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Heterocyclic Letters
(www.heteroletters.org) Vol. 1, No. 1, (2011), 61-67

A NEW PROTOCOL FOR THE SYNTHESIS OF 2-AMINOTHIOPHENES THROUGH THE GEWALD REACTION IN SOLVENT-FREE CONDITIONS.

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Abstract: A new set of green conditions have been developed for the preparation of tetrasubstituted 2-aminothiophene derivatives through the Gewald reaction between the respective ketones, ethyl cyanoacetate and elemental sulfur in the presence of morpholine. The synthesis was carried out under solvent-free conditions by stirring components at room temperature.

Keywords: 2-Aminothiophenes, Gewald reaction, Green chemistry, Solvent-free

1. Introduction

Thiophene is the backbone of several important products, including pharmaceuticals,[1] dyes,[2] and agrochemicals.[3] In addition, this S-heterocyclic core is present in many natural products,[4] several of which show antibacterial,[5] antifungal,[6] antiamoebic,[7] antioxidant,[8] antitumor,[9] anticoagulant and antithrombotic[10] activities. Within this family, the 2-aminothiophenes occupy a special position as important intermediates in synthesis because they provide building blocks for several types of heterocyclic systems.[11] The most convergent and well-established approach for the preparation of 2-aminothiophenes is the Gewald method, which involves the three-component reaction of a ketone, an activated nitrile and elemental sulfur in the presence of morpholine as catalyst.[11,12]

Solvent-free reactions are an interesting alternative approach, mainly when these conditions eliminate the use of a solid support or solvent from the reaction.[13] Solid supported reactions do not entirely meet the definition of solvent-free, however, because an appreciable amount of solvent is sometimes necessary to promote the absorption of the reactants and is always required for the extraction of products at the workup.[14]

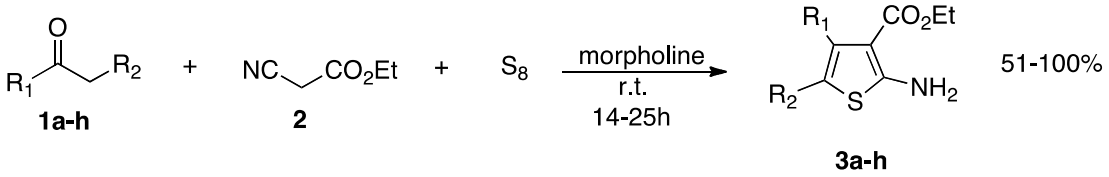
Thus far, little research has been reported on the Gewald reaction under solvent-free conditions; many reports use a microwave-assisted synthesis and solid support instead.[15] However, two studies in 2004 reported the "one pot" synthesis of polysubstituted aminothiophenes using polyethylene glycol as a soluble polymer support[15a-b] and, in 2005, a third paper[15c] described this reaction with basic aluminum oxide as the solid support.

The application of microwave irradiation in chemical reactions is useful because it enhances the reaction rates and, in many cases, the selectivity.[16,17] These technologies are used in the field of green chemistry because they avoid organic solvents, but their drawbacks are that they require energy and specialized equipment. One of the principles of green chemistry is that reactions at room temperature are preferred because they minimize the environmental impact of productive activities due to energy matrices.[18a]

In the continuation of our studies toward the development of new methodologies under green chemistry approaches,[18] herein we reported a mild, efficient and simple "one pot" Gewald synthesis of tetrasubstituted 2-aminothiophene derivatives **3a-h**.

2. Results and Discussion

In the present study, several ketones, 1a-h (aliphatic and aromatic), were reacted with ethyl cyanoacetate **2** and elemental sulfur in the presence of morpholine as catalyst. This methodology was carried out in solvent-free conditions at room temperature (Scheme 1).



Scheme 1. Synthesis of 2-aminothiophenes in solvent-free conditions.

Our approach is an elegant and simple methodology. We used a mixture of reactants at room temperature in the presence of morpholine that led to the 2-aminothiophenes **3a-h** as products in excellent yields (51-100%) and purities (Scheme 1, Table 1). Furthermore, the application of our methodology to the cyclohexanone **1e** (and its derivatives **1f-g**) led to the respective products (**3e-g**) in good yield and purity. However, when cyclopentanone was used as substrate, good yields were not observed (Table 1, entries 4 and 5). These observations were in agreement with those reported by Pett and co-workers[19] using the classical Gewald synthesis. Interestingly, the reaction of (3*R*)-methylcyclohexanone 1g led to the 5-methyl-regioisomer **3g** as the unique product, as detected by NMR (Table 1, entry 7), without formation of the 7-methyl-regioisomer. In contrast, the literature shows that reaction of 3-methylcyclohexanone with malonitrile and sulfur produces a mixture of two regioisomeric products.[20]

The synthesis of ethyl 2-amino-4-phenylthiophene-3-carboxylate **3h** with acetophenone as precursor[12] was reported to occur in yields not higher than 43% over two steps.[21]More recently, a "one pot" synthesis of this compounds class was reported with reasonable yields. However, this reaction was carried out in two sequential steps at a temperature of 55 °C under an argon atmosphere, using ethanol as solvent and glacial acetic acid and morpholine as reactants.[21] Now, we have been able to prepare 2-aminothiophene **3h** (Table 1, entry 8) in 51% yield in a "one pot" synthesis using our simple methodology.

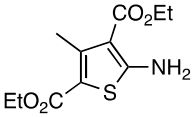
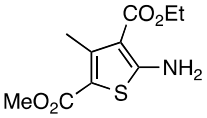
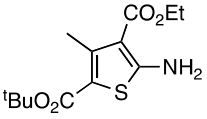
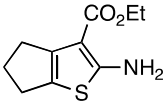
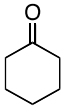
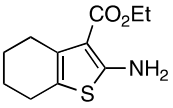
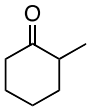
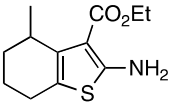
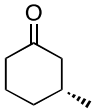
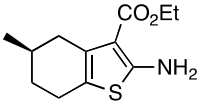
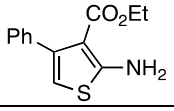
Further investigations into the scope of such reactions are underway.

Ethanol is the standard solvent for Gewald transformations in most liquid and solid phase protocols.[3] We describe here a more environmentally friendly protocol because organic solvents were avoided during the reaction process.[18] Moreover, our procedure is more cost effective and meets the principles of Green Chemistry which are, in our opinion, an economical solution to some environment problems caused by synthetic activities.

The 2-aminothiophenes could serve as precursors for many useful biologically active molecules.[22]With these facts in mind, the partition coefficient log *P* values of the synthesized molecules were calculated (Table 1) and found to be between 3.6 and 5.1. This range is in agreement with estimated values (between 2.0 and 5.0) for good lipophilicity and solubility.

Thus, log *P* is a useful parameter in drug discovery and development. This parameter is a good predictor of molecular transport properties across cell membranes and an indicator of protein binding characteristics for the 2-aminothiophene activities discussed above.[23]

Table 1. Gewald Synthesis of 2-aminothiophene derivatives **3a-h** produced via Scheme 1.

Entry (Compound)	Ketone **(1)** R_1	Ketone **(1)** R_2	2-Aminothiophene **(3)**	Reaction conditions Solvent free Yield (%)[a] (time, h)	Mp (ºC)	log*P*[b]
1 **(3a)**	CH_3	CO_2Et		82(14)	108-109	4.2 ± 0.5
2 **(3b)**	CH_3	CO_2Me		70(14)	114-115	3.6 ± 0.5
3 **(3c)**	CH_3	$CO_2{}^tBu$		78(14)	114-115	4.9 ± 0.5
4 **(3d)**				60(24)	92-93	4.0 ± 0.4
5 **(3e)**				75(14)	112-113	4.6 ± 0.4
6 **(3f)**				100(14)	74-75	5.1 ± 0.4
7 **(3g)**				77(14)	68-69	5.1 ± 0.4
8 **(3h)**	Ph	H		51(25)	98-99	4.5 ± 0.6

[a]Isolated yield;[b]Theoretical values of log P were calculated using commercially available ACD LAB/log *P* release 10, product version 10.08.

3. Experimental Section

Materials and methods

IR spectra were obtained on a Nicolet Magna IR-FT spectrometer as potassium bromide pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker 500 spectrometer (500 MHz ^1H NMR and 100 MHz ^{13}C NMR) with a FT-NMR system. Data for ^1H NMR are reported as follows: chemical shift (δ) and multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, qt: quintuple, dq: doublet of quartets, br: broad). GLC analyses were performed on a GC-2010

Shimadzu Corporation FID instrument equipped with a 30 m x 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 reported.

General experimental procedure for the synthesis of 2-aminothiophenes:
An equimolar(5 mmol) mixture of powdered sulfur and morpholine was stirred until total dissolution of the sulfur. After, the ethyl cyanoacetate (5 mmol) and the ketone (5 mmol) were added to the reactionalmixture, which was stirred at room temperature for the time mentioned in Table 1. After completion of the reaction, as monitored by TLC, the crude product was purified by silica gel column chromatography with 10:1 hexane:ethyl acetate as eluent to afford the pure 2-aminothiophenes **3a-g** and 5:1 hexane:ethyl acetate to purify **3h**.

Diethyl 5-amino-3-methyltiophene-2,4-dicarboxylate (Table 1, entry 1, **3a**): R_f = 0.56 (4:1 n-hexane/ethyl acetate); mp. 108-109 °C (Lit[12]. mp 108-110 °C); IR (KBr): 3408 $\nu_{(NH)}$, 3294 $\nu_{(NH)}$, 1682 $\nu_{(C=O)}$, 1660 $\nu_{(C=O)}$, 1587 $\nu_{(NH)}$, 1529 $\nu_{(C=C)}$, 1232 $\nu_{(C-N)}$ 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 ($M^{+\cdot}$, 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 = 0.51 (4:1 n-hexane/ethyl acetate); mp. 114-115 °C; IR (KBr): 3437 $\nu_{(NH)}$, 3325 $\nu_{(NH)}$, 1672 $\nu_{(C=O)}$,1649 $\nu_{(C=O)}$, 1591 $\nu_{(NH)}$, 1533 $\nu_{(C=C)}$, 1254 $\nu_{(C-N)}$ 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: R_t: 22.66 min.; *m/z* (%): 243 ($M^{+\cdot}$, 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 = 0.67 (4:1 n-hexane/ethyl acetate); mp. 114-115 °C (Lit[24]. mp 116-117 °C); IR (KBr): 3427 $\nu_{(NH)}$, 3305 $\nu_{(NH)}$, 1668 $\nu_{(C=O)}$, 1587 $\nu_{(NH)}$, 1529 $\nu_{(C=C)}$, 1265 $\nu_{(C-N)}$ 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: R_t: 23.68 min.; *m/z* (%): 285 ($M^{+\cdot}$, 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 = 0.77 (4:1 n-hexane/ethyl acetate); mp. 92-93 °C (Lit[12]. mp 91-92 °C); IR (KBr): 3467 $\nu_{(NH)}$, 3415 $\nu_{(NH)}$, 1730 $\nu_{(C=O)}$, 1520 $\nu_{(NH)}$, 1275 $\nu_{(C-N)}$ 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: R_t: 15.28 min.; *m/z* (%): 211 ($M^{+\cdot}$, 33), 165 (100), 137 (18), 110

(10), 104 (17), 77 (11).

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (Table 1, entry 5, **3e**): R_f = 0.73 (4:1 n-hexane/ethyl acetate); mp. 112-113 °C (Lit[12]. mp 115 °C); IR (KBr): 3404 $\nu_{(NH)}$, 3300 $\nu_{(NH)}$, 1647 $\nu_{(C=O)}$, 1597 $\nu_{(NH)}$, 1576 $\nu_{(C=C)}$, 1275 $\nu_{(C-N)}$ cm^{-1}. ^1H 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: R_t: 20.90 min.; *m/z* (%): 225 ($M^{+\cdot}$, 49), 197 (2), 179 (100), 151 (56), 125 (13), 91 (12).

Ethyl 2-amino-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (Table 1, entry 6, **3f**): R_f = 0.63 (4:1 n-hexane/ethyl acetate); mp. 74-75 °C (Lit[25]mp 68-70 °C); IV (KBr): 3413 $\nu_{(NH)}$, 3305 $\nu_{(NH)}$, 1643 $\nu_{(C=O)}$, 1593 $\nu_{(NH)}$, 1570 $\nu_{(C=C)}$, 1269 $\nu_{(C-N)}$ cm^{-1}. ^1H 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: R_t: 21.23 min.; *m/z* (%): 239 ($M^{+\cdot}$, 56), 193 (100), 178 (10), 151 (57), 125 (15), 105 (4), 91 (8).

Ethyl 2-amino-5*R*-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (Table 1, entry 7, **3g**):R_f = 0.63 (4:1 n-hexane/ethyl acetate); mp. 68-69 °C (Lit[26]mp 71 °C); IR (KBr): 3427 $\nu_{(NH)}$, 3315 $\nu_{(NH)}$,1649 $\nu_{(C=O)}$, 1579 $\nu_{(NH)}$, 1491 $\nu_{(C=C)}$, 1281 $\nu_{(C-N)}$ cm^{-1}. $[\alpha]_D^{25}$(0.014; CH_2Cl_2)= +87.9°. ^1H 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: R_t: 21.22 min.; *m/z* (%): 239 ($M^{+\cdot}$, 50), 193 (100), 178 (67), 165 (19), 151 (13), 137 (7), 104 (6), 91 (10).

Ethyl 2-amino-4-phenylthiophene-3-carboxylate (Table 1, entry 8, **3h**): R_f = 0.65 (4:1 n-hexane/ethyl acetate); mp. 98-99 °C (Lit[12]mp 98-99 °C); IR (KBr): 3427 $\nu_{(NH)}$, 3313$\nu_{(NH)}$, 1651 $\nu_{(C=O)}$, 1583 $\nu_{(NH)}$, 1525 $\nu_{(C=C)}$, 1282 $\nu_{(C-N)}$ cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.93 (3H, t, *J* = 7.1 Hz), 4.03 (2H, q, *J* = 7.1 Hz), 6.06 (1H, s), 6.08 (2H, br s), 7.29 (5H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 59.7, 105.7, 106.3, 127.0, 127.4, 129.1, 138.7, 141.8, 164.0, 165.9; GC-MS: R_t: 15.67 min.; *m/z* (%): 247 ($M^{+\cdot}$, 67), 201 (100), 172 (39), 146 (12), 128 (19), 102 (6), 77 (7).

4. Conclusion

In conclusion, we have described in this paper an efficient and convenient modification to the Gewald reaction carried out in solvents-free conditions. The reaction leads to 2-aminothiophene derivatives in moderate to excellent yields.

Acknowledgments

We are grateful to Conselho de DesenvolvimentoCientífico e Tecnológico (CNPq) for a fellowship to J. S. B. F.

5. References

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