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AN EFFICIENT SYNTHESIS OF 2-AMINOBENZOTHIAZOLE AND ITS DERIVATIVES IN IONIC LIQUIDS

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ABSTRACT: The 2-aminobenzothiazole moiety and its derivatives have immense importance in medicinal and pharmaceutical chemistry as a potent biologically active molecules. The synthesis of 2-aminobenzothiazole derivatives carried out from substituted phenyl thiourea which is synthesized by substituted aniline in ionic liquid (1-butyl-3-methylimidazolium) bisulphate ($[BMIM]^+[HSO_4]^-$), (1-butyl-3-methylimidazolium) tetrafluoroborate ($[BMIM]^+[BF_4]^-$) and (1-butyl-3-methylimidazolium) hexafluorophosphate ($[BMIM]^+[PF_6]^-$). Further N-alkylation at amino group of synthesized 2-aminobenzothiazoles was carried out with alcohol using conc. H_2SO_4 and Schiff bases are also prepared by reaction of substituted 2-aminobenzothiazoles and aromatic aldehydes. ILs are green alternate of volatile organic solvents and they are beneficiary environmentally and economically. The reactivity, reaction rate and yield were enhanced by using ILs and the products were recovered by simple filtration. 2-N-alkylaminobenzothiazoles and Schiff base derivatives are very important structural units in many medicinal compounds. The synthesized compounds can show many biological activities like antitumor, antimicrobial and anti analgesic. The characterization of synthesized compounds was done by elemental and spectral analysis.

INTRODUCTION: Heterocyclic chemistry is one of the most complex branch of organic chemistry. Heterocyclic compounds show high degree of structural diversity. They are accepted as economically useful therapeutic agents. Synthetically produced heterocycles are useful as agrochemicals and pharmaceuticals and play an important role in human life. Nitrogen and Sulphur containing heterocycles represent the core structural units of biologically active compounds.

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The current research is based on development of simple, efficient and general synthetic routes under environment friendly conditions. Heterocyclic ring systems containing nitrogen and sulphur exhibit potent pharmacological activities. Heterocycles have enormous potential as the most promising molecules for the design of new drugs. Ionic liquids (ILs) have applications in dissolution[1] processes, liquid-liquid separations, catalysis [2], extraction and Organic synthesis [3], nanomaterials synthesis [4], ring opening metathesis and polymerization reactions [5]. ILs are excellent solvents as the alternative of volatile organic solvents (VOs) in more environmental benign green technology. ILs offer thermal and chemical stability, very low vapour pressures, non-flammability and ability to act as catalyst.

2-aminobenzothiazoles derivatives show considerable biological [6] and medicinal activities which prompted interest in the development of an efficient green synthesis [7] also used as anticancer agents [8].

There are several methods and conditions reported for the synthesis of substituted 2-aminobenzothiazoles [9], but we tried to make the procedure efficient and simple. In the present work green solvent common IL is used in order to improve the yield.

MATERIAL AND METHODS: Melting points were taken in open glass capillary tube using Gallenkamp melting point apparatus and are uncorrected. The purity of synthesized compounds were checked by thin layer chromatography (TLC) and visualized by UV light or in iodine chamber. The IR Spectra were recorded in KBr on SHIMADZU 8400S FTIR Spectrophotometer and wave no. is given in cm^{-1}. The ^1H NMR were recorded on JEOL AL Spectrometer in $CDCl_3$/Me_2SO-d_6 using TMS as an internal standard at 300.15 MHz, respectively and chemical shift were measured in δ ppm. The elemental analysis (C, H and N) were performed using vario-III analyser at CDRI Lucknow.

The substituted aniline, bromine and chemicals required for ILs which are commercially available were purchased from Sigma Aldrich and used without further purification.

General Method of preparation of substituted 2-aminobenzothiazole (3a-b): Substituted aniline (0.1mol) on reaction with potassium thiocyanate (0.1mol) in the presence of IL (2.0 ml) gives substituted thiourea. Further, in a round bottom flask substituted thiourea (0.1mol) mixed with chloroform was stirred for 15 minutes on a mechanical stirrer. Then a mixture of bromine in chloroform was added drop wise at 0-5^oC with stirring. When bromine was completely added in the mixture further refluxed it for 4 hrs and filtered.

4-methoxy-6-nitro- 2 - aminobenzothiazole (3a): Yellow solid, M.P.: 162 ^oC, IR (KBr, *v/cm*$^{-1}$): 3505, 3300, 1640, 1610, 1540, 1525, 1470, 1345, 1150. ^1H NMR (300.15 MHz, Me_2SO-d_6): δ 8.56 (S, 1H, Ar-H), 7.91 (S, 1H Ar-H), 3.95 (S, 2H, -C-NH_2), 3.63 (S, 3 H, -OCH_3).

6-chloro - 2 - aminobenzothiazole (3b): Yellow solid, M.P.: 197 ^oC, IR (KBr, *v/cm*$^{-1}$): 3458, 3260, 3082, 1634, 1532, 1444, 1302, 1275, 762. ^1H NMR (300.15 MHz, Me_2SO-d_6): δ 7.56-7.31 (m, 3H, Ar-H), 5.39 (S, 2H, –C-NH_2).

General Method of alkylation of substituted 2-aminobenzothiazole (4a-b): The reaction of 2-aminobenzothiazole (0.1mol) and alcohol (0.1mol) in the presence of Conc. H_2SO_4 (5.0 ml) and ILs (2.0 ml) at 100 °C in the air and the product obtained as N-alkylated benzothiazole**.**

N-ethyl-(4-methoxy-6-nitro - 2 - aminobenzothia zole) (4a and 4b): Red solid, M.P.: 207 ^oC, IR (KBr, *v/cm*$^{-1}$): 3490, 2850, 1640, 1610, 1540, 1525, 1470, 1425, 1345, 1150. ^1H NMR (300.15 MHz, Me_2SO-d_6): δ 8.50 (S, 1H, Ar-H), 7.88 (S, 1H Ar-H), 3.92 (S, 1H, -C-NH-C-), 3.62 (S, 3H, -OCH_3), 3.05 (q, 2H, -CH_2-CH_3), 0.95 (t, 3H, -CH_3).

N-ethyl-(6-chloro – 2 -aminobenzothiazole) (4a and 4b): Pale yellow solid, M.P.: 209 ^oC, IR (KBr, *v/cm*$^{-1}$): 3455, 2880, 1634, 1615, 1532, 1444, 1302, 1275, 762. ^1H NMR (300.15 MHz, Me_2SO-d_6): δ 8.15-7.50 (m, 3H, Ar-H), 3.94 (S, 1H, –C-NH-C-), 3.02 (q, 2H, -CH_2-CH_3), 0.97 (t, 3H, -CH_3).

General Method of preparation of Schiff base derivatives of substituted 2-aminobenzothiazole (5a-b): Mixture of 2-aminobenzothiazole (0.01mol) and aromatic aldehyde (0.01mol) is taken in mortar add conc. H_2SO_4 (0.25 ml), water (5 ml) and ILs (2.0 ml) and stirred at room temperature for 30-40 minutes. After the completion of the reaction add 25 ml water. Now filter the separated solid and wash with water and crystalized from ethanol.

Schiff base derivative of (4-methoxy-6-nitro-2-amino benzothiazole) (5a): Orange solid, M.P.: 202 ^oC, IR (KBr, *v/cm*$^{-1}$): 1965, 1640, 1610, 1540, 1525, 1470, 1440, 1345, 1150. ^1H NMR (300.15 MHz, Me_2SO-d_6): δ 8.53 (S, 1H, Ar-H), 7.89 (S, 1H Ar-H), 7.44 (S, 1H, -N=CH-), 7.20 (m, 5H, protons of phenyl ring), 3.63 (S, 3 H, -OCH_3).

Schiff base derivative of (6-chloro-2-aminobenzothiazole) (5b): Yellow solid, M.P.: 192 ^oC, IR (KBr, *v/cm*$^{-1}$): 2860, 1975, 1610, 1530, 1440, 1428, 1310, 1270, 760. ^1H NMR (300.15 MHz, Me_2SO-d_6): δ 7.56-7.31 (m, 3H, Ar-H), 7.48

(S, 1H, -N=CH-), 7.23 (m, 5H, protons of phenyl ring).

Note: In all above methods the progress of the reaction controlled by TLC.

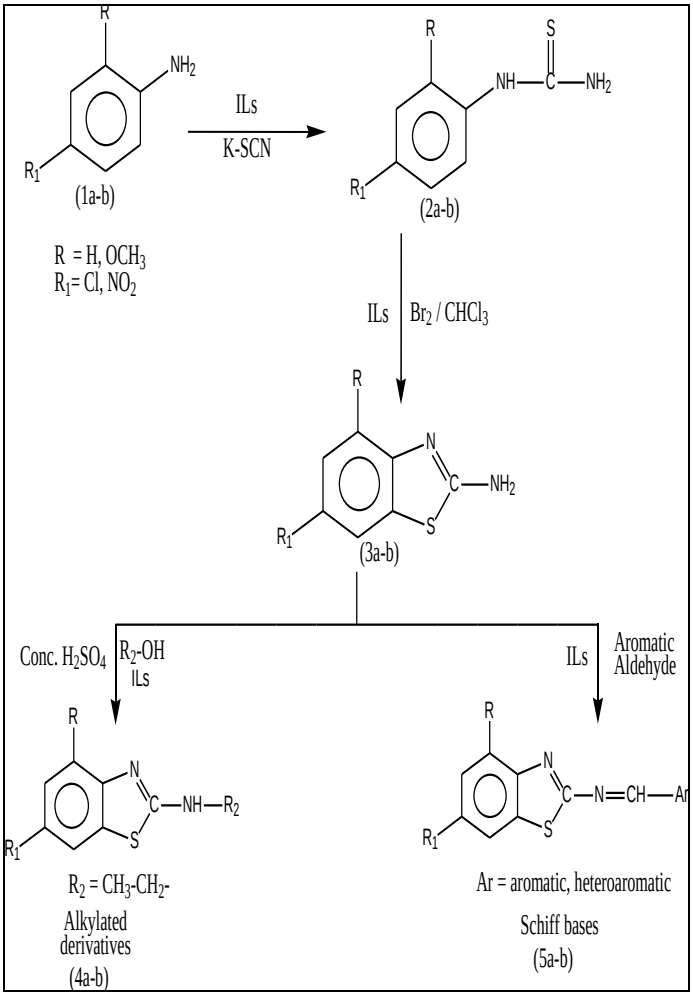
RESULTS AND DISCUSSION: Substituted phenyl thioureas were prepared by the reaction of substituted aniline with potassium thiocyanate in the presence of ionic liquids [10] (ILs) as catalyst at ambident temperature. These synthesized thiourea undergoes cyclization to give corresponding 2-aminobenzothiazoles (**3a-b**) in ILs [11]. The synthesized 2-aminobenzothiazoles were further treated with alcohol in the presence of Conc. H_2SO_4 and ILs to form corresponding N–alkylated substituted benzothiazoles [12-13] (**4a-b**). In other reaction substituted benzothiazoles were treated with aldehyde (Aromatic and heteroaromatic) to form corresponding Schiff bases [14-15] (**5a-b**). The product formation depends on the nature of the attached substituent's means the more electrons releasing group would give more amount of the product than those compounds which have electron attracting groups. Synthesis of all of these compounds shown in the **Scheme 1**.

The proposed structure of synthesized compounds is well supported by elemental analysis and spectral data. The structural assignments to the new compounds were based on their elemental analysis and spectral (IR and ^{1}H NMR) data. The formation of substituted 2-aminobenzothiazoles and their alkylated and Schiff base derivatives was confirmed by ^{1}H NMR and IR spectra. IR spectrum showed sharp absorption bands at 3550-3490 cm^{-1} and 3340-3285 cm^{-1} due to asymmetric and symmetric vibrations of primary amino group respectively in substituted 2-aminobenzothiazole (**3a-b**).

In N-alkylated derivatives of substituted 2-aminobenzothiazoles absorption bands at 3340-3285 cm^{-1} is absent that indicate the absence of $–NH_2$ group and one absorption band at 3550-3490 cm^{-1} is present due to the presence of –NH group. In Schiff base derivatives of substituted 2-aminobenzothiazole absorption bands at 3550-3490 cm^{-1} and 3340-3285 cm^{-1} due to primary amino group are absent and absorption band at 1610 cm^{-1} is present due the –C=N- group.

The appearance of multiplets at δ 8.56-7.31, δ 8.50-7.50 and δ 8.53-7.31 ppm due to aromatic protons for the compounds (**3a-b**), (**4a-b**) and (**5a-b**) respectively. A singlet is observed at δ 3.95 ppm for the compound (**3a**) due to presence of methoxy ($-OCH_3$) group and δ 5.39 ppm for the compound (**3a** & **3b**) due to the presence of $–NH_2$ group.

The appearance of a singlet in the range δ 3.94-3.92 due to the presence of (-NH-) group for the compounds (**4a-b**). The appearance of quartet in the range δ 3.02-3.05 ppm due to the presence of ($–CH_2$-) group and appearance of triplet in the range δ 0.95-0.97 ppm due to the presence of ($-CH_3$) group for the compounds (**4a-b**). A singlet is observed in the range δ 7.44-7.48 due the presence of (-N=CH-) group for the compounds (**5a-b**). The absence of the –NH peak in IR and NMR spectra in compounds (**5a-b**) clarify the synthesis of Schiff bases.



SCHEME: 1

CONCLUSION: 2-aminobenzothiazoles and their derivatives possess a wide range of biological properties hence their moieties are centre of current interest among number of researchers around the world. Among the three different moieties under study, substituted 2-aminobenzothiazoles, their alkylated derivatives and their Schiff bases the last one show more biological properties.

The fundamental goal of medicinal chemistry is the development of new anticancer therapeutic agents. The sufficient amount of an anticancer drug to kill tumor cells is generally toxic to the normal cells and leads to many side effects. In the recent years, special search for the discovery of novel anticancer drugs with fewer side effects than the conventional anticancer drugs has been done. Various alkylated benzothiazole derivatives have been reported as potent anticancer drugs. Benzothiazole derivatives have considerable medicinal and biological properties [6]. The other biological activities of benzothiazole derivatives are antimalarial, antidiabetic, analgesic [16], anti-inflammatory, anti-microbial and anti-tubercular etc.

Here we have carried out the synthesis of compounds in different ionic liquids namely (1-butyl-3-methylimidazolium) bisulphate ($[BMIM]^+[HSO_4]^-$), (1-butyl – 3 - methylimidazolium) tetrafluoroborate ($[BMIM]^+[BF_4]^-$) and (1-butyl-3-methyl imidazolium) hexafluorophosphate ($[BMIM]^+[PF_6]^-$). The catalytic activity and the yields of products is lesser affected by the cationic part of the ILs while it is greatly affected by the Bronsted acidity of anionic part of the ILs. So here we have obtained the excellent yield of product in (1-butyl-3-methylimidazolium)bisulphate ($[BMIM]^+[HSO_4]^-$), while moderate yield in later two ILs namely (1-butyl-3-methylimidazolium) tetra fluoroborate ($[BMIM]^+[BF_4]^-$) and (1-butyl-3-methyl imidazolium) hexafluorophosphate ($[BMIM]^+[PF_6]^-$). The comparative yield of product shown in **Table 1**.

TABLE 1: COMPARATIVE %YIELD OF THE PRODUCTS

Compound	% Yield in $[BMIM]^+[HSO_4]^-$	% Yield in $[BMIM]^+[BF_4]^-$	% Yield in $[BMIM]^+[PF_6]^-$
3a.	94	85	82
3b.	92	80	75
4a.	90	78	76
4b.	91	82	79
5a.	93	76	80
5b.	90	79	83

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REFERENCES:

1. Swatloski RP, Spear SK, Holbrey JD and Rogers RD: Dissolution of Cellose with Ionic Liquids. Journal of American chemical Society 2002; 124: 4974-4975.
2. Ratti R: Ionic Liquids: Synthesis and Applications in Catalysis. Advances in Chemistry 2014; 1-16.
3. Kuchenbuch A and Giernoth R: Ionic Liquids beyond Simple Solvents: Glimpses at the State of the Art in Organic Chemistry. Chemistry Open reviews 2015; 4: 677 –681.
4. Ferraz R, Prudêncio C, Vieira M, Fernandes R, Noronha JP and Petrovski Z: Ionic Liquids Synthesis – Methodologies. Organic Chemistry Current Research. 2015; 4: 1-2.
5. Vygodskii YS, Shaplov AS, Lozinskaya EI, Filippov OA, Shubina ES, Bandari R and Buchmeiser MR: Ring-Opening Metathesis Polymerization (ROMP) in Ionic Liquids: Scope and Limitations. Macromolecules. 2006; 39: 7821-7830.
6. Bondock S, Fadaly W and Metwally MA: Enaminonitrile in heterocyclic synthesis: Synthesis and antimicrobial evaluation of some new pyrazole, isoxazole and pyrimidine derivatives incorporating a benzothiazole moiety, European Journal of Medicinal Chemistry. 2009; 44: 4813-4818.
7. Bhoi MN, Borad MA and Patel HD: Synthetic Strategies For Fused Benzothiazoles: Past, Present, And Future. Synthetic Communications. 2014; 44: 2427–2457.
8. Shabana AA, Butler IS, Gilson DFR, Jean-Claude BJ, Mouhri ZS, Mostafa MM and Mostafa SI: Synthesis, characterization, anticancer activity and DNA interaction studies of new 2-aminobenzothiazole complexes; crystal structure and DFT calculations of $[Ag(Habt)_2]ClO_4$. Inorganica Chimica Acta 2014; 423: 242-255.
9. Khatun N, Jamir L, Ganesh M and Patel BK: A one-pot strategy for the synthesis of 2-aminobenzothiazole in water by copper catalysis. RSC Advances. 2012; 2: 11557-11565.

10. Xiao M L, Chen F H, Chen Z J, Guo B S, Lv X H and Tang W M: Facile synthesis of thiourea derivatives in ionic liquid, Chinese Chemical Letters 2007; 18: 258.
11. Bhavsar A, Makone S and Shirodkar S: Synthesis of Benzimidazole and Benzthiazole Derivatives by Using Ionic Liquids. International Journal of Advanced Research in Science, Engineering and Technology 2016; 3: 2485-2487.
12. Li F, Shan H, Kang Q and Chen L: Regioselective N-alkylation of 2-aminobenzothiazoles with benzylic alcohols. Chemistry Communications. 2011; 47: 5058–5060.
13. Natrajan A and David W: Facile N-alkylation of acridine compounds in Ionic liquids. U.S. Patent 2012, US 8293908 B2 20121023.
14. Etaiw SEH, Abd El-Aziz DM, Abd El-Zaher EH and Ali EA: Synthesis, spectral, antimicrobial and antitumor assessment of Schiff base derived from 2-aminobenzothiazole and its transition metal complexes. 2011; 79: 1331-1337.
15. Bhoi MN, Borad MA, Panchal NK and Patel HD: 2-Aminobenzothiazole containing novel Schiff bases derivatives: Search for new Antibacterial agents. International Letters of Chemistry, Physics and Astronomy. 2015; 53: 106-113.
16. Raju DN, Devi DVRS, Aghastina DG, Rao KG and Kumar KS: Synthesis, Characterization and Analgesic Activity of Some Novel Substituted 2-Amino Benzothiazole Derivatives. World Journal of Pharmacy and Pharmaceutical Sciences 2015; 4: 1815-1821.

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