NJC

PAPER

View Article Online
View Journal | View Issue

Cite this: *New J. Chem.*, 2021, 45, 6724

Aiding the versatility of simple ammonium ionic liquids by the synthesis of bioactive 1,2,3,4-tetrahydropyrimidine, 2-aminothiazole and quinazolinone derivatives†

Praachi Kakati, ‡ Preeti Singh, ‡ Priyanka Yadav and Satish Kumar Awasthi *

Received 18th January 2021,
Accepted 10th March 2021

DOI: 10.1039/d1nj00280e

rsc.li/njc

Simple ammonium ionic liquids [ILs] are efficient, green, environmentally friendly catalysts in promoting the Biginelli condensation reaction, Hantzsch reaction and Niementowski reaction to afford 1,2,3,4-tetrahydropyrimidine, 2-aminothiazole and quinazolinone derivatives respectively by eliminating the need for harmful volatile organic solvents. These [ILs] are air and water stable, easy to prepare and cost-effective. The effects of the anions and cations present in [IL] on reactions were investigated. The results clearly indicated that the Biginelli condensation reaction, Hantzsch reaction and Niementowski reaction were heavily influenced by the acidity of [IL], and among various ammonium ionic liquids, $[Et_3NH][HSO_4]$ showed the best catalytic activity. Furthermore, [IL] could be easily separated and reused with a slight loss of its activity. This technique provided a good alternative way for the industrial synthesis of 1,2,3,4-tetrahydropyrimidinones, 2-aminothiazoles and quinazolinones. The present processes are eco-friendly methods for the synthesis of these derivatives authenticated by several green parameters, namely, *E*-factor, process mass intensity, reaction mass efficiency, atom economy, and carbon efficiency.

1. Introduction

In recent years, 1,2,3,4-tetrahydropyrimidine derivatives have received significant attention owing to their diversified range of biologically active compounds. Because of their excellent biological profile, tetrahydropyrimidinones constitute an important class of heterocyclic compounds in pharmaceutical and medicinal chemistry, which has attracted the attention of many researchers.[1–3] There are various natural and synthetic tetrahydropyrimidinone analogs available, which display a wide range of pharmaceutical properties, namely, anticancer,[4] antiviral,[5] antihypertensive,[6] calcium channel blocking,[7] antitubercular,[8] anti-inflammatory,[9] antimicrobial,[10] and insecticidal activities.[11] Various biologically active compounds that contain hydropyrimidinone scaffolds such as (a) 5-fluorouracil displaying anticancer activity,[12] (b) SQ 32926 exhibiting antihypertensive activity,[13] (c) monastrol (having a hydropyrimidine-2-thione motif) specifically inhibiting the mitotic kinesin Eg5[14] and (d) Mon-97 exhibiting anticancer activity[15a] are represented in Fig. 1.

In addition to this, we have two other interestingly versatile heterocyclic class of compounds, namely 2-aminothiazoles and quinazolinones with very unique biological and pharmacological activities under consideration. Of them, 2-aminothiazole is a commonly occurring structural unit in various important drug molecules such as (e) 2-oxo-*N*-(4-phenylthiazol-2-yl)-2*H*-chromene-3-carboxamide that exhibits antifungal and antibacterial activities, whereas (f) *N*-(4-phenylthiazol-2-yl)thiazol-2-amine exhibits anti-inflammatory activity (Fig. 1).[15b] Moreover, quinazolinone falls in the class of fused structural motifs with its derivatives showcasing a wide range of bio-activity such as (g) mackinazolinone acting as an antidepressant, and (h) rutaecarpine showing antithrombotic activity among others (Fig. 1).[15c]

Because of broad biological applications displayed by 1,2,3,4-tetrahydropyrimidines, 2-aminothiazoles and quinazolinones, the establishment of more versatile and flexible methodology to synthesize these compounds is still required. There is an urgent need for methodologies that are cost-effective and accomplished with readily accessible starting materials, which can follow the principle of atom economy. Literature survey portrays various methods for the synthesis of tetrahydropyrimidinones like using organocatalysts,[16] Pd/C,[17] Si-[SbSipim][PF_6],[18]

Chemical Biology Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India. E-mail: satishpna@gmail.com; Tel: +91 9582087608

† Electronic supplementary information (ESI) available: Materials and characterization techniques, calculation of green chemistry parameters, ^{1}H NMR, ^{13}C NMR and ESI-MS spectra of all compounds are provided, associated with this article. Brief statements as noted in text: supporting figures and supporting tables. CCDC 1959600 (**4k**) and CCDC 1963534 (**6j**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1nj00280e

‡ Both the authors shared the equal authorship.

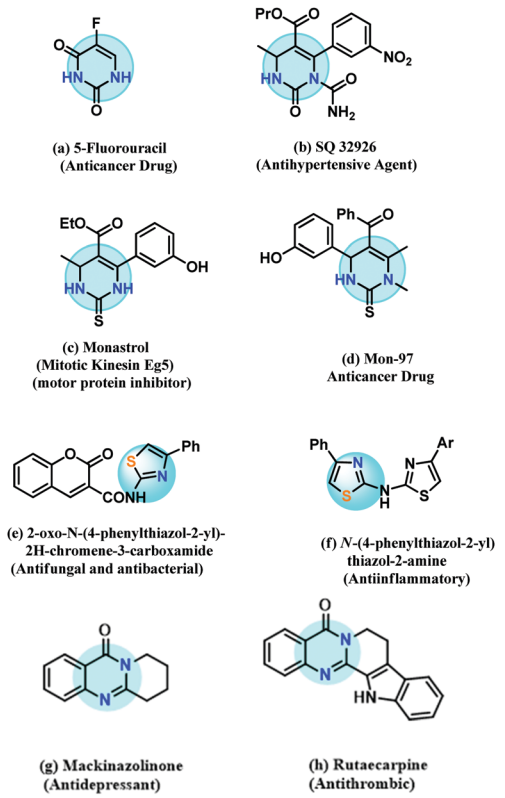


Fig. 1 Biologically active compounds based on 1,2,3,4-tetradihydropyrimidine-2-thione/one, 2-aminothiazoles and quinazolinones.

$Yb(PFO)_3$,[19] $ZrCl_4$,[20] and Fe_3O_4@C@OSO_3H[21] catalysts. Similarly, 2-aminothiazoles and quinazolinones have been previously synthesized in the presence of Fe_3O_4 nanoparticle-*N*-halo reagents,[22] palladium(II) acetate,[23] nanochitosan-I_2,[24] SiO_2-Cl,[25] TCCA-*p*-TSA[26] as well as by using H-Y-zeolite,[27] alum,[28] and Nafion-H[29] as catalysts respectively. The available approaches (detailed in Table 4 of the manuscript and Tables S12 and S13 of ESI†) mainly involve the extensive use of hazardous organic solvents, multistep reactions, lower yields, need for special instruments and apparatus, longer reaction time, complex characterizations of desired products, tedious workup procedures and metal-based catalysts. Metal-based catalysts are generally harmful and problematic to use because even if trace amounts of toxic metals are present in pharmaceutical materials, it can cause severe health hazards to people.[30] Therefore, industrially as well as pharmaceutically, the synthetic methodologies that may utilise metal-free approaches are always in demand.[31]

Moreover, the synthetic strategies must satisfy the principle of green chemistry metrices.[32] Therefore, all these features must be carefully considered where all the reactions should be carried out in an eco-friendly medium accompanying various advantages such as simple work-up procedures, non-toxicity, higher yielding products and its easy isolation.[33]

1.1 Motivation and strategy

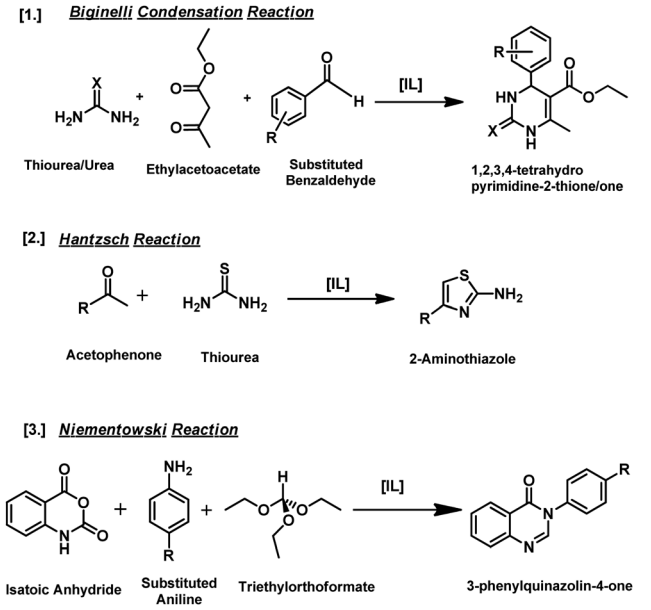
For the development of useful synthetic methodologies for synthesizing heterocyclic compounds, we sought for cleaner and greener technologies for the formation of 1,2,3,4-tetrahydropyrimidinones, 2-aminothiazoles and quinazolinones. Herein, we report a new synthetic method by utilising simple ammonium ionic liquids. [ILs] have increasingly attracted attention in both academics and industrial fields[34–37] and they display various important features that make them suitable and sustainable alternative for synthetic methodologies. Ionic liquids exhibit unique physiochemical properties that may attribute to their special structure and interaction between ions, such as they exhibit very low vapour pressure that produces virtually no hazardous vapours and non-flammability. The additional advantage of these simple ammonium [ILs] is that they provide easy isolation of products and are themselves recyclable as well as recoverable, so that they can be further used in subsequent reactions. Keeping these features as well as with the objective to incorporate metal-free synthesis, we utilised the simple ammonium [ILs] as catalysts in the synthesis of heterocyclic compounds such as 1,2,3,4-tetrahydropyrimidin-2-thiones/ones, 2-aminothiazoles and quinazolinones.

By utilising the simple ammonium [ILs] in the synthesis of heterocyclic compounds, we would like to report herein the one-pot multicomponent reactions. Multicomponent reactions (MCRs)[38] involve the coupling of three or more simple and flexible components in a one-pot medium, generating a complex structure by the simultaneous formation of two or more bonds.[37] Eco-friendly methodologies that reduce the number of synthetic steps and waste-free techniques are among the special advantages of MCRs, which add to their green credentials. To the best of our knowledge, this is the first report wherein simple ammonium ionic liquids are utilised in the synthesis of exceedingly biologically significant 1,2,3,4-tetraydropyrimidine-2-one/thiones, 2-aminothiazoles as well as quinazolinones (Scheme 1(1–3)).

2. Results and discussion

2.1 Catalytic evaluation

2.1.1 Effects of different ammonium ILs on the Biginelli condensation reaction. The model reaction between urea (**1b**), ethyl acetoacetate (**2**), benzaldehyde (**3**) and IL was performed (Table 1). In order to check the efficacy of simple ammonium ionic liquids, six different types of ionic liquids were tested and analysed. The effect of different [ILs] was investigated by varying the cation and anion counterparts. It is apparent from Table 1 that the activity of ionic liquids was strongly affected by the anionic counterpart. Excellent yields were obtained with the $[HSO_4]$ anion. However, when a salt with phosphate anion such as $[Me_3NH][H_2PO_4]$, $[Et_3NH][H_2PO_4]$ and $[Pr_3NH][H_2PO_4]$ was used, the reaction yield was found to be lower than those obtained with $[HSO_4]$ anions. Table 1 also shows that the yield of the product is affected by the presence of cations in the ionic liquid as well. The yield of the desired product 1,2,3,4-tetrahydropyrimidin-2-one was found to be highest in the presence of ionic liquid $[Et_3NH][HSO_4]$ with 15 mol% (0.029 g) as the optimal amount increasing, which had no effect on the



Scheme 1 (1) Synthesis of 1,2,3,4-tetrahydropyrimidine-2-thione/one promoted by ionic liquids. (2) Synthesis of 2-aminothiazoles promoted by ionic liquids. (3) Synthesis of 3-phenylquinazolin-4-one promoted by ionic liquids.

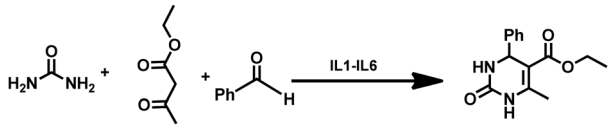
reaction yield. The reason may be attributed to the acidic property of the ammonium ionic liquid. Hence, the overall increasing order for the yield of the reaction is $[Pr_3NH][H_2PO_4]$ < $[Pr_3NH][HSO_4]$ < $[Me_3NH][H_2PO_4]$ < $[Et_3NH][H_2PO4]$ < $[Me_3NH][HSO_4]$ < $[Et_3NH][HSO_4]$ *i.e.* 61%, 65%, 76%, 77%, 78% and 80%, respectively. The correlative data are listed in Table 1.

2.1.2 Optimization of the reaction parameters on the Biginelli condensation reaction on the yield of 1,2,3,4-tetrahydropyrimidin-2-one (4) in the presence of $[Et_3NH][HSO_4]$[a]

Effect of the amount of ionic liquids and solvents. The influence of the quantity of IL3 $[Et_3NH][HSO_4]$ and the solvent on the reaction was also examined carefully. A control experiment using 1 : 1 : 1 ratio (*i.e.* urea 1 mmol, ethyl acetoacetate 1 mmol, benzaldehyde 1 mmol) was first conducted in the absence of catalyst, and it was observed that the reaction has failed to occur under such conditions, which eventually necessitates the presence of the catalyst to afford the desired product 1,2,3,4-tetrahydropyrimidinone. We have also investigated the influence of the quantity of $[Et_3NH][HSO_4]$, which was analysed for 0 to 20 mol% loading of the IL3. It is evident from Fig. 2 that on increasing the quantity of IL3, the formation of product was found to be higher. However, the yield did not continue improving when the quantity was raised to 20 mol% or above. It was also observed that on varying the solvents such as water, ethanol, methanol and acetonitrile, there was no such hike observed in the percentage yield of the product. In this context, the desired 1,2,3,4-tetrahydropyrimidinone was obtained efficiently with 15 mol% (0.029 g) loading of IL3 under solvent-free conditions (Fig. 2).

Effect of time on the yield of products promoted by $[Et_3NH][HSO_4]$. It was noted that the reaction time played a pivotal role in enhancing the reaction kinetics. To analyse the effect of time, we performed a model reaction in a distinct range of time between 0 and 55 min. The conversion percentage was found to be increasing on increasing the time from 5 min to 45 min. The maximum conversion percentage was obtained at 45 minutes; however, on further increasing the time period, there was no hike in the yield of the reaction. Therefore, the optimum time period for the coupling reaction was found to be around 45 minutes. The results are demonstrated in Fig. 3.

Table 1 Effect of different types of [ILs] on the Biginelli condensation reaction



Entry	Types of ionic liquid	Time/min	Temperature (°C)	Amount mol%	Yield[a] (%)
1	$[Me_3NH][HSO_4]$ IL1	5	100	5	Trace
2	$[Me_3NH][HSO_4]$ IL1	15	100	5	15
3	$[Me_3NH][HSO_4]$ IL1	25	100	5	25
4	$[Me_3NH][HSO_4]$ IL1	35	50	5	38
5	$[Me_3NH][HSO_4]$ IL1	45	50	5	42
6	$[Me_3NH][HSO_4]$ IL1	55	50	5	42
7	$[Me_3NH][HSO_4]$ IL1	45	R.T.	10	56
8	$[Me_3NH][HSO_4]$ IL1	45	R.T.	15	78
9	$[Me_3NH][HSO_4]$ IL1	45	R.T.	20	78
10	$[Me_3NH][H_2PO_4]$ IL2	45	R.T.	15	76
11	$[Et_3NH][HSO_4]$ IL3	35	R.T.	15	68
12	**$[Et_3NH][HSO_4]$ IL3**	**45**	**R.T.**	**15**	**80**
13	$[Et_3NH][HSO_4]$ IL3	45	R.T.	20	80
14	$[Et_3NH][H_2PO_4]$ IL4	45	R.T.	15	77
15	$[Pr_3NH][HSO_4]$ IL5	45	R.T.	15	65
16	$[Pr_3NH][H_2PO_4]$ IL6	45	R.T.	15	61

[a] Yield refers to isolated yields.

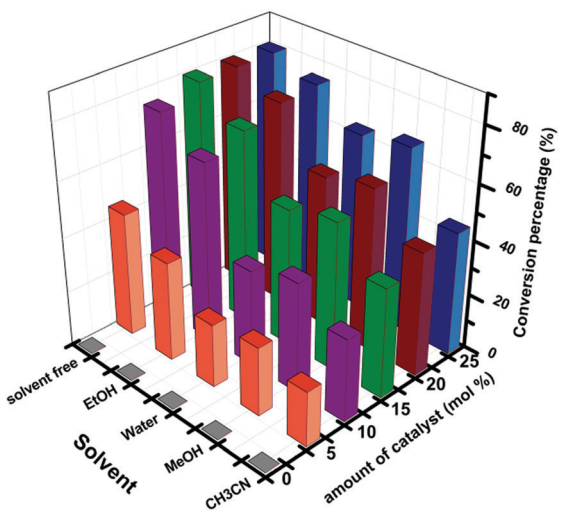


Fig. 2 Effect of the amount of ionic liquids and solvents.[a] Reaction conditions: urea (1 mmol), ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), and IL 15 mol%.

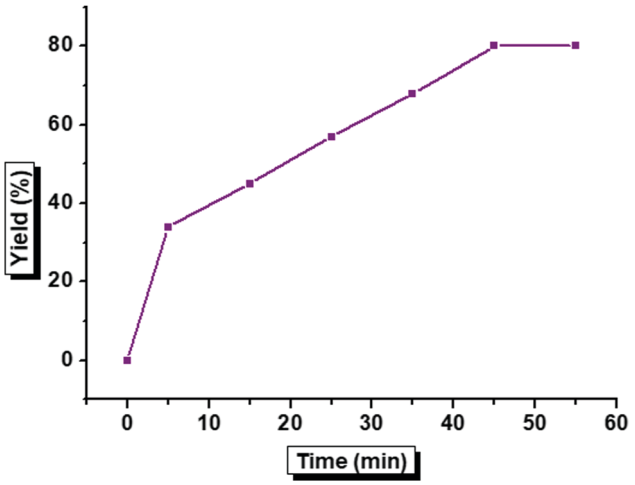


Fig. 3 Reaction kinetics of the Biginelli condensation reaction. Conditions: urea (1 mmol), ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), and IL (15 mol%).

2.1.3 Substrate scope. The optimized reaction conditions were then tested for the construction of 15 compounds involving thiourea/urea and substituted aldehydes. To explore the scope and versatility of this methodology, a series of thiourea/urea (**1a**/**1b**), ethyl acetoacetate (**2**) and substituted benzaldehydes (**3**) were coupled under the established optimal reaction conditions (Table 2). All the compounds were conveniently prepared by taking $[Et_3NH][HSO_4]$ in good to moderate yields by a one-pot methodology. Though all the products were formed, it was noted that the protocol was highly effective with urea as compared to thiourea to yield the corresponding 1,2,3,4-tetrahydropyrimidine-2-one products (comparing **4a** with **4b** in Table 3). Furthermore, in order to investigate the efficiency of this methodology, it was also extended for the electron-withdrawing as well as electron-donating species in substituted benzaldehydes. It was noted that the substituted benzaldehydes containing electron-withdrawing groups (chloro/fluoro/bromo) were highly efficient for the conversion of desired 1,2,3,4-tetrahydropyrimidine-2-thione/ones (**4**) with high conversion percentage yields ranging from 87% to 94% (**4g**, **4h**, **4i**, **4j**, **4k**, **4l**, **4m**, **4n**, and **4o**). Next, the scope of electron-donating groups was also evaluated for the Biginelli condensation reaction and the protocol exhibited resulting in moderate yields ranging between 80% and 85% (**4a**, **4b**, **4c**, **4d**, **4e**, and **4f**). The most distinguished characteristics of this protocol were high conversion percentage, reaction devoid of unwanted side products, wide substrate applicability, extensive functional group tolerance and recoverable ionic liquid.

Table 2 Optimization of the reaction condition for the synthesis of 1,2,3,4-tetrahydropyrimidin-2-one[a]

Amount of $[Et_3NH][HSO_4]$ mol%	Temperature (°C)	Time	Yield[b] (%)
0	100	6 h	NR
5	100	2 h	42
10	100	1.5 h	56
15	100	1.5 h	65
15	50	1 h	78
15	R.T.	55 min	80
15	**R.T.**	**45 min**	**80**
15	R.T.	35 min	68
20	R.T.	45 min	80
25	R.T.	45 min	80

[a] Reaction conditions: urea (1 mmol), ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), IL (15 mol%). [b] Isolated yields.

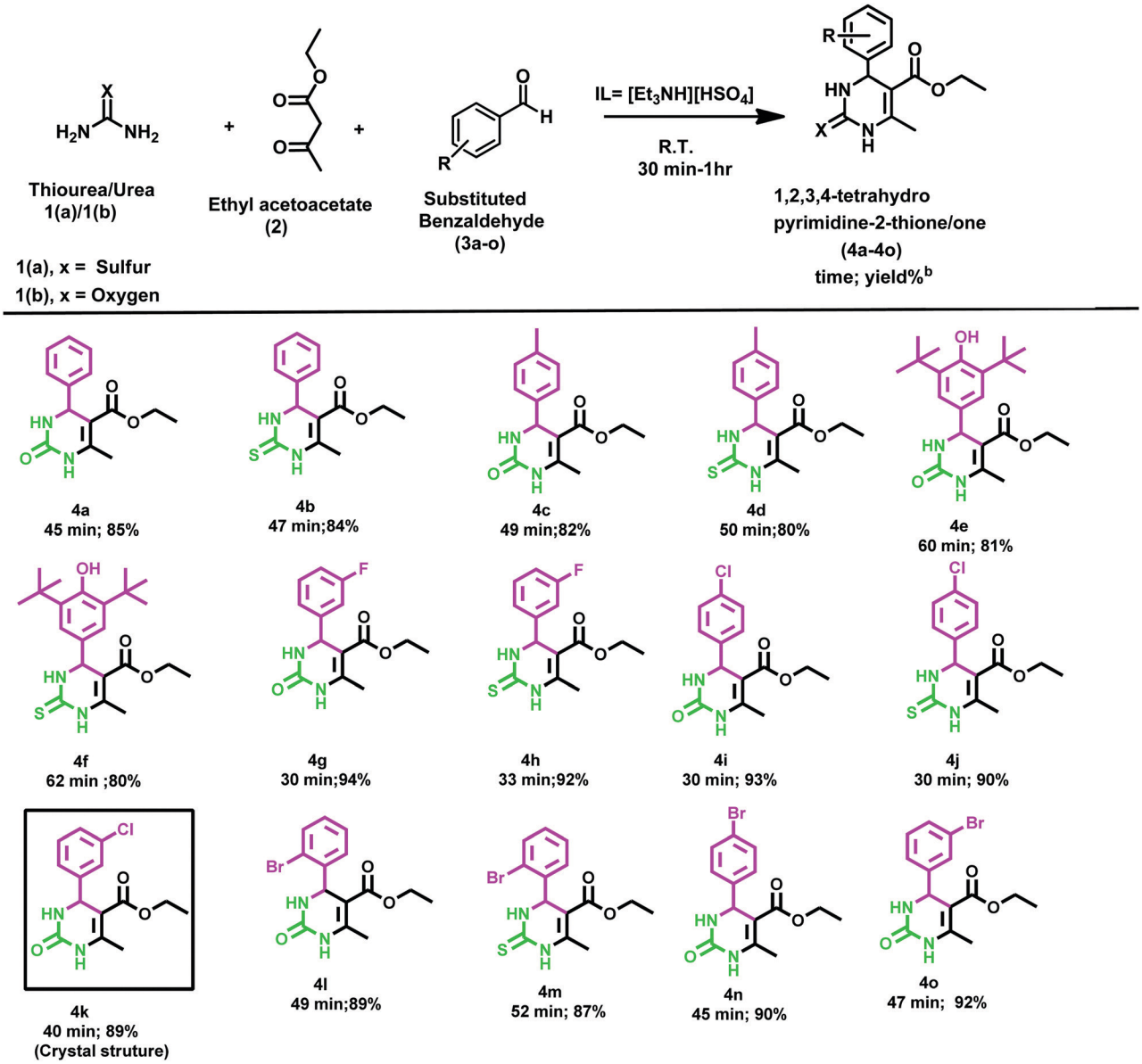
2.1.4 Comparison of the catalytic activity of $[Et_3NH][HSO_4]$ with the previously reported catalyst/ionic liquids. A comprehensive literature survey suggests that the synthesis of 1,2,3,4-tetrahydropyrimidine-2-thione/ones promoted by a simple ammonium ionic liquid displayed its predominance over previously reported protocols (Table 4). To the best of our knowledge, this is the first time that highly efficient $[Et_3NH][HSO_4]$ was employed for the synthesis of tetrahydropyrimidine derivatives. $[Et_3NH][HSO_4]$ catalysed protocol is superior in terms of ambient reaction conditions, extensive functional group tolerance and recoverability and reusability of an ionic liquid. Additionally, the present study replaces the use of hazardous organic solvents with an approach which is solvent- and waste-free under room temperature conditions within a duration of 30 min to an hour. Thus, the present study is an alternative for the synthesis of tetrahydropyrimidine moieties.

2.1.5 Single-crystal X-ray diffraction (XRD) analysis of 4k. In order to validate the formation of synthesized 1,2,3,4-tetrahydropyrimidine-2-thione/ones and to authenticate this approach, we chose to perform single-crystal X-ray diffraction analysis of compound **4k**.

Furthermore, after getting the perfect Wilson curve of compound **4k** (Fig. S1 of ESI†), the crystal structure of synthesized compound **4k** was solved using the WinGX (shelx method) and Olex2.1.2 software.[42,43] The ORTEP 3 was utilized for the graphics of the crystal structure **4k** and the same is represented in Fig. 4 along with the CCDC number. The detailed crystallographic studies of compound **4k** revealed that the arrangement of the compound in the crystal lattice is stabilized by the H-bonding interaction between O-atom of carbonyl and H-atom of $-CH_3$ with a distance of 2.76 Å and an angle of 124°. All other parameters such as crystal data and structure refinement table (Table S1, ESI†), fractional atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) (Table S2, ESI†), bond lengths (Table S3, ESI†) and bond angles (Table S4, ESI†) are provided in the ESI† of this article.

2.1.6 Proposed reaction mechanism. A plausible reaction mechanism has been proposed for the one-pot multicomponent reaction of 1,2,3,4-tetrahydropyrimidin-2-one/thiones promoted by a simple ammonium ionic liquid $[Et_3NH][HSO_4]$ as outlined in Fig. 5. First, the ionic liquid $[Et_3NH][HSO_4]$ as a Lewis acid participates in the reaction which activates the aromatic aldehyde followed by the nucleophilic addition of urea or thiourea which forms the *N*-acylimine intermediate. Then, this intermediate interacts with ethyl acetoacetate enolate to produce an open-chain intermediate ureide followed by intramolecular cyclization. Finally, aromatization of dihydropyrimidinone under air atmosphere would afford desired 1,2,3,4-tetrahydropyrimidin-2-one/thiones.

Table 3 Substrate scope for the synthesis of 1,2,3,4-tetrahydropyrimidine-2-thione/ones (**4**)[a]



[a] Reaction Conditions: urea/thiourea (1 mmol), ethyl acetoacetate (1 mmol), substituted aromatic aldehydes (1 mmol), IL (15 mol%). [b] Yield refers to isolated yields.

2.2 Utility of $[Et_3NH][HSO_4]$ in the formation of bioactive 2-aminothiazoles and quinazolinones

With the aim to explore the versatility of simple ammonium ionic liquids and its catalytic proficiency in organic synthesis, we report herein $[Et_3NH][HSO_4]$ catalysed 2-aminothiazole and quinazolinone synthesis. An inexpensive and commercially available reagent that has a high tolerance to different functional groups, IL3 has been shown to mediate a wide variety of 2-aminothiazole formation in an efficient and selective manner. It has also been successfully able to carry out the synthesis of a wide range of quinazolinone in a sustainable manner. To the best of our knowledge, a synthetic approach to 2-aminothiazoles and quinazolinones from simple ammonium ionic liquids has not been reported so far.

2.2.1 Catalytic parameters for the synthesis of 2-aminothiazole. To optimize the reaction, we began by choosing acetophenone (**5**), thiourea (**1a**), resublimed iodine and $[Et_3NH][HSO_4]$ as model substrates to establish the reaction. Table 5 demonstrates that by varying the amounts of $[Et_3NH][HSO_4]$ and temperature of the reaction, the percentage yield of 2-aminothiazole was also affected. Intensifying the amount of IL up to 15 mol% exhibits a noteworthy alteration in the percentage yields. Though, an additional increment in the amount of IL, *i.e.*, up to 30 mol% or more, resulted in no change in the conversion of percentage yield. This may be because of the exhaustion of the IL or attainment

Table 4 Comparing excellence of $[Et_3NH][HSO_4]$ with previously reported catalysts for the synthesis of tetrahydropyrimidinones

Catalyst	Solvent	Temperature	Time	Yield (%)	Ref.
(2*S*,4*R*)-4-Tosylamido-*N*-(2,4,6-triphenylbenzene) pyrrolidine2-carboxamide	THF/dioxane	R.T.	96 h	60	16
Pd/C (10% w/w)	Methanol	R.T.	24–48 h	71	17
Si-[SbSipim][PF_6]	EtOH (reflux)	100 °C	3.5 h	80	18
Yb(PFO)$_3$	SF[b]	120 °C	4 h	87	19
$NH_4NH_2PO_4$/MCM-41	SF[b]	100 °C	6 h	72	39
[PEG-DAIL][Cl]	Toluene	80 °C	5 h	85	40
ZnO@SBA-15	EtOH	65 °C	2.5 h	82	41
$ZrCl_4$	EtOH	Ultrasound	35 min	75	20
Fe_3O_4@C@OSO_3H	SF[b]	80 °C	20 min	93	21
$[Et_3NH][HSO_4]$	**SF[b]**	**R.T.**	**30–45 min**	**90**	**PW[a]**

[a] Present work. [b] Solvent free.

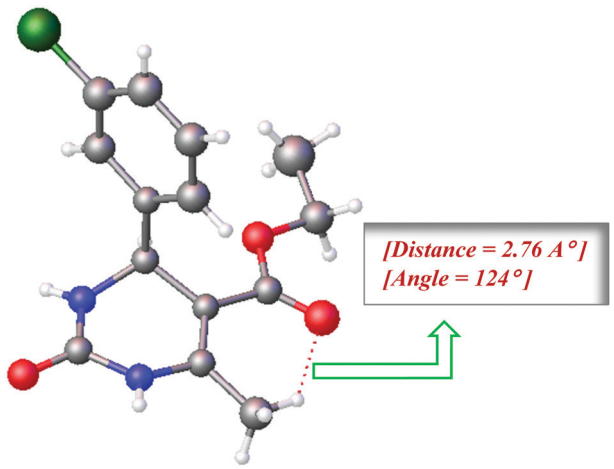


Fig. 4 X-ray crystallographic structure of compound **4k** (CCDC 1959600†).

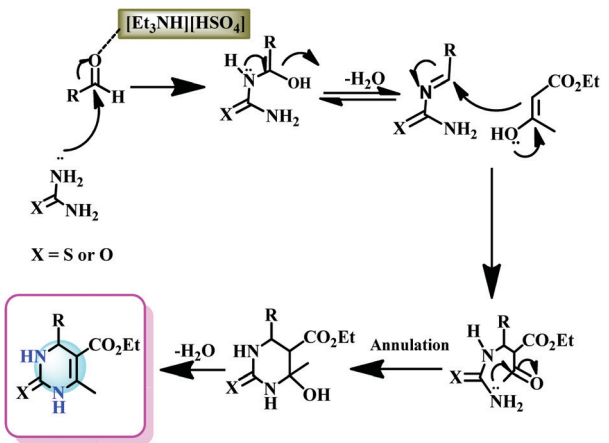


Fig. 5 Proposed mechanism for the synthesis of 1,2,3,4-tetrahydropyrimidine-2-thione/ones promoted by $[Et_3NH][HSO_4]$.

of the maximum conversion efficacy of the IL. Concurringly, temperature and time also play a pivotal role in affecting the reaction kinetics to large extents. Therefore, with the view of studying the effect of these two parameters, a varied range of temperature (room temperature to100 °C) was used to carry out the model reaction for different time periods (30 min–12 h). Conclusively, by using 15 mol% (0.029 g) of the IL at 40 °C for a reaction time of 0.5 hours, the percentage yield (92%) was found to be maximum. Our methodology here proves to be superior to the previously reported methods (Table S12, ESI†) in terms of ambient reaction conditions of temperature and time in solvent free protocol to give excellent yields. It has been observed that even after prolonged reaction time and increase in temperature, no significant change has been perceived.

2.2.1.1 Substrate scope for the synthesis of 2-aminothiazole derivatives. Using the optimized reaction conditions, we further inspected the opportunity of using thiourea (2 mmol), and various substituted ketones (1 mmol). A series of 2-aminothiazoles were synthesized in good to excellent yields by screening an array of ketones having electron-withdrawing as well as electron-donating groups, as displayed in Table 6. We can successfully conclude that ketones comprising electron-donating groups have better yields (**6j**, **6k**, and **6l** of Table 6) than the ones with electron-withdrawing groups (**6e**, **6f**, **6h**, and **6i** of Table 6).

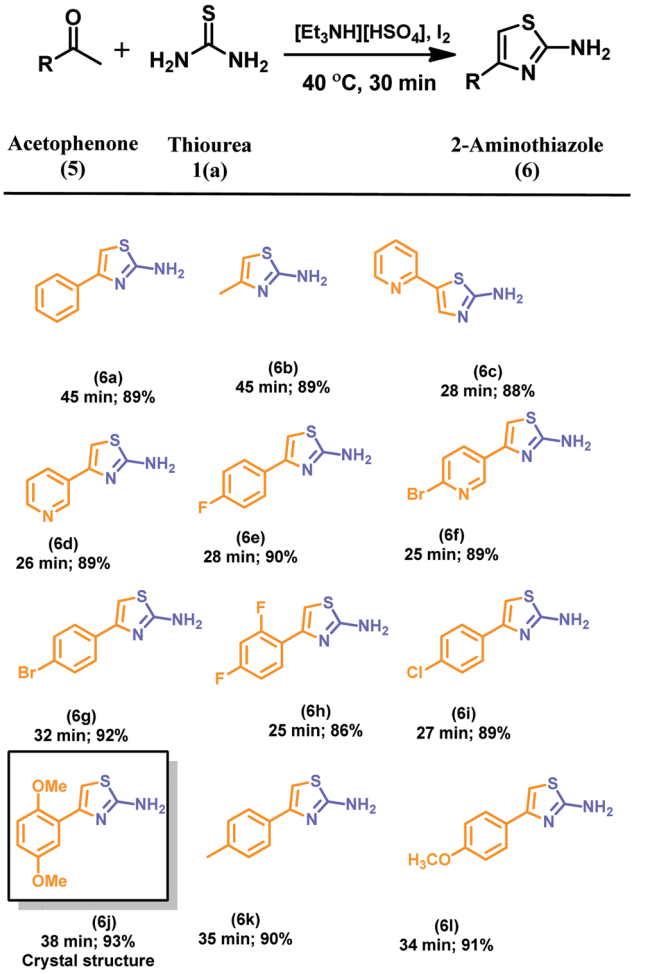
2.2.1.2 Plausible mechanism of the reaction. In the first step, in the presence of active iodine, thiourea was oxidised to furnish the electrophilic thionic intermediate (A). In the second step, acetophenone can enolize to 1-phenylethenol, promoted by protonation. Thereafter, 1-phenylethenol was attacked by sulfur of intermediate (A) to provide α-sulfur substituted ketone (B).

Table 5 Optimization of the reaction condition for the synthesis of 2-aminothiazole[a]

Amount of $[Et_3NH][HSO_4]$ mol%	Temperature (°C)	Time	Yield[b] (%)
0	100	12 h	72
5	100	8 h	77
10	80	6 h	83
10	40	3 h	83
15	**60**	**60 min**	**85**
15	40	30 min	92
15	rt	55 min	87
20	40	30 min	92
20	70	30 min	92
30	80	30 min	92

[a] Reaction conditions: acetophenone (1 mmol), thiourea (2 mmol), resub I_2 (1 mg), IL (15 mol%). [b] Isolated yields.

Table 6 Substrate scope for the synthesis of 2-aminothiazoles (**6a–6l**)[a]



[a] Reaction conditions: acetophenone (1 mmol), thiourea (2 mmol), resublimed I_2 (1 mg), IL (15 mol%).

In the third step, the nitrogen atom of its imine group promotes an intramolecular nucleophilic attack on the carbonyl carbon to facilitate 2-amino-4-phenyl-4,5-dihydrothiazol-4-ol (C), which thereby eliminates a molecule of water to give the final product 4-phenylthiazol-2-amine. The reaction mechanism pathway is outlined in Fig. 6.

Further, to confirm the formation 2-aminothiazoles, single crystal X-ray analysis of compound **6j** was performed. The crystal structure of compound **6j** is presented in Fig. 7, whereas the crystal packing diagram of 100, 010 and 001 planes are provided in Fig. S1 (ESI†). The hydrogen bonding of two molecules of **6j** shows an interesting interaction between O···H (*i.e.* between the oxygen atom of methoxy and the hydrogen atom of amine). The other parameters such as refinement table, fractional atomic coordinates, anisotropic displacement parameters, bond length, bond angles and hydrogen atom coordinates are provided in ESI† as Tables S6–S11.

2.2.2 Catalytic parameters for the synthesis of quinazolinone. For the optimization process, we chose the model reaction of isatoic anhydride (**7**), *p*-bromoaniline (**8**), triethyl orthoformate

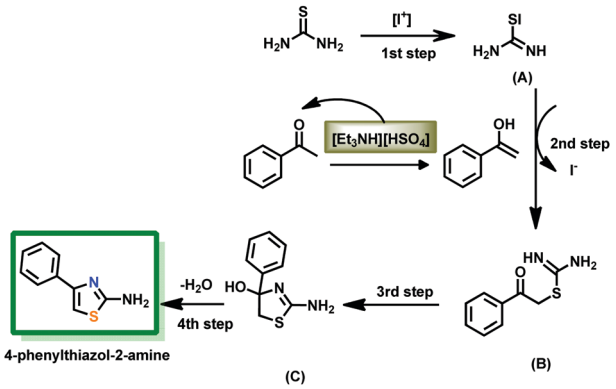


Fig. 6 Proposed mechanism for the synthesis of 2-aminothiazoles promoted by $[Et_3NH][HSO_4]$.

(TEOF) (**9**) in the presence of ionic liquid $[Et_3NH][HSO_4]$ to establish the process. By varying the amounts of $[Et_3NH][HSO_4]$, time and temperature of the reaction, the percentage yield of quinazolinone was affected, as shown in Table 7. It was found that by increasing the amount of IL3 to 15 mol%, had a spectacular impact on the yield of the product, but its further increment to 30 mol% had no such observational change. Furthermore, to introspect the pivotal role of time and temperature on the reaction, a varied range of temperature (room temperature to 100 °C) was used to carry the model reaction for a time range of (20 min–12 h). Conclusively, by using 15 mol% (0.029 g) of ionic liquid for a time of 20 mins at room temperature, a maximum percentage yield of 95% of the product was obtained. It was established that no further increase in temperature or prolong reaction time had any such significant change in the reaction yield. Our protocol surpassed the previously reported methods (Table S13, ESI†) of synthesis of this reaction as they had demonstrated the use of microwave irradiations, high temperature conditions and longer time duration, which we have established here under ambient reaction conditions.

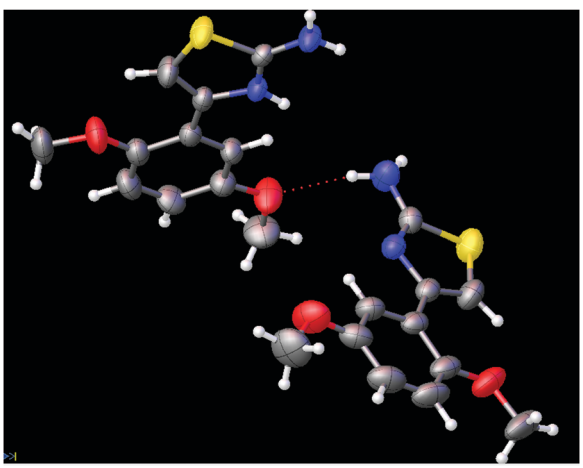


Fig. 7 Crystal structure of compound **6j** showing hydrogen bonding CCDC 1963534.†

Table 7 Optimization of the reaction condition for the synthesis of quinazolinones[a]

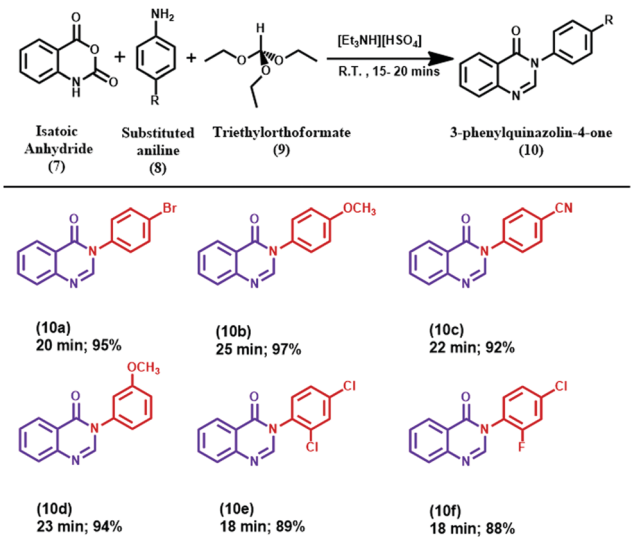
Amount of $[Et_3NH][HSO_4]$ mol%	Temperature (°C)	Time	Yield[b] (%)
0	100	12 h	80
5	100	6 h	82
10	80	1 h	85
10	40	45 min	87
10	R.T.	35 min	90
15	40	35 min	90
15	**R.T.**	**20 min**	**95**
20	R.T.	20 min	95
20	60	20 min	95
30	70	20 min	95

[a] Reaction conditions: isatoic anhydride (1 mmol), aniline (1 mmol), triethylorthoformate (1 mmol), IL (15 mol%). [b] Isolated yields.

2.2.2.1 Substrate scope for the synthesis of quinazolinone derivatives. Availing the optimized reaction conditions, we further synthesized a series of quinazolinones using isatoic anhydride (1 mmol), TEOF (1 mmol) and differently substituted anilines (1 mmol) to obtain derivatives having both electron-donating and electron-withdrawing substituents with good to excellent yields (Table 8). It was deciphered that anilines with electron-donating substituents generate products with very high yield (**10b**, **10d**). On the contrary, electron-withdrawing substituted anilines lead to moderate yield of products (**10a**, **10c**, **10e**, and **10f**).

2.2.2.2 Plausible reaction mechanism. We propose a plausible reaction mechanism for the one-pot multicomponent reaction for the synthesis of 3-phenyl quinazolin-4-one promoted by a simple ammonium ionic liquid, $[Et_3NH][HSO_4]$, as outlined in Fig. 8.

Table 8 Substrate scope for the synthesis of quinazolinones (**10a–10f**)[a]



[a] Reaction conditions: isatoic anhydride (1 mmol), substituted aniline (1 mmol), triethylorthoformate (1 mmol), IL (15 mol%).

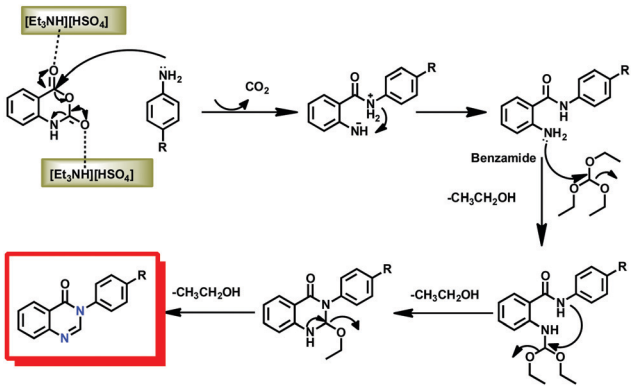


Fig. 8 Proposed mechanism for the synthesis of quinazolinone promoted by $[Et_3NH][HSO_4]$.

First, the ionic liquid activates the carbonyl group of isatoic anhydride followed by the nucleophilic attack by the lone pair electrons of aniline with the release of carbon dioxide. In the next step, there is the release of ethanol group and further attack of lone pair of electrons of the amine group in benzamide to triethylorthoformate. Finally, there is the loss of two ethanol groups and a ring closing reaction to yield the final product.

2.3 Preparation and characterizations of ionic liquid $[Et_3NH][HSO_4]$

2.3.1 Preparation of triethylammonium sulfate $[Et_3NH][HSO_4]$. The ionic liquid was synthesized by the previously reported method.[44a,b] Synthesis of IL was carried out in a 500 mL round-bottomed flask, which was immersed in a hot water bath and fitted with a reflux condenser. Then, 98% of sulfuric acid (98 g, 1.0 mol) solution in water was added dropwise into the trimethylamine (101 g, 1.0 mol) solution at 60 °C in 1 hour. After the addition, the reaction mixture was stirred for an additional period of 1 hour at 70 °C to ensure that the reaction had proceeded to completion. Traces of water were removed by heating the residue at 80 °C under high vacuum until the weight of the residue remained constant. The yield of $[Et_3NH][HSO_4]$ was 98%. ^{1}H NMR (DMSO-d_6): δ (ppm) 1.08 (t, J_1 = 8.32 Hz, J_2 = 8.73 Hz, 9H), 2.92 (q, 6H), 6.61 (brs, 1H), represented in Fig. 9.

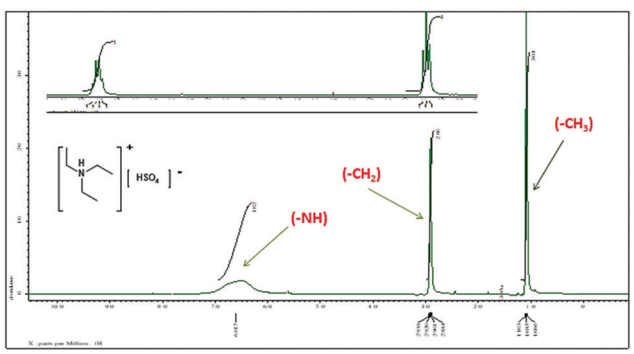


Fig. 9 Illustration of the ^{1}H NMR spectrum of $[Et_3NH][HSO_4]$.

2.3.2 Thermal studies

Differential scanning calorimetry (DSC). Differential scanning calorimetry (DSC) is a method which is widely used to observe the thermal behaviour of the ionic liquid $[Et_3NH][HSO_4]$.[45] This technique offers important advantages such as the small quantity of samples required for the experiment, rapidity of measurement, versatility and precision of temperature control. DSC of the ionic liquid has been performed in the temperature range (−100 to 400 °C). The DSC thermogram for the ionic liquid is given in Fig. 10. In the DSC curve, there is only one thermal transition, *i.e.* an endothermic peak at 300 °C, which is due to the melting transition of the ionic liquid.

Thermogravimetric analysis (TGA). Thermogravimetric analysis (TGA) was recorded to procure an insight into the stability of synthesised ammonium ionic liquid $[Et_3NH][HSO_4]$, as represented in Fig. 11. The thermogram curve shows two different regions. The weight loss in the first region, *i.e.* at 150–250 °C, is due to the loss of absorbed water and organic solvents. However, the main weight loss in the second region, *i.e.* at 330 °C, elucidates the complete decomposition of $[Et_3NH][HSO_4]$.

2.3.3 Toxicity of ammonium ionic liquid $[Et_3NH][HSO_4]$.

The very important consideration before commercialization of any process employing chemicals is the concept of toxicity. The reports on the toxicity of the reported ammonium ionic liquid $[Et_3NH][HSO_4]$ are limited.[46] However, on the basis of previously reported studies,[47–49] we have concluded that due to their simple construction from an acid and a base, we can expect toxicity similar to the parent amines and acids. Generally, quaternary ammonium ionic liquid toxicity depends upon the cation structure and chain length (longer alkyl chain increases toxicity), and hence, this can be minimized by choosing alkyl amines having a shorter chain length, which is considered in the present study. Hence, the overall order for the toxicity of quaternary ammonium ionic liquids, with some exceptions is $[Me_3NH][HSO_4] \leq [Et_3NH][HSO_4] < [Pr_3NH][HSO_4]$. We would like to point out that triethylamine does not bio-accumulate and the highest toxicity potential of triethyl is through inhalation, which is vastly reduced when bound in an ionic complex. Moreover, the hydrogen sulfate ions are not toxic in the dilute form. Considering corrosiveness, the hydrogen sulfate salts are acidic (pK_a of the HSO_4^- anion in dilute solution is approx. 2); however, they are significantly less than concentrated sulfuric acid and other strong acids. Briefly, corrosion could be a concern for process safety and equipment compatibility and needs to be considered carefully before designing ionic liquids.

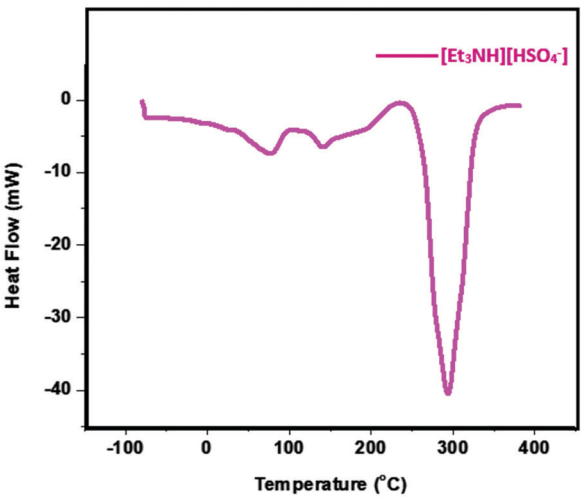


Fig. 10 Differential scanning calorimetry (DSC) curve of $[Et_3NH][HSO_4]$.

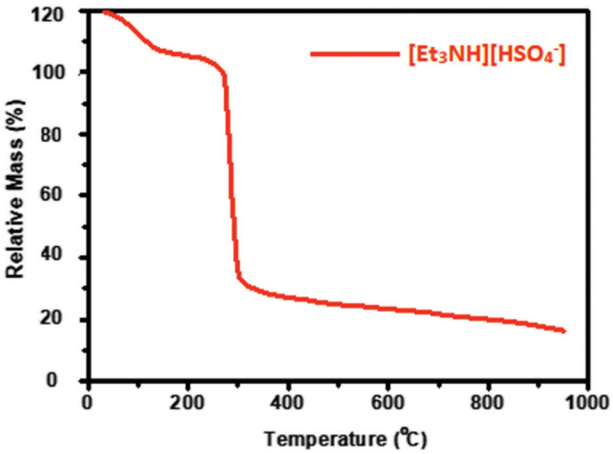


Fig. 11 Thermogravimetric analysis (TGA) curve of $[Et_3NH][HSO_4]$.

3. Experimental section

3.1 General information

Commercial solvents and reagents were used as received. All other reagents used were of analytical grade and obtained from Spectrochem and Merck. Double-distilled water was used throughout the experiment. Melting points are uncorrected. The thermal stability of ammonium ionic liquid $[Et_3NH][HSO_4]$ was determined using a PerkinElmer Pyris diamond TGA/differential thermal analyser. For obtaining the data, the sample was heated from room temperature to 1000 °C in N_2 atmosphere at a heating rate of 10 °C min^{-1} and gas flow of 200 mL min^{-1}. Differential scanning calorimetry (DSC) was used to investigate the thermal stability of the ionic liquid $[Et_3NH][HSO_4]$. The data were recorded by a conventional modulated differential scanning calorimetry (MDSC) method using a Q200 V24.11 Build 124 model. Thin-layer chromatography was performed on Merck pre-coated silica gel aluminium plates with 60 F_{254} indicator. The structural assignments of synthesised compounds were based on ^1H NMR, ^{13}C NMR, mass spectroscopy and single-crystal X-ray diffraction analysis. Nuclear magnetic resonance (NMR) was acquired at 400 MHz and 100 MHz for ^1H NMR and ^{13}C NMR respectively using a JEOL JNM-ECS 400 spectrometer instrument with $CDCl_3$ and DMSO-d_6 as solvents. TMS was taken as the reference in NMR, and data were processed with its delta software. Coupling constant (J) is reported in Hertz and chemical shift values are reported in ppm for ^1H NMR, and multiplicities are as follows: s (singlet), d (doublet), dd (double

doublet), t (triplet) and m (multiplet). High-resolution mass spectroscopy was carried out using an Agilent ESI-TOF mass spectrometer. X-ray analysis was carried out using an Oxford Diffraction Xcalibur four-circle diffractometer equipped with a Eos CCD detector using graphite mono-chromatized Mo-Kα radiation (λ = 0.71073 Å). For the single X-ray crystallography, crystals of compound **4k** and **6j** were grown in ethanol solvent at room temperature by slow evaporation of solution growth method.

3.2 General procedure for the synthesis of 1,2,3,4-tetrahydropyrimidine-2-thione/ones using $[Et_3NH][HSO_4]$ (4a–4o)

To an equivalent mixture of thiourea/urea (**1a**/**1b**) (1 mmol), ethyl acetoacetate (**2**) and substituted benzaldehyde (**3**), quaternary ammonium ionic liquid $[Et_3NH][HSO_4]$ (loading of 15 mol%) was added. The reaction mixture was stirred at room temperature for about 30–45 min. The progress of the reaction was monitored by TLC (eluent = *n*-hexane/EtoAc = 9/1). After completion of the reaction, the organic layer was extracted using ethyl acetate, which was further dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by recrystallization from ethanol or by column chromatography wherever required to obtain the pure desired 1,2,3,4-tetrahydropyrimidine-2-thione/ones (**4a–4o**) products. Finally, the product was confirmed by several known techniques such as ^{1}H NMR, ^{13}C NMR, High Resolution Mass Spectroscopy (HR-MS) and single-crystal X-ray diffraction analysis.

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a). White crystalline solid; M.P. = 200–202 °C. (206–207 °C).[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.56 (s, 1H), 6.94–6.79 (m, 5H), 6.26 (brs, 1H), 3.56 (q, J = 7.2 Hz, 2H), 1.85 (s, 3H), 0.68 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.63, 152.98, 147.65, 144.56, 128.13, 127.16, 126.42, 99.95, 59.33, 54.64, 13.95, 8.40. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}N_2O_3$: 260.1177; found 261.1247 [M + H].

Ethyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b). White crystalline solid; M.P. = 200–201 °C (208–209 °C).[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.27 (s, 1H), 8.64 (s, 1H), 7.11–6.97 (m, 5 H), 5.15 (s, 1H), 3.88 (q, 2H), 2.16 (s, 3H), 0.97 (t, J_1 = 8.01 Hz, J_2 = 7.98 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.63, 165.62, 144.28, 143.34, 129.04, 127.36, 126.35, 101.95, 60.02, 55.40, 18.36, 14.63. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}N_2O_2S$: 276.0928; found 277.1007 [M + H].

Ethyl-6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c). White crystalline solid; M.P. = 204–206 °C (206–207 °C).[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.034 (s, 1H), 7.19 (d, J = 8.12 Hz, 2H), 7.08 (d, J = 8.31 Hz, 2H), 5.26 (s, 1H), 4.03 (q, 2H), 2.93 (s, 1H), 2.30 (s, 6H), 1.17 (t, J_1 = 8.12 Hz, J_2 = 8.32 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 170.78, 158.24, 152.49, 146.72, 141.72, 133.86, 131.41, 105.29, 64.42, 59.42, 25.92, 23.13, 19.07.

Ethyl-6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d). White crystalline solid; M.P. = 207–208 °C. ^{1}H NMR (400 MHz, CDCl3) δ ppm: 9.18 (s, 1H), 8.52 (s, 1H), 6.92 (d, J = 8 Hz, 2H), 6.82 (d, J = 8 Hz, 2H), 5.02 (s, 1H), 3.79 (q, 2H), 2.06 (s, 3H), 2.03 (s, 3H), 0.89 (t, J_1 = 8.12 Hz, J_2 = 8.01 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.50, 165.60, 144.10, 140.42, 137.38, 129.07, 126.66, 101.97, 60.02, 54.95, 21.00, 17.79, 14.03. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}N_2O_2S$: 290.1098; found 291.1172 [M + H].

Ethyl-4-(4-hydroxy-3,5-ditertbutylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e). White crystalline solid; M.P. = 210–212 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.48 (s, 1H), 7.36 (s, 2H), 5.10 (s, 1H), 3.84 (brs, 3H), 2.74 (q, 2H), 1.41 (s, 18H), 0.95 (t, J_1 = 8.33 Hz, J_2 = 8.46 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 191.93, 190.64, 159.83, 137.51, 127.97, 127.80, 127.32, 126.52, 53.75, 53.56, 34.14, 31.12, 30.13, 29.17. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{32}N_2O_4$: 388.2362; found 389.2421 [M + H].

Ethyl-4-(4-hydroxy-3,5-ditertbutylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f). White crystalline solid; M.P. = 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.28 (s, 1H), 7.15 (s, 2H), 4.88 (s, 1H), 3.98 (brs, 3H), 2.51 (q, 2H), 0.93 (s, 18H), 0.75 (t, J_1 = 8.23 Hz, J_2 = 8.13 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 191.69, 184.38, 176.86, 160.08, 137.53, 128.24, 127.32, 110.49, 53.67, 45.49, 34.42, 29.97, 12.88, 8.54. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{32}N_2O_3S$: 404.2134; found 405.2213 [M + H].

Ethyl-4-(3-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g). White crystalline solid; M.P. = 209–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.94 (s, 1H), 7.08 (dd, J = 12.2, 7.6 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 11.3 Hz, 1H), 6.74 (t, J = 8.4 Hz, 1H), 5.13 (s, 1H), 3.86 (q, 2H), 2.14 (s, 3H), 0,97 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 170.62, 165.67, 158.09, 153.26, 152.18, 134.80, 127.18, 118.48, 118.26, 104.57, 64.53, 59.26, 23.15, 19.05.

Ethyl-4-(3-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h). White crystalline solid; M.P. = 213–214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.88 (s, 1H), 9.26 (s, 1H), 7.12 (dd, J = 13.5, 7.84 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.78–6.84 (m, 2H), 5.13 (s, 1H), 3.91 (q, 2H), 2.17 (s, 3H), 1.00 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.62, 168.71, 158.09, 153.26, 152.18, 134.87, 127.18, 119.14, 118.93, 104.57, 64.53, 59.26, 23.15, 19.05. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}FN_2O_2S$: 294.0838; found 295.0885 [M + H].

Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i). White crystalline solid; M.P. = 202–204 °C (215–216 °C).[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.26 (s, 1H), 7.78 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.24 (s, 1H), 5.13 (s, 1H), 3.97 (q, J = 7.1 Hz, 2H), 2.24 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 163.10, 149.93, 146.62, 141.69, 129.77, 126.24, 126.01, 96.74, 57.13, 51.38, 15.78, 12.01. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}ClN_2O_3$: 294.0775; found 295.0838 [M + H].

Ethyl-4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j). White crystalline solid; M.P. = 208–210 °C (180–181 °C).[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.50 (s, 1H), 8.86 (s, 1H), 7.05 (d, J = 6 Hz, 2H), 6.90 (d, J = 7 Hz, 2H), 4.93 (s, 1H), 3.96 (q, 2H), 1.97 (s, 3H), 0.93 (t, J_1 = 8.01 Hz, J_2 = 8.21 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 194.51, 167.71, 167.17, 130.97, 130.62, 128.96, 128.23, 101.13, 61.59, 54.23, 26.30, 13.98. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}ClN_2O_2S$: 310.0535; found 311.0615 [M + H].

Ethyl-4-(3-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k). Yellowish white crystalline solid; M.P. = 210–212 °C (188–189 °C).[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.02 (s, 1H), 7.51 (s, 1H), 7.17 (d, J = 12.4 Hz, 1H), 7.10–7.14 (m, 2H), 5.14 (, 1H), 3.94 (q, 2H), 2.20 (s, 3H), 1.05 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.36, 151.45, 147.51, 145.96, 132.38, 128.69, 126.08, 125.53, 123.78, 98.01, 58.30, 53.02, 17.02, 13.01. HRMS (ESI): m/z calcd for $C_{14}H_{15}ClN_2O_2S$: 294.0769; found 295.0838 [M + H].

Ethyl-4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l). White crystalline solid; M.P. = 198-200 °C (201-202 °C).[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.97 (s, 1H), 7.37 (d, J = 7.1 Hz, 1H), 7.11 (t, J = 7 Hz, 2H), 6.96 (t, J = 7.2 Hz, 1H), 5.59 (s, 1H), 5.24 (s, 1H), 3.81 (q, 2H), 2.23 (s, 3H), 0.89 (t, J_1 = 8.12 Hz, J_2 = 8.33 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.30, 151.12, 148.08, 141.35, 131.60, 128.10, 127.43, 127.01, 121.56, 97.48, 58.37, 53.30, 16.93, 12.94. HRMS (ESI): m/z calcd for $C_{14}H_{15}BrN_2O_3$: 338.0266; found 339.0340 [M + H].

Ethyl-4-(2-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m). White crystalline solid; M.P. = 201–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.46 (s, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.90 (d, J = 8,1 Hz, 1H), 6.66 (dd, J = 10.2, 6.5 Hz, 2H), 5.13 (s, 1H), 2.43 (q, 2H), 1.77 (s, 3H), 0.43 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppms: 182.53, 177.73, 170.76, 147.30, 132.77, 131.21, 130.67, 128.78, 121.86, 104.05, 59.88, 43.70, 12.20, 6.95. HRMS (ESI): m/z calcd for $C_{14}H_{15}BrN_2O_2S$: 354.0038; found 357.0061 [M + H].

Ethyl-4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n). Yellowish white crystalline solid; M.P. = 208–210 °C (212–213 °C).[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.26 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.11 (s, 1H), 5.32 (s, 1H), 4.04 (q, J = 7.1 Hz, 2H), 2.30 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.74, 152.96, 147.88, 143.62, 131.44, 128.53, 121.23, 100.05, 59.80, 54.65, 18.48, 14.19. HRMS (ESI): m/z calcd for $C_{14}H_{15}BrN_2O_3$: 338.0274; found 339.0352 [M + H].

Ethyl-4-(3-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4o). Yellowish white crystalline solid; M.P. = 201–204 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.53 (s, 1H), 7.00 (t, J = 8.2 Hz, 1H), 6.83 (s, 1H), 6.79 (d, J = 7.1 Hz, 1H), 6.59 (m, 1H), 4.64 (s, 1H), 3.43 (q, 2H), 1.71 (s, 3H), 0.56 (t, J_1 = 8.11 Hz, J_2 = 7.98 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.13, 151.29, 147.23, 145.95, 129.15, 128.78, 128.27, 123.00, 120.55, 97.85, 58.11, 52.88, 16.83, 12.76. HRMS (ESI): m/z calcd for $C_{14}H_{15}BrN_2O_3$: 338.0266; found 339.0339 [M + H].

3.3 General procedure for the synthesis of 2-aminothiazoles using $[Et_3NH][HSO_4]$ (6a–6l)

Using the optimized reaction conditions, initially, acetophenone (1 mmol), thiourea (2 mmol) and resublimed iodine were taken in a round-bottomed flask and 15 mol% $[Et_3NH][HSO_4]$ was added to the reaction mixture. All the contents were heated at 40 °C for 30 min. The progress of the reaction was monitored by thin-layer chromatography (eluent = n-hexane/EtoAc = 9/1). The crude product was purified by recrystallization from ethanol to obtain the pure desired 2-aminothiazoles (**6a–6l**) products. Finally, the product was confirmed by several known techniques such as ^{1}H NMR, ^{13}C NMR, high-resolution mass spectroscopy (HR-MS) and single-crystal X-ray diffraction analysis. Melting points of the compounds were also taken.

4-Phenylthiazol-2-amine (6a). Light yellow coloured crystalline solid; M.P. = 150 °C (151–153 °C).[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.77–7.75 (d, J = 7.89 Hz, 2H), 7.39–7.35 (m, 2H), 7.30 (d, J = 7.1 Hz, 1H), 6.70 (s, 1H), 5.30 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.23, 158.23, 128.91, 119.68, 118.11, 117.09, 111.86. HRMS (ESI): m/z calcd for $C_9H_8N_2S$: 176.0412; found 177.0485 [M + H].

4-Methylthiazol-2-amine (6b). Yellow coloured solid; M.P. = 42–43 °C (45–46 °C).[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.24 (s, 1H), 4.95 (brs, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.42, 153.90, 104.16, 15.00. HRMS (ESI): m/z calcd for $C_4H_6N_2S$: 114.0252; found 115.0325 [M + H].

4-(Pyridin-2-yl)thiazol-2-amine (6c). Yellow coloured solid; M.P. = 144–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.40 (d, J = 10.59 Hz, 1H), 7.71 (dd, 1H), 7.53 (dd, 1H), 7.09–6.98 (m, 2H), 5.72 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.37, 150.61, 141.81, 134.76, 128.45, 127.41, 125.78, 101.81. HRMS (ESI): m/z calcd for $C_8H_7N_3S$: 177.0361; found 178.0445 [M + H].

4-(Pyridin-3-yl)thiazol-2-amine (6d). Yellow coloured solid; M.P. = 175–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.68 (s, 1H), 8.13 (d, J = 8.12 Hz, 1H), 7.74 (d, J = 8.08 Hz, 1H), 6.97 (m, 1H), 6.49 (s, 1H), 6.21 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 167.76, 146.92, 146.37, 146.07, 131.76, 129.59, 122.28, 101.85. HRMS (ESI): m/z calcd for $C_8H_7N_3S$: 177.0361; found 178.0428 [M + H].

4-(4-Fluorophenyl)thiazol-2-amine (6e). Yellow coloured solid; M.P. = 103–104 °C (102–103 °C).[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.72 (t, J_1 = 7.2 Hz, J_2 = 6.8 Hz, 2H), 7.05 (t, J_1 = 8.3 Hz, J_2 = 8.6 Hz, 2H), 6.63 (s, 1H), 5.19 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 167.45, 148.30, 130.06, 126.62, 114.40, 114.19, 100.40. HRMS (ESI): m/z calcd for $C_9H_7FN_2S$: 194.0311; found 195.0381 [M + H].

4-(3-Bromopyridin-2-yl)thiazol-2-amine (6f). Yellow coloured solid; M.P. = 182–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.48 (s, 1H), 7.82 (d, J = 14.4 Hz, 1H), 7.15 (d, J = 17.2 Hz, 1H), 6.71 (s, 1H), 5.28 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 166.40, 146.51, 144.40, 141.89, 139.61, 137.34, 135.05, 112.66. HRMS (ESI): m/z calcd for C_8H_6BrN3S: 254.0948; found 2555.9556 [M + H].

4-(4-Bromophenyl)thiazol-2-amine (6g). Yellow coloured solid; M.P. = 180–181 °C (180–183 °C).[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.63 (t, J = 7.69 Hz, 2H), 6.95 (m, 2H), 6.53 (s, 1H), 5.10 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 167.65, 148.50, 130.26, 126.82, 114.60, 114.39, 100.60. HRMS (ESI): m/z calcd for $C9H_7BrN_2S$: 253.9521; found 254.9594 [M + H].

4-(2,4-Difluorophenyl)thiazol-2-amine (6h). Yellow coloured solid; M.P. = 153–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.73–7.67 (m, 1H), 6.59–6.53 (m, 3H), 5.91 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.10, 161.11, 160.25, 153.58, 131.76, 120.98, 111.20, 105.18, 103.83. HRMS (ESI): m/z calcd for $C_9H_6F_2N_2S$: 212.0219; found 213.0291 [M + H].

4-(4-Chlorophenyl)thiazol-2-amine (6i). Yellow coloured crystalline solid; M.P. = 163–164 °C (161–162 °C).[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.70 (d, J = 8.13 Hz, 2H), 7.33 (d, J = 8.16 Hz, 2H), 6.69 (s, 1H), 4.98 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.66, 145.77, 127.63, 126.06, 123.41, 122.41, 96.02. HRMS (ESI): m/z calcd for $C_9H_7ClN_2S$: 210.0018; found 211.0086 [M + H].

4-(2,5-Dimethoxyphenyl)thiazol-2-amine (6j). Yellow coloured crystalline solid; M.P. = 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.66 (d, J = 3.2 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 5.00 (brs, 2H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.60, 152.43, 150.33, 149.21, 117.53, 116.26, 115.11, 114.77, 96.02, 59.97, 59.57. HRMS (ESI): m/z calcd for $C_{11}H_{12}N_2O_2S$: 236.0609; found 237.0751 [M + H].

4-(*p*-Tolyl)thiazol-2-amine (6k). Yellow coloured crystalline solid; M.P. = 135–136 °C (136–137 °C).[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.65 (d, J = 8.23 Hz, 2H), 7.17 (d, J = 8.23 Hz, 2H), 6.63 (s, 1H), 5.19 (brs, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 167.43, 151.37, 137.60, 132.03, 129.36, 125.96, 102.04, 21.34. HRMS (ESI): m/z calcd for $C_{10}H_{10}N_2S$: 190.0565; found 191.0639 [M + H].

4-(4-Methoxyphenyl)thiazol-2-amine (6l). Yellow coloured crystalline solid; M.P. = 205–206 °C (206–207 °C).[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.72 (d, J = 8.01 Hz, 2H), 6.90 (d, J = 8.12 Hz, 2H), 6.56 (s, 1H), 5.91 (brs, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.33, 161.32, 156.94, 130.56, 127.62, 116.20, 102.02, 57.28. HRMS (ESI): m/z calcd for $C_{10}H_{10}N_2OS$: 206.0514; found 207.0589 [M + H].

3.4 General procedure for the synthesis of 3-phenylquinozolin-4-one using $[Et_3NH][HSO_4]$ (10a–10f)

To equimolar amounts of isatoic anhydride (1 mmol), aniline (1 mmol), triethylorthoformate (1 mmol), 15 mol% of the ionic liquid $[Et_3NH][HSO_4]$ was added and the reaction mixture was stirred at room temperature for about 2 h. The progress of the reaction was monitored using the medium of thin-layer chromatography (TLC) (eluent = *n*-hexane/EtoAc = 9/1). After the reaction goes to completion, the crude product was extracted using ethyl acetate, which was then further purified by recrystallisation using ethanol to obtain the pure 3-phenylquinozolin-4-one product. Finally, the product was characterised using spectroscopic techniques such as ^{1}H NMR, and ^{13}C NMR, which confirm its synthesis. Melting points of the compounds were also taken.

3-(4-Bromophenyl)quinazolin-4(3H)-one (10a). Light yellow coloured crystalline solid; M.P. = 192–193 °C (188–190 °C).[53] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.35–8.33 (d, J = 7.5 Hz, 1H), 8.08 (s, 1H), 7.83–7.75 (m, 2H), 7.69–7.67 (d, J = 8.5 Hz, 2H), 7.57–7.53 (t, J_1 = 7 Hz, J_2 = 7.7 Hz, 1H), 7.33–7.28 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 160.54, 147.75, 145.48, 136.41, 134.77, 132.84, 128.63, 127.84, 127.67, 127.16, 123.16, 122.18.

3-(4-Methoxyphenyl)quinazolin-4(3H)-one (10b). Light yellow coloured crystalline solid; M.P. = 182–183 °C (180 °C).[53] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.39–8.37 (d, J = 7.75 Hz, 1H), 8.13 (s, 1H), 7.82–7.77 (m, 2H), 7.58–7.541 (t, J_1 = 6.75 Hz, J_2 = 8 Hz, 1H), 7.37–7.28 (d, J = 8.75 Hz, 2H), 7.07–7.05 (d, J = 8.75 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 161.03, 159.92, 147.91, 146.44, 134.50, 130.18, 128.15, 127.55, 127.16, 122.39, 114.84, 77.37, 55.63.

3-(4-Chlorophenyl)quinazolin-4(3*H*)-one (10c). Light yellow coloured crystalline solid; M.P. = 200–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.39 (d, J = 7.5 Hz, 1H), 8.13 (s, 1H), 7.80–7.90 (m, 4H), 7.64 (d, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 160.27, 147.58, 144.64, 141.06, 135.12, 133.54, 128.18, 127.91, 127.82, 127.28, 117.81, 113.16.

3-(3-Methoxyphenyl)quinazolin-4(3*H*)-one (10d). Light yellow coloured crystalline solid; M.P. = 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.40 (d, J = 7.8 Hz, 1H), 8.16 (s, 1H), 7.79–7.85 (m, 2H), 7.57–7.60 (m, 1H), 7.48 (t, J = 8.0 Hz, 1H), 6.99–7.07 (m, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 160.72, 160.43, 147.77, 146.12, 138.48, 134.64, 130.43, 127.70, 127.54, 127.21, 122.36, 119.11, 115.11, 112.84, 77.36, 55.58.

3-(2,4-Dichlorophenyl)quinazolin-4(3*H*)-one (10e). Light yellow coloured crystalline solid; M.P. = 192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.52 (s, 1H), 8.34 (d, J = 7.5 Hz, 1H), 8.08 (s, 1H), 7.75–7.83 (m, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.08, 146.42, 143.45, 139.99, 133.93, 132.35, 129.02, 126.99, 126.72, 126.63, 126.09, 123.27, 122.65, 120.88.

3-(4-Chloro-2-fluorophenyl)quinazolin-4(3*H*)-one (10f). Light yellow coloured crystalline solid; M.P. = 183–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.56 (s, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.13 (s, 1H), 7.77–7.83 (m, 2H), 7.54–7.58 (m, 1H), 7.36 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.05, 156.34, 155.23, 141.47, 138.22, 133.97, 132.20, 129.62, 128.03, 127.16, 126.36, 124.75, 123.87, 115.74.

4. Conclusions

In conclusion, simple ammonium ionic liquids $[Et_3NH][HSO_4]$ are highly efficient, environmentally benign, atom economic, and facile protocol for the synthesis of bioactive 1,2,3,4-tetrahydropyrimidine-2-thione/ones as well as 2-aminothiazoles and quinazolinones *via* a multicomponent reaction. Remarkable advantages of this protocol are as follows: (I) the Biginelli condensation reaction was in good agreement with the green chemistry parameters like *E*-factor (0.42), process mass intensity (1.42), reaction mass efficiency (70%), atom economy (88%) and carbon efficiency (80%); (II) the Hantzsch reaction for the synthesis of 2-aminothiazoles and Niementowski reaction for the synthesis of quinazolinones was found to be very effective and selective in the presence of $[Et_3NH][HSO_4]$; (III) this protocol features high functional group compatibility and easily accessible starting materials; (IV) one-pot sequential transformation was easily achieved; and (V) the ionic liquid is easily recovered and could be reused for at least six consecutive cycles. The stability of synthesized 1,2,3,4-tetrahydropyrimidine-2-thione/ones and 2-aminothiazoles were affirmed by single-crystal X-ray

crystallographic technique. Moreover, this protocol is plausible to be fruitful for the widespread organic transformations and for the synthesis of a pharmaceutically pertinent architecture.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Praachi Kakati: conceptualization, methodology, software, visualization, writing-original draft preparation. Preeti Singh: conceptualization, methodology, software, visualization, writing-original draft preparation. Priyanka Yadav: software, validation, writing, reviewing and editing. Satish K. Awasthi: supervision.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

All authors thank Department of chemistry, University of Delhi for providing the necessary facilities and USIC, University of Delhi for DSC, TGA, Single crystal XRD, ^{1}H NMR, ^{13}C NMR and Mass spectral data. PK is thankful to DST-INSPIRE for providing Junior Research Fellowship. PS and PY are thankful to UGC (University Grant Commission), India for providing Senior Research Fellowship. SKA is thankful to SERB (SERB/F/9974/2016-17), New Delhi, for financial support.

References

1 R. W. Lewis, J. Mabry, J. G. Polisar, K. P. Eagen, B. Ganem and G. P. Hess, Dihydropyrimidinone positive modulation of δ-subunit-containing γ-aminobutyric acid type A receptors, including an epilepsy-linked mutant variant, *Biochemistry*, 2010, **49**, 4841–4851.

2 J. P. Wan and Y. Pan, Recent advance in the pharmacology of dihydropyrimidinone, *Mini-Rev. Med. Chem.*, 2012, **12**, 337–349.

3 L. S. Jeong and G. Buenger, Mc Cormack, J. J.; Cooney, D. A.; Zhang, H.; Marquez, V. E. Carbocyclic analogues of the potent cytidine deaminase inhibitor 1-(β-D-ribofuranosyl)-1,2- dihydropyrimidin-2-one (Zebularine), *J. Med. Chem.*, 1998, **41**, 2572–2578.

4 T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber and T. J. Mitchison, Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen, *Science*, 1999, **286**, 971–974.

5 X. Zhu, G. Zhao and X. Zhou, *et al.*, 2,4-Diaryl-4,6,7,8-tetrahydroquinazolin- 5(1*H*)-one derivatives as anti-HBV agents targeting at capsid assembly, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 299–301.

6 S. A. Karnail, N. S. Brian and E. U. Steven, *et al.*, Dihydropyrimidine calcium channel blockers. 3, 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl- 5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents, *J. Med. Chem.*, 1991, **34**, 806–811.

7 B. Jauk, T. Pernat and C. O. Kappe, Design and synthesis of a conformation- ally rigid mimic of the dihydropyrimidine calcium channel modulator SQ 32,926, *Molecules*, 2000, **5**, 227–239.

8 K. N. Venugopala, S. K. Nayak, M. Pillay, R. Prasanna, Y. M. Coovadia and B. Odhav, Synthesis and antitubercular activity of 2-(substituted phenyl/benzyl-amino)-6-(4-chlorophenyl)-5-(methoxycarbonyl)-4-methyl-3,6- dihydropyrimidin-1-ium chlorides, *Chem. Biol. Drug Des.*, 2013, **81**, 219–227.

9 A. E. S. Wael, F. N. Ibrahim, A. H. Adel and R. Abdel, C-furyl glycosides, II: synthesis and antimicrobial evaluation of C-furyl glycosides bearing pyrazolines, isoxazolines, and 5,6-dihydropyrimidine-2(1*H*)-thiones, *Monatsh. Chem.*, 2009, **140**, 365–370.

10 T. B. Shah, A. Gupte, M. R. Patel, V. S. Chaudhari, H. Patel and V. C. Patel, Synthesis and in vitro study of biological activity of heterocyclic N-mannich bases of 3,4-dihydropyrimidine-2(1H)-thiones, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2010, **49**, 578–586.

11 Z. M. Nofal, H. H. Fahmy, E. S. Zarea and W. El-Eraky, Synthesis of new pyrimidine derivatives with evaluation of their anti-inflammatory and analgesic activities, *Acta Pol. Pharm.*, 2011, **68**, 507–517.

12 B. Salehian, *et al.*, Clinical Trials in Management of Anaplastic Thyroid Carcinoma; Progressions and Set Backs: A Systematic Review, *Int. J. Endocrinol. Metab.*, 2019, **17**, 67759.

13 J. J. Vicente and L. Wordeman, The quantification and regulation of microtubule dynamics in the mitotic spindle, *Curr. Opin. Cell Biol.*, 2019, **60**, 36–43.

14 F. J. Meng, L. Shi, G. S. Feng, L. Sun and Y. G. Zhou, Enantioselective Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones through Organocatalytic Transfer Hydrogenation of 2-Hydroxypyrimidines, *J. Org. Chem.*, 2019, **84**, 4435–4442.

15 (*a*) D. W. MacMillan, The advent and development of organocatalysis, *Nature*, 2008, **455**, 304–308; (*b*) X. Gao, Y. M. Pan, M. Lin and Z. P. Zhan, Facile one-pot synthesis of three different substituted thiazoles from propargylic alcohols, *Org. Biomol. Chem.*, 2010, **8**, 3259–3266; (*c*) F. Xie, Q. Chen, R. Xie, H. Jiang and M. Zhang, MOF-Derived Nanocobalt for Oxidative Functionalization of Cyclic Amines to Quinazolinones with 2-Aminoarylmethanols, *ACS Catal.*, 2018, **8**, 5869–5874.

16 S. Saha and J. N. Moorthy, Enantioselective Organocatalytic Biginelli Reaction: Dependence of the Catalyst on Sterics, Hydrogen Bonding, and Reinforced Chirality, *J. Org. Chem.*, 2011, **76**, 396–402.

17 S. Sepehri, S. Soleymani, R. Zabihollahi, M. R. Aghasadeghi, M. Sadat, L. Saghaie, H. R. Memarian and A. Fassihi, Design, synthesis and anti -HIV-1 evaluation of a novel series of 1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives, *Chem. Biodiversity*, 2018, **15**, 1700502.

18 L. Q. Kang, D. Y. Jin and Y. Q. Cai, Silica-Supported Ionic Liquid Si-[SbSipim][PF6]: An Efficient Catalyst for the Synthesis of 3,4- Dihydropyrimidine-2-(1H)-ones, *Synth. Commun.*, 2013, **43**, 1896.

19 M. Wu, J. Yu, W. Zhao, J. Wu and S. Cao, One-pot synthesis of difluoromethyl-containing dihydropyrimidinones catalyzed by Yb(PFO)3 under solvent and dehydrating agent free conditions, *J. Fluorine Chem.*, 2011, **132**, 155–159.
20 H. Kumar and A. Parmar, Ultrasound promoted ZrCl4 catalyzed rapid synthesis of substituted 1,2,3,4-tetrahydropyrimidine-2-ones in solvent or dry media, *Ultrason. Sonochem.*, 2008, **15**, 129–132.
21 S. F. T. Hatkehlouei, B. Mirza and S. Soleimani- Amiri, Solvent-Free One-Pot Synthesis of Diverse Dihydropyrimidinones/Tetrahydropyrimidinones Using Biginelli Reaction Catalyzed by Fe3O4@C@OSO3H, *Polycyclic Aromat. Compd.*, 2020, 1–17.
22 M. Sadeghi, J. Safari and Z. Zarnegar, Synthesis of 2-aminothiazoles from methylcarbonyl compounds using a Fe3O4 nanoparticle-N-halo reagent catalytic system, *RSC Adv.*, 2016, **6**, 64749.
23 B. Chen, S. Guo, X. Guo, G. Zhang and Y. Yu, Selective Access to 4-Substituted 2-Aminothiazoles and 4-Substituted 5-Thiocyano-2-aminothiazoles from Vinyl Azides and Potassium Thiocyanate Switched by Palladium and Iron Catalysts, *Org. Lett.*, 2015, **17**, 4698–4701.
24 J. Safari, Z. Abedi-Jazini, Z. Zarnegar and M. Sadeghi, Nano-chitosan: A biopolymer catalytic system for the synthesis of 2-aminothiazoles, *Catal. Commun.*, 2016, **77**, 108–112.
25 H. Karade, M. Sathe and M. P. Kaushik, An efficient method for the synthesis of 2-aminothiazoles using silica chloride as a heterogeneous catalyst, *Catal. Commun.*, 2007, **8**, 741–746.
26 H. Nagarajaiah, A. K. Mishra and J. N. Moorthy, Mechanochemical solid-state synthesis of 2-aminothiazoles, quinoxalines and benzoylbenzofurans from ketones by one-pot sequential acid- and base-mediated reactions, *Org. Biomol. Chem.*, 2016, **14**, 4129.
27 M. Bakavoli, O. Sabzevari and M. Rahimizadeh, H-Y-zeolites induced heterocyclization: Highly efficient synthesis of substituted-quinazolin-4(3H)ones under microwave irradiation, *Chin. Chem. Lett.*, 2007, **18**, 533–535.
28 Ali A. Mohammadi and S. S. Sadat Hossini, KAl(SO4)2·12H2O (Alum) Catalyzed One-Pot Three-Component Synthesis of 2-Alkyl and 2-Aryl-4(3H)-quinazolinone under Microwave Irradiation and Solvent Free Conditions, *Chin. J. Chem.*, 2011, **29**, 1982–1984.
29 G. Ezikiel, T. Yakaiah and G. Venkat Reddy, Shanthan Rao, P. Nafion-H: An Efficient and Recyclable Heterogeneous Catalyst for the One-Pot Synthesis of 2,3-Disubstituted 4-(3H)-Quinazolinones under SolventFree Microwave Irradiation Conditions, *Synlett*, 2006, 2507–2509.
30 K. Van Aken, L. Strekowski and L. Patiny, Eco Scale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters, *J. Org. Chem.*, 2006, **2**, 3.
31 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, 1998.
32 P. T. Anastas and M. M. Kirchhoff, Origins, current status, and future challenges of green chemistry, *Acc. Chem. Res.*, 2002, **35**, 686–694.
33 K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perryand and M. Stefaniak, Green chemistry tools to influence a medicinal chemistry and research chemistry based organization, *Green Chem.*, 2008, **10**, 31–36.
34 P. Sledz, M. Mauduit and K. Grela, Olefin metathesis in ionic liquids, *Chem. Soc. Rev.*, 2008, **37**, 2433–2442.
35 C. Maton, N. Vos and C. V. Stevens, Ionic liquid thermal stabilities: decomposition mechanism and analysis tools, *Chem. Soc. Rev.*, 2013, **42**, 5963–5977.
36 J. P. Hallett and T. Welton, Room temperature ionic liquids: solvent for synthesis and catalysis, *Chem. Rev.*, 2011, **111**, 3508–3576.
37 S. Anwar, I. M. Baltork, S. Tangestaninejad, M. Moghadam, V. Mirkhani, A. R. Khosropour, A. L. Isfahani and R. Kia, New pyridinium based ionic liquid as an excellent solvent-catalyst system for the one-pot three component synthesis of 2,3-disubstituted quinolones, *ACS Comb. Sci.*, 2014, **16**, 93–100.
38 P. Singh, P. Yadav, A. Mishra and S. K. Awasthi, Green and Mechanochemical One-Pot Multicomponent Synthesis of Bioactive 2-amino-4H-benzo[b]pyrans via Highly Efficient Amine-Functionalized SiO2@Fe3O4 Nanoparticles, *ACS Omega*, 2020, **5**(8), 4223–4232.
39 R. Tyebee and M. Ghadamgahi, Solvent free one-pot multi-component synthesisof 3,4-dihydropyrimidin-2(1H)-ones catalyzed bymesoporous NH4H2PO4/MCM-41 as anenvironmentally friendly, cheap, and effective catalyst, *Arabian J. Chem.*, 2017, **10**, S757–S764.
40 N. D. Kadam and R. V. Jayaram, Poly Ethylene Glycol Based Dicationic Acidic Ionic Liquid [PEG-DAIL][Cl] Used as Cost Effective and Recyclable Catalyst for Biginelli Reactions, *Curr. Catal.*, 2018, **7**(1), 52–59.
41 N. D. Kadam and R. V. Jayaram, Poly Ethylene Glycol Based Dicationic Acidic Ionic Liquid [PEG-DAIL][Cl] Used as Cost Effective and Recyclable Catalyst for Biginelli Reactions, *Curr. Catal.*, 2018, **7**(1), 52–59.
42 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: A complete structure solution, refinement and analysis program, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.
43 L. J. Farrugia, ORTEP 3 for windows, *J. Appl. Crystallogr.*, 1997, **30**, 565.
44 (*a*) J. Weng, C. Wang, H. Li and Y. Wang, Novel quaternary ammonium ionic liquids and their use as dual solvent-catalysts in the hydrolytic reaction, *Green Chem.*, 2006, **8**, 96–99; (*b*) C. Wang, L. Guo, H. Li, Y. Wang, J. Weng and L. Wu, Preparation of simple ammonium ionic liquids and their applications in the cracking of dialkoxypropanes, *Green Chem.*, 2006, **8**, 603–607.
45 *Differential Scanning Calorimetry*, ed. G. Hohne, W. Hemminger and H. J. Flammersheim, Springer, Berlin, 2003, p. 298.
46 A. George, A. Brandt, K. Tran, S. M. S. N. S. Zahari, D. K. Marcuschamer, N. Sun, N. Sahitsuksanoh, J. Shi, V. Stavila, R. Parthasarathi, S. Singh, B. Holmes, T. Welton,

B. A. Simmons and J. P. Hallet, Design of low-cost ionic liquids for lignocellulosic biomass pretreatment, *Green Chem.*, 2015, **17**, 1728.

47 J. Pernak, J. Rogoza and I. Mirska, Synthesis and antimicrobial activities of new pyridinium and benzimidazolium chlorides, *Eur. J. Med. Chem.*, 2001, **36**(4), 313–320.

48 K. M. Docherty and C. F. Kulpa, Toxicity and antimicrobial activity of imidazolium and pyridinium ionic liquids, *Green Chem.*, 2005, **7**, 185.

49 D. J. Couling, R. J. Bernott, K. M. Docherty, J. K. Dixon and E. J. Maginn, Assessing the factors responsible for ionic liquid toxicity to aquatic organisms via quantitative structure–property relationship modelling, *Green Chem.*, 2006, **8**, 82–90.

50 C. K. Jadhav, A. S. Nipate, A. V. Chate, V. D. Songire, A. P. Patil and C. H. Gill, Efficient Rapid Access to Biginelli for the Multicomponent Synthesis of 1,2,3,4-Tetrahydropyrimidines in Room-Temperature Diisopropyl Ethyl Ammonium Acetate, *ACS Omega*, 2019, **4**(27), 22313–22324.

51 T. M. Potewar, S. A. Ingale and K. V. Srinivasan, Catalyst-free efficient synthesis of 2-aminothiazoles in water at ambient temperature, *Tetrahedron*, 2008, **64**, 5019–5022.

52 D. V. Jawale, D. L. Lingampalle, U. R. Pratap and R. A. Mane, One-pot synthesis of 2-aminothiazoles in PEG-400, *Chin. Chem. Lett.*, 2010, **21**, 412–416.

53 G. W. Kabalka and A. R. Mereddy, Microwave promoted synthesis of functionalized 2-aminothiazoles, *Tetrahedron Lett.*, 2006, **47**, 5171–5172.

