SYNTHESIS OF HETEROCYCLES FROM ACETYLENIC CARBONYL COMPOUNDS AND DINUCLEOPHILIC REAGENTS (REVIEW)

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The literature on reactions of sulfur, oxygen, and nitrogen-containing dinucleophilic reagents with acetylenic carbonyl compounds is reviewed. The mechanisms of some reactions are discussed.

The reactions of acetylenic carbonyl compounds with dinucleophilic reagents such as glycols, dithiols, hydroxythiols, and aminothiols are being used to an ever-increasing extent in the synthesis of heterocycles. Thanks to the simplicity and ease of the experimental procedures and the high yields of heterocycles obtained, such reactions are receiving increasing attention.

To date, a considerable amount of experimental data have appeared on the reactions of conjugated acetylenes with dinucleophilic reagents, principally nitrogenous, which has been reviewed [1-6].

The material covered in reviews [1-5] includes the literature only up to and including 1976. In addition, the synthesis of N, O, and S heterocycles by the reaction of acetylenic ketones with dinucleophilic reagents, most of which has been reported recently, lies outside the range of these reviews. A review published in 1981 [6] dealt with the synthesis of heterocycles from vinyl, diacetylenic, and nitrogenous binucleophiles.

We have now systematized recent information on methods of synthesis of heterocycles by the reaction of acetylenic carbonyl compounds with dinucleophilic reagents other than N,N-dinucleophiles, and it is shown that routes to heterocycles from dinucleophilic reagents and acetylenic carbonyl compounds are diverse. The presence of two nucleophilic centers favors the occurrence of "double addition" to the triple bond, either synchronously or by intramolecular heterocyclization of the intermediate monoadducts by addition of a second nucleophilic group to conjugated $C{=}C$ or $C{=}O$ bonds. The literature on the reactions of these acetylenes with dinucleophiles to give heterocycles by cyclization of intermediate monoadducts with loss of a molecule of alcohol, and on dehydrative cyclization, is reviewed.

REACTIONS OF ACETYLENIC CARBONYL COMPOUNDS WITH GLYCOLS AND HYDROXYACIDS

The triple bond shows a tendency to add a variety of reagents, especially by nucleophilic attack, which is rationalized in terms of both steric and electronic factors [7-9]. Even greater reactivity is displayed by acetylenes in which the triple bond is activated by electron-acceptor groups, especially the carbonyl group. Conjugation in the system $R^1{-}C{\equiv}C{-}C(R){=}O$ polarizes the triple bond to such an extent that the nature of the polarization is independent of R and R^1, and consequently determines the order of addition of the various nucleophiles.

Studies of the kinetics of the reaction of piperidine with α-acetylenic ketones has shown that the reactivities of the latter decrease in the sequence terminal > aryl-substituted > alkly-substituted. Bulky substituents at the triple bond considerably retard the reactions [10].

Reactions of acetylenic carbonyl compounds with O,O-dinucleophilic reagents are usually carried out in the presence of strongly basic catalysts.

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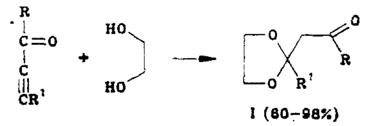
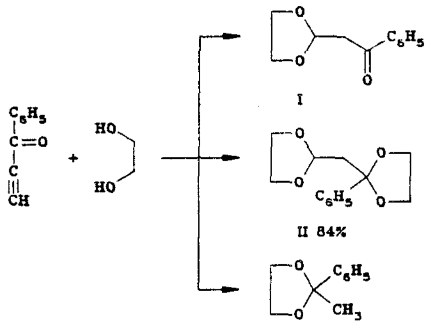
The reaction of substituted and terminal acetylenic ketones with ethylene glycol in the presence of sodium diglycollate in dry tert-butanol with cooling (0-5°C) affords 2-substituted 1,3-dioxolanes (I) [11].



I (80–98%)

$R=C_3H_7, C_6H_5$; $R^1=H, C_6H_5$

Benzoylacetylene reacts with an excess of ethylene glycol in the presence of toluene-p-sulfonic acid in boiling benzene to give high yields of 2-phenyl-2,2-methylene-bis-1,3-dioxolane (II) [8].



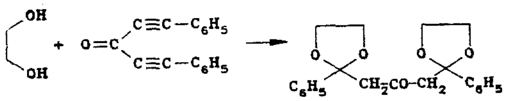
I

II 84%

III 52%

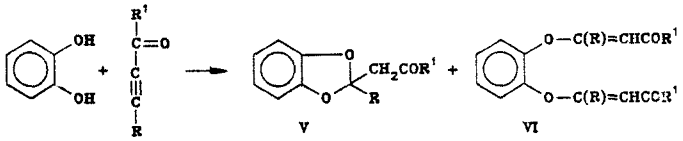
When equimolar amounts of benzoylacetylene, toluene-p-sulfonic acid, and ethylene glycol are used, 2-methyl-2-phenyl-1,3-dioxolane (III) is obtained as the sole product, but when toluene-p-sulfonic acid is present in catalytic amounts, 30% of the starting benzoylacetylene is recovered, together with 34% of the 1,3-dioxolane (II) and 14% of 2-phenyl-1,3-dioxolane (I).

Di(phenylethynyl) ketone reacts with ethylene glycol in THF in the presence of sodium to give the cyclic diacetal (IV) [13].



IV 86%

The reaction of pyrocatechol with acetylacetylenes and propiolic acid esters in the presence of potassium carbonate gives the 2-substituted benzo-1,3-dioxoles (V) and o-phenylenedivinyl ethers (VI) [14].



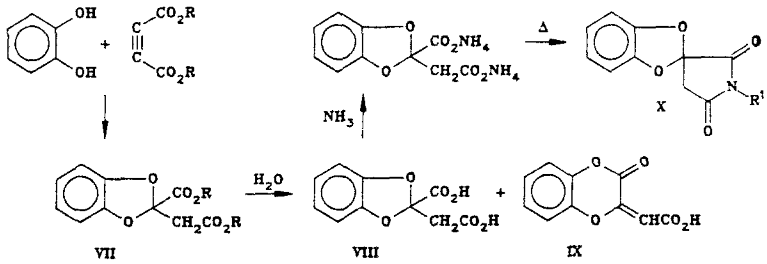
V

VI

$R=H, CH_3, C_6H_5$; $R^1=CH_3, C_6H_5, p\text{-}C_6H_4CH_3, OCH_3, OC_2H_5$

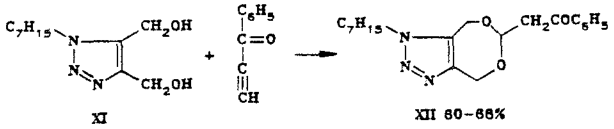
Aryl ethynyl ketones react with pyrocatechol on prolonged heating in benzene in the presence of triethylamine to give 74-88% yields of the 2-acylmethyl-1,3-benzodioxoles (V) [15].

The reaction of pyrocatechol with esters of acetylenedicarboxylic acid in alcohol in the presence of sodium methoxide or ethoxide affords the benzo-1,3-dioxoles (VII) [16], which on alkaline hydrolysis give 2-carboxy-2-carboxymethylbenzo-1,3-dioxole (VIII) and its rearrangement produce 2-carboxymethylene-3-oxobenzo-1,4-dioxane (IX). Vacuum pyrolysis of the ammonium salts of the dicarboxylic acid (VIII) gives the spirosuccinimides (X) [16].

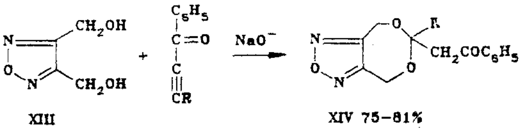


$R=CH_3, C_2H_5; R^1=H, CH_3$

1-Heptyl-4,5-bishydroxymethyl-1,2,3-triazole (XI) reacts on heating with benzoylacetylene in dioxane or THF in the presence of catalytic amounts of sodium to give high yields of the cyclic acetal (XII) [13, 17].



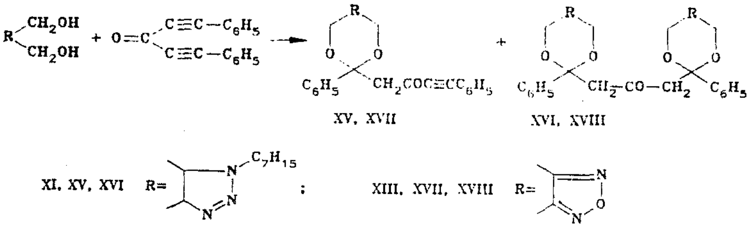
Under similar conditions, 3,4-bishydroxymethyl-1,2,5-oxadiazole (XIII) reacts with benzoylacetylene and 1-benzoyl-2-phenylacetylene to give the cyclic acetals (XIV) [13].



$R=H, C_6H_5$

The diols (XI) and (XIII) react with di(phenylethynyl) ketone in THF in the presence of sodium at either one or both the triple bonds, giving mixtures of the cyclic acetals (XV) and (XVI) and the diacetals (XVII) and (XVIII) [13].

The diols considered in this review, in which the hydroxyl groups possess the same acidity, react synchronously with activated acetylenes at both OH groups. This may be the reason for the fact that no O-monoadducts were isolated in these reactions.



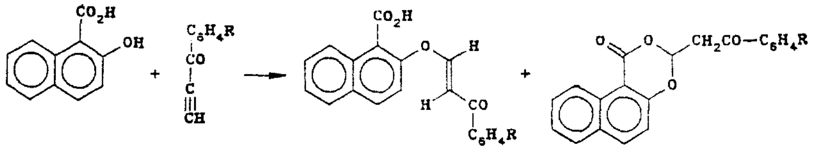
In hydroxyacids, the hydroxyl groups differ markedly in their acidity. For instance, in the case of salicylic acid, disregarding the mutual influence of the groups, the pK_a values for phenol and benzoic acid are 10.00 and 4.18, respectively. However, the pK_a of salicylic acid is 3.00, i.e., it is a stronger acid than benzoic. This "anomaly" may be explained in terms of the ortho-effect of the substituent [18]. It may be that the reactions discussed below between hydroxyacids and acylacetylenes involve an initial stage in which O-monoadducts are formed (addition of the aromatic OH to the C≡C bond), which then undergo intramolecular cyclization (addition of the carboxyl OH to the conjugated C=C bond).

The reaction of salicylic and 2-hydroxy-3-naphthoic acids with acylacetylenes in benzene in the presence of triethylamine leads to the formation in high yields of 2-substituted benzo-1,3-dioxen-4-ones (XIX) and naphtho-1,3-dioxen-4-ones (XX) [16].

XIX, XX

XIX $R=C_6H_4$; $R^1=H$ (75%), CH_3 (57%), OCH_3 (92%), Cl (76%); XX $R=C_{10}H_6$; $R^1=H$ (79%), OCH_3 (42%), Cl (54%)

On reacting 2-hydroxy-1-naphthoic acid with terminal acetylenes, in addition to the cyclic compounds (XXII), the trans-adducts (XXI) were isolated, in a ratio of 1:1 [15].



XXI XXII

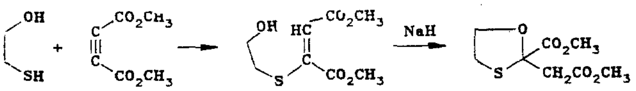
XXI R=H (47%), p-OCH_3 (49%), p-Cl (45%); XXII R=H (34%), p-OCH_3 (42%), p-Cl (41%)

REACTIONS OF ACETYLENIC CARBONYL COMPOUNDS WITH HYDROXYTHIOLS, MERCAPTOACIDS, AND DITHIOLS

The nucleophilicity of thiols in analogous reactions and solvents is known to be much greater than that of alkoxides. This is believed to be due to the greater polarizability of the sulfur atom as compared with oxygen [9]. The effects of various factors on the relative nucleophilicities of oxygen and sulfur-containing anions have been discussed by Kooyman in a review [19].

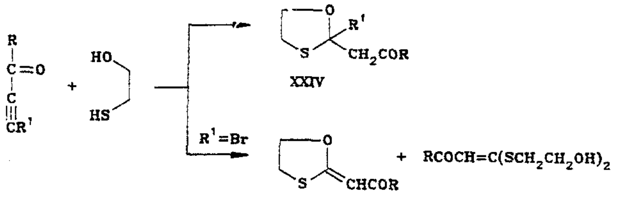
In the reactions of hydroxythiols with activated acetylenes discussed below, it has been shown that the initial step in the reaction is addition of thiolate anion to the C≡C bond with the formation of the S-monoadducts.

The reaction of equimolar amounts of 1,2-mercaptoethanol with acetylene-dicarboxylic ester at 0°C gave dimethyl (2-hydroxyethylthio)fumarate, which cyclized on treatment with sodium hydride in dry toluene to give the substituted 1,3-oxathiolane (XXIII) [20].



XXIII

2-Acylmethyl-1,3-dioxolanes (XXIV) have been obtained by the reaction between α-acetylenic ketones and 1,2-mercaptoethanol in chloroform in the presence of potassium carbonate or in alochol in the presence of triethylamine (yields 35-40%) [21].

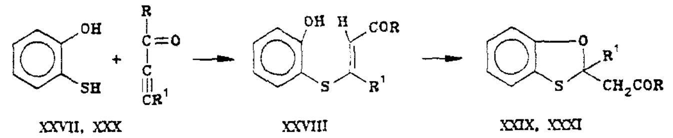


XXV XXVI

XXIV $R=C_6H_5$, m-$C_6H_4NO_2$, C_4H_3S; $R^1=H$, C_4H_9, C_6H_5; XXV, XXVI $R=C_6H_5$, C_4H_3S, 2-C_2H_5—C_4H_2S

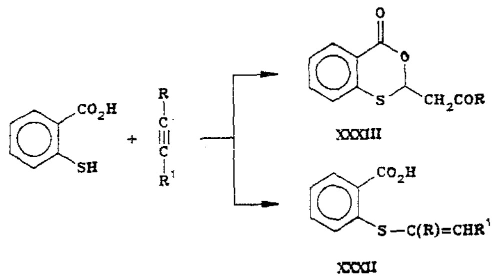
In an analogous synthesis of 2-acylmethylene-1,3-oxathiolanes (XXV) from 1,2-mercaptoethanol and 1-bromo-2-acylacetylenes, in addition to (XXV) the α-ketoketene mercaptals (XXVI) were isolated, which on prolonged heating in chloroform gave (XXV) with the elimination of a molecule of mercaptoethanol [22].

o-Mercaptophenol reacts with methyl propiolate in DMSO in the presence of potassium tert-butoxide at 80-100°C to give 2-methoxycarbonylmethyl-1,3-benzoxathiole (XXIX) and a mixture of trans- and cis-vinyl sulfides (XXVIII) in a ratio of 1:4 [23].



XXVII—XXIX R=OCH_3, R^1=H; XXX, XXXI R=CH_3, C_6H_5, C_4H_3S, C_4H_3Se; R^1=H, C_4H_9, C_6H_5, C_4H_3S

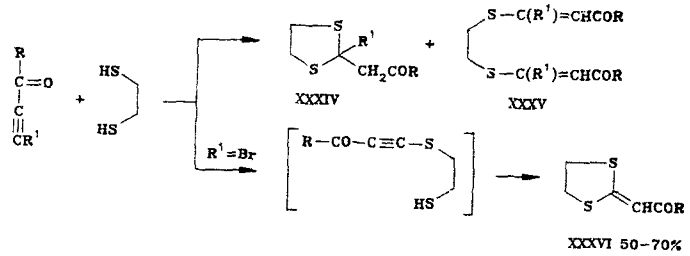
The reaction of o-mercaptophenol with α-acetylenic ketones of diverse structure in alcohol in the presence of triethylamine affords high yields (70-98%) of 2-acylmethylbenzo-1,3-oxathioles (XXXI) [24, 25]. The reaction proceeds via the intermediate formation of ketovinyl sulfides, which cyclize readily to (XXXI).



XXXII R=R^1=CO_2CH_3; XXXIII R=C_6H_5 (51%), p-$C_6H_4OCH_3$ (53%)

Reaction of o-mercaptosalicylic acid with acetylenedicarboxylic ester in alcohol gives the S-monoadduct (XXXII) (58% yield) [26, 27], and with terminal acetylenic ketones in benzene in the presence of triethylamine it affords the cyclic compounds (XXXIII) with a lactone structure [15].

2-Acylmethyl-1,3-dithiolanes (XXXIV) have been obtained by the reaction of equimolar amounts of 1,2-ethanedithiol with acetylenic ketones [28, 29], and with propiolate esters [30] in chloroform in the presence of potassium carbonate or in alcohol in the presence of triethylamine.



XXXIV, XXXV R=OCH_3, OC_2H_5, C_6H_5, m-$C_6H_4NO_2$, C_4H_3S; R^1=H, C_4H_9, C_6H_5; XXXVI R=C_6H_5, C_4H_3S

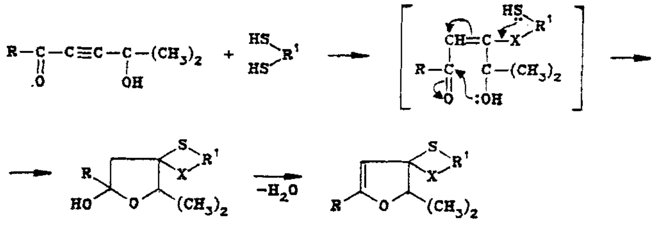
When 1,2-ethanedithiol reacts with two moles of an acetylenic ketone, in addition to the 1,3-dithiolanes (XXXIV) there are formed mixtures of E,E-and E,Z-1,4-bis(ketovinyl)dithiooethanes (XXXV) in a ratio of 3:1 [29].

A method has been developed for the preparation of 2-acylmethylene-1,3-dithiolanes (XXXVI) by the reaction of 2-acyl-1-bromoacetylenes with ethane-1,2-dithiol in alcohol at 20°C in the presence of triethylamine [31]. During the reaction, intermediate acetylenic mercaptosulfides are formed, these then cyclizing to (XXXVI).

Reaction of 1,2-mercaptoethanol, ethane-1,2-dithiol, or o-phenylene-dithiol with acylethynylcarbinols in chloroform in the presence of potassium carbonate gives 5-hydroxytetrahydrofuran-3-spiro-2'-(1,3-oxathiolanes) (XXXVII), -2'-(1,3-dithiolanes) (XXXVIII), and -2'-benzo-1,3-dithioles (XXXIX) [32, 33].

On heating (XXXVII) or (XXXVIII) in aprotic solvents, spontaneous dehydration takes place with the formation of the spiro-derivatives of 4,5-dihydrofuran (XL) [33].

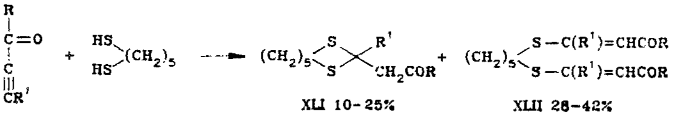
The reaction of acylacetylenes with pentane-1,5-dithiol in chloroform in the presence of potassium carbonate gives 2-acylmethyl-1,3-dithiacylo-octanes (XLI) and 1,5-bis[1-oxo-



XXXVII-XXXIX (52-65%) XL

XXXVII $R=C_6H_5$, C_4H_3S; $R^1=CH_2CH_2$; $X=O$; XXXVIII $R=C_6H_5$, C_4H_3S; $R^1=CH_2CH_2$, $X=S$; XXXIX $R=C_6H_5$, C_4H_3S; $R^1=C_6H_4$; $X=S$

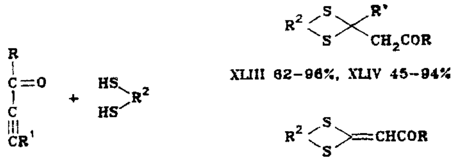
1-phenyl(2-thienyl)-4-thiabuten-2-yl]-pentanes (XLII) [34].



XLI 10-25% XLII 28-42%

$R=C_6H_5$, C_4H_3S; $R^1=H$, C_6H_5

The syntheses of 2-acylmethyl- and 2-acylmethylenebenzo-1,3-dithioles (XLIII, XLV) and 1,3-dithiolo[4,5-b]quinoxalines (XLIV, XLVI) have been effected by reacting acylacetylenes and 1-bromo-2-acyl-acetylenes with o-phenylenedithiol and quinoxaline-2,3-dithiol in alcohol, chloroform, or DMSO in the presence of basic catalysts (triethylamine, potassium carbonate) [35, 36].



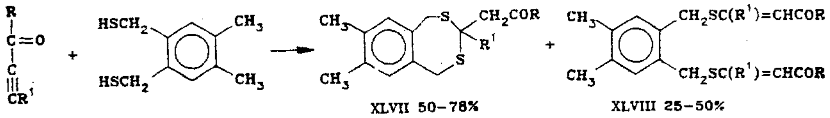
XLIII 62-96%, XLIV 45-94%

XLV 83-88%, XLVI 54-59%

XLIII $R=CH_3$, C_6H_5, C_4H_3S; $R^1=H$, C_4H_9, C_6H_5, C_4H_3S; $R^2=C_6H_4$; XLIV $R=C_6H_5$, C_4H_3S; $R^1=H$, CH_3OCH_2, C_6H_5; $R^2=2,3$-quinoxalyl: XLV $R=C_6H_5$, C_4H_3S; $R^2=C_6H_4$; XLVI C_6H_5, C_4H_3S; $R^2=2,3$-quinoxalyl

The reaction of dithiols with 1-bromo-2-acylacetylenes involves direct nucleophilic replacement of the bromine at the ethynyl carbon atom [37, 38], followed by cyclization of the intermediate acyl ethynyl sulfides.

The reaction of 1,2-dimethyl-4,5-di(mercaptomethyl)benzene with acylacetylenes and methyl propiolate in chloroform in the presence of potassium carbonate, or in methanol in the presence of triethylamine, has in our hands given substituted 1,5-dihydrobenzo[e]-2,4-dithiepines (XLVII) and 1,2-di-(acylvinylthiomethyl)-4,5-dimethylbenzenes (XLVIII) [30, 39].



XLVII 50-78% XLVIII 25-50%

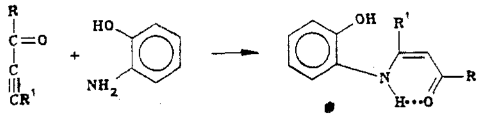
$R=CH_3$, OCH_3, C_6H_5, C_4H_3S; $R^1=H$, C_6H_5, p-$C_6H_4CH_3$

When an excess of the acetylenic ketone was used, the yields of the 2,4-dithepines (XLVII) decreased, but that of (XLVIII) increased to 70-80%.

SYNTHESIS OF N,O HETEROCYCLES BY THE REACTION BETWEEN ACETYLENIC CARBONYL COMPOUNDS AND AMINOPHENOLS, AMINOALCOHOLS, AND CARBOXYLIC ACID o-HYDROXYAMIDES

Different functional groups in the dinucleophilic compounds react with the activated triple bond in different ways. The addition of amines to activated acetylenes is known to proceed readily in the absence of catalysts [40, 41], whereas the addition of alcohols is catalyzed by strong bases such as alkali metal alkoxides [11, 42-45].

In the reactions of acetylenic carbonyl compounds with N,O-dinucleophiles, the amino-group adds readily to the triple bond, but the hydroxyl group frequently does not react.

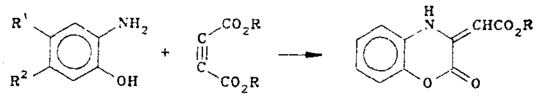


XLIX, L

XLIX R=C_6H_5, R^1=COC_6H_5; L R=C_6H_5 (83%), p-$C_6H_4CH_3$ (79%), p-$C_6H_4OCH_3$ (59%), R^1=H

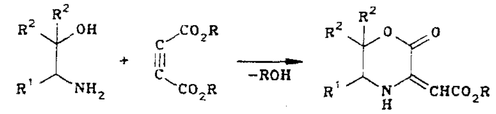
The reaction of dibenzoylacetylene with o-aminophenol in a 1:4 mixture of alcohol and ether at a boil [46], or in THF [47], affords 84-87% yields of the aminovinyl ketones (XLIX) in the cis-form, in which the free OH group is retained. The reaction of o-aminophenol with terminal acetylenic ketones proceeds similarly in benzene with heating, to give (L) [15].

The reactions of acetylenedicarboxylic esters with o-aminophenol and β-aminoethanol under various conditions to give respectively 1,4-benzoxazin-2-one and 1,4-oxazin-2-one have been described in reviews [1-3]. The reaction of acetylenedicarboxylic esters with 4,5-disubstituted 2-aminophenols and with substituted β-aminoethanols at 20°C in alcohol affords the 3-alkoxycarbonylmethylene-1,4-benzoxazin-2-ones (LI) and 3-alkoxycarbonylmethylene-3,4,5,6-tetrahydro-1,4-oxazin-2-ones (LII) [48].



LI

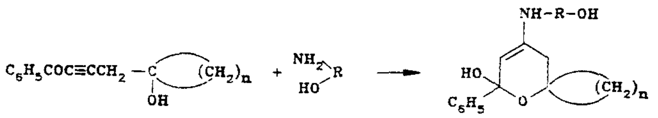
R=CH_3, C_2H_5; R^1=H, Cl, NO_2; R^2=H, Cl, CH_3



R=CH_3, C_2H_5; R^1=H, CH_3; R^2=H, CH_3

LII

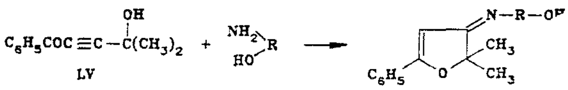
The 2,3-dihydro-α-pyrans (LIII, LIV) have been obtained by reacting α-acetylenic ketones with o-aminophenol and β-aminoethanol in a 1:4 mixture of alcohol and ether with heating [46].



LIII R=C_6H_4; LIV R=CH_2CH_2; n=4,5

LIII 75%, LIV 71%

The acetylenic ketone (LV) reacts with o-aminophenol and β-aminoethanol under similar conditions to give the corresponding 3-imino-2,3-dihydrofurans (LVI) [46].

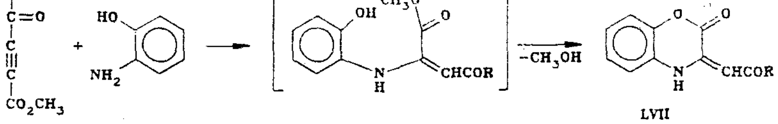


LV

LVI 70-78%

R=C_6H_4, CH_2CH_2

Acetylenic esters of γ-ketoacids behave in their reactions with dinucleophiles in a similar way to acetylenedicarboxylic esters. The reaction of methyl acylpropiolates with o-aminophenol in a 1:4 mixture of alcohol and ether with heating affords the substituted 3,4-dihydro-2H-1,4-benzoxazin-2-ones (LVII) [46].

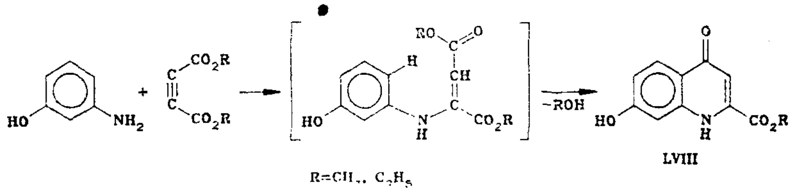


LVII

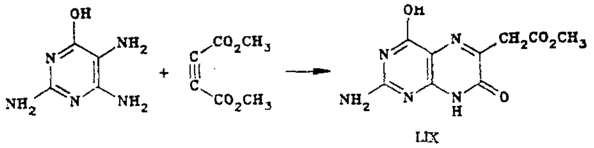
R=C_3H_7, C_6H_5

This reaction involves the intermediate formation of aminovinyl ketones, which cyclize to the benzoxazines (LVII) with the elimination of a molecule of alcohol.

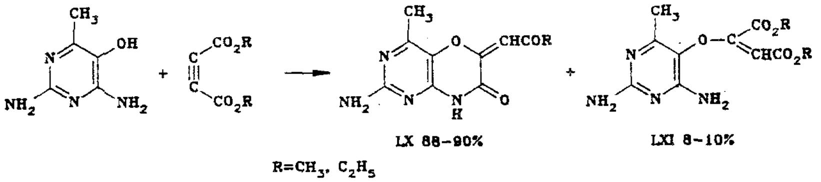
The reaction of acetylenedicarboxylic ester with m-aminophenol at 20°C affords 2-methoxycarbonyl-7-hydroxy-1H-quinolin-4-one (LVIII) [49]. The reaction appears to proceed via the aminofumarate, which undergoes intramolecular cyclization to (LVIII).



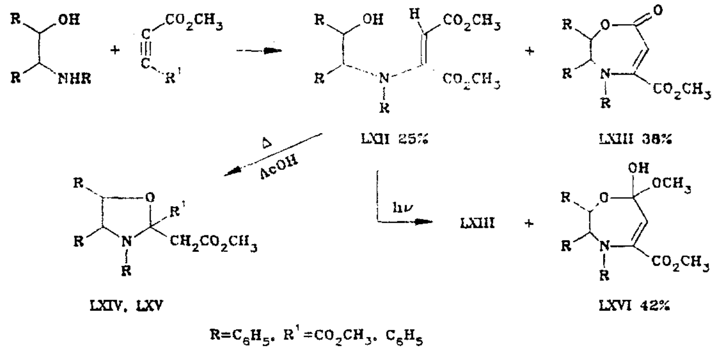
2,4,5-Triamino-6-hydroxypyrimidine reacts with acetylenedicarboxylic ester to give pyrimido[4,5-b]-1,4-pyrazin-2-one (LIX) [50]. Only the amino-groups in the 4 and 5-positions of the pyrimidine ring are involved in the reaction, confirming that the amino-group is more nucleophilic than the hydroxy-group.



The reaction of 2,4-diamino-5-hydroxy-6-methylpyridine with acetylene-dicarboxylic esters in methanol gives 2-amino-6-alkoxcarbonylmethylene-4-methylpyrimido[5,4-b]-8H-1,4-oxazin-7-ones (LX) and hydroxyethylene-1,2-dicarboxylates (LXI), which on prolonged heating in alcohol cyclize to (LX) [50].



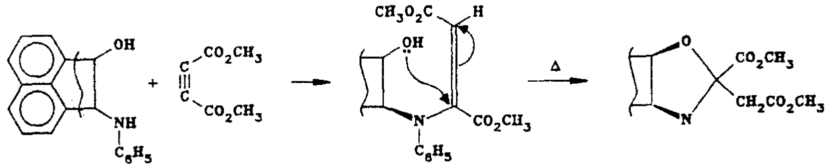
The reaction of erythro-1,2-diphenyl-2-(phenylamino)ethanol with acetylenedicarboxylic ester in boiling benzene affords the aminomaleate (LXII), but in alcohol at 20°C, in addition to this compound there is also formed 4-methoxycarbonyl-2-oxo-5,6,7-triphenyl-2,5,6,7-tetrahydro-1,5-oxazepine (LXIII) [51]. Heating this compound (LXII) in glacial acetic acid gives cis-3,4,5-triphenyl-2-methoxycarbonylmethyl-1,3-oxazolidine (LXIV).



UV irradiation of (LXII) in benzene in the presence of acetic acid gave (LXIII) and 2-methoxy-4-methoxycarbonyl-2-hydroxy-5,6,7-triphenyl-2,5,6,7-tetrahydro-1,5-oxazepine (LXVI). The latter was formed by nucleophilic addition of the hydroxy-group to the carbonyl group in the aminomaleate (LXII) [51].

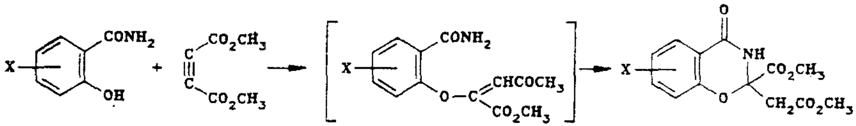
On heating 1,2-diphenyl-2-(phenylamino)ethanol with methyl phenylpropiolate in xylene in the presence of triethylamine, 2-methoxycarbonyl-methyl-2,3,4,5-tetraphenyl-1,3-oxazolidine (LXV) is formed. The reaction proceeds via the intermediate aminovinylcarboxylate, which cyclizes to (LXV) as a result of nucleophilic addition of the hydroxyl group to the conjugated C=C bond [51].

cis-1-Hydroxy-2-phenylaminoacenaphthene reacts with acetylenedicarboxylic ester to give the aminofumarate (LXVII), which on heating in glacial acetic acid cyclizes to oxazolidino-[4,5-a]acenaphthene (LXVIII) [51].



LXVII 72% LXVIII 80%

A method has been developed for the preparation of benz-1,3-oxazin-4-ones (LXIX) involving the reaction of acetylenedicarboxylic ester with salicylamides in the presence of sodium methoxide in methanol on prolonged heating [52-54].



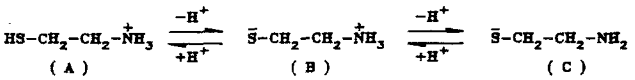
LXIX 45-93%

LXIX X=H, Br, Cl, CH_3O

The reaction of 1-hydroxy-2-naphthylamide with acetylenedicarboxylic ester in methanol in the presence of sodium methoxide takes place extremely slowly to give the substituted naphtho-1,3-oxazin-4-one (LXX) [52].

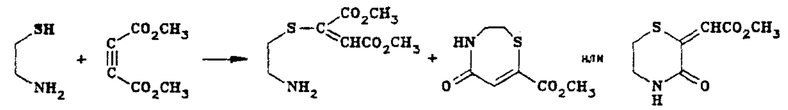
REACTIONS OF ACETYLENIC CARBONYL COMPOUNDS WITH 1,2-AMINOTHIOLS AND o-MERCAPTOBENZAMIDES

Aminothiols, being bifunctional compounds, are able to react either at the amino-group or the sulfhydryl group. The combination of acidic and basic properties in a single molecule makes possible the existence of the aminothiols as internal salts, namely the zwitterion B [55]. Varying the pH of the medium may create the conditions for the conversion of the ammonium salt (A) via the zwitterion (B) into the free base (C) [56, 57].



$$\underset{(A)}{HS-CH_2-CH_2-\overset{+}{N}H_3} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \underset{(B)}{\bar{S}-CH_2-CH_2-\overset{+}{N}H_3} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \underset{(C)}{\bar{S}-CH_2-CH_2-NH_2}$$

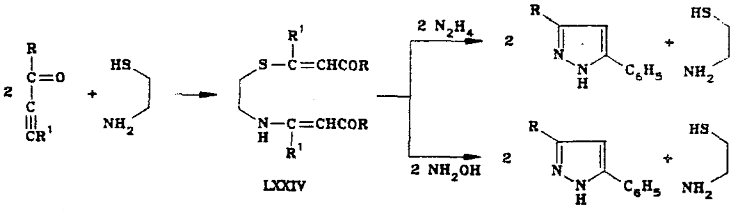
β-Mercaptoethylamine is an example of an aminothiol in which the acidity of the SH-group is so much greater than the acidity of the amino-group that removal of a proton occurs almost exclusively from the mercapto-group [58].



LXXI 25% LXXII 21% LXXIII

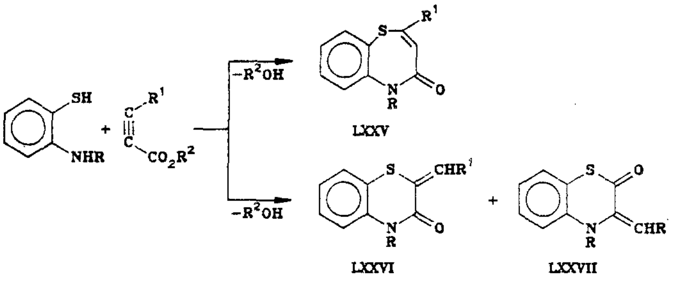
β-Mercaptoethylamine reacts with acetylenedicarboxylic ester in ether with cooling to give 6,7-dihydro-1,5-thiazepin-2-one (LXXII) or 5,6-dihydro-1,4-thiazin-2-one (LXXIII) and the S-monoadduct (LXXI). As a result of studies of the chemical behavior of the cyclic compound, Mushkalo and Lanovaya [59] conclude that the most likely structure is that with a seven-membered ring (LXXII).

The reaction of α-acetylenic ketones with β-mercaptoethylamine in alcohol in the presence of sodium methoxide, or in chloroform in the presence of potassium carbonate, gives 1,4-bis(acylvinyl)-1-thia-4-azabutanes (LXXIV), which on heating with hydroxylamine hydrochloride or with hydrazine hydrate in the presence of potassium carbonate give isoxazoles and pyrazoles [60].



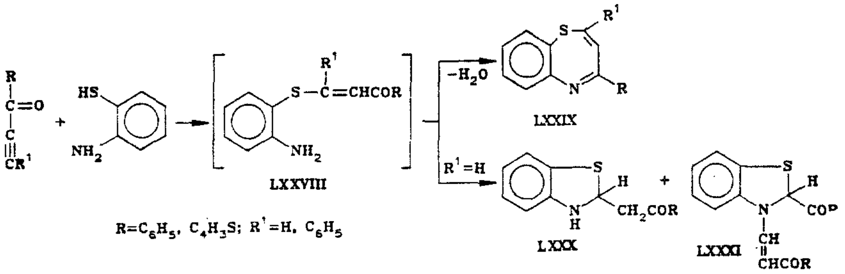
$R=R^1=C_6H_5$; $R=C_4H_3S$, $R^1=C_6H_5$

Substituted benzo-1,5-thiazepin-2-ones (LXXV) are obtained by reacting o-aminothiophenol or N-methyl-o-aminothiophenol with propiolic or methylpropiolic acid in ether [59, 61].



LXXV R=H, CH_3; R^1=H (93%), CH_3 (44%); R^2=H; LXXVI, LXXVII R=H, CH_3; $R^1=CO_2H$, CO_2CH_3, $CO_2C_2H_5$; R^2=H, CH_3, C_2H_5

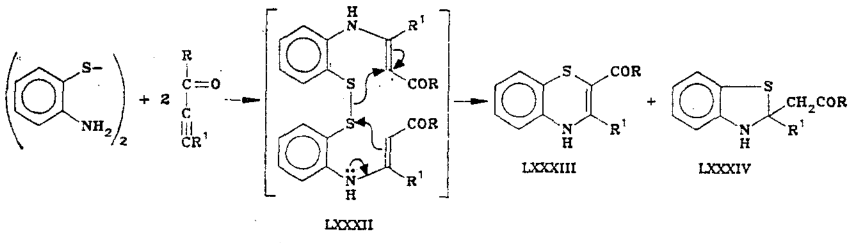
The reactions of o-aminothiophenol or N-methylthiophenol with acetylene-dicarboxylic acid or its esters normally lead to 2-alkoxycarbonylmethylene-3,4-dihydrobenzo-1,4-thiazin-3-ones (LXXVI) and its isomers, 3-alkoxy-carbonylmethylene-3,4-dihydrobenzo-1,4-thiazin-2-ones (LXVII) [62-67]. In ether, this reaction gives high yields (91-98%) of (LXVII) only [68].



$R=C_6H_5$, C_4H_3S; R^1=H, C_6H_5

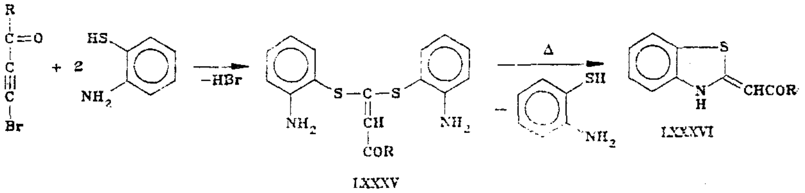
Reaction of o-aminothiophenol with α-acetylenic ketones in methanol at 20°C in the absence of a catalyst or in the presence of triethylamine gives the 1,5-benzothiazepines (LXXIX) [69, 70]. Terminal α-acetylenic ketones react with o-aminothiophenol in alcohol in the presence of triethylamine on heating to give 2-acylmethyl-4,5-benzothiazolines (LXXX) and 3-acylvinyl-2-acylmethyl-4,5-benzothiazolines (LXXXI). The latter are formed by vinylation of the NH group in (LXXX) by a further molecule of the acetylenic ketone [69, 71]. The reaction involves the intermediate formation of the acylvinyl sulfides (LXXVIII).

Heating o-aminophenyl disulfide with acetylenic ketones or esters of propiolic acid in ethanol or DMF under nitrogen gives high yields of the benzo-1,4-thiazines (LXXXIII) and benzo-1,3-thiazolines (LXXXIV), together with small amounts of 2,3-dihydrobenzothiazoles [72 - 74]. The reaction is assumed to involve the intermediate formation of the enamine (LXXXII), followed by fission of the S—S bond.

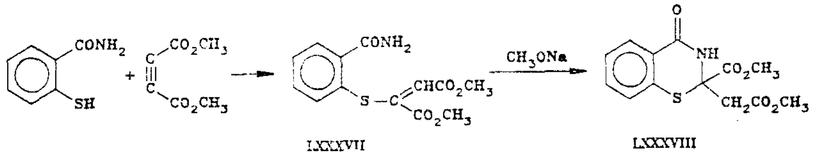


$R=CH_3$, OCH_3, OC_2H_5; R^1=H, C_6H_5

The reaction of o-aminothiophenol with 1-bromo-2-acylacetylenes in methanol in the presence of a catalyst (triethylamine or KOH) gives the ketene mercaptals (LXXXV), which on heating in vacuo undergo intramolecular cyclization with loss of o-aminothiophenol to give the 2-acylmethyl-4,5-benzothiazolines (LXXXVI) [75].



o-Mercaptobenzamide reacts with acetylenedicarboxylic ester in anhydrous methanol on heating to give the vinyl sulfone (LXXXVII), which cyclizes on treatment with methanolic sodium methoxide at 65°C to give the 2-substituted 1,3-benzothiazin-4-one (LXXXVIII) [26].



Compound (LXXXVIII) can also be obtained directly by reacting o-mercaptobenzamide with acetylenedicarboxylic ester in the presence of a catalytic amount of sodium methoxide. In this case, double addition to the triple bond takes place, and although the mercapto-group adds without a catalyst, a basic catalyst such as sodium methoxide is required to activate the amino-group [27].

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NITRATION OF 4-METHYL-5,6-DIHYDRO-2H-PYRAN AND SOME ASPECTS OF THE PREPARATION AND ISOMERIZATION OF NITRODIHYDROPYRANS

M. S. Sargsyan, S. A. Mkrtumyan,
and A. A. Gevorkyan

UDC 547.812:542.958.1

The reaction of 4-methyl-5,6-dihydro-2H-pyran with acetyl nitrate to give additive and substitutive nitration products has been examined. It is shown that the addition product, 4-acetoxy-4-methyl-3-nitro-tetrahydropyran, is deacylated on treatment with bases to give an α,β-unsaturated nitro-compound which isomerizes under the reaction conditions to a β,γ-unsaturated nitro-compound. 4-Acetoxy-4-nitromethyltetrahydropyran behaves similarly.

It has previously been shown that the addition of acetyl nitrate to 4-methylenetetrahydropyran can be used to obtain nitro-derivatives of dihydro- and tetrahydropyrans, which are of interest as convenient intermediates for the synthesis of functional derivatives of di- and tetrahydropyran [1]. Continuing these studies, we have examined the addition of acetyl nitrate to 4-methyl-5,6-dihydro-2H-pyran and the chemical properties of the reaction products.

The reaction of acetyl nitrate with 4-methyl-5,6-dihydro-2H-pyran proceeds as readily as with 4-methylenetetrahydropyran, to give a mixture of the adduct (I) and the substitution products (II-IV) in a ratio of 7:3. Variations in the temperature of the reaction did not affect this ratio at all, probably in consequence of the independent reaction pathways. In fact, separate experiments showed that the nitroacetate (I) showed no tendency to lose acetic acid under the reaction conditions. Furthermore, it did not undergo deacylation in the presence of sulfuric acid in acetic anhydride, and in the presence of hydrochloric acid only hydrolysis occurred to give 4-hydroxy-3-nitrotetrahydropyran (V). It must therefore be assumed that the unsaturated nitro-compounds (II-IV) are formed in a different way. In all likelihood, nitroacylation leads to the tetrahydropyranilium carbocation as an intermediate, which in addition to reacting with the nucleophile, also undergoes deprotonation.

According to PMR and GC, the major component of the deprotonation products (II-IV) is 4-methyl-3-nitro-3,6-dihydro-2H-pyran (II). In other words, deprotonation of the intermediate tetrahydropyranilium carbocation gives, as would be expected, the nonconjugated

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