(New) 5-Substituted-4H-4-amino-3-mercaptopo-1,2,4-triazoles with Increased Complexing Capabilities

VASILE-NICOLAE BERCEAN1*, ANDREEA-ANDA CREANGĂ1,2, VALENTIN BADEA1, CĂLIN DELEANU3, CAROL CSUNDERLIK6

1 Politehnica University Timișoara, Faculty of Industrial Chemistry and Environmental Engineering, 6, Carol Telbisz 6, 300001, Timișoara, Romania
2 University of Medicine and Pharmacy “Victor Babes”, 2 P-ta Eftimie Murgu, 300041, Timișoara, Romania
3 Institute of Macromolecular Chemistry “Petru Poni”, 41A leea Grigore Ghica Voda, 6600, Iasi, Romania

Five 5-substituted-4H-4-amino-3-mercaptopo-1,2,4-triazoles have been synthesized, in a single step, through the reaction of hydrazides of o-hydroxy-benzoic, p-hydroxy-benzoic, 3,4,5-trihydroxy-benzoic, o-amino-benzoic and p-amino-benzoic acids with carbon disulfide in ethanolic potassium hydroxide, followed by the reaction of the intermediate N''-acyl-dithiocarbazates with hydrazine hydrate. The products were characterized by mass, IR, 1H-NMR and 13C-NMR spectroscopy.

Keywords : 4H-4-amino-5-(hydroxy-phenyl)-substituted-3-mercaptopo-1,2,4-triazole, 5-(amino-phenyl)-substituted-4H-4-amino-3-mercaptopo-1,2,4-triazole

5-Substitued-4H-4-amino-3-mercaptopo-1,2,4-triazoles, their derivatives, as well as their coordination complexes, are biologically active compounds, showing antibacterial [1-4], anti-fungal [1,5], tuberculostatic [6,7], antihelmintic [8], antimicrobial [9], antiviral [10], anti-HIV [11], and antitumoral [12,13] activities.

The purpose of our work was to synthesize (new) 4H-4-amino-5-aryl-3-mercaptopo-1,2,4-triazoles (1) with -OH and -NH2 groups on the benzenic ring, compounds with increased complexing capabilities and which can serve as starting material for new functional derivatives with potential biological activity (Schiff bases, Mannich bases, glycosidic derivatives [14-16]).

Among the synthesis methods of 5-substituted 4H-4-amino-3-mercaptopo-1,2,4-triazoles (1) presented in literature, the ones using accessible starting materials are shown in scheme 1.

According to the literature data, 4H-4-amino-5-aryl-3-mercaptopo-1,2,4-triazoles (1) with R= 2-HO-C6H4- and 2(4)-H2N-C6H4- substituents can be synthesized by treating thiocarbohydrazide (6) with the corresponding carboxylic acids [8].

Among the synthetic routes presented in scheme 1, we choose for the synthesis of 4H-4-amino-3-mercaptopo-5-aryl-1,2,4-triazoles (1a-e) the reaction of the corresponding hydrazides with carbon disulfide in ethanolic potassium hydroxide, followed by the cyclization with hydrazine hydrate of the intermediate N''-acyl-dithiocarbazates, without their isolation, method which we used for the synthesis of others 5-substituted 4H-4-amino-3-mercaptopo-1,2,4-triazoles [17].

Experimental part
Materials and methods

The reagents were commercial products (Chimopar, Merck, Fluka) and used as received. Hydrazides (4a-e) were obtained according to the literature, by hydrazinolysis of the corresponding ethylic esters (3a-e) [18].

Mass spectra GS-MS was performed on a Agilent G1701DA apparatus using methanol as carrier solvent. 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 F254 Merck using benzene : ethyl acetate 1:1 (v/v) as eluant.

IR spectra were recorded in KBr pellet, on a Jasco FT/IR-410 spectrophotometer (br-broad; s-strong; m-medium; w-weak, γ-out of plane vibration; sk-skeletal vibration; ν-stretching vibration; δ-deformation vibration). 1H-NMR and 13C-NMR spectra were recorded on a Bruker Avance AC200 and Bruker Avance DRX400 spectrometer in DMSO-d6, using TMS as reference; chemical shifts are reported in ppm and the coupling constants in Hz.

Preparation of 5-substitued-4H-4-amino-3-mercaptopo-1,2,4-triazoles (1a-e)

Hydrazide (4a-e) (0.02 mol) was dissolved in a solution of 0.03 mol KOH / 20 mL ethanol and 0.03 mol carbon disulfide was added dropwise, at room temperature. The

Scheme 1. Synthetic routes to 5-substituted 4H-4-amino-3-mercaptopo-1,2,4-triazoles (1)
formed suspension was maintained at room temperature for 2 h, then 0.04 mol hydrazine hydrate was added dropwise. After 2 h, half of the reaction volume was distilled, 0.04 mol hydrazine hydrate was added, the solution was refluxed for 4 h, then cooled at room temperature, adjusted to pH ~ 1 with concd. HCl, filtered, and products (1a-e) were separated by filtration and recrystallized from ethanol 50%.

4H-4-amino-5-(2-hydroxy-phenyl)-3-mercaptopo-1,2,4-triazole (1a)
Crem-coloured powder, \( \eta = 65\% \), m.p. = 210-213°C; GS-MS \((m/z) = 208(100\%\, M^+); 137\) (17.52%); 120 (20.61%).
\[
\begin{align*}
\text{IR(KBr, cm}^{-1}): v_{C-H} &= 3428; v_{\text{N-NH}} &= 3294; v_{\text{N-NH}} &= 3196; \\
v_{\text{C-O}} &= 3028; v_{\text{C=O}} &= 1631; v_{\text{N}} &= 1493; \delta_{\text{N}} &= 746m, 693m; \\
\delta (\text{DMSO-d}_6, 200 MHz): &13.79 (s, 1H, -NH); 10.30 (s, 1H, -OH); 7.48 (d, 1H, =7.5 Hz, 6'-H), 7.37 (t, TH, =7.8 Hz, 4'-H), 7.05 (d, 1H, =7.8 Hz, 2'-H), 6.92 (t, 1H, =7.5 Hz, 5'-H), 6.55 (s, 2H, -NH) \\
\delta (\text{DMSO-d}_6, 50 MHz): &164.9 (5'-C); 155.9 (2'-C); 148.9 (3'-C); 131.9 (4'-C); 130.6 (6'-C); 119.0 (3'-C); 116.2 (3'-C); 112.9 (1'-C)
\end{align*}
\]
4H-4-amino-5-(4-hydroxy-phenyl)-3-mercaptopo-1,2,4-triazole (1b)
White powder, \( \eta = 80\%\), m.p. = 260-263°C; GS-MS \((m/z) = 208 (100\%\, M^+); 137\) (35.10%); 119 (23.40%).
\[
\begin{align*}
\text{IR(KBr, cm}^{-1}): v_{\text{C-O}} &= 3475; v_{\text{N-NH}} &= 3306; v_{\text{N-NH}} &= 3279; \\
v_{\text{C=O}} &= 3017; v_{\text{C=O}} &= 1612; v_{\text{N}} &= 1481; \delta_{\text{N}} &= 733m, 691m; \\
\delta (\text{DMSO-d}_6, 400 MHz): &13.76 (s, 1H, -NH); 10.02 (s, 1H, -OH); 7.90 (d, 2H, =8.6 Hz, 2'-H, 6'-H), 6.81 (d, 2H, =8.6 Hz, 3'-H, 5'-H), 5.75 (s, 2H, -NH)\; \delta (\text{DMSO-d}_6, 100 MHz): &166.4 (5'-C); 159.4 (4'-C); 149.6 (3'-C); 129.7 (2'-C, 6'-C); 116.5 (1'-C); 115.3 (3'-C, 5'-C)
\end{align*}
\]
4H-4-amino-5-(3,4,5-trihydroxy-phenyl)-3-mercaptopo-1,2,4-triazole (1c)
Brown powder, \( \eta = 50\%\), m.p. = 250°C; GS-MS \((m/z) = 3391; v_{\text{N-NH}} &= 3316; v_{\text{N-NH}} &= 3285; \\
v_{\text{C=O}} &= 3017; v_{\text{C=O}} &= 1618; v_{\text{N}} &= 1526; \delta_{\text{N}} &= 754m; \\
\delta (\text{DMSO-d}_6, 200 MHz): &13.68 (s, 1H, -NH); 1.91 (brs, 3H, 3'-OH, 4'-OH, 5'-OH); 7.13 (s, 2H, 2'-H, 6'-H), 5.73 (s, 2H, -NH)\; \delta (\text{DMSO-d}_6, 50 MHz): &166.0 (5'-C); 149.1 (3'-C); 145.6 (3'-C, 5'-C); 135.6 (4'-C); 115.6 (1'-C); 107.1 (2'-C, 6'-C)

Results and discussions
Reaction of hydrazides (4a-e) with carbon disulfide in ethanolic KOH, was performed without the isolation of the intermediate N''-acyl-dithiocarbazates (5a-e), which treated with hydrazine hydrate at reflux, lead to 5-aryl-4H-4-amino-3-mercaptopo-1,2,4-triazoles (1a-e), with good yields in the case of para-oriented substituents and modest yields in the case of ortho-oriented substituents.

In our attempt to synthesize the compound with the -NH$_2$ group in the ortho position, a mixture of triazole (1d) and oxadiazole (2) was obtained. The 1H-NMR spectra of this mixture indicates a ratio between the 4H-4-amino-5-(2-amino-phenyl)-3-mercaptopo-1,2,4-triazole (1d) and 5-(2-amino-phenyl)-3-mercaptopo-1,2,4-oxadiazole (2) of 2:1. The GS-MS results indicated, as well, the presence of the two compounds. The two compounds could not be separated by recrystallization.

The 13C-NMR spectra of compounds (1a-e) evidence only the presence of thione tautomeric form (C=S) through the signals with \( \delta = 164.9-166.4 \) ppm, corresponding to exocyclic C=S bonds and through the signals with \( \delta = 13.61-13.79 \) ppm corresponding to N-H proton.

The COSY NMR spectra of compounds 1b, e evidence the direct coupling of the amino group protons (-NH$_2$) with the aromatic protons: 2'-H, 3'-H, 5'-H and 6'-H.

Mixture of 4H-4-amino-5-(2-amino-phenyl)-3-mercaptopo-1,2,4-triazole (1d) and 5-(2-amino-phenyl)-3-mercaptopo-1,2,4-oxadiazole (2)
Yellow powder (1.8 g crude product); m.p. = 152-160°C; GS-MS \((m/z) = 207 (100\% \, \text{M}^+ \, \text{triazole}); 136 (17.64\%); 118 (30.4\%); 193 (100\% \, \text{M}^+ \, \text{oxadiazole}); 120 (77.5\%); 104 (31.25\%)

4H-4-amino-5-(4-phenyl-3-mercaptopo-1,2,4-triazole (1e)
Yellow powder, \( \eta = 83\%\), m.p. = 243-247°C; IR (KBr, cm$^{-1}$): \( \nu(\text{OH}) = 3351 \, \text{m}, \nu(\text{N-H}) = 3269 \, \text{m}; \delta (\text{DMSO-d}_6, 200 MHz): \nu(\text{C=O}) = 1653 \, \text{m}, \nu(\text{C=O}) = 1616 \, \text{m}, \delta (\text{DMSO-d}_6, 50 MHz): 165.9 (5'-C); 150.8 (4'-C); 149.9 (3'-C); 129.0 (2'-C, 6'-C); 113.0 (3'-C, 5'-C); 112.5 (1'-C)

http://www.revistadichemie.ro

REV CHIM. (Bucharest) • 62 • No. 1 • 2011
COSY spectra of compound 1e

2D $^1$H-$^1$C HMBC spectra of compound 1b

2D $^1$H-$^1$C HMBC spectra of compound 1e
Analyzing 2D $^1$H-$^1$C HMBC spectra, long distance coupling $J_{3-C,-NH_2}$ and $J_{5-C,-NH_2}$ of 3-C and 5-C carbon atoms with the protons of the NH$_2$ group is observed, coupling which confirms the presence of the amino group grafted on the triazolic ring.

**Conclusions**

Four compounds, $^4$H-4-amino-5-(2-hydroxy-phenyl)-3-mercapto-1,2,4-triazole ($\text{1a}$), $^4$H-4-amino-5-(4-hydroxy-phenyl)-3-mercapto-1,2,4-triazole ($\text{1b}$), $^4$H-4-amino-5-(3,4,5-trihydroxy-phenyl)-3-mercapto-1,2,4-triazole ($\text{1c}$) and $^4$H-4-amino-5-(4-amino-phenyl)-3-mercapto-1,2,4-triazole ($\text{1e}$), have been synthesized using a different method from the one presented in literature. The four compounds were characterized accordingly.

**References**

15. ŞIŞU, I., BERCEAN, V., BADEA, V., CAPROIU, M.T., ŞIŞU, E., Rev. Chim. (Bucharest), 60, nr. 9, 2009, p.884
18.e) *** BEILSTEINS, Handbuch der Organischen Chemie, Verlag von Julius Springer, 14, I, 1933, p.570

Manuscript received: 15.06.2010