Photomediated Synthesis

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External-Photocatalyst-Free Visible-Light-Mediated Synthesis of Indolizines

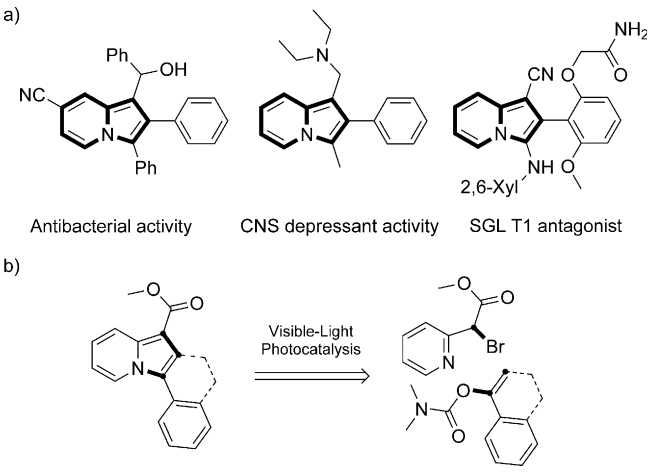
*Basudev Sahoo, Matthew N. Hopkinson, and Frank Glorius**

Dedicated to Stephen L. Buchwald on the occasion of his 60th birthday

Abstract: *A visible-light-mediated synthesis of valuable polycyclic indolizine heterocycles from easily accessed brominated pyridine and enol carbamate derivatives has been developed. This process, which operates at room temperature under irradiation from readily available light sources, does not require the addition of an external photocatalyst. Instead, an investigation into the reaction mechanism indicates that the indolizine products themselves may be in some way involved in mediating and accelerating their own formation. Preliminary studies also show that these simple heterocyclic compounds may be capable of facilitating other visible-light-mediated transformations.*

The harvesting of energy from visible light, the most abundant part of the solar spectrum, is a sustainable and cost-effective approach to activate chemical transformations.[1,2] However, most organic compounds do not themselves absorb in the visible region and strategies must be employed that allow for the efficient and selective transfer of energy from visible light to the reactants of interest. This can be achieved through the use of photocatalysts, which are capable of either passing on energy directly to the visible-light-inactive reagents or of engaging in single-electron-transfer (SET) events from their photoexcited states. Furthermore, photocatalysis can also provide access to interesting and often exotic reactivity pathways not commonly observed in the absence of light. Recent years have seen a resurgence of interest in photocatalysis with visible light, particularly SET-based photoredox activation processes.[3]

Inspired by these transformations, we envisaged that photocatalysis by visible light could open up mild and general synthetic routes to valuable heterocyclic compounds. In this regard, we identified the indolizine core as a promising target for investigation.[4] Indolizines are widely found as structural motifs in various pharmaceutical compounds,[5] while the reduced form is the key feature of the extensive indolizidine natural product family (Scheme 1 a).[6] Although many strategies have been employed to build up the heterocyclic core of these compounds under thermal conditions,[4,7] to the best of our knowledge, only one photochemical route to indolizines, involving irradiation with UV light, has been reported to date.[8]



Scheme 1. a) Selected examples of the indolizine motif in pharmaceuticals; b) proposed visible light photoredox-catalyzed synthesis of indolizines.

A visible-light-mediated synthesis of indolizines **3** starting from brominated 2-pyridine acetic acid ester derivatives **1** and enol carbamates **2** was designed, taking advantage of well-established light-induced SET processes from a photocatalyst (Scheme 1 b). Our envisaged mechanism is shown in Scheme 2. Initial excitation of a transition-metal/polypyridyl complex of the type commonly employed in photoredox catalysis ([PC]) would be followed by single-electron transfer to the brominated pyridine substrate **1a** to afford a radical anion $\mathbf{1a}^{\bullet-}$ and the oxidized photocatalyst $[PC]^{+}$. Mesolytic loss of a bromide ion from $\mathbf{1a}^{\bullet-}$ would then deliver an alkyl radical **A**, which could in turn add to the enol carbamate derivative **2a**. Oxidation of the resulting radical **B** to cation **D** could then occur either as part of a radical-chain process with another molecule of **1a** or by SET with the oxidized photocatalyst $[PC]^{+}$, thereby regenerating the ground-state species and closing the photoredox catalytic cycle. Subsequent trapping of the cation in **D** by the intramolecular pyridine nitrogen atom followed by a series of proton-transfer steps and elimination of a carbamic acid derivative would finally deliver the desired indolizine heterocycle **3aa**.

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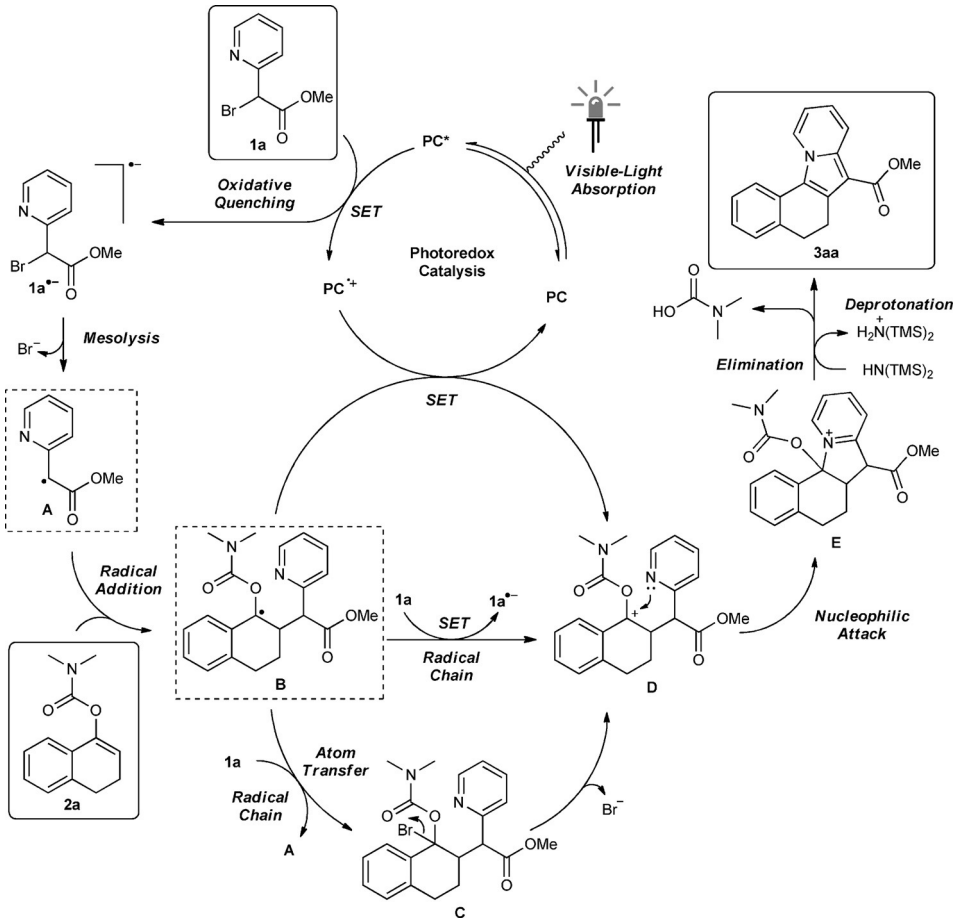
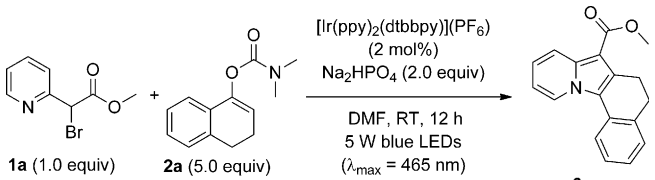


Scheme 2. Envisaged mechanism for the visible light photoredox-catalyzed synthesis of indolizines.

Here, we report the successful realization of this concept in a visible-light-mediated route to unprecedented polycyclic indolizines, which proceeds under mild conditions upon irradiation with readily available blue light-emitting diodes (LEDs). As explained below, however, this process does not in fact require the use of an external photocatalyst. Instead, initial experiments point towards an interesting mechanistic scenario, wherein the polycyclic indolizine products themselves play a role in facilitating their own formation.

As an initial test reaction, the simple brominated pyridine **1a** was treated with the bicyclic enol carbamate **2a** (5 equiv) in *N*,*N*-dimethylformamide (DMF) in the presence of the inorganic base Na_2HPO_4 and the organometallic photosensitizer $[Ir(ppy)_2(dtbbpy)](PF_6)$ (ppy = 2-phenylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine), which has been widely employed in photoredox catalysis. The desired tetracyclic indolizine product **3aa** was generated in 62% yield (GC) after 12 h at room temperature under irradiation by blue LEDs ($\lambda_{max} = 465$ nm). A control reaction performed in the dark confirmed the necessity of visible light. A more interesting observation was made, however, upon conducting the reaction in the absence of the photocatalyst $[Ir(ppy)_2(dtbbpy)](PF_6)$. Rather than shutting down the reactivity as expected, carrying out the process under the same conditions without the iridium complex had little impact on the reaction outcome, with **3aa** being delivered in a comparable yield of 52% (GC, Scheme 3). Extensive optimization studies involving the screening of different solvents, bases, light sources, protected enol substrates, and reagent stoichiometries led to an improvement in the yield of **3aa** to 77% (63% yield of isolated product) by using α,α,α-trifluorotoluene as the solvent and hexamethyldisilazane (HMDS) as the base.[9] As before, a control reaction performed without irradiation by visible light was unproductive (1% GC yield), thus verifying the photomediated nature of the process.

The results of a study into the scope and limitations of the process with a variety of different pyridines **1** and enol carbamates **2** are shown in Table 1. While an electron-withdrawing substituent on the brominated pyridine substrates was required to sufficiently activate the compounds towards photoactivation, a range of different ester groups could be applied to



Scheme 3. Preliminary investigations and control experiments.

afford the corresponding indolizines **3aa**–**3da**. The cyano-substituted substrate **1e** was also tolerated, but was significantly less effective, with **3ea** isolated in only 16% yield. A range of different functional groups including halogens, aryl, alkyl, methoxy, and trifluoromethyl groups were tolerated either on the pyridine ring or on various enol carbamates **2** derived from the 1-tetralone core. Access to indolizines with substituents on the pyridine ring has been comparatively rarely reported by alternative synthetic methods. Although a considerable excess of the olefinic coupling partners **2** (5 equiv) was required to ensure a reasonable yield of the product **3**, in all cases the unincorporated enol carbamate could be recovered from the reaction mixture and subsequently recycled. As with all photomediated processes, the

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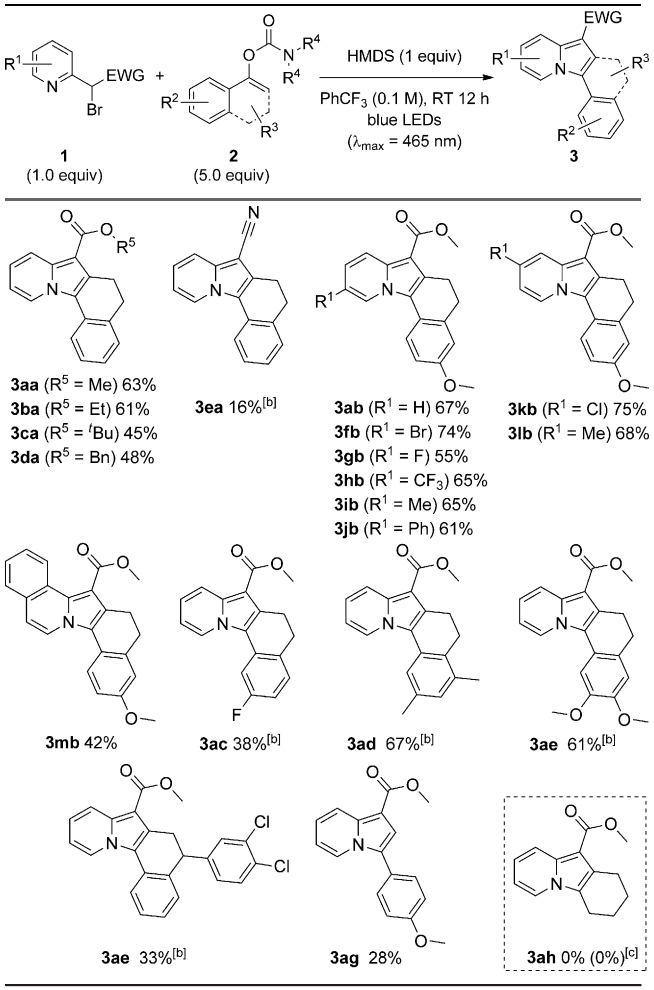
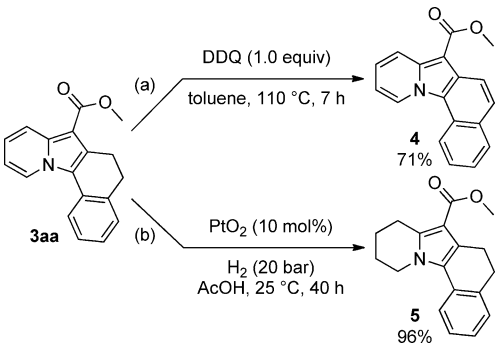
Table 1: Scope and limitations of the visible-light-mediated synthesis of indolizines **3** with various brominated pyridines **1** and enol carbamates **2**.[a]



[a] Reactions were conducted on a 0.20 or 0.30 mmol scale. See the Supporting Information for experimental details. R^4 = methyl unless otherwise stated. [b] R^4 = ethyl. [c] Reaction conducted in the presence of $[Ir(ppy)_2(dtbbpy)](PF_6)$ (2 mol%). EWG = electron-withdrawing group.

reaction progress could also be easily regulated simply by switching the light irradiation on and off.[9] In most cases, the indolizines **3** were isolated in moderate to good yields of up to 75%, although compound **3ag**, which does not possess a tethered aryl group, was generated in a much lower yield of 28%. Unfortunately, however, the all-alkyl-substituted indolizine **3ah** was not formed either under the standard conditions or in the presence of $[Ir(ppy)_2(dtbbpy)](PF_6)$.

The indolizine products from these reactions represent a novel class of tetracyclic or, in the case of **3mb**, pentacyclic, heteroaromatic scaffold, which could warrant further investigation in the context of pharmaceutical or materials chemistry. Moreover, as demonstrated for product **3aa**, subsequent facile oxidation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) can give easy access to the corresponding fully aromatic compounds (**4**, 71%), while hydrogenation with Adams catalyst (PtO_2) provides the reduced fused-pyrrole derivatives (**5**, 96%, Scheme 4).



Scheme 4. Derivatization of indolizine **3aa**.

With the scope of the process established, a series of mechanistic experiments were conducted, with the aim of understanding how energy from visible light is apparently harnessed during the reaction in the absence of an external photocatalyst. Firstly, the reaction between **1a** and **2a** was performed in the presence of the radical scavengers TEMPO and galvinoxyl. In both cases, a complete shutdown of reactivity was observed, thus indicating the involvement of radical intermediates. Moreover, an ESI mass spectrum of the reaction performed in the presence of TEMPO exhibited signals consistent with adducts formed between this radical scavenger and the proposed radical intermediates **A** and **B** (Scheme 2).[9] At this stage, we sought to identify the species present in the reaction mixture that was responsible for absorbing visible light in lieu of a photocatalyst. Thus, absorption spectra were recorded for all reaction components both on their own and in combination. As expected, the spectra for the substrates **1a** and **2a** and for the base HMDS in $PhCF_3$ did not reveal any notable absorption of either visible or near-UV light ($\lambda > 300$ nm, Figure 1a).[10] An absorption spectrum of the indolizine **3aa** recorded under the same conditions, however, exhibited a range of peaks with a maximum in the near-UV region at 340 nm and shoulders at 328 nm and 372 nm. Irradiating at either wavelength resulted in a detectable fluorescence emission at 442 nm (excited-state lifetime, $\tau = 4$ ns). A selection of variously substituted indolizines have been previously shown to exhibit fluorescence properties, with some having found applications in solar cells and in sensors for analyte detection.[11] The implication that the reaction products could themselves play a role in mediating their own formation was also supported by an analysis of the reaction kinetics. As shown in Figure 1b, a plot of the yield of **3aa** as a function of the reaction time revealed a slight parabolic curve consistent with the expected acceleration of the reaction rate as the product concentration increases over time. Furthermore, spiking the mixture with increasing amounts of preformed **3aa** led to a small, but notable, corresponding increase in the initial reaction rate.[9]

A Stern–Volmer luminescence quenching analysis of the reaction also indicated that a mechanism of the type shown in Scheme 2 with the indolizine product replacing the external photocatalyst is plausible. Excitation of **3aa** at 372 nm in the presence of various amounts of **1a** revealed quenching of the fluorescence at 442 nm by the brominated substrate, while

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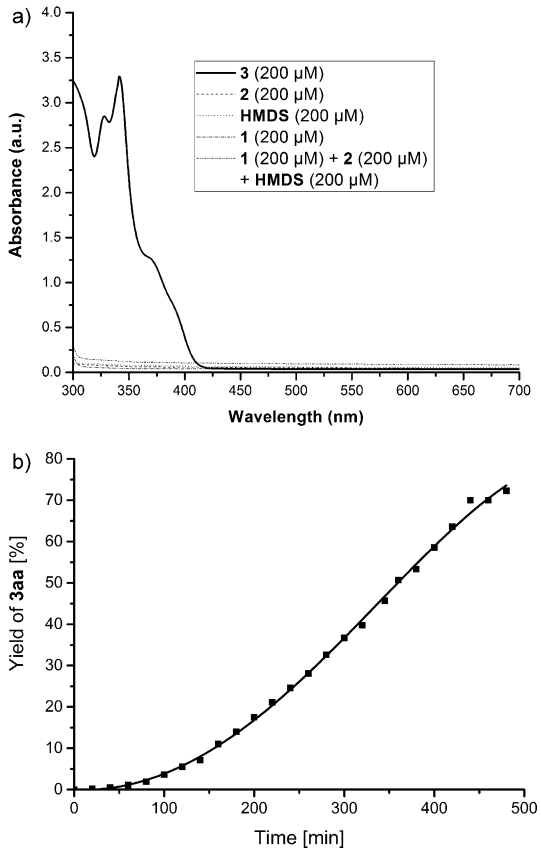
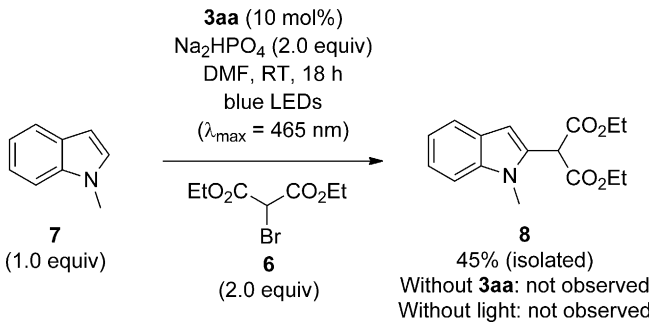


Figure 1. a) Absorption spectra of substrates **1a**, **2a**, the base HMDS, and indolizine **3aa**; b) reaction profile of the visible-light-mediated synthesis of **3aa**.

similar experiments with the other reaction components had no significant effect on the emission intensity.[12]

Chemical transformations where the products serve to mediate their own formation are of fundamental interest, as they enable compounds to self-replicate and multiply.[13] An examination of the absorption spectrum of indolizine **3aa** and the emission maximum of the blue LED light source used, however, would seem to argue against the direct involvement of the indolizine in self-replication.[14] No significant absorption was observed for **3aa** above approximately 410 nm, while blue LED visible-light sources were used with $\lambda_{max} =$ 465 nm.[15] At this stage, we tentatively propose that the emission tail of the blue LEDs at wavelengths shorter than the emission maximum could be sufficient to excite the indolizine and initiate a radical-chain process of the type outlined in Scheme 2.[16,17] Alternatively, a photoactive species derived from the indolizine products with greater absorption at longer wavelengths may form in low concentrations and mediate the reaction. Finally, the implication from these studies that simple polycyclic indolizine heterocycles can play a role in harvesting energy from visible light and initiate or otherwise facilitate photochemical reactions was tested by employing indolizine **3aa** as a photosensitizer in a different transformation. In a proof of principle experiment, **3aa** was used in place of $[Ru(bpy)_3]Cl_2$ (bpy = 2,2′-bipyridine) for the radical addition of bromomalonate **6** to 1-methylindole **7** reported by Stephenson and co-workers.[18] The successful conversion into the alkylated indole product **8** observed after 18 h at room temperature (45% yield of isolated product, Scheme 5) suggests that this scaffold could find applications in photochemical synthesis and could provide a starting point for further studies.



Scheme 5. Application of indolizine **3aa** as a photosensitizer in the addition of ethyl bromomalonate **6** to 1-methylindole **7**.

In conclusion, we have developed a novel visible-light-mediated synthetic method that gives access to functionally diverse indolizines under mild conditions. The tetracyclic and pentacyclic structures obtained by using this route represent a new class of heterocyclic scaffold, which may be of interest in pharmaceutical or fluorescent materials research. Control reactions showed that this process proceeds effectively in the absence of an external photocatalyst, and mechanistic studies seem to implicate the indolizine products, or species derived from them, as playing a role in absorbing energy from visible light and mediating their own formation. Furthermore, the successful application of one of these simple polycyclic heterocycles as a photosensitizer in a different transformation suggests that these compounds may be of interest for photochemical synthesis.

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[9] See the Supporting Information for more details.

[10] Absorption spectra were also recorded of combinations of the reaction components at higher concentrations to investigate any potential excited donor–acceptor (EDA) complexes. No such effect was observed in any of the cases (see the Supporting Information for more details). For an example of EDA complexes, see E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750.

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[12] The potential for single-electron oxidation of the excited singlet indolizine **3aa** was evaluated by cyclic voltammetry. An irreversible oxidation wave was observed at an estimated excited-state potential of $E_{1/2}(\mathbf{3aa}^{+}/\mathbf{3aa}^{*}) = -1.9$ V versus Ag/AgCl, thus implying that **3aa*** is highly reducing (see the Supporting Information).

[13] As the purest class of such reactions, autocatalytic processes have found many roles across the chemical sciences; for a review on autocatalysis, see A. J. Bissette, S. P. Fletcher, *Angew. Chem. Int. Ed.* **2013**, *52*, 12800; *Angew. Chem.* **2013**, *125*, 13034.

[14] Indolizine **3aa** is not thought to be acting as a genuine autocatalyst in any of the cases. The increase in the initial rate observed upon adding additional **3aa** would be expected to be greater if this compound was a true autocatalyst. Also, the cyclic voltammetry data of **3aa** indicates that the oxidized form generated upon SET to **1a** is not stable and would lead to decomposition (see the Supporting Information for more details).

[15] An emission spectrum of the blue LEDs did not reveal significant emission at wavelengths below ca. 410 nm (see the Supporting Information). Carrying out the reaction using one blue LED (5 W, $\lambda_{max} = 465$ nm) as the irradiation source fitted with a long-pass filter at 455 nm, however, resulted in only a 15% yield of **3aa** (GC yield, cf. 55% GC yield in the absence of the filter). Indolizine **3aa** was formed in 48% GC yield using the same light source with a long-pass filter at 400 nm. These results would seem to imply that the visible-light tail of the blue LEDs at wavelengths below 455 nm (and above 400 nm) is mostly responsible for the observed reactivity.

[16] The involvement of EDA complexes formed between the indolizine products and the other reaction components was also ruled out by a series of absorption studies (see the Supporting Information for more details).

[17] The involvement of radical chains in this process is supported by the success of the reaction using the thermal radical initiator dibenzoyl peroxide. Conducting the reaction between **1a** and **2a** in the presence of this species (0.5 equiv) at 105 °C without light resulted in the formation of **3aa** in 26% yield (see the Supporting Information for more details).

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