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Facile Reductive Amination of Aldehydes with Electron-Deficient Anilines by Acyloxyborohydrides in TFA: Application to a Diazaindoline Scale-Up

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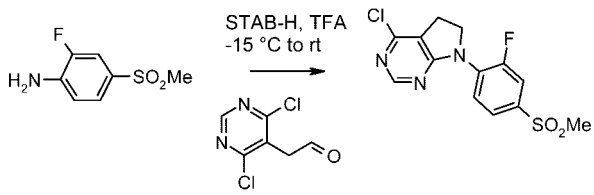
Received January 27, 2009



A scale-up of diazaindoline **1** was achieved in four stages and 32% overall yield. The key step involved rapid reductive amination of aldehyde **8** with aniline **5** by sodium triacetoxyborohydride (STAB-H) and TFA followed by ring closure of intermediate amine **9** to compound **1** in the same pot. These reaction conditions were also applied to facile reductive aminations with anilines known to have little reactivity under STAB-H/AcOH conditions. Spectral data supported the tris(trifluoroacetoxy)borohydride anion (**16**) as the active reducing agent.

Diazaindoline **1** is a useful intermediate in the synthesis of preclinical GPR119 receptor agonists.[1,2] Our metabolic pathways drug discovery team recently required ca. 200 g of **1** for analogue synthesis and scale-up campaigns. The original five-step synthesis of **1** (used for medicinal chemistry purposes) and the four-stage scale-up route are shown in Scheme 1. The first two steps of both syntheses were similar and involved cyclization of commercially available diethyl allylmalonate (**2**) to pyrimidine **3** followed by deoxychlorination to **4**. At this point, the two routes diverged.

In the original synthesis, commercially available sulfonylaniline **5** was deprotonated with NaH, and the resulting sodium salt was reacted with **4** to give anilinopyrimidine **6**. Low temperature (−78 °C) ozonolysis of **6** followed by treatment with $NaBH_4$ afforded the primary alcohol **7**. Finally, formation of the mesylate of **7** and cyclization in situ provided **1**.

From a scale-up perspective, we considered use of NaH to be undesireable owing to handling issues and significant hydrogen gas production. The ozonolysis of **6** was of even greater concern in view of the highly energetic ozonide intermediates[3] and cryogenic conditions involved. For these reasons, we pursued an alternative synthesis of **1** for scale-up applications with the goals of shortening the synthesis, avoiding chromatography, and eliminating hazardous procedures.

We proposed a new route to **1** from aniline **5** and the known aldehyde **8**[4] via the reductive amination/ring-closure sequence shown in Scheme 1. We felt that the putative amine intermediate (**9**) would readily cyclize to **1** in situ under the appropriate conditions. A few accounts of one-pot reductive amination/cyclization syntheses of diazaindolines with sodium triacetoxyborohydride (STAB-H) and AcOH are known in the literature,[5] although yields are variable. Encouraged by these reports, we prepared a nominal amount of allyldichloropyrimidine **4** by the route shown in Scheme 1 and oxidatively cleaved the double bond to afford the requisite aldehyde **8**.

Reductive amination of **8** with **5** was investigated using STAB-H[6] in CH_2Cl_2 both with and without AcOH cosolvent. Reactions were monitored by a combination of HPLC and LCMS. Adding STAB-H portionwise to a mixture of **5** and **8** in CH_2Cl_2/AcOH resulted predominantly in reduction of **8** to the corresponding primary alcohol. The results were improved by adding a CH_2Cl_2 solution of **8** dropwise to a mixture of **5** and STAB-H in CH_2Cl_2/AcOH. Under these conditions, some formation of **9** (ca. 30% by HPLC) occurred overnight at rt; however, none of the cyclized product **1** was observed. Performing the same reaction without AcOH produced very little of **9** (<5% conversion).

We next evaluated TFA as cosolvent (10−30 equiv) and found that it gave a much cleaner and faster reaction. Reasonable formation of **9** was achieved by cooling a mixture of **5** and **8** in TFA followed by portionwise addition of STAB-H; however, we found that dropwise addition of a CH_2Cl_2 solution of **8** to a mixture of **5** and STAB-H in TFA gave a cleaner reaction and avoided dialkylation of **5**.

Accordingly, STAB-H (1.5 equiv) was dissolved in neat TFA, and the solution was charged with **5** (1 equiv). After the mixture was stirred for a few minutes[7] at rt, it was cooled to −15 °C, and a solution of **8** (1.1 equiv) in CH_2Cl_2 was added dropwise. The reaction mixture was immediately checked by HPLC and LC−MS which showed clean formation of **9** (>92%); moreover, little or no aldehyde reduction was observed. After the mixture was stirred for 10 min, workup afforded **9** in 83% yield (Table

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(7) Solutions prepared from STAB-H and TFA lose their effectiveness over time and should be used immediately following preparation for optimum results.

10.1021/jo900157z CCC: $40.75 © 2009 American Chemical Society
Published on Web 04/07/2009

SCHEME 1

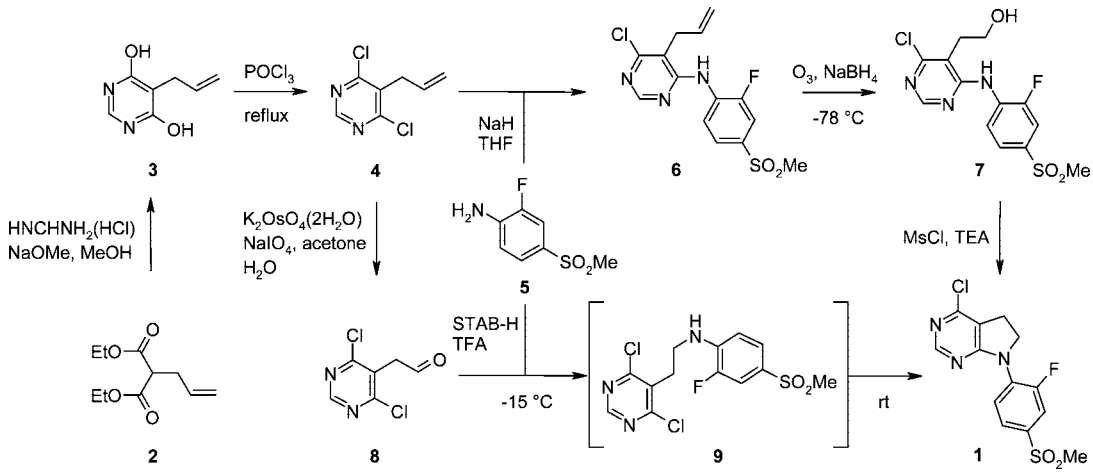


TABLE 1. Reaction Conditions and Results for Reductive Aminations of Aldehydes 8, 11, and 14 with Electron-Deficient Anilines 5, 10, and 13 by Solutions Prepared from STAB-H and TFA[a]

aniline (equiv)	aldehyde (equiv)	STAB-H (equiv)	time	product	% yield[b]
5 (1)	**8** (1.05)	(1.5)	5 min[c]	**9**	83
5 (1)[d]	**8** (1.1)	(1.4)	18 h[e]	**1**	69
10 (1)	**11** (2.3)	(4)	10 min[f]	**12**	92
13 (1)	**14** (1)	(2)	10 min[f]	**15**	82[g]

[a] A solution of aniline and STAB-H in neat TFA (10−30 equiv) was treated dropwise with a solution of aldehyde in CH_2Cl_2. [b] Isolated yield. [c] −15 °C. [d] 0.96 mol scale. [e] −15 °C to rt overnight. [f] rt. [g] Hydrochloride salt.

1). Peforming the same procedure at −15 °C and allowing the reaction mixture to warm to rt with stirring overnight effected complete cyclization of **9** to diazaindoline **1** in the same pot.

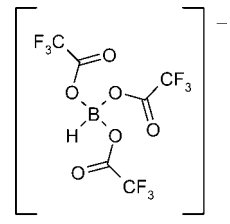
Interestingly, whereas the small amount of **9** generated under STAB-H/AcOH conditions did not readily cyclize to **1**; this cyclization occurred smoothly with TFA as cosolvent. Thus, TFA facilitated both the reductive amination and ring-closure steps.

To determine if our results with STAB-H/TFA were unique for reactants **5** and **8** or were applicable to other weakly basic amines, we explored the reaction of 2,4-dinitroaniline (**10**) with cyclohexanecarboxaldehyde (**11**) (Scheme 2). This reaction is reported[8] to occur slowly under STAB-H/AcOH conditions; the published yield of **12** is 61% after 4 d with 5 equiv of STAB-H and 4−5 equiv of **11**. In contrast, the STAB-H/TFA conditions (Table 1) produced complete reaction *immediately following aldehyde addition*. The product (**12**) was isolated in 92% yield following workup and trituration with hexanes.

We also investigated reaction of 2,4,6-trichloroaniline (**13**) with benzaldehyde (**14**) (Scheme 2). There is speculation[8] that STAB-H-mediated reductive aminations of aliphatic aldehydes with **13** proceed through an enamine intermediate; this is primarily based on the lack of reactivity of **13**[8,9] (under STAB-H/AcOH conditions) with benzaldehyde (**14**) which cannot form an enamine. Remarkably, the STAB-H/TFA reductive amination of **14** with **13** occurred within minutes (>87% by HPLC); the product (**15**) was isolated as its hydrocholoride salt in 82% yield (Table 1).

The mechanism of reductive aminations by solutions prepared from STAB-H in TFA is difficult to determine; however, the actual reducing agent does not appear to be STAB-H. For example, dissolving STAB-H (a white powder) in excess TFA followed by rotary evaporation and drying under high vacuum afforded a viscous oil; mass balance of this material together with its ^{13}C NMR spectrum suggested significant substitution of the STAB-H acetate groups by trifluoroacetic acid; moreover, electrospray mass spectral analysis of a solution of **13** and STAB-H in TFA showed strong base peaks matching aniline **13** and the tris(trifluoroacetoxy)borohydride anion (**16**).

Interestingly, treating excess TFA with $NaBH_4$ (caution: significant hydrogen gas evolution occurs along with a mild exotherm) is known to generate **16**.[10] Treatment of this solution with **13** and subsequent dropwise addition of a solution of **14** in CH_2Cl_2 also effected rapid reductive amination to **15**; however, not all of **13** was consumed, and the reaction produced more byproducts compared to the STAB-H/TFA method. This result also supported the intermediacy of **16** as the reducing agent in the reductive amination reactions summarized in Table 1.



16

Assuming the reductive amination reactions shown in Table 1 proceed by a mechanism involving hydride reduction of an iminium ion, it appears that TFA solutions of acyloxyborohydrides promote this process, especially with severely electron deficient anilines.

With practical procedures in hand for synthesis of **1**, we turned our attention to its scale-up. All of the scaled reactions were performed in graduated 6 or 16 L fixed-glass, jacketed laboratory reactors (quench volumes ca. 10−30 L). Workups and phase splits were performed in the reactor; however, for

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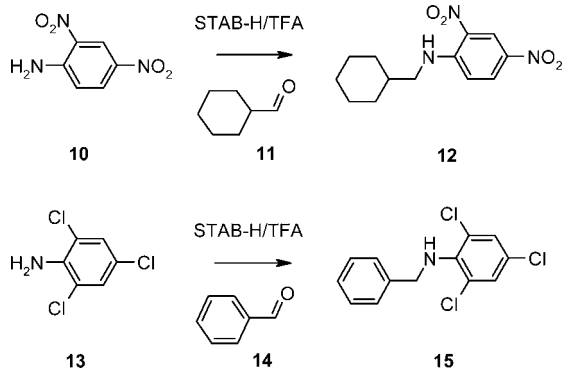
SCHEME 2



10 11 12 13 14 15

convenience, the final organic phase was often removed from the reactor, dried, and concentrated by rotovap.

Allyldihydroxypyrimidine **3**[4] was prepared on 2.2 mol scale from formamidine hydrochloride and diethyl allylmalonate **2** in the presence of sodium methoxide/methanol. Solvent removal and neutralization with 6 N HCl afforded **3** which was collected by filtration in 76% yield. Deoxychlorination of **3** with $POCl_3$ at reflux temperature effected clean conversion to the dichloropyrimidine **4**[4] in 82% yield.

We next evaluated oxidative cleavage of allylpyrimidine **4** to aldehyde **8**.[4] The two most common methods employed for this type of transformation are ozonolysis (which we wished to avoid) or use of catalytic osmium tetroxide in the presence of stoichiometric oxidants[11] such as $NaIO_4$ at ambient temperatures. We chose to evaluate the latter conditions, but replaced OsO_4 with $K_2OsO_4 \cdot (2\ H_2O)$, which is a more stable, less volatile, and easier to handle solid.[12] The scaled synthesis of **8** was accomplished by portionwise addition of $NaIO_4$ to a mixture of **4** (1.45 mol) in acetone/water containing 3 mol % of $K_2OsO_4 \cdot (2\ H_2O)$. Following an aqueous reductive workup, aldehyde **8** was obtained as a solid in 74% yield.

Reductive amination of **8** with **5** was performed on a ca. 1 mol scale. We chose to first dissolve aniline **5** in TFA (12 equiv) with cooling and then add the STAB-H portionwise at −15 °C. Following the STAB-H charge, the mixture was stirred for a few minutes, and a CH_2Cl_2 solution of **8** was added dropwise; after the reaction mixture was warmed to rt and stirred overnight, formation of **1** was complete. Following workup, the crude material was triturated with EtOAc/MeOH to afford **1** as a crystalline solid (216 g, 69% yield).

In conclusion, a practical laboratory scale-up of diazaindoline **1**, a useful intermediate in the synthesis of novel GPR119 receptor agonists,[1] was achieved in four stages and 32% overall yield without chromatography. The new route circumvented an ozonolysis reaction in the first-generation approach and shortened the synthesis by one step. A key synthetic discovery involved the facile reductive amination of aldehyde **8** with aniline **5** by STAB-H and TFA. The TFA cosolvent facilitated both the formation of intermediate amine **9** and its subsequent ring closure to diazaindoline **1**. In addition, the STAB-H/TFA methodology was useful for rapid reductive amination of aldehydes with other weakly basic anilines (e.g., **10** and **13**) known to have little or no reactivity under STAB-H/AcOH conditions. Mass and NMR spectral data supported the tris(trifluoroacetoxy)borohydride anion (**16**) as the active reducing agent in these transformations. Details of the medicinal chemistry synthesis of **1** and the structure−activity relationships of GPR119 receptor agonists derived from this compound are planned for a future publication.

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Experimental Section

(4,6-Dichloro-5-pyrimidinyl)acetaldehyde (8). A 16 L fixed-glass jacketed laboratory reactor (32 L quench volume) was charged with **4** (274 g, 1.45 mol), acetone (3.8 L), and water (3.8 L). The solution was cooled to 15 °C (jacket control = 15 °C), and $K_2OsO_4 \cdot (2\ H_2O)$ (18 g, 49.3 mmol) was added followed by the addition of $NaIO_4$ (1.24 kg, 1.8 mol) in eight portions over 1 h while maintaining the reaction temperature below 40 °C. Following this addition, the reaction mixture was stirred at rt for 1 h. The resulting suspension was filtered; the filtrate was returned to the reactor, and the acetone was removed by distillation at reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (5 × 1 L), and the combined organic layers were washed with 10% $Na_2S_2O_3$ (2 × 3.5 L) and brine, dried over Na_2SO_4, filtered, and concentrated to afford **8**[4] as a light amber solid (203.7 g, 74% yield). This material was used without purification. An analytical sample was obtained by recrystallization from CH_2Cl_2/heptane: mp 89−91 °C (lit.[4] mp 84−86 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.72 (s, 1H), 8.86 (s, 1H), 4.21 (s, 2H); Anal. Calcd for $C_6H_4Cl_2N_2O$: C, 37.73; H, 2.11; N, 14.67. Found: C, 37.81; H, 2.02; N, 14.77.

[2-(4,6-Dichloro-5-pyrimidinyl)ethyl][2-fluoro-4-(methylsulfonyl)phenyl]amine (9). Compound **5** (1 g, 5.29 mmol) was dissolved in TFA (5 mL) at rt, and the solution was cooled to −15 °C; STAB-H (1.68 g, 7.93 mmol) was added portionwise. The mixture was stirred for 10 min, and a solution of **8** (1.06 g, 5.55 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After 5 min, the mixture was poured into ice-cold satd $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with satd $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford a solid which was triturated with hexanes and filtered to afford **9** as a light beige solid (1.6 g, 83% yield). An analytical sample was obtained by recrystallization from CH_3CN: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.77 (s, 1H), 7.51 (dd, J = 8, 2 Hz, 1H), 7.48 (dd, J = 11, 2 Hz, 1H), 6.94 (br t, J = 8 Hz, 1H), 6.72 (br m, 1H), 3.50 (br q, J = 7 Hz, 2H), 3.08 (s, 3H), 3.06 (t, J = 7 Hz, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 162.2, 156.8, 150.0 (d, J_{CF} = 243 Hz), 141.6 (d, J_{CF} = 12 Hz), 131.2, 126.5 (d, J_{CF} = 6 Hz), 125.7 (d, J_{CF} = 2 Hz), 114.0 (d, J_{CF} = 21 Hz), 110.8 (d, J_{CF} = 4 Hz), 44.8, 40.0 (obscured by solvent multiplet), 29.9; ESI MS m/z 364 $[M + H]^+$. Anal. Calcd for $C_{13}H_{12}Cl_2FN_3O_2S$: C, 42.87; H, 3.32; N, 11.54. Found: C, 42.79; H, 3.22; N, 11.51.

4-Chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1). A 6 L fixed-glass jacketed laboratory reactor (12 L quench volume) was charged with TFA (850 mL). The contents of the reactor were cooled to −10 °C, and **5** (181 g, 0.96 mol) was added. The reactor's jacket temperature was set to −25 °C, and when the solution reached −15 °C, STAB-H (293.7 g, 1.39 mol) was added. After the solution was stirred for a few minutes, a solution of **8** (203.7 g, 1.07 mol) in CH_2Cl_2 (550 mL) was added dropwise over 1 h while maintaining the reaction temp at ca. −15 °C. Stirring was continued at −15 °C for 30 min, and the reaction mixture was then allowed to warm to rt overnight. The reaction mixture was diluted with 1,2-dichloroethane (1 L), and the majority of CH_2Cl_2 and TFA was removed by distillation at reduced pressure (ca. 50 mbar; jacket temperature = 25−30 °C). The reaction mixture was diluted with CH_2Cl_2 (1 L) and neutralized by slow addition of 10% Na_2CO_3 (6 L) to pH 7−8. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 L). The combined organic layers were washed with brine (1.5 L), dried over Na_2SO_4, filtered, and concentrated. The crude

material was stirred with 1:1 EtOAc/MeOH (250 mL) for 2 h, and compound **1** was collected by filtration as a light beige crystalline solid (216 g, 69% yield): mp 165−167 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.29 (s, 1H), 7.94 (br t, J = 8 Hz, 1H), 7.89 (dd, J = 11, 2 Hz, 1H), 7.79 (dd, J = 8, 2 Hz, 1H), 4.20 (t, J = 8 Hz, 2H), 3.27 (s, 3H), 3.22 (t, J = 8 Hz, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 166.2, 158.0, 155.5 (d, J_{CF} = 254 Hz), 152.7, 139.3 (d, J_{CF} = 6 Hz), 132.5 (d, J_{CF} = 11 Hz), 126.6 (d, J_{CF} = 2 Hz), 124.2 (d, J_{CF} = 3 Hz), 120.1, 116.5 (d, J_{CF} = 23 Hz), 50.7 (d, J_{CF} = 5 Hz), 44.0, 24.7; ESI MS m/z 328 $[M + H]^+$. Anal. Calcd for $C_{13}H_{11}ClFN_3O_2S$: C, 47.64; H, 3.38; N, 12.82. Found: C, 47.54; H, 3.32; N, 12.60.

(Cyclohexylmethyl)(2,4-dinitrophenyl)amine (12). STAB-H (847 mg, 4 mmol) was dissolved in TFA (7 mL) at rt. Compound **10** (183 mg, 15 wt % water, 0.852 mmol) was added, and the mixture was stirred for 10 min at rt. A solution of **11** (224 mg, 2 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 10 min, the mixture was poured slowly into ice-cold satd $NaHCO_3$ solution. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with satd $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford a dark orange oil which was triturated with hexanes and stirred for 1 h at rt. The mixture was filtered, washed with hexanes, and dried under high vacuum to afford **12**[8] as a bright yellow solid (218 mg, 92% yield): HPLC purity (LCMS) >99%; mp 80−83 °C (lit.[8] mp 76−78 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.12 (d, J = 3 Hz, 1H), 8.64 (br, 1H), 8.23 (dd, J = 10, 3 Hz, 1H), 6.89 (d, J = 10 Hz, 1H), 3.23 (t, J = 6 Hz, 2H), 1.89−1.65 (m, 6H), 1.36−1.11 (m, 3H), 1.13−0.98 (m, 2H); ESI MS m/z 278 $[M - H]^-$.

2,4,6-Trichloro-*N*-(phenylmethyl)aniline[9] Hydrochloride (15·HCl). Compound **13** (196 mg, 1 mmol) was dissolved in neat TFA (1 mL) at rt; STAB-H (424 mg, 2mmol) was added, and the mixture was stirred for 5 min at rt. A solution of **14** (106 mg, 1 mmol) in CH_2Cl_2 (1 mL) was then added slowly dropwise over 5 min. The reaction mixture was stirred for 10 min at rt and then poured into a mixture of ice and satd $NaHCO_3$ solution. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a colorless oil. This material was dissolved in heptane (10 mL); 4 N HCl/*p*-dioxane (0.22 mL, 0.88 mmol) was added, and the mixture was stirred for 10 min at rt. The product (**15**·HCl) was collected by filtration as a white solid (265 g, 82% yield): HPLC purity (LCMS) > 99%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (br, 2H), 7.39 (d, J = 7 Hz, 2H), 7.27 (s, 2H), 7.30−7.20 (m, 3H), 4.80 (s, 2H); ^{13}C NMR (CD_3OD, 101 MHz) δ 134.4, 133.9, 131.7, 129.7, 129.3, 129.1, 128.9, 128.6, 52.5; ESI MS m/z 286 $[M + H]^+$ (100), 288 $[M + 2 + H]^+$ (97), 290 $[M + 4 + H]^+$ (32).

Acknowledgment. We thank David M. Black for performing the ESI MS analyses on solutions prepared from TFA and STAB-H.

Supporting Information Available: Procedures for synthesis of **3** and **4**; ^{1}H and ^{13}C NMR spectra (including expansions) of **1**, **9**, and **15**·HCl; analytical HPLC conditions; HPLC chromatogram (LCMS) of **15**·HCl; ESI mass spectrum of **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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