Triethylamine-Mediated Transformation of Phosphonates into Phosphonamidates

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Abstract: Organophosphorus compounds such as phosphonamidates are gaining attention across different fields of chemistry, with interesting applications as pharmaceuticals, or pesticides. However, practical application of phosphonamidates is complicated by their difficult syntheses which often involve expensive or unstraightforward reagents and harsh conditions. To remedy these issues, we present a flexible, room temperature synthesis for novel *P*-alkylphosphonamidates without the need for intermediary purification. Commonly available phosphonates are first chlorinated by use of oxalyl chloride and phosphonylaminium salts are used to mediate the harsh reactivity of phosphonochloridates, giving rise to the desired products. We demonstrate the compatibility of our protocol with primary and secondary amines, as well as with different phosphonate esters. The proposed pathway also enables the synthesis of primary phosphonamidates using ammonium acetate as a cheap and safe alternative for ammonia. In future research, this protocol will also enable the synthesis of bioactive targets that are incompatible with current protocols.

Introduction

Phosphonic acids and their various derivatives have long been targeted in organic synthesis due to their many applications, e.g. as flame retardants,[1] pharmaceuticals[2,3] or pesticides (Figure 1, **1-4**).[4,5] More recently, however, greater attention has also been paid to phosphonamidates, e.g. in antivirals such as the HIV drug tenofovir alafenamide (**5**) and in the DOPO (9,10-dihydro-9-oxa-10-phospha-phenanthrene-10-oxide) class of flame retardants (**6**).[2,6–8] In the design of bioactive compounds for medicinal or other applications, this moiety attracts attention by serving as a bioisostere to both sulfonamide[9–11] and carboxamide moieties[6,11,12]. Whereas phosphonates are generally highly resistant to hydrolysis,[13] phosphonamidates are more easily hydrolyzed and thus often more suitable as prodrugs.[6,7]

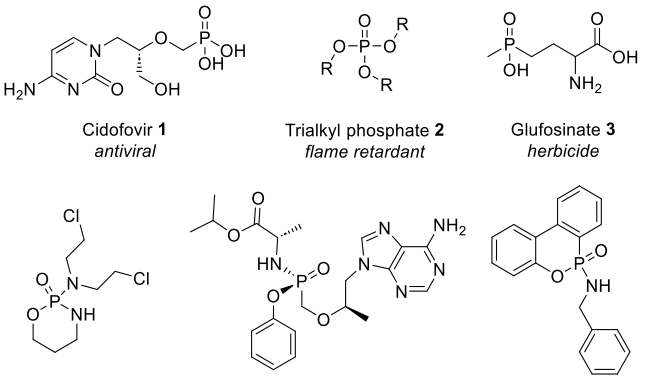
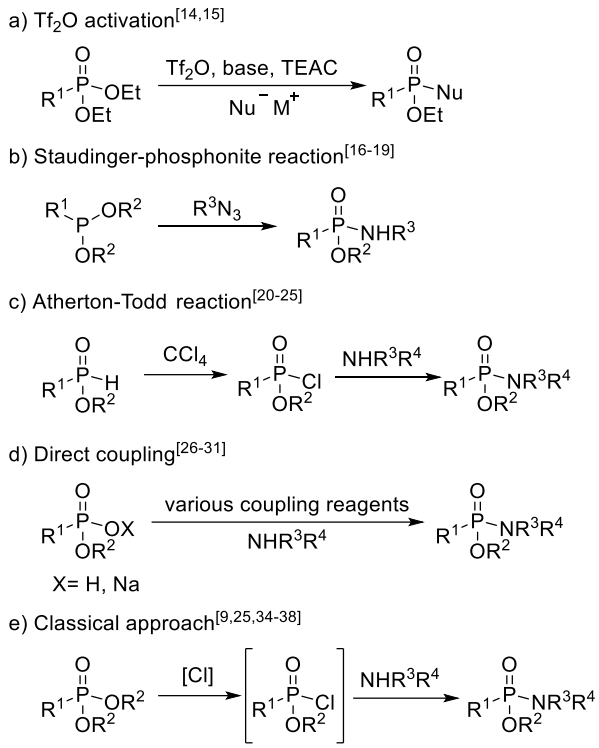


Figure 1. Representative examples of organophosphorus-compounds and their applications.

Recent literature shows various methods for the synthesis of the phosphonamidate functional group. In 2018, Kang *et al.*, demonstrated the synthesis of mixed phosphonates via a triflic acid-mediated activation of the corresponding symmetrical phosphonates.[14] Even though they did not expand their scope to other nucleophiles, this was published only a couple months later by the Maulide group (Scheme 1a).[15] Besides mostly evaluating secondary amines, their protocol also requires the deprotonation of the corresponding nucleophile, which hampers the compatibility with sensitive nucleophiles.[15]



Scheme 1. Overview of commonly used methodologies for the synthesis of phosphonamidate moieties.

Other methodologies include the use of the Staudinger-phosphonite reaction[16–19] (Scheme 1b), the Atherton-Todd reaction[20–25] (Scheme 1c) or direct coupling methods[26–31] (Scheme 1d). Even though the Staudinger-phosphonite and Atherton-Todd reactions are both straightforward and efficient reactions, their starting products must be synthesized separately and are either expensive or difficult to obtain. Moreover, the Staudinger-phosphonite reaction subsequently needs azides for the desired amide coupling, whereas the Atherton-Todd reaction generally employs CCl_4 for the necessary chlorination. These reagents come with substantial hazards, so avoiding their use is highly desirable. The direct coupling methodology usually starts from phosphonate mono-acids or salts and avoids the need for chlorinating agents by using coupling reagents, but the necessary coupling reagents are expensive and the final yields are often low.[28–31]

The most common and broadly applied route is a two-step sequence starting from symmetrical phosphonates (Scheme 1e). These phosphonates can be obtained either via a Michaelis-Arbuzov reaction[32] or by Hirao coupling[33]. The first step of this sequence is the chlorination of the phosphorus-center with chlorination agents such as oxalyl chloride or thionyl chloride, followed by substitution with the desired nucleophile.[9,25,34–38] This method also has its disadvantages: chlorinating agents often lack chemoselectivity and thus yield both the mono- and dichlorinated product.[39] This can be circumvented by partially hydrolysing the diester and selectively chlorinating the resulting mono-ester[9,36,37,40], but this adds a laborious additional purification step that reduces conversion and recovery rates. In light of these disadvantages, there is an unmet need for a straightforward and mild method for the synthesis of a wide array of phosphonamidates.

Via common transformations such as the Michaelis-Arbuzov reaction[32] or the Hirao coupling, dialkyl phosphonate esters can be readily accessed from the corresponding halides and in some cases, these products are even commercially available. Additionally, by choosing a mild chlorinating agent like oxalyl chloride, we can avoid dichlorination of the initial dialkyl phosphonate, as these desired monochlorinations can be found in literature for similar methodologies.[38,41–46] This approach also negates the need for an extra (partial) hydrolysis step, as mentioned before.

Additionally, in order to reduce the inherent reactivity of phosphonochloridates and omit (extensive) cooling during the phosphonamide coupling, literature revealed a possible solution in the use of phosphonylaminium salts. Some of these salts have already been described as phosphonylating agents for the formation of phosphonates or phosphonamidates, using pyridine and triethylamine as the corresponding amines (Figure 2).[14,47–51] To the best of our knowledge, the first of these types of adducts to be reported were adducts of pyridine, picoline and 2,6-lutidine and various dialkyl halophosphates, and the stability of the resulting salts **7** was studied with ^{31}P NMR.[47,48] This work concluded that lower temperatures and more sterically hindered pyridines, such as 2,6-lutidine, improved the stability of salts **7**. Contrastingly, recent work by Kang *et al.* seemingly encountered no stability issues when generating salts **8** with the use of triflic anhydride, indicating that the stability of these compounds differs depending on the nature of the phosphorus center.[14] Their work subsequently employs these cations as intermediates in the synthesis of mixed phosphonates. Triethylaminium cations **9**, in turn, have been described in a series of papers by Hirschmann and Smith in the synthesis of phosphonylated amino acids.[49–51] Comparison between the phosphonylaminium salts and the corresponding phosphonochloridates revealed that these salts are clearly superior in the formation of both phosphonate esters and their corresponding amides.

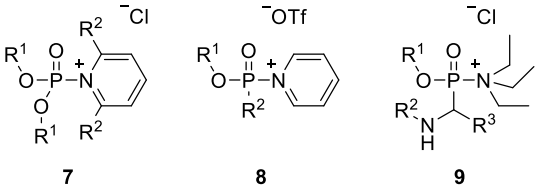
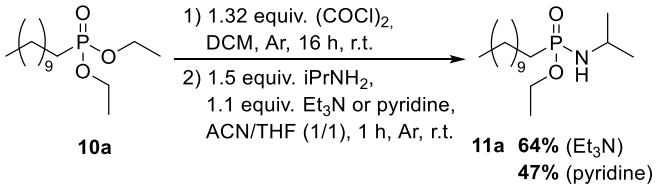


Figure 2. Phosphonylaminium salts described in literature.[14,47–51]

In this work, we present a room-temperature coupling method for the synthesis of novel phosphonamidates, starting from commonly available symmetrical phosphonates. A mild chlorinating reagent such as oxalyl chloride is employed to avoid side reactions in the chlorinating step. Meanwhile, phosphonylaminium salts are employed to mediate the amide coupling. Additionally, aniline derivatives could be included under reflux conditions. This combination of reagents and conditions allows for a mild synthesis of the desired phosphonamidates, which makes it useful in the synthesis of novel pharmaceutical or agrochemical target structures.

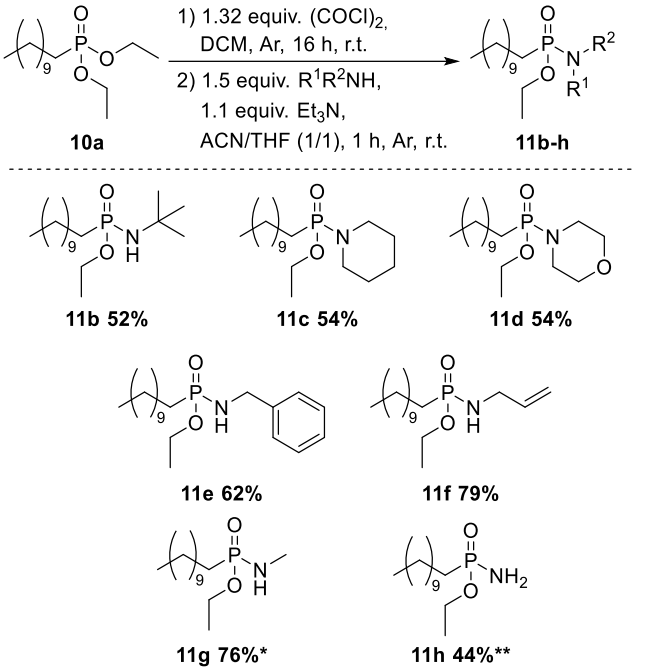
Results and Discussion

Convinced by the application potential of these phosphonylaminium salts, we chose to compare pyridine and triethylamine as mediators for the synthesis of phosphonamidates using diethyl undecylphosphonate and isopropylamine as model substrates (Scheme 2).[14,49–51] Diethyl undecylphosphonate **10a** is a novel compound, but readily accessible via Michaelis-Arbuzov coupling of triethyl phosphite and undecyl bromide with a yield of 79%.[52–54] Chlorination of this compound with oxalyl chloride at room temperature delivered the monochloride in sufficient purity to be directly used in the next step. To evaluate the potency of the phosphonylaminium salts, the phosphonochloridate was diluted in THF and stirred in the presence of pyridine or triethylamine. Afterwards, this solution was added dropwise to a second solution with the desired nucleophile dissolved in acetonitrile. As the isolated yields indicate, triethylamine is superior to pyridine in the synthesis of phosphonamidate **11a**. Spectroscopic analyses indicate a larger amount of the corresponding hydrolysis products in the reaction mixture with pyridine than triethylamine, thus explaining the difference in final yield. This indicates that the triethylamine-mediated method is better suited for the envisioned addition-elimination reaction with amines such as isopropylamine.



Scheme 2. Comparison between triethylamine and pyridine for the coupling of diethyl undecylphosphonate and isopropylamine

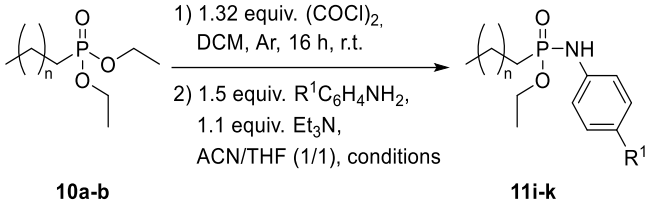
A logical next step was to investigate the scope of the reaction. With only few exceptions[38], literature reports on the synthesis of *P*-alkylphosphonamidates focus on the usage of secondary amines, either deprotonated or not.[15,34,55–57] To expand on this, we chose to include both primary and secondary amines, with a focus on primary amines. Replacing isopropylamine from Scheme 2 with other common amines like *tert*-butylamine, piperidine or morpholine resulted in similar, rather modest, yields for all three phosphonamidates (**11b-d**, Scheme 3). Subsequently, benzylamine and allylamine were selected as alternative primary amines, both being included in the final phosphonamidate in good yields (**11e** and **11f**, Scheme 3).



Scheme 3. Synthesis of different ethyl undecylphosphonamidates with various amines. *performed with 3 equiv. of a 9 w% solution of $MeNH_2$ in ACN. **performed with 2 equiv. NH_4OAc and 2.7 equiv. Et_3N.

Lastly, the conditions were adapted to evaluate the use of methylamine, used as a commercial solution in acetonitrile. Using 3 equivalents of methylamine led to a yield of 76% (**11g**, Scheme 3). To our satisfaction, the conditions could be extended further for the synthesis of primary phosphonamidates, using ammonium acetate as the source of the nitrogen-nucleophile. Slight adaptation of the conditions, compensating for the used acetate salt, resulted in a yield of 44% of ethyl undecylphosphonamidate (**11h**, Scheme 3). This also marks the first time that these primary phosphonamidates have been synthesized from ammonium salts such as ammonium acetate.

However, switching to aniline as a less nucleophilic amine did not allow for good conversion towards the target product under standard conditions and no pure product **11i** could be obtained (Scheme 4 and Table 1). Since the phosphonamidate coupling took longer to reach completion, we opted to evaluate p-anisidine as a more nucleophilic aniline derivative. Even though the reaction with p-anisidine progressed similarly to the other evaluated amines, this modification did not prove to be effective to ensure the isolation of the corresponding product **11j**. Interestingly, stirring the mixture with aniline under reflux conditions resulted in a cleaner conversion towards the corresponding product **11i** with 65% yield. Subsequently, the more nucleophilic p-anisidine was used under similar conditions allowing the isolation of product **11j** in a higher yield of 74%. Lastly, this modification towards heating conditions for reaction with aniline also resulted in the isolation of product **11k** in a 54% yield, starting from diethyl pentylphosphonate **10b**.

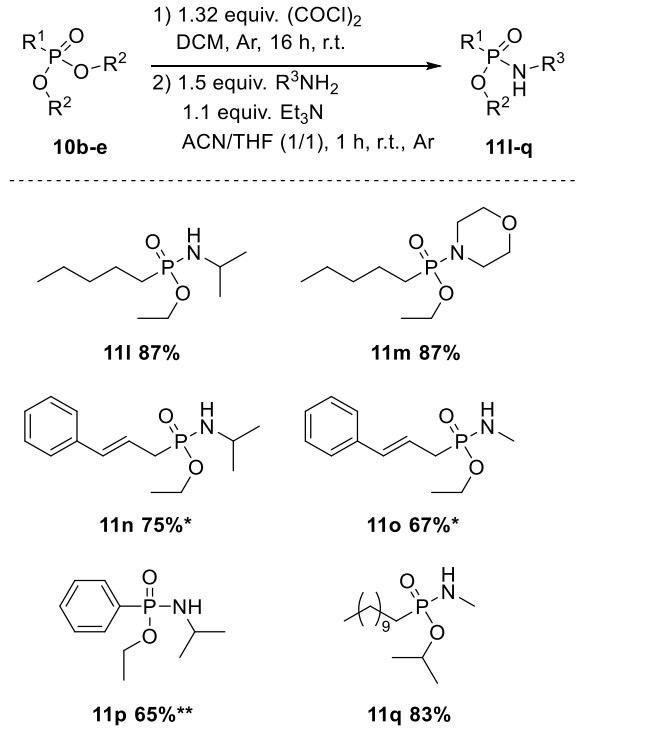


Scheme 4. Attempted synthesis of phosphonamidates with aniline derivatives as nucleophiles (see Table 1).

Table 1. Evaluated conditions for the synthesis of aniline-based phosphonamidates **11i-k**.

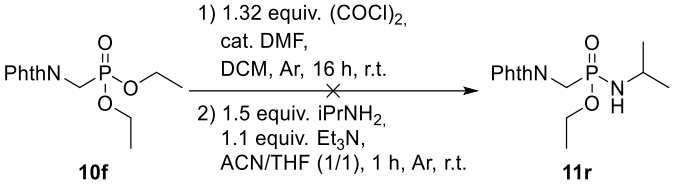
Product	n	R^2	Conditions	Yield (%)
11i	9	H	20 h, Ar, r.t.	/
11j	9	OMe	4 h, Ar, r.t.	/
11i	9	H	2 h, Ar, reflux	65
11j	9	OMe	2 h, Ar, reflux	74
11k	3	H	2 h, Ar, reflux	54

After diethyl undecylphosphonate **10a**, we successfully extended the scope of our method and achieved good results for diethyl pentylphosphonate **10b**, diethyl cinnamylphosphonate **10c** and diethyl phenylphosphonate **10d**, with isopropylamine, morpholine or methylamine (**11l-p**, Scheme 5). Only for the chlorination of the cinnamyl- and phenylphosphonate, the chlorination conditions had to be adapted slightly. Finally, an exemplary synthesis with diisopropyl undecylphosphonate **10e** was included to show the compatibility of our method with other dialkyl phosphonates (**11q**, Scheme 5).



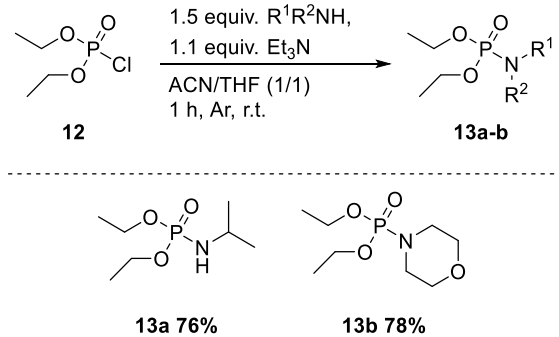
Scheme 5. Synthesis of different phosphonamidates with different phosphonates. *step 1: + cat. DMF. **step 1: + cat. DMF and reflux overnight.

Evaluating our conditions on diethyl (phthalimidomethyl)phosphonate **10f** revealed that the proposed conditions were incompatible with the proposed aminomethylphosphonate (**11r**, Scheme 6). At first glance, this appears to be in contrast with the papers by Hirschmann and Smith, who have described these types of couplings on aminomethylphosphonates. However, they chlorinate the corresponding mono-ester rather than directly chlorinating the diester. This difference is thus most likely responsible for this difference in compatibility.



Scheme 6. Attempted synthesis of aminomethylphosphonamidate **11r**.

In contrast to the *P*-alkyl phosphonamidates synthesized thus far in this paper, reactions with common phosphorochlorides have been reported before, thereby providing the opportunity to compare our conditions with those mentioned in the literature. When substituting the phosphonate substrate with commercial diethyl chlorophosphate **12** and evaluating the reaction with both isopropylamine and morpholine (Scheme 7), we were able to synthesize products **13** in 76 and 78% yield, respectively. This is in contrast to the reactions with diethyl undecylphosphonate, where a higher yield was achieved with isopropylamine then morpholine. In literature, *N*-isopropylphosphoramidate **13a** has been synthesized in 98% yield, using diisopropylethylamine in DCM, indicating that the impact of these conditions differs greatly between different types of phosphorus moieties.[38] The morpholine-based product **13b**, on the other hand is reported in the literature in 70% yield via the benzotriazole surrogate and with microwave heating.[58] Our method does not require heating, uses commercially available diethyl chlorophosphate **12**, is safer and does not require an extra synthesis step to make the surrogate reagent. Finally, an iodine-mediated synthesis investigated by Peng and coworkers, starting from triethylphosphite instead of diethyl chlorophosphate, in turn outperforms our method.[59] The major drawback, aside from the use of DCM, is that their methodology needs trivalent phosphorus centers, for which the corresponding alkylphosphonites are notoriously difficult to synthesize.



Scheme 7. Benchmarking against literature formation of diethyl phosphoramidates **13a** and **13b**.

Conclusion

In conclusion, we have demonstrated a straightforward two-step method for the synthesis of *P*-alkylphosphonamidates without the need for cooling in the amide coupling or deprotonation of the desired nucleophile. The discussed methodology uses easily obtainable starting products and reagents to ensure a broad applicability in end products. Chlorination with oxalyl chloride at room temperature eliminates the risk of contaminating side products in the final mixture and the use of phosphonylaminium salts to mediate the amide coupling proved to be crucial for the formation of a novel class of *P*-alkylphosphonamidates. The scope of the proposed conditions was shown to include a wide array of primary and secondary amines with good yields, most notably allylamine and methylamine. Similarly, primary phosphonamidates could be synthesized in the same way, for the first time using ammonium acetate as nucleophile. Other phosphonates could be included with good yields. The scope could subsequently be extended to less nucleophilic aniline derivatives as well, requiring reflux conditions to ensure successful isolation of the target. These results indicate that this mild synthesis protocol could be used to synthesize a wide array of bioactive target structures. In future work, evaluation of other nucleophiles, such as alcohols or thiols may open up further applications for the use of phosphonylaminium salts.

Experimental Section

The instrumentation, description of the experiments and characterisation data can be found in the supplementary information.

The synthesis of ethyl *N*-isopropyl-*P*-undecylphosphonamidate **11a** is described as example for the general procedure used. Under argon atmosphere, oxalyl chloride (1.32 equiv.; 0.42 mL, 4.8 mmol) is added dropwise to a stirred solution of the corresponding phosphonate **10a** (3.7 mmol, 1 equiv.) in 20 mL dry DCM. This solution is stirred for 16 hours at room temperature and the conversion is monitored via ^{31}P-NMR. After completion of the reaction, solvent is evaporated under reduced pressure to yield a crude mixture of phosphonochloridate. Due to the instability of the compound, the crude compound is immediately used in subsequent reactions. The corresponding phosphonochloridate and triethylamine (1.1 equiv.; 825 µL; 4.0 mmol) were dissolved in 30 mL dry THF under argon atmosphere and left stirring for 30 min at room temperature, after which the reaction mixture was analysed using ^{31}P-NMR. Isopropylamine (1.5 equiv.; 5.5 mmol) was dissolved in 30 mL dry ACN under argon atmosphere, while stirring at room temperature. The solution containing the phosphonochloridate was added dropwise to the amine solution at room temperature and stirred for 1h (monitored with ^{31}P-NMR). Subsequently, the excess hydrochloride salts were removed via filtration, upon addition of diethyl ether and the solvent was evaporated under reduced pressure. The title compound was additionally purified using normal phase automated column chromatography (SiO_2, EtOAc:hexane 3:1 v:v, 5% Et_3N, gradient MeOH 0-7 v%), after which 1.78 g of product **11a** was obtained as a yellowish oil with a yield of 64%.

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Data Availability Statement

The data that support the findings in this study are available in the supplementary material of this article.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amines • phosphorus • phosphonamidate synthesis • phosphonochloridate • amide coupling

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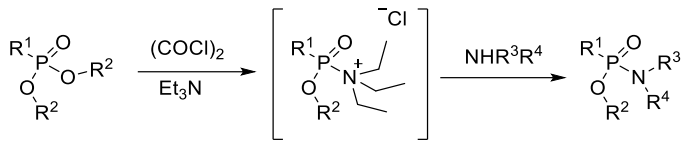

This work presents a flexible, straightforward methodology to synthesize phosphonamidates starting from commonly available phosphonates, and demonstrates the use of phosphonylaminium salts to mediate the harsh reactivity of phosphonochloridates. Our methodology is demonstrated on primary amines, secondary amines, ammonium acetate, aniline derivatives and different phosphonate diesters.

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