Simple One-Pot Synthesis of Thioureas From Amine, Carbon Disulfide and Oxidants In Water

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Abstract: The present study reports the new facile methodology for synthesis of symmetrical and asymmetrical thioureas by an one-pot reaction of amine, carbon disulfide and oxidants: hydrogen-peroxide, ethylenediamine tetraacetic acid (EDTA)/sodium percarbonate system or air. The structures of the synthesized compounds were confirmed by FTIR, ^{1}H and ^{13}C NMR and MS methods. Reaction mechanism has been proposed on the basis of reaction intermediate isolation and their structure determination. The synthetic benefits of the presented methods are reflected in the simplicity of procedure, mild reaction conditions, short reaction times, recycling of solvent, high purity and yield of products, absence of dangerous by-products and technological applicability at industrial scale. Considering commercial importance of the thioureas, it can be suggested that the implementation of the optimal synthesis of thiourea, based on presented methods, would provide concurrent alternative to the existing technologies in use, at the industrial level of production.

Keywords: hydrogen peroxide; percarbonate; air; reaction mechanism.

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INTRODUCTION

Thiourea is a compound which contains sulfur and nitrogen atoms which make its properties liable to oxidation by a large number of oxidants, resulting in different products including ureas, sulfur oxides and nitrogen. Such a sulfur-containing compound has a special importance for industrial applications. It has been extensively employed in various fields of science, industry and technology such as rubber industry[1], for agricultural application[2,3], substance which improves ripening of certain fruit species[4], analytical chemistry[5,6], photo catalysis[7], electronic industry, including electronic modulators and electro-acoustic devices[8], electro-optic components[9] and polarization filters[10]. However, thiourea is well known environmental organic pollutant, with carcinogenic consequences[11] and can act as a serious allergenic component[12]. Moreover, thiourea induces hypothyroidism[13], causes the damage to pulmonary endothelial cells and possibly mesothelial lining cells in animal organism[14]. Also, in previous works it was shown that thioureas inhibits nitrification in soil and water[15].

Thiourea is also used in the production of thioureas derivatives[16] and also as additive for plastic materials[17]. In organic chemistry, it is used for preparation of heterocyclic compounds[18]. Depending on the substituents, these heterocyclic compounds possess antihelmintic, antibiotic and immunosuppressant activity[19,20].

When thioureas are oxidized, variuos products are obtained depending on the structure of the starting compound, oxidizing agent and pH[21]. Oxidation using hydrogen peroxide in the presence of ruthenium complex leads to the production of formamide disulphide, thiourea three oxide and sulfate[22]. Recent research indicates that some of 2-aminothiazoline derivatives of thiourea are inhibitors of enzymes such as kinurenine-3-hydroxylase[23], or possess inhibitors activity against enzyme cyclindependent kinase[24]. Certain 2-aminothiazole derivatives of 4-hydroxy-chromen-2-one were obtained and the first step was the synthesis of *N*-alkyl (aryl) and *N,N*-dialkyl thioureas from the ammonium isothiocyanate and an appropriate amine in water at 80 − 90 °C[25]. Also, *N,N*-dialkyl-*N'*-alkyl thioureas may be prepared from dialkylamine and carbon disulfide in the presence of sodium hydroxide[26]. As described in previous works, there are common routes where substituted thioureas synthesis involve reactions of anilines with sodium or ammonium thiocyanate in the presence of strong acids, trifluoroacetic acid (TFA) or

concentrated HCl, aroyl isothiocyanates with amines, followed by basic hydrolysis, silicon tetraisothiocyanate with primary and secondary amines, unsubstituted thioureas with primary alkyl amines at 170–180 °C[27]. In addition, thiourea could be obtained by reaction of isothiocyanates with ammonia or amines[28], primary amines with carbon disulfide, aqueous ammonia and the presence of mercury acetate[29], and disubstituted cyanamides with hydrogen chloride and LiAlHSH[30] or hydrogen sulfide in the presence of ammonia[31]. Recently, a new and efficient reagent 1-benzotriazole-1-carbothioamide was used for the preparation of mono and *N*,*N*-disubstituted thioureas. 1-Benzotriazole-1-carbothioamide was prepared in 84% yield from 1-cyanobenzotriazole in 1,2-dimethoxyethane (DME) saturated with gaseous hydrogen sulfide[32].

A series of *N*-aroyl-*N′*-substituted thiourea derivatives have been prepared in good to excellent yields under the condition of solid-liquid phase transfer catalysis using polyethylene glycol-400 (PEG-400) as the catalyst[33]. Also, *N*-benzoyl-*N*'-carboxyl substituted thiourea derivatives have been synthesized by the reaction of benzoyl isothiocyanate with amino acids. The reaction conditions were experimentally investigated and the preliminary biological tests showed that some of the *N*-aroyl-*N′*-substituted thiourea derivatives had excellent plant growth promotion activities[34], for example, the promoting effects on wheat growth.

Carbamoyl isothiocyanates can be used for the synthesis of 1,3-disubstituted and 1,1,3-trisubstituted thiourea derivatives in the reaction with alkyl or aryl amines. These reagents make the purification trivial, without the later inclusion of a protection step. The carbamate increases the reactivity of the isothiocyanate, permitting formation of thiourea even with hindered amines. A second amine can be coupled to the carbamoyl thiourea using EDC (1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide) forming 1,3-disubstituted and 1,1,3-trisubstituted guanidines through either stepwise, or one-pot synthesis[35]. Several thiourea and urea derivatives were prepared by the reaction of 4-amino-pyrazoles with substituted isothiocyanates or isocyanates in acetone[36]. The new compounds were isolated in satisfactory yields (42-70%). However, reported methods of thiourea syntheses encountered some drawbacks which demand the development of efficient and eco-friendly methods applicable on industrial production level.

Syntheses of symmetrical and asymmetrical thioureas by an one-pot reaction of amine, carbon disulfide and oxidants: hydrogen-peroxide, ethylenediamine tetraacetic acid (EDTA)/sodium percarbonate system or air was performed in this work. Mechanism of thiourea synthesis was established on the basis of isolation and identification of the reaction

intermediates. This paper represents a practical extension of our research into new methods of synthesis of sulfur related compounds in convenient reaction medium[37-39], characterized by the procedure simplicity, high purity and yields of the obtained products, recycling of solvents and absence of dangerous by-products in efflunet water. There are numerous of operationally simple catalytic synthesis methods performed in water as a reaction medium[40,41]. This fact is especially important considering that potentially dangerous carbon disulfide was used as a reagent.

EXPERIMENTAL

Materials

All materials used for synthesis of symmetrical and asymmetrical thioureas were provided by Sigma-Aldrich, and used without purification.

Instrumental methods

Mass spectra were obtained on a Thermo Finnigan Polaris Q ion trap mass spectrometer, including TraceGC 2000 (ThermoFinnigan Corp., Austin, TX, USA). Polaris Q ion trap GC/MS system with electron ionization (EI), and direct insertion probe (DIP) techniques was used. DIP mode has been used to introduce the sample and EI/MS technique to acquire the spectra. Ionization conditions were as follows: ion source temperature 200 °C, maximum energy of electron excitation 70 eV, corona current 150 μA. The obtained data were processed using Xcalibur™ 1.3 software.

GC analysis was also performed on Perkin-Elmer gas chromatograph series 8700, equipped with flame ionization detector and columns filled with: 10% of SP-2410 at Supelcort (100/120) and 5% of OV-210 at Chromosorb WH/P (80/100).

Chromatographic conditions:

- injector temperature 230 °C
- detector temperature 270 °C
- column temperature-program mode: Supelcort column 50 °C→5 °C/min→150 °C; Chromosorb WH/P column 50 °C→5 °C/min→130 °C
- carrier gas: nitrogen (99.99 %)
- nitrogen flow: 25 cm^3/min.
- air flow: 250 cm^3/ min (99.99 %)
- hydrogen flow: 25 cm^3/ min (99.99 %)
- column: inner diameter 2 mm, length 30 m

^{1}H and ^{13}C NMR measurements were performed on a Varian Gemini 2000 (200/50 MHz) instrument at 25 ^{o}C. Chemical shifts (δ) were reported in part per million (ppm) relative to tetramethylsilane (δ_H=0 ppm) in ^{1}H NMR, and to dimethyl sulfoxide (δ_C=39.5 ppm) in ^{13}C NMR, using the residual solvent peak as a reference standard. Fourier-transform infrared (FTIR) spectra were recorded in transmission mode using a BOMEM (Hartmann&Braun) spectrometer.

Elemental analysis was performed on the VARIO EL III Elemental analyzer, and the results of analysis are in good agreement with theoretical values (±0.2%).

Fourier-transform infrared (FTIR) spectra were recorded in transmission mode using a BOMEM (Hartmann&Braun) spectrometer.

HPLC (high performance liquid chromatograph) was performed on Spectra System P4000 equipped with UV detector, column Zorbax SB-C8, mobile phase benzene/methanol (HPLC grade) (9:1), isocratic mode.

Determination of cations concentrations in water solution from thioureas semi-industrial production plant was performed by the use of inductively coupled plasma mass spectrometry (ICP-MS) using an Agilent 7500ce ICP-MS system (Waldbronn, Germany) and Perkin Elmer Analyst 200, MHS 15 (Waltham, MA, USA). ICP-MS was equipped with an octopole collision/reaction cell, Agilent 7500 ICP-MS ChemStation software, a MicroMist nebulizer and a Peltier cooled (2.0 °C) quartz Scott-type double pass spray chamber. Standard optimization procedures and criteria were specified in the manufacturer's manual instruction.

*General procedure for the synthesis of symmetric (**S**) thioureas by using hydrogen peroxide as oxidant, exemplified by preparation of N,N,N',N'-tetraethylthiourea* - Method **S-m1**

In a three necked round bottom flask, 500 cm^3, equipped with a reflux condenser, dropping funnel, thermometer and magnetic stirrer were immersed into 110 cm^3 of water and 34.0 cm^3 (0.32 mol) of 98.0% diethyl amine. Afterward, 10.2 cm^3 (0.16 mol) of 98.0% carbon disulphide (water was added a top layer to prevent pressure development above the carbon-disulfide in a dropping funnel) was added with efficient stirring and providing temperature of reaction mixture between 35 and 40^{o}C for 1 h. Oxidation of diethylammonium carbamodithioic acid was performed by addition of 46.40 cm^3 (0.18 mol; 13.2% solution was prepared by dissolution of 178.6 cm^3 (2.08 mol) of 35.0% hydrogen-peroxide in 406.5 cm^3 of deionized water) of hydrogen-peroxide solution keeping the reaction temperature in the range 40 - 45 ^{o}C for 1 h. The formation of the suspended product, during the addition of the solution of hydrogen-peroxide, was observed.

Reaction product was subjected to vacuum for 5 min (10 kPa), filtered using a vacuum filter, whereby thiourea and sulfur were obtained as a filtration cake. The obtained material was dissolved in

ethanol:dichloromethane mixture (1:1), and suspension was filtered to give 4.8 g of sulfur, and thiourea was in a filtration solution. After solvent evaporation pure product was obtained by recrystallization from methanol followed by column chromatography purification (silica gel 60, 230–400 mesh) using methanol/dimethylformamide (9:1) as a mobile phase. After solvent evaporation and product drying at 50 °C for 10 hours, yield 27.60 g of *N,N,N',N'*-tetraethylthiourea (82%), m.p. 76-78 °C (78 °C[42]). The purity of the product was determined by GC analysis (99.0%). All other asymmetrical thioureas were synthesized in an analogous manner to described method **S-m1**, and reuslts of the synthesis are presented in Table I.

Analogous methodolgies were performed for symmetric thiourea synthesis in the presence of EDTA/percarbonate system, *i.e*. *in situ* generated peracetic acid, method **S-m2**, and air, method **S-m3**. Procedure, according to method **S-m3**, was performed in a mildly pressurized system to provide higher oxygen concetration in a reaction medium. Results of thioureas synteses according to methods **S-m2** and **S-m3** are presented in Table I.

*General procedure for the synthesis of asymmetric (**AS**) thioureas by using hydrogen peroxide as oxidant, exemplified by preparation of N,N,N'-triethylthiourea* - Method **AS-m1**

In a three necked round bottom flasks, 500 cm^3, equipped with a reflux condenser, dropping funnel, thermometer and magnetic stirrer were immeresed into 110 cm^3 of water and 17.0 cm^3 (0.16 mol) of 98.0% diethyl amine. Afterward, 10.2 cm^3 (0.16 mol) of 98.0% carbon disulphide (water was added as a top layer to prevent pressure development above the carbon-disulfide in a dropping funnel) was added with efficient stirring and providing temperature of reaction mixture between 35 and 40 °C for 1 h. Oxidation of diethylammonium carbamodithioic acid was performed by addition of 23.20 cm^3 (0.09 mol; 13.2%) of hydrogen-peroxide maintaining the reaction temperature in the range 40 - 45 °C for 1 h. The formation of the suspended product, during the addition of the solution of hydrogen-peroxide, was observed. Afterwards, 12.55 cm^3 (0.16 mol) of 68 % of ethylamine and 23.20 cm^3 (0.09 mol) of 13.2% hydrogen-peroxide followed by maintaining the temperature in the range 40 - 45 °C for additional 1 h.

Reaction product was subjected to vacuum for 5 min (10 kPa), filtered using a vacuum filter, whereby thiourea and sulfur were obtained as a filtration cake. The filtration cake was dissolved in ethanol:dichloromethane mixture (1:1 vol.), and obtained suspension was filtered to give a filtration cake of 4.8 g of sulfur, and thiourea was in a filtration solution. Pure product was obtained by recrystallization from methanol followed by column chromatography purification (silica gel 60, 230–400 mesh) using methanol/dimethylformamide (9:1) as mobile phase. After solvent evaporation and product drying at 50 °C for 10 hours, yield 9.0 g of *N,N,N'*-triethyl thiourea (*$Et_2NC(S)NHEt$*) (34%), 86-88 °C (87-88 °C[42]) was obtained. The purity of the product was determined by GC analysis (99.0%).

Method **AS'-m1**

In a three necked round bottom flask, 500 cm^3, equipped with a reflux condenser, dropping funnel, thermometer and magnetic stirrer were immersed into 110 cm^3 of water and 34.0 cm^3 (0.32 mol) of 98.0% diethyl amine. Afterward, 10.2 cm^3 (0.16 mol) of 98.0% carbon disulphide was added with efficient stirring and providing temperature of reaction mixture between 35 and 40 ^oC for 1 h. Continuous addition of 15% hydrochloric acid solution was performed until pH reach 2, *i.e*. no precipitation of waxy diethyl carbamodithioic acid was observed. Decantation of supernatant solution, washing of precipitate with distilled water, and addition of 12.55 cm^3 (0.16 mol) of 68 % of ethylamine and 23.20 cm^3 (0.09 mol) of 13.2% hydrogen-peroxide was followed by maintaining the temperature in the range 40 - 45 ^oC for additional 1 h. Purification of reaction product, performed according to procedure described by Method **AS-m1**, gave 23.30 g of *N,N,N'*-triethyl thiourea (88%; GC purity 99.2%), 86-88 ^oC (87-88 ^oC[42]). Results of asymmetrical thioureas synthesis, according to **AS'-m1** method, are presented in Table 1. In an analogous manner was performed assymetrical thiourea synthesis in presence of the EDTA/percarbonate system, **AS'-m2**, and air, **AS'-m3** method, and results of thioureas syntheses are presented in Table 1.

All synthesized thioureas obtained by above presented methods have identical MS, FTIR, ^1H and ^{13}C NMR data to literature ones. Yield was presented for **S-m2** and **AS'-m2** methods of thiourea synthesis.

Diethylcarbamodithioic acid (**K**, $C_3H_7NS_2$), yield 56 % (99.0% HPLC); m.p. 136-138 ^oC (143-144 ^oC[43]);

Tetraethylthiuram disulfide (TETD) (**L**, $C_{10}H_{20}N_2S_4$), yield 58 % (99.0% HPLC); m.p. 71 ^oC (72 ^oC[37]);

N,N,N'-triethylthiourea - (**1a,** $C_7H_{16}N_2S$), yield 88% (99.1% HPLC); 86-88 ^oC (87-88 ^oC[42]);

N,N,N',N'-tetraethyl thiourea (**1b,** $C_9H_{20}N_2S$), yield 79% - (99.5% HPLC), m.p. 76-78 ^oC (78 ^oC[42]);

N'-(4-chlorophenyl)-N,N-dimethyl thiourea (**2a,** $C_9H_{11}ClN_2S$), yield 76% (99.4% HPLC); m.p. 150-152 °C (150–152 °C[44]);

N'-(4-bromophenyl)-N,N-dimethyl thiourea (**2b,** $C_9H_{11}BrN_2S$), yield 72% (99.3% HPLC); m.p. 165-166 °C (165–167 °C[45]);

N,N-dimethyl-N'-(4-nitrophenyl)thiourea (**2c,** $C_9H_{11}N_3O_2S$), yield 69% (99.2% HPLC); m.p. 123-125 °C (124–126 °C[46]);

N,N'-Dibenzyl thiourea (**3a,** $C_{15}H_{16}N_2S$), yield 71 % (99.4% HPLC); m.p. 137–138 °C (138–139 °C[47]);

N,N'-Diphenylthiourea (**3b,** $C_{13}H_{12}N_2S$), yield 69 % (98.9% HPLC); m.p. 151-153 ^oC (152 ^oC[48]);

Bis(4-methylphenyl)thiourea (**3c,** $C_{15}H_{16}N_2S$),yield 74 % (98.8% HPLC) mp 180-182 ^oC (182 ^oC[48]);

Bis(4-ethylphenyl)thiourea (**3d,** $C_{17}H_{20}N_2S$), yield 70 % (98.7% HPLC); m.p. 140-142 ^oC (142 ^oC[48]);

Bis(2-methoxyphenyl)thiourea (**3e**,$C_{15}H_{16}N_2O_2S$), yield 71 % (98.8% HPLC); m.p. 130-132 ^oC (132 ^oC [48]);

1-Ethyl-3-(2-methoxyphenyl)thiourea (**4a,** $C_{10}H_{14}N_2OS$), yield 62% (98.8% HPLC); m.p. 98 - 100 ^oC (99-101 ^oC[49]);

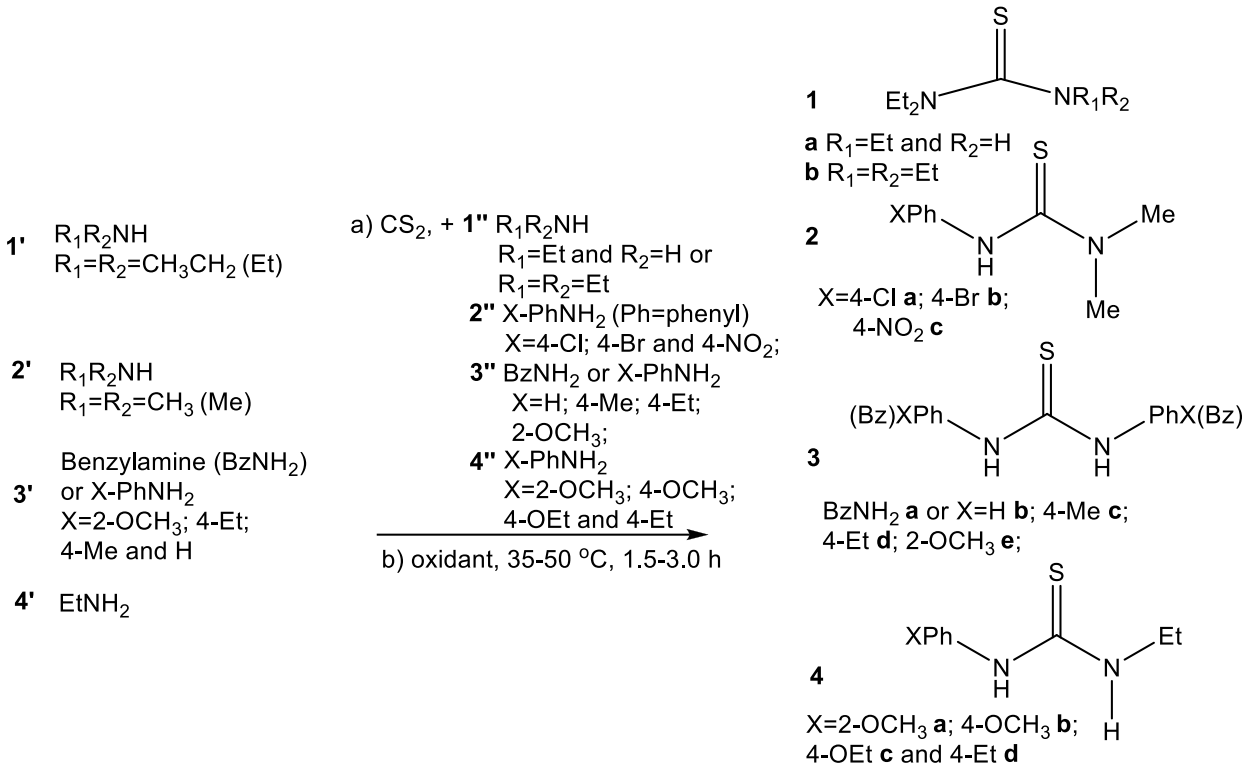
1-Ethyl-3-(4-methoxyphenyl)thiourea (**4b,** $C_{10}H_{14}N_2OS$), yield 75% (98.9% HPLC); m.p. 126 - 128 °C (125-130 °C[49]);

1-(4-Ethoxyphenyl)-3-ethylthiourea (**4c,** $C_{11}H_{16}N_2OS$), yield 73% (99.0% HPLC); m.p. 106 - 108 °C (105-109 °C[49]);

1-Ethyl-3-(4-ethylphenyl)thiourea (**4d,** $C_{11}H_{16}N_2S$), yield 69% (99.1% HPLC); m.p. 87-89 °C (85-90 °C[49]);

RESULTS AND DISCUSSION

A new method for the synthesis of symmetrical and asymmetrical thioureas, series **1 - 4**, is presented on Scheme 1 using *mono*- and *di*-substituted alkyl and aryl amine, carbon disulfide and different oxidants. Three oxidizing agents were used: hydrogen peroxide (method **m1**), *in situ* generated peracetic acid (EDTA/percarbonate system) (method **m2**) and air (method **m3**). Synthesis of thiourea from alkyl and aryl amine and carbon disulfide, without oxidative agent, does not give any appreciable quantity of thiourea. This result indicates that the role of the oxidant is the crucial one for the successful thiourea synthesis. A great number of alkyl amines were used but only dimethyl amine, ethyl amine and diethyl amine gave satisfactory yield of thiourea. Furthermore, a variety of aryl amines: benzylamine ($BzNH_2$) and substituted anilines (X-$PhNH_2$) where X is: 2- and 4-OCH_3, 4-Cl, 4-Br, 4-Me, 4-Et, 4-OEt and 4-NO_2 substituent were used for thioureas synthesis. The reaction takes place in one batch in the water as the reaction medium, without the presence of a catalyst and without isolation of the intermediate from the reaction mixture.



Scheme 1. General method applied for symmetric and asymmetric thiourea synthesis

Study of the influences of synthesis parameters on reaction yield and purity of thiourea products were performed and optimal synthesis of thiourea was established. According to the optimal methods, described in the experimental part, a series of thioureas have been obtained and results are given in Table I.

Table I. Yields and purities of thiourea obtained by appropriate synthesis method

Compound	Yield-Purity/%	Method*	Yield-Purity/%	Method	Yield-Purity/%	Method
1a	82-99.2	AS'-m1	88-99.1	AS'-m2	42-99.0	AS'-m3
1b	72-99.1	S-m1	79-99.5	S-m2	39-98.9	S-m3
2a	73-99.0	AS'-m1	76-99.4	AS'-m2	33-98.7	AS'-m3
2b	71-99.1	AS'-m1	72-99.3	AS'-m2	36-98.8	AS'-m3
2c	62-99.5	AS'-m1	69-99.2	AS'-m2	39-99.0	AS'-m3
3a	63-99.3	S-m1	71-99.4	S-m2	38-99.0	S-m3
3b	64-99.2	S-m1	69-98.9	S-m2	34-98.9	S-m3
3c	65-99.0	S-m1	74-98.8	S-m2	41-99.1	S-m3
3d	62-98.9	S-m1	70-98.7	S-m2	40-99.2	S-m3
3e	68-98.8	S-m1	71-98.8	S-m2	33-99.3	S-m3
4a	57-98.9	AS'-m1	62-98.8	AS'-m2	36-99.0	AS'-m3
4b	71-99.0	AS'-m1	75-98.9	AS'-m2	34-99.2	AS'-m3
4c	70-98.8	AS'-m1	73-99.0	AS'-m2	42-99.3	AS'-m3
4d	66-98.9	AS'-m1	69-99.1	AS'-m2	40-99.0	AS'-m3

*__S__ and __AS__ designate metods used for symmetric and asymmetric thioureas synthesis, respectively.

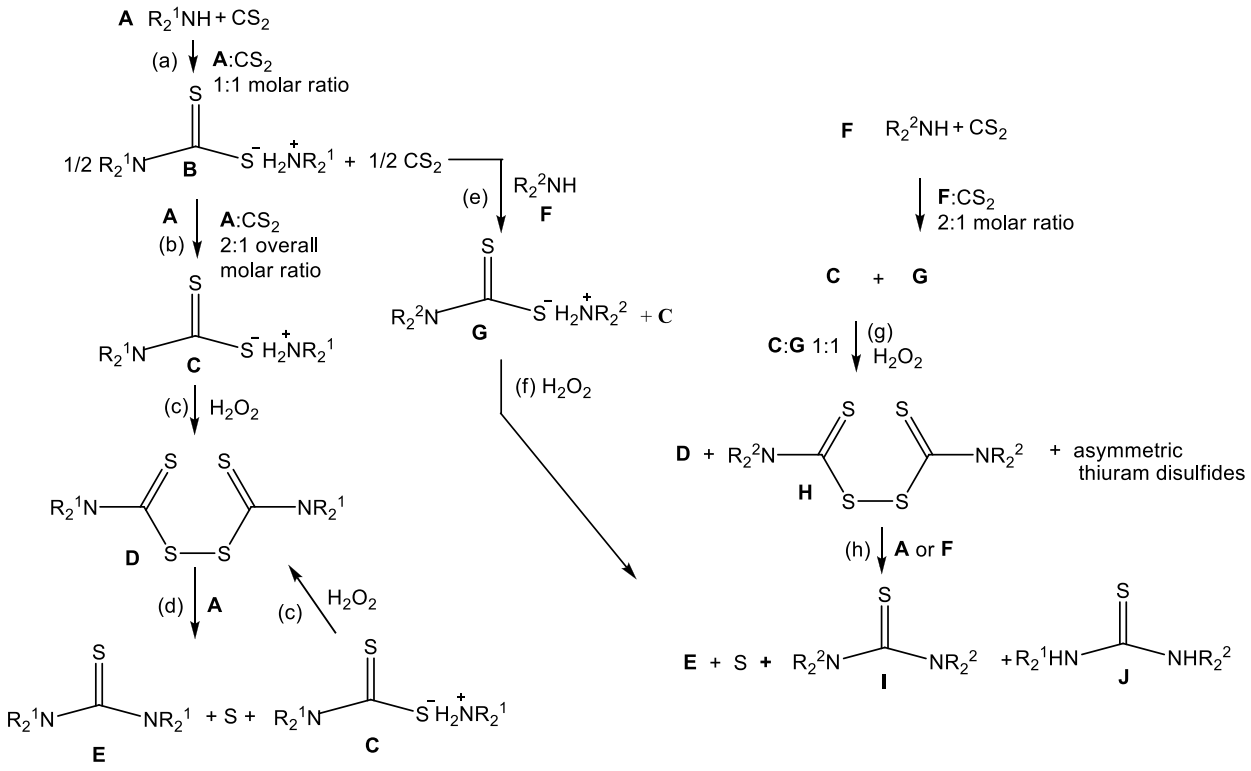
On the basis of the results presented in Table I, it could be observed that satisfactory yields and purities of the thioureas were obtained according to the optimal methods **m1** and **m2**. Highest yield and purity were obtained using EDTA/percarbonate system, somewhat lower with hydrogen peroxide and lowest using air as oxidant. Longer reaction time, air flow change or air enriched oxygen did not contribute to appreciable increase of the reaction yield of thiourea obtained by method **m3**. Fairly higher reaction yields of thioureas were obtained with pure oxygen, around 7-13%, which indicate that oxygen diffusional transport resistance exist at gas/liquid interface and in a bulk of solution. This means that controllable generation of oxidative species in a homogeneous EDTA/percarbonate system had benefitial effect on increased reaction yields obtained by method **m2**.

Recycling of the reaction residual solution was performed by using water without prior purification. This method offered satisfactory improvement to overall synthesis method regardless to heterogeneity of residual solution and amine oxidation by-products. Determination of the amine content as well as oxidation potential in recycled water was used for calculation of reactant ratio for design of subsequent reaction. Lower yield in second cycle was obtained, 5-10%, while difficulties encountered with purification of obtained product (purity 85-92%) was solved by simple purification with active carbon. Purity of obtained product, after filtration and

purification procedure, was 95-98%, which offers acceptable alternative for improvement of overall production technology. Otherwise, the design of water purification was based on simple treatment with calcium hydroxide, heating at 40-50 ^{o}C for 15 min and filtration produce effluent water which satisfied criteria prescribed by EPA effluent limition guidelines for waste water. Benefits of the use of both technologies will be subject of detail techno-economic analysis.

According to the results shown in Table I, the highest yields were obtained in the synthesis of asymmetric alkylthiourea of 88% for **1a** and 79% for **1b** obtained by using method **m2**. Higher basicity (nucleophilicity) of aliphatic (alkyl) amines contributes to the better reactivity in the first reaction step, *i.e.* nucleophilic addition on thicarbonyl group of carbon disulfide (Scheme 2). Additionally, flexible alkyl chain could be easily adapted, in the course of formation of transition state, in the low energy structure with minima interactions in transition states, and thus lower activation energy is a consequence.

Study of the reaction mechanism of thiourea synthesis in the presence of hydrogen peroxide has been performed by means of isolation and identification of the reaction intermediates and characterization by using ^{1}H and ^{13}C NMR and GC MS/MS methods. Results of this study indicate that thiourea synthesis reaction take place in a three steps. If, in the first step, amine **A** reacts with carbon-disulfide, at molar ratio of 1:1, corresponding alkyl(aryl) ammonium salt of dithiocarbamoic acid **B** was obtained (Scheme 2; path (a)). Further transformation of **B** by reacting with amine **A**, at 2:1 molar ratio of amine:carbon disulfide, produces compound **C** (Scheme 2; path (b)). Thus, in the first step, if the molar ratio amine: carbon disulfide is 1:1, the half quantity of the present carbon disulfide reacts with the whole amount of present amine producing alkyl(aryl) ammonium salt of dithiocarbamic acid. Interrupting mixing and allowing the reaction mixture to equilibrate, unreacted carbon disulfide will separate at the bottom of reaction flask. Measured volume of separated fraction corresponds to 95% of the extent of reaction (with respect to formation of compound **B**). Continuation of the reaction mixture mixing, followed by addition of hydrogen peroxide, enable the completion of the reaction producing tetraalkyl thiuramdisulfide **D**. On the basis of presented results it was necessary to use two-fold molar excess of amine, relative to carbon-disulfide, to provide synthesis of tetraalkyl thiuramdisulfide (compound **D**).



Scheme 2. Proposed reaction mechanism of symmetric and asymmetric thiourea synthesis in presence of hydrogen peroxide

The second stage of reaction represents oxidation of the obtained alkyl(aryl) ammonium salt of dithiocarbamic acid, compound **C**, by hydrogen peroxide, and the resulting product is tetralkylthiuram disulfide, compound **D**, accompanied with the formation of amine **A**. Released amine **A**, reacts with a compound **D**, in third step, producing thiourea **E**, sulfur and the alkyl(aryl) ammonium salt of dithiocarbamoic acid **C**. Slow addition of hydrogen peroxide provides oxidation of alkyl(aryl) ammonium salt of dithiocarbamoic acid to tetraalkylthiuram disulfide, compound **D**, by maintaining the temperature of reaction mixture in the range 35 - 50 ^{o}C. In a such way of repeated cycles the reaction successively take place until the complete conversion of the compound **D** to symmetrical thiourea is accomplished.

Study of the reaction mechanism of asymmetric thiourea synthesis was performed in an analogous way to symmetric one, considering that complex mixture of asymmetric and symmetric reaction intermediate and thiourea products could be obtained. Synthesis procedure was performed by reacting of amine **A** and carbon-disulfide in a molar ratio 1:1 in the first step of reaction (Scheme 2; path (a)), producing alkyl(aryl) ammonium salt of dithiocarbamoic acid

B. In a subsequent step, the addition of equimolar quantity of amine **F** to residual CS_2 (Scheme 2; path (e)) was accompanied with the formation of the mixture of symmetric and asymmetric alkyl(aryl) salt of dithiocarbamoic acid. Main product was consisted from almost equimolar quantity of salts **G** and **C**, as well as minor fraction of assymetric salt (less than 4% according to HPLC analysis). Addition of hydrogen peroxide to the reaction mixture (Schema 2; path (f)) causes oxidation of compounds **G** and **C** producing mainly symmetric thiuramdisulfide, as well as minor fraction of asymmetric one. Liberated amines **A** and **F** exert heterolytic cleavage of disulfide bonds in symmetric thiuramdisulfide producing compounds **E**, **I** and **J**, at almost similar content if used amines, both **A** and **F**, are either monoalkyl or dialkyl amine. In a similar fashion, as for symmetric thiourea synthesis, reaction took place until whole quantity of amine and carbon disulfide were exhausted. In the case of thiourea synthesis when monoalkyl amine **A** and dialkyl amine **F** were used, obtained product contain highest quantity of symmetric *N*,*N'*-dialkyl thiourea, asymmetric and symmetric *N*,*N*,*N'*,*N'*-tetraalkyl thioureas were found to be of significanlty lower quantity. Such results suggested that thiourea content was mainly dictated by the amine reactivity, *i.e.*, amine nucleophilicity.

Also, synthesis of asymmetric thiourea was performed according to an alternative method: two separate solutions containing alkyl(aryl) ammonium salt of dithiocarbamoic acids **C** and **G**, combined with immediate addition of hydrogen peroxide. By the addition of hydrogen-peroxide the both salts were oxidized to symmetric and asymmetric thiuramdisulfide, and liberated amines **A** and **F** further successively reacted in the next step with present thiuramdisulfide in a cyclic manner until the termination of reaction. The symmetric and asymmetric thiourea **E**, **I** and **J**, at almost similar content, as in previous study, were obtained. Difficulties encountered with the separation and purification of the product mixture to obtain pure asymmetric thiourea indicate impracticability of this method for asymmetric thiourea synthesis.

Evidence that the reaction took place according to the reaction Scheme 2, were demonstrated experimentally in the following manner: the mechanism was proved by the isolation of intermediates and products of the reaction, similar to the method applied in the previous work[38,39].

*Analysis of the intermediary products in the syntheses of symmetric thiourea***:** Following Following the procedure described by Method **S-m1** immediately after addition of amine **A**, *e.g*. diethyl amine, in the first intial step of reaction a sample of the reaction mixture was withdrawn, acidified by addition of diluted HCl (10% vol.) and in this manner the formation of insoluble waxy precipitate of diethyl carbamodithioic acid was evidenced (comp. **K**). Results of ^{1}H and ^{13}C NMR and FTIR characterization of the raw product, as well as HPLC analysis showed that isolated material contains 96% of comp. **K**. Using unpurified product in the next experiment, *i.e* dispersion in appropriate volume of water and following by addition of the hydrogen peroxide and equimolar quantity of amine **A** with respect to compound **C**, produced a suspension containing sulfur and *N,N,N',N'*-tetraalkylthiourea. After filtration and dissolution of the obtained filtration cake in ethanol and repeated filtration gave product which mostly contains sulfur, and the solution was tetraalkyl thiourea in ethanol (example: *N,N,N',N'*-tetraethyl thiourea - comp. **1b**). Syntheses of tetraethylthiuram disulfide (TETD; **L**) was performed from diethyl carbamodithioic acid and diethyl amine and addition of the hydrogen peroxide, which confirmed that reaction step (c) produced thiuram disulfide derivatives. Subsequent reaction step (d), *i.e*., reaction of TETD with diethyl amine and hydrogen peroxide, yielded *N,N,N',N'*-tetraethyl thiourea.

*Analysis of the intermidary products in the syntheses of asymmetric thiourea***:** In a similar manner of the mechanistic study of symmetric thiourea synthesis the assumed mechanism of asymmetric thiourea synthesis was studied. After isolation of water-insoluble diethyl carbamodithioic acid, unpurified product was used in subsequent experiment, *i.e* dispersing it in appropriate volume of water followed by addition of hydrogen peroxide and equimolar ratio of ethyl amine, produce a sulfur and *N,N,N'*-triethylthiourea (**1a**).

Reaction of TETD, dispersed in water, with ethylamine at 1:1 molar ratio following by slow addition of hydrogen peroxide produced *N,N,N''*-triethylthiourea (**1a**). The presence of the sulphur, as a product of decomposition of TETD in reaction mixture after filtration, was almost stoichiometrically equal to the value obtained by calculation in respect to the reaction yield.

According to presented, it could be stated that satisfactory reaction yields obtained by methods **m1**-**m3** and simple work-up on synthesis of thiourea allow implementation of optimized laboratory technology on semi-industrial level. It was also confirmed that reaction by-product was not present in water, while concentration of alkyl(aryl) ammonium of dithiocarbamoic acid

and tetraalkylthiuram disulfide have been determined to be under maximum permissible contamination limit. Innovative methods, especially method **m2**, could be widely used for thiourea synthesis at industrial level of production.

CONCLUSION

Presented work describes the optimal synthesis of thioureas from alkyl and aryl amines, carbon disulfide and three oxidants: hydrogen peroxide, *in situ* generated per acetic acid (EDTA/percarbonate) and air. A high conversion of starting materials into products was achieved using EDTA/percarbonate (62%-88%), hydrogen peroxide produced lower yields (57%-82%), and the lowest yield was obtained using air (36%-42%). The synthetic method, developed in laboratory provides a good opportunity for applications at semi-industrial level. The present innovative method provides an efficient method for the preparation of symmetrical or assymetrical thioureas. This method has several unique advantages, such as: simple procedure, mild reaction conditions, avoiding hazardous organic solvents, use of moderately toxic and inexpensive reagents, short reaction times and high product yields. This environmentally friendly process represents a suitable option to existing methods.

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ИЗВОД

ЈЕДНОСТАВНА ЈЕДНОСТЕПЕНА СИНТЕЗА ТИОУРЕА ИЗ АМИНА, УГЉЕН-ДИСУЛФИДА И РАЗЛИЧИТИХ ОКСИДАНАСА У ВОДИ

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Резултати приказани у овом раду дају једноставне методе за синтезу симетричних и асиметричних тиоуреа у једностепеној реакцији из амина, угљен-дисулфида и оксидационих средстава: водоник-пероксида, систем етилендиаминтетрасирћетна киселина/натријум-перкарбонат и ваздух. Структура синтетисаних једињења је потврђена на основу резултата FTIR, ^{1}H и ^{13}C NMR спектроскопије и MS спектрометрије. Теакциони механизам је предложен на бази изоловања интермедијера реакције и утврђивања њихове структуре. Погодности наведених метода се огледају у једноставности операција, благим реакционим условима, кратким реакционим временима, могућности рециклирања растварача, високог приноса и чистоће производа, одсуства опасних споредних производа и могућност примене освојених технологија на индустријском нивоу производње. Разматрајући комерцијални значај тиоуреа, може се нагласити да примена оптималних синтеза тиоуреа, базираних на приказаним методама у овом раду, на индустријском нивоу производње обезбеђује конкурентске алтернативе технологијама које се тренутно примењују у индустријској пракси.

RUNNING TITLE

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SIMPLE ONE-POT SYNTHESIS OF THIOUREAS

REFERENCES

1. A. Puig, P. Ormad P, J. Sarasa, E. Gimeno, J. L. Ovelleiro, *J Chromatogr* **733** (1996) 511

2. U.D. Pete, C. M. Zade, J. D. Bhosale, S. G.Tupe, P. M. Chaudhary, A. G. Dikundwar, R. S. Bendre, *Bioorg Med Chem Lett* **22** (2012) 5550

3. T. Perez-Ruiz, C. Martinez-Lozano, V. Tomas, R. Casajus, *Talanta* **42** (1995) 391

4. A. N. de Oliveira, H. de Santana, C. T. B. V Zaia, D. A. M Zaia, *J Food Compos Anal* **17** (2004) 165

5. Z. He, F. Wu, H. Meng, L. Ling, L. Yuan, Q. Luo, Y.e. Zeng, *Anal Sci* 15 (1999) 381

Z. He, F. Wu, H. Meng, L. Ling, L. Yuan, Q. Luo and., *Anal. Sci., 1999, 15, 381*–384

6. K. R. Koch, *Coord Chem Rev* **216–217** (2001) 473

7. P. Calza, C. Medana, C. Baiocchi, E. Pelizzetti, *J Photoch Photobio* **189** (2007) 380

8. C. Puzzarini, *J Phys Chem A* **116** (2012) 4381

9. V. Circu, A. S. Mocanu, C. Rosu, D. Manaila-Maximean, F. Dumitrascu,
J Therm Anal Calorim 107(2012) 877

10. M. H. Chao, B. M. Kariuki, K. D. M. Harris, S. P. Collins, D. Laundy, *Angew Chem Int Ed* **42** (2003) 2982

11. E. R. Munoz, *Mutat Res* **517** (2002) 231

12. P. E. McCleskey, R. A. Swerlick, *Cutis* **68** (2001) 387

13. W. Y Chan, T. B. Ng, *J Exp Zool* **273** (1995) 160

14. S.N. Giri, A. B. Combs, *Toxicol Appl Pharm* **16** (1970) 709

15. M. R. Smyth, J. G. Osteryoun, Anal Chem **49** (1977) 2310

16. K.M. Thakar, D. J. Paghdar, P. T. Chovatia, H. S. Joshi, *J Serb Chem Soc* 70 (2005) 807

17. B. Mertschenk, F. Beck, W. Bauer, *Thiourea and Thiourea Derivatives*. *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, 2002, Berlin.

18. L. Nagarapu, N. Ravirala, *Indian J Chem* **37B** (1998) 39

19. D. Lednicer, L. A. Mitscher, G. I. Georg, Wiley-Interscience Publication, John Wiley & Sons, Inc **4** (1990) 95

20. M. E. Azab, M. M. Youssef, E. A. El-Bordan, *Molecules* **18** (2013) 832

21. S. Sahu, P. R. Sahoo, S. Patel, B. K. Mishra, *J Sulfur Chem* **32** (2011) 171

22. D. Chatterjee, S. Rothbart, R. van Eldik, *Dalton T* **42** (2013) 4725

23. S. Rover, M. A. Cesura, P. Huguenin, A. Szente, *J Med Chem* **40** (1997) 4378

24. K. S. Kim, S. D. Kimball, R. N. Misra, D.B. Rawlins, *ibid.*, **45** (2002) 3905

25. N. Vukovic, S. Sukdolak, S. Solujic, T. Milosevic, *Arch Pharm* **341** (2008) 491

26. R. M. Maddani, K. R. Prabhu, *J Org Chem* **75** (2010) 2327

27. J. G. Erickson, *J Org Chem* **21** (1956) 483

28. G.P. Slater, J. F. Manville, *J Chromatogr* **648** (1993) 433

29. L. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins, W. A. Lott, *J Am Chem Soc* **73** (1951) 906

30. M. Koketsu, Y. Fukuda, H. Ishihara, *Tetrahedron Lett* **42** (2001) 6333
31. W. Hillebrand, *Ind Eng Chem Prod RD* **23** (1984) 476
32. A. R. Katritzky, N. Kirichenko, B. V. Rogovoy, J. Kister, H. Tao, *Synthesis* (2004) 1799
33. Y. Zhang, T. Wei, L. M. Gao, *Synth Commun* **31** (2001) 3099
34. Z. Li, Y. Zhang, Y. Wang, *Phosphorus Sulfur* **178** (2003) 293
35. B. R. Linton, A. J. Carr, *J Org Chem* **65** (2000) 1566
36. B. K. Kaymakçıoglu, S. Rollas, *J Pharm Sci* **26** (2005) 97
37. M. M. Milosavljević, A. D. Marinković, J. M. Marković, D. V. Brković, M.M. Milosavljević, *Chem Ind Chem Eng Q* **18** (2012) 73
38. M. M. Milosavljević, D. Z. Mijin, S. S. Milisavljević, N. N. Elezović, J. K. Milanović, *Monatsh Chem* **144** (2013) 1833
39. M. M. Milosavljević, A. D. Marinković, S. D. Petrović, M. Sovrlić, *Chem Ind Chem Eng Q* **15** (2009) 257
40. B. Movassagh, M. Soleiman-Beigi, *Monatsh Chem* **139** (2008) 927
41. M. Soleiman-Beigi, Z. Taherinia, *J Sulfur Chem* **35** (2014) 470
42. P. W. Preisler, *J Am Chem Soc* **71** (1949) 2849
43. L. Malatesta, *Gazz Chim Ital* **69** (1939) 629
44. J. Zakrzewski, *Phosphorus Sulfur* **187** (2009) 1880
45. A. M. Demchenko, V. A. Yanchenko, V. V. Kisly, M. S. Lozinskii, *Chem Heterocyc Compd* **41** (2005) 668
46. H. Pint-Lin, *Huaxue Xuebao* **26** (1960) 1
47. A. Q. Hussein, J. C. Jochims, *Chem Ber* **112** (1979) 1956
48. P. P. Kumavat, A. D. Jangale, D. R. Patil, K. S. Dalal, J. S. Meshram, D. S. Dalal, *Environ Chem Lett* **11** (2013) 177
49. A. Yahyazadeh, Z. Ghasemi, *Eur Chem Bull* **2** (2013) 573.