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Lewis Acid–Doped Natural Phosphate: New Catalysts for the One-Pot Synthesis of 3,4-Dihydropyrimdin-2(1*H*)-one

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Abstract: Inexpensive and readily available natural phosphate doped with metal halides is used to efficiently catalyze the three-component condensation reaction of an aldehyde, a beta-keto ester, and urea to afford the corresponding dihydropyrimidin-2(1*H*)-ones in high yields.

Keywords: Biginelli reaction, catalysis, condensation, pyrimidinones

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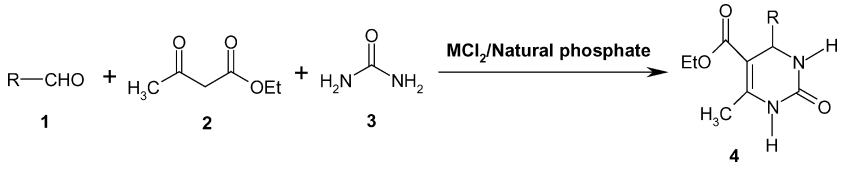
3,4-Dihydropyrimidin-2(1*H*)-ones and related compounds exhibit a wide range of pharmacological activities[1] such as antiviral, antibacterial, and anti-flammatory properties. The biologically active dihydropyrimidinones have been recently reviewed.[2] The simple and direct method for the synthesis of dihydropyrimidin-2-ones, reported first by Biginelli in 1893, involves the one-pot condensation of an aldehyde, a beta-keto ester, and urea under strongly acidic conditions.[3] Recently, several improved procedures have been reported using a variety of catalysts such as manganese acetate,[4] ytterbium/resin,[5] clay,[6] and zirconium chloride.[7] More recently, other processes in this area have been developed using zinc chloride,[8] heteropoly-acid $Ag_3PW_{12}O_{40}$,[9] cadmium chloride,[10] $SnCl_2$, $2H_2O/LiCl$,[11] potassium hydrogen sulfate,[12,13] ionic liquid/ultrasound irradiation,[14] and Cu/microwave.[15] A recent review has been also published.[16]

However, we have used the natural phosphate (NP) alone or doped as the heterogenous catalyst for several reactions such as Claisen–Schmidt condensation,[17] nitrile hydratation,[18] α-hydroxyphosphonates synthesis,[19] Knoevenagel condensation,[20] alkene epoxidation,[21] flavonones synthesis,[22] and Michael addition.[23] NP has been used also as a Lewis acid catalyst or as support in Friedel–Crafts alkylation,[24] 1,3-dipolar cycloaddition,[25] nucleoside synthesis,[26] and building blocks for polyamide nucleic acids synthesis.[27] In this work, we report a convenient and efficient one-pot synthesis of dihydropyrimidin-2-ones by condensation of tree components aldehydes, beta-keto esters, and urea (Scheme 1), catalysed for the first time by natural phosphate doped with $ZnCl_2$, $CuCl_2$, $NiCl_2$, and $CoCl_2$.

First of all, we tested the activity of NP alone in the Biginelli reaction. The yields of dihydropyrimidin-2-ones obtained after 48 h of reaction time are poor (10–20%). Thereafter, the use of NP doped with metal halides as catalysts for this reaction was investigated. Reactions were carried out under a variety of conditions that were designed to optimize the system in a general way. For an initial evaluation of activity of $ZnCl_2$/NP, we studied the influence of amount of the catalyst in the condensation of benzaldehyde, ethyl acetocetate, and urea. The yield of dihydropyrimidinone **4a** increased as the weight of catalyst increased. This result indicate that $ZnCl_2$/NP is effectively a good catalyst for this reaction (Table 1). Although the increase is not dramatic from 0.2 g of the catalyst to 1 g, we decided to continue optimization with 0.2 g of catalyst.



Scheme 1.

Table 1. Effect of the weight of $ZnCl_2$/NP in the synthesis of product **4a** (24 h)

Yield (%)	Weight of $ZnCl_2$/NP (g)
62	0.2
80	0.3
95	0.5
98	1

Furthermore, the metal halide effect was also examined. Thus, we have tested $CuCl_2$/NP, $NiCl_2$/NP, and $CoCl_2$/NP in this reaction. To evaluate the catalytic activity of these materials in comparison with $ZnCl_2$/NP and NP alone, we carried out the condensation of benzaldehyde, ethyl acetoacetate, and urea to afford the product **4a**. The kinetic curves of these reactions, as shown in Figure 1, indicate clearly the promoting effect of metal halides. For example the yields obtained after 24 h of reaction time are 13, 37, 48, 52, and 62% using NP, $NiCl_2$/NP, $CuCl_2$/NP, $CoCl_2$/NP, and $ZnCl_2$/NP, respectively. It appears that $ZnCl_2$/NP is the most active catalyst.

As a result of the optimization of the reaction conditions, we found that increased yields were observed when the reaction was conducted in 5 ml of toluene using 1 mmol of aldehyde and ethyl acetoacetate, 3 mmol of urea, and 0.2 g of catalyst. To determine the scope and limitation of the reaction, the optimum conditions were applied to other substrates as shown in Table 2. All products were isolated and analysed by ^1H and ^{13}C NMR. It

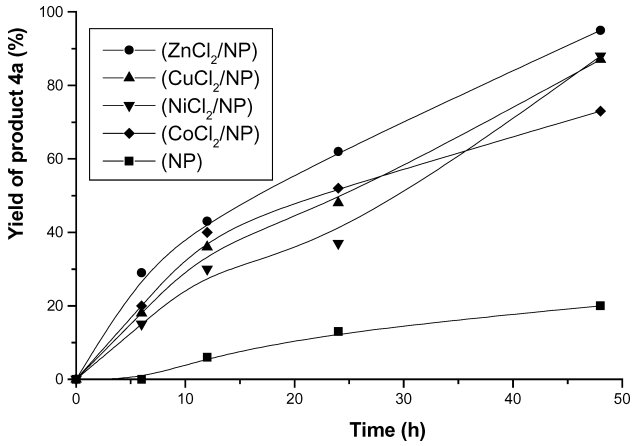


Figure 1. Kinetic curves of product **4a** synthesis using NP alone or doped with $ZnCl_2$, $CuCl_2$, $NiCl_2$, and $ZnCl_2$.

Table 2. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones catalyzed by NP and MCl_2/NP

Product	R	Catalyst Yield (%)[a] [Time (h)] NP	$ZnCl_2$/NP	$CuCl_2$/NP	$NiCl_2$/NP	$CoCl_2$/NP
4a	Ph-	20 (48)	95 (48)	87 (48)	88 (48)	73 (48)
4b	4-Cl-C_6H_4-	15 (48)	84 (48)	78 (48)	76 (48)	80 (48)
4c	4-MeO-C_6H_4-	13 (48)	90 (48)	80 (48)	83 (48)	78 (48)
4d	3-MeO-C_6H_4-	10 (48)	94 (48)	76 (48)	81 (48)	79 (48)
4e	3-O_2N-C_6H_4-	10 (48)	90 (48)	70 (48)	74 (48)	87 (48)
4f		11 (48) 29 (72)	79 (48) 89 (72)	53 (48) 79 (72)	50 (48) 76 (72)	64 (48) 80 (72)

[a]Yields of isolated products.

can be seen that for all substrates the yields obtained are good. The only example where yield is low is for the synthesis of product **4f**. In this case, the electronic effect of the furanyl group probably made the reaction less favorable. However, the yields obtained using different doped materials are in the range of 50–79% after 48 h, which can be increased to 76–89% with longer reaction times (72 h). More interestingly, for the other products aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents all reacted very well, giving good yields. However, it can be seen that for all cases (Table 2) $ZnCl_2$/NP is the most active catalyst for the Biginelli reaction.

In summary, we have reported an efficient and convenient route to the heterogeneous one-pot synthesis of 3,4-dihydropyrimidin-2-ones using metal halide–doped natural phosphate. The yields of products obtained are very good for a range of substrates and demonstrate that these doped materials are both highly active and versatile.

EXPERIMENTAL

Preparation of the Catalysts

Natural phosphate comes from an extracted ore in the region of Khouribga (Morocco). A portion of 100–400-μm grain size was isolated, washed with water, calcined at 900°C for 2 h, washed again, calcined at 900°C for 0.5 h, and ground (63–125 μm) to give the NP catalyst. The structure of calcined phosphate NP is similar to that of fluorapatite $Ca_{10}(PO_4)_6F_2$, as shown by the X-ray diffraction pattern and IR spectroscopy. The chemical composition was determined to be Ca (54.12%), P (34.24%), F (3.37%), Si (2.42%), S (2.21%),

C (1.13%), Na (0.92%), Mg (0.68%), Al (0.46%), Fe (0.36%), K (0.04%), and other metals less than 6 ppm. The specific surface area of NP was determined by the BET method from the adsorption–desorption isotherm of nitrogen at its liquid temperature (77 K). The total pore volume was calculated by the BJH method at $P/P_0 = 0.98$. The NP shows a very low surface area ($1-2\,m^2\,g^{-1}$) together with a low total pore volume ($V_T = 0.007\,cm^3/g^{-1}$). The preparation of MCl_2/NP [M = Zn, Ni, Cu or Co] was as follows: 10 mmol of MCl_2 and 10 g of NP were mixed in 100 ml of water and then evaporated to dryness under vacuum and dried for 2 h at 150°C before use.

Typical Procedure for 3,4-Dihydropyrimidin-2(1*H*)-ones Synthesis

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (3 mmol), and catalyst (0.2 g) was stirred in refluxing toluene (5 mL). After the appropriate time, the solid catalyst was removed by filtration and washed with methanol. The solution was evaporated under vacuum and the crude product was purified by recrystallization in ethanol and identified by ^{1}H and ^{13}C NMR.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, 4a: Mp 209–210°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.12 (t, $J = 7.2$ Hz, 3H), 2.29 (s, 3H), 4.02 (q, $J = 7.2$ Hz, 2H), 5.19 (d, $J = 2.7$ Hz), 7.27–7.42 (m, 5H), 7.76 (s, 1H), 9.21 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.1, 17.9, 54.2, 59.3, 99.5, 126.4, 127.4, 128.5, 145.0, 148.5, 152.3, 165.5. HR-FAB-MS: calc. for $C_{14}H_{17}O_3N_2$ (261.30): 261.1239 ($[M+H]^+$, 100%); found: 261.1233.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4b: Mp 213–214°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.09 (t, $J = 6.7$ Hz, 3H), 2.24 (s, 3H), 3.97 (q, $J = 6.7$ Hz, 2H), 5.14 (d, $J = 3.1$ Hz), 7.23 (d, $J = 7.3$ Hz), 7.38 (d, $J = 7.3$ Hz), 7.76 (s, 1H), 9.23 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.9, 18.7, 54.3, 60.1, 99.7, 129.0, 129.2, 132.7, 144.6, 149.6, 152.8, 166.2. HR-FAB-MS: calc. for $C_{14}H_{16}O_3N_2Cl$ (295.75): 295.0849 ($[M+H]^+$, 100%); found: 295.0840.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4c: Mp 202–203°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.09 (t, $J = 7$ Hz, 3H), 2.23 (s, 3H), 3.70 (s, 3H), 3.97 (q, $J = 7$ Hz, 2H), 5.09 (d, $J = 3.1$ Hz), 6.87 (d, $J = 8.6$ Hz), 7.15 (d, $J = 8.6$ Hz), 7.65 (s, 1H), 9.13 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 15.0, 18.6, 54.3, 55.9, 60.1, 100.5, 114.6, 128.3, 138.0, 148.9, 153.1, 159.4, 166.3. HR-FAB-MS: calc. for $C_{15}H_{19}O_4N_2$ (291.33): 291.1345 ($[M+H]^+$, 29.8%); found: 291.1351.

5-Ethoxycarbonyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4d: Mp 223–224°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.09

(t, $J = 6.9$ Hz, 3H), 2.23 (s, 3H), 3.70 (s, 3H), 3.98 (q, $J = 6.9$ Hz, 2H), 5.12 (d, $J = 3.1$ Hz), 6.78–7.24 (m, 4H), 7.67 (s, 1H), 9.13 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 15.0, 18.7, 54.7, 55.9, 60.1, 100.2, 113,1, 113.3, 119.2, 130.4, 147.3, 149.3, 153.2, 160.2, 166.3. HR-FAB-MS: calc. for $C_{15}H_{19}O_4N_2$ (291.33): 291.1345 ($[M + H]^+$, 100%); found: 291.1342.

5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4e: Mp 223–224°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.08 (t, $J = 7$ Hz, 3H), 2.28 (s, 3H), 4.02 (q, $J = 7$ Hz, 2H), 5.32 (d, $J = 2.8$ Hz), 7.63–8.15 (m, 4H), 7.89 (s, 1H), 9.36 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.0, 17.9, 53.6, 59.4, 98.4, 121.1, 122.4, 130.2, 133.0, 147.0, 147.8, 149.4, 151.8, 165.1. HR-FAB-MS: calc. for $C_{14}H_{16}O_5N_3$ (306.30): 306.1090 ($[M + H]^+$, 45.3%); found: 306.1082.

5-Ethoxycarbonyl-4-(2-furfuryl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4f: Mp 209–210°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.12 (t, $J = 6.9$ Hz, 3H), 2.22 (s, 3H), 3.99 (q, $J = 6.9$ Hz, 2H), 5.20 (d, $J = 2.7$ Hz), 6.08 (s, 1H), 6.33 (s, 1H), 7.52 (s, 1H), 7.71 (s, NH), 9.20 (s, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.1, 17.7, 47.8, 59.2, 96.8, 105.3, 110.3, 142.1, 149.3, 152.4, 155.9, 165.0. HR-FAB-MS: calc. for $C_{12}H_{15}O_4N_2$ (251.26): 251.1032 ($[M + H]^+$, 100%); found: 251.1025.

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