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Note

One-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones catalyzed by acidic ionic liquid

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3,4-Dihydropyrimidin-2(1*H*)-ones have been synthesized via one-pot reaction of aromatic aldehydes, ethyl acetoacetate and urea or thiourea catalyzed by room temperature ionic liquid [hmim]HSO_4. It has been observed that the proposed method is fast, efficient and environmentally benign. The reaction time is 15 ~ 55 min with the yields between 82 ~ 97 %.

Keywords: Acidic ionic liquid, Biginelli reaction, solvent-free, 3,4-dihydropyrimidin-2(1*H*)-ones, synthesis

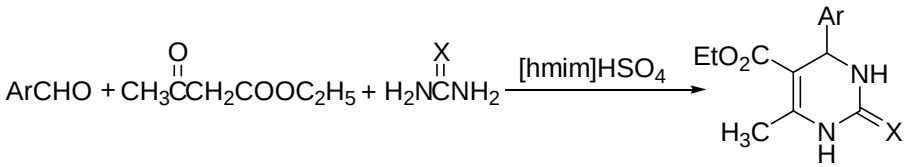
In recent years, dihydropyrimidinones and their derivatives have been shown to display a range of useful physiological and pharmacological properties[1]. They have emerged as the integral backbones of several calcium channel blockers[2], antagonists[1], antihypertensive agents[3] and anticancer drugs[4]. Thus, synthesis of the dihydropyrimidinone derivatives has received much attention continuously. In 1893, Biginelli reported a simple and straightforward procedure starting from aromatic aldehydes, β-dicarbonyl compounds and thiourea under strong acidic conditions with low yields and long time[5]. Therefore, the development of an efficient and versatile catalyst for Biginelli reaction is an active ongoing research area and there is scope for further improvements toward milder reaction conditions and better yields. Many improved procedures have been reported using PPE[6], lanthanide compounds[7,8] and various Lewis acids[9,10] as promoters. Recently, NH_4Cl[11], ionic liquids[12] and heteropolyacid[13] have also been used for Biginelli reaction. However, some of the methods employed have drawbacks, for example using expensive reagents, prolonged reaction time, unsatisfactory yield, etc. Therefore, the development of an inexpensive, facile and effective method for the synthesis of dihydropyrimidinone derivatives is desirable.

Room temperature ionic liquids (RTILs) have received increasing attention as potential "greener" alternatives to volatile organic solvent, and they have been investigated extensively as solvent or catalyst for many important organic reactions because of their special properties such as negligible vapour pressure, tunable polarity, high thermal stability, good solvating ability, ease of recyclability and potential to enhance reaction rates and selectivity[14]. They have also been referred as " designer solvents ", as their properties can be altered by the fine tuning of parameters such as the choice of organic cation, inorganic anion and alkyl chain attached to the organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent and catalyst, catering for the needs of a particular process. Task-specific ionic liquids, which have a functional group in their framework, have been successfully employed as efficient catalyst or dual catalyst-solvent for a variety of reactions[15].

In continuing our endeavor in green synthesis and using ionic liquids as a recyclable, eco-friendly reaction medium to enhance rates and selectivity[16], we report herein, a one-pot synthesis of dihydropyrimidinones (**Scheme I**) catalyzed by task-specific acidic ionic liquid [hmim]HSO_4, which is found to be a simple, highly-yielding, time saving and environmentally friendly method.

Results and Discussion

In our initial study, we used 4-chlorobenzaldehyde as a representative reactant in order to optimize the reaction conditions. As shown in **Table I**, the reaction proceeded efficiently in acidic ionic liquid [hmim]HSO_4, [emim]HSO_4 and [bmim]HSO_4 (Entries 1-3). However, only moderate yield of **4b** was obtained when [bmim]H_2PO_4 was employed (Entry 4). The catalytic performance of [emim]HSO_4, [bmim]HSO_4 and [hmim]HSO_4 was found to be same indicating that there was little impact of the cation on the catalytic activity. Attempts to perform the reaction in [bmim]Br, [bmim]BF_4 and [bmim]PF_6 led only very low yields of the products even at prolonged reaction time. These results suggest that the catalytic activity of the ionic liquids on the condensation reaction was dependent on the Brőnsted acidity of the counteranion. The catalytic performance of the ionic liquids with hydrogen sulphate counteranion was



1 **2** **3** **4**

Scheme I

found to be better than that of the other employed ionic liquids under the same reaction conditions. Probably, this is due to the high Brőnsted acidity of hydrogen sulphate counteranion. So [hmim]HSO_4 was chosen for all further study in this work.

Table I — The condensation reaction of 4-chlorobenzaldehyde, ethyl acetoacetate and urea in different acidic ionic liquids[a]

Entry	RTILs	Yield (%)[b]
1	[hmim]HSO_4	93
2	[emim]HSO_4	90
3	[bmim]HSO_4	92
4	[bmim]H_2PO_4	62

[a] Reaction conditions: 1 mmole 4-chlorobenzaldehyde, 2 mmoles ethyl acetoacetate and 1 mmole urea, 0.2 mL ionic liquid.

[b] Isolated yields.

The reusability and recycling of [hmim]HSO_4 was also investigated. For the condensation reaction of 4-chlorobenzaldehyde, ethyl acetoacetate and urea, after completion of the reaction, 2 mL H_2O was added into the reaction mixture, and the solid was collected by filtration. The filtrate was extracted with diethyl ether for elimination of the unreacted reactants. The extract was dried under vacuum at 90°C for 2 hr to eliminate any water. The recycled [hmim]HSO_4 was reused for subsequent reactions. The catalytic activity of [hmim]HSO_4 did not show any significant decrease even after five runs.

Experimental Section

Melting points were recorded on an electrothermal apparatus and uncorrected. ^{1}H NMR (400 MHz) spectra were determined with a Brucker AVANCE 400 spectrometer (DMSO-d_6) using TMS as an internal standard. IR spectra (cm^{-1}) were measured with a WQF-510 spectrometer. RTILs employed in the paper were prepared according to the literature[17].

A mixture of aromatic aldehydes 1 mmole, ethyl acetoacetate 2 mmoles and urea or thiourea 1mmol in [hmim]HSO_4 (0.2 mL) was heated at 80-85°C for 15-55 min. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, washed with 2 mL water and filtered. The solid was recrystallized from 95% ethanol to afford the desired 3,4-dihydropyrimidin-2(1*H*)-ones **4a** ~ **4n**. The results were shown in **Table II**. All the products were fully characterized by IR, ^{1}H NMR and melting point, which were consistent with the literature data.

4a: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, *J*=7.1 Hz, 3H), 2.29 (s, 3H), 3.91 (q, *J*=7.1 Hz, 2H), 5.65 (d, *J*=2.7 Hz, 1H), 7.21-7.47 (m, 4H), 7.73 (s, 1H), 9.28 (s, 1H); IR (KBr): 3426, 3336, 2977, 1660, 1616, 1524 cm^{-1}.

4b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, *J*=7.1 Hz, 3H), 2.26 (s, 3H), 3.95 (q, *J*=7.2 Hz, 2H) , 5.16 (d, *J*=2.8 Hz, 1H), 7.25 (d, *J*=8.8 Hz, 2H), 7.40 (d, *J*=8.8 Hz, 2H), 7.76 (s, 1H), 9.23 (s, 1H); IR (KBr): 3420, 3246, 3107, 2983, 1708, 1648, 1487 cm^{-1}.

4c: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, *J*=7.2 Hz , 3H), 2.23 (s, 3H), 3.95 (q, *J*=7.2 Hz, 2H), 5.07 (d, *J*=3.2 Hz, 1H), 6.71 (d, *J*=8.4 Hz, 2H), 7.01 (d, *J*=8.4 Hz, 2H), 7.63 (s, 1H), 9.10 (s, 1H), 9.30 (s , 1H); IR (KBr): 3420, 3241, 3115, 2984, 1682, 1650, 1515 cm^{-1}.

4d: ^{1}H NMR (DMSO-d_6, 400 MHz): δ1.07 (t, *J*=7.2 Hz, 3H), 2.25 (s, 3H), 3.70 (s, 3H), 3.97 (q, *J*=7.2 Hz, 2H), 5.07 (d, *J*=2.8 Hz, 1H), 6.84 (d, *J*=8.4 Hz , 2H), 7.16 (d, *J*=8.4 Hz , 2H), 7.65 (s, 1 H), 9.15 (s, 1H); IR(KBr) ν: 3418, 3241, 3114, 2959, 1705, 1646, 1513cm^{-1}.

4e: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, *J*=7.2 Hz, 3H), 2.25 (s, 3H), 3.95 (q, *J* =7.2 Hz, 2H), 5.05 (d, *J*=3.2 Hz, 1H), 6.69 (d, *J*=8.0 Hz, 1H), 5.95 (s, 2H), 6.73 (s, 1H), 6.85 (d, *J*=8.0 Hz , 1H), 7.68 (s, 1H), 9.15 (s, 1H); IR (KBr): 3418, 3230, 3105, 2965, 1700, 1640, 1501 cm^{-1}.

4f: ^{1}H NMR(DMSO-d_6, 400 MHz): δ 1.07 (t, *J*=7.2 Hz, 3H), 2.24 (s, 3H), 3.95 (q, *J*=7.2 Hz, 2H), 5.12 (s, 1H), 7.20-7.33 (m, 5H), 7.70 (s, 1H), 9.17 (s, 1H); IR

Table II —Synthesis of dihydropyrimidinone derivatives in acidic ionic liquid [hmim]HSO_4

Entry	Ar-	X	Time (min)	M.p. (lit) (°C)	Yield(%)
4a	2- ClC_6H_4-	O	45	217-219 (216-218)[20]	92
4b	4-ClC_6H_4-	O	30	215.5-217 (215-216)[19]	93
4c	4-HOC_6H_4-	O	55	227-228 (226-228)[19]	87
4d	4-$CH_3OC_6H_4$-	O	15	203-205 (201-202)[19]	93
4e	3,4-$(OCH_2O)C_6H_3$-	O	45	188-189 (188-189)[19]	97
4f	C_6H_5-	O	15	202-204 (203-204) [18]	86
4g	4-HO-3-$CH_3OC_6H_3$-	O	15	233-234.5 (231-232) [18]	95
4h	3-$NO_2C_6H_4$-	O	30	228-230 (226-227) [20]	93
4i	C_6H_5-	S	20	205-206 (206-208)[20]	82
4j	2-ClC_6H_4-	S	45	205-206 (203-205) [20]	92
4k	4-ClC_6H_4-	S	50	184-186 (180-182) [20]	90
4l	3-$NO_2C_6H_4$-	S	50	207-208 (208-209)[20]	91
4m	4-HOC_6H_4-	S	50	171-173 (170-173)[20]	88
4n	4-HO-3-$CH_3OC_6H_3$-	S	30	190-192 (191-193)[20]	89

(KBr): 3415, 3235, 3111, 2939, 1702, 1644, 1601 cm^{-1}.

4g: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.15 (t, *J*=7.1 Hz, 3H), 2.25 (s, 3H), 3.16 (s, 3H), 3.95 (q , *J*=7.1 Hz, 2H), 5.08(d, *J*=3.5 Hz, 1H), 6.56 – 6.61 (m, 1H), 6.70 – 6.81 (m, 2H), 9.01 (s, 1H), 9.55 (s, 1H), 10.20 (s, 1H); IR (KBr): 3415, 3175, 2997, 1687, 1586, 1517,1197 cm^{-1}.

4h: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.07 (t, *J*=7.1 Hz, 3H), 2.51 (s, 3H), 3.97 (q, *J*=7.1 Hz, 2H), 5.30 (d, *J*=3.3 Hz, 1H), 7.61-7.72 (m, 2H), 7.83 (s, 1H), 8.03-8.12 (m, 2H), 9.25 (s, 1H) ; IR (KBr): 3333 , 3210 , 3112 , 2965 , 1707 , 1632 , 1525 cm^{-1}.

4i: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, *J*=7.1 Hz, 3H), 2.27 (s, 3H), 4.01 (q, *J*=7.1 Hz, 2H), 5.15 (d, *J*=3.2 Hz, 1H), 7.19-7.38 (m, 4H), 9.58 (s, 1H), 10.31(s, 1H); IR (KBr): 3239, 3115, 2980, 1720, 1695, 1653, 1223, 1088cm^{-1}.

4j: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.07 (t, *J*=7.1 Hz, 3H), 2.33 (s, 3H), 3.96 (q, *J*=7.1 Hz, 2H), 5.61(d, *J*=3.0 Hz, 1H), 7.23-7.38 (m, 3H), 7.41-7.43 (m, 1H), 9.62 (s, 1H), 10.35 (s, 1H); IR (KBr): 3371, 3272, 3179, 1617, 1478, 1415, 1086 cm^{-1}.

4k: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, *J*=7.1 Hz, 3H), 2.31 (s, 3H), 3.98 (q, *J*=7.1 Hz, 2H), 5.19(d, *J*=3.4 Hz, 1H), 7.22 (d, *J*=8.4 Hz, 2H), 7.45 (d, *J*=8.4 Hz, 2H), 9.65 (s, 1H), 10. 38 (s, H); IR (KBr): 3338, 3171, 2979, 1669, 1568, 1459 cm^{-1}.

4l: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.07 (t, *J*=7.1 Hz, 3H), 2.35 (s, 3H), 3.97 (q, *J*=7.1Hz, 2H), 5.33 (d, *J*=3.6 Hz, 1H), 7.66 (m, 2H), 8.01-8.17 (m, 2H), 9.71 (s, 1H), 10.39 (s, 1H); IR (KBr) ν: 3182, 2993, 1712, 1657, 1598, 1529,1475, 1191 cm^{-1}.

4m: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.11 (t, *J*=7.1 Hz, 3H), 2.29 (s, 3H), 4.01 (q, *J*=7.1 Hz, 2H), 4.99 (d, *J*=3.6 Hz, 1H), 6.67 (d, *J*=8.4 Hz, 2H), 7.02 (d, *J*=8.4 Hz, 2H), 9.40 (s, 1H), 9.53 (s, 1H), 10.31 (s, 1H); IR (KBr): 3507, 3347, 3238, 3117, 1731, 1667, 1643, 1591, 1228 cm^{-1}.

4n: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.07 (t, *J*=7.1 Hz, 3H), 2.52 (s, 3H), 3.86 (q, *J*=7.1 Hz, 2H), 3.99 (s, 3H), 5.09 (d, *J*=3.6 Hz, 1H), 6.56 (m, 1H), 6.67-6.81(m, 2H), 8.91 (s, 1H), 9.49 (s, 1H), 10.16 (s, 1H); IR (KBr): 3409, 3171, 3001, 1691, 1583, 1517, 1192 cm^{-1}.

Conclusion

An efficient, time saving and environmentally friendly method for the one-pot synthesis of dihydropyrimidinones using task-specific acidic ionic liquid [hmim]HSO_4 as catalyst has been developed.

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