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Brian D. Judkins [a], David G. Allen [a], Tracey A. Cook [a], Brian Evans [a] & Tsarina E. Sardharwala [a]
[a] Receptor Chemistry Unit, Glaxo Wellcome Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY

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A VERSATILE SYNTHESIS OF AMIDINES FROM NITRILES *VIA* AMIDOXIMES

Brian D. Judkins*, David G. Allen, Tracey A. Cook,
Brian Evans, and Tsarina E. Sardharwala

Receptor Chemistry Unit, Glaxo Wellcome Research and Development,
Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY.

Abstract: Benzamidines were prepared conveniently from benzonitriles in good yield *via* catalytic hydrogenation of intermediate benzamidoximes in acetic acid/acetic anhydride.

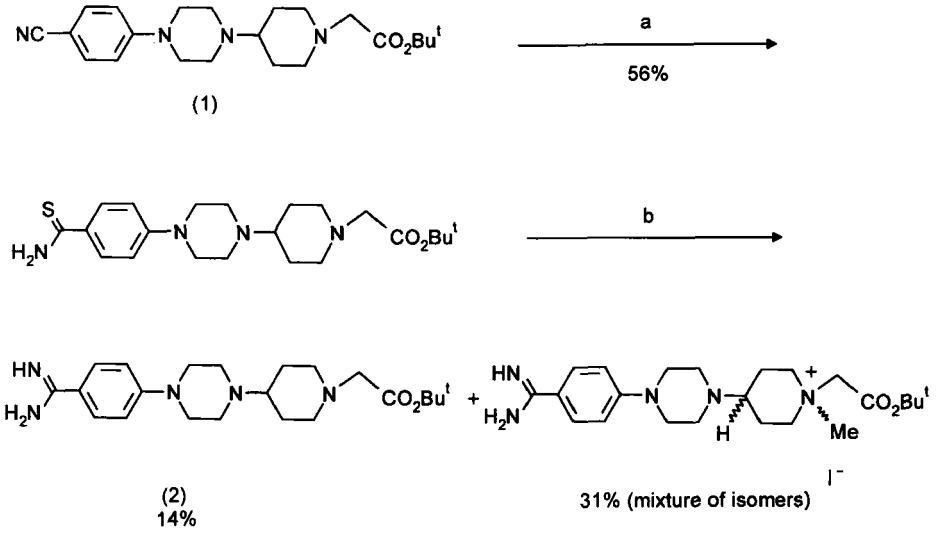
Introduction

The conversion of nitriles into amidines represents an important part of the synthesis of a number of pharmacologically active molecules, e.g. fibrinogen antagonists[1], thrombin inhibitors[2], and recently reported factor Xa inhibitors[3]. The existing routes to amidines from nitriles include (a) the Pinner method (*via* the imidate)[4], (b) conversion *via* the thioamide and thioimidate and reaction with ammonium acetate[5], and recently (c), a direct copper catalysed reaction of nitriles with amines[6]. In order to prepare some benzamidine containing fibrinogen antagonists, we required an efficient conversion of benzonitriles into benzamidines.

*To whom correspondence should be addressed

This is illustrated by the poor yielding (7%) conversion of the benzonitrile (1) into the benzamidine (2) due to competing quaternisation of the piperidine nitrogen that accompanied the use of the thioamide route (FIG.1). The Pinner method was unsuitable due to the acid lability of the *tert*-butyl ester group during attempted imidate formation, while the corresponding methyl ester of (1) formed an insoluble hydrochloride which could not be induced to react.

FIG. 1



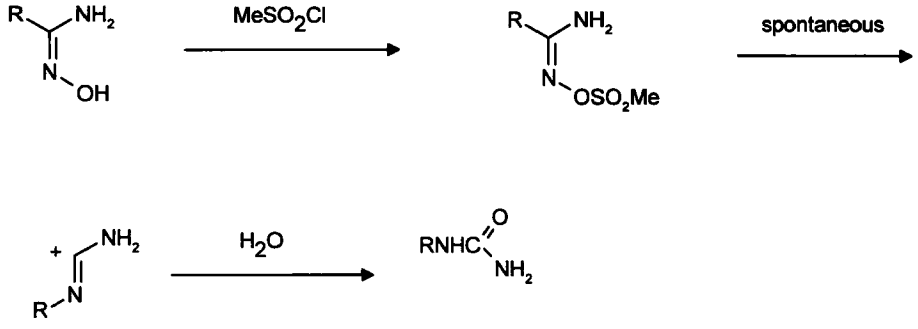
(a) $H_2S/Et_3N/DMF$ (b) MeI/Me_2CO then $NH_4OAc/MeOH$

We therefore investigated an alternative route *via* amidoximes. In contrast to the above routes, the use of amidoximes to prepare amidines has been sparsely reported. Whilst hydrogenation of amidoximes to amidines has been reported to proceed under forcing conditions[7] (e.g. Raney nickel at 60° and 3atm. hydrogen),

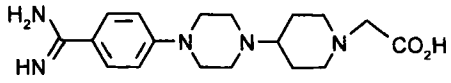
we reasoned that the N-O bond would be weakened, and hence made more susceptible to hydrogenation, by attachment of an electron withdrawing substituent to the oxygen atom. This hypothesis was supported by analogy with the Tiemann rearrangement[8] (FIG.2) in which O-sulphonylation of amidoximes promotes a spontaneous rearrangement with N-O bond cleavage to form ureas upon quenching with water.

FIG. 2

The Tiemann rearrangement



As a result we investigated hydrogenation of O-acetylamidoximes[9] in which the N-O bond would be expected to be of intermediate stability, and found these to be readily reduced to amidines under mild conditions. The scope and limitations of this reaction have been examined using some readily available benzonitriles, and the optimised conditions applied to the large scale synthesis (1kg) of the fibrinogen antagonist GR144053 (3).



(3)

Results

Amidoxime formation

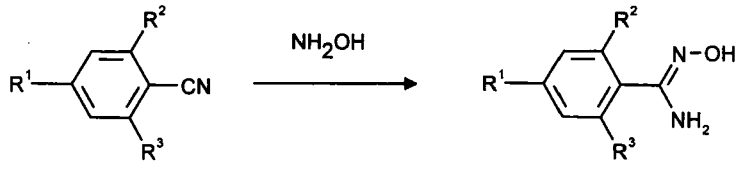
A variety of aromatic nitriles (4) were converted to (Z)-amidoximes (5) by either published procedures[9] (Method A - see Table 1), or when this failed [e.g. (4i), where the only product isolated was 2,6-dimethylbenzamide], by using a modified procedure (Method B - Table 1). 2,6-Dimethylbenzonitrile proved less reactive than the other examples, and prolonged heating with excess reagents was required using the conditions of Method B to give a low yield of the previously unreported 2,6-dimethylbenzamidoxime, together with 2,6-dimethylbenzamide.

Amidine formation

Amidoximes (5) were hydrogenated over 10% palladium on carbon at 1atm. pressure in glacial acetic acid containing acetic anhydride (1.5 equivs.) for 2-4 h to afford the acetate salts of the amidines (6) directly (Table 2)[10]. In a few cases (Examples 5b-d) the reaction proceeded slowly (16h) in the absence of acylating agent, but as other examples, e.g. (5a, R=F), were only partly hydrogenated under these conditions, we routinely performed all hydrogenations in the presence of acetic anhydride. The intermediate O-acetates are rapidly formed (<10min. by

Table 1

Preparation of amidoximes



(4) (5)

(4)	R^1	R^2	R^3	% Yield (5)	Method
a	F	H	H	90	B
b	Me	H	H	92	B
c	CF_3	H	H	91	B
d	Me_2N	H	H	81	A
e	MeO_2C	H	H	60	B
f	H	H	OMe	93	A
g	H	H	Me	77	A
h	H	H	Et	67	A
i	H	Me	Me	16	B

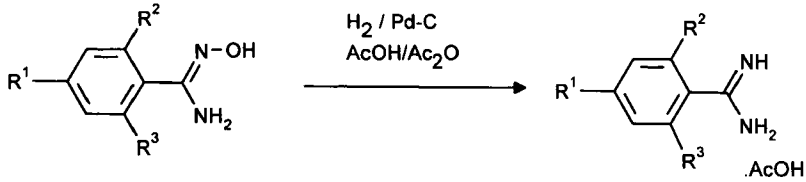
Method A = $NH_2OH.HCl/Na_2CO_3/EtOH\text{-}H_2O/80°/16h$
Method B = $NH_2OH.HCl/KOBu^t/MeOH\text{-}PhMe/70\text{-}80°/17h$

t.l.c.), and in the case of (5c) the O-acetate was isolated and characterised before being hydrogenated to (6c) in quantitative yield.

Importantly, as can be seen from examples 6f-i, this method was successful for those systems containing *ortho* substituents for which the Pinner method fails[11]. Also the hitherto unknown 2,6-dimethylbenzamidine could be prepared using this route. Trifluoroacetic anhydride (TFAA) could also be used as the acylating agent, e.g. (5a) could be converted into (6a) presumably *via* the corresponding O-

Table 2

Preparation of Amidines



(5) (6)

(5)	R^1	R^2	R^3	% Yield (6)	M.p. of (6)
a	F	H	H	84	215 (sub)
b	Me	H	H	94	241 (sub)
c	CF_3	H	H	99	220 (sub)
d	Me_2N	H	H	90	235-238 (dec)
e	MeO_2C	H	H	94	138-142[a]
f	H	H	OMe	94	192-195
g	H	H	Me	45	196-198
h	H	H	Et	18	133-135[b]
i	H	Me	Me	56	241 (dec)

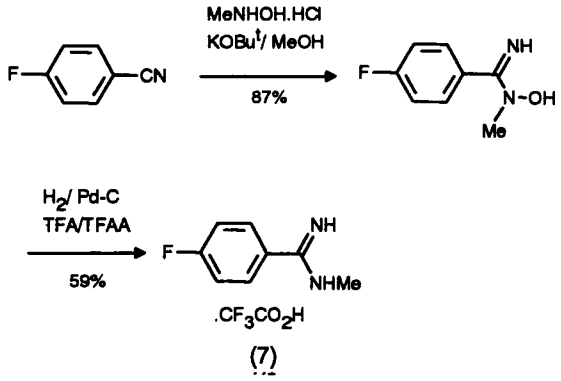
[a] - free base, [b] - trifluoroacetate salt (see experimental)

trifluoroacetate. Although of no advantage in the case of (5a), use of TFAA/TFA was advantageous in the case of the N-alkylamidine (7) which was prepared from 4-fluorobenzonitrile in good yield (FIG.3), in contrast to the poor yield obtained using acetic acid/ acetic anhydride (<5%).

Application to synthesis of fibrinogen antagonists

We have found this method to be applicable for the synthesis of a large number of our fibrinogen antagonists[12] including the large scale preparation (1kg) of

FIG. 3



(7)

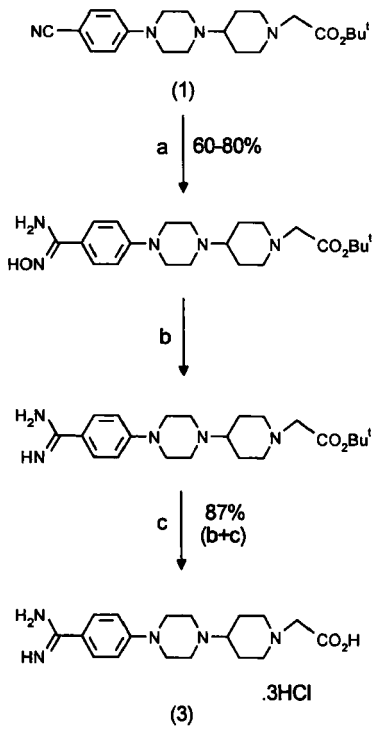
GR144053 (3)[13], which was obtained from the nitrile (1) in 75% overall yield (FIG.4), a major improvement on the 7% yield obtained using the thioamide route.

Summary

We have described a straightforward procedure using mild conditions for converting benzonitriles into benzamidines. The procedure is compatible with a wide range of functional groups, and enables the synthesis of *ortho* substituted benzamidines, which are difficult to synthesise using existing methods. In addition the route was suitable for scale-up, as illustrated in the synthesis of GR144053 (3).

Experimental

NMR spectra were obtained on a Bruker AC-250MHz instrument with TMS as internal standard. Mass-spectra were carried out using a Hewlett-Packard HP-engine instrument. Infra-Red spectra were performed on a Perkin-Elmer 1750



(adapted with permission from ref. 13, copyright 1994, American Chemical Society)

(a) Method A (see text), (b) H_2/Pd-C/Ac_2O/AcOH, (c) 5M HCl

instrument, and CHN analyses were carried out on a Leco CHNS/932 analyser. Thin layer chromatography (TLC) was carried out on polygram plastic backed silica gel plates. The benzonitriles (apart from 4i) were available commercially.

Formation of Amidoximes

Method A

(Z)-2-Methoxybenzamidoxime (5f)

2-Methoxybenzonitrile (2.99g, 22.46mmol), hydroxylamine hydrochloride (5.75g,

82.73mmol), and sodium carbonate (4.11g, 38.06mmol) were dissolved in water (60ml)-ethanol (7ml), the solution gently stirred for 5min., then heated under reflux for 3h under nitrogen. The solution was cooled, the solvents were removed *in vacuo*, and the residue was triturated with water (100ml). The product was collected by filtration and dried *in vacuo* to afford the title compound as a colourless solid: (2.24g, 60%). The water triturate was extracted with dichloromethane (4x80ml) and the organic extracts were dried (Na_2SO_4), and evaporated *in vacuo* to give a further batch of product: (1.22g, 33%).

NMR δ (DMSO) 9.45 (1Hs, -OH), 7.42 (2Hm, 2xArH), 7.12 (1Hd, ArH-3), 7.00 (1Hdd, ArH-5), 5.65 (2H brs $-NH_2$) and 3.85 (3Hs, -OMe).

TLC (cyclohexane-ether 1:1) $R_f = 0.06$.

(Z)-2-Ethylbenzamidoxime (5h)

2-Ethylbenzonitrile (2.46g, 18.75mmol), hydroxylamine hydrochloride (4.78g, 68.78mmol), and potassium carbonate (4.85g, 35.09mmol) were dissolved in water (25ml) - ethanol (40ml), the solution gently stirred for 10min., then heated under reflux for 41h. The solution was cooled, the solvents removed *in vacuo*, and the residue partitioned between water (15ml) and dichloromethane (2x20ml). The combined organic extracts were dried (Na_2SO_4), evaporated *in vacuo*, and the residue purified by flash chromatography over silica gel (Merck 9385, 75g), with cyclohexane-ether (9:1-1:1) and ether eluants to give initially the *title compound* as colourless crystals (1.24g, 40%) m.p. 103-105°, followed by 2-ethylbenzamide (0.93g, 33%), m.p. 155-157° (lit.[14] 153°). Data for (5h):

NMR δ (DMSO) 9.32 (1Hs, -OH), 7.15-7.4 (structured m, 4xArH), 5.75 (2H brs - NH_2), 2.73 (2Hq, $-CH_2$), and 1.15 (3Ht, -Me).

Found, C, 65.7; H, 7.4; N, 17.0. $C_9H_{12}N_2O$ requires C, 65.8; H, 7.4; N, 17.1%

(Z)-4-Dimethylaminobenzamidoxime (5d)

4-Dimethylaminobenzonitrile (2.74g, 18.74mmol), hydroxylamine hydrochloride (4.78g, 68.83mmol), and sodium carbonate (3.42g, 32.26mmol) were dissolved in water (80ml)-ethanol (20ml), the solution gently stirred for 10min., then heated under reflux for 17h. On cooling in ice, the title compound crystallised out. The precipitate was collected by filtration, washed with water (10ml), and dried at 60°/2mm. Hg to give the title compound as colourless crystals: (2.73g, 81%).

NMR δ (DMSO) 9.32 (1Hs, -OH), 7.53 and 6.71 (2x2H, AA'BB', 4xArH), 5.64 (2Hs, $-NH_2$), and 2.95 (6Hs, 2xMe).

Method B

(Z)-4-Trifluoromethylbenzamidoxime (5c)

Hydroxylamine hydrochloride (1.52g, 21.87mmol), and potassium *tert*-butoxide (2.46g, 21.93mmol) were added to a solution of 4-trifluoromethylbenzonitrile (10.04g, 58.68mmol) in methanol (10ml)-toluene (140ml) and the mixture stirred at 75-80° under nitrogen for a total of 17h, with further additions of hydroxylamine hydrochloride (1.52g, 21.87mmol), and potassium *tert*-butoxide (2.46g, 21.93mmol) after 2,4, and 6h[15]. The solvents were removed *in vacuo*, the residue treated with water (100ml), and extracted with dichloromethane

(4x150ml). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound as a colourless solid (11.85g, 98%).

NMR δ (DMSO) 10.0 (1Hs, -OH), 7.93 and 7.76 (2x2H, AA'BB', 4xArH), and 6.05 (2Hs, $-NH_2$).

TLC (cyclohexane-ether 1:1) $R_f = 0.28$.

(Z)-2,6-Dimethylbenzamidoxime (5i)

A solution of 2,6-Dimethylbenzonitrile[16] (2.50g, 19.1mmol) in methanol (10ml)-toluene (40ml) at 75° was repeatedly treated with hydroxylamine hydrochloride (654mg, 9.55mmol) and potassium *tert*-butoxide (1.07g, 9.55mmol) every 3-4h (20 portions each, total reaction time 96h). The solvents were removed *in vacuo*, and the residue was partitioned between water (100ml) and ethyl acetate (100ml). The residue was purified by flash chromatography over silica gel (Merck 9385) with cyclohexane-ether (5:1) eluant to recover unreacted starting nitrile (1.47g, 59% recovery). Elution with ether afforded the *title compound* as a colourless solid (0.53g, 17%).

NMR δ (DMSO) 9.2 (1Hs, -OH), 7.23 (1Hdd, H-4), 7.10 (2Hd, H-3&H-5), 5.8 (2Hbrs, $-NH_2$), and 2.32 (6Hs, 2xMe).

Further elution with ether gave 2,6-dimethylbenzamide as a colourless solid (0.627g, 22%).

NMR δ (DMSO) 7.8 and 7.55 (2H, 2xbrs, NH_2), 7.21 (1Hdd, H-4), 7.10 (2Hd, H-3&H-5), and 2.32 (6Hs, 2xMe).

Formation of Amidines

4-Trifluoromethylbenzamidine, acetate (6c)

(Z)-4-Trifluoromethylbenzamidoxime (5c) (1.5g, 7.348mmol) was dissolved in glacial acetic acid (40ml) and acetic anhydride (1.04ml, 11.02mmol) added. After 5min. TLC indicated complete acylation of the starting material. The solution was added to 10% palladium on carbon (0.24g) and hydrogenated at 23°/1atm. for 2h. The mixture was filtered through hyflo and the filter pad washed with glacial acetic acid (15ml). The combined filtrate and washings were evaporated *in vacuo* and the residue co-evaporated four times with n-heptane (to remove acetic acid) and dried *in vacuo* to give the *title compound* as a colourless solid (1.81g, 99%), m.p. 220° (sub.)

NMR δ (DMSO) 9.60 (4H brs, NH's), 8.20 (4H AA'BB', 4xArH), and 1.80 (3Hs, -OAc)

Found C, 48.5; H, 4.6; N, 10.8. $C_8H_7F_3N_2.CH_3COOH$ requires C, 48.4; H, 4.5; N, 11.3%

Synthesis of (6c) via isolation of (Z)-4-Trifluoromethylbenzamidoxime, acetate:

(Z)-4-Trifluoromethylbenzamidoxime (5c) (120mg, 0.59mmol) was dissolved in glacial acetic acid (5ml) and acetic anhydride (83μl, 0.88mmol) added. After 5min., the solvent was removed *in vacuo* to afford the product (0.14g, 97%).

NMR δ (DMSO) 7.85-8.00 (4H AA'BB', 4xArH), 7.10 (2H brs $-NH_2$), and 2.20 (3Hs, -OAc).

IR ν_{max} 3440, 1720, and 1630 cm^{-1}.

mass-spec found: 247 (MH^+)

A solution of the preceding intermediate (40mg, 0.16mmol) was hydrogenated over 10% palladium on carbon (10mg) in glacial acetic acid (10ml) for 1h. Work-up as above gave (6c) in quantitative yield.

2-Ethylbenzamidine, trifluoroacetate (6h)

(Z)-2-Ethylbenzamidoxime (5h) (568mg, 3.459mmol) was hydrogenated as described for (6c) over 10% palladium on carbon (600mg) in acetic acid (20ml)-acetic anhydride (1ml) for 4h. The crude product was purified by preparative HPLC (Dynamax 60A C18 8μM 25cm. x 4.6mm. i.d. column, eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water, and (ii) acetonitrile, gradient profile 90:10 (i):(ii) to 50:50 (i):(ii) over 15min., flow rate 45ml/min.) to afford after R_T11-12min. the *title compound* as colourless crystals (313mg, 35%), m.p.133-135°.

NMR δ (DMSO) 9.55 (2H brs $-NH_2$), 9.35 (2H brs $-NH_2$), 7.37-7.63 (structured m, 4xArH), 2.70 (2Hq, $-CH_2$), and 1.20 (3Ht, -Me).

Found C, 50.1; H, 5.1; N, 10.55. $C_9H_{12}N_2.CF_3CO_2H$ requires C, 50.4; H, 5.0; N, 10.7%

2-Methoxybenzamidine, acetate (6f)

(Z)-2-Methoxybenzamidoxime (5f) (1.50g, 9.03mmol) was hydrogenated over 10% palladium on carbon (290mg) in acetic acid (45ml)-acetic anhydride (1.28ml, 13.5mmol) as described for (6c) for 4h. Work-up as for (6c) gave crude product which was recrystallised from ethanol to afford the *title compound* as a colourless

crystalline solid: (1.86g, 94%), m.p. 192-195°.

NMR δ (DMSO) ca.10.5 (4Hvbr, 4 NH's), 7.60 (1Ht, Ar H-4), 7.50 (1Hd, Ar H-6), 7.24 (1Hd, Ar H-3), 7.12 (1Ht, Ar H-5), 3.88 (3Hs, -OMe), and 1.72 (3Hs, -OAc).

Found C, 56.8; H, 6.8; N, 13.0. $C_9H_{12}N_2.CH_3CO_2H$ requires C, 57.1; H, 6.7; N, 13.3%

4-Dimethylaminobenzamidine, acetate (6d)

(Z)-4-Dimethylaminobenzamidoxime (5d) (100mg, 0.56mmol) was hydrogenated over 10% palladium on carbon (0.29g) in acetic acid (10ml)-acetic anhydride (0.079ml, 0.84mmol) as described for (6c) for 4h. Work-up as for (6c) gave crude product which was recrystallised from ethanol to afford the *title compound* as a colourless crystalline solid: (119mg, 90%), m.p. 235° (dec.).

NMR δ (DMSO) ca.10.0 (4Hvbr, 4 NH's), 7.74 and 6.82 (2x2H, AA'BB', 4xArH), 3.06 (6Hs, 2xMe), and 1.72 (3Hs, -OAc).

Found C, 59.1; H, 7.6; N, 18.2. $C_9H_{13}N_3.CH_3CO_2H$ requires C, 59.2; H, 7.7; N, 18.5%

2,6-Dimethylbenzamidine, acetate (6i)

(Z)-2,6-Dimethylbenzamidoxime (5i) (120mg, 0.73mmol) was hydrogenated over 10% palladium on carbon (0.29g) in acetic acid (10ml)-acetic anhydride (0.103ml) as described for (6c) for 4h. Work-up as for (6c) gave crude product which was recrystallised from isopropanol-isopropyl acetate (1:9) to afford the *title*

compound as a colourless crystalline solid: (85mg, 56%), m.p. 241° (dec.).

NMR δ ($CDCl_3$) 7.35 (1Ht, H-4), 7.20 (2Hd, H-3&H-5), 3.4 (4Hvbr, 4xNH's), 2.32 (6Hs, 2xMe), and 1.72 (3Hs, -OAc).

Found C, 62.0; H, 7.7; N, 13.1. $C_9H_{12}N_2.CH_3CO_2H.0.25H_2O$ requires C, 62.1; H, 7.8; N, 13.2%

Acknowledgements

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