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FORMATION OF SOME HETEROCYCLES BASED ON HYDROGEN CYANIDE

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Cyanogen chloride (prepared from hydrogen cyanide) has been used to prepare chlorosulfonyl isocyanate which can be adopted as the starting material in syntheses of N-methyl-N-phenyl-sulfuric diamides whose ortho derivatives are cyclized to give substituted (1H)-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxides.

Nuçleophilic substitution of cyanogen chloride with sodium benzenesulfinate produces benzenesulfonyl cyanide - the starting material for production of substituted 1,2,4-oxadiazoles.

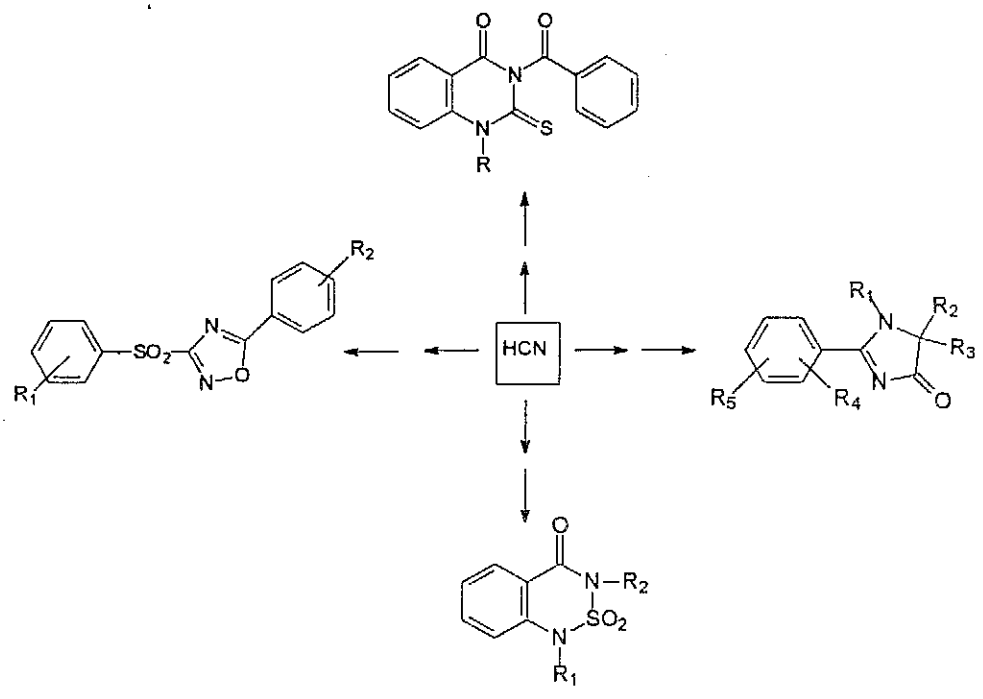
Hydrogen cyanide itself was used in the Strecker synthesis of aminonitriles which served for preparation of substituted imidazolines.

The nucleophilic substitution of benzoyl chloride and potassium thiocyanide gave benzoyl isothiocyanate which was further transformed into derivatives of substituted 2-thioxo-4-quinazolones.

Biologically active substances of predominantly heterocyclic nature have often been synthesized from simple, very reactive compounds, such as hydrogen cyanide and its derivatives, e.g., cyanogen chloride, chlorosulfonyl isocyanate, sulfamoyl chloride and, as the case may be, potassium thiocyanate.

The present communication summarizes preparations of biologically active

compounds (predominantly pesticides) synthesized at the Department of Organic Chemistry with the help of the above-mentioned derivatives of hydrogen cyanide (Scheme I). With the aim of optimization of preparations of these compounds, the kinetics and mechanisms of the cyclization and solvolytic reactions have been studied, too. The solvolysis rates of pesticides are important for predicting their degradation course in nature.

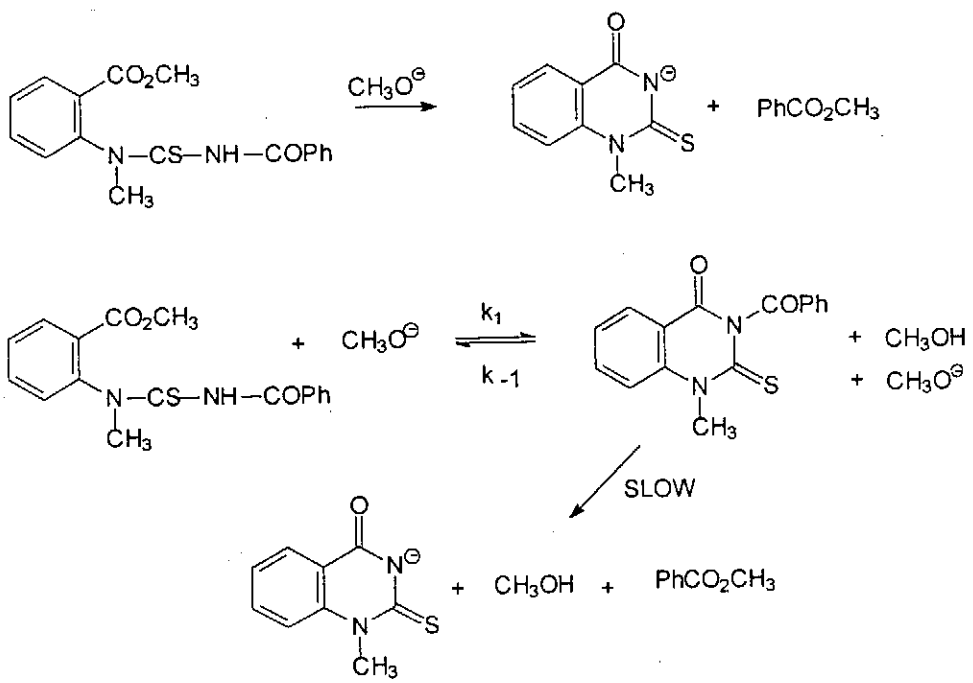


Scheme I

Aromatic thioureides having a methoxycarbonyl group at ortho position are cyclized in the presence of methoxide to give 2-thioxo-4-quinazolone derivatives. In the respective paper[1] we described the investigation of kinetics and mechanism of cyclization of 1-benzoyl-3-(2-methoxycarbonylphenyl)-thiourea. The reactive species proper is the monoanion of this substance, and the reaction shows a nonlinear increase in its rate with increasing concentration of methoxide. But the rate increase with methoxide concentration continues even after the whole of the substrate has been transformed into the monoanion. This additional rate increase was explained by formation of the dianion. In order to confirm the suggested mechanism, we prepared a compound in which the hydrogen at the first nitrogen atom was replaced by a methyl group to prevent the formation of the dianion. But when studying the methoxide-catalyzed reaction of 1-benzoyl-3-methyl-3-(2-methoxycarbonylphenyl)thiourea, we found

that it reacts in a quite different way.

The reaction takes place in two stages considerably differing in rates. In the first, faster stage, the anion of initial substance cyclizes to 1-methyl-3-benzoyl-2-thioxo-4-quinazolone. The reaction is reversible, the concentration of 1-methyl-3-benzoyl-2-thioxo-4-quinazolone decreases with increasing concentration of methanolate. In the second stage, the benzoyl group rearrangement in the given substance from nitrogen to sulfur and subsequent methanolysis to 1-methyl-2-thioxo-4-quinazolone take place. The rate-determining step is the methanolysis for $[CH_3O^{(-)}] < 4\times10^{-3}$ mol l^{-1} and the benzoyl group rearrangement for higher methanolate concetrations[2]. (Scheme II).



Scheme II

Sulfonamides represent another group of compounds synthesized in our laboratory. We prepared several substituted sulfonamides by a reaction of sulfamoyl chloride with the respective substituted anilines[3]. The products are structuraly similar to substituted ureas and can possess herbicidal effects. We have found that the 2-methoxycarbonyl derivatives can undergo either cyclization or solvolytic reactions depending on the medium. We studied the kinetics and mechanism of solvolysis in aqueous or methanolic medium. The unsubstituted derivative (N-methyl-N-phenylsulfuric diamide) is solvolyzed by the addition-elimination mechanism in neutral medium. In the presence of lyate

ion, however, the reaction takes the ElcB course[3]. When studying the solvolysis mechanism of the N-methyl-N-(2-methoxycarbonylphenyl)sulfuric diamide we have found a considerable acceleration of the solvolytic reaction as compared with that of the unsubstituted derivative. In the respective paper this phenomenon was explained by a catalytic effect of neighbouring group[3].

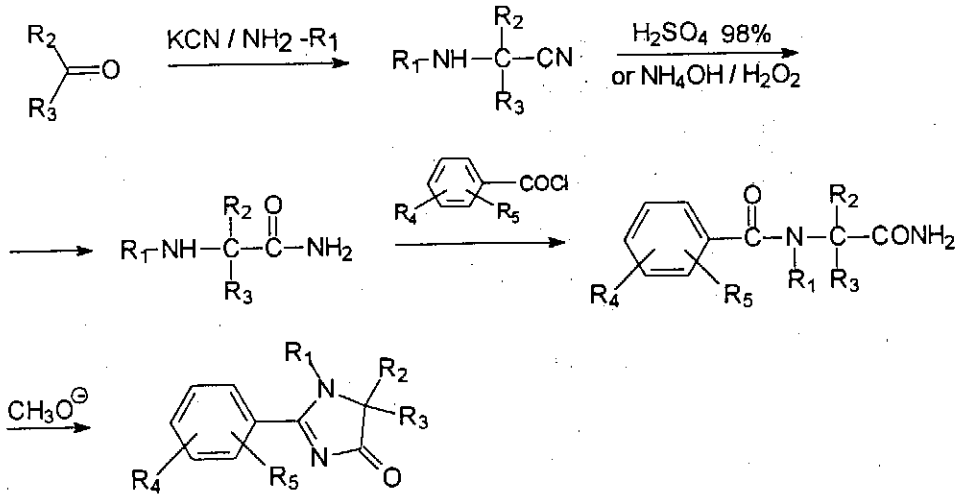
The cyclization of N-(2-methoxycarbonylphenyl)-N)-isopropylsulfuric diamide in the presence of sodium methoxide represents one of the industrial production methods of the commercial herbicide Bentazon (3-(1-methylethyl)-(1H)-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide). R_1 = H, R_2 = $CH(CH_3)_2$ (Scheme I, bottom formula).

We have studied kinetics and mechanism of cyclization of the three derivatives: N-(2-methoxycarbonylphenyl)sulfuric diamide, N-(2-methoxycarbonylphenyl)-N-methylsulfuric diamide and N-(2-methoxycarbonylphenyl)-N′-methylsulfuric diamide. The cyclization rate was measured in the aqueous media of butylamine, ethanolamine, morpholine, and glycinamide buffers. In strongly basic buffers, such as butylamine and ethanolamine, the cyclization takes the same mechanism for all the three compounds. The reaction rate increases with increasing concentration of buffers and the reaction is subject to general base catalysis. The methyl substituent has the following effect: the derivative with a methyl group at the first nitrogen atom (N) is cyclized twice as fast as the unsubstituted derivative, whereas the derivative with a methyl group at the end nitrogen atom (N′) cyclizes more slowly by a factor of 100.

The unsubstituted derivative, (N-(2-methoxycarbonylphenyl)sulfuric diamide), shows a different reaction course in less basic morpholine and glycinamide buffers. The reaction exhibits the general base catalysis at low concentration of base like in the butylamine and ethanolamine buffers, but with increasing base concentration the reaction mechanism is changed and the reaction gradually becomes independent of the base concentration. The general base catalysis is changed into a specific base catalysis, with the rate independent of the base concentration and dependent on hydroxyl ion concentration, i.e. on pH (Ref.[4]).

Another interesting group of compounds studied by us involves imidazolinones. These compounds belong among the newest types of herbicides which effectively destroy the dicotyledonous weeds, show no mutagenic activity, and are almost nontoxic for mammals and fish[5].

The starting aminonitriles were prepared by the Strecker synthesis. The aminonitriles were hydrolyzed to aminoamides by the peroxide catalyzed process in aqueous ammonia or by acid hydrolysis with sulfuric acid. The acylation was performed with substituted benzoyl chlorides[6], and the subsequent cyclization was accomplished in methanolic sodium methoxide. The derivatives prepared are given in Scheme III.



R_1: H; CH_3

R_2: CH_3

R_2; R_3: $(CH_2)_5$

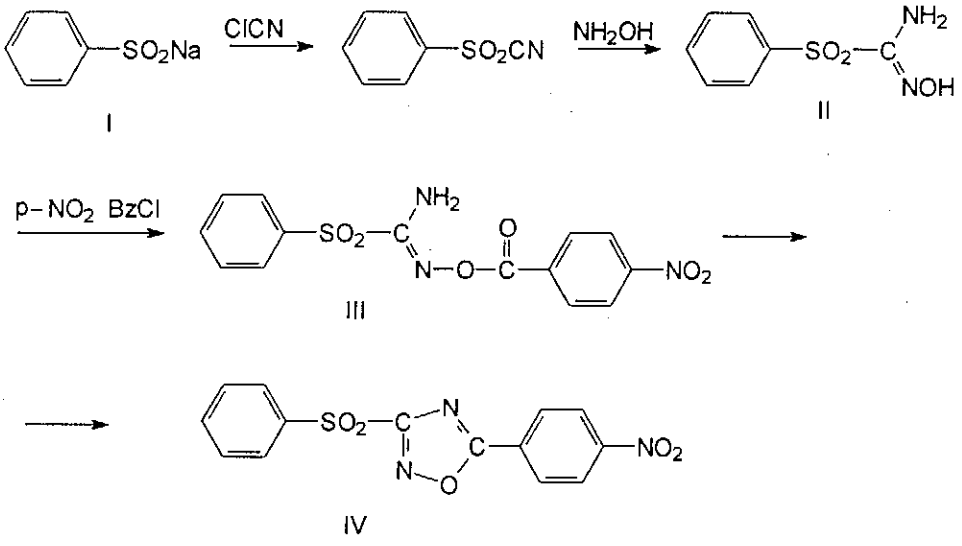
R_3: CH_3; C_2H_5; i-C_3H_7; i-C_4H_9; C_6H_5; 4-NO_2-C_6H_4-

R_4; R_5: H; 2CH_3; 4-CH_3; 2-OCH_3; 4-OCH_3; 2-CO_2CH_3; 2-NO_2; 2-Cl; 4-Cl; 2,6-diCl; 3,5-diNO_2

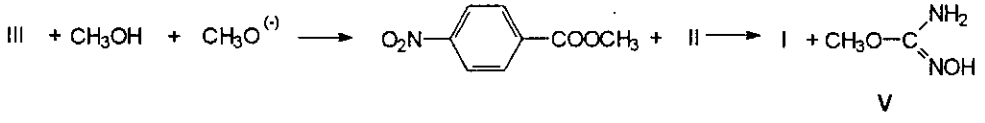
Scheme III

Recently, we have started research work concerning kinetics and mechanism of cyclization reactions giving imidazoline derivatives. First of all we have found that the N-methyl derivatives (R_1 = CH_3) are cyclized faster than the unsubstituted ones by a factor of 500. Next we have found some side reactions accompanying the cyclization, for instance the formation of azoxy derivative from nitro compound[7], hydrolysis of ortho-standing ester group, nucleophilic substitution of the fluorine atom by methoxy group in the 2,6-difluoro derivative. However, the 2,6-dichloro derivative does not cyclize even after 100 h boiling in 1M methoxide. These reactions will be studied in more detail later.

Reaction of cyanogen chloride withe sodium benzenesulfinate (I) gives phenylsulfonylcyanide which adds hydroxylamine to form phenylsulfonyl-formamidoxime (II) which can be acylated with 4-nitrobenzoyl chloride. The resulting phenylsulfonyl-O-(4-nitrobenzoyl)formamidoxime (III) undergoees cyclization in basic medium to give 5-(4-nitrophenyl)-3-phenylsulfon-1,2,4-oxadiazole (IV).



We studied the cyclization course in toluene and methanol. In toluene, the cyclization catalyzed with sodium methoxide or triethylamine produces oxadiazole IV. In methanolic sodium methoxide no cyclization takes place, a two-step reaction proceeding instead. The first step (ca 10 times faster) is methanolysis to methyl 4-nitrobenzoate and the starting oxime II which decomposes in the second, slower step to give sodium benzenesulfinate and a substance which was assigned structure V according to its mass spectra.



Acknowledgements

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