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Supramolecular synthesis of 3,4-dihydropyrimidine-2(1*H*)-one/thiones under neat conditions

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Abstract

An efficient solvent free method for the synthesis of various 3,4-dihydropyrimidin-2(1*H*)-one/thiones in excellent yields using sulfonated β-cyclodextrine as recyclable catalyst is described. Sulfonated β-cyclodextrine was found to be efficient, recyclable heterogeneous catalyst and showed rate enhancements, high yields and short reaction times in this transformation.
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Keywords: Cyclodextrine; Recyclable catalyst; Heterogeneous; Dihydropyrimidine

The Biginelli dihydropyrimidine synthesis [1], first described in 1891, consists of the condensation of urea, an aldehyde, and a 1,3-ketoester. This condensation reaction has been used for the synthesis of dihydropyrimidin-2-ones, which have attracted considerable interest because of their wide applications as calcium channel blockers, antihypertensive agents, α-1a-antagonists and neuropeptide Y (NPY) antagonists [2,3]. Moreover, some bioactive alkaloids such as batzelladine B containing the dihydropyrimidine unit have been isolated from marine sources, which show anti-HIV activity [4]. However, this method suffers from the drawbacks such as the lower yields of the desired products (20–40%) particularly in case of substituted aldehydes and loss of sensitive functional groups during the reaction. Therefore, in the recent years several improved methodologies mainly using $BF_3{\cdot}OEt_2$/CuCl [5], lanthanide triflate [6], indium trichloride [7], vanadium(III) chloride [8], cupric chloride [9], LiBr [10], zirconium(IV) chloride [11], lithium perchlorate [12], and polymer-supported ytterbium(II) reagent [13], as well as Bronsted acids, such as *p*-toluene sulfonic acid [14], silica sulfuric acid [15], $KHSO_4$ [16], $H_3PMo_{12}O_{40}$ [17], montmorillonite KSF [18], natural HEU-type zeolite [19], and HY-zeolite [20], have been employed as heterogeneous catalyst for the synthesis of dihydropyrimidinones. Recently ionic liquids have also been used as catalysts for Biginelli reaction [21–23]. However, most of these methods require expensive reagents, long reaction time, harsh reaction conditions, tedious work-up procedure, give unsatisfactory yields and moreover use of homogeneous catalysts which are difficult in separation from reaction mixture for reuse. Furthermore, ionic

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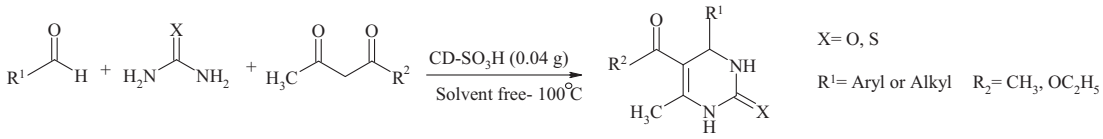

Scheme 1. CD–SO_3H-catalyzed Biginelli reaction.

liquids with imidazole as the cation are relatively expensive, which hinders their industrial applications. Moreover, typical ionic liquids consist of halogen containing anions (such as $[PF_6]^-$, $[BF_4]^-$, $[CF_3SO_3]^-$ and $[(CF_3SO_2)_2N]^-$) which in some regard limit their ''greenness'' [24–26]. Therefore, in spite of a large number of methods reported for this transformation, there is still need to develop a more efficient, simple, milder and high yielding protocol using reusable and environmentally friendly catalyst. Biopolymers have some properties, which make them attractive alternative for conventional organic or inorganic supports for catalytic applications. Recently, science and technology are shifting emphasis on environmentally friendly and sustainable resource and processes. In this regard, biopolymers are attractive candidates to explore for supported catalysis [27,28]. Several interesting biopolymers have been utilized as a support for catalytic applications, such as alginate [29], gelatin [30], starch [31,32], and chitosan derivatives [33]. Cyclodextrins (CDs) are cyclic oligomers of D-glucose and are named α-, β- and γ-CD for hexamer, heptamer and octamer, respectively [34]. They have a toroidal cyclic structure with secondary hydroxyl glucose C-2 and C-3 on their more open face and the primary C-6 hydroxyl on the opposite secondary face [35]. Their ability to bind organic molecules in the hydrophobic central cavity has provided a basis for the construction of receptor models [36]. It is widely accepted that the binding forces involved in the inclusion-complex formation are van der Waals interactions, hydrophobic interactions, hydrogen bonding and electrostatic interactions between charged parts of guest molecule and CDs [37]. In this letter, we would like to report a simple effective approach to the Biginelli reaction products using sulfonated β-cyclodextrine as the catalyst under solvent free conditions (Scheme 1).

Sulfonated β-cyclodextrine was readily prepared by reaction of CD with chlorosulfonic acid.

1. Experimental

Synthesis of sulfonated β-cyclodextrine: To a magnetically stirred mixture of β-cyclodextrine (5.00 g, 4.5 mmol) in $CHCl_3$ (20 mL), chlorosulfonic acid (1.00 g, 9 mmol) was added dropwise at 0 °C during 2 h. After addition was completed, the mixture was stirred for 2 h to remove HCl from reaction vessel. Then, the mixture was filtered and washed with methanol (30 mL) and dried at room temperature to obtain sulfonated β-cyclodextrine as white powder (5.28 g). The $-SO_3H$ content was measured by titration method and showed 0.52 mequiv./g.

General procedure: A mixture of aldehyde (2 mmol), β-dicarbonyl compound (2 mmol), urea or thiourea (3 mmol), and β-cyclodextrine–SO_3H (0.04 g), was heated with stirring at 100 °C for 2 h. The reaction was followed by TLC. Then, the reaction mixture dissolved in ethanol and filtered off to remove the catalyst. Evaporation of the ethanolic solution gave a solid which recrytallised to afford pure product. Products were identified by comparison with authentic samples and by ^1H and ^{13}C NMR and their melting points.

Spectroscopic data for selected products.

Entry 1: Mp 228–230; ^1H NMR (300 MHz, DMSO-d_6): δ 9.16 (br s, 1 H, NH), 7.78 (br s, 1 H, NH), 7.22–7.36 (m, 5H), 5.25 (d, 1H, J = 2.4 Hz), 2.24 (s, 3H), 2.07 (s, 3H); ^{13}C NMR: δ 194.4, 158.5, 152.1, 147.8, 136.9, 127.7, 113.9, 109.6, 55.1, 53.3, 30.18, 18.8. *Entry 2*: Mp 165–167 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 9.16 (br s, 1 H, NH), 7.78 (br s, 1 H, NH), 7.16 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 5.20 (d, 1H, J = 3.0 Hz), 3.72 (s, 3H), 2.28 (s, 3H), 2.07 (s, 3H); ^{13}C NMR: δ 194.4, 158.5, 152.1, 147.8, 136.4, 127.7, 113.9, 109.6, 55.1, 53.3, 30.2, 18.8. *Entry 3*: Mp 226–228; ^1H NMR (300 MHz, DMSO-d_6): δ 9.40 (br s, 1 H, NH), 8.21 (d, 2H, J = 8.4 Hz), 7.93 (s, 1H), 7.51 (d, 2H, J = 8.7 Hz), 5.39 (s, 1H), 2.32 (s, 3H), 2.19 (s, 3H); ^{13}C NMR: δ 194.0, 152.0, 151.6, 149.1, 146.7, 127.7, 123.8, 109.5, 53.1, 30.7, 19.1. *Entry 10*: Mp 192–194 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 8.86 (br s, 1H, NH), 7.26 (br s, 1 H, NH), 4.04 (m, 2H), 3.96 (t, 1H, J = 3.6 Hz), 2.18 (s, 3H), 1.68 (m, 1H), 1.19 (t, 3H, J = 7.1 Hz), 0.82 (d, 3H, J = 6.9 Hz), 0.74 (d, 3H, J = 6.8 Hz); ^{13}C NMR: δ 165.8, 153.2, 148.4, 98.2, 59.1, 55.5, 34.6, 18.5, 17.7, 16.0, 14.2.

Table 1
Effect of solvent under different reaction conditions for Biginelli reaction.

Entry	Solvent	Time (h)	Yield (%)
1	Toluene	3	Trace
2	Ethanol	3	Trace
3	None	3	83

Table 2
β-Cyclodextrine–SO_3H-catalyzed synthesis of dihydropyrimidinones/thiones.

Entry	R^1	R^2	X	Yield (%)[a,b]	Mp (°C) found	Mp (°C) reported
1	C_6H_5	CH_3	O	83	228–230	223–236 [42]
2	4-MeO–C_6H_4	CH_3	O	80	165–167	168–170 [42]
3	4-$O_2NC_6H_4$	CH_3	O	91	226–228	230 [42]
4	C_6H_5	OC_2H_5	O	89	200–202	201–203 [42]
5	4-O_2N–C_6H_4	OC_2H_5	O	93	205–207	207–210 [42]
6	4-MeO–C_6H_4	OC_2H_5	O	89	196–198	199–201 [42]
7	4-Cl–C_6H_4	OC_2H_5	O	88	210–212	210–212 [42]
8	3-Cl–C_6H_4	OC_2H_5	O	92	190–192	193–195 [42]
9	4-Me–C_6H_4	OC_2H_5	O	89	212–214	215–216 [42]
10	$(CH_3)_2$ CH	OC_2H_5	O	73	192–194	194–195 [42]
11	C_6H_5	OC_2H_5	S	86	205–207	208–210 [43]
12	4-MeO–C_6H_4	OC_2H_5	S	74	146–148	150–152 [43]
13	4-Me–C_6H_4	OC_2H_5	S	85	190–192	192–194 [43]
14	4-Cl–C_6H_4	OC_2H_5	S	71	193–195	192–194 [43]

[a] Yields refer to isolated products.
[b] All the reactions completed within 2 h.

2. Results and discussion

We first examined the reaction of benzaldehyde, acetyl acetone and urea in toluene, ethanol and also under solvent free conditions at 100 °C. The results showed that the highest yield of the products was achieved under solvent free conditions (Table 1).

Using these optimized reaction conditions, the scope and efficiency of this solvent free approach was explored for the synthesis of a wide variety of substituted 3,4-dihydropyrimidin-2(1*H*)-ones and results are summarized in Table 2. All the aforementioned reactions (Table 2) proceeded expeditiously, delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both, electron-donating and electron-withdrawing substituents; substrates with electron-withdrawing groups gave relatively higher yields. These three-component condensation reactions also proceeded smoothly with thiourea (Table 2, entries 11–14) and were completed within 120 min. In all cases, the pure product was isolated by simple filtration, without any chromatography or cumbersome work-up procedure. After the reaction, the catalyst can be easily separated from the product and reused without any decrease in its activity. For example, the reaction of benzaldehyde, acetyl acetone and urea afforded the corresponding 3,4-dihydropyrimidine-2(1*H*)-one in 83, 80, and 80% isolated yield over three cycles. In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-

Table 3
Comparison of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihidropyrimidine-2(1*H*)-one using different catalysts.

Entry	Catalyst	Time (h)	Yield (%)	Reference
1	Montmorillonite KSF	48	82	[18]
2	Sulfuric acid	18	71	[1]
3	Zeolite	12	80	[20]
4	Silica sulfuric acid	6	91	[15]
5	$BF_3{\cdot}OEt_2$/CuCl	18	71	[5]
6	$H_3PMo_{12}O_{40}$	5	80	[17]
7	CD–SO_3H	2	89	This work

dihydropyrimidin-2(1*H*)-one (Table 2, entry 4) in the presence of montmorillonite KSF, sulfuric acid, zeolite, silica sulfuric acid, $BF_3{\cdot}OEt_2$/CuCl, $H_3PMo_{12}O_{40}$ and CD–SO_3H with respect to the reaction times (Table 3). The yield of product in the presence of CD–SO_3H is comparable with these catalysts. However, other catalysts in Table 3 required longer reaction times than CD–SO_3H.

3. Conclusion

In summary, we have developed a simple and new procedure for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-one/thiones by three-component condensation in one pot using β-cyclodextrine–SO_3H as catalyst under solvent free condition. This method offers several advantages such as catalyst recyclability, inexpensive catalyst, environmental friendly procedure, short reaction time, high yields, simple work-up procedure and easy isolation.

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References

[1] For the first account of this reaction, see:
(a) P. Biginelli, Gazz. Chim. Ital. 21 (1981) 497, for reviews, see:;
(b) C.O. Kappe, Acc. Chem. Res. 33 (2000) 879;
(c) C.O. Kappe, QSAR Comb. Sci. 22 (2003) 630.
[2] (a) C.O. Kappe, Eur. J. Med. Chem. 35 (2000) 1043;
(b) C.O. Kappe, O.V. Shishkin, J. Uray, P. Verdino, Tetrahedron 56 (2000) 1859;
(c) K.S. Atwal, G.C. Rovnyak, S.D. Kimball, et al. J. Med. Chem. 33 (1990) 2629.
[3] G.C. Rovnyak, S.D. Kimball, B. Beyer, et al. J. Med. Chem. 38 (1995) 119.
[4] A.D. Patil, N.V. Kumar, W.C. Kokke, et al. J. Org. Chem. 60 (1995) 1182.
[5] E.H. Hu, D.R. Sidler, U.H. Dolling, J. Org. Chem. 63 (1998) 3454.
[6] Y. Ma, C.T. Qian, L.M. Wang, et al. J. Org. Chem. 65 (2000) 3864.
[7] A. Brindban, J.U. Jana, J. Org. Chem. 65 (2000) 6270.
[8] G. Salitha, G.S.K. Reddy, et al. Tetrahedron Lett. 44 (2003) 6497.
[10] M. Gohain, D. Prajapati, J.S. Sandhu, Synlett (2004) 235.
[11] G. Maiti, P. Kundu, C. Guin, Tetrahedron Lett. 44 (2003) 2757.
[12] C.V. Reddy, M. Mahesh, P.V.K. Raju, et al. Tetrahedron Lett. 43 (2002) 2657.
[13] J.S. Yadav, B.V.S. Reddy, R. Srinivas, et al. Synthesis (2001) 1341.
[14] A. Dondoni, A. Massi, Tetrahedron Lett. 42 (2001) 7975.
[15] T. Jin, S. Zhang, T. Li, Synth. Commun. 32 (2002) 1847.
[16] P. Salehi, M. Dabiri, M.A. Zolfigol, et al. Tetrahedron Lett. 44 (2003) 2889.
[17] S. Tu, F. Fang, S.L. Zhu, T.X. Zhang, Q. Zhuang, Synlett (2004) 537.
[18] M.M. Heravi, K. Bakhtiari, F.F. Bamoharram, Catal. Commun. 7 (2006) 373.
[19] F. Bigi, S. Carloni, B. Frullanti, et al. Tetrahedron Lett. 40 (1999) 3465.
[20] M. Tajbakhsh, B. Mohajerani, et al. J. Mol. Catal. 236 (2005) 216–219.
[21] J.J. Peng, Y.Q. Deng, Tetrahedron Lett. 42 (2001) 5917.
[22] M. Li, W.S. Guo, L.R. Wen, et al. J. Mol. Catal. A: Chem. 258 (2006) 133.
[23] R.W. Zheng, X.X. Wang, H. Xu, J.X. Du, Synth. Commun. 36 (2006) 1503.
[24] P. Wasserscheid, R. Hal, A. Bösmann, Green Chem. 4 (2002) 400.
[25] J. Fraga-Dubreuil, K. Bourahla, et al. J. Catal. Commun. 3 (2002) 185.
[26] V.R. Rani, N. Srinivas, M.R. Kishan, et al. Green Chem. 3 (2001) 305.
[27] R. Breslow, Acc. Chem. Res. 13 (1980) 170.
[28] J.H. Clark, D.J. Macquarrie, Green Chemistry and Technology, Blackwell, Abingdon, 2002.
[29] W.L. Wei, H.W. Zhu, C.L. Zhao, et al. React. Funct. Polym. 59 (2004) 33.
[30] C. Creechio, P. Ruggiero, M.D.R. Pizzigallo, Biotechnol. Bioeng. 48 (1995) 585.
[31] H. Gliemann, U. Nickel, S. Schneider, J. Raman Spectosc. 29 (1998) 89.
[32] K. Huang, L. Xue, Y.C. Hu, M.Y. Huang, Y.Y. Jiang, React. Funct. Polym. 50 (2002) 199.
[33] E. Guibal, Prog. Polym. Sci. 30 (2005) 71.
[34] J. Szejtli, Cyclodextrin Technology, Kluwer Academic Publishers, Dordrecht, 1988.
[35] Y. Cao, X. Xiao, R. Lu, Q. Guo, J. Mol. Struct. 660 (2003) 73.
[36] S. Li, W.C. Purdy, Chem. Rev. 92 (1992) 1457.
[37] J. Szeitli, Chem. Rev. 98 (1998) 1743.