ChemPubSoc Europe

DOI: 10.1002/chem.201604739

CHEMISTRY
A European Journal
Communication

Synthetic Methods

CuOTf-Catalyzed Selective Generation of 2-Aminopyrimidines from Carbodiimides and Diaryliodonium Salts by a Triple C(sp^3)–H Functionalization

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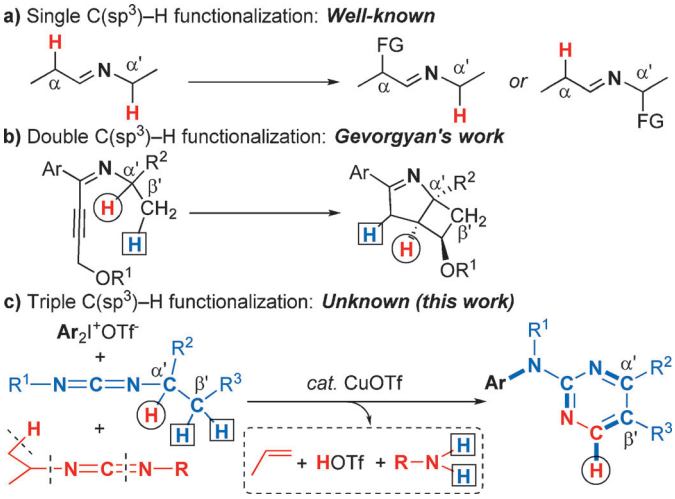
Abstract: The selective C(sp^3)–H bond functionalization is an ideal and atom-economical method in organic synthesis. In this work, 2-aminopyrimidines are generated from a Cu-catalyzed reaction between carbodiimides and diaryliodonium salts, by cleavage of four C(sp^3)–H, one C–N, and one C=N bonds in the carbodiimides. It is the first triple C(sp^3)–H bond functionalization neighboring a C=N bond. The selective synthesis of 2-aminopyrimidines is controlled by the amount of the diaryliodonium salts. The novel mechanism involving a C–N formation/1,5-H shift/1,7-H shift/6π-electrocyclic ring-closing/aromatization is well elucidated by the detection of important intermediates and DFT calculations.



Scheme 1. C(sp^3)–H functionalization neighboring a C=N bond.

The direct functionalization of C(sp^3)–H bonds has become a fantastic field in modern synthetic organic chemistry, because it provides a streamlined and step-economical synthesis of desired compounds without preactivation of the coupling partners.[1] The low reactivity and site selectivity of C(sp^3)–H bonds are two major challenges for C(sp^3)–H bond functionalizations. To deal with these problems, various directing groups and catalytic systems have been utilized to lower activation energies and control the selectivity.[2] As important directing groups, imines could also be nitrogen sources used to avoid the waste of elements. Therefore, the functionalization of α,α'-C(sp^3)–H bonds neighboring a C=N bond has received much attention. The major strategy in this area was based on the acidity of C(sp^3)–H bonds (Scheme 1 a).[3] For example, the groups of Oshima, Walsh, and others have succeeded in achieving the regioselective α'-arylation of 2-azaallyl anions from imines.[4] However, due to the large distance to directing groups and low acidity, the β'-C(sp^3)–H bond functionalization is considered as a challenging but valuable subject.[5] Gevorgyan et al. reported the formation of fused pyrroline products by an unusual transformation of alkynyl imines, in which two C–H bonds at α' and β' positions of the imine were cleaved by two sequential 1,5-H shifts (Scheme 1 b).[6] Thereafter, this C(sp^3)–H functionalization strategy by multiple sequential H-shifts/cyclizations is rare due to three difficulties: 1) the suitability of the conjugated system as H acceptor, 2) the intrinsic inertness of the remote C(sp^3)–H bond, and 3) the control of the H-shift selectivity. To deal with these difficulties we used carbodiimide, an aza-allene structure, as H acceptor. As far as we are aware, the challenging triple C(sp^3)–H bond functionalization neighboring a C=N double bond has not been reported (Scheme 1 c).

2-Aminopyrimidines are found in a wide range of drug molecules and are important for their biological activities (Scheme 2).[7] This skeleton is usually prepared by the condensation reaction of 1,3-dicarbonyl compounds with guanidines or by substitution of pyrimidines using amine nucleophiles by a C–N bond formation.[8] These methods generally involve a multi-step synthesis, expensive reagents that are not readily available, and harsh reaction conditions.[8] We are interested in the bond cleavage and recombination of carbodiimides to construct heterocyclic compounds.[9] Here, we report a Cu-catalyzed reaction between carbodiimides and diaryliodonium salts to synthesize 2-aminopyrimidines by a combined cleav-

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/chem.201604739.

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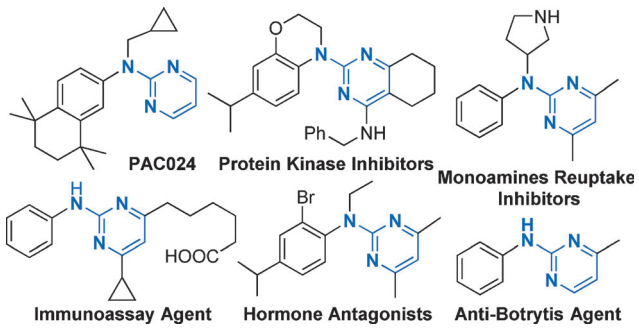
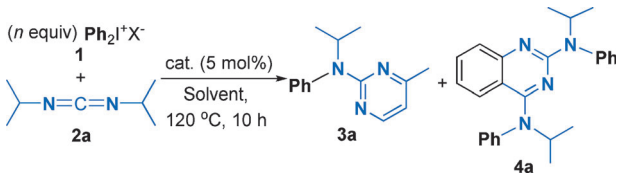


Scheme 2. Representative examples of 2-aminopyrimidines with biological activities.

age of four C(sp^3)–H, one C–N, and one C=N bonds in the carbodiimides (Scheme 1c). It is the first triple C(sp^3)–H functionalization neighboring a C=N bond.

The reaction of diphenyliodonium salts (X = PF_6^-, Cl^- or OTf^-) and *N*,*N*′-diisopropylcarbodiimide **2a** (*i*PrN=C=N*i*Pr, DIC) was first examined under various conditions. As a control experiment, a diphenyliodonium salt (X = PF_6^-) was heated with **2a** in DCE at 120 °C for 10 h, but no product was observed (Table 1, Entry 1). When a reaction with an 1:1 molar ratio of

Table 1. Optimization of the reaction conditions.

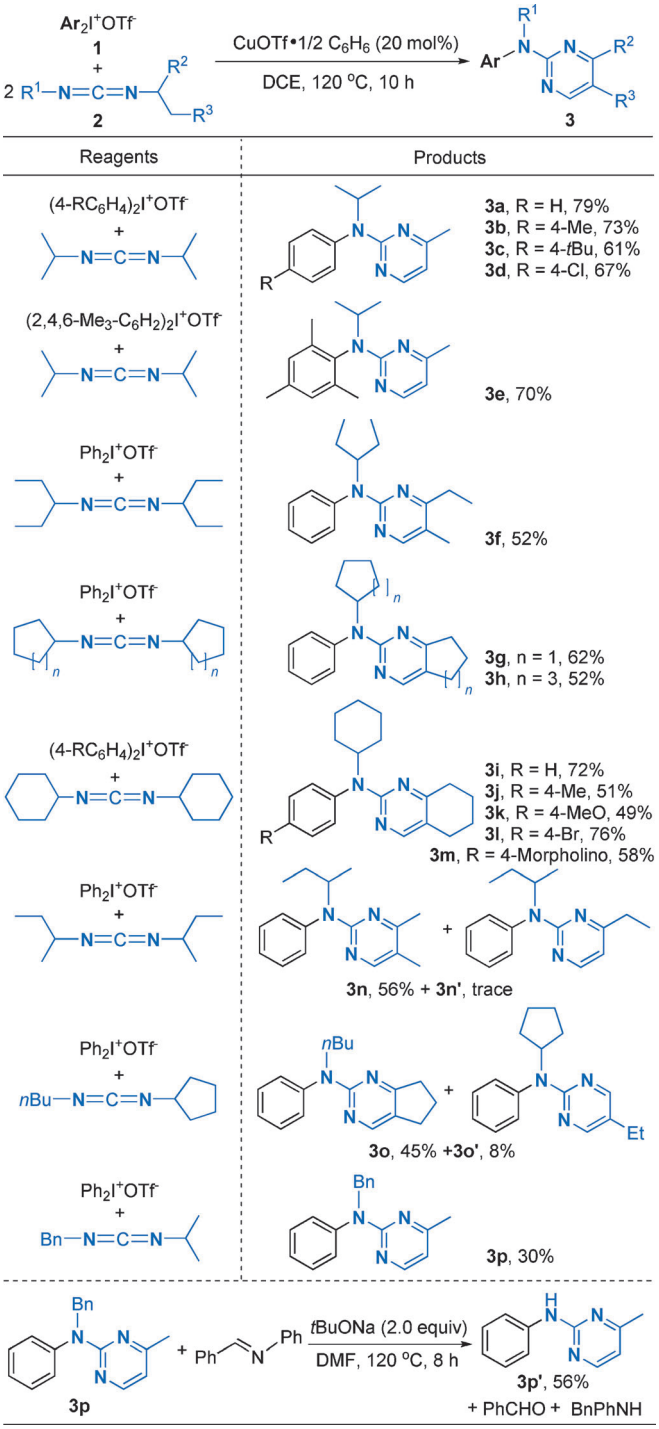


Entry	Solvent	X	*n*	Cat.	Yield **3a**[a] [%]	Yield **4a**[a] [%]
1	DCE	PF_6^-	1.0	None	–	–
2	DCE	PF_6^-	1.0	CuOTf·1/2 C_6H_6	13	34
3	DCE	PF_6^-	0.5	CuOTf·1/2 C_6H_6	28	–
4	THF	PF_6^-	0.5	CuOTf·1/2 C_6H_6	–	–
5	MeCN	PF_6^-	0.5	CuOTf·1/2 C_6H_6	10	–
6	Toluene	PF_6^-	0.5	CuOTf·1/2 C_6H_6	<5	–
7	DCE	OTf^-	0.5	CuOTf·1/2 C_6H_6	59	–
8	DCE	Cl^-	0.5	CuOTf·1/2 C_6H_6	<5	–
9	DCE	OTf^-	0.5	$Cu(OAc)_2$	13	–
10	DCE	OTf^-	0.5	CuCl	<5	–
11	DCE	OTf^-	0.5	$Cu(OTf)_2$	55	–
12[b]	DCE	OTf^-	0.5	CuOTf·1/2 C_6H_6	79	–
13[b]	DCE	OTf^-	1.5	CuOTf·1/2 C_6H_6	7	46
14[b]	DCE	OTf^-	2.0	CuOTf·1/2 C_6H_6	–[c]	49

[a] Isolated Yield. [b] 20 mol% catalyst was used. [c] Only trace amounts were isolated.

the diphenyliodonium salt (X = PF_6^-) and **2a** was carried out in the presence of CuOTf·1/2 C_6H_6 in DCE at 120 °C for 10 h, two pyrimidine derivatives **3a** and **4a** were isolated in 13% and 34%, respectively (Table 1, Entry 2). The unexpected product **3a** drew our interest, because it was generated from one diphenyliodonium salt and two DIC molecules by an unusual mechanism. Then, we screened various reaction conditions, such as the ratio of the two substrates, and the used solvents, Cu and iodonium salts (Table 1, Entries 3–14). Finally, we found that **3a** could be obtained in 79% isolated yield by using CuOTf·1/2 C_6H_6 (20 mol%) as catalyst in DCE at 120 °C for 10 h (Table 1, Entry 12).

Scheme 3 summarizes representative results obtained from the Cu-catalyzed reaction of diaryliodonium salts and carbodiimides. Various functional groups on the phenyl ring of diaryliodonium salts, including methoxy, amino, and halogen



Scheme 3. Synthesis of 2-aminopyrimidine derivatives **3a–p.**

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groups (**3d**, **3k**–**m**), could be tolerated. Carbodiimides containing at least one α' hydrogen and two β' hydrogens were suitable to provide different 2-aminopyrimidines (**3a**–**p**). Cycloalkyl-substituted carbodiimides led to the formation of bicycle-fused 2-aminopyrimidines (**3g**–**m**). When *s*BuN=C=N*s*Bu was utilized, **3n** was obtained as the main product, and only traces of **3n′** were observed. When unsymmetrical carbodiimides, such as *n*BuN=C=NCyp and BnN=C=N*i*Pr, were utilized, isomers **3o** and **3p** were obtained as the major products. This is mainly owing to the less steric hindrance of *n*Bu or Bn compared to secondary alkyl groups, which leads to a more smooth reaction of the N atom connected to primary *n*Bu or Bn with the diaryliodonium salts. As for **3p**, the Bn group could be removed to form **3p** (Scheme 3),[10a] which was reported to have *anti*-botrytis activity.[7d] The structure of **3l** was confirmed by X-ray crystallographic analysis (Figure 1).[10b] It contains a pyrimidine ring and three N atoms, which indicates that two carbodiimides molecules participated in this reaction with a novel cleavage of C(sp^3)–H, C–N, and C=N bonds.

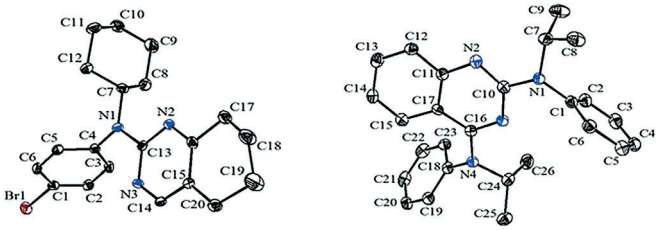
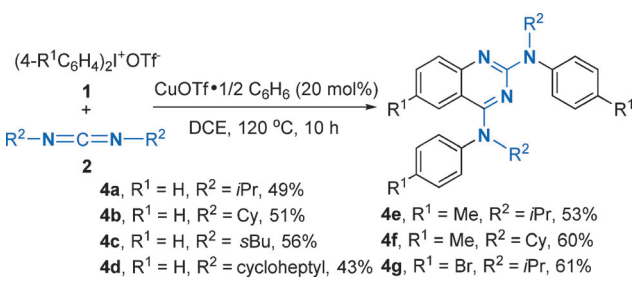


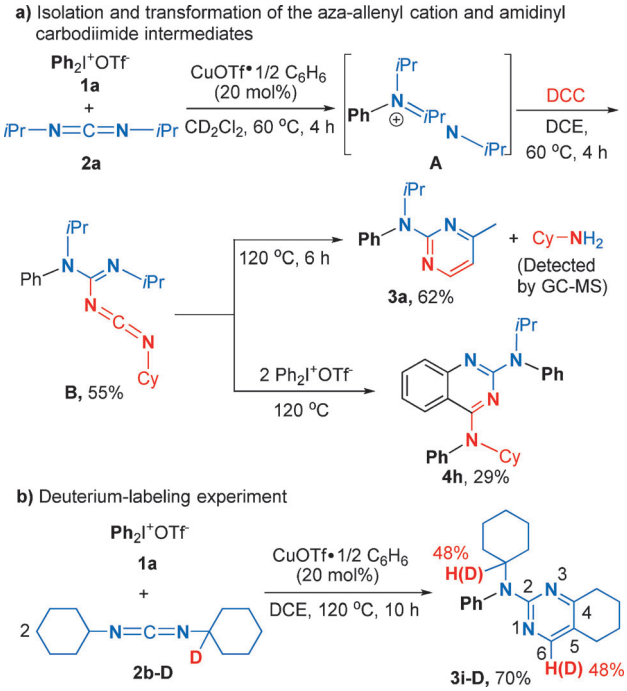
Figure 1. Molecular structure of **3l** and **4a**. All hydrogen atoms are omitted for clarity, and ellipsoids are shown at the 30% probability level.

When an excess of the diphenyliodonium salt was utilized under the same conditions, the benzopyrimidine **4a** became the major product (Table 1, Entry 14). Furthermore, various benzopyrimidines **4b**–**g** could be obtained in a similar procedure (Scheme 4). The structure of **4a** was confirmed by X-ray crystallographic analysis (Figure 1).[10b] **4a** was constructed from two DIC and three diphenyliodonium salt molecules. It clearly shows that the amount of iodonium salts can control this reaction pathway and lead to totally different products.

These interesting results motivated us to explore the reaction mechanisms for formation of **3** and **4** (Scheme 5). Based on related work on iodonium salt chemistry,[11,12] a highly active cation **A** could be considered as a key intermediate.



Scheme 4. Synthesis of benzopyrimidines **4a**–**g**.



Scheme 5. Mechanistic studies.

When **1a** was allowed to react with one equivalent of **2a** at 60 °C for 4 h, the aza-allenyl cation intermediate **A** was formed in a quantitative yield as detected by in situ NMR spectroscopy (Scheme 5a). **A** is relatively electron deficient, and could be nucleophilically attacked by another carbodiimide, yielding the amidinyl carbodiimide **B** along with a release of cyclohexene and a small amount of **3a**. When **B** was heated to 120 °C, **3a** was obtained in 62% yield. On the contrary, when an excess of the iodonium salt was added to **B** at 120 °C, **4h** could be obtained. These results show that **A** and **B** are two key intermediates in this process and the amount of the iodonium salt controls the formation of **3a** or **4h**. Furthermore, deuterated dicyclohexylcarbodiimide (**2b-D**) was allowed to react with **1a** to provide **3i-D** (Scheme 5b). There was 48% (maximum 50%) D incorporation at the C6 position of the pyrimidine ring in **3i-D**, which unambiguously indicates that the hydrogen atom at the C6 position should originate from the α'-H atom of the carbodiimide.

To gain more mechanistic information, DFT calculations were carried out with the Gaussian 09 program package.[13] The optimized structures of all the minima and transition states were fully calculated at the B3LYP[14]/LANL2DZ (for Cu)/6–31+G* (for other elements) level in the gas phase. The computational results of a possible pathway for the formation **3a** is shown in Scheme 6. Based on former computational work,[15] the diphenyliodonium salt could react with Cu^{I} to form a Ph–Cu^{III} species as **Int-1**. Followed by the coordination and insertion of carbodiimide, the aza-allenyl **Int-3** is constructed. It could be nucleophilically attacked by another carbodiimide molecule to give **Int-4**, which is the rate-determining step and requires 20 kcal mol^{-1} energy. After an olefin elimination, the amidinyl carbodiimide **Int-5** is generated.

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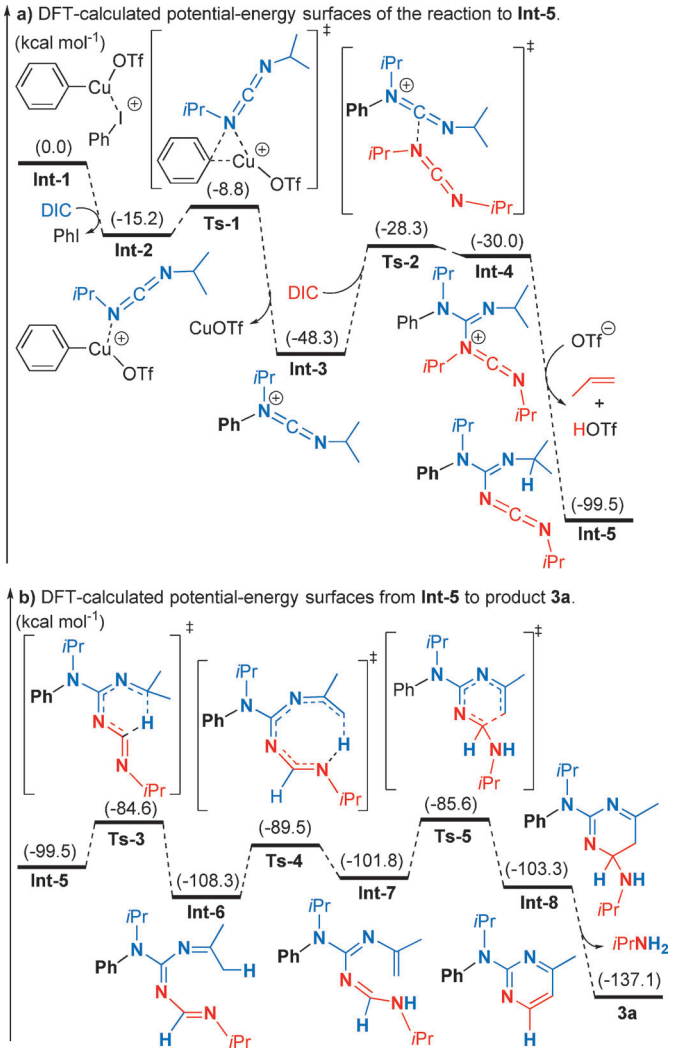

Scheme 6. DFT-calculated potential-energy surfaces of the reaction to generate **3a**.

Int-5 is a key intermediate and can go through three possible pathways, depending on the amount of diaryliodonium salts. When using an excess of diaryliodonium salts, the reaction would finally yield **4a** (see the Supporting Information). These computational results agree with the experiments in Scheme 5a. When there is no iodonium salt, a Friedel–Crafts type nucleophilic attack would need 27.9 kcal mol^{-1} (see the Supporting Information), which is evidently a higher barrier than that of the 1,5-H shift (**Ts-3,** 14.9 kcal mol^{-1}). A 1,5-H shift in **Ts-3** was proven by the deuterium-labeling experiment in Scheme 5b. The triple C(sp^3)–H functionalization process from **Int-5** to **3a** includes a 1,5-H shift (**Ts-3**)/1,7-H shift (**Ts-4**)/6π-ERC (**Ts-5**, ERC = electrocyclic ring-closing)/aromatization. It is a reasonable reaction pathway, because all the energy barriers were less than 20 kcal mol^{-1}. The complete mechanism is given in the Supporting Information.

In summary, we successfully developed a Cu-catalyzed reaction to synthesize 2-aminopyrimidines from carbodiimides and diaryliodonium salts by a triple C(sp^3)–H bond functionalization neighboring a C=N double bond. More interestingly, this novel mechanism undergoes a C–N formation/1,5-H shift/1,7-H shift/6π-ERC/aromatization and involves a triple C(sp^3)–H bond, C–N bond, and C=N bond cleavage. The whole mechanism was well elucidated by the detection of important intermediates, deuteration experiments, and DFT calculations.

Acknowledgements

This work was supported by the Natural Science Foundation of China (nos. 21572005, 21372014), and the "973" program from the National Basic Research Program of China (2012CB821600).

Keywords: 2-aminopyrimidines · C(sp^3)–H functionalization · carbodiimide · diaryliodonium salts · hydrogen shift

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Manuscript received: October 9, 2016
Accepted Article published: ■■ ▮▮, 0000
Final Article published: ■■ ▮▮, 0000

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COMMUNICATION

Synthetic Methods

Y. Chi, H. Yan, W.-X. Zhang, Z. Xi**

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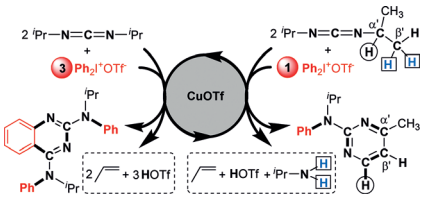
CuOTf-Catalyzed Selective Generation of 2-Aminopyrimidines from Carbodiimides and Diaryliodonium Salts by a Triple C(sp^3)–H Functionalization



Triple C(sp^3)-H Functionalization: Two Cu-catalyzed reactions between carbodiimides and diaryliodonium salts are achieved to provide various amino-substituted pyrimidines. The selective synthesis of 2-aminopyrimidines is controlled by the amount of diaryliodonium salts. It is the first triple C(sp^3)–H functionalization neighboring a C=N bond. The novel mechanism via C-N formation/1,5-H shift/1,7-H shift/6π-ERC/aromatization (ERC = electrocyclic ring-closing) for 2-aminopyrimidines is well elucidated by the detection of intermediates and DFT calculation.

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