooled to room temperature. The crystal product was collected by filtration, purified by washing with distilled water, and dry to give 6.48 gam UHP (69.01% yield), white crystal; IR v(cm<sup>-1</sup>) 3428, 3348, 1607, 1152.

**General procedure for oxidation of disulfide with UHP.** To a solution of di-*tert*-butylsulfide (10.0 g, 56 mmol, 1 equiv) in 50 ml CH<sub>3</sub>CO<sub>2</sub>H at 0°C was added UHP (8.29 g, 112 mmol, 2 equiv) in small portion over 30 min. The mixture was stirred at 0°C for 12 h.

The resulting mixture was hydrolyzed with cool water (50 ml) and extracted with EtOAc (3 x 30 ml). The organic extracts were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel by using as eluent a 4:1 mixture of *n*-hexane and EtOAc to yield a pure compound as a colorless liquid (10.0 g, 92%).

**(tert-butyl) 2-methylpropane-2-sulfinothioate (4a);** R<sub>f</sub> = 0.66 (hexane/EtOAc: 4/1); <sup>1</sup>H NMR (500 Hz, CDCl<sub>3</sub>) δ (ppm): 1.58 (s, 9H (OS(CH<sub>3</sub>)<sub>3</sub>)), 1.40 (s, 9H, (SC(CH<sub>3</sub>)<sub>3</sub>). <sup>13</sup>C NMR (125 Hz, CDCl<sub>3</sub>) δ (ppm): 59.4, 48.7, 32.2, 24.1.

**Phenyl benzenesulfinothioate (4b).** The general procedure was followed with 1.09 g (5.0 mmol, 1 equiv) of diphenyl disulfide, 5.0 ml CH<sub>3</sub>CO<sub>2</sub>H at 0°C, 740 mg (10 mmol, 2 equiv) of UHP. Chromatography delivered 1.089 g (93%) of **4b**. yellow solid; R<sub>f</sub> = 0.65 (hexane/EtOAc: 4/1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ (ppm) 7.54–7.49 (m, 5H, *aromatic*), 7.34–7.27 (m, 5H, *aromatic*). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ (ppm) 130.5, 130.3, 129.7, 129.4, 129.3, 129.0, 128.7, 125.5.

**Allyl prop-2-ene-1-sulfinothioate (4c).** The general procedure was followed with 731.5 mg (5 mmol, 1 equiv) of diallyl disulfide, 5.0 ml CH<sub>3</sub>CO<sub>2</sub>H at 0°C, 740 mg (10 mmol, 2 equiv) of UHP. Chromatography delivered 722.3 mg (89%) of **4c**; R<sub>f</sub> = 0.63 (hexane/EtOAc: 4/1); oily substance that smells like garlic; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ (ppm) 5.88–5.68 (m, 2H); 5.42–5.14 (m, 4H); 3.75–3.70 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ (ppm) 132.8, 125.7, 124.4, 119.3, 59.8, 35.6.

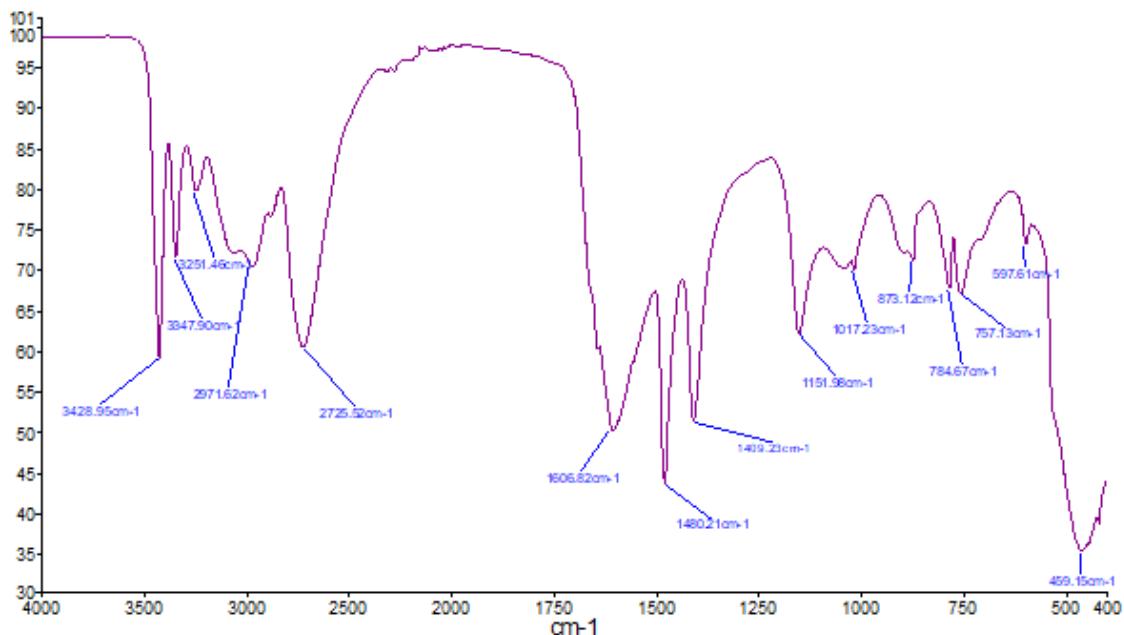
### 3. Results and discussion

Firstly, UHP was synthesized from urea and hydrogen peroxide in the different molar ratios and reaction time (Tab. 1). The result showed that at the 1:1.2 molar ratio of urea/hydrogen peroxide, after 15 min of reaction at 60°C, UHP was obtained at 69.01% yield as a white crystal.

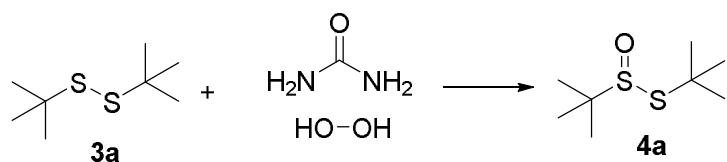
Tab. 1. Effect of molar ratio and reaction time on the UHP yield

Entry	Molar ratio Urea : H <sub>2</sub> O <sub>2</sub>	Reaction time (min)	Yield (%)
1	1:1	5	51.78
		15	55.02
		30	54.03
2	1:1.2	5	58.15
		15	<b>69.01</b>
		30	67.54
3	1:1.5	5	61.20
		15	66.09
		30	64.17

UHP was characterized by IR spectrum shown as Fig. 2 and in agreement with the data in the literature [8]: ( $\text{cm}^{-1}$ )  $\nu_{\text{NH}}$ : 3428.95, 3347.90,  $\nu_{\text{C=O}}$  1606.82,  $\nu_{\text{C-N}}$ : 1151.96. Initial investigation involved developing the oxidation reaction between di-*tert*-butyl disulfide **3a** and UHP at the molar ratio of 1:1 as a model reaction (Scheme 1). Firstly, reaction was carried out in  $\text{CH}_2\text{Cl}_2$  as a solvent. After stirring at 0°C until disappearance of the starting materials (12h, monitoring reaction by TLC) the desired product **4a** was obtained in 50% yield.



*Fig. 2. IR spectrum of urea hydrogen-peroxide*



*Scheme 1. Synthesis of compound 4a*

To optimize this reaction, a series of solvents to screen the oxidation reaction was investigated including  $\text{CH}_2\text{Cl}_2$ , THF,  $\text{C}_6\text{H}_5\text{-CH}_3$ ,  $\text{CH}_3\text{CO}_2\text{H}$ ,  $\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$ ,  $\text{CH}_3\text{OH}$  and  $\text{C}_2\text{H}_5\text{OH}$ . In several cases, the solvent could strongly accelerate or slow down the reaction. The reaction was carried out in polar protic solvents (entry  $\text{CH}_3\text{CO}_2\text{H}$ ,  $\text{CH}_3\text{OH}$  and  $\text{C}_2\text{H}_5\text{OH}$ ) that could give thiosulfinate compounds from moderate to excellent yield up to 86% with  $\text{CH}_3\text{CO}_2\text{H}$  as the best solvent (Tab. 2). On the contrary, the reaction

could afford the desired product in low yield in non-polar aprotic solvent (entry CH<sub>2</sub>Cl<sub>2</sub>, THF, toluene).

*Tab. 2. Effect of different solvents on the oxidation reaction yield*

Solvent	CH <sub>2</sub> Cl <sub>2</sub>	THF	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	CH <sub>3</sub> CO <sub>2</sub> H	CH <sub>3</sub> OH	C <sub>2</sub> H <sub>5</sub> OH
Yield of <b>4a</b>	50%	53%	34%	86%	80%	78%

Besides, the influence of the molar ratio between disulfide **3a** and UHP was also studied. The reaction was carried out at room temperature in CH<sub>3</sub>CO<sub>2</sub>H at 0°C, at the disulfide **3a** : UHP molar ratio of 1:1, 1:2, 1:3 and 1:4 respectively. It was observed that the reagent molar ratio also exhibited a significant effect on the reaction yield. The desired thiosulfinate compound was obtained in the best yield at the molar ratio of 1:2 with excellent selectivity. Using the excess of UHP, the reaction could give the desired product in low yield and low selectivity caused by further oxidation reaction of thiosulfinate to give sulfone compound (Tab. 3).

*Tab. 3. Effect of the disulfide **3a** : UHP molar ratio on the oxidation reaction yield*

Molar ratio	1:1	1:2	1:3	1:4
Yield of <b>4a</b>	86%	92%	78%	75%

It was found that the yield reaction was significantly affected by the reaction time. The oxidation reaction at 0°C proceeded inefficiently, affording only 30% yield after 2h of stirring. As expected, increasing the reaction time led to a dramatic enhancement in the reaction rate. The best yield of 92% was obtained after 12h at 0°C and it seemed that the reaction might complete after stirring 12h at the molar ratio disulfide **3a** : UHP of 1:2 (Tab. 4).

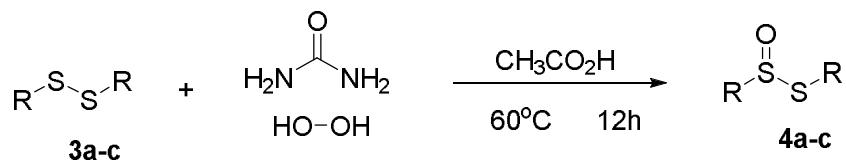
*Tab. 4. Effect of the temperature on the oxidation reaction yield*

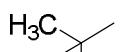
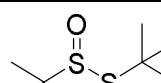
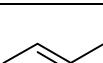
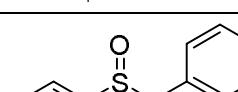
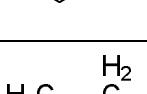
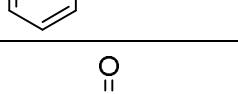
Reaction time	2h	6h	10h	12h	14h	16h
Yield of <b>4a</b>	30%	52%	86%	92%	93%	92%

Finally, the study was then extended to the oxidation reaction of UHP with different disulfide compounds. The reaction carried out for 12h at 0°C in CH<sub>3</sub>CO<sub>2</sub>H, at the disulfide : UHP molar ratio of 1:2. Experimental results showed that the nature of disulfide structure exhibited a significant effect on the reaction yield. The oxidizing agent UHP was compatible with the oxidation reaction of

alkyl, aryl or allyl disulfide to thiosulfinate correspondingly in very good to excellent yield up to 92% (Tab. 5).

*Tab. 5. Synthesis of compound 4*



Entry	Disulfide <b>3</b>		Thiosulfinate <b>4</b>		
	No.	R	No.	Structure	Yield (%)
1	<b>3a</b>		<b>4a</b>		92
2	<b>3b</b>		<b>4b</b>		93
3	<b>3c</b>		<b>4c</b>		89

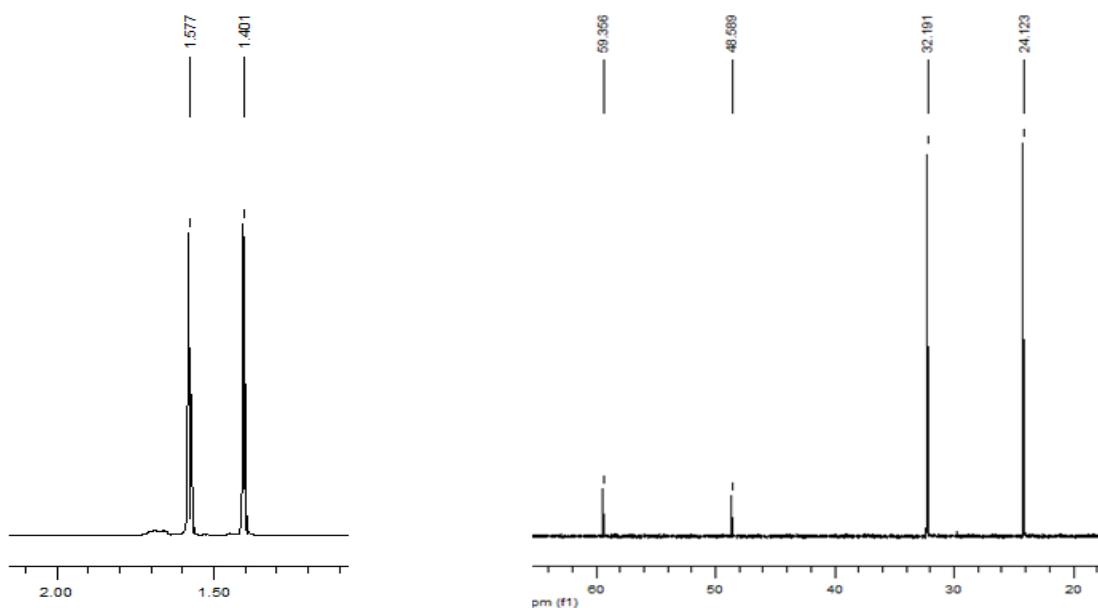


Fig. 3.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectrum of compound **4a**

The  $^1\text{H}$ -NMR spectrum of compound **4a** displayed two single peaks at 1.40 and 1.57 ppm corresponding to 18 protons of  $(\text{CH}_3)_3\text{C-S}$  and  $(\text{CH}_3)_3\text{C-SO}$  groups. Furthermore, in the spectrum of  $^{13}\text{C}$ -NMR, signals are clearly observed for all carbon atoms.

#### **4. Conclusion**

In summary, we have reported a very simple procedure for preparation of UHP and its application for the oxidation reaction. This complex has emerged a useful oxidizing agent for disulfides to thiosulfinates. Using 2 equivalents of UHP, the methodology was efficient and compatible with versatile disulfides as starting materials. We have found that the optimal condition of this reaction is at  $0^\circ\text{C}$ , at the 1:2 molar ratio of disulfide : UHP, in  $\text{CH}_3\text{CO}_2\text{H}$  as a solvent and after 12h magnetic stirring, desired products were obtained from very good to excellent yield up to 92%. It was evident that this pathway could be streamlined to better yield and better stereoselectivity for this reaction in the future.

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## ĐIỀU CHẾ VÀ ÚNG DỤNG URÊ HYDRO PEROXIT CHO PHẢN ÚNG TỔNG HỢP THIOSULFINATE

**Tóm tắt:** Phức chất urê hydro peroxit (UHP) đã được điều chế từ urê và hydro peroxit, đặc trưng bởi FT-IR. Phức chất UHP có thể được sử dụng làm tác nhân ôxi hóa cho phản ứng không kim loại của disulphit để tạo thành các hợp chất thiosulfinate. Điều này được thể hiện bởi các phản ứng xảy ra trong điều kiện nhẹ nhàng ở 0°C trong dung môi  $CH_3CO_2H$ , tương thích và rất hiệu quả với một loạt các dẫn xuất ankyl, aryl hoặc allyl disulphit để tổng hợp trực tiếp các hợp chất thiosulfinate với hiệu suất lên tới 92% và độ chọn lọc cao.

**Từ khóa:** Phản ứng ôxi hóa; disulphit; thiosulfinate; urê hydro peroxit.

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