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First Gewald reaction ignited by sodium polysulfide: greener ultrasound-promoted synthesis of substituted 2-aminothiophenes in the absence of catalyst

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SHORT COMMUNICATION

First Gewald reaction ignited by sodium polysulfide: greener ultrasound-promoted synthesis of substituted 2-aminothiophenes in the absence of catalyst

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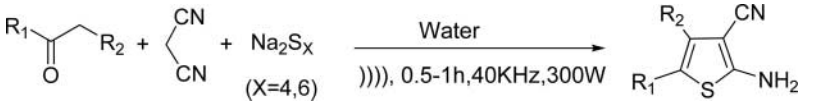
In this paper, a modified and facile Gewald reaction triggered by sodium polysulfide in the absence of catalytic base was developed. This approach involves a one-pot ultrasound-irritated aqueous reaction between ketones or aldehydes, malononitrile, and sodium polysulfide, which are converted into the corresponding 2-aminothiophene derivatives in moderate to high yields. In comparison with conventional methods, the prominent features of this sonocatalyzed procedure are experimental simplicity, good functional group tolerance, atom efficiency, and the use of water as a green solvent.



Keywords: Gewald reaction; 2-aminothiophene; sodium polysulfide; ultrasound, one-pot synthesis

1. Introduction

In heterocyclic chemistry, the thiophene scaffold is found in certain natural products and is also incorporated in several synthetic compounds (*1*). Highly functionalized 2-aminothiophene derivatives are utilized in the synthesis of a variety of agrochemicals (*2*), dyes (*3*), and pharmacologically active compounds (*4*). It is noteworthy to mention that both the top-selling drugs Olanzapine **1** (antipsychotic) and Tinoridine **2** (non-steroidal anti-inflammatory) bear the 2-aminothiophene nucleus. Moreover, 2-aminothiophenes were found to have various biological applications, such as a potent apoptosis inducer **3** (*5*) and an agonist of allosteric enhancers (AE) **4** at the adenosine A1 receptor (A1AR) (*4c*) (Figure 1).

Well-established synthetic procedures for the formation of the thiophene scaffold include Paal–Knorr thiophene synthesis (*6*), Fiesselmann reaction (*7*), Gewald synthesis (*8*), and Hinsberg reaction (*9*). These traditional name reactions use a variety of sulfur sources such as phosphorus sulfides **5**, Lawesson's reagent **6** for Paal–Knorr thiophene synthesis, thioglycolic acid **7** for Fiesselmann synthesis, elemental sulfur **8** for Gewald's method, and diethyl thiodiacetates **9** for Hinsberg syntheses (Figure 2).

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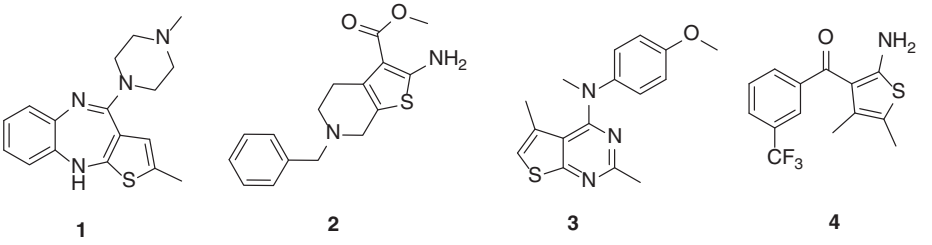

Figure 1. Pharmacologically important multisubstituted 2-aminothiophenes derivatives.

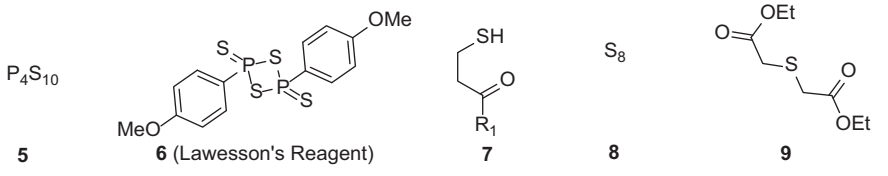

Figure 2. Sources of sulfur utilized in thiophene synthesis.

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The prevalence of 2-aminothiophenes-substituted compounds has resulted in a continuous demand for the development of flexible and greener synthetic methods for this structural moiety. The most convergent and classical approach for the preparation of these thiophene moieties is Gewald's method described by Karl Gewald over 50 years ago (*10*). It consists of the base-catalyzed condensation of a ketone or aldehyde bearing a CH_2 group with α, β-ketonitrile to form an olefin, followed by cyclic condensation with elemental sulfur (*4a*).

Many modifications mediated by excess amount of base have been recently developed, including using a solid support (*11*) and microwave irradiation combined with an insoluble polymer (*12*) or soluble polymer support (*13*). Considerable emphasis has been placed on catalyst screening: morpholine, diethylamine, triethylamine, KF-alumina (*14*), ionic liquid (*12*), etc. In contrast, far less attention has been paid to the development of a completely new approach to 2-aminothiophenes utilizing alternative sulfur sources. To the best of our knowledge, there is no literature precedent for the synthesis of 2-aminothiophenes **13** utilizing Na_2S_X instead of the sparingly water-soluble elemental sulfur as the sulfur atom source. We herein report a new Gewald methodology that involves a one-pot sequential two-step environmentally friendly process that avoids hazardous solvent and catalyst.

2. Results and discussion

Initially, water-soluble Na_2S that gives strongly alkaline solutions used in reducing organic nitro compounds (*15*) and manufacturing of sulfur dyes (*16*), insecticides (*17*) and fungicides (*18*) attracted our attention as an alternative sulfur source. We proposed that Na_2S would be a valid S_8 alternative that when coupled with synthetic intermediate **14a** (Scheme 3) would afford 2-aminothiophene **13a**. Disappointedly, the aqueous solution obtained in this reaction was complex, and the target product was not observed when using Na_2S as the sulfur source according to mass spectrometric analysis. We speculated that Na_2S could be hydrolyzed to H_2S in water that drove the reaction medium to a strong reducing condition. Consequently, malononitrile **11** and

Table 1. Optimization of reaction conditions in the presence of sodium polysulfide.

				With sonication[a]		Without sonication[b]	
Entry	Na_2S_X	Temperature (°C)	Solvent	Time (h)	Yield (%)	Time (h)	Yield (%)[c]
1	$X = 1$	70	Ethanol	0.5	–	2	–
2	$X = 1$	70	H_2O	0.5	–	2	–
3	$X = 4$	70	Ethanol	0.5	61	2	59
4	$X = 4$	70	H_2O	0.5	73	2	54
5	$X = 4$	70	Acetonitrile	0.5	34	2	31
6	$X = 4$	70	PEG-200	0.5	48	2	33
7	$X = 6$	70	Ethanol	0.5	81	1	61
8	$X = 6$	70	H_2O	0.5	84	1	47
9	$X = 6$	70	Acetonitrile	0.5	64	1	43
10	$X = 6$	70	PEG-200	0.5	59	1	21

Notes: [a]Reaction condition: The ultrasonic frequency was kept at 40 kHz and the ultrasonic power was kept at 300 W.
[b]Reaction condition: The mixture was kept silent under high stirring condition.
[c]Isolated yields.

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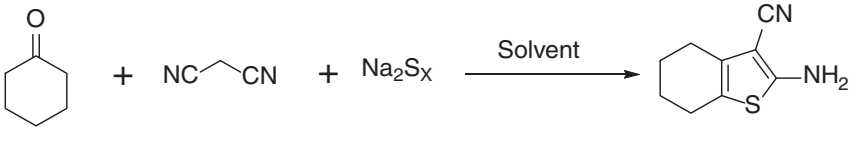
the presumed intermediate **14a** might be reduced under these strong reducing conditions. Subsequently, Na_2S_X (sodium polysulfides) was selected for further investigation. Sodium polysulfide containing two or more atoms of sulfur in the molecule is used chiefly in the manufacture of sulfur dyes (*19*), insecticides (*20*), batteries (*21*), and synthetic vulcanized rubber (*22*). Moreover, this water-soluble granular powder is widely used as ligands in coordination chemistry (*23*).

When Na_2S_4 was selected as the sulfur donor in refluxing ethanol, to our delight, we observed the precipitation of the desired product **13a** after the volume was reduced by evaporation followed by the addition of cold water. In view of this encouraging result, we decided to search for a suitable Na_2S_X and solvent in our subsequent tests. The screening/optimization results of the reaction are depicted in Table 1. The reaction yield increased with the increase in the molar fraction of sulfur in Na_2S_X. When Na_2S_X was Na_2S_6, the yield of **13a** (84%, Entry 8) after 30 min was better than that with Na_2S_4 (73%, Entry 6). On the whole, improvements in rates and yields of all trials are observed when the reactions were carried out in the polar protic solvent, ethanol and water, in comparison with the polar aprotic solvent acetonitrile. Ultrasound-assisted conditions proved to be excellent in all cases where traditional heating had a low efficiency even with prolonged reaction times. Consequently, the results demonstrate that the optimum reaction condition (Entry 8) for effective synthesis of **13a** is the presence of aqueous Na_2S_6 (Scheme 1).



10a **11** **12** **13a**

Scheme 1. Synthesis of 2-aminothiophene **13a.**

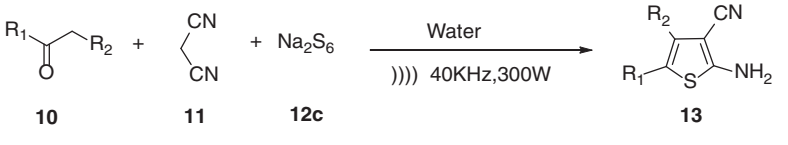
With the optimized conditions in hand, the versatility and generality of the reaction was investigated with a variety of aldehydes and ketones. We found that the above method utilizing aldehydes with small substituent groups (R_2) could render high yields and fast reaction rate (Table 2, Entries b, c and d). According to Table 2, malononitrile and Na_2S_6 proved to be optimal reagents for this reaction, both α-methylene aldehydes and cyclic ketone are well tolerated using this protocol to

Table 2. Synthesis of 2-aminothiophenes via Scheme 2.

Entry	Substrate R_1	Substrate R_2	Time (h)	Product	Yield (%)[a]
a	$-(CH_2)_4-$		0.5	**13a**	84
b	H	Et	0.5	**13b**	79
c	H	Me	0.5	**13c**	86
d	H	*i*-Pr	0.5	**13d**	90
e	H	*i*-Bu	0.5	**13e**	77
f	H	*n*-Bu	0.5	**13f**	79
g	H	*n*-Pr	0.5	**13g**	68
h	H	Ph	1	**13h**	76
i	H	$PhCH_2$	1	**13i**	57
j	Ph	H	1	**13j**	68
k	4-Me-Ph	H	1	**13k**	42
l	$-(CH_2)_3-$		0.5	**13l**	63

Note: [a]Isolated yields.

give desired products in excellent yield. Alkyl-substituted aldehydes and ketones are more reactive than aromatic-substituted substrates in this protocol to afford desired products with satisfactory yields and shortened reaction time. This phenomenon is consistent with relative reactivities of the various ketones and aldehydes toward nucleophilic addition. It is noteworthy to mention that the amino- and cyano-groups in the product remain intact after the reaction, providing useful functional groups for further synthetic elaborations. The structures of the isolated products **13a-l** were determined by physical and spectroscopic data including melting points, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectra and are consistent with previously reported structural data for 2-aminothiophenes (*14*, *24*) (Scheme 2).



Scheme 2. Synthesis of 2-aminothiophene derivates **13**.

A possible mechanism is outlined in Scheme 3. The first step of the proposed improved Gewald reaction is a Knoevenagel condensation of an activated nitrile with a α-methylene carbonyl component (ketone or aldehyde) to produce an isolable α,β-unsaturated nitrile intermediate **14**, which is then thiolated at the cyano-group with Na_2S_X. When the sulfur attack occurs at the cyano *cis* to the R_2 bearing group, an intramolecular hydrogen abstraction can occur to give a 1,3-diene-enamine intermediate. This nucleophilic intermediate can subsequently cyclize and aromatize to give the thiophene product. This presumptive reaction mechanism is significantly different from the traditional Gewald reaction route described by Sabnis *et al*. (*4a*).

Obviously, high-intensity ultrasound irradiation gives rise to the formation, growth, and implosive collapse of bubbles provoking a microenvironment with consequently high local temperatures and pressures in water (*24*); this so-called cavitation accelerates the reaction rate and shortens the reaction time, which is conducive to the mass transfer and accelerating chemical procedure for 2-aminothiophene synthesis.

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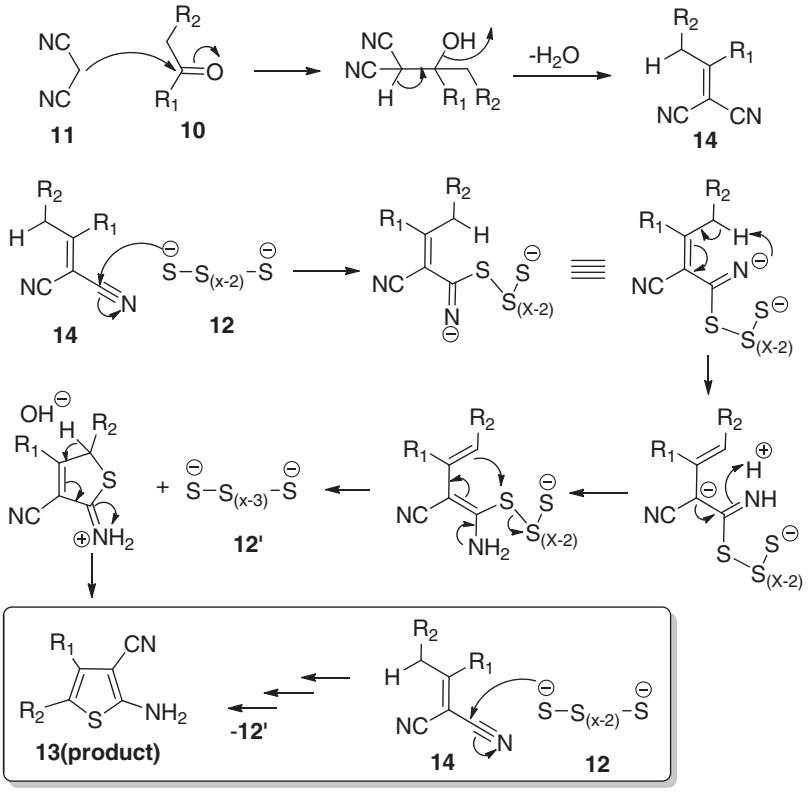

Scheme 3. Plausible mechanism for the formation of 2-aminothiophenes in the presence of sodium polysulfide.

3. Conclusions

In summary, we described a facile and practical method toward the synthesis of multisubstituted 2-aminothiophenes in good yields using sodium polysulfide as the substitute for elemental sulfur. The present work could find diverse applications in view of the power of the retro Gewald synthesis as a valid and green alternative. Further studies to develop new clean methodology toward the synthesis of biologically active sulfur compounds are in progress.

4. Experimental section

All the substrates and solvents were commercially available and purified before use. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AV-300 spectrometer at 300.13 and 75.47 MHz, respectively. The mass spectrometric analyses (HRMS) were performed using a JMS-700 MStation High Resolution JEOL Mass Spectrometer with a source temperature of 230°C, an ionization energy of 70 eV, and an ionization trap current of 300 A. Melting points were measured with a differential scanning calorimeter (Shimadzu DSC-50) and were uncorrected. The standard heating rate for all compounds was 10°C/ min. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner. The flask was located at the maximum energy area in the cleaner and addition or removal of water was used to control the temperature of the water bath.

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4.1. *General experimental procedure*

A 50 ml round-bottomed flask was charged with α-methylene carbonyl compound **10** (5 mmol), malononitrile **11** (5 mmol), and 25 ml H_2O, which was stirred for 20 min under heating or ultrasound irradiation. Subsequently, sodium polysulfide **12** (5 mmol) was added and stirred at 70°C under conventional heating or ultrasound irradiation. The mixture became turbid at the end of the reaction, which was poured into cold water. The crude product was isolated by filtration and was further purified by recrystallization with ethanol to afford pure 2-aminothiophenes. All the products were isolated, and their isolated yields are given in Table 2. Identities of the products were established by comparison of their physical and spectral data with those of reported compounds.

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