

Microwave-Assisted Brønsted Acidic Ionic Liquid-Promoted
One-Pot Synthesis of Heterobicyclic Dihydropyrimidinones by a
Three-Component Coupling of Cyclopentanone,
Aldehydes, and Urea

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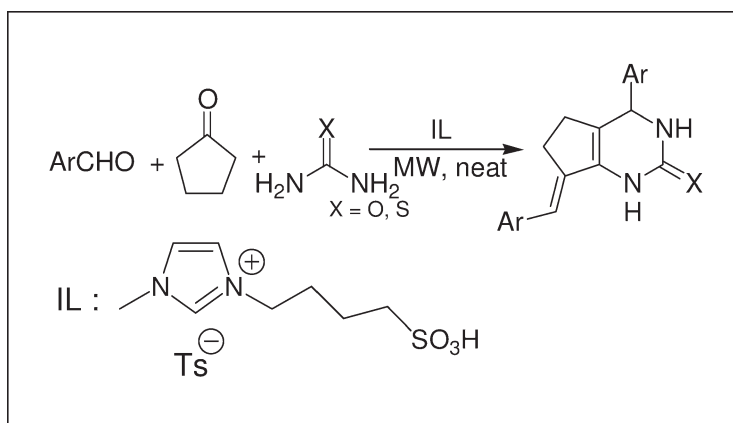
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A simple and efficient method has been developed for the synthesis of heterobicyclic dihydropyrimidinone derivatives through a solvent-free one-pot three-component condensation of aromatic aldehydes, cyclopentanone, and urea or thiourea in the presence of Brønsted acidic ionic liquid under microwave irradiation. The catalyst can be reused at least six times without any noticeable decrease in catalytic activity.

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INTRODUCTION

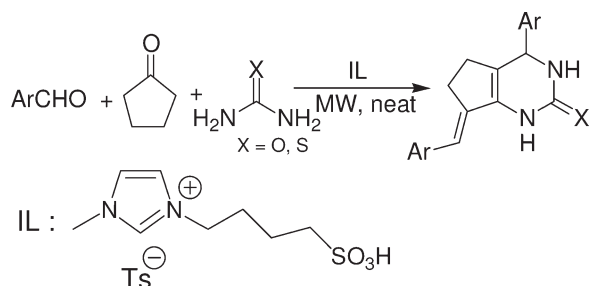
Dihydropyrimidinones and their derivatives are a very important class of bioactive compounds because of their pharmacological properties [1]. They are known to exhibit a wide range of biological activities, such as calcium channel blockers [2], antihypertensive agents [3], α -adrenergic antagonists [4], and neuropeptide Y antagonists [5]. The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety in the molecules [6]. Most notable among these are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors [7]. Therefore, such a wide spectrum of biological activity allows consideration of the dihydropyrimidinone structural unit as one of the most important drug-like scaffolds.

The Biginelli reaction, which was discovered more than a century ago is one of the most important reactions in the synthesis of dihydropyrimidinones based on acid-catalyzed three-component condensation of 1,3-dicarbonyl compound, aldehyde, and urea [8]. The scope of the original condensation reaction was gradually

extended by variation of all three building blocks, allowing access to a large number of structurally diversified multifunctionalized dihydropyrimidinones [9]. The use of the common open-chain β -dicarbonyl compounds in Biginelli reactions has been extended to the use of cyclic β -diketones, β -ketolactones, cyclic β -diesters or β -diamides, benzocyclic ketones, and α -keto acids.

Microwave- (MW-) promoted reactions have been attracting increasing research interest from chemists in recent years, not only because these reactions exhibit some particular or unexpected reactivities in some cases but also because they are significantly useful for green chemistry [10]. In our corresponding investigations, we have reported few MW-promoted multicomponent coupling reactions for various chemical transformation as well as synthesis of useful heterocyclic compounds [11]. The application of Brønsted acidic task-specific ionic liquids (TSILs) as catalytic materials is growing continuously in the catalytic field. Combining the useful characteristics of solid acids and mineral acids, TSILs have been synthesized to replace traditional mineral liquid acids, such as hydrochloric acid and sulfuric acid in chemical reactions. In view of green chemistry, the

Scheme 1



substitution of harmful liquid acids by reusable TSILs is the most promising catalyst in chemistry [12].

Recently, it was found that some fused pyrimidinones carrying an arylidene moiety are potential antitumor agents [13]. In addition, some of these analogues also showed a distinctive pattern of selectivity toward individual cell line, such as that of leukemia [14]. Because of the various therapeutic utility of arylidene heterobicyclic pyrimidinones, a number of synthetic procedures for this type of derivatives were developed using different protocols [15]. Pan and coworkers described an efficient alternative for the synthesis of these fused pyrimidinones by a three-component condensation with aromatic aldehyde, cyclopentanone, and urea or thiourea in presence of stoichiometric amounts of TMSCl as additional reagent and mixed DMF/CH₃CN as reaction solvent appeared to be necessary to obtain satisfactory results [16a]. Very recently, Xu and Shen revealed that ytterbium chloride could efficiently promote this one-pot three-component condensation under solvent-free conditions without using any additional reagents [16b]. In connection with our earlier work on the synthesis of dihydropyrimidinones [17], herein we report an efficient Brønsted acidic ionic liquid catalyzed this Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea for the synthesis of arylidene heterobicyclic pyrimidinones using MW irradiation under solvent-free conditions (Scheme 1). To the best of our knowledge, this is the first report of a functionalized ionic liquid-catalyzed synthesis of heterobicyclic dihydropyrimidinones.

RESULTS AND DISCUSSION

The experimental procedure is very simple. To optimize the reaction conditions, the reaction of benzaldehyde, cyclopentanone, and urea was selected as the model in presence of catalytic amount of acidic ionic liquid under MW irradiation. The best result was obtained when the reaction of cyclopentanone, benzaldehyde, and urea was carried in a 2:2:1.2 mole ratio in presence of acidic ionic liquid (5 mol %) under MW irradiation (250 W, 90°C) for 5 min. In a blank reaction, without acidic ionic liquid, no desired product was

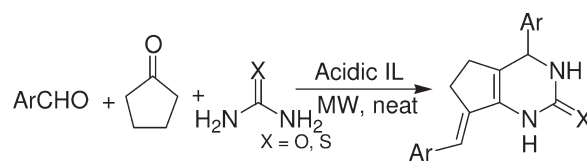
obtained in 5 min. But, very low yield (10–15%) was obtained after longer time irradiation (15–20 min).

Under these optimized conditions, the reaction between various aromatic aldehydes and cyclopentanone in presence of urea was investigated (Table 1). It was found that all the reactions proceeded smoothly to give the corresponding arylidene pyrimidinones in high yields. Both aromatic aldehydes bearing electron-donating and electron-withdrawing gave excellent yields. The mildness of the procedure makes it very selective, as it tolerates a variety of functionalities, including bromo, chloro, fluoro, methoxy, nitro, and methylenedioxy groups. The present procedure was equally effective for thiourea also. The results are summarized in Table 1, which clearly demonstrates the generality and scope of the reaction with respect to various aromatic aldehydes. No organic solvents were required to isolate the product from the reaction mixture. Only ethanol was used for recrystallization to provide analytically pure samples. Use of just 5 mol % IL is sufficient to push the reaction forward. Higher amount of IL did not improve the reaction forward.

Our interest in the preparation of novel scaffolds prompted us to attempt the extension of this reaction to condensations of cyclohexanone and/or aliphatic aldehydes in the Biginelli-type reaction. Unfortunately, the

Table 1

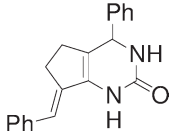
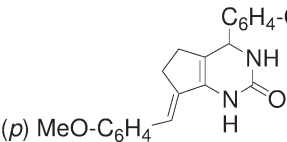
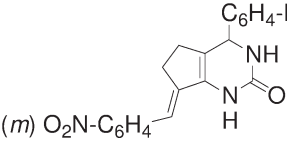
IL promoted microwave-assisted one-pot synthesis of pyrimidinone.



Entry	Ar	X	Time (min)	Yield ^a (%)	Ref.
1	Ph	O	5	82	16a
2	4-MeC ₆ H ₄	O	5	73	16a
3	4-MeOC ₆ H ₄	O	5	64	16a
4	4-BrC ₆ H ₄	O	5	77	16b
5	4-ClC ₆ H ₄	O	5	79	16a
6	4-FC ₆ H ₄	O	5	91	16a
7	2-ClC ₆ H ₄	O	5	68	16a
8	4-NO ₂ C ₆ H ₄	O	5	83	16a
9	3-NO ₂ C ₆ H ₄	O	5	67	16a
10		O	5	82	
11	1-Naphthyl	O	6	84	16b
12	Ph	S	10	82	16a
13	4-MeC ₆ H ₄	S	12	64	16b
14	4-ClC ₆ H ₄	S	10	78	16a
15	4-FC ₆ H ₄	S	8	73	16b
16	4-NO ₂ C ₆ H ₄	S	18	75	16a

^a Yields refer to isolated pure product.

Table 2
Comparison of the present protocol with recently reported methods.

Entry	Product	Present method		Reported method [16b]		Reported method [16a]	
		Time	Yield (%) ^a	Time	Yield (%) ^b	Time	Yield (%) ^c
1		5 min	82	3 h	79	2–3 h	93
2		5 min	64	5 h	69	2–3 h	86
3		5 min	67	5 h	50	2–3 h	78

^a Present reaction conditions: acidic ionic liquid (5 mol%) at 90°C (250 W microwave).

^b Reported reaction conditions: 3 mol% YbCl₃ at 90°C.

^c Reported reaction conditions: stoichiometric amount of TMSCl in DMF/CH₃CN solvent at rt.

reaction did not produce the corresponding benzylidene pyrimidinones under the present reaction conditions, instead leads to multiple products whose identities are yet to be established.

The recovery and reusability of the ionic liquid were investigated. After completion of the reaction, crushed ice (20 g) was added to the reaction mixture and the solid product was filtered. The aqueous layer consisting of the acidic IL was extracted with diethyl ether (5 mL) to remove the organic impurities. The catalyst was recovered after removal of water under reduced pressure and reused for subsequent reactions. It showed the same activity as a fresh catalyst with out any loss of activity in terms of yield and purity. After six recycles, the catalyst had a high activity and gave the desired product in good yield (78%, entry 1).

The efficiency of the present protocol can be realized by comparing some of the results presented here with recently reported two methods as shown in the Table 2, which compares reaction time, yields, and reaction conditions. Thus, it is clear from the Table 2 that the present protocol can act as an effective method with respect to times and reaction conditions.

The mechanism of this reaction is uncertain. The reaction may proceed through the formation of acyl imine intermediate, by the reaction of the aldehyde with urea and activated acid [16a]. Another hypothesis is that dibenzylidene cyclopentanone is the key intermediate

produced by reaction of benzaldehyde with cyclopentanone in presence of acidic IL [16b].

CONCLUSIONS

In conclusion, the present MW-assisted one-pot procedure provides an efficient synthesis of heterobicyclic dihydropyrimidinones by acidic IL-catalyzed condensation of aldehyde, cyclopentanone, and urea or thiourea under solvent-free conditions. We believe our procedure will find important applications in the synthesis of biologically active scaffolds to cater the needs of academia as well as pharmaceutical industries. Further exploration of this chemistry and biological evaluation of the synthesized scaffolds are in progress and will be reported in due course.

EXPERIMENTAL

Melting points were determined on a glass disk with an electrical bath and are uncorrected. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were run in DMSO-*d*₆ solutions. IR spectra were taken as KBr plates. Elemental analyses were done by Perkin–Elmer autoanalyzer. The synthesis of the Brønsted acidic ionic liquid, 1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]Ts was carried out using a method similar to that reported [18].

Typical procedure for the synthesis of 4-benzo[1,3]-dioxol-5-yl-7-benzo[1,3]dioxol-5-ylmethylene-1,3,4,5,6,7-hexahydrocyclopentapyrimidin-2-one (entry 10, Table 1). To a mixture of piperonal (300 mg, 2 mmol), cyclopentanone (177 μ L, 168 mg, 2 mmol), and urea (72 mg, 1.2 mmol) acidic ionic liquid (39 mg, 5 mol %) was added. The mixture was irradiated in a MW reactor (CEM, Discover) at 90°C (250 W) for 5 min as required to complete the reaction. The mixture, after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5–10 min. the solid separated was filtered under suction (water aspirator), washed with ice-cold water (20 mL) and then recrystallized from hot ethanol to afford pure product (320 mg, 82%) as white powder. mp 253–255°C; IR (KBr): 1679, 1492, 1452, 1242 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ = 8.61 (s, 1H), 7.07 (s, 1H), 6.87 (s, 3H), 6.79–6.71 (m, 3H), 6.52 (s, 1H), 5.98 (s, 4H), 5.04 (s, 1H), 2.76 (s, 2H), 2.76 (br, 1H), 2.48 (br, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 153.5, 147.9, 147.8, 146.9, 145.9, 137.9, 137.7, 136.3, 132.5, 122.6, 120.1, 118.1, 116.9, 108.9, 108.5, 107.8, 107.2, 101.4, 101.3, 57.4, 28.7, 28.6; Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.51; H, 4.54; N, 7.01.

The catalyst recovered for the aqueous layer was dried under vacuum and reused for subsequent reactions.

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