International Journal of Chemical, Materials and Biomolecular Sciences
ISSN: 2415-6620
Vol:8, No:7, 2014

Technologies of Acylation of Hydroxyanthraquinones

Dmitry Yu. Korulkin, Raissa A. Muzychkina

***Abstract*—**In review the generalized data about different methods of synthesis of biological activity acylated hydrohyanthraquinones is presented. The basic regularity of a synthesis is analyzed. Action of temperature, pH, solubility, catalysts and other factors on a reaction product yield is revealed.

***Keywords*—**Aminoacidic acylation, hydroxyanthraquinones, nucleophilic exchange, physiologically active substances.

I. Introduction

AMONG high-performance low-toxicity medicine preparations, especially, preparations of selective action, an important place is occupied by the derivatives of anthraquinone. This is well proven in the literature on biological activity of anthracene-containing plants, natural anthraquinones, their synthetic analogues and phytopreparations, and it should be noted that synthetic analogues have wider spectrum of biological activity.

One of the most perspective directions of chemical modification of hydroxyanthraquinones is acylating reaction.

II. Results and Discussion

The process of acylation of hydroxyanthraquinones enhances stability of aromatic system against oxidation, protects hydroxyl groups from further transformations thereby reducing the number of by-products, increases solvability of compounds, which is important for the choice of conditions of biological tests of any compounds weakly soluble or insoluble in water and physiological solution.

Hydroxyanthraquinones are acylated by aliphatic and aromatic aldehydes, ketones, acids, anhydrides. An important role plays reducing acylation by acetic anhydride or benzoilchloride in the dioxane solution in the presence of zinc dust. Acylation reactions may be carried out selectively in one of two α-, hydroxy-, in α-hydroxy- in the presence of β-hydroxy and vice versa, in pyridine [see in Fig. 1].

Reactions of acylation of chrysophanol, aloe-emodin, emodin, physcion, their amino- and halogen substitutes were carried out with acetic anhydride, benzenesulfochloride, alkyl phosphorous acids, salts of dialkyldithiophosphorous acids, isocyanates of dialkyldithiophosphorous and phosphonic acids, aminoacids, etc. Except for acetic anhydride all other acylating agents were used for the first time [1].

Dmitry Yu. Korulkin is with the Department Chemistry and Chemical Technology, al-Farabi Kazakh National University, Almaty, CO 050040 Kazakhstan (corresponding author to provide phone: 727-387-1751; fax: 727-292-3731; e-mail: Dmitriy.Korulkin@kaznu.kz).

Raissa A. Muzychkina is with the Department Chemistry and Chemical Technology, al-Farabi Kazakh National University, Almaty, CO 050040 Kazakhstan (e-mail: rmuz@mail.ru).

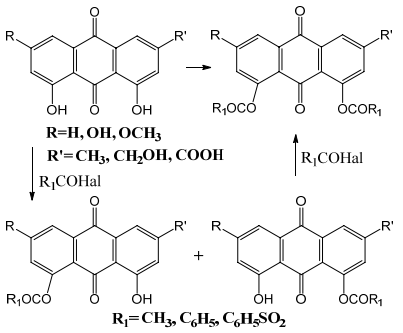

Fig. 1 Halogenanhydride acylation of hydroxyanthraquinones

It should be noted that in these reactions different reactivity of 4- and 5-OH-groups was most clearly pronounced, i.e. all experiments gave 2-mono- and di-substituted, with the yield of isomer in 4-OH group of chrysophanol and in 5-OH group of emodin and physcion up to 50%. The usage of pyridine in contrast to other alkaline agents enabled to get only monoacylated products after 4-5 hour heating, and if the temperature raised quickly, the products of complete acylation dominated in the reaction [1]. 2-methyl-4,5-bis-benzoilamino-anthraquinone was detected in the reverse reaction of chrysophanol with benzamide and in the reaction of 2-methyl-4,5-diaminoanthraquinone with benzoil chloride [2].

Reactions of phosphorylation of hydroxyanthraquinones significantly widen possibilities of directed changes in biological activity of modified products as compared with traditional activity of P-organic substances and other classes of compounds. There are very few publications devoted to phosphorylation of anthraquinones, therefore we studied all parameters which could increase the yield of target products in interactions with various phosphorous syntons [3]. For example, phenols and thiophenols with PCl_3 phosphorylation of chrysophanol gives yield of 40-47% [see in Fig. 2].

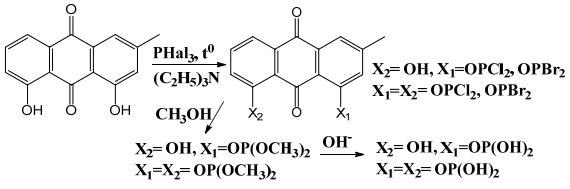

Fig. 2 P-acylation of chrysophanol

Chloroanhydrides of phosphorous acid are thermolabile; at temperatures above 70^0 they give partial resinification in all solvents, therefore optimal solvents are tetrahydrofurane and dioxane in the presence of triethylamine [see in Fig. 3].

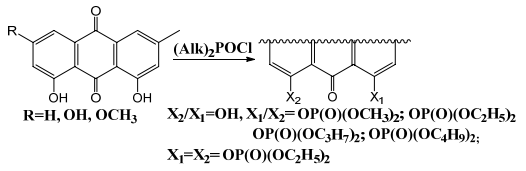

Fig. 3 Chloroanhydride P-acylation of anthraquinones

The sum of monosubstituted dialkylphosphates was divided into the mixtures of sorbents chromatin/silicic acid 1:1 with the usage of eluents of opposite polarity. Dichloroanhydrides of phosphorous acid easily undergo the reactions of nucleophilic exchange of one and two chlorine atoms [4].

In the reactions of dichloroanhydride of methylphosphonic and ethylphosphonic acids in the ratio 2:1 with chrysophanol the following dimeric structures were obtained [see Fig. 4]:

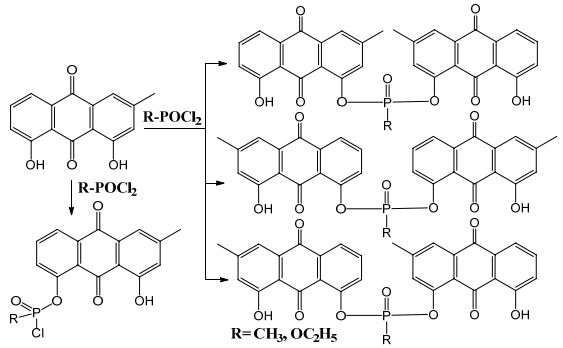

Fig. 4 P-acylic dimerization of chrysophanol

M^+ 568 in mass-spectra of methylphosphones was not detected, but intensive signals of the fragments with m/z 331, 284, 254, 237, 209, 198, 169, 151 were in good agreement with the main directions of fragmentation of anthraquinone molecules [see in Fig. 5]:

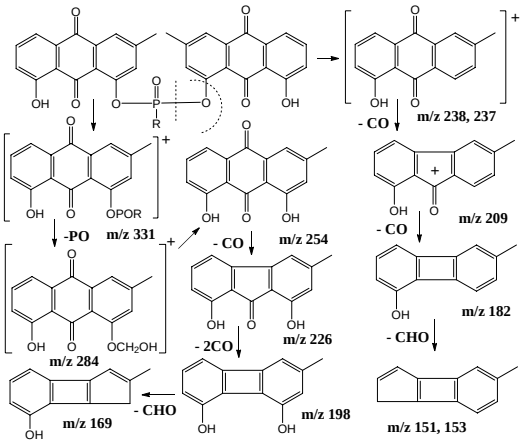

Fig. 5 MS-fragmentation of P-acylic anthraquinones

α- and β-halogen- derivatives of natural hydroxyl-anthraquinones interact with salts of thio- and dithioalkyl-phosphorous acids even at room temperature, with a decrease in the yield of target thiophosphates in the series C_1-C_3 and → C_6H_5 → $C_6H_4CH_3$ [5].

The increase in temperature promotes increase in the yield, it should be noted that the best catalytic admixture in these reactions turned out to be one-valence copper [see in Fig. 6]:

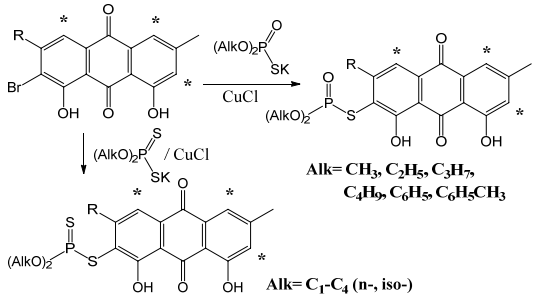

Fig. 6 Thiophosphorylation of chrysophanol

The yields with β-bromides (mono- and di-) are 17-28% higher than the yields with α-bromides, which can be explained by their better spatial accessibility [6] [See in Fig. 7].

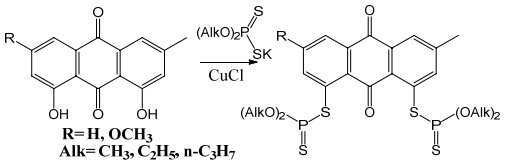

Fig. 7 Alkylthiophosphorylation of anthrquinones

In spite of actively developing chemistry of isocyanates, we could not find publications on phosphorylation of hydroxyanthraquinones by isocyanato-phosphorous acids and carried out such reactions in the presence of triethylamine at temperatures varying from room temperature to 60^0C [3] [see in Fig. 8].

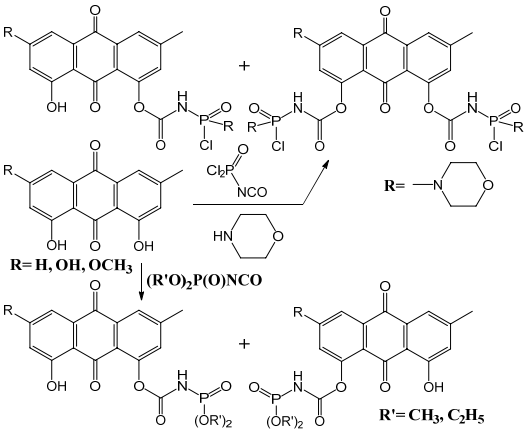

Fig. 8 Isocyanatophosphorylation of anthrquinones

We have worked out conditions of selective monophosphorylation in aromatic system, in carbonyl and

hydroxyl groups of anthraquinone molecules, which considerably extend possibilities of targeted creation of biologically active compounds.

Most interesting in terms of biological activity are dimeric structures with phosphorous-containing fragments, isocyanates, alkyldithio-phosphonates and biophosphites. It was shown that the presence of anthraquinone fragment reduced toxicity of such derivatives [1], [7].

Interactions of chrysophanol, physcion and emodin with dimethyl- and trimethylphosphites go easily with acetyl derivatives [see in Fig. 9]:

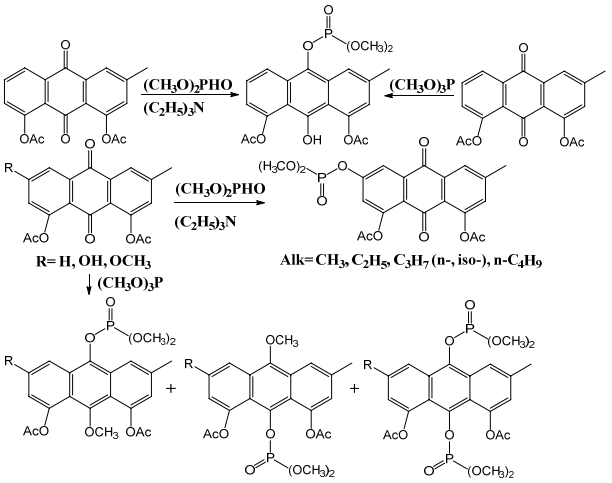

Fig. 9 Alkoxyphosphorylation of anthrquinones

Salts of phosphorous monothio-acids with isomeric anions, i.e. anions constructed similar to thion-thiol ambident triads, may exhibit dual reactivity in alkylation and acylation reactions. For example, in the interactions with bromides of hydroxyanthraquinones high yield of exchange products of bromine atom was obtained [8].

Interaction of hydroxyanthraquinones with aminoacids or their haloidoanhydrates yields either acylation of hydroxyl groups or their exchange for the aminoacid residue. The aminoacid residue can be also inserted through the exchange reaction of haloid atoms both in α- and β-positions of hydroxyanthraquinones. The scheme of the above reactions is presented below [see in Fig 10].

It should be noted that in the acylation reactions in pyridine different reactivity is observed not only for *α*- and β-hydroxygroups but also for α,α- and β,β-hydroxygroups, which depends on their location in the rings of anthraquinone molecule, presence and nature of other substituting groups, for example, hydroxygroups of chrysophanol, emodin, aloe-emodin, rhein, etc [1], [9].

Possibilities for insertion of amino acid fragments with preservation of COOH-group increases solvability and bio-accessibility of such derivatives but increase in pH influences toxicity of such derivatives. Amino acid derivatives with terminal NH_2-group exhibits higher antitumor activity on the same cultures [10].

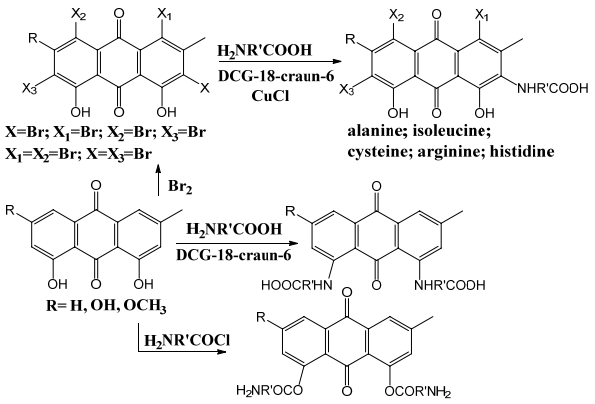

Fig. 10 Aminoacylation of hydroxyanthrquinones

III. Conclusion

The aforesaid enables to consider the acylation methods as a perspective for modifications of biologically active anthraquinones with a number of useful properties.

Acknowledgment

Authors are grateful to the Foundation the First President of the Republic of Kazakhstan – the Leader of the Nation for award of financial support.

References

[1] R.A.Muzychkina, D.Yu.Korulkin, *The anthraquinones*, Almaty: MV-Print, 2013.
[2] R.A.Muzychkina, *Natural Anthraquinones. Biological Properties and Physicochemical Characteristics*, Moscow: Phasis, 1998.
[3] H.N.Ghosh, *J. Photochem. Photobiol*., vol. 73, no. 1, pp. 17-22, 1993
[4] L. Bloomer, *J. Org. Chem*., vol. 58 no. 27, pp.7906-7912, 1993.
[5] K.Katsuura, *Tetrahedron Lett*., no. 1, pp. 9-12, 1985.
[6] K.Nakamura, T.Assai, T.Hara, *Bull. Chem. Soc. Japan*, vol. 56, no. 5, pp. 1435-1439, 1983.
[7] C. Y.Chen, Y.Lu, Z.N. Chen, *Acta Univ. Med. Second. Shanghai*, vol. 21, pp. 488-491, 2001.
[8] J.V.Bergman, *J. Amer. Chem. Soc.*, vol. 113, no. 18, pp. 6982-6998, 1991
[9] Z. T.Zhang, Y. J.Du, Q. G.Liu, Y.Liu, *Nat. Prod. Res. Dev.*, vol. 13, pp. 45-47, 2001.
[10] C. H.Chen, C. Y.Shaw, C. C.Chen, Y. C. H.Tsai, *J. Nat. Prod.,* vol. 65, pp. 740-741, 2002.