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Optimized Synthesis and Simple Purification of 2,5-Diamino-thiophene-3,4-dicarboxylic Acid Diethyl Ester

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Optimized Synthesis and Simple Purification of 2,5-Diamino-thiophene-3,4-dicarboxylic Acid Diethyl Ester

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Abstract: A stable diamino thiophene was synthesized in high purity with a three-fold increase in yield over previous reports via simple crystallization using inexpensive reagents.

Keywords: diamino thiophene, Gewald reaction, one-pot reaction

INTRODUCTION

Thiophenes constitute an interesting class of compounds that has attracted much attention in the areas of organic synthesis and materials science alike. Their synthetic appeal is due in part to their pharmaceutical properties, which include antiulcer and antiviral/antitumor properties,[1,2] along with other biological agents including human leukocyte elastases,[3] allosteric enhancers,[4] and nonpeptide antagonists,[5] to name but a few. These properties have resulted in the preparation of many thiophene derivatives including amino analogues, shown in Fig. 1, which are ideal precursors for new pharmaceutical products with high biological availabilities.[6] Not only do thiophenes possess desired pharmaceutical properties, they also exhibit outstanding properties suitable for functional materials such as organic light-emitting diodes[7,8] and field effect transistors.[9–13] These ideal properties stem from

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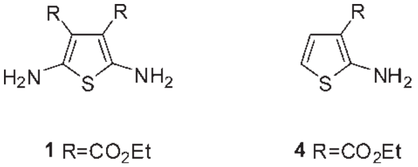


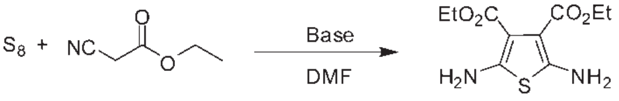
1 R=CO_2Et
2 R=CN
3 R=H

4 R=CO_2Et
5 R=CN

Figure 1. Mono- and diamino thiophene derivatives.

their reversible oxidation[14,15] and their semiconductor-like behavior obtained upon p-doping,[16] in addition to their capacity to undergo oxidative polymerization leading to conducting polymers.[17–19]

Our interest in amino thiophenes stemmed from the finding that they are useful precursors in the synthesis of conjugated functional materials via Schiff bases.[20–30] These novel materials are synthesized in a simple fashion without any of the challenging reaction conditions or purification protocols encountered with their vinylenic analogs. The ideal precursor for the Schiff base materials is **3**; however, it is extremely unstable and spontaneously decomposes under ambient conditions. For such reasons, **1** and **2** are suitable alternatives for new functional materials owing to their electron-withdrawing groups, which render them air stable. Although the synthesis of monoamino thiophenes (**4** and **5**)[31–34] consists simply of a Knoevenagel condensation from 1,4-dithiane-2,5-diol with either malononitrile or ethylcyano acetate,[3,4,31–39] the syntheses of the diamino precursors **1** and **2** are unfortunately not as trivial. The synthesis of **1** is not only challenging because of its low yield (8%), but it is also plagued with numerous purifications required to remove the unreacted elemental sulfur with toxic solvents such as CS_2 and multiple flash chromatography. Very little effort[40,41] has focused on the optimization of the synthetic protocol of **1** and its derivatives beyond Gewald's original report[42,43] (Scheme 1). This is particularly surprising given the pharmaceutical importance of amino thiophenes. The long reaction times involving upward of 1 week and time-consuming multiple purification steps concomitant with residual sulfur contamination unfortunately do not lend themselves to large-scale pharmaceutical or functional materials productions. We therefore set out to optimize the synthesis of **1** through judicious choice of reagent stoichiometry



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Scheme 1. General synthetic scheme leading to **1**.

and other parameters that would simplify its purification and increase the yield while making the synthesis amenable to large-scale synthesis.

Previous examples of the Gewald reaction were done using copious amounts of N,N-dimethylformamide (DMF) to dissolve the elemental sulfur leading to homogeneous reaction conditions. As an alternative to these methods, we first examined the use of ethanol as a suitable solvent for this reaction because the excess volumes of DMF renders product isolation extremely difficult and results in low yields. The reaction to afford **1** in ethanol requires heating to sufficiently solubilize the elemental sulfur and to drive the reaction. Even though **1** is highly stable at room temperature, it decomposes upon heating. The effect of reaction temperature upon the product formation was therefore examined according to Table 1. The solvent amounts and the stoichiometries of the reaction were also studied. The main advantage of this approach is the reduced number of polymeric by-products, which in turn simplifies the purification because the product is obtained in relatively high purity after one silica flash-chromatographic column. Despite the easier purification, the desired product is still obtained in only low yields.

Although the exact Gewald reaction mechanism is still unclear, it can be rationalized according to that proposed in Scheme 2. The use of an organic base to drive the reaction is evident from the proposed mechanism and the general one shown in Scheme 1. The base is further required to digest the allotrope S_8 elemental sulfur and to make a reactive linear zwitterionic species.[44] This ring-opening process is further favored by polar solvents such as DMF. However, the use of large volumes of this solvent is problematic for product isolation. We therefore examined the Gewald reaction using minimal amounts of DMF and various reagent stoichiometries as reported in Table 2. As shown in entry 5, this method offers a means to manage the amount of sulfur reagent and hence control the quantity of unreacted sulfur, making for an easier purification. By pouring the reaction mixture into water and then recrystallizing the filtered solid in a mixture of ethylacetate/hexanes, **1** can be obtained easily in >98% purity, void of any sulfur contamination. Furthermore, yields that are three times greater than previous reports are possible by this method. The notable advantages of the present methodology are the mild reaction conditions, short reaction times, increased yield, and purification by simple crystallization in ethylacetate/hexanes with no multiple flash chromatography.

EXPERIMENTAL

All reagents were used as received from Aldrich without further purification. Triethylamine was distilled under reduced pressure prior to use, whereas anhydrous DMF was obtained from a GlassContour solvent purification system. The reported melting point is uncorrected.

Table 1. Effect of reaction temperature and time, concentration, and stoichiometry upon the yield of **1** using absolute ethanol as the solvent[a]

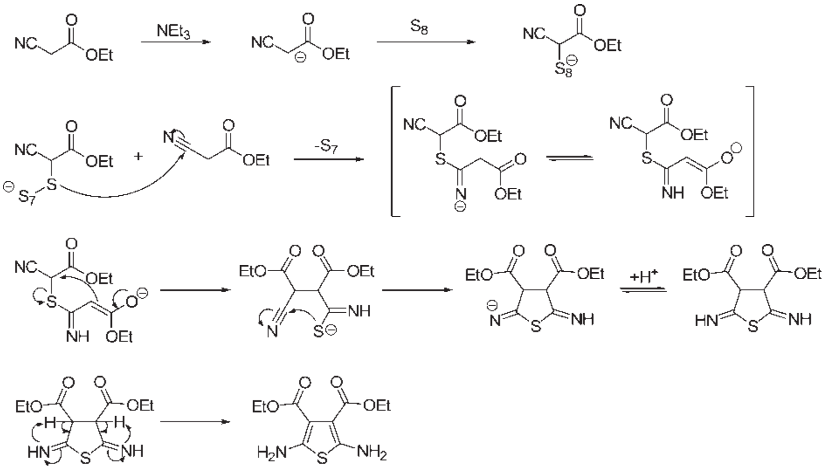
Entry	Ethylcyano acetate (equivalents)	Sulfur (equivalents)	$NHEt_2$ (equivalents)	EtOH[b] (mL)	Reaction temperature (°C)	Reaction time (h)	Yield **1** (%)[c]
1	1	2	1	150	Reflux	2.5	<1
2	1	1.2	1	150	80	2	1
3[d]	1	1	1	150	80	2	<1
4	1	2	1	150	45	2.5	1
5	1	3	10	130	45	16	0
6	1	2	1	150	45	2.5	1
7	1	2	1	75	45	2	3
8	1	2	1	75	45	2	3

[a] The reactions were performed using 1 g of sulfur without any additional conditions other than those reported in the table.

[b] Absolute ethanol.

[c] Isolated yield either by crystallization in ethylacetate/hexanes or by silica flash chromatography.

[d] Addition of CS_2 to digest any unreacted sulfur.



Scheme 2. Proposed mechanism for the Gewald reaction of **1**.

General Procedure

The optimized general procedure for the synthesis of **1** is the following. Elemental sulfur (1 g, 31.2 mmol) was added to DMF (5 mL) along with ethylcyanoacetate (7.12 g, 62.3 mmol) and triethylamine (1 mL, 7.1 mmol) and then stirred at room temperature for 60 h. The resulting slurry was

Table 2. Effects of stoichiometry and reaction times upon the yield and purity of **1**[a]

Entry	Ethylcyano acetate (equivalents)	Sulfur (equivalents)	Et_3N (equivalents)	Reaction time (h)	Yield[b]	Purity (%)[c]
1	1	0.5	0.5	18	0	—
2	1	0.5	0.5	48	14	<80
3	1	0.5	0.5	48	12	85
4	1	1	0.5	60	22	—
5	1	1	0.25	60	24	98
6	1	1	0.05	60	0.2	<50
7	1	1	0.25	60	22	94
8	1	0.5	0.25	60	17	—

[a] The reactions were performed at room temperature using 1 g of sulfur in 5 mL of DMF. See the experimental description for more details.

[b] Isolated yield after crystallization in ethylacetate/hexanes.

[c] The purity of the crystallized samples was measured by NMR using *tert*-butyl benzene as an internal standard in deuterated acetone and by elemental analysis.

filtered and then poured into water (125 mL). The resulting precipitate was filtered, and the product (1.94 g, 24%) was obtained as yellow needles upon recrystalization from a mixture of ethylacetate/hexanes. Mp: 155–156°C. ^{1}H NMR (acetone-d_6): $\delta = 6.17$ (s, 2H), 4.12 (q, 4H, $J = 7.1$ Hz), 1.27 (t, 6H, $J = 7.0$ Hz). ^{13}C NMR (DMSO-d6): $\delta = 165.6$, 148.9, 104.5, 60.4, 14.8. Analytically calculated for $C_{10}H_{14}N_2O_4S$ (258.30): C, 46.50; H, 5.46; N, 10.85; O, 24.74; S, 12.41. Found: C, 46.57; H, 5.46; N, 10.65; S, 12.44. EI-MS: m/z 258.1 ([M]+, 80%), 212 ([M-C2H5O]+, 100%).

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