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IONIC LIQUIDS –CATALYZED A GREEN SYNTHESIS OF 3, 4-DIHYDROPYRIMIDIN- 2 (1H) - ONES UNDER SOLVENT- FREE CONDITIONS

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ABSTRACT

Ionic liquids (ILs) Triethyl ammonium dihydrogen phosphate efficiently catalyzes the condensation reaction of ethyl acetoacetate, aldehydes, and urea or thiourea a three-component reaction under solvent-free conditions. The reaction proceeds rapidly and affords the corresponding 3, 4-dihydropyrimidin-2 (1H)-ones in high yields, short reaction times, simple procedure.

KEYWORDS: Ionic liquids, Triethyl ammonium dihydrogen phosphate [Et_3NH] [H_2PO_4], 3, 4-dihydropyrimidin-2 (1H)-ones, solvent- free.

INTRODUCTION

The developing of new multi-component reactions and improving known multi-component reactions are an area of considerable current Interest.[1, 2] Ionic liquids (ILs) have attracted more and more attentions as the green reaction medium alternative to organic solvents for their low volatility, negligible vapour pressure, reasonable thermal stability, outstanding recyclability and reusability. In recent years, Triethyl ammonium dihydrogen phosphate, due to its acidic and stable nature, has been found to be a suitable replacement for various homogeneous two-phase catalysts[3] and extraction.[4] The importance of 3, 4-dihydropyrimidin- 2 (1H)- ones and core as a pharmacophore is well established due to the pharmacological activities[5, 6] of its various derivatives; antiviral, antitumour, antibacterial and antiflammatory properties. In addition, the 2- oxodihydropyrimidine-5 – carboxylate core unit is found in nature[7, 8] and in potent HIVgp-120-CD_4- inhibitors, therefore many synthetic methods for the synthesis of this heterocyclic scaffold have been developed.[9] Recently,

many synthetic methods for preparing these compounds have been reported including classical conditions, with microwave and ultrasound irradiation and by using Lewis acid as well as protic acid promoters such as zirconium (IV) chloride[10], indium (III) bromide[11], H_2SO_4[12], HOAc[13], montimorillonite KSF[14], polyphosphate ester (PPE)[15], BF_3-OEt_2/CuCl/HOAc[16] and conc. HCl[17, 18]. No doubt, these methods are good in terms of reactivity; however they suffer form the drawbacks of long reaction time, moderate yield, use of toxic organic solvents, the requirement of special apparatus, or harsh reaction conditions. Following our systematic studies directed towards the development of practical, safe, and environmentally friendly procedures for several important organic transformations.[19]

In this context, we report a simple and environmentally benign methodology for the synthesis of 3, 4- dihydropyrimidin-2 (1H)-ones via direct three –component condensation reaction between aldehydes, ethyl acetoacetate, and urea or thiourea using catalytic amounts of Triethyl ammonium dihydrogen phosphate under solvent-free condition (**Scheme 1**).

MATERIALS AND METHODS

All chemical were purchased from Marck, Aldrich and Rankem Chemical companies and used without further purification. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. The progresses of the reactions were monitored by TLC (thin layer chromatography). IR spectra were recorded on Perkin –Elmer FT spectrometer in KBr disc. 1H NMR spectrometer in $CDCl_3$ and DMSO as a solvent and chemical shift values are recorded in units δ relative to tetramethylsilane (Me_4Si) as an internal standard.

1.1. General procedure for the synthesis of 3, 4- dihydropyrimidin-2 (1H)-ones (**1-14**)

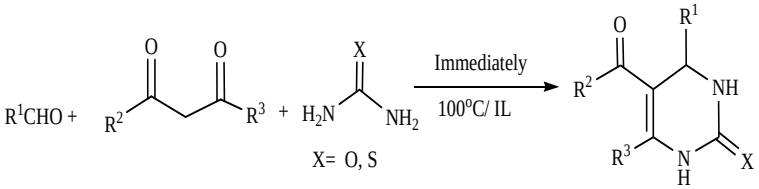
A mixture of aromatic aldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea or thiourea (3 mmol) and [Et_3NH] [H_2PO_4] (10 mol %) was heated with stirring at 100 ^oC for appropriate time in (>1 min). After completion of reaction confirmed by TLC, the reaction mixture was dissolved in ethanol and poured into water to furnish the crude products. The crude was further purified by column chromatography by using ethyl acetate: n- Hexane (2:8) eluent and get the corresponding 3, 4- dihydropyrimidin-2 (1H)-ones (**1-14**). IR, ^1H NMR, mass elemental analysis and melting points.

Spetra data: Ethyl 6-methyl-2-thioxo-4-p-tolyl-1,3,4-tetrahydropyrimidine-5-carboxylate(13) ^1H NMR (400MHz, DMSO-d_6): δ 10.30 (s, 1H, NH), 9.61 (s, 1H, NH) 7.12 (d, 2H, *J*= 8.0

Hz, ArH), 6.90 (d, 2H, *J*= 8.0 Hz, ArH), 5.12 (s, 1H, CH), 4.00 (q, 2H, *J*=6.8 Hz, OCH_2CH_3), 3.72 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 1.11 (t, 3H, J= 6.8 Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, DMSO-d6): δ 174.0, 165.1, 158.7, 144.7, 135.7, 127.6, 113.9, 100.9, 59.5, 55.0, 53.4, 17.1, 14.0. IR (KBr): 3313, 3171, 3106, 2985, 1667, 1610, 1575, 1509, 1461, 1371 cm^{-1}.

RESULTS AND DISCUSSION

As a part of our ongoing investigation in developing a versatile and efficient method for synthesis of heterocyclic compounds.[19] herein, we reported efficient synthetic method for the synthesis of 3, 4- dihydropyrimidin-2 (1H)-ones from ethyl acetoacetate, substituted aromatic aldehyde and urea or thiourea in the presence of Triethyl ammonium dihydrogen phosphate $[Et_3NH]$ $[H_2PO_4]$ (**Scheme 1**). The three –component, cyclocondensation reaction may be preformed under relatively simple reaction conditions by heating together the three components, an aromatic aldehyde, ethyl acetoacetate, urea or thiourea, in the ratio of 2: 2: 3 and the catalyst (10 mol%), at 100 ^oC with stirring. After the completion of the reaction, as indicated by TLC, the reaction mixture was dissolved in ethanol and poured in water to furnish the crude products. The crude was further purified by column chromatography by using ethyl acetate: n-Hexane as indicated in Table 1.



Scheme 1

Table 1: Triethyl ammonium dihydrogen phosphate –catalyzed synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones under solvent- free condition at 100 ^oC

DHMP	R^1	R^2	R^3	X	Yield (%)[a]	Mp	(^oC)
						Found	Reported
1	C_6H_5	OEt	Me	O	97	202	201-203[20]
2	4-NO_2-C_6H_4	OEt	Me	O	97	208	207-210[20]
3	4-OMe-C_6H_4	OEt	Me	O	92	200	199-201[20]
4	4-Cl-C_6H_4	OEt	Me	O	90	214	210-212[20]
5	4-Me-C_6H_4	OEt	Me	O	90	210	208-210[11]
6	C_6H_5	OMe	Me	O	97	208	207-

							210[20]
7	4-NO_2-C_6H_4	OMe	Me	O	93	238	235-237[20]
8	4-OMe-C_6H_4	OMe	Me	O	90	192	191-193[20]
9	4-Cl-C_6H_4	OMe	Me	O	91	204	204-207[16]
10	C_6H_5	Me	Me	O	80	236	233-236[20]
11	C_6H_5	OEt	Ph	O	79	158	157-159[16]
12	C_6H_5	OBn	Me	O	83	166	165-166[21]
13	4-$CH_3C_6H_5$	OEt	Me	S	92	214	192-194[15]
14	CH-$(CH_3)_2$	OEt	Me	O	80	170	170-172[22]

[a]Isolated yields

The resulted presented in the Table indicate the scope and generality of the method, which is efficient, not only for urea or thiourea, but also for aliphatic as well as aromatic aldehydes. An important feature of this method is that electron releasing or withdrawing groups gave excellent yields in high purity. It is pertinent to note that Triethyl ammonium dihydrogen phosphate catalyst gave consistently higher yields with aliphatic aldehydes, entry **14** as against the moderate yields[23,24] reported earlier.

CONCLUSION

In conclusion, the Ionic liquids (ILs) Triethyl ammonium dihydrogen phosphate has been employed as a novel, mild, and very efficient catalyst for the convenient synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones in excellent yields from wide variety of aldehyde. In addition, low-cost of catalyst, solvent-free conditions, environmental friendliness, easy availability make this methodology a valid contribution to the existing processes in the field of 3, 4-dihydropyrimidin-2 (1H)-one derivatives synthesis.

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