

1, 3, 5-Tris (2-hydroxyethyl) Isocyanurate Functionalized SBA-15 (THEIC-SBA-15): as a Novel Heterogeneous Nano-Catalyst for the One-Pot Three-Component Synthesis of Tetrahydrobenzo [b] Pyrans in Water

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Abstract: 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized SBA-15 is used as a novel, highly efficient, and recyclable heterogeneous nano-catalyst for the one-pot 3-component synthesis of tetrahydro benzo [b] pyran derivatives. These unique derivatives were synthesized through the condensation reactions of the enolizable compounds, different aldehydes, and malononitrile (or ethyl cyanoacetate) under the mild reaction conditions, in the short reaction times, and gives excellent yields in the refluxing H₂O as a green solvent. The accuracy of synthesizing functionalized SBA-15 was confirmed with FT-IR spectroscopy. Then the catalyst was characterized by scanning electron microscopy (SEM), transition electron microscopy (TEM), and surface area analysis (BET). TEM images demonstrated that the synthesized catalyst had a hexagonal structure. Simplicity in the operation, rapidity, high yields, low cost, mild reaction conditions, catalyst with low loading, evading the usage of toxic change metals, stability, and the catalyst reusability are the main advantages of the proposed protocol.

Keywords: Nano-catalyst; Mesoporous material; SBA-15; Tetrahydrobenzo [b] pyrans; Green chemistry.

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1. Introduction

In recent years, the development of green protocols in the chemical and industrial processes has attracted great attention among the various research groups all over the world. The heterogeneous catalysts compared to the homogeneous ones, can offer remarkable advantages according to the reusability and stability in the chemical reactions [1-4]. Therefore, the design of a heterogeneous catalyst with higher activity and efficiency has been directed towards the research and development of new stable supports, complexes, and other catalytic species on nanostructured materials. Due to the higher surface area and thermal stability of the silica-based mesoporous materials compared to other nano-structures, they are the most attractive for such purposes [5-8]. Silica-based mesoporous materials are appropriate to be functionalized owing to the accessibility of the functional hydroxyl groups [9-11]. SBA-15, as

mesoporous silica with 2D, ordered channels, and higher stability compared to MCM-types, is an excellent candidate for the different types of catalytic applications. Silica-based mesoporous materials such as SBA-15 have opened an active area in the scientific research and organic synthesis for their use as catalyst-immobilization matrixes [12-15].

These materials display a large specific surface area, narrow pore-size distribution in between two to ten nm, tunable pore size, thermal, chemical, and mechanical stability, highly uniform pore distribution, high adsorption capacity, and an ordered porous network for the fast diffusion and easy access of the substrates and reaction products—especially, SBA-type materials that possess more silanol groups, larger pore sizes, and thicker walls. The silanol functionalization groups on the surface of the mesoporous materials mainly enhance their catalytic ability in the organic reactions [16-19].

Nowadays, the development of environmentally friendly and efficient procedures for the synthesis of interesting biological compounds has been a major issue in academic and industrial researches [16]. Multicomponent reactions (MCRs) have appeared as an important and attractive research area in the organic and medicinal chemistry [20]. MCR methodologies can improve the atom economy and offer efficiency and diversity in the synthesis of the complex molecules, particularly heterocyclic compounds, in a fast and often simple procedure. In such reactions, three or even a lot of reactants gather together in a single response vessel to make the new products that have specified portions of all the components. From the environmental and economic viewpoints, MCRs are well known as valuable tools for the preparation of structurally diverse drug-like compounds [16, 21-24].

Also, numerous organic reactions have been done in the water as a green solvent and reaction medium. It has several advantages, such as abundance, availability, non-polluting nature, inexpensive, and safety [16, 21, 25, 26]. Recently, tetrahydro benzo [b] pyrans have attracted great attention due to their biological and pharmacological properties [27-29]. Furthermore, they are the structural unit of many natural products, which are generally found in the comestible fruits and vegetables [27]. These compounds have various properties such as anti-tumoral, anticoagulant, anticancer, anti-HIV, spasmolytic, antioxidant, diuretic, and anti-anaphylactic activity [27, 30, 31]. Also, some 2-aminotetrahydropyrans have been reported as suitable biological, cosmetics, and photoactive materials (Fig. 1) [30, 32, 33]. Due to the distinct aforementioned properties of 4H-pyrans, different procedures have been reported for the synthesis of 4H-pyrans in the presence of several catalysts such as SBPPSP [33], SnCl₂/Nano SiO₂ [34], TSA, Nano-TiO₂/H14[NaP5W30O110] [35], Nano-ZnO [36], [HMIM]C(CN)₃ [37], TFE [38], Supported-KF [39], Na₂CO₃ [26], Urea [40], [γ -Fe₂O₃@HAp Si (CH₂)₃ AMP] [32], Nanozeolit [41], Fe₃O₄@SiO₂-imid-PMA [42], Aminopropylated silica gel [43] DBSA [44], potassium phthalimide (POPI) under mechanochemical ball-milling conditions [45], Borax, [BMIm]BF₄ [25], K₃PO₄ [44]. However, some limitations such as toxic or expensive catalysts, reagents, and solvents, high catalyst loading, harsh reaction conditions, the use of heavy metals, low yields, long reaction times, and tedious work-up procedures are associated with many of the reported catalytic methods for the synthesis of 4H-pyran derivatives. Moreover, in many of the proposed methods, catalysts are not recyclable.

Therefore, the development of a green and efficient process in order to the synthesis of 4H-pyrans is of great importance to overcome these drawbacks. There is no previous report on the use of 1, 3, 5-tris (2-hydroxyethyl) isocyanurate (THEIC) for the functionalization and modification of SBA-15. The heteroaromatic isocyanurate ring of THEIC has three flexible and nonpolar alkyl arms and is well known for its binding ability to the transition metals.

Furthermore, it is thermally very stable and is used to enhance the physical properties of a wide variety of polyurethanes, polyureas, and polyesters as coating materials in the commercial systems. These unique properties, as well as other significant properties associated with SBA-15, make 1, 3, 5-tris (2-hydroxyethyl) isocyanurate functionalized SBA-15 (SBA-15-THEIC (1), Scheme 1) as a promising nanomaterial, catalyst or support depending on the used conditions compared to the other modified SBA-15 materials. As part of our interest in the developing new eco-friendly, efficient, and green methodologies and explore the application of isocyanurate functionalized materials in different fields as well as MCRs, we herein will report catalytic activity of the THEIC functionalized SBA-15 (1) nanomaterial as a novel, green, reusable, and highly effective heterogeneous nano-catalyst for the one-pot three-component synthesis of tetrahydro benzo [b] pyran derivatives under the reflux conditions in water (Scheme 1).

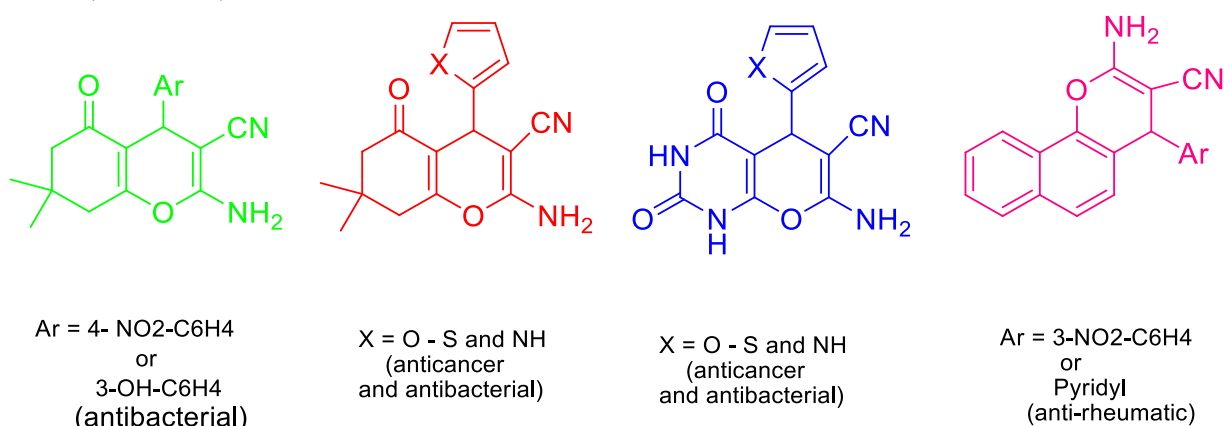
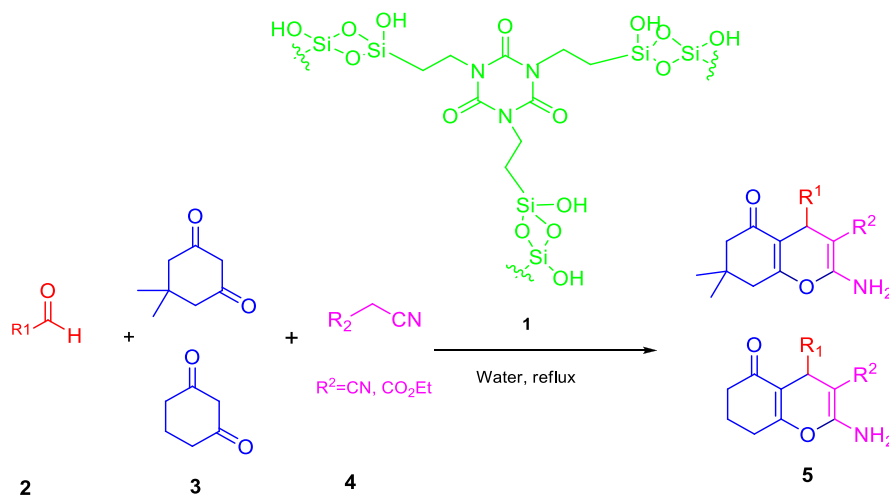


Figure 1. Selected examples of biologically and pharmacologically active 4H-pyrans



Scheme 1. One-pot three-component reaction of aldehydes, enolizable compounds, and malononitrile catalyzed by THEIC functionalized SBA-15 (1) nanomaterial.

2. Materials and Methods

2.1. General.

All chemicals were purchased from Sigma Aldrich and used as received. IR spectra were recorded on a Shimadzu FT-IR-8400S spectrophotometer in the KBr pellet. The development of the responses was evaluated by TLC using Merck 0.2 mm silica gel 60 F-254 Al-plates. Melting points were determined in the capillary tubes in the Electrothermal 9100

apparatus. Transmission electron microscopy (TEM) images were obtained using EM10C-100 kV of Zeiss Company, Germany. Scanning electron microscopy (SEM) images were collected with a sigma of Zeiss Company, Germany. ¹H NMR (500 MHz) spectra were obtained using a Bruker DRX-500 AVANCE spectrometer in DMSO at ambient temperature. The BET specific surface area of the catalyst was obtained using equipment ASAP 2020™ micromeritics, and the ultrasonic probe used is TOPSONICS (20 kHz-400W) model.

2.2. General process for the synthesis of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized SBA-15.

In a traditional synthesis procedure, 2 g of the Pluronic P123 block copolymer and HCl solution (2 M) were stirred at 40 °C until P123 completely dissolved and the homogenous mixture observed. Afterward, 4.50 g TEOS was added slowly to the mixture and was stirred for 24 h. Subsequently, the obtained mixture was transferred into the Teflon autoclave for hydrothermal treatment and heated at 100 °C for 24 h. The resulted gel was filtered, washed, and dried at 100 °C for 12 h. Finally, template removal carried out by calcination for 6 h at 540 °C. To modification of the mesoporous SBA-15, 1 mmol of 1, 3, 5-tris (2-hydroxy ethyl) isocyanurate, and 3 mmol of 4-toluenesulfonyl chloride were mixed in a test tube in the acetone media. The obtained mixture was placed in an ultrasonic probe at 60 °C for 1h. In the next step, 261 mg of SBA-15 was added to the test tube, and the reaction mixture was syndicated at 60 °C for 1.5 h. The white solid was achieved, filtered, and dried under the vacuum.

2.3. General process for the synthesis of 2-amino-4H-chromene derivatives in the water.

A mixture of aldehydes (2, 1 mmol), dimedone or 1, 3-cyclohexanedione (3, 1 mmol), malononitrile or ethyl cyanoacetate (4, 1 mmol), and 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized SBA-15 (10 mg) was added to a 50-mL round-bottom flask equipped with a magnetic bar and condenser, and the mixture reaction was stirred under the reflux conditions in the 3ml of water for the mentioned time shown in Tables 2 and 3, respectively. The progress of the reaction was monitored by TLC as well as precipitating out of the products from the reaction mixture. After completion of the reaction, the solvent was evaporated under the reduced pressure. Then 5 mL of EtOH was added to the combination to simplify the separation of the heterogeneous catalyst during the recrystallization from EtOH to give pure products. All of the compounds were characterized by ¹H-NMR, IR, and melting point data.

2.4. Selected spectroscopic data.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(5a): IR (KBr) 3379,3180,2189,1676,1635,1365,1215 cm⁻¹; ¹H-NMR (500 MHz, DMSO-d₆) δ= 0.95 (s, 3H, CH₃), 1.11 (s, 3H, CH₃), 2.20 (d, J=16.05 Hz, 1H), 2.30 (d, J=16.05 Hz, 1H), 2.50 (s, 2H, CH₂), 4.38 (s, 1H, CH), 7.05 (s, br, 2H, NH₂), 7.18 (d, J= 8.25 Hz, 2H, Ar), 7.36 (d, J= 8.25 Hz, 2H, Ar). 2-Amino-4-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4g): IR (KBr) 3496, 3402, 3323, 3253, 2192, 1676, 1654, 1602, 1367, 1211cm⁻¹; ¹H-NMR (250 MHz, DMSO-d₆) δ= 1.00 (s, 3H), 1.06 (s, 3H), 2.08 (d, J = 16.25 Hz, 1H) 2.23 (d, J = 16.25 Hz, 1H), 2.54 (m, 2H), 3.74 (s, 3H), 4.10 (s, 1H), 6.53 (m, 1H), 6.81 (m, 2H), 6.97 (s, 2H), 8.90 (s, 1H).

3. Results and Discussion

The SBA-15 mesoporous silica was synthesized according to the described procedure by Shylesh and Singh [36]. The obtained catalyst was then characterized using various techniques including transmission electron microscopy (TEM), scanning electron microscopy (SEM), Fourier transforms infrared (FTIR) spectroscopy, and BET surface area analysis. The IR spectrum of THEIC functionalized SBA-15 (1) shows the presence of organic functional groups in the material framework. Indeed, the observed peaks at 2927 and 2850 cm^{-1} are assigned to the C–H stretching of aliphatic moieties. Moreover, the peak which has been appeared at 1699 cm^{-1} is qualified for the widening vibrations of the isocyanurate ring. On the other hand, THEIC-SBA-15 (1) showed peak at 1080 cm^{-1} corresponding to the asymmetric and symmetric vibrations of Si–O (siloxane) bonds. The broad peak appeared about 3200–3600 cm^{-1} is attributed to O–H bonds of the silanol groups.

The surface area and pore size distribution were calculated using BET and BJH methods, respectively (Fig. 2). The N₂-sorption isotherms indicated that the pore sizes of all samples are in the mesoporous range. The materials exhibited a type IV isotherm pattern with H1 hysteresis loops, which are characteristics of the mesoporous structure. This mesoporous material [THEIC-SBA-15 (1)] showed a specific surface area close to 832 m^2/g , volume pore $\approx 1.08 \text{ cm}^3/\text{g}$, and average pore diameter: 5.35 nm (Fig. 3).

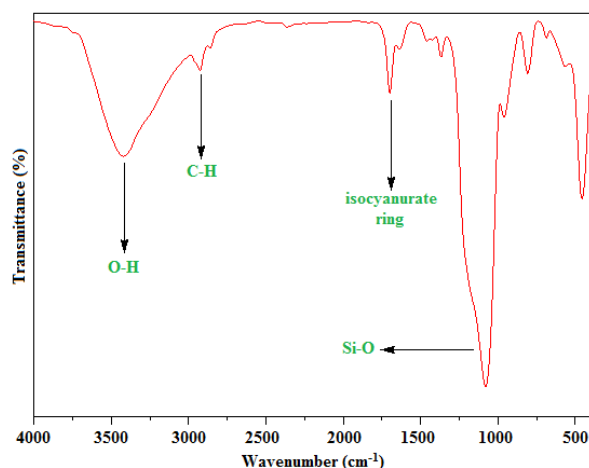


Figure 2. FT-IR spectrum of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized SBA-15 (THEIC functionalized SBA-15).

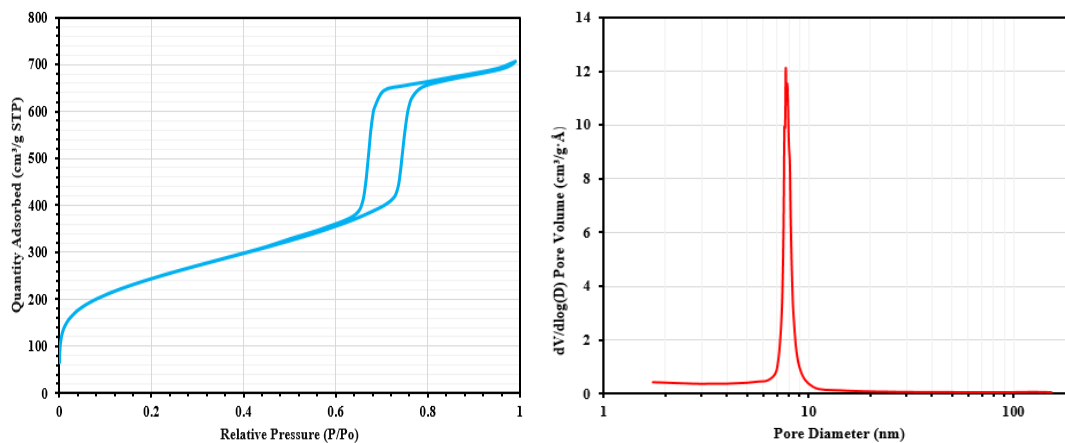


Figure 3. BET & BJH analyses of the (THEIC functionalized SBA-15) nano-catalyst.

TEM images demonstrated that the mesostructured THEIC-SBA-15 (1) exhibits ordered hexagonal structure (Fig. 4). Moreover, the comparison SEM images of SBA-15 and <https://biointerfaceresearch.com/>

THEIC-SBA-15 indicated the surface modification, the morphology of a sample, and nanoparticles. Also, the morphology of the sample was saved without noteworthy change during the modification process (Fig. 5).

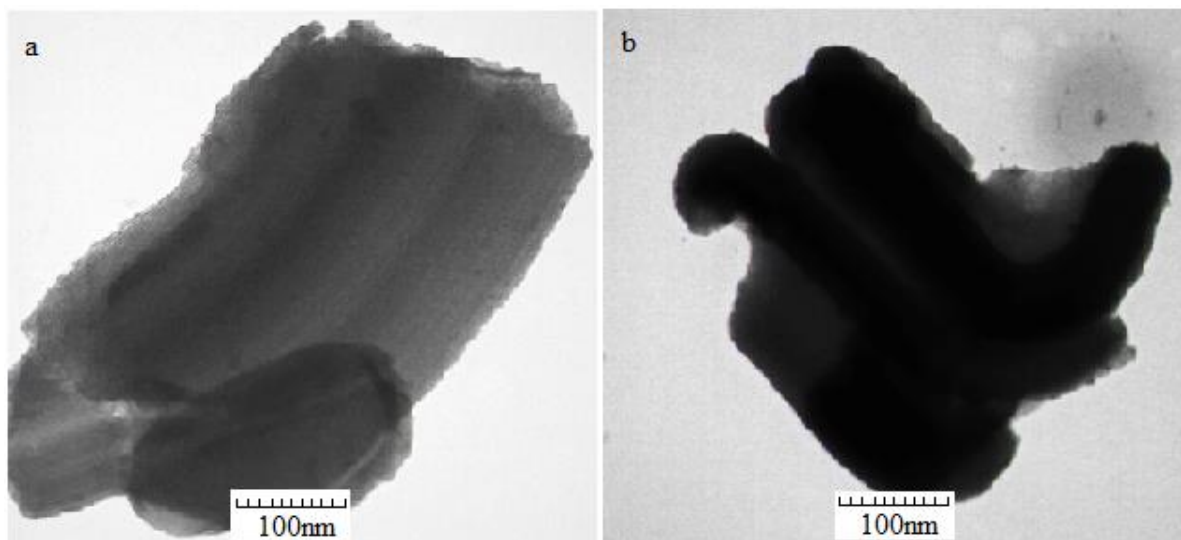


Figure 4. TEM images of a) SBA-15, and b) THEIC-SBA-15.

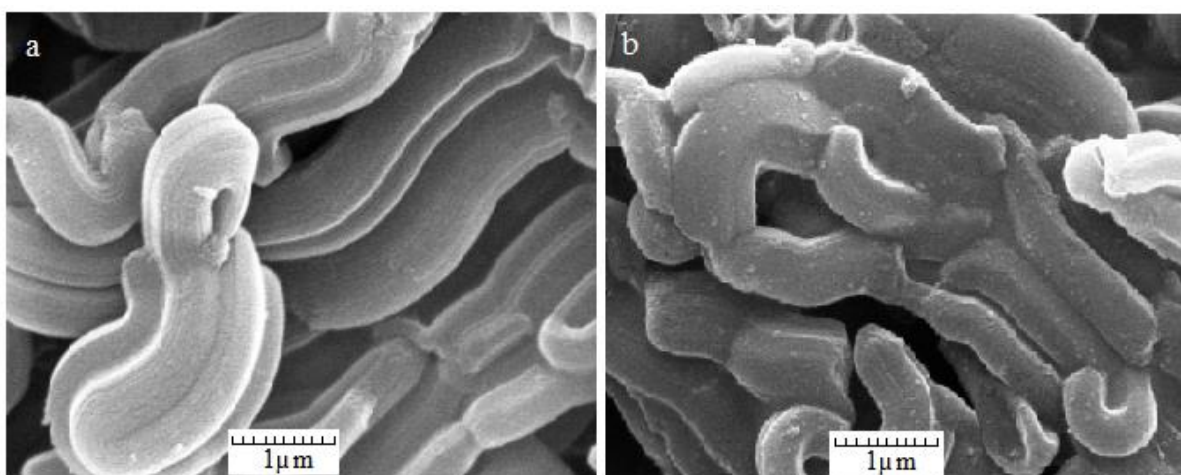


Figure 5. SEM images of a) SBA-15, and b) THEIC-SBA-15.

Table 1. Optimization of the one-pot three-component reaction of dimedone, 4-chlorobenzaldehyde, and malononitrile under various conditions.

Entry	Amount of Catalyst (mg)	Solvent	Temp (°C)	Time (min)	Yield (%)
1	-	-	100	240	50
2	5	H ₂ O	Reflux	39	80
3	10	H ₂ O	Reflux	24	90
4	15	H ₂ O	Reflux	23	90
5	10	H ₂ O	60	50	75
6	10	Aceton	Reflux	50	50
7	10	EtOH	Reflux	50	30
8	10	CCl ₄	Reflux	50	60
9	10	DMSO	Reflux	95	40
10	10	CHCl ₃	Reflux	245	45
11	10	-	-	40	55

To examine the catalytic activity of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized SBA-15 (1) and finding the optimal conditions, the three-component reaction and heteroannulation of 4-chlorobenzaldehyde (2a), dimedone (3a, pK_a = 5.23) and

malononitrile (4) (1:1:1 molar ratio) was studied as the model reaction. The results have been summarized in Table 1.

Initially, the effect of temperature, type of solvent, and amount of the loaded catalyst was examined on the model reaction. Maximum 50% of the desired product (2-amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene) (5a) was isolated under the solvent-free and catalyst-free conditions even at 100 °C after 4 hours (entry 1). Remarkably, it was detected that the use of 5 mg of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized SBA-15 (1) as a catalyst, significantly enhanced the production of the wanted product (5a) under the reflux conditions in the water (entry 2). Increasing of the loaded catalyst to 10 mg, afforded higher produce of the wanted product (5a) in the shorter reaction time under similar conditions (entry 3). However, further increasing the amount of the loaded catalyst had no significant impact on the yield and reaction time (entry 4). Moreover, the desired product was obtained in lower yield and longer reaction time at 60 °C compared to the reflux temperature in H₂O (entry 5). On the other hand, lower yields of the desired product (5a) were obtained, when the model reaction was investigated using 10 mg catalyst loading of THEIC-SBA-15 (1) in other solvents such as acetone, EtOH, CCl₄, DMSO, CHCl₃, under the reflux conditions (entries 6-10). Finally, the desired product (5a) was obtained in the lower yield when the reaction carried out in Ball-milling under the solvent-free conditions (entry 11). As a result, we suggested that the H₂O is an effective and green solvent; also, reflux conditions and 10 mg of catalyst loading of THEIC-SBA-15 (1) were selected as the optimal conditions for the synthesis of 4H-chrome derivatives.

To obtain the optimized reaction conditions, different derivatives of 2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4H-chromene (5a-k) were prepared under the optimal reaction conditions (1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized SBA-15 loading of 10 mg in H₂O under the reflux conditions) using various aromatic carbocyclic, heterocyclic or α , β -unsaturated aldehydes (2a-l) in high to excellent yields. Furthermore, when 1,3-cyclohexanedione (3b, pK_a = 5.26) was used as the enolizable component, the corresponding 2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4H-chromene derivatives (5l-r) were also achieved in high to admirable yields (see Table 2). After completion of the reaction (monitored by TLC), the catalyst 1 was easily isolated from the reaction mixture by the simple filtration.

The obtained results (Table 2) clearly shows that the desired products (5) were prepared with excellent yield under the optimized conditions in the short reaction times. Moreover, the rate of reactions was considerably influenced by the nature of the substituents on the aromatic ring of the aldehydes. Hence, aromatic aldehydes having electron-donating groups required the longer reaction time compared to the electron-withdrawing groups under similar conditions (Tables 2 and 3). These findings imply that the nucleophilic attack of the corresponding imine-ketene resonance form of malononitrile (4') to the activated aldehydes containing withdrawing groups occurs faster than ones having the electron-donating groups (Scheme 2). Consequently, corresponding Knoevenagel intermediates (III) for the aldehydes containing withdrawing groups will be formed faster. Furthermore, cinnamaldehyde (2j), furfural (2i), and thiophene-2-carbaldehyde (2h), which are susceptible to polymerization under the acidic conditions, reacted under optimal reaction conditions to afford the corresponding products, as well as, due to the lower reactivity of the ethyl cyanoacetate, the desired product was obtained in the longer reaction time compared to malononitrile (compound 5k).

Table 2. Synthesis of derivatives of 2-amino-5-oxo-5, 6, 7, 8-tetrahydro-4H-benzo[b] pyran (5) via condensation of dimedone or 1, 3-cyclohexanedione, different aldehydes and malononitrile or ethyl cyanoacetate in the presence of THEIC-SBA-15 (1).

Entry	R-CHO	Carbon acid (R ²)	Product (5)	Time (min)	Yield (%)	Mp (Obsd) (°C)	Mp (lit) (°C)	Reference
1	4-ClC ₆ H ₄ (2a)	CN	5a	24	92	206-209	207-209	[46]
2	3-NO ₂ -C ₆ H ₄ (2c)	CN	5c	20	95	212-214	214-216	[47]
3	C ₆ H ₆ (2d)	CN	5d	29	93	227-231	226-228	[46]
4	4-MeOC ₆ H ₄ (2f)	CN	5f	29	88	200-203	198-200	[46]
5	Vanillin (2g)	CN	5g	38	92	230-234	230-238	[48]
6	2-Thienyl (2h)	CN	5h	28	94	209-214	210-212	[49]
7	2-Furfural (2i)	CN	5i	29	95	220-224	220-223	[50]
8	Cinnamaldehyde (2j)	CN	5j	30	90	180-183	182-184	[51]
9	4-ClC ₆ H ₄ (2a)	COOEt	5k	60	80	150-154	153-154	[48]
10	4-ClC ₆ H ₄ (2a)	CN	5l	31	92	224-228	226-230	[49]
11	4-NO ₂ -C ₆ H ₄ (2b)	CN	5m	23	92	231-235	234-236	[52]
12	C ₆ H ₆ (2d)	CN	5o	34	90	235-239	239-241	[53]
13	4-HOC ₆ H ₄ (2e)	CN	5q	37	90	232-236	234-236	[53]
14	2-Furfural (2i)	CN	5r	35	89	232-236	234-235	[49]
15	2-ClC ₆ H ₄ (2k)	CN	5n	30	95	208-213	210-212	[52]
16	4-MeC ₆ H ₄ (2l)	CN	5p	35	85	220-226	223-225	[53]

Recyclability of the catalyst is another important aspect of this efficient, non-toxic, and eco-friendly heterogeneous nano-catalyst. In this part of the manuscript, the recycling of the catalyst was examined in the model reaction. The nano-catalyst was separated after completion of the reaction and washed with some ethanol, then dried in the oven at 70 °C. It has been shown that the THEIC-SBA-15 (1) could be recovered and reused at least three times in the subsequent runs without significant loss in its catalytic activity (Fig. 6).

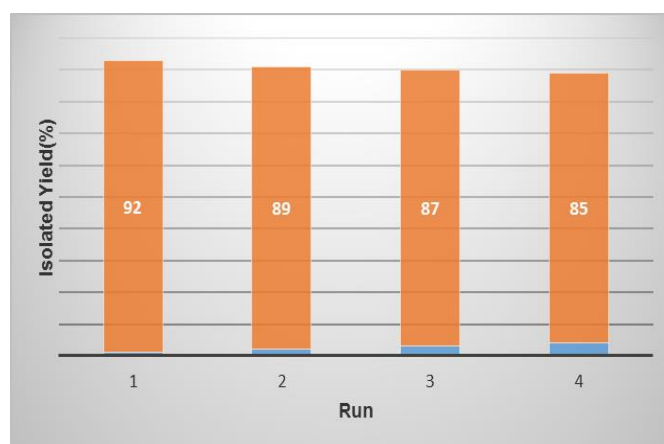


Figure 6. Reusability of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized SBA-15 (1) as nano-catalyst for the synthesis of tetrahydrobenzo [b] pyran.

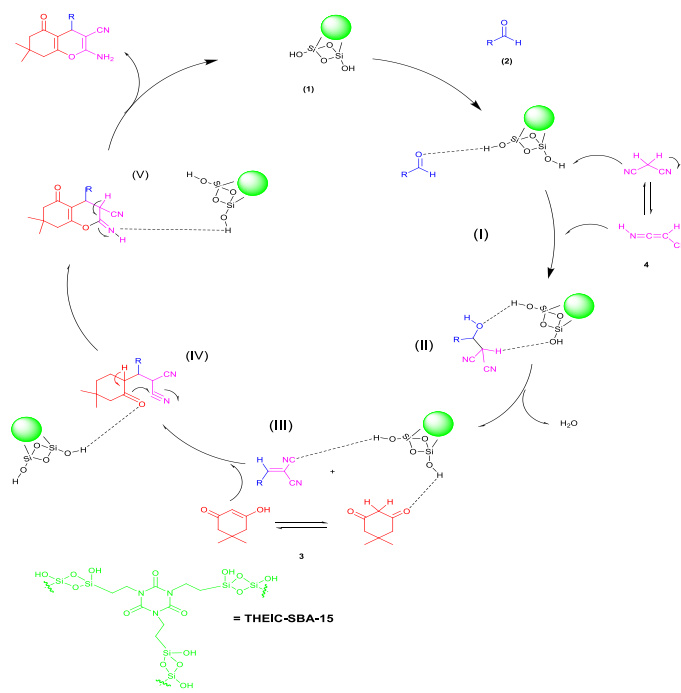
Table 3. Comparison of the catalytic efficiency of THEIC-SBA-15 (1) with the other reported catalysts for the synthesis of compound 5a.

Entry	Catalyst	Solvent	Temp (°C)	Time (min)	Yield (%)	Reference
1	Borax	EtOH	Reflux	10	82	[44]
2	Nano-ZnO	Water	80	30	95	[37]
3	Aminopropylated silica gel	Water	70	90	92	[44]
4	Urea	Water-EtOH	r.t	7h	93	[32]
5	Nano-TiO ₂ /H ₁₄ [NaP ₃ W ₃₀ O ₁₁₀]	EtOH-US	40	15	94	[36]
6	Alumina supported KF	EtOH	Reflux	120	92	[26]

To demonstrate the efficiency of the present procedure for the synthesis of different 4H-pyran derivatives, the obtained results in Table 3 are compared with those of the previously

reported procedures in the literature. THEIC-SBA-15 (1) shows higher catalytic activity in comparison to several of the others in terms of catalyst loading, evading the usage of toxic transition metals, corrosive reagents, or toxic solvents, product yield and required reaction time.

The proposed mechanism for the one-pot three-component reaction of aldehydes, different 1,3-dicarbonyl compounds, and malononitrile catalyzed by THEIC-SBA-15 (1) is shown in Scheme 2. It can be offered that the hydroxyl groups on the surface of THEIC-SBA-15 (1) are responsible for the initial activation of both carbonyl groups of aldehydes (2) and malononitrile (4) by hydrogen bonding to facilitate nucleophilic addition (Knoevenagel condensation) of the corresponding imine-ketene resonance form of malononitrile (4') on the activated aldehydes (I) and formation of intermediate (II). Then in the next step, the cyanocinnamionitrile intermediate was formed with the elimination of water molecule (III). The THEIC-SBA-15 (1) is also can increase enol form (3'), the concentration of 1,3-dicarbonyls and subsequent Michael addition to form the intermediate (IV) followed by heteroannulation of this obtained intermediate and its final tautomerization in the presence of THEIC-SBA-15 (1), as a heterogeneous nano-catalyst, affords the corresponding products 5.



Scheme 2. A plausible mechanism for the one-pot three-component reaction of aldehydes 2, different 1,3-dicarbonyl compounds and malononitrile/ethyl cyanoacetate (4) catalyzed by THEIC-SBA-15 (1) in water.

4. Conclusions

In the presented work a green, facile, new environmentally benign, and highly efficient one-pot three-component methodology has been advanced in order to the synthesis of the wide range of pharmaceutically interesting substituted tetrahydro benzo [b] pyrans in the presence of 1,3,5-Tris(2-hydroxyethyl) isocyanurate functionalized SBA-15, as a new and efficient heterogeneous catalyst via one-pot condensation of aldehydes, malononitrile, and dimedone or 1,3-cyclohexanedione in the water under the reflux condition. This procedure offers several advantages, including high yields, mild reaction conditions, the simplicity of the operation, and short reaction time. Also, this catalyst can be easily recovered and reused for several runs without significant loss of catalytic activity.

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Conflicts of Interest

The authors declare no conflict of interest.

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