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Nanocrystalline SiO_2–$HClO_4$: A novel, efficient and green catalyst for the three-component synthesis of pyrimidine derivatives

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Abstract

Nanocrystalline SiO_2–$HClO_4$, as a newly reported catalyst, has been used as an efficient and reusable catalyst for the synthesis of pyrimidine derivatives. The procedure can be successfully applied to the efficient synthesis of mono substituted pyrimidine derivatives, using triethylorthoformate, ammonium acetate, methyl ketone derivatives. In practice, this method is a combination of a satisfactory synthesis and more significantly easy product isolation and purification. A simple, high yielding method in the presence of perchloric acid–functionalized silica nanosphere as a catalyst is described.

Keywords: Three-component reaction; pyrimidine derivative; perchloric acid–functionalized silica nanosphere; methyl ketones.

Introduction

Nano-sized compounds have novel and significant applications in comparison to the bulk compounds [1−4].Advancement in nanotechnology leads to the production of nanosized silica, which has been widely used as filler in engineering composite. In many systems, heterogeneous catalysts usebifunctional structures [5-6]. A bifunctional catalyst has both active metal nanoparticles and a high surface

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area support [7].Two types of functional groups, siloxane (Si-O-Si) and silanol (Si-OH) [8-10] can react on silica surface [11-12]. Pyrimidine is an important heterocycle with a variety of biological activities [13]. In general, most of these methods involve multiple synthetic steps, which often require harsh reaction conditions or reagents that are not readily available, making these methods unsuitable for use in the synthesis of pyrimidine libraries. Herein, we describe a simple, single step synthesis pyrimidines using a combination of ketones, triethylorthoformate, ammonium acetate that represents a significant improvement over existing methods of pyrimidine synthesis. A few methods are available for the synthesis of the pyrimidine ring system with this method such as $ZnCl_2$ [14], TsOH [15], TBBDA [16]. These procedures have problems such as long reaction times, use of solvent, potential hazards and difficulty in preparation.

Experimental

General

Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies and were used as purchased, without further purification. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrum Gx, KBr pellets were used for solid samples. ^{1}H and ^{13}C NMR spectra were measured with BrukerAvance 300 and 500 MHz FT NMR spectrometers with $CDCl_3$ and $(CD_3)_2CO$ as solvent and TMS as internal standard. Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer. Weight change curve in nitrogen was measured on a TA instrument of TGA Q50 V6.3 with maximum heating rate of 10 °C/min. Scanning electron microscopy (SEM) of the particles was carried out using a Jeol JDM 840A instrument. Samples were prepared by dispensing drops of an aqueous suspension of particles on to a glass plate. Transmission electron microscopy (TEM) analysis was performed by a Zeiss model EM900 instrument. Wide-angle X-ray diffraction (XRD) measurements were performed at room temperature on a Philips PW 1820 diffractometer using Ni-filtered Co-Kα radiation (λ=0.15418 nm). N_2physisorption at liquid nitrogen temperature was obtained by a SHIBATA APP. SA-1100 surface area analyzer and standard multipoint BET

analysis methods were carried out. Samples were degassed in flowing N_2 for 2 h at 250 °C before N_2physisorption measurements were obtained. UV-Vis spectra were recorded on Agilent, 8453, UV-Vis spectrometer.

Preparation of silica perchloric acid nanosphere

Silica nanosphere (2.0 g, 5 wt%) was dispersed in dry diethylether (30 mL, 0.7134 g/mL) and stirred in a round-bottomed flask. $HClO_4$ (0.14 g, 1 mmol, 70% aq solution) was added at room temperature. After the addition was completed, the mixture was stirred for 3 h. Evaporation of the solvent on a rotary evaporator gave silica perchloric acid nanosphere (SPA-NS) as a white solid. Silica perchloric acid nanosphere were characterized by XRD, FT-IR, BET and TGA spectra and also by SEM and TEM images [17].

General procedure for the synthesis of Pyrimidin derivatives

A mixture of the methyl ketone (1 mmol), triethylorthoformate (3 mmol), ammonium acetate (3 mmol) and the catalyst (containing 0.012 mmol H^+) was stirred at 85 ˚C. After completion of the reaction, as monitored by TLC, the reaction mixture was centrifuged for 5 min. Then, the clear liquid was separated and crushed ice (10 mL) and methanol was added to the reaction mixture and stirred thoroughly. On solidification, the crude product was filtered, dried, and purified. Pyrimidin derivatives were confirmed by using IR, ^{1}H-NMR, ^{13}C-NMR spectra data. The physical data of known compounds were identical with other reported [14,16].

Selected spectral data

4-Phenylpyrimidine (1)

FT- IR (KBr) ν(Cm^{-1}) = 1577 (C=N), 1536 (C=C). ^{1}H-NMR ($CDCl_3$) δ(ppm) = 7.55-7.59 (m, 3H, ArH), 7.79-7.81 (d, 1H, *J*=5.35 Hz, H^5Pyrimidine), 8.14-8.16 (m, 2H, ArH), 8.82-8.83 (d, 1H, *J*=5.34 Hz, H^6Pyrimidine), 9.33 (s, 1H, H^2Pyrimidine).

4-(4-Bromophenyl)pyrimidine (2)

FT- IR (KBr) ν(Cm^{-1}) = 1574-1590 (C=N), 1538 (C=C).^{1}H-NMR ($CDCl_3$) δ(ppm) = 7.67-7.69 (d, 2H, *J*= 8.53 Hz, ArH), 7.73-7.74 (d, 1H, *J*=5.36 Hz, H^5Pyrimidine), 8.00-8.01 (d, 2H, *J* =8.54 Hz, ArH), 8.81-8.82 (d, 1H, *J*= 5.34 Hz, H^6Pyrimidine), 9.30 (s, 1H, H^2Pyrimidine). ^{13}C-NMR ($CDCl_3$) δ(ppm) = 117.1 (2CH), 126.4 (CH), 129.43 (CH), 132.7 (CH), 135.7(C), 157.8 (C), 159.4 (CH), 163.3 (C).

4-(4-Chlorophenyl)pyrimidine (3)

FT- IR (KBr) ν(Cm^{-1}) = 1578-1594 (C=N), 1539 (C=C). ^{1}H-NMR ($CDCl_3$-d^6) δ(ppm) = 7.62-7.64 (d, 2H, *J*=8.58 Hz, ArH), 8.12-8.13 (d, 1H, *J*= 5.29 Hz, H^5Pyrimidine), 8.24-8.26 (d, 2H, *J*=8.55 Hz, ArH), 8.88-8.89 (d, 1H, *J*=5.33 Hz, H^6Pyrimidine), 9.26 (s, 1H, H^2Pyrimidine). ^{13}C-NMR ($CDCl_3$) δ(ppm) = 118.1 (2CH), 129.6 (CH), 130.0 (2CH), 135.6 (2CH), 136.9, 159.1 (C), 159.6 (C), 162.2 (C).

4-(4-Flourophenyl)pyrimidine (4)

FT- IR (KBr) ν(cm^{-1}) = 1581- 1601 (C=N), 1542 (C=C),^{1}H-NMR ($CDCl_3$) δ(ppm) = 7.23-7.27 (t, 2H, ArH), 7.74-7.76 (d, 1H, *J*=5.34 Hz, H^5Pyrimidine), 8.15-8.19 (m, 2H, ArH), 8.82-8.83 (d, 1H, *J*=5.38 Hz, H^6Pyrimidine), 9.31 (s, 1H, H^2Pyrimidine). ^{13}C-NMR ($CDCl_3$) δ(ppm) = 116.5 (CH), 116.7 (2CH), 117.0 (CH), 129.7 (CH), 129.8 (CH), 157.4 (CH), 159.0 (C), 163.6 (C), 166.3 (C).

4-(4-Nitrophenyl)pyrimidine (5)

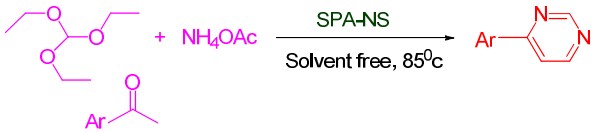
FT- IR (KBr) ν(Cm^{-1}) = 1577 (C=N), 1546 (C=C), 1521- 1349 (NO_2). ^{1}H-NMR ($CDCl_3$) δ(ppm) = 7.84-7.86 (d, 1H, *J*=5.25 Hz, H^5Pyrimidine), 8.32-8.34 (d, 2H, *J*=7.13 Hz, ArH), 8.41-8.43 (d, 2H, *J*=7.00 Hz, ArH), 8.93-8.94 (d, 1H, *J*=5.19 Hz, H^6Pyrimidine), 9.4 (s, 1H, H^2Pyrimidine). ^{13}C-NMR ($CDCl_3$) δ(ppm) = 118.0 (2CH), 124.6 (2CH), 128.6 (2CH), 142.6 (CH), 158.4 (CH), 159.7 (C), 161.9 (C).

4-(4-Methylphenyl)pyrimidine (6)

FT- IR (KBr) ν(cm^{-1}) = 1579-1611 (C=N), 1540 (C=C).^{1}H-NMR ($CDCl_3$) δ(ppm) = 2.39 (s, 3H, Me) 7.36-7.37 (d, 2H, *J*=7.7 Hz, ArH), 8.05-8.06 (d, 1H, *J*=5.4Hz, H^5Pyrimidine), 8.11-8.13 (d, 2H, J=7.76 Hz, ArH), 8.82-8.83 (d, 1H, *J*=5.36 Hz, H^6Pyrimidine), 9.2 (s, 1H, H^2Pyrimidine). ^{13}C-NMR ($CDCl_3$) δ(ppm) = 21.8 (Me), 117.6(CH), 127.7 (2CH), 130.5 (2CH), 134.0 (CH), 142.1 (CH), 158.7 (C), 159.5 (C), 163.3 (C).

Results and discussion

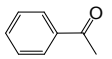
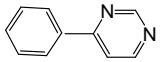
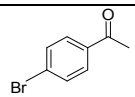
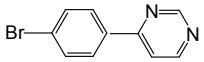
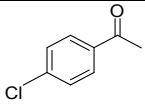
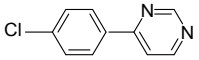
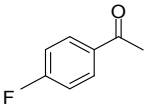
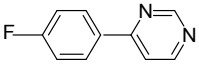
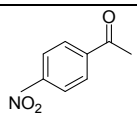
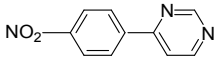
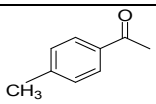
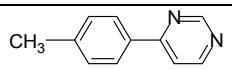
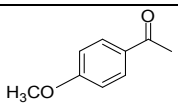
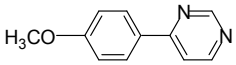
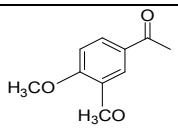
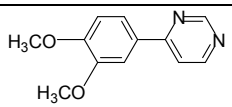
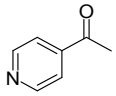
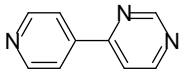
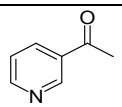
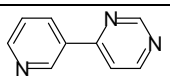
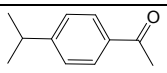
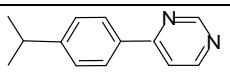
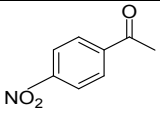
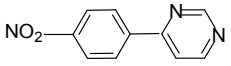
As a part of our current studies on the design of routes for the preparation of heterocyclic compounds [17-18],we herein disclose a simple and convenient method for the efficient synthesis of 4-substituted pyrimidine derivatives under solvent-free catalyzed by perchloric acid–functionalized silica nanosphere (SPA-NS) (Scheme 1, Table 1).



Scheme 1. Synthesis of 4-substituted pyrimidine derivatives

These reactions proceeded cleanly to produce pyrimidine derivatives in good yields (Entries 1-12, Table 1). This synthesis accommodated acetophenonederivatives with an electron-donating group and an electron-withdrawing group (Entries 2-12, Table 1).

Table1. Pyrimidine derivatives catalyzed by perchloric acid–functionalized silica nanosphere

Entry	Ketone	Product	Time(h)	Yield (%)
1			11	60
2			11	62
3			13	62
4			14	58
5			11	58
6			14	55
7			16	55
8			17	60
9			8	65
10			9	65
11			14	52
12			12	60

The presence of an electron withdrawing group such as a halogen at the 4-position of the phenyl ring produced entries 2-5. Substitution of the methyl group of acetophenone with larger alkyl groups had a dramatic effect on the pyrimidine synthesis (Entry 6, Table 1). Bulky isopropyl group substitution significantly reduced the product yield (Entry 11, Table 1).

The advantages to use (SPA-NS) as a catalyst [Figure 1,2] are as follows:

1. The preparation of (SPA-NS) is easy.
2. It can be separated by simple methods.
3. The catalyst could be used at least five times.
4. The present methodology offers simple and green procedure rather than other method.

To optimize the reaction conditions, we selected the synthesis (1) as a model reaction. The better yields were obtained with the use of solvent free at 85 °C (Table 2).Perchloric acid–functionalized silica nanosphere is an excellent catalyst over other catalysts (Table 3).

The catalyst could be used at least five times without any change in the activity. The reusability of this catalyst is exemplified by the synthesis (1)in the presence of the recycled catalyst, which gave the product in 70, 65, 62, 60 and 57% yields after five runs (Figure 1).

A plausible mechanism for the coupling reaction is shown in Scheme 2. Perchloric acid–functionalized silica nanosphere activated acetal with the starting enamine and the reaction of vinylamidine 2 with another acetal.Species and the surface of SPA-NS are active [16].

Table 2. Effect of different condition and temperature for preparation of compound (1)

Condition	Temperature(°C)	Time (h)	[a]Yield(%)
CH_2Cl_2	80	8	63
$CHCl_3$	80	8	51
CH_3OH	80	12	10
CH_3CN	80	11	12
n-Hexane	80	10	17
Solvent-free	75	6	59
Solvent-free	85	11	70
Solvent-free	100	6	65

[a]Isolated yield

Table 3. The activity of various catalysts on the reaction of compound (1)

Catalyst	Temperature(°C)	Time (h)	[a]Yield(%)
$ZnCl_2$ [14]	100	72	70
TBBDA [16]	110-120	13	66
(SPA-NS)	85	11	70

If SiO_2 (amorphous) was directly used as a catalyst, the yield of product (1) was 41 % after 18 h. The yield of product (1) was 45% after 16 h by silica nanosphere, and 50 % (1) after 15 h by ordinary SiO_2-$HClO_4$ as a catalyst.

We have compared acidic catalysts. Some of these catalysts had difficult recovery and purification (Table 4).

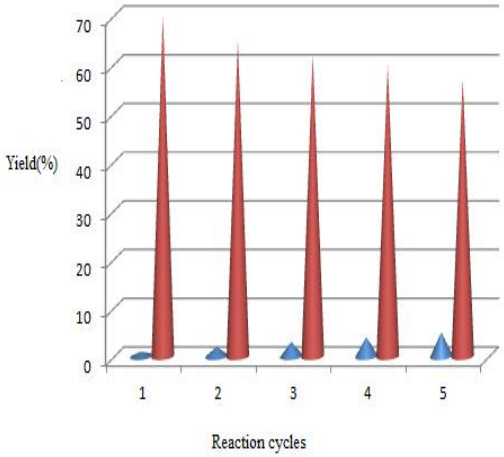
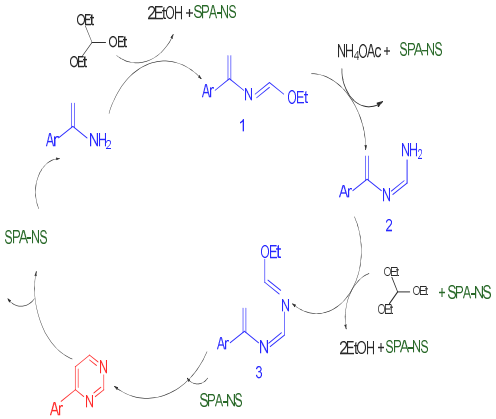


Figure 1. Reusability of the catalyst



Scheme 2. A Plusible Mechanism

Table 4. The activity of acidic catalysts on the reaction of compound (1)

Entry	Catalyst	Time (h)	Yield (%)	Runs of Reusability
1	Nano-SiO_2-$HClO_4$ (85 °C)	11	70	5
2	ordinary SiO_2-$HClO_4$(100 °C)	15	50	3
3	ordinary-SiO_2-H_2SO_4(100 °C)	14	51	3
4	ordinary-SiO_2-H_3PO_4(100 °C)	15	50	3
5	Nano-SiO_2-H_3PO_4(85 °C)	12	73	5

Conclusion

Thus far, we have discribed a simple and efficient synthesis of 4-phenylpyrimidine derivatives *via* a perchloric acid–functionalized silica nanosphere catalyzed reaction of a functionalized enamine, or an R-acidic ketone, with an orthoester and ammonium acetate. The advantages of this new method are efficient yields, shorttime, recyclability of the catalyst, green method and mild condition.

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