

SYNTHESIS AND REACTIONS OF *N*-ETHYNYL-HETEROCYCLES

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Abstract – Synthesis of *N*-ethynyl-heterocycles by elimination, nucleophilic substitution, isomerization, benzotriazole intermediates and other methods are reviewed. The reactions of *N*-ethynyl-heterocycles including additions, cycloadditions and polymerizations are discussed.

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INTRODUCTION

Alkynes play a significant role as building blocks in synthetic organic chemistry.^{1a} Ynamines, created by the direct linking of amino nitrogen atom with alkyne, are very useful functionalized alkynes; the electron donating ability of the nitrogen atom makes them synthetically effective due to their high regioselectivity in reactions with a variety of electrophiles. During recent decades, the preparation and synthetic utility of ynamines in organic and related fields have been explored.¹ However, synthetic applications of ynamines have remained relatively limited because of the difficulty experienced in preparation and handling of ynamines due to their high reactivity and sensitivity toward hydrolysis.^{1d} Thus, modifications to thermally stable ynamines without decreasing the reactivity afforded a challenging approach to improve their synthetic utility. An important example of this approach includes functionalized acetylenes containing 'push-pull' systems, with an electron-donating group at one end and an electron-withdrawing group at the other end of the triple bond, as pioneered in the Hsung^{1c} and Ishihara groups.²

Ynamines containing an acetylene moiety linked to a heterocyclic nitrogen atom have recently gained importance in organic synthesis. Heterocycle-substituted alkynes possess more conformational rigidity than other heteroatom-substituted alkynes or ynamines. Potentially, they can co-ordinate to metals, be chiral, and afford useful stereoselective methodologies for novel heterocyclic compounds. This review summarizes the synthesis and applications of *N*-ethynyl-heterocycles (Scheme 1). The first section describes their synthesis by eliminations, nucleophilic substitutions, isomerizations, benzotriazole mediated reactions and by other miscellaneous methods. The section on synthetic utility includes addition, rearrangement, cycloaddition and polymerization reactions. Besides including the important contributions from other workers, this review also covers the methodologies developed in our group along with some

$$\text{R}-\text{C}\equiv\text{C}-\text{R}^1$$

alkynes

$$\text{R}-\text{C}\equiv\text{C}-\text{NR}_2$$

ynamine

$$\text{R}-\text{C}\equiv\text{C}-\text{N} \bigcirc$$

N-ethynyl-heterocycle

Scheme 1

Synthetic routes to *N*-ethynyl-heterocycles can be broadly classified into three main pathways: elimination, nucleophilic substitution, or isomerization.

1.1.1 From trichloroenamines

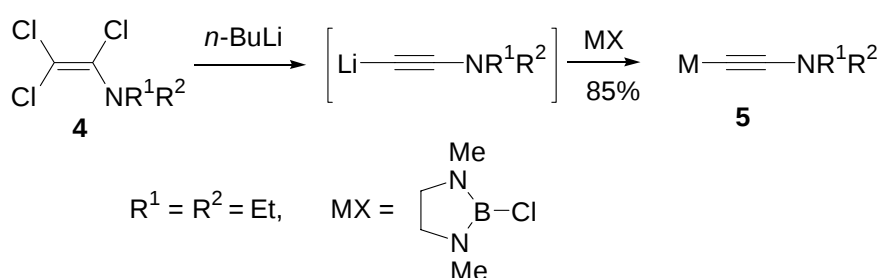
$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{Cl}_3\text{C}-\text{C}-\text{NR}^1\text{R}^2 \\
 \mathbf{1}
 \end{array}
 \xrightarrow{\text{PPh}_3}
 \begin{array}{c}
 \text{Cl} \quad \text{Cl} \\
 \backslash \quad / \\
 \text{C}=\text{C} \\
 / \quad \backslash \\
 \text{Cl} \quad \text{NR}^1\text{R}^2 \\
 \mathbf{2}
 \end{array}
 \xrightarrow{n\text{-BuLi}}
 \left[\text{Cl}-\text{C}\equiv\text{C}-\text{NR}^1\text{R}^2 \right]$$

$$\downarrow \text{LiNR}^3\text{R}^4$$

$$\left[\begin{array}{c} \text{Li} \quad \text{NR}^3\text{R}^4 \\ \backslash \quad / \\ \text{C}=\text{C} \\ / \quad \backslash \\ \text{Cl} \quad \text{NR}^1\text{R}^2 \end{array} \right]
 \xrightarrow{-\text{LiCl}}
 \begin{array}{c}
 \text{R}^3 \quad \text{R}^1 \\
 \backslash \quad / \\
 \text{N} \equiv \text{N} \\
 / \quad \backslash \\
 \text{R}^4 \quad \text{R}^2 \\
 \mathbf{3}
 \end{array}$$

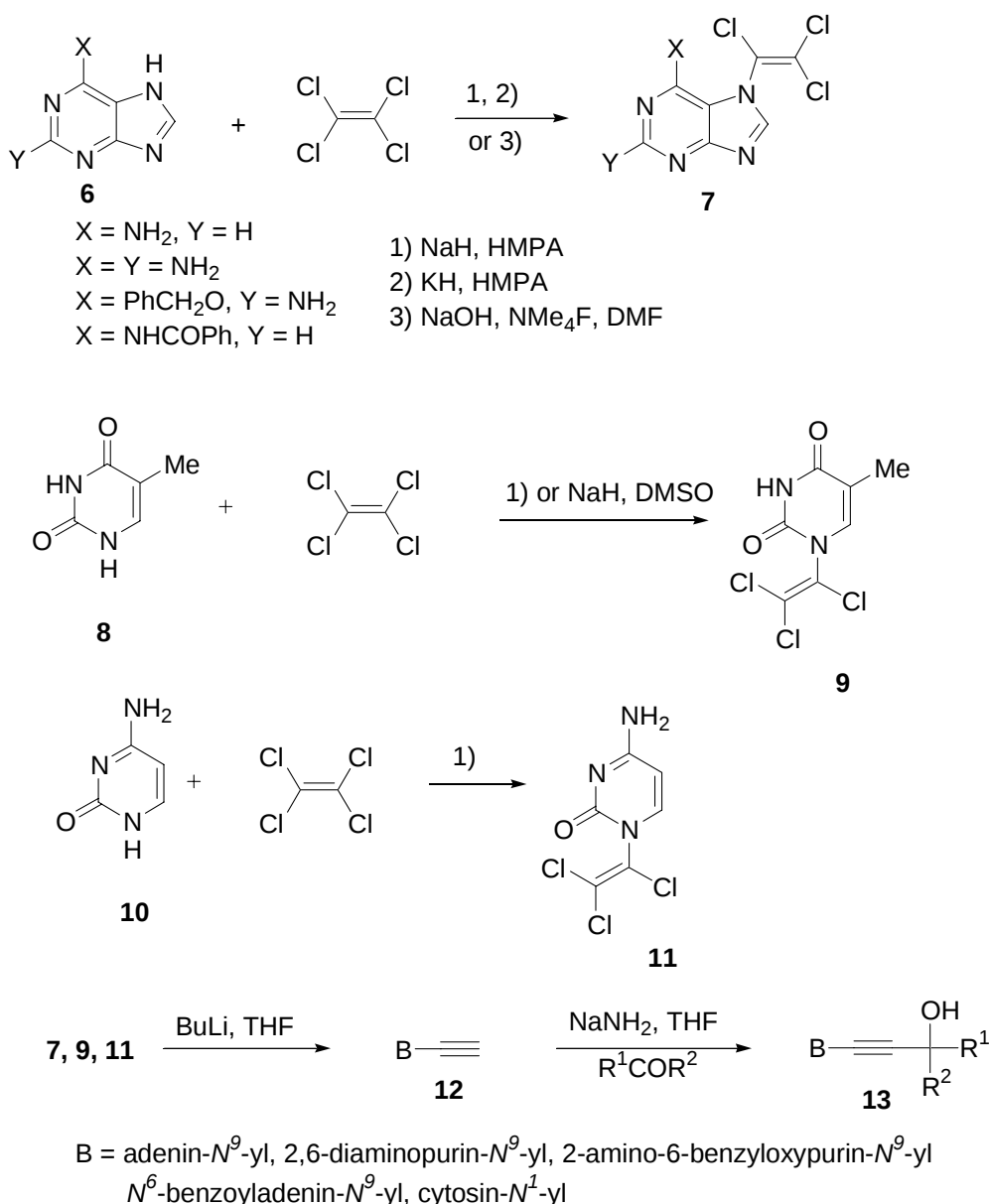
$\text{R}^1, \text{R}^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$
 $\text{R}^3, \text{R}^4 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2, (\text{CH}_2)_5$

Trichloroenamines (**4**) can also undergo elimination to lithiated ynamines which can be trapped by halides to furnish hetero-substituted ynamines (**5**) (Scheme 3).⁶



Heterocyclic ynamines (**12**) derived from nucleic acid bases were reported by Ramachandra⁷ using a

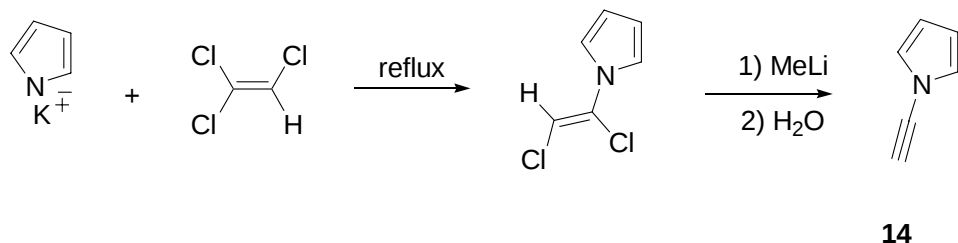
similar method. Ynamines (**12**) are synthetic intermediates for the preparation of new analogues with therapeutic potential and also exhibit some interesting biological properties such as a substrate of moderate activity for adenosine deaminase from calf intestine.⁷ In addition, they could serve as starting materials for unsaturated acyclic nucleoside analogues⁸ and become synthons of the corresponding polymers (polyacetylenes) containing nucleic acid bases, which can inhibit *E. coli* RNA polymerase.⁹ Reactions of nucleic acid bases and related heterocycles (**6**, **8**, **10**) with tetrachloroethylenes in hexamethylphosphoric triamide gave the corresponding chloroenamines (**7**, **9**, **11**) which were converted into ynamines (**12**) by using BuLi in THF. Deprotonation of **12** followed by trapping with ketone give propargyl alcohol (**13**) (Scheme 4).⁷ Further isomerization of **13** can form nucleic acid allenols which serve as analogues of nucleosides with antiretroviral activity.^{10,11}



Scheme 4

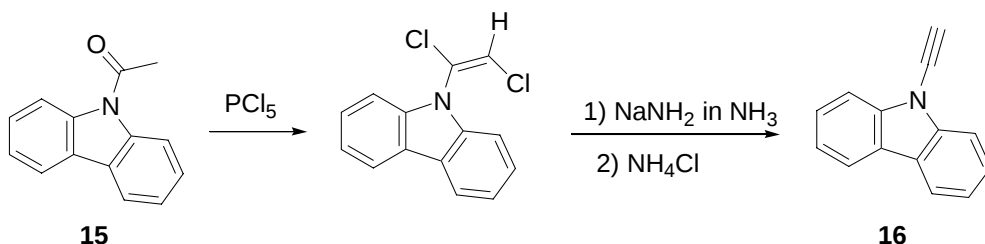
1.1.2 From α,β -dichloroenamines

α,β -Dichloroenamines can also undergo elimination when treated with alkylolithiums to give heterocyclic ynamines. Using this procedure, the synthesis of a useful polymerization precursor of diacetylene, pyrrole *N*-ethynylpyrrole (**14**) was achieved by Paley *et al.* (Scheme 5).¹²

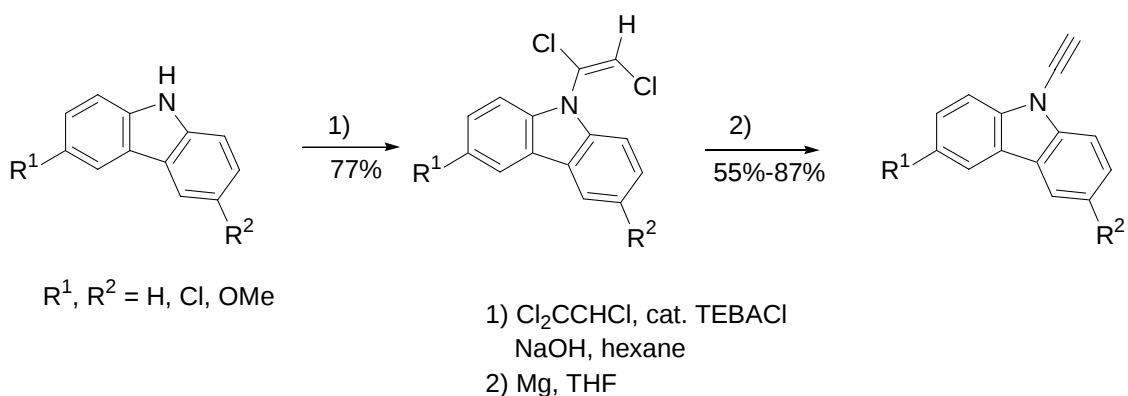


Scheme 5

Likewise, 9-ethynylcarbazole (**16**) was first synthesized from *N*-acetylcarbazole (**15**) by successive treatment with phosphorus pentachloride and with potassium hydroxide or sodium amide in liquid ammonia (Scheme 6).¹³ Twenty five years later this method was modified by Pielichowski by using phase transfer alkylation and subsequent reductive dehalogenation by Mg (Scheme 7).¹⁴



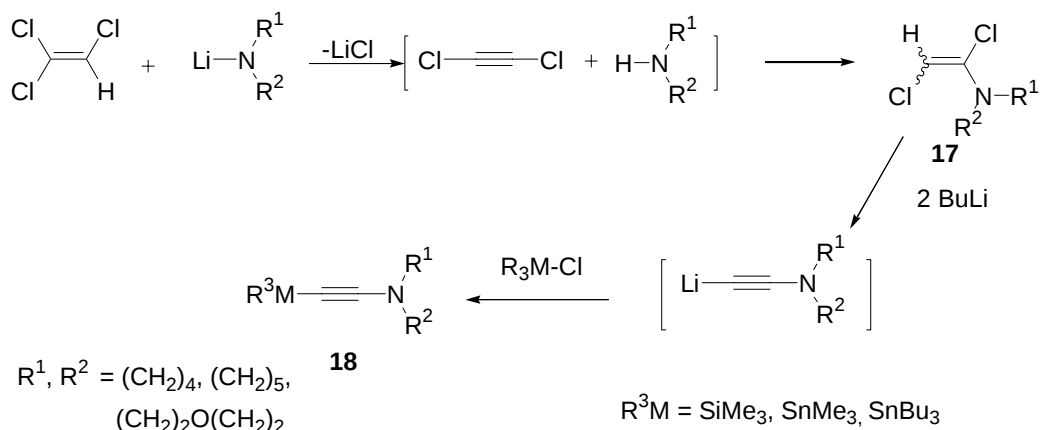
Scheme 6



Scheme 7

Himbert developed a simple, one-pot synthesis of silylated and stannylated heterocyclic ynamines (**18**).¹⁵ The 1,2-dichlorovinyl compounds (**17**) could be formed by dehydrohalogenation of trichloroethylene, which adds to piperidine and morpholine to give the enamine derivatives. The unstable dichlorovinyl compounds were not isolated but were directly reacted with two equivalents of butyllithium to form the lithium acetylides. After treatment with chlorotrimethylsilane, chlorotrimethylstannane or

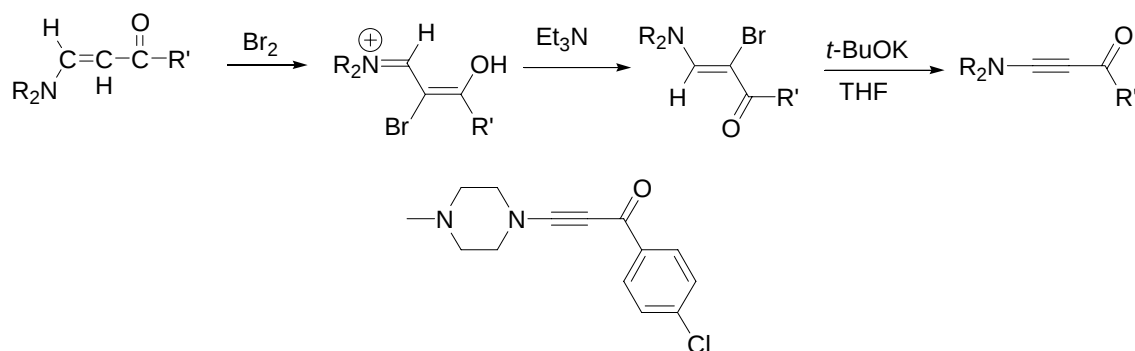
chlorotributylstannane these acetylides furnished the easily isolable metallated ynamines (**18**) (Scheme 8).



Scheme 8

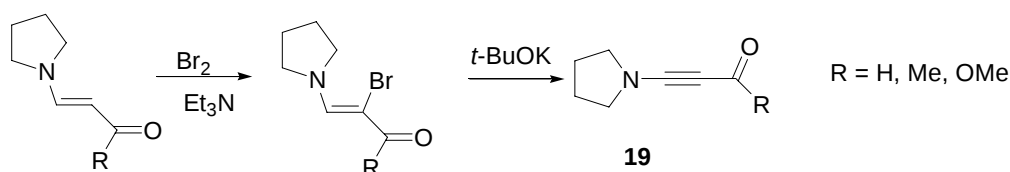
1.1.3 From β -haloenamines

dehydrohalogenation of β -haloenamines having an alkyl group in a β position is difficult and the corresponding ynamines are obtained from the β -lithioenamine *via* halogen-metal exchange¹⁶. However, when an electron-withdrawing group is present β to the amino group, vinyloungous amides, carbamates and ureas have been transformed into their ethynylogs for which the term “push-pull acetylenes” is used. The second commercially available ynamine, 1-(4-chlorophenyl)-3-(4-methyl-1-piperazinyl)-2-propyn-1-one was made by this method (Scheme 9).¹⁷



Scheme 9

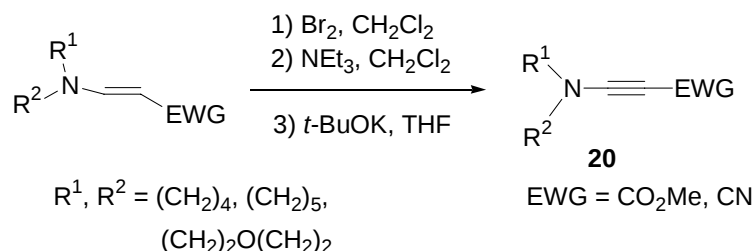
Further extension of this methodology leads to a series of ‘push-pull’-acetylenes (**19**), which were used in solid-state polymerization giving crystals with stacked molecules (Scheme 10).¹⁸



Scheme 10

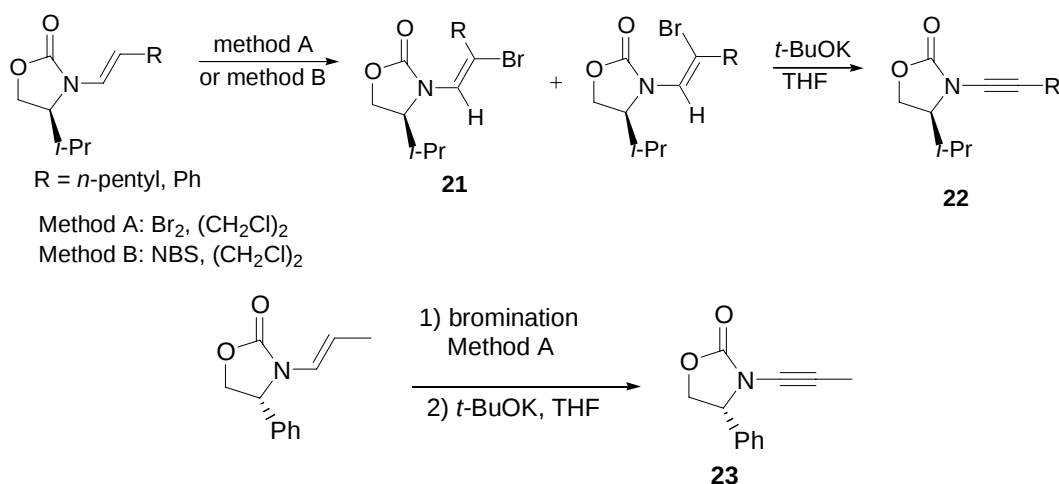
Similarly, ynamine esters and nitriles (**20**), which are useful precursors in pyran synthesis by

hetero-Diels-Alder reaction as the 2π electron component, were prepared according to this method (Scheme 11).¹⁹



Scheme 11

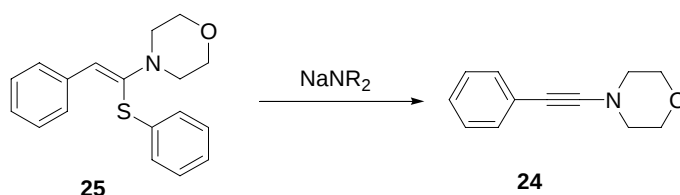
Hsung reported the preparation of ynamides (**22**) from enamides (**21**) via bromination followed by base-induced elimination of the *Z*-bromoenamides (**21**). After exploring a variety of conditions, they found that method A worked well for enamides where R is an alkyl substituent, and method B for enamides where R is an aromatic substituent. Also, the chiral ynamide (**23**), the first chiral equivalent and electron deficient variant of Ficini's *N,N*-diethyl-1-amino-1-propyne, was prepared by this method in 50% yield (Scheme 12).²⁰



Scheme 12

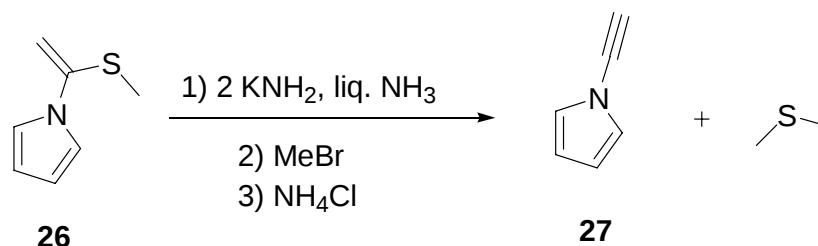
1.1.4 From ketene S, *N*-acetals

Ynamines can be prepared from *S*, *N*-acetals. 4-Phenylethynylmorpholine (**24**) is obtained by slow addition of β -methylthio- β -morpholinestylene (**25**) under nitrogen to sodium amide in boiling piperidine (Scheme 13).^{21,22}



Scheme 13

Thioamides and the corresponding ketene *S*, *N*-acetals are easily synthesized from amides by treatment with phosphorus pentasulfide alone or with alkylation, respectively. Both undergo elimination to ynamines on heating with excess of sodium or potassium amide. Using this method, Trofimov reported the synthesis of *N*-ethynylpyrrole (**27**) by the treatment of methyl vinyl thioether (**26**) with potassium amide in liquid ammonia (Scheme 14).²³

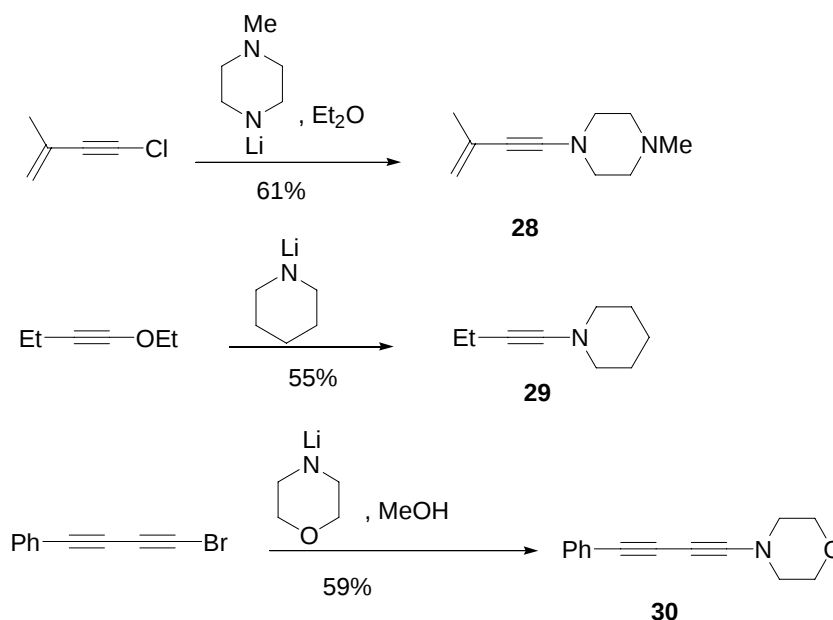


Scheme 14

1.2 By nucleophilic substitution

1.2.1 From alkyne and metal amides and tertiary amines

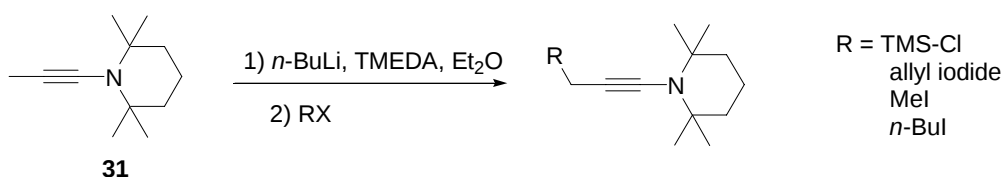
This is a general method to prepare tertiary ynamines (**28**, **29**, **30**) and involves nucleophilic substitution of the leaving group from substituted alkyne by metal amides and tertiary amines (Scheme 15).^{24,25}



Scheme 15

1.2.2 By functionalization of ynamines

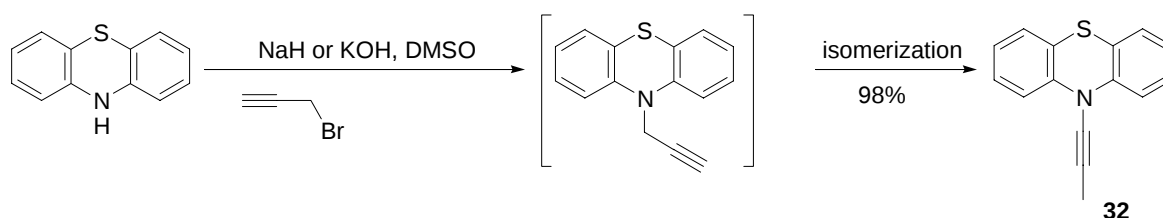
The propargyl protons of alkynyl substituted ynamines are acidic enough to be deprotonated with a strong base and the corresponding resonance-stabilized anion reacts with electrophiles at either the α - or γ -position. For example, the lithiated tetramethylpiperidino substituted ynamine (**31**) underwent γ -alkylation with a variety of electrophiles (Scheme 16).²⁶



Scheme 16

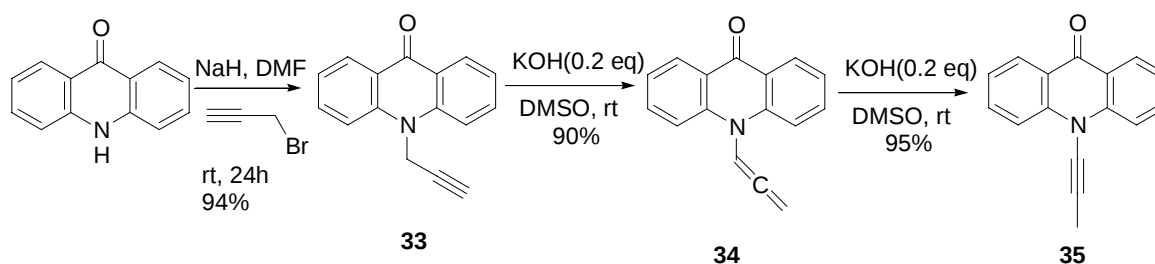
1.3 By isomerization reactions

Among the various methods for the preparations of ynamines, base-induced isomerization appears to be one of the most efficient. Reaction of propargyl bromide with phenothiazine in presence of sodium hydride led to the isolation of ynamine (**32**) (Scheme 17).²⁷



Scheme 17

In a recent report, the vinylogous ynamide (**35**) was prepared in 80% overall yield from acridone under similar conditions.²² It was found that isomerization of the propargylated acridone (**33**) can be stopped at the vinylogous allenamide intermediate (**34**) stage, but by extending the reaction time, isomerization of **34** led to **35** (Scheme 18).²⁸



Scheme 18

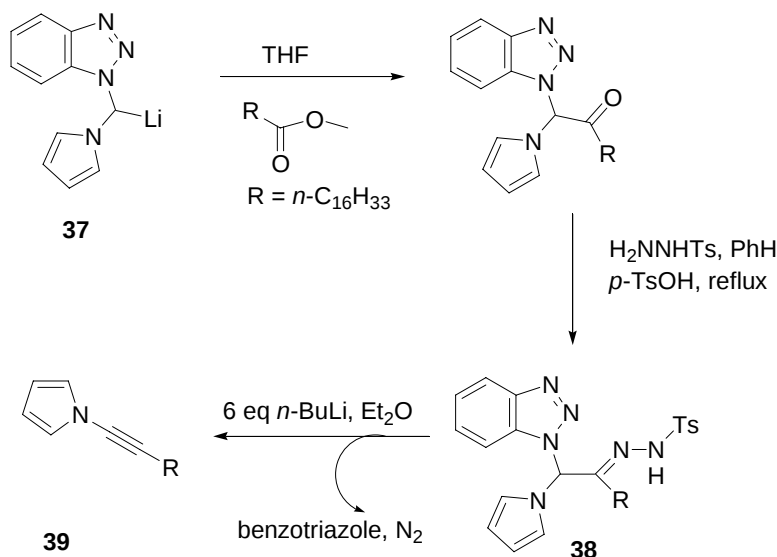
Using the same protocol, Fischer *et. al.* synthesized chiral ynamine (**36**).²⁹ Beginning with a chiral secondary amine, **36** was obtained in moderate yields upon reaction with propargyl bromide followed by isomerization with potassium *tert*-butoxide (Scheme 19).



Scheme 19

1.4 From benzotriazole intermediates

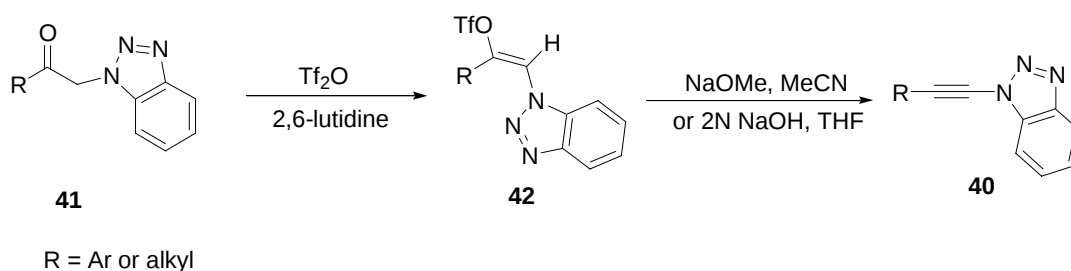
Our group has developed a convenient method for the construction of various alkynes from aromatic and aliphatic esters.³⁰ Acylation of carbanion (**37**) and subsequent tosylhydrazone formation gives **38** which undergoes Shapiro-type elimination, followed by the loss of benzotriazole and nitrogen, to generate pyrrole-ynamine (**39**) (Scheme 20).



Shapiro-type elimination

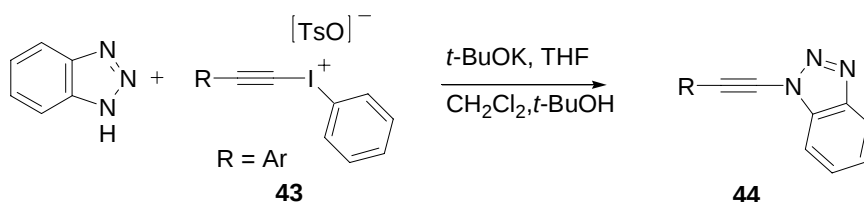
Scheme 20

Benzotriazole ynamines (**40**) can be generated from *N*-(acyl-methyl)benzotriazoles (**41**) via enol triflates (**42**) by treatment with either sodium methoxide or aq. sodium hydroxide (Scheme 21).³¹



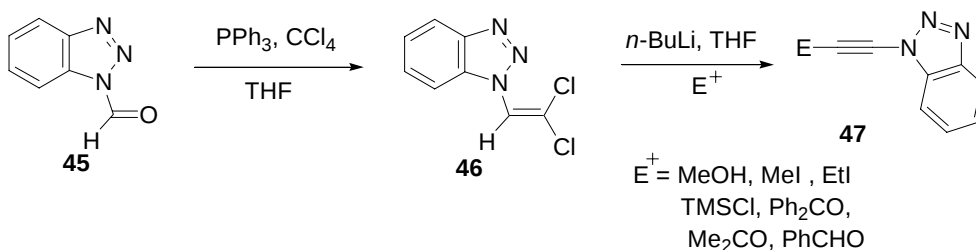
Scheme 21

Tosylate salts have also been used in the synthesis of benzotriazole ynamines (**44**) via reaction of alkynyliodonium salts (**43**) with benzotriazole (Scheme 22).³²



Scheme 22

Recently, we devised a method to prepare various functionalized *N*-ethynylbenzotriazoles (**47**) from the commercially available 1-formylbenzotriazole (**45**) in two steps *via* lithiation-substitution of the intermediate dichlorovinylbenzotriazole (**46**) (Scheme 23).³³

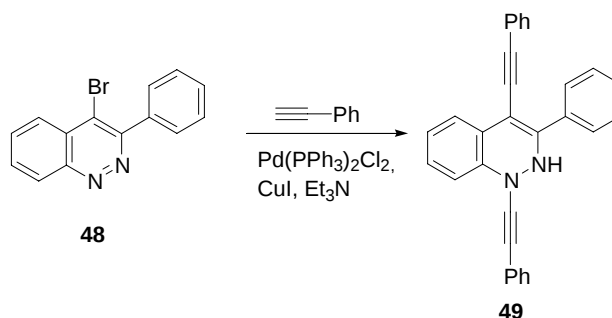


Scheme 23

1.5 Miscellaneous methods

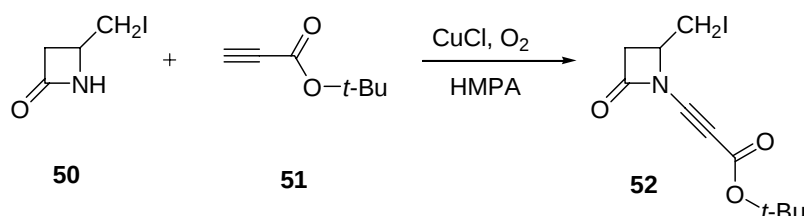
1.5.1 From metal-mediated coupling reactions

Bromocinnoline derivatives (**48**) were found to undergo palladium catalyzed amination when treated with phenylacetylene in the presence of palladium catalysts and copper(I) salts to give the phenyl-ethynyl-heterocycle (**49**) (Scheme 24).³⁴



Scheme 24

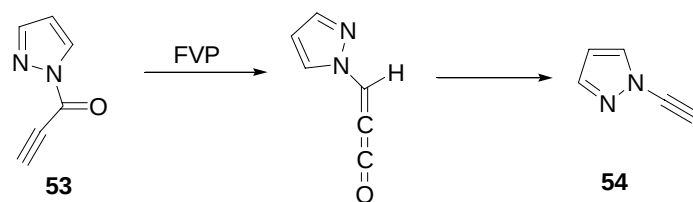
A Cu(I) mediated oxidative process that was intended for coupling *t*-butyl propiolate (**50**) to the alkyl halide (**51**) (Scheme 25) resulted in the unexpected formation of the β -lactam ynamide (**52**).³⁵



Scheme 25

1.5.2 By flash vacuum pyrolysis

Brown was able to detect the pyrazoloynamines (**54**) as a minor product when subjecting amide (**53**) to flash vacuum pyrolysis (Scheme 26).³⁶ This component is believed to be formed by rearrangement of **53** with migration from N-1 to N-2, followed by the loss of CO from the resultant propadienone and 1,2-hydride shift.

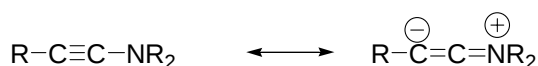


Scheme 26

2 REACTIONS OF *N*-ETHYNYL-HETEROCYCLES

2.1 Reactivity of *N*-ethynyl-heterocycles

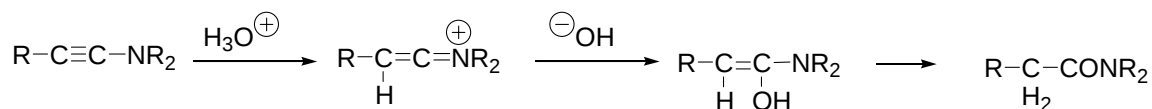
The N atom directly bonded to a carbon carbon triple bond makes ynamines a more effective nucleophile due to the resonance interaction between nitrogen and the triple bond (Scheme 27).



Scheme 27

The substituents on the nitrogen atom play a very important role in determining the reactivity of ynamines. So far, the most reactive ynamines are those bearing an alkyl group on the nitrogen, which in some cases makes it difficult to utilize them without special precautions to avoid their hydration or polymerization. However, a *N*-heterocycle substituent can stabilize ynamines by steric as well as electronic effects. For example, *N*-morpholinoacetylene has been the reagent of choice when other ynamines bearing alkyl substituents on the nitrogen atom are difficult to handle.^{1a}

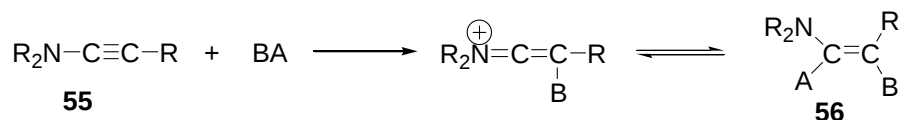
Ynamines can react as if they were electrophiles, especially under acid catalysis, when reactions probably proceed *via* a ketene-iminium intermediate (Scheme 28).³⁷



Scheme 28

2.2 Addition reactions

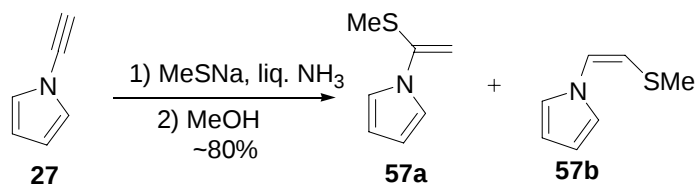
The addition of ynamine to a polar molecule of type $\text{A}^{\delta-}-\text{B}^{\delta+}$ leads to a ketene-immonium salt intermediate (55) which can be trapped by nucleophiles to give adducts (56) (Scheme 29).^{1a}



Scheme 29

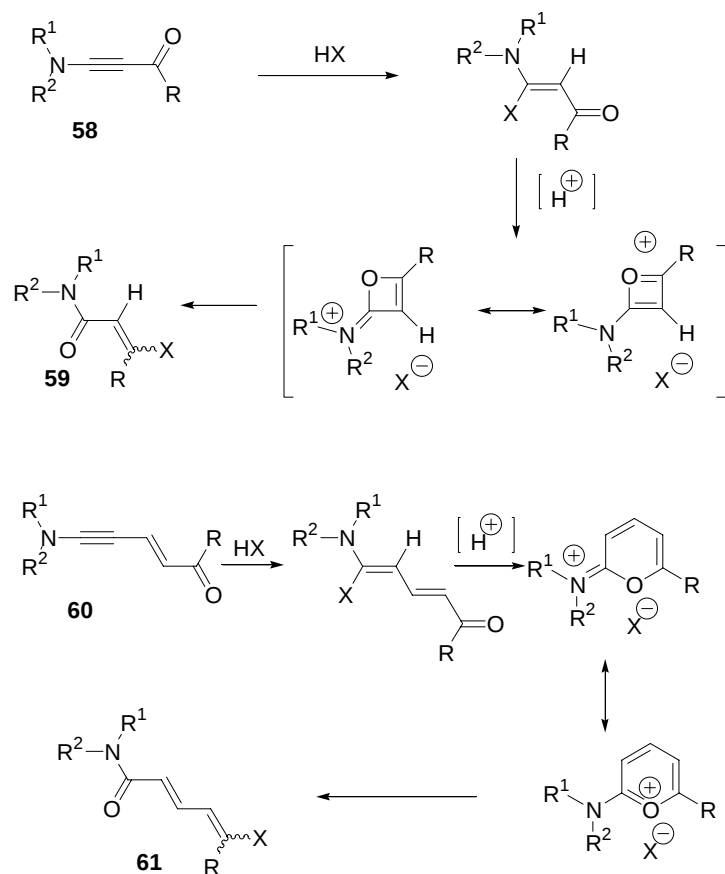
Likewise sodium methanethiolate adds to ethynylpyrrole (27) to give the substituted vinylpyrroles (57a)

and **(57b)** (Scheme 30).²³



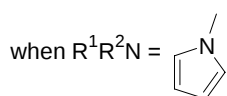
Scheme 30

Dialkylaminopropinals (**58**, **60**) react with hydrogen halides or acids as conjugated “push-pull” (PP) acetylenes to generate dienes in high yield via addition of hydrogen halides or acids (Scheme 31).³⁸ Rearrangement of dienes to 2-aminopyrylium salts occurred by further treatment of the dienes with acid, which ring-opened on reaction with nucleophiles to form amides (**59**, **61**).



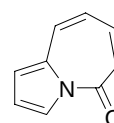
when $R^1R^2 = -(CH_2)_2O(CH_2)_2-$, $X = PhO^-$

Y: 66%



$X = PhO^-$

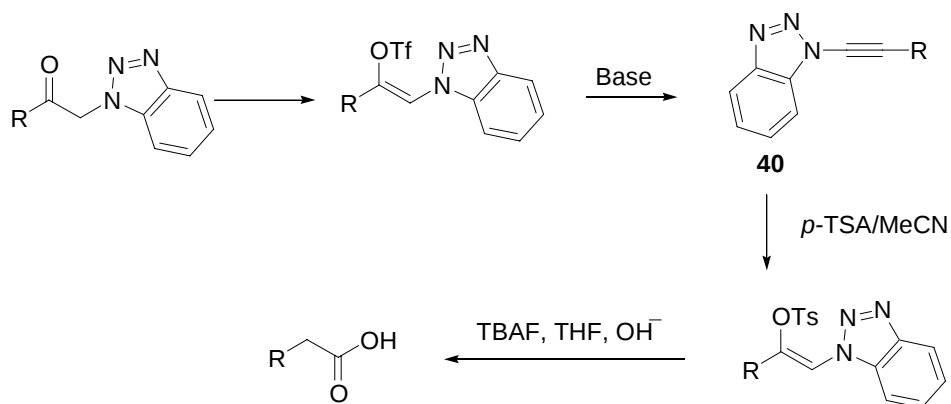
cyclized product isolated in 70%



Scheme 31

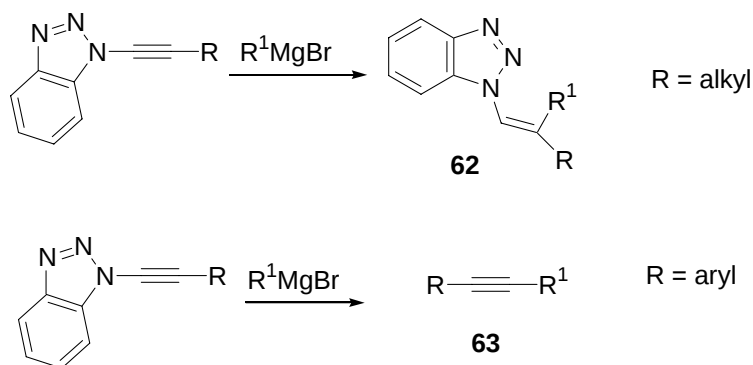
Our group has developed an efficient one-carbon homologation procedure for carboxylic acids and esters.³⁰ Synthesis of the benzotriazole ynamine (**40**) from *N*-(acyl-methyl)benzotriazoles is followed by

addition reaction of *p*-toluenesulfonic acid and by treatment with a base to give the homologated carboxylic acids and esters (Scheme 32).



Scheme 32

Recently, we found that treatment of 1-alkylethynylbenzotriazoles with Grignard reagents in dry toluene at $-45\text{ }^\circ\text{C}$ to $20\text{ }^\circ\text{C}$ afforded only the *cis* addition products (**62**) in high yields instead of the expected substitution products (**63**), which could be formed from 1-arylethynylbenzotriazoles under similar conditions (Scheme 33).³⁹



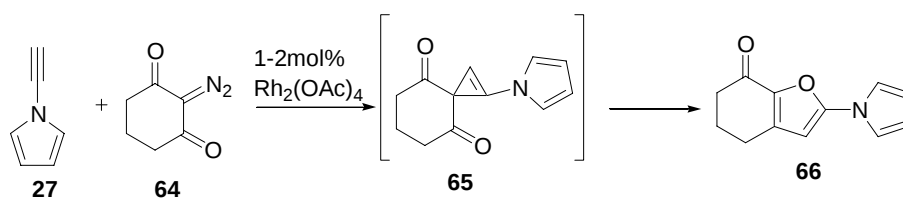
Scheme 33

2.3 Cycloaddition reactions

N-Ethynyl-heterocycles can react as two electron components in cycloaddition reactions.

2.3.1 [2+1] Cycloadditions

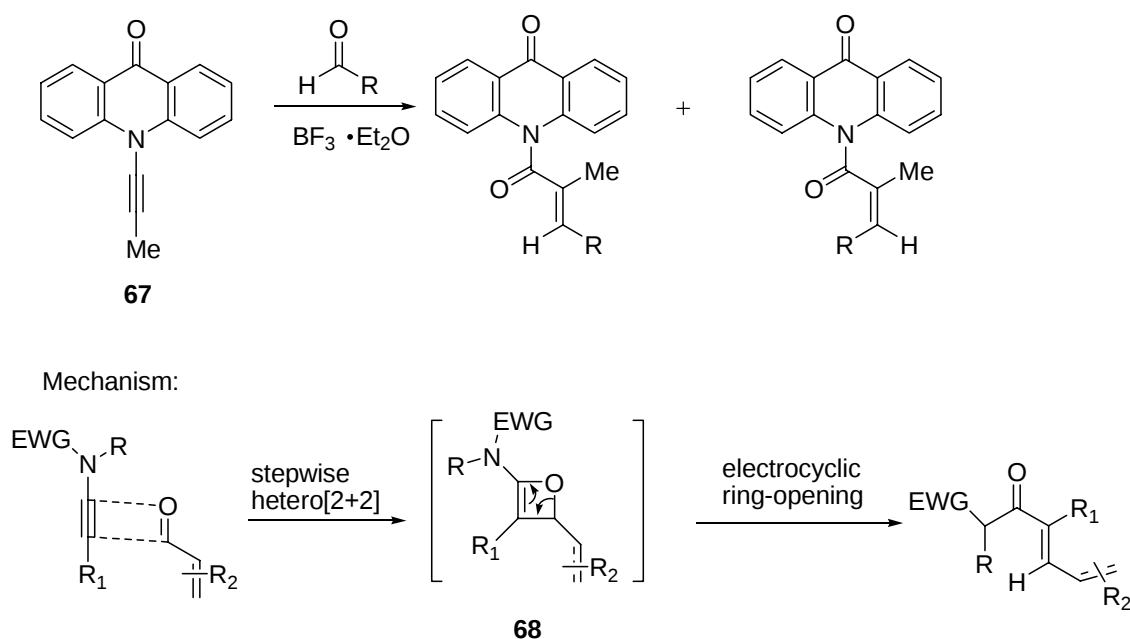
Pirrung has found that *N*-ethynylpyrrole (**27**) can react as a two electron component in [2+1] cycloadditions (Scheme 34) with the rhodium carbenoid generated from (**64**).⁴⁰ The intermediate cyclopropene (**65**) can not be isolated since it undergoes ring opening and recyclization to afford furan (**66**).



Scheme 34

2.3.2 [2+2] Cycloadditions

Hsung reported the first reactivity study of an electron deficient ynamine toward aldehyde in hetero [2+2] cycloaddition reactions promoted by Lewis acids.⁴¹ Treatment of various aldehydes with 10-propynyl-9(10*H*)-acridone (**67**) in $\text{BF}_3 \cdot \text{Et}_2\text{O}$ provided a highly stereoselective synthesis of trisubstituted alkenes (Scheme 35). As shown in the mechanism, hetero [2+2] cycloaddition reactions of electron- deficient ynamines with aldehydes could lead to an oxetene intermediate (**68**), which undergoes an electrocyclic ring opening to give the alkane.

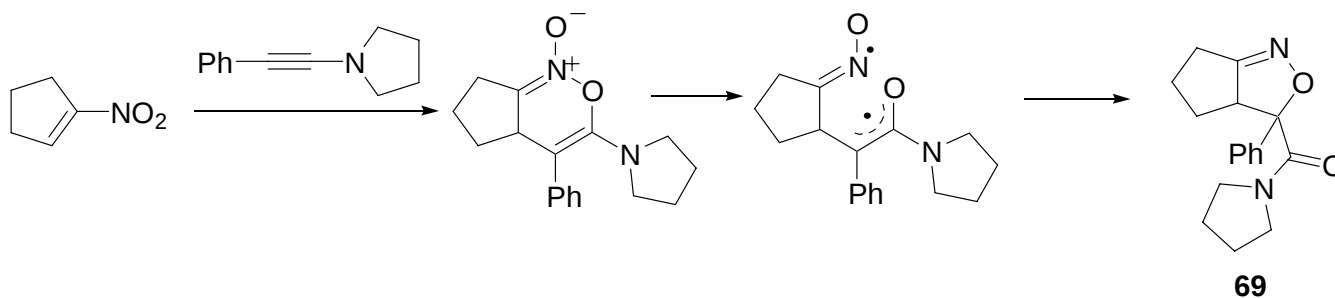


Scheme 35

2.3.3 [4+2] Cycloadditions

2.3.3.1 [4+2] Cycloaddition of nitroalkenes with ynamines

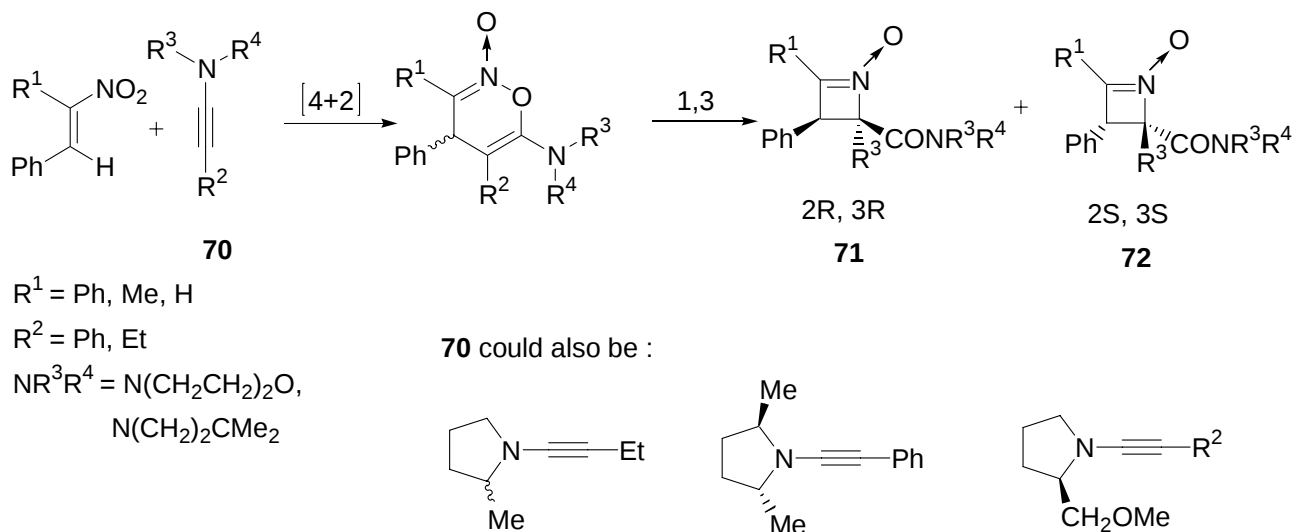
Pennings reported the reaction of 1-nitrocyclopentene with 1-phenyl-2-(1-pyrrolidiny)acetylene to generate compound (**69**) (Scheme 36).⁴²



Scheme 36

Four-membered cyclic nitrones represent a relatively new class of heterocycles with an extremely reactive

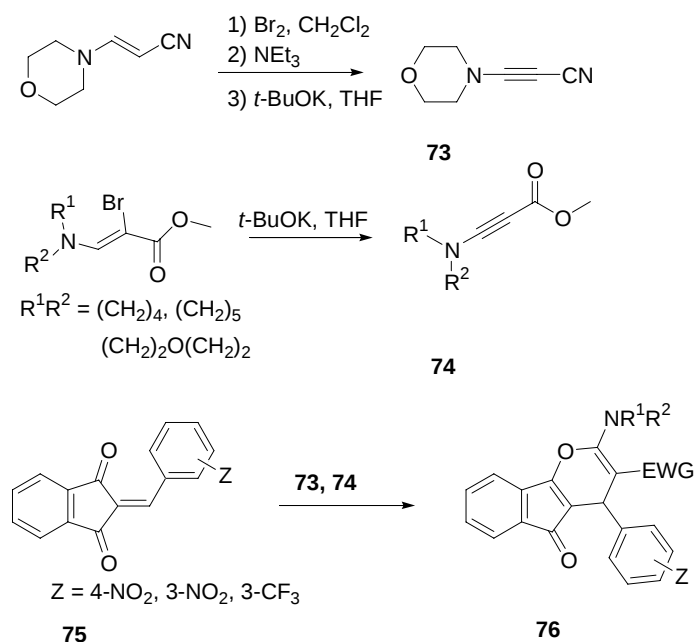
nitronone moiety. A series of four-membered cyclic nitrones (**71**, **72**) can be synthesized with high stereoselectivity by reaction of nitroalkenes and ynamines (**70**) (Scheme 37).⁴³



Scheme 37

2.3.3.2 Hetero-Diels-Alder reaction

Dell reported a hetero-Diels-Alder approach to synthesize pyrans (**76**) by reaction of ynamine nitrile (**73**) and ynamine ester (**74**) with **75** (Scheme 38).⁴⁴

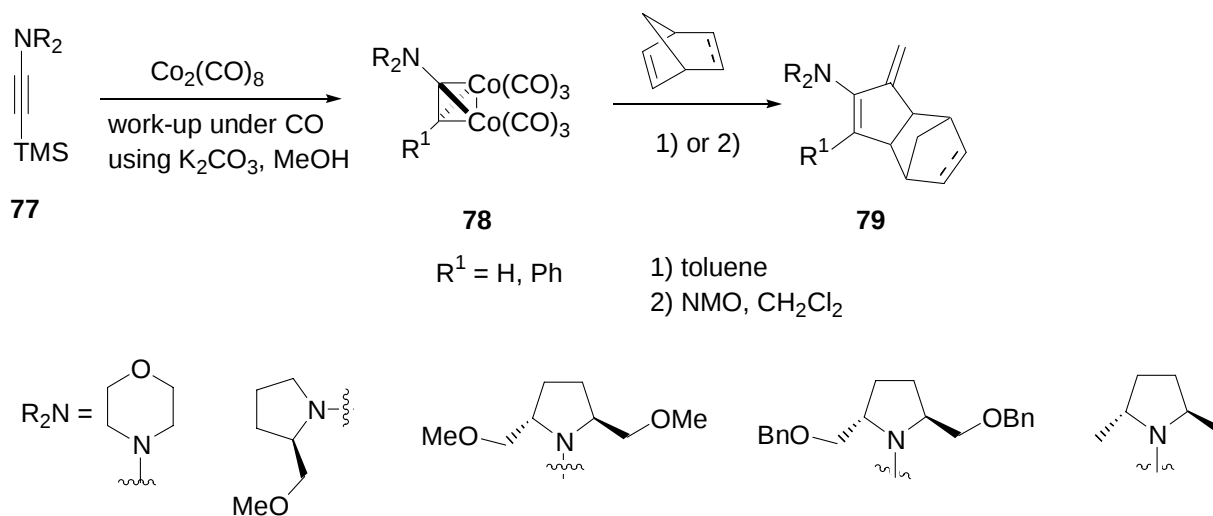


Scheme 38

2.3.4 Metal-mediated cycloadditions

Pericas reported an elegant utilization of chiral ynamine (**77**) in a Pauson-Khand reaction which involves complexation of the ynamines as the dicobalt hexacarbonyl complex (Scheme 39).⁴⁵ Complexes (**78**) were very stable, could be stored under CO atmosphere for months, and could be purified by

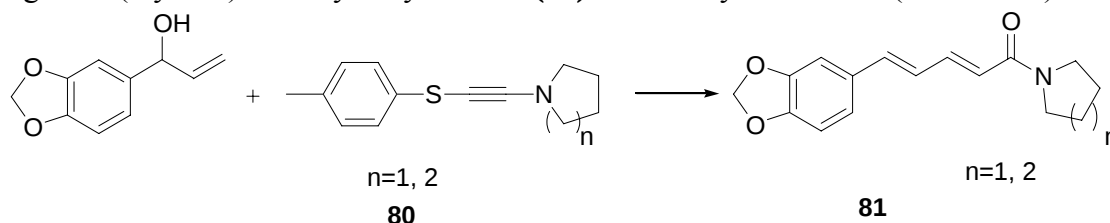
chromatography. Pauson-Khand reaction of **78** with norbornene or norbornadiene generated cycloadducts (**79**) as diastereomeric mixtures.



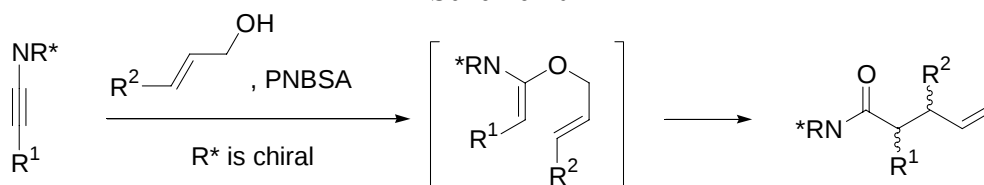
Scheme 39

2.4 Ynamine-Claisen rearrangement

The Ynamine-Claisen rearrangement was first developed by Ficini, in which the reaction of an allylic alcohol with ynamines affords the rearranged γ,δ -unsaturated amides *via* the ketene *N,O*-acetal intermediate.⁴⁶ Takeshi *et.al* used this method for the stereocontrolled synthesis of conjugated dienamides (**81**) starting from (aryltio)heterocyclic ynamines (**80**) and an allylic alcohol (Scheme 40).⁴⁷

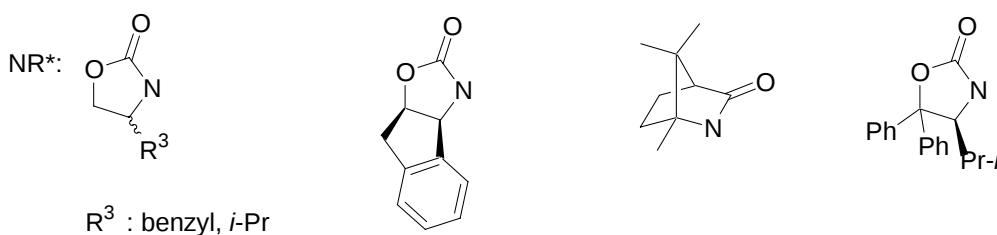


Scheme 40



PNBSA: *p*-nitrobenzenesulfonic acid

R^1 : Ph, *n*-pentyl, *n*-Bu, *i*-Pr, cyclohexyl, R^2 : Me, Ph, CH_2OBn

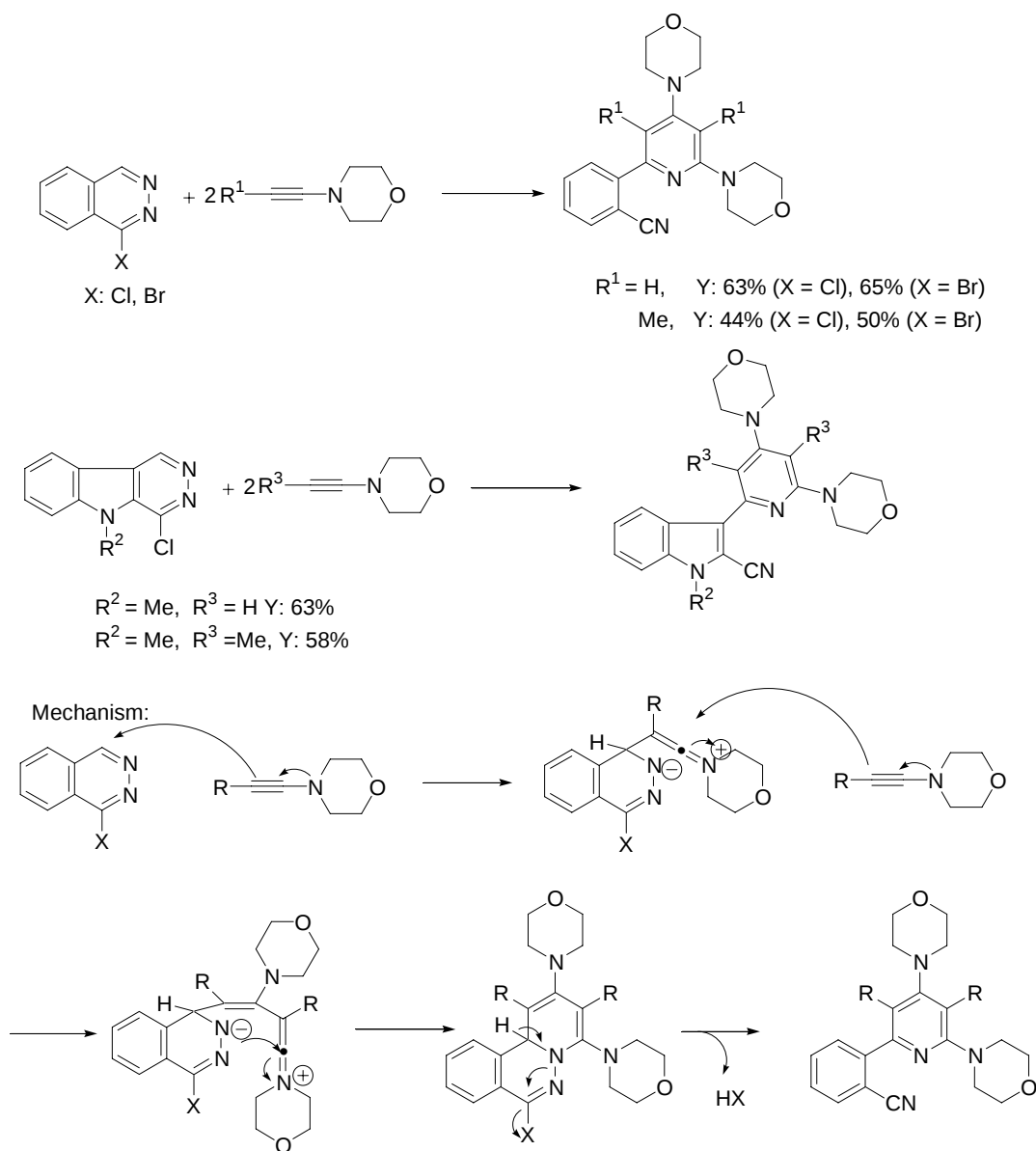


Scheme 41

Recently, Hsung has extended the application of this method by the reaction of chiral heterocyclic ynamide with allylic alcohol to give ketene *N,O*-acetal intermediates followed by stereoselective rearrangement to furnish Ficini-Claisen products (Scheme 41).⁴⁸

2.5 Ynamines as nucleophiles

The triple bond of ynamine is electron rich because of the electron donating ability of nitrogen. It can attack electron deficient carbon as a nucleophile to form a new carbon-carbon bond. Iwamoto *et al.* reported the synthesis of penta-substituted pyridines and 3-(2-pyridyl)indoles by this methodology and established a new N-N bond cleavage reaction of pyridazine through nucleophilic attack by ynamines (Scheme 42).^{49,50}

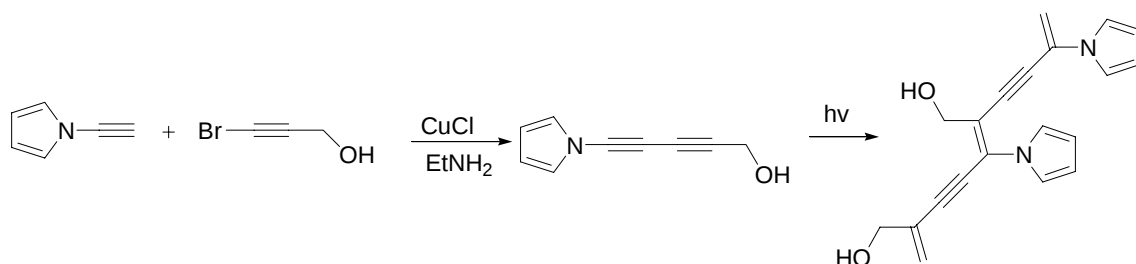


Scheme 42

2.6 Polymerization

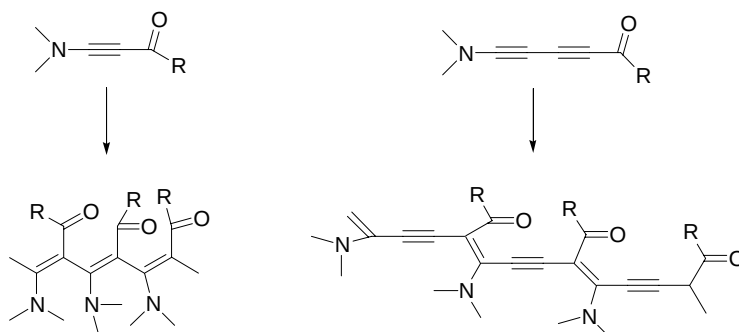
Paley investigated the synthesis, vapor growth, polymerization and characterization of thin films of novel

diacetylene derivatives of pyrrole which readily polymerize to poly(diacetylenes) (Scheme 43).¹²



Scheme 43

Likewise, Berger reported solid-state polymerization of crystalline stacked ‘push-pull’ acetylenes (Scheme 44).⁴¹



Scheme 44

3 CONCLUSION

The role of *N*-ethynyl-heterocycles in organic synthesis has grown tremendously over the last 20 years. Their diverse range of activity allows them to act as stabilized ynamines, and to be precursors to make heterocycles, alkaloids and functionalized polyacetylenes. The extension of this area offers promising synthesis both in biomedical and material science.

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