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Synthetic aspects of the chemistry of *p*,π-unsaturated amines

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ABSTRACT. The review covers the electrophilic and nucleophilic addition of mono- and bi-functionalised reagents to ynamino-carbonyl compounds to 1,3-enynes possessing an enamine or ynamine group. Amines of this type are synthons for preparing five-, six-, seven- and eight-membered rings with two heteroatoms as well as condensed ring systems. The effect of the structure of the acetylenic compound on the mode of interaction has been analysed. Special features of the intra- and inter-molecularity of the reactions were discussed. Data are presented in 1,3-dipolar cycloaddition with all three types of amine.

The bibliography contains 108 references.

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I. Introduction

Acetylenes and their nitogen-containing derivatives play an important role in modern organic chemistry, as indicated in a number of reviews[1–3] and monographs.[4–7]

Over the last ten years, acetylene chemistry has developed along non-classical lines, and there has been particular emphasis on the study of 1,3-enynes possessing an ynamine (I) or enamine groups (II) and of ynaminocarbonyl compounds of type (III).

$$\underset{(I)}{R_2NC{\equiv}CCH{=}CR_2'}, \quad \underset{(II)}{R_2NCH{=}CHC{\equiv}CR'}, \quad \underset{(III)}{R_2NC{\equiv}CCOX},$$

where X = H, R′, OR′.

The reactivity of such compounds is different from that of the corresponding 1,3-enynes and acetylenecarbonyl compounds, and the amino group reactivity differs from that of simple tertiary amines. Unsaturated nitrogen-containing systems of this type, which are obtainable from the commercially available diacetylene[1], vinylacetylene and propargyl alcohol, are valuable synthons for the preparation of five-, six-, seven- and eight-membered heterocyclics with two heteroatoms, as well as condensed systems. In addition, alkenylynamines and ynaminocarbonyl compounds are synthetically useful starting materials for the synthesis of novel types of polyfunctionalised compound.

The study of reactions of *p*,π-conjugated unsaturated amines with bifunctional compounds, and research into structural effects, the nature of the reagent and the factors affecting the course of the reaction, have provided the basis for new routes to synthetically important compounds. The chemistry of ynamines has particularly developed in this direction during recent years, and their participation in multi-step syntheses of terpenes, steroids[8], vitamin D_3 [9] and peptides[5] has been noted. Conjugated ynamines with acceptor groups are especially valuable in this respect. They are considerably more active than simple and vinylacetylenic ynamines; furthermore, they possess reaction centres which offer wider scope for synthetic applications.

In one of the recent reviews, Shrot[2] states that "in the synthesis of heterocycles the triple bond serves as a latent carbonyl function, participating in the usual carbonyl condensations as well as in heteronucleophilic addition, being equivalent to vinylation at a heteronucleophilic centre". Developing the concept of "alkynes as pseudo-carbonyl compounds", the author formulated an orientation principle which is governed largely by electronic effects; other factors are not considered.

In heterocyclic syntheses from *p*,π-unsaturated amines (I–III), the pattern of behaviour is more complex.

II. The interaction of *p*,π-unsaturated amines with mono-functionalised electrophiles and nucleophiles

1. Reactions of alkenylynamines

The first compounds with an ynamine structure (in the phenothiazine series) were obtained by chance in 1958. In 1961, while studying the nucleophilic replacement of halogen at sp^2- and *sp*-carbon atoms, Belgian chemists developed a number of methods of preparing this class of compound. Around the same time, further syntheses of ynamines were carried out by Viehe et al. (FRG), Ficini et al. (France), Arens et al. (Holland), A A Petrov et al. (USSR) and by a number of chemists in the United States.[5]

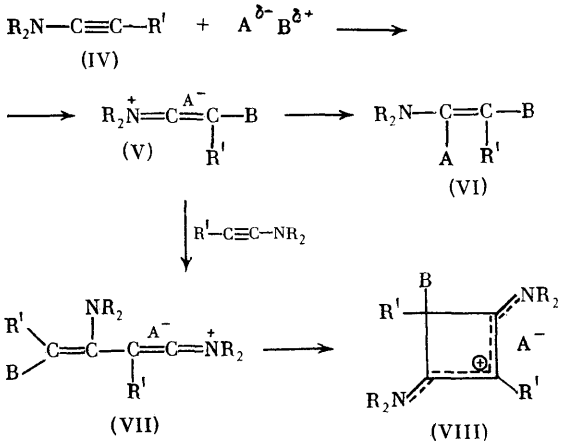
Contrasting with acetylenic hydrocarbons, conjugated *p*,π-unsaturated ynamines are strong nucleophiles.

By interaction of ynamines (IV) with a polar molecule, $A^{\delta-}B^{\delta+}$, reaction proceeds at the C_2-atom with formation of a ketenimminium salt (V) (Scheme 1).

It is quite probable that the mechanism involves addition of B^+ at the nitrogen atom. Such an interaction would not be unlike that of the corresponding enamines,[6] but in the case of ynamines no stable salts have been formed. In the meantime, Drenth[10] reported a kinetic study of the acid-catalysed hydration of ynamines by stopped flow technique, which confirmed the formation of N-protonated intermediates with subsequent charge transfer to the C_2-atom of the acetylene group. The rate constant for the hydration of ynamines is 2000 times greater than that for the hydration of enamines. This is because the process of transferring a proton from the nitrogen atom

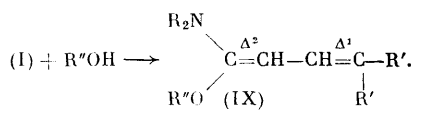
to the β-carbon of the ynamine is concerted, the separation and addition of the proton being accomplished in one step.

Scheme 1

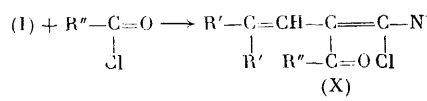


The pathway by which the ketenimminium salt is transformed is dependent on the reagent. Thus, on treatment with electrophilic reagents having a weakly nucleophilic anion, the salt (V) undergoes subsequent reaction with a second ynamine molecule rather than with the anion; in this way, an enamine-ketenimminium intermediate (VII) is formed, which subsequently undergoes intramolecular C-alkylation to form a π-cyclobutenyl cation (VIII) via addition of B^+ to the corresponding cyclobutadiene.[11]

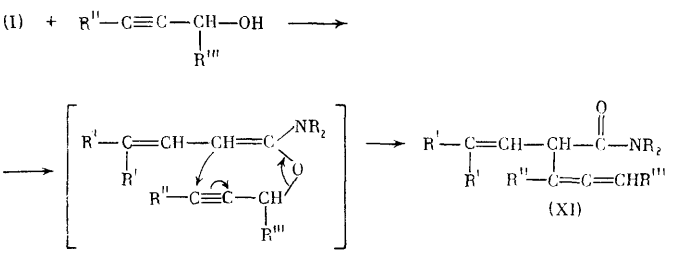
The reactivity of 1-dialkylaminoalk-3-en-1-ynes is noticeably less than that of simple ynamines. Thus, interaction with electrophilic reagents having a weakly nucleophilic anion, e.g. phenols, proceeds with the formation of vinylketene O,N-acetals, namely 1-dialkylamino-1-(aryloxy or alkoxy)-1,3-pentadienes, rather than cyclobutenium salts (VIII) as described above. Reaction proceeds regio- and stereo-specifically across the Δ^2-bond with formation of a *cis*-adduct.[12]



Ketenimminium salts (V) react with electrophilic reagents having strongly nucleophilic anions by addition of the anion A^-. Thus, treatment of 1-dialkylaminoalk-3-en-1-ynes with acetyl chloride or benzoyl chloride affords 1-dialkylamino-1-chloro-2-acetyl(benzoyl)-1,3-pentadienes (X) which are readily distillable.[13]

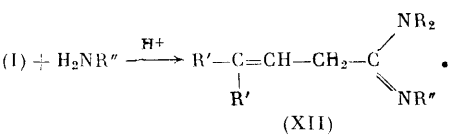


In certain cases, the ketenimminium salts (V) are sufficiently nucleophilic in themselves, and participate in Claisen rearrangement. Thus, branched dialkylamides of β-allenecarboxylic acids (XI) have been prepared by reaction of 1-dialkylamino-3-penten-1-ynes with propargyl alcohol.[14] Reaction with propargyl alcohol derivatives proceeds quite readily since the electron-accepting acetylene group increases the acidity of the alcohol.

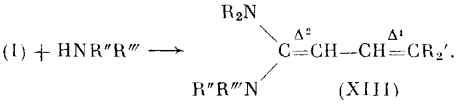


Reaction of vinylacetylenic ynamines with nucleophiles proceeds only by acid catalysis. Thus, for nitrogen-containing analogues of propargyl alcohol the amino-Claisen rearrangement does not take place.

In catalysed reactions of 4-alkyl-1-dialkylamino-3-penten-1-ynes with primary amines, the amino group attaches to the C_1-atom of the multiple bond, but the interaction is complicated by protropic rearrangement involving the participation of the second labile hydrogen of the amino group with the formation of per-N-substituted amidines of 4-alkyl-3-pentenoic acids (XII).[15]

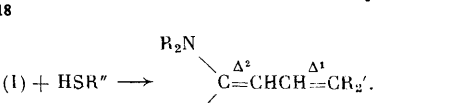


Reactions of 1-dialkylamino-4-methyl-3-penten-1-ynes with secondary aliphatic, aromatic and heterocyclic amines proceed regioselectively and with *cis*-stereospecificity across the acetylenic bond with formation of conjugated vinylketone aminals (XIII).[16,17]



From data on the reactivity of primary and secondary amines, it is clear that weakly basic amines are more reactive than highly basic amines since the latter inhibit acid catalysis. However, this is only true within a limited range of the basicity constant. Butylamine (pK_B = 3.2) and cyclohexylamine (pK_B = 3.34) are far less reactive than aniline (pK_B = 9.37). Secondary heterocyclic amines (piperidine, pK_B = 2.88) react far less than N-alkylaromatic amines (N-methylaniline, pK_B = 9.15) even though there is significant steric hindrance in the latter. *p*-Nitroaniline does not take part in the addition since its nucleophilic acitivity is low.

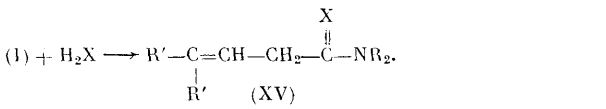
The addition of aliphatic and aromatic thiols proceeds across the acetylenic bond with the formation of vinylketone N,S-thioacetals (XIV).[18]



Reaction is not stereospecific. Reaction is regioselective and proceeds in the same manner as those described above, i.e. by attack of the nucleophile at the C_1-atom of the aminoenyne. However, mixtures of *Z*- and *E*-Δ^2-isomers are formed. The isomeric composition varies significantly and reproducible results cannot be achieved. This is because sulphur-functionalised ethylenes readily isomerise—a well-known observation in sulphur chemistry.

It cannot be excluded that a radical mechanism is involved in parallel with an electrophilic process. The interaction of (I) with RSH differs significantly from the reaction of simple ynamines. Thus, addition of propenethiol to the latter is accompanied by thio-Claisen rearrangement with formation of thioamides.[5]

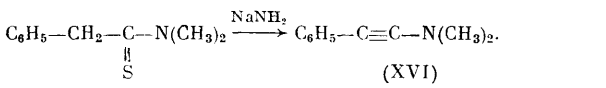
The group $R_2NC{\equiv}C-$, is a masked carboxylic acid amide function. Thus, addition of compounds of the type H_2X (X = O, S, Se) to 1-dialkylamino-3-alken-1-ynes affords β,α-ethylenecarboxylic acid amides, thioamides and selenoamides, respectively (XV).[19,20]



(XV)

The thiol group displays significantly higher acidity and nucleophilicity than the hydroxyl group in similar compounds. Thus, reactions with H_2S and H_2Se proceed far more readily than reaction with water, the reactivity of the reagents increasing in the order O < S < Se.

In the case of thioamides, reaction can be reversed, i.e. synthesis of ynamines can be based on thioamides. The corresponding amides do not participate in the reverse reaction.[5]

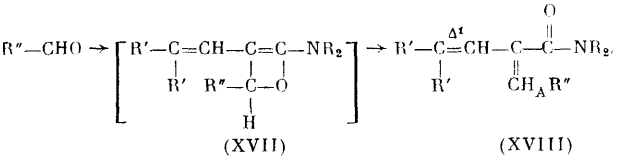


(XVI)

By comparison, the hydration of aminoenynes is not in itself of great interest. However, one should recall that this reaction has been applied in the dehydrative syntheses of functionalised carboxylic acid derivatives and in peptide synthesis.[5,20]

Thus, summarising the reactions of vinylacetylenic ynamines with simple nucleophiles, it should be noted that the nucleophile attacks the C_1-atom of the hetero-substituted acetylene bond, as is the case with the reactins of ynolethers, ynamines and enynolethers.

Alkenylynamines react with compounds containing polar multiple bonds, e.g. $>C=O$ (aldehydes, ketones, carboxylic acid esters) via intermediate formation of cycloaddition products, as is the case with simple ynamines.[26] Thus, substituted amides of unsaturated carboxylic acids (XVIII) are obtained in 60–65% by reaction of (I) with both aliphatic and aromatic aldehydes in the absence of catalyst.[21]



(XVII) (XVIII)

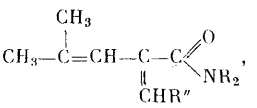
It is likely that reaction proceeds through an intermediate oxete, formed by the synchronous addition of the carbonyl atom group to the triple bond. Thus, for the reaction of 1-diethylamino-4-methyl-3-penten-1-yne with butanal, the ^1H NMR spectrum displays, in addition to signals from product (XVIII), a weak triplet (4.23 p.p.m.), which would correspond to the protons of the oxete ring in (XVII). This signal was absent when the spectrum was retaken after 2 days. Intermediates of type (XVII) have been isolated from the reaction of ynolethers with ketones.[22]

The ^1H NMR spectrum of (XVIII) (Table 1) confirms the formation of only one Δ^2-isomer. For structural confirmation, the experimental values of the chemical shifts of proton H_A were in agreement with those calculated according to the formula:[54]

$$\delta_H = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}.$$

From the data presented, it is clear that the experimental values are close to the values for the *cis*-isomer, and noticeably different from those calculated for the *trans*-isomer. The *cis*-structure for (XVIII) is consistent with the proposal that reaction proceeds via a stereo-defined oxete ring. The isomeric composition at the Δ^1-unsaturation corresponds approximately with the proportion of double bond isomers in the starting ynamine—30% *trans*-isomer and 70% *cis*-isomer. Thus, the double bond in the starting ynamine (I) does not take part in the reaction.

Table 1. Chemical shifts of vinylic protons



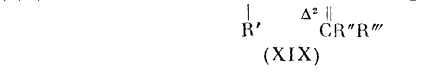
where R″ = CH_3 (XVIIIa), C_2H_5 (XVIIIb), C_3H_7 (XVIIIc).

for *cis*- and *trans*-isomers at the Δ^2-bond.

Compound	δ_H (found) p.p.m.		δ_H(calculated), p.p.m.	
	cis	*trans*	*cis*	*trans*
(XVIIIa)	5.52	—	6.00	6.45
(XVIIIb)	6.36	—	6.74	7.42
(XVIIIc)	6.56	—	7.01	7.69

According to the literature,[23] alkylamines readily react with ketones. However, reaction of alkenylynamines with ketones, under the conditions of the aldehyde addition, was not possible, except in the case of alkenylynamines (II) with cyclohexanone. Here, the yield is only 50% and the amount of catalyst had to be doubled.

Acetone and acetophenone react with alkenylynamines in the presence of a stoichiometric amount of $MgBr_2$. The latter is known to activate the carbonyl group of ketones by complex formation which increases the δ^+ charge on the carbon atom.[21]



(XIX)

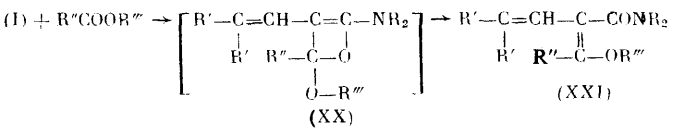
Reaction is regioselective, as with aldehydes; however, in the case of acetophenone stereospecificity is reduced with the formation of Δ^2-isomers in 67:33 proportion.

Thus, it has been shown, that alkenylynamines react with aldehydes regioselectively and stereospecifically at the triple bond in the presence of a catalytic amount of BF_3-etherate. Ketones only participate in the reaction in the presence of stoichiometric amount of $MgBr_2$ with the same regioselectivity, but reduced stereo-specificity.

The decrease in the electrophilic activity of the carbonyl group from ketones to carboxylic acid esters explains the lower activity of the latter in reactions with alkenylynamines. $MgBr_2$-ethereate serves as catalyst only with addition of ethyl acetate, and only on heating.

With carboxylic acid esters, there is a marked difference of reactivity between aliphatic and aromatic compounds. Methyl

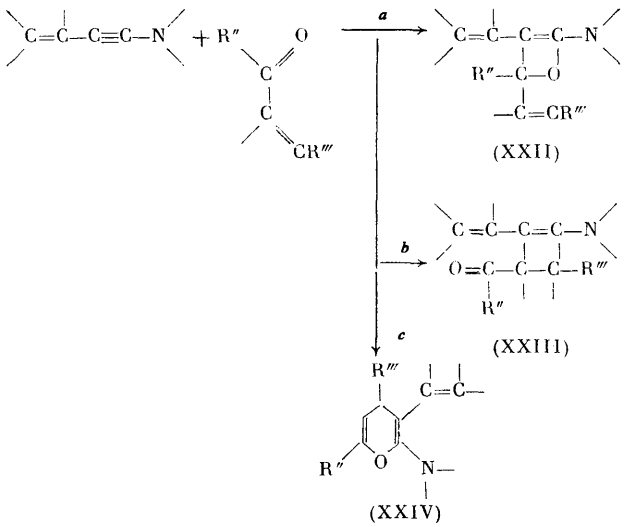
benzoate adds to alkenylynamines only in the presence of a stoichiometric amount of boron fluoride, the product yield being around 6–7%. The majority of unreacted methyl benzoate can be removed by distillation. The unconverted alkenylynamines polymerise, which evidently explains the low yield of adducts (XXI).[24]



(XX) (XXI)

Cycloaddition is strictly chemoselective, reaction taking place only at the triple bond of ynamine. A [2 + 2]-cycloaddition is involved. The intermediate oxete (XX) is unstable, and is immediately converted to the dialkylamides of the corresponding carboxylic acid.

For cycloaddition of α,β-unsaturated aldehydes and ketones to alkenylynamines, there are several possible pathways (*a*–*c*).[25]



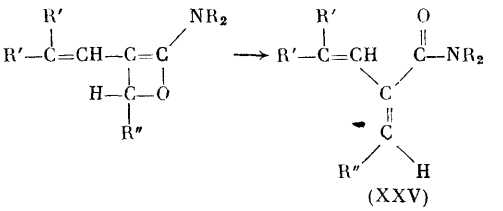
(XXII) (XXIII) (XXIV)

The more probable cisoid conformation should favour route *c* ([4 + 2]-cycloaddition), and the transoid conformation should favour route *b*. It has been shown, in fact, that [2 + 2]-cycloaddition of carbonyl compounds across the C=C bond (route *b*) is characteristic of cyclic ketones having a fixed transoid conformation.[26]

On the same theme, a study has been made of the reaction between alkenylynamines and α,β-unsaturated carbonyl compounds. Here is it assumed that rotation around the C–C bond is more rapid than the interconversion of the *cis*- and *trans*-conformers. For cinnamaldehyde one might anticipate reaction by all three pathways. It has been shown that, on reaction with 1-diethylamino-1-propyne, adducts are formed only by routes *a* and *c*.[27,28] In this particular example reaction takes place only on the carbonyl group (route *a*).

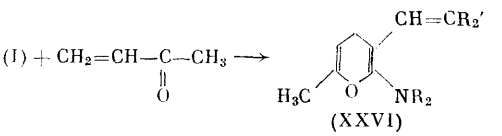
Phenylpropional might be expected to add with formation of products via a cyclobutadiene intermediate, as is characteristic of the reaction of alkenylynamines with activated acetylenes.[29,30] However, in the case of alkenylynamines, addition takes place only across the aldehyde group (route *a*) via an oxete intermediate.

^{1}H NMR spectral data confirms that only Δ^2-isomer is formed. The intermediate oxete undergoes electrocyclic ring opening by the most sterically favourable pathway. Thus, as with aliphatic and aromatic aldehydes[26], the *E*-isomer is formed.



(XXV)

Alkenylynamines react with methyl vinyl ketones by [4 + 2]-cycloaddition (route *c*) to give (XXVI).[25]



(XXVI)

Only scant reference to 4*H*-pyrans is given in the literature. Nevertheless, interest in this class of compound is great, primarily because 4*H*-pyrans are useful starting materials for the synthesis of pyrylium salts and unsaturated 1,5-diketones.[31] It is interesting to note that methyl vinyl ketone reacts with enamines either by heterocyclisation to give dihydro-4*H*-pyrans or by proton transfer to give unsaturated carboxamides.[32] Such proton transfer is not possible with ynamines since the system is fully unsaturated. As illustrated above, alkenylynamines can serve as valuable reagents for the synthesis of dialkylamino-4*H*-pyrans.

Summarising, the relative reactivity of the C=C and C=O group in α,β-unsaturated aldehydes and ketones determines the mode of addition to alkenylynamines.

2. Reactions of vinylacetylenic enamines, $R_2N-CH=CH-C\equiv CR'$, with mono-functionalised agents

In contrast with acetylenic hydrocarbons, en- and yn-amines readily participate in electrophilic reactions, and as a consequence the addition of nucleophilic reagents can take place, both in the presence and absence of mineral acid. However, with aminoenyne systems, the nature of the addition process is dependent on whether the amino group is attached to the ethylenic or acetylenic fragment.

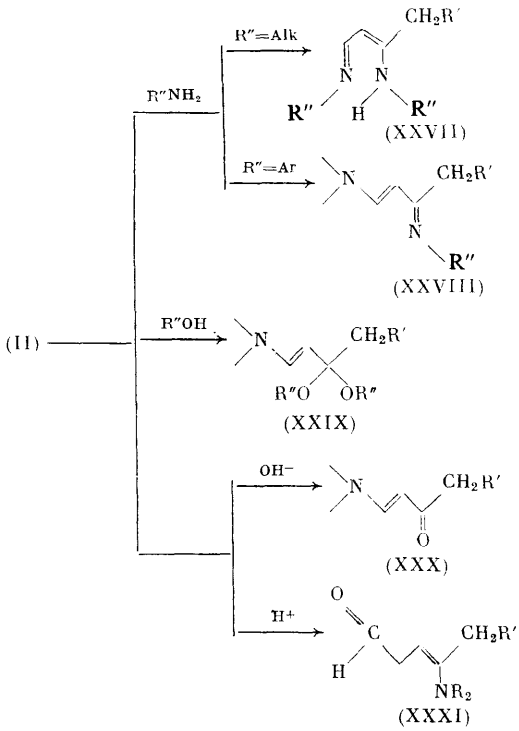
Thus, enamines $R_2N-CH=CH-C\equiv CR'$ (II) react with primary aliphatic amines to give vinylogous and potentially tautomeric aminocrotonaldimines (XXVII) via transamination; on the other hand, reaction with arylamines proceeds with formation of (XXVIII) (Scheme 2).[33,34]

Base-catalysed addition of alcohols leads to vinylogous amide acetals (XXIX).[35] Depending on reaction conditions, hydration of (II) can provide β-aminovinyl ketones or β-aminocrotonoaldehydes.[35,37]

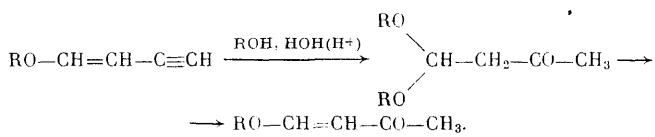
It should be pointed out that compounds (XXVII) are of potential synthetic utility. Thus, subsequent C-alkylation and hydrogenation affords N-monosubstituted 1-aminoalkanes as synthons for the nucleophilic incorporation of the 4-aminobutyl group (R = H).[36]

It is interesting to note that the reaction of 1-alkoxy-1-butene-3-ynes with alcohols affords primarily the C_1-adducts, hydration of

Scheme 2



which leads to β-ketoacetals, thence β-alkoxyvinyl ketones by thermolysis.[4]



According to Engelhardt[38], vinylacetylene undergoes 1,4-addition with secondary amines.

$$R_2NH + CH_2{=}CH{-}C{\equiv}CH \rightarrow R_2N{-}CH_2{-}CH{=}C{=}CH_2.$$

Badanyan reported the same mode of addition with tert-aminomethyl derivatives[39], i.e. the additional amino function has no effect on the reaction.

$$R_2N{-}CH_2{-}C{\equiv}C{-}CH{=}CH_2 + R_2'NH \rightarrow$$
$$\rightarrow R_2N{-}CH_2{-}CH{=}C{=}CH{-}CH_2{-}NR_2'.$$

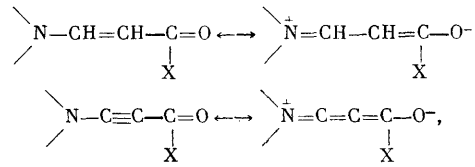
Because the chemistry of enamines (II) has already been the subject of a review[1] and a monograph[4], the present article covers only general trends in the reactions of this compound class in relation to other types of amine.

3. Reaction of ynaminocabonyl compounds, $R_2NC{\equiv}CCOX$ (III), with mono-functionalised reagents

The chemistry of enaminocarbonyl compounds has been well documented in a monograph[40] and in a number of review articles published in recent years[2,41]. Acetylene analogues of carbonyl compounds, first prepared some 100 years after the corresponding ethylenic derivatives, have been studied somewhat less. Data on their relative reactivity are few, and there have been no surveys in this area.

A study has been made of the electronic effects of donor and acceptor groups in ethylenic and acetylenic dialkylaminocarbonyl compounds on the electron density in the molecule by ^{13}C NMR spectroscopy. The constants for spin-spin interaction, $^{13}C-{}^{13}C(^1J_{CC})$, of the double and triple bonds in en- and yn-amines have been determined (Table 2) (pulse sequence inadequate with decoupling of the signals from ^{13}C-isomers[42]).

It has been shown that, in the case of en- and yn-aminocarbonyl compounds, the value is somewhat less than that calculated by the simple additive principle. This is a consequence of the delocalisation of the multiple bonds as a result of direct polar conjugation, through the double (triple) bond, involving the lone pair on the nitrogen atom and the π-system of the carbonyl fragment. This can be expressed by the following canonical forms:



X = H, R′, OR′.

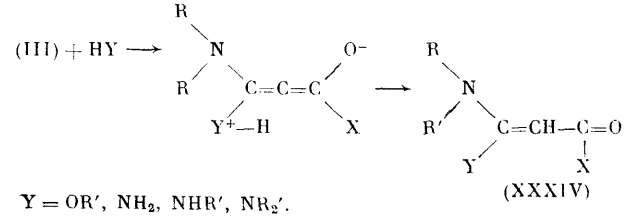
The contribution of the bipolar resonance forms was computed to be around 30% for enaminocarbonyl compounds and in excess of 50% for the acetylene analogues.

By analysis of the chemical shifts in the ^{13}C NMR spectra of the carbon atoms of the triple bond of substituted ynamines, relative to the corresponding values for ethylenic analogues, there is evidence of opposite polarisation of the orthogonal π-system of the triple bond in ynamines containing acceptor groups. This effect explains the unusually low value for the shielding contribution from the dialkylamino group adjacent to the C-atom of the multiple bond.

The data obtained on the structure of ynaminocarbonyl compounds confirms that the conjugation of donor and acceptor groups with the multiple bond has a profound effect on the distribution of electron density in the molecule, and, thereby, on the reactivity of this class of compound. Carbonyl-containing dialkylaminoacetylenes thus have unique properties, differing from those of both simple ynamines[5,26] and acetylenic ketones.[43]

While simple ynamines react with mono-functionalised compounds only after initial protonation,[44] ynaminocarbonyl compounds react with alcohols, ammonia and amines in the absence of catalyst even at room temperature (ynaminoaldehydes) or at 60–70 °C (ynamino-ketones and -carboxylic acid esters).[45,46]

A detailed study of the mechanism, stereochemistry and kinetics of addition[47] have shown that the limiting step in the process is the nucleophilic attack of the alcohol or amine at the C_3 carbon atom. The bipolar compound formed is stabilised by proton transfer, so that in polar aprotic solvents the (*E*)-isomer is formed (by intramolecular proton transfer) whereas in protic solvents the product is a mixture of *E*- and *Z*-isomers (possibly formed via intermolecular protonation). Interconversion of the *E*- and *Z*-forms takes place on increasing the temperature.



Y = OR′, NH_2, NHR′, NR_2'.

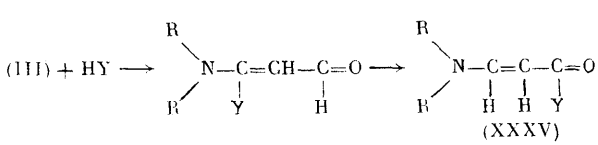
Table 2. ^{13}C Chemical shifts and $^{13}C-^{13}C$ spin-spin coupling constants of β-substituted enamines and ynamines[a].

No.	Formula	^{13}C NMR spectral data						
		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	$^1J_{3,4}$
1	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}H=\overset{4}{C}H-\overset{5}{C}H_2-\overset{6}{C}H_3$	12.75	45.03	136.94	99.64	24.75	16.90	79.2
2	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}H=\overset{4}{C}H-\overset{5}{C}H=\overset{6}{C}H_2$	13.33	45.38	141.57	99.41	138.19	103.43	77.2
3	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}H=\overset{4}{C}H-\overset{5}{C}HO$[b]	11.54 14.74	42.74 50.22	159.14	100.99	188.21	—	71.8
4	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}H=\overset{4}{C}H-\overset{5}{C}O-\overset{6}{C}H_3$[b]	13.01	44.42	150.67	96.83	192.83	27.47	70.8
5	$\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}H=\overset{4}{C}H-\overset{5}{C}O-O\overset{6}{C}H_3$[b]	13.30	45.31	157.09	83.48	169.37	49.88	72.8
6	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}\equiv\overset{4}{C}-\overset{5}{C}H_3$	12.87	48.94	83.39	57.36	3.18	—	189.2
7	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}\equiv\overset{4}{C}-\overset{5}{C}H=\overset{6}{C}H-\overset{7}{C}H_3$[c]	13.17	48.85	99.73	63.19	112.15	128.30	174.1
8	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}\equiv\overset{4}{C}-\overset{5}{C}H=\overset{6}{C}H-\overset{7}{C}O-\overset{8}{C}H_3$[d]	13.15	48.22	110.89	70.86	126.79	126.79	175.6
9	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}\equiv\overset{4}{C}-\overset{5}{C}O-\overset{6}{C}H_3$	13.03	47.95	104.80	77.79	180.19	31.39	186.5
10	$(\overset{1}{C}H_3-\overset{2}{C}H_2)_2N-\overset{3}{C}\equiv\overset{4}{C}-\overset{5}{C}O-O\overset{6}{C}H_3$	12.94	47.66	98.76	65.44	155.70	50.98	177.0

[a] *trans*-Isomers: chemical shifts given in p.p.m. (TMS) with a precision of ±0.05 p.p.m.; $^{13}C-^{13}C$ spin-spin coupling constants given in Hz and with a precision of ±0.2 Hz. [b] In compound 3 the signals from atoms C(1) and C(2) are doublets, and in compounds 4 and 5 there is noticeable broadening due to restriction of internal rotation around the C–N bond. [c] C(7) 15.47 p.p.m. [d] C(7) 194.98 p.p.m.; C(8) 26.96 p.p.m.

The addition of mono-functionalised nucleophiles to activated acetylenes is a second order reaction. The rate of reaction increases in parallel with 1) the basicity of the reagents (amines add more easily than alcohols, and secondary amines more rapidly than primary amines and ammonia), 2) the electrophilicity of the reactive centre at C_3 (the rate of addition decreases in the order: ynamino-aldehydes > ynaminoketones > aminoacrylic acid esters), and 3) the polarity of the solvent (as a result of enhanced solvation of the bipolar transition state).

It has been shown that the products obtained by addition of simple alcohols to ynaminodehydes undergo rearrangement to the isomeric aminoacrylic acid esters on heating or on treatment with protic or Lewis acids. Formally, the alkoxy group migrates from C_3 to the carbonyl group. Ynamino-ketones and -esters do not undergo such a transformation.[45,48]



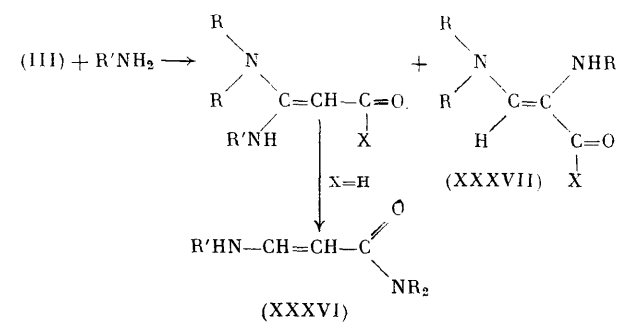
(III) + HY → N–C=CH–C=O → N–C=C–C=O, (XXXV)

X = H, Y = OCH_3, OC_2H_5.

3-Dimethylaminoacrylic acid esters are obtained in the *E*-configuration in 55–60% yield.

The rearrangement takes place via an oxete intermediate with migration of an oxygen atom and the dimethylamino group.[45]

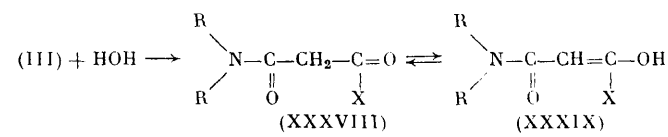
The products of addition of amines to ynaminoaldehydes underwent rearrangement far less smoothly, and a low yield of 3-aminoacrylic acid dimethylamide was obtined, i.e. a similar oxygen migration takes place with participation of an amino group.



(III) + R′NH₂ → N–C(R)=CH–C(X)=O + N–C(H)=C(NHR′)–C(X)=O (XXXVII); X=H → R′HN–CH=CH–C(=O)–NR₂ (XXXVI)

By addition of ammonia and amines to ynamino-aldehydes and -ketones, isomeric adducts are also formed by inverse attack of nitrogen at the C_2-atom of the multiple bond to give (XXXVII).[49]

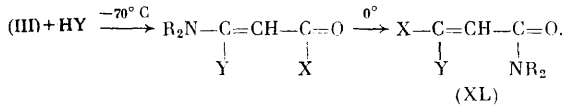
Hydration of ynaminocarbonyl compounds proceeds in neutral media at 20 °C (with ynaminoaldehydes) and at 60–70 °C (with ynamino-ketones and -esters).[45]



(III) + HOH → N–C(R)–CH_2–C(X)=O ⇄ N–C(R)=CH–C(X)–OH. (XXXVIII) (XXXIX)

The β-ketoamides obtained exist as a mixture of keto and enol tautomers. According to ^{1}H NMR spectral data the proportion of the enol form in $CDCl_3$ varies from 4% (for esters, X = OMe) to 20% for ketones (X = Me). Acids readily add to the triple bond of ynaminocarbonyl compounds.[45,48] The geometry of the product is determined by the nature of the acceptor group. For aldehydes, the reaction is stereospecific, for ketones it is highly stereoselective in favour of the *trans*-adduct (*Z*-configuration), while esters afford both *cis*- and *trans*-adducts in approximately equal amount.

In the overwhelming majority of cases the initial adducts undergo facile rearrangement to the corresponding substituted α,β-ethylenic carboxylic acid dialkylamides (XL) (amino-, mercapto- and hydroxycarboxylic acid derivatives).

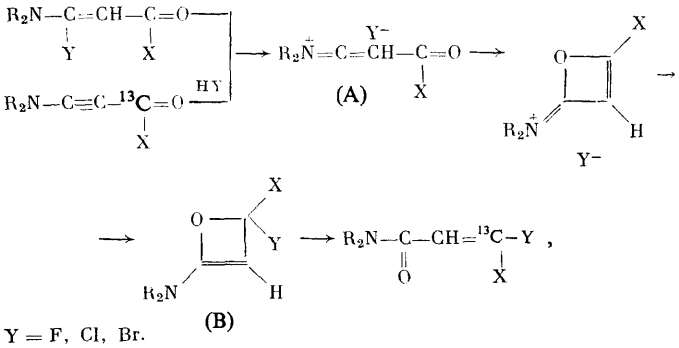


(XL)

Rearrangement does not take place, or proceeds to a small extent, only in the case of dimethylaminopropiolic acid esters (X = OMe) or on addition of HF (Y = F). The adducts formed in these reactions are stable, even on heating.

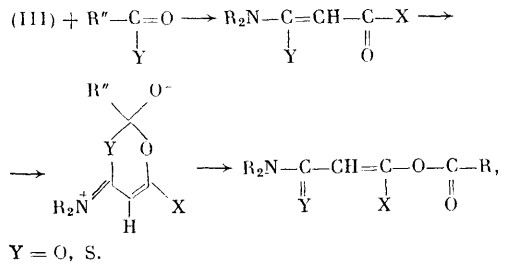
An oxete mechanism has been invoked only for the addition of hydrogen halides to ynaminocarbonyl compounds, as shown in Scheme 3.[45,50,51]

Scheme 3



Y = F, Cl, Br.

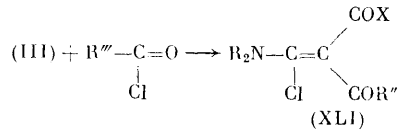
The mechanism of the rearrangement is quite different for the addition of carboxylic and thiocarboxylic acids. Here, there is intramolecular formation of an intermediate six-membered bipolar compound, which is subsequently cleaved stereospecifically.[50]



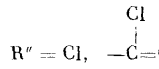
Y = O, S.

In such cases, the obtained *cis*-product isomerises to the thermodynamically more stable *trans*-product on heating to 60–70 °C.

Acylation of ynaminocarbonyl compounds has been examined by a study of the reaction with phosgene and oxalyl chloride.[52] It has been shown that these reagents add across the triple bond of activated ynamines to give (XLI), as would be anticipated from considerations of the electron density.

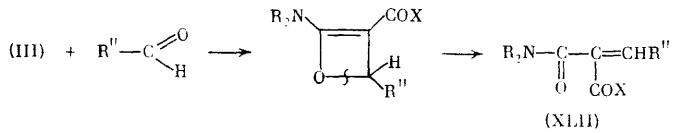


(XLI)



The products obtained are extremely reactive, participating in heterocyclisation with a number of bifunctional reagents.

The interaction of aldehydes with ynaminocarbonyl compounds proceeds in a totally different manner. Here, there is an analogy with the reactions of ynamines (I). Thus, [2 + 2]-cycloaddition of the carbonyl group to the triple bond of the activated acetylene takes place at 0–5 °C in methylene chloride with formation of an oxete intermediate.

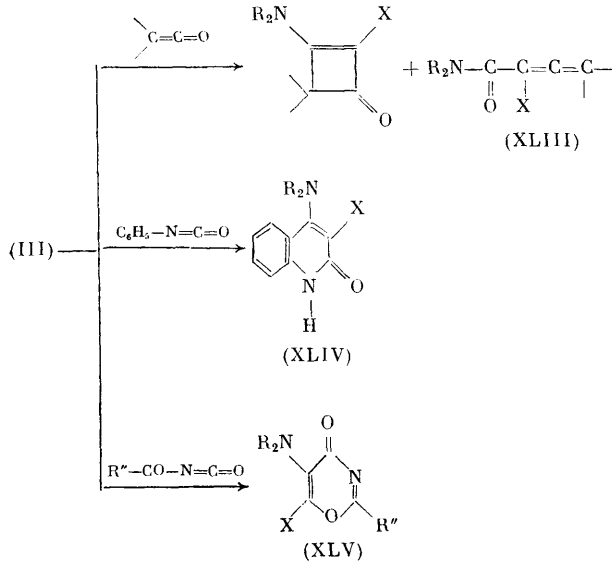


(XLII)

Stereospecific ring opening of the oxete leads to the corresponding unsaturated carboxylic acid amides (XLII), having a *cis*-configuration.[53]

The reaction of heterocumulenes with ynaminocarbonyl compounds affords cyclic products by [2 + 2]- [4 + 2]-cycloaddition[54,55] (Scheme 4)

Scheme 4



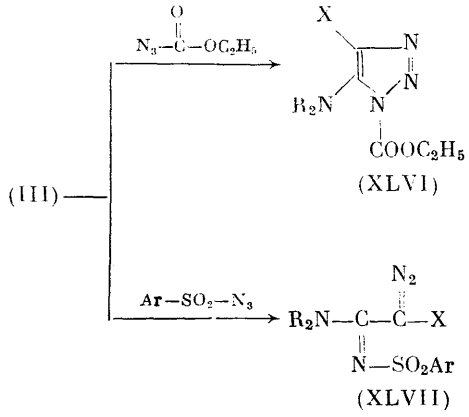
(XLIII)

(XLIV)

(XLV)

Ynaminocarbonyl compounds participate in reaction with 1,3-dipolar compounds in the same way as ynamines and acetylenecarbonyl compounds.[45] Thus, substituted triazoles are formed in high yields by interaction with ethyl azidoformate at 65 °C.

Arylsulphonyl azides, however, yield products derived primarily by triazole cleavage, the corresponding triazole analogues of (XLVI) being formed only in small amounts.[56]



III. Heterocyclisation involving *p*,π-unsaturated amines and bifunctionalised reagents

The reactions of enamines (II) with bifunctional compounds provide a general route to five- and six-membered heterocycles. In this capacity, enamines (II) have been described in reviews[1,2] as three-carbon synthons.

In acidic media, enamines (II) are protonated with the formation of a conjugated carbenium ion, ($R_2N-CH=CH-\overset{+}{C}=CH_2 \longleftrightarrow R_2\overset{+}{N}=CH-CH=C=CH_2$), which, on further reaction, dictates the structure of the final product. Thus, reaction of the conjugated carbenium ion with reagents having adjacent functionality proceeds with participation of the C_1- and C_3-atoms, leading to the formation of 5-substituted isoxazoles and pyrazoles (XLVIII),[57,58] 2-substituted 4-alkylpyrimidines (XLIX), (L)[59–61] and 3-substituted 2,4-dialkylpyridines (LI)[57,62–65] (Scheme 5).

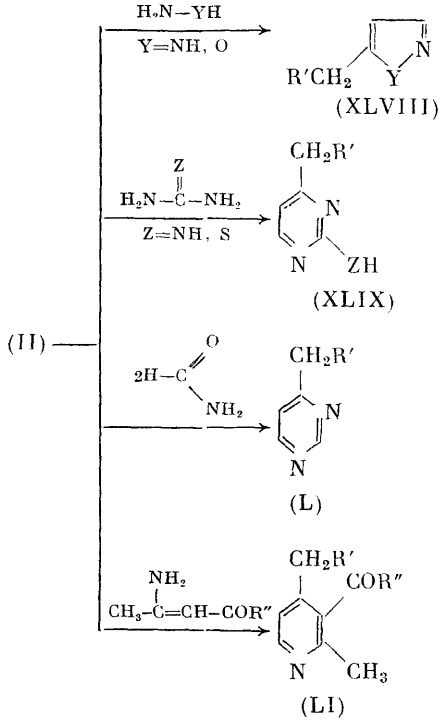
Since under acid catalysis the reaction of the carbocation with the nucleophile is the key step prior to cyclisation, the structure of the final product will, to a large extent, be determined by the activity of the electrophilic centres at C_1 and C_3 of the conjugated carbocation. For enamines (II), the electrophilic centre at C_1 has the greater effect, which accordingly determines the direction of the reaction.[66]

In this connection, one should especially emphasise the preparative value of the method since, by using β-dicarbonyl compounds or 1-alkoxy-1-alken-3-ynes as starting material in such ring syntheses, one obtains a mixture of 3- and 5-substituted isoxazoles and pyrazoles and a mixture of 2,4- and 2,6-dialkyl-substituted pyridines.[66]

Ring syntheses with enamines (II) take place via direct nucleophilic attack. Thus, 4-alkylpyrimidines (L) are obtained in high yield by treatment of (II) with formamide. Evidently, reaction proceeds by transamination of the dialkylamino group with the formation of a foramido compound which decarbonylates to give an imine; the latter then reacts with a second molecule of formamide to give the 4-methylpyrimidine (L).[61]

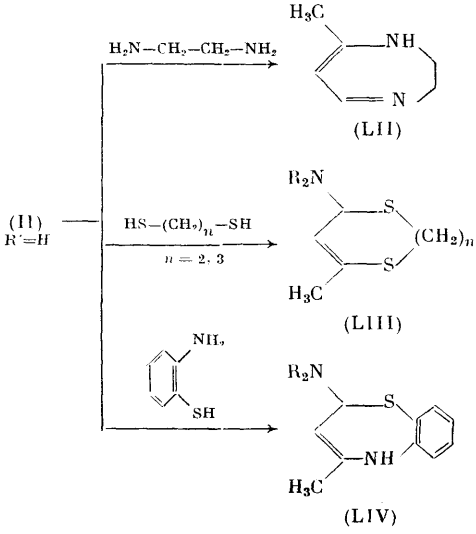
The same is true for the reaction of β-amino-α,β-ethyleneketones which afford 3-functionalised 4-alkylpyridines (LI).[64] Of the several possible routes by which reaction takes place, the most likely involves transamination of the function at the C_1 electrophilic centre with the primary amine group; this would be accompanied by intramolecular cyclisation via attack of the methine function at C_3, leading to the formation of the 2,4-disubstituted pyridine. The isolation of transamination products and literature data on the configuration of enaminoketones and enaminonitriles would support this pathway.[66]

Scheme 5



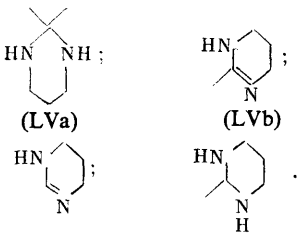
The formation of 2,3-dihydro-1,4-diazepines (LII) by reaction of enamines (II) with 1,2-diaminoethane is in accord with the above-described cyclisation via transamination (Scheme 6).[67–69]

Scheme 6



The interaction of 1-dialkylamino-1-buten-3-ynes with 1,2-ethanedithiol 1,3-propanedithiol also proceeds with involvement of the reactive C_1- and C_3-atoms of the conjugated system with the formation of 7-dialkylamino-5-methyl-7*H*-2,3-dihydro-1,4-dithiepines and 2-alkylamino-4-methyl-8*H*-6,7-dihydro-1,5-dithiocins, respectively (LIII).[70,71] In contrast with the reaction of 2-aminothiophenol with alkenylynamines, interaction with enamines (II) proceeds by 1,3-attack of the conjugated system to give the corresponding 2-dialkylamino-4-methyl-5*H*-1,5-benzothiazepines (LIV).[70,72]

Normally, the reaction of enamines (II) with 1,3-difunctionalised reagents would be expected to give heterocyclics with a large ring size. However, this is not always the case. Thus, the reaction of 1,3-butadiyne with 1,3-diaminopropane leads to the formation of a bis-adduct of the type XXVII, rather than an 8-membered ring; C-cleavage of these adducts affords the corresponding tetrahydro- and hexahydro-pyrimidines (LV):[35]



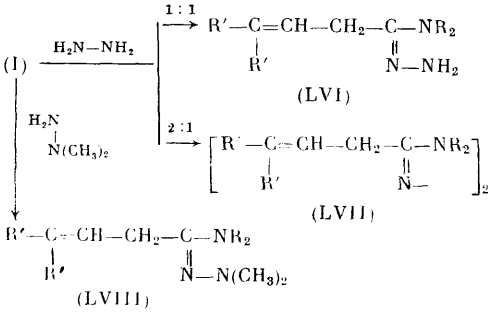
(LVa) (LVb) (LVc) (LVd)

Pyrroles with a variety of substitution patterns are obtainable by other routes, notably via 1,4-addition. Here, the synthesis can be achieved with butadiyne and ammonia or primary amines in the presence of copper salts.[1,4,73]

Since the starting enamines (II) can be obtained by direct interaction of diacetylene with secondary amines, the syntheses described above are potentially interesting from an industrial viewpoint. However, in planning synthetic routes from enamines (II), the commercially available 1,1-dimethoxy-3-butanone, which is obtaining from diacetylene, cannot be used as an equivalent.[74]

Ynamines (I) behave in a quite different way with bifunctional reagents. Thus, reaction with compounds having adjacent nucleophilic centres, such as hydrazine and hydroxylamine, affords acyclic adducts with participation of only the C_1 electrophilic centre of the ynamine (Scheme 7).[75] Amidrazones (LVI) based on 3-pentenoic acids are thereby produced in a manner not unlike the addition of hydrazine to ω-diethylaminophenylacetylene.[76]

Scheme 7

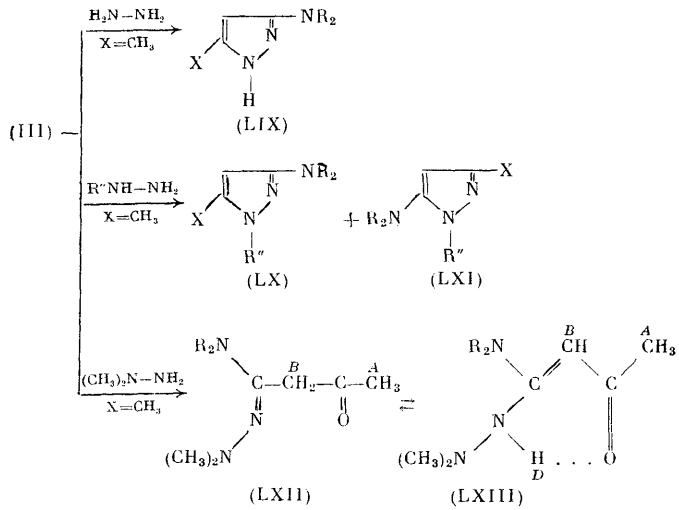


By adjusting the proportion of the reactants, e.g. by increasing the amount of hydrazine, it is possible to isolate adducts (LVII).[57] The reaction of ynamines (I) with non-symmetrical dialkylhydrazines leads in the same way to poly-N-substituted amidrazones (LVIII).[75]

The reaction of vinylacetylenic ynamines with hydrazine is markedly different from the reaction of vinylacetylenic enamines in that only the acetylene bond participates with the formation of monoadducts; the latter readily react with a second ynamine molecule. This observation is in keeping with the unusual mechanistic features of nucleophilic attack at an acetylenic bond in conjugation with a donor group.[77]

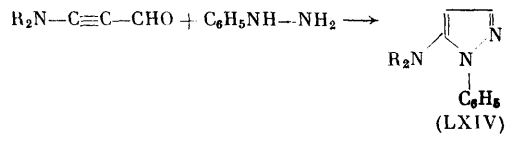
A study has also been made of the interaction of ynaminocarbonyl compounds (III) with supernucleophiles, such as hydrazine, alkyl- and phenyl-hydrazines, and unsymmetrical dimethylhydrazine. The reaction of 4-dialkylamino-3-butyn-2-ones with hydrazine proceeds with involvement of the C_1 and C_3 electrophilic centres to give 3(5)-dialkylamino-5(3)-methylpyrazoles in 56–63% yield (LIX) [78,79] (Scheme 8).

Scheme 8



The interaction of 4-dialkylamino-3-butyn-2-ones with monosubstituted hydrazines (methyl, propyl, and phenyl) leads in all cases to a mixture of isomeric products (LX) and (LXI),[79] as a result of the alternative approaches of the hydrazine group to the reactive centre of the ynaminoketone. According to ^{1}H NMR spectroscopic data and GLC analysis, the proportion of the two isomers in all cases is 3:4.

The obtained results would indicate that the reactivity of the two electrophilic centres in (III) is approximately equal. However, with ynaminoaldehydes, in which the activity of the carbonyl group is higher, the free amino group of the hydrazone predominantly attacks the carbonyl group. Thus, reaction of diethylaminopropynal with phenylhydrazine afforded predominantly isomer (LXIV) by attack of the free amino group on the carbonyl group.[80]



Ynaminoketones react on heating with the unsymmetrical dimethylhydrazine by exclusive attack at the reactive C_1 centre to give the corresponding N,N-dimethyl-3-oxobutanamidrazones (LXII, LXIII).[79]

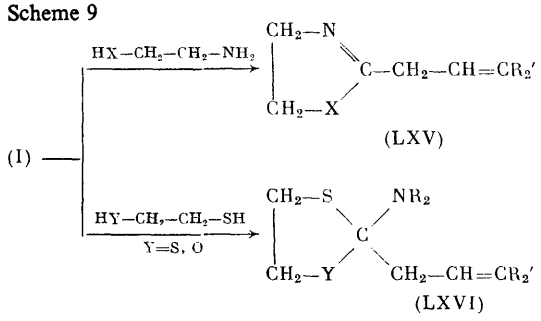
The ^{1}H NMR spectrum of (LXII) displayed signals in the region 2.10 p.p.m. corresponding to the methyl group of the acetyl fragment (H_A) and at 3.40 p.p.m. corresponding to the protons of the methylene group (H_B).

However, the enol tautometer (LXIII), stabilised by intramolecular hydrogen bonding, is present together with the keto form. The enol form is responsible for the signal at 1.84 p.p.m., corresponding to the methyl group (H_A), the signal at 5.00 p.p.m. corresponding to the vinyl proton (H_B), and the weak signal at 7.30 p.p.m. corresponding to the proton (H_D) of the hydroxyl group. The infrared spectra also reveal absorption at around 3400 cm^{-1} which can be ascribed to the associated hydroxyl group.

Thus, ynaminoketones react with hydrazine and its monosubstituted derivatives at both the C_1 and C_3 reactive centres affording a regioisomeric mixture of the corresponding pyrazoles. The unsymmetrical N,N-dimethylhydrazine adds exclusively across the triple bond of 1-dialkylamino-1-butyn-3-one with the formation of an acyclic product existing as a tautomeric mixture of keto and enol forms.

Treatment of alkenylynamines with aliphatic 1,2-dinucleophiles containing nitrogen, oxygen and sulphur functionality afford five-membered heterocyclics by attack of the two nucleophilic centres at the C_1 electrophilic centre (Scheme 9).

Scheme 9

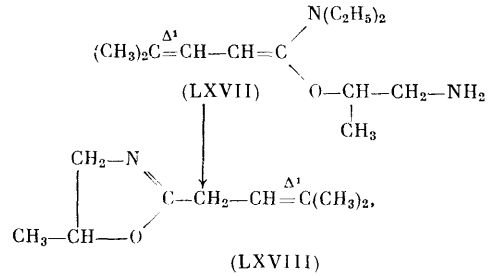


Thus, interaction of 1-dialkylamino-3-penten-1-ynes (I) with 1,2-diaminoethane and ethanolamine gave the corresponding 2-(2-buten-1-yl)imidazolines and 2-(2-buten-1-yl)oxazolines (LXVI), respectively.[81] In these reactions, 2-substituted imidazolines and oxazolines were formed by cleavage of the dialkylamino group. The non-conjugated ethylenic group at the 2-position of the side chain is thereby left intact, confirming the regioselectivity of reaction at the triple bond.

Regioselectivity is the same with sulphur-containing binucleophiles (2-mercaptoethanol, ethanedithiol), the corresponding products being 2-dialkylamino-(2-buten-1-yl-1,3-oxathiolanes and 2-dialkylamino-(2-buten-1-yl)1,3-dithiolanes (LXVI).[81]

The reactivity of nitrogen-, oxygen-, and sulphur-containing reagents towards alkenylynamines (I) increases with their acidity as a consequence of electrophilic catalysis of the addition process. Reagents which are more acidic than water (2-mercaptoethanol and 1,2-ethanedithiol) interact with alkenylynamines (I) in the absence of acid, while reactions with 1,2-diaminoethane and ethanolamine require the presence of a catalytic amount of acid, which is in accordance with the rule outlined above.[12,17]

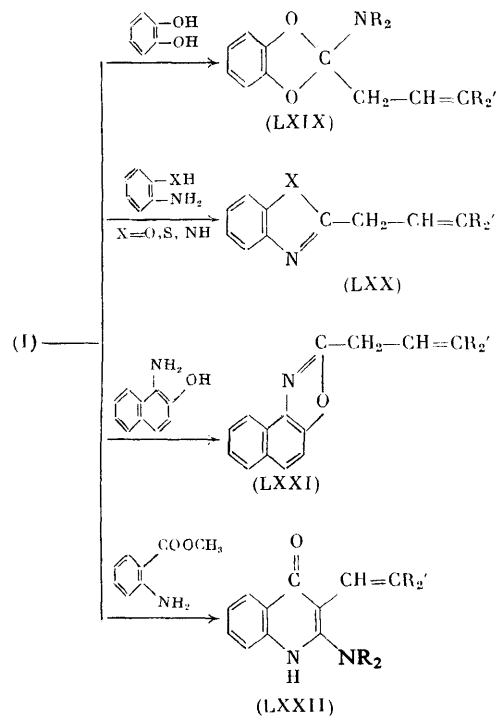
Reactions of alkenylynamines (I) with ethanolamine proceed similarly, but a two-stage process is involved with methylethanolamine. Thus, according to ^{1}H NMR spectral data, the product of reaction between methylethanolamine and 1-diethylamino-3-penten-1-yne affords, in addition to the expected cyclic product, a vinylketene O,N-acetal (LXVII), which is converted into the oxazoline (LXVIII) during the course of the reaction.[82] The isolation of the acyclic product (LXVII) is evidently a consequence of steric hindrance in the formation of the ring.



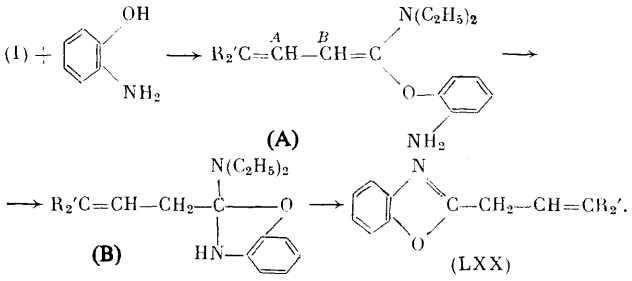
In order to determine the effect of the structure of the reagent and the stereochemistry of ring closure, a study has been made of reactions with aryl and naphthyl 1,2-dinucleophiles in which the nucleophilic residues are stereo-defined (Scheme 10). The interaction of alkenylynamines (I) with catechol (pK_a 9.44) proceeds on cooling to give the corresponding 2-dialkylamino-2-[3-methyl-2-buten-1-yl]-1,3-benzodioxoles (LXIX) in 70% yields.[83,84]

The reaction of alkenylynamines (I) with *o*-aminophenol, *o*-aminothiophenol, and *o*-phenylenediamine afforded the respective benzoxazole,[84,86] benzothiazole[85] and benzimidazole[84,87] derivatives of general structure (LXX), in which the side chain unsaturation at the 2-position is non-conjugated.

Scheme 10

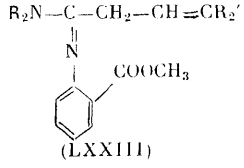


In the reaction of 1-diethylamino-(4-methyl)3-penten-1-yne with *o*-aminophenol it is possible to isolate all the intermediates.[84] Reaction proceeds smoothly and is exothermic; moreover, it is initiated by attack of the hydroxyl group since phenols react with ynamines at a much greater rate than amines. This is also confirmed by ^{1}H NMR spectral measurements during the reaction, which display proton signals at 4.78 p.p.m. (H_B, 1H) and 5.85 p.p.m. (H_A, 1H); according to the literature values for fragment $R_2'C=CH-CH=C(OPh)NR_2$ [12], these correspond with the signals for the vinylic protons of compounds of type (A). At the end of the reaction these signals have completely disappeared. When (A) could no longer be detected, the residue was shown to contain compound (B) which, on distillation, affords (LXX) by cleavage of the diethylamino group.



It was also shown that the condensation takes place with naphthalene derivatives. Thus, 1-amino-2-naphthol gave naphth[1,2-*d*]oxazoles (LXXI).[88]

If the difunctionalised reagent possesses groups which are different in nature, e.g. methyl anthranilate, then reaction with alkenylynamines takes place at C_1 and C_2 to give a six-membered ring without cleavage of the dialkylamino group, i.e. 2-dialkylamino-3-(2-methyl-1-propenyl)-4-quinolones (LXXII).[89] Reaction proceeds in two stages under acid catalysis. The intermediate (LXXIII), formed by initial addition of methyl anthranilate to the starting ynamine (I), was isolated.[69]



In the above-described reaction, the alkenylynamines (I) behave as rather unusual acylating agents, from which a number of 5-membered benzo-condensed 1,3-heterocyclics can be prepared with a non-conjugated unsaturated residue at the 2-position. Ynamines participate in the same type of heterocyclisation.[90]

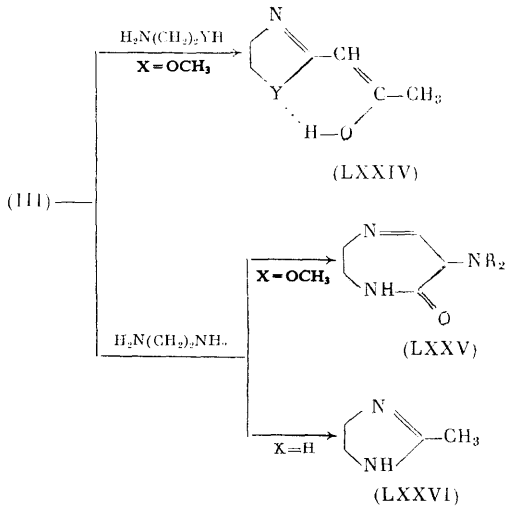
By comparing reactivity data for the reactions of alkynamines and alkenylynamines with *o*-phenylenediamine, *o*-aminothiophenol, and *o*-aminophenol, one arrives at the qualitative conclusion that, in the absence of acidic catalysis, addition becomes more facile with an increase in the acidity of the functional group in the order $NH_2 < OH < SH$. This is possibly associated with autocatalysis of the nucleophilic addition.

Thus it has been shown that the reaction of alkenylynamines (I) with bifunctional reagents containing nitrogen, oxygen and sulphur proceeds stepwise via initial atack at the electrophilic C_1 atom of the ynamine to give 5-membered heterocyclics with two heteroatoms and an unconjugated phenyl-type group at the 2-position. The interaction of aromatic *o*-substituted dinucleophiles proceeds by a concerted mechanism through a cyclic, 5-membered, resonance-stabilised transition state.

Acetylenic ynaminocarbonyl compounds (III) should display electrophilicity by virtue of the ynamine residue in conjugation with a polar carbonyl group. In fact, reactions with both mono- and dinucleophiles proceed without acid catalysis. Data on the reactivity of ynaminocarbonyl compounds show that they react in a different manner to ynamines[26], alkenylynamines and acetylenic ketones.[43]

Thus, in reactions with aliphatic 1,2-dinucleophiles, the nature of the heteroatom and the carbonyl group have a pronounced effect. For example, reactions of 4-dialkylamino-3-butyn-2-ones with 1,2-diaminoethane and 2-aminoethanol afford the corresponding 1-(2-imidazolinyl)-1-propen-2-ols[91,92] and 1-(2-oxazolinyl)-1-propen-2-ols (LXXIV) [91] (Scheme 11).

Scheme 11



The formation of imidazoline and oxazoline derivatives takes place as a result of a two-fold attack at the α-carbon atom of the acetylene group, i.e. the orientation of attack is the same as in reactions with ynamines[90] and conjugated ynamines.[81] According to one finding[93], 1-mercapto-2-aminoethane adds to acetylenic ketones at the β-carbon atom of the acetylene group under basic catalysis.

The geometry of the final product (LXXIV) is determined by stabilisation of the enol form through intramolecular hydrogen bonding. The literature does make reference to imidazolines having a completely enolised β-ketoalkyl residue.[94]

The course of the reaction is dependent on the nature of the carbonyl group. Thus, dialkylaminopropiolates react with 1,2-diaminoethane with the participation of both electrophilic centres to give 5-dialkylamino-2,3-dihydro-1,4-diazepin-7-ones (LXXV) in 68% yield.

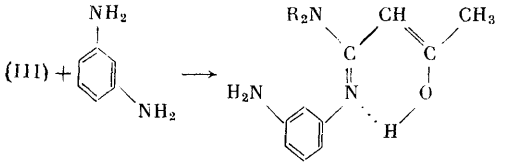
Evidently, the lower electrophilicity of the C_1 and C_3 centres in ynaminoesters, compared with ynaminoketones, is responsible for the concerted 1,3-attack of the bifunctional nitrogen-containng bases, the final outcome being the formation of diazepine derivatives. The facile intramolecular nuclophilic replacement of the methoxy group of the ester also dictates this mode of cyclisation.

With ynaminoaldehydes (III, X = H) the electrophilicity of the two centres is so high that two 1,2-diaminoethane molecules attack each of the reaction centres twice, affording a bis-adduct which

undergoes carbon-carbon bond cleavage with formation of 2-methyl-2-imidazoline (LXXVI).[97] This type of reaction is similar to that described earlier.[35]

The interpretation of ynaminocarbonyl compounds with aromatic 1,2-dinucleophiles leads to a different result. The reduced nucleophilicity of *o*-phenylenediamine relative to 1,2-diaminoethane, is responsible for the different mode of reaction with ynaminoketones. Thus, 4-dialkylamino-3-butyn-2-ones react with o-phenylenediamine to give seven-membered heterocyclic derivatives, namely 7(α)-R'-2-dialkylamino-4-methyl-3H-1,5-benzodiazepines (LXXVII) [95] (Scheme 12).

An NMR spectral study of the reaction between 4-dimethylamino-3-butyn-2-one and *m*-phenylenediamine was conducted in an NMR tube (i.e. non-preparatively) in order to elucidate the initial attack of the aromatic diamine. On heating in $CDCl_3$, *m*-phenylenediamine adds slowly to the ynaminoketone across the triple bond with the formation of an iminoenol tautometer (LXXXIII) as the final product.



X = CH_3.

(LXXXIII)

Of all the nucleophilic reagents studied, only *m*-phenylenediamine reacted to give a sufficiently stable iminoenol tautometer. The extent of conjugation, involving the two double bonds (C=C and C=N), the aromatic ring, and the hydroxyl group, is sufficient to provide such stabilisation. It is likely that, in the case of *o*-phenylenediamine, enolisation of the intermediate adduct favours ring closure to the benzodiazepine (LXXVIII).

The 1,3-mode of attack with *o*-phenylenediamine is again evident in the reaction with methyl 3-dialkylaminopropiolate, providing LXXVIII.[96]

The orientation of the reaction of acetylenic ketones with *o*-phenylenediamine is the same as that of ynaminoketones.[98]

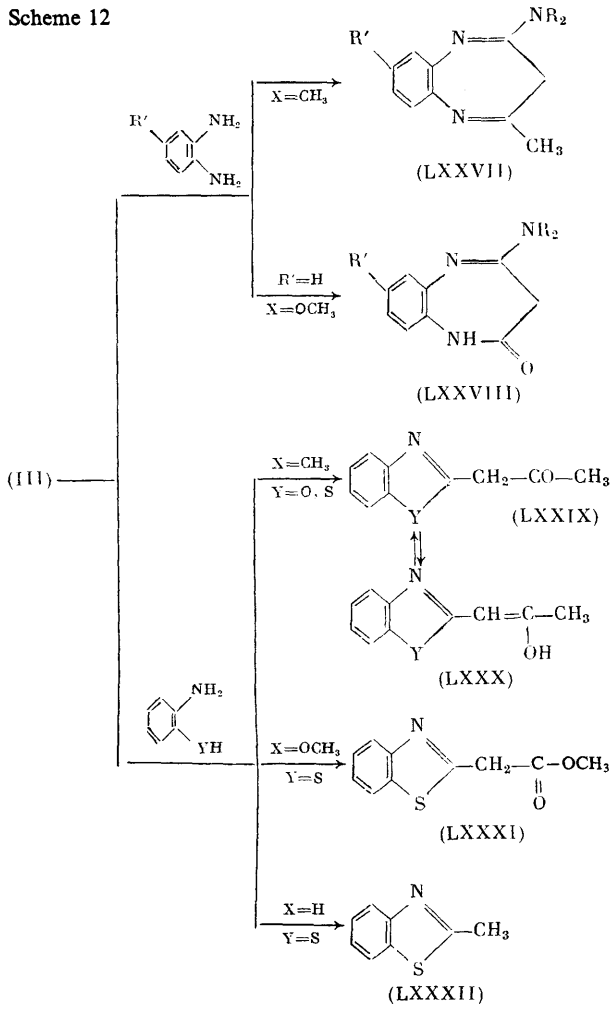
Treatment of 4-dialkylamino-4-butyn-2-ones with *o*-aminophenol and *o*-aminothiophenol afforded the corresponding fused 5-membered heterocyclics, namely 1-(2-benzoxazolyl)-2-propanone and 1-(2-benzothiazolyl)-2-propanone, which exist as a mixture of keto (LXXIX) and enol (LXXX) tautomers.[91]

Reaction of methyl 3-dialkylaminopropiolate with *o*-aminophenol and *o*-aminothiophenol affords 2-carbomethoxymethylbenzoxazole and 2-carbomethoxymethylbenzothiazole, respectively, (LXXXI).[96]

Just as in reaction with ethylenediamine, 3-(dialkylamino)propynal with *o*-aminothiophenol affords a product via double addition across both reaction centres; C–C bond cleavage then takes place to give 2-methylbenzothiazole (LXXXII).[97]

Thus, it has been shown that ynaminocarbonyl compounds react in the same way as simple ynamines, irrespective of the nature of the acceptor group. The course of the heterocyclisation of conjugated ynamines with acceptor groups depends both on the character of the carbonyl group and the nature of the nucleophile. Cyclisation with aliphatic nucleophiles depends on the acceptor ability of the carbonyl function. With weak nuclophiles (aromatic diamines) only 1,3-addition takes place, independent of the nature of the carbonyl group, and only the ynamine residue is involved in the reaction with nucleophiles containing hydroxyl and sulfhydryl groups. The preparation of five- and seven-membered heterocyclics containing two

Scheme 12

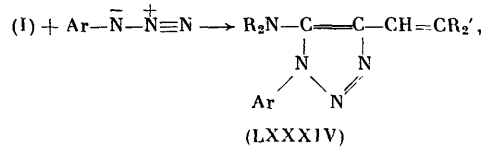


heteroatoms (nitrogen, oxygen, or sulphur) can thus be achieved by choosing a suitable carbonyl-containing ynamine and dinucleophile.

IV. 1,3-Dipolar cycloaddition

The 1,3-dipolar activity of both types of amine, (I) and (II), has been studied in order to assess the activating effect of the dialkylamino group on the reactivity of the α,β-unsaturation in conjugation with the π-system. It is known that acetylenic ynamines react with 1,3-dipoles to give 5-membered heterocyclics.[5,99] In the 1,3-dipolar cycloaddition of a variety of vinylacetylenic compounds, the double bond of the conjugated enyne system is significantly more reactive than the disubstituted triple bond.[99]

1-Aryl-4-vinyl-5-dialkylamino-1,2,3-triazoles (LXXXIV) were obtained by interaction of 1-dialkylamino-3-buten-1-ynes with aromatic azides.[100,101]

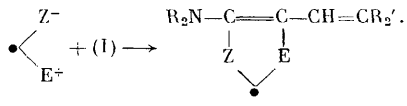


(LXXXIV)

Thus, the 1,3-dipole attacks the acetylenic bond rather than the terminal ethylenic bond with retention of the dialkylamino group.

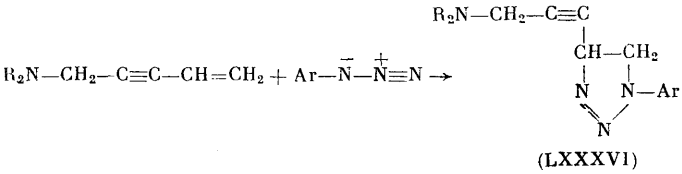
In all cases, addition of aryl azides to alkenylynamines (I) proceeds regiospecifically with the formation of only one isomer as has been confirmed by TLC and NMR spectroscopic studies of the product. The data accord well with literature values for the 1,3-dipolar cycloaddition of aryl azides with compounds having highly polar unsaturations, e.g. alkoxyacetylenes,[102] ynamines,[103,104] and acetylenic ketones and acids.[105,106]

The results obtained by studying the reactions of other octet-stabilised 1,3-dipoles (benzonitrile *N*-oxide, C-*p*-F-phenyl-*N*-nitrilimines) with alkenylynamines confirm the generality of the cycloaddition, which proceeds regioselectively at the acetylenic function independent of the structure of the ethylene fragment (LXXXV).



(LXXXV)

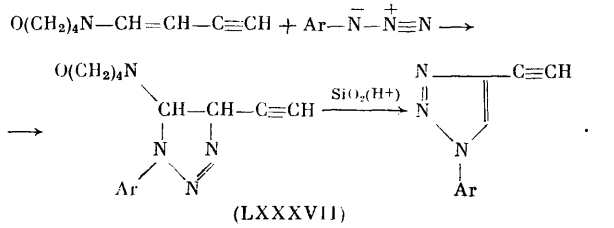
It is important to note that the incorporation of a methylene group between the nitrogen function and the vinylacetylene group significantly affects the order of addition of the 1,3-dipole, by comparison with alkenylynamines (I). The interaction of 1-diethylamino-4-penten-2-yne with aromatic azides leads to 1-aryl-4-(3-diethylamino-1-propynyl)-Δ^2-triazolines (LXXXVI).[101] In this reaction it is generally found that the terminal double bond of the vinylacetylene group is the more reactive unsaturation.[99]



(LXXXVI)

Thus, in vinylacetylenic compounds having an amino group on an unsaturation, the nitrogen atom activates the α,β-unsaturation for the addition of 1,3-dipoles. Where the amino group is not bonded to the unsaturation, the regioselectivity is determined by the position of the bond. This is supported by data obtained from the reaction between 1,3-dipoles and enamines (II).

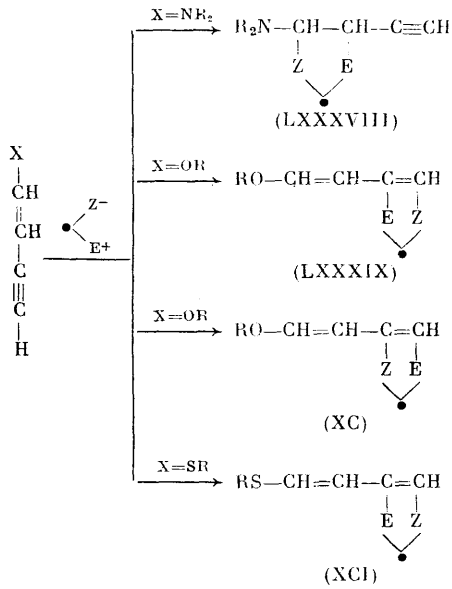
Thus, 1-morpholino-1-but-3-yne with aromatic azides affords 1-aryl-4-ethynyl-5-*N*-morpholino-Δ^2 triazolines (LXXXVII),[101] i.e. addition of the 1,3-dipole proceeds exclusively at the disubstituted ethylenic bond.



(LXXXVII)

In contrast, addition of 1,3-dipoles to 1,3-enynyl ethers and thioethers takes place at the terminal acetylene group with formation of 5-membered heterocyclics (LXXXIX), (XC) and (XCI) [101,107] (Scheme 13).

Scheme 13



(LXXXVIII)

(LXXXIX)

(XC)

(XCI)

Thus a study of 1,3-dipolar cycloaddition with both types of vinylacetylenic amine, (I) and (II), has shown that the conjugated *p*,π-system serves as dipolarophile, interacting with 1,3-dipolar systems in the usual manner. However, the amino group in such dipolarophiles has a specific directing influence on the cycloaddition.

The fact that conjugation with the amino group activates the α,β-unsaturation confirms the electrophilic nature of the reaction. However, the readiness of amines (I) and (II) to undergo electrophilic addition, as mentioned in earlier sections, and the requirement of an acid catalyst for nucleophilic addition, would suggest that the anomalous behaviour of the nitrogen-containing *p*,π-conjugated system is associated with the involvement of the nitrogen atom in the initial stage the cycloaddition, as is observed in the reactions of α,β-unsaturated tri-valent phosphorus compounds.[99,108]

The subsequent stabilisation of the system is effected by formation of the heterocyclic ring with participation of the α,β-unsaturation.

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