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Simple one-pot synthesis of thioureas from amines, carbon disulfide and oxidants in water

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Abstract: The present study reports a new facile methodology for the synthesis of symmetrical and asymmetrical thioureas by a one-pot reaction of the required amine, carbon disulfide and an oxidant, *i.e.*, hydrogen peroxide, ethylenediaminetetraacetic acid (EDTA)/sodium percarbonate system or air. The structures of the synthesized compounds were confirmed by IR, ¹H- and ¹³C-NMR and MS methods. A reaction mechanism is proposed based on the isolation of reaction intermediate and the determination of their structure. The synthetic benefits of the presented methods are reflected in the operational simplicity, mild reaction conditions, short reaction times, solvent recycling, high purity and yield of the products, absence of dangerous by-products and technological applicability on an industrial scale. Considering the commercial importance of thioureas, it should be emphasized that implementation of the optimal synthesis of thiourea determined in this study for industrial production could provide a concurrent alternative to the existing technologies in use.

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

INTRODUCTION

Thiourea is a compound that contains sulfur and nitrogen atoms, which make it susceptible to oxidation by a large number of oxidants, resulting in different products including ureas, sulfur oxides and nitrogen. Such sulfur-containing compounds have a special importance for industrial applications. It has been extensively employed in various fields of science, industry and technology such

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as in the rubber industry,¹ for agricultural applications,^{2,3} as a substance that improves the ripening of certain fruit species,⁴ in analytical chemistry,^{5,6} as a photocatalyst,⁷ in the electronic industry, including electronic modulators and electro-acoustic devices,⁸ electro-optic components⁹ and polarization filters.¹⁰ However, thiourea is a well-known environmental organic pollutant, with carcinogenic consequences¹¹ and presents a serious allergenic component.¹² Moreover, thiourea induces hypothyroidism,¹³ causes the damage to pulmonary endothelial cells and possibly mesothelial lining cells in animal organisms.¹⁴ In addition, it was shown that thioureas inhibit nitrification in soil and water.¹⁵

Thiourea is also used in the production of thiourea derivatives¹⁶ and also as an additive for plastic materials.¹⁷ In organic chemistry, it is used for the preparation of heterocycles.¹⁸ Depending on the substituents, this heterocycle possesses anthelmintic, antibiotic and immunosuppressant activities.^{19,20}

When thioureas are oxidized, various products are obtained depending on the structure of the starting compound, oxidizing agent and pH.²¹ Oxidation using hydrogen peroxide in the presence of a ruthenium complex led to formamidine disulphide, thiourea trioxide and sulfate.²² Recent research indicated that some 2-aminothiazoline derivatives of thiourea are inhibitors of enzymes, such as kinurenine-3-hydroxylase,²³ or possess inhibitor activity against the enzyme cyclin-dependent kinase.²⁴ Certain 2-aminothiazole derivatives of 4-hydroxychromen-2-one were obtained and the first step was the synthesis of *N*-alkyl(aryl) and *N,N*-dialkyl thioureas from ammonium isothiocyanate and an appropriate amine in water at 80–90 °C.²⁵ Moreover, *N,N,N'*-trialkylthioureas may be prepared from a dialkylamine and carbon disulfide in the presence of sodium hydroxide.²⁶ As described in previous works, there are common routes in which the synthesis of substituted thioureas involve reactions of anilines with sodium or ammonium thiocyanate in the presence of strong acids, trifluoroacetic acid (TFA) or concentrated HCl, aryl isothiocyanates with amines followed by basic hydrolysis, silicon tetrakisothiocyanate with primary and secondary amines, and 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 LiAlHSH³⁰ 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. 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 was prepared in good to excellent yields under the condition of solid–liquid phase transfer catalysis using poly(ethylene glycol)-400 (PEG-400) as the catalyst.³³ The promoting

effects of some compounds on wheat growth have been tested preliminarily. In addition, *N*-benzoyl-*N'*-carboxy-substituted thiourea derivatives were 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 compounds had excellent plant growth promotion activities.³⁴

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

The syntheses of symmetrical and asymmetrical thioureas by a one-pot reaction of the appropriate amine, carbon disulfide and an oxidant, *i.e.*, hydrogen peroxide, the ethylenediaminetetraacetic acid (EDTA)/sodium percarbonate system or air, was investigated in this work. The mechanism of thiourea synthesis was established based on the isolation and identification of the reaction intermediates. This study represents a practical extension of on-going research into new methods for the synthesis of sulfur-related compounds in a convenient reaction medium.^{37–39} The proposed method is characterized by operational simplicity, high purity and yields of the obtained products, recycling of the solvents and absence of dangerous by-products in the effluent water. There are numerous operationally simple catalytic synthesis methods performed in water as the reaction medium.^{40,41} This fact was 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

The mass spectra were obtained on a Thermo Finnigan Polaris Q ion trap mass spectrometer, including TraceGC 2000 (Thermo Finnigan Corp., Austin, TX, USA). A Polaris Q ion trap GC/MS system with electron ionization (EI), and direct insertion probe (DIP) tech-

niques were used. The DIP mode was used to introduce the sample and the EI-MS technique to acquire the spectra. The 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.

The ¹H- and ¹³C-NMR measurements were performed on a Varian Gemini 2000 (200/50 MHz) instrument at 25 °C. Chemical shifts (δ) are reported in part per million (ppm) relative to tetramethylsilane (δ_H = 0 ppm) for ¹H-NMR, and to dimethyl sulfoxide (δ_C = 39.5 ppm) for ¹³C-NMR, using the residual solvent peak as a reference standard.

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

Elemental analysis was realized on the Vario EL III elemental analyzer, and the results of analysis were in good agreement with the theoretical values (±0.2 %).

High performance liquid chromatograph (HPLC) was performed on Spectra System P4000 equipped with a UV detector (240 nm) and a Zorbax SB-C8 column. Benzene:methanol (HPLC grade, 9:1) was used as the mobile phase at a flow rate of 0.8 ml min⁻¹ in the isocratic operational mode.

The data on the characterization of the synthesized compounds are given in Supplementary material to this paper.

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

In a 500 cm³ three necked round bottom flask equipped with a reflux condenser, dropping funnel, thermometer and magnetic stirrer were added 110 cm³ of water and 34.0 cm³ (0.32 mol) of 98.0 % diethylamine. Subsequently, 10.2 cm³ (0.16 mol) of 98.0 % carbon disulphide (water was added as a top layer to prevent pressure development above the carbon disulfide in the dropping funnel) was added over 1 h under efficient stirring and maintaining the temperature of the reaction mixture between 35 and 40 °C. Oxidation of diethylammonium salt of diethylcarbamidithioic acid was performed by addition of 46.40 cm³ of hydrogen peroxide solution (0.18 mol; a 13.2 % solution was prepared by dissolution of 178.6 cm³ (2.08 mol) of 35.0 % hydrogen peroxide in 406.5 cm³ of deionized water) keeping the reaction temperature in the range 40–45 °C for 1 h. Formation of the suspended product was observed during the addition of the hydrogen peroxide solution.

The reaction product was subjected to vacuum for 5 min (10 kPa) and then filtered using a vacuum filter, whereby thiourea and sulfur were obtained as the filtration cake. The obtained material was mixed with a 1:1 mixture of ethanol and dichloromethane and the suspension was filtered to give 4.8 g of sulfur and a filtrate containing the thiourea. After solvent evaporation, the pure product was obtained by recrystallization from methanol followed by column chromatography (silica gel 60, 230–400 mesh) using methanol/dimethylformamide (9:1) as the mobile phase. After solvent evaporation and product drying at 50 °C for 10 h, 27.60 g of *N,N,N',N'*-tetraethylthiourea (82 %) were obtained, m.p.: 76–78 °C (lit.: 78 °C⁴²). The purity of the product was determined by GC analysis (99.0 %). All other symmetrical thioureas were synthesized in an analogous manner to the described method S-m1, and the results of the syntheses are presented in Table I.

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

TABLE I. Yields (%) and purities (HPLC method, %) of the thioureas obtained by different synthesis methods

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

^aS and AS designate methods used for the synthesis of symmetric and asymmetric thioureas, respectively

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

To a 500 cm³ three necked round bottom flask equipped with a reflux condenser, dropping funnel, thermometer and magnetic stirrer were added 110 cm³ of water and 17.0 cm³ (0.16 mol) of 98.0 % diethylamine. Subsequently, 10.2 cm³ (0.16 mol) of 98.0 % carbon disulphide (water was added as a top layer to prevent pressure development above the carbon disulphide in the dropping funnel) was added over 1 h under efficient stirring and maintaining the temperature of the reaction mixture between 35 and 40 °C. Oxidation of diethylammonium salt of ethylcarbamidithioic acid was performed by addition of 23.20 cm³ (0.09 mol; 13.2 %) of hydrogen peroxide maintaining the reaction temperature in the range 40–45 °C for 1 h. The suspended product formed during the addition of the hydrogen peroxide solution. Afterwards, 12.55 cm³ (0.16 mol) of 68 % ethylamine and 23.20 cm³ (0.09 mol) of 13.2 % hydrogen peroxide was added into reaction mixture and the temperature kept in the range 40–45 °C for an additional 1 h.

Reaction product was worked up as described above for the S-m1 method. *N,N,N'*-Triethylthiourea (Et₂NC(S)NH₂) was obtained in 34 % yield (9 g), m.p.: 86–88 °C (lit. 87–88 °C⁴²). The purity of the product was determined by GC analysis (99.0 %).

Method AS'-m1

In a 500 cm³ three-necked round bottom flask equipped with a reflux condenser, dropping funnel, thermometer and magnetic stirrer was added 110 cm³ of water and 34.0 cm³ (0.32 mol) of 98.0 % diethylamine. Subsequently, 10.2 cm³ (0.16 mol) of 98.0 % carbon disulphide was added over 1 h under efficient stirring and maintaining the temperature of the reaction mixture between 35 and 40 °C. Continuous addition of 15 % hydrochloric acid solution was performed until the pH reached 2, *i.e.*, no precipitation of waxy diethylcarbamidithioic acid was observed. Decantation of the supernatant solution, washing of precipitate with distilled water, and addition of 12.55 cm³ (0.16 mol) of 68 % of ethylamine and 23.20 cm³ (0.09 mol) of 13.2 % hydrogen peroxide were followed by maintaining the temperature in the range 40–45 °C for an additional 1 h. Purification of reaction product, performed according to

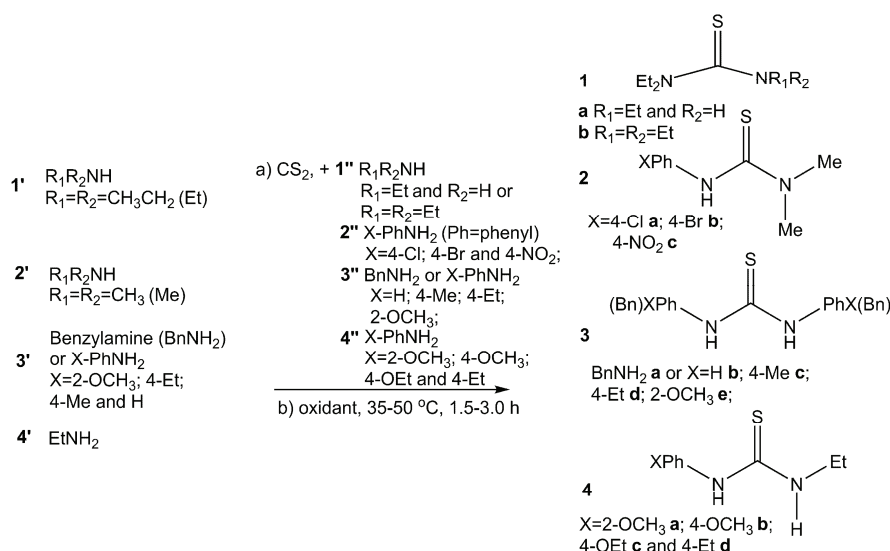
procedure described under Method AS-m1 gave 23.30 g of *N,N,N'*-triethylthiourea (88 %; GC purity 99.2 %), m.p.: 86–88 °C (Lit. 87–88 °C⁴²). Results of asymmetrical thioureas synthesis according to the AS'-m1 method are presented in Table I.

In an analogous manner, the syntheses of the asymmetrical thioureas were performed in presence of the EDTA/percarbonate system, AS'-m2, and air, AS'-m3 methods, and the results of these thioureas syntheses are presented in Table I.

The MS, FTIR, ¹H- and ¹³C-NMR data for all thioureas synthesized by the above-presented methods were identical to those given in the literature.

RESULTS AND DISCUSSION

A new method for the synthesis of symmetrical and asymmetrical thioureas, series 1–4, using mono- and di-substituted alkyl and aryl amines, carbon disulfide and different oxidants is presented in Scheme 1. Three oxidizing agents were used: hydrogen peroxide (method m1), *in situ* generated peracetic acid (EDTA/percarbonate system) (method m2) and air (method m3). The synthesis of thioureas from alkyl and aryl amines and carbon disulfide without an oxidative agent did not give any appreciable quantity of the thioureas. This result indicates that an oxidant plays a crucial role in the successful synthesis of thioureas. A large number of alkyl amines were used but only dimethylamine, ethylamine and diethylamine gave satisfactory yields of the thioureas. Furthermore, a variety of aryl amines: benzylamine (BnNH₂) and substituted anilines (X-PhNH₂) where X was: 2- and 4-OCH₃, 4-Cl, 4-Br, 4-Me, 4-Et, 4-OEt and 4-NO₂ substituents, were used for the synthesis of thioureas. The reaction occurred in one batch in 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 the synthesis of symmetric and asymmetric thioureas.

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

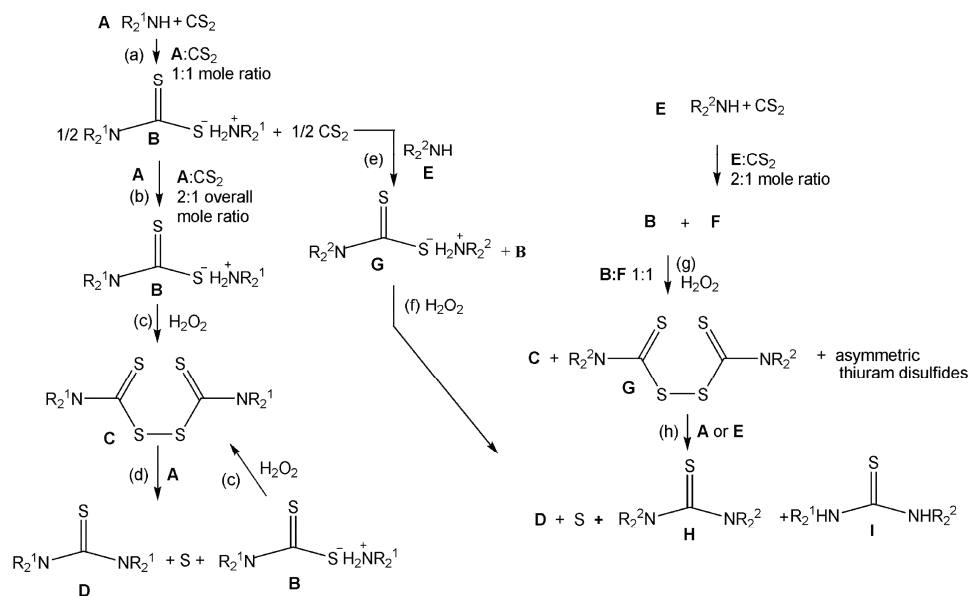
Based on the results presented in Table I, it could be observed that satisfactory yields and purities of the thioureas were obtained according to the optimal methods m1 and m2. The highest yields and purities were obtained using the EDTA/percarbonate system, somewhat lower with hydrogen peroxide and the lowest using air as the oxidant. Longer reaction times, airflow change or air enriched with oxygen did not contribute to appreciable increases in the reaction yields of the thioureas obtained by method m3. Moderately higher reaction yields of thioureas were obtained with pure oxygen, around 7–13 %, which indicates that oxygen diffusional transport resistance exists at the gas/liquid interface and in the bulk solution. This means that controllable generation of oxidative species in the homogeneous EDTA/percarbonate system had a beneficial effect on increasing the reaction yields obtained by method m2.

Recycling of the residual reaction solution was performed by using water without prior purification. This method offered satisfactory improvement to the overall synthesis method regardless of the heterogeneity of the residual solution and amine oxidation by-products. Determination of the amine content, as well as the oxidation potential, in recycled water was used for the calculation of the ratio of the reactants for the design of the subsequent reaction. A lower yield was obtained in second cycle, 5–10 %, while difficulties encountered with purification of the obtained product (purity 85–92 %) were solved by simple purification with active carbon. The purity of the obtained product, after filtration and purification procedure, was 95–98 %, which offers an acceptable alternative for the improvement of the overall production technology. Otherwise, the design of water purification was based on simple treatment with calcium hydroxide, heating at 40–50 °C for 15 min and filtration, which produced effluent water that satisfied the criteria prescribed by the EPA effluent limitation guidelines for wastewater. The benefits of the use of both technologies will be the subject of detailed techno-economic analysis.

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

Reaction mechanism

Synthesis of symmetric thioureas. The reaction mechanism of the synthesis of thioureas in the presence of hydrogen peroxide was studied by the isolation and identification of the reaction intermediates and their characterization by ^1H - and ^{13}C -NMR, and GC/MS methods. The obtained results indicated that the synthesis reaction involved three steps. In the first step, at a mole ratio of 1:1, amine **A** reacts with carbon disulfide giving the corresponding alkyl(aryl) ammonium salt of carbamodithioic acid **B** (Scheme 2; path a). Further transformation of **B** by reaction with amine **A** at a 2:1 mole ratio of amine:carbon disulfide produces compound **B** (Scheme 2; path b). Thus, in the first step, if the mole ratio amine:carbon disulfide was 1:1, half quantity of the present carbon disulfide reacts with the whole amount of present amine producing alkyl(aryl) ammonium salt of carbamodithioic acid. If the mixing was interrupted and the reaction mixture allowed to equilibrate, unreacted carbon disulfide separated at the bottom of the reaction flask. The measured volume of the separated fraction corresponded to 95 % of the extent of reaction (with respect to the formation of compound **B**). Continuation of the mixing, followed by addition of hydrogen peroxide, enabled completion of the reaction producing tetraalkylthiuram disulfide **C**. Based on the presented results, it was necessary to use a two-fold molar excess of amine, relative to carbon disulfide, to provide synthesis of tetraalkylthiuram disulfide (compound **D**).



Scheme 2. Proposed reaction mechanism for the synthesis of symmetric and asymmetric thioureas in the presence of hydrogen peroxide.

The second stage of the reaction represents the oxidation of the obtained alkyl(aryl) ammonium salt of carbamodithioic acid, compound **B**, by hydrogen peroxide, the resulting product being tetraalkylthiuram disulfide, compound **C**, accompanied with the formation of amine **A**. In the third step, the released amine **A** reacts with compound **C** producing thiourea **D**, sulfur and the alkyl(aryl) ammonium salt of carbamodithioic acid **B**. The slow addition of hydrogen peroxide provides oxidation of the alkyl(aryl) ammonium salt of dithiocarbamoic acid to tetraalkylthiuram disulfide, compound **C**, by maintaining the temperature of reaction mixture in the range 35–50 °C. In such a way of repeating cycles, the reaction successively occurred until complete conversion of compound **C** to symmetrical thioureas was accomplished.

Synthesis of asymmetric thioureas. The reaction mechanism of the synthesis of asymmetric thioureas was investigated in an analogous way to that used to study the symmetric ones, considering the complex mixture of asymmetric and symmetric reaction intermediates and thiourea products that could be obtained. The synthesis was performed by reacting amine **A** and carbon disulfide in a mole ratio 1:1 in the first step of the reaction (Scheme 2; path a), producing the alkyl(aryl) ammonium salt of carbamodithioic acid **B**. In the subsequent step, the addition of an equimolar quantity of amine **E** to the residual CS₂ (Scheme 2; path e) was accompanied with the formation of a mixture of symmetric and asymmetric alkyl(aryl) salts of carbamodithioic acid. Main product consisted of almost equimolar quantities of salts **F** and **C**, as well as a minor fraction of the asymmetric salt (less than 4 % according to HPLC analysis). Addition of hydrogen peroxide to the reaction mixture (Scheme 2; path f) resulted in the oxidation of compounds **F** and **C**, producing mainly symmetric thiuram disulfide, as well as a minor fraction of the asymmetric one. The liberated amines **A** and **E** exerted heterolytic cleavage of the disulfide bonds in the symmetric thiuram disulfides producing compounds **E**, **H** and **I**, in almost similar amounts as the used amines, both **A** and **E** are either monoalkyl or dialkyl amines. In a similar fashion as in the synthesis of symmetric thioureas, the reaction occurred until all the amine and carbon disulfide were exhausted. In the case of the thiourea synthesis in which monoalkyl amine **A** and dialkyl amine **E** were used, the obtained product contained the highest quantity of symmetric *N,N'*-dialkyl thiourea. The asymmetric and symmetric *N,N,N',N'*-tetraalkyl thioureas were found in significantly lower quantities. Such results suggested that thiourea content was mainly dictated by the amine reactivity, *i.e.*, the nucleophilicity of the amine.

In addition, the synthesis of asymmetric thioureas was realized according to an alternative method, *i.e.*, immediate addition of two separate solutions containing alkyl(aryl) ammonium salt of carbamodithioic acids, **C** and **F**, were mixed with hydrogen peroxide. On addition of hydrogen peroxide, both salts were oxidized to symmetric and asymmetric thiuram disulfide, and the liberated amines **A**

and **E** further successively reacted in the next step with the present thiuram disulfide in a cyclic manner until termination of the reaction. The symmetric and asymmetric thioureas **E**, **H** and **I** were obtained in almost similar amounts as in the previous study. Difficulties encountered with the separation and purification of the product mixture to obtain pure asymmetric thiourea indicated the impracticability of this method for the synthesis of asymmetric thioureas.

Evidence that the reaction occurred according to reaction Scheme 2, were demonstrated experimentally in the following manner: the mechanism was proved by the isolation of intermediates and products of the reaction, similarly to methodology applied in previous studies.^{38,39}

Analysis of the intermediary products

Syntheses of symmetric thioureas. Following the S-m1 procedure, immediately after addition of amine **A**, e.g., diethylamine, in the first initial step of the reaction, a sample of the reaction mixture was withdrawn, acidified by addition of dilute HCl (10 vol. %) and in this manner the formation of an insoluble waxy precipitate of diethylcarbamdithioic acid was evidenced (compd. **J**). The results of ¹H- and ¹³C-NMR and FTIR characterization of the raw product, as well as HPLC analysis showed that the isolated material contained 96 % of compound **J**. Using the unpurified product in the next experiment, *i.e.*, dispersion in appropriate volume of water followed by the addition of hydrogen peroxide and an equimolar quantity of amine **A** with respect to compound **C**, a suspension containing sulfur and *N,N,N',N'*-tetraalkylthiourea was produced. After filtration and suspension of the obtained filtration cake in ethanol and repeated extraction a solid product that mostly consisted of sulfur and a combined ethanolic solution containing a tetraalkylthiourea (example: *N,N,N',N'*-tetraethylthiourea – compd. **1b**) was obtained. Synthesis of tetraethylthiuram disulfide (TETD; **K**) was performed from diethylcarbamdithioic acid and diethylamine and addition of hydrogen peroxide, which confirmed that reaction step (c) produced thiuram disulfide derivatives. The subsequent reaction step (d), *i.e.*, reaction of TETD with diethylamine and hydrogen peroxide yielded *N,N,N',N'*-tetraethylthiourea.

Syntheses of asymmetric thioureas. In a similar manner to that employed in the mechanistic study of symmetric thiourea synthesis, the assumed mechanism of asymmetric thiourea synthesis was studied. After isolation of the water-insoluble diethylcarbamdithioic acid, the unpurified product was used in the subsequent reaction, *i.e.*, dispersion in an appropriate volume of water followed by the addition of hydrogen peroxide and an equimolar ratio of ethylamine, whereby sulfur and *N,N,N'*-triethylthiourea (**1a**) were produced. The amount of sulfur, as a product of decomposition of TETD in reaction mixture after filtration, was almost stoichiometrically equal to the value obtained by calculation with respect to the reaction yield.

Accordingly, it could be stated that the satisfactory reaction yields obtained by methods m1–m3 and the simple work-up in the synthesis of thioureas allow the optimized laboratory technology to be implemented on a semi-industrial level. It was also confirmed that the reaction by-product was not present in water, while the determined concentrations of alkyl(aryl)ammonium salt of carbamodithioic acid and tetraalkylthiuram disulfide were under maximum permissible contamination limit. The suggested innovative methods, especially method m2, could be widely used for the synthesis of thioureas on an industrial scale.

CONCLUSIONS

The presented work describes the optimal synthesis of thioureas from alkyl and aryl amines, carbon disulfide and three oxidants: hydrogen peroxide, *in situ* generated peracetic acid (EDTA/percarbonate) and air. High conversion of the starting materials into the products was achieved using EDTA/percarbonate (62–88 %), hydrogen peroxide gave lower yields (57–82 %), while the lowest yields were obtained using air (36–42 %). The synthetic method developed in the laboratory provides a good opportunity for applications at semi-industrial levels. The present innovative method provides a powerful and versatile method for the preparation of symmetrical or asymmetrical thioureas. This method has several unique advantages, such as: simple operation, mild reaction conditions, avoidance of hazardous organic solvents, the 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.

SUPPLEMENTARY MATERIAL

The data on characterization of the synthesized compounds are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

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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 једноступеној реакцији из амина, угљен-дисулфида и оксидационих средстава: водоник-пероксида, система етилендиаминтетрасирћетна киселина/натријум-перкарбонат и ваздуха. Структура синтетисаних једињења је потврђена на

основу резултата IR, ^1H - и ^{13}C -NMR спектроскопије и масене спектрометрије. Реакциони 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 могућности 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.

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