THE CHEMISTRY OF FURAZANS

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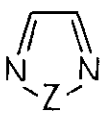
Abstract — Syntheses, chemical reactivity and physical properties of furazans are presented.

I. INTRODUCTION

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



Z = O, S, Se, Te

1

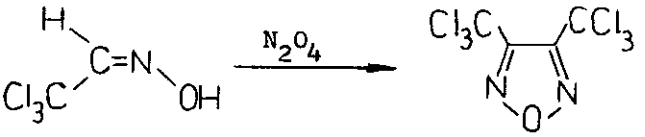
1,2,5-Thia- and selenadiazoles have been the subject of numerous publications,[1-8] while telluradiazoles, so far, are rather uncommon species[9]; the present review, a continuation of our former papers, concerning 1,2,5-thia- and selenadiazoles[3,4,10] is dealing with 1,2,5-oxadiazoles i.e. furazans, having in view their syntheses, reactivity and physical properties.

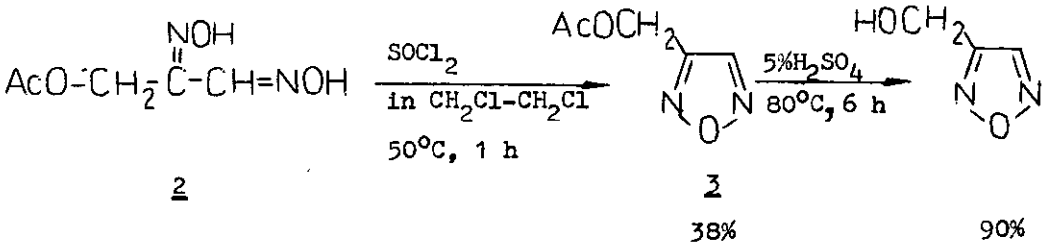
Benzo-fused analogs and N-oxides (furoxans) of the above compounds, especially benzofuroxans, important synthons of biologically active quinoxaline-di-N-oxides[11-17] cover a large area of literature[18-20] and this topic is not included here.

II. SYNTHESES

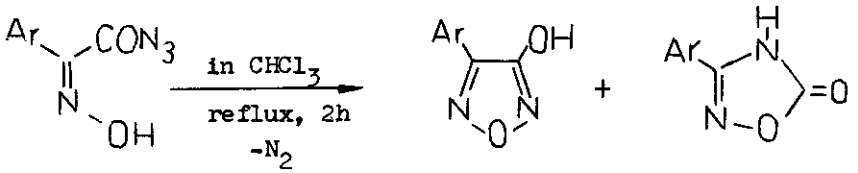
Among recently described synthetic approaches of furazans, the following ones ought to be presented.

Z-Chloral oxime oxidized by nitrogen tetroxide gave way to 3,4-bis(trichloromethyl)furazan[21], and dioxime 2 treated with thionyl chloride yielded 3, which could be hydrolyzed to hydroxymethylfurazan[22,23].

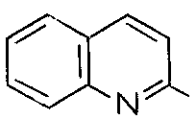


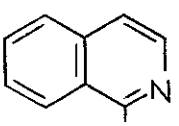


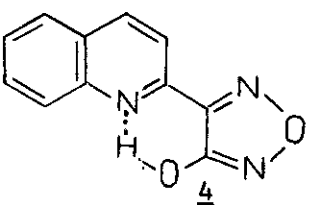
In the thermolysis of α-oximino-α-(N-heteroaryl)acetylazides in $CHCl_3$ medium, 4-substituted 3-hydroxyfurazans 4 and 5 have been obtained, along with trace amounts of 1,2,4-oxadiazole derivatives[24].



Ar =

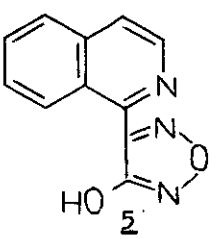






4

70%



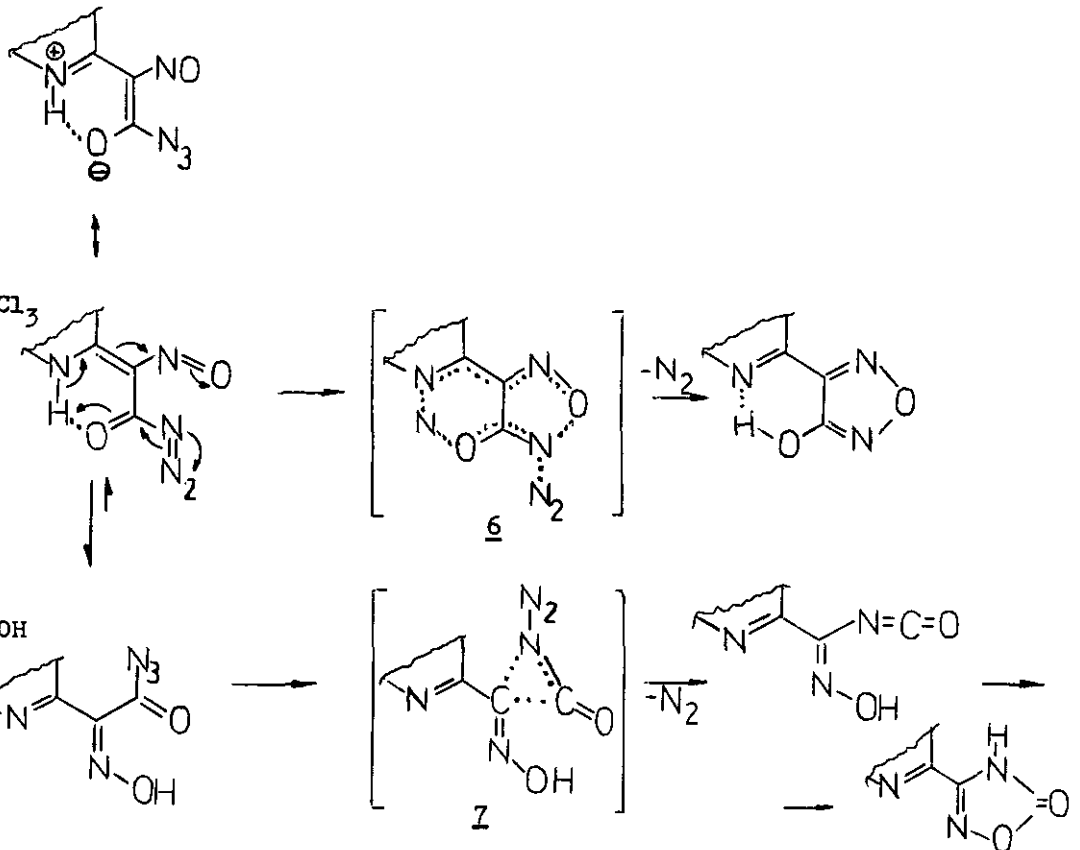
5

58%

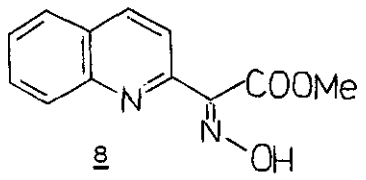
However when $CHCl_3$ was replaced by EtOH as solvent, 1,2,4-oxadiazole derivatives were found to be the major products. This fact can be explained by the difference in the stability of transition states in the solvent of low polarity, i.e. 6 in $CHCl_3$ and in the polar solvent, i.e. 7 in EtOH.

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 10[24].



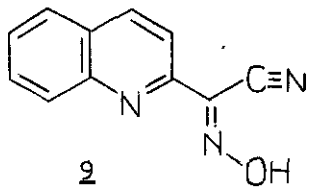
8

H_2NOH, aq. NaOH

room temp., 4 days, next 100°C, 4 h

4

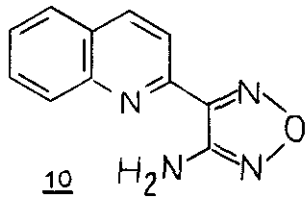
25%



9

H_2NOH, aq. NaOH

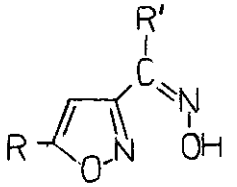
reflux, 1 h



10

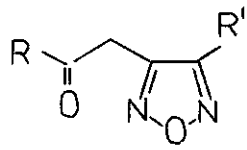
16%

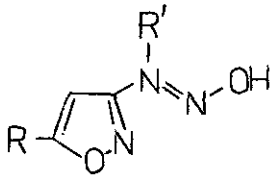
Z-Oximes of 3-acylisoxazoles can rearrange into furazans in the presence of base, and E-oximes do not rearrange under these conditions, this fact being probably due to the failure of the E – Z isomerization[25-27].



aq. 20% KOH in EtOH

reflux, 2 h

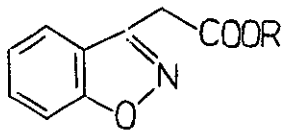




no rearrangement

R	R'
Me	Ph
Ph	Ph

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].

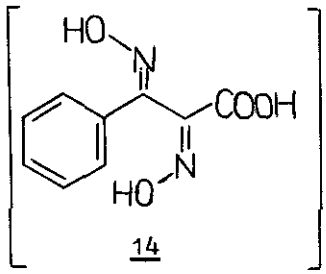


12

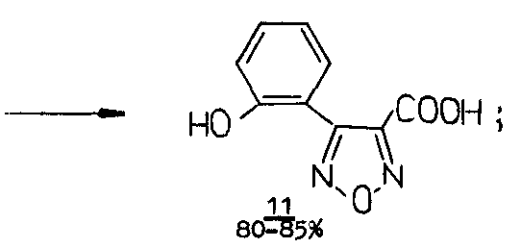
R=Me, Et

i-Amyl NO_2, MeONa

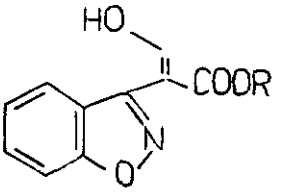
0°C, 4 h



14

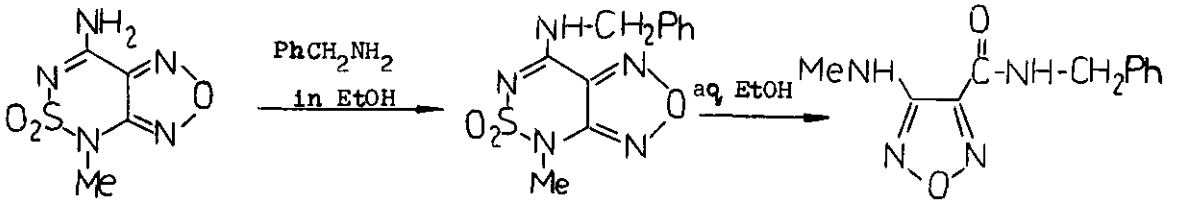


11
80–85%



13 /the minor product/

Aminofurazancarboxamide 15 can be obtained by treatment of 16 with benzylamine and the subsequent hydrolysis of the formed 17[30].

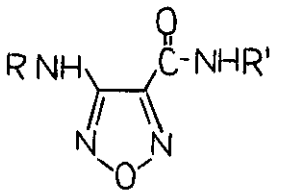


16

17
80%

15
70%

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

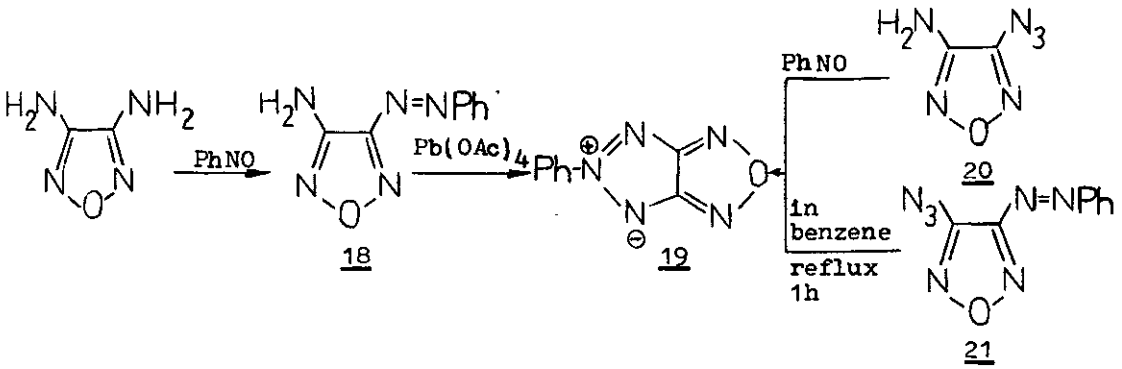


R = H, alkyl

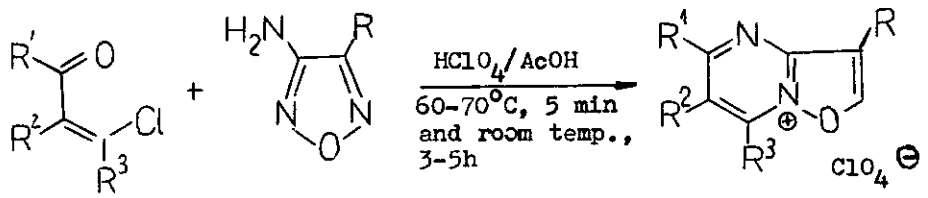
R' = alkyl, aryl, amino

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 $Pb(OAc)_4$ into a relatively unknown mesoionic triazolofurazan 19. The reaction proceeds via the nitrene intermediate[8].

Triazolofurazan 19 can be also obtained directly from 20 by its treatment with nitrosobenzene[31], or by thermolysis of 21; furazanoazides are serving here as nitrene generators[32,33].



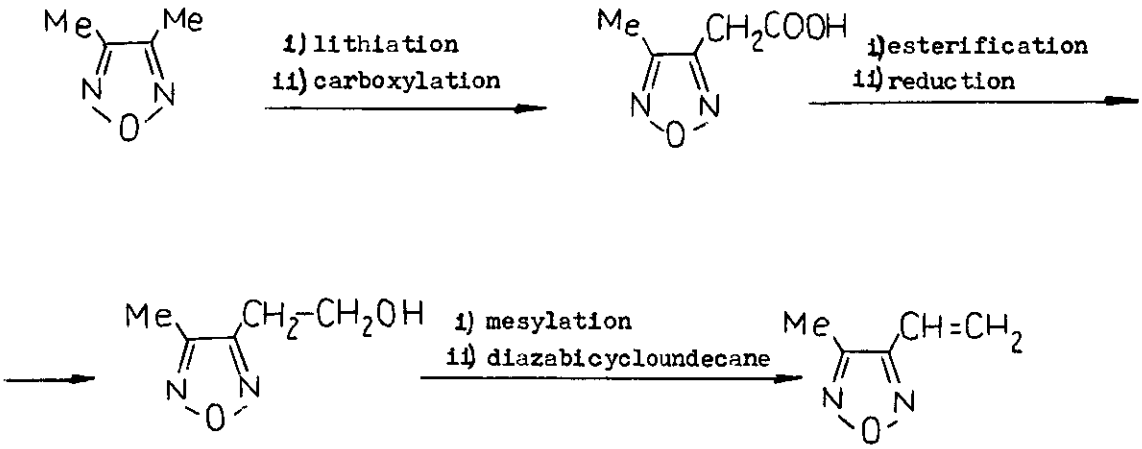
Furazanopyrimidinium salts containing bridgehead nitrogen atom are rather new species, too. An example of the synthesis of such heterocycles is the reaction of 4-substituted 3-aminofurazans with β-chlorovinylcarbonyl compounds in the acidic medium[34].



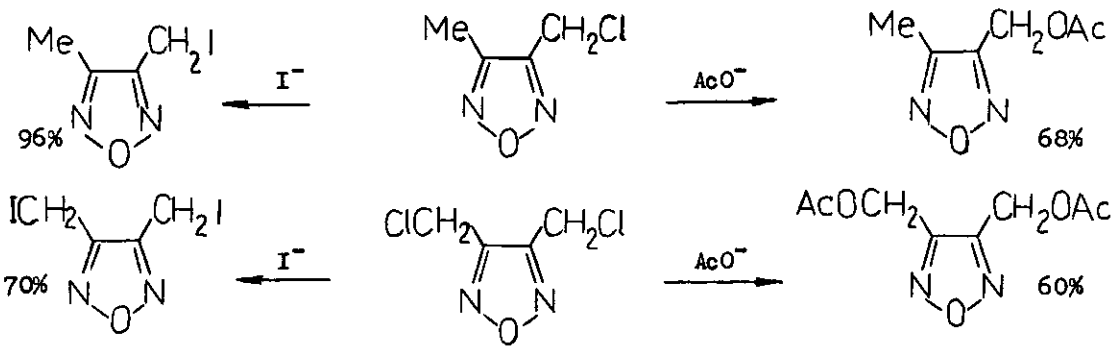
R	R^1	R^2	R^3	yield
Me	Me	H	Me	73%
Me	Ph	H	Me	70%
Ph	Me	H	Me	76%
Ph	H	Me	Me	82%

III. CHEMICAL REACTIVITY

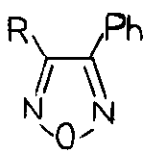
In the investigation of chemical reactivity of furazans, 3,4-dimethylfurazan was converted into 3-methyl-4-vinylfurazan[35]:



The following nucleophilic substitution reactions of chloromethylfurazans were performed[36]:



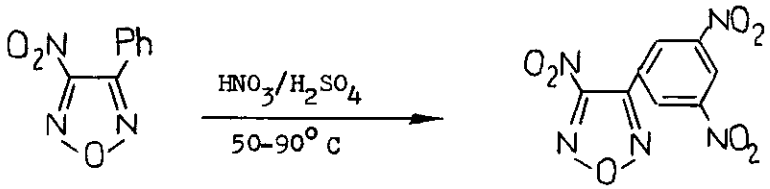
As the example of electrophilic substitution, the nitration of 22 was accomplished[37].



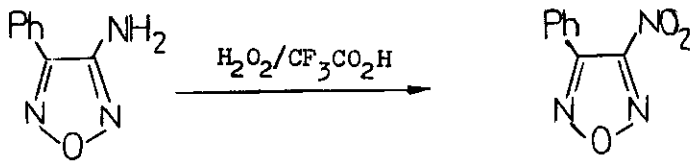
22

R = H, Me, Ph, NO_2, COOH

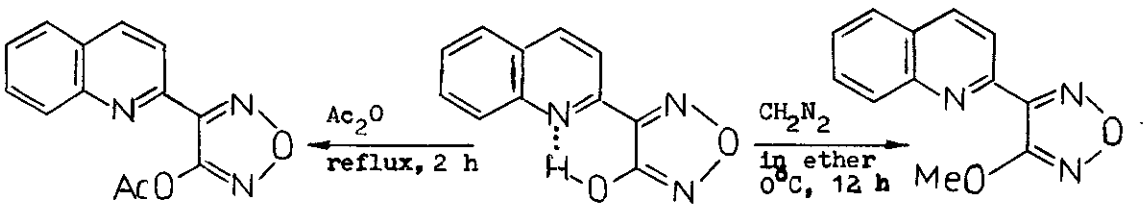
The furazanyl substituent directs in ortho and para positions, however, in the presence of electron-withdrawing substituents this effect decreases, and the meta substitution takes place. E.g.:



The oxidation of 3-amino-4-phenylfurazan with an excess of 85% H_2O_2 in CF_3COOH affords 3-phenyl-4-nitrofurazan[38,39].

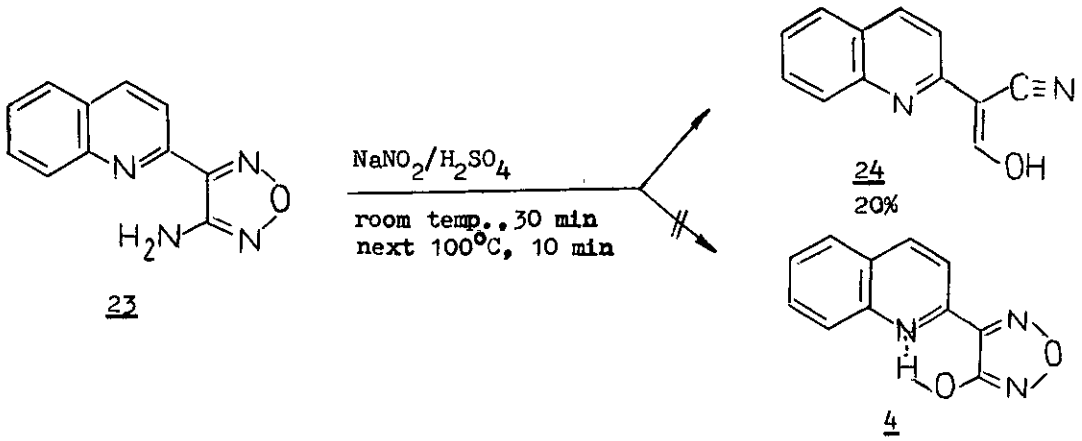


4-Substituted 3-hydroxyfurazan 4 undergoes acetylation and methylation to give the corresponding derivatives[24]:



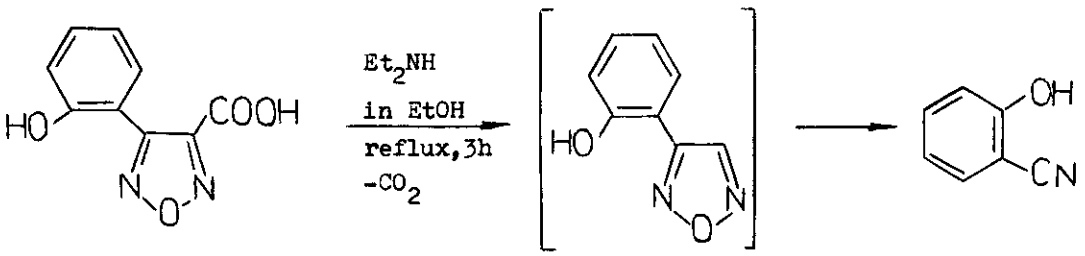
82% 4 100%

When 23 was treated with nitrous acid, 24 resulting from the ring fission was obtained instead of the expected hydroxy derivative 4[24].

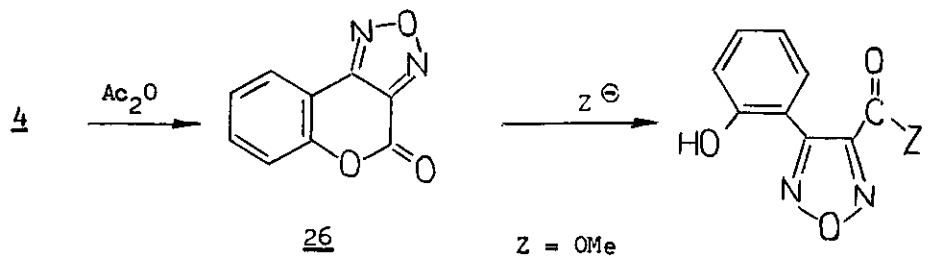


23

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].



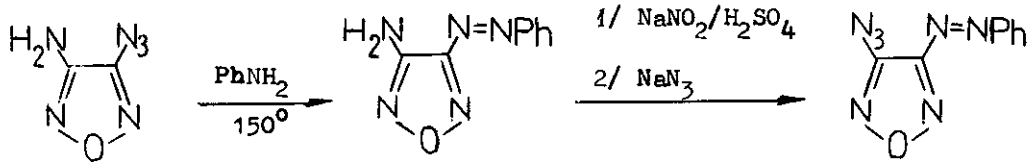
11 25



26
80%

Z = OMe
OEt
NMe_2
NEt_2

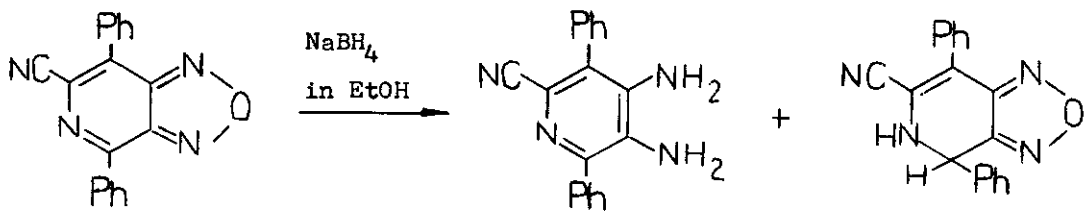
The reaction of 20 with aniline results in the azo compound 18, which can be converted into azide 21[32]:



20 18 21

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 obtained[40].

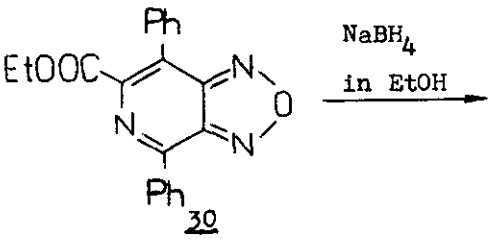
For example, the reduction of pyridofurazan 27 leads to diaminopyridine 28 and dihydropyridofurazan 29, in the ratio relative to the reaction temperature:



27 28 29

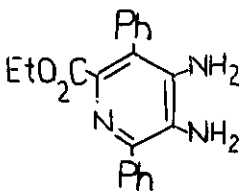
room temp., 1h	4%	65%
reflux, 10 min.	79%	-

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.

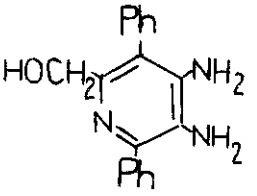


30

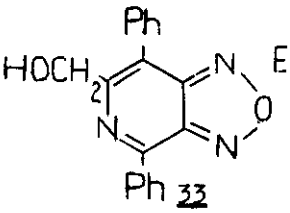
$NaBH_4$ in EtOH



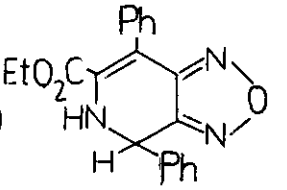
31



32



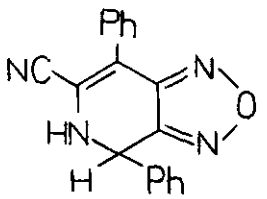
33



34

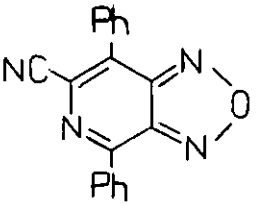
room temp.	1 h		41%
	18 h	21%	
reflux	1 h	39%	
	12 h	sole product	

The obtained dihydropyridofurazans were oxidized with sodium hydroxide to afford the corresponding pyridofurazans[40], e.g.:



29

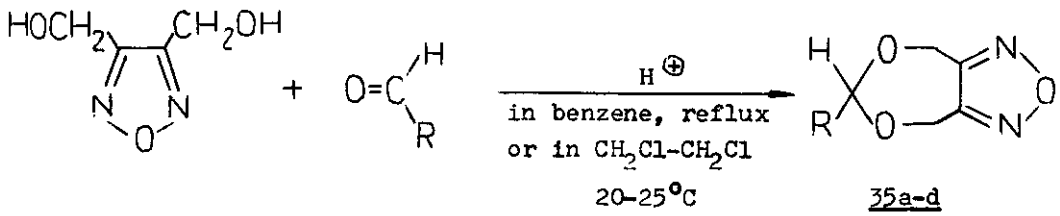
NaOH in EtOH
room temp., 90min.

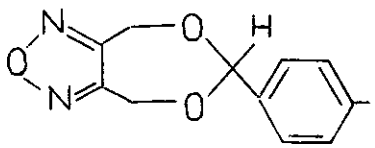


27

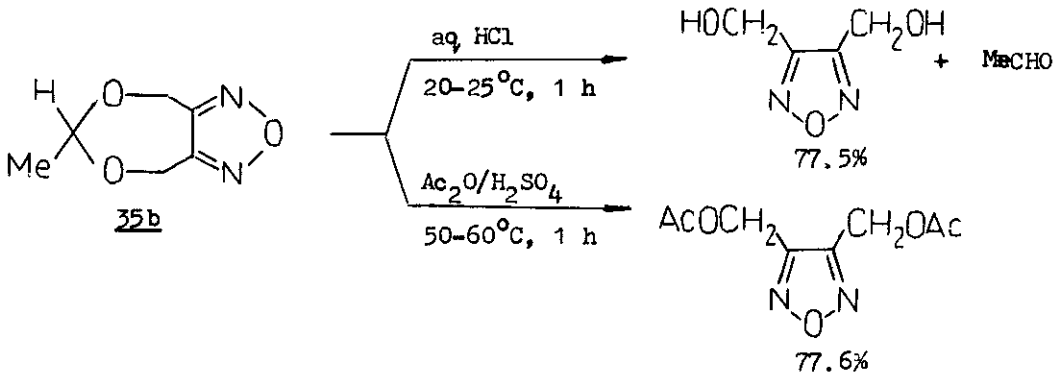
50%

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].

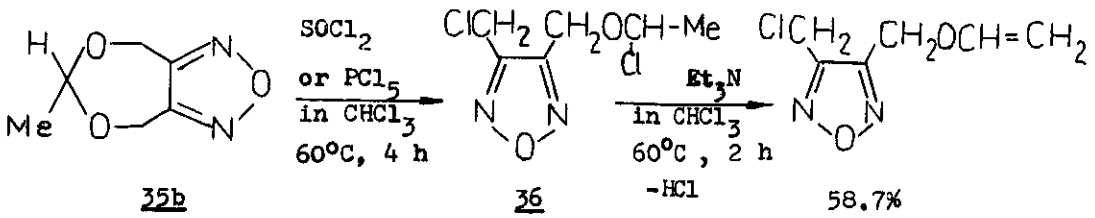


	a	b	c	d
R:	H	Me	Ph	
yield % :	58.6	66.7	64,3	33.5

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

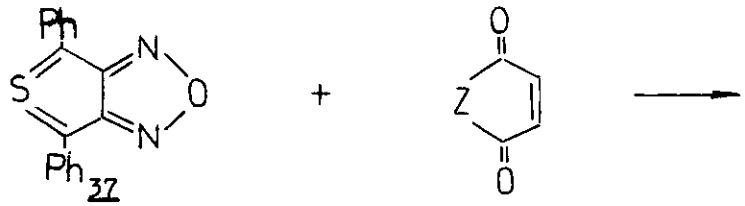


In the reaction of 35b with thionyl chloride or phosphorus pentachloride, the dioxepane ring is opened to afford the ether 36, which by HCl elimination can be converted into its vinyl derivative[41].



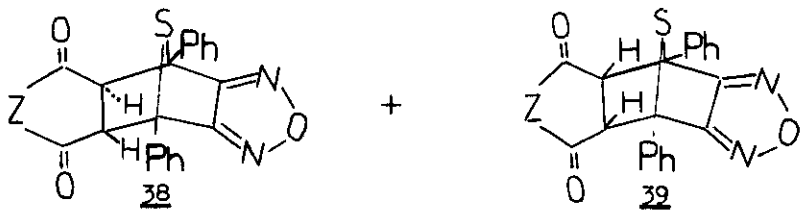
35b 36

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



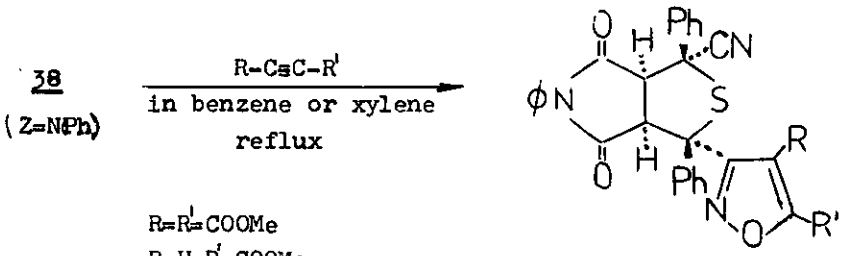
37

Z = NH, NMe, NPh and other

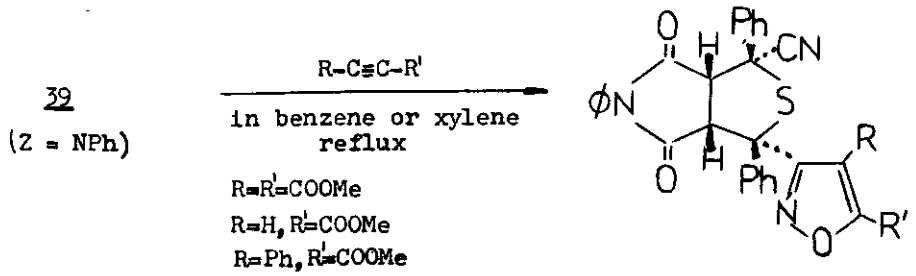


38 exo 39 endo

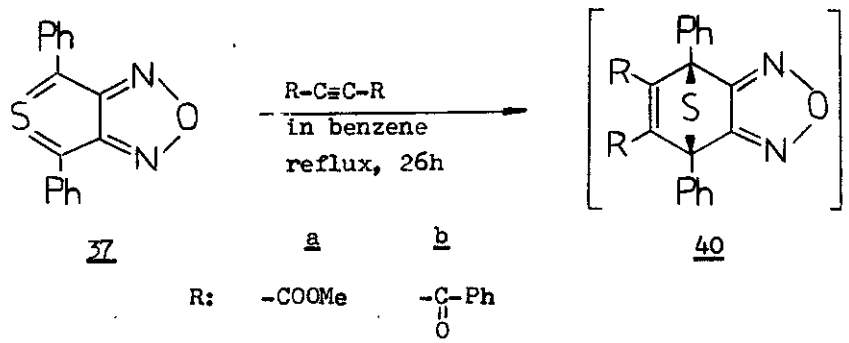
The thermolysis of 38 and 39 under mild conditions resulted in the furazan ring cleavage to nitrile and nitrile oxide moieties, which could be trapped as 1,3-cycloadducts by acetylenes or olefins[43-45].



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



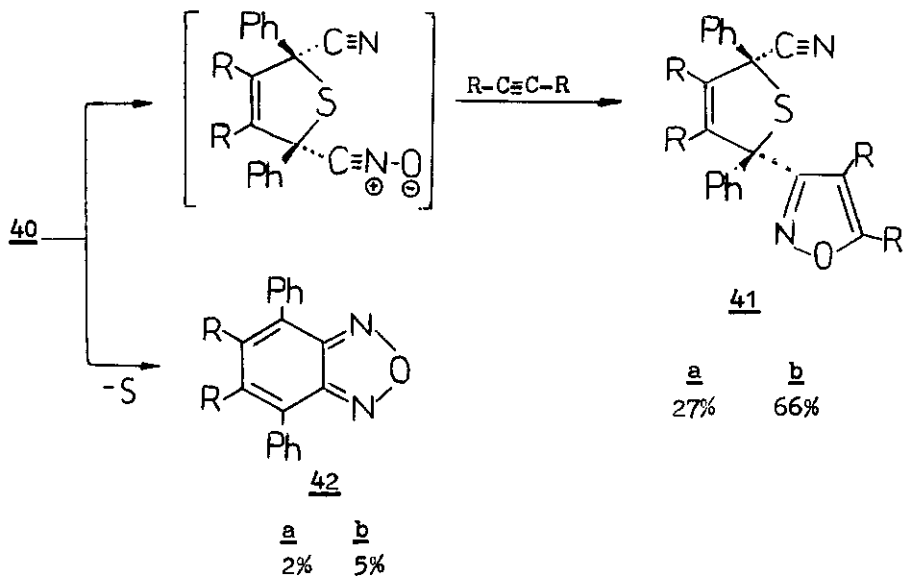
However, the reaction of 37 with acetylenes, instead of the expected highly strained **thianorbornene** 40, leads to 41 and 42. These compounds are formed via the intermediate 40; the furazan **ring** opening of 40 and the subsequent cycloaddition reaction with the second dipolarophile molecule lead to the 1:2 adduct 41, while desulfurization of 40 under the reaction conditions gives way to the minor product 42[46].



37 40

a b

R: -COOMe -C(=O)-Ph



41

a b

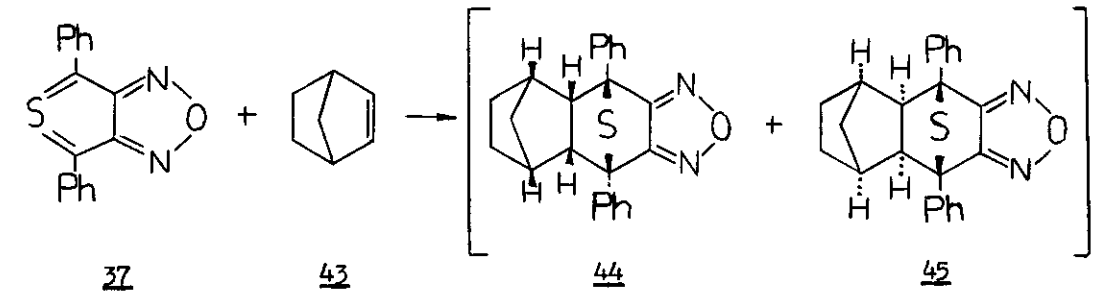
27% 66%

42

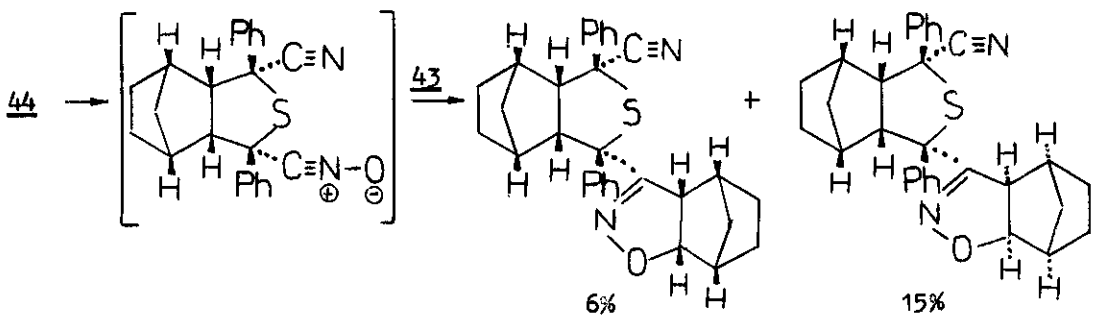
a b

2% 5%

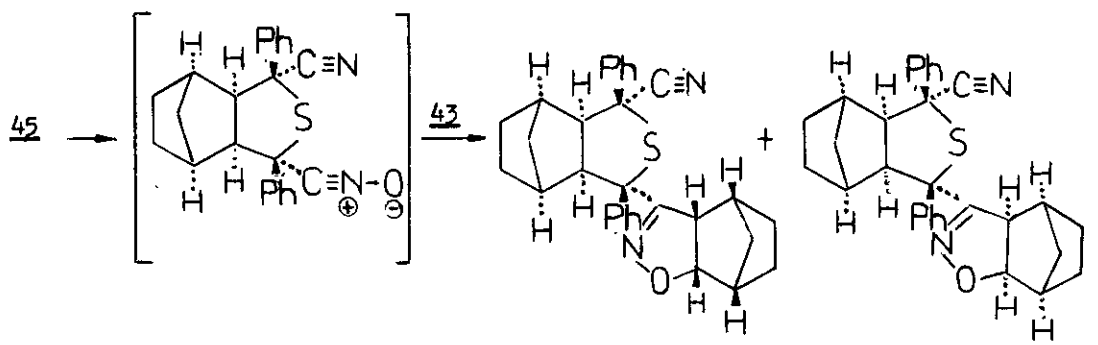
In the reaction of 37 with norbornene 43, as with acetylenes, no strained cycloadducts 44 and 45 were detected; although not formed, they are believed to be intermediates in the formation of four stereoisomeric 1:2 adducts, resulting in the following way[47]:



37 43 44 45



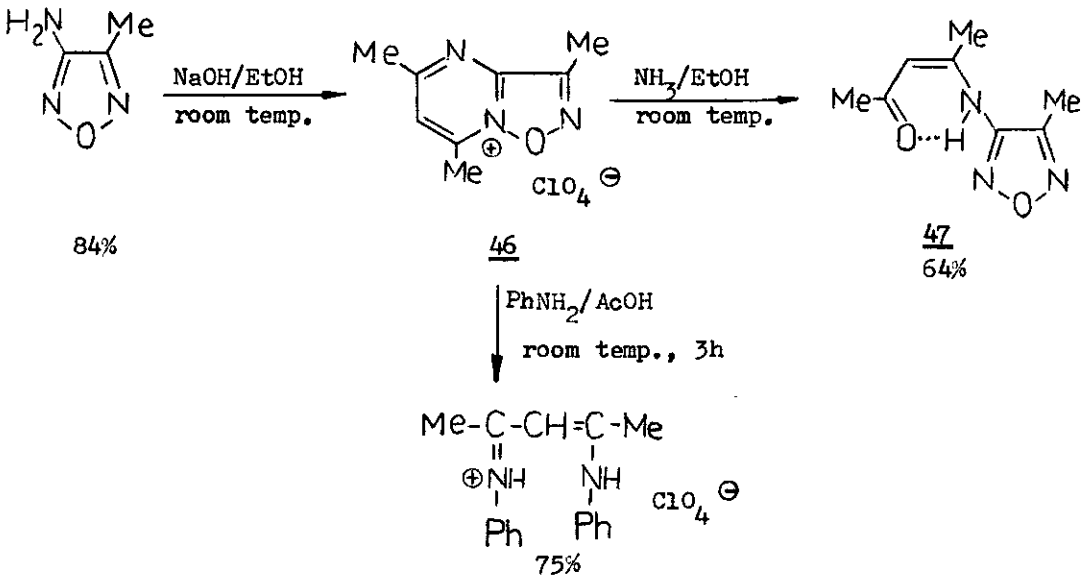
6% 15%



23% 22%

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-methylfurazan, and with ethanolic NH_3 the derivative 47 is formed. Action of aniline in acetic acid converts 46 into acetylacetone dianil perchlorate[34].



IV. PHYSICAL PROPERTIES

Among physicochemical investigations of furazans an attention ought to be paid to ^1H and ^{13}C NMR spectroscopy of 3,4-dimethylfurazan[48,49], ^{13}C NMR spectroscopy of 4-substituted 3-phenylfurazans[50], as well as the ^1H NMR spectroscopy of furazanopyrimidinium salts of the type 46[34]. In the study of furazancarboxylic acid 11 derivatives, the X-ray crystal structure analysis of its methyl ester was performed[28].

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Received, 17th February, 1984