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Green Synthesis of (2*E*,2'*E*)-1,1'-(4,6-Dihydroxy-1,3-phenylene)bis-3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-prop-2-en-1-ones[1]

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Abstract—A series of new (2*E*,2'*E*)-1,1'-(4,6-dihydroxy-1,3-phenylene)bis-3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-ones have been synthesized by Claisen-Schmidt condensation of 1-(5-acetyl-2,4-dihydroxyphenyl)-1-ethanone and 3-aryl-1-phenylpyrazole-4-carboxaldehydes under ultrasound and microwave irradiation. These green methods enjoy the advantages of short reaction times, high yields, operational simplicity and are environmentally benign. The synthesized compounds have been characterized by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and screened for their antimicrobial activity.

Keywords: Bis-chalcones, pyrazole-4-carboxaldehydes, green synthesis, ultrasound irradiation, microwave irradiation, antimicrobial activity

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INTRODUCTION

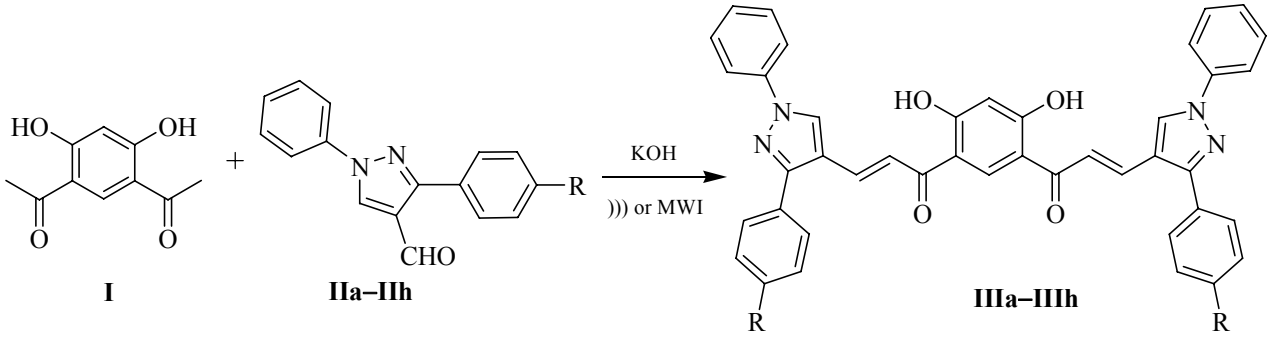
Eco-friendly chemical processes is a vital part of modern chemical research and development. The use of ultrasound [1] and microwaves [2] to accelerate chemical reactions has proven to be a particularly important tool for achieving the green chemistry goals. Microwave-assisted organic reaction enhancement (MORE) is nowadays a well established technique for the synthesis of various heterocycles. Virtually any thermally driven reaction can be accelerated by microwave irradiation. The spectacular results such as shorter reaction time, experimental simplicity and selectivity have clearly indicated the advantages of this technique over conventional heating. Similarly, the advantages of ultrasound-assisted synthesis include higher yields, shorter reaction times and milder reaction conditions as compared with conventional method. Chalcones have been reported to possess various biological activities such as antimicrobial [3], anti-inflammatory [4], analgesic [5], antiplatelet [6], antiulcerative [7], antimalarial [8], anticancer [9], antiviral [10], antileishmanial [11], and antioxidant [12] activities.

Chalcones are also potential intermediates for the synthesis of biodynamic heterocycles. Pyrazole derivatives are well established in the literature as important biologically active heterocyclic compounds. They are the subject of many research studies due to their widespread potential biological activities such as anti-inflammatory [13], antimicrobial [14], antiviral [15], antitumour [16], and anticonvulsant [17] activities. Our research group has made considerable efforts to design and put into practice innovative synthetic protocols adopting more eco-sustainable approaches [18–20]. As a part of our research program on green synthesis, here we report an environmentally benign synthesis of bis-chalcones with a view to study the ease of formation and to evaluate their antimicrobial activity.

Antimicrobial activity. All the synthesized compounds were screened for their antimicrobial activity against two strains of gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), two strains of gram-negative bacteria (*Echerichia coli, Pseudomonas aeruginosa*), as well as three strains of fungi (*Aspergillus niger*, *Penicillium italicum* and *Fusarium oxysporum*). Standard antibiotic drugs *Amoxicillin* for bacteria and *Mycostatin* for fungi were used at a concentration of 100 mg/mL for comparison. The antimicrobial activity been evaluated by filter paper disc method [21] after dissolving in DMF to attain a 100 mg/mL solution. The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were

[1] The text was submitted by the authors in English.

Scheme 1. Microwave assisted synthesis of bis-chalcones **IIIa–IIIh**



R = H (**a**), CH_3 (**b**), OCH_3 (**c**), Cl (**d**), OH (**e**), F (**f**), Br (**g**), NO_2 (**h**).

measured in millimeters at the end of the incubation period of 3 days at 37°C for *Echerichia coli* and at 28ºC for other bacteria and fungi. DMF alone showed no inhibition zone. Among the compounds screened **IIIb**, **IIId,** and **IIIf** showed good antibacterial activity. Compounds **IIId** and **IIIf** showed good antifungal activity (Scheme 1).

EXPERIMENTAL

The purity of the compounds was checked by the silica gel F_{254} (Merck). All the reagents and solvents were reagent grade and were used without further purification. Microwave-assisted reactions were carried out in Milestone multi SYNTH microwave system. Sonication was performed using Shanghai BUG40-06 ultrasonic cleaner (with a frequency of 25, 40, and 59 kHz and a nominal power 250 W). Melting points were determined in open capillaries and are uncorrected. IR spectra were taken on a Shimadzu FTIR 8400S spectrophotometer. NMR spectra were registered on Bruker Avance II 400 MHz spectrometer and mass spectra were recorded on a Shimadzu mass spectrometer. Elemental analysis was performed by using Thermo Finnigan CHNS analyzer.

Experimental data ara shown in the table.

General procedure for synthesis of (2*E*,2'*E*)-1,1'-(4,6-dihydroxy-1,3-phenylene)bis-3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-ones. *a. Conventional method.* A mixture of 1-(5-acetyl-2,4-dihydroxy phenyl)-1-ethanone (**I**) (1 mmol), appropriate 3-aryl-1-phenyl pyrazole-4-carboxaldehydes (**IIa–IIh**) (2 mmol) and potassium hydroxide (5 mmol) in ethanol (15 mL) was taken in a round-bottom flask and stirred at room temperature for 16–20 h. the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice and acidified with dil. HCl. The solid separated was filtered and recrystallized from methanol as yellow powder.

Physical data of compounds **IIIa–IIIh**

Comp. no.	mp, °C	Conventional method		Ultrasound irradiation method		Microwave irradiation method	
		time, h	yield, %	time, min	yield, %	time, min	yield, %
IIIa	214	16	65	85	81	5	90
IIIb	223	18	63	95	80	6	85
IIIc	230	16	61	85	83	6	90
IIId	245	20	60	90	85	5	87
IIIe	241	18	62	95	80	6	85
IIIf	239	18	64	90	82	5	89
IIIg	256	20	60	95	85	6	90
IIIh	251	19	61	85	82	5	86

b. Ultrasound method. A mixture of 1-(5-acetyl-2,4-dihydroxy phenyl)-1-ethanone (**I**) (1 mmol), appropriate 3-aryl-1-phenyl pyrazole-4-carboxaldehydes (**IIa–IIh**) (2 mmol), potassium hydroxide (5 mmol) in ethanol (10 mL) was taken in a round-bottom flask and irradiated in a water bath at 55–60°C with the ultrasonic cleaner for 85–95 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was treated as above.

c. Microwave method. A mixture of 1-(5-acetyl-2,4-dihydroxy phenyl)-1-ethanone (**I**) (1 mmol), appropriate 3-aryl-1-phenyl pyrazole-4-carboxaldehydes (**IIa–IIh**) (2 mmol) and potassium hydroxide (5 mmol) in ethanol (5 mL) was taken in a quartz tube and inserted into Teflon vial with screwed cap and then subjected to microwave irradiation at 160 W for 5–6 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was treated as above.

Compound IIIa. IR spectrum, ν, cm^{-1}: 3432 (OH), 1635 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.50 s (1H, Ar-H_5), 7.25–7.46 m (20H, Ar-H), 7.72 d (2H, =C_α-H, J = 15.7 Hz), 8.01 d (2H, =C_β-H, J = 15.7 Hz), 8.15 s (1H, Ar-H_2), 8.31 s (2H, pyrazole-H), 13.65 s (2H, OH). ^{13}C NMR spectrum, δ, ppm: 191.58, 170.01, 153.67, 139.13, 136.49, 136.15, 134.73, 133.39, 129.59, 129.27, 128.98, 127.94, 119.69, 118.73, 117.93, 113.71, 105.16. Found, %: C 77.07; H 4.67, N 8.58. $C_{42}H_{30}N_4O_4$. Calculated, %: C 77.05; H 4.62; N 8.56. M 655 $[M + H]^+$.

Compound IIIb. IR spectrum, ν, cm^{-1}: 3440 (OH), 1636 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.31 s (6H, CH_3), 6.48 s (1H, Ar-H_5), 7.20 d (2H, =C_α-H, J = 15.6 Hz), 7.29–7.38 m (10H, Ar-H), 7.41–7.52 m (4H, Ar-H), 7.86 d (4H, Ar-H), 8.07 d (2H, =C_β-H, J = 15.6 Hz), 8.18 s (1H, Ar-H_2), 8.29 s (2H, pyrazole-H), 13.72 s (2H, OH). ^{13}C NMR spectrum, δ, ppm: 191.69, 170.22, 154.07, 139.3, 139.1, 136.9, 133.5, 129.7, 129.6, 129.3, 128.7, 127.7, 127.5, 119.4, 118.4, 117.9, 113.8, 105.3, 21.35(CH_3). Found, %: C 77.46; H 5.07, N 8.24. $C_{44}H_{34}N_4O_4$. Calculated, %: C 77.40; H 5.02; N 8.21. M 683 $[M + H]^+$.

Compound IIIc. IR spectrum, ν, cm^{-1}: 3419 (OH), 1640 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.71 s (6H, OCH_3), 6.45 s (1H, Ar-H_5), 7.22 d (2H, =C_α-H, J = 15.4 Hz), 7.40-7.57 m (10H, Ar), 7.59 d (4H, Ar), 7.74 d (4H, Ar), 8.02 d (2H, =C_β-H, J = 15.4 Hz), 8.14 s (1H, Ar-H_2), 8.27 s (2H, pyrazole-H), 13.76 s (2H, –OH). ^{13}C NMR spectrum, δ, ppm: 184.7, 160.7, 154.3, 139.2, 139.1, 136.9, 131.1, 130.2, 129.5, 129.3, 128.7, 127.7, 127.7, 124, 122.5, 119.9, 114.2, 105.3, 55.3. Found, %: C 73.96; H 4.83, N 7.89. $C_{44}H_{34}N_4O_6$. Calculated, %: C 73.94; H 4.79; N 7.84. M 715 $[M + H]^+$.

Compound IIId. IR spectrum, ν, cm^{-1}: 3423 (OH), 1641 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.75 s (1H, Ar-H_5), 6.86 d (2H, =C_α-H, J = 16.2 Hz), 7.34–7.49 m (10H, Ar-H), 7.79 d (4H, Ar-H), 7.63 d (4H, Ar-H), 7.92 d (2H, =C_β-H, J = 16.2 Hz), 8.12 s (1H, Ar-H_2), 8.28 s (2H, pyrazole-H), 13.65 s (2H, OH). ^{13}C NMR spectrum, δ, ppm: 188.1, 152.6, 139.4, 134.9, 133.4, 130.9, 130.1, 129.7, 129.1, 127.5, 126.9, 125.4, 123.5, 119.5, 118.2, 117.9, 113.7, 102.6. Found, %: C 69.74; H 3.93, N 7.76. $C_{42}H_{28}Cl_2N_4O_4$. Calculated, %: C 69.71; H 3.90; N 7.74. M 723 $[M + H]^+$.

Compound IIIe. IR spectrum, ν, cm^{-1}: 3418 (OH), 1634 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.91 s (2H, OH), 6.79 s (1H, Ar-H_5), 6.86 d (2H, =C_α-H, J = 15.7 Hz), 7.32–7.51 m (10H, Ar-H), 7.61 d (4H, Ar-H), 7.84 d (4H, Ar-H), 8.02 d (2H, =C_β-H, J = 15.7 Hz), 8.09 s (1H, Ar-H_2), 8.31 s (2H, pyrazole-H), 13.72 s (2H, –OH). ^{13}C NMR spectrum, δ, ppm: 187.9, 157.7, 140.6, 135.0, 134.2, 130.2, 130.1, 129.5, 129.2, 127.4, 126.3, 125.7, 123.4, 120.5, 119.2, 115.9, 114.6, 103.5. Found, %: C 73.48; H 4.43, N 8.18. $C_{42}H_{30}N_4O_6$. Calculated, %: C 73.46; H 4.40; N 8.16. M 687 $[M + H]^+$.

Compound IIIf. IR spectrum, ν, cm^{-1}: 3415 (OH), 1641 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.48 s (1H, Ar-H_5), 7.10 d (2H, =C_α-H, J = 16.1 Hz), 7.26 m (4H, Ar), 7.35–7.67 m (10H, Ar), 7.75 d (4H, Ar), 7.95 d (2H, =C_β-H, J = 16.1 Hz), 8.10 s (1H, Ar-H_2), 8.34 s (2H, pyrazole-H), 13.71 s (2H, OH). ^{13}C NMR spectrum, δ, ppm: 190.3, 157.1, 140.0, 137.2, 135.1, 134.5, 131.9, 130.5, 128.3, 128.2, 126.6, 125.1, 122.9, 121.4, 119.5, 117.7, 115.7, 103.3. Found, %: C 73.08; H 4.13, N 8.14. $C_{42}H_{28}F_2N_4O_4$. Calculated, %: C 73.04; H 4.09; N 8.11. M 691 $[M + H]^+$.

Compound IIIg. 3418(OH), 1636 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.78 s (1H, Ar-H_5), 7.09 d (2H, =C_α-H, J = 16.2 Hz), 7.32–7.50 m (10H, Ar), 7.52 d (4H, Ar), 7.73 d (4H, Ar), 7.92 d (2H, =C_β-H, J = 16.2 Hz), 8.07 s (1H, Ar-H_2), 8.17 s (2H, pyrazole-H), 13.82 s (2H, –OH). ^{13}C NMR spectrum, δ, ppm: 188.3, 153.0, 139.9, 135.4, 134.1, 130.7, 130.3, 129.0, 128.5, 127.3, 126.2, 126.0, 124.3, 120.3, 119.2, 116.2, 114.8, 103.9. Found, %: C 62.12; H 3.49, N 6.93. $C_{42}H_{28}Br_2N_4O_4$. Calculated, %: C 62.09; H 3.47; N 6.90. M 810 $[M + H]^+$.

Compound IIIh. IR spectrum, ν, cm^{-1}: 3420 (OH), 1632 (C=O). ^1H NMR spectrum, δ, ppm: 6.71 s (1H, Ar-H_5), 7.20 d (2H, =C_α-H, J = 15.6 Hz), 7.36–7.50 m (10H, Ar), 7.82 d (4H, Ar), 7.98 d (4H, Ar), 8.02 d (2H, =C_β-H, J = 15.6 Hz), 8.09 s (1H, Ar-H_2), 8.28 s (2H, pyrazole-H), 13.73 s (2H, OH), ^{13}C NMR spectrum, δ, ppm: 189.9, 153.0, 138.6, 135.8, 134.0, 133.8, 131.02, 130.7, 129.3, 128.2, 127.4, 125.9, 122.3, 120.5, 119.5, 117.9, 115.7, 104.4. Found: C 67.80; H 3.81, 11.32. $C_{42}H_{28}N_6O_8$. Calculated, %: C 67.74, H 3.79, N 11.29. M 745 $[M + H]^+$.

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