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Reactions of acetylenes in superbasic media. Recent advances

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The main advances in the chemistry of acetylene in superbasic media achieved over the last five years are analyzed. Particular emphasis is placed on the ethynylation of aldehydes and ketones and C-, N- and O-vinylation. The cascade assembly of complex molecules in which ethynylation and vinylation are consecutive steps is considered.
The bibliography includes 369 references.

Contents

I. Introduction

The chemistry of acetylene is an important and swiftly developing area of organic synthesis. Most of transformations involving acetylene are addition reactions, which are fundamentally atom-economical and are accompanied by heat evolution, *i.e.*, these processes are energy-efficient. Thus, they perfectly comply with the green chemistry principles, which are a goal of the modern organic synthesis.

The proper acetylene is an unavoidable product of oil refining and gas and coal processing. The ethylene production alone gives off hundreds of thousands tons of acetylene.

In the 1970s, acetylene was displaced from the basic organic synthesis by cheap ethylene and propylene. However, the time of readily accessible crude oil is coming to an end. Some analysts already believe that the return to acetylene as a basic industrial chemical feedstock that can also be obtained from coal is inevitable.[1–4] The future will show whether this will really happen.

Currently calcium carbide — the traditional source of acetylene — can be prepared using wood charcoal instead of coke.[5] This makes acetylene a renewable raw material. Currently, carbide-based acetylene is again becoming an important chemical raw material in the countries having no natural hydrocarbons of their own. For example, 15 mln tons of calcium carbide per year is already produced in China.[6]

In fine organic synthesis, acetylene has never lost the top position,[7] which has only consolidated with time. This is due to high reactivity and unique chemical plasticity of acetylene.[8–14]

This is indicated, in particular, by the constant extension of the synthetic potentials of acetylene cross-coupling with aryl and hetaryl halides[15–17] and pyrrole and indole cross-coupling with haloacetylenes on active surfaces of metal oxides and salts.[18–22] New, in principle, data on the mechanism of addition reactions of chalcogen organic compounds to acetylenes in the presence of palladium catalysts were obtained.[23–26] Original studies of non-catalytic electrophilic addition of chalcogen halides to carbon–carbon triple bond are being developed.[27–34] The synthesis, structure and reactions of acetylene metal complexes,[35,36] including carbene type ones,[11,37] are being investigated. The number of publications devoted to reactions of acetylene catalyzed by gold compounds grows in the avalanche-like manner.[38–43] The radical addition reactions to the triple bond are getting a second wind and conquer new application areas.[44–47] More traditional reactions such as intramolecular cyclization of functionalized acetylenes[48,49] and intermolecular annulation involving them[50–58] are also being developed.

However, currently, reactions that proceed through carbanionic intermediates of various nature, *viz.*, Favorskii reactions (acetylene – allene isomerization, vinylation and ethynylation) are at the center of attention. These reactions are atom-economical, energy efficient and environmentally safe and they are based on available raw materials. As a rule, these reactions are catalyzed by alkali metal hydroxides or alkoxides, which can form isolable complexes (Tedeschi complexes) with acetylene,[59] *i.e.*, these reactions may be regarded as involving metal complexes. This revival

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of the Favorskii reaction reveals the key trends and characteristic features of the modern organic synthesis.

The concentration and reactivity of carbanions are known to increase in the presence of strong bases. Therefore, it became usual practice to stimulate the Favorskii reactions by superbasic media, reagents and catalysts.[60–63] During the last decades, this concept has been systematically developed by the authors of this review.[60–67] Today superbases are also used in acetylene chemistry by other researchers.[68–73]

In recent years, a number of unexpected breakthrough results have been obtained along this line. The brief analysis of these results is the subject of the present review. Here we mainly discuss the works published after 2007 when the latest review devoted to this subject was published [63] (earlier works are cited only for comparison).

II. Ethynylation

Propargyl alcohols formed upon Favorskii ethynylation of carbonyl compounds find wide use in fine and basic organic synthesis. They served for the development of preparation methods of acetylenic ethers,[74,75] unsaturated ketones [76,77] and heterocyclic compounds.[78,79] They are used in the synthesis of isoprenoids (including the industrial production of isoprene),[4] carotenoids,[1] vitamins A and E,[80] fragrance compositions,[81] anti-mite agents, herbicides, corrosion inhibitors, and non-ionic surfactants.[1,61]

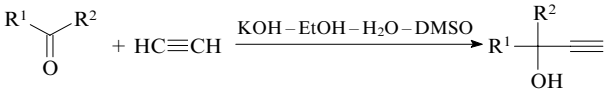
1. Ethynylation of ketones

Whereas propargyl alcohols from aliphatic and alicyclic ketones and acetylene are usually formed by the Favorskii reaction in nearly quantitative yields and without significant experimental problems, alkyl (het)aryl ketones, which are more prone to enolization, react with difficulty, and, correspondingly, the yields of ethynylation products are, in this case, relatively low. To increase the reaction efficiency, it is necessary to considerably increase pressure, which reduces the process safety and adds more requirements to the process equipment. In some cases, more complicated modifications of the Favorskii reaction are used. For example, Iotsitch reagents (alkynylmagnesium halides) or alkali metal acetylides are used as ethynylating reagents.

Before our studies,[82] the Nazarov modification [83] was considered to be the best procedure for the Favorskii synthesis of tertiary propargyl alcohols. The necessity of continuous supply of acetylene and ketone under pressure, the use of fire-hazardous diethyl ether and a large excess of alkali complicate the application of this method both in laboratory and in industry.

It was found [82] that in the KOH–EtOH–H_2O–DMSO superbasic system, alkyl (het)aryl ketones readily react with acetylene under atmospheric pressure (10–15 °C, 2 h) to give propargyl alcohols **1** in an up to 91% yield (Scheme 1). The reaction is selective: only in some cases, traces of acetylenic diols are detected in the crude product by ^{1}H NMR.

Scheme 1



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

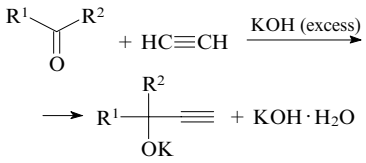
1 (⩽91%)

The molar ratio of the reaction components ketone : KOH : EtOH : H_2O is 1 : 1 : 0.5 : 0.5.

The efficiency of the synthesis is evidently due to an increase in the activity of the catalytic system and a change in the physicochemical properties of the medium upon the use of hydrated potassium hydroxide (KOH · 0.5 H_2O) and ethanol. Under these conditions, an equilibrium homogeneous catalytic system containing the potassium cation and hydroxide, ethoxide and acetylide ions is formed. This changes not only the base concentration in the solution (because KOH is completely dissolved in the reaction medium) but also the base nature: due to the poor solvation of anions, including acetylide anion, in DMSO, their activity sharply increases. The reactivity of undissociated potassium hydroxide molecules also increases due to loosening of its ion pair (elongation of the K—O bond according to quantum chemical data).[84]

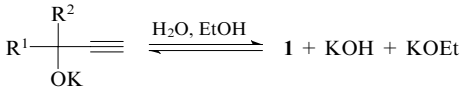
Usually, the Favorskii reaction is carried out at a large excess of KOH powder in a dry solvent [83] and, initially, alcoholate is formed instead of the propargyl alcohol, as the liberated water (1 equiv.) is trapped by the solid-phase alkali, *i.e.*, the reaction is not catalytic (Scheme 2).

Scheme 2



Under conditions of ketone ethynylation that we found (see Scheme 1) in which 1 equiv. of KOH and 0.5 equiv. of each water and ethanol (see above) are used per equiv. of ketone, propargyl alcohol **1** is liberated from the formed alcoholate under the action of water and ethanol, *i.e.*, the reaction is thus switches to a catalytic mode (Scheme 3).

Scheme 3



This is supported by the fact that ethynylation of acetophenone also proceeds with 0.5 equiv. of KOH with respect to ketone, the preparative yield of the corresponding propargyl alcohol being 78%.

The important preparative advantages of the new method include the use of acetylene under atmospheric pressure, replacement of diethyl ether by fire- and explosion-safe and non-toxic dimethyl sulfoxide and a considerable decrease in the amount of KOH, which makes this method attractive not only for a research laboratory but also for low-tonnage chemical production.

The recent report [85] on the synthesis of tertiary propargyl alcohols using acetylene (generated *in situ* from calcium carbide and water) in DMSO in the presence of caesium carbonate (50 mol.%) at 60 °C seems ambiguous and certainly this requires independent experimental verification. The unusual stability of tertiary propargyl alcohols at elevated temperature in the presence of large amounts of strong bases (calcium hydroxide, caesium carbonate and the product of its hydrolysis, caesium hydroxide) is surprising. Tertiary propargyl alcohols are known to undergo the

reverse Favorskii reaction under these conditions, *i.e.*, to decompose to ketones and acetylene. Moreover, the proposed method for the synthesis can in no way be referred to as a green chemistry process, as it is accompanied by the formation of large amounts of slime (calcium hydroxide with the remainder of calcium carbide, starting compounds, target products, dimethyl sulfoxide and acetylene polymers), which is difficult to dispose of. Furthermore, the idea of preparing propargyl alcohols using calcium carbide, although claimed by the authors as pioneering, is far from being new. Back in the 1930s, followers of Academician A E Favorskii prepared tertiary acetylenic alcohols and glycols using calcium carbide as the source of acetylene.[86,87] Later, this approach was the subject of some patents[88,89] and was included in a monograph.[90]

2. Ethynylation of aldehydes

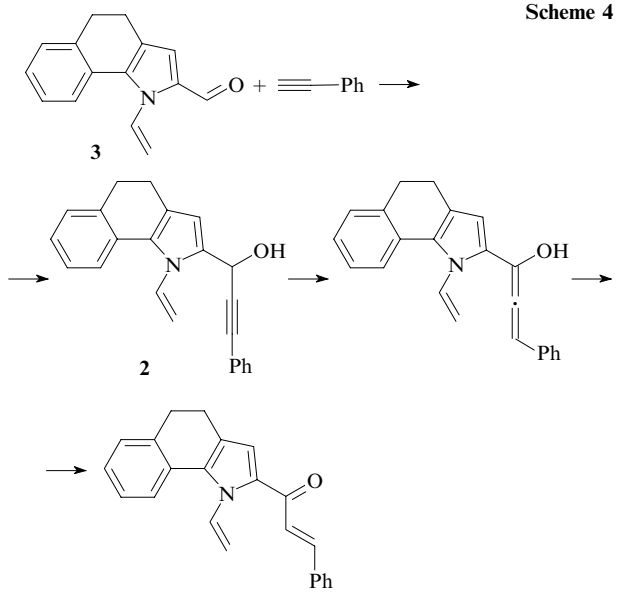
Secondary propargyl alcohols are no less practically significant than the tertiary homologues.[91–95] In the last decade, due to the development of enantioselective methods for the synthesis of secondary propargyl alcohols,[96–100] the interest in this class of functionalized acetylenes has even more enhanced.

Secondary propargyl alcohols are most often synthesized by the addition of the acetylide anion to the carbonyl group of aldehydes.[101–105] This implies preliminary preparation of metal acetylides from terminal acetylenes and highly reactive organometallic reagents. These reactions are, as a rule, not atom-economical, comprise numerous steps and are sensitive to air and moisture.

The few known reactions of aliphatic aldehydes with acetylene in the presence of potassium hydroxide[106–108] are unsuitable for the preparation of secondary propargyl alcohols of the aromatic series.

In the KOH–DMSO superbasic system, secondary propargyl alcohols can be obtained rather smoothly only from aliphatic aldehydes; phenylpropargyl alcohol has not been synthesized as yet under these conditions.[108] This is due to easy prototropic isomerization of this compound to allene alcohol and then to vinyl phenyl ketone, which is polymerized by the anionic mechanism. This isomerization was also observed in attempted preparation of propargyl alcohol **2** from 1-vinyl-4,5-dihydrobenzo[*g*]indole-2-carbaldehyde (**3**) and phenylacetylene in the KOH–DMSO system (Scheme 4).[109]

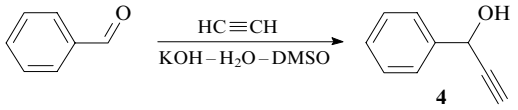
Scheme 4



It is evident that the acetylene–allene isomerization, which occurs in the KOH–DMSO system at room temperature at a high rate,[61] can be suppressed by decreasing the basicity of the medium. For this purpose, the ternary system KOH–H_2O–DMSO was tested as the ethynylation catalyst.

A study of benzaldehyde ethynylation (Scheme 5) demonstrated that the addition of water (10 vol.% with respect to DMSO) at a temperature of −5 to −7 °C results in phenylpropargyl alcohol **4** being formed in a 67% yield (upon complete conversion of benzaldehyde).[110]

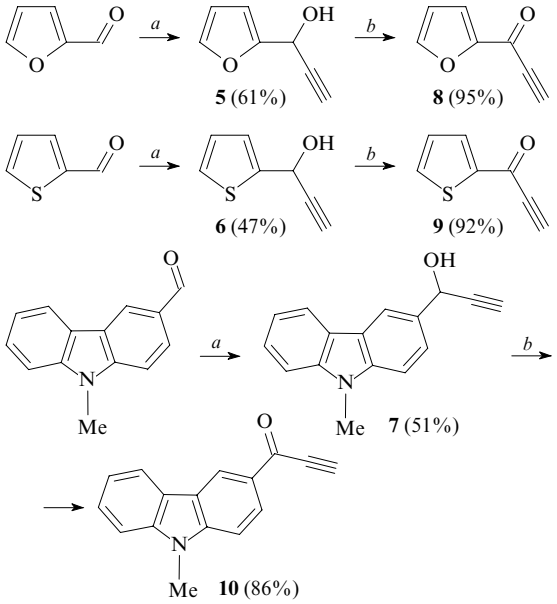
Scheme 5



As noted above, the role of water in the KOH–H_2O–DMSO system is, first of all, to optimize the basicity of the medium, which provides control over the acetylene–allene isomerization. It is important that this is accompanied by homogenization, *i.e.*, the potassium hydroxide concentration in the solution increases. In addition, the reaction mixture has a low freezing point, which allows the reaction to be conducted at lower temperature (this, naturally, suppresses the side processes).

These conditions proved to be suitable for the synthesis of secondary propargyl alcohols **5**–**7** from heteroaromatic aldehydes (Scheme 6).[110] The reaction is selective, giving no acetylenic diols.

Scheme 6



(*a*) HC≡CH, KOH–H_2O–DMSO;
(*b*) O_2, TEMPO, $Fe(NO_3)_3 \cdot 9H_2O$, NaCl;
TEMPO is (2,2,6,6-tetramethylpiperidin-1-yl)oxyl

Thus, direct ethynylation of aromatic and heteroaromatic aldehydes with acetylene was accomplished for the first time at atmospheric pressure in the KOH–H_2O–DMSO system with controlled basicity.[110]

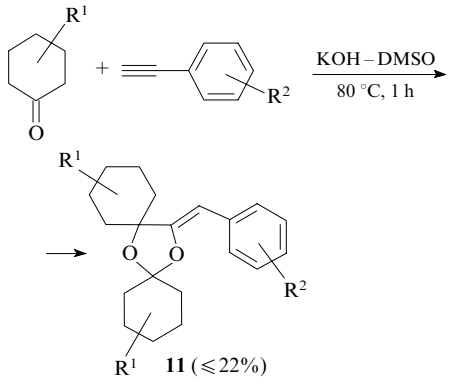
The developed method has been successfully used to prepare hetaryl ethynyl ketones **8**–**10** (see Scheme 6),[111] which serve as the starting compounds for the synthesis [112, 113] and functionalization [114] of aromatic and heterocyclic compounds.

3. Spirocyclization of cyclic ketones

Studies of carbon–carbon bond formation reactions by nucleophilic addition of acetylide ions to carbonyl group are being in progress.[8, 9, 61, 115, 116] Owing to their diverse properties, the resulting propargyl alcohols are readily converted to various polycyclic structures;[9, 61, 115] among these, attention is drawn by spirocyclic ketals as fragments of many natural compounds encountered in plants, animals and microorganisms.[117, 118]

The ethynylation of ketones in the KOH–DMSO superbasic suspension was used to produce new dispirocyclic systems **11** (Scheme 7).[119] Cyclohexanones and arylacetylenes, which form *in situ* tertiary propargyl alcohols capable of subsequent spirocyclization, were chosen for this purpose.

Scheme 7

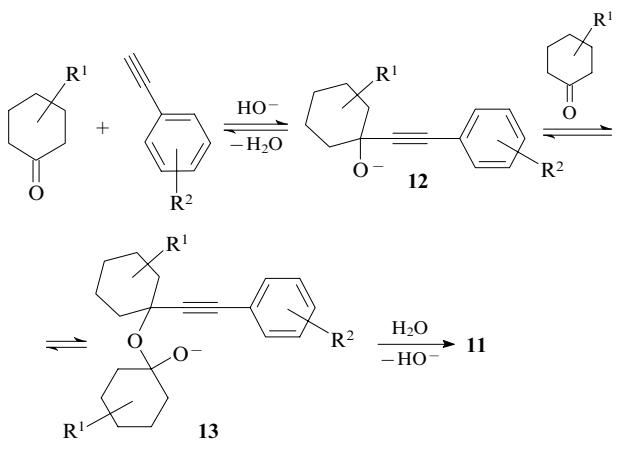


R^1 = H, Me; R^2 = H, Alk, Ar, F

The reaction is stereoselective, dispiro ketals **11** being formed as *Z*-isomers. Other reaction products are unsaturated ketones (see Section III).

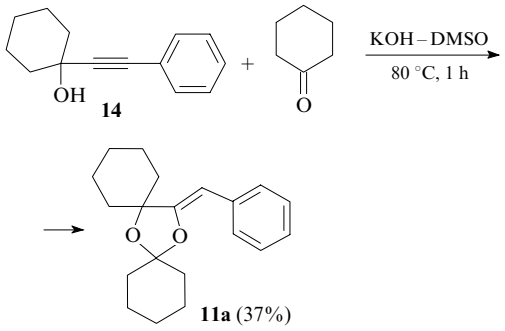
The synthetic route to compounds **11** includes the formation of the tertiary propargyl alcoholate **12**, which then adds to a second ketone molecule. The hemiketal anion **13** thus formed adds regioselectively to the ethynyl group of the same molecule according to the rule of nucleophilic *trans*-addition to a triple bond (Scheme 8).[120]

Scheme 8



The tandem sequence **12** → **13** → **11** was confirmed by the reaction of 1-phenylethynylcyclohexanol (**14**) with cyclohexanone (Scheme 9).

Scheme 9



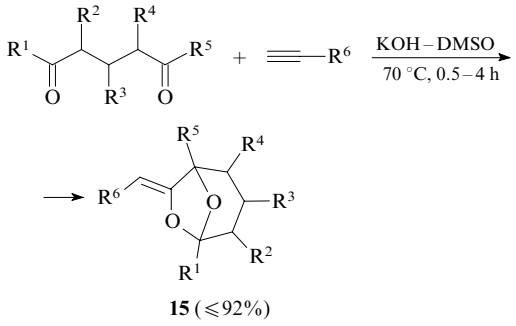
Thus, one more simple route to dispiro ketals from accessible starting compounds has been outlined.

The synthetic potential of these reactions is very high also due to the fact that dispirocyclic ketals **11** are analogues of known cytostatic,[121, 122] antibacterial [123] and antimalarial [122] agents. Despite moderate yields, the one-pot synthesis of dispiro ketals from accessible reactants under facile conditions can be of preparative value because syntheses of their analogues are labour-consuming and multistep processes.[117, 123]

4. Cascade cyclization of 1,5-diketones

In superbasic systems like alkali metal hydroxide (alkoxide)–DMSO, 1,5-diketones undergo one-pot cascade cyclization with acetylenes to give 7-alkylidene-6,8-dioxabicyclo[3.2.1]octanes **15** of the *Z*-configuration (in the case of aryl- and hetarylacetylenes, Scheme 10).[124]

Scheme 10



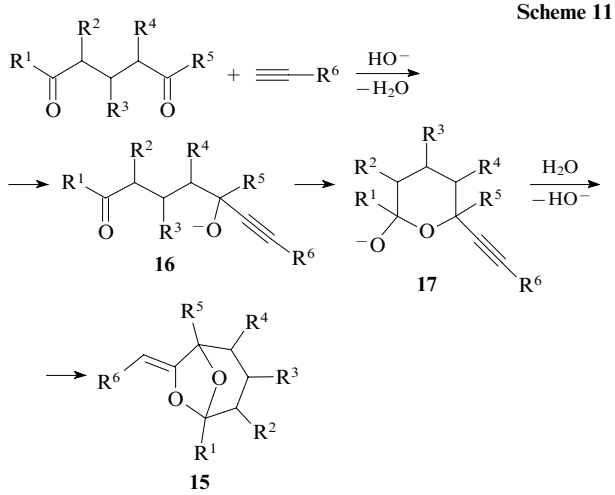
R^1 = Ar, Het; R^2 = H, Alk, Ar; R^1–R^2 = $(CH_2)_4$;
R^3 = H, Alk, Ar; R^4 = H, Alk, Ar; R^5 = Ar, Het;
R^4–R^5 = $(CH_2)_4$; R^6 = H, Ar, Het

The reaction is also diastereoselective. 1,5-Diketones that exist as single diastereomers are converted to only one diastereomer of bicyclooctane. A mixture of two 1,5-diketone diastereomers affords two bicyclooctane diastereomers in the same ratio as the initial diketones.

The reaction starts with the attack of the acetylene carbanion on one of the carbonyl groups (ethynylation, Scheme 11). The acetylenic keto alcohol anion **16** thus formed adds intramolecularly to the remaining carbonyl group, thus closing the tetrahydropyran ring in compound **17**. This new oxygen-centred anion attacks the triple bond (intramolecular vinylation), thus completing the cyclization. In the case of aryl and hetarylacetylenes, an arylmethylene

moiety is stereoselectively formed in the *Z*-configuration, which is in line with the classical mechanism of nucleophilic *trans*-addition to acetylenes.[120]

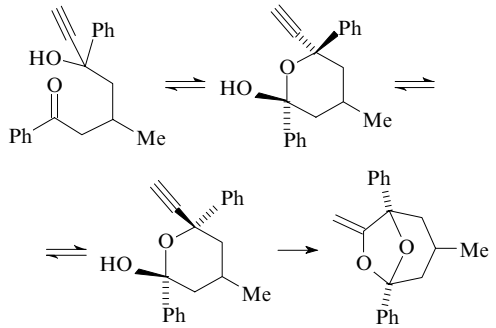
Scheme 11



For R^1, R^2, R^3, R^4, R^5 and R^6, see Scheme 10

The reaction diastereoselectivity is controlled at the last cyclization step (see Scheme 11), which is possible only in the case where the hydroxy group and the triple bond occupy *cis*-positions with respect to the distorted tetrahydropyran ring plane. It is evident that the mutual arrangement of these groups depends on the configurations of the two asymmetric centres, which can change as all of the cascade steps are reversible (Scheme 12).

Scheme 12



The structures resembling bicyclic ketals **15** are frequently encountered in the living nature[125–128] and are also used as building blocks in fine organic synthesis.[129–132]

III. Vinylation

The vinylation reaction was discovered by Academician A E Favorsky in relation to addition of ethanol to methylacetylene in the presence of potassium hydroxide. Since then, nucleophilic addition of molecules with an active hydrogen atom to a triple bond has found wide use not only in the fine organic synthesis but also in industry.[1, 61–63, 133, 134] Superbasic media increased the vinylation rates by many orders of magnitude, thus providing a quantum leap in the chemistry of enol ethers. Today it is possible to vinylate methanol in the liquid phase under atmospheric pressure,[135] which has been recently considered impossible.[136] Easy vinylation occurs for allyl alcohol,[137] although W Ju Reppe, an outstanding authority in the industrial chemistry of acetylene, stated that it cannot be vinylated.[136] In superbasic systems, vinylation can be conducted even for secondary acetylenic alcohols,[138, 139] which are difficult to vinylate under conventional conditions. The steroid alcohol cholesterol abundant in living nature has been successfully vinylated with acetylene.[140] Nowadays the cholesterol vinyl ether is a readily accessible building block in the steroid chemistry, a monomer for the preparation of optically active and liquid-crystalline polymers.[134, 140]

Owing to superbasic catalysts, it was possible for the first time to perform chemo- and regioselective vinylation of chemical 'chameleons' such as oximes[141, 142] and amidoximes,[134, 143, 144] which can behave as C-, N- and O-nucleophiles. This resulted in the synthesis of previously unknown series of functional nitrogen-containing vinyl ethers — promising synthons for the synthesis of heterocyclic compounds and special polymers.

Elemental chalcogens are vinylated by acetylene in superbasic media to give divinyl sulfide,[61, 134, 145–150] divinyl selenide[61, 134, 147, 148] and divinyl telluride[61, 134, 145, 147, 148] — high-performance cross-linking agents, organoelement synthons and volatile precursors of nanostructured chalcogens and metal chalcogenides for semiconductor and optoelectronic devices.

In the KOH–hexamethylphosphoric triamide superbasic system, one-pot vinylation of elemental phosphorus takes place.[134, 151, 152] It was confirmed experimentally that these new phosphines can serve as ligands in catalytically active palladium complexes[153] and replace triphenylphosphine obtained *via* toxic phosphorus chlorides.

In the case of elemental chalcogens and phosphorus, the species that add to acetylene are chalcogen- and phosphorus-centred anions (apparently including nano-sized anionic species) formed upon destruction of crystals of these elements induced by hydroxide ions.[152]

1. C-Vinylation

The last decade has witnessed an increase in the number of publications devoted to addition reactions of carbon-centred nucleophiles (mainly carbonyl compounds) to acetylenes. The most vigorous research is concerned with vinylation of 1,3-dicarbonyl compounds in the presence of transition metal salts and complexes.[154–169] The addition of arylacetonitriles[170–175] to acetylene or mono- and disubstituted acetylenes under phase transfer catalysis in aqueous alkaline solutions and in superbasic CsOH ($CsOBu^t$)–*N*-methylpyrrolidone systems was reported.[176, 177]

It is beyond doubt that of most interest is vinylation of ketones — an extensive and readily accessible class of C-nucleophiles.

a. Vinylation of ketones

It was demonstrated using a few examples that thermal intramolecular vinylation of ketones containing a triple bond is possible.[178, 179] It was also reported[180] that cyclohexanone adds to acetylene in the presence of $(Bu^tO)_2$ giving an adduct in a 2.6% yield (ketone conversion of 5.1%).

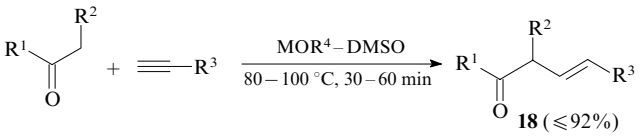
Meanwhile, until recently, there were no reported examples of ketone addition to a carbon–carbon triple bond in the presence of bases. The reasons why the base-catalyzed vinylation of this important class of compounds with acetylenes did not receive any attention were both theoretical and experimental. Theoretically, transition of an oxygen-centred anion (enolate anion) to the corresponding carbanion is thermodynamically unfavourable.[181] Considering the available experimental data, instead of vinylation,

more likely would be the formation of tertiary propargyl alcohols (ethynylation), ketone self-condensation and deprotonation of terminal acetylenes as CH-acids yielding carbanions, which are, in the general case, inert with respect to an attack by ketone carbanions.

However, this reasoning, which casts doubt on the probability of base-catalyzed vinylation of ketones with acetylenes, does not take into account the possible electrophilic assistance from the alkali metal cation.[61] Furthermore, tertiary propargyl alcohols — the expected products of ketone ethynylation — dissociate on heating according to the reverse Favorskii reaction yielding the starting compounds. Hence, at elevated temperature in the presence of bases, the addition of deprotonated ketones (carbonyl carbanions) to acetylene is, in principle, possible.

Indeed, recent publications describe successful nucleophilic regio- and stereoselective addition of ketone carbanions to aryl- and hetarylacetylenes in MOH–DMSO superbasic suspensions (M = Na, K, Cs)[182–185] and in homogeneous superbasic systems, KOH–Bu^{t}OH–DMSO [186] and KOBu^t–DMSO (Scheme 13).[187]

Scheme 13

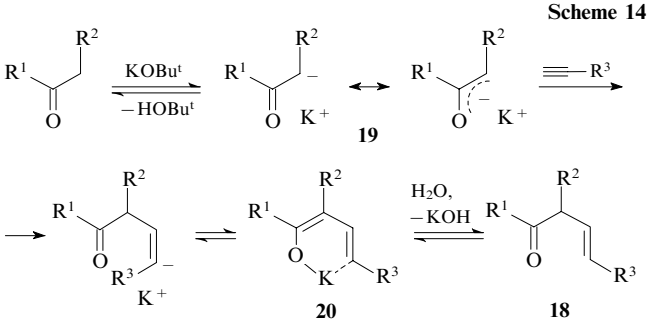


R^1 = Alk, Ar, Het; R^2 = H, Alk, Ar; $R^1–R^2$ = $(CH_2)_n$ (n = 3–5, 10); R^3 = Ar, Het; M = Na, K, Cs; R^4 = H, Bu^t

Thus, contrary to the formerly existing views, it was demonstrated that the reaction of ketones with acetylenes in the presence of superbases at elevated temperatures does not follow the Favorskii reaction route but ketones add to the carbon–carbon triple bond as C-nucleophiles yielding β,γ-unsaturated ketones **18** of *E*-configuration. This reaction occurs for aliphatic, cycloaliphatic and alkylaromatic ketones, aryl- and hetarylacetylenes.

Like all other processes of base-catalyzed vinylation with acetylenes, this reaction proceeds as nucleophilic addition of deprotonated ketone (enolate anion) **19** to a triple bond. These reactions usually afford adducts of *Z*-configuration (concerted *trans*-addition of nucleophiles with simultaneous transfer of a proton of the medium or a reactant to the carbanionic centre being formed).[120] The observed violation of the *trans*-addition was attributed [187] to the formation of six-membered 6p-electron pseudoaromatic chelate complex **20** with the participation of the potassium cation, which fixes the *E*-configuration (Scheme 14).

Scheme 14

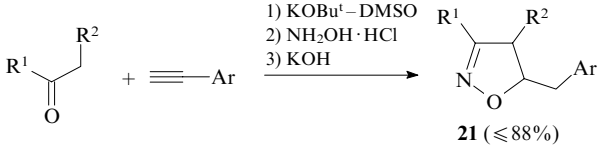


β,γ-Unsaturated ketones **18** are reactive building blocks for organic synthesis [188, 189] and key intermediates in the design of some drugs.[190–194] The known syntheses of such ketones (unlike the thermodynamically more stable α,β-isomers, which are easily prepared by crotonic condensation) are labour-consuming and multistep and often require exotic starting reactants and/or occur under metal complex catalysis.[195–208]

The discovery of base-catalyzed vinylation of ketones with acetylenes (see Scheme 13) basically extends the traditional views on reactivity of acetylenes and ketones and qualitatively enhances the accessibility of β,γ-ethylenic ketones.

This reaction is valuable as the first step in the syntheses of more intricate molecules (without preliminary isolation of the adducts). As an example, consider the one-pot synthesis of Δ^2-isoxazolines **21** from ketones, arylacetylenes and hydroxylamine (Scheme 15).[209] The ketone is treated first with arylacetylene in the KOBu^t–DMSO system (100 °C, 30 min) and then with water and hydroxylamine hydrochloride (70 °C, 1.5–3.5 h) and with KOH (70 °C, 30 min).

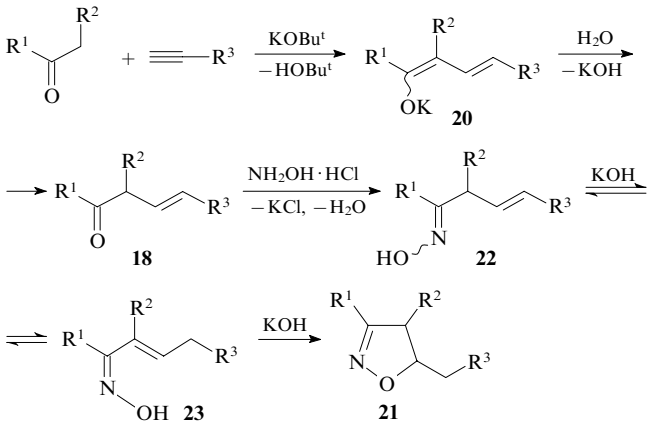
Scheme 15



R^1 = Alk, Ar; R^2 = H, Alk, Ar; $R^1–R^2$ = $(CH_2)_4$, $(CH_2)_2CHMeCH_2$

The formation process of Δ^2-isoxazolines **21** includes the following steps (Scheme 16): potassium dienolate (the adduct of ketone with arylacetylene) **20** reacts with hydroxylamine (*via* the corresponding β,γ-unsaturated ketone **18**) to give β,γ-unsaturated ketoxime **22**. Upon the addition of KOH, it apparently isomerizes to α,β-unsaturated ketoxime **23**, which then cyclizes.

Scheme 16



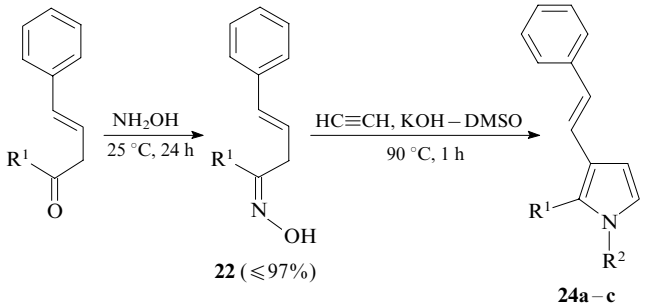
The addition of the oximate anion to the β,γ-position (without preliminary isomerization) is unlikely, as β-substituted styrenes are very weak electrophiles.

5-Benzyl-Δ^2-isoxazolines **21** are promising pharmacophores;[210–212] in particular, they are active against some tuberculosis strains (*Mycobacterium tuberculosis* H_{37} Ra and H_{37}Rv).[213–215]

Recently, it was shown that β,γ-unsaturated ketoximes **22** react with acetylene in the KOH–DMSO superbasic

system (90 °C, 1 h) being stereoselectively converted to 3-(*E*)-styrylpyrroles **24** (Scheme 17).[216]

Scheme 17



24: R^1 = Ph, R^2 = CH=CH_2 (**a**, yield 35%);
R^1 = 2-Naph, R^2 = CH=CH_2 (**b**, 33%), R^1 = 4-PhC_6H_4,
R^2 = H (**c**, 38%); Naph is naphthyl

3-(*E*)-Styrylpyrroles **24** are heterocyclic analogues of stilbene, the derivatives of which occur in nature (the natural antioxidants resveratrol[217–219] and pterostilbene[220]) and are used in medicine[218, 220, 221] and optoelectronics (data recording and storage devices,[222] nonlinear-optical materials).[223–225] The known methods for the synthesis of styrylpyrroles are limited to the Wittig reaction of 3-formyl-1-methylpyrrole with appropriate phosphorus ylides[226] and reduction of 1-protected 3-benzoylpyrrole followed by dehydration of the resulting secondary alcohol.[227–230] Despite the moderate yields of 3-styrylpyrroles from β,γ-unsaturated ketoximes, their preparation according to Scheme 17 may become of preparative value as a one-pot stereoselective synthesis from available reactants (actually from ketones and acetylenes).

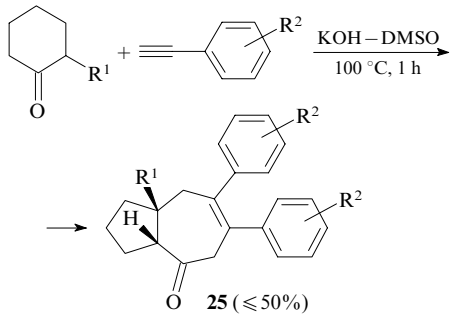
b. Vinylation of 2-alkylcyclohexanones with arylacetylenes: synthesis of hexahydroazulenones

In recent years, researchers have paid particular attention to the search and development of reactions in which several carbon–carbon bonds are formed in one preparative step and valuable polycyclic molecules can be regio- and stereoselectively obtained.[231–234] Among these molecules, azulenones attract attention as selective inhibitors of human immunodeficiency virus.[235–239]

Approaches to diastereoselective synthesis of substituted azulenones are limited to intramolecular cyclization of β-aryl α-diazo ketones catalyzed by rhodium salts[240–243] and cycloaddition of 2-acyl 2-phenyl ketenes to acetylenic ethers.[235]

It was found that 2-alkylcyclohexanones and arylacetylenes are diastereoselectively self-assembled in a KOH–DMSO suspension to 8a-alkyl-6,7-diphenyl-1,2,3,3a,8,8a-hexahydroazulen-4(5*H*)-ones **25** (Scheme 18).[244]

Scheme 18



R^1 = Me, Et; R^2 = H, 4-Me, 4-Ph, 3-F

The reaction obviously starts from the vinylation of ketone with arylacetylene (Scheme 19). The resulting adduct **26** is ethynylated by a second arylacetylene molecule. The oxygen-centred anion of acetylenic alcohol **27** rearranges with ring contraction (*via* elimination of the hydride ion) to α,β-acetylenic ketone **28**, which closes a seven-membered ring *via* intramolecular base-catalyzed C-vinylation involving the vinyl carbanion.

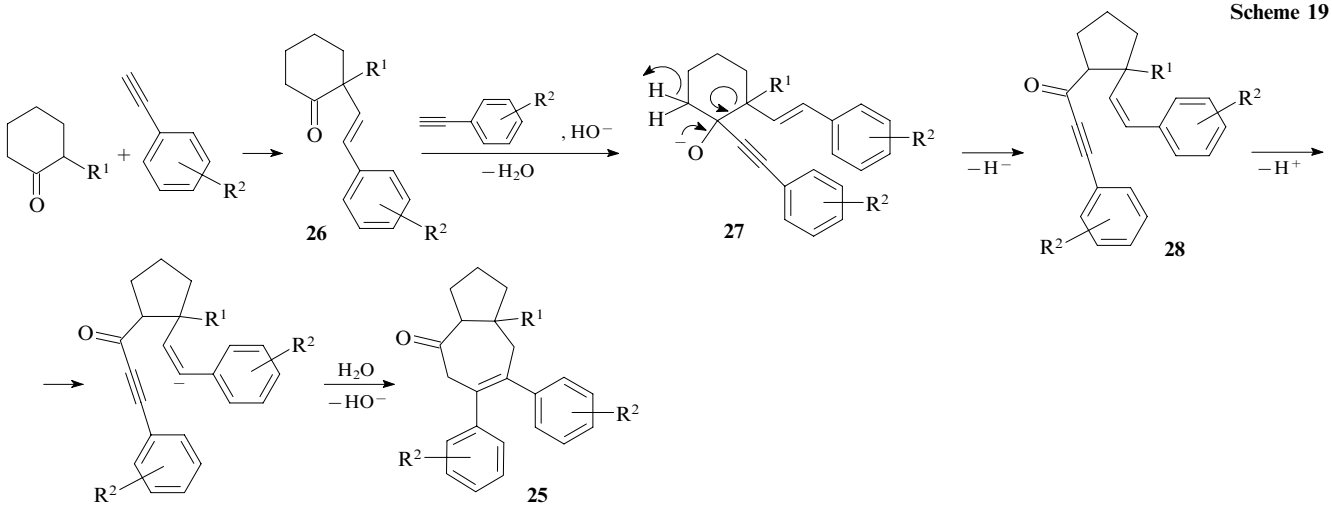
During this process, as many as four carbon–carbon bonds are formed in one preparative step from simple reactants (ketones, acetylenes, KOH), and a pharmaceutically important bicyclic system is diastereoselectively formed.

c. Vinylation of ketones with propargyl and allenyl ethers

Under the action of KOH–DMSO or KOBu^t–DMSO superbases (100 °C, 1 h), ketones add to propargyl ethers[245] (accessible representatives of functionalized acetylenes) both at the internal and terminal positions (Scheme 20). This furnishes 1 : 1 *Z*-adducts **29** and 1 : 2 *E*-adducts **30** in approximately equal amounts.

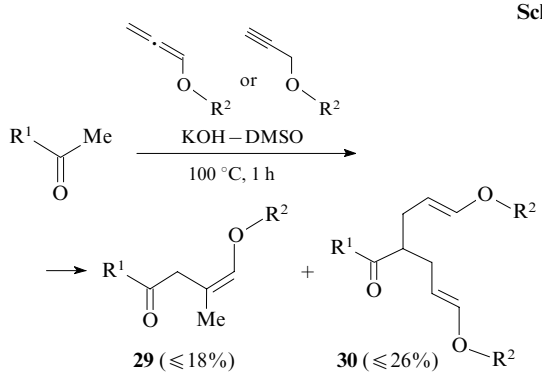
Since at 20 °C (KOH–DMSO, 15 min), propargyl ethers are already rapidly isomerized to the corresponding

Scheme 19



allenes,[61] then at 100 °C, ketones actually react with allenyl ethers. Indeed, under the described conditions, the same results were obtained for propargyl and for corresponding allenyl ethers (see Scheme 20).

Scheme 20

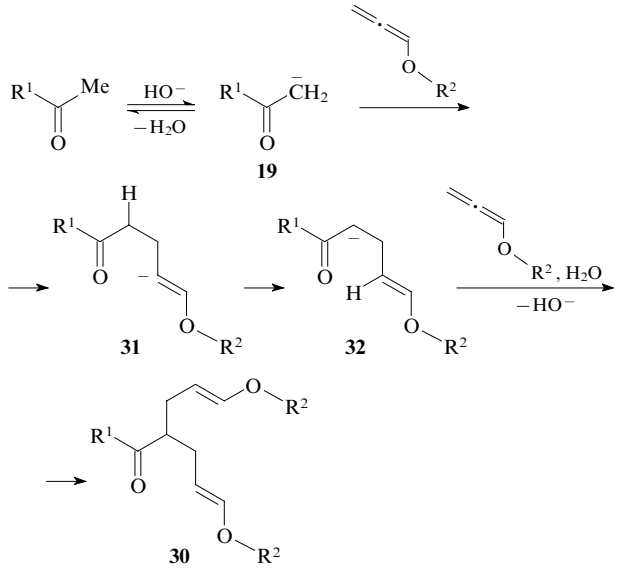


R^1 = Ph, 4-PhC_6H_4; R^2 = Me, Bu^n

Whereas monoadducts **29** are quite expected products,[246] the formation of bis-adducts **30** needs to be explained. A surprising fact is also the absence of monoadducts at the terminal carbon atom in the reaction mixture.

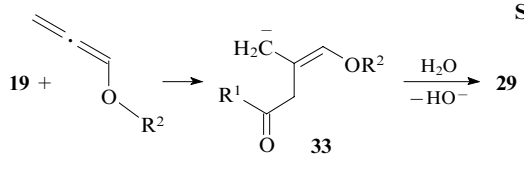
Apparently, vinyl carbanion **31** — the primary adduct of deprotonated ketone **19** (R^2 = H) (Scheme 21) at the terminal position of the allene — is not quenched at this step by a proton of the medium. Instead, intramolecular proton transfer takes place. The α-carbanion **32** thus formed adds to the terminal carbon atom of a second allenyl ether molecule.

Scheme 21



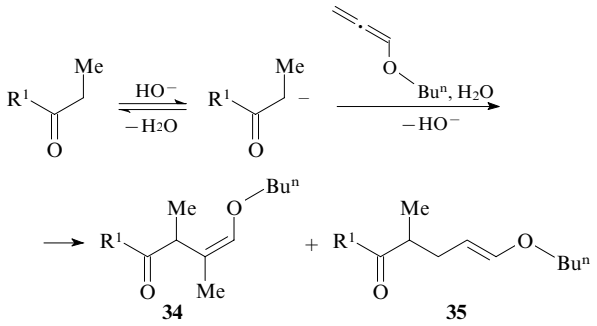
This does not take place upon the attack of the central carbon atom of allene (Scheme 22), because the resulting allyl carbanion **33** is less basic than vinyl carbanion **31**;[247] moreover, the carbanionic centre in adduct **33** is sterically more accessible for the attack by a proton of the medium.

Scheme 22



This interpretation is confirmed by the fact that a branching at the ketone carbanion centre prevents the formation of the bis-adduct. For example, the reaction of propionylbenzene and 2-propionylthiophene with allenyl butyl ether (Scheme 23) affords only both types of monoadducts **34** and **35**.

Scheme 23



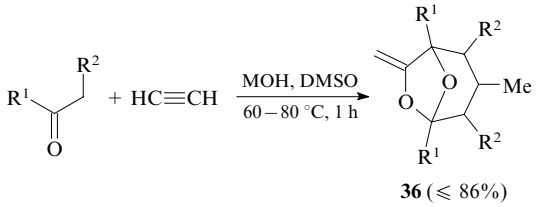
R^1 = Ph, 2-Th; Th is thienyl

Thus, a one-pot stereoselective route to new families of promising synthetic intermediates representing a combination of ketone and enol ether fragments in one molecule was outlined.

d. One-pot synthesis of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes from ketones and acetylene

The vinylation and ethynylation reactions taking place in superbasic media are currently developed in unexpected ways, being implemented more and more often in various combinations as successive steps in the cascade assemblies of intricate carbo- and heterocyclic systems (δ-carbolines,[248] pyrrolopyridines,[249] dispirocyclic ketals,[119] hexahydroazulenones[244] and so on). An example is the diastereoselective one-pot synthesis of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **36** from two ketone molecules and two acetylene molecules (Scheme 24).[250]

Scheme 24



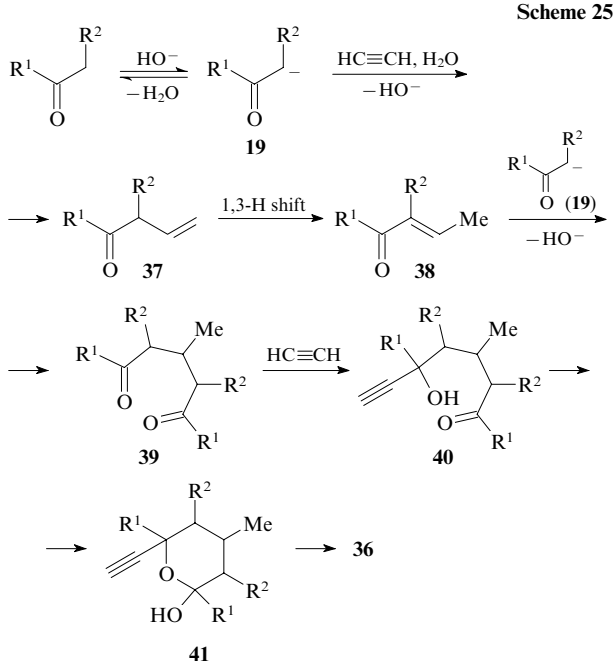
R^1 = Ar, Het; R^2 = H, Alk; M = Na, K, Cs

A specific feature of this unique reaction is its high (up to 100%) diastereoselectivity, despite the presence of 3 to 5 asymmetric carbon atoms in molecules **36**.

A probable pathway to **36** (Scheme 25) includes the addition of ketone carbanion **19** to acetylene (ketone C-vinylation). Adduct **37** undergoes prototropic isomerization to α,β-unsaturated ketone **38**, which is again attacked by the ketone carbanion furnishing 1,5-diketone **39**, which is ethynylated by a second acetylene molecule. Acetylenic keto alcohol **40** is vinylated in its hemiacetal form **41**, thus completing the assembly of molecule **36**.

The 6,8-dioxabicyclo[3.2.1]octane scaffold is a structural moiety of insect pheromones (frontalin, brevicomin, multistriatin, bullerone),[251–253] hormones of warm-blooded species,[254, 255] marine toxins (palytoxin).[256]

Scheme 25

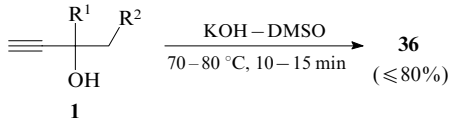


Functionalized 6,8-dioxabicyclo[3.2.1]octanes serve as the starting compounds for the preparation of δ,ε-unsaturated ketones,[257] 1,5-diketones,[258] substituted pyridines,[259] cyclopentane-1,2-diols,[260] di-[261] and tetrahydropyrans[262] and polysaccharide analogues.[263, 264] Structures like bicyclic ketals **36** are still approached by complicated routes with development of multistep procedures.[265–270]

e. Diastereoselective dimerization of tertiary propargyl alcohols

Tertiary propargyl alcohols **1**, the products of ethynylation of alkyl (het)aryl ketones with acetylene,[82] diastereoselectively cyclodimerize in a KOH–DMSO superbasic system to give 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **36** (Scheme 26).[271]

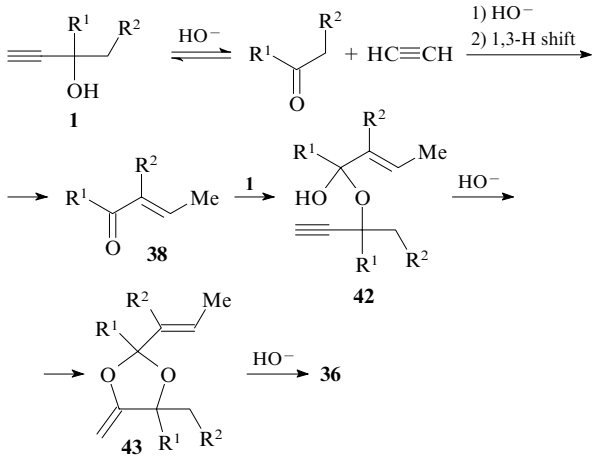
Scheme 26



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

Apparently, on heating in the presence of a base, tertiary propargyl alcohol **1** partly decomposes by the reverse Favorskii reaction to give ketone and acetylene (Scheme 27). The ketone is vinylated with acetylene, and the 1,3-prototropic shift in the adduct gives α,β-unsaturated ketone **38**, which reacts with a second propargyl alcohol **1** molecule to form hemiketal **42**. The latter closes a 1,3-dioxolane ring *via* intramolecular vinylation. Nucleophilic cyclization of diene **43** furnishes methylenedioxabicyclo[3.2.1]octane **36**.

Scheme 27



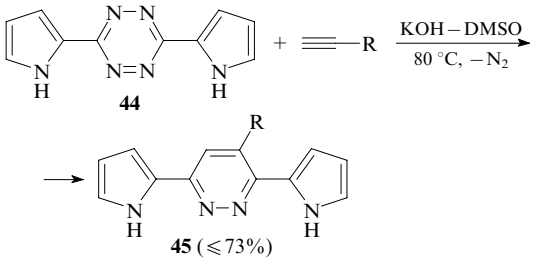
Cyclodimerization smoothly occurs in an excess of acetylene, which suppresses the reverse Favorskii reaction by shifting the equilibrium towards propargyl alcohol **1**. This synthesis[271] is a convenient alternative approach to 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **36**.[250]

f. Base-catalyzed [4 + 2]-cycloaddition of acetylenes to 3,6-di(pyrrol-2-yl)-1,2,4,5-tetrazine

The [4 + 2]-cycloaddition of acetylenes to tetrazines is used to obtain substituted pyridazines — versatile intermediates of multipurpose organic synthesis.[272–282]

However, dipyrrolyltetrazine **44** does not cyclize with acetylenes under conditions[283–286] usual for this type of reactions. Apparently, π-donor pyrrole substituents considerably increase the energy of the vacant orbital of tetrazine diene, which interferes with cycloaddition. Meanwhile, the expected reaction giving pyridazines **45** easily occurs in the KOH–DMSO system (Scheme 28).[287]

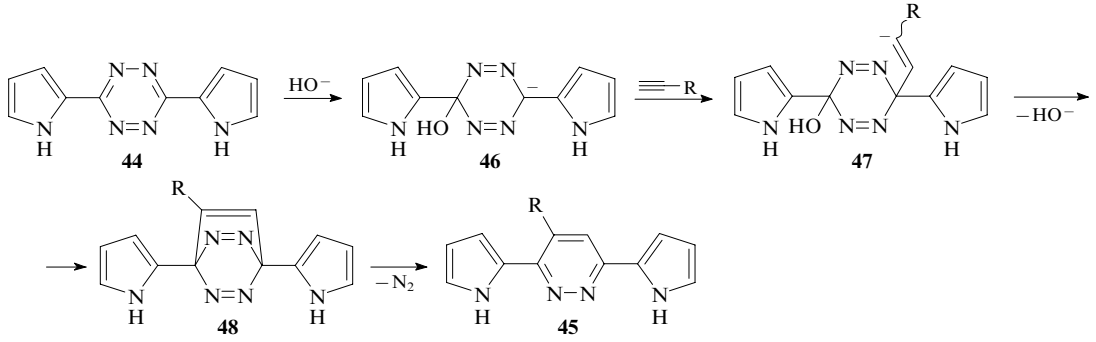
Scheme 28



R = H, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-FC_6H_4, 4-BrC_6H_4, *p*-biphenyl

The review[288] that considers in detail the cycloaddition of acetylenes to tetrazines gives no examples of the base-

Scheme 29

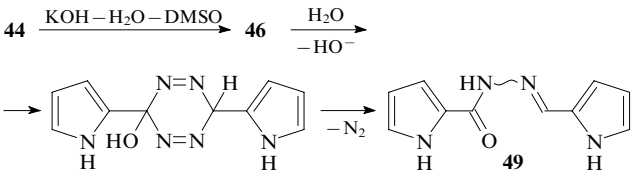


catalyzed version of this reaction. Thus, this cyclization is the first example of base-catalyzed [4+2]-cycloaddition of acetylenes to tetrazines.

Evidently, carbanion **46** — the hydroxide ion adduct with tetrazine **44** (the reaction of tetrazine with alkalis is known)[289] — adds to acetylene (Scheme 29). Vinyl carbanion **47** substitutes intramolecularly the hydroxide ion, and extrusion of a nitrogen molecule from primary cycloadduct **48** leads to pyridazine **45**. Hence, the hydroxide ion acts as a catalyst in this case.

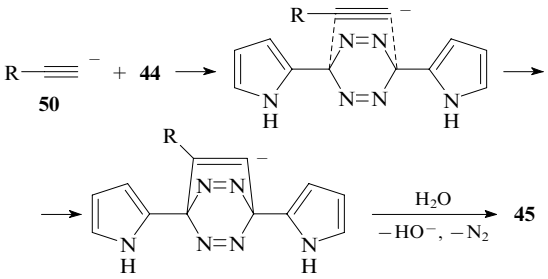
Tetrazine **44** reacts with the KOH–H_2O–DMSO system in the absence of acetylene (80 °C) to be converted to carbohydrazine **49** (Scheme 30),[287] thus confirming the formation of primary carbanion **46** — the tetrazine **44** adduct with the hydroxide ion.

Scheme 30



An alternative mechanism or a parallel pathway for [4+2]-cycloaddition of acetylenic carbanion **50** to tetrazine **44** (Scheme 31) has been discussed:[287] the higher HOMO energy of acetylide anion **50** (compared with that of unionized acetylene) compensates for the higher LUMO level of the diene (tetrazine **44**).

Scheme 31



According to publications,[288, 290, 291] for the inverse electron demand Diels–Alder reaction to occur, the difference between the tetrazine LUMO energy and the dienophile HOMO energy should amount to 4–5 eV. Quantum chemical calculations (by the MP2/cc-pVTZ//B3LYP/cc-pVTZ method) demonstrated[287] that the energy difference between the tetrazine **44** LUMO and acetylene HOMO is ~10–12 eV. However, on going to acetylenide ions **50**, this difference decreases to ~4 eV, which promotes more effective overlap of the frontier orbitals of the reacting species and, hence, facilitates the [4+2]-cycloaddition.

The reaction considered (see Scheme 28) opens up an easy route to 3,6-dipyrrolylpyridazines **45**, which are promising synthetic intermediates and monomers for electrically conducting polypyrroles with pyridazine spacers.

2. N-Vinylation

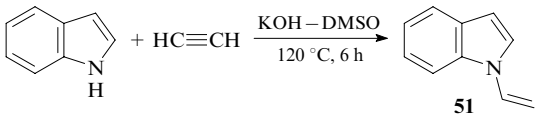
Although vinylation of NH-acids with acetylenes in the presence of bases has been known for a long time (see, for example, publications[136, 292–294]), the interest in this reaction still persists.

a. Vinylation of indole with acetylene

Poly(1-vinylindole), which is a close analogue of poly(9-vinyl)carbazole widely used for the fabrication of modern optoelectronic materials,[295–299] had been hardly accessible until recently due to the lack of a convenient method for the preparation of the 1-vinylindole monomer (**51**). The known methods were unsuitable for a real industrial process either due to low yields[300–304] or due to engineering complexity (high pressure,[305, 306] high explosiveness,[305, 306] necessity to handle potassium metal[292]).

Recently, an effective method for vinylation of indole with acetylene under atmospheric pressure in the KOH–DMSO superbasic system has been developed (Scheme 32).[307]

Scheme 32



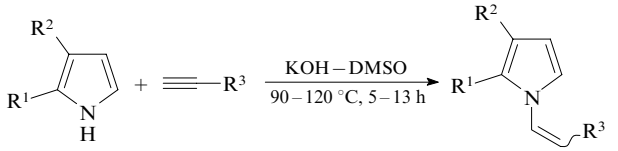
Under the developed conditions, 1-vinylindole (**51**) is obtained in a 94% yield and with > 99% purity after single vacuum distillation of the crude product (without fractionation).[307] It is important that the process is conducted under atmospheric pressure of acetylene and at moderate temperature with natural ions (K^+, HO^-) serving as the catalysts and a non-toxic high-boiling solvent (DMSO). This method opens up real prospects for the more extensive use of 1-vinylindole not only in laboratory but also in industry.

b. Vinylation of pyrroles with (het)arylacetylenes

The most direct approach to the synthesis of 1-styrylpyrroles **52** is vinylation of pyrroles with arylacetylenes. Recently, transition metal catalysis has been successfully used for this type of reactions.[308–311] However, base-catalyzed synthesis may become a more facile and environmentally safe method for the preparation of pyrrole analogues of stilbene. This suggestion follows from the known fact of easy nucleophilic addition of (het)arylpyrroles to unsubstituted acetylene in the KOH–DMSO system.[294] In the same system, pyrroles, indoles and di- and triazoles are readily isopropenylated by a propyne–allene mixture.[312] Recently, similar reports appeared (without references to the above-mentioned publications) about KOH–DMSO-catalyzed addition of azoles (mainly indoles) to arylacetylenes.[313, 314]

Simultaneously, as a continuation of earlier research,[294, 312] vinylation of a broad range of 2- and 2,3-substituted pyrroles with aryl- and hetarylacetylenes was successfully implemented in the same superbasic system (Scheme 33).[315]

Scheme 33



52 (⩽ 94%)

R^1 = H, Alk, Ar, Het; R^2 = H, Alk, Ar; R^3 = Ar, Het

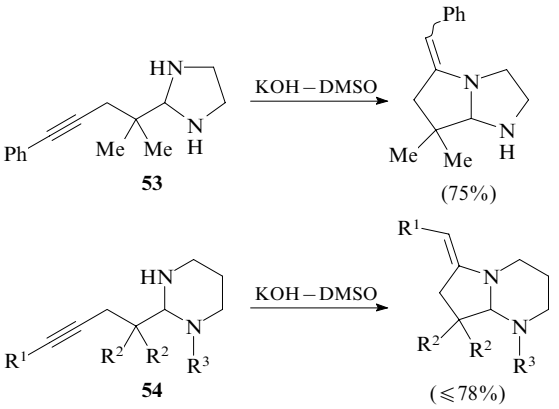
In this case, the vinylation stereochemistry is kinetically controlled, while the product ratio is dictated by subsequent

isomerization, *i.e.*, it is the thermodynamic result that depends on both the pyrrole and acetylene structures and the reaction conditions. This allows for producing single *E*- or *Z*-isomers of adducts **52**. This reaction solves the problem of synthesis of pure isomers of pyrrole-containing stilbene analogues.

Recently, the K_3PO_4–DMSO system was successfully used for N-vinylation of heterocycles by arylacetylenes (120 °C, 24 h).[316] Especially efficient was this catalyst for vinylation of imidazoles, which selectively gives *Z*-adducts in high yields. However, the addition of pyrrole and benzotriazole to phenylacetylene in this system gives moderate yields of adducts (38% and 13%, respectively), although high *Z*-selectivity of the reaction is retained. Morpholine is not vinylated at all under these conditions. Apparently, during the reaction, a minor amount of KOH is generated by hydrolysis of K_3PO_4 with water present in a trace amount in hygroscopic DMSO.

In the KOH–DMSO system, the intramolecular vinylation of alkynyltetrahydroimidazoles **53** or -hexahydropyrimidines **54** proceeds even at room temperature (Scheme 34).[317]

Scheme 34



R^1 = Ph, 4-FC_6H_4, 4-$F_3CC_6H_4$, 2-Th; R^2, R^3 = H, Me

3. O-Vinylation

Direct vinylation of alcohols with acetylene in superbasic media is of permanent interest. Most recently, attention has been drawn again to calcium carbide as a possible source of acetylene in the preparation of vinyl ethers.[6] As noted above, the reason is that acetylene is now becoming a renewable raw material due to the advent of calcium carbide production process from charcoal.[5] An alcohol–calcium carbide system may be classified as superbasic, in view of high basicity of calcium hydroxides and alkoxides formed in the reaction and especially the initial carbide as a metal acetylide. The first examples of vinylation of alcohols using calcium carbide were reported in our early works of the 1960s.[318, 319] Later, a method of alcohol vinylation using calcium carbide was claimed in a U.S. patent.[320] Since then, the method has not been further developed.

a. Vinylation of hydroxyl-containing furan derivatives

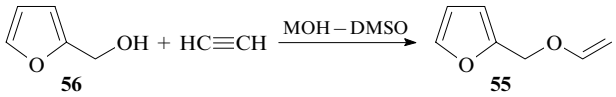
Furan derivatives are quite abundant in nature [321, 322] and are used to prepare drugs [323–328] and as modifying additives to electrolytes of lithium ion cells.[329–333]

2-Vinyloxymethylfuran (**55**) could become a promising monomer and building block for organic synthesis provided it is available. This highly reactive carrier of the furan ring can be used to obtain new furan derivatives: acetals, thioacetals, acylals, heterocyclic compounds and polymers.

Meanwhile, the reported synthesis of compound **55** from 2-hydroxymethylfuran (**56**) and acetylene [334, 335] is poorly practicable and has low efficiency: vinylation was carried out under acetylene pressure in the presence of KOH at a temperature of 125–160 °C and was accompanied by heavy resinification, which hampered the isolation and purification of the vinyl ether (yield 45% –68%).

It has been shown recently [336] that in the MOH–DMSO superbasic catalytic systems (M = Na, K), the reaction of 2-hydroxymethylfuran (**56**) with acetylene (Scheme 35) under elevated pressure occurs at lower temperature (75–85 °C), the yield of 2-vinyloxymethylfuran (**55**) being increased to 80%.

Scheme 35

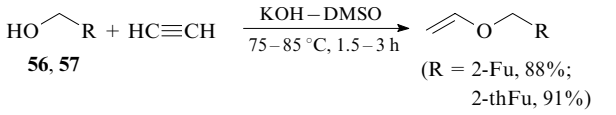


M = Na, K

When added to lithium sulfur battery electrolytes (1% amount), vinyl ether **55** or acetals synthesized from **55** increase the specific discharge capacity.[336]

Even more facile, effective and industrially feasible method for the vinylation of furan alcohols is based on the use of acetylene under atmospheric pressure in the KOH–DMSO system (Scheme 36).[337]

Scheme 36

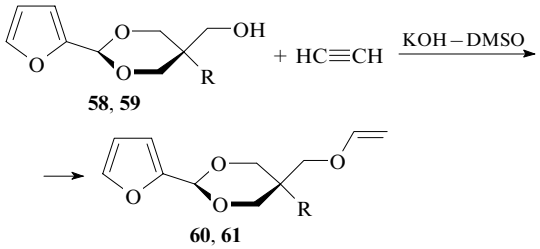


R = 2-Fu (**56**), 2-thFu (**57**); Fu is furyl, thFu is tetrahydrofuryl

Finally, the conditions were found for virtually quantitative vinylation of commercially available 2-hydroxymethylfuran (**56**) and 2-hydroxymethyltetrahydrofuran (**57**), close derivatives of furfural (the product of hydrolysis of pentosane raw materials).[338–340]

In the KOH–DMSO system, vinylation of *cis*-5-alkyl-5-hydroxymethyl-2-(2-furyl)-1,3-dioxane **58** or **59** under atmospheric (100 °C, 3 h) or increased acetylene pressure (85–90 °C, 3 h) occurs stereoselectively to give *cis*-5-alkyl-5-vinyloxymethyl-2-(2-furyl)-1,3-dioxane **60** or **61** in a yield of up to 93% (Scheme 37).[341]

Scheme 37



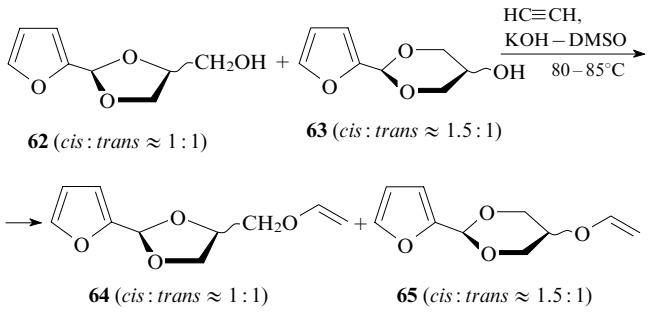
R = Me (**58**, **60**), Et (**59**, **61**)

Thus, an effective and stereoselective method for the synthesis of new functional 1,3-dioxanes containing furan

rings and vinyloxy groups suitable for further modification was developed.

In the KOH–DMSO superbasic suspension, dioxolane **62** and dioxane **63** (synthesized by heating glycerol and furfural in benzene in the presence of *p*-toluenesulfonic acid) representing a mixture of *cis*- and *trans*-isomers react with acetylene to give the corresponding vinyl ethers **64** and **65** in a total yield of 88%–90% (Scheme 38).[342] In the obtained vinyl ethers **64** and **65**, the ratio of structural and configuration isomers remains almost the same as in the starting alcohols **62** and **63**.

Scheme 38

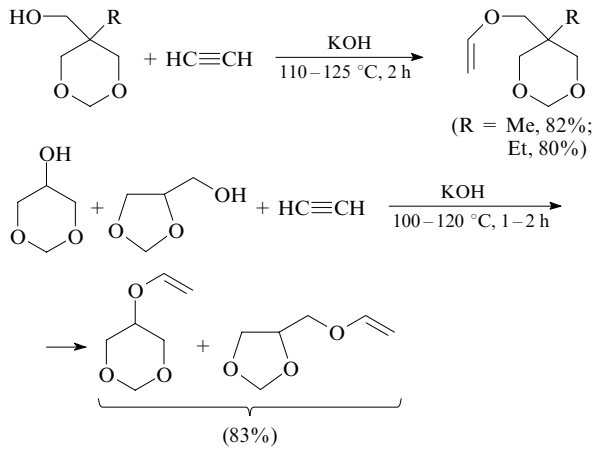


62 (*cis* : *trans* ≈ 1 : 1) **63** (*cis* : *trans* ≈ 1.5 : 1)

64 (*cis* : *trans* ≈ 1 : 1) **65** (*cis* : *trans* ≈ 1.5 : 1)

Interestingly, the vinylation of hydroxy-containing dioxanes and dioxolanes (derived from glycerol and other triatomic alcohols) in the presence of KOH without DMSO (Scheme 39) efficiency proceeds also under rather mild conditions (100–125 °C, 1–2 h).[343] Apparently, in this case, the role of the second superbase component is played by cyclic acetal structures capable of complex formation with potassium cation (similar to complex formation of alkali metal cations with crown ethers).

Scheme 39



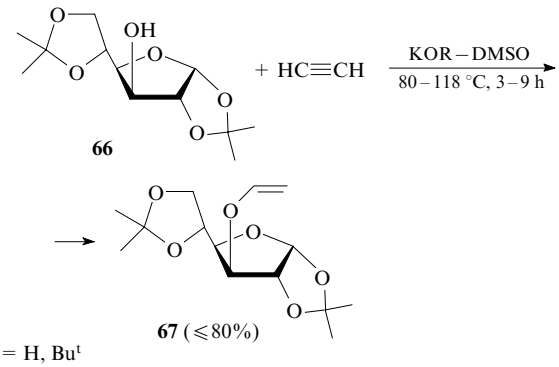
b. Vinylation of sugars and cellulose

The broad availability, optical purity and the presence of several easily transformable functional groups makes sugars unique chiral synthons. The additional functionalization by selective modification at one or several hydroxy groups markedly increases their synthetic potential and opens up new prospects for up-to-date asymmetric synthesis.[344, 345] Vinyl ethers of sugars and their derivatives are especially valuable chiral reagents due to versatile reactivity of the enol function and importance of the obtained products including oligosaccharides and hybrid carbohydrate polymers.

Compared with the known methods for the preparation of carbohydrate vinyl ethers, direct vinylation of sugars with acetylene in the presence of alkali metal hydroxides or alkoxides can provide the basis for a more facile and effective industrial process. In addition, such catalysts are safer and more readily accessible than mercury salts[346–348] or rare and noble metal complexes,[349, 350] which are used most often to catalyze reactions resulting in sugar vinyl ethers.

Certain advances along this line were attained upon vinylation of some glucose derivatives with acetylene.[351] Glucofuranose **66** was found to react with acetylene in the KOH–DMSO or KOBu^t–DMSO system under atmospheric (107–118 °C) or elevated pressure (the initial pressure at room temperature is 12–14 atm, 80–89 °C) to give vinyl ether **67** in a 68%–70% or 80% yield, respectively (Scheme 40).[351]

Scheme 40



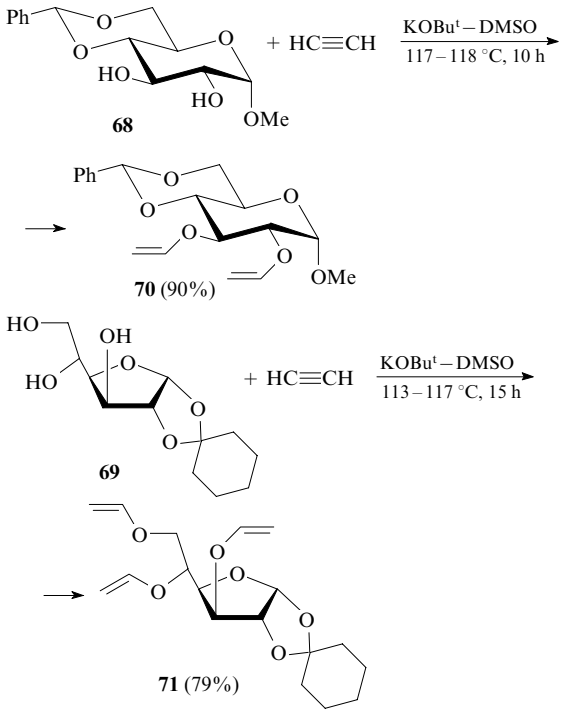
66

67 (⩽80%)

R = H, Bu^t

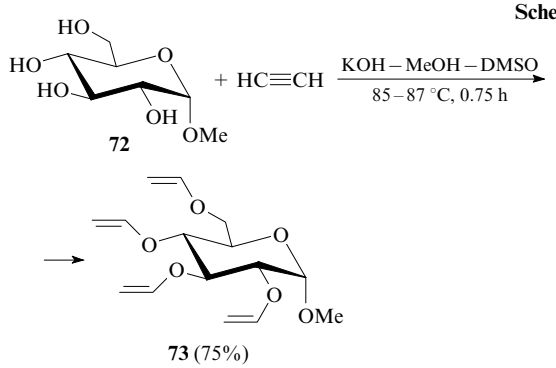
In the KOBu^t–DMSO system, the glucose derivatives **68** and **69** are exhaustively vinylated with acetylene under atmospheric pressure to give di- (90% yield) and trivinyl (79% yield) ethers **70** and **71**, respectively (Scheme 41).[351]

Scheme 41



Glucopyranoside **72** and acetylene were converted under pressure in the KOH–MeOH–DMSO system to tetravinyl ether **73** (Scheme 42).[351, 352]

Scheme 42



72 **73** (75%)

Recently, various sorts of cellulose were successfully vinylated with acetylene under elevated pressure in the MOH–DMSO and MOH–THF systems (M = Na, K) (Scheme 43).[353] Depending on the reaction conditions, the degree of replacement of hydroxy groups by vinyloxy groups was 0.11–1.22, while the yield of vinylated cellulose varied from 41% to 89%.

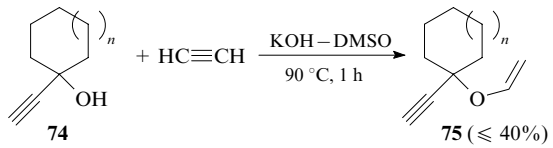
c. Vinylation of tertiary propargyl alcohols

Since tertiary propargyl alcohols rapidly decompose into ketones and acetylene in the presence of bases (reverse Favorskii reaction), it seemed quite natural that their base-catalyzed vinylation with acetylene has not been reported in the literature. Meanwhile, this vinylation can be implemented if its rate is much higher than the rate of the reverse Favorskii reaction.

As noted above, the classical vinylation of alcohols with acetylene was substantially advanced in the last decades (in particular, the reaction rate was increased) owing to the use of superbasic catalytic systems,[61–63] which enabled vinylation of propargyl alcohol[354] and secondary propargyl alcohols.[138, 139] Thus, one could hope that superbasic systems would accelerate vinylation to a higher extent than the reverse Favorskii reaction.

Indeed, by treating 1-ethynylcycloalkanols **74** with acetylene under elevated pressure in the KOH–DMSO system, vinyl ethers of tertiary propargyl alcohols **75** were prepared for the first time (Scheme 44).[355]

Scheme 44

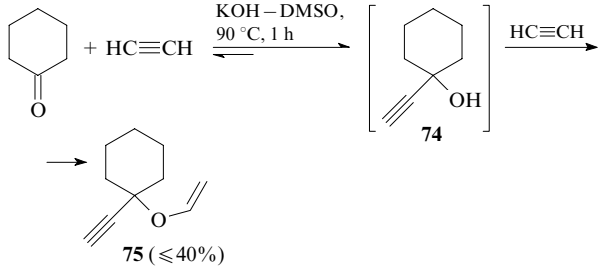


74 **75** (⩽ 40%)

n = 1, 2

Then it was demonstrated in relation to the reaction of cyclohexanone with acetylene that vinyl ethers **75** can be obtained in one preparative step by heating ketones with acetylene under the same conditions (Scheme 45).[356]

Scheme 45

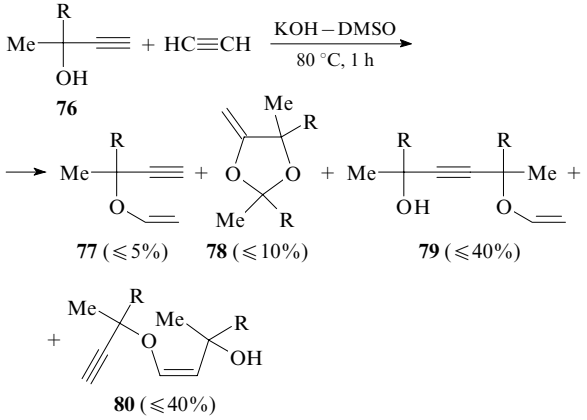


74 **75** (⩽40%)

The increased acetylene concentration in the liquid phase (resulting from high acetylene solubility in DMSO, especially under pressure) forces the equilibrium towards the formation of 1-ethynylcyclohexanol **74**, which nucleophilically adds to acetylene.

Dialkylethynylmethanols **76** react with acetylene to give, apart from expected vinyl ethers **77**, also 5-methylene-1,3-dioxolanes **78**, monovinyl ethers of acetylenic diols **79** and self-vinylation products **80** (Scheme 46).[357]

Scheme 46

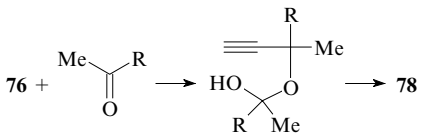


76 **77** (⩽5%) **78** (⩽10%) **79** (⩽40%) **80** (⩽40%)

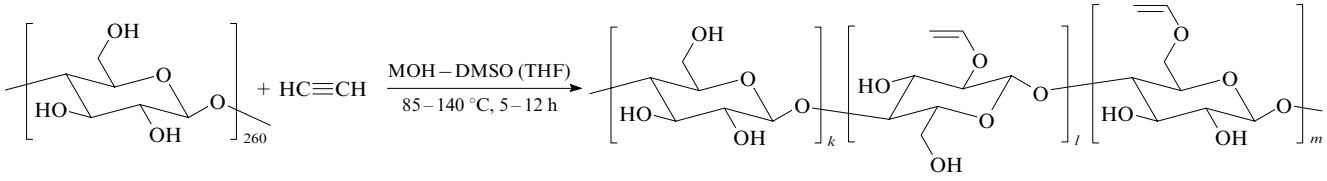
R = Me, Et

5-Methylene-1,3-dioxolanes **78** result from nucleophilic addition of the starting propargyl alcohol **76** to ketone (formed upon the reverse Favorskii reaction) and subsequent intramolecular vinylation of hemiacetal **81** (Scheme 47).

Scheme 47

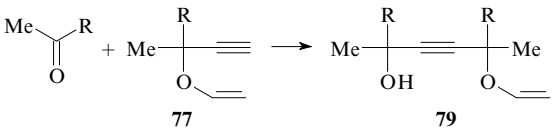


Scheme 43



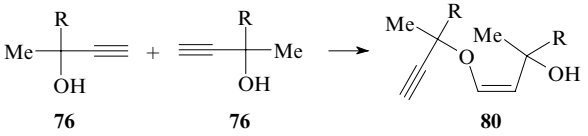
Monovinyl acetylenic diol ethers **79** are formed upon ethynylation of ketones existing in equilibrium by vinyl ethers of tertiary acetylenic alcohols **77** (Scheme 48).

Scheme 48



The stereoselectivity of self-vinylation (formation of adducts **80** of *Z*-configuration, Scheme 49) complies with the known rule of concerted nucleophilic *trans*-addition to a triple bond.[120]

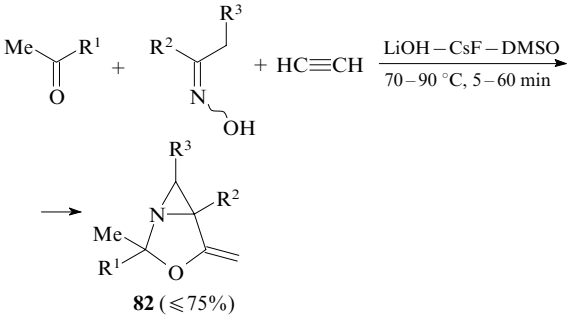
Scheme 49



d. Synthesis of 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes

In the LiOH–CsF–DMSO superbasic system, the three-component reaction of ketones, ketoximes and acetylene leads to selective formation of a new class of heterocycles — 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes **82** (Scheme 50).[358]

Scheme 50

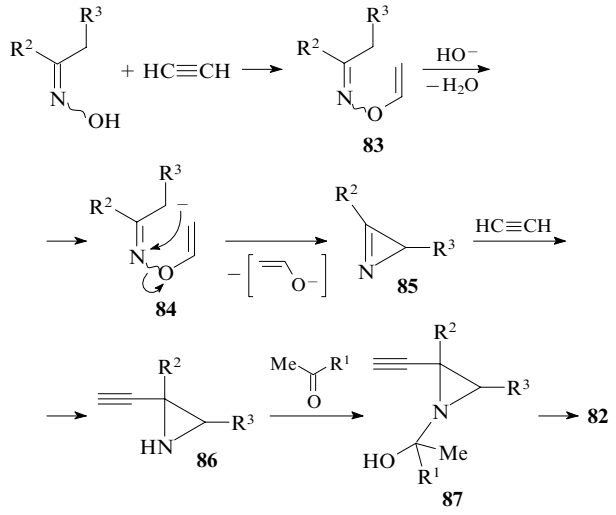


R^1 = Me, Bu^t; R^2 = Ph, 2-Naph, 2-Th, 1-Pyr;
R^3 = H, Bu^t; Pyr is pyrenyl

Presumably, the reaction starts with O-vinylation of ketoxime (Scheme 51). Then under the action of the superbase, *O*-vinylketoxime **83** is deprotonated at the α-position relative to the oxime function. The carbanion **84** formed substitutes the vinyloxy group in the same molecule, thus closing the azirine ring of compound **85**. The latter adds acetylene carbanion at the C=N double bond (aza-analogue of the Favorskii ethynylation). Then ethynylated aziridine **86** attacks the ketone carbonyl group by the nitrogen atom to give ethynylated amino alcohol **87**, which forms a bicyclic structure upon intramolecular vinylation.

The synthesized 4-methylene-3-oxa-1-azabicyclo[3.1.0]-hexanes **82** are structural analogues of the natural and synthetic molecules with clear-cut biological activities (immunomodulators,[359] antimicrobial agents[360] and drugs for treating glaucoma[361] and Alzheimer disease).[362] Since products **82** are synthesized by a simple one-step method from readily accessible starting compounds, they can be expected to form a basis for drug development.

Scheme 51



e. Quantum chemical consideration of the nucleophilic addition to acetylene in the KOH–DMSO system

The formation of nucleophilic species and their addition to acetylene were studied in relation to the reaction of methanol and acetoxime with acetylene in a KOH–DMSO superbasic system by the MP2/6-311++G**//MP2/6-31+G* method with inclusion of one DMSO molecule in combination with the polarizable continuum model (PCM).[363]

The calculations show that the reaction of methanol and acetoxime with the KOH–DMSO system affords stable complexes $MeOH \cdot KOH \cdot DMSO$ and $Me_2C{=}NOH \cdot KOH \cdot DMSO$ with formation energies of -10.4 and -17.7 kcal mol^{-1}, respectively. The K–O bond length increases by 0.262 and 0.236 Å, respectively. Then the complexes $MeOK \cdot DMSO \cdot H_2O$ and $Me_2C{=}NOK \cdot DMSO \cdot H_2O$ are formed. In these complexes, nucleophiles occur as contact ion pairs with a weakened interaction between the cation and the anion. Thus, the reaction of the acetylene molecule with the anionic complexes to give the vinylation products proceeds *via* low-stability pre-reaction complexes and then *via* transition states with a typical *trans*-distortion of the acetylene molecule.[364]

According to calculations, the total cycle of methanol and acetoxime vinylation comprising the generation of a nucleophilic species, its addition to the triple bond, protonation of the carbanion to give the final product and regeneration of the superbasic catalyst is accomplished in the coordination environment of the potassium cation.

The estimates of the activation barriers for the nucleophilic addition of methanol (23.9 kcal mol^{-1}) and acetoxime (30.9 kcal mol^{-1}) to acetylene are in qualitative agreement with the experiment.

IV. Conclusion

The reactivity of acetylenes in the presence of strong bases still brings surprises for researchers. The fundamental reason is the amphoteric nature of acetylenes, *i.e.*, the

ability to simultaneously function as electrophilic and nucleophilic reagents. In the presence of strong bases (superbases), this dual nature of acetylenes is most pronounced — they are deprotonated to a higher extent; in addition, the anions that attack the triple bond and the acetylide anions are more reactive owing to desolvation. Combinations of these competing processes (acetylene deprotonation and addition of anions to the triple bond) provides the possibility of new reactions, which are often one-pot multistep assemblies of intricate structures. As superbasic catalysts and reagents, suspensions and solutions of alkali metal hydroxides or alkoxides in polar non-hydroxyl-containing solvents (dimethyl sulfoxide, *N*-methylpyrrolidone or hexamethylphosphoric triamide) proved efficient. They are distinguished by high and easily controllable (by small water or alcohol additives) basicity, ready accessibility and convenient use. An especially important feature of this type of superbases is a change in the catalytic activity depending on the nature of the alkali metal and the structure and concentration of the base. As a rule, the reactions take place in a complex equilibrium heterogeneous system in which the base is represented by both dissolved molecules and various nanoclusters and solid-state particles (submicron- and micron-sized crystals).

It is in the KOH–DMSO and KOBu^t–DMSO systems that nucleophilic addition of ketones to aryl- and hetaryl-acetylenes was recently accomplished for the first time to stereoselectively give β,γ-ethylene ketones of *E*-configuration (a new general reaction of carbon–carbon bond formation),[182–187] which discloses previously unknown aspects of acetylene and ketone chemistry. It was already found out that this reaction can be used for high-performance one-pot synthesis of Δ^2-isoxazolines directly from ketones, acetylenes and hydroxylamine.[209] It has became the basis for one-pot synthesis of hexahydroazulenones from 2-alkylcyclohexanones and arylacetylenes,[244] and 6,8-dioxabicyclo[3.2.1]octanes (the scaffold of some insect pheromones of the frontalin series and hormones of warm-blooded species) from two ketone molecules and two acetylene molecules.[250] It is evident that this is only the first advances in the utilization of the discovered reaction by organic synthesis. The scope of its applicability is still to be extended, in particular, it could be used for functionalized acetylenes (propargyl ethers form the first example).[245] The obtained products, especially β,γ-ethylene ketones, which are still difficult to prepare, could be used as synthons and intermediates in the design of intricate molecules.

The KOH–DMSO system provided easy hydroamination of acetylenes with pyrroles[315] and indoles,[307, 315] successful vinylation with acetylene of various furan alcohols[336, 337, 341, 342] and glucose derivatives.[351, 352] Of obvious practical interest is effective vinylation of cellulose performed in the same superbasic systems,[353] which would open up new, in principle, opportunities for modification of cellulose-based materials.

The information presented in the review indicates that the studies of reactions of acetylenes in superbasic catalytic systems become more and more popular. The nucleophilic addition to acetylenes in the alkali metal hydroxide (alkoxide)–dimethyl sulfoxide type systems is already being systematically studied at the modern quantum chemical level.[84, 363–369] This occurs in parallel with enhancement of the interest in the whole chemistry of acetylene as an economic and environmentally clean source of important organic products.

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