Recent Advances in the Synthesis of Thiophene Derivatives by Cyclization of Functionalized Alkynes

Raffaella Mancuso † and Bartolo Gabriele †,*

Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, Via P. Bucci, 12/C, Arcavacata di Rende (CS) 87036, Italy

† These authors contributed equally to this work.

* Author to whom correspondence should be addressed; E-Mail: bartolo.gabriele@unical.it; Tel.: +39-098-449-2813; Fax: +39-098-449-2044.

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Abstract: This review is intended to highlight some recent and particularly interesting examples of the synthesis of thiophene derivatives by hetero cyclization of readily available S-containing alkyne substrates.

Keywords: alkynes; catalysis; cyclization; heterocyclization; thiophenes

1. Introduction

Substituted thiophenes are among the most important aromatic heterocyclic derivatives. Many molecules incorporating the thiophene nucleus have, in fact, shown important pharmacological activities [1–4]. Moreover, thiophene derivatives find large application in material science [5–15] and in coordination chemistry [16,17], and as intermediate in organic synthesis [18,19].

The classical approaches to substituted thiophenes are mainly based on condensation-like reactions or on subsequent functionalization of the thiophene ring [20–30]. However, during the last years, innovative approaches to the regioselective synthesis of substituted thiophenes starting from acyclic precursors have been developed, mainly based on heterocyclization of functionalized alkynes [31].
In this review, we will highlight some recently developed efficient and selective syntheses of thiophene derivatives by cyclization of readily available S-containing alkyne substrates, which have allowed a significant step forward toward a direct and atom-economical entry to this very important class of aromatic heterocycles. As a matter of fact, these processes may allow the construction of the thiophene ring with the desired substitution pattern in a regiospecific manner and in only one step, usually with high atom economy (particularly in the case of cycloisomerization reactions), and starting from readily available starting materials (as the acetylenic S-containing precursors can be easily prepared in a few steps from commercially available compounds through simple synthetic steps).

As will be seen, many of these cyclization reactions leading to thiophenes have been performed under mild conditions (even at rt, in particular with iodocyclizations) in classical organic solvents, either dipolar aprotic (such as N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), or MeCN), apolar or slightly polar (such as toluene, THF, or CH₂Cl₂), or protic ones (such as MeOH). However, particularly during the last years, the possibility to carry out these processes in unconventional solvents, such as ionic liquids (ILs) has been successfully verified. This has allowed the easy and convenient recycling of the reaction medium and/or of the catalyst (in the case of metal-catalyzed heterocyclizations).

We have structured the review into different Sections. Section 2 will deal with metal-catalyzed or base-promoted heterocyclizations, while in Section 3 iodocyclization reactions will be discussed. Carbocyclization of S-containing alkyne substrates is the topic of Section 4. In Section 5, some miscellaneous methods that cannot be classified into the previous categories are treated. We would like to point out here that most of the mechanisms shown in this review are based on mechanistic pathways proposed by the authors, on the basis of the existing knowledge and, in some cases, of some additional experimental evidences (product stereochemistry, reactivity pattern of the substrates, and so on). Only in a few cases these hypotheses have been corroborated by computation calculations (one example is the iodocyclization of 1-mercapto-3-yn-2-ols 23 in ionic liquids, Section 3, while, to the best of our knowledge, no kinetic studies have been reported so far. Another aspect worth mentioning concerns the reaction conditions reported in the review: they refer to the optimized conditions, usually established after a careful study on the influence of the reaction parameters (such as the catalyst loading, reagents molar ratios, solvent, temperature and so on) on substrate reactivity and product yield.

2. Synthesis of Thiophene Derivatives by Metal-Catalyzed or Base-Promoted Heterocyclization of S-Containing Alkyne Substrates

Metal-catalyzed heterocyclization of functionalized alkynes bearing a suitably placed heteronucleophilic group is a powerful methodology for the regioselective and atom-economical synthesis of substituted heterocycles starting from readily available acyclic substrates (Scheme 1, Y = heteroatom) [31–49]. The generally accepted mechanism for this important transformation involves the electrophilic activation of the triple bond by coordination to the metal center, followed by either exo or endo cyclization (ensuing from intramolecular nucleophilic attack by the –YH group to the coordinated triple bond) and protonolysis (Scheme 1).
Scheme 1. Metal-catalyzed heterocyclization of functionalized alkynes bearing a suitably placed nucleophilic group leading to heterocycles through activation of the triple bond by the metal species followed by intramolecular nucleophilic attack by the heteronucleophile and protonolysis.

This is probably connected with the “poisoning” effect exerted by the sulfur atom on the metal catalyst, owing to its strong coordinating and adsorptive properties [50,51]. Nevertheless, progress in organometallic catalysis has recently permitted to develop several important processes involving the metal-catalyzed carbon-sulfur bond formation [52–55]. Although most of these processes concern the formation of sulfuratet acyclic molecules, during the last years several important S-cyclization reactions, involving the formation of the C-S bond and leading to S-heterocycles, have been developed.

The first example of the formation of thiophenes by a metal-catalyzed cycloisomerization approach of alkynylthiol derivatives was reported in 2000 by our research group [56]. It concerned the reaction of (Z)-2-en-4-yne-1-thiols 1 (readily obtainable from the corresponding (Z)-2-en-4-yn-1-ols [57]) in N,N-dimethylacetamide (DMA) as the solvent or under solventless conditions at 25–100 °C, carried out in the presence of a particularly simple catalytic system, consisting of PdI$_2$ (1 mol %) in conjunction with KI (2 mol %) (Table 1). The use of KI was necessary in order to make PdI$_2$ soluble and to stabilize the formation of the catalytically active species PdI$_4^{2-}$. With low-boiling substrates, solventless conditions were used to facilitate product recovery. In other cases, several polar solvent were tested (a polar solvent was necessary to ensure the dissolution of the ionic catalyst), and, between them, DMA gave the best results in terms of substrate reactivity and product yield. Substrates bearing a terminal as well as an internal triple bond could be employed, while alkyl as well aryl substitution was tolerated on the double bond and at C-1 (Table 1) [56]. One indubitable advantage of this new protocol consisted in the practically neutral conditions employed for realizing the thiocyclization, as compared with the strongly basic conditions previously used ($t$-BuOK in $t$-BuOH in the presence of 18-crown-6), which were not compatible with base-sensitive substrates such as those bearing a terminal triple bond [58].

Mechanistically, the reaction is believed to proceed through anti 5-exo-dig intramolecular nucleophilic attack by the thiol group to the triple bond coordinated to Pd(II), with formal elimination of HI, followed by protonolysis and aromatization or vice versa (Scheme 2; anionic iodide ligand are omitted for clarity). This mechanistic hypothesis was in agreement with the experimental observation that substrates bearing a terminal triple bond were more reactive with respect to those bearing an internal triple bond. With an internal triple bond, in fact, Pd(II) coordination is less favored for steric reasons. A nucleophilic attack by the –SH group on the triple bond, with Pd(II) being coordinated from the opposite site (anti attack), was also in agreement with the significantly higher reactivity observed with substrates unsubstituted at C-3 with respect to enynethiols substituted at C-3 (Table 1, compare Entries 5 and 6).
This is clearly related to the fact that an anti-coordination of the triple bond to Pd(II) may be less efficient, for steric reasons, in the presence of a substituent at C-3 [56].

Table 1. PdI₂/KI-catalyzed cycloisomerization of (Z)-2-en-4-yne-1-thiols 1 to substituted thiophenes 2

| Entry | 1 | T (°C) | Solvent | t (h) | 2 | Yield of 2 (%) |
|-------|---|--------|---------|-------|---|----------------|
| 1 c   |   | 100    | none    | 2     |   | 36             |
| 2     |   | 100    | none    | 1     |   | 71             |
| 3     |   | 100    | DMA     | 1.5   |   | 58             |
| 4     |   | 100    | DMA     | 15    |   | 44             |
| 5     |   | 100    | DMA     | 8     |   | 56             |
| 6     |   | 25     | DMA     | 1     |   | 89             |

a: Unless otherwise noted, all cycloisomerization reactions were carried out under nitrogen using 1:KI:PdI₂ molar ratio of 100:2:1. For the reactions carried out in DMA, substrate concentration was 2 mmol of 1 per mL of DMA; b: Isolated yield based on starting 1; c: The reaction was carried out with 2 mol % of PdI₂.

Scheme 2. Proposed mechanistic pathways for the PdI₂-catalyzed cycloisomerization of (Z)-2-en-4-yne-1-thiols 1 leading to thiophenes 2 [56].
More recently, a strictly related method has been published, regarding the metal-free cyclization of 4-en-1-yn-3-yl acetates 3 to give 2,4-disubstituted thiophenes 5 through the intermediate formation of (Z)-2-en-4-yne-1-thiolate derivatives 4, formed in situ by allylic nucleophilic substitution with KSAc followed by base-promoted deacylation (Scheme 3) [59]. Intermediates 4 were then converted into thiophenes 5 by 5-exo-dig cyclization and aromatization. The reaction has been applied to the synthesis of several 2,4-disubstituted thiophenes, but presented limitations due to the strong basic conditions employed (for example, the reaction could not be applied to substrates bearing a terminal triple bond) and to the need for the presence of an electron-withdrawing group (EWG) at the C-4 of the starting material (Scheme 3) [59].

Scheme 3. Synthesis of 2,4-disubstituted thiophenes 5 from 4-en-1-yn-3-yl acetates 3 by sequential allylic nucleophilic substitution with KSAc followed by base-promoted deacylation, to give (Z)-2-en-4-yne-1-thiolate derivatives 4, and base-promoted thiocyclization [59].

![Scheme 3 Diagram]

(R = alkyl, aryl; EWG = CO2Me, COMe)

Scheme 4. Synthesis of 3-cyano-2-(vinylthio)thiophenes 8 from 2-(1,3-dithiolan-2-ylidene)-4-ynenitriles 6 by NaH-induced ring opening, to give (Z)-1-en-4-yne-1-thiolates 7, followed by 5-exo-dig cyclization and aromatization [60].

![Scheme 4 Diagram]

(R1 = alkyl, aryl; R2 = aryl)

In a similar way, 3-cyano-2-(vinylthio)thiophenes 8 were obtained from 2-(1,3-dithiolan-2-ylidene)-4-ynenitriles 6 by NaH-induced ring opening of the 1,3-dithiolan-2-ylidene group (ensuing from
deprotonation of the methylene moiety bonded to sulfur), leading to the corresponding \((Z)-1\)-en-4-yn-1-thiolates 7, followed by 5-\(exo\)-dig cyclization and aromatization (Scheme 4) [60]. Interestingly, the similar substrates 1,1-\(bis\)(ethylthio)-1-en-4-ynes 9, bearing an electron withdrawing group, such as the carbonyl, at the 2 position, reacted in a rather different way when treated with a base such as DBU. In this case, in fact, the intermediate formation of \(gem\)-dialkylthiovinylallenes 10 took place, followed by 5-\(exo\)-dig \(S\)-cyclization and 1,3-migration of the ethyl group from sulfur to the benzylic carbon, eventually leading to substituted thiophenes 11 in good to high yields (Scheme 5) [61].

**Scheme 5.** Synthesis of thiophenes 11 from 1,1-\(bis\)(ethylthio)-1-en-4-ynes 9 by DBU-induced isomerization to \(gem\)-dialkylthiovinylallenes 10 followed by 5-\(exo\)-dig \(S\)-cyclization and 1,3-migration of the ethyl group [61].

![Scheme 5 Diagram](image)

An interesting approach to multifunctionalized thiophene 16 from 1,1,6,6-\(tetrakis\)(ethylthio)-2,5-\(bis\)(trifluoromethyl)hexa-1,5-dien-3-yne (12) has been reported, based on treatment of 12 with a mixture of trifluoroacetic acid and water (TFA-H\(_2\)O 9:3) at 75 °C for 2 h (Scheme 6) [62].

**Scheme 6.** Synthesis of \(S\)-ethyl 2-(5-(ethylthio)-4-(trifluoromethyl)thiophen-2-yl)-3,3,3-trifluoropropanethioate (16) from 1,1,6,6-\(tetrakis\)(ethylthio)-2,5-\(bis\)(trifluoromethyl)hexa-1,5-dien-3-yne (12) through the intermediate formation of 5-(3,3-\(bis\)(ethylthio)-1,1,1-trifluoroprop-2-en-2-yl)-2-(ethylthio)-3-(trifluoromethyl)thiophene (15) [62].

![Scheme 6 Diagram](image)
Formation of S-ethyl 2-(5-(ethylthio)-4-(trifluoromethyl)thiophen-2-yl)-3,3,3-trifluoropropane-thioate (16) is explained to occur by triple bond protonation to give stabilized carbocation 13 followed by sulfur attack to the carbocation and nucleophilic attack of the trifluoroacetate anion to the resulting sulfonylum cation 14. This leads to the formation of 5-(3,3-bis(ethylthio)-1,1,1-trifluoroprop-2-en-2-yl)-2-(ethylthio)-3-(trifluoromethyl)thiophene intermediate (15), which has been isolated under appropriate conditions, and which upon hydrolysis leads to the final product 16 (Scheme 6) [62]. A one-pot C-S coupling/heterocyclization approach to substituted thiophenes 19 has been recently reported [63]. It involves the Pd-catalyzed reaction of (Z)-1-bromo-1-en-3-ynes 17 with triisopropylsilanethiol (1.2 equiv), carried out in the presence of Xantphos as ligand and lithium hexamethyldisilazane (LiHMDS) as the base, to give (Z)-(1-en-3-nylthio)triisopropylsilanes 18, followed by 5-endo-dig cyclization, induced by desilylation with tetrabutylammonium fluoride (TBAF) (Scheme 7) [63].

Scheme 7. Synthesis of thiophenes 19 from (Z)-1-bromo-1-en-3-ynes 17 by Pd-catalyzed coupling with triisopropylsilanethiol, to give (Z)-(1-en-3-nylthio)triisopropylsilanes 18, followed by one-pot 5-endo-dig cyclization, induced by desilylation with tetrabutylammonium fluoride (TBAF) [63].

Further functionalization of the final product, to give thiophenes 21 and 22, could be introduced by reacting purified (Z)-triisopropyl-(5-(2-phenylethynyl)oct-4-en-4-ylthio)silane (20) with CsF in the presence of a suitable electrophile, such as dimethyl disulfide or p-chlorobenzaldehyde, and molecular sieves 4A (Scheme 8) [63].

A 5-endo-dig S-cyclization was also involved in the synthesis of substituted thiophenes 24 by Pd-catalyzed heterocyclodehydration of readily available 1-mercapto-3-yn-2-ols 23, recently reported by our research group [64]. The cyclization reaction is catalyzed by PdI2 in conjunction with an excess (10:1 molar ratio) of KI, and takes place either in MeOH at 50–100 °C (Table 2) or in an ionic liquid, such as BmimBF4, at 80 °C. These are optimized conditions, after a careful study on the influence of the reaction parameters (such as the KI:PdI2 molar ratio, the catalyst loading, and so on) on substrate reactivity and product yield. In the case of the reactions carried out in BmimBF4, the catalyst-solvent system could be recycled several times without appreciable loss of activity (Table 3) [64]. This protocol generalized the previous finding by Aponick and coworkers, who reported the Au/Ag-catalyzed
transformation of 1-mercapto-4-phenylbut-3-yn-2-ol into 2-phenylthiophene, carried out using 5 mol % of Au[P(t-Bu)₂(o-biphenyl)]Cl and 5 mol % of AgOTf in THF at 40 °C in the presence of molecular sieves 4A [65]. The heterocyclodehydration process takes place by 5-endo-dig intramolecular nucleophilic attack of the thiol group to the triple bond coordinated to the metal center, with elimination of HI, followed by dehydration and protonolysis or vice versa (Scheme 9; anionic iodide ligands are omitted for clarity) [64].

Scheme 8. Synthesis of 3-(methylthio)-2-phenyl-4,5-dipropylthiophene (21) and (4-chlorophenyl)(2-phenyl-4,5-dipropylthiophen-3-yl)methanol (22) from (Z)-triisopropyl (5-(2-phenylethynyl)oct-4-en-4-ylthio)silane (20) by CsF-induced 5-exo-dig S-cyclization in the presence of a suitable electrophile (dimethyl disulfide or p-chlorobenzaldehyde respectively) [63].

Table 2. PdI₂/KI-catalyzed heterocyclodehydration of 1-mercapto-3-yn-2-ols 23 to substituted thiophenes 24 a [64].
### Table 2. Cont.

| Entry | 23 | PdI$_2$ (mol %) | T (°C) | t (h) | 24 | Yield of 24 (%)$^b$ |
|-------|----|----------------|--------|-------|----|-------------------|
| 7     | ![Structure](image1) | 1 | 50 | 8 | ![Structure](image2) | 85 |
| 8     | ![Structure](image3) | 1 | 50 | 8 | ![Structure](image4) | 52$^c$ |
| 9     | ![Structure](image5) | 2 | 80 | 3 | ![Structure](image6) | 85 |

$^a$: All cycloisomerization reactions were carried out in MeOH as the solvent (0.5 mmol of starting thiol 23 per mL of MeOH) in the presence of PdI$_2$ and KI (KI:PdI$_2$ molar ratio of 10). Conversion of substrate was quantitative; $^b$: Isolated yield based on starting 23; $^c$: Substrate conversion was 74%.

### Table 3. Recyclable catalytic synthesis of substituted thiophenes 24 by PdI$_2$/KI-catalyzed heterocyclodehydration of 1-mercapto-3-yn-2-ols 23 in BmimBF$_4$ $^a$ [64].

![Diagram](image7)

| Entry | 23 | 24 | Yield of 24 (%)$^b$ |
|-------|----|----|-------------------|
|       | ![Structure](image8) | ![Structure](image9) | Run 1 | Run 2 | Run 3 | Run 4 | Run 5 | Run 6 | Run 7$^c$ |
| 1     | ![Structure](image10) | ![Structure](image11) | 81 | 83 | 80 | 79 | 79 | 78 | 79 |
| 2     | ![Structure](image12) | ![Structure](image13) | 71 | 72 | 71 | 70 | 70 | 71 | 69 |
| 3     | ![Structure](image14) | ![Structure](image15) | 78 | 77 | 77 | 76 | 76 | 77 | 76 |
| 4     | ![Structure](image16) | ![Structure](image17) | 67 | 66 | 67 | 66 | 66 | 65 | 65 |

$^a$: All cycloisomerization reactions were carried out at 80 °C for 24 h in BmimBF$_4$ as the solvent (0.2 mmol of starting thiol 23 per mL of BmimBF$_4$) in the presence of PdI$_2$ (1 mol %) and KI (KI:PdI$_2$ molar ratio of 10). Conversion of substrate was quantitative; $^b$: Isolated yield based on starting 23; $^c$: Run 1 corresponds to the 1st experiment, the next runs to recycles.
Scheme 9. Proposed mechanistic pathways for the PdI2-catalyzed heterocyclodehydration of 1-mercapto-3-yn-2-ols 23 leading to thiophenes 24 [64].

Copper-promoted or –catalyzed cyclization of S-containing alkyne derivatives to give thiophenes has also been reported. Thus, (Z)-1-en-3-ynyl(butyl)sulfanes 25 were converted into the corresponding substituted 3-halothiophenes 27 (X = Cl or Br) when treated with 2 equiv of CuX2 in MeCN (X = Cl) or THF (X = Br) as the solvent (Scheme 10) [66]. The process is believed to proceed through CuX2-promoted 5-endo-dig S-cyclization, to give the sulfonium salt 26, followed by reductive elimination with simultaneous nucleophilic attack by the X⁻ anion to the butyl group bonded to the sulfur atom of 26 (Scheme 10) [66].

Scheme 10. Synthesis of thiophenes 27 from (Z)-1-en-3-ynyl(butyl)sulfanes 25 by CuX2-promoted 5-endo-dig S-cyclization, to give the sulfonium salt 26, followed by elimination of BuX and Cu(0) [66].

In a strictly related process, 2-aryl-3-halothiophenes 30 were obtained in moderate yields from but-3-ynyl(butyl)sulfanes 28, when working in the presence of 4 equiv of CuX2 (X = Cl, Br) in DMA under air at 100 °C for 12 h, through the intermediate formation of dihydrothiophenes 29 (Scheme 11) [67].
Scheme 11. Synthesis of 2-aryl-3-halothiophenes 30 from but-3-ynyl(butyl)sulfanes 28 by CuX$_2$-mediated 5-endo-dig S-cyclization, elimination of BuX and Cu(0), and in situ oxidation of dihydrothiophene intermediates 29 [67].

![Scheme 11](image)

(R = H, 2-Me, 4-OMe, 4-Cl, 3-CF$_3$; X = Cl, Br)

The Cu(I)-catalyzed tandem addition of terminal alkynes to 1-phenylsulfonylalkylidenethiiranes 31/cycloisomerization has allowed a convenient synthesis of functionalized thiophenes 33 (Table 4) [68].

Table 4. CuCl/DBU-catalyzed tandem addition/cycloisomerization of 1-phenylsulfonylalkylidenethiiranes 31 with terminal alkynes leading to thiophenes 33 $^{a}$ [68].

| Entry | 31 | 1-Alkyne | t (h) | 33 | Yield of 33 (%) $^{b}$ |
|-------|----|----------|------|----|------------------------|
| 1     | ![](image) | ![image](image) | 10   | ![image](image) | 91 |
| 2     | ![image](image) | ![image](image) | 10   | ![image](image) | 86 |
| 3     | ![image](image) | ![image](image) | 8    | ![image](image) | 68 |
| 4     | ![image](image) | ![image](image) | 10   | ![image](image) | 65 |
| 5     | ![image](image) | ![image](image) | 10   | ![image](image) | 67 |
| 6     | ![image](image) | ![image](image) | 12   | ![image](image) | 68 |
| 7     | ![image](image) | ![image](image) | 5    | ![image](image) | 91 |
| 8     | ![image](image) | ![image](image) | 14   | ![image](image) | 76 |

$^{a}$ [68]
Reactions were carried out in toluene at 50 °C or under reflux with a molar ratio of 31: alkyne:CuCl of 1:1.5:0.2, in the presence of DBU (10 mol % with respect to 31). The reaction is believed to proceed through base-promoted formation of an alkynylcopper intermediate, whose regiospecific attack to the C-2 of the thiirane ring affords (Z)-1-phenylsulfonyl-1-en-4-yne-2-thiolate intermediate 32. 5-Endo-dig cyclization of the latter, ensuing from intramolecular nucleophilic attack of the thiolate group to the triple bond coordinated to CuCl, followed by protonolysis and isomerization, eventually leads to the final thiophene derivative 33 (Scheme 12) [68].

**Scheme 12.** Formation of thiophenes 33 by CuCl/DBU-catalyzed tandem addition/cycloisomerization of 1-phenylsulfonylalkylidenethiiranes 31 with terminal alkynes through the intermediate formation of (Z)-1-phenylsulfonyl-1-en-4-yne-2-thiolate 32 [68].

An interesting approach to 2,5-disubstituted thiophenes 38, starting from 1-bromoalkynes 34 and Na₂S (5 equiv) in the presence of Cul (15 mol %) and 1,10-phenanthroline (20 mol %), in DMF at 70 °C, has been recently developed (Scheme 13) [69]. The proposed mechanism starts with the Cu(I)-catalyzed formation of 1,3-diynes 35, followed by sulfide attack to the triple bond to give enynethiolate intermediate 36. Cu-promoted 5-endo-dig cyclization of the latter, ensuing from intramolecular attack by the sulfur atom to the triple bond coordinated to Cul, leads to 3-thienylcopper complex 37, from which the final product is formed by protonolysis (Scheme 13) [69].
Scheme 13. Synthesis of thiophenes 38 from 1-bromoalkynes 34 and Na₂S by CuI-induced 5-endo-dig S-cyclization of enynethiolate intermediate 36, formed by sulfide addition to 1,3-diynes 35, deriving in their turn from CuI-catalyzed homocoupling of 34 [69].

\[
\text{R} \equiv \equiv \text{Br} + \text{Na}_2\text{S} \cdot 9\text{H}_2\text{O} \xrightarrow{\text{Cul (15\%)}, \text{1,10-phen (20\%)}, \text{DMF, 70°C, 6 h}} \text{S} \equiv \equiv \text{R} \xrightarrow{-\text{Cu(I)}} \text{S} \equiv \equiv \text{R} \quad (\text{R = aryl, heteroaryl})
\]

The direct, metal-free conversion of 1,3-diynes 39 to thiophenes 40, by reaction with a 3-fold excess of NaSH or Na₂S•9H₂O in DMF at 25–80 °C for 1–48 h, has also been reported, as exemplified in Scheme 14 [70].

Scheme 14. Metal-free synthesis of thiophenes 40 from 1,3-diynes 39 and Na₂S [70].

(R¹ = aryl, heteroaryl; R² = aryl, alkyl)

3. Synthesis of Thiophene Derivatives by Iodocyclization of S-Containing Alkyne Substrates

The iodocyclization of suitably functionalized alkynes is a very important synthetic tool for the direct preparation of iodine-containing carbo- and heterocycles starting from readily available starting materials [71–79]. The utility of the method is further demonstrated by the possibility to elaborate the final products through various cross-coupling reactions (such as Heck, Suzuki-Miyaura, and Sonogashira reactions). The process is usually carried out under mild conditions, and takes place through intramolecular nucleophilic attack of the nucleophilic group of the substrate to the iodonium ion formed by the reaction between the triple bond and the electrophilic iodine species (indicated with I⁺); both exo and endo cyclization modes are possible, as shown in Scheme 15. The process is usually carried out in the presence of a base, to buffer the acid generated during the process.
Iodocyclization of alkynes bearing a suitably placed nucleophilic group leading to iodinated carbo- or heterocycles [71–79].

\[
\begin{align*}
\text{YH} & \quad \text{I}^+ \\
\text{YH} & \quad \text{R} \\
\text{R} & \quad \text{I} \\
\text{Y} & \quad \text{H} \\
\text{Y} & \quad \text{R} \\
\end{align*}
\]

(YH = nucleophilic group; I\(^+\) = electrophilic iodine species)

Recently, several novel approaches to iodinated thiophenes have been reported, starting from readily available sulfur-containing alkynes. As an extension of the previously reported syntheses of 3-iodofuran and 3-iodopyrrole derivatives by the iodocyclization of 3-yne-1,2 diols [80–84] and N-protected 1-amino-3-yn-1-ols [80,85], respectively, our research group has reported a particularly facile and convenient synthesis of 3-iodothiophenes 41 by dehydrative iodocyclization of 1-mercapto-3-yn-2-ols 23, according to Scheme 16 [86]. Reactions were carried out in MeCN at room temperature for 5 h, using molecular iodine as the electrophilic iodine species (2–3 equiv) and NaHCO\(_3\) as the base (1–3 equiv). Iodine-induced 5-endo-dig cyclization was followed by dehydration with aromatization to give 41 in fair to high yields (65%–88%, Scheme 16) [86].

\[
\begin{align*}
\text{SH} & \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \\
\text{R}_1 & \quad \text{R}_2 \quad \text{R}_3 \\
\text{41} & \quad (65-88\%) \\
\text{MeCN, rt, 5 h} \\
\text{I}_2 (2-3\text{ equiv}) & \quad \text{NaHCO}_3 (1-3\text{ equiv}) \\
\end{align*}
\]

(R\(_1\) = H, alkyl; R\(_2\) = H, alkyl, alkynyl; R\(_3\) = alkyl, alkenyl, aryl, heteroaryl)

Interestingly, the process also took place in an ionic liquid bearing a basic anionic moiety, such as 1-ethyl-3-methylimidazolium ethylsulfate (EmimEtSO\(_4\)), as the solvent, in the absence of external bases [87]. As reported in Table 5, the reaction medium could be recycled several times without significantly affecting the reaction outcome. Theoretical calculations have confirmed the role of the ethylsulfate anion in the deprotonation of the thiolic group of the substrate [87].

A thioether or thioester group can also act as intramolecular nucleophile in an iodocyclization process, eventually leading to a thiophene derivative. Thus, 5-(4-(benzylthio)but-1-ynyl)-2-methoxyphenyl acetate 42 was easily transformed into 5-(3-iodothiophen-2-yl)-2-methoxyphenol 45 in almost quantitative yield by a three-step procedure, involving iodocyclization (carried out with I\(_2\) in CH\(_2\)Cl\(_2\) at room temperature), to give dihydrothiophene 44, followed by oxidation with DDQ and deacylation with K\(_2\)CO\(_3\) in MeOH (Scheme 17) [88].
Table 5. Recyclable and base-free synthesis of 3-iodothiophenes 41 by iodo-heterocyclization of 1-mercapto-3-yn-2-ols 23 in EmimEtSO4 \(^a\) [87].

| Entry | 23 | 41 | Yield of 41 (%) \(^b\) |
|-------|----|----|----------------------|
|       |    |    | Run 1 | Run 2 | Run 3 | Run 4 | Run 5 | Run 6 | Run 7 \(^c\) |
| 1     | ![Structural formula](image1) | ![Structural formula](image2) | 70 | 68 | 70 | 71 | 72 | 70 | 72 |
| 2     | ![Structural formula](image3) | ![Structural formula](image4) | 65 | 67 | 68 | 62 | 65 | 65 | 60 |
| 3     | ![Structural formula](image5) | ![Structural formula](image6) | 77 | 68 | 67 | 69 | 68 | 70 | 71 |
| 4 \(^d\) | ![Structural formula](image7) | ![Structural formula](image8) | 77 | 73 | 70 | 65 | 61 | 60 | 60 |
| 5 \(^e\) | ![Structural formula](image9) | ![Structural formula](image10) | 81 | 73 | 76 | 75 | 72 | 73 | 74 |

\(^a\): Unless otherwise noted, all iodocyclization reactions were carried out at rt for 24 h in EmimEtSO4 as the solvent (0.25 mmol of starting thiol 23 per mL of EmimEtSO4) in the presence of 1 equiv of I\(_2\). Conversion of substrate was quantitative; \(^b\): Isolated yield based on starting 23; \(^c\): Run 1 corresponds to the 1st experiment, the next runs to recycles; \(^d\): The reaction was carried out with a I\(_2\):substrate molar ratio of 2; \(^e\): The reaction was carried out with a I\(_2\):substrate molar ratio of 1.5.

Scheme 17. Synthesis of 5-(3-iodothiophen-2-yl)-2-methoxyphenol 45 by 5-endo-dig iodocyclization of 5-(4-(benzylthio)but-1-ynyl)-2-methoxyphenyl acetate 42 to give 5-(3-ido-4,5-dihydrothiophen-2-yl)-2-methoxyphenyl acetate 44 (through the intermediate formation of sulfonium ion salt 43) followed by oxidation and deacylation [88].
As concerns the mechanism leading to 44, as shown in Scheme 17, the initial iodo cyclization is followed by nucleophilic attack by the iodide anion on the benzyl group of the sulfonium intermediate 43. In a similar way, (Z)-1-en-3-ynyl(butyl)sulfanes 46 were smoothly converted into 3-iodothiophenes 47 when treated with 1.1 equiv of I\(_2\) in CH\(_2\)Cl\(_2\) or 1,2-dichloroethane (DCE) at rt or 70 °C for 5 min–2 h, as shown in Table 6 [89,90].

Table 6. Synthesis of 3-iodothiophenes 47 by iodo cyclization of (Z)-1-en-3-ynyl(butyl)sulfanes 46 \(^a\) [89,90].

| Entry | 46 | Solvent | t | T | Yield of 47 (%) \(^b\) |
|-------|----|---------|---|---|-----------------------|
| 1     | SBu\(\text{Ph}\)\(\text{Ph}\) | CH\(_2\)Cl\(_2\) | 5 min | rt | 82 |
| 2     | SBu\(\text{OMe}\)\(\text{MeO}\) | CH\(_2\)Cl\(_2\) | 5 min | rt | 92 |
| 3     | SBu\(\text{Cl}\)\(\text{Cl}\) | CH\(_2\)Cl\(_2\) | 15 min | rt | 77 |
| 4     | SBu\(\text{Bu}\)\(\text{Bu}\) | CH\(_2\)Cl\(_2\) | 20 min | rt | 65 |
| 5     | SBu\(\text{Ph}\)\(\text{HO}\)\(\text{Me}\)\(\text{Me}\) | CH\(_2\)Cl\(_2\) | 30 min | rt | 84 |
| 6     | SBu\(\text{Ph}\)\(\text{Bu}\) | DCE | 2 h | 70 °C | 80 |
| 7     | SBu\(\text{Bu}\)\(\text{Bu}\) | DCE | 2 h | 70 °C | 68 |

\(^a\): I\(_2\) was added dropwise in the appropriate solvent; \(^b\): Isolated yield based on starting 46.

3,4-Dihalodihydrothiophenes 49 have been obtained in moderate to excellent yields (39%–98%) by the iodo cyclization of S-4-hydroxybut-2-ynyl ethanethioate 48, carried out with an excess of I\(_2\) or IBr (2–3 equiv) in CH\(_2\)Cl\(_2\) at rt for 1 h, according to Scheme 18 [91,92]. These products could be conveniently converted into the corresponding 3,4-dihalothiophenes 50 through oxidation with DDQ and then further elaborated by the Heck or Sonogashira reactions [91].
Scheme 18. Synthesis of 3,4-dihalodihydrothiophenes 49 by iodocyclization of S-4-hydroxybut-2-ynyl ethanethioate 48 and their oxidation into 3,4-dihalothiophenes 50 [91,92].

Mechanistically, the idocyclization process is believed to occur through I2- or IBr-induced formation of an allenic carbocation 51 (with simultaneous formation of HOI), followed by iodide (or bromide) attack to give an iodoallene (or bromoallene) intermediate 52 (Scheme 19). Reaction of the latter with HOI affords the iodonium intermediate 53, which then undergoes intramolecular nucleophilic attack by the sulfur atom to give sulfonium cation 54. Deacylation of the latter by the previously generated hydroxide anion eventually affords 3,4-dihalodihydrothiophenes 49 (Scheme 19) [91,92].

Scheme 19. Proposed mechanism for the formation of 3,4-dihalodihydrothiophenes 49 by iodocyclization of S-4-hydroxybut-2-ynyl ethanethioate 48 [91,92].

Starting from S-4-oxobut-2-ynelethanethioates 55, the formation of 3,4-diodothiophenes 56 could be obtained directly, using 3 equiv of I2 in nitromethane at rt for 5 h (Scheme 20) [92].

Scheme 20. Synthesis of 3,4-diiodothiophenes 56 by iodocyclization of S-4-oxobut-2-ynelethanethioates 55 [92].
4. Synthesis of Thiophene Derivatives by Carbocyclization of S-Containing Alkyne Substrates

Only a few methods have been reported so far in the literature for the synthesis of thiophenes through carbocyclization of S-containing acetylenes. To the best of our knowledge, the first catalytic example of such an approach was reported by our research group in 1999 [93]. It involved the PdI2/KI-catalyzed carbonylative carbocyclization of dipropargyl sulfide (57) to afford a mixture of 3,4-bis(methoxycarbonylmethylene)tetrahydrothiophene (58, 39%, Z,Z,E,E ca. 1:1) and 3,4-bis-(methoxycarbonylmethyl)thiophene (59, 3%), which could be treated directly, without further purification, with Et3N in CH2Cl2 at 60 °C for 3 h to selectively give the novel thiophene derivative 59 in 40% isolated yield based on starting 57 (Scheme 21). The carbonylation reaction was carried out in MeOH as the solvent at 40 °C and under 20 atm of a 3:1 mixture of CO-air, in the presence of 0.5 mol % of PdI2 and 5 mol % of KI for 5 h [93].

**Scheme 21.** Synthesis of 3,4-bis(methoxycarbonylmethyl)thiophene (59) by PdI2-catalyzed oxidative carbonylative carbocyclization of dipropargyl sulfide 57 followed by base-promoted isomerization [93].

The carbonylative carbocyclization process started with the formation of a methoxycarbonylpalladium iodide intermediate 60 from the reaction between PdI2, CO, and MeOH [49,94–100], followed by the insertion of the triple bond of 57 into the palladium-carbon bond to give complex 61, stabilized by the chelation from the second triple bond (Scheme 22; anionic iodide ligands are omitted for clarity). Further insertion of the triple bond leads to the carbocyclized vinylpalladium intermediate 62, from which the final product 58 is obtained from nucleophilic displacement by MeOH. In the last step, Pd(0) was generated, which is then reoxidized back to PdI2 according to a mechanism involving initial oxidation of 2 mol of HI (also ensuing from the carbonylation process) to give I2, followed by oxidative addition of I2 to Pd(0) [49,94–100] (Scheme 22).

Later on, the anionic carbocyclization of some dipropargyl sulfides was studied, using t-BuOK in THF at rt for 1 min [101]. The reaction of (3-phenylprop-2-ynyl)(prop-2-ynyl)sulfane (63) led to a 1:1 diastereoisomeric mixture of 2-styrylthiophene (65) in 70% yield, through a mechanism involving the formation of diallenyl sulfide 64 as intermediate (Scheme 23). Similar results were obtained with (4,4-dimethylpent-2-ynyl)(3-phenylprop-2-ynyl)sulfane [101].
Scheme 22. Proposed mechanism for the formation of bis(methoxycarbonylmethylene)-tetrahydrothiophene (58) by PdI₂-catalyzed oxidative carbonylative carbocyclization of dipropargyl sulfide (57) [93].

Scheme 23. Formation of 2-styrylthiophene (65) by base-promoted carbocyclization of (3-phenylprop-2-ynyl)(prop-2-ynyl)sulfane (65) [101].

A more complicated reaction mixture was observed from the reaction of bis(3-phenylprop-2-ynyl)sulfane, with formation of products deriving from radical cycloaromatization besides the expected vinylthiophene. A radical cycloaromatization mechanism was also at work in the case of bis(4-methylpent-4-en-2-ynyl)sulfane (66) with formation of 6-methyl-4-(prop-1-en-2-yl)-4,5-dihydrobenzo[c]thiophene 68 in 36% yield, through the formation of the diradical intermediate 67 [101] (Scheme 24).

A propargyl-allenyl isomerization was also the first step in the formation of β-allyl thiophene derivatives 73 starting from functionalized allyl(4-en-2-ynyl)sulfanes 69, using DBU as the base in THF at rt [102]. As shown in Scheme 25, the initially formed eneallyl intermediate 70 underwent thio-Claisen rearrangement (TCR) to give trienethione 71. Deprotonation of the latter followed by
intramolecular conjugate addition afforded 5-methylene-2,5-dihydrothiophene 72, whose aromatization led to the final thiophene derivative 73 [102].

**Scheme 24.** Formation of 6-methyl-4-(prop-1-en-2-yl)-4,5-dihydrobenzo[c]thiophene (68) by base-promoted carbocyclization of bis(4-methylpent-4-en-2-ynyl)sulfane (66) [101].

![Scheme 24](image)

**Scheme 25.** Synthesis of β-allyl thiophene derivatives 73 by base-promoted isomerization/thio-Claisen rearrangement/conjugate addition/aromatization of allyl(4-en-2-ynyl)sulfanes 69 [102].

![Scheme 25](image)

An interesting tandem thermal rearrangement/carbocyclization process of dipropargylic disulfides 74, leading to a mixture of 1,3-dihydrothieno[3,4-c]thiophenes 75 and thienyl disulfides 76, has been reported recently [103]. As shown in Table 7, the reaction takes place in CHCl₃, MeCN, or DMSO as the solvent at 60–70 °C for 1.5–160 h [103].

Mechanistically, the reaction leading to 75 is believed to occur via an initial double [2,3]-sigmatropic rearrangement to give diallenyl disulfides 77, which may then undergo a [3,3]-sigmatropic rearrangement to give 2,3-dimethylene-1,4-dithione 78, followed by a double conjugate addition of the
sulfur atoms to the double bonds of 78, to give 1,4-dihydrothieno[3,4-c]thiophene 79, and isomerization (Scheme 26, path a). On the other hand, 76 may be formed by dimerization of the thyl radical intermediate 80, formed in its turn from 79 by the action of O₂ (Scheme 26, path b). Accordingly, the formation of 76 could be minimized working in the absence of air under argon atmosphere (entry 2, Table 8) [103].

**Table 7.** Synthesis of 1,3-dihydrothieno[3,4-c]thiophenes 75 and thienyl disulfides 76 by tandem thermal rearrangement/carbocyclization process of dipropargylic disulfides 74

| Entry | 74 | Solvent | t (h) | T (°C) | 75 | 76 | Yield of 75 (%) b | Yield of 76 (%) b |
|-------|----|---------|-------|--------|----|----|-------------------|-------------------|
| 1     | ![74](image1) | CHCl₃   | 1.5   | 60     | ![75](image2) | ![76](image3) | 13                | 27                |
| 2⁺    | ![74](image1) | CHCl₃   | 2     | 60     | ![75](image2) | ![76](image3) | 73                | 7                 |
| 3     | ![74](image1) | CHCl₃   | 160   | 60     | ![75](image2) | ![76](image3) | 54                | 11                |
| 4     | ![74](image1) | DMSO    | 24    | 70     | ![75](image2) | ![76](image3) | 0                 | 45                |
| 5     | ![74](image1) | CHCl₃   | 24    | 60     | ![75](image2) | ![76](image3) | 45                | 8                 |
| 6     | ![74](image1) | MeCN    | 16    | 60     | ![75](image2) | ![76](image3) | 36                | 12                |

a: The mixture 75+76 was isolated by column chromatography. Products 75 and 76 were not separated; b: Yield based on starting 74, referred to the isolated overall yield of 75+76 and based on the 75:76 molar ratio as determined by ¹H-NMR; c: The reaction was carried out under argon atmosphere.
Scheme 26. Proposed mechanistic pathway for the formation of 1,3-dihydrothieno[3,4-c]-thiophenes 75 and thienyl disulfides 76, by tandem thermal rearrangement/carbocyclization of dipropargylic disulfides 74 [103].

Table 8. Multicomponent synthesis of ethyl 2-(2-(dimethylamino)thiophen-3-yl)-2-oxoacetate derivatives 84 starting from acetylenic esters 81, tetramethylthiourea 82, and ethyl bromopyruvate 83 a [104].

| Entry | 81 | 84 | Yield of 84 b (%) |
|-------|----|----|------------------|
| 1     | MeO2C=CO2Me | EtO2C=CO2Me | 90 |
| 2     | EtO2C=CO2Et  | EtO2C=CO2Et  | 85 |
| 3     | Ph=CO2Et     | EtO2C=Ph     | 74 |
| 4     | MeO2C=CO2Me  | EtO2C=CO2Me  | 73 |
| 5     | EtO2C=CO2Et  | EtO2C=CO2Et  | 75 |

a: All reactions were carried out with an equimolar amount of 81, 82, and 83 (2 mmol per 15 mL of CH2Cl2); b: Isolated yield.
5. Synthesis of Thiophene Derivatives by Miscellaneous Methods Starting from Functionalized Alkyne Substrates

Miscellaneous methods that cannot be classified into the previous categories are reviewed here. Acetylenic esters can be useful precursors for the construction of the thiophene ring. Thus, ethyl 2-(2-(dimethylamino)thiophen-3-yl)-2-oxoacetate derivatives 84 have been conveniently synthesized through a multicomponent approach, employing acetylenic esters 81, tetramethylthiourea 82, and ethyl bromopyruvate 83 as starting materials [104]. Reactions were carried out in CH₂Cl₂ at rt using equimolar amounts of 81, 82, and 83, to afford the corresponding thiophenes 84 in good to high yields (Table 8) [104].

The proposed reaction mechanism involves the formation of a 1,5-dipolar intermediate 85 from the reaction between 81 and 82, followed by nucleophilic attack by the carbanion to 83 to give the organic salt 86. The final thiophene derivative 84 is then formed from 86 by elimination of HBr to give the dipolar intermediate 87, followed by intramolecular nucleophilic attack, affording dihydrothiophene 88, and elimination of dimethylamine (Scheme 27) [104].

**Scheme 27.** Proposed mechanism for the formation of ethyl 2-(2-(dimethylamino)thiophen-3-yl)-2-oxoacetate derivatives 84 starting from acetylenic esters 81, tetramethylthiourea 82, and ethyl bromopyruvate 83 [104].

In a similar way, trialkyl 4-arylthiophene-2,3,5-tricarboxylates 93 were obtained in moderate yields (30%–50%) from the reaction between dialkyl acetylenedicarboxylates 89, KSCN, and 3-aryl-2-cyanoacrylates 90, carried out in MeCN at rt for 6 h, through the intermediate formation of the organic salt 91, which undergoes cyclization with loss of KCN (to give dihydrothiophene derivative 92) followed by elimination of HCN (Scheme 28) [105].

Another useful utilization of acetylenic diesters for the thiophene synthesis has been reported recently. It involves the reaction between β-oxodithioesters 94 and dialkyl acetylenedicarboxylates 89 (1:1 molar ratio) carried out in the presence of an equimolar amount of dimethylaminopyridine (DMAP) in CH₂Cl₂ at rt for 3–5 min (Scheme 29) [106]. The process takes place through α-deprotonation of 94 by DMAP and intermolecular conjugate addition (from nucleophilic attack by the sulfur atom to the triple bond of 89, to give anionic intermediate 95), followed by intramolecular conjugate addition to give
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Dihydrothiophene 96, and elimination of Me₂S, eventually leading to dialkyl thiophene-2,3-dicarboxylate derivatives 97 (Scheme 29) [106].

Scheme 28. Synthesis of trialkyl 4-arylthiophene-2,3,5-tricarboxylates 93 starting from dialkyl acetylenedicarboxylates 89, KSCN, and 3-aryl-2-cyanoacrylates 90 [105].

\[
\text{CO}_2\text{R} + \text{KSCN} + \text{EtO}_2\text{C}-\text{CN} \rightarrow \text{Ar-S} + \text{EtO}_2\text{C}-\text{CO}_2\text{R}
\]

(R = Me, Et; Ar = Ph, p-MeC₆H₄, p-ClC₆H₄, p-O₂NC₆H₄)

Scheme 29. Synthesis of dialkyl thiophene-2,3-dicarboxylate derivatives 97 starting from β-oxodithioesters 94 and dialkyl acetylenedicarboxylates 89 in the presence of DMAP [106].

\[
\text{MeS} + \text{CO}_2\text{R} \rightarrow \text{MeS} + \text{CO}_2\text{R}
\]

(R = Me, Et; R' = alkyl, aryl, heteroaryl, ferrocenyl)

A mechanism involving a conjugate addition by a thiolate anion to an activate triple bond was also at work in a modification of the classical Fiesselmann thiophene synthesis [107], involving the reaction between acetylenic ketones 98 and methyl thioglycolate 99 to give methyl thiophene-2-carboxylates 100 (Scheme 30) [108]. Reactions were carried out by dissolving an equimolar amount of 98 and 99 in THF at 0 °C followed, after 2 h, by the addition of a 1:2 mixture of CsCO₃/MgSO₄ in MeOH and stirring at rt for 2 h [108].
Scheme 30. Synthesis of methyl thiophene-2-carboxylates 100 from acetylenic ketones 98 and methyl thioglycolate (99) in the presence of CsCO3, MgSO4, and MeOH [108].

A particularly convenient approach to 2,4-disubstituted thiophenes 104, based on a sequential three-component Sonogashira coupling/Fiesselmann-type cyclocondensation, has been reported recently [109]. Thus, the reaction between (hetero)aroyl chlorides 101 and terminal alkynes 102 (1.1 equiv) (carried out at rt in THF for 2 h, in the presence of 2 mol % of PdCl2(PPh3)2, 4 mol % of Cul, and 1.05 equiv of Et3N) was followed by the addition of EtOH, ethyl thioglycolate 103 (1.2 equiv) and DBU (1.5 equiv), to give, after stirring for 12–24 h at rt, thiophene derivatives 104 in moderate to excellent yields (32%–97%, Table 9). The method has also been successfully applied to the synthesis of luminescent terthiophenes and pentathiophenes [109].

Table 9. Synthesis of ethyl thiophene-2-carboxylates 104 starting from sequential Sonogashira coupling between (hetero)aroyl chlorides 101 and terminal alkynes 102/Fiesselmann-type cyclocondensation [109].

| Entry | 101 | 102 | 104 | Yield of 104 (%) |
|-------|-----|-----|-----|-----------------|
| 1     | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | 97 |
| 2     | ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) | 88 |
An interesting approach to regioisomeric 2,3,5-triaryl-4-trifluoromethylthiphene 107 and 108, based on 1,3-dipolar cycloaddition between 1-aryl-3,3,3-trifluoro-1-propynes 105 and 1,3-dithiolium-4-olates 106 (1:1 molar ratio), was developed some years ago (Scheme 31) [109]. Reactions were carried out in xylenes at 120 °C for 20–32 h [110].
Scheme 31. Synthesis of 2,3,5-triaryl-4-trifluoromethylthiophenes 107 and 108 from 1-aryl-3,3,3-trifluoro-1-propynes 105 and 1,3-dithiolium-4-olates 106 [110].

6. Conclusions

The development of novel, efficient and selective methods for the construction of the thiophene ring starting from acyclic precursors is a very important target in current organic synthesis, in view of the high significance of the products obtained and of the more and more stringent requirements in the direction of a sustainable chemistry. In this regard, the synthesis of thiophene derivatives by heterocyclization of readily available S-containing alkyne substrates has proved to be a valuable and reliable approach, and it is destined to assume a central role in the next future for the one-step production of this particularly important class of heterocyclic derivatives. Recent progress in organometallic catalysis has also recently opened the way to the use of metal catalysis for promoting S-heterocyclization reactions leading to thiophenes under particularly mild and efficient reaction conditions. Further progress will allow developing other novel synthetic routes characterized by even more efficiency and selectivity under environmentally friendly conditions.

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Conflicts of Interest

The authors declare no conflict of interest.

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