SYNTHESIS OF FURO[3,2-*b*]PYRROLE-5-CARBOXHYDRAZIDES AND THEIR Cu, Co AND Ni COMPLEXES

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Abstract: Carboxhydrazides **3** were synthesized by reaction of substituted furo[3,2-*b*]pyrrole-5-carboxhydrazides **1** with 4-oxo-4*H*-chromene-2-carboxaldehyde **2** in the presence of 3-methyl-benzenesulfonic acid in ethanol. Carboxhydrazides **3** were used as ligands for synthesis of Cu, Co and Ni complexes **4**.

Keywords: furo[3,2-*b*]pyrrole, chromene, carboxhydrazide, complex

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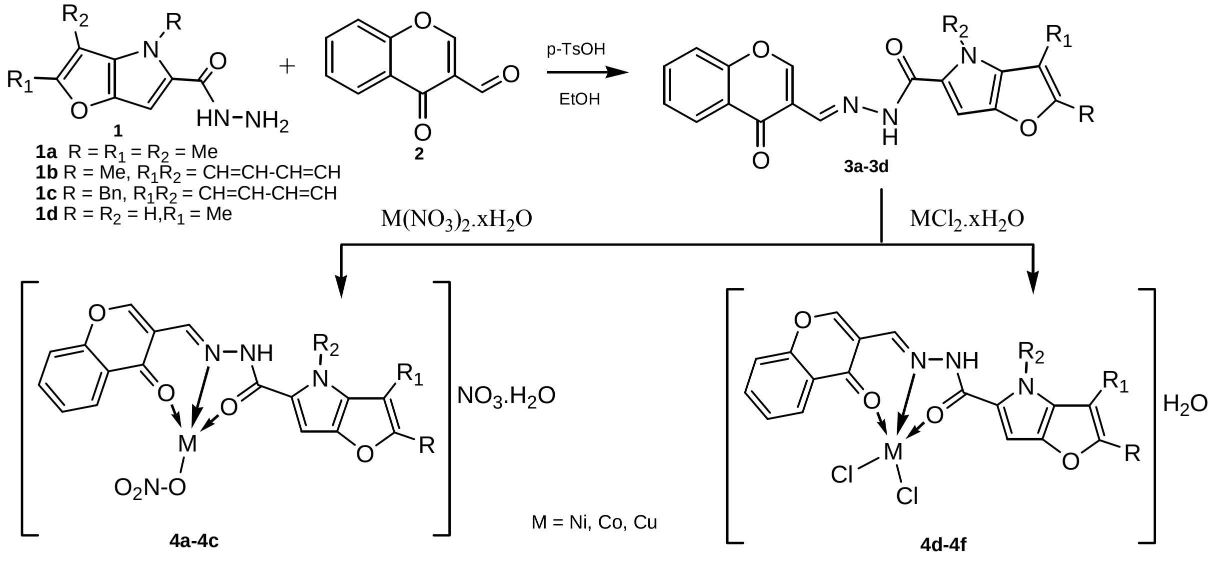
1. Introduction

Carboxhydrazides and their derivatives represent an interesting class of compounds which exhibits antitumor [1], antimicrobial [2], analgesic and anti-inflammatory [3] activities. Complexes of carbohydrazides are also known for their boological activity. La (I) and Sm (II) complexes of 6-hydroxy chromone-3-carbaldehyde benzoyl hydrazone were tested against tumor cell lines including human promyelocytic leukemia cell line HL-60 and lung adenocarinoma epithelial cell line A-549 [4]. Zn(II) complex of 4-oxo-4*H*-chromene-3-carbaldehyde thiosemicarbazone binds to DNA and possess significant anioxidant activity [5]. The present study is a follow-up paper to our previous research dealing with the synthesis and reactions of furo[3,2-*b*]pyrrole system [6,7] and the study of its biological activity. E.g. the effect of *N'*-{[5-(R-Phenyl)furan-2-yl]methylene}-2-[3-(trifluoromethyl)phenyl]-4*H*-furo[3,2-*b*]pyrrole-5-carboxhydrazides on inhibition of photosynthetic electron transport in spinach chloroplasts and chlorophyll content in the antialgal suspensions of *Chlorella vulgaris* were investigated [8].

2. Experimental

Melting points of products were determined on a Kofler hot plate apparatus and are uncorrected. All solvents were predistilled and dried appropriately prior to use. ^{1}H NMR spectra were obtained on a 300 MHz spectrometer VARIAN GEMINI 2000 in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. Elemental analyses were measured on EAGER 300 apparatus. Electronic spectra vere measured in nujol mull on Specord 200 (Analytical Jena) in the range 50,000 – 9,000 cm^{-1}.



Scheme 1

2.1 Synthesis of ligands ***3***

A mixture of furo[3,2-*b*]pyrrole-5-carbohydrazide **1** (10 mmol) and 4-oxochromene-3-carboxaldehyde **2** (10 mmol) was heated for 1–4 h at 50–60 °C in ethanol (20 cm^3) in the presence of 4-methylbenzenesulfonic acid. The solid products were filtered off, dried and crystallized from ethanol.

2.1.1N’-[(4-Oxo-4H-chromen-3-yl)methylene]-2,3,4-trimethyl-furo[3,2-b]pyrrole-5-carboxhydrazide (tmfupy) ***3a***

For $C_{20}H_{17}N_3O_4$ (363.4): Mp 251-255 °C; react. time 2.5h; yield: 81%; ^{1}H NMR ($CDCl_3$): 10.98 (1H, brs, NH); 8.93 (1H, s, H-2); 8.69 (1H, s, H-9); 8.20 (1H, d, *J* = 2.5 Hz, H-5); 7.95 (1H, d, *J* = 7.2 Hz, H-6); 7.68 (1H, ddd, *J* = 8.1, 7.3, 1.6 Hz, H-7); 7.50 (1H, d, *J* = 8.4 Hz, H-8); 6.57 (1H, s, H-6’); 4.05 (3H, s, CH_3); 2.36 (3H, s, CH_3); 2.21 (3H, s, CH_3).

2.1.2 N’-[(4-Oxo-4H-chromen-3-yl)methylene]-4-methyl-[1]benzofuro[3,2-b]pyrrole-5-carboyhydrazide (mebfupy) ***3b***

For $C_{22}H_{15}N_3O_4$ (385.4): Mp 241-245 °C; react. time 1h; yield 85%; ^{1}H NMR ($CDCl_3$): 11.71 (1H, brs, NH); 8.83 (1H, s, H-2); 8.55 (1H, s, H-9); 8.16-7.72 (4H, m, H-2’, H-3’, H-4’, H-5’); 7.36-7.22 (4H, m, H-5, H-6, H-7, H-8); 7.15 (1H, s, H-6’); 4.31 (3H, s, CH_3).

2.1.3 N’-[(4-Oxo-4H-chromen-3-yl)methyene]-4-benzyl-[1]benzofuro[3,2-b]pyrrole-5-carboxhydrazide(bzbfupy) ***3c***

For $C_{28}H_{19}N_3O_4$ (461.5): Mp 263-266 °C; react. time 4h; yield 82%; ^{1}H NMR ($CDCl_3$): 11.69 (1H, brs, NH); 8.81 (1H, s, H-2); 8.56 (1H, s, H-9); 8.17-7.75 (4H, m, H-2’, H-3’, H-4’, H-5’); 7.39-7.29 (4H, m, H-5, H-6, H-7, H-8); 7.27-7.16 (5H, m, Ph); 7.13 (1H, s, H-6’); 5.65 (2H, s, CH_2).

2.1.4 2-Methyl-N’-[(4-oxo-4H-chromen-3-yl)methylene]-4H-furo[3,2-b]pyrrole-5-carboxhydrazide(mefupy) ***3d***

For $C_{18}H_{13}N_3O_4$ (335.3): Mp 253-256 °C; react. time 2.5h; yield 60%; ^{1}H NMR (DMSO-d_6): 11.53 (1H, s, NH); 11.46 (1H, brs, NH); 8.84 (1H, s, H-2); 8.19-8.16 (2H, m, H-5, H-9); 7.87 (1H, ddd, *J* = 7.2, 6.9, 1.5 Hz, H-7); 7.75 (1H, d, *J* = 7.8 Hz, H-8); 7.57 (1H, ddd, *J* = 8.1, 6.9, 1.2 Hz, H-6); 7.01 (1H, s, H-6’); 6.27 (1H, s, H-3’).

2.2 Synthesis of complexes ***4***

Ligand **3** (0.5 mmol) was dissolved in acetone (10 cm^3) at 70 °C. A solution of metal (M^{2+}) nitrate or chloride [$Ni(NO_3)_2.6H_2O$, $Co(NO_3)_2.6H_2O$, $CoCl_2.6H_2O$, $CuCl_2.2H_2O$] (0.5 mmol) was added dropwise. Precipitate which was formed immediately, was filtered off, washed with acetone (3 x 15 cm^3) and dried.

2.2.1 [Ni(tmfupy)NO$_3$]NO$_3$.H$_2$O ***4a***

Yield: 80%; Anal. Calcd. for $C_{20}H_{19}N_5NiO_{11}$ (564.1); C, 42.58; H, 3.40; N, 12.42; Ni, 10.41. Found: C, 42.97; H, 3.21; N, 12.57; Ni, 11.69 %.

2.2.2 [Co(mebfupy)NO$_3$]NO$_3$.H$_2$O ***4b***

Yield: 88%; Anal. Calcd. for $C_{22}H_{17}CoN_5O_{11}$ (586.3); C, 45.07; H, 2.92; N, 11.94; Co, 10.05. Found: C, 46.96; H, 2.71; N, 12.07; Co, 11.54 %.

2.2.3 [Co(mefupy)NO$_3$]NO$_3$.H$_2$O ***4c***

Yield: 78%; Anal. Calcd. for C, 40.31; H, 2.82; N, 13.06; Co, 10.99. Found: C, 42.12; H, 2.70; N, 13.33; Co, 11.72 %.

2.2.4 [Cu(tmfupy)Cl$_2$]H$_2$O ***4d***

Yield: 81%; Anal. Calcd. for $C_{20}H_{19}Cl_2CuN_3O_5$ (515.8); C, 46.57; H, 3.71; N, 8.15; Cu, 12.32. Found: C, 45.45; H, 3.62; N, 7.79; Cu, 11.95 %.

2.2.5 [Cu(bzbfupy)Cl$_2$]H$_2$O ***4e***

Yield: 93%; Anal. Calcd. for $C_{28}H_{21}Cl_2CuN_3O_5$ (613.9); C, 54.78; H, 3.45; N, 6.84; Cu, 10.35. Found: C, 52.03; H, 3.02; N, 6.48; Cu, 10.84 %.

2.2.6 [Co(mefupy)Cl$_2$]H$_2$O ***4f***

Yield: 77%; Anal. Calcd. for $C_{18}H_{15}Cl_2CoN_3O_5$ (483.2); C, 44.74; H, 3.13; N, 8.70; Co, 12.20. Found: C, 45.06; H, 3.24; N, 9.30; Cu, 11.45 %.

2.2.7 [Cu(mefupy)Cl$_2$]H$_2$O ***4g***

Yield: 84%; Anal. Calcd. for $C_{18}H_{15}Cl_2CuN_3O_5$ (487.8); C, 44.32; H, 3.10; N, 8.61; Cu, 13.03. Found: C, 45.16; H, 3.07; N, 9.04; Cu, 12.88 %.

3. Results and discussion

N'-[(4-Oxo-4*H*-chromen-3-yl)methyene]-2-R^1-3-R^2-4-R-furo[3,2-*b*]pyrrole-5-carboxhydrazides **3a-3d** were synthesized in 60 – 85% yields by reaction of **1** with **2** in ethanol in the presence of 4-methylbenzenesulfonic acid by heating at 50 - 60° C for 1 - 4h (Scheme 1).

The ^1H NMR spectra of compounds **3a – 3d** displayed signals of H-2 pyran protons in the 8.81-8.93 ppm range, H-6 pyrrole protons in the 7.36 – 7.95 ppm range and signals due to CH=N bonded protons in the 8.19 – 8.69 ppm range. The chemical shifts and the multiplicity confirmed the proposed structures.

Carboxhydrazides **3** were subsequently used as ligands in complexation reactions with solutions of metal (M^{2+}) chlorides or nitrates [$Ni(NO_3)_2.6H_2O$, $Co(NO_3)_2.6H_2O$, $CoCl_2.6H_2O$, $CuCl_2.2H_2O$] in acetone at 70 °C. Complexes **4** were obtained in high yields (78-93%).

Structures of **4** were determined by the elemental analyses and electronic spectra. Electronic spectrum of hexacoordinated Ni (II) ion shows transitions at 10000 ($^3A_{2g} \rightarrow {}^3T_{2g}$)

and 16000 cm^{-1} ($^{3}A_{2g} \rightarrow {}^{3}T_{1g}$). The third transition ($^{3}A_{2g} \rightarrow {}^{3}T_{1g}$), which is probably overlapped, should be at about 26000 cm^{-1} (Fig.1).

Electronic spectra of hexacoordinated Co(II) shows weak transitions at 15000 cm^{-1} ($^{4}T_{1g} \rightarrow {}^{4}A_{2g}$) and transitions at 19000 cm^{-1} ($^{4}T_{1g} \rightarrow {}^{4}T_{1g}(P)$). Next transitions over 20000 cm^{-1} could be overlaped by strong charge-transfer transitions (Fig.2).

Hexacoordinated Cu(II) ion has tetragonal symmetry with transitions up to 10000 cm^{-1} ($^{2}B_{1g} \rightarrow {}^{2}A_{1g}$) and 16000 cm^{-1} ($^{2}B_{1g} \rightarrow {}^{2}B_{2g}$) (Fig.3).

Electronic spectrum of tetracoordinated Co(II) ion shows characteristic transitions in the area of 15000 – 16000 cm^{-1} ($^{4}A_{2} \rightarrow {}^{4}T_{1}(P)$) (Fig. 4).

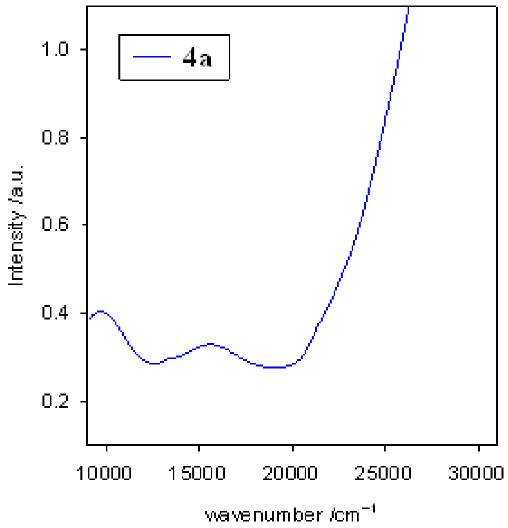


Figure 1

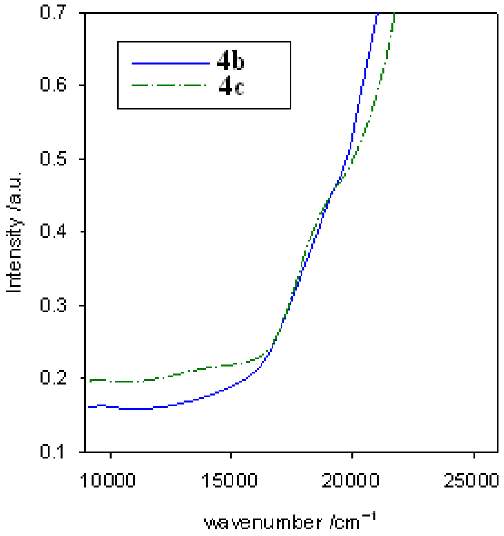


Figure 2

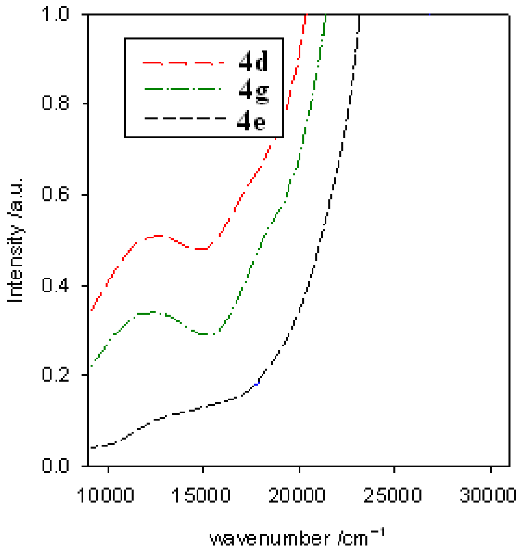


Figure 3

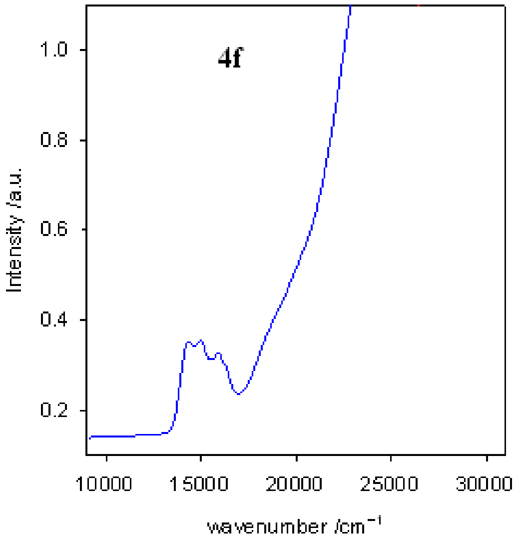


Figure 4

4. Conclusion

Furo[3,2-*b*]pyrrole-5-carboxhydrazides **1** reacted with substituted with 4-oxo-4*H*-chromene-2-carboxaldehyde **2** to give *N'*-[(4-oxo-4*H*-chromen-3-yl)methyene]-2-R^{1}-3-R^{2}-4-

R-furo[3,2-*b*]pyrrole-5-carboxhydrazides **3**, which served asligands for synthesis of synthesis of Cu, Co and Ni complexes **4**.

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