HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 2: (1), 2012, 31-36**

A SOLVENTLESSSYNTHESIS OF 2-AMINOTHIOPHENES VIA THE GEWALD REACTION UNDER ULTRASONIC CONDITIONS

Bruno Dias de C. F. dos Santos[1], Josué S. Bello Forero[1], Erika M. de Carvalho[2], Joel Jones Junior[1,*] andFlavia M. da Silva[1,*].

[1]Departamento de QuímicaOrgânica - Instituto de Química - UFRJ- CP 68.584, 21941-972, Rio de Janeiro, RJ, Brazil – e-mail: soa@soa.pro.br
[2]Instituto de TecnologiaemFármacos, Far-Manguinhos, RuaSizenandoNabuco, 100, 21041-250, Rio de Janeiro, RJ, Brazil

Abstract- A simple, fast and efficient one-pot, three-component,solventlessprocedure for the synthesis of 2-aminothiophene derivatives under ultrasonic conditionswas developed. The combined advantages of sonochemistry, such as mild reaction conditions, good yield and short reaction times, enabled progress to be made on the synthesis of 2-aminothiophenes via the Gewald reaction.

Keywords: 2-aminothiophenes, Gewald reaction, Green Chemistry, Ultrasound

1. Introduction

2-Aminothiophene is an important heterocyclic scaffold of medicinal and therapeutic interest.[1] This moiety is present in many relevant molecules, several of which show antibacterial,[2] antifungal,[3] antiamoebic,[4]antioxidant,[5]antitumor,[6]anticoagulant andantithrombotic[7] activities. The 2-aminothiophene scaffold is also present in some commercially available drugs such as olanzapine, an antipsychotic agent, utilized for the treatment of schizophrenia and bipolar disorder.[8]This S-heterocyclic system has also found utility in a diverse range of other research areas,[9]which includes dye chemistry,[10] agro chemistry[11] and electronic devices.[12]In light of their wide use, many synthetic approaches have been developed to generate these heterocycles.[13]To a certain extent, most ofthese methodologies remain restricted due to the unavailability, high cost, air or moisture sensitivity, and/or specificity of substrates.[14] Among the currently available synthetic methodologies, the Gewald reaction is the most enabling and versatile approach to functionalized 2-aminothiophenes.[15] The reaction can be carried out in a *one-pot*method starting from ketones, cyano-methylenes and elemental sulfur.

A survey of the literature revealed that several modifications appeared after the original publications of Gewald and co-workers. Among them, the use of microwave irradiation,[16] ionic liquids,[17] solar energy,[18] PEG (Polyethylene Glycol) as a soluble polymer support[19] and organocatalysts[20]wasfrequently explored.

Since the first report about the effect of ultrasound on chemical reactions in 1927 by Richards and Looms[21] involving rate studies on the hydrolysis of dimethyl sulfate, ultrasound has been

investigated intensively in organic synthesis. Ultrasound has been utilized to accelerate a number of synthetic organic transformations.[22] Ultrasonic irradiation, with its advantages of convenient operation, mild reactions conditions, short reactions times and high efficiency, has become particularly popular in recent years.Numerous examples using these conditions for the constructionof heterocycles with remarkable properties have been reported in the literature.[23] The notable effect of ultrasound observed during organic reactions is due to cavitation,[24] a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in the irradiated liquid. Cavitation induces very high temperatures and pressures inside the bubbles, leading to turbulent flow of the liquid and enhanced mass transfer.[25]

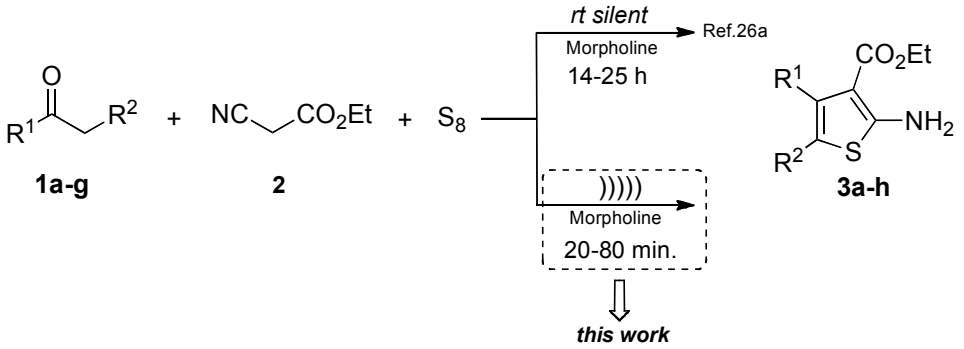
As a continuation of our studies toward the development of new methodologies for green chemical approaches,[26] herein we report a mild, efficient and simple one-pot Gewald synthesis of tetrasubtituted 2-aminothiophene derivatives in ultrasound media.

2. Results and discussion

Recently,[26a] we reported a green route for the synthesis of substituted 2-aminothiophenes through a simple base-catalyzed, *one-pot* reaction of ketones, cyanomethylenes and elemental sulfur under solvent-free conditions (Scheme).

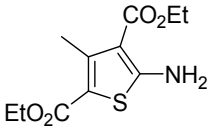
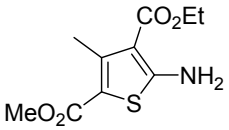
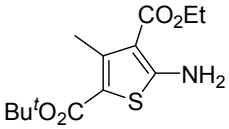
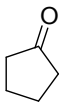
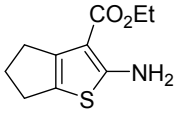
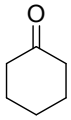
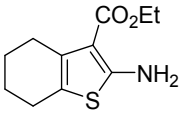
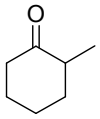
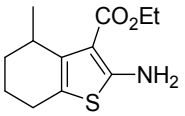
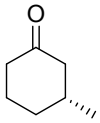
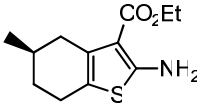
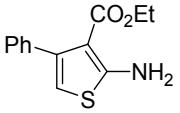
Although the procedure furnishes products in high preparative yields, the prolonged reaction times (14-25 h) diminish the efficiency of the method. To address this issue an alternative approach to synthesize the 2-aminothiophenes was sought. We envisioned that the 2-aminothiophene core can be prepared under sonication with reduced reaction times (20-80 min.) (General Reaction Scheme).

We first investigated the synthesis of the known compound diethyl 5-amino-3-methyltiophene-2,4-dicarboxylate **3a**as a model reaction to test our hypothesis. We found that the desired product, 2-aminothiophene **3a,** could readily be synthesized as a pure product (TLC) in 78% yield (Table) from an equimolar mixture of ethyl acetoacetate, ethyl cyanoacetate, elemental sulfur and morpholine that was sonicated for 40 min.



General Reaction Scheme

Table

Comp.	Ketone		Product	Conditions rtsilent		Ultrasound		ConventionalGewald reaction* Yield(%)
	R^1	R^2		Yield (%)	Time (h)	Yield(%)	Time (min.)	
3a	CH_3	CO_2Et		82	14	78	40	32
3b	CH_3	CO_2Me		70	14	77	30	---
3c	CH_3	CO_2Bu^t		78	14	61	40	---
3d				60	24	55	40	45
3e				75	14	65	20	82
3f				100	14	40	80	---
3g				77	14	70	40	---
3h	Ph	H		51	25	NR	80	---

*using ethanol as the solvent at 50-60 ºC

The results of additional experiments demonstrated that our ultrasound-assisted approach could be used to increase the reaction rate for the synthesis of 2-aminothiophenes in comparable yields to the conventional,silent method. The reaction produced 2-aminothiophene derivatives in moderate to good yields (40-78%). A range of β-ketoesters and cyclic ketones were surveyed to determine the scope and generalizability of this ultrasonic solvent-free process. Cyclohexanone**1e** (and its derivatives **1f-g**) performed very well in terms of yield and quality of the crude material; however, cyclopentanone resulted in poor yields (Table 1). These observations are in agreement with those reported by Pett and co-workers,[27]who used classical methods for the Gewald synthesis.The formation of the desired product did not occur even after 80 minutes of sonication for the aromatic ketone acetophenone starting material, **1h**.

In summary, we have developed an efficient synthesis of 2-aminothiophenes under sonication, which providedeasy access to the desired products. This approach provides an attractive method to both easily generate products and independently vary substituents in a single step.

3. Experimental Section:

Materials and methods:

Sonication was performed in a US Ultra Cleaner 800 Unique USC800 with a frequency of 40KHz. IR spectra were obtained on a Nicolet Magna IR-FT spectrometer as potassium bromide pellets.^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 spectrometer (500 MHz ^{1}H NMR and 100 MHz ^{13}C NMR) with an FT-NMR system. The data for ^{1}H NMR are reported as follows: chemical shift (δ) and multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, qt: quintet, dq: doublet of quartets, br: broad). GLC analyses were performed on a GC-2010 Shimadzu Corporation FID instrument equipped with a 30 m × 0.5 μm DB-5ms capillary column. Mass spectra were recorded with a mass selective detector (Shimadzu Corporation QP2010S) interfaced to a capillary gas chromatograph. Reaction progress was monitored using thin-layer chromatography on Silufol PF254 TLC aluminum sheets. Column chromatography was carried out using Merck Kieselgel 60 (0.040-0.063 mm) with n-hexane/ethyl acetate as the eluent. All reagents were purchased from Merck or Aldrich Chemical Co. and used as received, unless otherwise stated. The spectral data of known compounds were in accordance with those previously reported in the literature.

General experimental procedures for the synthesis of 2-aminothiophenes:

An equimolar (3 mmol) mixture of powdered sulfur and morpholine was stirred until the sulfur was completely dissolved. Then the ethyl cyanoacetate (3 mmol) and the ketone (3 mmol) were added to the reaction mixture, which was subjected to ultrasound irradiation (See Table for reaction times). Reaction progress was monitored by TLC until the reaction was complete.The crude product was purified by silica gel column chromatography with 10:1 hexane:ethyl acetate as the eluent to afford the pure 2-aminothiophenes **3a-g**. In some cases, it was necessary to perform a recrystallization with 4:1 hexane:ethyl acetate to achieve greater purity.

Diethyl 5-amino-3-methyltiophene-2,4-dicarboxylate (Table 1, entry 1, **3a**): R_f = 0.60 (10:1 hexane/ethyl acetate); mp. 109-110 °C (Lit.[9]mp 108-110 °C); IR (KBr): 3408 ν(NH), 3294 ν(NH), 1682 ν(C=O), 1660 ν(C=O), 1587 ν(NH), 1529 ν(C=C), 1232 ν(C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.33 (3H, t, *J* = 7.1 Hz), 1.37 (3H, t, *J* = 7.1 Hz), 2.70 (3H, s); 4.26 (2H, q, *J* = 7.1 Hz); 4.31 (2H, q, *J* = 7.1Hz); 6.60 (2H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 14.6, 16.3, 60.2, 60.6, 108.6, 108.7, 148.2,163.1, 166.3, 166.4; GC-MS: R_t: 23.55 min.; *m/z* (%): 257 (M+·, 88), 229 (2), 211 (100), 183 (45), 166 (30), 139 (18), 111 (9), 66 (9).

4-ethyl 2-methyl 5-amino-3-methylthiophene-2,4-dicarboxylate (Table 1, entry 2, **3b**): R_f = 0.52 (10:1 hexane/ethyl acetate); mp. 116-117 °C; IR (KBr): 3437 ν(NH), 3325 ν(NH), 1672 ν(C=O),1649 ν(C=O), 1591 ν(NH), 1533 ν(C=C), 1254 ν(C-N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.37 (3H, t, *J* =7.1 Hz), 2.70 (3H, s), 3.79 (3H, s), 4.32 (2H, q, *J* = 7.1 Hz), 6.53 (2H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 16.3, 51.7, 60.3, 108.2, 108.9, 148.6, 163.4, 166.2, 166.3; GC-MS: Rt: 22.66 min.; *m/z* (%): 243 (M+·, 57), 212 (8), 197 (100), 166 (47), 154 (8), 139 (15), 110 (13), 66 (22).

2-*tert*-butyl 4-ethyl 5-amino-3-methylthiophene-2,4-dicarboxylate (Table 1, entry 3, **3c**): R_f = 0.58 (10:1 hexane/ethyl acetate); mp. 116-117°C (Lit.[20]mp 116-117 °C); IR (KBr): 3427 ν(NH), 3305 ν(NH), 1668 ν(C=O), 1587 ν(NH), 1529 ν(C=C), 1265 ν(C-N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.37 (3H, t, *J* = 7.0 Hz), 1.53 (9H, s), 2.67 (3H, s), 4.31 (2H, q, *J* = 7.0 Hz), 6.45 (2H, br s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 16.2, 28.6, 60.2, 81.3, 108.7, 110.5, 147.1, 162.5, 166.0, 166.4; GC-MS: Rt: 23.68 min.; *m/z* (%): 285 (M+·, 10), 229 (52), 212 (8), 183 (100), 166 (9), 139 (5), 127 (4), 111 (7).

Ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (Table 1, entry 4, **3d**): R_f = 0.65 (10:1 hexane/ethyl acetate); mp. 91-92 °C (Lit.[9]mp 91-92 °C); IR (KBr): 3467 ν(NH), 3415 ν(NH), 1730 ν(C=O), 1520 ν(NH), 1275 ν(C-N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (3H, t, *J* = 7.13 Hz), 2.30 (2H, qt, *J*= 7.1 Hz), 2.66-2.75 (2H, m), 2.77-2.86 (2H, m), 4.24 (2H, q, *J* = 7.1 Hz), 5.64 (2H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 27.4, 29.1, 31.0, 59.6, 103.1, 121.5, 142.9, 166.0, 166.5; GC-MS: Rt: 15.28 min.; *m/z* (%): 211 (M+·, 33), 165 (100), 137 (18), 110

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (Table 1, entry 5, **3e**): R_f = 0.64 (10:1 hexane/ethyl acetate); mp. 116-117 °C (Lit.[9]mp 115 °C); IR (KBr): 3404 ν(NH), 3300 ν(NH), 1647 ν(C=O), 1597 ν(NH), 1576 ν(C=C), 1275 ν(C-N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (3H, t, *J* = 7.0 Hz), 1.69-1.83 (4H, m), 2.45-2.54 (2H, m), 2.65-2.75 (2H, m), 4.25 (2H, q, *J* = 7.0 Hz), 5.78 (2H, br s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.7, 23.0, 23.4, 24.7, 27.1, 59.6, 106.0, 117.9, 132.6, 161.8, 166.3; GC- MS: Rt: 20.90 min.; *m/z* (%): 225 (M+·, 49), 197 (2), 179(100), 151 (56), 125 (13), 91 (12).

Ethyl2-amino-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (Table 1, entry 6, **3f**): R_f = 0.55 (10:1 hexane/ethyl acetate); mp. 71-72 °C (Lit.[21]mp 68-70 °C); IV (KBr): 3413 ν(NH), 3305 ν(NH), 1643 ν(C=O), 1593 ν(NH), 1570 ν(C=C), 1269 ν(C-N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17 (3H, d, *J* =6.8 Hz), 1.33 (3H, t, *J* = 7.1 Hz), 1.57-1.68 (1H, m), 1.69-1.81 (2H, m), 1.81-1.95 (1H, m), 2.42-2.55 (2H, m), 3.19-3.32 (1H, m), 4.29 (1H, dq, *J* = 7.2 and 11.2 Hz), 4.32 (1H, dq, *J* = 7.2 and 11.2 Hz), 5.87 (2H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 18.6, 21.7, 24.8, 29.8, 30.0, 59.6, 105.3, 117.5, 137.8, 162.4, 166.0; GC-MS: Rt: 21.23 min.; *m/z* (%): 239 (M+·, 56), 193 (100), 178 (10), 151 (57), 125 (15), 105 (4), 91 (8).

Ethyl2-amino-5*R*-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (Table 1, entry 7, **3g**): R_f = 0.54 (10:1 hexane/ethyl acetate); mp. 68-71 °C (Lit.[22]mp 71 °C); IR (KBr): 3427 ν(NH), 3315 ν(NH),1649 ν(C=O), 1579 ν(NH), 1491 ν(C=C), 1281 ν(C-N) cm^{-1}. $[\alpha]^{25}$ (0.014; CH_2Cl_2)= +87.9°.^{1}H NMR (500 MHz,$CDCl_3$) δ: 1.05 (3H, d, *J* = 6.6 Hz), 1.34 (3H, t, *J* = 7.1 Hz), 1.36-1.47 (1H, m), 1.68-1.91 (2H, m), 2.17(1H, ddt, *J* = 9.8, 17.5 and 2.0 Hz), 2.47-2.59 (2H, m), 2.92 (1H, dd, *J* = 4.5 and 17.3 Hz), 4.26 (2H, q, *J* =7.1 Hz), 5.94 (2H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7, 21.9, 24.5, 29.1, 31.5, 35.5, 59.6, 105.8,117.5, 132.6, 162.1, 166.2; GC-MS: Rt: 21.22 min.; *m/z* (%): 239 (M+·, 50), 193 (100), 178 (67), 165 (19), 151 (13), 137 (7), 104 (6), 91 (10).

References

1. Norris, R. K. Aminothiophenes and Their Derivatives. In *Chemistry of Heterocyclic Compounds:* Thiophenes and Its Derivatives; Gronowitz, S., eds.; John Wiley and Sons: New York, 1986, Part Two, vol. 44.

2. Foroumadi, A.; Mansouri, S.; Kiani, Z.; Rahmani, A. *Eur. J. Med. Chem.* **2003***,* 38, 851-854.
3. Al-Omran, F.; Mohareb, R. M.; El-Khair, A. A. *J. Heterocyclic Chem.***2002***, 39*, 877-883.
4. Bharti, N.; Shailendra.; Sharma, S.; Naqvi, F.; Azam, A. *Bioorg. Med. Chem.***2003**,*11*, 2923-2929.
5. Meotti, F. C.; Silva, D. O.; dos Santos, A. R. S.; Zeni, G.; Rocha, J. B. T.; Nogueira, C. W. *Environ. Toxicol. Pharmacol.*2003,37, 37-44.
6. Gobbi, S.; Rampa, A.; Bisi, A.; Belluti, F.; Piazzi, L.; Valenti, P.; Caputo, A.; Zampiron, A.; Carrara, M. *J. Med. Chem.***2003**,46, 3662-3669.
7. Lee, K.; Park, C. W.; Jung, W-H.; Park, H. D.; Lee, S. H.; Chung, K. H.; Park, S. K.; Kwon, O. H.; Kang, M.; Park, D-H.; Lee, S. K.; Kim, E. E.; Yoon, S. K.; Kim, A. *J. Med. Chem.***2003**,*46*, 3612-3622.
8. Meltzer, H. Y.; Fibiger, H. C.*Neuropsychopharmacology***1996**, *14*, 83-85.
9. Pinto, I. L.; Javerst, R. L.; Serafinowska, H.T. *Tetrahedron Lett.* **2000**, *41*, 1597-1600.
10. Hallas, G.; Choi, J-H. *Dyes pigments***1999**, 40, 99-117.
11. Puterová, Z; Bobula, T.; Végh, D. *J. Heterocyclic Chem.* **2008**, 45, 201-207.
12. Rost, C.; Karg, S.; Riess,W.; Loi, M. A.; Murgia, M.; Muccini, M. *Appl. Phys. Lett.*. **2004**, *85*, 1613.
13. Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocyclic Chem*. **1999**, *36*, 333.
14.Sabnis, R. W. *J. Sulfur. Chem*. **1994**, *16*, 1.
15. *a)*Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber*.**1966**, *99*, 94; *b)* Gewald, K.; Schinke, E. *Chem. Ber*.**1966**, *99*, 2712.
16. *a)*Sridhar**,** M.; Rao**,** R. M.; Baba, N. H. K.;Kumbhare, R. M.*Tetrahedron Lett.* **2007***, 48*, 3171-3172.; *b)* Hoener, A. P. F.; Henkel, B.; Gauvin,J-C. *Synlett***2003**, *1*, 63-66.
17. Hu, Y.; Wei P.; Huang, H.; Han S. Q.; Ouyang P. Q.. *Synth. Commun.* **2006**,*36*, 1543-1548.
18.Mekheimer, R. A.; Ameen, M. A.; Sadek, K. A. *Chin. Chem. Lett*. **2009**, *19*, 788-790.
19. Huang, Y.; Dömling, A. *Mol Divers.***2011**, *15*, 3-33.
20. Wang, T.; Huang, X-G.; Liu, J.; Li, B.; Wu, J-J.; Chen, K-X.; Zhu, W-L.; Xu, X-Y.; Zeng, B-B. *Synlet* **2010***, 9*, 1351-1354.
21. Rechards, W. T.; Loomis, A. L. *J. Am. Chem. Soc*. **1927**, *49*, 3086.
22. *a)* Mason, T. J. *Chem. Soc. Rev*. **1997**, *26*, 443.; *b)* Cravotto, G.; Cintas, P. J. *Chem. Soc. Rev*. **2006**, *35*, 180.
23 Cella, R.; Stefani, H. A. *Tetrahedron***2009**, *65*, 2619.
24. Vanhille, C.; Campos-Pozuelo, C. *Ultrason. Sonochem*. **2012**, *19*, 217.
25. Ruiz, E.; Rodríguez, H.; Coro, J.; Niebla, V.; Rodríguez, A.; Martínez-Alvarez, R.; de Armas, H. N.; Suaréz, M.; Martín, N. Ultrason. Sonochem. 2012, 19, 221.
26. *a)* Bello Forero, J. S.; De Carvalho, E. M.; Jones Jr., J.; Da Silva, F. M. *Heterocyclic Lett*. **2011**, *1*, 61.; b)Da Silva, F. M.; De Lacerda, P. S. B.; Jones Jr, J.; *Quim. Nova***2005**, *28*, 103; c*)* Da Silva, F. M.; Jones Jr, J.*Quim. Nova***2001**, *24*, 646; d*)* Da Silva, F. M.; Jones Jr, J.*Can. J. Chem*. **1999**, *77*, 624.
27. Peet, N. P.; Sunder, S.; Barbuch, R. J. *J. Heterocycl. Chem*. **1986**, *23*, 129-134.

Received on October 4, 2011.