Green methodologies for the synthesis of 2-aminothiophene

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Abstract
Pollution and the rising energy demand have prompted the design of new synthetic reactions that meet the principles of green chemistry. In particular, alternative synthesis of 2-aminothiophene have recently focused interest because 2-aminothiophene is a unique 5-membered S-heterocycle and a pharmacophore providing antiprotozoal, antiproliferative, antiviral, antibacterial or antifungal properties. Here, we review new synthetic routes to 2-aminothiophenes, including multicomponent reactions, homogeneously- or heterogeneously-catalyzed reactions, with focus on green pathways.

Keywords 2-Aminothiophene · Green chemistry · Sustainable synthesis · Gewald methodology · Multicomponent reactions

Introduction
In chemistry, the development of heterocyclic synthetic methodologies is a crucial field. More than 75% of all biologically active compounds possess a heterocyclic moiety (Jampilek 2019). Thiophene is a particularly interesting scaffold because it is a bioisostere of the phenyl groups, which is found in a wide range of active drugs and both natural and synthetic medicines (Jarvest et al. 1999; Doré et al. 2004). Within the thiophene family, 2-aminothiophenes have been shown to confer biological applications in a variety of areas, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral agents (Kasprzyk et al. 2021).

As examples, we can highlight compound A known as RS-C-5966451, described for its broad-spectrum antiviral properties (Fig. 1) (Thakur et al. 2007), derivative B, named PD 81,723, for its adenosine A1 receptor agonist used to reduce necrosis, apoptosis and inflammation for renal ischemia-reperfusion (Fig. 1) (Narlawar et al. 2010; Park et al. 2012), and structure C, called tinoridine, for its non-steroidal anti-inflammatory assets (Fig. 1) (Kalariya et al. 2015).

The constant advancement of efficient procedures to assemble complex structures with a high value in the pharmaceutical field is required in medicinal chemistry and, more specifically, drug discovery. Regarding 2-aminothiophenes, it is worth noting that thiophenes are 5-membered aromatic scaffolds whose synthesis was initially described by Campagne and Foye in the 1950s (Campagne and Foye 1952). Several years later, in the 1960s, Gewald developed and standardized the reaction, which explains why the
reaction bears his name (Gewald et al. 1966; Singla et al. 2018). A carbonyl derivative 1, a nitrile 2 and a sulfur source are frequently used in this reaction to yield 3. Frequently, methodologies often lead to the formation of a trisubstituted thiophene ring with an electron-withdrawing group—particularly negative mesomeric effects like carboxamide, ester or cyano function on the C3 position (Fig. 2) (Minetto et al. 2005; Revelant et al. 2011; Gouda et al. 2020; Hwang et al. 2020; Ibrahim and Mohareb 2020).

Mechanistically, the first step consists of a Knoevenagel condensation in basic medium, between the carbanion 4 and the ketone 1, followed by the dehydration of 5 to afford 6. In a second step, the generated carbanion 7 reacts with the elemental sulfur S₈ to yield 8. Finally, ring closure occurs to give 9 and then 3 after the aromatization and the departure of S₇ (Fig. 3) (Sabnis et al. 1999). The elemental sulfur S₈ is often used for the synthesis of 2-aminothiophenes is known to exhibit low toxicity in the environment against organisms (Kuklińska et al. 2013).

Research groups from all over the world are always looking for new and very effective ways to make 2-aminothiophenes, using different methods (Aurelio et al. 2008; Wang et al. 2010; Scheich et al. 2010; Aly et al. 2011; Oza et al. 2012; Ma et al. 2013; Thanna et al. 2016; Desantis et al. 2017; Pathania et al. 2019; Rezaei-Seresht et al. 2021). In fact, 2-aminothiophenes continue to raise an interest in both organic synthesis and medicinal chemistry. Interestingly, the synthesis of 2-aminothiophenes is a lot more well known than the synthesis of 3-aminothiophene, mostly because 2-aminothiophenes synthetic routes are, for now, more accessible than 3-aminothiophene (Han et al. 2018; Novanna et al. 2019; Batsyts et al. 2019; Irgashev et al. 2021). For
example, the main strategy to synthesize 3-aminothiophenes is Thorpe–Ziegler cyclization, which often requires precursor synthesis (Dagoneau et al. 2019).

Consistently, articles describing the synthesis of 2-aminothiophenes continue to increase. In recent years, research on the development of greener conditions to synthesize 2-aminothiophenes has soared. The development of green chemistry is a necessity in chemistry, and the synthesis of multiple 2-aminothiophenes does not do away with this rule (Horváth and Anastas 2007a; Anastas and Eghbali 2010). Work dealing with the uses of classical multicomponent reactions has been realized. Reactions relating to the application of a new catalyst or methodology in both homogeneous and heterogeneous pathways have also been observed in the last few years.

As examples of the possibilities 2-aminothiophenes can offer, some research is articulated around the integration of the 2-aminothiophene moiety into ferrocenes (Rodlovskaya and Vasnev 2020). Their utilization as dye is likewise well documented (Sabnis 2016). Implementations in photovoltaic cells have also been related (Stylianakis et al. 2010). Moreover, 2-aminothiophene was considered as a central scaffold on which modifications could be realized to obtain more complex molecules (Adib et al. 2015; Abdelwahab et al. 2016; Abaee et al. 2017; El-Mekabaty et al. 2017). Despite their importance in various application fields, only a few reviews on their methods of synthesis have been published, and if they do, they usually focus on the Gewald methodology (Nylund and Johansson 2010; Puterová et al. 2010; Huang and Dömling 2011; Bello Forero et al. 2013). The latest work that describes 2-aminothiophenes synthesis is from prior to 2011 (Nylund and Johansson 2010).

Here, we report in a comprehensive review the different approaches used to synthesize 2-aminothiophene-based derivatives over the last decade (2011–2022). Synthetic pathways were divided into categories based on the type of option they provide, such as green alternatives, multicomponent reactions, homogeneously and heterogeneously catalyzed reactions and miscellaneous reactions. Because of the novelty of the new synthetic routes to get 2-aminothiophenes, the green conditions have particularly caught our eye. The use of environmentally friendly solvents will also be specified when encountered.
Principles of Green Chemistry

Green chemistry has become one of the first incentives for organic chemists and industries to encourage sustainable processes. Until the early 2000s, only the yield and purity of the product were important and there was a lack of consideration for the environmental component (de Marco et al. 2019). Over the years, the concerning for the generation of pollution, the toxicity associated and the necessity to care about the treatment of wastes has grown. The attempts to develop greener chemical processes, less harmful, with a better atom economy, more adapted solvents or green methodologies to eliminate solvents have become a point of interest. Thereafter, less energy-consuming synthesis by means of milder conditions or the use of catalysts as well as the employment of renewable-based chemicals was carried out (Fig 4).

Since 1998, many efforts have followed the emerging interest and the introduction of the concept of “green chemistry” by Anastas through 12 principles (Anastas and Warner 1998). By definition, the 12 principles of green chemistry depict the greenest solution for each chemical consideration (Fig. 5). From a global perspective, the reduction or removal of toxic solvents, chemicals and processes is underlined. The willingness to develop less energy-consuming methodologies, including the acceleration of chemical reactions by means of catalysis, for example, has promoted emulation among researchers. Finally, a consideration of the risk component has also raised interest in these principles to minimize the environmental and occupational risks inherent to industrial activities (Kurniawan et al. 2021; Sajid and Plotka-Wasylko 2022).

Green alternative methodologies

At first, we will focus on the newly developed sustainable alternative strategies to synthesize 2-aminothiophenes, using Gewald methodologies or original pathways. Green approaches often involve eco-responsible solvents, non-polluting catalysts or environmentally friendly purification (Hrováth and Anastas 2007b; Anastas and Eghbali 2010).

In 2013, Liang and co-workers proposed for the first time a 2-aminothiophene synthesis following Gewald conditions in water as the solvent in a reaction ignited by sodium polysulfides in catalyst-free conditions under ultrasound activation (Liang et al. 2013). The variant of the classical process consisted of the reaction of ketones $9a$–$l$ with malononitrile $2a$ and elemental sulfur $S_8$ in water under sonification at 40 kHz and 300 W at 70 °C for 0.5–1 h, and 12 different 2-aminothiophenes $10a$–$l$ were synthesized in 42–90% yields after recrystallization from ethanol (Fig. 6).

In 2013, Ma et al. reported the synthesis of 14 distinct 2-aminothiophenes ($13a$–$n$) using an $N$-methylpiperazine-functionalized polyacrylonitrile fiber as a catalyst, whose synthesis is depicted in Fig. 7 (Ma et al. 2013). 2,5-Dihydroxy-1,4-dithiane $11$ reacted with nitriles $2a$–$c$ or $12d$–$n$ and polyacrylonitrile fiber in ethanol under reflux for 4 h to yield $13a$–$n$ in 65–91% after purification by silica gel chromatography. This green methodology allows functionalization of position 3 of the 2-aminothiophene moiety, while having the advantage of employing a catalyst that can be reused at least ten times.

Another study involving water as a solvent was described in 2014 by Abaee et al. By analogy to the Gewald methodology, a range of 14 2-aminothiophenes ($15a$–$n$) were...
The reaction of the corresponding ketones \(14a-g\) with nitriles \(2a,b\) and elemental sulfur \(S_8\) in a mixture of triethylamine and water at room temperature led to the desired 2-aminothiophenes \(15a-n\) in 75–98% yields after recrystallization from a mixture of ethyl acetate and hexanes. An efficient method for the preparation of 2-aminothiophenes was reported by Shearouse and his team in 2014 (Shearouse et al. 2014). Using mechanochemistry, ketones \(16a-f\) reacted with \(2c\) and elemental sulfur \(S_8\) under high-speed ball milling (HSBM) for 24 h, affording \(17a-f\) in 12–41% yields after purification by silica gel chromatography (Fig. 9). The authors also mentioned a reaction time reduction of up to 30 min by coupling HSBM to a heat gun (14–53%). These conditions were shown to synthetized as presented in Fig. 8 (Abaee and Cheraghi 2014). The reaction of the corresponding ketones \(14a-g\) with nitriles \(2a,b\) and elemental sulfur \(S_8\) in a mixture of triethylamine and water at room temperature led to the desired 2-aminothiophenes \(15a-n\) in 75–98% yields after recrystallization from a mixture of ethyl acetate and hexanes. An efficient method for the preparation of 2-aminothiophenes was reported by Shearouse and his team in 2014 (Shearouse et al. 2014). Using mechanochemistry, ketones \(16a-f\) reacted with \(2c\) and elemental sulfur \(S_8\) under high-speed ball milling (HSBM) for 24 h, affording \(17a-f\) in 12–41% yields after purification by silica gel chromatography (Fig. 9). The authors also mentioned a reaction time reduction of up to 30 min by coupling HSBM to a heat gun (14–53%). These conditions were shown to
be advantageous over the conventional thermal methods for forming 2-aminothiophenes (17a–f).

In 2014, Xu and colleagues demonstrated the benefits of the high-speed vibrating milling (HSVM) methodology as described in Fig. 10 (Xu et al. 2014). Cyclic ketone 18a–h, malonodinitrile 2a, elemental sulfur S8 and diethylamine were used in the process. After 30 min under HSVM, 19a–h were obtained in 42–94% yields after purification by silica gel chromatography (Fig. 10).

An efficient method for the construction of a series of 2-aminothiophenes (21aa–bu) mediated by basic ionic liquid as a greener solvent alternative was depicted in 2014 by Rao Kaki et al. (Fig. 11) (Kaki et al. 2015). They succeeded the synthesis of 2-aminothiophenes from ketones 20a–u with malonodinitrile 2a or ethyl cyanoacetate 2b and elemental sulfur S8 in 1-butyl-3-methylimidazolium hydroxide ([bmIm]OH) at 60 °C for 2 h, yielding 28 different 2-aminothiophenes 21aa–bu in 35–92% yields after purification by silica gel chromatography (Fig. 10).

In 2015, 23 2-aminothiophenes (25a–w) have been synthesized by Luo et al. following a one-pot regioselective metal-free methodology whose synthesis is portrayed in Fig. 12 (Luo et al. 2015). The authors applied thioamides 22a–v as a source of sulfur in the reaction with a series of alkynes 23a–c in alcohol 24a–c as solvent under reflux for 7 h to afford 2-aminothiophenes 25a–w in 35–96% yields after purification by silica gel chromatography.
They proposed a mechanism to describe their one-pot synthesis, which is presented in Fig. 13. The aldol condensation would form the intermediate A, which would then react proceeding a 5-exo-dig cyclization to furnish the zwitterionic specie B. Then, protonation of B would occur in an alcoholic solvent to give C, which would be subsequently followed by the addition of a corresponding alkoxide to aromatize the structure and afford 25a.

In 2015, Li and co-workers reported a synthetic pathway to synthesize a 2-aminothiophene (21ba) in water. They
used polyacrylonitrile fiber functionalized by 4-dimethylaminopyridine as a catalyst (Li et al. 2015). 2,5-Dihydroxy-1,4-dithiane reacted with ethyl cyanoacetate and the catalyst in water at 80 °C to give \(21\) in 92% yield after purification by silica gel chromatography (Fig. 14). This strategy showed the advantage of using a low catalyst loading with better yields than those obtained with 4-dimethylaminopyridine alone (79% yield).

In 2017, Shaabani et al. developed a new methodology for the synthesis of 2-aminothiophenes (23aj–bj) with a Gewald strategy realized in eutectic solvents (Shaabani et al. 2017). Starting from ketones \(22\) that reacted with nitriles \(2a,b\), sodium hydroxide and elemental sulfur \(S_8\), afforded 2-aminothiophenes \(23aj–bj\) in 68–88% yields after filtration and crystallization from ethanol (Fig. 15). The deep eutectic solvent used in this synthetic pathway was based on choline chloride mixed with urea.

Another methodology reporting alternative solvents was described in 2017 by Akbarzadeh and Dekamin and is disclosed in Fig. 16 (Akbarzadeh and Dekamin).
They applied alkyl ketones 24a–i in the reaction with corresponding nitriles 2a,b and elemental sulfur S₈ in eco-friendly PEG-600 under ultrasonic conditions at room temperature for 10 to 50 min to form 2-aminothiophenes 25aa–bi in 29–98% yields after filtration and recrystallization from ethanol (Fig. 16).

**Fig. 14** Synthesis of 2-aminothiophene 21ba from 2,5-dihydroxy-1,4-dithiane 11 and ethyl cyanoacetate 2b. Reagents and conditions: a fiber (1 mol% based on aminopyridine group), H₂O, 80 °C, 92% yield. The use of the fiber in water as a solvent renders the methodology environmentally friendly. PANp-AP-3Fs in the figure represents polyacrylonitrile fiber functionalized by 4-dimethylaminopyridine

**Fig. 15** Synthesis of 2-aminothiophenes 23aj–bj from ketones 22a–j and nitriles 2a,b. Reagents and conditions: a sodium hydroxide, elemental sulfur S₈, choline chloride/urea, 2–3 h, 60 °C, 68–88% yields. The use of eutectic solvent composed of environmentally compatible choline chloride/urea is interesting from a green chemistry point of view as well as the energy-efficient purification

**Fig. 16** Synthesis of 2-aminothiophenes 25aa–bi from ketones 24a–i and nitriles 2a,b. Reagents and conditions: a elemental sulfur S₈, PEG-600, room temperature, 10–50 min, 29–98% yields. PEG-600 is known to be an eco-friendly solvent and is used here under ultrasonic conditions at room temperature. PEG-600 in the caption means polyethylene glycol 600
Multicomponent reactions

Multicomponent reactions are reactions realized with more than two reagents following a one-pot methodology. This kind of reaction is a great tool in medicinal chemistry because it allows the synthesis of large series easily in one step instead of pathways with many stages and tedious conditions (Dömling et al. 2012; John et al. 2021). Multicomponent reactions are interesting tools to synthesize 2-aminothiophenes and interest around the obtention of 2-aminothiophene moiety soared up. In general, multicomponent reactions are really attractive eco-friendly procedures due to their atom economy, mild conditions, high yields and their general compatibility with green solvents (Cioc et al. 2014).

In 2013, Venkata Rao and his team developed the synthesis of sixteen 3,4-substituted-2-aminothiophenes (28a–p) from trimethyl orthoacetate 26 (Venkata Rao et al. 2013). As described in Fig. 17, the reaction of 26 with the corresponding alcohol at 80 °C for 24 h led to dinitriles 27a–p. In a second step, compounds 27a–p reacted with malonodinitrile 2a, elemental sulfur S8 and triethylamine in THF at 60 °C for 2–3 h, giving 2-aminothiophenes 28a–p in 26–84% yields after purification by silica gel chromatography.

In 2013, Chen et al. described the synthesis of 2-(2-aminothiophene)-benzimidazoles (31a–t) using 3-multicomponent reactions involving nitriles 29a–f with aldehydes 30a–f, elemental sulfur S8 and piperidine in ethanol under reflux for 1.5 h, providing 2-aminothiophenes 31a–t in 69–86% yields after purification by silica gel chromatography (Fig. 18) (Chen et al. 2013).

In 2016, Zeng and co-workers developed a method to afford 2-aminothiophenes (35a–n) from 4-thiazolidinone derivatives in catalyst-free conditions, whose synthesis is shown in Fig. 19 (Zeng et al. 2016). The first step was the synthesis of the 4-thiazolidinone moiety by the reaction of thiocyanates 32a–h with nitrile 2d and acyl chlorides 33a,b in the presence of potassium hydroxide in anhydrous N,N-Dimethylformamide at room temperature overnight. Then, the hydrolysis of ester with TFA in dichloromethane for 24 h at room temperature gave 34a–n in 84–91% yields after crystallization from a mixture of dichloromethane and methanol. Thereafter, reduction of 34a–n occurred with NaBH4 in water to yield 35a–n in 36–83% after purification by silica gel chromatography (Fig. 19). In addition, the authors proposed a plausible mechanism to explain the reduction, pictured in Fig. 20. Firstly, the reduction and deprotonation of 4-thiazolidinone 34a–n would lead to carboxylates A, followed by the cleavage of the C–N bond, resulting in the generation of aldehyde B. Then, intramolecular cyclization would yield to C, which would subsequently lose carbon dioxide to form dihydrothiophene D. The final step would be the aromatization of thiophene to obtain the desired products 35a–n after dehydration.

Fig. 17 Synthesis of 2-aminothiophenes 28a–p from orthoacetate 26 and malonodinitrile 2a. Reagents and conditions: a ROH, malonodinitrile 2a, 24 h, 80 °C; b malonodinitrile 2a, 60 °C, 3 h; c elemental sulfur S8, triethylamine, 60 °C, 15 min, 26–84% yields

Fig. 18 Synthesis of 2-aminothiophenes 31a–t from benzimidazoles 29a–f and aldehydes 30a–f. Reagents and conditions: a elemental sulfur S8, piperidine, ethanol, reflux, 1.5 h, 69–86% yields
In 2018, Mari et al. described a new way to synthesize ten different 2-aminothiophenes (42a–j) in two steps via 4-multicomponent reactions (Mari et al. 2018). Aiming to optimize reaction conditions, the authors tested several solvents and the best conditions are those disclosed in Fig. 21. The reaction between n-butyl amine 36, β-ketoesters 37a–i, aryl isothiocyanates 38a–c and 1,2-diaza-1,3-dienes 39a–k at room temperature for 9.5–23.5 h yielded dihydrothiophene 40a–j in 40–69% after purification by silica gel chromatography. 2,5-Dihydrothiophenes 40a–j were then successively treated with Amberlyst™ 15H in a mixture of acetone and water to hydrolyze the hydrazone moiety with the departure of 41a–k. In these conditions, they isolated in 70–83% the 5-aminothiophene–2,4-dicarboxylates 42a–j after purification by flash silica gel chromatography. However, conservation of electron-withdrawing group on C3 position seems necessary for this methodology.
In 2019, Kavitha et al. reported the synthesis of 2-aminothiophenes (45a–j) following a 4-component Gewald reaction employing L-proline as an organocatalyst (Kavitha et al. 2019). Readily available starting materials were used in the synthesis presented in Fig. 22. Coumarin 43 reacted in the presence of tetrabutylammonium tribromide in acetic acid for 2 h at room temperature, followed by the addition of cyanoacetamide 2c in ethanol under reflux for 2 h to afford 44 in 88% yield over two steps after recrystallization from methanol. Then, the 4-multicomponent reactions were used and 44 reacted with malonodinitrile 2a, elemental sulfur S₈ and various aryl aldehydes in the presence of 10 mol% of L-proline in ethanol at room temperature, 5–8 h, 66–81% yields.
temperature to lead 45a–j in 66–81% yields after recrystallization from methanol, acetonitrile, acetone or ethyl acetate.

In 2020, Nguyen et al. developed a one-pot synthesis of two steps starting with the reaction between cyanoaryl 46a–p with α,β-unsaturated ketones 47a–p and DBU in dimethyl sulfoxide at room temperature for 30 min to give transitorily 48aa–pp. The second stage involved 48aa–pp with DABCO and elemental sulfur S₈ at 80 °C for 16 h to afford compounds 49aa–pp in 45–77% yields after two steps after purification by silica gel chromatography (Fig. 23) (Nguyen et al. 2020). This methodology allowed the substitution of the C3 position with aryl groups, with 31 derivatives explored.

In 2021, Nguyen et al. described one-pot base-catalyzed 3-multicomponent reactions from chalcones 50aa–ad or 51a–f with α-cyanoacetates 2d, 52a–e and elemental sulfur S₈ to obtain 51aa–aae and 54aa–fa (Nguyen et al. 2021). Firstly, 30 chalcones 50aa–ad reacted with cyanoacetate 2d to get 51aa–ada in 54–82% yields after purification. Secondly, the nature of the cyanoacetate has been customized: 2d, 52a–e reacted with chalcone 50aa and afforded six different 2-aminothiophenes 53aa–aae in 72–86% yields after purification. In the end, nature of the aryl moieties grafted on chalcone has been modified and poured in reaction with 51a–f and 2d to yield 54aa–fa in 48–70% after purification (Fig. 24). In total, 41 compounds were synthesized in 48–82% yields after purification by silica gel chromatography. A second step was written up by Kao et al. (Kao et al. 2018). The first step was the reaction between alkynes 59a–f, nitriles 58a–h, L-proline and Hantzsch ester in ethanol at 70 °C to give 60aa–hf in 44–99% yields. At a second time, phosphorus pentasulfide was employed in ethanol at 80 °C for 3 h

Interestingly, these synthetic pathways allowed the formation of 2-aminothiophenes, considered unobtainable via the Gewald reaction by the authors (Nguyen et al. 2021).

### Catalyzed reactions

#### Homogeneously catalyzed reactions

Homogeneously catalyzed reactions are realized with a catalyst in the same phase as the reactants. The organocatalysis is an excellent example of this kind of catalyzed reaction (Shelke et al. 2018). Homogeneous catalysis often moves away from stoichiometric processes using organic catalysts; hence, it is considered as a strong green alternative and is often enough to render the reaction as green compatible (Kitanosono et al. 2018).

In 2014, Ge and his team investigated a novel direct synthesis of 2-aminothiophenes catalyzed by Cu(II) from thioamides and symmetric alkynes (Ge et al. 2014). After a first optimization, the best conditions are those described in Fig. 25. The reaction of thioamides 55a–o with alkynes 56a,b and copper acetate (II) in dimethylacetamide at 80 °C yielded to 16 2-aminothiophenes 57a–p in 38–91% after purification by silica gel chromatography.

Another method that uses L-proline and Hantzsch ester was written up by Kao et al. (Kao et al. 2018). The first step was the reaction between alkynes 59a–f, nitriles 2d or 58a–h, L-proline and Hantzsch ester in ethanol at 70 °C to give 60aa–hf in 44–99% yields. At a second time, phosphorus pentasulfide was employed in ethanol at 80 °C for 3 h.

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**Fig. 23** Synthesis of 2-aminothiophenes 49aa–pp from nitriles 46a–p and α,β-unsaturated ketones 47a–p.

Reagents and conditions: (a) DBU (5 mol%), dimethyl sulfoxide, room temperature, 30 min; (b) DABCO (20 mol%), elemental sulfur S₈, 80 °C, 16 h, 45–77% yields. Note: DBU and DABCO in the caption represent 1,8-diazabicyclo(5.4.0)undec-7-ene and 1,4-diazabicyclo[2.2.2]octane, respectively.
Fig. 24  Synthesis of 2-aminothiophenes 51aaa-ada, 53aaa-aee and 54aa-fa from chalcones 50aa-ad, 51a-f and nitriles 2d, 52a-e. Reagents and conditions: a DABCO, dimethyl sulfoxide, 80 °C, 30 min, and then elemental sulfur S₈, 80 °C, 16 h, 54–82% yields; b DABCO, dimethyl sulfoxide, 80 °C, 30 min, and then elemental sulfur S₈, 80 °C, 30 min, 72–86% yields; c DABCO, dimethyl sulfoxide, 80–100 °C, 30 min, and then elemental sulfur S₈, 80–100 °C, 30 min, 48–70% yields. Note: DABCO in the caption represent 1,4-diazabicyclo[2.2.2]octane.

Fig. 25  Synthesis of 2-aminothiophenes 57a-p from thioamides 55a-o and alkynes 56a,b. Reagents and conditions: a copper acetate (II) (10 mol%), dimethylacetamide, 80 °C, 4–6 h, 38–91% yields.
Fig. 26 Synthesis of 2-aminothiophenes 61aa–hf from alkynes 59a–f, nitriles 2d, 58a–h. Reagents and conditions: a L-proline, Hantzsch ester in ethanol, 70 °C, 44–99% yields; b P₄S₁₀ in ethanol, 80 °C, 3 h, air, 9–95% yields.

Fig. 27 Synthesis of 2-aminothiophenes 66a–e from aldehyde 62a–e. Reagents and conditions: a methyl acrylate, DABCO in methanol, room temperature, 72 h; b Boc₂O, 4-Dimethylaminopyridine in dichloromethane, room temperature, 3 h; c triphenylphosphine (20 mol%) in toluene, 110 °C, 1.5 h, 31–59% yields. DABCO and Boc₂O in the caption mean 1,4-diazabicyclo[2.2.2]octane and di-tert-butyl decarbonate, respectively.
to afford 61aa–ia in 9–95% yields after purification by flash chromatography (Fig. 26).

In 2021, Zenkov et al. depicted the synthesis of five 2-aminothiophene-5-aryl-substituted with adamantane (66a–e) as shown in Fig. 27 (Zenkov et al. 2021). The synthesis consisted in a Morita–Baylis–Hillman reaction in the presence of methyl acrylate and corresponding aldehyde 62a–e with DABCO in methanol at room temperature for 72 h to afford 63a–e in 35–79% yields after purification by flash chromatography. Thereafter, 63a–e reacted with di-t-butyl dicarbonate (Boc₂O), 4-Dimethylaminopyridine in dichloromethane at room temperature for 3 h to give 64a–e in 40–75% yields. The last step was the reaction between carbonates 64a–e with adamantane isothiocyanate 65 and triphenylphosphine in toluene at 110 °C for 1.5 h to provide desired 2-aminothiophenones derivatives 66a–e in 31–59% yields after purification by flash chromatography.

Heterogeneously catalyzed reactions

Heterogeneously catalyzed reactions are realized with a catalyst that is not in the same phase as the reactants. The most common examples in organic chemistry are palladium-catalyzed reactions (Liu and Corma 2018). In the same way as homogeneous catalysis, heterogeneous catalysis respects green chemistry principles (Anastas and Eghbali 2010). In the last decade, the methodologies for the synthesis of 2-aminothiophenes that used transition metal-catalyzed reactions have seen a surge in popularity. All of the synthetic pathways involving heterogeneous catalysts through the Gewald methodology are summarized in Fig. 28.

In 2011, Ren et al. reported a strategy starting with ketone 1, corresponding nitrile 2a,b, elemental sulfur S₈ and Mg/La mixed oxide-based catalysts (Ren et al. 2011). The authors also described the advantageous microwave irradiation (4–8 min) over batch conditions in ethanol (50–85 min).

In 2013, Tayebee and his team found ZnO nanoparticles as an efficient catalyst to afford ten different 2-aminothiophenes. The reaction of aldehydes or ketones 1 with malonodinitrile 2a, elemental sulfur S₈ and nano-ZnO (2.5 mol%) at 100 °C for 6 h gave the desired 2-aminothiophenes 3a in 37–86% yields after purification by silica gel chromatography (Tayebee et al. 2013).

In 2015, Bai et al. proposed using NaAlO₂ as an eco-catalyst for the novel synthesis of 2-aminothiophenes from ketones 1 with nitriles 2a,b and elemental sulfur S₈ in ethanol in the presence of NaAlO₂ for 10 h. A total of 18 different 2-aminothiophenes 3a,b were obtained in 26–94% yields after purification by preparative thin-layer chromatography (Bai et al. 2015).

In 2016, Javadi et al. presented their work dealing with catalysis of Gewald reactions with ZnO/nanoclinoptilolite as a new nanocomposite (Javadi and Tayebee 2016). They have reported the synthesis of 2-aminothiophenes 3a obtained from ketones or aldehydes 1 with malonodinitrile 2a and ZnO/nanoclinoptilolite (0.05 g) at 100 °C for 4 h. The desired 2-aminothiophenes were afforded in 30–76% yields after purification by silica gel chromatography.

In 2018, Shafighi et al. disclosed the synthesis of six 2-aminothiophenes using MgO–CeO₂ nanocomposite as catalysts (Shafighi et al. 2018). Using this material, characterized by X-ray diffraction and field emission scanning electron microscopy (FE-SEM), 2-aminothiophenes 3c were obtained using ketones 1 with cyanoacetamide 2c and elemental sulfur S₈ in ethanol under reflux for 10 h in 76–89% yields after filtration and washes with ethanol.

In 2017, Erfaninia et al. described an efficient procedure for the synthesis of 2-aminothiophenes 3a using recyclable ZnFe₂O₄ nanoparticles with an average size of 40 nm (Erfaninia et al. 2018). Nanoparticles were characterized by X-ray diffraction, Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy, inductively coupled plasma mass spectrometry (ICP-MS), differential reflectance spectroscopy, thermogravimetric analysis, vibrating-sample magnetometer and elemental analysis. Starting from the ketones 1 with malonodinitrile 2a and elemental sulfur S₈ in the presence of ZnFe₂O₄ nanoparticles at 2.5 mol% for 4 h at 100 °C, 2-aminothiophenes 3e were obtained in 25–80% yields after precipitation in cold water.

In 2018, Saadati-Moshtaghin et al. described a new, facile way to synthesize 2-aminothiophenes 3a using Fe₃O₄-modified nanoparticles (Saadati-Moshtaghin and Zonoz 2018). They enabled the synthesis of a scope of eight distinct 2-aminothiophenes 3 from commercially available ketones 1 with malonodinitrile 2a, elemental sulfur S₈ and a catalytic amount of aminopropyl-modified silica-coated magnetite nanoparticles (0.05 g/10 mmol) under solvent-free condition, in 56–88% yields after purification by silica gel chromatography. This method showed the advantage of allowing the removal of the catalyst with a magnet.

In 2018, Rezaei-Seresht and his team developed a total of 13 examples of 2-aminothiophenes (Rezaei-Seresht et al. 2021). Still following the Gewald methodology, ketones 1 reacted with malonodinitrile 2a or ethyl cyanoacetate 2b,
elemental sulfur $S_8$ and $\text{Fe}_3\text{O}_4$ graphene oxide functionalized with morpholine moiety ($\text{Fe}_3\text{O}_4@\text{rGO–NH}$) at a concentration of 0.1 g/mmol, allowing the synthesis of 2-aminothiophenes $3a,b$ in 40–95% yields after precipitation in water. The magnet can also be used to get the catalyst back. After a few washes with ethanol and acetone and drying under a vacuum for 24 h at room temperature, the catalyst can be reused.

In 2021, Gao et al. described the green synthesis of six classical 2-aminothiophenes $3a$ using $\text{ZnO}@\text{SiO}_2–\text{NH}_2$ nanoparticles (Gao et al. 2021). The material, with a grain particles or nanoclinoptilolite: $\text{NaAlO}_2$; $\text{MgO}$, $\text{CeO}_2$, $\text{Fe}_2\text{O}_3$, $\text{SiO}_2$; $\text{ZnFe}_2\text{O}_4$; $\text{ZnO}$, $\text{SiO}_2$; $\text{Fe}_3\text{O}_4$). DMF, M.W., NPs and NCPs in the figure represent N,N-dimethylformamide, microwave, nanoparticles and nanoclinoptilolite, respectively.

![Fig. 28](image_url)

**Fig. 28** Heterogeneously catalyzed reactions of 2-aminothiophenes $3a–c$ from ketones $1$, nitriles $2a–c$ and elemental sulfur $S_8$. In the last 10 years, reactions were realized from various metal oxides acting as catalysts as main green-compatible aspect ($\text{MgO}$, $\text{La}_2\text{O}_3$; $\text{ZnO}$ nanoparticles or nanoclinoptilolite; $\text{NaAlO}_2$; $\text{MgO}$, $\text{CeO}_2$, $\text{Fe}_3\text{O}_4$, $\text{SiO}_2$; $\text{ZnFe}_2\text{O}_4$; $\text{ZnO}$, $\text{SiO}_2$; $\text{Fe}_3\text{O}_4$). DMF, M.W., NPs and NCPs in the figure represent N,N-dimethylformamide, microwave, nanoparticles and nanoclinoptilolite, respectively.

In 2021, Gao et al. described the green synthesis of six classical 2-aminothiophenes $3a$ using $\text{ZnO}@\text{SiO}_2–\text{NH}_2$ nanoparticles (Gao et al. 2021). The material, with a grain $40–95\%$ yields after precipitation in water. The magnet can also be used to get the catalyst back. After a few washes with ethanol and acetone and drying under a vacuum for 24 h at room temperature, the catalyst can be reused.

In 2021, Gao et al. described the green synthesis of six classical 2-aminothiophenes $3a$ using $\text{ZnO}@\text{SiO}_2–\text{NH}_2$ nanoparticles (Gao et al. 2021). The material, with a grain particles or nanoclinoptilolite: $\text{NaAlO}_2$; $\text{MgO}$, $\text{CeO}_2$, $\text{Fe}_2\text{O}_3$, $\text{SiO}_2$; $\text{ZnFe}_2\text{O}_4$; $\text{ZnO}$, $\text{SiO}_2$; $\text{Fe}_3\text{O}_4$). DMF, M.W., NPs and NCPs in the figure represent N,N-dimethylformamide, microwave, nanoparticles and nanoclinoptilolite, respectively.

![Fig. 29](image_url)

**Fig. 29** Synthesis of 2-aminothiophene $68$ from 2-iodothiophene $67$. Reagents and conditions: $\text{a}$ ammonia, copper iodide (I), trisodium phosphate, PEG-400/$\text{H}_2\text{O}$, $100 \degree\text{C}$, 15 h, 50% yield. The use of a mixture composed of PEG-400 and water as solvent gives an environmentally friendly aspect. PEG-400 in the caption represents polyethylene glycol 400
size of 70–90 nm was characterized by FTIR, transmission electron microscopy, X-ray diffraction and FE-SEM and has been used as a catalyst for a Gewald reaction. Ketones 1, malonodinitrile 2a, elemental sulfur S₈ and ZnO@SiO₂–NH₂ (0.02 g/5 mmol) reacted in solvent-free conditions for 4–8 h at 100 °C, to give 2-aminothiophenes 3 in 27–96% yields after precipitation in cold water.

**Miscellaneous**

In 2011, Chen et al. dealt with a methodology to synthesize 2-aminothiophene 68, as shown in Fig. 29 (Chen et al. 2011). Starting from 2-iodothiophene 67 with copper iodide (I), aqueous ammonia and trisodium phosphate in a mixture of PEG-400 and water at 100 °C for 15 h, 2-aminothiophene 68 was obtained in a 50% yield after purification by silica gel chromatography.

In 2014, Han et al. reported the synthesis of 2-aminothiophenes 70a–n in moderate to good yields (48–83%) from cyclopropanes 69a–n, elemental sulfur S₈ and morpholine in N,N-dimethylformamide at 60 °C for 48 h after purification on preparative thin-layer chromatography (Fig. 30).

In 2017, Zhang et al. described the synthesis of 2-aminothiophenes using 1,1-difluoroalkenes 71a–j and N,N-disubstituted β-keto thioamides 72a–n with potassium carbonate in catalyst-free conditions. After optimizations realized by the authors, the best conditions disclosed in Fig. 31 consisted of the use of potassium carbonate in dimethyl sulfoxide at 120 °C for 4 h under an inert atmosphere to afford the 27 N,N-substituted 2-aminothiophenes 73aa–jh in 73–91% yields after purification by silica gel chromatography.

A mechanistic study has also been suggested by the authors and is found in Fig. 32A. Starting with the addition of the enolate equivalent A to 71a–j followed by the elimination of fluoride would generate B. Still, in the basic medium, the thiolate intermediate C would react following an unfavored 5-endo-trig cyclization into dihydrothiophene D. The final step would be the aromatization of the structure 73aa–jh after the generation of the carbene E and intramolecular hydride migration. An X-ray structure has been realized by the authors to confirm the structure of 73fa (Fig. 32B, Fig. 33).

In 2020, Zhang et al. reported a novel series of 26 different 2-aminothiophenes (Zhang et al. 2020). The general procedure is proposed in Fig. 34 and occurred by cyclization of 12 gem-dibromo 74a–l or six gem-dichloro 77m–r with seven tertiary β-ketothioamide 75a–g and aqueous solution of potassium carbonate in dimethyl sulfoxide at 120 °C for 4 h under an argon atmosphere to afford 76aa–rc in 50–92% yields after purification by silica gel chromatography. The reaction substituted 2-aminothiophenes using a chemo- and regioselectivity methodology.

In 2022, Duvauchelle et al. described a novel catalyst-free regioselective methodology to graft a trifluoromethyl alkyl group on the C3 position of 2-aminothiophenes (Duvauchelle et al. 2022). The reaction between 2-bromo-5-nitrothiophene 77 with phenyl boronic acid 78 under Suzuki–Miyaura coupling conditions formed the intermediate 79 in 86% yield after purification. Then, the reduction of the nitro function in amine was realized in the presence of hydrazine hydrate in absolute ethanol at 50 °C for 15 min, followed by the addition of Raney nickel to smoothly afford

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**Fig. 30** Synthesis of 2-aminothiophenes 70a–n from cyclopropanes 69a–n. Reagents and conditions: a elemental sulfur S₈, morpholine, N,N-dimethylformamide, 60 °C, 48 h, 48–83% yields

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| R₁ | R₂ | R₃ | R₄ |
|----|----|----|----|
| CN | CN | H  | H  | R₁ = CN, R₂ = H, R₃ = F, R₄ = H |
| CN | CN | p-CH₃| H  | R₁ = CN, R₂ = p-CH₃, R₃ = H, R₄ = H |
| CN | CN | p-CH₃| Cl | R₁ = CN, R₂ = p-CH₃, R₃ = Cl, R₄ = H |
| CN | CN | o-CH₃| Cl | R₁ = CN, R₂ = o-CH₃, R₃ = Cl, R₄ = H |
| CN | CN | p-OPh| Cl | R₁ = CN, R₂ = p-OPh, R₃ = Cl, R₄ = H |
| CN | CN | p-OPh| Br | R₁ = CN, R₂ = p-OPh, R₃ = Br, R₄ = H |
80 (90% yield after purification). The last step was the regioselective trifluoromethyl alkylation on the C3 position in the presence of α-trifluoromethyl ketones in toluene under reflux for 2–4.5 h to obtain 81a–l in 69–93% yields (Fig. 35A). All the purification was done by flash silica gel chromatography. The X-ray diffraction of 81d has been realized to confirm the structure (Fig. 35B).

**Conclusion**

We reported here the newly explored synthetic pathways for 2-aminothiophenes in the last decade (2011–2022). We emphasized the innovative methodologies available to realize the synthesis of 2-aminothiophenes. As a lack of literature on work gathering conditions has been observed, we had the feeling the time was right to propose this highlight. The review started with a brief description of bioactive 2-aminothiophenes, followed by a global background on the Gewald synthesis of 2-aminothiophenes. Then, considerations of novel green pathways were proposed; it was the same regarding catalyzed reactions and multicomponent reactions, allowing the formation of the desired moiety. We focused our work on the synthesis of 2-aminothiophenes and showed the organic possibilities of this scaffold have soared in terms of conditions, starting materials and willingness for chemists to propose greener synthetic conditions.
**Fig. 32** A Mechanistic studies for the synthesis of 2-aminothiophenes 73aa–jh proposed by Zhang et al. through a 5-endo-trig cyclization. B X-ray structure of 73fa realized to confirm the conformation.

**Fig. 33** X-ray structure of 73fa
Fig. 34 Synthesis of 2-aminothiophenes 76aa–rc from gem-dibromo 74a–i or gem-dichloro 77m–r and tertiary β-ketothioamide 75a–g. Reagents and conditions: a potassium carbonate, dimethyl sulfoxide, 120 °C, 4 h, 75–92% yields; b potassium carbonate, dimethyl sulfoxide, 120 °C, 4 h, 50–88% yields.
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Author contributions ZB was responsible for the management of the work and overall supervision. The authors contributed to the data preparation, drafted and revised the manuscript. All authors have read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.
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