

Organic Reactions in Ionic Liquids: Ionic Liquid-promoted Efficient Synthesis of Disubstituted and Trisubstituted Thioureas Derivatives

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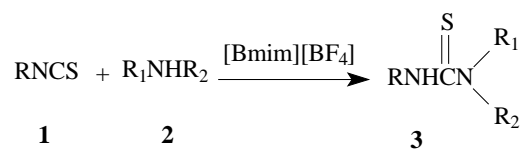
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Abstract: In ionic liquid [Bmim][BF₄], a series of disubstituted and trisubstituted thiourea derivatives were synthesized from phenyl and butyl isothiocyanate with a variety of amine in excellent yield.

Keywords: Phenyl isothiocyanate, butyl isothiocyanate, thiourea, ionic liquid.

The three categories of agents against the human immunodeficiency virus (HIV) are nucleoside analogs, protease inhibitors and the recently introduced non-nucleoside reverse transcriptase inhibitors¹, such as thiourea derivatives. The bioactivities² and reactions³ of thiourea derivatives has been a topic of research interest for over a century. The popular synthetic method⁴ is the direct reaction of isothiocyanate with amine. However these methods are limited due to harsh reaction condition^{4c}, long reaction time^{5,3a}, low yield^{4b}, and using toxic solvent, such as benzene⁵, toluene^{4h}, acetonitrile⁶, DMF^{4d}, dichloro methane^{4a}, xylene^{4f}, THF^{2c}, acetone^{3a} and ethyl alcohol^{4g} *etc.* Therefore to develop a simple, mild, efficient and environmental more benign synthetic methods of thiourea derivatives is still urgent.

Scheme 1



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In recent years, the room temperature ionic liquids are attracting increasing interest as 'green' recyclable alternative to classical molecular solvents for synthetic organic chemistry⁷. To date, some of the more important reactions carried out in ionic liquids show rate acceleration effect then that in conventional solvents⁸. We examined the reaction of isothiocyanate and amine in ionic liquid, which acted both as reaction media and promoter (**Scheme 1**).

The reaction of phenyl isothiocyanate with aniline in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [Bmim][BF₄] could complete nearly within 10 min to give N,N'-diphenylthiourea (**Table 1**, Entry 1) almost in quantitative yield. The reaction of phenyl isothiocyanate with a variety of aromatic amines were investigated. This reaction is general and applicable to various aromatic amines including: 1-naphtylamine, 2-amino-pyridine, and substituted phenyl amine bearing various different groups, such as methyl, chloro, and hydroxy (**Table 1**, Entries 1-6). In order to explore the generality of the method developed for synthesis of thiourea derivatives, we carried out the experiment of phenyl isothiocyanate with a variety of aliphatic primary and second amine and obtained corresponding disubstituted and trisubstituted thioureas (**Table 1**, Entries 7-10). Furthermore, the reaction of butyl isothiocyanate with aniline and butyl amine also was conducted to form the corresponding 1,3-disubstituted thioureas in excellent yield (**Table 1**, Entries 11, 12).

Table 1 Synthesis of disubstituted and trisubstituted thiourea derivatives in ionic liquid [Bmim][BF₄]^a

Entrv	RNCS	R ₁ NHR ₂	Reaction condition (min)	Yield ^b (%)
1	PhNCS	C ₆ H ₅ NH ₂	10	98
2		<i>p</i> -MeC ₆ H ₄ NH ₂	10	97
3		<i>p</i> -ClC ₆ H ₄ NH ₂	10	99
4		<i>o</i> -HOC ₆ H ₄ NH ₂	20	85
5		2-NH ₂ C ₃ H ₄ N	25	90
6		1-naphtylamine	10	96
7		C ₆ H ₅ CH ₂ NH ₂	5	96
8		<i>n</i> -C ₄ H ₉ NH ₂	5	98
9		C ₆ H ₅ CH ₂ NHCH ₃	7	97
10		(<i>n</i> -C ₄ H ₉) ₂ NH	5	99
11	<i>n</i> -BuNCS	C ₆ H ₅ NH ₂	10	95
12		<i>n</i> -C ₄ H ₉ NH ₂	10	97

^aAll reactions were run with isothiocyanate (2 mmol) and amine (2.4 mmol) in ionic liquid [Bmim][BF₄] (2 mL) at 25 °C.

^b Isolated yield based on isothiocyanate.

The mp, IR and ^1H NMR of all the products were consistent with the literature data. The ionic liquid can be recovered after extracting out the product and followed by drying at vacuum. The recovered ionic liquid solvent can be reused without decrease of the yield. The representative results are summarized in **Table 1**.

The present method represents the first example of the ionic liquid-promoted reaction of isothiocyanates with amines, it has many obvious advantages, compared to those reported in the literature, including high efficiency, generality, high yield, simple operation, environmentally more benign and recyclibility. In conclusion, we have demonstrated that the synthesis of disubstituted and trisubstituted thiourea derivatives can be performed rapidly in ionic liquid [Bmim][BF₄] in excellent yields. The ionic liquid plays the dual role of solvent and promoter.

Experimental

Melting points were determined on digital melting point apparatus and the thermometer was not corrected. Infrared spectra were recorded on a VECTOR22 (Bruker). Nuclear magnetic resonance spectra were recorded on AVANCE DMX 400 (Bruker) spectrometer. The ionic liquids [Bmim][BF₄] were synthesized according to reported procedures⁹. The other materials are commercially available and were used without further purification.

General procedure for the N-alkylation of heterocyclic compounds

Isothiocyanate (2 mmol) and corresponding amine (2.4 mmol) were added to ionic liquid [Bmim][BF₄] (2 mL), the mixture was stirred at room temperature for 5-25 min (reaction condition see **Table 1**). The product was extracted with ether (3 × 10 mL). The combined ethereal phase was evaporated under reduced pressure to give crude product. The crude product were purified by recrystallization to give the corresponding thiourea derivatives. After filtration of the product the rest viscous ionic liquid was further washed with a mixture of ether-ethyl acetate (1:1) and dried at 80°C under reduced pressure and reused in subsequent runs.

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