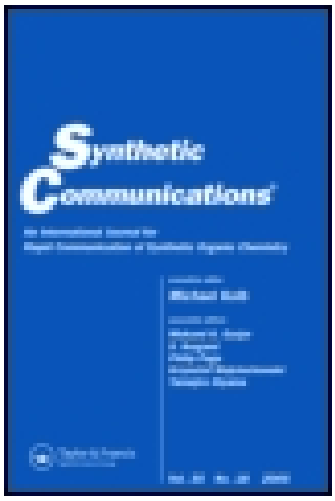

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# Basic Ionic Liquid [bmIm]OH Mediated Gewald Reaction as Green Protocol for the Synthesis of 2-Aminothiophenes

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# Basic ionic liquid [bmIm]OH mediated Gewald reaction as green protocol for the synthesis of 2-aminothiophenes

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## Abstract

A simple, efficient and environmental friendly procedure was developed based on 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:** Basic ionic liquid, [bmIm]OH, 2-aminothiophenes, Gewald reaction, Ionic liquid, 4-alkoxythiophenes

## 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 non-volatility, non-flammability, thermal stability, and controlled miscibility[1]. They are also referred as ‘‘designer solvents’’ as 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[2].

Multisubstituted 2-aminothiophene scaffolds derived from Gewald reaction (GR) attracted considerable attention in the design of several biologically active molecules [3]. Ample data has been accumulated highlighting their biological utility as synthons in the development of atypical antipsychotic agents (Fig 1, 1)[4], antiinflammatory agents (**2**), allosteric enhancers of adenosine $A_1$ receptor (**3, 5**)[5-7], I$\kappa$B kinase $\beta$ (IKK$\beta$) inhibitors (**4**) [8] and antitubercular agents (**6**) [9].

A typical GR involves base catalyzed condensation of a ketone with an activated nitrile in the presence of sulfur to obtain functionalized 2-aminothiophenes [10]. Majority of GR applications include use of organic bases such as morpholine[11,12], triethylamine [13,14],

piperidine [15], pyridine and diethylamine [16] etc. making it environmental unfriendly which necessitated 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 DCC with cyanoacetic acid and an imidazolium-based IL as soluble support in GR was studied by Hu *et al.*, however this methodology lacks versatility [17,18]. For instance IL-ester cannot be prepared with activated nitriles such as malononitrile and ethylcyanoacetate. Further product isolation by base-catalyzed hydrolysis and recovery of IL from alkoxide solution is prohibitively tedious process. Though, a basic ionic liquid [TMG] [Lac] (1,1,3,3-tetramethylguanidine lactate) has been explored as solvent and catalyst in synthesis of 4,5-dialkyl-2-aminothiophenes, the utility of the method has not been studied for 4-aryl and 4-alkoxy-2-aminothiophenes [19]. 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,[20] and Markovnikov addition of N-heterocycles to vinyl esters[21] etc. 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 multi-component one-pot green protocol, different alkylketones, activated nitrile, and sulfur was 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 [22-24]. For example, in the literature **2a** was obtained in 61% yield after 8 h using Calcined Mg-Al hydrotalcite as the base at 60ºC in EtOH, [22] while **2a** was obtained in 88% yield in present method, similarly **2g-2j** were also obtained in high yields. Several reviews and papers on the Gewald reaction and its improvements propose that 2-aminothiophene ring is formed from the aliphatic ketones such as **1a-j** during the multi-step 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 further reactions.

Encouraged with the results, utility of [bmIm]OH has been studied 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 low 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 ylidenes **4b-4g** [25, 26] and **7a-7i** [27] by Knoevenagel condensation followed by [bmIm]OH catalyzed cyclisation with sulfur yielded respective 4-aryl-2-aminothiophenes, 2,3,4,5-tetrasubstitued thiophenes (Table 2) and 4-alkoxy-2-aminothiophenes (Table-3) in good yields. Demonstrating that [bmIm]OH is efficient in sulfur addition and cyclisation 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 cyclisation with sulfur, [bmIm]OH can be utilized efficiently for sulfur addition and cyclisation to yield 2-aminothiophenes.

Remarkably, [bmIm]OH is very promising for the synthesis of 4-alkoxy-2-aminothiophenes (Scheme 3**)** in high yields. Since, in our previous experiments[27] use of organic bases for sulfur addition and cyclisation of ylidenes **7a-i** resulted in black color masses, which consequently necessitated us tedious column purification process. Whereas with aqueous inorganic bases (aqueous KOH or NaOH), nucleophilic displacement of **7a** with hydroxyl and subsequent formation of 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, dried under vacuum at 90 $^{0}$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 3 runs without loss of activity (Table 1, **2k-l**) highlighting it as a greener approach.

In conclusion, the present study highlights the task-specific basic ionic liquid [bmIm]OH as an useful environmental-friendly solvent and catalyst in GR. The results delineated in Table 1-3 demonstrate its versatility for the synthesis of functionalized 2-aminothiophenes.

## EXPERIMENTAL DATA

Synthesis of 4,5-alkyl-2-aminothiophenes (**2a-2j**): general procedures are described as those of compound **2i**.

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

**2-Amino-6-Benzyl-4,5,6,7-Tetrahydrothieno[2,3-*C*]Pyridine-3-Carbonitrile (2i)**

Red color solid; $^{1}$H NMR (400 MHz, $CDCl_3$): δ = **7**.31 (m, 5H), 4.68 (s, 2H), 3.69 (s, 2H), 3.40 (s, 2H), 2.80 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): 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 $(M+H)^+$.

Synthesis of 4-aryl-2-aminothiophenes (**5a-g**) and 4-alkoxy-2-aminothiophenes (**8a-h**): general procedures are described as those of compound **8b**.

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

**2-Amino-4-Ethoxythiophene-3-Carbonitrile (8b)**

Brown colour solid; Mp 134 ºC (lit. [27] 134 ºC); IR (KBr): 3439, 3320, 3213, 2972, 2199, 1631, 1557 $cm^{-1}$.; $^{1}$HNMR (400MHz, $CDCl_3$): δ = 5.18 (s, 1H), 4.79 (s, 2H, $NH_2$), 4.01 (q, *J* = 6.8 Hz, 2H), 1.40 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100MHz, $CDCl_3$): δ = 160.4, 154.2, 113.9, 82.6, 78.9, 59.0, 15.1; MS ($ESI^+$): *m/z* = 169.1 (M+H).

## SUPPLEMENTARY MATERIAL

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

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

| S.No. | R1 | $R_2$ | X | %yield | Ref. |
|---|---|---|---|---|---|
| 2a | $CH_3$ | $CH_3$ | CN | 88 | 22 |
| 2b | | | COOEt | 72 | 22 |
| 2c | $(CH_2)_3$ | | CN | 85 | -- |
| 2d | | | COOEt | 67 | 23 |
| 2e | $(CH_2)_4$ | | CN | 88 | 23 |
| 2f | | | COOEt | 88 | 23 |
| 2g | $(CH_2)_5$ | | CN | 87 | 24 |
| 2h | | | COOEt | 86 | 24 |
| 2i | $CH_2$-N($CH_2PH$)-$CH_2$ | | CN | 92 | -- |
| 2j | | | COOEt | 90 | -- |
| 2k | $(CH_2)_4$ | | CN | 88[a] | -- |
| 2l | | | | 85[b] | -- |

[a]second recycling of IL, Ref. = Reference

[b]third recycling of IL

**Table 2.** Yields of 4-aryl-2-amino/2,3,4,5-tetrasubstituted thiophenes using [bmIm]OH as catalyst

| S.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 | $CH_2Ph$ | Ph | Ph | CN | 74 | 26 |
| 5d | 4-BrPh | $CH_3$ | 4-BrPh | H | CN | 69 | 25 |
| 5e | 3,4-$(OCH_3)_2Ph$ | $CH_3$ | 3,4-$(OCH_3)_2Ph$ | H | CN | 67 | -- |
| 5f | $CH_3$ | $CH_2COOEt$ | $CH_3$ | COOEt | CN | 86 | -- |
| 5g | $CH_3$ | $CH_2COOEt$ | $CH_3$ | COOEt | COOEt | 84 | 17 |

**Table 3.** Yields of 4-alkoxy/alkylamino-2-aminothiophenes using [bmIm]OH as catalyst

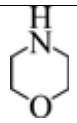
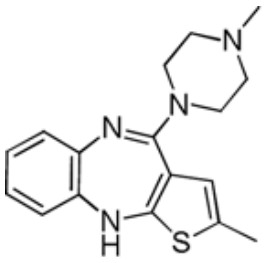
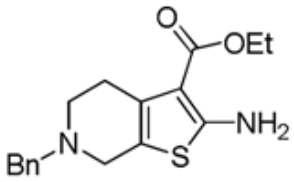
| S. No. | $R_1$ | %yield |
|---|---|---|
| 8a | $O\text{-}CH_3$ | 72 |
| 8b | $O\text{-}CH_2CH_3$ | 84 |
| 8c | $O\text{-}(CH_2)_2\text{-}CH_3$ | 68 |
| 8d | $O\text{-}(CH_2)_3\text{-}CH_3$ | 74 |
| 8e | $O\text{-}CH_2\text{-}CH(CH_3)_2$ | 72 |
| 8f | $O\text{-}CH_2\text{-}CH_2\text{-}CH(CH_3)_2$ | 76 |
| 8g | $O\text{-}(CH_2)_7\text{-}CH_3$ | 82 |
| 8h | $O\text{-}CH_2\text{-}Ph$ | 35 |
| 8i |  | 91 |

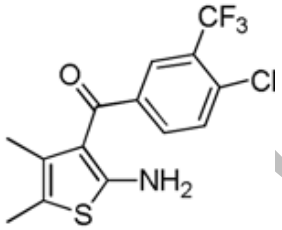
**Figure 1**. 2-aminothiophene analogues in clinics (**1**&**2**) or in preclinical development (**3-6**)



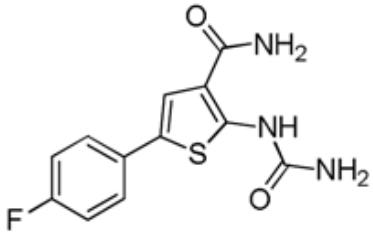
Olenzepine (1)



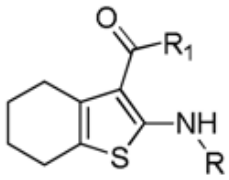
Tinoridine (2)



(3)



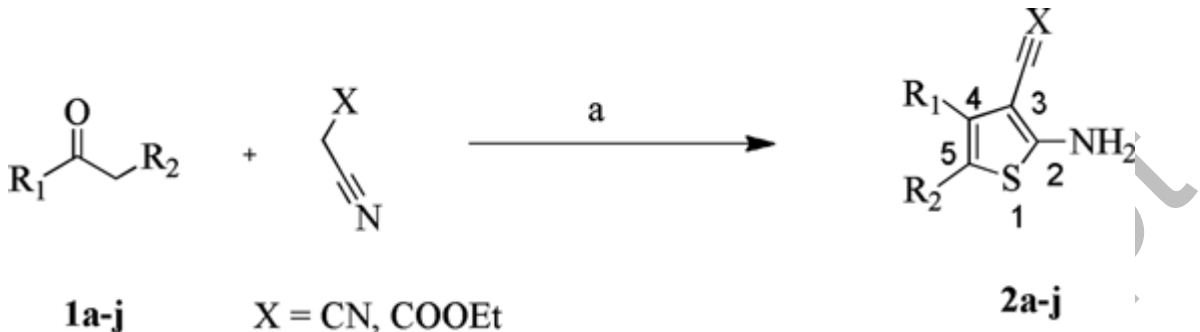
(4)



(5) R = H, $R_1$ = 4-ClPh

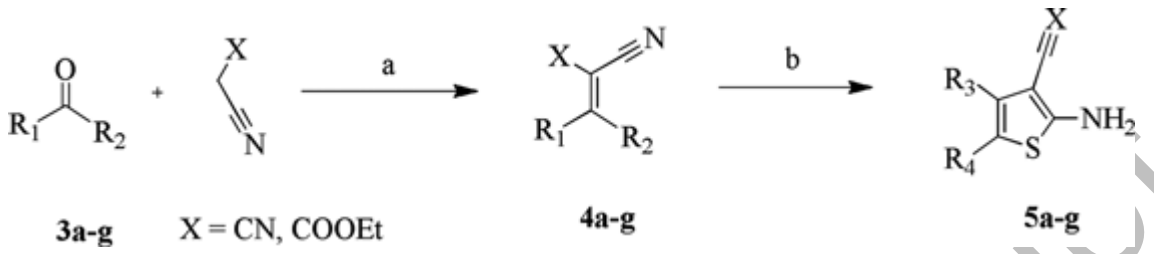
(6) R = CO-cy-Pr $R_1$ = $NH_2$

**Scheme 1.** Synthesis of 4,5-alkyl-2-aminothiophenes: Reagents and conditions; a) 1equiv. $S_8$, 1.2 equiv. [bmIm]OH, 60 ºC, 2h.




**1a-j** X = CN, COOEt **2a-j**

**Scheme 2.** Synthesis of 4-aryl-2-amino/2,3,4,5-tetrasubstituted thiophenes: Reagents and conditions; a) $NH_4OAc$, toluene, reflux.; b) 1equiv. $S_8$, 1.2 equiv. [bmIm]OH, 60 ºC, 4h.




**3a-g** X = CN, COOEt **4a-g** **5a-g**

**Scheme 3.** Synthesis of 4-alkoxy/alkylamino-2-aminothiophenes: Reagents and conditions: a) i) R-OH (3 equiv.), 24 h, 80 °C; (ii) $CH_2(CN)_2$, 60 °C, 3 h; [27] b) 1equiv. $S_8$, 1.2 equiv. [bmIm]OH, 60 °C, 4h; c) $CH_2(CN)_2$, 60 °C, 3 h; d) 1equiv. $S_8$, 1 equiv.KOH (aqueous), 60 °C, 15 min.