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REGULAR ARTICLE

Efficient and selective catalytic N-Alkylation of pyrimidine by ammonium Sulfate@Hydro-thermal carbone under eco-friendly conditions

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Abstract. An efficient and inexpensive method for the *N*-alkylation of pyrimidines using ammonium sulfate coated Hydro-Thermal-Carbone (HTC) (AS@HTC) as reused heterogeneous catalyst was developed. The catalyst was characterized by several analytical techniques such as SEM, XRD, and FTIR. The effect of various parameters was studied including catalyst loading, mole ratio, to achieve excellent selectivity and yields in 80–90%. Significantly, the present protocol offers the use of an inexpensive and environmentally friendly catalyst and simple workup. The simplicity of the procedure, excellent yield of the products, and the recyclability of the catalyst are the main advantages of this method.

Keywords. Heterogeneous catalysis; AS@HTC; N-alkylation; pyrimidines.

1. Introduction

The key advantages of heterogeneous catalysts are environmental compatibility, operational simplicity, nontoxicity, ease of separation, and low cost.[1,2] Different materials have been studied as heterogeneous catalysts. For instance, porous carbon materials are of interest in many applications because of their high surface area, physicochemical properties, stability, low density, and wide availability.[3,4] Furthermore, they are used extensively as sorbents for separation processes, gas storage, and as supports for many important catalytic processes.[5–7] On the other hand, carbon materials have been used as a catalyst for various organic reactions. For instance, Akhil *et al.,*[8] reported that Cu_2O nanoparticles supported hydrothermal carbon microspheres as a catalyst for propargylamine synthesis, whereas Filoklis *et al.,*[9] worked on esterification of levulinic acid into ethyl levulinate catalyzed by sulfonated hydrothermal carbon. Moreover, Biradar *et al.,*[10] used molybdenum nanoparticle supported on the carbon microsphere for epoxidation reaction. On the other hand, Reddy and Patil[11] examined the importance of solid acid sulfated Zirconium catalysts in environmentally benign processes and in a diverse range of organic and fine chemical syntheses. Furthermore, a new type of solid acid that is promoted by a sulfate ion (introduced from H_2S0_4, or $(NH_4)_2S0_4$) such as SO_4^{2-}/ZrO_2, SO_4^{2-}/TiO_2, and SO_4^{2-}/Fe_2O_3, has been developed and used as a powerful catalyst for various acid-catalyzed reactions, such as the skeletal isomerization of butane to isobutane, the acylation of benzene derivatives by acyl chlorides, and the ring-opening isomerization of cyclopropane.[12,13]

The most popular and mildest reaction of glycosylation is the Vorbruggen variant[14–16] of the Hilbert–Johnson reaction making use of a fully protected sugar or acyclic chains and coupling it with a silylated nucleobase in the presence of Lewis acids (typically

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$SnCl_4$ or TMSOTf). Also, an effective synthesis of nucleosides using glycosyl chlorides as glycosyl donors in the absence of Lewis acid has been developed by Mao *et al.,*[17] It is worth noting that several catalysts were used in the silylating reaction of the nucleobase, for instance, ammonium sulfate,[18–21] ammonium chloride[22] and trimethylsilyl chloride.[23,24]

The coupling reaction at one of the nitrogen atoms in the nucleobases and its analogs is the most effective method for introducing certain substituents with desired functionalities into the heterocyclic base, for instance, acyclovir and analogs.[25,26] In addition, the N_1-alkylation of pyrimidines affords the important building blocks for PNAs (Peptide Nucleic Acids), which have been widely described in the literature as therapeutic and biomolecular tools.[27]

For this purpose, several bases, such as potassium carbonate[36] sodium hydride[37] and potassium hydroxide[38] have been used. Although most of the above methodologies have their own synthetic values, they also have limitations. For instance, they all require the use of dimethylformamide or dimethylacetamide as a solvent with a cumbersome workup of the reaction mixture. The yields are moderate at best. Furthermore, mixtures of mono, di and *O*-alkylated products, as well as a small amount of condensation product, are formed. Hence, there is still a need for milder and suitable methods for the synthesis of these interesting *N*-alkylated pyrimidines. Here we report a synthetic approach which is novel and efficient in several aspects such as yield, reaction conditions, and selectivity. In this context, heterogeneous catalysis was proposed to be a promising alternative.

We report herein for the first time, the use of hydrothermal carbon microsphere as a support for loading of ammonium sulfate and its application as an efficient catalyst for the *N*-alkylation of pyrimidine. This report is a continuation of our previous work on heterogeneous catalysis.[39–41] Ammonium sulfate coated HTCs was found to be an excellent catalyst for the practical, simple and efficient synthesis of some *N*1-alkylpyrimidines using new conditions of Hilbert-Johnson reaction.[42,43] These reactions are carried out using a catalytic amount of AS@HTC (ammonium sulfate/hydrothermal carbon) and HMDS (hexamethyldisilazane) as a silylating agent in MeCN.

2. Experimental methods

2.1 *Characterization techniques*

All the reagents and solvents for synthesis and analysis were commercially available and used directly. The stretching vibration frequency of the catalyst was recorded by FTIR spectroscopy in the range of 400–4000 cm^{-1} using a Bruker vertex 70 DTGS spectrometer. Spectrometer XRD measurements were performed on an XPERT-MPD Philips diffractometer using $CuK^{\bullet}$ radiation as the X-ray source in the range of 20°–80°. Morphology of the microstructures was carried out on a VEGA3 TESCAN microscope equipped with an energy dispersive X-ray spectrometer (EDAX TEAM). Liquid chromatography was performed on silica gel (Merck 60, 220–440 mesh; eluents: dichloromethane – Methanol). ^1H and ^{13}C NMR spectra were recorded at 300 MHz a Brucker Avance spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent, and internal standard and coupling constant (J) in Hz. HRMS was performed on a Thermo Scientific LTQ Orbitrap XL equipped with an electrospray source, and the data was processed with Xcalibur.

2.2 *(Thermo Scientific)*

2.2a *Preparation of hydrothermal carbon [HTC]*: Hydrothermal carbon (HTC) was synthesized according to the reported route.[3,4] In a typical synthesis procedure, 10.00 g of glucose was dissolved in 20.00 mL of distilled water and transferred to a Teflon-lined autoclave and placed in an oven at 180 °C for 24 h. The dark brown carbonaceous material obtained was separated by filtration, washed with distilled water (3 x 30 mL) followed by an ethanol wash (1 x 30 mL) and placed for drying overnight at 100 °C. Four grams were obtained (40% yield).

2.2b *Preparation of the heterogeneous catalyst AS@HTC*: Using wet impregnation method, $(NH_4)_2SO_4$ (30 mg) was dissolved in 10 mL of H_2O in the presence of a desired amount of HTC (70 mg). The suspended HTC was stirred at 80 °C for 2 h. The water was removed by rotary evaporation and the remaining solid was dried in an oven at 100 °C for 12 h. $(NH_4)_2SO_4$ and HTC were taken in different mass to get different compositions of $(NH_4)_2SO_4$ doped HTC. The catalysts AS@HTC were then ready to use. Characterization (P-XRD, IR, EDX and SEM) of $(NH_4)_2SO_4$, doped on HTC composite was limited to the most active catalyst AS@HTC with a weight percentage of 30% $(NH_4)_2SO_4$ and 70% HTC.

2.3 *General procedure for the synthesis of N_1-alkylated pyrimidines*

A mixture of pyrimidine (1.00 mmol), AS@HTC (50 mg) in 1.5 mL of HMDS was heated under reflux for 2 h (First step). After that, a clear oil of 2,4-bis (trimethylsilyloxy) pyrimidine was dissolved in 2.5 mL of anhydrous acetonitrile and then 2 eq. of the alkylating agent (ethyl acetate bromide or propargyl bromide) was added (second step). The reaction mixture was then stirred for 12 h at 80 °C. The

resulting mixture was filtered and the solvent was evaporated to dryness. The crude product was purified by column chromatography over silica gel by using CH_2Cl_2/MeOH (9.6/0.4) as eluent to give the desired product.

3. Results and Discussion

3.1 *Characterization of AS@HTC*

3.1a *FT-IR of AS@HTC*: The FTIR of Figure S1 (Supplementary Information) showed a strong absorption band at 3447 cm^{-1} which can be assigned to O–H stretching vibration of adsorbed water molecules[44] and surface hydroxyl groups. The absorption bands at 1636 cm^{-1} is attributed to C=C stretching vibrations,[8] which can be clearly observed the HTC and AS@HTC before and after use. Compared to the ammonium sulfate FTIR spectrum, the absorption peak at 1401 cm^{-1} correspond to NH_4^+ ion.[44,45] The vibration bands located at 1115 cm^{-1} and 620 cm^{-1} are clearly visible in the AS@HTC and ammonium sulfate FTIR spectrum, demonstrating the presence of the –SO– groups. All of the correlation bands produced chemical bonds in the carboxyl group were weakened after carbonization and ammonium sulfate treatment which indicated that the side chain groups were cleaved in the experiment. From this analysis, it is possible to qualitatively conclude that there were many -SO- groups in the AS@HTC catalyst.

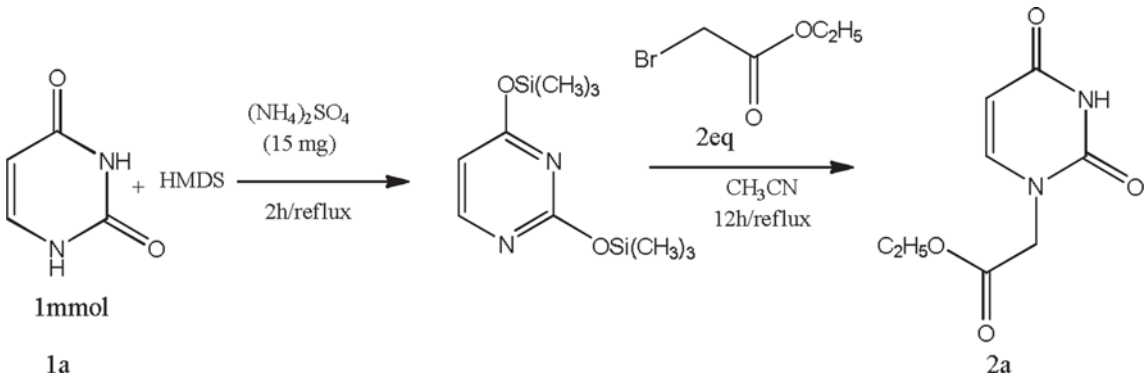
3.1b *X-ray diffraction*: The XRD patterns of samples HTC, $(NH_4)_2SO_4$, AS@HTC, and reused AS@HTC are shown in Figure S2, Supplementary Information. For HTC sample, XRD spectrum shows a broad peak at $2\theta = 18–28°$ (Figure S2(a)) which is attributed to (0 0 2) planes of amorphous carbon.[48] The XRD patterns of AS@HTC and reused AS@HTC display a similar pattern as $(NH_4)_2SO_4$ mascagnite phase (JCPDS: 00-007-0002) with a less intense broad peak at $2\theta = 18–28°$. However, it should be noted that this carbon framework is still amorphous and far away from graphitization. We can then conclude that XRD analysis further proved the adsorption of ammonium sulphate on the surface of HTC.

3.1c *Scanning electron microscopy (SEM)*: The morphology of HTC, $(NH_4)_2SO_4$, AS@HTC, and reused AS@HTC were elucidated by the scanning electron microscope (SEM) (Figure S3, Supplementary Information). The elements present in the catalyst sample (C, S, O and N) from EDS characterization are given in Table S1, Supplementary Information. The surface of the pure HTC consists mainly of aggregates of uniform and interconnected carbon spheres (Figure S3a, Supplementary Information). Compared to the pure HTC, the surface of the AS@HTC catalyst clearly shows the uniform impregnation of ammonium sulfate on the HTC support (Figure S3b, Supplementary Information) and the particles of the catalyst are uniformly nanosized. The reused AS@HTC present also the same motif as a fresh one. We can also observe a loose irregular network structure due to the porous nature of the materials which probably caused by the adsorption of ammonium sulfate on the surface of HTC. Therefore, the larger amounts of pores and larger pore size would increase the accessibility of ammonium sulfate into the carbon bulk of HTC.

Additionally, the adsorption of the ammonium sulfate on the surface of HTC was confirmed by the composition of the catalyst using energy-dispersive X-ray spectroscopy (EDX). The analysis showed the presence of nitrogen, sulfur and oxygen elements with a weight percentage of 8.71%, 6.18% and 28.39%, respectively. We notice here a decrease of sulfur weight percentage (3.99%) after the 4th reused reaction (Table S1, Supplementary Information).

3.1d *Catalytic study*: To optimize the reaction conditions with the use of AS@HTC as a catalyst for the Hilbert-Johnson reaction, a different set of reactions were carried out using different molar ratios of AS@HTC and substrates. The reaction of uracil **1a** with Bromo-ethylacetate was studied as a model reaction to provide compound **2a** (Scheme 1).

The results of the survey of the catalyzed reaction indicated that the reaction proceeded well using the heterogeneous catalyst AS@HTC, which turned out to be the best choice (Table S2, Supplementary Information). In this study, Hilbert-Johnson's reaction was used as a reference and showed that the addition of HMDS and AS appears to be important for the reaction to proceed (40% yield) (Table S2, entry 1, Supplementary Information). According to the Hilbert-Johnson reference reaction, the amount of AS used is 15 mg (Table S2, Supplementary Information), and shows that the efficiency (80% yield) is mainly affected by HTC support added at the start of the reaction. When HTC was added in the second step, the yield did not exceed 70%. On the other hand, addition of HMDS, AS@HTC and alkylating agent in one step, causes deactivation of the reaction giving a yield less than 35%.



Scheme 1. Hilbert–Johnson reaction.

Table 1. The mole ratio influence of HTC and $(NH_4)_2$ SO_4 on the synthesis of product 2a.

	AS@HTC Catalysts		
Entry	Mass of AS (mg)	Mass of HTC (mg)	Yield 2a (%)
1	15	10	51
2	15	15	60
3	15	35	80[a]
4	15	60	80
5	5	35	60
6	10	35	71
7	20	35	80

Optimal condition: One pot: first step: uracil [1mmol], HMDS (1.5 mL), AS@HTC (50 mg), reflux for 2 h. second step: alkylating agent (2 eq), 2.5 mL CH_3CN, reflux for 12 h.

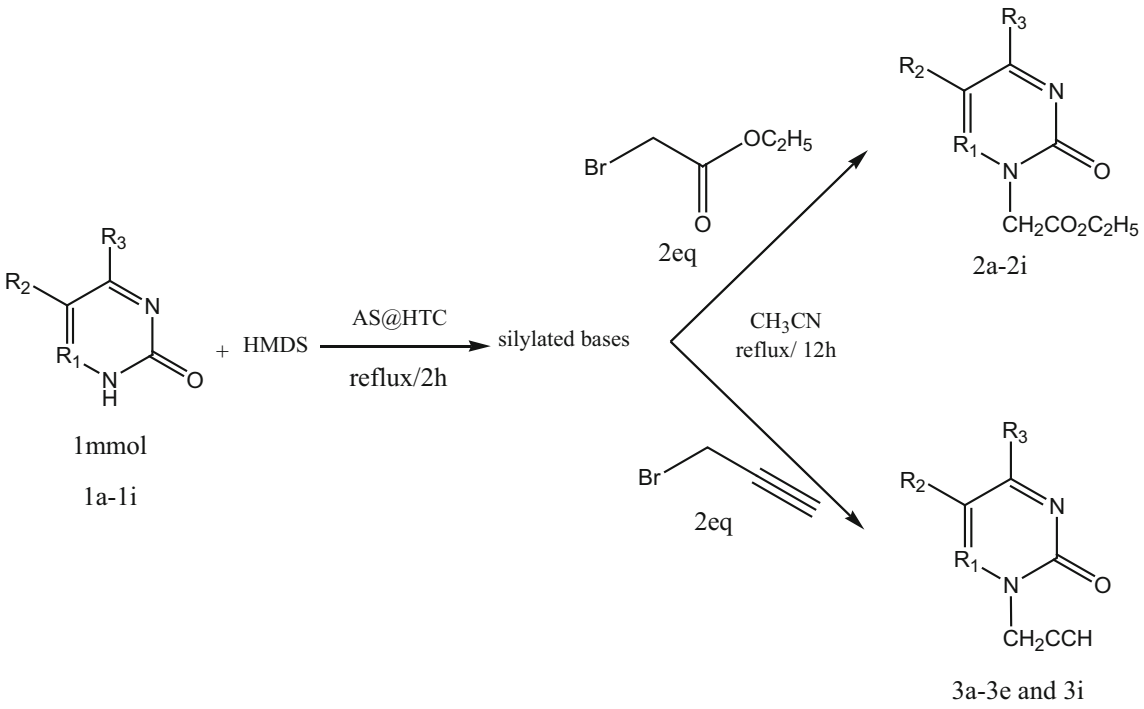
To understand the possible influence of $(NH_4)_2$ SO_4 and to optimize the reaction condition, the amount of the HTC was fixed at 35 mg (Table 1), and the amount of $(NH_4)_2$ SO_4 was varied between 5–30 mg. The results in Table 1 showed that the yield increased until stabilizes at 80% (entries 3, 5, 6,). Furthermore, increasing the amount of HTC, from 15 to 60 mg, enhanced the reaction yield until it stabilizes at a 80% yield. The reaction showed an excellent selectivity towards the desired product **2a**.

Therefore, the optimal amount of AS and HTC for the reaction was 15 and 35 mg, respectively. In addition, solvent effects were examined and CH_3CN afforded the best result (80%) and hence it was solvent of choice for all reactions. Using $ClCH_2CH_2Cl$ afforded a moderate yield (62%) of the corresponding **2a**. For comparison, some other support and catalysts are tested (Table S3, Supplementary Information). Replacing the $(NH_4)_2$ SO_4 with $ClSi(CH_3)_3$ gave no improvement in reaction yield which did not exceed 42%. Furthermore, the substitution of HTC by other support (SiO_2, K10) negatively affected the reaction yield and efficiency (Table S3, Supplementary Information).

Table 2. Generalization of the reaction conditions with 2-bromo-ethylacetate and propargyl bromide.

Entry	Nucleobases	Product	Yield[a] %	Yield[b] %
1	Uracil **1a**	**2a**	70	80
2	Thymine **1b**	**2b**	83	90
3	5-fluoro uracil **1c**	**2c**	78	80
4	5-chloro uracil **1d**	**2d**	87	90
5	5-bromo uracil **1e**	**2e**	71	72
6	5-iodo uracil **1f**	**2f**	62	65
7	6-azauracil **1g**	**2g**	61	69
8	6-azathymine **1h**	**2h**	65	70
9	Cytosine **1i**	**2i**	70	80
10	Uracil **1a**	**3a**	76	87
11	Thymine **1b**	**3b**	89	94
12	5-fluoro uracil **1c**	**3c**	70	72
13	5-chloro uracil **1d**	**3d**	68	70
14	5-bromo uracil **1e**	**3e**	67	68
15	Cytosine **1i**	**3i**	90	94

Conditions: [a] **One pot:** first step: Nucleobase (1 mmol), HMDS (1.5 mL), $(NH_4)_2$ SO_4 (15 mg), reflux for 2 h. second step: alkylating agent (2eq), HTC (35 mg), 2.5 mL CH_3CN, reflux for 12 h. [b]**One pot:** first step: Nucleobase (1 mmol), HMDS (1.5 mL), AS@HTC (50 mg), reflux for 2 h, second step; alkylating agent (2 eq), 2.5 mL CH_3CN, reflux for 12 h.



1a- R_1=C, R_2=H, R_3=OH **2a-** R_1=C, R_2=H, R_3=OH **3a-** R_1=C, R_2=H, R_3=OH,

1b-R_1=C, R_2=CH_3, R_3=OH **2b-**R_1=C, R_2=CH_3, R_3=OH **3b-**R_1=C, R_2=CH_3, R_3=OH

1c-R_1=C, R_2=F, R_3=OH **2c-**R_1=C, R_2=F,R_3=OH **3c-**R_1=C, R_2=F, R_3=OH

1d-R_1=C, R_2=Cl, R_3=OH **2d-**R_1=C, R_2=Cl, R_3=OH **3d-**R_1=C, R_2=Cl, R_3=OH

1e-R_1=C, R_2=Br, R_3=OH **2e-**R_1=C, R_2=Br, R_3=OH **3e-**R_1=C, R_2=Br, R_3=OH

1f-R_1=C, R_2=I, R_3=OH **2f-**R_1=C, R_2=I, R_3=OH **3i-**R_1=C, R_2=H, R_3=OH

1g- R_1=N, R_2=H, R_3=OH **2g-**R_1=N, R_2=H, R_3=OH

1h- R_1=N, R_2=CH_3, R_3=OH **2h-** R_1=N, R_2=CH_3, R_3=OH

1i- R_1=C, R_2=H, R_3=NH_2 **2i-**R_1=C, R_2=H, R_3=NH_2

Scheme 2. General reaction.

To demonstrate the versatility of the developed protocol, a number of pyrimidines with various substituents (Table 2, **1b–1)** were subjected to the optimized reaction conditions. The reactions proceeded efficiently providing the desired *N*1-alkylated pyrimidines in excellent yields and selectivity (Scheme 2). The mono alkylation reaction is free from any side-product formation, such as *N*1, N3-dialkylated nucleobases, O-alkylation, and condensation products. The assignment of all structures was established on the basis of IR, ^{1}H- and ^{13}C-NMR, mass spectrometry. (12c).

1,2,3-Triazoles are present in several compounds with assorted biological activities such as anticancer, antibacterial, antifungal, and antiviral properties.[49] Furthermore, mono-propargyl pyrimidines are generally used as starting material for the synthesis of triazolo-nucleosides[50–52] and triazolo-nucleotides.[53] Therefore, the synthesis of mono-propargyl pyrimidine **3a–3e** and **3i** were studied by treating several

Table 3. Recycling of the catalyst (AS@HTC).

Nucleobase	Product	Catalyst	Yield %
Uracil	**2a**	Fresh	80
Uracil	**2a**	1st run	70
Uracil	**2a**	2nd run	70
Uracil	**2a**	3rd run	70

Conditions: One pot: first step: uracil (1mmol), HMDS (1.5 mL), AS@HTC (50 mg), reflux for 2 h, second step: alkylating agent (2 eq), 2.5 mL CH_3CN, reflux for 12 h.

pyrimidines with propargyl bromide under the same optimized reaction conditions, and the results are reported in Table 2 (entries 10–15). The desired products were obtained in good to excellent yields. The structures of the N_1-alkylated pyrimidines **3a–3e** and **3i** (Scheme 2) were determined from their spectral (NMR 1H, 13C, and Mass) data and found to agree with the literature.[30, 32, 54, 55]

3.2 *Recycling of the catalyst*

The reusability of the AS@HTC catalyst was studied to evaluate catalyst robustness. Table 3 summarizes the results of three consecutive catalytic runs performed using the catalyst under optimized reaction conditions. After each reaction, the catalyst was recovered by filtration, washed twice with CH_2Cl_2 and CH_3CN at room temperature to remove both polar and non-polar adsorbents, then air-dried in the oven at 100 °C and activated at 180 °C (4 h) before reuse (Table 3). After completion of the first reaction affording the corresponding product in 80% yield, the catalyst was recovered and a fresh reaction was then performed under same conditions. The products for 2nd and 3rd were obtained in good yields (70%). Thus, this catalyst system could be used for at least 3 cycles with negligible change in its activity. Also, the PXRD and FTIR of the reused catalyst did not reflect any changes. On the other hand, the results in Table 3 shows, low loss of uracil conversion to **2a** even after three consecutive runs. The milder conditions used in this case prevented the formation of secondary compounds and thus the catalyst is not deactivated by poisoning.

4. Conclusions

We have reported for the first time a highly efficient, convenient and practical method for the synthesis of a wide range of N1-alkylated pyrimidine in mild reaction conditions using As@HTC as heterogeneous catalyst. The sequences and reactions conditions have therefore been carefully optimized to produce the final compounds in the most straight forward and convenient way and with the maximum purity and overall yield. Significantly, the present protocol offers the use of an inexpensive and environmentally friendly catalyst and simple reaction operation. Notably, simple work-up, moisture-tolerance and ease handling of reagents make this method a viable alternative to existing methodologies.

Supplementary Information (SI)

Experimental information and supplementary figures and tables are available at www.ias.ac.in/chemsci.

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