ORGANIC AND PHYSICAL CHEMISTRY USING CHEMICAL KINETICS: PROSPECTS AND DEVELOPMENTS

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Nova Science Publishers, Inc.
New York

In: Organic and Physical Chemistry Using Chemical Kinetics ... ISBN: 978-1-60021-763-0
Editors: Y.G. Medvedevskikh, et al. pp. 251-255

Chapter 19

SUGAR CARBAMIDES

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ABSTRACT

The results of experimental researches on the synthesis of sugars derivatives with glycosylamide and thioamide bonds have been presented in this work. The possibility of using their in the preparative chemistry of sugars, some fields of medicine and agriculture has been shown.

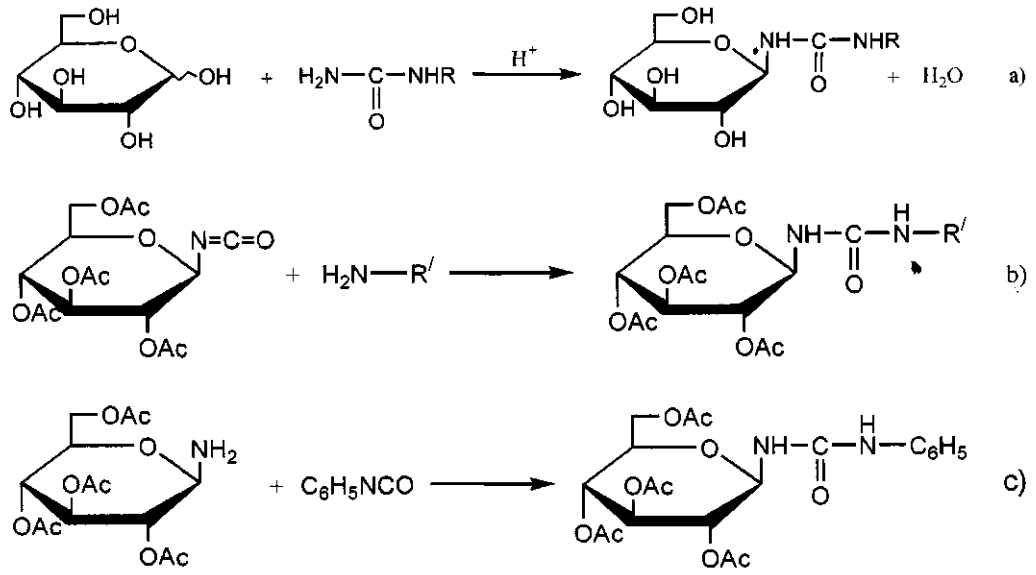
Keywords: monosaccharides, glycosylisotiocyanates, glycosyltiocyanates, glycosylureas, glycosylnitrozometylureas.

The study of the reactions with the participation of glycosyl bonds is important not only for the theory of carbohydrates structure and reactional ability of carbohydrates. They represent a significant interest and solution for a number of important problems of organic, bioorganic chemistry, and molecular biology, fermentative catalysis, since the glycosyl bond is one of the most important structural elements of many biologically active compounds.

The bioorganic chemistry laboratory of the Institute of Chemistry and Chemical Technology under the National Academy of Science of the Kyrgyz Republic is conducting studies in the area of kinetics, mechanisms of catalysis of carbohydrate reactions and development of new methods of synthesis of the physiologically active compounds with the N-glycosylamide bonds (derivatives of the sugar carbamides) for their application in medicine and other industries. Among the practically important properties of this type of derivatives of the sugar carbamides is the high hydrolytic stability as compared to the simple N-glycosides of alkyl(aryl)amines. Chemical connection of sugars with the unprotected hydrocsyl groups with the biologically active compounds at the account of stable N-

glycosylamide bonds will lead to the growth of solution in water, decrease of toxic and change of selective action of the preparations [1, 2].

Two bases approaches are used in the synthesis of sugar carbamides: direct interaction of carbohydrates with carbamides and their analogs in the conditions of acid catalysis (a) and interaction of acetylation N-glycosylisothiocyanates with amines (b) or interaction of acetylation N-glycosylamines with arylisothiocyanates (c) [3].



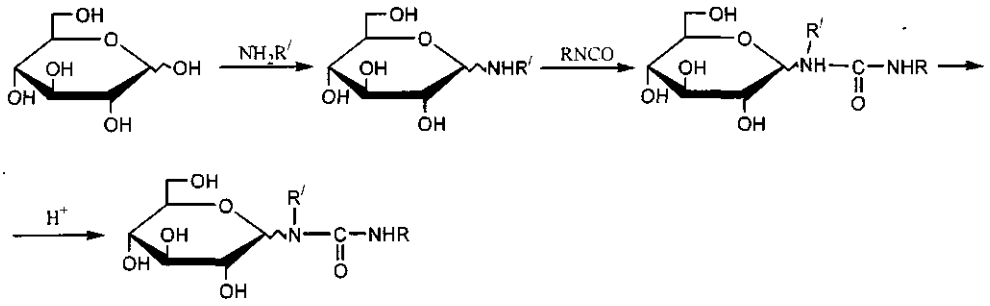
The first direct approach requires a long stand of the reaction mixture under high temperature. In the crystal form the product could be receive only after the fermentative splitting of un-reacted glucose. In the further studies [4-6] the direct method was somewhere improved and applied to other mono- and disaccharides, however, there were no principal changes in the synthesis methods.

The second approach - amination glycosylisothiocyanates was suggested by E. Fisher [3,7]. The method was widely used in the synthesis of analogs of glycoproteins and nucleosides of pirimidine and geterocyclic derivatives of the carbohydrates [7-8].

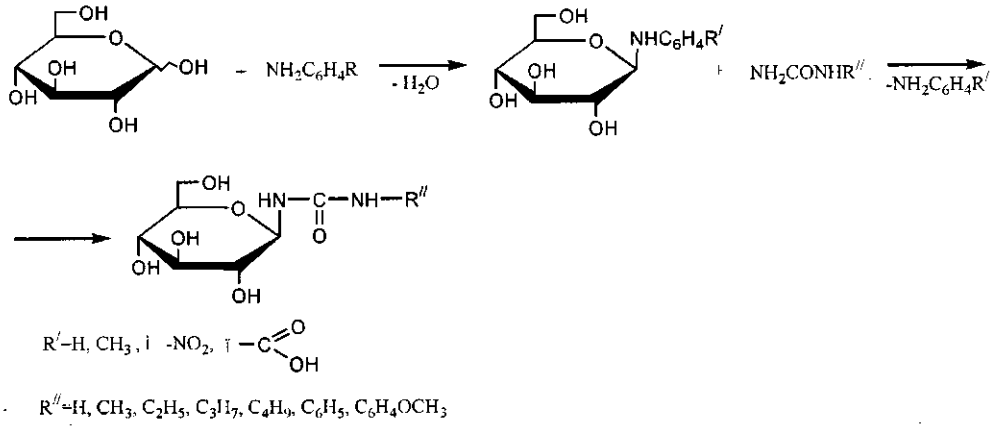
The version of the isothiocyanates method of E. Fisher is based on the interaction between alkyl- and arylisothiocyanates with glycosylamines, produced, for example, though hydrogenezation glycosylazids [3].

These methods have many stages and require preliminary protection of the OH-groups, followed by the removal of protective functions. The advantages of E. Fisher's method include its universality - the ability to introduce ureido (thioureido) fragments in any position of the carbohydrate ring with the presence of amino group in this position.

The works of [9, 10] suggest a simplified isothiocyanates synthesis of glycosylureas. According to this method, in the beginning they receive anomerical mixture of N-alkylglycosylamines, conduct the condensation with isocyanates and receive anomerical mixture of N-alkylglycosylamines, conduct the condensation with isocyanates and receive anomerical mixture of N-alkylglycopyranosylthioureas. After the processing of this mixture with the ant acid the β-anomer of N-alkyl-N/-glycopyranosylthiourea is separated.



The authors suggest a new more effective method of synthesis of N-glycosylcarbamides with the use of N-arylglycozides [11, 12]. The kinetic studies have shown that the replacement of the glycosyl hydrocsyl by N-arylaglycon leads to the growth of the reaction properties of C_1 in the reactions of nucleophilic addition and replacement, easing introduction of aglycons with small basic in the conditions of acid catalysis.



To receive N-glycosylureas on the reaction of N-transglycosylation, it is enough to heat the mixture of ureido derivatives and N-arylglycozides for a short period (10-30 min.) in an alcohol environment with some small addition of mineral acid until the mixture becomes homogenous.

The scheme shows that arylamine plays the role of nucleophilic catalyst reaction of direct condensation of monosaccharide with the ureido derivatives. That is why in order to simplify the synthesis of N-glycosylureas, one can go without N-arylglycozid and instead use the catalyst additions of arylamine [13, 14].

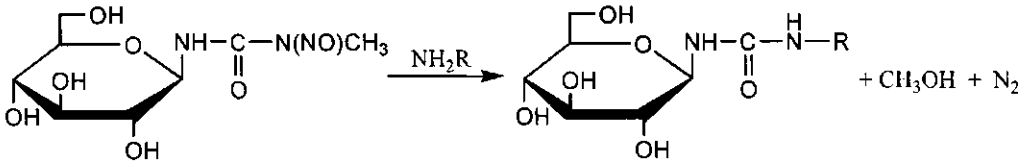
When using the small basic m-nitroanilin as a catalyst, β-anomerical forms of glucopyranosylureas are mostly formed. The stability of N-glycosylamid bond allows to recommend these fragments as a connecting bridge between sugars and biologically active compounds for the receiving sugar derivatives as drugs. The use of sugar carbamides is limited mostly to N-glycosylureas, which are recommended for technical reasons. Currently, a more important tendency is developing which leads to their applications in the area of medical-biological problems. The sugar derivatives with N-nitrozo-N-alkylcarbamide fragments deserve a special attention due to their important role in the chemical therapy of the cancer diseases [15, 16].

The interest to compounds of this class arouse after the discovering of high antileucemia activity of 1-methyl-1-nitrozourea [15]. Methods of synthesis of N-nitrozocarbamide fragments in the carbohydrate rings were worked out to get select acting antitumour remedies [17, 18, 19, 20].

Comparative methods of pharmaco-toxicological research help to ascertain [2, 19] that adding of N-nitrozo-N-metylurea on the glycosyl center leads to the sharp lowering of toxic activity of the antitumour preparation and to changing of spectrum of its activity to a number of experimental swelling models. It is shown, that toxic and selective actions of carbohydrate analogs of nitrozometylurea depend on the monosaccharide carrier of the cytosine agent.

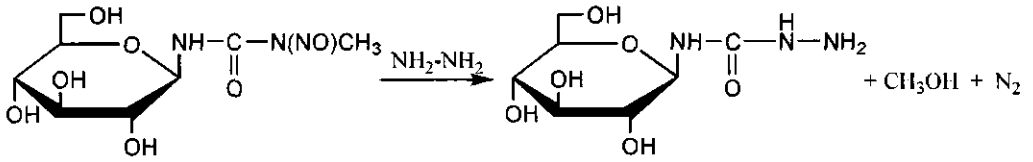
N-nitrozo derivatives of N-glycosylureas attract attention to them not only as perspective antitumour preparations also as compounds with high reactional ability on the bases of which new methods of the carbohydrate derivative synthesis can be developed.

The authors in their works [21, 22] show that N-nitrozo derivative of carbohydrates can easily come into the reaction of substitution on carbonil group of N-aglicon witch the help of interaction of amines witch the development of sugar carbohydrate derivatives.



The described reaction opens great possibilities for the synthesis of different N-glycosylation derivatives witch carbamide bridges including such derivatives of sugar, the synthesis of which by methods of direct interaction of nucleophilic agents with a glycoside center, turns out to be difficult for poor reactional ability of the attack amino group.

The example of it can be shown by reaction of N-glycosylation semicarbazids [22].



The developed method of getting of glycosylation semicarbazids with N-glycosyl bond and the final reactional amino group opens wide possibilities in the chemistry of semicarbazid derivatives.

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