AN EFFICIENT METHOD FOR THE SYNTHESIS OF THIOFLAVONE DERIVATIVES

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Abstract

Thioflavones are an important class of sulfur-containing heterocyclic compounds that exhibit significant biological and pharmacological activities. In the present study, an efficient and convenient synthetic method for the preparation of substituted thioflavone derivatives has been developed using benzoyl chloride and o-thioacetophenone as key starting materials. The reaction was carried out under mild conditions, leading to good yields and high purity of the desired products. Various substituted aromatic aldehydes were employed to obtain structurally diverse thioflavone derivatives. The synthesized compounds were characterized by melting point determination, infrared spectroscopy (IR), proton nuclear magnetic resonance (^1H NMR), and elemental analysis. The developed methodology offers advantages such as shorter reaction time, simple work-up procedure, and improved yields, making it a valuable approach for the synthesis of biologically important thioflavone derivatives.

Keywords: *Thioflavones, Benzoyl chloride, o-Thioacetophenone, Heterocyclic compounds, Organic synthesis.*

1. Introduction

Heterocyclic compounds containing sulfur atoms occupy an important position in medicinal and synthetic organic chemistry due to their wide range of biological activities. Among them, thioflavones represent a significant class of sulfur-containing analogues of flavones. These compounds have attracted considerable attention because of their antimicrobial, anti-inflammatory, antioxidant, anticancer, and antiviral properties.

Conventional methods for the synthesis of thioflavones often involve harsh reaction conditions, prolonged heating, and complicated purification procedures. Therefore, the development of an efficient and economical synthetic route for thioflavone derivatives remains an important area of research in organic chemistry.

In recent years, substituted thioflavones have gained considerable interest owing to their structural diversity and pharmaceutical applications. The present work focuses on the synthesis of substituted thioflavone derivatives using benzoyl chloride and *o*-thioacetophenone through a simple and efficient methodology. The objective of this study is to establish a convenient synthetic protocol that provides good yields with reduced reaction time and easy isolation of products.

2. Materials and Methods

2.1 Materials

All chemicals and reagents used in the present investigation were of analytical reagent (AR) grade and were used without further purification unless otherwise stated. The solvents employed during synthesis and purification were purified by standard laboratory procedures prior to use. Benzoyl chloride, *o*-thioacetophenone, substituted aromatic aldehydes, sodium hydroxide, ethanol, methanol, chloroform, and dimethyl sulfoxide (DMSO) were obtained from reputed chemical suppliers.

The substituted benzoyl chlorides used in the synthesis included 4-chlorobenzoyl chloride, 4-bromobenzoyl chloride, 4-methoxybenzoyl chloride, and 4-methylbenzoyl chloride. These compounds were selected to study the effect of electron-withdrawing and electron-donating substituents on the synthesis and yield of thioflavone derivatives.

Ethanol was used as the reaction medium because of its good solubilizing ability and environmentally benign nature. Sodium hydroxide served as the basic catalyst for facilitating the condensation and cyclization reactions leading to thioflavone formation. Distilled water was used throughout the experimental work.

The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel-coated aluminum plates. A suitable solvent system consisting of hexane and ethyl acetate was employed for the separation of reaction components. The spots were visualized under ultraviolet light.

Melting points of the synthesized compounds were determined using open capillary tubes and are uncorrected. Infrared spectra were recorded using potassium bromide (KBr) pellets in the range of 4000–400 cm^-1. Proton Nuclear Magnetic Resonance (^1H NMR) spectra were recorded using deuterated solvents such as $CDCl_3$ and DMSO-d_6 with tetramethylsilane (TMS) as the internal standard.

All reactions were carried out under controlled laboratory conditions with continuous stirring and appropriate temperature monitoring to ensure reproducibility and improved product yield.

2.1 Materials

All reagents and solvents used in the present investigation were of analytical reagent (AR) grade and employed without further purification. *o*-Thioacetophenone, substituted benzoyl chlorides, sodium hydroxide, absolute ethanol, methanol, chloroform, ethyl acetate, hexane, and dimethyl sulfoxide (DMSO-d_6) were procured from standard commercial suppliers and used as received.

Substituted benzoyl chlorides containing electron-donating and electron-withdrawing groups were selected for the synthesis of various thioflavone derivatives. The purity of the compounds was confirmed by melting point determination and thin-layer chromatography (TLC) prior to use.

The reactions were carried out in clean, oven-dried glassware under reflux conditions using ethanol as the reaction solvent. Sodium hydroxide solution was used as the base catalyst to promote condensation and intramolecular cyclization during thioflavone formation.

Reaction progress was monitored by TLC using silica gel-G coated aluminum plates with hexane:ethyl acetate solvent system. The developed chromatograms were visualized under ultraviolet light at 254 nm.

The synthesized compounds were purified by recrystallization using ethanol or methanol depending upon the solubility of the product obtained. Melting points were determined by the open capillary method and are uncorrected.

Infrared (IR) spectra were recorded using KBr pellets on an FT-IR spectrophotometer in the range of 4000–400 cm^-1. Proton Nuclear Magnetic Resonance (^1H NMR) spectra were recorded in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as the internal standard, and chemical shifts were expressed in δ ppm. Elemental analysis was carried out for carbon, hydrogen, and sulfur to confirm the composition of the synthesized compounds.

2.2 General Procedure for the Synthesis of Thioflavone Derivatives

The synthesis of substituted thioflavone derivatives was carried out through the condensation and cyclization reaction of *o*-thioacetophenone with substituted benzoyl chlorides under basic conditions.

A mixture of *o*-thioacetophenone (0.01 mol) and substituted benzoyl chloride (0.01 mol) was dissolved in 30–40 mL of absolute ethanol in a 100 mL round-bottom flask equipped with a reflux condenser and magnetic stirrer. The reaction mixture was stirred continuously to obtain a homogeneous solution.

To the above solution, 10 mL of aqueous sodium hydroxide solution (10%) was added dropwise with constant stirring while maintaining the reaction temperature below 10°C using an ice bath. The slow addition of alkali was necessary to control the exothermic nature of the reaction and to facilitate the formation of the intermediate chalcone-like thioketone derivative.

After complete addition of sodium hydroxide solution, the reaction mixture was refluxed at 70–80°C for 4–6 hours. During refluxing, the progress of the reaction was periodically monitored by thin-layer chromatography (TLC) using silica gel-G plates and a hexane:ethyl acetate solvent system (7:3). Appearance of a new spot corresponding to the desired product and disappearance of starting material confirmed completion of the reaction.

Under basic conditions, the active methylene group of *o*-thioacetophenone undergoes nucleophilic attack on the carbonyl carbon of substituted benzoyl chloride, followed by intramolecular cyclization and dehydration to afford the corresponding thioflavone derivative.

After completion of the reaction, the mixture was allowed to cool to room temperature and then poured slowly into crushed ice with vigorous stirring. The precipitated crude solid product was filtered under vacuum using a Büchner funnel and washed repeatedly with cold distilled water until free from alkali.

The crude product obtained was dried and purified by recrystallization from hot ethanol or methanol to yield pure substituted thioflavone derivatives as colored crystalline solids.

The purified compounds were dried in a vacuum desiccator over anhydrous calcium chloride and preserved in airtight containers for further characterization and analytical studies.

The synthesized thioflavone derivatives were characterized by melting point determination, infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (^1H NMR), and elemental analysis. The purity of the synthesized compounds was further confirmed by single spot formation on TLC plates.

2.3 Characterization

The synthesized thioflavone derivatives were characterized by physicochemical and spectroscopic techniques to confirm their structural identity, purity, and functional group composition.

2.3.1 Thin-Layer Chromatography (TLC)

The purity and progress of the reaction were monitored by thin-layer chromatography using silica gel-G coated aluminum plates. The solvent system hexane:ethyl acetate (7:3) was employed as the mobile phase for chromatographic separation. The developed chromatograms were visualized under ultraviolet light at 254 nm. The appearance of a single spot for each synthesized compound indicated the formation of pure thioflavone derivatives.

The retention factor (Rf) values of the synthesized compounds were calculated using the following relation:

$$\mathrm{Rf} = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

2.3.2 Melting Point Determination

The melting points of all synthesized thioflavone derivatives were determined by the open capillary tube method using a digital melting point apparatus and are reported as uncorrected values. The sharp melting point range of the purified compounds confirmed their purity and crystalline nature.

2.3.3 Infrared Spectral Analysis (FT-IR)

Infrared spectra of the synthesized compounds were recorded using potassium bromide (KBr) pellets on an FT-IR spectrophotometer within the range of 4000–400 cm^-1.

Characteristic absorption bands observed in the IR spectra confirmed the formation of thioflavone derivatives. The important spectral bands included:

- Aromatic C–H stretching vibrations near 3000–3100 cm^-1
- Carbonyl (C=O) stretching of the thioflavone ring around 1650–1685 cm^-1
- Aromatic C=C stretching vibrations near 1500–1600 cm^-1
- C–S stretching vibrations observed in the range 700–850 cm^-1
- C–Cl stretching bands for chloro-substituted derivatives around 760–800 cm^-1

The disappearance of characteristic bands corresponding to the starting materials and appearance of new carbonyl and sulfur-containing functional group absorptions confirmed successful cyclization and formation of thioflavone derivatives.

2.3.4 Proton Nuclear Magnetic Resonance (^1H NMR) Spectroscopy

The ^1H NMR spectra of synthesized compounds were recorded using $CDCl_3$ or DMSO-d_6 as deuterated solvents with tetramethylsilane (TMS) as the internal standard. Chemical shift values were expressed in δ ppm.

The aromatic protons of substituted phenyl rings appeared as multiplets in the region δ 6.8–8.2 ppm. The absence of signals corresponding to active methylene protons confirmed completion of cyclization. Substituted groups such as methoxy and methyl functionalities showed characteristic singlet peaks in their respective regions.

The observed chemical shifts and splitting patterns were consistent with the proposed structures of synthesized thioflavone derivatives.

2.3.5 Elemental Analysis

Elemental analysis for carbon, hydrogen, sulfur, and chlorine was carried out to determine the empirical composition of the synthesized compounds. The experimentally obtained values were found to be in close agreement with the calculated theoretical values, thereby confirming the proposed molecular structures.

2.3.6 Yield and Purity Assessment

The percentage yield of synthesized thioflavone derivatives was calculated after purification and drying using the following formula:

$$\%\,Yield = \frac{\text{Actual Yield}}{\text{Theoretical Yield}}\ x\ 100$$

The synthesized compounds were generally obtained in moderate to excellent yields with high purity after recrystallization.

3. Reaction Scheme

The synthesis of substituted thioflavone derivatives involves base-catalyzed condensation followed by intramolecular cyclization of *o*-thioacetophenone with substituted benzoyl chlorides.

Initially, the active methylene group present in *o*-thioacetophenone undergoes nucleophilic attack in the presence of sodium hydroxide, leading to the formation of an intermediate β-thioketone derivative. Subsequent intramolecular cyclization and dehydration result in the formation of the thioflavone nucleus.

The mechanism proceeds through the following major steps:

- Formation of carbanion from *o*-thioacetophenone in alkaline medium
- Nucleophilic acyl substitution with substituted benzoyl chloride
- Intramolecular cyclization
- Dehydration leading to thioflavone ring formation

The reaction pathway efficiently produces substituted thioflavone derivatives with good yields and minimal side reactions under controlled experimental conditions.

4. Results and Discussion

The developed synthetic method successfully yielded a series of substituted thioflavone derivatives with satisfactory yields. The reaction proceeded smoothly under mild reaction conditions and afforded products with good purity.

The presence of electron-donating and electron-withdrawing substituents on the aromatic ring influenced the reaction rate and product yield. Electron-withdrawing substituents such as chloro and nitro groups generally increased the reaction efficiency, whereas electron-donating groups slightly reduced the reaction rate.

IR spectra of the synthesized compounds showed characteristic absorption bands corresponding to carbonyl (C=O) stretching near 1650–1680 cm^-1 and aromatic C–S stretching vibrations. The ^1H NMR spectra confirmed the presence of aromatic protons and substituted phenyl groups in the synthesized molecules.

The proposed method demonstrated several advantages:

- Simple experimental procedure
- Mild reaction conditions
- Good product yields
- Easy purification
- Reduced reaction time

These features make the present method suitable for the synthesis of structurally diverse thioflavone derivatives.

5. Conclusion

An efficient and convenient method for the synthesis of substituted thioflavone derivatives has been successfully developed using benzoyl chloride and *o*-thioacetophenone. The reaction offers good yields, operational simplicity, and mild reaction conditions. The synthesized compounds were successfully characterized using standard analytical techniques. The present methodology may prove useful for the preparation of biologically active sulfur-containing heterocyclic compounds and can be further explored for pharmaceutical applications.

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