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Organocatalytic Application of Ionic Liquids: [bmim][$MeSO_4$] as a Recyclable Organocatalyst in the Multicomponent Reaction for the Preparation of Dihydropyrimidinones and -thiones

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Abstract: The organocatalytic potential of 1-butyl-3-methylimidazolium-based room-temperature ionic liquids has been investigated for the synthesis of dihydropyrimidinones and -thiones by a one-pot multicomponent reaction involving an aldehyde, a β-keto ester or β-diketone, and urea or thiourea in excellent yields in short time. Factors that influence the efficiency of the ionic liquid as a catalyst were examined such as the anion and the imidazolium cation, particularly the influence of C2 substitution in the latter. The ionic liquid can be recovered and reused for five consecutive reactions without significant loss of catalytic efficiency. The applicability of the methodology for large-scale reaction highlights its potential for bulk synthesis.

Key words: ionic liquid, organocatalyst, multicomponent reaction, dihydropyrimidinone, dihydropyrimidinethione

Multicomponent reactions (MCRs)[1] have been recognized as a new tool that provides timely synthetic support[2] to medicinal chemists by the rapid construction of complex structural frameworks in a convergent and atom-economical fashion.

The 1,4-dihydropyrimidine moiety is a versatile pharmacophoric feature, as compounds with this structural framework exhibit a broad range of biological activity, e.g. calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors, and antibacterial, anti-inflammatory, fungicidal, and anticancer agents etc.[3] Therefore, there has been continued interest from synthetic organic and medicinal chemists in the development of newer methodologies for this class of compounds that comprise of a three-component reaction involving an aldehyde, a β-keto ester or β-diketone, and urea.[4] Recent efforts involve the use of a Brønsted acid[5] or base,[6] metal Lewis acids,[7] organocatalysts,[8] and heterogeneous catalysts,[9] and nonconventional techniques, such as microwave, ultrasound, high pressure, and grindstone chemistry.[10]

Recently there has been increasing concern centered around the tight legislation on the maintenance of 'greenness' in synthetic pathways and processes.[11] Green chemistry strongly influences chemical research, and there is an insistence on the use of 'greener' reaction conditions.[12] The major focus is on improving reaction media; volatile organic solvents amount to >85% of mass utilization in a typical chemical manufacturing process, and, as recovery efficiency is less than satisfactory, they are major contributors to environmental pollution.[13] The use of alternative reaction media is a priority in the development of sustainable chemistry, for which water and ionic liquids (ILs) are main contenders. There has been an upsurge of the use of water as an alternative reaction medium in various organic reactions,[14] however, its popularity has yet to reach its zenith due to the poor aqueous solubility of organic compounds; efforts being are made to overcome this problem by using surfactants[15] which may also play an unprecedented role in the reaction.[16] Ionic liquids, on the other hand, are hailed as the green solvents of the future.[17] Therefore, the use of ionic liquids in multicomponent reactions has a perfect synergy in ecocompatible synthesis.[18] However, the innocuous behavior of ionic liquids is under debate[19] and their green image is under scrutiny[20] on the grounds of combustibility,[21] toxicity,[22] and biodegradability.[23] These have generated momentum in terms of the non-solvent applications of ionic liquids.[24]

In the pursuit of exploring the organocatalytic efficiency of ionic liquids,[25] we describe herein the potential of room-temperature ionic liquids (RTILs) as organocatalysts for the synthesis of 1,4-dihydropyrimidinones and -thiones in a one-pot, three-component reaction of an aldehyde, a β-keto ester or β-diketone, and urea or thiourea.

The use of ionic liquids in multicomponent reactions to form 1,4-dihydropyridines has involved: (i) ionic-liquid-phase organic synthesis (IoLiPOS), wherein one of the substrates is supported on the ionic liquid,[26] and (ii) the use of ultrasound/microwave irradiation.[27] There are few reports on the use of ionic liquids, such as 1-butyl-3-methylimidazolium tetrafluoroborate and 1-butyl-3-methylimidazolium chloroaluminate (10–40 mol%), as organocatalysts.[28] However, the toxicity of 1-butyl-3-methylimidazolium-based ionic liquids is dependent on the counteranion, and halide, tetrafluoroborate, and hexafluorophosphate based ionic liquids are more toxic than alkyl sulfate containing ionic liquids.[29] Chloroaluminate anion containing ionic liquids are susceptible to decomposition in contact with moisture liberating corrosive HCl.

Therefore, in order to identify a more ecocompatible ionic liquid as an organocatalyst, a model reaction was exam-

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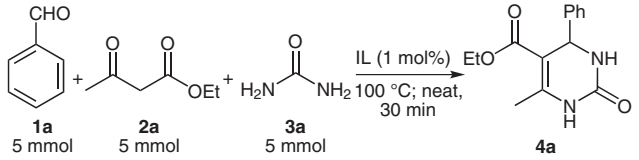
ined comprising of a mixture of benzaldehyde (**1a**, 5 mmol), ethyl acetoacetate (**2a**, 5 mmol), and urea (**3a**, 5 mmol) which was treated with various 1-butyl-3-methylimidazolium-based room-temperature ionic liquids (1 mol%) (Scheme 1) at 100 °C for 30 minutes (Table 1).



Scheme 1 The synthesis of dihydropyrimidinone **4a** catalyzed by room-temperature ionic liquids

Table 1 The Catalytic Effect of Various Ionic Liquids in the Synthesis of Dihydropyrimidinone **4a** (see Scheme 1)[a]

Entry	Ionic liquid[b]	Yield[c,d] (%) of **4a**
1	[bmim][Br]	70
2	[bmim][PF_6]	55
3	[bmim][BF_4]	80
4	[bmim][$MeSO_4$]	90
5	[bmim][$MeSO_3$]	72
6	[bmim][HSO_4]	79
7	[bmim][NTf_2]	67
8	[bmim][NCN_2]	71
9	[bmim][OH]	73
10	[bmim][HCO_2]	55
11	[bmim][OAc]	75
12	[bmim][N_3]	65
13	[bmim][ClO_4]	68
14	[Hmim][BF_4]	70
15	[H-2-mim][BF_4]	50
16	[H-1,2-dimim][BF_4]	45
17	$NaMeSO_4$	41
18	–	trace

[a] Reaction conditions: benzaldehyde (**1a**, 5 mmol), ethyl acetoacetate (**2a**, 5 mmol), urea (**3a**, 5 mmol), ionic liquid (1 mol%), 100 °C (oil bath), 30 min.
[b] [Hmim] = 1-methylimidazolium; [H-2-mim] = 2-methylimidazolium; [H-1,2-dimim] = 1,2-dimethylimidazolium.
[c] Isolated yield of **4a** (recrystallized from EtOAc).
[d] Wherever applicable the unreacted **2a** was recovered.

The ionic liquid 1-butyl-3-methylimidazolium methyl sulfate {[bmim][$MeSO_4$]} containing the less toxic alkyl sulfate anion proved to be the most effective. However, apart from the toxic effect of the associated anion, significant influence by the counteranion on the organocatalytic properties of the ionic liquid was observed which is in conformity with earlier observations.[25] The poor catalytic effect of sodium methyl sulfate (Table 1, entry 17) showed that the imidazolium-based cationic moiety is also essential for the catalytic power of these ionic liquids. However, the effect of the imidazolium-based cationic moiety on the catalytic efficiency of the ionic liquid is influenced by the nature of substitution on the imidazole ring. A 1,3-disubstituted imidazolium moiety is required for better catalytic potency; the corresponding ionic liquids derived from 1-methylimidazolium, 2-methylimidazolium, and 1,2-dimethylimidazolium cations are less effective (entry 3 vs. entries 14–16). However, the C2 hydrogen of the 1,3-disubstituted imidazolium cation appears to be a crucial feature[25] as [bmim]-based ionic liquids devoid of the C2 hydrogen, such as [bdmim], exhibited inferior catalytic efficiency (Table 2).

Table 2 Catalytic Efficiency of Various [bmim]-Based Ionic Liquids Devoid of C2 Hydrogen of the Imidazole Moiety in Dihydropyrimidinone **4a** Formation (Scheme 1)[a]

Entry	Ionic liquid[b]	Yield[c] (%)
1	[bdmim][Br]	45
2	[bdmim][PF_6]	35
3	[bdmim][BF_4]	50
4	[bdmim][$MeSO_4$]	51
5	[bdmim][HSO_4]	58
6	[bdmim][NTf_2]	47
7	[bdmim][NCN_2]	45
8	[bdmim][OAc]	50

[a] Reaction conditions: benzaldehyde (**1a**, 5 mmol), ethyl acetoacetate (**2a**, 5 mmol), urea (**3a**, 5 mmol), RTIL (1 mol%), 100 °C (oil bath), 30 min.
[b] [bdmim] = 1-butyl-2,3-dimethylimidazolium.
[c] Isolated yield of **4a** (recrystallized from EtOAc).

To identify the optimum reactions conditions the [bmim][$MeSO_4$]-catalyzed three-component reaction of benzaldehyde (**1a**), ethyl acetoacetate (**2a**), and urea (**3a**) was performed under various conditions (Table 3).

The best result was obtained when the reaction was performed using 1 mol% of the ionic liquid at 100 °C for 30 minutes, affording dihydropyrimidinone **4a** in 90% yield (Table 3, entry 2). The use of lower amounts (0.1 mol%) of the ionic liquid required a longer time period to afford comparable results (entry 1). No beneficial effect in terms of reduction of the reaction time was observed when the catalyst load was increased (entry 4). Decreasing the reaction temperature had a detrimental effect on product yield (entries 6–8). The use of larger amounts (5–10 mol%) of the ionic liquid did not provide any beneficial effect in terms of reducing the reaction time (entry 4) or reaction temperature (entries 9 and 10).

Table 3 Optimization of Various Reaction Parameters for [bmim][$MeSO_4$]-Catalyzed Dihydropyrimidinone **4a** Formation[a]

Entry	[bmim][$MeSO_4$] (mol%)	Time (min)	Temp (°C)	Yield[b] (%)
1	0.1	45	100	89[c]
2	1	30	100	90
3	5	30	100	92
4	10	15	100	60[d]
5	10	30	100	95
6	1	30	60	trace[d]
7	1	60	80	81
8	1	30	80	51[d]
9	5	30	60	trace[d]
10	5	30	80	62[d]

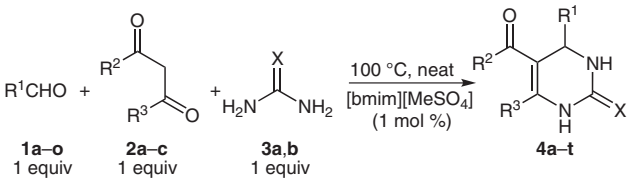
[a] Reaction conditions: benzaldehyde (**1a**, 5 mmol), ethyl acetoacetate (**2a**, 5 mmol), urea (**3a**, 5 mmol), [bmim][$MeSO_4$].
[b] Isolated yield of **4a** (recrystallized from EtOAc).
[c] Reaction was carried out on a 25-mmol scale for ease of handling of the ionic liquid.
[d] Unreacted **2a** was recovered.

To establish the scope and generality of [bmim][$MeSO_4$] as an organocatalyst for the synthesis of dihydropyrimidinones and -thiones **4a–t**, various aryl, heteroaryl, and aliphatic aldehydes **1a–o** were treated with urea or thiourea **3a**,**b** and 1,3-dicarbonyl compounds **2a–c** and the results are summarized in Table 4.

In all cases, the reaction proceeded smoothly to afford the corresponding dihydropyrimidinones and -thiones **4a–t** in excellent yields (80–91%) in short reaction times (25–45 min). The reaction is compatible with a variety of functional groups such as alkoxy, hydroxy, dimethylamino, nitro, acetyl, and nitrile as well as with acid-sensitive substrates (entries 18 and 19). The β-keto esters **2a** and β-diketones (acyclic or cyclic) **2b**,**c** react smoothly with urea or thiourea **3a**,**b** and aldehydes **1a–o** to give the corresponding dihydropyrimidinone and -thione derivatives. Thiourea (**3b**) exhibited greater reactivity than urea (**3a**) (Table 4, cf. entry 2 vs. 3 and 12 vs. 13). The β-keto ester **2a** exhibited greater reactivity over the β-diketone **2b** (entry 1 vs. 2) and cyclic β-diketone **2c** reacted relatively sluggishly compared to the acyclic β-diketone **2b** (entry 3 vs. 15).

We realized that the advantages of using of ionic liquids as organocatalysts over conventional organocatalysts would lie in the feasibility of their reuse. Hence we decided to study the reuse of [bmim][$MeSO_4$] in the three-component reaction to give dihydropyrimidinone **4a** (Table 5). In each case [bmim][$MeSO_4$] was recovered after product isolation and the recovered ionic liquid was reused for the next four consecutive reactions. The desired dihydropyrimidinone **4a** was obtained in very good yields

Table 4 The [bmim][$MeSO_4$]-Catalyzed Synthesis of Dihydropyrimidinones and -thiones[a–c]



Entry	R^1	R^2	R^3	X	Time (min)	Product	Yield[d] (%)
1	Ph	OEt	Me	O	30	**4a**	90
2	Ph	Me	Me	O	40	**4b**	88
3	Ph	Me	Me	S	25	**4c**	83
4	4-$MeOC_6H_4$	OEt	Me	O	30	**4d**	87
5	4-$MeOC_6H_4$	OEt	Me	S	30	**4e**	82
6	4-$Me_2NC_6H_4$	OEt	Me	O	25	**4f**	82
7	2,4,6-$Me_3C_6H_2$	OEt	Me	O	30	**4g**	85
8	4-HOC_6H_4	OEt	Me	O	30	**4h**	90
9	3-HOC_6H_4	Me	Me	S	25	**4i**	90
10	4-AcC_6H_4	OEt	Me	O	30	**4j**	91
11	4-NCC_6H_4	OEt	Me	O	30	**4k**	85
12	4-$F_3CC_6H_4$	OEt	Me	O	45	**4l**	86
13	4-$F_3CC_6H_4$	OEt	Me	S	35	**4m**	89
14	3-$O_2NC_6H_4$	OEt	Me	O	30	**4n**	88
15	Ph	$(CH_2)_3$		S	70	**4o**	80
16	4-*i*-PrC_6H_4	$(CH_2)_3$		S	65	**4p**	80
17	1-naphthyl	OEt	Me	O	20	**4q**	84
18	2-thienyl	Me	Me	S	40	**4r**	90
19	2-furyl	Me	Me	S	40	**4s**	85
20	Cy	OEt	Me	O	20	**4t**	82

[a] Reaction conditions: aldehyde (5 mmol), β-dicarbonyl compound (5 mmol), urea/thiourea (5 mmol), [bmim][$MeSO_4$] (1 mol%), 100 °C (oil bath).
[b] R^2 = OEt, R^3 = Me **2a**, R^2 = R^3 = Me **2b**, R^2,R^3= $(CH_2)_3$ **2c**.
[c] X = O **3a**; X = S **3b**.
[d] Isolated yield of the corresponding dihydropyrimidinone and -thione **4** (recrystallized from EtOAc). All compounds have been characterized by IR and NMR spectroscopy and MS spectrometry. The spectral data of known compounds are available in the Supporting Information.

without significant loss of catalytic activity of [bmim][$MeSO_4$].

The feasibility of large-scale synthesis was next demonstrated by the reaction of benzaldehyde (**1a**, 25 mmol) with equimolar amounts of ethyl acetoacetate (**2a**) and urea (**3a**) performed in the presence of 1 mol% of [bmim][$MeSO_4$] to afford dihydropyrimidinone **4a** in 90% yield.

Table 5 Reuse of [bmim][$MeSO_4$] for Synthesis of Dihydropyrimidinone **4a**[a]

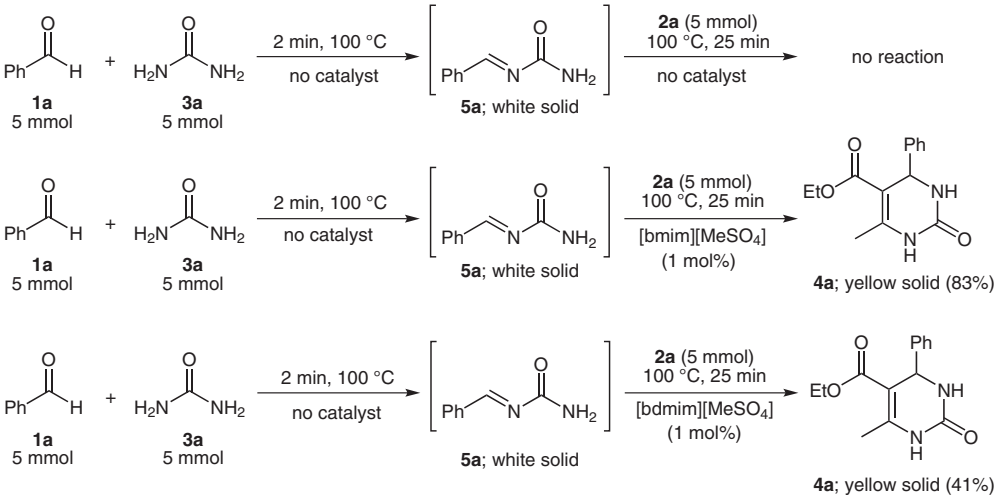
Entry	Use	Yield[b,c] (%)
1	1st	90
2	2nd	88
3	3rd	84
4	4th	82
5	5th	79

[a] Reaction conditions: benzaldehyde (**1a**, 5 mmol), ethyl acetoacetate (**2a**, 5 mmol), urea (**3a**, 5 mmol), [bmim][$MeSO_4$] (1 mol%), 100 °C (oil bath), 30 min.
[b] After each experiment the ionic liquid was recovered and the recovered ionic liquid was used as the organocatalyst for the subsequent batch/entry of reaction.
[c] Isolated yield of dihydropyrimidinone **4a** (recrystallized from EtOAc).

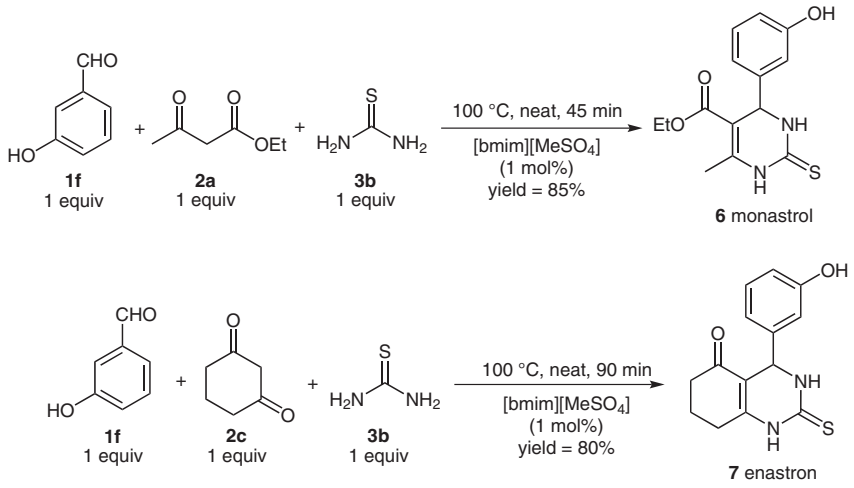
We next attempted to understand the mechanistic course of the reaction under the catalytic influence of the ionic liquid. The three-component reaction of an aldehyde, a β-dicarbonyl compound and urea has been proposed to proceed by three distinctive routes: (i) intermediate formation the imine or iminium salt of the aldehyde and the urea which undergoes subsequent nucleophilic attack by the active methylene carbon of the β-dicarbonyl compound through its enol form followed by intramolecular cyclocondensation, (ii) formation of the Knovenagel adduct of the β-dicarbonyl compound and the aldehyde and subsequent aza-Michael reaction with urea followed by intramolecular cyclodehydration, and (iii) formation of enaminone through aza-Michael reaction of urea with the enol form of the β-dicarbonyl compound and subsequent aldol-type reaction of its enamine moiety with the aldehyde followed by cyclodehydration.[30] To understand the role of the ionic liquid in the course of the reaction the following sets of experiments were performed: equimolar mixtures of (a) benzaldehyde (**1a**) and ethyl acetoacetate (**2a**), (b) urea (**3a**) and ethyl acetoacetate (**2a**), and (c) benzaldehyde (**1a**) and urea (**3a**) were heated at 100 °C in the presence and absence of [bmim][$MeSO_4$].

In the case of reactions under options (a) and (b) the starting materials remained unchanged (TLC) even after maintaining the reaction mixture at 100 °C for 3–6 hours. These eliminate the possibility of the reaction following the Knovenagel and enaminone routes. However, in case of the option (c) a white solid precipitated within a short period of time (~2 min) even in the absence of the ionic liquid and complete consumption of the starting materials took place (TLC). This suggests that the reaction proceeds through the initial formation of the imine **5** which, however, need not require any catalytic assistance although the solid product formation occurs almost immediately (<1 min) in the presence of the ionic liquid (Scheme 2). The solid product **5a** was next treated with ethyl acetoacetate (**2a**) in the presence and absence of [bmim][$MeSO_4$]; treatment of the solid product **5a** [obtained in the absence of catalyst] with ethyl acetoacetate (**2a**) at 100 °C in the absence of catalyst for 30 minutes gave no dihydropyrimidinone **4a**, but treatment of **5a** with ethyl acetoacetate (**2a**) in the presence of [bmim][$MeSO_4$] (1 mol%) at 100 °C for 25 minutes afforded dihydropyrimidinone **4a** in 83% yield. Therefore, the ionic liquid exhibits its distinct and indispensable role during the reaction of the active methylene carbon of ethyl acetoacetate (**2a**) (presumably through its enol form) with the imine **5a** and in the subsequent cyclodehydration step. However, the reaction of the white solid **5a** with ethyl acetoacetate (**2a**) at 100 °C for 25 minutes in the presence of [bdmim][$MeSO_4$] produced dihydropyrimidinone **4a** in a lower yield (40%) and highlighted the important contribution of the C2 hydrogen of the 1,3-dialkylimidazolium moiety in the activation process.

Endeavors to synthesize 1,4-dihydropyrimidinones are mostly driven by their known biological importance. One of these biologically important classes is mitotic kinesin Eg5 inhibitors and the first report of monastrol (**6**)[31] in 1999 stimulated the synthesis of dihydropyrimidinones and dihydropyrimidinethiones to establish structure–



Scheme 2 Assessment of the role of [bmim][$MeSO_4$] in the course of dihydropyrimidinone **4a** formation during the three-component reaction



Scheme 3 Synthesis of bioactive dihydropyrimidinones **6** and **7** catalyzed by [bmim][$MeSO_4$]

activity relationships to generate more effective mitotic kinesin Eg5 inhibitors as well as generating novel leads in diverse therapeutic areas. This has led to the discovery of enastron (**7**) as a more potent mitotic kinesin Eg5 inhibitor.[32] Hence we extended our methodology to the synthesis of monastrol (**6**) and its analogue enastron (**7**), both these molecules were formed in excellent yields in a short reaction time (Scheme 3).

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer in DMSO with residual undeuterated solvent (DMSO; 2.54 ppm for ^{1}H NMR, 40.45 ppm for ^{13}C NMR) using Me_4Si as an internal standard. Chemical shifts (δ) are given in ppm and *J* values are given in Hz. The melting points were measured in Perkin-Elmer Micro DSC. The IR spectra were recorded on KBr pellets in a Nicolet Impact 410 FTIR spectrophotometer. Mass spectra were recorded on advance Bruker Daltonics® MALDI-TOF-TOF mass spectrometer [for MALDI] and HRMS on Bruker Maxis®. Solvent evaporation was performed under reduced pressure (Buchi rotary evaporator). Chemicals were purchased from Aldrich, Lancaster and Fluka Chemicals and used as received.

Characterization data for new compounds are provided below; those for known compounds in the Supporting Information.

Ethyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a); Typical Procedure

A mixture of benzaldehyde (**1a**, 0.61 g, 5 mmol), ethyl acetoacetate (**2a**, 0.65 g, 5 mmol, 1 equiv), and urea (**3a**, 0.38 g, 5 mmol, 1 equiv) was stirred magnetically at 100 °C in the presence of [bmim][$MeSO_4$] (0.012 g, 1 mol%). After completion of the reaction (30 min, TLC) the mixture was diluted with H_2O (1 mL) and EtOAc (5 mL). The organic layer was separated and the crude product was recrystallized (EtOAc) to afford **4a** (1.17 g, 90%). The aqueous layer containing the ionic liquid was subjected to rotary evaporation at 80 °C under reduced pressure for 20 min to afford the recovered ionic liquid which was used/reused for 5 subsequent fresh batches of reaction of **1a** (0.534 g, 5 mmol), **2a** (0.65 g, 5 mmol, 1 equiv), and **3a** (0.3 g, 5 mmol, 1 equiv) to afford **4a** in 90, 88, 84, 82, and 79% yields, respectively, after usual workup and purification.

On a large-scale operation, the reaction of benzaldehyde (**1a**, 5.34 g, 50 mmol), ethyl acetoacetate (**2a**, 6.5 g, 50 mmol, 1 equiv), and urea (**3a**, 3.0 g, 50 mmol, 1 equiv) was stirred at 100 °C in the presence of [bmim][$MeSO_4$] (0.125 g, 1 mol%) for 30 min to afford **4a** (11.7 g, 90%) after usual workup and purification.

Ethyl 4-Mesityl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g)

Mp 262 °C.

IR (KBr): 3430, 2926, 2855, 1698, 1642, 1598, 1456, 1231, 1094 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.88 (t, *J* = 8.0 Hz, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 2.29 (s, 6 H, CH_3), 3.78 (q, *J* = 6.5 Hz, 2 H, CH_2), 5.76 (s, 1 H, CH), 6.75 (s, 2 H, ArCH), 7.27 (br s, 1 H, NH), 9.02 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.15, 17.97, 20.79, 51.29, 59.31, 97.37, 136.02, 136.98, 137.47, 146.82, 151.20, 166.01.

HRMS: *m*/*z* = 302.1620 (M + 1).

1-[4-(3-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (4i)

Mp 250 °C.

IR (KBr): 3434,2347, 1620, 1443, 1320, 1180 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.13 (s, 3 H, $COCH_3$), 2.30 (s, 3 H, CH_3), 5.20 (d, *J* = 3.6 Hz, 1 H, CH), 6.63–6.66 (m, 3 H, ArCH), 7.11 (t, *J* = 8.0 Hz, 1 H, ArCH), 9.45 (s, 1 H, NH), 9.69 (s, 1 H, OH), 10.23 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.65, 30.76, 54.27, 110.80, 113.87, 115.14, 117.64, 130.05, 144.75, 157.97, 174.39, 195.33.

HRMS: *m*/*z* = 285.0650 (M + Na^+).

Ethyl 4-(4-Acetylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)

Mp 202 °C.

IR (KBr): 3435, 1770, 1641, 1227, 1092 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.09 (t, *J* = 6.8 Hz, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 3.31 (s, 3 H, $COCH_3$), 3.97 (q, *J* = 6.8 Hz, 2 H, CH_2), 5.20 (s, 1 H, CH), 7.36 (d, *J* = 7.6 Hz, 2 H, ArCH), 7.79 (br s, 1 H, NH), 7.91 (d, *J* = 7.6 Hz, 2 H, ArCH), 9.24 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.52, 18.20, 27.18, 54.12, 59.75, 99.08, 126.97, 129.01, 136.37, 149.24, 150.17, 152.38, 165.63, 197.94.

HRMS: *m*/*z* = 325.1142 (M + Na^+).

Ethyl 6-Methyl-2-thioxo-4-[4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m)
Mp 218 °C.

R (KBr): 3429, 2920, 1652, 1577, 1456, 1325, 1111 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.08 (t, 3 H, J = 7.2 Hz, CH_3), 3.33 (s, 3 H, CH_3), 4.00 (q, 2 H, J = 6.8 Hz, CH_2), 5.25 (s, 1 H, CH), 7.42 (d, 2 H, J = 8.0 Hz, ArCH), 7.73 (d, 2 H, J = 8.0 Hz, ArCH), 9.72 (br s, 1 H, NH), 10.44 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.42, 17.59, 54.08, 60.18, 100.46, 123.26, 226.08, 126.11, 127.59, 127.74, 128.57, 128.89, 129.20, 146.01, 146.14, 148.24, 165.39, 174.75.

HRMS: m/z = 367.0710 ($M + Na^+$).

4-(4-Isopropylphenyl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (4p)
Mp 217 °C.

IR (KBr): 3427, 3246, 2956, 1624, 1454, 1373, 1180 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.81–1.96 (m, 4 H, CH_2CH_3), 2.19–2.31 (m, 4 H, CH_2CH_3), 2.49–2.70 (m, 4 H, CH_2), 2.77–2.86 (m, 1 H, CH), 5.14 (d, J = 2.8 Hz, 1 H, CH), 7.05–7.19 (m, 4 H, ArCH), 9.64 (br s, 1 H, NH), 10.55 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.32, 24.30, 26.90, 33.41, 36.78, 52.10, 109.56, 126.84, 126.87, 128.33, 141.24, 146.44, 151.09, 196.74.

HRMS: m/z = 323.1202 ($M + Na^+$).

Monastrol (6)
A mixture of 3-hydroxybenzaldehyde (**1f**, 0.534 g, 5 mmol), ethyl acetoacetate (**2a**, 0.65 g, 5 mmol, 1 equiv), and thiourea (**3b**, 0.3 g, 5 mmol, 1 equiv) was stirred magnetically at 100 °C in the presence of [bmim][$MeSO_4$] (0.012 g, 1 mol%). After completion of the reaction (45 min, TLC) the mixture was diluted with H_2O (1 mL) and EtOAc (5 mL). The organic layer was separated and the crude product was recrystallized (EtOAc) to afford **6** (1.24 g, 85%).[31]

Enastron (7)
A mixture of 3-hydroxybenzaldehyde (**1f**, 0.534 g, 5 mmol), cyclohexane-1,3-dione (**2c**, 0.56 g, 5 mmol, 1 equiv), and thiourea (**3b**, 0.3 g, 5 mmol, 1 equiv) was stirred magnetically at 100 °C in the presence of [bmim][$MeSO_4$] (0.012 g, 1 mol%). After completion of the reaction (90 min, TLC) the mixture was diluted with H_2O (1 mL) and EtOAc (5 mL). The organic layer was separated and the crude product was recrystallized (EtOAc) to afford **7** (1.09 g, 80%).[32]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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