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Ir(III)-Catalyzed Oxidative Annulation of Phenylglyoxylic Acids with Benzo[*b*]thiophenes

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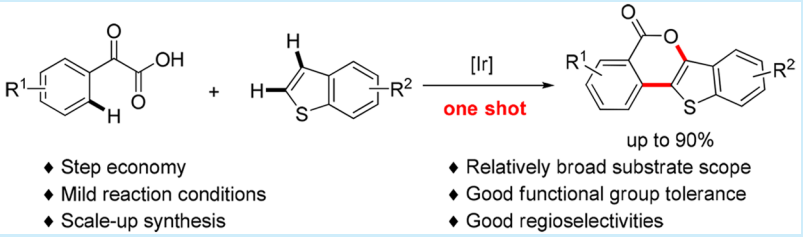
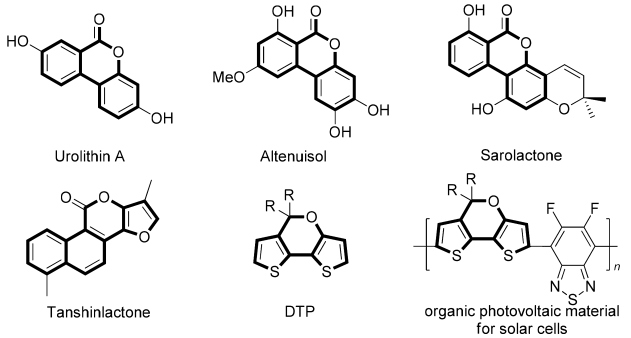
Supporting Information



ABSTRACT: An Ir(III)-catalyzed oxidative annulation of phenylglyoxylic acids with benzo[*b*]thiophenes for the construction of benzothieno[3,2-*c*][2]benzopyranones in one step is disclosed. Three C−H cleavages and C−C/C−O bond formations are involved in this reaction. This protocol features a relatively broad substrate scope, good functional group tolerance, good regioselectivities, mild reaction conditions, and scale-up synthesis.

The dibenzopyranone scaffold is often encountered in natural products, bioactive molecules, organic functional materials, and synthetic intermediates.[1−3] In particular, their thieno analogues are important structural units for various organic optoelectronic materials such as organic photovoltaic (OPV) materials.[3] For example, 5*H*-dithieno[3,2-*b*:2′,3′-*d*]pyran (DTP) is known as one of the most efficient donors for organic photovoltaics (Scheme 1).[3b] Therefore, a number of methods have been reported for the synthesis of dibenzopyranones, including Baeyer−Villiger oxidation of fluorenones,[4] oxidation of the benzylic C−H bonds of 6*H*-benzo[*c*]chromenes,[5] intramolecular coupling of aryl 2-halobenzoates,[6] sequential cross-coupling of 2-halobenzaldehydes with 2-hydroxyarylboronic acids/lactionization,[7] intramolecular lactonization of biarylcarboxylic acid derivatives,[8] and transition-metal-catalyzed carbonylation of 2-arylphenols.[9] Despite the reliability, these methods often suffer from disadvantages such as tedious synthetic routes, inaccessible synthetic precursors, and poor substrate scope. More importantly, very few examples have been reported on the construction of the thieno analogues of dibenzopyranones, which to an extent limits the rapid diversification of the dibenzopyranone structures and further hinders the exploration of their applications in organic optoelectronic materials. Thus, it is still in high demand to establish a straightforward and efficient pathway toward thieno-dibenzopyranone analogues.

Scheme 1. Selected Examples of Dibenzopyranone Derivatives



In the past decade, transition-metal-catalyzed chelation-assisted oxidative C−H/C−H cross-coupling/intramolecular cyclization between two (hetero)arenes has emerged as a highly efficient strategy for the construction of fused (hetero)aromatic structures and complex molecules due to high atom and step economy.[10] In this context, You and co-workers reported a facile two-step synthesis of thieno[3,2-*c*][2]benzopyranones through rhodium-catalyzed oxidative C−H/C−H cross-coupling of (hetero)aromatic carboxylic acids with heteroarenes and subsequent palladium-catalyzed intramolecular oxidative lactonization (Scheme 2a).[10e] Herein, we disclose an iridium-catalyzed oxidative cyclization of phenylglyoxylic acids with benzo[*b*]thiophenes to construct benzothieno[3,2-*c*][2]benzopyranones via multiple oxidative C−H activation and C−C/C−O formations in one step (Scheme 2b). This reaction features a relatively broad substrate scope, good functional group tolerance, mild reaction conditions, good regioselectivities, and scale-up synthesis.

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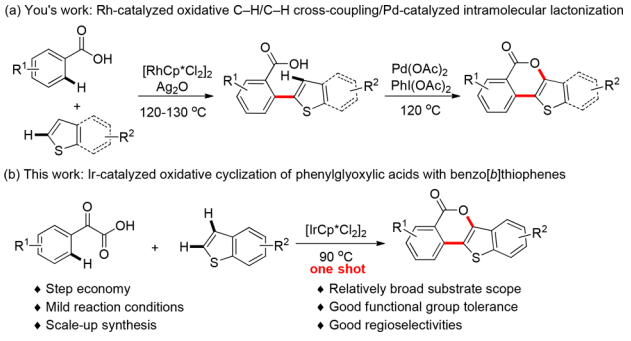
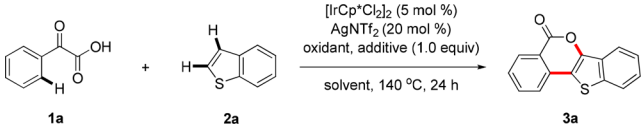
Scheme 2. Synthesis of Thieno-dibenzopyranone Analogues



Our investigation was initiated with the reaction of benzoic acid and benzo[*b*]thiophene **2a** in the presence of $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), Ag_2O (3.0 equiv), and 1-AdCOOH (1.0 equiv) in 1,2-dichloroethane (1.0 mL) at 140 °C. The desired product 5*H*-[1]-benzothieno[3,2-*c*][2]benzopyran-5-one **3a** was obtained in a 22% NMR yield. Phenylglyoxylic acid **1a** was found to be a better substrate for this reaction, giving **3a** in a 36% yield (Table 1, entry 1). No other regioisomer was observed. Thus, phenylglyoxylic acid **1a** was selected as the model substrate. Switching from $[IrCp^*Cl_2]_2$ to other catalysts, such as $IrCl_3$, $[RhCp^*Cl_2]_2$, $[Ru(p\text{-cymene})Cl_2]_2$, and $Pd(OAc)_2$, led to no formation of **3a** (Table S1, entries 3–6). No reaction was observed in the absence of $[IrCp^*Cl_2]_2$ (see Table S1 in Supporting Information, entry 7).

Table 1. Optimization of Reaction Conditions[a,b]



1a 2a 3a

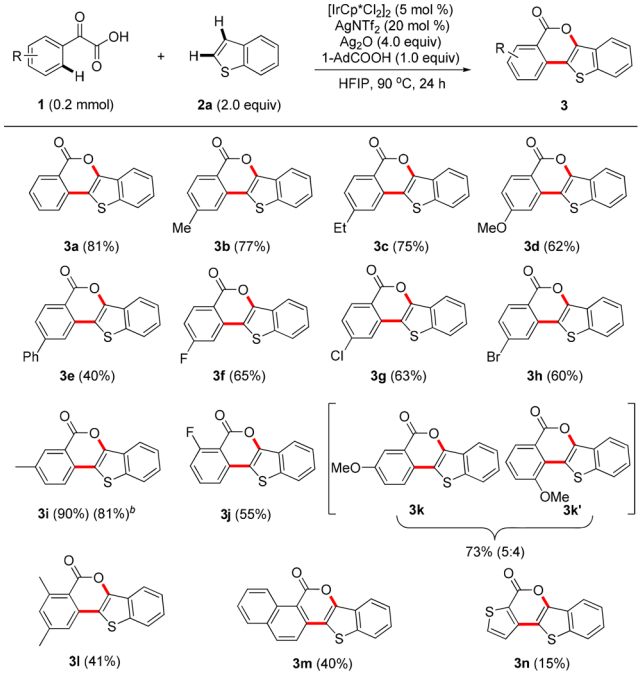
entry	oxidant (equiv)	additive	solvent	yield (%)
1	Ag_2O (3.0)	1-AdCOOH	DCE	36
2[c]	Ag_2O (3.0)	1-AdCOOH	DCE	20
3	Ag_2O (3.0)	1-AdCOOH	HFIP	56
4	Ag_2O (3.0)	1-AdCOOH	TFE	22
5	Ag_2O (3.0)	1-AdCOOH	toluene	20
6	Ag_2O (3.0)	1-AdCOOH	^{t}BuOH	trace
7	Ag_2O (3.0)	1-AdCOOH	DMAc	n.d.
8	Ag_2O (3.0)	1-AdCOOH	DMSO	n.d.
9	Ag_2CO_3 (3.0)	1-AdCOOH	HFIP	12
10	AgOAc (3.0)	1-AdCOOH	HFIP	20
11	$Cu(OAc)_2$ (3.0)	1-AdCOOH	HFIP	n.d.
12	Ag_2O (3.0)	TFA	HFIP	32
13	Ag_2O (3.0)	AcOH	HFIP	42
14	Ag_2O (3.0)	PivOH	HFIP	38
15	Ag_2O (3.0)	$TsOH{\cdot}H_2O$	HFIP	26
16[d]	Ag_2O (3.0)	1-AdCOOH	HFIP	64
17[e]	Ag_2O (3.0)	1-AdCOOH	HFIP	50
18[d]	Ag_2O (4.0)	1-AdCOOH	HFIP	81
19[d,f]	Ag_2O (4.0)	1-AdCOOH	HFIP	70
20[d,g]	Ag_2O (4.0)	–	HFIP	66

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), oxidant, additive (1.0 equiv), and solvent (1.0 mL) were stirred at 140 °C for 24 h. [b]Isolated yields. [c]The reaction was carried out under air. [d]90 °C for 24 h. [e]80 °C for 24 h. [f]Without $AgNTf_2$. [g]Without 1-AdCOOH. n.d. = not detected. 1-AdCOOH = 1-adamantanecarboxylic acid.

A slightly decreased yield was afforded when the reaction was conducted under air (entry 2). Further optimization of solvents showed that 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was the most effective (entry 3). Other polar solvents such as 2,2,2-trifluoroethanol (TFE), toluene, *N*,*N*-dimethylacetamide (DMAc), DMSO, and ^{t}BuOH gave no product or low conversions (entries 4–8). Investigations on the oxidants revealed that Ag_2O was the best oxidant. Other silver oxidants such as Ag_2CO_3 and AgOAc proved to be less effective, whereas copper oxidants such as $Cu(OAc)_2$ were totally ineffective for this transformation (entries 9–11). 1-AdCOOH was proposed to work as a proton shuttle to promote the C–H cleavage.[11] The attempts with other acidic additives, including 2,2,2-trifluoroacetic acid (TFA), AcOH, PivOH, and $TsOH{\cdot}H_2O$, gave inferior yields (entries 12–15). A slightly increased yield was obtained when the reaction was performed at 90 °C (entry 16). Lowering the temperature to 80 °C resulted in a diminished yield (entry 17). Further optimization of the amounts of oxidant indicated that 4.0 equiv of Ag_2O was the most suitable, giving the desired product **3a** in an 81% yield (entry 18). Diminished yields were obtained when the reactions were conducted in the absence of either $AgNTf_2$ or 1-AdCOOH (entries 19 and 20). Finally, the optimal reaction conditions consisted of $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), Ag_2O (4.0 equiv), and 1-AdCOOH (1.0 equiv) in HFIP (1.0 mL) at 90 °C for 24 h under N_2 (entry 18).

With the optimized reaction conditions in hand, we next investigated the substrate scope with regard to α-keto carboxylic acids. As summarized in Scheme 3, a diverse set of benzothieno[3,2-*c*][2]benzopyranones bearing both electron-donating and -withdrawing groups could be synthesized in moderate to excellent yields. A variety of functional groups such as methyl, ethyl, methoxy, phenyl, fluoro, chloro, and bromo

Scheme 3. Scope of α-Keto Carboxylic Acids[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), Ag_2O (4.0 equiv), and 1-AdCOOH (1.0 equiv) in HFIP (1.0 mL) at 90 °C for 24 h under N_2. [b]2.0 mmol scale.

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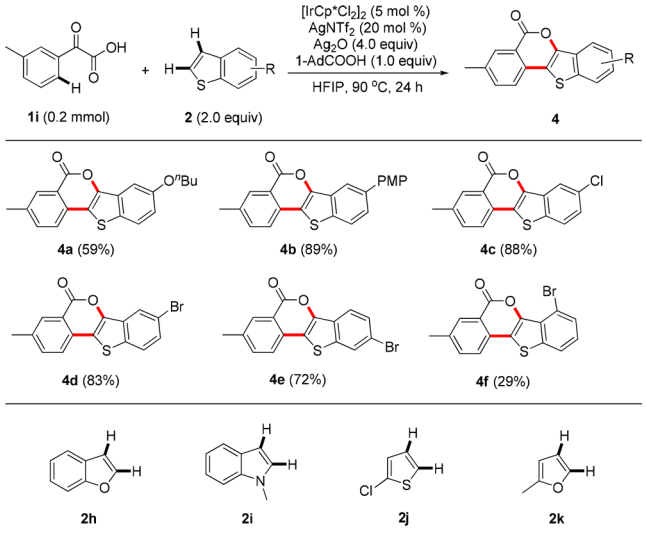
could be tolerated under the standard conditions (**3b**–**j**). Further investigation on the substrate scope indicated that a set of phenylglyoxylic acids bearing substituents at the *ortho*-, *meta*-, and *para*-positions of the aromatic ring smoothly underwent the reactions to provide the desired products in moderate to excellent yields (**3b**–**l**). However, a mixture of regioisomeric products was observed when 3-methoxyphenylglyoxylic acid was used as the substrate (**3k** and **3k′**). 1-Naphthylglyoxylic acid was also a suitable substrate for this reaction (**3m**). In addition, heteroaromatic substrates such as 2-oxo-2-(thiophen-2-yl)acetic acid were applicable in this transformation, providing the corresponding products in relatively low yields (**3n**). Notably, a gram-scale synthesis was carried out, further indicating the practicality of this protocol (**3i**).

Next, the substrate scope of benzothiophenes was investigated (Scheme 4). We were pleased that both electron-donating and -withdrawing substituents were well tolerated, giving the corresponding products in moderate to good yield (**4a**–**d**). Functional groups including butoxy, bromo, and chloro were all compatible, which offered opportunities for further transformations (**4a**, **4c**–**f**). However, a significantly diminished yield was observed when 4-bromo benzothiophene was attempted, probably owing to the high steric hindrance (**4f**). Regrettably, other heteroarenes such as benzofuran (**2h**), *N*-methylindole (**2i**), 2-chlorothiophene (**2j**), and 2-methylfuran (**2k**) failed to undergo this annulation.

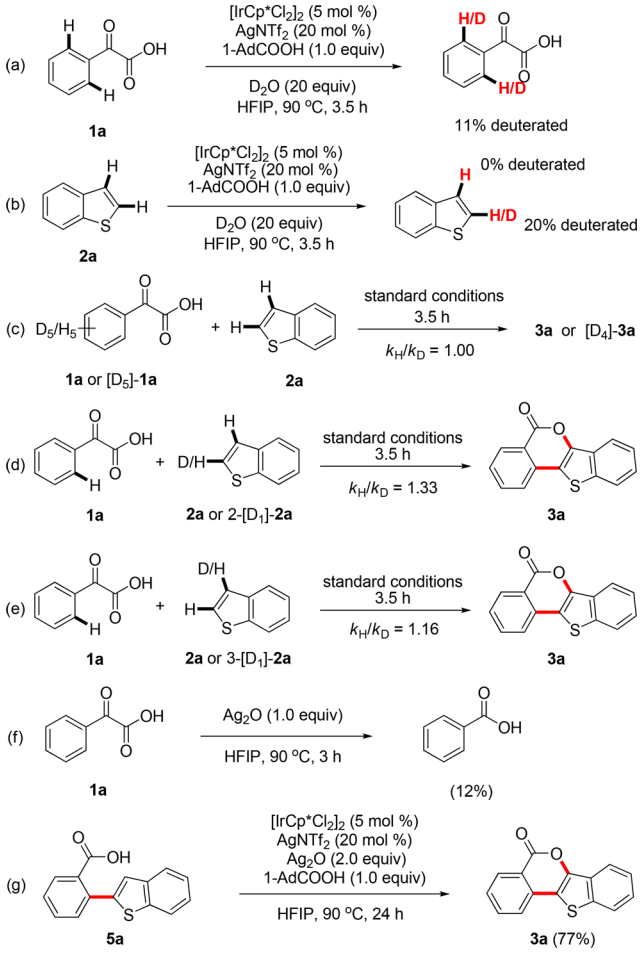
Scheme 4. Scope of Benzo[*b*]thiophenes[a]



[a]Reaction conditions: **1i** (0.2 mmol), **2** (0.4 mmol), $[IrCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), Ag_2O (4.0 equiv), and 1-AdCOOH (1.0 equiv) in HFIP (1.0 mL) at 90 °C for 24 h under N_2.

To gain insight into the reaction mechanism, the deuterium-labeling experiments of phenylglyoxylic acid **1a** and benzothiophene **2a** were conducted, respectively (Scheme 5). A significant H/D scrambling was observed for phenylglyoxylic acid **1a** when **1a** was treated with D_2O (20.0 equiv) in the absence of **2a** (11% D) (Scheme 5a). Similarly, the exposure of benzo[*b*]thiophene **2a** alone to the catalytic conditions with D_2O led to 20% deuterium incorporation at the α-position, whereas no deuterium exchange was found at the β-position (Scheme 5b). These results indicate that the C–H activation processes of both substrates were reversible.

Scheme 5. Mechanistic Experiments



Additionally, kinetic isotopic effect (KIE) experiments for both coupling partners were carried out. The parallel reactions of **2a** with **1a** or $[D_5]$-**1a** were carried out under the standard conditions, giving a KIE value of 1.00 (Scheme 5c). Similarly, two parallel reactions between **1a** and **2a**/2-$[D_1]$-**2a** did not give a significant KIE value (k_H/k_D = 1.33) (Scheme 5d). Parallel experiments of **1a** with **2a**/3-$[D_1]$-**2a** provided a similar result (k_H/k_D = 1.16) (Scheme 5e). These results revealed that the C–H cleavages might not be involved in the turnover-limiting step.[12] In addition, treatment of **1a** with 1.0 equiv of Ag_2O in HFIP for 3 h gave benzoic acid in a 12% yield (Scheme 5f). This result suggested that phenylglyoxylic acids could convert into the corresponding benzoic acids in the presence of Ag_2O by decarboxylation. Furthermore, the smooth transformation of 2-(benzo[*b*]thiophen-2-yl)benzoic acid **5a** into the desired product **3a** under the present catalytic system indicated that **5a** might be the intermediate of this reaction (Scheme 5g).

Next, several well-known radical inhibitors such as TEMPO, 2,6-di*tert*-butyl-pcresol (BHT), and ascorbic acid were added into the reaction of **1a** with **2a** (see Table S2 in Supporting Information). It was found that these radical inhibitors could significantly suppress the reaction and no product **3a** was detected in the presence of 1.0 equiv of the radical inhibitors, thus indicating that a radical process may be involved in this reaction.

Based on the above experimental results and previous reports,[13−15] a plausible mechanism for this oxidative

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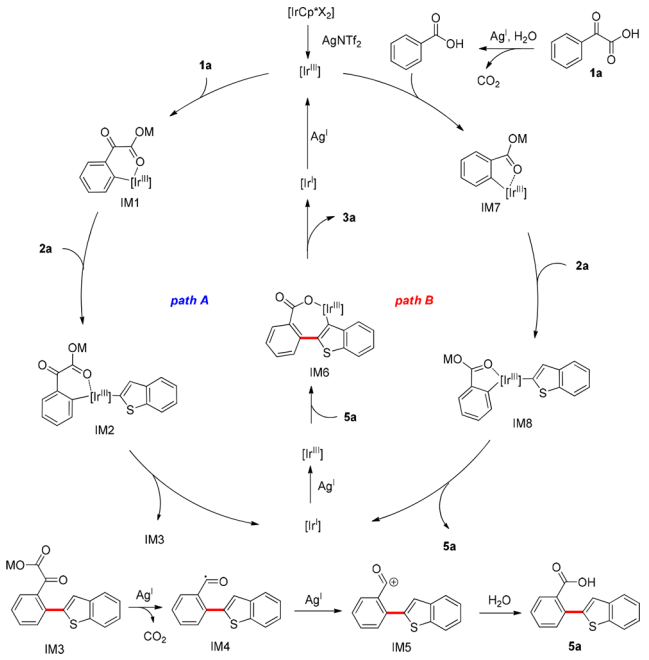
annulation is shown in Scheme 6. Initially, the reaction of $[IrCp^*Cl_2]_2$ with $AgNTf_2$ affords a cationic iridium species,

Scheme 6. Plausible Mechanism



which then coordinates to the carbonyl group of α-keto acid **1a** and induces the *ortho* C−H cleavage to deliver a cyclometalated Ir(III) intermediate **IM1**.[16] Following C−H activation occurring at the α-position of **2a** leads to **IM2**, which subsequently undergoes a reductive elimination to afford **IM3** and release the Ir(I) species. In the presence of Ag_2O, the bi(hetero)aryl α-keto acid **IM3** would undergo decarboxylation to give an acyl radical species **IM4**, which then undergoes another Ag-mediated oxidation to give the cationic species **IM5**. Following nucleophilic attack by H_2O gives the bi(hetero)aryl carboxylic acid **5a**.[17] Next, C−H iridation at the β-position of the thiophene moiety of **5a** with Ir(III) delivers **IM6**, which then undergoes a reductive elimination to provide the desired product **3a** with the release of an Ir(I) species. Finally, the Ir(I) species is oxidized by Ag_2O to regenerate the reactive Ir(III) species to complete the catalytic cycle (path A). Alternatively, similar to the transformation process from **IM3** to **5a**, the α-keto acid **1a** could first undergo a decarboxylation to deliver the benzoic acid. Then carbonyl-directed C−H activation at the *ortho* position of the benzoic acid gives **IM7**, which subsequently reacts with **2a** to afford an Ir(III) intermediate **IM8**. The following reductive elimination of **IM8** and intramolecular oxidative C−H lactonization provide the desired product **3a** (path B). Because the carboxylic acid substrates showed lower efficiencies than the corresponding α-keto carboxylic acids, this reaction might mainly proceed via path A. However, the possibility of path B could not be excluded at the current stage.

In conclusion, we have demonstrated an Ir(III)-catalyzed oxidative annulation of (hetero)aromatic α-keto carboxylic acids with benzothiophenes for the construction of benzothieno[3,2-*c*][2]benzopyranones via triple C−H activation and C−C/C−O formations in one step. This reaction features a relatively broad substrate scope, good functional group tolerance, good regioselectivities, mild reaction conditions, and scale-up synthesis. The present protocol is expected to provide opportunities for the exploration of novel optoelectronic materials based on dibenzopyranone structures. Further investigations on the reaction mechanism and extension of the substrate scope are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01033.

Experimental procedures and spectroscopic characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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