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Electrochemically Initiated Tandem and Sequential Conjugate Addition Processes: One-Pot Synthesis of Diverse Functionalized Isoindolinones

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Abstract: A tandem aldol–heterocyclization–rearrangement reaction and one-pot sequential Michael addition allowed a direct access to highly functionalized 3-isoindolinones containing quaternary carbon centers. The desired products are obtained under mild conditions and in short reaction times by galvanostatic electrolysis in a divided cell. A further tandem intramolecular heterocyclization reaction leading to synthetically relevant hemiaminal derivatives has been established with suitable Michael acceptors.

Keywords: electrosynthesis; hemiaminals; isoindolinones; one-pot Michael addition; tandem reactions

Due to the ever-increasing concern for the environment and health, the search for new synthetic methodologies remains a task of great interest for the organic chemistry community, especially for the achievement of building block molecules with applications in biological and medicinal chemistry.

As well established by several literature reports, many advantages in terms of sustainability and green chemistry, are offered by domino or tandem[1] reactions and one-pot multicomponent[2] processes that provide valuable synthetic targets while avoiding inconvenient multistep protocols and tedious purification of intermediates.

On the other hand, the electrochemical methodology also stands out as a powerful tool to induce useful chemical transformations with reduced waste production and improved atom economy thanks to the use of the practically mass-free electron as reagent or catalyst.[3]

On these grounds, some research groups in the electro-organic area are currently exploring the possibility to perform domino reactions by means of electrochemical activation, so combining virtues and benefits of both strategies in solving specific synthetic issues.[4]

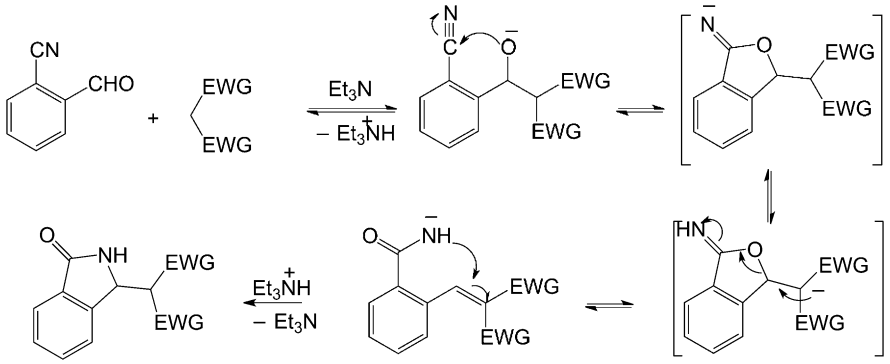
Hitherto, most of the domino reactions induced in an electrochemical way are Knoevenagel–Michael processes that have been successfully exploited in the synthesis of biologically relevant heterocyclic compounds, such as bis-tetronic acids,[5] bispyrazoles,[6] 2-amino-*4H*-chromenes and their derivatives[7] etc.

Recently, inspired by the interesting works of Ramström et al.,[8] one of the authors and co-workers successfully assessed a base-promoted tandem reaction to directly access 3-functionalized isoindolinone scaffolds containing dicarbonyl moieties, by aldol addition to 2-cyanobenzaldheyde (2-CNC_6H_4CHO), followed by heterocyclization and rearrangement *via* an aza-Michael reaction (Scheme 1).[9]

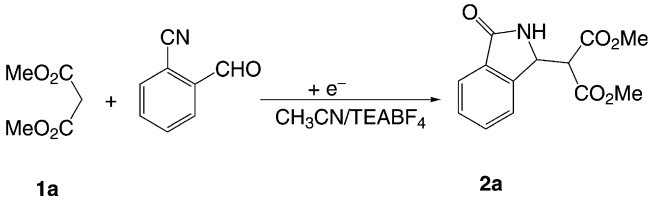
As well documented in the literature, the isoindolinone framework frequently appears in many natural[10] and pharmaceutical products,[11] therefore straightforward methods to assemble related structures incorporating suitable functionalities for further molecular processing, are still highly desirable.

In the light of the above considerations and following on from our previous investigations on the galvanostatic activation of C–H acid compounds,[12] we envisaged the chance to design an electrochemical version of this useful tandem reaction and further speculated on the electrocatalytic method for exploring the possible second reactivity of the isoindolinone skeleton with alkylating agents.

Herein we present the scope and limitations of the electroreductively-catalyzed tandem reaction of 1,3-dicarbonyl compounds and 2-CNC_6H_4CHO and a se-



Scheme 1. Proposed reaction pathway for the base-catalyzed synthesis of isoindolinones.



Scheme 2. Electrochemically induced tandem reaction of **1a**.

quential one-pot addition to Michael acceptors leading to isoindolinone derivatives containing quaternary carbon centers.

The effectiveness of the electrochemical route was firstly checked using dimethyl malonate (**1a**) as a reference compound (Scheme 2) and performing the electrolysis in the presence of 2-CNC_6H_4CHO under a variety of conditions as reported in Table 1.

Since no conversion of starting materials was observed by performing the electrolysis in an undivided cell (entry 1), the following experiments were carried out in the cathodic side of a U-shaped two-compartments cell fitted with a glass (G-4) separator septum; this strategy proved to be successful as the tandem reaction efficiently took place affording **2a**, under the optimized conditions (Table 1, entry 4), in 87% isolated yield.

Quite interestingly, with respect to the conventional chemical method,[9] the electrochemical approach allowed for lower catalyst loading (4% of electricity *vs.* 100% Et_3N) and shorter reaction time (0.75 h *vs.* 18 h).[13]

With this result in hand, we felt encouraged to explore the substrate scope for this process, so a series of symmetrical and unsymmetrical 1,3-dicarbonyl compounds (**1b–l**) was electrolyzed in the presence of 2-CNC_6H_4CHO accordingly to the optimized conditions reported in Table 1, entry 4 (Scheme 3).

As showed in Table 2, the scope of this electrocatalytic reaction may be successfully extended to the use of both β-diesters, β-keto esters and β-diketones affording the isoindolinone derivatives with very satisfactory yields and complete chemo- and regioselectivity in almost all the cases.

Interestingly, excellent conversions of starting materials and short reaction times were observed with the class of malonates, regardless of the steric hindrance of the two alkyl substituents (**1b–e**); conversely, significant drops in reactivity or selectivity were noticed when electrogenerated enolates arising from

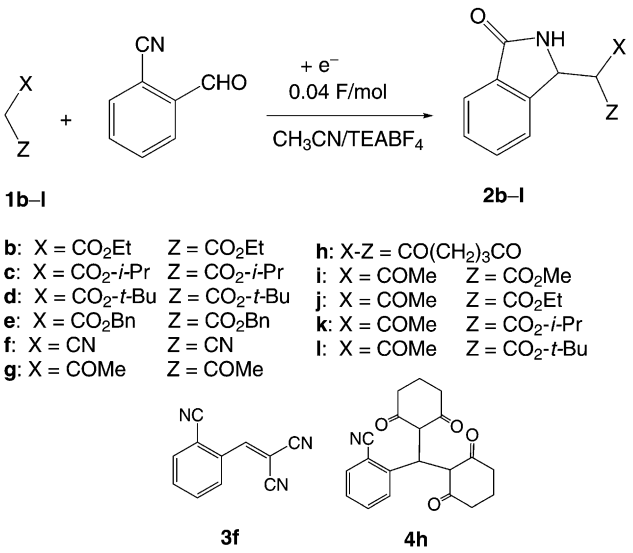
Table 1. Electrochemically induced tandem reaction of 2-CNC_6H_4CHO and **1a**.

Entry	Electrolysis method[a]	Current density D [mA/cm^2]	Current quantity [F/mmol of **1a**]	Reaction time [h]	Yield [%] of **3a**[b]
1	A	2	0.1	24	–
2	B	2	0.08	0.5	76
3[c]	B	2	0.08	0.5	83
4[c]	B	5	0.04	0.75	87

[a] Method A: a solution of **1a** (1 mmol) in CH_3CN/$TEABF_4$ (3 mL/0.1 mmol) was electrolyzed in an undivided cell, at room temperature, using Pt anode and cathode, under galvanostatic conditions. At the end of electrolysis 2-CNC_6H_4CHO was added and the reaction prolonged for 24 h. Method B: **1a** (1 mmol) in CH_3CN/$TEABF_4$ (3 mL/0.08 mmol (entries 2 and 3) or 0.04 mmol (entry 4)) was electrolyzed at the cathodic compartment of a U-divided cell, Pt anode and cathode, under galvanostatic conditions. 2-CNC_6H_4CHO (1 mmol) was added after the potential was switched off.

[b] Yields refer to chromatographically pure **2a**

[c] Electrolyses were performed in the presence of 2-CNC_6H_4CHO (1 mmol).



Scheme 3. Electrochemically induced tandem reaction of **1b–l**.

highly enolizable active methylene compounds (**1f–h**) or β-keto esters (**1i–l**) were used as nucleophiles.

However, in these cases, convenient increases in reaction rate and yield could be achieved upon performing the electrolysis under neat conditions (Table 2, entries 7, 10–13).

By comparing selected data collected for **1d**, **1f** and **1h** with the those obtained using the conventional base-promoted method we could further remark several differences of the electro-induced method with respect to the chemical one. Substrate **1d**, for example, which displays very high reactivity and selectivity under electrochemical conditions (Table 2, entry 3), suffered a strong dependence on the steric hindrance of the ester substituents when standard chemical conditions were used: in such a case, **1d** showed a very low conversion (<15%) after long reaction times (18 h). Again, while the attempt to obtain isoindolinone **2f** under basic condition was totally ineffective resulting in complete decomposition of the starting

Table 2. Electrochemically induced tandem reaction of 2-CNC_6H_4CHO and **1b–l**.

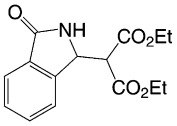
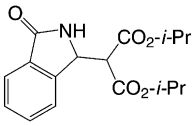
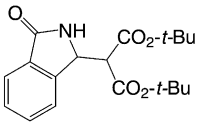
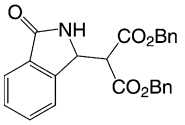
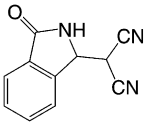
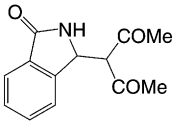
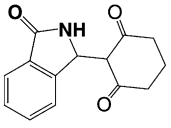
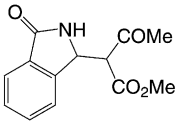
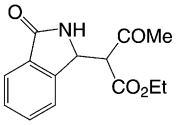
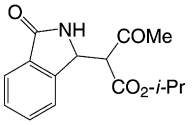
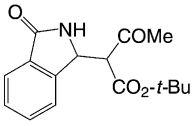
Entry	Substrate **1**	Product	Reaction time [h]	Yield [%][a]	*dr*[b]	Et_3N (stoich.)	
						Reaction time	Yield [%] (*dr*)
1	**1b**	 **2b**	0.5	73	–		
2	**1c**	 **2c**	0.5	93	–		
3[c]	**1d**	 **2d**	0.5	98	–	18 h	<15
4	**1e**	 **2e**	2.5	65	–		
5	**1f**	 **2f** (**3f**)	1	59 (20)[d]	–	18 h	dec.
6	**1g**	 **2g**	21	52	–		
7[e,f]	**1g**	**2g**	7	65	–		
8	**1h**	 **2h** (**4h**)	1	– (84)[g]	–	18 h	64

Table 2. (Continued)

Entry	Substrate **1**	Product	Reaction time [h]	Yield [%][a]	*dr*[b]	Et_3N (stoich.)	
						Reaction time	Yield [%] (*dr*)
9	**1i**	 **2i**	12	70	50:50		
10[e]	**1i**	**2i**	5	74	50:50		
11[e]	**1j**	 **2j**	5	71	50:50		
12[e]	**1k**	 **2k**	4	84	53:47		
13[e]	**1l**	 **2l**	1	92	70:30 (85:15)[h]	18 h	87 (60:40)

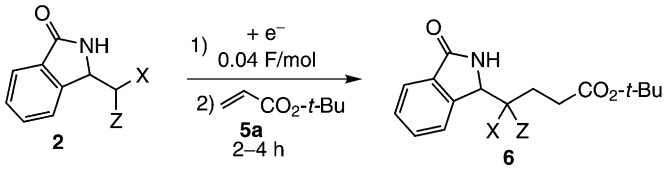
[a] Yields refer to chromatographically pure products.
[b] Diastereoisomeric ratios have been calculated on the ground of ^{1}H NMR spectra on crude products.
[c] This reaction performed on 3 mmol scale of 2-CNC_6H_4CHO using D = 15 mA/cm^2 led to the product **2d** in 95% isolated yield.
[d] Value in parentheses refers to isolated product **3f**.
[e] Electrolysis was performed using solvent-free conditions: see Experimental Section for details.
[f] This reaction was performed on a 3-mmol scale of 2-CNC_6H_4CHO using D = 15 mA/cm^2 and led to the product **2** in 67% isolated yield.
[g] Value in parentheses refers to isolated product **4h** (isolated yield calculated with respect to **1h**).
[h] Value in parenthesis refers to *dr* after recrystallization.

materials, the electrochemical route allowed us to achieve the desired product (Table 2, entry 5) in reasonable yield. Conversely, the electrolysis of 1,3-cyclohexanedione **1h** in the presence of 2-CNC_6H_4CHO did not afford isoindolinone **2h** in appreciable yield, rather leading to the product **4h** as a result of an electro-initiated cascade Knoevenagel–Michael reaction process.

Given the presence of several adjoined functionalities and reactive sites, the isoindolinone derivatives of type **2** also intrigued us as potential building blocks for the quick assembly of heterocyclic frameworks with enhanced molecular diversity.

Taking into account our preceding investigations on the electro-catalyzed Michael and related addition reactions,[14] several isoindolinone derivatives **2** were submitted to electrolysis under the conditions reported in Scheme 3 and tested in the conjugate addition to *tert*-butyl acrylate **5a** – chosen as a model Michael acceptor.

As indicated in Scheme 4, we were pleased to observe that the process turned out completely chemo- and regioselective, leading to the exclusive formation

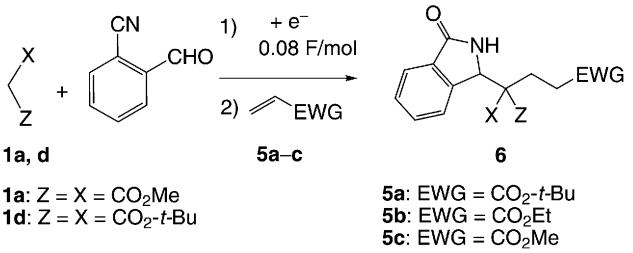


2	6	yield
2a	**6aa**	95%
2d	**6da**	95%
2e	**6ea**	92%
2g	**6ga**	66%
2l (*dr* = 70:30)	**6la**	74% (*dr* > 95:5)

Scheme 4. Electrochemically induced Michael addition of **5a** to isoindolinone derivatives **2**.

of the Michael adducts **6**, with good to excellent yields, in short reaction times and under mild conditions for almost all the substrates.

Indeed, as already noted for the tandem process, the moderate reactivity of the isoindolinone deriva-



Scheme 5. Electrochemically initiated tandem reaction and one-pot sequential Michael addition.

tive **2g** confirmed the reduced nucleophilic ability of electro-generated enolates arising from highly enolizable active methylene compounds.[15]

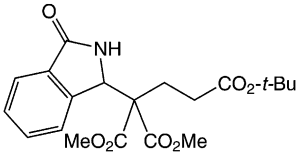
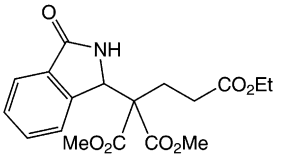
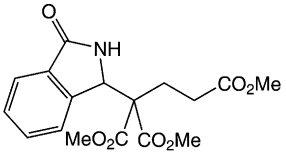
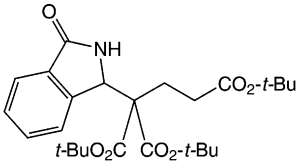
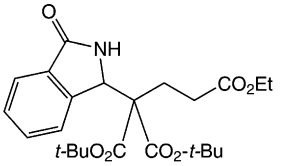
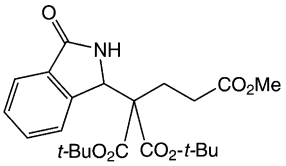
Notably, concerning the stereochemical aspects, the electro-catalyzed process proved to be highly diastereoselective as the product **6la** was achieved with a *dr* >95:5, irrespective of the diastereomeric ratio of the starting material **2l**.[16]

With these results in hand, we focused our next efforts to ascertain whether both these cathodically-initiated processes could be paired in a one-pot procedure directly leading to isoindolinone derivatives **6**.

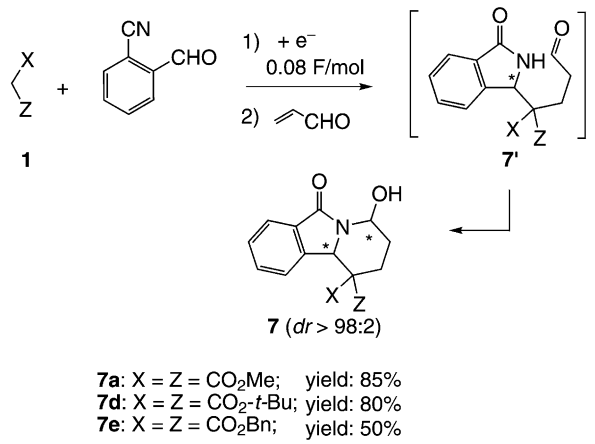
To this end, active methylene compounds **1a**, **d** were electrolyzed in the presence of 2-CNC_6H_4CHO and Michael acceptors **5a–c** were subsequently added to the cathodic compartment after 0.08 F/mol of electricity had been passed (Scheme 5).

To our delight, highly functionalized isoindolinone derivatives **6** containing quaternary carbon centers were smoothly achieved as exclusive reaction products in 67–85% overall yields (Table 3), with no significant loss in selectivity with respect to the above two-

Table 3. Electrochemically-induced isoindolinones synthesis and sequential one-pot Michael addition to **5a–c**.

Entry	Substrate **1**	**5**	**6**		Reaction time [h][a]	Yield[b]
1[c]	**1a**	**5a**	**6aa**		18	85%
2[c]	**1a**	**5b**	**6ab**		5	83%
3[c]	**1a**	**5c**	**6ac**		2	67%
4[d]	**1d**	**5a**	**6da**		1	91%
5[d]	**1d**	**5b**	**6db**		2	75%
6[d]	**1d**	**5c**	**6dc**		2	76%

[a] Reaction time refers to the overall process of synthesis of **6**.
[b] Yields refer to chromatographically pure products.
[c] Current density: 4 mA/cm^2.
[d] Current density: 2 mA/cm^2.



Scheme 6. Electrochemically initiated one-pot access to tricyclic hemiaminal derivatives.

step synthesis. In such a way, that is, bypassing the isolation of isoindolinone intermediates **2**, an important improvement in terms of simplicity, reduction of waste disposal and solvent/electrolyte amount has been demonstrated.

A further useful finding on this subject was disclosed by us using an appropriate dielectrophile as the acceptor. As is well-known, in the presence of amidomalonates, α,β-unsaturated aldehydes display a sequential reactivity which gives access to cyclic hemiaminals, an important class of heterocyclic compounds with a wide range of synthetic applications.[17] A similar tricyclic skeleton is found, for example, in indolizidine-based biologically active compounds.[18]

In order to assess whether a similar reactivity could be found with isoindolinone derivatives, acrolein was added to the electrolyzed solutions of **1** and 2-CNC_6H_4CHO. As shown in Scheme 6, jointly to the 1,2-addition, we were pleased to observe a further cyclization involving the amidic group of the isoindolinone moiety to give the unprecedented tricyclic isoindolinone derivatives **7** with the hemiaminal functionality, a feature that can open the way to new interesting synthetic investigations. As expected this finding was achieved as the overall goal of a one-pot process of two sequential electro-induced tandem reactions.

Remarkably, in all the cases examined, products **7** were obtained with a high level of diastereoisomeric purity. Preliminary 2D NMR experiments (ROESY and NOESY) showed cross-peaks between the hydrogen atom on the hydroxy functionality and the one on the isoindolinone moiety so indicating that, in the most abundant diastereoisomer, the asymmetric atoms should have the configurations (*RR*, *SS*) (see Supporting Information for details). Moreover, Spartan calculations indicated that the diastereoisomer (*RR*, *SS*) form is *ca.* 4 kcal/mol more stable than the other (*RS*, *SR*) form.

In conclusion, the electrochemical activation of C–H acid compounds proved to be an efficient, selective and convenient strategy to accomplish the synthesis of 3-substitued isoindolinones *via* tandem reactions with 2-CNC_6H_4CHO. The products are obtained in good to high yields, under mild conditions and short reaction times, by constant current electrolysis, using a catalytic amount of electricity. Compared with the conventional base-catalyzed procedure, the electrochemical method can, in turn, be considered as a viable alternative with promising features of versatility or even the only route to obtain the desired products.

A further study on the second reactivity of these valuable compounds successfully proved the effectiveness of the electrochemical activation to also promote a sequential one-pot conjugate addition to activated olefins providing highly functionalized isoindolinones containing quaternary carbon centers. Furthermore, the direct one-pot access to tricyclic hemiaminal derivatives **7** in highly diastereoselective fashion has been demonstrated as a consequence of an electrocatalytic process constituted by two-sequential tandem reactions.

Experimental Section

General Remarks

Reaction times and conditions are detailed in the respective tables. Constant current electrolyses were performed using using a Hewlett–Packard DC Power Supply Model E3612 A .The experiments were carried out in a U-divided glass cell separated through a porous G-4 glass plug. Platinum spirals (apparent area 2.5 or 5 cm^2) were used as anode and cathode. In all the experiments the anolyte was constituted by a solution of $TEABF_4$ 0.1 M in CH_3CN.

Typical Experimental Procedure for Electrochemically Induced Synthesis of Isoindolinones in CH_3CN (2a–f)

A solution of **1** (1.1 mmol) and 2-CNC_6H_4CHO (1.0 mmol) in $CH_3CN/TEABF_4$ (0.6 mL/0.04 mmol) was electrolyzed at room temperature, under galvanostatic conditions (current density and quantity as reported in Table 2). At the end of the electrolysis, the reaction was prolonged at room temperature under magnetic stirring until TLC disappearance of 2-CNC_6H_4CHO. The mixture was then concentrated under vacuum and purified by silica gel chromatography (CH_3Cl: AcEt = 9:1).

Typical Experimental Procedure for Electrohemically Induced Synthesis of Isoindolinones under Solvent-Free Conditions (2g–l)

A solution of **1** (0.5 mL), 2-CNC_6H_4CHO (1.0 mmol) and $TEABF_4$ (0.05 mmol) was electrolyzed at room temperature, under galvanostatic conditions (current density and quantity

as reported in Table 1). At the end of the electrolysis, the reaction was prolonged at room temperature under magnetic stirring until TLC disappearance of 2-CNC_6H_4CHO. The mixture was then concentrated under vacuum and purified as reported above.

Typical Experimental Procedure for Electrochemically Initiated Tandem Reaction and One-Pot Sequential Michael Addition (6)

A solution of **1** (1.0 mmol) and 2-CNC_6H_4CHO (1.0 mmol) in CH_3CN/$TEABF_4$ (0.6 mL/0.08 mmol) was electrolyzed at room temperature, under galvanostatic conditions (current density and quantity as reported in Table 3). At the end of the electrolysis, the reaction was prolonged at room temperature under magnetic stirring until TLC disappearance of 2-CNC_6H_4CHO; The Michael acceptor **5a–c** (1.05 mmol) was subsequently added. The mixture was kept under stirring up to completion of the reaction (TLC disappearance of isoindolinone intermediate), concentrated under vacuum and purified as reported above.

Typical Experimental Procedure for Electrochemically Initiated Single-Step Synthesis of Hemiaminal Derivatives (7)

A solution of **1** (1.0 mmol) and 2-CNC_6H_4CHO (1.0 mmol) in CH_3CN/$TEABF_4$ (0.6 mL/0.08 mmol) was electrolyzed at room temperature, under galvanostatic conditions (current density and quantity as reported in Table 3). At the end of the electrolysis, the reaction was prolonged at room temperature under magnetic stirring until TLC disappearance of 2-CNC_6H_4CHO; acrolein (1.2 mmol) was subsequently added. The mixture was kept under stirring up to completion of the reaction (TLC disappearance of isoindolinone intermediate), concentrated under vacuum and purified as reported above.

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