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SYNTHESIS OF DERIVATIVES OF CHLOROSUBSTITUTED FLAVONE

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ABSTRACT

As a part of study, we have synthesized chloro-substituted flavone derivative from flavanone which is obtained by cyclization of 1-(4-chlorophenyl)-3-(2-hydroxyphenyl) propane-1,3-dione with various substituted aromatic benzaldehyde by using a catalytic amount of piperidine under solvent of ethanol. The entire reported compound has 72–80 percentage of isolated yield. All synthesized compounds were characterized by Mass ^{1}H NMR and IR Spectroscopy.

Keywords: Flavonoids, Flavone, Flavanone, Aromatic aldehyde, Piperidine

INTRODUCTION

Flavonoids involve a group of naturally occurring compounds. They are a major constituent of many fruits, vegetables, beverages, and secondary metabolites. Flavonoids' family members (e.g. flavones, isoflavones, and neoflavones) possess many medicinal proper. Flavones which are a class of flavonoids constructed on the backbone of 2-phenylchromen-4-one together from flavones extra flavonoids are

bioflavonoids, derived from 3-phenylchromen-4-one structure neoflavonoids. Flavonoids are one of the largest groups of polyphenolics which are widely distributed in fruits, vegetables, and plant kingdoms [1]. Flavonoids are classified as chalcones, flavanones, Flavones, Isoflavones, Aurones, Neoflavones and Bio flavones. [2]. Flavonoids are crucial for plant growth development and reproduction [3]. Flavonoids are a major class of plant secondary metabolites [4]. Flavanones have attracted considerable attention because of their interesting biological activities like anti-oxidants [5], anti-hypertensive [6] anti-microbial [7], antibacterial [8], anti-fungal [9], and anti-viral [10]. Epidemiological appraisals recommend that the systematic consumption of flavonoids protects humans against various diseases accompanying oxidative stress such as Alzheimer's disease [11], arteriosclerosis [12], cancer [13], [14] and aging [15]. Flavones is a very important special residence not only in the dominion of nature but also in synthetic organic chemistry. They exhibit various biological and medicinal interest [16-20]. Flavanones are synthesized by cyclo condensation of 1,3-propanediones with various substituted aromatic aldehyde [21]. 1,3-propanediones abbreviate aromatic aldehyde through its reactive methylene group [22]. In the present work, 1-(2-hydroxy phenyl) 1, 3 propanedione was condensed with Halo substituted benzaldehyde and Chorosubstituted derivatives to give several substituted flavanones.

Experimental

General methods and materials

All solvents and reagents were picked up since Merck India Ltd and are of AR Grade and recycled without further purification. Melting Points were unwavering by the open capillary method and were uncorrected. Thin-layer chromatography (TLC) was implemented on silica. The spots were visualized by exposure to iodine vapor Nuclear magnetic resonance (NMR) spectra were recorded on a 400-MHz spectrometer for ^{1} HNMR. IR spectra of the compounds accomplished in potassium bromide (KBr) disks on a Bruker IR spectrometer. Mass spectra were recorded on a Waters ZQ-4000 spectrometer. The yields of the synthesized compounds were revealed for the isolated product.

Preparation of 2-acetylphenyl 4-chlorobenzoate (3)

o-hydroxy acetophenone (0.05 mmol) was dissolved in 30 ml of NaOH (10%) with the addition of p-Chlorobenzoyl Chloride (0.05mmol) in a 100 mL round bottom (RB) flask. This reaction mixture was shaken for about half an hour. After

completion of the reaction, the reaction mixture was poured into a 500 mL separating funnel. The desired product was separated, then filtered, washed with help of sodium bicarbonate (10%). Reaction mixture Raines again with water. Recrystallized from absolute ethanol. **m.p. 65^{o} C, yield 75%**

Preparation of 1-(4-chlorophenyl)-3-(2-hydroxyphenyl) propane-1, 3-dione. (4)

2-acetyl phenyl 4-chlorobenzoate was dissolved in dry pyridine (40 ml) in 50 ml RBF. The solution warmed at the temperature of 60^{o} C. Then crushed KOH (15 g) was added slowly with constant stirring at R.T. Reaction. Progress of the reaction was monitored by using a TLC plate. After four hours of heating, the reaction mixture was acidified by adding ice-cold dip.HCl (1:1). The brownish-yellow solid product thus separated was filtered, washed with $NAHCO_3$ (10%). Then wash again with cold water. Recrystallized using ethanol acetic acid mixture to acquire 1(4-chlorophenyl)-3-(2-hydroxyphenyl), **m.p. 110^{o} C, yield 74%.**

Preparation of 3-benzoyl 2-(4 fluro phenyl) - 4-cholrophenyl flavanone. (6a)

1-(4-chlorophenyl)-3-(2-hydroxyphenyl) propane-1,3-dione (0.012 mol) mixed with 4-flurobenzaldehyde (0.012 mol) in 25 ml of ethanol and piperidine (0.5 mol) in the 250 RBF. It was refluxed for 15-20 min. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mass was cooled to R.T. It was acidified with dil. HCl (1:1) and the desired product were separated. Recrystallized from ethanol-acetic acid mixture to get product **(6a)**

Preparation of 3-benzoyl 2-(4-bromo phenyl) - 4-cholrophenyl flavanone (6b)

1-(4-chlorophenyl)-3-(2-hydroxyphenyl) propane-1,3-dione (0.012 mol) mixed with 4-bromobenzaldehyde (0.012 mol) in 25 ml of ethanol and piperidine (0.5 mol) in the 250 RBF. It was refluxed for 15-20 min. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mass was cooled to R.T. It was acidified with dil. HCl (1:1) and the desired product were separated. Recrystallized from ethanol-acetic acid mixture to get the product **(6b)**

Preparation of 3-benzoyl 2-(4-nitro phenyl) - 4-cholrophenyl flavanone (6c)

1-(4-chlorophenyl)-3-(2-hydroxyphenyl) propane-1,3-dione (0.012 mol) mixed with 4-nitro benzaldehyde (0.012 mol) in 25 ml of ethanol and piperidine (0.5 mol) in the 250 RBF. It was refluxed for 15-20 min. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mass was cooled to R.T. It was acidified with dil. HCl (1:1)

and the desired product were separated. Recrystallized from ethanol-acetic acid mixture to get the product **(6c)**

Preparation of 3-benzoyl 2-(4 methyl phenyl) - 4-cholrophenyl flavanone (6d)

1-(4-chlorophenyl)-3-(2-hydroxyphenyl) propane-1,3-dione (0.012 mol) mixed with 4-methyl benzaldehyde (0.012 mol) in 25 ml of ethanol and piperidine (0.5 mol) in the 250 RBF. It was refluxed for 15-20 min. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mass was cooled to R.T. It was acidified with dil. HCl (1:1) and the desired product were separated. Recrystallized from ethanol-acetic acid mixture to get the product **(6d)**

Preparation of 3-benzoyl-2 (4 Fluro phenyl) 4-cholrophenyl flavone (7a)

A mixture of 3-benzoyl 2-(3-nitro phenyl) - 4-chlorophenyl flavanone (**6a)** (0.01mol) and iodine crystal was reflexed in DMSO (20 ml) for about 10 min in 250 ml RBF. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mixture was cooled to R.T. The solid product was obtained, separated, It was washed with sodium thiosulphate solution. Finally Recrystalline from ethanol acetic acid mixture to get the 3-benzoyl-2 (4 Fluro phenyl) 4-cholrophenyl flavone**. (7a). m.p. 125^{o} C, yield 72%.**

Preparation of 3-benzoyl-2 (4 Bromo phenyl) 4-chlorophenyl flavone (7b)

A mixture of 3-benzoyl 2-(3-nitro phenyl) - 4-chlorophenyl flavanone (**6b)** (0.01mol) and iodine crystal was reflexed in DMSO (20 ml) for about 10 min in 250 ml RBF. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mixture was cooled to R.T. The solid product was obtained, separated, It was washed with sodium thiosulphate solution. Finally Recrystalline from ethanol acetic acid mixture to get the 3-benzoyl-2 (4 Fluro phenyl) 4-cholrophenyl flavone**. (7b). m.p. 160^{o} C, yield 75%.**

Preparation of 3-benzoyl-2 (4 nitro phenyl) 4-cholrophenyl flavone (7c)

A mixture of 3-benzoyl 2-(4-nitro phenyl) - 4-cholrophenyl flavanone (**6c)** (0.01mol) and iodine crystal were reflexed in DMSO (20 ml) for about 10 min in 250 ml RBF. Progress of the reaction was monitored by using a TLC plate. After completion of the reaction, the reaction mixture was cooled to R.T. The solid product was obtained, separated, It was washed with sodium thiosulphate solution. Finally Recrystalline from ethanol acetic acid mixture to get the 3-benzoyl-2 (4 fluro phenyl) 4-

cholrophenyl flavone **(7c). m.p. 152° C, yield 79%.**

Preparation of 3-benzoyl-2 (4 bromo phenyl) 4-cholrophenyl flavone (7d)

A mixture of 3-benzoyl 2-(4 methyl phenyl) - 4-cholrophenyl flavanone (**6d)** (0.01mol) and iodine crystal was reflexed in DMSO (20 ml) for about 10 min. After the cooling reaction mixture was diluted with water. The solid product thus separated was washed with sodium thiosulphate solution and then with water. Finally it was crystalline from ethanol acetic acid mixture to get the compound 3-benzoyl-2 (4 Bromo phenyl) 4-cholrophenyl flavone. **(7d). m.p. 160° C, yield 80%.**

Result and Discussion

We have synthesized a series of chloro-substituted flavone derivatives **7(a-d)** by flavanone derivative which was prepared by cyclization of 1-(4-chlorophenyl)-3-(2-hydroxyphenyl **(4)** with various substituted aromatic benzaldehyde **5(a-d)** by using a catalytic amount of piperidine under solvent of ethanol. To begin with, commercially available o-hydroxy acetophenone reacted with p-Chlorobenzoyl Chloride in presences of NaOH to obtain 2-acetyl phenyl 4-chlorobenzoate by literature method [23]. 1-(4-chlorophenyl)-3-(2-hydroxyphenyl) propane-1,3-dione was obtained by 2-acetyl phenyl 4-chlorobenzoate under catalyst amount of BVT in Pyridine by using potassium hydroxide. The synthesis compound was purified by column chromatography. All synthesis compound **7(a-d)** are characterized by various spectroscopic techniques like ^{1}H NMR, IR, and mass. Compound **7a** was purified by column chromatography and its structure was confirmed by 1 H-NMR**.** Compound **7a** confirmed by NMR peaks of aromatics proton appears δ 6.3-9.1 as multiplet. IR absorption band appears at 3424 cm-^{1} for aromatics proton .band appears at 1603 cm-^{1} indicates –C=O group while band appears at 840 and 1178 cm^{-1} for Ar- Cl and Ar-F stretching respectively. LC-MS spectra show a peak at m/z 379.

Spectral data of flavone derivatives

3-benzoyl-2 (4 fluro phenyl) 4-cholrophenyl flavone (7a)

Molecular formula: yield: **72%**, **m.p. 125 °C,** IR (KBr) cm^{-1} : 3424 (-CH Aromatic str), 1603(>C=O str), 840 (Ar-Cl str); 1178 (Ar-F str); ^{1} H NMR (DMSO-d6), 400 MHz, δ (ppm): 6.3 (m, 3H), 6.4(m, 5H), 7.01 (dd, 2H), 7.02 (d, 1H), 9.1(m,1H), mass: 379 (M+1).

3-benzoyl-2 (4 bromo phenyl) 4-cholrophenyl flavone (7b)

Molecular formula yield: **75%**, **m.p. 160 °C,**IR (KBr) cm^{-1} : 3014 (-CH Aromatic str), 16014(>C=O str), 829 (Ar-Cl str), 529

(Ar-Br str); ^{1} H NMR (DMSO-d6), 400 MHz, δ (ppm): 7.5 (m, 1H), 7.6(d, 2H), 7.7(d, 2H), 8.2 (d, 2H), 8.3 (m, 3H), 8.4 (d, 1H), 9.1(m,1H), mass: 440 (M+1).

3-benzoyl-2 (4 nitro phenyl) 4-cholrophenyl flavone (7c)

Molecular formula: **79%**, **m.p. 152^{o}C**, IR (KBr) cm^{-1} : 3058 (-CH Aromatic str), 1709(>C=O str), 854 (Ar-Cl str) , 1314 (Ar-NO_2 str); ^{1} H NMR (DMSO-d6), 400 MHz, δ (ppm): 6.7 (m, 1H), 7.4(d, 4H), 7.6(d, 2H), 8. (d, 2H), 8.4(dd,1H), 8.8(d, 1H), 9.1(m,1H), mass: 406 (M+1).

3-benzoyl-2 (4 bromo phenyl) 4-cholrophenyl flavone (7d)

Molecular formula: **80 %**, **m.p. 160 ^{o}C** IR (KBr) cm$^{-1:}$ 3186 (-CH Aromatic str), 1599 (>C=O str), 840 (Ar-Cl str); ^{1} H NMR (DMSO-d6), 400 MHz, δ (ppm): 6.7 (m, 1H), 7.4(d, 4H), 7.6(d, 2H), 8. (d, 2H), 8.4(dd,1H), 8.8(d, 1H), 9.1(m,1H), mass:375 (M+1).

CONCLUSION

We have synthesized four derivatives of flavone like Fluro, Nitro, Bromo, and Methyl. The yield of these flavone derivatives was found to be in the range of 68-88%. The purity of compounds was established by TLC. The synthesized compounds were further established by mass, ^{1} H NMR, and IR spectral studies. Based on spectral data, it was demonstrated that all synthesized flavone derivatives come across the standard values of various spectral techniques.

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