

Synthesis of 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanone and Thioflavones from 4-Methoxybenzoic acid and o-Thioacetophenone.

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Abstract

Thioflavanones and Thioflavones have wide applicability as a growth regulating agent in agricultural field. Investigation of study of different derivatives of thioflavanones and thioflavones are attention in present day context. The present study explored the synthesis and characterization of series of ortho substituted phenyl derivatives of thioflavanones and thioflavones. Mercaptophenylethanone and 4-methoxybenzoic acid are taken as the starting material. The synthesized compounds are characterized using sophisticated analytical techniques such as UV-Vis, FT-IR, GC-MS, and NMR. The characterization reveals the complete synthesis of fluoro, bromo, nitro and methyl substituted 3-(4-methoxybenzoyl)-2-(4-substituted phenyl) thioflavanone derivatives as well as 3-(4-methoxybenzoyl)-2-(4-substituted phenyl) thioflavone derivatives.

Keywords- Thioflavanone, Thioflavone, Mercaptophenylethanone, Aldehyde.

Introduction

Flavonoids shows wide spread diversity mainly due to the changes in B- and Cring locations, degree of hydroxylation, oxidation, and saturation of ring are and found in nature [1,2]. 4-thioflavonol is the important subclasses of flavonoids which exhibits antioxidant properties in the food and health sciences [3,4]. 4-thioflavonols and their derivatives have been reported to possess potent biological properties such as anticancer, antimicrobial and green pesticides etc. [5,6].

They are universally distributed in plants with a wide range of biological and pharmacological activities such as antifungal, antimicrobial, neuroprotective, antioxidant, HIV inhibitory and anticancer activities [7,8]. Moreover, Sulphur containing compounds usually possess good biological activities, which can be speculated by their ability to scavenge free radicals, high potential of chelating metal cations and capacity of affecting key redox enzymes [9]. However, despite the fact that the conversion of the carbonyl (C=O) group in 2-phenylchromone framework into thiocarbonyl (C=S) group has been usually described as a feasible strategy [8,12], the inhibitory potential against cholinesterase enzymes of sulfurcontaining flavonols have been much less reported [10,11]. Thioflavanones have a skeleton of a thiochroman-4-one ring with aryl groups in the 2-position. Their biological activities have recently been investigated in anticipation of improved bioavailability compared to flavanones.

Ehsan Ullah Mughal reported that 4-thioflavones exhibited higher activity than that of their corresponding flavone analogues and also investigated compounds having substituents like F, OMe and NO₂ at 4-position in Ring-B exhibited improved activity [12]. Sulphur atoms at 4-position of flavones on improve their biological activity. Jae In Lee reported Synthesis of

Thioflavanones by the Regioselective Cyclization of 1-(2-Benzylthio) phenyl-3-phenyl-2-propen-1-ones with Hydrobromic Acid [13]. However, in the number of publications, thiochromones lag much behind the oxygen analogues δ chromones. This is due not only to the lower accessibility of the sulfur-containing building blocks, their unpleasant odour and the tendency to form disulfides, but also to the lower reactivity of the thiopyrone ring, which is a direct consequence of replacement of the oxygen atom by the less electronegative sulphur atom. Thioflavanones constrain the cellular proliferation of human breast cancer with weak.

cytotoxicity and exhibit antioxidative activity against nitric oxide (NO). They also have antileishmanial activity against *Leishmania panamensis* and exhibits better antifungal activity against fungi, such as *Cryptococcus neoformans* and *Epidermophyton floccosum* than fluconazole. Several methods for synthesizing thioflavanones have been described through the construction of thiochroman-4-one ring as a key step [14]. Thioflavanones derivatives were synthesized by the 1,4-addition by using phenylzinc chloride [15], diarylcuprates [16,17], thiochromones in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2$ [18].

We have synthesized a series of compounds of substituted 3-(4-methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanones and Thioflavones. The key intermediates were prepared in four steps. Cyclization of Mercaptophenyl Ethanone **1** with 4-Methoxybenzoic acid **2** in the presence phosphorus oxychloride to give 2-Acetyl-4-methoxyphenyl benzothioate (**3**). The compound 2-Acetylphenyl benzothioate (**3**) treated with BVT/KOH in in dry pyridine to obtained 1-(2-Mercaptophenyl)-3-(4-Methoxyphenyl) propane-1,3-dione (**4**). The reaction of 1-(2-Mercaptophenyl)-3-(4-Methoxyphenyl) propane-1,3-dione (**4**) with 4-substituted aldehyde [**5(a-e)**] in presence of ethanol and piperidine gave 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanone [**6(a-e)**].

3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavone [**7(a-e)**] derivatives were synthesized by reacting 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanone [**6(ae)**] with iodine in ethanol.

Experimental General methods and materials

All chemicals such as starting materials and reagents were commercially available and used without further purification. The reaction was monitored by thin layer chromatography, which was performed on Merck percolated plates (silica gel. 60 F254, 0.25 mm) and was visualized by fluorescence quenching under UV light (254 nm). Melting Points were determined by open capillary method and were uncorrected. 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 down field from Tetramethylsilane. Mass spectra were recorded on a Waters ZQ-4000 spectrometer. The yields of the synthesized compounds were revealed for the isolated product.

Synthesis of 2-Acetyl-4-Methoxyphenyl benzothioate (3)

1-(2-Mercaptophenyl) Ethanone (0.1 Mol) and 4-Methoxybenzoic acid (0.1 Mol) 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 with HCl . Thus the solid product obtained was filtered washed with water. It was crystallized from ethanol to 2-Acetyl-4-Methoxyphenyl benzothioate (**3**).

Synthesis of 1-(2-Mercaptophenyl)-3-(4-Methoxyphenyl) propane-1,3-dione. (4)

2-acetyl-4-Methoxyphenyl benzothioate (**3**) was dissolved in dry pyridine (40 ml) in 250 ml RBF. The solution warmed at the temperature of 70° 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, washed with NaHCO_3 (10%). Then wash again with cold water. Recrystallized using ethanol acetic acid mixture to acquire 1-(2-Mercaptophenyl)-3-(4-Methoxyphenyl) propane-1,3-dione (**4**) **Synthesis of 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanone [6(a-e)]**

1-(2-Mercaptophenyl)-3-(4-Methoxyphenyl) propane-1,3-dione (**4**) (0.01Mol) mixed with 4substituted 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 40 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)]**

Synthesis of 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavones [7 (a-e)]

A mixture of 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanones **[6(a-e)]**. (0.01Mol) and iodine crystal was refluxed in ethanol (50 ml) for about 1 hour 55 min in 100 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. We obtained the product substituted 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavones. **[7(a-e)]** Finally, recrystallize from methanol.

Result and Discussion

Table-1. Physical data of synthesized compounds 6 (a-e).

Entry	Compound	R	Reaction Time (Min)	Yield (%)	M.P. (°C)
1	6a (A16)	F	1 h 25 min	77	180
2	6c (A18)	Br	1 h 24 min	68	179
3	6d (A19)	NO ₂	1 h 18 min	76	168
4	6e (A20)	CH ₃	1 h 40 min	65	266

Table 4.1. Physical data of synthesized compounds 7 (a-e).

Entry	Compound	R	Reaction Time (Min)	Yield (%)	M.P. (°C)
1	7a (A16)	F	1 h 20 min	78	121
2	7c (A18)	Br	1 h 40 min	65	160
3	7d (A19)	NO ₂	1 h 10 min	79	189
4	7e (A20)	CH ₃	1 h 55 min	60	180

This research work was focused on the rational approach to synthesised of 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanone and Thioflavones. Synthesized compounds (7 a-e) were characterized by IR, NMR, mass spectral analyses. Spectral data of all synthesized compounds were in full agreement with the proposed structures. IR spectrum of compound **7a** showed absorption bands at 3365 cm⁻¹ assigned to the aromatic C–H stretch. The peak for >C=O group was observed at 1631 cm⁻¹. The peaks at 1528 was allocated for (C-O of Flavone). IR absorption bands at 1070 which was due to the presence of C-F bonds. In ¹H NMR spectra, all protons were appreciated according to the estimated chemical shift and integral values. The mass spectrum of **7a** displayed a molecular ion peak at m/z = 364 (M+1) which is in agreement with the molecular formula C₂₂H₁₅FO₂S. IR spectrum of compound **7b** exhibited absorption bands at 3352 cm⁻¹ assigned to the aromatic C–H stretch. The peaks at 1528 was allocated for (C-O of Flavone). IR absorption bands at 622 which was due to the presence of C-Cl bonds. Absorption band at 1631 cm⁻¹ is due to C-O of carbonyl group. In ¹H NMR spectra, all protons were appreciated according to the estimated chemical shift and integral values. The ¹H-NMR spectrum of **7b** showed a multiplet at 6.5 and 8.0 for corresponds to 12 H of aromatic proton. A singlet at d 3.5 was due to methoxy 3H proton. The mass spectrum of **7b** displayed a molecular ion peak at m/z = 379 (M+1) which is in agreement with the molecular formula C₂₂H₁₅ClO₂S. In the reaction scheme having weak electron withdrawing group's such as 4-Cl and 4-F with methoxy substituent to afford the target products **7a** and **7b** in moderate yield. Which compound **7d** having electron withdrawing (NO₂) group obtained very good. Compound **7e** having electron donating group (-OCH₃) resulted low yield. Other compound acquired moderate yield.

Spectral Data

3-(4-Methoxybenzoyl)-2-(4-Fluorophenyl) Thioflavone (7a)

Molecular formula: $C_{22}H_{15}FO_2S$, Yield: 78 %, M.P.121 °C, IR (KBr) cm^{-1} : 3365 (-CH Aromatic str) 1631 ($>C=O$ str), 1528 (C-O of Flavone), 1070 (Ar-F str), Mass: 363 (M+1). **3**

3-(4-Methoxybenzoyl)-2-(4-Bromophenyl) Thioflavone 7c

Molecular formula: $C_{22}H_{15}BrO_2S$, Yield: 65 %, M.P.160 °C, IR (KBr) cm^{-1} : 2343 (-CH Aromatic str), 1626 ($>C=O$ str), 1506 (C-O of Flavone), 623 (Ar-Br str): Mass: 424 (M+1).

3-(4-Methoxybenzoyl)-2-(4-Nitrophenyl) Thioflavone 7d

Molecular formula: $C_{22}H_{15}NO_4S$: Yield: 79 %, M.P. 186 °C, IR (KBr) cm^{-1} : 2981 (-CH Aromatic str), 1575 ($>C=O$ str), 1505 (C-O of Flavone), 1475 (Ar- NO_2 str): 1H NMR (DMSO-d₆), 400 MHz, δ 3.4 (s, 3H, OCH_3), 6.5 (m, 6H), 8. (m, 6H) Mass: 389 (M+1).

3-(4-Methoxybenzoyl)-2-(4-methylphenyl) Thioflavone 7e

Molecular formula: $C_{22}H_{12}ClFO_2S$, Yield: 60 %, M.P.180 °C, IR (KBr) cm^{-1} : 2981 (-CH Aromatic str), 1788 ($>C=O$ str), 1657(C-O of Flavone), : Mass: 361 (M+1).

Conclusion

We report a series of synthesis of substituted 3-(4-methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanones and Thioflavones by multistep reaction. We have synthesized substituted 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavone derivative **[7(a-e)]** by the reaction of substituted 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanones **[6 (a-e)]** in the presence of iodine crystal in ethanol as solvent . Starting with cyclization of Mercaptophenyl ethanone **1** with 4-Methoxy benzoic acid **2** in the presence phosphorus oxychloride to give 2-Acetyl-4-Methoxyphenyl benzothioate (**3**). The compound 2-Acetylphenyl benzothioate (**3**) treated with BVT/KOH in in dry pyridine to obtained obtained 1-(2-Mercaptophenyl)-3-(4-Methoxyphenyl) propane-1,3-dione (**4**). The reaction of 1-(2-Mercaptophenyl)-3-(4-Methoxyphenyl) propane-1,3-dione (**4**) with 4-substituted aldehyde **[5(a-e)]** in presence of Ethanol and piperidine gave 3-(4-Methoxybenzoyl)-2-(4-substituted phenyl) Thioflavanones **[6(a-e)]**.

Electron withdrawing group's such as 4-Cl and 4-F with methoxy substituent to afford the target products **7a** and **7b** in moderate yield. compound **7d** having electro withdrawing (NO_2) group obtained very good. Compound **7e** having electron donating group ($-OCH_3$) resulted low yield. Other compound acquired moderate yield. All synthesized compounds were characterized by IR, 1H NMR, and mass spectra. All the compounds were obtained in good to moderate yields.

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