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3-Aryl-5-furylpyrazolines and Their Biological Activities

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ABSTRACT: *Aryl-furyl substituted pyrazolines* **2a–c** *and* **4a–c** *were prepared by the reaction of* α,β*-unsaturated carbonyl compounds with hydrazine or phenyl hydrazine. N-chloroacetyl derivatives* **3a–c** *were obtained by the N-acetylation of* **2a–c**. *The antibacterial activities of synthesized pyrazolines were examined by employing the disk-diffusion technique. All synthesized compounds showed antibacterial effects in 1200* μ*g concentration.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:345–347, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10159

INTRODUCTION

Pyrazoline derivatives constitute an interesting class of organic compounds with diverse chemical and pharmacological applications [1–3]. Pyrazolines can be synthesized from α,β-unsaturated carbonyl compounds and hydrazines. They are reported to be potential extractants and powerful drugs [4].

α,β-Unsaturated ketones **1a–c** were obtained by Claisen–Schmidt reactions of furfural and p-substituted acetophenones [5,6]. On heating **1a–c** with hydrazine hydrate the corresponding pyrazolines **2a–c** were obtained in good yield [7]. *N*-Acetylation of **2a–c** was achieved with chloroacetylchloride in the presence of triethylamine to give **3a–c** (Scheme 1) [8].

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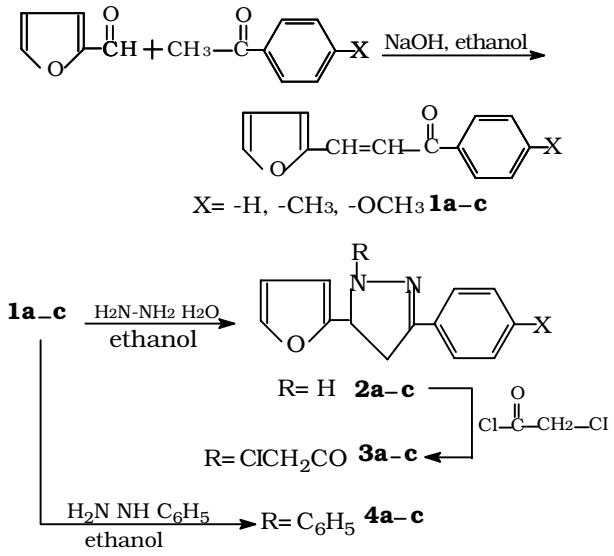
RESULT AND DISCUSSION

Data of the prepared pyrazoline derivatives are given in Table 1. IR and ^{1}H NMR spectral data of prepared chalcones and pyrazoline derivatives are given in Table 2. All newly synthesized compounds analyzed satisfactorily for nitrogen and structures were confirmed on the basis of their IR and ^{1}H NMR spectral data. IR spectra of these compounds showed moderately strong band around 1495–1499, 1390–1121, and 1255–1251 cm^{-1} characteristic for the C=N, C–N, and N–N groups. In the ^{1}H NMR spectra the characteristic signal due to CH–$\underline{CH_2}$–N protons appeared at δ 3.4–3.6. The NH and aromatic protons appeared as a multiplet at δ 6.1–8. The signal due to furyl N–$\underline{CH}$–CH_2 protons appeared δ 6.2–7.

Antimicrobial Activity

The pyrazolines **2–4** were screened for their in vitro antimicrobial activity against some bacteria employing the disk-diffusion technique. The test organism employed were *Salmonella thypimurium* TA 100 hi, *Kluyveromyces fragilis*, *Serratia marcescens* NRRL 3284, *Pseudomonas aeruginosa* ATCC 27853, *Rhodotorula rubrum*, *Aoremonas hydrophila* ATCC 7966, *Enterococcus faecalis* ATCC 15753, *Corynebacterium xerosis* UC 9165, *Micrococcus luteus* LA 2971, *Bacillus megaterium* DSM 32, *Listeria monocytogenes*



SCHEME 1

Scoot A, *Proteus vulgaris* FMC 1, *Mycobacterium smegmatis* CCM 2067, *Bacillus subtilis* IMG 22, *Staphylococcus aureus* Cowan 1, and *Escherichia coli* DM. The diameters of zones of inhibition were measured at 300, 600, and 1200 μg concentration. Although antibacterial effects of all synthesized compounds were generally found to be very low in lower concentrations, they showed better antibacterial effect in 1200 μg concentration.

EXPERIMENTAL

General Data

Melting points were determined in open capillary tubes on digital Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded KBr with a Mattson 1000 FT-IR spectrometer. The ^{1}H NMR spectra were run on Varian EM-360, 60 MHz spectrometers using TMS as internal reference.

TABLE 1 Data of Pyrazolines **2–4**

	Yield (%)	*mp (°C)*	
2a	65	105	Yellowish brown
2b	50	104	Yellowish brown
2c	70	125	Yellow
3a	70	32	Brown
3b	68–70	34	Brown
3c	75	38	Dark brown
4a	60	122	Light yellow
4b	65	112	Yellow
4c	68	133	Light yellow

Elemental analyzes were performed at Firat University with a Perkin-Elmer 240-B elemental analyzer. Starting chemicals were obtained from Fluka or Aldrich.

*Synthesis of 3-Aryl-5-(2-furyl)-2-pyrazolines (**2a–c**)*

A solution of the respective 0.02 mol furfural p-substituted acetophenone **1a–c** and 0.02 mol hydrazine hydrate in 30 ml ethanol was refluxed for 3 h. The reaction mixture was cooled and kept at 0°C overnight. The resulting solid was crystallized from ethanol–hexane (3:1).

*Synthesis of 3-Aryl-1-chloroacetyl-5-(2-furyl)-2-pyrazolines (**3a–c**)*

A mixture 0.02 mol pyrazoline **2a–c**, 0.02 mol chloroacetyl chloride, and triethylamine in 40 ml dry benzene was left at room temperature overnight. The reaction mixture was evaporated to dryness by suction and the remaining solid product was recrystallized from an appropriate solvent.

*Synthesis of 3-Aryl-5-(2-furyl)-1-phenyl-2-pyrazolines (**4a–c**)*

A solution of 0.02 mol **1a–c** and 0.02 mol phenyl hydrazine in 50 ml ethanol was refluxed for 8 h. The reaction mixture was cooled and kept at 0°C overnight. The resulting solid was crystallised from glacial acetic acid.

Preparation of Microorganism Culture

All the chemical samples and the standard antibiotics, in amount of 300, 600, and 1200 μg, were injected into empty sterilized antibiotic discs having a dimeter of 6 mm (Schleicher & Schüll No: 2668, Germany). The discs injected only with chloroform were used as control. All the bacteria mentioned above were incubated at 30 ± 0.1°C for 24 h by inoculation into Nutrient Broth (Difco) and the yeasts studied were incubated in Sabourand Dextrose Broth (Difco) for 24 h. Mueller Hinton Agar (oxoid) and Sabourand Dextrose Agar sterilized in separate flasks and cooled to 45–50°C were distributed to sterilized petri dishes having a diameter of 9 cm, by using 15-ml pipettes. Cultures (1 ml) of bacteria (10^5 bacteria per ml) and yeast (10^4 yeast cell per ml) prepared as mentoined above were incubated for 24 h after the food medium in the petri dishes had been distributed homogenously. Dishes injected with extracts were

TABLE 2 IR and ^{1}H NMR Spectral Data of **1–4**

	IR Spectra (μ_{max} cm^{-1})	*^{1}H NMR Spectra δ (DMSO)*
1a	3150, 3030, 1664, 1600, 1580, 1555, 1450, 1256, 1016, 750, 700	6.2 (d, 1H, ar. CH═C), 6.5 (d, 1H, C═CH—CO), 7.2–7.5 (m, 6H, 3H furyl CH, 3H ar. C—H), 7.8 (m, 2H, ar. CH).
1b	3120, 3030, 2960, 1850, 1660, 1600, 1580, 1555, 1450, 1256, 1016	2.2 (s, 3H, —CH_3), 6.2 (d, 1H, ar. CH═C), 6.5 (d, 1H, C═CH—CO), 7–7.8 (m, 7H, 3H furyl CH, 4H ar. CH).
1c	3125, 3020, 2962, 2840, 1659, 1600, 1580, 1553, 1450, 1260, 1173, 1017	3.8 (s, 3H, OCH_3), 6.3 (d,1H, ar. CH═C), 6.5 (d, 1H, C═CH—CO), 6.8–6.9 (d, 2H, furyl H_3—H_4), 7.3 (m, 5H, 1H furyl H_2 ve 4H ar. CH)
2a	3332, 3150, 3020, 2960, 2836, 1673, 1600, 1513, 1410,1255, 1175, 1017	3.6 (d, 2H, —CH_2), 5.2 (t, 1H, —CH), 6.2 (d, 1H, —NH), 6.8 (s, 2H, furyl H_3, H_4), 7–8 (m, 6H, 5H ar. CH ve 1H furyl H_2).
2b	3329, 3150, 3020, 2960, 2836, 1673, 1600, 1251, 1174, 1029, 1015	2.8 (s, 3H, —CH_3), 3.6 (d, 2H, —CH_2), 5.3 (t, 1H, —CH), 6.1 (d, 1H, —NH), 6.8 (m, 2H, furyl H_3—H_4), 7.4–8 (m, 5H, 4H ar. CH ve 1H furyl H_2).
2c	3333, 3120, 2837, 1672, 1661, 1256, 1030, 1015	3.4 (s, 2H, —CH_2), 4.1 (s, 3H, OCH_3), 4.8 (m, 1H, —CH), 6.6 (d, 1H, —NH), 7–8.3 (m, 7H, 3H furyl CH, 4H ar. CH).
3a	3160, 3090, 2840, 1680, 1609, 1520, 1251, 1044, 765	2.2 (s, 2H, CO—CH_2—Cl), 3.6–3.8 (d, 2H, —CH_2), 5.3 (t, 1H, —CH), 6.3 (d, 2H, furyl H_3, H_4), 7–8.2 (m, 6H, 5H ar. CH, 1H furyl H_2).
3b	3115, 3000, 2960, 2866, 1682, 1613, 1435, 1013, 1025, 760	2.2 (s, 2H, CO—CH_2—Cl), 2.8 (s, 3H, —CH_3), 3.7 (d, 2H, —CH_2), 5.3 (m, 1H, —CH), 6.5 (m, 2H, furyl H_3, H_4), 7.2–8.2 (m, 5H, 4H ar. CH, furyl H_2).
3c	3100, 3020, 2955, 2840, 1677, 1601, 1512, 1450, 1258, 1020, 752	2.6 (s, 2H, CO—CH_2—Cl), 3.4 (m, 2H, —CH_2), 4.1 (s, 3H, OCH_3), 4.8 (s, 1H, CH), 7.3–8.4 (7H, 3H furyl CH ve 4H ar. CH).
4a	3125, 3020, 2920, 1597, 1495, 1450, 1393, 1251, 1121	5 (d, 2H, —CH_2), 5.3 (t, 1H, —CH), 6.2 (m, 2H, furyl H_3—H_4), 7–7.8 (m, 11H, 10H ar. CH ve 1H furyl-H_2).
4b	3150, 3020, 2920, 1597, 1498, 1390, 1324, 1251, 1121	2 (s, 3H, —CH_3), 3.5 (d, 2H, —CH_2), 5 (m, 1H, —CH), 6.2 (m, 2H, furyl H_3—H_4), 6.5–7.5 (m, 10H, 9H ar. CH ve 1H furyl-H_2).
4c	3117, 3020, 2922, 2837, 1609, 1499, 1391, 1280, 1254, 1180, 1122	3.6 (d, 2H, —CH_2), 4.1 (s, 3H, —OCH_3) 5.5 (m, 1H, CH), 7.1–8 (m, 12H, 9H, ar. CH ve 3H, furyl-CH).

kept on the solid agar medium by pressing slightly [9–13].

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