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Catalytic application of task specific ionic liquid on the synthesis of benzoquinazolinone derivatives by a multicomponent reaction

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ABSTRACT

Benzoquinazolin-2-one derivatives were synthesized by using a catalytic amount of task specific ionic liquid, [1-methyl-3-(4-sulfobutyl)imidazolium-4-methylbenzenesulfonate] through a one-pot multicomponent Biginelli reaction of α-tetralone, aldehyde, and urea/thiourea in excellent yields within a short reaction time. Mechanism studies suggest that the reaction proceeds through iminium intermediate and C2-H of the TSIL plays a major role on its catalytic activity. The catalyst has been reused four times without any significant loss in catalytic activity. Large scale reaction by using this TSIL suggests the applicability of this methodology for bulk synthesis of quinazolinone derivatives.

Multicomponent reactions (MCRs) have been proved to be a new tool in organic and medicinal chemistry as it provides rapid building of complex structure in a convergent and atom economical way.[1]

The quinazolinone moiety has a resourceful pharmacophoric feature and is present in many naturally occurring compounds. Thus it is of great importance to chemists and biologists. Compounds with this structural framework are also clinically useful and possess a wide range of biological activities such as antiviral, antimalarial, anticonvulsant, antibacterial, diuretic, hypnotic, hypoglycemic, antitumoral, and antihypertensive.[2] The Biginelli reaction, which was discovered more than a century ago is one of the most important reactions for the synthesis of dihydropyrimidinones by a three-component coupling of 1,3-dicarbonyl compounds, aldehydes, and urea.[3] Several improved procedures have been developed mainly based on 1,3-dicarbonyl compounds.[3c–f] However, only a few protocols have been reported using cyclic aryl ketones for the Biginelli condensation which produced quinazoline derivatives.[4] But these methodologies suffer from some stern drawbacks like use of TMSCl,[4a,e] HCl,[4b,d] $HClO_4$,[4g] $FeCl_3$,[4f] and other limitations such as narrow substrate scope and[4c] long reaction time.[4f] Thus, the quest remains for a practical and convenient method.

A new class of reaction medium has emerged–*ionic liquids* (ILs) that have been projected as green solvents. The tight legislation to maintain greenness in synthetic processes directs to prevent the generation of waste, avoid the use of auxiliary substances, and minimize the energy requirement.[5] The aspect of hazardness of the use of volatile organic solvents as auxiliary substances can be addressed by the use of *ionic liquids*[6] and the generation of waste and the consumption of energy can be minimized by the acceleration of reaction rates through the use of catalysts. However, there are some unresolved environmental, health, and safety issues in the use of ILs as solvents in large quantities.[7–9] Thus, its use in small quantities become an alternate choice to exploit the benefits of ILs.[10] The application of Brønsted acidic task-specific ionic liquids (TSILs) as catalytic materials is growing continuously in the field of catalysis.[11] Combining the useful characteristics of solid acids and mineral acids, TSILs have been applied to replace traditional mineral liquid acids, such as hydrochloric acid and sulfuric acid in chemical reactions. After the report by Forbes and Davis for the synthesis of a new class of phosphonium- and imidazolium ion-based ionic liquids equipped with a pendant acidic sulfonic acid moiety, Brønsted acidic ionic liquids (BAILs) have drawn considerable attention.[12] BAILs are more preferable over the traditional ionic liquids as these combine strong acidity with the use of nonvolatile ionic liquids. As a result many transformations have been carried out using this type of acidic IL.[11]

In continuation of our efforts toward the development of green methodologies using task specific ionic liquids (TSILs),[10b–f] we present in this study the use of 1-methyl-3-(4-sulfobutyl)imidazolium-4-methylbenzenesulfonate as a catalyst for the synthesis of benzoquinazolin-2-one and -2-thione in a one-pot, three-component reaction of α-tetralone, an aldehyde, and urea or thiourea (Scheme 1).

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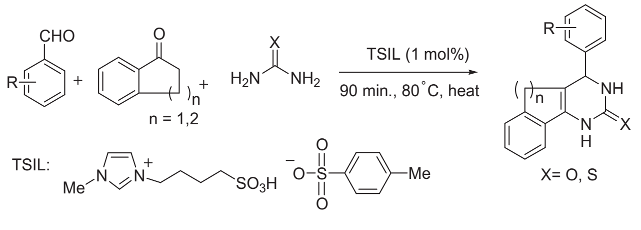


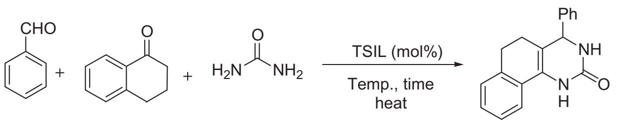
Scheme 1. Synthesis of quinazolinones catalyzed by TSIL.

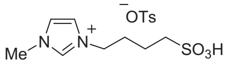
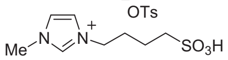
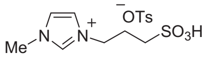
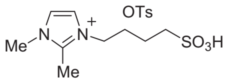
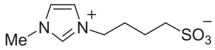
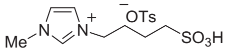
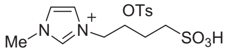
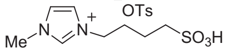
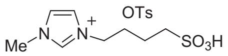
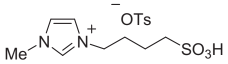
To find out a suitable TSIL, a model reaction was chosen by using benzaldehyde (1 mmol), α-tetralone (1 mmol), and urea (1 mmol) in the presence of different TSILs and the results are summarized in Table 1.

From Table 1 it is evident that TSIL **A** (Table 1, entry 2) was the most efficient catalyst which provided 85% yield within 90 min. It was also observed that catalytic efficiency depends on electronic environment and physiochemical properties of TSIL. With decreasing chain length of TSIL **B** catalytic properties decreased (Table 1, entry 3).[13] The poor catalytic effect was observed when C2-H was replaced by C2-Me (TSIL **C**) and afforded 56% yield in 90 min (Table 1, entry 4). It suggests that C2-H plays a crucial role to catalyze the reaction.[10g] Reaction without catalyst afforded very poor yield (<10%). It is worthy to mention that the Biginelli reaction for the synthesis of dihydropyrimidinones proceeded very well under catalyst and solvent-free conditions.[3f] It was also clear from Table 1 that the use of lower amount of catalyst decreased the yield, but use of higher quantity of catalyst did not improve the yield. Neither higher temperature (100 °C) nor longer reaction time (120 min) improved the yield of reaction (Table 1, entries 8 and 9). Moderate yield was obtained at lower temperature (Table 1, entry 10). Moreover, *p*-toluenesulfonic acid is not so effective like TSIL (**A**). Finally, the optimized condition for this reaction was chosen as use of 1 mol % catalyst (TSIL **A)** at 80 °C for 90 min (Table 1, entry 2).

To explore the generality and scope, several structurally diverse aldehydes were treated with α-tetralone (1 mmol) and urea/thiourea (1 mmol) under optimized reaction conditions and the results are summarized in Table 2. Both aromatic aldehydes substituted with electron donating group or electron withdrawing group underwent clean conversion to the desired products. The catalyst was compatible with various functional groups such as –Br (Table 2, entry 2) and $–NO_2$ (Table 2, entries 3 and 4). These reactions suggest the mildness of the catalyst. Acid sensitive aldehyde (piperonal) was also unaffected under these reaction conditions (Table 2, entries 7 and 8). The acid-sensitive heterocyclic substrate such as 2-thiophenecarboxaldehyde efficiently afforded the desired product without accompanying self-condensation (Table 2, entry 9). In general all the reactions were clean. No formation of undesired product was found. It is notable to mention that the pure product was isolated from the reaction mixture without use of any chromatographic method. Only ethanol was used for recrystallization to get the analytically pure products.

Table 1
Optimization of reaction conditions[a]



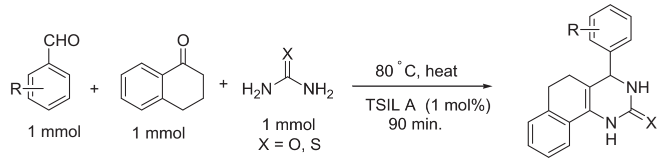
Entry	Catalyst	Mol (%)	Temp (°C)	Time (min)	Yield[b] (%)
1[c]	 (**A**)	0.5	80	90	49
2	 (**A**)	1	80	90	85
3	 (**B**)	1	80	90	68
4	 (**C**)	1	80	90	56
5	 (**D**)	1	80	90	52
6	 (**A**)	2	80	90	86
7	 (**A**)	5	80	90	86
8	 (**A**)	1	100	90	86
9	 (**A**)	1	80	120	85
10	 (**A**)	1	60	120	52
11	–	–	80	90	<10
12	*p*-Toluenesulfonic acid	1	80	90	24

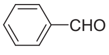
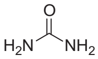
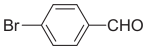
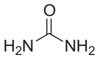
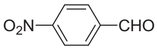
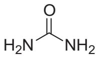
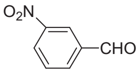
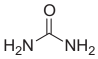
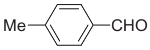
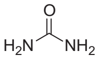
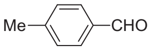
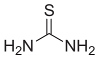
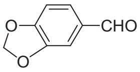
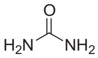
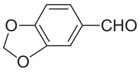
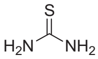
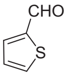
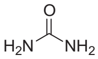
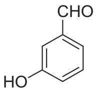
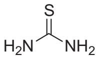
[a] Reaction conditions: benzaldehyde (1 mmol), α-tetralone (1 mmol), and urea (1 mmol) in neat conditions.

[b] Isolated yield.

[c] Reaction was carried out on 5 mmol.

Table 2
TSIL catalyzed synthesis of tetrahydro-1*H*-benzo[*h*]quinazolin-2-ones/2-thiones



Entry	Substrate	Urea/thiourea	Yield[a] (%)
1			85
2			82
3			68
4			70
5			80
6			80
7			78
8			82
9			82
10			80

[a] Isolated yield.

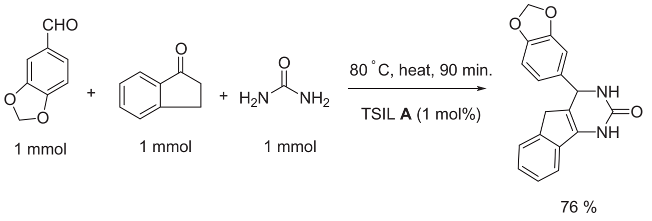
Table 3
Reusability of TSIL **A**[a]

Use/ cycle[b]	Scale[c] (mmol)	Amount used[d] (g)	Amount recovered[e] (g)	Recovered[f] (%)	Yield[g] (%)
Fresh	25	0.098	0.090	91	84
1st	22	0.086	0.078	90	83
2nd	20	0.076	0.071	88	83
3rd	17	0.066	0.057	86	82
4th	15	0.058	0.050	84	82

[a] Benzaldehyde and α-tetralone (1 equiv) were treated with urea (1 equiv) in the presence of TSIL **A** (1 mol %) at 80 °C for 90 min.
[b] Indicates the status of the IL use.
[c] The amount of benzaldehyde, α-tetralone, and urea used in reaction.
[d] The amount of TSIL **A** used.
[e] The amount of TSIL **A** recovered.
[f] Indicates to the recovered TSIL **A**.
[g] Yield of the 4-phenyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinazolin-2-one urea (5 mmol) using 1 mol % catalyst.

We have successfully synthesized another biologically active compound 4-benzo[1,3]dioxol-5-yl-1,3,4,5-tetrahydro-indeno[1,2-*d*]pyrimidin-2-one[14] using piperonal, 1-indanone, and urea giving moderate yields in 90 min (Scheme 2).

The reusability of the catalyst is an important benefit especially for commercial applications. We planned to evaluate the possibility of recovery and reuse of TSIL **A**. After completion of the reaction the TSIL **A** was recovered and four consecutive reaction cycles were performed without any significant loss in the catalytic activity or product yields. The recovery efficiency was 91–84% with 84–82% yields of the 4-phenyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinazolin-2-one (Table 3).

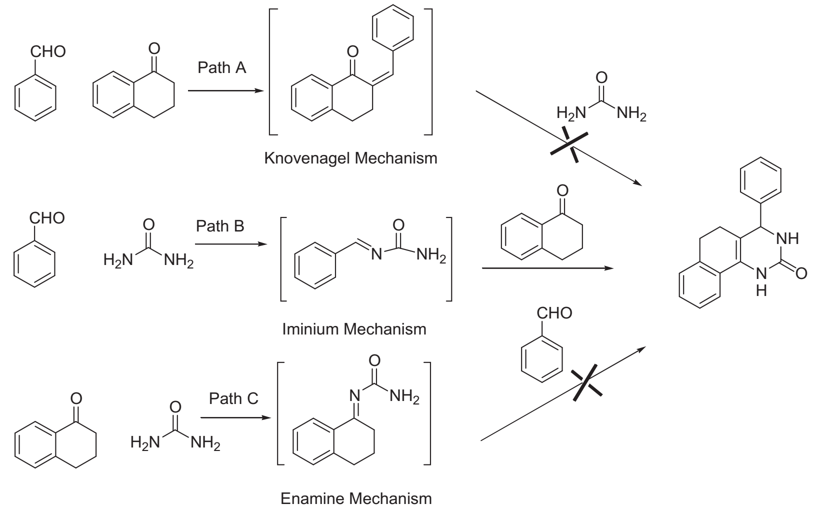


Scheme 2. Synthesis of 4-benzo[1,3]dioxol-5-yl-1,3,4,5-tetrahydro-indeno[1,2-*d*]pyrimidin-2-one.

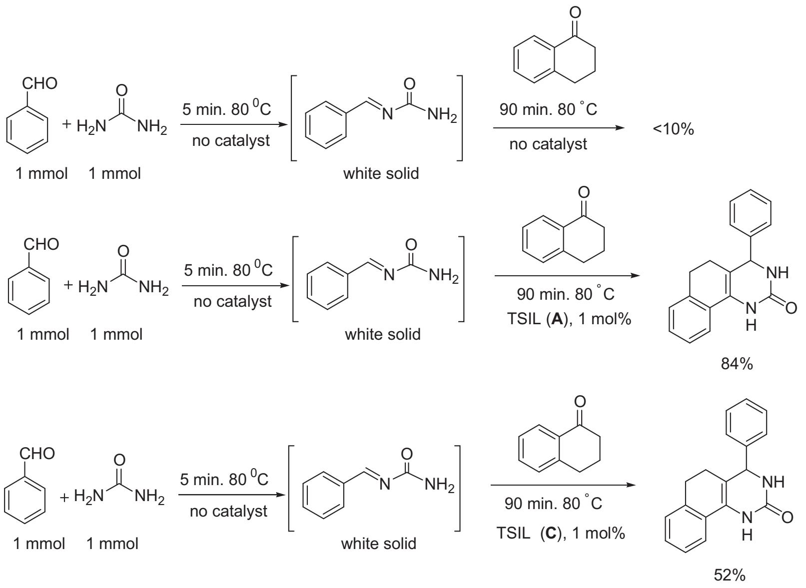
Then we performed large scale preparation of 4-phenyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinazolin-2-one by the reaction of benzaldehyde (50 mmol), α-tetralone (50 mmol), and urea (50 mmol) in presence of 1 mol% TSIL **A** which afforded 84% yield in 90 min.

Finally we have tried to understand the mechanistic course of the reaction under the catalytic influence of TSIL. The three-component reaction among α-tetralone, benzaldehyde, and urea have been proposed to progress by three characteristic pathways (Scheme 3): (a) Knovenagel adduct formation of aldehyde and α-tetralone followed by *aza*-Michael addition of urea and after that intramolecular cyclodehydration (Path A), (b) intermediate formation of iminium moiety by condensation between benzaldehyde and urea, followed by attack through enol form of α-tetralone to the iminium moiety (Path B), (c) enaminone formation by condensation of urea with α-tetralone followed by subsequent aldol type reaction of enaminone with that of aldehyde by cyclodehydration to give the expected product (Path C).[15] To understand the role of ionic liquid in the three-component reaction, three sets of reactions have been performed: equimolar mixture of benzaldehyde and α-tetralone (path A), benzaldehyde and urea (path B), and α-tetralone and urea (path C) were heated at 80 °C in the presence and absence of TSIL **A**. In the path A and path C no reaction took place. The starting materials remain unchanged (TLC) even after two hours in path A and C. This result eliminates the Knovenagel (path A) and enaminone (path C) routes. Interestingly in the absence or in the presence of TSIL **A** a white solid was obtained even after five minutes (path B) which is shown in Scheme 4. This suggests the three-component reaction has been taking place through iminium mechanism.[16] The obtained white solid (imine) product has been treated with α-tetralone in the absence and in the presence of TSIL **A** (Scheme 4). In the absence of TSIL very low amount (<10%) of desired product was obtained but in the presence of TSIL **A** the required product 4-phenyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinazolin-2-one was obtained in 84% yield. Therefore TSIL **A** shows its divergent and essential task during the reaction of active methylene carbon of α-tetralone (through its enol form) with that of imine and followed by cyclodehydration step. However the imine (white solid) was treated with α-tetralone in the presence of TSIL **A** (Table 1, entry 4), devoid of C2-H, moderate yield of product (56%) was obtained. This suggests that C2-H plays a crucial role in the course of the reaction probably activating the aldehydic oxygen through hydrogen bond formation.[10g]

In conclusion, we have demonstrated the remarkable catalytic activity of a TSIL for the practical and convenient synthesis of benzoquinazolinone derivatives using only 1 mol % catalyst. Our



Scheme 3. Probable reaction pathway.



Scheme 4. The role of TSIL in three-component reaction.

observation suggests that the reaction proceeds through iminium intermediate and C2-H plays a major role on its catalytic activities. This protocol has the advantages of operational simplicity, reusability of the catalyst, no need of column chromatographic separation, and shorter reaction time. It is also applicable for large scale synthesis and expected to be attractive for academic and industrial use due to its environmentally benign reaction conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.011.

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