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A Modified Method for the Synthesis of Thiopheneacetic Acid Derivatives from Aromatic Thioamides

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Abstract. *Thiophene derivatives are of significant importance in medicinal chemistry owing to their broad spectrum of biological and pharmacological activities. However, the preparation of thiopheneacetic acid derivatives via existing methods remains challenging, typically requiring multiple synthetic steps, harsh conditions, and prolonged reaction times. In this study, a modified and efficient method for the synthesis of thiopheneacetic acid scaffolds is presented. The target compounds were prepared from the reaction of aromatic thioamides possessing an active methylene group with β-bromo-β-aroylpropionic acids in DMF at 90 °C. The optimal reaction conditions, including solvent, temperature, base amount, and molar ratio of starting materials, were systematically investigated to maximize efficiency. Under the optimized conditions, a series of structurally diverse thiopheneacetic acid derivatives were synthesized in good isolated yields (62–80%) within short reaction times (60 min). The progress of the reactions and the purity of the synthesized products were successfully monitored and confirmed using thin-layer chromatography (TLC) and melting point measurements. This method offers a straightforward and practical approach to thiopheneacetic acids, providing advantages over conventional multi-step protocols in terms of operational simplicity and reduced reaction time. The improved synthetic efficiency aligns with the principles of green chemistry and SDG 12 (Responsible Consumption and Production).*

Keywords: *Thiopheneacetic Acid; Thioamide; B-Bromo-B-Aroylpropionic Acid; Green Chemistry; Anti-Inflammatory; Analgesic*

1. Introduction

Thioamides are of significant importance in medicinal chemistry owing to their broad spectrum of biological activities, including antibacterial, antifungal, and herbicidal properties *(Sarkis & Faisal, 1985)*. For instance, the compound Tritiozine acts as an analgesic and gastric acid antisecretory agent *(Schroeder, 1955) (Figure 1)*. Furthermore, thioamides serve as valuable and versatile synthons in the construction of five- and six-membered heterocycles, as well as in the development of anion sensors *(Martínez-Máñez & Sancenón, 2003)*.

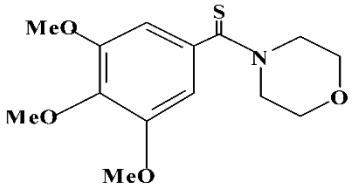


Figure 1. Chemical structure of Tritiozine, an analgesic and gastric acid antisecretory agent *(Schroeder, 1955)*.

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Thiophenes constitute an important class of heterocycles with diverse properties and applications. They exhibit a wide range of biological activities, including anti-inflammatory, antimicrobial, and antifungal properties *(Taylor & Dowling, 1997)*. Furthermore, certain thiophene derivatives are recognized as antibiotics and anti-allergic agents, while polythiophenes have found extensive applications in recent years, particularly in biosensors, gas sensors, organic transistors, and solar cells *(Baudry et al., 1993) (Figure 2)*.

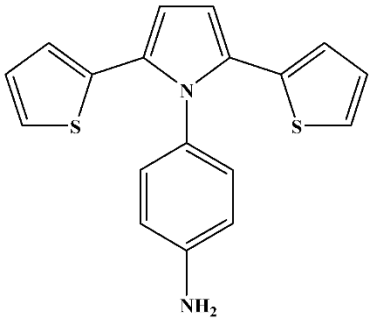


Figure 2. Chemical structure of di(thiophen-2-yl)-1H-pyrrol-1-yl phenylamine *(Baudry et al., 1993)*.

2. Methods

2.1. Materials and Instrumentation

All materials and solvents used in this study were purchased from Merck, Fluka, and Aldrich and were used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard; $CDCl_3$ and DMSO-d_6 were used as solvents. Mass spectra were obtained on a Micromass Platform II mass spectrometer at 70 eV using the electron impact (EI) ionization method. Melting points were determined on a Stuart Scientific SP2 melting point apparatus and are reported uncorrected.

2.2. Separation and Identification of Products

Thin-layer chromatography (TLC) plates containing a fluorescent indicator active at 254 nm (Merck) were used to monitor the progress of the reactions. For the separation and purification of the products, recrystallization from an appropriate solvent was employed, and in some cases, column chromatography on neutral silica gel (Merck) was used.

2.3. Synthesis of Thioamides Containing Active Methylene

In a 100 mL round-bottom flask equipped with a magnetic stirrer and a condenser, a mixture of aldehyde (50 mmol), sulfur (70 mmol, 2.24 g), and morpholine (150 mmol, 13 mL) was prepared. The reaction mixture was stirred at 130 °C for 5 h. The progress of the reaction was monitored by TLC. After completion, the mixture was cooled to 70 °C. The contents were then transferred to a 100 mL beaker containing 40 mL of methanol. After 2 h, the precipitated thioamide crystals were filtered, washed with cold methanol (10 mL), and the pure thioamides were obtained in good to excellent yields (73–94%). The Willgerodt–Kindler reaction was employed for the synthesis of thioamides *(Sarkis & Faisal, 1985)*. A notable feature of this method is that the resulting products are solid and can all be recrystallized from methanol in high yield *(Figure 3)*.

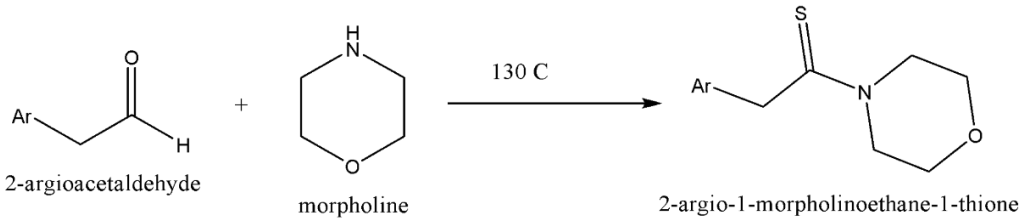
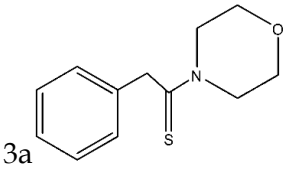
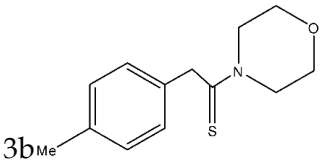
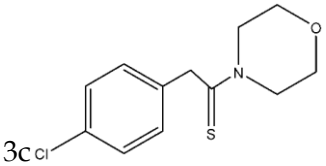


Figure 3. Synthesis of thioamides bearing an active methylene group via the Willgerodt–Kindler reaction *(Sarkis & Faisal, 1985).*

Table 1. Synthesis of thioamides bearing an active methylene group via the Willgerodt–Kindler reaction.[a]

Entry	Ar	Product	Yield (%)
1	Ph	 3a	94
2	4-Tolyl	 3b	91
3	4-ClC_6H_4	 3c	73

[a] Reaction conditions: aldehyde (50 mmol), sulfur (70 mmol), morpholine (150 mmol), 130 °C, 5 h.

2.4. Synthesis of Acidic Precursors: Benzoyl Propionic Acid and Toluoyl Propionic Acid

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirrer and a condenser, a mixture of succinic anhydride (68 mmol, 6.8 g) and arene (benzene or toluene, 236 mmol) was prepared. Then, aluminum trichloride (150 mmol, 20 g) was added to the flask. The reaction mixture was stirred at 100 °C for 30 min. The temperature was then lowered using an ice bath, and cold water was added dropwise. Subsequently, steam distillation was performed. After distillation, the contents of the flask were decanted. To the decanted liquid, a drop of concentrated hydrochloric acid was added, and the resulting white precipitate was filtered and dried. To the solid remaining from the decantation, 150 mL of water and 35 g of sodium carbonate were added, and the mixture was stirred at 100 °C for 3 h. The mixture was then filtered, and the filter cake was washed with boiling water (2 × 10 mL). To the filtrate, 1 mL of concentrated hydrochloric acid was added, and the resulting white precipitate was filtered, dried, and combined with the precipitate from the previous step to afford the acidic precursors as white solids. Due to the lengthy and multi-step nature of the reaction pathway, the obtained products were isolated in moderate yields *(Figure 4).*

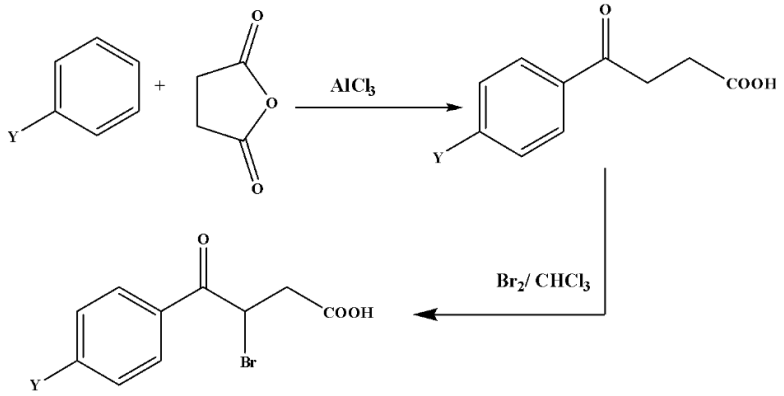
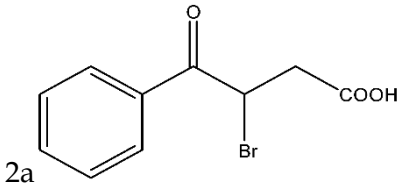
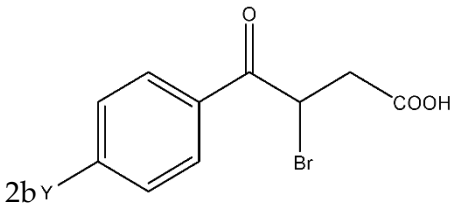


Figure 4. Synthesis of the acidic precursors *(Martínez-Máñez & Sancenón, 2003).*

Table 2. Synthesis of the acidic precursors. [b]

Entry	Product	Yield (%)
1	H  2a	59
2	Me  2b	52

[b] Reaction conditions: succinic anhydride (68 mmol), arene (236 mmol), $AlCl_3$ (150 mmol), 100 °C, 30 min.

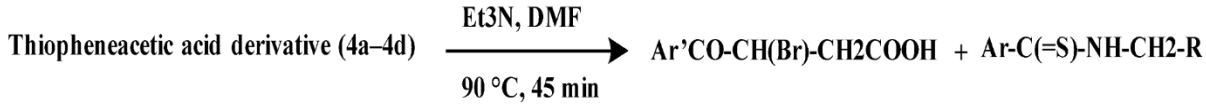
2.5. Synthesis of β-Bromo-β-aroylpropionic Acids

The β-bromo-β-aroylpropionic acid derivatives (β-bromo-β-benzoylpropionic acid and β-bromo-β-toluoylpropionic acid) used as electrophilic precursors in this study were prepared according to a previously reported standard bromination procedure *(Jios et al., 2006)* with minor modifications, or were obtained from commercial sources and used without further purification. Specifically, the corresponding benzoylpropionic or toluoylpropionic acid (2a–2b) was treated with bromine (Br_2) in an appropriate solvent under controlled conditions to afford the desired brominated precursors. The completion of the bromination step was monitored by TLC, and the structures were confirmed by their melting points and spectral data prior to use in the subsequent cyclization step.

2.6. General Procedure for the Synthesis of Thiopheneacetic Acids (4a–4d)

In a 25 mL round-bottom flask equipped with a magnetic stirrer and a condenser, a mixture of thioamide **1** (1 mmol) and DMF (1.5 mL) was prepared. While the mixture was stirred vigorously at 90 °C, the acidic precursor **2** (β-bromo-β-aroylpropionic acid, 1 mmol) was gradually added. The reaction mixture was stirred for 45 min at 90 °C. Subsequently, triethylamine (1 mmol, 0.14 mL) was added, and the mixture was stirred for an additional 15 min at 90 °C. The progress of the reaction was monitored by TLC. After completion, the mixture was cooled to room temperature, dissolved in ethyl acetate (10 mL), and the organic

phase was washed with water (2 × 10 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on neutral silica gel using an ethyl acetate/hexane mixture (8:1, v/v) as the eluent to afford the pure thiopheneacetic acid derivatives **4a–4d** in 62–80% isolated yields.



3. Results and Discussion

3.1. Synthesis of Thiopheneacetic Acids from Thioamides Bearing an Active Methylene Group

3.1.1. Optimization of the Reaction Solvent

To determine the optimal solvent, the reaction of thioamide 1 with the acidic precursors (β-bromo-β-benzoylpropionic acid and β-bromo-β-toluoylpropionic acid) was investigated in various solvents at 90 °C. As shown in Table 3, the reaction proceeded with the highest conversion in DMF (88%) after 60 min, compared to toluene, DMSO, and isopropanol. Therefore, DMF was selected as the optimal solvent for further optimization steps *(Figure 5)*.

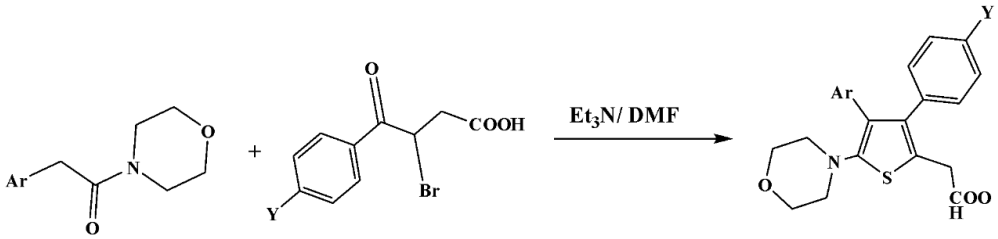


Figure 5. Synthesis of thiopheneacetic acids *(Jios et al., 2006)*.

Table 3. Effect of solvent on the reaction of thioamide with the acidic precursor.[c]

Entry	Solvent	Conversion (%) in 60 min
1	Toluene	31
2	DMSO	39
3	Isopropanol	42
4	DMF	88

[c] Reaction conditions: thioamide (1 mmol), acidic precursor (1 mmol), triethylamine (1 mmol), 90 °C.

3.1.2. Optimization of the Reaction Temperature

To determine the optimal temperature, the reaction of thioamide 1 with the acidic precursors in DMF was investigated at various temperatures. As presented in Table 4, at temperatures below 90 °C, the reaction did not proceed significantly; however, at 90 °C, the reaction reached 92% conversion. Increasing the temperature to 100 °C did not improve the conversion. Therefore, 90 °C was selected as the optimal temperature for all subsequent reactions.

Table 4. Effect of temperature on the reaction of thioamide with the acidic precursor in DMF.[d]

Entry	Temperature (°C)	Conversion (%) in 60 min
1	60	37
2	70	54
3	80	81
4	90	92
5	100	92

[d] Reaction conditions: thioamide (1 mmol), acidic precursor (1 mmol), DMF (1.5 mL), triethylamine (1 mmol).

3.1.3. Optimization of the Amount of Triethylamine

To determine the optimal amount of triethylamine, the reaction was investigated in DMF at 90 °C using different amounts of triethylamine. The results are summarized in(*Table 5)*.
When a 0.25:1 ratio of triethylamine to thioamide was used, the reaction did not proceed significantly. However, a considerable improvement was observed with increasing amounts of triethylamine. When a 1:1 ratio was employed, the reaction reached 92% conversion. Consequently, 1 mmol of triethylamine per 1 mmol of thioamide was used in the remaining reactions.

Table 5. Effect of triethylamine amount on the reaction of thioamide with the acidic precursor in DMF.[e]

Entry	Triethylamine (mmol)	Conversion (%) in 60 min
1	0.25	46
2	0.5	59
3	0.75	78
4	1	92
5	1.25	92

[e] Reaction conditions: thioamide (1 mmol), acidic precursor (1 mmol), DMF (1.5 mL), 90 °C.

3.1.4. Optimization of the Amount of Thioamide

To determine the optimal amount of thioamide, the reaction was investigated in DMF in the presence of triethylamine using different amounts of thioamide. As shown in (*Table 6*) when a 0.25:1 ratio of thioamide to the acidic precursor was used, the reaction did not proceed significantly; however, with increasing amounts of thioamide, a considerable improvement was observed. When a 1:1 ratio was employed, the reaction was completed within 60 min. Therefore, 1 mmol of thioamide per 1 mmol of the acidic precursor was used for the remaining reactions.

Table 6. Effect of thioamide amount on the reaction with the acidic precursor in DMF.[f]

Entry	Thioamide (mmol)	Yield (%)
1	0.25	31
2	0.5	53
3	0.75	77
4	1	82
5	1.25	78

6	1.5	59

[f] Reaction conditions: acidic precursor (1 mmol), DMF (1.5 mL), triethylamine (1 mmol), 90 °C, 60 min.

3.1.5. Synthesis of Thiopheneacetic Acids from Thioamides Bearing an Active Methylene Group

After optimizing the reaction conditions, the reaction of thioamides bearing different substituents with the acidic precursors was carried out according to the general procedure (Section 2.6) in DMF at 90 °C. Finally, upon the addition of triethylamine, the reaction was completed. The results indicate that under these conditions, thiopheneacetic acid derivatives 4a–4d were obtained in good isolated yields (62–80%) within a short reaction time, as summarized in Table 7. The completion of the reactions was monitored by TLC, and the purity of the final products was confirmed by their sharp melting points, which were consistent with the expected structures.

Table 7. Synthesis of thiopheneacetic acid derivatives (4a–4d) via the reaction of thioamides with acidic precursors.[g]

Entry	Ar	Y	Product	Yield (%)
1	Ph	H	4a	80
2	Ph	Me	4b	78
3	4-Tolyl	H	4c	76
4	4-Tolyl	Me	4d	62

[g] Reaction conditions: thioamide (1 mmol), acidic precursor (1 mmol), DMF (1.5 mL), triethylamine (1 mmol), 90 °C, 45 min.

3.2. Proposed Mechanism for the Synthesis of Thiopheneacetic Acids

A plausible mechanism involves the initial deprotonation of the thioamide 1 by triethylamine to form a reactive anion, which then attacks the α-bromo ketone 2 via an SN^2 pathway in DMF at 90 °C, giving a linear β-keto thioamide intermediate. Subsequent intramolecular cyclization and dehydration afford the fully conjugated thiophene ring, yielding the final thiopheneacetic acid derivatives 4a–4d (Figure 6).

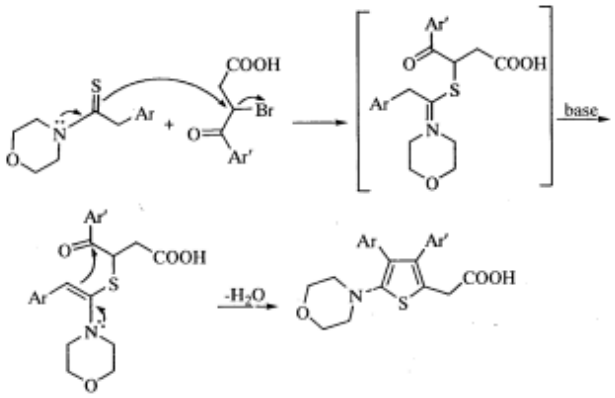


Figure 6. Scheme of Proposed mechanism for the synthesis of thiopheneacetic acids from aromatic thioamides.

Conclusions

In this study, a modified and efficient method was developed for the synthesis of thiopheneacetic acid derivatives from simple thioamides. The present method addresses the limitations of conventional multi-step procedures by employing a straightforward protocol that proceeds smoothly in DMF at 90 °C in the presence of triethylamine as a base. Under the optimized conditions, a series of structurally diverse thiopheneacetic acid derivatives (**4a–4d**) were obtained in good isolated yields (62–80%) within short reaction times. The proposed mechanism involves the deprotonation of the thioamide, an SN^2 attack on the α-bromo ketone, intramolecular cyclization, and subsequent dehydration/aromatization to form the fully conjugated thiophene ring.

This protocol offers several notable advantages over previously reported methods, including: (1) significantly reduced reaction time; (2) operational simplicity in workup and product isolation; (3) mild reaction conditions; and (4) good to excellent product yields. Although the use of DMF and triethylamine presents some environmental limitations compared to ideal green solvents, the improved synthetic efficiency (fewer steps and reduced time) aligns with the principles of Green Chemistry and **SDG 12 (Responsible Consumption and Production)** by minimizing energy consumption and chemical waste. The synthesized compounds serve as promising scaffolds for further pharmacological evaluation, given the well-documented biological properties of thiophene-based derivatives. Overall, this work provides a practical and efficient synthetic strategy for the preparation of thiopheneacetic acids from readily available starting materials.

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Conflicts of Interest

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the result.

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