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Lewis basicity of water for a selective monodehalogenation of α,α–dihaloketones to α–haloketones and mechanistic study

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Abstract.
The Lewis base character of the greenest reagent water has been explored over its nucleophilic property for an organic transformation. Utilizing this concept, a new strategy for the highly controlled and selective mono-dehalogenation of α,α-dihaloketones has been discovered and reported in this manuscript. Extending this concept, first direct conversion of propargylic acetates to corresponding α-iodoketones *via* α,α-dihaloketones has also been efficiently achieved under metal free conditions. During the later process, water has been concurrently employed as a nucleophile and a Lewis base. Employing this type of dual reactivity of water may be for the first time in the context of organic synthesis. Control experiments supported the involvement of the enoalte as an intermediate during the monodehalogneation process.

Keywords: α,α-dihaloketones; α-haloketones; Lewis base; propargylic acetates; Water.

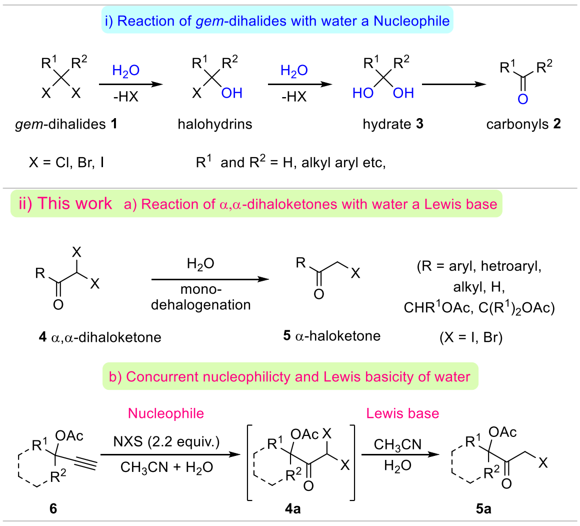
Introduction

Water is a universal solvent with unique properties like readily available, non-toxic, non-flammable.[1] Since most of the biological and natural transformations have been performed in water, it is a highly appealing solvent for bio-mimetic synthetic chemistry.[2] Employing water as a solvent in organic reactions has already been largely explored because of various advantages over organic solvents.[3] The work by Breslow[4] and Sharpless[5] initiated and inspired the development of catalysis and synthetic protocols employing water as the solvent. Since the solubility of most of the organic compounds is poor in water and solubility is generally a prerequisite for reactivity, many of the organic transformations are incompatible with water. Apart from being utilised as a solvent, water exhibits diverse chemical reactivities as it can act as a Brønsted acid, Brønsted base, nucleophile and in principle as a Lewis base. However, first three chemical properties are well explored for various synthetic transformations in organic synthesis. The fourth property i.e., Lewis basicity is more studied in inorganic chemistry whereas less explored in the context of organic synthesis.

The *gem*-dihalides[6] are useful functional groups in organic synthesis in particular as surrogates for carbonyl compounds and carbenes. Reaction of gem-dihalides **1** with water is a well known[7] method (Scheme 1A) for the synthesis of carbonyl compounds **2** (ketones from internal dihalides -CX_2-; and aldehydes from terminal dihalides, -CHX_2). In this process water acts as a nucleophile to displace the halide ions (X^-) for the generation of a carbonyl-hydrate **3**. α,α-Dihaloketones[8] are a novel bi-functional building blocks available for organic synthesis. The reductive dehalogenation reaction (mono- as well as di-) of simple gem-dihalides and α,α-dihaloketones has been reported in the literature,[9] by employing mostly KI or NaI as the Lewis base. To the best of our knowledge so far there are no other Lewis bases have been employed for this purpose.[10]

Our research groups main focus is on the exploration of novel reactivity of propargylic alcohols and propargylic acetates.[11] Recently, we reported an acetoxy directed, highly efficient dihalohydration process for the generation of α,α-diiodo(dibomo)-α'-acetoxyketones **4** from the reaction of propargylic acetates **6** with NIS/NBS under metal free conditions.[12]

During the process of exploring the synthetic utility of the α,α-diiodo(dibomo)-α'-acetoxyketones, we discovered a novel Lewis base reactivity of water. Herein we report a highly selective mono-dehalogenation process of α,α-dihaloketones **4** for the synthesis of α-haloketones **5** (Scheme 1B) employing a non-halide and ultimate green Lewis base, i.e., water. It is noteworthy to mention here that, this type of reaction between *gem*-dihalides and water is unconventional and contrary to the classical reaction where water acts as a nucleophile to produce carbonyl compounds (scheme 1A). Furthermore, the concurrent dual reactivity of water, i.e., nucleophilicity and Lewis basicity in the context of organic synthesis has also been reported for the first time for the direct conversion of propargylic acetates to α-iodo-α'-acetoxyketones.

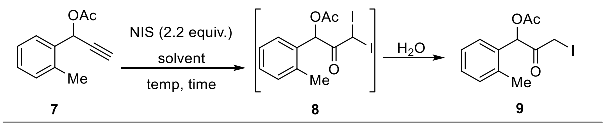


Scheme 1: i) Reactivity of water as a nucleophile with *gem*-dihalides, ii) Water as a Lewis base with α,α-dihaloketones and concurrent nucleophilicity and Lewis basicity of water (This work)

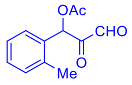
Results and Discussions

Our initial investigation started with the reaction between propargylic acetate **7** and NIS in acetonitrile. When the secondary propargylic acetate **7** was heated with NIS (2.2 equiv.) in acetonitrile at 80 °C (entry 1, Table 1), the diiodo-hydration process found to be slower and took 2 h for complete consumption of **7**.

Table 1: Discovery of mono-dehalogenation of α,α-diiodo-α'-acetoxyketones employing water as a Lewis base and reaction optimization



entry	solvent	temp (°C)	time (h)	yield (%)	(8 : 9)
1	MeCN	80	2	—	(1 : 0.15)
2	MeCN	100	2	—	(1 : 0.3)
3	MeCN	100	6	—	(1 : 1)
4	MeCN+H_2O (1:1)	100	5	70	only **9**
5	MeCN+H_2O (1:1)	100	15 min	94	only **8**
6	MeCN+H_2O (1:1)	100	3	—	(1 : 1)
7	MeCN+H_2O (1:1)	120	1	29	only **9**


10 not observed

(*via* nucleophilicity of water)

But to our surprise, the ^{1}H-NMR of the isolated compound from this reaction shows a (1 : 0.15) inseparable mixture of α,α-diiodo-α'-acetoxyketone **8** and a new product, i.e., α-iodo-α'-acetoxyketone **9**.

At this stage, to get **9** as the exclusive product and to confirm its structure, we next increased the temperature to 100 °C and kept the reaction for 2 h and 6 h (entries 2 & 3). Interestingly, a gradual increase in the amount of **9** was observed from 2 h to 6 h, as the isolated respective product mixtures shows (1 : 0.3) and (1 : 1) ratios of **8** and **9**. We next performed the reaction in a 1:1 mixture of acetonitrile and water at 100 °C (entry 4). To our delight, this condition resulted in the exclusive formation of α-iodo-α'-acetoxyketone **9** in 70% yield after 5 h. Further increase in the temperature to 120 °C gave poor yield of **9** (entry 7). It is noteworthy to mention here that, subjecting the propargylic acetate **7** to same conditions as entry 4, but for 15 min (entry 5) resulted in only α,α-diiodo-α'-acetoxyketone **8** in 94% yield, whereas after 3 h (entry 6) gave a 1:1 mixture of **8** and **9**. These observations (entries 4-6) suggests that the α-iodo-α'-acetoxyketone **9** may not be directly forming from propargylic acetate **7** but may be *via* the α,α-diiodo-α'-acetoxyketone **8** as there was no propargylic acetate **7** but only diiodoketone **8** present after 15 min (entry 5) and only monodiodoketone after 5 h.

To confirm the intermediacy of the **8**, we subjected the diiodoketone **8** to standard reaction conditions (eq. 1, Figure 1). After 4.5 h at 100 °C, it gave cleanly the monoiodoketone **9**. Hence the formation of **9** from propargylic acetate **7** is *via* a reductive mono-deiodination of the intermediate **8**. From the entries 3 and 4 (Table 1) it is clear that NIS may not have any role on the conversion of **8** to **9** but water may be playing a key role, as the reaction was faster when excess water was used (compare entries 3 ad 4). To verify this hypothesis, we next treated the diiodoketone **8** with 1:1 CH_3CN:H_2O at 100 °C in the absence of any NIS (eq. 2, Figure 1). After 5 h, a smooth conversion of **8** to **9** was observed. Furthermore, heating the diiodoketone **8** in anhydrous CH_3CN under N_2-atmosphere, both with and without NIS (eq. 3), failed to produce any of the mono-iodoketone **9** even after 18 h at 100 °C. These experiments, strongly supports the involvement of water as the Lewis base and rule out the role of either NIS or the by-product succinimide during the conversion of **8** to **9**. It is very interesting and surprising that, during this process the water is acting as a mild Lewis base but not as nucleophile, as there was no detection of corresponding α-ketoaldehyde **10**. Furthermore, the mono-iodoketone **9** was found to be very stable upon heating in a 1:1 mixture of CH_3CN and water at 100 °C for 24 h. There was no detection of any of the deiodinized product methylketone **11** (eq. 4, Figure 1). Therefore, this process is very selective towards the formation of mono-iodoketones.

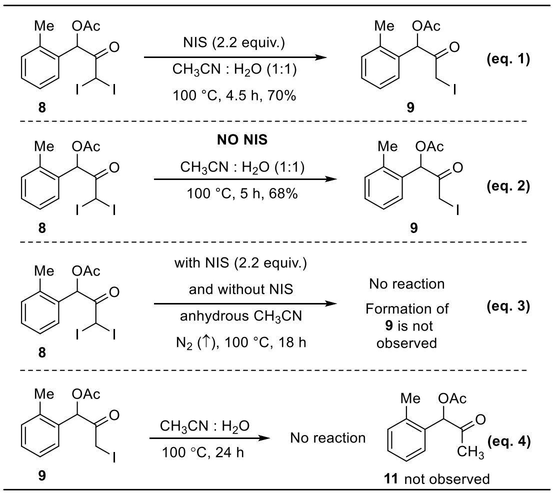
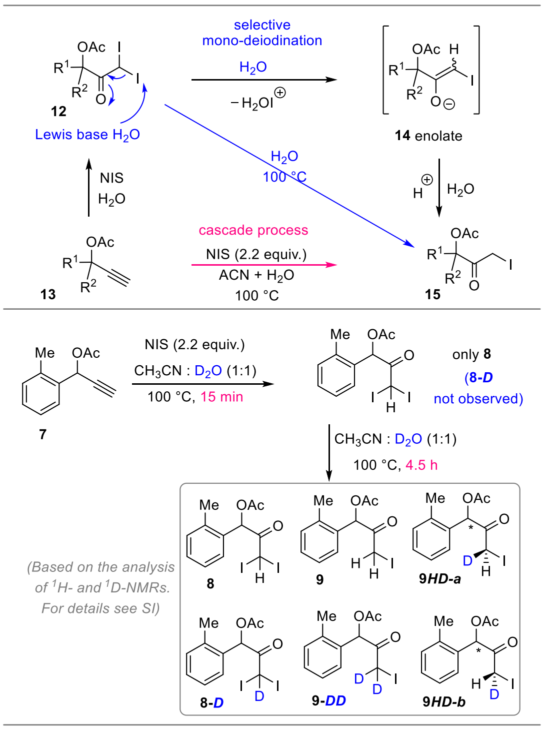


Figure 1: Control experiments to support a) an intermediacy of the diiodoketone **8**; b) role of water as a Lewis base; and c) selectivity for mono-deiodination process

Based on the above control experiments and observations, we proposed a possible mechanism (Scheme 2A). The reaction of the initially formed diiodoketone **12** (from propargylic acetate **13**) with water (Lewis base) leads to the formation of α-iodoenolate **14** *via* a mono-deiodination process. This **14** under reaction conditions will be protonated to give the corresponding α-iodoketone **15**.

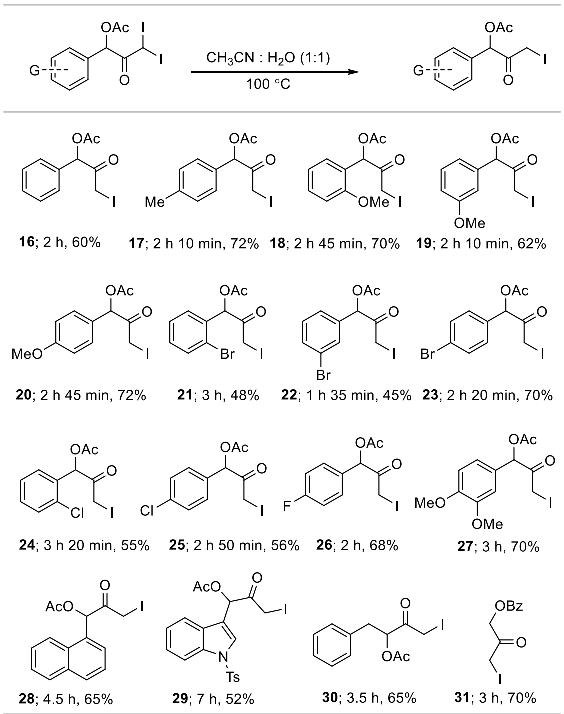


Scheme 2: Possible mechanism and deuterium experiments

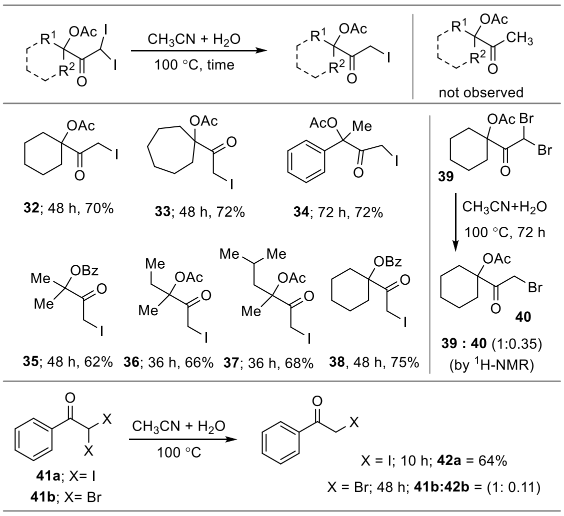
In order to get evidence for the existence of the enolate **14** during the proposed mechanism, we have performed D_2O based control experiments (Scheme 2B). Accordingly, the propargylic acetate **7** was treated with NIS in CH_3CN and D_2O (1:1) at 100 °C. After 15 min, the reaction cleanly provided the diiodoketone **8** without any deuterium incorporated product **8-D**. On the other hand, the α,α-diiodo-α’-acetoxyketone **8** was also treated with CH_3CN and D_2O (1:1) at 100 °C for 4.5 h. The ^{1}H-NMR analysis of the reaction mixture shows a mixture of six possible compounds **8**, **8-*D***, **9**,**9-*HDa***, **9-*HDb***, and **9-*DD*** with mono- and di-deuterium incorporations (for details see the supporting information). These experiments clearly supports the existence of the enolate structure **14** during the mono-deiodination process.

After discovering the water (Lewis base) promoted, highly selective and controlled mono-deiodination of α,α-diiodo-α’-acetoxyketones for the generation of α-iodo-α’-acetoxyketones, we next focused to evaluate the generality of this transformation (Table 2). Accordingly a wide array of α,α-diiodo-α’-acetoxyketones possessing a 2°-acetoxy group were employed under standard reaction conditions. Various functional groups such as OMe, F, Cl, and Br, are found to be compatible under reaction conditions at different positions on the benzene ring to provide access to corresponding α-iodo-α’-acetoxyketones **16-27**, in good yields. 1-Naphthyl-, 3-indolyl- and aliphatic propargylic acetates were also successfully employed to synthesize α-iodo-α’-acetoxyketones **28-30**. From the table 2, it is observed that there is no strong electronic effects of the substituent on the reaction rates. But among the three regio-isomeric compounds (*o*-, *m*-, & *p*-) for a particular substituent, *ortho*-isomer is taking more time than *para*- followed by *meta*-isomer. Furthermore, a primary propargylic acetate was also efficiently transformed into mono-iodoketone **31**.

Table 2: Scope study for *sec*- and *pri*-acetoxy-diiodoketones



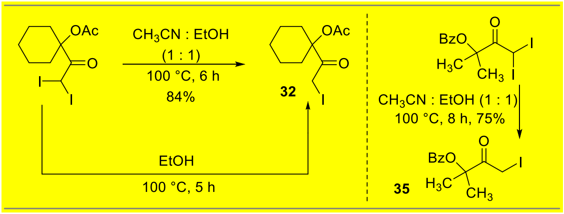
Subsequently, attention has been focused on 3°-acetates (Scheme 3). To our surprise, the conversion of di-iodoketones of this kind to corresponding α-iodoketones, found to be relatively slower (2-3 days) than their secondary counterparts under standard reaction conditions. After 48 h, the reaction was completed to give **32** in 70% yield. This may be due to the steric bulk created by the quaternary centre. Next structurally divergent di-iodoketones with 3°-acetates were employed under standard reaction conditions. All the substrates underwent smooth mono-dehalogenation process to afford the corresponding α-iodoketones **33-38** in good yields (62-75%).



Scheme 3: a) Scope study for tert-acetoxy-diiodoketones; b) verifying this strategy to simple dihaloketones

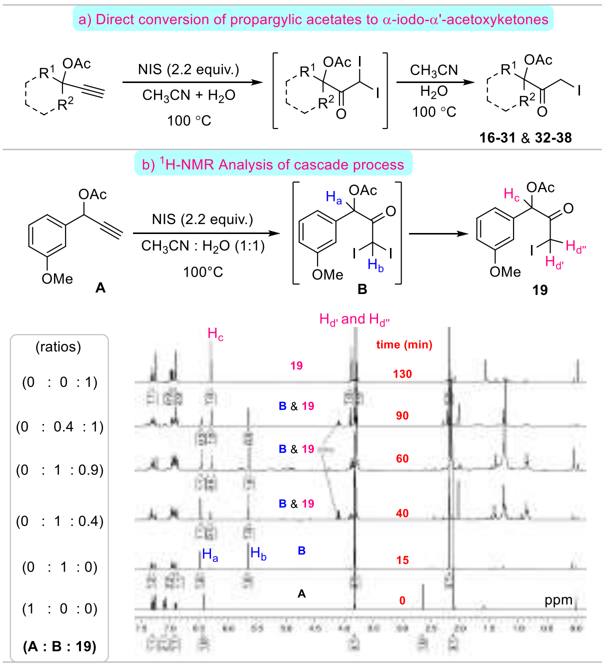
When an α,α-dibromoketone **39** was subjected to these conditions, only about 35% conversion to mono-bromoketone **40** was observed after 72 h. Furthermore, we also employed simple α,α-dihaloketones[13] such as α,α-diiodo- and α,α-dibromo-acetophenones **41a** and **41b**. The diiodoketone **41a** provided the corresponding α-iodoacetophenone **42a** in 65% yield after heating in CH_3CN+H_2O mixture at 100 °C for 10 h. Whereas the dibromoacetophenone **41b** afforded only a trace (~11%) of mono-debrominated product **42b** even after 48 h under standard conditions.

Next, to further prove the existence of the enolate intermediate and to support that the mono-deiodination occurs via the Lewis basicity of the water, we have also performed the reaction in presence of ethanol (a Lewis base) with two diiodoketones (Scheme 4). Delightfully, the efficient formation (84% and 75%) of the corresponding mono-iodoketones **32** and **35** was observed. These experiments again supports the fact that the Lewis basicity of water is responsible for the mono-deiodination via the enoate intermediate.



Scheme 4: Employing ethanol as the Lewis base to further support the enolate intermediate

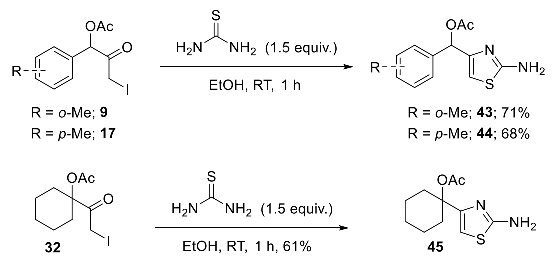
In order to improve the synthetic efficiency and accessibility of this transformation, we aimed at developing a cascade process for the synthesis of α-iodo-α'-acetoxyketones directly from the corresponding propargylic acetates without the isolation of the respective dihaloketones (Scheme 5a). In this process the water has been concurrently employed as a nucleophile as well as a Lewis base in a sequential manner. To the best of our knowledge this simultaneous dual reactivity of was not reported before for organic synthesis. The nucleophilicity of water transforms the proaprgylic acetates into corresponding α'-acetoxy-α,α-dihaloketones, whereas the Lewis basicity converts α'-acetoxy-α,α-dihaloketones into α'-acetoxy-α-haloketones by a highly controlled mono-dehalogenation process.



Scheme 5: a) Cascade conversion of propargylic acetates to α-iodo-α'-acetoxyketones under metal free conditions; b) ^{1}H-NMR analysis for the cascade formation of mono-iodoketone **19** from propargylic acetate **A** *via* di-iodoketone **B**

Accordingly, various propargylic acetates (secondary as well as tertiary) were treated with NIS (2.2 equiv.) in $CH_3CN:H_2O$ at 100 °C. All the substrates underwent the cascade process smoothly to generate α-iodo-α'-acetoxyketones **16-31** and **32-38**. And all these cascade processes found to be as efficient as the two-step strategy. To the best of our knowledge there are no reports on the direct conversion of propargylic acetates into the corresponding α-halo-α'-acetoxyketones[14] hence this strategy constitutes the first of such a cascade transformation. Furthermore this process is metal and catalyst free. The cleanliness of the discovered cascade process has been shown by ^{1}H-NMR monitoring of the conversion of propargylic acetate **A** to α-iodo-α'-acetoxyketone **19** *via* the α,α-diiodo-α'-acetoxyketone **B**. The ratios of compounds **A**, **B** and **19,** and an overlay diagram of ^{1}H-NMR spectra of the reaction mixtures at various time intervals after workup is depicted in scheme 5b

Finally, the synthetic utility of the derived α-iodoketones[15] as building blocks[16] in organic synthesis has been highlighted by converting them to bioacitive thiazoles.[17] Accordingly, compounds **9**, **17** & **32** were individually treated with 1.5 equiv. of thiourea in ethanol at RT. After 1 h, the corresponding thiazoles **43-45** were isolated in good yields (Scheme 6).



Scheme 6: Conversion of α-iodoketones to bioactive thiazoles

Conclusions

In conclusion we have discovered and developed a new strategy for the highly selective and controlled mono-dehalogenation of α,α–dihaloketones. The Lewis base character of the greenest reagent water has been explored and utilized over its nucleophilic property for this new transformation. This process is contrary to the classical reaction between gem-dihalides ad water, where water acts as a nucleophile. Extending this concept, first direct conversion of propargylic acetates to corresponding α-iodo-α'-acetoxyketones *via* α,α-diiodo-α'-acetoxyketones has also been efficiently achieved under metal free conditions. This later cascade transformation describes the concurrent dual reactivity of water as a nucleophile followed by a Lewis base. This may be the first of its own type.

Experimental Section

Representative general experimental procedure for synthesis of α-haloketones from α,α-dihaloketones employing water as the Lewis base:

The solution of α,α-di-haloketone (1 equiv.) was taken in a sealed tube containing (1:1) mixture of CH_3CN and H_2O. This resulting solution was refluxed at 100 °C. Reaction mixture was diluted with brine solution (10 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the crude reaction mixture by flash column chromatography (9:1; hexane:EtOAc) gave the α-haloketone.

For full details of all experiments, and spectroscopic data for all new compounds see the Supporting Information

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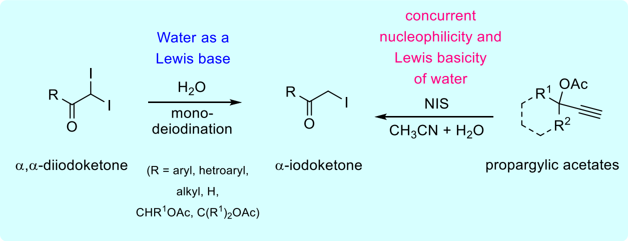

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