BASIC IONIC LIQUID [bmIm]OH–MEDIATED GEWALD REACTION AS GREEN PROTOCOL FOR THE SYNTHESIS OF 2-AMINOTHIOPHENES

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GRAPHICAL ABSTRACT

Abstract A simple, efficient, and environmental friendly procedure was developed based on the Gewald reaction for the synthesis of 2-aminothiophenes using a basic ionic liquid [bmIm]OH as both catalyst and solvent. Besides being a green protocol, the method offers advantages of successful synthesis of a variety of alkyl, aryl, alkoxy, and alkylamino-2-aminothiophenes in good yields.

Keywords 4-Alkoxythiophenes; 2-aminothiophenes; basic ionic liquid; [bmIm]OH; Gewald reaction; ionic liquid

INTRODUCTION

Ionic liquids (ILs) have attracted growing interest in the context of green organic synthesis. Initially they were introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility.[1] They are also referred to as “designer solvents” because their physical and chemical properties could be...
tailor-made by a careful choice of cation and anion. Recently, the development of task-specific ionic liquids (TSILs) with special functions to suit the specific requirements of a reaction has become an attractive field. Besides their inherent advantages as reusable homogenous supports, reagents, and catalysts with green credentials, the additional enabling tunable features made them more popular. These TSILs often serve the dual role of catalyst as well as reaction media.

Multisubstituted 2-aminothiophene scaffolds derived from Gewald reaction (GR) attracted considerable attention in the design of several biologically active molecules. Ample data has been accumulated, highlighting their biological utility as synthons in the development of atypical antipsychotic agents (Fig. 1, 1), anti-inflammatory agents (2), allosteric enhancers of adenosine A1 receptor (3, 5), IκB kinase β (IKKβ) inhibitors (4), and antitubercular agents (6).

A typical GR involves base-catalyzed condensation of a ketone with an activated nitrile in the presence of sulfur to obtain functionalized 2-aminothiophenes. The majority of GR applications include use of organic bases such as morpholine, triethylamine, piperidine, and pyridine and diethylamine, making it environmentally unfriendly. This caused us to investigate GR using TSILs. Surprisingly, very few such attempts were reported in the literature. The application of an IL ester, prepared by coupling of N,N'-dicyclohexylcarbodiimide (DCC) with cyanacetic acid and an imidazolium-based IL as soluble support in GR was studied by Hu et al.; however, this methodology lacks versatility. For instance, IL ester cannot be prepared with activated nitriles such as malononitrile and ethylcyanooacetate. Further product isolation by base-catalyzed hydrolysis and recovery of IL from alkoxide solution is prohibitively tedious process. A basic ionic liquid, [TMG][Lac]

![Figure 1. 2-Aminothiophene analogues in clinics (1 and 2) or in preclinical development (3-6).](image-url)
(1,1,3,3-tetramethylguanidine lactate), has been explored as solvent and catalyst in the synthesis of 4,5-dialkyl-2-aminothiophenes, but the utility of the method has not been studied for 4-aryl and 4-alkoxy-2-aminothiophenes. Hence the development of a versatile and robust protocol involving TSIL was felt as an urgent need for the synthesis of functionalized 2-aminothiophenes.

Recently a TSIL [bmIm]OH has been successfully utilized to catalyze Michael addition of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles and Markovnikov addition of N-heterocycles to vinyl esters. The versatility of this TSIL as green reaction media and catalyst prompted us to study its utility in GR to get 2-aminothiophenes.

RESULTS AND DISCUSSION

As our key interest is to develop a multicomponent, one-pot, green protocol, different alkylketones, activated nitrile, and sulfur were condensed in one pot using [bmIm]OH as catalyst and solvent (Scheme 1). Interestingly, the yields of 2-aminothiophenes (2a–2j, Table 1) are better than the reported procedures. For example, in the literature 2a was obtained in 61% yield after 8 h using calcined Mg-Al hydrotalcite as the base at 60 °C in EtOH, whereas 2a was obtained in 88% yield in the present method. Similarly, 2g–2j were also obtained in good yields. Several reviews and papers on the Gewald reaction and its improvements propose that a 2-aminothiophene ring is formed from the aliphatic ketones such as 1a–j during the multistep reaction sequence: condensation, base-promoted activation, and addition of sulfur and ring closure. Hence it can be presumed that [bmIm]OH is efficient to catalyze condensation as well as sulfur addition process in the synthesis of 4,5-alkyl-2-aminothiophenes. The additional advantage of this green methodology is that the final products are pure enough (>90%) for spectral analysis and to proceed to further reactions.

Encouraged with the results, we studied the utility of [bmIm]OH in the synthesis of 4-aryl-2-aminothiophenes, 2,3,4,5-tetrasubstitued thiophenes (Scheme 2), and 4-alkoxy-2-aminothiophenes (Scheme 3). Condensation of acetophenone (3a), activated nitrile, and sulfur using [bmIm]OH in one pot resulted in poor yield (<40%) of 2-aminothiophene 5a. Conversely, reaction of ylidene 4a with sulfur using [bmIm]OH as catalyst resulted in good yield (77%) of 5a. Similarly synthesis of different yldienes 4b–4g and 7a–7i by Knoevenagel condensation followed by

Scheme 1. Synthesis of 4,5-alkyl-2-aminothiophenes, reagents and conditions: (a) 1 equiv. S8, 1.2 equiv. [bmIm]OH, 60 °C, 2 h.
[bmIm]OH-catalyzed cyclization with sulfur yielded respective 4-aryl-2-aminothiophenes, 2,3,4,5-tetrasubstituted thiophenes (Table 2), and 4-alkoxy-2-aminothiophenes (Table 3) in good yields, demonstrating that [bmIm]OH is efficient in sulfur addition and cyclization of ylidenes though not effective in Knoevenagel condensation of these ketones. Hence we propose that in the modified two-step Gewald method (i.e., Knoevenagel condensation followed by cyclization with sulfur), [bmIm]OH can be utilized efficiently for sulfur addition and cyclization to yield 2-aminothiophenes.

Remarkably, [bmIm]OH is very promising for the synthesis of 4-alkoxy-2-aminothiophenes (Scheme 3) in good yields. In our previous experiments,[27] use of organic bases for sulfur addition and cyclization of ylidenes resulted in black masses, which consequently necessitated tedious column purification. With aqueous inorganic bases (aqueous KOH or NaOH), nucleophilic displacement of 7a occurred with hydroxyl and subsequently formed 2-amino-4-hydroxythiophene (9) as the major product. Using [bmIm]OH no such side products were observed. The final compounds are separated from the IL simply by washing with diethyl ether or ethyl acetate. The residual ionic liquid was washed with diethyl ether and dried under vacuum at 90 °C for 2 h to eliminate any water trapped from moisture. Weight of the ionic liquid lost in the washings was adjusted and reused for subsequent reactions. The ionic liquid has been reused in three runs without loss of activity (Table 1, 2k–l), making it a greener approach.

Scheme 2. Synthesis of 4-aryl-2-amino/2,3,4,5-tetrasubstituted thiophenes, reagents and conditions: (a) NH₄OAc, toluene, reflux; (b) 1 equiv. S₈, 1.2 equiv. [bmIm]OH, 60 °C, 4 h.

Table 1. Yields of 4,5-alkyl-2-aminothiophenes using [bmIm]OH as catalyst

| No. | R₁    | R₂    | X      | Yield (%) | Ref. |
|-----|-------|-------|--------|-----------|------|
| 2a  | CH₃   | CH₃   | CN     | 88        | 22   |
| 2b  | (CH₂)₃ | COOEt | CN     | 72        | 22   |
| 2c  | (CH₂)₄ | CN    | 85     | —         |      |
| 2d  | (CH₂)₅ | COOEt | 87     | 23        |      |
| 2e  | (CH₂)₆ | CN    | 88     | 23        |      |
| 2f  | (CH₂)₇ | COOEt | 88     | 24        |      |
| 2g  | (CH₂)₈ | CN    | 87     | 24        |      |
| 2h  | CH₂-N(CH₂PH)-CH₂ | CN | 92 | — |      |
| 2i  | COOEt | CN    | 90     | —         |      |
| 2j  | CN    | COOEt | 88     | —         |      |
| 2k  | (CH₂)₉ | CN    | 88     | —         |      |
| 2l  | CN    | 85     | —      | —         |      |

*Second recycling of IL.

*Third recycling of IL.

Note: Ref., reference.
Table 2. Yields of 4-aryl-2-amino/2,3,4,5-tetrasubstituted thiophenes using \([\text{bmIm}]\text{OH}\) as catalyst

| No. | R_1 | R_2       | R_3 | R_4 | X   | Yield (%) | Ref. |
|-----|-----|-----------|-----|-----|-----|-----------|------|
| 5a  | Ph  | CH_3      | Ph  | H   | CN  | 77        | 25   |
| 5b  | 4-MeOPh | CH_3 | 4-MeOPh | H   | CN  | 62        | 26   |
| 5c  | Ph  | CH_3Ph    | Ph  | Ph  | CN  | 74        | 26   |
| 5d  | 4-BrPh | CH_3     | 4-BrPh | H   | CN  | 69        | 25   |
| 5e  | 3,4-(OCH_3)Ph | CH_3 | 3,4-(OCH_3)Ph | H   | CN  | 67        | —    |
| 5f  | CH_3 | CH_3COOEt | CH_3 | COOEt | CN | 86        | —    |
| 5g  | CH_3 | CH_3COOEt | CH_3 | COOEt | COOEt | 84       | 17   |

Table 3. Yields of 4-alkoxy/alkylamino-2-aminothiophenes using \([\text{bmIm}]\text{OH}\) as catalyst

| No. | R_1         | Yield (%) |
|-----|-------------|-----------|
| 8a  | O-CH_3      | 72        |
| 8b  | O-CH_3CH_3  | 84        |
| 8c  | O-(CH_3)_2CH_3 | 68      |
| 8d  | O-(CH_3)_2CH_3 | 74      |
| 8e  | O-CH_2-CH(CH_3)_2 | 72      |
| 8f  | O-CH_2-CH(CH_3)_2 | 76      |
| 8g  | O-(CH_3)_2-CH_3 | 82      |
| 8h  | O-CH_3 - Ph  | 35        |
| 8i  | H N O        | 91        |
In conclusion, the present study highlights the task-specific basic ionic liquid [bmIm]OH as an useful environmentally friendly solvent and catalyst in GR. The results delineated in Tables 1–3 demonstrate its versatility for the synthesis of functionalized 2-aminothiophenes.

EXPERIMENTAL

4,5-Alkyl-2-aminothiophenes (2a–2j)

For the synthesis of 4,5-alkyl-2-aminothiophenes (2a–2j), the general procedures are the same as those of compound 2i.

A mixture of N-benzyl-4-piperidone (1i, 380 mg, 2 mmol), malononitrile (132 mg, 2 mmol), sulfur (64 mg, 2 mmol), and basic ionic liquid (bmIm)OH (380 mg, 2.4 equiv.) was heated to 60 °C for 2 h. The reaction mixture was cooled to room temperature and washed with diethyl ether or ethyl acetate (3 × 40 mL), and the organic layers were concentrated under vacuum to obtain an oily crude product. The crude product was dissolved in ether/hexane (3:1, 50 mL) mixture, insoluble material was decanted, and the organic layer was concentrated to 1/4 of the volume and kept in a refrigerator. The precipitate that formed was filtered and dried.

2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carbonitrile (2i)

Red color solid; 1H NMR (400 MHz, CDCl3): δ = 7.31 (m, 5H), 4.68 (s, 2H), 3.69 (s, 2H), 2.80 (t, J = 6.0 Hz, 2H), 2.63 (t, J = 6.0 Hz, 2H). 13C NMR (100 MHz, CDCl3): δ = 160.5, 137.8, 130.9, 129.9, 128.4, 127.3, 117.8, 115.1, 88.2, 61.7, 50.7, 49.5, 24.6. MS (ESI): m/z = 270.1 (M+H)+.

4-Aryl-2-aminothiophenes (5a–g) and 4-Alkoxy-2-aminothiophenes (8a–h)

The syntheses of 4-aryl-2-aminothiophenes (5a–g) and 4-alkoxy-2-aminothiophenes (8a–h) are the same as described for those of compound 8b.

A mixture of 2-(1-ethoxyethylidene)malononitrile[27] (7b, 272 mg, 2 mmol), sulfur (64 mg, 2 mmol), and basic ionic liquid (bmIm)OH (380 mg, 2.4 mmol) was allowed to stir at 60 °C for 4 h. The reaction mixture was cooled to room temperature and washed with diethyl ether or ethyl acetate (3 × 30 mL), and organic layers were concentrated to 1/4 of the volume and kept in a refrigerator. The precipitate that formed was filtered and dried.

2-Amino-4-ethoxythiophene-3-carbonitrile (8b)

Brown solid; mp 134 °C (lit.[27] 134 °C); IR (KBr): 3439, 3320, 3213, 2972, 2199, 1631, 1557 cm−1; 1H NMR (400 MHz, CDCl3): δ = 5.18 (s, 1H), 4.79 (s, 2H, NH2), 4.01 (q, J = 6.8 Hz, 2H), 1.40 (t, J = 6.8 Hz, 3H). 13C NMR (100 MHz, CDCl3): δ = 160.4, 154.2, 113.9, 82.6, 78.9, 59.0, 15.1; MS (ESI+): m/z = 169.1 (M+H).
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SUPPLEMENTARY MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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