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Synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives of acid sensitive aldehydes catalyzed by lanthanum nitrate in ionic liquids

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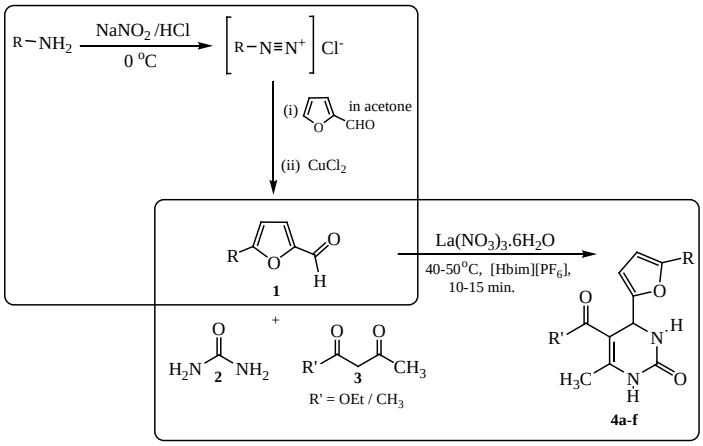
ABSTRACT



Synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives (**4a-f**) of acid sensitive aldehydes catalyzed by lanthanum nitrate in ionic liquids is described. The method offers use of inexpensive, readily available and efficient Lewis acid catalyst in an environment benign process with excellent yields in short reaction time and easy product isolation with high purity.

Keywords: Lanthanum nitrate, 3,4-dihydropyrimidin-2(1H)-ones, acid sensitive aldehyde, ionic liquids

INTRODUCTION

Dihydropyrimidin-2(1H)-ones (DHPMs) are calcium channel blockers, antihypertentive agents, α_{1a}-adrenergic antagonists and neuropeptide Y(NPY) antagonists.[1-5] They are found as core units in many marine alkaloids such as batzelladine and crambine, which have been found to be potent HIV gp-120CD4 inhibitors.[6] Consequently, synthesis of this heterocyclic core is currently of much importance. In recent years, room-temperature ionic liquids (ILs) have emerged as a powerful alternative to conventional molecular organic solvents or catalysts due to their particular properties, such as undetectable vapour pressure, wide liquid range, as well as the ease of recovery and reuse.[7-11] The ILs have also been used as catalysts for Biginelli reaction.[12-13]

The regular interest on Biginelli compounds leading to the development of nitractin, a derivative of 2-furfuraldehyde, that has excellent activity against the virus of trachoma group and antibacterial activity.[14] Generally under strongly protic or Lewis acidic conditions the poor yields of DHPMs derived from the acid sensitive aldehydes are observed along with side products.[15-16] Therefore, the development of a neutral alternative would extend the scope of the useful Biginelli reaction. The present protocol constitutes a practical and effective method for the synthesis of DHPMs derivatives of acid sensitive aldehydes catalyzed by lanthanum nitrate in ILs.

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RESULTS AND DISCUSSION

The reaction between ethyl acetoacetate (1.0 mmol), 2-furfuraldehyde (1.0 mmol), urea (1.3 mmol), and $La(NO_3)_3.6H_2O$ (0.1 mmol) in aqueous solution gave 5-(ethoxycarbonyl)-6-methyl-4-(furyl)-3,4-dihydropyrimidin-2(1H)-ones (**4a**) in 5% yield, in water:ethanol (1:1) 28% and in ethanol 80%. In ILs viz; [Hbim][Br], [Hbim][BF_4] and [Hbim][PF_6] 84%, 92%, 94% yield of **4a** was obtained (**Table 1**). Poor yields of DHPMs was observed when the reactions was performed in the absence of $La(NO_3)_3.6H_2O$ (**Table 1**). Hence all the reactions were carried out using $La(NO_3)_3.6H_2O$ as catalyst and [Hbim][PF_6] as solvent.

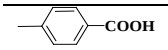
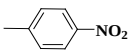
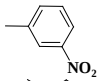
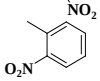
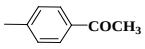
The reaction of 2-furfuraldehyde, urea and ethyl acetoacetate in the presence of a catalytic amount of $La(NO_3)_3.6H_2O$ in ILs was carried out at different temperatures under similar experimental conditions. The reaction rate was slow at ambient temperature, but improved with increasing the temperature. The optimum temperature was found to be 50 °C.

Table 1. Synthesis of 5-(ethoxycarbonyl)-6-methyl-4-(furyl)-3,4-dihydropyrimidin-2(1H)-ones (**4a**) in different reaction conditions.

Entry	Solvents	Catalyst	Time (min.)	Yields (%)[a]
1	H_2O	$La(NO_3)_3.6H_2O$	120	5
2	H_2O:EtOH (1:1)	$La(NO_3)_3.6H_2O$	240	28
3	EtOH	$La(NO_3)_3.6H_2O$	240	80
4	CH_3CN	$La(NO_3)_3.6H_2O$	300	55
5	CH_2Cl_2	$La(NO_3)_3.6H_2O$	300	40
6	[Hbim][Br]	-	90	12
7	[Hbim][BF_4]	-	60	18
8	[Hbim][PF_6]		60	24
9	[Hbim][Br]	$La(NO_3)_3.6H_2O$	20	84
10	[Hbim][BF_4]	$La(NO_3)_3.6H_2O$	15	92
11	[Hbim][PF_6]	$La(NO_3)_3.6H_2O$	15	94

[a]Isolated yields

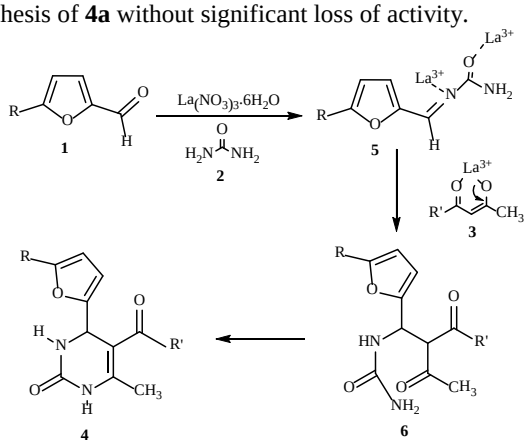
Table 2. $La(NO_3)_3.6H_2O$ catalyzed synthesis of dihydropyrimidin-2(1H)-ones (**4**) in ILs.

R	R´	X	Product	Time (min.)	Yield (%)[b]	M.P. (°C)[c]
H	OEt	O	**4a**	10	94	206[17]
	OEt	O	**4b**	15	94	< 250
	OEt	O	**4c**	15	92	175-176
	Me	O	**4d**	15	90	189-190
	Me	O	**4e**	15	88	220-224
	Me	O	**4f**	15	93	220 (dec.)

[a]All products were characterized by ^{1}H NMR and IR spectroscopy; [b]Isolated yield; [c]Observed melting point

All the substituted 2-furfuraldehydes carrying either electron-donating or electron-withdrawing substituents gave excellent yields of DHPMs. Thus, many pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. The nature and position of the groups in the aromatic ring have minor effect on the yields of corresponding DHPMs (**Table 2**). The three component reaction afforded uniformly high yields, regardless of the different substituted β-diketones (**3**) or aldehydes (**1**). Another important aspect of this procedure is the survival of variety of functional groups such as -NO_2, -COOH and –$COCH_3$.

Further, the recovery of the product is relatively simple as compared to organic solvents. The products were easily isolated by dilution with solvent and filtration of the precipitated DHPMs. The DHPMs, thus isolated were homogeneous on TLC and pure enough for all practical purposes. After work-up procedure, the ionic liquid remaining in the filtrate can be recovered by removing the solvent through heating and then drying under vacuum for 4h. The reaction of **1a** with **2** and ethylacetoacetate in the presence of $La(NO_3)_3.6H_2O$ in [Hbim][PF_6] afforded **4a** in 94, 92, 87 and 82 % yields by reuse of recovered ionic liquid in four cycles. Thus the ionic liquid could be reused at least four successive runs for the synthesis of **4a** without significant loss of activity.



Scheme 1. Mechanism proposed for Biginelli condensation.

According to the mechanism suggested by Kappe[18] the reaction may proceed through imine formation from the aldehyde and urea, subsequent addition of the carbanion derived from 1,3-dicarbonyl compounds to the imine followed by cyclodehydration to afford DHPMs. The La^{3+} is capable of bonding with the carbonyl oxygen of the aldehydes as well as that of the β-keto ester to form enolate intermediate (Scheme 1).

CONCLUSION

In conclusion, some DHPMs derivatives have been synthesized using acid sensitive aldehydes and their derivatives catalyzed by $La(NO_3)_3.6H_2O$ in ILs. The method offers use of inexpensive, readily available and efficient Lewis acid catalyst in an environment benign process with excellent yields in short reaction time and easy product isolation with high purity.

EXPERIMENTAL

All melting points were determined on a Thomas Hoover Unimelt melting point apparatus and uncorrected. IR spectra (ν_{max},

cm^{-1}) were recorded on a Shimadzu IR 435 spectrometer. Electronic spectra (λ_{max}, nm) were obtained by Perkin Elmer, Lambda 35 UV-Vis spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance 300 spectrometer using TMS as internal standard (chemical shift in ppm). The symbols s, d, t, q and m stand for singlet, doublet, triplet, quartet and multiplet respectively. The electron spray ionization mass spectra (ESI-MS) were recorded on Waters, LCT micromass.

GENERAL PROCEDURE

The aldehydes were prepared using minor modification of the reported procedure.[19] The A solution of an appropriate *β*-diketone (1 mmol), corresponding aldehyde (1 mmol), urea (1.3 mmol), and $La(NO_3)_3.6H_2O$ (0.1 mmol) immobilized in ionic liquid [Hbim][PF_6] was stirred at 50-60°C for 15 min. After the completion of the reaction, water (20 mL) was added to the reaction mixture and it was allowed to stand for 10 min. at room temperature. The precipitated product was filtered, and washed with water:ethanol (1:1). The product was recrystallized from ethanol to afford the pure DHPMs. The filtrate thus obtained was concentrated at 80-90 °C under reduced pressure for 4h to afford the ionic liquid.

The spectroscopic data of selected compounds is given below:

5-(Ethoxycarbonyl)-6-methyl-4-(4-carboxy-furyl)-3,4-dihydropyrimidin-2(1H)-ones (4b).

IR (KBr, cm^{-1}): 3280, 1735, 1659, 1619, 1596, 1462; ^{1}H NMR (DMSO-d_6, 300 MHz, δ in ppm): 2.15 (s, 3H, CH_3), 5.4 (s, 1H), 2.2 (s, 3H, CH_3), 7.85 (s, 1H, NH), 6.2 (d, *J*=3.3 Hz, 1H, H-3′), 7.01 (d, *J*=3.3 Hz, 1H, H-4′), 7.82 (d, *J*=7.8 Hz, 2H, H-2″ & H-6″), 8.12 (d, *J*=8.1 Hz, 2H, H-3″ & H-5″), 9.3 (s, 1H, NH); ESI-MS: 371.119 (M+1).

5-(Ethoxycarbonyl)-6-methyl-4-(4-nitrophenyl-furyl)-3,4-dihydropyrimidin-2(1H)-ones (4c).

IR (KBr, cm^{-1}): 3297, 1677, 1660, 1640, 1463; ^{1}H NMR (DMSO-d_6, 300 MHz, δ in ppm): 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 5.4 (s, 1H, H-4), 7.3 (d, *J*=3.7 Hz, 1H, H-3′), 7.54 (d, *J*=3.7 Hz, 1H, H-4′), 7.6 (s, 1H, NH), 7.90 (d, *J*=8.8 Hz, 2H, H-2″ & H-6″), 8.52 (d, *J*=8.8 Hz, 2H, H-3″ & H-5″), 9.4 (s, 1H, NH); ESI-MS: 394.206 (M+Na), 352.166, 252.231.

5-Acetyl-6-methyl-4-(3-nitrophenyl-furyl)-3,4-dihydropyrimidin-2(1H)-ones (4d).

IR (KBr, cm^{-1}): 3297, 1677, 1660, 1640, 1463; ^{1}H NMR (DMSO-d_6, 300 MHz, δ in ppm): 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 5.79 (s, 1H, H-4), 7.3 (d, *J*=3.7 Hz, 1H, H-3′), 7.5 (d, *J*=3.7 Hz, 1H, H-4′), 7.72 (s, 1H, NH), 8.25-7.74 (m, 4H, H-3″-H-6″), 9.4 (s, 1H, NH); ESI-MS: 342.416 (M+1).

5-Acetyl-6-methyl-4-(4-acetylphenyl-furyl)-3,4-dihydropyrimidin-2(1H)-ones (4e).

IR (KBr, cm^{-1}): 3295, 1679, 1661, 1642, 1460; ^{1}H NMR (DMSO-d_6, 300 MHz, δ in ppm): 2.02 (s, 3H, CH_3) 2.35 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 5.8 (s, 1H, H-4), 6.3 (d, *J*=3.8 Hz, 1H, H-3′), 6.5 (d, *J*=3.8 Hz, 1H, H-4′), 7.60 (s, 1H, NH), 7.64 (d, *J*=8.8 Hz, 2H, H-2″, H-6″), 8.1 (d, *J*=8.8 Hz, 2H, H-3″ & H-5″), 9.3 (s, 1H, NH); ESI-MS: 339.142 (M+1).

5-Acetyl-6-methyl-4-(2-nitrophenyl-furyl)-3,4-dihydropyrimidin-2(1H)-ones (4f).

IR (KBr, cm^{-1}): 3297, 1677, 1660, 1640, 1463; ^{1}H NMR (DMSO-d_6, 300 MHz, δ in ppm): 2.20 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 5.20 (s, 1H, H-4), 7.03 (d, *J*=3.7 Hz, 1H, H-3′), 7.16 (br s, 1H, H-4′); 7.47 (s, 1H, NH), 7.68-8.01 (m, 4H, Ar-H), 9.28 (s, 1H, NH); ESI-MS: 364.246 (M+Na), 342.316 (M+1).

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