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The molecular structure n-{2,2,2-trichloro-1-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethyl}acet- and Thioacetamide.

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ABSTRACT

X-ray diffraction analysis revealed the molecular structure of N-{2,2,2-trichloro-1-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethyl}acet - and thioacetamides as substrate and intermediate in the synthesis of 7H-1,3,4-thiadiazole[3,2-a][1,3,5]triazine. X-ray diffraction study was carried out for co-crystals of these compounds derived from the reaction mixture after the early termination of the process.

Keywords: X-ray diffraction studies, Lawson reagent, 2-amino-1,3, 4-thiadiazole, 7H-1,3,4-thiadiazole[3,2-a] [1,3,5] triazine

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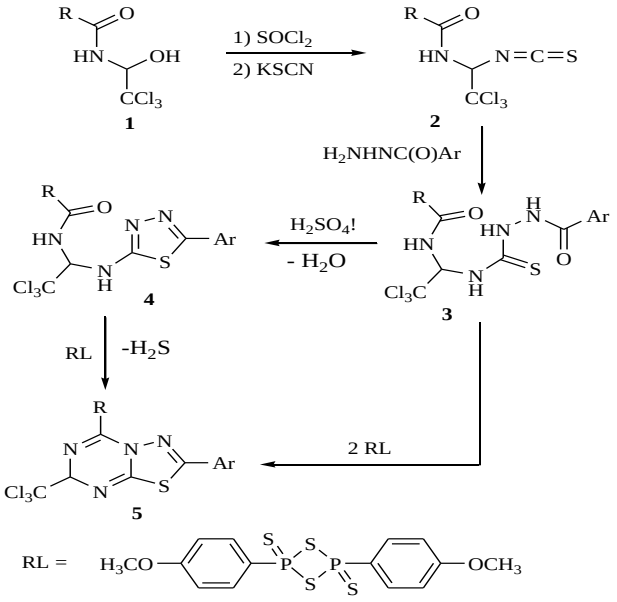
INTRODUCTION

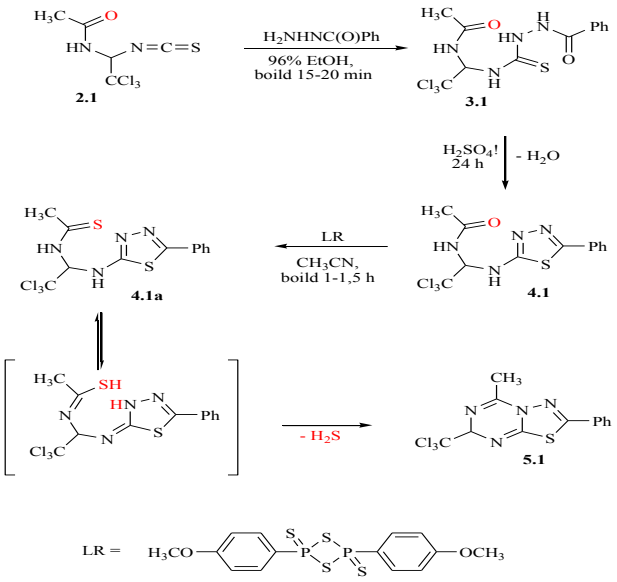
Products of the condensation of chloral and amides of carboxylic acids **(1)** have been successfully applied in an organic synthesis [1,2]. Thus, on their basis a number of N-isothiocyanatealkilamides of carboxylic acid **(2)** [3-6] has been obtained, and they are the polyfunctional reagents widely used in the synthesis of various heterocyclic systems [1,7,8]. For example, some amidoalkilated derivativeses of 2-amino-1,3,4-thiadiazole **(4)** have been synthesized via the stage of intermediate thiosemicarbazide **(3)** formation on the basis isothiocyanate **(2)** [9]. Compounds **(4)** appeared to be the promising building blocks for the synthesis of condensed heterocyclic systems [10-12]. According to [13] the reaction of the amidoalkilated derivatives of 2-amino-1,3,4-thiadiazole **(4)** and reagent Lawson leaded to the formation of the corresponding derivatives of 7H-1,3,4-thiadiazole[3,2-a][1,3,5]triazine **(5)**.

Scheme 1



But intermediate compounds of transformation (**4**)→(**5**) have not been isolated, despite of numerous attempts and changes of the reaction conditions [13].

Scheme 2



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To prove the assumption that the formation of bicyclic compounds (**5**) happens with the formation of intermediate N-substituted thioamides, we have synthesized another representative of reagents (**4**) – *N*-{2, 2, 2-trichloro-1-[(5-phenyl-1, 3, 4-thiadiazol-2-yl) amino] ethyl} acetamide (**4.1**) (Scheme 2). Compound (**4.1**) appeared to be more suitable for research of heterocyclization, because after the prior process termination, the co-crystals of compounds (**4.1**) and (**4.1a**) was able to be extracted from reaction mixture.

Those co-crystals were suitable for X-ray diffraction study. However, the attempts to obtain an individual form of *N*-{2, 2, 2-trichloro-1-[(5-phenyl-1, 3, 4-thiadiazol-2-yl) amino] ethyl} thioacetamide (**4.1a**) failed, despite of changes in the duration of heating and the ratio of reactants. As well as using P_2S_5 did not lead to the desired result.

The detailed review of the synthesis of compound (**5.1**), its spectral characteristics and X-ray diffraction studies will be presented in a separate publication.

EXPERIMENTAL

Melting points were determined in open capillaries and not adjusted. IR spectra were recorded in KBr tablets on the instrument Spectrum BX II, mass spectra - the device VG7070, desorption of ions from solution samples in *meta*-nitrobenzyl alcohol conducted beam of argon atoms with 8 keV energy. ^{1}H NMR spectra were measured on a spectrometer Varian VXR-200 (standard TMS). Chemical shifts (δ) are given in ppm downfield. *J* values are in Hz. Monitoring the progress of the reaction and the identity of the compounds obtained was performed by TLC (Silufol UV-254, eluent - chloroform: acetone - 3:1).

N-(1-{[(2-benzoylhydrazino)carbonothioyl]amino}-2,2,2-trichloroethyl)acetamide (**3.1**). A mixture of 20 mmol isothiocyanate (**2.1**) [3] and 20 mmol benzohydrazide in 20-25 ml of ethanol was boiled for 15-20 minutes, and then left for 12 hours at 293-298 K. The precipitate was filtered, dried and used without purification for further reaction. The rest quantity of compound (**3.1**) was obtained from the filtrate after removal of the solvent. Yield 76.2%. mp = 513-514 K (for EtOH); R_f = 0.2; IR (KBr): ν_{max} = 3380, 3268, 3100, 2930, 1649, 1604, 1595, 1505, 1483, 1332, 1259, 1130 см$^{-1}$; ^{1}H NMR: δ = 1.91 (s, 3H, CH_3), 7.20 (m, 1H, NHCHNH), 7.52-7.94 (m, 6H, C_6H_5, NH), 8.94-8.96 (d, 1H, *J*=7.80, NH), 10.22 (s, 1H, NH), 10.68 (s, 1H, NH). MS (FAB): m/z = 384 $[M+H]^+$. Anal. calc. for $C_{12}H_{13}Cl_3N_4O_2S$ (383.69): C, 37.57; H, 3.42; Cl, 27.72; N, 14.60; S, 8.36. Found: C, 37.54; H, 3.45; Cl, 27.77; N, 14.68; S, 8.32.

N-{2,2,2-trichloro-1-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethyl}acetamide (**4.1**). 10 mmol of compound (**3.1**) was dissolved in 10-15 mL of concentrated sulfuric acid. The mixture was left for 24 hours at 293-298 K, and then poured on 30-40 g of ice. The precipitate was filtered, thoroughly washed with water and dried. Yield 97.4%. mp = 503-504 K (for HAc); R_f = 0.12; IR (KBr): ν_{max} =3310, 3134, 2975, 2954, 1670, 1657, 1542, 1490, 1368, 1256, 1122, 1105, 1044, 885, 810, 773 см$^{-1}$; ^{1}H NMR: δ = 1.98 (s, 3H, CH_3), 6.76-6.81 (m, 1H, NHCHNH), 7.48-7.80 (m, 5H, C_6H_5), 7.94 (prs, 1H, NH), 8.95 (prs, 1H, NH). MS (FAB): m/z = 366 $[M+H]^+$. Anal. calc. for $C_{12}H_{11}Cl_3N_4OS$ (365.67): C, 39.42; H, 3.03; Cl, 29.09; N, 15.32; S, 8.77. Found: C, 39.40; H, 3.10; Cl, 29.12; N, 15.37; S, 8.74.

The mixture of (10 mmol) N-{2,2,2-trichloro-1-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethyl}acetamide (**4.1**) and (10 mmol) of Lawson reagent was boiled for 1-1,5 hours in 10-12 ml of acetonitrile. The reaction mixture was filtered hot, the filtrate was cooled to 293-298 K, poured into 7-12 ml of 5-7% aqueous solution of sodium hydroxide. The precipitate formed was filtered, washed with water 2×25 ml, and dried. Crystals for X-ray diffraction studies were grown by recrystallization from acetonitrile. mp = 487-488 K.

X-ray diffraction study: crystals of the co-crystallizate (**4.1**)**/**(**4.1a**) are orthorhombic, $C_{12}H_{11}Cl_3N_4O_{0.75}S_{1.25}$, at 298K *a* = 10.9746(6), *b* = 12.5655(9), *c* = 11.6275(8) Å, V = 1603.44(18) Å^3, M_r = 369.67, Z = 4, space group $Pna2_1$, d_{calc}= 1.531 g/cm^3, μ(MoK_α) = 0.735 mm^{-1}, F(000) = 752. Data collection was performed on an «Xcalibur-3» diffractometer (MoK_α radiation, CCD-detector, graphite monochromator, ω-scanning, $2\theta_{max}$= 60°). 6218 reflections was collected (3094 independent, R_{int}= 0.029).

Structure was solved by direct methods and refined against F^2 by full-matrix least squares procedure using OLEX2 program package [14] using SHELXS and SHELXL modules [15]. All non-hydrogen atoms were refined in anisotropic approximation. Hydrogen atom positions were initially located from difference electron

density maps and constrained to ride on their parent atoms, with $U_{iso} = 1.2U_{eq}$ (except $U_{iso} = 1.5U_{eq}$ for methyl groups). Atom O(1) of the amide group was partially substituted with the S(2) atom (relative site occupancies of O(1)/S(2) are 0.75/0.25). Methyl group bonding to the C(11) atom was disordered over two sites with relative occupancies of 0.65/0.35. The C(11)–O(1) and C(11)–S(2) bond lengths were constrained to have fixed values of 1.25(1) Å and 1.63(1) Å, respectively. Also the C(11)–C(12) and C(11)–C(12A) bonds were fixed to be approximately equal to within 0.005 Å. Thermal parameters of C(11), C(12), C(12A), O(1) and S(2) atoms were constrained to be approximately isotropic to within 0.01 – 0.001. Final refinement was converged at wR_2 = 0.095 for all 2826 reflections (R_1 = 0.042 for 2087 reflections with F>4σ(F), S = 1.02). The bond angles and bond lengths are given in Tables 1 and 2, respectively. And the atomic coordinates and equivalent isotropic thermal parameters in Table 3.)

Table 1: Bond angles (degrees) in the structures (4.1) and (4.1a)

A group of Atoms	Angle, degrees	A group of Atoms	Angle, degrees
C(8)-S(1)-C(7)	87.0(2)	C(2)-C(1)-C(7)	122.0(3)
N(1)-C(7)-S(1)	112.9(3)	C(2)-C(1)-C(6)	118.8(4)
N(1)-C(7)-C(1)	123.7(3)	C(11)-N(4)-C(9)	123.1(3)
C(1)-C(7)-S(1)	123.4(3)	C(8)-N(2)-N(1)	111.6(3)
C(8)-N(3)-C(9)	120.9(3)	C(4)-C(5)-C(6)	121.2(5)
Cl(1)-C(10)-Cl(2)	108.6(2)	N(3)-C(9)-C(10)	110.9(3)
Cl(3)-C(10)-Cl(1)	109.0(2)	N(3)-C(9)-N(4)	113.7(3)
Cl(3)-C(10)-Cl(2)	109.0(2)	N(4)-C(9)-C(10)	109.6(3)
C(9)-C(10)-Cl(1)	110.2(3)	C(3)-C(2)-C(1)	120.8(4)
C(9)-C(10)-Cl(3)	110.5(3)	C(2)-C(3)-C(4)	119.6(6)
C(9)-C(10)-Cl(2)	109.5(2)	N(4)-C(11)-S(2)	123.7(5)
N(3)-C(8)-S(1)	121.9(3)	N(4)-C(11)-C(12)	120(1)
N(2)-C(8)-S(1)	114.1(3)	N(4)-C(11)-C(12)*	112.1(7)
N(2)-C(8)-N(3)	124.0(4)	C(12)-C(11)-S(2)	113(1)
C(7)-N(1)-N(2)	114.4(3)	C(12)A-C(11)-S(2)	124.3(8)
C(5)-C(6)-C(1)	120.0(5)	O(1)-C(11)-N(4)	125.5(6)
C(5)-C(4)-C(3)	119.6(5)	O(1)-C(11)-C(12)	114(1)
C(6)-C(1)-C(7)	119.2(4)	O(1)-C(11)-C(12)*	121.6(9)

* Data relating to the structure (**4.1a**)

Table 2: Bond lengths (Å) in the structures (4.1) and (4.1a)

Bond	Bond lengths, Å	Bond	Bond lengths, Å
S(1)-C(7)	1.740(3)	N(1)-N(2)	1.383(5)
S(1)-C(8)	1.738(4)	C(6)-C(1)	1.387(5)
Cl(1)-C(10)	1.765(4)	C(6)-C(5)	1.367(7)
Cl(3)-C(10)	1.758(4)	C(4)-C(5)	1.354(8)
Cl(2)-C(10)	1.786(4)	C(4)-C(3)	1.387(7)
S(2)-C(11)	1.620(2)	C(1)-C(2)	1.377(7)
C(7)-N(1)	1.291(5)	N(4)-C(9)	1.435(5)
C(7)-C(1)	1.467(6)	N(4)-C(11)	1.361(6)
N(3)-C(8)	1.345(5)	C(2)-C(3)	1.373(7)
N(3)-C(9)	1.427(5)	C(12)-C(11)	1.521(1)
C(10)-C(9)	1.531(5)	C(12)-C(11)*	1.522(9)
C(8)-N(2)	1.302(4)	C(11)-O(1)	1.265(2)

* Data relating to the structure (**4.1a**)

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Table 3: The atomic coordinates (×10^4) and equivalent isotropic thermal parameters (Å^2×10^3) in the structures (4.1) and (4.1a)

Atom	x	y	z	U(eq)
S(1)	4186.8(7)	2139.9(7)	4888.3(10)	43.0(2)
Cl(1)	4226.8(10)	5570.1(9)	6940.6(12)	67.8(4)
Cl(3)	3932.5(12)	5337.4(9)	9378.3(12)	68.9(3)
Cl(2)	1903.9(9)	4919.9(8)	7865.9(13)	60.0(3)
S(2)*	5467(3)	2498(7)	9725(9)	67(2)
C(7)	5714(3)	1769(2)	4845(4)	37.9(8)
N(3)	3638(3)	3233(2)	6822(3)	46.7(8)
C(10)	3518(3)	4815(3)	8032(4)	41.4(9)
C(8)	4501(3)	2726(3)	6210(4)	38.4(8)
N(1)	6320(3)	2091(3)	5731(3)	45.5(8)
C(6)	7165(4)	407(3)	4181(5)	58.2(12)
C(4)	7209(4)	-191(4)	2247(6)	72.6(16)
C(1)	6242(3)	1122(3)	3921(4)	41.9(9)
N(4)	3346(3)	3048(2)	8855(3)	52.2(9)
N(2)	5635(2)	2649(2)	6527(3)	46.6(8)
C(5)	7633(4)	-234(4)	3340(6)	67.7(15)
C(9)	3897(3)	3645(3)	7939(4)	38.9(8)
C(2)	5827(4)	1180(4)	2805(5)	59.4(11)
C(3)	6297(5)	528(4)	1967(6)	77.5(14)
C(12)	3380(30)	1855(16)	10570(20)	84(8)
C(12A)	3181(13)	2245(9)	10714(13)	80(4)
C(11)	3996(3)	2609(4)	9731(5)	67.0(13)
O(1)	5144(3)	2630(5)	9828(8)	61.7(16)

* Data relating to the structure (**4.1a**)

Atom coordinates and crystallographic parameters have been deposited to the Cambridge Crystallographic Data Centre (CCDC **1024563**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

In the crystal, two types of molecules with either amide (N(4)–C(11)–O(1), fig. 1) or corresponding thioamide (N(4)–C(11)–S(2), fig. 2) group occupy the equivalent positions, forming a co-crystallizate. Relative site occupancies are 0.75/0.25. Geometrical parameters of both molecules, excepting the above mentioned amide or thioamide groups, are identical. Planar configuration of the N(3) atom and the N(3)–C(8) bond length of 1.345(5) Å (mean value is 1.339 Å [14]) indicates conjugation between the π-system of the thiadiazole ring and the lone electron pair of the N(3) atom. Phenyl ring is slightly turned relatively the plane of thiadiazole ring (the N(1)–C(7)–C(1)–C(6) angle is 31.8(6)º) that, however, does not violate the π-conjugation between rings (the C(1)–C(7) bond length of 1.467(6) Å is close to mean value of 1.470 Å [16] for conjugated π-system).

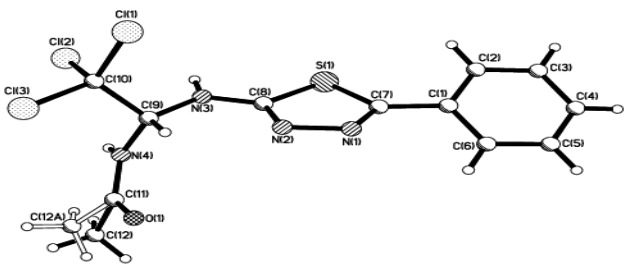

Figure 1: The molecular structure of compound N-{2,2,2-trichloro-1-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethyl}acetamide's (4.1) according to X-Ray

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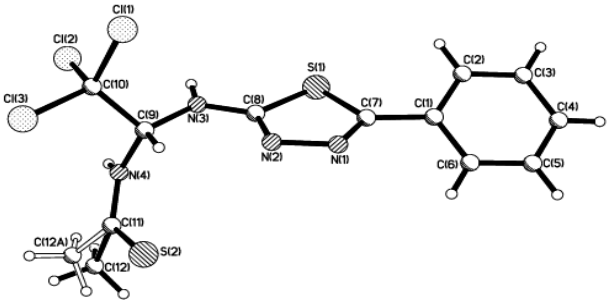
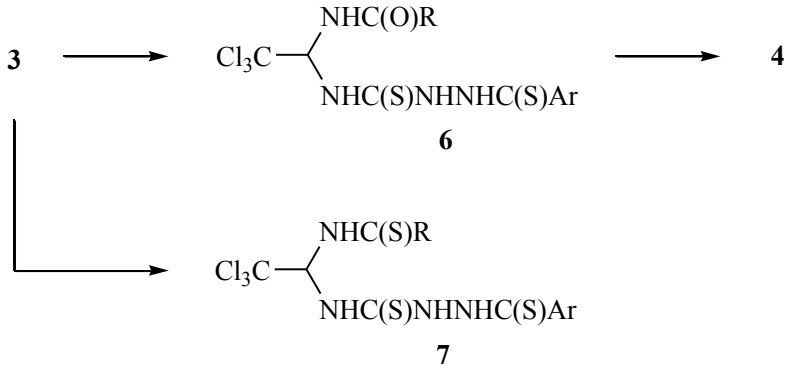


Figure 2: The molecular structure of compound N-{2,2,2-trichloro-1-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethyl}thioacetamide's (4.1a) according to X-Ray

Molecules form chains along the (100) crystallographic direction due to formation of hydrogen bonds N(3)–H(3)…N(1)' (x-0.5, 0.5-y, z; H…N' 2.05 Å, N–H…N' 159º). These chains are linked with the halogen bonds C(10)–Cl(2)…C(2) (0.5-x, 0.5+y, 0.5+z; Cl…π' 3.390 Å, C–Cl…C' 155.9º).

It should be mentioned that cyclization of reagents (**3**) with an excess of reagent Lawson seems to be much more complex process. We can predict the reaction of both amide and ureyide fragments to form compounds (**6**), which are then converted into the compound (**4**), followed by cyclization as described above:



Or the formation of acyclic compounds (**7**) takes place. Perhaps in this case the spontaneous cyclization occurs to form 1,3,5-thiadiazole derivatives common to compounds (**4.1**), but the lower yield of products of cyclization (**3**)→(**5**) compared to (**4**)→(**5**) [13] indicates side processes.

It should be also noted that any cyclization of products of condensation of isothiocyanate with thiohydrazides was not described in the literature.

Undoubtedly the study of the mechanism of reagents (**3**) and (**4**) cyclization requires further investigation and promotes the application of such heterocyclic sintons, that will be shown later.

CONCLUSION

As a result in the reaction of synthesis of 7H-1,3,4-thiadiazole[3,2-a][1,3,5]triazine derivatives on the basis of N-{2,2,2- trichloro-1-[(5-aryl-1,3,4-thiadiazol-2-yl)amino]ethyl}amides carboxylic acids, the intermediate substance has been identified. The molecular parameters of N-{2,2,2-trichloro-1-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethyl}acet- and thioacetamides have been identified using X-ray analysis.

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