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Synthesis, properties and biological activity of thiophene: A review

Raghav Mishra*, K.K. Jha, Sachin Kumar, Isha Tomer

College of Pharmacy, Teerthankar Mahaveer University, Delhi Road, Moradabad(UP), India

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ABSTRACT

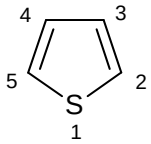
Thiophene nucleus has been established as the potential entity in the largely growing chemical world of heterocyclic compounds possessing promising pharmacological characteristics. The similar compounds synthesized through different routes bear variable magnitudes of biological activities. The knowledge of various synthetic pathways and the diverse physicochemical parameters of such compounds draw the especial attention of medicinal chemists to produce combinatorial library and carry out exhaustive efforts in the search of lead molecules. The present review provides a broad view of the synthesis and properties of compounds having thiophene nucleus.

Keywords Heterocycles, Thiophene: Synthesis, Properties, Biological Activity.

INTRODUCTION

As the world's population increases and health problems expand accordingly, need to discover new therapeutics will become even more diring. The design of drug molecules arguably offers some of the greatest hopes for success in present and future era. Heterocyclic compounds are widely distributed in nature and are essential for life. There are vast numbers of pharmacologically active heterocyclic compounds many of which are in regular clinical use[1]. The investigational approaches towards Structure- Activity Relationship focusing the search of optimized candidates have become immensely important.

Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulphur as heteroatom with the formula C_4H_4S. Thiophene and its derivatives exist in petroleum or coal. Thiophene is taken from the word *theion*, the Greek word for sulfur, and another Greek word *phaino* which means shinning. Thiophene structure can be found in certain natural products and is also incorporated in several pharmacologically active compounds.



Thiophene

In medicinal chemistry, thiophene derivatives have been very well known for their therapeutic applications. The simple thiophenes are stable liquids which closely resemble the corresponding benzene compounds in boiling point and even in smell[2]. They occur in coal tar distillates. The discovery of thiophene in coal tar benzene provides one of the classic anecdotes of organic chemistry.

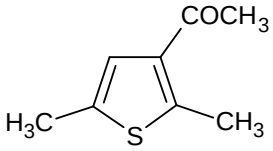
Thiophene was discovered as a contaminant in benzene[3]. It was observed that isatin (1H-indole-2, 3- Dione) forms a blue dye if it is mixed with sulfuric acid and crude benzene. Victor Meyer was able to isolate the substance responsible for this reaction. The compound was found to be a heterocyclic compound- Thiophene.

Thiophene has a structure that is analogous to structure of pyrrole, and due to pie electron cloud, it behave like extremely reactive benzene derivative.

A) ROUTES FOR THIOPHENE NUCLEUS FORMATION

A principal route to alkyl substituted thiophene is the reaction of a dicarbonyl compound with phosphorus pentasulphide[4].

An alternative route that has been used is the Friedel- Crafts acylation followed by Wolff-Kishner reduction. Thiophene acylate preferentially in the α-position and thus 2-acyl-5-alkylthiophenes can also be accessed by this route from 2-alkyl thiophenes. When both α-positions are alkyl substituted, acylation occurs in the β-position to produce 3-acyl-2, 5-dialkylthiophenes such as 2, 5-dimethyl- 3-acetylthiophene **(1)**.



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Synthetic approaches to the construction of thiophene and substituted thiophene have been efficiently developed. Thiophene ring can be constructed from non-heterocyclic precursors by two reaction pathways[5]:

1. Construction of thiophene ring from appropriately substituted open chain precursors:
This method involves the introduction of sulphur into a starting material containing the complete carbon skeleton.
2. The functionalization at the positions α and β to the sulphur atom of the preconstructed thiophene nucleus:

This method employ either the reaction of a mercaptoacetate with a 1, 3-dicarbonyl compound or the reaction of a thiodiacetate with a 1,2-dicarbonyl compound.

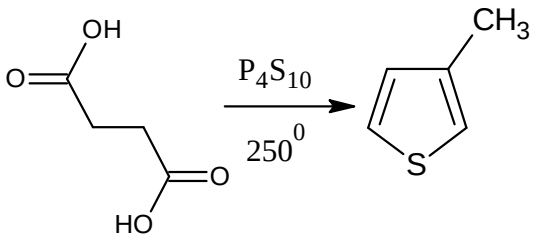
Depending upon the following reaction pathways, various synthetic procedures have been developed, leading to different substituted thiophene.

A.1.) MAJOR SYNTHETIC PROCEDURES

Well known or major synthetic procedure includes: Paal- Knorr Thiophene synthesis, Fiesselmann Thiophene synthesis Gewald Aminothiophene synthesis and Hinsberg Synthesis.

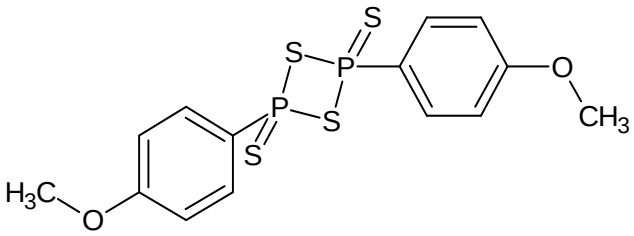
i) Paal- Knorr Thiophene Synthesis

This reaction is also known as Paal Thiophene Synthesis. 1, 4-Dicarbony1 compounds can be reacted with a source of sulfur to give thiophene.



Paal Thiophene Synthesis

Source of sulfur used are traditionally phosphorus sulfides, latterly Lawesson's reagent(LR)[6], or bis(trimethylsilyl) sulfide[7].

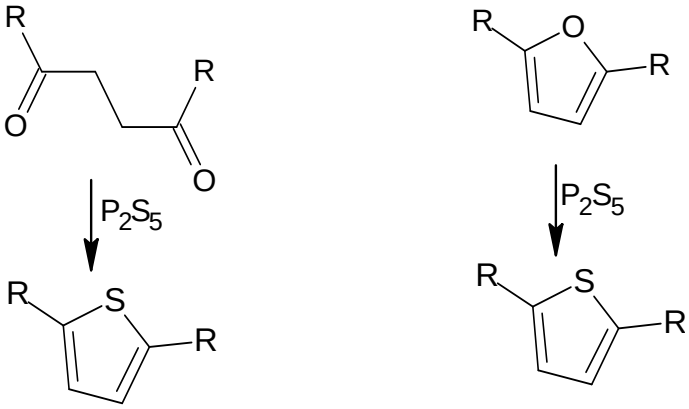


Lawesson's Reagent

Paal and Knorr individually described the initial examples of condensation reactions between 1, 4- diketones and primary amines, which became to known as the Paal- Knorr pyrrole synthesis[8]. The basic mechanism of this synthetic procedure involves cyclization of 1,4-diketones, either in the presence of a primary amine (Paal- Knorr pyrrole synthesis), in the presence of a sulphur source (Paal Thiophene synthesis), or by dehydration of the diketone itself (Paal Furan synthesis)[9].

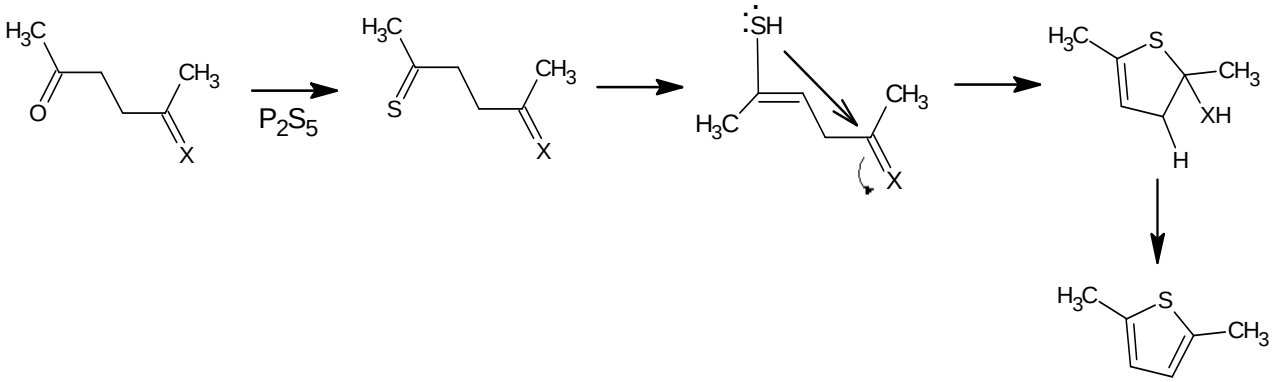
Reagents such as phosphorus pentasulfide or Lawesson's reagent act as sulfurizing agents as well as dehydrating agents, allowing a reaction pathway that could lead first to the formation of furans. This hypothesis was tested by Campaigne and coworkers in 1952. They were able to prove that Paal Thiophene Synthesis could not proceed via furan as intermediate. Instead it went through the formation of a thione. To prove this they conducted parallel experiments. Direct comparisons were made between the reactions of 2,5-hexanedione and 1,2- dibenzoylethane with

P_2S_5 and the reactions of 2,5-dimethylfuran and 2,5-diphenylfuran under the Paal Thiophene Synthesis conditions. Reactions utilizing the diketones provided a greater yield of the thiophene suggesting that the furan is not an essential intermediate in the reaction pathway, but rather a by-product[10].



R= CH_3	70% Yield	13% Yield
R= Ph	25% Yield	0 % Yield

Based on the above observations, it was proposed that the mechanism involves initial formation of thione (X = O or S), which is followed by tautomerization and cyclization. Aromaticity drives the facile elimination of either H_2O or H_2S resulting in the thiophene product.



Reaction mechanism involved in Paal Thiophene Synthesis

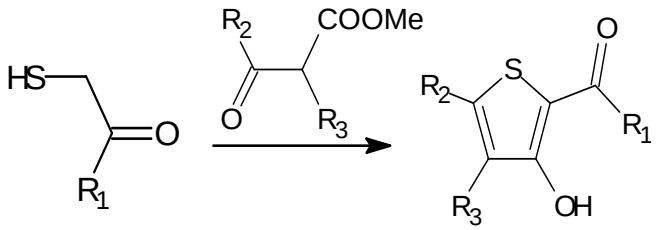
This synthetic method for thiophene had been subjected to considerable variations and improvements over time. The standard procedure for the Paal Thiophene Synthesis is to use phosphorus pentasulphide as the sulphur atom source. The product is always a mixture containing furan due to the dehydrating effect of P_2S_5 as an additional property.

A number of other reagents had been developed to take care of the sulphur source and dehydration. Hydrogen sulphide, in the presence of an acid catalyst, was found to be more efficient than phosphorus pentasulphide at converting ketones to thione.

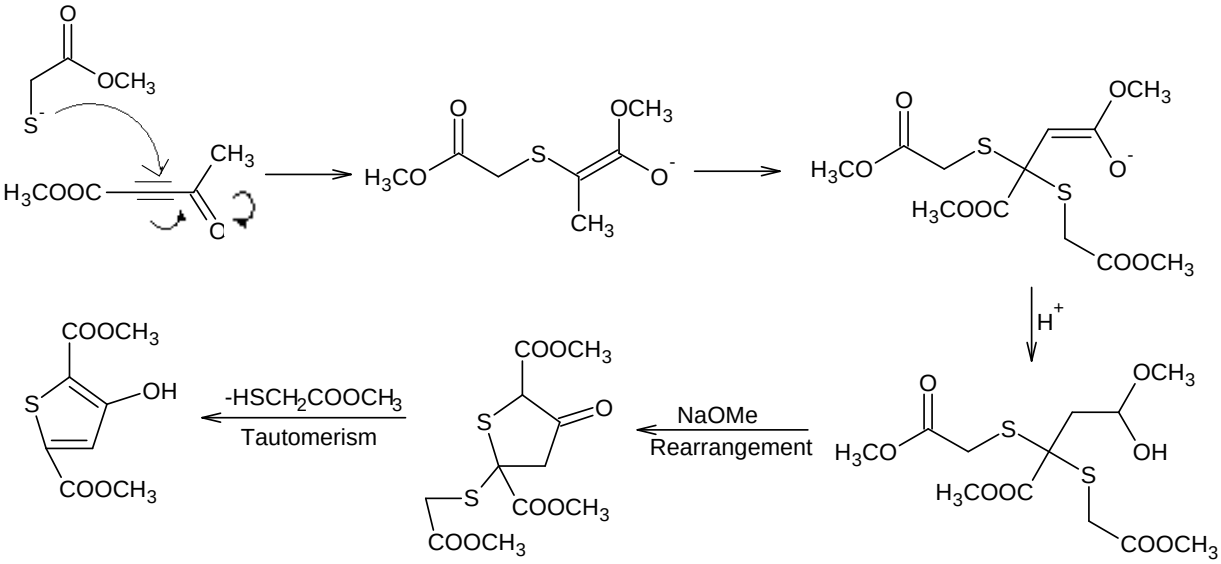
ii) Fiesselmann Thiophene Synthesis

Condensation reaction of thioglycolic acid with α, β- acetylenic esters, which upon treatment with base result in the formation of 3- hydroxyl- 2- thiophenecarboxylic acid[11].

Fiesselmann Thiophene Synthesis is an extension of Woodward condensation of thioglycolic acid[12] and α, β- unsaturated ester in the presence of base to produce 2-carbomethoxy-3-ketotetrahydrothiophene.



Fiesselmann Thiophene Synthesis proceeds through consecutive base-catalyzed 1, 4- conjugate addition reactions to form thioacetal. Treatment with stronger base results in the formation of an enolate while intramolecular reaction through Dieckmann condensation leads to the formation of a ketone. Eliminating methylthioglycolate and tautomerization propelled by aromaticity provides the 3-hydroxyl thiophene dicarboxylate.

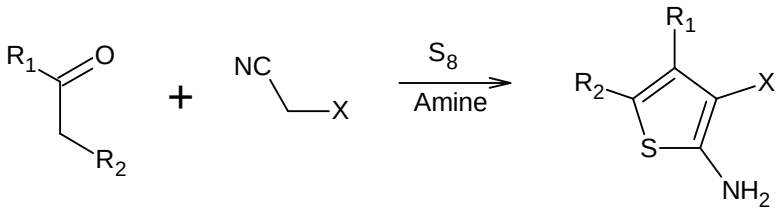


Reaction mechanism involved in Fiesselmann Thiophene Synthesis

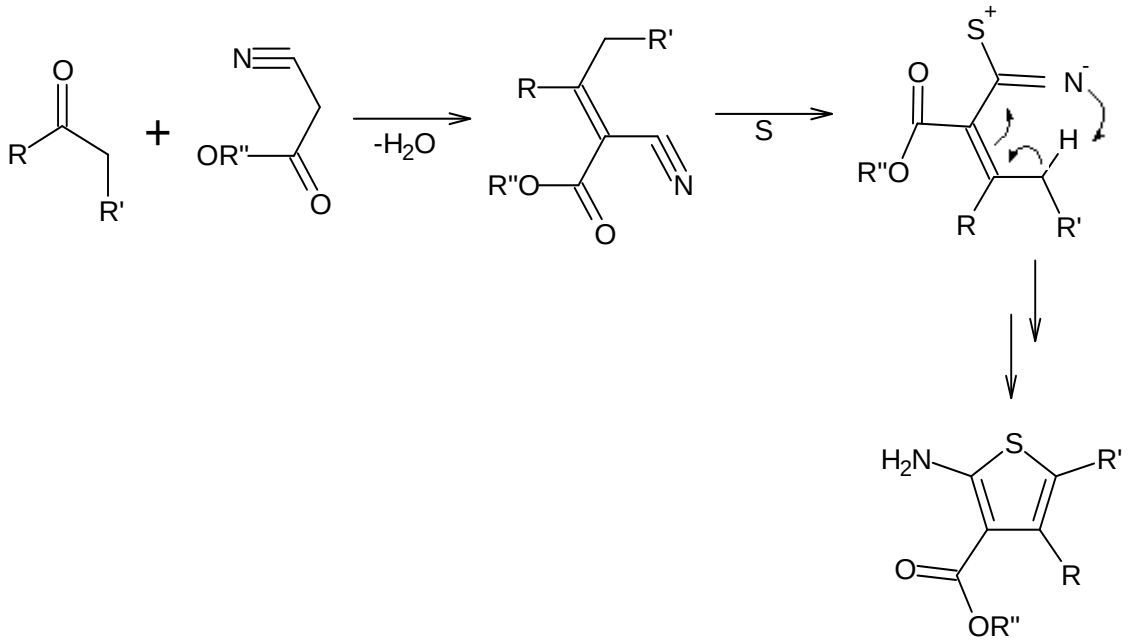
Therefore, thiophene can be synthesized from reactions of thioglycolic acid derivatives and β -keto esters, α, β -dihalo esters and α - and β -halovinyl esters, along with the corresponding nitriles, ketones and aldehydes. Furthermore, a variety of α-mercaptocarbonyl systems can be used in place of the thioglycolic acid derivatives and this extends the applicability of this reaction[9].

iii) Gewald Aminothiophene Synthesis

This method was reported by Gewald in 1966[13]. Gewald synthesis is the usual route to 2-aminothiophenes. It consists of the base-catalyzed condensation of a ketone having an a CH_2 group with a β-ketonitrile to form an olefin, followed by cyclisation with elemental sulfur.



The first step in the mechanism of the Gewald reaction is the Knoevenagel condensation of an activated nitrile with a ketone or aldehyde to produce an acrylonitrile. The product of this condensation is then thiolated at the methylene position. The sulfurated compound initially decays to the mercaptide compound which then undergoes a cyclization reaction via mercaptide attack at the cyano group. Base-catalyzed tautomerization affords the 2-aminothiophene[14].

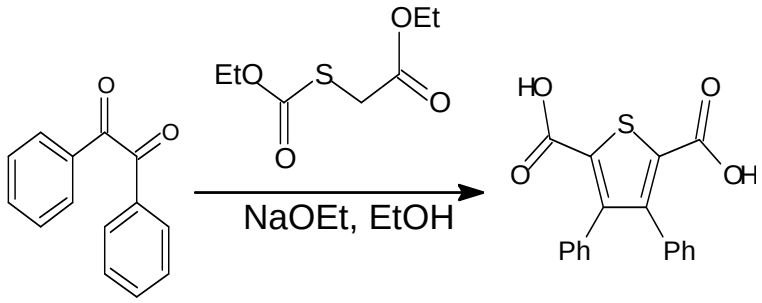


Reaction mechanism involved in Gewald Aminothiophene Synthesis

Gewald Aminothiophene reaction had been used to produce different substituted 2-aminothiophenes like 5-alkoxy-2- aminothiophene[15], 2,4-diaminothiophenes[16], 4-alkyl-2-aminothiophene[17] and 5-alkyl-2- aminothiophene[18].

iv) The Hinsberg Synthesis

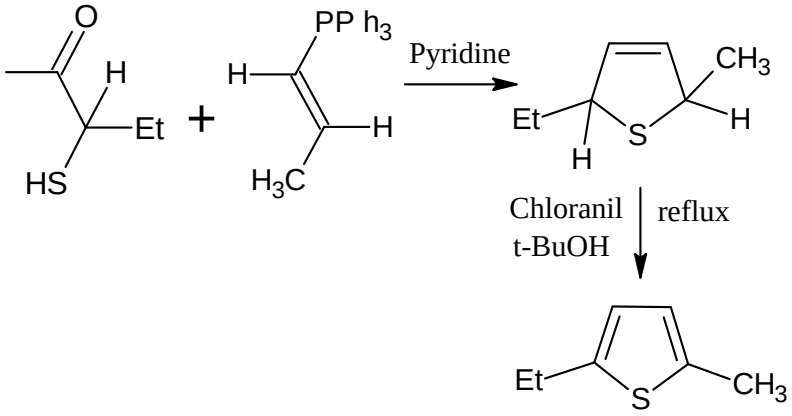
Two consecutive aldol condensations between a 1, 2-dicarbony1 compound and diethy1 thiodiacetates gives thiophene. The immediate product is an ester-acid produced[19] by a Stobbe-type mechanism but the reactions are often worked up via hydrolysis to afford an isolated diacid.



A.2.) GENERAL SYNTHETIC PROCEDURES

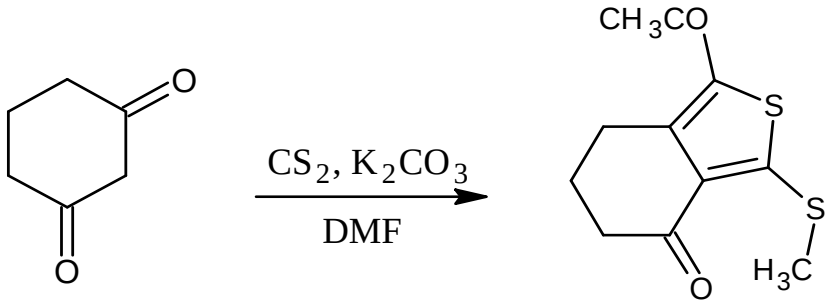
i) From thiocarbony1 compounds

2-Keto-thiols added to alkenyl phosphonium ions followed by ring closure via Witting reaction gives 2, 5-dihydrothiophenes which can be dehydrogenated[20].



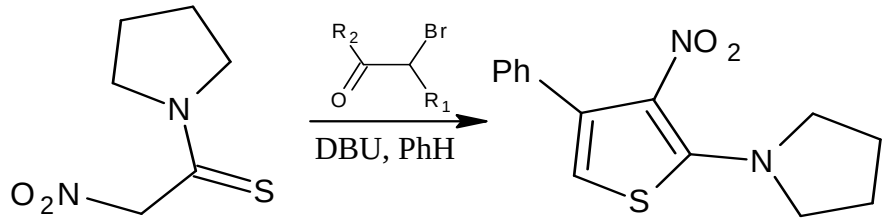
ii) Using carbon disulfide

2-alkylthiophenes[21] can be synthesized by the addition of a carbanion to carbon disulfide with a subsequent S-alkylation.



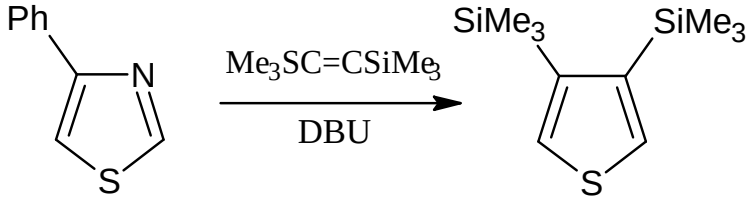
iii) From thio-nitroacetamides

The S-alkylation of thio-nitroacetamides with 2-bromoketones produces 2-amino-3-nitrothiophenes[22].



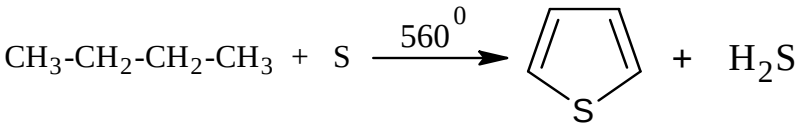
iv) From thiazoles

When thiazoles are heated strongly with an alkyne, generates 2, 5- unsubstituted thiophenes. Though the conditions are vigorous, excellent yield can be obtained.

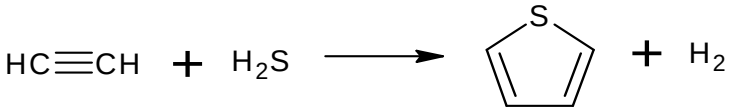


A.3.) SYNTHESIS ON INDUSTRIAL SCALE

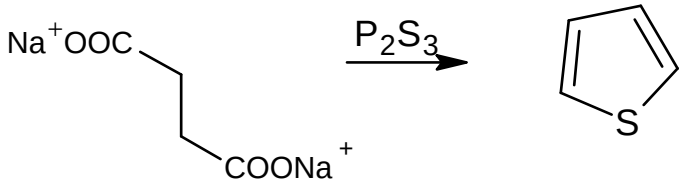
i) Thiophene can be synthesized on industrial scale by the high temperature reaction between n-butane and Sulfur.



ii) Thiophene can be synthesized by passing a mixture of acetylene and hydrogen sulfide through a tube containing alumina at 400°C. This method is commercially used.



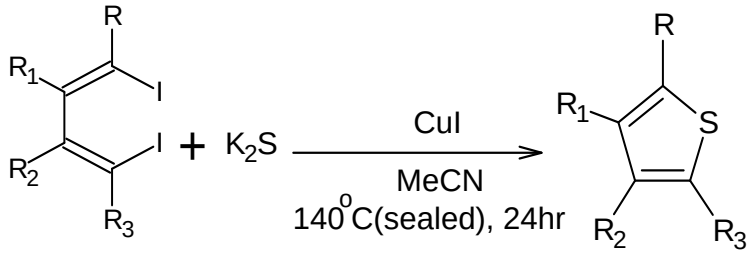
iii) Thiophene may also be prepared by heating sodium succinate with phosphorous trisulphide.



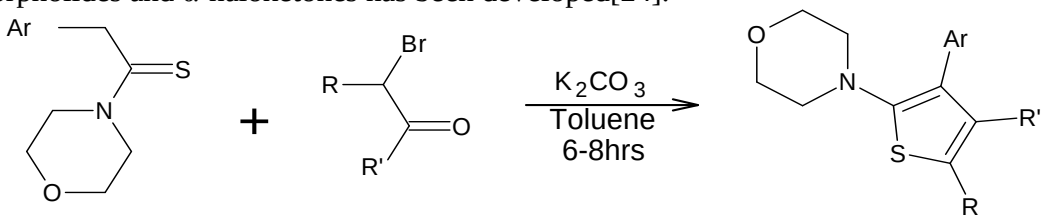
A.4.) MISCELLANEOUS SYNTHETIC PROCEDURES

Various other methods have been reported for synthesizing substituted thiophene. Some of them are as follows:

i) Copper-catalyzed tandem S-alkenylation of potassium sulfide with 1, 4-diiodo-1, 3-dienes enables an efficient synthetic approach to variously substituted thiophenes[23].

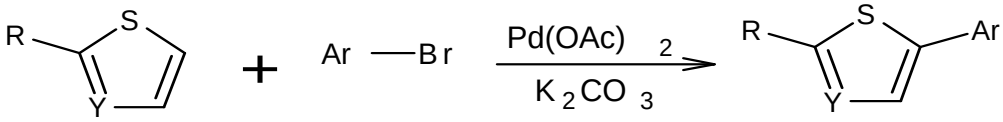


ii) An efficient one-step method for the synthesis of highly substituted thiophenes from thiomorpholides and α-haloketones has been developed[24].



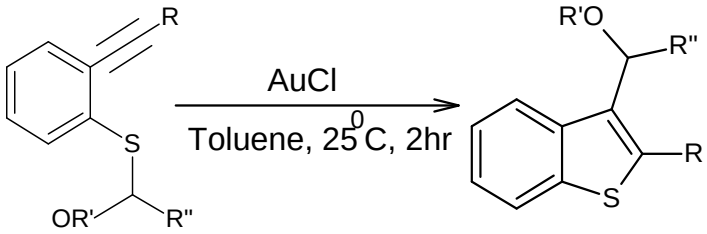
iii) Conditions for the palladium-catalyzed direct arylation of a wide range of heterocycles with aryl bromides employ a stoichiometric ratio of both coupling partners, as well as a substoichiometric quantity of pivalic acid, which results in significantly faster reactions.

An evaluation of the influence of the nature of the aryl halide has also been carried out[25].



Y= CH(R= alkyl, CHO, COOEt, OMe); N (R= H, Alkyl)

iv) A gold-catalyzed carbothiolation provided an atom-economic way of synthesizing sulfur-containing heterocycles such as 2,3-disubstituted benzothiophenes[26].



B) BEHAVIOUR OF THIOPHENE NUCLEUS

Knowledge of the behavior of heterocyclic systems under conditions of the principal reactions is required to perform the directed synthesis of important compounds practically and particularly of biological significance.

Thiophene derivatives comprise a significant portion of the organosulfur compounds in petroleum and in other products from fossil fuels[27], being obtainable as by-products of petroleum distillation. Different studies related to their biodegradation[28] and catalytic hydro

desulfuration[29] have been carried out. Coordination chemistry of such compounds has received recent attention because of its relevance to metal-catalysed hydro desulfuration of fossil fuels[30].

Thiophene display coordination properties closer to those of arenes than thioethers. On comparing the ionization potential of thiophene(8.9ev) and benzene (9.3ev), it is found that thiophene is slightly more nucleophilic than benzene. Ab initio calculations[31] seem to indicate accumulation of negative charge on 2- or 5- carbon atom and a positive charge on sulfur atom.

Coordination can occur through sulfur atom, through the 2- and 5- carbon or both(η^1) or through π- clouds of C(2)= C(3) or C(4)= C(5) bonds (η^2) or both(η^4).

Thiophene-based compounds have also found widespread use in modern drug design[32], biodiagnostics[33], electronic and optoelectronic devices[34] and conductive and electroluminescent polymers[35]. Also several reviews of various aspects of thiophene coordination and reactivity in transition metal complexes have been reported[36].

B.1.) PHYSICAL BEHAVIOUR OF THIOPHENE

Thiophene is the simplest aromatic compound containing sulfur atom and it shares some similar chemical properties with benzene. At room temperature, thiophene is a colorless liquid with a mildly pleasant odor reminiscent of benzene, with which thiophene shares some similarities. The high reactivity of thiophene toward sulphonation is the basis for the separation of thiophene from benzene, which are difficult to separate by distillation due to their similar boiling points (4°C difference at ambient pressure).

Thiophene is considered aromatic, although theoretical calculations suggest that the degree of aromaticity is less than that of benzene. This could be demonstrated by its ability to undergo substitution reaction.

Thiophene is a toxic and flammable aromatic compound. It is insoluble in water but soluble in most organic solvents including alcohol and ether. Melting Point of thiophene is -38°C while boiling point is 84°C.

Critical temperature of Thiophene has been determined by sealed- tube method and is found to be 579.4K. From the heat of combustion and from the values of thermochemical bond energies, a resonance energy of 20 Kcal./mol was calculated for thiophene. Dipole moments were used in connection with estimation of electron distribution and substituent effect in thiophene and for conformation of molecular orbital calculations(MO)[37].

Table1: Dipole moment of thiophene(in debyes)

Solvent	Dipole Moment
CCl_4	0.562, 0.003
Cyclohexane	0.53

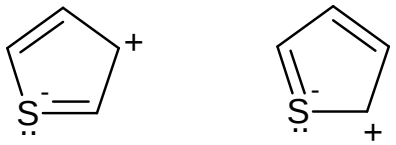
Table2: Dipole moment of 2 substitutedthiophene(in debyes)

Group(R_2)	Solvent	Dipole Moment
Br	CCl_4	1.39
Cl	Dioxane	0.01

Table3: Dipole moment of 2 substitutedthiophene(in debyes)

Group(R_3)	Solvent	Dipole Moment
Br	Benzene	1.13
CHO	Dioxane	2.94

The "electron pairs" on sulfur are significantly delocalized in the pi electron system[38]. Thiophene has a higher degree of stabilization than the analogous furan. This is due to the fact that sulphur has a lager bonding radius (length) and therefore sulphur could tolerate a positive charge better as a result of inductive pull towards sulphur[39]. These contributions to its stability can be envisaged from the canonical form of thiophene.



A **B**

B.2.) CHEMICAL BEHAVIOUR OF THIOPHENE

Thiophene is a chemically stable compound, readily available, and the chemistry of thiophene and its derivatives has been a constant matter of investigation[40]. It is the simplest representative of an aromatic structure bearing sulfur.

Thiophenes do not undergo the oxidation typical of a sulfides. Thiophene undergoes electrophilic substitution: nitration, sulfonation, halogenation, Friedel-Crafts acylation etc. Even the thiophene can undergo Reimer-Tiemann reaction and coupling diazonium salts formation.

Heat of combustion indicates resonance stabilization to the extent of 22-28 K.Cal./mol, somewhat less than resonance energy of benzene(36K.Cal./mol). On the basis of these properties, thiophene is considered as aromatic. Thiophene have structure that are analogous to structure of pyrrole, where nitrogen in pyrrole carries a hydrogen atom, the oxygen or sulfur carries an unshared pair of electrons in an sp^2 hybridized orbital. Thiophene obeys the $4n + 2\ \pi$ electron rule, and it is generally considered to be aromatic[41]. Its structure can be assumed to be derived from benzene by the replacement of two annular CH groups by sulfur. The sulfur atom in this five membered ring acts as an electron donating heteroatom by contributing two electrons to the aromatic sextet, and thiophene is thus considered to be an electron-rich heterocycle.

Considerable recent attention has been given to investigations into modifications of substituents in the presynthesized thiophene structure. In addition many studies were devoted to the use of

various thiophene derivatives in the synthesis of linearly and angularly polyannelated, including previously unknown heterocyclic systems.

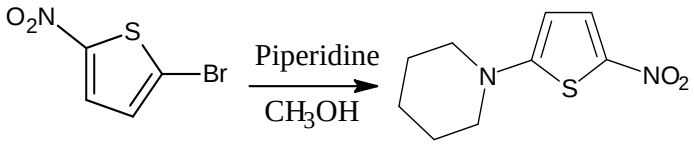
It has been interesting for sometimes in the isosteric replacement of benzene in pharmacologically active agents. The thiophene moiety has usually served as replacement of choice[42].

a. Reactions with oxidizing reagents

The thiophene ring system is relatively stable to oxidants and side-chains can be oxidized to carboxylic acid groups.

b. Reactions with nucleophilic reagents

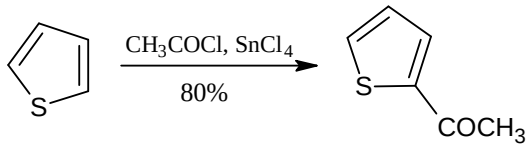
Nucleophilic displacements proceed atleast hundred times faster than for benzenoid counterparts. This is because of the participation of the sulfur in the delocalization of charge in the Meisenheimer intermediate[43].



c. Reactions with electrophilic reagents

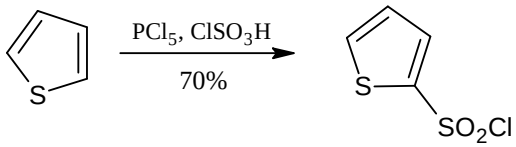
i) Acylation

The Friedel-Crafts acylation of thiophenes generally gives good yield under controlled conditions. Acylation with anhydrides in presence of phosphoric acid[44] is an efficient method.



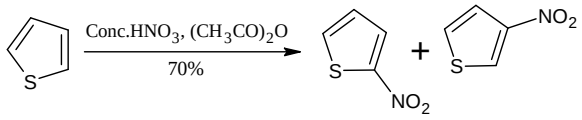
ii) Sulfonation

Sulfonation of thiophene by sulphuric acid gives thiophene-2-sulfonic acid. and 2-chlorosulfonation[45] is efficient.



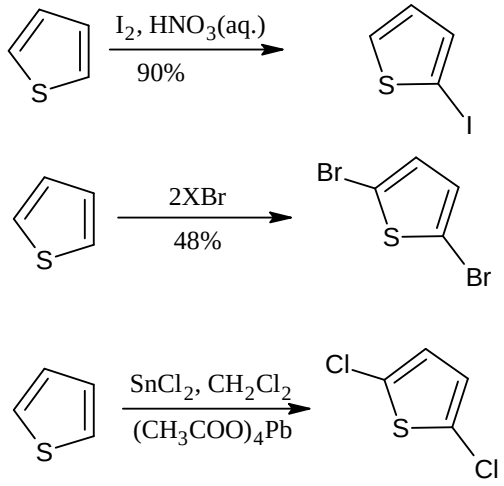
iii) Nitration

Nitration of thiophene should be carried out in the absence of nitrous acid as it can lead to an explosive reaction[46]. To prevent this, acety1 nitrate or nitronium tetraflouroborate[47] are satisfactory. The major 2-nitro-product is accompanied by approximately 10% of the 3- nitro isomer[48].



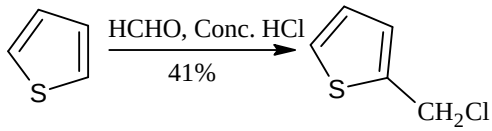
iv) Halogenation

At room temperature halogenation of thiophene occurs readily and is rapid even at -30^0 C in the dark. The rate of halogenation of thiophene, at 25^0 C, is about 10^8times that of benzene[49].



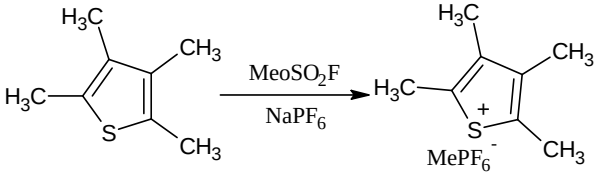
v) Condensation With Aldehydes And Ketones

Hydroxy alkyl thiophenes are unstable under the reaction conditions; chloroalkylation can however be achieved[50]. Care is needed in choosing condition; there is a tendency for formation of either di-2-thienylmethanes[51] or 2, 5-bis(chloromethy1)thiophene[52] .



d. Addition at sulfur

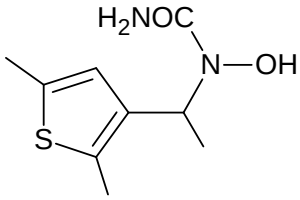
Thiophene sulfur can add electrophilic species. Thiophenium salts[53] though not formed efficiently from thiophene itself, are produced in high yields with polyalky1-substituted thiophenes[54]. The sulfur in such salts is probably tetrahedral i.e. the sulfur is sp^3 hybridised.



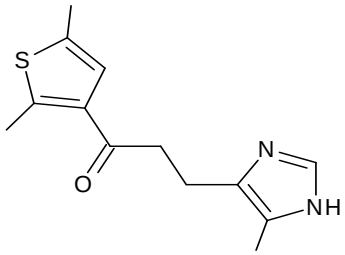
C) BIOLOGICAL ACTIVITY AND SOME ASPECTS OF PRACTICAL USE OF THIOPHENE

In medicinal chemistry, thiophene derivatives have been very well known for their therapeutic applications. Many thiophene derivatives have been developed as chemotherapeutic agents and

are widely used. Thiophene nucleus is one of the most important heterocycles exhibiting remarkable pharmacological activities. Thiophene moiety carrying compounds exhibit various activities like for example 1-[1- (2, 5- dimethylthiophen- 3- yl) ethyl]- 1-hydroxyurea **(2)** shows antiinflammatory activity; the maleate salt of 1-(2,5-dimethylthiophen- 3- yl)- 3-(5- methyl- 1 H-imidazol- 4- yl) propan-1-one **(3)** act as serotonin antagonists and is used in the treatment of Alzheimer's disease. The latter has also been employed in the formulation of inks for computer printers by the Xerox Group[55] and as a raw material for herbicides/ pesticides[56].

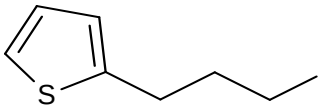


(2)

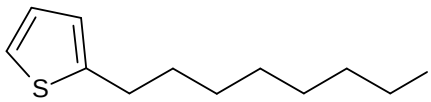


(3)

2-butylthiophene **(4)** has been employed as a raw material in the synthesis of anticancer agents and 2-octylthiophene **(5)** has been employed in the synthesis of anti-atherosclerotic agents such as **(6)**.



(4)



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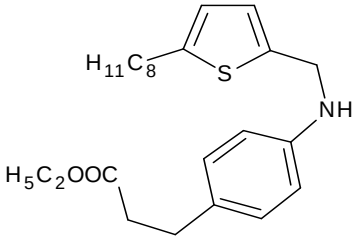
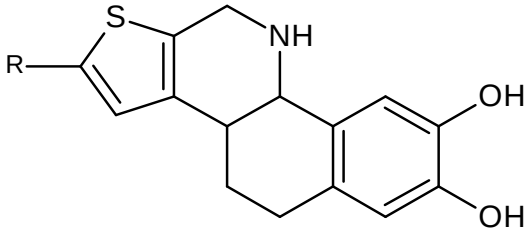


(6)

It also has applications in metal complexing agents and in the development of insecticides. The higher alkylated thiophenes **(7)** also have other uses like 2-hexylthiophene has been used extensively as a raw material in patents relating to liquid crystals.



(7)

R= C_2H_5-C_6H_{13}

As far as biological activity is concerned, fused hetero-aromatic systems are often of greater interest than monocyclic compounds.

Thiophene can be fused with various heterocyclic systems giving rise to various new heterocyclic system with enhanced biological activity. Thienopyrimidines occupy a special position among these compounds.
Along with some other pyrimidine systems containing an annelated five-membered hetero-aromatic ring, thienopyrimidine are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites.

Certain thienopyrimidine derivatives exhibit antiallergic[57], antibacterial[58], antidepressant[59], antidiabetic[60], analgesic and anti-inflammatory[61] activities.

CONCLUSION

The analytical and other informational data, available in literature so far, have rendered thiophenes significantly important class of heterocyclic compounds and their applications in ever challenging chemotherapy of various ailments/ infections etc. since last two decades immensely hiked interests of medicinal chemist and biochemist.

This particular review article, in reference, would extend great deal of help to researchers in reckoning and determining the best and most productive, economical, suggestive and conclusive access to various thiophenes of clinical importance superseding other compounds of their class.

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