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An efficient one-pot synthesis of dihydropyrimidinones catalyzed by zirconium hydrogen phosphate under solvent-free conditions

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A simple, efficient, and practical procedure for the Biginelli reaction using zirconium hydrogen phosphate [$Zr(H_2PO_4)_2$] as a novel solid acid catalyst is described under solvent-free conditions in high yields. The catalyst exhibited remarkable reactivity and it is reusable.

Key Words: Biginelli reaction; solvent-free; zirconium hydrogen phosphate; dihydropyrimidinones, recyclable catalyst

Introduction

Several dihydropyrimidinones and their derivatives are pharmacologically potent calcium channel blockers, antihypertensive agents, α-adrenergic antagonists, and neuropeptide Y(NPY) antagonists.[1] These compounds also exhibit a broad range of biological activities[2] such as antiviral, antitumor, antibacterial, anti-inflammatory, antioxidant, and FATP4 inhibitor properties. Furthermore, the 2-oxodihydropyrimidine-5-carboxylate core unit is found in many marine natural products including batzelladine alkaloids, which have been found to be HIV-gp-120 CD_4 inhibitors.[3] Therefore, the preparation of this heterocyclic core unit has attracted the attention of many organic chemists. The simple and direct method originally reported by Biginelli[4] involves

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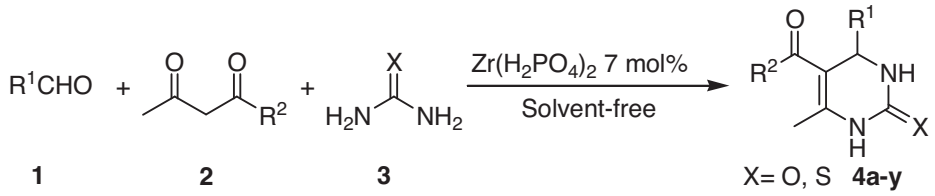
the one-pot condensation of β-ketoester with an aldehyde and urea under strongly acidic conditions, but the reaction suffered from drawbacks such as low yields, long reaction time, and strong corrosion equipment. For this transformation, several methods were improved, such as using $ZrCl_4$,[5] $InBr_3$,[6] $Mn(OAc)_3.2H_2O$,[7] $ZnCl_2$,[8] TMSCl,[9] $FeCl_3$/Si-MCM-41,[10] and ionic liquid.[11] However, some of these one-pot procedures generally require strong protic or Lewis acids, prolonged reaction times, and high temperature. Consequently, there is scope for further modification towards mild reaction conditions, increased variation of the substituents, and improved yields.

Solvent-free conditions are especially important for providing an eco-friendly system. Currently, much emphasis has been given to the use of inorganic reagents in organic reactions, as these reactions often provide the milder conditions and easier work up than similar reactions using organic reagents.[12]

In the recent past, metal phosphates have attracted considerable attention as solid acid catalysts.[13] The activity of these materials is attributed to the Brønsted acidity of hydroxyl groups and the Lewis acidity of the metal center. In particular, zirconium phosphates have been used in catalytic reactions such as esterification, dehydration of alcohols, isomerization of olefins, and Aza-Diels-Alder reactions.[14] Zirconium hydrogen phosphate [$Zr(H_2PO_4)_2$] is a new water-tolerant solid acid catalyst that possesses high activity, is stable in the presence of excess water, is recoverable by simple filtration, and is reusable without any treatments such as calcination.[15]

In continuation of our studies on the development of novel synthetic methodologies in a heterogeneous system,[16] we report herein the synthesis of a variety of 3,4-dihydropyrimidin-2(1H)-ones using zirconium hydrogen phosphate as a water-tolerant solid acid catalyst in the condensation reaction of β-ketoester with urea (or thiourea) and various aromatic aldehydes without any solvent (Scheme).



Scheme

Experimental

Melting points were recorded using an Electrothermal IA 9100 melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ on a Varian Mercury Plus 300 MHz and mass spectra were taken by Micromass Quattro LC-MS-MS instruments. Benzaldehyde was purified by distillation. The other chemicals were of commercial grade and used without further purification.

General Procedure for the Synthesis of DHPMs: Catalyst was prepared according to the literature.[15] A mixture of benzaldehyde (3 mmol, 0.32 g), ethyl acetoacetate (3 mmol, 0.39 g), urea (4.5 mmol, 0.27 g), and the catalyst (7% mmol) was finely mixed together in a test tube at 90 °C for 1 h. After cooling, the reaction mixture was poured onto crushed ice (50 g) and stirred for 10 min. The precipitate was filtered under suction

and washed with cold water (20 mL) to remove excess urea. After that the solid was dissolved in ethanol and filtered to remove the catalyst and purified further by recrystallization (hot ethanol).

5-Ethoxycarbonyl-4-(2,4-dimethoxyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1H)-one (4g)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.11 (3H, t, J=7.03 Hz, CH_3CH_2O), 2.39 (3H, s, CH_3), 3.77 (3H, s, CH_3O), 3.83 (3H, s, CH_3O), 4.05 (2H, q, J=7.03 Hz, CH_3CH_2O), 5.64 (1H, d, J=2.93 Hz, CH), 5.77 (1H, s, NH), 6.37 (1H, dd, J=8.2 Hz, J=2.34 Hz, Ar-H), 6.44 (1H, d, J=2.34 Hz, Ar-H), 6.94 (1H, d, J=8.2 Hz, Ar-H), 8.45 (1H, s, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.43, 18,73, 49.78, 55.57, 55.59, 60.08, 98.75, 98.96, 103.91, 122.77, 127.48, 148.36, 154.15, 158.01, 160.75, 166.17. MS, m/z: $[M+1]^+$ 321.17.

5-Ethoxycarbonyl-4-(2,3-dimethoxyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1H)-one (4h)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.11 (3H, t, J=7.03 Hz, CH_3CH_2O), 2.39 (3H, s, CH_3), 3.86 (3H, s, CH_3O), 3.90 (3H, s, CH_3O), 4.04 (2H, q, J=7.03 Hz, CH_3CH_2O), 5.65 (1H, s, NH), 5.70 (1H, d, J=2.63 Hz, CH), 6.71 (1H, dd, J=7.91, J=1.46 Hz, Ar-H), 6.84-6.98 (2H, m, Ar-H), 8.56 (1H, s, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.42, 18,77, 50.38, 56.06, 60.09, 60.94, 98.73, 112.55, 118.96, 124.40, 136.07, 146.52, 148.54, 152.96, 153.61, 166.02. MS, m/z: $[M+1]^+$ 321.10.

5-Ethoxycarbonyl-4-(3,4-dihydroxyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1H)-one (4j)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.11 (3H, t, J=7.03, CH_3CH_2O), 2.22 (3H, s, CH_3), 3.98 (2H, q, J=7.03, CH_3CH_2O), 4.98 (1H, d, J=3.23, CH), 6.47-6.65 (3H, Ar-H), 7.60 (1H, s, NH), 8.78 (1H, s, -OH), 8.88 (1H, s, -OH), 9.10 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.81, 18,43, 54.18, 59.80, 100.51, 114.38, 115.84, 117.83, 136.68, 145.17, 145.63, 148.18, 152.90, 166.15. MS, m/z: $[M+1]^+$ 293.01.

5-Ethoxycarbonyl-4-(2,4,6-trimethoxyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1H)-one (4m)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.99 (3H, t, J=7.03 Hz, CH_3CH_2O), 2.14 (3H, s, CH_3), 3.70 (6H, s, 2 × CH_3O), 3.74 (3H, s, CH_3O), 3.82 (2H, q, J=7.03 Hz, CH_3CH_2O), 5.74 (1H, d, J=1.17, CH), 6.16 (2H, s, Ar-H), 6.91 (1H, s, NH), 8.95 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.63, 18,46, 45.58, 55.78, 56.19, 59.11, 91.38, 96.74, 114.22, 148.58, 152.80, 159.62, 160.62, 166.52. MS, m/z: $[M+1]^+$ 351.13.

5-Ethoxycarbonyl-4-(2,4,5-dimethoxyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1H)-one (4n)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.05 (3H, t, J=7.03 Hz, CH_3CH_2O), 2.25 (3H, s, CH_3), 3.35 (3H, s, CH_3O), 3.62 (3H, s, CH_3O), 3.76 (3H, s, CH_3O), 3.92 (2H, q, J=7.03 Hz, CH_3CH_2O), 5.38 (1H, d, J=3.07, CH), 6.62 (1H, s, Ar-H), 6.67 (1H, s, Ar-H), 7.22 (1H, s, NH), 9.90 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.78, 18,36, 50.03, 56.48, 56.93, 57.27, 59.61, 98.45, 99.24, 113.61, 124.20, 142.76, 149.04, 149.85, 151.99, 152.79, 166.07. MS, m/z: $[M+1]^+$ 351.12.

5-Ethoxycarbonyl-4-(2,4-dimethoxyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1H)-thione (4u)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.02 (3H, t, J=7.03 Hz, CH_3CH_2O), 2.24 (3H, s, CH_3), 3.69 (3H, s, CH_3O), 3.73 (3H, s, CH_3O), 3.88 (2H, q, CH_3CH_2O), 5.37 (1H, d, J=3.52, CH), 6.42 (1H, dd, J=8.20, J=2.05, Ar-H), 6.50 (1H, J=2.05, Ar-H), 6.89 (1H, d, J=8.20, Ar-H), 9.18 (1H, s, NH), 10.17 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.66, 17.69, 49.67, 55.86, 56.16, 60.01, 99.11, 100.25, 105.20, 123.91, 129.18, 145.61, 158.34, 160.89, 165.90, 174.64. MS, m/z: $[M+1]^+$ 337.14.

Results and discussion

Zirconium hydrogen phosphate [$Zr(H_2PO_4)_2$] is a new water-tolerant solid acid catalyst. The activity of this material is attributed to the Brønsted acidity of dihydrogenphosphate groups and the Lewis acidity of zirconium metal.

A number of aromatic and aliphatic aldehydes were used with ethyl acetoacetate and urea or thiourea to illustrate the generality of the condensation. These results are summarized in the Table.

Table. Zirconium hydrogen phosphate-catalyzed synthesis of dihydropyrimidinones under solvent-free conditions.

Entry	R^1	R^2	X	Time (h)	Yield[a] (%)	Mp(°C) found	Mp(°C) reported
4a	C_6H_5-	EtO-	O	1	88	207-208	206[17]
4b	4-(Me)-C_6H_4-	EtO-	O	1	81	216-217	215-216[18]
4c	4-(Cl)-C_6H_4-	EtO-	O	1	92	214-215	213-215[17]
4d	4-(NO_2)-C_6H_4-	EtO-	O	1	77	210-211	209-212[17]
4e	3-(OH)-C_6H_4-	EtO-	O	1	58	184-186	167-170[17]
4f	4-(OH)-C_6H_4-	EtO-	O	1	86	236-237	236-238[19]
4g	2,4-(MeO)-C_6H_3-	EtO-	O	1	91	210-211	-
4h	2,3-(MeO)-C_6H_3-	EtO-	O	1	85	185-186	-
4i	2,5-(MeO)-C_6H_3-	EtO-	O	1	94	214-216	212[10]
4j	3,4-(OH)-C_6H_3-	EtO-	O	1	89	243-244	-
4k	4-NMe_2-C_6H_4-	EtO-	O	1	82	256-257	257-258[21]
4l	3-(MeO)-4-(OH)-C_6H_3-	EtO-	O	1	89	238-239	232-233[22]
4m	2,4,6-(MeO)-C_6H_2-	EtO-	O	1	76	255-256	-
4n	2,4,5-(MeO)-C_6H_2-	EtO-	O	1	80	208-209	-
4o	C_6H_5-	Me-	O	1	95	236-237	234-235[23]
4p	4-(Me)-C_6H_4-	Me-	O	1	92	230-231	228-229[23]
4q	4-(Cl)-C_6H_4-	Me-	O	1	97	228-230	215-216[23]
4r	C_6H_5-	Me-	S	1,5	73	233-235	183(dec.)[17]
4s	C_6H_5-	EtO-	S	2	82	208-209	208-210[18]
4t	4-(Me)-C_6H_4-	EtO-	S	2	79	192-193	192-194[18]
4u	2,4-(MeO,)-C_6H_4-	EtO-	S	2	93	163-164	-
4v	CH_2CH_2-	EtO-	O	1	43	210-211	212-214[24]
4y	$(CH_3)_2CH$-	-OEt	O	1	67	191-193	194[25]

[a]Isolated yield.

The procedure gives products in good yields and avoids problems associated solvent use (cost, handling, safety, pollution). Decreased reaction times are also realized because of increased reactivity of the reactants in the solid state and the fact that water as a reaction product is evaporated at the reaction temperature at 90 °C. Importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents all reacted very well, giving moderate-to-excellent yields of the desired products using the catalyst. The activity

of the recycled $Zr(H_2PO_4)_2$ was also examined according to the typical experimental conditions. We obtained the desired products in 88%, 87%, and 85% yields after 1-3 runs, respectively (entry **4a**).

In conclusion, we have described a simple and general method for the synthesis of dihydro- pyrimidinones by using a reusable $Zr(H_2PO_4)_2$ solid acid catalyst. The method offer several advantages including high yields, environmentally friendly procedure, short reaction times, simple work-up procedure, and easy isolation, making it a useful process for the synthesis of DHPMs. Moreover, the catalysis is not affected by water released from the reaction.

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