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Synthesis of Some Novel Chalcone Containing Pyrazole Moiety

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ABSTRACT

A green, efficient and rapid procedure for the synthesis of novel chalcone derivatives containing pyrazole moiety has been developed through the condensation of various pyrazole aldehyde and ketone, in the presence of Potassium Hydroxide (KOH) in Ethanol (EtOH). This method has the advantages of operational simplicity, and high yield of products via a simple experimental and work-up procedure.

Keywords: Pyrazole, Chalcone, Novel, Condensation, Green

INTRODUCTION

Chalcone and its derivatives represent important class of compounds and its intensive scientific studies throughout the world. Chalcones are abundantly present in nature starting from ferns to higher plants [1]. Numbers of naturally occurring chalcones have been isolated from different plant species especially from Asteraceae, Leguminosae and Moraceae families [2]. Chalcones have often been used in traditional medicine and chalcones have therefore been studied and reported to possess many beneficial biological effects as antimicrobial, antifungal, anti-inflammatory, antioxidant, cytotoxic, antitumor, antimalarial and chemopreventive activities [3-6].

Chalcones are valuable synthones in the synthesis of many active pharmaceutical drugs like Auwers synthesis of flavones [7] and biosynthesis of flavonoids [8]. Claisen-Schmidt condensation between acetophenone and benzaldehyde gives chalcone [9]. This reaction is catalyzed by both acids and bases under homogeneous or heterogeneous conditions. Several researchers have reported the synthesis of chalcone by using different catalysts like zeolites and hydrotalcites [10], zinc oxide [11], organolithium [12], $KF–Al_2O_3$ [13], modified phosphates [14], to get a better specification of chalcone products with higher yield and low by-products.

In addition to their numerous biological activities, chalcones find a pronounced application in synthetic organic chemistry. Many heterocycles are synthesized by using chalcone [15] and as synthons for the synthesis of many pharmaceuticals [16]. Having such a varied pharmacological activity and synthetic utility, chalcones have attracted chemists to develop a large number of synthetic methodologies for their synthesis around the world.

MATERIALS AND METHODS

All chemicals used for the synthesis of the compounds were obtained specially from Sigma Aldrich and SD Fine chemicals. Melting points were recorded by using simple open capillaries and are uncorrected. Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded in 400 MHz NMR spectrophotometer by using Deuterated Dimethyl Sulfoxide (DMSO-d_6) as solvent and Tetramethylsilane (TMS) as an internal standard. The Infra-Red (IR) spectra were recorded using Fourier Transform Infrared (FT-IR) spectrophotometer Model RZX (Perkin Elmer). By using Electro Spray method (ES), mass spectra were recorded on Macromass mass spectrophotometer (Waters). Using Thin Layer Chromatography (TLC) purity of the synthesized compounds was checked. TLC silica gel coated plates obtained from Merck as stationary phase and mobile phase were mixture of ethyl acetate/hexane (20:80).

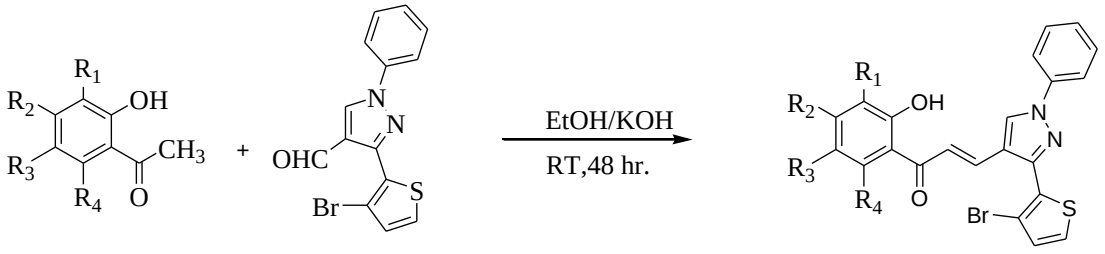
General procedure

In 40 ml of ethanol, mixture of 1 (0.01 mol) and 2 (0.01 mol) was dissolved and contents placed in ice bath at 0°C. In this reaction mixture, 2 g KOH pellets were added for maintaining temperature below 5°C. The reaction mixture was stirred for 48 h at room temperature. Then this reaction mixture was poured in ice cold water and acidified with 2 M HCl. Yellow solid was obtained and separated by filtration, washed with cold water.

Product was recrystallized from ethanol. Using this typical experimental procedure, other analogs were prepared of this series. The physical data of the compounds 3(a-g) were recorded in Table 1. Their structures have been confirmed by analyzing method such as ^{1}H-NMR, mass and IR spectra.

IR (3c) (cm^{-1}): 1059 (C-Cl), 1226 (C-O), 1533 (C=C), 1572 (C=N), 1640 (C=O), 3142 (O-H). ^{1}H-NMR (3c) (DMSO-d_6) δ ppm: 6.9964-7.0185 (d, 1H, Ar-H, J=8.84 Hz), 7.2724-7.2857 (d, 1H, Ar-H, J=7.4 Hz), 7.4234-7.4419 (m, 1H, Ar-H, J=7.4 Hz), 7.5186-7.6017 (m, 3H, Ar-H), 7.6885-7.7268 (d, 1H, CH=C-, J=15.32 Hz), 7.8278-7.8648 (m, 2H, Ar-H), 7.9182-7.9380 (d, 2H, Ar-H), 8.0810-8.0870 (d, 1H, Ar-H, J=2.4 Hz), 9.4580 (s, 1H, pyrazole-H), 12.5847 (s, 1H, Ar–OH). ES-MS (3c) (m/z): 487.25 (M+1), 489.25 (M+3), 491.25 (M+5).

IR (3f) (cm^{-1}): 1058 (C-Cl), 1227 (C-O), 1500 (C=C), 1567 (C=N), 1641 (C=O), 3104 (O-H). ^{1}H-NMR (3f) (DMSO-d_6), δ ppm: 2.3755-2.5379 (s, 3H, -CH_3), 6.9549 (s, 1H, Ar-H), 7.2598-7.2730 (d, 1H, Ar-H. J=5.28 Hz), 7.3986-7.4356 (m, 1H, Ar-H), 7.5554-7.5949 (m, 2H, Ar-H), 7.6930-7.7312 (d, 1H, CH=C-, J=15.28 Hz), 7.8034-7.8564 (m, 2H, Ar-Hz), 7.9172-7.9367 (m, 2H, Ar-H), 8.0937 (s, 1H, Ar-H), 9.4535 (s, 1H, pyrazole-H), 12.6797 (s, 1H, Ar–OH). ES-MS (3f) (m/z): 501.2 (M+1), 503.2 (M+3), 505.2 (M+5) (Scheme 1).



1(a-g) **2** **3(a-g)**

Scheme 1: Synthesis of series of various (E)-3-(3-(3-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one

Table 1: Physical data of compounds 3(a-g)

Compound	R_1	R_2	R_3	Melting point (°C)	Yield (%)
3a	H	H	H	152-154	68
3b	H	H	CH_3	196-198	65
3c	H	H	Cl	182-184	78
3d	Cl	H	Cl	212-214	81
3e	H	H	F	202-204	71
3f	H	CH_3	Cl	142-144	76
3g	H	H	Br	160-162	73

RESULTS AND DISCUSSION

The chalcone derivatives were synthesized successfully having good yields. The newly synthesized compounds were analyzed from ^{1}H-NMR, melting point range, IR, mass spectral analysis. Using disc diffusion method, newly synthesized compounds were screened for antimicrobial activity.

Antimicrobial activity

Compounds 2 and 3(a-g) were screened for their antimicrobial activity against *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923) by paper disc diffusion method using gentamycin as a reference standard drug. Antifungal activity was screened against *Candida sp*., using nystatin as standard drug. At 100 µg/ml concentration, all the tests were evaluated. The culture media was Muller Hinton agar. After 24 h of incubation at 37°C the zone of inhibition was measured in mm. Microbial data for 2 and 3(a-g) as summarized in Table 2.

Table 2: Antimicrobial analysis data of 2 and 3(a-g)

S. No.	Compound number	*Escherichia coli* (ATCC 25922)	*Pseudomonas aeruginosa* (ATCC 27853)	*Staphylococcus aureus* (ATCC 25923)	*Candida sp.,*
1	2	No Zone	No Zone	No Zone	No Zone
2	3a	No Zone	No Zone	No Zone	No Zone
3	3b	No Zone	No Zone	No Zone	No Zone
4	3c	No Zone	No Zone	No Zone	No Zone
5	3d	No Zone	No Zone	No Zone	No Zone
6	3e	No Zone	No Zone	No Zone	No Zone
7	3f	No Zone	No Zone	No Zone	No Zone
8	3g	No Zone	No Zone	No Zone	No Zone
9	Gentamycin	28 mm	23 mm	32 mm	-
10	Nystatin	-	-	-	23 mm

CONCLUSION

The newly synthesized compounds were screened for their antimicrobial activity against *Candida sp*., and Gram-negative as well as Gram-positive bacterial strains. The synthesized compounds do not shown any activity as compared to standard drug. Chalcones are intermediate in the biosynthesis of flavonoid. They are a very valuable compounds whether from bioactivity aspects or from organic synthesis aspects. Chalcones exhibit diverse pharmacological activities and can serve as synthons for synthesis of heterocyclic compounds. Due to these reasons, various preparation procedures were developed by many working Scientist and groups, including ecofriendly protocol.

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