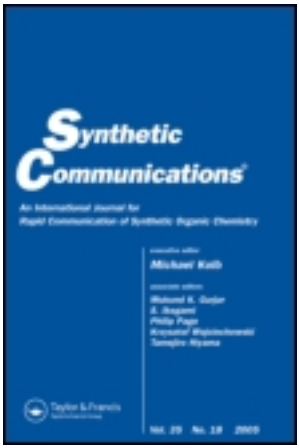

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Organic Reactions in Ionic Liquids: Gewald Synthesis of 2-Aminothiophenes Catalyzed by Ethylenediammonium Diacetate

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ABSTRACT

Ionic liquids based on 1-butyl-3-methylimidazolium tetrafluoroborate ($BmimBF_4$) and 1-butyl-3-methylimidazolium hexafluorophosphate ($BmimPF_6$) were used as reusable alternatives to volatile organic solvents (VOCs) for ethylenediammonium diacetate (EDDA) catalyzed Gewald synthesis of 2-aminothiophenes. Significant rate enhancement and improvement of the yield were observed. The ionic liquids containing

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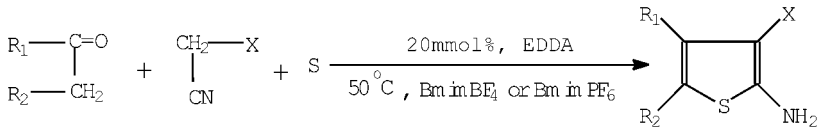
catalyst EDDA were recycled several times with no decreases in yields and reaction rates.

Key Words: 2-Aminothiophene; Gewald reaction; Ionic liquids; Knoevenagel condensation.

2-Aminothiophenes derivatives are important intermediates for pharmaceuticals, dyes, conducting polymers, agriculture, and other related materials.[1,2] The most elegant and simple version of the Gewald reaction, involving three-component condensation of a ketone, aldehyde, or β-dicarbonyl compound, an active nitrile, and elemental sulfur in the presence of base (Sch. 1), is the most well-established route to the synthesis of 2-aminothiophenes containing electron-withdrawing groups in the 3-position.[2] The Gewald-thiophene synthetic procedures usually require 0.5–1.0 molar equivalents of organic amines such as Et_3N, Et_2NH, diisopropylethylamine (DIPEA), morpholine, piperidine, etc.,[2,3] and the use of volatile organic solvent. Many modifications of this synthesis have been developed recently, including heterogenous catalysis,[4] Lewis acid catalysis,[1a] solid support,[5] microwave irradiation,[6] etc. However, these conditions indispensably need the use of organic base and volatile organic solvent, yet usually need long reaction times and sometimes give low yields. Therefore, the improvement on Gewald synthesis of 2-aminothiophenes is still a challenge in organic synthesis.

In recent years, room-temperature ionic liquids (RTILs) have attracted increasing interest as green and reusable reaction media.[7] Our recent research has revealed that the ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate ($BmimBF_4$) and 1-butyl-3-methylimidazolium hexafluorophosphate ($BmimPF_6$) could be used as recyclable reaction medium for ethylenediammonium diacetate (EDDA)-catalyzed Knoevenagel condensation between aldehydes or ketones with active methylene compounds.[8] It is known that the Knoevenagel condensation is a key step in the Gewald reaction.[2,4] Herein, we wish to report our preliminary results on the application of



1 **2** **3** **4**

Scheme 1.

EDDA as a reusable catalyst in the Gewald 2-aminothiophenes synthesis using ionic liquids as recyclable reaction medium.

For this study, $BmimBF_4$ and $BmimPF_6$ were synthesized according to the procedures reported in the literature.[9] The results are summarized in Table 1. All products were characterized by ^{1}H-NMR, IR, and melting points that were consistent with the literature data. As delineated in Table 1, different carbonyl compounds were examined and found to be generally applicable. The ionic liquid $BmimPF_6$ gave the same excellent results as $BmimBF_4$. Moreover, the ionic liquid containing catalyst EDDA could be typically recovered and reused with no appreciable decrease in yields and reaction rates. To investigate the catalytic influence of EDDA in detail, we separately carried out the reaction of cyclohexanone and malononitrile with EDDA (first step). The Knoevanagel condensation product was isolated and cyclized to 2-aminothiophenes by elemental sulfur in the presence of the catalyst under the same experimental conditions (second step). We found that the first step of the reaction is completed in 2 h and could hardly take place in the absence of catalyst. The second step of the reaction proceeded smoothly in the presence of catalyst, whereas, in the absence of catalyst, reaction was very slow and never attained completion. From the rate of reaction of both the steps, it can be concluded that the EDDA not only catalyzed the condensation step but also functioned as an effective catalyst in the cyclization step. We believe our method exhibited pronounced rate accelerations and gave high yields. For example, the literature[3] reported **4c** was obtained in 47% yield after 24 h using Et_2NH as the base at 70°C in t-BuOH. In our experiment, **4c** was obtained in 61% yield using 20 mol% EDDA as the base after 8 h at 50°C in $BmimBF_4$. The literature[4] reported **4a** was obtained in 61% yield after 8 h using Calcined Mg-Al Hydrotalcite as the base at 60°C in EtOH, while **4a** was obtained in 71% yield after 6 h using our method.

In conclusion, we demonstrated that the one-pot Gewald synthesis of 2-aminothiophenes can effectively be performed in the ionic liquids $BmimBF_4$ or $BmimPF_6$ catalyzed by EDDA. The present method has many obvious advantages compared to those reported in the literature, including being environmentally more benign, the generality, the shorter reaction times, the higher yields, and the potential for recycling of ionic liquids and catalyst EDDA.

EXPERIMENTAL

Melting points were determined on 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

Table 1. Gewald Synthesis of 2-Aminothiophenes in $BmimBF_4$ Catalyzed by EDDA.

Entry	R_1	R_2	X	Time/h	Yield/%	Mp[a]/°C	Lit.mp/°C
1 **4a**	CH_3	CH_3	CN	6	71	139–140	141–142[2a]
2 **4a**	CH_3	CH_3	CN	6	69[b]	139–140	
3 **4b**	CH_3	CH_3	$CO_2C_2H_5$	8	65	89–90	91–92[2a]
4 **4c**	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	8	61	106–107	108–109[2a]
5 **4d**	H	CH_3	$CO_2C_2H_5$	6	59	44–45	46[2a]
6 **4e**		— $(CH_2)_4$—	CN	3	89	146–147	147–148[2a]
7 **4e**		— $(CH_2)_4$—	CN	3	87[c]	146–147	
8 **4e**		— $(CH_2)_4$—	CN	3	88[d]	146–147	
9 **4e**		— $(CH_2)_4$—	CN	3	87[b]	146–147	
10 **4f**		— $(CH_2)_4$—	$CO_2C_2H_5$	4	84	113–114	115[2a]
11 **4g**		— $(CH_2)_3$—	$CO_2C_2H_5$	6	65	89–90	91[2a]

[a]Melting points were uncorrected.
[b]$BmimPF_6$ was used as solvent.
[c–d]Second and third recycling of $BmimBF_4$ containing the catalyst EDDA.

on a BRUKER-400 MHz spectrometer using $CDCl_3$ as the solvent, with trimethylsilane (TMS) as an internal standard. All materials are commercially available and were used without further purification.

General Procedure for the Gewald Reaction

Carbonyl compound (2 mmol), malononitrile, or ethyl cyanoacetate (2 mmol) and sulfur (2 mmol) were added in ionic liquid $BmimBF_4$ or $BmimPF_6$ (2 mL). The reaction mixture was stirred for 3–8 h at 50°C. Reaction was monitored by thin-layer chromatography (TLC). After the reaction, the resulting mixture was extracted with Et_2O (3 × 10 ml). The combined ethereal solution was evaporated to give the crude product, which was purified by recrystallization or preparative TLC (silica gel). After isolation of the product, the remainder of the ionic liquids containing catalyst EDDA was dried for 2 h under vacuum at 50°C. The next run was performed under identical reaction conditions.

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