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SILICA SUPPORTED PERCHLORIC ACID ($HCLO_4$-SIO_2) AS ECO-FRIENDLY REUSABLE CATALYSTS FOR GREEN SYNTHESIS OF TETRAHYDROBENZO[B]PYRAN DERIVATIVES BY GRINDING METHOD

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Abstract:-Silica supported perchloric acid ($HClO_4$-SiO_2) is explored as reusable catalyst for the synthesis of 4*H*-benzo[b]pyran derivatives from one-pot three component condensation of aldehydes, dimedone and malononitrile by using grinding method. This method provides several advantages including environmental friendliness, short reaction times, high yields and a simple work-up procedure.

Keywords : Silica supported perchloric acid ($HClO_4$-SiO_2), aldehyde, dimedone, malononitrile, tetrahydrobenzo[b]pyran.

Introduction

Benzopyrans and their derivatives, in particular have shown several biological and pharmacological properties, such as spasmolytic, diuretic, antianaphylactin, antisterility and anticancer agents [1]. The polyfunctionalized benzopyrans were used as cosmetics, pigments and biodegradable agrochemicals [2]. Due to their applications, the syntheses of heterocyclic derivatives of these ring systems have great importance in medicinal chemistry and organic synthesis. Strategies for the synthesis of these compounds have varied from one-pot to multi-step approaches [3]. Recently, there have been many methods reported for the preparation of 4*H*-benzo[b]pyrans through two-component or three-component condensations including the use of microwave irradiation [4], ultrasonic irradiation [5] or use of (diethylamino) propylated silica [6], hexadecyltrimethyl ammonium bromide (HTMAB) [7], hexadecyldimethyl ammonium bromide (HDMBAB) [8], (s)-proline [9] and rare earth perfluorooctanoate [$RE(PEO)_3$] [10] as catalysts. Each of the protocols has its own merit, with at least one of the drawbacks of low yield, long reaction times, harsh reaction conditions and tedious work-up procedures. Hence, improved methods for multicomponent synthesis of tetrahydrobenzo[b]pyran using inexpensive and less toxic reagents coupled with simple reaction conditions and easier work-up procedures are required.

Grinding method has increasingly been used in organic synthesis in recent years compared with traditional methods. Many organic reactions by grinding has been reported such as Grignard reaction [11], Reformatsky reaction [12], Aldol condensation [13], Dieckmann condensation [14], phenol coupling reaction [15], reduction [16] and synthesis of dicyclopropanes by grinding method [17].In the past few years, silica supported catalysts gained much attention in organic synthesis because of their unique features like high efficiency due to large surface area, high mechanical, and thermal stabilities, greater selectivity, low toxicity, reusability, and high selectivity. Moreover, the catalysts are simple, secure and easy in handling. By-products and wastages could also be minimized using these catalysts Silica supported perchloric acid ($HClO_4$-SiO_2) has emerged as a powerful approach in the synthesis of propargyl indoles [18].Octahydro-quinazolin-2, 5-diones [19], imidazo[1,2-a] pyridines [20],tetrahydropyranylation [21] of alcohols and phenols, synthesis of heterocyclic pyrazoles and pyranyl pyridines [22], α-amino phosphonates [23], Biginelli condensation [24], Hantzsch condensation [25], synthesis of homoallylicamines & quinazolinones [26].

As part of our work on one-pot multicomponent reactions by grinding for the synthesis of tetrahydrobenzo[b]pyran derivative of biological importance, we wish to report a general and highly efficient procedure for the preparation of this kind of compounds. It is achieved *via* a one-pot three component condensation reactions between aromatic aldehyde **1(a-k)**, malononitrile **2** and dimedone **3** using $HClO_4$-SiO_2 as a catalyst. (Scheme 1)

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EXPERIMENTAL

The melting points of compounds were uncorrected and taken in an open capillary using a paraffin bath. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique.

Preparation of $HClO_4$-SiO_2 catalysts: A 70% aqueous perchloric acid (1.8 g, 12.5 mmol) was added to a suspension of SiO2 (230 400 mesh, 23.7 g) in ether (70 ml). The mixture was concentratedand the residue was heated at 100°C for 72 h under vacuum to give $HClO_4$-SiO_2 (0.5 mmol/g) as free flowing powder (50 mg=0.025 mmol of $HClO_4$). [27].

General procedure for the synthesis of tetrahydrobenzo[b]pyran derivatives:

A mixture of an aromatic aldehyde **1 (a-k)** (1 mmol), malononitrile **2** (1 mmol) and $HClO_4$-SiO_2 (5mol%) was stirred for 1-2 min. and in resulting mixture dimedone **3** (1 mmol) was added and ground at room temperature with pestle in mortar. The completion of reaction was monitored by TLC. Solid was filtered, dried and crystallized from ethanol. The products **4 (a-k)** were confirmed by comparisons with authentic samples. IR, ^{1}H NMR and mass spectra.

Spectral data of principal compounds

(4a) IR (KBr, cm^{-1})V_{max} 3282, 3250, 3045, 2992, 2980, 2245, 1655, 1600, 1480, 740, 700.
^{1}H NMR ($CDCl_3$, δ ppm): 1.02(3H, s, CH_3), 1.12 (3H, s, CH_3), 2.23 (2H, s, CH_2), 2.57 (2H, s, CH_2), 3.08 (2H, br., s, NH_2), 4.30 (1H, s, CH), 7.27 (5H, s, ArH).
MS: m/z (%) 294.

(4b) IR (KBr, cm^{-1})V_{max} 3400, 3300, 3040, 2990, 2985, 2970, 2245, 1680, 1610, 1515, 840.
^{1}H NMR ($CDCl_3$, δ ppm): 0.97 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.15 (2H, s, CH_2), 2.50 (2H, s, CH_2), 3.28 (2H, br., s, NH_2), 3.70 (3H, s, OCH_3), 4.10 (1H, s, CH), 6.87–6.98 (4H, m, ArH).
MS: m/z (%) 324.

(4c) IR (KBr, cm^{-1})V_{max} 3300, 3200, 3045, 2990, 2975, 2240, 1650, 1610, 1490, 850.
^{1}H NMR ($CDCl_3$, δ ppm):1.01 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.24 (2H, s, CH_2), 2.60 (2H, s, CH_2), 3.08 (2H, br., s, NH_2), 4.30 (1H, s, CH), 7.30 (4H, s, ArH).
MS: m/z (%) 328.

(4e) IR (KBr, cm^{-1})V_{max} 3300, 3200, 3045, 2990, 2975, 2240, 1680, 1600, 1450, 770.
^{1}H NMR ($CDCl_3$, δ ppm): 1.09 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.20 (2H, s, CH_2), 2.55 (2H, s, CH_2), 3.05 (2H, br., s, NH_2), 4.88 (1H, s, CH), 7.29 (4H, s, ArH).
MS: m/z (%) 328.

(4f) IR (KBr, cm^{-1})V_{max} 3650, 3327, 3165, 2191, 1664.
^{1}H NMR ($CDCl_3$, δ ppm): 1.07 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.16–2.25 (m, 2H, CH_2), 2.45 (s, 2H, CH_2), 4.26 (s, 1H, CH), 5.34 (s, 2H, NH_2), 6.75–7.03.
MS: m/z (%) 296.

(4i) IR (KBr, cm^{-1})V_{max} 3498, 3308, 3258, 2195, 1678.
^{1}H NMR ($CDCl_3$, δ ppm): 1.05 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.20–2.22 (m, 2H, CH_2), 2.43 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.29 (s, 1H, CH), 5.25 (s, 2H, NH_2), 6.60–6.78 (m, 3H, ArH), 6.80 (s, 1H, OH).
MS: m/z (%) 327.

(4j) IR (KBr, cm^{-1})V_{max} 3400, 3300, 3050, 2995, 2980, 2245, 1680, 1600, 730.
^{1}H NMR ($CDCl_3$, δ ppm): 1.00 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.28 (2H, s, CH_2), 2.55(2H, s, CH_2), 3.05 (2H, br., s, NH_2), 4.44 (1H, s, CH), 6.18–7.37 (3H, m, ArH).
MS: m/z (%) 284

(4k) IR (KBr, cm^{-1})V_{max} 3400, 3300, 3050, 2990, 2985, 2240, 1680, 1600, 730.
^{1}H NMR ($CDCl_3$, δ ppm): 1.02 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.30 (2H, s, CH_2), 2.54 (2H, s, CH_2), 3.05 (2H, br., s, NH_2), 4.44 (1H, s, CH), 6.18–7.37 (3H, m, ArH).
MS: m/z (%) 301.

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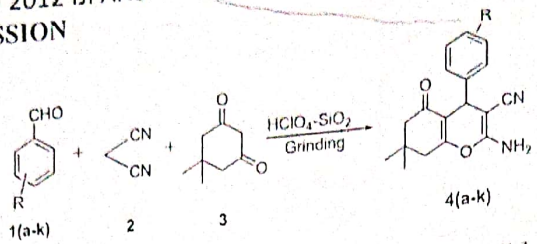
RESULT AND DISCUSSION



Scheme 1: Synthesis of tetrahydrobenzo[b]pyran

In continuation of our research work on the development of novel synthetic methodologies [28,29], herein, we would like to report the greener synthesis of tetrahydrobenzo[b]pyran derivatives by grinding using ecofriendly catalyst i.e $HClO_4$-SiO_2.

To optimize the reaction conditions we have chosen, 4-chlorobenzaldehyde **1c**, malononitrile **2** and dimedone **3** as the model reaction as shown in Table 1.

In order to verify the role of grinding, we have examined the model reaction stirred and left standing for overnight, reaction remain incomplete. To make this method simple, economical and efficient, we have used a glass mortar and pestle to repeat this experiment under the same conditions. The reaction complete within 10 min with excellent yields. Also, we observed that, the reaction in the absence of $HClO_4$-SiO_2 does not proceed under similar conditions even after grinding for 30 min (Table 1, entry 1). The same reaction was carried out in the absence of grinding, the result was showing approximately 65% conversion of reactants into the products (entry 2). Further we have observed that, the model reaction was carried out in presence of 5 mol% of $HClO_4$-SiO_2 followed by grinding was found to be most effective (Table 1, entry 3).

Table 1: Optimization of reaction condition for model reaction (**4c**)

Entry	Reaction condition	Yield (%)[a]
1	Grinding without $HClO_4$-SiO_2	No reaction
2	Stirring with $HClO_4$-SiO_2 for 3 hr	65
3	Grinding using $HClO_4$-SiO_2	88

[a]Isolated yield.

Use of 5 mol% of catalyst is sufficient to push the reaction forward. Higher amount of the catalyst did not improve catalyst for this reaction, as shown in (Table 2).

Table 2:-Screening of catalyst concentration on model reaction.

Entry	Catalyst (mol %)	Yield (%)[a]
1	1	46
2	2	50
3	3	67
4	4	70
5	5	88
6	6	88

[a]Isolated Yields.

The scope and generality of the present method were then further demonstrated by reaction of various aldehydes with malononitrile and dimedone. In all cases good yields and selectivity were obtained as shown in Table 3.

We have also observed that the electronic effects and nature of substituents on the aromatic ring showed strongly obvious effects in terms of reaction time and yield. When aromatic aldehydes

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containing electron donating groups (-OMe, -OH) were employed a longer reaction time was required than those reaction encountered with electron withdrawing groups (-NO_2, -X) on aromatic ring.

Table 3: .Synthesis of tetrahydrobenzo[b]pyran derivatives catalysed by sodium hypochlorite[a].

Entry	R	Product	Time(min)	Yield (%)[b]	M.P (°C)	
					Found	Reported
1	H	4a	12	82	229-230	229-231
2	4-OMe	4b	12	84	199-200	199-201
3	4-Cl	4c	10	88	209-211	208-210
4	2-Cl	4d	10	86	214-216	215-216
5	3-OH	4e	25	80	235-237	236-238
6	4-OH	4f	22	87	212-214	214-215
7	2-NO_2	4g	10	88	182-183	180-182
8	3-NO_2	4h	12	86	213-215	213-214
9	4-OH,3-OMe	4i	25	84	228-230	229-231
10	2-Furyl	4j	25	86	217-119	218-220
11	2-Thionyl	4k	15	85	210-113	210-212

[a]*Reaction condition:* **1(a-k)** (1 mmol), **2** (1 mmol), **3** (1 mmol) and (5 mol%) of $HClO_4$-SiO_2 by grinding method.

[b]Isolated yield.

Reusaility of the catalysts:- After completion of the reaction, the catalysts were separated from the reaction mixture by simple filtration and treated with ethyl acetate. Organic layer was sepaerated, and the obaitned catalyst was dried. This step ensured to purify catalyst free from any residual product. After drying, the asobainedcatalyst was used again to in a next batch of experiments. Under similar reaction conditions, the recycled catalysts were found active, with only slight reduction of activityfor four to five consecutive

Experiments.(**Table 4**)

Table 4

Entry	1	2	3	4	5
Cycle	Fresh	First reuse	Second reuse	Third reuse	Fourth reuse
Yield	88	87	87	86	85

The proposed mechanism for this reaction is as given in Figure 1. The mechanism suggests that in **step-1** Knoevenagel condensation takes place to form the α-cynocinnamonitrile derivative. In **step-2** the active methylene of dimedone reacts with the electrophilic C=C double of α-cynocinnamonitrile giving the intermediate 6, which tautomerizes into 7. The latter is then cyclized by nucleophilic attack of the OH group on the cyano (CN) moiety, giving intermediate 8. Finally, the expected product 4 is afforded by tautomerization (8→4).

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Mechanism:

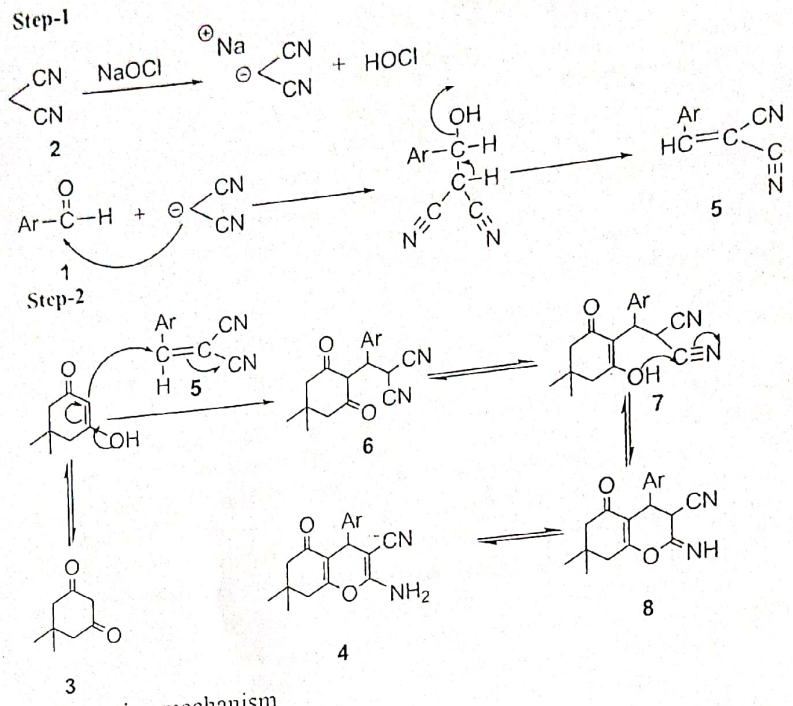

Figure 1 Proposed reaction mechanism

Conclusion

In conclusion, the procedure demonstrated that the reaction using grinding is faster and show an efficient catalytic activity of $HClO_4$-SiO_2 for a one-pot synthesis of tetrahydrobenzo[b]pyran derivative. It is significant that experimental procedure is very simple and more efficient than originally reported traditional reaction. The significant advantages offered by this methodology are operational simplicity, general applicability to all type of aldehyde, mild reaction condition, and excellent yield of product, environmentally benign and with no harmful organic solvent.

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