Sulfated Zirconia-catalyzed One-pot Benign Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones under Microwave Irradiation

Dalip Kumar,* M. Swapna Sundaree, and Braja Gopal Mishra*
Chemistry Group, Birla Institute of Technology & Science, Pilani-333031, India

(Received June 21, 2006; CL-060703; E-mail: dalipk@bits-pilani.ac.in)

Sulfated zirconia has been demonstrated as an efficient catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under microwave irradiation and conventional heating. The solid acid catalyst is found to be highly active for the one-pot condensation of aldehydes, urea and β-dicarbonyl compound, affording variety of 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields with high purity. The low cost catalyst has exhibited remarkable reactivity and recycled without any significant loss of activity.

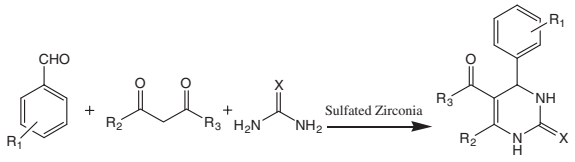
In recent years, organic synthesis involving greener process is being explored world wide due to stringent environment regulations.[1,2] Homogeneous, corrosive liquid acid catalysts, such as H_2SO_4, HCl, and complexes of BF_3 are frequently used in organic synthesis. However, processes involving conventional acids are inherently associated with problems such as high toxicity, corrosion, catalyst waste, difficulty in separation and recovery. Replacement of these conventional acids by solid catalyst is highly desirable to achieve effective catalyst handling, product purification and to decrease waste production. In the last decade, sulfated metal oxides have received considerable attention as potentially benign solid acid catalysts that possess very high catalytic activity and even superacidity.[1–3] Sulfated zirconia has been demonstrated to be efficient catalyst for several industrially important reactions under mild reaction conditions.[2–8] The sulfated zirconia catalyst is known to possess both Brønsted and Lewis acidity, the relative concentration of which depends on the procedure of preparation and the pretreatment temperature.[2,3] Generation of acidic sites on sulfated oxides thought to proceed by a two-stage reaction mechanism involving grafting of the sulfate species during impregnation step followed by dehydration of the grafted species at higher temperatures.[2,9] The strength of the surface acidic sites in case of sulfated zirconia has been found to be greater than many conventional solid acid catalysts such as silica–alumina, clays, and zeolites.[1–3]

Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones has received significant attention in natural and synthetic organic chemistry because of their promising therapeutic and pharmacological properties.[10–12] Some of 3,4-dihydropyrimidin-2(1*H*)-ones has been evaluated as antihypertensive agents, calcium channel blockers, and α_{1a} antagonists. Recently, monastrol has been identified as a lead compound of a new class of anticancer agents.[13] Several marine alkaloids bearing the dihydropyrimidone nucleus with interesting biological activities have also been isolated.[14] First synthesis of these dihydropyrimidones was reported by Biginelli involving one-pot condensation of β-dicarbonyl compound, aldehyde, and urea under strongly acidic conditions.[15] The major drawback of this method was the low to moderate yields that are frequently encountered when using substituted aromatic aldehydes. Since then various reagents have been employed for this conversion includes, among others: $BF_3 \cdot OEt$, $FeCl_3$, $InCl_3$, $BiCl_3$, $LaCl_3$, $LiClO_4$, Iodine, clays, etc.[16] Some of these methods suffer from drawbacks such as stoichiometric amounts of catalysts, purification of products, extended reaction time and moderate yields. Recently, use of microwave irradiation as an unconventional energy source has greatly improved the time and yield of Biginelli reaction under solvent-free conditions.[17,18] In view of environment constraints and biological importance of 3,4-dihydropyrimidin-2(1*H*)-ones, a rapid protocol that proceeds under catalytic condition and in quantitative yield is highly desirable.

Considering the vast scope of sulfated zirconia for acid-catalyzed organic reactions, we have described herein the potential of this solid acid catalyst for the synthesis of aforementioned 3,4-dihydropyrimidin-2(1*H*)-ones in a multi-component condensation approach. Using sulfated zirconia we obtained 3,4-dihydropyrimidin-2(1*H*)-ones in high yields from a neat mixture of aryl aldehyde, urea and β-dicarbonyl compound (Scheme 1). Initially we varied the amount of sulfated zirconia catalyst and observed that 100 mg was sufficient for effective conversion. Excessive amount of the catalysts does not increase the yields significantly. The microwave-accelerated condensation of three components was found to complete in a time span of 90–120 s. Under similar condition, aromatic aldehydes and heteroarylaldehyde afforded the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in high yields and purity. The β-dicarbonyl compounds such as acetylacetone and benzoylacetone were also found equally effective as ethyl acetoacetate, and corresponding products were achieved in high yields. Furthermore, replacing urea with thiourea, thio analogues of 3,4-dihydropyrimidin-2(1*H*)-ones were obtained. Variation of different substituents and functional groups in the substrates, demonstrates the generality of this procedure. The sulfated zirconia catalyst was easily separated by taking the neat reaction mixture into methanol and followed by simple filtration.

The reaction (Sl No.1, Table 1) was also performed in different solvent such as methanol, acetonitrile, and tetrahydrofuran at 80 °C. We found that in methanol, the conversion was fastest (2 h) with 90% yield of the product. Whereas, the condensation of the three components in acetonitrile (70%, 6 h), tetrahydrofuran (64%, 10 h) and under neat condition (89%, 3 h) at 80 °C afforded product in moderate to good yield.

The used sulfated zirconia catalyst was reactivated by heat treatment at 400 °C for 1 h in air. The regenerated catalyst was

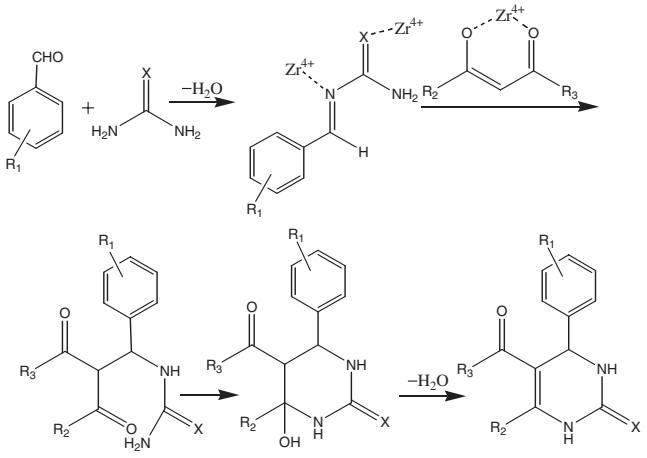


Scheme 1.

Table 1. Sulfated zirconia-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under microwave irradiation

Sr No[a]	R_1	R_2	R_3	X	Time /s	Yield /%[b]	Mp[16]/°C
1	H	Me	OEt	O	90	86	198–200
2	*p*-NO_2	Me	OEt	O	60	94	206–207
3	*m*-NO_2	Me	OEt	O	90	91	228–229
4	*p*-Cl	Me	OEt	O	90	91	213–215
5	*p*-OMe	Me	OEt	O	120	79	199–201
6	*o*-OH	Me	OEt	O	120	90	201–202
7	H	Me	OEt	S	120	90	194–196
8	*p*-OMe	Me	OEt	S	120	83	130–132
9	2-furyl	Me	OEt	O	120	90	210–212
10	H	Me	Me	O	90	91	233–234
11	*p*-OMe	Me	Me	O	120	84	167–170
12	*p*-NO_2	Me	Me	O	90	94	230–232
13	H	Me	Ph	O	90	88	203–204
14	*p*-OMe	Me	Ph	O	90	81	218–220
15	H	Me	Ph	S	90	93	229–231

[a]All the products were identified by their physical and spectral data (^{1}H NMR and IR). [b]Isolated yields.



Scheme 2.

used for three consecutive cycles without significantly loosing its activity (Sl No. 2, yields, 94%, 1st; 91%, 2nd; 89%, 3rd).

Mechanistically, initial condensation of the aldehyde and urea probably leads to acyl iminium intermediate. It is likely that the imine formation is accelerated in the presence of Brønsted acidic sites of the sulfated zirconia. The enolic content of the β-dicarbonyl compounds is further enhanced in the presence of sulfated zirconia by coordination with surface Zr^{4+} ions. Nucleophilic addition of the enolic β-dicarbonyl compounds to the acylimine intermediate, followed by cyclization and dehydration, affords the 3,4-dihydropyrimidin-2(1*H*)-one derivatives (Scheme 2).

General procedure under solvent-free conditions: A neat mixture of *m*-nitrobenzaldehyde (1 mmol), urea (1.5 mmol), ethyl acetoacetate (1 mmol), and sulfated zirconia (100 mg) in a beaker was exposed to microwave for three successive irradiation of 30 s each with cooling and mixing interval of 30 s (90 s). The reaction mixture was cooled and the ensuing solid contents were treated with hot methanol followed by filtration under hot condition. The final product was recovered from the solution which upon recrystallization from ethyl acetate afforded the pure ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Sr No. 3) in 91% yield, mp 228–229 °C (lit. mp 226–227 °C).[17] IR (KBr): 3300, 3120, 1710, 1690, 1630 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.12 (t, 3H, $J = 7.5$ Hz, CH_3), 2.28 (s, 3H, CH_3), 4.03 (q, 2H, $J = 7.5$ Hz, OCH_2), 5.33 (d, 1H, $J = 3.0$ Hz, H-4), 7.62–7.75 (m, 2H, Ar–H), 7.96 (brs, 1H, NH), 8.07–8.18 (m, 2H, Ar–H), 9.34 (brs, 1H, NH).

Synthesis of ethyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in solution: A methanolic solution (5 mL) of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), and sulfated zirconia (100 mg) was heated at 80 °C for 2 h. After completion of reaction, sulfated zirconia was removed by simple filteration under hot conditions. The methanol was distilled off and the residue obtained was recrystallised from ethanol to afford the pure product.

In conclusion, we have described a novel application of sulfated zirconia catalyst for a facile and rapid synthesis of structurally diverse 3,4-dihydropyrimidin-2(1*H*)-ones. Furthermore, this method is suitable for generating diverse libraries of potentially biological active 3,4-dihydropyrimidin-2(1*H*)-ones.

Financial support from the institute is gratefully acknowledged.

References

1 A. Corma, A. Garcia, *Chem. Rev.* **2003**, *103*, 4307.
2 A. Corma, *Chem. Rev.* **1995**, *95*, 559.
3 X. M. Song, A. Sayari, *Catal. Rev. Sci. Eng.* **1996**, *38*, 320.
4 A. Clearfield, G. P. D. Serrette, A. H. Khazi-Syed, *Catal. Today* **1994**, *20*, 295.
5 B.-Q. Xu, W. M. H. Sachtler, *J. Catal.* **1997**, *167*, 224.
6 J. Sommer, R. Jost, M. Hachoumy, *Catal. Today* **1997**, *38*, 9.
7 B. H. Davis, R. A. Keogh, R. Srinivasan, *Catal. Today* **1994**, *20*, 219.
8 Y. Sun, S. Ma, Y. Du, L. Yuan, S. Wang, Y. Jun, F. Deng, F. Xiao, *J. Phys. Chem. B* **2005**, *109*, 2567.
9 a) K. Arata, M. Hino, *Appl. Catal.* **1990**, *59*, 197. b) A. Clearfield, G. P. D. Serrete, A. H. Khazi-Syed, *Catal. Today* **1994**, *20*, 295.
10 a) C. O. Kappe, *Tetrahedron* **1993**, *49*, 6937. b) C. O. Kappe, *Acc. Chem. Res.* **2000**, *33*, 879.
11 B. Jauk, F. Belaj, C. O. Kappe, *J. Chem. Soc., Perkin Trans. 1* **1999**, 307.
12 C. O. Kappe, *Eur. J. Med. Chem.* **2000**, *35*, 1043.
13 T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber, T. J. Mitchison, *Science* **1999**, *286*, 971.
14 Z. D. Aron, L. E. Overman, *Chem. Commun.* **2004**, 253.
15 P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360.
16 a) E. H. Hu, D. R. Sidler, U.-H. Dolling, *J. Org. Chem.* **1998**, *63*, 3554. b) J. Lu, H. Ma, *Synlett* **2000**, 63. c) B. C. Ranu, A. Hazra, U. Jana, *J. Org. Chem.* **2000**, *65*, 6270. d) K. Ramalinga, P. Vijayalakshmi, T. N. B. Kaimal, *Synlett* **2001**, 863. e) J. Lu, Y. Bai, Z. Wang, B. Yang, H. Ma, *Tetrahedron Lett.* **2000**, *41*, 9075. f) M. S. Manhas, S. N. Ganguly, S. Mukherjee, A. K. Jain, A. K. Bose, *Tetrahedron Lett.* **2006**, *47*, 2423. g) A. Stadler, C. O. Kappe, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1363, and references therein.
17 a) K. Tanaka, F. Toda, *Chem. Rev.* **2000**, *100*, 1025. b) R. S. Varma, *Green Chem.* **1999**, *1*, 43.
18 C. O. Kappe, D. Kumar, R. S. Varma, *Synthesis* **1999**, 1798.

Published on the web (Advance View) August 26, 2006; doi:10.1246/cl.2006.1074