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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

SYNTHESIS AND TRANSFORMATIONS OF POLYFUNCTIONAL CARBONYL COMPOUNDS

Specialty: 2306.01 Organic chemistry

Field of science: Chemistry

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BAKU – 2021

The work was performed at the Department of Chemistry, Faculty of Biology-Chemistry Ganja State University.

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GENERAL CHARACTERISTICS OF THE WORK

Relevance and state-of-the-art of the topic. The alkylation reactions of β-dicarbonyl compounds, which are widely used for the preparation of complex organic substances, are one of the developing areas of organic synthesis. Respectively, the synthesis and reactions of phosphorus analogs of β-dicarbonyl compounds are particularly relevant. The synthesis of functionally substituted carbo- and heterocyclic compounds based on low-step reactions of these compounds is particularly important in producing biologically active and optically active materials.

The presented thesis covers the synthesis of derivatives of furan, resorcinol, cyclohexa-2,5-dione, phosphonoacetaldehyde, phosphonoacetate, and other classes of compounds using condensation reactions of polycarbonyl compounds and their phosphorus analogs with halogenated alkanes, including structural and mechanistic studies.

The dissertation work is part of research program of the Department of Organic Chemistry of Baku State University (state registration No. 0112Az 2041) on the title «Synthesis and study of functional organic compounds».

The object and the subject of the research. Synthesis of polyfunctional carbonyl compounds, as well as their phosphorus analogs and aromatic carbonyl compounds. Preparation of functionally substituted different classes (furan, resorcinol, oximes, hydrazones, hydroxyquinone derivatives, lactones, etc.) of compounds based on the conversion of synthesized substances.

The aim and objectives of the work. This study was carried out to solve the following goals: a) obtaining of various heterocyclic compounds as a result of the reaction of carbonyl compounds with mono- and polyhalogenated reagents by a simple preparative method; b) To use the potential of alkylation reactions for the synthesis of polycarbonyl compounds by adding a new carbonyl fragment to the original carbonyl substances; c) to identify the reasons for the low productivity of alkylation reactions by studying the interaction of various factors (temperature, solvent, substrate, reagent, catalyst) separately; d) on the base of the acylation reaction to obtain derivatives of phenols containing two acetyl groups in the aromatic ring and to study some of their chemical properties.

Research methods. The structure of the synthesized compounds was studied by IR, ^{1}H, and ^{13}C NMR spectroscopy and X-ray analysis methods. The conformational analysis of α-phosphoryl carbonyl compounds in different media (acidic, basic, and neutral) was carried out by ^{1}H NMR spectroscopy.

The main theses of the defense:

1. Synthesis of polyfunctional furan and benzene derivatives based on the reaction of dimethylacetonedicarboxylate with mono- and polyhalogenated compounds.

2. Obtaining enol esters of 1,4-dimethyldicarboxylate-2,5-cyclohexadione by condensation of methyl 4-chloroacetoacetate with di- and trihaloalkanes in presence of potassium carbonate in dimethyl sulfoxide medium.

3. Synthesis of functional substituted compounds by the interaction of carbonyl compounds containing the active methylene group with α-bromopropionate and bromacetal.

4. Synthesis of hydroquinone compounds containing an acetyl group, then performing some substitution reactions in the carbonyl group and aromatic ring.

Scientific novelty. Polyfunctional furans were synthesized as a result of a one-step reaction of dimethyl acetonedicarboxylate with mono- and polyhalogen compounds. It was found that besides the initial alkylation reaction of the ketone, potassium carbonate and dimethyl sulfoxide take part in a competitive self-condensation reaction to form resorcinol derivatives. It has been experimentally confirmed that the condensation of methyl 4-chloroacetoacetate with di- and trihaloalkanes is a multi-stage process. It has been found that this compound is readily converted to 1,4-dimethyldirobaxylate-2,5-cyclohexadione in high yield in presence of potassium carbonate and dimethyl sulfoxide. At the next stage, the O-alkylation of the latter leads to the formation of corresponding enol ethers. On the other hand, it has been shown that methyl 4-acetoacetate is converted to an aromatic compound in presence dry potassium carbonate.

The stability and reactivity of phosphonate conformers were studied in various media by ^{1}H NMR.

The introduction of formyl fragment to phosphonic aldehyde, phosphonacetate and phosphonacetonitrile backbone was achieved by

their alkylation with bromocetal in the presence of alkali metal.

The theoretical and practical value of the work. Alkylation of carbonyl compounds and their phosphorus analogs makes it possible to obtain new types of polyfunctional compounds, in turn, are starting materials for the synthesis of biological active furan and other heterocyclic systems.

The research outcomes can be useful to scientific and pedagogical staff working in the field of chemistry of phosphorus and heteroaromatic compounds of fine organic synthesis.

Applicant's personal contribution to the research. The applicant was directly involved in the realization and preparation of the dissertation. She studied the recent world literature on the synthesis and transformation of polycarbonyl compounds, summarized collected data, and demonstrated her personal approach in a literature review. The applicant took an active part in lab experiments in synthesis and purification of compounds (by vacuum distillation, crystallization methods), as well as in studying their structures by physicochemical research methods (NMR, X-ray). Regarding to reaction mechanisms she expressed her views in her single-authored articles.

Approbation and application: 15 scientific papers have been published on the topic of the dissertation, including 9 articles (6 in foreign journals), 6 abstracts (1 at an international conference). The essential part of the work was presented at international and local conferences in Russia and Azerbaijan: conferences devoted to the national leader Heydar Aliyev's anniversaries (Baku, 2014-2016; Ganja, 2015), All-Russian Conference dedicated to Chemistry and Technology of Heterocyclic Compounds (Ufa, 2017), International Conference of Young Researchers (Baku, 2013), International All-Russian Conference (Moscow, 2015).

Name of the organization where the dissertation work is carried out: Ganja State University.

The structure and scope of the thesis. The thesis consists of an introduction part, three chapters (literature review, discussion of results, experimental part), results, references to the literature used (243 titles), and 34 figures, in total, covered in 180 pages. The main part of the work is 162853 characters.

The *first chapter* (46511 characters) is a literature survey on the

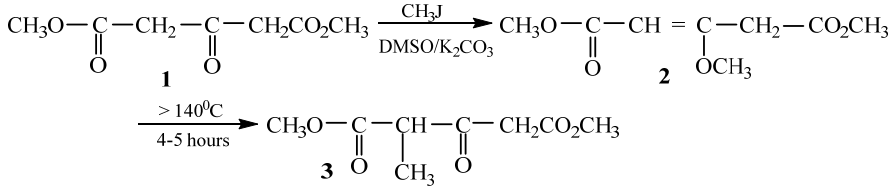
chemistry of carbonyl compounds, mainly over the past 10 years.

The *second chapter* (65602 characters) discusses the results obtained in the study of the synthesis and transformation of polyfunctional carbonyl compounds.

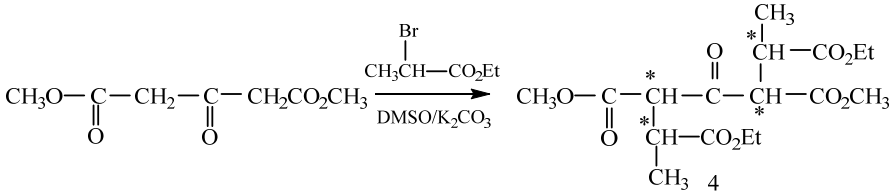
The *third chapter* (42479 characters) describes the methods of the experimental part of the study and the physicochemical characteristics of the synthesized compounds.

THE MAIN CONTENT OF THE WORK

1. **Alkylation of dimethyl acetonedicarboxylate with mono- and polyhalogen compounds.** Only O-alkylation product was obtained by the reaction of dimethyl acetondycarboxylate (1) with methyl iodide in presence of potassium carbonate in dimethyl sulfoxide medium at 40-60°C. The latter is converted to a C-alkylation product at 140-150°C and above.



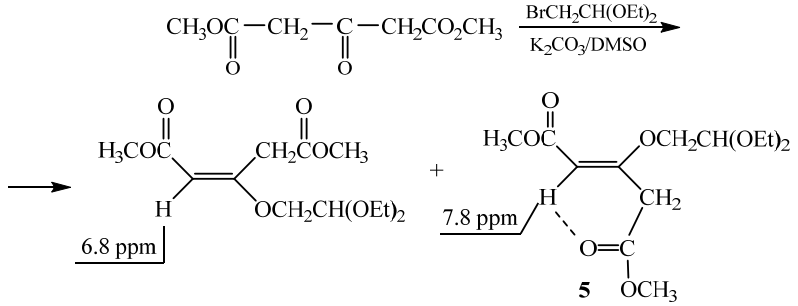
Alkylation of compound (**1**) with α-bromopropionate runs on the both active methylene groups.



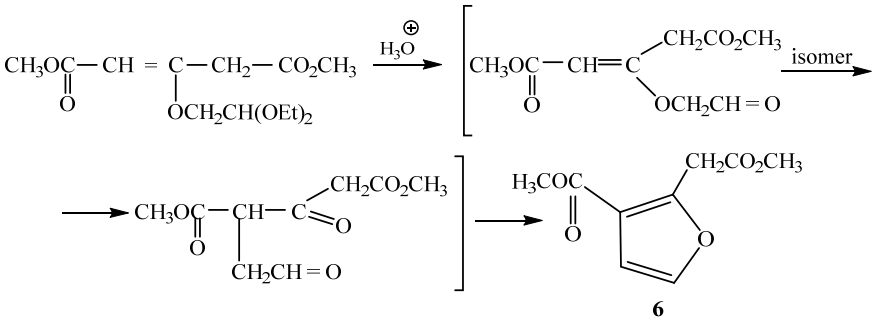
Although the formation of compound (**4**) initially occurs with the O-alkylation reaction, it can also be considered as the complete conversion of the latter to C-alkylation compounds under the influence of temperature.

The presence of four asymmetric carbon atoms in the synthesized compound is also reflected in NMR spectra, which means that this compound consists of a mixture of multiple stereoisomers.

The study of the alkylation reactions of compound (**1**) with halide acetals has great theoretical and practical importance. The aim was to synthesize tetracarbonyl compound by adding another active methylene and carbonyl group to the structure of compound (**1**), which belongs to the class of tricarbonyl compounds containing two active methylene groups. The reaction of (**1**) with bromoacetaldehyde diethyl acetal was carried out in the presence of potassium carbonate in a dimethyl sulfoxide environment. But the alkylation of ketone (**1**) with bromocetal occurs mainly at the oxygen atom, which lead to formation of O-alkylation product (**5**). The ^{1}H and ^{13}C NMR spectra confirmed that the latter consists of a mixture of two geometric isomers.



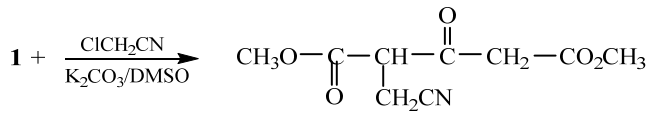
It was found that isomerization does not occur when the compound (**5**) is heated for 3-4 hours at 140-150°C. On the other hand, the aldehyde obtaining from the hydrolysis of this compound readily isomerized to the C-alkylation product, in turn lead to formation of furan (**6**).



Due to the sterical hindrance created by the acetal moiety in compound (**5**), it can be assumed that such isomerization does not take place since it prevents the attacking of methylene group to the carbanion. However, the formylmethylenolic ether obtained by hydrolysis

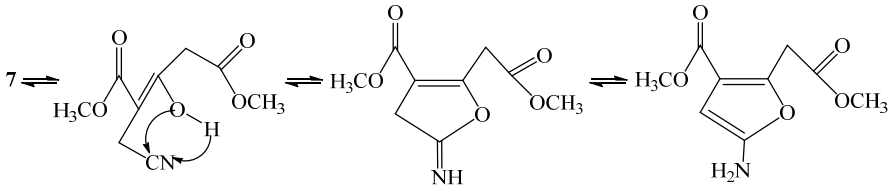
of this compound readily isomerized in an acidic medium to C-formyl methyl acetonedicarboxylate and then to the furan derivative (**6**).

The insertion of the nitrile moiety in the active methylene group of triketone (**1**) has great preparative importance. Thereby the interaction of compound (**1**) with chloroacetonitrile was studied. The reaction was carried out in various solvents and conditions, and it was shown that only the *C*-alkylation product (**7**) is obtained in a potassium carbonate/ dimethyl sulfoxide reaction system.



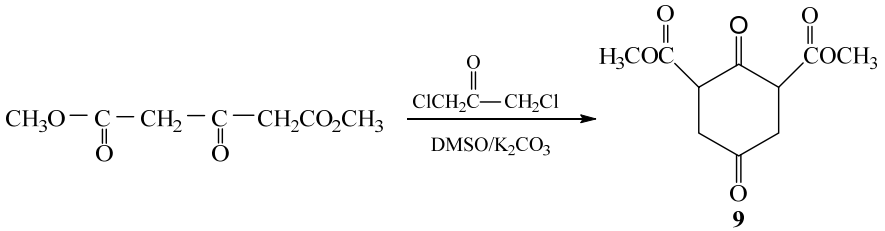
7

In an acidic medium, compound (**7**) undergoes sequential intramolecular transformations (prototropic isomerization, addition) to form α-aminofuran (**8**).



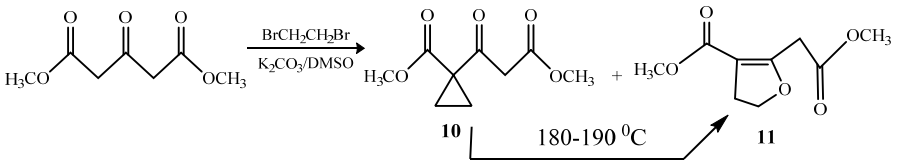
8

Alkylation of compound (**1**) with biselectrophilic 1,3-dichloroacetone takes place at both active methylene groups and leads to the formation of cyclohexanedione derivative (**9**).



9

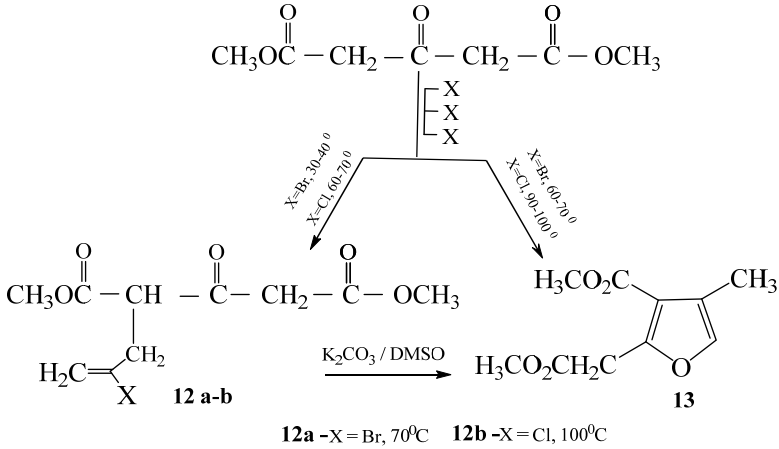
The reaction of dimethyl acetonedicarboxylate (**1**) with 1,2-dibromoethane in the presence of potassium carbonate in dimethyl sulfoxide at 50-60°C for 6-8 hours lead to the formation of C,C-alkylation (**10**) and C,O-alkylation (**11**) products.



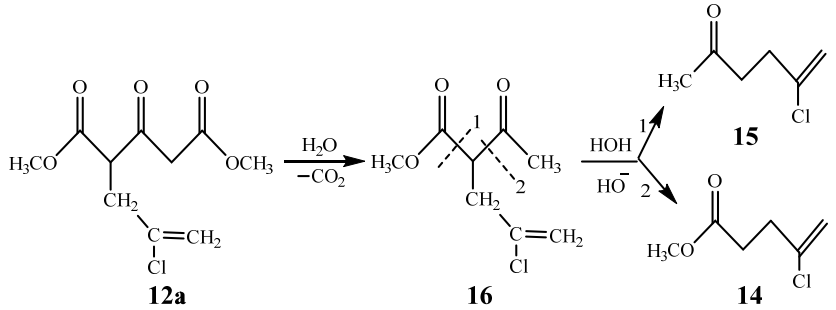
Probably under this reaction condition any of the methylene groups of substrate (**1**) can undergo alkylation because of the same activity of both methylene groups. Then, the ring closure of the formed intermediate in the C- and O-alkylation directions leads to the formation of cyclopropane (**10**) and furan (**11**) derivatives.

Isomerization of compound (**10**) into (**11**) as a result of recyclization-cyclization at 180°C was confirmed by ^{1}H and ^{13}C NMR spectra.

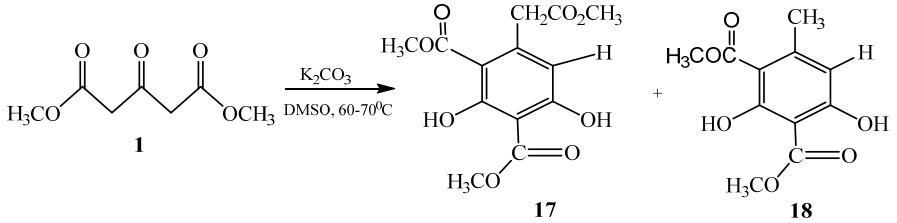
The study of the reactions of alkylation of acetone dicarboxylate (**1**) with 1,2,3-trihalopropanes suggests that the direction of the reaction depends on a number of factors, including the nature of the halogen and the reaction temperature. If halogen is the bromine reaction runs at 30-40^{0}C and in the case of chlorine, it runs at 60-70°C which generally give rise formation of alkylation products (**12a,b)**. When the condensation is carried out at 70°C (x = Br) and 90-100 °C (x = Cl), the formation of the furan derivative (**13)** takes place.



Then compound (**12a)** undergoes destructive transformations to form keto- and acidic derivatives (**14-16)**. The proposed mechanism for the formation of these compounds is described in the corresponding section of the thesis.

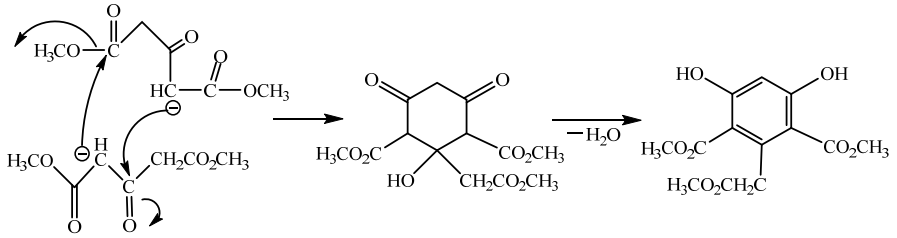


Amorphous crystals precipitated upon neutralization of the aqueous phase by the hydrochloric acid. The precipitate was confirmed to be a mixture of two resorcinol derivatives. By recrystallization from this mixture were isolated 5-methoxycarbonylmethyl-4,6-di(methoxycarbonyl)resorcinol (**17)** and 5-methyl-4,6-di (methoxycarbonyl)resorcinol (**18)**.



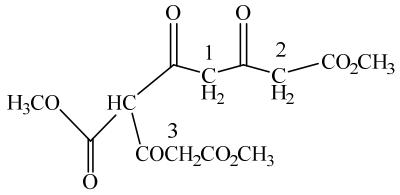
The mechanism of the formation of products (**17)** and (**18)** can be described as follows. The presence of active methylene and ester groups in 1,3-dimethyl acetonedicarboxylate facilitates the formation of the $CH_3OCO\bar{C}H–CO–CH_2CO_2CH_3$ carbanion in dimethyl sulfoxide in the presence of potash at the first stage. Probably the resulting carbanion is subsequently converted to resorcinol by a single or multi-step transformation.

A one-stage reaction is possible only in the case of its simultaneous (synchronous) Claisen condensation and the aldol-type mechanism.



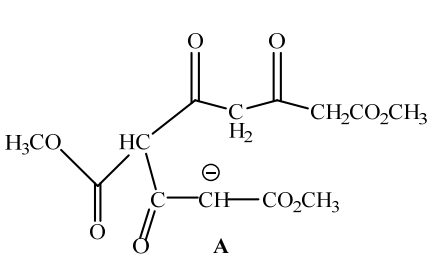
The formation of only one resorcinol isomer can take place in this reaction pathway.

When the reaction proceeds through a multi-stage scheme, in the first stage, Claisen condensation leads to the formation of a ketone (**X**), containing three active methylene groups (1, 2, 3).

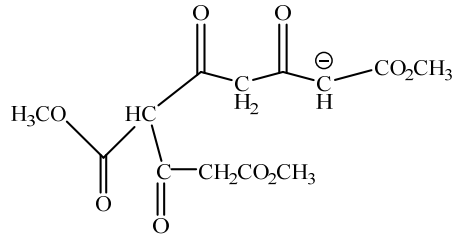


X

From a theoretical and sterical point of view, since the 2nd and 3rd methylene groups have the same probability of forming a carbanion, one can imagine the formation of two different carbanions (carbanions A and B).

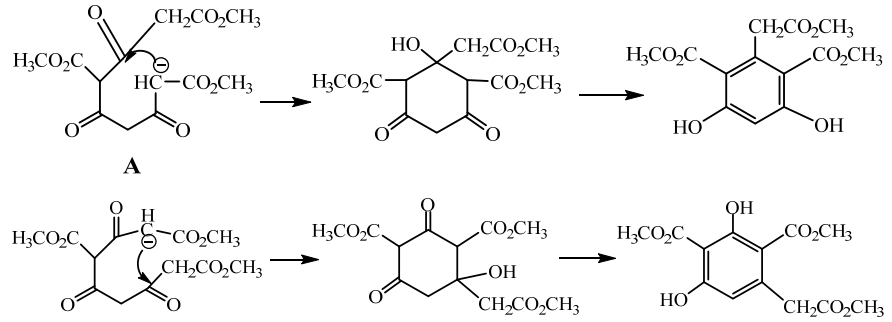


A



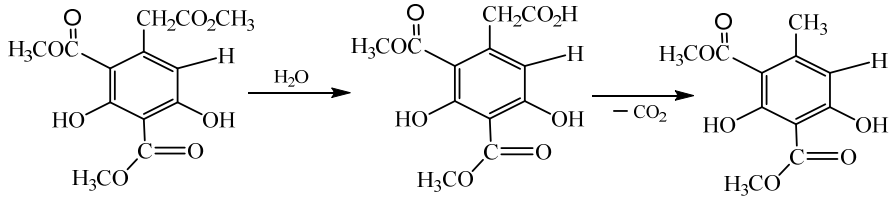
B

Since these carbanions are different, the resorcinol compounds they form need not be the same and must be obtained as isomers.



Since resorcinol obtained from carbanion A has a symmetrical

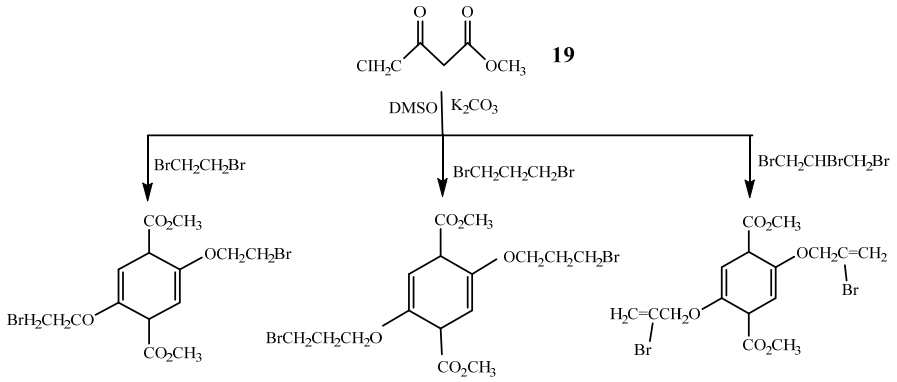
molecule, OH groups are equivalent and should give one signal in the nuclear magnetic resonance (NMR) spectrum. The presence of two OH peaks in the NMR spectrum confirms the formation of the obtained resorcinol from the B anion. Thus, self-condensation of dimethyl-1,3-acetonedicarboxylate leads to the formation of 2,4-dihydroxy-6-(2-methyl-2-hydroxyethyl) phthalate as a result of a multistep reaction. At the first stage, Claisen condensation occurs, and then the carbanion B lead to the formation unsymmetrical resorcinol molecule. The formation of a single isomer can be explained by its energetic stability. The formation of the second possible resorcinol isomers was not observed. The formation of compound (**18)** takes place by hydrolysis and decarboxylation of a part of compound (**17)** under the reaction conditions.



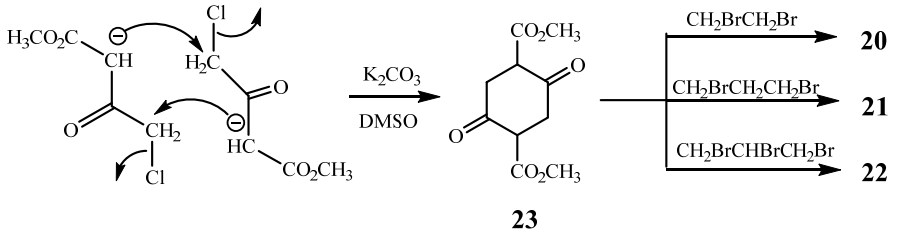
17 **18**

2. Interaction of methyl 4-chloro-3-oxobutanoate with polyhaloalkanes. The presence of an active chlorine atom in the α-position in methyl 4-chloro-3-oxobutanoate causes special functional properties. It can be assumed that this compound behaves differently from β-dicarbonyl compounds in the alkylation process that could impact reaction to proceed in different pathways. Therefore, the reaction of methyl 4-chloro-3-oxobutanoate (**19)** with di- and trihalogenated alkanes is of theoretical and synthetic interest.

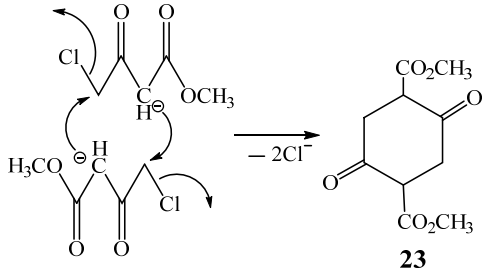
The reaction of methyl 4-chloro-3-oxobutanoate (**19)** with 1,2-dibromethane, 1,3-dibromopropane and 1,2,3-tribromopropane at 40-60°C in the presence of potassium carbonate in dimethyl sulfoxide medium give rise to the formation of enol ethers: dimethyl 2,5-bis(2-brometoxy)cyclohexa-2,5-diene-1,4-dicarboxylate (**20)**, dimethyl 2,5-bis(3-bromopropoxy) cyclohexa-2,5-diene-1,4-dicarboxylate (**21)**, dimethyl 1,4-dimethyldicarboxylate-2,5-bis(2-bromopropen-2-yloxy)-cyclohexa-2,4-diene (**22).**



Probably as a result of intermolecular condensation of compound 19 the formation of dimethyl 2,5-dioxocyclohexane-1,4-dicarboxylate takes place at the first stage (**23**). The latter is O-alkylated with the mentioned dihaloalkanes to form compounds (**20-22**). This hypothesis is proved experimentally. Thus, we found out that 2,5-dimethoxycarbonyl 1,4-cyclohexandione (**23**) is formed from (**19**) at room temperature and under certain conditions, and this intermediate (**23**) is converted to (**20-22**) upon reaction with alkyl halides.

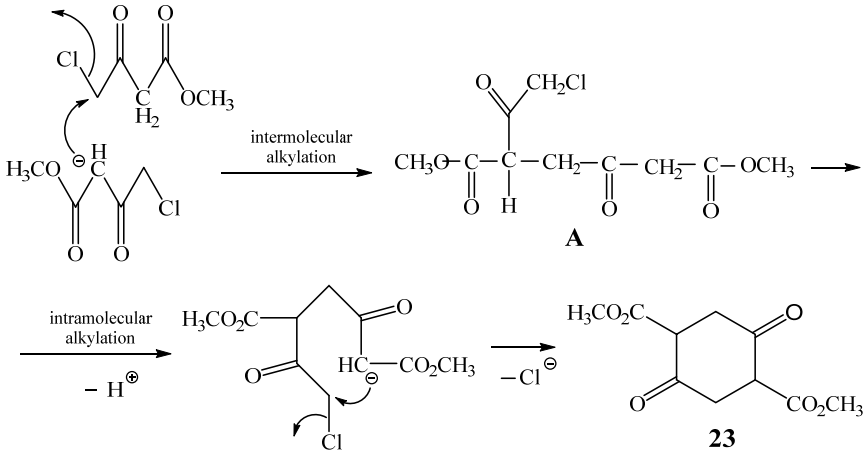


Speaking about the mechanical nuances of the formation of cyclohexadione (**23**), it should be noted that, despite the structural similarity between substrates (**1**) and (**19**), the structure of (**19**), in contrast to substrate (**1**), allows the chloromethyl group to act as a new reaction center. It was found that self-condensation of substrate (**19**) during the formation of cyclohexadione (**23**) occurs only by acting of active methylene (CH_2) and chloromethyl (CH_2Cl) groups. The formation of cyclohexadione (**23**) can be shown by a one- and two-step mechanism. The mechanism of a one-step reaction can be considered as a synchronous cyclization of two carbanion molecules.



23

If the reaction proceeds in a multistep process, the intramolecular cyclization of intermediate A, appeared in the first stage of reaction, leads to the formation final product.

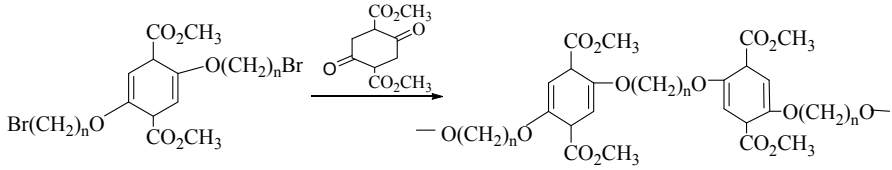


A

23

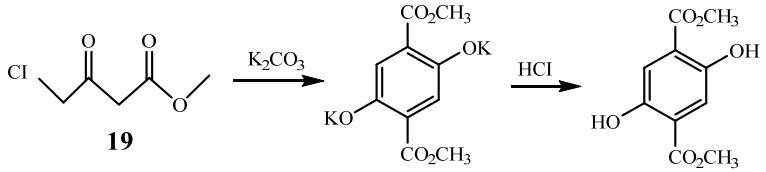
As can be seen from the considered schemes, the absence of Claisen condensation in these transformations can be explained only by the activity of the chloromethyl (CH_2Cl) fragment.

In the course of this reaction, the formation of polymer glassy crystals as byproducts was observed. These polymer compounds can be considered as a condensation product of substances (**20)** and (**21)** with diketone (**23)**. A detailed study of the obtained polymer is the subject of an additional investigation.



It should be noted that this polymer substance was not prepared by alkylation of compound (**23)** with 1,2,3-tribromopropane. Thus, this is explained by the inactivity of the bromine atom in the resulting substance (**22)**.

We have shown for the first time that compound (**19)** is directly converted to an aromatic compound in presence of potassium carbonate. The reaction leads to the formation of potassium phenolate derivative (**24)** under exothermic conditions. And the latter is converted into 1,4-dimethyl dicarboxylate dihydroquinone (**25)** upon treatment with hydrochloric acid.



19 **24** **25**

The structure of compounds (**24)** and (**25)** was elucidated by ^{1}H and ^{13}C NMR spectroscopy. Moreover, the structure of (**25)** was investigated by the X-ray method.

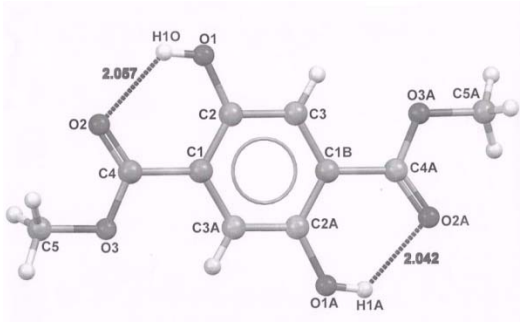


Figure 1. Molecular structure of (**25)**.

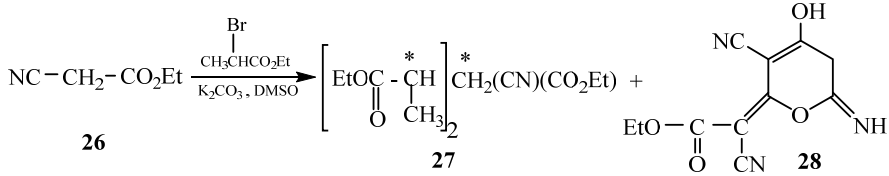
It can be imagined that, since the molecule of (**25)** has a symmetrical structure, the length of the intramolecular hydrogen bonds should be the same. However, it is clear from the results of the X-ray analysis that the length of one hydrogen bond is 2.042 and the other is 2.057, which means they have different values. The reason for this can be the formation of these bonds at different stages. The structure of the synthesized products was confirmed by ^{1}H and ^{13}C NMR spec-

troscopy.

Although methyl 4-chloro-3-oxobutanoate (**19)** belongs to the class of β-dicarbonyl compounds, it behaves differently in alkylation reactions and does not form C-alkylation products and furan derivatives. This is due to the active chlorine atom in the structure of (**19)**.

3. Reactions of β-dicarbonyl compounds with ethyl-α-bromopropionate and halide acetals. Alkylation of compounds containing an active methylene group is widely reported in the literature. In this section, we discuss the reactions of acetylacetone, acetoacetic ether, ethyl nitrile acetate with ethyl α-bromopropionate and halide acetals. The specific properties of the alkylating agent used in these reactions have led to interesting new results.

The study of this reaction is of synthetic and stereochemical importance. Theoretically, the starting materials used in both reactions are likely to form a carbanion in presence of potassium carbonate, and due to their high stability in dimethyl sulfoxide, other reactions are possible in addition to the alkylation reactions. The reaction of ethyl nitrile acetate (**26)** with ethyl-α-bromopropionate in presence of in presence of potassium carbonate in dimethyl sulfoxide medium at 60-70°C for 6-8 hours lead to the formation of only the C,C-alkylation product 2,4-dimethyl-3-cyano-3-ethoxycarbonylpentadionic acid diethyl ester (**27)**. However, a detailed investigation of the reaction system made it possible to determine the formation of (**28)** (extracted from the aqueous phase) as a second product.



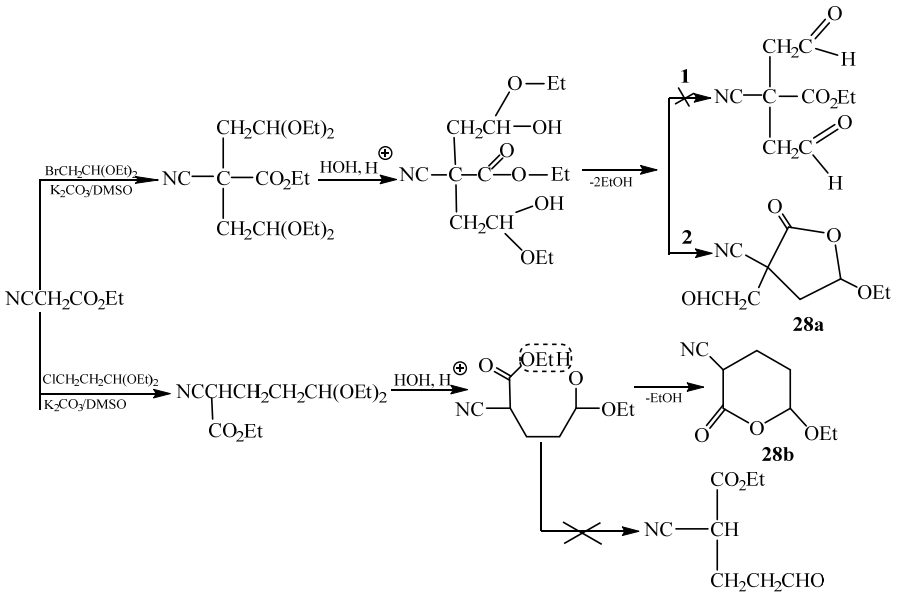
26 **27** **28**

Probably formation of an oxynane derivative (**28)** can be considered as the Claisen condensation of three molecules of ethyl nitrile acetate and latter intramolecular addition of an enol group to nitrile group in condensation product.

Since there are three chiral centers in (**27)**, the presence of 8 stereoisomers in the reaction product is inevitable, and the ^{1}H and ^{13}C nuclear magnetic resonance spectra were used to study the composition.

It is well known that while enantiomers give the exact same spectrum the spectra of diastereomers differ. By evaluating the nature and intensities of signals in the spectrum of diastereoisomers, it is possible to comment on the composition of the mixture. Thus, the presence of signals in the ^{1}H NMR spectrum of compound (**23)** at 1.28 d, 1.25 d, 1.37 d, 3.0 q, 3.1 q, and 3.2 q ppm indicates that there are three diastereoisomers in the mixture in a ratio of 1:2:3.

The alkylation of ethyl nitrile acetate with bromoacetaldehyde diethyl acetal in the presence of potassium carbonate in dimethyl sulfoxide medium led to the formation of dialkylation product. When this reaction is carried out with chloropropionaldehyde diethyl acetal, only the monoalkylation product is formed. Polyfunctional γ-butyrolactone (**28a)** and δ-valeriolactone (**28b)** were obtained by hydrolysis of the resulting acetals.

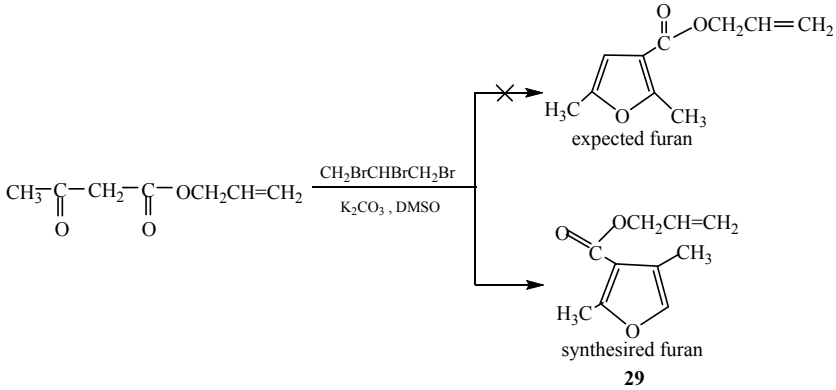


An unusual course of these reactions can be explained by the conformation of the intermediates.

4. Synthesis of functionally substituted furans on the base of β-dicarbonyl compounds. The synthesis of furan and its derivatives is always a point of great interest. These compounds can be synthesized in organic synthesis by various synthetic approaches as well as on the

base of 1,3-dicarbonyl compounds. Being valuable chemicals in organic synthesis, they also have strategic importance in the industry.

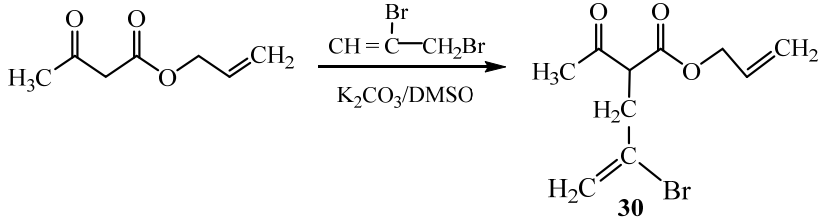
In continuation of our study carried out in organic chemistry department at Baku State University, the reaction of allyl acetoacetate with 1,2,3-tribromopropane was studied. The reaction was carried out at 60-70°C in presence of potassium carbonate in dimethyl sulfoxide medium for 6-8 hours and 2,4-dimethyl-3-allyloxycarbonylfuran (**29)** was synthesized with 60% yield.



29

The formation of compound (**29)** proceeds through sequential alkylation, elimination, rearrangement, intramolecular O-alkylation, and prototropic isomerization stages.

Recent studies have shown that the use of 2,3-dibromopropene-1 or tribromopropane in this reaction system leads to the formation of C-alkylation product 2-bromopropene-2-yl allyl acetate (**30)**. The reaction was carried out in in presence of potassium carbonate in dimethyl sulfoxide environment at 30-40°C for 3-4 hours.



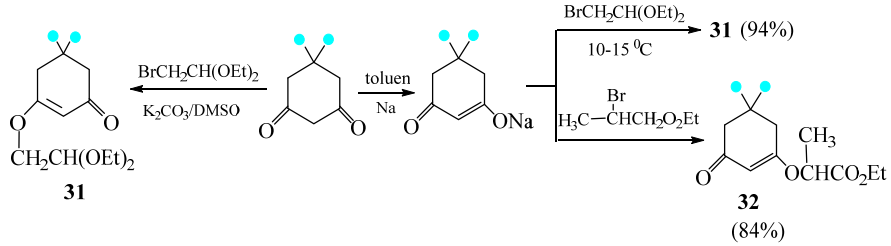
30

To understand the formation mechanism of furan derivative (**29)**, we studied the structure of intermediate (**30)**, a C-alkylation product isolated from the reaction system and its rearrangement into com-

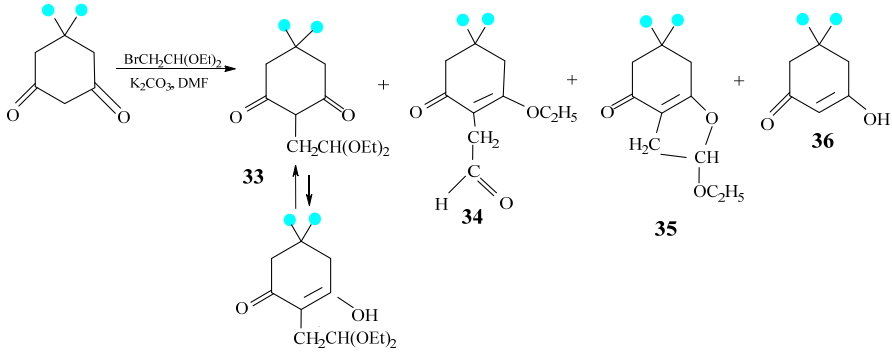
pound (**29**). Interestingly, the elimination of hydrogen bromide (HBr) was sufficient for ring-closing of intermediate (**30**) to give expected furan, but the reaction proceeded through a more complex transformation scheme, resulting in the formation of compound (**29**).

The incorporation of a formyl moiety into an active methylene group by alkylation methods has great importance in organic synthesis. One of the approaches for «protecting» the formyl group of haloaldehydes is using them in the form of acetals.

For the first time, the reaction of dimedone with diethyl bromoacetal was carried out in K_2CO_3/DMSO and K_2CO_3/DMF systems or in Na/toluene system, and it was found that in dimethyl sulfoxide and toluene medium the formation of O-alkylation product **31** takes place. In presence of sodium in toluene medium, the yield of this product (**31**) is increased up to 94%. Using the enolate obtained in this way, various enol esters of dimedone can be obtained.



This reaction was carried out under similar conditions in dimethylformamide (DMF). In contrast to the reactions described above, a mixture of several substances was obtained here. The main product of the reaction is the product of C-alkylation and its transformations: enol ether, bicyclic furan, and dimedone (in enol form).



Formation of substances (**34)** and (**35)** from the enolate (**33)** can be considered as the result of intramolecular O-alkylation of enolate-anion in two possible directions.

5. Conformational transitions in phosphonates in different media. It is important to know the conformation about the reactants used in chemical research, since reaction ability also depends on their conformation. For this purpose, the ^{1}H NMR method was used to study the conformation of phosphonacetate in neutral, acidic and basic media as a representative of α-phosphoryl-α-carbonyl compounds. The signals of the P–CH_2 group are the main characteristic parameter of the spectrum. It was found that in a neutral medium, the P-CH_2 group of phosphonacetate appears as a doublet, which indicates a free transition of spatial isomers (Figure 2).

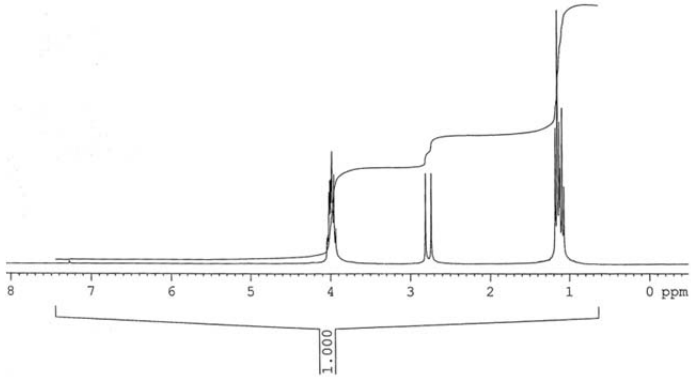
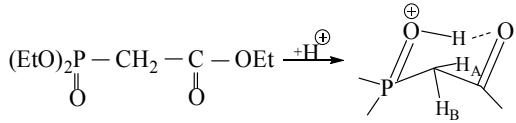


Figure 2. ^{1}H NMR spectrum of triethylphosphonoacetate

The insertion of a proton into the system prevents free rotation. The protonated phosphorus group forms a six-membered cyclic structure due to hydrogen bonding with carbonyl oxygen. If we imagine this structure as a chair conformer, it becomes clear that protons of P-CH_2 group give two doublets in the spectrum since they are not chemically equivalent (Figure 3).



This closed conformation, caused by protonation, not only activates the phosphoryl, carbonyl and active methylene groups of the

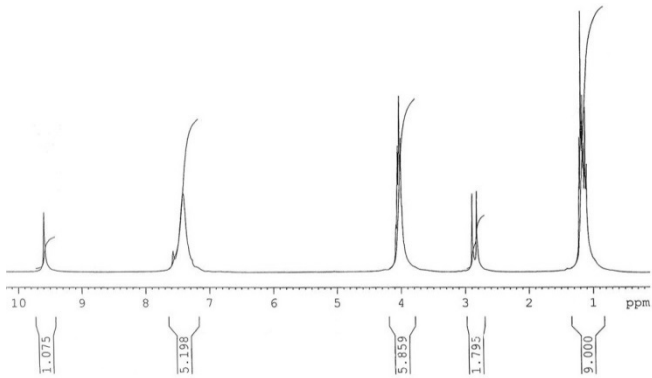
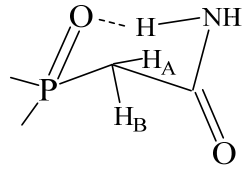


Figure 3. ^{1}H NMR spectrum of protonated triethylphosphonoacetate

substrate towards nucleophilic reagents but also makes these reaction centers easy targets for attack by external reagents because of the steric suitability of the cyclic structure. It should be noted that in neutral mediums the closed conformer of phosphonamides is formed due to the amide N-H and phosphoryl group, and two doublets of the same intensity are observed in the spectrum (Figure 4).



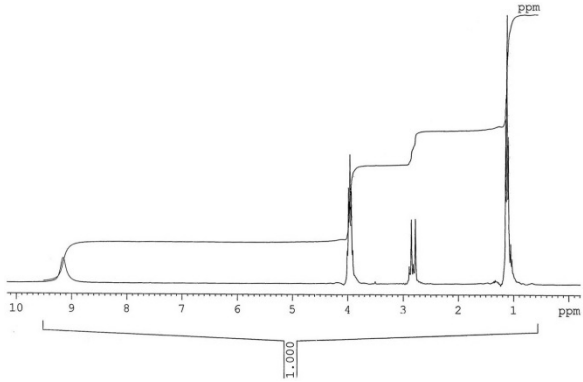
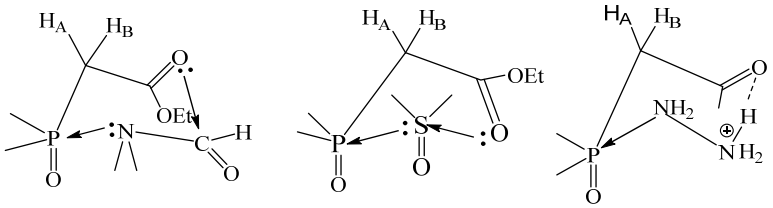


Figure 4. ^{1}H NMR spectrum of phosphonacetamide

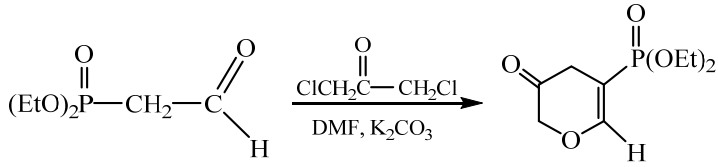
The formation of binucleophilic compounds, including closed conformers in solvents, is not excluded. Phosphonacetate in equivalent

proportions forms stable molecular adducts with a cyclic structure due to coordination with dimethylformamide, dimethyl sulfoxide and hydrazine hydrate. Consequently, the signals characterizing the P-CH_2 group appears in the spectrum as a quartet, and not as a doublet.



Naturally, the activity of such closed conformers decreases towards the nucleophilic reagents. Finally, by converting α-phosphoryl-α-carbonyl compounds into stable closed conformers, depending on the environment, it is possible to achieve changes in their chemical activity towards the nucleophilic and electrophilic reagents.

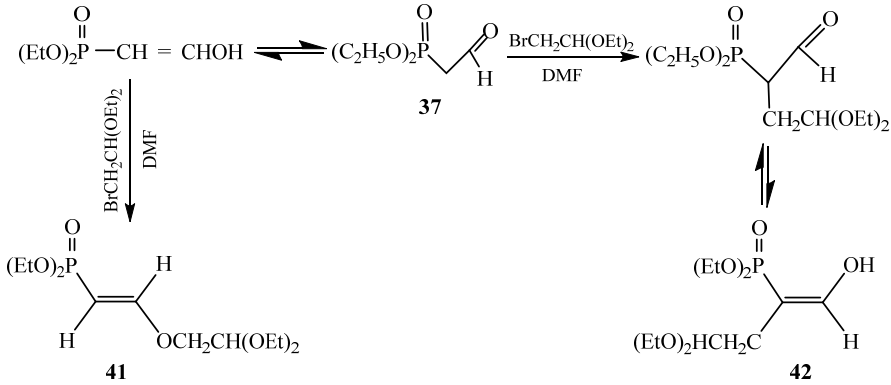
6. Reactions of carbonyl substrates containing an α-phosphoryl group with functionally substituted organohalogen reagents. Although the alkylation of organic phosphorus compounds containing an active methylene group has been studied for a long time by researchers, a number of problems remain unresolved. For this reason, we studied the reactions of phosphonoacetaldehyde (**37**), which is active in alkylation reactions, and phosphonacetate (**38**) and phosphonitrile (**39**), which are relatively inactive in these reactions, with bromoacetal, an alkylating agent. As a result of the interaction of phosphonoacetaldehyde (**37**) with bis(chloromethyl)ketone in presence of potassium carbonate in dimethylformamide medium at 60-70°C for 3 hours, a compound (**40**) containing a phosphoryl group in the side chain was synthesized with a yield of 30%.



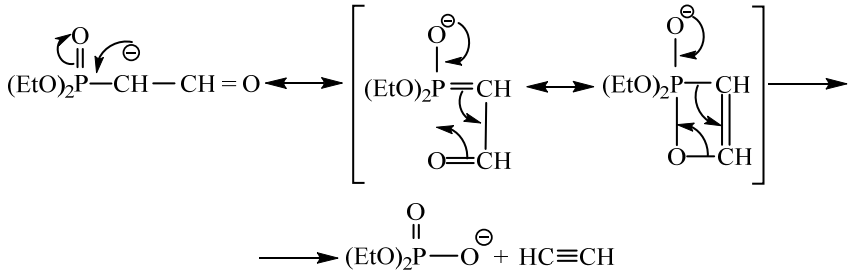
37 **40**

Probably the intermediate obtained at the initial stage of C-alkylation of the substrate with bis(chloromethyl)ketone undergoes prototropic isomerization and O-alkylation with the formation of **(40)**. The

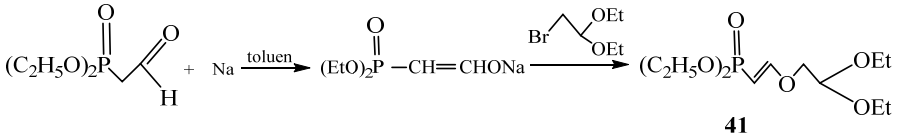
reaction of phosphonoacetaldehyde (**37**) with bromoacetaldehyde diethyl acetal in presence of potassium carbonate in dimethylformamide media led to two products: an O-alkylation product (**41**) (main product) and a minor C-alkylation product (**42**). The overall yield in this reaction did not exceed 20%.



Since the phosphonoacetaldehyde give an ambident ion in the catalytic environment, the process ends with O- and C-alkylation due to the participation of both centers in the alkylation. Probably the reason for the low overall yield of alkylation products in this process is due to the transformation of the intermediate carbanion into phosphorus ylide, and the latter is decomposed into phosphate and acetylene by the intramolecular Wittig reaction.

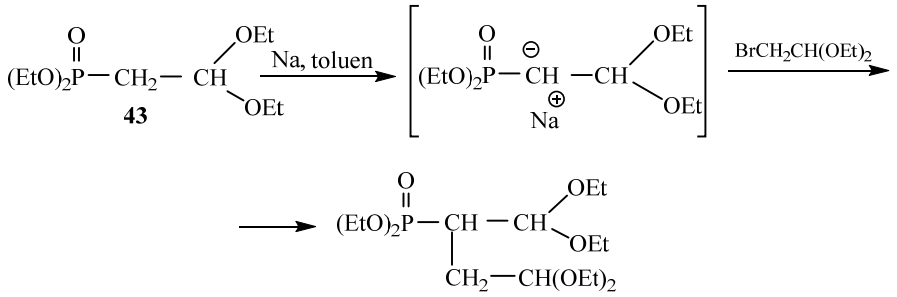


The second reason is the possibility of alternative nucleophilic reactions of dimethyl sulfoxide towards the phosphoryl group. By treating phosphonoacetaldehyde with sodium at 30-40°C, its enolate is obtained, which is alkylated with bromocetal in order to synthesize the aforementioned enolate ester (**41**) in high yield.



41

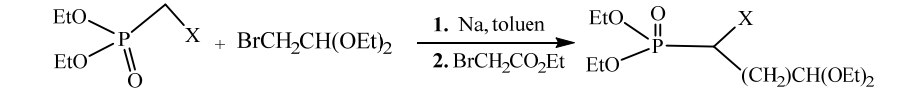
The aim of the phosphonoacetaldehyde reaction with bromocetal was to achieve a C-alkylation product for synthesizing polycarbonyl phosphorus-containing heterocycles and other derivatives on its basis. For this, in the presence of sodium, the reaction of diethyl 2,2-diethoxyethylphosphonate with bromoacetaldehyde diethyl acetal in toluene medium was carried out and the product of mono-C-alkylation (**44**) was obtained with a yield of ~ 43%.



43 **44**

The CH_2 groups of ethoxy radicals of acetal fragments in the proton spectrum give separate resonance signals due to their anisotropic nature.

Under the same conditions, the alkylation of phosphonates (**46**) and (**47**) with bromoacetal lead to the formation of only the C-alkylation product.



46-47

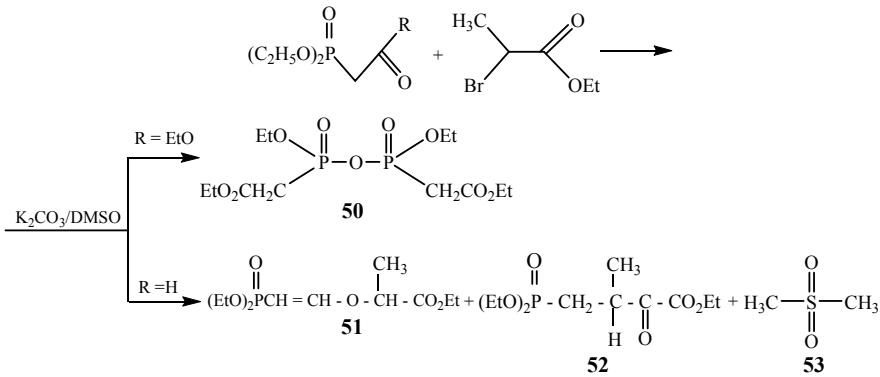
X= CO_2Et (**46**); CN (**47**)

48-49

X= CO_2Et (**48**); CN (**49**)

The reaction of phosphonacetate (**46**) with ethyl-α-bromopropionate (potassium carbonate/dimethyl sulfoxide, 60-70°C, 8 hours) was not lead to any alkylation product. Only phosphonacetic ester anhydride (**50**), ethyl esters of dimethylmalein and dimethylfumaric acid were extracted from the reaction mixture by deep vacuum distillation.

Considering the chemical activity of phosphonoacetaldehyde and α-bromopropionate in the alkylation reactions, the study of their condensation reaction has synthetic and theoretical importance. Carrying out this reaction at 40-50°C led to the formation of a mixture of O-alkylation product **(51)** with low yield, the Darzan reaction product **(52)**, dimethyl sulfone **(53)**, diethyl esters of maleic and fumaric acid.

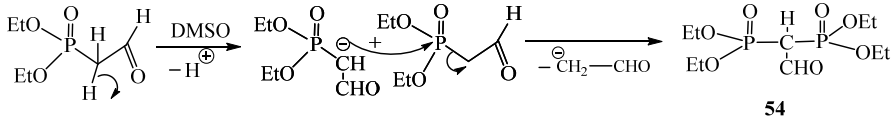


The formation of numbers of compounds in this reaction is associated with the occurrence of several alternative reactions in the process. In order to investigate these cases, the detailed examination phosphonoacetaldehyde and α-bromopropionate reaction with dimethyl sulfoxide and potassium carbonate were studied. It was found that α-bromopropionate generates the $CH_3BrC^-{-}CO_2Et$ carbanion in the K_2CO_3/DMSO system, and that the latter enters into a nucleophilic substitution reaction with another bromopropionate molecule, which leads to the formation of ethyl esters of maleic and fumaric acids. With the addition of this carbanion to the carbonyl group and rearrangement, the formation of Darzan's reaction product **(52)** taking place. The formation of dimethyl sulfone **(53)** can be considered as a product of the reaction of phosphonoacetaldehyde with dimethyl sulfoxide. Since dimethyl sulfoxide has a basic nucleophilic property, it also acts as a reactant in this reaction.

Thus, we see that the reaction of phosphonoacetaldehyde with α-bromopropionate in presence of K_2CO_3/DMSO causes different competitive reactions under the influence of both components of this system, which leads to the decreasing of alkylation products yields.

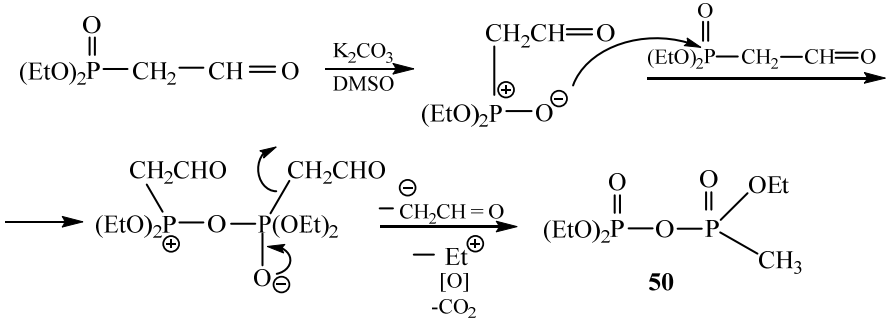
Self-condensation of phosphonoacetaldehyde in dimethyl sulfox-

ide at 60-80°C (8 hours) gives *hem* diethoxyphosphoryl acetaldehyde (**54**). In this reaction, dimethyl sulfoxide exhibits basic property that causes the release of the proton from the active methylene group, and the resulting anion condenses with the second aldehyde molecule to form (**54**).



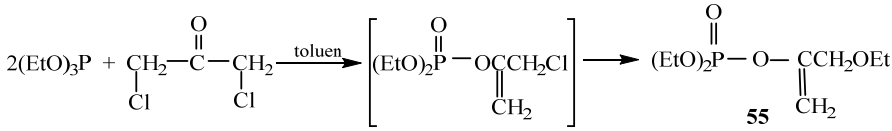
54

In the presence of potassium carbonate in this reaction, condensation ends with the formation of a phosphate group.



50

6.1. Reaction of 1,3-dihaloacetone with triethyl phosphite. 1,3-Dihaloacetone can be used in the synthesis of diphosphonates containing two active methylene groups. It is known that the route of reactions of α-halogencarbonyl compounds with trialkyl phosphites is ambiguous and proceeds according to the Arbuzov or Perkov scheme, depending on the nature of the halogen and the solvents used in the reaction. When we study 1,3-dichloroacetone reaction with triethyl phosphite in toluene in 1: 2 ratio, the result was unexpected. In the phosphate ether obtained according to the Perkov reaction, the second chlorine atom was replaced by an ethoxy group, without entering into the Arbuzov reaction.



55

At the second stage, this course of the reaction can be explained

by the nucleophilic attack of the phosphite moiety on the phosphate group. The resulting six-coordination substance decomposes into the final product (**55)**.

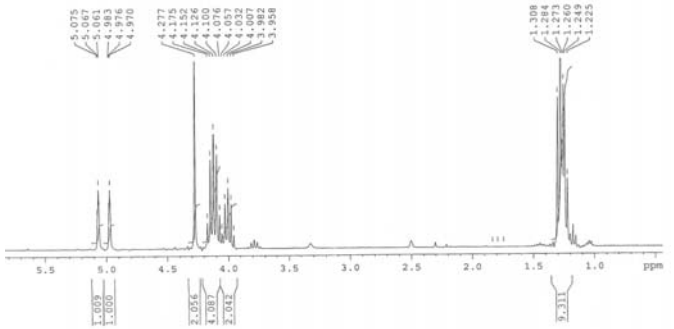
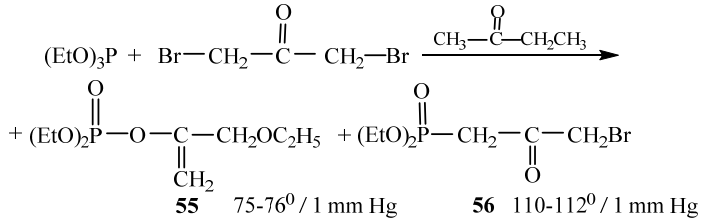


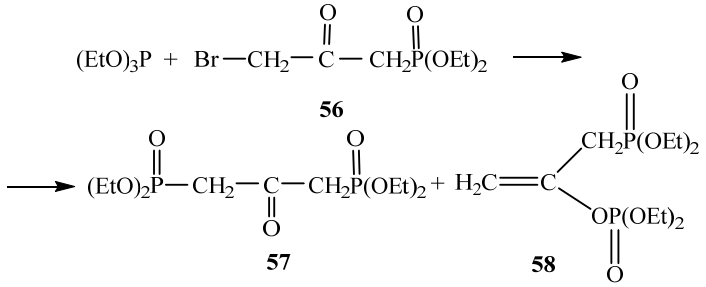
Figure 5. ^{1}H NMR spectrum of compound (**55)**.

The 1,3-dibromoacetone reaction with triethyl phosphite was carried out in methyl ethyl ketone, a polar solvent, and it was determined that the reaction proceeds in two directions with the formation of Arbuzov and Perkov products.



55 75-76^{0} / 1 mm Hg **56** 110-112^{0} / 1 mm Hg

As can be seen, the second bromine atom is retained in the product obtained according to the Arbuzov scheme. Thanks to the different boiling points, both compounds were extracted by distillation. The reaction of this compound (**56)** with phosphites lead to the formation of diphosphonate (**57)** and phosphate (**58)** derivatives.



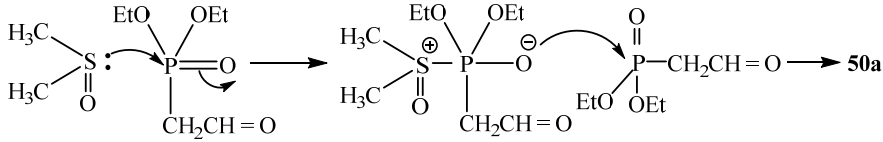
56

57 **58**

The presence of an active methylene group in the synthesized compounds allows them to be used in organic synthesis.

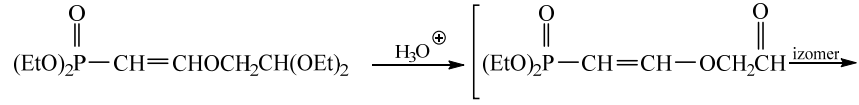
6.2. The factors influencing the alkylation of α-phosphorylated carbonyl compounds. Alkylation of carbonyl compounds is usually carried out in presence of potassium carbonate in dimethyl sulfoxide or dimethylformamide. Having basic (also nucleophilic) properties, dimethyl sulfoxide will be interacting with carbonyl compounds containing an active methylene group involved in the reaction. In this point of view, the phosphoryl, carbonyl and active methylene groups of α-phosphorylated carbonyl compounds can react with dimethyl sulfoxide. The attack of DMSO on phosphoryl and methylene groups leads to substitution reaction on the phosphorus atom (due to the P-C, P-O bonds fission), and the attack on the carbonyl group ends with carbon-carbon bond fission.

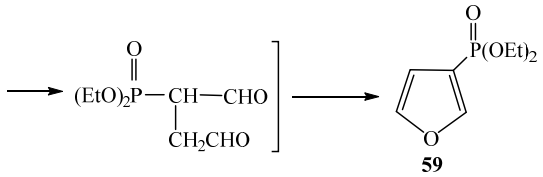
Dimethylsulfone is a reaction product of nucleophilic attack of dimethylsulfoxide on the carbonyl group of phosphonoacetaldehyde. The catalyzed action of dimethyl sulfoxide on the phosphoryl group gives rise to substance (**50a)**.



One of the factors that determine the direction and speed of the reaction is the stability of conformers of substrates and depends on how their active sites are sterically suitable for the reagent attacks.

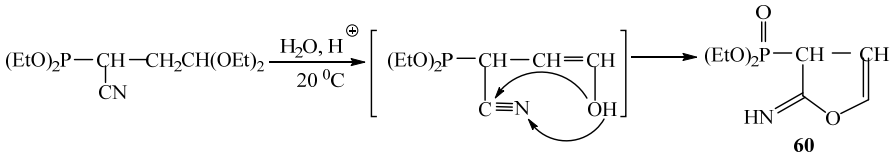
7. Some transformations of compounds on the base of phosphonates. Acetals obtained by alkylation of the active methylene group of organophosphorus compounds are widely used in the synthesis of aldehydes, heterocyclic compounds, hydrazones, and oxides, some examples of which we will disclose here on the basis of synthesized substrates. Series aldehydes and furans were obtained by hydrolysis of synthesized phosphorylated acetals.





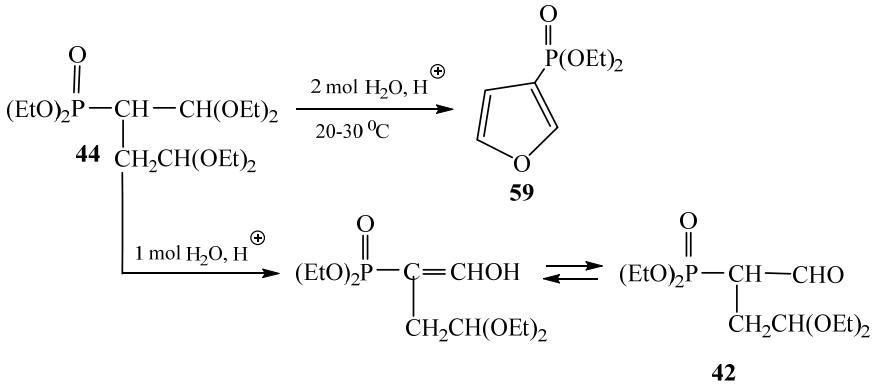
59

Aldehyde, obtained by hydrolysis of diethylacetal of α-cyano-phosphonacetic aldehyde, is converted to furan, resulted by enolating and addition to nitrile group.



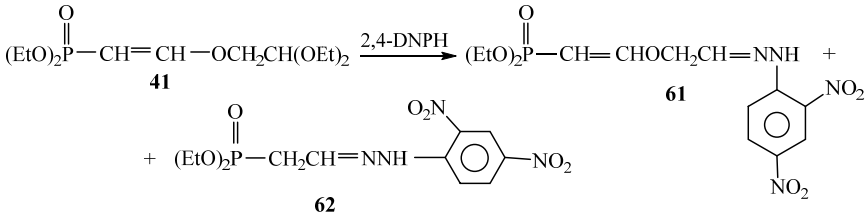
60

The phosphorilfuran is obtained by hydrolysis of diacetal (**44**). When the water ratio is 1:1, the hydrolysis takes place in the acetal moiety, close to the phosphoryl group, which is in aldo-enolic tautomeric form.

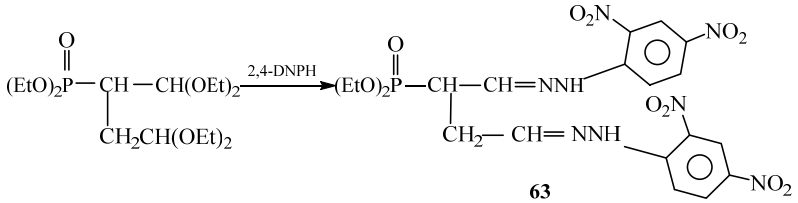


42

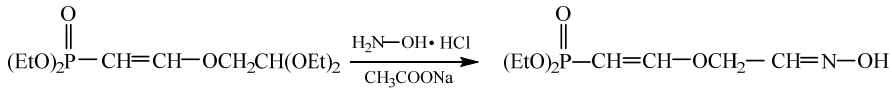
It is known that indole and its derivatives can be obtained on the basis of hydrazones by Fischer reaction. Using various carbonyl compounds and hydrazones, it is possible to obtain indole derivatives containing functional groups in both pyrrole and benzene rings. In this regard, the synthesis of hydrazones containing different functional groups is a point of great interest. We used synthetic acetals to obtain hydrazones. Mixture of two hydrazones were obtained by the reaction of acetal **41** with 2,4-dinitrophenylhydrazine.



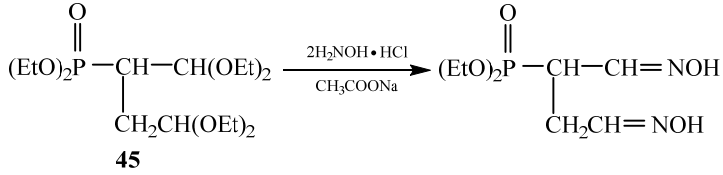
Dihydrazones were prepared using diacetals.



It is more suitable to use acetals in the synthesis of oximes, since aldehydes (ketones) undergo additional condensation reactions in an acidic or alkaline medium. In using acetals, it should be taken considering that the hydrolysis of acetals is possible only in acidic media. Therefore, during the synthesis of oximes on the base of acetals should be created an acidic environment, to hydrolyze them to aldehydes for the interaction with hydroxylamine.



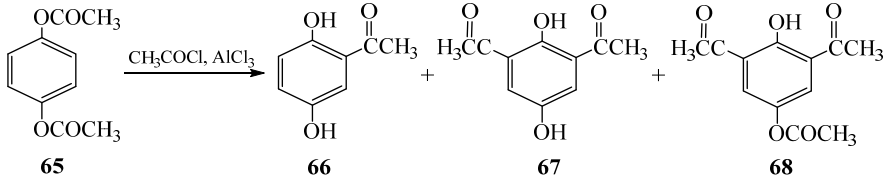
Acetal (**41**) was used in the synthesis of the oxime (**64**), which is according to nuclear magnetic resonance spectra, consists of two isomers. Since the nuclear magnetic resonance spectra of *syn*- and *anti*-isomers differ, it is possible to calculate their ratio in the mixture. In this reaction, dioxime was obtained using a diacetal.



The oxime yield depends on many factors, including the sequence of reactions of the reactants. The synthesized oximes are decomposed

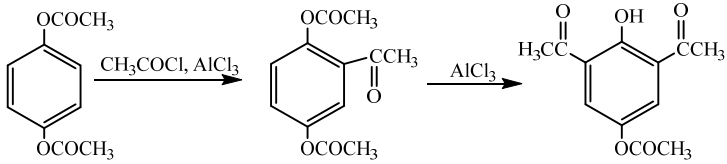
at high temperatures (> 200°C). Some oximes can be widely used in material science as complexones.

8. The acylation reaction of 1,4-diacetylhydroquinone. The synthesis of aromatic diketones with high synthetic potential and the study of their chemical properties have a great interest. In this regard, the acylation of 4-acetoxyphenyl acetate (**65)** in the presence of aluminum chloride in dichloroethane was studied. As a result of the reaction, 2-acetyl-1,4-hydroquinone (**66)**, 2,6-diacetyl-1,4-hydroquinone (**67)** and 2,4,6-triacetylhydroquinone (**68)** were obtained.



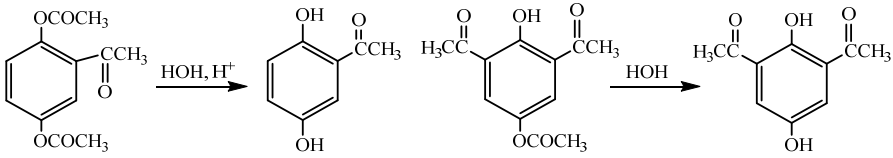
65 **66** **67** **68**

It was found that the yield of the products depends on the reaction time, the decomposition temperature of the intermediate complexes and the reaction conditions is carried out. Here, the formation of compound 68 can be considered as a Fritz rearrangement of the first acylation product in presence of aluminum chloride.



65 **68**

The formation of (**66)** and (**67)** should be considered as a result of the hydrolysis of acylation products.

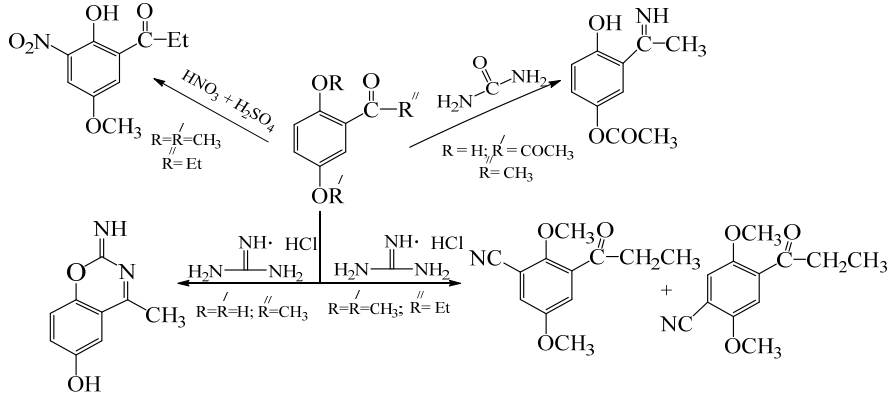


66 **68** **67**

2,6-Diacetyl-4-methoxyphenol was synthesized by acylation of 1,4-dimethoxybenzene, and its structure was studied by ^{1}H, ^{13}C NMR spectroscopy as well as by X-ray diffractometry.

Series novel hydroquinone derivatives have been synthesized by

interaction of electrophilic and nucleophilic reagents with the carbonyl groups and aromatic rings of the acylated derivatives of various hydroquinones.



9. Synthesis of oximes based on aromatic ketones and NMR studies of their structures. In literature presented many works on using various physical and chemical methods in the study of the synthesis, properties and stereochemistry of ketoximes. The most modern and efficient of them is the use of ^{13}C and ^{15}N NMR data analysis. From the ^{13}C NMR spectra of series ketoximes, it is clear that the signal of the sin-located methyl group to OH-group is detected in an upfield region than the signal of anti-counterpart, and this difference $\Delta\delta$ (syn-anti) is about 5-7 ppm in the *E*- and *Z*-isomers of methyl phenyl ketoximes. Thus, based on this, the authors believed that using this value («constant») it can be possible to determine *E*- and *Z*-configuration of ketoximes. In the ^{13}C NMR spectrum of the E-isomer, the signal of the methyl group is observed at 10-14 ppm, while in the Z-isomer it is appearing between 15-21 ppm.

To clarify the versatility of this idea, we synthesized a ketoxime based on 1,4-dimethoxy-2-acetylbenzene and carried out structural studies. İnterestingly, only one isomer was obtained, and the signal of the methyl group in this isomer is observed at 18 ppm of ^{13}C NMR spectrum. Based on the above-mentioned presented literature data, this isomer can be attributed to the *Z*-configuration, but our X-ray studies have shown that, on the contrary, this oxime has the *E*-configuration (Figure 6).

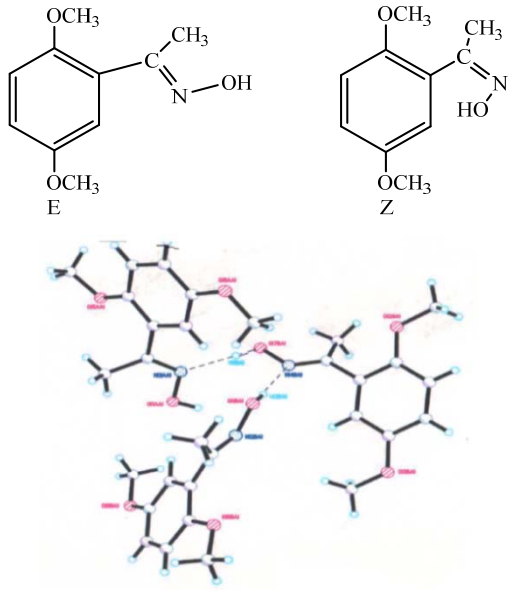
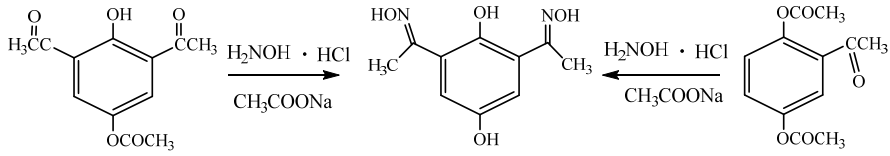


Figure 6. Molecular structure of oxime derived from 1,4-dimethoxyacetyl-2-acetylbenzene

Therefore, it can be concluded that the presented literature method is not applicable in all cases, because of shielding of the methyl group could be arisen by the influence of many other groups in the aromatic ring. Thus, the use of this approach for studying the structure of oximes is ineffective, since it is important to take into account the effect of functional groups on the shielding of the methyl group.

For the first time, 2,6-diacetylhydroquinone dioxime (**69**) was synthesized by interaction of (**54**) and 4-acetyloxy-2-acetylphenyl acetate. This dioxime is a dark dye due to the electronic transitions in its structure.



68 **69** **66**

The interaction of hydroquinone-based carbonyl compounds with some nucleophilic and electrophilic reactants has also been studied and lead to interesting results.

CONCLUSIONS

1. The study of reactions of dimethylacetonedicarboxylate and other active methylene substrates with mono- and polyhalogen compounds showed that depending on the nature of the reactant, the solvent and the temperature process runs towards the formation of O-, C-, C-C-alkylation products or their (O- and C-alkylates) mixtures. The conversion of O-alkylation products into C-alkylation products (and vice versa) is also taking place.
2. It was found that the reactions of methyl 4-chloroacetoacetate with di- and trihaloalkanes are a two-step process leading to the formation of enol esters of 1,4-dimethyldicarboxylate cyclohexadione-2,5.
3. The reactions of α-phosphoryl-α-carbonyl compounds with α-bromopropionate and bromoacetaldehyde diethyl acetal in K_2CO_3/DMSO and sodium/toluene systems were studied. It was shown that the synthesized compounds play an important role in the building of furans, hydrazones, and oxides.
4. The factors influencing the conformation of α-phosphoryl-α-carbonyl compounds have been studied. It has been shown that in the presence of polar solvents (dimethyl sulfoxide, dimethylformamide) and binucleophiles (hydrazine hydrochloride, etc.), α-phosphoryl-α-carbonyl compounds are capable to form stabile closed conformers.
5. The detailed study of each reaction component as well as reaction mechanisms of alkylation reactions showed that, as a rule, the due to real-time participation of substrates and reactants in competitive self-condensation reactions diminish the chemoselectivity of the process.
6. Hydroquinone derivatives containing one and two acetyl groups were synthesized by acylation of 1,4-diacetylhydroquinone, and their reactions in the acetyl group and aromatic ring were studied.

The results of the thesis are presented in the following works

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