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IMIDIC ACID DERIVATIVES IN THE SYNTHESIS OF 1,3-DIAZINES

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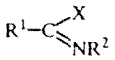
Imidic acids are hypothetic tautomeric forms of amides, which are not observed in free form.

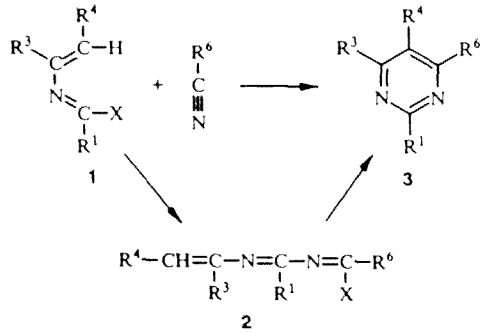
But their derivatives, like anhydrides, esters, and chlorides, are useful starting materials to synthesis of heterocyclic nitrogen compounds. In our studies we are interested in the N-vinyl or N-phenylimidoyl chlorides, bromides, or dichlorophosphates.



R^1 = alkyl, aryl; $R^2 = R^4—CH=CR^3—$, $R^5—C_6H_5—$; X = Cl, $OPOCl_2$, Br

These compounds were prepared by previously developed methods based on Beckmann rearrangement of α,β-unsaturated ketoximes [1], reaction of alkyl ketones with nitriles in the presence of phosphoryl chloride [2], or interaction of phosphorus pentachloride or complex triphenylphosphinebromine on adequate amides.

In our study, we examined the potential use of reaction of N-vinyl and N-phenylimidoyl compounds with nitriles, cyanamide, and its derivatives in the synthesis of 1,3-diazines, especially amino derivatives of pyrimidines and quinazolines. The studies on the reaction of N-vinylimidoyl compounds with nitriles have led us to elaboration of a new method useful in the synthesis of pyrimidine derivatives [3]. N-Vinylimidoyl compounds **1** contain 2-azabutadiene moiety, hence, one could expect that the reaction with compounds having a triple CN bond would proceed as a typical thermal cycloaddition with reversed electron demand.



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However, the reaction of N-vinylimidoyl compounds with cyanamide and dimethyl cyanamide ($R^6 = NR_2$) did not directly yield the expected 4-aminopyrimidines, but the linear products as 1-amino-1-chloro-2,4-diaza-1,3,5-hexatriene salts (**2**) were obtained in the acidic reaction environment. Effective atomic charges calculated by the MNDO method in starting N-vinylimidoyl compounds also indicated that the C—X bond is highly polarized and may easily undergo a heterolytic cleavage with formation of iminocarbenium cation on the contrary to halogen-derivative coupled carbon arrangement. The presence of the lone electron pair of nitrogen atoms greatly facilitates this process. The formed iminocarbenium cation is susceptible to an attack of nucleophilic agents like the nitrogen atom of nitrile, and the reaction rate depends on the nucleophilicity of the attacking agent. The forming linear intermediate product has an amino group, and a salt is formed in the acidic media, whose electron density distribution is disadvantageous for cyclization. Neutralization of the salt in anhydrous media allows us to obtain a free linear intermediate product that easily undergoes cyclization to 4-aminopyrimidine derivarives **3** ($R^6 = NR_2$).

The yields of pyrimidine derivatives depend on structure of the substituent present in the position 6 (R^4) of intermediate product **2**. Electron acceptor substituent increases the yield of the cyclization reaction. So the yields of the forming 5-arylpyrimidines **3** range from 50-80% for a 4-nitrophenyl substituent, whereas 5-alkylpyrimidines are obtained merely with yields of about 30% [3, 4].

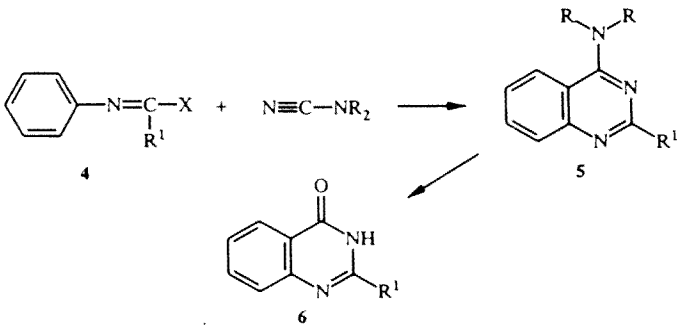
The reaction of N-(2-pyridylvinyl)imidoyl chlorides obtained by Beckmann rearrangement of the oximes of 4-pyridyl-3-methyl-3-buten-2-ones, with cyanamide or its alkyl derivatives in the presence of $TiCl_4$, gives the 5-pyridyl-4-aminopyrimidines (**3**) (R^4 = 2-, 3-, 4-pyridyl) with excellent yields [5].

N-Vinylimidoyl compounds having the amino substituent in position 1 ($R^1 = NR_2$) were prepared in a reaction of alkyl ketones with cyanamide and dimethyl cyanamide [6]. The structure of the obtained compounds was proved by their hydrolysis to urea derivatives. Their reaction with the nitrile nitrogen atom proceeds with more difficulty, therefore, it is better to transform them into reactive nitrilium salts in the presence of the Lewis acid-type catalyst. The forming intermediate derivatives of 1,3-diamino-2,4-diazahexatriene easily undergo a cyclization to 2,4-diaminopyrimidine derivatives **3** ($R^1 = R^6 = NR_2$). 5-Alkyl-2,4-diaminopyrimidines were obtained by this method, with yields exceeding 60%.

However, if nitrilium salts contain a phenyl group in position 4 ($R^4 = R^5—C_6H_4$), 1-aminoisoquinoline derivatives are also formed as a result of the intramolecular cyclization of the iminocarbenium cation. A ratio of heterocyclic products depends in this case on the electron effect of the substituents presented at the benzene ring. Electron-acceptor and electron-donor substituents increase the possibility to obtain 5-phenyl-2,4-diaminopyrimidines and 1-aminoisoquinolines respectively [6].

A reaction of N-phenylimidoylchlorides **4** with cyanamide and dimethyl cyanamide gives 4-aminoquinazolines **5** with good yields [7, 8].

It is possible to obtain cyclic products with satisfactory yields when a Lewis acid-type catalyst is used to facilitate a closure of the quinazoline ring. Excellent results are achieved with titanium tetrachloride as a catalyst. However, titanium tetrachloride forms a very stable complex with the forming aminoquinazolines. Their cleavage, requiring severe conditions, also results in the hydrolysis of the quinazolines unsubstituted at the amine nitrogen to 4-quinazolones **6**.



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It should be noted that the presented method for synthesis of 1,3-diazines is simple and effective in most cases and is also based on easily available raw materials. The presented results of our studies do not cover all the potentialities of this method. It can be also used to synthesize other nitrogen heterocyclic arrangements.

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