Intrinsic catalytic activity of an acidic ionic liquid as a solvent for synthesis of 2-amino thiazole derivatives

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Abstract: A greener methodology for the synthesis of 2-amino thiazole derivatives using an ionic liquid was developed where the ionic liquid is used as an inherent reaction catalyst and a solvent. Rapid, one-step, novel approach for the transformation of acetophenone and thiourea using ionic liquid has been developed at room temperature to form synthesis of 2-amino thiazole derivatives. The developed procedure is appropriate to numerous types of substituted synthesis of 2-amino thiazole derivatives are synthesized. The developed methodology offers mild reaction condition, short reaction time, and fair to excellent yields. This is one of the easiest and environmentally benign protocols for synthesis of synthesis of 2-amino thiazole derivatives.

Keywords: Ionic liquid, Aminothiazoles, Heterocyclic compounds, 1-methyl pyrrolodine-2-one

Introduction:

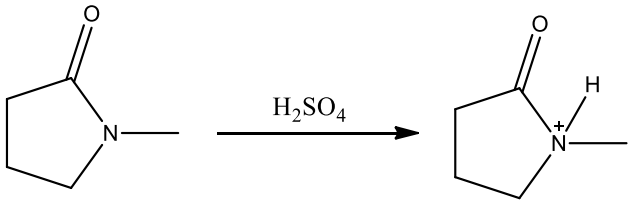
Thiazole ring is used as buildings blocks in many natural compounds as well as in vitamin B1 (thiamine), penicillin and carboxylase. Furthermore 2-aminothiazoles have been engaged in the synthesis of t important drugs essential for the treatment of schizophrenia,[1] inflammation,[2] cancer,[3] and bacterial infection[4]. They have been widely used as anti-inflammatory, insecticidal compounds[5-7].Thiazole is useful pharmacophore with a variety of biological activities.[8] various substituted thiazole have demonstrate for their antifungal activity. The thiazole derivatives show very important utility in medicinal chemistry and has found wide application in drug developments for the treatment of anticonvulsant[9], Diuretics[10], pesticidal[11], antituberclosis[12-13]. 2-Aminothiazole heterocycles have also found a wide range of applications in drug discovery and development due to their inimitable properties such as antiplatelet,[14] antiprion[15]

In view of the importance of 2-aminothiazole and its derivatives, a number of procedures have been developed to prepare this class of heterocyclic compound. Among them, the predominant method is Hantzsch condensation of α-bromoketone with thiourea, Also, 2aminothiazoles could be produced by solvent free synthesis under microwave irradiation in presence of iodine, thiourea and acetophenone,[16] treatment of α-bromoketone and thiourea in presence of PEG-400 gives 2-aminothiazoles,[17] There are several synthetic methods have been reported for the preparation of 2-aminothaizole derivatives treating α –halocarbonyl campound with thiourea[18] phenyl acetylene or styrene with N-bromosuccinimide in the presence of thiourea, reaction of α –tosyloxyketones[19], iodine [20]. Other reported methods include synthesis using various catalysts such as ionic liquid[21], $NaICl_2$[22], cylodextrin, ammonium 1,2-molybdophosphate [23,24], silica chloride[25], oxidative cyclisation using CBr4 [26]

Recently our research group worked on synthesis of 2-amonothiazole derivatives and we synthesize 2-amino thiazole derivatives by using oxone and Iodobenzene reaction system in aq. Acetonitrile solvent system[27] with connection to this we are expanding our research work in the same direction but this time we explore use of ionic liquids as solvent. In current years the use of ionic liquids as solvent has been popular as a greener approach for the synthesis of organic compounds. The use of ionic liquid has some advantages over conventional reaction solvent system. The advantages of ionic liquids are recyclability, low toxicity, high chemical stability, low viscosity, catalytic activity, short reaction time, high polarity. Taking into consideration these advantages of ionic liquid we decided to use ionic liquid as solvent system. Brønsted acidic ionic liquid used for the synthesis of quinazolines[28]. In order to develop more sustainable organic synthesis by using eco-friendly solvents, here the efficacy of an ionic liquid as a solvent as well as a catalyst for the synthesis of 2-aminothiazole derivatives has been tested.

Result and Discussion

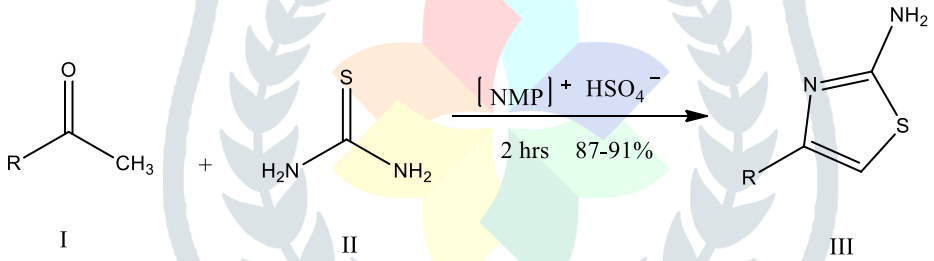
We have developed a new methodology for the synthesis of 2-amino thiazole derivatives using an ionic liquid as a green solvent. For the present study, we prepared a Brønsted acidic ionic liquid. The obtained ionic liquid was used as a catalyst for the synthesis of 2-amino thiazole derivatives. The ionic liquid was synthesized by a reported procedure and used for 2-amino thiazole derivatives (Scheme 1)[33]



1-Methylpyrrolidin-2-one N-Methyl-2-Pyrrolidone hydrogen sulphate

Schematic presentation of synthesis of N-methyl-2-pyrrolidone hydrogen sulphate

The literature explains that cyclisation reaction is always carried out in the presence of a catalyst. So we decided to reaction in presence of ionic liquid which acts as solvent and show acidic catalytic activity. Stating we added acetophenone and thiourea in the ionic liquid to give the corresponding 2-amino thiazole. (Table 1, Scheme 2). The entire the reactions were carried out at room temperature and atmospheric pressure. Required reaction time for completion of reaction is 2-3 hours. Greatest efficiency of the ionic liquid in terms of yield and reaction rate was found to be outstanding for p-methyl acetophenone, the reaction completed within 1.25 hours, and the yield was 91% (entry 3, Table 1).



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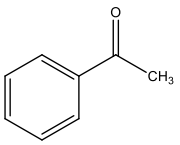
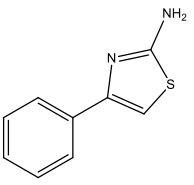
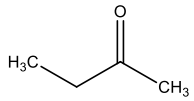
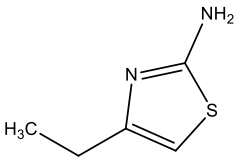
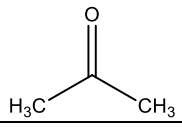
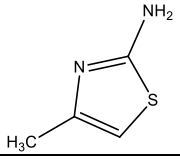
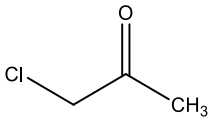
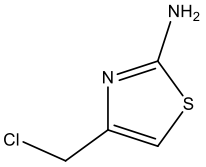
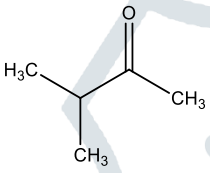
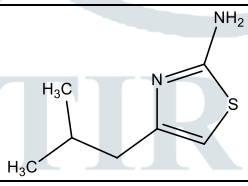
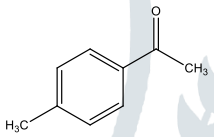
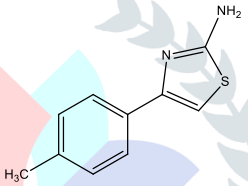
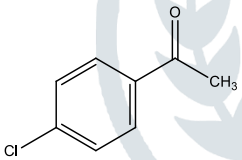
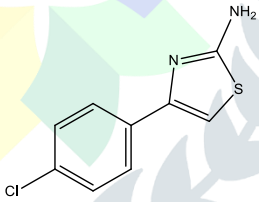
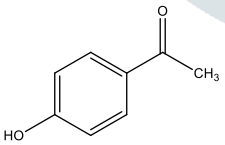
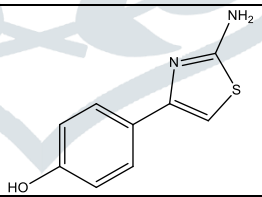
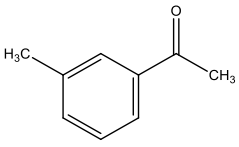
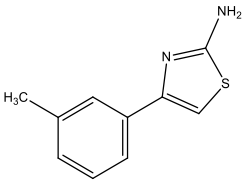
1. R= C_6H_5 2. R= CH_3 3. R= CH_2CH_3 4. R= $CH(CH_3)_2$ 5. R= CH_2-Cl 6. R= C_6H_4-CH_3 7. R= C_6H_4- OCH_3 8. R = C_6H_4-NH_2 9. R= C_6H_4-Br

Table 1: Aliphatic and aromatic ketones are converted into aminothiazoles

Sr. No	Substrate	Product	Time (hrs)	Yield %
1			1.45	91

2			1.40	89
3			1.50	86
4			1.45	89
5			1.30	88
6			1.45	90
7			120	84
8			120	85
9			1.35	85

[a]Reaction conditions: substrate (1 equiv), Thiourea 2 eq. in presence of 5 ml of ionic liquid at room temperature. [b]Isolated yields by column chromatography and structures were confirmed by comparison of ^{1}H NMR and Mass Spectrometer with authentic materials.

To investigate generality of the reaction variety of substrates were reacted with optimized reaction condition. In order to study the promising and general applicability of the developed methodology, various substituted acetophenone containing different functional groups were subjected to this transformation. We

observed that electron donating as well as electron withdrawing groups provided significant yield of products. A variety of functional groups including, methyl, ethyl, were well tolerated and gave good yield (table 1, entry 2,6,). All formed products were characterized by comparing spectral properties and comparing their physical properties with that of reported compounds in the literature. Detail data is presented in the experimental section. All 2-aminothiazoles showed characteristic features

Experimental

Melting points were determined with Melting point apparatus using open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker spectrometer at 400 MHz. he reactions were monitored by TLC using 0.25 mm E-Merck silica gel 60 mesh precoated plates, which were visualized with UV light

Preparation of $[NMP]^+ [HSO4]^-$

1-Methyl-2-pyrrolidinone (0.2mol) was charged into a 250 mL three necked flask equipped with a magnetic stirrer. Then equimolar concentrated sulphuric acid (98 wt%) was added drop wise slowly into the flask at 80 1C for 12 h. The mixture was washed with ether three times to remove non-ionic residues and dried in vacuum using a rotary evaporator to obtain the clear and viscous $[NMP]^+[HSO4]^-$[28] which was used for preparation of 2-aminothiazole derivatives without any further purification (Scheme 1).

General experimental procedure for synthesis of 2-aminothiazole derivatives:

Substituted ketone (1 mmol), and thiourea (2 mmol), mixed in [NMP] (5mL) were placed in a 25mL round bottom flask fitted with a water condenser. The reaction mixture was stirred at room temperature for desired time mentioned in Table 1, and then a sufficient amount of cold water was added. The precipitated product was filtered from the reaction mixture by addition of a sufficient amount of water into the reaction mixture and washed with water. For the purpose of recycling and reusability of the ionic liquid, water was evaporated from the solvent under vacuum and as such used for the next reaction. During the progress of the reaction consumption of the reactant as well as conversion of the product was confirmed by TLC. The results of time required for reaction and corresponding yields are summarized in Table 1. It was observed that ionic liquid has very high activity and gives excellent conversion for reaction of acetophenone.

Table 1, Entry 1, (4-phenylthiazol-2-amine**), IR (KBr)**, cm^{-1}: 3320, 3189, 2920, 1616, 1520,cm^1. **^{1}H NMR** (400 MH_Z, $CDCl_3$); δ, ppm: 7.72-7.76 (d, j =7.7, 2H), 7.33-7.36 (d, j =7.4, 2H), 7.30-7.35 (m, 2H), 5.75 (br, s, 2H). Colorless solid

Table 1, Entry 2, (4-ethylthiazol-2-amine**), IR (KBr),** cm^{-1}: 3330, 3187, 2926, 1362 cm^{-1}. **^{1}H NMR** (400 MH_Z, $CDCl_3$); δ, ppm: 1.22(t, 3H), 3.07(q, 2H), 6.44 (s, 1H), 6.99 (br, s, 2H).

Table 1, Entry 3, (4-methylthiazol-2-amine**), IR (KBr),** cm^{-1}: 3225, 3092, 2926, 1616, 1519, 1367 cm^{-1}, **^{1}H NMR** (400 MH_Z, $CDCl_3$); δ, ppm: 7.67 (d, J=7.7, 2H), 7.29(d, J=7.5, 2H), 2.34(s, 3H), 6.2 (s,2H),
Table 1, Entry 4, 4-(chloromethyl) thiazol-2-amine**, IR (KBr),** cm^{-1}: 3320, 3182, 2906, 1626, 1519, 1327 cm^{-1}. **^{1}H NMR** (400 MH_Z, $CDCl_3$); δ, ppm: 7.51 (d, j =7.8, 2H), 7.0 (d, j =7.4, 2H), 6.21 (s,2H), 7(br s, 2H).

Table 1, Entry 5, (4-isobutylthiazol-2-amine**), IR (KBr),** cm^{-1}: 3315, 3172, 2916, 1369 cm^{-1}. **^{1}H NMR** (400 MH_Z, $CDCl_3$); δ, ppm: 2.22(s, 3H), 6.48(s, 1H), 6.95 (s, 2H, NH_2)

Table 1, Entry 6, 4-(p-tolyl) thiazol-2-amine, **IR (KBr),** cm^{-1}: 3402, 3240, 1500, 715; **^{1}H NMR** (400 MHz, $CDCl_3$); δ, ppm: d 7.65(d, *J* = 6.8, 2H), 7.12 (d, *J* = 7.2, 2H), 7.10 (s, 1H), 6.92 (s, 2H);

Table 1, Entry 7, 4-(4-Chlorophenyl) thiazol-2-amine, **IR (KBr),** cm^{-1}: 3400, 2900,1629,1570,1487,735; **^{1}H NMR** (400 MHz, $CDCl_3$,); δ, ppm: 7.19 (1H, S, thiazole C-H), 7.50 (2H, J= 8.4 Hz Ar-H), 7.69 (2H, J= 8.4 H, Ar-H), 8.82 (s, 2H, NH_2)

Table 1, Entry 8, 4-(4-Hydroxyphenyl) thiazol-2-amine; **IR(KBr),** cm^{-1}: 3435, 2927, 1625, 1520, 1425, 824; **^{1}H NMR** (400 MHz , $CDCl_3$); δ, ppm: 6.61 (d, J = 8.5 Hz, 2H, Ar-H), 6.70 (s, 1H, thiazole), 6.91 (s, 2H, NH_2), 7.57 (d, J = 8.5 Hz, 2H, Ar-H), 9.52 (s, OH).

Table 1, Entry 9, 4-(3-Methylphenyl) thiazol-2-amine, **IR(KBr),** cm^{-1}: 3400, 2910, 1521,1600, , 1448, 715; **^{1}H NMR** (400 MHz, $CDCl_3$): δ, ppm: 2.34(s, 3H, CH_3), 6.85 (s, 1H, thiazole), 7.00 (s, 2H, NH_2), 6.95 (d, J =7.8 Hz, 1H, Ar-H), 7.20 (t, 1H, J = 7.9 Hz, Ar-H), 7.48 (d, J = 7.9Hz, 1H, Ar-H), 7.30 (s, 1H, Ar-H).

RESULT AND DISCUSSION:

To expand a suitable methodology for formation of 2-aminothiazole, initially the plane ketone (1 mmol), and thiourea (2 mmol), mixed in [NMP] (5mL) were placed in a 25mL round bottom flask fitted with a water condenser. The reaction mixture was stirred at room temperature for desired time and then a sufficient amount of cold water was added. The precipitated product was filtered from the reaction mixture by addition of a sufficient amount of water into the reaction mixture and washed with water as expected product was obtained in exceptional yields in 1-2 hrs. Completion of the reaction was monitored by Thin Layer Chromatography (TLC). After completion of reaction, workup carried out as given in experimental procedure, pure product was isolated by column chromatography.

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