Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis A: Chemical 271 (2007) 14–17
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

$Y(NO_3)_3.6H_2O$: A novel and reusable catalyst for one pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions

Nitin S. Nandurkar, Mayur J. Bhanushali, Malhari D. Bhor, Bhalchandra M. Bhanage*

Department of Chemistry, Institute of Chemical Technology, N. Parekh Marg, Matunga, Mumbai 400019, India

Received 23 January 2007; received in revised form 15 February 2007; accepted 16 February 2007
Available online 22 February 2007

Abstract

Yttrium(III) nitrate hexahydrate [$Y(NO_3)_3.6H_2O$] as a catalyst for organic reaction is described for the first time. The catalytic activity is demonstrated using Biginelli reaction as a model under solvent-free conditions. Excellent yields of dihydropyrmidinones are obtained at 70 °C within a short reaction time (10–50 min) and the catalyst is also recyclable. Other advantages over the classical method include greater substrate compatibility, faster reaction rates and easy workup procedures.

Keywords: Biginelli reaction; Yttrium(III) nitrate hexahydrate; Dihydropyrimidinones; Solvent-free conditions; Three component synthesis

1. Introduction

Dihydropyrimidinones (DHPMs) and their derivatives are well known heterocyclic units in the realm of natural and synthetic organic chemistry due to their therapeutic and pharmacological properties [1]. They are medicinally important as calcium channel blockers, antihypertensive agents, alpha-la-antagonists and neuropeptide Y(NPY) antagonists [2]. Moreover, several alkaloids containing the dihydropyrimidinones as a core unit have been isolated from marine source, which also showed interesting biological properties [3,4].

The classical synthesis of DHPMs was first reported by the Italian chemist Pietro Biginelli in 1893, involving a one pot condensation of an aldehydes, β-ketoester and urea under strongly acidic conditions [1a]. However, this method suffers from low yields (20–40%) of desired products. In order to improve the efficiency of Biginelli reaction, many Lewis acid catalysts have been developed such as $Cu(OTf)_2$ [5], $BF_3{\cdot}OEt_2$ [6], $LaCl_3{\cdot}H_2O$ [7], $ZrCl_4$ [8], $Sr(OTf)_2$ [9], $In(OTf)_3$ [10], $ZnCl_2$ [11], $FeCl_3{\cdot}6H_2O$ [12], $RuCl_3$ [13] L-proline [14] and $Ce(NO_3)_3{\cdot}6H_2O$ [15]. More recently, the use of $PhB(OH)_2$ in acetonitrile under reflux for 18 h [16], metal triflimide in water for 24 h [17]. Other works have been devoted to the use of ionic liquids [18], microwave irradiation [19] and ultrasonic mediated methods [20]. However, in spite of their potential utility, many of the existing procedures require strongly acidic conditions, longer reaction time and use of organic solvents. Therefore, the search for milder and environmentally acceptable catalytic method for performing the Biginelli reaction has been the subject of recent focus.

In recent years, development of efficient and new catalytic systems for various organic transformations is an active ongoing research area and the scope for further improvement towards milder reaction conditions. To our knowledge, neither $Y(NO_3)_3{\cdot}6H_2O$ nor its derivatives have been explored as a catalyst for any of the organic transformations. Herein, we introduce for the first time $Y(NO_3)_3{\cdot}6H_2O$ as a novel catalyst for this synthetically useful three component condensation under solvent free conditions (Scheme 1). The catalyst exhibited remarkable activity and reusability affording high yields of desired products within a short reaction time (10–50 min).

2. Experimental

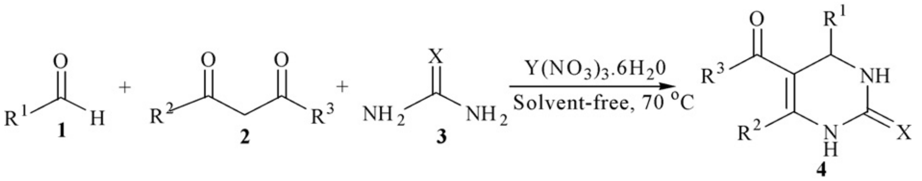
2.1. General

All compounds were identified by comparison of their spectral data and physical properties with those of the authentic sample and all yields refer to isolated products. Melting points were determined in a capillary tube and are uncorrected. ^{1}H

---

* Corresponding author. Tel.: +91 22 24145616; fax: +91 22 24145614.
E-mail addresses: bhalchandra_bhanage@yahoo.com, bmb@udct.org (B.M. Bhanage).

1381-1169/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2007.02.021



Scheme 1.

NMR and ^{13}C NMR spectra were recorded on Varian-400 NMR spectrometer using TMS as internal standard. IR spectra were recorded on Perkin-Elmer 100 spectrochem series using KBr pellets. Mass spectra were recorded on Finnigan mass spectrometer (MAT XL95). $Y(NO_3)_3{\cdot}6H_2O$ (99.9%) was purchased from Lancaster (Alfa Aesar) and used as it is. All other solvents and reagents were purchased from Lancaster and S.D. Fine Chemicals Ltd. India and used without any further purification.

2.2. General procedure for synthesis of 3,4-dihydropyrimidin-2(1H)-ones

A mixture of aldehyde (5 mmol), 1,3-dicarbonyl compound (5 mmol), urea or thiourea (5 mmol) and $Y(NO_3)_3{\cdot}6H_2O$ (0.25 mmol) was heated at 70 °C under stirring. The reaction was monitored by TLC using ethyl acetate/hexane (4:6) as eluent. After completion, the reaction mixture was cooled, poured into cold water and stirred for 5 min. The solid was suction filtered and the filtrate was evaporated to get back the original catalyst. The residual solid was washed with cold water (20 ml × 2 ml) and recrystallized from ethyl acetate or ethanol to afford pure product.

2.3. Physical and spectral data of unknown products

Compound **4p**: Solid, mp 241–243 °C. IR (KBr): 3414, 3105, 1702, 1628 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 10.0$ (s, 1H, NH), 7.90 (s, 1H, NH), 7.23–7.31 (m, $J = 8.0$ Hz, 5H_{arom}, CH), 5.21 (s, 1H, CH), 1.21 (s, 9H, $C(CH_3)_3$), 1.13 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6): $\delta = 28.2$, 29.1, 31.5, 43.4, 56.3, 109.1, 121.1, 126.2, 127.3, 145.0, 153.6, 158.2, 203.1. MS: $m/z = 314$ (M+), 257, 237.

Compound **4q**: Solid, mp 198–200 °C. IR (KBr): 3436, 3312, 1724, 1668 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 9.61$ (s, 1H, NH), 7.93 (s, 1H_{arom}, CH), 7.84 (d, 1H_{arom}, CH), 7.56 (s, 1H, NH), 7.31 (m, $J = 8.0$ Hz, 2H_{arom}, CH), 5.41 (s, 1H, CH), 1.23 (s, 9H, $C(CH_3)_3$), 1.14 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6): $\delta = 28.4$, 29.6, 32.1, 43.1, 57.8, 107.1, 121.4, 125.3, 128.6, 129.8, 130.3, 145.7, 153.6, 157.6, 202.1. MS: $m/z = 393$ (M+), 336, 313, 237.

Compound **4r**: Solid, mp 194–196 °C. IR (KBr): 3465, 3283, 1705, 1644 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 9.71$ (s, 1H, NH), 8.53 (s, 1H, NH), 7.0–7.2 (m, 3H_{arom}, CH), 5.42 (s, 1H, CH), 1.2 (s, 9H, $C(CH_3)_3$), 1.11 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6): $\delta = 28.4$, 29.6, 32.1, 43.8, 56.1, 107.1, 123.6, 124.9, 126.7, 140.3, 153.6, 159.6, 202.8. MS: $m/z = 320$ (M+), 263, 237.

Compound **4s**: Solid, mp 196–198 °C. IR (KBr): 3306, 3312, 1700, 1657 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 9.35$ (s, 1H, OH), 9.30 (s, 1H, NH), 7.60 (s, 1H, NH), 7.12 (d, $J = 8.0$ Hz, 2H_{arom}, CH), 6.62 (d, $J = 8.0$ Hz, 2H_{arom}, CH), 5.43 (s, 1H, CH), 1.21 (s, 9H, $C(CH_3)_3$), 1.10 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6): $\delta = 28.5$, 29.3, 32.1, 45.4, 56.3, 108.7, 115.1, 127.4, 135.6, 153.6, 156.8, 158.0, 203.7. MS: $m/z = 330$ (M+), 273, 237.

Compound **4t**: Solid, mp 197–199 °C. IR (KBr): 3430, 3300, 1705, 1660, 1531, 1356 cm^{-1}. 1H NMR (DMSO-d_6): $\delta = 10.0$ (s, 1H, NH), 8.52 (s, 1H, NH), 7.6–7.8 (m, 3H_{arom}, CH), 5.41 (s, 1H, CH), 1.24 (s, 9H, $C(CH_3)_3$), 1.14 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6): $\delta = 27.3$, 29.1, 31.1, 44.4, 55.3, 107.3, 123.3, 126.3, 131.4, 131.7, 144.4, 147.1, 153.6, 157.6, 201.9. MS: $m/z = 393.5$ (M+), 336.5, 301, 237.

Compound **4u**: Solid, mp 194–195 °C. IR (KBr): 3441, 3296, 1665, 1613 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 9.71$ (s, 1H, NH), 7.92 (s, 1H, NH), 6.6–6.7 (m, $J = 8.0$ Hz, 3H_{arom}, CH), 5.93 (s, 2H, O_2CH_2), 5.41 (s, 1H, CH), 1.2 (s, 9H, $C(CH_3)_3$), 1.1 2 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6): 28.1, 28.8, 32.5, 41.6, 44.7, 92.4, 107.3, 109.5, 111.3, 120.7, 121.8, 146.1, 147.1, 153.9, 158.1, 202.7. MS: $m/z = 358$ (M+), 301, 237.

3. Results and discussion

To evaluate the effect of catalyst under different reaction conditions, the reaction of benzaldehyde, ethyl acetoacetate and urea was selected as a model reaction and the results are presented in Table 1. The best result was achieved by carrying out the reaction with (0.05:1:1:1) mole ratio of catalyst, benzaldehyde, ethyl acetoacetate and urea at 70 °C. Although ethanol and acetonitrile were found to be effective, considering stringent environmental

Table 1
Effect of catalysts under different reaction conditions for condensation of benzaldehyde, ethyl acetoacetate and urea[a]

No	Solvent	Catalyst (mol%)	Time	Yield[b] (%)
1	Toluene	$Y(NO_3)_3{\cdot}6H_2O$ (5)	1 h	74
2	Ethanol	$Y(NO_3)_3{\cdot}6H_2O$ (5)	1 h	98
3	EDC	$Y(NO_3)_3{\cdot}6H_2O$ (5)	1 h	78
4	CAN	$Y(NO_3)_3{\cdot}6H_2O$ (5)	1 h	98
5	THF	$Y(NO_3)_3{\cdot}6H_2O$ (5)	1 h	77
6	H_2O	$Y(NO_3)_3{\cdot}6H_2O$ (5)	1 h	30
7	None	$Y(NO_3)_3{\cdot}6H_2O$ (10)	20 min	96
8[c]	None	$Y(NO_3)_3{\cdot}6H_2O$ (5)	20 min	97, 94, 90
9	None	$Y(NO_3)_3{\cdot}6H_2O$ (2)	20 min	77
10	None	Without catalyst	1 h	28
11	None	YCl_3 (5)	20 min	79
12	None	$Y_2\ (SO_4)_3{\cdot}8H_2O$ (5)	20 min	45

[a] Reaction condition: benzaldehyde (5 mmol), ethylacetoacetate (5 mmol), urea (5 mmol) and catalyst in solvent (25 ml, entries 1–6) at 70 °C.

[b] Isolated yield.

[c] Catalyst was recycled for three times.

Table 2
$Y(NO_3)_3{\cdot}6H_2O$-catalyzed synthesis of dihydropyrimidinones under solvent free conditions

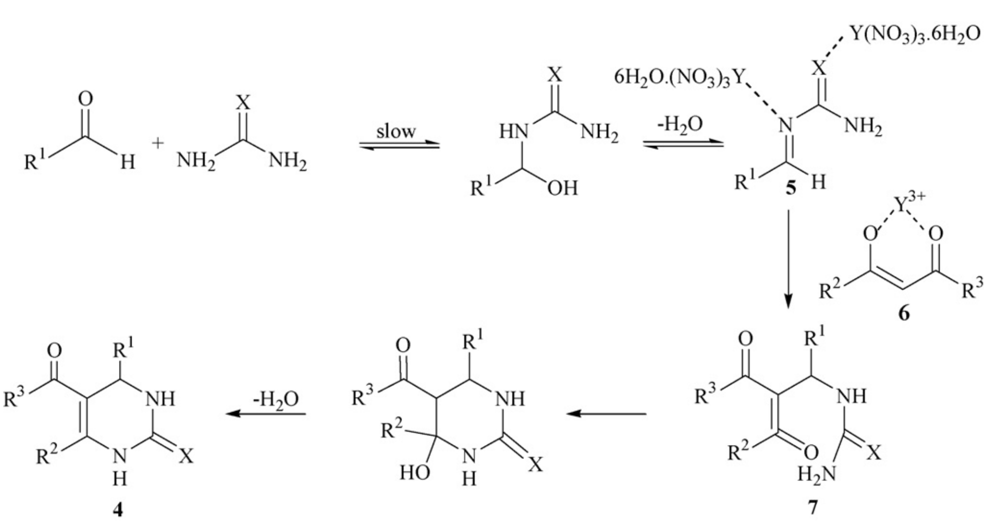
No	R^1	R^2	R^3	X	Yield (%)	Time (min)	Mp (°C) found	Mp (°C) reported
4a	C_6H_5	CH_3	OC_2H_5	O	97	20	207–208	206–208[9]
4b	$4\text{-}O_2NC_6H_4$	CH_3	OC_2H_5	O	94	10	208–210	211–213[11]
4c	$4\text{-}HOC_6H_4$	CH_3	OC_2H_5	O	93	30	237–239	237–238[9]
4d	$4\text{-}CH_3OC_6H_4$	CH_3	OC_2H_5	O	95	40	202–203	202–203[12]
4e	$4\text{-}Me_2NC_6H_4$	CH_3	OC_2H_5	O	94	12	256–258	253–254[9]
4f	$4\text{-}ClC_6H_4$	CH_3	OC_2H_5	O	93	10	216–217	215–216
4g	$C_7H_5O_2$[a]	CH_3	OC_2H_5	O	92	45	194–196	–
4h	$4\text{-}Cl\text{-}3\text{-}O_2NC_6H_3$	CH_3	OC_2H_5	O	85	30	239–241	–
4i	$4\text{-}CH_3C_6H_4$	CH_3	OC_2H_5	O	80	45	213–214	205–206[9]
4j	$3\text{-}O_2NC_6H_4$	CH_3	OC_2H_5	S	88	35	205–206	206–207[9]
4k	C_6H_5	CH_3	OCH_3	O	96	20	208–209	212–213[9]
4l	$4\text{-}CH_3OC_6H_4$	CH_3	OCH_3	S	82	45	149–150	150–152[12]
4m	$4\text{-}HOC_6H_4$	CH_3	OCH_3	O	93	30	229–230	260(dec)[11]
4n	2-Furyl	CH_3	OCH_3	O	85	50	214–216	217–219[11]
4o	C_6H_5	C_6H_5	OC_2H_5	S	80	50	156–157	157–159[6]
4p	C_6H_5	$C(CH_3)_3$	$C(CH_3)_3$	O	91	40	241–243	–
4q	$3\text{-}BrC_6H_4$	$C(CH_3)_3$	$C(CH_3)_3$	O	80	45	198–200	–
4r	2-Thienyl	$C(CH_3)_3$	$C(CH_3)_3$	O	73	45	194–196	–
4s	$4\text{-}HOC_6H_4$	$C(CH_3)_3$	$C(CH_3)_3$	O	70	20	196–198	–
4t	$4\text{-}Cl\text{-}3\text{-}O_2NC_6H_3$	$C(CH_3)_3$	$C(CH_3)_3$	O	73	30	197–199	–
4u	$C_7H_5O_2$[a]	$C(CH_3)_3$	$C(CH_3)_3$	O	40	35	194–195	–

[a] Piperanal.

regulations, solvent free reactions are desired. Therefore, we intended the Biginelli reaction under solvent free conditions (entries 7–10). The effect of different catalyst on the reaction system was tested and the results showed that the catalytic activity of yttrium(III) nitrate hexahydrate was better than that of the yttrium(III) chloride and yttrium(III) sulfate octahydrate. It may be due to the strong electron withdrawing ability of the nitrate ion, which reduced the density of the electron cloud around yttrium(III) ion. So yttrium(III) ion could accept the electron easily favoring the reaction to proceed smoothly.

The activity of the recycled catalyst was also examined under the optimized conditions and the desired product were obtained in 97, 94, 90% yields after 1–3 runs, respectively (entry 8c). The recycled catalyst after each run was characterized by FT-IR. It showed the same characteristic peaks at 721, 835 and 1393 cm^{-1} (N–O stretch) indicating coordinated nitrate ion similar to the original unused catalyst.

In order to study the generality of the procedure, a series of Biginelli compounds having different steric and electronic properties were synthesized using the optimized conditions. The results are presented in Table 2. The three-component condensation reaction proceeds smoothly at 70 °C under solvent free conditions and was completed in 20 to 50 min (entries **4a**–**4u**). Aromatic aldehydes containing both electron donating and electron withdrawing groups afforded high yields of the desired products with high purity. More importantly acid sensitive aldehydes such as 2-furfural, which normally gives low yields underwent smooth condensation without formation of any side products (entry **4n**). Thiourea also gives similar results for the generation of S-analogues of dihydropyrimidinones. The



Scheme 2.

effect of 1,3-dicarbonyl compound having different steric and electronic properties, such as ethyl benzoyl acetate and methyl acetoacetate was also investigated and high yields were obtained (entries **4k**–**4o**). Therefore, the present protocol has the ability to tolerate the variations in all the three components.

The catalyst was subjected for the three-component condensation of sterically hindered 1,3-diketone, aldehydes and urea, which is a challenging task. It exhibited remarkable activity affording moderate to good yields of bulky dihydropyrimidinones within a short reaction time (entries **4p**–**4u** have not been previously reported).

According to the mechanism suggested by Kappe [21], A proposed reaction mechanism for the Y(III)-catalyzed Biginelli condensation via acyl imine intermediate is presented in Scheme 2. The reaction of the aldehydes and urea/thiourea generates an acylimine intermediate (5) stabilized by $Y(NO_3)_3{\cdot}6H_2O$ through a coordinate bond owing to its empty orbital. Interception of this iminium ion intermediate by activated 1,3-dicarbonyl compound (6) produces an open-chain ureide (7) which subsequently undergo cyclization and dehydration to afford the corresponding dihydropyrimidinone (4).

4. Conclusion

In conclusion, $Y(NO_3)_3{\cdot}6H_2O$ has shown to be an excellent catalyst for one pot synthesis of large size dihydropyrimidinones under solvent free conditions. The protocol offers several advantages such as catalyst recyclability, high yields of product, short reaction time, simple work up procedures and easy isolation making it an important supplement to the existing methods. Further work is in progress to extrapolate the catalytic activity of Yttrium(III) nitrate hexahydrate to other organic transformations.

Acknowledgment

Financial assistance from Technical Education Quality Improvement Program (TEQIP) by Government of India is kindly acknowledged.

References

[1] (a) P. Biginelli, Gazz. Chem. Ital. 23 (1893) 360;
(b) C.O. Kappe, Tetrahedron 49 (1993) 6937;
(c) C.O. Kappe, W.M. Fabian, M.A. Semones, Tetrahedron 53 (1997) 2803;
(d) C.O. Kappe, Acc. Chem. Res. 33 (2000) 879.

[2] (a) K.S. Atwal, G.C. Rovnak, S.D. Kimballs, D.M. Floyd, S. Moreland, B.N. Swanson, D.Z. Gougoutas, J. Schewartz, K.M. Smillie, M.F. Malley, J. Med. Chem. 33 (1990) 2629;
(b) K.S. Atwal, G.C. Rovnyak, B.C. O'Reilly, J. Schewartz, J. Org. Chem. 54 (1989) 5898.

[3] (a) B.B. Snider, Z. Shi, J. Org. Chem. 58 (1993) 3828;
(b) L.E. Overman, M.H. Rabinowitz, P.A. Renhowe, J. Am. Chem. Soc. 117 (1995) 2657.

[4] (a) B. Snider, J. Chen, A.D. Patil, A. Freyer, Tetrahedron Lett. 37 (1996) 6977;
(b) A.D. Patil, N.V. Kumar, W.C. Kolle, M.F. Bean, A.J. Freyer, C. De Brosse, S. Mali, A. Truneh, D.J. Faulkaer, B. Carte, A.L. Breen, R.P. Hertzverz, R.K. Johenson, J.W. Westley, B.C.M. Ports, J. Org. Chem. 60 (1995) 1182.

[5] A.S. Paraskar, G.K. Dewker, A. Sudalai, Tetrahedron Lett. 44 (2003) 3305.

[6] E.H. Hu, D.R. Sidler, U.H. Dolling, J. Org. Chem. 63 (1998) 3454.

[7] J. Lu, Y. Bai, Z. Wang, B. Yang, H. Ma, Tetrahedron Lett. 41 (2000) 9075.

[8] C.V. Reddy, M. Mahesh, P.V.K. Raju, T.R. Babu, V.V.N. Reddy, Tetrahedron Lett. 43 (2002) 2657.

[9] W. Su, J. Li, Z. Zheng, Y. Shen, Tetrahedron Lett. 46 (2005) 6037.

[10] R. Ghosh, S. Maitti, A. Chakraborty, J. Mol. Catal. A: Chem. 217 (2004) 47.

[11] Q. Sun, Y. Wang, Z. Ge, T. Cheng, R. Li, Synthesis (2004) 1047.

[12] J. Lu, H. Ma, Synlett (2000) 63.

[13] S.K. De, R.A. Gibbs, Synthesis (2005) 1748.

[14] J. Marby, B. Ganem, Tetrahedron Lett. 47 (2006) 55.

[15] M. Adib, K. Ghanbary, M. Mostofi, M.R. Ganjali, Molecules 11 (2006) 649.

[16] A. Debache, B. Boumoud, A. Mouna, A. Belfaitah, S. Rhouati, B. Carboni, Tetrahedron Lett. 47 (2006) 5697.

[17] I. Suzuki, Y. Suzumura, K. Takeda, Tetrahedron Lett. 47 (2006) 7861.

[18] J. Peng, Y. Deng, Tetrahedron Lett. 42 (2001) 5917.

[19] C.O. Kappe, D. Kumar, R.S. Varma, Synthesis (1999) 1799.

[20] X. Zhang, Y. Li, C. Liu, J. Wang, J. Mol. Catal. A: Chem. 253 (2006) 207.

[21] C.O. Kappe, J. Org. Chem. 62 (1997) 7201.