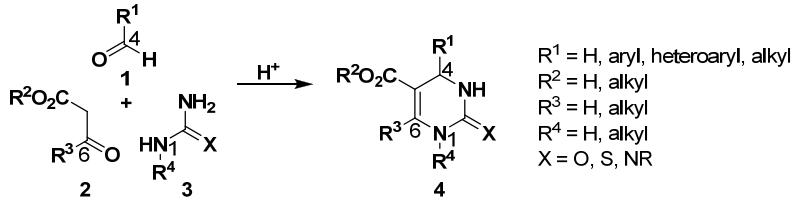
THE BIGINELLI REACTION: DEVELOPMENT AND APPLICATIONS

Reported by Eric Woerly November 24, 2008

INTRODUCTION

The combination of an aldehyde **1**, β-keto ester **2**, and urea **3** under acid catalysis to give a dihydropyrimidine **4** (Scheme 1) was first reported by Pietro Biginelli in 1893.[1] Referred to as the Biginelli reaction, this one-pot condensation reaction generates compounds with pharmacological activity, including calcium channel modulation, mitotic kinesin Eg5 inhibition, and antiviral and antibacterial activity.[2] Although the original reaction conditions suffered from poor yields and a limited substrate scope, the recent discovery of dihydropyrimidine biological activity has led to a renewed exploration of the reaction conditions, revealing a variety of compatible solvents, acid catalysts, and an expanded substrate scope. Most recently, the development of asymmetric methods has allowed the generation of enantioenriched dihydropyrimidines. Further, the reaction manifold has been extended from its solution-phase origins to include microwave assisted, solid-phase, and fluorous-phase reactions. The gradual development of the Biginelli reaction over the past 115 years, coupled with the biological study of the resulting compounds, has provided an entryway into the relatively unexplored dihydropyrimidine compounds.

Scheme 1. General Biginelli Reaction.



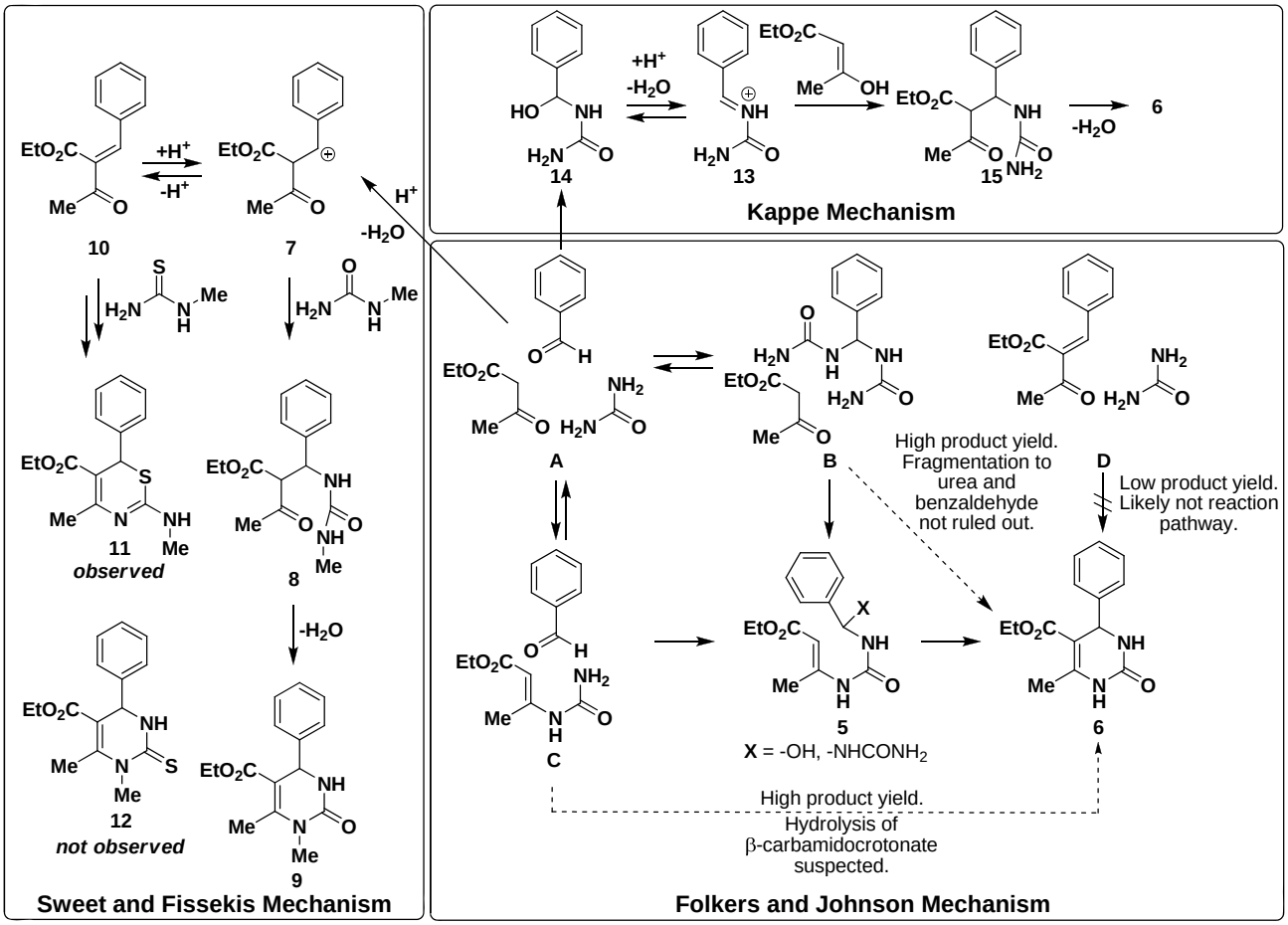
MECHANISTIC STUDIES

The first mechanistic studies of the Biginelli reaction were conducted by Folkers and Johnson forty years after Biginelli's initial report.[3] Four possible combinations of the three reaction components were examined for the generation of dihydropyrimidine **6** (Figure 1): (**A**) the termolecular reaction between benzaldehyde, ethyl acetoacetate, and urea, (**B**) the combination of ethyl acetoacetate and benzal-bisurea, (**C**) the reaction of benzaldehyde and ethyl β-carbamidocrotonate, and (**D**) the reaction of ethyl α-benzalacetoacetate and urea. Folkers and Johnson based their mechanistic conclusions on reaction yields and visual observation. They proposed that the simultaneous combination of the three reaction components in **A** was improbable. **D** was ruled out on the basis of the low reaction yields (2%).

In contrast, **B** and **C** gave high yields of **6** (80%). The authors note that **B** may undergo fragmentation of the benzal-bisurea, regenerating the three reaction components, which may then form the product by another pathway. Further, the authors posit that the β-carbamidocrotonate in **C** hydrolyzes to the original three reaction components. Therefore, they conclude that **6** is likely formed from cyclization of **5**, which can be generated from either **B** or **C**.

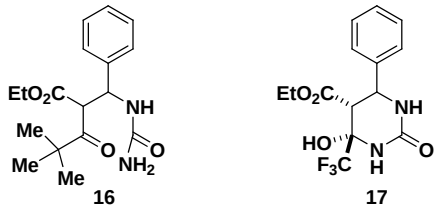
A second mechanistic proposal was suggested by Sweet and Fissekis forty years after Folkers' pioneering work.[4] This proposal involves an aldol condensation between benzaldeyde and ethyl acetoacetate to form a stabilized carbenium ion **7**. Trapping with *N*-methylurea gives **8**, which can cyclize to form **9** (Figure 1). The observation that independently prepared **10** reacts with *N*-methylurea under acidic conditions to generate **9** provides evidence in support of this mechanism. Evidence against this mechanism is provided by Kappe,[5] who found that reaction of **10** with *N*-methylthiourea produces thiazine **11** and not dihydropyrimine **12**, which is the observed product under standard Biginelli conditions (catalytic amounts of HCl, refluxing ethanol).

Figure 1. Mechanistic Proposals for the Biginelli Reaction.



Kappe further explored the mechanism of the Biginelli reaction using NMR spectroscopy and trapping experiments.[5] He proposes the formation of *N*-acyliminium **13** from benzaldehyde and urea via an unobservable (^{1}H NMR) hemiaminal **14** (Figure 1). Interception of **13** with the enol tautomer of ethyl acetoacetate gives **15**, the precursor to dihydropyrimidine **6**. Kappe suggests that the first step, formation of **14**, is rate limiting, thus preventing the observation of intermediates **13** and **15** by NMR. However, evidence to support this mechanism was provided by two trapped species, **16**[6] and **17**[7] (Chart 1). Use of a sterically bulky β-keto ester allows isolation of ureide **16**, which has been independently converted to the dihydropyrimidine product. In a similar fashion, the electron-deficient nature of the trifluoromethyl group destabilizes the carbocation intermediate necessary for dihydropyrimidine formation, allowing the isolation of **17**, whose relative configuration has been confirmed by single crystal X-ray analysis. This intermediate is converted to the corresponding dihydropyrimidine via *p*-toluenesulfonic acid mediated dehydration. Kappe's proposal is currently the accepted mechanism for the Biginelli reaction.

Chart 1. Observed Intermediates to Support the Kappe Mechanism.

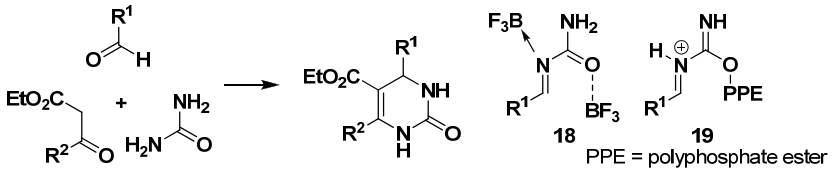


REACTION ADVANCEMENTS

Improved Reaction Conditions

With a deeper mechanistic understanding of the Biginelli reaction, several advancements were made to address the poor and variable yields (20-70%) and limited substrate scope often associated with this reaction. Conditions that support the formation and reaction of *N*-acyliminium ion **13** provide one route to improving the Biginelli reaction. Hu and coworkers report consistently high yields when the reaction proceeds in the presence of BF_3•OEt_2 and CuCl in a mixture of acetic acid and THF (Figure 2).[6] A Lewis acid activated acyl imine **18** is proposed to be an intermediate in this reaction. Likewise, Kappe and Falsone report that polyphosphate ester in THF provides increased reaction yields (Figure 2).[8] An activated enol phosphate **19** is the proposed intermediate for this reaction. Overall, these two methods are comparable, both providing improved yields over the original Biginelli conditions.

Figure 2. Modifications to Original Biginelli Reaction Conditions.

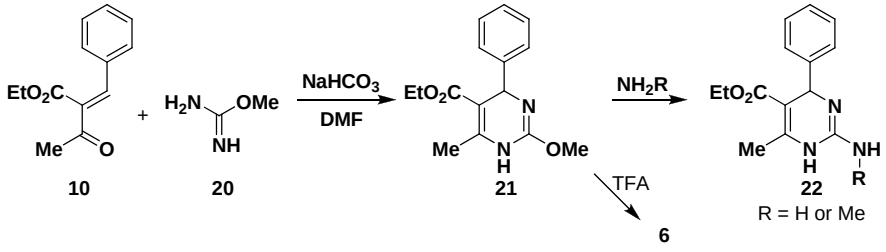


Entry	R^1	R^2	Yield (%) Lewis acid[a]	PPE[b]	Original[c]
1	C_6H_5	Me	94	94	71
2	4-(NO_2)-C_6H_4	Me	91	77	54
3	3,4-$(F)_2$-C_6H_3	Me	81	84	66
4	4-(OMe)-C_6H_4	Et	79	NA	40

[a] 1.3 eq BF_3•OEt_2, 10 mol % CuCl, 10 mol % AcOH in THF, reflux, 18 hr
[b] PPE, THF, reflux, 15 hr
[c] catalytic H_2SO_4, EtOH, reflux, 18 hr
NA = not attempted

Atwal and coworkers introduced a modification to the original Biginelli reaction that affords high product yields and the preparation of previously inaccessible dihydropyrimidines.[9] The Atwal modification (Scheme 2) involves reaction of preformed unsaturated keto esters (i.e. **10**) with a protected urea **20** to give a 2-substituted dihydropyrimidine **21**. Deprotection with trifluoroacetic acid (TFA) affords the dihydropyrimidine product **6**, while deprotection with ammonia or a primary amine gives the previously inaccessible amino pyrimidines **22**. While this modification expands the substrate scope of the Biginelli reaction, the presynthesis of **10** and added deprotection step depart from the convenience of the one-pot reaction conditions.

Scheme 2. Atwal Modification.

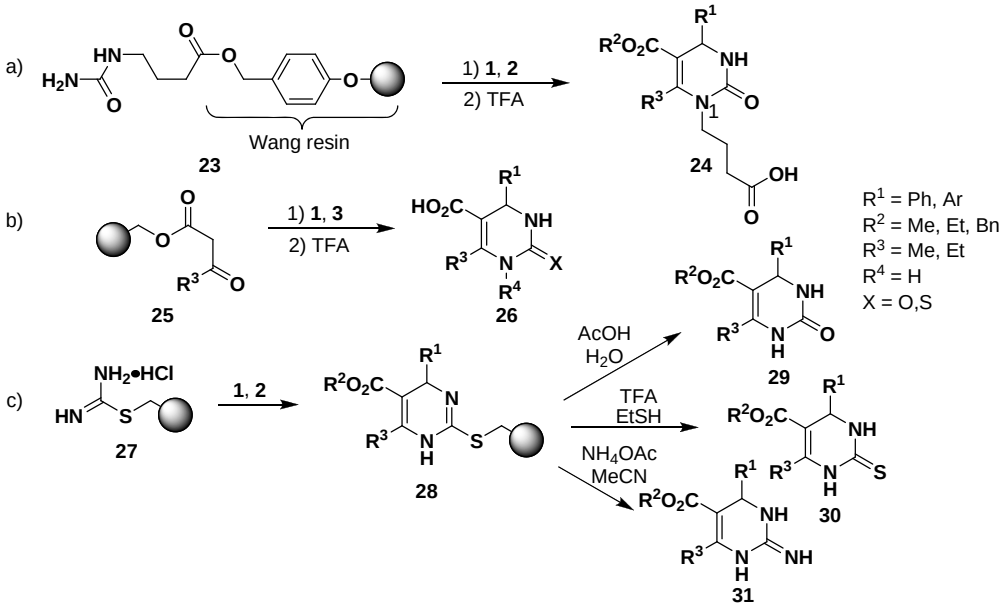


Library Synthesis

The therapeutic potential of dihydropyrimidines is highlighted by their diverse biological activity.[2] To explore this activity, libraries of dihydropyrimidines have been generated using microwave, solid-phase, and fluorous-phase technologies.[10] These libraries have the potential to provide a number of novel compounds for biological testing. Kappe and Stadler report the automated microwave-assisted generation of dihydropyrimidines utilizing $Yb(OTf)_3$.[11] They were able to prepare a forty-eight compound library within a twelve hour time span including a variety of aryl, heteroaryl, and alkyl aldehydes, *N*-substituted ureas, and carbon acids including β-keto esters and β-keto amides.

Solid-phase synthesis provides another method for accessing a diverse collection of dihydropyrimidines. The use of a large excess of reagents in solid-phase synthesis provides high product yields. Also, non-resin bound byproducts are easily washed away. This approach has allowed dihydropyrimidines to be synthesized in high yield and purity, eliminating the need for further purification. A variety of polymer-supported building blocks have been explored, including attachment of the linker to the urea and β-keto ester components. Wipf and Cunningham provided the first example of a solid-phase Biginelli reaction using a resin bound urea **23** (Figure 3a).[12] Formation of the dihydropyrimidine and cleavage from the resin with TFA produces the N(1) substituted product **24**.

Figure 3. Solid-phase Approaches to the Biginelli Reaction.

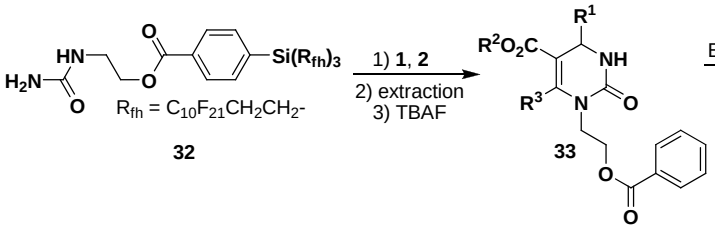


Kappe and coworkers further explored the scope of the solid-phase application by using a β-keto ester immobilized reagent **25** (Figure 3b).[13] This strategy yields 5-carboxylic acid dihydropyrimidines **26** upon cleavage from the resin, as well as N(1) unsubstituted compounds. In another application, Kappe utilized a polymer bound thiuronium salt **27**[14] (Figure 3c). After completion of the Biginelli reaction, the resin bound dihydropyrimidines **28** could be cleaved under different conditions to yield dihydropyrimidines **29**, thiopyrimidines **30**, or 2-iminodihydropyrimidines **31**. This method provides an alternative to Atwal's synthesis of aminopyrimidines **22**. These solid-phase methods allow for the synthesis of diverse dihydropyrimidines in high yield and purity, and has the potential for automation.

Curran and coworkers have adapted fluorous-phase chemistry toward the synthesis of dihydropyrimidines.[15] Fluorous-phase strategies are based on the ability for highly fluorinated compounds to partition into a fluorinated solvent. The reaction mixture can be purified by a liquid-liquid extraction if the byproducts are not soluble in the fluorinated solvent. Curran has prepared

fluorinated ureas **32**, which underwent the Biginelli reaction and were cleanly extracted into fluorinated hexanes (Figure 4). Desilylation affords N(1) substituted dihydropyrimidines **33**. The yields for the fluorous-phase reaction are comparable to reactions preformed under standard Biginelli reaction conditions (Figure 4); however, the fluorous methodology requires the synthesis of fluorinated ureas and use of expensive fluorinated solvents.

Figure 4. Fluorous Biginelli Reaction.



Entry	R^1	R^2	R^3	Yield (%) Fluorous	Yield (%) Original[a]
1	C_6H_5	Et	Me	71	74
2	4-(OMe)-C_6H_4	Et	Me	69	78
3	2-naphthyl	Me	CH_2Bn	mixture	33

[a] With desilylated version of **32**

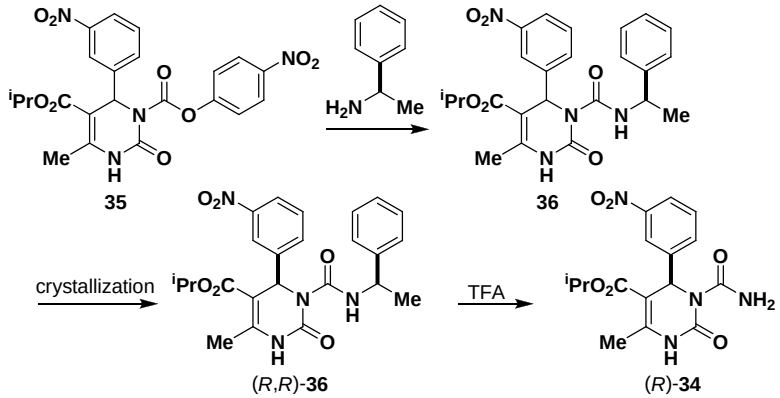
ENANTIOENRICHED DIHYDROPYRIMIDINES

Dihydropyrimidines are inherently chiral molecules. Interestingly, the lone stereogenic center greatly influences the biological activity of the dihydropyrimidine. For example, the *R* enantiomer of dihydropyrimidine SQ 32926 **34** (Scheme 3), an antihypertensive agent, is >400-fold more potent than the *S* enantiomer.[16] Consequently, obtaining enantioenriched material is essential to reliably assess the biological activity of the dihydropyrimidine. Over time, several methods have been developed to give enantioenriched material, including resolution and asymmetric syntheses.

Resolution

Until recently, the only method for obtaining enantioenriched dihydropyrimidines was chemical resolution. Atwal and coworkers resolved racemic **35** through the generation of diastereomeric N(3) substituted dihydropyrimidines **36**[17] (Scheme 3). Separation by fractional crystallization, followed by cleavage of the chiral amine gave (*R*)-**34** in 99:1 e.r. To date, no general method has been developed for the chemical resolution of dihydropyrimidines.

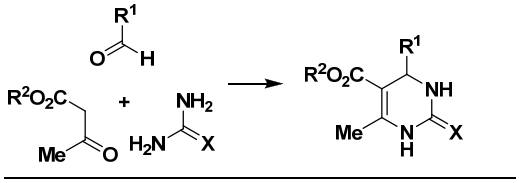
Scheme 3. Synthesis of SQ 32926 34.



Asymmetric Biginelli Reaction

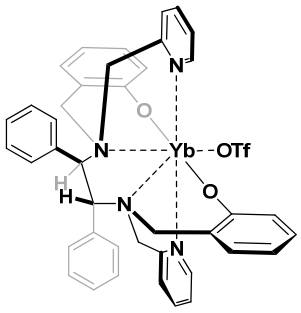
Several methods have been developed for the asymmetric synthesis of enantioenriched dihydropyrimidines. The first of these methods to give synthetically useful enantiomeric ratios was reported by Zhu and coworkers in 2005, over one-hundred years after discovery of the Biginelli reaction.[18] Zhu found that the use of chiral ytterbium catalyst **37** allowed for dihydropyrimidines to be synthesized in high yield and enantioselectivity (Figure 5). The ytterbium catalyst is recoverable and can be recycled several times without diminishing the product e.r.

Figure 5. Asymmetric Syntheses of Dihydropyrimidines.



Entry	R^1	R^2	X	e.r. Yb catalyst[a]	e.r. BA catalyst[b]
1	C_6H_5	Et	O	95:5 (*R*)	NA
2	3-NO_2-C_6H_4	^{i}Pr	O	99.5:0.5 (*R*)	90:10
3	2-Cl-C_6H_4	Et	S	99:1 (*R*)	96:4

[a] 10 mol % Yb catalyst, THF, rt
[b] 10 mol % Bronsted acid (BA) catalyst, CH_2Cl_2, rt
NA = not attempted



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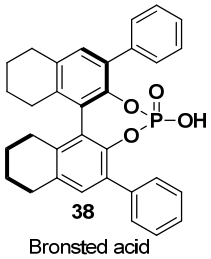
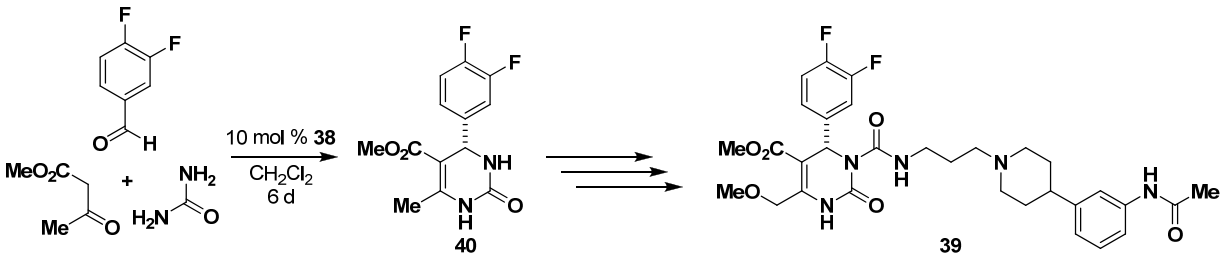


38
Bronsted acid

A second protocol for the synthesis of enantioenriched dihydropyrimidines was introduced by Gong and coworkers.[19] This organocatalytic reaction utilizes a chiral phosphoric acid **38** to generate dihydropyrimidines with moderate enantioselectivities (Figure 5). This method has been employed by Goss and Schaus in the synthesis of MCH1-R inhibitor SNAP-7941 **39** (Scheme 4), which has been shown to induce weight loss in guinea pigs and rats.[20] Using **38**, Goss and Schaus were able to prepare the dihydropyrimidine **40**, the precursor to **39**, in 96% yield and 94.5:5.5 e.r.

Scheme 4. Synthesis of SNAP-7941 39.



40 39

CONCLUSION

The development of the Biginelli reaction has advanced considerably since its discovery 115 years ago. Mechanistic insights have provided rational modifications to the experiment protocols, allowing dihydropyrimidines to be synthesized in high yield. The interesting and diverse biological activity of dihydropyrimidines has been explored through the generation of libraries of compounds via

microwave, solid-phase, and fluorous-phase technologies. Most recently, asymmetric methods have been developed to give enantioenriched dihydropyrimidines. The frontier of the Biginelli reaction will continue to be developed as new asymmetric methods are reported and as the biological importance of this class of compounds is explored in greater detail.

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