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Yttria-Zirconia–Based Lewis Acid Catalysis of the Biginelli Reaction: An Efficient One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones

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Abstract: Yttria-zirconia–based Lewis acid efficiently catalyzes the three-component cyclocondensation reaction of aldehyde, β-keto ester, and urea or thiourea in refluxing acetonitrile to produce the corresponding dihydropyrimidones in high yields.

Keywords: Biginelli reaction, dihydropyrimidone, yttria-zirconia–based Lewis acid

One-pot coupling of three or more compounds, often called multicomponent reaction, has attracted a great deal of attention in recent years for the synthesis of complex organic molecules.[1] The Biginelli reaction is constituted by a one-pot, acid-catalyzed cyclocondensation of an aldehyde, a β-keto ester, and urea, leading to 3,4-dihydropyrimidin-2-(1*H*)-one (DHPM) (Scheme 1). DHPM derivatives have attracted considerable interest in recent times because of their promising therapeutic[2a] and biological activities[2b] such as antiviral, antitumor, antibacterial, and anti-inflammatory activities. In addition, 4-aryldihydropyrimidones have emerged as potent calcium channel blockers, antihypertensive agents, α_{1a}-adrenergic antagonists, and neuropeptide antagonists.[3] Furthermore, the dihydropyrimidinone-5-carboxylate core unit is found in many marine natural products including batzelladine alkaloids, which are potent HIV gp-120-CD_4 inhibitors.[4]

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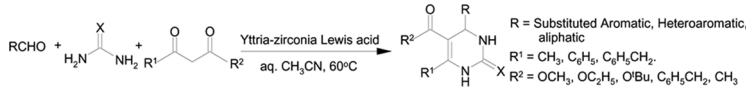


Scheme 1. Synthesis of dihydropyrimidones (DHPM) by Biginelli cyclocondensation reaction using yttria-zirconia–based Lewis acid.

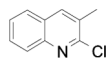
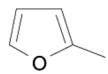
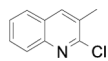
The most simple and straightforward procedure, reported by Biginelli in 1893, involves a one-pot condensation of ethylacetoacetate, benzaldehyde, and urea under strong acidic conditions.[5] However, low yields in the case of substituted aromatic and aliphatic aldehydes[3a,5] led to the development of multistep strategies that produce somewhat higher overall yields but lack the simplicity of the one-pot, one-step synthesis.[3a,6] Several methods for the Biginelli DHPM synthesis have been documented in the literature. These involve the use of protic acids and Lewis acid catalysts such as AcOH and $BF_3 \cdot OEt_2$.[7a] HCl and $FeCl_3$[7b] and $LaCl_3 \cdot 7H_2O$,[7c] YbOTf,[7d] polyphosphate-ester,[7e] $InCl_3$,[7f] $InBr_3$,[7g] $LiClO_4$,[7h] $FeCl_3 \cdot 6H_2O$,[7i] zirconium(IV) chloride,[7j] $Mn(OAc)_3 \cdot 2H_2O$.[7k] In addition to the zeolites,[8a] ionic liquids,[8b] microwave irradiation,[8c,8d] ultrasound,[8e] and KSF clay[8f] have also been employed for Biginelli's condensation reaction.

Recently, NH_4Cl,[9a] *N*-butyl-*N*,*N*-dimethyl-α-phenylethylammoniumbromide,[9b] boric acid,[9c] triflates of Bi[9d(i)] and Cu,[9d(ii)] chlorides of Cd[9e(i)] and Zn[9e(ii)] combination of TMSCl/NaI,[9f] $Ag_3PW_{12}O_{10}$ (as water-tolerant catalyst),[9g] and polyaniline-bismoclite[9h] have been reported to catalyze the Biginelli reaction to give DHPMs.

However, in spite of their potential utility, many of these methods involve expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions, longer reaction times, high temperatures, unsatisfactory yields, and incompatibility with other functional groups. Therefore, the development of new methods would extend the scope of the useful Biginelli reaction. Yittria-zirconia-based Lewis acid catalyst was widely used as solid acid catalyst for varied organic transformations, for example, for the Diel–Alder reaction,[10a] acylation of alcohols, thiols, and amines[10b] in our group. Herein, we report an efficient synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones catalyzed by yttria-zirconia-based Lewis acid catalyst.

In a general experimental procedure, when β-keto ester (1 equiv.), aldehyde (1 equiv.), and urea (1.3 equiv.) were refluxed together in the presence of 10 mol% of yttria-zirconia catalyst in 10% aq. acetonitrile at 60 °C, the mixture underwent cyclocondensation to afford the corresponding dihydropyrimidones in good to excellent yields. A wide range of structurally varied β-dicarbonyl compound, aldehyde, and urea were condensed by this procedure to produce the corresponding dihydropyrimidones. The results are reported in Table 1. Both β-keto ester and

Table 1. Synthesis of dihydropyrimidones (DHPM)[a] by Biginelli cyclocondensation reaction using yttria-zirconia–based Lewis acid

Entry	R^1	R^2	R	X	Time (h)	Yield[b] (%)
1	Me	OEt	C_6H_5	O	7	94
2	Me	OEt	4-(CH_3)-C_6H_4	O	6	95
3	Me	OEt	4-(OMe)-C_6H_4	O	6	92
4	Me	OEt	3-(OMe)-C_6H_4	O	4	91
5	Me	OEt	2,4-$(OMe)_2$-C_6H_3	O	6	81
6	Me	OEt	3,4-$(OMe)_2$-C_6H_3	O	10	80
7	Me	OEt	3,4,5-$(OMe)_2$-C_6H_2	O	5	92
8	Me	OEt	2-(OMe)-6-(Me)-C_6H_3	O	7	80
9	Me	OEt	4-(OH)-3-(OMe)-C_6H_3	O	5	86
10	Me	OEt	2-(OH)-C_6H_4	O	5	93
11	Me	OEt	2,6-$(OH)_2$-3-(CO_2Me)-4-(Me)-C_6H	O	15	70
12	Me	OEt	4-(CI)-C_6H_4	O	6	90
13	Me	OEt	2-(CI)-C_6H_4	O	9	72
14	Me	OEt	C_6H_4-CH=CH (E)	O	7	80
15	Me	OEt	4-$[N(Me)_2]$-C_6H_4	O	8	95
16	Me	OEt		O	16	67
17	Me	OMe	4-(Me)-C_6H	O	5	80
18	Me	O'Bu	C_6H_5	O	7	94
19	Me	$C_6H_5CH_2$	C_6H_5	O	8	56
20	Me	OEt	4-(OH)-C_6H_5	O	5	88
21	Me	OMe		O	7	86
22	Me	O'Bu	4-(OH)-3-(OMe)-C_6H_3	O	7	80
23	$C_6H_5CH_2$	OMe	C_6H_5	O	16	82
24	Me	OEt	C_6H_5	S	4	96
25	$C_6H_5CH_2$	OMe		S	16	69
26	C_6H_5	OEt	C_6H_5	S	12	62
27	C_6H_5	OEt	3,4-$(OMe)_2C_6H_4$	S	9	72
28	Me	Me	4-(NO_2)-C_6H_4	S	15	75
29	Me	Me	4-(OMe)-C_6H_4	O	6	92
30	Me	Me	3,4-$(OMe)_2$-C_6H_3	O	8	67
31	Me	Me	3,4,5-$(OMe)_3$-C_6H_2	O	10	84
32	Me	Me	4-(OH)-3-(OMe)-C_6H_3	O	5	71
33	Me	Me	2-(Cl)-C_6H_4	O	9	71

(*Continued*)

Table 1. Continued

Entry	R^1	R^2	R	X	Time (h)	Yield[b] (%)
34	Me	Me	2,6-$(OH)_2$-3-(CO_2Me)-4-(Me)-C_6H	O	10	56
35	Me	Me	C_6H_5-CH=CH (*E*)	O	6	88
36	Me	OEt	$C_6H_5CH_2$	O	10	86
37	Me	OEt	C_2H_5	O	14	75
38	Me	Me	$(CH_3)_2CH$	O	17	73

[a]Products were characterized by spectral data and also by comparison with authentic samples.
[b]Isolated yield.

β-diketone participated in this reaction readily. A wide variation in alkyl groups of β-dicarbonyl compounds was tolerated in this procedure. A variety of substituted aromatic, aliphatic and heterocyclic aldehydes were subjected to the condensation reaction efficiently. Aromatic aldehydes carrying either electron-withdrawing or donating groups afforded high yields of products. Acid-sensitive aldehydes such as furfural, phenylacetaldehyde, and cinnamaldehyde worked well without the formation of any side product, which are normally observed in the presence of either protic or Lewis acids. In addition to its simplicity and milder reaction conditions, the method was found to be effective even with aliphatic and α,β-unsaturated aldehydes, which normally give poor yields in the presence of either protic or Lewis acids because of their decomposition or polymerization under acidic conditions. Another important feature of this procedure is the survival of a variety of functional groups such as olefins, ethers, esters, nitro, and halides under the reaction conditions. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2-(1*H*)-thiones, which are also of great interest with regard to biological activity.[2] Thus, variations in all three components have been accommodated very comfortably.

In summary, the present procedure demonstrates an efficient yttria-zirconia-based Lewis acid catalysis of the cyclocondensation of 1,3-dicarbonyl compound, aldehyde, and urea or thiourea and is a much improved modification of Biginelli reaction. In addition to its simplicity and milder reaction conditions, this method has the ability to tolerate a wide variety of substitutions in all three components, which is lacking in many of the existing procedures. Thus, this procedure offers easy access to the substituted dihydropyrimidin-2-(1*H*)-ones and thiones with varied substitution patterns in very high yields. Additionally, the other advantages of this method are simple operation, easy workup,

and recyclability of the catalyst. We believe our procedure will find important applications in the synthesis of dihydropyrimidones to cater the needs of academia as well as pharmaceutical industries.

EXPERIMENTAL

Materials and Equipment

All reactions were run under an air atmosphere. Chromatographic separations were done using EM SiO_2-60 (300–400 mesh) as the stationary phase. The IR spectra were recorded on a Perkin-Elmer spectrophotometer 683B or 1605FT-IR and adsorptions are expressed in centimeters^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on Brucker AC-200 instruments using tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained with a Finningen MAT mass spectrometer. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer. The diffractogram of x-ray powder diffraction pattern was recorded on a Rigaku diffractometer model D/Max. IIIVC with N-filtered Cu-Kα radiation. Fourier transform infrared (FTIR) spectrum of pyridine adsorbed on the yttrium-based catalyst was recorded on a Nicolet 60 SXB FTIR spectrometer. The temperature programmed description (TPD) profile (ammonia) of the yttrium-based catalyst was recorded on a Sorbstar apparatus. Determination of specific surface area was carried out by BET (Brunner–Emmett–Teller) N_2 adsorbtion using a Omnisorp 100CX apparatus. Solvents were purified and dried by standard procedures before use according to reported procedure.[11] Petroleum ether refers to the fraction collected in boiling range 60–80 °C.

The catalyst was prepared and characterized following the literature procedure.[10a] The catalyst was calcined at 573 K before use.

Synthesis of Catalyst

The catalyst was prepared by mixing aqueous solutions of yttrium nitrate and zirconyl nitrate in the molar ratio 16:84, to which aqueous ammonia (28%) was added under vigorous stirring until a pH of 8.5 was achieved and precipitate was formed. Washing with deionized water, drying at 110 °C for 24 h, treating with sulfuric acid (4M), drying at 120 °C, and subsequent programmed calcinations at 500 °C for 3 h at a heating rate of 2 °C min^{-1} resulted in a highly acidic material. The chemical composition of the final catalyst [determined by X-ray fluorescence (XRF) technique] was found to be 82.6 mol% Zr, 15.6 mol% Y, and 1.8 mol% S.

The physicochemical characterization of the catalyst was carried out by titration, TPD, scanning electron microscopy (SEM), and N_2 adsorption techniques.

General Procedure

Benzaldehyde (1 equiv), ethyl acetoacetate (1 equiv), and urea (1.3 equiv) in aqueous CH_3CN were refluxed together at 60–65 °C in the presence of yttria-zirconia (10 mol%) for 7 h (Table 1). After completion of the reaction as indicated by thin-layer chromatography (TLC), the reaction mixture was filtered under hot condition for catalyst recovery and washed with aq. acetonitrile. The filtrate, after cooling to room temperature, was poured into crushed ice, and the resulting solid was filtered to give the crude product, which was recrystallized from hot methanol to afford the pure product in 94% yield.

Spectral Data for Selected Products

Ethyl-6-methyl-2-oxo-4-(2-methyl-6-methoxy)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Entry 8, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3432, 3257, 1650, 1574, 1439. ^1H NMR (200 MHz, $CDCl_3$): 1.13 (t, 3H, $J = 4$ Hz), 2.33 (s, 3H), 2.53 (s, 3H), 3.82 (s, 3H), 3.97–4.06 (q, 2H, $J = 6$ Hz), 5.83 (s, 1H), 6.75–6.85 (m, 3H), 7.15 (t, 1H, $J = 2$ Hz), 7.86 (s, 1H), 8.80 (s, 1H). ^{13}C NMR (200 MHz, DMSO-d^6): 12.79, 17.03, 18.28, 48.22, 54.29, 57.74, 95.92, 108.47, 121.68, 126.62, 129.19, 136.27, 146.37, 150.06, 157.75, 164.93. Mass ($C_{16}H_{20}N_2O_4$, 304.21): 304, 289, 275, 257, 243, 231, 215, 201, 183, 155.

Ethyl-6-methyl-2-oxo-4-(4-methyl-3-carbomethoxy-2,6-dihydroxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Entry 11, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3483, 3400, 3262, 3018, 1713, 1644, 1582, 1437, 1364. ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, 3H, $J = 6$ Hz), 1.90 (s, 3H), 2.48 (s, 3H), 3.04 (s, 1H), 3.95 (s, 3H), 4.27 (q, 2H, $J = 6$ Hz), 4.99 (s, 1H), 5.52 (s, 1H), 5.60 (s, 1H), 6.24 (s, 1H), 2.22 (s, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.5, 29.6, 57.1, 57.9, 60.1, 99.7, 103.4, 113.2, 113.7, 116.1, 116.5, 117.0, 118.5, 145.0, 149.0, 151.4, 152.7, 167.8, 169.9, 170.3. Mass: 365 ($M^+ + 1$), 346, 335, 332, 318, 304, 291, 285, 274, 259, 235, 203, 183, 175, 150, 137, 105, 77. Anal. calcd. for $C_{17}H_{20}N_2O_7$ (364.35): found: C, 55.89; H, 5.34; N, 7.85. Required: 56.04; H, 5.53; N, 7.69.

Ethyl-4-(2-chloroquinolin-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Entry 16, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3555, 3385, 3206, 3080, 1699, 1643, 1462, 1377. ^1H NMR (200 MHz, $CDCl_3$): δ 1.07 (t, 3H, $J = 4$ Hz), 1.85 (b, 1H), 2.55 (s, 3H), 4.07 (q, 2H, $J = 8$ Hz), 5.99 (s, 1H), 7.46 (t, 1H), 7.75 (t, 1H, $J = 4$ Hz), 7.79 (d, 1H, $J = 4$ Hz), 7.95 (s, 1H), 8.01 (d, 1H, $J = 4$ Hz), 8.46 (s, 1H). Mass: 345 (M^+), 330, 316, 310, 300, 280, 272. Anal. calcd for $C_{17}H_{16}ClN_3O_3$ (345.78): found: C, 58.79; H, 4.56; N, 12.31. Required: C, 59.05; H, 4.68; N, 12.15.

Methyl-6-methyl-2-oxo-4-furfuryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Entry 21, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3415, 3413, 2513, 1697, 1644, 1426, 1218. ^1H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 3.62 (s, 3H), 5.27 (s, 1H), 6.05 (s, 1H), 6.25 (s, 1H), 7.34 (s, 1H), 7.55 (s, 1H), 9.15 (s, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.5, 29.1, 49.2, 95.9, 103.7, 108.7, 140.1, 147.9, 151.4, 154.5, 164.2. Mass: 236 (M^+), 219, 208, 193, 182, 177. Anal. calcd. for $C_{11}H_{12}N_2O_4$ (236.226): found: C, 55.79; H, 5.09; N, 8.52. Required: C, 55.88; H, 5.12; N, 8.47.

Methyl-6-benzyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Entry 23, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3523, 3424, 3238, 3088, 3018, 1700, 1643, 1432, 1229, 1217. ^1H NMR (200 MHz, $CDCl_3$): δ 3.61 (s, 3H), 4.00 (q, 2H, $J = 12$ Hz), 5.37 (s, 1H), 6.30 (s, 1H), 7.24 (s, 10 Hz), 7.89 (s, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 30.7, 36.5, 51.1, 55.4, 101.8, 126.4, 126.9, 127.8, 128.7, 136.2, 143.6, 148.1, 153.5, 165.8. Mass: 304 (M^+ H_2O), 276 (304 CO), 231 (322 $PhCH_2$), 216 (231 CH_3), 200, 199, 187, 173. Anal. calcd. for $C_{19}H_{18}N_2O_3$ (322.36): found: C, 69.51; H, 5.99; N, 9.21. Required: C, 69.66; H, 5.84; N, 9.06.

Ethyl-2-thiooxo-6-phenyl-4(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Entry 27, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3346, 3176, 3053, 2935, 2915, 1901, 1682, 1457. ^1H NMR (200 MHz, $CDCl_3$): δ 0.83 (t, 3H, $J = 6$ Hz), 3.81–3.98 (m, 8H), 5.50 (d, 1H, $J = 4$ Hz), 6.84–7.00 (m, 3H), 7.35–7.44 (m, 5H), 7.71 (s, 1H), 7.88 (s, 1H). Mass: 398 (M^+), 369, 352, 325, 309, 293, 283, 261, 250, 220,

208, 165, 151, 129, 105, 91, 77, 65. Anal. calcd. for $C_{21}H_{22}N_2O_4S$ (398.48): found: C, 63.43; H, 5.402; N, 6.915. Required: C, 63.30; H, 5.56; N, 6.91.

5-Acetyl-6-methyl-2-oxo-4-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine (Entry 32, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3415, 3325, 3295, 1698, 1665, 1455. ^1H NMR (200 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.25 (s, 3H), 3.73 (s, 3H), 5.15 (s, 1H), 6.58 (d, 1H, $J = 8$ Hz), 6.67 (d, 1H, $J = 8$ Hz), 6.83 (s, 1H), 7.666 (s, 1H), 8.85 (b, 1H), 9.07 (b, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.8, 28.0, 52.2, 53.9, 107.6, 109.6, 113.6, 116.9, 133.4, 144.3, 145.7, 145.8, 150.3, 192.7. Mass: 276 ($M^+ + 1$) 275, 260, 243, 232, 271. Anal. calcd. for $C_{14}H_{16}N_2O_4$ (276.29): found: C, 60.95; H, 5.38; N, 10.01. Required: C, 60.86; H, 5.47; N, 10.14.

5-Acetyl-6-methyl-2-oxo-4-(4-methyl-2-carbomethoxy-2,6-dihydroxy-phenyl)-1,2,3,4-tetrahydro-pyrimidine (Entry 34, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3248, 1721, 1696, 1625, 1461. ^1H NMR (200 MHz, $CDCl_3$): 1.76 (s, 3H), 2.38 (s, 3H), 2.50 (s, 3H), 3.95 (s, 3H), 4.93 (s, 1H), 5.96 (s, 1H), 6.31 (s, 1H), 7.06 (s, 1H), 8.97 (s, 1H), 12.12 (s, 1H). Mass ($C_{16}H_{18}N_2O_6$, 334.34): 334, 316, 301, 291, 285, 274, 259, 243, 216, 204, 182, 175.

5-Acetyl-6-methyl-2-oxo-4-cinnamyl-1,2,3,4-tetrahydropyrimidine (Entry 35, Table 1)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3276, 3201, 1692, 1642, 1609, 1462, 1378, 1364, 1232. ^1H NMR (200 MHz, $CDCl_3$): 2.32 (s, 3H), 2.45 (s, 3H), 5.03 (d, 1H), 7.09–7.52 (m, 5H), 7.81 (s, 1H). Mass ($C_{15}H_{16}N_2O_2$, 256.15): 256, 241, 224, 213, 179, 165, 153, 141, 128.

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