CONSTRUCTION OF SUBSTITUTED 2-PYRAZOLINES

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Abstract. *The 2-pyrazoline core is a very interesting five-membered heterocycle composed of three carbon atoms and two nitrogen atoms in adjacent positions. Diversely substituted 2-pyrazolines provide highly versatile applications such as biological active agent developments, fluorescence probes as fluorophores, and chemo-sensors. Based on literature studies, versatile synthetic approaches have been employed for the preparation of differently substituted 2-pyrazolines. In this context, the well-studied synthetic strategies for substituted 2-pyrazolines were summarized.*

Contents

1. Introduction

Pyrazolines, as dihydro derivatives of pyrazoles, are an important class of heterocyclic compounds containing one double bond and two nitrogens at adjacent positions in the five-membered ring. On the basis of the position of the double bond, three types of pyrazolines are possible: 1-pyrazoline, 2-pyrazoline, and 3-pyrazoline (Figure 1a), of which 2-pyrazoline is the most studied due to its higher stability and shows wide applications.

Being electron-rich nitrogen heterocycles, substituted pyrazoline derivatives play an important role in diverse biological activities. They are constantly incorporated into the structures of numerous important medical and biochemical agents that exhibit diverse biological activities including anti-bacterial, anti-fungal, anti-viral, anti-parasitic, anti-tubercular, anti-inflammatory, anti-cancer, anesthetic, analgesic, and insecticidal properties (Figure 1b).[1-3] For example, 5-(3-indolyl)-1-(4-sulfamylphenyl)-3-trifluoromethyl pyrazoline **1** exhibits inhibitory activity against cyclooxygenase-2 (COX-2) and lipoxygenase (LOX).[4] The pyrazolyl pyrazoline **2** is a dual anti-inflammatory–anti-microbial agent.[5] Pyrazolines **3**-**6**, with different substituents, exhibit various biological activities including tyrosine kinase inhibitory, antitubercular, urease and glucosidase inhibitory, and anti-malarial activities. Meanwhile, 1,3-diaryl-2-pyrazolines, with their rigid but only partly unsaturated central pyrazoline ring, are well-known fluorescent compounds with tunable photophysical properties, which can be tuned by altering the substitution pattern in the N-1, C-3, or even C-5 phenyl rings. These compounds are widely used in analytical chemistry or chemical biology as fluorescence probes or chemo-sensors.[6-8] For example, *in vivo*-formed pyrazolines **7** and **8** can serve as fluorescence probes for organelles or tubulin imaging.[9,10] Additionally, fluorescent aryl-pyrazolines show wide applications in electroluminescence, organic electronics, and material science.[11-13]

The first synthesis of the pyrazoline ring was described by Knorr and Blank in 1885 by the reduction of 1,3-diphenyl-5-methylpyrazole with sodium and ethanol. Pioneered by Knöevenagel and Fisher, substituted 2-pyrazoline rings are directly constructed by α,β-unsaturated aldehydes or ketones with hydrazines, which is mostly used and accepted as a simple method for preparation of 2-pyrazolines until now.[14] To our delight, some other strategies for the construction of substituted 2-pyrazolines are explored as well with the development of modern synthetic chemistry. In this account, we summarized the most

representative methods for the synthesis of 2-pyrazolines, and selective examples are shown for each synthetic method.

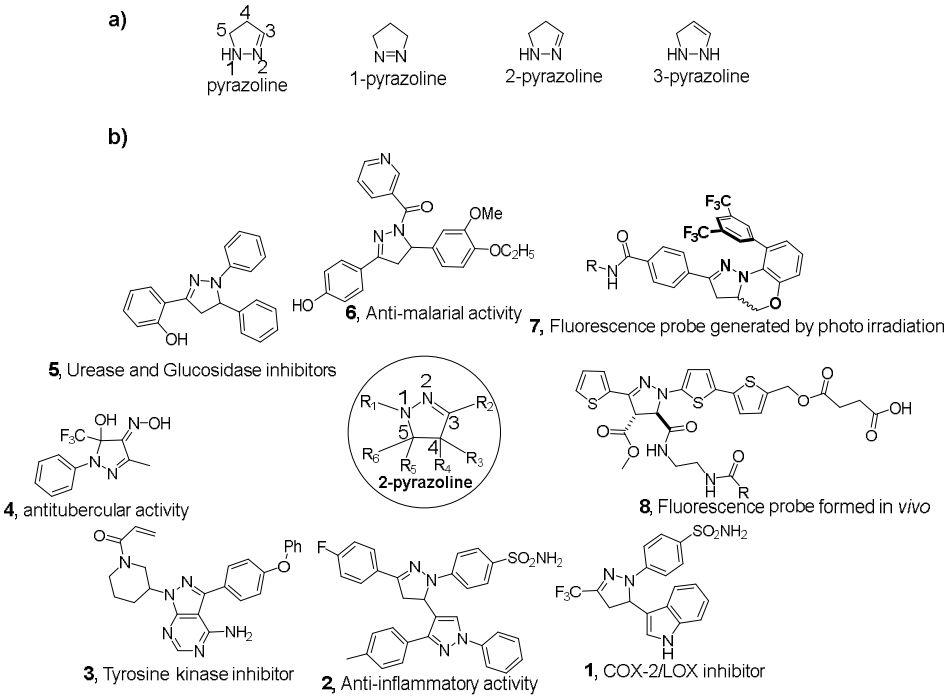


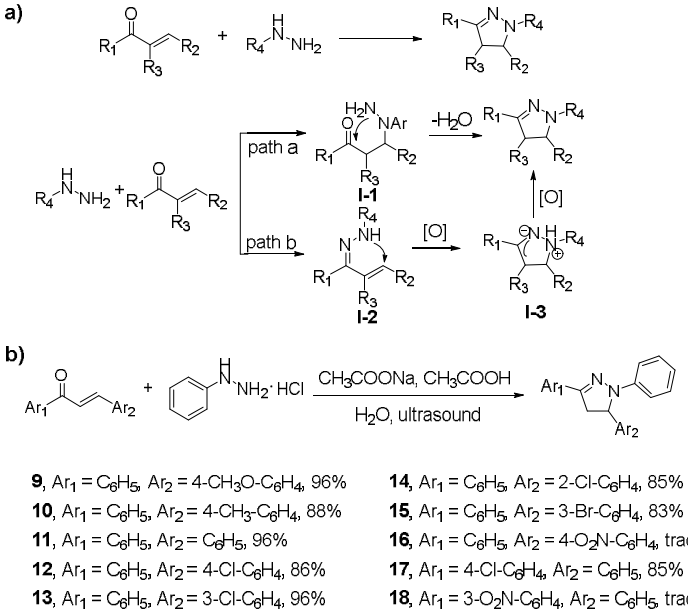
Figure 1. a) Chemical structure of pyrazoline scaffold. b) Different pyrazoline-containing structures with related biological activities and fluorescence applications.

2. Reactions between hydrazines and α,β-unsaturated enones

Among the synthetic approaches to 2-pyrazolines, the reaction between hydrazine and α,β-unsaturated enones is the most commonly used. As shown in Scheme 1a, two possible mechanisms have been reported for the reaction of different α,β-enones with various hydrazine derivatives. The first mechanism involves the formation of aza-Michael intermediate **I-1** through 1,4-addition, followed by cyclization with elimination of water to give 2-pyrazolines. In the other mechanism, hydrazine **I-2** is formed, which undergoes a subsequent oxidative cyclization to give the corresponding 2-pyrazolines. The reactions are commonly catalyzed by an acid, such as acetic acid. As shown in Scheme 1b, Li and co-workers reported a practical and convenient procedure for the synthesis of 2-pyrazolines in sodium acetate-acetic acid aqueous solution using various α,β-unsaturated ketones, and phenylhydrazine.[15] Under ultrasound irradiation, different 1,3,5-triaryl-2-pyrazolines **9**-**17** were obtained at room temperature with high yields (83-96% yield except for NO_2- substituted analogs **16** and **18**).

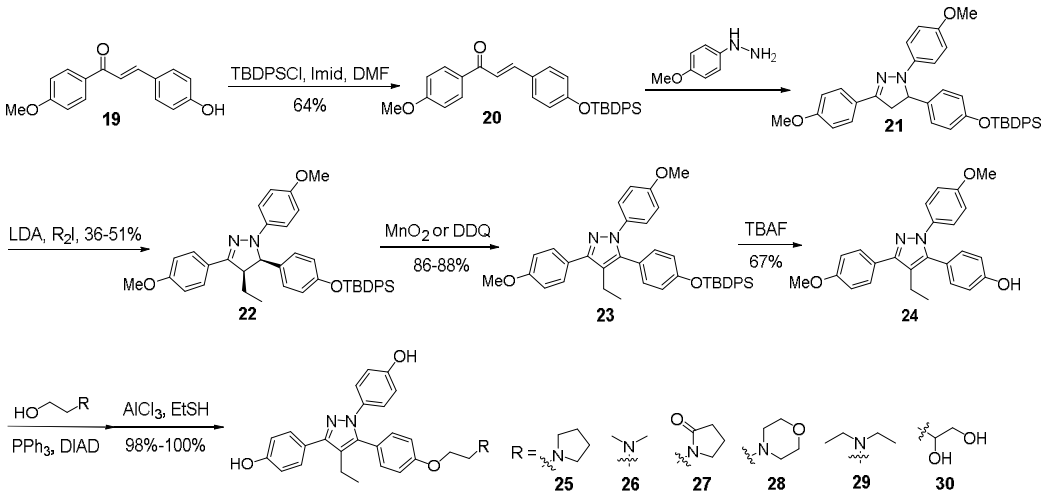
This synthetic approach to 2-pyrazolines from hydrazine and α,β-unsaturated enone is widely used for the construction of bioactive compounds. For example, Katzenellenbogen and Huang synthesized a series of 1,3,5-triaryl-4-alkylpyrazoles, in which the 2-pyrazolines rings were constructed by the reactions of hydrazines and α,β-unsaturated enones (Scheme 2).[16] These pyrazoles with a basic or polar side chain, as the ligands for the estrogen receptor (ER), were found to have selective estrogen receptor modifiers (SERMs) activity. The basic synthetic routes are shown in Scheme 2. α,β-Unsaturated ketone **19** was prepared by aldol condensation of 4-methoxyacetophenone and 4-hydroxybenzaldehyde. Enone **19**, protected as its silyl ether **20**, followed the typical 2-pyrazoline formation pathway by reacting with 4-methoxyl henylhydrazine in DMF to give pyrazoline **21** in 74% yield. Then, through alkylation with ethyl iodide, pyrazoline **22** was

obtained in 36% yield, which was oxidized with either MnO_2 or DDQ to afford the desired pyrazole **23**. The silyl protecting group was replaced with several side chains, followed by demethylation to afford the desired ligands **25**-**30**.



9, $Ar_1 = C_6H_5$, $Ar_2 = 4\text{-}CH_3O\text{-}C_6H_4$, 96%
10, $Ar_1 = C_6H_5$, $Ar_2 = 4\text{-}CH_3\text{-}C_6H_4$, 88%
11, $Ar_1 = C_6H_5$, $Ar_2 = C_6H_5$, 96%
12, $Ar_1 = C_6H_5$, $Ar_2 = 4\text{-}Cl\text{-}C_6H_4$, 86%
13, $Ar_1 = C_6H_5$, $Ar_2 = 3\text{-}Cl\text{-}C_6H_4$, 96%
14, $Ar_1 = C_6H_5$, $Ar_2 = 2\text{-}Cl\text{-}C_6H_4$, 85%
15, $Ar_1 = C_6H_5$, $Ar_2 = 3\text{-}Br\text{-}C_6H_4$, 83%
16, $Ar_1 = C_6H_5$, $Ar_2 = 4\text{-}O_2N\text{-}C_6H_4$, trace
17, $Ar_1 = 4\text{-}Cl\text{-}C_6H_4$, $Ar_2 = C_6H_5$, 85%
18, $Ar_1 = 3\text{-}O_2N\text{-}C_6H_4$, $Ar_2 = C_6H_5$, trace

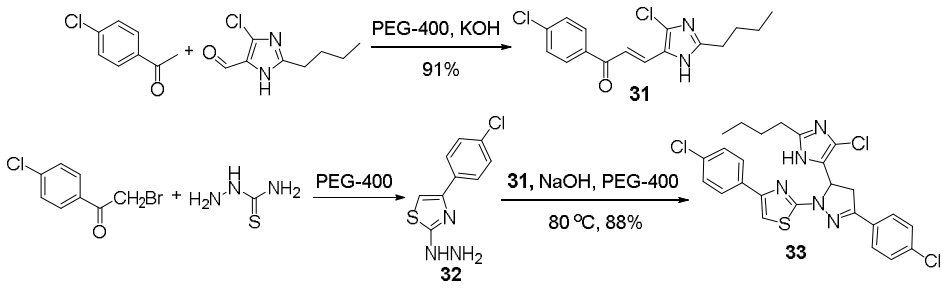
Scheme 1. a) Main mechanisms for the formation of 2-pyrazolines. b) Synthesis of 1,3,5-triaryl-2-pyrazolines in the NaAc-HAc aqueous under ultrasound.



Scheme 2. Regioselective synthesis of pyrazole derivatives **25**-**30**.

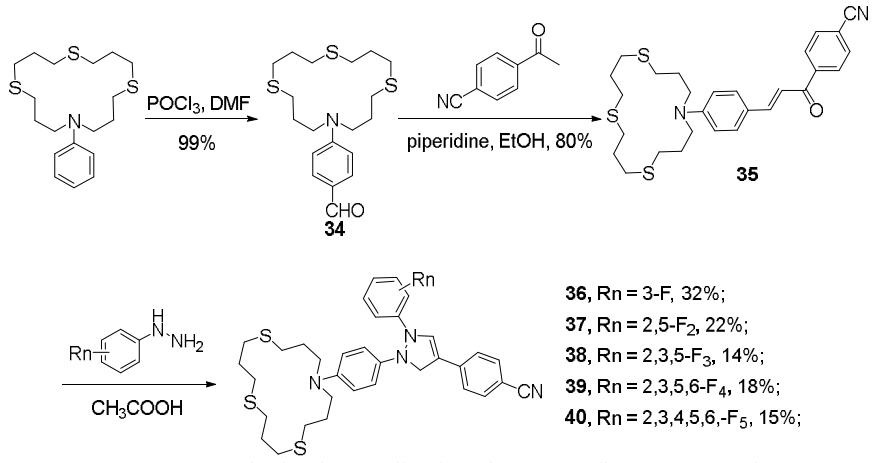
This pyrazoline formation can also be catalyzed under basic conditions. Dawane and co-workers reported a series of 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1*H*-imidazol-5yl)-2-pyrazoline derivatives, most of which show potent antibacterial and antifungal activity.[17] The key

pyrazoline-ring construction was performed under basic condition. The synthesis of one representative compound **33** is shown in Scheme 3, α,β-unsaturated carbonyl compound **31** was prepared by Claisen-Schmidt condensation *via* the reaction of substituted 4-chloroacetophenone and 2-butyl-4-chloro-5-formyl-imidazole in PEG-400 at 40 ºC in 91% yield. On the other hand, 4-(4'-chlorophenyl)-2-hydrazinothiazole **32** was prepared by the treatment of 4-chloro-α-bromoketone with thiosemicarbazide in PEG-400 (10 mL) at 40 ºC. Finally, hydrazine **32** reacted with α,β-unsaturated ketone **31** in the presence of NaOH in PEG-400 to give 2-pyrazoline **33** in 88% yield.



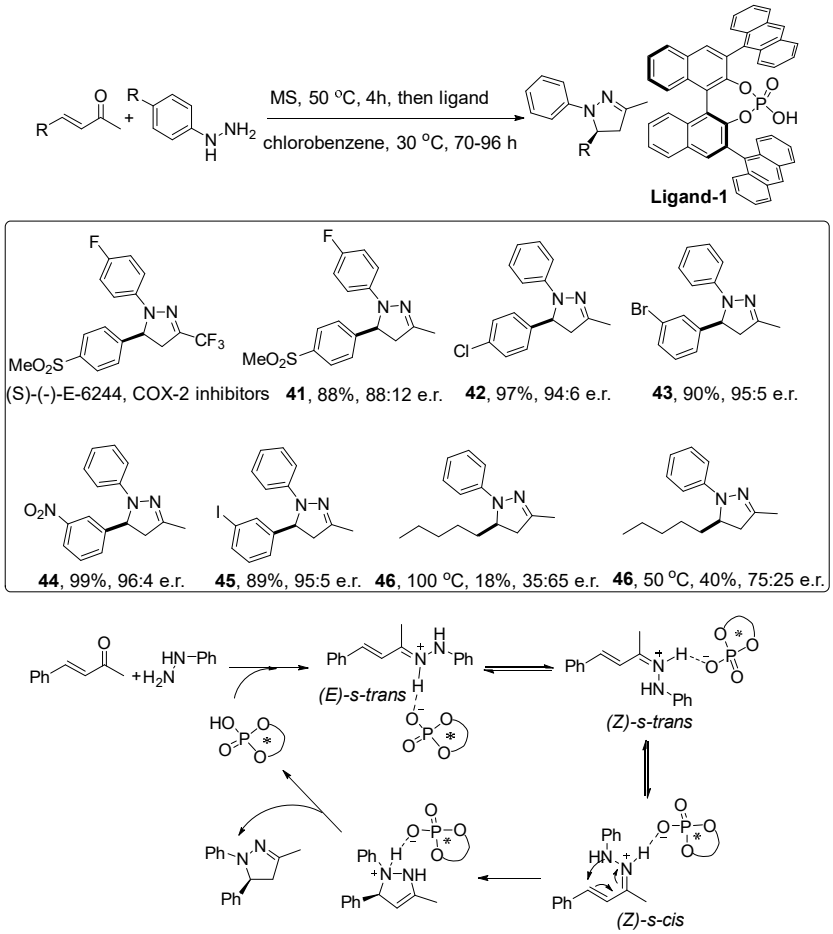
Scheme 3. Synthesis of 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1*H*-imidazol-5yl)-2-pyrazoline **33**.

Using this synthetic method, some 1,3-diaryl-2-pyrazoline-based fluorescence probes or sensors were constructed. For example, Fahrni and co-workers developed pyrazoline-based Cu(I) fluorescence sensors (Scheme 4).[18] Installation of a formyl group into the crown ether ligand afforded aldehyde **34**. The α,β-unsaturated carbonyl compound **35** was obtained by reacting aldehyde **34** with 4-acetylbenzonitrile. A mixture of chalcone **35** and the corresponding fluoro-substituted phenylhydrazines in acetic acid afforded the corresponding 2-pyrazoline fluorophores **36**-**40**. In the absence of the analyte, the fluorescence emission was strongly quenched due to a fast intramolecular photoinduced electron transfer (PET) process from the electron-rich aniline donor (D) to the excited fluorophore (A*) acting as the electron acceptor. The formed radical ion pair (D^+–A^-) undergoes nonradiative charge recombination back to the initial ground state. Binding of the copper cation to the ligand results in a less favorable donor potential, which slows down the kinetics for PET quenching and thus increases the fluorescence intensity to have a fluorescence "turn-on" signal.



Scheme 4. Synthesis of pyrazoline-based copper(I) fluorescence probe.

Enantioselective synthesis of 2-pyrazolines starting from α,β-unsaturated ketones and hydrazine was investigated by the List group.[19] Initially, the electrocyclization of the benzylideneacetone-derived phenylhydrazone (Scheme 1a, path b) in the presence of chiral phosphoric acid **ligand-1** gave 2-pyrazoline **41** in 88% yield with an enantiomeric ratio of 88:12 (Scheme 5). Compound **41** as well as its 3-trifluoromethyl analog (*S*)-**E-6244** are patented COX-2 inhibitors. Then direct cyclizations between enones and phenylhydrazines were performed under the catalysis of acid **ligand-1**. The enantioselective synthesis of 2-pyrazolines **42**-**46** was achieved in high yields and 75:25-96:4 e.r. values (Scheme 5). The catalytic mechanism is shown in Scheme 5. Phenylhydrazine reacted with the α,β-unsaturated ketone to afford a linear (*E*)-hydrazone. Then, through sequential C=N double-bond isomerization and C–C single-bond rotation, the reactive conformer (*Z*)-hydrazone was formed with the chiral acid binding through hydrogen bonds. The (*Z*)-hydrazone transformed into 3-pyrazoline through a 6π-electrocyclization. Subsequent isomerization and deprotonation then gave the thermodynamically more stable 2-pyrazoline.

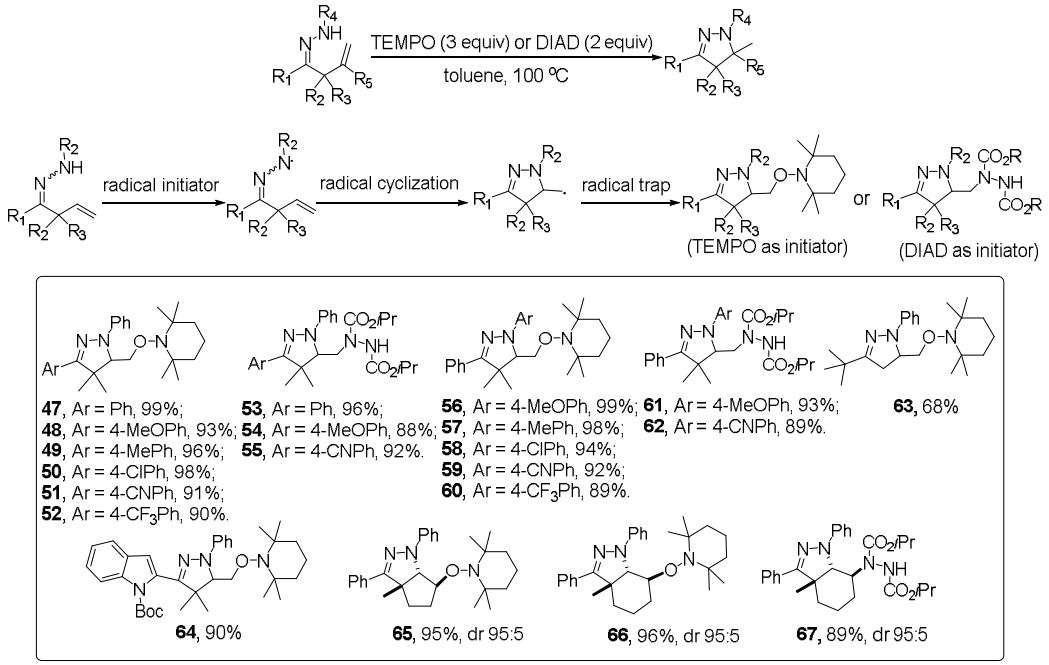


Scheme 5. Enantioselective synthesis of 2-pyrazolines starting from α,β-unsaturated ketones and phenylhydrazine.

3. Intramolecular amination of β,γ-unsaturated hydrazones

Among the great effort toward the efficient synthesis of substituted 2-pyrazolines, the direct cyclization/amination of β,γ-unsaturated hydrazones is an attractive method due to the easy availability of

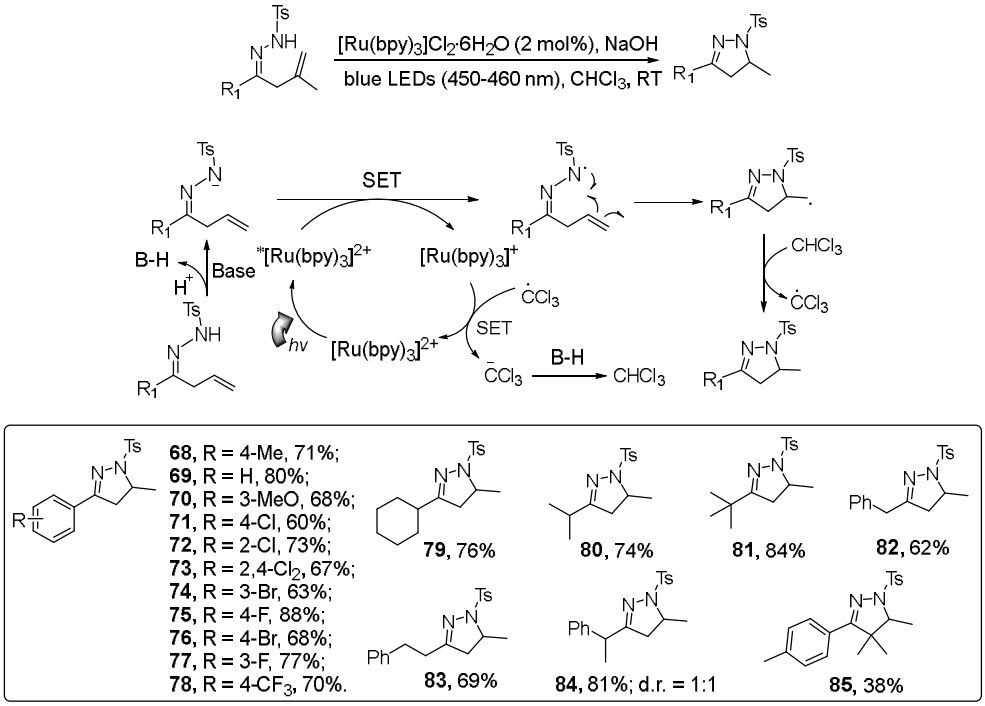
the β,γ-unsaturated hydrazone substrates and diverse functionalization of the double bond. Free radical cyclizations have found wide applications in the synthesis of carbocyclic and heterocyclic compounds. Han and co-workers reported direct hydrazone intramolecular amination through nitrogen-centered radical cycloaddition to synthesize 2-pyrazoline derivatives.[20] As shown in Scheme 6, the β,γ-unsaturated hydrazones, reacted with radical initiator TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or DIAD (diisopropyl azodicarboxylate) to afford nitrogen-centered hydrazone radicals by a hydrogen atom transfer (HAT) process. Then, the formed hydrazone radicals underent 5-*exo-trig* cyclization to give the corresponding pyrazoline ring and the exocyclic carbon-centered radicals could be trapped immediately by TEMPO or DIAD. The substrate scope included a wide range of functionalized aromatic-, and aliphatic-analogs can tolerate the present radical protocols (representative examples **47**-**67** in Scheme 6).



Scheme 6. Hydrazone radical promoted intramolecular vicinal difunctionalization of alkenes to the synthesis of pyrazolines with representative examples.

Instead of using stoichiometric TEMPO or DIAD as radical initiators to generate hydrazonyl radicals, Xiao and co-workers reported a direct transformation of the N–H bond into an *N*-centered radical by photocatalysis to generate the substituted 2-pyrazolines.[21] By testing the reaction conditions, it was found that the photocatalyst, base, and light source were all critical for this transformation. Eventually, it was found that β,γ-unsaturated hydrazones can efficiently transform into 2-pyrazolines in the presence of $[Ru\text{-}(bpy)_3]Cl_2{\cdot}6H_2O$, NaOH, visible light (450-460 nm) in chloroform. A possible reaction mechanism is shown in Scheme 7. Deprotonation of the hydrazone under basic conditions afforded an anionic intermediate. Then, single-electron oxidation of this anionic intermediate by the excited state of the photocatalyst ($*[Ru(bpy)3]^{2+}$) gave the *N*-centered radical and $[Ru(bpy)3]^{+}$ through a reductive quenching process. A 5-*exo-trig* cyclization of the *N*-centered hydrazonyl radical gave the *C*-centered pyrazoline radical. Subsequent H-transfer from $CHCl_3$ to *C*-centered radical afforded the final 2-pyrazoline, together with the generation of trichloromethyl radical, which reacted with $[Ru(bpy)3]^{+}$ to regenerate the photocatalyst ($[Ru\text{-}(bpy)3]^{2+}$) through a single electron transfer process. Regarding the substrate scope, a range of β,γ-unsaturated hydrazones bearing electron-donating and electron-withdrawing groups at either the

2, 3-, or 4-position of the aromatic ring underwent the desired reaction smoothly to give the corresponding 3-aryl-2-pyrazolines **68**-**78**. Moreover, the reaction also proceeded efficiently with aliphatic hydrazones **79**-**84** and 3-dimethyl-2-pyrazoline **85**.

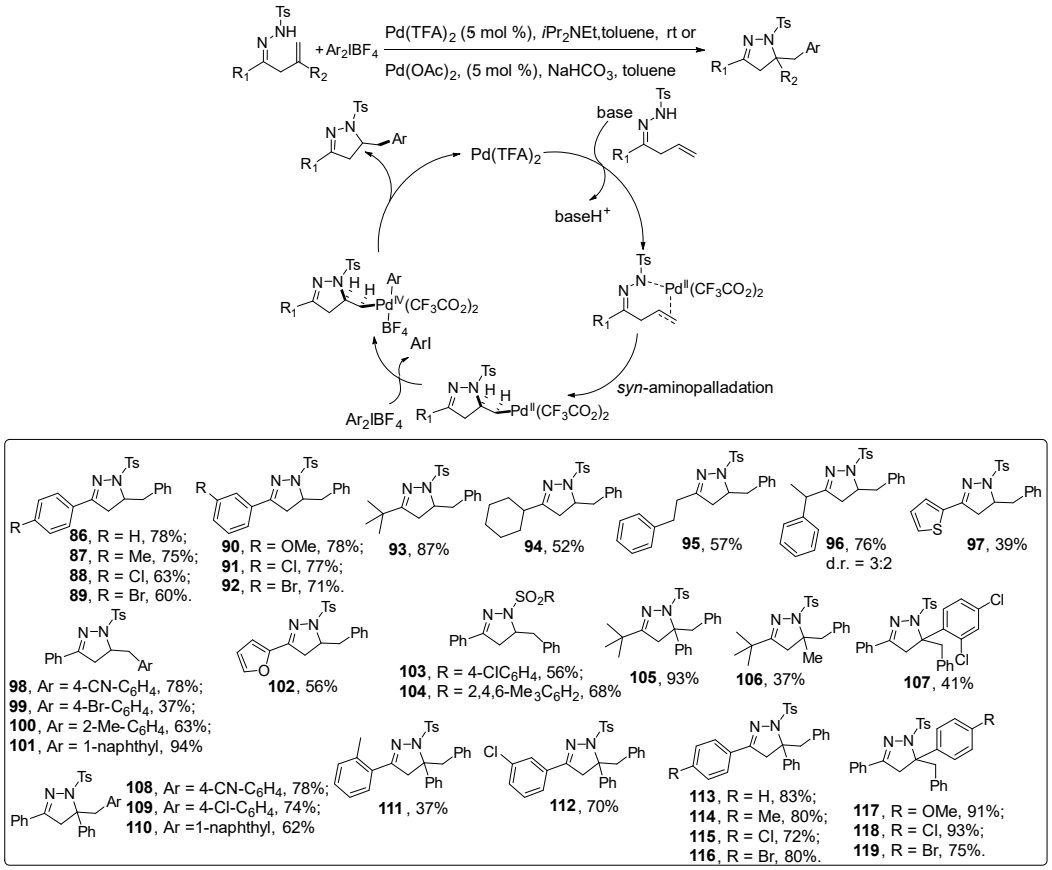


Scheme 7. Photocatalytic N-radical hydroamination of β,γ-unsaturated hydrazones.

Palladium-catalyzed alkene difunctionalization through C−N bond formation has been established as a powerful and widely applied synthetic tool for the construction of diverse nitrogen heterocycles.[22] In 2017, Xiao and co-workers reported the palladium-catalyzed alkene aminoarylation of β,γ-unsaturated hydrazones to synthesize substituted 2-pyrazolines.[23] As shown in Scheme 8, the β,γ-unsaturated hydrazones with terminal alkene (R_2=H) can efficiently transform into 5-benzyl-2-pyrazolines **86**-**104** in the presence of $Pd(TFA)_2$ (5 mol%), $^iPr_2NEt$, and diaryliodonium salts in toluene (Scheme 8). This protocol features excellent functional group compatibility at the C3-position of pyrazolines. Moreover, by the installation of an aryl group at the 2-position of the alkene (R_2=Ph), the desired 2-pyrazolines **105**-**119** with a tetrasubstituted carbon center at C5 were obtained in 37-93% yields (Scheme 8) when using $Pd(OAc)_2$ as the catalyst and $NaHCO_3$ as the base. The plausible mechanism for this aminoarylation reaction involves a Pd(II)/(IV) catalytic cycle. After deprotonation of the hydrazone under basic conditions, the formed anionic-alkene coordinate to the catalyst $Pd(TFA)_2$ followed by intramolecular *syn*-amino-palladation leads to an alkylpalladium complex. The diaryliodonium salt serves not only as an aryl source but also as a terminal oxidant. Thus, the oxidation of the above alkylpalladium complex forms a transient Pd(IV) intermediate. Reductive elimination of Pd(IV) intermediate affords the pyrazoline and regenerates Pd(II) catalyst to complete the catalytic cycle.

Besides the palladium-catalyzed intramolecular amination of β,γ-unsaturated hydrazones, the Cu-promoted intramolecular alkene-amination was also explored for 2-pyrazoline synthesis. Li and co-workers reported the Cu-catalyzed intramolecular amination of β,γ-unsaturated hydrazones to obtain versatile functionalized 2-pyrazolines.[24,25] The proposed reaction mechanism is shown in Scheme 9. Deprotonation of the hydrazone under basic conditions affords the anionic intermediate, which coordinates

with the Cu(II) catalyst. Intramolecular aminocupration of the above complex occurred upon alkene activation by a copper(II) catalyst to form an alkyl-copper intermediate. Then this intermediate underwent homocleavage to form the pyrazoline radical intermediate. On the other hand, different nucleophiles reacted with the Cu(II) catalyst to form Cu(II)-complex. The pyrazoline radical coupled with the Cu(II)-complex to generate an alkyl-copper intermediate, which was followed by a reductive elimination process to form the desired 2-pyrazolines with different substituents at C5 and Cu(I). Finally, Cu(I) was oxidized by DMSO to regenerate Cu(II). When β,γ-unsaturated hydrazones were allowed to react with simple amines, a direct diamination afforded the corresponding aminomethyl-functionalized pyrazolines such as compounds **120**-**132**. Meanwhile, following this protocol, aminoazidation, aminohalogenation, and aminothiocyanation were realized by using different nucleophilic reagents such as NaN_3, halide salts, and KSCN, which could replace the role of amines and convert to the corresponding Cu(II) complexes. In the end, a series of C5 functionalized 2-pyrazolines **133**-**144** were obtained.

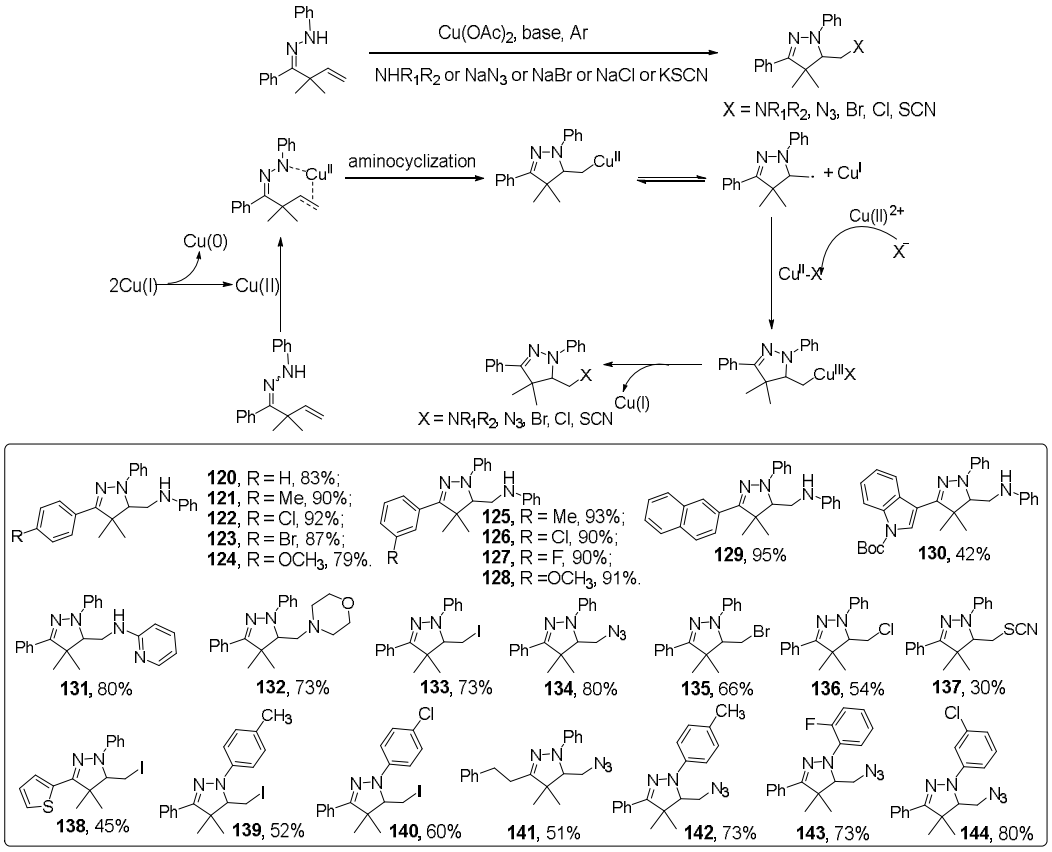


Scheme 8. Palladium-catalyzed, diaryliodonium-mediated aminoarylation reaction of the inactivated alkenes in β,γ-unsaturated hydrazones.

4. 1,3-Dipolar cycloaddition between nitrile imine and alkenes

As a highly reactive member of the nitrilium betaine 1,3-dipole family, the nitrile imine (NI) exhibits a versatile reactivity with a range of nucleophiles, in addition to more conventional dipolarophiles.[26,27] The nitrile imine-related reactions have a wide array of applications ranging from chemical synthesis to biorthogonal ligation and materials chemistry. Different alkenes, as the dipolarophiles react with NI dipoles,

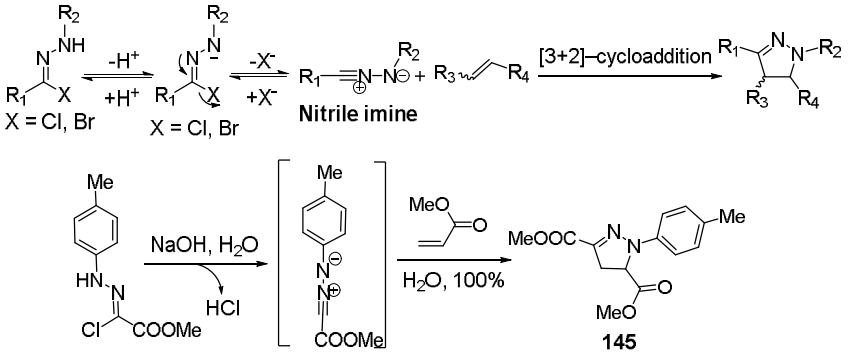
could afford different 2-pyrazolines through [3+2]-cycloadditions (Scheme 10), which represents an alternative way to synthesize 2-pyrazolines. The first generation of nitrile imines (NIs) from hydrazonyl chloride can be traced back to the work of Huisgen in 1959.[28] As shown in Scheme 10, the hydrazonyl halides, can transform into the NI by removal of the halogen hydride, which then reacted with alkenes to afford the corresponding 2-pyrazolines. Unsurprisingly, the relative formation of NI intermediate was highly pH-dependent, with the NI dipole formation becoming increasingly favorable with increasing pH. The pK_a of the hydrazonyl halide had a significant impact on the rate of NI generation, as the deprotonation of the species was the rate-determining step of the reaction.[29] This NI-based [3+2]-cycloaddition occurred smoothly in water, which significantly broads its application in biological systems. As shown in Scheme 10, the hydrazonyl chloride methyl formate, reacted with methyl acrylate in the presence of 0.1 M sodium hydroxide in water to afford the 2-pyrazoline **145** in the quantitative yield.[30]



Scheme 9. Copper-mediated intramolecular amination of β,γ-unsaturated hydrazones and further functionalization of terminal alkene.

Excluding hydrazonyl chlorides, tetrazoles are the most common precursor to the NI dipole, which can form NI through the expulsion of the N-3 and N-4 atoms of the heterocycle as a molecule of nitrogen. This de-nitrogenation process can be initiated in either a thermal or a photochemical way (Scheme 11a). Offering efficiency, exquisite spatiotemporal control, and mild reaction condition, photochemistry plays a vital role in organic synthesis and biological studies. Therefore, the photoinduced tetrazole-alkene cycloaddition was intensively studied as a bioorthogonal reaction to form 2-pyrazolines *in vivo*.[31] As shown in Scheme 11b, a hand-held benchtop UV lamp was sufficiently robust to initiate the photoactivated nitrile imine formation

and the 1,3-dipolar cycloaddition reactions between diaryl nitrile imine and alkenes proceeded efficiently to afford diaryl pyrazolines **146-157** with 62-100% yields within 2 hours.[32] To illustrate the utility of this mild photoactivation procedure in synthesizing highly functionalized pyrazolines, a water-soluble pyrazoline analog **159** (which contains an isomeric core while retaining three key hydrophobic appendages of **Nutlin-3**,[33] a potent MDM2 inhibitor) was prepared with the photoactivated tetrazole-styrene reaction as the key step. Since the 1,3-diaryl-2-pyrazolines are fluorophores and exhibited tunable photophysical properties by changing the substituents in the aryl rings, this photo-induced tetrazole-alkenes [3+2]-cycloaddition was employed as a fluorogenic ligation strategy in bioorthogonal chemistry, so-called "photoclick" reaction.[34]

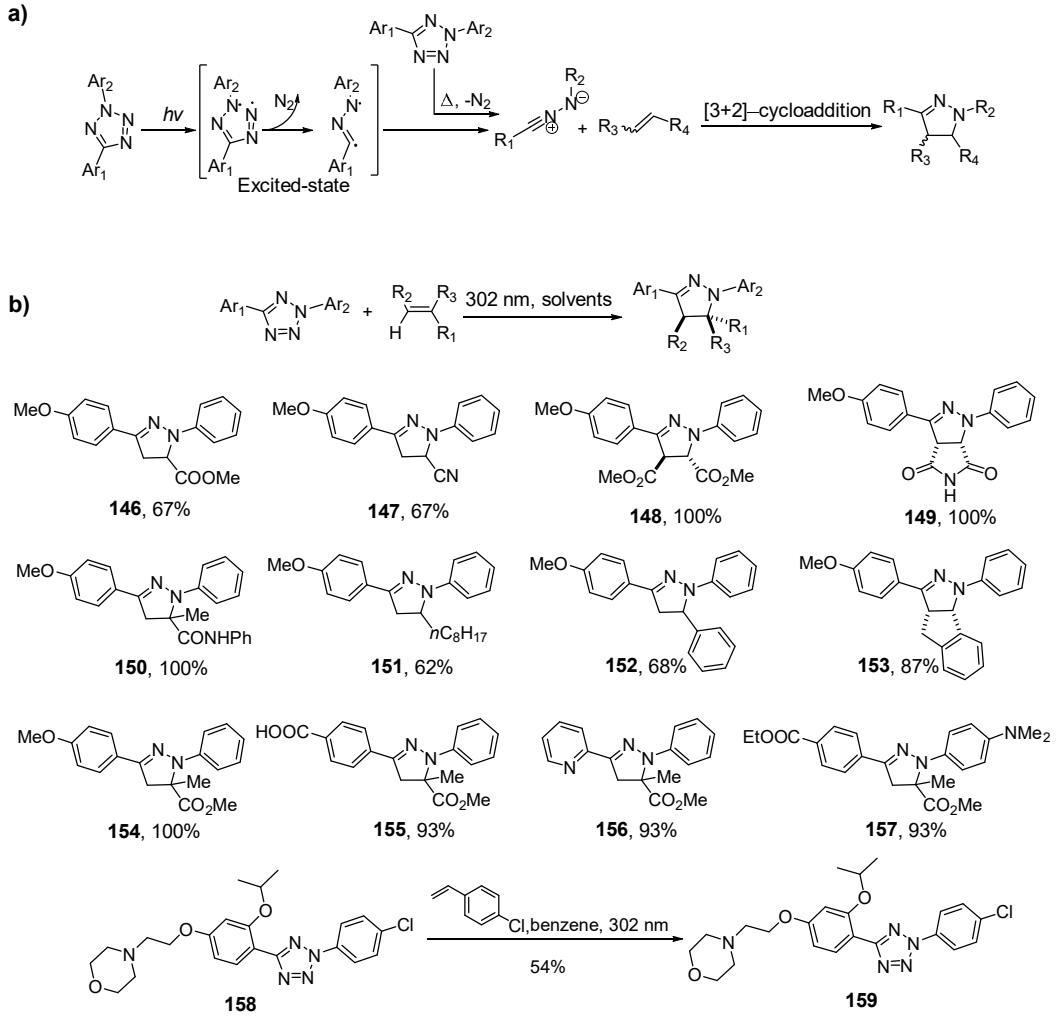


Scheme 10. Nitrile imine generation using hydrazonyl halides and nitrileimine-alkene-based [3+2]-cycloaddition to synthesize 2-pyrazolines.

The photoinducible tetrazole-alkene cycloaddition reaction ("photoclick chemistry") involves the UV light-induced breaking of the tetrazole ring to generate *in situ* a highly reactive nitrile imine dipole. To reduce phototoxicity (302 nm UV light) to the living systems and increase spatiotemporal control, a visible-light-induced tetrazole-alkene bioorthogonal reaction was designed.[10] By fusing the tetrazole ring into linear α,α-linked oligothiophenes, the molar absorptivity and absorption wavelengths can be tuned to the visible region with maintaining the ring-rupture reactivity of tetrazole. As shown in Scheme 12a, 5-(thiophen-2-yl)tetrazole was coupled with phenyl(thiophen-2-yl)iodonium salts **160** in the presence of $Cu(OAc)_2$ and NEt_3 affording tetrazole fused oligothiophene **161**. Then, through hydrolysis, esterification, reduction, and substitution, a negatively charged succinate at the distal thiophene ring was appended to improve the water solubility of tetrazole **161**. To test the ability of this tetrazole ring rapture can be activated by visible light to form the fluorescence pyrazoline and applied in biological systems, a fumarate-docetaxel conjugate **163** was synthesized and incubated in living cells, which could bind to microtubules. When the tetrazole **162** was incubated in cells and irradiated by 405 nm light, the nitrile imine formed and reacted with fumarate-docetaxel conjugate **163** to generate the fluorescence pyrazoline derivative **164**.

To minimize the interference caused by autofluorescence, fluorescence probes with emissions in the red or near-infrared region are highly desirable for diverse applications in living systems. For this *in situ*-formed pyrazoline fluorophores, the red to near-infrared emissive pyrazolines was realized by extending π-conjugation and introducing electronic functional groups.[35] As shown in Scheme 12b, tetrazole **165** with ethyl 4-vinylbenzoate substituent at C3 and bisthiophene at N1 can react with dimethyl fumarate through visible light-induced cycloaddition to afford pyrazoline **166**, which exhibits near-infrared fluorescence with the emission maximum at 644 nm in aqueous buffer. The photoactivatable fluorophores as "turn-on" fluorescence activated by light, are valuable tools for tracking the dynamics of biological molecules or super-resolution fluorescent imaging. Recently, An and co-workers reported a dual-activated pyrazoline fluorophore **169**, which needs to be activated by sequenced azide-alkyne click reaction and photoinduced intramolecular tetrazole-alkene cycloaddition (Scheme 12c).[36] This photoactivatable fluorogenic azide-alkyne click reaction presents a high signal-to-noise ratio fluorescence with precise spatiotemporal control of the fluorescent signal. However, 1,3-diaryl-2-pyrazoline fluorophores derived from

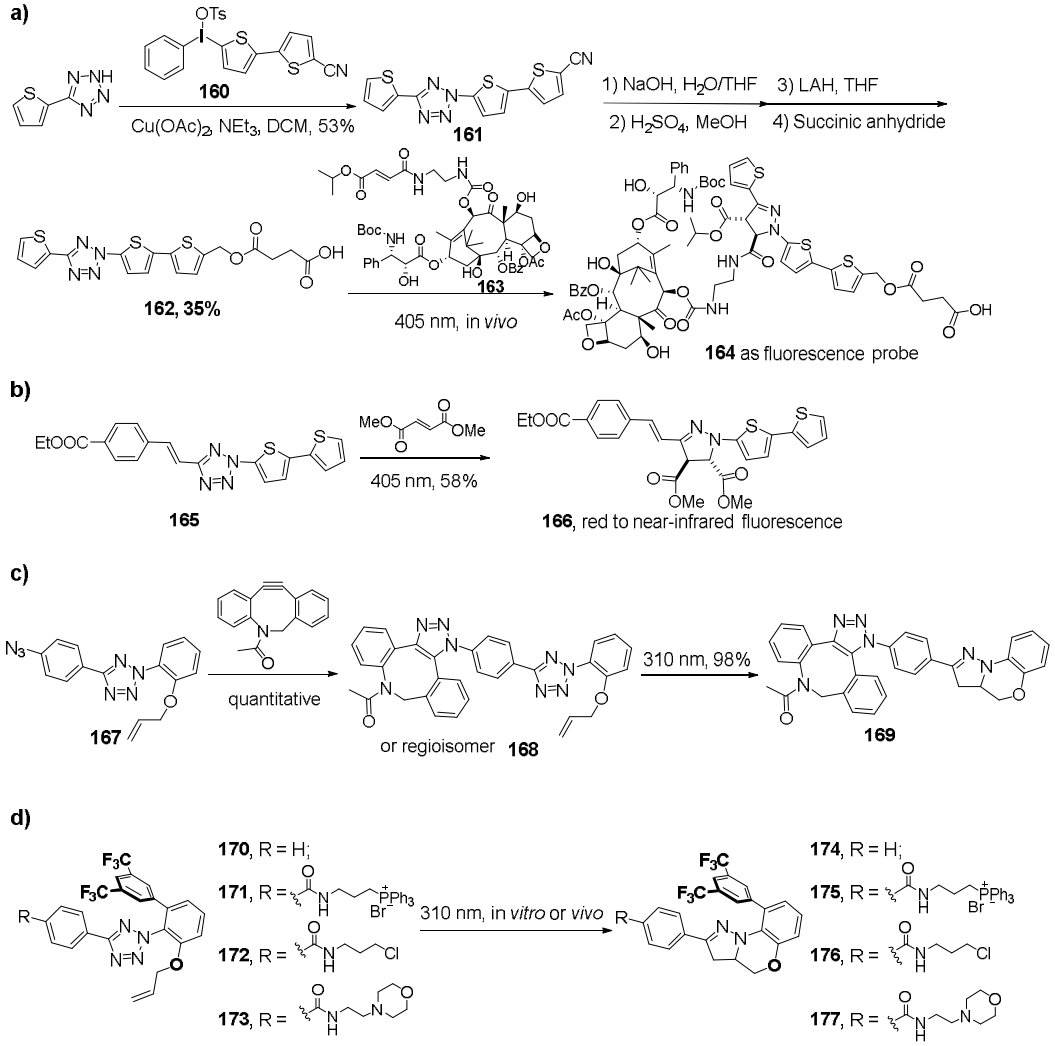
photo-triggered, intramolecular tetrazole-ene cycloaddition, were found to be less emissive in polar solvents with low fluorescent quantum yield due to the excited-state protonation of imine of the 2-pyrazoline ring, which limits their extensive application in biological systems. To address this issue, An and co-workers reported a sterically shielded pyrazoline, which exhibits improved brightness and stability in protic solutions (Scheme 12d).[9] This fluorescence enhancement was explained by the steric effect and fluoro-involved hydrogen bonding to prevent the excited-state protonation process. Through the installation of different ligands (compounds **170**-**173**), the fluorescence imaging of organelles at low concentrations was realized by these photoactivatable fluorophores.



Scheme 11. a) Thermal- or photo-induced nitrile imine formation followed by [3+2]-cycloaddition for the 2-pyrazoline synthesis. b) UV-light induced diaryl tetrazole-alkene cycloaddition to form 2-pyrazolines.

Sydnones are mesoionic compounds that are typically represented as cationic oxadiazole species with an exocyclic anionic oxygen atom,[37] which was also reported in the early time that can react with alkenes from 1,3-addition and CO_2-evolution to afford 2-pyrazolines.[38] For example diaryl sydnone **178** reacted with

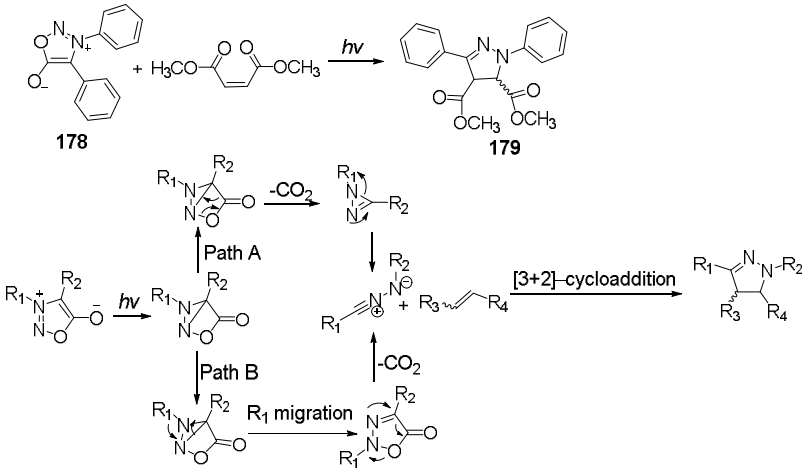
dimethyl maleate in the presence of light, affording the 1,3-diaryl-2-pyrazoline **179** (Scheme 13).[39] It was proposed that photolysis of arylsydnone derivates activates a mechanistic pathway by which the sydnone expels CO_2 to generate the reactive NI intermediate. As shown in Scheme 13, the photolysis of sydnone would generate a diazirine species through intramolecular addition to diazonium followed by elimination of CO_2 in path A.[40] Meanwhile, Kato hypothesised that N-aryl group migration could enable NI formation directly (path B).[41]



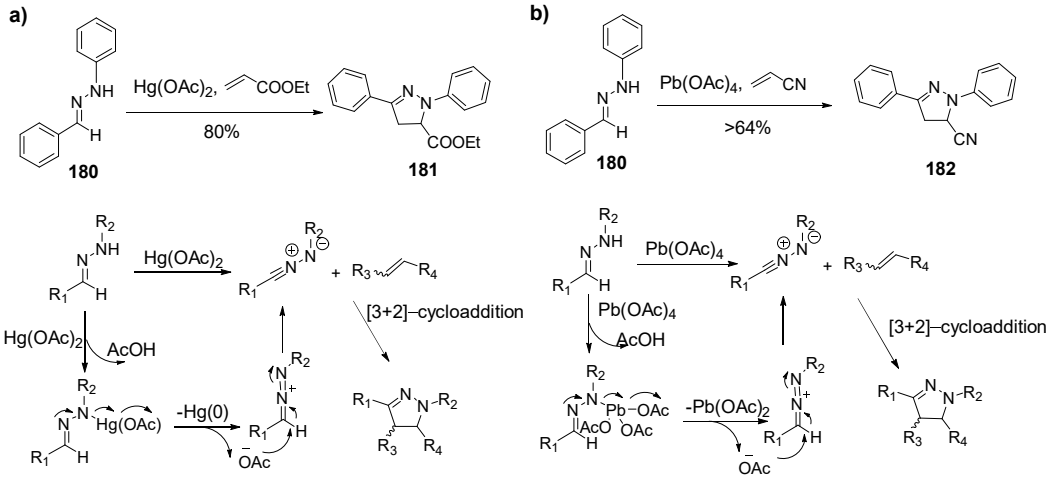
Scheme 12. a) Synthesis of visible light active terthiophene-tetrazole and generation of the pyrazoline fluorophore with docetaxel ligand. b) The red to near-infrared pyrazoline fluorophore obtained by photoclick tetrazole-ene cycloaddition. c) Tetrazole-ene-based photoactivatable fluorophore used in click chemistry as "click-on" probe. d) 1,3-Diaryl-2-pyrazolines with improved fluorescence intensity in water.

Besides the above-mentioned precursors, NI can also be accessed directly from the corresponding aldehyde hydrazones through an oxidative process by heavy metals. As shown in Scheme 14a, hydrazone **180**, reacted with ethyl acrylate in the presence of mercury(II) acetate affording the corresponding

2-pyrazoline **181** in a high yield.[42] This process involved the oxidation of aldehyde hydrazone *via* the loss of two hydrogens by mercuric acetate to generate the NI intermediate. Meanwhile, lead tetraacetate was also proved as an efficient oxidant for the oxidation of aldehyde hydrazine **180** in a similar manner as mercuric acetate to afford pyrazoline **182** (Scheme 14b).[43]



Scheme 13. Photoinduced sydnones-alkene [3+2]-cycloaddition to form 2-pyrazoline and the two hypothesized mechanisms of NI formation *via* sydnone photolysis.

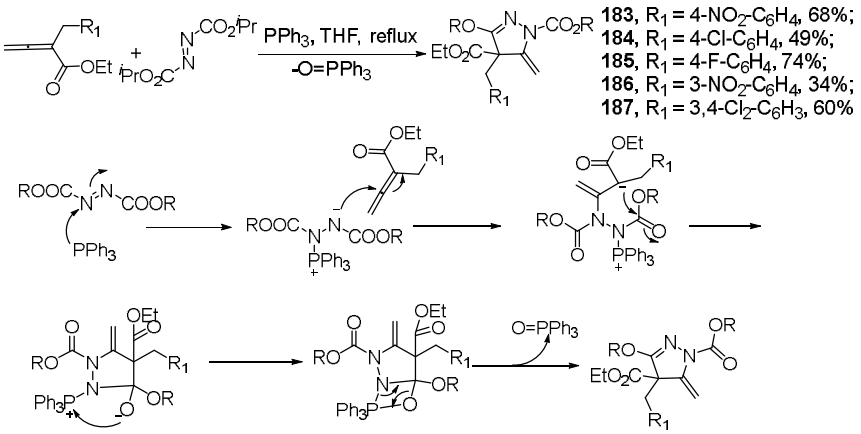


Scheme 14. Nitrile imine formation from hydrazones through metal-catalysis for 1,3-dipole [3+2]-cycloaddition with alkenes.

5. Through Huisgen zwitterions

In early times, Huisgen reported the formation of a zwitterion by the reaction of triphenylphosphine and dimethyl azodicarboxylate.[44] The Huisgen zwitterions could be used to synthesize pyrazolines through a series of annulation reactions with electron-deficient alkenes, carbonyls, or imines. Nair and co-workers reported a way to synthesize functionalized pyrazolines by triphenylphosphine-mediated reaction of dialkyl azodicarboxylates with allenic esters (Scheme 15).[45] The phosphine first reacts with the azo-ester to form the zwitterion. Then the nitrogen anion attacks the electron-deficient double bond of the allene ester to give a

tetrahedral intermediate, in which the carbanion reacts with the ester to form the heterocyclic five-membered ring. Finally, the triphenylphosphine oxide is eliminated *via* a process resembling the Wittig reaction to give 2-pyrazoline. A series of 2-pyrazolines **183**-**187** were synthesized by using this protocol in 34-74% yields.



Scheme 15. Formation of functionalized pyrazolines by reaction of PPh_3-DIAD Zwitterion with allene.

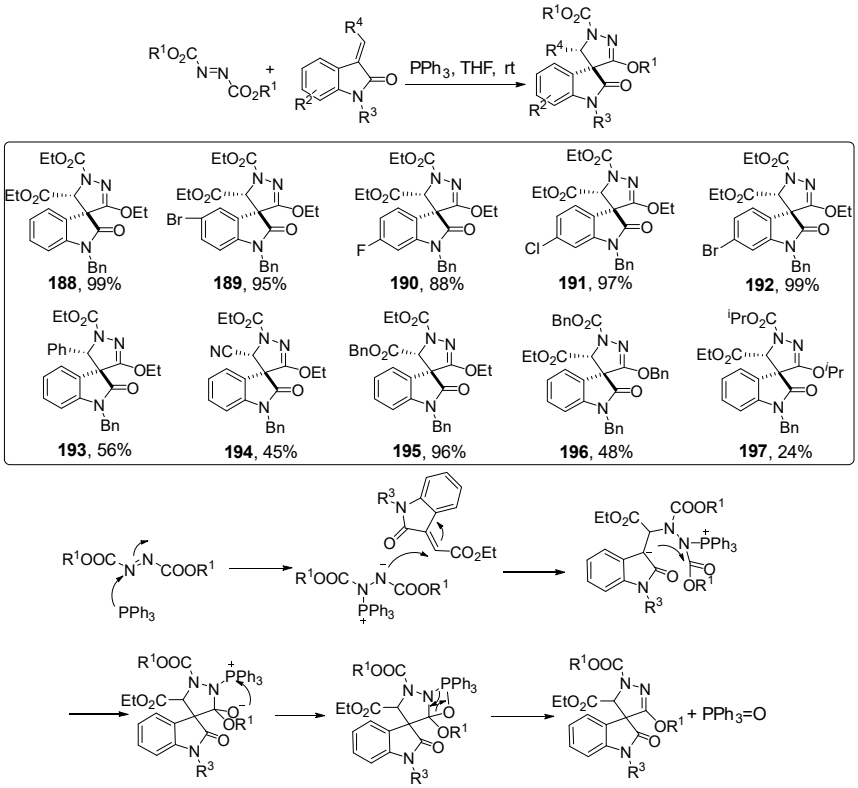
He and co-workers reported an annulation reaction between 3-alkylidene oxindoles and Huisgen zwitterions as a new route to spirooxindole-pyrazolines.[46] As shown in Scheme 16, by processing a similar reaction mechanism as Scheme 15, a series of spirooxindole-pyrazolines **188**-**197** were obtained in 24-99% yields.

Wang and co-workers reported that Huisgen zwitterions reacted with 2-acylaziridines instead of electron-deficient alkenes to synthesize a class of 2-pyrazolines **198**-**202** bearing carbamate group at the C5 position (Scheme 17).[47] The reaction process initiated by the nucleophilic addition from Huisgen zwitterion to the carbonyl group of 2-acylaziridine followed by removing triphenylphosphine oxide to form the heterocyclic ring. Then the nitrogen in the aziridine attacks the ester followed by a series of ring rearrangements to give the final 2-pyrazoline.

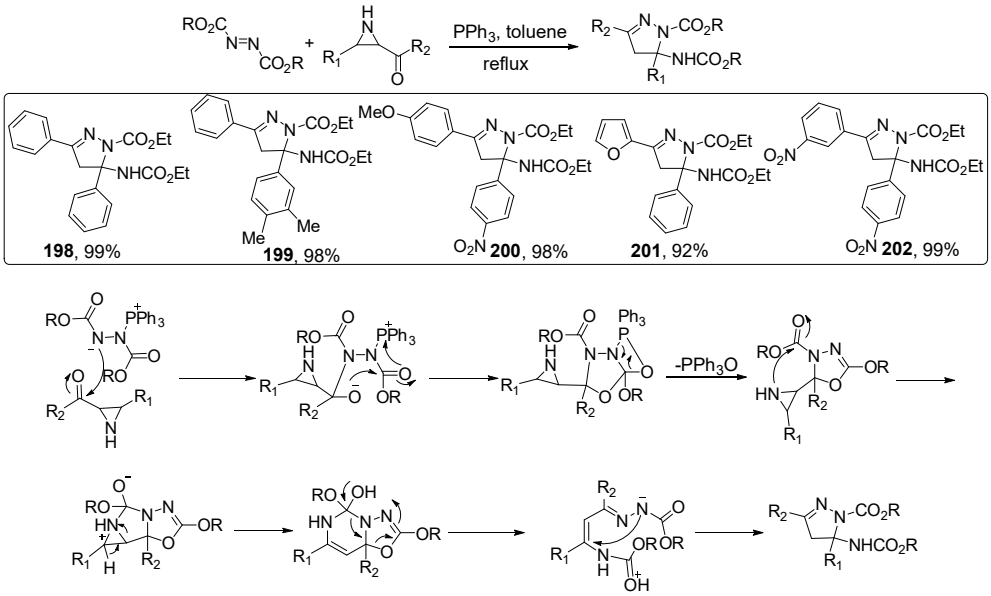
6. Other methods

The 2-pyrazoline can also be constructed from a diazo compound and α,β-unsaturated alkenes.[48] An aliphatic diazo compound, such as diazomethane, reacted with simple α,β-unsaturated esters to initially give a 1-pyrazoline in which the nitrogen atom is linked to the α-carbon atom of the carbonyl compound. Through proton transfer, 1-pyrazoline was prone to transform into a more stable 2-pyrazoline. As shown in Scheme 18, diazomethane reacted with different *o*-hydroxychalkones affording 4-phenyl-5-carbonyl-2-pyrazolines **203**-**208** in 65-85% yields.[49]

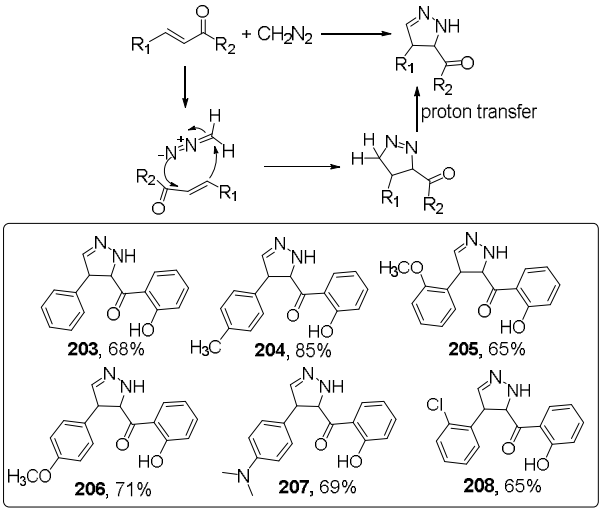
In 2008, Beller and co-workers reported a zinc-promoted hydrohydrazination of terminal alkynes to synthesize 2-pyrazolines.[50] Various phenylhydrazine with 3-butanol in the presence of a stochiometric amount of $Zn(OTf)_2$ led to the formation of 1-aryl-3-methyl -2-pyrazolines **209**-**217** in high yields (Scheme 19). Hu and co-workers reported a regio- and enantioselective Cu-catalyzed [3+2]-cycloaddition of propargylic acetates with monosubstituted hydrazines to stereoselectively construct optically pure 2-pyrazolines **218**-**241** in the presence of chiral ligand **S-L$_1$** (Scheme 20).[51] The possible reaction mechanism is shown in Scheme 20. The propargylic acetate transformed into a Cu-allenylidene complex, which then regio- and enantioselectively reacted with phenyl hydrazine through [3+2]-cycloaddition to afford 3-pyrazoline. Finally, the 3-pyrazoline underwent spontaneous 1,3-proton migration leading to thermodynamically more stable 2-pyrazolines. The steric congestion imparted by the phenyl group of hydrazines close to the copper center was proposed to explain the observed regioselectivity. By employing a structurally rigid tridentate ketimine P,N,N-ligand, the chiral 2-pyrazolines were generated in high enantiomeric excess (up to 96% ee).



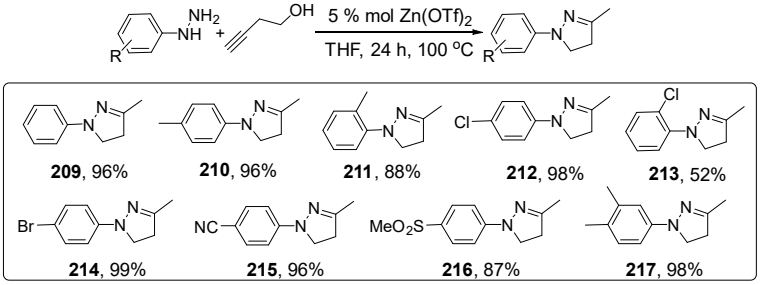
Scheme 16. Synthesis of spirooxindole-pyrazolines by using Huisgen zwitterions and3-alkylidene oxindoles.



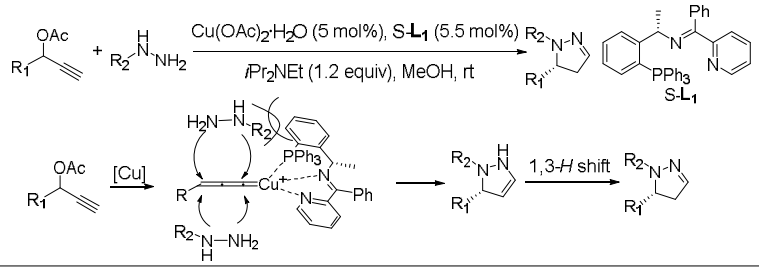
Scheme 17. Synthesis of pyrazolines *via* Domino reaction of Huisgen zwitterions with aziridines.



Scheme 18. Formation of 2-pyrazolines by the reactions of diazomethane and α,β-unsaturated alkenes.



Scheme 19. Reactions of arylhydrazines with 3-butanol to various substituted pyrazolines.



218, R_1 = Ph, R_2 = Ph, 90% yield, 94% ee;
219, R_1 = 2-ClC_6H_4, R_2 = Ph, 92% yield, 90% ee;
220, R_1 = 3-ClC_6H_4, R_2 = Ph, 91% yield, 94% ee;
221, R_1 = 4-ClC_6H_4, R_2 = Ph, 89% yield, 92% ee;
222, R_1 = 4-FC_6H_4, R_2 = Ph, 90% yield, 91% ee;
223, R_1 = 4-BrC_6H_4, R_2 = Ph, 93% yield, 92% ee;
224, R_1 = 4-$CF_3C_6H_4$, R_2 = Ph, 88% yield, 91% ee;
225, R_1 = 4-MeC_6H_4, R_2 = Ph, 87% yield, 92% ee;
226, R_1 = 4-MeOC_6H_4, R_2 = Ph, 91% yield, 84% ee;
227, R_1 = 2-naphthyl, R_2 = Ph, 97% yield, 95% ee;
228, R_1 = 2-thienyl, R_2 = Ph, 91% yield, 87% ee;
229, R_1 = Me, R_2 = Ph, 87% yield, 85% ee;
230, R_1 = Bn, R_2 = Ph, 85% yield, 94% ee;
231, R_1 = Ph, R_2 = Ph, 90% yield, 94% ee;
232, R_1 = Ph, R_2 = 4-MeC_6H_4, 95% yield, 94% ee;
233, R_1 = Ph, R_2 = 4-MeOC_6H_4, 91% yield, 94% ee;
234, R_1 = Ph, R_2 = 4-$CF_3C_6H_4$, 84% yield, 95% ee;
235, R_1 = Ph, R_2 = 4-BrC_6H_4, 96% yield, 96% ee;
236, R_1 = Ph, R_2 = 4-FC_6H_4, 92% yield, 94% ee;
237, R_1 = Ph, R_2 = 4-ClC_6H_4, 88% yield, 96% ee;
238, R_1 = Ph, R_2 = 3-ClC_6H_4, 89% yield, 93% ee;
239, R_1 = Ph, R_2 = 2-ClC_6H_4, 45% yield, 94% ee;
240, R_1 = Ph, R_2 = 2-MeC_6H_4, 65% yield, 94% ee;
241, R_1 = Ph, R_2 = $HOCH_2CH_2$, 70% yield, 92% ee.

Scheme 20. Cu-catalyzed [3+2]-cycloaddition of propargylic acetates with monosubstituted hydrazines.

7. Conclusion

The construction of 2-pyrazolines has been developed intensively in recent decades due to their versatile biologic activities and wide applications as fluorescence probes. In this current context, we summarized the general synthetic strategies to synthesize 2-pyrazoline including reactions between hydrazines and α,β-unsaturated enones, intramolecular amination of β,γ-unsaturated hydrazones, 1,3-dipolar cycloaddition between different nitrile imines and alkenes, Huisgen zwitterions involved transformations, cycloaddition between diazo compounds and α,β-unsaturated alkenes, and alkyne involved cyclization reactions. All these methodologies proceeding in different pathways would facilitate the synthesis of more valuable 2-pyrazoline compounds in the identification of promising medicinal candidates or chemical biology applications. Meanwhile, it is always encouraging to develop more advanced methods to construct substituted 2-pyrazolines by referring to the current synthetic ways.

Acknowledgments

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