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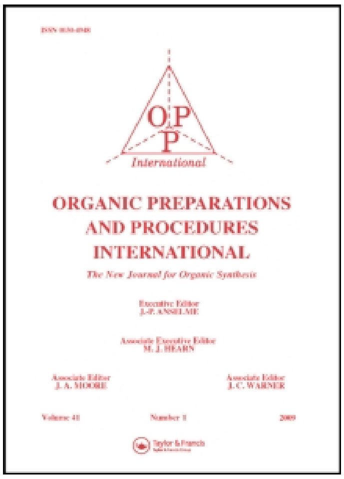

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REACTIONS OF ACETYLENES WITH HYDRAZINES. A REVIEW

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REACTIONS OF ACETYLENES WITH HYDRAZINES. A REVIEW[†]

Wolfgang SUCROW

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[†] *Dedicated to Prof. F. Bohlmann on the occasion of his 60th birthday*

REACTIONS OF ACETYLENES WITH HYDRAZINES. A REVIEW

Wolfgang SUCROW

Laboratory of Organic Chemistry, University of Paderborn
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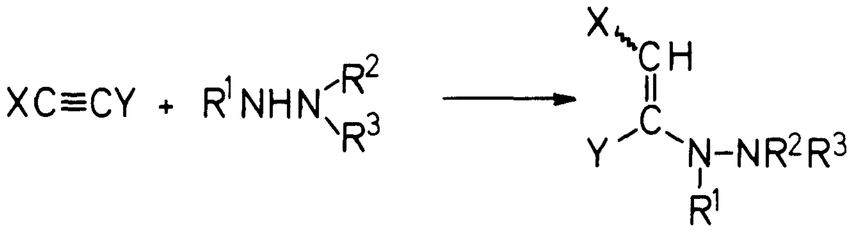
INTRODUCTION AND SCOPE OF THE REVIEW

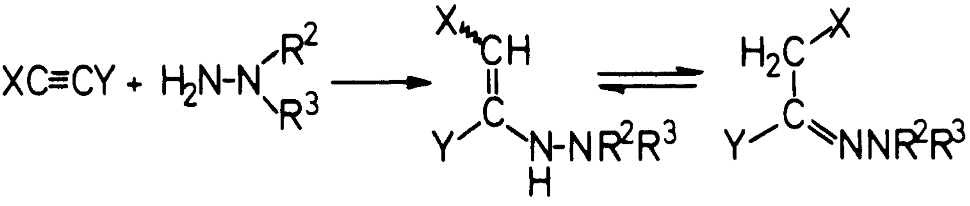
The addition of hydrazines to acetylenic esters or to acetylene dicarboxylic esters has recently been reviewed by George, Khetan and Gupta[1] and Baumgarth.[2a-c] The purpose of this review is to focus on the structure of the primary addition products of hydrazines to acetylenic compounds and on the subsequent products. Cycloaddition reactions to acetylenic compounds will not be considered.

The addition of hydrazines is in practice restricted to triple bonds bearing at least one acceptor group X. If the hydrazine adds through an NHR-group, enehydrazines of type A will result, with the formation of two diastereomers (E and Z) being possible. If the addition takes place through an unsubstituted amino group, a tautomeric equilibrium between an enehydrazine of form B and/or a hydrazone of form C may be established.



X = acceptor group

A



X = acceptor group B C

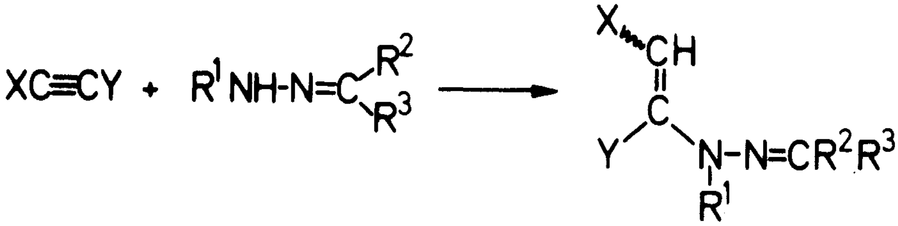
It seemed reasonable to discuss these two types separately and consider the enehydrazines incapable of tautomerization (type A) first and the others (type B/C) later. Most of the enehydrazines/hydrazones are very labile compounds which should be handled with great care. In deep freezers (- 30°) they may, as a rule, be kept for some time without degradation.

Since a great number of the compounds discussed in this review are prepared from dimethyl acetylene-dicarboxylate or methyl propiolate these starting materials will be designed as DMAD and MP, respectively.

I. ENEHYDRAZINES INCAPABLE OF TAUTOMERIZATION

1. Enehydrazones

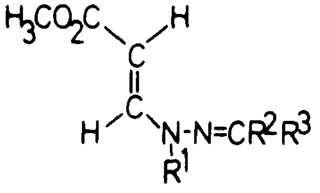
A prominent group of enehydrazine derivatives incapable of tautomerization is formed by the addition of hydrazones of type D to triple bonds to yield the enehydrazones of type E.



D E

X = acceptor group

Most of the compounds described in the literature are derived mainly from a large number of hydrazones and dimethyl acetylenedicarboxylate (DMAD) or methyl propiolate (MP). Compounds 1 and 2[3,4] may serve as typical examples for enehydrazones derived from aliphatic hydrazines and 3 as representative of these derived from benzaldehyde hydrazones;[5,6] only one phenylhydrazone adduct (to DMAD) has been described.[7]



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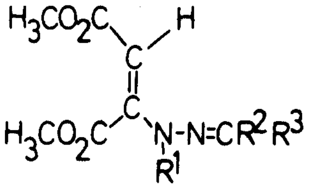

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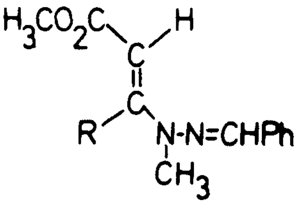


3

a) $R^1 = R^2 = R^3 = CH_3$

b) $R^1 = C_2H_5$ $R^2 = CH_3$ $R^3 = H$

c) $R^1 = CH_3$ $R^2,R^3 = (CH_2)_4$

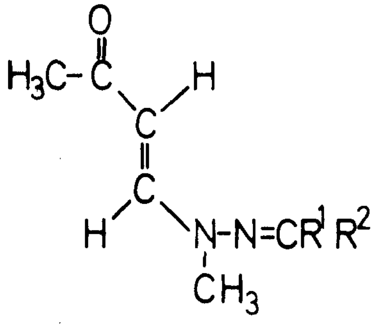
a) $R = H$

b) $R = CO_2CH_3$

The configurations of the double bonds are E as is easily recognized in the acrylic ester derivatives such as 1 and 3a from the $J_{2,3}$ coupling constants of 13—13.5 cps.[4-6] Trisubstituted olefins as 2a-2c and 3b are recognized as maleic ester derivatives by the chemical shifts of their vinyl protons which, as a rule, do not differ much from those of H-2 of the acrylic ester analogues; the additional ester group in the maleic ester derivatives has little influence on the chemical shift. Compounds 1a-2c have absorptions at δ 4.4-4.9 ppm and 3a and 3b at about δ 5. The vinyl proton of a fumaric ester derivative would appear at lower field by at least 1 ppm.[8,9]

The exclusive formation of E-adducts resembles the predominant syn-addition of amines to acetylenic esters.[10] However, this was shown to be a consequence of thermodynamic control.[11,12] Kinetic control led to considerable amounts of anti-addition (Z-products) which under normal conditions, rearranged in a secondary reaction to E-products which thus seem to originate from syn-additions. In the case of addition of hydrazones, no Z-adducts could be observed, not even in case where liquid products were investigated without purification.

Ethynyl ketones have also been used to prepare the corresponding enehydrazones.[3,5] 1-Butyn-3-one gave addition products 4a and 4b with a number of hydrazones. The coupling constants of 4a and 4b, ranging from 12.5-13.5 cps, indicate an E-configuration about the C=C double bonds. The same configuration is observed for the addition products of phenyl ethynyl ketone and propiolaldehyde;[3] this is also probably true for the products derived from dibenzoylacetylene[13] and phenylpropiolaldehyde (e.g. 5).[3]



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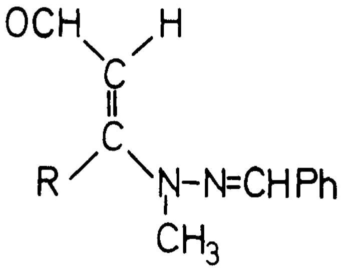
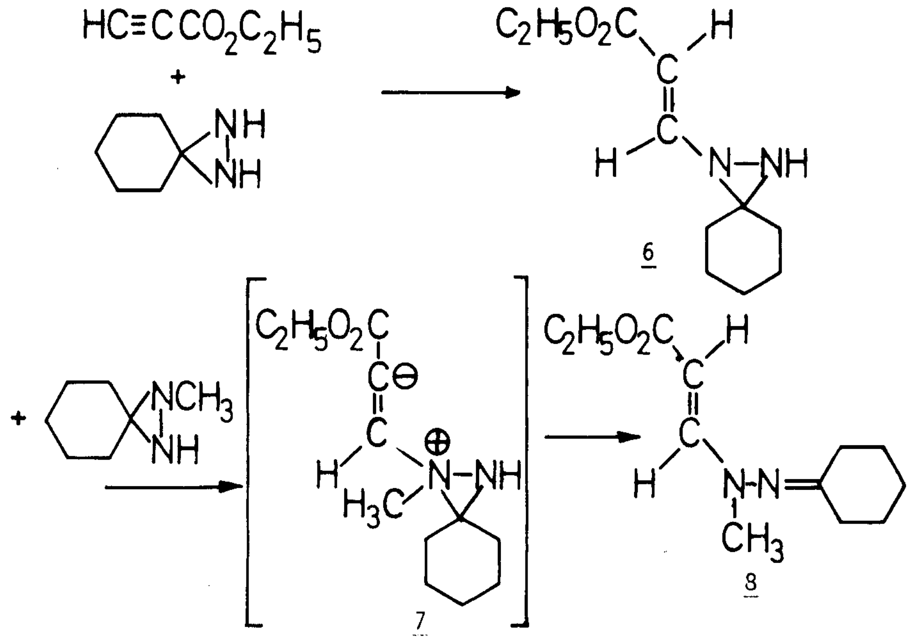


5

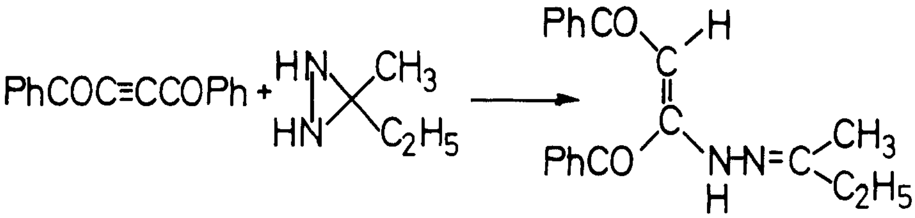
a) R^1 = H R^2 = Ph b) $R^1 = R^2 = CH_3$

Some enehydrazones were obtained by rearrangements of diaziridine adducts to acetylenic compounds;[13] ethyl propiolate and 3,3-pentamethylenediaziridine gave adduct 6 (see also Ref.[14]). 1-Methyl-3,3-pentamethylenediaziridine adds through the more nucleophilic methyl-substituted nitrogen to give the unstable zwitterion 7 which rearranges to the enehydrazone 8; 8 was also obtained from ethyl propiolate and cyclohexanone methylhydrazone. The configurations of 6 and 8 were established to



be E by the coupling constants of 13 cps; 6 was, however, accompanied by a small amount of the Z-isomer with a coupling constant of 8.5 cps.

With substrates such as diethyl acetylenedicarboxylate, dibenzoylacetylene and hexafluoro-2-butyne, the rearrangement occurred even with N-unsubstituted diaziridines (e.g. 9 independently prepared from

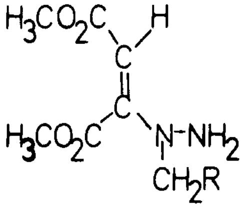


9

dibenzoylacetylene and 2-butanone hydrazone).[13] Compound 9 might be expected to tautomerize to the hydrazone form but actually exhibits a vinyl signal in the nmr.

2. Enehydrazines

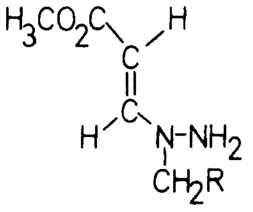
Addition of methylhydrazine to DMAD in ether or methylene chloride leads to the formation of the exceptional enehydrazine 10a.[15] As with 7, the more nucleophilic methyl-substituted nitrogen adds to the triple bond. The E-configuration suggested by the vinyl proton at 4.56 ppm was confirmed by other spectroscopic means such as X-ray crystal structure.[16] The crystalline compound 10a is stable enough to be kept in deep freeze for some weeks, but is very reactive otherwise giving a variety of products under mild conditions (see below). Compound 10a forms hydrazones with carbonyl compounds, e.g. the above cited 3b with benzaldehyde and 2a with acetone;[15] adduct 10b derived from benzylhydrazine behaves similarly.[17] Addition of methylhydrazine to MP gives 11a[15] which could not be purified, but adduct 11b[15] with benzylhydrazine is a sufficiently stable crystalline compound (2-H 4.83 ppm, J = 13.5 cps). The symmetrical 1,2-dimethylhydrazine forms the adducts 12a (J = 13 cps)[18] and 12b (vinyl proton at 4.47 ppm),[15,18] both being liquids.



10

a) R = H

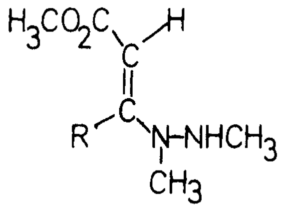
b) R = Ph



11

a) R = H

b) R = Ph

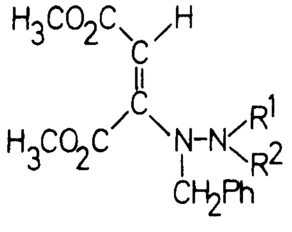


12

a) R = H

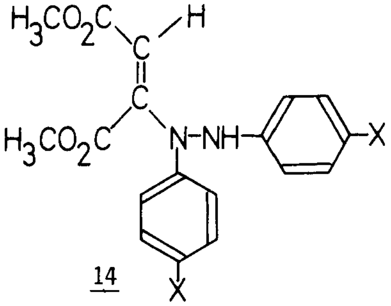
b) R = CO_2CH_3

There is no doubt that adduct 13a prepared by Diels and Reese in 1935[19] also has the E-configuration like 12b and this may also be true for enehydrazines 13b-13d and 14a-14c[19-21]; 13b was obtained in two stereo(?)isomeric forms. Compounds 13b and 14a-14c are starting materials for interesting cyclization reactions (see below).



13

a) R^1 = H R^2 = CH_2Ph
b) R^1 = Ph R^2 = CH_2Ph
c) R^1 = H R^2 = Ph
d) R^1 = R^2 = CH_2Ph

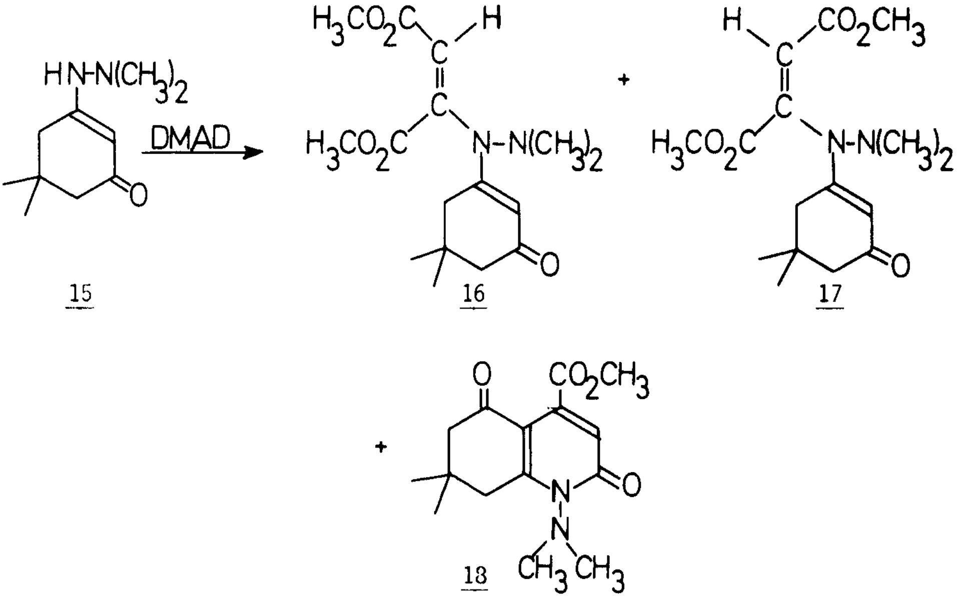


14

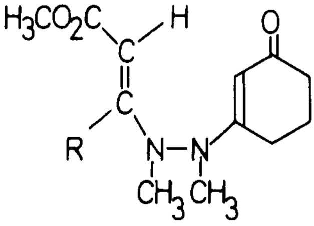
a) X = H
b) X = CH_3
c) X = Cl

The hydrazine 15 from dimedone and 1,1-dimethylhydrazine adds to DMAD in tetrahydrofuran to give the diastereomeric adducts 16 and 17 together with the cyclized product 18.[9] Compounds 16 and 17 exhibit the typical shift difference of the vinyl protons δ 5.47 ppm for 16 and δ 6.87 for 17 in E- and Z-enehydrazines.

Addition of the enehydrazine from 1,3-cyclohexanedione and 1,2-dimethylhydrazine to MP or DMAD gave only the adducts of E-configuration 19a or 19b along with cyclization products 20a, 20b, 21a and 21b.[22] Formazanes have also been added to DMAD to give the adducts 22a and 22b



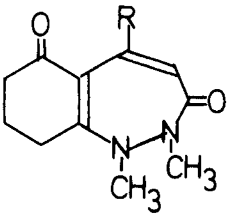
15 16 17 18



19

a) R = H

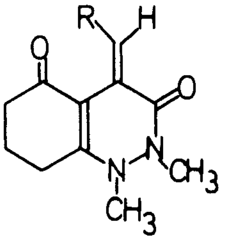
b) R = CO_2CH_3



20

a) R = H

b) R = CO_2CH_3

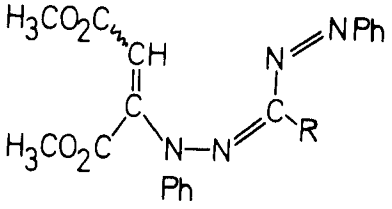


21

a) R = H

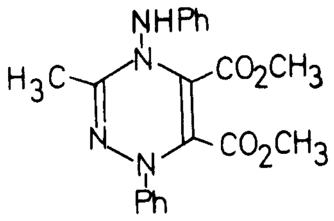
b) R = CO_2CH_3

of unknown configuration with 23 being the main product in one case.[23]



22

a) R = H b) R = CH_3

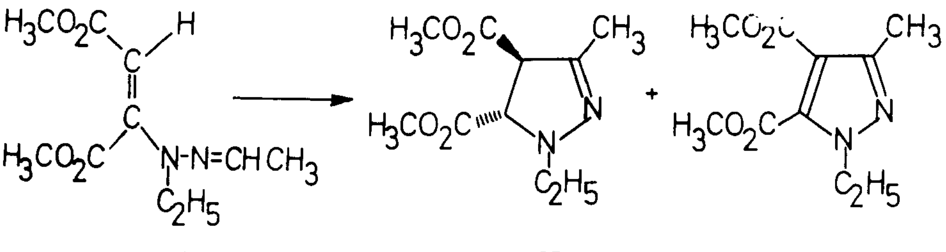


23

II. FORMATION OF PYRAZOLINES FROM HYDRAZONES

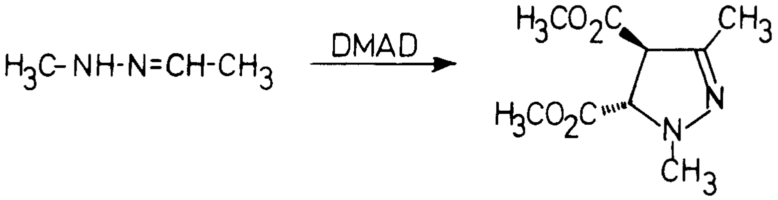
Upon heating in inert solvents and in the presence or absence of acidic catalysts, enehydrazones may undergo an electrocyclic ring closure to pyrazolines. The mechanism of this cyclization has been discussed by Elguero, Jacquier and Marzin.[24] The enehydrazones may be prepared separately or generated in situ.

With the purely aliphatic enehydrazone 24, 38 % of pyrazoline 25 and 56 % of the corresponding pyrazole 26 were obtained in boiling xylene.[3]



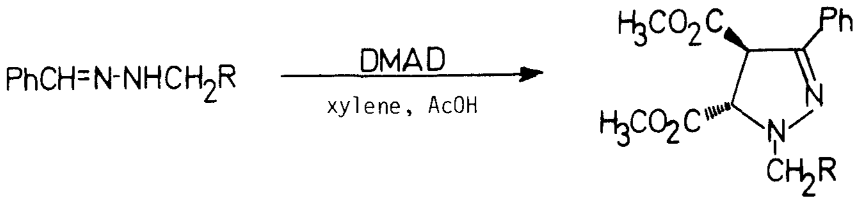
24 25 26

The coupling constant $J_{4,5}$ = 11.5 cps observed in hexadeuterobenzene for 25 cannot serve to determine its configuration unambiguously; it was shown to be trans by the addition of shift reagent. Some similar pyrazolines were prepared in good yields from methylhydrazones of aliphatic aldehydes and DMAD in boiling xylene without isolation of the enehydrazone intermediates;[6] their configuration was probably trans also.



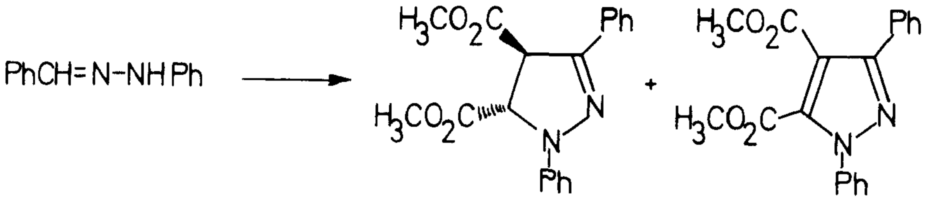
27

Benzaldehyde methyl- and benzylhydrazone formed the dimethyl trans-pyrazolinedicarboxylates 28a and 28b with DMAD in mixtures of xylene and acetic acid;[25] a small amount of the cis-isomer of 28b was also detected.



28

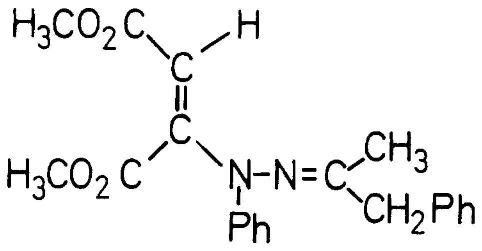
a) R = H b) R = Ph



29 30

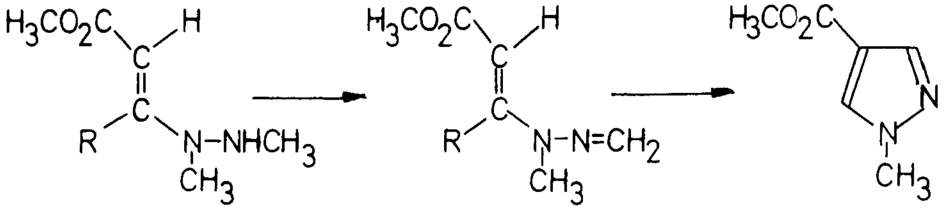
Heating a mixture of benzaldehyde phenylhydrazone with DMAD gave small amounts of pyrazoline 29 (no proof for trans-configuration given) and its dehydrogenation product 30 in 16% yield[7] along with a by-product resulting from Diels-Alder and retro Diels-Alder reactions. Such compounds will not be considered in this review. The dehydrogenation is believed to be caused by DMAD.

Benzyl methyl ketone phenylhydrazone behaved differently with DMAD and gave only the enehydrazone 31.[7]



31

The preparation of pyrazolines from hydrazones and MP is less straightforward. Dehydrogenation of the enehydrazines 12a and 12b led to the simple enehydrazones 32a and 32b. Compound 32a on warming in xylene/ acetic acid gave pyrazole 33;[18] no pyrazoline could be isolated.



12

a) R = H

b) R = CO_2CH_3

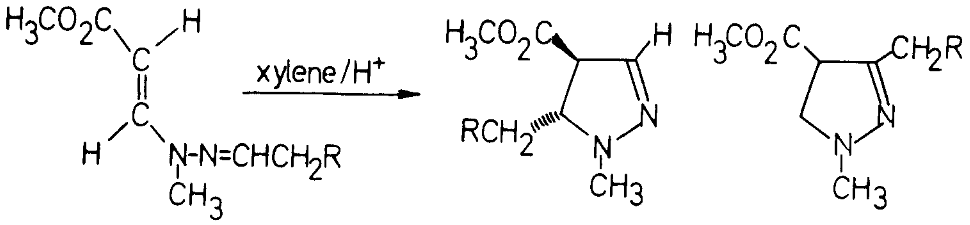
32

a) R = H

b) R = CO_2CH_3

33

Enehydrazones from MP and methylhydrazones of aliphatic aldehydes as 34 did not give the expected pyrazolines 36 but their isomers 35.[6] The



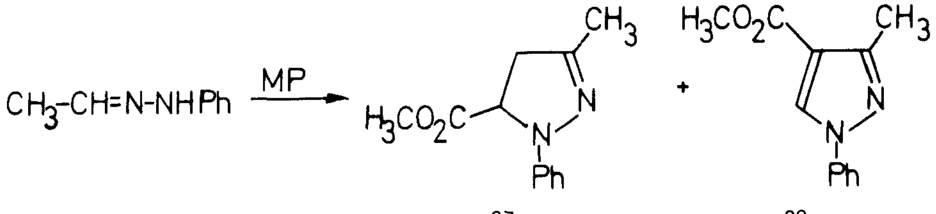
34

35

36

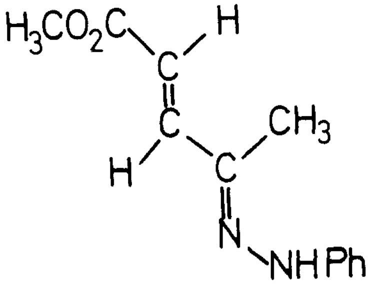
a) R = H b) R = CH_3 c) R = C_2H_5

authors believe that during the course of the reaction, the two nitrogens exchange their positions via a diaziridine intermediate. Interestingly, this reaction path is not followed in the case of phenylhydrazones of aliphatic aldehydes. When acetaldehyde phenylhydrazone and MP were heated in xylene in the presence of small amounts of p-toluenesulfonic acid, 60% of still another type of pyrazoline 37 and 15% of the "expected" isomer but dehydrogenated to the corresponding pyrazole 38 were isolated[26] along with small amounts of other products which are not discussed for the reasons given above. In cold carbon tetrachloride only 38 was formed.



37 38

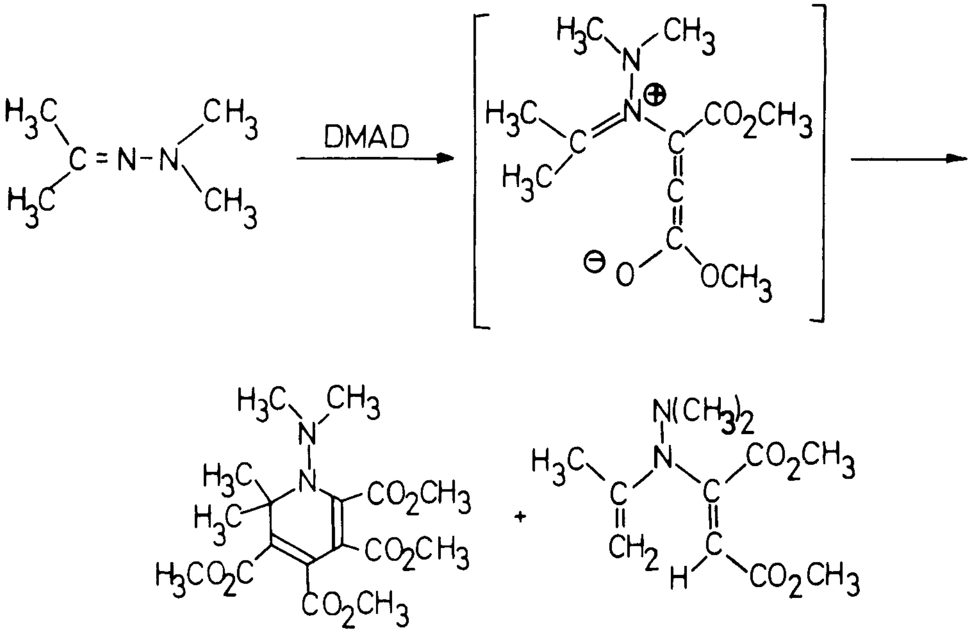
Similar results have been obtained with a number of other arylhydrazones of aliphatic and aromatic aldehydes. The formation of 38 is interpreted in terms of a nucleophilic attack of the NH on the triple bond via a normal enehydrazone with subsequent cyclization and dehydrogenation. The formation of 37, however, is explained by a nucleophilic attack of the hydrazone carbon on MP, forming the intermediate 39 which has been



39

isolated in small amount and which is believed to cyclize to the pyrazoline 37 in its syn-form with the acrylic ester double bond and the NHPh on the same side of the C=N double bond.

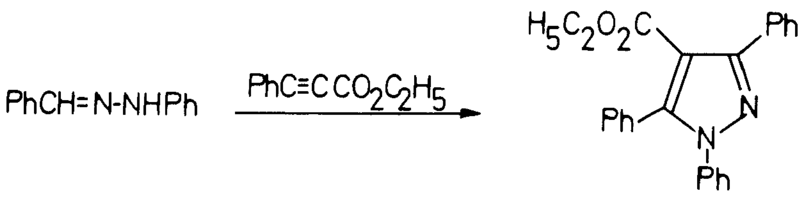
A nucleophilic attack through nitrogen has also been observed with acetone N,N-dimethylhydrazone on DMAD to give compounds 40 and 41.[27]



40

41

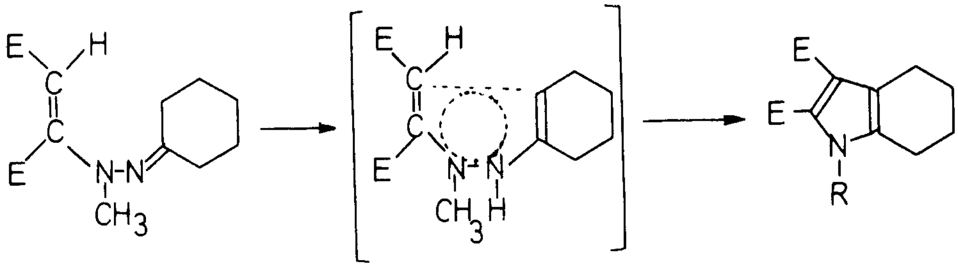
Ethyl phenylpropiolate and benzaldehyde phenylhydrazone give a pyrazole 42 with the expected substituent pattern,[28] but with propionaldehyde phenylhydrazone a 2:1 product results which is believed to be a pyrazolone derivative.



42

III. FISCHER CYCLIZATION OF ENEHYDRAZONES AND ENEHYDRAZINES

Enehydrazones derived from ketone methylhydrazones give a Fischer-type cyclization reaction on heating in xylene or toluene with small amounts of acetic acid.[3]

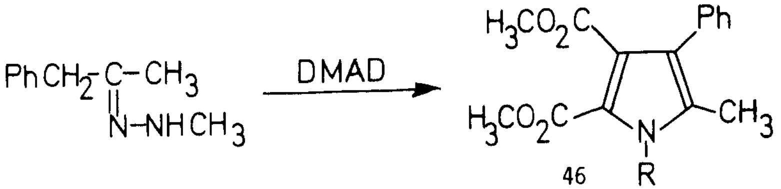


43 44 45

$E = CO_2CH_3$

a) $R = CH_3$ b) $R = H$

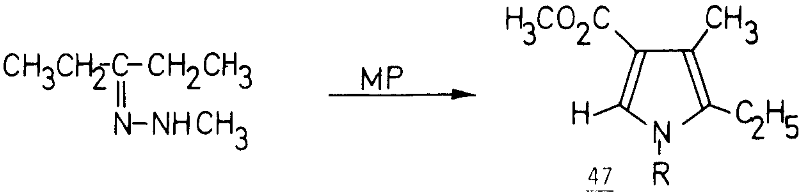
Compound 45a has been isolated in 40% and 45b in 12% yield. Similar results were obtained when cyclohexanone methylhydrazone and DMAD are boiled in xylene.[4] Baumes, Jacquier and Tarrago have very carefully examined this reaction,[4] generally without isolation of the enehydrazone intermediate. Further typical examples are given below.



46

a) $R = CH_3$

b) $R = H$ 30 % (1:1)

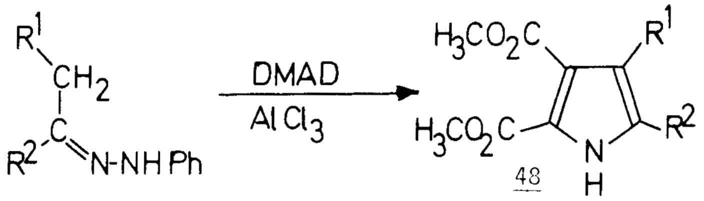


47

a) $R = CH_3$

b) $R = H$ 20 % (1:1)

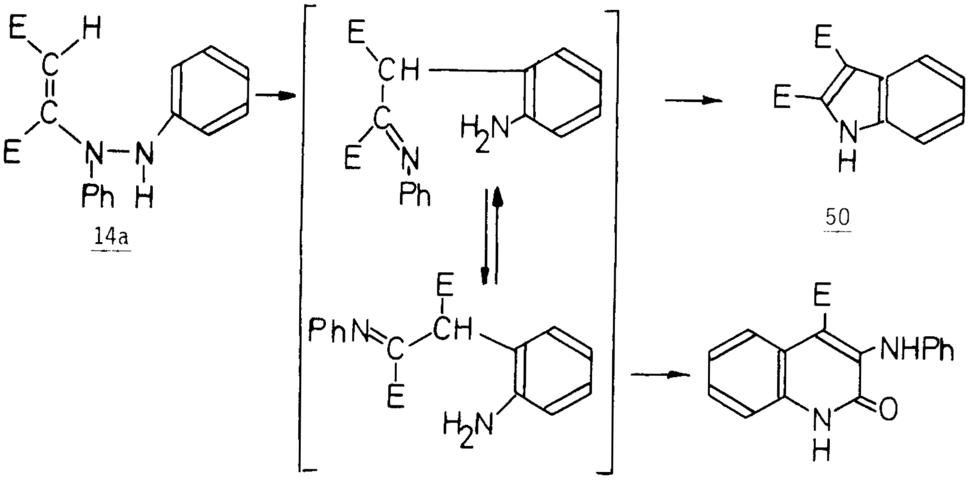
In the presence of DMAD and aluminum chloride, ketone phenylhydrazones do not undergo the normal Fischer indole synthesis but the Fischer-type cyclization of the (non-isolated) enehydrazones. N-Unsubstituted pyrroles are exclusively formed in good yields.[29]



48

a) R^1 = H R^2 = Ph
b) R^1 = C_2H_5 R^2 = Ph
c) R^1 = Ph R^2 = CH_3
d) R^1,R^2 = $-(CH_2)_4-$

Enehydrazines with a phenyl substituent at N-2 are prone to a normal Fischer indole synthesis. Thus Diels and Reese[20] found that heating the enehydrazine 14a in xylene afforded a 70% yield of dimethyl 2,3-indoledicarboxylate 50, while in pyridine a 55% of quinolone 51 was obtained; obviously both were formed through the common intermediate 49.



14a

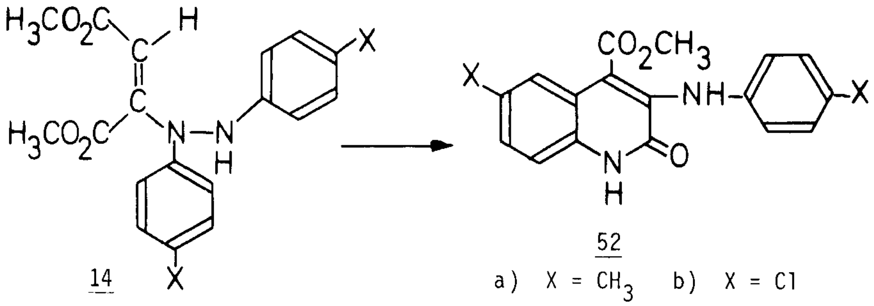
50

E = CO_2CH_3

49

51

These reactions were later extended to the substituted derivatives 14a, 14b and 54.[21] While 14a and 54 yielded only the corresponding quinolones 52a and 55, 14b gave both the quinolone 52b and the indole 53 in good yields.

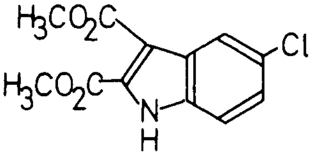


14

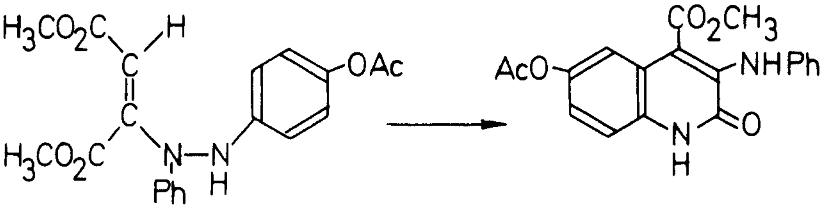
a) X = CH_3
b) X = Cl

52

a) X = CH_3 b) X = Cl



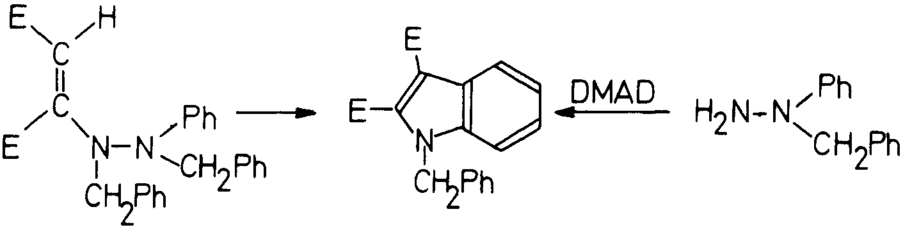
53



54

55

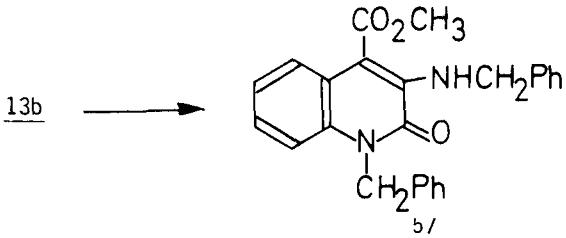
Finally, the enehydrazine 13b yielded both the indole 56 and the quinolinone 57; 56 could also be obtained from 1-benzyl-1-phenylhydrazine and DMAD.[19]



13b

56

E = CO_2CH_3

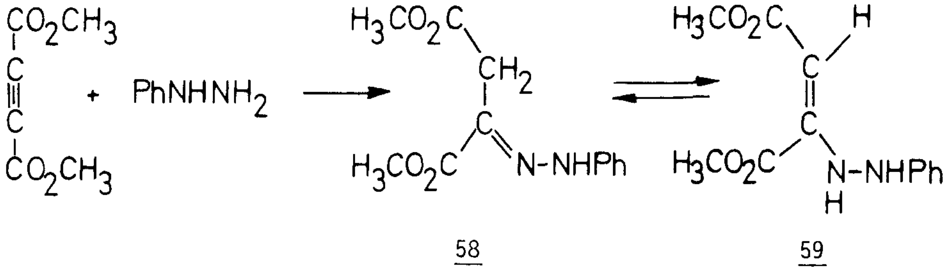


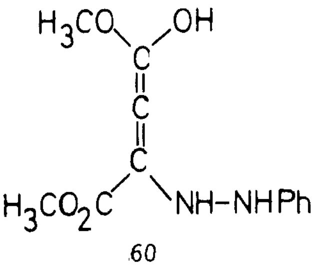
57

IV. ENEHYDRAZINE-HYDRAZONE TAUTOMERS

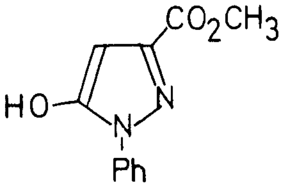
1. Addition of Hydrazine to Dimethyl Acetylenedicarboxylate and Methyl Propiolate

As early as 1889, Buchner[30] established that the addition product of phenylhydrazine to DMAD in ether was dimethyl oxaloacetate phenylhydrazone.[31] Later, Heindel, Kennewell and Pfau studied this reaction in more detail;[32] in ethanol it gave a high yield of a 4:1 mixture of the hydrazone 58 and the enehydrazine 59, separated by crystallization. The hydrazone methylene group exhibits a singlet at 3.72 ppm, the enehydrazine vinyl-H one at 4.84 ppm. Though 59 is the less stable isomer, its tautomerization to 58 is extremely slow under neutral conditions. Therefore, 59 is probably not an intermediate in the formation of 58, but the allenic enol 60 is believed to kinetically control the reaction by the different rates of an NH-shift to the hydrazone 58 or an OH-shift to the enehydrazine 59. Part of the product 58 is always cyclized to the pyrazolone 61.





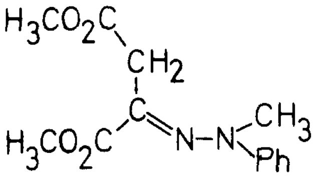
60



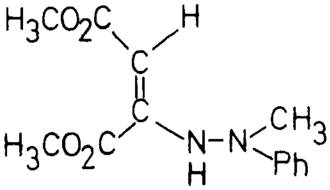
61

Other authors found only the hydrazone form upon addition of phenylhydrazine to DMAD.[33,34] This is also true for a number of substituted phenylhydrazines as p-chloro-, 2,5-dichloro-, 2,4,6-trichloro-, 2- and 4-nitro- and 2,4-dinitrophenylhydrazine and N,N-diphenylhydrazine.[32-35] In contrast to the phenyl- and 4-nitrophenylhydrazones, the 2,4-dinitrophenylhydrazone cannot be cyclized to a pyrazolone.

p-Tolylhydrazine gave only the enehydrazine form.[32] Hydrazone 62[32,35,36] and enehydrazine form 63[32] have been found as adducts of N-methyl-N-phenylhydrazine to DMAD.

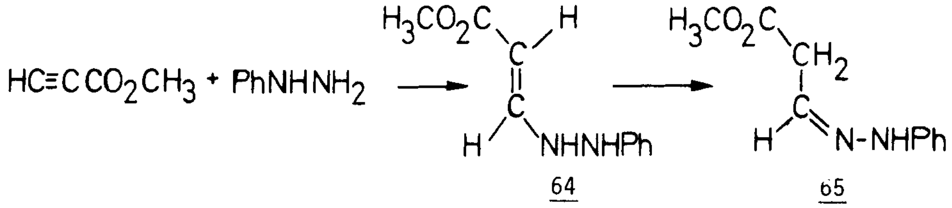


62

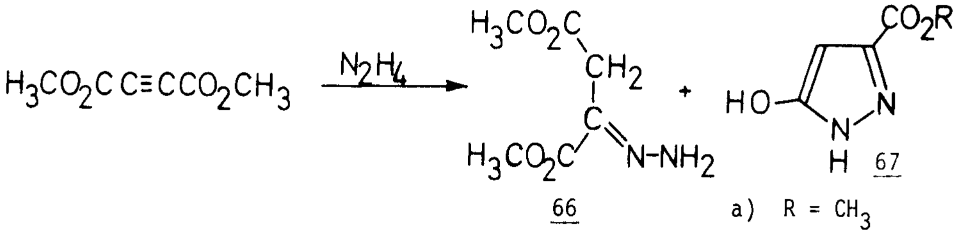


63

It is interesting to note that addition of phenylhydrazine to MP in ether gives the enehydrazine 64 (J = 13 cps) exclusively, but in chloroform solution at room temperature this is quantitatively isomerized to methyl formylacetate phenylhydrazone 65.[37]

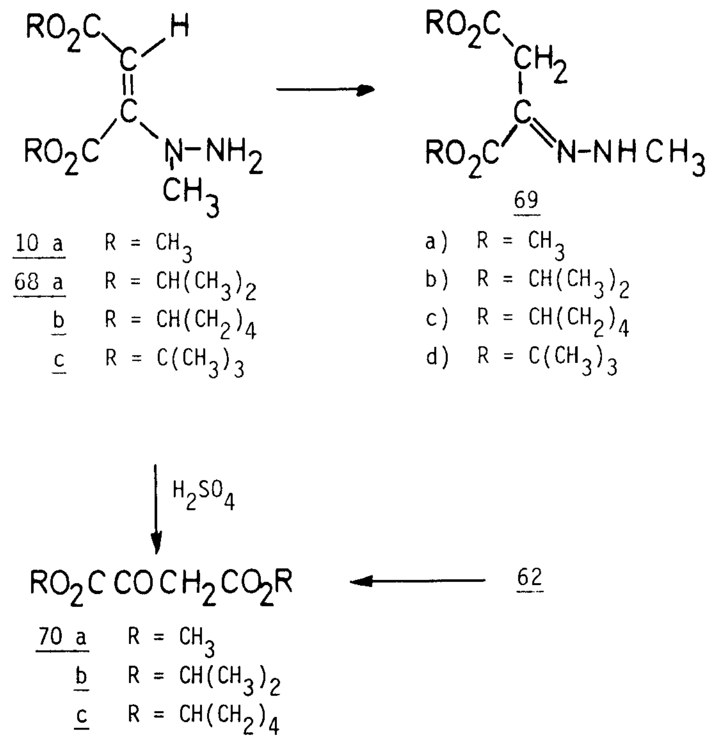


Early studies of the addition of unsubstituted hydrazine to DMAD and diethyl acetylenedicarboxylate led to the pyrazolone esters 67a or 67b exclusively.[38] However, careful reinvestigation of this reaction by Heindel et al.,[32] afforded dimethyl oxaloacetate hydrazone 66 (CH_2, s, 3.50 ppm) as the primary adduct along with the pyrazolone.



a) $R = CH_3$
b) $R = C_2H_5$

The homologue 69a could be observed in the nmr as a rearrangement product of 10a; it has the structure of a dimethyl oxaloacetate methylhydrazone.[39] Space demanding ester groups stabilize the methylhydrazones 69b-69d which were obtained from the corresponding enehydrazines 68a-68c in chloroform at room temperature as crystalline compounds.[40] The enehydrazines 10a and 68a and 68b and the methylphenylhydrazone 62 have been hydrolyzed to the corresponding dialkyl oxaloacetates;[35,40] for 10a we have recommended this procedure as a convenient method to prepare dimethyl oxaloacetate 70a, particularly, when performed as a one-pot procedure starting from methylhydrazine and DMAD.[41]



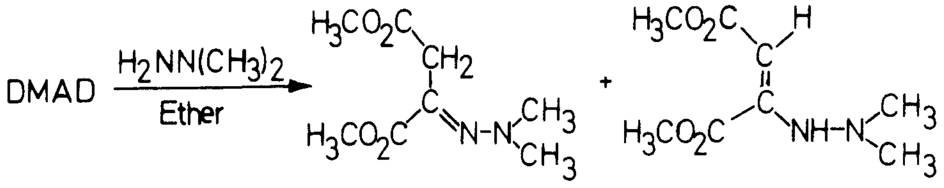
10 a R = CH_3
68 a R = $CH(CH_3)_2$
b R = $CH(CH_2)_4$
c R = $C(CH_3)_3$

69
a) R = CH_3
b) R = $CH(CH_3)_2$
c) R = $CH(CH_2)_4$
d) R = $C(CH_3)_3$

62

70 a R = CH_3
b R = $CH(CH_3)_2$
c R = $CH(CH_2)_4$

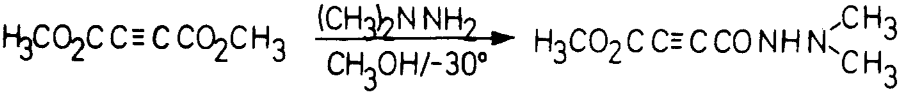
Addition of N,N-dimethylhydrazine to DMAD in boiling ether has been reported to yield dimethyl oxaloacetate dimethylhydrazone 71.[27] A complete nmr investigation of a product obtained in cold ether revealed, however, that a 72:28 mixture of the hydrazone and enehydrazine form 72 was present.[42]



71   72

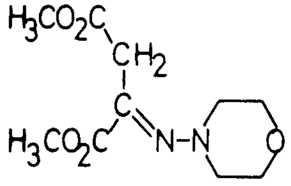
These results compare well with the 86:14 equilibrium mixture obtained from 1,1-dimethylhydrazine and diethyl oxaloacetate in carbon tetrachloride described by Yakimovich and Khrustalev,[43] while Ahlbrecht and Henk[44] report an opposite figure for the product from dimethylhydrazine and dimethyl oxaloacetate in DMSO.

It is interesting to note that the reaction between 1,1-dimethylhydrazine and DMAD in methanol at low temperature leads preferentially to the dimethylhydrazide 73.[27] Hydrazone 74 from N-aminomorpholine and DMAD though formed only as a by-product in methanol/water (see below), is obtained in 54% yield in toluene.[36]

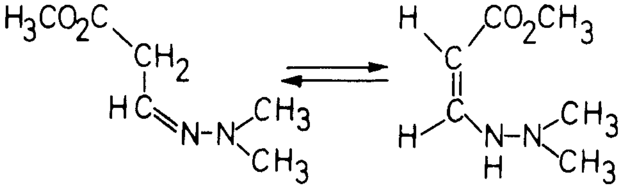


$$H_3CO_2CC{\equiv}CCO_2CH_3 \xrightarrow[CH_3OH/-30^\circ]{(CH_3)_2NNH_2} H_3CO_2CC{\equiv}CCONHN(CH_3)_2$$

73



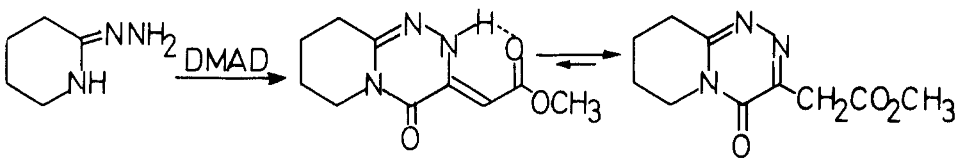
74



75 76

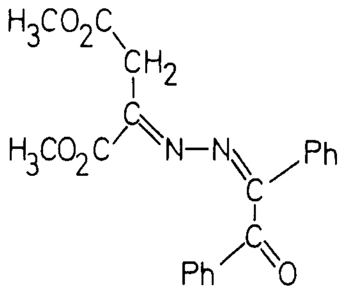
Another tautomeric mixture, 60% of the hydrazone 75 relative to 40% of the Z-enehydrazine 76 (J = 8.5 cps.), was observed in carbon disulfide after addition of N,N-dimethylhydrazine to MP in ether.[42] Ahlbrecht and Henk[45] reported an equilibrium of 96% hydrazone and 4% Z-enehydrazine in bromobenzene for the ethyl ester from N,N-dimethylhydrazine and ethyl formylacetate.

Brugger, Wamhoff and Korte[46] carefully examined the tautomers obtained upon addition of amidrazones on DMAD; e.g. 78 by far predominates in deuterochloroform. This is a special case of the enehydrazine-hydrazone tautomerism discussed in this section. Similar compounds have been examined by LeCount and Greer (see below).[47,48]

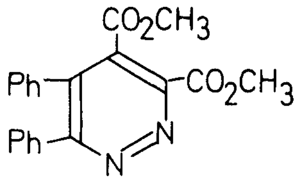


77 78

Addition of benzil monohydrazone to DMAD in methanol affords the oxaloacetic ester derived azine 79 along with some pyridazine 80.[49] Under different reaction conditions, particularly with 4,4-disubstituted benzils pyridazines may become the main products.

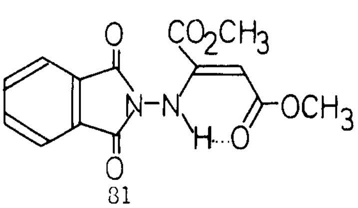


79

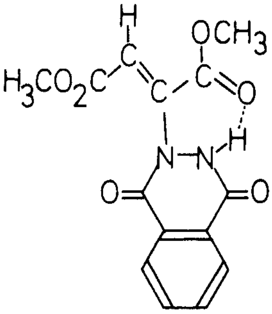


80

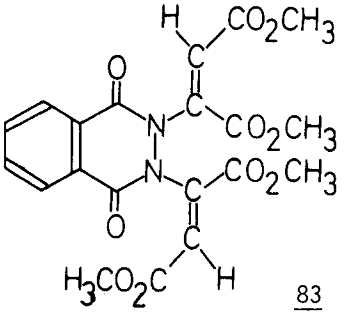
A number of adducts from acetylenic esters with carbonyl substituted hydrazines have been described, but only few of these have spectroscopically established structures. Compounds 81 and 82 are enehydrazines with fumaric ester configurations while 83 contains a fumaric and a maleic ester group.[50]



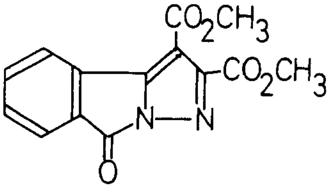
81



82



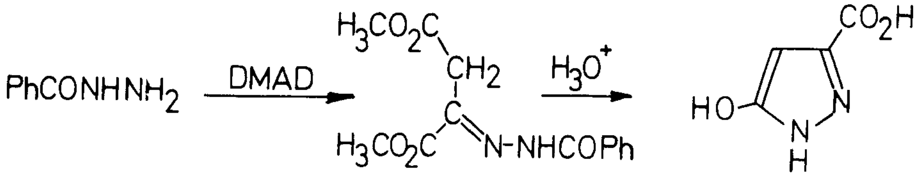
83



84

While N-aminophthalimide forms 81 in methanol, 84 is obtained in dioxane in equally good yield.

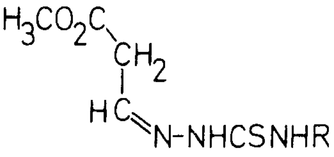
Aroylhydrazines add to DMAD in methanol to give dimethyl oxaloacetate aroylhydrazones, e.g. 85, which on acid treatment form pyrazolonecarboxylic acid 86.[51]



85

86

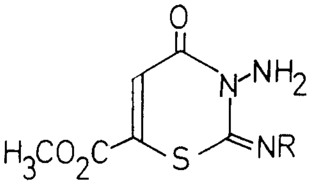
Thiosemicarbazides add to MP to give the methyl formylacetate thiosemicarbazones 87a and 87b while with DMAD the heterocycles 88a and 88b result.[33] Thiohydrazides, however, lead to 1,3,4-thiadiazoles, as e.g. 89 and 90.[52]



87

a) $R = CH_3$

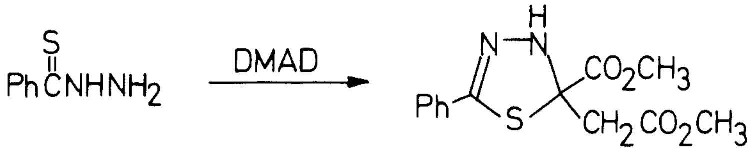
b) $R = Ph$



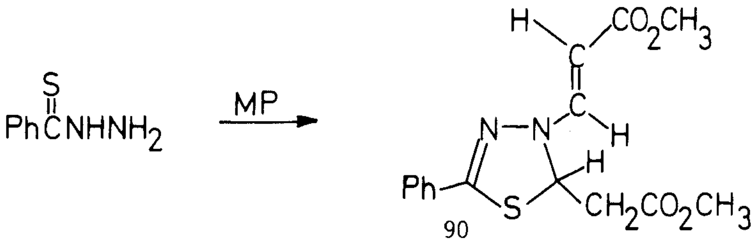
88

a) $R = CH_3$

b) $R = Ph$

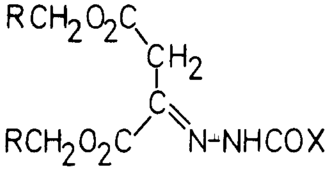


89

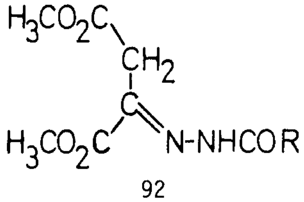


90

Other adducts written as oxaloacetates are 91a-91c[33,53,54] and 92a-92c.[33,55]



91



92

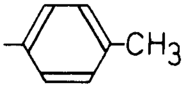
a) R = H X = OC_2H_5

b) R = CH_3 X = NH_2

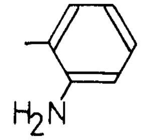
c) R = H X = CH_2CN

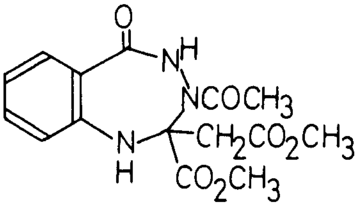
a) R = Ph

b) R =



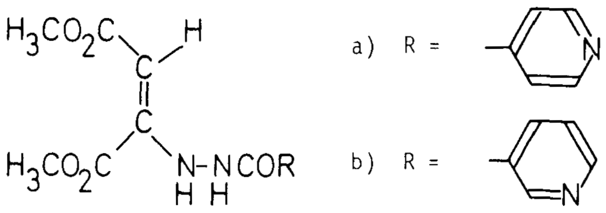
c) R =





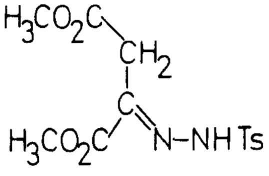
93

Treatment of 92c with acetic anhydride gives the triazepinone 93.[55] Adducts 94a and 94b, written as enehydrazines[56] in aqueous acid also give compounds of type 86.

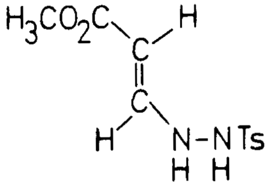


94

It is noteworthy that p-toluenesulfonylhydrazine forms the hydrazone 95 with DMAD while with MP, the enehydrazine 96 is generated (J = 13.5 cps), both in good yields.[57]

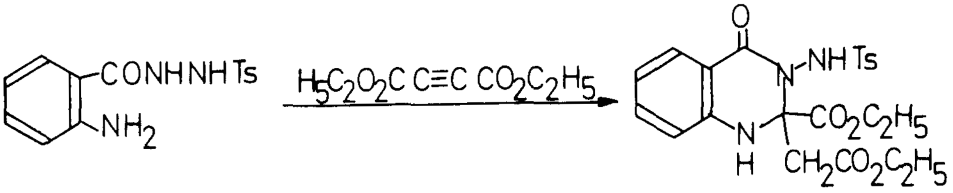


95



96

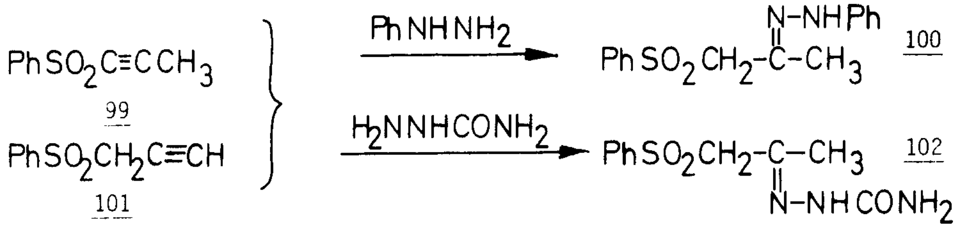
Treatment of diethyl acetylenedicarboxylate with the tosylhydrazide 97 gives the quinazolone derivative 98.[55]



97

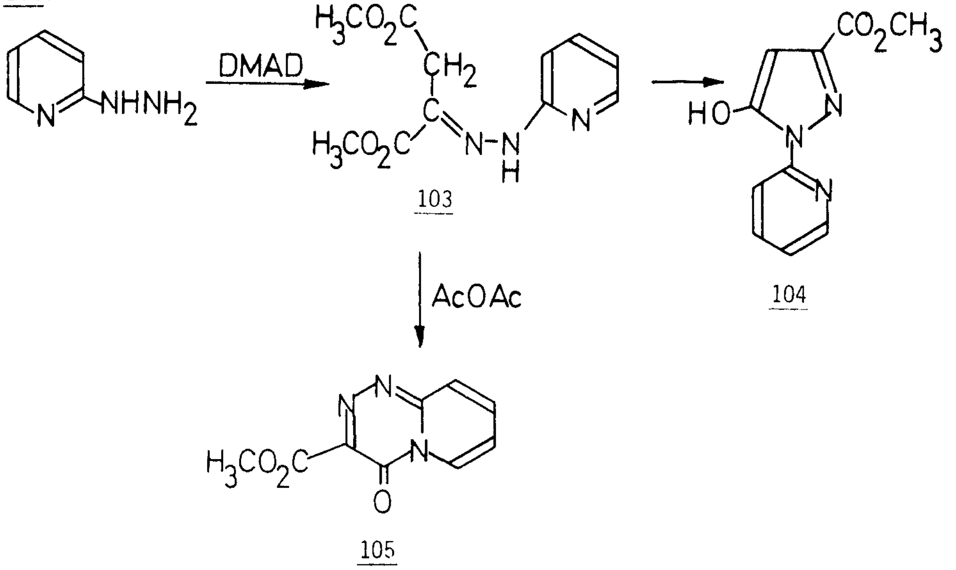
98

The ethynyl sulfone 99 also adds phenylhydrazine or semicarbazide to give the phenylhydrazone 100 or the semicarbazone 102.[58] The same compounds are obtained from the isomeric phenylpropargyl sulfone 101.

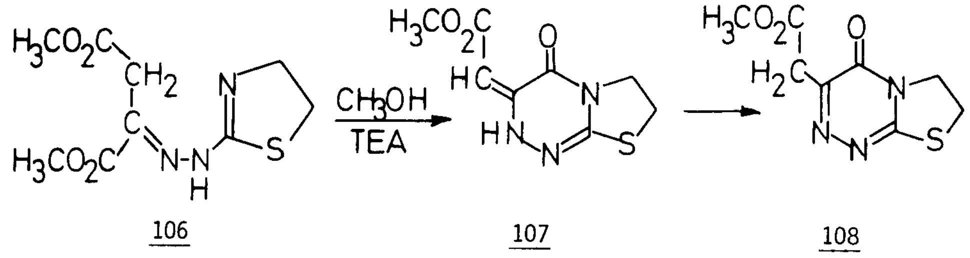


Finally, the structure of dimethyl oxaloacetate hydrazones has been established for most of the adducts of heteroaryl hydrazines to DMAD.

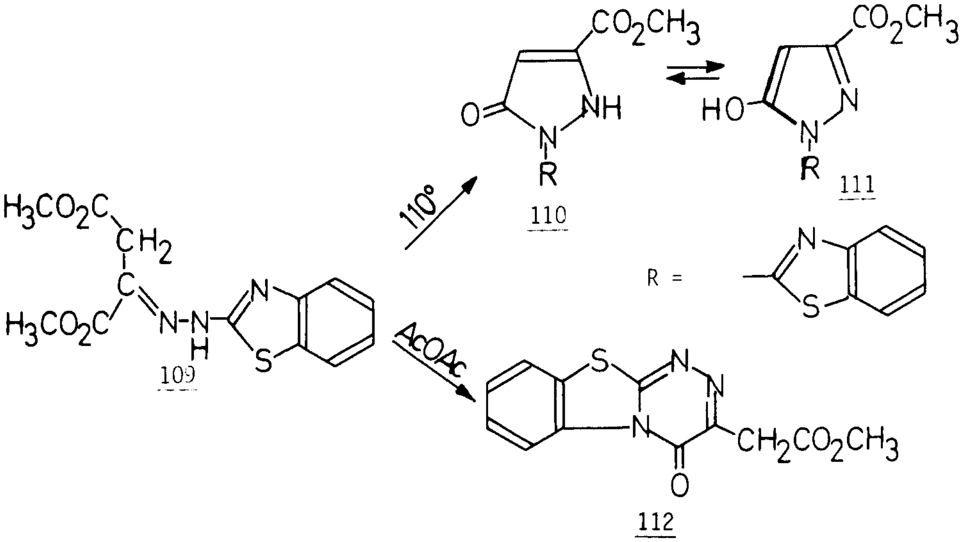
2-Pyridylhydrazine in cold ethanol forms the hydrazone 103;[46,48] occasionally this reaction may, however, go on to give the pyrazolone 104.[34]



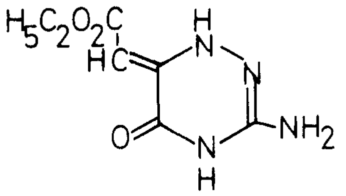
With acetic anhydride 103 cyclizes to the triazinone 105.[47,48] 2-Quinolylhydrazine gave only the pyrazolone.[34] Oxaloacetic ester hydrazones corresponding to 103 have also been obtained from 3-chloro-1-hydrazino-5-nitroisoquinoline,[34] 3-chloro-6-hydrazinopyridazine,[59] and 1-hydrazinophthalazine.[34,47,48] The latter compound can be cyclized to two tautomeric triazinones in the same way as mentioned for 77 and 78 (see above), this is also true for the hydrazone 106.[47,48]



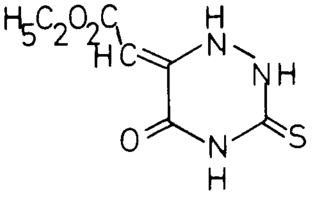
Other hydrazones similar to 106 can be cyclized either to triazinones or to pyrazolones.[47,48] In the case of 109 both reactions can be achieved.



Triazinones 113 and 114 were obtained from reactions between diethyl acetylenedicarboxylate and N-aminoguanidine or thiosemicarbazide.[54]



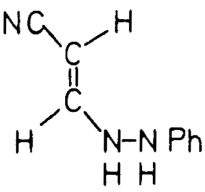
113

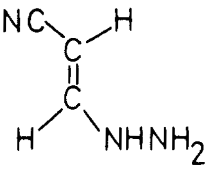


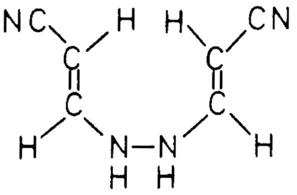
114

2. Addition of Hydrazines to Cyanoacetylenes

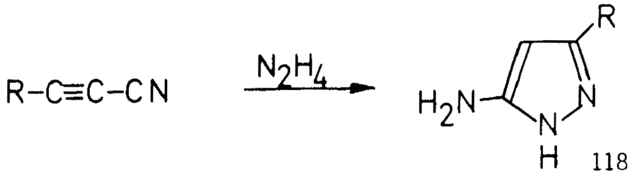
Cyanoacetylene adds phenylhydrazine to give the E-enehydrazine 115 (J = 14 cps), while hydrazine affords what is a mixture of 116 and 117.[60]


115


116

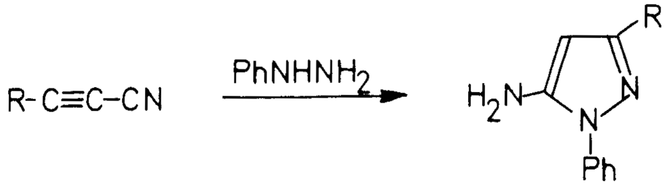

117

Alkynoic acid nitriles are reported to give aminopyrazoles with hydrazine and phenylhydrazine.[61]



118

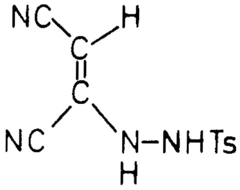
a) R = C_5H_{11}
b) R = Ph

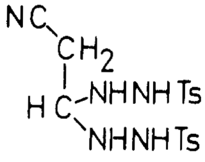


119

a) R = C_5H_{11}
b) R = Ph

Tosylhydrazine adds to dicyanoacetylene to give the enehydrazine 120 with a probable E-configuration,[57] but from cyanoacetylene the


120
Ts = Tosyl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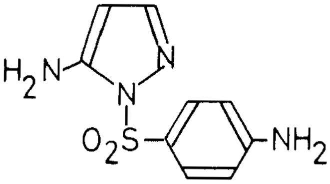
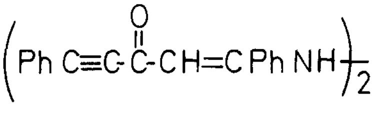

122

hydrazidine 121 is formed. Other benzenesulfonic acid hydrazides were found to give aminopyrazoles as e.g. 122.[62]

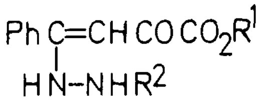
V. PYRAZOLES FROM ACETYLENIC KETONES AND ALDEHYDES

This topic has been reviewed earlier.[62] Only very few enehydrazines and no simple hydrazones have been reported from the addition of hydrazines to the triple bonds of ethynyl ketones or acetylenic aldehydes. Thus 1,5-diphenyl-1,4-pentadiyn-3-one adds hydrazine at low temperature in methanol to give the bis-enehydrazine 123 (vinyl-H at 5.51 ppm).[64] Aryl- and aroylhydrazines have been added to phenylethynylglyoxylic esters to give e.g. 124a and 124b.[65]



$(PhC\equiv C-\overset{O}{\overset{\|}{C}}-CH=CPhNH)_2$

123



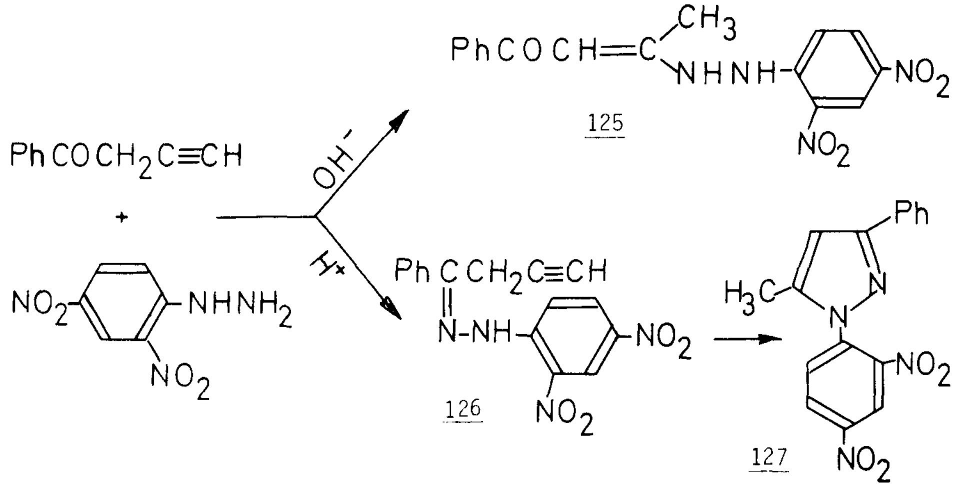
$Ph\underset{HN-NHR^2}{\underset{|}{C}}=CHCOCO_2R^1$

124

a) $R^1 = C_2H_5$ $R^2 = Ph$

b) $R^1 = CH(CH_3)_2$ $R^2 = PhCO$

Base-catalyzed addition of 2,4-dinitrophenylhydrazine to 1-phenyl-3-butyn-1-one affords the enehydrazine 125 after shift of the multiple



bond. In acidic medium the 2,4-dinitrophenylhydrazone 126 is formed which under acid catalysis cyclizes to the pyrazole 127.[66]

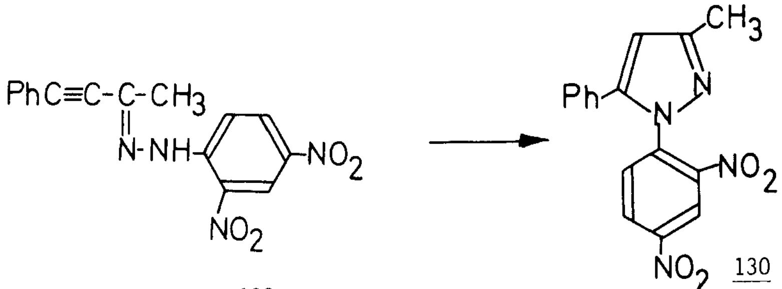
Benzoylacetylene adds phenylhydrazine[67] or semicarbazide[68] at both the C=O double and the C≡C triple bond.

$$\mathrm{PhCOC{\equiv}CH} \longrightarrow \mathrm{Ph\,C({=}N{-}NHR){-}CH_2{-}CH{=}N{-}NHR}$$

128

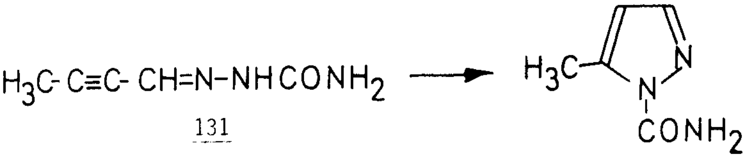
a) R = Ph b) R = $CONH_2$

Generally, 2,4-dinitrophenylhydrazine,[64,66-69] p-nitrophenylhydrazine,[28,67,68,70,71] semicarbazide[68,70-73] and p-toluenesulfonylhydrazine[74] form the usual carbonyl derivatives with ethynyl aldehydes and ketones. Some of the resulting 2,4-dinitro-[64,66,67] and one 4-nitrophenylhydrazone[67] have been cyclized in acidic medium to the corresponding 1-(2,4-dinitrophenyl)- and 1-(4-nitrophenyl)pyrazoles, e.g.[67]



129

130

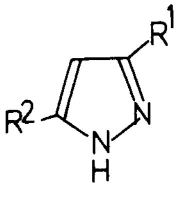


131

132

The semicarbazone 131 of tetrolaldehyde cyclized under the influence of KOH to the pyrazole 132.[72] Hydrazine is reported to give azines with tetrolaldehyde[72] and phenylpropiolaldehyde[72] while phenylhydrazine gave two isomeric phenylhydrazones with the latter aldehyde.[70]

On the other hand, cyclic products, i.e. the pyrazoles 133a-133e were reported as products of the reactions between hydrazine and propiolaldehyde,[72] phenylpropynone,[75] 3-nonyn-2-one,[71] 1-phenyl-2-octyn-1-one,[76] and ethyl phenylethynylglyoxylate.[65]

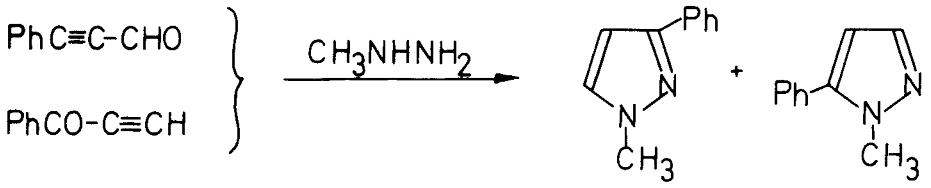


133

a) $R^1 = R^2 = H$
b) $R^1 = Ph \quad R^2 = H$
c) $R^1 = C_5H_{11} \quad R^2 = CH_3$
d) $R^1 = C_5H_{11} \quad R^2 = Ph$
e) $R^1 = Ph \quad R^2 = CO_2C_2H_5$

Unsymmetrical hydrazines may give two isomeric pyrazoles with most ethynyl ketones and acetylenic aldehydes. Very often both are formed at the same time while no open-chained intermediate can be isolated. This makes it even more difficult to decide which is the initial step in these pyrazole formations. The problem may be illustrated by the following example.

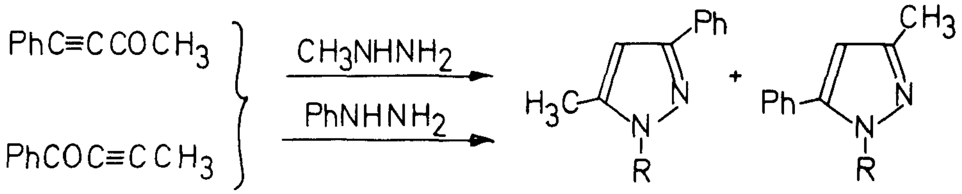
Phenylpropiolaldehyde and benzoylacetylene give the same 2:8-mixture of the isomeric pyrazoles 134 and 135 with methylhydrazine in acidic ethanol.[67] Compound 135 may have been formed from phenylpropiolaldehyde



134 135

by the initial attack of the unsubstituted nitrogen on the aldehyde carbonyl group (i.e. via an ethynyl aldehyde hydrazone) or by attack of the substituted N-1 on C-3 (i.e. via an enehydrazine). Conversely, 134 may have been formed from phenylpropiolaldehyde either by an attack of the unsubstituted nitrogen on C-3 (i.e. via an enehydrazine) or by attack of the substituted N-1 on the carbonyl group. A same reasoning can be applied to benzoylacetylene as a starting material.

The following pair of isomeric phenylbutynones showed a similar behaviour with respect to methyl- and phenylhydrazine;[67] in the case of



136 137

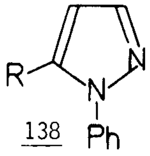
a) $R = CH_3$ b) $R = Ph$

methylhydrazine, however, the relation of 136a to 137a differed from one ketone to the other.[67] Other authors[70,73] found different ratio in acetic acid. A thorough discussion of the possible reaction paths has been published by Coispeau, Elguero and Jacquier.[67]

As was pointed out earlier for 7 and 10a, alkylhydrazines may well react preferentially with the more nucleophilic alkylated nitrogen. On the other hand, methylhydrazine is known to give methylhydrazones with simple ketones. For phenylhydrazine the unsubstituted nitrogen is generally believed to be the more nucleophilic one. Yet, in some cases phenylhydrazine has undoubtedly reacted preferentially with its substituted nitrogen.[77,67] Finally, in the presence of acid initial protonation of the hydrazines may change these patterns.

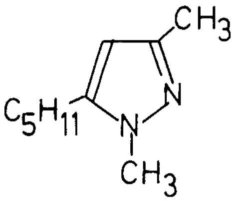
Propiolaldehyde gives 1-phenylpyrazole 138a with phenylhydrazine,[72,78] tetrolaldehyde is reported to afford the pyrazole 138b possibly indicating an initial formation of the phenylhydrazone.[72]

Phenylpropiolaldehyde and phenylhydrazine give pyrazole 138c in acetic acid[70] or ethanol *via* the phenylhydrazone mentioned above[67] in poor yield. 3-Nonyn-2-one forms a pyrazole of the probable structure 139[71] with methylhydrazine. For the reaction between methylhydrazine and butynone[67] or 1-phenyl-1-butyn-3-one[73] the two possible pyrazoles have been recorded.

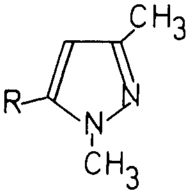


138

a) R = H
b) R = CH_3
c) R = Ph

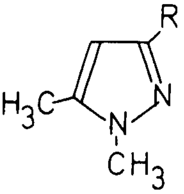


139



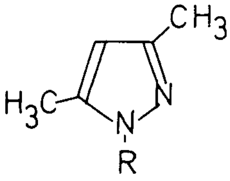
140

a) R = H
b) R = Ph



141

a) R = H
b) R = Ph

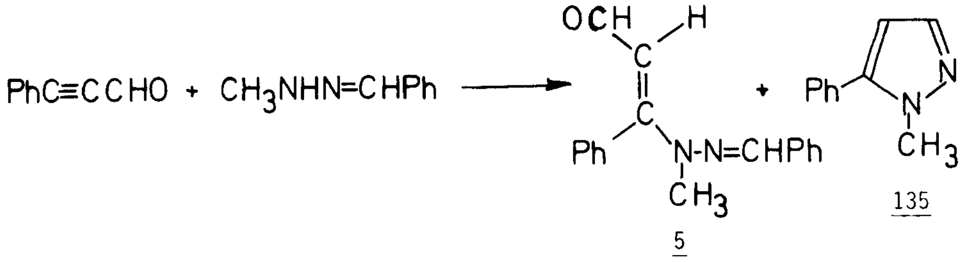


142

a) R = CH_3
b) R = Ph

3-Pentyn-2-one, expectedly, gives only one pyrazole 142a or 142b with methyl- or phenylhydrazine.[67]

1-Methyl-5-phenylpyrazole 135 has also been obtained in good yield when the preparation of the above mentioned enehydrazone 5 from propiolaldehyde with benzaldehyde N-methylhydrazone was carried out in acetic acid instead of ethanol. Similarly, the enehydrazone 143 has been cyclized to the pyrazole 144 with acetic acid.[65]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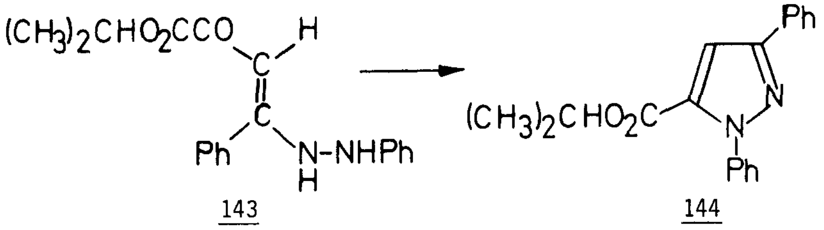
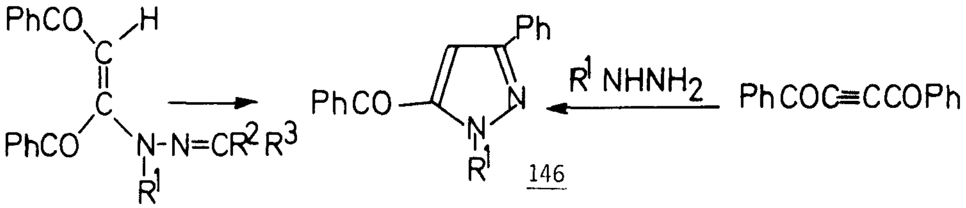
135


143

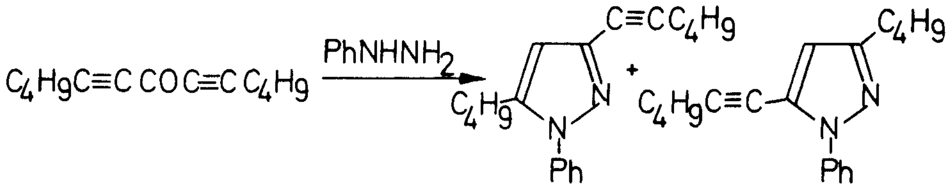
144

A number of enehydrazones 9 and 145a-145c has been prepared from dibenzoylacetylene and, alternatively, the hydrazones or the diaziridines. Boiling these enehydrazones in ethanolic hydrochloric acid gave the pyrazoles 146a-146c which could, however, also be prepared from dibenzoylacetylene and the simple alkylhydrazines.[13]


146

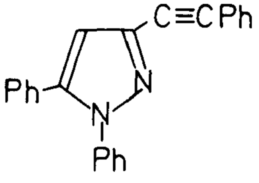
9 $R^1 = H$ $R^2 = CH_3$ $R^3 = C_2H_5$ a) $R = H$
145a $R^1 = CH_3$ $R^2 = R^3 = CH_3$ b) $R = CH_3$
b $R^1 = CH(CH_3)_2$ $R^2 = R^3 = CH_3$ c) $R = CH(CH_3)_2$
c $R^1 = CH_3$ $R^2 = (CH_2)_5$

Two isomeric pyrazoles 147 and 148 resulted when 5,8-triadecadiyn-7-one and phenylhydrazine were kept in methanol at room temperature, while 1,5-diphenyl-1,4-pentadiyn-3-one gave only 149 in boiling methanol.[64]



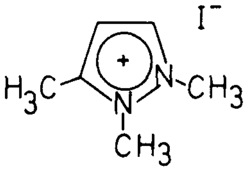
147

148

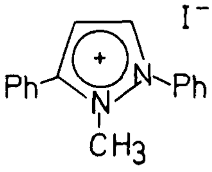


149

1,2-Dimethylhydrazine and 1-methyl-2-phenylhydrazine add to acetylenic aldehydes and ketones in the presence of molar amounts of hydroiodic acid to give the pyrazolium compounds. Thus butynone forms 150 with the former and phenylpropiolaldehyde a mixture of 151 and 152 with the latter.[67]



150



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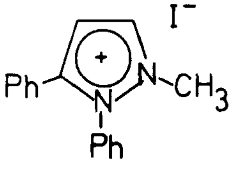


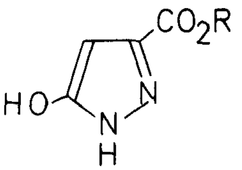
152

VI. PYRAZOLONES FROM ACETYLENIC ESTERS

Pyrazolones which are a very important group of organic compounds, are usually prepared from hydrazines and β-keto esters. Reviews on the topic[79,80] show that relatively few pyrazolones were obtained from acetylenic esters. Only the latter will be considered in this review.

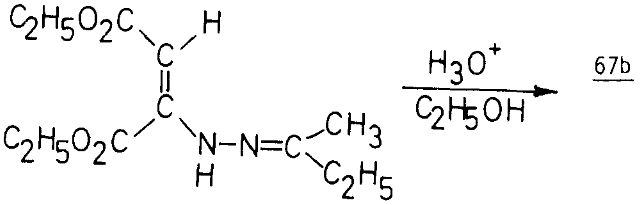
According to their most important tautomeric forms, simple pyrazolin-5-ones[81,82] will be written as 2-pyrazolin-5-ones throughout this review while pyrazolin-3-ones[82,83] and particularly pyrazolones with ester substituents[25,84] will be written as hydroxypyrazoles. In a paper cited above,[48] two tautomeric forms of a pyrazolone could be studied separately.

It was mentioned above that the hydrazone 66 from DMAD and hydrazine cyclizes to give the pyrazolone 67a.



67a R = CH_3
67b R = C_2H_5
86 R = H

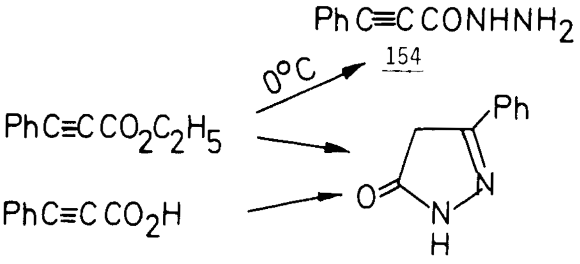
The ethyl ester 67b is obtained when diethyl acetylenedicarboxylate reacts with hydrazine hydrate,[38] both probably *via* an intermediate corresponding to 66. The hydrazone 153 affords 67b on acid solvolysis.[13]



153

Hydrolysis of the dimethyl oxaloacetate aroylhydrazones 85[51] and 94a and 94b[56] give the carboxylic acid 86.

Ethyl phenylpropiolate is cyclized with hydrazine hydrate at room temperature to the phenylpyrazolone 155,[85,86] but at 0° phenylpropiolhydrazide 154 is formed, which on heating above its melting point gives also 155.[85,86] Compound 154 is probably an intermediate in the formation of 155 at higher temperature. Compound 155 can also be obtained from the free phenylpropiolic acid[85,87] but was found to be accompanied by varying amounts of azine 156[87] in that case. The same is true for aryl substituted phenylpropiolic acids.[87]



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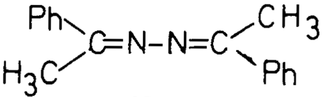
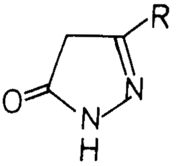
155



156

Ethyl propiolate and tetrolate give pyrazolones 157a and 157b[88,89] with hydrazine hydrate.



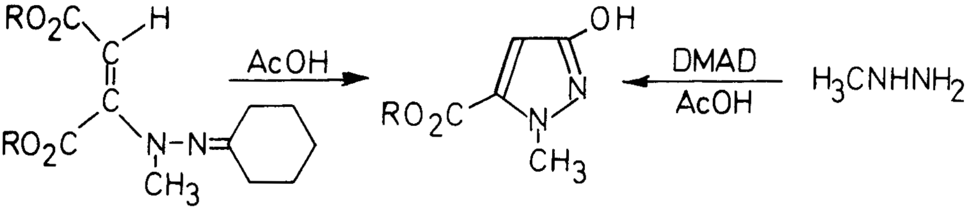
a) $R = H$

b) $R = CH_3$

157

Unsymmetrical hydrazines may lead to isomeric pyrazolinones. As with acetylenic ketones and unsymmetrical hydrazines, different pathways may be envisaged for the formation of pyrazolones; they were discussed by Coispeau and Elguero.[90]

Treatment of aliphatic enehydrazones with acetic acid gives 1-alkyl-3-hydroxy-5-pyrazolecarboxylic esters in poor yields,[13,25] e.g. 159a from 158.

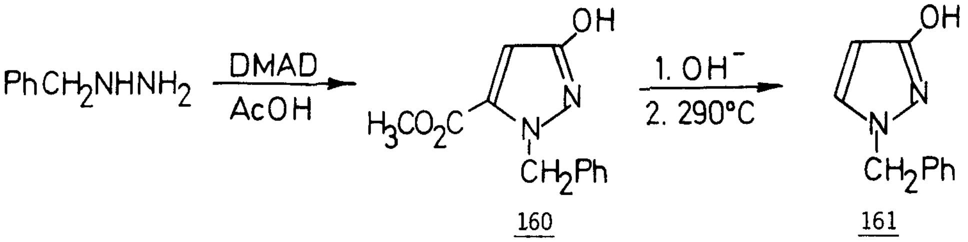


158 $R = C_2H_5$

159

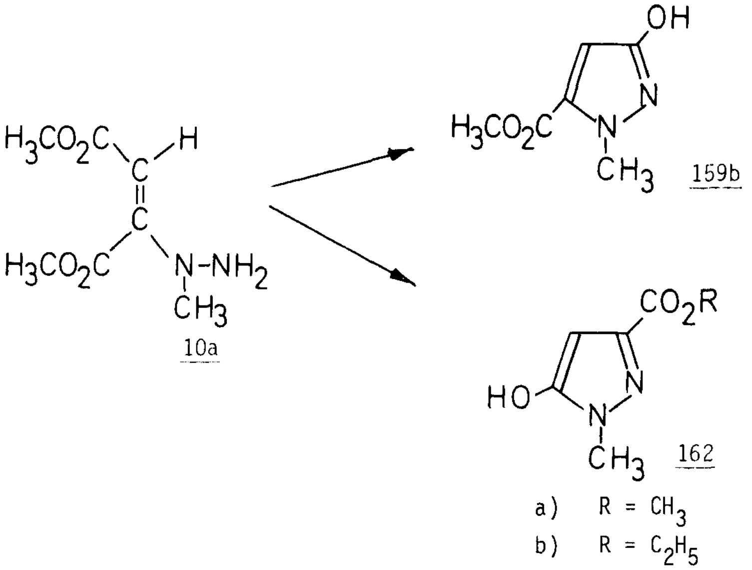
a) $R = C_2H_5$

b) $R = CH_3$



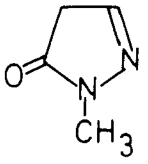
Better yields have been realized when alkylhydrazines were heated with acetylenedicarboxylic esters; e.g. 159b and 160 were prepared in this way.[13,25] 1-Alkyl-3-hydroxy-5-pyrazolecarboxylic acids from saponification of the esters, in contrast to the isomeric 5-hydroxy-3-carboxylic acids, can easily be decarboxylated to give the 1-alkyl-3-hydroxypyrazoles, e.g. 161.[25]

Two isomeric hydroxypyrazoles can be prepared from the enehydrazine 10a. Thus in acetic acid 10a yields the expected cyclization product 159b in excellent yield. Surprisingly, when heated without a solvent or in non polar solvents as chloroform or xylene, the isomeric methyl 1-methyl-5-hydroxy-3-pyrazolecarboxylate 162a is obtained in high yield along with small amounts of 159b which can be removed by crystallization or chromato-



graphy; the ethyl ester 162b can be obtained similarly.[39] In ethanol, about equal amounts of both isomers are formed. The mechanism of the formation of 162a is not yet well understood.[39] Obviously, the two nitrogens exchange their positions and the above mentioned hydrazone 69a is the immediate result of this process. Consequently, the methylhydrazones 69b-69d could also be cyclized to the different 1-methyl-5-hydroxy-3-pyrazolecarboxylic esters.[40]

Ethyl propiolate in ether gave pyrazolone 163 with methylhydrazine,[91] again this is not the expected cyclization product of the enehydrazine 11a described above. Products 164a and 164b[92,93] formed from ethyl propiolate and tetrolate respectively, with substituted benzylhydrazines were claimed in patents.



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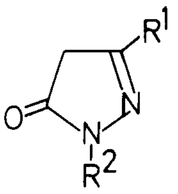
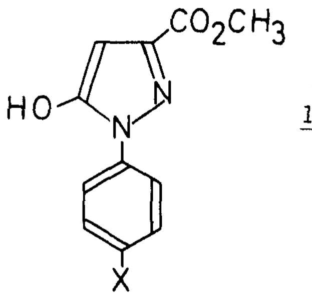


164

a) $R^1 = H \quad R^2 = CH_2\underline{p}C_6H_4Cl$
b) $R^1 = H \quad R^2 = CHCH_3\underline{p}C_6H_4F$

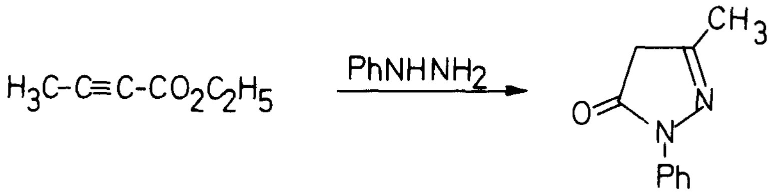
Phenylhydrazine leads to 1-phenylpyrazolinones in these reactions. The previously mentioned dimethyl oxaloacetate phenylhydrazone 58[30,32-34] when warmed with or without acid gives methyl 5-hydroxy-1-phenyl-3-pyrazolecarboxylate 61.[32-34] This reaction has also been described for the corresponding *p*-methyl-, *p*-chloro- and *p*-nitrophenylhydrazones to give the derivatives 165a-165c.[32,33]



61 X = H
165a X = CH_3
b X = Cl
c X = NO_2

The formation of some pyrazolones (104, 110/111 and others) similar to 61 but derived from hydrazinoheterocycles,[34,48] has been mentioned above.

Propiolic esters normally form 3-substituted 1-phenylpyrazolin-5-ones with phenylhydrazine (e.g. 166 from ethyl tetrolate).[94] A number of homologues with alkyl groups other than methyl have been prepared,[95,96] all in moderate yields. Somewhat better yields can be achieved in the presence of NaOMe, NaOEt or KO-t-Bu in alcohols. In such cases, however, the direction of addition is reversed. Thus ethyl tetrolate with phenylhydrazine in the presence of NaOEt gives 3-hydroxy-5-methyl-1-phenylpyrazole 167,[97] isomeric to 166. Ethyl propiolate with phenylhydrazine in the presence of KO-t-Bu gives the 3-hydroxypyrazole[97] 168 in good yield. MP when treated with phenylhydrazine in the presence of NaOMe, however, gave mainly the



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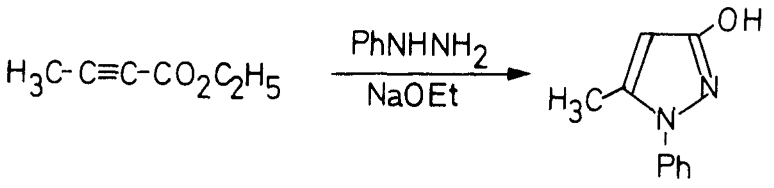
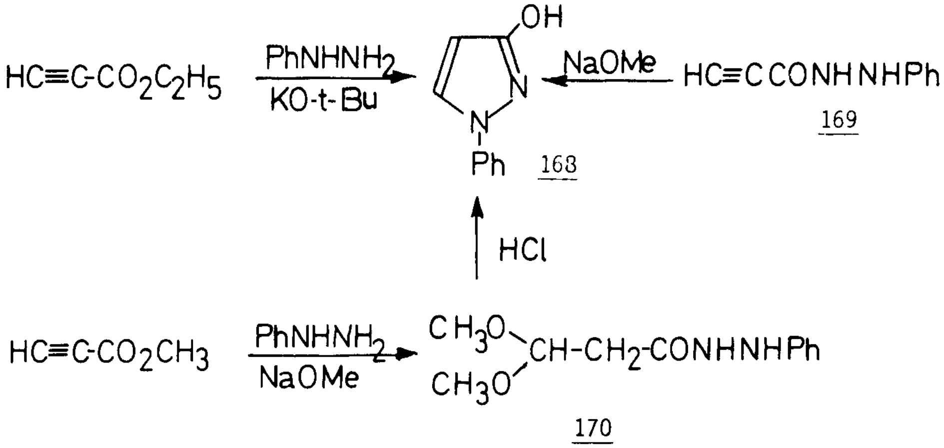
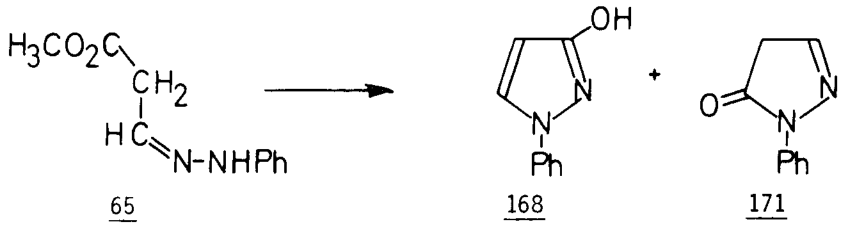


167

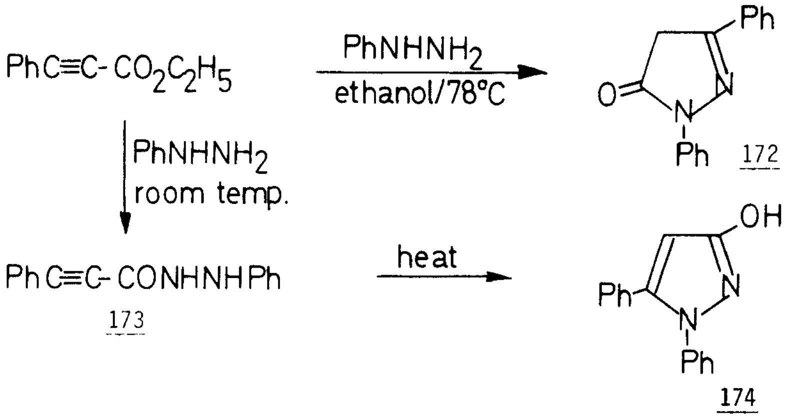
phenylhydrazide 170 which could be cyclized to 168 with acid.[37] Cyclization of propiolylphenylhydrazide 169 proceeded to 168[37] under basic conditions; no yields were given.



When methyl formylacetate phenylhydrazone 65 is treated with acetic acid, a mixture of 168 and its isomer 171 results.[37]

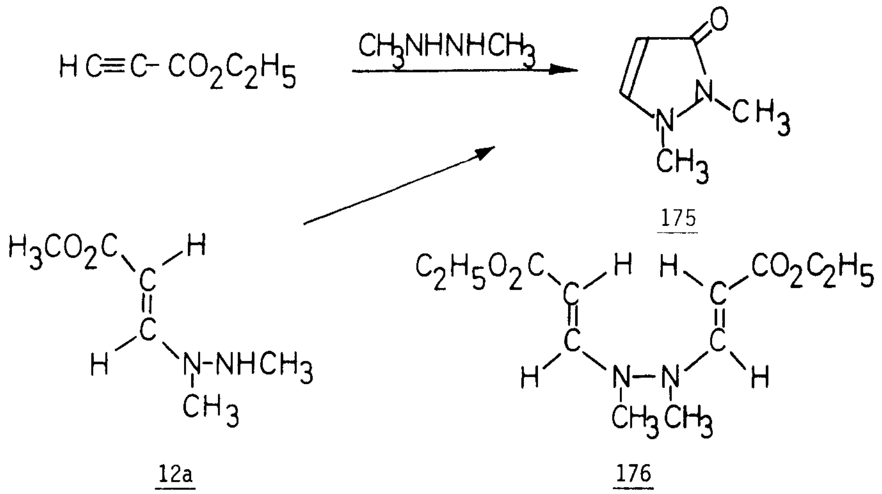


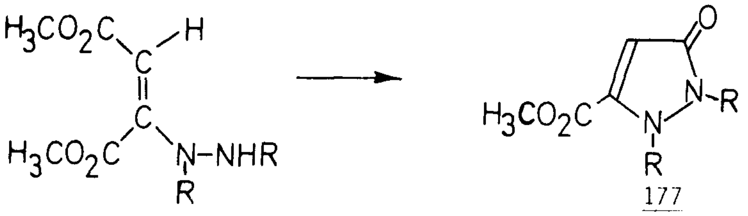
A similarly clear cut situation is found with ethyl phenylpropiolate. In boiling ethanol, a quantitative yield of the pyrazolin-5-one 172 was obtained with phenylhydrazine.[86] At room temperature with the ester or better free phenylpropiolic acid, phenylhydrazide 173 was obtained which on heating cyclized to the isomeric pyrazolin-3-one 174.[86] The latter has also been prepared by treating ethyl phenylpropiolate with phenylhydrazine in the presence of KO-*t*-Bu[97] and by heating phenylpropiolamide with phenylhydrazine.[96] Boiling a solution of phenylpropiolic acid and phenylhydrazine in benzene also gave 174 in good yield.[87] This reaction has also



been applied to *m*- and *p*-chlorophenylpropiolic acid.[87]

Products blocked in a pyrazol-3-in-5-one structure are formed from symmetrically disubstituted hydrazines and acetylenic esters. Thus 1,2-dimethylhydrazine and ethyl propiolate gave compound **175**. The enehydrazine **176** was presumably also formed but not characterized.[91] Compound **175** was also obtained by the acid-catalyzed cyclization of the enehydrazine **12a** described above.[18] Similarly, the enehydrazines **12b**[18] and **14a**[19] gave pyrazolinones **177a** and **177b**.[18,19]





$\underline{12b}$ R = CH_3

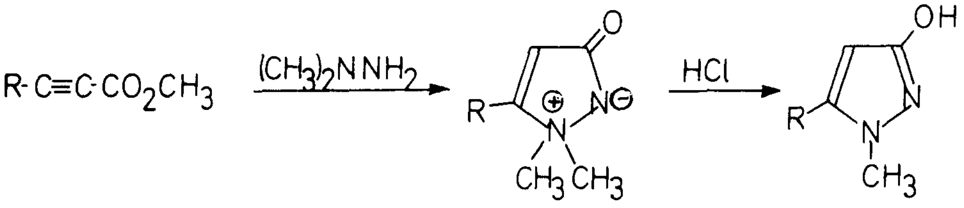
$\underline{14a}$ R = Ph

$\underline{177}$

a) R = CH_3

b) R = Ph

The addition of 1,1-dialkylhydrazines to acetylenic esters in methanol/water at 0^0 leads in moderate yields to nicely crystalline pyrazolium betaines.[36,98] Thus 1,1-dimethylhydrazine gives 178a and 178b with MP and DMAD, respectively.



$\underline{178}$

a) R = H

b) R = CO_2CH_3

$\underline{179}$

a) R = H

b) R = CO_2CH_3

$RCH_2CH_2CONHN(CH_3)_2$

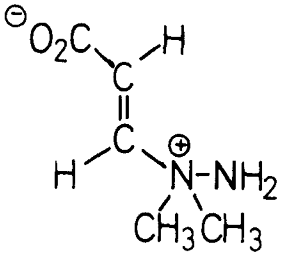
$\underline{180}$

a) R = H b) R = CO_2CH_3

Protonation of 178a and 178b with hydrochloric acid and heating the resulting hydrochlorides gives the hydroxypyrazoles 179a and 179b along with methyl chloride. Hydrogenolysis of 178a and 178b gives the hydrazides 180a and 180b respectively; this constitutes a formal proof of structure.

The formation of such pyrazolium betaines may be related to the above described observation that acetylenic esters tend to give the acid hydrazides in alcohols at low temperatures. The formation of the monodimethylhydrazide 73[27] from DMAD is the most relevant example for this type of reaction. It is also possible that pyrazolium betaines such as 178a and

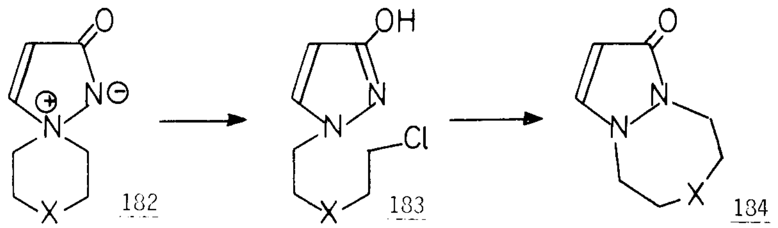
178b are formed via an acid hydrazide rather than from an enehydrazine. On the other hand, a recent paper by Dalton, Demeral and Elmers[99] describes the formation of the open-chained betaine 181 from MP and 1,1-dimethylhydrazine in water. Better yields of 181 and similar betaines are obtained using propiolic acid and 1,1-dialkylhydrazines in methanol or ethanol. Though no experimental evidence is given thus far, 181 may also be able to cyclize to 178a.



181

Pyrazolium betaines have also been prepared by Lockley and Lwowski[100] through cycloadditions between the unstable N-aminoisocyanates and acetylenic esters. In this reaction different structural patterns result; the products bear ester or phenyl groups in position 4 of the pyrazolium ring.

The pyrolysis of the betaine hydrochlorides becomes clearer in the case of the betaines 182a and 182b derived from N-aminopiperidine and N-aminomorpholine. These give the hydroxypyrazoles 183a and 183b without a loss of haloalkane which remains part of the molecule enabling these products to recyclize (via hydrochlorides) to the pyrazolinones 184a and 184b.

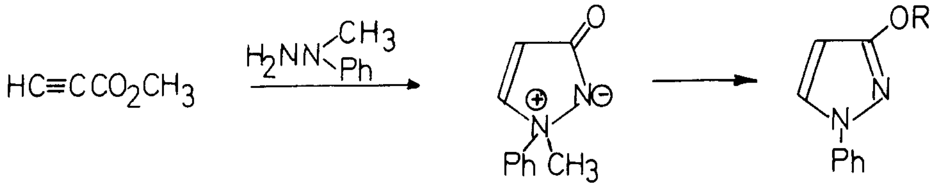


182 183 184

a) X = CH_2 a) X = CH_2 a) X = CH_2

b) X = O b) X = O b) X = O

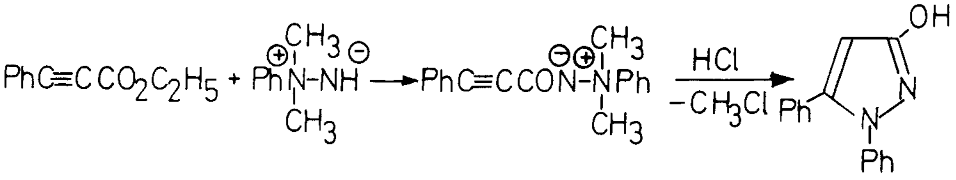
1-Methyl-1-phenylhydrazine and MP give the betaine 185 which can be degraded *via* the hydrochloride to 168 or thermally rearranged to 186.



185

168 R = H

186 R = CH_3



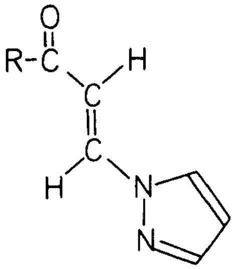
187 174

1,1-Dimethyl-1-phenylaminimine, prepared from 1,1-dimethyl-1-phenylhydrazinium chloride with sodium ethylate, reacts with ethyl phenylpropiolate to give the betaine 187 which with hydrochloric acid gives the pyrazolinone 174 and loss of two equivalents of methyl chloride.[101]

VII. ENEHYDRAZINES FROM HYDRAZINE DERIVED HETEROCYCLES

The reactions of acetylenecarboxylic esters with nitrogen containing heterocycles have been reviewed.[102,103] In the present review, additions of heterocycles through the hydrazine portion of the molecule to acetylenic compounds will be considered. Cycloaddition reactions to acetylenic compounds will not be discussed. The addition of diaziridines to triple bonds has been treated earlier in this review.

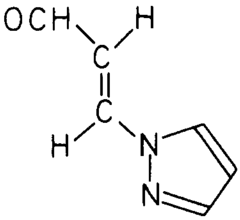
Pyrazole adds to MP to give the E-adduct 188a (J = 14 cps).[104] In the same manner, butynone and pyrazole give 188b.[105] Nmr measurements show that 1,2,4-triazole, benzotriazole and tetrazole also form adducts of E-configuration with butynone;[105] 2:1 adducts are also observed.



188

a) $R = OCH_3$

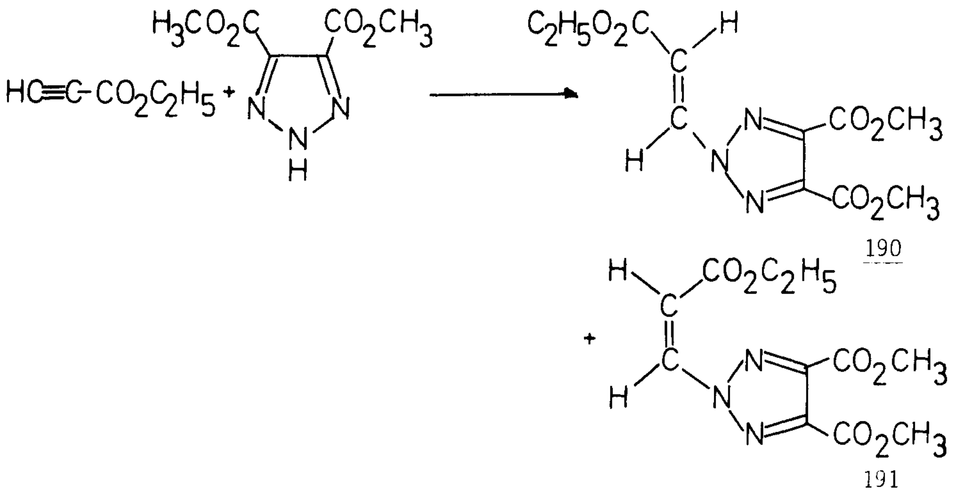
b) $R = CH_3$



189

Although the configurations of the adducts of pyrazole to methyl tetrolate[104] and of pyrazole and substituted pyrazoles to propiolaldehyde claimed in a patent[106] were not investigated, all of them, however, are probably E, e.g. 189.[106]

As has been shown for amine adducts to acetylenic esters, the E-configuration may be a consequence of a thermodynamic equilibration. In this respect, the reactions between 1,2,3-triazoles and acetylenic compounds give interesting insights. The triethylamine catalyzed addition of dimethyl 1,2,3-triazole-4,5-dicarboxylate and 4-phenyltriazole to ethyl propiolate in acetone has been carefully examined by Tanaka and Miller.[107] 1,2,3-Triazoles add through their N-2 to the triple bond, forming a mixture of E- and Z-adducts (14 cps and 10 cps respectively). Initially, more Z-adduct is formed establishing the kinetic preference for *anti*-addition; eventually, the E-adduct predominates;[107] see e.g. 190-193.



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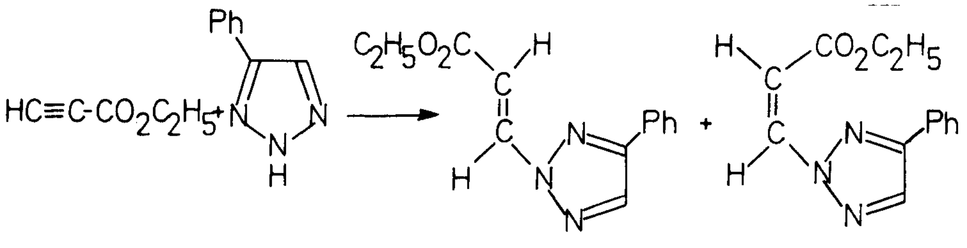
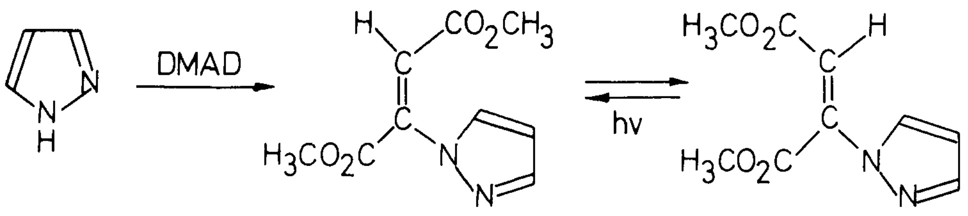
191



192

193

The addition of pyrazole to DMAD can also be understood in such terms. Initially, Reimlinger and Moussebois detected the E-adduct 195 in carbon tetrachloride but not Z-isomer 194; a 1:1 mixture of E and Z could, however, be obtained by sensitized illumination of 195.[104,108] Later, Huisgen, Giese and Huber[11] demonstrated that under carefully controlled



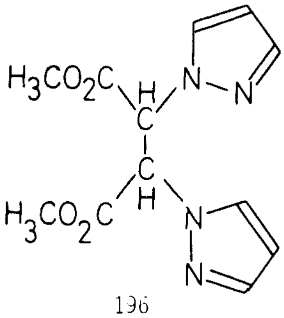
194

195

conditions, the reaction of pyrazole with DMAD in methanol led to the Z-adduct (194) of anti-addition as the predominant product; in dioxane 25% of this adduct could still be observed. This establishes that in reality the E-adduct is the product of thermodynamic control.

On the other hand the adducts of 2,3,4-trimethylpyrazole,[109] of dimethyl 1,2,3-triazole-4,5-dicarboxylate,[107] and of indazole[110] have been described as presumably Z, but this assignment may be regarded with some doubt.

The addition of pyrazoles to DMAD is largely accompanied by the formation of 2:1 adducts. Pyrazole always gives the succinic ester 196 as a by-product.[104,109,111] In the cases of 3,5-dimethylpyrazole,[109] 1,2,3-triazole,[110] benzotriazole[110] and 1,2,4-triazole[110] only the 2:1-adducts were obtained. No diastereomers were detected. Normally, the carbon-nitrogen bond is formed through N-1, but in the case of indazole one molecule is bonded through N-1 and the other through N-2 (197).[110]



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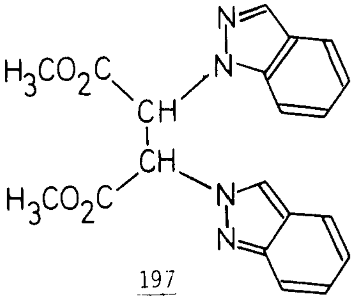
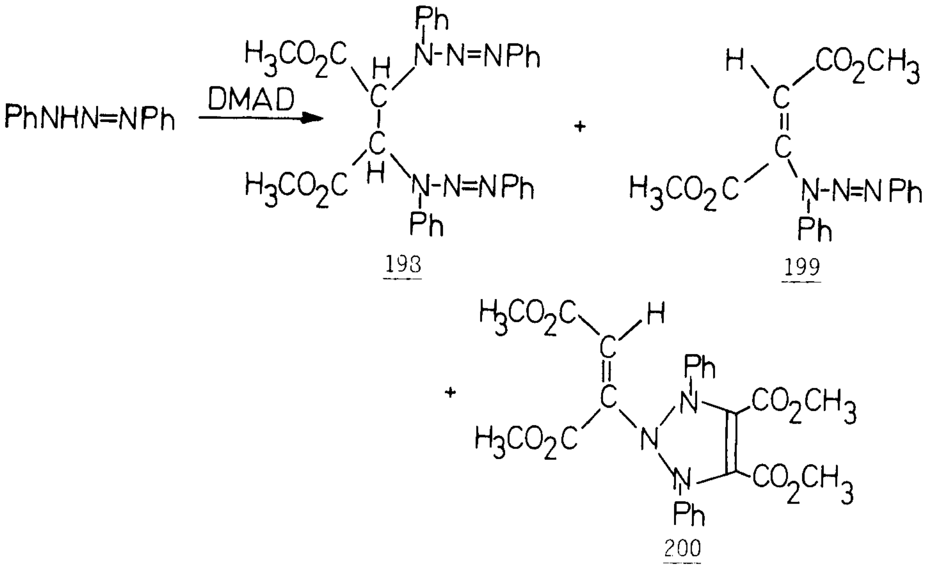
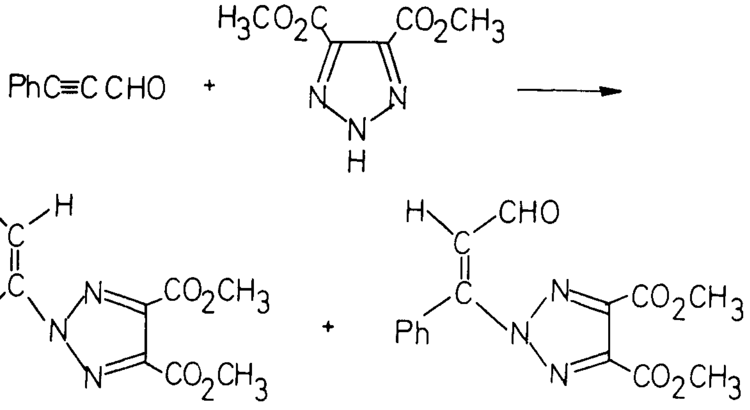


197

A succinic ester derivative 198[110] also resulted from the reaction between 1,3-diphenyltriazene and DMAD; only traces of 199 were detected and some 200 was formed by addition of the triazole generated by the cycloaddition of DMAD and 1,3-diphenyltriazene.[110]



198 199 200

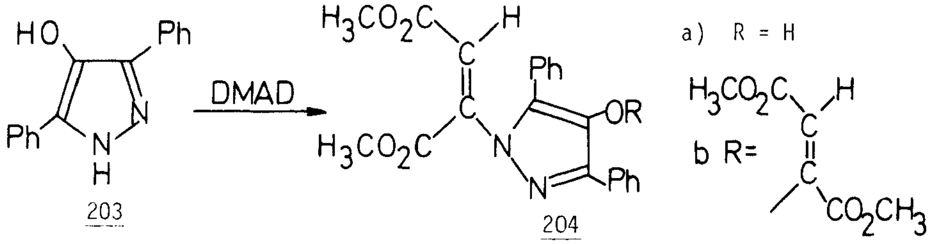


201 202

Only one adduct of uncertain configuration was obtained from ethyl phenylpropiolate and ethyl 5-phenyl-1,2,3-triazole-4-carboxylate.[107] With dimethyl 1,2,3-triazole-4,5-dicarboxylate, phenylpropiolaldehyde formed the two isomers 201 and 202, with other triazoles, the adducts were just prepared and studied by nmr.[107]

4-Hydroxypyrazole 203 reacted with DMAD preferentially at nitrogen (204a) and both at nitrogen and hydroxyl but with different configurations

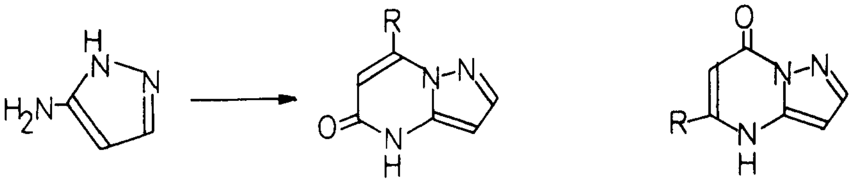
(204b).[112]



203

204

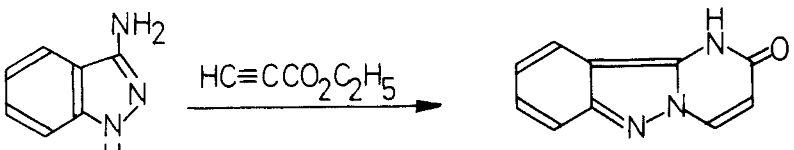
Bicyclic addition products are obtained from 3-aminopyrazoles and acetylenic esters; the pyrazole nitrogen adds to the triple bond while the amino group attacks the ester. Thus with 3-aminopyrazole MP and phenylpropiolate give only 205a and 205b respectively.[113] Methyl tetrolate gives



205
a) R = H
b) R = Ph
c) R = CH_3

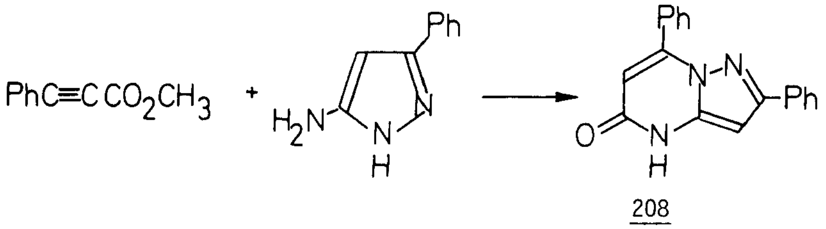
206
a) R = CH_3
b) R = CO_2CH_3

both 205c and 206a but DMAD only the unexpected 206b.[113] Similar results are obtained with 3-aminotriazoles.[114,115] 3-Aminoindazole gives 207 with ethyl propiolate[116,117]; the corresponding pyrazolopyrimidones are obtained

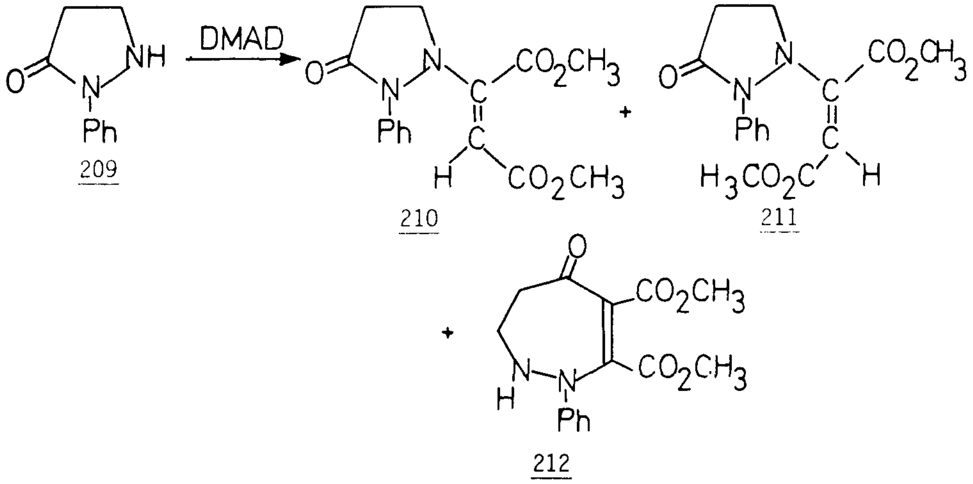


207

from 4,5,6,7-tetrahydro-3-aminoindazole and ethyl propiolate, tetrolate or phenylpropiolate.[118] 3-Amino-5-phenylpyrazole gives 208 with methyl phenylpropiolate.[119]

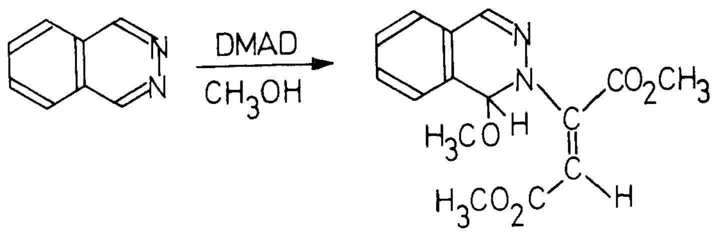


Some pyrazolidinones have also been added to DMAD. In the case of the 2-phenyl derivative 209 the two isomers 210 and 211 and a ring-enlarged diazepinone 212 *(by internal cycloaddition/-reversion) were formed;*[120,121]

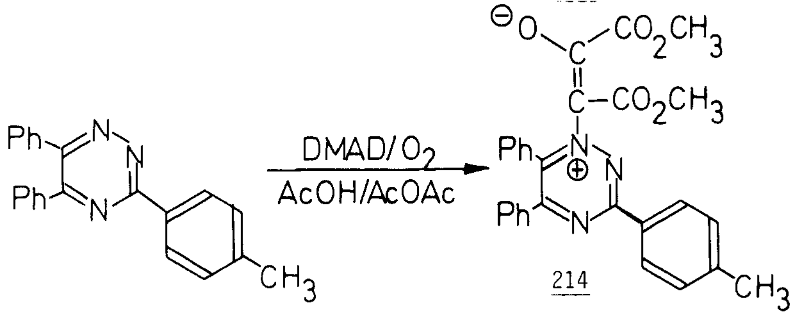


the same is true for different C-methyl- and -dimethyl derivatives. The 2-benzyl-5-methylpyrazolidinone forms only one adduct to which the maleic ester structure has been assigned on the basis of the vinyl signal at 5.2 ppm.[122] A hexahydropyridazinone has also been used but gave only a ring enlarged N-aminoazepinone derivative.[122] 3-Cyanomethylpyrazolidine adds to DMAD to give a mixture of the two stereoisomeric 1:1 adducts but hexafluoro-2-butyne adds to each of the nitrogens to give products of uncertain configurations.[123]

Finally, two unusual addition reactions shall be mentioned. Phthalazine adds to DMAD in methanol to give compound 213 (vinyl-H at 6.36 ppm).[124] A triazine adds DMAD in the presence of oxygen to give the stable, deeply colored zwitterion 214.[125] Two similar compounds have also been described.



213

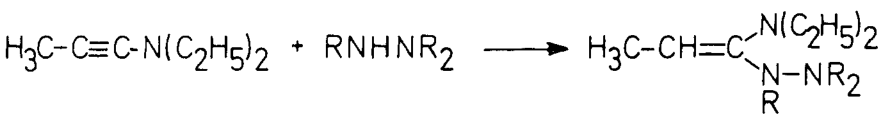


214

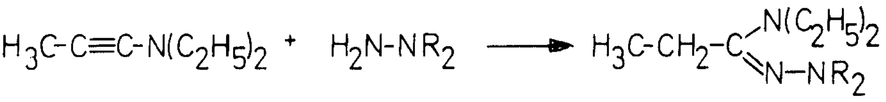
VIII. ADDITION OF HYDRAZINES TO YNAMINES AND DIACETYLENES

1. Addition to Ynamines

Ynamines add hydrazines at C-1. This is one of the rare cases that the addition is favoured by a donor group.

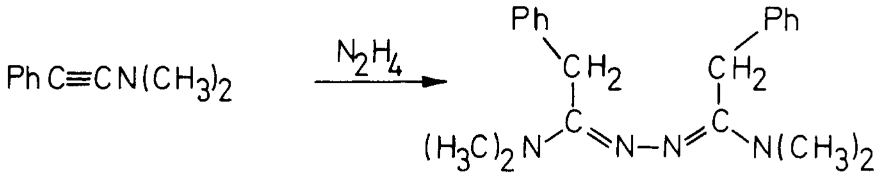


$$H_3C-C\equiv C-N(C_2H_5)_2 + RNHNR_2 \longrightarrow H_3C-CH=C\begin{matrix}N(C_2H_5)_2\\ \underset{R}{N}-NR_2\end{matrix}$$



$$H_3C-C\equiv C-N(C_2H_5)_2 + H_2N-NR_2 \longrightarrow H_3C-CH_2-C\begin{matrix}N(C_2H_5)_2\\ =N-NR_2\end{matrix}$$

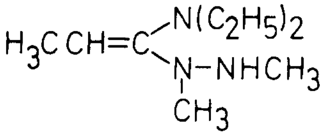
Ynamines give geminal enamino-enehydrazines with 1,2-di- and tri-substituted hydrazines but amidrazones with mono- or 1,1-disubstituted hydrazines. Thus Viehe, Fuks and Reinstein prepared the crystalline azine 215 from dimethylamino phenylacetylene and hydrazines.[126]



215

A similar but liquid azine has been obtained from 1-diethylaminopropyne.[127]

The reaction of this ynamine with hydrazines in carbon tetrachloride was more extensively investigated. Four different enehydrazines of type 216 could be observed by nmr but were not isolated; they were extremely labile and no configurations were given. Five amidrazones of type 217 were distillable liquids; those derived from monosubstituted hydrazines were sensitive to air.[127] Similar results were reported for the addition of hydrazine to 1-dialkylamino-3-penten-1-ynes.[128]



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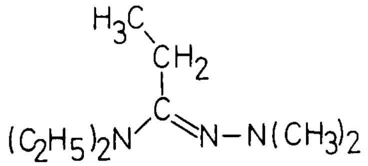
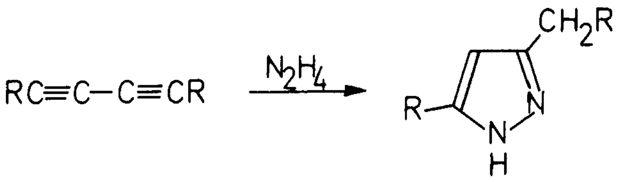


217

2. Addition to Diacetylenes

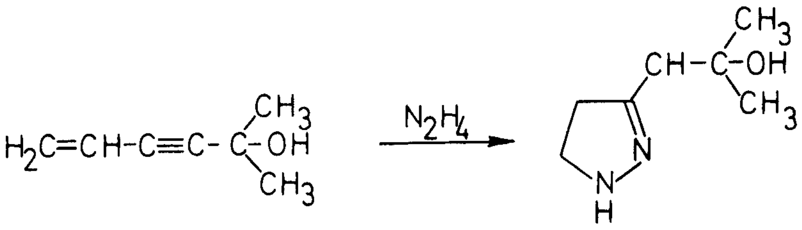
Even though diacetylenes react easily with hydrazines to pyrazoles, no open-chained adducts have been so far reported. In 1968, two groups described the formation of pyrazoles from diacetylenes and hydrazine in good yields.[129,130]



218

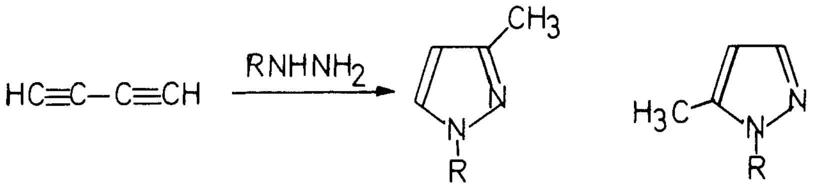
a) R = H
b) R = CH_3
c) R = Ph
d) R = CH_2OH

The formation of pyrazolines from butenynylcarbinols and hydrazine hydrate in good yields had previously been described.[131]



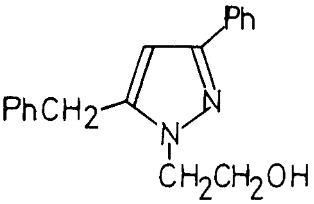
219

Anhydrous monoalkylhydrazines preferentially lead to the 3-alkylpyrazoles 140a and 220a while in water the formation of 5-alkylpyrazoles 141a and 221a and 221b is preferred.[132] Diphenyldiacetylene gave only 222 with hydroxyethylhydrazine.[132] Semicarbazide gives the two isomers 220b and 132, but from 1,3-pentadiyne only 223 was obtained.[133]



140a R = CH_3
220a R = C_2H_5
b R = $CONH_2$

141a R = CH_3
221a R = C_2H_5
b R = $CH_2\text{-}CH_2OH$
132 R = $CONH_2$



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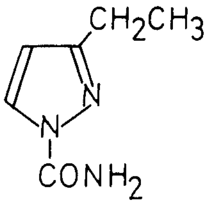
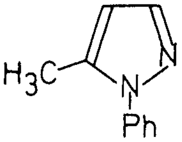


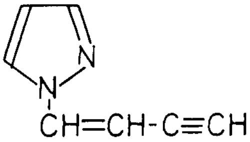
223

Compound 218a has also been prepared by first adding primary or secondary amines to diacetylene followed by hydrazine. In this way 138b was obtained with phenylhydrazine.[134]

Base-catalyzed additions of pyrazoles to diacetylene gave the simple adducts, e.g. 224.[135]



138b



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