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ABSTRACT

of the dissertation for the degree of Doctor of Science

«NEW APPROACHES IN SYNTHESIS AND DETERMINATION OF STRUCTURE-PROPERTY PARAMETERS OF BIOLOGICALLY ACTIVE COMPOUNDS ON THE BASE OF ACTIVEMETHYLENE REAGENTS AND SUBSTRATES CONTAINING POLARIZED DOUBLE-BOND»

Speciality: 2306.01 – Organic chemistry

Field of science: Chemistry

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The work was performed at the scientific laboratory of «Fine Organic Synthesis» attached to the department of organic chemistry of Baku State University.

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INTRODUCTİON

Relevance and elaboration of the topic. Synthesis of polyfunctional 4H-pyran, pyridine, imidazo-pyridine, pyrazole and etc. on the basis of activated (polarized) double bonded compounds, with valuable biological activity, studying relationship between structure and properties, investigation of their applications is point of perspective. The products of multicomponent interaction of ketones, ethers, nitriles and ylidens containing polarized double bond with active methylene compounds, amines, isonitriles, alcohols, thiols, etc., which contain polarized double bond are important compounds and form the basis of many practically-valuable substances.

Thus, these compounds demonstrates fungicidal, insecticidal, stimulant, antispasmolitic, as well as anti-tick, anti-virus, anti-tumor, anti-bacterial, anti-shock and anti-fungal etc. physiological activities. In addition, heterocyclic compounds containing sulfur are effective additives to oils and fuels, antioxidants, corrosion inhibitors, etc. These can be considered as an indicator of the relevance of the studied scientific topic.

Despite the fact that since the beginning of the XIX century, many multicomponent reactions based on polarized double-bonded compounds have been carried out, and different reaction conditions have been proposed, the interest in this field has not decreased and non-investigated directions still remain.

By the given above, there are parts that need to be studied in the field of multicomponent reactions based on polarized double-bonded compounds, the study of this topic is relevant and has a practical importance.

Object and subject of research. The object of research is polarized double-bonded compounds and active methylene reagents. In order to show the importance of these compounds from the point of view of organic chemistry, pyridine, pirane, imidazo- and imino-pyridine, pyridopyrimidine, pyranopyridine, isoquinolines on the of them were synthesized. The role of non-covalent interactions, π-stackings, hydrogen bonds in the formation of the crystal lattice of polyfunctional compounds synthesized as the subject of research and solutions of practically valuable derivatives were investigated by

Nuclear Magnetic Resonance (NMR) spectroscopy and their biological activity were studied.

The purpose and objectives of the study. The main goals of presented investigation work is transformation of Michael adduct, obtained from the Michael addition reaction of active methylene compounds to chalcones, and development of synthesis methods of functionally substituted compounds, carrying out of three-component non-catalyst interactions of benzylidenemalononitriles with malononitrile and various amines (ethilendiamine, 1,3-diaminopropane, benzylamine, furfurilamine, thiophenylamine and (S)-(-)-1-phenylamine) that forms polyfunctional imidazo, pyrido- iminopyridines, multicomponent reaction of izatilidenmalononitriles, malononitrile and ethylenediamine (or 1,3- diaminopropane) giving corresponding spirocyclic piridine derivatives, and forming substituted 4H-pyrans by Michael addition reactions of izatilidenemalononitrile with acetoacetanilide (or ethyl ester of 4-chloroacetoacetatic acid).

Additional goals of the work was the investigation of the structure of obtained multifunctional compounds by modern physical methods and screening of their antimicrobial and antibacterial activity.

Research methods. Syntheses were carried out in the «Fine Organic Synthesis» Laboratory by using appropriate synthetic methods. The crystal structures of synthesized compounds were studied by the Brucker APEX II CCD difractometer. The ^{1}H, ^{13}C and two-dimensional Nuclear Magnetic Resonance spectrums were recorded in dimethylsulfoxide (D_6) on a Brucker Avance spectrometer. Thin layer chromatography was monitored on UB-254 Silufol board by Ultra Violet lamp. Electron Spray Ionization Mass Spectra was used for mass-spectroscopy.

The main provisions:

The reasons of various directions of Michael addition of chalcones with active methylene compounds depend on the conditions. The interaction of Michael's adducts with ethylenediamine (or malononitrile) has also been studied. Functional bicyclic compounds were synthesized by the reaction of the Michael adducts with ethylenediamine (or malononitrile).

It has been find out that the reaction of benzylidenemalononitriles with acetoacetanilide runs in different directions depending on the

ratio of reagents and according to the reaction corresponding substituted tricyclic pyranopyridine (or pyridine) derivatives are formed.

Convertion to corresponding 4H-piran derivatives of the product of interaction of 5-acetyl-2-amino-6-methyl-4-phenyl-4H-pyrane-3-carbonitrile that is the Michael's adduct with various active methylene compounds and the probable mechanism of the reaction the was studied. Also, for the first time it was established that the acetyl-substituted 1,4,5,6-tetrahydroropyridine-3-carbonitrile derivative that is Michael adduct in an alcohol solution, in the presence of amines have been regrouped.

Also, for the first time it was established that in alcoholic conditions, in the presence of amines, acetyl-substituted 1,4,5,6-tetrahydropyridine-3-carbonitrile derivative that is Michael's adduct have regrouped. By one-pot three component condensation benzylidenemalononitriles with various electrodonors and electroacceptor-substituents, malononitrile and ethylenediamine (or monobasic amines) substituted imidazopyridine (or iminopyridine) derivatives were synthesized. It is also carried out the one-pot three-component condensations of benzelidenmalanonitriles, malononitrile and 1,3-diaminopropane and corresponding new dihydropyrido[1,2-*a*]pyrimidine derivatives were synthesized with good yields.

It has been investigated reactions of carbonylic acrylonitrile derivatives with polarized double bonds and acetylacetanilide, benzoylacetone, ethyl ester of 4-chloroacetoacetic acid and malononitrile.

By one-pot three-component interaction of isatylidenemalononitriles, malononitrile and ethylendiamine dihydro-1H-spiro[imidazo[1,2-*a*]piridine-7,3'-indoline derivatibes were obtained, while by using 1,3-diaminopropane as an amine in the same reaction the corresponding spirocyclic tetrahydrospiro[indoline-3,8'-pyrido[1,2-*a*]pyrimidine derivatives were obtained. It was developed the path of synthesis of corresponding spirocyclic tetrahydropyridine derivatives with appropriate spiro structure by one-pot three-component condensation of isatylidenemalononitrile, malononitrile and 2-thiophenmethylamine (or furfurylamine).

Possible mechanism of one-pot three-component reaction of phenylethylidenmalonitrile with malononitrile and acetoacetanilide was proposed. It was also found that reaction of two moles of malono-

nitrile with two moles of acetoacetanilide lead to formation of substituted isoquinoline derivative.

Investigations of reaction mechanisms and structures of products, capabilities of a modern type Nuclear Magnetic Resonance spectrometer operating at 300 MHz and X-ray analysis were carried out and comparative analysis of the results were performed. Studies have shown that the results are consistent.

The scientific novelty of the work. It has been identified that by carrying out Michael's addition of benzoylacetone to chalcones in a solvents and in the presence of different bases, the reaction is directed in different paths by formation of different functionally substituted derivatives. The formation of functional cyclic derivatives from the interaction of Michael's adducts with ethylenediamine (or malononitrile) has been established.

For the first time, by one-pot interaction of benzylidenemalononitriles with acetoacetanilide (2:1) in the presence of 7 mol% piperazine hydrate in a methanol medium (or in the presence of piperidine in a benzene medium) tricyclic pyranopyridine derivatives have been synthesized. It was identified that the substituted pyridine derivatives formed by the Michael addition of benzylidenmalononitriles and acetoacetanilide (1:1 ratio) in the presence of 7 mol% piperazine hydrate (or methylpiperazine, piperidine, triethylamine) using methanol (or ethanol, benzene, chloroform), the elimination of acetyl group from the molecule at the boiling point of methanol (or ethanol) takes place and as a result of regrouping the new substituted pyridines are formed.

It was found that by interaction of Michael’s adduct 5-acethyl-2-amino-6-methyl-4-phenyl-4H-pirane-3-carbonitrile with dimedone, benzoylacetone, dibenzoilmethane, ethyl esters of acetoacetic-, 4-chloroacetoacetic and benzoicacetic acids cycle was opened and reclosing takes place resulting another 4H-pyran derivative was formed.

Benzylidenemononitriles, with various electrodonor and electroacceptor substituents were used in one-pot three-component condensation with malononitrile and ethylenediamine by obtaining of derivatives of imidazopyridine. It was established that when using para-elektroacceptor (or electrodonor) substituted benzylidenmalo-

nonitriles then dihydroimidazo-pyridine's, but by using dihalogen substituted benzilidenmalononitriles then tetrahydroimidazopiridine derivatives production was observed at first time. F···F bonds were found in the derivative of the corresponding dihydroimidazo-pyridine's obtained on the basis of para-fluorobenzylidenemalononitrile. When using 1,3-diaminopropane in the same reaction, obtaining substituted dihydropyrido[1,2-*a*]pyrimidine derivatives, but using furfurylamin (and or 2-thiophenemethylamine) formation of 2,6-diaminodihydropyridine derivatives was observed.

From one-pot catalyst-free tree-component condensation of benzyldenmalononitriles, malononitrile and various amines (benzylamine, thiophenylamine and (S)-(-)-1-phenylethylamine) corresponding imino and diaminopyridine derivatives were synthesized in methanol solution. It was also observed that by using 2-amino-5-bromopyridine as amine in reaction above corresponding terpiridine derivative was obtained.

By carrying out one-pot tree-component interaction of isatylidenemalononitrile (or bromo-substituted isatylidenemalononitrile), malononitrile and ethylenediamine the substituted dihydroimidazopyridines were formed, whereas using 1,3-diaminopropane as amine results corresponding substituted dihydropyrido[1,2-*a*]pyrimidine derivatives. So as by one-pot-tree-component interaction of isathylidenemalononitrile, malononitrile, and furfurylamine (or 2-thiophenemethylamine) as new spirodiaminodihydropyridines can be synthesized. In addition, there has been developed effective synthesis of cyanospiro[indoline-3,4'-piran] derivatives by Michael addition of isatylidenemalononitrile with ethyl ether of benzoylacetone, acetoacetanilide and 4-chloroacetoacetic acid.

The corresponding derivatives, contatining polarized double bond has been obtained by Knoevenagel condensation of 3-oxo-3-thiophene-2-yl-propannitryle with aromatic and heteroaromatic aldehydes in non-catalyst (or 1-2 drops of methylpiperazine) ethanol solution, and then addition them to active methylene compounds have been investigated and established the formation of substituted cyclohexanone a pirane derivatives. Also by Michael addition of 2-(thiophene-2-carbonyl)acrylonitrile derivatives to malononitrile at room temperature, in methanol in the presence of (S)-(-)-1-phenyl-

ethylamine there has been observed the formation of substituted 4H-pyran derivatives.

It has been carried out the synthesis of substituted tetrahydroisoquinoline derivatives by one-pot three-component interaction of 1-phenylethylidenemalononitrile with malononitrile and acetoacetanilide at room temperature, in ethanol solution, in the presence of 7 mol% piperazine hydrate.

The inhibitory activity of number of synthesized compounds against microorganisms has been studied and the effect of functional groups on biological activity has been reported. It was found that inhibitory activity is associated with the hydrophobicity of the molecule, as well as lipophilic properties.

The practical importance of the work. The synthesis and identification of areas of application of physiologically active substances with medicinal and pharmaceutical properties, allows the development of suitable methods for the synthesis of new types of compounds and has theoretical and practical significance.

Functionally substituted derivatives of synthesized 4H-pyran, pyridine, imidazopyridine, imino-pyridine, pyridopyrimidine, pyranopyridine and tetrahydroisoquinoline were tested in various fields and found to be antimicrobial, bactericidal, etc. properties (test report is attached).

The results of the research can be useful for research staff as well as students.

Approbation and publication of the work. 38 Scientific works on the topic of the dissertation were published, including 26 articles (11 published abroad), 12 theses (7 are international). The main parts of the work were presented at the International and Republic Conferences in Russian Federation, United States of America (USA), Georgia and Azerbaijan Republics: 8th Eurasian meeting on Heterocyclic Chemistry (Tbilisi, Georgia, 2014), International Conference on Organic Chemistry (Las Vegas , USA, 2016), Russian Conference of young scholars, dedicated to the 100th anniversary of the Republic of Bashkortostan, Chemistry and Technology of Heterocyclic compounds (Ufa, 2017), Advances in synthethesis and complexing – The Fourth International Scientific Conference (Moscow, Russia, 2017), The VII, VIII, XI and XII Republican scientific conferences of doc-

toral students, masters and young researchers «Actual problems of Chemistry» dedicated to 90, 91, 94, 96th anniversary of National Leader Heydar Aliyev (Baku, 2013, 2014, 2017, 2018, 2019)

Name of the organization where the dissertation work is performed. The dissertation work was carried out at the scientific laboratory of «Fine Organic Synthesis» of the Organic Chemistry department at Baku State University in accordance with the theme (State Registration Number №01101 Az 0048).

The volume and structure of the dissertation. The dissertation consists of 287 pages (333 307 characters) and consists of introduction, 5 chapters, results, 284 references, 67 pictures, appendices.

Introduction (15 039 characters) contain the relevance, purpose, scientific novelty and practical significance of the work.

First chapter (94 070 characters) provides an overview of the literature of the last decade, mainly on research with polarized double-bonded compounds.

Second chapter (86 196 characters) consists of discussion of results obtained during the synthesis of functionally substituted compounds based on polarized double-bonded compounds.

In third chapter (6 821 characters) the solutions of some substances on the basis of polarized double bonded compounds studied by NMR are presented.

In fourth chapter (6 325 characters) the regularities obtained during the study of antimicrobial activity of derivatives of synthesized functionally substituted compounds were given.

The fifth chapter (119 457 characters) is devoted to the experimental methods used in research.

Personal contribution of the author. During the fullfilment of dissertation, the analysis of recent world literature reviews on the topic, experiments, analysis of nuclear magnetic resonance spectrums of reaction products, preparation of articles, were realized by author directly.

SUMMARY OF WORK

The literature provides extensive information on the Michael coupling reaction of active methylene compounds to polarized double-bonded compounds. However, there is still a need for scientific

research in this area. In view of the above, the dissertation presents the synthesis of practically valuable compounds on the basis of polarized double-bonded substrates and active-methylene compounds and devoted to the solution of important issues such as the study of mechanisms reactions and biological activities of synthesized compounds.

Investigation of alkylation reaction of unsaturated ketones with active methylene compounds

First of all, we synthesized corresponding syclohexanon derivative (1) by Michael addition of benzoylacetone to unsaturated ketones (chalcones) in benzene, in presence of dry piperidine catalyst. When using wet piperidine as catalyst in the reaction above the open-structured piperidinium salt of 3-hydroxy-7-oxo-3,5,7-triphenylene heptanoic acid (2) was formed. Besides, it has been established that when carrying out the same reaction in the presence of triethylamine and in methanol medium, the appropriate cyclic ketoalcohol's formations was observed (3), but when using piperidine or sodium methylate (or ethylate) in an alcoholic medium, the methyl (or ethyl) esters of 3-hydroxy-7-oxo-3,5,7-triphenyl-heptanoic acid were synthesized (Figure 1). As can be seen from the results, methyl (or ethyl) alcohol, which was taken as a solvent for reaction conditions, included as a component in the reaction. Our research has shown that when nitro-substituted chalcone was taken in the process, esters of 3-hydroxy-7-oxo-3,5,7-triphenyl-heptanoic acid (6, 7) were obtained.

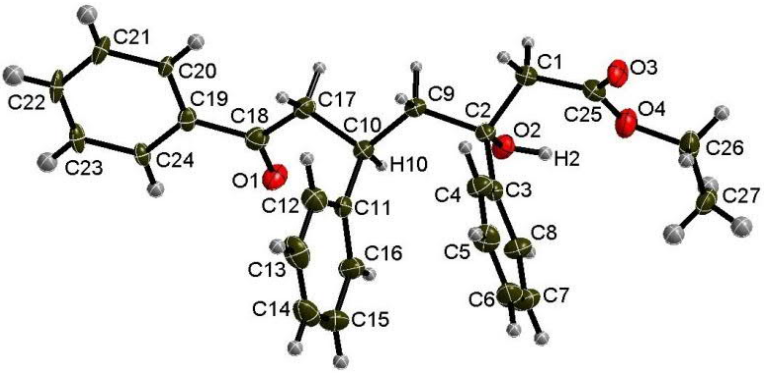
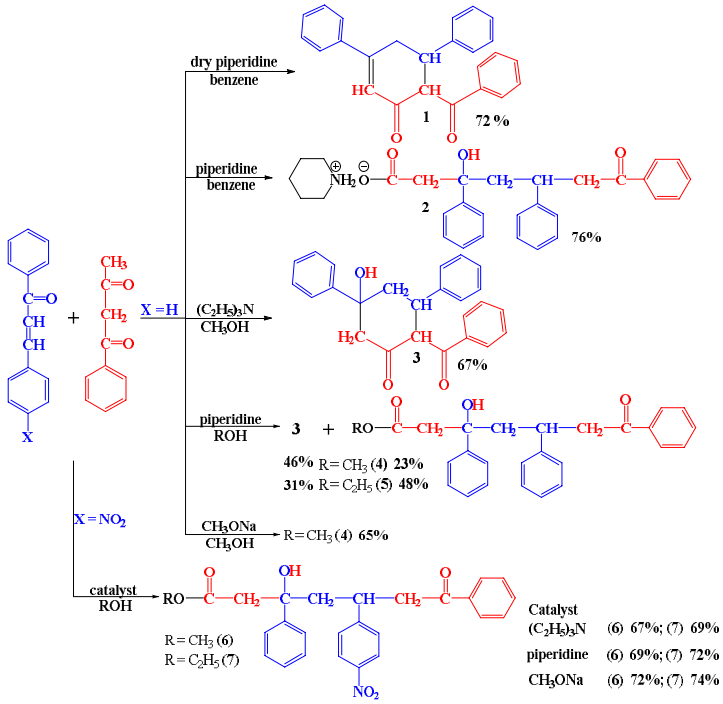
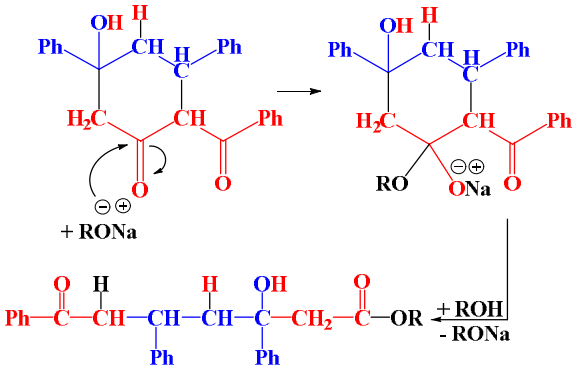


Figure 1. Molecular structure of compound 5.



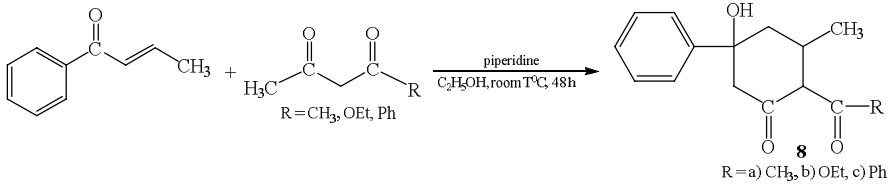
Extensive information is provided in the literature about the mechanism of production of cyclic ketoalcohols, as well as cyclohexanone derivatives. In our opinion, the production of open-structured esters goes through the formation of cyclic keto alcohol. The probable mechanism of the reaction is as follows:



According to the above supposed reaction mechanism, the carbonyl group in the cyclic keto alcohol molecule is first attacked by

the nucleophile. By breaking the carbon-carbon (C-C) bond in the intermediate the ethers of 3-hydroxy-7-oxo-3,5,7-triphenyl-heptanoic acid are obtained.

Interaction of crotonophenone with acetylacetone, acetoacetic acid and benzoylacetone. Continuing our research in interaction of crotonophenone with acetylacetone, acetoacetic ester and benzoylacetone in ethanol (or benzene) medium, in the presence of piperidine, at room temperature for 24 hours was carried out. As a result of reaction, the corresponding substituted cyclohexanone derivatives were formed. ^{1}H and ^{13}C nuclear magnetic resonance experiments confirmed the formation of compounds shown in the reaction scheme (8).



Reaction of chalcone's alkylation products with ethylenediamine and malononitrile

Interaction of Michael adduct synthesized on the basis of dibenzoylmethane with ethylenediamide in the presence of HCl, at boiling point of ethanol for 4 hours was carried out. As X-ray of reaction product so ^{1}H, ^{13}C and two-dimensional nuclear magnetic resonance spectrums confirmed the formation of phenyl(5,7,8a-triphenyl-1,2,3,7,8,8a-hexahydroimidazo[1,2-*a*]pyridin-6-yl)metanone (9).

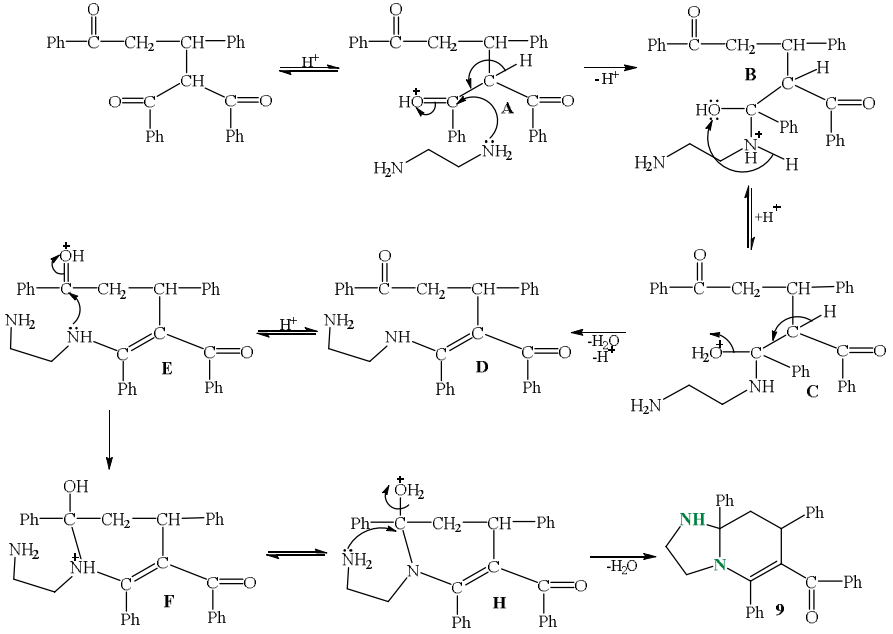
Investigations as well as nuclear magnetic resonance studies, suggest that the probable mechanism of the reaction is as follows.

In our opinion, first the Michael adduct combines with proton of acid to form the intermediate A. The nitrogen atom of one of the amine groups in ethylenediamine attacks the carbon atom of the double bond in A with free electron pair and by elimination the proton converted into B. After then, C-intermediate is formed by the protonation of OH group in the B. Continuing the process, D-intermediate is formed by separation of water and protons from C. In the presence of a proton intermedate-D convertes to E, in which double nitrogen's

electrons attack more polarized carbon atom and converted to F. After the hydrogen migration of F turns to intermediate compound H. In the resulting H, another nitrogen atom attacks the quaternary carbon atom with an electron pair and combines phenyl(5,7,8a-triphenyl-1,2,3,7,8,8a-hexahydroimidazo[1,2-*a*]pyridin-6-yl)metanone (compound 9) occurs with the separation of water.

In ^{1}H NMR spectrum double dublets at 2.29 ppm of two protons of methylene (CH_2) group attached to the nitrogen atom in the cycle, and at 2.78 ppm of two protons of the methylene (CH_2) group attached to the other nitrogen atom of the cycle, triplet at 3.03 ppm, of one proton of the methine (CH) group bonded to the ring, double dublet at 3.42-3.64 ppm of two protons of methylene (CH_2) group in six-membered cycle and multiplet signal at 6.81-7.77 ppm of 20 protons of 4 aromatic rings confirm the formation of compound (9) shown in the scheme above.

X-ray (Figure 2), ^{13}C, two-dimensional Correlation spectroscopy (COSY), and other nuclear magnetic resonance experiments also showed the formation of the substance (9).



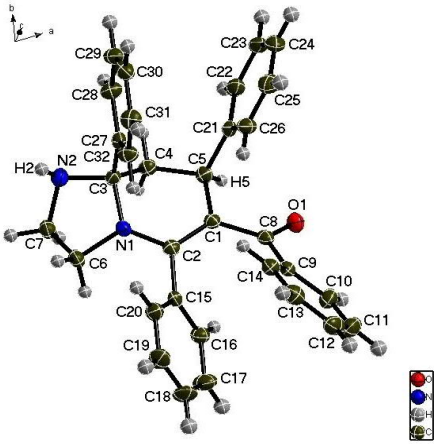
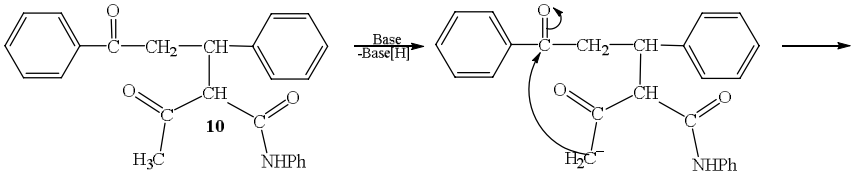
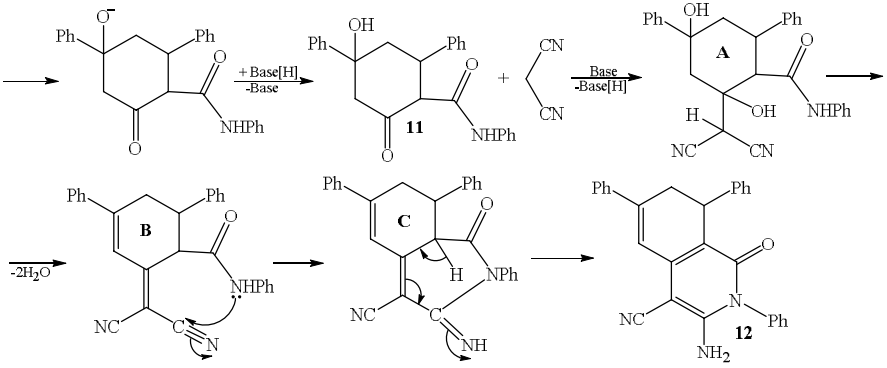


Figure 2. Molecular structure of compound (9) (CCDC: 2017791)

It was found that by reaction of the synthesized Michael's adduct 2-acethyl-5-oxo-N,3,5-triphenylpentanamide (10) with malononitrile in the acetonitrile medium and in the presence of ethylenediamine compound (10)-3-amino-2,6,8-triphenyl-7,8-dihydroisoquinoline-1(2H)-one was synthesized.

The probable mechanism of this reaction has been proposed as follows. According to this mechanism, the methyl group is first converted to corresponding anion in the presence of base. The resulting anion attacks the carbon atom of the carbonyl group, which is the electrophilic center, and cyclohexanone anion forms. After then new anion combines with hydrogen to form compound 11. In base conditions, the simultaneous separation of water and the attack of the malononitrile anion to carbonyl group of the cycle provides formation of A-intermediate. Elimination of water from A gives B-intermediate. The nitrogen atom in the amide fragment then attacks the carbon atom of the nitrile group, which is another electrophilic center, with free electron pair and C was formed, and 3-amino-2,6,8-triphenyl-7,8-dihydroisoquinoline-1 (2H) -on (12) was obtained as a result of migration of hydrogen.





The experiments X-ray, ^{1}H and ^{13}C NMR also confirm the results (figure 3).

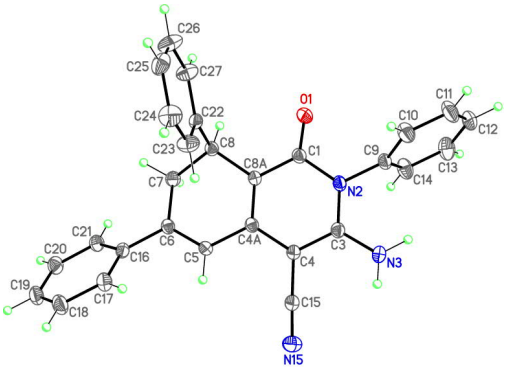


Figure. 3. Molecular structure of 3-amino-2,6,8-triphenyl-7,8-dihydroisoquinoline-1 (2H)-on (12) (CCDC: 2058071)

In contrast to the literature, the Michael adducts that formed in these reactions, depending on the conditions, were obtained in a cyclic or non-cyclic form. Thus, from reaction of benzoyl acetone to chalcones in an alcoholic medium in the presence of aqueous piperidine the corresponding esters of 3-hydroxy-7-oxo-3,5,7-triphenyl-heptanoic acid have been e formed. Ethers of named acid were also been obtained when triethylamine and sodium methylate were used as catalysts in this reaction. In our opinion, the first cyclic Michael adduct is formed. Then a cycle is opened under appropriate conditions and esters of open-structured 3-hydroxy-7-oxo-3,5,7-triphenyl-heptanoic acid were obtained.

Also, in contrast to the literature, by the interaction of the product of Michael's addition of dibenzoylmethane to 1,3-di-phenyl-2-propene-1-one-2-benzoyl-1,3,5-triphenylpentane-1,5-dion with ethylenedi-

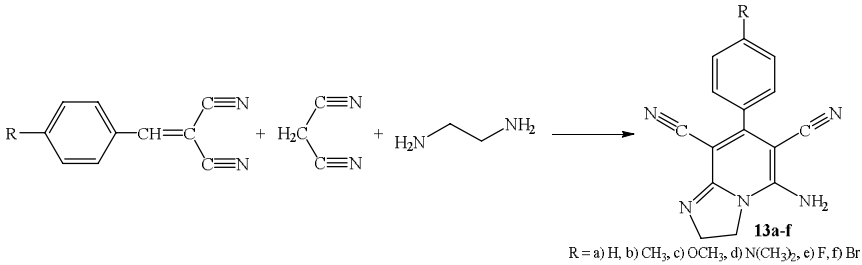
amine at the boiling point of ethanol, in the presence of HCl, the effective synthesis of imidazo[1,2-*a*]pyridine derivative was carried out.

Also, for the first time by interaction of 2-acethyle-5-oxo-N,3,5-triphenylpentanamide and malononitrile of in acetonitrile medium, in the presence of catalytic quantity of piperidine or methylpiperazine, under boiling conditions 3-amino-2,6,8-triphenyl-7,8-dihydroisoquinoline-1(2H)-one (12) have been synthesized.

One-pot three-component reaction of benzylidenemalononitriles with malononitrile and amines

Recently, multicomponent reactions have become an efficient method of synthesis. This method is more convenient, mainly from the point of view of environmental safety. Multicomponent reactions are widely used in organic synthesis and the pharmaceutical industry, are of particular importance in the synthesis of heterocyclic compounds with structural differences.

In this part of our study, by three-component condensation of various mono-substituent benzilidydenmalononononitriles, malonodinitrile and ethylenediamine was carried out in methanol, without catalyst, accomplished by formation of appropriate dihydroimidazo[1,2-*a*]pyridines (13a-f). For research benzylidenemalononitriles consists of an electrodonor and electroaceceptor groups were taken. The advantage of the proposed path is that the reactions are carried out at room temperature and at non-catalyst conditions. Reactions were carried out for 48-72 hours. Significant decreasing of reaction time (up to 175 minutes) were observed when using a microwave irradiation condition. The results of Nuclear Magnetic Resonance (NMR) and X-ray of synthesized samples are given in Figure 4-6.



The singlet at 3.97 ppm corresponding to four protons of two methylene groups in the imidazole cycle, the multiplet at 7.39-7.62 ppm

corresponding to five protons of the aromatic ring, and at 8.14 ppm of two protons of amin (NH_2) group on the ^1H NMR spectrum confirms production of 5-amino-7-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (13a). ^{13}C and other Nuclear Magnetic Resonance (NMR) experiments also confirm this result.

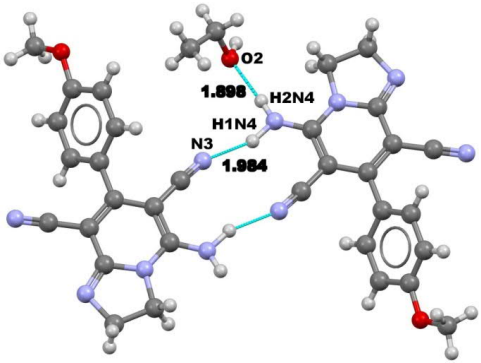


Figure 4. Molecular structure of 13c

From X-Ray results of 13c (figure 4) there are intermolecular hydrogen bonds. Hydrogen bond is formed between the nitrogen atom of the nitrile group in one molecule and the nitrogen atom of the NH_2 group in another molecule. Also, hydrogen bond between oxygen of ethanol molecule used as a solvent and nitrogen of NH_2 in 5-amino-7-(4-methoxyphenyl)-2,3-dihydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (13c) molecule was observed.

Analysis of the molecular structure of 13e (Figure 5) shows that both the intermolecular non-covalent F•••F bond and hydrogen bond between nitrogen atom of nitrile group in one molecule and nitrogen of amine group (NH_2) in other molecule are present.

The probable mechanism of the reaction is as follows. At first, by action of ethylenediamine the hydrogen atom from the malondinitrile molecule breaks down and the corresponding nucleophile-carboanion formed, then it attackes the electrophilic center (group CH) in the benzylidenmalononitrile producing intermediate adduct. In the obtained adduct, the CN group is converted to the C=NH. Nitrogen in the ethylenediamine molecule attacks the carbon atom of the C=NH group with an electron pair, forming I-intermediate. After the migration of hydrogen, the nitrogen in the I-intermediate attacks the carbon

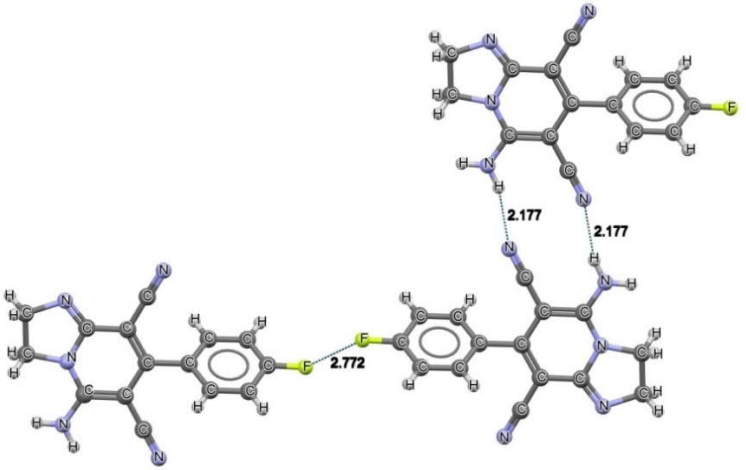
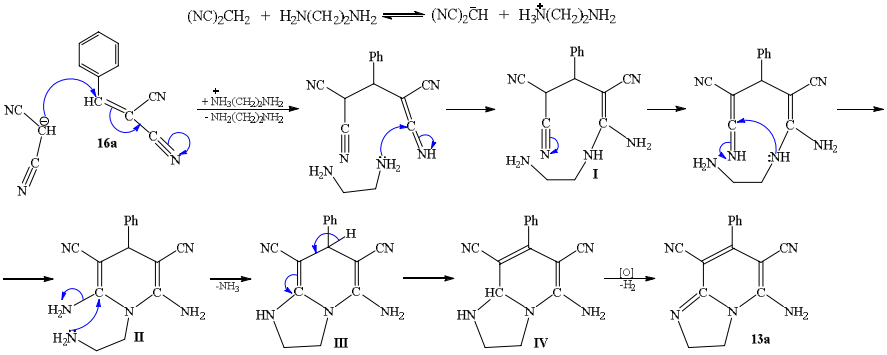


Figure 5. Molecular structure of 13e

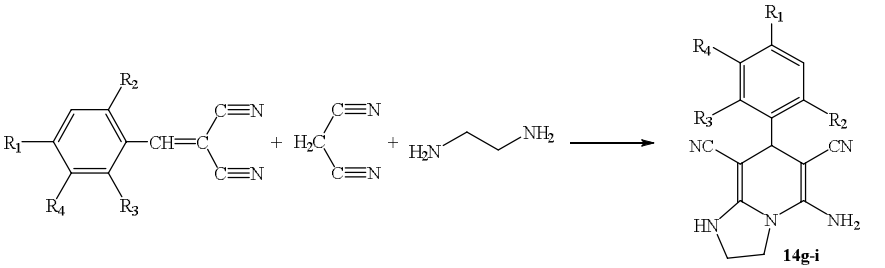
atom of the other nitrile group in the molecule with its electron pair, and forms intermediate-II. In the resulting adduct II, the nitrogen atom of the amine group attacks the carbon atom of the double bond in the cycle and results separation of ammonia and by producing intermediate III. In III-intermediate, the transfer of electron density from one carbon atom to another leads formation of IV. After that, the oxidation of IV-intermediate by air oxygen forms dihydroimidazo[1,2-*a*]pyridine ring.



^{1}H, ^{13}C and COSY NMR confirmed obtaining of 5-amino-7-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (13a).

Three-component condensation of various di-halogen-substituted benzylidenemalononitriles, malononitrile and ethylenediamine was

carried out in methanol medium, without catalyst, and established synthesis of corresponding tetrahydroimidazo[1,2-*a*]pyridines (14g). In our opinion, this reaction also goes with the mechanism above. However, under the influence of dihalogen substituent, III-intermediate does not undergo further processes (oxidation).



g) $R_1=R_2=Cl$, h) $R_2=R_3=Cl$, i) $R_3=R_4=Cl$

Analysis of the molecular structure of 14h (Figure 6) shows formation of two types of hydrogen bonds between molecules. One between nitrogen atom of the NH_2 group of one molecule and oxygen atom of water, and other between oxygen atom of water and the nitrogen atom of the nitrile group of another molecule. Hydrogen bond is also formed between the chlorine atom in the benzene ring of one molecule and the nitrogen atom of imidazole ring of another molecule.

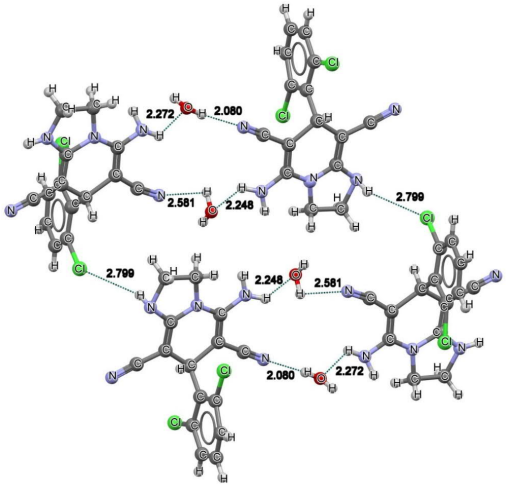


Figure 6. Molecular structure of 14h.

The formation of various types of hydrogen bonds in the molecule also had an effect on the formation of the crystal lattice.

^{1}H, ^{13}C NMR experiment confirmed obtaining 5-amino-7-(2,4-dichloro-phenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (14g) (figure 7 and 8).

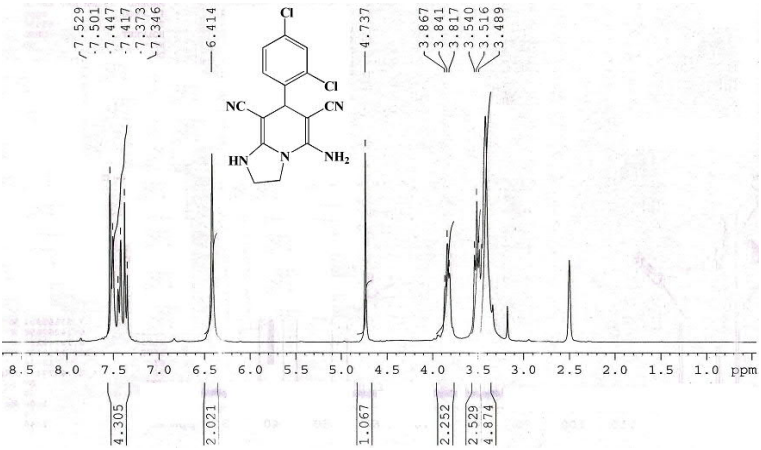


Figure 7. ^{1}H NMR spectrum of 5-amino-7-(2,4-dichlorophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (14g)

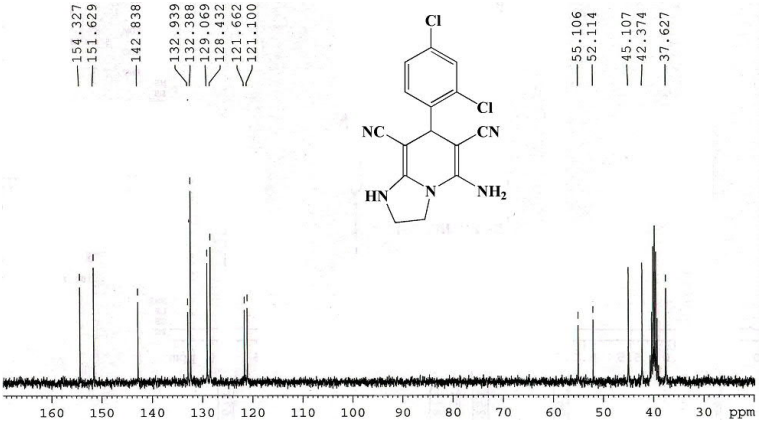
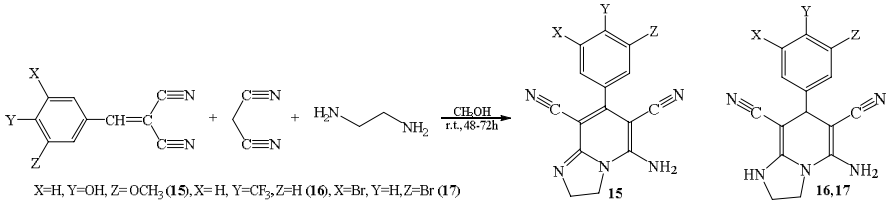


Figure 8. ^{13}C NMR spectrum of 5-amino-7-(2,4-dichlorophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (14g)

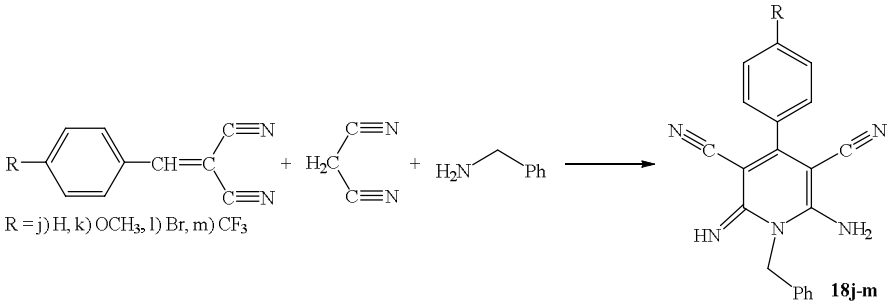
One-pot three-component interaction of 2-[(4-hydroxy-3-methoxy-phenyl)methyliden]propandinitrile, 2-(4-trifluorobenzene)malononitrile and 2-(3,5-di-bromobenzylidene)malononitrile with malononitrile and ethylenediamine under the same reaction conditions was carried out. If use 2-[(4-hydroxy-3-metoxyphenyl]methyliden]propandinitrile

and benzylidenemalononitrile the corresponding dihydroimidazo[1,2-*a*]piridine derivative (15) and when using and 2-(3,5-dibromobenzylidene)maononitrile the appropriate tetrahydroroimidazo [1,2-*a*]pyrimidines (16, 17) production takes place.



^{1}H, ^{13}C NMR spectrums confirmed producing of 5-amino-7-(4-hydroxy-3-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (15).

Formation of dihydroimino[1,2-*a*]pyridines (18j-m) by non-catalyst one-pot three-component condensation of various mono-substituted benzylidenemalononitriles, malononitrile and benzylamine in a methanol medium.



The ^{1}H NMR spectrum contains dublet at 4.62 ppm corresponding to two protons of the methylene (CH_2) group attached to the nitrogen, multiplet at 7.24-7.53 ppm of two protons of amin (NH_2) and ten proons of aromatic ring, triplet at 8.10 ppm of ptoron of NH confirms formation of 6-amino-1-benzyl-2-imino-4-phenyl-1,2-dihydropyridine-3.5-dicarbonitrile (18j) shown in the reaction scheme above. ^{13}C Nuclear Magnetic Resonance (NMR) spectrum also confirmed this result.

Continuing of research of reactions of benzylidenemalononitrile one-pot three component condensation of various mono-substituted benzylidenemalononitriles such as benzylidenemalononitile, 2-(4-

fluorobenzylidene)malononitrile, 2-(4-methylbenzylidene)malononitrile with malononitrile and furfurilamine (or 2-thiophenemethylamine) in a catalyst-free conditions and methanol medium the correspondong 2,6-diaminodihydropyrimidines (19, 20) and iminodihydropyridine (21) were obtained. ^{1}H, ^{13}C, NMR and X-Ray confirmed the formation of compounds above (Figure 9).

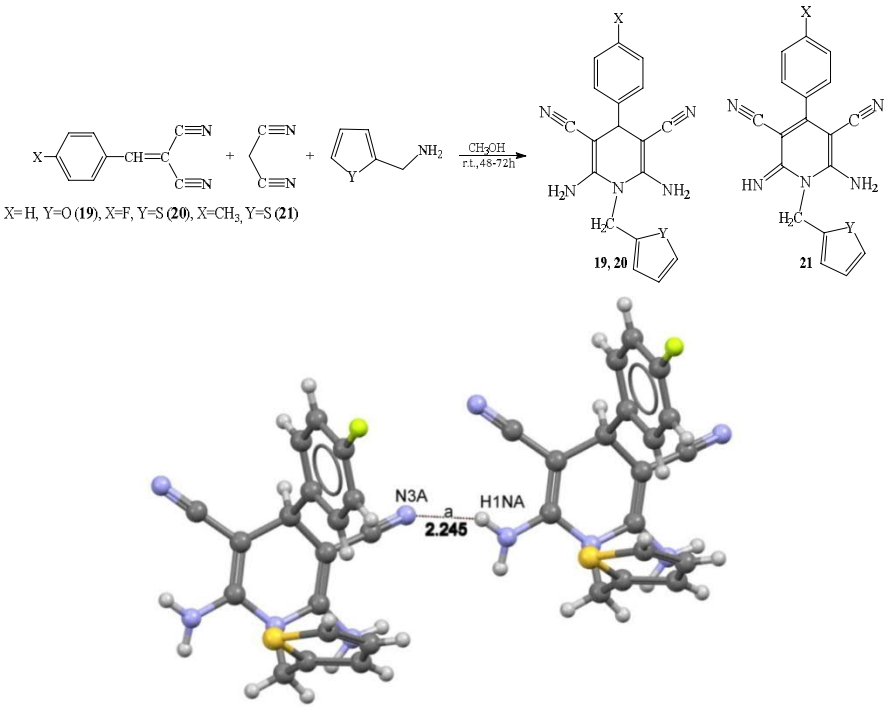
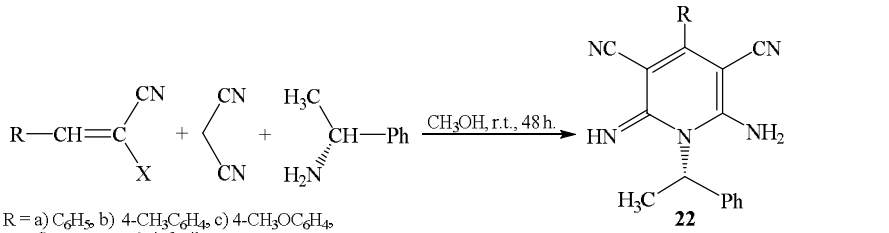


Figure 9. Molecular structure of 20.

Analysis of molecular structure of 20 (Figure 9) shows that the hydrogen bond between nitrogen atom of amino (NH_2) group of one molecule and the nitrogen atom of the nitrile group of another molecule formed. The thiophene and aromatic ring are perpendicular to the dihydropyridine ring.

In our subsequent research, by one-pot, three-component interaction of phenyl, tolyl-, p-methoxyphenyl, p-fluorophenyl-substituted benzylidenecyanoacetamide (or thiophenelidencyanoacetamide with malononitrile and (S)-(-)-1-phenylethylamine in methanol medium at room temperature has been the corresponding piridine derivatives

were synthesized. Not-depending on whether the reaction is carried out with benzylidenemalononitriles or benzylcyanoacetamides, however, the same reaction product was found.



R = a) C_6H_5, b) 4-$CH_3C_6H_4$, c) 4-$CH_3OC_6H_4$, d) 4-F-C_6H_4, e) tiofenil
X = $CONH_2$, CN

R = a) C_6H_5, b) 4-$CH_3C_6H_4$, c) 4-$CH_3OC_6H_4$, d) 4-F-C_6H_4, e) tiofenil

The possible mechanism of reaction is given in dissertation in detail.

^1H, ^{13}C NMR spectrums of synthesized 6-amino-2-imino-4-phenyl-1-(1-phenylethyl)-1,2-dihydropyridine-3,5-dicarbonitrile (compound 22a) are shown in Figure 10 and 11.

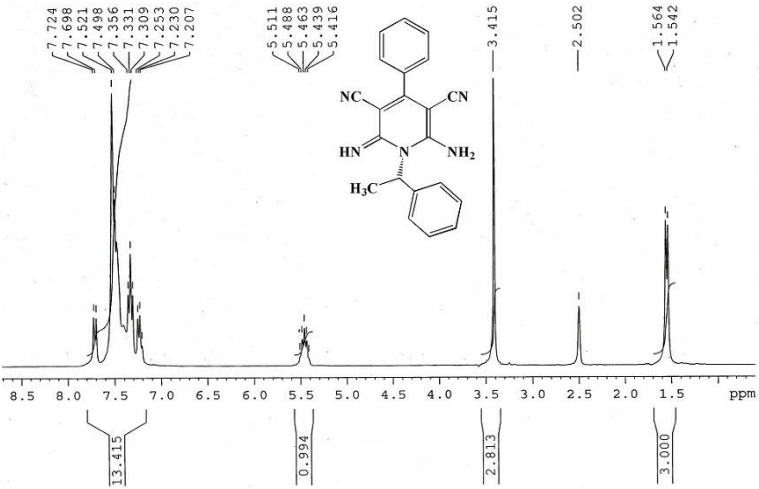


Figure 10. ^1H NMR spectrum of 22a.

^1H NMR spectrum contains dublet at 1.55 ppm according to three protos of methyl (CH_3) group, quartet at 5.46 ppm of protons of methine (CH) group connected to aromatic ring, multiplet at 7.21-7.72 ppm corresponding to ten protons of two aromatic rings, one proton of the NH group and two protons of the amin (NH_2) group and confrims structure of 6-amino-2-imino-4-phenyl-1-(1-phenylethyl)-1,2-

dihydropyridine-3,5-dicarbonitrile (22a). The ^{13}C NMR experiment also reaffirmed this result.

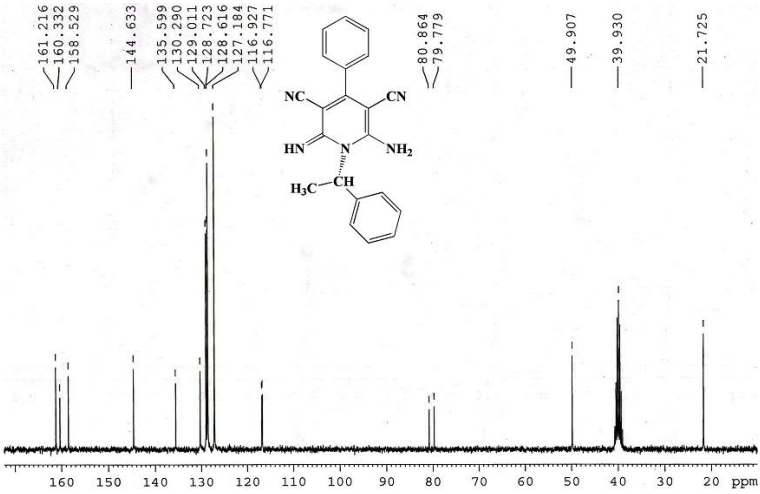
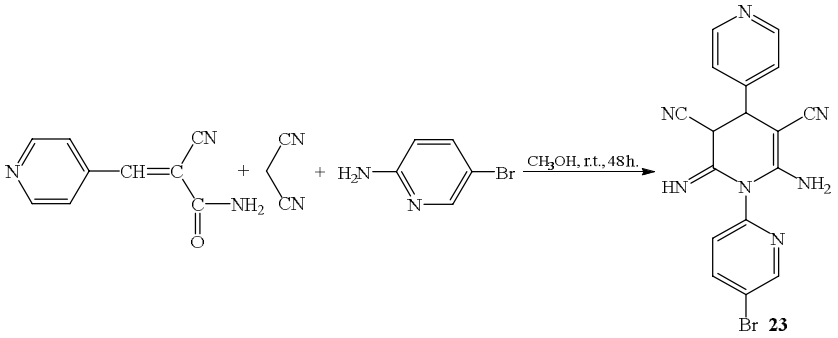


Figure 11. ^{13}C NMR spectrum of 22a.

Also, the appropriate terpiridine derivative (23) was synthesized by one-pot, three-component condensation under the same reaction conditions of pyridinelidenecyanoacetamide with malononitrile and 2-amino-5-bromopyridine.

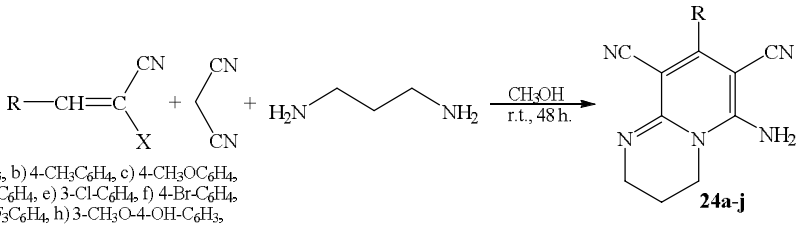


23

The ^{1}H NMR spectrum containing dublets at 4.61 ppm corresponding to one proton of the methine (CH) group and at 4.91 ppm of one proton of another methine (CH) of iminopyridine ring, at 7.32 ppm of proton of methine of 4-bromosubstituted pyridine, singlet at 7.66 ppm corresponding to one proton of the other CH group of 4-bromosubstituted pyridine, dublet at 7.67 ppm, corresponding to one

proton of last CH group of 4-bromosubstituted pyridine, singlets at 7.82 ppm of proton of the imin (=NH) group, at 7.97 ppm of two protons of amino (NH_2), dublets at 8.67 ppm of two protons of two CH groups of pyridine ring, and at 8.78 ppm of two CH of pyridine ring confiormes formation of 6'-amino-5-bromine-2'-imino-3',4'-dihydro-2'H-[2,1': 4',4''-terpyridine]-3',5'-dicarbonitrile (23). The ^{13}C NMR spectrum also reconfirmed this result.

Continuing of research, we have studied one-pot, three-component interaction of various ylidenecyanoacetamides (or ylidenemalononitrile) with malononitrile and 1,3-diaminopropane methanol and at room temperature, for 24-48 hours and established obtaining of new substitited dihydropirido[1,2-*a*]pirimidines (1,2a-j) no matter does ylidenecyanoacetamide or ylidenemalononitrile was used as compound with polarized double bond.



R = a) C_6H_5, b) 4-$CH_3C_6H_4$, c) 4-$CH_3OC_6H_4$, d) 4-F-C_6H_4, e) 3-Cl-C_6H_4, f) 4-Br-C_6H_4, g) 4-$CF_3C_6H_4$, h) 3-CH_3O-4-OH-C_6H_3, j) tiofenil

X = $CONH_2$, CN

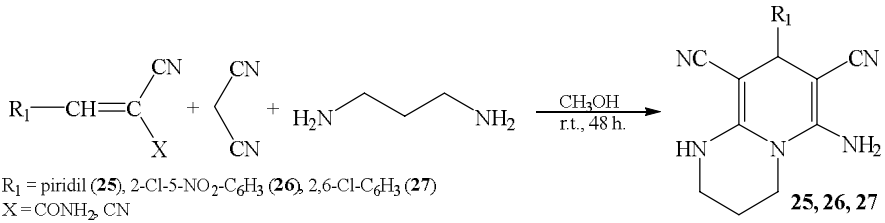
The probable mechanism of reaction is the same with the mechanism of synthesis of 13a given above.

Signals in ^1H NMR spectrum are multiplet at 1.94 ppm corresponding to two protons of methylene (CH_2) in the center of propyl fragment of the cycle, triplet at 3.86 ppm, corresponding to two protons of another methylene (CH_2) group attached to nitrogen, multiplet at 7.41-7.52 ppm corresponding to five protons of aromatic ring and a singlet at 7.84 ppm corresponding to two protons of the amin (NH_2). All signals confirm obtaining of 6-amino-8-phenyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrimidine-7,9-dicarbonitrile (24a) and this thesis also affirmed by ^{13}C NMR.

When using as polarized double bonded compound pyridinelidencyanoacetamide (or pyridinelidenmalononitrile), 2-chloro-5-nitrobenzylidencyanoacetamide (or 2-chloro-5-nitrobenzylidenmalononitrile), 2,6-dichlorobenzylidenecyanoacetamide (or 2,6-dichlorobenzyliden-

malononitrile) in one-pot, three-component interaction with malononitrile and 1,3-diaminopropane dihydropyrido[1,2-*a*]pyrimidines was not obtained but, but suitable tetrahydropyrido[1,2-*a*]pyrimidine derivatives (25, 26, 27) have been identified.

The ^{1}H NMR spectrum contains multiplets at 1.88 ppm corresponding to two protons of the methylene (CH_2) group, and at 3.13 ppm corresponding to two protons of the methylene (CH_2) group attached to a fully substituted nitrogen atom, and at 3.60 ppm of two protons of methylene (CH_2) group attached to the NH, singlets at 4.06 ppm corresponding to one proton of CH of aromatic ring, at 6.27 ppm corresponding to two protons of amino (NH_2) group, at 6.90 ppm corresponding to one proton of the NH group, dublets at 7.18 ppm corresponding to two protons of the 2CH group of the pyridine ring, and at 8.51 ppm of two protons of other 2CH of piridine ring affirms that the product of reaction is 6-amino-(pyridine-4-il)-1,3,4,8-tetrahydro-2H-pirido[1,2-a]pyrimidine-7,9-dicarbonitrile (25). This result also confirmed by ^{13}C NMR.



R_1 = piridil (**25**), 2-Cl-5-NO_2-C_6H_3 (**26**), 2,6-Cl-C_6H_3 (**27**)
X = $CONH_2$, CN

25, 26, 27

By our mind, the possible mechanism of obtaining of these compounds is the same with mechanism of obtaining 24a-j described in detail in the dissertation.

In the literature, in multicomponent reactions of benzylidenemalononitriles, malononitrile (other activemethylene compounds) with amines, as amino-components aminopyridines, aminopyrimidines and aminoacids were used. But using ethylendiamine and 1,3-diaminopropane were not presented.

In contrast to the literature, ethyleneamine and 1,3-diaminopropane were used for the first time in these reactions. Thus, by one-pot three component interaction of various mono-substituted benzylidenemalononitriles (exept 2-(4-(trifluoromethyl)benzylidenemalononitrile or benzylidenecyanoacetamides with malononitrile and eth-

ylendiamine it has been found that dihydroimidazo[1,2-*a*]pyridines are formed. When using dihalogen-substituted benzylidenemalononitriles (except disubstituted 2-[(4-hydroxy)-3-methoxyphenyl)metiliden]propandinitrile) the formation of corresponding tetrahydroimidazo[1,2-*a*]pyridines has been identified. In our opinion, benzene ring of dihalogen-substituted benzylidenemalononitriles is involved by positive inductive coupling tetrahydroimidazo[1,2-*a*]pyridines are quite resistant to subsequent oxidation.

When a similar three-component reaction is carried out in the presence of 1,3-diaminopropane, a new substituted dihydropyrido [1,2-*a*]pyrimidine was synthesized. But when using substituted benzylidenemalononitriles (or benzylidenecyanoacetamides) in this reaction obtaining of tetrahydropyrido[1,2-*a*]pyrimidine derivatives has been observed.

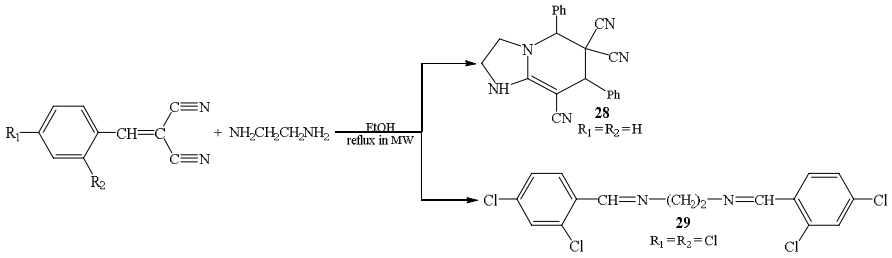
It was established that when furfurylamine or 2-thiophenmethylamine used in multicomponent interaction then 2,6-diaminodihydropyridine derivatives obtained.

Also, for the first time, from one-pot, three-component interaction of mono-substituted benzylidenemalononitriles (or benzylidenecyanoacetamides) with malononitrile and benzylamine then derivatives of iminodihydropyridine derivatives were identified as reaction products. When a three-component reaction was carried out in the presence of (*S*)-(-)-1-phenylethylamine, optically substituted iminodihydropyridine was obtained.

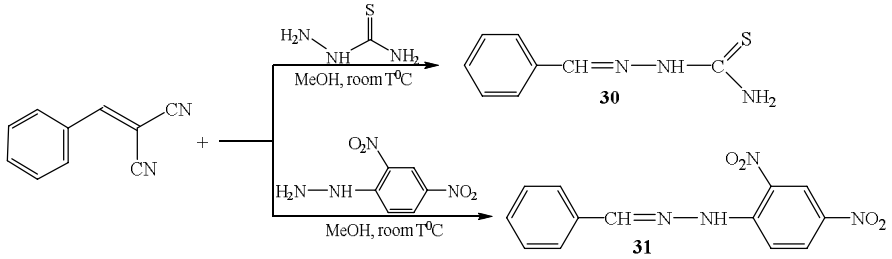
Interaction of benzylidenmalononitriles with ethylenediamine, thiosemicarbazide and 2,4-dinitrophenylhydrazine

By reflux of benzylidenemalononitrile with ethylenediamine in ethanol under ordinary conditions or microwave irradiation new bicyclic heterocyle 5,7-diphenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6,6,8(5H)-tricarbonitrile (28) has been was obtained. Interaction of 2-(2,4-di-chlorobenzylidene)malononitrile with ethylenediamine under the same reaction conditions the corresponding azomethine (29) was formed.

^{1}H, ^{13}C NMR spectrums confirmed synthesis of 5,7-diphenyl-1,2, 3,7-tetrahydroimidazo[1,2-*a*]pyridine-6,6,8(5H)-tricarbonitrile (28) and corresponding azometine (29).



There was also carried out one-pot, three-component reaction between benzyldenemalononitrile, malononitrile and thiosemicarbazide (or 2,4-dinitrophenylhydrazine) and established that malononitrile doesnt involved in process and by elimination of ammonia and malononitrile fragments formation of azomethane derivatives (30 and 31) was determined and structures were confirmed by ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectrums.

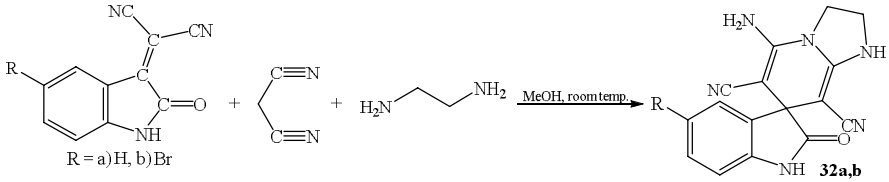


Synthesis of functionally substituted isatylidenemalononitriles

Spirooxindols, which show biological activity, are the main components of many natural compounds and drugs. Isatylidenemalononitriles are important synthons in organic synthesis and widely used in obtaining spirooxyindols and 3.3'-disubstituted oxyindols. During the synthesis of spirooxindols, Michael addition, cyclo-addition and sometimes even domino reactions are widely used. In addition, in the literature, there are many researching works dedicated to interactions of dialkyl phosphite, diphenyl phosphite, α,β-unsaturated ketones with activemethylene.

One-pot three-component reaction of isatylidenemalononitrile with malononitrile and amines. In this part of our study, by one-pot three-component interaction of isatylidenemalononitrile (or bromo isatylidenemalononitrile) with malononitrile and ethylenediamine in

methanol and at room temperature was carried out. Only corresponding dihydroimidazopyridine derivative (32a,b) was obtained as a reaction product.



The probable mechanism of reaction is similar to the mechanism of obtaining of 13a and described in detail in the dissertation.

The ^{1}H and ^{13}C NMR spectrums characterized the structures of the synthesized 32a are shown in Figure 12 and 13.

The ^{1}H NMR spectrum contains triplet at 3.55 ppm of four protons of two methylene (CH_2) groups attached to a nitrogen atom, singlet at 6.43 ppm corresponding to two protons of amino (NH_2) group, multiplet at 6.82-7.19 ppm of four protons of the aromatic ring, a singlet at 7.57 ppm corresponding to one proton of the NH group, and a singlet at 10.33 ppm of one proton of the NH group and confirms structure of 5-amino-2'-oxo-2,3-dihydro-1H-spiro[imidazo[1,2-*a*]pyridine-7,3'-indoline]-6,8-dicarbonitrile (32a). ^{13}C NMR once again affirms the result above.

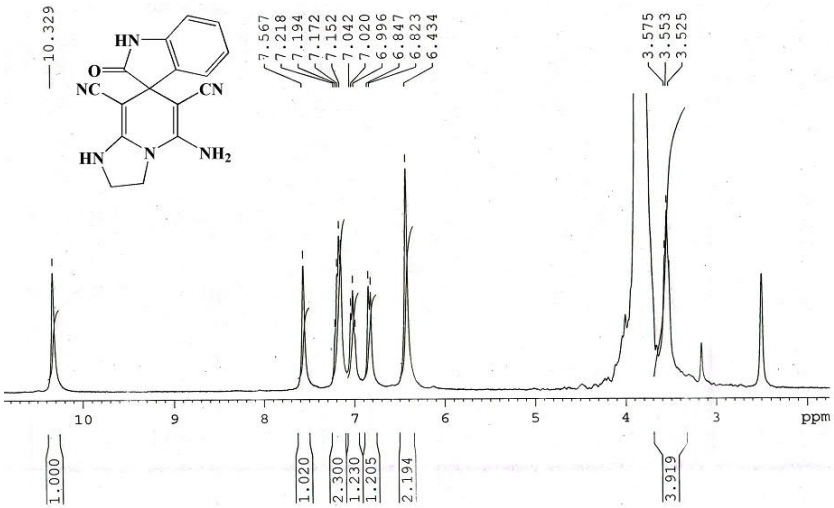


Figure 12. ^{1}H NMR spectrum of 32a

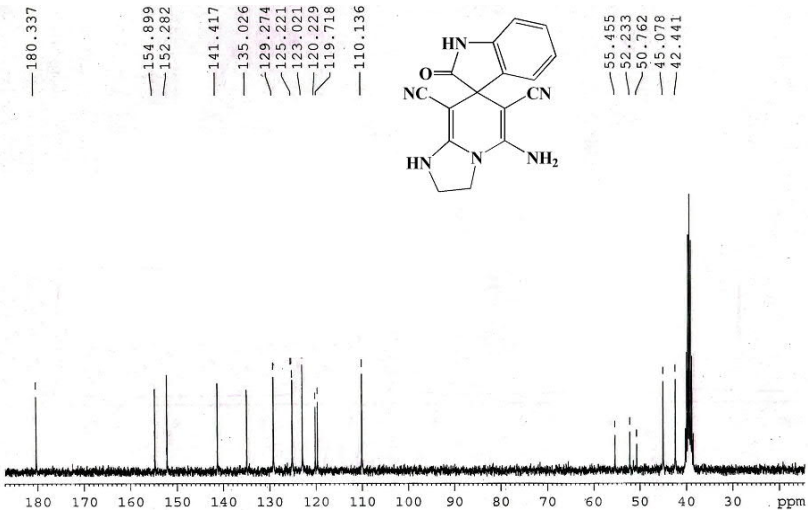
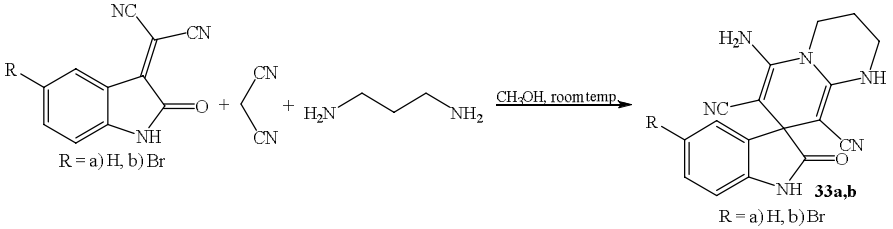


Figure 13. ^{13}C NMR spectrum of 32a

In continuation of the research, by one-pot three-component reaction of isatylidenemalononitriles with malononitrile and 1,3-diaminopropane carried out in a methanol at room temperature the formation of a tetrapirido[1,2-*a*]pyrimidine derivative (33a,b) with good yields was observed. The mechanism of reaction path is the same with formation of pyrido[1,2-*a*]pyrimidine derivatives (24a-j) and the dissertation provides detailed information.



The ^{1}H NMR spectrum contains multiplet at 1.92 ppm corresponding to two protons of methylene (CH_2) group in the center of cyclic propyl fragment, and triplet at 3.17 ppm corresponding to two protons of the methylene (CH_2) group attached to nitrogen atom, triplet at 3.62 ppm of to two protons of the CH_2 group attached to another nitrogen atom, multiplet in the interval 6.33-7.19 ppm of three protons of the aromatic ring, two protons of the amin (NH_2) group and one proton of the NH group, singlet at 10.24 ppm corresponding

to one proton of another NH group confirms obtaining of 6'-amino-2-oxo-1',2',3',4'-tetrahydrospiro[indoline-3,8'-pyrido[1,2-*a*]pyrimidine]-7',9'-dicarbonitril (33a) in reaction scgheme given above. The X-ray (Figure 14) and ^{13}C NMR also confirm this result.

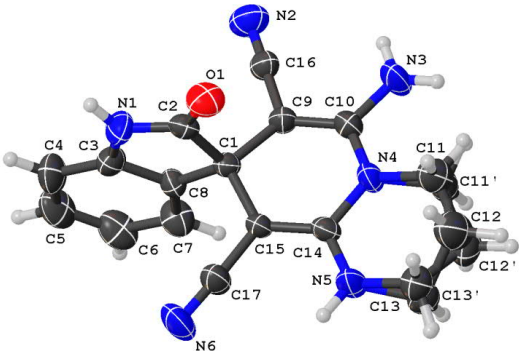
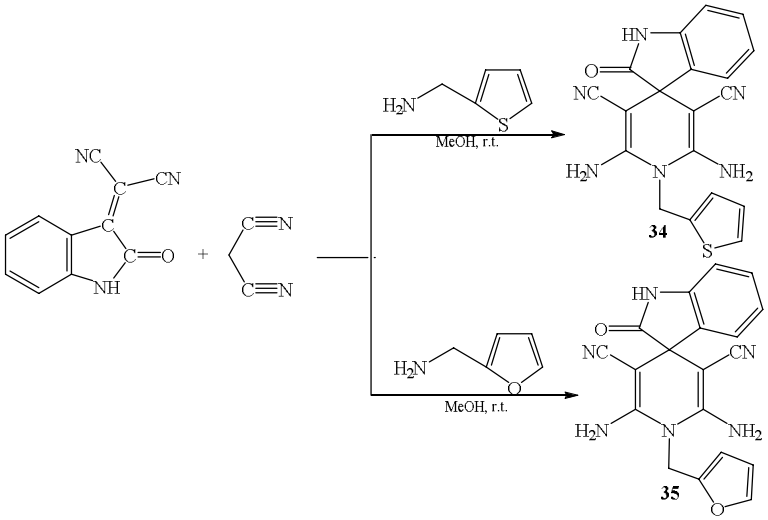


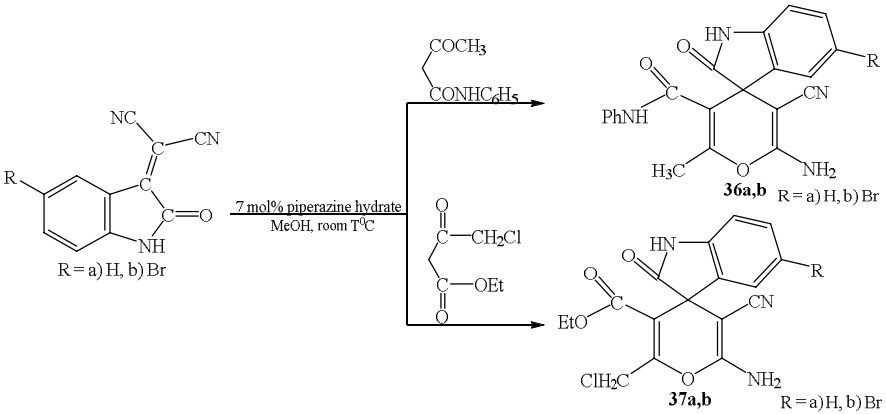
Figure. 14. Molecular structure of 33a

In our next study, correeponding derivative of diaminodihydropyridine (34, 35) was synthesized by one-pot, three-component interaction of isatylidenemalononitrile with malononitrile and furfurylamine (or 2-thiphenmethylamine).



Reaction of isatylidenemalononitrile with acethyl acetanilide and 4-ethyl ester of chloroacetoacetic acid. By Michael addition of isatylidenemalononitrile (or 2-(5-bromo-2-oxoindoline-3-iliden)ma-

lanonitrile with acetoacetanilide (or ethyl ester of 4-chloroacetoacetic acid in methanol, at room temperature, in the presence of 7 mol% pyperazine hydrate (or methyl piperazine) The corresponding cyano-spiro[indoline-3,4'-piran] – derivatives (36a,b and 37a,b) were synthesized.



The molecular structure of the synthesized 37a studied by X-ray is shown in Figure 15.

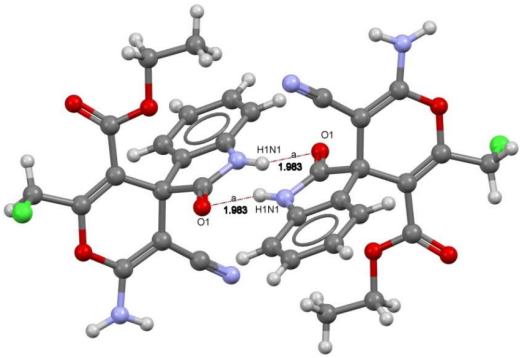


Figure 15. Molecular structure of 37a

From the analysis of the molecular structure of the synthesized compound 35a, it can be concluded that there are intermolecular hydrogen bonds in crystal lattice between nitrogen atom of the NH group of one molecule and oksigen of N−C=O group of the other molecule.

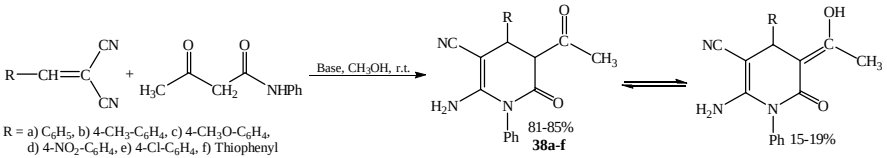
It is also established one-pot three-component synthesis path of di-

aminodihydropyridine derivative by interaction of isatylidenemalononitriles, malononitrile and furfurylryamine (or 2-thiophenemethylamine). In addition, by Michael addition of isatylidenemalononitriles to acetacetanilide and ethyl ester of 4-chloroacetic acid in the presence of pyperazine hydrate (or methyl piperazine) appropriate cyanospiro[indoline-3,4'-piran] derivatives obtaining has been developed.

Michael addition of benzylidenemalononitriles or ylidenecyanoacetoamides to activemethylene compounds

Benzylidenemalononitriles or ylidenecyanoacetoamides are compounds with polarized double bond. Nitrile and amide groups, which are electrowithdrawing groups, polarize double bond in these compounds. As a result, the interaction of these compounds with nucleophilic agents in the presence of various bases results formation of functionally substituted derivatives.

Michael addition of benzylidenemalononitriles with acetoacetanilide and keto-enol tautomerism in Michael's adducts. Corresponding pyridine derivatives were synthesized by Michael addition of substituted benzylidenemalononitriles (R = a-e) or thiophenylidenemalononitriles (R=f) with acetoacetanilidine in the presence of various bases (piperidine, piperazine hydrate, methylpiperazine, triethylamine), in a methanol, at room temperature. nuclear magnetic resonance (NMR) studies (38a-f) confirmed the presence of keto-enol tautomerism in the solution systems of the compounds. Based on the integrated intentions of the signals, 85% were found to be in keto and 15% in enol form.



R = a) C_6H_5, b) 4-CH_3-C_6H_4, c) 4-CH_3O-C_6H_4, d) 4-NO_2-C_6H_4, e) 4-Cl-C_6H_4, f) Thiophenyl

Michael addition of 2,6-dichlorobenzylidenemalononitrile and acetoacetanilide in the presence of various bases (piperidine, piperazine hydrate, methylpiperazine, triethylamine) in methanol medium at 60-65°C for 4-6 minutes was carried out. Nuclear Magnetic Resonance (NMR) studies of the obtained 5-acetyl-2-amino-4-(2,6-dichlorophe-

nyl)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (compound 39) showed the presence of a stable enol form in the solution. In our opinion, the predominance of the enol form (83.51%) in this compound is due to the fact that the hydrogen atom of the hydroxyl group (OH) takes place in formation of intramolecular hydrogen bond. ^{1}H and ^{13}C NMR spectrums of 39 are shown in Figure 16 and 17.

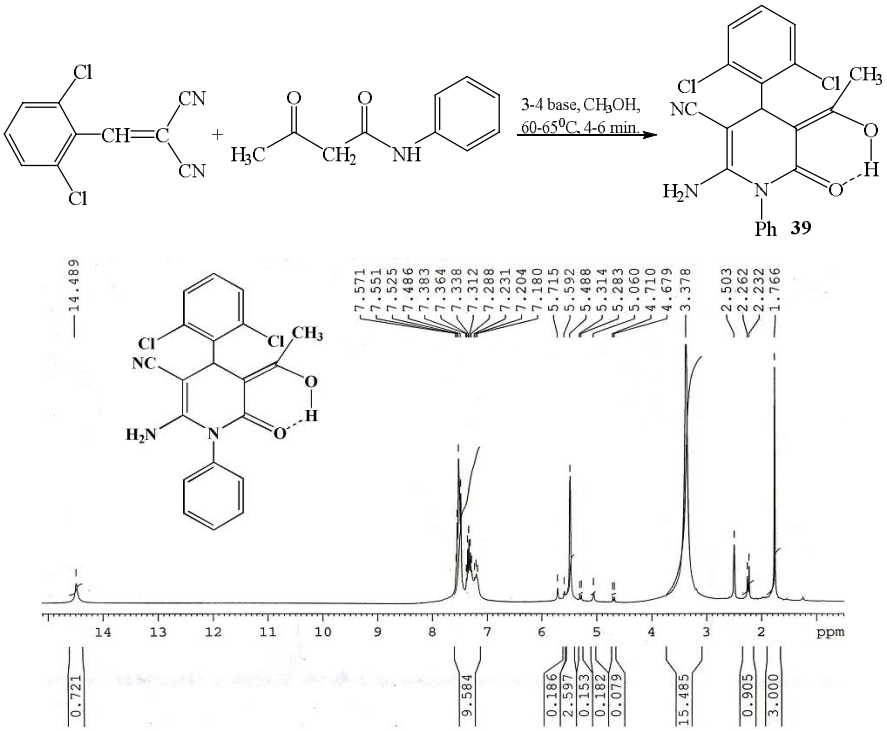


Figure 16. ^{1}H NMR spectrum of (Z)-2-amino-4-(2,6-dichlorophenyl)-5-(1-hydroxyethylidene)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (39).

Also, the Michael addition of 2-(2-chloro-5-nitrobenzylidene)malononitrile with acetoacetanilide in the presence of various bases (piperidine, piperazine hydrate (7 mol%), methylpiperazine, triethylamine) for 24 hours at room temperature was carried out. Initial crystals were observed after 15 minutes reaction. Analysis of the nuclear magnetic resonance (NMR) spectra of these crystals confirmed the formation of compound-40. Reaction product also contained compound-41.

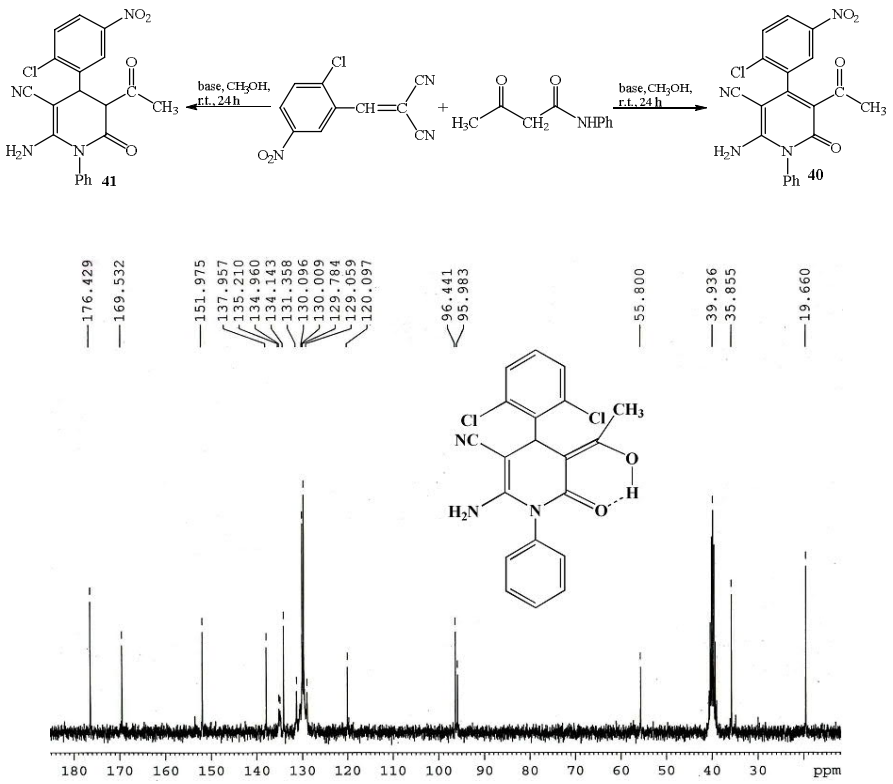
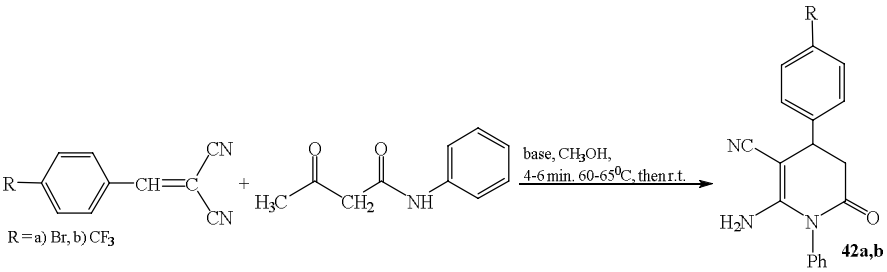


Figure 17. ^{13}C NMR spectrum of (Z)-2-amino-4-(2,6-dichlorophenyl)-5-(1-hydroxyethylidene)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (39).

The Michael addition of 2-(4-bromobenzylidene)malononitrile and 2-(4-(trifluoromethyl)benzylidenemalononitrile with acetoacetanilide in the presence of various different bases (piperidine, piperazine hydrate, methylpiperazine, triethylamine in methanol medium, at a 60-650C for 4-6 minutes and keeping at room temperature for 48 hours after drying was carried out. NMR studies have determined the separation of an acetyl group attached to a pyridine ring from molecule. The corresponding spectrums contain double dublets at 5.88 ppm (42a) and 5.93 ppm (42b) of the protons of amin (NH_2), and at 2.75-3.44 ppm (42a) and 2.78–3.26 ppm (42b) of protons of methylene (CH_2) group, and triplet at 3.95 ppm of proton of CH (42a) and at 4.07 ppm protons of CH (42b).



Observing doublet-dublet at 2.78–3.17 ppm corresponding to two protons of methylene (CH_2) group, a triplet at 3.95 ppm corresponding to one proton of the methine (CH) group attached to an aromatic ring, singlet 5.88 ppm corresponding to two protons of the amin (NH_2) and multiplet at 7.21-7.62 ppm confirms obtaining of 2-amino-4-(4-bromophenyl)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (42a). The ^{13}C NMR spectrum also reaffirmed this result.

The molecular structure of the synthesized 42a X-ray is given in Figure 18.

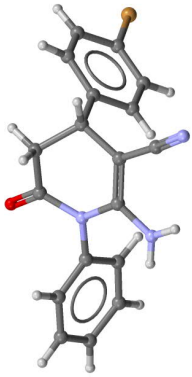
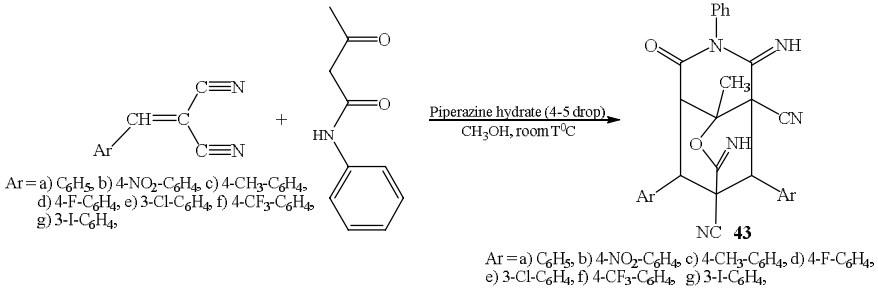


Figure 18. Molecular structure of 42a.

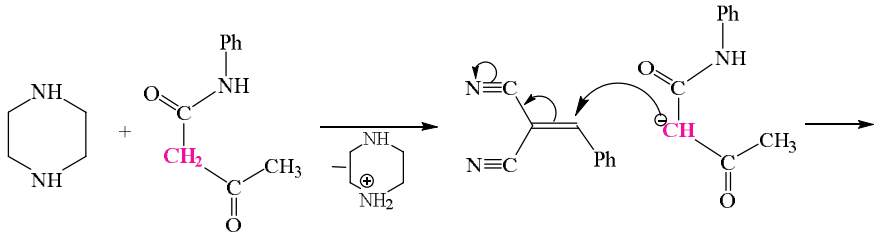
Synthesis of tricyclic compounds by Michael addition of benzylidenemalononitriles to acetoacetanilide

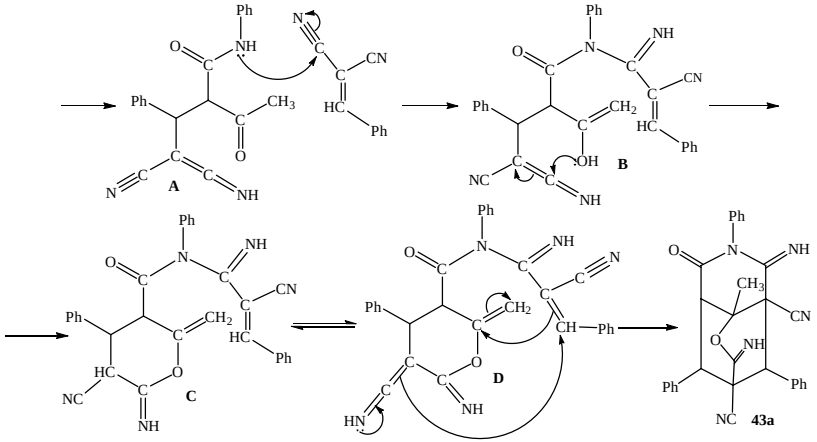
Continuing research, it has been established that by interaction of 2 moles of benzylidenemalononitrile with acetoacetanilide in methanol as solvent at room temperature, in the presence of bases such as piperazine hydrate (or methylpiperazine), only corresponding tricyclic heterocycles (43a-g) was found as result of reaction.



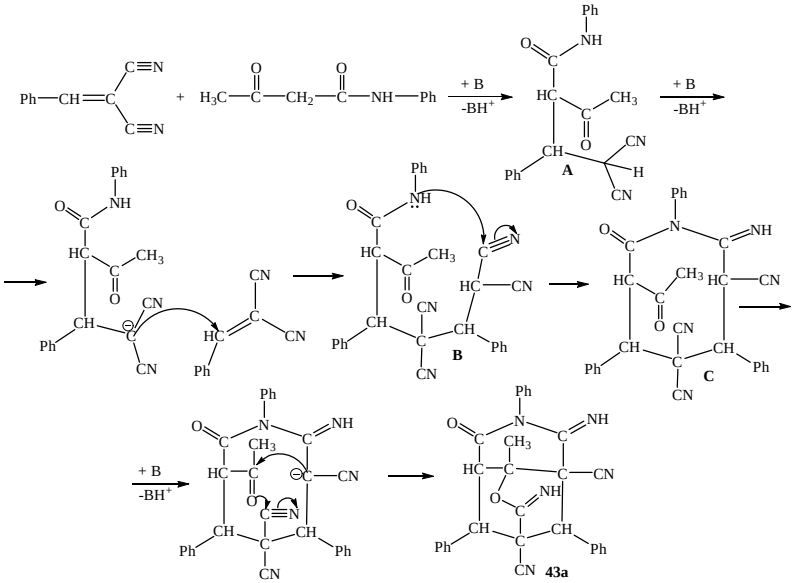
The singlet at 1.91 ppm of three protons of the methyl (CH_3) group, dublet at 3.95 ppm of one proton of methine (CH) group attached to aromatic ring, dublet at 4.49 ppm of one proton of methine (CH) group attached to N−C=O, singlet at 4.94 ppm of one proton of methine (CH) group attached to another aromatic, multiplet at interval 7.37 ppm - 7.64 ppm to fifteen protons of three aromatic rings, singlet at 7.88 ppm of one proton of NH, singlet at 9.20 ppm of oproton of another NH in ^{1}H NMR spectrum confirms obtaining of 2.5-diimino-8*a*-methyl-7-oxo-4,6,9-triphenyltetrahydro-2H-3,8-metano-pyrano[3,2-c]pyridine-3,4*a*(4H,5H)-dicarbonitrile (43a). The X-Ray and ^{13}C NMR spectrum also confirm this result.

We have proposed two possible mechanisms of formation of heterocycle: a) by nucleophilic attack with an electron pair of NH of A−Michael adduct formed as conversion product on the carbon atom of the nitrile group (CN) in the second arylidenemalononitrile molecule and forms B. The acethyl group in the B-intermediate is then enolized. The C-intermediate is formed as a result of nucleophilic attack of electron pair of oxygen atom of OH group of the enol form to the carbon atom of the nitrile group. In the last stage, as a result of double cyclization of C-intermediate the tricyclic pyrano[3,2-c]pyridine derivative (43a-g) is formed.





b) According to the second probable mechanism, the nucleophilic agent (corresponding anion) formed as a result combination of two electroacceptor nitrile groups in the Michael adduct (A), attacks electrophilic center of another benzylidenmalononitrile molecule on the =CH and form intermediate B. Then, nucleophilic attack by the electron pair of the nitrogen atom in the NH group to the carbon of nitrile group and carbanion formed in C by action of base attacks to carbon of carbonyl group and oxygen of carbonyl group attacks carbon of nitril group simultaniously and give compound 43a.



In subsequent studies, 2,5-diimino-8a-methyl-7-oxo-4,6,9-trife-nil-tetrahydro-2H-3,8-methanopyrano[3,2-c]pyridine-3,4*a*(4H,5H)-di-carbonitrile (43a) refluxed in ethanol in the presence of iodine and hydrazine hydrochloride by resulting of 5-acethyl-2,4-dioxo-3,6-diphenyl-3-aza-bicyclo[3.1.0]hexane-1-carbonitrile (44), whereas when reflux 44 in ethanol and in the presence of hydrazine hydrochloride monocyclic substance (45) was formed.

Molecular structures studied by X-ray of the of 43a-45 compounds are shown in Figure 19-20.

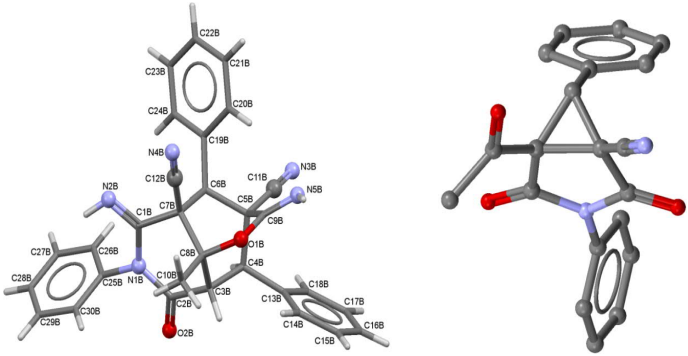


Figure 19. Molecular structure f 43a and 44

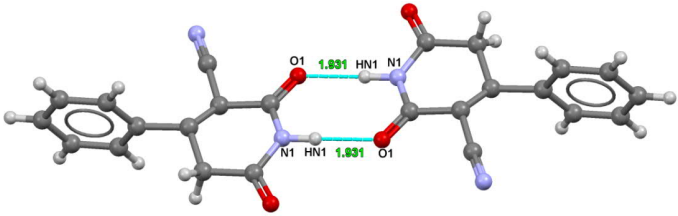
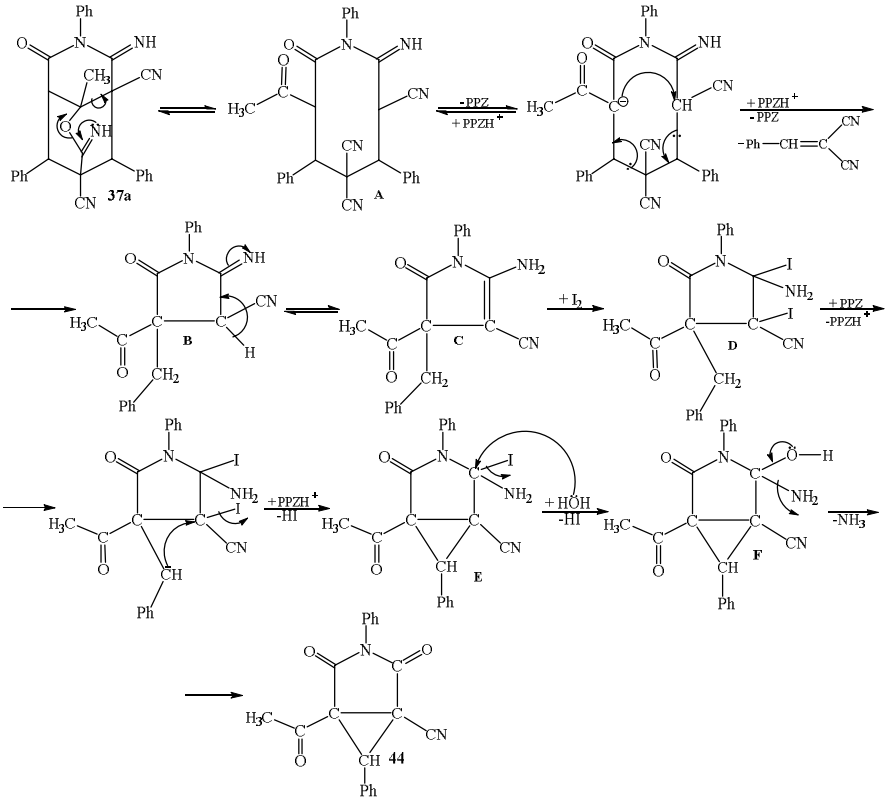


Figure 20. Molecular structure of 45.

According to supposed mechanism of the reaction path, the tricycle 37a ion converted into A-intermediate as a result of redistribution of electron density. The attack of the nucleophilic particle of the anion formed in the intermediate A on the CH group in in the presence of the piperazine base, the redistribution of the electron density, and breaking of the carbon-carbon bonds takes place the destruction of molecule and by the reason of separation of benzylidenemalononitrile B-intermediate was formed. Redistribution of electron density also occurs in B-intermediate, and by addition of hydrogen to the NH group the C-intermediate was observed. D-intermediate has been ob-

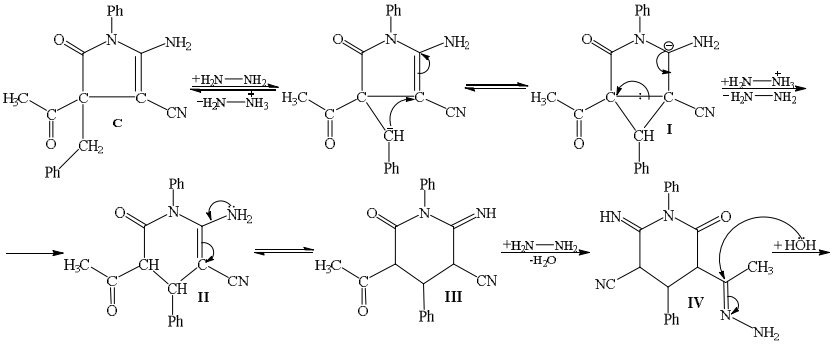
tained by adding iodine to the double bond of C. Under the influence of base, the D-intermediate converts to corresponding anion. Relatively positive-charged carbon atom (nucleophilic particle) in the obtained anion attacks the negative-charged carbon atom (electrophilic center) and by separation of HI three-membered cycle and E-intermediate was formed. In the next stage, as a result of attack of the oxygen atom of water molecule on the carbon atom to which the iodine is bonded, HI is released from molecule and F-intermediate obtained. In final stage, the electron density of oxygen atom is transferred to the carbon atom in the F-intermediate, and compound 44 was formed by separating ammonia.

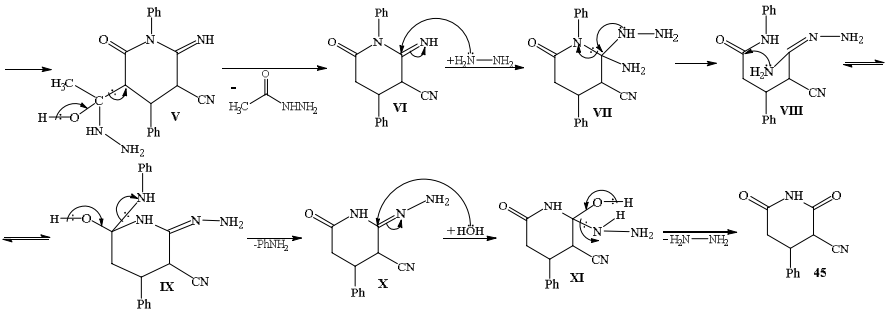


When tricycle reacts with hydrazine hydrate, reaction occurs in a manner similar to the probable mechanism described above. In our opinion, the resulting C-intermediate converted into suitable anion in the presence of hydrazine hydrate. As a result of nucleophilic attack

of negative carbon of double bond, the intermediate I is formed. Hydrogen of the quaternary ammonium salt transferred to I, and electron density rearranges correspondingly and carbon−carbon bond was breaken down by forming II. By fransferring electron pair of NH_2 to double bond and replacing electron density at another carbon of double bond, intermediate II was converted to III. Electron pair of nitrogen in hydrazine electrophilic carbon atacks acethyl group of III and as a result of water elimination hydrazone (IV) was formed. The nucleophilic attack of electron pair of oxygen in the separated water to the carbon atom of the hydrazone stimulates formation V. In resulting intermediate V, the electron density on the hydroxyl group is transferred to a carbon of acethydrazine by forming VI.

Then, nitrogen atom of hydrazine attacks carbon atom of imin group with the higher electrophilicity in the VI and the intermediate VII formes. In new VII-intermediate the electron pair of nitrogen atom is transferred to the carbon atom and also transfering of electron density to the nitrogen where phenyl group was bonded results the breaking of the C-N bond and forming VIII. In the next stage, a nucleophilic attack occurs on the electrophilic carbon of carbonyl (C=O) group with electron pair of nitrogen atom of the NH_2 and converting of VIII to IX takes place. As a result of transferring of electron density from the hydroxyl group to the carbon atom in IX, and further from carbon to nitrogen provides separation of aniline and obtaining X. The electron pair of oxygen in the water hydroxyl group of water attacks the carbon atom of imine group in X, and XI-intermediate is formed. At last stage, by transferring electron density from hydroxyl to carbon and eliminating of hydrazine 2,6-dioxo-4-phenylpiperidine-3-carbonitrile (compound 45) was synthesized.

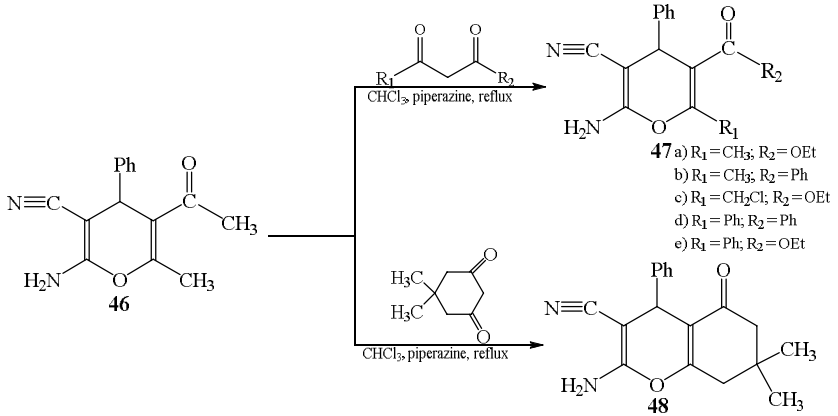




Alkylation of 5-acethyl-2-amino-6-methyl-4-phenyl-4h-pyrane-3-carbonitrile with various active-methylene reagents

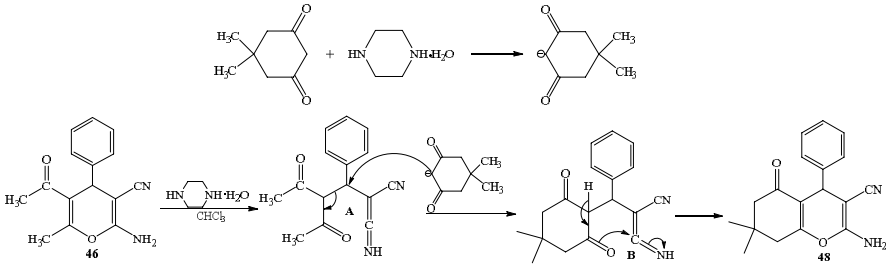
It was carried out reaction of 5-acethyl-2-amino-6-methyl-4-phenyl-4H-pyrane-3-carbontrile (46) with acetoacetic ester (or dimedone, benzoylacetone, ethyl ester of 4-chloroacetoacetic acid, dibenzoylmethane and ethyl ester of benzoylacetic acid) in chloroform, in the presence of 7% mol of piperazine hydrate in mw-irradition and synthesized corresponding 4H-pirane-3-carbonitrile derivatives.

^{1}H and ^{13}C NMR spectrums confirmed formation of corresponding substituted pirane derivatives (47a-e and 48) shown in the reaction scheme.



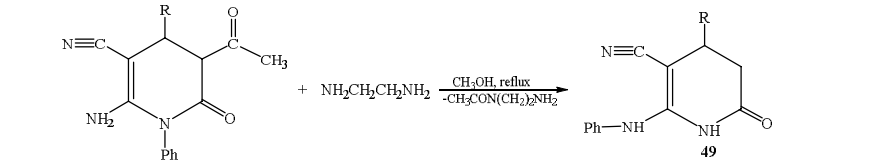
According to the supposed reaction mechanism, the corresponding anion formed by action of piperazine hydrate on dimedone molecule. The pyran ring is opened, and the nucleophilic attack of anion of the dimedone to the obtained adduct (A) results formation of B-inter-

mediate. B converted to enol form and by nucleophilic atack of electron pair of the oxygen atom of the enol form to imine carbon corresponding 4H-pyrane-ring (48) is formed. The probable mechanism of reaction is given below:



Rearrangements in acethyltetrahydropyridine derivatives

By continuing our research in this filed, by Michael addition of benzylidenemalononitriles and thiophenylidenemalononitrile with acetoacetanilide the appropriate 1,4,5,6-tetrahydropyridine-3-carbonitriles were obtained. The obtained acetyltetrahydropyridine derivatives were acted by ethylenediamine at reflux conditions in methanol. Studies have shown separation of acetyl group that leads to rearrangement in molecule and formation of new pyridine derivatives.



R= a) Ph, b) 4-$CH_3C_6H_4$, c) 4-F-C_6H_4, d) 4-Br-C_6H_4, e) 3-I-C_6H_4, f) 2,6-Cl-C_6H_3, g) thiophenyl, h) 4-$CH_3OC_6H_4$, i) 4-$NO_2C_6H_4$,

R= a) Ph, b) 4-$CH_3C_6H_4$, c) 4-F-C_6H_4, d) 4-Br-C_6H_4, e) 3-I-C_6H_4, f) 2,6-Cl-C_6H_3, g) thiophenyl, h) 4-$CH_3OC_6H_4$, i) 4-$NO_2C_6H_4$,

As singlet at 2.33 ppm corresponding to three protons of acetyl methyl (CH_3) in molecule of initial compound, so as two dublets at 4.09 and 4.27 ppm corresponding to two methine (CH) and singlet at 5.92 ppm corresponding to protons of amin (NH_2) disappear in the ^{1}H NMR spectrum of the synthesized compounds. Instead of them we observed double dublet at 2.69 and 3.10 ppm, of formed CH_2, triplet at 3.94 ppm of CH, and two singlets at 8.86 and 10.22 ppm of corresponding to two NH protons.

Double dublet at 2.69 ppm corresponding to one proton of methylene (CH_2), and double dublet at 3.10 ppm of another proton of

methylene (CH_2) group, bonded to aromatic ring, triplet at 3.94 ppm of one proton of the CH group, multiplet at 6.96–7.42 ppm corresponding to ten protons of two aromatic rings, singlets at 8.86 ppm of one proton of NH and at 10.22 ppm of one proton of other NH group confirms formation of 2-anilino-6-oxo-4-phenyl-1,4,5,6-tetrahydro-pyridine-3-carbonitrile (49a) shown in the reaction scheme. X-ray (Figure 21) and ^{13}C NMR spectrum also confirm this result.

Considering the molecular structure of the 2-anilino-4-(4-methoxyphenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitryl (49h), it is clear that hydrogen bonds are formed in two states of the crystal lattice. Thus, hydrogen bonds have formed between NH nitrogen atom of the pyridone cycle of one molecule and the nitrogen atom of nitrile group of another molecule, as well as between the oxygen atom of the C=O group of the pyridone cycle of one molecule and the NH group of another molecule.

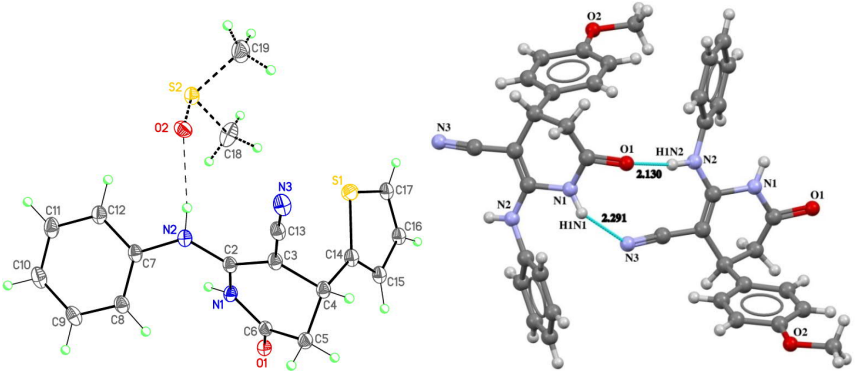
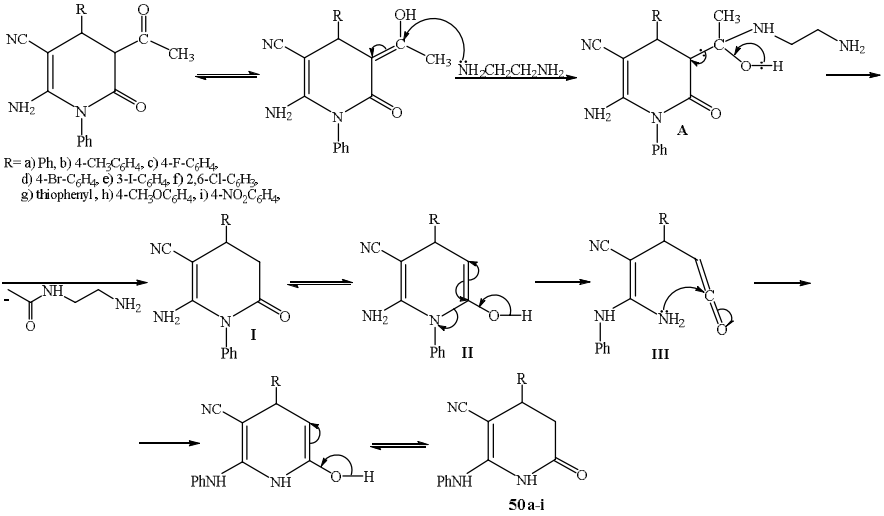


Figure 21. Molecular structures of (49g) and (49h).

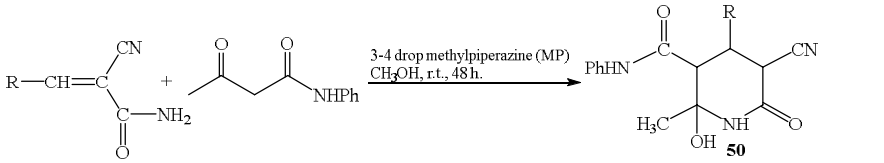
According to the probable reaction mechanism, 5-acethyl-2-amino-1,4,5,6-tetrahydropyridine-3-carbonitrile derivatives are converted to the corresponding enol form in appropriate conditions. Electron pair of nitrogen of amine group in the ethylenediamine molecule, attacks the carbon of enol form as nucleophile to form A-intermediate. As result of dehydration occured in A the B-intermediate was formed. The C-intermediate is formed by the nucleophilic addition of water and the elimination of protons in B. Then by appropriate transfering of electron pair in C and elimination of amide of acetic acid intermediate I was obtained. In the next stage, I-intermediate reaction

turns into the enol form (II). In the enol-form (II), a cycle is opened by transfering of electron density resulting III. Finally, electron pair of nitrogen of amine group atacks as nuclophile to the carbon of ketene fragment that is electrophilic center by resulting new cycle and by appropriate transfering of electrondensity reaction product was formed.



Michael addition of some ylidenecyanoacetamides to active-methylene compounds

As a continuation of research, we carrierd out Michael addition of some ylidenecyanoacetamides with acetoacetanilide in methanol solution, in the presence of catalytic amount of methylpiperazine (MP), at room temperature for 24-48 hours resulting obtaining of new substituted pyridone derivatives (50a-e).



The ^{1}H NMR spectrum containing singlet at 1.51 ppm corresponding to three protons of methyl (CH_3), dublet at 3.21 ppm of one

proton of methine (CH) group attached to amide group, triplet at 4.04 ppm of methine (CH) group bonded to aromatic ring, dublet at 4.48 ppm according to one proton of CH group combined with nitrile group, singlet at 6.20 ppm of one proton of hydroxyl (OH), multiplet at interval 6.96-7.48 ppm corresponding to ten protons of two aromatic rings, singlets 8.94 ppm of one proton of the NH at 9.78 ppm of one proton of the other NH confirm obtaining 5-cyano-2-hydroxy-2-methyl-6-oxo-N,4-diphenylpiperidine-3-carboxamide (50a). ^{13}C NMR spectrum also confirmed this result.

The molecular structure determined by X-ray of the synthesized compound (50d) is given in Figure 22.

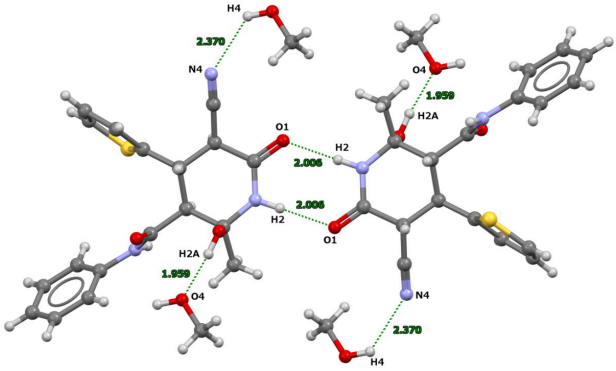


Figure 22. Molecular structure of dimer of compound 50d

The molecular structure of obtained compound 50d shows that hydrogen bond formed as between oxygen of carbonile group of amide fragment of one molecule and nitrogen of pyridone ring of other molecule so between nitrogen atom of NH group of amide fragment of one molecule and oxygen atom of carbonyl group of second molecule in crystal lattice. In addition, between oxygen atom of methanol taken as solvent and nitrogen atom of the nitrile group and the hydroxyl group of other molecule hydrogen bonds are formed in the crystal lattice (Figure 23).

X-Ray analysis confirmed that in addition to the intermolecular hydrogen bonds, T-type interactions are present between hydrogen of aromatic ring of one molecule and π-system of thiophene ring of another molecule. Thus, the intermolecular hydrogen bonds and «T-shaped» interactions affect the formation of crystal lattice (Figure 23).

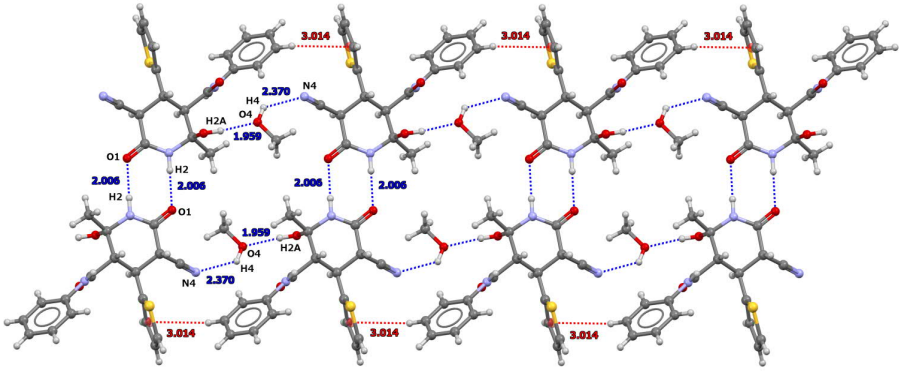
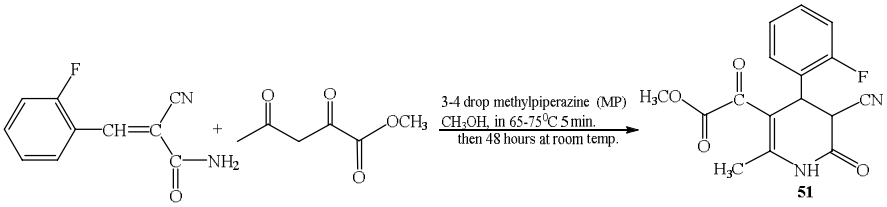


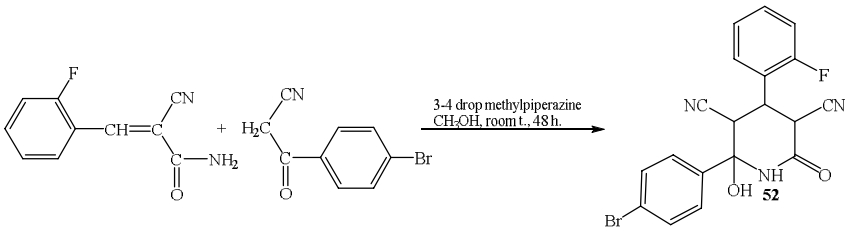
Figure 23. Molecular structure of crystal lattice of 50d.

Also, tetrahydropiridone derivative (51) was synthesized by Michael addition of 2-fluorobenzylidenecyanoacetamide and methyl acetopyruvate in catalytic quantities of methylpiperazine (MP) and in methanol solution at 65-70°C for 5 minutes.

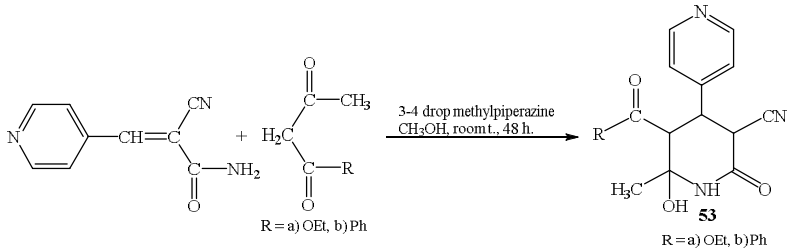


^{1}H NMR spectrum containing singlets at 1.81 ppm corresponding to three protons of methyl group, at 3.70 ppm of three protons of methoxy (CH_3O), a dublet at 4.43 ppm corresponding to one proton of methine (CH) group associated with nitrile group, doublet at 4.54 ppm of one proton of methine (CH) and four protons of the aromatic ring, and singlet at 9.41 ppm of one proton of the NH confirm obtaining of methyl ester of 2-(5-cyano-4-(2-fluorophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-yl)-2-oxoacetate (51). ^{13}C Nuclear Magnetic Resonance (NMR) spectrum also confirms this result.

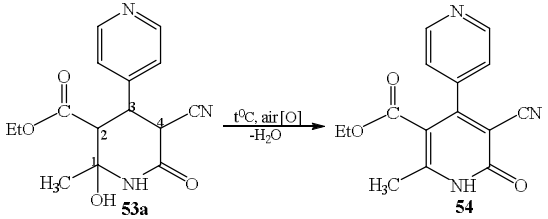
Michael addition of 4-bromobenzoylacetonitrile to 2-fluorobenzylidenecyanoacetamide with polarized double bond was carried out in the presence of catalytic amount of methylperazine (MP) in methanol at room temperature resulting new derivative of tetrahydroropyridone (52) with high yield.



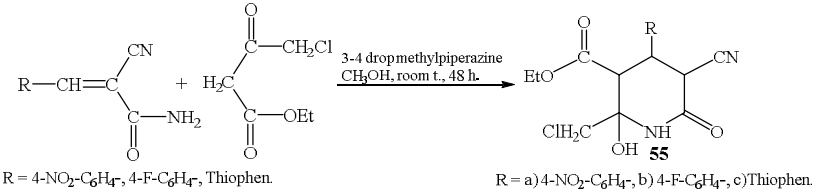
It should be noted that when carrying out Michael addition of benzoylacetone and acetoacetic acid to 2-cyano-3-(pyridine-4-yl)acrylamide under the same reaction conditions new tetrahydroro-pyridone derivatives (53a,b) were obtained with high yield.



Studies have shown that when 53a-compound is heated, water is released from 1-2 positions, and hydrogen atoms from positions 3-4 oxydazied with air oxygen so it converted to 54.



Also, it was established that by Michael addition of ethyl ester of 4-chloroaceticacid to 2-cyano-3-(4-nitrophenyl)acrylamide, 2-cyano-3-(thiophen-2-yl)acrylamide or 2-cyano-3-(4-fluorophenyl)acrylamide under the same reaction conditions obtaining of tetrahydro-pyridone derivatives (55a,b,c) with high yields was determined.



Thus, the availibility of keto-enol tautomerism if Micahel adducts obtained by Michael addition of acetoacetanilide to mono-substituted benzyldenemalononitriles was established. NMR spectrums confirms that bulk of these adducts are in keto form. However, in contrast to the benzylidenemalononitriles mentioned above, Michael addition of acetacetanilide to 2,6-dichlorobenzylidenemalononitrile mainly in enol form, and this fact determined by Nuclear Magnetic Resonance. In our opinion, an intramolecular hydrogen bond is formed between the oxygen atom of the enol form and the oxygen atom of the carbonyl group in Michael's adduct. For this reason, the reaction product can remain stable in enol form. In addition, the Michael addition of 2-(2-chloro-5-nitrobenzylidene)malononitrile with malononitrile and acetoacetanilide was carried out by using different bases and formation of two products was determined.

It was found that the result of Michael addition of 2-(4-bromobenzylidene)malononitrile and 2-(4-(trifluoromethyl)benzylidene)-malononitrile to acetoacetanilidine is non-acethyl-substituted pyridone derivatives.

Also, in contrast to the relevant reactions in the literature, tricyclic pyrano[3,2-c]pyridine derivatives were obtained from the reaction of 2 moles of substituted benzylidenmalononitriles with 1 mole of acetoacetanalide. When acting with iodine to obtained tricyclic pyrano[3,2-c]piridine in the presence of piperazine hydrate the bicyclic (three- and five-membered) 5-acetyl-2,4-dioxo-3,6-di-phenyl-3-azabicyclo[3.1.0]-hexane-1-carbonitrile was synthesized. By interaction of tricyclic pyrano[3,2-c]pyridine derivative with hydrazine hydrate formation of 2,6-dioxo-4-phenyl-pyperidine-3-carbonitrile has been identified.

When synthesized acethyl-substituted 1,4,5,6-tetrahydropyridine-3-carbonitriles have been refluxed in the presence of the base, new substituted pyridone derivatives were identified as a result of regrouping in the pyridone cycle with separation of the acethyl-group.

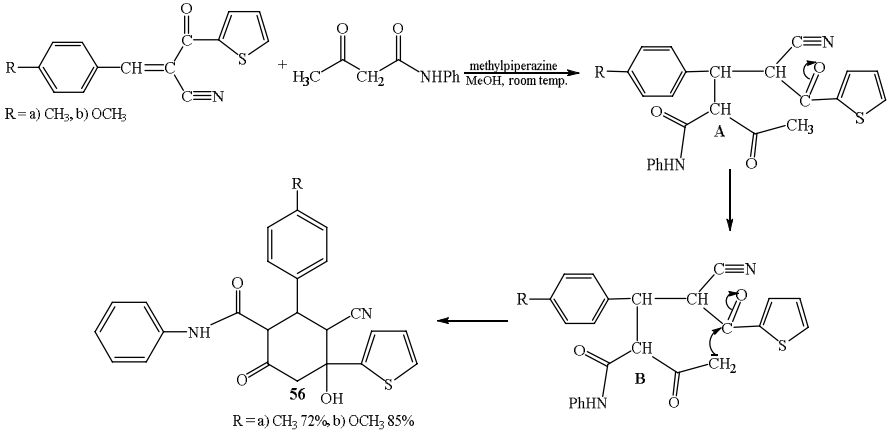
Synthesis of polarized double-bonded compounds and their Michael's addition with activemethylene compounds

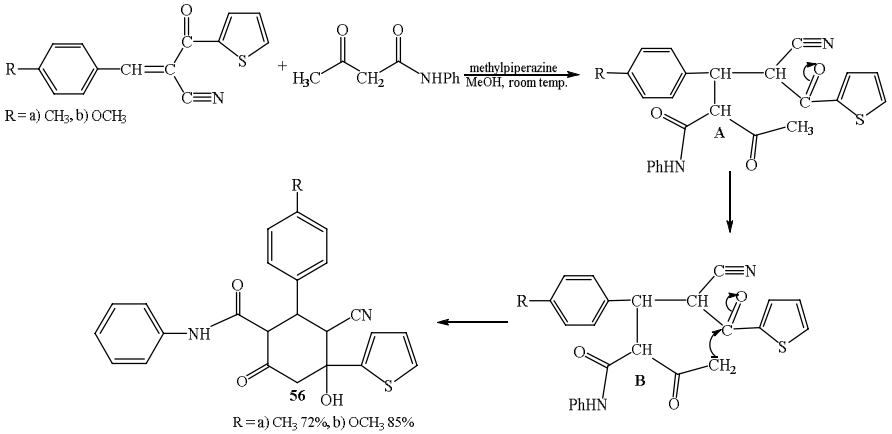
Carbonylacrylonitriles are also class of compounds with polarized (activated) double bond. Double bond in these compounds, is activated (polarized) by the nitrile and carbonyl groups, which are the

electrowithdrawing groups. As a result of negative mesomeric effect (-M) of carbonyl and nitrile groups of carbonylacrylonitriles, the electron density of double bond attached carbon atoms changes. Therefore, nucleophilic addition can easily occur in these systems. Also in unsaturated ketones, the double bond is in an active (or polar) state, so it can easily undergo various nucleophilic fusion reactions.

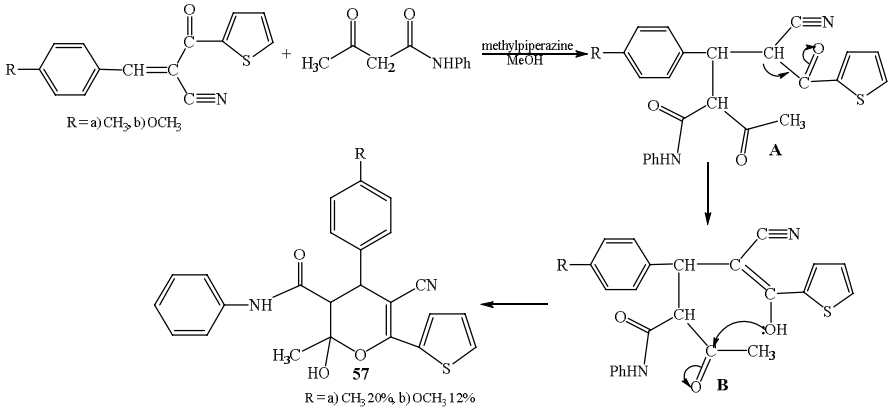
Michael addition of 2-(thiophene-2-carbonyl)acrylonitriles with acetoacetanilide. Michael addition of 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile and 3-(4-metoxyphenyl)-2-(thiophene-2-carbonyl)-acrylonitrile acetylation to acetoacetanilide was carried out in methanol solution with 2-3 drops of methylpiperazine. Obtaining of corresponding pirane derivatives was established as result of reaction.

The ^{1}H NMR spectrum containing singlet at 2.23 ppm corresponding to three protons of methyl (CH_3) group, a doublet at 2.79 ppm corresponding to one proton of methine (CH) group attached to the nitrile group, triplet at 3.50 ppm of one proton of methine (CH) attached to the aromatic ring, singlet at 3.63 ppm corresponding to one hydroxyl (OH)-proton, singlet at 4.06 ppm of two protons of the CH_2, dublet at 4.28 ppm a doublet corresponding to one proton of methine (CH) group joined to the amide group, multiplet at 6.97-7.48 ppm of nine protons of aromatic ring and 3 protons of the thiophenyl group, and singlet at 9.94 ppm corresponding to one proton of the NH confirmed obtaining of 3-cyano-4-hydroxy-6-oxo-N-phenyl-4-(thiophene-2-il)-2-(p-tolil)cyclohexane-1-carboxamide (56a). ^{13}C NMR spectrum also confirms this result.



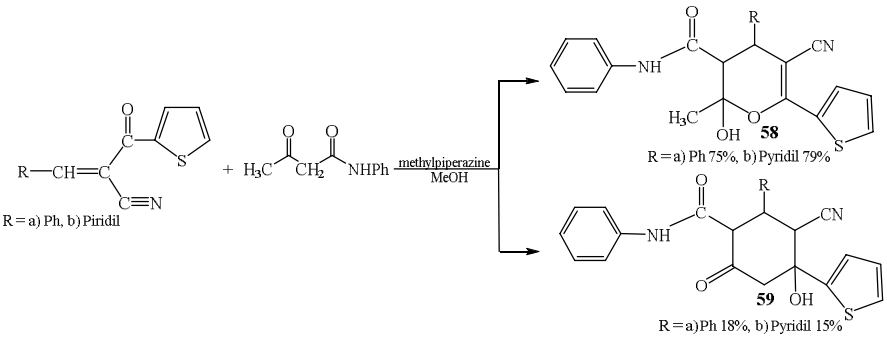


Further studies revealed that in Michael addition of 2- (thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile and 3-(4-metoxyphenil)-2- (thiophene-2-carbonyl)acrylonitrile with asetoastanilide formation of pyrane derivatives (57a, b) was observed.



Also, by Michael addition of Knoevenagel adduct obtained from the pyridine aldehyde (or benzaldehyde) and 3-oxo-3-(2-thienyl)propionitrile in ethanol-water solution with acetoacetanilide in the presence of 2-3 drops methylpiperazine of 3,4-dihydro-2H-pyran derivatives synthesized with high yield and cyclohexanon derivatives also synthesized but with low yield.

The probable mechanism of this reaction is the saw with the reaction mechanism of compounds 56 and 57 and is given in detail in the dissertation.



The molecular structures of synthesized compounds 58a and 58b are shown in Figure 24.

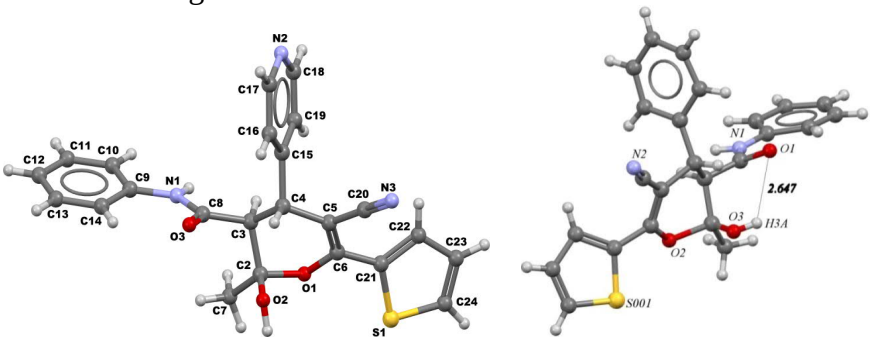


Figure 24. Molecular structures of 58a and 58b

Molecular structure of 58a-compound (Fig. 24) shows that an intramolecular hydrogen bond length 2,647 nm is formed between oxygen atom of amide and hydroxyl oxygen.

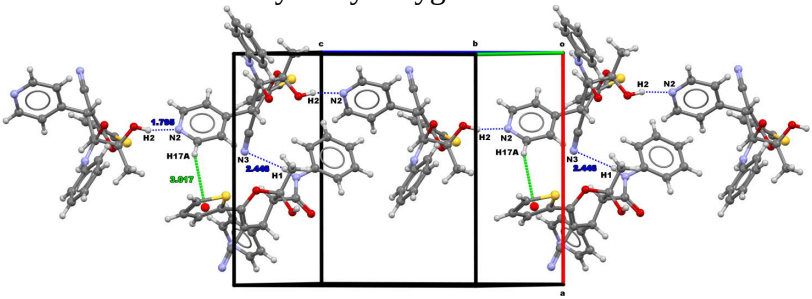


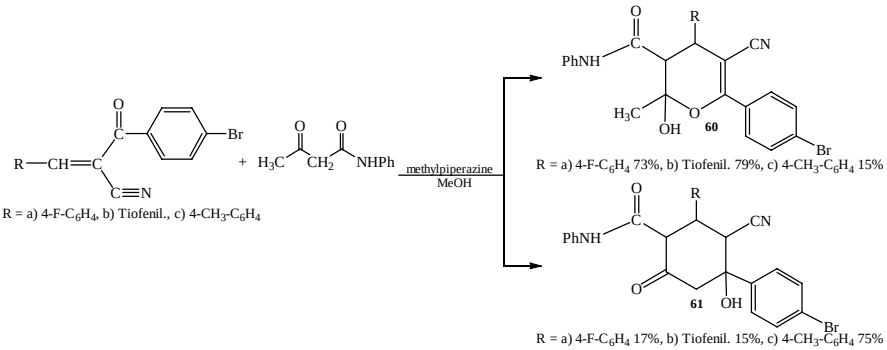
Figure 25. Fragment of crystal lattice of 58b. Broken lines describes intermolecular hydrogen bonds H···N, H···N and T-shape C–H···π interaction sistemi across bc diagonal

Analysis of the molecular structure of the 58b-compound (Figure

25) shows that between oxygen of hydroxyl group of one molecule and nitrogen of pyridyl ring of other molecule intermolecular hydrogen bonds have been formed.

Michael addition of 2-(4-bromobenzoyl)-3-(4-fluorophenyl)acrylonitriles with acetoacetanilide

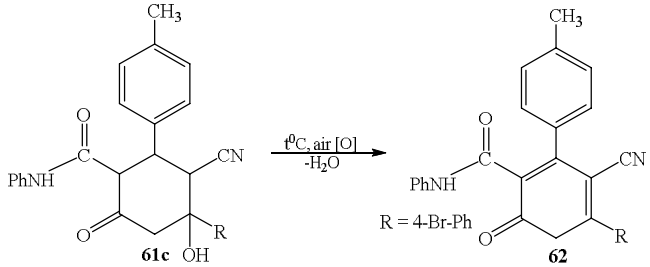
In our next study, Michael adition of 2-(4-bromobenzoyl)-3- (4-fluorophenyl)acrylonitrile, 2-(4-bromobenzoyl)-3-(thiophen-2-yl)acrylonitrile and 2-(4-bromobenzoyl)-3-(p-tolyl)acrylonitrile with acetoacetanilide was carried out at room temperature, in methanol solution, in the presence of 2-3 drops of methylpiperazine. It was determined formation as substituted hexanone so corresponding pirane derivatives when using 2-(4-bromo-benzoyl)-3-(4) fluorophenyl)acrylonitrile and 2-(4-bromobenzoyl)-3-(thiophene-2-yl)acrylonitrile as carbonylacrylonitrile in the same reaction conditions, formation of cyclohexanone derivatives with high yield has been observed. However, when use 2-(4-bromo-benzoyl)-3-(p-tolyl)acrylonitrile as compound with polarized double bond, cyclohexanone with high yield and pirane derivatives with low yield were obtained.



The ^{1}H NMR spectrum contains singlet at 1.71 ppm corresponding to three protons of methyl (CH_3), doublet at 3.02 ppm of one proton of methine (CH) group bonded to amide group, singlet at 3.52 ppm of one proton of hydroxyl (OH), dublet at 4.35 ppm according to one proton of the methine (CH) group attached to aromatic ring, multiplet at 7.00-7.97 ppm corresponding to thirteen protons of aromatic ring and singlet at 9.85 ppm corresponding to one proton of the

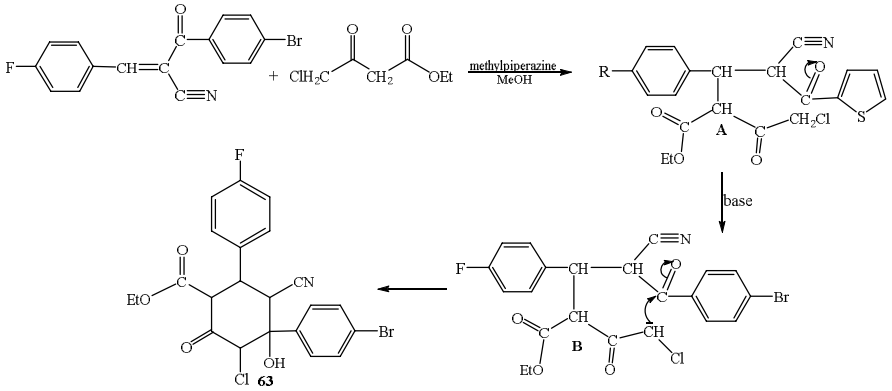
NH group confirm obtaining of 6-(4-bromophenyl)-5-cyano-4-(4-fluorophenyl)-2-hydroxy-2-methyl-N-phenyl-3,4-dihydro-2H-pyran-3-carboxamide (60a) and ^{13}C NMR spectrum also reaffirms the structure of 60a.

It should be noted that when reflux 4-(4-bromophenyl)-3-cyano-4-hydroxy-6-oxo-N-phenyl-2-(p-tolyl)cyclolo-hexane-1-carboxamide (61c) in ethanol and re-crystallized water molecule eliminates from structure and takes place oxidation by air oxygen and formation of 62.



Michael addition of some carbonylacrylonitriles with malononitrile, benzoylacetone and ethyl ester of 4-chloroacetoacetic acid

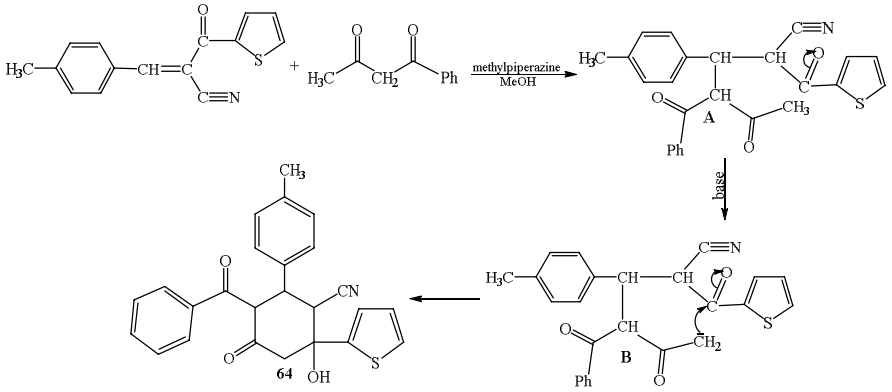
In the next stage of our research, the Michael addition of ethyl ester of 4-chloroacetoacetic acid with 2-(4-bromobenzoyl)-3-(4-fluorophenyl)acrylonitrile was carried out at room temperature, in the presence of methanol and using 2-3 drops of methylpiperazine. According to the reaction, a substituted hexanone derivative (63) was obtained.



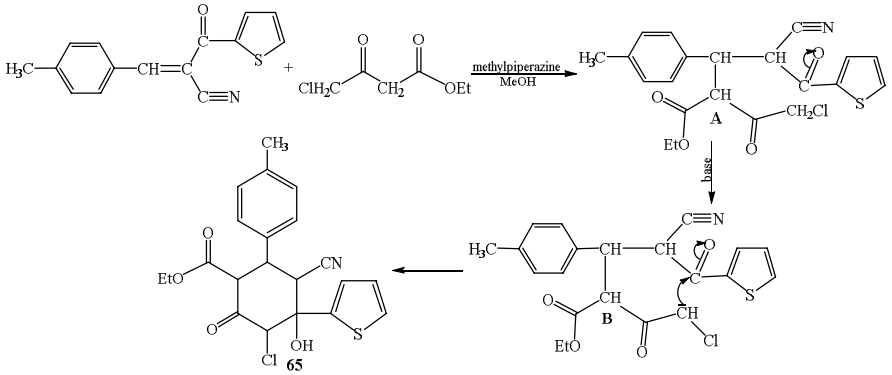
^{1}H and ^{13}C NMR spectrums confirmed obtaining of 4-(4-bromo-

phenyl)-3-chloro-5-cyano-6-(4-fluorophenyl)-4-hydroxy-2-oxycyclohexane-1-carboxylic acid (63).

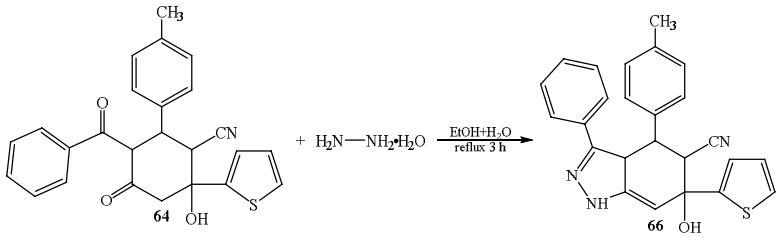
In our next study, Michael addition of benzoylacetone to 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile at room temperature and methanol medium was carried out by obtaining of substituted derivative of cyclohexanone (64).



Michael addition of ethyl ester of 4-chloroacetoacetic acid with 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile was carried out at the same conditions and appropriate cyclohexanone derivative (65) was synthesized.



The interaction of 5-benzoyl-2-hydroxy-4-oxo-2-(thiophene-2-il)-6-(p-tolyl)cyclohexane-1-carbonitrile (64) with hydrazine was carried out by reflux in ethanol-water solution and 6-hydroxy-3-phenyl-6-(thiophene-2-il)-4-(p-tolyl)-3a,4,5,6-tetrahydro-1H-indazole-5-carbonitrile (66) was obtained.

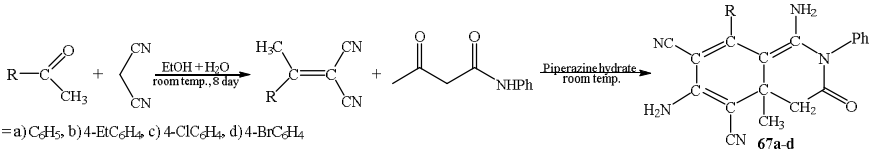


^{1}H NMR spectrum contains singlet at 2.11 ppm corresponding to three protons of methyl (CH_3) group, doublet at 3.15 ppm of one proton of the methine (CH) group attached to aromatic ring, singlet at 3.50 ppm corresponding to one proton of the hydroxyl group, doublet at 4.51 ppm characterizing proton of methine (CH) attached to the nitrile (CN) group, multiplet at 6.59-7.43 ppm of protons of two aromatic rings and a 3 protons of the thienyl group, and a singlet at 12.87 ppm corresponding to one proton of NH confirms obtaining 6-hydroxy-3-phenyl-6-(thiophene-2-il)-4-(p-tolil)-3a,4,5,6-tetrahydro-1H-indazole-5-carbonitrile (66). ^{13}C Nuclear Magnetic Resonance (NMR) spectrum also reaffirmed this result.

The probable mechanism of reaction is described in detail in the dissertation.

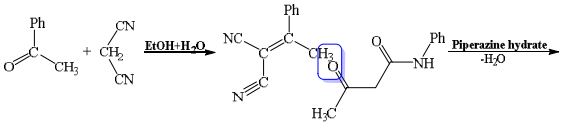
Synthesis of functionally-substituted bicyclic compounds based on substituted arylethylidenemalononitriles

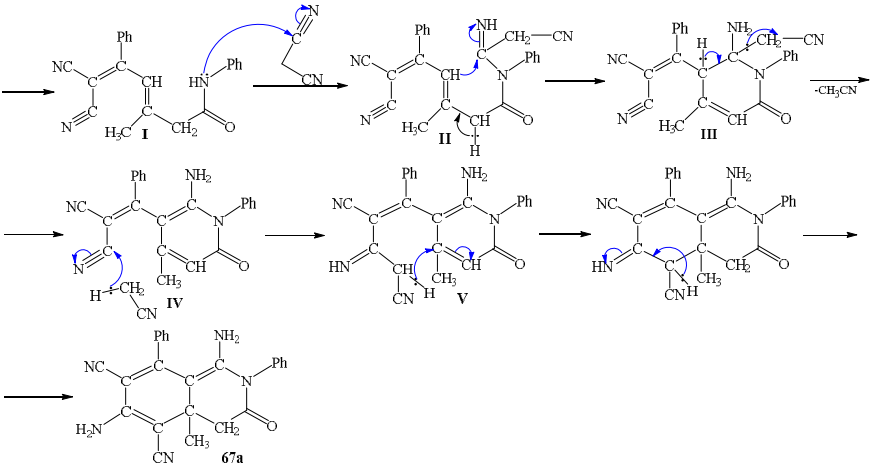
Formation of various tertahydroisoquinoline-5,7-dicarbonitrile derivatives (65a-d) was established by reaction of Knovenagel adducts obtained by interaction of substituted acetophenols with malononitriles and acetoacetanilide at room temperatire and ethanol-water solution and using piperazine hidrate.



R = a) C_6H_5, b) 4-EtC_6H_4, c) 4-ClC_6H_4, d) 4-BrC_6H_4

The probable mechanism of reaction is:





Molecular structures of synthesized compounds 67a studied by X-Ray presented in Figure 26.

^{1}H NMR spectrum contains singlet at 1.51 ppm corresponding to three protons of methyl (CH_3) group, double-doublet at 3.02 m.p. of two protons of methylene (CH_2), multiplet at 7.18-7.57 ppm corresponding to ten protons of two aromatic rings and four protons of two amin (NH_2) groups confirm formation of 1,6-diamino-4*a*-methyl-3-oxo-2,8-diphenyl-2,3,4,4*a*-tetrahydroisoquinoline-5,7-dicarbonitrile (67a). ^{13}C NMR spectrum also confirms this result.

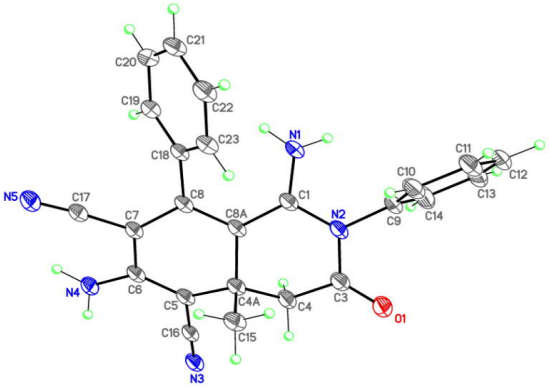


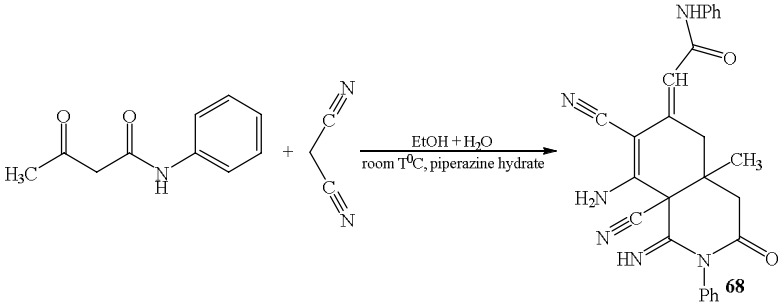
Figure 26. Molecular structure of 1,6-diamino-4a-methyl-3-oxo-2,8-diphenyl-2,3,4,4a-tetrahydroisoquinoline-5,7-dicarbonitrile (67a)

In contrast to the literature, at first time we carried out the reaction of obtained mono-substituted arylethyldenmalonitriles with aceto-

acetanilide and production of various substituted tetrahydroisoquinoline-5,7-dicarbonitrile derivatives was observed.

Reaction of acetoacetanilide with malononitrile

For the first time, by interaction of malononitrile with acetoacetanilide in an aqueous solution of ethanol, at room temperature, in the presence of piperazine hydrate (8-amino-7,8*a*-dicyano-1-imino-4*a*-methyl-3-oxo-2-phenil-1,3,4,4*a*,5,8*a*-hexahydroisoquinoline-6(2H)-iliden)-N-phenyl-acetamide (68) has been identified.



Molecular structure of synthesized (8-amino-7,8*a*-dicyano-1-imino-4*a*-methyl-3-oxo-2-phenil-1,3,4,4*a*,5,8*a*-hexahydroisoquinoline-6(2H)-yliden)-N-phenyl-acetamide (compound 68) presented in Figure 27.

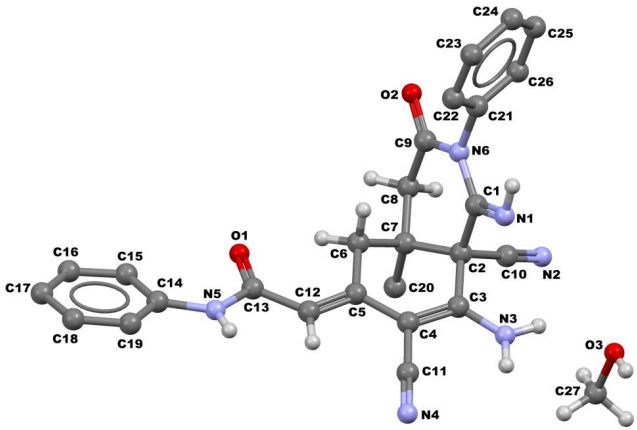
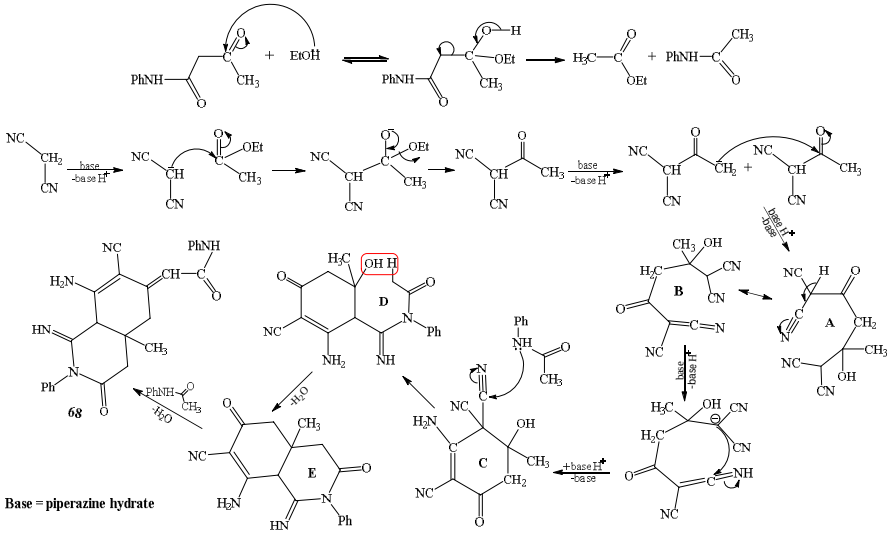


Figure 27. Molecular structure of 68

In our opinion, according to the probable reaction mechanism, ethyl alcohol first attacks the carbonyl group in the acetoacetanylide

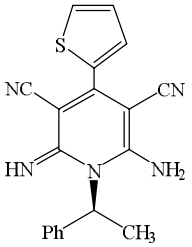
molecule, the C-C bond is broken, and intermediate is decomposed to ethyl ester of acetic acid and acetanilide molecules. Under the action of the base, acetyl malononitrile is formed as a result of the attack of malanonitrile on the ethyl ether of the corresponding anion acetic acid. The corresponding acetyl malanonitrile anion formed by the action of the base forms A-intermediate with a nucleophilic attack on the carbonyl group of another acetyl malononitrile molecule. The A-intermediate intermediate is then converted to the B-intermediate intermediate as a result of the electron density distribution. In base conditions, a corresponding anion formed by combining electron-acceptor nitrile groups combine to carbon and by atack of imine fragment to carbon C-intermediate is obtained. D-intermediate obtained as the result of nucleophilic atack with the electron pair of nitrogen of NH to the carbon atom of the nitrile group of the C-intermediate. Then, as a result of condensation in D-intermediate, water is separated and the E-intermediate formed, which finally reacts with acetanilide by production of compound 68.



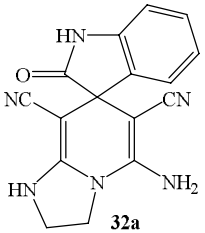
Investigation of solution systems of some substances obtained on the basis of compounds with polarized double bond by NMR.

(S)-(-)-6-Amino-2-imin-1-(1-phenylethyl)-4-(thiophene-2-yl)-1,2-dihydropyridin-3,5-dicarbonitrile solution by diffusion order

spectroscopy (DOSY) NMR. (S)-(-)-6-amino-2-imin-1-(1-phenyl-ethyl)-4-(thiophene-2-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (25e) and 5-amino-2'-oxo-2,3-dihydro-1H-spiro[imidazo[1,2-a]pyridine-7,3'-indoline]-6,8-dicarbonitrile (32a) were studied in the presence of β-cyclodextrin (β-CD) using Nuclear Magnetic Resonance (NMR).



25e



32a

It was found that the value of the diffusion coefficient was significantly reduced in the β-CD + sample mixture (25e). This suggests that there is some kind of interaction between β-cyclodextrin (β-CD) and compound. 2D nuclear Overhauser effect (NOESY) and 2D Rotating frame Overhause Effect Spectroscopy (ROESY) Nuclear Magnetic Resonance studies were also performed for the mixture to determine the type of interaction. Studies have shown that the value of the diffusion coefficient decreases sharply due to the hydrogen bond formed between the water (residual water of the solvent and the hygroscopic water of the sample) and studied compound. In other words, an intermolecular hydrogen bond is formed between the water molecules, the β-CD, and the sample. In addition, Nuclear Magnetic Resonance (NMR) studies have shown that, depending on the conditions, there are different types of proton exchange interactions between the spirolytic 5-amino-2'-oxo-2,3-dihydro-1H-spiro[imidazo[1,2-a]pyridine-7,3'-indoline]-6,8-dicarbonitrile (compound 32a) and the hydroxyl groups of β-CD.

Study of new dihydroimidazo-, tetrahydroimidazopyridines by NMR and X-ray. Solutions and solids of the studied dihydroimidazopyridines were examined by NMR and X-ray. In ^{13}C NMR spectrums of all synthesized dihydroimidazopyridines shooted at 22°C, increasing signals of carbons near C≡N was observed. To get acquainted with the dynamic behavior of these systems, the ^{13}C NMR spectrums were recorded at +22°C ÷ +90°C, and a contraction

(or accumulation) of the indicated carbon signals was detected at 90°C. In addition, it was observed that in the crystal structure of the studied compounds, the bond lengths C−C, C=C, C=N in the six-member cycles deviate from the literature data. (The literature values of these communication lengths are 1.54, 1.34, 1.38 A°, respectively. Figure 28).

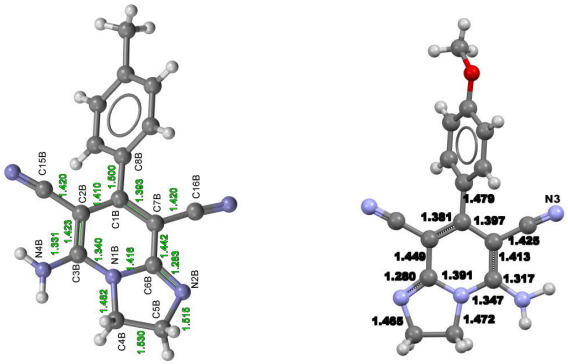
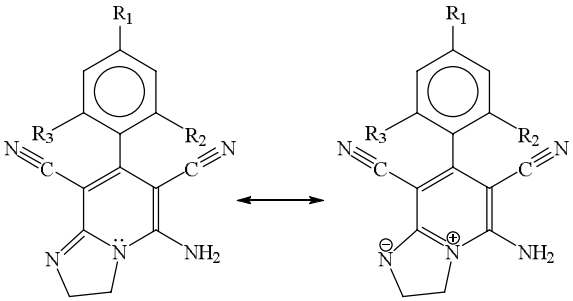


Figure 28. Molecular structures of (13b) and (13c)

Based on the results of Nuclear Magnetic Resonance (NMR) and X-ray, we can note that the expansion of the ^{13}C NMR signals of the carbons attached to nitrile (C≡N) groups of six-membered ring is the result of distribution of electron density of nitrogen electrons between five- and six-membered, and distribution between six-membered conjugated rings of dihydroimidopyridines.



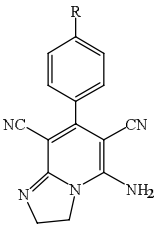
Investigation of biologicaly activities of synthesized compounds

In view of the above, 2-amino-3-cyanopyridines (1-16) were tested against gram-negative *Escherichia coli* and gram-positive Bacillus subtilis bacteria at a single concentration of 200 μg/ml. Studies have

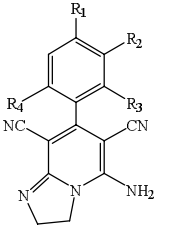
shown that only 12 compounds have a high antimicrobial effect. Repeated tests revealed the maximum inhibitory concentration (MIC) and half of the maximum inhibitory concentration IC50. The MIC concentration for e-coli bacteria is 577 μg / ml, for B-subtilis is 288 μg/ml, and for MCF-7 cells taken from human breast cancer is 95 cytotoxic concentration. μg / ml was determined.

If we compare 12 with 10, we see that in 12, bromine is in the place of hydrogen. It can be concluded that bromine, acting as an acceptor of hydrogen bonds or a donor of halogen bonds, has antimicrobial properties by combining with hydrophobic properties. However, other compounds (11 and 13) did not show antimicrobial properties, despite the presence of polar groups such as methoxy (-OCH_3) and trifluoromethyl (-CF_3), which are involved in the formation of hydrogen bonds in the para-position. In addition, antimicrobial properties were not observed in compounds 5 and 15, despite the presence of bromine in the para-position.

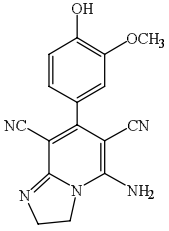
Therefore, when explaining the antimicrobial activity of compound 12, it is necessary to take into account that in addition to hydrophobicity, it also has lipophilic properties due to the N-benzyl fragment. This property is not possible due to the steric difficulty of the phenyl fragment in compounds 5 and 15.



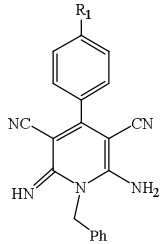
1. R=H (16a); **3.** R=CH_3 (16b); **5.** R=Br (16f); **6.** R=F (16e); **7.** R=OCH_3 (16c); **8.** R=$N(CH_3)_2$ (16d)



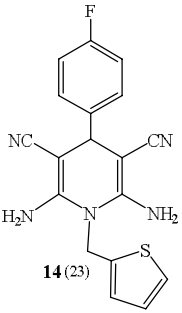
2. R_1=R_2=H, R_3=R_4=Cl (17h) **4.** R_1=R_4=Cl, R_2=R_3=H (17g)



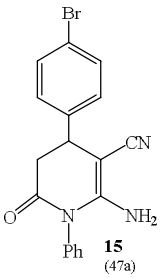
9 (18)



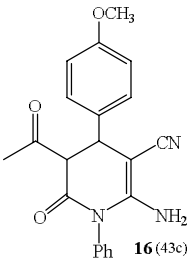
10. R_1=H (21j); **11.** R_1=OCH_3 (21k); **12.** R_1=Br (21l); **13.** R_1=CF_3 (21m)



14 (23)



15 (47a)



16 (43c)

RESULTS

1. Obtaining of corresponding esters of 3-hydroxy-7-oxo-3,5,7-triphenylheptanoic acid by Michael addition of benzoylacetone to chalcones in the presence of piperidine (or triethylamine, sodium methylate) in alcohol solution presented at first time.
2. At first time by reflux of 2-benzoyl-1,3,5-triphenylpentane-1,5-dione that is Michaels adduct with ethylenediamine in ethanol solution and using catalytic amount of hydrogen chloride (HCl) the substituted imidazo[1,2-*a*]pyridine derivative was formed, so interaction of 2-acethyl-5-oxo-N,3,5-triphenylpentanamide that is also Michaels adduct with malononitrile in acetonitrile solution by using ethylenediamine resulted 3-amino-2,6,8-triphenyl-7,8-dihydroisoquinoline-1(2H)-one.
3. Multicomponent interaction of benzylidenemalononitriles, malononitrile and ethylenediamine in methanol solution at non-catalyst conditions was carried out by resulting of substituted dihydroimidazo[1,2-*a*]piridines and substituted tetrahydroimidazo[1,2-*a*]pyridines, but when using in the same reaction 1,3-diaminopropane and furfurilamine (2-thiophenylmethylamine) as formation of 2,6-diaminodihydropyridine derivatives was established.
4. At first time, one-pot three-component interaction of monosubstituted benzylidenemalononitriles (benzylidenecyanoacetamides), malononitrile and benzylamine at room temperature and methanol medium formed substituted iminodihydropyridines, but using (S)-(-)-1-phenylethylamines as amine, results obtaining of chiral iminodihydropyridines and by three-component interaction of pyridinylidencyanoacetamide, malononitrile and 2-amino-5-bromopyridine synthesis of substituted terpyridine derivatives was observed.
5. By reflux in ethanol (or in microwave irradition) of benzylidenmalononitrile with ethylenediamine 5,7-diphenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6,6,8(5H)-tricarbonitrile obtained, interaction of 2-(2,4-dichlorobenzylidene)malononitrile with ethylenediamine results diazometine, when benzylidenemalononitrile interacts with such nucleophilic agents as thio-

semicarbazide (or 2,4-dinitrophenylhydrazine), formation of 1-benzyliden-2-(2,4-dinitrophenyl)hydrazine derivatives and 2-benzylidenhydrazine-1-carbothioamide was identified.

6. In contrast of literature, by one-pot, three-component interaction of isatylidenemalononitriles (or bromo-substituted isatylidenemalononitriles) with malononitrile and ethylenediamine obtaing of substituted dihydroimidazopyridines was observed, so as by one-pot three-component interaction of isatylidenemalononitriles with malononitrile and furfurilamine (or 2-thiophenmethylamine) obtaining spiro-structured diaminodihydropyridines, and by Michael addition isatylidenemalononitrile acetoacetanilide and ethyl ester 4-chloroacetoacetic acid effective synthesis of cyanospiro[indoline-3,4'-pyrane] derivative was established.
7. At first time by Michael addition of benzoylacetone to benzylidenemalononitrile in varius conditions 4H-pyrane derivatives were synthesized. Also obtaining of three cyclic pyrano[3,2-c]pyridine derivatives and substituted tetrahydropyridines were established by Michael addition of acetoacetanilide to benzylidenemalononitrile at the same reaction conditions.
8. Keto-enol tautomerism was investigated by Nuclear Magnetic Resonance (NMR) in acethyl substituted pyridine derivatives synthesized by Michael addition of acetoacetanilide to mono- and di-substituted benzylidenemalononitriles. It was established that monosubstituted derivatives are in keto-form but disubstituted derivatives are in enol-form. By using modern oppofunities of NMR spectroscopy various heterocyclic systems were investigated and interesting results were observed about dynamic transitions.
9. At first time by one-pot interaction of 2 moles of substituted benzylidenemalononitriles and 1 mole of acetoacetanilide threecyclic pyrano[3,2-c]pyridine derivatives were obtained. Obtained three cyclic pyrano[3,2-c]pyridine derivatives interacted with iodine and hydrazine hydrochloride with interesting results.
10. Michael's adduct 5-acethyl-2-amino-6-methyl-4-phenyl-4H-pyrane-3-carbonitrile was interacted with ether active methylene compounds in chlorophorm solution and in the presence piperazine hydrate resulting substituted 4H-pyrane derivative. At first time acethyl substituted 1,4,5,6-tetrahydropyridine-3-carbonitrile de-

rivative that is Michael's adduct was refluxed in base conditions using alcohol solution accomplishing elimination of acethyl group and rearrangement of pyridone ring and resulting pyridone derivative. It was also established that rearrangement doesnt take place in aproton solvent.

11. By Michael addition of activemethylene compounds to various Knoevenagel adducts cyclohexanone derivatives obtained with high yield and pyrane derivatives with low yield obtained depended on nature of functional substituents.

12. By one-pot Michael addition of malononitrile to 3-phenyl-2-(thiophene-2-carbonyl)acrylonitrile or 3-(thiophene-2-yl)-2-(thiophene-2-carbonyl)acrylonitrile in the presence of optically-active (S)-(-)-1-phenylethylamine catalyst resulted optically-active 4H-pyrane derivatives.

13. Inhibitory activity againist microorganisms and antibacterial activity relationship between antibacterial activity of molecule and its hydrofobic and lipofilic nature.

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