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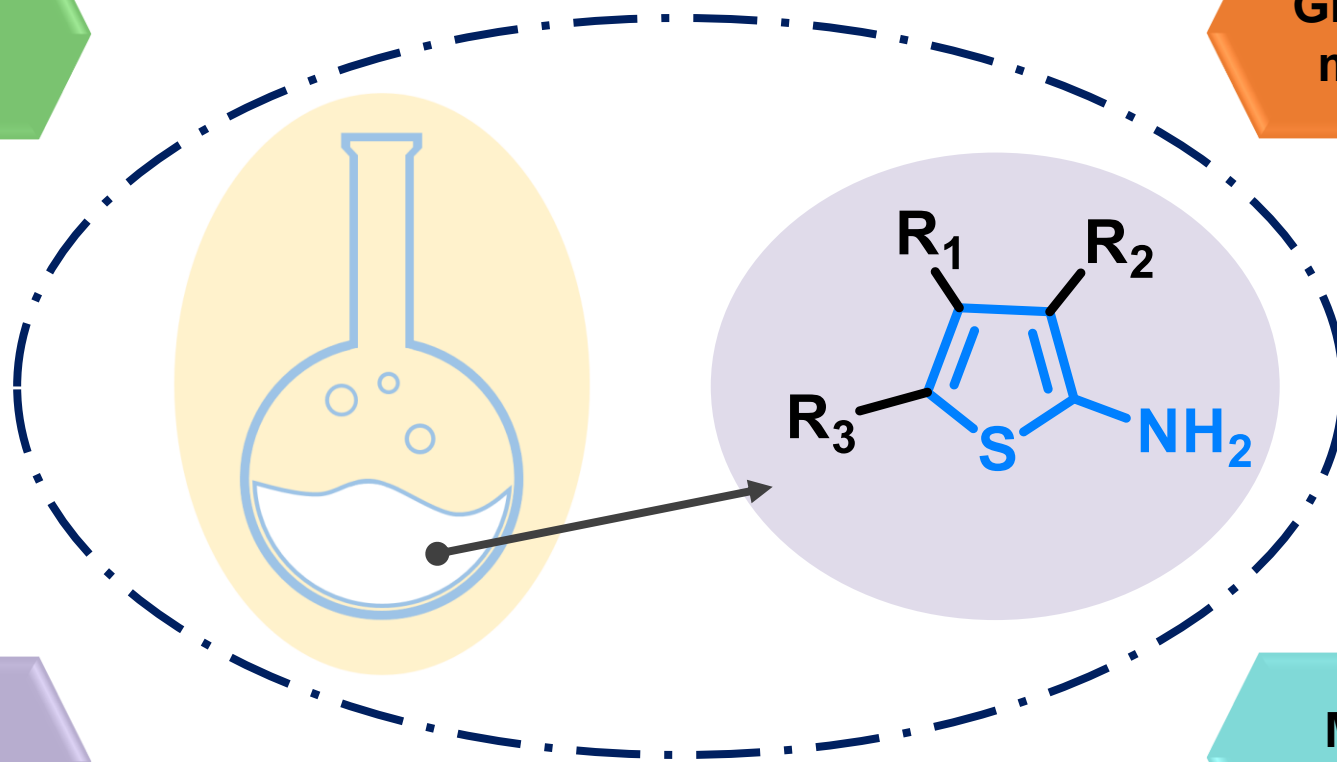
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# Synthetic methodologies of 2-aminothiophenes

Multicomponent reactions

Green alternative methodologies



Catalyzed reactions

Miscellaneous reactions

# 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

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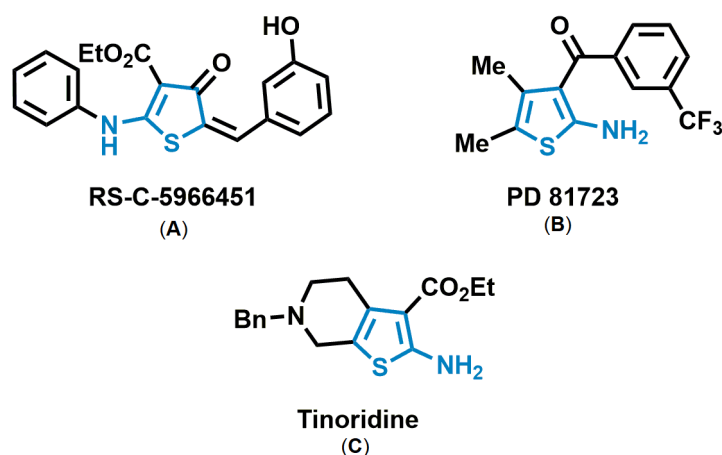
## Abbreviations

[bmIm]OH	1-butyl-3-methylimidazolium hydroxide	Boc <sub>2</sub> O	Di-tert-butyl dicarbonate
DABCO	1,4-Diazabicyclo[2.2.2]octane	DBU	1,8-Diazabicyclo[5.4.0]undéc-7-ène
DMF	N,N-Dimethylformamide	EWG	Electron-withdrawing group
FE-SEM	Field Emission Scanning Electron Microscopy	FT-IR	Fourier-transform infrared spectroscopy
HSBM	High-speed ball milling	HSVM	high-speed vibrating milling
Hz	Hertz	ICP-MS	Inductively coupled plasma mass spectrometry
NCP	nanoclinoptilolite	NP	Nanoparticle
PEG	Polyethylene glycol	P-PANF	Polyacrylonitrile fibre
PPh <sub>3</sub>	Triphenylphosphine	S <sub>8</sub>	Elemental sulfur
SiO <sub>2</sub>	Silicon dioxide	W	Watt

## 1. Introduction

In chemistry, the development of heterocycle synthetic methodologies is a crucial field. More than 75% of all biologically active compounds possess a heterocycle moiety (Jampilek 2019). Thiophene is a particularly interesting scaffold because it is a bioisostere of the phenyl groups, which are found in a wide range of active drugs and both natural and synthetic medicinal (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).

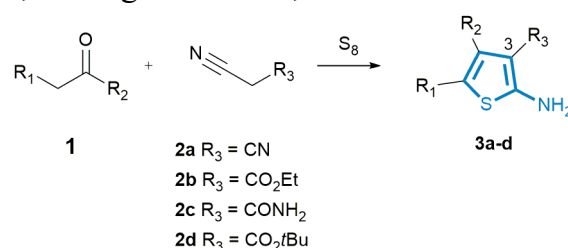
As examples, we can highlight compound **A** known as **RS-C-5966451**, described for its broad-spectrum antiviral properties (Fig. 1)(Thakur et al. 2007), derivative **B**, named **PD 81723**, for its adenosine A1 receptor agonist used to reduce necrosis, apoptosis and inflammation for renal ischemia-reperfusion (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).



**Fig. 1** This review focuses on the recent methodologies reporting the synthesis of 2-aminothiophenes. These compounds are known to confer various biological activities and some

of them are or were FDA approved. Structure (A) represents the structure of compound named **RS-C-5966451** interesting for its broad-spectrum antiviral properties. Structure (B) represents the structure of compound called **PD 81723** exhibiting anti necrosis properties. Structure (C) corresponds to **tinoridine** that demonstrated non-steroidal anti-inflammatory effect.

The constant advancement of efficient procedures to assemble complex structures with 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 Campaigne and Foye in the 1950s (Campaigne 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).



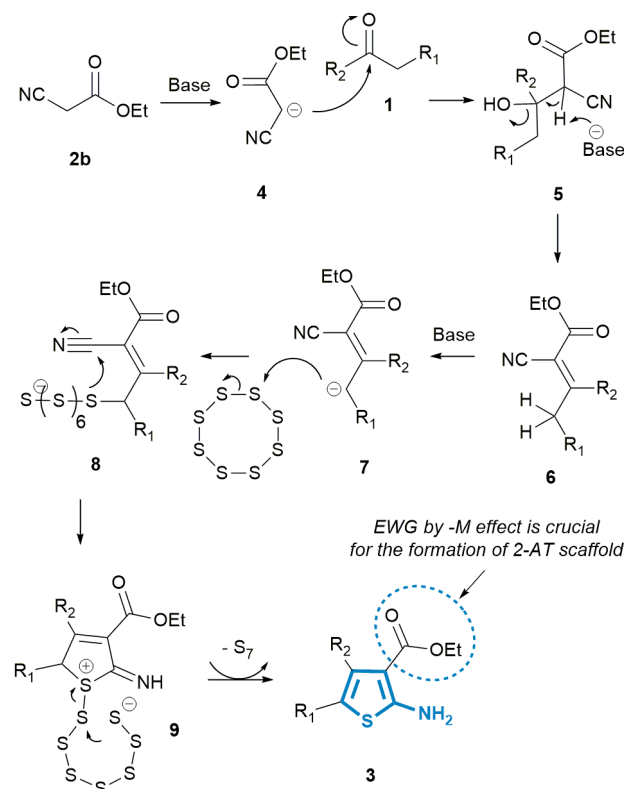
**Fig. 2** This review describes the various synthetic pathways to obtain 2-aminothiophenes whose classical conditions follow the Gewald synthesis. The 2-aminothiophene **3** synthesis from ketone **1** and nitriles **2a-d** in the presence of elemental sulfur  $S_8$  is shown (Puterová et al. 2010; Huang and Dömling 2011). Due to the use of nitrile derivatives, the position 3 is often substituted with an electron-withdrawing group.

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  $S_8$  to yield **8**. Finally, ring closure occurs to give **9** then **3** after the aromatization and the departure of  $S_7$  (Fig. 3)(Sabnis et al. 1999). The elemental sulfur  $S_8$  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-amiothiophenes 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 (Rodlovskaia 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; S. Bello Forero et al. 2013). The latest work that describes 2-aminothiophenes synthesis is from prior to 2011 (Nylund and Johansson 2010).



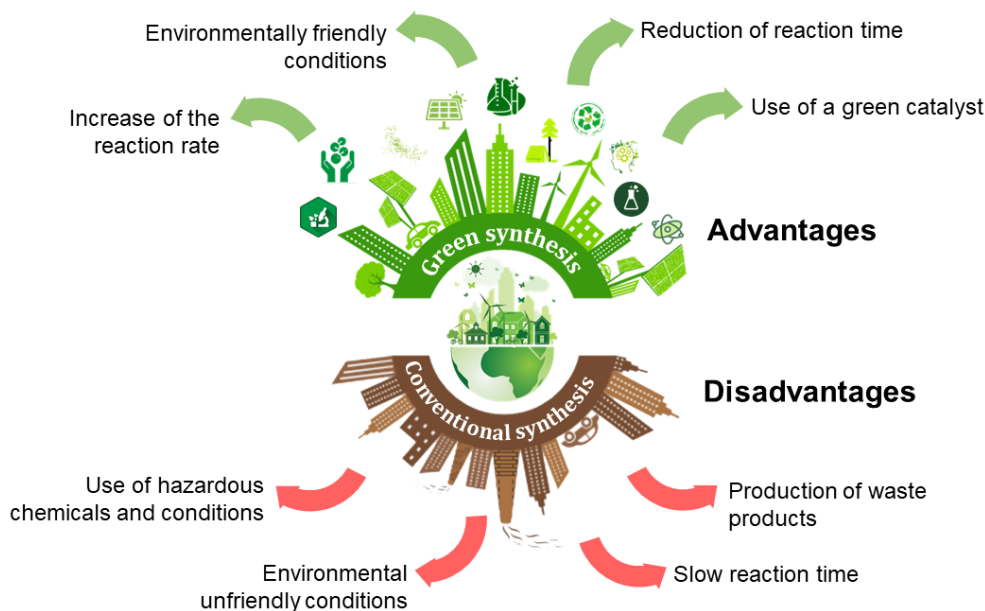
**Fig. 3** Mechanism of formation of 2-aminothiophene **3** following Gewald methodology (ketone **1**, ethyl cyanoacetate **2b**, elemental sulfur  $S_8$  and a base). With this strategy, the importance of an electron-withdrawing group in position 3 of the thiophene is highlighted. Note: EWG in the figure represents electron-withdrawing group.

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, homogeneous and heterogeneous 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.

## 2. Green Chemistry principles

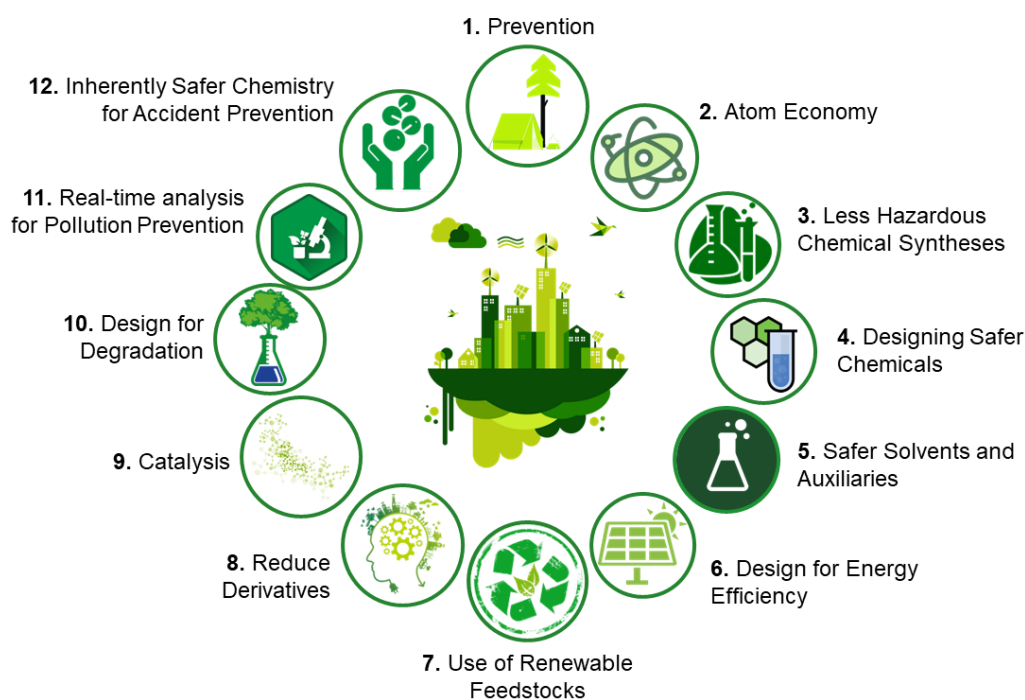
Green chemistry has become one of the first incentive for organic chemists and industries to encourage sustainable processes. Until the early 2000s, only the yield and purity of the

product were important and there was a lack of consideration for the environmental component (de Marco et al. 2019). Over the years, the concern 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 has 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 were carried out (Fig 4).



**Fig. 4** Advantages of Green Chemistry processes over conventional chemistry synthesis. Globally, Green Chemistry demonstrates higher reaction rates, more environmentally friendly reaction conditions, reduction of the reaction time and the use of green catalyst over conventional batch synthesis (2000; Horváth and Anastas 2007b).

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 Płotka-Wasyłka 2022).



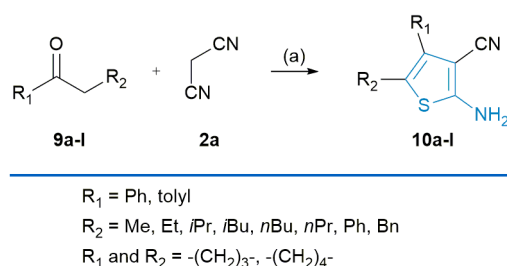
**Fig. 5** Graphical representation of the 12 principles of Green Chemistry proposed by Anastas and Warner in 1998 (Anastas and Warner 1998). 1°) **Prevention**, *i.e.*, it is easier to prevent the generation of waste rather than treat or clean it. Recently, the concept of process mass intensity, which is equal to the ratio of the weight of all used material (solvents, chemicals, purification) over the weight of the active drug produced, has been defined (Jimenez-Gonzalez et al. 2011). 2°) **Atom economy** is defined by the ratio between the molecular weight of atoms utilized over the molecular weight of all the reactants. In other words, it shows the number of atoms that are incorporated into the desired products by comparison with wasted atoms (Trost 1995a, 2002). 3°) **Less Hazardous Chemical Syntheses**: when applicable, chemical processes and substances used should be safe for humans and the environment (Anastas et al. 2000). 4°) **Safer Chemicals** implies that it is preferable to synthesize a compound with low toxicity even if its activity is lower than its toxic analog. 5°) **Safer Solvents and Auxiliaries**. Solvents are often responsible for 50 to 80% of the mass in a standard batch and the removal or the use of safer solvents is one of the biggest but trickiest issues for chemists to reduce environmental pollution (Zhou et al. 2019). 6°) **Design for Energy Efficiency**. The use of room temperature and atmospheric pressure should be prioritized (Koel and Kaljurand 2006; Moseley and Kappe 2011; Sajid and Plotka-Wasyłka 2022). 7°) **Use of renewable feedstocks** indicates the importance of using bio-based chemicals when possible rather than depleting material (Lange 2015). 8°) **Reduce Derivatives** demonstrates the need to avoid protection and deprotection steps in synthetic pathways when possible to minimize waste generation. 9°) **Catalysis**: the use of reagents most likely as a selective catalyst is the best way to achieve a reaction (Trost 1995b). 10°) **Design for Degradation** shows the importance of the “benign by design” strategy in avoiding toxicity persistence in the environment (Horváth and Anastas 2007a). 11°) **Real-time analysis for Pollution Prevention**: monitoring reactions with analytical processes enables the control or detection of toxic products (Kurniawan et al. 2021). 12°) **Inherently Safer Chemistry for Accident Prevention** known as the “Safety Principle” indicates the necessity to develop the best conditions to minimize risks, *i.e.*, explosions, fires, or toxic substances releases (2000).

### 3. 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 environment-friendly purification (Horváth and Anastas 2007b; Anastas and Eghbali 2010).

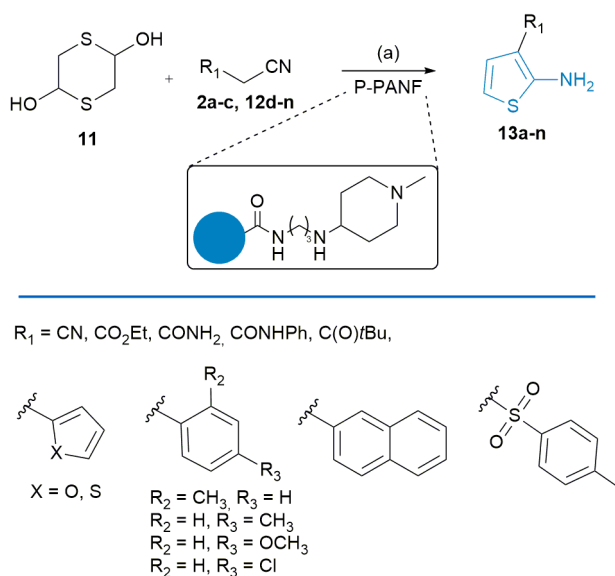


In 2013, Liang and co-workers proposed for the first time a 2-aminothiophene synthesis following Gewald conditions in water as the solvent in a reaction ignited by sodium polysulfides in catalyst-free conditions under ultrasound activation (Liang et al. 2013). The variant of the classical process consisted of the reaction of ketones **9a-l** with malonodinitrile **2a** and elemental sulfur S<sub>8</sub> in water under sonification at 40 kHz and 300 W at 70 °C for 0.5-1h, twelve different 2-aminothiophenes **10a-l** were synthesized in 42–90% yields after recrystallization from ethanol (Fig. 6).



**Fig. 6** Synthesis of 2-aminothiophenes **10a-l** from ketones **9a-l** and malonodinitrile **2a**. Reagents and conditions: (a) Disodium hexasulfide, H<sub>2</sub>O, 0.5–1h, 70 °C, sonification at 40 kHz, 300 W, 42–90% yields. The use of water as a solvent as well of sonification activation are part of Green Chemistry principles.

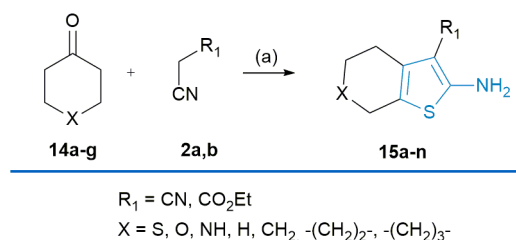
In 2013, Ma *et al.* reported the synthesis of fourteen distinct 2-aminothiophenes (**13a-m**) using an N-methylpiperazine functionalized polyacrylonitrile fiber as a catalyst, whose synthesis is depicted in figure 7 (Ma et al. 2013). 2,5-dihydroxy-1,4-dithiane **11** reacted with nitriles **2a-c** or **12d-n** and polyacrylonitrile fiber in ethanol under reflux for 4 hours 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.



**Fig. 7** Synthesis of 2-aminothiophenes **13a-n** from 2,5-dihydroxy-1,4-dithiane **11** and nitriles **2a-c**, **12d-n**. Reagents and conditions: (a) elemental sulfur S<sub>8</sub>, polyacrylonitrile fiber, 8 mol%, ethanol under reflux, 65–91% yields. Polyacrylonitrile fiber in this methodology is used as a renewable catalyst. Note: P-PANF in the figure represents polyacrylonitrile fiber.

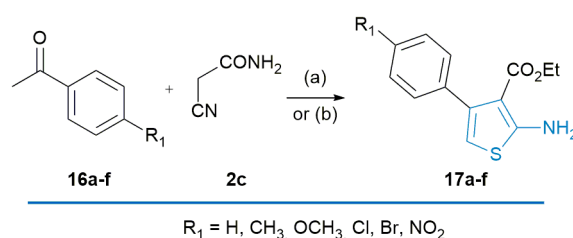
Another study involving water as a solvent was described in 2014 by Abaee *et al.* By analogy to the Gewald methodology, a range of fourteen 2-aminothiophenes (**15a-n**) were synthesized as presented in figure 8 (Abaee and Cheraghi 2014). The reaction of

the corresponding ketones **14a-g** with nitriles **2a,b** and elemental sulfur S<sub>8</sub> 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.



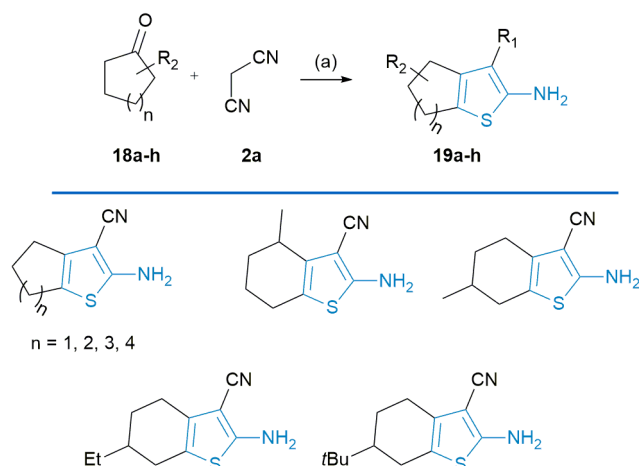
**Fig. 8** Synthesis of 2-aminothiophenes **15a-n** from ketones **14a-g** and nitriles **2a,b**. Reagents and conditions: (a) elemental sulfur S<sub>8</sub>, H<sub>2</sub>O/triethylamine (2:1 v/v), room temperature, 6h, 75–98% yields. The use of water as solvent at room temperature with a good atom-economy makes the reaction green compatible.

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<sub>8</sub> under high-speed ball milling (HSBM) for 24 hours, 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 minutes 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**).



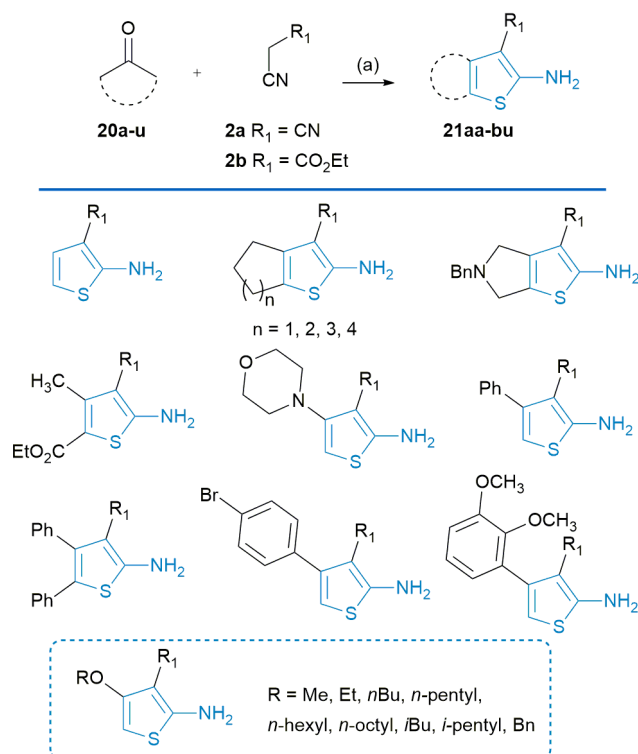
**Fig. 9** Synthesis of 2-aminothiophenes **17a-f** from ketones **16a-f** and nitrile **2c**. Reagents and conditions: (a) HSBM methodology, elemental sulfur S<sub>8</sub>, room temperature, 24h, 12–41% yields; (b) heat-assisted HSBM, 30 min, 14–53% yields. The mechanochemistry process at room temperature allows the absence of solvent for the reaction and respects Green Chemistry principles. Note: HSBM in the caption represents high-speed ball milling.

In 2014, Xu and colleagues demonstrated the benefits of the high-speed vibrating milling (HSVM) methodology as described in figure 10 (Xu et al. 2014). Cyclic ketone **18a-h**, malonodinitrile **2a**, elemental sulfur S<sub>8</sub>, and diethylamine were used in the process. After 30 minutes under HSVM, **19a-h** were obtained in 42–94% yields after purification by silica gel chromatography.



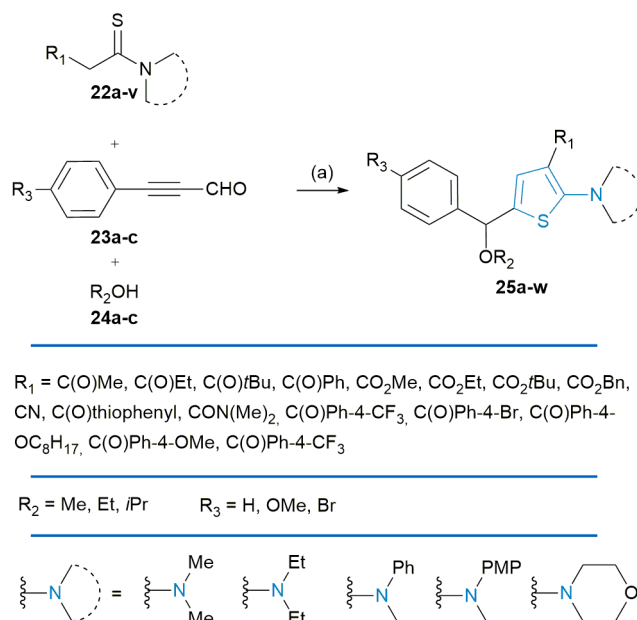
**Fig. 10** Synthesis of 2-aminothiophenes **19a-h** from ketones **18a-h** and malonodinitrile **2a**. Reagents and conditions: (a) diethylamine, elemental sulfur  $S_8$ , HSVM, 43–94% yields. The use of HSVM process renders the synthetic pathway Green compatible. Note: HSVM in the caption means high-speed vibrating milling.

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. 8) (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  $S_8$  in 1-butyl-3-methylimidazolium hydroxide ([bmIm]OH) at 60 °C for 2 hours, yielding twenty-eight different 2-aminothiophenes **21aa-bu** in 35–92% yield after filtration. The process of carrying out the synthesis of 2-aminothiophene in ionic liquids was still very little described in the literature (Hu *et al.* 2006).



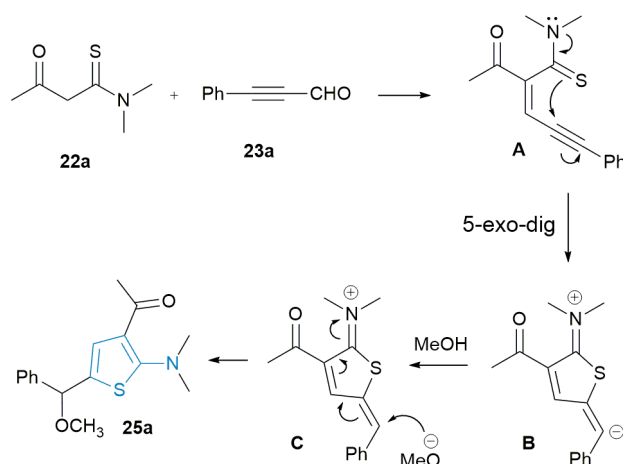
**Fig. 11** Synthesis of 2-aminothiophenes **21aa-bu** from ketones **20a-u** and nitriles **2a,b**. Reagents and conditions: (a) elemental sulfur  $S_8$  in [bmIm]OH, 60 °C, 2h, 35–92% yields. The use of ionic liquid as solvents is a trend in Green Chemistry that respects Green Chemistry principles. Note: [bmIm]OH in the caption represents 1-butyl-3-methylimidazolium hydroxide.

In 2015, twenty-three 2-aminothiophenes (**25a-w**) have been synthesized by Luo *et al.* following a one-pot regioselective metal-free methodology whose synthesis is portrayed in figure 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 hours to afford 2-aminothiophenes **25a-w** in 35–96% yields after purification by silica gel chromatography.



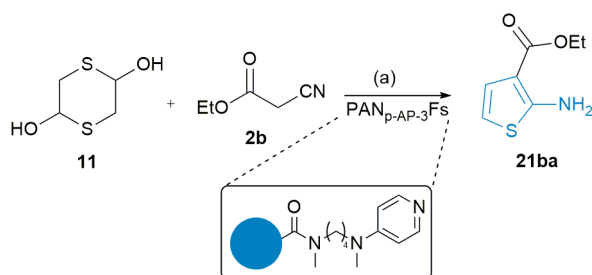
**Fig. 12** Synthesis of 2-aminothiophenes **25a-w** from thioamides **22a-v**, alkynes **23a-c** and alcohols **24a-c**. Reagents and conditions: (a) reflux, nitrogen atm, 7h, 35–96% yields. The methodology shows a good atom economy and a metal-free regioselective pathway that respects Green Chemistry principles.

They proposed a mechanism to describe their one-pot synthesis, which is presented in figure 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**.



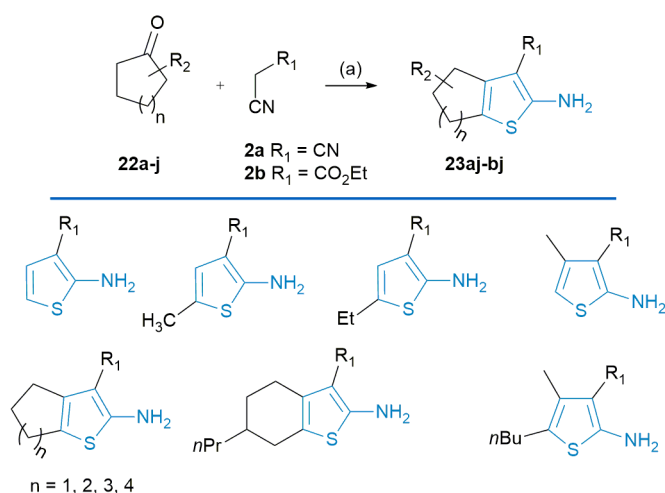
**Fig. 13** Mechanism of formation of 2-aminothiophene **25a** from thioamide **22a** and the aldehyde **23a** described by Luo *et al.* The mechanism demonstrates the good atom economy with as only waste a molecule of water.

In 2015, Li and coworkers 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 **11** reacted with ethyl cyanoacetate **2b** and the catalyst in water at 80 °C to give **21ba** 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).



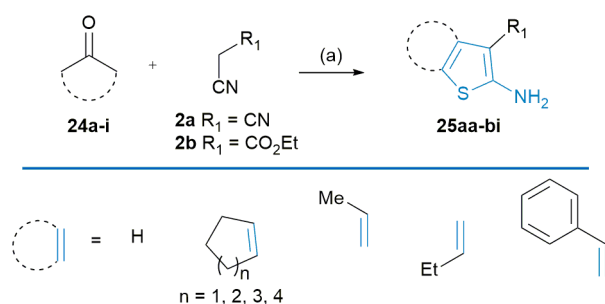
**Fig. 14** Synthesis of 2-aminothiophene **21ba** from 2,5-dihydroxy-1,4-dithiane **11** and ethyl cyanoacetate **2b**. Reagents and conditions: (a) fiber (1 mol% based on aminopyridine group), H<sub>2</sub>O, 80 °C, 92% yield. The use of the fiber in water as a solvent renders the methodology environmentally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

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 **22a-j** that reacted with nitriles **2a,b**, sodium hydroxide, and elemental sulfur S<sub>8</sub>, 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.



**Fig. 15** Synthesis of 2-aminothiophenes **23aj-bj** from ketones **22a-j** and nitriles **2a,b**. Reagents and conditions: (a) sodium hydroxide, elemental sulfur S<sub>8</sub>, choline chloride/urea, 2–3h, 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.

Another methodology reporting alternative solvents was described in 2017 by Akbarzadeh and Dekamin and is disclosed in figure 13 (Akbarzadeh and Dekamin 2017). They applied alkylketones **24a-i** in the reaction with corresponding nitriles **2a,b** and elemental sulfur S<sub>8</sub> in eco-friendly PEG-600 under ultrasonic conditions at room temperature for 10 to 50 minutes to form 2-aminothiophenes **25aa-bi** in 29–98% yields after filtration and recrystallization from ethanol.

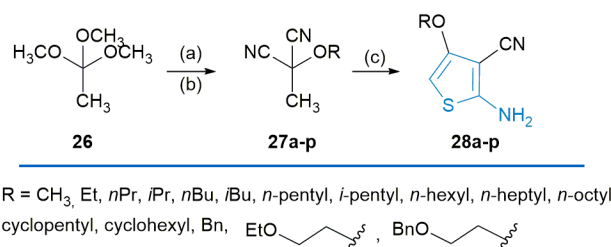


**Fig. 16** Synthesis of 2-aminothiophenes **25aa-bi** from ketones **24a-i** and nitriles **2a,b**. Reagents and conditions: (a) elemental sulfur S<sub>8</sub>, PEG-600, room temperature, 10–50 min, 29–98% yields. PEG-600 is known to be an eco-friendly solvent and is used here under ultrasonic conditions at room temperature. Note: PEG-600 in the caption means polyethylene glycol 600.

#### 4. Multicomponent reactions

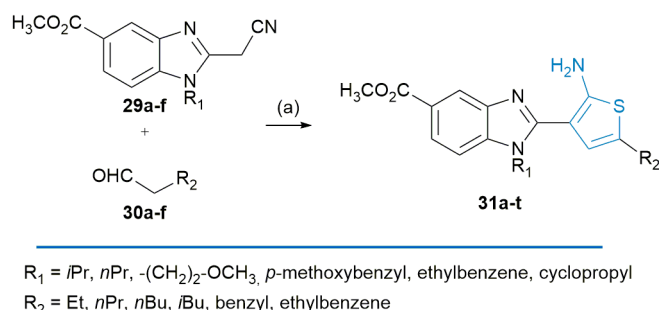
Multicomponent reactions are reactions realized with more than two reagents following a one-pot methodology. This kind of reaction is a great tool in medicinal chemistry because it allows the synthesis of large series easily in one step instead of pathways with many stages and tedious conditions (Dömling 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 figure 17, the reaction of **26** with the corresponding alcohol at 80 °C for 24 hours led to dinitriles **27a-p**. In a second step, compounds **27a-p** reacted with malonodinitrile **2a**, elemental sulfur S<sub>8</sub> and triethylamine in THF at 60 °C for 2–3h, giving 2-aminothiophenes **28a-p** in 26–84% yields after purification by silica gel chromatography.



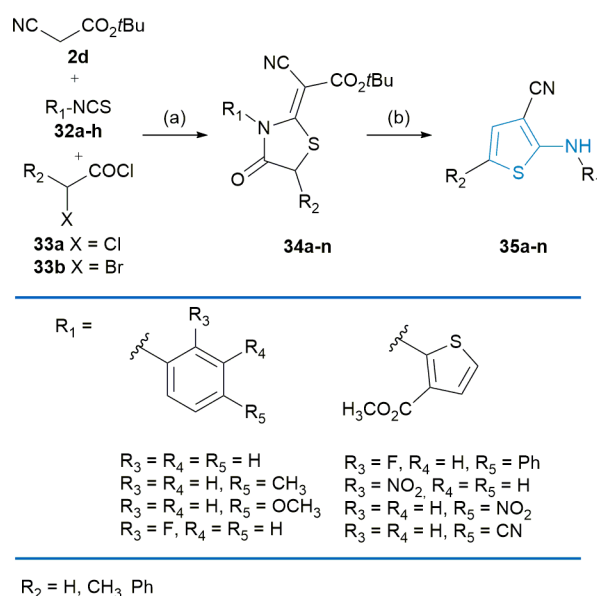
**Fig. 17** Synthesis of 2-aminothiophenes **28a-p** from orthoacetate **26** and malonodinitrile **2a**. Reagents and conditions: (a) ROH, malonodinitrile **2a**, 24h, 80°C; (b) malonodinitrile **2a**, 60 °C, 3h; (c) elemental sulfur S<sub>8</sub>, triethylamine, 60 °C, 15 min, 26–84% yields.

In 2013, Chen *et al.* described the synthesis of 2-(2-aminothiophene)-benzimidazoles (**31a-t**) using a 3-multicomponent reactions involving nitriles **29a-f** with aldehydes **30a-f**, elemental sulfur S<sub>8</sub>, and piperidine in ethanol under reflux for 1.5h, providing 2-aminothiophenes **31a-t** in 69–86% yields after purification by silica gel chromatography (Fig. 18)(Chen *et al.* 2013).



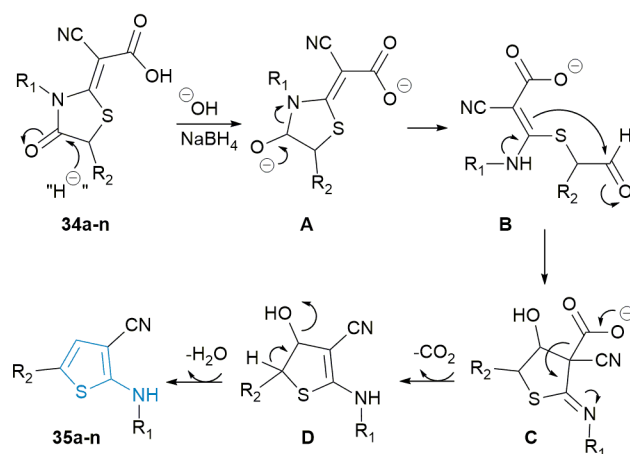
**Fig. 18** Synthesis of 2-aminothiophenes **31a-t** from benzimidazoles **29a-f** and aldehydes **30a-f**. Reagents and conditions: (a) elemental sulfur S<sub>8</sub>, piperidine, ethanol, reflux, 1.5h, 69–86% yields.

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 figure 16 (Zeng *et al.* 2016). The first step was the synthesis of the 4-thiazolidinone moiety by the reaction of thioisocyanates **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 hours 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 NaBH<sub>4</sub> in water to yield **35a-n** in 36–83% after purification by silica gel chromatography.



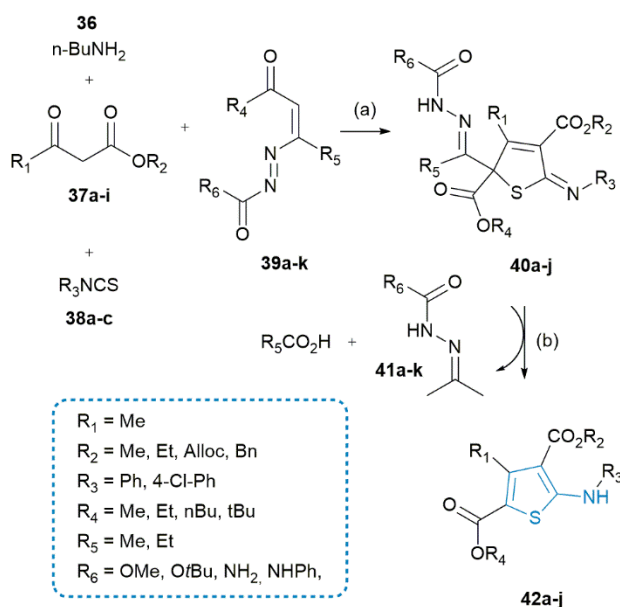
**Fig. 19** Synthesis of 2-aminothiophenes **35a-n** from thioisocyanates **32a-h**, acyl chlorides **33a,b** and nitrile **2d**. Reagents and conditions: (a) potassium hydroxide, dry N,N-Dimethylformamide, room temperature, overnight, 68–80% yields; (b) trifluoroacetic acid, dichloromethane, room temperature, 24h, 84–91% yields; (c) Sodium borohydride, H<sub>2</sub>O, 15 °C, 0.5–24h, 36–83% yields.

In addition, the authors proposed a plausible mechanism to explain the reduction, pictured in figure 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. 20** Mechanism of formation of 2-aminothiophenes **35a-n** proposed by Zeng and co-workers. The mechanism shows the departure of water and carbon dioxide as only wastes.

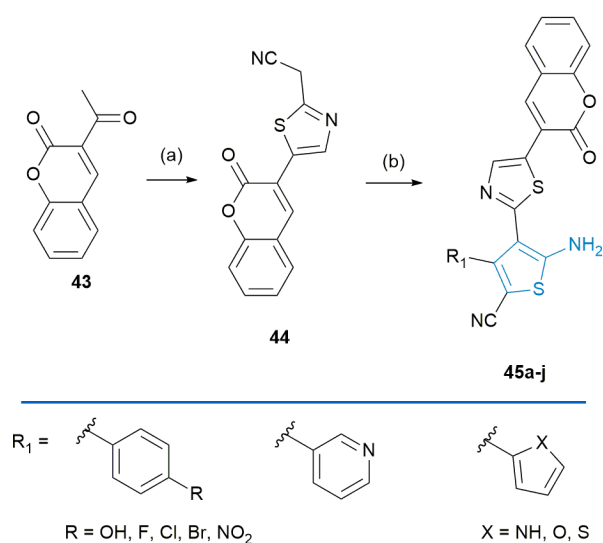
In 2018, Mari *et al.* described a new way to synthesize ten different 2-aminothiophenes (**42a-j**) in two steps *via* a 4-multicomponent reactions (Mari *et al.* 2018). Aiming to optimize reaction conditions, the authors tested several solvents and the best conditions are those disclosed in figure 21. The reaction between *n*-butyl amine **36**,  $\beta$ -ketoesters **37a-i**, aryl isothiocyanates **38a-c**, and 1,2-diaza-1,3-dienes **39a-k** at room temperature for 9.5–23.5 hours 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. This method allowed the introduction of diverse functions on the 2-aminothiophene moiety in mild conditions with good yields. However, conservation of electron-withdrawing group on C3 position seems necessary for this methodology.





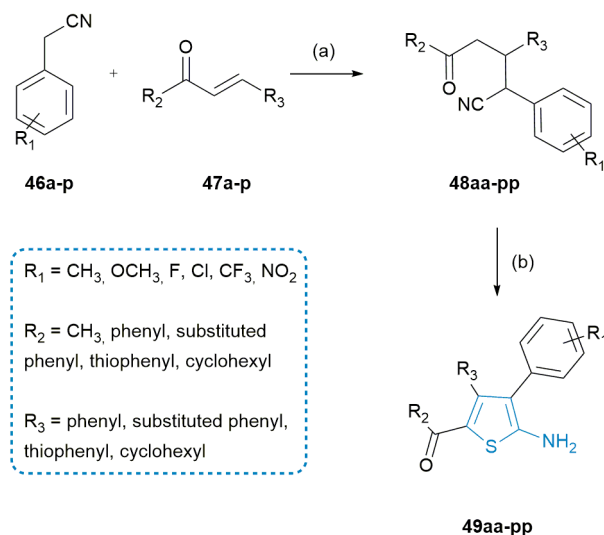
**Fig. 21** Synthesis of 2-aminothiophenes **42a-j** from *n*-butyl amine **36**,  $\beta$ -ketoesters **37a-i**, aryl isothiocyanates **38a-c**, and 1,2-diaza-1,3-dienes **39a-k**. Reagents and conditions: (a) methanol, room temperature, 9.5–23.5h, 40–69% yields; (b) Amberlyst™ 15H, acetone/H<sub>2</sub>O, room temperature, 70–83% yields. Note: Amberlyst™ 15H is a strong acidic resin.

In 2019, Kavitha *et al.* reported the synthesis of 2-aminothiophenes (**42a-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 figure 22. Coumarin **43** reacted in the presence of tetrabutylammonium tribromide in acetic acid for 2 hours at room temperature, followed by the addition of cyanoacetamide **2c** in ethanol under reflux for 2 hours to afford **44** in 88% yield over two steps after recrystallization from methanol. Then, the 4-multicomponent reactions was used and **44** reacted with malonodinitrile **2a**, elemental sulfur S<sub>8</sub>, and various aryl aldehydes in the presence of 10 mol% of L-proline in ethanol at room temperature to lead **45a-j** in 66–81% yields after recrystallization from methanol, acetonitrile, acetone or ethyl acetate.



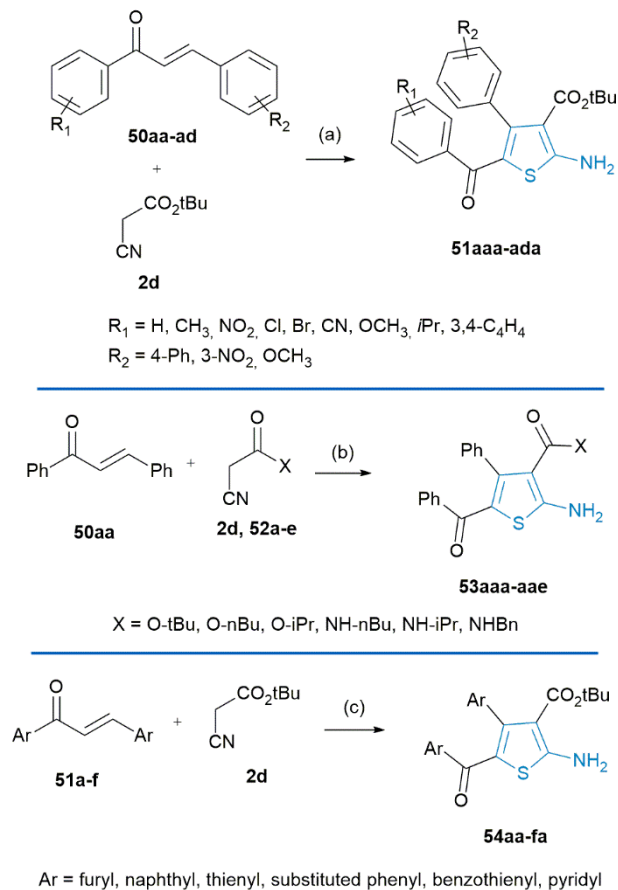
**Fig. 22** Synthesis of 2-aminothiophenes **45a-j** from coumarin **43** and cyanoacetamide **2c**. Reagents and conditions: (a) tetrabutylammonium tribromide, acetic acid, room temperature, 2h then cyanoacetamide **2c** in ethanol, reflux, 2h, 88% yield; (b) malonodinitrile **2a**, aryl aldehydes, elemental sulfur S<sub>8</sub>, L-proline (10 mol%) in ethanol, room temperature, 5–8h, 66–81% yields.

In 2020, Nguyen *et al.* developed a one-pot synthesis of two steps starting with the reaction between cyanoaryls **46a-p** with  $\alpha,\beta$ -unsaturated ketones **47a-p** and DBU in dimethyl sulfoxide at room temperature for 30 minutes to give transiently **48aa-pp**. The second stage involved **48aa-pp** with DABCO, and elemental sulfur S<sub>8</sub> at 80 °C for 16 hours to afford compounds **49aa-pp** in 45–77% yields over 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 thirty-one derivatives explored.



**Fig. 23** Synthesis of 2-aminothiophenes **49aa-pp** from nitriles **46a-p** and  $\alpha,\beta$ -unsaturated ketones **47a-p**. Reagents and conditions: (a) DBU (5 mol%), dimethyl sulfoxide, room temperature, 30min; (b) DABCO (20 mol%), elemental sulfur  $\text{S}_8$ , 80 °C, 16h, 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.

In 2021, Nguyen *et al.* described a one-pot base-catalyzed 3-multicomponent reactions from chalcones **50aa-ad** or **51a-f** with  $\alpha$ -cyanoacetates **2d**, **52a-e**, and elemental sulfur  $\text{S}_8$  to obtain **51aaa-aae** and **54aa-fa** (Nguyen et al. 2021). First, thirty chalcones **50aa-ad** reacted with cyanoacetate **2d** to get **51aaa-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 **53aaa-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, forty-one compounds were synthesized in 48–82% yields after purification (trituration in methanol for thirty-nine compounds and flash chromatography for two molecules). We can notice here the lack of diversity in the C3 position with only the alkyl ester moiety introduced. Interestingly, these synthetic pathways allowed the formation of 2-aminothiophenes, considered unobtainable *via* the Gewald reaction by the authors (Nguyen et al. 2021).



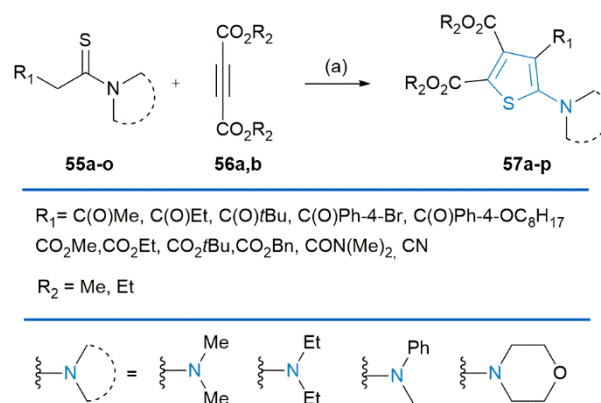
**Fig. 24** Synthesis of 2-aminothiophenes **51aaa-ada**, **53aaa-aae** and **54aa-fa** from chalcones **50aa-ad**, **51a-f** and nitriles **2d**, **52a-e**. Reagents and conditions: (a) DABCO, dimethyl sulfoxide, 80 °C, 30 min then elemental sulfur S<sub>8</sub>, 80 °C, 16h, 54–82% yields; (b) DABCO, dimethyl sulfoxide, 80 °C, 30 min then elemental sulfur S<sub>8</sub>, 80 °C, 30min, 72–86% yields; (c) DABCO, dimethyl sulfoxide, 80–100 °C, 30 min then elemental sulfur S<sub>8</sub>, 80–100 °C, 30 min, 48–70% yields. Note: DABCO in the caption represent 1,4-diazabicyclo[2.2.2]octane.

## 5. Catalyzed reactions

### 5.1. Homogeneous catalyzed reactions

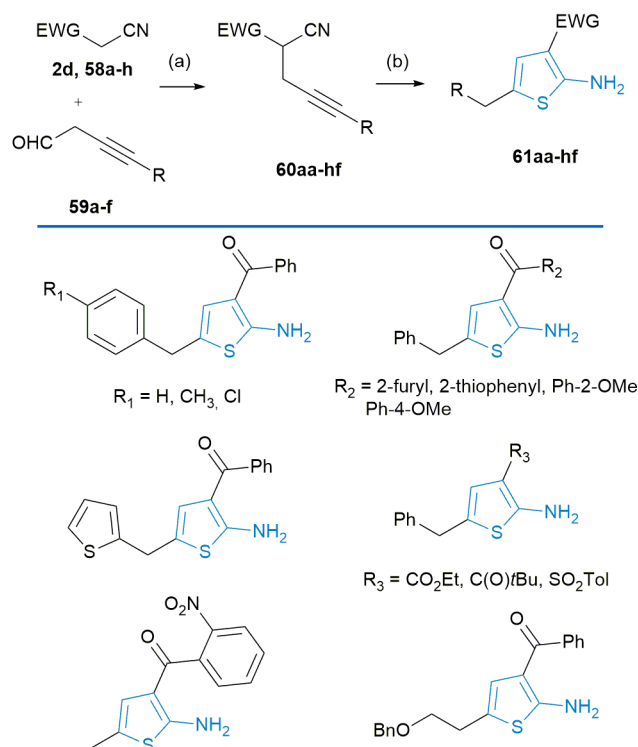
Homogeneous catalyzed reactions are realized with a catalyst in the same phase as the reactants. The organocatalysis is an excellent example of this kind of catalyzed reaction (Shelke et al. 2018). Homogeneous catalysis often moves away from stoichiometric processes using organic catalysts, hence it 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, best conditions were those described in figure 25. The reaction of thioamides **55a-o** with alkynes **56a,b** and copper acetate (II) in dimethylacetamide at 80 °C yielded to sixteen 2-aminothiophenes **57a-p** in 38–91% after purification by silica gel chromatography.



**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, 4–6h, 38–91% yields.

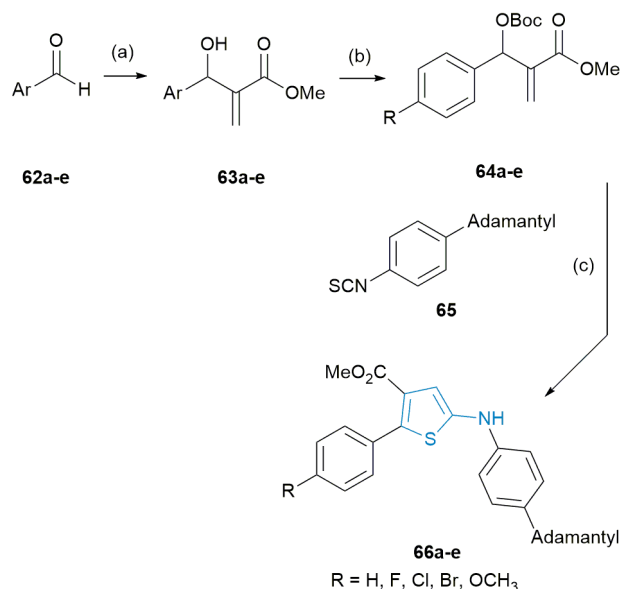
Another method that uses L-proline and Hantzsch ester was written up by Kao *et al* (Kao *et al.* 2018). The first step was the reaction between alkynes **59a-f**, nitriles **2d** or **58a-h**, L-proline, and Hantzsch ester in ethanol at 70 °C to give **60aa-hf** in 44–99% yields. At a second time, phosphorus pentasulfide was employed in ethanol at 80 °C for 3 hours to afford **61aa-ia** in 9–95% yields after purification by flash chromatography (Fig. 26).



**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) P<sub>4</sub>S<sub>10</sub> in ethanol, 80 °C, 3h, air, 9–95% yields.

In 2021, Zenkov *et al.* depicted the synthesis of five 2-aminothiophene-5-aryl-substituted with adamantane (**66a-e**) as shown in figure 27 (Zenkov *et al.* 2021). The synthesis consisted in a Morita-Baylis-Hillman reaction in presence of methyl acrylate and corresponding aldehyde **62a-e** with DABCO in methanol at room temperature for

72 hours to afford **63a-e** in 35–79% yields after purification by flash chromatography. Thereafter, **63a-e** reacted with di-tert-butyl dicarbonate ( $\text{Boc}_2\text{O}$ ), 4-Dimethylaminopyridine in dichloromethane at room temperature for 3 hours 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 hours to provide desired 2-aminothiophenes derivatives **66a-e** in 31–59% yields after purification by flash chromatography.



**Fig. 27** Synthesis of 2-aminothiophenes **66a-e** from aldehyde **62a-e**. Reagents and conditions: (a) methyl acrylate, DABCO in methanol, room temperature, 72h; (b)  $\text{Boc}_2\text{O}$ , 4-Dimethylaminopyridine in dichloromethane, room temperature, 3h; (c) Triphenylphosphine (20 mol%) in toluene, 110 °C, 1.5h, 31–59% yields. Note: DABCO and  $\text{Boc}_2\text{O}$  in the caption mean 1,4-diazabicyclo[2.2.2]octane and di-tert-butyl decarbonate.

## 5.2. Heterogeneous catalyzed reactions

Heterogeneous 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 pallado-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 figure 28.

In 2011, Ren *et al.* reported a strategy starting with ketone **1**, corresponding nitrile **2a,b**, elemental sulfur  $\text{S}_8$  and Mg/La mixed oxide-based catalysts (Ren et al. 2011). The authors also described the advantageous microwave irradiation (4–8 minutes) over batch conditions in ethanol (50–85 minutes). The expected products **3** were afforded in 80–92% yields after purification by silica gel chromatography.

In 2013, Tayebie 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  $\text{S}_8$  and nano ZnO (2.5 mol%) at 100 °C for 6 hours gave the desired 2-aminothiophenes **3a** in 37–86% yields after purification by silica gel chromatography (Tayebie et al. 2013).

In 2015, Bai *et al.* proposed using  $\text{NaAlO}_2$  as an ecocatalyst for the novel synthesis of 2-aminothiophenes from ketones **1** with nitriles **2a,b**, and elemental sulfur  $\text{S}_8$  in ethanol in the presence of  $\text{NaAlO}_2$  for 10 hours. A total of eighteen 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 hours. The desired 2-aminothiophenes were afforded in 30–76% yields after purification by silica gel chromatography.

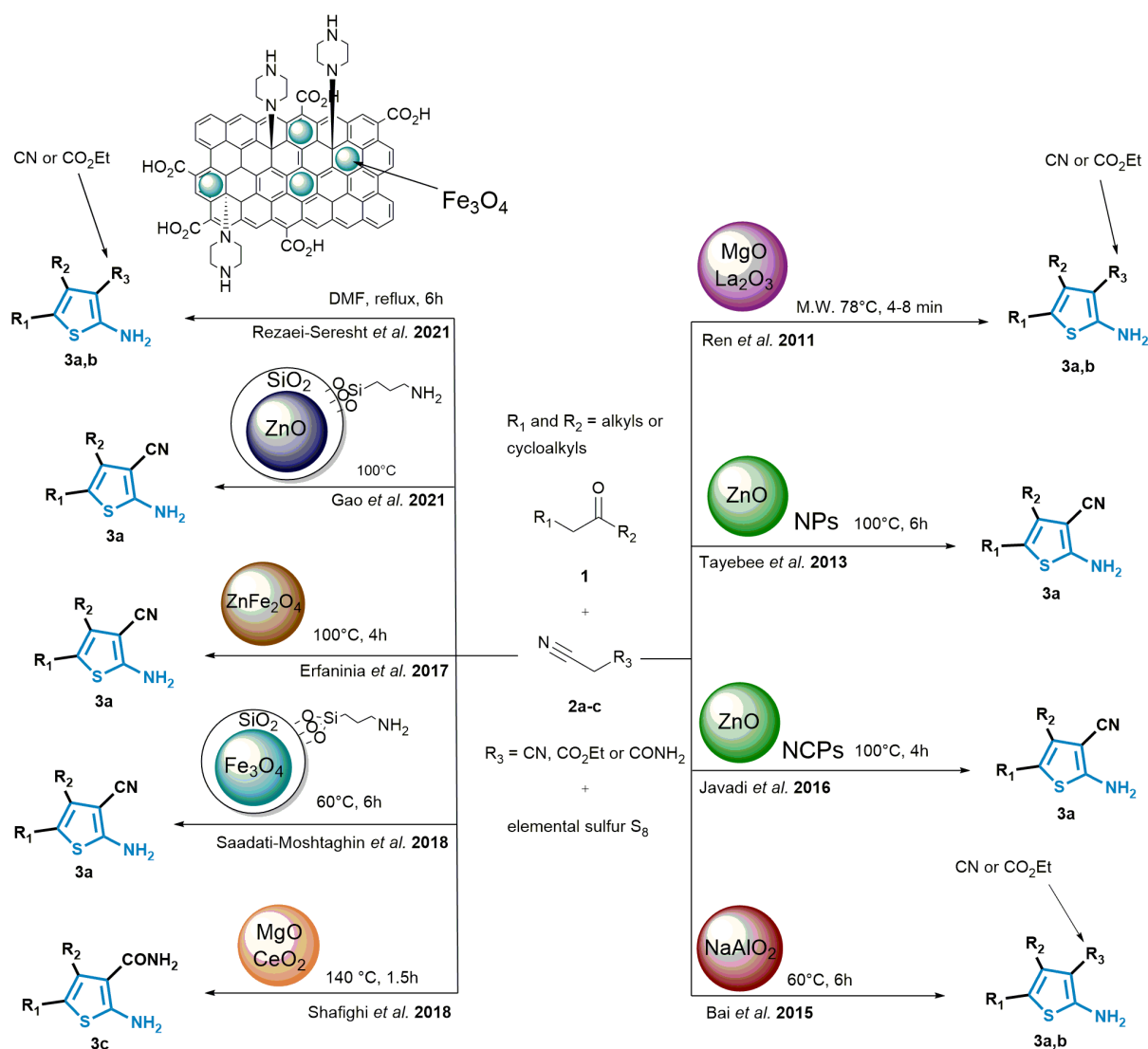
In 2018, Shafighi *et al.* disclosed the synthesis of six 2-aminothiophenes using MgO-CeO<sub>2</sub> nanocomposite as catalysts (Shafighi et al. 2018). Using this material, characterized by X-ray diffraction, field emission scanning electron microscopy (FE-SEM), 2-aminothiophenes **3c** were obtained using ketones **1** with cyanoacetamide **2c** and elemental sulfur S<sub>8</sub> in ethanol under reflux for 10 hours 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 ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles with an average size of 40 nm (Erfaninia et al. 2018). nanoparticles were characterized by X-ray diffraction, Fourier-transform infrared spectroscopy (FT-IR), scanning electron microscope, 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 S<sub>8</sub> in the presence of ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles at 2.5 mol% for 4 hours at 100 °C 2-aminothiophenes **3** 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 Fe<sub>3</sub>O<sub>4</sub> 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 S<sub>8</sub> and a catalytic amount of aminopropylmodified 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 thirteen 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<sub>8</sub> and Fe<sub>3</sub>O<sub>4</sub> graphene oxide functionalized with morpholine moiety (Fe<sub>3</sub>O<sub>4</sub>@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 hours at room temperature, the catalyst can be reused.

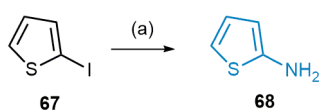
In 2021, Gao *et al.* described the green synthesis of six classical 2-aminothiophenes **3a** using ZnO@SiO<sub>2</sub>-NH<sub>2</sub> nanoparticles (Gao et al. 2021). The material, with a grain size of 70–90 nm was characterized by FT-IR, transmission electron microscopy, X-ray diffraction and FE-SEM, and has been used as a catalyst for a Gewald reaction. Ketones **1**, malonodinitrile **2a**, elemental sulfur S<sub>8</sub>, and ZnO@SiO<sub>2</sub>-NH<sub>2</sub> (0.02 g/5 mmol) reacted in solvent-free conditions for 4–8 hours at 100 °C, to give 2-aminothiophenes **3** in 27–96% yields after precipitation in cold water.



**Fig. 28** Heterogeneous catalyzed reactions of 2-aminothiophenes **3a-c** from ketones **1**, nitriles **2a-c** and elemental sulfur  $S_8$ . In the last ten years, reactions were realized from various metal oxides acting as catalysts as main Green-compatible aspect (MgO, La<sub>2</sub>O<sub>3</sub>; ZnO nanoparticles or nanoclioptilolite; NaAlO<sub>2</sub>; MgO, CeO<sub>2</sub>, Fe<sub>3</sub>O<sub>4</sub>, SiO<sub>2</sub>; ZnFe<sub>2</sub>O<sub>4</sub>; ZnO, SiO<sub>2</sub>; Fe<sub>3</sub>O<sub>4</sub>). Note: DMF, M.W., NPs, NCPs in the figure represent N,N-Dimethylformamide, microwave, nanoparticles and nanoclioptilolite.

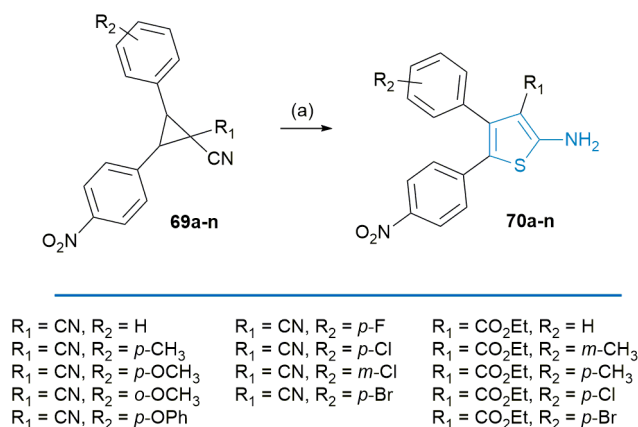
## 6. Miscellaneous

In 2011, Chen *et al.* dealt with a methodology to synthesize 2-aminothiophene **68**, as shown in figure 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 hours, 2-aminothiophene **68** was obtained in a 50% yield after purification by silica gel chromatography.



**Fig. 29** Synthesis of 2-aminothiophene **68** from 2-iodothiophene **67**. Reagents and conditions: (a) ammonia, copper iodide (I), trisodium phosphate, PEG-400/H<sub>2</sub>O, 100 °C, 15h, 50% yield. The use of a mixture composed of PEG-400 and water as solvent gives an environmentally friendly aspect. Note: PEG-400 in the caption represents polyethylene glycol 400.

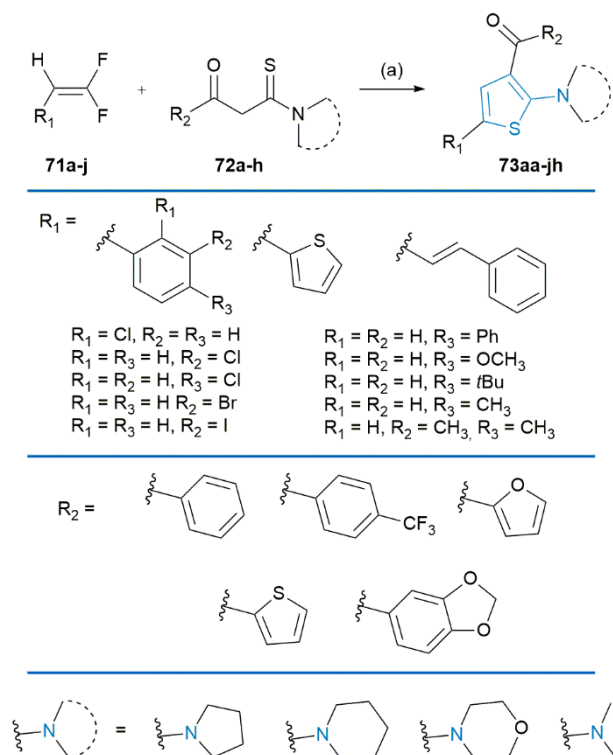
In 2014, Han *et al.* reported the synthesis of 2-aminothiophenes **70a-n** in moderate to good yields (48–83%) from cyclopropanes **69a-n**, elemental sulfur S<sub>8</sub> and morpholine in N,N-Dimethylformamide at 60 °C for 48 hours after purification on preparative thin-layer chromatography (Fig. 30).



**Fig. 30** Synthesis of 2-aminothiophenes **70a-n** from cyclopropanes **69a-n**. Reagents and conditions: (a) elemental sulfur S<sub>8</sub>, morpholine, N,N-Dimethylformamide, 60 °C, 48h. 48–83% yields.

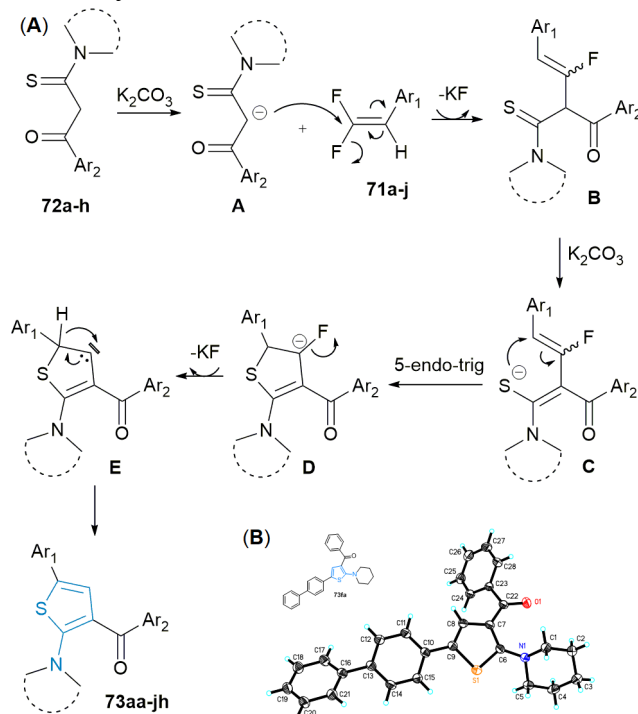
In 2017, Zhang *et al.* described the synthesis of 2-aminothiophenes using 1,1-difluoroalkenes **71a-j** and N,N-disubstituted β-keto thioamides **72a-n** with potassium carbonate in catalyst-free conditions. After optimizations realized by the authors, the best conditions disclosed in figure 31 consisted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





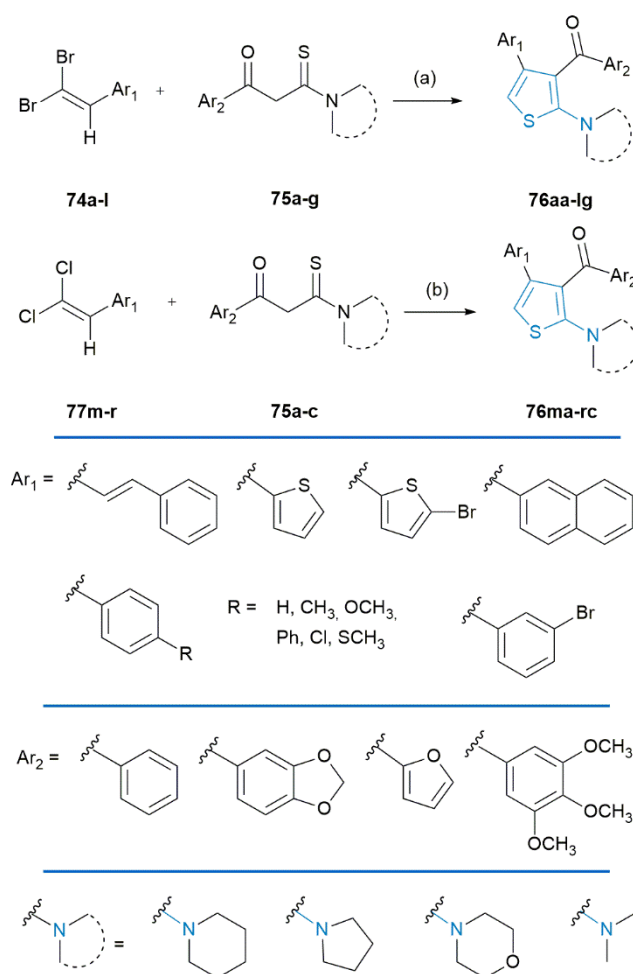
**Fig. 31** Synthesis of compounds **73aa-jh** from difluoroalkenes **71a-j** and N,N-disubstituted  $\beta$ -keto thioamides **72a-n**. Reagents and conditions: (a) potassium carbonate, dimethyl sulfoxide, 120 °C, 4h, Ar, 73–91% yields.

A mechanistic study has also been suggested by the authors and is found in figure 32A.<sup>80</sup> 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. 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.

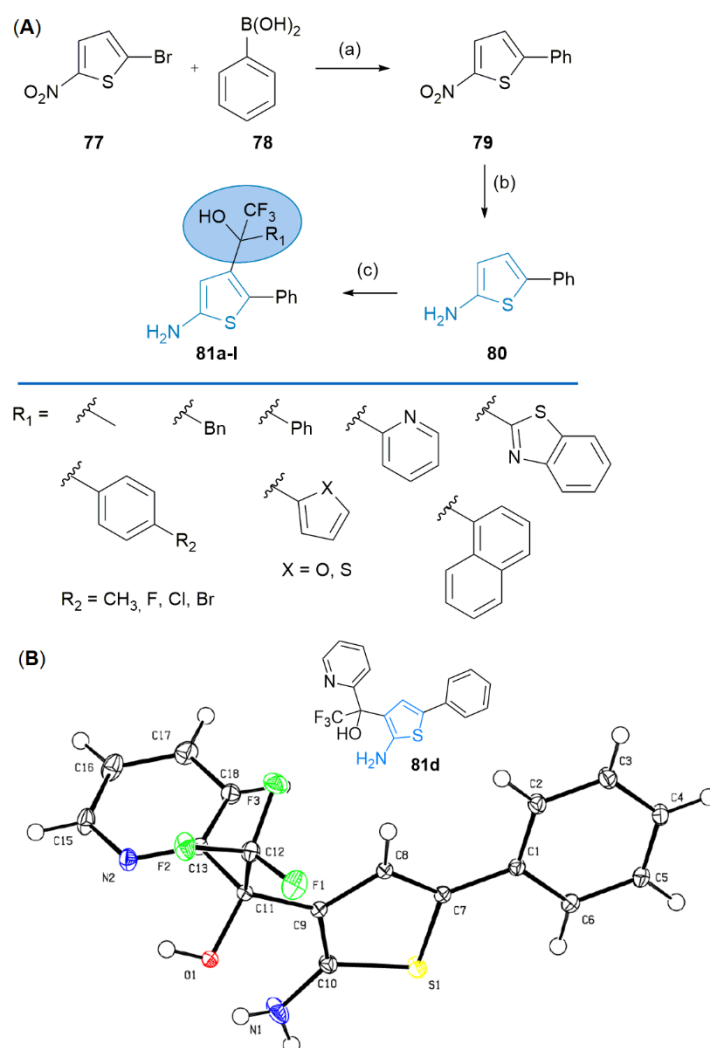
In 2020, Zhang *et al.* reported a novel series of twenty-six different 2-aminothiophenes (Zhang *et al.* 2020). The general procedure is proposed in figure 33 and occurred by cyclization of twelve gem-dibromo **74a-l** or six gem-dichloro **77m-r** with seven tertiary  $\beta$ -ketothioamide **75a-g** and aqueous solution of potassium carbonate in dimethyl sulfoxide at 120 °C for 4 hours 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.



**Fig. 33** Synthesis of 2-aminothiophenes **76aa-rc** from gem-dibromo **74a-l** or gem-dichloro **77m-r** and tertiary  $\beta$ -ketothioamide **75a-g**. Reagents and conditions: (a) potassium carbonate, dimethyl sulfoxide, 120 °C, 4h, 75–92% yields; (b) potassium carbonate, dimethyl sulfoxide, 120 °C, 4h, 50–88% yields.

In 2022, Duvauchelle *et al.* described a novel catalyst-free regioselective methodology to graft a trifluoromethylalkyl 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 **80** (90% yield after purification). The last step was the regioselective

trifluoromethyl alkylation on the C3 position in the presence of  $\alpha$ -trifluoromethyl ketones in toluene under reflux for 2–4.5 hours to obtain **81a-l** in 69–93% yields (Fig. 34A). All the purification was done by flash silica gel chromatography. The X-ray diffraction of **81d** has been realized to confirm the structure (Fig. 34B).



**Fig. 34 (A)** Synthesis of 2-aminothiophenes **81a-l** from 2-bromo-5-nitrothiophene **77**. Reagents and conditions: (a) Pd(PPh<sub>3</sub>)<sub>4</sub>, sodium carbonate [2M], toluene/ethanol under reflux, 15h, 86% yield; (b) hydrazine hydrate, ethanol, 50 °C, 15 min then Ni Raney, 50 °C, 45 min, 90% yield over 2 steps; (c)  $\alpha$ -trifluoromethyl ketones, toluene, reflux, 2–4.5h, 69–93% yields. **(B)** X-ray structure of **81d** realized to confirm the conformation.

## 7. Conclusions

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.

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### **Author Contributions**

ZB was responsible for the management of the work, overall supervision. The authors contributed to the data preparation, drafted, and revised the manuscript. All authors have read and approved the final manuscript.

### **Conflicts of interest**

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

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