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Comparative efficiency of metal phosphates as a protomer in multi-component condensation reaction

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Abstract

This work was aimed to investigate the efficiency of various metal phosphates as a protomer in the synthesis of multi-component condensation reaction. The multi-component reaction employed in this work was a ternary condensation between urea/thiouea, an aldehyde and 1,3-dicorbonyl compound. The metal phosphates utilized as a protomer in condensation reaction were mono and dibasic phosphates of sodium and potassium metals (NaH_2PO_4, KH_2PO4 and K_2HPO4). The efficiency of these phosphates were investigated in a common solvent; glacial acetic acid which is a very cheap and cost-effective. Six different condensation products (4a-4f) were obtained by using different aldehydes and 1,3-dicorbonyl compound to ensure reproducibility of the reaction. The structures of all compounds were confirmed on the basis of spectral data (IR and ^{1}HNMR). Among the metal phosphates used, KH_2PO_4 demonstrated excellent efficiency as a protomer in terms of excellent yields and purity as compared to other phosphates.

Keywords: Metal phosphates, Protomer, Multi-component reaction, Ternary condensation, Efficiency

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INTRODUCTION

Biginelli 3,4-dihydropyrimidine-2-(1*H*)-one (DHPM) [1] multi-component reaction compounds are popular because of their many interesting biological activities such as calcium channel modulators [2-5], analgesic [6], anticancer [7], antioxidant agents [8], anti-inflammatory [9], antimicrobial [10] and neuropeptide antagonists [11]. The original Biginelli reaction was carried out by refluxing a mixture of the three components such as ethyl acetoacetate, benzaldehyde and urea in presence of ethanol catalyzed by small amount of HCl [1] which often resulted in poor to moderate yields of desired products [12].

Therefore, several improved reaction protocols for the synthesis of Biginelli compounds have been reported, either by modification of the classical one-pot Biginelli reaction, novel multi-step methods, use of combinatorial approaches or microwave irradiation techniques [13-16].

Literature survey revealed that yields of Biginelli compounds have been improved by employing different catalysts such as polyphosphate ester (PPE) [12], Bronsted acids viz. *p*-toluenesulfonic acid [17] potassium hydrogen sulphate [18] and chloroacetic acid [19], Lewis acids viz. Yb $(OTf)_3$ [13], $InCl_3$ [20], $CuCl_2$. [21], $SnCl_2$. [22], BF3.OEt_2 [23] and $ZrCl_4$ [24]. Besides these catalysts, recently $Pb(NO_3)_2$ [25], NaCl [26] alkaline phosphates [27-29] and sulphates [30] have been also employed for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one compounds.

In recent years, multi-component reactions have attracted the attention of organic chemists because they are more efficient and cost effective. Further, these reactions can be carried out without isolation of the intermediates (One pot and one step synthesis) and avoid the protection-deprotection strategies in the synthesis as well as time consuming purification processes [16]. The only disadvantage resides with such type of reactions is the low % yields of target products due to possibly formation of by-products.

As a part of ongoing research to synthesize 3, 4-dihydropyrimidine-2-(1*H*)-one derivatives, this work was aimed to check the efficiency of various metal phosphates as protomer in the multi-component dihydropyrimidine synthesis. Initially, different solvents were attempted where glacial acetic acid was optimized to be suitable solvent as far as the yields of the products were concerned. The various metal phosphates employed were NaH_2PO_4, KH_2PO_4 and K_2HPO_4. All these catalysts are inexpensive and nontoxic. Thus in the present work efforts were taken to improve the yields of Biginelli compounds through eco-friendly procedure.

MATERIAL AND METHODS

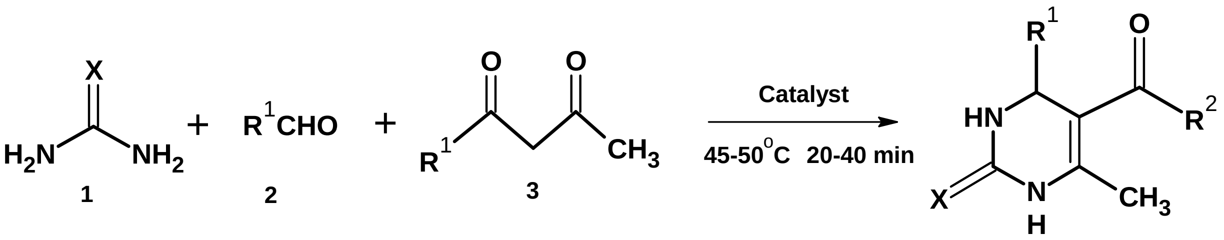
Materials

All the chemicals used were of synthetic grade and procured from Loba Chemie, Mumbai, India. The melting points were determined in open capillary tubes and are uncorrected. The purity of compounds was checked by TLC on silica gel G plates. IR spectra were recorded on Shimadzu FT-IR spectrophotometer. ^{1}HNMR spectra were recorded in DMSO (d6) and / or $CDCI_3$ on Varian Mercury YH-300 NMR spectrophotometer.

Synthesis of 5- acetyl / ethoxycarbonyl, 4-aryl / substituted aryl, 6-methyl, 3, 4-dihydropyrimidine-2-one / thione

A mixture of urea / thiourea (0.05 mol), appropriate aldehyde (0.05 mol), acetyl acetone / ethyl acetoacetate (0.05 mol) and metal phosphate (0.05 mol) in 20 mL of glacial acetic acid solvent was heated at 45 -50° C under magnetic stirring for 20-40 min (Scheme 1). The progress of reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was poured onto crushed ice and stirred for few minutes. The resulting solid was filtered at vacuum, washed with water and recrystallized from hot ethanol to afford the pure product. The % yields and meting points are reported in Table 1.

Scheme 1 Synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one / thione derivatives (4a-4f)



Scheme 1

4 (4a-4f)

R^1 = aryl, substituted aryl

R^2 = CH_3, OC_2H_5

X = O, S

Spectroscopic data of synthesized compounds

5- acetyl, 6-methyl, 4-phenyl, 3, 4-dihydropyrimidine-2(1H)-one (4a)
IR (KBr, cm^{-1}): 3259 (N-H), 3082 (C-H aromatic), 2943 (C-H aliphatic *asym*), 2910 (C-H aliphatic *sym*), 1601 (C=C aromatic), 1490 (C=C pyrimidine cyclic),1699 (C=O ketone), 1674 (C=O amide), 1456 (C-N ring), 705 (phenyl bending); ^{1}HNMR (δppm): 8.68 (s, 2H, NH), 2.11 (s, 3H, CH_3), 2.36 (s, 3H, $COCH_3$), 5.38 (s, 1H, CH), 7.25-7.42 (m, 5H, ArH).

5- acetyl, 6-methyl, 4-(4-methoxyphenyl), 3, 4-dihydropyrimidine-2(1H)-one (4b)
IR (KBr, cm^{-1}): 3228 (N-H), 3051 (C-H aromatic), 2910 (C-H aliphatic *asym*), 2839 (C-H aliphatic *sym*), 1593 (C=C aromatic), 1558 (C=C pyrimidine cyclic), 1718 (C=O ketone), 1653 (C=O amide), 1383 (C-N ring), 1070 (C-O-C), 827 (phenyl bending); ^{1}HNMR (δppm): 8.04 (s, 2H, NH), 2.10 (s, 3H, CH_3), 2.34 (s, 3H, $COCH_3$), 5.38 (s, 1H, CH), 7.20-7.26 (m, 4H, ArH), 3.79 (s, 3H, OCH_3).

5- acetyl, 6-methyl, 4-phenyl, 3, 4-dihydropyrimidine-2(1H)-thione (4c)
IR (KBr, cm^{-1}): 3319 (N-H), 3093 (C-H aromatic), 2904 (C-H aliphatic *asym*), 2821 (C-H aliphatic *sym*), 1589 (C=C aromatic), 1531 (C=C pyrimidine cyclic), 1651 (C=O ketone), 1230 (C=S thiocarbonyl), 1415 (C-N ring), 729 (phenyl bending); ^{1}HNMR (δppm): 9.66-10.18 (s, 2H, NH), 2.138 (s, 3H, CH_3), 2.36 (, 3H, $COCH_3$), 5.33 (s, 1H, CH), 7.28 (s, 5H, ArH).

5- ethoxycarbonyl, 6-methyl, 4-phenyl, 3, 4-dihydropyrimidine-2(1H)-one (4d)
IR (KBr, cm^{-1}): 3244 (N-H), 3115 (C-H aromatic), 2980 (C-H aliphatic *asym*), 1600 (C=C aromatic), 1495 (C=C pyrimidine cyclic), 1725 (C=O ester), 1652 (C=O amide), 1418 (C-N ring), 1091 (C-O-C), 703 (phenyl bending); ^{1}HNMR (δppm): 8.06 (s, 2H, NH), 2.34 (s, 3H, CH_3), 1.16 (t, 3H, CH_3), 4.02 (q, 2H, CH_2), 5.39 (s, 1H, CH), 7.23-7.32 (m, 5H, ArH).

5- ethoxycarbonyl, 6-methyl, 4-(4-methoxyphenyl), 3, 4-dihydropyrimidine-2(1H)-one (4e)
IR (KBr, cm^{-1}): 3280 (N-H), 3115 (C-H aromatic), 2984 (C-H aliphatic *asym*), 2835 (C-H aliphatic *sym*), 1615 (C=C aromatic), 1514 (C=C pyrimidine cyclic), 1725 (C=O ester), 1652 (C=O amide), 1467 (C-N ring), 1087 (C-O-C), 844 (phenyl bending); ^{1}HNMR (δppm): 8.16 (s, 2H, NH), 2.33 (s, 3H, CH_3), 1.14 (t, 3H, CH_3), 4.03 (q, 2H, CH_2), 5.34 (s, 1H, CH), 7.22-7.23 (m, 4H, ArH), 3.78 (s, 3H, OCH_3).

5- ethoxycarbonyl, 6-methyl, 4-phenyl, 3, 4-dihydropyrimidine-2(1H)-thione (4f)
IR (KBr, cm^{-1}): 3327 (N-H), 3101 (C-H aromatic), 2901 (C-H aliphatic *asym*), 2810 (C-H aliphatic *sym*), 1670 (C=C aromatic), 1500 (C=C pyrimidine cyclic), 1725 (C=O ester), 1282 (C=S thioamide), 1410 (C-N ring), 1085 (C-O-C), 694 (phenyl bending); ^{1}HNMR (δppm): 9.36-9.96 (s, 2H, NH), 2.35 (s, 3H, CH_3), 1.15 (t, 3H, CH_3), 4.01 (q, 2H, CH_2), 5.29 (s, 1H, CH), 7.23-7.30 (s, 5H, ArH).

RESULTS AND DISCUSSION

The results obtained from tertiary condensation of urea or thiourea, aldehydes and 1,3-dicarbonyl compounds leading to formation of 4, 5-disubstituted, 3, 4-dihydropyrimidine-2(1*H*)-one / thione derivatives catalyzed by NaH_2PO_4, KH_2PO_4 and K_2HPO_4 are shown in Table 1. It is evident that all products were obtained in satisfactory yields (moderate to excellent) in glacial acetic acid solvent. Previously ethanol was employed as a solvent for present reaction following the similar experimental conditions. However results obtained were poor in terms of yields and purity of the compounds in presence of ethanol. Glacial acetic acid is a cheap solvent and is being used in various reactions. Further, all metal phosphates are cheap and nontoxic.

Table 1 Data showing the % yield and melting point of the compounds obtained by using various metal phosphates

DHPM	X	R1	R2	NaH_2PO_4		KH_2PO_4		K_2HPO_4		M.P. (°C) (Reported)
				Yield (%)	M.P. (°C) (Found)	Yield (%)	M.P. (°C) (Found)	Yield (%)	M.P. (°C) (Found)	
4a	O	C_6H_5	CH_3	81	223-225	96	228-230	76	226-228	232-234^a
4b	O	4- $OCH_3C_6H_5$	CH_3	79	175-177	94	178-180	73	176-178	182-183^b
4c	S	C_6H_5	CH_3	78	226-227	90	231-233	72	232-233	-----
4d	O	C_6H_5	OC_2H_5	66	192-195	89	204-206	50	200-202	202-203^a
4e	O	4- $OCH_3C_6H_5$	OC_2H_5	90	188-190	91	201-204	85	200-205	200-202^b
4f	S	C_6H_5	OC_2H_5	84	170-172	88	202-204	77	203-205	205-207^a

^{a}: Ref. 29; ^{b}: Ref. 24; DHPM: 3,4-dihydropyrimidine-2-(1H)-one

Therefore it was thought worthwhile to optimize and compare the efficiency of metal phosphates as a protomer in multicomponent reaction in presence of glacial acetic acid solvent. All metal phosphates had demonstrated their ability to act as protomer in multi-component Biginelli 4, 5-disubstituted, 3,4-dihydropyrimidine-2(1*H*)-one / thione synthesis in glacial acetic acid. It was found that the metal phosphates employed differed in their efficiency in terms of yields and purity (M.P.) (Table 1). To check the protomer efficiency of catalyst and reproducibility of the reaction, different aldehydes and 1, 3-dicarbonyl compounds were reacted with urea and thiourea to give six different Beginelli compounds.

It can be seen that, catalyzing the reaction by NaH_2PO_4 resulted in good yields of all products. However, the lower meting points of these products (than the reported) indicated low purity of the compounds. On the other hand, the catalyst K_2HPO_4 has displayed satisfactory results. Moderate to good yields of all compounds were obtained with some exceptional compounds. Further, all compounds were obtained in pure form as evidenced by melting points closer to those reported one.

As indicated in Table 1, catalyzing the reaction by KH_2PO_4 gave superior results over the other two metal phosphates both in terms of yields and purity. All compounds were obtained in excellent yields. Melting points of all compounds were found to be much closer to reported substances indicating high purity of the compounds. In addition to that, KH_2PO_4 was found to be reusable catalyst and can be employed for second run which was recovered by filtration after first run. For second run almost similar yields of all compounds were obtained. The reusability of NaH_2PO_4 was also examined. However, NaH_2PO_4 resulted in formation of somewhat viscous mass and therefore was difficult to recover unlike KH_2PO_4. Only small fraction of NaH_2PO_4 was recovered and therefore was not used for further analysis. The catalyst K_2HPO_4 was found to be non reusable as no fractions were obtained after its first run.

It is well known that Biginelli reaction is an acid catalyzed versatile one pot multi-component reaction for the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one / thione derivatives. The reaction occurs via formation of metal-enolate ion pairs and metal-*N*-acylimine intermediates which govern the overall progress of Biginelli reaction. The stabilization of *N*-acylium intermediate by the cation of the catalyst is the exact mechanism involved in this reaction [31-33].

It was observed that all metal phosphates had efficiently catalyzed the Biginelli reaction with 1, 3- dicarbonyl compounds which could be because of stabilization of intermediate and increased reactivity of enolate tautomer of 1, 3- dicarbonyl compounds towards *N*-acylimine species [30]. Further, due to softness and high polarizability of K^+ than Na^+ [34], in coordination with enol tautomer, KH_2PO_4 produced high yields of the compounds [30]. Variation in the % yield of compounds was also examined by using different ratios of the reactants. It was found that the reactants when used in equimolar quantities (1:1:1:1 of urea / thiourea: aldehyde: 1, 3-dicarbonyl compound: catalyst) produced best results. Also in this method the reaction time had been considerably reduced (20-40 min) indicating the increased reactivity of the reactants in glacial acetic acid solvent.

CONCLUSION

In the present investigation, KH_2PO_4 in glacial acetic acid was found to be superior catalyst over NaH_2PO_4 and K_2HPO_4 in terms of purity and yields of Biginelli compounds, even though all of them have given satisfactory results. In addition to that KH_2PO_4 demonstrated its reusability in multi-component condensation reaction also. Further, all catalysts employed were nontoxic and very cheap. In conclusion, the method was found to be simple, less time consuming, cost effective and eco-friendly.

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