A Practical Synthesis of Indole-Based Heterocycles Using an Amidoaluminum-Mediated Strategy

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Abstract: A large number of biologically active compounds consist of an indole scaffolding. Because of this, chemists are continually searching for more efficient means through which to successfully synthesize the required alkaloids. In our recent effort to synthesize indole-based p38 inhibitors and gramines, we found that a series of indole-based indole-3-carboxamides could be efficiently synthesized from various indole-3-carboxylates using an amidoaluminum-mediated strategy. The treatment of ethyl indole-3-carboxylates bearing a range of substitution patterns on the indole ring with various amidoaluminum complexes, led to the corresponding 1*H*-indole-3-carboxamides in yields up to 75%. Reduction by diisobutylaluminum hydride afforded the corresponding gramines in 63–85% yield. This is the first reported example of amidoaluminum complexes of type $Al_2(CH_3)_4(NR_2)_2$ promoting facile amidation of relatively inert indole esters. This particularly promising approach has resulted in the first strategy for generating medicinally important alkaloids of this type.

Key words: indoles, amination, aluminum, esters, alkaloids

The diversity and significance of indole-based heterocycles as key biologically active alkaloids suggests that development of a versatile synthesis would have broad utility in medicinal research. Most challenges facing modern chemists in synthesizing indole-based alkaloids, such as those shown in Figure 1 and Figure 2, is the synthesis of the indole moiety itself. Although methods[1] have been reported for the synthesis of various indole-based carboxamides, few methods have been reported for the synthesis of indole-based alkaloids with C-3 amide linkers (Scheme 1). Herein, we report a highly efficient synthetic strategy for generating indole-3-carboxamides and gramines from commercially available raw materials.

A common method for generating gramines from indoles is by Mannich reaction with dimethylamine and formaldehyde,[2,3] however, complimentary extension to various substituted indoles either do not work as well or not take place at all. The lack of available methods for generating ring-A substituted gramines, in addition to indole-3-carboxamides, presented a novel synthetic challenge that attracted our attention. We recently reported a highly efficient fluoroboric acid (HBF_4) catalyzed synthesis of various substituted indole-3-carboxylates in excellent yields using readily available *o*-nitrobenzaldehydes and ethyl diazoacetate under moderate conditions.[4]

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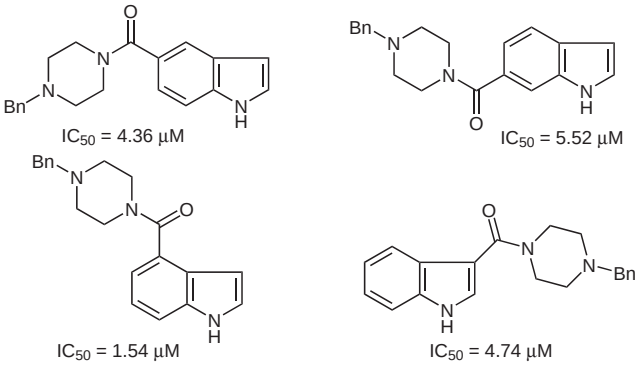


Figure 1 Known indole-based heterocyclic inhibitors of p38α

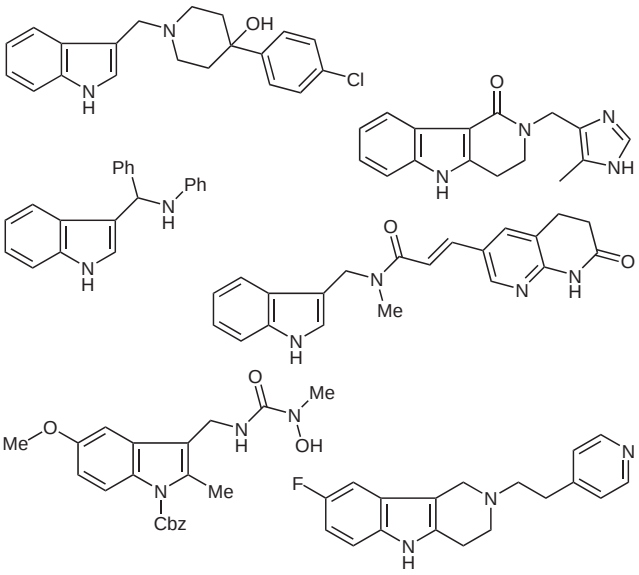
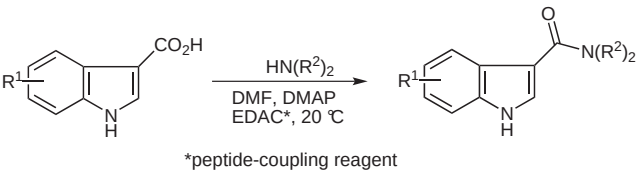


Figure 2 Biologically active gramines

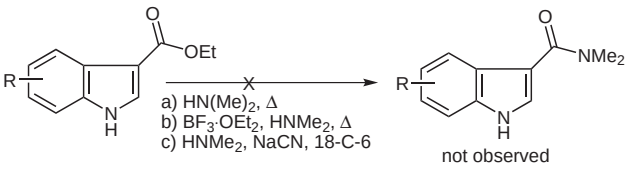


Scheme 1 Modern synthesis of indole-based 3-carboxamides

The two-step indole synthesis involves the synthesis of 2-aryl-3-hydroxypropenoic acid esters, followed by reduction over Pd/C. This method is simple and efficient, and provides access to functionalized indole esters as a possi-

ble substrate for carboxamides and gramine synthesis through an amidation–reduction sequence.

The diversity of synthetic tools available for amidating esters suggested amidation of indole-3-carboxylates would occur quite readily, however, our initial attempts at converting indole esters **1a**–**e** into the corresponding amides **2a**–**e** were unsuccessful using conventional methodology (Scheme 2). This failure underlies our efforts in developing a method that efficiently transforms indole-3-carboxylates into indole-based carboxamides and gramines.



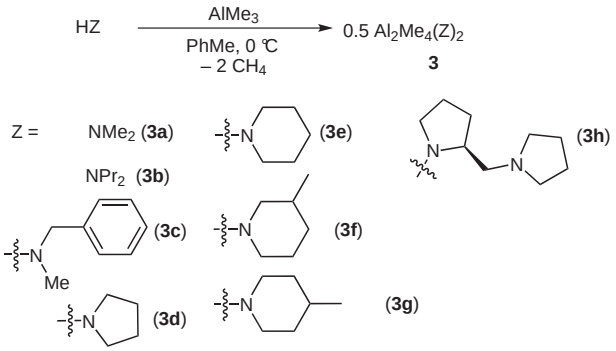
1a R = H
1b R = 5-MeO
1c R = 6-MeO
1d R = Br
1e R = 5,6-(MeO)$_2$

Scheme 2 Failed amidation attempts

Trimethylaluminum reacts with ammonia and secondary amines in a 1:1 ratio at room temperature with evolution of methane, to give dimethylaluminum amides.[5a,b] A quantitative procedure for converting esters into various carboxamides was reported by Weinreb[5a] and Ha[5b] using the amidoaluminum complex $Al_2(CH_3)_4(NMe_2)_2$. Insights from this transformation suggested that such aluminum complexes might be efficient at generating indole-based carboxamides from various indole esters, such as those shown in Scheme 2. Generating a range of amidoaluminum complexes **3** in toluene at 0 °C (Scheme 3), and then heating at 100 °C in the presence of various N-protected indole-3-carboxylates **4a**–**d** (Table 1), resulted in the formation of carboxamides **5a**–**k** in 58–81% isolated yield. Table 1 shows that an assortment of amidoaluminum complexes are capable of efficiently amidating a variety of indole esters with varying substitution patterns. The direct formation of indole-based 3-carboxamides using amidoaluminum complexes is noteworthy, particularly since this type of transformation was reported to be ineffective for the reaction with pentafluorophenyl indole-3-carboxylates.[6]

It was previously reported[7] that lithium aluminum hydride (LAH) reduction of indole-3-carboxamide proceeded satisfactorily, however, initial attempts at reducing **5a**–**d** with LAH failed, yielding instead 3-methylindoles as the major product. Substituting diisobutylaluminum hydride (DIBAL-H; 1 M in toluene) for LAH, resulted in facile amide reduction, generating **6a**–**k** in 65–93% yield (Table 2).

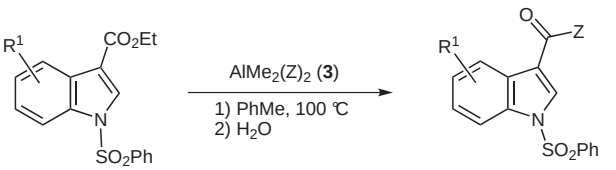
Facile formation of 3-methylindoles in the LAH reduction of amides prompted our investigation into the possibility of generating these indole amides directly from unprotected 1*H*-indole-3-carboxylates via indolene-type intermediates. Although direct amidation of N-protected indole-3-



Scheme 3 Amidoaluminum complexes **3a**–**h** generated in situ from $Al(Me)_3$

carboxylates using amidoaluminum complexes proceeded in good yield (Scheme 3, Table 1), eliminating unwanted protection and deprotection steps would be valuable. Despite the potential utility of this transformation, no synthetically useful examples of direct indole carboaluminations have been reported in the literature.

Table 1 Synthesis of *N*-(Phenylsulfonylamide)-indole-3-carboxamides **5a**–**k** Using Amidoaluminum Complexes **3**



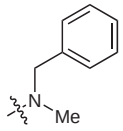
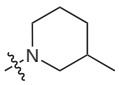
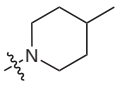
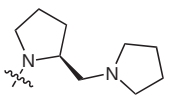
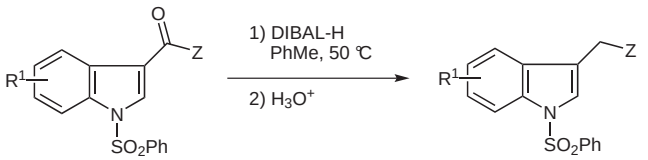
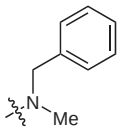
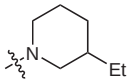
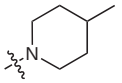
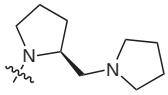
Entry	Indole	R^1	Z	Product	Yield (%)
1	**4a**	H	NMe_2	**5a**	77
2		H	N(*n*-Pr)$_2$	**5b**	65
3		H		**5c**	63
4		H		**5d**	69
5		H		**5e**	58
6		H		**5f**	81
7		H		**5g**	71
8		H		**5h**	64
9	**4b**	5-MeO	NMe_2	**5i**	73
10	**4c**	6-MeO	NMe_2	**5j**	64
11	**4d**	5-Br	NMe_2	**5k**	61

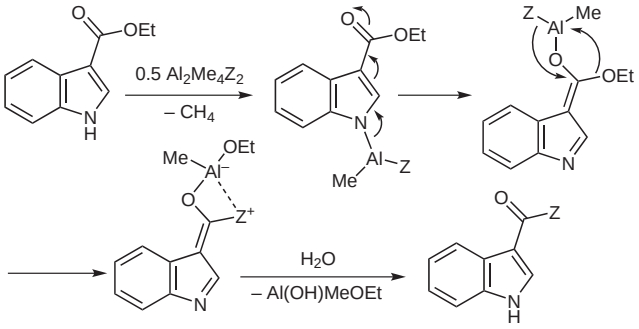
Table 2 Synthesis of *N*-(Phenylsulfonylamide)gramines **6a–k** Using DIBAL-H



Entry	R^1	Z	Product	Yield (%)
1	H	NMe_2	**6a**	91
2	H	$N(n\text{-}Pr)_2$	**6b**	87
3	H		**6c**	88
4	H		**6d**	93
5	H		**6e**	79
6	H		**6f**	82
7	H		**6g**	85
8	H		**6h**	80
9	5-MeO	NMe_2	**6i**	87
10	6-MeO	NMe_2	**6j**	90
11	5-Br	NMe_2	**6k**	65

Addition of amidoaluminum complexes **3a–h** to various 1*H*-indole-3-carboxylates **1a–d** in toluene (Table 3), resulted in substantial gas evolution. Acidic aqueous work-up resulted in the formation of amides **2a–k** in 41–65% yield. Subsequent reduction with DIBAL-H resulted in the formation of gramines **7a–k** in 63–85% yield.

Carbometalation is well accepted as a mechanistic step in reactions such as Heck coupling and olefin polymerization.[8] We believe that direct amidoalumination of N-protected indole-3-carboxylates **4** (Table 1) proceeds by a similar route (Scheme 4). Indirect amidoalumination of unprotected 1*H*-indole-3-carboxylates **1** (Scheme 5) is unknown, and presumably proceeds via a 1,4-shift, with the initial metalation occurring at the indolic nitrogen, resulting in the liberation of methane.



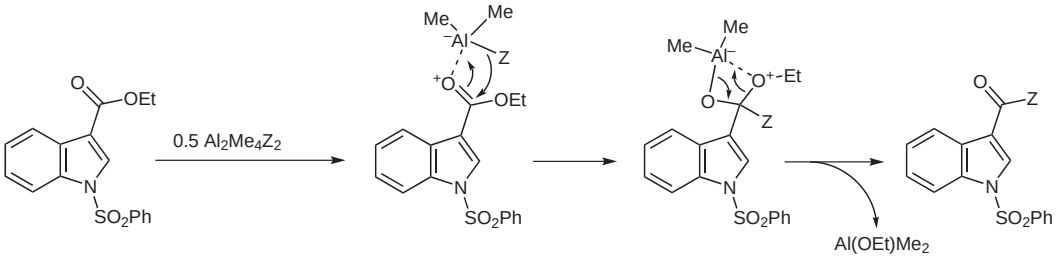
Scheme 5 Indirect amidoalumination (pathway B)

In summary, we have developed a novel approach to the construction of various indole-based alkaloids without the need for protecting groups, using easily accessible amidoaluminum complexes $[Al_2(CH_3)_4(NR_2)_2]$ and indole-3-carboxylates in toluene. A study on the scope of this process, as well as its application to natural product synthesis, is currently underway in our laboratories.

The chemical shifts (δ) are expressed in ppm relative to TMS, and C_6D_6 was used as the solvent. All organometallic operations were performed under a dry nitrogen atmosphere with standard Schlenk techniques. All of the glass flasks were flamed under vacuum and filled with nitrogen prior to use. Column chromatography was performed with silica gel (40–140 mesh). Anhydrous grade solvents were purchased from Aldrich Chemicals and used without further purifications. All indole esters were synthesized by known procedure.[4] Toluene solutions of trimethylaluminum and DIBAL-H were purchased from Aldrich Chemical company and used as received.

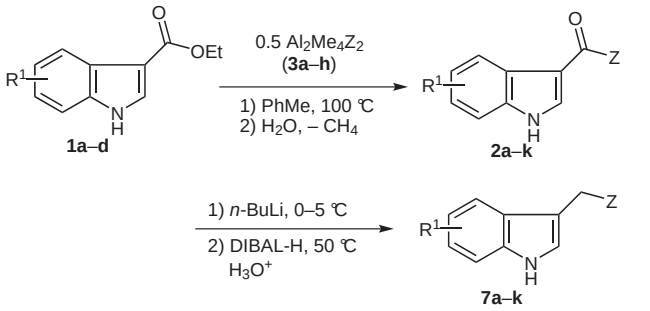
Synthesis of Amidoaluminum Complexes in Toluene: (*S*)-(–)-1-(2-Pyrrolidinylmethyl)pyrrolidinylamino-dimethyl Aluminum (3h); Typical Procedure

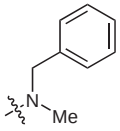
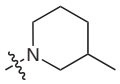
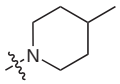
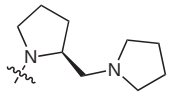
A solution of (*S*)-(–)-1-(2-pyrrolidinylmethyl)pyrrolidine (3.0 g, 0.019 mol) in toluene (100 mL) was added to a 250 mL reaction flask under N_2 to form a clear yellow solution. Me_3Al in toluene (2 M, 9.7 mL, 0.019 mol) was added to the solution over 15 min at 0–5 °C, resulting in gas evolution and a mild exotherm. The reaction mixture retained a clear yellow appearance. The reaction mixture was allowed to warm to r.t., then allowed to stir until gas evolution ceased (1–2 h). The solution was used directly with no further purification.



Scheme 4 Direct amidoalumination (pathway A)

Table 3 Synthesis of Gramines from Unprotected 1*H*-Indole-3-carboxylates **1a–d** Using DIBAL-H



Entry	Indole	R^1	Z	Yield of **2** (%)	Yield of **7** (%)
1	**1a**	H	NMe_2	**2a** (59)	**7a** (85)
2		H	N(*n*-Pr)$_2$	**2b** (42)	**7b** (79)
3		H		**2c** (55)	**7c** (73)
4		H		**2d** (58)	**7d** (81)
5		H		**2e** (41)	**7e** (65)
6		H		**2f** (62)	**7f** (75)
7		H		**2g** (61)	**7g** (79)
8		H		**2h** (75)	**7h** (74)
9	**1b**	5-MeO	NMe_2	**2i** (65)	**7i** (77)
10	**1c**	6-MeO	NMe_2	**2j** (63)	**7j** (81)
11	**1d**	5-Br	NMe_2	**2k** (57)	**7k** (63)

Synthesis of *N*-(Phenylsulfonyl)indole-3-carboxamides: (*S*)-[1-(Phenylsulfonyl)-1*H*-indol-3-yl][2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]methanone (5h); Typical Procedure

Ethyl (*N*-phenylsulfonyl)indole-3-carboxylate (**4a**; 1.75 g, 0.006 mol) was dissolved in toluene (3 mL) inside a 100 mL reaction flask under N_2. A toluene solution of **3h** (20 mL, 0.006 mol, ~0.28 M) was added to the slurry over 10 min at r.t., resulting in a 2–3 °C exotherm. The reaction mixture was heated to reflux for 18 h, allowed to cool to r.t., then H_2O (2 mL) was added to the reaction mixture over 10 min, resulting in gas evolution and a mild exotherm. Solids were removed by filtration to yield a dark biphasic filtrate. The organics were collected, washed with H_2O (5 mL) and brine (5 mL), and then dried over anhydrous Na_2SO_4. The organics were concentrated under reduced pressure, then purified by flash chromatography on silica gel (THF–EtOH, 10:1) to give a dark, tacky solid. Triturating the tacky solid with cyclohexane (50 mL) yielded **5h**.

Yield: 1.5 g (64%); light-brown powder.

^{1}H NMR (400 MHz, C_6D_6): δ = 8.23 (d, *J* = 8.4 Hz, 1 H), 7.76 (d, *J* = 7.7 Hz, 1 H), 7.68 (m, 1 H), 7.66 (m, 1 H), 7.55 (s, 1 H), 7.04 (t, *J* = 7.3 Hz, 2 H), 6.61 (m, 3 H), 4.17 (dd, *J* = 13.3, 1.3 Hz, 1 H), 3.18 (d, *J* = 13.4 Hz, 1 H), 2.70 (td, *J* = 8.2, 2.3 Hz, 1 H), 2.59 (dd, *J* = 11.2, 4.7 Hz, 1 H), 2.50–2.32 (m, 6 H), 1.89 (q, *J* = 8.9 Hz, 1 H), 1.78 (m, 1 H), 1.53 (m, 5 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 138.6, 136.0, 132.8, 128.6, 126.4, 124.7, 124.1, 123.0, 122.3, 120.9, 113.8, 62.7, 61.9, 54.7, 54.6, 50.0, 30.3, 23.5, 22.6.

Anal. Calcd for $C_{24}H_{27}N_3O_3S$: C, 65.8; H, 6.22; N, 9.6. Found: C, 66.1; H, 6.43; N, 9.4.

Reduction of Indole-3-carboxamides Using DIBAL-H: 3-[(3-Methylpiperidin-1-yl)methyl]-1*H*-indole (7f); Typical Procedure

(1*H*-Indol-3-yl)(3-methylpiperidin-1-yl)methanone (**2f**; 2.3 g, 9.5 mmol) was dissolved in toluene (50 mL) inside a 100 mL reaction flask, under nitrogen. A solution of *n*-BuLi (2.5 M in hexanes, 3.8 mL, 9.5 mmol) was added to the reaction mixture over a 10 min period at 0–5 °C, resulting in a mild exotherm. After stirring for an additional 15 min, a solution of DIBAL-H in toluene (1.5 M, 6.6 mL, 10 mmol) was added to the reaction mixture over a 5 min period at 0–5 °C. No exotherm was observed. The reaction mixture was allowed to warm to r.t., then stirred at 50 °C for 16 h. After cooling to r.t., MeOH (1.9 mL) was added to the reaction mixture over a 10 min period, resulting in the formation of solids that were removed by Buchner filtration. The filtrate was concentrated under reduced vacuum, then purified by flash chromatography on silica gel (THF–EtOH, 10:1) to give **7f**.

Yield: 1.7 g (75%); light-brown powder; mp 145–148 °C (Lit.[9] 144–146 °C).

IR (ATR): 3230 (NH), 2510 (CH), 1555, 1501, 1335, 885, 730 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.88 (s, 1 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 7.18 (d, *J* = 2.2 Hz, 1 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 6.96 (t, *J* = 7.3 Hz, 1 H), 3.56 (s, 2 H), 2.82–2.72 (br, 2 H), 1.86–1.76 (br t, 1 H), 1.66–1.34 (br, 5 H), 0.86–0.73 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 136.7, 128.1, 124.8, 121.3, 119.5, 118.7, 111.7, 111.6, 61.8, 54.2, 53.8, 33.2, 31.1, 25.6, 20.1.

Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.56; H, 8.59; N, 12.33.

Synthesis of 1*H*-Indole-3-carboxamides: (*S*)-(1*H*-Indol-3-yl)[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]methanone (2h); Typical Procedure

Ethyl indole-3-carboxylate (**1a**; 3.4 g, 0.019 mol) was dissolved in toluene (60 mL) inside a 250 mL reaction flask under a N_2 atmosphere. A toluene solution of **3h** (100 mL, 0.019 mol, ~0.19 M) was added to the slurry over 10 min at r.t., resulting in substantial gas evolution. The reaction mixture was refluxed for 16 h, then allowed to cool to r.t. with stirring. H_2O (7 mL) was added to the reaction mixture over 5 min to give a slurry (the addition of H_2O was moderately exothermic with moderate gas evolution). Solids were removed by filtration and washed with THF (100 mL). The filtrates were combined and concentrated to a solid under reduced pressure and the residue was purified by flash chromatography on silica gel (THF–EtOH, 10:1) to give **2h**.

Yield: 4.5 g (75%); free-flowing, white powder; mp 139–140 °C.

IR (ATR): 3230, 2510 (NH, CH), 1725, 1654, 1555, 1501, 1335, 885, 730 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 10.90 (s, 1 H), 8.35 (d, *J* = 7.7 Hz, 1 H), 7.39 (d, *J* = 7.7 Hz, 1 H), 7.20–7.13 (m, 2 H), 6.91 (br, 1 H), 4.75–4.48 (br, 1 H), 3.31–3.03 (br, 2 H), 2.98–2.72 (br, 1 H), 2.63–

2.24 (br, 5 H), 1.75 (1 H, m), 1.66 (m, 1 H), 1.52 (br, 4 H), 1.40 (m, 1 H), 1.32–1.14 (br, 1 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 166.6, 136.3, 122.3, 121.3, 120.7, 112.0, 111.9, 58.7, 54.4, 30.1, 28.8, 27.6, 23.6.

Anal. Calcd for $C_{18}H_{23}N_3O$: C, 72.7; H, 7.8; N, 14.13. Found: C, 72.31; H, 7.56; N, 14.35.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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