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Research Article

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Ultrasound-promoted synthesis of 2-aminothiophenes accelerated by DABCO utilizing PEG-200 as solvent

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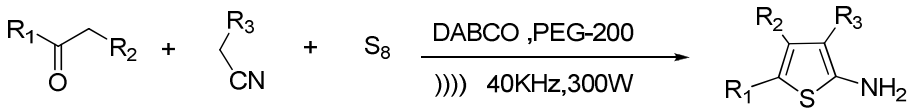
ABSTRACT



An expeditious and greener one-pot procedure was developed for the synthesis of multisubstituted 2-aminothiophene derivatives. In the presence of catalytic amount of DABCO, ketones or aldehydes, dicyanomethane and elemental sulfur were converted into the corresponding 2-aminothiophene derivatives in moderate to high yields in PEG-200 under sonication.

Keywords: Gewald reaction, 2-Aminothiophenes, DABCO, PEG-200, Ultrasound

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INTRODUCTION

The Gewald reaction of α-methylene carbonyl compounds, cyanoacetic acid derivatives or malononitrile and elemental sulfur yielding highly substituted 2-aminothiophenes has been provided instantaneous access to the never ending assembly of screening libraries with diverse functionality[1].In addition to the top-selling drug Olanzepine[2] and Tinoridine[3], an increasing number of drug candidates based on privileged 2-aminothiophene scaffolds have been found to exhibit a variety of pharmacological activities, such as anti-bacterial[4], anti-fungal[5], anti-inflammatory[6], antihypertensive[7], anti-HIV[8], antitumor[7,9], and anti-filarial [10].

Notably, the convergent and well-established classical approach to the Gewald's method mediated by basic catalyst, such as morpholine[1b, 11], diethylamine[12], triethylamine[13], KF-alumina[14], etc. suffers from drawbacks such as prolonged reaction time and moderate yield, high temperature, excess amount of hazardous catalyst and solvents. The prevalence of 2-aminothiophenes substituted compounds has required continuously development of flexible synthetic methods and effective promoter for this structural moiety.

To the best of our knowledge, a large number of organic reactions can be carried out in higher yield, shorter reaction time and milder conditions under ultrasonic irradiation than that in classical conditions[15]. On the other hand, the widely available polymer PEG as a promising solvent for organic reactions has received considerable attention in the arena of organic synthesis because of green, sustainable and environmental benign chemical processes[16].Herein, we wish to report an efficient one-pot sonication procedure for the synthesis of 2-aminothiophenes via intramolecular cyclization promoted by catalytic amount of DABCO (1,4-diazabicyclooctane) in PEG-200.

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 DRX-300 AVANCE spectrometer at 300 and 75MHz, respectively. The mass spectrometric analyses (HRMS) were performed using a JMS-700 MStation High Resolution JEOL Mass Spectrometer with a source temperature of 230^{o}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.

RESULTS AND DISCUSSION

An effective catalytic base needs to be identified first in our preliminary attempts process. Initially, cyclohexanone ,malononitrile and sulfur were chosen to survey the sonochemical effects on the synthesis of **3ea**. The model reactions(Scheme 1) were carried out in a commercially available ultrasound cleaning bath (40 kHz, 300W) in EtOH at ambient temperature in the presence of various catalytic amount of bases.

The screening results of the reaction were summarized in Table 1. Classical Gewald reaction bases, such as morpholine and piperidine were used to mediate the reaction, however, giving low yields (entries 1 and 2). The reaction also gave trace amount of desired product in the presence of *N*-Methylimidazole (entry 6). Amidine bases containing nitrogen atoms, such as 1,8-Diazabicyclo[5.4.0]undec-7-ene(DBU), 1,5-Diazabicyclo [4.3.0] non-5-ene(DBN), were tested to catalyze the three-component condensation and had no obvious promotion on the yield . By using isoquinoline or 4-methylimidazole and a prolonged reaction time up to 3 h, it could have a higher yield of 77% and 79%, respectively. Albeit, if this reaction was conducted with 5 mol% DABCO, the yield could raise up to 89% in a shorter time (entry 11).Therefore, we chose entry 11 in the next step to investigate the scopes and the limitations of the DABCO-catalyzed Gewald reaction. In general, improvements in rates and yield of all trials are observed when reactions were carried out under sonication compared with classical condition.

Scheme 1. Synthesis of 2-aminothiophene (3ea)

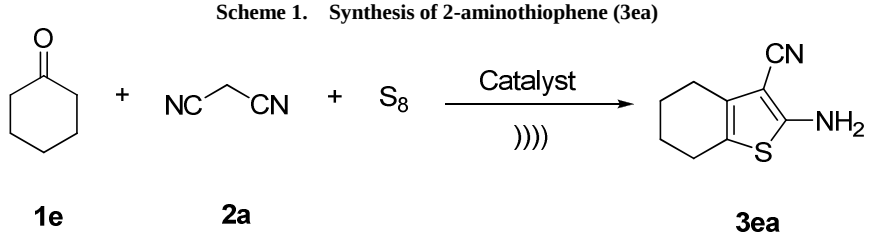


Table 1 Optimization of reaction conditions in the presence of catalytic amount of base

Entry	Catalyst	mol%	With sonication[a]		Without sonication[b]	
			Time(h)	Yield(%)[c]	Time(h)	Yield(%)[c]
1	Morpholine	20	2	53	12	45
2	Piperidine	20	2	41	11	37
3	DBU	10	3	68	10	33
4	DBN	10	3	63	11	44
5	Isoquinoline	20	3	77	20	65
6	4-Methylimidazole	20	3	79	13	54
7	N-Methylimidazole	20	1.5	14	10	Trace
8	1,4-Diazacyclohexane	20	1.5	58	10	43
9	Pyridine	20	3	41	15	35
10	DABCO	10	0.5	71	10	61
11	DABCO	5	0.5	89	10	68
12	DABCO	1	1	84	10	71

[a] *Reaction condition: The ultrasonic frequencies of 40 kHz, the ultrasonic power was kept at 300 W.*
[b] *Reaction condition: The mixture was kept silent under high stirring condition.*
[c] *Isolated yields.*

In the next step the scope and efficiency of the solvents was explored under the optimized condition of 5mol% DABCO. The model reaction was carried out in different solvents such as dimethylformamide(DMF), dimethylsulfoxide (DMSO), 1,2-dichloroethane, toluene, tetrahydrofuran (THF), acetonitrile, ethanol, PEG-200, PEG-400 and water at room temperature using 5mol% of DABCO as catalyst (Table 2). The desired product (**3ea**) was observed in ethanol, methanol, DMF, PEG and water whereas the results showed that no product were obtained even prolonged the reaction time in 1,2-dichloroethane and toluene. PEG-200 gave the highest yield (95%) of **3ea**.

The excellent yield in PEG-200 may be explained in terms of markedly improved solubility of elemental sulfur under sonication . From another point of view, it is assumed that PEG-200 also acts as a phase transfer catalyst and helps in bringing the aqueous reagent and organic reagent together. Another suggestion is that PEG-200 stabilizes the transition state **4** promoting the cyclization in the reaction rate.

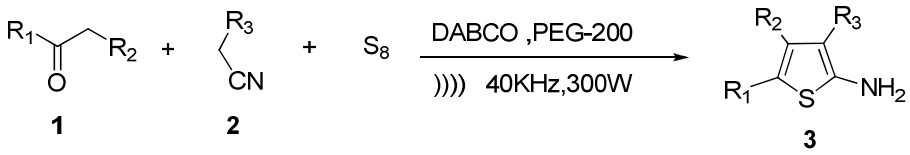
Table 2 .DABCO catalyzed synthesis of 2-aminothiophene (3ea) in different solvent

Entry	Solvent	Time(min)	Yield(%)[d]
1	Ethanol	30	89
2	Methanol	30	43
3	H_2O	30	67
4	THF	60	Trace
5	DMF	30	52
6	1,2-Dichloroethane	60	—
7	Toluene	60	—
8	PEG-200	30	95
9	PEG-400	30	31

[d]*Isolated yields.*

With the optimized conditions in hand, the versatility of the reaction was investigated with a variety of α-methylene carbonyl compounds and cyano derivatives. According to Table 3, malononitrile and ethylcyanoacetate proved to be suitable substrates for this reaction，both α-methylene aldehydes and cyclic ketones are well tolerated in this protocol to give desired products in excellent yield. It is noteworthy to mention that cyano and ester groups of 2-aminothiophenes remain intact after the reaction, which leaves easy handles for further synthetic elaborations.

Scheme 2. Synthesis of 2-aminothiophene derivates (3aa-3fb)

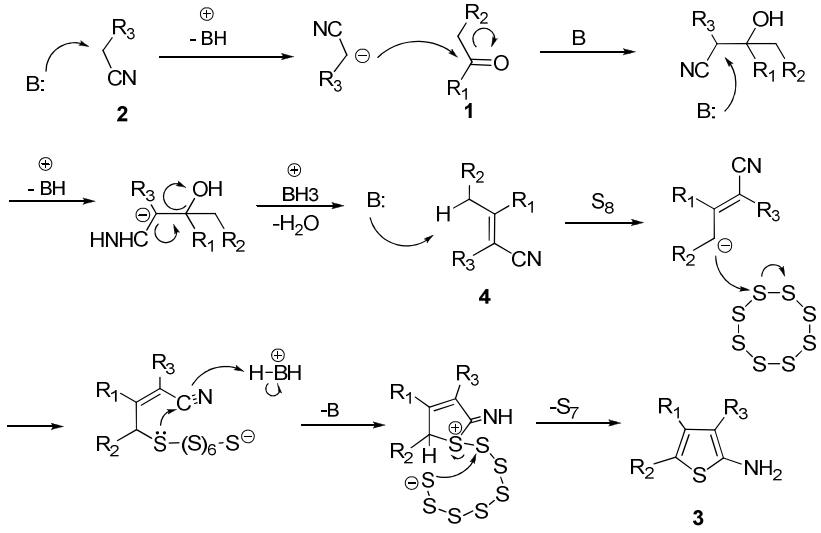


1 **2** **3**

Entry	Substrate **1**		**2**	Time (min)	Product **3**	Yield(%)
	R_1	R_2	R_3			
1	H(**1a**)	Et(**1a**)	CN(**2a**)	30	**3aa**	91
2	H(**1a**)	Et(**1a**)	COOEt(**2b**)	30	**3ab**	90
3	H(**1b**)	i-Propyl(**1b**)	CN(**2a**)	20	**3ba**	95
4	H(**1b**)	i-Propyl(**1b**)	COOEt(**2b**)	20	**3bb**	89
5	H(**1c**)	n-Propyl(**1c**)	CN(**2a**)	20	**3ca**	93
6	H(**1c**)	n-Propyl(**1c**)	COOEt(**2b**)	20	**3cb**	90
7	H(**1d**)	Ph(**1d**)	CN(**2a**)	15	**3da**	92
8	H(**1d**)	Ph(**1d**)	COOEt(**2b**)	15	**3db**	79
9	-$(CH_2)_3$- (**1e**)		CN(**2a**)	40	**3ea**	94
10	-$(CH_2)_3$- (**1e**)		COOEt(**2b**)	40	**3eb**	81
11	-$(CH_2)_4$- (**1f**)		CN(**2a**)	30	**3fa**	89
12	-$(CH_2)_4$- (**1f**)		COOEt(**2b**)	30	**3fb**	82

A possible mechanism is speculated and described in Scheme 3, The first step of the Gewald reaction is a Knoevenagel condensation of an activated nitrile with a α-methylene carbonyl component (ketone or aldehyde) to produce an α-β-unsaturated nitrile intermediate mediated by DABCO, which is then thiolated at the γ -methylene group with elemental sulfur. The sulfurated compound undergoes cyclization to form the thiophene structure, followed by an aromatization rearrangement. Upon irradiation with high intensity ultrasound, acoustic cavitation occurs and gives rise to the formation, growth, and implosive collapse of bubbles in PEG-200 with consequent high local temperatures and pressures. Thus, cavitation serves as a means of concentrating the diffuse energy of sound to accelerate the Gewald reaction.

Scheme 3. The reaction mechanism of the Gewald reaction



CONCLUSION

In conclusion, a simple, efficient, and environmentally benign methodology towards the synthesis of 2-aminothiophenes has been reported.The use of DABCO as an effective basic promoter supports the practical utility of this procedure for a wide variety of substrates. PEG-200 not only acts as phase transfer catalyst but also as clean, recyclable and low cost solvent by significantly enhancing the intramolecular cyclization. Further studies to develop new clean methodology towards the synthesis of biologically active compounds are in progress.

Acknowledgments
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