

Proceeding Paper

Synthesis of 6-(4-Chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines: Comparative Evaluation of Dehydrosulfurization Methods of Starting 4-Chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides [†]

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† Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry; Available online: <https://ecsoc-26.sciforum.net>.

Abstract: Derivatives of 1,3,5-oxadiazine are of interest to pharmacy, medicine, and agriculture as potential biologically active substances. These compounds have found wide application in organic synthesis and supramolecular chemistry. In this paper, we discuss and compare the effectiveness of two approaches to the dehydrosulfurization of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides resulting in the formation of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines. Dicyclohexylcarbodiimide (DCC) or a mixture of iodine with triethylamine was used as a dehydrosulfurizing agent. It is shown that in the case of using DCC, the target products are predominantly formed in high yields. However, the use of the I₂ + Et₃N mixture made it possible to obtain several new compounds of this class, which could not be obtained under the DCC action. The structure of all new compounds was confirmed by ¹H and ¹³C NMR spectroscopy data.

Keywords: synthesis; 4*H*-1,3,5-oxadiazine; dicyclohexylcarbodiimide; dehydrosulfurization

Citation: Lominoga, E.R.; Zadorozhnii, P.V.; Kiselev, V.V.; Kharchenko, A.V. Synthesis of 6-(4-Chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines: Comparative Evaluation of Dehydrosulfurization Methods of Starting 4-Chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides. *Chem. Proc.* **2022**, *4*, x. <https://doi.org/10.3390/xxxxx>

Academic Editor(s):

Published: 15 November 2022

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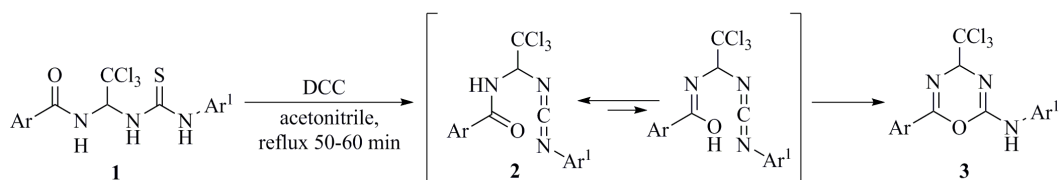
1. Introduction

Derivatives of 1,3,5-oxadiazine are of great interest in medicine, pharmacy, and agriculture as biologically active substances [1–4]. For example, these substances exhibit antibacterial [5–9], antifungal [8,9], antitumor [3,10], insecticidal [11], herbicidal [12], and larvicidal [13,14] activity. 1,3,5-Oxadiazine derivatives can be used in human practice as ionic liquids [15], polymers [16], and explosives [17], as well as in organic and supramolecular chemistry for the synthesis of molecular clips and other compounds [1,18–21].

To date, only two natural compounds containing the 1,3,5-oxadiazine ring are known. The first is the alkaloid Fissoldhimine from a plant of the genus *Fissistigma oldhamii* isolated in 1994 [22]. The second is the alkaloid Alboinon from the ascidians of the genus *Dendroa grossularia* [23], isolated in 1997. Mostly, substances with this cycle are obtained synthetically, using cycloaddition reactions [6–9,24–28], intramolecular cyclization of diols [11,29,30], bisamidals [1], or transformation of other cycles [17,31].

Previously, we developed a new method for the synthesis of 4*H*-1,3,5-oxadiazine derivatives (**3**) based on the dehydrosulfurization of *N*-amidoalkylated thioureas (**1**) by the action of dicyclohexylcarbodiimide (DCC) (Scheme 1) [32–35]. It is assumed that carbodiimide **2** is formed as an intermediate, which is then closed to oxadiazine **3**. This method makes it possible to obtain 1,3,5-oxadiazine derivatives in sufficiently high

yields, but it is very limited in terms of the variety of possible substituents of the thioureide fragment. In some cases, products **3** could not be isolated from the reaction mixture. Therefore, we were forced to look for other dehydrosulfurizing agents, which, for example, can be used without heating. In this work, we proposed to synthesize 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines based on 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides using a mixture of I₂ and Et₃N for dehydrosulfurization.



Scheme 1. Synthesis of 4*H*-1,3,5-oxadiazine derivatives (**3**) using dicyclohexylcarbodiimide as a dehydrosulfurizing agent.

2. Materials and Methods

¹H NMR (400 MHz) and ¹³C 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's progress and the compounds' purity were monitored by TLC on Silufol UV-254 plates using a chloroform/acetone mixture (3:1) as an eluent.

Synthesis of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides (1a-t). *N*-Amidoalkylated thioureas **1a-e,g-p** were previously obtained by the addition of the corresponding arylamines **5** to 4-chloro-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)benzamide (**4**) according to the general procedure described in [32–34]. Thioureas **1f,q-t** were obtained for the first time by a similar method.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-(4-ethoxy-2-nitrophenyl)thioureido)ethyl)benzamide (1f). Yellow solid; yield 89%; mp. 202–204 °C (MeCN); *R*_f = 0.56. ¹H NMR: δ 10.30 (s, 1H, NH), 9.35 (br. s, 1H, NH), 8.36 (d, *J* = 9.3 Hz, 1H, NH), 7.90 (d, *J* = 8.3 Hz, 2H, H_{arom.}), 7.60 (d, *J* = 8.3 Hz, 2H, H_{arom.}), 7.51–7.46 (m, 3H, H_{arom.}), 7.29 (dd, *J* = 9.3, 8.3 Hz, 1H, CH), 4.14 (q, *J* = 6.8 Hz, 2H, CH₂), 1.35 (t, *J* = 6.8 Hz, 3H, CH₃). ¹³C NMR: δ 182.9 (C=S), 164.7 (C=O), 155.7, 145.6, 136.8, 131.9, 131.7, 129.6, 128.5, 124.8, 119.9, 109.4 (arom.), 101.5 (CCl₃), 70.6 (CH), 64.2 (CH₂), 14.4 (CH₃). Anal. Calcd (%) for C₁₈H₁₆Cl₄N₄O₄S (526.21): C, 41.09; H, 3.06; N, 10.65; S, 6.09. Found: C, 41.05; H, 3.04; N, 10.69; S, 6.12.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-(2-chloro-4-nitrophenyl)thioureido)ethyl)benzamide (1q). Yellow solid; yield 91%; mp. 206–208 °C (MeCN); *R*_f = 0.52. ¹H NMR: δ 10.49 (s, 1H, NH), 9.50 (d, *J* = 7.8 Hz, 1H, NH), 8.96 (d, *J* = 9.3 Hz, 1H, NH), 8.40 (m, 1H, H_{arom.}), 8.30–8.28 (m, 1H, H_{arom.}), 8.21–8.18 (m, 1H, H_{arom.}), 7.91 (d, *J* = 8.8 Hz, 2H, H_{arom.}), 7.61 (d, *J* = 8.3 Hz, 2H, H_{arom.}), 7.48 (dd, *J* = 7.8, 9.3 Hz, 1H, CH). ¹³C NMR: δ 181.6 (C=S), 165.0 (C=O), 144.1, 142.0, 136.8, 131.9, 129.6, 128.4, 127.9, 127.4, 124.7, 122.1 (arom.), 101.0 (CCl₃), 70.5 (CH). Anal. Calcd (%) for C₁₆H₁₁Cl₅N₄O₃S (516.60): C, 37.20; H, 2.15; N, 10.85; S, 6.21. Found: C, 37.16; H, 2.13; N, 10.88; S, 6.25.

4-Chloro-*N*-(2,2,2-trichloro-1-(3-(2-nitrophenyl)thioureido)ethyl)benzamide (1r). Yellow solid; yield 86%; mp. 149–151 °C (MeCN); *R*_f = 0.53. ¹H NMR: δ 10.58 (s, 1H, NH), 9.46 (d, *J* = 8.3 Hz, 1H, NH), 8.60 (d, *J* = 9.3 Hz, 1H, NH), 8.02 (m, 1H, H_{arom.}), 7.91 (d, *J* = 8.3 Hz, 2H, H_{arom.}), 7.75–7.68 (m, 2H, H_{arom.}), 7.61 (d, *J* = 8.3 Hz, 2H, H_{arom.}), 7.50–7.47 (m, 2H, CH + 1H_{arom.}). ¹³C NMR: δ 182.5 (C=S), 164.8 (C=O), 144.6, 136.8, 133.5, 132.5, 131.9, 130.0, 129.6, 128.5, 126.9, 124.7 (arom.), 101.4 (CCl₃), 70.6 (CH). Anal. Calcd (%) for C₁₆H₁₂Cl₄N₄O₃S (482.16): C, 39.86; H, 2.51; N, 11.62; S, 6.65. Found: C, 39.82; H, 2.49; N, 11.63; S, 6.69.

4-Chloro-N-(2,2,2-trichloro-1-(3-(3-nitrophenyl)thioureido)ethyl)benzamide (1s).

Pale yellow solid; yield 88%; mp. 226–228 °C (MeCN); $R_f = 0.36$. $^1\text{H NMR}$: δ 10.93 (s, 1H, NH), 9.35 (d, $J = 7.8$ Hz, 1H, NH), 8.69 (s, 1H, $H_{\text{arom.}}$), 8.32 (d, $J = 9.8$ Hz, 1H, NH), 8.02–8.00 (m, 1H, $H_{\text{arom.}}$), 7.91–7.89 (m, 3H, $H_{\text{arom.}}$), 7.68–7.60 (m, 3H, $H_{\text{arom.}}$), 7.52 (dd, $J = 7.8, 9.8$ Hz, 1H, CH). $^{13}\text{C NMR}$: δ 180.7 (C=S), 164.8 (C=O), 147.5, 140.1, 136.9, 131.8, 129.9, 129.5, 128.6, 128.5, 119.0, 116.8 (arom.), 101.4 (CCl_3), 70.0 (CH). Anal. Calcd (%) for $\text{C}_{16}\text{H}_{12}\text{Cl}_4\text{N}_4\text{O}_3\text{S}$ (482.16): C, 39.86; H, 2.51; N, 11.62; S, 6.65. Found: C, 39.84; H, 2.47; N, 11.65; S, 6.70.

4-Chloro-N-(2,2,2-trichloro-1-(3-(4-nitrophenyl)thioureido)ethyl)benzamide (1t).

Yellow solid; yield 92%; mp. 205–207 °C (MeCN); $R_f = 0.45$. $^1\text{H NMR}$: δ 11.05 (s, 1H, NH), 9.35 (d, $J = 8.3$ Hz, 1H, NH), 8.45 (d, $J = 9.3$ Hz, 1H, NH), 8.25 (d, $J = 8.8$ Hz, 2H, $H_{\text{arom.}}$), 7.96 (d, $J = 8.8$ Hz, 2H, $H_{\text{arom.}}$), 7.90 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 7.61 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 7.49 (dd, $J = 8.3, 9.3$ Hz, 1H, CH). $^{13}\text{C NMR}$: δ 180.2 (C=S), 164.8 (C=O), 145.2, 142.7, 136.8, 131.8, 129.5, 128.5, 124.5, 121.3 (arom.), 101.2 (CCl_3), 69.9 (CH). Anal. Calcd (%) for $\text{C}_{16}\text{H}_{12}\text{Cl}_4\text{N}_4\text{O}_3\text{S}$ (482.16): C, 39.86; H, 2.51; N, 11.62; S, 6.65. Found: C, 39.82; H, 2.49; N, 11.65; S, 6.68.

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

Method A: Target products were obtained by dehydrosulfurization of thioureas (1) with dicyclohexylcarbodiimide according to the procedure described in [32–35].

Method B: A solution of 11 mmol (2.79 g) of iodine and 30 mmol (4.2 mL) of triethylamine in 10 mL of DMF was added in portions over 40 min to a solution of 10 mmol of thiourea 1 in 15 mL of DMF with stirring. The reaction mixture was left for 2–4 h at room temperature, the precipitated sulfur was filtered. The target product was precipitated from the filtrate with an aqueous solution of sodium thiosulfate (1%, 250 mL). The precipitate formed was filtered, washed with water (2×50 mL), and dried. The product was purified by recrystallization from an appropriate solvent.

4H-1,3,5-Oxadiazine derivatives **3a-e,g-p** were obtained earlier by method A, all necessary constants and spectral data are given in [32–34]. Compounds **3f,q-t** were obtained for the first time.

6-(4-Chlorophenyl)-N-(4-ethoxy-2-nitrophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (3f). Yellow crystals; yield 47% (method B); mp. 148–150 °C (MeCN); $R_f = 0.78$. $^1\text{H NMR}$: δ 9.61 (s, 1H, NH), 8.02 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 7.88–7.85 (m, 1H, $H_{\text{arom.}}$), 7.68 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 7.52 (s, 1H, $H_{\text{arom.}}$), 7.35–7.33 (m, 1H, $H_{\text{arom.}}$), 5.59 (s, 1H, CH), 4.12 (q, $J = 6.8$ Hz, 2H, CH_2), 1.35 (t, $J = 6.8$ Hz, 3H, CH_3). $^{13}\text{C NMR}$: δ 154.9 (C=N), 152.0 (C=N), 146.0, 142.3, 137.7, 129.0, 128.9, 127.8, 127.1, 123.9, 120.4, 109.6 (arom.), 102.7 (CCl_3), 79.3 (CH), 64.1 (CH_2), 14.4 (CH_3). Anal. Calcd (%) for $\text{C}_{18}\text{H}_{14}\text{Cl}_4\text{N}_4\text{O}_4$ (489.98): C, 43.93; H, 2.87; N, 11.38. Found: C, 43.89; H, 2.85; N, 11.41.

N-(2-Chloro-4-nitrophenyl)-6-(4-chlorophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (3q). Yellow crystals; yield 37% (method A) and 59% (method B); mp. 180–182 °C (MeCN); $R_f = 0.74$. $^1\text{H NMR}$: δ 9.71 (s, 1H, NH), 8.55 (d, $J = 8.8$ Hz, 1H, $H_{\text{arom.}}$), 8.39 (s, 1H, $H_{\text{arom.}}$), 8.25 (d, $J = 8.8$ Hz, 1H, $H_{\text{arom.}}$), 8.19 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 7.69 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 5.78 (s, 1H, CH). $^{13}\text{C NMR}$: δ 155.1 (C=N), 148.7 (C=N), 136.6, 132.0, 129.8, 129.3, 129.1, 128.9, 128.2, 124.7, 123.1, 121.9 (arom.), 102.4 (CCl_3), 81.3 (CH). Anal. Calcd (%) for $\text{C}_{16}\text{H}_9\text{Cl}_5\text{N}_4\text{O}_3$ (482.52): C, 39.83; H, 1.88; N, 11.61. Found: C, 39.78; H, 1.83; N, 11.65.

6-(4-Chlorophenyl)-N-(2-nitrophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (3r). Yellow crystals; yield 64% (method B); mp. 163–165 °C (MeCN); $R_f = 0.51$. $^1\text{H NMR}$: δ 9.88 (s, 1H, NH), 8.15–8.05 (m, 4H, $H_{\text{arom.}}$), 7.75–7.68 (m, 3H, $H_{\text{arom.}}$), 7.36–7.33 (m, 1H, $H_{\text{arom.}}$), 5.67 (s, 1H, CH). $^{13}\text{C NMR}$: δ 152.0 (C=N), 145.4 (C=N), 140.5, 137.8, 134.3, 132.2, 131.7, 129.0, 127.7, 125.3, 124.4, 124.1 (arom.), 102.4 (CCl_3), 79.2 (CH). Anal. Calcd (%) for $\text{C}_{16}\text{H}_{10}\text{Cl}_4\text{N}_4\text{O}_3$ (448.08): C, 42.89; H, 2.25; N, 12.50. Found: C, 42.87; H, 2.23; N, 12.54.

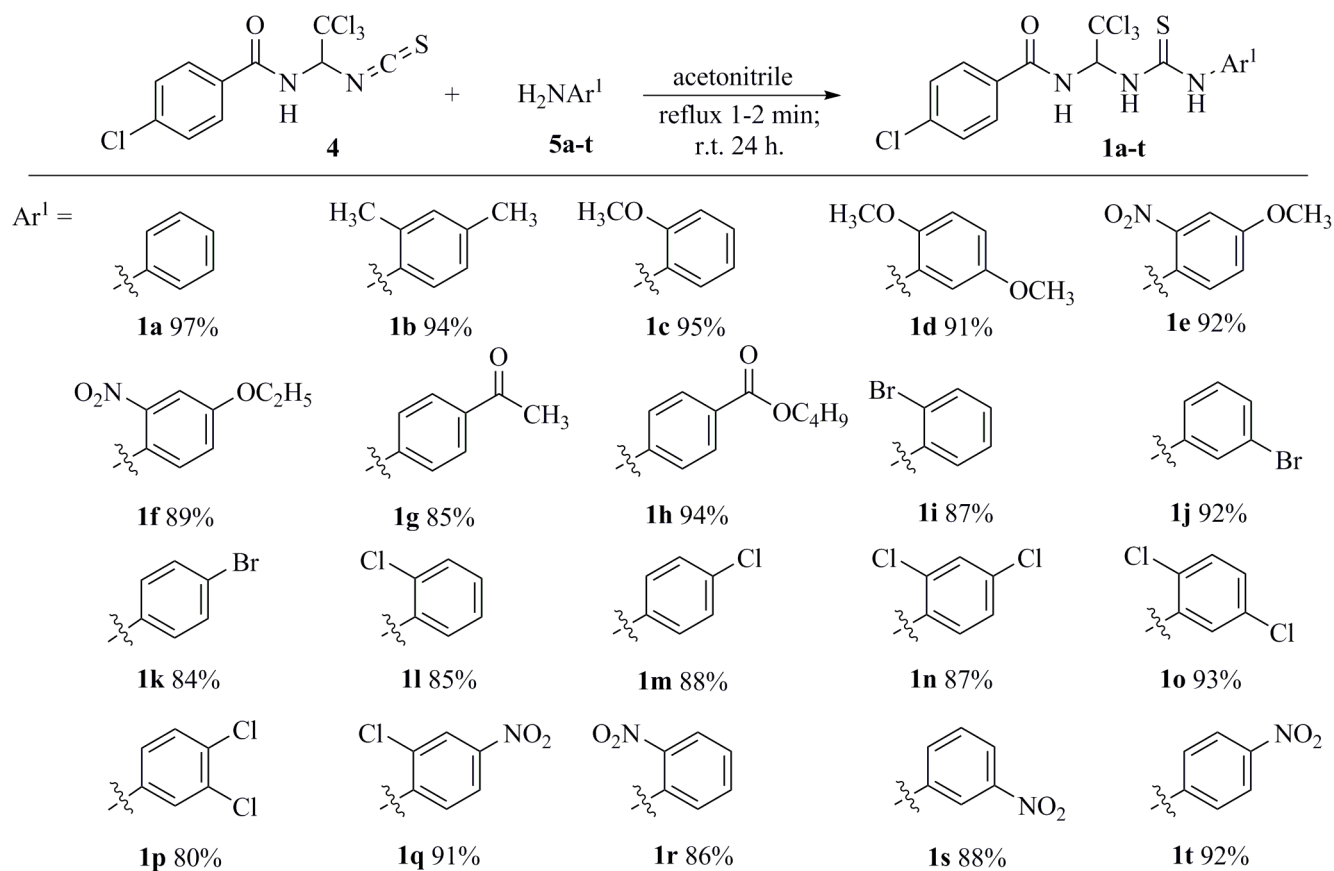
6-(4-Chlorophenyl)-N-(3-nitrophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (3s). Yellow crystals; yield 59% (method B); mp. 170–172 °C (MeCN); $R_f = 0.64$. ^1H

NMR: δ 10.32 (s, 1H, NH), 8.92 (s, 1H, $H_{\text{arom.}}$), 8.05 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 7.94–7.88 (m, 2H, $H_{\text{arom.}}$), 7.71 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 7.65–7.61 (m, 1H, $H_{\text{arom.}}$), 5.80 (s, 1H, CH). ^{13}C NMR: δ 152.1 (C=N), 148.0 (C=N), 154.1, 139.6, 137.7, 130.0, 129.0, 128.8, 127.9, 124.4, 116.9, 112.7 (arom.), 102.8 (CCl_3), 79.2 (CH). Anal. Calcd (%) for $\text{C}_{16}\text{H}_{10}\text{Cl}_4\text{N}_4\text{O}_3$ (448.08): C, 42.89; H, 2.25; N, 12.50. Found: C, 42.86; H, 2.22; N, 12.53.

6-(4-Chlorophenyl)-N-(4-nitrophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine (3t). Yellow crystals; yield 22% (method A) and 45% (method B); mp. 175–177 °C (MeCN); $R_f = 0.65$. ^1H NMR: δ 10.48 (s, 1H, NH), 8.25 (d, $J = 9.3$ Hz, 2H, $H_{\text{arom.}}$), 8.05 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 7.94 (d, $J = 9.3$ Hz, 2H, $H_{\text{arom.}}$), 7.71 (d, $J = 8.3$ Hz, 2H, $H_{\text{arom.}}$), 5.80 (s, 1H, CH). ^{13}C NMR: δ 152.1 (C=N), 144.9 (C=N), 144.7, 141.5, 137.7, 129.0, 128.9, 127.8, 124.9, 118.1 (arom.), 102.6 (CCl_3), 79.2 (CH). Anal. Calcd (%) for $\text{C}_{16}\text{H}_{10}\text{Cl}_4\text{N}_4\text{O}_3$ (448.08): C, 42.89; H, 2.25; N, 12.50. Found: C, 42.86; H, 2.22; N, 12.52.

3. Results and Discussion

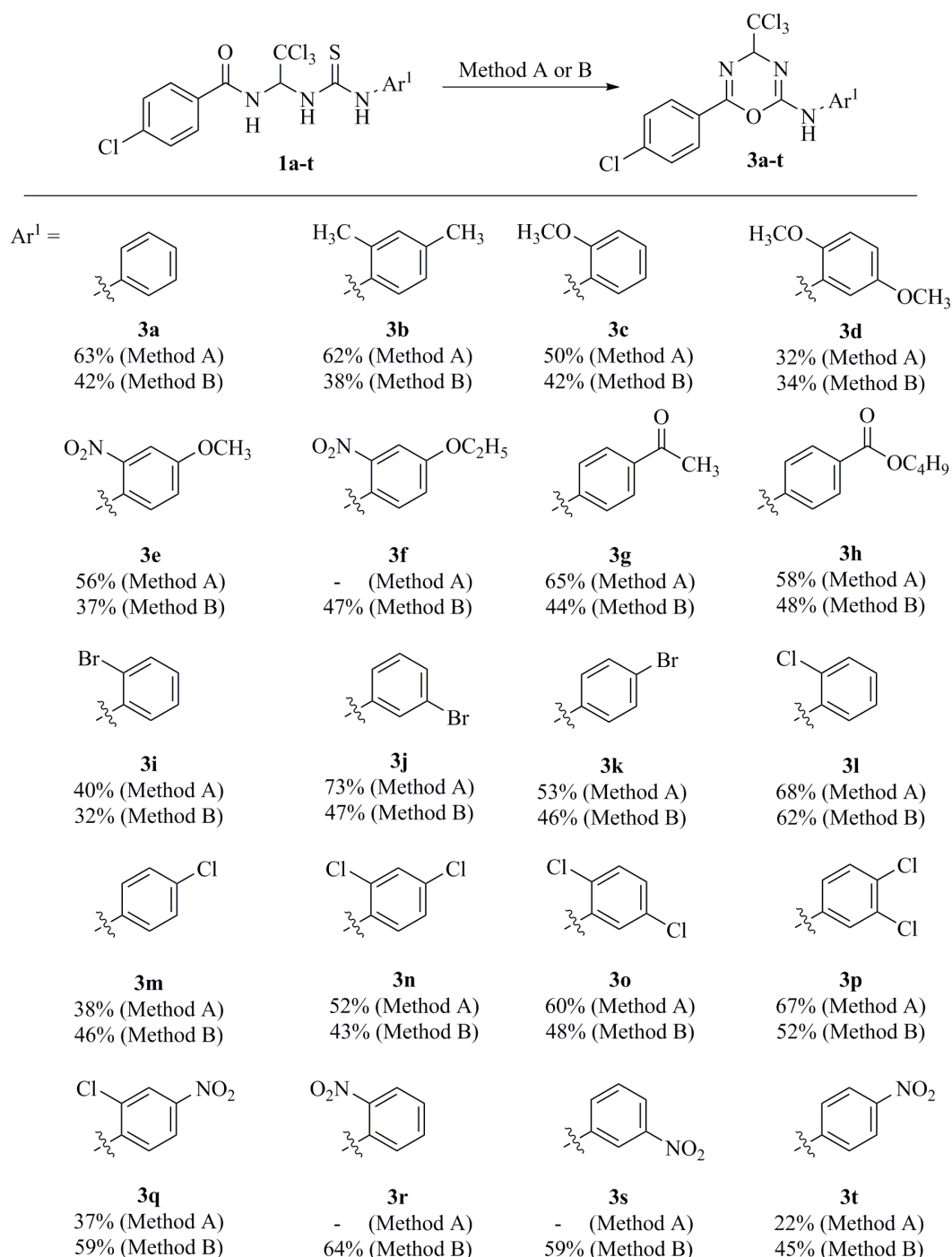
Amidoalkylated thioureas **1a-t** were obtained by the addition of arylamines **4a-t** to 4-chloro-*N*-(2,2,2-trichloro-1-isothiocyanoethyl)benzamide (**5**) according to the general procedure described in [32–34] (Scheme 2). Thioureas **1f,q-t** were obtained for the first time, other representatives of this series of compounds were known earlier. Due to the presence of several reaction centers, compounds **1a-t** are of interest for the synthesis of heterocycles by the reaction of intramolecular cyclization. In addition, these compounds are structural analogs of Salubrinal [36–41] and are of interest as potential inhibitors of GADD34:PP1.



Scheme 2. Synthesis of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides (**1a-t**).

Dehydrosulfurization of thioureas (**1**) with dicyclohexylcarbodiimide, as shown earlier [32–35], leads to the formation of 4*H*-1,3,5-oxadiazine derivatives **3** (Scheme 3). Using this method (Method A), we obtained several representatives of this class of

compounds in fairly high yields. However, in most cases, due to the resinification of the reaction mixture, products **3** could not be isolated. Therefore, we empirically searched for other possible dehydrosulfurizing agents. We chose to use a mixture of I₂ and Et₃N in DMF (Method B). The use of this method made it possible to exclude heating of the reaction mixture and, as a result, to avoid its gumming.



Scheme 3. Synthesis of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines (**3a-t**). **Method A:** 1.1 DCC, CH₃CN, reflux 50–60 min. **Method B:** 1.1 I₂, 3.0 Et₃N, DMF, r.t. 2–4 h.

The use of DCC as a dehydrosulfurizing agent mainly allowed obtaining the target products with high yields. (Figure 1). However, the use of a mixture of I₂ and Et₃N made it possible to obtain compounds **3f**, **3r**, and **3s**, which could not be obtained under the action of DCC.

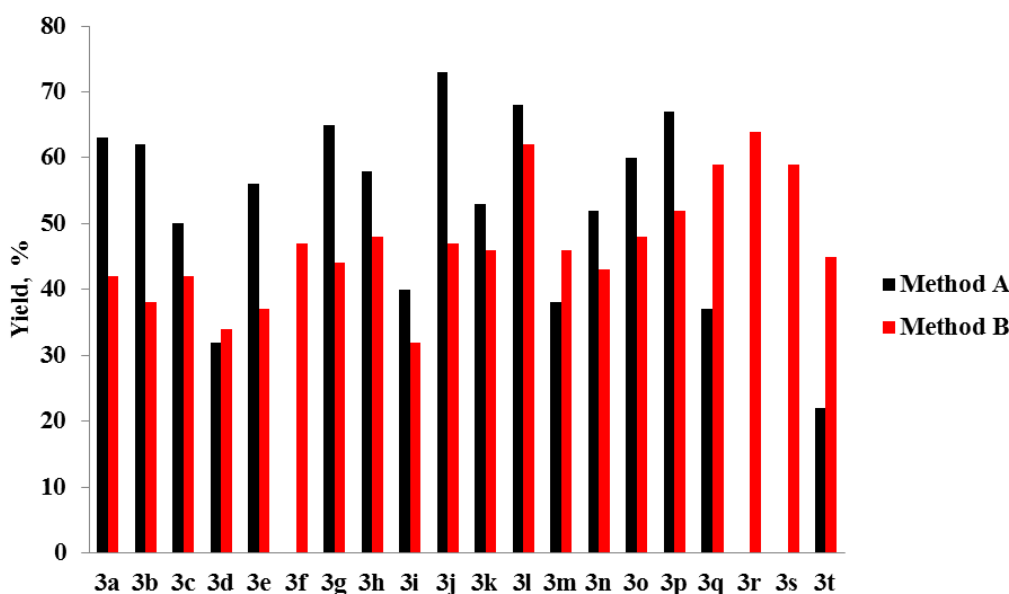


Figure 1. Estimation of the yield ratio of 4*H*-1,3,5-oxadiazines **3** depending on the method used for dehydrosulfurization of starting thioureas **1**.

The structure of all compounds was confirmed by ^1H and ^{13}C NMR spectroscopy data (see supporting information and [32–34]). The starting thioureas **1** in the ^1H NMR spectra were characterized by the presence of three NH protons, one of which appeared as a singlet (11.1–10.3 ppm), and the other two—as a doublet or a broadened singlet at 9.5–8.4 ppm. Oxadiazines **3** were characterized by the presence of only one NH proton signal, which appeared at 10.5–8.7 ppm. The involvement of the amide and thioureide fragments in the cyclization was indicated by the fact that in the starting thioureas **1** the CH signal of the proton located near the trichloromethyl group manifested itself as a doublet of doublets at 7.6–7.1 ppm, while in oxadiazines **3**, it appeared as a singlet at 5.80–5.50 ppm. In the ^{13}C NMR spectra of thioureas **1**, the most characteristic signals were C=S and C=O carbons at 183–180 and 165–164 ppm, respectively. In the ^{13}C NMR spectra of products **3**, there were no signals of C=S and C=O carbons, but signals of two C=N carbons were observed at 155–144 ppm.

4. Conclusions

In this work, we have proposed a new method for the dehydrosulfurization of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides (**1**) leading to the formation of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines (**3**). As a dehydrosulfurizing agent, we have proposed to use a mixture of iodine with triethylamine. The efficiency of using DCC and $\text{I}_2 + \text{Et}_3\text{N}$ for the dehydrosulfurization of thioureas **1** has been compared. It has been shown that the target products are predominantly formed in high yields when using DCC. However, the use of a mixture of I_2 and Et_3N makes it possible to obtain several new compounds of this class, which cannot be obtained under the action of DCC.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: ^1H NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(4-ethoxy-2-nitrophenyl)thioureido)ethyl)benzamide (**1f**); Figure S2. ^{13}C NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(4-ethoxy-2-nitrophenyl)thioureido)ethyl)benzamide (**1f**); Figure S3. ^1H NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(2-chloro-4-nitrophenyl)thioureido)ethyl)benzamide (**1q**); Figure S4. ^{13}C NMR spectra of

4-chloro-*N*-(2,2,2-trichloro-1-(3-(2-chloro-4-nitrophenyl)thioureido)ethyl)benzamide (**1q**); Figure S5. ¹H NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(2-nitrophenyl)thioureido)ethyl)benzamide (**1r**); Figure S6. ¹³C NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(2-nitrophenyl)thioureido)ethyl)benzamide (**1r**); Figure S7. ¹H NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(3-nitrophenyl)thioureido)ethyl)benzamide (**1s**); Figure S8. ¹³C NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(3-nitrophenyl)thioureido)ethyl)-benzamide (**1s**); Figure S9. ¹H NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(4-nitrophenyl)thioureido)ethyl)benzamide (**1t**); Figure S10. ¹³C NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(4-nitrophenyl)thioureido)ethyl)benzamide (**1t**); Figure S11. ¹H NMR spectra of 6-(4-chlorophenyl)-*N*-(4-ethoxy-2-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3f**); Figure S12. ¹³C NMR spectra of 6-(4-chlorophenyl)-*N*-(4-ethoxy-2-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3f**); Figure S13. ¹H NMR spectra of *N*-(2-chloro-4-nitrophenyl)-6-(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3q**); Figure S14. ¹³C NMR spectra of 4-*N*-(2-chloro-4-nitrophenyl)-6-(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3q**); Figure S15. ¹H NMR spectra of 6-(4-chlorophenyl)-*N*-(2-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3r**); Figure S16. ¹³C NMR spectra of 6-(4-chlorophenyl)-*N*-(2-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3r**); Figure S17. ¹H NMR spectra of 6-(4-chlorophenyl)-*N*-(3-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3s**); Figure S18. ¹³C NMR spectra of 6-(4-chlorophenyl)-*N*-(3-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3s**); Figure S19. ¹H NMR spectra of 6-(4-chlorophenyl)-*N*-(4-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3t**); Figure S20. ¹³C NMR spectra of 6-(4-chlorophenyl)-*N*-(4-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3t**).

Author Contributions: V.V.P.; methodology, formal analysis, investigation. P.V.Z.; conceptualization, methodology, writing—original draft, formal analysis, investigation, visualization, project administration. V.V.K.; validation, resources, writing—review and editing. A.V.K.; validation, supervision, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

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