Journal of Saudi Chemical Society (2014) **18**, 269–275

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Synthesis and antimicrobial screening of tetra Schiff bases of 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene

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Received 12 May 2011; accepted 6 July 2011
Available online 20 July 2011

KEYWORDS

Tetra Schiff base;
1,3,4-Thiadiazole;
Antibacterial;
Antifungal

Abstract In the present study, novel tetra Schiff bases were synthesized by condensation of 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene with different aromatic aldehydes. The chemical structures were confirmed by means of IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. All compounds were screened for antibacterial (*Staphylococcus aureus* ATCC-9144, *Staphylococcus epidermidis* ATCC-155, *Micrococcus luteus* ATCC-4698, *Bacillus cereus* ATCC-11778, *Escherichia coli* ATCC-25922, and *Pseudomonas aeruginosa* ATCC-2853) and antifungal (*Aspergillus niger* ATCC-9029 and *Aspergillus fumigatus* ATCC-46645) activities by paper disc diffusion technique. The minimum inhibitory concentrations (MICs) of the compounds were also determined by agar streak dilution method. Among the synthesized compounds 1,2,4,5-tetra[5-(4-nitrobenzylideneamino)-1,3,4-thiadiazole-2-yl]benzene **7** was found to be the most potent antimicrobial activity with MICs of 3.4, 2.1, 1.2, 2.0, 3.1, 2.4, 1.1, and 1.7 μg/mL against the above mentioned respective strains.

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Peer review under responsibility of King Saud University.
doi:10.1016/j.jscs.2011.07.007

Production and hosting by Elsevier

1. Introduction

Schiff bases represent an important class of organic compounds, especially in the medicinal and pharmaceutical fields. Thus, development and synthesis of novel Schiff base derivatives as potential chemotherapeutics still attract the attention of organic and medicinal chemist (Bharti et al., 2010; da Silva et al., 2011; Rosu et al., 2011). Many studies reported the biological activities of Schiff bases, including their anticancer, antibacterial, antifungal, and herbicidal activities (Gudipati

et al., 2011). Schiff bases, derived mostly from variety of heterocyclic rings, were reported to possess a broad spectrum and a wide variety of biological activities including antiviral, anticancer, cytotoxic, antimicrobial, antibacterial, anticonvulsant, etc. (Hranjec et al., 2011). A number of Schiff bases have been tested for antibacterial, antifungal, anticancer and herbicidal activities (Prasad et al., 2011; Pulate et al., 2011).

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and increasing number of multi-drug resistant microbial pathogens with particular relevance for Gram-positive bacteria. In spite of the large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotic resistant bacterial strains in the last decades constitutes a substantial need for the new class of antibacterial agents.

The varied biological activities of 1,3,4-thiadiaziles and their analogs have been known from the beginning of the 20th century (Bhat et al., 2011; Gilani et al., 2010). Literature survey revealed that slight modification in the structure can result in qualitative as well as quantitative changes in the activity (Alagawadi and Alegaon, 2010; Dong et al., 2010; Bhat et al., 2011). This prompted us to undertake the synthesis of various novel tetra Schiff bases derived from 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene and characterized using IR, ^{1}H NMR, ^{13}C NMR, and Elemental analysis with the aim of having improved activity. The synthesized compounds were screened for their antibacterial activity against four Gram-positive bacteria (*Staphylococcus aureus* ATCC-9144, *Staphylococcus epidermidis* ATCC-155, *Micrococcus luteus* ATCC-4698 and *Bacillus cereus* ATCC-11778), three Gram-negative bacteria (*Escherichia coli* ATCC-25922, *Pseudomonas aeruginosa* ATCC-2853 and antifungal (*Aspergillus niger* ATCC-9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique. The minimum inhibitory concentrations (MICs) of the compounds were also determined by agar streak dilution method.

2. Experimental

2.1. Measurements

The melting points were taken in an open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FT-IR spectrometer MB 104 with KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 300 NMR spectrometer operating at 400.13 and 100.77 MHz, respectively. Microanalyses were obtained with an Elemental analyses system GmbH VarioEL V300 element analyzer. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF254, 200 mesh) aluminium plates (E Merk) and visualized in UV chamber. IR, ^{1}H NMR, ^{13}C NMR and elemental analysis were consistent with the assigned structures.

2.2. Synthesis

2.2.1. Synthesis of 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene **2**

A mixture of pyromellitic acid **1** (0.01 mol, 2.54 g) and (0.04 mol, 3.64 g) of thiosemicarbazide with (15 mL) of phosphorusoxy chloride was refluxed gently for 15 h, the completion of the reaction mixture monitored by TLC. After cooling, 125 mL of water was added, the mixture was then refluxed for 10 h, filtrated, and neutralized with potassium hydroxide. The precipitate was washed with water and recrystallized from (ethanol-water) to give the desired product. (Yield 80%). mp > 360 °C; IR (KBr) cm^{-1}: 3325–3298 (ν_{NH2}), 3081 (ν_{C-H}), 1610 ($\nu_{C=N}$), 1534 ($\nu_{C=C}$). ^{1}H NMR (DMF-d_6) δ ppm 8.87 (s, 2H, NH_2) (D_2O exchange, disappeared), 8.76 (s, 2H, NH_2) (D_2O exchange, disappeared), 8.70 (s, 2H, NH_2) (D_2O exchange, disappeared), 8.62 (s, 2H, NH_2) (D_2O exchange, disappeared), 7.50 (s, 1H, ar-H), 7.44 (s, 1H, ar-H). ^{13}C NMR (DMF-d_6) δ ppm 143.22–148.31 (6C, ar-C), 137.11–140.40 (8C, thiadiazole carbons). Anal. Found (calc.) for $C_{14}H_{10}N_{12}S_4$ (%): C, 35.44 (35.43); H, 2.13 (2.12); N, 35.41 (35.42), S, 27.04 (27.03).

2.2.2. General method of synthesis **3**–**10**

A mixture of 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene (0.01 mol) and appropriate aromatic aldehyde (0.04 mol) was dissolved in 35 mL of absolute ethanol. The mixture was then refluxed for 20–24 h with stirring, the completion of the reaction mixture monitored by TLC. After cooling to room temperature, a solid was obtained. The crude product was filtered, dried and recrystallized from ethanol.

2.2.2.1. 1,2,4,5-Tetra[5-benzylideneamino-1,3,4-thiadiazole-2-yl]benzene ***3***. (Yield: 87%). mp 220–221 °C; IR (KBr) cm^{-1}: 3100 (ν_{C-H}), 1612 ($\nu_{C=N}$), 1560 ($\nu_{C=C}$). ^{1}H NMR (DMF-d_6) δ ppm 8.02–8.05 (d, 1H, ar-H), 7.95–8.01 (d, 1H, ar–H), 7.63–7.67 (d, 1H, ar–H), 7.57–7.60 (d, 1H, ar–H), 7.51–7.54 (d, 1H, ar–H), 7.50 (s, 1H, ar–H), 7.44–7.47 (d, 1H, ar–H), 7.40 (s, 1H, ar–H), 7.29–7.33 (d, 1H, ar–H), 7.19–7.22 (m, 3H, ar–H), 7.11–7.14 (m, 3H, ar–H), 7.00–7.03 (m, 3H, ar–H), 6.83–6.86 (m, 4H, ar–H), 5.74 (s, 1H, –CH = N–), 5.70 (s, 1H, –CH = N–), 5.63 (s, 1H, –CH = N–), 5.58 (s, 1H, –CH = N–). ^{13}C NMR (DMF-d_6) δ ppm 138.15–147.13 (12C, ar–C), 132.43–137.34 (12C, ar–C), 130.56–134.78 (6C, ar–C), 125.02–129.15 (8C, thiadiazole carbons), 115.31–119.40 (4C, –C = N–). Anal. Found (calc.) for $C_{42}H_{26}N_{12}S_4$ (%): C, 61.01 (61.00); H, 3.18 (3.17); N, 20.33 (20.32), S, 15.50 (15.51).

2.2.2.2. 1,2,4,5-Tetra[5-(4-methylbenzylideneamino)-1,3,4-thiadiazole-2-yl]benzene ***4***. (Yield: 73%). mp 200–201 °C; IR (KBr) cm^{-1} 3090 (ν_{C-H}), 1615 ($\nu_{C=N}$), 1560 ($\nu_{C=C}$). ^{1}H NMR (DMF–d_6) δ ppm 8.08–8.10 (d, 1H, ar–H), 7.97–8.00 (d, 1H, ar–H), 7.84–7.87 (d, 1H, ar–H), 7.61–7.65 (d, 1H, ar–H), 7.51 (s, 1H, ar–H), 7.53–7.55 (d, 1H, ar–H), 7.45–7.47 (d, 1H, ar–H), 7.43 (s, 1H, ar–H), 7.28–7.31 (m, 2H, ar–H), 7.21–7.25 (m, 2H, ar–H), 7.18–7.20 (m, 2H, ar–H), 6.02–7.07 (m, 2H, ar–H), 6.77–6.80 (m, 2H, ar–H), 5.79 (s, 1H, –CH = N–), 5.73 (s, 1H, –CH = N–), 5.66 (s, 1H, –CH = N–), 5.60 (s, 1H, –CH = N–). ^{13}C NMR (DMF–d_6) δ ppm 140.12–145.78 (12C, ar–C), 134.12–136.46 (12C, ar–C), 130.20–134.13 (6C, ar–C), 125.26–130.24 (8C, thiadiazole carbons). Anal. Found (calc.) for $C_{46}H_{34}N_{12}S_4$ (%): C, 62.57 (62.56); H, 3.87 (3.88); N, 19.04 (19.03), S, 14.51 (14.52).

2.2.2.3. 1,2,4,5-Tetra[5-(4-hydroxybenzylideneamino)-1,3,4-thiadiazole-2-yl]benzene ***5***. (Yield: 80%). mp > 360 °C; IR (KBr) cm^{-1} 3435 (ν_{O-H}), 3095 (ν_{C-H}), 1613 ($\nu_{C=N}$), 1560