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THE USE OF MICROWAVE ACTIVATION IN THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS. (REVIEW)*

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Published data on the successful application of microwave activation in the chemistry of various heterocycles over the last two years are discussed.

Keywords: microwave, ring opening, recyclization, chemical transformations.

The use of microwaves to accelerate chemical reactions began in 1986 [1, 2]. Since that time a series of reviews on the use of microwave technology in organic synthesis have been published. The reviews in [3-8] provide information on achievements in this region, and earlier papers were reviewed in [9-12]. However, there have not so far been any reviews on the application of microwaves in the chemistry of heterocyclic compounds. In the present work we discuss published data of the last two years on the use of microwaves in the synthesis and various transformations of heterocyclic compounds.

1. GENERAL REMARKS

The action of UHF radiation on a substance can give rise to various effects leading to the release of heat [9]. In organic synthesis the effect involving the polarization of dielectrics has found greatest use.

It is known that the molecules of polynuclear substances (including heterocycles) in an electrostatic field strive to adopt a position such that their dipoles are arranged in one direction. Here the frequency of the radiation (2540 MHz) is of the same order as the rotational frequencies of the molecules. Therefore microwaves give rise to forced rotation of the molecules. As a result of intermolecular collisions the energy is distributed among other degrees of freedom, and heating of the substance occurs. Here the heat is as it were generated *in situ* in the body of the solid and is not transferred by convection from its outer boundary as in the case of normal heating. This leads to a more uniform distribution of heat, the absence of significant local areas of overheating, and consequently a decrease in the amount of side products.

2. THE TECHNIQUE OF THE MICROWAVE EXPERIMENT

At the present time there is a fairly large number of microwave ovens specially designed for laboratory use, but in the overwhelming majority of cases microwave syntheses mean the use of ordinary domestic microwave ovens. Compared with the special laboratory ovens the domestic ovens have a series of disadvantages: they do not

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contain devices for measuring the temperature of the irradiated sample, do not provide the facility of focusing the radiation, and do not even make it possible to vary the power of the radiation. The various levels of energy in domestic microwave ovens are only achieved by periodically switching off a source giving radiation of fixed power. This can give rise to problems if the mixture is cooled too quickly. Nevertheless, the comparatively low cost of the domestic ovens makes them extremely accessible. Moreover, in spite of the limitations domestic microwave ovens are quite suitable for many synthetic reactions, and several reactions can be carried out in the oven at the same time.

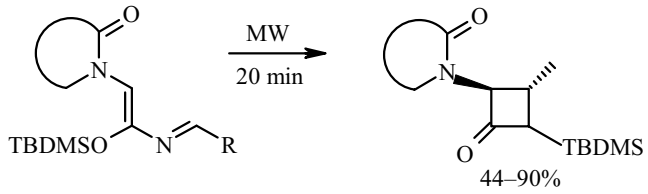
It is very important that microwave heating often makes it possible to dispense with a solvent and a reflux condenser and to conduct the reaction in an open vessel. In this case the temperature of the reaction mixture is not restricted to the boiling point of the solvent, and the reaction takes place considerably more quickly.

If the reaction mixture absorbs the microwave radiation insufficiently well, it is necessary to use either a solid support that absorbs the radiation well (e.g., graphite) or to introduce other additives (e.g., polar solvents). Each method has its disadvantages: the introduction of an active support reduces the advantages of the microwave method of heating to zero, since the heat in this case arises at the interface between the reaction mixture and the support and not in the body of the reaction medium. The use of volatile solvents in a microwave experiment can lead to explosion as a result of the ignition of the vapors and it is difficult to remove many high-boiling solvents after the reaction.

Sometimes the reaction requires the presence of a catalyst. In this case it is most convenient to use a heterogeneous catalyst, since it is easier to separate the organic reaction products from the catalyst. For acid catalysis it is usual to employ zeolites, certain clays, and silicon or aluminum oxides; for base catalysis it is possible to use the hydroxides of alkali and alkaline-earth metals. (The use of palladium and nickel hydrogenation catalysts has also been reported.) The use of homogeneous catalysts in microwave synthesis has so far been restricted to metal-complex catalysis. A review has been devoted to the use of phase-transfer catalysis under the conditions of microwave activation [5].

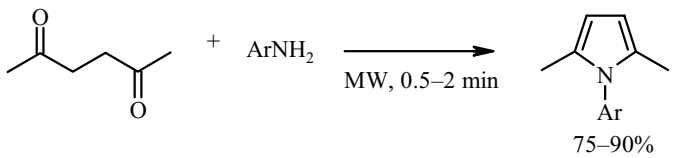
3. SYNTHESIS OF HETEROCYCLIC COMPOUNDS

In papers on the use of microwave activation in the chemistry of heterocycles greatest attention has been paid to their synthesis. In spite of the fact that the authors use well authenticated methods for the production of the heterocyclic compounds, the use of microwaves makes these reactions even more attractive. Thus, according to the microwave procedure proposed in [13] for the cyclization of 1,3-azadienes to 2-azetidinones, as under classical conditions only the *trans*-3,4-disubstituted β-lactams are formed:



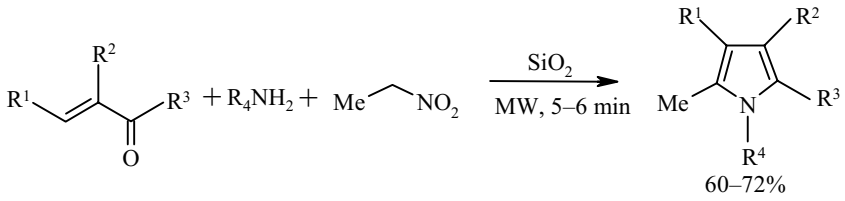
If the substituents of the azadiene contain a chiral center, the reaction takes place stereoselectively, and the ratio of the isomers varies between 56:46 and 90:10.

It was shown [14] that the formation of N-arylpyrroles from anilines and γ-diketones under microwave conditions takes only a few minutes:



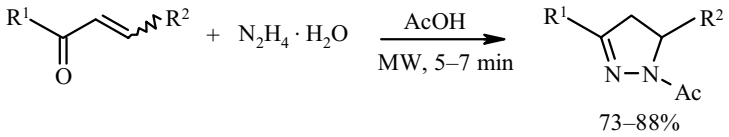
Such high-speed methods deserve to be called express syntheses. In fact, the investigator's time is only spent on isolation of the reaction product.

Pyrroles can also be obtained with good yields in the course of the three-component condensation of α,β-unsaturated carbonyl compounds with amines and nitroalkanes under the conditions of microwave treatment [15]:



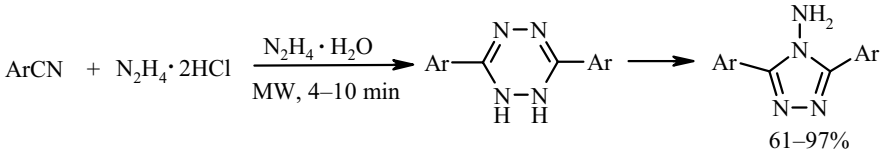
In this work it was possible not only to reduce the reaction time from 16-18 h to 5-6 min but also to increase the yield by 10-30%.

Microwave irradiation of α,β-unsaturated carbonyl compounds with hydrazine in glacial acetic acid leads to the corresponding N-acylpyrazolines [16]:



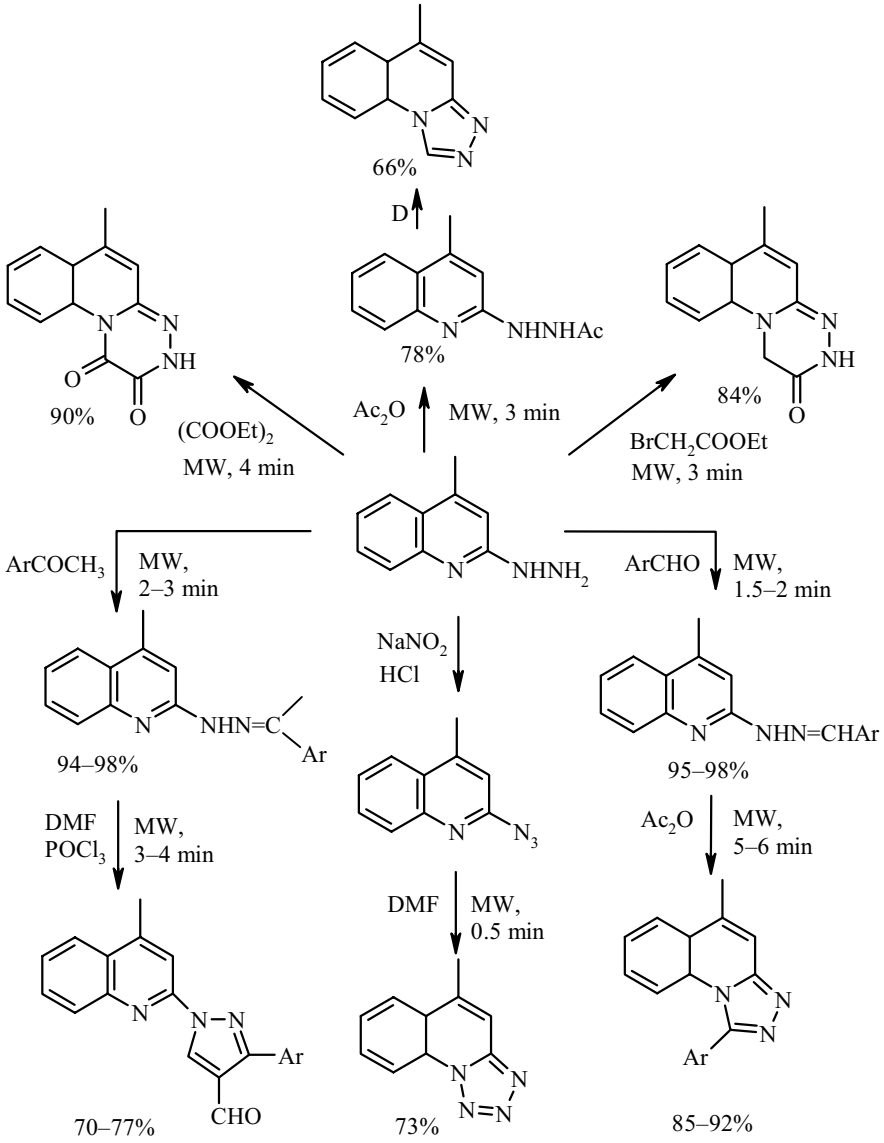
The authors note that realization of the reaction under classical conditions would require 5.5-8 h, i.e., the reaction rate is increased by approximately 60 times.

A series of symmetrical 4-amino-3,5-diaryl-1,2,4-triazoles were obtained by the express reaction of aromatic nitriles with hydrazine hydrochloride in the presence of an excess of hydrazine hydrate in ethylene glycol [17]:

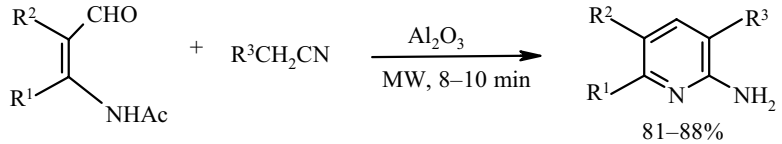


Of great interest is the paper [18] on the microwave synthesis of a series of biologically active condensed five- and six-membered nitrogen heterocycles from 2-hydrazino-4-methylquinoline. In each case the microwave treatment made it possible not only to reduce the reaction time considerably (by 40-200 times) but also to increase the yield of the nitrogen heterocycles. This work demonstrates how promising the complex use of microwave activation is at all stages of the synthesis of heterocyclic compounds, including the synthesis of their precursors (Scheme 1).

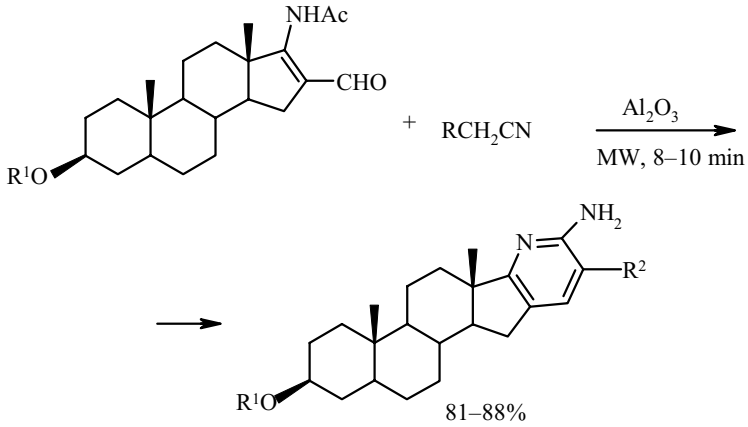
Scheme 1



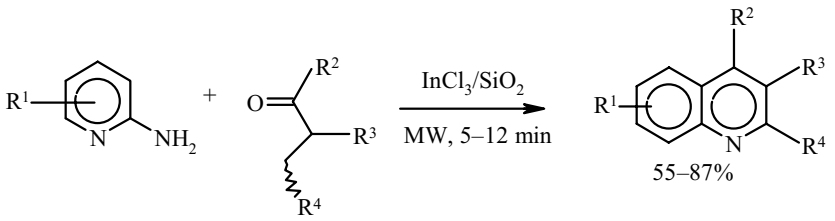
The condensation of β-formylenamides with cyanomethylenes at basic aluminum oxide under microwave conditions leads to α-aminopyridines [19]:



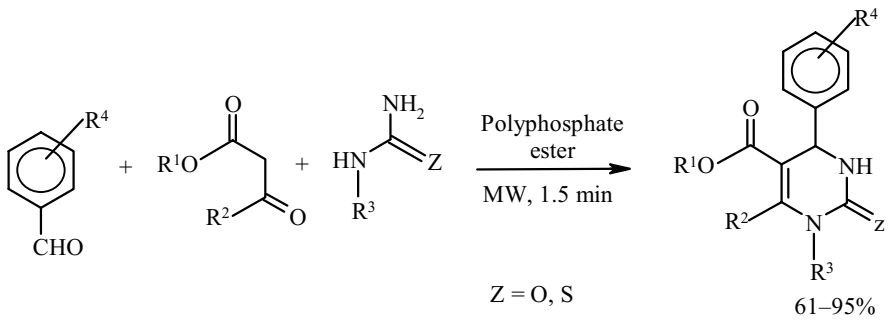
In this work a series of annellated α-aminopyridines and even α-aminoquinolines were obtained. The application of this reaction in the chemistry of steroids is not without interest:



A microwave version of the Skraup synthesis of substituted quinolines in the presence of indium(III) chloride on silica gel has been proposed [20]:

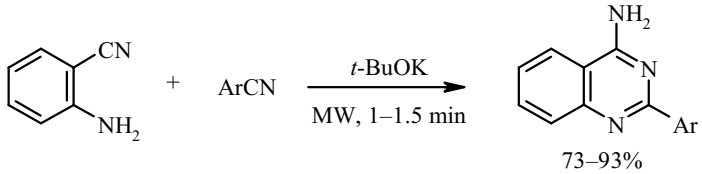


A procedure was developed for the express synthesis of 4-aryl-3,4-dihydropyrimidin-2-(1H)-ones according to Biginelli [21]:

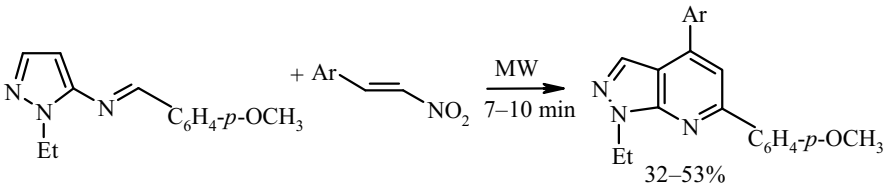


The high rate of the reaction and the possibility of varying the substituents make the proposed method very suitable for the combinatorial synthesis of heterocyclic compounds.

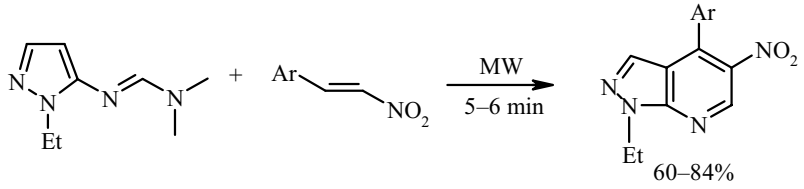
Aryl cyanides react with anthranilonitrile, leading to the corresponding 4-aminoquinazolines after a very short microwave treatment in the presence of potassium *tert*-butoxide [22]:



Pyrazolopyridines are formed with good yields in the reaction of pyrazolylimines and nitroalkenes with microwave activation [23]:

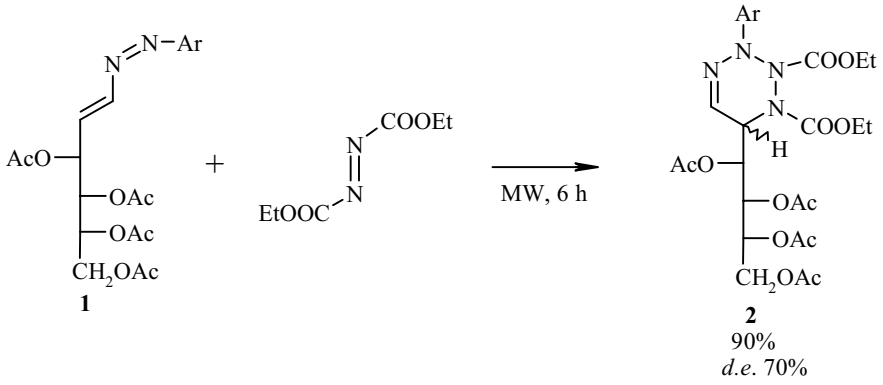


If the aryl group of the imine is replaced by an amino group, it is possible to obtain nitro-substituted pyrazolopyridines:



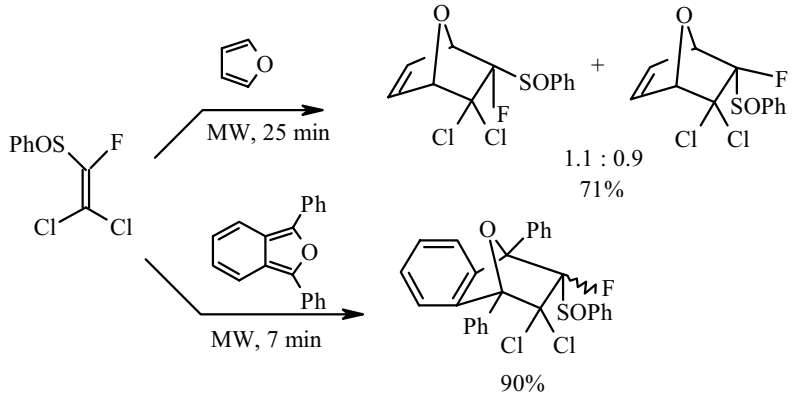
The authors emphasize that the reactions do not go at all on certain substrates with normal heating.

The Diels–Alder reaction of homochiral 1,2-diaza-1,3-butadienes (**1**) with diethyl azodicarboxylate, leading to 1,2,3,6-tetrahydro-1,2,3,4-tetrazines (**2**), is accelerated significantly by microwave radiation, and the formation of the new chiral center is accompanied by high stereoselectivity [24]:



It was emphasized that under normal conditions this condensation would require 30 days.

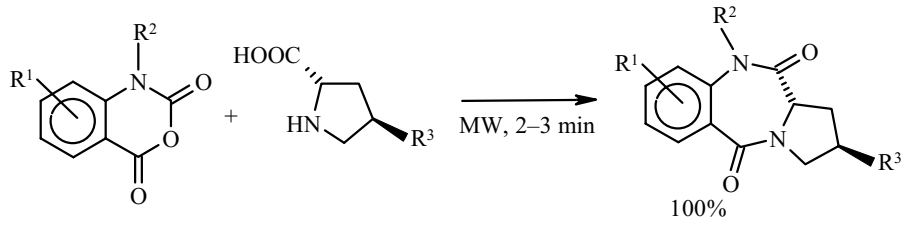
The cycloaddition of furan and 1,3-diphenylisobenzofuran to trihalogenoethenylsulfenylbenzenes by the Diels–Alder reaction under microwave radiation was described in [25]:



The substitution of the *trans* chlorine atom in the initial diene by fluorine in reaction with furan under the same conditions leads to an increase in the stereoselectivity (ratio of diastereoisomers 2:1).

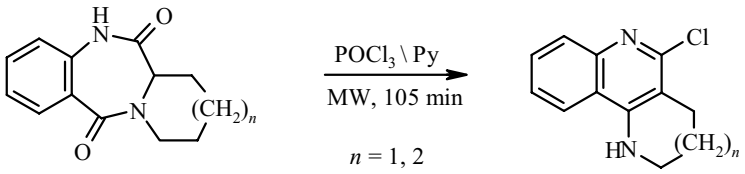
4. CHEMICAL TRANSFORMATIONS OF HETEROCYCLES UNDER MICROWAVE CONDITIONS

Their recyclizations and transformations are rightly considered some of the most interesting reactions of heterocyclic compounds. There are several examples of such reactions among publications devoted to the reactions of heterocycles under microwave conditions. Thus, isatoic anhydrides react with *L*-proline with the formation of benzodiazepinediones [26]:



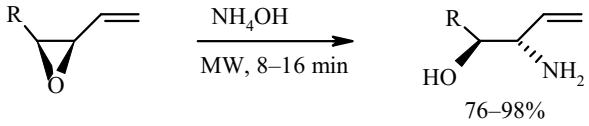
The reaction conditions are so mild that epimerization does not occur at any of the chiral centers.

In work by other authors [27] the benzodiazepinediones themselves were recyclized under microwave conditions:

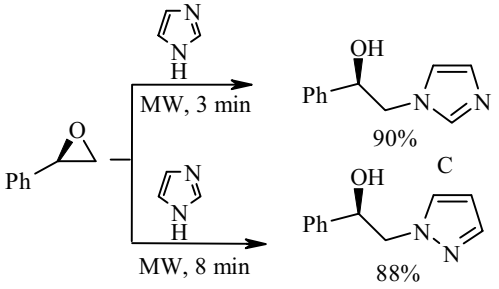


In this case the microwave radiation reduces the reaction time by only a third, which hardly justifies the use of the microwave technique. Such an insignificant increase in the reaction rate is probably due to the fact that under the conditions proposed by the authors, as under classical conditions, the reaction takes place in boiling pyridine. The use of a more high-boiling base would possibly be more effective.

Several examples of the application of microwave activation to reactions in which opening of the heterocycle occurs are known. Thus, Swedish authors [28] have studied the aminolysis of vinyloxiranes under microwave conditions:

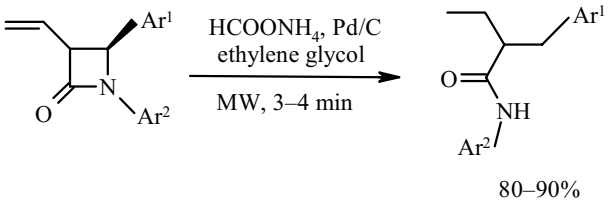


The reaction is stereospecific and regioselective, and nucleophilic attack takes place predominantly at the carbon atom at the vinyl group. The use of microwave activation in this case makes it possible not only to reduce the reaction time from four days to a few minutes but also to increase the yields by 10-50%. Moreover, the microwave technique makes it possible even to bring substrates that are inert under classical conditions into the reaction. The nucleophilic opening of the oxirane ring is probably sensitive to steric factors even under the conditions of microwave treatment. The addition of imidazole and pyrazole to 1-phenyloxirane takes place exclusively at the $C_{(2)}$ atom [29]:

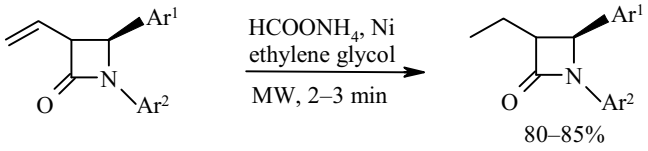


Without microwave activation the reaction requires a catalyst (toluenesulfonic acid), takes several hours, and gives a low yield, particularly in the case of pyrazole.

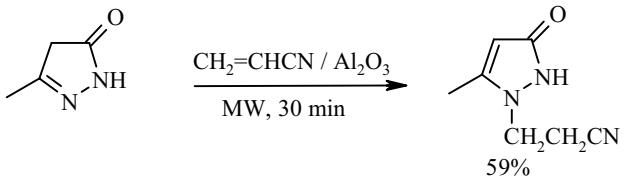
It is known [30] that in the series of 4-aryl-2-azetidinones under microwave conditions a palladium catalyst leads, in addition to other processes, to hydrogenolysis of the C–N bond of the β-lactam ring. The ester and amide groups are not affected.



It is interesting that unlike the palladium catalyst under the same conditions Raney nickel only reduces the multiple bonds:

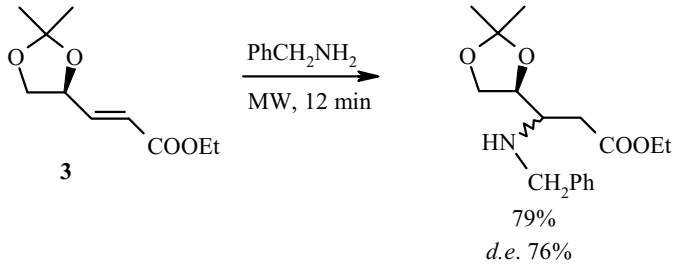


The use of microwave technology in a series of reactions leading to functionalization of the heterocycle has been described. Of particular interest is work on the Michael addition of acetonitrile to 5-methyl-3-pyrazolone [31] at neutral aluminum oxide or aluminum oxide modified with sodium hydroxide under microwave conditions. By means of the reaction it is possible to insert a cyanoethyl group at position 1 of the heterocycle:



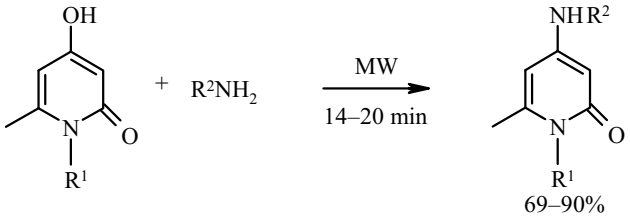
The authors emphasize in particular that the pyrazolone acts as a nucleophile in this reaction, and addition at other possible nucleophilic centers does not occur.

The microwave Michael addition of aliphatic amines to the chiral dioxolane (**3**), containing an ethoxycarbonylvinyl substituent, is described in one of our own papers [32]:

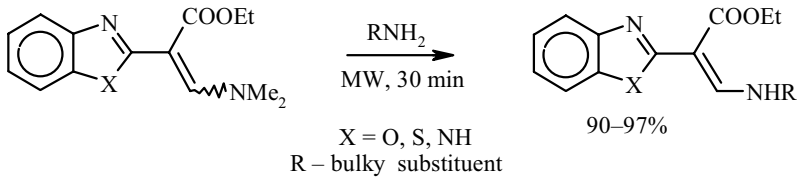


We note that, although the heterocycle does not take a direct part in the reaction, by having a chiral carbon atom it has a considerable effect on the configuration of the newly formed asymmetric center; addition is highly stereoselective.

A group of authors [33] have developed a method for nucleophilic substitution of the hydroxy group in 4-hydroxy-6-methyl-2(1H)-pyridones by an amino group with microwave activation:

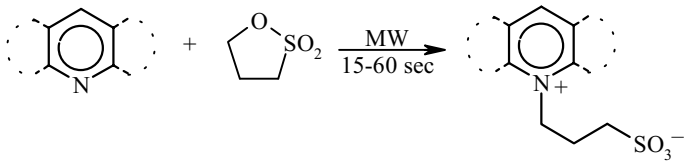


Another example of nucleophilic substitution with microwave treatment is transamination in the series of heterocyclic enamines [34]. Here, as seen from the scheme, the heterocycles are not affected, demonstrating the mild conditions of the reaction.

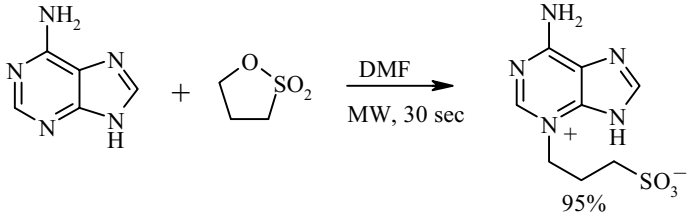


The reaction is stereoselective, and the most thermodynamically stable imine isomer is formed preferentially. The ratio of the isomers for the studied substrates ranges from 93:7 to 100:0.

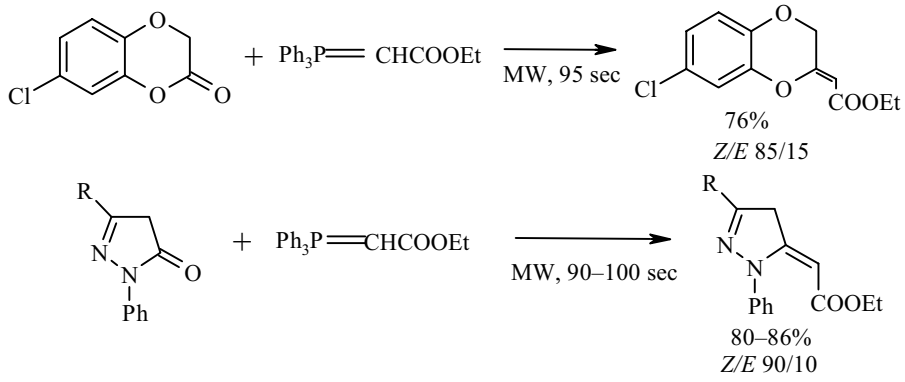
An express method for the sulfopropylation of pyridine and its condensed analogs has been described [35]. This is one of the fastest microwave reactions – it takes no longer than 1 min.



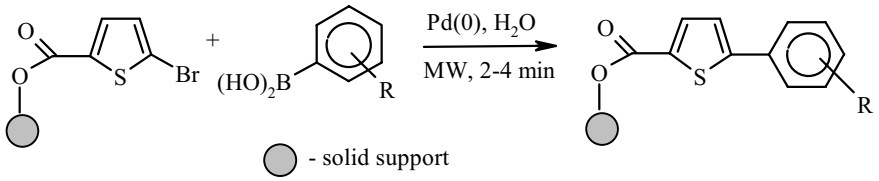
The regioselectivity of the reaction merits special mention, as demonstrated by the case of the sulfopropylation of adenine:



There is a report on the successful application of microwave activation in the Wittig reaction between the carbonyl groups of γ,δ-lactones, γ,δ-lactams, and pyrazolones and stabilized phosphorus ylides [36]:

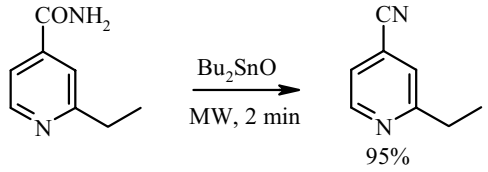


A microwave procedure was developed for solid-phase Suzuki cross coupling in the presence of catalytic amounts of palladium and traces of water. The reaction is general in nature; there are examples of its use with heterocyclic substrates [37]:



The use of the microwave technique in this case not only reduces the reaction time by two orders of magnitude but also completely suppresses the side reaction (hydrolysis of the ester groups), which usually reduces the yield of the arylated thiophenes by 10-45%.

The method for the transformation of primary heterocyclic amides into the corresponding nitriles, proposed in [38], may have great practical significance:



The reaction, catalyzed by dibutylstannyl oxide, takes place with high yields under microwave conditions in only a few minutes. The mildness of the conditions makes this transformation particularly promising in the chemistry of heterocyclic compounds.

The publications on the use of microwave activation in the chemistry of heterocyclic compounds included in the present review comprise approximately half of all the papers on microwave organic synthesis. Almost all the experiments discussed in the review were carried out in domestic microwave ovens, and most of them (more than two thirds) were carried out in the absence of a solvent. The main advantage of the method is a reduction in the reaction time to a few minutes. (The reaction rate here is increased by 2-3 orders of magnitude.)

The simplicity and the economy of the microwave experiment, the ease of its automation, and the availability of sources of microwave radiation make it possible to hope that microwave synthesis will in the near future occupy a worth-while place in the heterocyclic chemist's arsenal.

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