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Letter

Photocatalytic Keto- and Amino-Trifluoromethylation of Alkenes

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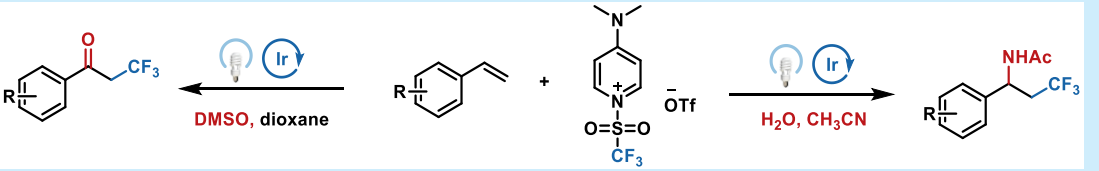
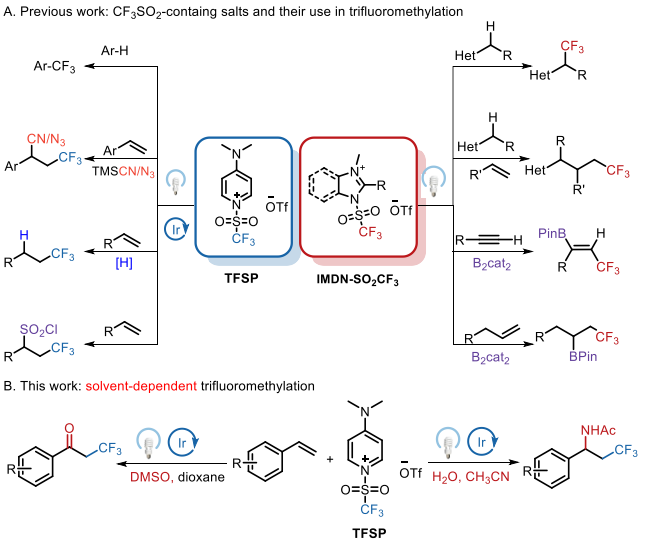


ABSTRACT: Efforts to develop alternatives to triflic anhydride (Tf_2O) as a trifluoromethylation reagent continue due to its limitations, including volatility, corrosiveness, and moisture sensitivity. Described herein is the use of a trifluoromethylsulfonylpyridinium salt (**TFSP**), easily obtained by a one-step reaction of Tf_2O with 4-dimethylaminopyridine, as a reagent for the trifluoromethylative difunctionalization of alkenes by photoredox catalysis. DMSO and CH_3CN are suitable solvents for achieving keto- and amino-trifluoromethylation of alkenes, respectively, with good functional group tolerance.

The distinct electronic properties of the trifluoromethyl group (CF_3), such as its strong electron-withdrawing capacity (σ_m = 0.43, σ_p = 0.54) and high lipophilicity (Hansch constant π = 0.88),[1] have made it a useful tool for modifying the physicochemical properties of organic molecules. As a result, a large number of CF_3-containing pharmaceuticals have been developed, including flecainide, efavirenz, and tipranavir. Given the great value of introducing a CF_3 group for altering the biological activity of compounds, extensive research efforts have been devoted to developing new trifluoromethylation reagents for the installation of a CF_3 group.[2] Despite the existence of various reagents, such as $TMSCF_3$,[2g] CF_3SO_2Na,[2i] Togni Reagents,[2f] TT-$CF_3^+OTf^-$,[3] and the Umemoto reagent,[4] certain limitations, such as high volatility or cost, have prompted further investigations for the development of efficient reagents.

Triflic anhydride (Tf_2O) is a highly reactive and versatile reagent commonly used in organic synthesis.[5] Its primary application is activating C−OH bonds by converting alcohols or phenols into triflates, allowing for the subsequent nucleophilic substitution or cross coupling.[6] In 2018, Tf_2O was first identified as a trifluoromethylation reagent by the group of Qing.[7] They found that Tf_2O can be activated by pyridine to form a $CF_3SO_2^-N^+$ intermediate, which can undergo desulfonylation to release a $CF_3\bullet$ radical under photoredox conditions. This finding has served as inspiration for other research groups to explore the radical trifluoromethylation using Tf_2O in the presence of a pyridine derivative as an activator.[8] While Tf_2O is efficient as a trifluoromethylation reagent, it does have some disadvantages, such as high volatility, corrosiveness, and moisture sensitivity. To address these challenges, two alternative CF_3SO_2-containing salts have been developed, an imidazolium salt (IMDN-SO_2CF_3)[9] and a pyridinium salt (TFSP) (Scheme 1A).[10] The imidazolium salt

Scheme 1. CF_3SO_2-Containg Salts and Their Use in Trifluoromethylation



(IMDN-SO_2CF_3), developed by Wang and his colleagues, has shown promising capabilities in enabling the C(sp^3)−H trifluoromethylation of azines[9b] and the trifluoromethylation-borylation of unsaturated hydrocarbons.[9a] Although the TFSP

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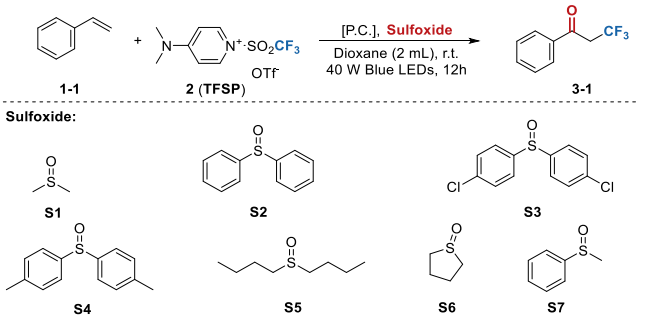
pyridinium salt was previously known,[11] it was first developed as a trifluoromethylation reagent by our research team.[10,12]

As mentioned above, when using Tf_2O as a trifluoromethylation reagent, the presence of pyridine is required to activate Tf_2O by forming a crucial $CF_3SO_2^-N^+$ intermediate.[7,8] However, this intermediate has not been isolated and characterized, probably because of its low stability, and as a result it has not been utilized as a trifluoromethylation reagent. In sharp contrast, the TFSP salt, which can be easily obtained by a one-step reaction of Tf_2O with 4-dimethylaminopyridine, is a stable and easy-to-handle solid, which makes it a highly practical trifluoromethylation reagent.[12a,c] We have discovered that TFSP can effectively facilitate C−H trifluoromethylation of (hetero)arenes[12a] and various trifluoromethylations of alkenes,[10,12b,c] such as azido- and cyano-trifluoromethylation,[10] hydro-trifluoromethylation,[12b] and sulfonyl-trifluoromethylation.[12c] These trifluoromethylative difunctionalization reactions allow for the incorporation of a second functional group in addition to the CF_3 group, which has become an active research area.[13] However, for the installation of the second group X, only a C−X single bond was constructed using TFSP. We are then interested in the introduction of a second group Y by constructing C═Y double bonds with the use of TFSP. We find that a DMSO/dioxane cosolvent allows for keto-trifluoromethylation of alkenes with TFSP. Interestingly, the use of CH_3CN as a reaction solvent leads to amino-trifluoromethylation products. Herein we describe the solvent-dependent trifluoromethylative difunctionalization of alkenes under photocatalytic conditions (Scheme 1B).

Keto-trifluoromethylation of alkenes, which was pioneered by us[14] and has been further developed by other research groups,[15] usually occurs via a single electron transfer to generate a CF_3• radical, which attack alkenes to form a C−CF_3 bond. Prompted by the shortcomings of these approaches, such as the stoichiometric use of oxidants or the high cost of trifluoromethylation reagents, we direct our investigation toward employing TFSP to carry out this reaction under photoredox conditions. Styrene (**1-1**) was used as the model substrate, and DMSO was selected as the keto oxygen source in our optimization process, as summarized in Table 1. Initially, we explored a range of photocatalysts (entries 1−6) and observed that the use of Ir(ppy) as the photocatalyst in conjunction with DMSO as the solvent produced the desired product, albeit with a low yield of 16% (entry 1). We subsequently found that TFSP is reactive to DMSO and will be transformed by DMSO into an unknown species. Therefore, we experimented with a mixed solvent system (see the Supporting Information for details) comprising DCM or 1,4-dioxane (entries 7 and 8). This approach improved the yield to 35%, with dioxane being preferred to avoid the complexities encountered with DCM. Further experimentation with different sulfoxides to identify an effective oxygen source (entries 9−17) established that DMSO was superior for generating the targeted product. Prolonging the reaction time to 24 h enhanced the yield to 37% (entry 10). Notably, when DMSO was used in 10 equiv, we succeeded in increasing the yield significantly to 54% (entry 18). Further increasing the loading of DMSO did not increase the yield (entry 19). Reducing the photocatalyst loading to 2.5 mol % resulted in a similar yield (entry 20).

Equipped with the optimal conditions as detailed (Table 1, entry 20), we explored the substrate scope of the keto-trifluoromethylation of styrenes. Scheme 2 illustrates the broad

Table 1. Optimization of Keto-Trifluoromethylation Conditions[a]



entry	[P.C.]	sulfoxide	yield (%)[b]
1[c]	$Ir(ppy)_3$	**S1** (2 mL)	16
2[c]	$[Ir(dtbbpy)(ppy)_2]PF_6$	**S1** (2 mL)	7
3[c]	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**S1** (2 mL)	trace
4[c]	$Ru(bpy)_3Cl_2$	**S1** (2 mL)	N.D.
5[c]	$Ru(bpy)_3(PF_6)_2$	**S1** (2 mL)	trace
6[c]	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]BF_4$	**S1** (2 mL)	trace
7[d]	$Ir(ppy)_3$	**S1** (1 mL)	35
8[e]	$Ir(ppy)_3$	**S1** (1 mL)	35
9	$Ir(ppy)_3$	**S1** (2 equiv)	21
10[f]	$Ir(ppy)_3$	**S1** (2 equiv)	37
11	$Ir(ppy)_3$	**S2** (2 equiv)	7
12	$Ir(ppy)_3$	**S3** (2 equiv)	trace
13	$Ir(ppy)_3$	**S4** (2 equiv)	trace
14	$Ir(ppy)_3$	**S5** (2 equiv)	6
15	$Ir(ppy)_3$	**S6** (2 equiv)	20
16[f]	$Ir(ppy)_3$	**S6** (2 equiv)	25
17	$Ir(ppy)_3$	**S7** (2 equiv)	16
18[f]	$Ir(ppy)_3$	**S1** (10 equiv)	54
19[f]	$Ir(ppy)_3$	**S1** (12 equiv)	51
20[f,g]	$Ir(ppy)_3$	**S1** (10 equiv)	53

[a]Reaction conditions: substrate **1-1** (0.2 mmol), **2**, sulfoxide, and photocatalyst [P.C.] (3 mol %) in 1,4-dioxane (2 mL) were irradiated with 40 W blue LEDs at r.t. for 24 h under a N_2 atmosphere. [b]Yield was determined by ^{19}F NMR using $PhOCF_3$ as an internal standard. [c]DMSO was used as the reaction solvent instead of dioxane. [d]DCM (1 mL) was used as a cosolvent. [e]Dioxane (1 mL) was used as a cosolvent. [f]The reaction time was 24 h. [g]Using 2.5 mol % $Ir(ppy)_3$.

applicability of the reaction, indicating that a diverse array of styrenes could undergo keto-trifluoromethylation. A variety of functional groups, including nitrile, ester, halogen, boronic ester, and silicon groups, were shown to be compatible with the process. The reaction was found to be successful regardless of the electronic nature of the substituents on the aryl ring, with electron-donating, electron-neutral, and electron-withdrawing groups all yielding the desired products. Styrenes with varying electronic properties could be successfully transformed into their corresponding keto-trifluoromethylation products with moderate yields. Even styrenes containing a reactive silicon or a boronic ester group could be used without compromising the integrity of these groups, as seen in products **3-12** and **3-13**. Besides terminal alkenes, internal alkenes are also reactive toward this process (**3-6**, **3-13** and **3-14**). For all of the above reactions, only moderate yields were obtained, partly due to the occurrence of deprotonative trifluoromethylation, which resulted in the formation of CF_3-alkenes in approximately 20% yields. The reaction has been successfully applied in the synthesis of analogs of fenofibrate[16] (**3-15**) and

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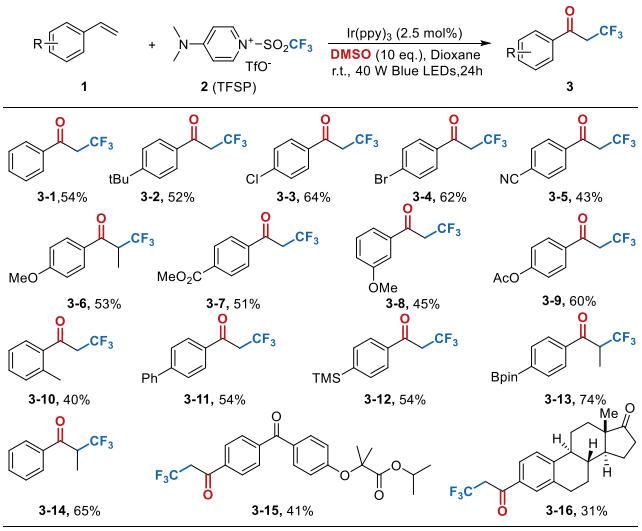
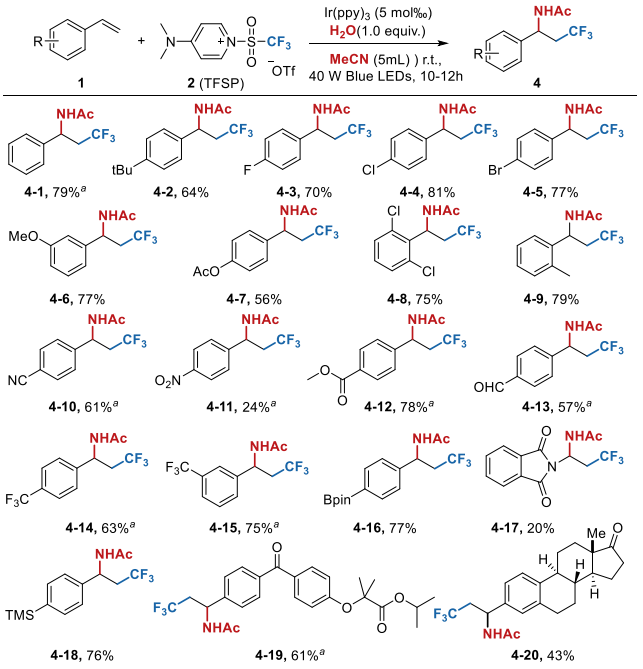
Scheme 2. Substrate Scope of Keto-Trifluoromethylation[a]



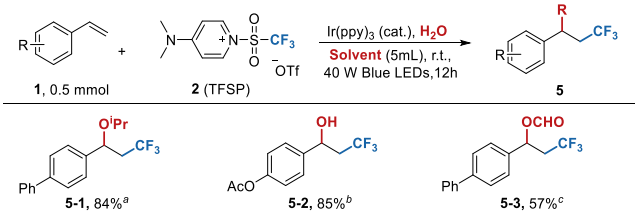
[a]Isolated yields are shown. Reaction conditions: substrate **1** (0.5 mmol), **2** (1.0 mmol), $Ir(ppy)_3$ (0.0125 mmol, 2.5 mol %), DMSO (354 μL, 5 mmol), and dioxane (5 mL) at room temperature for 24 h under the irradiation of LED lights (450 nm) under a N_2 atmosphere.

Scheme 3. Amino-Trifluoromethylation of Alkenes[b]



[a][Ir(dtbbpy)(ppy)$_2$]PF_6 was used as a catalyst. [b]Isolated yields are shown. Reaction conditions: substrate **1** (0.5 mmol), **2** (0.9 mmol), $Ir(ppy)_3$ (0.0025 mmol, 0.5 mol %), H_2O (0.5 mmol), and CH_3CN (5 mL) at room temperature for 10−12 h under the irradiation of LED lights (450 nm) under a N_2 atmosphere.

Scheme 4. Trifluoromethylative Bifunctionalization of Styrene[d]



[a]Using ^{i}PrOH as a solvent without H_2O. [b]Using acetone as a solvent. [c]Using DMF as a solvent. [d]Isolated yields are shown. Reaction conditions: substrate **1** (0.5 mmol), **2** (1.0 mmol), $Ir(ppy)_3$ (0.0125 mmol, 2.5 mol %), H_2O (0.5 mmol), and solvent (5 mL) at room temperature for 12 h under the irradiation of LED lights (450 nm) under a N_2 atmosphere.

estrone[17] (**3-16**), which are used to treat abnormal blood lipid levels and symptoms caused by estrogen deficiency in peri- and postmenopausal women, respectively. This process is ineffective for the trifluoromethylation of aliphatic alkenes.

We found that using CH_3CN as the solvent leads to amino-trifluoromethylation product **4-1**. Subsequent optimization of the reaction conditions (see the Supporting Information for details) identified that employing 0.5 mol % $Ir(ppy)_3$ as the photocatalyst yields the amino-trifluoromethylation product with good efficiency. A broad range of electron-rich and electron-neutral substrates with a variety of functional groups proved to be compatible with the aminotrifluoromethylation (Scheme 3). However, electron-deficient substrates (**4-10** to **4-15**) exhibit lower reactivity toward this process when $Ir(ppy)_3$ is employed as the catalyst, which is likely due to the difficulty in oxidizing electron-deficient benzyl radical intermediates. Notably, the use of [Ir(dtbbpy)(ppy)$_2$]PF_6 as a photocatalyst was especially effective for transforming electron-deficient substrates. The superior performance of [Ir(dtbbpy)(ppy)$_2$]-PF_6 can be attributed to its higher oxidation potential ($E^{ox}_{1/2}[Ir^{IV}/Ir^{III}]$ = +1.21 V vs SCE) when compared with that of $Ir(ppy)_3$ ($E^{ox}_{1/2}[Ir^{IV}/Ir^{III}]$ = +0.77 V vs SCE), favoring the oxidation of the challenging electron-deficient benzyl radicals. The reaction's compatibility with reactive functional groups like Bpin and TMS could permit further diversification of the products (**4-16** and **4-18**). Besides aryl alkenes, enamines could also be transformed into the desired products (**4-17**). Furthermore, the reaction was successful in producing CF_3-substituted amide products **4-19** and **4-20**, derivatives of fenofibrate and estrone, respectively.

Apart from keto- and amino-trifluoromethylation, our study also investigated the use of different solvents to expand the applicability of trifluoromethylative bifunctionalization of alkenes. As shown in Scheme 4, a variety of solvents can be employed to achieve diverse trifluoromethylative bifunctionalization products, further exemplifying the practicality of this trifluoromethylation protocol.

To illustrate the synthetic utility, the reactions were performed on gram scales (Scheme 5), yielding product **3-9** (1.08 g) in a 55% yield and product **4-18** (1.09g) in a 72% yield, respectively. It should be noted that the deprotonative trifluoromethylation byproduct **3-9′** is also formed in the case of keto-trifluoromethylation with a 17% yield.

Further evidence was gathered to deepen our understanding of the reaction mechanism. It was found that DMSO is crucial to the success of keto-trifluoromethylation, suggesting that DMSO is the keto oxygen source (Scheme 6a). The absence of the desired product when either the photocatalyst $Ir(ppy)_3$ or light exposure is omitted confirms that the trifluoromethylation reactions proceed via a photoredox-catalyzed pathway. Moreover, when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical scavenger, was introduced to the reaction, the yields of desired products were dramatically decreased and TEMPO−

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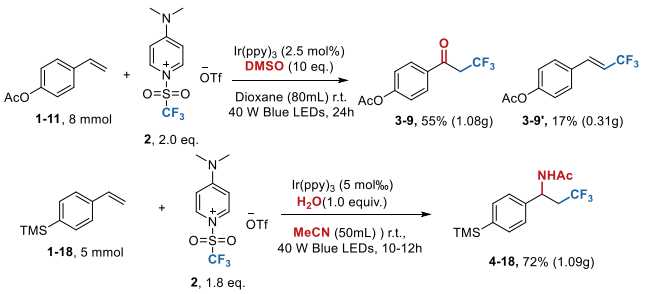
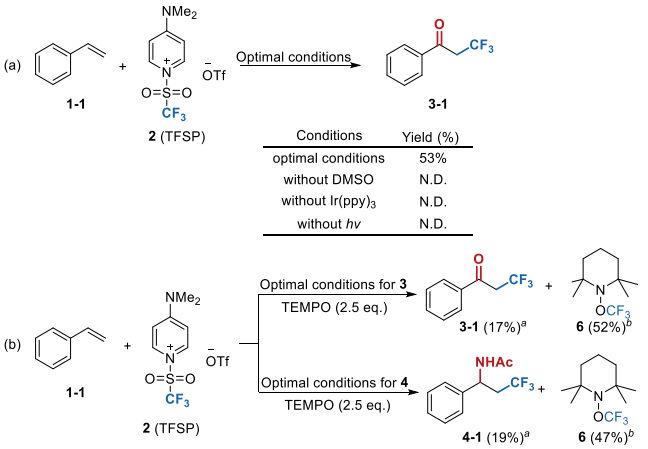
Scheme 5. Gram-Scale Reactions[a]



[a]Isolated yields are shown.

Scheme 6. Investigative Insights into the Mechanism[c]

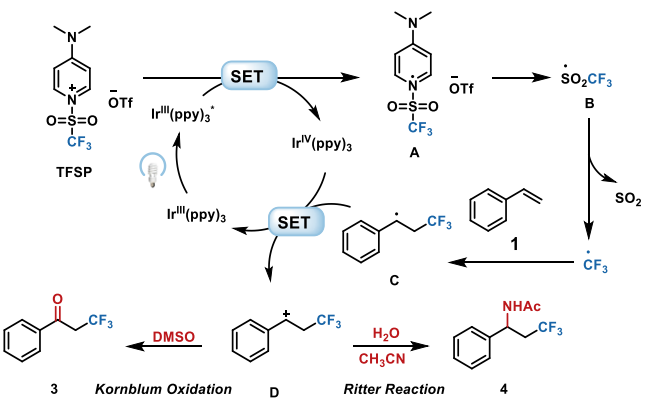


[a]The yield was calculated based on substrate **1-1**. [b]The yield was calculated based on TFSP. [c]All yields are determined by ^{19}F NMR spectroscopy.

CF_3 was generated as a byproduct, as illustrated in Scheme 6b. These findings strongly suggest that the trifluoromethylation of styrene operates through a radical mechanism.

Based on the mechanistic investigation and our previous studies,[10,12] we propose a plausible mechanism, as shown in Scheme 7. The photoreductive cleavage of TFSP by the excited-state photocatalyst results in the formation of radical **A**, which then undergoes homolysis to produce DMAP and radical **B**. The radical **B** then converts to the CF_3• radical via the elimination of SO_2. The CF_3• radical is subsequently trapped by styrene to generate benzyl radical intermediate **C**, which is oxidized to produce carbocation **D**. The Ritter reaction and Kornblum oxidation give the final amino-trifluoromethylation and keto-trifluoromethylation products, respectively.

Scheme 7. Plausible Reaction Mechanism



In conclusion, we have developed a photoredox-catalyzed keto- and amino-trifluoromethylation of alkenes with TFSP. TFSP, easy to prepare and convenient to handle, can act as a trifluoromethyl radical source under reductive conditions. The distinctive solvent-dependent keto- and amino-trifluoromethylation processes show a good level of functional group tolerance. The synthetic practicality was further demonstrated by gram-scale reactions and the synthesis of pharmaceutical derivatives.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c00447.

Materials and methods; experimental procedures; optimization studies; and ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, IR, and MS data (PDF)

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Notes

The authors declare no competing financial interest.

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