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STUDY OF THE SYNTHESIS METHODS OF 1,3-ARYL(HETERYL)PROPENONE

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In this work, we refer to the study of recent specialized literature, where some syntheses methods of chalcone derivatives are described. These substances show a very pronounced anticancer activity, having a protective action in the cellular system. They present interest due to their biological properties, such as anti-inflammatory, antioxidant, cytotoxic and antihistamine properties, etc. These important biological properties are the basis of the current research intended to obtain them synthetically. The bibliographic data refers to the synthesis of 1,3-aryl (heteryl) propenones, which are described in several reviews. The main focus is on the synthesis methods of chalcones, which allow us to obtain pure reaction products, short reaction time and high yields. Also, synthesis methods with the use of solid-based heterogeneous catalysts are described, which, in turn, are very active, durable and more economical and can be used for three synthesis cycles, without significant loss of catalytic activity. The synthesis methods studied were: aldol and crotonic condensation, Claisen-Schmidt reaction, Suzuki reaction, coupling of alkynes with aldehydes, microwave irradiation, etc.

Keywords: *chalconnes, condensation Claisen-Schmidt, synthesis, synthetic.*

STUDIUL METODELOR DE SINTEZĂ PENRU 1,3-ARIL(HETERIL)PROPENONE

Prin articolul dat se prezintă studiul literaturii de specialitate, în care sunt descrise unele metode de sinteză a derivaților chalconici. Aceste substanțe au o activitate anticancerigenă foarte pronunțată, având o acțiune de protecție în sistemul celular. Ele prezintă interes datorită proprietăților biologice pe care le manifestă: antiinflamatorii, antioxidante, citotoxice și antihistaminice ș.a. Aceste propietăți biologice importante stau la baza cercetărilor actuale pentru a le obține pe cale sintetică. Datele bibliografice se referă la sinteza 1,3-aril(heteril)propenonelor, care sunt descrise într-un șir de articole de generalizare. O atenție deosebită este acordată metodelor de sinteză a chalconelor care să permită obținerea produșilor de reacție puri, timp de riacție scurt, randamente rentabile. Sunt descrise metode cu utilizarea catalizatorilor eterogeni cu bază solidă, care, la rândul lor, sunt foarte activi, durabili și mai economici și care pot fi folosiți la trei cicluri de sinteză fără pierderi semnificative ale activității catalitice. Metodele de sinteză studiate au fost: condensarea aldolică și crotonică, reacția Claisen-Schmidt, reacția Suzuki, cuplarea alchinelor cu aldehidele, iradierea cu microunde etc.

Cuvinte-cheie: *chalcone, condensare Claisen-Schmidt, sinteză, sintetic.*

Introduction

The chalcones represents α, β-unsaturated carbonyl compounds, which have a benzene ring at the ends and is most often substituted. This place can be taken by any heterocycle, such as pyridine, piperidine, furan, thiophene, etc. In general, these compounds are named propenones.

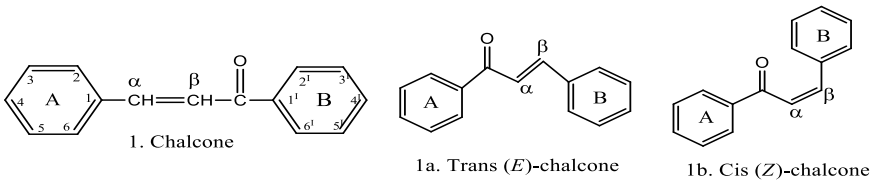


Fig.1. The structural formula of chalcones.

The chalcone is the trivial name for substances with 1,3 diphenyl-prop-2-en-1-one structure and are part of the family of flavonoid compounds [1]. They are also known as benzylideneacetophenones or benzalacetophenones. The name chalcone was proposed by the Polish chemist Kostaneki Stanislaw. In most of the cases, the aromatic rings are hydroxylated. Chalcones are unsaturated ketones, containing the reactive ketoethylene group -CO-CH═CH-. The presence of -CO-CH═CH- chromophore group gives them a color, which varies depending of other auxochrome groups. Chalcones are open chains flavonoids where two phenyl groups are linked via carbonyl system of three unsaturated α, β carbons. The numbering of carbon atoms in chalcone molecule is carried out according to (Fig.1). Chalcones are widely distributed in nature and they are found in plants such as *Ruscus, Angelica, Clycyrhaza*, etc. Through a stereospecific reaction catalyzed by isomerase

enzymes, in plants they are converted into (2S) flavones *2*. This similarity in structure between chalcones and flavones explains their simultaneous presence in plants. Common compounds of the flavonoid class 2 contain a phenyl group in position 2 of the benzo-(γ)-pyrone (Fig.2). The flavonoids *2* differ by saturation, size and substituents of (γ)-pyrone ring called the ring C.

The ethylene bond between C_2 and C_3 in the C ring of flavones **2** generates the conjugation between the A and B rings. Thus, the structure of flavones rings becomes more stable than that of the other flavonoids. Although antocyanidins **3** (Fig.2) differ by the absence of carbonyl group in the C ring, their biological properties are similar. Chalcones **1** are ring and chains isomers of flavonoids.

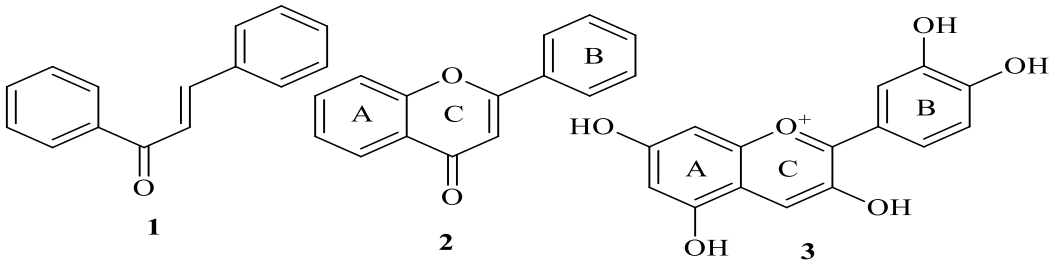


Fig.2. Structural formulas: 1-chalcone, 2-flavone, 3- anthocyanin.

It has been shown that α ketone groups β unsaturated from chalcone skeleton 1 confer all the active biological properties that have been detected, since in all bioactive molecules ketone groups are present and their removal causes the loss of the active principle [2,3]. These substances have a pronounced anticancer activity, having a protective action in the cellular system. Also, they are of interest due to their anti-inflammatory, antioxidant, cytotoxic and antihistamines properties. These important biological properties are the basis of current research to obtain them synthetically. Likewise, these characteristics highlighted the necessity of choosing these compounds for researcher's investigations.

We will refer to the study of recent specialized literature on the synthesis of chalcones compounds. In the specialized literature the prior attention is given to synthesis methods of chalcones which allow us to obtain pure reaction products with high yields. The studied synthesis methods are: aldol and crotonic condensation, Claisen-Schmidt reaction, Suzuki reaction, coupling reaction of alkynes with aldehydes, etc.

Background

Synthesis of 1,3-aril(ethereal)propenones.

Aldol and crotonic condensation. A known method for chalcones synthesis is aldol and crotonic condensation. The condensation reactions are one of the most important enolic reactions of carbonyl compounds. Condensation reactions are combining two or more molecules, usually with elimination of a small molecule such as water or *en* alcohol. In a basic environment, aldol condensation involves the nucleophilic addition of an enolate ion to another carbonyl group. Under acidic conditions, the enol serves as a weak nucleophile, attacking the activated (protonated) carbonyl group.

The product, α, β-hydroxy ketone or an aldehyde, is named aldol, because it contains both an aldehydes group and an alcoholic hydroxyl group. The aldol product can through deshydratation form an α, β-unsaturated carbonyl compound. Generally, this takes place after heating, under acid or base catalysis (Fig.3).

Variants of Claisen-Shmidt reactions. Chalcones are also obtained by the Claisen-Schmidt method, in acid or base catalysis. The formation of C-C bonds in the aldol condensation step is facilitated by the groups with –I effect, and less delayed by the +I effect on the carbonyl component.

Claisen-Shmidt condensation is the most common method in homogeneous phase or solid-liquid phase, using alkaline catalysts. It is alsow known that hydroxylchalcones have the property to cyclize during the Claisen-Shmidt reaction into flavones. To optimize this type of synthesis methods, it is necessary to use the initial compounds that contain protected groups or to use the synthesis based on the Friedel-Crafts reaction. In comparison with other Claisen-Shmidt reactions, this reaction needs longer reaction time anhydrous conditions, which is the reason why they are less used. To reduce this shortcoming, the scientists proposed the synthesis of chalcones derivatives by microwave irradiation.

Synthesis of chalconic derivatives by Claisen-Schmidt method, in acid or base catalysis:

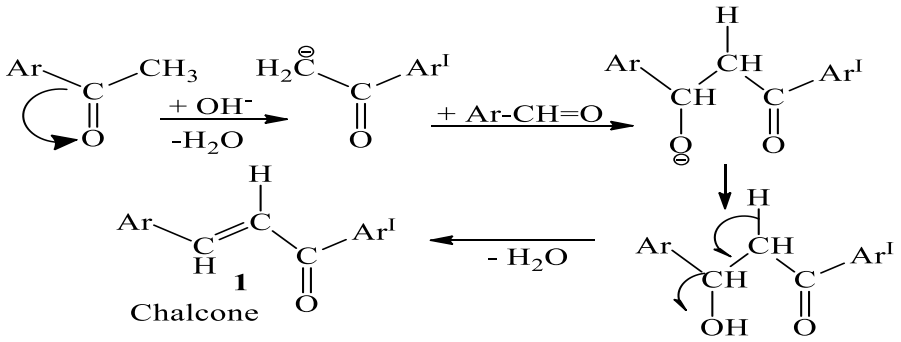


Fig.3. The condensation mechanism of aldehydes and ketones in the basic environment.

The classic method of Claisen-Schmidt reaction in acid environment takes place according the following mechanism:

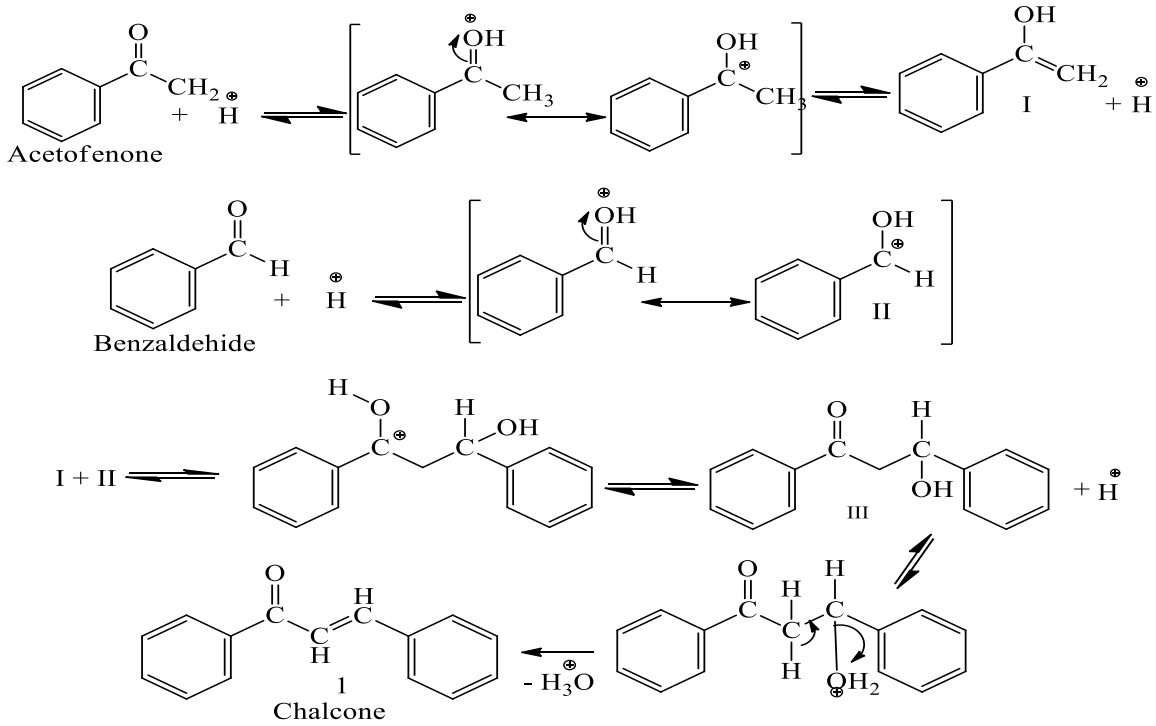
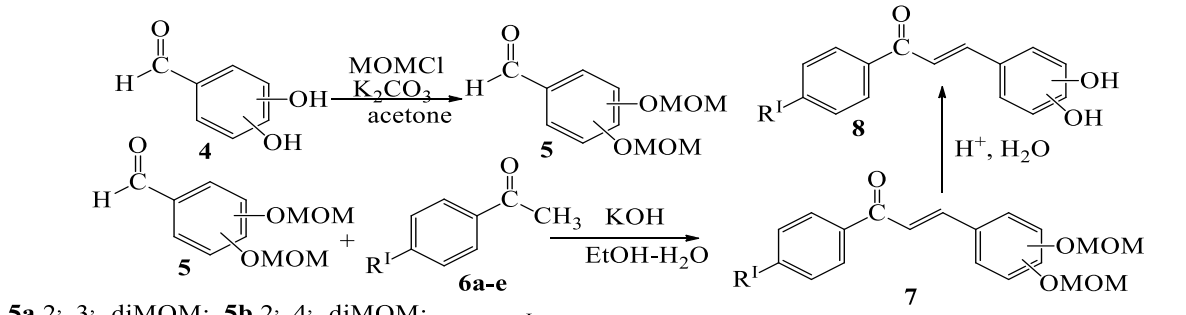


Fig.4. The aldehydes and ketone condensation mechanism in acid environment following the Claisen-Schmidt method.

In these reactions, the condensation takes place between the aromatic aldehydes with acetophenones. In the case of acidic catalyze, in most of the cases mineral acids are used (HCl, H_2SO_4) and in the basic one alkaline bases are used (NaOH, KOH). The catalyst is chosen according to the nature of the substituent attached to the benzene nuclei. In case of electron-acceptor substituents (-Cl, -NO_2, -SO_3H, -CN) base catalysis is preferred, and in the case of electron donor's substituents (-R, -OR, -OH, -NR_2) base catalysis is preferred. The chalcones antioxidant properties are mainly due to the two aryl rings and their substituents. Thus, the hydroxyl group is one of the key substituents that enhance the antioxidant activity of chalcones, mainly due to the ease with which they are transformed into fragments containing phenoxy groups, through the hydrogen transfer mechanism. The hydroxyl substituent is one of the most spread in chalcones from natural sources. In one of the researched methods for obtaining chalcones containing hydroxyl groups, a tactic is used to protect them. The chalcones derivatives were synthesized through Clainsen-Schidt condensation (basic catalysis) of benzaldehyde containing methoxymethyl groups protected with para-substituted acetophenones followed by acid-catalyzed hydrolysis. The protected bezaldehydes with methoxymethyl groups (MOM) **5**, which were prepared by the treatment of the respective benzaldehyde **4** with chloromethyl ether (MOMCl) under basic conditions

(K_2CO_3/acetone), were successfully transformed into chalcones derivatives **8a-y** with two hydroxyl groups at the aromatic ring of benzaldehyde:



5a 2', 3'- diMOM; **5b** 2', 4'- diMOM;
5c 2', 5'- diMOM; **5d** 3', 4'- diMOM;
5e 3', 5'- diMOM

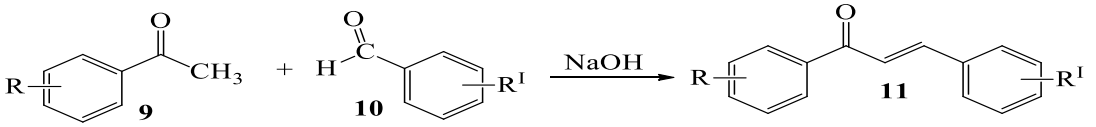
6a-e R^I = -H, -CH_3, -OCH_3, -OH, -Cl

8a = 77%, **8b** = 86%, **8c** = 86%, **8d** = 38%, **8e** = 58%,
8f = 71%, **8g** = 22%, **8h** = 58%, **8i** = 25%, **8j** = 35%,
8k = 81%, **8l** = 64%, **8m** = 82%, **8n** = 53%, **8o** = 89%,
8p = 83%, **8q** = 91%, **8r** = 79%, **8s** = 59%, **8t** = 58%,
8u = 83%, **8v** = 85%, **8w** = 62 %, **8x** = 56%, **8y** = 52%.

8a, 8f, 8k, 8p, 8u R^I = -H,
8b, 8g, 8l, 8q, 8v R^I -CH_3,
8c, 8h, 8m, 8r, 8w R^I -OCH_3,
8d, 8i, 8n, 8s, 8x R^I -OH,
8e, 8j, 8o, 8t, 8y R^I -Cl

Fig.5. General synthesis method of chalcones which contains hydroxyl groups.

LAHSASNI S.A. proposed the synthesis of some chalcones derivatives applying the Clainsen-Schmidt condensation between acetophenols **9** and benzaldehydes **10** [4]:



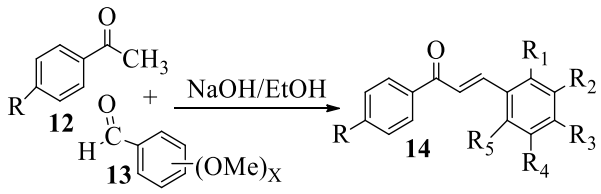
9a R = 3-OH,
9b R = 4-NO_2
9c R = 4-Br,

10a R^I = 3-NO_2
10b R^I = 3,5-OCH_3
10c R^I = 4-Br
10d R^I = 3-OH

11a R = 3-OH, R^I = 3-NO_2	67 %
11b R = 3-OH, R^I = 3,5-OCH_3	60 %
11c R = 3-OH, R^I = 4-Br	85 %
11d R = 4-Br, R^I = 3-OH	79 %
11e R = 4-NO_2, R^I = 3-OH	65 %

Fig.6. Synthesis scheme of chalcones analogues which contain substituted aromatic rings.

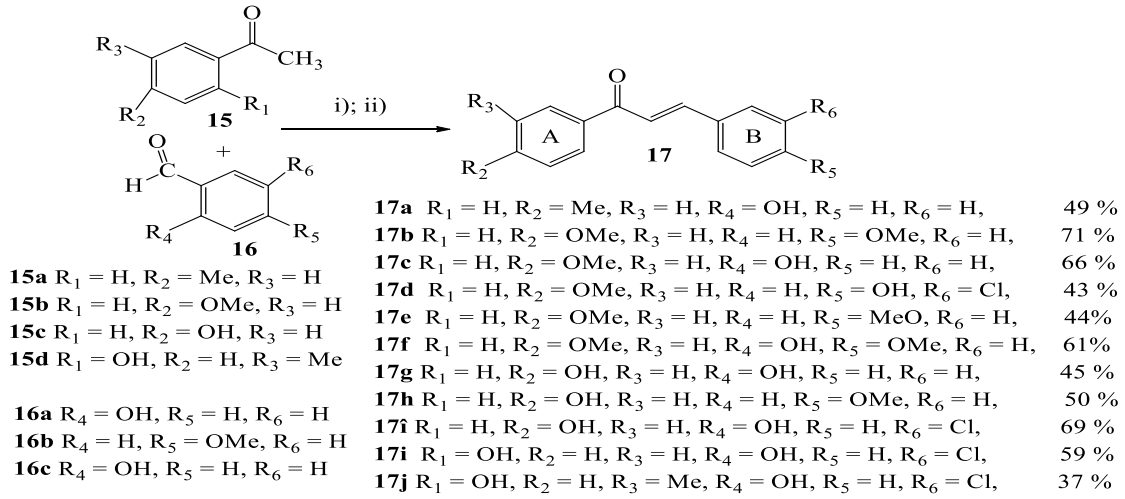
The Claisen-Schmidt reaction has a wide application in chalcones synthesis. Thus, chalcones and their derivatives can be synthesized in the laboratory, having as reactants acetophenones or its derivatives **12,** benzaldehyde and its derivatives **13** and alkane base as NaOH, KOH or NaH as catalyst in a polar solvent [5].



14a R = H, R_1 = OCH_3, R_2, R_3, R_4, R_5 = H	27%
14b R = H, R_2 = OCH_3, R_1, R_3, R_4, R_5 = H	86%
14c R = H, R_3 = OCH_3, R_1, R_2, R_4, R_5 = H	57%
14d R = H, R_1, R_2 = OCH_3, R_3, R_4, R_5 = H	41%
14e R = H, R_1, R_3 = OCH_3, R_2, R_4, R_5 = H	51%
14f R = H, R_1, R_4 = OCH_3, R_2, R_3, R_5 = H	72%
14g R = Br, R_3 = OCH_3, R_1, R_2, R_4, R_5 = H	68%
14h R = Br, R_1, R_3 = OCH_3, R_2, R_4, R_5 = H	87%
14i R = Br, R_1, R_4 = OCH_3, R_2, R_3, R_5 = H	98%

Fig.7. The use of Claisen-Schmidt reaction in the synthesis of substituted chalcones.

In order to create more favorable conditions for the synthesis of the same chalcone derivatives, microwave irradiation can also be used [6]:



Reagents and conditions: i) EtOH, NaOH solution of 50%, MW, 80°C, 2-4 h; ii) HCl de 10%.
Fig.8. The synthesis scheme of chalconic derivatives by microwave irradiation.

It should be mentioned that WANDER A. S. and his collaborators from the Institute of Chemistry from Brasilia [7], succeeded in obtaining a series of chalcones **20a-i** using also the Claisen-Schmidt reaction:

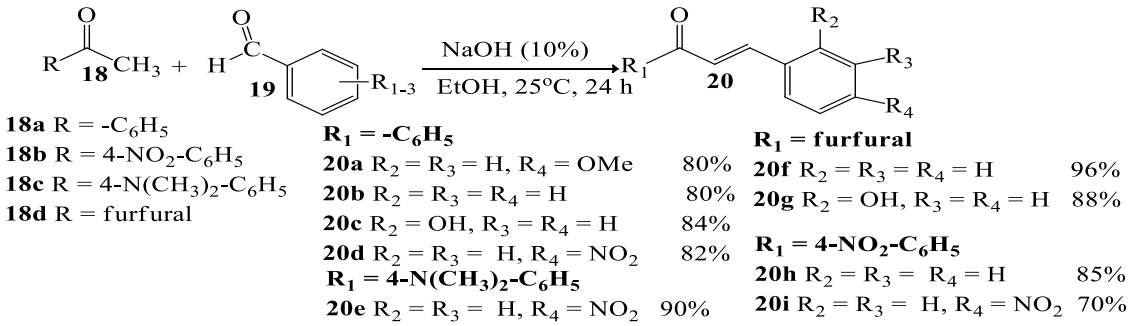
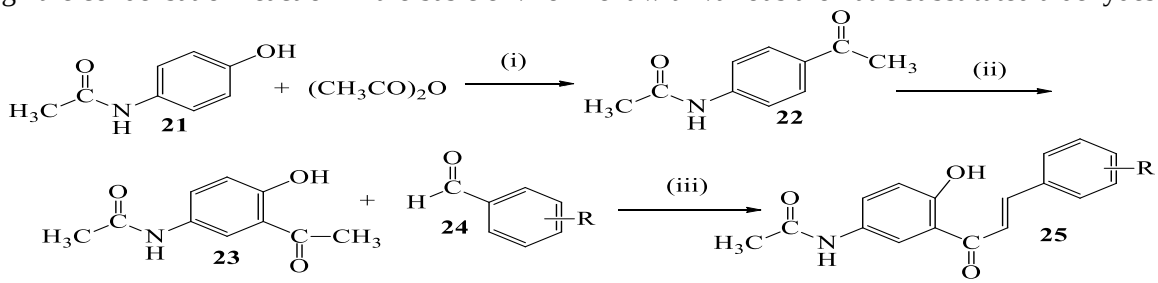


Fig.9. Synthesis scheme of substituted chalcones derivatives **20a-i**.

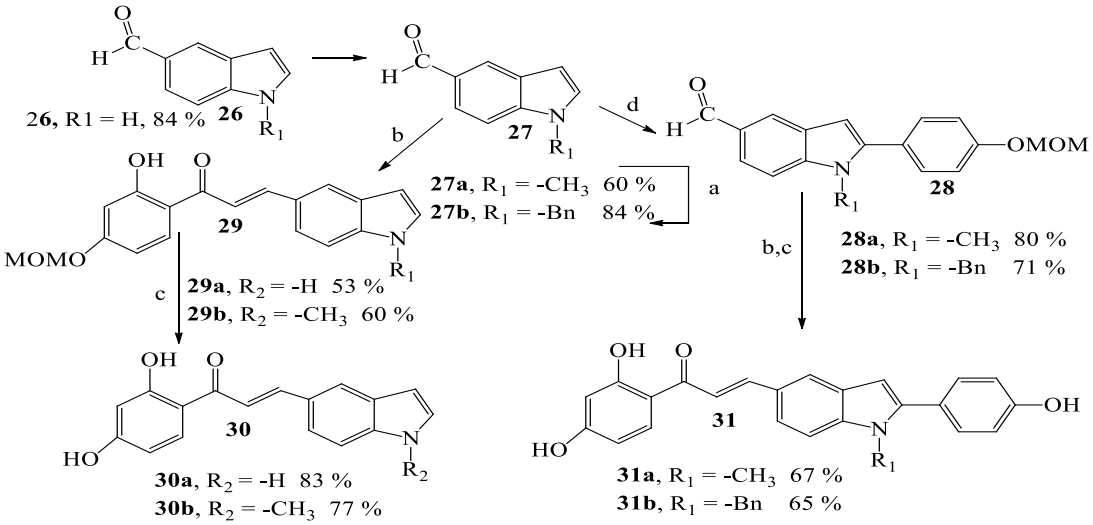
In Claisen-Schmidt reaction are also used catalysts such as: sodium nitrate $NaNO_3$ and natural phosphate (NP) [8]. The yields of the final products are 70-96%. The aldol condensation of benzaldehyde with acetone and acetophenone were investigated on hydrotalcite KF and KNO_3 deposited on aluminum La_2O_3, in which zeolite X contain Cs and Mg groups and aluminum-magnesium hydroxide hydrate [9].

It was possible to synthesize a series of chalcones from N-(3-acetyl-4-hydroxyphenyl) –acetamide **21** through the condensation reaction in the basic environment with various aromatic substituted aldehydes **24.**



Reagents and conditions: (i) H_2SO_4(c), la 50-60°C, 15 min.; (ii) $AlCl_3$, 130°C, 3h; NaOH/EtOH, 25°C, 18-24h.
Fig. 10. Synthesis scheme of (E)-N-(3-cinnamoyl-4-hydroxyfenyl)acetamides **25a-j**.

Chalcones of the given type **25a-j** are obtained with high yields, and their structure was confirmed by various spectral methods [10], as in the Claisen-Schmidt reaction different solid catalysts are used, such as the Co (II) complex with pyridine polymers. The most useful polymer proved to be the Co (II)-4vinylpyridine-styrene copolymer, because no secondary compounds are obtained after the reaction [11]. The synthesis of chalcone derivatives containing indole group also refers to the Claisen-Schmidt reaction:

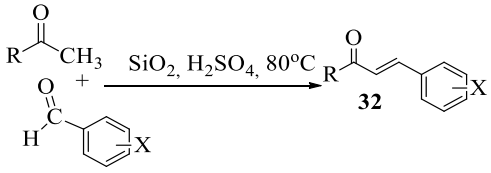


Reagents and conditions: (**a**) NaH (60% *w*/*w*), CH_3I (for **27a**) or BnBr (for **27b**), DMF, from 0°C up to 25°C, 12 h; (**b**) **29a, b**, NaOH (5 M), EtOH, from 0°C up to 25°C, 48 h; (**c**) **30a, 30b**, HCl (12 M), MeOH/THF, from 0°C up to 40°C, 1 h; (**d**) **28a, 28b**, Ag_2O, 2-nitrobenzoic acid, $Pd(OAc)_2$, DMF, 25°C, 24 h.

Fig. 11. Synthesis scheme of chalcone derivatives **31a, b** containing indole.

A shortcoming of the Claisen-Schmidt method used in the synthesis of ester chalcones is the difficult recovery of the catalyst. EKANAYAKE U. G. obtained secondary reaction products that led to the formation of reaction products with low yields. As a solution, solid-based heterogeneous catalysts can be used, which, in turn, can be very active, durable and more economical. Magnesium oxide nanosheets can be used as such type of catalyst. The two-dimensional heterogeneous MgO catalyst was synthesized using salt recovered from seawater using the atmospheric pressure plasma method. The catalytic activity of MgO nanosheets was compared with irregular MgO nanoparticles. With this type of catalyst, the conversion of acetophenone with benzaldehyde is 90 %. An advantage of this catalyst is that it can be used in three synthesis cycles without significant loss of catalytic activity [12]. Similarly, acyclic ionic liquid catalysts functionalized with $–SO_3H$ groups can be used in the Claisen-Schmidt reaction and are recyclable [13].

Aldol and crotonic condensation. The condensation reaction in solid phase was studied by different researchers [13,14,15]. In the case of reaction between aromatic aldehydes with cyclic ketones in the presence of a catalytic amount of $NH_4H_2PO_4/SiO_2$, in the absence of organic solvents, a series of substituted bis-benzylidene chalcones **32a-u** were obtained with high yields. The given method is easy to perform and has a general character for all types of aromatic aldehydes. Likewise, for the given method $Mg(HSO_4)_2$, 1,5,7-(trizabicyclo(4,4,0)-dec-5-ene or SiO_2 can be used as catalyst [16-18].

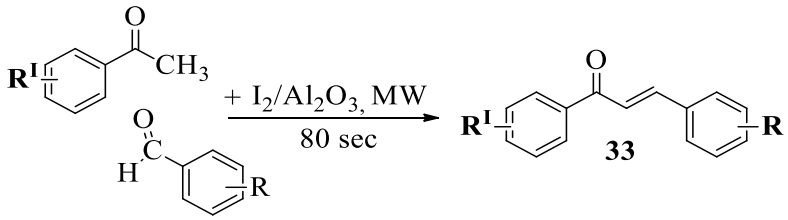


R = 4-bifenil		**R = 9H-fluorenil**	
32a X = H	91%	**32k** X = H	95%
32b X = p-NH_2	94%	**32l** X = p-NH_2	94%
32c X = m-NH_2	92%	**32m** X = m-NH_2	94%
32d X = m-Br	95%	**32n** X = m-Br	95%
32e X = p-Cl	95%	**32o** X = p-Cl	96%
32f X = m-Cl	95%	**32p** X = m-Cl	95%
32g X = p-$N(CH_3)_2$	94%	**32q** X = p-$N(CH_3)_2$	95%
32h X = p-OH	94%	**32r** X = p-OH	94%
32i X = p-OCH_3	92%	**32s** X = p-OCH_3	96%
32î X = p-CH_3	94%	**32t** X = p-CH_3	96%
32jX = p-NO_2	96%	**32u** X = p-NO_2	96%

Fig.12. Synthesis method of substituted chalcones derivatives **32a-u**.

The synthesis of some chalcone derivatives was achieved using Zn(L-proline)$_2$ as a harmless catalyst, obtaining reaction products with yields of 79-92%. The eminence of this method lies in the use of water as a non-toxic, cheap and non-flammable solvent. Moreover, the Zn(L-proline)$_2$ catalyst can be recovered and reused several times, without it significantly losing of its qualities [19].

In recent literary investigations, the method of obtaining chalcones **33a-g** is described using as catalyst molecular iodine soaked on aluminum oxide and using microwave irradiation without any solvent [20].



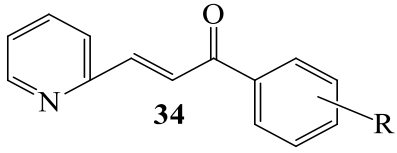
33a R^I, R = H, 95%
33b R^I = H, R = 4-OH, 93%
33c R^I = 2-OH, R = H, 91%
33d R^I = 4-OH, R = 4-OH, 94%
33e R^I = OCH_3, R = Cl 88%
33f R^I = H, R = 4-NO_2, 82%
33 g R^I = 4-OH, R = 3,4-OH, 86%

Fig.13. Synthesis method of chalcones derivatives **33a-g**, conditions of molecular iodine catalyst soaked on aluminum oxide.

Under these conditions, the synthesis of polyhydroxychalcones **33d**, **33g**, can be achieved by the reaction of acetophenones with benzaldehyde, both containing –OH groups. The given reaction is carried out without using the protection of functional groups, which is impossible to carry out in synthesis reactions catalyzed by alkaline bases. The molecular iodine acts as Lewis acid, which facilitates the enolization of the hydroxyl aryl ketone, simultaneously activating the carbonyl and hydroxyl groups in benzaldehyde. The neutral aluminum powder serves to increase the catalytic surface. The chalcones synthesis reaction, which contains hydroxyl groups by condensation in acidic medium without protecting the OH groups, has been successfully carried out by several organic scientists [21]. As catalyst $SOCl_2$ was used and ethanol with 81-93% yield of final products [22]. The combination of these reaction conditions with continuous reflux and microwave technology is a relatively new method applied in organic synthesis. This technique offers many advantages, both in technical and economic aspects. This synthesis technique of chalcones derivatives was successfully realized using mixed solution of phenylacetylenes and benzaldehydes in 1,2-dichloroethane. Initially, the solution mixture is continuously dropped in the reaction vessel which is placed in a reactor equipped with microwaves (50 W). The crude product solutions are collected from the discharge tube and then purified by chromatographic methods. Chalcones are obtained with a yield of 84-91% [23].

Recent research describes the special biological activity of organic compounds containing aromatic pyridine ring. It should be mentioned that these activities are more pronounced if the pyridinic fragment is part of the chalcones structure [24-26].

Methods for the synthesis of chalcones derivatives **34a-k** containing the pyridinic ring as a base are proposed:

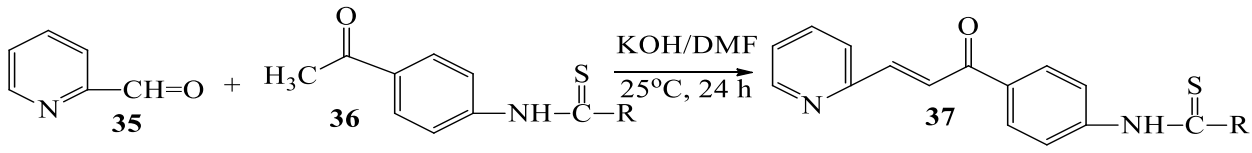


34a R = 2-Cl 66 %; **34b** R = 3-Cl 61 %; **34c** R = 4-Cl 38 %;
34d R = 2-OCH_3 54 %; **34e** R = 3-OCH_3 55 %;
34g R = 4-OCH_3 68 %;**34h** R = 2-OH 39 %; **34i** R = 3-OH 37 %;
34j R = 2-F 63 %; **34k** R = 4-F 63 %;

Fig.14. The structure of chalconic derivatives containing the pyridine fragment.

The method used was aldol condensation, where picolinaldehyde is used as aldehydes. These compounds possess antioxidant activity and have been compared with *Quercetin* and *Trolox* [27].

Synthesis methods of derivatives of the given type are also known when 1-(pyridin-2-yl)ethanone and substituted aromatic aldehydes are used in the Claisen-Schmidt condensation reaction [28]. The researchers of the Department of Chemistry of the Faculty of Chemistry and Chemical Technology from Moldova State University (USM) have investigated the obtaining of 3-(4-(3-pyridin-2-yl)acryloyl)phenyl-1-(alkyl)arylthioureas **35a** with analogous structure according to the scheme:

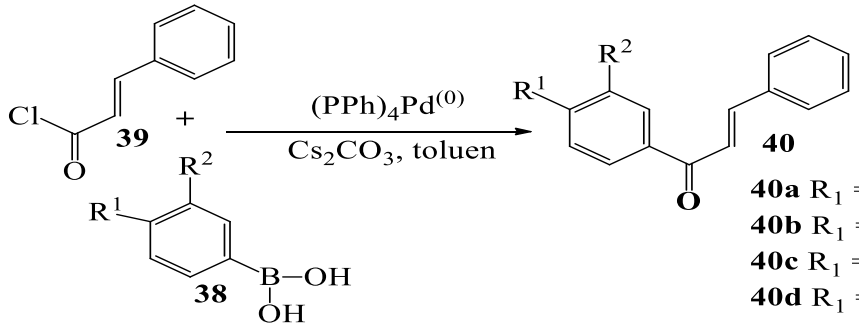


37a R = -NH-CH_2-CH_2-OH	80%	**37f** R = -NH-(o-OH)-C_6H_5	68%
37b R = -N-$(CH_2)_4O$ (morfolina)	89%	**37g** R = -NH-(p-Br)-C_6H_5	82 %
37c R = -NH-C_6H_5	75 %	**37h** R = -NH-(o-Br)-C_6H_5	79 %
37d R = -NH-(p-CH_3)-C_6H_5	82 %	**37j** R = -NH-(p-$COOC_2H_5$)-C_6H_5	78%
37e R = -NH-(o-OCH_3)-C_6H_5	79 %	**37i** R = -NH-Py	87%

Fig.15. Synthesis of 3-(4-(3-pyridin-2-yl)acryloyl)phenyl-1-(alkyl)aryltioureas **35a-i**.

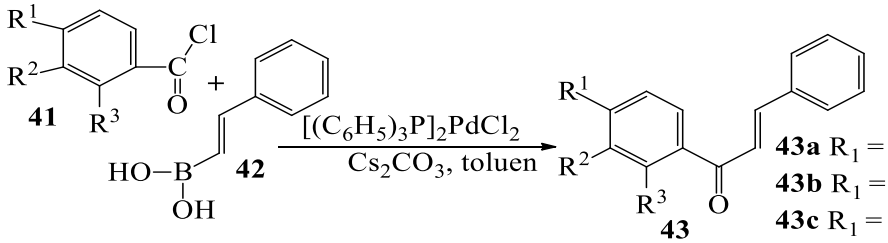
4-Acetylphenyltioureas **36** were synthesized by addition of the corresponding amines to 1-(4-isothiocyanatophenyl) ethanone similar to methods described in the literature [29]. Condensation of thioureas **36** with 2-pyridinecarboxaldehyde (picolinaldehyde) **35** under base catalysis leads to 1,3-arylpyridylpropenones **37a-i** with thiourea groups.

The Suzuki reaction. In the contemporary literature a new way for chalcones syntheses based on Suzuki reaction is mentioned [30]. As a result, the researchers were able to obtain chalcones **40a-d**, **43a-e** in two ways: by the interaction of activated cinnamic acid **39** with phenylboronic acids ($FB(OH)_2$) **38** (Scheme 12) or by coupling activated benzoic acids with (E)-styrylboronic acid, which can also be called phenylvinylboronic acid **42**:



40a R_1 = H, R_2 = H	51%
40b R_1 = H, R_2 = NO_2	47%
40c R_1 = OMe, R_2 = H	44 %
40d R_1 = OMe, R_2 = OMe	41%

Fig.16. Obtaining chalcones **40a-d** upon the interaction of cinnamoyl chloride with substituted phenylboronic acids.



43a R_1 = H, R_2 = H, R_3 = H	93 %
43b R_1 = H, R_2 = CF_3, R_3 = H	77 %
43c R_1 = H, R_2 = H, R_3 = CF_3	90 %
43d R_1 = H, R_2 = NO_2, R_3 = H	68 %
43e R_1 = OMe, R_2 = H, R_3 = H	87 %

Reagents and conditions: solvent – THF; catalyst – $[(C_6H_5)_3P]_2PdCl_2$ in the presence of the non-basic reagent n-Bu_4N^+, HF_2^-.

Fig.17. Obtaining chalcones **43a-e** at the interaction of benzoyl chloride with (E)-styrylboronic acid.

The first synthesis attempts were carried out on the coupling between cinnamoyl chloride **39** and different diphenylboronic acids **38** (Fig.12), using the following reaction conditions: solvent – THF; catalyst – $[(C_6H_5)_3P]_2PdCl_2$ in the presence of the non-basic reagent tetra-n-butylammoniumfluoride (n-Bu_4N^+, HF_2^-). Unfortunately, this catalytic system led to the formation of a complex mixture of products, which disfavored the obtaining of high yields products. Better yields were obtained using the following conditions: solvent – anhydrous toluene; catalysts – tetrakis(triphenylphosphine)palladium at 0°C; base – cesium carbonate. This reaction is also effective for the synthesis of phenylboronic acids **38** containing electron donating or accepting substituents.

Researchers from India [31] succeeded to synthesize chalcones following a new method based on BF_3-Et_2O, which allow the obtaining of high yields products (75-96%). They employed in the synthesis reaction different acetophenones and substituted benzaldehydes using an equivalent of 0.5 mol of boron trifluoride diethylether (BF_3-Et_2O). The most of the compounds were formed within 15-150 min, exclusively obtaining products with the trans bonds. The reaction mixture was washed with water to remove complexes with BF_3 and after their recrystallization, for obtaining pure chalcones with high yields. It should be mentioned that in the presence of KOH and NaOH the reaction lasted a much longer time (2 - 4 days), with high probability of side reactions, such as Cannizzaro reaction. Using the Indian synthesis method described above, no side reactions were observed.

In comparison with existing methods, the advantage of this method is high yields of resulting products, short reaction time and lack of side reactions, avoiding the need for column chromatography and solvents, as well as tolerance of functional groups sensitive for bases (esters, amides). Disadvantages include the difficulty of working with BF_3 and its relatively high costs.

Coupling of alkynes with aldehydes. The coupling reaction of aromatic alkynes with aldehydes in ionic solution was also applied to the synthesis of chalcones containing different substituents in the benzene nuclei, 1-butyl-3-methyl-1-H-imidazole-4-methylbenzenesulfonate (BmimOTs) and 1-ethyl-3methyl-1-H-imidazole-4-methylbenzenesulfonate (EmimOTs) were used as ionic liquids. The respective reagents are more efficient and recyclable for such reactions. They favor the formation of only E isomers of chalcones, which can be easily purified. This method avoids the use of Lewis acids and heavy metals. It was found that if the aldehydes contain electron donors or acceptors, the reaction proceed favorably, without the formation of secondary products. However, it was observed that when aliphatic alkynes are used, it is not possible to isolate the reaction products [32]. The optimization study of the coupling-isomerization reaction demonstrated that the use of propargylic alcohol and microwave heating allows chalcone synthesis in only 8-25 min with yields higher than 96%, using reduced amounts of base [33].

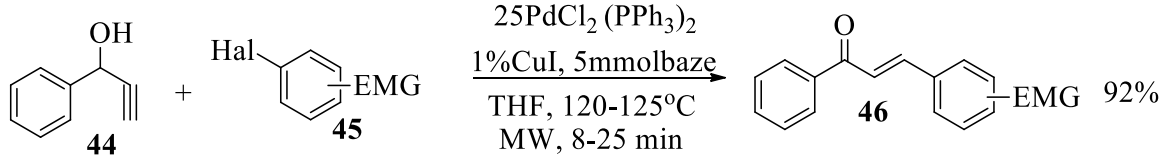


Fig.18. Synthesis of chalcone derivatives **46** from propargylic alcohol under microwave conditions.

Synthesis of nitro-chalcones and aminochalcones. Nitrochalcones also play a special role in chalcones chemistry. In the specialized literature the nitrochalcones synthesis are described [34].

Thus, during the nitration of benzylidene acetophenones at low temperatures, acetic anhydride was used as a solvent and a mixture of 2- and 4-nitrochalcone isomers was obtained together with secondary products [35]:

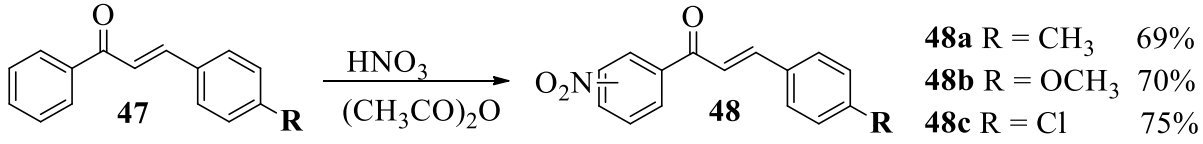
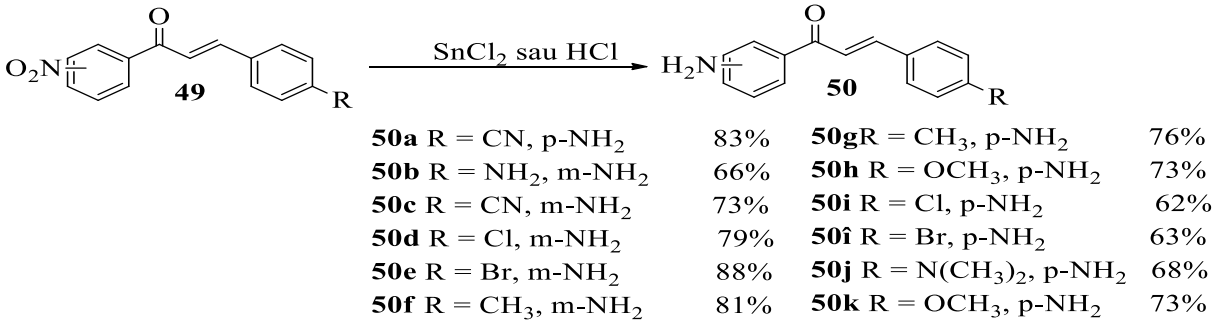


Fig.19. Synthesis of nitrochalcone derivatives **48a-c**.

The solubility studies show that the suitable solvent for the separation of these isomers can be diethyl ether or benzene. The reactions yields are 69-75 % and chlorine derivatives are more effective for obtaining. Direct condensation of aminobenzaldehydes with acetophenones proceeds unsuccessfully, low yields and impure reaction products. To exclude these difficulties, aminochalcones are more commonly obtained by reducing nitrochalcones. The optimal effective reduction method is considered to be treatment with $SnCl_2$ or HCl. Depending on the position of the nitro group in compounds **49**, the reaction yield ranges from 62 to 88%.

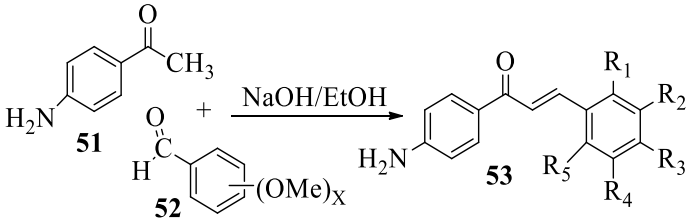


50a R = CN, p-NH_2	83%	**50g**R = CH_3, p-NH_2	76%
50b R = NH_2, m-NH_2	66%	**50h** R = OCH_3, p-NH_2	73%
50c R = CN, m-NH_2	73%	**50i** R = Cl, p-NH_2	62%
50d R = Cl, m-NH_2	79%	**50î** R = Br, p-NH_2	63%
50e R = Br, m-NH_2	88%	**50j** R = $N(CH_3)_2$, p-NH_2	68%
50f R = CH_3, m-NH_2	81%	**50k** R = OCH_3, p-NH_2	73%

Fig.20. Transformation scheme of nitrochalcones into aminochalcones.

The nitro group can be replaced by bromine. The method consists in treating of nitrochalcones with silver bromide under illumination in glacial acetic acid. Halogenochalcones can be obtained from aminochalcones through the diazotization reaction. However, the reaction did not achieve practical applications at this time, because the direct condensation of halogenobenzaldehydes with the corresponding acetophenones is more effective for obtaining of chalcones. The given conclusion results from the comparison of the reaction yields of the final products. When the halogenochalcones are obtained through the diazotization reaction, the reaction yields are between 26-39%, and through the direct condensation reaction yields are 49-89%.

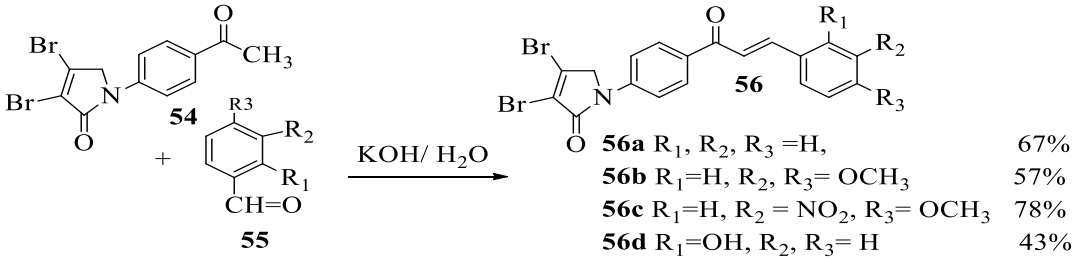
SUWITO H. et al. have achieved the synthesis of aminochalcones and their derivatives containing -OCH_3 groups, using the Claisen-Schmidt reaction in which the acetophenone **51** or its derivatives react with benzaldehyde or its derivatives **52** using an alkaline base, such as NaOH, KOH or NaH as a catalyst in a polar solvent [36]:



53a R_1 = OCH_3, R_2, R_3, R_4, R_5 = H	75%
53b R_2 = OCH_3, R_1, R_3, R_4, R_5 = H	86%
53c R_3 = OCH_3, R_1, R_2, R_4, R_5 = H	75%
53d R_1, R_2 = OCH_3, R_3, R_4, R_5 = H	80%
53e R_1, R_3 = OCH_3, R_2, R_4, R_5 = H	98%
53f R_1 , R_2, R_3, R_4, R_5 = H	42%

Fig.21. The structure of synthesized aminochalcones **53a-f**.

The scientists in this research area proposed the synthesis of some 4'-aminochalcone's derivatives from dibromoaleimide [37, 38]. The Claisen-Schmidt condensation reaction of 4'-ethyl 3,4-dibromoaleimide with various arylaldehydes under basic conditions offers the possibility of obtaining 4'-aminochalcones using dibromoaleimide:



56a R_1, R_2, R_3 =H,	67%
56b R_1=H, R_2, R_3= OCH_3	57%
56c R_1=H, R_2 = NO_2, R_3= OCH_3	78%
56d R_1=OH, R_2, R_3= H	43%
56e R_1, R_2 = H, R_3= Cl	78%

Fig.22. Synthesis of 4'-aminochalcone based on dibromoaleimide.

The present research revealed the synthesis of 4'-aminochalcone based on dibromoaleimide **56a-e**, which potentially serves as model structure in designing the syntheses of some antibacterial drugs.

As mentioned in contemporary literature, one of the main questions of chalcones chemistry is their small molecular size, but has the opportunity to be structurally modified. Thus, we have the possibility to modify and correlate the process of structure-physical-chemical properties. Due to this fact, these compounds possess a

wide spectrum of biological activity and can serve as synthetic chalcones derivatives, which are of increased interest for fine organic synthesis and the pharmaceutical industry [39, 40]. In order to obtain and research new biological properties of these materials, the emphasis is placed on the development of new synthesis methods of synthetic chalcones derivatives. This fact allows us to know more deeply the molecular mechanisms of action and in particular the identification of groups that increase these properties.

This success in the therapeutic effect allows synthetic chalcones derivatives to be applied to the discovery of new drugs, pharmaceutical forms, using modern strategies such as nano-formulations to increase their bioavailability with prolonged effect. Synthetic chalcones derivatives have been shown to possess a broad spectrum of biological activities [41]. A special emphasis is given to the anticancer activity against some types of cancer cells and the antibacterial, antioxidant, antiviral activity, etc.

However, further clinical studies, fully understanding the mechanisms of action at the cellular level and establishing the correlation between the structure of synthetic chalcones derivatives and pharmacological action, especially for anticancer and antimicrobial activity, still need to be investigated.

Conclusions

Based on the existing bibliographic data regarding the synthesis methods of chalcones derivatives, it can be concluded that this field is well studied. Also, according to literature data, these substances have a very pronounced anticancer activity, having a protective action in the cellular system.

High interest is shown due to their biological properties such as: anti-inflammatory, antioxidant, cytotoxic and antihistaminic properties, etc. These important biological properties are the basis of current research to obtain them synthetically. The bibliographic data refer to the synthesis of 1,3-aryl(heteryl)propones, which are described in a series of summary articles. The main attention is paid to the synthesis methods of chalcones that allow us to obtain pure reaction products, short reaction time and profitable yields. Methods using solid-based heterogeneous catalysts are described, which, in turn, are highly active, durable, more economical and can be used in three synthesis cycles without significant loss of catalytic activity. The studied synthesis methods were: aldol and crotonic condensation, Claisen-Schmidt reaction, Suzuki reaction, coupling of alkynes with aldehydes, microwave irradiation, etc.

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