## COMMUNICATION / COMMUNICATION

# An ionic liquid mediated Friedel–Crafts addition of arenes to isothiocyanates

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**Abstract:** A new protocol is developed for the synthesis of *N*-substituted thioamides, employing arenes and isothiocyanates in 1-butyl-3-methylimidazolium chloroaluminate ionic liquid, [bmim]Cl·2AlCl<sub>3</sub>, as a homogenous Lewis acid catalyst and solvent. The effect of Lewis acidity and the stoichiometry of the ionic liquid on the extent of product formation is studied. Studies reveal that a progressive increase in yields was observed with increasing Lewis acidity, and two equivalents of [bmim]Cl·2AlCl<sub>3</sub> was the optimal amount for the reaction. A distinct *para* selectivity for the incoming thioamido group on activated arenes was observed under ambient conditions.

Key words: arenes, isothiocyanates, Friedel-Crafts, ionic liquids, thioamides.

**Résumé :** On a développé un nouveau protocole pour la synthèse de thioamides *N*-substitués qui fait appel à l'utilisation d'arènes et d'isothiocyanates dans du chloroaluminate de 1-butyl-3-méthylimidazolium, [bmim]Cl·2AlCl<sub>3</sub>, un liquide ionique qui agit comme catalyseur acide de Lewis homogène et comme solvant. On a étudié l'effet de l'acidité de Lewis et la stoechiométrie du liquide ionique sur le niveau de formation du produit. Les études révèlent qu'une augmentation progressive des rendements peut être observée avec une augmentation de l'acidité de Lewis et que deux équivalents de [bmim]Cl·2AlCl<sub>3</sub> correspond à la quantité optimale pour la réaction. Dans les conditions ambiantes, on a observé une sélectivité *para* pour le groupe thioamido qui s'insère sur les arènes activés.

Mots clés : arènes, isothiocyanates, Friedel-Crafts, liquides ioniques, thioamides.

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#### Introduction

Room temperature ionic liquids have attracted considerable attention as novel reaction media, offering cleaner and environmentally benign protocols to a number of chemical processes (1). An appropriate amalgamation of properties possessed by these liquids, such as high thermal stability, reusability, nonvolatility, and excellent solvating ability has undoubtedly made them the most protean and promising solvents of the future (2). The most interesting feature of ionic liquids is the extensive flexibility they offer in terms of alteration of properties such as density, viscosity, Lewis acidity, hydrophobicity, hydrophilicity, etc. (3). This feature of ionic liquids has enabled chemists to design and engineer them so that a proper equilibrium of properties is attained, making them the most suitable and compatible solvents for several chemical processes (4–8). derivatives as useful building blocks in organic syntheses has been recently reviewed (9). Thioamides are a class of compounds that comprise a variety of derivatives that possess diverse physiological properties such as antigastric, antiulcer, antidiabetic, antitubercular, fungistatic, etc. (10). Besides, they have been technically applied in a number of commercial applications as vulcanisation promoters, antioxidants, corrosion inhibitors, etc. (10). Activated arenes are known to undergo Lewis acid mediated amidation (11, 12) and thioamidation (13, 14) with isocyanates and isothiocyanates, respectively. In contrast to the Lewis acid mediated amidation of arenes with isocyanates, thioamidation with isothiocyanates has been particularly attractive, as the former procedure often suffers from the disadvantage of low yields of products. The isothiocyanato group is one of the excellent acceptors of nucleophiles, and its reactivity has been aptly utilized in various synthetic procedures (15). With Lewis acids, the isothiocyanato group is known to

The significance of thioamides and their polyfunctional

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form a charged complex containing electrophilic carbon (16), which is believed to be involved as an intermediate in its reaction with arenes.

#### **Results and discussion**

Over the last two years, our group has developed considerable interest in investigating the Friedel–Crafts (17–19) and condensation (20, 21) reactions in the Lewis acidic chloroaluminate ionic liquids. As a part of our ongoing venture to exploit chloroaluminate ionic liquids for newer reactions, we present herein an account of the execution of 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·AlCl<sub>3</sub> ( $0.67 \ge N > 0.50$ ; *N* is the apparent mole fraction of AlCl<sub>3</sub> in the ionic liquid) mediated addition of activated arenes to isothiocyanates (Scheme 1).

We anticipated an exhortive result in the case of activated arenes such as phenols, and they were therefore an obvious choice for the preliminary investigations. A reaction performed in [bmim]Cl did not fetch any product. The encouraging results obtained in the subsequent investigations carried out in [bmim]Cl·AlCl<sub>3</sub>, N = 0.67, prompted us to plan a systematic study aimed at the optimization of Lewis acidity and stoichiometry of the ionic liquid and time of reaction, to develop an ambient protocol for thioamidation. 2,5-Xylenol, being sufficiently reactive, was preferred as a model substrate for these optimizations.

To study the effect of the Lewis acidity of  $[\text{bmim}]\text{Cl}\cdot\text{AlCl}_3$  (0.67  $\ge N \ge 0.50$ ) on the extent of product formation, a series of ionic liquids with varying Lewis acidities were prepared. The molar proportion of 2,5-xylenol, phenyl isothiocyanate, and ionic liquid was maintained at 1:1:1 at room temperature for 24 h, and the extent of conversion in terms of the percentage yield of the product obtained in each case was compared. The results reflected that an increase in the Lewis acidity resulted in an increase in the percentage yield of product formed, but in all the cases the yields were too low to be quantitative. The yield increased from 0% to 30% as *N* increased from 0.50 to 0.63, progressively, and only 64% yield was realized for [bmim]Cl·AlCl<sub>3</sub>, N = 0.67.

The [bmim]Cl·AlCl<sub>3</sub>, N = 0.67, was an obvious choice for all further investigations. With a view to obtain an optimal yield of the product, we further planned to study the effect of stoichiometry of [bmim]Cl·AlCl<sub>3</sub>, N = 0.67, on the extent of product formation. A series of experiments were planned in which the molar proportion of 2,5-xylenol and phenyl isothiocyanate was fixed at 1:1 and varying amounts of [bmim]Cl·AlCl<sub>3</sub>, N = 0.67, ranging from 1 to 2.5 mole equivalents, was added. The reaction time was 24 h at room temperature. The results indicated that the optimal product formation calls for the use of at least 2 mole equivalents of [bmim]Cl·AlCl<sub>3</sub>, N = 0.67. No significant increase in yields was observed with a further increase in stoichiometry of the ionic liquid.

To optimize the time for the thioamidation procedure, a series of experiments were planned in which the molar proportion of 2,5-xylenol, phenyl isothiocyanate, and [bmim]Cl·AlCl<sub>3</sub> (N = 0.67) was maintained at 1:1:2 at room temperature for different time periods (ranging from 2–12 h). The yields of the product formed at different time in-

Scheme 1. The [bmim]Cl·AlCl<sub>3</sub> (0.67 = N > 0.50) catalyzed addition of arenes to isothiocyanates.

Ar-H + R-NCS 
$$(-R \text{ is alkyl or aryl group})$$
 [bmim]Cl·AlCl<sub>3</sub> S  
0.67  $\ge$  N>0.5 Ar NH-R

tervals were compared. The results indicated that the optimal time for the reaction is 8 h, beyond which no substantial increase in yield was observed. No improvement in yield was realized, even after a prolonged reaction time of 30 h.

To generalize the procedure and to study the effect of substituents on product formation, a variety of arenes were screened under optimized conditions. The results obtained are indicative of successful thioamidation of activated arenes (Table 1). The reaction of phenyl isothiocyanate did not occur with benzene, but with *m*-xylene 83% yield of the product was obtained. In terms of yields and selectivity, the method is comparable to a nitromethane–AlCl<sub>3</sub> system (13). In general, aryl isothiocyanates fetched better yields than alkyl isothiocyanates. In contrast to a number of classical carbonylation procedures, an exquisite *para*-selectivity was observed in reaction even with the arene that has both *ortho* positions unblocked (entry 5). In the case of substrates with the *para* position blocked, such as *p*-xylene and *p*-cresol, no reaction was observed.

The present methodology can be easily extended to *ortho* carbonylation of benzoic acids, i.e., conversion of benzoic acids to phthalic acids and also for conversion of phthalic acids to homophthalic acids, which are synthetically versatile intermediates (22, 23). In addition, the method can serve as an advantageous alternative to the synthesis of certain benzoic acids and benzyl amines, which cannot be synthesized by other methods.

#### Conclusion

In effect, we found 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·AlCl<sub>3</sub> (N = 0.67), to be a homogenous Lewis acidic medium for Friedel–Crafts type addition of activated arenes to isothiocyanates, thus eliminating the use of conventional obnoxious or volatile solvents such as halogenated hydrocarbons, nitromethane, and carbon disulphide. Homogenous catalysis, reduced reaction times, ambient conditions, and exquisite *para*-selectivity are some of distinctively notable advantages offered by the novel procedure.

#### Experimental

The ionic liquids used in the present study were prepared as per the procedures reported earlier (24, 25). In a typical experimental procedure for thioamidation of arene, to the weighed quantity of the arene (5 mmol) and isothiocyanate (5 mmol), the ionic liquid [bmim]Cl·AlCl<sub>3</sub> (N = 0.50-0.67, 5–15 mmol (as specified in the text)) was added, and the reaction mixture was stirred for a specified time at room temperature. All additions were carried out under a nitrogen atmosphere glove box. The reactions were quenched with 6 mol L<sup>-1</sup> HCl under cold conditions. The resultant solution

Table 1	. The	[bmim]	Cl·AlCl <sub>2</sub>	$(\Lambda$	V = 0.6	57)	mediated	addition	of	arenes	to	isothiocy	anates.
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Entry	Arene	Isothiocyanate	Thioamide	% Yield <sup>a</sup>
1	С	€ NCS	C <sub>e</sub> H <sub>e</sub> NH	80
2	$\Diamond$	₩CS	C <sub>6</sub> H <sub>5</sub> NH	83
3	ССС	<b>NCS</b>	C <sub>8</sub> H <sub>5</sub> NH	85
4	ГСС	€ NCS	C <sub>6</sub> H <sub>5</sub> NH	92
5	OMe	<b>NCS</b>		81
6	СС	<b>NCS</b>	C <sub>6</sub> H <sub>5</sub> NH COH	79
7	С	CI NCS	p-CI-C <sub>6</sub> H₄-NH OH	82
8	Ċ.	CI NCS	p-CI-C <sub>6</sub> H <sub>4</sub> -NH	88
9	СТ <sub>он</sub>	CI NCS	p-CI-C <sub>6</sub> H <sub>4</sub> -NH	82
10	OMe	CI NCS	ρ-Cŀ-C <sub>e</sub> H₄-NH Come	88
11	С	CI CI NCS	р-CI-C <sub>6</sub> H <sub>4</sub> -NH	92
12	С	NCS	Ch-NH Ch-NH	72
13	СС	NCS	Ch-NH CH	69
14	С	∕~ <sub>NCS</sub>	EI-NH CH	66

Note: Reactions carried out at room temperature for 8 h.

<sup>a</sup>Indicates isolated yields.

was extracted using ethyl acetate (3  $\times$  10 mL). The combined organic extracts were dried using anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to obtain the crude

product. The crude products were chromatographed using silica gel column chromatography to yield pure thioamides, which were characterized by physical constants, IR, and

NMR. The analytical and spectral data was consistent with that reported in the literature (13).

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