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SOME NEW HETEROCYCLISATIONS BASED ON *N*-(2,2-DICHLORO-1-ISOTHIOCYANATOETHYL)BENZAMIDE DERIVATIVES

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Abstract: Based on the readily available *N*-(2,2-dichloro-1-(2-(4-methylbenzoyl)-hydrazine-1-carbothioamido)ethyl)benzamide, the corresponding *N*-(2,2-dichloro-1-((5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)amino)ethyl)benzamide and 5-(*p*-tolyl)-1,3,4-thiadiazol-2-amine were obtained. The products were received in acceptable yields and were isolated from the reaction mixture without any particular difficulty. The structure of the compounds obtained was confirmed by ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry data.

***Keywords*:** 1,3,4-Oxadiazole; 1,3,4-Thiadiazole; Isothiocyanate; Synthesis

Introduction

Heterocyclic compounds, as a special class of organic compounds, are of great practical interest for many areas of human activity such as medicine and pharmacy,[1,2] agriculture,[3] materials science,[4] electronics[5] and many others[6].

Therefore, the search for new and expanding the scope of application of known reagents for the synthesis of heterocyclic compounds is a very

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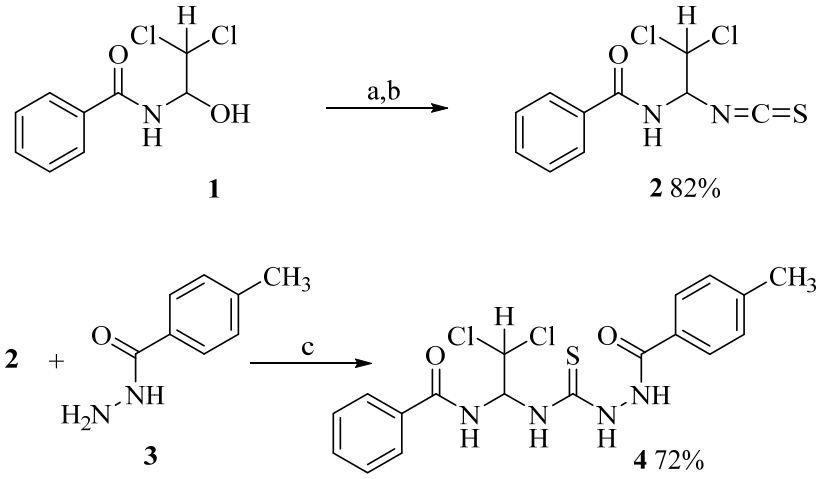
important and urgent task. Previously, *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides[7] were successfully used to synthesize derivatives of 1,3,5-oxadiazines,[8,9] 1,3,4-oxa(thia)diazols[7] and other heterocyclic compounds[7,10]. In this paper, we have briefly reported the attempts to introduce *N*-(2,2-dichloro-1-isothiocyanatoethyl)benzamide (**2**)[11] derivatives into similar transformations.

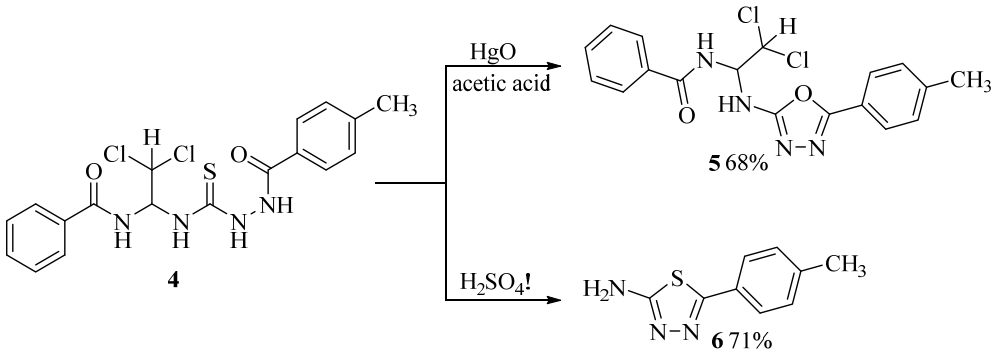
Results and Discussion

The compound (**2**) was obtained on the basis of *N*-(2,2-dichloro-1-hydroxyethyl)benzamide (**1**) sequentially acting on it with thionyl chloride and KSCN. Addition of *para*-toluic hydrazide (**3**) to isothiocyanate (**2**) resulted in the formation of *N*-(2,2-dichloro-1-(2-(4-methylbenzoyl)hydrazine-1-carbothioamido)ethyl)benzamide (**4**) (Scheme 1). The preparation of (**4**) was carried out in acetonitrile, which greatly facilitated the isolation of the product and allowed it to be obtained in high yields and of sufficient purity for use in further conversions without any purification. The compound (**4**) was not described in the literature before.



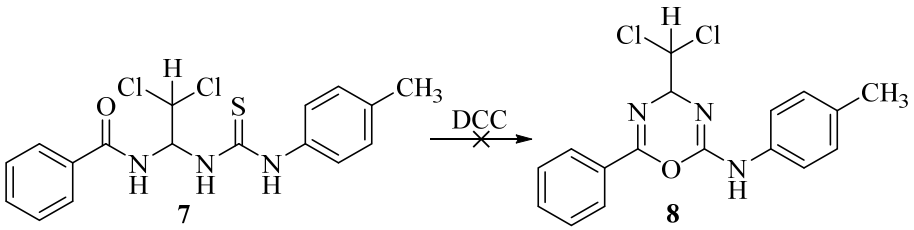
Scheme 1. Synthesis of *N*-(2,2-dichloro-1-(2-(4-methylbenzoyl)hydrazine-1-carbothioamido)ethyl)benzamide (**4**). Reagents and conditions: a) $SOCl_2$, CCl_4, reflux – 1-1.2 h; b) KSCN, acetonitrile, stirring – 1.5-2 h; c) isothiocyanate (**2**), *p*-toluic hydrazide (**3**), EtOH, reflux – 2-4 minutes.

To close the oxadiazole cycle, a 50% excess of HgO was used as the dehydrosulfurization agent. The reaction was carried out during refluxing for 40-60 minutes without formation of by-products. The effect on thiosemicarbazide (**4**) with concentrated sulfuric acid led not only to the elimination of water, followed by formation of a 1,3,4-thiadiazole ring, but also to the splitting off alkylamide moiety. At the same time, 5-(*p*-tolyl)-1,3,4-thiadiazol-2-amine (**6**) was formed.



Scheme 2. Synthesis of *N*-(2,2-dichloro-1-((5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)amino)ethyl)benzamide (**5**) and 5-(*p*-tolyl)-1,3,4-thiadiazol-2-amine (**6**).

While attempts to synthesize 4-(dichloromethyl)-6-phenyl-*N*-(*p*-tolyl)-4*H*-1,3,5-oxadiazin-2-amine (**8**) based on substituted thiourea (**7**) (Scheme 3), by analogy with works,[8,9] were still unsuccessful.



Scheme 3. Interaction of *N*-(2,2-dichloro-1-(3-(*p*-tolyl)thioureido)ethyl)-benzamide (**7**) with dicyclohexylcarbodiimide (DCC).

The structures of the compounds obtained were confirmed by ^{1}H, ^{13}C

NMR spectroscopy and mass spectrometry data. In ^{1}H NMR spectra, the signal of the methine proton located in the dichloromethyl group is in the region of 6.04-6.02 ppm and is manifested as the doublet of doublet of doublets (ddd) for the compounds (**4**) and (**5**). The proton signal of dichloromethyl group is observed in the region of 6.53-6.52 ppm and is manifested as the doublet (d). The proton signal of amide, hydrazide and amino groups is observed in the region of 9.35-7.55 ppm. In ^{13}C NMR spectrum of the compounds (**5**) in the region of 185-181 and 166-165 ppm, there are no signals C=S and C=O (hydrazide) carbons, characteristic for the starting compound (**4**). In this case, carbon signals of two C=N groups located in the region of 162-158 ppm are observed. The presence of the signal of the amide carbon atom (C=O) in the region of 166-165 ppm, CH – in the region of 66-65 ppm and $CHCl_2$ – in the region of 73-72 ppm is characteristic in ^{13}C NMR spectra of all compounds.

The mass spectra of electron impact (EI) turned out to be poorly informative because of the high lability of the compounds (**4**), (**5**). Thus, for the compound (**5**), the intensity of the molecular ion peak did not exceed 1.0%, as for the compound (**4**) – it was not observed at all. FAB Spectra were more informative.

Experimental

^{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. 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. 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).

Synthesis of N-(2,2-dichloro-1-isothiocyanatoethyl)benzamide (2).[11] 12 mmol of thionyl chloride was added to the suspension of 10 mmol (2.34 g) *N*-(2,2-dichloro-1-hydroxyethyl)benzamide (**1**)[12] in 30-35 mL of CCl_4. The mixture was refluxed for 1-1.2 hours. After completion of the reaction, the solution was still warm filtered, and the filtrate was evaporated on a rotary evaporator. The residue after evaporation was treated with hexane (2×10 mL), filtered and dissolved in 30-35 mL of anhydrous acetonitrile. 10 mmol (0.97 g) of carefully dried KSCN was added in portions to the resulting solution. The reaction mixture was being stirred for 1.5-2 hours. The precipitated KCl was filtered off, the filtrate was evaporated on a rotary evaporator without raising the heating temperature above 55-60 °C. The residue after evaporation was treated with water (3×50 mL), filtered and dried at room temperature for 48 hours. The product was recrystallized from acetonitrile. Light yellow crystals; yield 82% (2.26 g); mp. 114-116 °C (MeCN); R_f = 0.82 (chloroform/acetone – 3:1). ^{1}H NMR: *δ (ppm)* 9.80 (d, *J* = 7.3 Hz, 1H, NH), 7.92-7.90 (m, 2H, $H_{arom.}$), 7.63-7.53 (m, 3H, $H_{arom.}$), 6.58 (d, *J* = 5.4 Hz, 1H, $CHCl_2$), 6.27 (dd, *J* = 7.3, 5.4 Hz, 1H, CH). Anal. Calcd. (%) for $C_{10}H_8Cl_2N_2OS$ (275.15): C, 43.65; H, 2.93; Cl, 25.77; N, 10.18; S, 11.65. Found: C, 43.63; H, 2.91; Cl, 25.80; N, 10.21; S, 11.67.

Synthesis of N-(2,2-dichloro-1-(2-(4-methylbenzoyl)hydrazine-1-carbothioamido)ethyl)benzamide (4). An equimolar amount (1.50 g) of *para*-toluic hydrazide in 12-15 mL of MeCN was added to the solution of 10 mmol (2.75 g) of isothiocyanate (**2**) in 18-20 mL of MeCN. The mixture

was reflux for 2-3 minutes and left for 24 hours. The precipitate, which formed, was filtered off, washed with 10-12 mL of MeCN and dried at room temperature for 48 hours. The product was recrystallized from acetonitrile. White crystals; yield 72% (3.06 g); mp. 168-170 °C (MeCN); R_f = 0.72 (chloroform/acetone – 3:1). ^{1}H NMR: *δ (ppm)* 9.35 (d, *J* = 6.8 Hz, 1H, NH), 7.92-7.90 (m, 2H, $H_{arom.}$), 7.85 (brs, 1H, NH), 7.75-7.73 (m, 1H, $H_{arom.}$), 7.57-7.55 (m, 1H, NH), 7.52-7.47 (m, 3H, $H_{arom.}$), 7.35-7.30 (m, 3H, $2H_{arom.}$+NH), 6.53 (d, *J* = 6.4 Hz, 1H, $CHCl_2$), 6.04 (ddd, *J* = 6.8, 6.8, 6.4 Hz, 1H, CH), 2.35 (s, 3H, CH_3). ^{13}C NMR: *δ (ppm)* 180.4 (C=S), 165.8, 164.1 (C=O), 140.6, 138.2, 138.1, 137.6, 131.1, 129.6, 129.5, 129.0, 128.3, 121.9 (arom.), 72.9 ($CHCl_2$), 64.9 (CH), 21.1 (CH_3). MS (FAB): m/z 275 $[M+H]^+$. Anal. Calcd. (%) for $C_{10}H_8Cl_2N_2OS$ (275.15): C, 43.65; H, 2.93; Cl, 25.77; N, 10.18; S, 11.65. Found: C, 43.62; H, 2.90; Cl, 25.81; N, 10.22; S, 11.68.

Synthesis of N-(2,2-dichloro-1-((5-(p-tolyl)-1,3,4-oxadiazol-2-yl)amino)ethyl)benzamide (5). 15 mmol (3.25 g) of HgO and 50-55 mL of glacial acetic acid were added to 10 mmol (4.25 g) of compound (**3**). The mixture was reflux for 40-60 minutes. The completion of the reaction was determined by TLC method. The reaction mixture was cooled for one hour at room temperature; the precipitate was filtered off, washed with acetonitrile (2×5 mL) and dried. The product was recrystallized from ethyl alcohol. White crystals; yield 68% (2.66 g); mp. 206-208 °C (EtOH); R_f = 0.46 (chloroform/acetone – 3:1). ^{1}H NMR: *δ (ppm)* 9.18 (brs, 1H, NH), 8.66 (brs, 1H, NH), 7.90-7.88 (m, 2H, $H_{arom.}$), 7.75-7.73 (m, 2H, $H_{arom.}$), 7.60-7.56 (m, 1H, $H_{arom.}$), 7.52-7.48 (m, 2H, $H_{arom.}$), 7.37-7.34 (m, 2H, $H_{arom.}$), 6.52 (d, *J* = 5.9 Hz, 1H, $CHCl_2$), 6.02 (ddd, *J* = 6.8, 6.8, 5.9 Hz, 1H, CH), 2.37 (s, 3H, CH_3). ^{13}C NMR: *δ (ppm)* 166.3 (C=O), 161.8, 158.4 (C=N), 140.7, 133.0, 131.9, 129.7, 128.3, 127.5, 125.2, 121.1 (arom.), 72.5

($CHCl_2$), 65.7 (CH), 21.0 (CH_3). MS (FAB): m/z 391 $[M+H]^+$. Anal. Calcd. (%) for $C_{18}H_{16}Cl_2N_4O_2$ (391.25): C, 55.26; H, 4.12; Cl, 18.12; N, 14.32. Found: C, 55.24; H, 4.10; Cl, 18.17; N, 14.36.

Synthesis of 5-(p-tolyl)-1,3,4-thiadiazol-2-amine (6).[13] 40 mL of concentrated sulfuric acid was added to 10 mmol (4.25 g) of compound (**4**). The mixture was left for 24 hours at room temperature, then, it was poured into a vessel with crushed ice. The precipitate was filtered and washed with water (3×25 mL) and then dried. The product was recrystallized from ethyl alcohol. Light yellow crystals; mp. 219-221 °C (EtOH); R_f = 0.53 (chloroform/acetone – 3:1). Anal. Calcd (%) for $C_9H_9N_3S$ (191.25): C, 56.52; H, 4.74; N, 21.97; S, 16.76. Found: C, 56.50; H, 4.71; N, 22.00; S, 16.79.

Synthesis of N-(2,2-dichloro-1-(3-(p-tolyl)thioureido)ethyl) benzamide (7) was carried out according to the known procedure described in [14]. Light yellow crystals; mp. 130-132 °C (MeCN); R_f = 0.74 (chloroform/acetone – 3:1). Anal. Calcd (%) for $C_{17}H_{17}Cl_2N_3OS$ (382.30): C, 53.41; H, 4.48; Cl, 18.55; N, 10.99; S, 8.39. Found: C, 53.38; H, 4.45; Cl, 18.58; N, 11.02; S, 8.42.

Conclusions

The two new compounds: *N*-(2,2-dichloro-1-(2-(4-methylbenzoyl)hydrazine-1-carbothioamido)ethyl)benzamide (**4**) and *N*-(2,2-dichloro-1-((5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)amino)ethyl)benzamide (**5**) were synthesized. The structures of the compounds obtained were confirmed by ^1H, ^{13}C NMR spectroscopy and mass spectrometry data.

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