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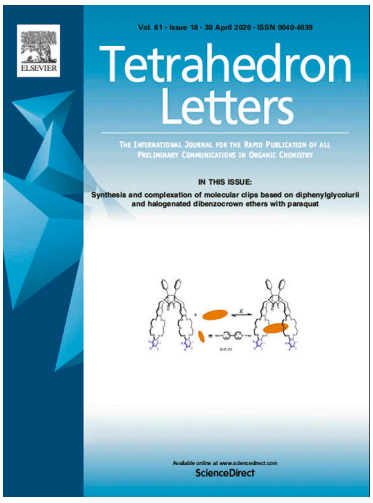

Novel, Green and Sustainable Route for Synthesis of 5-Aryl-4-Phenyl-1,2,4-Triazolidine-3-Thiones

Mayuri Patil, Pradeep Mhaldar, Vrushali Mahadik, Dattaprasad M. Pore

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Graphical Abstract

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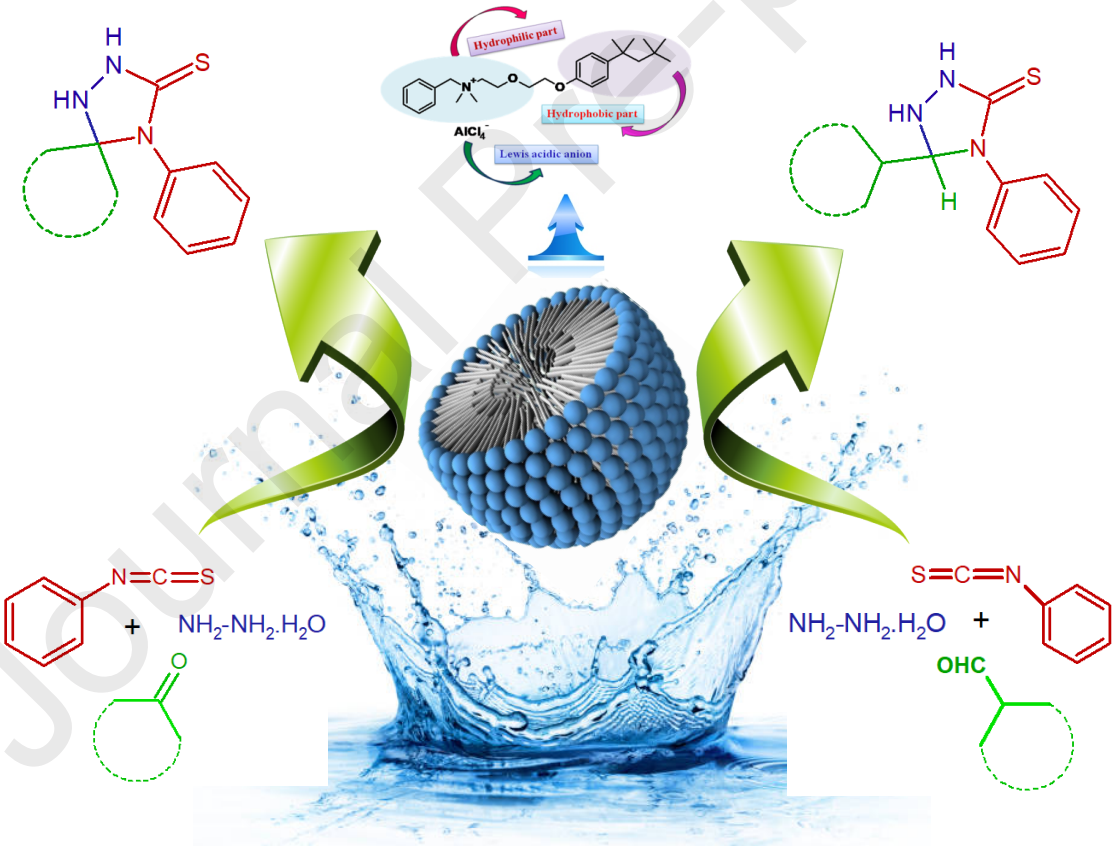
NOVEL, GREEN AND SUSTAINABLE ROUTE FOR SYNTHESIS OF 5-ARYL-4-PHENYL-1,2,4-TRIAZOLIDINE-3-THIONES

Mayuri Patil [a], Pradeep Mhaldar [a], Vrushali Mahadik [a] and Dattaprasad M. Pore,*[a]



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NOVEL, GREEN AND SUSTAINABLE ROUTE FOR SYNTHESIS OF 5-ARYL-4-PHENYL-1,2,4-TRIAZOLIDINE-3-THIONES

Mayuri Patil [a], Pradeep Mhaldar [a], Vrushali Mahadik [a] and Dattaprasad M. Pore,*[a]

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Abstract
A highly efficient, one-pot, novel and greener straightforward multi-component approach has been disclosed for the facile synthesis of 5-aryl-4-phenyl-1,2,4-triazolidine-3-thiones from reaction of phenyl isothiocyanate, hydrazine hydrate and diverse aromatic aldehydes / cyclic ketones / isatins in the presence of a novel Lewis acid-surfactant-combined catalyst. High yields, use of ambient temperature and water as a universally accepted green solvent, easy work-up procedure and isolation of product, high atom economy makes the present method attractive, sustainable and economical.

Keywords: Surfactant, Lewis acid, Triazole, Phenylisothiocyanate.

1. Introduction

The discovery of environment friendly synthetic track for 'drug-resembling' heterocyclic compounds from easily available precursors in eco-benign solvents is gaining significant interest in the sectors like pharmaceuticals, academic circles and manufacturing.[1] In recent years, the substitution of toxic and explosive organic solvents as reaction medium by green solvent water which is safe, good-natured, environment-friendly, cheap and with unrivaled reactivity and selectiveness that cannot be achieved in traditional organic solvents is the major driving force behind cleaner processes.[2] In contrast to these advantages, the low solubility of several organic compounds in this media reflects the biggest downside of use of water as a solvent.[3] An introduction of the phase transfer catalysts or surfactants is one of the way to circumvent this problem. Because of non-toxicity, bio-compatibility, bio-degradability, miscibility and reactivity with aqueous as well as numerous non-aqueous solvents through the creation of micelles with hydrophobic interior and hydrophilic crown in ambient environment, the utility of surfactant in water is a greener substitute for toxic organic solvents in organic synthesis.[4]

Due to the unique possible deeds on biological systems, nitrogen-containing scaffolds are imperative motifs in pharmaceutical products among various heterocycles. Triazole is a well known heterocyclic scaffold that has been very enticing as a consequence of its broad array of applications in pharmaceuticals, agrochemicals (Fungicide-Prothioconazole Fig. 1a, Insecticide-Triazophos Fig. 1b),[5] dyes, photographic material, corrosion inhibition.[6] Moreover, they are found to exhibit a variety of biological activities such as antiviral,[7] antiepileptic,[8] antiallergic,[9] anticancer,[10] anti-HIV,[11] antimicrobial activities against Gram-positive bacteria and β_3-adrenergic receptor agonist.[12] Interestingly, 1,2,4-triazole core has been included in a extensive collection of therapeutically significant drugs including anti-inflammatory, Sedatives, antianxiety, CNS depressant (Triazolam, Fig. 1c), anticancer agent (Letrozole, Fig. 1d), antiviral drug (Ribavirin, Fig. 1e). Owing to these multifarious applications, we persuit for investigating a novel synthetic route for the construction of functionalized triazoles.

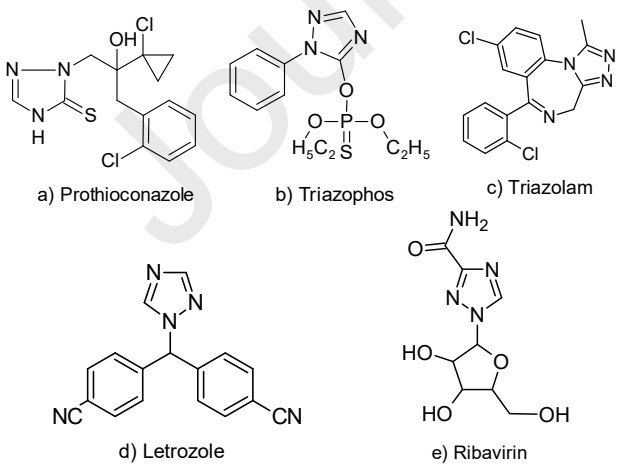


Fig. 1: Therapeutic drugs containing triazole skeleton

e of basic reagents.[13-19] Our research group investigated two component routes for the synthesis of 1,2,4-triazolidine-3-thiones viz, [C_{16}MPy]$AlCl_3Br$ catalyzed reaction of aldehyde and thiosemicarbazide, synthesis of novel spiro-1,2,4-triazolidine-3-thione from isatin and thiosemicarbazide in presence of glycine nitrate.[20-21] Several research groups reported different catalysts for the synthesis of 1,2,4- triazole-3-thiones.[22-27] Recently, our research group has also investigated multicomponent route for synthesis of 1,2,4- triazole-3-thiones from sulfamic acid catalyzed reaction of aldehyde, trimethyl silyl isothiocyanate with hydrazine hydrate.[28] In continuation with our interest in designing the new routes for synthesis of 1,2,4- triazole-3-thiones , in present work, we have investigated novel route for synthesis of diverse class of 1,2,4-triazolidine-3-thiones by carrying [BZT]+ AlCl4- catalyzed multi component reaction of Aldehydes / Isatin / Cyclic ketone, hydrazine hydrate and PhSNCS in water solvent at room temperature under the umbrella of green chemistry.

Initially, we focused our attention towards designing of catalyst. The most efficient tool in organic synthesis is Lewis acid catalysis.[29] Water-labile character of most of the Lewis acids restricts the reactions under anhydrous conditions. Also, most of the organic reactants do not usually dissolve in water. Hence, to tackle the solubility issue, the catalyst should contain surfactant counterpart that would help reactants to solubilise in aqueous media. In this perspective, we designed the surfactant catalyst having water-stable Lewis acidic constituent for the acid-catalyzed reactions in water.[30] 'Lewis acid-surfactant-combined catalyst' (LASC), would perform both as a catalyst to activate the reactants as well as a surfactant to increase the solubility in water by forming micellar aggregation.

2. Result and Discussion:

Primarily, our experimentation commenced with the design and synthesis of novel Lewis acid-surfactant-combined catalyst (LASC) which would construct the micelles in water, enabling its use as a solvent system to solubilise organic reactants and Lewis acidic counter ion helps to accelerate the rate of reaction with increasing the product yield. (Fig.2)

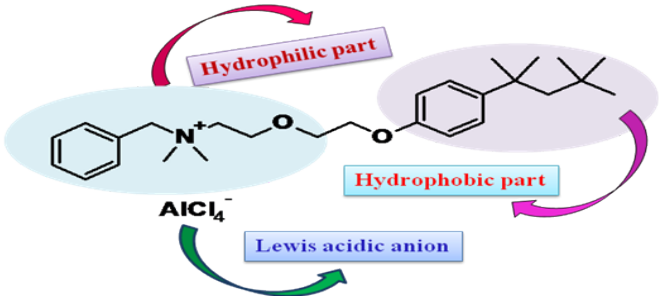
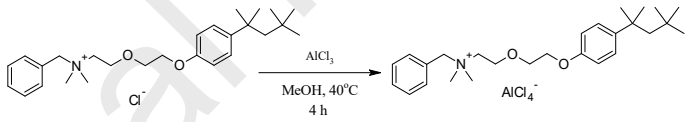


Fig. 2: Lewis acid surfactant combined catalyst $[BZT]^+$ $AlCl_4^-$

The synthesis of LASC, $[BZT]^+$ $AlCl_4^-$ was carried out by the reaction of $AlCl_3$ and benzethonium chloride $[BZT]^+[Cl]^-$ in methanol at 40°C for 4h furnished LASC (Scheme-1) which was characterized by IR, ^1H, ^{13}C, ^{27}Al NMR, ESI-MS and TGA analysis.



Scheme 1: Synthesis of Novel Lewis acidic surfactant, $[BZT]^+$ $AlCl_4^-$

FTIR spectrum of $[BZT]^+$ $[AlCl_4]^-$ shows the band at 2952 cm^{-1} and 2893 cm^{-1} due to C-H symmetric and asymmetric stretching vibrations in methylene and methyl group. The stretching bands at 1241cm^{-1} and 1118 cm^{-1} correspond to alkyl aryl ether and alkyl ether, respectively. The absorption band displayed at 1060 cm^{-1} indicates presence of C-N stretching vibrations.

The structure of LASC was also in well accordance with ^1H and ^{13}C NMR. The peak at δ 74.28 ppm in ^{27}Al NMR spectrum of LASC (Fig.3) confirmed the existence of Al possessing tetrahedral geometry.[31-32] Furthermore, in the mass spectrum of LASC, the peak observed at m/z 169 assist the formation of $AlCl_4^-$ as a counter ion.

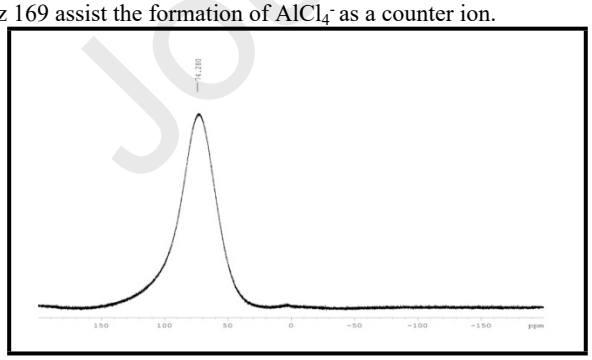


Fig. 3: ^{27}Al NMR spectrum of LASC catalyst, $[BZT]^+$ $[AlCl_4]^-$

The thermal stability of catalyst was evaluated by thermo gravimetric analysis (TGA) and differential thermo gravimetric analysis (DTA) in the temperature range of 25 to 600 °C in an air atmosphere at 10 °C/min (Fig. 4). Initially, the weight loss of 11.01% was observed in the temperature range of 25-148.26 °C may be accredited to the loss of physically adsorbed water molecules in the catalyst. The second weight loss of 14.53% in the range of 148.26-198.97 ° C due to the loss and decomposition of $AlCl_4^-$ anion. The further largest weight loss of 57.67 % is

due tal oxides at 594.01°C.

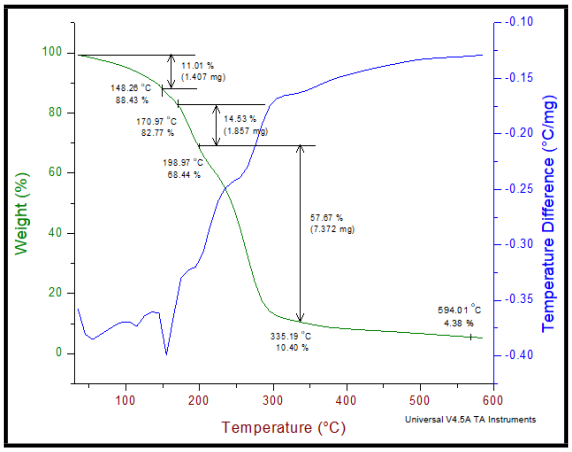
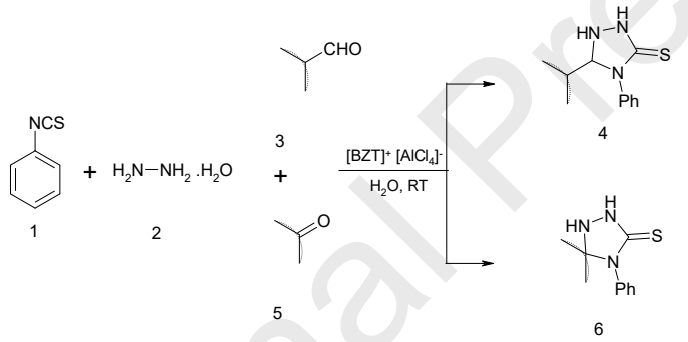


Fig.4: TGA/DTA plot of $[BZT]^+$ $[AlCl_4]^-$

The critical micelle concentration (CMC) of aqueous surfactant solution was calculated by using conductometry method by measuring the conductance as a function of surfactant concentration. The plot of equivalent conductance (λ) versus surfactant concentration is shown in Fig. 5. The equivalent conductance of the solution decreases with increasing surfactant concentration. The CMC of the $[BZT]^+$ $[AlCl_4]^-$ surfactant was found to be 0.005 mol.dm^{-3}.

Fig. 5: Equivalent conductance as a function of concentration

Following this major achievement, the attention was turned towards exploring catalytic efficiency of synthesized LASC catalyst for the synthesis of 5-aryl- 4-phenyl-1,2,4-triazolidine-3-thiones. In our ongoing research in the elaboration of new and expedient synthetic protocols for constructing bioactive heterocycles, herein we reveal a swift approach for the synthesis of 5-aryl- 4-phenyl-1,2,4-triazolidine-3-thiones from aldehyde, hydrazine hydrate and phenyl isothiocyanate using catalytic amount of $[BZT]^+$ $[AlCl_4]^-$ in water at ambient temperature (Scheme-2).



Scheme 2: Synthesis of 5-aryl-4-phenyl-1,2,4-triazolidine-3-thiones and Spiro-4-phenyl-1,2,4-triazolidine-3-thiones

The optimization of catalyst and solvent was carried out by using model reaction, phenyl isothiocyanate, hydrazine hydrate and benzaldehyde at ambient temperature. To explore the role of catalyst the model reaction was performed under catalyst-free condition in water and ethanol. However, the reaction failed to provide the desired product even after prolonged time (Table 1, entries 1-2). So screening of catalyst was carried out with K_2CO_3, *p*-TSA, NH_2-SO_3H, EPZ-10, SDS, Triton X 100, $AlCl_3$, 3-Methyl-1-sulphonic Acid Imidazolium Chloride $[Msim]^+$ Cl^-, $[BZT]^+$ $AlCl_4^-$ (Table 1, entries 3-13).

Table 1: Screening of catalysts for the formation of 4a

Sr. no	Catalyst	Catalyst load (mol %)	Solvent	Time (min)	Yield [b] (%)
1	-	-	Water	300	45[c]
2	-	-	Ethanol	120	70[c]
3	K_2CO_3	30	Ethanol	480	66
4	*p*-TSA	20	Ethanol	70	80
5	NH_2-SO_3H	20	Water	60	82
6	EPZ-10	30	Ethanol	100	73
7	$AlCl_3$	15	Water	90	78
8	$[Msim]^+$ Cl^-	20	Water	55	80
9	SDS	50	Water	90	65

11	$[BZT]^+ Cl^-$	20	Water	50	70
12	$[BZT]^+ AlCl_4^-$	25	Water	40	86
13	$[BZT]^+ AlCl_4^-$	20	Water	40	85
14	$[BZT]^+ AlCl_4^-$	15	Water	40	82
15	$[BZT]^+ AlCl_4^-$	10	Water	80	80
16	$[BZT]^+AlCl_4^-$	5	Water	80	79

[a] Reaction conditions: Benzaldehyde (1 mmol), phenyl isothiocyanate (1 mmol), hydrazine hydrate (1 mmol), specified catalyst, water (5 mL) at room temperature.
[b] Isolated yield; [c] undesired product

Basic catalyst K_2CO_3 led to the formation of desired product in low yield with very high reaction time (Table 1, entry 3). We observed that, in the presence of acid catalyst reaction proceed smoothly (Table 1, entries 4-8). Unexpectedly, the desired product was obtained in comparatively good yield within short reaction time with commercially available Sodium dodecyl sulfate (SDS), Triton X-100 and Benzethonium chloride surfactant in water (Table 1, entries 9-11). Pleasantly, in the presence of $[BZT]^+$ $[AlCl_4]^-$ best result was obtained (Table 1, entry 13). By comparing the catalytic activity of $[BZT]^+$ $[AlCl_4]^-$ with additional acidic, basic catalysts and surfactants under the optimal reaction conditions, it was found that LASC was superior to perform the reaction at room temperature.

Supported by these outcomes, the effect of the catalyst load on the reaction was examined. The 20 mol % of $[BZT]^+$ $[AlCl_4]^-$ was found to be adequate to promote this reaction (Table 1, entries 12-16). Excess amount of catalyst did not influence positively both in the yield and reaction time.

Due to the addition of surfactant initial suspended reaction mixture converted into a homogeneous white turbid emulsion indicating the creation of micelles or colloidal aggregates. [Fig. 6 (I)] Finally, white precipitate obtained point outs the completion of reaction. The formation of spherical emulsion droplets (micro bubbles) in water was confirmed by taking microscopic image of white turbid reaction mixture. [Fig. 6 (II)]

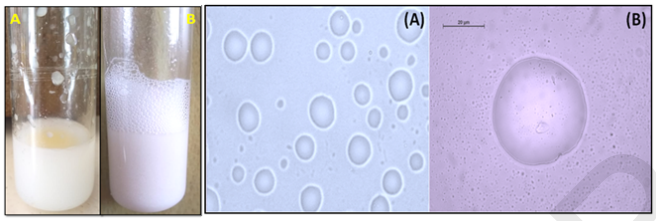
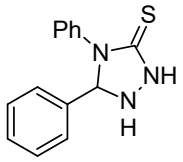


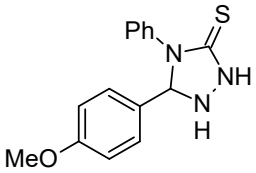
Fig. 6: (I) Reaction mixture at starting of reaction (A); reaction mixture after completion of reaction (B). **(II)** Microscopic image of the reaction mixture: Normal view (A); Magnified view (B). (Scale bar = 20 µm)

Noticeably, the workup for the reaction requires just filtration and simple washing with water followed by recrystalization in ethanol to obtain an extremely pure desired product. The IR, ^1H, ^{13}C NMR and Mass analysis validated the structure of the product. In the IR spectrum, the absorption bands of carbonyl of aldehyde and primary amine at 1710 cm^{-1} and 3350 $cm,^{-1}$ respectively, disappeared whereas the band at 1199 cm^{-1} was observed corresponding to C-S stretching of thiocarbonyl of 5-aryl-4-phenyl-1,2,4-triazolidine-3-thione. ^1H NMR spectrum indicates two D_2O exchangeable protons at δ = 9.26, 10.01 ppm of a secondary amine, respectively. In ^{13}C NMR, signal due to carbonyl of aldehyde disappeared and exhibited signal at δ = 178 ppm due to thiocarbonyl (C=S) functionality confirming the structure of product 4a. Mass spectrum is also in good agreement with the expected structure showing molecular ion peak at m/z 255. These spectroscopic analyses endorse the proposed structure 4a for the present conversion.

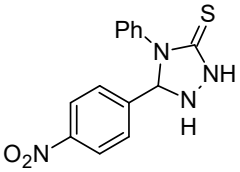
Table 2: Synthesis of combinatorial library of 5-aryl- 4-phenyl-1,2,4-triazolidine-3-thione.[a] & Spiro-4-phenyl-1,2,4-



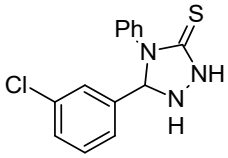
4a, 40 min; 84 %



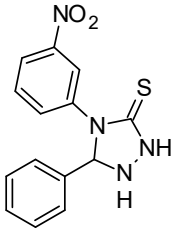
4b, 45min.; 82 %



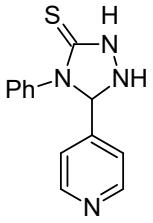
4c, 40 min.; 88 %



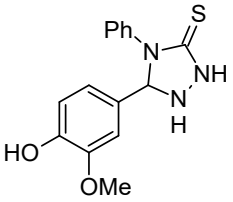
4d, 45 min.; 86 %



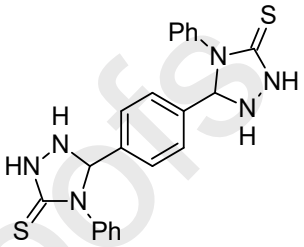
4m 45 min.; 82 %



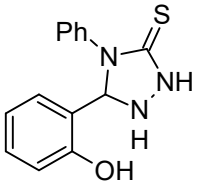
4f, 50 min.; 84 %



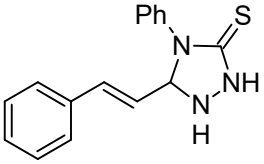
4g, 45 min.; 80 %



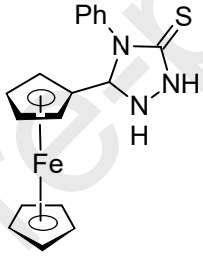
4h, 60 min.; 82 %



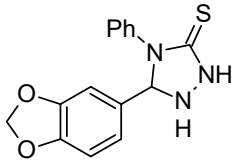
4i, 45 min.; 80



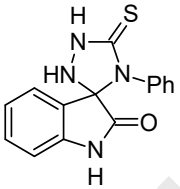
4j, 45 min.; 86 %



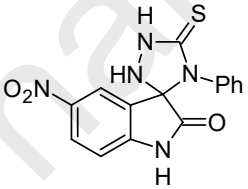
4k, 40 min.; 84 %



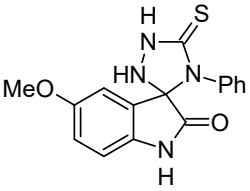
4l, 55 min.; 84 %%



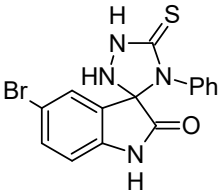
6a, 1.3 h.; 86 %



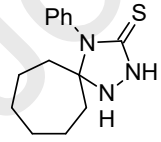
6b, 1.4 h.; 84 %



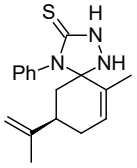
6c, 2 h.; 78 %



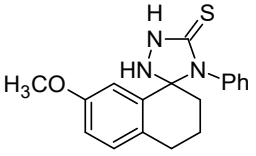
6d, 2 h.; 80 %



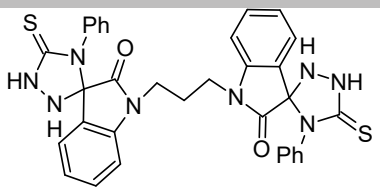
6f, 1.5 h.; 80 %



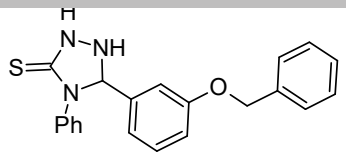
6g, 2 h.; 78 %



6h, 1.5 h.; 74 %



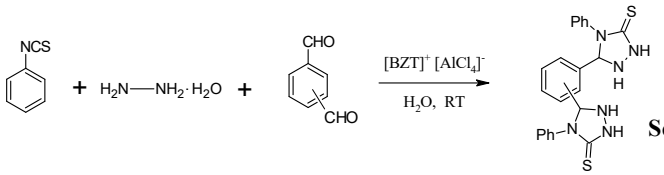
6e, 4 h.; 82 %



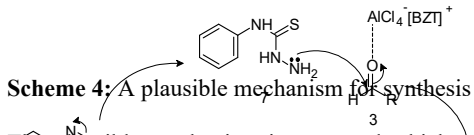
4e, 55 min; 80 %

[a] Reaction conditions: aldehyde/Isatin/Cyclic ketone (1mmol), Phenyl isothiocyanate (1mmol), Hydrazine hydrate (1mmol), Catalyst $[BZT]^+[AlCl4]^-$ (20 %), Water (5 mL), Room temperature.

With improved reaction conditions in hand, we expanded the scope of the reaction using various structurally diverse aromatic aldehydes (alicyclic, cyclic, aromatic, heteroaromatic and organometallic) as illustrated in Table 2. Aldehydes with electron-withdrawing (nitro, chloro) and electron-donating substituent's (methoxy, hydroxyl) were almost inevitably transformed into their respective targets. Interestingly, 4-nitro and 3-chloro benzaldehyde worked well yielding the corresponding products in excellent yield (Table 2, Products 4c, 4d). Ortho substituent containing aldehydes give somewhat lower yields which may be due to steric hindrance. Heteroaromatic and organometallic aldehydes such as pyridine-4-carboxaldehyde and ferrocene-2-carboxaldehyde yielded the desired product in excellent yield (Table 2, products 4f, 4k). Eventually, the competency of the reaction was examined using bis aldehyde namely terephthalaldehyde (Scheme 3) and found that reaction performed well with good yield (Table 2, product 4h).



Scheme 3: Synthesis of bis-5-aryl- 4-phenyl-1,2,4-triazolidine-3-thione

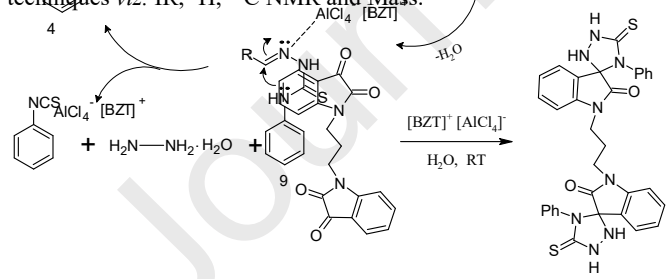


Scheme 4: A plausible mechanism for synthesis of 5-aryl- 4-phenyl- 1,2,4-triazolidine-3-thiones

The plausible mechanism is proposed which revealed that, the reaction proceeds *via*, the intermediate **7** which formed by the nucleophilic addition reaction of hydrazine hydrate **2** to thiocarbonyl carbon of phenyl isothiocyanate **1**. Further nucleophilic attack of NH_2 group of 7 to the carbonyl carbon of aldehyde **3** in acidic condition furnish **9** which undergo cyclization to yield product **4** (Scheme 4).

Then to investigate the generality of the protocol, cyclic ketones were used instead of aromatic aldehydes. Gratifyingly, reactions proceed efficiently leading to good yields of desired products. The results are depicted in Table 2.

Finally, Bis-isatin was used to assess the extent of reaction (scheme 5) and it was noticed that the reaction performed well with good yield (Table 2, product 6e). The formation of spiro-4-phenyl-1,2,4-triazolidine-3-thione (Table 2, product 6a) was verified by various spectral techniques *viz.* IR, ^1H, ^{13}C NMR and Mass.



Scheme 5: Synthesis of bis spiro-4-phenyl-1,2,4-triazolidine-3-thione

Conclusion:

In conclusion, we have investigated a novel, converging and robust greener protocol for the synthesis of structurally diverse 5-aryl-4-phenyl-1,2,4-triazolidine-3-thiones from reaction of phenylisothiocyanate, hydrazine hydrate and carbonyl compounds *viz* aldehydes / isatins / cyclic ketones in presence of $[BZT]^+$ $[AlCl_4]^-$ as an effective promoter. Use of water as an universal solvent, ambient temperature, the simple procedure, rapid, wide substrate scope, short reaction time, high yield and easy workup furnished high purity of products without tedious column chromatography are the green aspects of the present transformation.

Acknowledgements

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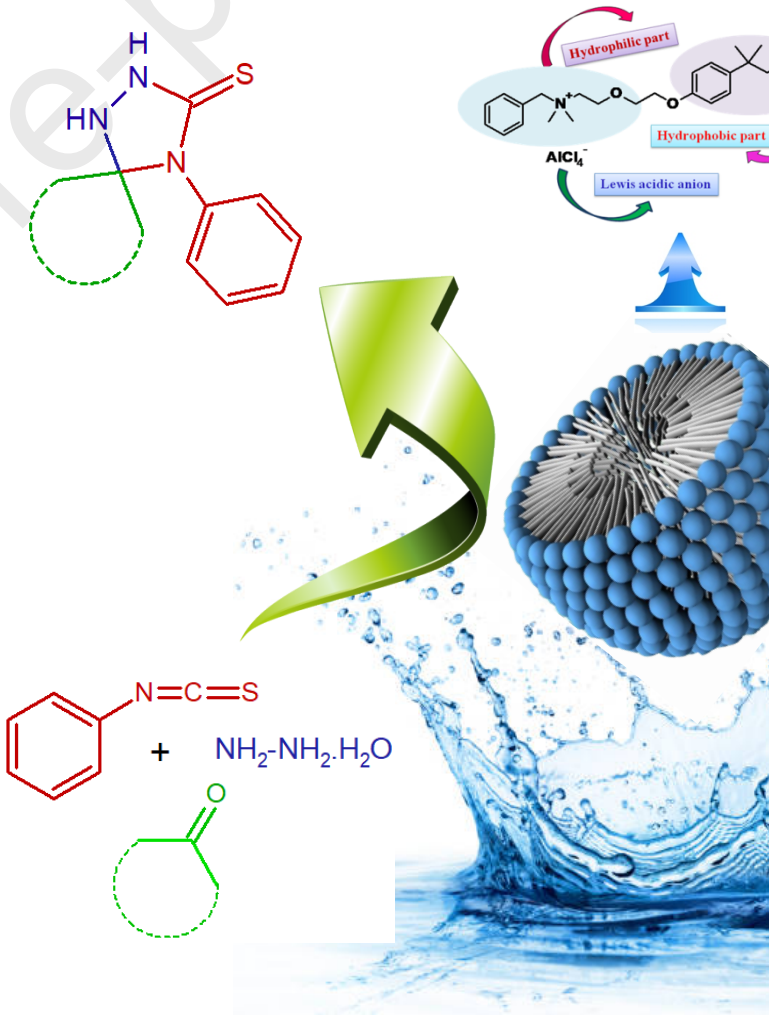
Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



NOVEL, GREEN AND SUSTAINABLE ROUTE FOR SYNTHESIS OF 5-ARYL-4-PHENYL-1,2,4-TRIAZOLIDINE-3-THIONES

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Highlights

- ✓ Investigated multicomponent synthesis of 5-aryl-4-phenyl-1,2,4-triazolidine-3-thiones