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New Facile One-Pot Synthesis of Isobutyl Thiocarbamate in Recycling Solvent Mixture

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Abstract: The specific objectives of the presented study were related to the optimization of the production process of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate; trial industrial production of *N*-ethyl-*O*-isobutyl thiocarbamate; and the evaluation of flotation efficiency of *N*-ethyl-*O*-isobutyl thiocarbamate using a real ore sample. The optimization of thiocarbamate syntheses were performed by varying the molar ratio of isobutyl alcohol, carbon disulfide, potassium hydroxide, reaction time, and reaction temperature. In the first step, one-pot reaction took place to produce alkyl xanthate and was followed with chlorination to give alkyl chloroformate (*O*-alkyl carbonochloridothioate); finally, thiocarbamates were obtained by the reaction with corresponding amines. *N*-alkyl-*O*-ethyl thiocarbamate was synthesized as a comparative flotation agent. The structure of the synthesized compounds was confirmed by IR, ^{1}H and ^{13}C NMR, and MS instrumental methods, and the purity was determined by gas chromatographic method and elemental analysis. The optimized methods gave high-purity products in a significant yield that was also confirmed by semi-industrial production of *N*-ethyl-*O*-isobutyl thiocarbamate. The optimized thiocarbamate synthesis, without isolation of intermediates, is of great importance from the aspect of green technologies. Flotation efficiency test results, using real copper and zinc ores, showed the highest activity of *N*-ethyl-*O*-isobutyl thiocarbamate. The optimal one-pot thiocarbamate synthesis provides a simple procedure with a high conversion degree, and, thus, offers valuable technology applicable at the industrial scale.

Keywords: alkyl xanthate; *N*,*N*-alkyl-*O*-isobutyl thiocarbamate; one-pot synthesis; flotation

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1. Introduction

The mining industry is currently facing significant challenges in identifying and adopting sustainable harvesting chemicals that can effectively recover valuable minerals. Oppositely, the exploitation of biomass-derived molecules presents an increasingly developed strategy for cleaner production that improves sustainability by reducing environmental impact [1–4]. The limited resources of the actual mining industry increase the need for development of more efficient collectors along with reducing environmental risks [5–11]. Since the beginning of the 20th century, alkyl xanthates have been significantly used as reagents for the flotation concentration of various minerals, sulfides, and oxides, due to their ability to bind to hydrophobic agents [12–14]. The collectors' differentiation is based on their strength to adapt to hydrophobic agents and also to air bubbles. The collector's activity can be improved by enhancing its interactions with the target compounds.

Various studies highlighted the importance of surface oxidation of sulfide minerals with respect to xanthate adsorption and their response to flotation [15,16].

In flotation processes, it is desirable to collect as many minerals as possible from the ore without transferring undesirable components, while selective recovery has to be achieved. Currently known oil- or water-insoluble scavengers are allyl alkyl xanthates, alkyl esters of alkyl thiocarbamates, and (alkoxycarbonyl) alkyl xanthates. Although a relatively large number of compounds within each of these classes is available as collectors, extensive studies have shown that the most effective oil collectors are allyl amyl xanthate, *O*-isopropyl *N*-ethyl thiocarbamate, and (ethoxycarbonyl) ethyl xanthate. Despite the minor increase in mineral recovery (about 1% relative to the other collectors), this small improvement is of great techno-economic importance. The exemplary ores that were processed by foam flotation with a collector insoluble in water are sulfides and oxides of copper, zinc, molybdenum, lead, iron, nickel, and cobalt. Such ores may contain valuable metals. Thiocarbamate collectors are used in quantities of about 30 g per ton of ore. The particular collector used in flotation processes depends mainly on the type and content of metal in the ore being processed. Some collectors have an advantage and are more universal than others due to their high mineral extraction potential. Thiocarbamate collectors can be employed with or without water, in combination with hydrocarbon oils, or with other oil collectors such as allyl xanthates. Further, thiocarbamate collectors can be added to the ore flotation process either alone or mixed with emulsifiers such as condensate nonyl phenol-ethylene oxide, organic sulfosuccinates, or sulfosuccinamates. In foaming flotation processes, foaming and conditioning agents (alkali or acid) are usually used with the collectors. The conditioning agents are added to adjust the pH of the ore and to achieve better selectivity and/or increased recovery values. Foaming agents produce stable foam during the flotation step, and methyl isobutyl carbinol, polypropylene glycols and glycol ethers, boric oil, and cresol are the most commonly used members.

Selectivity depends on the structure of the xanthate hydrocarbon chain (C-H), which affects flotation recovery. The efficiency and adhesive strength of the flotation reagent depends on the chain length and structure (branched or straight chains). Although longer xanthate chains are more efficient in flotation of sulfide minerals and, therefore, fewer collectors are needed to achieve the same sulfide recovery, increasing the solubility of the chains in water reduces their efficiency. Therefore, there is an optimal xanthate chain length for a particular flotation system [17]. The binding mechanism of the mineral collector depends on the type of collector and the nature and charge of the mineral surface and can occur by physisorption or chemical binding. In the case of physisorption, the collector does not interact with the mineral surface. The obtained structure is amorphous, and the Gibbs free adsorption energy is relatively low [18].

Thiocarbamates are thiocarbamic acid derivatives, namely, thiol and thion esters [19], and have pronounced biological activity [20] with a wide spectrum of action. They are used as fungicides [21–23], bactericides [22,24], herbicides [25,26], germicides [27], pesticides [28–30], insecticides [31,32], etc. Additionally, *O*-alkyl thiocarbamates are used as polymerization accelerators and selective flotation reagents [33]. Thiocarbamates can be obtained in the reaction of *O*,*S*-diester of dithiocarboxylic acid in aqueous or alcoholic solution with the primary or secondary amines, as well as in the reaction of monothiocarboxylic acid *O*-ester chloride with amines [34]. Preparation of thion- and thiolcarbamic esters is obtained in the reaction of alkaline xanthates, alcohol, and oxidizing agent [35]. The synthesis of thiocarbamates from thiols and isocyanates can be performed in the presence of catalysts with or without solvents [36]. In addition to the known synthetic methods [37–41], thiocarbamates can also be obtained from sodium or potassium xanthate in aqueous solution and primary or secondary amines, in the presence of elemental sulfur [42]. Thiocarbamates can also be obtained in high yield in the reaction of xanthate and amine in the presence of nickel(II) sulfate heptahydrate as a catalyst [43] or by the oxidation of amine salts of xanthogenic acid with hydrogen peroxide or sodium hypochlorite [44]. Methods for the alkyl thiocarbamate synthesis using reaction of alkyl dixanthates and amines in the presence

of an oxidizing agent have been described [45]. In the Newman–Kwart rearrangement (intermolecular isomerization) of *O*-thiocarbamate, S-thiocarbamate is obtained, which is used as herbicides in plant protection [46–49].

In our previous work, the methods for the synthesis of isobutylthiocarbamate in the reaction of the sodium salt of isobutylxanthate acetic acid and the corresponding amines were described, and three comparative methods starting from potassium isobutyl xanthate and amines in the presence of various oxidizing agents were reported [50]. *O*-Alkyl- and *O*-aryl thiocarbamates can be obtained in the reaction of dialkylthiocarbamoyl chloride, obtained by chlorination of thiuram disulfide and the corresponding alcohol. The synthesis requires the isolation and purification of dialkyl thiocarbamoyl chloride, which subsequently reacts with the corresponding alkoxide in the presence of tetra butyl ammonium bromide [51].

This paper is a continuation of our research in the field of thiocarbamate production. The reaction of the synthesis of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate (Figure 1) was performed in a one-step reaction process, where the first formed, alkyl xanthate [52,53], was oxidized by chlorine to alkyl chlorothioformate (*O*-ethyl chloromethanethioate). The corresponding amine was then added to the reaction mixture, and the alkyl thiocarbamate was formed. In practice, the resulting alkyl chlorothioformate is used as alkoxy thiocarbonylating agents. The synthesis of thiocarbamates can be accomplished with the purified alkyl chlorothioformates, but prior preparation and isolation is required. This step was avoided in the present study in order to achieve some benefits, such as production simplicity, techno-economical positive indicator related to environmental impact, and energy saving. Moreover, by the described synthesis process, the obtained dixantogenate was not separated from the reaction mixture; however, during chlorination it was converted into alkyl chlorothioformate, which thioacylates the amine to the corresponding thiocarbamate. In this way, the synthesis took place in one batch with subsequent isolation of the product followed by recycling of the reaction medium. The results obtained in the experimental part of the work indicated the possibility of applying the optimal synthesis procedure at the industrial scale. Additionally, testing of their flotation efficiency proved their possible application in the processes of copper and zinc ore processing.

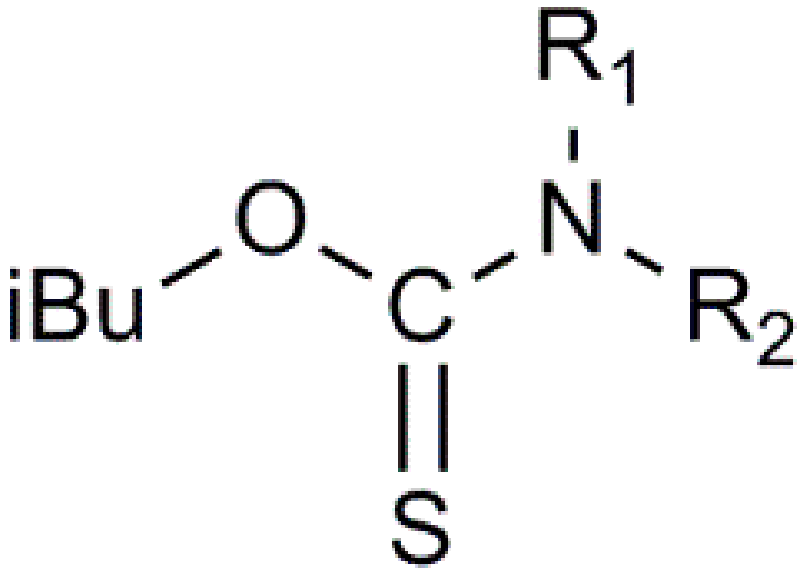


Figure 1. Structure of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate, where R1 is Et, Pr, iPr, Bu, iBu, secBu, iPen, cycPr, cycBu, cycPen, and cycHex, while R2 is H, Et, Pr, and Bu.

2. Experimental Part

2.1. Materials

All materials used are given in Supplementary Material.

2.2. Thiocarbamate Synthesis

In the experimental part, the synthesis of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate was performed starting from isobutanol, potassium hydroxide, and carbon disulfide. The first step was formation of the potassium isobutyl xanthate in the form of suspension in xylene. The obtained xanthate was then converted by chlorine to isobutyl/ethyl chlorothioformate, which gave the corresponding *O*-isobutyl thiocarbamate by the aminolysis with amines. The optimal conditions for the synthesis of *N*-ethyl-*O*-isobutyl thiocarbamate and *N*-ethyl-*O*-ethyl thiocarbamate were obtained by varying reaction time, molar ratio of reactants, and reaction temperature (Methods A, B, and C). The results of optimization are given in Table 1. Thereafter, the syntheses of *N*-alkyl-, *N*,*N*-dialkyl, and *N*-cycloalkyl-*O*-isobutyl thiocarbamates and *N*-alkyl-*O*-ethyl thiocarbamate were performed according to the, established optimized laboratory procedure. The obtained products were characterized by FTIR, ^{1}H, and ^{13}C NMR data, given in Tables S1–S4. Purity was determined by gas chromatographic method and confirmed by determination of elemental analysis of compounds. The results of these analyses are given in Tables S2 and S4.

Table 1. Optimization of synthesis of *N*-ethyl-*O*-isobutyl and *N*-ethyl-*O*-ethyl thiocarbamate.

Method		Reaction Conditions			GC %	Yield [d] %
		Time [c] h	Temperature [d] °C	Mols ratio/mol [b] iBuOH/KOH/CS_2/Cl_2/ $EtNH_2$:KOH		
iBuOC(S)NHEt	A	1.5/1.5/3.0–4.0/1.5	75–80/35–40/40–45/30–35	0.2/0.2/0.2/0.21/0.4:0.0	98.5	81.2
	B [e]	1.5/1.5/3.0–4.0/2.0	75–80/35–40/40–45/30–35	0.2/0.2/0.2/0.21/0.2:0.2	99.2	80.0
	C [f]	1.5/1.5/3.0–4.0/1.5	75–80/35–40/40–45/20–25	0.2/0.2/0.2/0.21/0.4:0.0	98.9	82.5
EtOC(S)NHEt	A	1.5/1.5/3.0–4.0/1.5	75–80/35–40/40–45/30–35	0.2/0.2/0.2/0.21/0.4:0.0	98.7	82.5
	B [e]	1.5/1.5/3.0–4.0/2.0	75–80/35–40/40–45/30–35	0.2/0.2/0.2/0.21/0.2:0.2	99.4	81.0
	C [f]	1.5/1.5/3.0–4.0/1.5	75–80/35–40/40–45/20–25	0.2/0.2/0.2/0.21/0.4:0.0	98.8	84.5

[a] The synthesis reaction takes place in xylene; [b] the molar ratio $EtNH_2$: KOH refers to aminolysis in the last phase of the synthesis reaction; [c] the first phase of the reaction time/the second phase of reaction time/the third phase of reaction time/the fourth phase of reaction time; [d] the first phase of reaction temperature/the second phase of reaction temperature/the third phase of reaction temperature/the fourth phase of reaction temperature; [e] the synthesis reaction takes place in xylene:water; [f] the synthesis reaction (aminolysis) takes place in a mixture of methylene chloride and water.

2.2.1. Optimal Laboratory Procedure for the Synthesis of *N*-Ethyl-*O*-Isobutyl Thiocarbamate (iBuOC(= S)NHEt) (Method A)

Into a 500-$cm^{3,}$ three-necked flask equipped with a reflux condenser, dropping funnel, thermometer, magnetic stirrer, calcium hydroxide and ammonium hydroxide exhaust gas washing bottle, and water vacuum pump to provide low vacuum, 11.4 g (0.20 mol) of 98.0% potassium hydroxide and 3.0 cm^3 of water were added. The heating was switched on and the potassium hydroxide was dissolved. Then, using a dropping funnel, a mixture of 18.8 g (0.21 mol) of 98.0% isobutanol and 250 cm^3 of xylene was added, with stirring and heating the reaction mixture to 75 to 80 °C for 1.5 h. The reaction mixture became silvery-white in color and quite viscous, so intensive mixing was necessary. After 1.5 h, the reaction mixture was cooled to 30 °C, and 12.3 cm^3 (0.21 mol) of 98.0% carbon disulfide was added dropwise for 1.5 h while maintaining the temperature of the reaction mixture between 35 and 40 °C. Obtained *O*-isobutyl xanthate was suspended in xylene. After that, 15 g (0.21 mol) of chlorine gas was bubbled into the reaction mixture over a period of 3 to 4 h at 40 to 45 °C, resulting in a suspension (due to formation of free sulphur). After the completion of chlorination, *O*-isobutyl chlorothioformate dissolved in xylene was obtained, and sulfur particles were suspended in the reaction mixture. When the formation of sulfur stopped, 32.02cm^3 (0.4 mol) of 70% ethyl amine was added dropwise while maintaining temperature between 30 to 35 °C for 1.5 h. After cooling, the reaction mixture was filtered and washed twice with hydrochloric acid (1:1) to the neutral reaction. Xylene was removed by distillation and reused for new reaction of synthesis. The product, *O*-isobutyl-*N*-ethyl

thiocarbamate, was purified using vacuum distillation and collected in a temperature interval of 119–124 °C (20 mmHg). The yield of product was 81.2% and purity, determined by GC chromatography, was 98.5%.

2.2.2. An Optimal Laboratory Procedure for the Synthesis of *N*-Ethyl-*O*-Ethyl Thiocarbamate (EtOC(= S)NHEt) (Method A)

An analogous experiment was performed in a synthesis of *N*-ethyl-*O*-ethyl thiocarbamate. The yield of product was 82.5% and purity, determined by GC chromatography, was 98.7%.

2.2.3. Optimal Laboratory Procedure for the Synthesis of *N*-Ethyl-*O*-Isobutyl Thiocarbamates (Method B)

Into a 500-$cm^{3,}$ three-necked flask equipped with a reflux condenser, dropping funnel, thermometer, magnetic stirrer, calcium hydroxide and ammonium hydroxide exhaust gas washing bottle, and water vacuum pump to provide low vacuum, 11.4 g (0.20 mol) of 98.0% potassium hydroxide and 3.0 cm^3 of water were added. The heating was switched on, which led to the dissolution of potassium hydroxide. Then, using a dropping funnel, a mixture of 18.8 g (0.21 mol) of 98.0% isobutanol and 250 cm^3 of xylene was added, with stirring and heating the reaction mixture from 75 to 80 °C for 1.5 h. The reaction mixture became silvery-white in color and quite viscous, so intensive mixing necessary. After 1.5 h, the reaction mixture was cooled to 30 °C, and 12.3 cm^3 (0.21 mol) of 98.0% carbon disulfide was added dropwise for 1.5 h while maintaining the temperature of the reaction mixture between 35 and 40 °C. Obtained isobutyl xanthate was suspended in xylene. After that, 40.0 cm^3 of water was added to the reaction mixture, resulting in dissolving the obtained isobutyl xanthate. After that, 15 g (0.21 mol) of chlorine gas was bubbled into the reaction mixture over a period of 3 to 4 h at 40 to 45 °C, resulting in suspension (due to the formation of free sulfur). After the chlorination was completed, *O*-isobutyl chlorothioformate dissolved in xylene was obtained, and sulfur particles were suspended in the reaction mixture. Then, 22.8 g (0.20 mol) of 49.0% potassium hydroxide solution and 16.01 cm^3 (0.2 mol) of 70.0% ethyl amine were added dropwise to the reaction mixture for 2.0 h while maintaining the temperature of the reaction mixture between 30 and 35 °C. After cooling, the reaction mixture was filtered. The sulfur was separated as a filtration cake, and the filtrate was transferred to a separatory funnel. The organic phase was separated from the aqueous portion and washed with hydrochloric acid (1: 1) until pH 7. The xylene was distilled under vacuum, using a water vacuum pump, and used for a new synthesis. The product was distilled under vacuum and collected at temperature intervals of 120–123 °C (20 mmHg). The yield of product was 80.0% and purity, determined using GC chromatography, was 99.2%.

2.2.4. An Optimal Laboratory Procedure for the Synthesis of *N*-Ethyl-*O*-Ethyl Thiocarbamate (Method B)

An analogous experiment was performed in a synthesis of *N*-ethyl-*O*-ethyl thiocarbamate. The yield of product was 81.0% and purity, determined by GC chromatography, was 99.4%.

2.2.5. Optimal Laboratory Procedure for the Synthesis of *N*-Ethyl-*O*-Isobutyl Thiocarbamate (Method C)

Into a 500-$cm^{3,}$ three-necked flask equipped with a reflux condenser, dropping funnel, thermometer, magnetic stirrer, calcium hydroxide and ammonium hydroxide exhaust gas washing bottle, and water vacuum pump to provide low vacuum, 11.4 g (0.20 mol) of 98.0% potassium hydroxide and 3.0 cm^3 of water were added. The heating was switched on, which led to the dissolution of potassium hydroxide. Then, using a dropping funnel, a mixture of 18.8 g (0.21 mol) of 98.0% isobutanol and 250 cm^3 of xylene was added, with stirring and heating the reaction mixture from 75 to 80 °C for 1.5 h. The reaction mixture became silvery-white in color and quite viscous, so intensive mixing necessary. After 1.5 h, the reaction mixture was cooled to 30 °C, and 12.3 cm^3 (0.2 mol) of 98.0% carbon disulfide was added dropwise for 1.5 while maintaining the temperature of the reaction mixture at

35 to 40 °C to give isobutyl xanthate, suspended in xylene. After that, 40.0 cm^3 of water was added to the reaction mixture, and the obtained xanthate was dissolved. The reaction mixture was transferred to a separatory funnel. The lower, aqueous portion of the xanthate solution was separated from the upper portion of the xylene. Xylene was reused for the next synthesis. After that, 15 g (0.21 mol) of chlorine gas were bubbled into the aqueous xanthate solution over a period of 3 to 4 h at 40 to 45 °C, resulting in suspension (due to formation of free sulfur). After the chlorination was completed, *O*-isobutyl chlorothioformate was obtained as a suspension with sulfur particles. Then, 250 cm^3 of dichloromethane was added to the reaction mixture, followed by dropwise addition of 32.02 cm^3 (0.4 mol) of 70.0% ethyl amine over 1.5 h while maintaining the reaction mixture temperature between 20 and 25 °C. After completion, the reaction mixture was filtered and the dichloromethane layer was washed with hydrochloric acid (1:1) to the neutral reaction and subsequently with 3000 cm^3 of water and dried over sodium sulfate. The xylene was distilled under vacuum, using a water vacuum pump, and used for a new synthesis. The product was distilled under vacuum and collected at temperature intervals of 119–123 °C (20 mmHg). The yield of product was 82.5% and purity, determined using GC chromatography, was 98.9%.

2.2.6. An Optimal Laboratory Procedure for the Synthesis of *N*-Ethyl-*O*-Ethyl Thiocarbamate (Method C)

An analogous experiment was performed in a synthesis of *N*-ethyl-*O*-ethyl thiocarbamate. The yield of product was 84.5% and purity, determined by GC chromatography, was 98.8%.

2.2.7. Laboratory Procedure for the Synthesis of *N*-Ethyl-*O*-Isobutyl Thiocarbamates Using a Recycled Xylene

Analogously to the synthesis described in Experimental Section 2.3, the *N*-ethyl-*O*-isobutyl thiocarbamates were prepared using recycled xylene. Namely, in experiment 2.3, product isolation performed by distillation of the xylene opens the possibility to study its use as medium for new thiocarbamate synthesis. The analogous reaction condition was defined except for molar ratio of reactants in the initial stage of xanthate formation. Namely, a 5% higher amount of KOH (0.21 mol) was used, compared to experiment 2.3, while the amounts of isobutanol and carbon disulfide remained the same (0.21 mol). Additionally, what should be pointed out is the small loss of xylene in the course of recycling (~2%). After product isolation and purification, the obtained yield was 83.0% and the purity (GC) was 99.0%. A slightly higher yield was obtained, compared to the one obtained in experiment 2.3, probably due to the small quantity of dissolved isobutanol (~1.5%) and carbon disulfide (~3%) in recycled xylene, determined using GC, which reacted with the added excess of KOH.

2.3. Laboratory Method for Defining the Reaction Mechanism of the Described Method for the Synthesis of O-Isobutyl Thiocarbamate

The proposed reaction mechanism was studied by isolation and identification of reaction intermediates, using FTIR, ^1H and ^{13}C NMR, and GC MS/MS spectroscopic methods. After the single-reaction step, the sample was taken, filtrated, dried at temperature from 50 to 60 °C, and analyzed in order to confirm that potassium alkyl xanthate and diethyl/dibutyl dixanthate were obtained as intermediates during the reaction. After the reaction was completed, the crude product was distilled under vacuum (20 mmHg) and analyzed. The results of the analysis are presented in Tables S1–S4.

2.4. Structural Instrumental Analysis

NMR spectroscopy was performed on a Bruker Avance III 500 spectrometer (Bruker (UK) Ltd., London, UK) equipped with a broad-band direct probe. The spectra were recorded at room temperature in deuterated chloroform ($CDCl_3$). Chemical shifts are expressed in ppm (δ) values relative to TMS (tetramethylsilane) in ^1H NMR spectra and residual solvent signal in ^{13}C NMR spectra.

EI (electron impact) mass spectra were recorded on a Thermo Finnigan Polaris Q ion trap mass spectrometer (Termo Finnigan, Austin, TX, USA), which included a Trace GC 2000 (ThermoFinnigan, Austin, TX, USA) and integrated GC-MS/MS system (Thermo Finnigan Austin, TX, USA). The DIP (direct insertion probe) mode was used to carry the samples to the column. Ionization conditions were ion source temperatures, 200 °C; maximum electron excitation energy, 70 eV; and current, 150 μA.

FTIR spectra were recorded in transmission mode on a BOMEM instrument (Hartmann & Braun, Frankfurt, Germany).

Elemental analysis was performed on a VARIO EL III Elemental analyzer (Elementar Analysensysteme GmbH, Langenselbold, Germany), and the obtained analysis results were in good agreement with the calculated values (±0.3%).

Gas chromatographic analysis was performed on a Perkin-Elmer 8700 apparatus (Perkin-Elmer, Waltham, MA, USA), equipped with a flame-ionizing detector and a filled column with 5% OV−210 on Gas-Chrom Q: length 2 m and diameter 0.3175 cm (1/8″).

Conditions for performing gas chromatographic analysis were:

- Injector temperature, 250 °C;
- Detector temperature, 270 °C;
- Column temperature program mode, 50 °C (5 min) → 10 °C/min → 130 °C (15 min);
- Carrier gas, nitrogen (purity 99.99%), flow of 1 cm^3/min;
- Air flow, 250 cm^3/min (purity 99.99%); and
- Hydrogen flow, 25 cm^3/min (purity 99.99%).

3. Results

3.1. Synthesis of Thiocarbamates

This work represents the continuation of our research on thiocarbamate synthesis [44,45,50,52]. The aim was to develop a new method applicable at the industrial scale, taking into account green technology principles. Namely, this paper describes the original process for the synthesis of thiocarbamate starting from xanthate, obtained in the first phase of the reaction. Hence, the phase of xanthate isolation was omitted, which is favorable for the implementation at the industrial scale and makes significant energy savings (drying of the final product and packaging). In addition, in the described process of thiocarbamate synthesis, the obtained xanthate/dixanthate was not also separated from the reaction mixture, but chlorinated and converted to chlorothioformates, which thioacylate the amine at final step giving thiocarbamate. Accordingly, the synthesis reaction takes place in one batch with recycling of the reaction medium.

The known process for the synthesis of alkyl chlorothioformate, carried out starting from potassium alkoxide and thiophosgene ($CSCl_2$) in a suitable alcohol as a reaction medium or tetrahydrofuran, at a temperature of −65 °C for a period of 1 h, was described [54]. If this reaction is performed in tetrahydrofuran (THF) or alcohol (ROH) as a solvent, it gives 81–91% alkyl chlorothioformate (ROC(=S)Cl,) where R is ethyl (Et), propyl (Pr), isopropyl (iPr), butyl (Bu), and isobutyl (iBu). In this synthesis reaction, a significant amount of byproduct *O*,*O*-dialkyl carbonothioate can be formed in the reaction of obtained alkyl chlorothioformate with unreacted alkoxide (Figure 2).

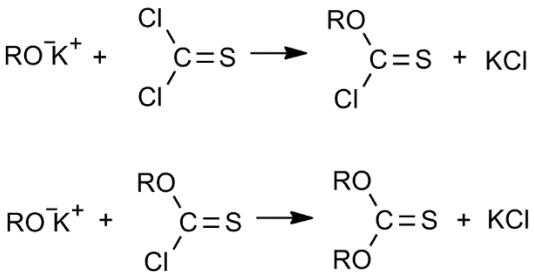


Figure 2. Reaction of thiophosgene with potassium alkoxide.

Furthermore, if the synthesis of alkyl thiocarbamate was performed starting from amine and alkyl chlorothioformate, obtained from thiophosgene and alcohol, the yields were very small. Namely, if the synthesis of methyl or ethyl chlorothioformate took place from thiophosgene and the corresponding alcohol, very low yields were obtained due to the decomposition of the resulting product into carbonyl sulfide (carbon thioxide) and alkyl chloride. Thermal decomposition of alkyl thioformates was particularly pronounced with n-butyl thioformate at an elevated temperature of 150 °C [53].

Additionally, a process for the alkyl chlorothioformates' synthesis was followed by separation and product purification [55] and subsequent use as alkoxy thiocarbonylating agents in thiocarbamate syntheses. The procedure took place by the reaction of xanthates (**1**, Figure 3) and Vilsmeier reagent (**2**, Figure 3), and the overall mechanism is a rather complex process with possible byproducts' formation.

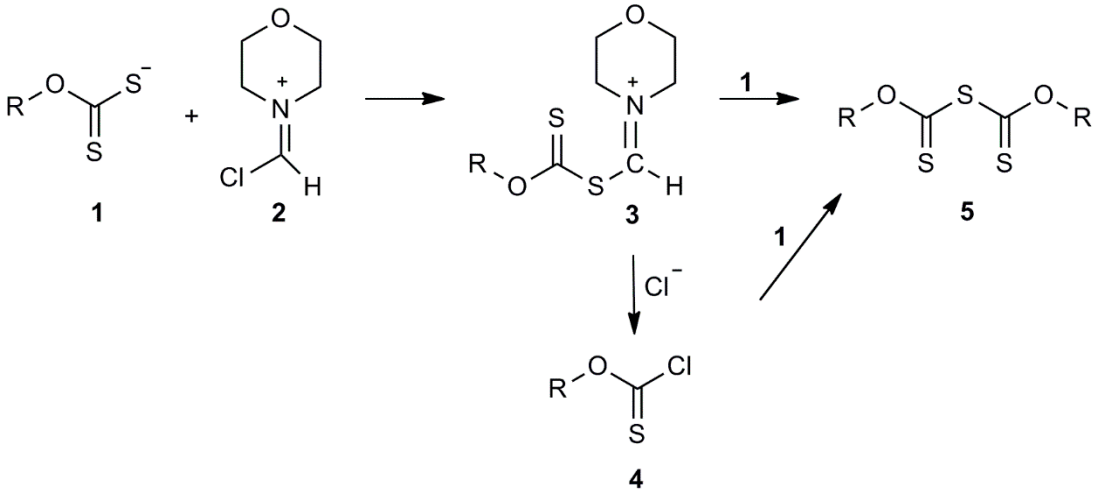


Figure 3. Alkyl chlorothioformate synthesis by reaction of alkyl xanthates and Vilsmeier reagent.

As can be seen from the reaction scheme shown in Figure 3, the resulting product, alkyl chlorothioformate **4**, can react with the unreacted xanthate **1** producing *O*,*O*-dialkyl thiodicarbonate **5**. The participation of the side reaction resulted in a significantly lower yield of the desired product. Except as stated, alkyl chlorothioformates are unstable compounds and easily decompose, especially at elevated temperatures [53]. This fact is important for consideration of the condition that has to be applied for its use as a reactant in alkoxy thiocarbonylation reactions.

Thus, the synthesis of alkyl thiocarbamates by aminolysis of *O*-alkyl chlorothioformates, obtained by the described procedures, is a rather complex process and not applicable at the industrial scale. The yield of alkyl thiocarbamates was small, due to the lower yield of alkyl chlorothioformate, as well as significant participation of a side reaction. In addition, the formed byproducts interfered with isolation of the desired product, i.e., alkyl chlorothioformate.

Another example of the synthesis of alkyl thiocarbamates by thioformylation of various amines using *O*-ethyl chlorothioformates has been described in the literature. *O*-ethyl thioformate was synthesized from triethyl orthoformate and hydrogen sulfide gas using sulfuric acid as Bronsted acid catalyst [56]. Except expensive chemicals, this process requires equipment with good sealing, generation, and manipulation with hydrogen sulfide as well as effluent gas treatment.

The main idea of this work was to design a new process according to the literature findings and observed deficiencies of the presented literature method. Development of the process without isolation of the obtained alkyl chlorothioformate and subsequent aminolysis provides a thiocarbamate product in one step. The idea to run the reaction continuously came from the fact that alkyl chlorothioformates are unstable and prone

to decomposition, especially at elevated temperatures [53]. It is important when they represent the starting material in the process of thiocarbamate production. Alkyl xanthate, formed in the reaction of isobutanol, potassium hydroxide, and carbon disulfide in xylene, was subjected to chlorine gas, giving alkyl chlorothioformates. The addition of amine to the reaction mixture produced alkyl thiocarbamate dissolved in xylene. The product was isolated by vacuum distillation, and xylene was recycled in the next synthesis reaction.

Thus, this study describes the developed method for the synthesis of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate, starting from isobutyl alcohol, potassium hydroxide, and carbon disulfide. In the first step, potassium isobutyl xanthate, in the form of a suspension in xylene, was obtained (Figure 3). Then, water was added to the reaction mixture to dissolve the resulting xanthate to obtain 50% solution. Next, chlorine was introduced into the reaction mixture, which oxidized the xanthate to the *O*-isobutyl dixanthate, a water-insoluble material that formed the suspension. Further, introduction of chlorine produced isobutyl xanthogenic acid chloride (isobutyl chlorothioformate), with the release of colloidal sulfur. The separated sulfur was suspended in the reaction mixture, and the resulting isobutyl chlorothioformate was dissolved in xylene. Thereafter, an amine was added and gave the product *O*-isobutyl thiocarbamate, also dissolved in xylene. After the synthesis was completed, the reaction mixture was filtered. The sulfur was separated as a filtration cake, and the filtrate was transferred to a funnel to separate the upper xylene solution, which contained *O*-alkyl thiocarbamate product. The xylene solution was dried over anhydrous sodium sulfate and distilled, yielding the isobutyl thiocarbamate. The reactions' scheme is presented in Figure 4.

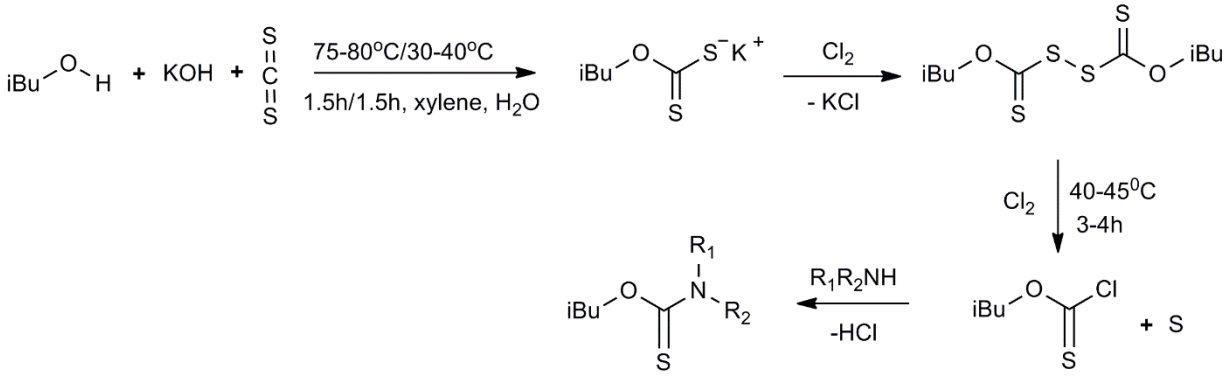


Figure 4. Chemistry of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate synthesis.

The synthesis of thiocarbamates, presented in this paper, is a one-pot synthesis that takes place through four subsequent steps (Figure 4). The first reaction step included the synthesis of potassium alkyl xanthate, starting from an alcohol, carbon disulfide, and potassium hydroxide. Introduction of chlorine gas, as an oxidizing agent, exerted dixanthates' formation by oxidation of xanthates, i.e., formation of a persulfide bond. A similar reaction of dixanthate synthesis, performed by xanthates' oxidation with iodine, has been described [2]. In the third phase, the continual introduction of chlorine performed heterolysis of a persulphide dixanthate bond by forming *O*-isobutyl chloroformate. In the fourth step, the amine reacted with the *O*-isobutyl chloroformate, producing thiocarbamate.

During the synthesis of alkyl thiocarbamate, a side reaction occurred, giving an undesirable product such as isobutyl xanthogenic acid anhydride (Figure 5). Further introduction of chlorine gas led to the formation of sulphene chloride [57] and *O*-isobutyl chlorothioformate. Decomposition of sulphene chloride to *O*-isobutyl chlorothioformate and sulfur provided thioacylating species. In this way, the reaction was almost quantitative, producing *O*-isobutyl chlorothioformate as a result of a stepwise process through side reactions, which provided reactivity regeneration.

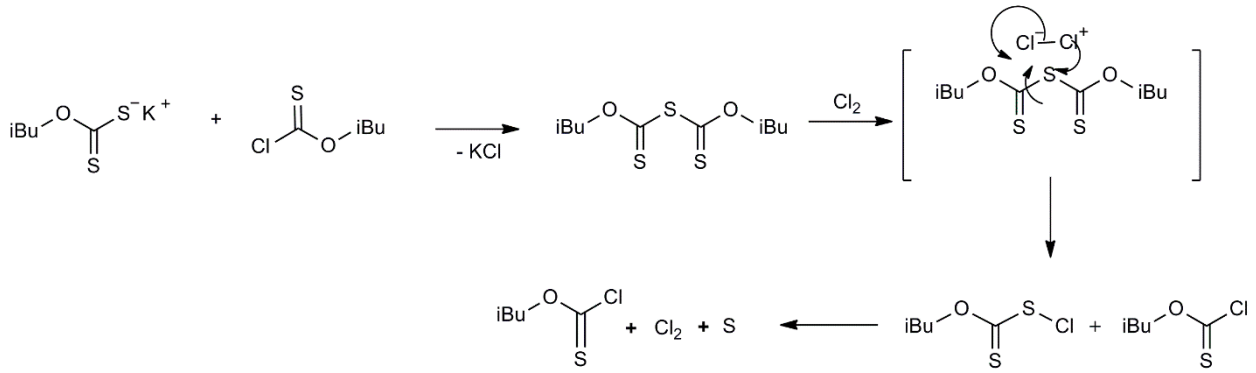


Figure 5. Side reaction mechanism in the course of alkyl thiocarbamate synthesis.

In the first step, loss of the reactivity of alkyl chloroformates was recovered by continual introduction of chlorine, which caused sequential transformation of isobutyl xanthogenic acid anhydride to reactive thioacylating agent. In this way, a negative effect of side reactions was compensated with almost quantitative transformation to alkyl chlorothioformate.

In general, the developed procedure was one-pot synthesis of thiocarbamate without *O*-alkyl chlorothioformate isolation. The simplicity of the developed process offers highly applicative technology, which was further applied at the industrial scale.

Moreover, the mechanism of this reaction was confirmed by isolation of intermediates *O*,*O*-diisobutyl dixanthate and *O*,*O*-diethyl dixanthate. The structure of the isolated intermediate was confirmed by IR and NMR MS instrumental methods (Tables S3 and S4).

Another side reaction could participate in an overall process, such as the one presented in Figure 2, but to a very small extent. If uncreated alkoxide **1** remained in the reaction mixture after the first phase, it could react with the *O*-isobutyl chlorothioformate **2**, and *O*,*O*-diisobutyl carbonothioate **3** would be formed (Figure 6)**.**

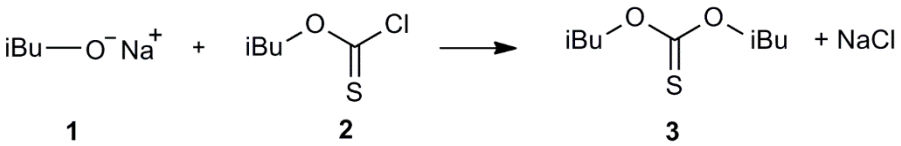


Figure 6. Reaction of alkyl alkoxides and *O*-isobutyl chlorothioformates.

The optimization experiments for the *N*-ethyl-*O*-isobutyl thiocarbamate synthesis are described as Methods A, B, and C. The same optimization experiments were also applied in a synthesis of *N*-ethyl-*O*-ethyl thiocarbamate. The obtained results of the optimized syntheses' procedures are presented in Table 1.

Based on the results shown in Table 1, it can be concluded that the highest yields were achieved using Method C. The yield of *N*-ethyl-*O*-isobutyl thiocarbamate was 82.5%, with the purity of 98.9%, and the yield of *N*-ethyl-*O*-ethyl thiocarbamate 84.5% with the purity of 98.8%. According to this method, the aminolysis reaction took place in methylene chloride after separation of xylene and sulfur from an aqueous solution of xanthates. In the synthesis described by Method A, the amount of amine was doubled. Satisfactory yield and purity were also achieved in Method A experiments (81.2; 98.5). In both the described processes, regeneration of ethyl amine was necessary, while in Method B, KOH was used to neutralize the separated HCl. In this reaction, a slightly lower yield of 80.0% was achieved, but the product was of the highest degree of purity (99.2%). Because there was no amine regeneration or use of methylene chloride, Method A was greatly simplified and the most favored for use at the industrial scale.

The experimental part describes an optimized laboratory procedure for the synthesis of *N*-ethyl-*O*-isobutyl thiocarbamate, and the synthesis of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate was performed analogously. The yields and purity

of the synthesized thiocarbamates, obtained according to optimal synthesis conditions using Methods A, B and C, are shown in Table 2.

Table 2. Results of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate synthesis.

R_1	R_2	Boiling Point [b]/°C				GC Analysis			Yield [c]/%		
		Method [a]			Lit.	Method [a]					
		A	B	C	[50]	A	B	C	A	B	C
Et	H	114–124	120–123	119–123	120–122	98.5	99.2	98.9	81.2	80.0	82.5
Pr	H	129–131	128–131	128–129	130–132	98.4	98.6	98.9	81.8	80.8	83.0
Bu	H	139–140	138–140	139–142	140–142	99.0	98.9	99.1	81.5	80.5	82.6
iPr	H	127–129	127–130	127–130	128–130	98.7	98.7	98.8	80.9	71.8	81.5
iBu	H	147–149	147–149	147–149	148–150	98.7	98.6	98.8	82.0	81.8	82.7
iPe	H	190–192	190–192	191–193	192–193	98.7	98.7	98.8	82.8	81.9	83.4
sBu	H	136–138	136–138	137–139	137–139	98.6	98.4	98.8	81.4	80.4	82.3
cycPr	H	133–136	133–136	134–137	134–136	98.6	98.6	98.8	78.9	77.0	79.3
cycPe	H	178–180	178–181	179–181	180–182	98.7	98.7	98.8	80.6	80.0	82.1
cycHe	H	177–179	177–180	178–180	179–180	99.0	98.9	99.2	81.4	81.0	82.8
Et	Et	142–145	143–145	144–147	144–146	98.7	98.9	99.1	82.4	81.9	83.0
Pr	Pr	176–178	176–179	178–180	178–179	99.1	99.0	99.2	83.3	82.5	83.9
Bu	Bu	190–192	190–192	191–193	192–194	99.2	99.0	99.3	83.6	83.0	83.8

[a] Reaction conditions: mol ratio, time of reaction, reaction temperature (presented in table are equal for all reactions). [b] Boiling point in vacuum of 20 mmHg. [c] Isolated yield.

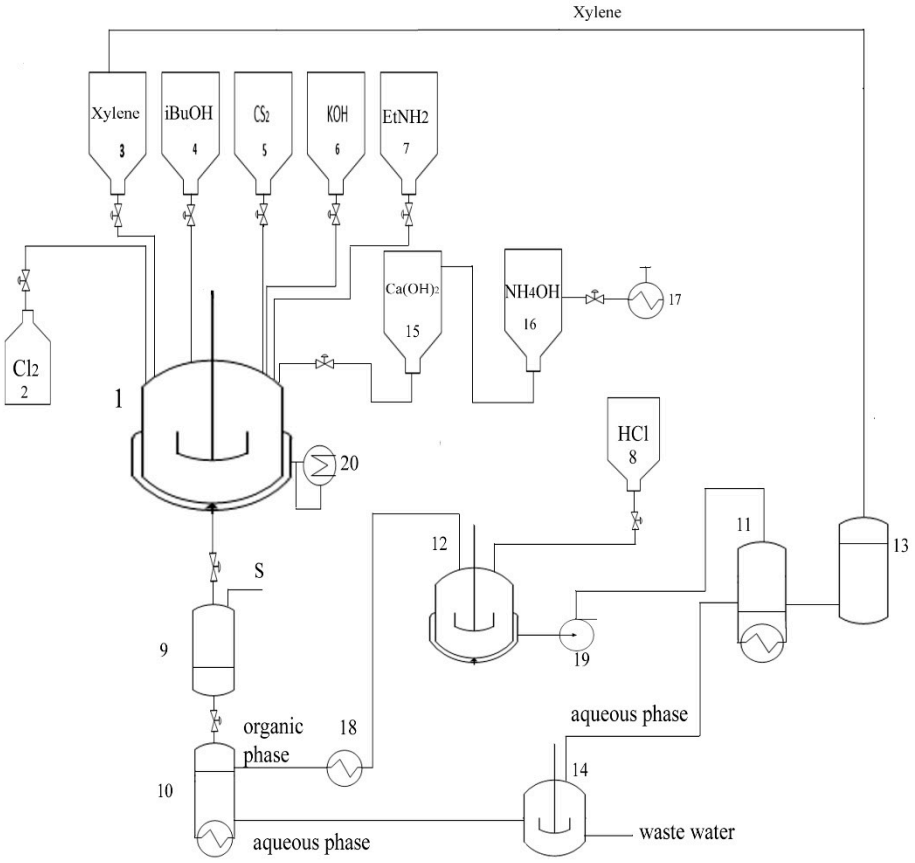
Based on the results presented in Table 2, it can be concluded that the application of these methods provided satisfactory yields and purity of the product. Comparing the described methods, it was concluded that the highest yields, of all products, were achieved according to Method C. The lower degree of conversions in Methods A and B probably was a consequence of side reactions and formed byproducts. Additionally, an increased yield of *N*-isoalkyl-*O*-isobutyl thiocarbamate was observed due to the distant position of the branching carbon with respect to nitrogen in the used amine. The yields obtained in method C in the synthesis of *N*-isopropyl, *N*-isobutyl, and *N*-isopentyl-*O*-isobutyl thiocarbamate were 81.5%, 82.7%, and 83.4%, respectively. It was evident that the steric interference of the alkyl groups to the nucleophilic center of the amine decreased with the increasing length of the aliphatic chain between the amino and carbon branching center. Furthermore, based on the results shown in Table 2, in the aminolysis, the yield of cyclic amines decreased from cyclohexyl to cyclopropylamine. The yield of the product obtained using cyclohexyl amine (82.8%) was negligibly higher than the yield of the products obtained using cyclopentyl (82.1%) and cyclopropyl (79.3%) amine. Such results indicated that the steric effects, of different conformational forms of cyclic amines, were the smallest in cyclohexylamine due to the equatorial position of the amino group. In addition, it was observed that higher yields were achieved in the reactions of secondary amines. The highest yield, of 83.9%, was achieved in the synthesis of *N*, *N*-dipropyl-*O*-isobutyl thiocarbamate.

As can be seen in Table 2, the Method B resulted in slightly lower yields of thiocarbamate with the sufficient purity; however, due to amine regeneration, Methods A and C were unsuitable to apply at the semi-industrial scale. The first phase, synthesis of xanthates, limited the final conversion rate. In the present paper, the yields of xanthate were about 87–88% [52].

Data from MS, FTIR, ^{1}H, and ^{13}C NMR spectra of the synthesized alkyl chlorothioformates are presented in Tables S1 and S2. Based on the presented data, the structure of the synthesized compounds was clearly confirmed. The results obtained in the experimental part of the work indicated high applicability of the optimal synthesis' procedure at the industrial level of production.

3.2. Semi-Industrial Synthesis

Based on the results of laboratory tests for the synthesis of *N*-alkyl, *N*,*N*-dialkyl, and *N*-cycloalkyl-*O*-isobutyl thiocarbamates, a semi-industrial synthesis of *N*-ethyl-*O*-isobutyl thiocarbamates was performed according to the technological scheme shown in Figure 7.



1. Reactor	7. Amine dozer	13. Distiller	19. Pump
2. Clorine dozer	8. HCl dozer	14. Neutralizer	20. Heater
3. Xylene dozer	9. Filter	15. $Ca(OH)_2$ washing bottle	21. Cooler
4. iBuOH dozer	10. Separator	16. NH_4OH washing bottle	
5. CS2 dozer	11. Separator	17. Pump	
6. KOH dozer	12. Neutralizer	18. Pump	

Figure 7. Proposed schematic presentation of the technological process of *N*-alkyl, *N*,*N*-dialkyl, and *N*-cikloalkyl-*O*-isobuthyl thiocarbamate.

The amounts of 60.0 kg (1.1 kmol) of 98% potassium hydroxide and 15 L of water were added to the 5-m^3 reactor (1). The heating started and the temperature of the reaction mixture was maintained at 65 °C. After that, stirring was switched on, and, simultaneously, 101.6 L (1.1 kmol) of isobutyl alcohol from the dispenser (4) and 3.25 m^3 of xylene from the dispenser (3) were added to the reactor. The reaction mixture was stirred while maintaining the temperature at 60 °C for 1.5 h. Thereafter, the reaction mixture was cooled to about 35 °C, and 61.5 L (1.0 kmol) of carbon disulfide was added from the dispenser (5). The addition of carbon disulphide was carried out for 2.5 h while maintaining a constant temperature of 35 °C. Then, 134 L of water were added, the reaction mixture was stirred for 5 min, and the obtained potassium isobutyl xantate dissolved. The obtained product was analyzed for active content substance, i.e., concentration of aqueous solution of xanthate 50.1%, content of three thiocarbonate 1.3%, and sulfide 0.3%, yield 88%. After

that, 78.5 kg (1.1 kmol) of chlorine gas from the chlorine bottle were introduced (5) for 4 h while maintaining a temperature of 40–45 °C, which resulted in the formation of a suspension due to the separation of sulfur in the reaction mixture. Then, 114.3 kg (1.0 kmol) of 49.0% potassium hydroxide solution from the dispenser (6) and 83.0 L (1.0 kmol) of 70.0% ethyl-amine from the dispenser (7) were added to the reaction mixture (vacuum was off) while maintaining the temperature of the reaction mixture from 30 to 35 °C for 2.0 h. The reaction mixture was filtered by means of a filter device (9), the sulfur being separated as a filtration cake and the filtrate transferred to the separator (10). The organic phase was separated from the aqueous portion, transferred by pump (18) to a neutralization vessel (12), and neutralized with hydrochloric acid (1: 1) until neutral. The aqueous phase was transferred to the neutralization vessel (14) and, after neutralization, discharged into the wastewater. After neutralization, the mixture was transferred to the separator (11), the aqueous part was transferred to a neutralizer (14), and the organic part was transferred to a distillation column (13), where the xylene was removed by vacuum distillation under 20 mmHg and temperatures of 120–122 °C and re-used for a new synthesis reaction. GC purity was obtained at 99.1%, with an achieved yield of 80.3%.

In the industrial production factory of CI "Župa" Kruševac, a trial production of three batches was performed according to the procedure described above. The obtained products were analyzed for the content of active substance, i.e., concentration of aqueous xanthate solution, trithiocarbonate, and sulfide content. The results of the semi-industrial trial production of *N*-ethyl-*O*-butylthiocarbamate under industrial conditions are given in Table 3.

Table 3. The results of the semi-industrial synthesis of *N*-ethyl-*O*-isobutyl thiocarbamate.

EXAMPLE	Reactants [a]								Reaction Conditions		Byproducts	Product		
	KOH		iBuOH		CS_2		Amine		Time [b]	Temp [c]	Sulphur	Yield		GC
	kg	kmol	kg	kmol	kg	kmol	m^3	kmol	h	°C	kg	kg	%	%
1	60.0	1.1	81.2	1.1	77.5	1.0	0.83	1.0	1.5/1.5	75/35	28.5	128.9	80.1	99.2
2	60.0	1,1	81.2	1.1	85.2	1.1	0.83	1.0	1.5/1.5	80/35	29.0	132.3	82.2	98.9
3	54.5	1.0	73.8	1.0	85.2	1.1	1.66	2.0	1.5/2.0	80/35	29.1	132.8	82.5	99.1

[a] The same amount of chlorine gas 78.5 kg (1.1 kmol) was used in all industrial tests. [b] The time of chlorine introduction and amine dosing is constant for all three industrial tests and presents at 4.0 h and 1.5 h, while the time for the first two reaction phases is varied. [c] Reaction temperature of dosage of the chlorine and amine is constant for all three industrial tests and represents 40 to 45 °C and 30 to 35 °C, while for the first two phases of the reaction it is varied.

Based on the results shown in Table 3, it can be seen that products yields were in the range from 80.1 to 82.5%, and the obtained products had a high degree of purity. In Experiment 2, raw materials were used in 10% higher amounts except for amine, and the aminolysis reaction was favored in the presence of an equivalent amount of KOH alkali compared to the amount of amine. Potassium hydroxide added to the reaction mixture during aminolysis acted as a neutralizing agent for hydrochloric acid released in the reaction. In Experiment 3, an amount of 10% excess of carbon disulfide was used, and the aminolysis reaction took place in the presence of a doubled amount of amine, while one part of the amine was used for neutralizing the separated hydrochloric acid. This procedure was more complex than Experiment 2 because it required subsequent regeneration of the amine. In addition, the yields were slightly higher than the yields achieved in Experiment 2.

The described process for the synthesis of *N*-alkyl, *N*,*N*-dialkyl, and *N*-cycloalkyl-*O*-isobuthyl thiocarbamate can be presented by a summary reaction:

$$2KOH + iBuOH + CS_2 + Cl_2 + EtNH_2 = iBuOC(S)NH(Et) + 2KCl + S + 2H_2O$$

Based on the described optimized synthesis procedure, it can be revealed that no by-products, other than sulfur, were generated, which can be commercially valuable after separation from the reaction medium and purification. Wastewater, generated in the synthesis process, does not contain potential pollutants having high ecological impact; thus,

existing treatment technology in the Chemical industry (CI) "Župa" Kruševac produces an effluent water in accordance with the Official Gazette of the Republic of Serbia. In that sense, the green technology aspects were completely assessed and a developed technological process for *N*-alkyl, *N*,*N*-dialky, and *N*-cycloalkyl-*O*-isobuthyl thiocarbamate synthesis is acceptable for the industrial level of production.

3.3. Confirmation of the Reaction Mechanism and Formation of the Intermediates

The assumed mechanism of the studied reaction (Figure 3) was confirmed by isolation and structure determination of the intermediates and products from the synthesis of *N*-ethyl-*O*-isobutyl/ethyl thiocarbamate (Tables S1 and S2). Namely, the intermediate compounds were isolated at a predefined reaction time and their structure was determined using spectrometric techniques (FTIR, NMR, MS). The characterization results of the isolated intermediates are given in Tables S3 and S4. In the first step of the reaction, potassium ethyl/isobutyl xanthate was formed, and, after, in the second, dialkyl dixanthate was obtained as intermediate during the reaction, according to proposed mechanism in Figure 4. The oxidation of alkyl xanthate by the chlorine produced dialkyl dixanthate, which, after isolation and structural characterization, gave crucial evidence for the reaction mechanism. The presence of the sulphur as a product of decomposition of sulphenamide in the reaction mixture after the filtration was nearly equal to the stoichiometric amount calculated yield according to the presented reaction mechanism. Based on the identification of the isolated compounds, the assumed mechanism of the reaction was proved.

3.4. Application of The Obtained N-Ethyl-O-Isobutyl Thiocarbamate at the Laboratory Level of Flotation of Ore Samples

Flotation efficiency testing results on a real sample of copper sulfide minerals for synthesized *N*-ethyl-*O*-isobutyl thiocarbamate produced in the Chemical Industry "Župa" Kruševac by the optimized laboratory procedure presented in this manuscript are presented in Table 4. Flotation experiments with copper ores in laboratory conditions were performed in flotation machines "Denver" with volume V = 2.8 L, on samples weighing 1 kg, under identical test conditions (fineness of ground material, flotation time, pH value). The results are presented as the mean value of a series of three experiments performed in the same way. The ore sample (Elacite, Bulgaria; copper content in the ore, 1.8515%) was ground to under 65 mesh with about 60% solids. The pH value was adjusted to 8.8 by adding lime. After adding 8.0 g/ton of methyl isobutyl carbinol, 2.6 g/ton of water-soluble dialkyl dithiophosphate collector, and 5.2 g/ton of one of the fat collectors, the ore pulp was conditioned to 20% solid for 1 min in a flotation cell and results were obtained after flotation for 5 min. The following results represent a comparison of the efficiency of *N*-ethyl-*O*-isobutyl thiocarbamate with *N*-ethyl-*O*-ethyl thiocarbamate, *N*-ethyl-*O*-isopropyl thiocarbamate (standard promoter for this ore), potassium amyl xanthate (KAmX), and potassium isobutyl xanthate (KiBuX).

Table 4. Flotation results obtained using synthesized compound, *N*-alkyl-*O*-isobutyl thiocarbamate (Methods A, B, and C) sample of real ore (Elacite, Bulgaria) at the laboratory level (copper content in ore, 1.8515%; OKCu, basic flotation (first flotation step); KKCu, extended flotation (second flotation step); UKCu, total floating copper; residues, copper residue).

Components	OKCu [%Cu]	KKCu [%Cu]	UKCu [%Cu]	Tailing [%Cu]
iButOC(S)NHEt (method A)	68.12	23.55	91.67	8.33
iButOC(S)NHEt (method B)	68.11	23.96	92.07	7.93
iButOC(S)NHEt (method C)	68.25	24.89	93.14	6.86
EtOC(S)NHEt (method C)	67.10	23.00	90.10	9.90
iPrOC(S)NHEt	68.00	23.54	91.54	8.46
KiBuX	66.85	24.07	90.92	9.08
KAmX	66.02	23.96	89.98	10.02

The flotation process was based on changing the surface properties of the mineral so that the mineral of interest acquired hydrophobic properties. When air bubbles were introduced, hydrophobic minerals were attached to the bubbles, carried out to the surface, and processed. The behavior of the mineral during foamy flotation was controlled by surface properties, which are a function of its chemistry, structure, and surface types resulting from reactions during processing. The nature of surface products resulting from the chemisorption of thiocarbamate is still in question.

Based on the results shown in Table 4, it can be seen that the highest flotation efficiency of copper was obtained using *N*-ethyl-*O*-isobutyl thiocarbamate obtained by Method C. Compared with the flotation efficiency of *N*-ethyl-*O*-isopropyl thiocarbamate, which was used as a standard promoter of this ore, *N*-ethyl-*O*-isobutyl thiocarbamate showed a better effect of copper concentration in ore flotation by 1.6%. This difference was significantly greater in experiments using obtained *N*-ethyl-*O*-ethyl thiocarbamate in this study, as with KAmX and KiBuX [52].

4. Conclusions

The laboratory procedure for the synthesis of *N*-alkyl-, *N*,*N*-dialkyl-, and *N*-cycloalkyl-*O*-isobutyl thiocarbamate was optimized in terms of synthesis parameters (reaction time, temperature, molar ratio of reactants, and solvent amount) and tested at a semi-industrial scale. The optimized reaction conditions for the procedure defined in this paper reduced the production of byproducts to a minimum. The structure of the synthesized compounds was confirmed by FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopy and MS spectrometry, and the purity was determined by GC analysis. Moreover, the proposed reaction mechanism was confirmed by isolation of intermediates and determination of their structures. Taking into account the importance of synthesized compounds as selective flotation reagents applying a new optimal process of their synthesis, significant improvements were achieved in terms of yield and purity of obtained compounds, simplicity of process, mild reaction conditions, high purity and product yield, short synthesis time, low environmental impact, and reducing amounts of byproducts. Due to the obtained advantages, the developed optimal technology is highly applicable at the industrial scale.

Flotation results obtained using synthesized *N*-ethyl-*O*-isobutyl thiocarbamate (Methods A, B, and C) on a real sample of copper ore minerals showed better effect of copper concentration in ore flotation by 1.6% compared to the standard *N*-ethyl-*O*-isopropyl thiocarbamate. Additionally, a higher concentration effect was achieved compared to the *N*-ethyl-*O*-ethyl thiocarbamate, potassium amyl xanthate, and potassium isobutyl xanthate.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/min11121346/s1, Figure S1: FTIR spectrum of *N*-ethyl-*O*-isobutyl thiocarbamate, Figure S2: FTIR spectrum of *N*-propyl-*O*-isobutyl thiocarbamate Figure S3: FTIR spectrum of *N*-butyl-*O*-isobutyl thiocarbamate, Figure S4: FTIR spectrum of *N*-sec butyl-*O*-isobutyl thiocarbamate, Figure S5: FTIR spectrum of *N*-isopropyl-*O*-isobutyl thiocarbamate, Figure S6: FTIR spectrum of *N*-isobutyl-*O*-

isobutyl thiocarbamate, Figure S7: FTIR spectrum of *N*-isopentyl-*O*-isobutyl thiocarbamate, Figure S8: FTIR spectrum of *N*-cyclopentyl-*O*-isobutyl thiocarbamate, Figure S9: FTIR spectrum of *N*-cyclohexyl-*O*-isobutyl thiocarbamate, Figure S10: FTIR spectrum of *N*,*N*-dipropyl-*O*-isobutyl thiocarbamate, Figure S11: FTIR spectrum of *N*-propyl-*O*-ethoxy thiocarbamate, Figure S12: FTIR spectrum of *N*,*N*-dipropyl-*O*-ethoxy thiocarbamate, Figure S13: ^{13}C NMR spectra of *N*-propyl-*O*-isobutyl thiocarbamate, Figure S14: ^{13}C NMR spectra *N*-sec butyl-*O*-isobutyl thiocarbamate, Figure S15: ^{13}C NMR spectra of *N*-isopropyl-*O*-isobutyl thiocarbamate, Figure S16: ^{13}C NMR spectra of *N*-isobutyl-*O*-isobutyl thiocarbamate, Figure S17: ^{13}C NMR spectra of *N*-isopentyl-*O*-isobutyl thiocarbamate, Figure S18: ^{13}C NMR spectra of *N*-cyclopentyl-*O*-isobutyl thiocarbamate, Figure S19: ^{13}C NMR spectra *N*-cyclohexyl-*O*-isobutyl thiocarbamate, Figure S20: ^{13}C NMR spectra of *N*,*N*-dipropyl-*O*-isobutyl thiocarbamate, Figure S21: ^{13}C NMR spectra of *N*,*N*-dibutyl-*O*-isobutyl thiocarbamate, Figure S22: ^{13}C NMR spectra of *N*,*N*-dipropyl-*O*-isobutyl thiocarbamate, Figure S23: GC-MS chromatogram for *N*-isobutyl-*O*-isobutyl thiocarbamate, Figure S24: GC-MS chromatogram for *N*-butyl-*O*-isobutyl thiocarbamate, Figure S25: GC chromatogram for *N*-ethyl-*O*-isobutyl thiocarbamate (method B), Figure S26: GC chromatogram for *N*-ethyl-*O*-isobutyl thiocarbamate (method A), Figure S27: GC chromatogram for *N*-ethyl-*O*-isobutyl thiocarbamate (method C), Table S1. ^{1}H and ^{13}C NMR data, and results of elemental analysis of synthesized *N*-alkyl, *N*,*N*-dialkyl and *N*-cycloalkyl-*O*-isobutyl thiocarbamates, Table S2: FTIR and MS data of *N*-alkyl, *N*,*N*-dialkyl and *N*-cycloalkyl-*O*-isobutyl thiocarbamate, Table S3: ^{1}H and ^{13}C NMR data, and results of elemental analysis of *O*,*O*-dialkyl dixanthates intermediates, Table S4: FTIR and MS data of *O*,*O*-dialkyl dixanthates intermediates.

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