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Research Article

Morpholine-Based Novel Ionic Liquid for Synthesis and Characterization of Triazolidinethiones and Their Biological Properties

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Abstract

Keeping the green chemistry approach in mind we have synthesized a novel morpholine-based ionic liquid $[NBMMorph]^+Br^-$. The structure of Ionic liquid was confirmed by spectral techniques *viz*. IR, ^1H NMR, and ^{13}C NMR, analysis. The synthesized novel IL $[NBMMorph]^+Br^-$ was utilized to prepare 1,2,4-triazolidine-3-thiones of biological significance. The $[NBMMorph]^+Br^-$ IL shows excellent catalytic activity, and a simple filtration technique can separate the thiazolidinedione products. The structure of the synthesized compounds were confirmed using IR and NMR techniques. All the synthesized compounds were screened for their antimicrobial activity. All compounds shows outstanding biological activity.

Keywords

Triazolidinethiones; morphiline; ionic liquid; biological properties

1. Introduction

In modern synthetic chemistry, developing heterocyclic compounds from simple precursors is a challenging and emerging area for the scientific community [1-6]. The five membered heterocycles with 3 nitrogen and 2 carbon atoms in the skeleton are known as Triazole, one of the prime class of heterocycles [7, 8]. The positions of nitrogen atoms divide triazoles into two categories *viz.* 1,2,3- and 1,2,4-triazoles. The variety of triazole compounds especially 1,2,4-triazoles are widely studied and owe a significant impact because of their curious pharmacological properties. The literature survey reveals that diversity of biological aspects of 1,2,4-Triazoles have been discovered through the analysis of antifungal, cytotoxic, antibacterial, anti-inflammatory, antidepressant, anti-tubercular, analgesic, and anticancer properties [9-17]. Additionally, plant growth regulating activity of triazole increases agriculture demand through research and development. Such biodiversity and applications imply the voyage for new synthetic methodologies in developing 1,2,4-triazole-based thiones derivatives amongst the researchers.

It is well known that organic chemistry is always on the edge of the pharmaceuticals, petrochemicals and biotechnology area. Organic synthesis can be simplified by using ionic liquids (ILs), well-known as eco-friendly catalysts, versatile reaction mediums, and safe solvents. ILs attributed to low vapor pressure, high chemical, thermal and electrochemical stability, significant viscosity and low flammability make them more suitable and important materials in synthetic methodologies. Organic synthesis, catalysis, extraction and CO_2/SO_2 capture are a few areas where ILs are widely applied [18]. The non-corrosive and non-volatile nature of ILs resists air oxidation. The recycling ability received notable research of interest in bromide-functionalized ILs and their application in synthesizing heterocycles [19, 20].

1,2,4-triazolidinethiones or their interrelated derivatives showed interesting biological properties, including acetylcholinesterase inhibition, anti-cancer, anti-HIV, antimycobacterial, anti-viral, antiepileptic, anti-allergic, antidepressant, carbonic anhydrase, and analgesic activities [20-27]. Nowadays, the design and synthesis of 1,2,4-triazolidine-3-thiones and evaluating their biological aspects are in challenging, demanding and advantageous research interest mode. The reported methods fail to follow the green synthetic approach or have no remarkable biological activities. Now it's time to replace hazardous methods with a greener and more sustainable process. Green chemistry is an emerging tool for maximizing the efficiency of eco-friendly processes and products and minimizing the generation of hazardous substances. The environmentally friendly solvents are known as Green solvents [28-31]. Many green solvents include ionic liquids, supercritical fluids, water, and supercritical water. These green solvents are much more eco-friendly, less toxic, and less hazardous than traditional volatile organic solvents (VOCs). Green chemistry helps to conserve natural resources and reduces pollution by eliminating waste and hazardous materials. Therefore, we design to adopt a green chemistry approach such as using green solvents and some catalyst with the solvent-free condition. Therefore, the main motivation to perform the present research work was the synthesis of 1,2,4-triazolidine-3-thiones by using novel ionic liquid for their bio-evaluation against antibacterial activity. We have disclosed an efficient, one-pot multi-component approach for 5-aryl–[1,2,4]triazolidine-3-thione from various aldehydes as precursors in the presence of the catalytic amount of synthesized IL. Ethanol is classified as an environmentally preferable green solvent because it is available by fermenting renewable sources, including sugars, starches, and lignocelluloses. Hence, we have used ethanol as a green solvent for

this transformation. The main merits of the present research work are the high practical yield, ease in the workup procedure, and novelty in multi-component strategy.

2. Experimental Section

2.1 General

The various substituted aldehydes (Alfa Aesar), thiosemicarbazide (spectrochem), morpholine (spectrochem), and *N*- butyl bromide (spectrochem) were used as received without further purification. The open capillary method was followed to determine the melting points of synthesized derivatives. IR spectra were recorded on a Shimadzu IR Affinity 1- S Diamond ATR spectrophotometer. NMR spectra were recorded on a Bruker AVANCE NEO 500 MHz FT-NMR spectrometer in DMSO-d_6 using tetramethylsilane as an internal standard.

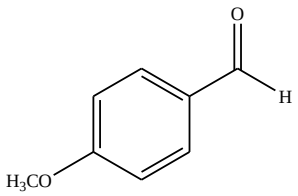
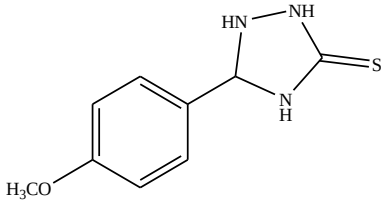
2.2 General Procedure for Synthesis of Ionic Liquid (NBMMorph]$^+$Br$^-$

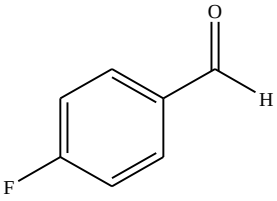
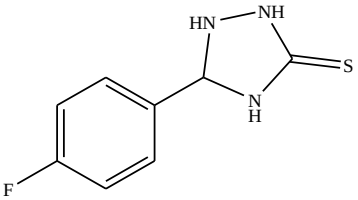
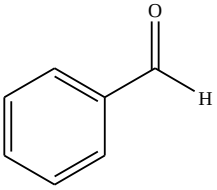
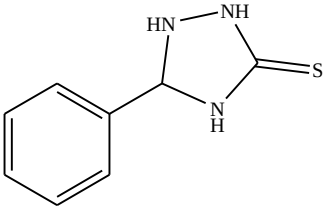
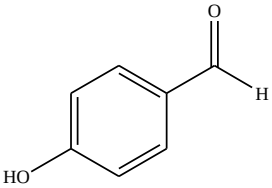
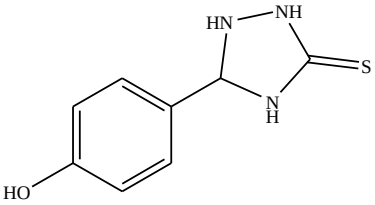
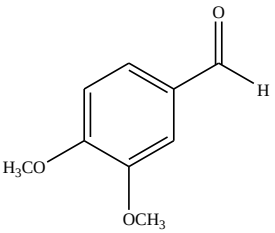
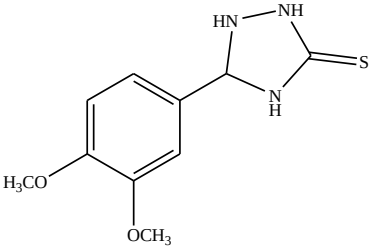
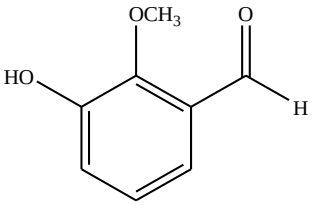
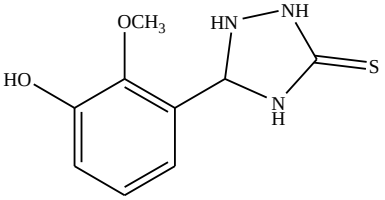
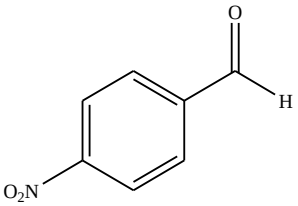
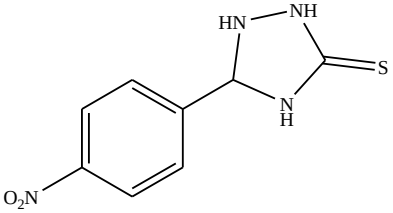
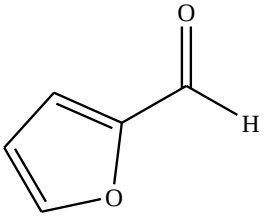
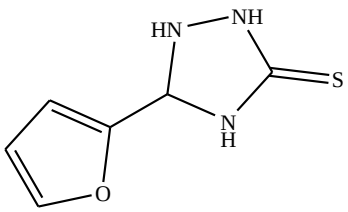
1 mmol of *N*-butyl bromide and 1 mmol of *N*-methyl morpholine were taken in 50 mL round bottom flask. This reaction mixture was heated in the sand bath for 5 hours. The progress of the reaction was monitored by using TLC. The corresponding semi-solid product was obtained in appreciable yield which was further allowed to filter. The obtained product was kept in a sealed amberlite bottle. The structure of the product was confirmed by UV, IR, ^{1}H and ^{13}C NMR.

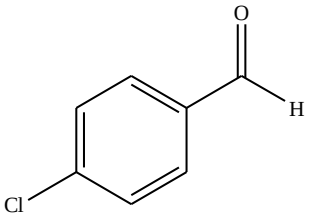
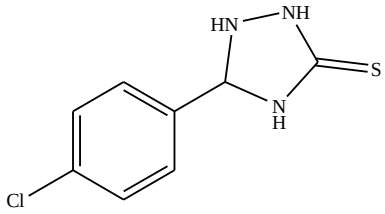
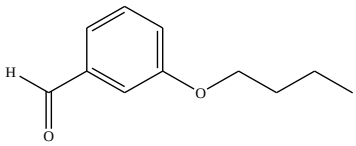
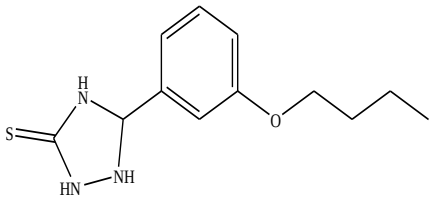
2.3 General Procedure for Synthesis of -5-Aryl-[1,2,4]Triazolidine-3Thiones Derivatives from Various Aldehyde

1 mmol of corresponding aldehyde and 1 mmol of thiosemicarbazide in ethanol were mixed in 25 mL round bottom flask. To the same mixture 10 mol% of synthesized acidic ionic liquid was added. The reaction mixture was allowed to stir for a specific time as mentioned in Table 1. To examine the movement of the reaction, the TLC method was used. After getting the confirmation from TLC about the completion of the reaction, the reaction mixture was added to ice-cold water, followed by rapid stirring. Then the product was separated by a simple filtration technique. After filtration the product was recrystallized with ethanol. The corresponding products were received in appreciable yield. The formation of expected product was confirmed by using IR and Melting point.

Table 1 Ionic liquid catalyzed library of 5-aryl –[1,2,4]triazolidine-3-thiones.

ENTRY	ALDEHYDE USED	PRODUCT	TIME [min]	YIELD (%)	MP.°C
1		 R1D	25	85	164

2		 R2D	30	53	200
3		 R3D	35	70	153
4		 R4D	25	68	235
5		 R5D	30	74	220
6		 R6D	30	65	210
7		 R7D	30	69	290
8		 R8D	35	94	170

9		 R9D	30	72	240
10		 R10D	25	95	160

*Reaction conditions at RT: Aldehyde (1 mmol), thiosemicarbazide (1 mmol), catalyst: 10 mol% $[NBMMorph]^+Br^-$, ethanol (5 ml).

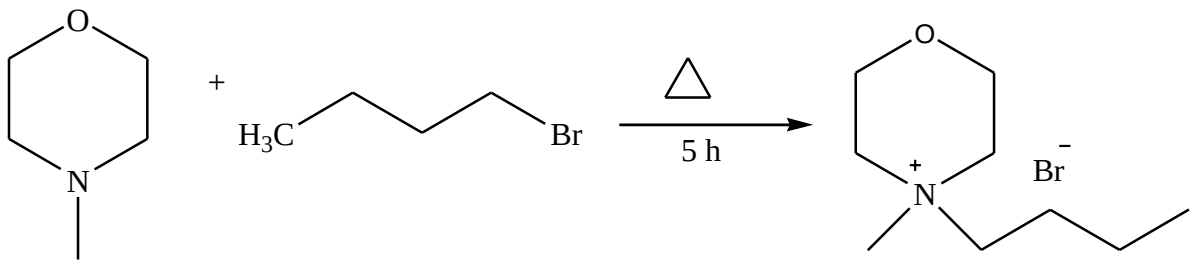
2.4 Antimicrobial Activity

All the synthesized compounds in the present work were examined for their biological activity such as antibacterial aspects of designed 5-aryl-[1,2,4]triazolidine-3-thiones derivatives from aldehyde on *pseudomonas aeruginosa.* The disc diffusion assay (Quantity per disc-10) method was used to determine the antibacterial properties & minimum inhibitory concentration (MIC) of different derivatives against gram-negative bacteria *pseudomonas aeruginosa.* The growth media was maintained at pH 6.7. All the derivatives show good results and exhibit antibacterial activities against tested microorganisms. The following conditions for the analysis include The Disc Diffusion Assay (Quantity per dise-10 µl) with inoculums used: 1 × 10 CFU/ml at incubation temperature: 37° C or the incubation Time of 24 hr in growth media of sterile nutrient agar at pH 6.7 against the bacterial culture of *Pseudomonas aeruginosa* [32-34].

3. Result and Discussion

3.1 Synthesis of Catalyst-Ionic Liquid – $[NBMMorph]^+Br^-$

Firstly we focused on the synthesis of catalyst by considering the advantages of morpholine, we decided to synthesize morpholine-based IL. First, we performed the reaction between Morpholine and *N*-butyl bromide at equimolar conditions. Scheme 1 shows a representation of the reaction between morpholine and *N*-butyl bromide. The reaction was carried out in a sand bath for 5 hours. The formation of desired IL was confirmed using spectral techniques, *i.e.,* IR, ^{1}H NMR (Figure 1) and ^{13}C NMR (Figure 2). All the spectral data is in accordance with the structure.



[NBMMorph]+Br -

Scheme 1 Synthesis of ionic liquid $[NBMMorph]^{+}Br^{-}$.

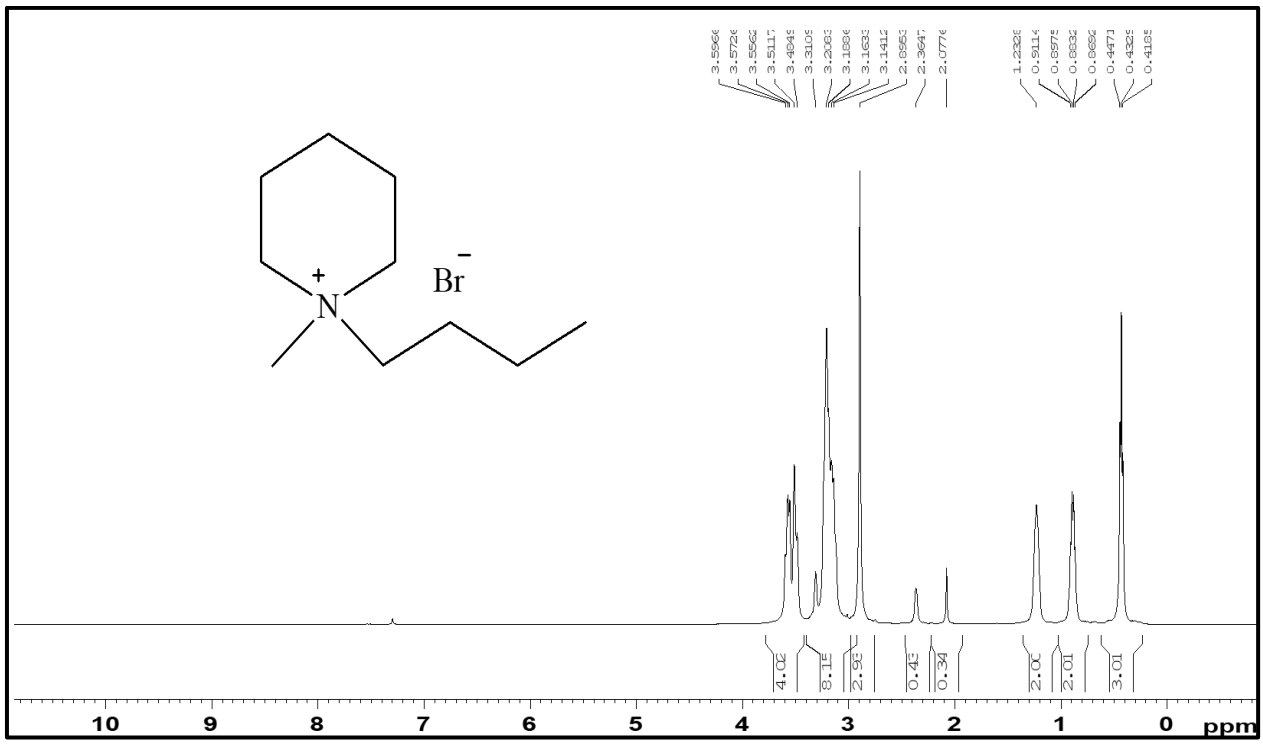


Figure 1 ^{1}H NMR of ionic liquid.

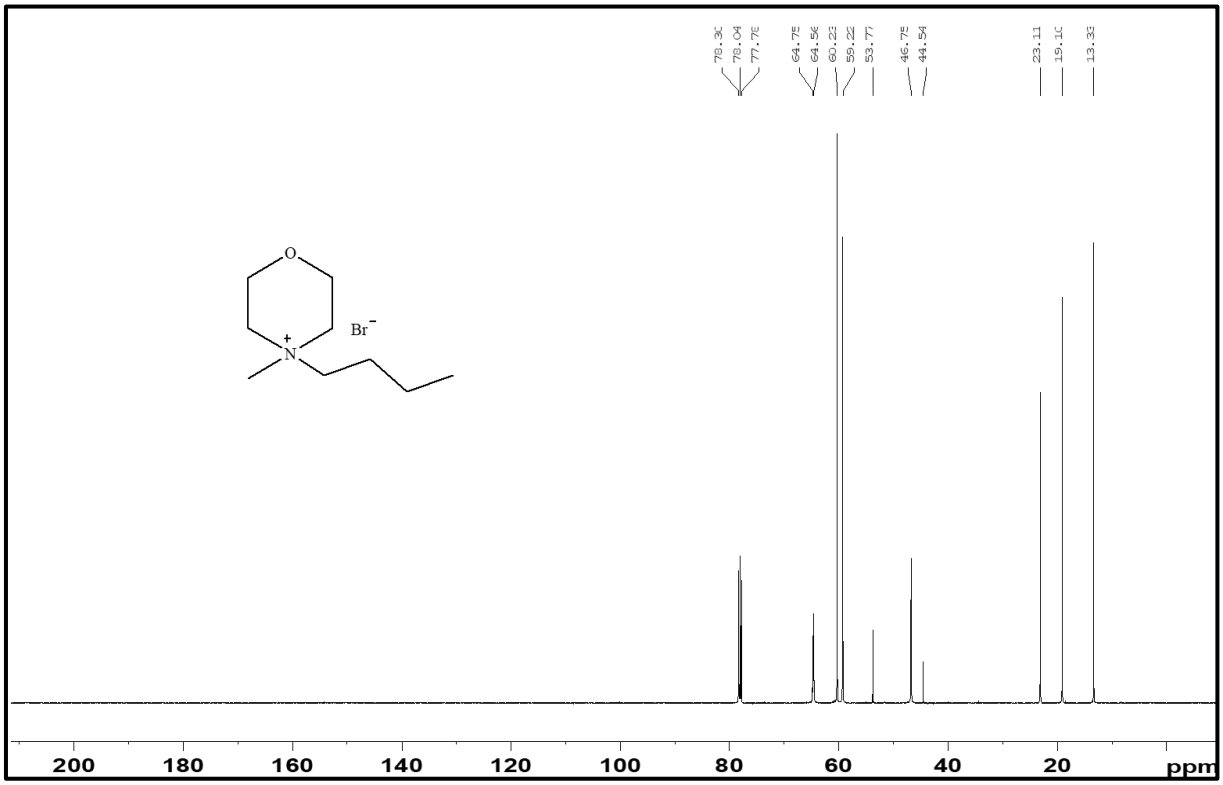
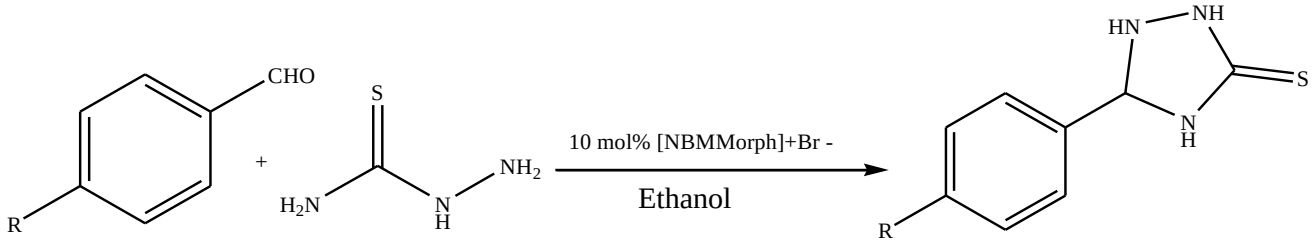


Figure 2 ^{13}C NMR of ionic liquid.

3.2 Synthesis of Target 1,2,4-Triazolidine-3-Thiones

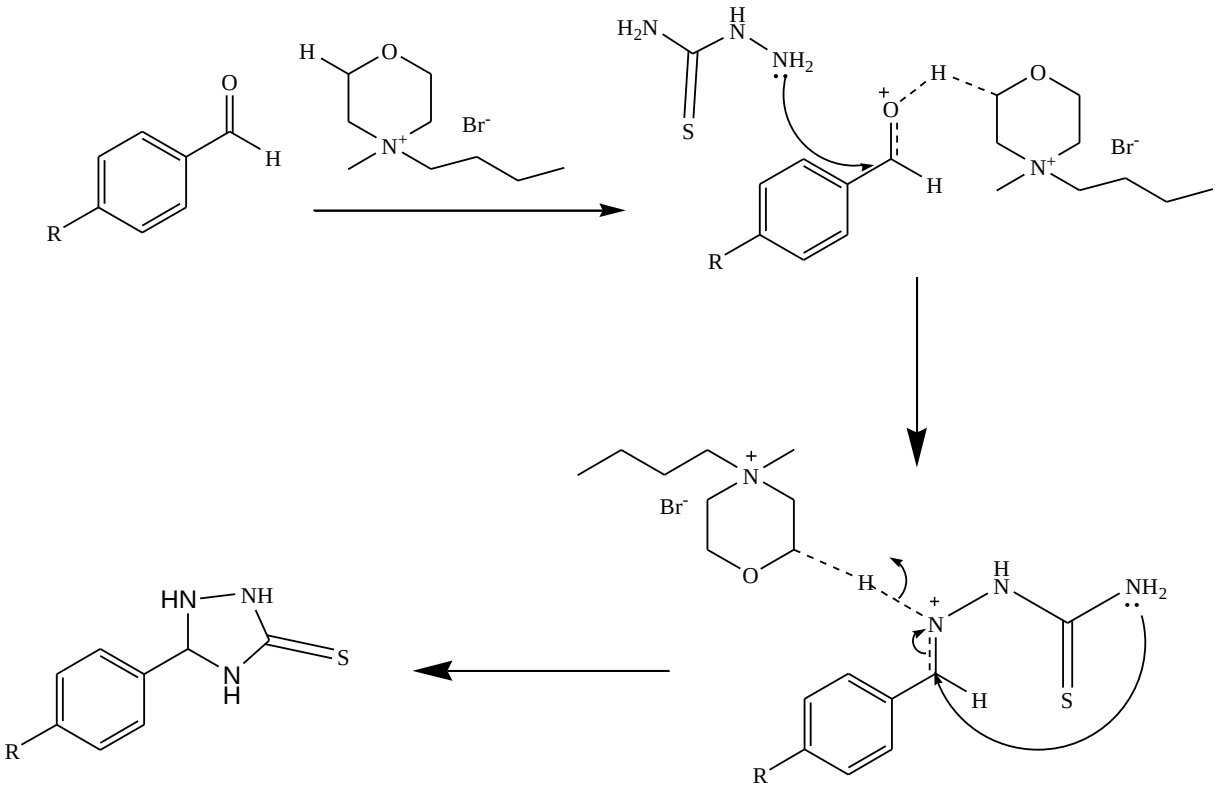
After the successful synthesis of IL we used the reaction between various substituted aldehydes and thiosemicarbazide to deliver the expected target products of 1,2,4-triazolidine-3-thiones in ethanol using synthesized acidic IL as catalyst (Scheme 2) at room temperature.



Scheme 2 Synthesis of 1,2,4-triazolidine-3-thione derivatives at room temperature.

The detailed mechanism of formation of target thiones is discussed in brief herein and shown in Scheme 3. When catalytic amount of IL was added to the starting aldehyde it forms complexation because the hydrogen in $–CH_2$ of morpholine near oxygen is more reactive. It forms a weak bond with the oxygen of carbonyl functionality in aldehyde. The highly soluble complexation indicates an increase in the charge on the oxygen of carbonyl moiety. Subsequently instability increase and the reactivity of the carbonyl group at the carbon center increases. Adding an equimolar quantity of thiosemicarbazide shows an attack of $–NH_2$ (hydrazine side of thiosemicarbazide) on carbon of carbonyl functionality. In order to achieve stability, the cyclization plays a pivotal role in forming a five-membered ring structure by the attack of $–NH_2$ (amine side of thiosemicarbazide) on carbon by

leaving the homogeneous (hydrophilic) IL in the last step of reaction work-up. The proposed mechanism for the transformation is given in Scheme 3.



Scheme 3 Proposed mechanism for the synthesis of 1,2,4-triazolidine-3-thione.

Initially, optimizing the reaction conditions for the synthesis of target compounds was crucial. In order to achieve the optimization of reaction conditions, we studied the reaction of anisaldehyde (1 mmol) and thiosemicarbazide (1 mmol) as the model reaction. The catalyst screening was done using various acidic catalysts such as sulphuric acid, *p*-TSA, CAN and synthesized ionic liquid $[NBMMorph]^+Br^-$ at room temperature (Table 2, entries 1-6). When H_2SO_4, *p*-TSA and CAN (Table 2, entries 1-3) were used as catalysts (20 mol%), we found that the time required to complete the reaction was significant and the yield of the product was low compared to the same loading of synthesized IL. However, loading the same 20 mol% of synthesized IL for the same reaction approach delivers superior results for the reaction time of 30 minutes along with about 78% product yield. Hence, we conclude that satisfyingly superior catalytic activity was found in the case of synthesized ionic liquid with excellent product yield in a short period of reaction time as compared with the other catalytic conditions.

Table 2 Optimization of reaction conditions.

Sr. No.	Catalyst	Loading (mol%)	Time (min)	Yield (%)
1	H_2SO_4	20	30	71.64
2	P-TSA	20	40	55.00
3	CAN	20	40	60.00
4	$[NBMMorph]^+Br^-$	20	30	78.00

5	[NBMMorph]$^{+}$Br^{-}	10	25	85.00
6	[NBMMorph]$^{+}$Br^{-}	05	35	74.00

*Reaction conditions at RT: Anisaldehyde (1 mmol), thiosemicarbazide (1 mmol), Solvent: ethanol (5 ml).

Further, optimizing IL loading by varying its amount (Table 2, entries 4-6) suggests that lesser reaction time and excellent product yield could be obtained under only 10 mol% loading of synthesized IL to drive the reaction forward (Table 2, entry 5). However, an increase in the amount of catalyst to 20 mol% indicates a slight decline in the product yield but the time to complete the transformation remains comparably the same (Table 2, Entries 4). Hence, it was concluded that to perform the present organic transformation, only 10 mol% of synthesized IL is enough as a catalyst.

The generality of the protocol was then investigated using a variety of aldehydes (Table 1, Entries 1-10). It was noted that whatever the nature of the substituent on the aldehyde, it furnished the expected substituted -5-aryl-[1,2,4]triazolidine-3thiones in good yields within a short reaction time. The reaction was also carried out using heterocyclic aldehyde, *i.e.,* furfuraldehyde (Table 1, Entry 8). This reaction proceeded well with an excellent yield of the desired product. The structure of all the synthesized products has been confirmed by IR and by comparing the melting points with available literature.

As 1,2,4 triazole derivatives are biologically important, we were interested in studying the biological importance of synthesized compounds. Hence we have screened all the synthesized compounds for their antimicrobial activity.

3.3 Antimicrobial Activity

Antibacterial activity is the most important characteristic of medical materials, to provide adequate protection against microorganisms, biological fluids, and aerosols, as well as disease transmission [10-18]. We have tested all synthesized derivatives of -5-aryl-[1,2,4]triazolidine-3thiones for the antimicrobial activity using disc diffusion assay as protocol (Figures 3A and 3B) and the results obtained are interpreted in Table 3. The antimicrobial activity is proven by observing the zone of inhibition. All the samples exhibited exceptional antimicrobial activity. Out of these R6D indicated fewer inhibitions zone. The compound R6D has phenolic -OH and methoxy group –OCH_3. The bacteria pseudomonas aeruginosa resists this derivative.

Figure 3 Test of antibacterial activity using disc diffusion assay (quantity per disc -10 µ) A) for R8D, B) for all synthesized 5-aryl-[1,2,4]triazolidine-3-thiones.

Table 3 Antibacterial activity of synthesized triazolidine-thiones derivatives using disc diffusion assay.

Sr.No.	SAMPLE ID	Inhibition zone diameter (mm) against *Pseudomonas aeruginosa.*
1	R1D	13
2	R2D	14
3	R3D	13
4	R4D	14
5	R5D	10
6	R6D	06
7	R7D	10
8	R8D	23
9	R9D	11
10	R10D	09

*No inhibition. The experiment was repeated three times.

R8D shows significant results. It shows more inhibitions zone (Figure 3). R8D is a compound having a furan ring in its structure. In this report, wet disc assay and agar well diffusion assay results werecompared testing the susceptibility of Pseudomonas aeruginosa. Based on the results it can be concluded that all the samples showed admirable antibacterial activity.

4. Conclusion

Herein we have synthesized an efficient and versatile IL ($[NBMMorph]^+Br^-$) based catalyst for the preparation of 5-aryl-[1,2,4]triazolidine-3-thiones. The formation of synthesized IL was confirmed by well know own spectroscopic techniques such as IR, NMR and Mass analysis. Compared to the hazardous catalyst, synthesized IL shows a superior response in terms of reaction time and yield of products. The derivatives of triazolidinediones were successfully derived by using IL as a catalyst in the present proposed protocol which signifies ease in workup procedures, lesser reaction time and a high yield of products. The derived all thiones derivatives were examined for their antibacterial properties using the disc diffusion method. Surprisingly, it was found that all the derived derivatives of thiones show excellent antibacterial properties against *Pseudomonas aeruginosa* with minimum inhibition concentration. To conclude, the merits of the present research work are the modified approach of synthetic protocol, synthesized bromide functionalized IL, and antibacterial properties of derived thiones. The biological properties of synthesized compounds could open a new window for the further application of these derivatives in pharmaceuticals, paint industries, agrochemicals, etc.

Author Contributions

Randive CS, Tamhane OS and Ghorpade RS performed experimental part. Dr. S. R, Kale, Dr. N. C. Dige and Dr. P. G. Mahajan discussed analysis of results. Dr. P. G. Mahajan and Dr. N. C. Dige designed proposed work, analysis of results and writing.

Competing Interests

The authors have declared that no competing interests exist.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Figure S1: ^{1}H NMR of Ionic liquid.
2. Figure S2: IR of R1D.
3. Figure S3: IR of R2D.
4. Figure S4: IR of R3D.
5. Figure S5: IR of R7D.
6. Figure S6: IR of R9D.
7. Figure S7: IR of R10D.

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