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One-Pot Synthesis of 1,3,5-Tribenzoylbenzenes by Three Consecutive Michael Addition Reactions of 1-Phenyl-2-propyn-1-ones in Pressurized Hot Water in the Absence of Added Catalysts

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Abstract: Cyclotrimerization of 1phenyl-2-propyn-1-one in pressurized hot water gave 1,3,5-tribenzoylbenzene in one pot in 65% yield after 7 min at 200°C, or in 74% yield after 60 min at 150°C. The reaction did not take place in the absence of water, and added base promoted the reaction at 250°C, suggesting a mechanism of three-consecutive Michael addition reactions. The reaction rates increased with temperature, but the yield of 1,3,5-tribenzoylbenzene decreased at the expense of formation of acetophenone as a side

Keywords: cycloaddition • highpressure chemistry • Michael addition • supercritical fluids • water chemistry product at higher temperatures. *p*-Methyl and *p*-chloro-substituents on the phenyl ring retarded and enhanced the reaction, respectively. A mechanism involving the enol of benzoylace-taldehyde at a branching point of the pathway leading to 1,3,5-tribenzoylbenzene and acetophenone was suggested.

Introduction

Typical organic reactions are often performed by the action of acid or base catalysts in organic solvents. These reactions usually require workup procedures, such as neutralization of

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the catalysts and removal of the solvents, which can cause deterioration of waste water quality and emission of volatile organic compounds(VOC) into the atmosphere, thus increasing the burden on the environment. Pressurized hot water near the critical point ($T_{\rm C}$ =374.15°C, $P_{\rm C}$ = 22.12 MPa) has various merits as an alternative reaction medium. Its high specific dielectric constant (ε_r) of 78 at room temperature drops in parallel with the decrease in its density to about 28 at 250 °C (cf. $\varepsilon_r = 28$ for ethanol and 33 for methanol at 25°C) and down to approximately 2 at 450 °C (cf. $\varepsilon_r = 2.3$ for benzene at 25 °C),^[1] enabling higher solubility/miscibility of organic compounds in this medium. Because the ionic dissociation of water is endothermic, its ion product of 10⁻¹⁴ at 25 °C increases with temperature and, because its ε_r drops at higher temperature, it reaches a maximum three orders of magnitude greater at temperatures of around 250°C under the saturated vapor pressure.^[2] These conditions facilitate various acid- or base-catalyzed organic reactions in water in the absence of added catalysts.^[3,4,5]

Herein, we report a one-pot cyclotrimerization reaction (Scheme 1) of 1-phenyl-2-propyn-1-one to produce 1,3,5-tribenzoylbenzene in the absence of any added catalyst. It is well known that monosubstituted acetylenes RC=CH undergo cyclotrimerization reactions to give substituted benzenes under the action of various transition-metal catalysts.^[6] Reppe's catalysts, consisting of nickel or cobalt carbonyls,

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Scheme 1. One-pot cyclotrimerization of 1-phenyl-2-propyn-1-one.

give mainly 1,2,4-trisubstituted benzenes, with lower amounts of the 1,3,5-isomers also generally obtained, and little, if any, of the 1,2,3-isomers.^[7] The Ziegler-type catalyst, a tri-isobutylaluminum-TiCl₄ system, has been used to cyclotrimerize 2-ethynylfuran.^[8] More recently, a (4-hydroxybutyrylcyclopentadienyl)Co- η^4 -COD catalyst (COD=1,5-cyclooctadiene) and a ruthenium(IV) precatalyst have been successfully used in the cyclotrimerization of acetylenes in aqueous solvents.^[9a,b] Furthermore, [Co(CO)₂(Cp)]-catalyzed (Cp=cyclopentadienyl) reactions have even been carried out in supercritical water.^[9c,d] All of the transitionmetal-catalyzed reactions, including the latter approach, have the same problem regarding the regioselective formation of 1,3,5-isomers from terminal acetylenes.

Whereas Sasaki and Suzuki had obtained 1,3,5-tri(2-furancarbonyl)benzene in 20% yield during the oxidation of 1-(2furyl)-2-propyn-1-ol with active manganese oxide,^[10] it was Balasubramanian et al. who first reported the unique formation of 1,3,5-tribenzoylbenzene by three consecutive Michael addition reactions of 1-phenyl-2-propyn-1-one in the presence of diethylamine as a catalyst in organic solvents such as dichloromethane, N,N-dimethylformamide (DMF), and toluene.^[11] Mechanistic studies of the cyclotrimerization reaction by Matsuda et al. revealed that the amine catalyst initially reacts with an alkynyl moiety to form an enaminoketone. Sequential condensation of this enamine with two additional molecules of aryl ethynyl ketone results in the formation of a cyclohexadiene, from which the amine is eliminated, thereby generating the central benzene ring.^[12] Our conjecture is based on the high OH⁻ concentration in pressurized hot water, which might be able to replace NH- $(C_2H_5)_2$ in the reported reactions (Scheme 2).

Because of its unique topology and ability to interact through hydrogen bonding and other weak interactions, 1,3,5-triaroylbenzene itself serves as a molecular host not only in solution but also in the solid phase.^[13] The tri(*p*-cyanophenyl) derivative was used as a ligand for a coordina-



Scheme 2. $X\!=\!NH(C_2H_5)_2$ in the previous work $^{[11,12]}$ and OH^- due to pressurized hot water in this work.

tion polymer,^[14] and tri(*p*-octyloxybenzoyl)benzene has been fabricated into a monolayer.^[15] When attached with poly-(oxyethylene) units, the resulting crownophanes crystallized as inclusion solids.^[16] Moreover, the propiolyl group has been introduced into a calixarene moiety, which was cyclotrimerized to form tri- and pentacalixarenes that served as host molecules for amines, polyamines, and C₆₀.^[17] 1,3,5-Tribenzoylbenzene serves, among other things, as key synthetic intermediates for the synthesis of dendrimers of various functions, including superparamagnetic polycarbenes and 1,3,3-trisubstituted 2-oxindoles.^[12b, 18, 19] Hyperbranched polymers with a high degree of branching, such as poly(aroxycarbonylphenylene)s and ferrocene-containing hyperbranched poly(aroylarylene)s have been prepared.^[20a,b] The physicochemical properties of disc-like molecules of medium size thus warrants further investigation, and herein we report a synthetic study of 1,3,5-triaroylbenzene in pressurized hot water.^[21]

Results and Discussion

Formation of 1,3,5-tribenzyolbenzenes: All reactions gave colorless powders in various amounts depending on the reaction conditions. The solid products were shown to be 1,3,5-tribenzyolbenzene on the following grounds: 1) Its melting point (118-119°C) was in good agreement with the reported melting point (119°C).^[11,12a,22] 2) A mass spectral parent peak at m/z 390, and a base peak at m/z 105 due to the fragment ion C₆H₅CO, and other fragmentation peaks agreed well with those of an authentic sample of 1,3,5-tribenzyolbenzene. 3) The FTIR spectra of a sample in a KBr disc showed peaks that were characteristic of conjugated carbonyl absorptions at 1660 cm^{-1.[22]} 4) The ¹H NMR spectrum showed a singlet at $\delta = 8.47$ ppm due to three protons at the 2-, 4-, and 6-positions on the inner benzene ring, multiplets ($\delta = 7.91 - 7.96$ ppm) due to six protons ortho to the carbonyls and remaining multiplets (9 H, $\delta = 7.57 - 7.71$ ppm) due to the three outer benzene rings.^[22] The identities of 1,3,5-tri(p-methylbenzoyl)benzene and 1,3,5-tri(p-chlorobenzoyl)benzene were confirmed by comparing their ¹H NMR spectra with those reported in the literature.^[22]

The effect of the amount of water on the yield of 1,3,5-tribenzoylbenzene: A series of experiments were performed at 250 °C (10 min) in which the amount of water was adjusted within the molar ratio 0–600 relative to one mole of 1phenyl-2-propyn-1-one as a starting material. The results are given in the Supporting Information (Table S1) and are summarized in Figure 1.

It is significant that 1,3,5-tribenzoylbenzene was not formed in the absence of water. Its yield increased sharply with increasing relative amounts of water, leveling off at a yield of approximately 55% upon introducing water in a 300:1 ratio with phenylpropynone. The results are interpreted in terms of the highest ion product of water at 250°C under saturated vapor pressure and catalysis of the reactions

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Figure 1. Changes in the amount of 1,3,5-tribenzoylbenzene with the relative amount of water for the reactions fixed at 250 °C for 10 min.

through latent H^+ or OH^- ions available from the large excess of water.

As described in the Experimental Section, possible catalytic metal sites on the inner wall of the reaction vessel were quenched by "aging". The inner wall may be regarded as being coated with oxide films of Fe_3O_4 (sometimes Fe_2O_3), NiO, and CrOOH. Even if these sites were crucial for the cyclotrimerization reaction, however, it was concluded that they would not provide a suitable reaction environment in the absence of water. According to the thermodynamic evaluation by Ziemniak,^[23] the concentration of the solubilized oxides are estimated to be 2.5, 0.6, and 0.01 ppb for Fe_3O_4 , NiO, and CrOOH, respectively, at temperatures of approximately 250°C, and these values decrease as the temperature increases.

The effects of reaction time and temperature: Temporal variation of the amounts of 1,3,5-tribenzoylbenzene formed when the reaction was performed in a 400-fold molar excess water was examined at temperatures of between 150–400 °C. The results are given in the Supporting Information (Table S2) and summarized in Figure 2.

Prolonged heating did not decrease the amount of 1,3,5tribenzoylbenzene once formed, showing that the final prod-



Figure 2. Temporal variation in the amounts of product 1,3,5-tribenzoylbenzene formed in 400-fold excess water at 150 (\odot), 200 (\triangle), 250 (\Box), 300 (\bullet), 370 (\blacktriangle), and 400 °C (\blacksquare).

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yield of 1,3,5-tribenzoylbenzene was 65% at 200°C after 7 min or 74% at 150°C after 60 min. The initial rates, which were estimated from the less reliable data after 1 min of reaction and the slopes of the rising curves in Figure 2, were greater as the temperature increased. However, the saturated yields of 1,3,5-tribenzoylbenzene became lower at higher temperatures. We also noted that most of the phenylpropynone starting material was lost during the early stages of the reactions. We determined the amount of unreacted starting materials by HPLC analysis and found that the molar amount was less than 1% after 1 min at 200°C. The observation strongly implies the presence of branching in the mechanism, in which product formation is accompanied by a loss of entropy (see below). This is not surprising given the nature of the cyclotrimerization reaction.

uct is thermally stable in hot pressurized water. The highest

Because the reaction vessel was sealed at ambient temperature and pressure, the water in the reactor was considered to be in equilibrium between the vapor and liquid phases below the critical point. At 150, 200, 250, 300, and 370 °C, the density of neat water is estimated to decrease in the order: 0.92, 0.86, 0.80, 0.71, and 0.45 g cm⁻³, and the internal pressure of the vessel increases in the order 0.48, 1.6, 4.0, 8.6, and 21 MPa, respectively. By definition of the supercritical state, only one phase, with a density of 0.35 g cm⁻³ and a pressure of 30 MPa, should be present at 400 °C. We found no drastic change in the temperature dependence of the formation of 1,3,5-tribenzoylbenzene on passing through the critical point (Figure 2).

The effect of the pH of water on the rates of the reaction: To provide support for the mechanism of the three consecutive Michael addition reactions for the formation of 1,3,5-tribenzoylbenzene, the pH of the aqueous solutions were adjusted to 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 at 25 °C by prior addition of measured amounts of aqueous hydrochloric acid (0.1 M) or sodium hydroxide (0.01 M) to pure water to make 10^{-3} , 10^{-4} , 10^{-5} , and $10^{-6} \text{ moldm}^{-3}$ solutions of HCl and NaOH. The effective pH values at 250 °C were calculated by using the relevant dissociation constants of water, hydrochloric acid, and sodium hydroxide, and the ionic activity coefficients reported in the literature,^[24] as described in the previous paper.^[5] The results are listed in Table 1.

The product yields of 1,3,5-tribenzoylbenzene in 400molar excess water after 1 min at 250 °C were less than 10% at pH 3–5, it rose gradually, and reached 48% at pH 7.2, as shown in Figure 3. No improvement in the accuracy of the

Table 1. Calculated pH values of the reaction media at 250 °C.

pH at 25 °C	pH at 250°C
3.0	3.0
4.0	4.0
5.0	5.0
6.0	5.3
7.0	5.6
8.0	7.2

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Figure 3. Effect of pH on the yield of 1,3,5-tribenzoylbenzene in 400-molar excess water at the earliest reaction time of 1 min at 250 °C.

measurements or in the analysis could establish a linear relationship between logarithm of the initial rate R of the product formation and pH (log $R \approx p$ H), which would be expected for a simple base catalysis in the rate-determining step of the reaction sequence. This would suggest that the Michael addition reaction involves stronger base catalysis and weaker acid catalysis. In the crossed aldol condensation in pressurized hot water, both V-shaped and linear plots are reported for the formation of benzalacetone and pentacenequinone,^[4a,5] respectively.

1-(p-Substituted phenyl)-2-propyn-1-ones: To extend the applicability of the cyclotrimerization reaction and to obtain experimental support for the mechanism, three 1-phenyl-2propyn-1-ones carrying a para substituent on the 1-phenyl ring, were studied. The results obtained by using a 400molar excess of water after 5 min at 200 °C are summarized in Table 2 and show that, during the earlier parts of the reactions, the p-chloro and p-methyl substituents seem to enhance and retard the reactions, respectively. The electronwithdrawing and -donating substituents differ in the Hammett σ_p^+ constants by 0.425, revealing the buildup of negative charges at the side chains of the phenyl ring in the transition state of the reaction. The 1-(2-naphthyl) derivative remained unreacted even after 6 min at 250 °C. Because even 1-(1-naphthyl)-2-propyn-1-one is reported to undergo the cyclotrimerization reaction to give the corresponding 1,3,5tri(1-naphthoyl)benzene under classical amine-catalyzed conditions in organic solvent,^[22] a steric effect could not be

Table 2. Reactions of 1-(substituted phenyl)-2-propyn-1-ones after 5 min at 200 °C.

Ar in ArCOC=CH	Yield [%]
1-phenyl	37.1
1-(<i>p</i> -methylphenyl)	33.6
1-(<i>p</i> -chlorophenyl)	49.0
1-(2-naphthyl)	0

invoked to explain the lack of reactivity in the hot pressurized water system used in this study. The lower solubility of the starting material due to the naphthyl moiety in the subcritical water could, however, be responsible for the lack of reactivity.

Formation of acetophenone as a byproduct and reaction mechanism: Acetophenone, as a byproduct, always accompanied the formation of tribenzoylbenzene. A mass spectral parent peak at m/z 120, a base peak at m/z 105 due to fragment ion C₆H₅CO, and other fragmentation peaks agreed well with those of an authentic sample of acetophenone. The FTIR spectra contained peaks that were characteristic of conjugated carbonyl absorptions at 1690 cm⁻¹. The ¹H NMR spectrum showed a singlet at δ =2.50 ppm (3H, CH₃), together with protons in the aromatic region δ =7.35–7.38 (2H), 7.44–7.47 (1H), and 7.85–7.90 ppm (2H).

Temporal variation in the production of acetophenone in a 400-fold molar excess of water was determined at 150– 400 °C, and the results are given in the Supporting Information (Table S3) and Figure 4. The amount of acetophenone gradually increased with reaction time. At approximately 300 °C, the molar yield of acetophenone became comparable to that of 1,3,5-tribenzoylbenzene, and the former became the more predominant product at higher temperatures.



Figure 4. Temporal variation in the formation of acetophenone in 400-fold excess water at 150 (\odot), 200 (\triangle), 250 (\Box), 300 (\bullet), 370 (\blacktriangle), and 400 °C (\blacksquare).

Although comparison of the GC-MS minor peaks to reference peaks held in the database, and the ¹H NMR spectrum of the crude reaction mixture both suggested the additional formation of 1-indenone and 4-(hydroxymethylene)-1,5-diphenyl-2-pentene-1,5-dione (dimer in Scheme 3), the amount of these byproducts was small. A precedent for the formation of 1-indenone is found in the formation of 3arylindenone from 1,3-diarylpropynones in superacids.^[26]

In addition to the observation that the starting 1-phenylpropynone disappeared sooner than the triketone formed,

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reaction.

Conclusion

the expense of the cyclization

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It has been established that the threefold Michael addition of 1phenyl-2-propyn-1-one gives cyclotrimerized 1,3,5-tribenzoylbenzene in good yield in pressurized hot water, in the absence of any organic solvent and added catalyst. In contrast to the use of triethylamine as a catalyst, which is a hazardous organic base, if not carcinogenic,[27] and an organic solvent such as dichloromethane, toluene, or DMF in the conventional organic preparative methods, the present approach of using pure water has the merit of reducing the burden on the environment. The size of the reaction vessel used in this work was miniaturized for rapid temperature equilibration in the metal salt bath and to conserve the starting material. It could, however, readily be scaled up

HPLC analysis of the material balance during the course of the reaction under various conditions revealed that, at temperatures, higher, then, approximately, 200%C, the matter

peratures higher than approximately 300 °C, the molar amounts of 1,3,5-tribenzoylbenzene and acetophenone accounted for all the starting materials consumed. At lower temperatures, the material balance was not satisfactory; the total amount of both of the products was considerably lower than that of the starting material consumed during the earlier part of the reaction.

All the results can be interpreted in terms of a plausible reaction mechanism given in Scheme 3. The nucleophilic addition of OH⁻ at the terminal ethynyl carbon of the phenylpropynone must be a rate-determining step, which would be followed by protonation of the vinylcarbanion to give the enol of benzoylacetaldehyde. This intermediate serves as an important branching point in the reactions. The reaction with a second molecule of 1-phenyl-2-propyn-1-one, although unfavorable in terms of reaction entropy, leads to the formation of 1,3,5-tribenzoylbenzene. The preparation of benzoylacetaldehyde by base-catalyzed aldol condensation of acetophenone with alkyl formate in nonhydrolytic solvents has been described in the literature,^[25a,b] and undergoes a hydroxide ion catalyzed reverse reaction to give acetophenone and a formate ion.^[25c] The latter reaction should be favorable in terms of reaction entropy and, therefore, fato a cylinder accommodating 100 cm³ of water. A continuous flow reactor used for the production of nanoparticles of various oxides^[28] could also be modified to produce 1,3,5-tribenzoyolbenzene at a rate of 1 kg per day.

An analysis of the byproducts formed provided hints for the mechanism of the reaction. A series of experiments showed unequivocally that the increased solubility of the starting carbonyl compounds, as a result of lowered dielectric constant and the higher ion product under saturated water vapor pressure of pressurized hot water at 250°C, are responsible for the successful addition reaction. It is clear that another merit of the pressurized hot water system as an alternative reaction media is the high temperature and consequent short reaction time, although we have to note that the selectivity of the parallel reactions at high temperatures, if present, could be lower than in lower temperature reactions. Finally, we would like to suggest that the process might be extended to sets of two or three different 1-aryl-2propyn-1-ones that should lead to unsymmetrically substituted 1,3,5-triaroylbenzenes, which are precursors of a number of interesting dendrimers.^[18,19] Such reactions have been successfully performed in organic solvents with added amine catalysts. Furthermore, the phenyl ring of 1-phenyl-2propyn-1-one can include a protected propiolyl group as a substituent. Deprotection of the formed 1,3,5-triaroylben-

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zene, followed by cyclotrimerization, is expected to produce unsymmetrically extended dendrimers, as reported by Matsuda and co-workers under classical conditions for nonaand dodecaketones. Such compounds, after conversion into the corresponding polydiazo derivatives followed by photolysis at cryogenic temperature, gave strongly paramagnetic super-high-spin organic compounds.^[18]

Experimental Section

Chemicals: 1-Phenyl-2-propyn-1-ol of chemical purity greater than 98 % was purchased from Tokyo Chemical Industry and used without further purification for the synthesis of 1-phenyl-2-propyn-1-one after oxidation with potassium permanganate supported on active manganese dioxide.^[29] The ¹H NMR and GC-MS spectra of the product, which was obtained in quantitative yield, agreed with those reported in the literature.^[30] Ultrapure water with a specific resistivity greater than 18.2 M Ω and TOC less than 20 ppb was obtained by treating tap water through a Millipore Milli-RX75 ultrapure water purification system. Other chemicals and solvents were commercially available and used as received. Aqueous hydrochloric acid (0.1 m) and sodium hydroxide (0.01 m) from Wako Pure Chemical Industries were used directly for pH-adjusted reactions.

Reaction vessel: A batch reactor (Figure 5 and Figure S1 in the Supporting Information) made of a SUS316 1/16-inch plug (Swagelok, No. SS-100-P), a 1/16-inch to 1/8-inch reducing connector (Swagelok, No. SS-



Figure 5. A SUS316 reaction vessel.

200-R-8), and a 1/8-inch to 1/2-inch reducing connector (Swagelok, No. SS-100-R-2) were fitted with a 1/2-inch cap (Swagelok, No. SS-810-C), and had an effective inner volume of 2.1 cm³.^[5] Prior to its use in experiments, the reactor was loaded with 2% aqueous hydrogen peroxide and conditioned for 1 h at 370 °C to remove any lubricants/oils that might remain from the manufacture of the Swagelok parts and possible catalytic metal sites on the inner wall, unless otherwise stated. The reactor was cleaned with acetone and dried prior to repeated use of about 10 and 5 times for the reactions carried out at 250 and 400 °C, respectively.

Heating, temperature control, and a typical run of the cyclotrimerization reaction: 1-Phenyl-2-propyn-1-one (0.0136 g) and water (0.751 g), making a molar ratio of 1:400, were introduced into the reaction vessel and the contents were purged with a stream of argon. The capped vessel was immersed in a metal salt bath (Taiatsu Techno, Model TBC-B600) preheated at 200, 250, 300, 370, or (400 ± 1) °C. The pressure in the reaction vessel was calculated to be 1.6, 4.0, 8.6, 21, or 30 MPa, respectively. After the given reaction time (1–10 min), heating was discontinued by remov-

ing the reactor from the heat bath and immersing it promptly in cold water. The reactor heat-up time was on the order of 30 s, which was generally short compared with the reaction times employed.

Analyses of the reaction mixture: GC–MS analyses were carried out with a Shimadzu GC–MS-QP2010 spectrometer. Into a column of Agilent DB-5MS, $1.5 \,\mu$ L aliquots of the solution of the products (dried over MgSO₄) in dichloromethane were injected with a split ratio of 100 with a flow rate of helium carrier gas of 28 cm s⁻¹. After being kept at 60°C for 4 min, the column was heated to 280°C at a rate of 20°Cmin⁻¹ and kept at 280°C for 45 min. NMR spectra were recorded with a Bruker AXS NMR Avance-400 spectrometer operating at 400 MHz, with samples dissolved in CDCl₃ and TMS as an internal standard. FTIR spectra were measured with a Shimadzu FTIR-8400S spectrometer, with solid samples in KBr discs.

For quantitative analyses, methanol was added to the reaction mixture in the reactor to make a homogeneous solution of a given amount in the range 15–20 cm³. An aliquot (1 μ L) was injected into a Shimadzu high-pressure liquid chromatograph analyzer (Prominence HPLC20) and developed with 50% aqueous acetonitrile under the flow rate of 1 mLmin⁻¹. The amounts of 1,3,5-tribenzoylbenzene and acetophenone produced were determined accurately by reference to added acetone as an internal standard and on the basis of calibration curves obtained independently for the pure samples. The variance of the yield data in these studies were dominated by the uncertainty of these manual processes and was estimated to be 5%.

The amount of substituted 1,3,5-tribenzoylbenzene was determined by NMR spectroscopic analysis of the crude reaction products with a given amount of 1,3,5-triacetylbenzene added as an internal standard.

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