TiO_2 nanoparticles/melamine Tri sulfonic acid for biginelli syntheis under solvent-free conditions

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Abstract:

TiO_2 nanoparticles/melamine Tri sulfonic acid (MTSA) supported on silica gel as an efficient catalytic system for simple, one pot, solvent-free and environmentally benign process for synthesis of dihydropyrimidines via Biginelli reaction at 110 °C is described. It was found that the catalyst is reusable and exhibited remarkable activity. The catalyst can be easily separated and reused several times without appreciable loss of activity. The availability and recoverability of the catalytic system with easy operation and work up make this catalytic system attractive for organic synthesis.

Keywords: TiO2 nano particles, Biginelli reaction, dihydropirimidinone, solvent-free.

Introduction

In recent years, use of eco-friendly applicable industrial and green catalysts has been interest. Thus, green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials[1].To realize this goal, in recent years, significant articles have appeared reporting efficient solvent free reactions[2]. This technique has many advantTiO2es such as reduced pollution, low cost, process simplicity, and easy work up. In addition, because of environmental acceptability, recently more attention has been paid to the application of inorganic solid acids in organic synthesis[3].

The use of solid acids as catalyst is important in the development of clean technologies, since it avoids drawbacks of environmental pollution and prevents corrosion of the conventional technologies [4]. As described in Scheme 1, MTSA, as an efficient solid acid, was easily prepared by addition of chloro sulfonic acid to melamine at room temperature. The reaction is very easy and clean, because the evolved HCl gas can be removed from the reaction vessel immediately. This solid acid is not soluble in water or common polar or nonpolar organic

solvents[5].

One-pot sequential multi-step reactions are increasing academic, economical and ecological interest because they address fundamental principles of synthetic efficiency and reaction design. [6]The Biginelli reaction, discovered by pietroBiginelli in 1893, is a multicomponent reaction (MCR)in a one-pot process that involves the cyclo condensation of di carbonyl compounds, aromatic aldehydes and urea. The products of this three–component synthesis were identified as 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs). [7]This important class of heterocyclic compounds has medicinal chemists due to pharmacological and biological properties such as antihypertensive, α-1a-antTiO2onism, neuropeptide Y(NPY) antTiO2onism, antibacterial, aniviral, antitumour, antioxidant and anti-inflammatory[8-11]. Batzelladine alkaloids containing dihydropyrines core have been found to show potent anti-HIV activity [12].

Classically this reaction was carried out in alcoholic solution of Bronsted acids such as HCl, H_2SO_4, acetic acid, and which usually gave very low yields [13-14]. With the awareness of environmental issues and importance of this reaction many improvements have been attempted by way of use of catalysts. [15-23]

In this work, we have investigated the application of TiO_2 nano particles/MTSA.$SiO_2$for synthesis of Biginelli condensation reaction under solvent-free condition.

Exprimental

The materials were purchased from Sigma–Aldrich and Merk and were used without any additional purification. ^{1}H NMR spectra were recorded on a BRUKER AVANCE (400) spectrometer using TMS as an internal standard and $CDCl_3$ as solvent. products were characterized by FT-IR and comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker Eqinox 55 spectrometer and the TEM of nanoparticles determined with VEGA/TESCAN scanning electron microscope.

Preparation of TiO_2 nanoparticle supported on silica gel

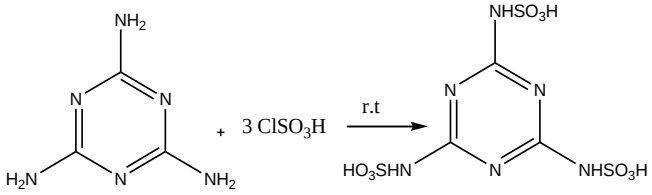
Aqueous $NaBH_4$ solution (30mL, 8 mmol/L) was placed in an ice bath. After cooling, 1.5g of silica gel was added to the solution. When 10mL of TiO_2NO_3 solution (1mmol/L) was added drop wise to this solution, the color of solution was turned yellow due to the formation of silver nanoparticles. After 30 min stirring, the solid was separated from solution by centrifuge. The yellow precipitate was washed with water for several times and oven-dried at 80 $^{\circ}$C. The

immobilized silver nanoparticles were stored in a dark colored bottle.

Preparation of Melamine Trisulfonic acid

A 50-mL suction flask was equipped with a constant pressure-dropping funnel. The gas outlet was connected to a vacuum system through adsorbing solution (water) and an alkali trap. Melamine (1.26 g, 10mmol) was charged in the flask, and Chloro sulfonic acid (3.5 g, 2 mL, 30mmol) in CH_2C_{l2} (10 mL) was added drop wise over a period of 30 min at room temperature. HCl gas was evolved immediately.

After completion of the addition, the mixture was shaken for 2 h, while the HCl was eliminated by suction. Then the mixture was washed with excess CH_2Cl_2 to remove the unreacted chlorosulfonic acid. Finally, MTSA was obtained as a white powder (3.3 g, 90%) [5].



Schem 1: Preparation of MSA

Acidic Capacity Determination of Melamin Sulfonic acid supported on Silica gel by titration

Suspension of 1 g of solid acid in 10 mL of distilled water was prepared and it was titrated with soda solution (0.1 M) in the presence of phenolphethalein. 170 mL was used to achieve eq point. Thus, the acid capacity was determined 17 mmol per 1 gram of acid.

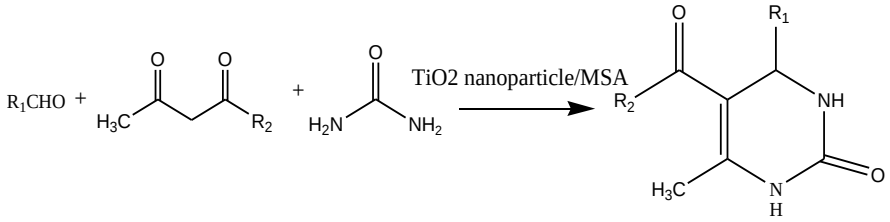
Typical procedure for preparation of 3,4-Dihydropyrimidin-2(1H)-ones in the presence of TiO2 nanoparticles/MTSA.SiO_2under solvent-free condition:

A mixture of aldehyde (1mmol), ethyl acetoacetate or acetyl acetone (1mmol), urea (3mmol), melamine Trisulfonic acid (0.2g), and TiO_2 nanoparticle.SiO_2 (0.05g) was heated with stirring at 110 ºC for 20 min. The progress of the reaction was monitored by TLC using (ethyl acetate/hexane(1:4)as eluent). After completion of the reaction, the product washed with crushed ice-cold water and the solid that separated was filtered to dissolve excess of urea in water. After that solid was dissolved in hot ethanol and filtered to remove the catalyst and purified further by recrystallization.

Results and discussion

The dimensions of nanoparticles were observed with TEM. The size of commercial synthesized TiO2 nanoparticles is about 53nm (Figure 1). The preparation of TiO_2 nanoparticles was investigated by UV-Vis spectroscopy. The broad peak in 390 nm was shown preparation of TiO2 in nano size (Figure 2).

The IR spectrum of MSA showed the broad O-H absorption in the region between 2600 and 3600cm^{-1}, strong S=O absorptions between 1150 and 1200cm^{-1}, strong S-O absorption at 650 cm^{-1}, and medium C=N absorption at 1620 cm^{-1}. This solid acid leads to a decrease in the pH from 7 to 2 and decomposed at 350 $^{\circ}C$.



Scheme 2

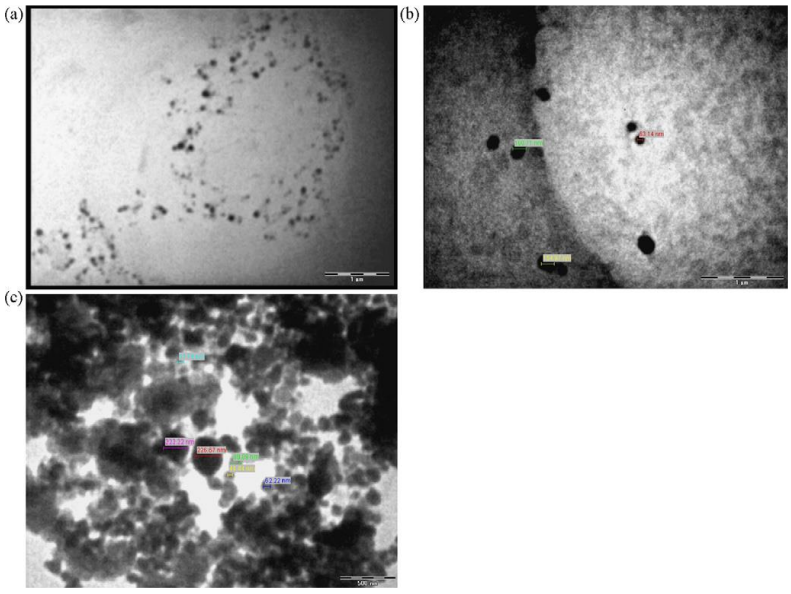


Fig.1.TEM imTiO_2e of (a)synthesized colloidal silver nanoparticle, (b) the TiO2 nanoparticles immobilized on silica gel (c) TiO2gregated silver nanoparticle

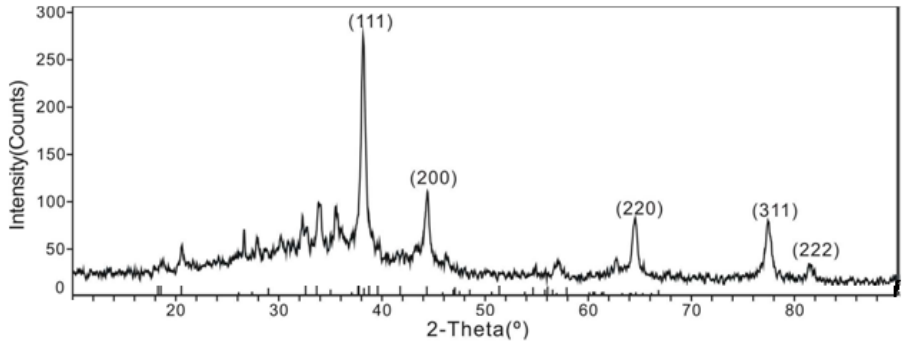


Fig.2.XRD pattern of the TiO_2 nanoparticles

The typical powder XRD pattern of the prepared nanoparticles is shown in Figure 3. The data shows diffraction peaks at 2θ= 38.2°, 44.4°, 64.6°, 77.5°, and 81.7°, which can be indexed to (111), (200),(220), (311), and (222) planes of pure silver (PDF № 04-0783). It confirmed that the main composition of the nanoparticles was silver.

Optimize the reaction conditions

In order to find the best reaction conditions, we started our study on the Biginelli reaction using MTSA.SiO_2 by model reaction (Scheme 2).

Benzaldehyde reacted with ethyl acetoacetate and urea in the presence of various amounts of catalyst. Different molar ratios of substrates were also examined. The optimum amounts were found to be 1:1:3:0.2 for benzaldehyde, ethyl acetoacetate, urea, MSA.SiO_2 respectively (Table 1).

Table1. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones in the presence of MSA.SiO_2

Com.	R_1	R_2	Time (min)	Yield (%)
4a	C_6H_5	OC_2H_5	20	94
4b	4-$OMeC_6H_4$	OC_2H_5	20	70
4c	4-ClC_6H_4	OC_2H_5	20	46
4d	C_6H_4CH=CH	OC_2H_5	20	41
4e	4-$OMeC_6H_4$	CH_3	20	46
4f	4-ClC_6H_4	CH_3	20	33
4g	C_6H_4CH=CH	CH_3	20	30

In the next steps, we investigated the application of TiO2 nanoparticles/MSA.SiO2 for the

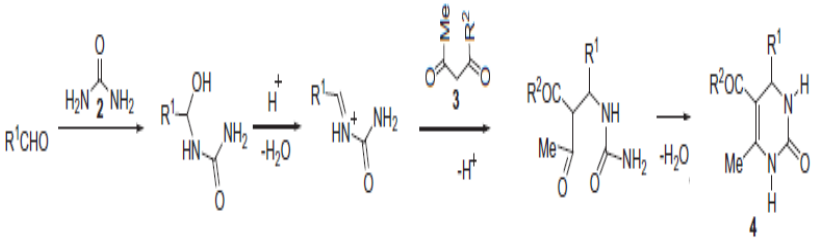
synthesis of various Biginelli type products by condensation of various aromatic aldehydes containing electron-donating and withdrawing groups with ethyl acetoacetate or acetyl acetone and urea (Table 2). In all cases, the three component reaction proceeded smoothly to give the corresponding 3,4-Dihydropyrimidin-2(1H)-ones in moderate to good yield. We have found that the best conditions were using 0.2 g of MTSA**,** 0.05 g of TiO2 nanoparticles.SiO_2 under solvent-free conditions at 110 $^{\circ}$C (Scheme 2).

Table 2. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones in the presence of TiO2 nanoparticles/MSA.SiO_2

Compond	R_1	R_2	Time (min)	Yield (%)	M.p. (ºC)	
					Found	Reported
4a	C_6H_5	OC_2H_5	20	73	201-202	206-207[31]
4b	4-ClC_6H_4	OC_2H_5	20	88	232-234	213-214[32]
4c	4-$OMeC_6H_4$	OC_2H_5	20	97	202-204	203-204[19]
4d	4-CNC_6H_4	OC_2H_5	20	87	200-201	-------
4e	4-C_6H_4CH=CH	OC_2H_5	20	82	212-214	229-230[33]
4f	C_6H_5	CH_3	20	70	232-235	232-235[18]
4g	4-ClC_6H_4	CH_3	20	87	230-232	212-213[34]
4h	4-$OMeC_6H_4$	CH_3	20	84	169-171	177-179[35]
4i	4-CNC_6H_4	CH_3	20	92	195-197	-------
4j	4-C_6H_4CH=CH	CH_3	20	86	229-230	230-232[35]

[a]The yields refer to the isolated pure products which were characterized from their spectral data and were compared with authentic sample.

According to the mechanism presented by kappe in 1997, a plausible mechanism for the present one- pot cyclo condensation of aromatic aldehyde, urea and 1,3- dicarbonyl compound is depicted in scheme (3).



Scheme 3. Plausible mechanism for Biginelli reaction

The products have been characterized by comparison of their physical and spectroscopic data with those of the authentic samples. The physical and spectroscopic data of the new compounds

are reported below.

4a.5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one

Colorless solid; m.p.201-202 °C; IR (KBr): 3240, 3110, 2974, 1722, 1705, 1649 cm^{-1}: ^1H NMR: δ 9.12 (S, 1H), 7.66 (S,1H), 7.28-7.16(m, 5H), 5.10(d, *J* 3.3HZ,1H), 3.94 (q, *J* 7.1 HZ, 2H), 2.18 (s, 3H), 1.04(t, *J* 7.1 HZ, 3H).

4b. 4-(4-chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one

Colorless solid; m.p.212-214 °C; IR (KBr): 3242, 1723, 1704, 1649 cm^{-1}: ^1H NMR: δ 9.20 (s, 1H), 7.82 (s,1H), 7.27(m, 5H), 5.11(d, *J* 1.16 HZ, 1H), 3.96 (q,*J*7.1HZ, 2H), 2.23 (s, 3H), 1.06(t,*J*7.2 HZ, 3H).

4c. 5-Ethoxycarbonyl-4-(4- methoxyphenyl) - 6-methyl-3,4-dihydropyrimidin-2(1H)-one

Colorless solid; m.p.200-201 °C; IR (KBr): 3246, 1700, 1642 cm^{-1}: ^1H NMR: δ9.20 (s, 1H), 7.69 (s, 1H), 7.16 (d, *J*8.6 HZ,2H), 6.90 (d, *J* 8.6HZ,2H), 5.09 (d, *J* 2.6 HZ, 1H), 4.52 (d,*J*3.6 HZ, 1H), 3.99(q, *J* 7.1 HZ, 2H), 3.72(s,3H), 2.26(s, 3H), 1.12 (t, *J* 7.1 HZ, 3H).

4e.5-Ethoxycarbonyl-6-methyl-4-Styryl-3,4-dihydropyrimidin-2(1H)-one

Colorless solid; m.p.232-234 °C; IR (KBr): 3245, 1724, 1700, 1650 cm^{-1}: δ_H 8.93 (s, 1H), 7.33 (s,1H), 7.20-6.99(m, 5H), 6.14(d, *J* 15.9HZ,1H), 5.99 (dd, *J*15.9 HZ, 6.0HZ, 1H), 4.52 (d,*J*3.6 HZ, 1H), 3.93-3.81(m, 2H), 2.00(s,3H),0.98(t,*J*7.1 HZ, 3H).

It is worthy to note that the catalytic system reused 3 consecutive times with only a slight variation in the yields of the corresponding products.Table3 demonstrates the usability of the catalyst after three runs in Biginelli condensation reaction.

Table3. Reusability of the TiO2 nanoparticles/MSA.SiO_2catalytic system under solvent-free synthesis of DHPMs [a]

Experiment	Cycle	Yield [b] (%)
1	1	97
2	2	95
3	3	94

Reaction conditions: 4-methoxy benzaldehyde (1mmol), ethyl acetoacetate (1mmol), urea (3mmol), TiO2 nanoparticles/MSA.SiO_2 (0.25 g), time (20 min). [b] Isolated yield.

Conclusion

TiO_2 nano particles/MSA is cheap readily available, eco-friendly, low in toxicity, highly stable towards humidity, high activity , recoverable by simple filtration and very high surface to volume ratios in nano structures have found more attention and efficient for promotion of Biginelli

condensation reaction. This catalytic system do not need special precautions for preparation, handling or storTiO2e and it can be stored at ambient temperature for months without losing their catalytic activity.

TiO2 nanoparticles/MSA.SiO_2 has been applied for the condensation of aromatic aldehydes, ethyl acetoacetate or acetylacetone and urea in a simple and straightforward protocol. Short reaction times, good yields, simplicity of operation, easy work up and environmentally friendly procedure are some advantTiO2es of this method.

Table4. Comparison of Catalytic Activity of other Lewis with TiO_2 nanoparticle/MSA .SiO_2under VariousConditions

Lewis acid	Time (h)	Yield (%)[b]	Solvent	Ref.
TiO2 nanoparticles/MSA.SiO_2	0.3	97	----	Present work
$Sr(NO_3)$	6	77.8	AcOH	24
Carbon-based solid acid	0.45	95	----	25
Silica sulfuric acid	6	91	EtOH	17
Natural HEU Zeolite	5	75	AcOH	25
HCl	24	50	EtOH	26
Iodine	4	95	Toluene	27
Nano CeO_2/Vinylpyridine	4.5	92	H_2O	28
Anchored sulfonic acid on SiO_2	8	90	Acetonitrile	29
$FeCl_3/Si(OEt)_4$	3	88	Isopropanol	30
$Y(OAc)_3.xH_2O$	4	92	AcOH	31

References

1. J.H. Clark, *Green Chem,***1**, 1, (1999).
2. M. Schnürch, M. Holzweber, M.D. Mihovilovic and P. Stanetty, *Green Chem.*, **9**, 139, (2007).
3. B.F. Mirjalili, M.A. Zolfigol, A. Bamoniri and A. Hazar, *J. Braz. Chem. Soc.*, **16**, 877 (2005).
4. R.W. Armstrong, A.P. Combs, P.A. Tempest, S.D. Brown and T.A. Keating, *Acc. Chem. Res.*, **29**, 123 (1996).
5. A.R. Kiasat and M. Fallah-Mehrjardi, *J. Braz. Chem. Soc.*, **19**, 1595. (2008).
6. M.A. Bigdeli, S. Jafari, G.H. Mahdavinia and H. Hazarkhani, *Catal. Commun.*, **8**, 1641 (2007).

7. P. Biginelli, *Gazz. Chim. Ital.*, ***23***, 360. (1893).
8. C.O. Kappe, *TetrahedronLett.*, **49**, 6937 (1993).
9. C.O. Kappe, *Acc. Chem. Res.*, **33**, 879 (2000).
10. J.P. Wan and Y. Liu, *Synthesis*, **23**, 3943 (2010).
11. A. Karamat, M.A. Khan and A. Sharif, *J. Chin. Chem. Soc.*, **57**, 1099 (2010).
12. A.D. Patil, N.V. Kumar, W.C. Kokke, M.F. Bean, A.J. Freyer, C. DeBrosse, S. Mai, A. Truneh and B. Carte, *J. Org. Chem.*, , **60**, 118 (1995).
13. K. Folkers, H.J. Harwood, T.B. Johnson, *J. Am. Chem. Soc.*, **54**, 3751 (1932).
14. K. Folkers and T.B. Johnson, *J. Am. Chem. Soc.*, ,**55**, 3784 (1933).
15. S.K.Kundu,A. Majee and A.Hajra, *Ind. J. chem.*, ,**48B**,408 (2009).
16. T. Jin, S. Zhang and T. Li, *Synth. Commun.*, , **32**, 1847 (2002).
17. P. Salehi, M. Dabiri, M.A. Zolfigol and M.A. BodTiO2hiFard, *Tetrahedron Lett.*, **44**, 2889 (2003).
18. S. Tu, F. Fang, S. Zhu, T. Li, X. Zhang and Q. Zhuang, *Synlett.*, **3,** 537 (2004).
19. H. Adibi, H.A. Samimi and M. Beygzadeh, *Catal. Commun.*, **8**, 2119 (2007).
20. Y. Yu, D. Liu, C. Liu and G. Luo, *Bioorg. Med. Chem. Lett.*, **17**, 3508 (2007).
21. E.H. Hu, D.R. Sidler and U.H. Dolling, *J. Org. Chem.*, **63**, 3454 (1998).
22. Y. Ma, C. Qian, L. Wang and M. Yang, *J. Org. Chem.*, **65**, 3864 (2000).
23. K.A. Kumar, M. Kasthuraiah, C.S. Reddy andC.D. Reddy, *Tetrahedron Lett.*, **42**,7873 (2001).
24. V. Mirkhani, M. Moghadam and S. Tangestaninejad, *J. Iran. Chem. Soc.*, **8**, 611 (2011).
25. G. Maiti, P. Kundu and C. Guin, *Tetrahedron Lett*, **44**, 2757 (2003).
26. M. Tajbakhsh, B. Mohajerani, M.M. Heravi and A.N. Ahmadi, *J. Mol. Catal. A. Chem.*, **236**,216 (2005).
27. S.K. De and R.A. Gibbs, *Synthesis*,**11**, 1748 (2005).
28. A.K. Mitra and K. Banerjee, *Synlett.*, **10**, 1509-1511. (2003).
29. T. Jin, S. Zhang and T. Li, *Synth. Commun.*, **32**, 1847-1851. (2002).
30. G.L. Zhang and X.H. Cai, *Synth. Commun.*, 2005, **35**, 829 (1993).
31. G. Aridoss and Y.T. Jeong, *Bull. Korean Chem. Soc.*,**31**, 863 (2010).