

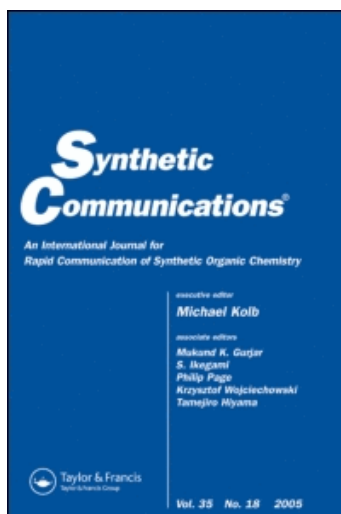
This article was downloaded by: [Monash University]

On: 20 June 2010

Access details: Access Details: [subscription number 907465080]

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Synthetic Communications

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597304>

### Convenient Synthesis of 2-Aminothiophene Derivatives by Acceleration of Gewald Reaction Under Ultrasonic Aqueous Conditions

Mohammad M. Mojtahedi<sup>a</sup>; M. Saeed Abaee<sup>a</sup>; Peyman Mahmoodi<sup>b</sup>; Mehdi Adib<sup>b</sup>

<sup>a</sup> Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran <sup>b</sup> School of Chemistry, University of Tehran, Tehran, Iran

Online publication date: 17 June 2010

**To cite this Article** Mojtahedi, Mohammad M. , Abaee, M. Saeed , Mahmoodi, Peyman and Adib, Mehdi (2010) 'Convenient Synthesis of 2-Aminothiophene Derivatives by Acceleration of Gewald Reaction Under Ultrasonic Aqueous Conditions', *Synthetic Communications*, 40: 14, 2067 – 2074

**To link to this Article:** DOI: 10.1080/00397910903219435

**URL:** <http://dx.doi.org/10.1080/00397910903219435>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

## CONVENIENT SYNTHESIS OF 2-AMINOTHIOPHENE DERIVATIVES BY ACCELERATION OF GEWALD REACTION UNDER ULTRASONIC AQUEOUS CONDITIONS

Mohammad M. Mojtahedi,<sup>1</sup> M. Saeed Abaee,<sup>1</sup>  
Peyman Mahmoodi,<sup>2</sup> and Mehdi Adib<sup>2</sup>

<sup>1</sup>Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran

<sup>2</sup>School of Chemistry, University of Tehran, Tehran, Iran

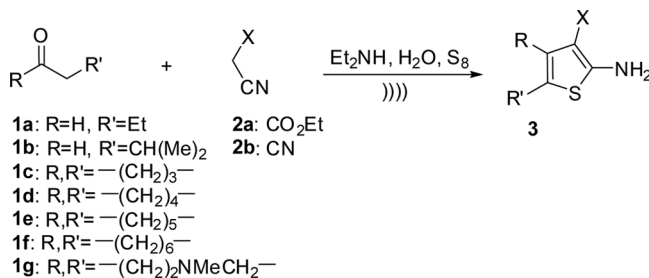
*Under ultrasound irradiation and in the presence of H<sub>2</sub>O/Et<sub>2</sub>NH, ethyl cyanoacetate or malononitrile can combine with  $\alpha$ -methylene carbonyl compounds and elemental sulfur to efficiently yield 2-aminothiophene derivatives within a few minutes. Products are easily obtained by simple filtration because of their spontaneous precipitation in the reaction mixtures.*

**Keywords:** 2-Aminothiophenes; aqueous conditions; Gewald reaction; ultrasound irradiation

In the past decade, several books,<sup>[1]</sup> reviews,<sup>[2]</sup> and papers<sup>[3]</sup> have been published that emphasize the extensive applications of ultrasonic irradiation in various types of organic transformations. Consequently, many protocols have been developed to carry out chemical reactions in shorter time periods and especially under more environmentally friendly conditions.<sup>[4]</sup> In another green chemistry front, multicomponent reactions (MCRs)<sup>[5]</sup> have increasingly gained popularity in synthetic organic chemistry<sup>[6]</sup> in recent years because they offer one-pot combinations of more than two reactants in one step, allowing direct access to complex target molecules. In this context, the one-pot cyclocondensation of ketones or aldehydes and  $\beta$ -substituted acetonitrile derivatives with elemental sulfur, known as the Gewald reaction,<sup>[7]</sup> has been one of the most well-studied MCRs in recent years. The reaction affords formation of 2-aminothiophenes with diverse pharmaceutical,<sup>[8]</sup> agrochemical,<sup>[9]</sup> and dye<sup>[10]</sup> properties. In addition, there are several natural products<sup>[11]</sup> and biologically active compounds<sup>[12]</sup> in which the 2-aminothiophene moiety serves as the basic structural framework. To extend the scope of the reaction, many alterations have been made to the original Gewald's base-catalyzed, two-component combination of  $\alpha$ -mercapto ketones with cyanoacetate<sup>[13]</sup> by varying the components<sup>[14]</sup> and the conditions.<sup>[15]</sup> The usual long reaction time periods required in most of the published procedures

Received April 18, 2009.

Address correspondence to Mohammad M. Mojtahedi, Chemistry and Chemical Engineering Research Center of Iran, P. O. Box 14335-186, Tehran, Iran. E-mail: abae@ccerci.ac.ir



**Scheme 1.** Ultrasound-mediated Gewald reactions in water.

are dramatically decreased by the use of microwave irradiation in combination with the use of additional reagents and catalysts.<sup>[16]</sup> In the present work, ultrasound irradiation is employed to conduct various Gewald reactions under inexpensive and environmentally friendly H<sub>2</sub>O/Et<sub>2</sub>NH conditions (Scheme 1). The reaction times have been considerably decreased to a few minutes and, because of the high polarity of the medium, products precipitate spontaneously, which allows their solvent-free separation from the reaction mixtures.

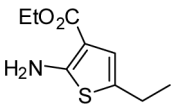
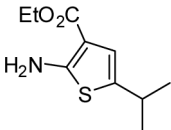
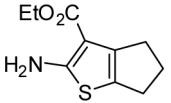
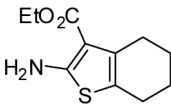
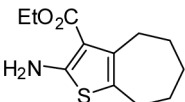
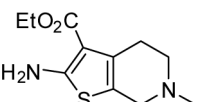
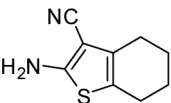
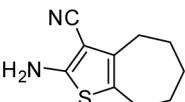
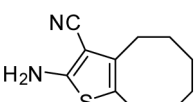
First, an equimolar mixture of 1-butanol **1a**, ethyl cyanoacetate **2a**, and sulfur was sonicated under various sets of conditions. The best results were obtained in the presence of H<sub>2</sub>O/Et<sub>2</sub>NH, leading to sole formation of ethyl 2-amino-5-ethylthiophene-3-carboxylate **3aa** within 5 min (Table 1, entry 1). The solid product precipitated by itself and was easily separated by simple filtration. A possible simultaneous thermal activation was excluded by conducting a temperature-controlled experiment. As a result, when a water bath was used to maintain the reaction temperature at 25 ± 1 °C, a similar yield was obtained for **3aa** after the same time period. Alternatively, in the absence of irradiation, the same mixture gave only low quantities of **3aa** after several hours, illustrating the crucial role of the sonication in the reaction. These observations suggest that the ultrasonic irradiation can significantly assist the reaction, presumably by providing the required energy of the transition state, as previously proposed by others.<sup>[17]</sup>

Reaction of 3-methylbutanol **1b** with **2a** proceeded equally well, leading to formation of **3ba** after 5 min of sonication (entry 2). Under the same conditions, cyclic ketones also gave their respective products in good yields (entries 3–6). The generality of the procedure was further shown by subjecting malononitrile to reaction with cyclic ketones, giving **3db**, **3eb**, and **3fb** in excellent yields (entries 7–9).

Based on these observations, a mechanistic pathway as depicted in Scheme 2 can be proposed in which an α-β-unsaturated nitrile intermediate is formed via a Knoevenagel condensation.<sup>[8a,18]</sup> This intermediate further adds to S<sub>8</sub> to form the thiophene structure after a ring-closure process, followed by an aromatization rearrangement.

In summary, we have furnished a rapid and efficient method for the preparation of substituted 2-aminothiophenes via condensation of carbonyl compounds with elemental sulfur and ethyl cyanoacetate or malononitrile under ultrasonic irradiation. The H<sub>2</sub>O/Et<sub>2</sub>NH medium is inexpensive, no extra additive or catalyst is required, and the conditions are environmentally safe and green. We can reach

**Table 1.** Ultrasound-promoted Gewald reactions

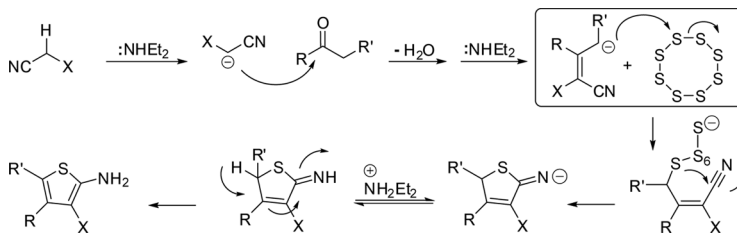
Entry	Substrate	Product	Time (Min.)	Yield (%) <sup>a</sup>
1	<b>1a + 2a</b>	 <b>3aa</b>	5	91
2	<b>1b + 2a</b>	 <b>3ba</b>	5	89
3	<b>1c + 2a</b>	 <b>3ca</b>	5	96
4	<b>1d + 2a</b>	 <b>3da</b>	5	97
5	<b>1e + 2a</b>	 <b>3ea</b>	7	88
6	<b>1g + 2a</b>	 <b>3ga</b>	3	87
7	<b>1d + 2b</b>	 <b>3db</b>	5	96
8	<b>1e + 2b</b>	 <b>3eb</b>	8	90
9	<b>1f + 2b</b>	 <b>3fb</b>	8	87

<sup>a</sup>Isolated yields.

a better conclusion by comparing the performance of the present work with some other reports available in the literature as illustrated in Table 2.

## EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC) and gas chromatography (GC). Fourier transform-infrared (FT-IR) spectra were recorded using



Scheme 2. The proposed mechanism.

KBr disks on a Bruker Vector-22 IR spectrometer, and absorptions are reported as wave numbers ( $\text{cm}^{-1}$ ). NMR spectra were obtained on a FT-NMR Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz as  $\text{CDCl}_3$  solutions, and the chemical shifts are expressed as  $\delta$  units with  $\text{Me}_4\text{Si}$  as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Elemental analysis was performed for compound **3ba** using a Thermo Finnigan Flash EA 1112 instrument. Aldehydes were purified using standard procedures prior to use. All other chemicals and reagents were purchased from commercial sources and were used without further purification. Sonication was performed using a Sartorius Ultrasonic homogenizer Labsonic P 230-V/50-Hz instrument with a frequency of 24 KHz and nominal power of  $460 \text{ W/cm}^2$ . In all reactions, the tip of the sonotrode was located in the same position just under the liquid surface in order to obtain optimal sonication and reproducible results.

### Typical Procedure for the Synthesis of 3aa

A mixture of **1a** (360 mg, 5 mmol), **2a** (565 mg, 5 mmol), and sulfur (160 mg, 5 mmol) in  $\text{H}_2\text{O}$  (1 mL) and  $\text{Et}_2\text{NH}$  (0.3 mL) was sonicated in a 10-mL test tube for an appropriate length of time (as indicated in Table 1) until TLC showed complete disappearance of the starting materials. In temperature-controlled experiments, reactions were performed in a water bath at  $25 \pm 1^\circ\text{C}$ . The product precipitated upon completion of the reaction. The pure product was obtained by recrystallization of the precipitates using an  $\text{EtOAc}$ /hexane mixture. Products were identified based on their melting points and spectral characteristics.

Table 2. Ultrasound-mediated Gewald reaction in comparison with some other methods

Energy type	Solvent requirement	Reference
Ultrasonic	$\text{H}_2\text{O}$	Present work
Thermal	$\text{MeOH}$ , $\text{Et}_2\text{O}$	Gütschow et al. <sup>[14b]</sup>
Thermal	EDDA, <sup>a</sup> $\text{Et}_2\text{O}$	Hu et al. <sup>[15a]</sup>
Microwave	Toluene, $\text{MeOH}$ , $\text{CH}_2\text{Cl}_2$ , DMF	Hoener et al. <sup>[16b]</sup>
Microwave	$\text{EtOH}$ , $\text{CH}_2\text{Cl}_2$	Sridhar et al. <sup>[16c]</sup>
Electrochemical	$\text{MeCN}$	Feroci et al. <sup>[15d]</sup>

<sup>a</sup>Ethylenediammonium diacetate.

## Data

**Ethyl 2-Amino-5-ethylthiophene-3-carboxylate (3aa).** Mp 73 °C (reported mp. 73 °C)<sup>[16c]</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.64 (s, 1H), 5.84 (s, 2H), 4.25 (q, 2H, *J* = 7.1 Hz), 2.60 (q, 2H, *J* = 7.5 Hz), 1.33 (t, 3H, *J* = 7.1 Hz), 1.22 (t, 3H, *J* = 7.5 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 165.5, 161.2, 128.5, 120.6, 106.2, 59.6, 23.0, 15.4, 14.5; IR (KBr) 3407, 3305, 1660, 1254 cm<sup>-1</sup>; MS *m/z* (%) 200 (M<sup>+</sup>, 25), 199 (100), 184 (80), 138 (86).

**Ethyl 2-Amino-5-isopropylthiophene-3-carboxylate (3ba).** Mp 68 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.63 (s, 1H), 5.80 (s, 2H), 4.25 (q, 2H, *J* = 7.1 Hz), 2.95–2.86 (m, 1H), 1.34 (t, 3H, *J* = 7.1 Hz), 1.24 (d, 6H, *J* = 6.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 165.5, 161.0, 134.2, 119.1, 106.0, 59.6, 29.5, 24.1, 14.6; IR (KBr) 3441, 3334, 1677, 1590 cm<sup>-1</sup>; MS *m/z* (%) 213 (M<sup>+</sup>, 35), 198 (100), 152 (40). Calcd. for C<sub>10</sub>H<sub>15</sub>NO<sub>2</sub>S: C, 56.31; H, 7.09. Found: C, 56.44; H, 7.12.

**Ethyl 2-Amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (3ca).** Mp 90 °C (reported mp. 89–90 °C)<sup>[15c]</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.83 (s, 2H), 4.25 (q, 2H, *J* = 7.1 Hz), 2.85–2.80 (m, 2H), 2.74–2.69 (m, 2H), 2.36–2.26 (m, 2H), 1.33 (t, 3H, *J* = 7.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 166.2, 165.8, 142.7, 121.4, 103.0, 59.4, 30.8, 28.9, 27.2, 14.4; IR (KBr) 3414, 3294, 1624, 1287 cm<sup>-1</sup>; MS *m/z* (%) 211 (M<sup>+</sup>, 100), 165 (70), 137 (15).

**Ethyl 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (3da).** Mp 113 °C (reported mp. 115 °C)<sup>[15c]</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.01 (s, 2H), 4.25 (q, 2H, *J* = 7.2 Hz), 2.71–2.69 (m, 2H), 2.48–2.46 (m, 2H), 1.75–1.73 (m, 4H), 1.33 (t, 3H, *J* = 7.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 166.6, 161.9, 132.4, 117.5, 105.5, 59.4, 27.0, 24.5, 23.3, 22.9, 14.5; IR (KBr) 3405, 3299, 1647, 1274 cm<sup>-1</sup>; MS *m/z* (%) 225 (M<sup>+</sup>, 100), 223 (90), 179 (51), 151 (24).

**Ethyl 2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylate (3ea).** Mp 87 °C (reported mp 89 °C)<sup>[16c]</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.74 (s, 2H), 4.28 (q, 2H, *J* = 7.2 Hz), 3.00–2.96 (m, 2H), 2.60–2.56 (m, 2H), 1.82–1.78 (m, 2H), 1.68–1.62 (m, 4H), 1.35 (t, 3H, *J* = 7.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 166.0, 159.7, 137.9, 121.4, 107.6, 59.6, 32.2, 28.7, 28.6, 27.8, 27.0, 14.5; IR (KBr) 3398, 3301, 1651, 1277 cm<sup>-1</sup>; MS *m/z* (%) 239 (M<sup>+</sup>, 9), 193 (8), 83 (100).

**Ethyl 2-Amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (3ga).**<sup>[8c]</sup> Mp 99 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.18 (s, 2H), 4.22 (q, 2H, *J* = 7 Hz), 3.37 (s, 2H), 2.82 (m, 2H), 2.67 (m, 2H), 2.43 (s, 3H), 1.30 (t, 3H, *J* = 7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 165.9, 162.4, 130.5, 113.9, 104.9, 59.5, 53.1, 52.3, 45.2, 27.1, 14.4; IR (KBr) 3394, 3262, 1667 cm<sup>-1</sup>.

**2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (3db).** Mp 145 °C (reported mp. 146–147 °C)<sup>[15c]</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.71 (s, 2H), 2.48–2.46 (m, 4H), 1.79 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 160.1, 132.3, 120.6, 115.6, 88.5, 24.5, 24.1, 23.4, 22.1; IR (KBr) 3445, 3328, 2196, 1521 cm<sup>-1</sup>; MS *m/z* (%) 178 (M<sup>+</sup>, 85), 150(100).

**2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carbonitrile (3eb).** Mp 125 °C (reported mp. 126 °C)<sup>[16c]</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.26 (s, 2H),

2.65–2.57 (m, 4H), 1.83–1.79 (m, 2H), 1.67–1.63 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  157.7, 136.9, 123.9, 115.9, 92.0, 31.9, 29.4, 29.2, 28.1, 27.2; IR (KBr) 3443, 3310, 2203  $\text{cm}^{-1}$ ; MS  $m/z$  (%) 192 ( $\text{M}^+$ , 100), 164 (35), 138 (25).

**2-Amino-4,5,6,7,8,9-hexahydrocycloocta[b]thiophene-3-carbonitrile (3fb).** Mp 107 °C (reported mp. 110 °C)<sup>[16c]</sup>;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.69 (s, 2H), 2.64–2.58 (m, 4H), 1.64–1.59 (m, 4H), 1.41–1.26 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  159.2, 135.1, 122.7, 115.8, 90.0, 31.5, 29.8, 26.1, 26.0, 25.8, 25.5; IR (KBr) 3428, 3334, 2194, 1619  $\text{cm}^{-1}$ ; MS  $m/z$  (%) 206 ( $\text{M}^+$ , 100), 178 (85), 163 (25).

## ACKNOWLEDGMENT

Partial financial support by the Ministry of Science, Research, and Technology of Iran is greatly appreciated.

## REFERENCES

1. Mason, T. J.; Lorimer, J. P. *Applied Sonochemistry: Uses of Power Ultrasound in Chemistry and Processing*; Wiley-VCH: Weinheim, 2002.
2. Cravotto, G.; Cintas, P. Power ultrasound in organic synthesis: Moving cavitation chemistry from academia to innovative and large-scale applications. *Chem. Soc. Rev.* **2006**, 35, 180–196.
3. (a) Cravotto, G.; Cintas, P. Forcing and controlling chemical reactions with ultrasound. *Angew. Chem. Int. Ed.* **2007**, 46, 5476–5478; (b) Zhang, Z. H.; Zha, Z. G.; Gan, C. S.; Pan, C. F.; Zhou, Y. Q.; Wang, Z. Y.; Zhou, M. M. Catalysis and regioselectivity of the aqueous Heck reaction by Pd(0) nanoparticles under ultrasonic irradiation. *J. Org. Chem.* **2006**, 71, 4339–4342.
4. (a) Abaee, M. S.; Hamidi, V.; Mojtahedi, M. M. Ultrasound-promoted aminolysis of epoxides in aqueous media: A rapid procedure with no pH adjustment for additive-free synthesis of  $\beta$ -aminoalcohols. *Ultrason. Sonochem.* **2007**, 15, 823–827; (b) Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. Ultrasound-promoted acetylation of alcohols in room-temperature ionic liquid under ambient conditions. *Green Chem.* **2003**, 5, 693–696; (c) Mojtahedi, M. M.; Saidi, M. R.; Shirzi, J. S.; Bolourtchian, M. Ultrasound-accelerated reductive coupling of imine or iminium ion generated in 5 M lithium perchlorate solution by lithium metal. *Synth. Commun.* **2001**, 31, 3587–3592; (d) Mojtahedi, M. M.; Javadpour, M.; Abaee, M. S. Convenient ultrasound-mediated synthesis of substituted pyrazolones under solvent-free conditions. *Ultrason. Sonochem.* **2007**, 15, 828–832.
5. (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005; (b) Domling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem. Int. Ed.* **2000**, 39, 3168–3210.
6. (a) Kappe, C. O. Recent advances in the Biginelli dihydropyrimidine synthesis: New tricks from an old dog. *Acc. Chem. Res.* **2000**, 33, 879–888; (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Multiple-component condensation strategies for combinatorial library synthesis. *Acc. Chem. Res.* **1996**, 29, 123–131.
7. (a) Gewald, K. Methods for the synthesis of 2-aminothiophenes and their reactions. *Chem. Heterocycl. Comp.* **1976**, 12, 1077–1090; (b) Sabnis, R. W. The Gewald synthesis. *Sulfur Reports* **1994**, 16, 1–17.
8. (a) Sabins, R. W.; Rangnekar, D. W.; Sonawane, N. D. 2-Aminothiophenes by the Gewald reaction. *J. Heterocycl. Chem.* **1999**, 36, 333–345; (b) Blackburn, T. P.; Davies,

- D. T.; Forbes, I. T.; Hayward, C. J.; Johnson, C. N.; Martin, R. T.; Piper, D. C.; Thomas, D. R.; Thompson, M.; Upton, N.; Ward, R. W. Isosteric replacement of the indole nucleus by benzothiophene in a series of pyrido[2,3-b]indoles with potential anxiolytic activity. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2589–2592; (c) Andersen, H. S.; Olsen, O. H.; Iversen, L. F.; Sørensen, A. L. P.; Mortensen, S. B.; Christensen, M. S.; Branner, S.; Hansen, T. K.; Lau, J. F.; Jeppesen, L.; Moran, E. J.; Su, J.; Bakir, F.; Judge, L.; Shahbaz, M.; Collins, T.; Vo, T.; Newman, M. J.; Ripka, W. C.; Møller, N. P. H. Discovery and SAR of a novel selective and orally bioavailable nonpeptide classical competitive inhibitor class of protein-tyrosine phosphatase 1B. *J. Med. Chem.* **2002**, *45*, 4443–4459.
9. Hagen, H.; Nilz, G.; Walter, H.; Landes, A. Herbicidal agents containing substituted 2-aminothiophene. German Patent 4039734, 1992.
10. Fu, T. L.; Wang, I. J. Synthesis and characterization of some novel polyfunctionally substituted indeno[2,1-b]thiophene compounds derived from indanones. *Dyes Pigments* **2008**, *76*, 590–595.
11. Koike, K.; Jia, Z. H.; Nikaido, T.; Liu, Y.; Zhao, Y. Y.; Guo, D. Echinothiophene, a novel benzothiophene glycoside from the roots of *Echinops grijissii*. *Org. Lett.* **1999**, *1*, 197–198.
12. Arhin, F.; Belanger, O.; Ciblat, S.; Dehbi, M.; Delorme, D.; Dietrich, E.; Dixit, D.; Lafontaine, Y.; Lehoux, D.; Liu, J.; McKay, G. A.; Moeck, G.; Reddy, R.; Rose, Y.; Srikumar, R.; Tanaka, K. S. E.; Williams, D. M.; Gros, P.; Pelletier, J.; Parr, T. R.; Far, A. R. A new class of small molecule RNA polymerase inhibitors with activity against Rifampicin-resistant *Staphylococcus aureus*. *Bioorg. Med. Chem.* **2006**, *14*, 5812–5832.
13. Gewald, K. Zur reaktion von  $\alpha$ -oxo-mercaptanen mit nitrilen. *Angew. Chem.* **1961**, *73*, 114–114.
14. (a) Tormyshev, V. M.; Trukhin, D. V.; Rogozhnikova, O. Y.; Mikhulina, T. V.; Troitskaya, T. I.; Flinn, A. Aryl alkyl ketones in a one-pot Gewald synthesis of 2-aminothiophenes. *Synlett* **2006**, 2559–2564; (b) Gütschow, M.; Schroter, H.; Kuhnle, G.; Eger, K. Synthesis of 4-isobutyl substituted thiophenes by Gewald reaction. *Monatsh. Chem.* **1996**, *127*, 297–303.
15. (a) Hu, Y.; Wei, P.; Huang, H.; Han, S. Q.; Ouyang, P. K. Synthesis of 2-aminothiophenes on ionic liquid phase support using the Gewald reaction. *Synth. Commun.* **2006**, *36*, 1543–1548; (b) Buchstaller, H. P.; Siebert, C. D.; Lyssy, R. H.; Frank, I.; Duran, A.; Gottschlich, R.; Noe, C. R. Synthesis of novel 2-aminothiophene-3-carboxylates by variations of the Gewald reaction. *Monatsh. Chem.* **2001**, *132*, 279–293; (c) Hu, Y.; Chen, Z. C.; Le, Z. G.; Zheng, Q. G. Organic reactions in ionic liquids: Gewald synthesis of 2-aminothiophenes catalyzed by ethylenediammonium diacetate. *Synth. Commun.* **2004**, *34*, 3801–3806; (d) Feroci, M.; Chiarotto, I.; Rossi, L.; Inesi, A. Activation of elemental sulfur by electrogenerated cyanomethyl anion: Synthesis of substituted 2-aminothiophenes by the Gewald reaction. *Adv. Synth. Catal.* **2008**, *350*, 2740–2746.
16. (a) Hesse, S.; Perspicace, E.; Kirsch, G. Microwave-assisted synthesis of 2-aminothiophene-3-carboxylic acid derivatives, 3H-thieno[2,3-d]pyrimidin-4-one and 4-chlorothieno[2,3-d]pyrimidine. *Tetrahedron Lett.* **2007**, *48*, 5261–5264; (b) Hoener, A. P. F.; Henkel, B.; Gauvin, J. C. Novel one-pot microwave-assisted Gewald synthesis of 2-acyl amino thiophenes on solid support. *Synlett* **2003**, 63–66; (c) Hesse, S.; Perspicace, E.; Kirsch, G. Microwave-assisted synthesis of 2-aminothiophene-3-carboxylic acid derivatives, 3H-thieno[2,3-d]pyrimidin-4-one and 4-chlorothieno[2,3-d]pyrimidine. *Tetrahedron Lett.* **2007**, *48*, 5261–5264; (d) Huang, W.; Li, J.; Tang, J.; Liu, H.; Shen, J. H.; Jiang, H. L. Microwave-assisted synthesis of 2-amino-thiophene-3-carboxylic derivatives under solvent-free conditions. *Synth. Commun.* **2005**, *35*, 1351–1357; (e) Zhang, H. Q.



- Yang, G. C.; Chen, J. N.; Chen, Z. X. Synthesis of thiophene derivatives on soluble polymer-support using Gewald reaction. *Synthesis* **2004**, 3055–3059.
17. (a) Wang, M. L.; Rajendran, V. Kinetics for dichlorocyclopropanation of 1,7-octadiene under the influence of ultrasound assisted phase-transfer catalysis conditions. *J. Mol. Catal. A: Chem.* **2007**, 273, 5–13; (b) Entezari, M. H.; Heshmati, A.; Yazdi, A. S. A combination of ultrasound and inorganic catalyst: Removal of 2-chlorophenol from aqueous solution. *Ultrason. Sonochem.* **2005**, 12, 137–141.
18. Barnes, D. M.; Haight, A. R.; Hameury, T.; McLaughlin, M. A.; Mei, J. Z.; Tedrow, J. S.; Toma, J. D. R. New conditions for the synthesis of thiophenes via the Knoevenagel/Gewald reaction sequence: Application to the synthesis of a multitargeted kinase inhibitor. *Tetrahedron* **2006**, 62, 11311–11319.