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Chemistry of 1-aza-1,3-enynes: achievements and key trends of development

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The data on the chemistry of 1-aza-1,3-enynes published in the past 15 years have been summarized and systematized. Achievements in the synthesis of these compounds, as well as their transformations into various acyclic and heterocyclic nitrogenous products, have been surveyed. Particular attention has focused on the addition reactions at the azomethine and/or carbon – carbon triple bonds. Practical applications of the products of these transformations, first of all, in synthesis of complex natural and biologically active compounds, are discussed.
The bibliography includes 161 references.

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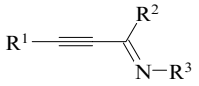
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I. Introduction

The persistent interest of organic chemists in 1-aza-1,3-enynes† is fuelled, among other factors, by the high synthetic potential of such compounds caused by the existence of a system of conjugated multiple bonds involving an sp^2-hybridized nitrogen atom, a triple carbon – carbon bond and an azomethine (aldimine or ketimine) bond.

The specific chemical structure of these systems determines their ability to add to nucleophilic, 1,3-dipolar and electrophilic reagents.[1,2] A unique feature of 1-aza-1,3-enynes is that their addition reactions are chemospecific or regiospecific, which enables the realization of the chemical design principle so that one of the multiple bonds can be involved in reaction while the other remains intact. For example, this strategy has been used to synthesize analogues of natural antibiotic thienomycin.[1] For this reason, 1-aza-1,3-enynes are believed to be convenient synthons for targeted synthesis of polyfunctional compounds, which are of interest for different areas of modern chemistry, such as organometallic, pharmaceutical and medicinal chemistry.[3]

Structures of 1-aza-1,3-enynes



R^1 = Alk, Ar, Het, $SiAlk_3$, $GeAlk_3$; R^2 = H, Alk, Ar, R^F, $SiAlk_3$, CO_2Alk; R^3 = Alk, Ar, Het, $P(O)Ph_2$, NH_2, NHAlk, NHAr, NHC(O)Ar, $NAlk_2$, NAr_2, NAlkAr, OH, OAlk, OAr, S(O)Alk, S(O)Ar, SO_2Alk, SO_2Ar, *etc.*; R^F is fluorine-containing alkyl group

It should be noted that, in the chemical literature, 1-aza-1,3-enynes are often referred to as alkynylimines, propargylimines, α,β-acetylenic aldimines, acetylenic azomethines and acetylenic ketimines. They actually denote the same 1-aza-1,3-enynes but containing definite functionalities; for example, β,γ-alkynyl-α-iminoesters are formally aza-1,3-enynes with an ester moiety.

† This refers to derivatives of propargyl aldehyde imine, which are treated as aza analogues of conjugated enynes in the context of the present review, the simplest of them being vinylacetylene.

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More than 15 years have passed since the moment of publication of the first review by Stadnichuk *et al.*[1] devoted to the chemistry of 1-aza-1,3-enynes. Since that, there have been published in this area of chemistry numerous studies that need to be summarized and systematized. Of spectral note is the review by Shimizu *et al.*[3] addressing conjugated imines, in which one of the considerable sections deals with 1-aza-1,3-enynes (alkynylimines).

Nearly all of the reactions considered in the review afford products in good yield, often higher than 80% or even 90%. In this context, we report the yields only when they are low or when there is only one example of some transformation.

In the present review, we focus on the potentialities of synthetic methods and the use of 1-aza-1,3-enynes as synthons for formation of different organic compounds and discuss mainly new data concerning the chemistry of 1-aza-1,3-enynes, trends in development of this field of science and recent quantum leaps. Some gaps in the study of such compounds and some important aspects that have received little attention of experts are also considered.

II. Basic methods of synthesis of 1-aza-1,3-enynes

The currently used methods of synthesis of 1-aza-1,3-enynes can be divided into the following groups:

— condensation of acetylenic aldehydes and ketones with primary amines;

— cross coupling of terminal alkynes;

— reactions with elimination of hydrocarbon halides and formation of multiple bonds in an aliphatic chain;

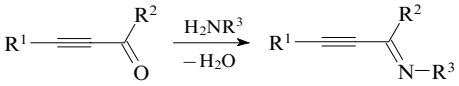
— special methods.

This classification is convenient since it allows one to easily determine the approach to synthesis of target compounds, as well as to predict the possibilities of introducing certain substituents into 1-aza-1,3-enynes, depending on the task.

II.1.Condensation of acetylenic aldehydes and ketones with amines

The general procedure for synthesis of 1-aza-1,3-enynes based on condensation of acetylenic aldehydes and ketones with primary amines is shown in Scheme 1.[1] Reactions with acetylenic aldehydes proceed under mild conditions in nearly quantitative yield.

Scheme 1



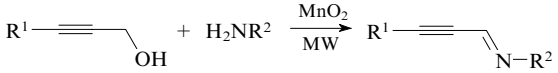
R^1 = Alk, Ar, Het, $SiMe_3$, $GeEt_3$; R^2 = H, Alk, Ar, Het; R^3 = Alk, Ar, NH_2, NHAlk, NHAr, NHC(O)Ar, $NAlk_2$, NAr_2, NAlkAr, OH, S(O)Alk, S(O)Ar, SO_2Alk, SO_2Ar, P(O)Ph_2

As a rule, 1-aza-1,3-enynes exist as a mixture of *Z* and *E* isomers,[4] with predominance of the latter.[5–7] Acetylenic ketones condense with aliphatic primary amines[8,9] to give *N*-alkyl-1-aza-1,3-enynes in the presence of titanium(IV) butoxide or ethoxide.[8] Acetylenic aldehydes and ketones react with hydrazines and hydrazides [R^3 = NH_2, NHAlk, NHAr, NHC(O)Ar, $NAlk_2$, NAr_2, NAlkAr] to yield alkynyl hydrazones,[10–12] and their reaction with hydroxylamine (R^3 = OH) leads to alkynyl oximes (see Scheme 1).[13]

Condensation with amides occurs less readily: in particular, propynals react with diphenylphosphoramide in the presence of titanium(IV) tetrachloride.[14] *tert*-Butylsulfinamide[15] and sulfonamides[16] react with acetylenic aldehydes and ketones to give corresponding 1-aza-1,3-enynes in the presence of titanium(IV) alkoxides, for example, titanium tetraethoxide (see Scheme 1).

In the presence of primary amines under MW irradiation, selective oxidants, such as MnO_2,[17] converts *in situ* propargyl alcohols into acetylenic aldehydes. This reaction is believed to be one of the most convenient routes to 1-aza-1,3-enynes (Scheme 2).

Scheme 2



R^1 = Pr^i, Bu^t, Ph, $SiMe_3$; R^2 = Alk, Ar, Het

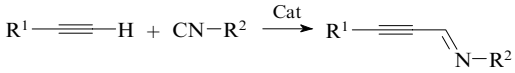
This method is applicable to the synthesis of silicon- and germanium-containing α,β-acetylenic aldimines. The silicon- and germanium-containing substituents in the initial propargyl alcohol remain intact after this transformation.[17]

II.2. Cross-coupling reactions of terminal alkynes

II.2.a. Coupling with aliphatic isonitriles

1-Aza-1,3-enynes form from terminal alkynes and aliphatic isonitriles in the presence of catalysts (Cat) — uranium,[18] thorium and rare earth complexes (Scheme 3).[19–23]

Scheme 3

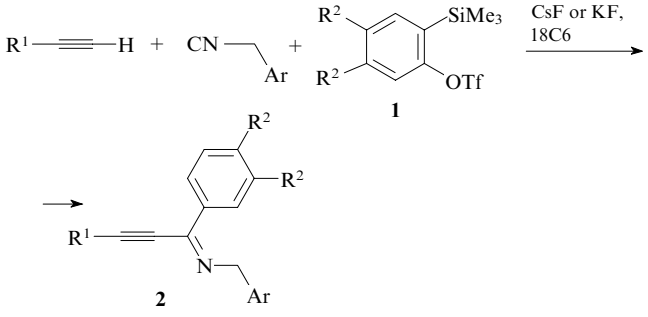


R^1 = Alk, Ar, $SiMe_3$; R^2 = Alk; Cat = $(\eta\text{-}C_5Me_5)_2ThMe_2$, $[(Et_2N)_3U][BPh_4]$

The stereoselectivity of this reaction can be controlled by varying the complexes. In particular, in the presence of catalytic amounts (1 mol.%–2 mol.%) of 'half-sandwich' yttrium complexes, the reaction affords in high yield 1-aza-1,3-enynes as the *Z* stereoisomer.[22] The use of thorium complex $(\eta\text{-}C_5Me_5)_2ThMe_2$ (Ref. 20) and cationic uranium complex $[(Et_2N)_3U][BPh_4]$ (Ref. 20) also leads exclusively to the *Z* isomer; however, with a lapse of time, the latter converts into the thermodynamically more stable *E* isomer.[18,20]

The reaction of terminal alkynes, (arylmethyl)isonitriles, and substituted 2-(trimethylsilyl)phenyl triflates **1** in the presence of caesium or potassium fluoride and 18-crown-6 (18C6) leads to *N*-arylmethyl-1-aza-1,3-enynes **2** (Scheme 4).[8]

Scheme 4



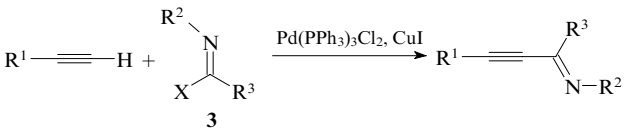
R^1 = Ar, Alk; R^2 = H, Me; Tf is trifluoromethanesulfonyl (triflyl)

It has been shown[24] that the use of carbodiimides instead of isonitriles under analogous conditions affords 2-aminoaryl-1-aza-1,3-enynes. The reaction of terminal alkynes with *tert*-butylisonitrile and aryl- or hetaryl bromides in the presence of palladium(II) acetate leads to corresponding acetylenic ketimines.[25]

II.2.b. Coupling with imidoyl halides

Currently, the most widely used method of synthesis of acetylenic ketimines is cross-coupling of terminal alkynes with imidoyl halides **3**. This route is often considered as a version of the Sonogashira reaction,[26,27] since it is catalyzed by palladium and copper compounds (Scheme 5).[28–30]

Scheme 5



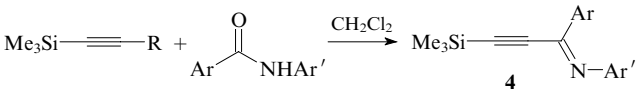
R^1 = Ar, Alk, $SiMe_3$; R^2 = Alk, Ar, CF_2Br; R^3 = Alk, Ar, OMe, NHAr; X = Cl, I

This route under mild conditions leads in good yield to acetylenic ketimines, including α-perfluoroalkyl-substituted derivatives.[31] The introduction of *N*-alkoxyimidoyl iodides into a similar reaction gives alkynyl oximes,[27] while the reaction with *N*-hydrazonyl chlorides in the presence of copper(I) iodide leads to alkynyl hydrazones.[32]

II.2.c. Coupling with carboxamides

The synthesis of silicon-containing acetylenic ketimines **4** from aromatic carboxamides and copper(I) trimethylsilylacetylenide has been reported by Movassaghi and Hill[33–35] (Scheme 6).

Scheme 6



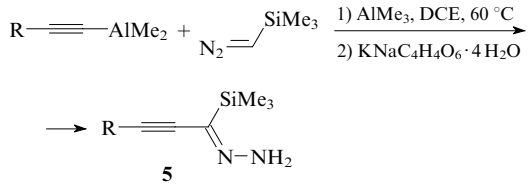
R = Cu, $SiMe_3$

The copper-free synthesis of 1-aza-1,3-enynes has been accomplished with the use of 1,2-bis(trimethylsilyl)acetylene (R = $SiMe_3$) in the presence of triphenylphosphine oxide trifluoromethanesulfonate.[36] The use of other alkynes in this reaction, as a rule, leads to formation of by-products — substituted quinolines.[36]

II.2.d. Coupling with trimethylsilyldiazomethane

Kumar *et al.*[37] have reported a new route to α-silicon-containing alkynyl hydrazones **5**. Dimethylaluminium(III) acetylenides react with trimethylsilyldiazomethane in the presence of an equimolar amount of trialkylaluminium in dichloroethane (DCE) for 24 h (Scheme 7).

Scheme 7



R = Alk, Ar, Het

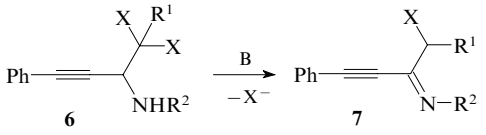
The target hydrazones are formed after the treatment of the reaction mixture with Rochelle salt for neutralizing the alkylaluminium derivatives.[37]

II.3. Reactions with elimination of hydrogen fluoride and chloride and formation of multiple bonds in the aliphatic chain

II.3.a. Dehydrohalogenation of halogen-containing propargylamines

Dehydrogenation of halogen-containing propargylamines **6** in the presence of strong bases (NaOH, NaOMe, $KOBu^t$) in THF leads to the corresponding acetylenic azomethines **7**.[38,39] Elimination of hydrogen halides affords the formation of the azomethine bond (Scheme 8).

Scheme 8



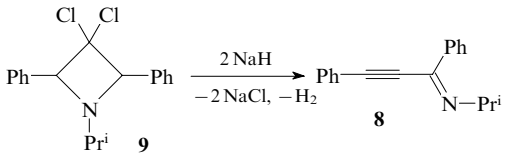
R^1 = H, Me, F, Cl; R^2 = Alk, Ar; X = F, Cl; B is base

This reaction enables the synthesis of fluoro and chloro derivatives of 1-aza-1,3-enynes, which are used as synthons for preparation of fluoro- and chloro-substituted heterocycles.

II.3.b. Dehydrohalogenation of dichloroazetidine

It has been suggested to synthesize acetylenic ketimine **8** from 3,3-dichloro-1-isopropyl-2,4-diphenylazetidine (**9**).[40] Elimination of two hydrogen chloride molecules under the action of NaH initiates ring opening and formation of conjugated triple and azomethine bonds (Scheme 9).

Scheme 9

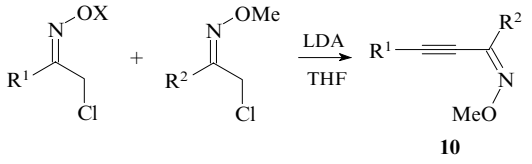


The reaction occurs in dimethyl sulfoxide in the presence of a sodium hydride excess at 50–60 °C; the yield is ~76%.

II.3.c. Condensation of α-chloro oxime esters

Cross-condensation of α-chloro oxime esters[41] in the presence of lithium diisopropylamide (LDA) leads to alkynyl oximes **10** predominantly as the *Z* isomers (Scheme 10).[42,43]

Scheme 10



R^1, R^2 = Alk, Ar; X = Ts, CO_2Et; Ts is *p*-toluenesulfonyl (tosyl)

It has been assumed that the reaction proceeds through the formation of intermediate 2-(iminomethyl)azacyclobutadiene with subsequent elimination of hydrogen cyanide.

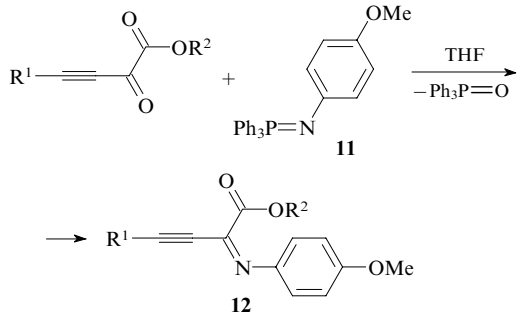
II.4. Special methods

Special methods of synthesis of 1-aza-1,3-enynes are of limited use since they afford only some compounds of this class.

II.4.a. Aza-Wittig reaction

β,γ-Alkynyl keto esters react with phosphinimine **11** to give β,γ-alkynyl-α-iminoesters **12** (formally 1-aza-1,3-enynes) (Scheme 11).[44,45] Phosphinimine **11** is synthesized from the corresponding azide and triphenylphosphine.

Scheme 11



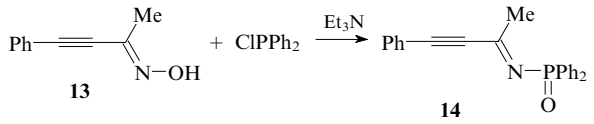
R^1 = Ar, Het, $SiAlk_3$; R^2 = Alk

The reaction occurs on heating under reflux in THF for 4 h and is currently used only for synthesis of β,γ-alkynyl-α-iminoesters **12**.

II.4.b. Phosphorylation of oximes

According to Graves *et al.*[46], 4-phenylbut-3-yn-2-one oxime (**13**) reacts with chlorodiphenylphosphine in the presence of Et_3N to give *N*-diphenylphosphinyl-1-aza-1,3-enyne **14** (Scheme 12).[47] Phosphorylation proceeds in anhydrous toluene at room temperature and is over in 1.5 h.

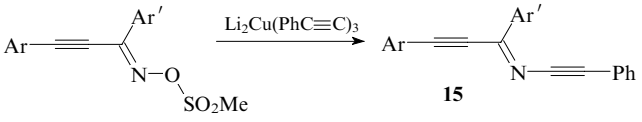
Scheme 12



II.4.c Alkynylation of oxime *O*-mesylates

To synthesize *N*-alkynyl-1-aza-1,3-enynes **15**, lithium–copper phenylacetylide is introduced into the reaction with alkynyl oxime mesylates.[48–50] The reaction proceeds in diethyl ether at low temperature (Scheme 13). The yields of this reaction are low (12%–31%).[48]

Scheme 13



N-Alkynyl-1-aza-1,3-enynes **15** are used in medicinal chemistry,[49,50] for example, in production of antitumour drugs.[51]

Thus, analysis of available data on the methods of synthesis of 1-aza-1,3-enynes shows that metal complex catalysis has been widely used in recent years, which has afforded otherwise hard-to-synthesize 1-aza-1,3-enynes. Using Lewis acids and d- and f-metal complexes as catalysts in the cross-coupling reactions of aliphatic isonitriles with terminal alkynes makes it possible to control stereoselectivity of formation of *E* (Ref. 18) or *Z* isomers of 1-aza-1,3-enynes.[22] Noticeable attention has been focused on the synthesis of fluoro- (Refs 31 and 52) and silicon-containing 1-aza-1,3-enynes. The latter is caused by the possibility of desilylation to 1-aza-1,3-enynes with a terminal triple bond, which can be introduced into alkyne–azide reactions (click chemistry reactions).

The increased interest of researchers in β,γ-alkynyl-α-iminoesters is caused by specific features of their structure, first of all, by their propensity to enolize. Noteworthy are reported methods of synthesis of 1-aza-1,3-enynes **2**,[8,24] since such reactions exclude the use of transition metal salts or complexes, which inevitably contaminate target products, and eliminate the need for subsequent refinement in the case of platinum metals.

III. Addition reactions at the azomethine bond

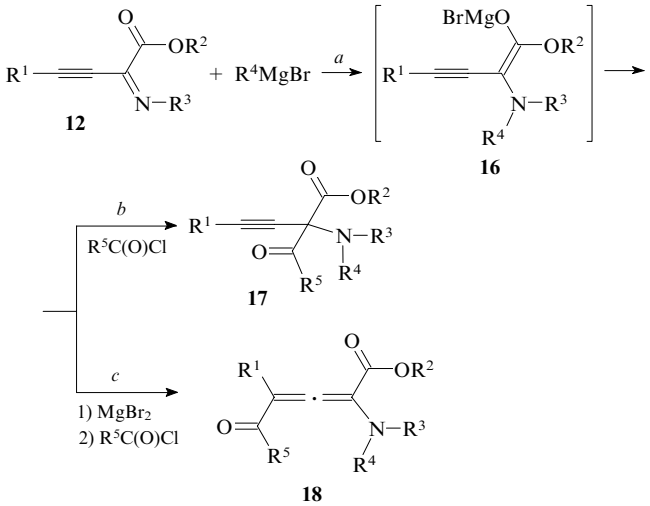
Mainly nucleophiles enter into the addition reactions at the azomethine bond of 1-aza-1,3-enynes. These reactions often proceed by the 1,2-addition mechanism. The nucleophile attack is, as a rule, directed at the most electrophilic atom of the azomethine group, *i.e.*, the carbon atom in the 2-position. Such a reaction is the most widely used method of synthesis of acetylene derivatives of α- and β-amino acids, amino alcohols and β-lactams.

III.1. Addition of organometallic reagents

The addition of Grignard reagents to 1-aza-1,3-enynes[1] usually occurs chemo- and regioselectively at the α-carbon of the azomethine group.[53]

However, the reaction of the Grignard reagent with β,γ-alkynyl-α-imino esters **12** (which are formally 1-aza-1,3-enynes) leads to alkylation of the nitrogen atom rather than the α-carbon atom (stage *a*). This has been attributed to a specific feature of the chemical structure of the initial compounds, namely to their propensity to enolization, which alters the direction of the nucleophilic attack.[45] The acylation of intermediate **16** with an excess of acyl chloride leads to difficult-to-synthesize α-alkynyl amino acids **17** (stage *b*) (Scheme 14). At the same time, the addition of

Scheme 14

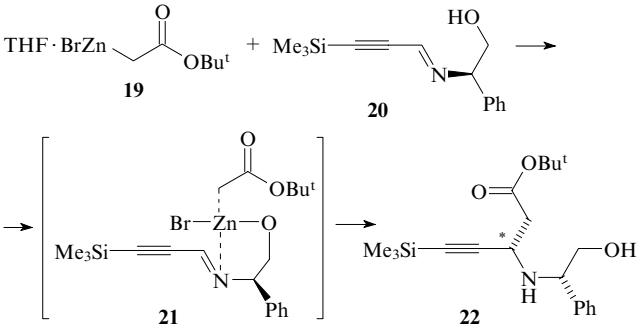


R^1 = Alkenyl, $SiAlk_3$, Ar, Het; R^2 = Et; R^3 = C_6H_4OMe-4; R^4 = Me, Et, Bn; R^5 = Alk, Ar, Het

$MgBr_2$ to the reaction mixture prior to the introduction of acyl chloride directs the electrophilic attack at the γ-carbon atom of intermediate **16** to give corresponding allenoates **18** (stage *c*).[45]

Organozinc compounds have been used with increasing frequency in synthesis in recent years. They are less reactive than their magnesium-containing analogues; however, when it is necessary to retain a functional group in the substrate, this weakness becomes an advantage. For example, the addition of Reformatsky reagent **19** to 1-aza-1,3-enyne **20** occurs by the classical mechanism[6] — at the azomethine bond and the α-carbon atom. However, stereospecificity of addition depends on the reactant ratio (Scheme 15).

Scheme 15



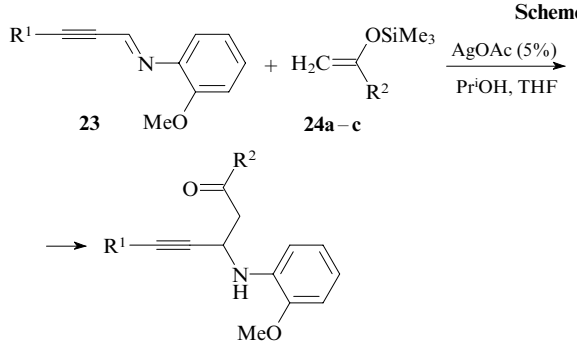
In has been highlighted that the reaction of equimolar amounts of the reactants presumably leads to intermediate zinc-containing chelate **21**, which can react with the second equivalent of the Reformatsky reagent to give the *S*,*S*-form of β-alkynyl-β-amino acid ester **22**.[6] Propargylamine **22** is a precursor of xemilofiban — a modern antiplatelet agent.

Zirconium-catalyzed enantioselective alkylation of *N*-aryl-1-aza-1,3-enynes with dialkylzinc in absolute isopropyl alcohol in the presence of a chiral polypeptide ligand (0.1 – 10 equiv.) has been described.[54] The method implies the preparation of optically pure substituted *N*-arylpropargylamines (60% – 85% yields).

III.2. Mannich-type addition

Reactions involving the azomethine bond are described in most of literature sources as Mannich-type reactions. A large body of studies has dealt with stereocontrolled reactions of 1-aza-1,3-enynes with CH-acids. There has been reported a catalytic enantioselective synthesis of β-aminoacetylene ketones[55] and β-aminoacetylene carboxylic acids[56] through the reaction of 1-aza-1,3-enynes **23** with acetone enol trimethylsilyl ether (**24a**), acetophenone enol trimethylsilyl ether (**24b**) or silyl ketene acetal **24c** in the presence of silver acetate and peptide chiral catalyst (Scheme 16).[57, 58]

Scheme 16

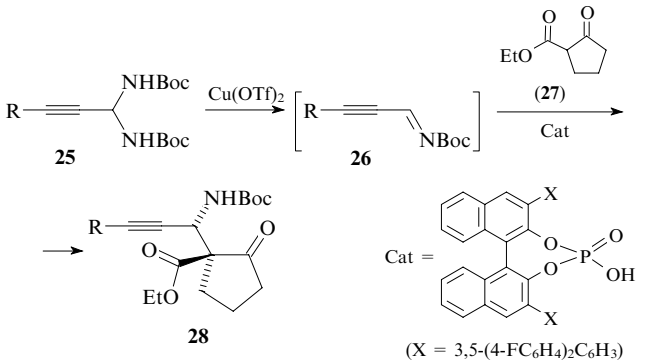


R^1 = Ar, Alk, $SiMe_3$; R^2 = Me (**24a**), Ph (**24b**), OPh (**24c**)

This reaction exemplifies the preparation of initial compounds intended for targeted synthesis of optically pure alkaloid sedamine derivatives.[55]

Acetylene aminals **25**, in the presence of copper(II) triflate, form *in situ* 1-aza-1,3-enynes **26**. The latter react with diethyl malonate and acetylacetone *via* a Mannich-type reaction to give the corresponding propargylamines.[59, 60] The use of chiral phosphoric acid, a 1,1′-binaphthyl-2,2′-diol [(*S*)-BINOL] derivative, as a catalyst in the reaction of 1-aza-1,3-enynes **26** with cyclic β-ketoester **27** in methylene chloride or toluene affords propargylamines **28** under mild conditions with high enantioselectivity and diastereoselectivity (Scheme 17).[60 – 63]

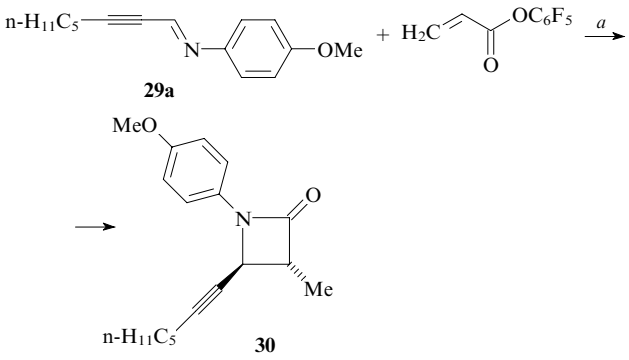
Scheme 17



R = Alk, Ar; Boc is *tert*-butoxycarbonyl

The reaction of 1-aza-1,3-enyne **29a** with perfluorophenyl acrylate in the presence of an iridium catalyst leads to alkyne-containing β-lactam **30**, existing predominantly in the *trans* configuration (Scheme 18).[64] The reaction proceeds in an excess of a mixture of perfluorophenyl acrylate, trialkylsilane and triphenyl phosphite, which provides the necessary stereoselectivity level of addition to give the corresponding *trans*-β-lactam in 58% yield.

Scheme 18



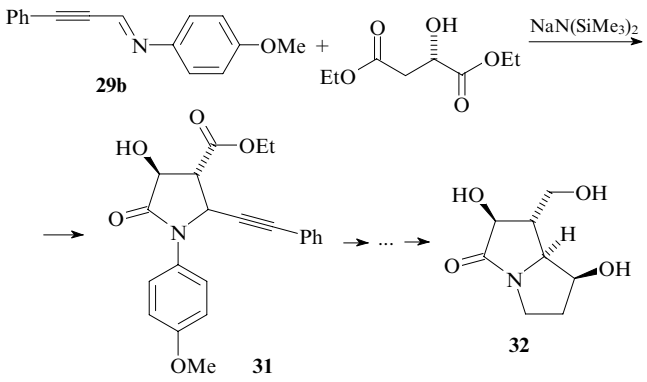
(*a*) [(cod)IrCl]$_2$, $(PhO)_3P$ (10%), Et_2MeSiH; cod is 1,5-cyclooctadiene

It has been reported[65] that *p*-anisidine and 3-phenyl-2-propynal imine (compound **29b**) react with diethyl (*S*)-malate in the presence of sodium bis(trimethylsilyl)amide to form substituted 2-pyrrolidone **31** (Scheme 19).

The latter has been used as a precursor in synthesis of pyrrolizidine alkaloid analogues, for example, compound **32**.[65]

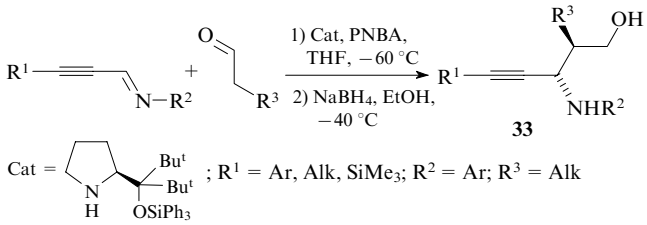
N-Aryl-1-aza-1,3-enynes react with aliphatic aldehydes under Mannich conditions in the presence of organic catalysts.

Scheme 19



An equimolar mixture of α,α-dialkylprolinol silyl ether and *p*-nitrobenzoic acid (PNBA) affords the necessary stereocontrol of the reaction leading to products **33** (Scheme 20).[66]

Scheme 20

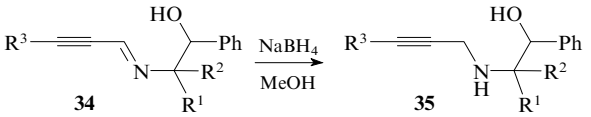


The addition reaction proceeds in THF at −60 °C and is over within 16–20 h, and the subsequent stage of reduction with sodium borohydride in ethanol leads to corresponding propargylaminoethanol **33** with high optical purity.

III.3. Ractions with sodium borohydride

Condensation of acetylenic aldehydes and aminoethanols leads to α,β-acetylenic aldimines **34**, and their reduction with sodium borohydride gives *N*-propargylaminoethanols **35** (Scheme 21).[67]

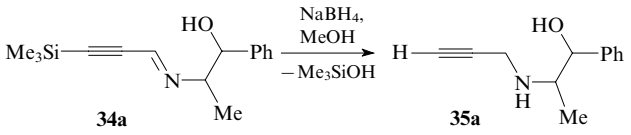
Scheme 21



N-Propargylaminoethanols **35** readily form air-stable crystalline hydrochlorides.[67] This is a one-pot route to 2-propargylaminoethanols, without isolation of intermediate alkynyliminoethanols. In this example, the role of sodium borohydride should be emphasized: it reduces the azomethine bond, while the triple bond remains intact; in the case of silicon-containing aldimine **34a**, sodium borohydride not only reduces the azomethine bond but also leads to the desilylation of the product (Scheme 22).

Hence, this method is applicable to synthesize *N*-propargylaminoethanols containing a terminal triple bond. The introduction of a terminal alkyne-containing moiety into

Scheme 22

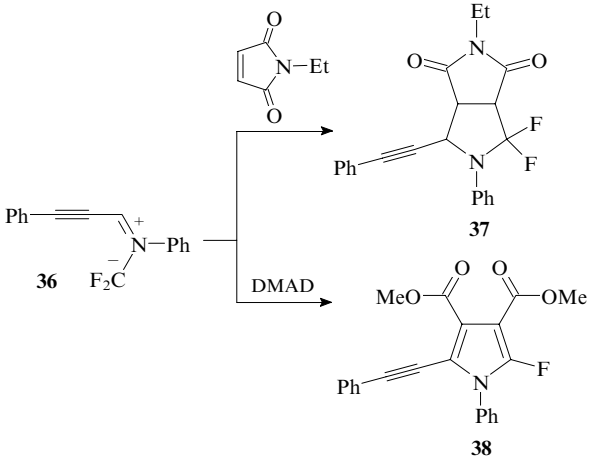


the starting molecule is realized through a one-pot route suitable for click reaction,[67] while isolation of the product as hydrochloride affords water-soluble derivatives.

III.4. Reaction with difluorocarbene

Aniline imine and 3-phenyl-2-propynal react with difluorocarbene, generated *in situ*, to give corresponding fluorinated azomethine ylide **36**. The latter adds to *N*-ethylmaleimide to form fluoro-containing tetrahydropyrrolo[3,4-*c*]pyrroledione **37**,[68] while the reaction of **36** with dimethyl acetylenedicarboxylate (DMAD) leads to substituted 2-fluoropyrrole **38** (Scheme 23).[69]

Scheme 23



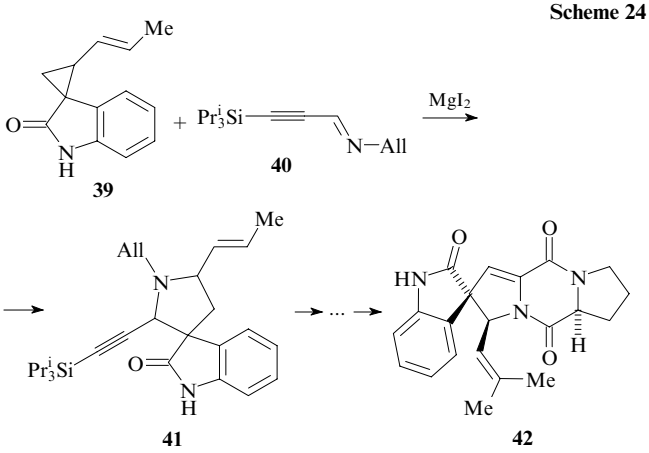
For lead-mediated generation of difluorocarbene from dibromodifluoromethane, common lead along with so-called 'active' lead, prepared by the reaction of lead acetate with sodium borohydride, is used as a reducing agent. It has been stated that the use of active lead decreases the reaction duration and increases the yields of target products.[69]

III.5. Addition of cyclopropane fragment

The addition of the cyclopropane fragment of spiro(cyclopropane-1,3′-oxindoles) **39** to 1-aza-1,3-enyne **40** leads to spiro(pyrrolidine-3,3′-oxindoles) **41**.[70,71] The reaction occurs in THF at 60–80 °C in the presence of an equimolar amount of magnesium iodide. The latter is believed to stabilize an intermediate species[70,71] formed upon opening of the cyclopropane moiety.[72] Marti and Carreira[72,73] have shown that 1-aza-1,3-enynes are key reagents in the synthesis of alkaloid Spirotryprostatin B (**42**), used in the treatment of leukemia (Scheme 24).

In this transformation, a classical approach of successive synthesis of alkaloid **42** is used: first, addition to the azomethine bond occurs, and then the triple bond is involved.[72] This protocol is an example of chemical design of a complex molecule based on 1-aza-1,3-enynes. The synthesis of alkaloid **42**, along with other examples,[74–78] demonstrates the possibilities of practical application of 1-aza-1,3-enynes.[79]

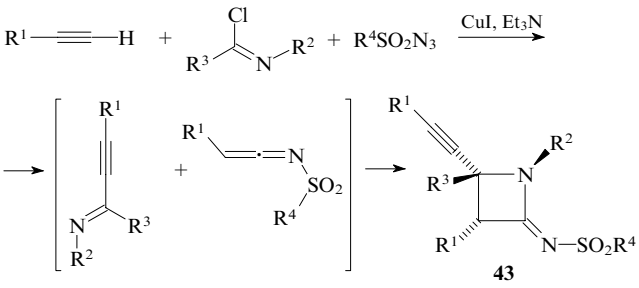
Scheme 24



III.6. Addition of ketenimines

A multicomponent stereoselective cascade synthesis of 4-alkynylazetidin-2-imines **43** from terminal alkynes, imidoyl chlorides and sulfonyl azide in the presence of copper(I) iodide as a catalyst and triethylamine has been described [80] (Scheme 25).[81]

Scheme 25



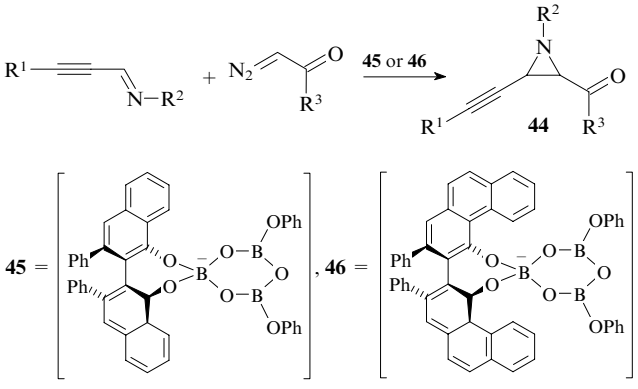
R^1, R^3 = Ar; R^2, R^4 = Ar, Alk

The authors convincingly prove that the reaction proceeds through the stage of formation of 1-aza-1,3-enynes,[81] while ketenimines are generated *in situ* in the course of reaction through decomposition of intermediate sulfonyl-1,2,3-triazoles — the products of Cu-catalyzed alkyne–azide cycloaddition.

III.7. Reactions with diazoacetic acid derivatives

The reaction of diazoacetic acid derivatives with α,β-acetylenic aldimines leads to alkyl-substituted aziridines **44** (Scheme 26).[82, 83] The reaction occurs in the presence of

Scheme 26



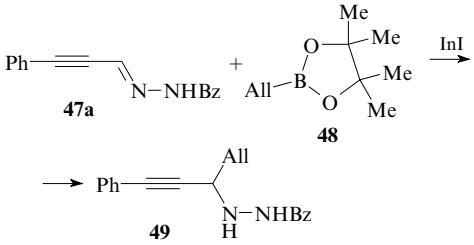
R^1 = Alk, Ar, $SiAlk_3$; R^2 = $CHAr_2$; R^3 = OEt, NHPh, $NHBu^n$

catalysts **45** and **46** (a protonated imine as a cation) based on boroxinates (*S*)-VANOL and (*S*)-VAPOL, respectively,[84] generated *in situ* from chiral biaryl ligands based on naphthalene and phenanthrene and $B(OPh)_3$ in the presence of azomethines. Sterospecificity of the resulting aziridines **44** depends on the reagent nature: for example, diazoacetamides form *cis*-aziridines, while diazoacetates form *trans*-aziridines.[82, 83]

III.8. Addition at the azomethine bond of 1-aza-1,3-enyne heteroanalogues

The addition reactions at the azomethine bond of N-substituted N-, O-, P- and S-derivatives of 1-aza-1,3-enynes are among the least studied processes involving 1-aza-1,3-enynes, since they have been studied only for some examples. In particular, the reaction of 3-phenyl-2-propynal *N*-benzoylhydrazone **47a** with pinacolyl allylboronate **48** in the presence of catalytic amounts of indium(I) iodide occurs exclusively as 1,2-addition (Scheme 27).

Scheme 27



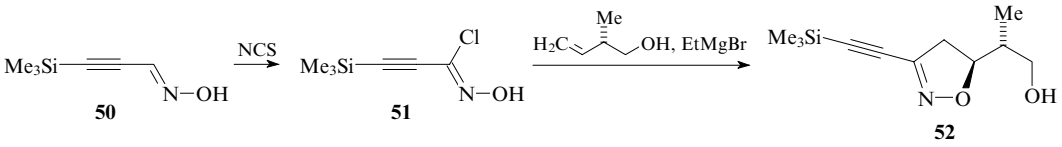
The reaction product — alkynyl-containing homoallyl hydrazide **49** — forms in quantitative yield in a methanol–toluene mixture.[85] Metal-free alkylation with allyltrichlorosilanes in the presence of a 200% excess of optically active (*R*)-methyl *p*-tolyl sulfoxide affords the target hydrazide predominantly in the *S*-configuration in 93% yield.[86, 87]

An example of synthesis of a dipole — nitrile oxide — from 1-aza-1,3-enyne has been reported.[88] Trimethylsilylpropynal oxime **50** reacts with *N*-chlorosuccinimide (NCS) to give hydroxyiminoyl chloride **51**. The latter, in the presence of the Grignard reagent, transforms into the corresponding nitrile oxide, which adds to optically pure (*S*)-2-methyl-3-buten-1-ol to form (*R*)-2-[(*S*)-3-trimethylsilylethynyl-4,5-dihydroisoxazol-5-yl]-1-propanol (**52**) (Scheme 28). Cycloaddition is chemoselective so that the triple bond and the trimethylsilyl substituent remain intact.[89]

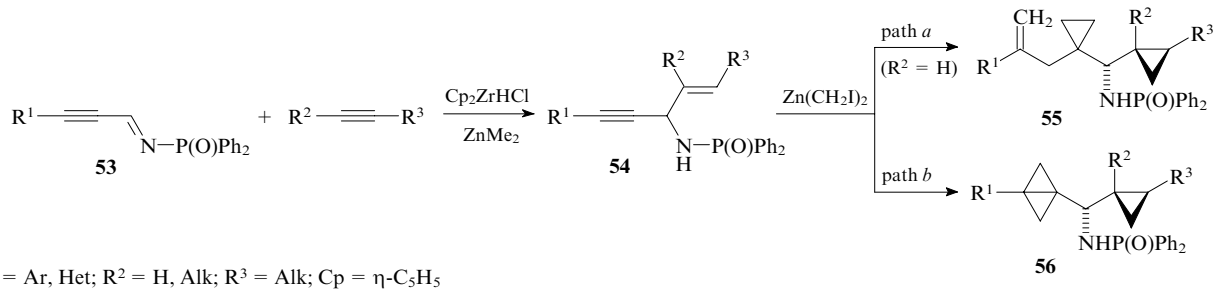
The use of *N*-diphenylphosphinyl-1-aza-1,3-enynes **53** as synthons in a domino multicomponent reaction catalyzed by organometallic compounds has been described [14, 90, 91] (Scheme 29). *N*-Diphenylphosphinyl-1-aza-1,3-enynes **53** react with alkenylzirconocenes in the presence of dimethylzinc [90] in toluene or methylene chloride. The reaction proceeds chemo- and stereoselectively to give α-alkenylpropargyl-*N*-diphenylphosphinylamides **54** in ~85% yield.[90]

The use of CH_2Cl_2 as a solvent in the presence of carbenoid $Zn(CH_2I)_2$ leads to triple cyclopropanation of intermediate α-alkenylpropargyl-*N*-diphenylphosphinylamides **54**. The use of terminal alkynes as starting materials drives the reaction towards dicyclopropanes **55** through route *a*, while disubstituted acetylenes as starting materials direct the reaction to uncommon bicyclo[1.1.0]butanes **56** in ~50% overall yield (route *b*).[14, 91] It remains unclear whether starting 1-aza-1,3-enynes **53**, in addition to inter-

Scheme 28



Scheme 29



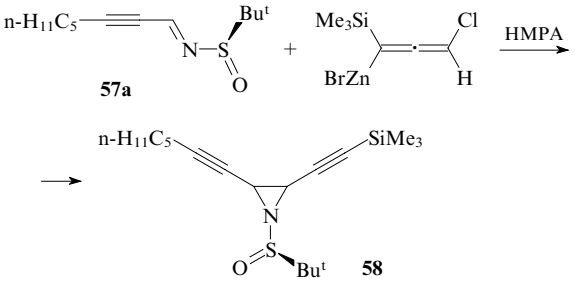
R^1 = Ar, Het; R^2 = H, Alk; R^3 = Alk; Cp = η-C_5H_5

mediate α-alkenylpropargyl-*N*-diphenylphosphinylamides **54**, can be subjected to cyclopropanation.

The reaction of (*R*)-*N*-*tert*-butylsulfinyl-1-aza-1,3-enynes **57a** (Ref. 92) with silicon-containing allenylzinc bromide in the presence of hexametapol (hexamethylphosphoramide, HMPA) leads to *cis*-2,3-dialkynylaziridine **58**.[93] According to these data,[93] in the reaction with 1-aza-1,3-enyne **57a**, like in the case of other azomethines, a 60-fold excess of hexametapol has a decisive effect on stereocontrol and provides predominantly *cis*-2,3-disubstituted isomers **58** (Scheme 30).[94–96]

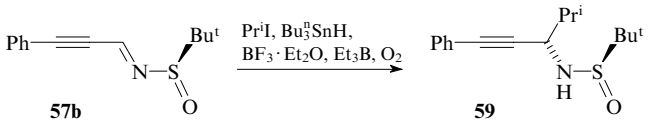
Isolation of optically pure diastereo- and enantiomeric aziridines requires additional purification of the product on silica gel.[93]

Scheme 30



Optically active (*R*)-*N*-*tert*-butylsulfinylimine-3-phenyl-2-propynal **57b** has been subjected to intermolecular radical alkylation with isopropyl iodide at the azomethine bond in the presence of boron trifluoride etherate, tri-n-butyltin hydride, triethylborane and molecular oxygen (Scheme 31).[15]

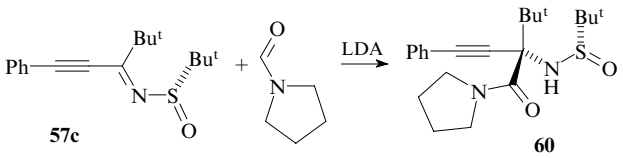
Scheme 31



The yield of product **59** was 80%. This reaction demonstrates an approach to synthesis of primary α-substituted propargylamines with high optical purity, since the *tert*-butylsulfinyl group can be easily removed.[15]

Diastereoselective addition of carbamoyl anion to *N*-*tert*-butylsulfinyl-1-aza-1,3-enyne **57c** with the *S*-configuration has been realized[97] (Scheme 32).

Scheme 32

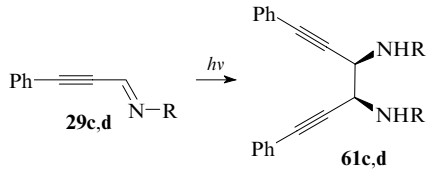


The reaction occurs under the action of lithium diisopropylamide in an excess of *N*-formylpyrrolidine in toluene at −73 °C to give product **60** in 73% yield. Removal of the *tert*-butylsulfinyl group enables the stereoselective synthesis of *S*-alkynyl-substituted α-amino acids.[97]

III.9. Processes driven by UV radiation

When exposed to UV radiation, *N*-alkyl-1-aza-1,3-enynes **29c**,**d** undergo dimerization (Scheme 33).[98] In the resulting stereoisomeric *N*,*N*′-dialkyl-1,2-dialkynylethylene-1,2-diamines **61c**,**d**, *meso* diamines predominate.

Scheme 33



R = Bu^t (**c**), Cy (**d**); Cy is cyclohexyl

Hydrazones of diacetylenic aldehydes and ketones react with sodium hydride to transform into 1-diazopenta-2,4-diynes, which are photolyzed to generate stable dialkynyl carbenes.[99–102] The latter are of interest as objects for studying triplet state photochemistry.

To summarize, it is necessary to underline that the substituent at the nitrogen atom of the azomethine bond has a decisive effect on the course of reaction. In addition, chemoselectivity of addition of various reagents to the azomethine bond inherent in 1-aza-1,3-enynes enables the synthesis of acyclic and heterocyclic compounds with a

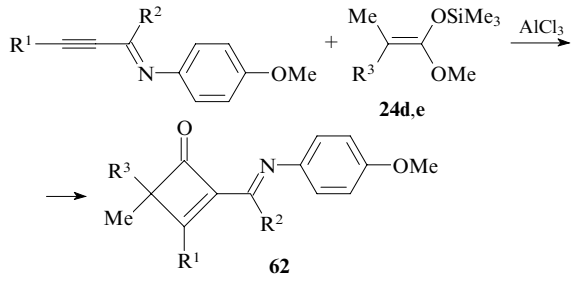
triple carbon – carbon bond. Such derivatives can serve as building blocks for further targeted synthesis of many organic compounds that are difficult to obtain.[66]

IV. Addition to the triple bond of 1-aza-1,3-enynes

Information on transformations involving only the triple bond of 1-aza-1,3-enynes is rather limited, and relevant data have not been updated over the past 15 years, except for a few studies. The nucleophilic addition of aromatic thiols to the triple bond of 1-aza-1,3-enynes, as well as the 1,3-dipolar cycloaddition of azides and diazomethane, has been described in detail by Stadnichuk *et al.*[1]

The reaction of 1-aza-1,3-enynes with ketene silyl acetals **24d**,**e** in the presence of an equimolar amount of a Lewis acid (aluminium chloride) occurs chemo- and regioselectively at the C≡C triple bond (Scheme 34).[103]

Scheme 34

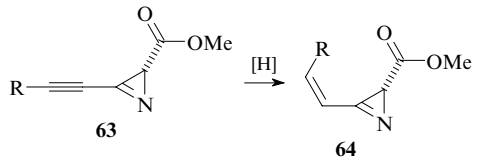


R^1 = Ar; R^2 = Ar, Het; R^3 = Me (**24d**), SEt (**24e**)

The reaction products — iminocyclobutenones **62** — form in 4 h when an excess of ketene silyl acetal in methylene chloride is used. These cyclobutenes can be further transformed into the corresponding β-lactams.[103, 104]

Reduction with hydrogen over Lindlar catalyst (palladium deposited on a neutral support, $CaCO_3$, and poisoned with lead and quinoline)[105] of formal 1-aza-1,3-enyne **63** involves only the triple bond, converting it into a double bond (Scheme 35).[106]

Scheme 35



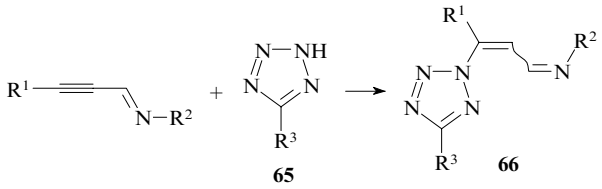
R = Alk

The reaction occurs in hexane at 0 °C for 20 min to give analogues of natural (*Z*)-dysidazirine **64**. This is one of few examples of stereoselective reduction of triple bond with retention of the azomethine moiety in the azirine ring.

The reaction of 1-aza-1,3-enynes with 5-substituted tetrazoles **65** proceeds chemo- and stereoselectively to give a mixture of *E* and *Z* imines of tetrazolylacroleins **66** (Scheme 36).[107]

At the triple bond of 1-aza-1,3-enynes, tetrazole is attached exclusively through the nitrogen atom in the 2-position. *N*-Aryl-1-aza-1,3-enynes react with tetrazoles only in the presence of triethylamine.

Scheme 36



R^1, R^2, R^3 = Alk, Ar

Silicon-containing acetylenic aldimines add to tetrazoles with elimination of the trimethylsilyl moiety.[107]

V. Reactions involving both the azomethine and triple bonds

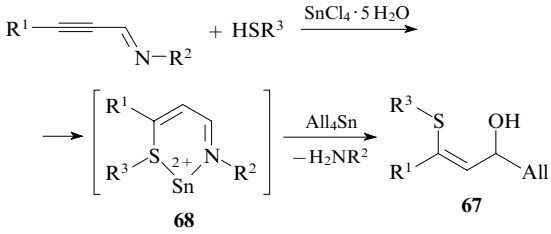
Reactions of 1-aza-1,3-enynes involving simultaneously the C≡C and C=N bonds became the subject of attention of chemists relatively recently. They are widely used since they reveal most fully the synthetic potential of 1-aza-1,3-enynes as a system of conjugated bonds.

V.1. Double nucleophilic addition

The nucleophilic attack at the triple and azomethine bonds of 1-aza-1,3-enynes leads to substituted allyl alcohols and allylamines. Initially, the nucleophile is added to the triple bond and, then, to the azomethine moiety.

Successive addition of thiols and tetraallyltin to 1-aza-1,3-enynes in the presence of tin chloride hydrate leads with high stereospecificity to (*Z*)-1-sulfenyl-1,5-alkadien-3-ones **67** (Scheme 37).[108]

Scheme 37

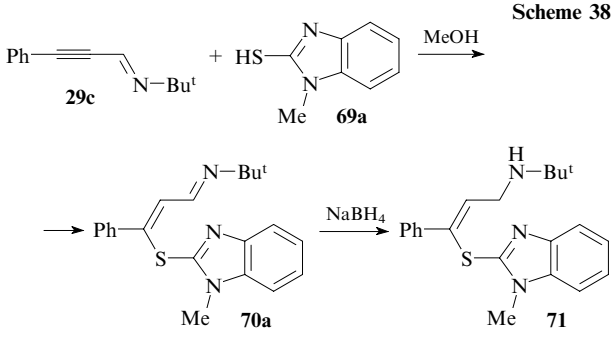


R^1, R^3 = Ar, Alk; R^2 = Ph, $SiMe_3$

The authors believe that the nucleophilic attack promoted by $SnCl_4 \cdot 5H_2O$ is directed at the triple bond of 1-aza-1,3-enyne. Intermediate chelated azadiene **68** is hydrolyzed in the presence of tin chloride hydrate to unsaturated aldehyde, which is alkylated at the carbonyl group by tetraallyltin to form target product **67**.[3, 108]

Successive addition, first, of heterocyclic thiol **69a** to the triple bond of azaenyne **29c** and then of the hydride ion to

Scheme 38

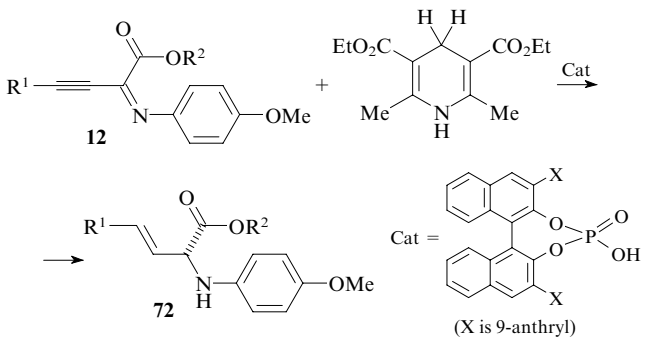


the azomethine moiety of intermediate **70a** reflects a new approach to the synthesis of benzimidazole-substituted allylamines **71** (Scheme 38).[109]

The reaction is carried out as a one-pot process, without isolation of intermediate azadienes. Product **71** is obtained as hydrochloride after the treatment with hydrochloric acid in acetone.[109]

Stereoselective organocatalytic hydrogenation of β,γ-alkynyl α-imino esters **12** (formally 1-aza-1,3-enynes), described in Ref. 44, involves both reactive bonds and affords optically pure *trans*-alkenyl α-amino esters **72** (Scheme 39).

Scheme 39



R^1, R^2 = Ar

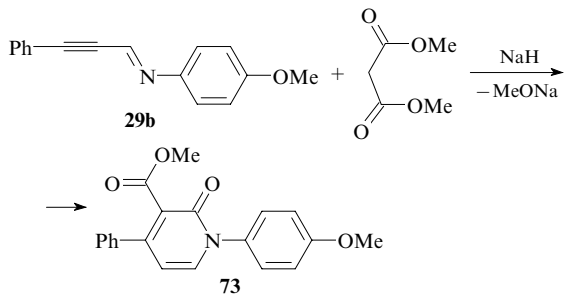
Asymmetric synthesis was realized using Hantzsch ester (as the hydride ion donor)[110] and the chiral catalyst based on a 1,1′-binaphthyl-2,2′-diol derivative.[44]

V.2. Intermolecular heterocyclization

V.2.a. Reactions with CH-acids

1-Aza-1,3-enynes, as well as their silicon- and germanium-containing analogues, react with malonic acid and monoethyl malonate to form dibasic acids of the vinylacetylene series.[1] Attempts to add diethyl malonate to 1-aza-1,3-enynes were unsuccessful.[1] However, according to Hanchiya *et al.*[111], varying the conditions of the reaction of CH-acids with 1-aza-1,3-enynes, for example, the use of strong bases and increasing reaction temperature and time, enables the synthesis of substituted 2-pyridones **73** from 1-aza-1,3-enyne **29b** and dimethyl malonate (Scheme 40).

Scheme 40

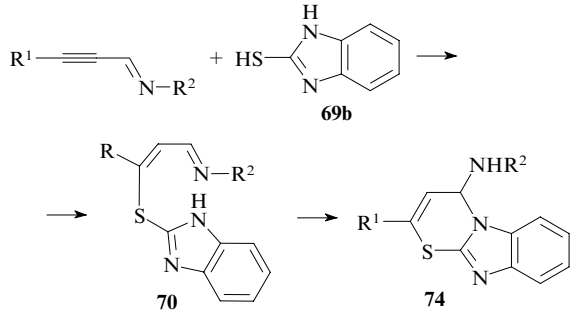


It should be noted that this reaction is realized as 1,4-addition, which is untypical of 1-aza-1,3-enynes.[1] Under analogous conditions, the use of β-keto esters in reactions with 1-aza-1,3-enynes leads to 3,4,5,6-tetrasubstituted 2-pyridones,[111,112] and the use of ethyl cyanoacetate derivatives as CH-acids affords 3,4,5-trisubstituted 2-iminopyridines.[113] Information on synthesis of such compounds is most comprehensively covered in the review by Shimizu *et al.*[3]

V.2.b. Addition of benzimidazole-2-thiols

The reaction of benzimidazole-2-thiol derivatives (**69b**) with *N*-alkyl-1-aza-1,3-enynes has been studied only for α,β-acetylenic aldimines. The reaction occurs in dry DMF at room temperature to give polynuclear heterocyclic sulfur-containing compounds **74** (Scheme 41).[114]

Scheme 41

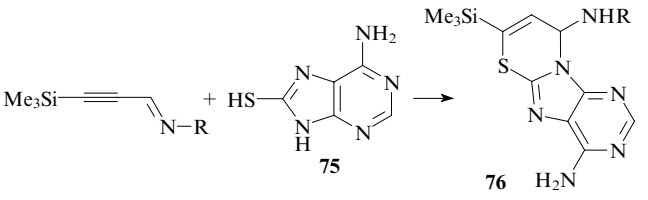


R^1 = Ph, Bu^t, $SiMe_3$; R^2 = Alk

Analysis of experimental data shows that, in the case of the reaction with 1-aza-1,3-enynes, thione–thiol tautomeric equilibrium typical of benzimidazole-2-thiols is shifted toward the thiol form. In addition to the thiol group, the reaction involves the second nucleophilic centre of benzimidazole-2-thiols — the unsubstituted pyrrole-type nitrogen atom, which attacks the electrophilic carbon atom of the azomethine group. Heterocyclization occurs through dinucleophilic [3 + 3] addition of benzimidazole-2-thiols to 1-aza-1,3-enynes. According to available data,[107] azoles (for example, tetrazoles) add to the multiple bonds of 1-aza-1,3-enynes much less readily than thiols.[1] It can be suggested that the thiol group of benzimidazole-2-thiol is first to react, and then the pyrrole nitrogen is also involved in the reaction with 1-aza-1,3-enynes.[115,116]

According to ^{1}H NMR, aliphatic imines of 3-trimethylsilyl-2-propynal react with a structural analogue of benzimidazole-2-thiol — adenine-8-thiol (6-amino-9*H*-purine-8-thiol, **75**) — to form silicon-containing [1,3]thiazinopurines **76** (Scheme 42).

Scheme 42

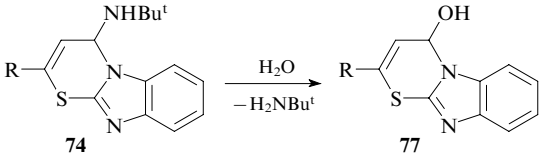


R = Alk

Quantum chemical density functional theory (DFT) calculations show that the isomer with two most distant amino groups is energetically most favourable.[117] Thus, it can be concluded that adenine-8-thiol **75** regioselectively adds to aliphatic imines of 3-trimethylsilyl-2-propynal, replacing the proton in the 9-position. Formation of one regioisomer is also driven by the steric factor — the presence of the primary amino group in the 6-position of initial adenine-8-thiol.

In a 1:1 water–alcohol solution, heterocyclization products **74** undergo hydrolysis accompanied by elimination of amine (for example, *tert*-butylamine) and formation of heterocyclic alcohols **77** (Scheme 43).[115]

Scheme 43

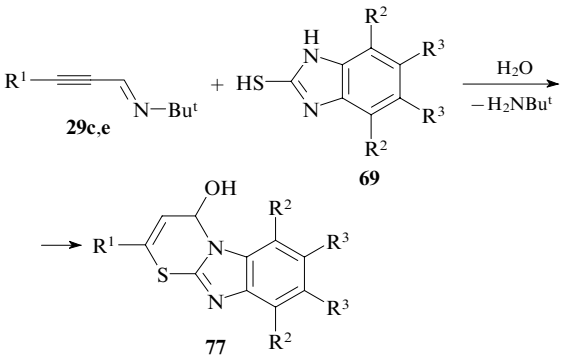


74 **77**

R = Ph, Bu^t

The addition of symmetrically substituted benzimidazole-2-thiols **69** to 1-aza-1,3-enynes **29c**,**e** in organic solvents (DMF or methanol) containing water traces followed by crystallization from aqueous ethanol of heterocyclization products — 4-amino[1,3]thiazino[3,2-*a*]benzimidazoles **74** — lead to [1,3]thiazino[3,2-*a*]benzimidazol-4-ols **77**. Hydrolysis accompanied by elimination of *tert*-butylamine occurs after the completion of the addition reaction (Scheme 44).[118]

Scheme 44



29c,**e** **69** **77**

R^1 = Ph (**29c**), Bu^t (**29e**); R^2, R^3 = H, Me, OMe

X-Ray crystallographic study of 6,9-dimethoxy-2-phenyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ol (R^1 = Ph, R^2 = OMe, R^3 = H; **77a**) has shown that this compound tends to form original dimers.[118] These dimers are one-dimensional constructions forming in the head-to-tail manner through hydrogen bonding of two enantiomeric molecules (Fig. 1). Crystallographic data make it possible to assume that formation of such molecular structures in the crystalline state is inherent in 4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ols **77**.

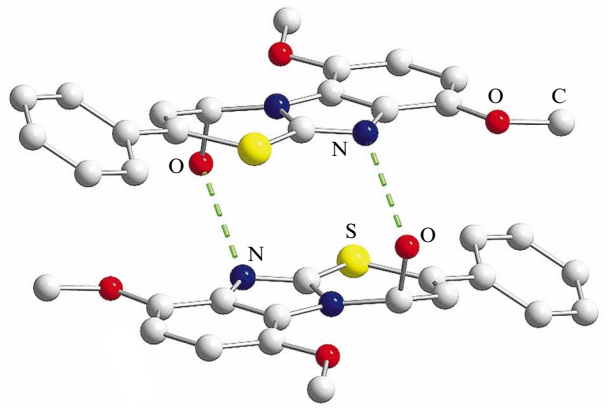
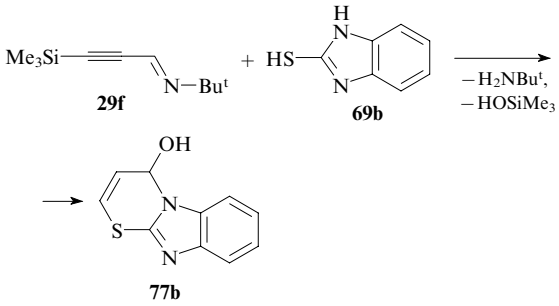


Figure 1. Intermolecular interactions in the crystal structure of 6,9-dimethoxy-2-phenyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ol (**77a**) (the H atoms are omitted).

The reaction of 3-trimethylsilyl-2-propyn-1-al *tert*-butylimine (**29f**) with benzimidazol-2-thiol (**69b**) in methanol is accompanied by not only the hydrolytic elimination of *tert*-butylamine but also the loss of the trimethylsilyl moiety in product **77b** (Scheme 45).[115] The reaction occurs with slight self-heating and is accompanied by some resinification of the reaction mixture.

Scheme 45



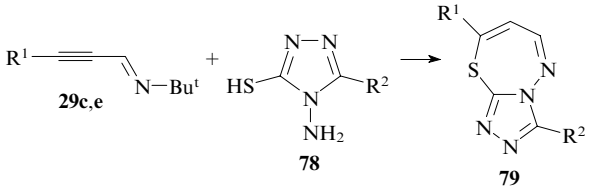
29f **69b** **77b**

It can be concluded that 1-aza-1,3-enynes are convenient synthons for targeted design of sulfur-containing polynuclear heterocyclic compounds — 4-amino[1,3]thiazino[3,2-*a*]benzimidazoles. The latter are readily hydrolyzed in aqueous alcohol solutions to substituted 4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ols.

V.2.c. Ractions with 4-amino[1,2,4]triazole-3-thiols

As in the case of benzimidazole-2-thiol derivatives, the reaction of 1-aza-1,3-enynes **29c**,**e** with 5-substituted 4-amino-3-sulfanyl[1,2,4]triazoles **78** is accompanied by heterocyclization. Along with the thiol group, which is added at the triple bond, the amino group of the initial triazole is also involved in the reaction. It attacks the azomethine bond of 1-aza-1,3-enyne and replaces the *tert*-butylamine moiety to form triazolo[3,4-*b*]-[1,3,4]thiadiazepine derivatives **79** (Scheme 46).[119]

Scheme 46



29c,**e** **78** **79**

R^1 = Ph (**29c**), Bu^t (**29e**); R^2 = H, Alk, Ar, 4-Py; Py is pyridyl

The reaction occurs under mild conditions (in methanol at room temperature) to give crystalline products in good yields. The direction of the reaction is independent of the nature of substituents at the triple bond of 1-aza-1,3-enynes **29c**,**e** and in the 5-position of [1,2,4]triazole-3-thiols **78**.

Available data demonstrate that [1,2,4]triazole-3-thiols analogously react with acetylenic aldehydes, but under more severe conditions: the reaction mixture should be heated under reflux in ethanol for 2 h in a nitrogen atmosphere. However, as has been shown,[120] not all of the 4-amino-3-sulfanyl[1,2,4]triazoles react readily with propy-

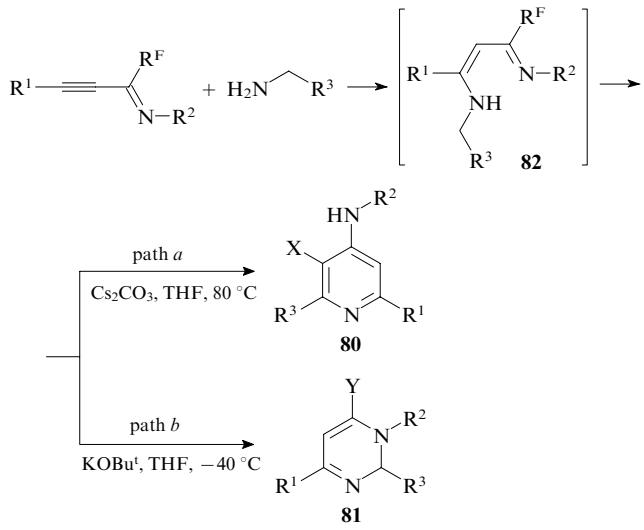
nals. In particular, the reaction of phenylpropiolaldehyde and 4-amino-5-(4-pyridyl)-3-sulfanyl[1,2,4]triazole leads to a difficult-to-separate mixture of products. The introduction of α,β-acetylenic aldimines instead of acetylenic aldehydes into the reaction with the above triazoles makes it possible to realize heterocyclization in good yields of 3,8-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines.[120]

This fact underlines the advantage of using α,β-acetylenic aldimines as compared with propynals in the synthesis of 3,8-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines.

V.2.d. Addition of benzylamines

The addition of benzylamines to perfluoroalkyl-substituted 1-aza-1,3-enynes in the presence of different bases proceeds through different pathways (Scheme 47).[121, 122]

Scheme 47



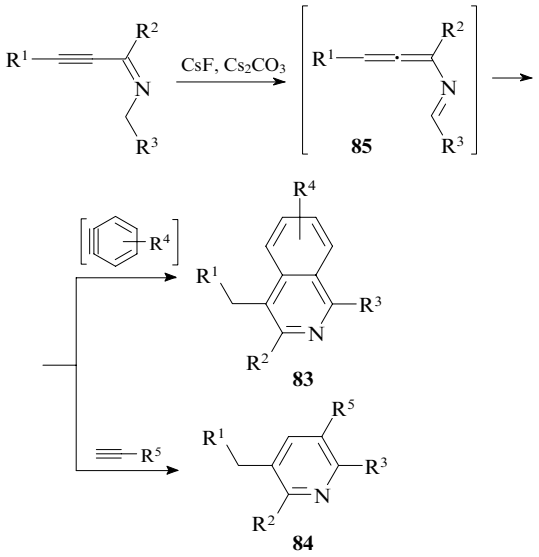
R^1, R^2, R^3 = Ar; R^F = CF_3, C_2F_5, C_3F_7; X = F, CF_3, C_2F_5; Y = CHF_2, CH_2F

Changing temperature, along with variation of alkali metal salts, makes it possible to control the chemoselectivity of the process. In particular, the reaction carried out in THF on heating under reflux with a caesium carbonate excess gives fluorinated 4-aminopyridines **80** (path *a*). The use of potassium *tert*-butoxide instead of a caesium salt and decreasing temperature to −40 °C leads to fluorinated dihydropyrimidines **81** (path *b*). It is believed[122] that, in both cases, benzylamine is first to add to the triple bond. Then, the perfluoroalkyl substituent (R^F) is involved in the reaction, which is accompanied by the cleavage of a fluorine–carbon bond. Then, depending on the nature of the base, intermediate **82** isomerizes to either 4-aminopyridine or dihydropyrimidine.

V.2.e. Aza-Diels–Alder reaction

N-Benzyl-1-aza-1,3-enynes react with dehydrobenzenes and terminal alkynes in the presence of caesium salts to form isoquinoline and pyridine derivatives (**83** and **84**, respectively).[8, 14, 123] The authors suggest that bases promote the isomerization of 1-aza-1,3-enynes into allenylimines **85**, which enter into an aza-Diels–Alder reaction with arynes or alkynes (Scheme 48).

Scheme 48



R^1, R^4 , R^5 = Alk, Ar; R^2, R^3 = Ar

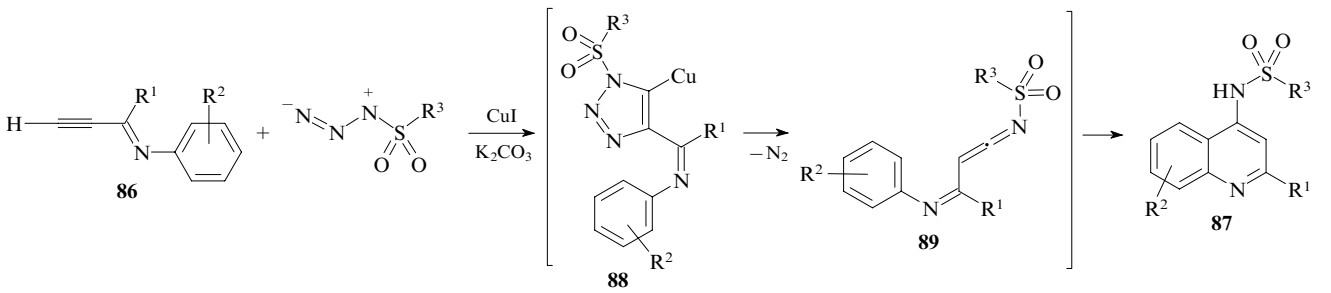
The reaction occurs in a reagent excess in a 4:1 acetonitrile–toluene mixture in the presence of an excess of caesium fluoride or carbonate. It is worth noting that the use of symmetric acetylenes as alkynes, in particular, diphenylacetylene, does not lead to target products.[8, 14]

V.2.f. Addition of sulfonyl azides

The addition of sulfonyl azides to terminal *N*-aryl-1-aza-1,3-enynes **86** in the presence of copper(I) iodide and K_2CO_3 occurs as a cascade reaction and affords 4-sulfonamidoquinolines **87** (Scheme 49).[124, 125]

The reaction cascade begins with the classical Cu-catalyzed cycloaddition of azides to terminal alkynes to form

Scheme 49



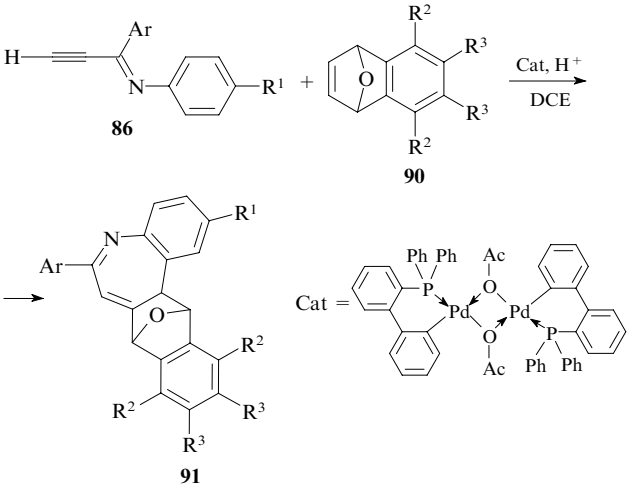
R^1 = Alk, Ar; R^2 = Me, OMe, Hal; R^3 = Ar

substituted 1,2,3-triazoles **88**. The latter decompose to unstable intermediate ketenimines **89**, which attack the aryl substituent at the nitrogen atom of 1-aza-1,3-enynes.[124, 125] If the benzene rings at the nitrogen and carbon atoms of the azomethine moiety have electron-donating substituents, the yields of target 4-sulfonamidoquinolines **87** increase.

V.2.g. Addition of oxabicyclic alkenes

Oxabicyclic alkenes **90** add to terminal *N*-aryl-1-aza-1,3-enynes **86** in the presence of phosphorus-containing palladacycle to form 5*H*-benzo[*b*]azepines **91** (Scheme 50).[28]

Scheme 50



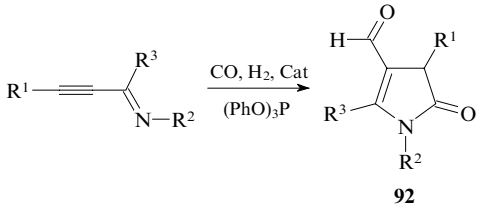
R^1 = H, Me, Et, OMe, Cl; R^2 = H, Me; R^3 = H, Me, F

The authors have studied in detail the factors that have an effect on the reaction course. The highest yields of the products were observed in nonpolar solvents (dichloroethane and toluene), while no reaction occurred in polar solvents, DMF or DMSO. The introduction of benzoic acid and an alkene excess increases the yield of the products, while no reaction is observed in the presence of Cs_2CO_3 or Et_3N.

V.2.h. Cyclohydrocarbonylation

Under heterophase conditions [bubbling a carbon monoxide – hydrogen mixture through a liquid reaction mass in the presence of a rhodium catalyst and triphenyl phosphite], *N*-alkyl-1-aza-1,3-enynes enter into the cyclocarbonylation reaction (Scheme 51).[126]

Scheme 51



R^1, R^2 = Alk; R^3 = Alk, Ar; Cat = [Rh(cod)(η^6-$C_6H_5BPh_3$)]

The products of oxo synthesis (4-formylpyrrolin-2-ones **92**) form in methylene chloride at temperature 75 – 90 °C and pressure 21 – 42 atm.[126, 127]

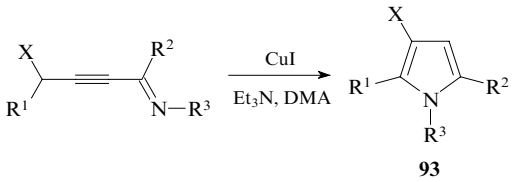
V.3. Intramolecular heterocyclization

In reactions of this type, linear 1-aza-1,3-enynes are converted into cyclic compounds. The tendency to such transformations is caused by the specific chemical structure of 1-aza-1,3-enynes. The direction of the reaction, as well as the structure of the products, are determined by the nature of substituents at the triple bond and at the nitrogen atom. Most of the reactions occur in the presence of catalysts — d-metal salts and complexes (Cu, Pd, Ru, *etc*.).

V.3.a. Synthesis of pyrroles

The synthesis of pyrrole derivatives **93** through cycloisomerization of 1-aza-1,3-enynes has been reported.[128, 129] The reaction is catalyzed by copper(I) iodide and triethylamine in *N*,*N*-dimethylacetamide (DMA) (Scheme 52).

Scheme 52



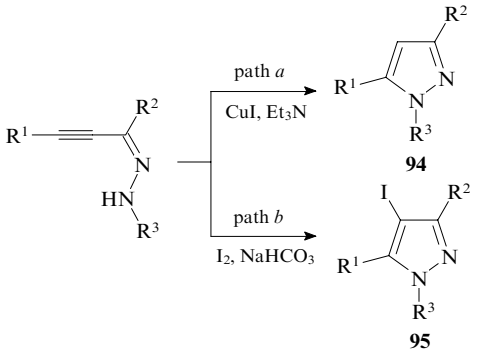
R^1 = Alk; R^2, R^3 = H, Alk; X = H, SAlk, SPh, SePh

In the case of 1-aza-1,3-enynes containing organosulfur and organoselenium substituents, the latter migrate into the 3-position of pyrrole **93**.[130 – 132] Cycloisomerization proceeds as a cascade of metal-catalyzed reactions involving isomerization of 1-aza-1,3-enynes into allenylimine, migration of the sulfenyl or seleno group and further transformation into substituted pyrrole.[133] This is an original method of synthesis of difficult-to-synthesize sulfur- and selenium-containing pyrroles and one of a few examples of participation of the substituent at the triple bond of 1-aza-1,3-enynes in the reaction.

V.3.b. Synthesis of pyrazoles

Hydrazones of acetylenic aldehydes and ketones in the *Z*-configuration are subjected to cycloisomerization into di- and trisubstituted pyrazoles **94** (path *a*, Scheme 53).[134] The reaction occurs in acetonitrile in the presence of copper(I) iodide and a base — triethylamine.[10, 11]

Scheme 53



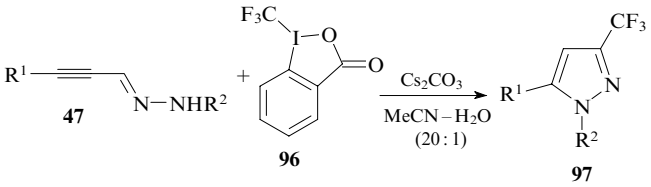
R^1 = Alk, Ar; R^2 = H, Me, Ph; R^3 = Ar

Heterocyclization of acetylenic hydrazones can also be promoted by molecular iodine to give 4-iodopyrazoles **95** (path *b*).[10, 135] Analogous scheme has been used to synthesize 4-fluorosubstituted pyrazoles;[136] in this case, the reaction is catalyzed by gold catalysts ($Ph_3PAuNTf_2$) in the

presence of a fluorination agent — 4-chloro-1-fluoromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor).

Hydrazones of acetylenic aldehydes in the presence of a fluoromethylation agent (hypervalent iodine compounds **96**) are cyclized into 3-trifluoromethyl-1,5-disubstituted pyrazoles **97** (Scheme 54).[137]

Scheme 54

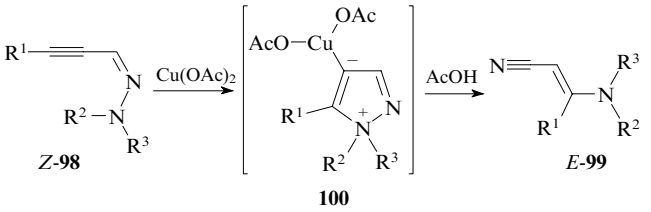


R^1 = Alk, Ar, Het; R^2 = Ar, Boc

This reaction demonstrates an approach to the synthesis of nonsteroidal anti-inflammatory drug Celecoxib, a representative of new-generation selective cyclooxygenase 2 inhibitors. Its analogues with trade names SC-560 (Ref. 138) and Mavacoxib [139] are already used in veterinary medicine.[140]

The *Z* isomers of propynal hydrazones **98** isomerize under mild conditions into (*E*)-3-aminoacrylonitriles **99** in the presence of copper(II) acetate in acetonitrile (Scheme 55).[141]

Scheme 55



R^1 = H, Alk, Ar; NR^2R^3 = NMe_2, NMePh, morpholino, piperidino

It has been suggested that isomerization occurs through intermediate pyrazole **100** with subsequent cleavage of the nitrogen–nitrogen bond.[141] It has been found that only the *Z* isomer of the initial hydrazone is involved in the reaction, while the *E* isomer does not isomerize even under more severe conditions. It should be noted that this is a rare example of the effect of configuration on the reactivity of the initial 1-aza-1,3-enyne.[141] It should be emphasized that almost no information is available on the reactivity of hydrazones obtained from asymmetric dialkyl hydrazides and acetylenic aldehydes or ketones. It cannot be ruled out that this is associated with their low reactivity.

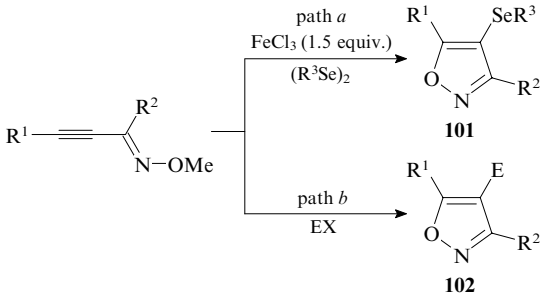
V.3.c. Synthesis of isoxazoles

Substituted isoxazoles have been synthesized from oximes [142] of acetylenic aldehydes and ketones.[143, 144] For example, under the action of iron(III) chloride in the presence of organic diselenides, methyl alkynyl oxime ethers isomerize into 4-selenyl-substituted isoxazoles **101** (path *a*, Scheme 56).[145]

Treatment of acetylenic aldehyde and ketone *O*-methyloximes with I_2, ICl, Br_2 and PhSeBr, leads to 4-halogen-substituted isoxazoles **102** (path *b*).[146–148]

An analogous scheme has been used to synthesize 4-fluoro-substituted isoxazoles.[140] In this case, gold- and

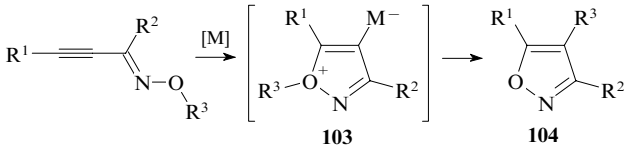
Scheme 56



R^1 = H, Ar, Alk; R^2, R^3 = Alk, Ar; E = I: EX = I_2, ICl; E = Br: EX = Br_2, PhSeBr

silver-based catalysts — [(IPr)AuCl] [IPr is 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] and (AgOTs) — are used. The reaction occurs in the presence of a fluorinating agent (Selectfluor) and $NaHCO_3$. Allyl and benzyl ethers of acetylenic aldehydes and ketones isomerize into substituted isoxazoles in the presence of $AuCl_3$,[149, 150] $AgBF_4$ (Ref. 151) and $Cu(OTf)_2$.[152] In the course of cycloisomerization, intermediate **103** undergoes the Claisen rearrangement. As a result of regioselective rearrangement, the allyl or benzyl substituent is shifted into the 4-position of target isoxazole **104** (Scheme 57).

Scheme 57



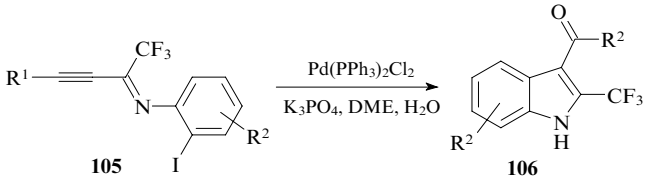
R^1 = H, Alk, Ar; R^2 = Ph, Me, Bu^t; R^3 = H, All, Bn; [M] = $AuCl_3$, $AgBF_4$, $Cu(OTf)_2$

It is worth noting that the presence of a proton donor — phenol — hinders the rearrangement and leads to the formation of 3,5-disubstituted isoxazole.[151]

V.3.d. Synthesis of indoles

N-(2-Iodoaryl)-2-trifluoromethyl-1-aza-1,3-enynes **105** cyclize in the presence of $Pd(PPh_3)_2Cl_2$, potassium phosphate and water to give 3-acyl-2-trifluoromethylindoles **106** (Scheme 58, the substituent positions in the initial compound are given).[153]

Scheme 58



R^1 = Alk, Ar; R^2 = H, 4-F, 4-Me, 5-OMe

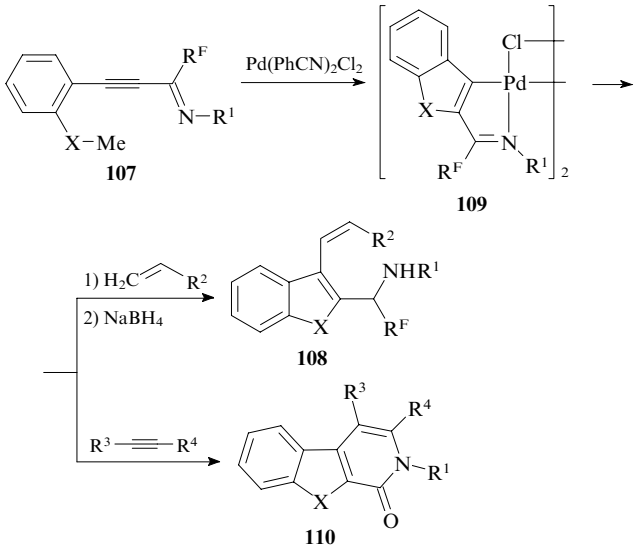
The reaction occurs in ethylene glycol dimethyl ether (DME) at 60 °C over a period of 30 min.[153] The presence of electron-donating substituents in aryl moieties at both the triple and double bonds promotes the reaction and increases the yield of target products. Conversely, the presence of

acceptor substituents suppresses the reaction and reduces the yield of indoles.

V.3.e. Synthesis of benzothiophenes and benzoselenophenes

Perfluoroalkyl-substituted propargylimines **107**, containing a sulfenyl or selenyl group, are used in synthesis of (*Z*)-3-alkenylbenzo[*b*]thiophenes **108** (X = S)[154] or (*Z*)-3-alkenylbenzo[*b*]selenophenes **108** (X = Se), respectively (Scheme 59).[155] It has been proved[52] that the synthesis of compounds **108** (X = Se) proceeds through the stage of formation of binuclear palladium(II) complex **109**. In addition to 1-aza-1,3-enynes **107**, the cascade of reactions involves the palladium complex $Pd(PhCN)_2Cl_2$ and alkenes — styrene or acrylates.

Scheme 59



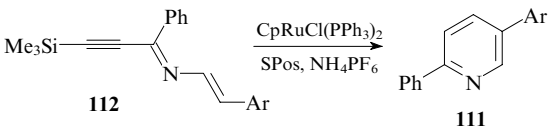
R^F = CF_3, C_2F_5, n-C_4F_9; R^1, R^3, R^4 = Ar; R^2 = CO_2Alk, Ph; X = S, Se

The reaction of palladacycles **109** with diaryl-substituted acetylenes leads to fused thiopheno- and selenophenopyridones **110**,[155] and the perfluoroalkyl substituent is eliminated in the course of reaction. The reaction occurs on heating in toluene and lasts for about 12 h.

V.3.f. Synthesis of pyridines

5-Aryl-2-phenyl-substituted pyridines **111** have been synthesized from silicon-containing *N*-vinyl-1-aza-1,3-enynes **112** (Scheme 60).[35] Heterocyclization is catalyzed by the ruthenium complex $CpRuCl(PPh_3)_2$ together with dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPos)[156] and ammonium hexafluorophosphate as the desilylating agent.[33]

Scheme 60

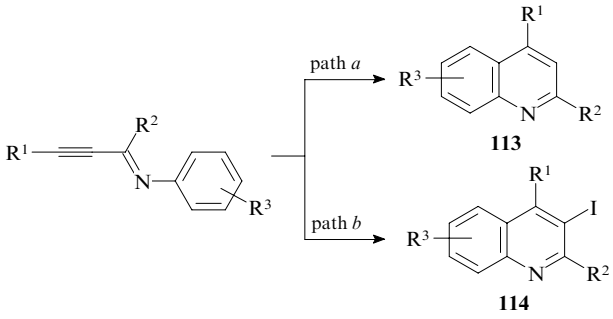


More complex fused heterocyclic systems can be synthesized analogously.[33] The reaction usually occurs in toluene at 105 °C for 19 h to give the products in good yield.[33,157]

V.3.g. Synthesis of substituted quinolines

Transformations leading to substituted quinolines in which *N*-aryl-1-aza-1,3-enynes are exclusively used have been studied in detail. In particular, α-fluoroalkyl derivatives cycloisomerize into quinolines **113** under the action of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[158] while α-aryl derivatives cycloisomerize in the presence of ruthenium[33,35] and palladium[159] complexes or vanadium carbonyl[160] (path *a*, Scheme 61).

Scheme 61



R^1 = H, CH_2SPh, CH_2OPh; R^2 = Ar, CF_3, C_2F_5; R^3 = Me, OMe

α-Fluoroalkyl-substituted 1-aza-1,3-enynes undergo electrophilic heterocyclization in an iodine excess in the presence of $(NH_4)_2[Ce(NO_3)_6]$ (CAN) to form 3-iodo-substituted quinolines **114** (path *b*).[31,161] The latter are suitable for further use in the Sonogashira reaction.[31,161]

VI. Conclusion

Information presented in this review demonstrates a significant advance in the chemistry of 1-aza-1,3-enynes achieved over the past 15 years. Along with upgrading the known methods of synthesis of 1-aza-1,3-enynes, new approaches, such as cross-coupling of terminal alkynes with isonitriles and carboxamides and aza-Wittig reaction, are actively developed. Development of efficient preparative methods of synthesis of 1-aza-1,3-enynes makes it possible to widely use compounds of this class in fine organic synthesis. Still poorly studied perfluoroalkyl-containing 1-aza-1,3-enynes are currently receiving ever increasing attention of chemists. However, as distinct from alkyl and aryl substituents, the effect of perfluoroalkyl groups on the reaction course and formation of final products has not been revealed so far. Along with the conventional use of metal complex catalysis in asymmetric synthesis involving 1-aza-1,3-enynes, organic catalysts, such as chiral phosphoric acids based on binaphthyldiol derivatives [(*S*)-BINOL] and boroxinates, have been used more and more widely in recent years. Practical application of 1-aza-1,3-enynes is represented by synthesis of biologically active compounds, in particular, modern drugs for the treatment of leukemia, anti-inflammatory drugs, *etc*. Finally, noteworthy is the appearance of new reagents — heterocyclic dinucleophiles (azolethiols). Their reactions with 1-aza-1,3-enynes can be regarded as a new route to the synthesis of fused heterocycles, which excludes the use of d-metal compounds.

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