International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 871-875 www.ijprajournal.com ISSN: 2456-4494

Synthesis of thiophene and Their Pharmacological Activity

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Date of Submission: 20-03-2025 Date of Acceptance: 30-03-2025

ABSTRACT

Thiophene is a five-membered heterocyclic compound, has garnered significant attention in pharmaceutical research due to its diverse pharmacological activities . This review focuses on the effective thiophene synthesis techniques, such as Fishwicksynthesis, Gewald synthesis, and the microwave-assisted Paal-Knorr reaction. Strong biological actions, including antibacterial, anti-inflammatory, anticancer, and effects on the central nervous system (CNS), are exhibited by the produced thiophene derivatives. Particularly, thiophene-based substances have demonstrated promise in the treatment of anxiety, depression, sedative-hypnotics, and psychoses.

Keywords:-: Thiophene, synthesis, pharmacological activities, antimicrobial, anti-inflammatory, anticancer, CNS effects

I. INTRODUCTION:-

Thiophene, which has the formula C4H4S, is a heterocyclic molecule having a planar five-membered ring. These are frequently utilized as building blocks in a variety of medications and agrochemicals. It is a white liquid that smells like benzene. It is similar to benzene in the majority of its reactions. In 1882, Viktor Meyer identified thiophene as a contaminant in benzene. Despite this, most people believe it smells like benzene. [1]One sulfur heteroatom makes up the five-membered ring of the favored heterocycle thiophene. Essential heterocyclic compounds, thiophene and its derivatives exhibit a wide range of characteristics and uses. Thiophene derivatives are used as corrosion inhibitors in material science and industrial chemistry. [2]

Thiophene and its derivatives exhibit various pharmacological activities:

1.Cancer

Cancer is a leading cause of death and its rate has been increasing[3].Heterocyclic compounds, including thiophene derivatives, indole, and thiazolone, have attracted considerable attention due to their antitumor activities

1. Antitumor: Thiophene derivatives (e.g., thiophene-2-carboxylic acid) against cancer cells .

2. Central Nervous System (CNS)

1. Antipsychotic: Thiophene derivatives (e.g., olanzapine) for schizophrenia.
2. .Antidepressant:Thiophene-based compounds (e.g., duloxetine) for depression.
3. Anxiolytic: Thiophene derivatives (e.g., tiapride) for anxiety.
4. Sedative-hypnotic: Thiophene-based compounds (e.g., thiopental) for sedation.

3. Infectious Diseases

1. Antibacterial: Thiophene derivatives (e.g., cefotiam) against bacteria. [4-5]
2. Antiviral: Thiophene-based compounds (e.g., thiophene-2-carboxylic acid) against viruses.
3. Antifungal: Thiophene derivatives (e.g., thiophanate-methyl) against fungi.

4. Pain and Inflammation

1. Analgesic: Thiophene derivatives (e.g., thiophenol) for pain relief.
2. Anti-inflammatory: Thiophene-based compounds (e.g., tiaprofenic acid) for inflammation [6]

5. Cardiovascular System

1. Antiarrhythmic: Thiophene derivatives (e.g., thiopental) for arrhythmias.
2. Vasodilator: Thiophene-based compounds (e.g., thiophene-2-carboxylic acid) for blood pressure.

6. Other Activities

1. Thiophene and its derivatives are well known for their anti-inflammatory properties, but they also have unintended side effects. We were able to control the activation of this

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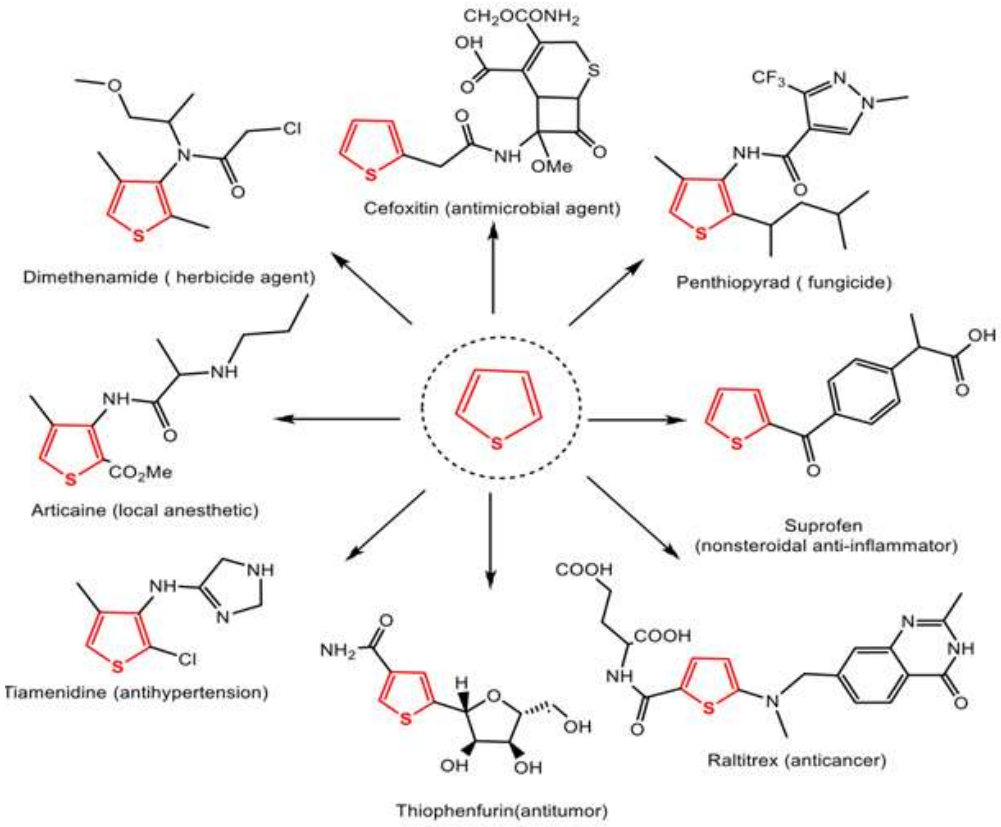
biologically active molecule by substituting it to the subpc structure. Thiophene-based compounds modulate immune responses.

2. They are antioxidants: They scavenge free radicals.
3. They are anti-diabetic: Thiophene derivatives (such as thiophene-2-carboxylic acid) treat diabetes.
4. They are immunomodulatory.

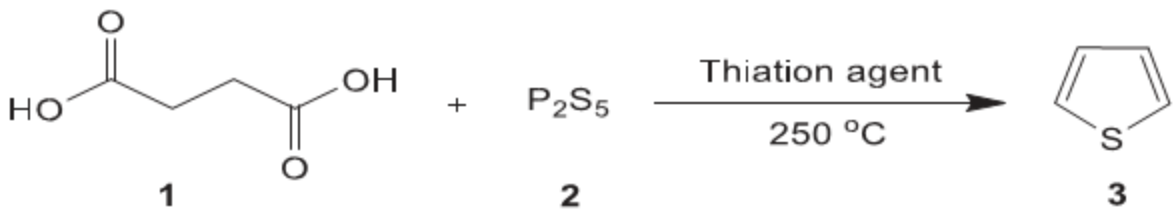


Scheme 1: Structures of important thiophene

SYNTHETIC METHODS FOR THE FORMATION OF THIOPHENE

1. Paal–Knorr synthesis

The reaction of dicarbonyl compounds with phosphorus pentasulphide (P2S5) was considered as a principal route to synthesize thiophenes.[38] Succinic acid could be reacted with P2S5 in presence of thiation agents such as Lawesson's reagentor 1,1,1,3,3,3hexamethyldisilathiane ((Me3Si)2S)[8] to give thiophene (3) (Scheme 2)



Scheme 2. Synthesis of 3-methylthiophene (3)

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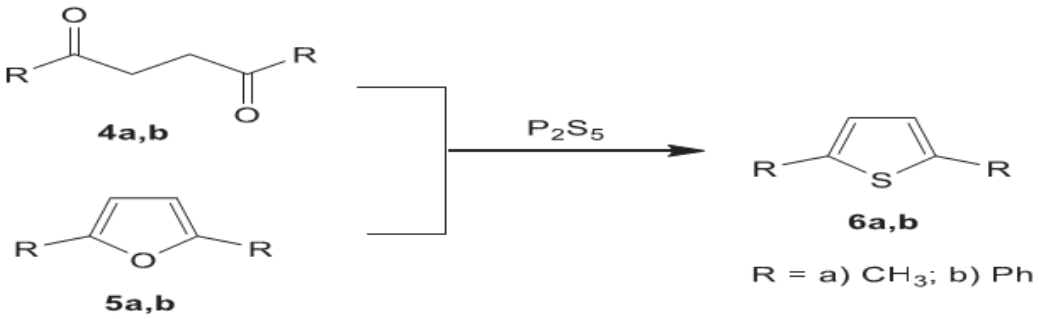
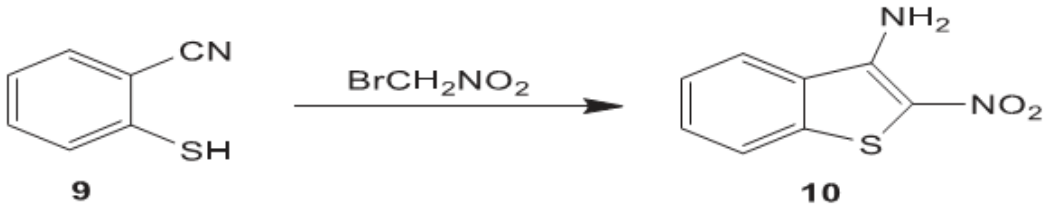
Reactions utilizing the diketones (i.e., thiophenes, 2,5-hexanedione (4a) and/or 1,2dibenzoylethane (4b)) give higher yield of corresponding 2,5-thiophene (6a, b) than the reactions of 2,5-dimethyl furan (5a) and/or 2,5-diphenyl furan (5b) with P2S5 under the Paal–Knorr thiophene synthesis conditions (Scheme 3)[9]



Scheme 3. Synthesis of 2,5-disubstituted thiophene (6a, b).

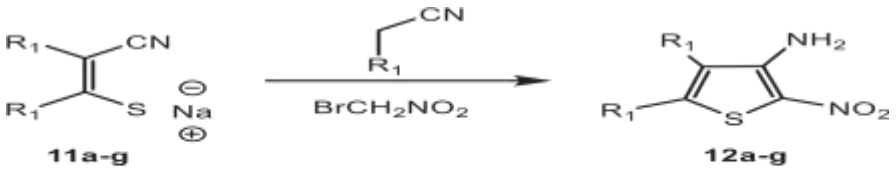
2. FISHWICK SYNTHESIS

Fishwick et al. described the preparation of 3-amino-2-nitrobenzo[b]thiophene (10) starting from 2-sulfanyl benzonitrile (9) and bromonitromethane (BNM) as depicted by Scheme 4[10]



Scheme 4. Synthesis of 3-amino-2-nitrobenzo[b]thiophene (10)

Synthesis of some 3-amino-2-nitrothiophenes (12a–g) started from the sodium salt of disubstituted 3-sulfanyl-2-propenenitriles (11a–g) and BNM, was also reported in yields ranging from 30 to 70% (Scheme 5)[11]



12	R_1	R_2
a	COOEt	NHPh
b	CN	NHPh
c	COOEt	SMe
d	CN	SMe
e	CONH	SMe
f	COOEt	NHMe
g	$PhSO_2$	NHPh

Scheme 5. Synthesis of 3-amino-2-nitrothiophenes (12a–g).

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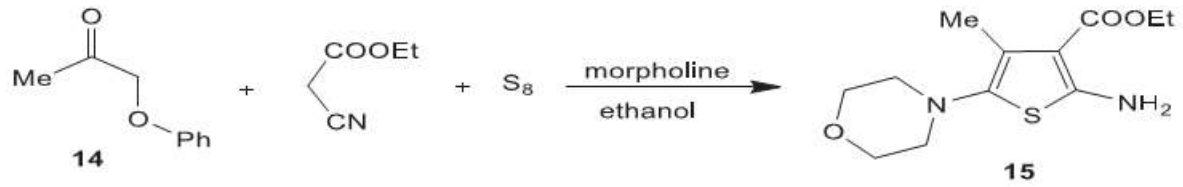
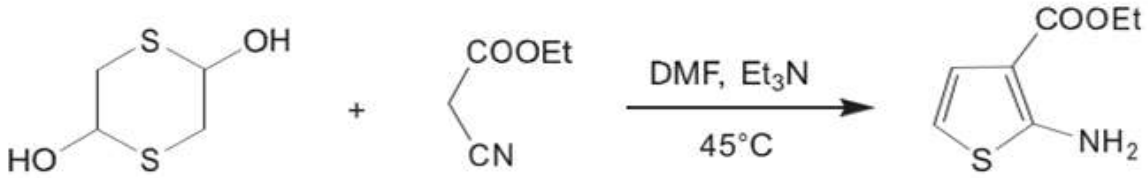
3.GEWALD SYNTHESIS

The introduction of 5-aryloxy alternative into 2-amino-3-ethyl acetate thiophene ring leads to the discovery of an unexpected transformation. The reaction of phenoxyacetone (15) with ECA and sulfur in the presence of morpholine, results not in the 5-phenoxythiophene but in 5-morpholinothiophene (16) in 21% yield as shown as by Scheme6[12]



Scheme 6. Synthesis of 5-morpholinothiophene (15).

The corresponding 2-amino thiophene-3-carboxylic acid ethyl ester (14a) has been prepared by another modified Gewald reaction through the base-catalyzed reaction with 2,5-dihydroxy-1,4-dithiane (17) and ECA (Scheme 7).[13,14,15]



Scheme 7. Synthesis of 2-aminothiophene-3-ethyl acetate (14a).

II. CONCLUSION

Thiophenes are important due to their many applications in pharmacology, industry, material science, and other fields. The thiophene ring was synthesized from non-heterocyclic substrates using two different chemical pathways. Sulfur is added to the entire carbon skeleton using the first technique, which uses substituted open-chain precursors. The first method involves using substituted open-chain precursors to add sulfur to the whole carbon skeleton. The best option for producing the thiophene nucleus and its derivative is Gewald's synthetic technique.

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