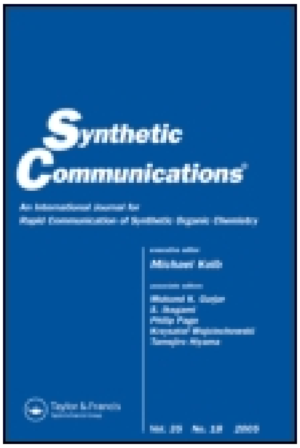

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Synthesis of 2-Aminothiophenes on Ionic Liquid Phase Support using the Gewald Reaction

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Synthesis of 2-Aminothiophenes on Ionic Liquid Phase Support using the Gewald Reaction

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Abstract: The first report of the use of task-specific ionic liquid as soluble support for the Gewald synthesis of 2-aminothiophenes is reported in this article. This synthetic method is simple and efficient, and the products are obtained in good to excellent yields with high purities, without the need for chromatographic purification.

Keywords: 2-Aminothiophene, Gewald synthesis, ionic liquids, soluble support

2-Aminothiophene derivatives are very important intermediates for pharmaceuticals, dyes, conducting polymers, agriculture, and other related materials.[1,2] The most common version of the Gewald reaction, involving multicomponent condensation of ketones or aldehydes, cyanoacetate, and elemental sulfur, is the most well-established route to the synthesis of 2-aminothiophenes containing electron-withdrawing groups in the 3-position and has attracted increasing interest since it was originally published in 1961 by Gewald.[2] Generally, Gewald–thiophene synthetic procedures require long reaction times for the condensation step and the resulting products require laborious purification.[2,3] Many modifications of this reaction have been developed recently, such as using solid support,[4]

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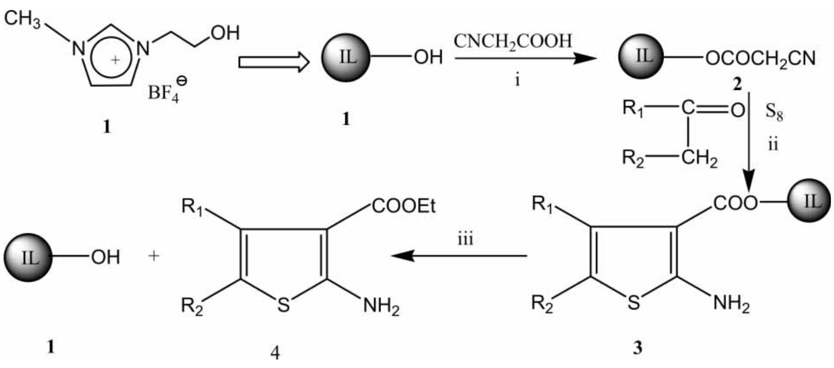
microwave irradiation combined with insoluble polymer support[5] or soluble polymer support,[6] heterogeneous catalysis,[7] and Lewis acid catalysis.[1a] However, some of these methods are limited by low loading capacity; difficulty of monitoring the reaction progress and configuration of polymer-bound products; use of large excess of reagents, expensive catalyst, or toxic volatile organic solvent; tedious workup; long reaction times; and sometimes low yields. Therefore, the improvement of Gewald synthesis of 2-aminothiophenes using a facile and efficient method with environmentally benign technologies is still very interesting in organic synthesis.

Recently, much attention has been focused on the use of ionic liquids (IL) as green reaction media; numerous chemical reactions can be carried out in ionic liquids.[8] More recently, IL formulations have been expanded to include ions with structurally and functionally complex side chains—the so called "task-specific ionic liquids" (TSIL).[9] One of the most elegant applications of functionalized IL has been pioneered by Bazureau et al., who used TSIL as supports for organic synthesis in an approach analogous to solid-phase synthesis, called ionic liquid-phase organic synthesis (IoLiPOS).[10] It has recently been extended by Miao and Chan who has shown it to be compatible with the Suzuki coupling and oligopeptides synthesis.[11] With these facts in mind, and in continuation of our interest in using IL as an ecofriendly medium in condensation reactions,[12] we report herein the new synthesis of 2-aminothiophenes using the IL as a soluble support for the Gewald reaction (Scheme 1).

As shown in Scheme 1, the reaction of **1** with a minor excess of cyanoacetic acid (1.2 equiv.) in the presence of dicyclohexyl carbodiimide (DCC) and a catalytic amount of 4-dimethylamino pyridine (DMAP) in dry MeCN produced the functionalized IL phase bond **2** through ester linkage. The disappearance of absorption for the hydroxyl group at 3598 cm^{-1} of **1** and the



Scheme 1. Reagents and conditions: (i) DCC (1 equiv.), DMAP (5%), cyanoacetic acid (1.2 equiv.), MeCN, rt, 12 h; (ii) ketone or aldehyde (1 equiv.), S_8 (1 equiv.), EDDA (0.1 equiv.), 50 °C; (iii) EtONa (0.5 equiv.), EtOH, rt, 6 h.

appearance of ester carbonyl and cyano at 1745 and 2200 cm^{-1} in the IR spectrum are clear evidence of the formation of **2**. Then Gewald reactions were carried out under solvent-free conditions catalyzed by ethylenediammonium diacetate (EDDA).[12a] The completion of the reaction was evidenced by the disappearance of cyano group and the appearance of amino group at 3413 and 3310 cm^{-1} in the IR spectrum of the products—the IL phase bond intermediates **3**. Treatment of **3** with NaOEt in ethanol resulted in a very efficient cleavage from IL support to provide the corresponding products **4** with high purity without the need for chromatographic purification. Compared to the conventional liquid synthesis methods, the IL phase bond intermediates were easily isolated and purified by simple filtration and washing with Et_2O to remove the minor unreacted materials and neutral by-product. Compared to the polymer-support methods, the most obvious advantages are the much higher loading capacity of the TSIL and no need for the use of a large excess of reagents, ^1H NMR and IR could be used readily to analyze the configuration of IL phase bond intermediates and products without detaching material from the ionic liquid-phase support in each step of the sequences in contrast to insoluble polymers as solid supports. Significantly, the three components were added in equivalent portions in the reaction, to allow standard analytical methods (^1H NMR, TLC) to be used conveniently to monitor reaction progress.

To establish the scope of this reaction, various ketones, aldehydes, and 1,3-dicarbonyl compounds were investigated. The results were summarized in Table 1; all the products were characterized by ^1H NMR, IR, and melting points, which were consistent with the literature data. As delineated in Table 1, our method was found to be generally applicable; all the products were obtained in good to excellent yields. Moreover, the IL phase **1** ([2-hydemim][BF_4]) could be typically recovered and reused with no appreciable decrease in yields and reaction rates after the workup as described in the literature.[10b]

Table 1. Synthesis of 2-aminothiophenes using ionic liquid as soluble support

Entry	Product	R_1	R_2	Time (h)	Yield (%)
1	4a	CH_3	CH_3	6	75
2	4b	CH_3CH_2	CH_3	6	77
3	4c	CH_3	$CO_2C_2H_5$	6	70
4	4d	CH_3	CO_2CH_3	6	69
5	4e	H	CH_3	5	68
6	4f	H	CH_3CH_2	5	67
7	4g		—$(CH_2)_4$—	3	91
8	4g		—$(CH_2)_4$—	3	89[a]
9	4g		—$(CH_2)_4$—	3	88[b]
10	4h		—$(CH_2)_3$—	5	83

[a,b] Second and third recycling of **1**.

In summary, we have successfully performed the Gewald reaction using ionic liquid as support. The use of this novel IL phase offers many advantages compared to previously reported methods including environmental friendliness, much higher loading capacity, easy isolation and purification of the products, shorter reaction times, higher yields, no need for use of large excess of reagents, compatibility with automatic manipulation, use of standard analytical methods (IR, NMR, TLC) to monitor reaction progress, and the recyclability of the soluble support.

EXPERIMENTAL

For this study, the functionalized ionic liquid 1-(2-hydroxylethyl)-3-methylimidazolium tetrafluorobate ([2-hydemim][BF_4]) **1** was prepared according to the literature.[10] Melting points were determined on a digital melting-point apparatus and were not corrected. Infrared spectra were recorded using KBr pellets on a Vector-22 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 400-MHz spectrometer using $CDCl_3$ as the solvent with TMS as an internal standard. All materials are commercially available and were used without further purification.

IL-Supported Cyanoacetic Ester 2

Cyanoacetic acid (12 mmol), and DCC (10 mmol), DMAP (0.5 mmol) were added to a solution of [2-hydemim][BF_4] **1** (10 mmol) in MeCN (50 ml). After vigorous stirring at rt for 12 h, the insoluble N,N′-dicyclohexylurea (DCHU) was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting crude product was washed successively with dry Et_2O (2 × 15 ml) and dried under vacuum to give the IL-supported cyanoacetic ester **2** in almost quantitative yield (99%). Pale yellow viscous liquid: IR (neat): 3170, 2200, 1745, 1578, 1453, 1170, 1072, 833 cm^{-1}; ^{1}H NMR: $\delta = 8.22$ (br s, 1H), 7.28 (t, 1H, J = 1.6 Hz), 7.20 (t, 1H, J =1.6 Hz), 4.05 (t, 2H, J = 4.8 Hz), 3.70 (s, 3H), 3.67 (t, 2H, J = 4.8 Hz), 3.40 (s, 2H).

General Procedure for the Synthesis of 2-Aminothiophenes

Carbonyl compound (5 mmol), S_8 (5 mmol), and EDDA (0.5 mmol) were added to **2** (5 mmol). The reaction mixture was stirred under solvent-free conditions for 3–6 h at 50 °C. The resulting mixture was filtered and washed with dry Et_2O (3 × 10 ml) and then dried under vacuum to give the IL-supported 2-aminothiophene **3**. The resulting **3** was added to a solution of EtONa (2.5 mmol) in ethanol (50 ml); the mixture was stirred at rt for

6 h. Upon completion of the reaction, the ethanol was removed under vacuum, and the expected product **4** was extracted with Et_2O (4 × 20 ml). The combined ethereal solution was evaporated to give the product **4** with high purity without the need for further chromatographic purification. The reaction progress of the Gewald and the following cleavage reactions could be easily monitored by IR, TLC, or ^1H NMR.

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