

SYNTHESIS OF FURO[3,2-*b*]PYRROLE-5-CARBOXYHYDRAZIDES 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

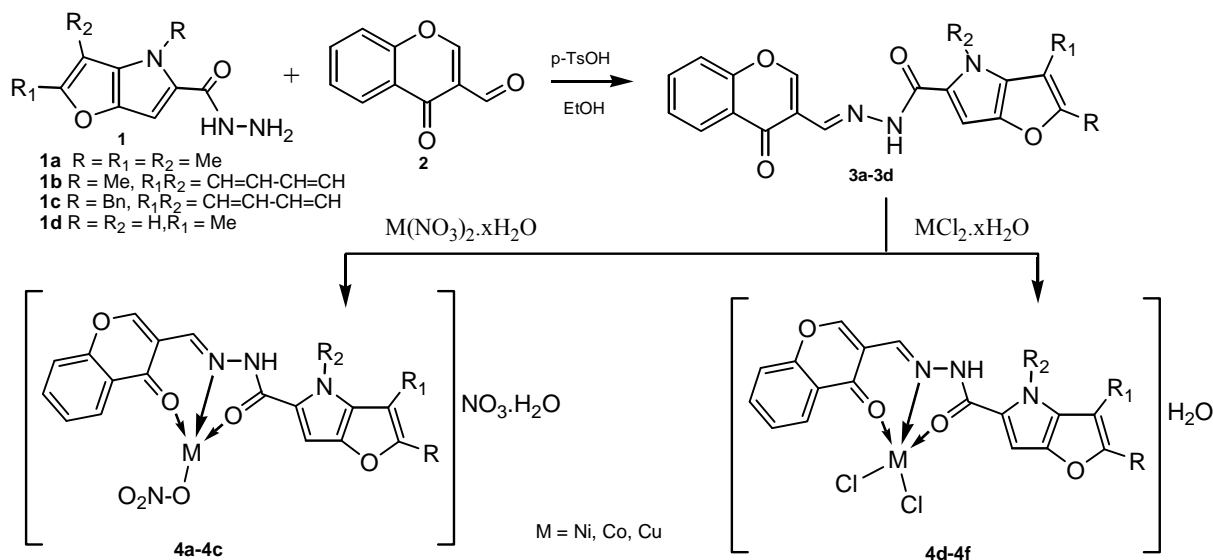
1. Introduction

Carboxhydrazides and their derivatives represent an interesting class of compounds which exhibits antitumor [1], antimicrobial [2], analgesic and anti-inflammatory [3] activities. Complexes of carboxhydrazides are also known for their biological activity. La (I) and Sm (II) complexes of 6-hydroxy chromone-3-carbaldehyde benzoyl hydrazone were tested against tumor cell lines including HL-60 and A-549 [4]. Zn(II) complex of 4-oxo-4*H*-chromene-3-carbaldehyde thiosemicarbazone binds to DNA and possess significant antioxidant 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 [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. ¹H NMR spectra were obtained on a 300 MHz spectrometer VARIAN GEMINI 2000 in CDCl₃ or DMSO-*d*₆ with tetramethylsilane as an internal standard. Elemental analyses were measured on EAGER 300 apparatus. Electronic spectra were 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 cm³) in the presence of 4-methylbenzenesulfonic acid. The solid products were filtered off, dried and crystallized from ethanol.

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

For C₂₀H₁₇N₃O₄ (363.4): Mp 251-255 °C; react. time 2.5h; yield: 81%; ¹H NMR (CDCl₃): 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, CH₃); 2.36 (3H, s, CH₃); 2.21 (3H, s, CH₃).

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

For C₂₂H₁₅N₃O₄ (385.4): Mp 241-245 °C; react. time 1h; yield 85%; ¹H NMR (CDCl₃): 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, CH₃).

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

For C₂₈H₁₉N₃O₄ (461.5): Mp 263-266 °C; react. time 4h; yield 82%; ¹H NMR (CDCl₃): 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, CH₂).

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

For C₁₈H₁₃N₃O₄ (335.3): Mp 253-256 °C; react. time 2.5h; yield 60%; ¹H 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 cm³) at 70 °C. A solution of metal (M²⁺) nitrate or chloride [Ni(NO₃)₂.6H₂O, Co(NO₃)₂.6H₂O, CoCl₂.6H₂O, CuCl₂.2H₂O] (0.5 mmol) was added dropwise. Precipitate which was formed immediately, was filtered off, washed with acetone (3 x 15 cm³) and dried.

2.2.1 [Ni(*tmfupy*)NO₃]NO₃.H₂O **4a**

Yield: 80%; Anal. Calcd. for C₂₀H₁₉N₅NiO₁₁ (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(*mefupy*)NO₃]NO₃.H₂O **4b**

Yield: 88%; Anal. Calcd. for C₂₂H₁₇CoN₅O₁₁(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*)NO₃]NO₃.H₂O **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*)Cl₂]H₂O **4d**

Yield: 81%; Anal. Calcd. for C₂₀H₁₉Cl₂CuN₃O₅ (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*)Cl₂]H₂O **4e**

Yield: 93%; Anal. Calcd. for C₂₈H₂₁Cl₂CuN₃O₅ (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*)Cl₂]H₂O **4f**

Yield: 77%; Anal. Calcd. for C₁₈H₁₅Cl₂CoN₃O₅ (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*)Cl₂]H₂O **4g**

Yield: 84%; Anal. Calcd. for C₁₈H₁₅Cl₂CuN₃O₅ (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)methylene]-2-R¹-3-R²-4-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 (M²⁺) chlorides or nitrates [Ni(NO₃)₂.6H₂O, Co(NO₃)₂.6H₂O, CoCl₂.6H₂O, CuCl₂.2H₂O] 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} → ³T_{2g}) and 16000 cm⁻¹ (³A_{2g} → ³T_{1g}). The third transition (³A_{2g} → ³T_{1g}), which is probably

overlapped, should be at about 26000 cm^{-1} (Fig.1). Electronic spectrum of hexacoordinated Co(II) ion shows characteristic transitions in the area of $15000 - 16000\text{ cm}^{-1}$ (${}^4A_2 \rightarrow {}^4T_1(P)$) (Fig. 2).

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

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

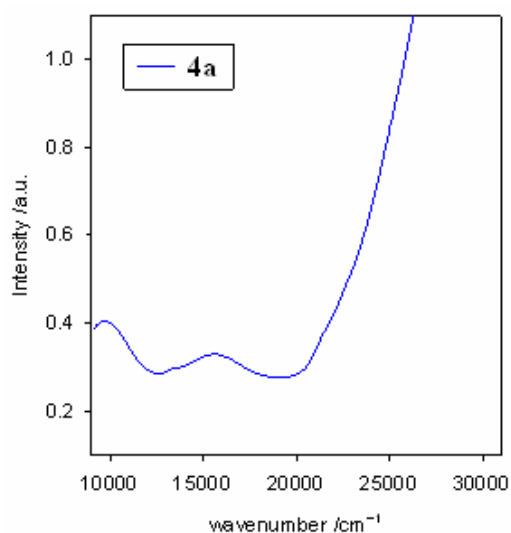


Figure 1

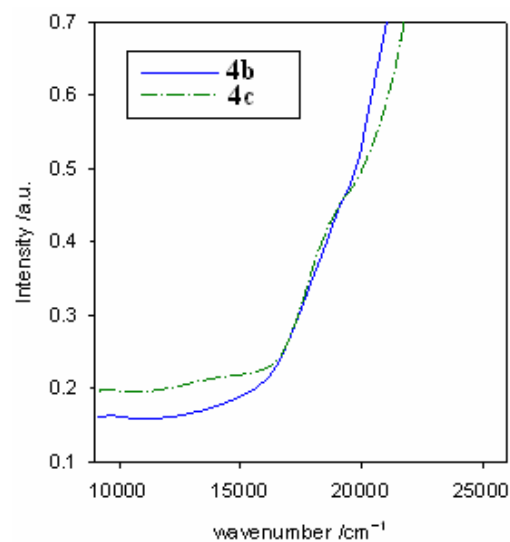


Figure 2

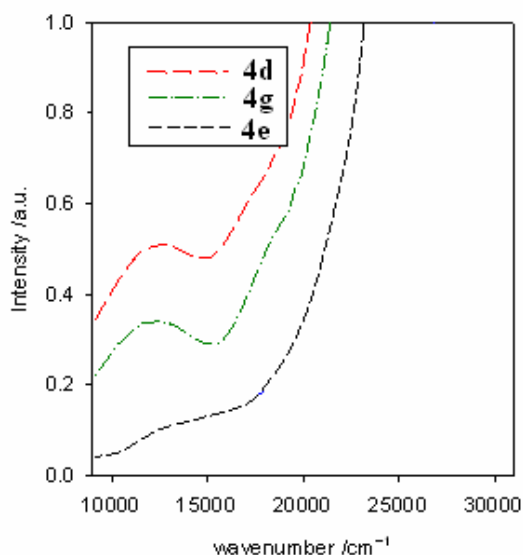


Figure 3

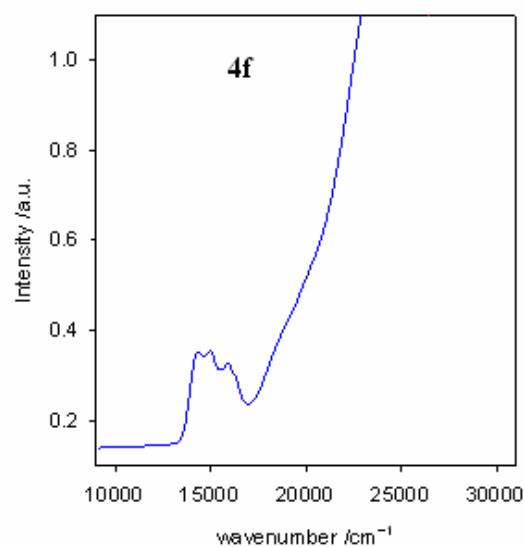


Figure 4

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)methylene]-2-*R*¹-3-*R*²-4-*R*-furo[3,2-*b*]pyrrole-5-carboxhydrazides **3**, which served as ligands for synthesis of synthesis of Cu, Co and Ni complexes **4**.

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