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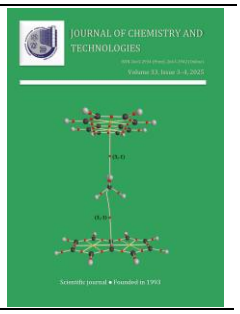

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SYNTHESIS OF *N,N′*-(((HYDRAZINE-1,2-DICARBONOTHIOYL)BIS(AZANEDIYL))BIS(2,2,2-TRICHLOROETHANE-1,1-DIYL))CARBOXAMIDES AND THEIR CYCLISATION INTO *N,N′*-(((1,3,4-THIADIAZOLE-2,5-DIYL)BIS(AZANEDIYL))BIS(2,2,2-TRICHLOROETHANE-1,1-DIYL))CARBOXAMIDES

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Abstract

1,3,4-Thiadiazole derivatives are widely used in science and technology as biologically active compounds, components of polymer and rubber compositions, dyes and varnishes, catalysts, as well as materials for microelectronics and nanotechnology. This work presents the synthesis of new bis-amidoalkylated derivatives of 2,5-diamino-1,3,4-thiadiazole. The preparation of these compounds is based on the reaction of oxidative dehydrosulfonation of *N,N′*-(((hydrazine-1,2-dicarbonothioyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))carboxamides using a mixture of iodine and triethylamine in DMF. The reaction was carried out at room temperature for two hours. This method yields target products in the range of 63–92 %. The advantage of the method is the absence of the need for expensive or hard-to-find reagents. NMR ^{1}H and ^{13}C spectroscopy confirmed the structure of the synthesized compounds. The ^{1}H NMR spectra of synthesized 1,3,4-thiadiazoles are distinguished by the presence of doublet signals corresponding to two NH protons observed in the 9.53–6.69 ppm range, along with a doublet of doublets assigned to the CH proton of the alkylamide fragment appearing at 6.77–6.69 ppm. The ^{13}C NMR spectra exhibit characteristic resonances of the C=O carbon at 168.8–164.7 ppm and the C=N carbon of the thiadiazole ring at 158.9–158.6 ppm. Furthermore, characteristics signals attributed to the CCl_3_ moiety and the CH carbon of the alkylamide fragment are observed at 101.5–101.2 and 70.0–69.4 ppm respectively.

Keywords: synthesis; 1,3,4-thiadiazole; oxidative dehydrosulfuration; dithiobiurea; carboxamide.

СИНТЕЗ *N,N′*-(((ГІДРАЗИН-1,2-ДІКАРБОНОТІОЇЛ)БІС(АЗАНДІЇЛ))БІС(2,2,2-ТРИХЛОРЕТАН-1,1-ДІЇЛ))КАРБОКСАМІДІВ ТА ЇХ ЦИКЛІЗАЦІЯ В *N,N′*-(((1,3,4-ТІАДІАЗОЛ-2,5-ДІЇЛ)БІС(АЗАНДІЇЛ))БІС(2,2,2-ТРИХЛОРЕТАН-1,1-ДІЇЛ))КАРБОКСАМІДІВ

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Анотація

Похідні 1,3,4-тіадіазолу знаходять широке застосування в науці та техніці як біологічно активні сполуки, компоненти полімерних та гумових композицій, барвників та лаків, каталізаторів, а також матеріали для мікроелектроніки та нанотехнологій. У цій роботі представлений синтез нових біс-амідоалкілованих похідних 2,5-діаміно-1,3,4-тіадіазолу. Одержання цих сполук засноване на реакції окиснювального дегідросульфування *N,N′*-(((гідразин-1,2-дикарбонотіоїл)біс(азандіїл))біс(2,2,2-трихлоретан-1,1-діїл))карбоксамідів із використанням суміші йоду та триетиламіну в ДМФА. Реакцію проводили за кімнатної температури протягом двох годин. Цей метод забезпечує вихід цільових продуктів у межах 63–92 %. Перевагою методу є відсутність потреби в дорогих або важкодоступних реагентах. Структура синтезованих сполук підтверджена за допомогою ЯМР ^{1}H і ^{13}C спектроскопії.

Ключові слова: синтез; 1,3,4-тіадіазол; окисне дегідросульфування; дитіобісечовини; карбоксамід.

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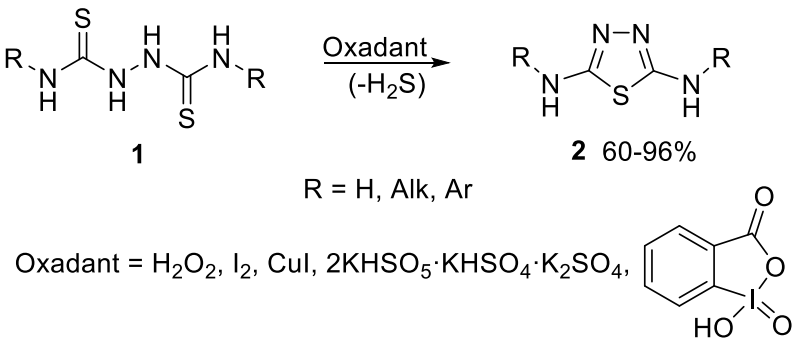
Introduction

Dithiobiureas and their derivatives attract the attention of researchers from various scientific fields due to their unique chemical, biological, and physical properties. They have found wide applications in organic synthesis, coordination, and medicinal chemistry. For organic synthesis, dithiobiureas are primarily of interest as multifunctional reagents. Due to the presence of the active –NHC(S)NHNHC(S)NH– group, these substances exhibit high reactivity, which makes them promising building blocks for the synthesis of complex organic molecules. They undergo elimination, substitution, and condensation reactions, forming a diverse range of heterocyclic compounds [1]. Additionally, dithiobiureas are effective ligands and are widely applied in coordination chemistry. They can coordinate with various metals, making these compounds promising for obtaining metal complexes with a specific set of properties [2–7]. Such complex compounds often exhibit high antimicrobial [5; 6] and antitumor activity [7], have anticorrosive properties [8; 9], and can be used as lubricant additives [10].

Dithiobiureas themselves also exhibit high biological activity. Among these compounds, effective antioxidants [11] and HIV-1 protease inhibitors [12] are known. In addition, these substances have a strong antifertility effect and can be used in veterinary medicine [13] and ichthyology [14], for example, the drug Metallibure.

Due to the presence of several reaction centers, dithiobiureas can be used to obtain a variety of heterocyclic compounds. One of the most characteristic reactions for these compounds is their oxidative desulfurization (ODS). This reaction is often used to obtain various derivatives of 2,5-diamino-1,3,4-thiadiazole [15] (Scheme 1). Hydrogen peroxide [16; 17], crystalline iodine [18], 2-iodoxybenzoic acid (IBX) [19], copper (I) iodide [20], potassium peroxymonosulfate [21], etc. [1] were used as oxidants. This reaction was carried out in basic media using triethylamine or K_2CO_3, and 1,3,4-thiadiazole derivatives were obtained in almost quantitative yields.



Scheme 1. Synthesis of 2,5-diamino-1,3,4-thiadiazole derivatives (2) based on dithiobiureas (1)

In addition, several methods have been developed for the synthesis of 2,5-diamino-1,3,4-thiadiazole derivatives **2** based on compounds **1** without the use of oxidizing reagents. For example, similar heterocyclization is achieved by boiling dithiobiureas in a mixture of pyridine and water [22], in DMF [23], or in ethanol [1].

We have recently reported the synthesis of *N*-amidoalkylated derivatives of dithiobiureas and their heterocyclization to the corresponding 2,5-diamino-1,3,4-thiadiazoles under the action of iodine and triethylamine in DMF [24]. In this work, we extend our research in this direction and report on the development of a method for the synthesis of bis-amidoalkylated dithiobiureas derivatives and their heterocyclization into new 2,5-diamino-1,3,4-thiadiazole derivatives.

Because 1,3,4-thiadiazole [25; 26] and alkylamide [27–33] fragments are well-known pharmacophore groups, it can be assumed that the obtained compounds will be of interest to pharmacy and medicine as potential biologically active substances.

Results and discussion

N-(2,2,2-Trichloro-1-isothiocyanatoethyl)carboxamides **3** [34] react quite easily with thiosemicarbazides to form the corresponding amidoalkylated dithiobiurea derivatives [24]. This prompted us to perform similar transformations with the previously obtained *N*-(2,2,2-trichloro-1-(hydrazinecarbothioamido)ethyl)acetamide **4** [35]. As a result, we received several new *N*,*N*′-(((hydrazine-1,2-dicarbonothioyl)bis(azane-

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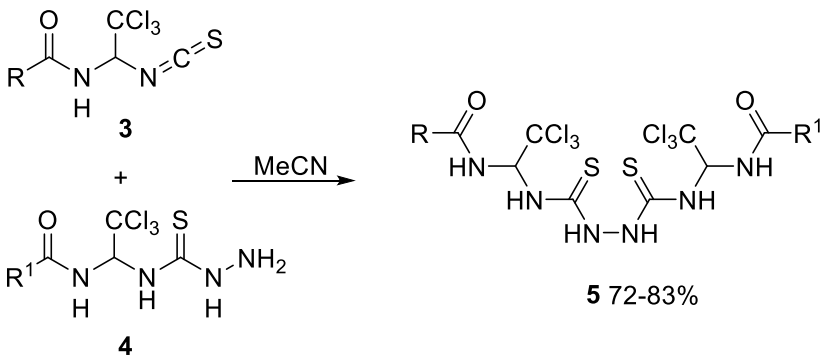
diyl))bis(2,2,2-trichloroethane-1,1-diyl))dicarboxamides (**5a-d**) (Scheme 2). The reaction was carried out in acetonitrile, and the reaction mixture was brought to a boil. The target products **5** precipitated from the reaction mixture quite quickly and almost quantitatively as a crystalline precipitate. The yields of the reaction products were 72–83 %.

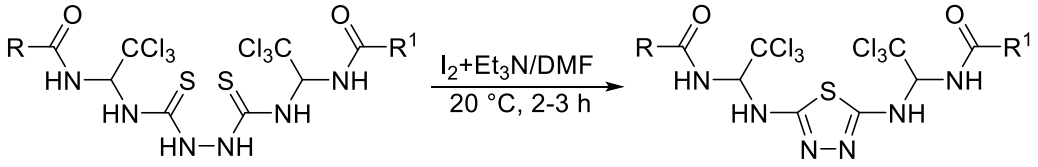


R = R^1 = CH=CH-C_6H_5 (**a**), C_6H_5 (**b**), *o*-$CH_3C_6H_4$ (**c**), *o*-ClC_6H_4 (**d**).

Scheme 2. Synthesis of *N,N′*-(((hydrazine-1,2-dicarbonothioyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))dicarboxamides (5a-d)

The structure of compounds **5a-d** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectra, the signals of the three NH protons were characteristic, typically appearing as broadened singlets at 10.62–8.15 ppm. The signals of the CH protons of the alkylamide fragment mainly overlapped with the signals of the aromatic rings, forming multiplet systems. In the ^{13}C NMR spectra, the signals of the carbon atoms in the C=S and C=O groups were indicative, appearing at 183.3-183.2 and 167.5–164.9 ppm, respectively. Also, characteristic were the signals of the CCl_3 group and the CH carbon of the alkylamide fragment, which appeared at 102.0–101.7 and 69.6–69.4 ppm, respectively.

The obtained *N,N′*-(((hydrazine-1,2-dicarbonothioyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))dicarboxamides (**5a-d**) readily undergo oxidative desulfurization with iodine to form bisamidoalkylated 2,5-diamino-1,3,4-thiadiazole derivatives **6** (Scheme 3). The yield of compounds 6 was 63–92 %.



R = R^1 = CH=CHC_6H_5 (**a**); C_6H_5 (**b**); *o*-$CH_3C_6H_4$ (**c**); *o*-ClC_6H_4 (**d**)

Scheme 3. Synthesis of *N,N′*-(((1,3,4-thiadiazole-2,5-diyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))diacetamide (6a-d)

The structure of the obtained *N,N′*-(((1,3,4-thiadiazole-2,5-diyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))diacetamide (**6a-d**) has been confirmed by ^{1}H and ^{13}C NMR spectroscopy data. In the ^{1}H NMR spectra of compounds **6**, the doublet signals of two NH groups, which appeared at 9.53–6.69 ppm, are characteristic, as well as the doublet-doublet signal of the CH proton of the alkylamide fragment, which appeared at 6.77–6.69 ppm. In the ^{13}C NMR spectra, the signals of the carbon atoms of the C=O group at 168.8–164.7 ppm and the C=N bond of the thiadiazole ring at 158.9–158.6 ppm are characteristic. In addition, the signals of the CCl3 group and the CH alkylamide fragment, which appeared at 101.5–101.2 and 70.0–69.4 ppm, respectively, are indicative.

Experimental

^{1}H NMR and ^{13}C NMR spectra were measured for solutions of the test substances in DMSO-d_6. When recording ^{1}H NMR and ^{13}C NMR spectra, the external magnetic field strengths were 400 MHz and 100 MHz, respectively. A Varian VXR-400 spectrometer was used to record them. Residual signals from the solvent were used as a

standard. Elemental analysis was performed on a LECO CHNS-900 instrument. Melting points were measured in open capillaries using an Electrothermal 9100 Digital Melting Point and were not corrected for temperature. R_f measurements, reaction progress control, and purity analysis of the obtained compounds were performed on Silufol UV-254 plates. A mixture of chloroform and acetone in a 3:1 ratio was used as the eluent.

*Synthesis of N,N'-(((hydrazine-1,2-dicarbonothioyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))dicarboxamides (**5a-d**).*

A mixture of equimolar amounts (10 mmol each) of previously purified *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamide **3** [34] and *N*-(2,2,2-trichloro-1-(hydrazinecarbothioamido)ethyl)carboxamide **4** [35] in 15 mL of acetonitrile was brought to a boil. The crystalline precipitate of product **5** almost immediately precipitated from the reaction mass. The mixture was left at 20 °C for 2–3 hours, then the precipitate was filtered, washed with acetonitrile (2 times 10 mL each), and dried. The yield was 71–83 %.

*(2E,2'E)-N,N'-(((Hydrazine-1,2-dicarbonothioyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))bis(3-phenylacrylamide) (**5a**).* White solid, yield 83 % (5.84 g); m.p. 176–178 °C; R_f = 0.2. NMR ^{1}H (DMSO-d_6), δ, ppm: 10.62 (br. s, 2H, NH), 10.27 (br. s, 2H, NH), 9.01 (d, *J* = 8.3 Hz, 2H, NH), 7.61-7.34 (m, 14H, 2C_6H_5CH=CH), 6.78 (br. s, 2H, CH). NMR ^{13}C (DMSO-d_6), δ, ppm: 183.2 (C=S), 165.5 (C=O), 141.1(C_6H_5<u>C</u>H=CH), 134.9, 130.0, 129.2, 128.1 ($C_{arom.}$), 120.8 (C_6H_5CH=<u>C</u>H), 101.6 (CCl_3), 70.0 (CH). Anal. Calcd (%) for: $C_{24}H_{22}Cl_6N_6O_2S_2$ (703.30): C, 40.99; H, 3.15; N, 11.95; S, 9.12. Found: C, 40.91; H, 3.07; N, 12.04; S, 9.19.

*N,N'-(((Hydrazine-1,2-dicarbonothioyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))dibenzamide (**5b**).* White solid, yield 74 % (4.82 g); m.p. 160–162 °C; R_f = 0.32. NMR ^{1}H (DMSO-d_6), δ, ppm: 10.23 (br. s, 2H, NH), 9.23 (s, 2H, NH), 8.32 (d, *J* = 8.3 Hz, 1H, NH), 8.15 (br. s, 1H, NH), 7.87-7.82 (m, 4H, 4$H_{arom.}$), 7.60–7.44 (m, 8H, 6$H_{arom.}$ + 2CH). NMR ^{13}C (DMSO-d_6), δ, ppm: 183.3 (C=S), 165.3 (C=O), 133.1, 132.1, 128.5, 127.4 ($C_{arom.}$), 101.7 (CCl_3), 69.6 (CH). Anal. Calcd (%) for: $C_{20}H_{18}Cl_6N_6O_2S_2$ (651.22): C, 36.89; H, 2.79; N, 12.91; S, 9.85. Found: C, 36.81; H, 2.72; N, 12.99; S, 9.90.

*N,N'-(((Hydrazine-1,2-dicarbonothioyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))bis(2-methylbenzamide) (**5c**).* White solid, yield 73% (4.96 g); m.p. 182-184 °C; R_f = 0.17. NMR ^{1}H (DMSO-d_6), δ, ppm: 10.30 (br. s, 2H, NH), 9.26 (d, *J* = 6.2 Hz, 2H, NH), 7.87 (d, *J* = 6.8 Hz, 2H, NH), 7.37-7.22 (m, 10H, 8$H_{arom.}$ + 2CH), 2.33 (c, 6H, 2CH_3). NMR ^{13}C (DMSO-d_6), δ, ppm: 183.2 (C=S), 167.5 (C=O), 136.0, 134.9, 130.9, 130.3, 127.1, 125.6 ($C_{arom.}$), 102.0 (CCl_3), 69.4 (CH), 19.7 (CH_3). Anal. Calcd (%) for: $C_{22}H_{22}Cl_6N_6O_2S_2$ (679.28): C, 38.90; H, 3.26; N, 12.37; S, 9.44. Found: C, 38.84; H, 3.21; N, 12.44; S, 9.38.

*N,N'-(((Hydrazine-1,2-dicarbonothioyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))bis(2-chlorobenzamide) (**5d**).* White solid, yield 72 % (5.18 g); m.p. 188–190 °C; R_f = 0.58. NMR ^{1}H (DMSO-d_6), δ, ppm: 10.31 (br. s, 2H, NH), 9.35 (br. s, 2H, NH), 8.17 (br. s, 2H, NH), 7.55-7.37 (m, 10H, 8$H_{arom.}$ + 2CH). NMR ^{13}C (DMSO-d_6), δ, ppm: 183.2 (C=S), 164.9 (C=O), 136.0, 134.8, 131.9, 130.2, 129.2, 127.1 ($C_{arom.}$), 101.7 (CCl_3), 69.5 (CH). Anal. Calcd (%) for: $C_{20}H_{16}Cl_8N_6O_2S_2$ (720.11): C, 33.36; H, 2.24; N, 11.67; S, 8.90. Found: C, 33.29; H, 2.18; N, 11.75; S, 9.01.

*Synthesis of N,N'-(((1,3,4-thiadiazole-2,5-diyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))dicarboxamides (**6a-d**).*

To a solution of 5 mmol of dithiobiurea **5** in 20 mL of DMF, a solution of 5.5 mmol (1.40 g) of iodine and 15 mmol (2.1 mL) of triethylamine in 15 mL of DMF was added dropwise with stirring. The reaction mixture was left at 20 ℃ for 2 hours. The sulfur precipitate was filtered, and the product **6** was precipitated from the filtrate using a 1 % aqueous sodium thiosulfate solution (250 mL). The precipitate that formed was filtered, washed with 60 mL of water, and dried. The product was purified by recrystallization from ethanol.

*(2E,2'E)-N,N'-(((1,3,4-Thiadiazole-2,5-diyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))bis(3-phenylacrylamide) (**6a**).* Yellow solid, yield 91 % (6.09 g); m.p. 182–184 °C (EtOH); R_f = 0.24. NMR ^{1}H (DMSO-d_6), δ, ppm: 8.95 (d, *J* = 8.8 Hz, 2H, NH), 8.04 (d, *J* = 8.8 Hz, 2H, NH), 7.59–7.53 (m, 6H, 4$H_{arom.}$+2C_6H_5C<u>H</u>=CH), 7.45-7.38 (m, 6H, $H_{arom.}$), 6.90 (d, *J* = 15.7 Hz, 2H, 2C_6H_5CH=C<u>H</u>), 6.69 (dd, *J* = 8.8, 8.8 Hz, 2H, CH). NMR ^{13}C (DMSO-d_6), δ, ppm: 164.7 (C=O), 158.6 (C=N), 140.9 (C_6H_5<u>C</u>H=CH), 134.6, 129.8, 129.0, 127.7 ($C_{arom.}$), 120.9 (C_6H_5CH=<u>C</u>H), 101.4 (CCl_3), 69.4 (CH). Anal. Calcd (%) for: $C_{24}H_{20}Cl_6N_6O_2S$ (669.22): C, 43.07; H, 3.01; N, 12.56; S, 4.79. Found: C, 43.00; H, 2.96; N, 12.63; S, 4.84.

N,N'-(((1,3,4-Thiadiazole-2,5-diyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-

*diyl))dibenzamide (**6b**).* Yellow solid, yield 92 % (5.68 g); m.p. 212–214 °C (MeCN); R_f = 0.33. NMR ^{1}H (DMSO-d_6), δ, ppm: 9. 21 (d, *J* = 8.3 Hz, 2H, NH), 7.88–7.85 (m, 4H, $H_{arom.}$), 7.81 (d, *J* = 8.8 Hz, 2H, NH), 7.60–7.46 (m, 6H, $H_{arom.}$), 6.77 (dd, *J* = 8.3, 8.8 Hz, 2H, CH). NMR ^{13}C (DMSO-d_6), δ, ppm: 166.4 (C=O), 158.9 (C=N), 133.3, 131.9, 128.3, 127.8 ($C_{arom.}$), 101.5 (CCl_3), 70.0 (CH). Anal. Calcd (%) for: $C_{20}H_{16}Cl_6N_6O_2S$ (617.15): C, 38.92; H, 2.61; N, 13.62; S, 5.19. Found: C, 38.87; H, 2.55; N, 13.68; S, 5.24.

*N,N'-(((1,3,4-Thiadiazole-2,5-diyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))bis(2-methylbenzamide) (**6c**).* Yellow solid, yield 63 % (4.06 g); m.p. 215–217 °C (MeCN); R_f = 0.58. NMR ^{1}H (DMSO-d_6), δ, ppm: 9.28 (d, *J* = 8.8 Hz, 2H, NH), 7.89 (d, *J* = 9.3 Hz, 2H, NH), 7.38–7.31 (m, 4H, $H_{arom.}$), 7.26-7.23 (m, 4H, $H_{arom.}$), 6.71 (dd, *J* = 8.8, 9.3 Hz, 2H, CH), 2.34 (s, 6H, CH_3). NMR ^{13}C (DMSO-d_6), δ, ppm: 168.8 (C=O), 158.9 (C=N), 136.0, 135.4, 130.4, 129.7, 127.3, 125.4 ($C_{arom.}$), 101.4 (CCl_3), 69.8 (CH), 19.4 (CH_3). Anal. Calcd (%) for: $C_{22}H_{20}Cl_6N_6O_2S$ (645.20): C, 40.95; H, 3.12; N, 13.03; S, 4.97. Found: C, 40.98; H, 3.10; N, 13.07; S, 4.93.

*N,N'-(((1,3,4-Thiadiazole-2,5-diyl)bis(azanediyl))bis(2,2,2-trichloroethane-1,1-diyl))bis(2-chlorobenzamide) (**6d**).* Yellow solid, yield 90 % (6.17 g); m.p. 190–192 °C (MeCN); R_f = 0.28. NMR ^{1}H (DMSO-d_6), δ, ppm: 9.53 (d, *J* = 7.3 Hz, 2H, NH), 7.99-7.94 (m, 2H, $H_{arom.}$), 7.52–7.41 (m, 8H, 6$H_{arom.}$+2NH), 6.73 (dd, *J* = 9.3, 7.3 Hz, 2H, CH). NMR ^{13}C (DMSO-d_6), δ, ppm: 166.1 (C=O), 158.8 (C=N), 135.8, 131.2, 130.0, 129.6, 129.1, 126.9 ($C_{arom.}$), 101.2 (CCl_3), 69.9 (CH). Anal. Calcd (%) for: $C_{20}H_{14}Cl_8N_6O_2S$ (686.03): C, 35.02; H, 2.06; N, 12.25; S, 4.67. Found: C, 34.96; H, 2.00; N, 12.32; S, 4.72.

Conclusion

In this study, we investigated the interaction of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides with *N*-(2,2,2-trichloro-1-(hydrazinecarbothioamido)ethyl)carboxamides, which led to the formation of a series of new bisamidoalkylated dithiobiurea derivatives. It was demonstrated that the obtained dithiobiureas readily undergo oxidative desulfurization with iodine to yield the corresponding 1,3,4-thiadiazole derivatives. The structure of the synthesized compounds was reliably confirmed by ^{1}H and ^{13}C NMR spectroscopy.

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