New 5-Substituted 2-Mercapto-1,3,4-Oxadiazoles, Intermediates in the Synthesis of 5-Substituted 4*H*-4-Amino-3-Mercapto-1,2,4-Triazoles

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Three novel 5-substituted 2-mercapto-1,3,4-oxadiazoles have been synthesized through the reaction of hydrazides of phenylacetic, 3-phenylpropionic and 4-phenylbutyric acids with carbon disulfide in ethanol, in the presence of potassium hydroxide at reflux, without the isolation of intermediates. The products were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Keywords: 2-benzyl-5-mercapto-1,3,4-oxadiazole, 2-mercapto-5-(2-phenyl-ethyl)-1,3,4-oxadiazole, 2-mercapto-5-(3-phenyl-propyl)-1,3,4-oxadiazole

Recent literature reports a large number of 5-substituted 2-mercapto-1,3,4-oxadiazoles (**1**) [1-4], as well as of 5-substituted 4*H*-4-amino-3-mercapto-1,2,4-triazoles (**2**) [5-10], displaying antimicrobial, antibacterial, antiinflamatory, anti-HIV activities, as well as cation complexing properties [11-12].

The synthesis of 5-substituted 4*H*-4-amino-3-mercapto-1,2,4-triazoles (**2**) showing the above-mentioned properties constitutes one of our preoccupations. Some of the possible sequences for their synthesis are presented in scheme 1.

Among these, reaction of 5-substituted 2-mercapto-1,3,4-oxadiazoles with hydrazine, under heating or microwaves [13,14], constitute an attractive synthetic option.

Since recently [15] the literature reports the synthesis of 4*H*-4-amino-5-benzyl-3-mercapto-1,2,4-triazole (**2**; R = C_6H_5-CH_2-) as a new compound with potential antibacterial and antifungal properties, we set as our goal its synthesis together with extending the series of such compounds to 4*H*-4-amino-3-mercapto-5-phenetyl-1,2,4-triazole (**2**; R = C_6H_5-CH_2-CH_2-) and 4*H*-4-amino-3-mercapto-5-(3-phenyl-propyl)-1,2,4-triazole (**2**; R = C_6H_5-CH_2-CH_2-CH_2-), respectively.

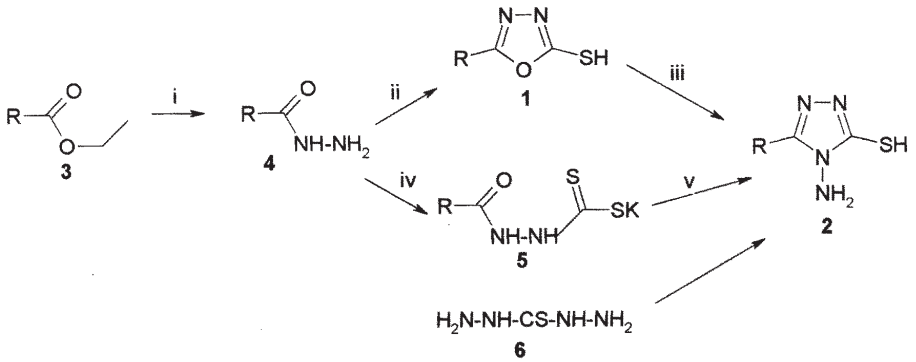
For their synthesis (**2a-c**) we prepared 2-benzyl-5-mercapto-1,3,4-oxadiazole (**1a**), 2-mercapto-5-(2-phenyl-ethyl)-1,3,4-oxadiazole (**1b**) and 2-mercapto-5-(3-phenyl-propyl)-1,3,4-oxadiazole (**1c**), respectively, starting from the ethyl esters of phenylacetic (**3a**), 3-phenylpropionic (**3b**) and 4-phenylbutyric acids (**3c**), through their hydrazinolysis and conversion of the hydrazides (**4a-c**) into oxadiazoles (**1a-c**) through the reaction with carbon disulfide and KOH in ethanol at reflux, without the isolation of the potassium salts of dithiocarbazic acids (**7a-c**) (scheme 2).

Experimental part

Materials and methods

The reagents and ethyl ester of phenylacetic acid (**3a**) were commercial products (Merck, Fluka, Aldrich) and used as received. Ethyl esters of 3-phenylpropionic acid (**3b**) and 4-phenylbutyric acid (**3c**) were obtained from the corresponding acid, according to the literature [16].

Melting points were determined on a Böetius PHMK (Veb Analytik Dresden) instrument, and thin-layer chromatography was carried out on silica gel-coated plates 60 F_{254} Merck using benzene:methanol 7:3 as eluant.



i=N_2H_4 ii= a) CS_2 / KOH / EtOH / Δt b) HCl [1,2] iii=N_2H_4 [5] iv= CS_2 / KOH / Et_2O / t.cam v=N_2H_4 [6-9]

Scheme 1. Possible syntheses of 5-substituted 4*H*-4-amino-3-mercapto-1,2,4-triazoles (**2**)

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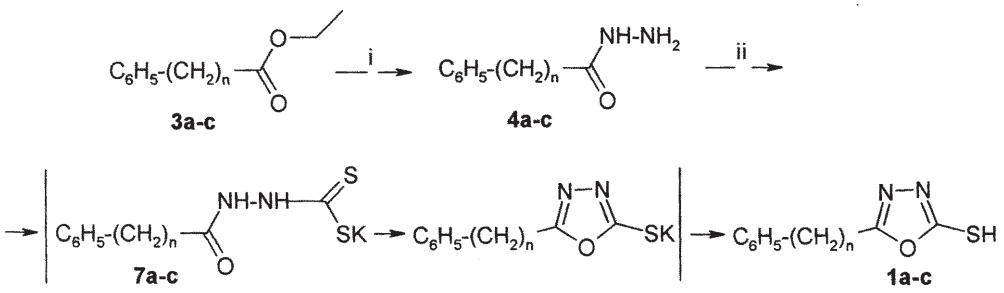

i= H_2N-$NH_2 \cdot H_2O$, Δ t; ii= a)CS_2 / KOH / EtOH, Δ t; b)HCl n= 1(**a**); 2 (**b**); 3(**c**)

Scheme 2. Synthesis of 5-substituted 2-mercapto-1,3,4-oxadiazoles

IR spectra were recorded in KBr pellet or in thin layer, on a Jasco FT/IR-410 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Advance AC200 spectrometer in DMSO-d_6, using TMS as reference; chemical shifts are reported in ppm and the coupling constants in Hz.

Synthesis of hydrazides **4a-c** by hydrazinolysis of esters **3a-c**

A mixture of 0.1 mol ethyl ester (**3a-c**) and 0.15 mol hydrazine hydrate 100% is heated at reflux for 8-15 h (10 h for **3a**, 8 h for **3b**, 15 h for **3c**). After distillation to dryness at ~80°C / 10 mmHg, the crude hydrazide is recrystallyzed.

Hydrazide of phenyl-acetic acid (**4a**)

White crystals (67% yield), m.p. = 113-115°C (ethanol) (lit. m.p. = 116°C [17]);

IR (cm^{-1}): ν_{NH2} = 3293s, ν_{NH} = 3199m, ν_{CHar} = 3028m, ν^{as}_{CH2} = 2944w, ν^{s}_{CH2} = 2872w, $\nu_{C=O}$ = 1644s, $\nu_{sk,ar}$ = 1527m, δ_{CH2} = 1454w, $\gamma_{sk,ar}$ = 771m, 703s

Hydrazide of 3-phenyl-propionic acid (**4b**)

White crystals (65% yield), m.p. = 98-101°C (ethanol) (lit. m.p. = 104-105°C [18]);

IR (cm^{-1}): ν^{as}_{NH2} = 3327s, ν^{s}_{NH2} = 3286s, ν_{NH} = 3175m, ν_{CHar} = 3060w, 3024w, ν^{as}_{CH2} = 2929w, ν^{s}_{CH2} = 2862w, $\nu_{C=O}$ =1 629s, $\nu_{sk,ar}$ = 1525m, δ_{CH2} = 1451w, $\gamma_{sk,ar}$ = 750m, 701s

Hydrazide of 4-phenyl-butyric acid (**4c**)

Off-white crystals (80% yield), m.p. = 76-78°C (benzene) (lit. m.p. = 78-79°C [19]);

IR (cm^{-1}): ν_{NH2} = 3301s, ν_{NH} = 3197m, ν_{CHar} = 3053w, 3025w, ν^{as}_{CH2} = 2943w, ν^{s}_{CH2} = 2865w, $\nu_{C=O}$ = 1638s, $\nu_{sk,ar}$ = 1523m, δ_{CH2} = 1455w, $\gamma_{sk,ar}$ = 746m, 703s

*Preparation of 5-substituted 2-mercapto-1,3,4-oxadiazoles (**1a-c**)*

Hydrazide **4a-c** (0.025 mol) is dissolved at room temperature in a solution of 0.025 mol KOH in 30 mL ethanol. CS_2 (0.0275 mol) is added dropwise; the resulting suspension is heated at reflux until the evolution of H_2S ceases (16 h for **1a**, 21 h for **1b**, 13 h for **1c**). The resulting solution is distilled to dryness at ~60°C / 10 mmHg, the residue is dissolved in 50 mL water, the solution is treated with active charcoal while hot, filtered, and the filtrate is brought to *p*H 1 with concd. HCl. Products **1a,b** are separated by filtration, and **1c** through extraction with diethyl ether, followed by distillation of the solvent to dryness.

2-Benzyl-5-mercapto-1,3,4-oxadiazole (**1a**)

White powder (31% yield), m.p. = 123-125°C;

IR (cm^{-1}): ν_{NH} = 3351w, 3170w, ν_{CHar} = 3081w, 3029w, ν^{as}_{CH2} = 2944w, $\nu_{C=N}$ = 1615m, $\nu_{sk,ar}$ = 1491s, δ_{CH2} = 1419w, $\gamma_{sk,oxadiazole}$ = 952m, $\gamma_{sk,ar}$ = 727m, 698m

δ_H (DMSO-d_6, 200 MHz): 7.40-7.26 (m, 5H, -Ph); 4.12 (s, 2H, -CH_2-)

δ_C (DMSO-d_6, 50 MHz): 177.9 (C=S); 162.7 (C=N); 133.3 ($\underline{C}_{Ph}$-CH_2); 128.9 (2 x C-o); 128.7 (2 x C-m); 127.4 (C-p); 31.1 (-CH_2-)

2-mercapto-5-(2-phenyl-ethyl)-1,3,4-oxadiazole (**1b**)

White powder (54% yield), m.p.= 90-92°C;

IR (cm^{-1}): ν_{NH} = 3136m, 3108m, ν_{CHar} = 3030w, ν^{as}_{CH2} = 2965m, ν^{s}_{CH2} = 2859w, $\nu_{C=N}$ = 1620m, 1568m, $\nu_{sk,ar}$ = 1499s, δ_{CH2} = 1450m, $\gamma_{sk,oxadiazole}$ = 943m, $\gamma_{sk,ar}$ = 733s, 701m

δ_H (DMSO-d_6, 200 MHz): 7.34-7.17 (m, 5H, -Ph); 3.09-2.93 (m, 4H, -$C\underline{H}_2$-$C\underline{H}_2$-)

δ_C (DMSO-d_6, 50 MHz): 177.7 (C=S); 163.2 (C=N); 139.3 ($\underline{C}_{Ph}$-CH_2-); 128.3 (2 x C-m); 128.2 (2 x C-o); 126.3 (C-p); 30.8 (Ph-CH_2-$\underline{C}H_2$-); 26.5 (Ph-$\underline{C}H_2$-CH_2-)

2-mercapto-5-(3-phenyl-propyl)-1,3,4-oxadiazole (**1c**)

Yellowish liquid (60% yield);

IR (cm^{-1}): ν_{NH} = 3151w, 3100, ν_{CHar} = 3084w, 3027, ν^{as}_{CH2} = 2945m, $\nu_{C=N}$ = 1619m, $\nu_{sk,ar}$ = 1495s, δ_{CH2} = 1455m, $\gamma_{sk,oxadiazole}$ = 947m, $\gamma_{sk,ar}$ = 747s, 701m

δ_H (DMSO-d_6, 200 MHz): 7.32-7.15 (m, 5H, -Ph); 2.74-2.63 (m, 4H, -$C\underline{H}_2$-CH_2-$C\underline{H}_2$-); 1.96 (quintet, 2H, *J* = 7.5 Hz, -CH_2-$\underline{C}H_2$-CH_2-)

δ_C (DMSO-d_6, 50 MHz): 177.6 (C=S); 163.6 (C=N); 140.6 ($\underline{C}_{Ph}$-CH_2-); 128.1 (2 x C-m); 128.1 (2 x C-o); 125.8 (C-p); 33.9 (Ph-$\underline{C}H_2$-CH_2-CH_2-); 26.6 (Ph-CH_2-CH_2-$\underline{C}H_2$-); 24.2 (Ph-CH_2-$\underline{C}H_2$-CH_2-)

Results and discussion

Hydrazinolysis of ethyl esters of phenylacetic (**3a**), 3-phenylpropionic (**3b**) and 4-phenylbutyric acids (**3c**) was achieved through a simplified procedure, without the use of ethanol as reaction medium, the characteristics of hydrazides (**4a-c**) obtained being similar to those reported in the literature [17-19].

The reaction of hydrazides **4a-c** with carbon disulfide in presence of KOH in ethanolic medium was performed without the isolation of the intermediates, potassium N''-acyl-dithiocarbazates **7a-c**, leading to 5-substituted 2-mercapto-1,3,4-oxadiazoles (**1a-c**). These were characterized accordingly, by thin-layer chromatography, melting point and IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{13}C-NMR spectra of compounds **1a-c** evidence the presence only of thione tautomeric forms (C=S) through

1a-c n = 1 (a); 2 (**b**); 3 (**c**)

the signals with δ = 177.7-177.9 ppm, corresponding to exocyclic C=S bonds. This interpretation corresponds to reports in literature on the thionic structure of other 5-substituted 2-mercapto-1,3,4-oxadiazoles [20,21].

Conclusions

Three new compounds, 2-benzyl-5-mercapto-1,3,4-oxadiazole (**1a**), 2-mercapto-5-(2-phenyl-ethyl)-1,3,4-oxadiazole (**1b**) and 2-mercapto-5-(3-phenyl-propyl)-1,3,4-oxadiazole (**1c**), intermediates in the synthesis of 5-substituted 4*H*-4-amino-3-mercapto-1,2,4-triazoles (**2**), have been synthesized and characterized accordingly.

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