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A New Approach to the Synthesis of 4*H*-1,3,5-Oxadiazine Derivatives

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Abstract: Derivatives of 1,3,5-oxadiazine are of great interest as potential biologically active compounds. In this work, we report on a new method for synthesizing 1,3,5-oxadiazine derivatives. The method is based on the elimination of hydrogen sulfide from *N*-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides by the action of dicyclohexylcarbodiimide (DCC). Presumably, at the first stage of the transformation, an intermediate carbodiimide is formed, which then enters into the [4+2] cycloaddition reaction with another DCC molecule to form the final products - *N*-(2,2,2-trichloro-1-(((2*Z*,4*E*)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4*H*-1,3,5-oxadiazin-4-ylidene)amino)ethyl)carboxamides. Target products were obtained in 68-89% yields. The structure of the obtained compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and mass spectrometry.

Keywords: Synthesis; 1,3,5-oxadiazine; dicyclohexylcarbodiimide; heterocyclization; thiourea.

1. Introduction

In recent years, 1,3,5-oxadiazine derivatives have attracted increased interest from researchers due to the high biological activity of these compounds and the number of their unique physical and chemical properties [1]. Compounds containing the 1,3,5-oxadiazine ring are able to interact with a variety of biological targets effectively. They have a high practical potential in the search for new drugs for the treatment of cancer [2-4], bacterial [5-10], and fungal infections [8, 9]. They have found wide application in supramolecular chemistry in the creation of molecular clips [11-18], in organic synthesis as intermediates for the preparation of alkaloids [19], 1,3,5-triazine derivatives [20], and other complexes acyclic and heterocyclic systems [1]. In addition, work is underway to study their thermal decomposition [21] and detonation properties [22]. Among the derivatives of 1,3,5-oxadiazines, two alkaloids are known: Fissoldhimine [23] and Alboinon [24], the insecticide Thiamethoxam [25-35], and the antitumor drug Synthazin [36].

The reactions of [5+1] [37], [4+2] [6-10, 38], [3+2+1] [39], [3+1+1+1] [40], and [2+2+2] [41] cycloaddition, as well as intramolecular cyclization of bisamidals [42], amidoalkylated thioureas [43, 44], and some other reagents with several reaction centers [45-48] are usually used for the synthesis of 1,3,5-oxadiazine derivatives. There are several works on the preparation of 1,3,5-oxadiazines based on other heterocycles [49, 50]. In this work, we report on the synthesis of *N*-(2,2,2-trichloro-1-(((2*Z*,4*E*)-3-cyclohexyl-2-(cyclohexylimino)-6-

phenyl-2,3-dihydro-4*H*-1,3,5-oxadiazin-4-ylidene)amino)ethyl)carboxamides based on *N*-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides.

2. Materials and Methods

IR spectra were recorded on a Spectrum BX II spectrometer in KBr pellets. A VG7070 instrument was used to record FAB mass spectra. Ions were desorbed from samples in *meta*-nitrobenzyl alcohol by an 8-keV argon beam. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured for solutions in DMSO-d_6 on a Varian VXR-400 spectrometer. Elemental analysis was performed on a LECO CHNS-900 instrument. The reaction and purity of the compounds were controlled by TLC on Silufol UV-254 plates using a chloroform/acetone (3: 1) mixture as eluent.

Synthesis of N-(1-amino-2,2,2-trichloroethyl)carboxamides (3a-f). $SOCl_2$ (12 mmol) was added to 10 mmol of the corresponding *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamide (**1**) [51] in 25 mL of CCl_4. The mixture was refluxed for 1.5-3 hours until the evolution of gaseous products ceased completely. The reaction mass was cooled, and the solvent was evaporated on a rotary evaporator. The dry residue (**2**) was treated with 10-12 mL of hexane, and the resulting suspension was filtered. The dry mass (**2**) was filled with 15 mL of MTBE, and 2 mL of an aqueous solution of ammonia (25%) was added. The mixture was stirred for 15 minutes, then left for half an hour. The ethereal layer was separated and evaporated on a rotary evaporator. The recrystallization purified the resulting product from a mixture of benzene: hexane (1:1).

N-(1-Amino-2,2,2-trichloroethyl)acetamide (3a). White crystals; yield 82% (1.68 g); mp 94-96°C (benzene:hexane = 1:1); R_f = 0.40. IR: ν_{max} 3427, 3331 (NH), 2923, 2872 (CH), 1652 (C=O) cm^{-1}. ^{1}H NMR: δ 8.42 (d, *J* = 8.8 Hz, 1H, NH), 5.25 (q, *J* = 7.3, 8.8, 7.3 Hz, 1H, CH), 2.60 (d, *J* = 7.3 Hz, 2H, NH_2), 1.90 (s, 3H, CH_3). ^{13}C NMR: δ 168.8 (C=O), 103.0 (CCl_3), 75.4 (CH), 23.8 (CH_3). FAB-MS: m/z 205 $[M+H]^+$. Anal. Calcd (%) for $C_4H_7Cl_3N_2O$ (205.46): C, 23.38; H, 3.43; N, 13.63. Found: C, 23.35; H, 3.45; N, 13.67.

N-(1-Amino-2,2,2-trichloroethyl)acrylamide (3b). White crystals; yield 87% (1.89 g); mp 95-97°C (benzene:hexane = 1:1); R_f = 0.75. IR: ν_{max} 3425, 3347 (NH), 2933, 2883 (CH), 1654 (C=O) cm^{-1}. ^{1}H NMR: δ 8.64 (d, *J* = 8.3 Hz, 1H, NH), 6.37 (dd, *J* = 10.2, 17.1 Hz, 1H, C<u>H</u>=CH_2), 6.18 (d, *J* = 17.1 Hz, 1H, =CH_2-*trans*), 5.70 (d, *J* = 10.2 Hz, 1H, =CH_2-*cis*), 5.36 (q, *J* = 7.8, 8.3, 7.8 Hz, 1H, CH), 2.70 (d, *J* = 7.8 Hz, 2H, NH_2). ^{13}C NMR: δ 166.7 (C=O), 130.8 (<u>C</u>H=CH_2), 124.9 (CH=<u>C</u>H_2), 102.5 (CCl_3), 77.4 (CH). FAB-MS: m/z 217 $[M+H]^+$. Anal. Calcd (%) for $C_5H_7Cl_3N_2O$ (217.47): C, 27.61; H, 3.24; N, 12.88. Found: C, 27.57; H, 3.22; N, 12.92.

N-(1-Amino-2,2,2-trichloroethyl)cinnamamide (3c) [52]. White crystals; yield 79% (2.32 g); mp 122-124°C (benzene:hexane = 1:1); R_f = 0.72. IR: ν_{max} 3433, 3339 (NH), 2928, 2874 (CH), 1658 (C=O) cm^{-1}. ^{1}H NMR: δ 8.65 (d, *J* = 8.8 Hz, 1H, NH), 7.60-7.59 (m, 2H, $H_{arom.}$), 7.54 (d, *J* = 15.6 Hz, 1H, C_6H_5CH=C<u>H</u>), 7.44-7.39 (m, 3H, $H_{arom.}$), 6.82 (d, *J* = 15.6 Hz, 1H, C_6H_5C<u>H</u>=CH), 5.44 (br. s, 1H, CH), 2.76 (br. s, 2H, NH_2). ^{13}C NMR: δ 166.7 (C=O), 140.7 (C_6H_5<u>C</u>H=CH), 135.7, 129.8, 128.9, 128.2 ($C_{arom.}$), 120.6 (C_6H_5CH=<u>C</u>H), 103.1 (CCl_3), 74.7 (CH). FAB-MS: m/z 293 $[M+H]^+$. Anal. Calcd (%) for $C_{11}H_{11}Cl_3N_2O$ (293.57): C, 45.00; H, 3.78; N, 9.54. Found: C, 44.97; H, 3.76; N, 9.59.

N-(1-Amino-2,2,2-trichloroethyl)benzamide (3d) [53]. White crystals; yield 89% (2.38 g); mp 97-99°C (benzene:hexane = 1:1); R_f = 0.60. IR: ν_{max} 3448, 3327 (NH), 2931, 2887 (CH), 1662 (C=O) cm^{-1}. ^{1}H NMR: δ 9.04 (d, *J* = 8.8 Hz, 1H, NH), 5.50-5.46 (m, 2H, $H_{arom.}$), 4.23-

4.07 (m, 3H, $H_{arom.}$), 3.59 (dd, *J* = 8.8, 7.3 Hz, 1H, CH), 2.78 (d, *J* = 7.3 Hz, 2H, NH_2). ^{13}C NMR: *δ* 168.8 (C=O), 135.8, 132.4, 131.2, 130.1 ($C_{arom.}$), 102.2 (CCl_3), 78.7 (CH). FAB-MS: m/z 267 $[M+H]^+$. Anal. Calcd (%) for $C_9H_9Cl_3N_2O$ (267.53): C, 40.41; H, 3.39; N, 10.47. Found: C, 40.38; H, 3.35; N, 10.51.

N-(1-Amino-2,2,2-trichloroethyl)-4-methylbenzamide (3e). White crystals; yield 92% (2.59 g); mp 110-112°C (benzene:hexane = 1:1); R_f = 0.47. IR: ν_{max} 3419, 3386 (NH), 3029 (CH), 1648 (C=O) cm^{-1}. ^1H NMR: *δ* 8.71 (d, *J* = 8.4 Hz, 1H, NH), 7.75 (d, *J* = 8.1 Hz, 2H, $H_{arom.}$), 7.29 (d, *J* = 8.1 Hz, 2H, $H_{arom.}$), 5.46 (q, *J* = 8.4 Hz, 1H, CH), 2.78 (d, *J* = 8.4 Hz, 2H, NH_2), 2.35 (s, 3H, CH_3). ^{13}C NMR: *δ* 165.6 (C=O), 141.6, 130.9, 128.8, 127.5 ($C_{arom.}$), 105.4 (CCl_3), 70.9 (CH), 21.0 (CH_3). FAB-MS: m/z 281 $[M+H]^+$. Anal. Calcd (%) for $C_{10}H_{11}Cl_3N_2O$ (281.56): C, 42.66; H, 3.94; N, 9.95. Found: C, 42.69; H, 3.90; N, 9.99.

N-(1-Amino-2,2,2-trichloroethyl)-2-bromobenzamide (3f). White crystals; yield 84% (2.91 g); mp 148-150°C (benzene:hexane = 1:1); R_f = 0.57. IR: ν_{max} 3411, 3382 (NH), 2947, 2892 (CH), 1657 (C=O) cm^{-1}. ^1H NMR: *δ* 8.74 (br. s, 1H, NH), 7.96-7.94 (m, 2H, $H_{arom.}$), 7.75-7.72 (m, 2H, $H_{arom.}$), 6.69 (br. s, 1H, CH), 3.02 (br. s, 2H, $H_{arom.}$). ^{13}C NMR: *δ* 166.9 (C=O), 136.8, 134.2, 132.2, 129.7, 123.8, 118.6 ($C_{arom.}$), 102.1 (CCl_3), 76.2 (CH). FAB-MS: m/z 345 $[M+H]^+$. Anal. Calcd (%) for $C_9H_8BrCl_3N_2O$ (346.43): C, 31.20; H, 2.33; N, 8.09. Found: C, 31.15; H, 2.29; N, 8.12.

Synthesis of N-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides (5a-f). A solution of 10 mmol of benzoyl isothiocyanate (**4**) in 7 mL of acetonitrile was added to 10 mmol of amino derivative **3** in 15 mL of MeCN. The mixture was brought to a boil and left at room temperature for 12 hours. The precipitate of thiourea **5** was filtered, washed with 10 mL of acetonitrile, and purified by recrystallization from the appropriate solvent.

N-((1-Acetamido-2,2,2-trichloroethyl)carbamothioyl)benzamide (5a). Pale yellow crystals; yield 89% (3.28 g); mp 188-190°C (MeOH); R_f = 0.80. IR: ν_{max} 3348, 3314, 2980 (NH), 2955, 2880 (CH), 1662 (C=O) cm^{-1}. ^1H NMR: *δ* 11.80 (d, *J* = 8.2 Hz, 1H, NH), 11.62 (s, 1H, NH), 9.35 (d, *J* = 8.3 Hz, 1H, NH), 8.04-8.01 (m, 2H, $H_{arom.}$), 7.65-7.62 (m, 2H, $H_{arom.}$), 7.55-7.52 (m, 2H, $H_{arom.}$+CH), 2.08 (s, 3H, CH_3). ^{13}C NMR: *δ* 182.7 (C=S), 170.0 (C=O), 166.4 (C=O), 135.7, 132.6, 129.2, 128.5 ($C_{arom.}$), 102.4 (CCl_3), 71.2 (CH), 18.9 (CH_3). FAB-MS: m/z 368 $[M+H]^+$. Anal. Calcd (%) for $C_{12}H_{12}Cl_3N_3O_2S$ (368.66): C, 39.10; H, 3.28; N, 11.40; S, 8.70. Found: C, 39.07; H, 3.25; N, 11.40; S, 8.70.

N-((1-Acrylamido-2,2,2-trichloroethyl)carbamothioyl)benzamide (5b). Pale yellow crystals; yield 90% (3.43 g); mp 180-182°C (MeCN); R_f = 0.72. IR: ν_{max} 3364, 3327, 2998 (NH), 2974, 2879 (CH), 1657 (C=O) cm^{-1}. ^1H NMR: *δ* 11.78 (br. s, 1H, NH), 11.57 (s, 1H, NH), 9.42 (d, *J* = 8.6 Hz, 1H, NH), 8.11-8.09 (m, 2H, $H_{arom.}$), 7.64-7.52 (m, 4H, 3$H_{arom.}$+CH), 6.34 (dd, *J* = 10.0, 17.4 Hz, 1H, C<u>H</u>=CH_2), 6.16 (d, *J* = 17.4 Hz, 1H, =CH_2-*trans*), 5.67 (d, *J* = 10.0 Hz, 1H, =CH_2-*cis*). ^{13}C NMR: *δ* 181.8 (C=S), 168.8 (C=O), 167.3 (C=O), 135.9, 132.7, 132.5, 129.6, 128.8, 125.9 ($C_{arom.}$+ CH=CH_2), 102.7 (CCl_3), 70.4 (CH). FAB-MS: m/z 380 $[M+H]^+$. Anal. Calcd (%) for $C_{13}H_{12}Cl_3N_3O_2S$ (380.67): C, 41.02; H, 3.18; N, 11.04; S, 8.42. Found: C, 40.99; H, 3.15 N, 11.09; S, 8.47.

N-((2,2,2-Trichloro-1-cinnamamidoethyl)carbamothioyl)benzamide (5c) [52]. Pale yellow crystals; yield 88% (4.02 g); mp 184-186°C (MeCN); R_f = 0.81. IR: ν_{max} 3358, 3318, 2987 (NH), 2968, 2877 (CH), 1656 (C=O) cm^{-1}. ^1H NMR: *δ* 11.64 (br. s, 1H, NH), 11.48 (s, 1H, NH), 9.22 (br. s, 1H, NH), 8.08-8.03 (m, 4H, $H_{arom.}$), 7.62-7.54 (m, 4H, $H_{arom.}$), 7.48 (d, *J* = 14.7 Hz, 1H, C_6H_5CH=C<u>H</u>), 7.42-7.37 (m, 2H, $H_{arom.}$+CH), 6.82 (d, *J* = 14.7 Hz, 1H, C_6H_5C<u>H</u>=CH), 6.72-6.70 (m, 1H, $H_{arom.}$). ^{13}C NMR: *δ* 182.0 (C=S), 168.2 (C=O), 166.8 (C=O),

141.4, 137.2, 136.8, 135.9, 135.3, 129.7, 129.5, 127.6, 127.4, 125.6 ($C_{arom.}$+CH=CH), 101.8 (CCl_3), 70.2 (CH). FAB-MS: m/z 456 $[M+H]^+$. Anal. Calcd (%) for $C_{19}H_{16}Cl_3N_3O_2S$ (456.77): C, 49.96; H, 3.53; N, 9.20; S, 7.02. Found: C, 49.94; H, 3.50; N, 9.25; S, 7.05.

N-((1-Benzamido-2,2,2-trichloroethyl)carbamothioyl)benzamide (5d). Pale yellow crystals; yield 93% (4.01 g); mp 182-184°C (MeCN); R_f = 0.78. IR: ν_{max} 3342, 3311, 2968 (NH), 2918, 2881 (CH), 1662 (C=O) cm^{-1}. ^{1}H NMR: δ 11.97 (d, J = 9.3 Hz, 1H, NH), 11.89 (s, 1H, NH), 9.66 (d, J = 7.8 Hz, 1H, NH), 7.99-7.93 (m, 4H, $H_{arom.}$), 7.69-7.51 (m, 7H, $6H_{arom.}$+CH). ^{13}C NMR: δ 182.4 (C=S), 166.9 (C=O), 166.0 (C=O), 135.7, 134.2, 132.8, 132.2, 128.5, 127.7, 127.3, 126.4 ($C_{arom.}$), 101.9 (CCl_3), 71.4 (CH). FAB-MS: m/z 430 $[M+H]^+$. Anal. Calcd (%) for $C_{17}H_{14}Cl_3N_3O_2S$ (430.73): C, 47.41; H, 3.28; N, 9.76; S, 7.44. Found: C, 47.37; H, 3.25; N, 9.80; S, 7.46.

N-(1-(3-Benzoylthioureido)-2,2,2-trichloroethyl)-4-methylbenzamide (5e). Pale yellow crystals; yield 91% (4.05 g); mp 192-194°C (MeCN); R_f = 0.82. IR: ν_{max} 3355, 3317, 2970 (NH), 2920, 2879 (CH), 1659 (C=O) cm^{-1}. ^{1}H NMR: δ 11.92 (d, J = 9.3 Hz, 1H, NH), 11.66 (s, 1H, NH), 9.40 (d, J = 8.3 Hz, 1H, NH), 8.01 (d, J = 7.8 Hz, 2H, $H_{arom.}$), 7.65 (d, J = 7.8 Hz, 2H, $H_{arom.}$), 7.62-7.55 (m, 2H, $H_{arom.}$+CH), 7.50-7.46 (m, 2H, $H_{arom.}$), 7.24 (d, J = 7.8 Hz, 2H, $H_{arom.}$), 2.40 (s, 3H, CH_3). ^{13}C NMR: δ 181.7 (C=S), 167.7 (C=O), 165.3 (C=O), 141.3, 132.7, 131.6, 130.2, 128.5, 128.3, 127.9, 127.7 ($C_{arom.}$), 100.9 (CCl_3), 70.4 (CH), 21.0 (CH_3). FAB-MS: m/z 444 $[M+H]^+$. Anal. Calcd (%) for $C_{18}H_{16}Cl_3N_3O_2S$ (444.76): C, 48.61; H, 3.63; N, 9.45; S, 7.21. Found: C, 48.58; H, 3.59; N, 9.49; S, 7.26.

N-(1-(3-Benzoylthioureido)-2,2,2-trichloroethyl)-2-bromobenzamide (5f). Yellow crystals; yield 86% (4.38 g); mp 178-180°C (MeCN); R_f = 0.69. IR: ν_{max} 3362, 3327, 2981 (NH), 2931, 2881 (CH), 1664 (C=O) cm^{-1}. ^{1}H NMR: δ 11.87 (br. s, 1H, NH), 11.62 (s, 1H, NH), 9.42 (br. s, 1H, NH), 8.01-7.82 (m, 4H, $H_{arom.}$), 7.60-7.54 (m, 6H, $5H_{arom.}$+CH). ^{13}C NMR: δ 181.0 (C=S), 168.1 (C=O), 166.4 (C=O), 137.3, 135.6, 134.8, 132.6, 131.5, 129.7, 129.4, 127.7, 123.1, 118.9 ($C_{arom.}$), 102.9 (CCl_3), 72.8 (CH). FAB-MS: m/z 508 $[M+H]^+$. Anal. Calcd (%) for $C_{17}H_{13}BrCl_3N_3O_2S$ (509.62): C, 40.07; H, 2.57; N, 8.25; S, 6.29. Found: C, 40.02; H, 2.54; N, 8.29; S, 6.33.

Synthesis of N-(2,2,2-trichloro-1-(((2Z,4E)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4H-1,3,5-oxadiazin-4-ylidene)amino)ethyl)carboxamides (8a-f). A mixture of 10 mmol of thiourea **5** and 20 mmol (4.13 g) of dicyclohexylcarbodiimide was poured into 40 mL of dry acetonitrile and refluxed for 40-50 minutes. The reaction mass was cooled, and the precipitated crystals were filtered and washed with 10 mL of MeCN. The final product was purified by recrystallization from methanol.

N-(2,2,2-Trichloro-1-(((2Z,4E)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4H-1,3,5-oxadiazin-4-ylidene)amino)ethyl)acetamide (8a). White crystals; yield 89% (4.81 g); mp 165-167°C (MeOH); R_f = 0.74. IR: ν_{max} 3368 (NH), 2918, 2854 (CH), 1717 (−N=C−O−C=N−C=N−), 1667 (C=O), 1626 (C=N) cm^{-1}. ^{1}H NMR: δ 8.47 (br. s, 1H, NH), 8.10-8.07 (m, 2H, $H_{arom.}$), 7.78-7.63 (m, 3H, $H_{arom.}$), 6.69 (d, J = 6.8 Hz, 1H, CH), 4.81-4.75 (m, 1H, cyclohexyl), 3.82 (br. s, 1H, cyclohexyl), 2.77-2.60 (m, 2H, cyclohexyl), 2.10 (s, 3H, CH_3), 1.92-1.17 (m, 18H, cyclohexyl). ^{13}C NMR: δ 171.0 (C=O), 159.1 (C=N), 150.9 (C=N), 141.8 (C=N), 133.6, 131.2, 129.6, 128.9 ($C_{arom.}$), 101.1 (CCl_3), 72.8 (CH), 56.2, 54.3, 34.0, 33.7, 29.0, 27.1, 26.0, 25.7, 25.4, 23.9, 23.4, 21.1 (CH_3+cyclohexyl). FAB-MS: m/z 540 $[M+H]^+$. Anal. Calcd (%) for $C_{25}H_{32}Cl_3N_5O_2$ (540.91): C, 55.51; H, 5.96; N, 12.95. Found: C, 55.48; H, 5.94; N, 12.99.

N-(2,2,2-Trichloro-1-(((2Z,4E)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4H-1,3,5-oxadiazin-4-ylidene)amino)ethyl)acrylamide (8b). White crystals; yield 84% (4.64 g); mp 166-168°C (MeOH); R_f = 0.73. IR: ν_{max} 3354 (NH), 2921, 2857 (CH), 1718 (−N=C−O−C=N−C=N−), 1665 (C=O), 1625 (C=N) cm^{-1}. ^1H NMR: δ 8.57 (br. s, 1H, NH), 8.11-8.09 (d, J = 7.3 Hz, 2H, $H_{arom.}$), 7.74-7.70 (m, 1H, $H_{arom.}$), 7.63-7.59 (m, 2H, $H_{arom.}$), 6.83 (d, J = 9.3 Hz, 1H, CH), 6.47 (dd, J = 17.0, 10.2 Hz, 1H, C<u>H</u>=CH_2), 6.22 (dd, J = 17.1, 2.3 Hz, 1H, =CH_2-*trans*), 5.62 (dd, J = 10.2, 2.2 Hz, 1H, =CH_2-*cis*), 4.83-4.77 (m, 1H, cyclohexyl), 3.85 (br. s, 1H, cyclohexyl), 2.76-2.59 (m, 2H, cyclohexyl), 1.82-1.09 (m, 18H, cyclohexyl). ^{13}C NMR: δ 169.2 (C=O), 158.6 (C=N), 149.8 (C=N), 140.9 (C=N), 133.4, 131.8, 130.6, 129.7, 129.2, 125.2 ($C_{arom.}$+ CH=CH_2), 99.8 (CCl_3), 70.8 (CH), 54.2, 53.3, 34.2, 33.6, 28.8, 26.8, 26.2, 25.4, 25.1, 23.7, 20.8 (cyclohexyl). FAB-MS: m/z 552 $[M+H]^+$. Anal. Calcd (%) for $C_{26}H_{32}Cl_3N_5O_2$ (552.93): C, 56.48; H, 5.83; N, 12.67. Found: C, 56.45; H, 5.80; N, 12.71.

N-(2,2,2-Trichloro-1-(((2Z,4E)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4H-1,3,5-oxadiazin-4-ylidene)amino)ethyl)cinnamamide (8c). White crystals; yield 86% (5.41 g); mp 172-174°C (MeOH); R_f = 0.81. IR: ν_{max} 3361 (NH), 2931, 2861 (CH), 1713 (−N=C−O−C=N−C=N−), 1664 (C=O), 1621 (C=N) cm^{-1}. ^1H NMR: δ 8.68 (d, J = 8.8 Hz, 1H, NH), 8.12-8.10 (m, 2H, $H_{arom.}$), 7.74-7.71 (m, 1H, $H_{arom.}$), 7.64-7.53 (m, 5H, $H_{arom.}$), 7.42-7.34 (m, 3H, 2$H_{arom.}$+CH), 6.93-8.85 (m, 2H, C_6H_5C<u>H</u>=C<u>H</u>), 4.83-4.77 (m, 1H, cyclohexyl), 3.82 (br. s, 1H, cyclohexyl), 2.76-2.60 (m, 2H, cyclohexyl), 1.82-1.08 (m, 18H, cyclohexyl). ^{13}C NMR: δ 167.6 (C=O), 157.4 (C=N), 150.8 (C=N), 142.0 (C_6H_5<u>C</u>H=CH), 141.0 (C=N), 136.7, 133.4, 131.8, 130.9, 130.2, 129.8, 129.2, 127.2, 125.7 ($C_{arom.}$+C_6H_5CH=<u>C</u>H), 102.3 (CCl_3), 72.3 (CH), 54.5, 53.0, 34.3, 33.4, 28.5, 26.4, 26.0, 25.1, 24.8, 23.6, 20.7 (cyclohexyl). FAB-MS: m/z 628 $[M+H]^+$. Anal. Calcd (%) for $C_{32}H_{36}Cl_3N_5O_2$ (629.02): C, 61.10; H, 5.77; N, 11.13. Found: C, 61.07; H, 5.74; N, 11.17.

N-(2,2,2-Trichloro-1-(((2Z,4E)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4H-1,3,5-oxadiazin-4-ylidene)amino)ethyl)benzamide (8d). White crystals; yield 73% (4.40 g); mp 149-151°C (MeCN); R_f = 0.87. IR: ν_{max} 3355 (NH), 2928, 2857 (CH), 1717 (−N=C−O−C=N−C=N−), 1660 (C=O), 1625 (C=N) cm^{-1}. ^1H NMR: δ 8.84 (d, J = 8.3 Hz, 1H, NH), 8.12 (d, J = 7.3 Hz, 2H, $H_{arom.}$), 7.87 (d, J = 7.3 Hz, 2H, $H_{arom.}$), 7.75-7.71 (m, 1H, $H_{arom.}$), 7.64-7.60 (m, 2H, $H_{arom.}$), 7.53-7.5 (m, 1H, $H_{arom.}$), 7.45-7.42 (m, 2H, $H_{arom.}$), 6.90 (d, J = 8.3 Hz, 1H, CH), 4.83-4.78 (m, 1H, cyclohexyl), 3.82 (br. s, 1H, cyclohexyl), 2.76-2.63 (m, 2H, cyclohexyl), 1.81-1.08 (m, 18H, cyclohexyl). ^{13}C NMR: δ 166.7 (C=O), 154.8 (C=N), 148.7 (C=N), 140.6 (C=N), 134.7, 133.8, 133.5 131.9, 130.9, 130.2, 129.7, 128.2 ($C_{arom.}$), 99.8 (CCl_3), 72.2 (CH), 54.8, 52.1, 33.3, 33.8, 29.2, 27.0, 26.4, 25.2, 25.3, 23.7, 21.1 (cyclohexyl). FAB-MS: m/z 602 $[M+H]^+$. Anal. Calcd (%) for $C_{30}H_{34}Cl_3N_5O_2$ (602.99): C, 59.76; H, 5.68; N, 11.61. Found: C, 59.72; H, 5.66; N, 11.65.

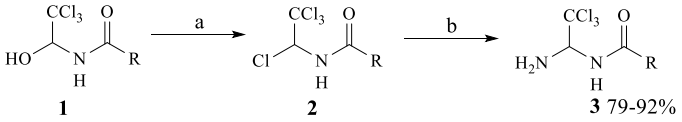
4-Methyl-N-(2,2,2-trichloro-1-(((2Z,4E)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4H-1,3,5-oxadiazin-4-ylidene)amino)ethyl)benzamide (8e). White crystals; yield 79% (4.87 g); mp 176-178°C (MeOH); R_f = 0.72. IR: ν_{max} 3377 (NH), 2924, 2849 (CH), 1714 (−N=C−O−C=N−C=N−), 1665 (C=O), 1624 (C=N) cm^{-1}. ^1H NMR: δ 8.34 (br. s, 1H, NH), 8.13 (d, J = 8.2 Hz, 2H, $H_{arom.}$), 7.76 (d, J = 7.8 Hz, 2H, $H_{arom.}$), 7.70-7.67 (m, 1H, $H_{arom.}$), 7.59-7.55 (m, 2H, $H_{arom.}$), 7.19 (d, J = 7.8 Hz, 2H, $H_{arom.}$), 6.92 (d, J = 8.6 Hz, 1H, CH), 4.83-4.78 (m, 1H, cyclohexyl), 3.80 (br. s, 1H, cyclohexyl), 2.76-2.62 (m, 2H, cyclohexyl), 2.36 (s, 3H, CH_3), 1.83-1.13 (m, 18H, cyclohexyl). ^{13}C NMR: δ 165.7 (C=O), 155.9 (C=N), 147.9 (C=N), 140.8 (C=N), 135.7, 133.7, 131.3, 128.6, 128.5, 128.3, 128.2, 127.6 ($C_{arom.}$), 95.5 (CCl_3), 73.0 (CH), 55.6, 52.5, 33.6, 33.5, 28.9, 26.8, 26.0, 25.5, 25.1, 23.6, 20.9

(cyclohexyl). FAB-MS: m/z 616 $[M+H]^+$. Anal. Calcd (%) for $C_{31}H_{36}Cl_3N_5O_2$ (617.01): C, 60.35; H, 5.88; N, 11.35. Found: C, 60.33; H, 5.85; N, 11.37.

2-Bromo-N-(2,2,2-trichloro-1-(((2Z,4E)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4H-1,3,5-oxadiazin-4-ylidene)amino)ethyl)benzamide (8f). White crystals; yield 68% (4.64 g); mp 98-100°C (MeOH); R_f = 0.45. ν_{max} 3358 (NH), 2930, 2847 (CH), 1718 (−N=C−O−C=N−C=N−), 1664 (C=O), 1632 (C=N) cm^{-1}. ^1H NMR: δ 9.21 (d, J = 8.8 Hz, 1H, NH), 8.17 (d, J = 7.3 Hz, 2H, $H_{arom.}$), 7.76-7.72 (m, 1H, $H_{arom.}$), 7.64-7.59 (m, 3H, $H_{arom.}$), 7.39-7.27 (m, 3H, $H_{arom.}$), 6.81 (d, J = 8.8 Hz, 1H, CH), 4.80-4.73 (m, 1H, cyclohexyl), 3.85 (br. s, 1H, cyclohexyl), 2.77-2.63 (m, 2H, cyclohexyl), 1.75-1.09 (m, 18H, cyclohexyl). ^{13}C NMR: δ 166.9 (C=O), 158.9 (C=N), 147.8 (C=N), 141.2 (C=N), 138.8, 134.7, 133.8, 132.9, 131.7, 128.6, 128.3, 127.6, 124.7, 119.9 ($C_{arom.}$), 101.0 (CCl_3), 72.4 (CH), 55.8, 53.0, 33.8, 33.4, 29.1, 26.8, 25.8, 25.7, 24.6, 23.4, 19.9 (cyclohexyl). FAB-MS: m/z 680 $[M+H]^+$. Anal. Calcd (%) for $C_{30}H_{33}BrCl_3N_5O_2$ (681.88): C, 52.84; H, 4.88; N, 10.27. Found: C, 52.81; H, 4.84; N, 10.31.

3. Results and Discussion

The starting *N*-(1-amino-2,2,2-trichloroethyl)carboxamides (**3**) were obtained in two stages based on *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamide (**1**) (Scheme 1). Initially, the hydroxyl group was replaced by chlorine under the action of thionyl chloride. The resulting chlorine derivatives **2** are solid, colorless substances easily hydrolyzed by atmospheric moisture. Therefore, immediately after receipt, they were used in further transformations. Amino derivatives **3** were synthesized by the action of a 25% aqueous ammonia solution on freshly prepared chlorine derivatives. Methyl *tert*-butyl ether was used as a solvent. After separating and evaporating the ether layer, amino derivatives **3** were obtained in 79-92% yields and of sufficient purity to be used in further transformations without additional purification.



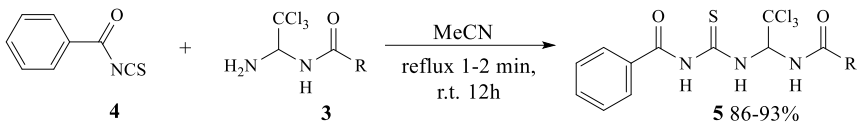
R = CH_3 (**a**), $CH{=}CH_2$ (**b**), $CH{=}CH{-}C_6H_5$ (**c**), C_6H_5 (**d**), $C_6H_4CH_3$ (**e**), 2-BrC_6H_4 (**f**).

Scheme 1. Synthesis of *N*-(1-amino-2,2,2-trichloroethyl)carboxamides (**3**). Reagents and conditions: **a** - $SOCl_2$, CCl_4, reflux 1.5-3 h; **b** - NH_3, MTBE, stirring 15 min, r.t. 30 min.

In the ^1H NMR spectra of the obtained products, the signal of the amino group appears as a doublet (rarely as a broadened singlet) at 2.78-2.70 ppm, and the CH signal of the proton appears as a quartet at 5.46-3.59 ppm, while in the case of starting compounds **1** it is represented by a doublet of doublets and slightly shifted to a weaker field (6.07-5.48 ppm) [51]. In the ^{13}C NMR spectra, the C=O signal of carbon appears at 168.8-165.6 ppm, while the CCl_3 and CH signals of carbon appear at 105.4-102.1 and 78.7-74.7 ppm, respectively. In the IR spectra of amino derivatives **3**, there is a characteristic intense broadened band at 3448-3411 cm^{-1} corresponding to the stretching vibrations of the amino group and a band corresponding to the C=O group at 1662-1648 cm^{-1}. Mass spectrometry data confirm the molecular weights of the resulting amino derivatives **3**.

The resulting *N*-(1-amino-2,2,2-trichloroethyl)carboxamides (**3**) readily react with benzoylisothiocyanate (**4**) to form the corresponding thioureas **5** (Scheme 2). *N*-((1-

Carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides (**5**) are formed in high yields (86-93%) and are easily isolated from the reaction mixture.

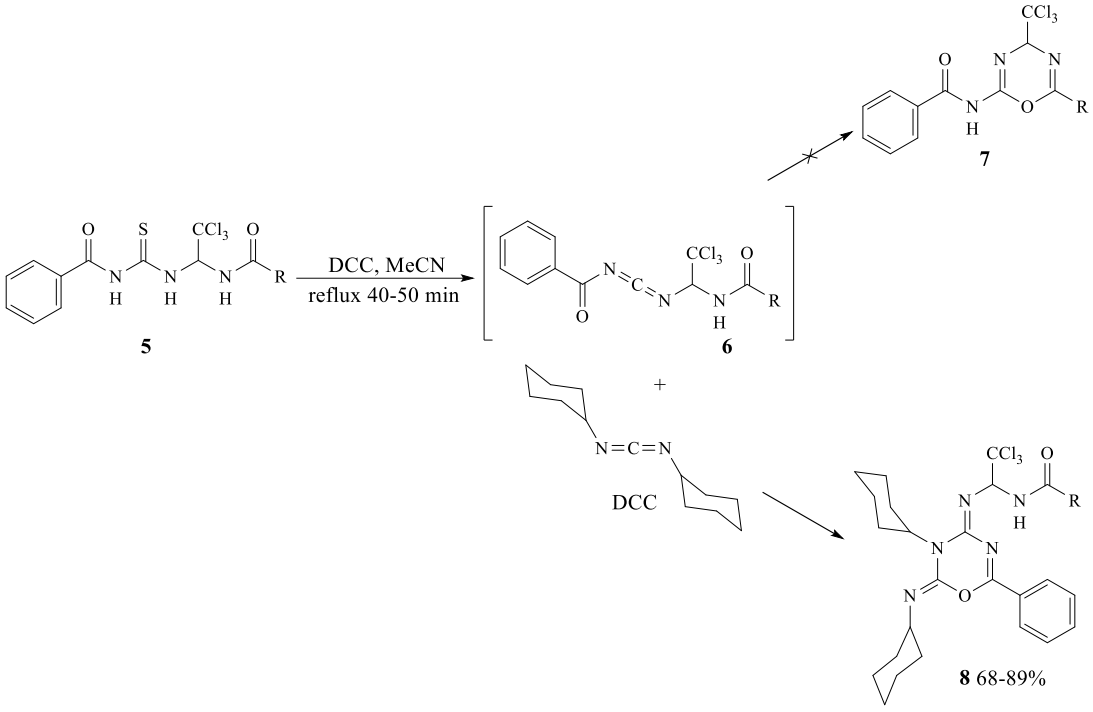


R = CH_3 (**a**), $CH=CH_2$ (**b**), $CH=CH-C_6H_5$ (**c**), C_6H_5 (**d**), $C_6H_4CH_3$ (**e**), 2-BrC_6H_4 (**f**).

Scheme 2. Synthesis of *N*-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides (**5**).

The ^{1}H NMR spectra of compounds **5a-f** are characterized by the presence of three NH proton signals, two of which are doublets at 11.97-11.78 and 9.66-9.35 ppm, and one is singlet at 11.89-11.48 ppm, while the CH signal of the proton shifted to the aromatic region. In the ^{13}C NMR spectra of thioureas **5**, a C=S carbon signal is observed at 182.7-181.0 ppm, as well as two C=O carbon signals at 170.0-166.9 and 166.0-167.3 ppm. Mass spectrometry data confirm the expected molecular weight of compounds **5**. In the IR spectra of the obtained thioureas, characteristics are the intense absorption bands of three NH and two C=O groups at 3364-2968 and 1664-1656 cm^{-1}, respectively.

Under the action of dicyclohexylcarbodiimide (DCC) on thioureas **5**, hydrogen sulfide is split off from the latter, and, presumably, carbodiimide **6** is formed. Carbodiimide **6** reacts with another DCC molecule to form the oxadiazine derivative **8**. It is noteworthy that the intramolecular cyclization of **6** with the formation of *N*-(6-R-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-yl)benzamides (**7**) does not occur (Scheme 3).



R = CH_3 (**a**), $CH=CH_2$ (**b**), $CH=CH-C_6H_5$ (**c**), C_6H_5 (**d**), $C_6H_4CH_3$ (**e**), 2-BrC_6H_4 (**f**).

Scheme 3. Synthesis of *N*-(2,2,2-trichloro-1-(((2*Z*,4*E*)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4*H*-1,3,5-oxadiazin-4-ylidene)amino)ethyl)carboxamides (**8**).

In the ^{1}H NMR spectra of oxadiazines **8**, two doublet signals of NH and CH protons are observed at 9.21-8.34 and 6.92-6.81 ppm, respectively. In the spectra of compounds like **7**, NH and CH protons appear as singlets at 10.17-8.71 and 5.80-5.50 ppm, respectively [43, 44].

This indicates that the alkylamide fragment does not take part in this transformation. At the same time, the presence of 22 characteristic signals of two cyclohexyl rings in the ^{1}H NMR spectrum indicates the passage of the [4+2] cycloaddition process. In addition, the addition of DCC to carbodiimide **6** and the formation of oxadiazines **8** is also confirmed by the data of mass spectrometry and ^{13}C NMR spectroscopy. Thus, the mass spectrometry data confirm the assumed molecular weight of compounds **8a-f**, and their ^{13}C NMR spectra lack the C=S signal, and only one C=O carbon signal at 171-166 ppm is observed. However, at the same time, these compounds are characterized by the presence of signals from three C=N groups in the region of 159-141 ppm. In the IR spectra of the obtained oxadiazines, the bands corresponding to the absorption of NH (3377-3354 cm^{-1}) and C=O (1667-1660 cm^{-1}) groups are of low intensity compared to the initial thioureas, but two intense bands in the region of 1718-1713 and 1632-1621 cm^{-1}, related to the symmetric and antisymmetric stretching vibrations of the group –N=C–O–C=N–C=N–.

4. Conclusions

We have developed a new method for the synthesis of 4*H*-1,3,5-oxadiazine derivatives based on the reaction of dehydrosulfurization of *N*-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides with a twofold excess of dicyclohexylcarbodiimide. Target products - *N*-(2,2,2-trichloro-1-(((2Z,4*E*)-3-cyclohexyl-2-(cyclohexylimino)-6-phenyl-2,3-dihydro-4*H*-1,3,5-oxadiazin-4-ylidene)amino)ethyl)carboxamides have been obtained in high yields, and complex spectral studies have reliably proved their structure.

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Conflicts of Interest

The authors declare no conflict of interest.

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