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Synthesis and Spectral Characteristics of Some New 4*H*-1,3,5-Oxadiazine Derivatives.

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ABSTRACT

In this paper, a method for the synthesis of some new 4*H*-1,3,5-oxadiazine derivatives was described. 4-Chloro-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)benzamide was used as the starting reagent, on the basis of which a series of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides was obtained. Dehydrosulfurization of the latter under the action of dicyclohexylcarbodiimide resulted in the formation of 4*H*-1,3,5-oxadiazine derivatives. The desired products were obtained in 12-65% yields. The structure of the compounds obtained was confirmed by complex spectral studies. The compounds obtained are of interest as potential biologically active substances.

Keywords: dehydrosulfurization, 1,3,5-oxadiazine, thioureas, *N*-amidoalkylated, heterocyclization

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INTRODUCTION

The derivatives of 1,3,5-oxadiazine are of great importance for medical chemistry and pharmaceutical industry [1,2], they are widely used in agriculture, the synthesis of polymers [2] and lithium batteries [3]. Such compounds exhibit a wide range of biological activity: antibacterial [4-9], fungicidal [6-8], antitumour [10,11], larvicidal [12-15] and herbicidal [16]. Substances with inhibitory activity against tubulin polymerase have been detected among the representatives of this class of compounds recently [17]. In addition, the 1,3,5-oxadiazine ring is a part of the alkaloid Alboinon, found in the ascidians of *Dendrodoa grossularia* [18]. The systems with the 1,3,5-oxadiazine ring act as scaffolds for the subsequent synthesis of cucurbituryls [2,19], triazines [20,21] and oligonitriles [22] as well.

Despite the fact that the chemistry of 1,3,5-oxadiazines is sufficiently developed, many of their derivatives are difficult to obtain or not known at all. Therefore, the urgency of searching for new directions for the use of promising reagents suitable for the synthesis of previously unknown derivatives of 1,3,5-oxadiazines is beyond question. This applies, in particular, to *N*-α-amidoalkylating reagents, which are successfully used to solve this problem [23,24].

We have previously shown that *N*-amidoalkylated thioureas can be easily converted to 1,3,5-oxadiazine derivatives [25,26]. To expand the scope of this approach in order to develop chemical libraries of multifunctional oxa-azaheterocycles, a number of new 1,3,5-oxadiazine derivatives have been obtained for pharmaceutical studies. The compounds obtained are of interest as potential biologically active substances.

EXPERIMENTAL

The melting point has been determined in open capillaries and has not been corrected. IR spectra have been recorded in KBr tablets using the device Spectrum BX II. The mass spectra of FAB have been recorded on the device VG7070, desorption of ions from solution samples in meta-nitrobenzyl alcohol being conducted by beam of argon atoms with 8 keV energy. ^{1}H NMR and ^{13}C spectra have been measured on spectrometer Varian VXR-400 (standard TMS). Chemical shifts (δ) have been given in ppm downfield. The constants value of the spin-spin interaction (J) is given in Hz. Elemental analysis was performed on a LECO CHNS-900 instrument. The monitoring of the reaction progress and identity of the compounds obtained has been performed by TLC (Silufol UV-254, eluent – chloroform: acetone – 3:1).

Synthesis of 4-chloro-N-(2,2,2-trichloro-1-hydroxyethyl)benzamide 3 [27] was carried out in the melt according to the procedure given in [28]. White solid; yield 92 % (2.81 g); m.p. 133-135 °C; R_f = 0.74. Anal. Calcd (%) for $C_9H_7Cl_4NO_2$ (302.96): C, 35.68; H, 2.33; Cl, 46.80; N, 4.62. Found: C, 35.65; H, 2.34; Cl, 46.83; N, 4.65.

Synthesis of 4-chloro-N-(2,2,2-trichloro-1-isothiocyanatoethyl)benzamide 4 was carried out according to the procedure given in [29]. Pale yellow crystals; yield 88 % (2.81 g); m.p. 114-116 °C; R_f = 0.81. Anal. Calcd (%) for $C_{10}H_6Cl_4N_2OS$ (344.03): C, 34.91; H, 1.76; Cl, 41.22; N, 8.14; S, 9.32. Found: C, 34.88; H, 1.74; Cl, 41.25; N, 8.17; S, 9.36.

General procedure for the synthesis of 4-chloro-N-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides 6a-h. Isothiocyanate **4** (3.44g, 10 mmol) was dissolved in 15-18 mL of $CHCl_3$, then portions, in order to avoid overheating, with intensive stirring during 7-10 min, 10 mmol of the appropriate amine **5a-h** was added. After adding the entire amine **5**, stirring was stopped and the reaction mixture was left at room temperature for 24 hours. The precipitate was filtered off and washed with 2×3 mL of $CHCl_3$, and then was dried for 24 h at r.t. and 5 h at 100 °C. These thioureas **6a-h** were used in subsequent transformations without further purification. Analytical samples of all of the compounds **6** were recrystallized from MeCN.

4-Chloro-N-(2,2,2-trichloro-1-(3-(o-tolyl)thioureido)ethyl)benzamide (6a). Light yellow solid; yield 84% (3.79 g); m.p. 211-213 °C; R_f = 0.78. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.06 (s, 1H, NH), 9.23 (br. s, 1H, NH), 7.87 (d, J = 8.3 Hz, 2H, $H_{arom.}$), 7.63-7.55 (m, 4H, 2$H_{arom.}$+CH+NH), 7.31-7.24 (m, 4H, $H_{arom.}$), 2.21 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.7 (s, C=S), 164.7 (s, C=O), 141.5 (s), 136.8 (s), 136.3 (s), 132.9 (s), 132.2 (s), 131.9 (s), 129.6 (s), 128.5 (s), 125.0 (s), 120.4 (s) (arom.), 102.0 (s, CCl_3), 70.5 (s, CH), 18.3 (s, CH_3); IR (KBr) (ν cm^{-1}): 3300 (NH), 2975, 2927, 2892 (CH), 1668 (C=O), 1634, 1605, 1595, 1565, 1538, 1483, 1477, 1402, 1336, 1311,

1297, 1231, 1176, 1155, 1122, 1090, 1051, 1006, 942, 878, 838, 821, 769, 728, 694, 682, 665, 610; FAB-MS: *m/z* 450 $[M+H]^+$. Anal. Calcd (%) for $C_{17}H_{15}Cl_4N_3OS$ (451.19): C, 45.26; H, 3.35; Cl, 31.43; N, 9.31; S, 7.11. Found: C, 45.23; H, 3.33; Cl, 31.47; N, 9.33; S, 7.14.

4-Chloro-N-(2,2,2-trichloro-1-(3-(4-ethoxyphenyl)thioureido)ethyl)benzamide (6b). Light yellow solid; yield 87% (4.19 g); m.p. 214-216 °C; R_f = 0.82. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.42 (s, 1H, NH), 9.35 (d, *J* = 8.4 Hz, 1H, NH), 8.56 (d, *J* = 9.1 Hz, 1H, NH), 7.90-7.88 (m, 2H, $H_{arom.}$), 7.85-7.83 (m, 2H, $H_{arom.}$), 7.62-7.60 (m, 4H, $H_{arom.}$), 7.28 (dd, *J* = 8.3, 9.3 Hz, 1H, CH), 3.77 (q, *J* = 7.0 Hz, 2H, $\underline{CH_2}CH_3$), 1.31 (t, *J* = 7.0 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.9 (s, C=S), 165.7 (s, C=O), 147.5 (s), 137.7 (s), 137.8 (s), 132.5 (s), 132.1 (s), 130.3 (s), 129.5 (s), 124.5 (s) (arom.), 101.6 (s, CCl_3), 70.7 (s, CH), 51.5 (s, $\underline{C}H_2CH_3$), 18.8 (s, $CH_2\underline{C}H_3$); IR (KBr) (*v* cm^{-1}): 3307 (NH), 2975, 2931, 2895 (CH), 1670 (C=O), 1634, 1609, 1595, 1569, 1535, 1484, 1472, 1400, 1337, 1302, 1295, 1231, 1177, 1155, 1122, 1078, 1051, 1008, 947, 882, 855, 834, 817, 787, 765, 732, 695, 681, 672, 614; FAB-MS: *m/z* 480 $[M+H]^+$. Anal. Calcd (%) for $C_{18}H_{17}Cl_4N_3O_2S$ (481.21): C, 44.93; H, 3.56; Cl, 29.47; N, 8.73; S, 6.66. Found: C, 44.91; H, 3.54; Cl, 29.51; N, 8.75; S, 6.69.

N-(1-(3-(4-Acetylphenyl)thioureido)-2,2,2-trichloroethyl)-4-chlorobenzamide (6c). Light yellow solid; yield 85% (4.07 g); m.p. 223-225 °C; R_f = 0.85. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H, NH), 9.28 (d, *J* = 7.8 Hz, 1H, NH), 8.27 (d, *J* = 9.3 Hz, 1H, NH), 7.97 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 7.89 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 7.74 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 7.61 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 7.51 (dd, *J* = 7.8, 9.3 Hz, 1H, CH), 2.55 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.6 (s, C=O), 181.1 (s, C=S), 164.7 (s, C=O), 138.8 (s), 136.9 (s), 134.4 (s), 132.5 (s), 130.2 (s), 129.7 (s), 127.5 (s), 125.4 (s) (arom.), 101.3 (s, CCl_3), 70.4 (s, CH), 27.1 (s, CH_3); IR (KBr) (*v* cm^{-1}): 3301 (NH), 2970, 2929, 2895 (CH), 1677 (C=O), 1672 (C=O), 1630, 1604, 1595, 1565, 1532, 1484, 1470, 1398, 1331, 1301, 1290, 1224, 1150, 1084, 1042, 1005, 942, 875, 852, 831, 815, 791, 763, 724, 695, 674, 662, 614; FAB-MS: *m/z* 478 $[M+H]^+$. Anal. Calcd (%) for $C_{18}H_{15}Cl_4N_3O_2S$ (479.20): C, 45.12; H, 3.16; Cl, 29.59; N, 8.77; S, 6.69. Found: C, 45.10; H, 3.18; Cl, 29.61; N, 8.79; S, 6.71.

Methyl-2-(3-(2,2,2-trichloro-1-(4-chlorobenzamido)ethyl)thioureido)benzoate (6d). Light yellow solid; yield 87% (4.31 g); m.p. 164-166 °C; R_f = 0.86. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H, NH), 9.33 (d, *J* = 8.3 Hz, 1H, NH), 8.54 (d, *J* = 9.3 Hz, 1H, NH), 7.92-7.90 (m, 2H, $H_{arom.}$), 7.86-7.84 (m, 1H, $H_{arom.}$), 7.73-7.71 (m, 1H, $H_{arom.}$), 7.59-7.54 (m, 4H, $H_{arom.}$), 7.31 (dd, *J* = 8.3, 9.3 Hz, 1H, CH), 3.77 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.0 (s, C=S), 166.1 (s, C=O), 164.7 (s, C=O), 138.8 (s), 136.8 (s), 132.4 (s), 132.0 (s), 130.2 (s), 129.5 (s), 128.4 (s), 127.4 (s), 125.3 (s), 124.4 (s) (arom.), 101.5 (s, CCl_3), 70.5 (s, CH), 52.1 (s, CH_3); IR (KBr) (*v* cm^{-1}): 3303 (NH), 2973, 2929, 2895 (CH), 1708 (C=O), 1670 (C=O), 1633, 1607, 1595, 1567, 1537, 1487, 1473, 1400, 1334, 1308, 1293, 1227, 1174, 1153, 1120, 1088, 1047, 1008, 945, 880, 858, 836, 817, 789, 768, 727, 691, 679, 668, 612; FAB-MS: *m/z* 494 $[M+H]^+$. Anal. Calcd (%) for $C_{18}H_{15}Cl_4N_3O_3S$ (495.20): C, 43.66; H, 3.05; Cl, 28.64; N, 8.49; S, 6.47. Found: C, 43.64; H, 3.02; Cl, 28.67; N, 8.52; S, 6.50.

4-Chloro-N-(2,2,2-trichloro-1-(3-(2,4-dibromo-6-methylphenyl)thioureido)ethyl)benzamide (6e). Light yellow solid; yield 86% (5.24 g); m.p. 221-223 °C; R_f = 0.78. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (d, *J* = 7.8 Hz, 1H, NH), 9.47 (br. s, 1H, NH), 8.26 (br. s, 1H, NH), 7.94-7.92 (m, 2H, $H_{arom.}$), 7.72 (br. s, 1H, $H_{arom.}$), 7.62-7.50 (m, 4H, $3H_{arom.}$+CH), 2.24 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.9 (s, C=S), 165.1 (s, C=O), 138.6 (s), 136.6 (s), 132.5 (s), 131.9 (s), 131.2 (s), 129.5 (s), 129.0 (s), 127.4 (s), 116.3 (s), 114.5 (s) (arom.), 101.5 (s, CCl_3), 70.3 (s, CH), 54.6 (s, CH_3); IR (KBr) (*v* cm^{-1}): 3314 (NH), 2977, 2929, 2890 (CH), 1671 (C=O), 1630, 1603, 1592, 1564, 1532, 1485, 1475, 1405, 1330, 1303, 1291, 1225, 1172, 1150, 1122, 1084, 1044, 1004, 942, 878, 852, 835, 812, 785, 763, 722, 693, 677, 664, 610; FAB-MS: *m/z* 606 $[M+H]^+$. Anal. Calcd (%) for $C_{17}H_{13}Br2Cl_4N_3OS$ (608.98): C, 33.53; H, 2.15; Br, 26.24; Cl, 23.28; N, 6.90; S, 5.26. Found: C, 33.55; H, 2.16; Br, 26.27; Cl, 23.31; N, 6.94; S, 5.24.

4-Chloro-N-(2,2,2-trichloro-1-(3-(2-iodophenyl)thioureido)ethyl)benzamide (6f). Light yellow solid; yield 82% (4.62 g); m.p. 217-219 °C; R_f = 0.75. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 1H, NH), 9.40 (d, *J* = 6.8 Hz, 1H, NH), 8.07 (br. s, 1H, NH), 7.92-7.89 (m, 3H, $H_{arom.}$), 7.63-7.61 (m, 2H, $H_{arom.}$), 7.58-7.53 (m, 1H, $H_{arom.}$), 7.44-7.41 (m, 2H, $H_{arom.}$), 7.07 (dd, *J* = 6.8, 5.4 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.1 (s, C=S), 164.7 (s, C=O), 140.4 (s), 138.9 (s), 136.8 (s), 132.0 (s), 129.7 (s), 128.6 (s) (arom.), 101.7 (s, CCl_3), 98.9 (s, arom.), 70.5 (CH); IR (KBr) (*v* cm^{-1}): 3262, 3190 (NH), 3063, 3014, 2964 (CH), 1646 (C=O), 1595, 1511, 1485, 1336, 1291, 1142, 1096, 1015, 907, 804, 759, 721, 663, 587; FAB-MS: *m/z* 562 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{12}Cl_4IN_3OS$ (563.06): C, 34.13; H, 2.15; Cl, 25.18; I, 22.54; N, 7.46; S, 5.69. Found: C, 34.10; H, 2.12; Cl, 25.21; I, 22.51; N, 7.49; S, 5.71.

4-Chloro-N-(2,2,2-trichloro-1-(3-(4-iodophenyl)thioureido)ethyl)benzamide (6g). Light yellow solid; yield 87% (4.90 g); m.p. 215-217 °C; R_f = 0.81. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.55 (s, 1H, NH), 9.23 (d, *J* = 6.8 Hz, 1H, NH), 8.07 (d, *J* = 8.8 Hz, 1H, NH), 7.88 (d, *J* = 7.8 Hz, 2H, $H_{arom.}$), 7.72 (d, *J* = 7.8 Hz, 2H, $H_{arom.}$), 7.60 (d, *J* = 7.8 Hz, 2H, $H_{arom.}$), 7.52 (dd, *J* = 6.8, 8.8 Hz, 1H, CH), 7.35 (d, *J* = 7.8 Hz, 2H, $H_{arom.}$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.3 (s, C=S), 164.6 (s, C=O), 138.3 (s), 137.4 (s), 136.9 (s), 131.8 (s), 129.4 (s), 128.5 (s), 125.2 (s) (arom.), 101.58 (s, CCl_3), 89.38 (s, arom.), 70.12 (s, CH); IR (KBr) (*v* cm^{-1}): 3313 (NH), 2978, 2931, 2892 (CH), 1673 (C=O), 1630, 1602, 1594, 1566, 1532, 1488, 1475, 1402, 1337, 1309, 1288, 1231, 1180, 1155, 1119, 1086, 1049, 1006, 943, 882, 861, 839, 821, 789, 766, 693, 681, 670, 611; FAB-MS: *m/z* 562 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{12}Cl_4IN_3OS$ (563.06): C, 34.13; H, 2.15; Cl, 25.18; I, 22.54; N, 7.46; S, 5.69. Found: C, 34.11; H, 2.16; Cl, 25.16; I, 22.55; N, 7.45; S, 5.72.

4-Chloro-N-(2,2,2-trichloro-1-(3-(4-fluorophenyl)thioureido)ethyl)benzamide (6h). Light yellow solid; yield 89% (4.05 g); m.p. 216-218 °C; R_f = 0.78. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H, NH), 9.24 (br. s, 1H, NH), 7.98 (br. s, 1H, NH), 7.88 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 7.61 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 7.55-7.47 (m, 4H, $H_{arom.}$), 7.23 (dd, *J* = 8.3, 8.3 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.8 (s, C=S), 164.5 (s, C=O), 160.5, 158.1 (d, *J* = 242.6 Hz), 136.82 (s), 134.62 (s), 131.81 (s), 129.39 (s), 128.54 (s), 125.81, 125.74 (d, *J* = 7.8 Hz), 115.58, 115.36 (d, *J* = 22.4 Hz), 101.68 (s, CCl_3), 70.2 (s, CH); IR (KBr) (*v* cm^{-1}): 3272, 3196, 3093 (NH), 3060, 2976, 2943, 2854, 2755 (CH), 1651 (C=O), 1593, 1536, 1504, 1484, 1326, 1300, 1250, 1219, 1132, 1083, 1040, 1014, 898, 804, 785, 729, 699, 657, 495; FAB-MS: *m/z* 454 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{12}Cl_4FN_3OS$ (455.15): C, 42.22; H, 2.66; Cl, 31.15; F, 4.17; N, 9.23; S, 7.04. Found: C, 42.20; H, 2.64; Cl, 31.19; F, 4.19; N, 9.25; S, 7.09.

General procedure for the synthesis of 6-(4-chlorophenyl)-N-aryl-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amines 9a-h. 5.5 mmole (1.13 g) DCC was added to 5 mmol of a thiourea **6a-h** in 20 mL of acetonitrile, and the mixture was reflux for 50-60 min. During the reaction, the precipitate of thioureas **6a-h** is gradually dissolved, and the solution turns highly yellow due to formation of dicyclohexyl thiourea. After the reaction completion, the solution was filtered hot, and the filtrate was left at r.t. for 24 h. The precipitated crystals were filtered off and washed with 2×5 mL of acetonitrile, then dried and recrystallized from the appropriate solvent.

6-(4-Chlorophenyl)-N-(o-tolyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (9a). White crystals; yield 22% (0.92 g); m.p. 151-153 °C; R_f = 0.77. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (br. s, 1H, NH), 8.07 (d, *J* = 7.8 Hz, 2H, $H_{arom.}$), 7.62-7.61 (m, 1H, $H_{arom.}$), 7.51 (d, *J* = 7.8 Hz, 2H, $H_{arom.}$), 7.18-7.12 (m, 2H, $H_{arom.}$), 7.05-7.02 (m, 1H, $H_{arom.}$), 5.41 (s, 1H, CH), 2.34 (s, 1H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.3 (s, C=N), 146.4 (s, C=N), 137.6 (s), 135.5 (s), 131.2 (s), 130.0 (s), 128.9 (s), 128.3 (s), 128.3 (s), 125.6 (s), 124.3 (s), 124.3 (s) (arom.), 95.5 (s, CCl_3), 79.7 (s, CH), 17.9 (s, CH_3); IR (KBr) (*v* cm^{-1}): 3417, 3238 (NH), 3185, 3047, 2872 (CH), 1722 (-N=C-O-C=N-), 1646 (C=N), 1595, 1536, 1511, 1497, 1479, 1331, 1292, 1241, 1135, 1013, 918, 812, 705, 615, 508; FAB-MS: *m/z* 416 $[M+H]^+$. Anal. Calcd (%) for $C_{17}H_{13}Cl_4N_3O$ (417.11): C, 48.95; H, 3.14; Cl, 34.00; N, 10.07. Found: C, 48.93; H, 3.12; Cl, 34.04; N, 10.10.

6-(4-Chlorophenyl)-N-(4-ethoxyphenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (9b). White crystals; yield 62% (2.77 g); m.p. 95-97 °C; R_f = 0.72. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.55 (s, 1H, NH), 8.03 (d, *J* = 8.7 Hz, 2H, $H_{arom.}$), 7.66 (d, *J* = 8.7 Hz, 2H, $H_{arom.}$), 7.58 (d, *J* = 9.1 Hz, 2H, $H_{arom.}$), 6.87 (d, *J* = 9.1 Hz, 2H, $H_{arom.}$), 5.63 (s, 1H, CH), 3.96 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 1.28 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.4 (s, C=N), 145.8 (s, C=N), 143.2 (s), 137.6 (s), 135.5 (s), 129.9 (s), 128.8 (s), 128.4 (s), 128.2 (s), 125.9 (s) (arom.), 101.1 (s, CCl_3), 79.6 (s, CH), 54.2 (s, $\underline{C}H_2CH_3$), 15.8 (s, $CH_2\underline{C}H_3$); IR (KBr) (*v* cm^{-1}): 3416, 3246 (NH), 3192, 3131, 3044, 2978, 2870 (CH), 1720 (-N=C-O-C=N-), 1644 (C=N), 1597, 1537, 1511, 1491, 1476, 1403, 1326, 1290, 1242, 1137, 1090, 1046, 1013, 920, 839, 808, 731, 705, 668, 610, 522; FAB-MS: *m/z* 446 $[M+H]^+$. Anal. Calcd (%) for $C_{18}H_{15}Cl_4N_3O_2$ (447.14): C, 48.35; H, 3.38; Cl, 31.71; N, 9.40. Found: C, 48.31; H, 3.36; Cl, 31.75; N, 9.42.

1-(4-((6-(4-Chlorophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-yl)amino)phenyl)ethan-1-one (9c). White crystals; yield 65% (2.89 g); m.p. 164-166 °C; R_f = 0.79. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H, NH), 8.03 (d, *J* = 8.8 Hz, 2H, $H_{arom.}$), 7.93 (d, *J* = 8.8 Hz, 2H, $H_{arom.}$), 7.81 (d, *J* = 8.8, 2H, $H_{arom.}$), 7.66 (d, *J* = 8.8 Hz, 2H, $H_{arom.}$), 5.73 (s, 1H, CH), 2.48 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.4 (s, C=O), 155.1 (s, C=N), 146.2 (s, C=N), 138.9 (s), 137.4 (s), 134.6 (s), 129.0 (s), 128.6 (s), 127.6 (s), 126.3 (s), 121.9 (s) (arom.), 101.9 (s, CCl_3), 79.7 (s, CH), 31.3 (s, CH_3); IR (KBr) (*v* cm^{-1}): 3419, 3343 (NH), 3186, 3096, 3073, 2998, 2925, 2887 (CH), 1732 (-N=C-O-C=N-), 1667 (C=O), 1657 (C=N), 1597, 1536, 1542, 1491, 1404, 1358, 1324, 1268, 1213, 1179, 1136, 1088, 1013, 960, 836, 803, 731, 494; FAB-MS: *m/z* 444 $[M+H]^+$. Anal. Calcd (%) for $C_{18}H_{13}Cl_4N_3O_2$ (445.12): C, 48.57; H, 2.94; Cl, 31.86; N, 9.44. Found: C, 48.54; H, 2.91; Cl, 31.89; N, 9.47.

Methyl-2-((6-(4-chlorophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-yl)amino)benzoate (9d). White crystals; yield 62% (2.86 g); m.p. 171-172 °C; R_f = 0.81. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H, NH), 8.01-7.99 (m, 2H, $H_{arom.}$), 7.88-7.84 (m, 3H, $H_{arom.}$), 7.52-7.49 (m, 3H, $H_{arom.}$), 5.70 (s, 1H, CH), 3.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9 (C=O), 154.2 (C=N), 145.5 (C=N), 140.0 (s), 137.7 (s), 134.3 (s), 130.6 (s), 128.8 (s), 128.7 (s), 127.7 (s), 126.8 (s), 126.1 (s), 121.8 (s) (arom.), 102.5 (s, CCl_3), 79.3 (s, CH), 52.4 (s, CH_3); IR (KBr) (ν cm^{-1}): 3240 (NH), 3061, 2930 (CH), 1727 (-N=C-O-C=N-), 1714 (C=O), 1657 (C=N), 1595, 1547, 1519, 1495, 1481, 1442, 1435, 1300, 1263, 1220, 1190, 1164, 1136, 1119, 1080, 1038, 965, 836, 798, 758, 714, 670; FAB-MS: *m/z* 460 $[M+H]^+$. Anal. Calcd (%) for $C_{18}H_{13}Cl_4N_3O_3$ (461.12): C, 46.89; H, 2.84; Cl, 30.75; N, 9.11. Found: C, 46.88; H, 2.81; Cl, 30.78; N, 9.09.

6-(4-Chlorophenyl)-N-(2,4-dibromo-6-methylphenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (9e). White crystals; yield 12% (0.69 g); m.p. 177-179 °C; R_f = 0.84. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H, NH), 7.94-7.92 (m, 2H, $H_{arom.}$), 7.76 (br. s, 1H, $H_{arom.}$), 7.66-7.64 (m, 2H, $H_{arom.}$), 7.56 (br. s, 1H, $H_{arom.}$), 5.54 (s, 1H, CH), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.0 (s, C=N), 147.3 (s, C=N), 137.4 (s), 135.9 (s), 131.3 (s), 130.1 (s), 129.1 (s), 128.4 (s), 128.2 (s), 125.7 (s), 116.0 (s), 115.3 (s) (arom.), 101.4 (s, CCl_3), 79.8 (s, CH), 18.2 (s, CH_3); IR (KBr) (ν cm^{-1}): 3235 (NH), 3058, 2932 (CH), 1727 (-N=C-O-C=N-), 1656 (C=N), 1595, 1545, 1521, 1497, 1480, 1445, 1435, 1300, 1261, 1218, 1191, 1161, 1136, 1122, 1078, 1037, 965, 835, 795, 758, 712, 670; FAB-MS: *m/z* 572 $[M+H]^+$. Anal. Calcd (%) for $C_{17}H_{11}Br_2Cl_4N_3O$ (574.90): C, 35.52; H, 1.93; Br, 27.80; Cl, 24.67; N, 7.31. Found: C, 35.49; H, 1.95; Br, 27.78; Cl, 24.70; N, 7.35.

6-(4-Chlorophenyl)-N-(2-iodophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (9f). White crystals; yield 33% (1.75 g); m.p. 149-151 °C; R_f = 0.74. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 1H, NH), 7.93 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 7.86-7.83 (m, 1H, $H_{arom.}$), 7.68-7.66 (m, 3H, $H_{arom.}$), 7.55 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 5.65 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.1 (s, C=N), 146.1 (s, C=N), 137.7 (s), 135.6 (s), 129.8 (s), 129.1 (s), 128.9 (s), 128.4 (s), 127.9 (s), 127.4 (s), 126.3 (s), 125.7 (s) (arom.), 102.8 (s, CCl_3), 79.2 (s, CH); IR (KBr) (ν cm^{-1}): 3412, 3279 (NH), 3093, 2974, 2916 (CH), 1724 (-N=C-O-C=N-), 1645 (C=N), 1594, 1527, 1390, 1336, 1292, 1212, 1134, 1091, 1052, 1012, 980, 842, 805, 730, 707, 643, 607, 484; FAB-MS: *m/z* 528 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{10}Cl_4IN_3O$ (528.98): C, 36.33; H, 1.91; Cl, 26.81; I, 23.99; N, 7.94. Found: C, 36.30; H, 1.89; Cl, 26.84; I, 23.97; N, 7.96.

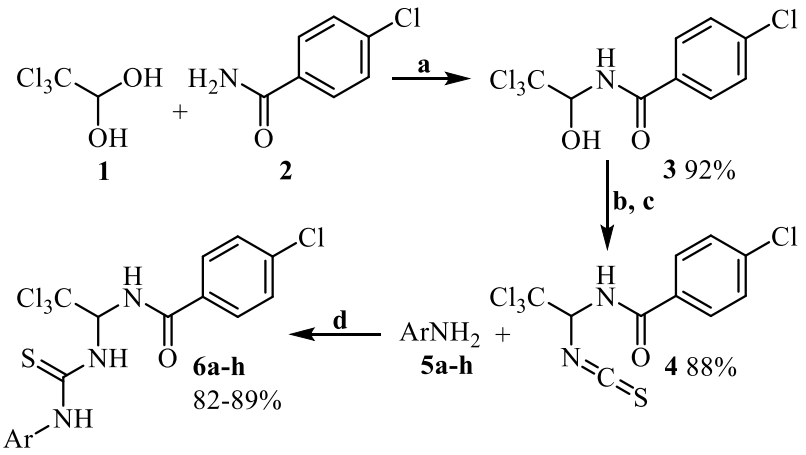
6-(4-Chlorophenyl)-N-(4-iodophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (9g). White crystals; yield 29% (1.53 g); m.p. 170-172 °C; R_f = 0.75. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.79 (s, 1H, NH), 8.04 (d, *J* = 7.8 Hz, 2H, $H_{arom.}$), 7.68-7.64 (m, 4H, $H_{arom.}$), 7.54 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 5.69 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.2 (s, C=N), 145.0 (s, C=N), 138.2 (s), 137.6 (s), 137.2 (s), 128.9 (s), 128.8 (s), 128.0 (s), 120.8 (s) (arom.), 103.0 (s, CCl_3), 85.7 (s, arom.), 79.3 (s, CH); IR (KBr) (ν cm^{-1}): 3415, 3281 (NH), 3097, 2925, 2889, 2855, 2782 (CH), 1722 (-N=C-O-C=N-), 1645 (C=N), 1589, 1530, 1485, 1397, 1335, 1285, 1249, 1215, 1132, 1089, 1041, 1013, 983, 821, 769, 731, 703, 646, 601, 491; FAB-MS: *m/z* 528 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{10}Cl_4IN_3O$ (528.98): C, 36.33; H, 1.91; Cl, 26.81; I, 23.99; N, 7.94. Found: C, 36.31; H, 1.93; Cl, 26.83; I, 24.01; N, 7.92.

6-(4-Chlorophenyl)-N-(4-fluorophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (9h). White crystals; yield 58% (2.44 g); m.p. 156-158 °C; R_f = 0.76. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H, NH), 8.04 (d, *J* = 8.3 Hz, 2H, $H_{arom.}$), 7.74-7.69 (m, 4H, $H_{arom.}$), 7.20-7.16 (m, 2H, $H_{arom.}$), 5.69 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.7, 156.3 (d, *J* = 239.4 Hz, arom.), 152.3 (s, C=N), 145.2 (s, C=N), 137.6 (s), 134.7 (s), 128.9 (s), 128.8 (s), 128.1 (s), 120.1, 120.0 (d, *J* = 7.3 Hz), 115.4, 115.2 (d, *J* = 22.4 Hz) (arom.), 103.1 (CCl_3), 79.3 (CH); IR (KBr) (ν cm^{-1}): 3415, 3283 (NH), 3097, 3076, 2925, 2853 (CH), 1724 (-N=C-O-C=N-), 1646 (C=N), 1596, 1537, 1509, 1489, 1401, 1327, 1291, 1216, 1132, 1091, 1013, 829, 810, 729, 607; FAB-MS: *m/z* 420 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{10}Cl_4FN_3O$ (421.07): C, 45.64; H, 2.39; Cl, 33.68; F, 4.51; N, 9.98. Found: C, 45.61; H, 2.35; Cl, 33.72; F, 4.49; N, 10.01.

RESULT AND DISCUSSION

Based on the readily available 4-chloro-*N*-(2,2,2-trichloro-1-hydroxyethyl)benzamide **3** [27], which is a condensation product of trichloroacetic aldehyde **1** and amide of *para*-chlorobenzoic acid **2**, through the intermediate 4-chloro-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)benzamide **4** [29], we obtained a series of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides **6** (Scheme 1) [30]. Compounds **6** are promising polyfunctional reagents, and we successfully used them as starting reagents for the synthesis of new 4*H*-1,3,5-

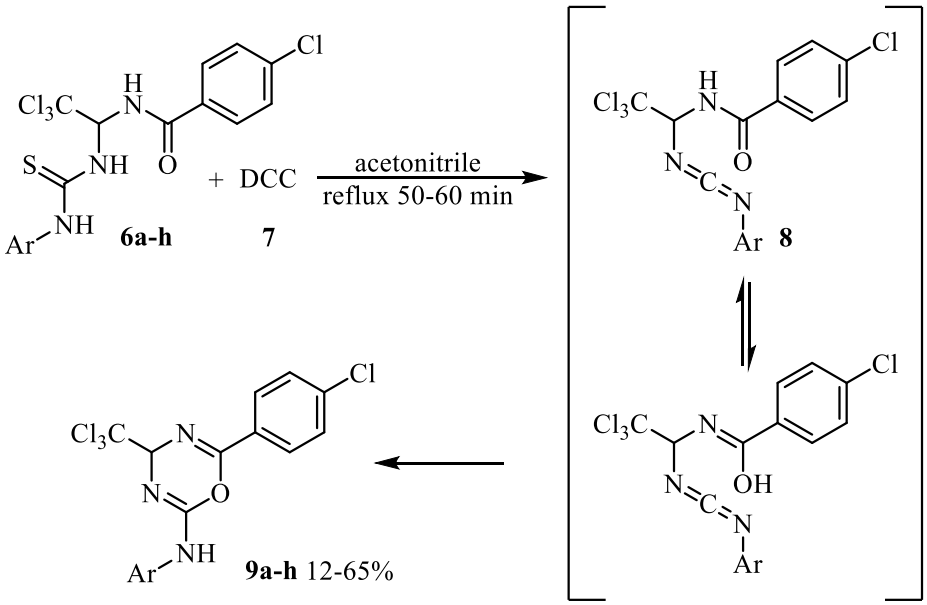
oxadiazines. The synthesis of thioureas **6** was first carried out in chloroform, which made it possible to obtain addition products with high yields and high purity.



Ar = 2-Me-C_6H_4 (**a**); 4-C_2H_5O-C_6H_4 (**b**); 4-$CH_3C(O)$-C_6H_4 (**c**); 2-$CH_3OC(O)C_6H_4$ (**d**); 2,4-diBr-6-Me-C_6H_2 (**e**); 2-I-C_6H_4 (**f**); 4-I-C_6H_4 (**g**); 4-F-C_6H_4 (**h**).

Scheme 1. Synthesis of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides 6. Reagents and conditions: a) t°, solvent-free, 10-20 min [28]; b) $SOCl_2$, CCl_4, reflux 1-1.2 h; c) KSCN, acetonitrile, stirred 1.5-2h; d) $CHCl_3$, reflux 2-3 min, r.t., 24 h.

Dehydrosulfurization of thioureas **6** was carried out under the action of dicyclohexylcarbodiimide **7**. No special study of the **6→9** transformation mechanism was made. However, it is quite probable that carbodiimide **8** was formed in the first stage of this transformation [31], and its cyclization led to the formation of derivatives of 4*H*-1,3,5-oxadiazines **9** (Scheme 2).



Ar = 2-Me-C_6H_4 (**a**); 4-C_2H_5O-C_6H_4 (**b**); 4-$CH_3C(O)$-C_6H_4 (**c**); 2-$CH_3OC(O)C_6H_4$ (**d**); 2,4-diBr-6-Me-C_6H_2 (**e**); 2-I-C_6H_4 (**f**); 4-I-C_6H_4 (**g**); 4-F-C_6H_4 (**h**).

Scheme 2. Synthesis of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines 9.

The structure of the compounds obtained was confirmed by complex spectral studies. In the ^{1}H NMR spectra of compounds **9**, the signal of the methine proton (5.7-5.4 ppm) located in the trichloromethyl group

was manifested as a singlet, while in compounds **6** it was in the form of a doublet doublet (7.6-7.1 ppm). The proton of the amino group in compounds **9** appeared in the region of 10.5-8.7 ppm in the form of a singlet, while for thioureas **6** there were three signals of protons of different amino groups in this region. In the ^{13}C NMR spectra of compounds **9** in the region of 155-145 ppm, carbon signals of two imino groups were observed, with no signals C=S (182-180 ppm) and amide C=O (165-164 ppm) carbons, characteristic for the starting thioureas. In the IR spectra of compounds **4** in the region of 1732-1720 and 1657-1644 cm^{-1}, intense absorption bands were observed, which were related to the symmetric and antisymmetric stretching vibrations of the −N=C−O−C=N− group [32]. All spectral data confirm the participation in the cyclization of both amide and thioureid fragments and indicate the formation of 4*H*-1,3,5-oxadiazine derivatives **9**.

CONCLUSION

We obtained a series of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides **6** based on the readily available 4-chloro-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)benzamide **4**. Dehydrosulfurization of the compounds **6** under the action of dicyclohexylcarbodiimide resulted in the formation of derivatives of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines **9**. The desired products were obtained in yields of 12-65%. The structure of the compounds obtained was confirmed by the complex spectral studies.

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