

An improved one-step synthesis of 1,4-dihydropyridines via a nano-sized MCM-41-SO₃H-catalyzed three-component Hantzsch reaction under solvent free conditions

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Abstract— An efficient and eco-friendly protocol for the one-step synthesis of 1,4-dihydropyridines using the nanosized MCM-41-SO₃H-catalyzed Hantzsch three-component reaction of an aromatic aldehyde, ethyl acetoacetate, and ammonium acetate is developed. The reaction was performed under mild conditions with good to excellent yields in the absence of any byproduct. As an innovation, the present study makes use of green and solvent free conditions for this reaction. Furthermore, the present method offers several other advantages such as simple work up, a remarkable reusability of the catalyst, and short reaction time (1.30-2.30 hour).

Index Terms— 1,4-Dihydropyridines, Green and solvent free conditions, Hantzsch reaction, Nano-sized MCM-41-SO₃H

INTRODUCTION

Multicomponent¹ and domino² reactions enable the creation of a number of bonds in a single operation and have recently been in the focus of attention as one of the most powerful emerging synthetic tools for the formation of molecular diversity and complexity.³ Moreover, these reactions offer significant advantages in terms of user and eco-friendliness because their use is associated with the step reduction and atom economy. 1,4-Dihydropyridines are among the drugs that help the treatment of cardiovascular disease,⁴ are involved in many other pharmacological activities⁵⁻⁹ and perform a prominent role in CNS-targeted chemical delivery systems.¹⁰ Furthermore, despite initial, largely unfounded, misgivings about their stability, 1,4-dihydropyridines have also proven to be very important synthetic intermediates, finding application in the preparation of a large number of nitrogen alkaloids.¹¹

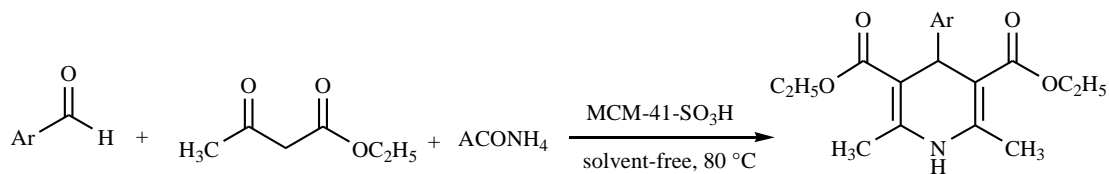
In order to model and broaden the understanding of these biological properties and to develop novel chemotherapeutic agents based upon the 1,4-DHP motif, a great deal of effort has been expended to develop effective and rapid methods for their synthesis. Generally speaking, 1,4-DHPs are synthesized adopting the Hantzsch method,¹² which involves cyclocondensation of an aldehyde, α - β -ketoester and ammonia either in acetic acid or under reflux in alcohols for long reaction times which characteristically leads to low yields.^{13,14} A quantity of modified methods have recently been worked out.^{15,16} Other procedures are made up of the use of microwaves,¹⁷ ionic liquids,¹⁸ high temperatures at reflux,¹⁹ TMSCl-NaI,²⁰ InCl₃,²¹ I₂,²² SiO₂/NaHSO₄,²³ SiO₂/HClO₄,²⁴ CAN,²⁵ Na and Cs-Norit carbons,²⁶ tetrabutylammonium hydrogen sulfate,²⁷ fermenting Baker's yeast,²⁸ organocatalysts²⁹ and metal triflates.³⁰ In recent years, further exciting possibilities have been opened up by the development of various new silica materials with ordered structure³¹ because of their ease of handling, enhanced reaction times, greater selectivity, simple workup, and recoverability of catalysts. Among the various heterogeneous catalysts, particularly, nano-sized MCM-41-SO₃H has advantages of low cost, ease of preparation, and catalyst recycling. In view of the fact that nano-sized MCM-41-SO₃H is an acid catalyst which has been used for the synthesis of 1,4-dihydropyridines, we set as our goal the development of synthesizing these biologically interesting heterocyclic compounds using MCM-41-SO₃H as a nanocatalyst.

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Results and discussion

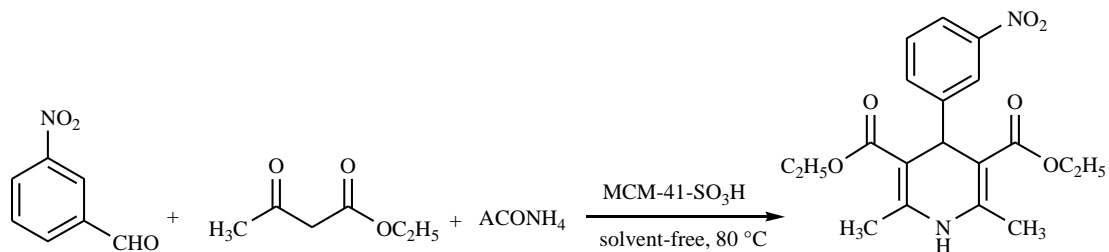
As part of our increasing interest in the nanosized MCM-41-SO₃H catalyzed reactions for some organic transformations,³² we had the opportunity to further explore its catalytic activity towards the synthesis of 1,4-dihydropyridines. Herein, we are to report a novel synthesis of 1,4-DHPs promoted by the catalytic amount of MCM-41-SO₃H under solvent free conditions with excellent yields. This method not only affords the products in excellent yields but also circumvents the problems associated with catalyst cost, handling, safety, and pollution. This catalyst is environmentally friendly for a range of organic transformations, non-volatile, recyclable, non-explosive, easy to handle, and thermally robust. Enhanced reaction times and improved selectivity were obtained in the presence of this heterogeneous catalyst. Considering the emerging importance of the heterogeneous catalyst, we are now going to explore the use of nanosized MCM-41-SO₃H as a recyclable catalyst for the synthesis of 1,4-DHPs.



Scheme1

We conducted a preliminary study in search of the best possible (the optimal) catalyst and solvent for the proposed transformation. In view of that, we used as a model the reaction involving 3-nitro benzaldehyde **1**, ammonium acetate **2** and 2 equiv. ethyl acetoacetate **3** in the presence of MCM-41-SO₃H, and the most significant and empirical data acquired are summarized in Scheme 2 and Table 1. As it can be observed, the best results were achieved with MCM-41-SO₃H (0.1 g) under solvent-free conditions, which gave the desired dihydropyridine derivative in 84% yield after 2 h under solvent-free conditions. The conditions developed for the model case were then applied to a variety of substrates. As shown in Table 2, the reaction of various aldehydes possessing either electron-donating or -withdrawing substituents with ethyl acetoacetate and ammonium acetate in the presence of MCM-41-SO₃H (0.1 g) afforded high yields of the corresponding 1,4-DHPs (75-95%) in short times. In all cases, crude products were obtained by extracting the reaction mixtures with ethyl acetate and then purified by crystallization from ethanol.

With these precedents in mind, we are now seeking to develop a new multicomponent procedure for the synthesis of dihydropyridines in such a way that it can transcend the aforementioned limitations and be complementary to the Hantzsch reaction.



Scheme2

To sum up, we have reported that MCM-41-SO₃H as a nanocatalyst is a highly efficient catalyst for the one-pot synthesis of a variety of 4-substituted-1,4-dihydropyridines by means of a three component condensation of an aldehyde, ethyl acetoacetate and ammonium acetate. The present method can be applied to a wide variety of substrates, including aromatic and heterocyclic aldehydes, and provides the corresponding 1,4-dihydropyridines in good to excellent yields. It should be noted that the proposed method brings important advantages such as short reaction times and economic viability of the catalyst, compared with conventional methods and other catalysts.

Reusability of the catalyst

Next, we investigated the reusability of MCM-41-SO₃H. With this end in view, we first put 3-nitro benzaldehyde **1**, ammonium acetate **2** and 2 equiv. ethyl acetoacetate **3** in the presence of MCM-41-SO₃H, under solvent free conditions. After the reaction was completed (monitored by TLC), the reaction mixture was extracted with ethyl acetate and subsequently purified by crystallization from ethanol. Furthermore, the catalyst was separated by simple filtration, and the recovered MCM-41-SO₃H was re-used in the succeeding reactions with no considerable reduction in activity even after three runs.

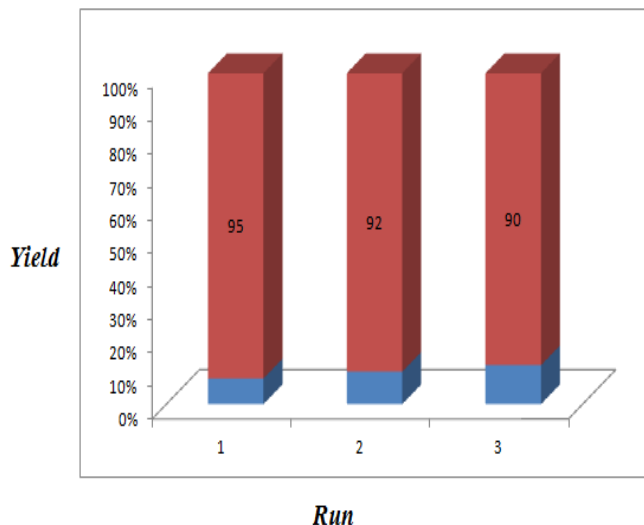


Fig1. Reusability of MCM-41-SO₃H

Synthesis and functionalization of MCM-41

In the present work, MCM-41 was modified to covalently anchor the sulfonic groups on the inside surface of the channels and provide the silica supported material with Bronsted acid properties. The MCM-41 was synthesized by using the cetyltrimethylammonium bromide (CTMABr) as the templating agent [35]. Then, the surfactant template was removed from the synthesized material through calcinations at 540 °C for 6 h.

MCM-41 was modified by means of a 100 mL suction flask equipped with a constant pressure dropping funnel containing chlorosulfonic acid (81.13g, 0.7mol) and a gas inlet tube for conducting HCl gas over an adsorbing solution. Into it was charged 60.0 g of MCM-41 and chlorosulfonic acid was then added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After the addition was completed, the mixture was shaken for 30 minutes, and the white solid (MCM-41-SO₃H) was obtained (115.9g).

MCM-41-SO₃H nanoreactor was characterized by scanning electron microscopy (SEM), and X-ray diffraction (XRD). The SEM image of mesoporous MCM-41-SO₃H was taken using 2 minutes gold coat for high magnification and is shown in Figure 2. XRD analysis was performed from 1.5° (2θ) to 10.0° (2θ) at a scan rate of 0.02° (2θ)/sec. The XRD patterns of the synthesized MCM-41-SO₃H sample are presented in Figure 3. The sample of MCM-41-SO₃H produced relatively well-defined XRD patterns, with one major peak along with three small peaks identical to those of MCM-41 materials.

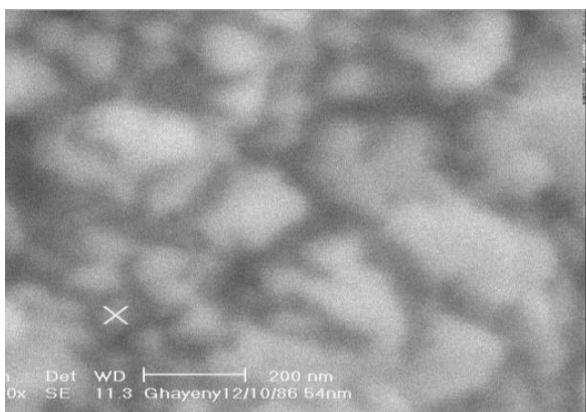


Fig2:SEM images of MCM-41-SO₃H

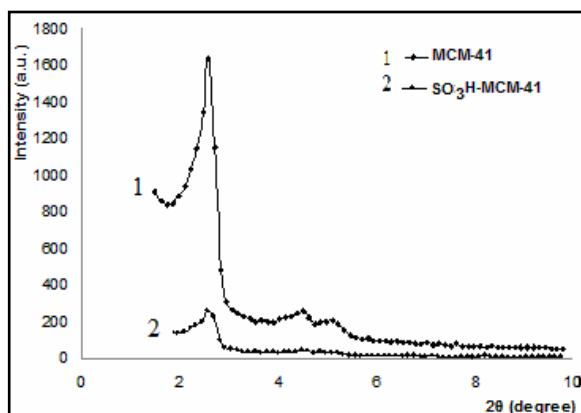
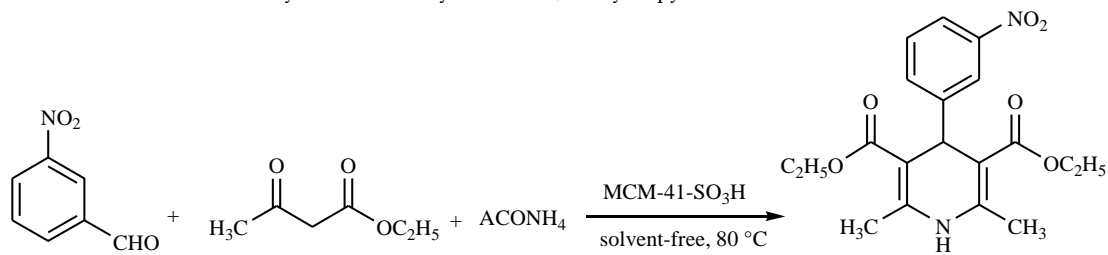


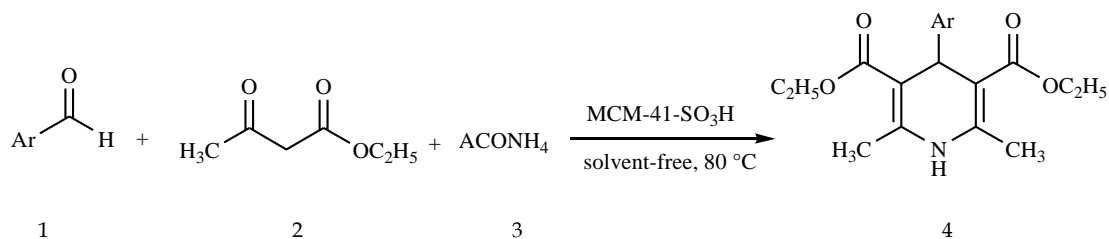
Fig3:XRD Patterns of MCM-41 and MCM-41-SO₃H

Table 1: MCM-41-SO₃H -catalyzed Hantzsch synthesis of 1,4-dihydropyridine under different conditions



Entry	Conditions	Solvent	Catalyst(g)	Time (h)	Yield (%)	R
1	MCM-41-SO ₃ H, 80 °C	C ₂ H ₅ OH	0.05	3.35	35.7	3-Nitro
2	MCM-41-SO ₃ H, 80 °C	H ₂ O	0.05	2.30	44	3-Nitro
3	MCM-41-SO ₃ H, 80 °C	CH ₃ CN	0.05	3.50	27	3-Nitro
4	MCM-41-SO ₃ H, 80 °C	None	0.03	3.30	48	3-Nitro
5	MCM-41-SO ₃ H, 80 °C	None	0.05	3	61	3-Nitro
6	MCM-41-SO ₃ H, 80 °C	None	0.08	2.30	76	3-Nitro
7	MCM-41-SO ₃ H, 80 °C	None	0.1	2	84	3-Nitro
8	MCM-41-SO ₃ H, 80 °C	None	0.15	2	84	3-Nitro
9	MCM-41-SO ₃ H, 100 °C	None	0.1	2	84	3-Nitro
10	MCM-41-SO ₃ H, 60 °C	None	0.1	4	58	3-Nitro

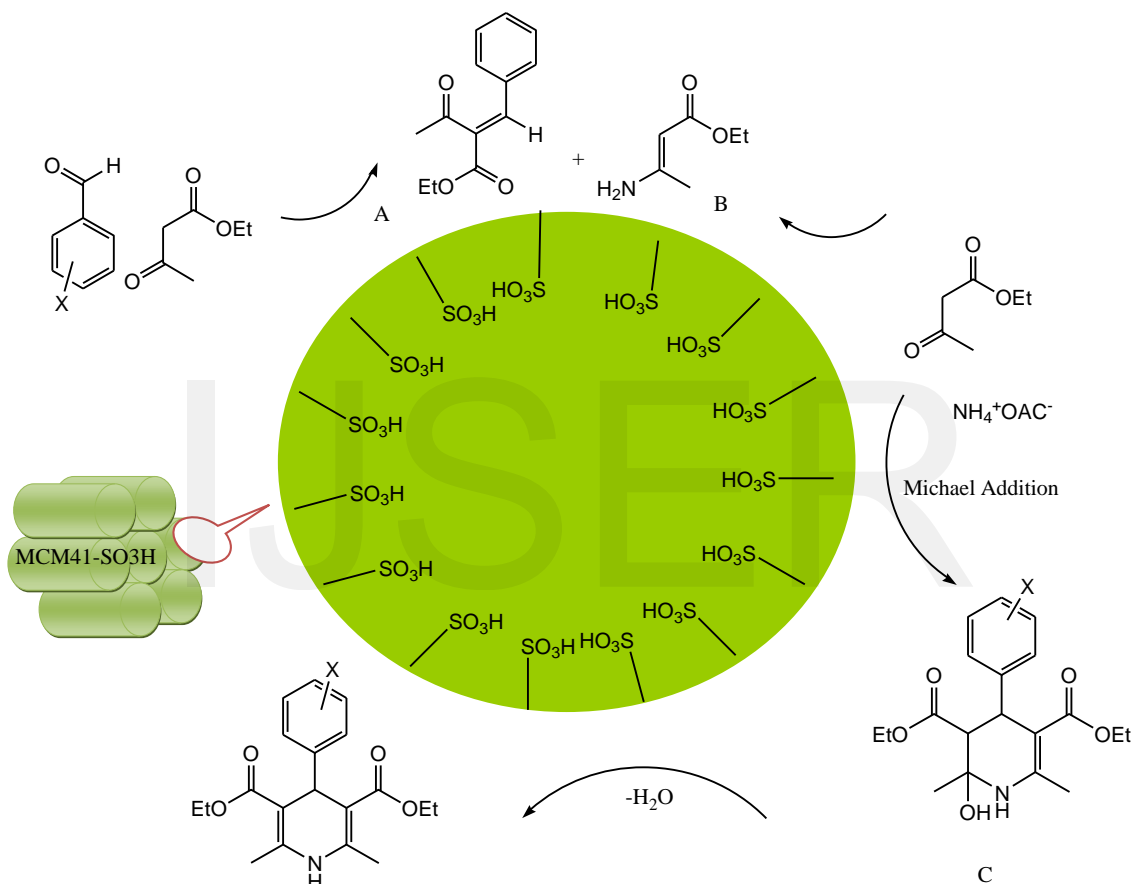
Table2:MCM-41-SO₃H -catalyzed Hantzsch synthesis of 1,4-dihydropyridines 4a-l



Product	Ar	Time (min)	Yield (%)	M.p. (°C)	
				Found	Reported
4a	4-Acetamido	2:10	85	236-242	---
4b	4-Benzyloxy	2:15	90	156-160	---
4c	4-choloro	2:10	86	138-141	145-147 ^[33]
4d	4-me	2	75	140-144	136-138 ^[33]
4e	4-Meo	1:35	80	140-150	158-160 ^[33]
4f	4-NO ₂	1:40	78	133-136	130-132 ^[33]
4g	Ph	2:15	90	155-156	156-158 ^[33]
4h	4-Hydroxy	1:30	83	226-228	225-229 ^[34]
4i	3-Nitro	2	84	161-163	163-165 ^[33]
4j	4-Bromo	2.30	90	164-165	162-164 ^[33]
4k	2-furyl	2.20	93	160-163	160-162 ^[33]
4L	2-thienyl	2.30	91	172-173	172-174 ^[33]

Treatment of one equivalent of 3-nitrobenzaldehyde and ammonium acetate with 2 equiv of ethyl acetoacetate in the presence of 0.1 gr of MCM-41-SO₃H as the catalyst under solvent free conditions resulted in 84% yield (entry 7). After that, the reaction conditions were optimized. The solvent free proved to be a much better condition in terms of yield and time of reaction (84% yield in 2 hours) than all others tested including ethanol (entry1), water (entry2), and acetonitrile (entry3) which afforded the desired product in moderate yields (35.7%, 44%, and 27% respectively). Under solvent free conditions as entry 8, there was no improvement in the reaction yield and time when we used 0.15 gr of the MCM-41-SO₃H. Furthermore, lower amounts of the catalyst (as in entries 4,5 and 6) caused in a lower yield and a longer time of reaction. No effect was observed by a rise in temperature (entry 9). However, a drop in temperature (entry 10) produced a lower yield and a longer time.

It seems that the reaction between an aldehyde, ethyl acetoacetate, ammonium acetate in the presence of MCM-41-SO₃H follows the pathway outlined in the following scheme.



First, the Knoevenagel condensation is created between one mol of the aldehyde and one mol of the ethyl acetoacetate (A). On the other hand, a condensation reaction is carried out between another mol of ethyl acetoacetate and the ammonium acetate (B). After that, Michael addition reaction occurs between these two intermediates. Finally, after the removal of water from the created molecule (C) the product is obtained.

In conclusion, we developed an efficient green methodology for the synthesis of 1,4-dihydropyridines using the nanosized MCM-41-SO₃H-catalyzed Hantzsch three-component reaction of an aromatic aldehyde, ethyl acetoacetate, and ammonium acetate. Short reaction time, reusability of the catalyst, eco-friendliness, good to excellent yields, and easy separation of the catalyst from the reaction are some important advantages of the methodology.

Experimental

Chemicals were obtained from Merck and Sigma-Aldrich and used without further purification. Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on an ABB Bomem ModelFTLA200-100 instrument. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts are reported (δ) relative to TMS, and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70eV ionization potential.

Synthesis of 1,4- dihydropyridines

A mixture of an aldehyde **1** (1 mmol), ethyl acetoacetate **2** (2 mmol), ammonium acetate **3** (2 mmol) and MCM-41- SO_3H (0.1g) was mixed in solvent free conditions for the appropriate time (Table 2, monitored by TLC). After completion of the reaction, the catalyst was filtered off and reaction mixture was poured in cold water and extracted with ethyl acetate. The organic layer was washed with brine and water and dried over Na_2SO_4 . After evaporation of the solvent, the crude yellow products were purified by crystallization from ethanol to afford 1,4-dihydropyridines **4** in 75-95% yields.

The spectral data of some representative products

Compound 4-a:

^1H NMR (300 MHz, CDCl_3): δ 1.16 (t, J=9 Hz, 6H), 1.55 (s, J=9 Hz, 6H), 2.15 (s, J=6 Hz 3H), 4.19 (q, J=3 Hz), 5 (s, J=5 Hz, 1H), 5.58 (s, J=5.58 Hz, 1H), 7.09 (s, J=7.09 Hz, 1H), 7.27 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3): δ 14.2, 19.6, 39.1, 59.7, 75.7, 104.1, 119.4, 128.5, 143.7, 167.5. IR (KBr): 1211, 1319, 1504, 1545, 1647, 1704 2978, 3085, 3214, 3316. Cm^{-1} ; MS(EI):m/e (%)=384 (100, M^+), 386 (26.5, M^+), 387 (3.7, M^+).

Compound 4-b:

^1H NMR (300 MHz, CDCl_3): δ 1.21 (t, J=7.1 Hz, 6H), 2.31 (s, J=2.31 Hz, 6H), 4 (q, J=6 Hz, 4H), 4.9 (s, J=4.9 Hz, 1H), 5 (s, J=5 Hz, 2H), 5.71 (s, J=5.71 Hz, 1H), 6.82 (d, J=6 Hz, 2H), 7.18 (d, J=3 Hz, 2H), 7.33 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3): δ 14.2, 19.5, 38.7, 59.6, 69.9, 104.3, 114.1, 127.5, 127.8, 128.5, 128.9, 134.6, 137.2, 140.6, 157.2, 167.7. IR (KBr):1234, 1377, 1488, 1649, 1695, 2927, 2982, 3356. Cm^{-1} ; MS(EI):m/e (%)=252 (100, M^+), 435 (9.44, M^+), 436 (2.3, M^+).

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