Inorganica Chimica Acta 471 (2018) 570–576

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Research paper

Pyrazoline derivatives of acryloyl substituted ferrocenyl ketones: Synthesis, antimicrobial activity and structural properties

Adrijana Burmudžija [a], Jovana Muškinja [a], Zoran Ratković [a,*], Marijana Kosanić [b], Branislav Ranković [b], Sladjana B. Novaković [c], Goran A. Bogdanović [c]

[a] Department of Chemistry, Faculty of Science, University of Kragujevac, Radoja Domanovića 12, 34000 Kragujevac, Serbia
[b] Department of Biology and Ecology, Faculty of Science, University of Kragujevac, Radoja Domanovića 12, 34000 Kragujevac, Serbia
[c] Vinča Institute of Nuclear Sciences, Laboratory of Theoretical Physics and Condensed Matter Physics, University of Belgrade, P.O. Box 522, 11001 Belgrade, Serbia

ARTICLE INFO

Article history:
Received 15 September 2017
Received in revised form 27 November 2017
Accepted 28 November 2017
Available online 2 December 2017

Keywords:
Ferrocenyl ketones
Enone system
Pyrazoline derivatives
Crystal structure
Antimicrobial activity

ABSTRACT

A series of ferrocenyl ketones were synthesized in reaction with ferrocene and corresponding substituted acryloyl chlorides, following previously described procedure. Synthesized products have conjugated enone system, which is suitable for further transformations. In a reaction with hydrazine in acidic medium (acetic acid) new pyrazoline derivatives were obtained. Their antimicrobial properties have been tested. Synthesized pyrazoline derivatives demonstrated expressed *in vitro* antimicrobial activity towards 12 strains of microorganisms inhibiting all tested bacteria and fungi. The most potent compound in all cases was sorbyl derivative; for bacteria activity was very close to streptomycin, and for fungi in one case the same as ketoconazole. It is established that this compound can be a new, potential antimicrobial agent with minimum inhibitory concentrations from 0.039 to 0.312 mg/mL. One of the starting compounds and two products were crystal substances, suitable for the single crystal X-ray diffraction analysis, which confirmed undoubtedly their structures.

1. Introduction

Chalcones (1,3-diaryl-2-propen-1-ones), and chalcone-like compounds (with similar enone system) are an important class of organic compounds, since they often represent core structure of many natural products and exhibit various pharmacological and biological activities. Antimicrobial [1–6], antioxidant [7–9], antifungal [5,6,10], antimalarial [11–13], anti-inflammatory [14,15] and anticancer activity [16–21] are well expressed and explored.Enone system presented in chalcones is the often a key part of substrates; it is almost planar and have *trans*-double bond. This structure enables various transformations of enone system, which could be easily converted into different heterocyclic derivatives, in reactions with urea, thiourea, hydroxylamine, hydrazine, guanidine [22,23], forming heterocyclic unit between aromates. Ferrocenyl derivatives are among the most promising organometallic compounds which can be used in microbiological research. In continuation of our interest in synthesis of ferrocene containing heterocycles exhibiting some biological activities [24–27], we expected that incorporation of pyrazoline fragment and the ferrocene scaffold into the same molecule might have an attracting structural result for development of novel antimicrobial agents.Herein we wish to report on synthesis, spectral characterization and evaluation of antimicrobial activity on some strains of microorganisms a series of novel Fc-pyrazoline derivatives, prepared from chalcone-like ketones (**2a**–**e**) and heterocyclic chalcone **2f**.All new products were characterized by their spectral data (IR, MS, ^{1}H NMR and ^{13}C NMR). Compounds **2c**, **3c** and **3f** gave crystals suitable for the X-ray analysis

2. Experimental

2.1. Chemistry

2.1.1. Materials and measurements

All starting chemicals were commercially available and used as received, except for the solvents being purified by distillation. Column chromatography were carried out using silica gel 60 (Merck, 230–400 mesh ASTM); for TLC was used Silica gel 60 F_{254}-precoated plates (Merck); layer thickness 0.2 mm. IR spectra: Perkin-Elmer Spectrum One FT-IR spectrometer with a KBr disc, ν in cm^{-1}. NMR spectra: Varian Gemini 200 MHz spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C), using $CDCl_3$ as the solvent and

* Corresponding author.
E-mail address: wor@kg.ac.rs (Z. Ratković).

https://doi.org/10.1016/j.ica.2017.11.061
0020-1693/

TMS as the internal standard. ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million (ppm) and were referenced to the solvent peak; $CDCl_3$ (7.26 ppm for ^{1}H and 76.90 ppm for ^{13}C). Multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (*J*) are in Hertz (Hz). Mass spectrometry was performed by Waters Micromass ZQ mass spectrometer and MassLynx software for control and data processing. Electro spray ionization in the positive mode was used. The electro spray capillary was set at 4.3 kV and the cone at 40 V. The ion source temperature was set at 125 °C and the nitrogen flow rates were 400 L/h and 50 L/h, for desolvation and cone gas flow respectively. The collision energy was 40 eV. The melting point of products was determined by using MelTemp1000 apparatus.

*2.1.2. Procedure for the synthesis of 1-ferrocenyl-2,4-hexadien-1-one (**2e**)*

The ferrocenyl ketone, 1-ferrocenyl-2,4-hexadien-1-one (sorbyl ferrocene), **2e**, was prepared by following procedure: sorbic acid, 1.12 g (10 mmol) was dissolved in a 150 mL of dried CH_2Cl_2, and 1 mL of PCl_3 was added. Closed vessel with solution was stirred overnight at room temperature. To this solution 1.98 g of ferrocene (10 mmol) was added following with 1.44 g (10 mmol) of anhydrous $AlCl_3$. Solution became deep blue from formed complex, and stirring was continued for next 2–3 h. Reaction mixture was poured out in 100 mL of 2 M HCl solution and shaken well. Organic phase was separated, and water layer was extracted with 50 mL of CH_2Cl_2. Combined organic layers were washed with 2 × 100 mL of water and dried over anhydrous Na_2SO_2. The main part of solvent was removed by distillation and concentrated crude mixture was filtered through SiO_2 pad. Separation of product was performed on SiO_2 column using CH_2Cl_2 as eluent. Deep red band belongs to ferrocenyl ketone **2e**. Solvent was evaporated by distillation and products crystalizes on standing.

Cinnabar red crystals; mp 139–140 °C; Yield 75%; IR (cm^{-1}): 3118, 3017, 1652, 1627, 1583, 1457, 1376, 1267, 1104, 1072, 1001; ^{1}H NMR: δ 1.89 (d, J = 5.4 Hz, 3H), 4.18 (s, 5H), 4.54 (t, J = 2.2 Hz, 2H), 4.83 (t, J = 1.8 Hz, 2H), 6.22–3.38 (m, 2H), 6.48 (d, J = 15.4 Hz, 1H), 7.27–7.44 (m, 1H); ^{13}C NMR: δ 18.8, 69.6, 70.0, 72.4, 80.7, 124.3, 130.5, 139.7, 141.2, 193.3.

*2.1.3. Synthesis of pyrazoline derivatives (**3a–f**)*

To a stirred solution of **2a–f** (10 mmol), in acetic acid (10 mL) hydrazine monohydrate (1.25 mL, 25 mmol) was added and reaction mixture was heated to reflux for 3 h. The solvent was evaporated under reduced pressure and water (50 mL) was added to the colored residue. Products were extracted from the reaction mixture with toluene or toluene/EtOAc (95:5) mixture. After removal of the main part of solvent the residue was filtered over SiO_2 pad. After evaporation of solvent oily residue was dissolved in ether, from which some of products **3a–f** crystallize on standing in deepfreeze.

*2.1.3.1. 1-(3-Ferrocenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (**3a**).* Light orange crystals; mp 184–185 °C; Yield 85%; IR (cm^{-1}): 3085, 1650 (CO), 1502 (C=Carom.), 1418, 1311, 1104, 1029, 1011; ^{1}H NMR: δ 2.33 (s, 3H), 3.06–3.15 (m, 2H), 3.91–4.01 (m, 2H), 4.18 (s, 5H), 4.39 (t, J = 1.8 Hz, 2H), 4.61 (t, J = 2.0 Hz, 2H); ^{13}C NMR: δ 21.4, 33.0, 43.3, 67.3, 69.4, 70.2, 75.4, 157.3, 168.5 (CO). ESI-MS (40 eV): m/z (%) = 296 (100%) $[M]^+$, 254 (35%), 185 (12%), 121 (39%), 43 (7%).

*2.1.3.2. 1-(5-Methyl-3-ferrocenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (**3b**).* Red-orange oil; Yield 81.2%; IR (cm^{-1}): 3086, 1648 (CO), 1498, 1413, 1314, 1106, 1027, 1006; ^{1}H NMR: δ 1.38 (d, J = 6.6 Hz, 3H), 2.31 (s, 3H), 2.65 (dd, J = 17.2, 3.4 Hz, 1H), 3.32 (dd, J = 17.2, 10.8 Hz, 1H), 4.19 (s, 5H), 4.39 (s, 2H), 4.57 (m, 1H), 4.63 (s, 2H); ^{13}C NMR: δ 20.3, 21.9, 41.6, 51.8, 67.2, 67.5, 69.4, 70.2, 75.7, 156.0, 168.3 (CO). ESI-MS (40 eV): m/z (%) = 310 (100%) $[M]^+$, 268 (31%), 185 (10%), 121 (27%), 43 (8%).

*2.1.3.3. 1-(5,5-Dimethyl-3-ferrocenyl-4,5-dihydro-1H-pyrazol-1-yl) ethanone (**3c**).* Cinnabar red crystals; mp 142 °C; Yield 61.2%; IR (cm^{-1}): 3086, 2929, 1651 (CO), 1498, 1405, 1314, 1105, 1012; NMR: δ ^{1}H NMR: δ 1.65 (s, 6H), 2.29 (s, 3H), 2.99 (s, 2H), 4.18 (s, 5H), 4.37 (t, J = 1.8 Hz, 2H), 4.57 (t, J = 2.0 Hz, 2H); ^{13}C NMR: δ 23.3, 26.3, 50.6, 62.8, 67.1, 69.3, 70.1, 72.3, 76.0, 153.6, 169.0 (CO). ESI-MS (40 eV): m/z (%) = 324 (100%) $[M]^+$, 283 (27%), 267 (63%), 185 (9%), 121 (27%), 43 (9%).

*2.1.3.4. 1-(4-Methyl-3-ferrocenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (**3d**).* Cinnabar red crystals; mp 78–79 °C; Yield 81.2%; IR (cm^{-1}): 3099, 2974, 1655 (CO), 1496, 1449, 1308, 1160, 1106, 1028, 997; ^{1}H NMR: δ 1.14–1.85 (m, 2H), 1.71 (s, 3H), 2.33 (s, 3H), 3.29–3.45 (m, 1H), 4.18 (s, 5H), 4.41 (m, 2H), 4.59 (m, 1H), 4.69 (m, 1H); ^{13}C NMR: δ 19.8, 21.3, 40.5, 51.9, 67.4, 67.5, 69.6, 69.9, 70.2, 75.7, 161.4, 168.9 (CO). ESI-MS (40 eV): m/z (%) = 310 (100%) $[M]^+$, 268 (32%), 185 (19%), 121 (33%), 44 (30%).

*2.1.3.5. (E)-1-(3-Ferrocenyl-5-propenyl-4,5-dihydro-1H-pyrazol-1-yl) ethanone (**3e**).* Red-orange oil; Yield 78.4%; IR (cm^{-1}): 3086, 1654 (CO), 1497, 1412, 1378, 1106, 1007; ^{1}H NMR: δ 1.71 (dt, J = 6.4, 1.3 Hz, 3H), 2.82 (dd, J = 17.0, 3.8 Hz, 1H), 3.32 (dd, J = 17.2, 11.2 Hz, 1H), 4.12 (s, 5H), 4.39 (m, 2H), 4.54 (dt, J = 3.8, 1.6 Hz, 1H), 4.66 (dt, J = 3.8, 1.8 Hz, 1H), 5.01 (ddd, J = 10.3, 5.6, 4.0 Hz, 1H), 5.48 (ddq, J = 15.2, 6.0, 1.0 Hz, 1H), 5.69 (ddd, J = 15.2, 6.1, 1.0 Hz, 1H); ^{13}C NMR: δ 21.8, 43.7, 55.9, 58.9, 67.1, 67.6, 69.3, 70.2, 70.4, 75.4, 108.9, 111.6, 117.2, 134.7, 148.4, 149.3, 155.8, 168.2 (CO). ESI-MS (40 eV): m/z (%) = 336 (100%) $[M]^+$, 294 (17%), 185 (6%), 121 (21%), 43 (7%).

*2.1.3.6. 1-(5-(Furan-2-yl)-3-ferrocenyl-4,5-dihydro-1H-pyrazol-1-yl) ethanone (**3f**).* Cinnabar red crystals; mp 153 °C; Yield 59.5%; IR (cm^{-1}): 3101, 1651 (CO), 1498, 1416, 1376, 1309, 1149, 1156, 1018, 1006; ^{1}H NMR: δ 2.32 (s, 3H), 3.39 (m, J = 17.2, 11 Hz, 2H), 4.21 (s, 5H), 4.41 (m, 2H), 4.51 (m, 1H), 4.75 (m, 1H), 5.63 (m, J = 11, 0.23 Hz, 1H), 6.35 (s, 2H), 7.34 (s, 1H); ^{13}C NMR: δ 21.8, 39.3, 52.6, 66.8, 67.9, 69.5, 70.2, 70.5, 75.2, 107.5, 110.6, 141.7, 156.1, 168.2 (CO). ESI-MS (40 eV): m/z (%) = 362 (100%) $[M-16]^+$, 320 (29%), 185 (4%), 121 (21%), 43 (10%).

2.2. Antimicrobial activity

Antimicrobial activities of tested compounds were evaluated against five strains of bacteria: *Staphylococcus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 6633), *B. cereus* (ATCC 10987), *Escherichia coli* (ATCC 25922) and *Proteus mirabilis* (ATCC 29906) and seven species of fungi: *Aspergillus flavus* (ATCC 9170), *A. fumigatus* (ATCC 1022), *Candida albicans* (ATCC 10259), *Penicillium italicum* (ATCC 10454) and *Trichophyton mentagrophytes* (ATCC 9533), *Geotrichum candidum* (ATCC 34614) and *Mucor mucedo* (ATCC 20094) obtained from the American Type Culture Collection (ATCC).

The bacteria isolates were picked from overnight cultures in Mueller-Hinton agar and suspensions were prepared in sterile distilled water. The turbidity of suspensions was adjusted by comparing with 0.5 McFarland's standard to approximately 10^8 CFU/mL.

Fungal suspensions were prepared from 3- to 7-day-old cultures that grew on a potato dextrose agar except for *C. albicans* that was maintained on Sabourad dextrose (SD) agar. The spores were rinsed with sterile distilled water, used to determine turbidity spectrophotometrically at 530 nm NCCLS [28]. The resulting suspensions were approximately 10^6 CFU/mL.