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Synthesis, Spectral Characteristics, and Molecular Structure of *N*-(2,2,2-Trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)carboxamides †

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Abstract

1,3-Thiazole derivatives are of interest in pharmacy, medicine, and agriculture as potential biologically active substances. We have proposed for the first time a convenient and effective method for the synthesis of amidoalkylated derivatives of 2-amino-1,3-thiazole. This approach is based on the reaction of amidoalkylated thioureas with α-halocarbonyl compounds. The reaction was carried out under stirring at 20 °C in ethanol with the addition of an equimolar amount of triethylamine to bind the released hydrogen halide. The yield of the obtained 1,3-thiazole derivatives was 68–75%. An attempt to carry out a counter-synthesis by amidoalkylation of the corresponding 2-amino-1,3-thiazole derivative was unsuccessful due to strong resinification of the reaction mass. The structure of the compounds obtained was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The structure was finally confirmed by X-ray structural analysis performed for *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)acetamide.

Keywords: 1,3-thiazole; thiourea; molecular structure; synthesis

1. Introduction

Heterocyclic compounds occupy a leading position in modern organic and medicinal chemistry due to their structural diversity and wide spectrum of biological activity. Among them, 1,3-thiazoles are of particular interest, which combine Sulfur and Nitrogen atoms in their structure [1]. This determines their unique electronic and physicochemical properties. The presence of a reactive 1,3-thiazole nucleus makes these compounds convenient platforms for synthetic modification and creation of new biologically active substances [1–4].

Many 1,3-thiazole derivatives exhibit various pharmacological properties, including anti-inflammatory [5–7], antimicrobial [8–10], antitumor [4], antifungal [11–13], and anticonvulsant [14,15]. Some of them have already become the basis of medicines used in clinical practice, while others are actively studied as promising pharmacophores. In addition, 1,3-thiazoles have found application in agriculture as fungicides, insecticides, and plant growth regulators [16], as well as in materials science as components of new functional materials. Despite significant progress in the chemistry of 1,3-thiazole, further research into new derivatives with specific properties is an urgent task. A promising direction in the creation of new biologically active substances is the combination of the

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thiazole ring with other pharmacophoric groups. In this study, we report the synthesis of amidoalkylated 1,3-thiazole derivatives. The alkylamide moiety is a well-known pharmacophore [17–23], and its combination with the 1,3-thiazole ring opens up prospects for the creation of compounds with potential pharmacological and pesticidal activity.

2. Materials and Methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured for DMSO-d_6 (Sigma-Aldrich, St. Louis, MO, USA) solutions on a Varian Agilent VNMRS 400 MHz spectrometer (Agilent Technologies, Inc., Santa Clara, CA, USA). Residual solvent signals were used as a standard. Elemental analysis was performed on a LECO CHNS-900 instrument (LECO Corporation, St. Joseph, MI, USA). The course of the reaction and the purity of the synthesized compounds were checked by TLC on Silufol UV-254 plates (Serva-Feinbiochemica GmbH & Co, Heidelberg, Germany), using a mixture of chloroform (Allhim, Kyiv, Ukraine) and acetone (WARCHEM, Warsaw, Poland) (3:1) as the eluent. Melting points were determined in open capillaries and were not corrected.

Synthesis of *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)carboxamides (**3**). A mixture of equimolar amounts (10 mmol) of monoamidoalkylated thiourea **1** [24,25], α-bromoacetophenone **2** (1.99 g) (Sigma-Aldrich, St. Louis, MO, USA), and triethylamine (1.4 mL) (Chimlaborreaktiv LLC, Brovary, Ukraine) in 40 mL of ethanol was stirred at room temperature for 3 h. During the reaction, the precipitate of thiourea 1 disappeared. The resulting solution was filtered, and the filtrate was evaporated at 20 °C and atmospheric pressure. After 24 h, the crystalline product was collected and purified by recrystallization from an appropriate solvent.

N-(2,2,2-Trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)acetamide (**3a**). Pale yellow crystals; yield 75%. mp 198–200 °C (EtOH). R_f = 0.49. ^{1}H NMR (DMSO-d_6), δ: 8.80 d (*J* = 7.3 Hz, 1H, NH), 8.51 d (*J* = 8.8 Hz, 1H, NH), 7.84 d (*J* = 7.3 Hz, 2H, $H_{arom.}$), 7.40–7.37 m (2H, $H_{arom.}$), 7.29–7.26 m (1H, $H_{arom.}$), 7.19 s (1H, $CH_{thiazole}$), 6.84 dd (*J* = 8.8, 7.3 Hz, 1H, CH), 1.96 s (3H, CH_3). ^{13}C NMR (DMSO-d_6), δ: 169.4 (C=O), 165.8 (C=N), 149.4 ($C=C_{thiazole}$), 134.5, 128.4, 127.3, 125.6 ($C_{arom.}$), 103.0 ($C=C_{thiazole}$), 101.5 (CCl_3), 69.8 (CH), 22.5 (CH_3). Anal. Calcd (%) for $C_{13}H_{12}Cl_3N_3OS$ (364.67): C 42.82; H 3.32; N 11.52; S 8.79. Found: C 42.74; H 3.27; N 11.61; S 8.84.

The crystals of compound **3a** are monoclinic, $C_{13}H_{12}N_3OCl_3S$, at −100.5 °C: a = 21.0525(5), b = 8.3440(2), c = 9.3233(2) Å, β = 94.339(2)°, V = 1633.06(7) Å^3, Mr = 364.67, Z = 4, space group $P2_1/c$, d_{calc} = 1.483 g cm^{-3}, μ(MoKα) = 0.689 mm^{-1}, F(000) = 744. The unit cell parameters and intensities of 18,926 reflections (2860 independent, R_{int} = 0.028) were measured on a Bruker APEX-II CCD diffractometer (Bruker Corporation, Billerica, MA, USA) (MoKα radiation, CCD detector, graphite monochromator, ω-scan mode, 2θmax = 50°). The structure was solved by direct methods using the OLEX2 program (version 1.5, Olexsys Ltd, Durham University, United Kingdom) [26] with the SHELXT (version 2014/5, Georg-August Universität Göttingen, Göttingen, Germany) [27] and SHELXL (version 2016/6, Georg-August Universität Göttingen, Göttingen, Germany) [28] software packages. The positions of hydrogen atoms were located from difference Fourier maps and refined using a riding model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms). Hydrogen atoms of the amino groups were refined isotropically. The structure was refined against F^2 by full-matrix least-squares in anisotropic approximation for all non-hydrogen atoms to wR_2 = 0.0861 for 2860 reflections (R_1 = 0.0332 for 2467 reflections with F > 4σ(F), S = 1.044). The final atomic coordinates, and crystallographic data for compound **3a** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44–1223-336,033; e-mail:

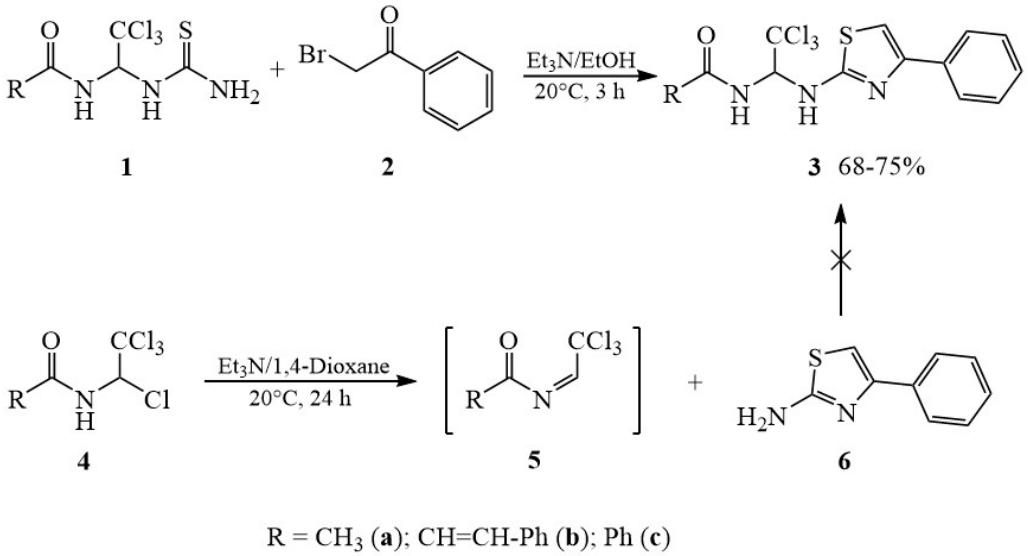
deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2489840).

N-(2,2,2-Trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)cinnamamide (**3b**). Pale yellow crystals; yield 68%. mp 214–216 °C (MeCN). R_f = 0.69. ^{1}H NMR (DMSO-d_6), δ: 8.99 d (*J* = 8.8 Hz, 1H, NH), 8.65 d (*J* = 8.8 Hz, 1H, NH), 7.85 d (*J* = 7.3 Hz, 2H, $H_{arom.}$), 7.59–7.55 m (3H, $H_{arom.}$ + $C_6H_5C\underline{H}$=CH), 7.42–7.37 m (5H, $H_{arom.}$), 7.29–7.26 m (1H, $H_{arom.}$), 7.21 s (1H, $CH_{thiazole}$), 7.00–6.91 m (2H, CH + C_6H_5CH=C$\underline{H}$). ^{13}C NMR (DMSO-d_6), δ: 165.7 (C=O), 164.8 (C=N), 149.4 (C=$C_{thiazole}$), 140.8 ($C_6H_5\underline{C}$H=CH), 134.6, 134.5, 129.7, 128.8, 128.3, 127.6, 127.3, 125.7 ($C_{arom.}$), 121.0 (C_6H_5CH=$\underline{C}$H), 103.1 (C=$C_{thiazole}$), 101.4 (CCl_3), 71.0 (CH). Anal. Calcd (%) for $C_{20}H_{16}Cl_3N_3OS$ (452.78): C 53.05; H 3.56; N 9.28; S 7.08. Found: C 53.12; H 3.49; N 9.37; S 7.14.

N-(2,2,2-Trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)benzamide (**3c**). Pale yellow crystals; yield 70%. mp 197–199 °C (MeCN). R_f = 0.84. ^{1}H NMR (DMSO-d_6), δ: 9.25 d (*J* = 8.3 Hz, 1H, NH), 8.39 d (*J* = 8.8 Hz, 1H, NH), 7.90–7.85 m (4H, $H_{arom.}$), 7.59–7.55 m (1H, $H_{arom.}$), 7.51–7.47 m (2H, $H_{arom.}$), 7.41–7.37 m (2H, $H_{arom.}$), 7.29–7.26 m (1H, $H_{arom.}$), 7.24 s (1H, $CH_{thiazole}$), 7.03 dd (*J* = 8.8, 8.3 Hz, 1H, CH). ^{13}C NMR (DMSO-d_6), δ: 166.6 (C=O), 165.7 (C=N), 149.3 (C=$C_{thiazole}$), 134.4, 133.4, 131.9, 128.5, 128.3, 127.7, 127.5, 125.6 ($C_{arom.}$), 103.6 (C=$C_{thiazole}$), 101.5 (CCl_3), 70.8 (CH). Anal. Calcd (%) for $C_{18}H_{14}Cl_3N_3OS$ (426.74): C 50.66; H 3.31; N 9.85; S 7.51. Found: C 50.58; H 3.27; N 9.92; S 7.60.

3. Results and Discussion

The starting *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides **1** were prepared previously [24,25]. These compounds readily reacted with α-bromoacetophenone **2** to give the corresponding *N*-amidoalkylated 1,3-thiazole derivatives **3** (Scheme 1). The reaction was carried out under stirring at 20 °C in ethanol with the addition of an equimolar amount of triethylamine to neutralize HBr. *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)carboxamides **3** were obtained in 68–75% yield. Attempts to perform the countersynthesis of compounds **3** by amidoalkylation of 4-phenylthiazol-2-amine **6** were unsuccessful. In this case, strong tarring of the reaction mixture was observed, and the product could not be isolated.



Scheme 1. Synthesis of *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)carboxamides (**3a–c**).

The structures of compounds **3** and **5** were confirmed by ^{1}H and ^{13}C NMR spectroscopy, as well as by X-ray structural analysis (see Figures S1–S7 and Tables S1–S4 in Supplementary Materials). In the ^{1}H NMR spectra, the characteristic doublet signals of

two NH protons appeared in the region of 9.25–8.39 ppm. In addition, the signals of two CH protons were indicative, one of which appeared as a singlet at 7.24–7.19 ppm and belongs to the thiazole ring, and the other appeared as a doublet of doublets at 7.03–6.84 ppm and corresponds to the alkylamide fragment. In the ^{13}C NMR spectra, the signals of carbon atoms C=O, CCl_3, and CH of the alkylamide fragment were characteristic, appearing in the region of 169.4–165.7, 101.5–101.4, and 71.0–69.8 ppm, respectively. Also indicative were the signals of the three carbon atoms of the thiazole ring, which appeared in the region of 165.8–164.8 (C=N), 149.4–149.3 and 103.6–103.0 (C=C) ppm.

For compound **3a**, an X-ray structural study was performed (Figure 1). The phenyl substituent at atom C1 is slightly non-coplanar with the thiazole ring plane (torsion angle C2–C1–C8–C13 -13.7(4)°) due to steric repulsion between the two rings (shortened intramolecular contacts H9. . .N1 2.51 Å and H13. . .C2 2.75 Å compared to the sums of van der Waals radii [29] of 2.68 Å and 2.84 Å, respectively). The amino group at the C3 substituent of the thiazole ring adopts a pyramidal configuration, with the sum of the valence angles centered on the nitrogen atom amounting to 346°. Atom C4 of the substituent is located in a nearly syn-periplanar orientation relative to the endocyclic N1–C3 bond, whereas the trichloromethyl group adopts an –ac conformation relative to the exocyclic C3–N2 bond (torsion angles N1–C3–N2–C4 18.0(3)°, C3–N2–C4–C5 −145.4(2)°). The methylcarbamoyl fragment is oriented orthogonally to the C3–N2 bond (torsion angle C3–N2–C4–N3 89.4(2)°) and is significantly rotated with respect to the N2–C4 bond (torsion angle N2–C4–N3–C6 −126.4(2)°). Conjugation between the π-orbital of the C6=O1 carbonyl group and the lone pair of electrons on atom N3 results in a planar configuration of the N3H amino group (sum of valence angles centered on the nitrogen atom is 359°).

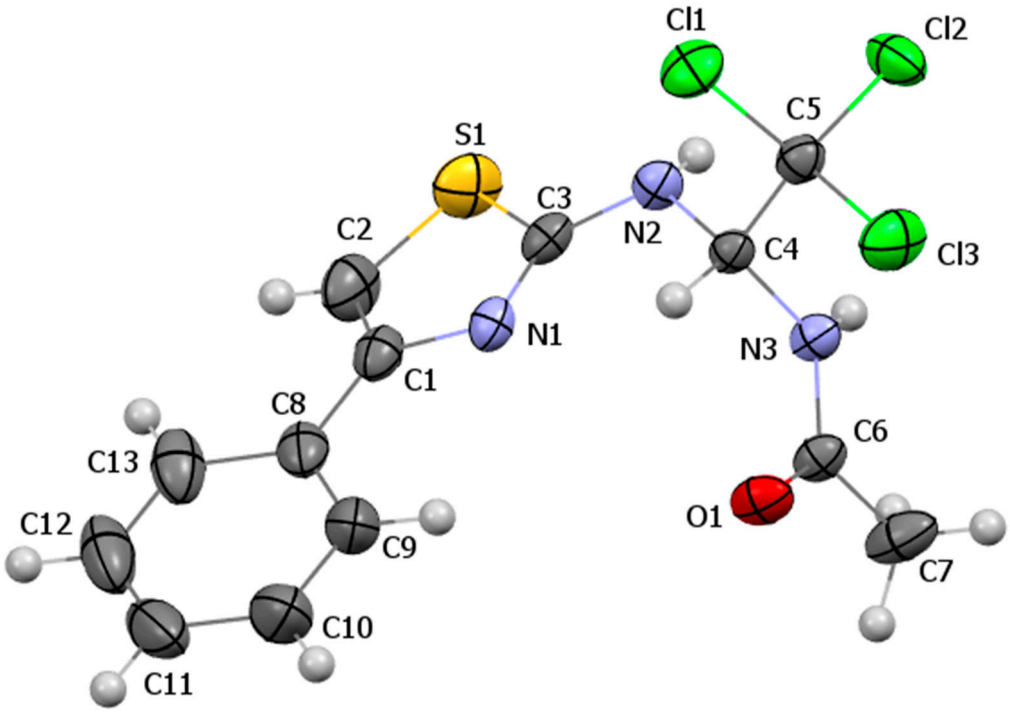


Figure 1. Molecular structure of compound **3a** according to XRD. Atoms are shown as 50% thermal ellipsoids.

In the crystal, molecules of **3a** form chains (Figure 2) along the crystallographic [001] direction, which are linked by intermolecular hydrogen bonds N2–H. . .O1′ (symmetry operation x, 1.5-y, 0.5+z; H2. . .O1 distance 2.22(2) Å, N2–H. . .O1 angle 144(2)°) and N3–H. . .O1′ (symmetry operation x, 1.5-y, 0.5+z; H3. . .O1 distance 2.15(3) Å, N3–H. . .O1 angle 148(2)°). The oxygen atom acts as a bifurcated proton acceptor in these hydrogen bonds.

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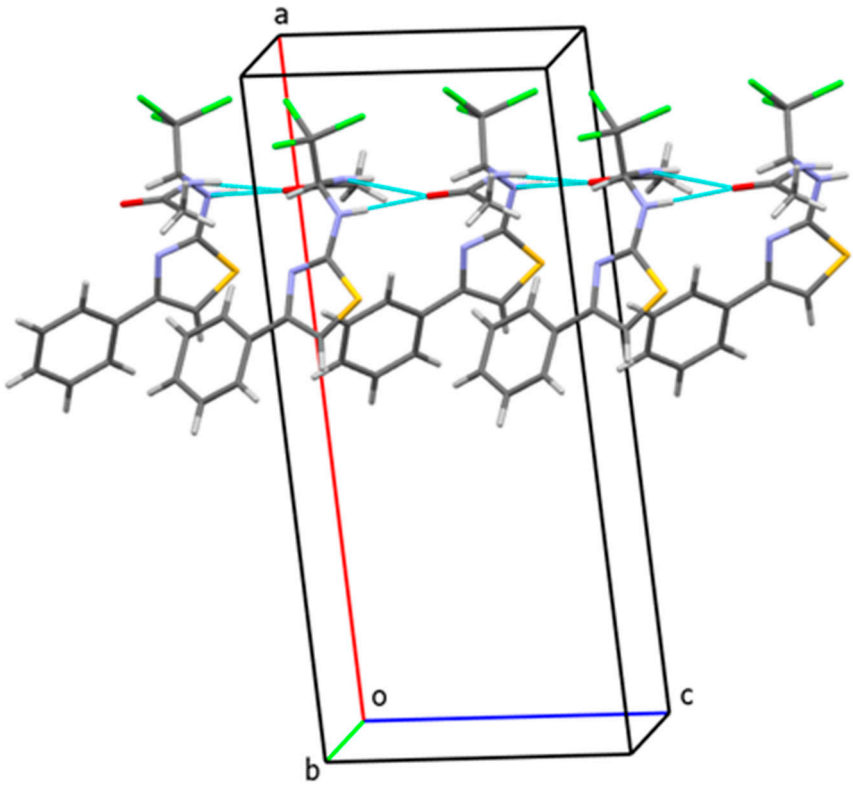


Figure 2. Chains of molecules **3a** along the crystallographic [001] direction. Hydrogen bonds are shown as blue lines.

4. Conclusions

We have developed a preparative method for the first time to synthesize *N*-amidoalkylated derivatives of 1,3-thiazole. The structure of the synthesized compounds has been reliably confirmed by ^{1}H and ^{13}C NMR spectroscopy and X-ray structural analysis. The obtained compounds are of interest as potential biologically active substances.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/engproc2026124045/s1, Figure S1: ^{1}H NMR (400 MHz, DMSO-d_6) spectra of *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)acetamide (**3a**); Figure S2: ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) spectra of *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)acetamide (**3a**); Figure S3: ^{1}H NMR (400 MHz, DMSO-d_6) spectra of *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)cinnamamide (**3b**); Figure S4: ^{13}C NMR (100 MHz, DMSO-d_6) spectra of *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)cinnamamide (**3b**); Figure S5: ^{1}H NMR (400 MHz, DMSO-d_6) spectra of *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)benzamide (3c); Figure S6: ^{13}C NMR (100 MHz, DMSO-d_6) spectra of *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)benzamide (3c); Figure S7: Molecular structure of compound **3a** according to XRD. Atoms are shown as 50 thermal ellipsoids; Table S1: Atomic coordinates ($\times 10^4$) and isotropic thermal parameters (Å^2 $\times$ 10^3) of atoms in *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)acetamide (**3a**); Table S2: Bond lengths (Å) in *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)acetamide (**3a**); Table S3: Angles (°) in *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)acetamide (**3a**); Table S4: Torsion angles (°) in *N*-(2,2,2-trichloro-1-((4-phenylthiazol-2-yl)amino)ethyl)acetamide (**3a**).

Author Contributions: Conceptualization, P.V.Z.; methodology, P.V.Z., Y.R.L., O.V.O. and P.V.R.; validation, V.V.K. and A.V.K.; formal analysis, Y.R.L., P.V.Z., P.V.R. and O.V.O.; investigation: Y.R.L., P.V.Z. and P.V.R.; resources, V.V.K.; writing—original draft preparation, P.V.Z.; writing—review and editing, V.V.K. and A.V.K.; visualization, P.V.Z.; supervision, A.V.K.; project administration,

P.V.Z.; funding acquisition, P.V.Z. All authors have read and agreed to the published version of the manuscript.

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