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Ionic liquid enabled sulfamoylation of arenes: an ambient, expeditious and regioselective protocol for aryl sulfonamides

Prashant U. Naik, Jitendra R. Harjani, Susheel J. Nara and Manikrao M. Salunkhe*

Department of Chemistry, The Institute of Science, 15-Madam Cama Road, Mumbai 400-032, India

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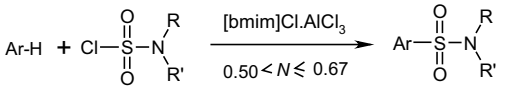
Abstract—The ionic liquid, 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·$AlCl_3$, $N = 0.67$ mediated syntheses of aromatic sulfonamides via electrophilic substitution of arenes is reported. The protocol serves as a distinctly expeditious and ambient route towards the syntheses of these pharmaceutically useful compounds, yielding quantitative conversions at room temperature within 5–30 min in most of the cases. The Lewis acidity and molar stoichiometry of the ionic liquid influences the extent of conversion. The method has been used for the syntheses of a diverse range of sulfonamides by variation of arenes and sulfamoyl chlorides. With monosubstituted benzenes, the protocol offers an added advantage of exclusive selectivity towards the formation of *para* substituted sulfonamides over the *ortho* products.

The utility of ionic liquids in catalysis and as neoteric solvents for various synthetic processes is now well recognised by chemists all over the world. The remarkable attributes possessed by them such as non-volatility, recyclability, thermal stability, diverse solvating ability and tunability have made them popular as environmentally benign counterparts to conventional reaction media.[1] The fact that the other ionic liquid-specific properties[2] such as Lewis acidity, viscosity, density, hydrophobicity, hydrophilicity, etc. can be tailored, has provided an enormous scope for innovation in the area of solvent engineering.

The realm of these unconventional reaction media began with molten salt chemistry, which subsequently evolved into the ambient temperature ionic liquids very frequently referred to as organoaluminates or chloroaluminate ionic liquids. This interesting class of liquids not only served the purpose of reaction media, but also acted as the catalyst[3] in Lewis acid mediated reactions. The major setback in their development and widespread acceptance is their water sensitive nature. Furthermore, a product of their reaction with water is corrosive HCl, which destroys the very purpose of these liquids being used as environmentally benign alternatives. This feature of chloroaluminates demands that they must be handled with exclusion of moisture-laden atmospheres, usually in a glove box. Despite these disadvantages, the chloroaluminates are often a preferred choice, firstly owing to their diverse solvating ability and variable Lewis acidity, which in an ensemble provides a tunable Lewis acidic medium for execution of reactions in a homogenous phase. Secondly, in certain reactions this conglomerate of properties has demonstrated a profound positive effect on the yield[4] or rate[5] or selectivity[6] of the reaction, when compared with the prototypical procedures.

Over the past three years, we have been engaged in exploring newer reactions in chloroaluminate ionic liquids[7] with emphasis on those reactions where their employment is aptly warranted.[5,8] To this end, we herein report the sulfamoylation of arenes with *N*,*N*-dialkylsulfamoyl chloride (Scheme 1) in Lewis acidic 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·$AlCl_3$, $0.50 < N \leqslant 0.67$ ionic liquid (N is the apparent



Scheme 1. Sulfamoylation of arenes in [bmim]Cl·$AlCl_3$, $N = 0.50$–0.67.

Keywords: Arene; Sulfamoyl chloride; Ionic liquid; Sufamoylation; *N*,*N*-Dialkylsulfonamide.
* Corresponding author. Tel./fax: +91-22-22816750; e-mail: mmsalunkhe@hotmail.com

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mole fraction of $AlCl_3$ in the liquid). Aromatic sulfonamides are of considerable importance owing to their bioactive nature. Compounds possessing this functionality have great potential as pharmaceuticals and over 30 drugs containing this moiety are presently in clinical use as antibacterials, diuretics, anticonvulsants, hypoglycemics and HIV protease inhibitors.[9] The conventional methods for synthesising *N*,*N*-dialkylsulfonamides includes chlorosulfonylation of arenes followed by the condensation of arylsulfonyl chloride with *N*,*N*-dialkylamine.[10] Besides these, other methods include, alkylation of sulfonamides with an alkyl halide,[11] oxidation of sulfonamides,[12] substitution of *N*,*N*-dichlorosulfonamide,[13] reaction of sulfinyl halides with hydroxylamine derivatives[14] and reaction of trialkylarylstannanes with sulfonyl isocyanates.[15] The electrophilic substitution of arenes with *N*,*N*-dialkylsulfamoyl chloride has not been investigated in great detail except for $AlCl_3$[16] and metal triflate[17] mediated sulfamoylation.

Yet another strategy for *N*,*N*-dialkylsulfonamide synthesis utilises the thia-Fries rearrangement of *O*-sulfamates to hydroxyl sulfonamides.[18] These reported protocols suffer from the disadvantage of both longer reaction times and high temperatures. For instance, in the $AlCl_3$ catalysed reactions, temperatures in the range of 70–80 °C were required for 4 h to obtain the optimal yields and in the case of the best metal triflate amongst those tried, that is $In(OTf)_3$, a temperature of 100 °C was required for 24 h for optimal product formation.[17] In contrast to these catalysts, [bmim]Cl·$AlCl_3$, $N = 0.67$ ionic liquid proved to be so effective that in an unoptimised experiment, with one mole equivalent of the ionic liquid, the reaction of piperidylsulfamoyl chloride with benzene was completed within 30 min at room temperature (as indicated by TLC). To the best of our knowledge, this is the first report on Lewis acid mediated sulfamoylation achieved at room temperature. Encouraged by these preliminary observations, we planned a systematic study wherein we monitored the influence of parameters such as molar stoichiometry, Lewis acidity of the ionic liquid and the time of reaction on the extent of conversion. The reaction of piperidylsulfamoyl chloride with benzene was selected as a model for all the further investigations.

To optimise the molar stoichiometry of [bmim]Cl·$AlCl_3$, $N = 0.67$ ionic liquid required for the reaction, we carried out several experiments and found that the conversions improved as the amount of ionic liquid was increased from 0 to 1 mol equiv and 1 mol equiv of [bmim]Cl·$AlCl_3$, $N = 0.67$ sufficed to afford almost quantitative conversions at room temperature after 30 min (Table 1).[19,20] The variation of the apparent mole fraction of $AlCl_3$ in chloroaluminate ionic liquids facilitates the variation of Lewis acidity of the medium. This feature of chloroaluminates prompted us to investigate the influence of variable Lewis acidity on the extent of conversion.[19,20] The reaction did not occur in basic ($N < 0.50$) and neutral ($N = 0.50$) ionic liquids even after a prolonged reaction time of 24 h. We observed that as the Lewis acidity of the ionic liquid was increased from $N = 0.50$ to 0.67, the percentage conversion increased progressively as was evident from the results obtained (Table 2).

Table 1. The effect of molar stoichiometry of [bmim]Cl·$AlCl_3$, $N = 0.67$ on the extent of conversion in the sulfamoylation of benzene with piperidylsulfamoyl chloride[a]

Molar equivalents of [bmim]Cl·$AlCl_3$, $N = 0.67$	Percentage conversion[b]
0.24	22
0.48	48
0.72	75
1.00	96

[a] Reactions performed at rt for 30 min.
[b] Conversions monitored by HPLC.[19]

Table 2. The effect of the Lewis acidity of [bmim]Cl·$AlCl_3$, $N = 0.50$–0.67 on the extent of conversion in the sulfamoylation of benzene with piperidylsulfamoyl chloride[a]

Mole fraction of $AlCl_3$ in the ionic liquid (N)	Percentage conversion[b]
0.56	20
0.59	53
0.63	72
0.67	96

[a] Reactions performed at rt with 1 mol equiv of ionic liquid.
[b] Conversions monitored by HPLC.[19]

Under the optimised conditions of molar stoichiometry, Lewis acidity of the ionic liquid and reaction temperature, we adjudged the catalytic efficacy of this liquid by monitoring the conversion as a function of time.[19,20] For the conversions to reach maximum, the optimal reaction time was 30 min (Table 3).

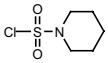
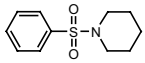
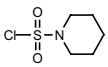
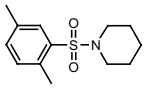
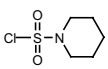
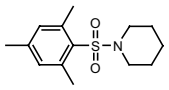
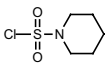
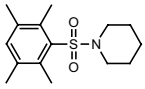
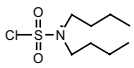
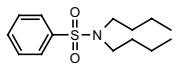
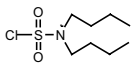
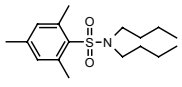
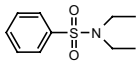
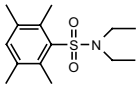
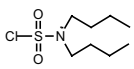
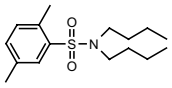
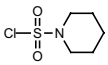
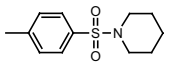
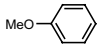
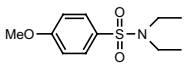
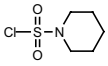
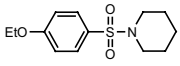
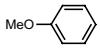
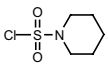
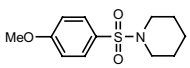
To extend the scope of the reaction and to generalise the procedure, we investigated the reaction of several arenes with a variety of *N*,*N*-dialkylsulfamoyl chlorides as sulfamoylating agents (Table 4). The reaction worked well with benzene, toluene, *p*-xylene, mesitylene, durene, alkoxy benzenes and naphthalene.[20] With alkoxy benzenes, (entries 11–13) the reaction was expeditious enough to afford good yields of the corresponding sulfonamides within 5 min at room temperature. An interesting feature that we observed with such arenes under the reported reaction conditions was no detectable dealkylation as was observed with the conventional $AlCl_3$ catalysed reactions, which resulted in a considerable reduction in yields of the corresponding sulfon-

Table 3. The effect of reaction time on the extent of conversion in the [bmim]Cl·$AlCl_3$, $N = 0.67$ mediated sulfamoylation of benzene with piperidylsulfamoyl chloride[a]

Reaction time (min)	Percentage conversion[b]
5	40
10	58
15	77
20	85
25	90
30	96

[a] Reactions performed at rt with 1 mol equiv of ionic liquid.
[b] Conversions monitored by HPLC.[19]

Table 4. The scope of [bmim]Cl·$AlCl_3$, $N = 0.67$ mediated sulfamoylations of arenes[a]

Entry	Arene	Sulfamoyl chloride	Time, temperature	Sulfonamide	Percentage yield[b]
1			30 min, rt		90
2			30 min, rt		92
3			30 min, rt		94
4			30 min, rt		89
5			30 min, rt		92
6			30 min, rt		88
7			30 min, rt		91
8			30 min, rt		87
9			30 min, rt		93
10			30 min, rt		89
11			5 min, rt		91
12			5 min, rt		88
13			5 min, rt		84
14			30 min, rt		88 (α:β = 94:6)[c]

[a] One mole equivalent of the ionic liquid was used.
[b] Indicates the yield of product isolated by column chromatography.
[c] Obtained by GC–MS.[21]

amides. On the other hand, $In(OTf)_3$ mediated sulfamoylations of alkoxy benzenes gave good yields of the corresponding sulfonamides, but the protocol affords poor regioselectivities in addition to the drastic reaction conditions.[17] The present protocol leads to exclusive selectivity for the *para* substituted sulfonamides with alkoxy benzenes. With alkoxy benzenes, longer reaction times (longer than 5 min) in the ionic liquid were detrimental for the formation of the desired sulfonamides because of the dealkylation. In the case of naphthalene, the protocol offers the best selectivity for the α-substituted product. The reaction of dibutylsulfamoyl chloride

with naphthalene (entry 14) resulted in an 88% yield of product in an α:β ratio of 94:6, (by GC–MS[21]), which confirmed the fact that the reaction conditions are promising for the formation of the kinetically favoured products over the thermodynamically favoured ones. Similarly, the reaction of naphthalene with diethylsulfamoyl chloride gave the corresponding sulfonamide in 87% yield (with α:β = 82:18[21]). It is noteworthy that, in terms of the isomer distribution observed for the naphthyl sulfonamides, the present protocol is distinctly complementary to the earlier one.[17] In the case of deactivated arenes such as chlorobenzene, no reaction was observed at room temperature. At higher temperatures however, we obtained a 65% yield of product within 30 min at 100 °C, which was exclusively *para*. To the best of our knowledge, the sulfonamides in entries 4, 6, 8 and 9 of Table 4 are unknown in the literature.

To conclude, the present protocol serves as an expeditious route to earlier methods, providing almost quantitative yields of aromatic sulfonamides under ambient conditions in most of the cases. In the case of monosubstituted benzenes, an added advantage is the regioselectivity offered by the procedure. The ionic liquid served a dual purpose of solvent as well as catalyst. The present method for effecting the sulfamoylation of arenes will therefore be a useful addition in the scientific literature.

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19. The conversion in all the cases was monitored on a reversed-phase HPLC using anisole as an external standard. The extent of conversion was monitored with respect to the formation of the product (λ_{max} 224 nm). The HPLC analysis was performed on a Merck Lachrome, equipped with the Inertsil ODS3 column (250 mm × 4.6 mm, 5μ) and a UV detector, which was tuned to measure the absorbance at 220 nm. The elution was performed with CH_3CN/aqueous buffer, pH 2.5 (0.05 M KH_2PO_4/H_3PO_4) taken in a 65/35 ratio by volume, maintaining a flow rate of 1 mL min^{-1}.
20. Typical experimental procedure: to the arene (5.5 mmol) and sulfamoyl chloride (5 mmol) was added [bmim]Cl·$AlCl_3$, $0.50 < N \leqslant 0.67$ (5 mmol or as specified in the text) and the reaction mixture stirred for a specified time at room temperature. All the additions were performed under N_2 atmosphere in a glove box. The reaction mixture was quenched by adding 6 M aq HCl solution under cold conditions. The product was extracted using (3 × 15 mL) of ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was chromatographed using toluene on a silica gel column to yield the purified product, which was characterised by melting point IR and ^1H NMR. Spectral data of 1-[(2,3,5,6-tetramethylphenyl)sulfonyl]-piperidine (Table 4, entry 4): mp 82–84 °C. IR (KBr): 2942, 2854, 1636, 1459, 1389, 1299, 1211, 1139, 1048, 922, 834, 726, 673, 621, 588, 527 and 487 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.57 (br s, 6H, 3 × –CH_2– cyclic), 2.27 (s, 6H, 2 × –CH_3), 2.54 (s, 6H, 2 × –CH_3), 3.15 (br s, 4H, 2 × –CH_2– cyclic) and 7.16 (s, 1H, 1 × C*H* arom.) ppm.
21. The GC–MS analysis was performed using a Shimadzu, QP-2010 instrument equipped with a dp-5 column. The detector temperature was set at 280 °C. The column was programmed initially at 60 °C for 15 min and then with a gradient of 10 °C/min to 270 °C.