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Synthesis, characterization and anti microbial activity of some novel chalcone compounds having benzyloxymonochloro resacetophenone moiety

S. S. Shah and Kirtikumar Goswami

Department of Chemistry, Shri U. P. Arts, Smt. M. G. Panchal Science & Shri V. L. Shah Commerce College, Pilvai(India)

ABSTRACT

*1– (2-hydroxy-3-chloro–4–benzyloxy) ethanone (HCBE) and chalcones were prepared by the coupling of benzyle bromide and 3-chloro resacetophenone then condensation with aromatic aldehyde(**3a-h**) then The newly synthesized compounds were evaluated for their characterization, antimicrobial activity and their physical properties.*

Keywords: benzyloxy, chloro-benzyloxy-resacetophenone, ketone aldehyde condensation, chalcones, phenone derivates antimicrobial activity

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INTRODUCTION

Chalcones are an important class of compounds which are good intermediates for the synthesis of various heterocyclic compounds like flavones, flavanones, flavanols, aurones, isoxazolines, anthocynins, pyrazolines,pyrimidines, quinoxalines, benzalcoumaranones.

The biological and industrial applications of chalcones are also found significant.Due to the presence of chromophor –CO-CH=CH- and other auxochromes, chalcones are colour compounds. These compounds exhibit high reactivity due toα:β-unsaturated un saturation present in the compounds. Chalcone is also known as 1,3-disubstituted-2-propene-1-ones.Kostanekci and Tambor[1] gave them the name “Chalcones.”

Chalcones are characterized by their possession of a structure in which two aromatic ring I and II are linked by an aliphatic three-carbon chain.

The chalcones have been found to be useful in providing structure of natural products like cynamaclurin[2], sakuranetin[3], ploretin[4], hemlocktanin[5], homoriodictyo[6],etc.

Keeping in view of biological importance of this group and their close relationship to flavones, flavanones, flavanols and dihidroflavonals, chalcones have been investigated since long time. It has been of great interest in their study as intermediates for substances of therapeutic importance[7]. Schraufstatter and Deutsch[8] and Calcinari[9] reported antibacterial properties of some chalcones, and have concluded that the bacteriostatic activity is due to their unsaturation.

ANTIMICROBIAL ACTIVITY

During the present century, chalcones and their derivatives are found to be much in use. Thus, some chalcones exhibited therapeutic properties eg. antiulcer activity, hypotensive activity etc. Antibiotic activity[10-11]have been shown by some chalcones due to presence of an enone function. It has been observed that the bacteriostatic or bactericidal properties get increased with the introduction of substituents like a nitro, bromo group at the α–position or a bromo or hydroxyl group at the β- position[10]. Some substituted chalcones and their derivatives possess biological properties eg. the growth of microbes[12], tuberclebecilli[13-14], malarial parasites[15], intestinal worms[16] etc. They also inhibit growth of several enzymes[17] and fungi[18-19]. Hypotensive property is associated with some chalcones[20]. Few substituted chalcones were tested for ability to protect adrenaline from destruction[21].

In heterocyclic derivatives of chalcones, isoxazolines have shown good antimicrobial, antitubercular[22], antiviral[23] and antifungal activities[24]. Pyrazolines are important nitrogen containing heterocycles possessing diverse biological activity[25-27]. Some pyrazoline derivatives have shown considerable promise as chemotherapeutic agents.

Doshiet al[28] reported some cyanopyridines as a potential antitubercular agents. Pyrimidine derivatives occupy a unique position as leiodynamic agents. Both are essential components of nucleic acid and also as therapeutic agents[29-30]. Some chalcone derivatives have been reported as anti inflammatory or antiallergic agents[31]. Furthermore, they found that chalcones with a 3,4-dihydroxy cinnamoyl structure strongly inhibited lipid peroxidation in cat liver microsomes[32]. The 3,4-dihydroxy chalcones are rapidly and extensively metabolized the systematic administration. These finding suggest that the chalcones may be promising non-toxic topical anti-inflammatory agents.

Antibacterial Activity

The purified products were screened for their antibacterial activity by using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method, was inoculated aseptically with 0.5 ml of 24 hrs old subculture of *Staphylococcus aureus* and *Escherichia coli* in separate conical flasks at 40^0-50^0C and mixed well by gentle shaking. About 25 ml of the contents of the flask were poured and evenly spread in petridish (90 mm in diameter) and allowed to set for two hrs. The cups (8mm in diameter) were formed by the help of borer in agar medium and filled with 0.1 ml (1 mg/ml) solution of sample in Acetone.

Antifungal Activity

A niger was employed for testing antifungal activity by cup-plate agar diffusion method. The culture was maintained on Sub rouse dextrose agar slants. Sterilized Sub rouse dextrose agar medium was inoculated with 72 hrs old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spreaded in a sterilized petridish and allowed to set for 2 hrs. The cups (8 mm in diameter) were punched in petridish and loaded with 0.1 ml (2 mg/ml) of solution of sample in Acetone. The plates were incubated at 20 – 25^0C for 72 hrs. After the completion of incubation period, the zones of inhibition growth is in the form of diameter in mm was measured. Along the test solution in each petridish one cup was filled up with solvent which acts as control. The zones of inhibition

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Buker spectrometer and 1 H NMR spectra in CDCl3 on Hitachi R-1500, 60 MHz spectrometer using TMS as an internal standard. All chemicals used were of laboratory grade.

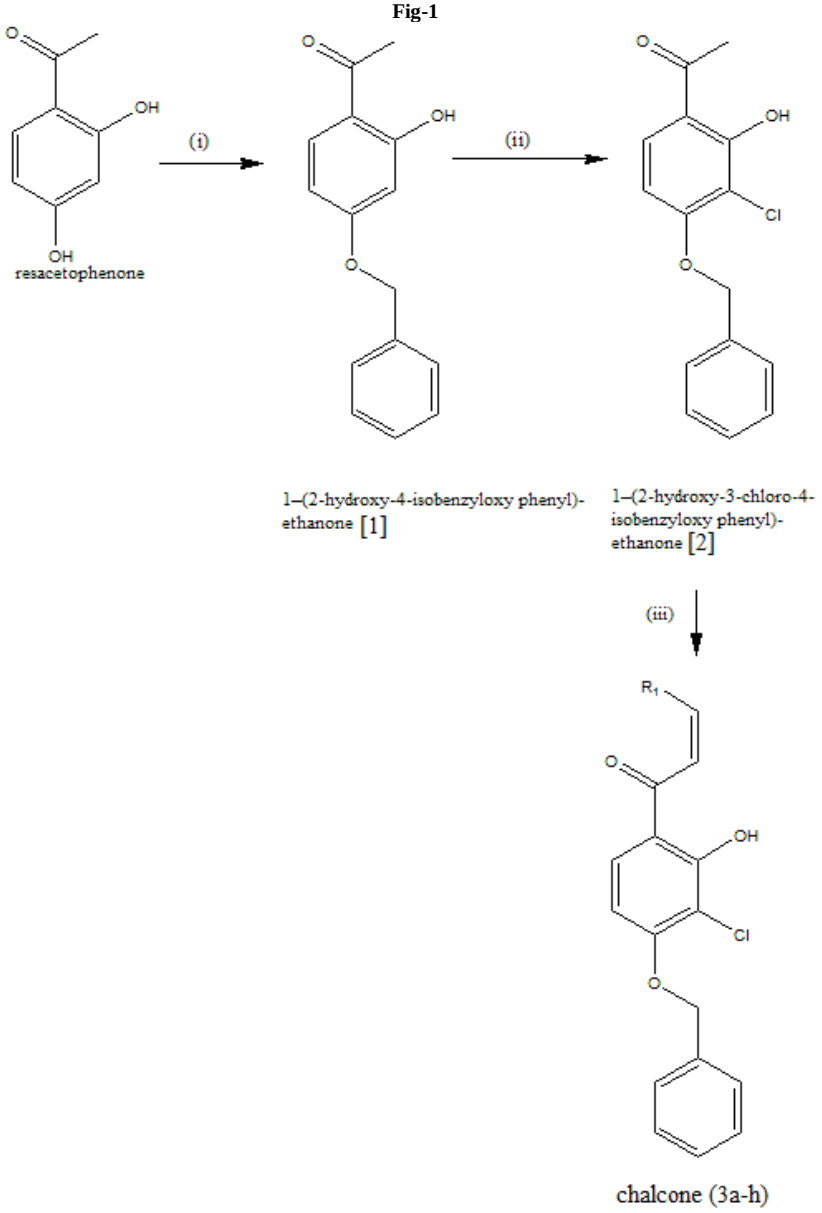
Preparation of 1-(2-hydroxy-4-benzyloxy phenyle) ethanone (1)

General procedure

A mixture resacetophenone (0.1 mol), K_2CO_3 (0.16 mol)and methanol (30 ml) stirred and then drop wise add benzyle bromide (0.12mol) then refluxed for 10 hrs. Allow it to coole at room temp then the access K_2CO_3 settled down the decant the organic layer, pour in the water acidify with HCl then filter it, wash with water, crystalline with ethanole.it give 50-60% yield.

Preparation of 1–(2-hydroxy–3-chloro-4–benzyloxy phenyl) ethanone (HCIBA) and chalcone is as given below.

Fig-1



Scheme 1 Reagents and conditions: i) K2CO3 & benzylebromide/S: methanole; ii) N-chlorosuccinimide & S:methanole / 6hrs; iii) Aldehyde & 50% NaOH in ethanole

(a) *R_1 =Benzaldehyde;* ***(b)*** *R_1 =4-Bromobenzaldehyde;* ***(c)*** *R_1 =4-Chlorobenzaldehyde;* ***(d)*** *R_1 =Anisaldehyde;* ***(e)*** *R_1 =3-Chlorobenzaldehyde;* ***(f)*** *R_1 =2-Clorobenzaldehyde;* ***(g)*** *R_1 =4-(N N-dimethylamino)benzaldehyde;* ***(h)*** *R_1 =3-Bromobenzaldehyde;*

Preparation of 1-(2-hydroxy-3-chloro-4-benzyloxy phenyle) ethanone (2)

1-(2-hydroxy-4-benzyloxy phenyle) ethanone (0.1 mole) was taken in 100 ml Methanol and stirred for clear solution. The reaction mixture was stirred and then N-Chlorosuccinimide was added slowly. The reaction mixture was stirred for 5-6 hours at RT. The reaction was monitored by TLC. The resulting product 1– (2-hydroxy–3-chloro-4–benyloxy phenyle) ethanone (HCIBA) was filtered and washed with Methanol. The obtained product was recrystallized in Methanol.

Preparation of chalcone (3a-h)

1– (2-hydroxy–3-chloro-4–benyloxy phenyle) ethanone (HCIBE) (0.10 mole) and aromatic aldehydes (0.10 mole) were dissolved in 100 ml Ethanol. The reaction was then treated with 195 ml ethanolic potassium hydroxide solution (0.125 moles) with constant stirring for 48 hours at room temperature. The reaction mass was monitored by TLC. The reaction mass was poured into cold water and acidify with hydrochloric acid. The obtained product was extracted with chloroform. Chloroform was distilled off. The obtained product was crystallized in methanol.[33,34, 35,36,37]

1-(2-hydroxy-3-chloro-4-benzyloxy phenyle) ethanone (2)

m.p 155-156°C; Mass;276.9 ; IR(KBr cm^{-1}): 2959(C-H str. vib.) 3070(-Aromatic C-H),1573, 1499,(C=C str. Vib.),884(-C – H o.o.p multi sub. benzene),1230, 1051(C-O-C str.vib), 3430(O-H str.vib), 1624(-C=O str.vib), 773(C-Cl str.vib),;^{1}H NMR 6.6 – 7.9 (s,7H,of the Ar-H) ,12.4 (s,1H, Ar-OH), 3.9 (2H,s, -CH_2-O-), 2.4 (3H,s, O=C-CH_3),; Yield 64%;

1-(2-hydroxy-3-chloro-4-Benzyloxyphenyl)-3- phenylprop-2-en-1-one [3a]:

m.p 138-139 °C; Mass;365.2 IR(KBr cm^{-1}): 3048(-Aromatic C-H),1573, 1497,(C=C str. Vib.),828(-C – H o.o.p multi sub. benzene),1228, 1063(C-O-C str.vib), 3430(O-H str.vib), 1637(-C=O str.vib), 718(C-Cl str.vib),975(CH=CH bending),;^{1}H NMR:8.2 -7.7 (m,12H, of the Ar-H) ,6.3-6.6 (m, 2H, -CH=CH-), 3.8 (d,2H, -CH_2-O-), Yield 54%;

1-(2-hydroxy-3-chloro-4-benzyloxyphenyl)-3-(4-bromophenyl) prop-2-en-1-one [3b]:

m.p 130-133°C; Mass; 443.9 IR(KBr cm^{-1}): 3069(Aromatic C-H),1560, 1490,(C=C str. Vib.),857(-C – H o.o.p multi sub. benzene),1230, 1052(C-O-C str.vib), 3470(O-H str.vib), 1624(-C=O str.vib), 748(C-Cl str.vib) 642(C-Br str.vib),937(CH=CH bending),; Yield 56%;

1-(2-hydroxy-3-chloro-4-benzyloxyphenyl)-3-(4-chlorophenyl) prop-2-en-1-one [3c]:

m.p 135-136°C; Mass;399.3 IR(KBr cm^{-1}): 3050(Aromatic C-H),1571, 1479,(C=C str. Vib.),831(-C – H o.o.p multi sub. benzene),1223, 1078(C-O-C str.vib), 3425(O-H str.vib), 1649(-C=O str.vib), 722(C-Cl str.vib),975(CH=CH bending),; Yield 58%;

1-(2-hydroxy-3-chloro-4-benzyloxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one [3d]:

m.p 137-139°C; Mass:394.8; IR(KBr cm^{-1}): 3070(Aromatic C-H),1574, 1491,(C=C str. Vib.),823(-C – H o.o.p multi sub. benzene),1231, 1072(C-O-C str.vib), 3443(O-H str.vib), 1636(-C=O str.vib), 737(C-Cl str.vib),978(CH=CH bending),; Yield 61%;

1-(2-hydroxy-3-chloro-4-benzyloxyphenyl)-3-(3-chlorophenyl) prop-2-en-1-one [3e]:

m.p 133-134°C; Mass;400.1; IR(KBr cm^{-1}): 3047(Aromatic C-H),1576, 1477,(C=C str. Vib.),829(-C – H o.o.p multi sub. benzene),1227, 1070(C-O-C str.vib), 3431(O-H str.vib), 1651(-C=O str.vib), 729(C-Cl str.vib),965(CH=CH bending),; Yield 56%;

1-(2-hydroxy-3-chloro-4-benzyloxyphenyl)-3-(2-chlorophenyl) prop-2-en-1-one [3f]:

m.p 135-136°C; Mass; 399.7 IR(KBr cm^{-1}): 3070(-Aromatic C-H),1574, 1492,(C=C str. Vib.),870(-C – H o.o.p multi sub. benzene),1219, 1060(C-O-C str.vib), 3470(O-H str.vib), 1627(-C=O str.vib), 773(C-Cl str.vib),958(CH=CH bending),; Yield 55%;

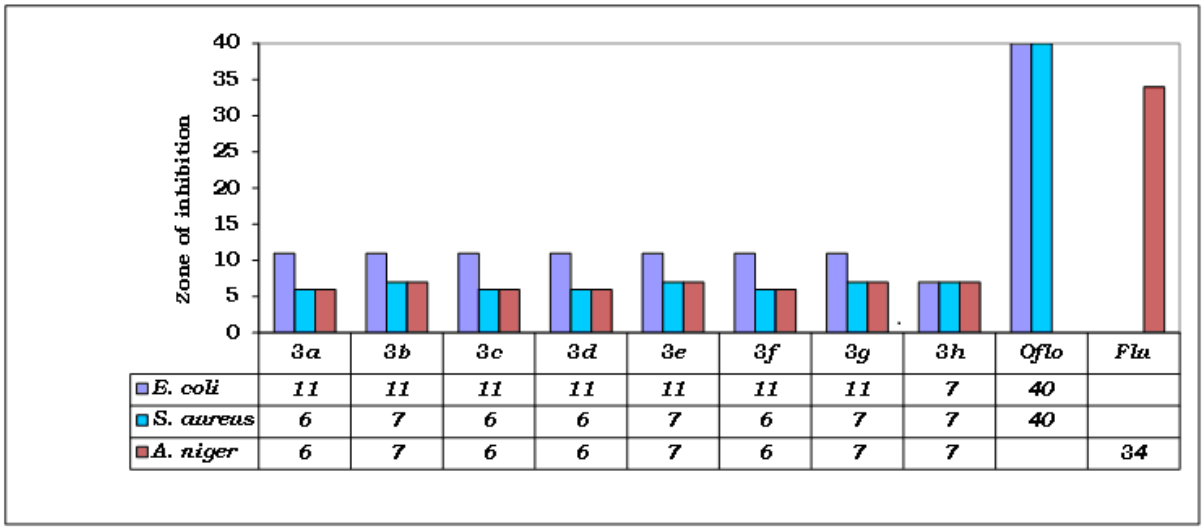
1-(2-hydroxy-3-chloro-4-benzyloxyphenyl)-3-(4-(N N-dimethyl) phenyl) prop-2-en-1-one [3g]:

m.p 141-142°C; Mass;407.7 IR(KBr cm^{-1}): 2966(C-H str.vib),; 3070(Aromatic C-H),1572, 1499,(C=C str. Vib.),831(-C – H o.o.p multi sub. benzene),1266, 1051(C-O-C str.vib), 3421(O-H str.vib), 1626(-C=O str.vib), 773(C-Cl str.vib),960(CH=CH bending), 1360(C-N str. vib); Yield 56%;

1-(2-hydroxy-3-chloro-4-benzyloxyphenyl)-3-(3-bromophenyl) prop-2-en-1-one [3h]:

m.p 135-136°C; Mass 443.6; IR(KBr cm^{-1}): 3055(Aromatic C-H),1569, 1492,(C=C str. Vib.),824(-C – H o.o.p multi sub. benzene),1227, 1061(C-O-C str.vib), 3439(O-H str.vib), 1625(-C=O str.vib), 757(C-Cl str.vib) 654(C-Br str.vib),978(CH=CH bending),;Yield 53%.

Fig-2 Microbial activity of 1–(2-Hydroxy–3-chloro-4–benzyloxyphenyl)ethanone chalcones from Aromatic Aldehydes



	3a	3b	3c	3d	3e	3f	3g	3h	Oflo	Flu
E. coli	11	11	11	11	11	11	11	7	40	
S. aureus	6	7	6	6	7	6	7	7	40	
A. niger	6	7	6	6	7	6	7	7		34

RESULTS AND DISCUSSION

In the present work, some novel chalcones of 1– (2-hydroxy–3-chloro-4–benzyloxyphenyl) ethanone (HCIBE) from 8 aldehydes have been prepared.

During the preparation work, it was found that most of the chalcones using aromatic aldehydes could be easily prepared by most convenient claisen-schmidt condensation method. The chalcones could be easily prepared at room temperature after 72 hours. It was found that the chalcones derived from aromatic aldehydes were stable and can be easily converted to its oxime/schief base.

During the preparation of chalcones using some aromatic aldehydes, it was found that chalcones could not be prepared by claisen-schmidt condensation. To establish a new synthetic process for chalcones, different reaction conditions were applied. From the results, it was found that the chalcones could be prepared from HCIBE using aliphatic aldehyde by refluxing the reaction mixture at 75 – 80^0 C temperature for 3 hours. Thus, a new developed synthetic process has been applied to prepare chalcones from HCIBE in the present work.

To check the applicability of the prepared compounds, they were screened for their antibacterial and antifungal activity by using cup-plate diffusion method. The antibacterial activity of each compound was compared with standard drug viz. Ofloxacin and antifungal activity was compared with standard drug viz. Fluconazole. The zone of inhibition was measured in millimeter. From the results, it may be generalized that the antibacterial activity on gram-positive and gram-negative bacteria of chalcones. Most of all compounds show moderate and poor antibacterial activity. The antifungal activity of each compound was found poor with compared to standard drug.

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