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N–N Bond Formation using an Iodonitrene as an Umpolung of Ammonia: Straightforward and Chemoselective Synthesis of Hydrazinium Salts

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Abstract. The formation of hydrazinium salts by N-N bond formation has typically involved the use of hazardous and difficult to handle reagents. Here, mild and operationally simple conditions for the synthesis of hydrazinium salts are reported. Electrophilic nitrogen transfer to the nitrogen atom of tertiary amines is achieved using iodosylbenzene as oxidant and ammonium carbamate as the N-source. The resulting process is highly chemoselective and tolerant to other functional groups. A wide scope is reported, including examples with bioactive molecules. Insights on the structure of hydrazinium salts were provided by X-ray analysis.

Keywords: Hydrazinium Salts; Electrophilic Nitrogen; Nitrene; Hypervalent Iodine; Amines

The N-N bond, typical of hydrazine derivatives, represents a structural motif of interest in drug discovery and modern synthesis. In fact, the heteroatom-heteroatom linkages (X-X, where X = N, O, S and P) are intriguing structural motifs of pharmacologically active molecules.[1] Examples of pharmaceutically relevant molecules bearing N-N bonds in hydrazine or hydrazinium motifs are collected in Figure 1. Hydrazinium salts have been studied for their antibacterial antispasmodic,[2] pain relief modulator,[3] and antihistaminic activities, and as precursors of alkylhydrazines, amines, and alkenes.[4,5]

The incorporation of the N-N moiety commonly relies on the use of hydrazine as a primary feedstock. However, hydrazine must be carefully handled due to its intrinsic toxic and explosive nature. Given the relevance of such functional groups in medicinal chemistry, synthetic methods to circumvent the use of hydrazine and low molecular weight hydrazine derivatives can provide improved and safer synthetic sequences.

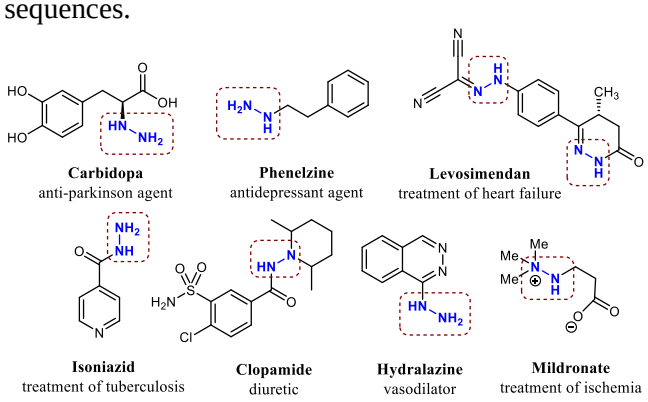
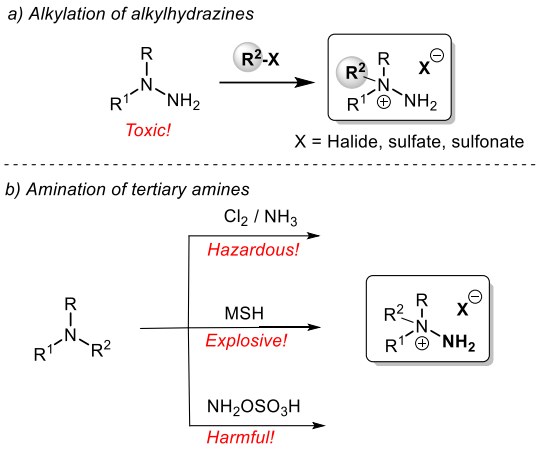


Figure 1. Biological relevant molecules including the N-N motif.

Few approaches are available for the synthesis of hydrazinium salts, the most common being alkylation of alkylhydrazines by reaction with alkyl halides, sulfates or sulfonates (Scheme 1, a).[6] An alternative approach involves the direct amination of tertiary amines with electrophilic nitrogen sources (Scheme 1, b).[7-10] The transfer of the amino group to form hydrazinium salts has been achieved using, 1) the *in situ* generation of chloramine from ammonia and

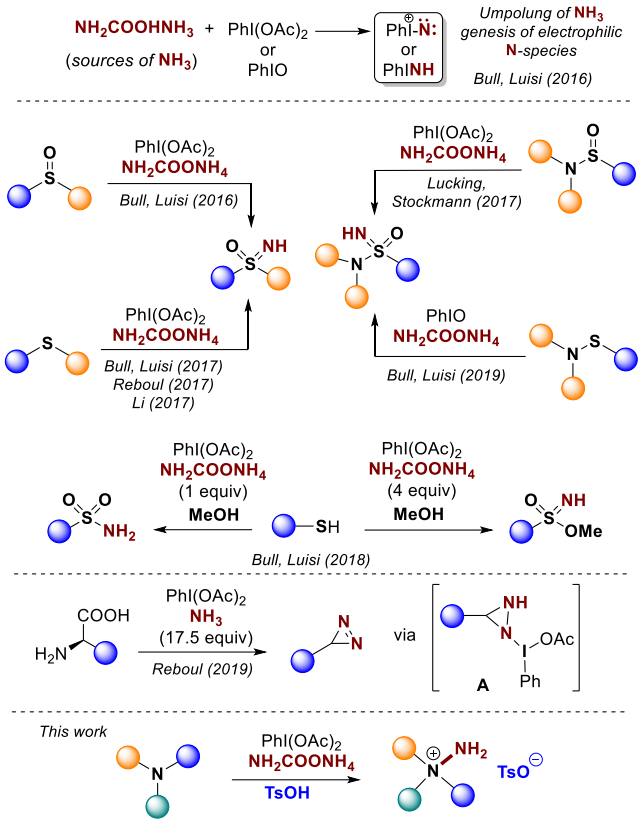
chlorine, which poses problems related to the use of toxic molecular chlorine; 2) the use of the explosive *O*-(mesitylsulfonyl)hydroxylamine (MSH) as the aminating agent; 3) the use of the corrosive and harmful hydroxylamine-*O*-sulfonic acid.



Scheme 1. Available approaches to hydrazinium salts.

As the amination of tertiary amines represents a strategy to avoid the use of hydrazine we envisaged applying safer amination reagents, generating umpolung ammonia using hypervalent iodine reagents. Here we report a new simple approach for the direct preparation of hydrazinium salts from tertiary amines using an electrophilic iodonitrene.

In 2016 we reported that an electrophilic *N*-species, as iodonitrene [PhIN]$^+$ (or iminoiodinane PhINH),[11] was generated by reacting a hypervalent iodine reagent ($PhI(OAc)_2$ or PhIO), with ammonium carbamate as a simple source of ammonia (Scheme 2).[12] This electrophilic *N*-species is able to react with sulfur compounds providing several iminated derivatives such as sulfoximines,[12,13] sulfonimidates and sulfonamides,[14] and sulfonimidamides[15] (Scheme 2). Reboul reported recently an elegant synthesis of 1,2-diazirine starting from α-aminoacids, using a combination of $PhI(OAc)_2$ and an excess of NH_3.[16] Diaziridine **A** resulting from the addition of an iodonitrene to an imine (Scheme 2), was proposed as an intermediate.



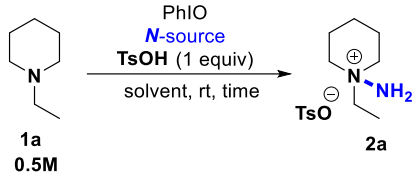
Scheme 2. Use of iodonitrene as source of electrophilic nitrogen.

We started our investigation using *N*-ethylpiperidine **1a** as model substrate; the results of the optimization study are collected in Table 1. First, we tested conditions successfully employed with sulfides and sulfoxides,[12,13a] using $PhI(OAc)_2$ (2.5 equiv) as the oxidant, and ammonium carbamate (2.0 equiv) as nitrogen source in MeOH. To our delight we were able to detect the expected hydrazinium salt **2a'** in 88% yield. However, isolation of a pure hydrazinium salt was complicated by the excess acetic acid derived from the oxidant. For this reason, PhIO[17] was selected as suitable hypervalent iodine reagent for this reaction. Importantly, the addition of 4-methylbenzenesulfonic acid (TsOH) to the reaction rendered the tosic acid-hydrazinium salt an easily separable solid. The optimized conditions used PhIO (2.5 equiv), NH_2COONH_4 (2 equiv) and TsOH (1 equiv) in acetonitrile at 0.5 M concentration (Table 1, entry 1). Under these conditions, hydrazinium salt **2a** could be obtained almost quantitatively as a flowing powder after 3 h reaction time.

Other N-sources, ammonium carbamate, ammonium carbonate ($(NH_4)_2CO_3$), ammonium acetate (NH_4OAc), and aqueous ammonia were also suitable providing very good yields of hydrazinium salt **2a** (Table 1, entries 2-4). The use of methanolic ammonia was unsuccessful returning only unreacted starting material (Table 1, entry 5). Furthermore, several solvents were successful using 2.5 equiv of

PhIO and 2 equiv of NH_4COONH_2. High yields (>90%) were obtained with *i*-PrOH, CH_2Cl_2, DMF and toluene (entries 7-10). In contrast, the use of MeOH returned a modest 53% yield of **2a** (entry 6), while CPME was unsuitable (entry 12). Interestingly, this reaction can be run in water obtaining 67% yield of the salt **2a** (Table 1, entry 11). Slightly lower yields were obtained reducing the reaction time and lowering the amount of the oxidant and N-source (Table 1, entries 16-17). As control reactions, two experiments were run in absence of the oxidant or the N-source (Table 1, entries 18-19) returning only unreacted starting material.

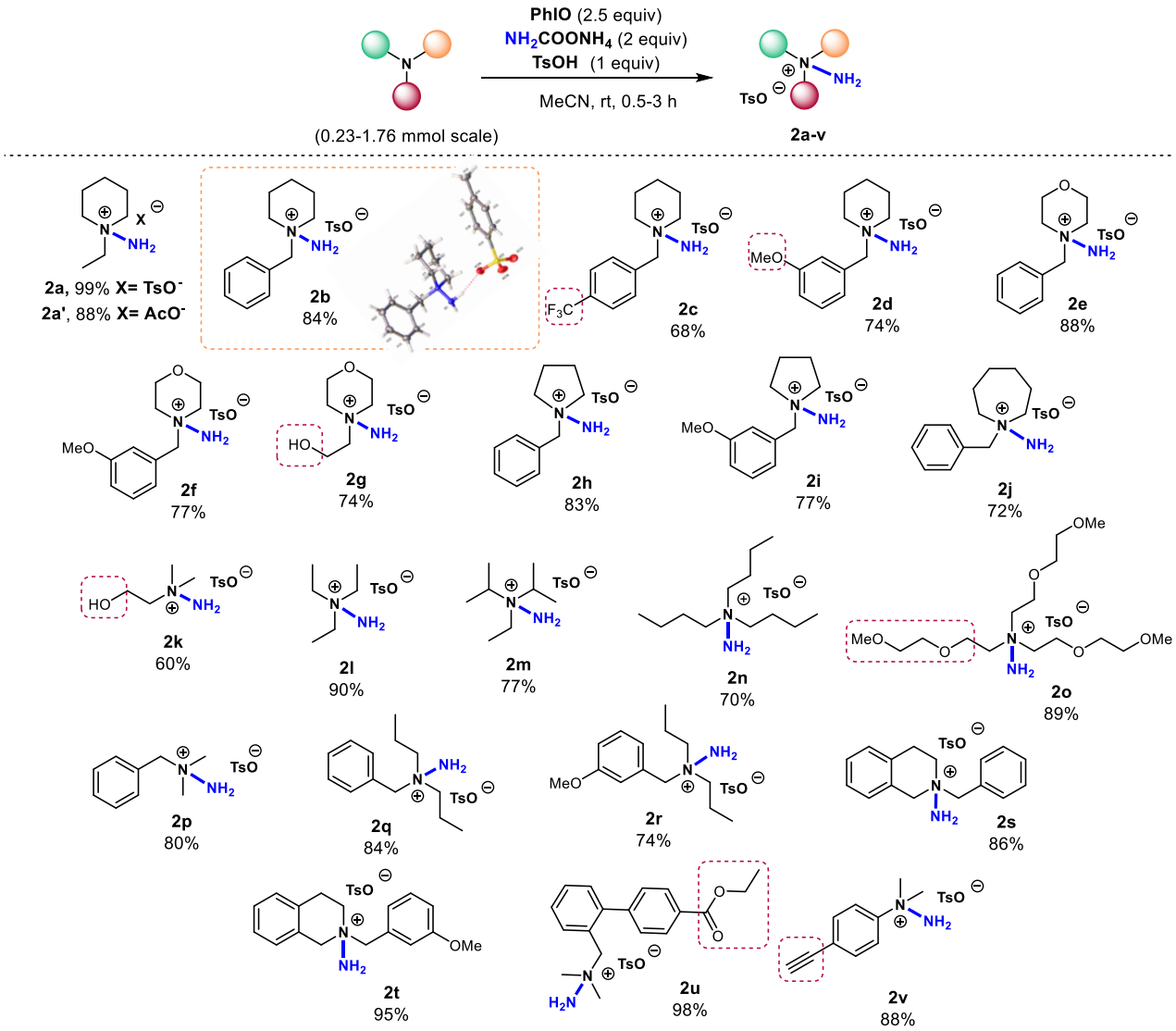
Table 1. Optimization study.



Entry	*PhIO (equiv)*	*N- source (equiv.)*	*Solvent* [a]	*t (h)*	*Yield (%)*[b]
1	2.5	NH_2COONH_4 (2)	MeCN	3	99
2	2.5	$AcONH_4$ (2)	MeCN	3	88
3	2.5	$(NH_4)_2CO_3$ (2)	MeCN	3	98
4	2.5	$NH_{3\ (aq)}$ (2)	MeCN	3	98
5	2.5	$NH_{3\ (MeOH)}$ (2)	MeCN	3	0
6	2.5	NH_2COONH_4 (2)	MeOH	3	53
7	2.5	NH_2COONH_4 (2)	*i*PrOH	3	98
8	2.5	NH_2COONH_4 (2)	toluene	3	94
9	2.5	NH_2COONH_4 (2)	CH_2Cl_2	3	98
10	2.5	NH_2COONH_4 (2)	DMF	3	93
11	2.5	NH_2COONH_4 (2)	H_2O	3	67
12	2.5	NH_2COONH_4 (2)	CPME	3	24
13	2.5	NH_2COONH_4 (2)	MeCN	2	99
14	2.5	NH_2COONH_4 (2)	MeCN	1	88
15	2.5	NH_2COONH_4 (2)	MeCN	0.5	87
16	1.5	NH_2COONH_4 (1)	MeCN	3	89
17	0.5	NH_2COONH_4 (2)	MeCN	3	25
18	0	NH_2COONH_4 (2)	MeCN	3	0
19	2.5	none	MeCN	3	0

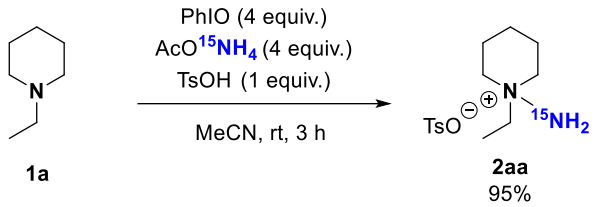
[a]Solvents: dimethylformamide (DMF), cyclopentylmethylether (CPME). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

With the optimal conditions in hand, we investigated the scope of this method using various tertiary amines (Scheme 3). Pleasingly, the reaction could be applied to different cyclic amines derived from piperidine, morpholine, pyrrolidine and azepane, furnishing the corresponding hydrazinium salts **2a-j** in good to excellent yields. The pure salts could be obtained by removing iodobenzene under high vacuum followed by precipitation and filtration (see Supplementary material). In the case of **2b**, the structure was unambiguously assigned by X-ray crystal diffraction.[18] Acyclic trialkyl amines were also suitable substrates, transformed to the corresponding hydrazinium salts **2k-o** in good to excellent yields. Other open-chain benzylic amines furnished salts **2p-r**, and **2u** with very good yields (>80%). The tetrahydroisoquinoline scaffold was also successfully employed leading to hydrazinium derivatives **2s**, **2t** with high yields. An aromatic amine was also tested with success in this *N*-transfer process, obtaining derivative **2v** with 88% yield. As reported in Scheme 2, the investigation of the scope of the reaction revealed functional group tolerance for this process. In fact, the presence of an hydroxyl group was tolerated as in the case of **2g** and **2k**, as well as the presence of carboxylic ester functionality or a triple bond as for **2u** and **2v**. Primary and secondary amines and other nitrogen containing compounds such as sulfonamides were unreactive under these conditions, while the use of imines led to the corresponding benzonitrile.[19]



Scheme 3. Scope for the hydrazinium salts.

Interestingly, the use of a ^{15}N-labelled N-source allowed for a selective introduction of a labelled amino group. Using 4 equiv of ^{15}N.ammonium acetate, 4 equiv of PhIO and 1 equiv of TsOH in MeCN, furnished the ^{15}N-labelled hydrazinium salt **2aa** with a 95% yield (Scheme 4).

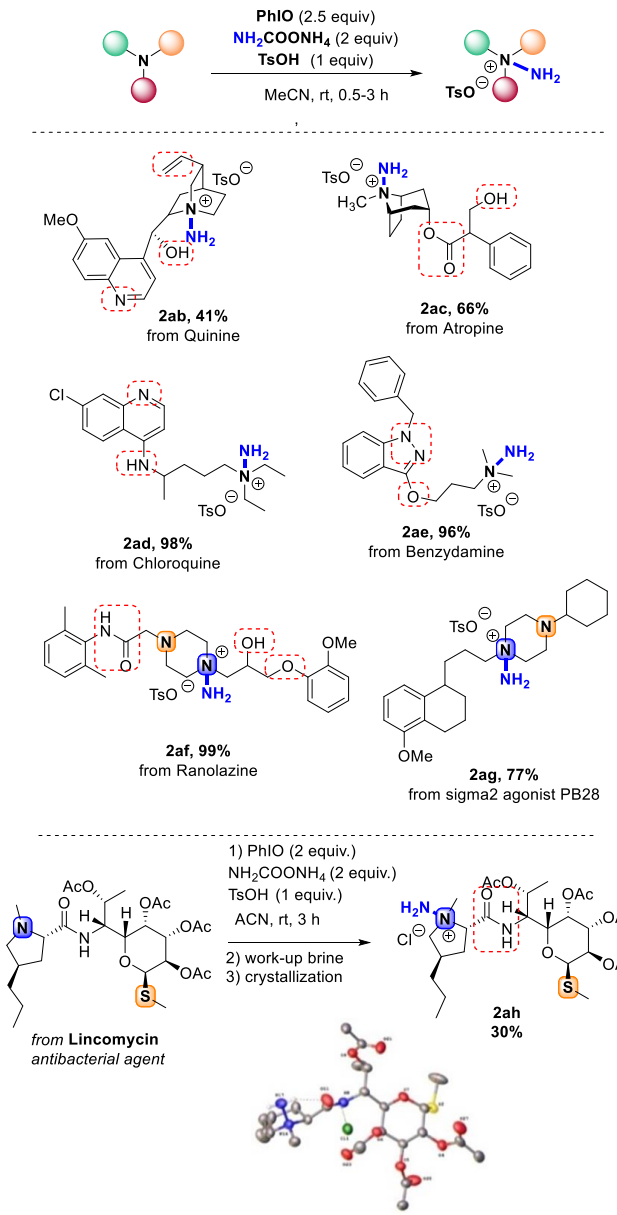


Scheme 4. Preparation of ^{15}N-labelled hydrazinium salt.

To further test the method, and evaluate chemoselectivity, several biologically active molecules containing multiple basic N-atoms or other nucleophilc sites were considered as substrates (Scheme 5). This electrophilic nitrogen transfer occurred on quinine and atropine with high chemoselectivity, installing the amino group on the nitrogen atom of the quinuclidine and tropane moiety of **2ab** and **2ac** respectively. A single diastereoisomer for both hydrazinium products was observed (Scheme 5, **2ab**, **2ac**).

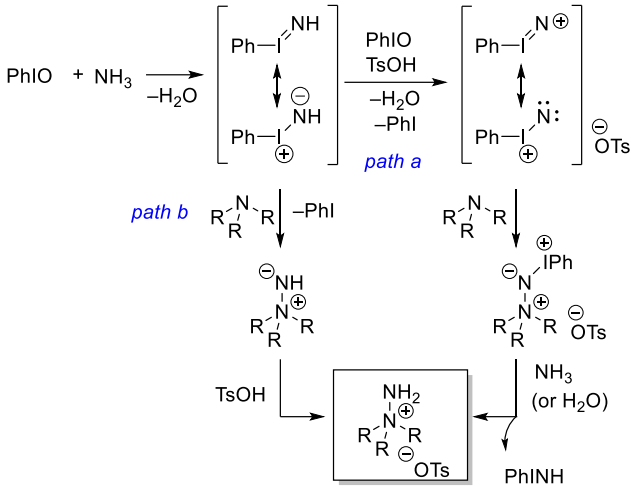
Selective amination of the tertiary amino group occurred with chloroquine, leading to hydrazinium salt **2ad** in 98% yield. Similarly, no interference was observed in the amination of benzydamine furnishing **2ae** in 96% yield. Remarkably, in the cases of ranolazine (antianginal agent) and Sigma-2 agonist PB28,[20] bearing two tertiary N-centers, the electrophilic nitrogen transfer takes place selectively only at one nitrogen atom of the piperazine ring leading to **2af** and **2ag**. By accurate ^{1}H NMR analysis it was possible to ascertain which position of the piperazine core was aminated (see Supplementary material). An unexpected result was obtained using peracetylated lincomycin bearing a sulfide moiety. To our surprise, in place of the expected sulfoximine derivative,[21] chemoselective amination occurred at the pyrrolidine nitrogen. The structure of the hydrazinium salt **2ah** was unambiguously assigned by

X-ray analysis[22] showcasing the chemoselectivity of this nitrogen transfer process.



Scheme 5. Hydrazinium salts of current drugs APIs.

Based on our previous findings,[12,13] the mechanism of the N-transfer could be rationalised as depicted in Scheme 6. Two possible pathways could be viable, involving either the iminoiodinane (path a) or the iodonitrene (path b). Both generate an electrophilic N-species to be attacked by the tertiary amine nucleophile. The selectivity for the tertiary amine substrates suggests significant nucleophilicity is required. In path b, the reagent can be further oxidized to the nitrene, with the subsequent cleavage of the N-I bond after amination. Protonation of the transferred N-atom, initially formed as an ylide, generates the salt form with the tosylate counter ion.



Scheme 6. Proposed mechanism.

In summary we have developed a new approach for the synthesis of hydrazinium salts starting from tertiary amines, and using an electrophilic N-transfer reaction. Compared to other available methodologies, this provides safer and milder conditions, with a hypervalent iodine reagent as the oxidizing species and ammonium carbamate as the nitrogen source. This procedure was applied to varied tertiary amines and displayed high tolerance to various functional groups. Examples of late-stage amination of relevant bioactive molecules and APIs have been also demonstrated. Further studies are ongoing in our laboratories in order to expand the applicability of this N-transfer methodology.

Experimental Section

General procedure for the preparation of hydrazinium salts. Ammonium carbamate (3 mmol) and iodosylbenzene (3.75 mmol) were added to a stirred solution of the tertiary amine (1.5 mmol) in acetonitrile (0.5 M, 3.0 mL), at 25 °C. p-Toluenesulfonic acid monohydrate (1.5 mmol) was added, and the reaction mixture stirred for 2 hours. After this time, the mixture was concentrated to remove acetonitrile. Removal of the remaining iodobenzene under high vacuum afforded the desired hydrazinium salt as flowing powder.

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COMMUNICATION

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