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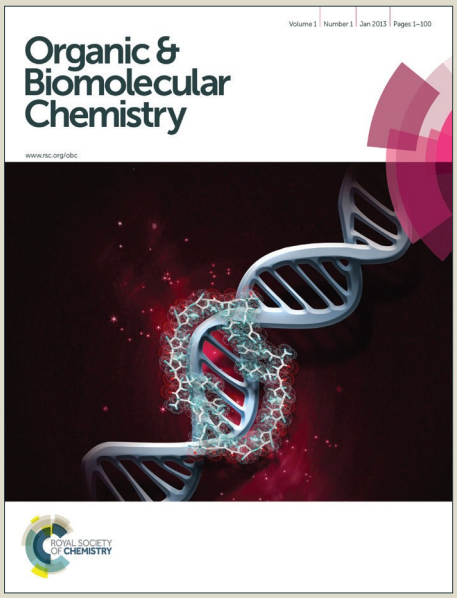

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PAPER

Chemoselective Acylation of Benzimidazoles with Phenylacetic Acids under Different Cu Catalysts to Fused Five-Membered N-Heterocycles or Tertiary Amides

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C-N bonds formation via a copper-catalyzed aerobic oxidative decarboxylative tandem protocols were realized. The phenylacetic acids which contain *ortho*-X (X = F or Br) on the aromatic ring will render fused five-membered heterocycle via a tandem aromatic nucleophilic substitution and aerobic oxidative decarboxylative acylation at C(sp^2)-H bond of benzimidazoles under $Cu(OAc)_2/K_2CO_3/BF_3{\cdot}Et_2O$ catalytic system. While with CuBr as catalyst and pyridine as base, N-acylation occurred and tertiary amides were obtained.

Introduction

N-Heterocycles are ubiquitous structure motifs in bioactive natural products, pharmaceuticals, organic materials and dyes. The construction of heterocycles is in the central of organic synthesis.[1] Along with the rapid development of organometallic chemistry, many efforts have been devoted to the synthesis and functionalizations of N-heterocycles via transition-metal-catalyzed coupling reactions. Also, within the application of this strategy, many complex fused heterocycles can be achieved via tandem reactions with simple and efficient synthetic operation accesses.[2]

Fused benzimidazoles, a special kind of N-heterocylces, represent a class of important compounds that display a broad range of biological functions,[3] therefore many synthetic methods have been developed toward them.[4] Among the fused benzimidazoles, the imidazoindanone-type structure such as 11H-benzo[4,5]imidazo[1,2-*a*]indol-11-one aroused our great interest because of their potential biological aitivities.[5, 6a-b] To our knowledge, there is only one example referred to the synthesis of such fused compounds through the reaction of *o*-fluorobenzaldehyde with benzimidazole, affording 11H-benzo[4,5]imidazo[1,2-*a*]indol-11-one only in 33% yield.[7]

Transition-metal-catalyzed decarboxylative couplings have attracted widespread attentions due to readily accessible starting materials, simple operation, and clean by-product (CO_2 only). Catalytic decarboxylative couplings of C(sp^2) (aromatic and alkenyl) and C(*sp*) (alkynyl) acids have been well studied, and decarboxylative coupling at an sp^3-hybridized carbon were also emerged as a hot topic recently.[8, 9] During our own efforts on oxidative decarboxylation coupling of phenylacetic acid with nucleophiles under Cu/O_2 conditions,[6c-f] we envisioned that the C(CO)-C bond can be formed via this strategy with the carbonyl-M at 2-position of benzimidazole as the nucleophile.[10] In conjunction with the tandem aromatic nucleophilic substitution[11] or Cu-catalyzed Ullmann coupling for the formation of a C-N bond,[12] the construction of the fused heterocycle can be expected (Figure 1).

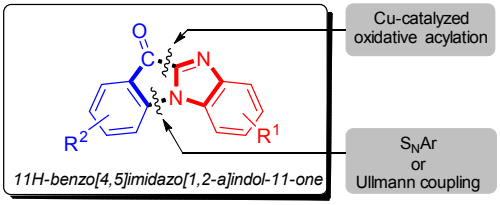

Figure 1. Retrosynthetic analysis of the fused benzimidazole

Results and discussion

To test our hypothesis, we firstly examined the Ullmann coupling-oxidative acylation tandem reaction using 2-Br phenyl acetic acid (**1a**) and benzimidazole (**2a**) as the model substrates (Table 1). When the reaction was conducted in DMSO in the presence of MeONa for 18 h at 120 °C under oxygen and catalyzed by 10 mol % of $Cu(OAc)_2$ and proline as the ligand, the desired fused heterocycle product **3aa** was obtained in 16% yield (entry 1). The catalytic system containing

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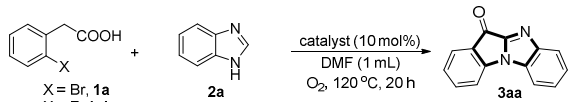
CuI, K_3PO_4 and DMEDA led to a moderate yield (entry 3). However, further screening of the catalyst, base and the ligand could not improve the reaction any more. We considered that the oxygen atmosphere might suppress the Ullmann process. Then we used 2-F phenylacetic acid (**1a'**) instead of **1a**, trying to construct the C-N bond via aromatic nucleophilic substitution (S_NAr). We were pleased to find that when $Cu(OAc)_2$ was used as the catalyst and K_2CO_3 as the base, **3aa** was obtained in 60% yield. The choice of base is crucial for this reaction. Except for K_3PO_4 and K_2CO_3, other bases tested didn't work well (entries 5-10). On the other hand, it was found that the Lewis acid additive $BF_3 \cdot Et_2O$ could promote this reaction, affording **3aa** in 65% isolated yield (entry 13). Finally, when the ratio of **1a'**:**2a** was changed to 1:1.4, a satisfied yield of 80% can be achieved. This result clearly indicated that our proposal for the tandem reaction to form fused N-heterocycles indeed works.

Table 1. Optimization of the reaction conditions for the cyclization of benzimidazole with *ortho*-halogenated phenylacetic acid [a]

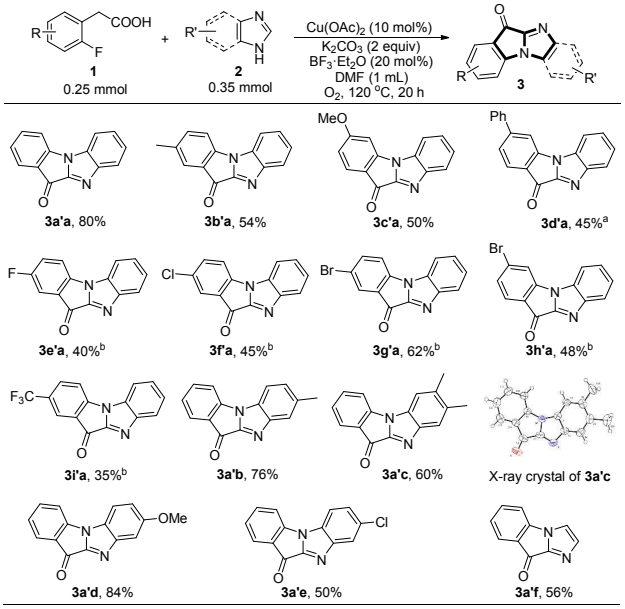


Entry	X	catalyst	Base	Additive/Ligand	Yield (%)[b]
1[c]	Br	$Cu(OAc)_2$	MeONa	proline	16
2[c]	Br	CuI	MeONa	proline	24
3[c]	Br	CuI	K_3PO_4	DMEDA	40
4	Br	CuI	K_3PO_4	DMEDA	trace
5	F	$Cu(OAc)_2$	K_3PO_4	-	56
6	F	$Cu(OAc)_2$	K_2CO_3	-	60
7	F	$Cu(OAc)_2$	Cs_2CO_3	-	0
8	F	$Cu(OAc)_2$	$NaHCO_3$	-	trace
9	F	$Cu(OAc)_2$	*t*-BuOK	-	trace
10	F	$Cu(OAc)_2$	$K_3PO_4 \cdot 3H_2O$	-	23
11	F	$Cu(OAc)_2$	K_2CO_3	$Fe(acac)_3$	trace
12	F	$Cu(OAc)_2$	K_2CO_3	$FeCl_3$	trace
13[d]	F	$Cu(OAc)_2$	K_2CO_3	$BF_3 \cdot Et_2O$	(65)[e]
14	F	$Cu(OAc)_2$	K_2CO_3	AcOH	0
15	F	$Cu(OAc)_2$	K_2CO_3	CuO	40
16[f]	F	$Cu(OAc)_2$	K_2CO_3	$BF_3 \cdot Et_2O$	95(80)

[a] Conditions: 2-bromophenylacetic acid (**1a**) or 2-fluorophenylacetic acid (**1a'**) (0.5 mmol), benzimidazole (**2a**) (0.25 mmol), base (0.5 mmol), solvent (1 mL), additive (0.05 mmol), O_2 (1 atm), 120 °C, 20 h; [b] GC yield. [c] DMSO as the solvent. [d] Under air. [e] Yields of the isolated product in parenthesis. [f] 0.25 mmol of **1a'** and 0.35 mmol of **2a**.

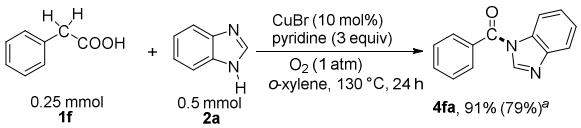
Next, we explored the substrate scope with respect to 2-fluorophenylacetic acids (**1a'**) and benzimidazoles (**2**) under the optimized reaction conditions (Scheme 1). It can be seen that a broad range of 2-fluorophenylacetic acids bearing an electron-donating group such as CH_3- and CH_3O- are good substrates for the tandem reaction with benzimidazole (**2a**) under the optimized conditions to give 11H-benzo[4,5]imidazo[1,2-a]indol-11-ones (**3a'a**) in moderate to good yields (**3b'a** and **3c'a**). For electron-withdrawing groups such as halogen and CF_3-, lower reaction temperature of 100°C was needed to achieve acceptable results (**3e'a**-**3i'a**). We then examined the reaction of 2-fluorophenylacetic acid (**1a'**) with a variety of benzimidazoles. The derivatives **2a**-**2d** with electron-donating groups on the benzene ring gave corresponding products in good yields. The structure of **3a'c** was confirmed by X-ray crystallographic analysis (See supporting information for details).[13] The electron-withdrawing Cl led to a moderate result. It is noteworthy that imidazole was also tolerated for this reaction, giving 9H-imidazo[1,2-*a*]indol-9-one (**3a'f**) in 56% yield.

Scheme 1. Substrate scope



[a] DMSO as the solvent; [b] These reactions were carried out at 100 °C

During our investigation of the parameters on the tandem reaction, we discovered that CuBr/pyridine system led to the direct oxidative N-acylation, affording imidazolium amide, which is also an important structural motif in a myriad of bioactive natural products, agrochemicals and pharmaceuticals.[14] The direct acylation from free carboxylate acid in the absence of an activating reagent is of great interest for environmentally benign synthesis. Thus we decided to expand this divergent pathway in detail by using phenyl acetic acid (**1f**) and benzimidazole (**2a**) as the standard substrates[15] (Scheme 2). It can be seen that the existence of both CuBr and pyridine was essential for the success of the reaction.



Variation:	
CuCl or $Cu(OAc)_2$ instead of CuBr:	0 %
Et_3N, bipyridine, 1,10-phen instead of pyridine:	0 %
p-xylene instead of *o*-xylene:	68%
120 °C instead of 130 °C:	11%
air instead of O_2:	74%

Scheme 2. Oxidative benzoylation of benzimidazole by phenyl acetic acid

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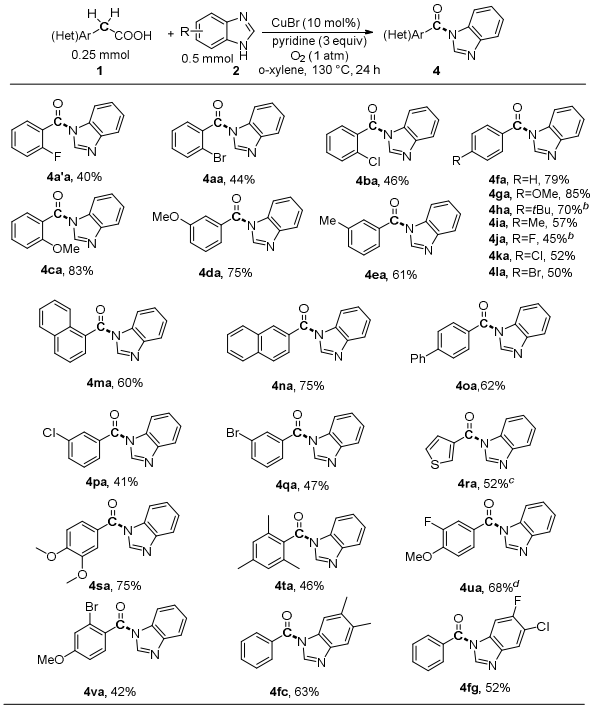
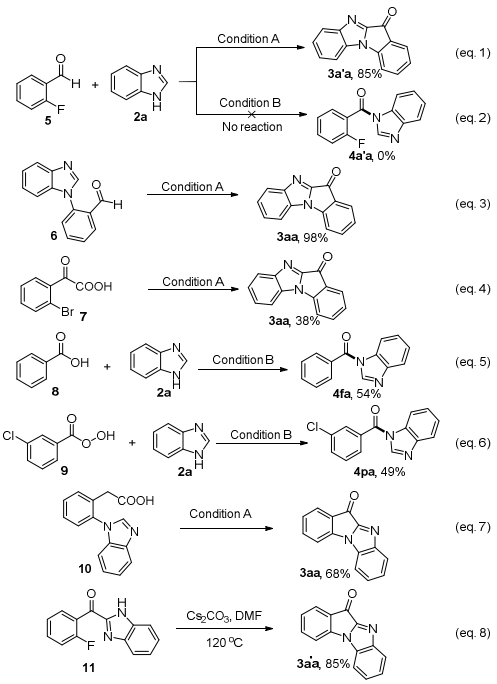
We next investigated the scope of this new reaction (Scheme 3). For 2-fluorophenylacetic acid (**1a'**) and 2-bromophenylacetic acid (**1a**), the model substrates of the tandem annulation, corresponding amides **4a'a** and **4aa** were afforded in moderate yields. The S_NAr reaction and Ullmann coupling were both highly suppressed under this condition and no **3a'a** was ever detected under this CuBr/Pyridine/O_2 system, neither under Condition A as well. *Ortho*-Cl phenylacetic acids also led to the amide products smoothly (**4ba**), providing the feasibility for further transformations. Both electron-donating and electron-withdrawing group substituted phenylacetic acids led to the products in good yields (**4ca**-**4ea**, **4ga**-**4la**, **4pa**-**4qa**, **4sa**-**4va**). Phenyl and polyphenylene substrates were all tolerated under the standard conditions to afford the corresponding desired products in good yields (**4ma**-**4oa**). Moreover, 3-thiophene acetic acid was compatible in this reaction as well (**4ra**). Finally, substitutions on the aromatic ring of benzimidazole were also proven to be compatible and the corresponding products were obtained in good yields (**4fc** and **4fg**). However, it is unlucky that under the CuBr/Pyridine/O_2 catalytic system, no reaction occurred for imidazole.



[a] Reaction Conditions: aromatic acetic acid (0.25 mmol), azole derivative (0.5 mmol), CuBr (10 mmol%), pyridine (0.75 mmol), *o*-xylene (1 mL), 130 °C, 24 h, under O_2 in a sealed tube. [b] 140 °C, 24 h. [c] 150 °C, 24 h. [d] 130 °C, 21 h.

Scheme 3. Substrate scope of N-acylation of benzimidazole [a]

To gain insight into the mechanism of this divergent reaction, some control experiments were carried out to find out the potential reaction intermediates (Scheme 4). In our previous work, we recognized that phenylacetic acids can be decarboxylatively transformed to benzaldehydes under [Cu]/O_2 conditions.[6] As shown in eq. 1 and 2, when 2-fluorobenzaldehyde was subjected to the reaction with benzimidazole (**2a**) under the standard "annulation condition" (A), a high yield of the fused heterocycle (**3aa**) was obtained while no aimed amide product **4a'a** was detected. In order to confirm that this is a tandem process, compound **6** was prepared according to the literature.[16] When it was subjected to condition A, almost quantitative amount of product **3aa** was obtained, which strongly support that aldehyde was one of the key intermediates for the annulation reaction, but not for the amidation. To get more information about the possible intermediates, compound **7** was exposed to the condition A as well, 38% of compound **3aa** was obtained, compared to *ortho*-bromo-phenylacetic acid **1a**, we could not rule it out as a possible intermediate. For decarboxylative amidation under condition B, the control experiments as in eq. 5 and eq. 6 indicated that the oxidation of phenylacetic acid led to the benzoic acid[17] or peroxybenzoic acid[18] which were efficient benzoylation reagents for this catalytic system. In order to figure out which step, S_NAr or aerobic oxidative decarboxylative acylation, occurred first in this tandem process, both compounds **10** and **11** were prepared[19] and subjected to Condition A, desired product were obtained in 68% and 85% yield. However, compound **11** was not observed or detected under either Condition A or Condition B, so we have reasons to believe that SNAr reaction occurred first to lead to C-N bond formation in the tandem process.



Condition A: $Cu(OAc)_2$ (10 mol%); $BF_3{\cdot}Et_2O$ (20 mol%); K_2CO_3 (2 equiv); DMF (1 mL); 120 °C; 18 h; O_2 (1 atm).
Condition B: CuBr (10 mol%); pyridine (3 equiv); o-xylene (1 mL); 130 °C; 24 h; O_2 (1 atm).

Scheme 4. Control experiments

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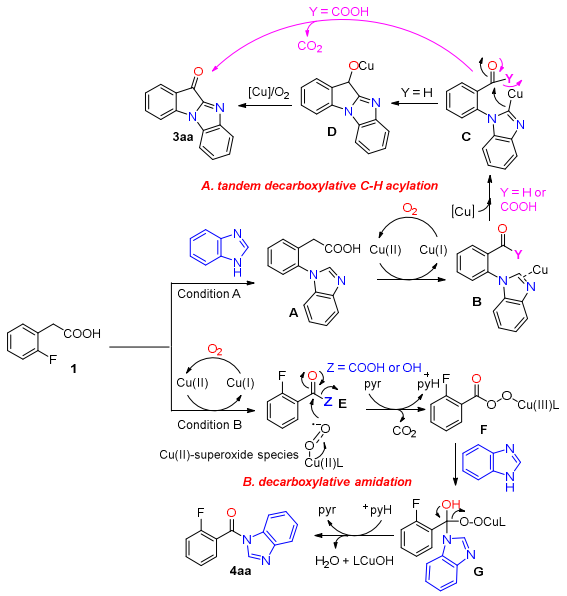

Scheme 5. Plausible mechanisms

Based on all of above control experiments, we gave a putative mechanism for these two divergent acylations: under condition A, C-N bond formation is occurred first to lead to intermediate **A** (**10**), which is further oxidized into intermediate **B** in the presence of Cu/O_2 system. If intermediate **B** is α-oxyphenylacetic acid, activated benzimidazole moiety will attack the newly formed carbonyl group to render product **3aa** by the release of CO_2, if intermediate **B** is aldehyde, after intramolecular attacking on the carbonyl group, intermediate **D** is formed, further oxidation eventually leads to the product **3aa**. For decarboxylative amidation (condition B in Scheme 5), phenylacetic acid **1a** is firstly oxidized into 2-oxo-2-phenylacetic acid, which might be further converted into benzoic acid via oxidative decarboxylation. Cu(II)-superoxide species was formed under O_2 atmosphere in the presence of pyridine as ligand, according to the literature,[18] this type of Cu(II)-superoxide species can react as a nucleophile (although very rare) to attack compound **E** to afford Cu(III)-peroxide intermediate **F**, which is very susceptible upon attacking by an electrophile, such as benzimidazole to give intermediate **G**. After elimination, desired product **4fa** is obtained.

Conclusions

In summary, we have developed a divergent reaction of o-halogenated phenylacetic acid with benzimidazole. Under different conditions, fused 11H-benzo[4,5]imidazo[1,2-*a*]indol-11-one or N-benzoylated benzimidazole can be formed respectively. The annulation process is based upon a tandem pathway through an aromatic nucleophilic substitution followed by an oxidative acylation. In both cases phenylacetic acids played as a novel benzoylation reagent. These reactions provide new synthetic routes to the fused N-acylated heterocycles. Further extension of this methodology and the mechanistic study are underway in our laboratory.

Experimental section

General

All experiments were conducted with a sealed pressure vessel. Flash column chromatography was performed over silica gel (200-300 mesh). ^{1}H NMR spectra were recorded on a Bruker AVIII-500M spectrometers, Chemical shifts (in ppm) were referenced to $CDCl_3$ (δ = 7.26 ppm) or DMSO-d_6 (δ = 2.54 ppm) as an internal standard. ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ (δ = 77.0 ppm) or DMSO-d_6 (δ = 40.45 ppm). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

General procedure for cyclization of benzimidazoles with *ortho*-flouro phenyl acetic acids

A sealed pressure vessel was charged with 2-fluorophenylacetic acids (0.25 mmol), benzimidazoles (0.35mmol), Cu $(OAc)_2$ (3.6 mg, 0.025 mmol), $BF_3\cdot Et_2O$ (7.1 mg, 0.05mmol), K_2CO_3 (69mg, 0.5mmol) and DMF (1 mL). The resulting solution was stirred at 120 ^{o}C under O_2 (O_2 was blowing into the system several times) monitored by TLC and GC for 20 hours. Upon completion of the reaction, the solvents were removed via rotary evaporator and the residue was purified with flash chromatography (silica gel, ethyl acetate: dichloromethane: petroleum ether: =1:1:4-1:1:10) to give the desired product 11H-benzo[4,5]imidazo[1,2-*a*]indol-11-one (**3aa**) as a yellow solid (44 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$),*c* 7.86 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 8.1 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$), δ 179.8, 148.9, 148.7, 143.2, 136.7, 129.8, 127.9, 127.3, 125.91, 125.8, 124.4, 123.9, 111.6, 111.1.

General procedure for benzoylation of benzimidazole by phenyl acetic acid

A sealed pressure vessel was charged with phenylacetic acids (0.25 mmol), benzimidazoles (0.5 mmol), CuBr (3.6 mg, 0.025 mmol), pyridine (60 mg, 0.75 mmol), and *o*-xylene (1 mL). The resulting solution was stirred at 130 ^{o}C under O_2 (O_2 was blowing into the system several times) monitored by TLC and GC for 24 hours. Upon completion of the reaction, the solvents were removed via rotary evaporator and the residue was purified with flash chromatography (silica gel, ethyl acetate: petroleum ether=1:4-1:10) to give the desired product (1H-benzo[*d*]imidazol-1-yl)(phenyl)methanone (**4fa**) as a white solid (44 mg, 79%). ^{1}H NMR: (500 MHz, $CDCl_3$), δ 8.22(s, 1 H), 8.21-8.19 (m, 1 H), 7.85-7.83 (m, 1 H), 7.82-7.80(m, 2 H), 7.71-7.68 (m, 1 H), 7.61-7.58 (m, 2 H), 7.47-7.42 (m, 2 H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 167.1, 144.0, 143.1, 133.2,132.8, 132.1, 129.5, 129.0, 125.8, 125.3, 120.5, 115.4.

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