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MICROWAVE-ASSISTED GEWALD SYNTHESIS OF 2-AMIMOTHIOPHENES USING FUNCTIONAL IONIC LIQUID AS SOLUBLE SUPPORT

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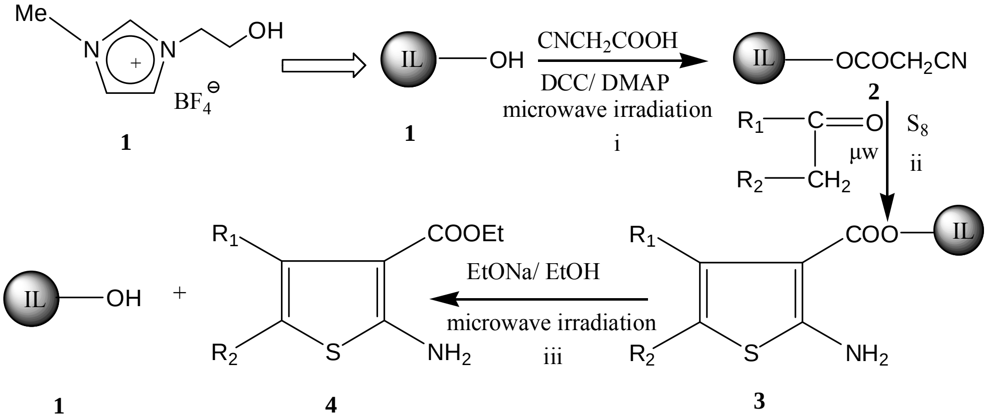
Abstract –A microwave-assisted liquid-phase Gewald synthesis of 2-aminothiophenes was developed using task-specific ionic liquid－[2-hydemim][BF_4] as soluble support. This new synthetic method is simple and efficient, and the products are obtained in good to excellent yields with high purities, without the need for chromatographic purification.

INTRODUCTION

2-Aminothiophenes 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 2-aminothiophenes containing electron-withdrawing groups in the 3-position and has attracted increasing interest since 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] microwave irradiation combined insoluble polymer support[5] or soluble polymer support,[6] heterogeneous catalysis,[7] Lewis acid catalysis,[1a] etc. However, these methods are usually limited by low loading capacity, using large excess of reagents, difficulty of monitoring the reaction progress and configuration of polymer-bound products, expensive catalyst or toxic volatile organic solvent, tedious workup, long reaction times and sometimes low yields obtained. Therefore, the improvement on Gewald synthesis of 2-aminothiophenes using facile and efficient method with environmental benign technologies is still very interesting in organic synthesis.

Recently, more attentions in room temperature ionic liquids research has been paid on the functionalized ionic liquids with special tasks,[8] which have been introduced as soluble supports in liquid-phase organic synthesis.[9-12] It has the advantages of the nature of homogeneous reaction, high loading capacity, wide range of solvents, simple monitoring technology, and low cost. Microwave irradiation has become an established tool in organic synthesis.[13] Hoffmann et al. reported ionic liquids could efficiently absorb microwave energy by which the reaction rate could be accelerated remarkably,[14] and the efficiency of microwave irradiation in the synthesis and applications of functionalized ionic liquids as soluble supports have been perfectly showed in the literatures.[9-12] Among various kinds of functionalized ionic liquids, 1-(2-hydroxylethyl)-3-methylimidazolium tetrafluorobate ([2-hydemim][BF_4]) (**1**) was the most widely used in the ionic liquids supported organic synthesis, for which has much lower viscosity compared to other kinds of functionalized ionic liquids.[9-12]

Having the above facts in mind, and in continuation of our interest in using IL as eco-friendly medium in condensation reactions.[15] We report herein a new synthetic approach of 2-aminothiophenes under microwave irradiation using the functionalized ionic liquid (**1**) as soluble supports for the Gewald reaction (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

For this study, [2-hydemim][BF_4] (**1**) was prepared according to the literature.[9] As shown in Scheme 1, the reaction of **1** with minor excess of cyanoacetic acid (1.2 equiv.) in the presence of dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) was irradiated with microwave under solvent-free condition for 5 min to give the functionalized ionic liquid-phase bond (**2**) through ester linkage. In contrast it would take overnight time to complete the reaction under conventional condition. The disappearance of absorption for the hydroxyl group at 3598 $cm^{-1}$of **1** and the appearance of ester carbonyl and cyano groups at 1745 and 2200cm^{-1} in the IR spectrum are clear evidences for the formation of **2**. Then Microwave-assisted Gewald reactions were carried out under solvent-free condition catalyzed by ethylenediammonium diacetate (EDDA),[15a] only 15 min was needed for the complete transformation from **2** to **3**. 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 ionic liquid-phase bond intermediates (**3**). Treatment of **3** with NaOEt in ethanol under microwave irradiation for 5 min resulted in a very efficient cleavage from IL support to provide the corresponding products (**4**) with high purity without the need for chromatographic purification. The comparison of entries 1 and 2 showed the reaction rates of the Gewald synthesis and the following cleavage step both could be accelerated remarkably by microwave irradiation. Compared to the conventional liquid synthesis methods, the ionic liquid-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 new soluble support and no need for the use of large excess of reagents. Besides, ^{1}H NMR and IR spectrum could be used readily to analyze the configuration of ionic liquid- phase bond intermediates and products without detaching material from the ionic liquid-phase support in each step of the sequences. Significantly, the three components were added in equivalent molar in the Gewald reaction, as allow TLC to be used conveniently to monitor the 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 ^{1}H NMR, IR spectrum and melting points that 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**) could be typically recovered and reused with no appreciable decrease in yields and reaction rates after the same workup as described in the literatures (Entries 9 and 10).[9b,12]

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

Entry	Product	R_1	R_2	Yield[a] (%)	mp[b] (°C)	Lit. mp (°C)
1	**4a**	Me	Me	76	89-90	91-92[2b]
2	**4a**	Me	Me	75[c]		
3	**4b**	Et	Me	78	39-40	41[16]
4	**4c**	Me	CO_2Et	73	106-107	108-109[2b]
5	**4d**	H	Me	71	44-45	46[2b]
6	**4e**	H	Et	78	72-73	73[2b]
7	**4f**	— $(CH_2)_4$—		90	113-114	115[2b]
8	**4f**	— $(CH_2)_4$—		88[d]	113-114	
9	**4f**	— $(CH_2)_4$—		89[e]	113-114	
10	**4g**	— $(CH_2)_3$—		85	89-90	91[2b]

a Isolated yield based on **2**. b Melting points were uncorrected. c The transformation form **2** to **3a** was completed after 6h at 50°C, and the following cleavage step was completed after 6h at rt. d-e Second and third recycling of **1**.

In conclusion, we have successfully performed the microwave-assisted Gewald synthesis of 2-aminothiophenes using hydroxyl-functionalized ionic liquids as supports. The presented methodology offers many advantages compared previous reported methods including being environmentally more benign, much higher loading capacity achieved due to lower molecular weight of functionalized ionic liquid, the isolation and purification of intermediates more easy, the shorter reaction times, the higher yields, no need for the use of large molar excess of reagents, the permission for using standard analytical methods (IR and NMR spectrum or TLC) to monitor reaction progress, without the need for chromatographic purification, the potential for recycling of the soluble support and compatible with automatic manipulation.

EXPERIMENTAL

Melting points were determined on digital melting point apparatus and were not corrected. Infrared spectra were recorded on a VECTOR-22 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a BRUKER-400 MHz spectrometer. MS spectra were recored on a HP 5989B mass spectrometer. Elemental analyses were performed on a Carlo Erba EA 1106 instrutment. The microwave irradiation was performed in a 100 mL flask equipped with mechanical stirrer and condenser in a CEM-MASS microwave oven. TLC was accomplished on Merck silica gel 60 F_{254} on aluminium sheets.

IL-Supported Cyanoacetic Ester (2)

Cyanoacetic acid (1.02 g, 12 mmol), DCC (2.07 g, 10 mmol) and DMAP (0.061 g, 0.5 mmol) were added to [2-hydemim][BF_4] (**1**) (2.14 g, 10 mmol). The mixture was irradiated in a flask for 5 min at a power of 150 W in the microwave oven with stirring. The mixture was cooled to rt and filtered to remove the urea. The filtrate was washed successively twice with dry Et_2O (2×15 mL) and dried under vacuum to give the IL-supported cyanoacetic ester (**2**) in almost quantitative yield (99%).

*Spectroscopic data for **2**:*

IR (neat): 3170, 2200, 1745, 1578, 1453, 1170, 1072, 833 cm^{-1}. ^{1}H NMR($CDCl_3$): $\delta = 8.22$ (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). EI-MS, m/z: 194 (M^+ for $C_9H_{12}N_3O_2^+$). Anal. Calcd for $C_9H_{12}N_3O_2BF_4$: C, 38.47; H, 4.30; N, 14.95. Φουνδ: X, 38.35; H, 4.42; N, 14.82.

General procedure for the synthesis of 2-aminothiophenes (**4**)

Carbonyl compound (5 mmol), S_8 (0.16 g, 5 mmol), EDDA (0.018 g, 0.5 mmol) were added to **2** (1.41 g, 5 mmol). The mixture was irradiated with microwave under solvent-free condition for 15 min at a power of 150 W. The cooled mixture was filtered and washed with dry Et_2O (4×10 mL), then dried under vacuum to give the IL-supported 2-aminothiophene (**3**). The resulting **3** was added to a solution of EtONa (0.034 g, 0.5 mmol) in ethanol (50 mL), the mixture was irradiated with microwave for 5 min at the same power. Upon completion of the reaction, the ethanol was removed under vacuum, 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 and NMR spectrum or TLC.

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