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.

\[
\begin{array}{c}
\text{N} \\
\text{Z} \\
\text{N}
\end{array}
\]

\( Z = \text{O, S, Se, Te} \)

1,2,5-Thia- and selenadiazoles have been the subject of numerous publications,\(^1\text{-}^8\) 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\(^3\text{-}^4,^{10}\) 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\(^11\text{-}^17\) cover a large area of literature\(^18\text{-}^20\) 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)acetylamides in CHCl₃ medium, 4-substituted 3-hydroxyfurazans 4 and 2 have been obtained, along with trace amounts of 1,2,4-oxadiazole derivatives²⁴.

\[
\text{ArCON}_3 \xrightarrow{\text{reflux, 2h}} \text{ArOH} + \text{ArN}_\text{O}=\text{O}
\]
However when CHCl₃ 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 CHCl₃ and in the polar solvent, i.e. Z in EtOH.

In CHCl₃ the less polar transition state 6 is more stable than the polar transition state Z, and therefore in CHCl₃ furazans are the major products. In EtOH however, where the polar transition state Z is stabilized, the formation of 1,2,4-oxadiazoles is favoured.

The plausible mechanism of the above reactions is as follows:

\[
\begin{align*}
\text{Hydroxyfurazan } 4 \text{ can be also obtained in the reaction of oxime } 8 \text{ with hydroxylamine and sodium hydroxide, while } 2 \text{ under similar conditions affords the amino derivative } 10^{24}. 
\end{align*}
\]
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. Z-Oximes rearrange to 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.

The furazancarboxylic acid was synthesized by reacting the ester and iso-amyl nitrite in the presence of sodium methylate, the minor product being benzoisoxazole. The reaction proceeds via the dioxime intermediate.

\[
\begin{align*}
\text{H}_2\text{NOH, aq NaOH} & \quad \text{room temp., 4 days, next 100°C, 4 h} \\
\text{H}_2\text{NOH, aq NaOH} & \quad \text{reflux, 1 h}
\end{align*}
\]

\[
\begin{align*}
\text{Z-Oximes} & \rightarrow \text{furazans} \\
\text{E-Oximes} & \not\rightarrow \text{furazans}
\end{align*}
\]
Aminofurazan-carboxamide \( \text{15} \) can be obtained by treatment of \( \text{16} \) with benzylamine and the subsequent hydrolysis of the formed \( \text{17} \)\(^{30} \).

In the similar way the following derivatives of \( \text{15} \) were synthesized.

\[
\text{R NH} \quad \text{C-NHR'}
\]

\[
\text{R = H, alkyl}
\]

\[
\text{R' = alkyl, aryl, amino}
\]

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 \( \text{18} \) is formed. This compound was converted by the action of \( \text{Pb(0Ac)}_4 \) into a relatively unknown mesionic triazolofurazan \( \text{19} \). The reaction proceeds via the nitrene intermediate.\(^3 \).
Triazolofurazan 12 can be also obtained directly from 20 by its treatment with nitrosobenzene\textsuperscript{31}, or by thermolysis of 21; furazanoazides are serving here as nitrene generators\textsuperscript{32,33}.

\[
\begin{array}{c}
\text{H}_2\text{N}-\text{N}-\text{NH}_2 \quad \xrightarrow{\text{PhNO}} \quad \text{H}_2\text{N}-\text{N}=\text{NPh} \\
\text{[18]} \quad \xrightarrow{\text{Pb(OAc)}_4} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{PhN} \quad \text{[19]} \\
\text{[21]} \quad \text{in benzene} \quad \text{reflux} \quad 1\text{h}
\end{array}
\]

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\textsuperscript{34}.

\[
\begin{array}{c}
\text{R}^1=\text{O} \quad + \quad \text{H}_2\text{N}-\text{N}=\text{NPh} \quad \xrightarrow{\text{[21]}} \quad \text{R}^4 \quad \text{N} \quad \text{ClO}_4^- \quad \Theta \\
\text{[20]} \quad \text{in benzene} \quad \text{reflux} \quad 1\text{h} \quad \text{60-70°C, 5 min} \quad \text{end room temp., 3-5h}
\end{array}
\]

\[
\begin{array}{c}
\text{R} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{yield} \\
\text{Me} \quad \text{Me} \quad \text{H} \quad \text{Me} \quad 73\% \\
\text{Me} \quad \text{Ph} \quad \text{H} \quad \text{Me} \quad 70\% \\
\text{Ph} \quad \text{Me} \quad \text{H} \quad \text{Me} \quad 76\% \\
\text{Ph} \quad \text{H} \quad \text{Me} \quad \text{Me} \quad 82\%
\end{array}
\]
III. CHEMICAL REACTIVITY

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

The following nucleophilic substitution reactions of chloromethylfurazans were performed:

As the example of electrophilic substitution, the nitration of 22 was accomplished.
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.:

![Chemical structure](image)

The oxidation of 3-amino-4-phenylfurazan with an excess of 85% H₂O₂ in CF₃COOH affords 3-phenyl-4-nitrofurazan³⁸,³⁹.

![Chemical structure](image)

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

![Chemical structures](image)

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 Ac₂O the lactone 26 was formed. This compound easily undergoes ring cleavage by nucleophilic reagents to yield the corresponding derivatives of 11 28.

\[
\begin{align*}
\text{Et}_2\text{NH} & \quad \text{in EtOH} \\
\text{reflux, 3h} & \quad \text{reflux} \\
\end{align*}
\]

\[
\begin{align*}
\text{11} & \quad \text{COOH} \\
\text{Et}_2\text{NH} & \quad \text{in EtOH} \\
\text{reflux, 3h} & \quad \text{reflux} \\
\end{align*}
\]

\[
\begin{align*}
\text{25} & \quad \text{HO} \\
\text{26} & \quad \text{HO} \\
\text{28} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{4} & \quad \text{Ac}_2\text{O} \\
\text{4} & \quad \text{Ac}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{24} & \quad 20\% \\
\end{align*}
\]
The reaction of 20 with aniline results in the azo compound 18, which can be converted into azide 21:

![Chemical reaction image]

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.

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

![Chemical reaction image]

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

\[
\text{EtOOC-} \begin{array}{c} \text{N} \text{=O} \\
\text{H} \end{array} \text{-EtOH, room temp., 90 min.}
\]

So far, very little is known on furazans fused with 1,3-dioxepane ring. For the synthesis of these heterocycles 3,4-dihydroxymethylfuran can be used; this compound undergoes smoothly the reaction with aldehydes to afford 1,3-dioxepanes, while with acetone the reaction is more difficult, the yield being only 10%.41
When hydrolyzed, 35b readily gives back the starting 3,4-dihydroxymethylfurazan and acetaldehyde, and with acetic anhydride 3,4-diacetoxyfurazan was obtained.

In the reaction of 35b with thionyl chloride or phosphorus pentachloride, the dioepane ring is opened to afford the ether 36, which by HCl elimination can be converted into its vinyl derivative 41.
Studying the reactivity of thienofurazans, the cycloaddition of 27 with maleimides was accomplished; this reaction leads to strained thianorbornane systems: exo-adducts 38 and endo-adducts 39.

\[ \text{Z} = \text{NH}, \text{NMe}, \text{NPh and other} \]

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.
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\( ^{46} \).
In the reaction of \( \text{77} \) with norbornene \( \text{43} \), as with acetylenes, no strained cycloadducts \( \text{44} \) and \( \text{45} \) 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:\(^{47}\):

\[
\text{77} + \text{43} \rightarrow \begin{cases} \text{44} \quad \text{45} \\ \text{44} \rightarrow \begin{cases} \text{44} \quad \text{43} \\ \text{45} \rightarrow \begin{cases} \text{45} \quad \text{43} \end{cases} \end{cases} \end{cases}
\]

- \( 44 \) to \( 45 \) and \( 43 \) is shown with 6% and 15% yield, respectively.
- \( 45 \) to \( 44 \) and \( 43 \) is shown with 23% and 22% yield, respectively.
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$^{34}$. 

![Chemical reactions and structures]

IV. PHYSICAL PROPERTIES

Among physicochemical investigations of furazans an attention ought to be paid to $^1$H 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 $^1$H 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