UDC 547.269+547.431
DOI: 10.15587/2312-8372.2018.124272

Abdo-Allah M.,
Mospanova E.,
Popov Ye.,
Isak A.

SEARCH FOR NEW BIOLOGICALLY ACTIVE COMPOUNDS BASED ON 6-METHYLURACIL-5-SULFOCHLORIDE AND ALCOHOLS

Проведено дослідження реакції взаємодії аліфатичних і ароматичних спиртів з 6-метилурацил-5-сульфохлоридів (МУСХ). Показано, що зручніше за все проводити взаємодію 6-метилурацил-5-сульфохлоріда з попередньо приготованим алкоголятом в надлишку вихідного спирту. Попередні дослідження (використання програми PAAS) показали, що серед отриманих сполук є такі, що проявляють антиоксидантні властивості і можуть бути використані в якості цитостатиків.

Ключові слова: *біологічно активні сполуки, синтез алкілсульфонатів на основі 6-метилурацил-5-сульфохлориду та алкоголятів, реакційна здатність.*

1. Introduction

Heterocyclic compounds are one of the most extensive and important in practice, classes of organic compounds. Methyluracil is one of the representatives of heterocyclic compounds, which recently find increasing use in organic synthesis, especially in the chemistry of pharmaceuticals, biologically active compounds. Esters of alkane and benzenesulfonic acids have acaricidal action. In agriculture, arylic esters of the simplest arylsulfonic acids are used to protect plants against ticks, which are active not only in larval stages, but also in mite eggs. The most active are 2-chloro- and 4-bromophenyl esters of 4-chlorobenzenesulfonic acid.

Aryl esters of arylsulfonic acids are obtained in good yield by the reaction of acid chloride of the corresponding sulfonic acids with alkali metal phenolates:

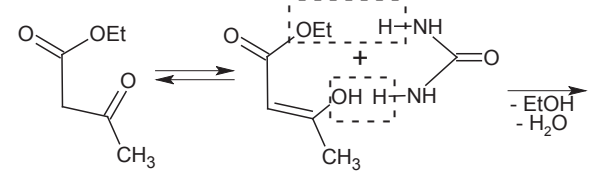
$$ArSO_2Cl+Ar_1ONa \rightarrow ArSO_2OAr_1+NaCl.$$

The reaction is carried out at a low temperature in an aqueous medium under good agitation conditions. The isolation of reaction products is not difficult, since esters of sulfonic acids are insoluble in water.

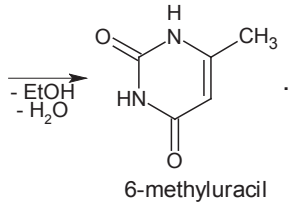
These compounds are widely distributed in nature, where they play a huge role in such key processes as the transmission of hereditary traits, respiration, photosynthesis, and the work of the enzymatic apparatus. It is not surprising that intensive studies of heterocycles are conducted in all industrialized countries. In chemistry, especially for synthetic chemists who know how to plan and carry out syntheses of complex heterocycles, the study of heterocyclic compounds is the most relevant direction. For this reason, research in the chemistry of heterocyclic compounds has both scientific-theoretical and practical significance.

2. The object of research and its technological audit

The object of research is methyluracil sulfochloride and the synthesis of alkyl and aryl sulfonates on its basis. Synthesis of these compounds for a long time represented a limited opportunity because of the difficult availability of the original methyluracil sulfochloride. The authors of [1, 2] attempted to synthesize uracil sulfochloride and methyluracil sulfochloride. However, the yield of these products did not exceed 24–29 % of the loaded. In addition, the synthesis of the starting 5-methyluracil was also ineffective. For its synthesis, the reaction of the reaction of acetoacetic ether and urea in an alcohol solution was used. The reaction mixture was kept for about a week at room temperature. The yield of the desired product did not exceed 40 %:

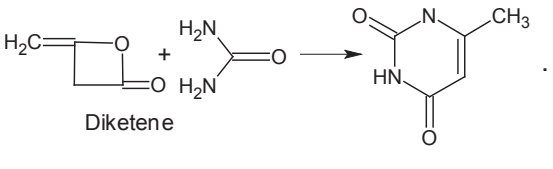


Acetoacetic ether



6-methyluracil

At present, methyluracil is an easily available product. It is obtained on an industrial scale with a high yield (over 90 %) by the interaction of diketene with urea according to the scheme:



Diketene

 © Abdo-Allah M., Mospanova E., Popov Ye., Isak A.

One of the most problematic places was the stage of sulfochloride formation. Only at the beginning of this century it was shown that if the reaction of methyluracil with chlorosulfonic acid is carried out in the presence of thionyl chloride, the yield of the desired product increases several times [3, 4]. In work [5] it was suggested that n-butyl ether MUSC can be used as a cytostatic, which shows the prospect of research in this direction.

3. The aim and objectives of research

The aim of research is studying the possibility of synthesizing new alkyl sulfonates by the interaction of MUSC with alcoholates of the corresponding alcohols. To achieve this aim it is necessary to accomplish the following tasks:

1. To work out the conditions for the synthesis of 6-methyluracio-5-sulfochloride with a higher yield.

2. To determine the elemental composition of the isolated compounds to confirm the structure of the obtained compounds.

4. Research of existing solutions of the problem

The introduction of the sulfochloride group – SO_2Cl into the molecule of the organic compound is widely used both for the preparation of R–SO_2Cl sulfochlorides and for the production of sulfonic acids followed by the hydrolysis of sulfochlorides. The latter method is one of the main ones in the preparation of alkane sulfonic acids, since alkane sulfonic acids are mainly obtained by photolytic sulfochlorination of alkanes with a mixture of SO_2 and Cl_2 when irradiated with ultraviolet rays.

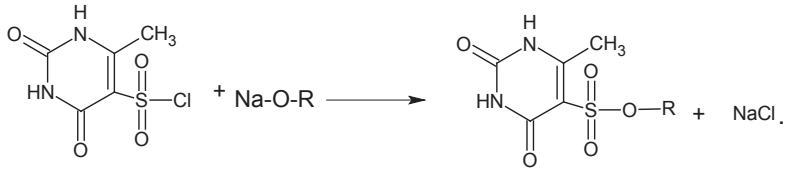
Sulfochlorides are *important intermediates* in the synthesis of sulfanilamide preparations. Compounds of this type are widely used for the preparation of amides, anilides, esters of sulfonic acids, herbicides, fungicides and other compounds. Among the various sulfonic acids and their derivatives, compounds with high pesticidal activity are found [6]. Fungicidal properties are found in many aromatic sulfonates [7, 8]. But practical application is not found, which is connected with their high phytocidal activity.

Herbicidal properties are possessed by salts of various sulfonic acids [8], many esters of sulfonic aliphatic, aromatic, alicyclic and heterocyclic series [7–11]. It is possible that among the methyluracil sulfonic esters there are compounds with similar properties.

Esters of sulfonic acids are usually obtained by reacting an alcohol, sulfochloride and a base (pyridine, triethylamine, dimethylaniline, anhydrous sodium acetate):

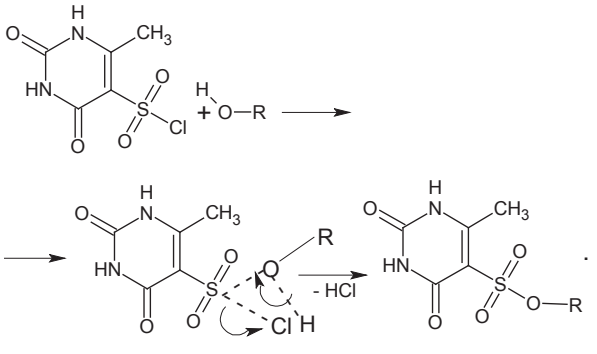
$$Ar\text{-}SO_2\text{-}Cl + R\text{-}OH \xrightarrow{\text{base}} Ar\text{-}SO_2\text{-}O\text{-}R + HCl\,.$$

Ethers of methyluracil sulfochloride and alcohols and phenols are obtained in good yield by the reaction of an acid chloride with alcoholates or phenolates of alkali metals:



This reaction is often carried out at room temperature or at a lower temperature to reduce the side reactions in which alkenes, ethers and alkyl halides are formed. It is found that in the case of 6-methyluracil-5-sulfochloride (MUSC) the same patterns are observed as in the alcoholysis of arylsulfochlorides. The interaction of MUSC with higher primary alcohols passes much faster and with higher yields compared with secondary alcohols and even more so with tertiary alcohols.

When studying the reaction of MUSC with alcohols, which are even weaker acids than water and in mixtures of alcohols, it is established that alcoholysis is carried out similarly to the hydrolysis of sulfochlorides and proceeds via the S_N2 mechanism [12–15]. However, the reaction rate in the first case is much smaller. The influence of the nature of alcohol on the alcoholic kinetics of MUSC shows that with increasing the length of the aliphatic radical, the acidity of the alcohol decreases and the rate constants for the formation of sulfoesters decrease. In this case, the alcoholysis reaction can proceed through the stage of formation of the intermediate complex of the structure:

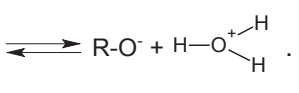


The repulsion and attraction of electrons within molecules is most expedient to consider with respect to some standard, which is usually chosen as hydrogen [16]. On the basis of the analysis, the induction effect of hydrogen in this paper is considered to be zero and chosen as a basis for comparison with other atoms and groups of atoms.

5. Methods of research

According to Ingold, the inductive effect is considered negative (–*I*-effect) if *X* in CH_3–X is more electronegative than carbon and positive (+*I*-effect) if carbon is more electronegative than *X*. With the extension of the carbon chain and its branching, the force the induction effect increases, which, in turn, leads to a decrease in the dissociation constant of alcohols as acids in their homologous series [17].

The alcohols are able to react with the sulfonic acid chlorides in the presence of a base to form the corresponding esters. Alcohols are able to exhibit both acidic and basic properties. As weak acids, alcohols dissociate over the O–H bond to form an alkoxide ion, thus forming a conjugated acid:



ISSN 2226-3780

Acidic properties of alcohols are evaluated by the acidity constant K_a:

$$R\text{-}OH+HOH \rightarrow R\text{-}O^{-}+H_3O^{+},$$

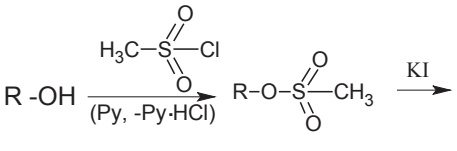
$$K_a = \frac{[R\text{-}O^{-}]\,[H_3O^{+}]}{[R\text{-}OH]},$$

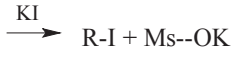
$$pK_a = -\lg K_a.$$

In an aqueous solution, the acidity of the alcohols decreases with increasing molecular weight (extension of the carbon chain) and oxygen branching. As weak acids, alcohols react with alkali, alkaline earth and some other metals, and with strong bases, for example, hydrides or metal amides, Grignard reagents.

Alcohols can behave the same way as weak Lewis bases, forming alkoxonium salts with strong mineral acids. Moreover, they can also form donor-acceptor complexes with Lewis acids. Typically, such reactions do not stop at this stage and lead to the nucleophilic substitution of the hydroxyl group or the elimination of water. Quantitatively, the basicity of the alcohols is estimated from the basicity constant pK_b or the associated acidity constant of the conjugated acid pK_{aH^+} [18].

Alcohols are weak bases, and their basicity increases with the length or branching of the hydrocarbon radical at the hydroxyl group. This effect is observed due to the growth of the positive inductive effect of the radical in this row, due to which the negative charge on the oxygen atom of the hydroxyl group increases. The hydroxyl group is also converted to a sulfate group, which is a good leaving group. For these purposes, the alcohol is first converted to a sulfonate, which is then subjected to a nucleophilic substitution reaction. As reagents for the modification of the hydroxyl group, methane sulfochloride or p-toluene sulfochloride is usually used:

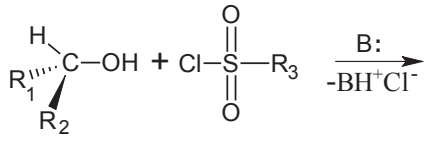


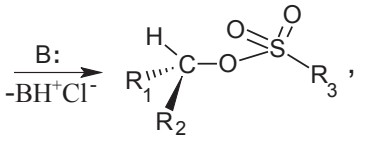


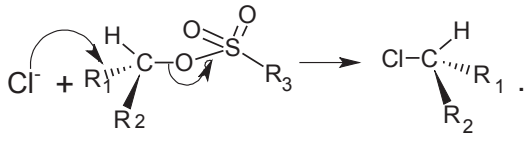
The action of aliphatic alcohols on aromatic and heterocyclic sulfochlorides readily yields esters of sulfonic acids. Primary alcohols react faster than secondary and much faster than tertiary alcohols, which are weaker acids. A selective formation of the primary ester of the sulfonic acid in the presence of secondary and tertiary alcohol groups is possible. Of greatest practical importance is the preparation of alkyl tosylates ($R–O–SO_2C_6H_4CH_3$), alkyl mesilates ($R–O–SO_2CH_3$) and alkyl trifluorates ($R–O–SO_2CF_3$).

The rate of interaction of sulfochlorides with alcohols is significantly influenced by the presence of bases. In the role of the base, pyridine is most often used, which simultaneously acts as a nucleophilic catalyst. Instead of pyridine, aliphatic tertiary amines, for example triethylamine, triethanolamine or pyridine, are often used for this purpose.

The sulfonates are excellent leaving groups and are easily replaced by a halogen atom by the S_N2 mechanism, with the following reversal of the configuration:







The source of the halide ion is usually the corresponding inorganic salt (NaBr, LiCl, CsF, KF, etc.). Dipolar aprotic solvents are used as the solvent: dimethylsulfoxide (DMSO), dimethylformamide (DMFA), acetonitrile. Substitution occurs, as a rule, with reversal of the configuration.

When studying the reaction of MUSC with alcohols, which are weaker bases than water and in a mixture of alcohols, it is established that alcoholysis is carried out, similarly to hydrolysis by the S_N2 mechanism, but the reaction rate in the former case is much less. The influence of the nature of alcohol on the alcoholic kinetics of MUSC shows that with an increase in the length of the aliphatic radical and an increase in the acidity of the alcohols, the rate constants of the acylation decrease.

Methanolysis is slower than hydrolysis, but 3–5 times faster than ethanolysis. The observed differences are due to a change in the enthalpy and entropy.

The method of aliphatic radical substitution of hydroxyl for a highly reactive group is a powerful preparative method in synthetic organic chemistry. This makes it possible to obtain from alcohols in two stages, in addition to halides, the most diverse compounds. For example, it can be ethers, carboxylic acid esters, acid amides and sulfamides, and the like.

6. Research results

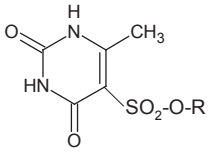
Methyluracil sulfochloride, previously purified by recrystallization from glacial acetic acid, is used for synthesis. The individuality of the product was determined by melting temperature and chromatography on plates of Silufol-254 (Chech Republic). Alcohols are previously making absolute by heating the original alcohol with precalcined quicklime or dehydrated copper sulfate.

In a three-necked flask with a mechanical stirrer and a reflux condenser, 0.055 g/sodium or potassium atom is dissolved in 100 ml of absolute alcohol ($C_1–C_{10}$) with vigorous stirring and cooling. After the evolution of hydrogen evolution ceased, 0.05 moles of methyluracil sulfochloride are added in small portions to the solution of the obtained alcoholate in stirring.

At the end of the exposure, excess alcohol is distilled off, the residue after removal of the alcohol is treated with hot water and filtered. After recrystallization, chromatographically pure alkyl sulfonates are isolated from a suitable solvent.

The obtained experimental data are presented in the Table 1.

Table 1

The physicochemical properties of the 5-alkylsulfonates 6-methyluracils of general formula 

No.	–O–R	Yield, %	T_m, °C	Found, %				Brutto formula	Calculated, %			
				C	H	N	S		C	H	N	S
01	$-CH_3$	95.4	215–216.5	32.63	3.61	12.27	14.56	$C_6H_8N_2O_5S$	32.73	3.66	12.72	14.56
02	$-C_2H_5$	92.8	299–299.4	36.04	4.28	11.88	13.76	$C_7H_{10}N_2O_5S$	35.89	4.30	11.96	13.69
03	$-C_3H_7$-*n*	89.8	192–194	38.58	4.89	11.22	13.08	$C_8H_{12}N_2O_5S$	38.70	4.87	11.28	12.91
04	$-C_3H_7$-*i*	74.5	275	13.61	4.82	11.17	13.11	$C_8H_{12}N_2O_5S$	38.70	4.87	11.28	12.91
05	$-CH_2CH_2OCH_3$	86.1	310	36.31	4.62	1173	12.21	$C_8H_{12}N_2O_6S$	36.36	4.57	11.60	12.13
06	$-C_4H_9$-*n*	88.7	196–196.5	41.11	5.43	10.78	12.33	$C_9H_{14}N_2O_5S$	41.19	5.38	10.68	12.23
07	$-C_4H_9$-*s*	72.1	283	41.26	5.31	10.54	12.29	$C_9H_{14}N_2O_5S$	41.19	5.38	10.68	12.23
08	$-C_4H_9$-*i*	78.2	261–261.5	41.24	5.30	10.61	12.35	$C_9H_{14}N_2O_5S$	41.19	5.38	10.68	12.23
09	$-C_4H_9$-*t*	88.5	>360	41.12	5.41	10.58	12.26	$C_9H_{14}N_2O_5S$	41.19	5.38	10.68	12.23
10	$-C_5H_{11}$-*n*	86.9	245–246	43.39	5.88	10.07	11.72	$C_{10}H_{16}N_2O_5S$	43.48	5.84	10.14	11.61
11	$-C_5H_{11}$-*i*	93.7	249–250	43.54	5.86	10.11	11.76	$C_{10}H_{16}N_2O_5S$	43.48	5.84	10.14	11.61
12	$-C_6H_{11}$-*cyclo*	88.0	>350	45.90	6.22	9.61	11.22	$C_{11}H_{16}N_2O_5S$	45.84	5.59	9.72	11.12
13	$-C_6H_{13}$-*n*	92.3	>330	45.48	6.22	9.90	11.16	$C_{11}H_{18}N_2O_5S$	45.52	6.25	9.65	11.05
14	$-C_6H_5$	94.8	198–199	46.88	3.51	9.91	11.45	$C_{11}H_{10}N_2O_5S$	46.81	3.57	9.92	11.36

Based on the data from Table 1, it is possible to say that the elemental composition of the obtained compounds is practically the same as the calculated content of these elements in the given compounds. This is one of the confirmations of the chemical structure of these structures.

7. SWOT analysis of research results

Strengths. Most of the given compounds obtained by the interaction of methyluracil sulfochloride with alcoholates are not described in the literature. The use of these compounds as a reactant promotes a faster reaction of the nucleophilic substitution of the chlorine atom in the sulfochloride for the alkoxy group. The rapid progress of the exchange reaction between SO_2Cl and the alcoholate significantly shortens the reaction time, and the formation of a pure product removes the investigator from the complex methods of purifying the reaction product.

Weaknesses. The weak side of the process is the fact that for the formation of alcoholate it is necessary to use absolute, that is, without moisture, alcohol. Many alcohols with water form azeotropic mixtures that can't be dispersed even with the use of powerful distillation columns, so for calculating alcohol use calcined quicklime or anhydrous copper sulfate. This entails a waste of expenditure.

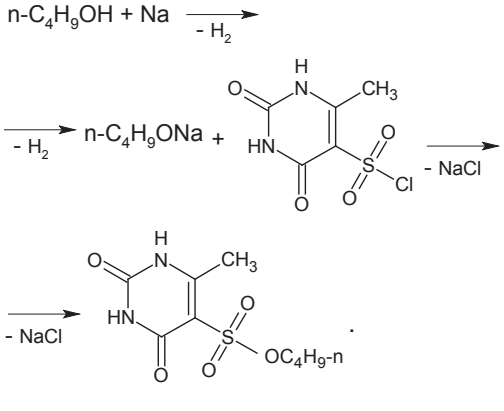
Opportunities. Preliminary screening for most of the compounds studied shows their high biological activity, so it is possible that among the synthesized compounds there are those that will find practical application in the future.

Threats. Methyluracil is used in medicine as an energy stimulant, and is also a part of nucleic acids, therefore it does not pose a threat to the objects of research. Analogues devoted to the synthesis of the interaction products of MUSC and alcohols have not been found in the literature.

8. Conclusions

1. In the course of the studies, the principle of sulfochlorination of methyluracil is changed. In order to increase the yield and improve the quality of the final product, the reaction of methyluracil with freshly distilled chlorosulfonic acid is carried out in an inert solvent such as dichloroethane, followed by the addition of thionyl chloride.

To improve the quality of synthesized compounds and simplify the synthesis, the used methyluracil is reacted with metallic sodium or potassium to form an alcoholate. Further, the obtained alcoholate reacts with the calculated amount of the sulfochloride, forming an almost chemically pure final product:



2. The preliminary biological activity of synthesized compounds and the possibility of using the obtained compounds as cytostatics are determined using the PAAS program. NMR spectroscopy and elemental analysis confirm the composition and structure of the obtained compounds, the data of which are given in Table 1.

ISSN 2226-3780

References

1. Khromov-Borisov N. V., Karlinskaya R. S. Sintezy i prevrashheniya proizvodnykh pirimidina. Sul'foproizvodnye tsitozina, 4-metiltsitozina i uratsila // Zhurnal obshhey khimii. 1957. Vol. 27, No. 9. P. 2518–2521.
2. Khromov-Borisov N. V., Karlinskaya R. S. Sintezy i prevrashheniya proizvodnykh pirimidina. Sul'firovanie proizvodnykh pirimidina // Zhurnal obshhey khimii. 1954. Vol. 24, No. 8. P. 2212–2215.
3. Pokhidni 6-metil-2,4-digidroksipirimidin-5-sul'fonamidu i sposib ikh oderzhannya: pat. 75516 UA. MPK A61P 31/12, C07D 239/69, A61P 31/04, A61K 31/505 / Pogorelova I. P., Isak A. D. Appl. No. 20040806492; Filed: 03.08.2004; Published: 17.04.2006. Bull. No. 4.
4. Pogorelova I. P., Orlov V. D., Isak A. D. Synthesis of 6-methyluracil-5-sulfonyl chloride // Russian Journal of Applied Chemistry. 2006. Vol. 79, No. 4. P. 631–633. doi:10.1134/s1070427206040240
5. Elderfield R. C., Prasad R. N. Synthesis of Potential Anticancer Agents. XI. Synthesis and Reactions of Derivatives of 6-Methyluracil-5-sulfonic Acid1, 2 // The Journal of Organic Chemistry. 1961. Vol. 26, No. 10. P. 3863–3867. doi:10.1021/jo01068a058
6. Sposib otrymannia 6-metyluratsyl-5-sulfokhlorydu: pat. 106558 UA. MPK A01N 25/00, C07C 307/00, A61K 31/08 / Abdo-Allah M., Shypydchenko M. V., Isak A. D. Appl. No. u 201511581; Filed: 23.11.2015; Published: 25.04.2016. Bull. No. 8.
7. Melnikov N. N. Pestitsidy. Khimiya, tekhnologiya i primenenie. Moscow: Khimiya, 1987. 712 p.
8. Halo-Substituted Cyanomethyl Benzenesulfonates: pat. US3873591A / Smith H. Q., Toukan S. S.; assignee: Pennwalt Corp. Published: 25.03.1975.
9. Fungicidal Compositions and processes using azonaphthol sulphonic acid derivatives: pat. GB1427516A; assignee: Imperial Chemical Industries Ltd. Published: 10.03.1976.
10. Double salt of copper alkyl phenolsulphonate an d basic calcium – useful as agricultural germicide: pat. DE2533102A1; assignee: Yonezawa Chemical Industries Co Ltd. Published: 27.01.1977.
11. Perfluoroalkanesulfonate ester Herbicides: pat. US3954828A / Fridinger T. L. Published: 04.05.1976.
12. Wegler H. K. Chemie der Pflanzenschuetz und Schudlingsbekampfungsmittell. Vol. 8. Berlin: Springer. Verlag, 1982. 485 p.
13. Jenkins F., Hambly A. Solvolysis of Sulphonyl Halides. I. The Hydrolysis of Aromatic Sulphonyl Chlorides in Aqueous Dioxan and Aqueous Acetone // Australian Journal of Chemistry. 1961. Vol. 14, No. 2. P. 190–212. doi:10.1071/ch9610190
14. Linetskaya Z. G., Sapozhnikova N. V. Kinetika gidroliza nekotorykh sul'fokhloridov aromaticheskogo i zhirnogo ryada // Doklady AN SSSR. 1952. Vol. 6, No. 4. P. 763–766.
15. Tommila E., Jutila J., Burstrom H. Hydrolysis and Alcoholysis of Sulphonic Esters // Acta Chemica Scandinavica. 1952. Vol. 6. P. 844–853. doi:10.3891/acta.chem.scand.06-0844
16. Reutov O. A. Teoreticheskie osnovy organicheskoy khimii. Moscow: MGU, 1964. 700 p.
17. Ingold K. Teoreticheskie osnovy organicheskoy khimii. Moscow: Mir, 1973. 1056 p.
18. Dneprovskiy A. S., Temnikova T. I. Teoreticheskie osnovy organicheskoy khimii. Leningrad: Khimiya, 1991. 560 p.

ПОИСК НОВЫХ БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ НА ОСНОВЕ 6-МЕТИЛУРАЦИЛ-5-СУЛЬФОХЛОРДА И СПИРТОВ

Проведено исследование реакции взаимодействия алифатических и ароматических спиртов с 6-метилурацил-5-сульфохлоридом (МУСХ). Показано, что удобней всего проводить взаимодействие 6-метилурацил-5-сульфохлорида с предварительно приготовленным алкоголятом в избытке исходного спирта. Предварительные исследования (использование программы PAAS) показали, что среди полученных соединений имеются такие, которые проявляют антиоксидантные свойства и могут быть использованы в качестве цитостатиков.

Ключевые слова: биологически активные соединения, синтез алкилсульфонатов на основе 6-метилурацил-5-сульфохлорида и алкоголятов, реакционная способность.

Abdo-Allah Masud, *Postgraduate Student, Department of Ecology, Institute of Chemical Technologies of the Volodymyr Dahl East Ukrainian National University, Rubizhne, Lugansk region, Ukraine, ORCID: https://orcid.org/0000-0002-8403-5301*

Mospanova Elena, *PhD, Associate Professor, Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine, e-mail: elena_mospanova@list.ru, ORCID: https://orcid.org/0000-0002-6575-5135*

Popov Yevgeniy, *Doctor of Technical Sciences, Professor, Department of Ecology, Institute of Chemical Technologies of the Volodymyr Dahl East Ukrainian National University, Rubizhne, Lugansk region, Ukraine, e-mail: popov@iht.lg.ua, ORCID: http://orcid.org/0000-0001-7941-5134*

Isak Alexandr, *PhD, Associate Professor, Department of General Chemistry Disciplines, Institute of Chemical Technologies of the Volodymyr Dahl East Ukrainian National University, Rubizhne, Lugansk region, Ukraine, e-mail: isak_ad@ukr.net, ORCID: https://orcid.org/0000-0002-9985-5011*

UDC 548.31
DOI: 10.15587/2312-8372.2018.124287

Artemev S.,
Shaporev V.,
Tsymbal B.

INVESTIGATION OF METHODS OF OBTAINING WHISKERS IN COMPOSITE MATERIAL

Досліджено методи отримання ниткоподібних кристалів у композиційному матеріалі. Зосереджено увагу на процесі отримання ниткоподібних кристалів хімічною взаємодією між газом та контактною речовиною, а також методом (пар – рідина – тверде). Показано перевагу проведення процесу конденсації крізь рідку фазу у порівнянні з процесом прямої конденсації з парової фази у тверду.

Ключові слова: *методи отримання ниткоподібних кристалів, композиційні матеріали, хімічна взаємодія між газом та контактною речовиною.*

1. Introduction

The methods of obtaining whiskers for a long time continue to be a rather urgent problem for the study of modern science. This is evidenced by an increase in the problems of these issues during scientific conferences and seminars, since any obtained experimental result deserves discussion and consideration. Scientists should clearly welcome

 © Artemev S., Shaporev V., Tsymbal B.