SYNTHESIS OF 3-(4-CHLOROBENZOYL)-2-(4-SUBSTITUTED PHENYL) THIOFLAVONES FROM BENZOYL CHLORIDE AND O-THIOACETOPHENONE

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Abstract

As a part of the study, we have synthesized 3-(4-Chlorobenzoyl)-2-(4-substituted phenyl) thioflavin derivatives by treating with 3-(4-Chlorobenzoyl)-2-(4-substituted phenyl) thioflavanone in the presence of iodine crystal in ethanol as solvent. The reaction of 1-(2-mercaptophenyl)-3-phenylpropane-1,3dione with 4-substituted aldehyde in the presence of ethanol and piperidine gave 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavanone. The reaction of 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavanone in the presence of iodine crystal in ethanol gave 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavone. The entire reported compound has 70–80 percent of isolated yield. All synthesized compounds were characterized by Mass ^{1}H NMR and IR Spectroscopy.

Keywords: *Flavonoids, Thioflavone, Thioflavanone, Substituted aldehyde, Piperidine.*

Introduction

Heterocyclic compounds embrace a special place among pharmaceutically significant natural products and synthetic compounds. The remarkable ability of heterocyclic nuclei to serve both as biomimetic and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs [1, 2]. Heterocyclic moieties are originating in many compounds, that have biological activity that depends mainly on their molecular structure [3]. Thio derivatives exhibit antibacterial [4], anticancer [5, 6] antiviral [7-8], antileishmanial [9], antimicrobial, [10] antibacterial [11], anticancer [12], anti-inflammatory [13,14], antiproliferative activity [15], anti-oxidant [16,17], antituberculosis [18,19], anti-inflammatory [20,21], anticonvulsants [22], antiproliferative [23]. Flavones, such as chrysin, apigenin, and luteolin, belong to the large group of plant.

Secondary metabolites are known collectively as flavonoids. These compounds exhibit of pharmacological properties counting antianxiety effects [24-25]. Flavones occur only in a relatively small food group that includes parsley, thyme, celery, and sweet red pepper [26], Yayli . N; Ayli. and co-worker synthesized 1,4-Diazaflavone pigment by a simple environmentally friendly microwave assisted one-pot method for the cyclization of 2-amino4-aza-chalcone 1 under solventless conditions using K-10 clay. [27]

Experimental

General methods and materials

Chemicals were purchased from Sigma Aldrich. Thin layer chromatography (TLC) was performed on aluminium aluminum-backed silica plate which was visualized by UV light. Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra of the compounds accomplished in potassium bromide (KBr) disks on a Bruker IR spectrometer. NMR spectra were recorded on a Bruker 400 MHz NMR spectrophotometer in DMSO and chemical shifts were recorded in parts per million downfield from tetramethylsilane. 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 benzothioate (3)

1-(2-Mercaptophenyl) ethanone (0.05 mmol) and 4-Chlorobenzoyl chloride (0.005) were added in 10 % NaOH with constant stirring and cooling. The reaction mixture was kept overnight and worked up dilution and acidification with ice-cold HCl. Thus the solid product obtained was filtered and washed with water. It was crystallized from ethanol to 2-acetylphenyl benzothioate (3).

Preparation of 1-(2-Mercaptophenyl)-3-phenylpropane-1,3-dione. (4)

2-Acetylphenyl benzothioate (3) was dissolved in dry pyridine (40 ml) in 250 ml RBF. The solution warmed at the temperature of 70^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 dil. HCl (1:1). The brownish-yellow solid product thus separated was filtered, and washed with $NaHCO_3$ (10%). Then wash again with cold water. Recrystallized using ethanol

acetic acid mixture to acquire 1-(2-Mercaptophenyl)-3-phenylpropane-1,3-dione (4).

Preparation of 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavanone. [6 (a-e)]

1-(2-Mercaptophenyl)-3-phenylpropane-1,3-dione **(4)** (0.01mol) mixed with 4-substituted aldehyde **[5(a-e)]** (0.012 Mol) in 25 ml of ethanol and piperidine (0.5 Mol) in the 250 RBF. It was refluxed for 1 hour 30 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. **[6(a-e)].**

Preparation of 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavone. [7 (a-e)]

A mixture of 3-(4-Chlorobenzoyl)-2-(4-substituted phenyl) thioflavanone (0.01Mol) [6 (a-e)**]** and iodine crystal was reflexed in ethanol (50 ml) for about 20 min in 50 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, and separated. Thus, we obtained the product substituted 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavone. **[7(a-e)]**. Finally, recrystallized from methanol.

Result and Discussion

Table - Physical data of synthesized compounds 7 (a-e)

Sr.No.	Compound	R	Reaction Time (Min)	Yield (%)	M.P. (^{0}C)
1	7a	F	1 h 12 min	70	149
2	7b	Cl	1 h 14 min	75	120
3	7C	Br	1 h 12 min	73	156
4	7d	NO_2	1 h 10 min	80	138
5	7e	CH3	1 h 14 min	76	141

The starting material 2-Acetylphenyl benzothioate **(3)** was prepared by reaction between 1-(2-Mercaptophenyl) ethanone (0.05 Mol) and 4-Chlorobenzoyl chloride in 10 % NaOH with constant stirring and cooling. The compound 2-Acetylphenyl benzothioate **(3**) was treated with BVT/KOH in dry pyridine to obtained acquire 1-(2-Mercaptophenyl)-3-phenylpropane-1,3-dione **(4).** The reaction of 1-(2-Mercaptophenyl)-3-phenylpropane-1,3-dione **(4)** with 4-substituted aldehyde **[5(a-e)]** in presence of ethanol and piperidine gave 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavanone. **[6 (a-e)].** Finally, 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavone**. [7(a-e)]** was synthesized by refluxed with 3-(4-Chlorobenzoyl)-2-(4-substitutedphenyl) thioflavanone. [6 (a-e)] in the presence of iodine crystal in ethanol as solvent.

All the synthesized compounds were characterized by IR, NMR, and mass spectral studies. The IR spectrum of 3-(4-Chlorobenzoyl)-2-(4-chlorophenyl) thioflavone **7b (A12)** showed the presence of C-H stretching at 3107 cm−1, a band for carbonyl group (C=O) stretching of **4H-**thiochromen-4-one ring at 1637 cm^{-1} while stretching at 1591 is due (C-O of flavone) and band observed at 682 for Ar –Cl. Whereas in ^{1}H NMR spectrum a multiplet around at 7.75-7.9 ppm for aromatic ring, a doublet at 8.4 and 9.20 ppm for aromatic protons to substituted thioflavone ring of compound **7b**. However, the formation of 3-(4-Chlorobenzoyl)-2-(4-chlorophenyl) thioflavone **7b (A12)** was confirmed observing mass spectrum at 384 (M+1). The mass spectra of these compounds show molecular ion peaks corresponding to their molecular formulae.

Spectral data:

3-(4-Chlorobenzoyl)-2-(4-fluorophenyl) thioflavin (7a)

Molecular formula $C_{22}H_{12}ClFO_2S$: yield: 70 **%**, m.p.149 ^{o}C, IR (KBr) cm^{-1}: 2972 (-CH Aromatic str), 1676 (>C=O str), 1219 (Ar-F str) : Mass: 367 (M+1).

3-(4-Chlorobenzoyl)-2-(4-chlorophenyl) thioflavin (7b)

Molecular formula: $C_{22}H_{15}O_4Cl$ yield: 75%, m.p. 119^{0}C. IR (KBr) cm^{-1}: 3107 (-CH Aromatic str), 1637 (> C = O str), 682 (Ar-Cl), 1591 (C-O of Flavone), ^{1}H NMR **(**DMSO-d6), 400 MHz, δ 7.75-7.90 (dd, 4H), 8.10 (d, 4H), 9.20 (d, 4H). mass: 384 (M+1).

3-(4-Chlorobenzoyl)-2-(4-bromophenyl) thioflavin (7c)

Molecular formula $C_{23}O_4H_{15}Br$: yield: 73 **%**, m.p. 117 **^{o}C** IR (KBr) cm^{-1}: IR spectrum, ν, cm^{-1}**:** 2971 (-CH Aromatic str), 1696(>C=O str), 11501 (C-O of Flavone); 558 (Ar-Cl str), 646 (Ar-Br str); (MS: *m/z*: $(M+H)^+$.: 429

3-(4-Chlorobenzoyl)-2-(4-nitrophenyl) thioflavin (7d)

Molecular formula: $C_{23}O_6H_{15}N$ yield: 80 **%.** m.p. 163 ^{o}C**,** IR (KBr) cm^{-1} : 2972 (-CH Aromatic str), 1593 (>C=O str),); 1699 (C-O of Flavone); 1054 (Ar-NO_2 str); ^{1}H NMR

(DMSO-d6), 400 MHz, δ (ppm): 3.3 (s, 3H, OCH_3), 6.8(d, 4H), 7.34 (d, 4H), 7.5 (m, 2H), 7.91 (m,2H), mass: 390 (M+1)

3-(4-Chlorobenzoyl)-2-(4-methyl phenyl) thioflavin (7e)

Molecular formula $C_{24}O_4H_{18}$: yield: 76 %, m.p. 141 ^oC, 2925 (-CH Aromatic str), 1717 (>C=O str),); 1684 (C-O of Flavone); 2820 (Ar-CH_3 str); 772 (Ar-Cl str). (MS: *m/z*: (M +H) : 364

Conclusion

In conclusion, a simple and efficient procedure for the synthesis of 3-(4-Chlorobenzoyl)-2-(4-substituted phenyl) thioflavone derivative by the reaction of 3-(4-Chlorobenzoyl)-2-(4-substituted phenyl) thioflavanone. [6 (a-e)] in the presence of iodine crystal in ethanol as solvent. These derivatives were synthesized starting from 1-(2-Mercaptophenyl) ethanone and 4-chlorobenzoyl chloride. Some. The compound containing the nitro group at the para position exhibits the highest yield among synthesized compounds. All synthesized compounds are characterized by IR, ^{1}HNMR, and Mass spectroscopic techniques.

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