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A new method for the synthesis of 4*H*-1,3,5-oxadiazine derivatives

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Abstract: A new, simple method for the synthesis of 4*H*-1,3,5-oxadiazine derivatives was developed based on the dehydrogenation reaction of *N*-amidoalkylated thioureas with dicyclohexylcarbodiimide. The reaction was carried out in acetonitrile under reflux for 50–60 min. The precipitated products were easily purified by crystallization from acetonitrile or ethanol. The yields were 30–70%. The structure of the synthesized compounds was determined by IR, ^{1}H NMR, ^{13}C NMR, MS and X-ray crystallography.

Keywords: dehydrosulfurization; dicyclohexylcarbodiimide; heterocyclization; 4*H*-1,3,5-oxadiazine; thiourea.

Introduction

Azines are of immense importance in medicinal chemistry and in the pharmaceutical industry. They are widely used in agriculture and in the production of polymers, semiconductors and dyes. Compounds containing a 1,3,5-oxadiazine ring that exhibit pronounced antibacterial, antifungal [1–5], antitumor [6] and insecticidal [7, 8] activities, are of special importance.

Though there are several preparative approaches for the synthesis of 1,3,5-oxadiazine derivatives, many such compounds remain difficult to synthesize. In most cases, the reactions of [4+2] cycloaddition of heterodienes to dienophiles [9–11], cyclodehydration of polyfluoro-containing bisamidales [12] and introduction of an oxygen atom into the imidazole ring by the Baeyer-Villiger reaction are used for the synthesis of these structures [13].

Another approach includes the use of *N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)amides of carboxylic acids [14, 15], which, due to the advantageous arrangement of the two reaction sites (amide and thioureide), are suitable for closing six-membered rings. For obtaining 4*H*-1,3,5-oxadiazine derivatives, 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides were used as starting materials. In these compounds, the *p*-chlorophenyl substituent promotes amide-imide tautomerism [16], facilitating ring closure.

Results and discussion

The addition reaction of amines **2** to 4-chloro-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)benzamide (**1**) [14, 15] furnished a series of *N*-amidoalkylated derivatives of thioureas **3** (Scheme 1). Thioureas **3** can be of interest in medicinal chemistry [17–19].

In this work, compounds **3** were successfully used in the synthesis of new 4*H*-1,3,5-oxadiazine derivatives. First, dehydrosulfurization of thioureas **3** was conducted at reflux in anhydrous acetonitrile with a 10% excess of dicyclohexylcarbodiimide (DCC) [20] for 50–60 min. During the reaction, the initially colorless solution turned bright yellow because of the formation of dicyclohexylthiourea. This reaction is assumed to involve the formation of intermediate carbodiimide **4** [14] followed by cyclization leading to the closure of the 1,3,5-oxadiazine ring (Scheme 2). Products **5** were obtained in acceptable yields and easily purified.

The structure of compounds **5a–h** was confirmed by spectral analysis. For example, in the IR spectra, strong absorption bands at 1725–1735 cm^{-1} and 1645–1655 cm^{-1} are observed. This absorption can be attributed to the symmetric and antisymmetric valence vibrations of a group -N=C-O-C=N- with certainty [21]. In the ^{1}H NMR spectra, the signal of the methine proton located at a trichloromethyl group appears as a singlet at 5.70–5.50 ppm, which is in a stronger field compared to 7.40–6.00 ppm for compounds **3**. A singlet for the amino group is observed at 10.20–8.70 ppm. This result is consistent with the participation of both amide and thiourea fragments in the cyclization. There are no signals of carbons C=S and C=O, typical for the starting thioureas, in the ^{13}C NMR spectra of compounds **5** near 180 and 165 ppm. Instead, carbon signals of two imino groups located in the range

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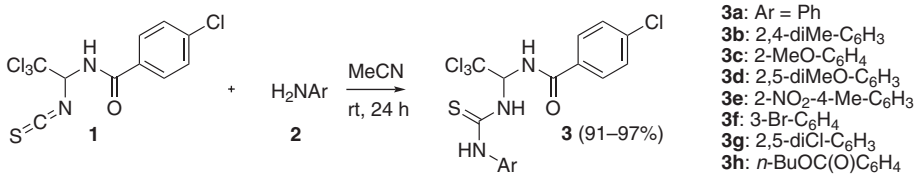
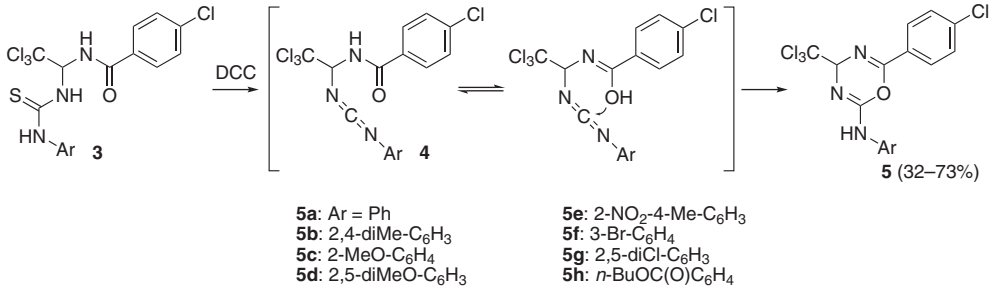


Scheme 1



Scheme 2

of 153–144 ppm can be seen. Because of the relative instability of compounds **5**, electron-impact mass spectra were uninformative. The intensity of the molecular ion peak does not exceed 1.0% in each case, and for some compounds, the molecular ion peak is not observed at all. The mass spectra recorded under fast-atom bombardment conditions are more informative. The molecular structure of compound **5d** was confirmed by an X-ray diffraction (XRD) study (Figure 1).

The oxadiazine ring is approximately flat [22, 23] to within 0.02 Å, and the N(3) atom also adopts a near-planar configuration with the sum of N-centered bond angles of 359(2)°. Both N(3)-C(2) 1.356(2) Å and N(3)-C(11) 1.405(2) Å bonds are slightly elongated compared to typical values of 1.339 Å and 1.353 Å, respectively [24], but are typical for arylamine derivatives of oxazole [25]. The {C(2), (N(3)-H(3), C(11)} fragment is almost coplanar with the oxadiazine ring and the {C(11)…C(16)} benzene moiety; the interfacial angles are 2.4° and 4.5°, respectively. That arrangement facilitates π-conjugation of the N(3) lone pair with the C(2)=N(2) moiety and the aromatic ring. The relative position of the ring is additionally stabilized by intramolecular hydrogen bonds. Both methoxy groups are deviated from the {C(11)…C(16)} benzene ring plane. The C(12)-C(13)-O(2)-C(17) torsion angle is 29.2(2)°. The C(11)-C(16)-O(3)-C(18) torsion angle of 14.1(2)° is slightly reduced due to the N(3)-H(3)…O(3) hydrogen bond. The *p*-chlorophenyl substituent is slightly rotated around the oxadiazine ring with the interfacial angle of 156(2)°, despite the presence of the attractive intramolecular contact C(6)-H(6)…N(1) 2.59 Å, for which the van der Waals radii sum is 2.67 Å. The C(1)-C(5) bond of 1.481(2) Å is elongated compared to a typical value of 1.463 Å [25], which indicates weakening of the π-conjugation between those rings.

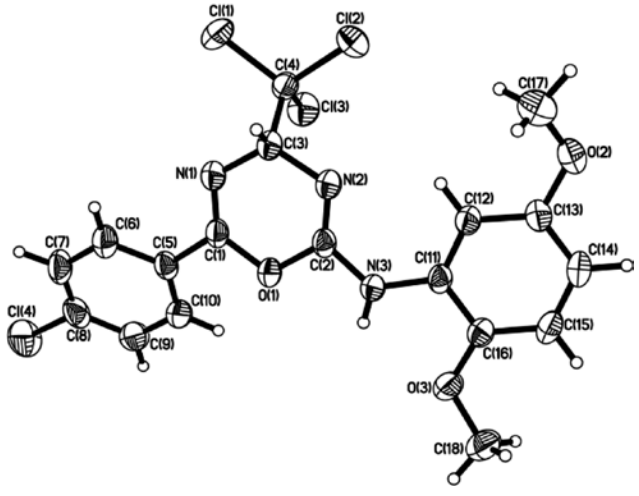


Figure 1 Molecular structure of 6-(4-chlorophenyl)-*N*-(2,5-dimetoxyphenyl)-4-(trichloro-methyl)-4*H*-1,3,5-oxadiazin-2-amine (**5d**) obtained from XRD data.

Conclusion

A new method for the synthesis of 4*H*-1,3,5-oxadiazines based on the dehydrosulfurization reaction of readily available *N*-amidoalkylated thioureas **3** was developed.

It allows obtaining cyclization products with acceptable yields and high degrees of purity.

Experimental

IR spectra were recorded in KBr pellets using a Spectrum BX II spectrometer. FAB mass spectra were recorded on a VG7070 instrument. Desorption of ions from the samples in *meta*-nitrobenzyl alcohol was carried out with a beam of argon atoms having an energy of 8 keV. EI mass spectra were recorded using a Kratos MS 890 spectrometer with direct sample injection into ion source; the temperature of the ionization chamber was 180–250°C and the ionization energy of the electrons was 70 eV. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded for solutions in DMSO-d_6 on a Varian VXR-400 spectrometer. Elemental analysis was performed on a LECO CHNS-900 instrument. Control of the reactions and the purity of compounds were performed by TLC on Silufol UV-254 plates eluting with chloroform/acetone (3:1).

General procedure for the synthesis of substituted thioureas 3a–h

The isothiocyanate **1** (3.44 g, 0.01 mol), prepared according to the method reported in [18], was dissolved in 15–18 mL of acetonitrile. Then, the solution was stirred vigorously and treated portion-wise, to avoid overheating, for 7–10 min, with 0.01 mol of the appropriate amine **2a–h**. After the addition was completed, stirring was stopped and the mixture was left at room temperature for 24 h. The resultant precipitate was filtered off, washed with acetonitrile (2×3 mL), and dried for 24 h at room temperature and then for 5 h at 100°C. The product **3a–h** was crystallized from EtOH.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-phenylthioureido)ethyl)benzamide (3a) Pale yellow solid; yield 97% (4.24 g); mp 214–216°C (dec); R_f = 0.72; ^{1}H NMR: δ 10.33 (s, 1H), 9.03 (d, J = 7.6 Hz, 1H), 7.96 (br. s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.51–7.44 (m, 5H), 7.35–7.31 (m, 2H), 7.15 (t, J = 7.1 Hz, 1H); ^{13}C NMR: δ 180.22 (C=S), 164.1 (C=O), 138.3, 136.8, 131.9, 129.2, 128.3, 127.9, 124.4, 123.0 (arom.), 101.8 (CCl_3), 70.2 (CH); IR: ν_{max} 3280 (NH), 3173, 3075 (CH), 1640 (C=O), 1592, 1550, 1506, 1483, 1329, 1272, 1135, 1081, 799, 695 cm^{-1}; FAB-MS: *m/z* 438 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}Cl_4N_3OS$ (437.18): C, 43.96; H, 3.00; Cl, 32.44; N 9.61; S, 7.33. Found: C, 43.91; H, 2.95; Cl, 32.49; N, 9.68; S, 7.35.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-(2,4-dimethylphenyl)thioureido)ethyl)benzamide (3b) Pale yellow solid; yield 94% (4.37 g); mp 210–211°C (dec); R_f = 0.75; ^{1}H NMR: δ 10.00 (s, 1H), 9.21 (br. s, 1H), 7.88 (d, J = 8.3 Hz, 2H), 7.62–7.57 (m, 3H), 7.12–7.07 (m, 3H), 2.29 (s, 3H), 2.17 (s, 3H); ^{13}C NMR: δ 181.5 (C=S), 164.4 (C=O), 136.8, 136.0, 134.7, 131.8, 131.2, 129.3, 128.6, 128.0, 127.6, 127.0 (arom.), 102.0 (CCl_3), 70.3 (CH), 20.6 (CH_3), 17.5 (CH_3). IR: ν_{max} 3310, 3258 (NH), 3094, 3027, 2942 (CH), 1654 (C=O), 1647, 1596, 1506, 1482, 1329, 1298, 1270, 1138, 798 cm^{-1}; FAB-MS: *m/z* 466 $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}Cl_4N_3OS$ (465.23): C, 46.47; H, 3.68; Cl, 30.48; N 9.03; S, 6.89. Found: C, 46.40; H, 3.64; Cl, 30.51; N, 9.08; S, 6.84.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-(2-methoxyphenyl)thioureido)ethyl)benzamide (3c) Pale yellow solid; yield 95% (4.44 g); mp 192–194°C (dec); R_f = 0.73; ^{1}H NMR: δ 9.85 (s, 1H), 9.20 (br. s, 1H), 8.09 (br. s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.74 (br. s, 1H), 7.56–7.49 (m, 3H), 7.17–7.16 (m, 1H), 7.03–7.01 (m, 1H), 6.92 (dd, J = 7.1, 6.9 Hz, 1H) 3.82 (s, 3H); ^{13}C NMR: δ 180.8 (C=S), 164.4 (C=O), 152.0, 136.7, 131.9, 129.4, 128.9, 128.1, 126.6, 126.3, 119.6, 111.2 (arom.), 101.7 (CCl_3), 70.3 (CH), 55.3 (CH_3O); IR: ν_{max} 3267 (NH), 3084, 3060, 2930, 2837 (CH), 1649 (C=O), 1595, 1535, 1505, 1483, 1463, 1332, 1259, 1130, 1109, 1029, 744 cm^{-1}; FAB-MS: *m/z* 468 $[M+H]^+$. Anal. Calcd for $C_{17}H_{15}Cl_4N_3O_2S$ (467.20): C, 43.70; H, 3.24; Cl, 30.35; N 8.99; S, 6.86. Found: C, 43.68; H, 3.21; Cl, 30.38; N, 9.03; S, 6.84.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-(2,4-dimethoxyphenyl)thioureido)ethyl)benzamide (3d) Pale yellow solid; yield 91% (4.52 g); mp 216–218°C (dec); R_f = 0.75; ^{1}H NMR: δ 9.95 (s, 1H), 9.29 (br. s, 1H), 8.24 (br. s, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.58–7.44 (m, 4H), 7.00 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H); ^{13}C NMR: δ 180.6 (C=S), 164.6 (C=O), 152.3, 146.1, 136.7, 131.3, 129.5, 128.4, 127.2, 112.2, 112.0, 111.0 (arom.), 101.6 (CCl_3), 70.2 (CH), 55.9 (CH_3O), 55.3 (CH_3O); IR: ν_{max} 3286, 3266 (NH), 2939, 2832 (CH), 1655 (C=O), 1609, 1595, 1549, 1509, 1482, 1279, 1246, 1137, 1115, 793 cm^{-1}; EI-MS: *m/z* 497 $[M]^+$ (2.6%). Anal. Calcd for $C_{18}H_{17}Cl_4N_3O_3S$ (497.23): C, 43.48; H, 3.45; Cl, 28.52; N, 8.45; S, 6.45. Found: C, 43.45; H, 3.43; Cl, 28.55; N, 8.49; S, 6.43.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-(4-methoxy-2-nitrophenyl)thioureido)ethyl)benzamide (3e) Pale yellow solid; yield 92% (4.71 g); mp 216–218°C (dec); R_f = 0.76; ^{1}H NMR: δ 10.33 (s, 1H), 9.41 (d, J = 7.8 Hz, 1H), 8.39 (d, J = 9.3 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.54–7.46 (m, 3H), 7.32 (dd, J = 9.3, 8.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR: δ 182.9 (C=S), 164.7 (C=O), 157.4, 145.8, 136.8, 131.9, 131.7, 129.5, 128.5, 124.9, 119.6, 109.0 (arom.), 101.5 (CCl_3), 70.6 (CH), 55.1 (CH_3O); IR: ν_{max} 3240 (NH), 3072, 3011, 2835 (CH), 1645 (C=O), 1598, 1530, 1510, 1333, 1263, 1132, 1030, 805, 728 cm^{-1}; FAB-MS: *m/z* 513 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}Cl_4N_4O_4S$ (512.18): C, 39.87; H, 2.76; Cl, 27.69; N, 10.94; S, 6.26. Found: C, 39.90; H, 2.74; Cl, 27.72; N, 10.98; S, 6.24.

***N*-(1-(3-(3-Bromophenyl)thioureido)-2,2,2-trichloroethyl)-4-chlorobenzamide (3f)** Pale yellow solid; yield 92% (4.75 g); mp 215–217°C (dec); R_f = 0.73; ^{1}H NMR: δ 10.63 (s, 1H), 9.24 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 9.3 Hz, 1H), 7.90–7.88 (m, 3H), 7.62–7.60 (m, 2H), 7.52 (dd, J = 9.3, 8.3 Hz, 1H), 7.42–7.32 (m, 3H); ^{13}C NMR: δ 180.4 (C=S), 164.6 (C=O), 140.1, 136.8, 131.8, 130.7, 129.4, 128.5, 127.5, 125.3, 121.8, 121.2 (arom.), 101.5 (CCl_3), 70.1 (CH); IR: ν_{max} 3290, 3238 (NH), 3091, 2940 (CH), 1651 (C=O), 1594, 1505, 1484, 1330, 1283, 1139, 706 cm^{-1}; FAB-MS: *m/z* 516 $[M]^+$. Anal. Calcd for $C_{16}H_{12}BrCl_4N_3OS$ (516.07): C, 37.24; H, 2.34; Cl, 27.48; N, 8.14; S, 6.21. Found: C, 37.21; H, 2.32; Cl, 27.51; N, 8.18; S, 6.19.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-(2,5-dichlorophenyl)thioureido)ethyl)benzamide (3g) Pale yellow solid; yield 93% (4.71 g); mp 213–215°C (dec); R_f = 0.73; ^{1}H NMR: δ 10.28 (s, 1H), 9.42 (s, 1H), 8.51 (s, 1H), 7.91–7.84 (m, 3H), 7.61–7.53 (m, 4H), 7.37 (s, 1H); ^{13}C NMR: δ 182.1 (C=S), 164.8 (C=O), 136.96, 136.8, 131.9, 131.0, 130.7, 129.6, 128.7, 128.5, 127.7, 127.3 (arom.), 101.4 (CCl_3), 70.5 (CH); IR: ν_{max} 3288 (NH), 3085, 2948, 2827 (CH), 1654 (C=O), 1595, 1502, 1483, 1331, 1137, 1094, 803, 740 cm^{-1}; FAB-MS: *m/z* 506 $[M]^+$. Anal. Calcd for $C_{16}H_{11}Cl_6N_3OS$ (506.04): C, 37.98; H, 2.19; Cl, 42.03; N, 8.30; S, 6.34. Found: C, 38.01; H, 2.16; Cl, 42.08; N, 8.26; S, 6.31.

Butyl-4-(3-(2,2,2-trichloro-1-(4-chlorobenzamido)ethyl)thioureido)benzoate (3h) Pale yellow solid; yield 94% (5.05 g); mp 211–213°C (dec); R_f = 0.75; ^{1}H NMR: δ 10.81 (s, 1H), 9.30 (d, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 9.3 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.52 (t, *J* = 8.8 Hz, 1H), 4.26 (t, *J* = 6.3 Hz, 2H), 1.68 (qi, *J* = 6.8 Hz, 2H), 1.40 (sx, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: δ 180.2 (C=S), 165.1, 164.7 (C=O), 143.1, 136.8, 131.8, 129.8, 129.4, 128.5, 125.4, 121.6 (arom.), 101.4 (CCl_3), 70.1 (CH), 64.2, 30.3, 18.8, 13.6 (*n*-Bu); IR: ν_{max} 3245 (NH), 3076, 2959, 2936, 2867 (CH), 1706, 1656 (C=O), 1537, 1501, 1481, 1310, 1279, 1126, 1015, 724 cm^{-1}; FAB-MS: *m/z* 538 $[M+H]^+$. Anal. Calcd for $C_{21}H_{21}Cl_4N_3O_3S$ (537.28): C, 46.95; H, 3.94; Cl, 26.39; N, 7.82; S, 5.97. Found: C, 46.97; H, 3.93; Cl, 26.43; N, 7.84; S, 5.94.

General procedure for the synthesis of 4*H*-1,3,5-oxadiazines 5a–h

DCC (1.13 g, 5.5 mmol) was added to 5 mmol of a thiourea **3a–h** in 20 mL of acetonitrile, and the mixture was heated under reflux for 50–60 min. During the reaction, the precipitate of thiourea **3a–h** gradually dissolved, and the solution turned yellow due to formation of dicyclohexylthiourea. After completion, the solution was filtered while hot, and the filtrate was left at room temperature for 24 h. The precipitated crystals were filtered off and washed with acetonitrile (2×5 mL), then dried and crystallized from the appropriate solvent indicated below.

6-(4-Chlorophenyl)-*N*-phenyl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (5a) White crystals; yield 63% (1.27 g); mp 146–148°C (EtOH); R_f = 0.71; ^{1}H NMR: δ 9.75 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.73–7.69 (m, 4H), 7.33 (m, 2H), 7.03 (m, 1H), 5.70 (s, 1H). ^{13}C NMR: δ 152.3 (C=N), 145.0 (C=N), 138.9, 138.2, 137.6, 129.7, 129.4, 128.7, 128.1, 121.8, 118.5 (arom.), 103.0 (CCl_3), 79.6 (CH); IR: ν_{max} 3414 (NH), 2928, 2854, 1731 (-N=C-O-C=N-), 1651 (C=N), 1602, 1540, 1446, 1318, 1131, 1091, 1021, 830 cm^{-1}; FAB-MS: *m/z* 404 $[M+H]^+$. Anal. Calcd for $C_{16}H_{11}Cl_4N_3O$ (403.10): C, 47.68; H, 2.75; Cl, 35.18; N 10.42. Found: C, 43.64; H, 3.18; Cl, 30.41; N, 10.47.

6-(4-Chlorophenyl)-*N*-(2,4-dimethylphenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (5b) White crystals; yield 62% (1.34 g); mp 150–152°C (EtOH); R_f = 0.74; ^{1}H NMR: δ 8.79 (s, 1H), 8.04 (d, *J* = 6.0 Hz, 2H), 7.62 (d, *J* = 6.0 Hz, 2H), 7.45–7.44 (m, 1H), 7.01–6.97 (m, 2H), 5.50 (s, 1H), 2.26 (s, 3H), 2.25 (s, 3H). ^{13}C NMR: δ 152.38 (C=N), 146.53 (C=N), 137.5, 133.8, 132.8, 131.5, 130.7, 128.8, 128.7, 128.2, 126.4, 124.6 (arom.), 103.3 (CCl_3), 79.5 (CH), 20.3 (CH_3), 17.7 (CH_3); IR: ν_{max} 3433 (NH), 3088, 3020, 2918, 2881 (CH), 1736 (-N=C-O-C=N-), 1648 (C=N), 1596, 1537, 1490, 1403, 1304, 1133, 1087, 1014, 832 cm^{-1}; FAB-MS: *m/z* 432 $[M+H]^+$. Anal. Calcd for $C_{18}H_{15}Cl_4N_3O$ (431.15): C, 50.14; H, 3.51; Cl, 32.89; N 9.75. Found: C, 50.11; H, 3.48; Cl, 32.92; N, 9.78.

6-(4-Chlorophenyl)-*N*-(2-methoxyphenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (5c) White crystals; yield 50% (1.08 g); mp 165–167°C (MeCN); R_f = 0.78; ^{1}H NMR: δ 8.80 (s, 1H), 8.18–8.16 (m, 3H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.01 (m, 2H), 6.91–6.90 (m, 1H), 5.60 (s, 1H), 3.87 (s, 3H). ^{13}C NMR: δ 152.5 (C=N), 149.2 (C=N), 145.6, 137.5, 129.2, 128.6, 128.1, 126.5, 123.3, 120.7, 120.1, 110.7 (arom.), 103.1 (CCl_3), 79.3 (CH), 55.5 (CH_3O); IR: ν_{max} 3407 (NH), 2962, 2933, 2883, 2838 (CH), 1732 (-N=C-O-C=N-), 1654 (C=N), 1600, 1540, 1483, 1463, 1402, 1324, 1290, 1253, 1209, 1138, 1105, 1089, 831 cm^{-1}; FAB-MS: *m/z* 434 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}Cl_4N_3O_2$ (433.12): C, 47.14; H, 3.03; Cl, 32.74; N 9.70. Found: C, 47.11; H, 3.00; Cl, 32.77; N, 9.75.

6-(4-Chlorophenyl)-*N*-(2,5-dimethoxyphenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (5d) White crystals; yield 32% (0.74 g); mp 157–159°C (MeCN); R_f = 0.74; ^{1}H NMR: δ 8.71 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 2H), 8.04 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 2H), 6.91–6.89 (m, 1H), 6.53–6.51 (m, 1H), 5.60 (s, 1H), 3.84 (s, 3H), 3.68 (s, 3H); ^{13}C NMR: δ 152.91 (C=N), 152.44 (C=N), 145.41, 142.76, 137.56, 129.23, 128.44, 128.04, 127.41, 111.42, 107.39, 106.48 (arom.), 103.06 (CCl_3), 79.37 (CH), 56.10 (CH_3O), 54.99 (CH_3O); IR: ν_{max} 3397 (NH), 3091, 2960, 2939, 2895, 2834 (CH), 1731 (-N=C-O-C=N-), 1649 (C=N), 1605, 1542, 1484, 1329, 1221, 1142, 1039, 835 cm^{-1}; FAB-MS: *m/z* 463 $[M]^+$. Anal. Calcd for $C_{18}H_{15}Cl_4N_3O_3$ (463.15): C, 46.68; H, 3.26; Cl, 30.62; N, 9.07. Found: C, 46.65; H, 3.24; Cl, 30.65; N, 9.10.

X-ray crystallographic analysis of 5d

Crystals of **5d** ($C_{18}H_{15}Cl_4N_3O_3$, M_r=463.13) are monoclinic, $P2_1/c$, *a* = 13.5203(4), *b* = 10.2156(3), *c* = 14.5892(5) Å, β = 102.021(3)°, V = 1970.85(11) Å^3, Z = 4, d_{Calc}=1 .561 g sm, μ (MoKα) = 0.626 mm^{-1}, F(000) = 944; 17744 reflections (5780 independent, R_{int}=0.024) were collected on an (Xcalibur-3) diffractometer at room temperature (MoKα radiation, CCD-detector, graphite monochromator, ω-scanning, 2θ max = 60°). The structure was solved by direct methods and refined against F^2 within anisotropic approximation for all non-hydrogen atoms by a full-matrix least squares procedure using the OLEX2 [26] program package with the SHELXS and SHELXL [27] modules. All H atoms were located from the difference electronic map and constrained to ride on their parent atoms with $U_{iso} = 1.2U_{eq}$ (except $U_{iso} = 1.5U_{eq}$ for methyl groups), except the H(3) atom that was refined isotropically without any constraints. Final refinement was converged at wR_2 = 0.095 for all 5766 reflections (R_1 = 0.038 for 4093 reflections with F > 4σ(F), S = 1.02). Atom coordinates and crystallographic parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 1438671). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

6-(4-Chlorophenyl)-*N*-(4-methoxy-2-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (5e) White crystals; yield 56% (1.34 g); mp 175–177°C (MeCN); R_f = 0.70; ^{1}H NMR: δ 9.66 (s, 1H), 8.02–8.01 (m, 2H), 7.91–7.86 (m, 1H), 7.69–7.67 (d, *J* = 8.3 Hz, 2H), 7.54 (s, 1H), 7.37–7.35 (m, 1H), 5.60 (s, 1H), 3.85 (s, 3H). ^{13}C NMR: δ 155.6 (C=N), 152.0 (C=N), 145.9, 142.2, 137.7, 128.9, 128.9, 127.8, 127.0, 124.1, 120.6, 109.1 (arom.), 102.7 (CCl_3), 79.2 (CH), 55.9 (CH_3); IR: ν_{max} 3326 (NH), 3096, 2933, 2853 (CH), 1728 (-N=C-O-C=N-), 1647 (C=N), 1583, 1516, 1314, 1288, 1127, 1090, 1034, 837, 813 cm^{-1}; FAB-MS: *m/z* 479 $[M+H]^+$. Anal. Calcd for $C_{17}H_{12}Cl_4N_4O_4$ (478.11): C, 42.71; H, 2.53; Cl, 29.66; N, 11.72. Found: C, 42.74; H, 2.50; Cl, 29.69; N, 11.75.

***N*-(3-Bromophenyl)-6-(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (5f)** White crystals; yield 73% (1.76 g); mp 148–150°C (EtOH); R_f = 0.72; ^{1}H NMR: δ 9.94 (s, 1H), 8.17 (s, 1H), 8.03 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.25 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 5.70 (s, 1H). ^{13}C NMR: δ

152.1 (C=N), 144.9 (C=N), 139.8, 137.6, 130.4, 128.8, 128.8, 127.9, 124.8, 121.6, 120.9, 117.1 (arom.), 102.9 (CCl_3), 79.1 (CH); IR: ν_{max} 3409 (NH), 3098, 3076 (CH), 1733 (-N=C-O-C=N-), 1652 (C=N), 1596, 1528, 1307, 1132, 1091, 830 cm^{-1}: FAB-MS: *m/z* 482 $[M]^+$. Anal. Calcd for $C_{16}H_{10}BrCl_4N_3O$ (481,99): C, 39.87; H, 2.09; Cl, 29.42; N 8.72. Found: C, 39.80; H, 2.01; Cl, 29.49; N, 8.75.

6-(4-Chlorophenyl)-*N*-(2,5-dichlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (5g) White crystals; yield 60% (1.42 g); mp 147–150°C (MeCN); $R_f = 0.73$; ^1H NMR: δ 9.34 (s, 1H), 8.33 (br. s, 1H), 8.14 (m, 2H), 7.68 (d, $J = 7.8$ Hz, 2H), 7.55–7.53 (d, $J = 8.8$ Hz, 1H), 7.22 (d, $J = 7.3$ Hz, 1H), 5.71 (s, 1H); ^{13}C NMR: δ 152.13 (C=N), 145.74 (C=N), 137.7, 133.1, 131.6, 130.6, 129.6, 129.2, 128.8, 127.8, 124.3, 123.2 (arom.), 102.8 (CCl_3), 79.1 (CH); IR: ν_{max} 3325 (NH), 3100, 2975, 2857 (CH), 1731 (-N=C-O-C=N-), 1654 (C=N), 1587, 1530, 1410, 1138, 1092, 830 cm^{-1}; FAB-MS: *m/z* 472 $[M]^+$. Anal. Calcd for $C_{16}H_9Cl_6N_3O$ (471.97): C, 40.72; H, 1.92; Cl, 45.07; N, 8.90. Found: C, 40.76; H, 1.89; Cl, 45.11; N, 8.94.

Butyl-4-((6-(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-yl)amino)benzoate (5h) White crystals; yield 58% (1.46 g); mp 86–89°C (MeCN); $R_f = 0.75$; ^1H NMR: δ 10.17 (s, 1H), 8.07 (d, $J = 8.3$ Hz, 2H), 7.94 (d, $J = 8.3$ Hz, 2H), 7.85 (d, $J = 8.3$ Hz, 2H), 7.71 (d, $J = 8.3$ Hz, 2H), 5.76 (s, 1H), 4.24 (t, $J = 5.9$ Hz, 2H), 1.68 (qi, $J = 6.8$ Hz, 2H), 1.43 (sx, $J = 7.3$ Hz, 2H), 0.93 (dd, $J = 7.3$, 6.8 Hz, 3H); ^{13}C NMR: δ 165.2 (C=O), 152.2 (C=N), 144.9 (C=N), 142.8, 137.6, 133.9, 130.1, 128.8, 127.9, 123.3, 117.8 (arom.), 102.8 (CCl_3), 79.7 (CH), 64.0, 30.3, 18.8, 13.6 (*n*-Bu); IR: $\nu_{max} = 3366$ (NH), 3199, 3076, 2961, 2875, 2732 (CH), 1712 (-N=C-O-C=N-), 1670 (C=O), 1600 (C=N), 1544, 1284, 1179, 1142, 1118, 1075, 833, 765 cm^{-1}; FAB-MS: *m/z* 506 $[M+3H]^+$. Anal. Calcd for $C_{21}H_{19}Cl_4N_3O_3$ (503.20): C, 50.13; H, 3.81; Cl, 28.18; N, 8.35. Found: C, 50.16; H, 3.78; Cl, 28.21; N, 8.38.

Supporting information

XRD data for compound **5d** are given in the online supplement.

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References

[1] El-Ziaty, A. K.; Shiba, S. A. Antibacterial activities of new (*E*)-2-Cyano-3-(3′,4′-dimethoxyphenyl)-2-propenoylamide derivatives. *Synth. Commun*. **2007**, *37*, 4043–4057.

[2] Patel, H. S.; Patel, K. B. Synthesis and biological activity of 3-[4*H*-(1,2,4)-triazolyl]-2,6-diaryl-1,3,5-oxadiazine-4-thione. *Phosphorus, Sulfur Silicon Relat. Elem*. **2009**, *184*, 2443–2452.

[3] Rambabu, N.; Viral, B. M.; Kirti, J. G. Synthesis and characterization of *N*-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2,6-diphenyl-4-thioxo-2*H*-1,3,5-oxadiazin-3(4*H*)-yl) benzenesulfonamide. *Der Pharma Chemica* **2012**, *4*, 511–516.

[4] Rambabu, N.; Ramachandran, D.; Viral, B. M.; Kirti, J. G. Synthesis, characterization and biological evaluation of 2,6-diphenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl) phenyl)-2*H*-1,3,5-oxadiazine-4(3*H*)-thione. *Der Pharma Chemica* **2012**, *4*, 639–643.

[5] Patel, K. H.; Mehta, A. G. Synthesis and antifungal activity of [(4-(2-naphthalenyl)thiazol-2-yl)-2-(substitutedphenyl)-6-phenyl-4-thioxo-1,3,5-oxadiazine]derivatives. *Der Chemica Sinica* **2012**, *3*, 1410–1414.

[6] Ke, S.; Cao, X.; Liang, Y.; Wang, K.; Yang, Z. Synthesis and biological properties of dihydro-oxadiazine-based heterocyclic derivatives. *Mini Rev. Med. Chem*. **2011**, *11*, 642–657.

[7] Ford, K. A.; Casida, J. E.; Chandran, D.; Gulevich, A. G.; Okrent, R. A.; Durkin, K. A.; Sarpong, R.; Bunnelle, E. M.; Wildermuth, M. C. Neonicotinoid insecticides induce salicylateassociated plant defense responses. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 17527–17532.

[8] Cattaneo, M. G.; Yafuso, Ch.; Schmidt, Ch.; Huang, Ch.; Rahman, M.; Olson, C.; Ellers-Kirk, Ch.; Orr, B. J.; Marsh, S. E.; Antilla, L.; et al. Farm-scale evaluation of the impacts of transgenic cotton on biodiversity, pesticide use, and yield. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 7571–7576.

[9] Shiba, S. A. Decomposition of 2-propenoyl azide derivatives. Synthesis and larvicidal activity of novel products. *Arch. Pharm. Pharm. Med. Chem*. **1998**, *331*, 91–96.

[10] Shiba, S. A. Synthesis and insecticidal activity of novel acrylonitrile derivatives. *Phosphorus, Sulphur Silicon Relat. Elem*. **1996**, *114*, 29–37.

[11] Assy, M. G.; Haiekl, A.; Moustafa, H. Y. Behavior of terephthaloyl isothiocyanate towards carbon and nitrogen reagents. *Phosphorus, Sulphur Silicon Relat. Elem*. **1995**, *106*, 179–185.

[12] Sokolov, V. B.; Aksinenko, A. Y.; Martynov, I. V. Hexafluoroacetone and methyl trifluoropyruvate acylimines in the cyclocondensation with amides. *Rus. J. Gen. Chem*. **2012**, *82*, 1180–1182.

[13] Shobana, N.; Farid, P. 1,3,5-Oxadiazines and 1,3,5-thiadiazines. In *Comprehensive Heterocyclic Chemistry III*, Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor R. J. K., Eds. Elsevier Ltd: Amsterdam, 2008; Vol. 9, pp 457–521.

[14] Lynch, J. K.; Huang, P.; Bai, H. Titanium tetraisopropoxide catalyzed synthesis of base-sensitive cyanoguanidine analogs. *Synth. Commun*. **2005**, *35*, 1–7.

[15] Zadorozhnii, P. V.; Kiselev, V. V.; Kharchenko, A. V. Synthesis of nitrogen-containing heterocycles based on *N*-(isothiocyanatoalkyl)carboxamides. In *Modern Directions in Chemistry, Biology, Pharmacy and Biotechnology*, Novikov, V. P., Ed. Lviv Polytechnic Publishing House: Lviv, 2015; pp 212–219.

[16] Laurella, S. L.; Sierra, M. G.; Furlong, J. J. P.; Allegretti, P. E. Substituent, temperature and solvent effects on the keto-enol EQUILIBRIUM in β-ketoamides: A nuclear magnetic resonance study. *Open J. Phys. Chem*. **2013**, *3*, 138–149.

[17] Boyce, M.; Bryant, K.; Jousse, C.; Long, K.; Harding, H. P.; Scheuner, D.; Kaufman, R. J.; Ma, D.; Coen, D. M.; Ron, D.; et al. A selective inhibitor of eIF2a dephosphorylation protects cells from ER stress. *Science* **2005**, *307*, 935–939.

[18] Liu, J.; He, K.-L.; Li, X.; Li, R.-J.; Liu, C.-L.; Zhong, W.; Li, S. SAR, cardiac myocytes protection activity and 3D-QSAR studies of salubrinal and its potent derivatives. *Curr. Med. Chem*. **2012**, *19*, 6072–6079.

[19] Komoike, Y.; Inamura, H.; Matsuoka, M. Effects of salubrinal on cadmium-induced apoptosis in HK-2 human renal proximal tubular cells. *Arch. Toxicol*. **2012**, *86*, 37–44.
[20] Ulrich, H. Chemistry and technology of carbodiimides; Wiley-VCH: New York, 2007.
[21] Burger, K.; Simmerl, R. Reaktionen mit in situ erzeugten hetero-1,3-dienen: 4-*H*-1,3,5-oxadiazine aus perhaloketonen und cyanamiden. *Synthesis* **1983**, *3*, 237–238.
[22] Onys'ko, P. P.; Sinitsa, A. A.; Pirozhenko, V. V.; Chernega, A. N. Synthesis of phosphorylated 1,3,5-oxadiazines via *N*-acyltrifluoroacetimidoilphosphonates. *Heteroatom Chem*. **2002**, *13*, 22–26.
[23] Kennard, K. K.; Byriel, K. A.; Woon, T. Ch.; Fairlie, D. P. Structure of a novel protonated oxadiazine: an unusual heterocycle from the cycloaddition of a ketone with nitriles. *Chem. Commun*. **1996**, *15*, 1731–1732.
[24] Bürgi, H.-B.; Dunitz, J. D. Structure correlation, Vol. 2. VCH: Weinheim, 1994, 741–784.
[25] Allen, F. H. The Cambridge Structural Database: a quarter of a million crystal structures and rising. *Acta. Cryst. B*. **2002**, *58*, 380–388.
[26] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. J. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst*. **2009**, *42*, 339–341.
[27] Sheldrick, G. M. A short history of SHELX. *Acta. Cryst*. **2008**, *A64*, 112–122.

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