Chapter 1
Synthesis and Biological Evaluation of Thiophene and Its Derivatives

Binoyargha Dam and Bhisma Kumar Patel

1.1 Introduction

Thiophene is a sulfur-containing aromatic heterocyclic compound that possesses a monocyclic five-member ring with sulfur as a heteroatom at position 1. Its chemical formula is C_4H_4S, and 2nd, 4th and 3rd, 5th positions are equivalent (Fig. 1.1) in an unsubstituted system. The chemical name of thiophene is thiacyclopentadiene. The word thiophene is derived from the Greek word *theion* meaning sulfur and *phaino* meaning shinning.

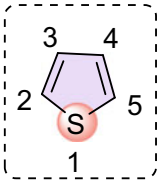
At room temperature, thiophenes are simple colorless liquids that are flammable having a sweet aroma reminiscent of benzene. They occur in coal tars and are discovered as contaminants in benzene. Thiophene and its derivatives are said to have various uses and properties. They are used in material science and industrial chemistry as corrosion inhibitors. They have prominent roles in the advancement of organic semiconductors [1] and the fabrication of organic light-emitting diodes (OLEDs) [2]. They also possess many pharmacological activities like anti-inflammatory [3], antimicrobial [4], antihypertensive [5] activities, etc. Structures of some thiophene moieties having medicinal activities are shown in Fig. 1.2.

B. Dam · B. K. Patel (✉)
Department of Chemistry, Indian Institute of Technology Guwahati, North Guwahati, Guwahati, Assam 781039, India
e-mail: patel@iitg.ac.in

B. Dam
Department of Chemistry, The Assam Royal Global University, Guwahati, Assam 781035, India

K. L. Ameta (ed.), *S-Heterocycles*, https://doi.org/10.1007/978-981-97-4308-7_1

Fig. 1.1 Thiophene



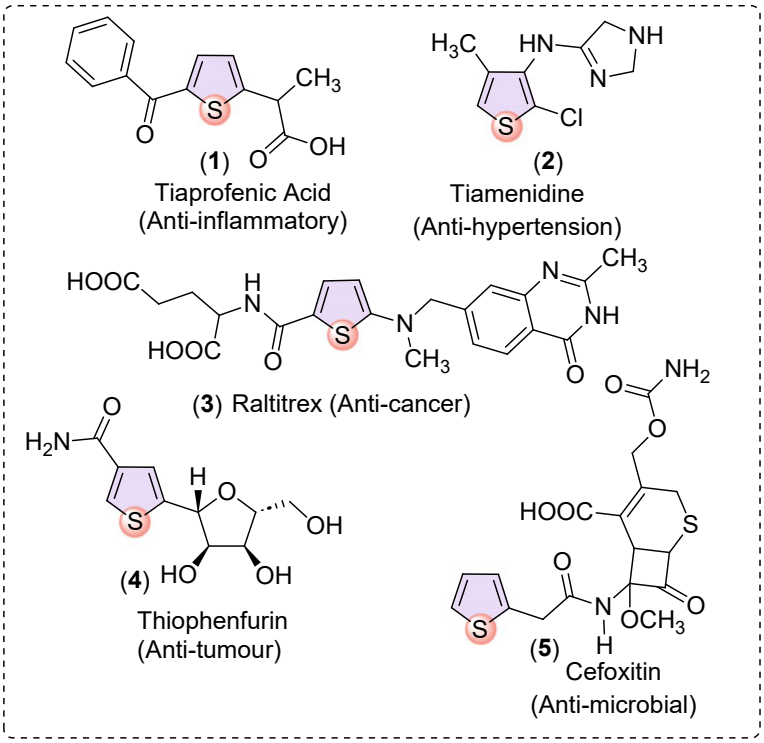
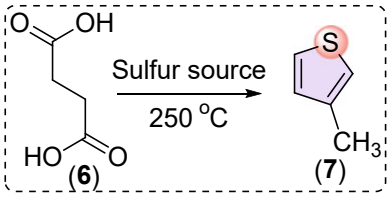


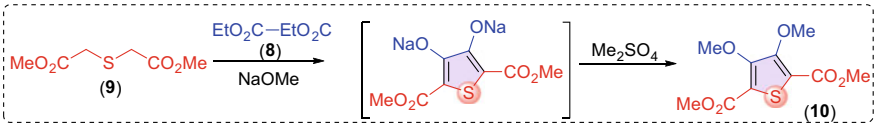
Fig. 1.2 Structures of a few medicinally active drugs containing thiophene moiety

1.2 General Approaches to Thiophene Ring Synthesis

Because of the various biological importance of thiophenes, this moiety has been classically synthesized in various ways. A few of these methods include Paal Knorr synthesis, Hinsberg synthesis, Fiessellmann synthesis, etc. In Paal Knorr synthetic procedure [6], 1,4-dicarbony1 compounds (**6**) were reacted with a sulfur surrogate to give thiophene derivatives (**7**) (Scheme 1.1). Traditionally used sulfur-based compounds are phosphorus sulfides, Lawesson's reagent, etc.

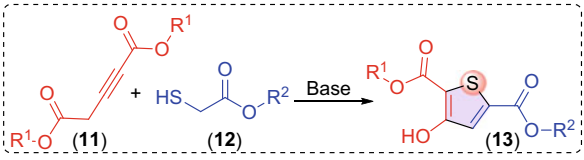
Scheme 1.1 Synthesis of thiophene derivatives by Paal Knorr method





Scheme 1.2 Hinsberg synthesis of thiophene derivatives

Scheme 1.3 Fiesselmann synthesis of thiophene derivatives



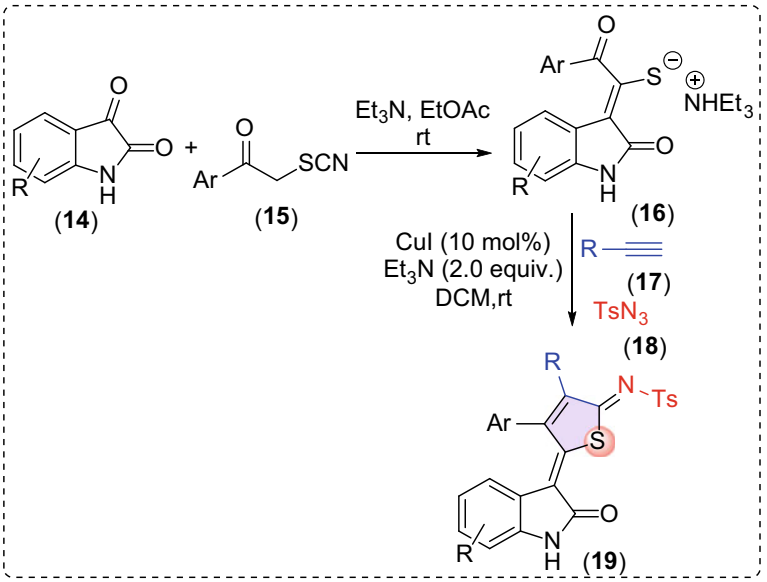
In Hinsberg synthesis [7], condensation of α-dicarbonyl compounds (**8**) and thioglycolic acid esters (**9**) in the presence of sodium alkoxide was carried out to yield thiophene-2,5-dicarboxylic acid derivatives (**10**) (Scheme 1.2).

In Fiesselmann synthesis [8], condensation of methyl thioglycolate (**12**) was carried out with dimethyl but-2-ynedioate (**11**) in the presence of a base to provide 3-hydroxy-2,5-thiophene carboxylate derivatives (**13**) (Scheme 1.3).

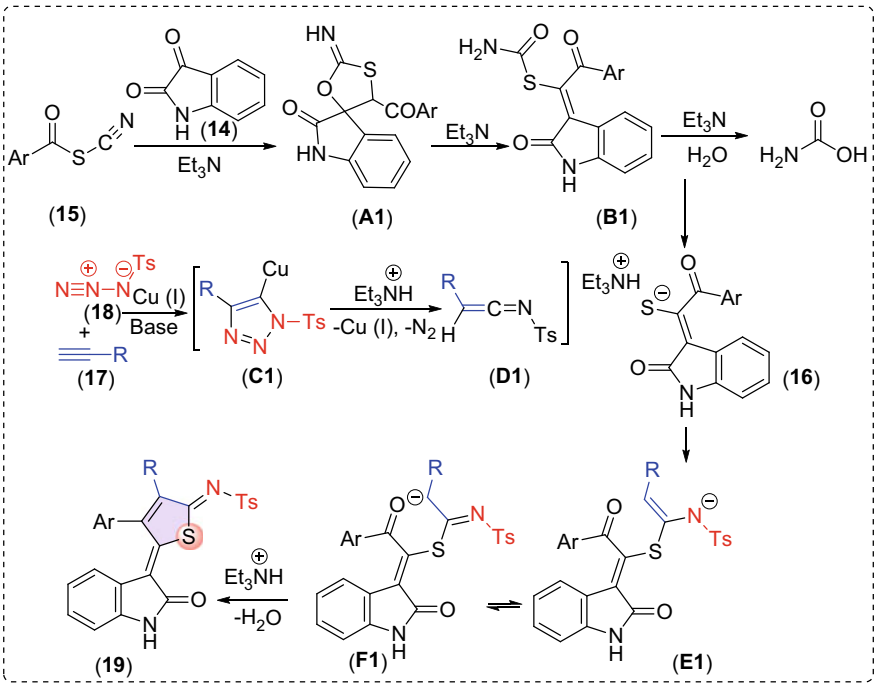
Aforementioned procedures are well-known classical methods for the synthesis of thiophene moieties. Because of many biological importance of thiophene derivatives, this moiety remains the subject of interest for many chemists and biologists. For this reason, scientists throughout the world are still focusing on the synthesis of this biologically relevant heterocycle. Some of the very latest reports are discussed herein in this chapter.

Li and co-workers used readily accessible triethylammonium 1-(2-oxoindolin-3-ylidene)-2-aroylethanethiolates (**16**) to synthesize diversely substituted thiophene derivatives (**19**) by copper(I)-catalyzed reaction of terminal alkynes (**17**) and *N*-sulfonyl azides (**18**) (Scheme 1.4) [9]. This reaction installed carbon–nitrogen, carbon–sulfur, and carbon–carbon bonds simultaneously, allowing the synthesis of functionalized thiophenes with a wide variety of substituents in one pot. A plausible mechanism for this domino process has been proposed as shown in Scheme 1.5.

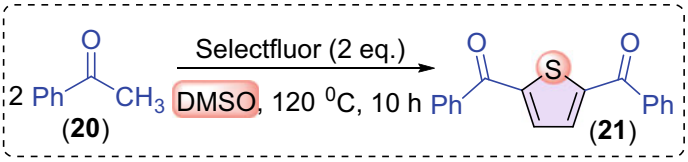
Firstly, triethyl amine-promoted [3 + 2]-between (**14**) and (**15**) leads to the formation of spiroindole (**A1**), which gives compound (**16**). Following that, the intermediate (**D1**), which is formed from copper-catalyzed cycloaddition of terminal alkynes (**17**) and *N*-sulfonyl azides (**18**), reacts with (**16**) to give anionic intermediate (**E1**).



Scheme 1.4 Synthesis of substituted thiophene derivatives (**19**) from (**16**)



Scheme 1.5 Reported mechanism for the synthesis of thiophene derivatives by Li and co-workers



Scheme 1.6 Selectfluor-promoted synthesis of thiophene moiety (**21**)

After tautomerization (**E1**) gives (**F1**), which underwent intramolecular nucleophilic addition to yield desired thiophene derivatives (**19**) [9] (Scheme 1.5).

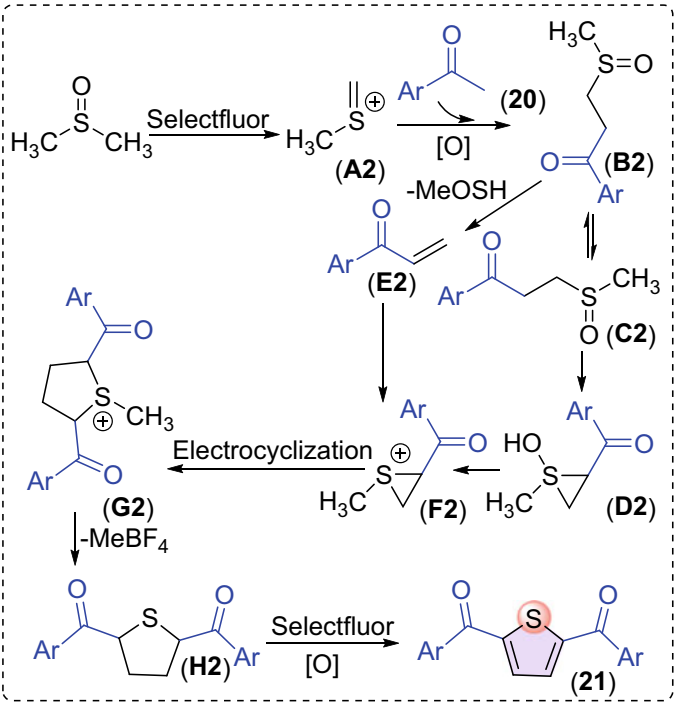
Recently, in the year 2023, Qiu and co-workers reported the synthesis of diacylthiophenes (**21**) from dimethyl sulfoxide (DMSO) and aryl methyl ketones (**20**) through selectfluor-promoted cyclization by simple solvent modification (Scheme 1.6) [10]. This method leads to the creation of new C–S and C–C bonds. Outstanding chemoselectivity, usage of easily available starting materials, and wide functional group tolerance were some added features of this protocol.

Scheme 1.7 shows a most probable mechanism as proposed by the authors [10]. Primarily, DMSO in the presence of select fluor gets converted to sulfonium cation (**A2**). Sulfonium cation then reacts with ketone (**20**) to form intermediate (**B2**). Following that, the intermediate (**B2**) underwent enol exchange to give intermediate (**D2**). The intermediate (**B2**) also eliminated MeOSH to give chalcone (**E2**). The intermediate (**D2**) gave (**F2**), which underwent intermolecular cycloaddition with (**E2**) to give intermediate (**G2**). Removal of methyl cation from (**G2**) leads to the formation of (**H2**), which underwent oxidative aromatization by selectfluor to yield desired thiophene (**21**).

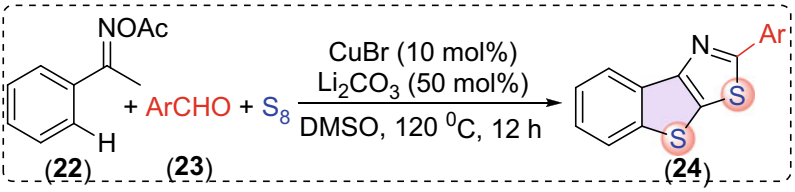
Deng and co-workers in the year 2018 reported a simplistic copper-catalyzed method to synthesize fused thieno[3,2-*d*]thiazole moieties (**24**) from methyl aromatic ketoxime acetates (**22**), aromatic aldehydes (**23**), and elemental sulfur (Scheme 1.8) [11]. The usefulness of this protocol was highlighted by the significant simplicity in one-pot organic transformations, high yield of products, application in gram-scale conditions, and potential applications in post-synthetic modifications.

Very recently, Li *and* co-workers developed a visible-light mediated method for the synthesis of 3-halobenzo[*b*]thiophenes (**27**). 2-Alkynylthioanisoles (**25**) and alkyl halides (**26**) were used as starting materials to synthesize diverse range of thiophene derivatives (Scheme 1.9) [12]. Reaction went smoothly in the presence of 10W blue LEDs at room temperature. THF was used as the solvent for this reaction. Further, after completion of reaction the synthesized product was subjected to many successful organic transformations.

Two separate mechanisms for bromo and iodocyclization were proposed by the research group as shown in Scheme 1.10. For bromocyclization, [**25** gets excited to (**25***)] and acted as a photosensitizer. This underwent an energy-transfer pathway with (**26**) to give (**26***), and the ground state (**25**) was regenerated. Bromide radical then gets formed from homolytic cleavage of (**26***). This bromide radical then reacted

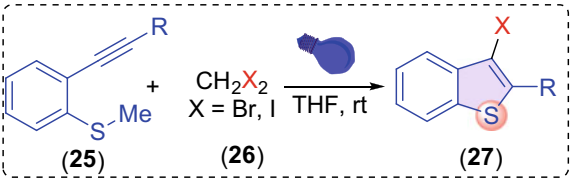


Scheme 1.7 Plausible mechanism for selectfluor-promoted synthesis of thiophene moiety



Scheme 1.8 Synthesis of fused thieno[3,2-*d*]thiazole moieties (**24**)

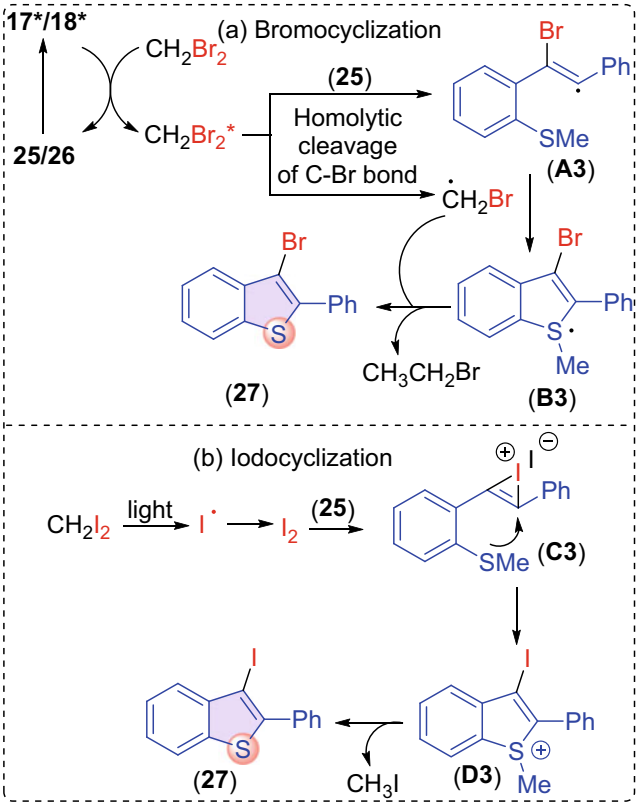
Scheme 1.9 Visible-light mediated synthesis of 3-halobenzo[*b*]thiophene derivatives (**27**)



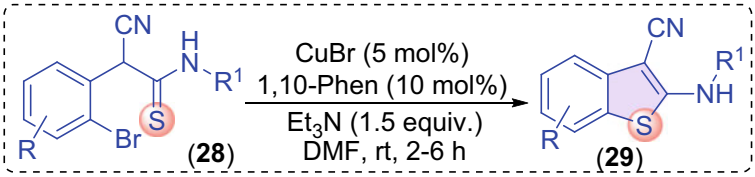
with alkynyl in (**25**) to generate intermediate (**A3**) in high regioselectivity. Consequently, this in situ generated radical reacted with the SMe part via intramolecular cyclization to give (**27**), which is the final product, along with the conversion of methyl radical into bromoethane. For iodocyclization, primarily, visible-light mediated homolytic cleavage of the C–I bond leads to the formation of an electrophilic iodine species (I_2) in situ, which then gets captured by the C–C triple bond in (**25**) to form an intermediate (**C3**). Following the intramolecular sulfur portion attack, the cationic intermediate (**D3**) was formed. Ultimately, the methyl group gets released to give the anticipated product (**27**) [12] (Scheme 1.10).

Peruncheralathan and research group reported the syntheses of various functionalized 2-aminobenzo[*b*]thiophenes (**29**) at room temperature by Ullmann coupling reaction (Scheme 1.11) [13]. Reaction was carried out using CuBr (5 mol%) and 1,10-phen (10 mol%). Further post-synthetic modification of newly synthesized thiophenes was carried out to synthesize quinolines in the presence of triflic acid.

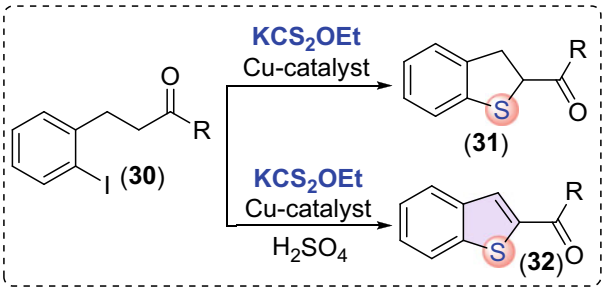
An efficient domino process was developed by Sekar et al. in the year 2020 for the syntheses of thiophenes (**31**) from 2-iodoketones (**30**) by using a copper catalyst



Scheme 1.10 Probable mechanism for visible-light mediated synthesis of (**27**)



Scheme 1.11 Synthesis of (**29**) by Ullmann coupling reaction

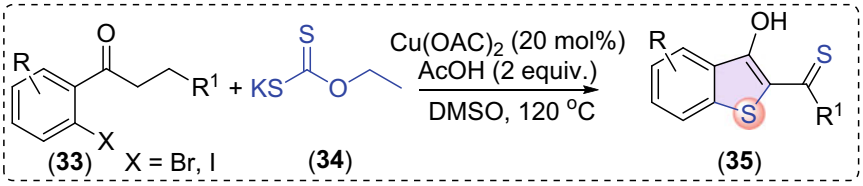


Scheme 1.12 Synthesis of (**31**) and (**32**)

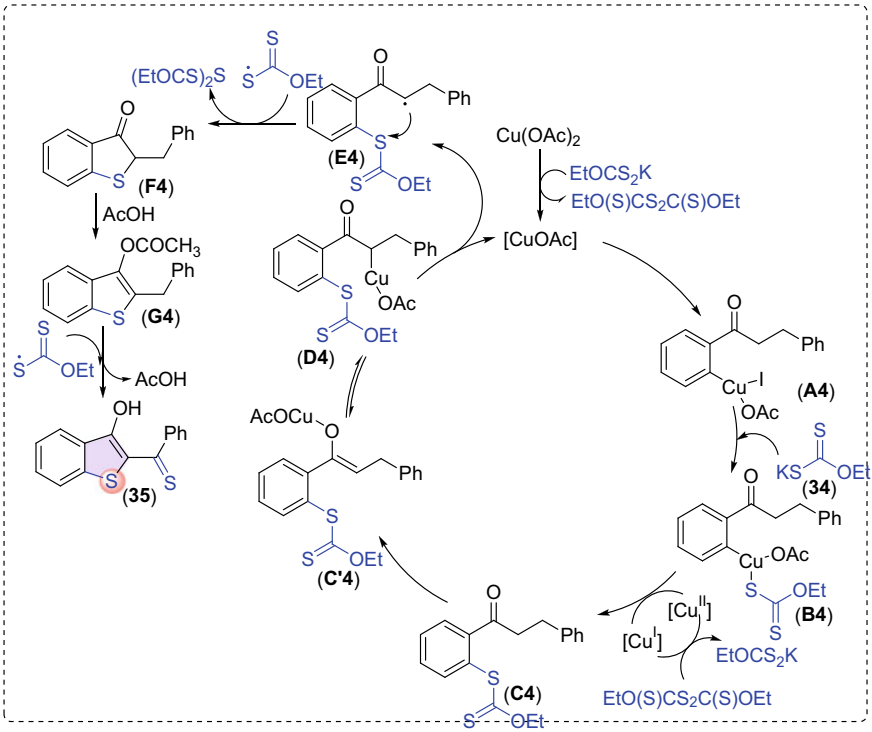
and xanthates the sulfur source. The process was also extended for the synthesis of 2-acylbenzo[*b*]thiophenes (**32**) using the in situ generated iodine from by product KI (Scheme 1.12) [14].

Sekar and research group again in the year 2021, reported a copper-catalyzed domino synthesis of thiophene derivatives (**35**) through radical cyclization of 2-iodophenyl ketones (**33**) and xanthate (**34**) as a sulfur surrogate (Scheme 1.13). After controlled experiments and literature survey, a probable mechanism was proposed by authors (Scheme 1.14). According to that, at first, 1-(2-iodophenyl)-3-phenylpropan-1-one (**33**) underwent oxidative addition in the presence of Cu(I) to form intermediate (**A4**), which then led to the formation of intermediate (**B4**) by ligand exchange with potassium ethyl xanthate (**34**). Reductive elimination of intermediate (**B4**) gave Cu(I) and xanthate ester. This Cu(I) gets oxidized to Cu(II) by the xanthate dimer, which reacts with the keto group of the xanthate ester and gives intermediate (**C4**). This (**C4**) underwent keto–enol tautomerism and gave (**D4**). Ultimately, (**D4**) underwent homolytic fission to give the radical intermediate (**E4**). Then, thiyl radical was generated through fission of the xanthate ester by in situ generated xanthate radicals which underwent cyclization to form (**F4**) (Scheme 1.14). Following that, a stable aromatic intermediate (**G4**) got formed from (**F4**), which eventually leads to the formation of desired thiophene moiety (**35**) [15].

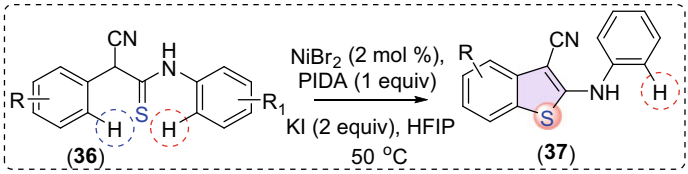
A catalytic site selective intramolecular C–S bond forming reaction has been reported by S. Peruncheralathan and his research group in the year 2018 (Scheme 1.15) [16]. The C–H bond functionalization of α-aryl-thioacetanilides (**36**) was resourcefully catalyzed by $NiBr_2$, resulting in (**37**).



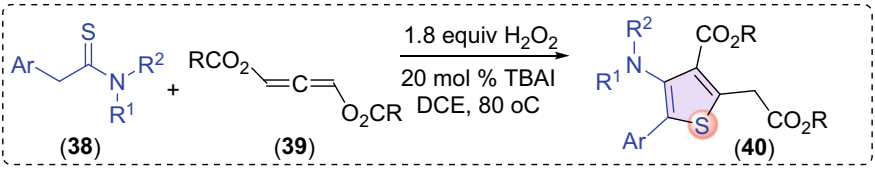
Scheme 1.13 Copper-catalyzed synthesis of thiophene derivatives (**35**)



Scheme 1.14 Plausible mechanism for domino synthesis of thiophene derivatives

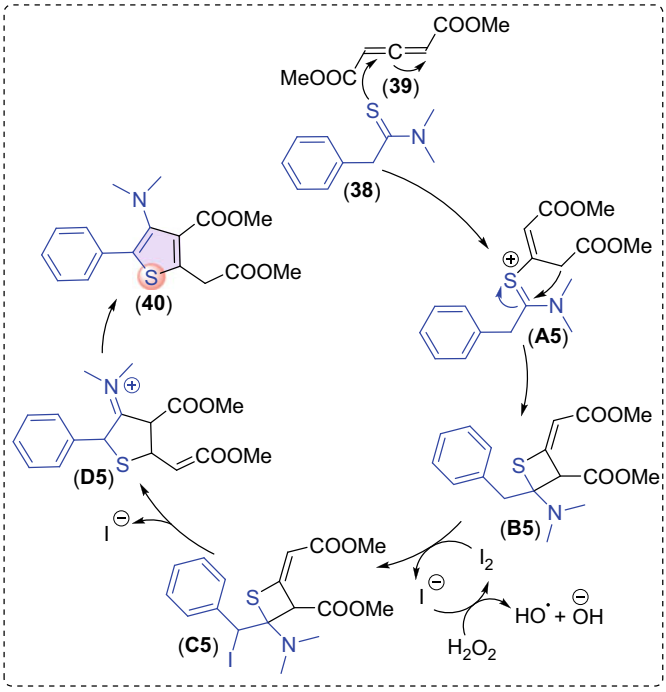


Scheme 1.15 $NiBr_2$-catalyzed synthesis of (**37**)



Scheme 1.16 TBAI-catalyzed synthesis of polyfunctionalized thiophenes (**40**)

Luo group in the year 2018 described a TBAI-catalyzed tandem thio-Michael addition/oxidative annulations reaction for the synthesis of substituted thiophene molecules (**40**) (Scheme 1.16). Thioamides (**38**) and allenes (**39**) were used as starting materials. This report discussed about a transition metal free oxidative cyclization procedure through 1,2-sulfur migration transformation protocol. Based on literature reports, a plausible mechanism was proposed as shown in Scheme 1.17. Primarily, arylthioamide (**38**) reacted with allene (**39**) to give intermediate (**A5**), this is then followed by an intramolecular nucleophilic ring closing reaction to give intermediate (**B5**). Following that, iodination of (**B5**) forms intermediate (**C5**), which underwent 1,2-sulfur migration to form intermediate (**D5**). At last, the intermediate (**D5**) underwent aromatization/oxidation to give thiophene derivatives (**40**) [17].



Scheme 1.17 Plausible mechanism for TBAI-catalyzed synthesis of polyfunctionalized thiophenes

1.3 Biological Activities of Thiopene Molecules

Heterocyclic compounds are known to play an important role in the exploration of biologically active molecules. In this regard, thiophene and its derivatives have been spotlighted of curiosity for almost two decades. Thiophene derivatives own extraordinary properties like anti-inflammatory, antianxiety, antifungal, antimicrobial, anticancer, and antipsychotic properties. Several marketed drugs like Olanzapine, Sertaconazole, Benzocyclidine, Tipepidine, Ticlopidine, Tioconazol, Clopidogrel, Tiquizium Bromide, Pasugrel, Timepidium, and Citizolam contain a thiophene nucleus in them. Structures of few of these medicinally active thiophene moieties are shown in Fig. 1.3.

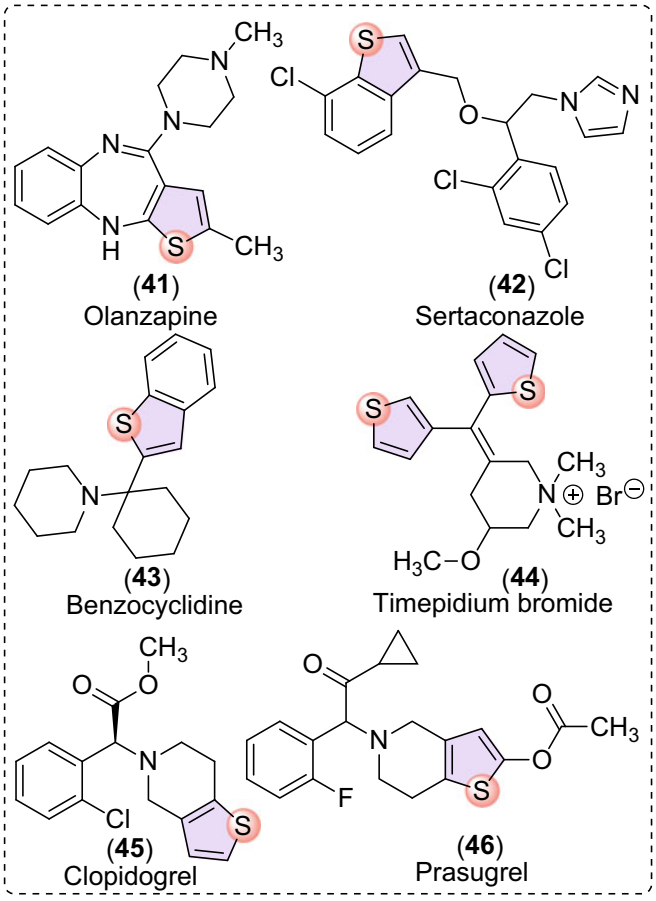


Fig. 1.3 Structures of Olanzapine, Sertaconazole, Benzocyclidine, Tiquizium Bromide, and Pasugrel

1.3.1 Anti-inflammatory Activity

Tiaprofenic acid (**1**), tenidap (**47**), tinoridine (**48**), and zileuton (**49**) (Fig. 1.4) are few examples of commercially available anti-inflammatory drugs with thiophene ring as pharmacophoric group. Tiaprofenic acid and tinoridine act as cyclooxygenase (COX) inhibitors [18, 19], whereas first three are non-steroidal anti-inflammatory drugs. Zileuton is a lipooxygenase (LOX) inhibitor [19].

COX enzymes are found in three forms. COX1 regulates various functions like platelet adhesiveness, produces prostaglandins from arachidonic acid, and is found in normal tissues [20, 21]. COX-2 are present in certain tissues like prostate, kidneys, and uterus. When a tissue gets damaged, their level enhances in body [22]. COX-3 are found in central nervous systems and are linked to the antipyretic effect of paracetamol [23–25].Other enzymes which are involved in inflammatory process are lipooxygenases (LOX). Several thiophenic molecules were being described as potential inhibitors of these enzymes. Filali and research group discovered that compound (**50**) (Fig. 1.5) presents inhibitory activity with an IC50 of 29.2 μM for 5-lipoxygenase [26]. Authors described that these potent activities were related to the presence of methoxy and methyl radicals in its structure. After a few years, Chiasson and co-workers synthesized a few compounds having benzothiophene moieties and phenolic acid fraction. Compounds (**51**) and (**52**) (Fig. 1.5) showed the best activities against polymorphonuclear leukocytes and HEK293 cells. This activity may correspond to the presence of methoxy and hydroxy group in the molecule [27].

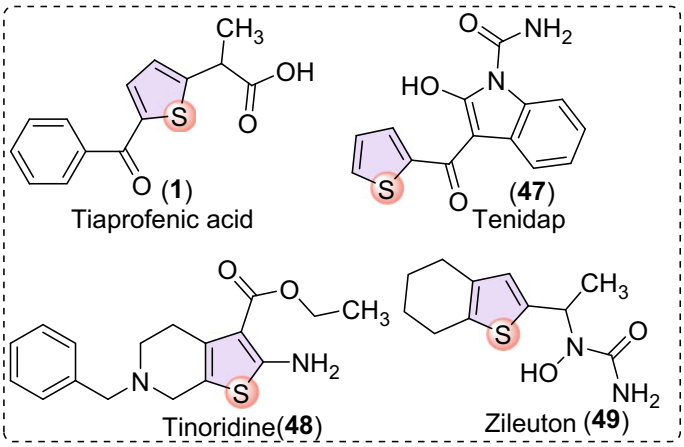


Fig. 1.4 Structures of few anti-inflammatory thiophene drugs

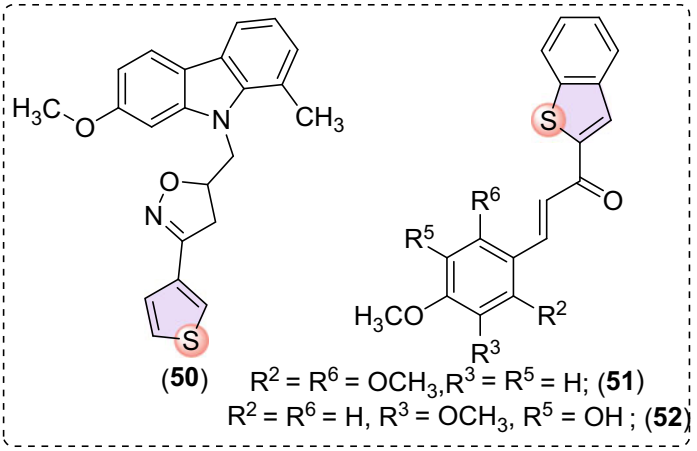


Fig. 1.5 Thiophene compounds possessing inhibitory activities against 5-lipoxygenase, polymorphonuclear leukocytes and HEK293 cells

1.3.2 Anticancer Activity

Cancer is a lethal disease accountable for growing death rate worldwide. It causes uncontrolled reproduction and multiplication of anomalous forms of the body's own cells. 2-Butylthiophene (**53**) had already been employed as a raw material in the synthesis of anticancer agents. Gunda and co-workers [28] synthesized a few new derivatives of thiophene and studied their in vitro cytotoxicity activities against colorectal adenoma cell line and breast cancer cell line. Among series of compounds synthesized by the researchers, compound (**54**) which had phenyl substituent showed the best anticancer activity (Fig. 1.6). Mohareb and research group in their work synthesized few thiophene derivatives, which were found to be active against breast adenocarcinoma cell, NCI-H460 (non-small lung cancer cell) and SF-268 (CNS cancer cells) [29]. Among various compound synthesized, compound (**55**) (Fig. 1.6) was found to contain higher cytotoxicity because of the presence of a chloro group.

1.3.3 Antioxidant Activity

A class of substituted thiophene derivatives was synthesized by Madhavi and research group, which were assessed for in vitro antioxidant activity by scavenging nitric oxide and 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals at 100 μM concentration [30]. Compound (**56**) (Fig. 1.7) was found to have maximum antioxidant activities as free radical scavengers in both the models.

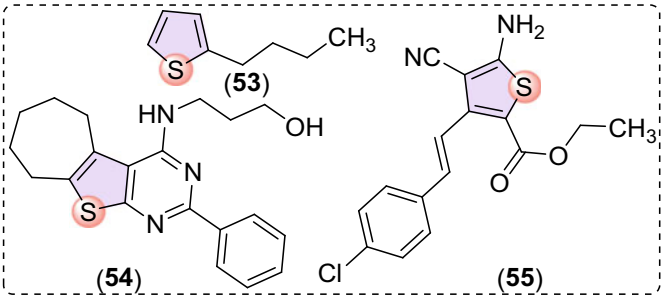
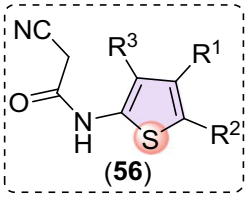


Fig. 1.6 Structures of 2-butylthiophene (**53**) and structures of two thiophene moieties (**54**, **55**) having anticancer activities

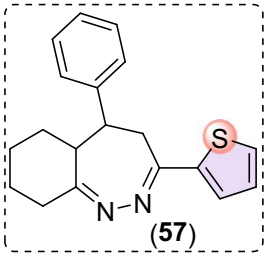
Fig. 1.7 Structure of a thiophene-based compound (**56**) found to have antioxidant activity



1.3.4 Antimicrobial Activity

Thiophene moieties are found to show high antimicrobial activities against several microbial infections. A series of thiophene analogues of chalcones were synthesized by Mazimba et al. [31] Synthesized compounds (**57**) (Fig. 1.8) were monitored for in vitro antimicrobial activities against *E. coli*, *C. Albicans*, *B. subtilis*, *S. Aureus,* and *P. Aeruginosa* using dilution method. Compounds were found to show superior antifungal and antibacterial activities.

Fig. 1.8 Structure of a thiophene-based compound (**57**) found to have antimicrobial activities



1.4 Conclusion

Since thiophene is of outmost importance for medicinal science, progress in the novel development for thiophene and their derivatives is a major concern among scientists. Some very recent and prominent strategies involved in constructing thiophene rings are discussed herein this chapter. Although the preparation of thiophenes has been widely studied, the synthesis of highly functionalized thiophenes needs special attention and is one of the challenges of organic chemistry. Some of the biological importance of the synthesized moieties is also discussed in this chapter.

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