RECENT DEVELOPMENTS IN THE CHEMISTRY OF YLIDENE AZOLONES

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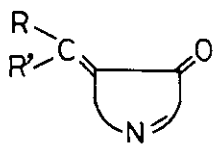
Abstract - The recent developments in the chemistry of ylidene azolones are reported and the literature data were critically discussed.

INTRODUCTION:

α,β-Unsaturated azolones are versatile reagents and their chemistry has, in the past, received considerable attention. Interest in the chemistry of this class of compounds has recently been revived[1-8]. Ylidene azolones have recently revealed several diverse interesting activities that have proved useful in heterocyclic synthesis[9]. Derivatives of the type 1 are generally obtained via condensation of active methylene heterocycles with aldehydes, ketones, orthoesters, amidines or nitriles. Such approaches are well familiar and known derivatives of several heterocyclic ring systems as well as their methods of preparation have been previ-



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iously surveyed[10]. In the present manuscript we are going to survey relevant important developments and utilities of this class of compounds. It was not the plan to make an encyclopedic scan for the subject but rather to survey in one article the literature on this class of compounds. This survey seems to be useful for heterocyclic chemistry instructors, researchers and students.

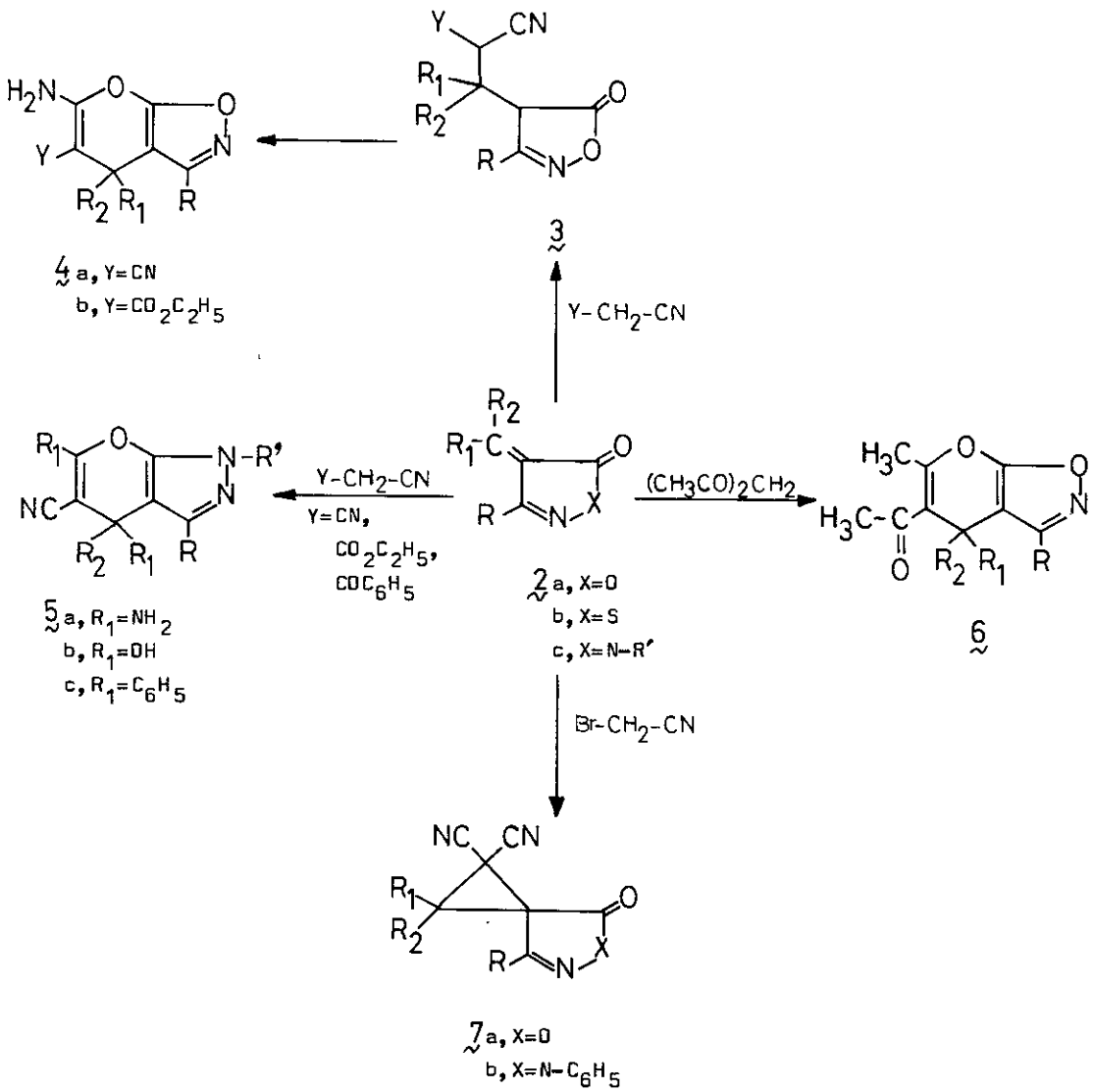
CHEMICAL PROPERTIES AND REACTIONS:

In compounds 1 the presence of a keto group adjacent to an α,β-unsaturated linkage activates the latter toward nucleophilic reagents. Thus, such double bonded systems behave like chalkones, enamino ketones and the β-keto enols[11-14]. Also

the presence of the α,β-unsaturated linkage activates the hetero ring toward a variety of reagents. The reactions that are going to be surveyed are those which take place at the double bond, at the ring carbonyl or on both moieties.

1- Reactivity toward active methylene reagents:

The exocyclic double bond in arylidene azolones has been observed to be highly active acceptor in Michael addition reactions.[1,4,15-19] Thus, malononitrile, ethyl cyanoacetate and benzoylacetonitrile have been reported to add to the exocyclic



4 a, Y=CN
b, Y=$CO_2C_2H_5$

3

5 a, $R_1=NH_2$
b, $R_1=OH$
c, $R_1=C_6H_5$

2 a, X=O
b, X=S
c, X=N-R'

6

7 a, X=O
b, X=N-C_6H_5

Chart 1

double bond in 4-arylidene-2-isoxazolin-5-one derivatives[17,18] (2a) and in 4-arylidene-2-pyrazolin-5-one derivatives[15,16] (2c). Harhash et al[17] have assigned the acyclic structure 3 for the formed products. Recently, Otto-Schmeltz[15] and Elnagdi et al[4,19] have proved, based on ^{1}H-NMR data, that these adducts are in fact the isomeric cyclic enaminopyrans 4 and 5. Acetylacetone afforded the pyrano [2,3-d]-isoxazole derivatives 6 on reaction with arylidene-isoxazolones under similar reaction conditions[17].

The reaction of bromomalononitrile with 2a and 2c has been reported to afford the corresponding cyclopropane derivatives 7a,b[20] probably formed via intermediacy of the acyclic Michael type adducts similar to those postulated by Harhash et al[17]. However, the possibility that the dicyanocarbene is the reactive species can not be ruled out[17] (cf. Chart 1). In contrast to these findings, Stachel et al[21] have recently reported a novel pyrrole synthesis via reaction of 2-phenyl-4-arylidene-2-oxazolin-5-ones (8a) with ethyl cyanoacetate. The authors[21] have shown that ethyl cyanoacetate effects ring cleavage of 8a to yield the isolable acyclic product 9 which could be cyclised into different pyrrolone derivatives (10 or 11) based on the cyclisation reaction conditions. The reactivity of 8a toward other activated methylene reagents has been recently investigated. Whereas the reaction with benzoylacetonitrile afforded the acyclic acid (12), the reaction with acetylacetone yielded the pyrano [3,2-d]oxazole derivatives 13[22] (cf. Chart 2).

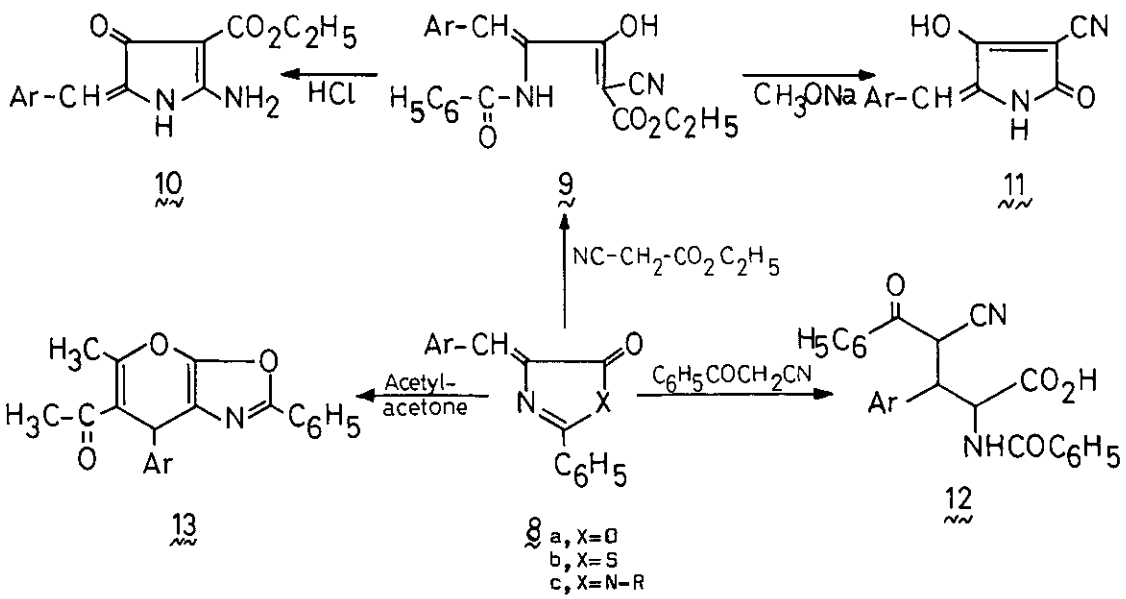
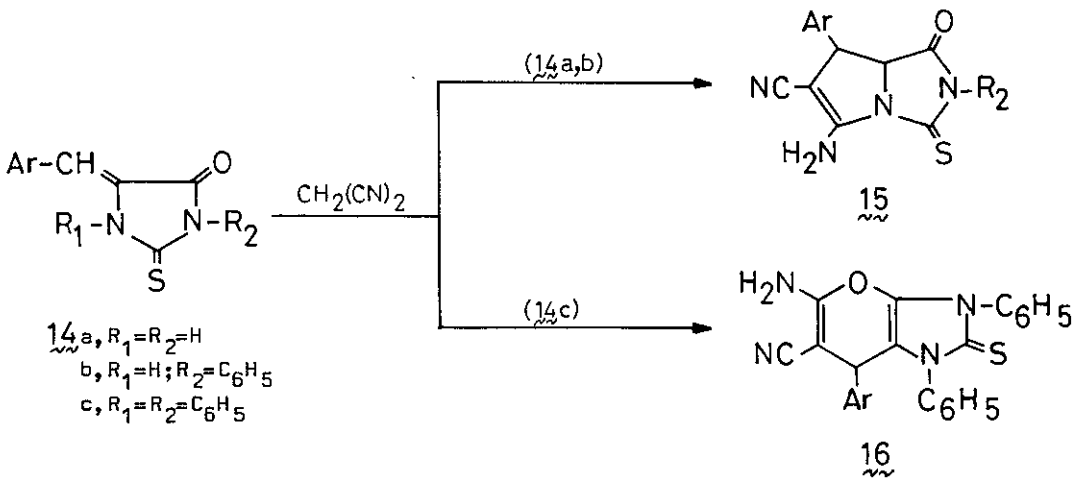


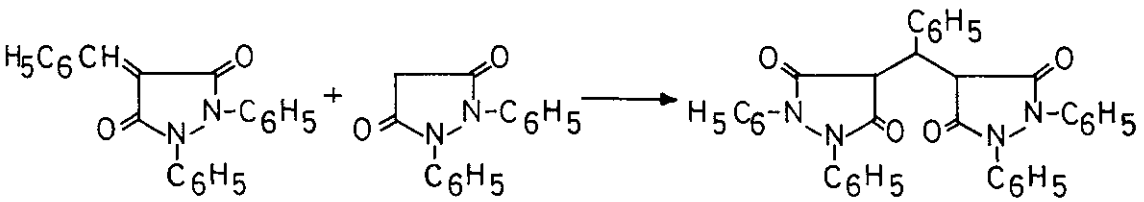
Chart 2

Recently, Daboun et al[9] reported that 5-arylidene-4-imidazolidinone-2-thiones 14 reacted with malononitrile to give pyrrolo[1,2-c]imidazoles (15) or pyrano[2,3-d]-imidazoles (16) according to the absence or presence of substituents at position 1.



14a, $R_1=R_2=H$
b, $R_1=H; R_2=C_6H_5$
c, $R_1=R_2=C_6H_5$

The double bond in arylidene azolones has been also reported to add to the active methylene azolones[23-25] to afford bis-adducts as shown from the following example:



Similar to the behaviour of benzylidene azolones, 1-phenyl-3-methyl-5-dimethyl-aminomethylene-2-pyrazolin-5-one reacted with active methylene reagents to give the pyrano[2,3-c]pyrazoline derivatives (18) probably formed via Michael type addition, elimination of dimethylamine and cyclisation (cf. Chart 3).[2]

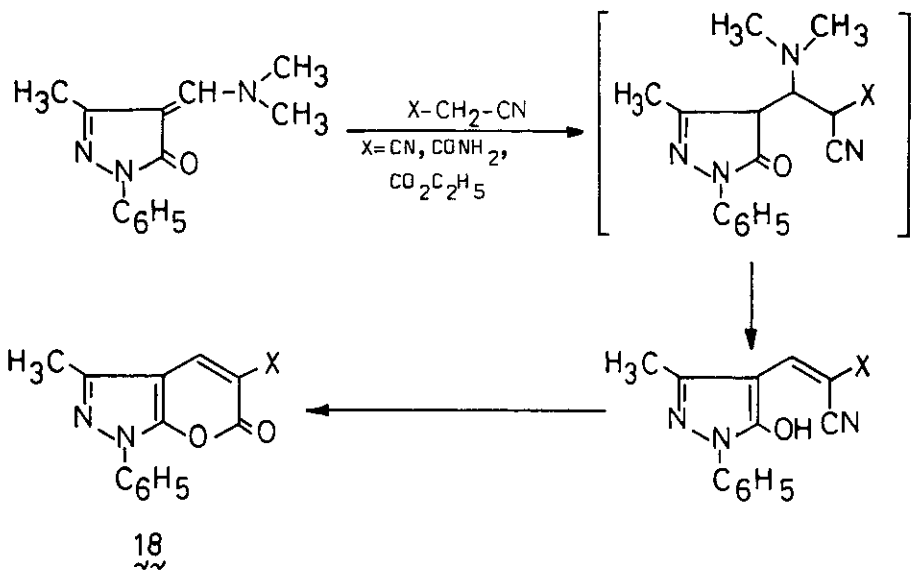


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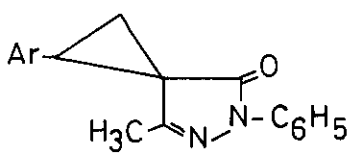
Chart 3

2- Reactions with diazomethane:

1-Phenyl-3-methyl-4-arylidene-5-pyrazolones (2c), 4-arylidene-2-oxazolin-5-ones (8a), 4-arylidene-2-thiazolin-5-ones (8b), 1,2-diphenyl-4-arylidene-2-imidazolin-5-ones (8c) and 1,3-diphenyl-5-arylidene-4-imidazolidinone-2-thione (14c) reacted with diazomethane to afford the corresponding cyclopropane derivatives 19, 20a,b,d and 21 respectively[26-37]. On the other hand, methylation as well as cyclopropane formation were observed when 2-phenyl-4-arylidene-2-imidazolin-5-ones (8c, R=H)[34] and 3-phenyl-5-arylidene-4-imidazolidinone-2-thione (14b)[36] reacted with ethereal



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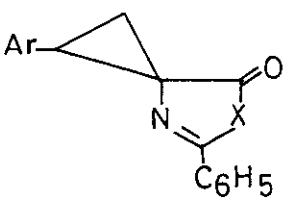
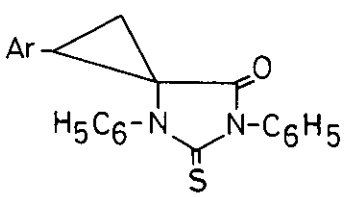


20a, X=O
b, X=S
c, X=N-CH3
d, X=N-C6H5



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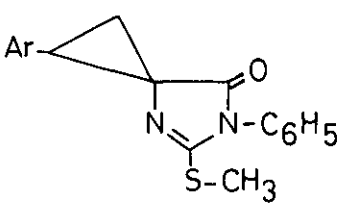

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diazomethane to afford 20c and 22 respectively.

In contrast to the above mentioned observations, 3-aryl-5-arylidene-2,4-thiazolidenediones (23a) reacted with ethereal diazomethane to yield the corresponding C-methylated derivatives (24)[38].

Treatment of 5-arylidene-4-thiazolidinone-2-thione (23b) with gaseous diazomethane gave mixtures of N-methyl and S-methyl derivatives (25 and 26)[39]. A linear correlation exists between the log of the relative yields (N-methyl/S-methyl) and substituent constants of the substitution group R'. Increasing the dielectric constants of the solvents increased the relative yields of N-methyl derivatives. In amines like triethylamine and aniline, only the S-methylthiazolone derivative is the sole isolable reaction product (cf. Chart 4).

It has been reported also that the exocyclic double bond in 27a appears stable toward the action of ethereal diazomethane and only the S-methyl derivatives 27b were formed[40]. On the other hand, 2-benzylmercapto-5-arylidene-2-thiazolin-5-ones (27d) afforded the C-methyl derivatives 28 together with the cyclopropane derivatives 29 on treatment with the same reagent[41].

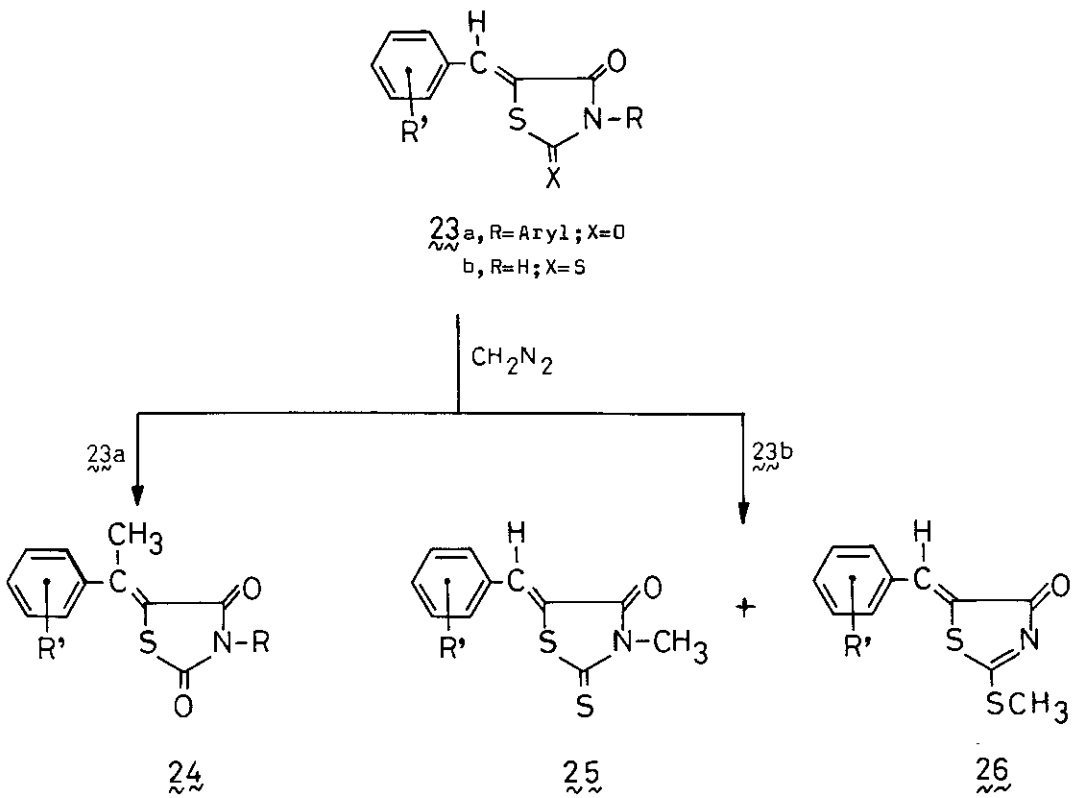
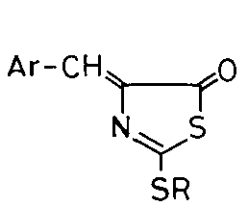
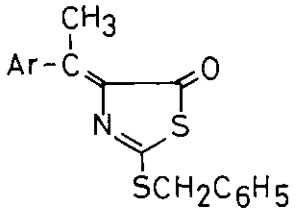


Chart 4



27 a, R=H; b, R=CH3; c, R=C2H5; d, R=CH2C6H5 (+ CH2N2)



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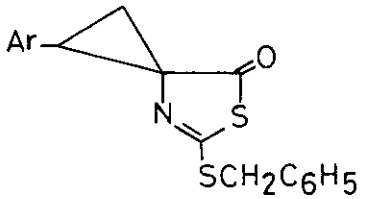

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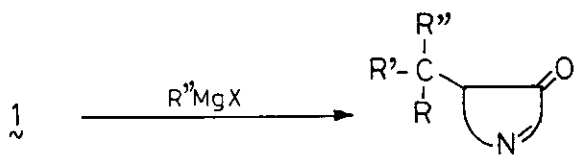
3- Reactions with Grignard reagents:

α,β-Unsaturated azolones are well known to undergo 1,4-addition of Grignard reagents on the activated double bond leading to the formation of saturated 4-aralkyl or alkyl substituted azolones (30).[24,25,36,37,42-70] Mustafa and Harhash[71] have reported that 4-arylidene-2-imidazolin-5-ones (8c) reacted with Grignard reagents via 1,2-addition of the reagent to the carbonyl group to afford the corresponding hydroxyimidazole derivatives 31. However, Awad et al[42] have corrected



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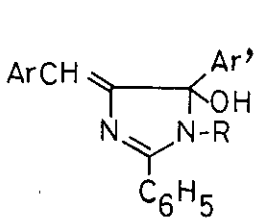
the structure of these products and proved that the reaction is really a typical 1,4-addition affording 32. These results were confirmed later when Asker et al[66,72] found that phenylmagnesium bromide reacted with 8c on the cold to give 32 (Ar'=Ph). On the other hand, compound 32 together with its oxidation products 33 and 34 were obtained when the reaction was conducted at the boiling point of the solvent.



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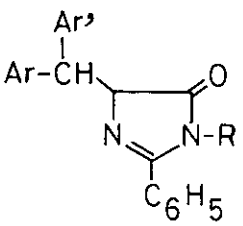

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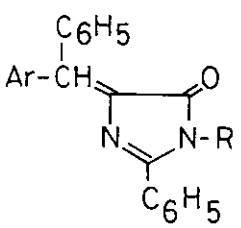

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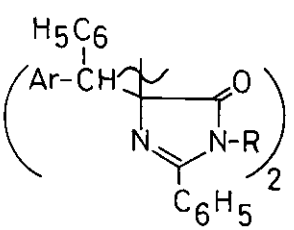

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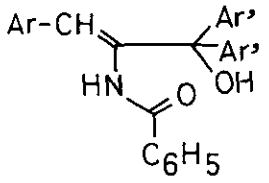
Whereas the oxazolone ring in 2-phenyl-4-arylidene-2-oxazolin-5-ones(8a) is readily opened by the action of arylmagnesium halides to give 1,1-diaryl-2-benzoylaminocinnamyl alcohol derivatives (35) together with 2-phenyl-4-arylidene-5,5-diaryl-2-oxazolines (36),[71,73,74] 1,4-addition of the reagent to the double bond conjugated with the carbonyl function, takes place upon treatment of 8a with



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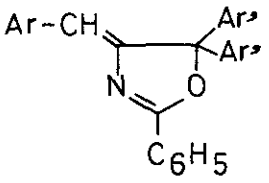

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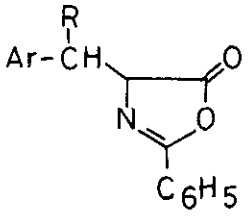

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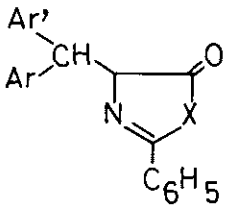
alkyl- and aralkylmagnesium halides to give 37[62,63]. No tertiary alcohol (or the corresponding thiazoline), which would have been formed by the 1,2-addition could be detected.

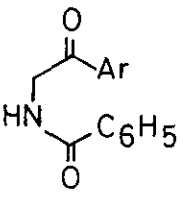
4-Friedel-Crafts reactions:

Treatment of 2-phenyl-5-arylidene-5(4H)-oxazolones (8a) with aromatic hydrocarbons in the presence of anhydrous aluminium chloride results in the formation of either 38a, formed by 1,4-addition of the hydrocarbon to the α,β-unsaturated system, or 39, formed via arylation and arylidene cleavage, depending upon several factors. Among these factors are the ageing of aluminium chloride, the temperature of the reaction and the presence of traces of moisture.[62,75,76]

When 4-arylidene-2-isoxazolin-5-ones (2a)[56,57] and 2-phenyl-4-arylidene-5(4H)-thiazolone (8b)[61] were treated with benzene in the presence of anhydrous aluminium chloride, 1,4-addition to the α,β-unsaturated carbonyl system took place with the formation of 40 and 38b. No products resulting from arylation or arylation and benzylidene cleavage have been isolated[61].



38 (a, X=O; b, X=S)



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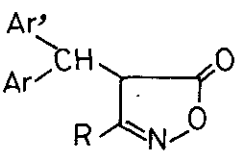

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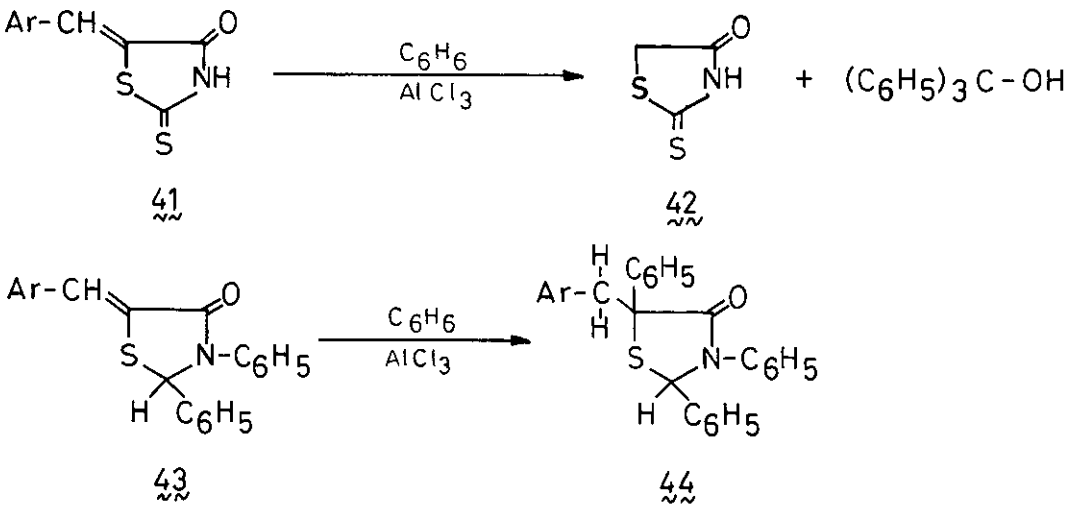
Snider et al[77] reported that the reaction of 5-arylidene-4-thiazolidinone-2-thione (41) with benzene and ⩾4 mol of aluminium chloride cleaved the arylidene substit-



uent to give 4-thiazolidinone-2-thione (42) and triphenylcarbinol.
Under similar conditions, 2,3-diphenyl-5-arylidene-4-thiazolidinones (43) added benzene to the unsaturated linkage to give the 2,3,5-triphenyl-5-arylmethyl-4-thiazolidinone derivatives 44.[77]

5- Reactivity in dipolar cycloaddition reactions:
Ylidene azolones seem to be interesting dienes and dienophiles. In this respect they can be considered as excellent starting materials in dipolar cycloaddition reactions. The utility of these reagents in the latter reactions has received relatively little attention. An interesting reaction of 3-phenyl-4-benzylidene-2-isoxazolin-5-one with α-chlorobenzaldehyde phenylhydrazone leading to the formation of 1,3,4-triphenylpyrazole-5-carboxylic acid (46) has been reported[78]. The reaction is beleived to proceed via the intermediacy of the spiro compound 45 which could not be isolated[78].
However, the reaction of the same benzylidene with benzonitrile oxide afforded the isolable spiro isoxazole derivative 47[79] (cf. Chart 5).
Other spiro pyrazoloneisoxazolines (48 and 49) have been also isolated from the reaction of 4-benzylidene-5-pyrazolones with N-oxides[80-82].

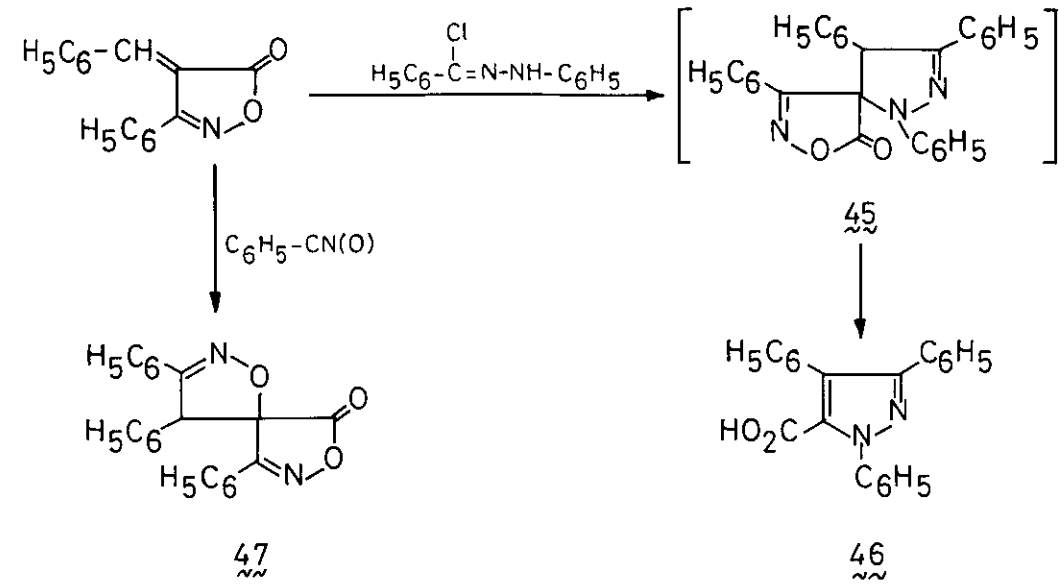
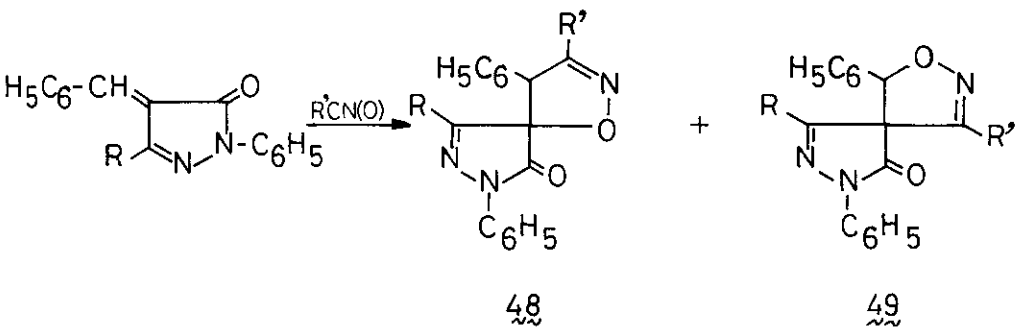


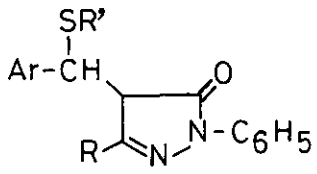
Chart 5



The exocyclic double bond in 5-(aroylmethylidene)-4-thiazolidinone-2-thiones added 2,3-dimethylbuta-1,3-diene to give the thiazolidinone spirocyclohexene derivatives 50.[83]

6- Action of sulphur compounds:

It has been reported that thiophenols undergo 1,4-addition to the activated exocyclic double bond of 4-arylidene-5-pyrazolones and 4-arylidene-3,5-pyrazolidinediones to give the corresponding adducts 51 and 52 respectively[25,69]. However, when 2-phenyl-4-arylidene-2-oxazolin-5-ones (8a) were treated with hydrogen sulphide or with thiols, they underwent simaltaneous addition of the sulphur compound to the exocyclic double bond followed by hetero-ring opening to give products such as 53.[62,84,85] On the other hand, treatment of 2-ethylmercapto-4-benzylidene-2-thiazolin-5-one with hydrogen sulphide in the presence of methanolic triethylamine affected the formation of 4-thiocarboxy-5-phenyl-2-thiazolidinethione (54), probably formed by 1,4-addition and hetero-ring opening followed by recyclisation via loss of ethylmercaptan[86,87]. Compound 54 was also obtained upon treatment of 2-carboxymercapto-4-benzylidene-2-thiazolin-5-one with hydrogen sulphide under the



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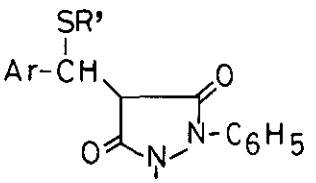

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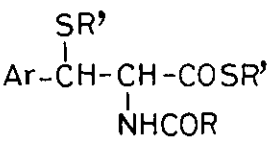

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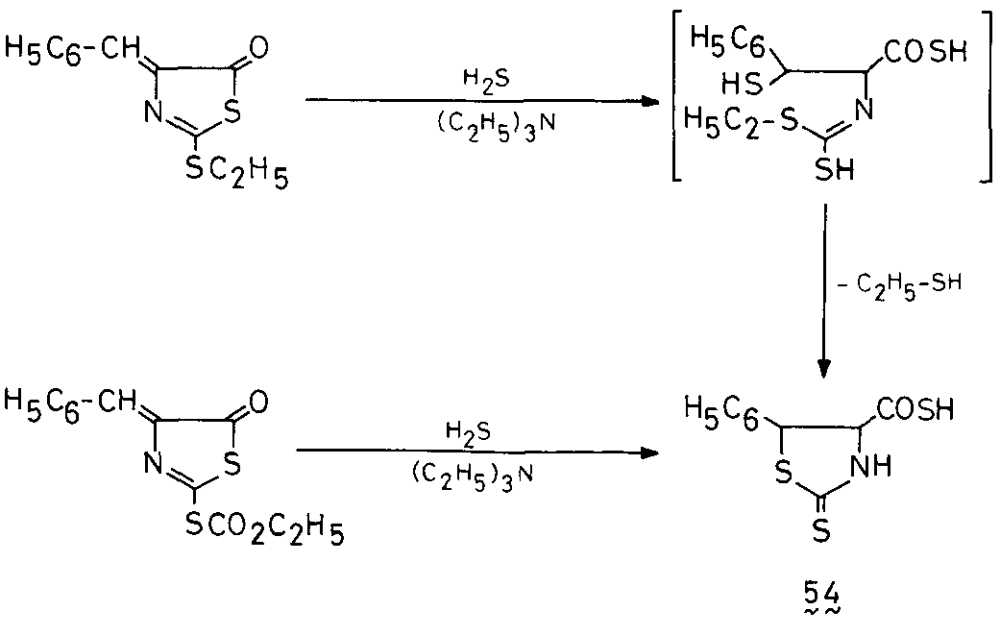

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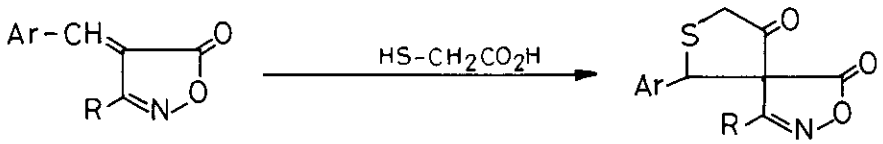
same reaction conditions[86]. Similar behaviour has been also reported with 2-ethylmercapto-4-isopropylidene-2-thiazolin-5-one[87].

Thioglycollic acid reacted with 4-arylidene-2-isoxazolin-5-ones to afford the



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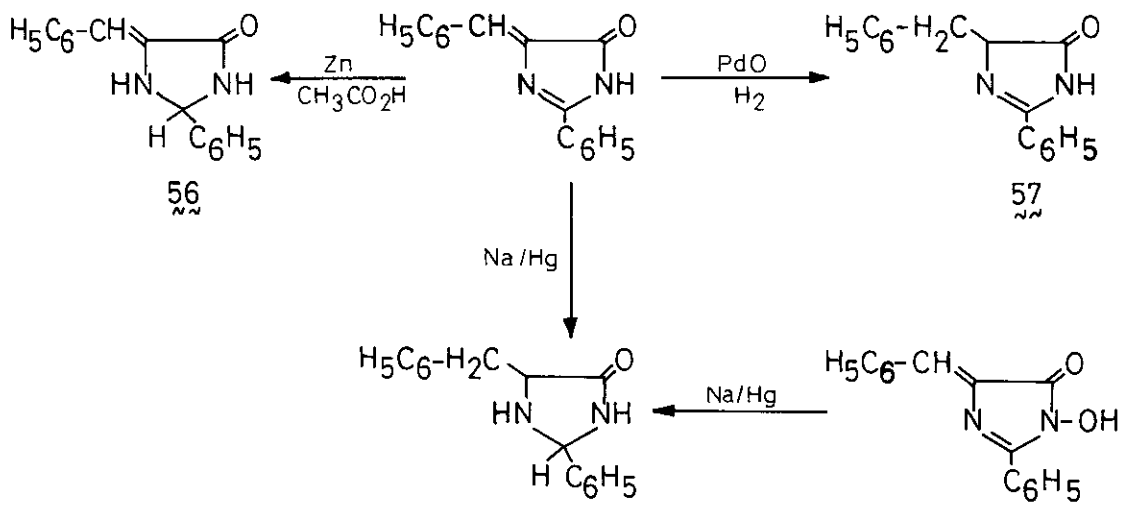
spiro products 55[17]. The reaction probably proceeds via addition of the reagent to the exocyclic double bond followed by water elimination.

7- Reduction:

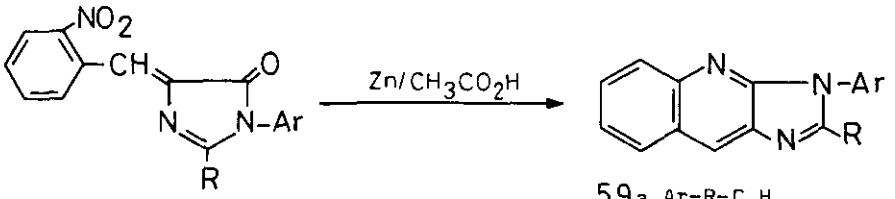
Reduction of 4-benzylidene-2-imidazolin-5-one afforded different products depending upon the applied reaction conditions. Thus, reduction using zinc dust and acetic acid resulted in saturation of the ring double bond with the formation of 56[88]. When using palladium oxide in the presence of hydrogen and ethanol, saturation of the exocyclic double bond takes place to afford 57[89]. On the other hand, saturation of both ring and exocyclic double bonds took place on using sodium amalgam in ethanol to yield 2-phenyl-4-benzyl-5-imidazolidone (58)[89]. Compound 58 could also be obtained by reducing 1-hydroxy-4-benzylidene-2-imidazolin-5-one with sodium amalgam in ethanol[90] (cf. Chart 6).



56 57 58

Chart 6

Treatment of the 4-nitrobenzylidene-5-imidazolone derivatives with zinc dust and acetic acid afforded the imidazolinoquinoline derivatives 59[91,92].



59 a, Ar=R=C_6H_5
b, Ar=C_6H_4-CH_3-p; R=SH

Kametani et al[93] found that treatment of 2-phenyl- and 2-methyl-4-(4,5-dialkoxy-2-nitrobenzylidene)oxazol-5-ones (60) with triethyl phosphite afforded the corresponding 2-phenyl- and 6,7-dialkoxy-2-methyloxazolo[5,4-b]quinolines (62), respectively. The simplest mechanism accounting for the formation of 62 involves initial reduction of the nitro group and formation of the nitrene 61, followed by one or

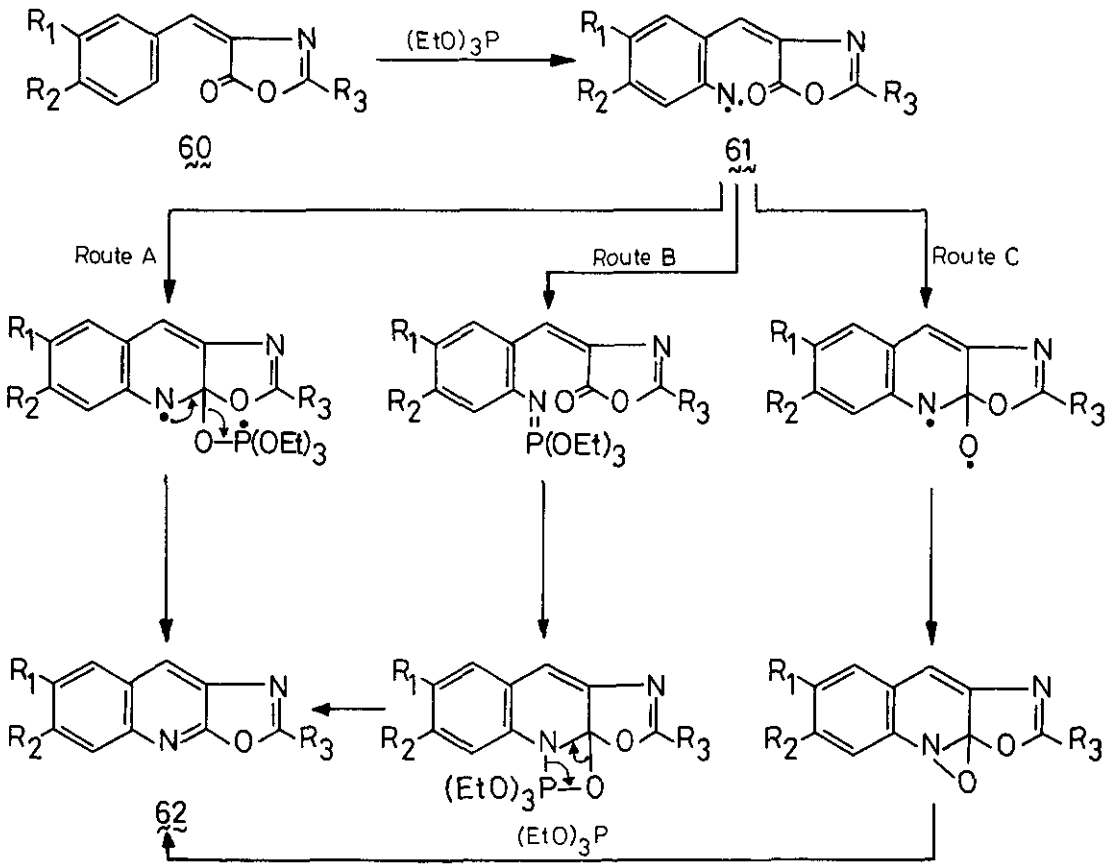


Chart 7

more of the routes A, B and C (cf. Chart 7).

Recently, the polarographic behaviour of 2-phenyl-4-benzylidene-2-oxazolin-5-one and 5-benzylidene-4-imidazolidinone-2-thione has been reported[94,95]. The reactions

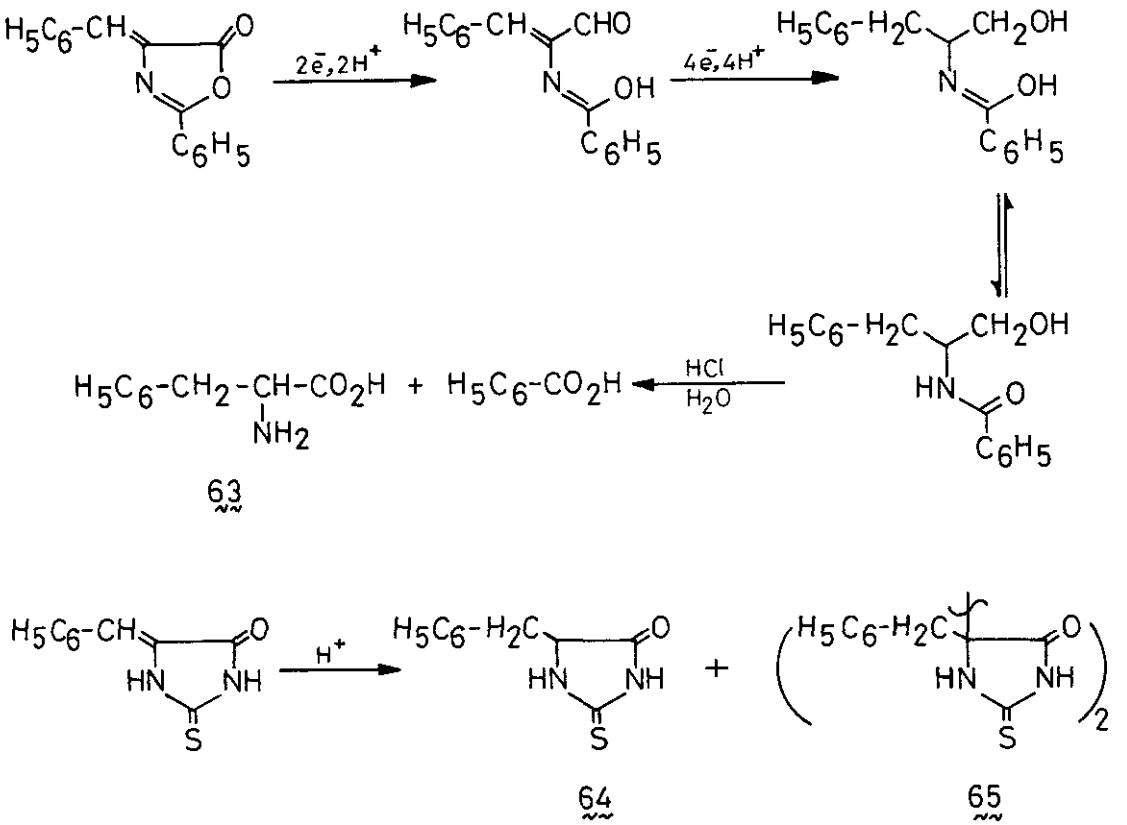


Chart 8

were suggested to proceed according to the mechanism shown in Chart 8. The reduction products 63, 64 and 65 were isolated, by controlled potential electrolysis experiments, and thus identified.

8- Action of ammonia derivatives:

It has been reported that 2-phenyl-4-arylidene-2-oxazolin-5-one derivatives (8a) react with hydroxylamine with ring opening to give the acyclic hydroxamic acid derivatives 66a and 67. In some cases ring closure of the formed hydroxamic acid derivatives 66a took place with the formation of the corresponding imidazolone derivatives 68. The nature of the end products was found to be dependent on the applied reaction conditions[90,96,97]. On the other hand, Mustafa et al[88] reported that on using N-phenylhydroxylamine, ring expansion took place with the formation of the

2,6-diphenyl-4-arylidene-2,3-dihydro-4H-1,2,5-oxadiazin-3-one derivatives (69). The authors suggested that the reaction proceeds via formation of the intermediate 69 (cf. Chart 9).

It has been reported[37,98,99] that the reaction of 2-phenyl-4-benzylidene-2-oxazolin-5-one (8a, Ar=C_6H_5) with hydrazine hydrate under mild reaction conditions afforded the acyclic hydrazide 70 (R=H). Subsequent treatment of 70 with hydrazine hydrate in boiling ethanol yielded either the hydrazino-oxazole derivatives 71 or

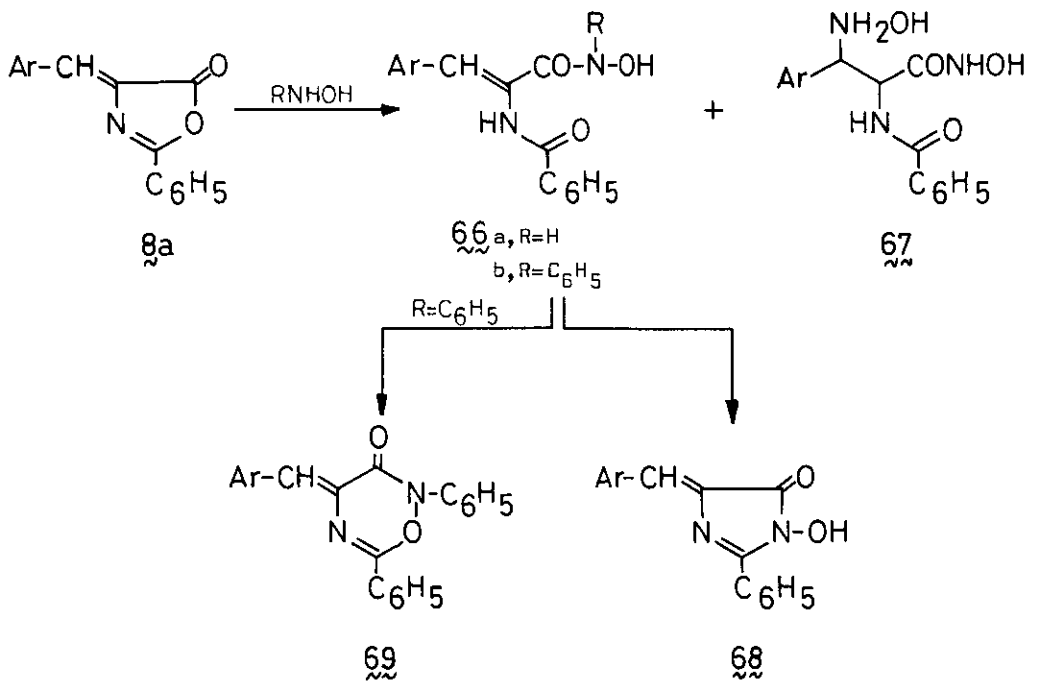


Chart 9

the pyrazolone derivatives 72 (R=H) (cf. route a in Chart 10). On the other hand, the reaction product of 8a with phenylhydrazine was found to be dependent on the applied reaction conditions. Thus, 8a reacted with phenylhydrazine in boiling ethanol to give the acyclic hydrazide 70 (R=C_6H_5). When the reaction was worked up in boiling glacial acetic acid the anilino derivatives 73 were the sole reaction products. Compounds 70 could be, however, converted into 73 on boiling in glacial acetic acid[88].

Iyengar et al[100] reported that the reaction of 8a with substituted hydrazines (phenyl, pyridyl, quinolyl and 1-isoquinolyl) leads to the formation of the pyrazolone derivatives 72 or the isomeric 75. The formation of 72 proceeds via the

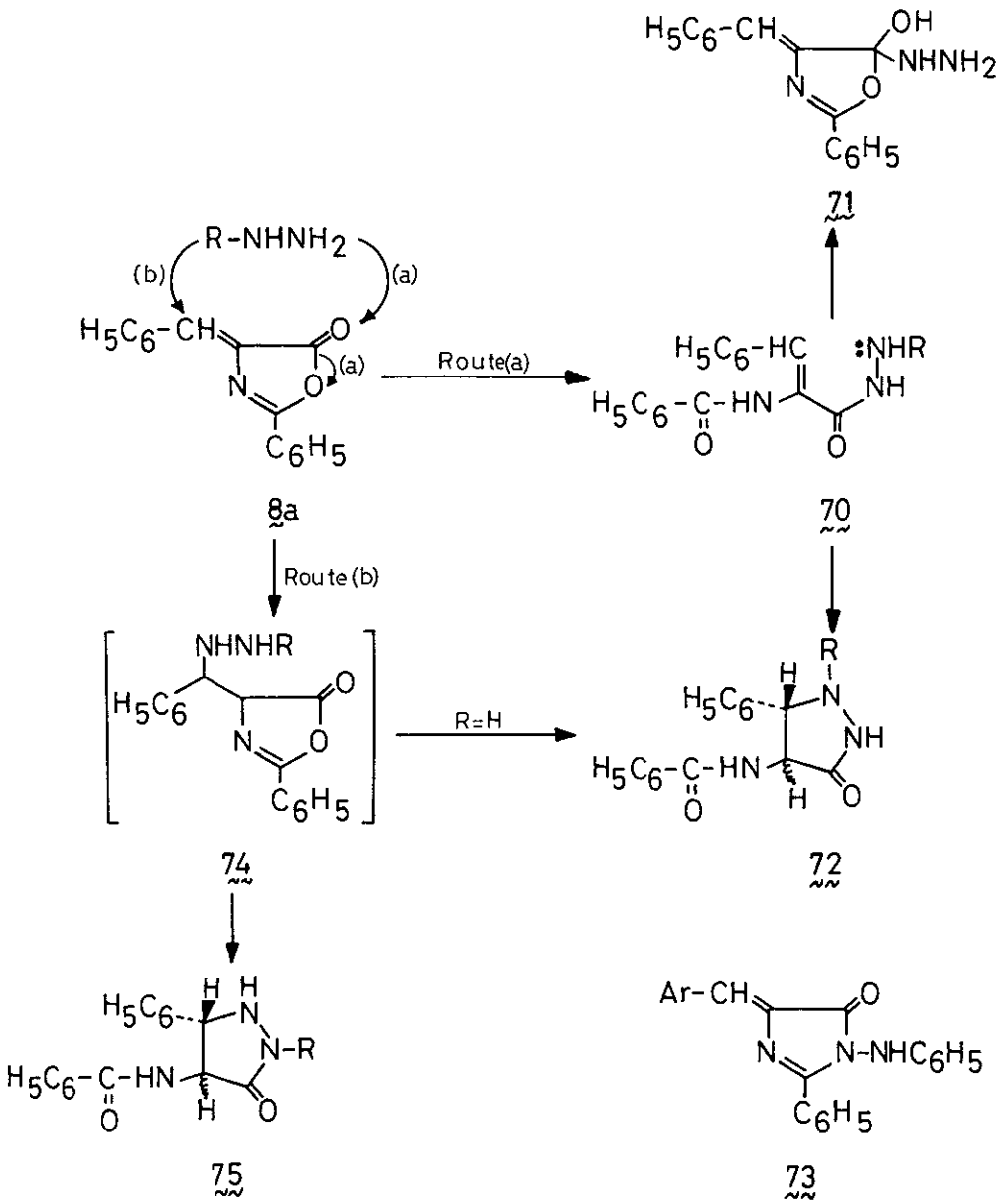
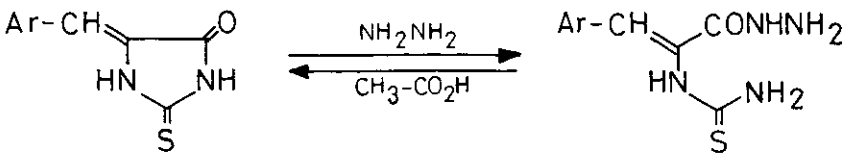


Chart 10

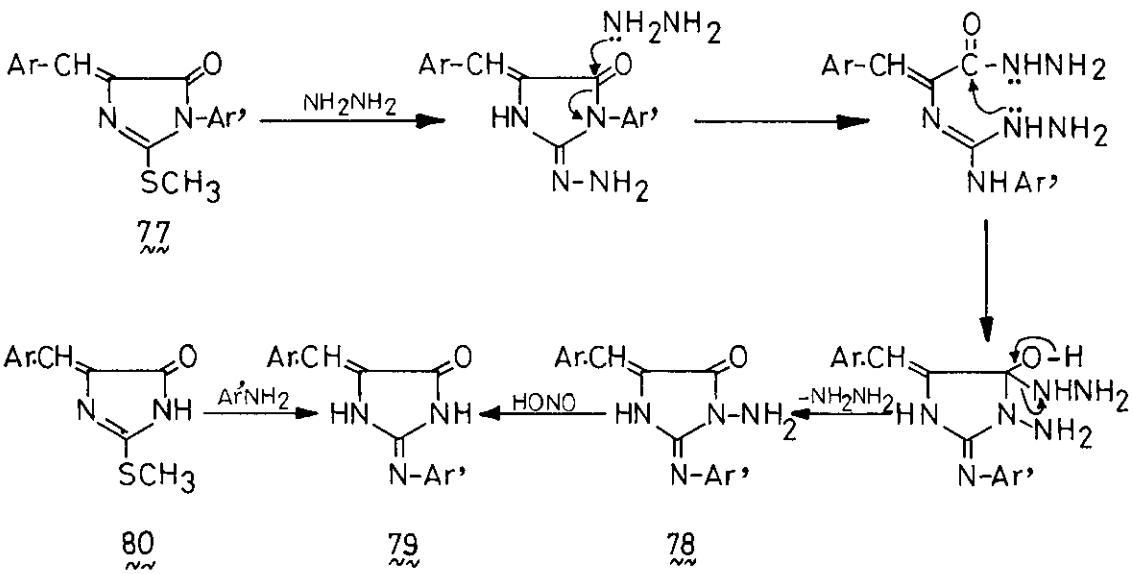
intermediacy of the isolable Michael adducts 70 (route a) whereas compounds 75 were formed, more probably, via the formation of the intermediates 74 (route b) (cf. Chart 10).

5-Arylidene-4-imidazolidone-2-thiones were converted into the hydrazides 76 on treatment with hydrazine hydrate. The latter 76 could be converted back into the starting materials when treated with acetic acid[101].



14a 76

Recently, Daboun and Ibrahim[102] reported an interesting rearrangement reaction of 1-aryl-2-methylmercapto-4-arylidene-2-imidazolin-5-ones (77) into 1-amino-2-arylimino-4-arylidene-5-imidazolidinones (78). The reaction was suggested to proceed

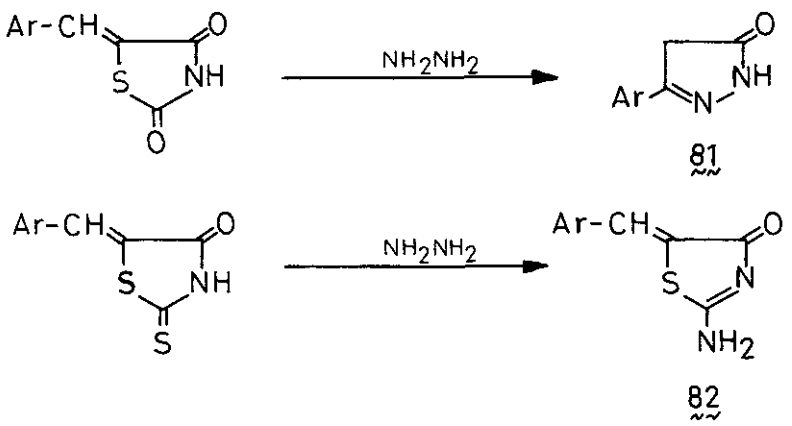


77 80 79 78

Chart 11

via the mechanism demonstrated in Chart 11. The formed products 78 were deaminated to 79 by the action of nitrous acid. Compounds 79 were also obtained via independent synthesis by the action of aromatic amines on the 2-methylmercapto-4-arylidene-2-imidazolin-5-one derivatives 80.

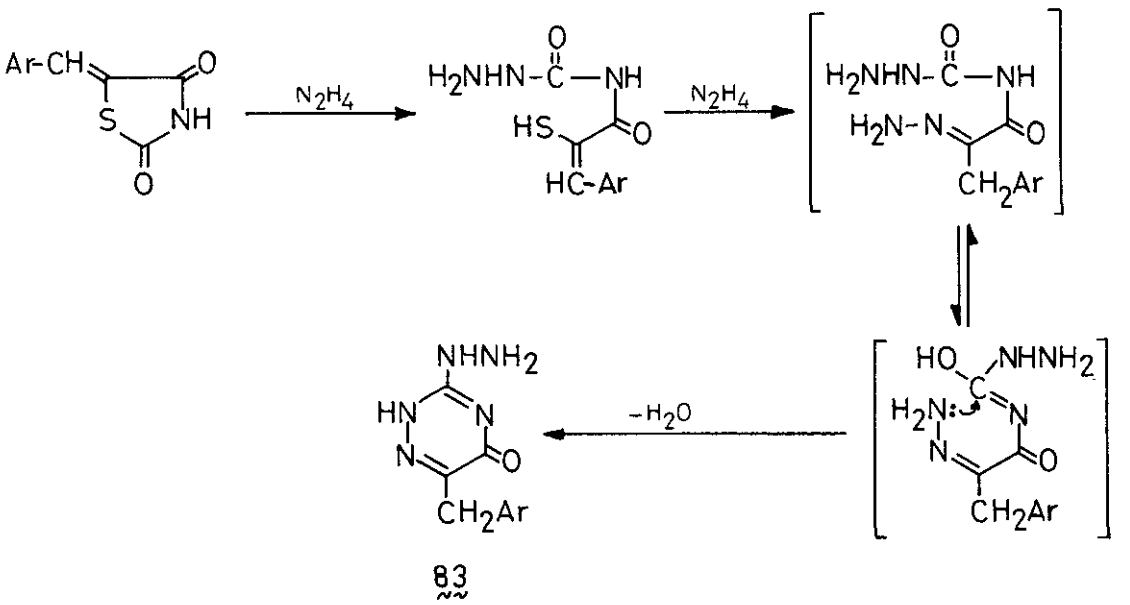
5-Arylidene-2,4-thiazolidinediones react with hydrazine to undergo ring cleavage followed by cyclisation to yield 5-aryl-3-pyrazolinones (81) in 55-70% yields. On the other hand, 5-arylidene-4-thiazolidinone-2-thiones on treatment with hydrazine gave 2-amino-4-arylidene-4-thiazolinones (82) in 35-50% yields[103].



81

82

However, Raouf et al[104] reported the synthesis of the triazinones 83 by the reaction of 5-(substituted benzylidene)-2,4-thiazolidinediones with hydrazine. The route

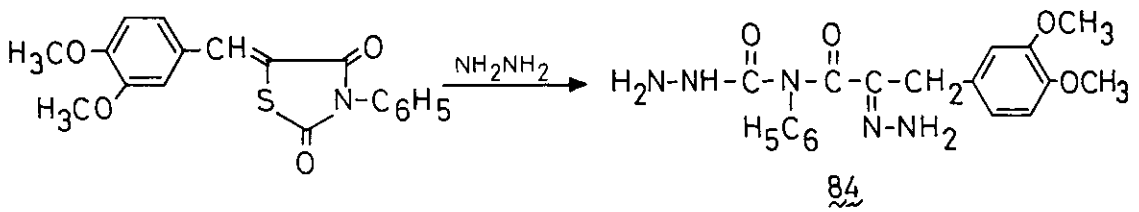


83

(Ar=6-Bromo-3,4-methylenedioxyphenyl,
6-Bromo-3,4-dimethoxyphenyl)

Chart 12

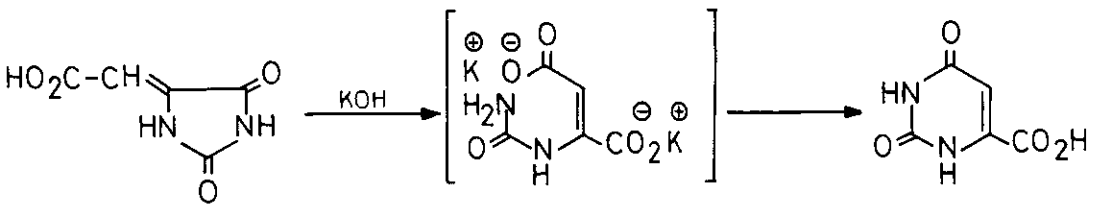
through which the transformation occurs is demonstrated in Chart 12. Ring cleavage of 5-(3,4-dimethoxybenzylidene)-3-phenyl-2,4-thiazolidenedione can be affected by the action of hydrazine to give 1-amino-3-phenyl-5ß-{[(3,4-dimethoxyphenyl)ethylidene]amino}biuret (84) with the evolution of hydrogen sulphide.[104]



84

9- Miscellaneous:

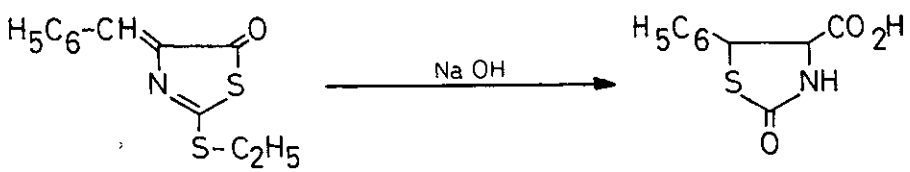
Several unusual reactions have been reported for ylidene azolones. The most interesting of these reactions will only be discussed here. It has been found that 5-carboxymethylidene-2,4-imidazolidinedione (85) reacted with boiling potassium hydroxide



85 86 87

solution with ring expansion to yield the pyrimidine derivative, orotic acid, 87. The reaction probably proceeds via the formation of the non-isolable intermediate salt 86[105,106].

Treatment of 2-ethylmercapto-4-benzylidene-5(4H)-thiazolone with sodium hydroxide solution afforded 4-carboxy-5-phenyl-2-thiazolidone (88). This rearrangement reaction proceeds via a hetero-ring opening, elimination of ethylmercaptan and subsequent recyclisation[86,87].



88

2-Trifluoromethyl-4-trifluoroacetylmethylene-5-oxazolidones (89) are converted into the 2-trifluoromethyl-4-trifluoroacetamino-2,5-dihydro-5-furanone derivatives (92) when they are heated for a long period at about 100°C. The rate of the reaction is strongly enhanced by the addition of an amine. These results make the mech-

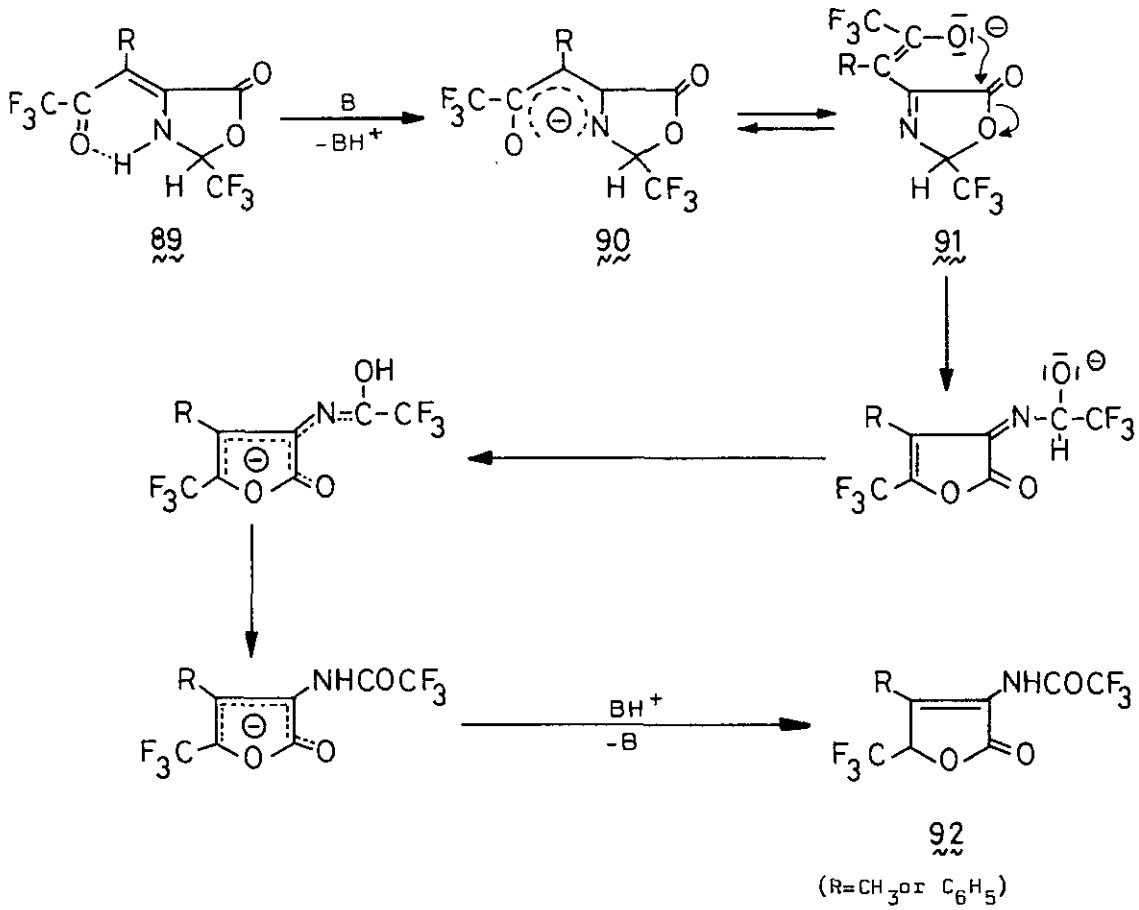
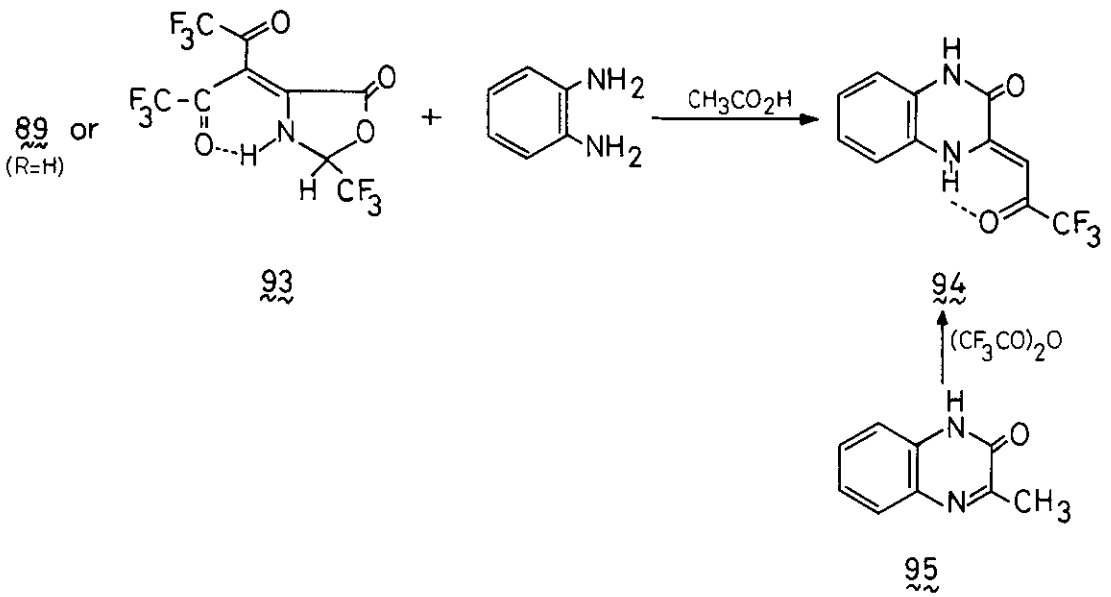


Chart 13

anism reported in Chart 13 more reasonable. The primary formation of an anion is very likely, since in the presence of ammonia or amine salts of the type $\underset{\sim\sim}{90}^{-}.N^{+}HR_1R_2R_3$ are isolated. In the anion $\underset{\sim\sim}{90}$ the enol-oxygen is in the required position for attack on the lactone $\underset{\sim\sim}{91}$[107].

An interesting reaction has been reported for $\underset{\sim\sim}{89}$ (R=H) and 2-trifluoromethyl-4-(bis-trifluoroacetylmethylene)-5-oxazolidone ($\underset{\sim\sim}{93}$) with o-phenylenediamine to give one and the same compound, 3-trifluoroacetylmethylene-1,2,3,4-tetrahydroquinoxalin-2-one ($\underset{\sim\sim}{94}$). Compound $\underset{\sim\sim}{94}$ could also be prepared via the reaction of 3-methyl-1,2-dihydroquinoxalin-2-one ($\underset{\sim\sim}{95}$) with trifluoroacetic anhydride[108].



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