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SYNTHESIS AND TRANSFORMATIONS OF HETEROCYCLIC COMPOUNDS UNDER THE INFLUENCE OF MICROWAVE RADIATION. (REVIEW)

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Published data on the synthesis and transformations of heterocyclic compounds with microwave treatment are analyzed and classified according to the types of products formed. The results of analogous reactions conducted with normal heating are given for comparison.

Keywords: heterocycles, microwave radiation, microwave heating.

The use of microwave radiation (MWR) with a frequency of 2450 MHz began in 1970-1980 in analytical chemistry to improve sample preparation and also the analysis of natural and synthetic samples [1]. Specialized equipment was created and developed [2, 3].

In the last decade MWR has been used more and more often in organic synthesis [4-7]. In most cases the investigations are carried out in domestic-type microwave ovens or in equipment for the preparation of samples and analysis (digests). Microwave equipment specially designed for carrying out organic reactions has also been created [8-10].

Microwave heating has attracted the attention investigators in that it makes it possible to shorten the length of reactions significantly, to increase their selectivity, and to increase the product yields, which is particularly important in the case of high-temperature processes that take a long time. The success of microwave synthesis is determined in most cases by the choice of solvent (it must be highly polar, e.g., DMF, ethanol) and mainly by the microwave heating regime, which can be performed in a closed or open system. Special sealed vessels have been created for the closed systems [7].

Continuous and pulsed heating are used. The latter is necessary in reactions in a closed vessel when there is a rapid rise in pressure [4]. According to the type of delivery of the microwave energy, the process is divided into single-mode irradiation, in which the electromagnetic energy is delivered to the object being heated in the form of an monochromatic focused beam, and the multimode regime used in domestic practise and characterized by random distribution of the energy in the working chamber containing the object being heated. The single-mode regime is energetically more favorable since it is characterized by minimal energy losses. However, it cannot be used for large quantities of reagents [11].

Below we examine published data on the synthesis and transformations of heterocyclic compounds in comparison with data obtained under normal heating conditions. The review includes three sections containing information on specific types of products: Compounds with an O-heterocycle (section 1); compounds with an N- or S-heterocycle (section 2); compounds containing two different heteroatoms in the ring (section 3).

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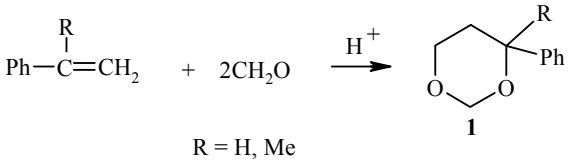
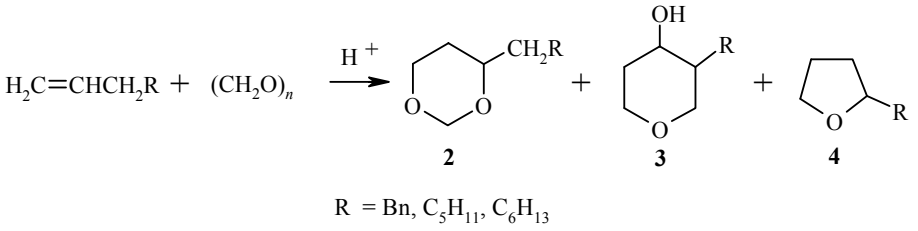
Most of the publications devoted to the application of MWR in organic chemistry relate to improvement of the production of the heterocyclic compounds used in the multistage syntheses of physiologically active substances.

1. SYNTHESIS OF COMPOUNDS WITH AN O-HETEROCYCLE

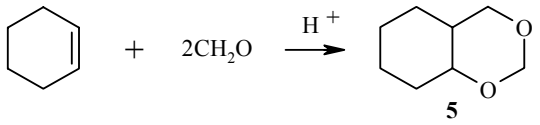
Microwave heating has been used successfully in the synthesis of a series of substituted 1,3-dioxanes. The formation of the latter, e.g., compounds **1**, during the condensation of various olefins with formaldehyde is on the average 2-6 times quicker than their synthesis with normal heating, in spite of the fact that the reactions take place in an open system at the boiling point of the reaction mixture [12].



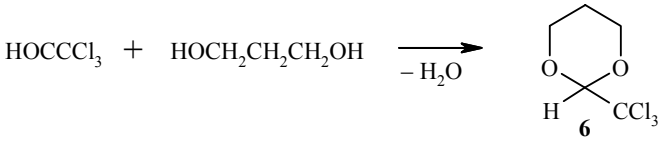
It was shown that the conversion of terminal olefins (1-heptene, 1-octene, 1-nonene) and the formation rate of the oxymethylation products **2**-**4** are increased when microwave heating is employed. It should be noted that the composition of the products **2**-**4** does not depend on the method of heating [13].



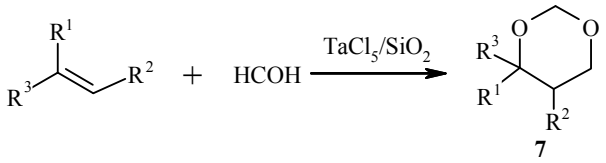
Similar results were obtained during the oxymethylation of cyclic olefins and of cyclohexene in particular [14]. The level of its conversion into 4,5-tetramethylene-1,3-dioxane (**5**) amounts to 75% after 35 min with microwave heating and 85% after 4 h with normal heating.



The synthesis of 2-(trichloromethyl)-1,3-dioxane (**6**) in a microwave reactor of the single-mode type takes 30 min, while it takes 8 h with traditional heating [15].



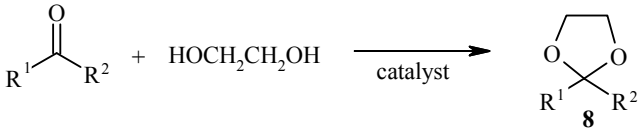
The optimum conditions were found for the production of 1,3-dioxane derivatives **7** by the condensation of olefins with formaldehyde with microwave heating in the presence of $TaCl_5$, deposited on silica gel, as catalyst [16]. The reaction takes 3-4 min, and the yields of the substituted 1,3-dioxanes amount to 85-90%, whereas the reaction with usual heating requires 10-13 h, and the yields of the products **7** are not greater than 80%.



7

R^1	R^2	R^3	Yield of **7**, %	R^1	R^2	R^3	Yield of **7**, %
H	H	Ph	90	H	Ph	Ph	85
Me	H	Ph	88	H	H	*p*-$O_2NC_6H_4$	80
H	Ph	Me	86	H	Me	*p*-MeC_6H_4	90
H	H	*p*-ClC_6H_4	85	H	Ph	Ph	85
H	Me	*p*-MeC_6H_4	88	H	H	$(CH_2)_8COOMe$	78

A series of 1,3-dioxolanes **8** were obtained with high yields (up to 96%) by the condensation of ethylene glycol with ketones and aldehydes with microwave heating in the presence of TsOH, $FeCl_3$, and Al_2O_3 as catalysts. The reactions took 2 min [17].



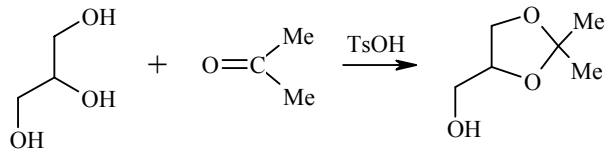
8

Initial aldehyde or ketone	Yield of **8**, %		
	TsOH	$FeCl_3$	Al_2O_3
$Me(CH_2)_5CHO$	96	97	75
PhCHO	81	77	90
m-$O_2NC_6H_4COCH_2Cl$	98	88	90
o-$MeOC_6H_4CHO$	90	95	92
$PhCH_2CH_2CHO$	88	91	95
p-$O_2NC_6H_4CHO$	97	83	96
p-ClC_6H_4CHO	96	97	91
$(CH_2)_6CO$	88	85	63

The microwave synthesis of 1,3-dioxolanes in the presence of I_2 was also studied. Here the products **8** were obtained in most cases with high yields and with reaction times of 3-7 min [18].

Initial aldehyde or ketone	Yield of **8**, %	Initial aldehyde or ketone	Yield of **8**, %
Benzaldehyde	85	Cyclohexanone	92
p-Nitrobenzaldehyde	83	Methylcyclohexanone	83
p-Chlorobenzaldehyde	90	Cholestanone	98
Anisaldehyde	87	Tetrahydrocarvone	98
Glutaraldehyde	55		

Isopropylideneglycerol – 4-hydroxy-2,2-dimethyl-1,3-dioxolane (**9**) – was synthesized with a yield of 84% in a flow-type microwave reactor for 1-2 min at 133°C. Under normal heating conditions the production of a comparable yield of **9** requires 12-24 h [8].

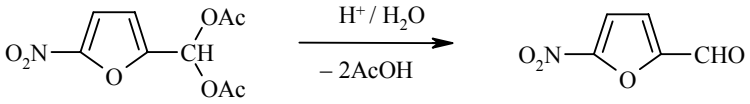


9

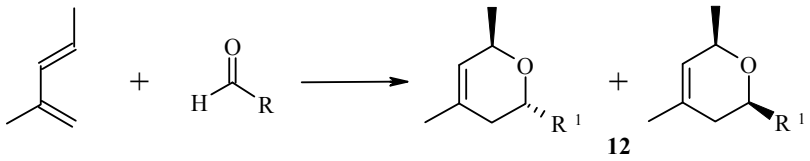
One of the effective methods for the production of heterocyclic compounds using microwave radiation is to conduct the reaction on solid mineral supports without a solvent. The advantages of this method include the absence of a solvent, the heating of which in an open microwave system is hazardous, and the disadvantages include the complexity of the temperature measurement and the small area of contact between the organic phase and the support. Montmorillonite K10 or KSF, silicon and aluminum oxides, and zeolites, which are active receivers of MWR, are used as supports [19]. For example, the acetalization of compound **10** with long-chain aldehydes by boiling in DMF in the presence of sulfuric acid requires 24-48 h. In a microwave system with montmorillonite KSF the reaction products **11** were obtained in 10 min with yields almost three times higher than the yields obtained with normal heating [11].

10 **11**

When microwave treatment was used for the deacetylation of 5-nitro-3-furfural diacetate at various supports the most effective was montmorillonite K10; the yield of 5-nitrofurfural after reaction for 2 min was 99%. With normal heating (50-60°C) the yield of the above-mentioned crude product after 5-6 h amounted to 83%, while the reaction could not be realized on montmorillonite K10 at 110°C [20].



The addition of methyl glyoxylate or dimethoxyacetaldehyde to 2-methylpenta-1,3-diene was studied under various heating conditions [11, 21]. Although there are no data on the temperature of the reaction mixture in the experiments with MWR and it is impossible to judge the actual reason for the acceleration of the reaction, it is nevertheless interesting that the authors of these papers were able to obtain the products **12** (a 75:25 mixture of *cis* and *trans* isomers) with very low-power microwave radiation (72 W). The best results (reaction time, product yield) from the reaction were obtained with microwave heating (table).

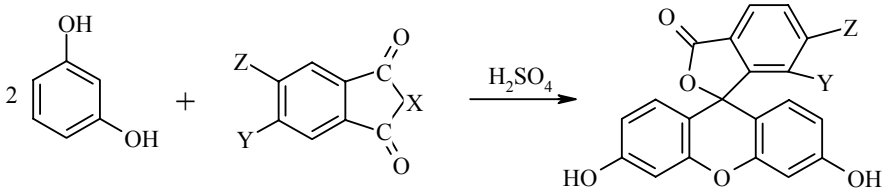


12

R	R^1	Solvent (catalyst)	Microwave heating			Normal heating (140°C)	
			Radiation power, W	*t*, min*	Yield of **12**, %	*t*, min*	Yield of **12**, %
$CH(OMe)_2$	CH_2OMe	Benzene ($ZnCl_2$)	600	5	82	240	0
$CH(OMe)_2$	CH_2OMe	Water ($ZnCl_2$)	600	15	76	480	54
$CH(OMe)_2$	CH_2OMe	– (–)	600	15	54	600	48
CO_2Me	CO_2Me	– (–)	72	10	96	360	65
CO_2Me	CO_2Me	Water (–)	72	8	80	180	82

* *t* is the reaction time.

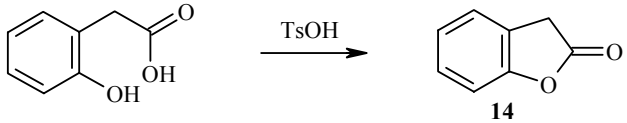
The synthesis of xanthene dyes **13** with yields of up to 60% by the condensation of resorcinol with acid anhydrides or amides in a microwave field took several minutes. With normal heating (150-170°C or the temperature of the melt in the presence of $ZnCl_2$) the length of the reaction was 5-6 h [22].



13

With X = O; Y = Z = H; Y = COOH, Z = OH; Y = COOH, Z = H; X = NMe, Y = NH_2, Z = H; Y = Z = H; Y = 6(5)-COOH, Z = 5(6)-OH; Y = 5(6)-COOH, Z = H; Y = 5(6)-NH_2, Z = H

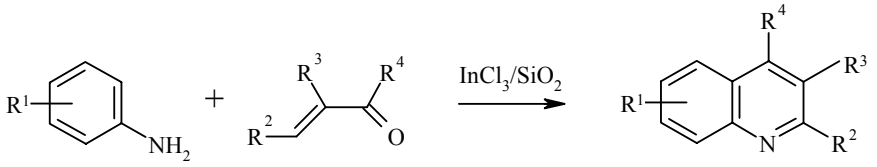
The microwave synthesis of coumaran-2-one (**14**) with a yield of 85% has been described [23].



14

2. SYNTHESIS OF COMPOUNDS WITH AN N- OR S-HETEROCYCLE

Single-stage methods have been proposed for the synthesis of the quinolines **15** [24] and polysubstituted pyrroles **16** [25] using MWR on silica gel without a solvent. The products **15** were formed in 1 min with high yields (81-87%).

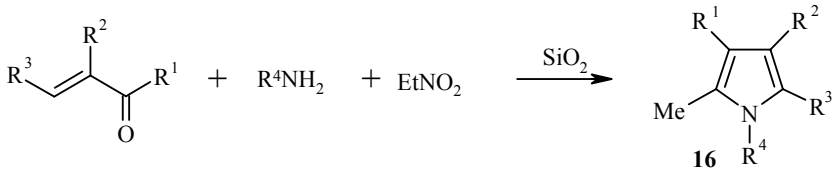


15

R^1	R^2	R^3	R^4	Yield of **15**, % (MWR, SiO_2)	R^1	R^2	R^3	R^4	Yield of **15**, % (MWR, SiO_2)
H	H	H	Me	85	4-Cl	H	H	Me	80
2-Me*	H	H	Me	81	4-Br	H	H	Me	80
3-Me	H	H	Me	84	2-Me-4-I	H	H	Me	83
4-Me	H	H	Me	85	1-Naphthyl	H	H	Me	82
2-OMe	H	H	Me	80	H	Me	H	*p*-$MeOC_6H_4$	81
4-OMe	H	H	Me	83	3-Cl	Me	H	H	83
3-OH	H	H	Me	81	H	Pr	Me	Me	55
3-Cl	H	H	Me	87					

* Here and subsequently the position of R^1 in the initial compound is indicated.

The yields of compounds **16** under analogous conditions amounted to 60-72%, which is approximately twice the yields obtained during the reaction in THF with normal heating.

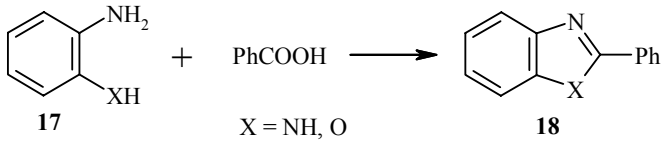


16

R^1*	R^3	R^4	Yield of **16**, %	
			SiO_2, MWR	THF, Δ
Ph	H	Bn	60	30
Ph	Ph	Bn	65	32
H	Me	*cyclo*-C_6H_{11}	60	32
Ph	H	PhCHMe	62	33
α-MeFur*[2]	Me	Bn	72	40

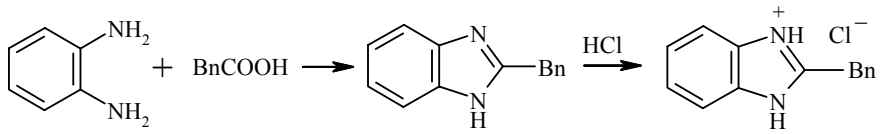
* R^2 = H.
*[2] Fur = furyl.

The heterocyclization of *o*-phenylenediamine and formic acid in a microwave field takes 3 min, and benzimidazole is formed with a yield of 70%. With normal heating a comparable yield of the latter was obtained after 3 h [26]. The authors of [22] synthesized 2-phenylbenzimidazole **18** (X = NH) and 2-phenylbenzoxazole **18** (X = O) by the heterocyclization of benzoic acid and *o*-phenylenediamine **17** (X = NH) or *o*-aminophenol **17** (X = O) respectively in a microwave field, but the yields of the products after microwave treatment for 2 min were not higher than 16%.



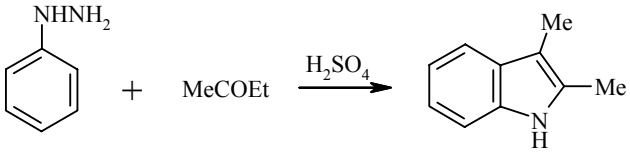
17 **18**

The heterocyclization of *o*-phenylenediamine and phenylacetic acid under analogous conditions was more successful, and the yield of the product 2-benzylbenzimidazole hydrochloride (**19**) after 7 min amounted to 79% [27].

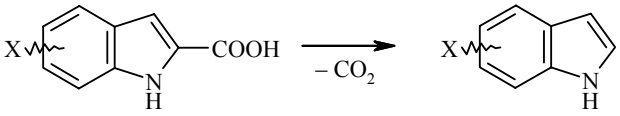


19

Microwave treatment mad it possible to synthesize 2,3-dimethylindole by the Fischer method with a yield of 65% in 1 min at 222°C [8].



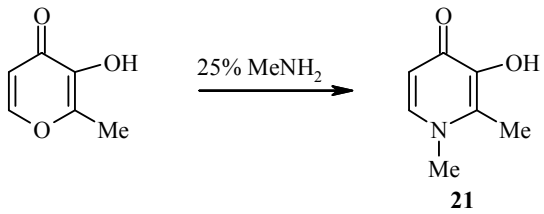
The synthesis of indoles **20** by the decarboxylation of indole-2-carboxylic acid and its substituted derivatives was realized successfully in a closed microwave system. The products **20** were obtained with high yields, and the reaction time was half the time taken with heating on an oil bath [28].



20

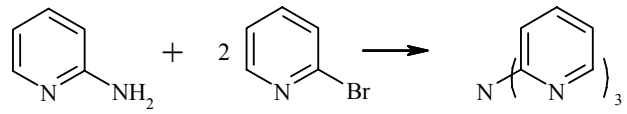
X	Yield of indole (**20**), %	X	Yield of indole (**20**), %
H	95	5-MeO	100
4-MeO	97	5-F	96
6-MeO	99	6-F	91

The synthesis of 3-hydroxy-1,2-dimethylpyridin-4-one (**21**) in a continuously operating microwave reactor took 1-3 min, and the yield of the pure product **21** amounted to 65%. With normal heating for 6 h the yield of the crude product **21** was 50% [8].



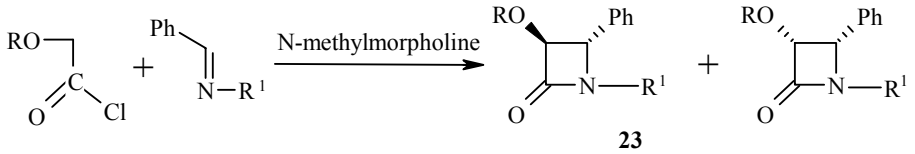
21

Approximately identical low yields (15-20%) of tri(2-pyridyl)amine (**22**) were obtained during microwave and thermal treatment of the reagents in ethanol. However, the reaction took 6 min in the first method and 16 h in the second [29].



22

The authors of [30, 31] not only found an effective method for the production of β-lactams **23** by microwave heating but also discovered that the power of the radiation had an effect on the stereochemistry of the products. Thus, at low power and, consequently with a low temperature in the reaction mixture the *cis* isomer predominated, while at high temperature (112°C) the *trans* isomer of the β-lactam **23** predominated.

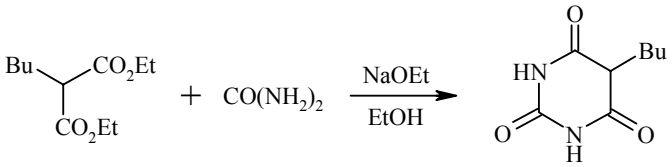


23

R = Bn, MeCO; R^1 = Me, Bn, $(MeO)_2C_6H_3CH_2$-*m*,*p*, $(MeO)_2C_6H_3$-*p*

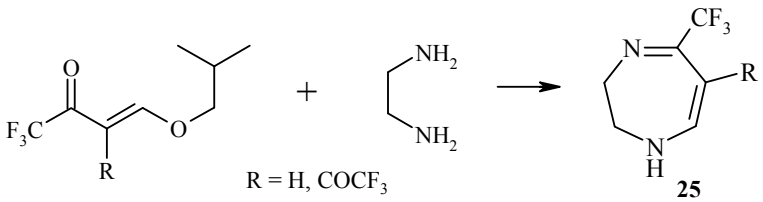
Reaction time, min	Reaction temp., °C	Yield of the *trans*/*cis* isomers of β-lactam **23** (R = Bn, R^1 = Me), %
1	69	16 / 84
2	75	20 / 80
3	94	45 / 55
4	96	45 / 55
5	112	55 / 45

The substituted barbituric acid **24** was synthesized with a yield of 80% by the action of microwave radiation [32].



24

The microwave synthesis of diazepines **25** with yields of 73-77% has been described [33].

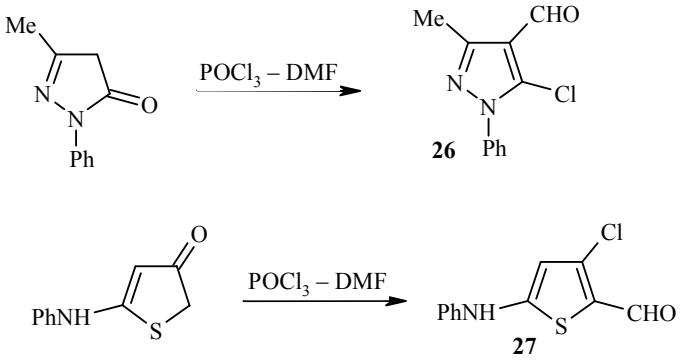


R = H, $COCF_3$

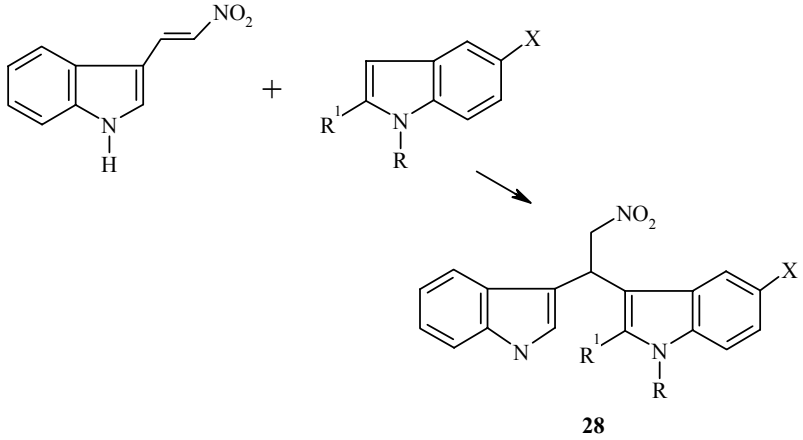
25

In the same work 12 derivatives of quinoxaline were obtained with yields of 73-93% according to the same scheme with *o*-phenylenediamine and its derivatives in place of ethylenediamine.

The use of microwave radiation and silica gel proved very effective in the Vilsmeier–Haack reaction. The aromatic compound and the Vilsmeier–Haack reagent ($POCl_3$–DMF) were deposited on previously activated silica gel. The products **26** and **27** were obtained in 1.5-2.5 min with yields of 66 and 64% respectively, which significantly exceed the yields obtained with ordinary heating [34].



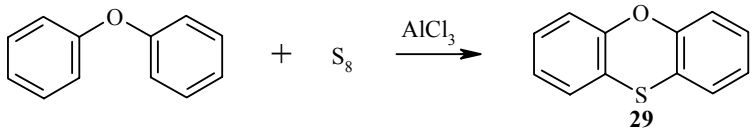
A convenient method was proposed for the synthesis of nitroethanes **28** containing two indole fragments by the reaction of 3-(2-nitrovinyl)indole with indole and its substituted derivatives on silica gel with microwave radiation. The products **28** were obtained with yields of 70-86% after 7-8 min. With normal heating similar yields of compounds **28** were obtained after 8-14 h [35].



R = R^1 = H, R = X = H, R^1 = Me; R = Me, R^1 = H, X = H, Br; R = Et, R^1 = X = H; R = Me; R = *i*-Pr, R^1 = X = H

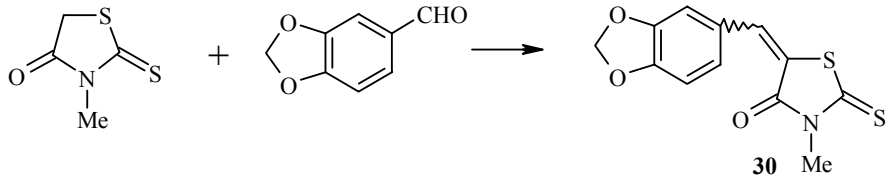
3. SYNTHESIS OF COMPOUNDS WITH A RING CONTAINING TWO DIFFERENT HETEROATOMS

A series of examples where microwave radiation was used in the synthesis of compounds containing two different heteroatoms in the ring are known. Thus, the phenoxathiin **29** was synthesized with a yield of 85% by microwave heating [36].



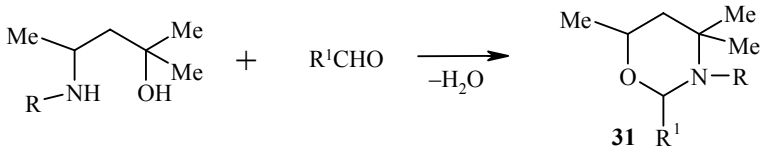
29

With microwave heating the condensation of N-methyl-2-thioxothiazolidin-4-one with piperonal on KF or Al_2O_3 was complete after 20 min, and the product yield amounted to 62%. With normal heating the same product was obtained after 5 min with a yield of not more than 20% [37].



30

It was shown that the cyclization of γ-amino alcohols with various aldehydes in a microwave field is 2-10 times as quick, depending on the type of substituent. The yields of the products **31** are comparable with the yields obtained by normal heating [38].



31

R = H, Me; R^1 = H, Me, *n*-Bu, *cyclo*-C_6H_{11}

The reviewed data on the synthesis and transformations of heterocyclic compounds with microwave heating show convincingly that with microwave treatment it is possible to reduce the shorten the process substantially and to increase the product yields.*

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