

THE CHEMISTRY OF FURAZANS

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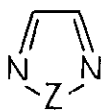
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Abstract — Syntheses, chemical reactivity and physical properties of furazans are presented.

I. INTRODUCTION

The chemistry of 1,2,5-heteradiazoles 1 is interesting from the theoretical and practical points of view.

1

Z = O, S, Se, Te

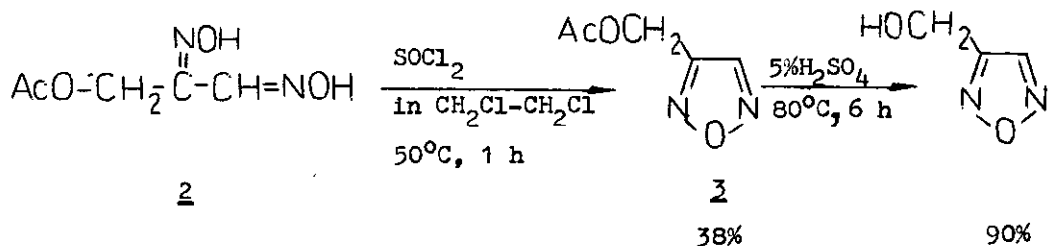
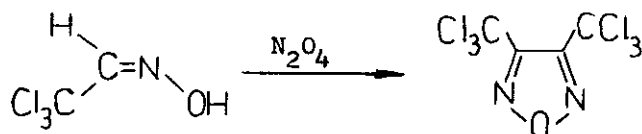
1,2,5-Thia- and selenadiazoles have been the subject of numerous publications,¹⁻⁸ while telluradiazoles, so far, are rather uncommon species⁹; the present review, a continuation of our former papers, concerning 1,2,5-thia- and selenadiazoles^{3,4,10} is dealing with 1,2,5-oxadiazoles i.e. furazans, having in view their syntheses, reactivity and physical properties.

Benzo-fused analogs and N-oxides (furoxans) of the above compounds, especially benzofuroxans, important synthons of biologically active quinoxaline-di-N-oxides¹¹⁻¹⁷ cover a large area of literature¹⁸⁻²⁰ and this topic is not included here.

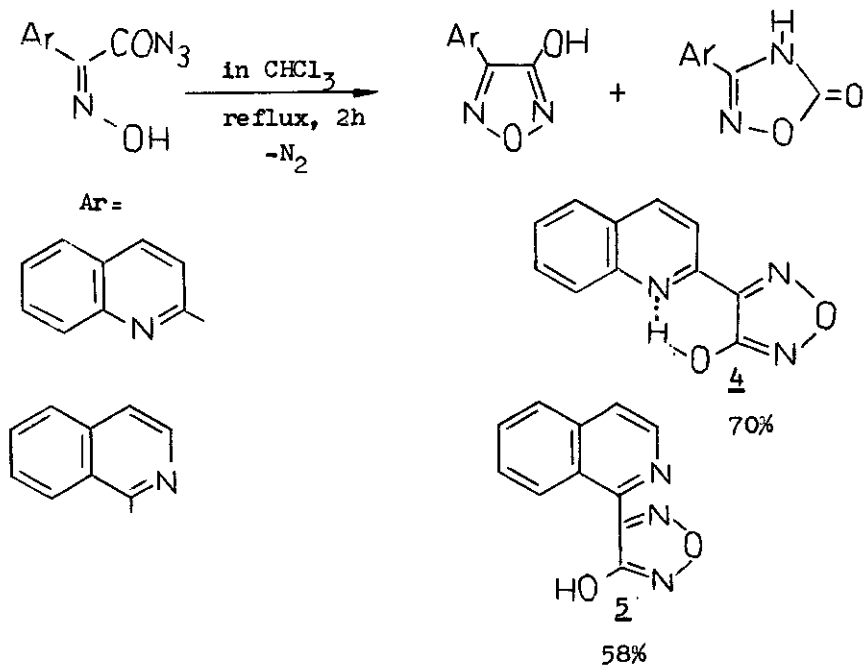
II. SYNTHESSES

Among recently described synthetic approaches of furazans, the following ones ought to be presented.

Z-Chloral oxime oxidized by nitrogen tetroxide gave way to 3,4-bis(trichloromethyl)furazan²¹, and dioxime 2 treated with thionyl chloride yielded 3, which could be hydrolyzed to hydroxymethylfurazan^{22,23}.



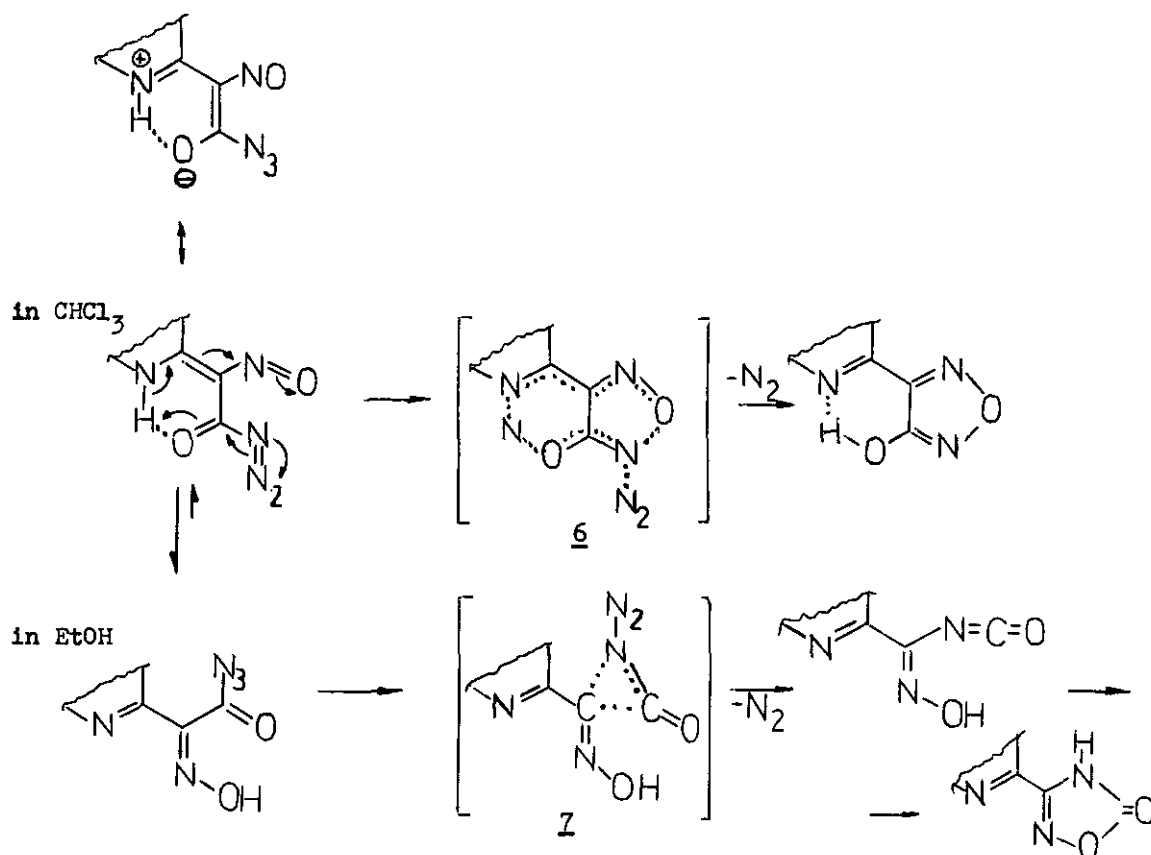
In the thermolysis of α -oximino- α -(N-heteroaryl)acetylazides in CHCl_3 medium, 4-substituted 3-hydroxyfurazans 4 and 5 have been obtained, along with trace amounts of 1,2,4-oxadiazole derivatives²⁴.



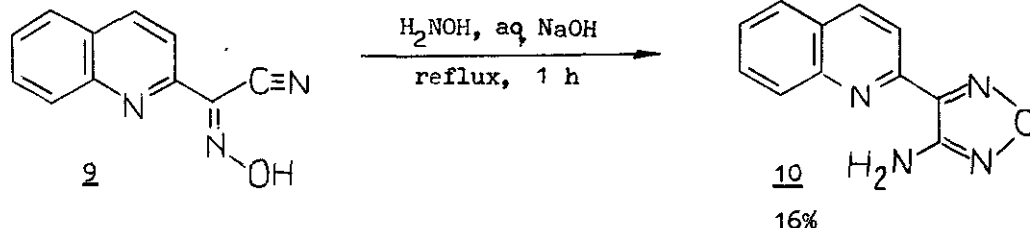
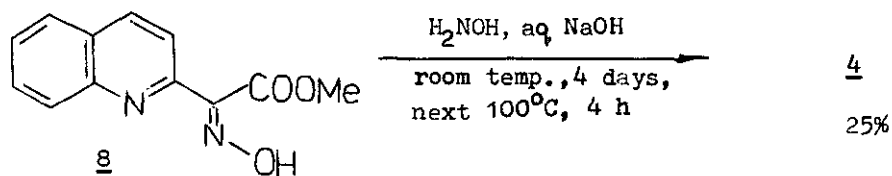
However when CHCl_3 was replaced by EtOH as solvent, 1,2,4-oxadiazole derivatives were found to be the major products. This fact can be explained by the difference in the stability of transition states in the solvent of low polarity, i.e. 6 in CHCl_3 and in the polar solvent, i.e. 7 in EtOH.

In CHCl_3 the less polar transition state 6 is more stable than the polar transition state 7, and therefore in CHCl_3 furazans are the major products. In EtOH however, where the polar transition state 7 is stabilized, the formation of 1,2,4-oxadiazoles is favoured.

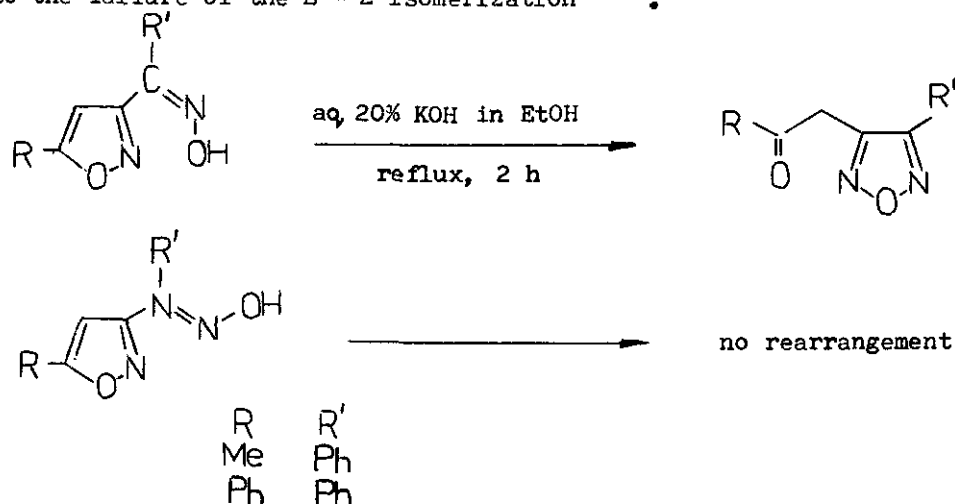
The plausible mechanism of the above reactions is as follows:



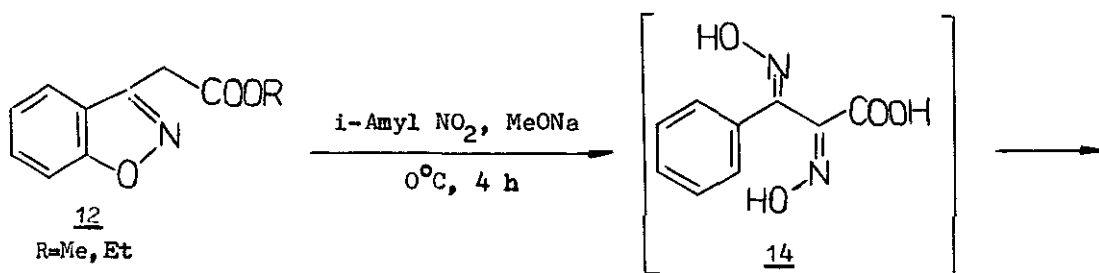
Hydroxyfurazan 4 can be also obtained in the reaction of oxime 8 with hydroxylamine and sodium hydroxide, while 9 under similar conditions affords the amino derivative 10²⁴.

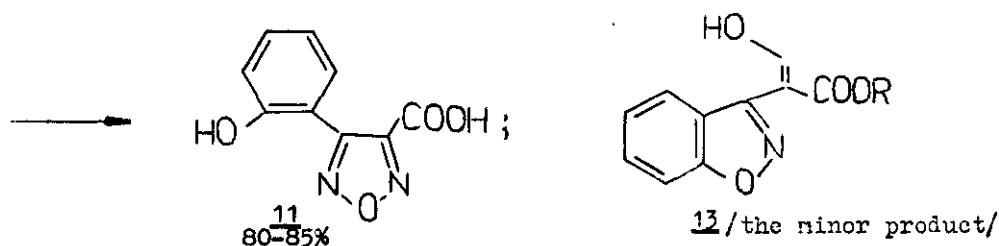


Z-Oximes of 3-acylisoxazoles can rearrange into furazans in the presence of base, and E-oximes do not rearrange under these conditions, this fact being probably due to the failure of the E - Z isomerization²⁵⁻²⁷.

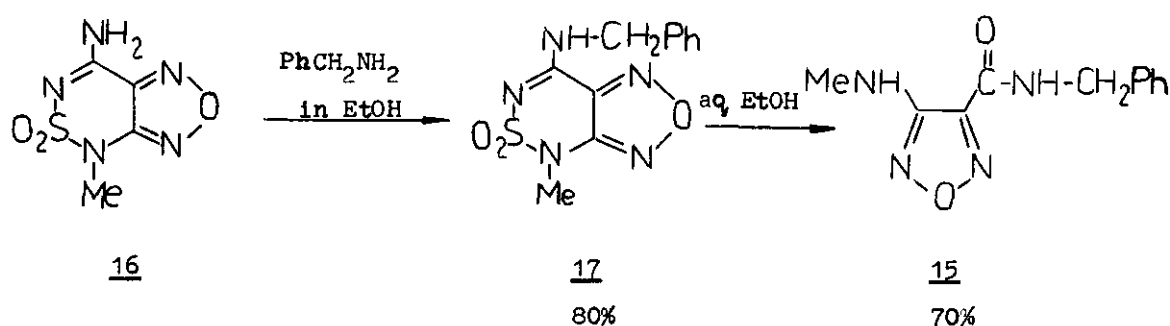


The furazancarboxylic acid 11 was synthesized by reacting the ester 12 and iso-amyl nitrite in the presence of sodium methylate, the minor product being benzoisoxazole 13. The reaction proceeds via the dioxime 14 intermediate^{28,29}.





Aminofurazancarboxamide 15 can be obtained by treatment of 16 with benzylamine and the subsequent hydrolysis of the formed 17³⁰.

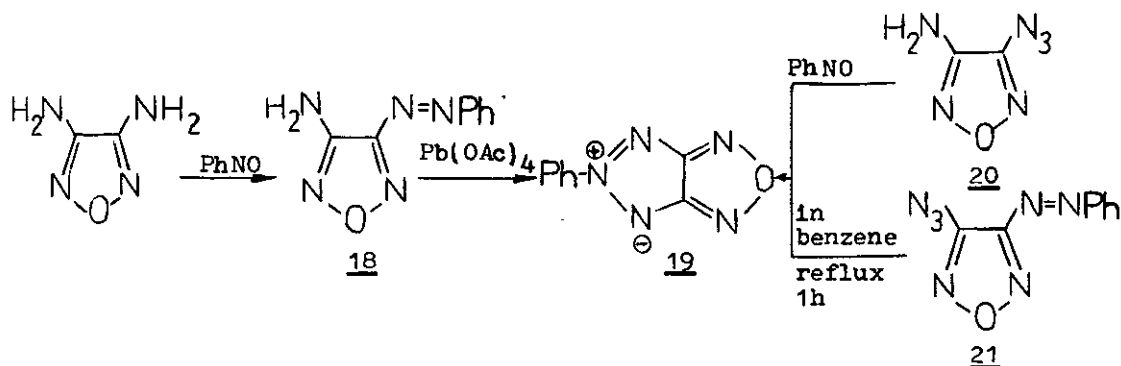


In the similar way the following derivatives of 15 were synthesized.

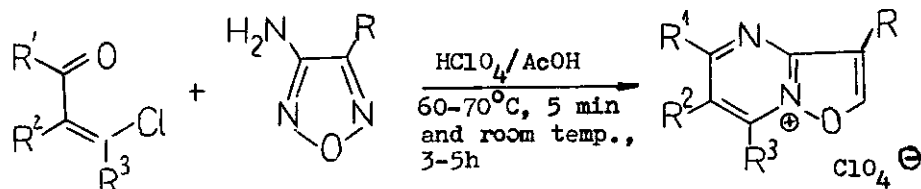


Fused furazans are an interesting class of heterocycles, and an attention ought to be paid to some synthetic approaches of these systems. In the reaction of 3,4-diaminofurazan with nitrosobenzene, the azofurazan 18 is formed. This compound was converted by the action of $\text{Pb}(\text{OAc})_4$ into a relatively unknown meso-ionic triazolofurazan 19. The reaction proceeds via the nitrene intermediate⁸.

Triazolofurazan 19 can be also obtained directly from 20 by its treatment with nitrosobenzene³¹, or by thermolysis of 21; furazanoazides are serving here as nitrene generators^{32,33}.



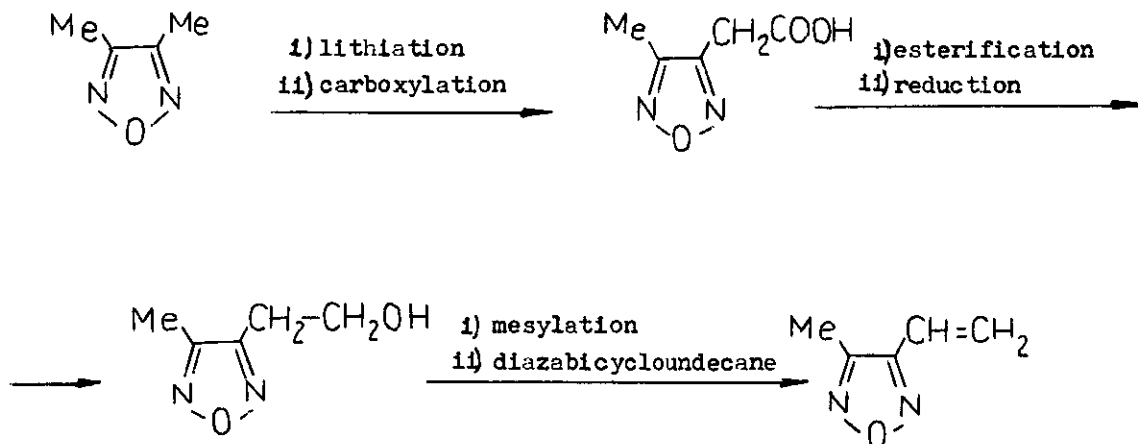
Furazanopyrimidinium salts containing bridgehead nitrogen atom are rather new species, too. An example of the synthesis of such heterocycles is the reaction of 4-substituted 3-aminofurazans with β -chlorovinylcarbonyl compounds in the acidic medium³⁴.



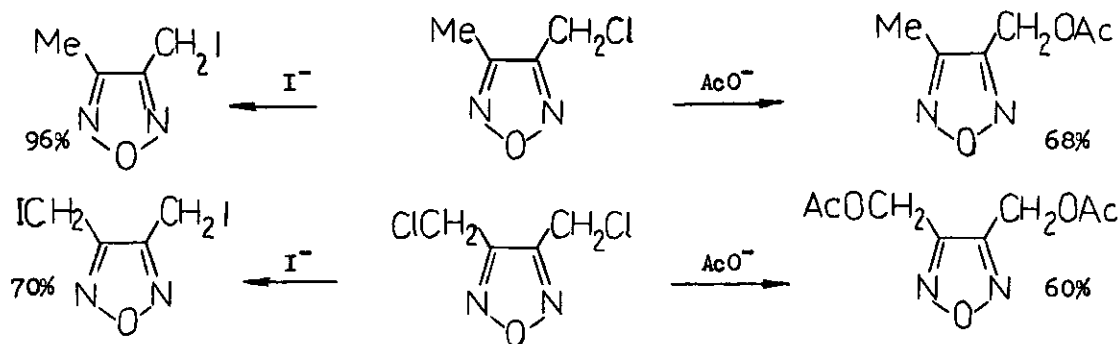
R	R ¹	R ²	R ³	yield
Me	Me	H	Me	73%
Me	Ph	H	Me	70%
Ph	Me	H	Me	76%
Ph	H	Me	Me	82%

III. CHEMICAL REACTIVITY

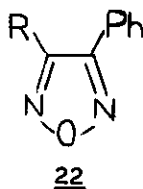
In the investigation of chemical reactivity of furazans, 3,4-dimethylfurazan was converted into 3-methyl-4-vinylfurazan³⁵:



The following nucleophilic substitution reactions of chloromethylfurazans were performed³⁶:

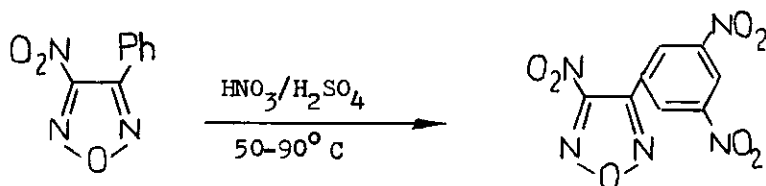


As the example of electrophilic substitution, the nitration of 22 was accomplished³⁷.

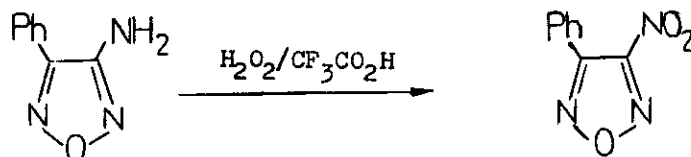


R = H, Me, Ph, NO₂, COOH

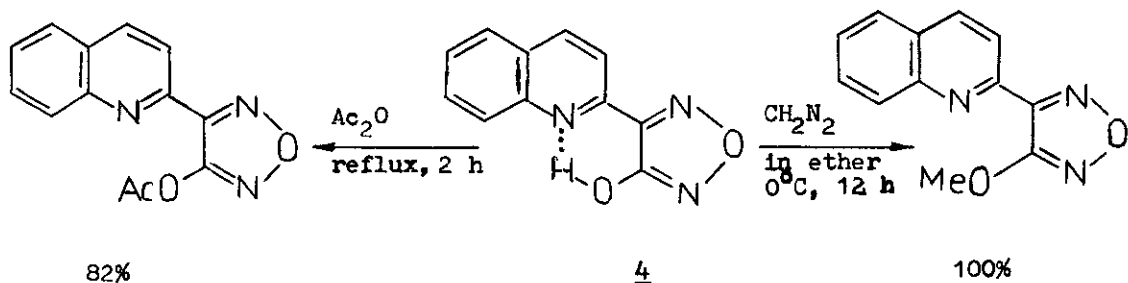
The furazanyl substituent directs in *ortho* and *para* positions, however, in the presence of electron-withdrawing substituents this effect decreases, and the meta substitution takes place. E.g.:



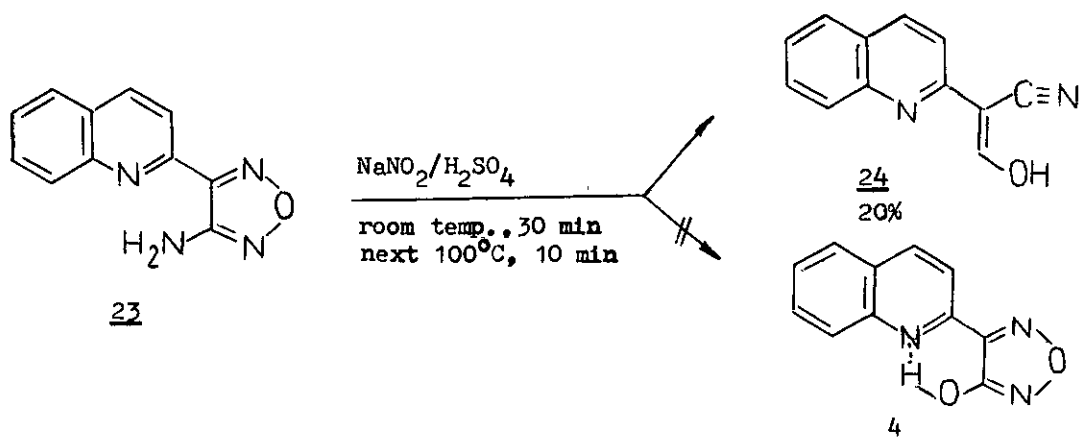
The oxidation of 3-amino-4-phenylfuran with an excess of 85% H_2O_2 in CF_3COOH affords 3-phenyl-4-nitrofuran^{38,39}.



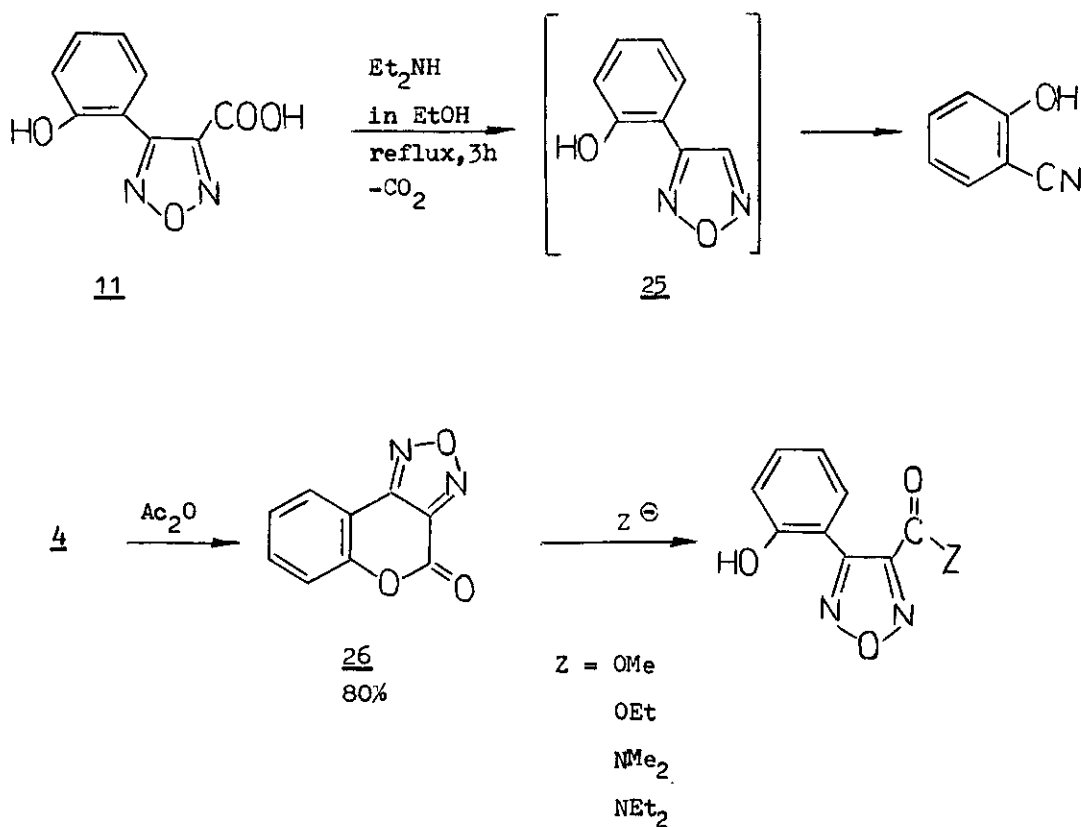
4-Substituted 3-hydroxyfuran 4 undergoes acetylation and methylation to give the corresponding derivatives²⁴:



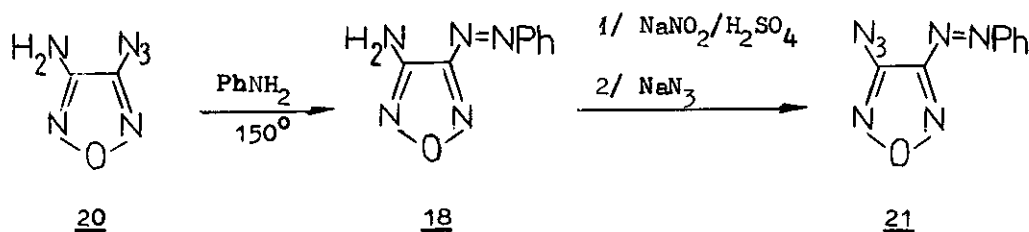
When 23 was treated with nitrous acid, 24 resulting from the ring fission was obtained instead of the expected hydroxy derivative 4²⁴.



The decarboxylation of the furazancarboxylic acid 11 in diethylamine gave 2-hydroxybenzonitrile, presumably via the intermediate 25; and with dehydrating agents, e.g. with Ac_2O the lactone 26 was formed. This compound easily undergoes ring cleavage by nucleophilic reagents to yield the corresponding derivatives of 11 ²⁸.

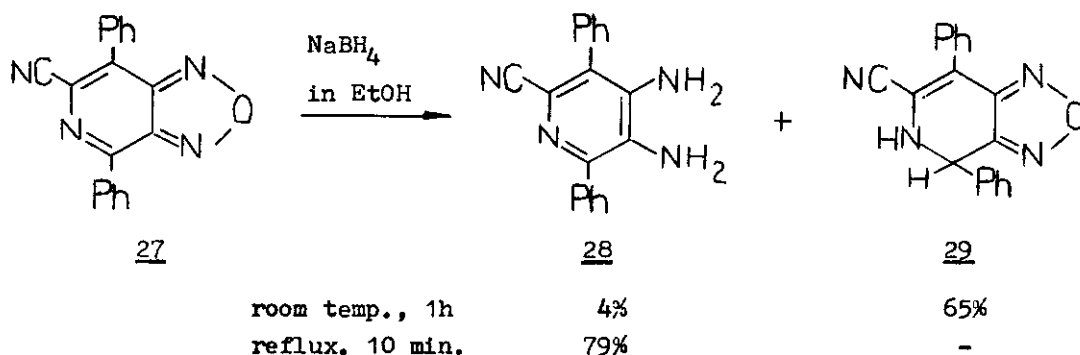


The reaction of 20 with aniline results in the azo compound 18, which can be converted into azide 21³²:

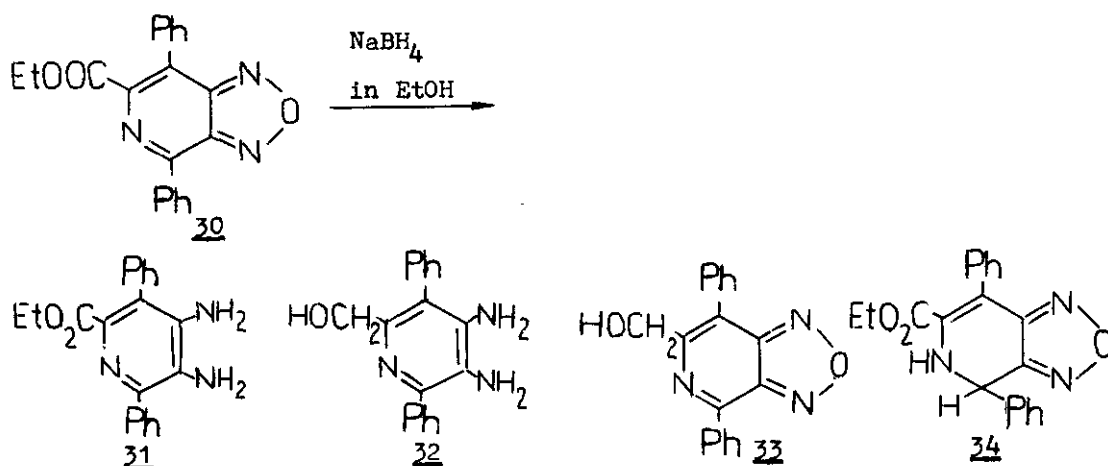


Among reactions of fused furazans, the following ones ought to be mentioned. Investigating the reactivity of pyridofurazans, their sodium borohydride reduction was performed. Depending upon the reaction conditions different products were obtained⁴⁰.

For example, the reduction of pyridofurazan 27 leads to diaminopyridine 28 and dihydropyridofurazan 29, in the ratio relative to the reaction temperature:



In the same procedure 30 can afford four products: at room temperature derivatives 32 and 34 are formed, while in boiling ethanol, in the first step the furazan ring reduction, resulting in 31 and 32, takes place.



room { 1 h
temp. { 18 h

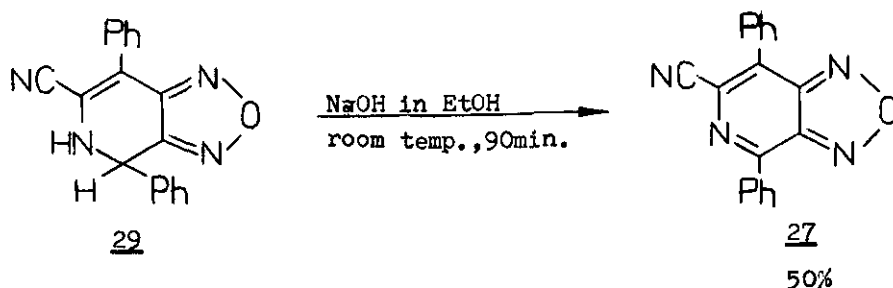
21%

re- { 1 h 39%
flux { 12 h

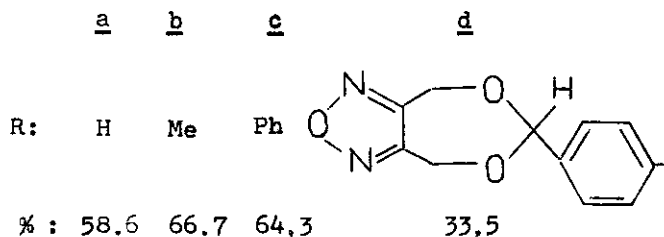
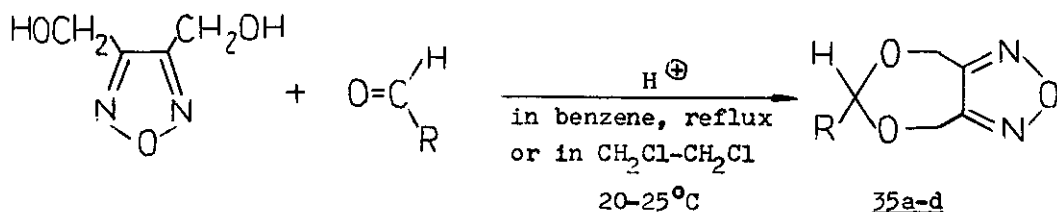
sole product

41%

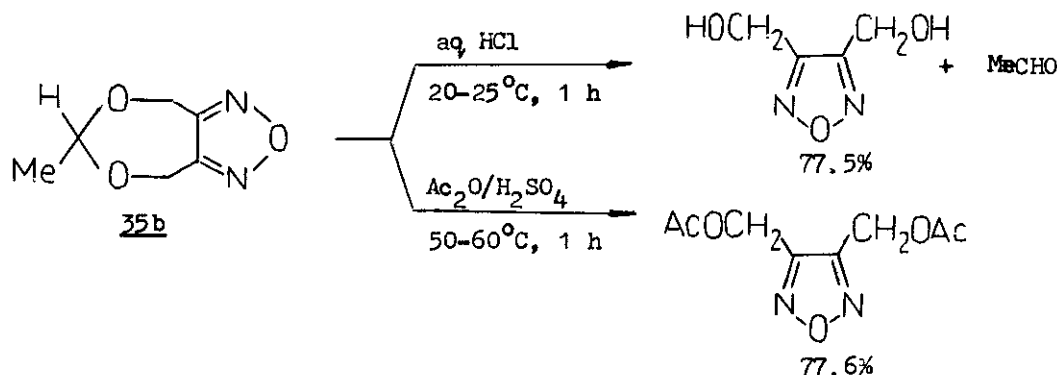
The obtained dihydropyridofurazans were oxidized with sodium hydroxide to afford the corresponding pyridofurazans⁴⁰, e.g.:



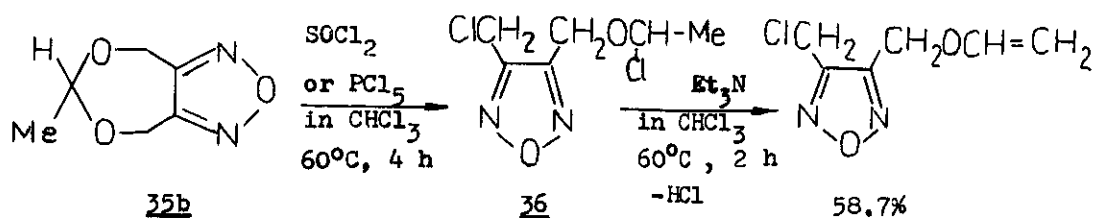
So far, very little is known on furazans fused with 1,3-dioxepane ring. For the synthesis of these heterocycles 3,4-dihydroxymethylfurazan can be used; this compound undergoes smoothly the reaction with aldehydes to afford 1,3-dioxepanes 35a-d, while with acetone the reaction is more difficult, the yield being only 10%⁴¹.



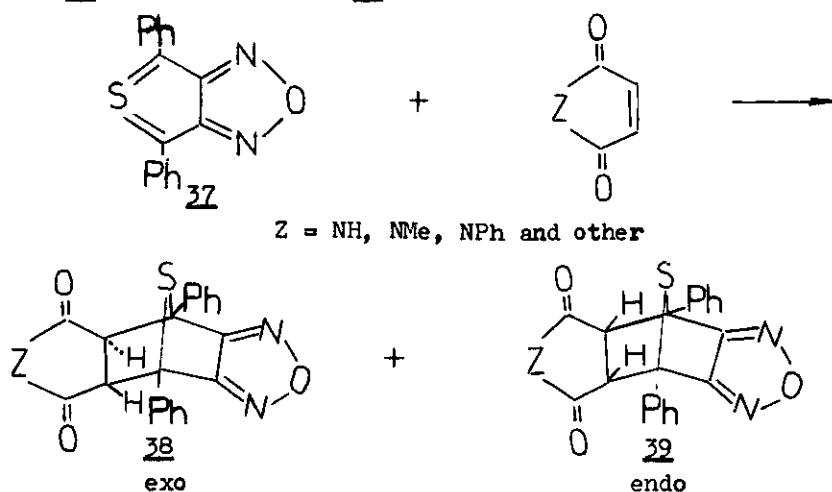
When hydrolyzed, 35b readily gives back the starting 3,4-dihydroxymethylfuran and acetaldehyde, and with acetic anhydride 3,4-diacetoxymethylfuran was obtained.



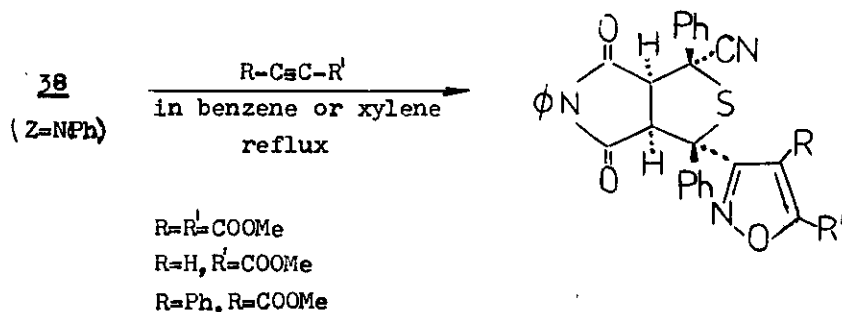
In the reaction of 35b with thionyl chloride or phosphorus pentachloride, the dioxepane ring is opened to afford the ether 36, which by HCl elimination can be converted into its vinyl derivative⁴¹.



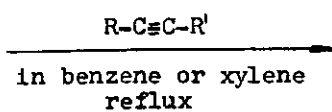
Studying the reactivity of thienofurazans, the cycloaddition of **37** with maleimides was accomplished; this reaction leads to strained thianorbormane systems: exo-adducts **38** and endo-adducts **39**⁴².



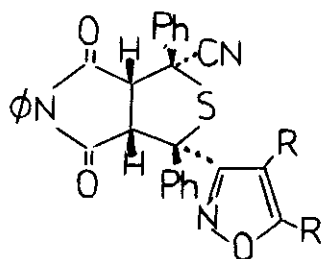
The thermolysis of **38** and **39** under mild conditions resulted in the furazan ring cleavage to nitrile and nitrile oxide moieties, which could be trapped as 1,3-cycloadducts by acetylenes or olefins⁴³⁻⁴⁵.



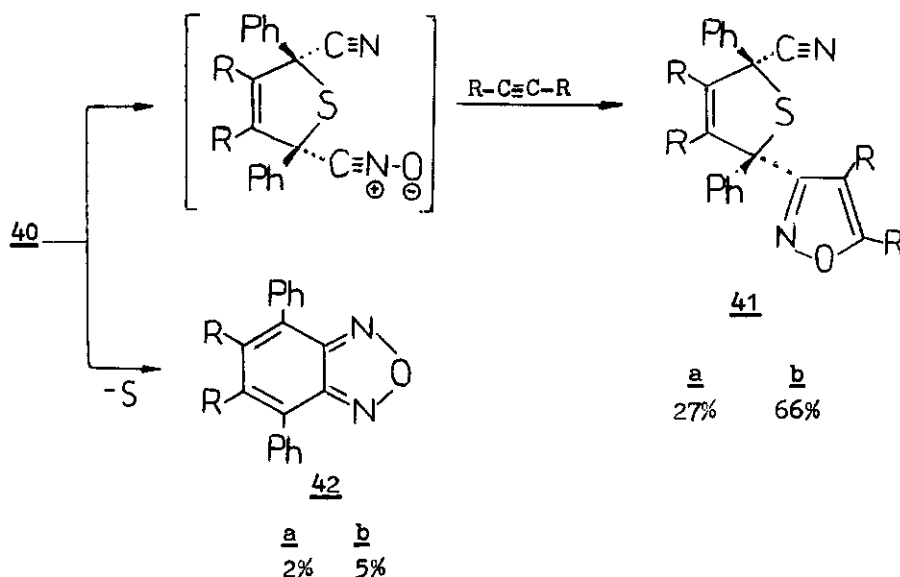
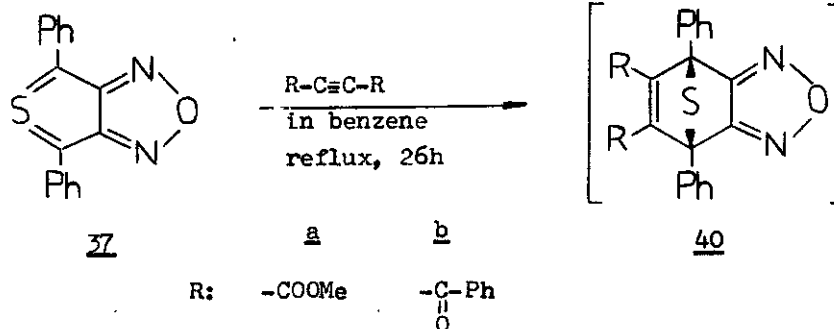
39
(Z = NPh)



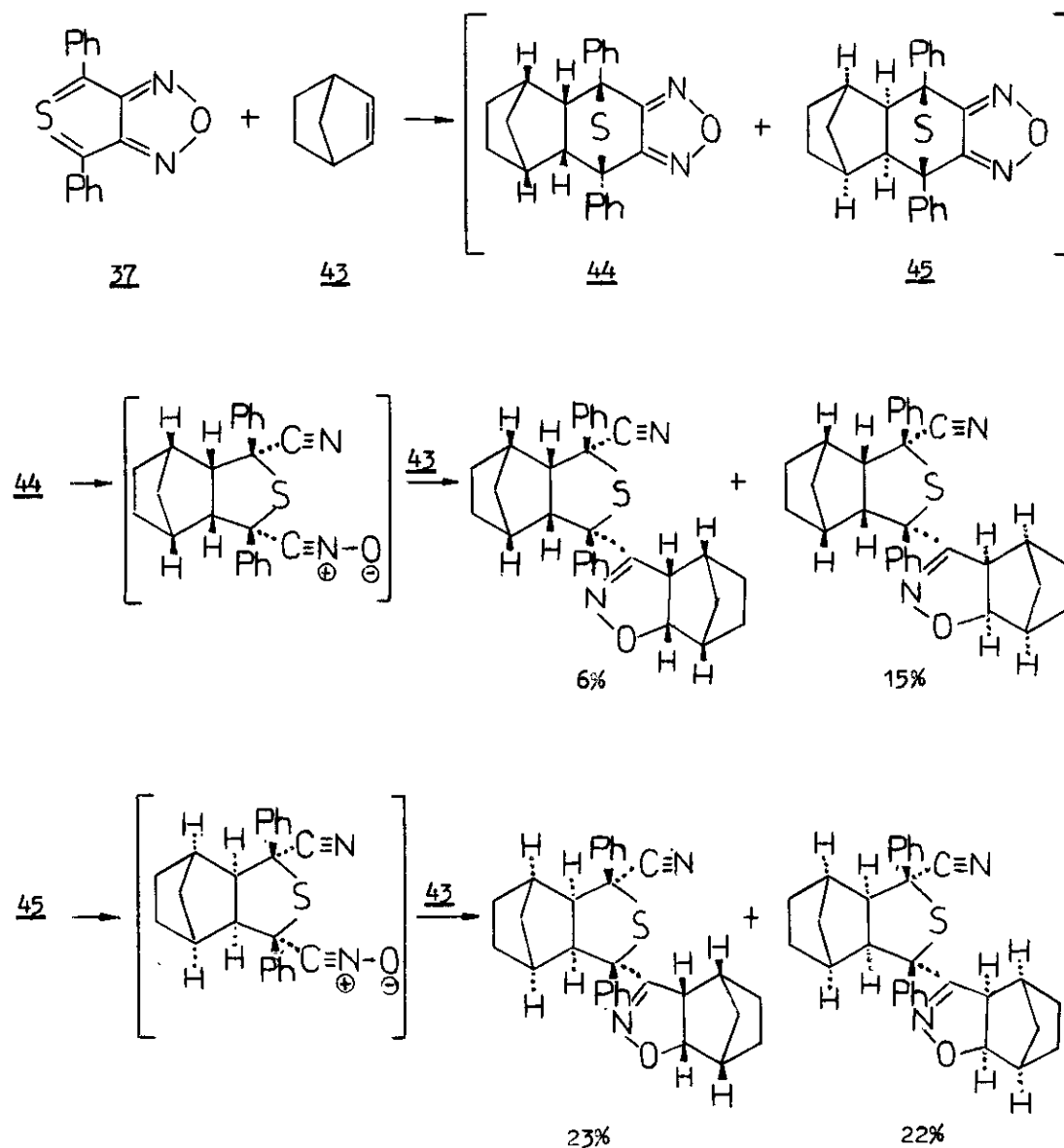
R=R'=COOMe
R=H, R'=COOMe
R=Ph, R'=COOMe



However, the reaction of 37 with acetylenes, instead of the expected highly strained thianorbornene 40, leads to 41 and 42. These compounds are formed via the intermediate 40; the furazan ring opening of 40 and the subsequent cycloaddition reaction with the second dipolarophile molecule lead to the 1:2 adduct 41, while desulfurization of 40 under the reaction conditions gives way to the minor product 42⁴⁶.

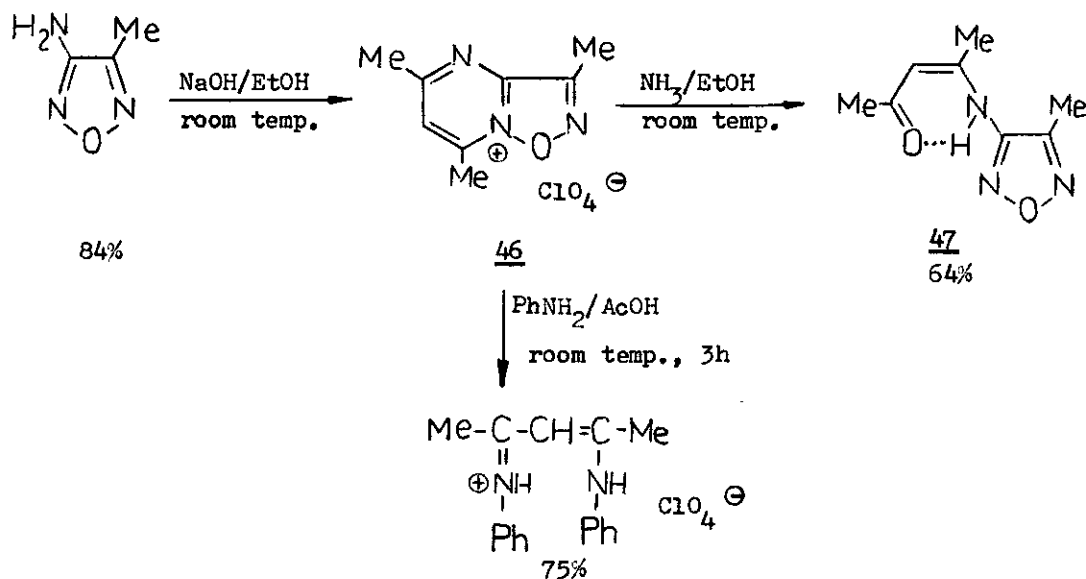


In the reaction of 37 with norbornene 43, as with acetylenes, no strained cycloadducts 44 and 45 were detected; although not formed, they are believed to be intermediates in the formation of four stereoisomeric 1:2 adducts, resulting in the following way⁴⁷:



In the study of furazanopyrimidinium salts their reactions with nucleophiles were performed.

These reagents open the pyrimidine ring; e.g. 46, treated with ethanolic NaOH yields 3-amino-4-methylfuran, and with ethanolic NH_3 the derivative 47 is formed. Action of aniline in acetic acid converts 46 into acetylacetone dianil perchlorate³⁴.



IV. PHYSICAL PROPERTIES

Among physicochemical investigations of furazans an attention ought to be paid to ^1H and ^{13}C NMR spectroscopy of 3,4-dimethylfuran^{48,49}, ^{13}C NMR spectroscopy of 4-substituted 3-phenylfurazans⁵⁰, as well as the ^1H NMR spectroscopy of furazano-pyrimidinium salts of the type 46³⁴. In the study of furazancarboxylic acid 11 derivatives, the X-ray crystal structure analysis of its methyl ester was performed²⁸.

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