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SYNTHESES OF HETEROCYCLIC COMPOUNDS UNDER MICROWAVE IRRADIATION

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Abstract – Microwave technique has been applied extensively in organic syntheses. In this paper, syntheses of different kinds of heterocyclic compounds under microwave irradiation were reviewed.

INTRODUCTION

In 1986 it was first reported that organic reactions could be accelerated in domestic microwave (MW) irradiation.[1] Although there were instances where the used vessels explored, rate enhancements of up to three orders of magnitude were also obtained. Thus microwave irradiation was simultaneously seen as beneficial through increased rates, yet hazardous with the equipment used. Despite the difficulties, microwave-assisted organic chemistry had experienced exponential growth with the last 17 years, and many groups had contributed to the approaches pursued. Now there are more than 1000 papers, including several reviews.[2-9]

The technique had been used to assist in oxidation, reduction, esterification and transesterification, deprotection and protection, cycloaddition, condensation, alkylation, aromatic and nucleophilic substitution, *N*-acylation, rearrangement and many other processes of significance to organic chemistry.[7] Microwave irradiation provided unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and the ease of manipulation.

Why does microwave irradiation speed up organic reactions? Microwave is a high frequency oscillating electric and magnetic field. Molecules with a permanent dipole that are subjected to this oscillating electric and magnetic field will try to align themselves with the field. As the field oscillates at 4.9×10^9 times/second, these molecules are continuously aligning and realigning with the field. This rapid motion and resulting intermolecular friction cause an intense internal heat that can increase up to 10℃ per second. This rapid heating is most often cited to be the reason behind the dramatically accelerated reaction rates using MW irradiation. At the same time, microwave heating is more homogeneous heating method

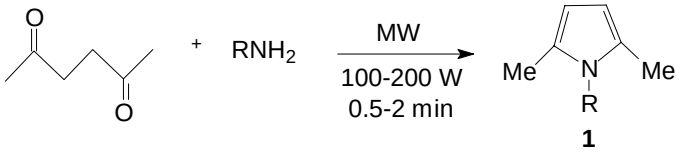
compared to the traditional heating. With traditional heating, heat is transferred to the reaction mixture through the vessel wall. This can cause localized overheating at the vessel walls, resulting in the formation of by-products and/or decomposition of products, especially with prolonged heating. However, in MW heating, MW radiation passes through the walls of vessel and heats only the reactants and solvent, avoiding local overheating at the reaction walls. This can eliminate side products and helps to explain the higher yields and purities often obtainable in MW-assisted syntheses in comparison to traditional methods, in often 1-10% of the time.[9]

MW had also been applied extensively in the synthesis of heterocyclic compounds which have wide-ranging biological activities. In this paper, we review the syntheses of different kinds of heterocyclic compounds under microwave irradiation.

1. Syntheses of five-membered heterocycles

1.1 Syntheses of pyrroles

Danks [10] studied the syntheses of pyrroles (**1**) by the reaction between hexane-2,5-dione and primary amines under microwave irradiation. When the aliphatic amines were used, a relatively short irradiation at low power setting was required to obtain high yields of the pyrroles. When the amines had greater steric interference, higher microwave power settings and longer irradiation times were required to produce pyrroles. When this synthesis was performed in thermal conditions, the reaction required 12 hours [11] to obtained similar yields of pyrrole to those obtained by the microwave route. (Scheme 1)



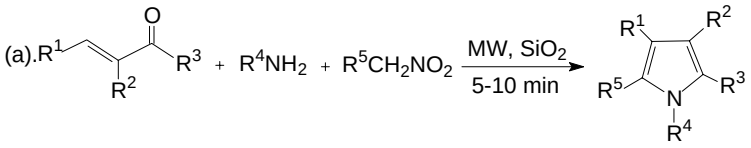
1

R	Yield(%)
$PhCH_2$	90
$PhCH_2CH_2$	90
Ph	90
m-ClC_6H_4	80
p-$MeOC_6H_4$	90
o-MeC_6H_4	85
2,4-$Me_2C_6H_3$	80
2,6-$Me_2C_6H_3$	75

Scheme 1

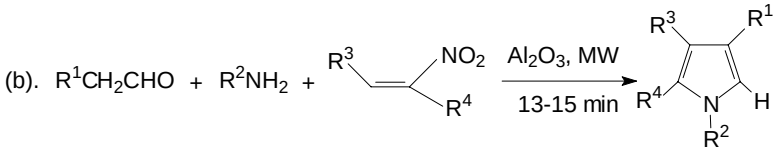
Ranu and coworkers [12] reported an efficient microwave-assisted one-pot syntheses of highly substituted alkylpyrroles (**2**, **3, 4**) by two alternative routes in a microwave oven: (a) coupling of an α,β-unsaturated carbonyl compound, an amine and a nitroalkane on the surface of silica gel and (b) coupling of a carbonyl compound, an amine and an α,β-unsaturated nitroalkene on the surface of alumina. (Scheme 2) Route (a) took 15 h to obtain 12-65% yield and Route (b) gave similar yield in 3-18 h under classical heating. [13]

And two procedures both needed samarium compounds as catalyst. However, the two routes only required no more than 15 min without samarium compounds as catalyst to give good yield under microwave irradiation.



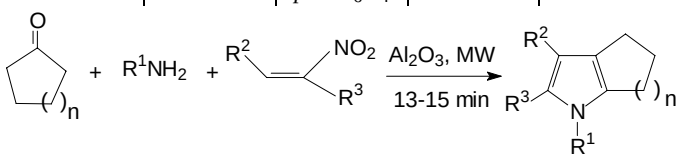
2

R^1	R^2	R^3	R^4	R^5	Yield (%)
Ph	H	H	$PhCH_2$	Me	60
Ph	H	H	$PhCH_2$	Et	62
Ph	H	Ph	$PhCH_2$	Me	65
Ph	H	Me	$PhCH_2$	Me	64
Ph	H	Me	$PhCH_2$	Et	66
H	H	Me	$PhCH_2$	Me	60
H	H	Me	⬡	Me	60
Ph	H	H	PhMeCH	Me	62
Ph	H	Me	PhMeCH	Me	66
Ph	H	H	Me_2CH	Me	64
2-Furyl	H	Me	Me_2CH	Me	68
2-Furyl	H	Me	$PhCH_2$	Me	72
2-Furyl	H	Me	*n*-Bu	Et	68
n-Pr	Et	H	$PhCH_2$	Me	60
n-Pr	Et	H	⬡	Me	65
Ph	H	H	*n*-Pr	Me	62
Ph	H	H	*n*-Bu	Me	61
Ph	H	Me	*n*-Bu	Me	65
$-(CH_2)_4-$		Me	*n*-Bu	Me	65



3

R^1	R^2	R^3	R^4	Yield (%)
Me	*n*-Pr	Ph	Me	74
Me	*n*-Bu	Ph	Me	71
Me	Me_2CH	Ph	Me	78
Me	$PhCH_2$	Ph	Me	75
Me	PhMeCH	Ph	Me	75
Et	*n*-Pr	Ph	Me	72
Et	*n*-Bu	Ph	Me	71
Me	*n*-Bu	*p*-ClC_6H_4	Me	76
Me	$PhCH_2$	*p*-ClC_6H_4	Me	78
Me	Me_2CH	*p*-ClC_6H_4	Me	80
Me	Me_2CH	*p*-ClC_6H_4	Et	81
Me	*n*-Bu	*p*-ClC_6H_4	Et	77



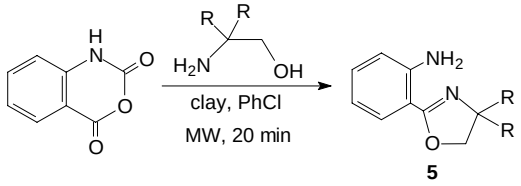
4

n	R^1	R^2	R^3	Yield (%)
1	*n*-Bu	Ph	Me	78
2	*n*-Bu	Ph	Me	84
2	$PhCH_2$	Ph	Me	81
2	PhMeCH	Ph	Me	79
3	*n*-Bu	Ph	Me	78
4	*n*-Bu	Ph	Me	74
1	$PhCH_2$	*p*-ClC_6H_4	Me	78
2	Me_2CH	*p*-ClC_6H_4	Me	85
2	$PhCH_2$	*p*-ClC_6H_4	Me	82
2	PhMeCH	*p*-ClC_6H_4	Me	80
2	*n*-Bu	*p*-ClC_6H_4	Me	78
1	$PhCH_2$	*p*-ClC_6H_4	Et	79
2	$PhCH_2$	*p*-ClC_6H_4	Et	82
2	Me_2CH	*p*-ClC_6H_4	Et	86
2	$PhCH_2$	*p*-FC_6H_4	Me	82

Scheme 2

1.2 Syntheses of oxazolines

Oxazoline is an important functionality as a protecting group [14] in organic synthesis. Reaction of isatoic anhydride with 2-aminoalcohol was carried out in dry chlorobenzene at 120℃ in the presence of acidic kaolinitic clay as the catalyst to furnish 2-(*o*-aminophenyl)oxazoline (**5**). It was presumed that the Lewis acidic sites of the catalyst assist the nucleophilic attack of the amino group on C-4 of isatoic anhydride, which was followed by cyclization to give the oxazoline. The final product was formed by the loss of carbon dioxide to give the free amine.[15] In thermal heating, it took 20 h using Lewis acid as catalyst. However, the reaction was completed for 20 min in a domestic microwave oven. (Scheme 3)

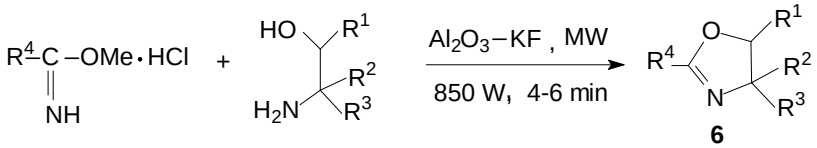


5

R	Yield (%)
Me	70
H	45

Scheme 3

Oussaid and coworkers [16] investigated the reaction of imino ethers hydrochlorides with ephedrine in the presence of potassium fluoride supported on alumina to synthesize oxazolines (**6**). In classical heating at 110℃ it required 24 h to give 65% yield. But in a domestic microwave oven it only required 5 min at 850 W to give 58-93% yield. (Scheme 4)

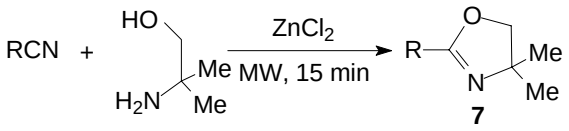


6

R^1	R^2	R^3	R^4	Yield (%)
H	H	H	Ph	71
Ph	Me	H	Ph	78
Ph	Ph	H	Ph	93
H	H	H		79
H	Et	H		58
Ph	Me	H		65
Ph	Ph	H		84

Scheme 4

Clarke and Wood [17] synthesized a number of 2-substituted 4, 4-dimethyl oxazolines (**7**) by condensation of readily available aromatic and aliphatic nitriles with 2-amino-2-methyl-1-propanol as both reactant and solvent, using zinc chloride as the Lewis acid catalyst. The reaction was generally clean, without the other by-product. The reaction proceeded well for both aromatic and heteroaromatic nitriles. Aromatic nitriles with either electron withdrawing or electron donating groups both gave good yields of products. Aliphatic nitriles also required longer reaction times to achieve comparable yields of products. The reaction required 15 min under microwave irradiation. Under classic heating, it required strongly acidic conditions in combination with high temperatures (130℃) over long reaction times (24 h) and proceeded in low yields. (Scheme 5)

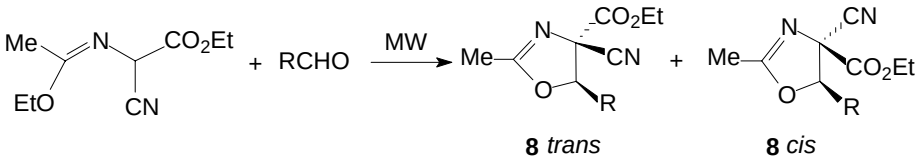


7

R	Yield (%)
Ph	78
p-BrC_6H_4	94
p-$NO_2C_6H_4$	88
p-$NH_2C_6H_4$	43
1-Na	61
p-$MeOC_6H_4$	77
m-$MeOC_6H_4$	94
o-$MeOC_6H_4$	59
o-MeC_6H_4	53
o-HOC_6H_4	76
o-NCC_6H_4	85
p-$Me_2NC_6H_4$	58
4-Py	83
$Ph(CH_2)_4$	67
p-$BrC_6H_4CH_2$	72

Scheme 5

Oxazolines (**8**) could also be synthesized with imidates and aldehydes in 1,3-dipolar cycloadditions.[18] The reaction was irradiated for 1-4.5 min by focused oven (Synthewave 402, Prolabo) to obtain 87-98% yield. Under thermal condition, it took 1-6 h to get comparable yields. (Scheme 6)



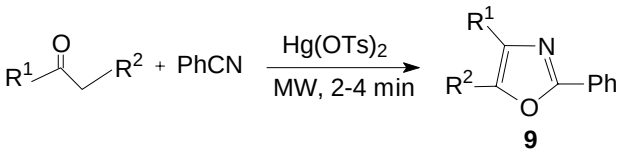
8 *trans* **8** *cis*

R	Ratio trans : cis	Yield (%)
Ph	87 : 13	93
2-Py	60 : 40	98
p-$MeOC_6H_4$	63 : 37	87
o-BrC_6H_4	63 : 37	97
o-HOC_6H_4	83 : 17	90
m-HOC_6H_4	72 : 28	94

Scheme 6

1.3 Syntheses of oxazoles

Oxazoles have attracted great interest due to their appearance as subunit of various biologically active natural products and their utilities as valuable precursors in many useful synthetic transformations.[19] They are well known for their antifungal activity and also have found application in drug development for the treatment of allergies, hypertension, inflammation and HIV infections.[20] Aromatic ketones and benzonitrile could be transformed directly into oxazoles (**9**) in the presence of $Hg(OTs)_2$ under microwave irradiation.[21] The reaction required 2-4 min in a domestic microwave oven. (Scheme 7) However, there is no general literature method for the direct preparations of 4-aryl-2-phenyloxazoles in classic heating.

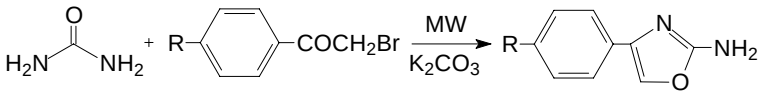


9

R^1	R^2	Yield (%)
Ph	H	51
p-ClC_6H_4	H	50
Ph	Me	85
p-MeC_6H_4	Me	83
p-ClC_6H_4	Me	86
p-FC_6H_4	Me	85
Ph	Et	79
p-ClC_6H_4	Et	71
CO_2Et	H	47
CO_2Et	Me	65

Scheme 7

Microwave irradiation of urea and substituted α–bromoacetophenone, deposited over K_2CO_3, (~100-115℃) for about 2-3 min, yielded the 2-aminooxazoles (**10**).[22] The reaction needed 160 sec in a domestic microwave oven (800 W) to give excellent yield. (Scheme 8) Under conventional heating, the K_2CO_3 mediated reaction was not facile and gave many by-products after 6-7 hours of heating in oil bath.

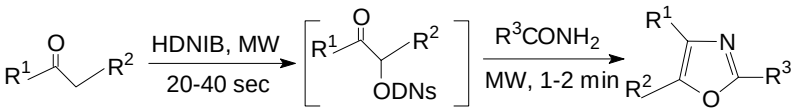


10

R	Yield (%)
Cl	94
NH_2	92

Scheme 8

Multi-substituted oxazoles (**11**) could also be synthesized by the reaction of amides with intermediary α-[(2,4-dinitrobenzene)sulfonyl]oxy ketone, formed *in situ* from the reaction of [hydroxyl-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene(HDNIB) with carbonyl compounds, under solvent-free microwave irradiation. Initial reaction of aromatic ketones with HDNIB was irradiated for 20-40 sec in an alumina bath to provide α-[(2,4-dinitrobenzene)sulfonyl]oxy ketone intermediates which were then converted to oxazoles with acetamide or benzamide under microwave irradiation for 1-2 min.[23] (Scheme 9) There are not examples to date for the preparation of substituted oxazoles directly from 1,3-dicarbonly compounds in thermal heating.



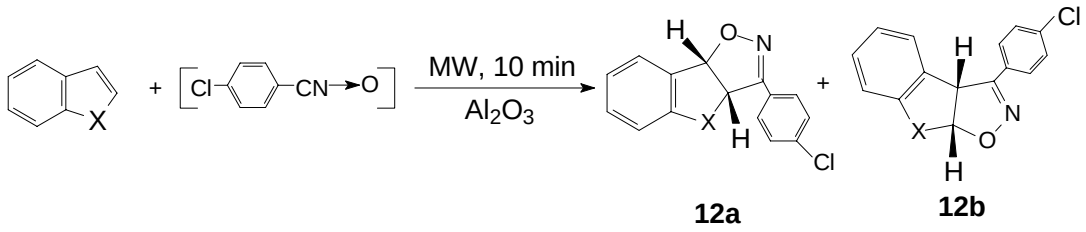
11

R^1	R^2	R^3	Yield (%)
Ph	H	Me	92
Ph	Me	Me	94
p-MeC_6H_4	Me	Me	94
p-ClC_6H_4	Me	Me	83
Me	COMe	Me	82
Me	CO_2Et	Me	58
Ph	CO_2Et	Me	91
Me	$CONEt_2$	Me	82
Ph	Ph	Me	70
Ph	Ph	Ph	68
Ph	H	Ph	77
Ph	Me	Ph	85
p-MeC_6H_4	Me	Ph	80
p-ClC_6H_4	Me	Ph	87
Me	COMe	Ph	87
Me	CO_2Et	Ph	74
Ph	CO_2Et	Ph	90
Me	$CONEt_2$	Ph	63

Scheme 9

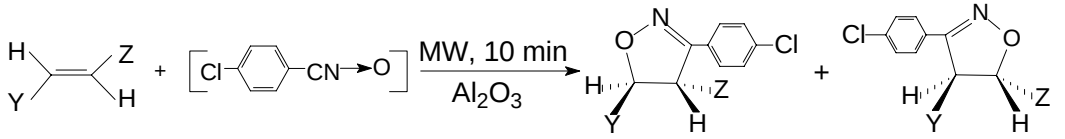
1.4 Syntheses of isoxazolines

Isoxazoles derivatives have been recognized as highly useful in medicinal chemistry, in particular, many trihalomethylated azoles are known to exhibit important biological activities in medicinal and agricultural scientific fields.[24] Syassi and coworkers [25] prepared isoxazolines (**12, 13, 14**) in good yields on solid mineral support in “dry media” in domestic microwave ovens. (Scheme 10)



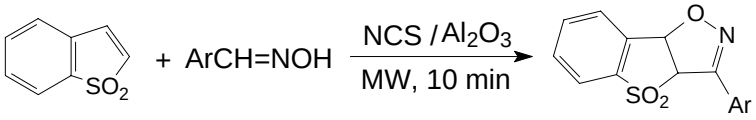
12a **12b**

X	Ratio **12a** : **12b**	Yield (%)
SO_2	100 / 0	85
CH_2	95 / 5	87



13a **13b**

Y	Z	Ratio **13a** : **13b**	Yield (%)
H	CO_2Bu-*n*	4 / 96	76
Ph	CO_2Et	70 / 30	75
Ph	COPh	25 / 75	67

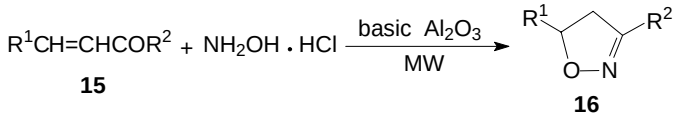


14

Ar	Yield (%)
Ph	84
p-MeC_6H_4	90
p-$MeOC_6H_4$	93
p-$NO_2C_6H_4$	95
o-ClC_6H_4	85
2,4,6-$(MeO)_3C_6H_2$	94
	87

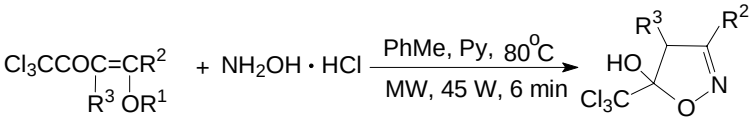
Scheme 10

Isoxazolines (**16, 18**) could also be obtained by the cyclocondensation of chalcones (**15**) and hydroxylamine hydrochloride on basic alumina [41] or 4-alkoxy-1,1,1-trichcloro-3-alken-2-ones (**17**) with hydroxylamine hydrochloride using toluene as solvent under microwave irradiation. [26] (Scheme 11) In classic heating, the reaction took 8-16 h to give 60-90% yield. However the reaction was completed in 6 min in a microwave oven. The average yields of products obtained by the microwave method were 10% higher than those obtained by the classic method. The advantages obtained by the use of microwave irradiation in relation to a classical method were demonstrated.



15 **16**

R^1	R^2	Yield (%)
p-$MeOC_6H_4$	Ph	63
	*p*-BrC_6H_4	67

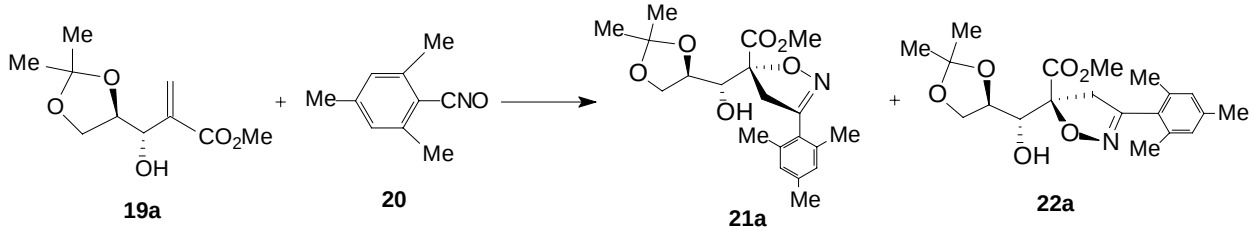


17 **18**

R^1	R^2	R^3	Yield (%)	
			Classical heating	MW
Et	H	H	78	78
Me	Me	H	82	95
Me	Et	H	86	90
Me	*n*-Pr	H	86	90
Me	*i*-Pr	H	81	95
Me	*Cyclo*-Pr	H	79	91
Me	*n*-Bu	H	80	85
Me	i-Bu	H	86	87
Me	*t*-Bu	H	81	95
Me	*n*-Hex	H	80	85
Me	Ph	H	90	90
Me	*p*-$NO_2C_6H_4$	H	87	82
H	-$(CH_2)_4$-		60	87

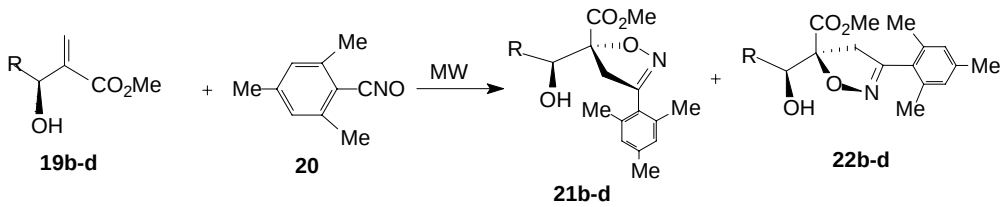
Scheme 11

Isoxazolines (**21, 22**) could also be prepared with 1,3-dipolar cycloaddition of mesitonotrile oxide (**19**) to Baylis-Hillman adducts (β-hydroxy-α-methylene esters) (**20**) proceeding regioselectively in good yields. Addition of Grignard reagent reversed the diastereoselectivity of the cycloaddition. If the reaction was completed at room temperature, longer reaction times are needed (24-78 h). When it was finished at 80℃, it still took 2-4 hour. It took only 1.5-4 min in a domestic microwave oven in an open vessel. So microwave irradiation strongly accelerated the reaction with only a small effect on its diastereoisomeric excess.[27, 28] (Scheme 12)



19a **20** **21a** **22a**

Lewis acid	Reaction time	Temperture	Yield (%)	Ratio **21** : **22**
-	2h	80℃	89	22 / 78
MeMgBr	48h	rt	50	95 / 5
MeMgBr	4min	MW	34	78 / 22

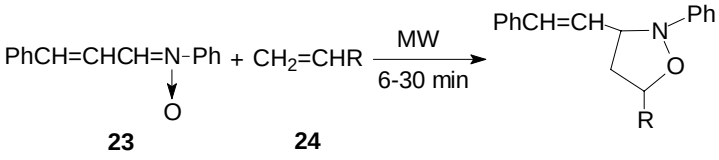


R	solvent	Lewis acid	Reaction time	Temperture	Yield (%)	Ratio **21** : **22**
	PhMe	-	2 h	80℃	92	26 / 74
	CH_2Cl_2	MeMgBr	43 h	rt	62	85 / 15
Ph	PhMe	-	4 h	80℃	92	42 / 58
Ph	CH_2Cl_2	MeMgBr	24 h	rt	57	61 /39
Ph	CH_2Cl_2	-	24 h	rt	96	48 / 52
Ph	PhCl	MeMgBr	4 min	MW	40	70 / 30
Ph	PhCl	-	1.5 min	MW	99	43 / 57
i-Pr	PhMe	-	2 h	80℃	99	5 / 95
i-Pr	CH_2Cl_2	MeMgBr	78 h	rt	35	95 / 5

Scheme 12

1.5 Syntheses of isoxazolidines

Baruah and coworkers [29] reported the first example of 1,3-dipolar cycloaddition reactions of unreactive nitrones (**23**) with typical unactivated alkenes (**24**) intermolecularly in a commercial microwave oven. The reaction proceeded efficiently in high yields at ambient pressure within few minutes and in the absence of solvent. In thermal heating, the reaction required 10 h - 4 d to give comparable yield. (Scheme 13)

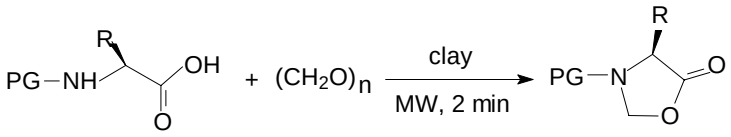


R	Yield (%)	
	MW	Classical method
Ph	90	80
CO_2Me	80	61
CN	80	66
p-MeC_6H_4	78	70
$ClCH_2$	76	65

Scheme 13

1.6 Syntheses of oxazolidinones

Reddy and coworkers [30] used microwave irradiation of *N*-protected 2-amino acids (**25**) and paraformaldehyde for 2 min to obtain the corresponding *N*-protected oxazolidinones (**26**) in excellent yields in microwave oven (600 W, operating at a frequence of 2450 MHz). (Scheme 14) This kind of reaction required 96 h with anhydrous magnesium sulfate in anhydrous dichloromethane at room temperature.[31]



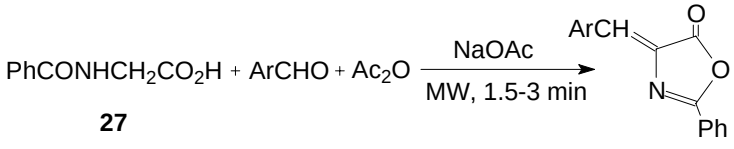
25 **26**

PG	R	Yield (%)
p-$MeC_6H_4SO_2$	Me	96
p-$MeC_6H_4SO_2$	Me_2CH	91
p-$MeC_6H_4SO_2$	Me_2CHCH_2	94
p-$MeC_6H_4SO_2$	$PhCH_2$	95
p-$MeC_6H_4SO_2$	$MeCH_2CHMe$	93
p-$MeC_6H_4SO_2$	$BnOC_6H_4CH_2$	95
MeCO	Me	92
MeCO	Me_2CH	90
MeCO	Me_2CHCH_2	93
MeCO	$PhCH_2$	91
PhCO	Me_2CH	93
PhCO	Me_2CHCH_2	92
PhCO	$PhCH_2$	94
PhCO	$MeCH_2CHMe$	91

Scheme 14

1.7 Syntheses of oxazolones

The cyclodehydration-condensation of hippuric (**27**), aromatic aldehydes and acetic anhydride took place easily and gave a series of 2-phenyl-4-arylidene-5(4*H*)-oxazolones (**28**) in good yields in the presence of sodium acetate in a domestic microwave oven.[32] In thermal condition, it needed 15 min to give comparable yield.[33] (Scheme 15)



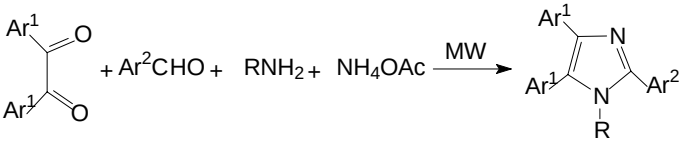
27 **28**

R	Yield (%)
Ph	78
p-ClC_6H_4	86
p-HOC_6H_4	85
o-HOC_6H_4	82
p-$NO_2C_6H_4$	89
p-$MeOC_6H_4$	73
PhCH=CH	66
2-Furyl	65

Scheme 15

1.8 Syntheses of imidazoles

The syntheses, reactions and biological properties of substituted imidazoles constitute a significant part of modern heterocyclic chemistry. Compounds with imidazole ring system have many pharmacological properties and play important roles in biochemical process.[34] The solvent-free microwave-assisted synthesis of substituted imidazoles was reported. Imidazoles (**29**) were obtained by the condensation of a 1,2-dicarbonyl compound with an aldehyde and an amine using acidic alumina, silica gel or Zeolite HY impregnated with ammonium acetate as the solid support.[35, 36] (Scheme 16)

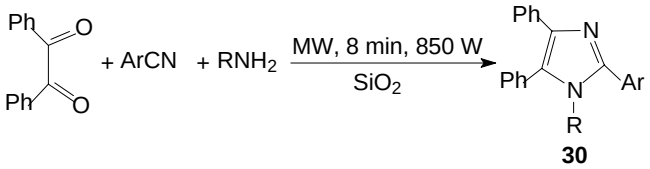


29

Ar^1	Ar^2	R	Yield (%)		
			SiO_2	Zeolite HY	Al_2O_3
Ph	Ph	Me	60	42	-
Ph	*p*-MeC_6H_4	Me	91	59	-
Ph	*p*-BrC_6H_4	Me	80	67	-
Ph	Ph	Et	74	56	-
Ph	*p*-MeC_6H_4	Et	70	77	-
Ph	*p*-BrC_6H_4	Et	62	82	-
Ph	Ph	*i*-Pr	81	71	-
Ph	Ph	CH_2=$CHCH_2$	85	57	-
Ph	*p*-BrC_6H_4	CH_2=$CHCH_2$	84	80	-
Ph	Ph	*i*-Bu	80	54	-
Ph	*p*-MeC_6H_4	*i*-Bu	85	54	-
Ph	Ph	C_6H_{11}	80	79	-
Ph	*p*-MeC_6H_4	C_6H_{11}	87	84	-
Ph	Ph	Ph	79	67	-
Ph	*p*-MeC_6H_4	Ph	74	83	-
Ph	Ph	$PhCH_2$	87	83	-
Ph	*p*-MeC_6H_4	$PhCH_2$	90	85	-
Ph	Ph	$PhCH_2CH_2$	-	-	80
Ph		$PhCH_2CH_2$	-	-	78
p-MeC_6H_4	Ph	$PhCH_2CH_2$	-	-	68
Ph	*p*-EtC_6H_4	*m*-$ClC_6H_4CH_2$	-	-	72

Scheme 16

Balalaie recently achieved a novel one-pot, three-component condensation of benzil, benzonitrile, derivatives and primary amines on the surface of silica gel with acidic character in a domestic microwave oven as a new efficient method to produce 1,2,4,5-tetrasubstituted imidazoles (**30**).[37] (Scheme 17) Carrying out the condensation in refluxing toluene for 29 h resulted in target compounds with comparable yields.

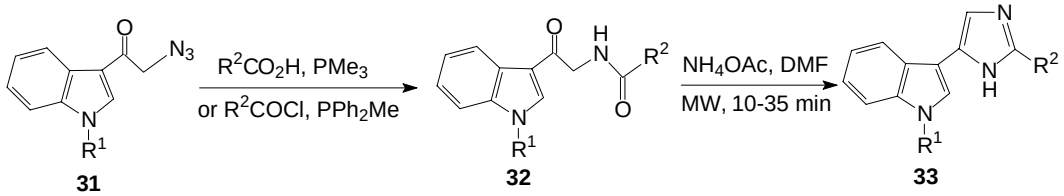


30

Ar	R	Yield (%)
Ph	$PhCH_2$	87
Ph	PhCHMe	92
p-MeC_6H_4	Me	78
p-MeC_6H_4	Et	87
p-MeC_6H_4	*i*-Bu	90
p-MeC_6H_4	$PhCH_2$	90
m-BrC_6H_4	$PhCH_2$	65
m-$NH_2C_6H_4$	$PhCH_2$	58

Scheme 17

Fresneda [38] described a two-step regioselective synthesis of 2,4-disubstituted imidazoles based on the reaction of α-azidoacetylindoles (**31**) with carboxylic acids in the presence of tertiary phosphines followed by cyclization of the resulting keto amides (**32**) by the action of ammonium acetate under microwave irradiation. The method was successfully applied to the synthesis of the antifungal nortopsentin D [2,4-bis(3-indolyl)imidazole]. Conversion of keto amides (**32**) into the correaponding 2, 4-disubstituted imidazoles (**33**) involved the use of ammonium acetate and heating of the resulting mixture. (Scheme 18) In thermal heating, the reaction required 12-16 h at 180℃ in dry DMF to give 25-75% yield. When the reaction was finished in a Synthewave 402 Prolabo microwave reactor (2.45 GHz, adjustable power within the range 0.300 W), it required for 10-35 min to give 50-75% yield.

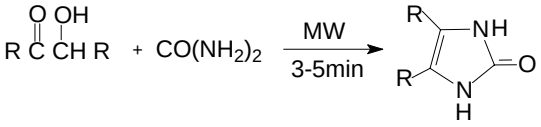


31 **32** **33**

R^1	R^2	Compound (**32**) Yield (%)	Compound (**33**) Yield (%)	
			Classical method	MW
Bn	3-indolyl	55	55	68
Bn	3-indolyl-CH_2	60	70	72
Bn	3-indolyl-CO	60	-	64
H	Me	75	50	67
H	$PhCH_2$	65	68	71
H	3-indolyl-CH_2	70	75	75
H	*m*-MeC_6H_4	55	70	73
H	2-Py	65	20	54
H	4-Py	71	72	50
H	3-indolyl	70	25	75

Scheme 18

The condensation of various acyloin with urea under microwave irradiation in the absence of solvent could give 4,5-disubstituted 4-imidazolin-2-ones (**34**).[39] Microwave irradiation was carried out with a modified domestic microwave oven for 3-5 min (2450 MHz, 500 W). The classic reaction conditions involved refluxing a mixture of an acyloin, urea in solvent with an acid as catalyst for 1-6 h. (Scheme 19)



34

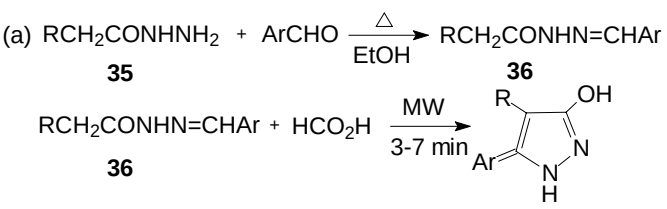
R	Yield (%)
Ph	65
2-Furyl	44
p-$MeOC_6H_4$	80
p-ClC_6H_4	61
m-ClC_6H_4	30
Et	54
n-Pr	51
-$(CH_2)_8$	40

Scheme 19

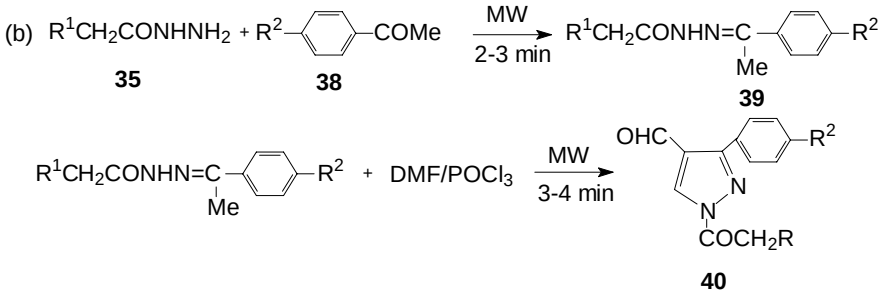
1.9 Syntheses of pyrazoles

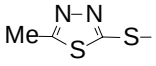
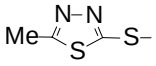
Kidwai and coworkers reported three methods to synthesize pyrazoles and pyrazoline:

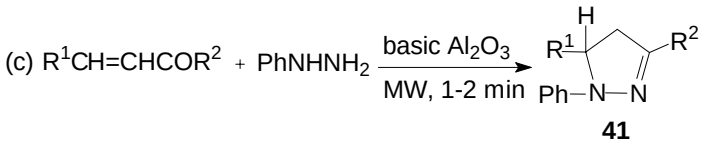
(a) Aromatic aldehydes were condensed with hydrazides (**35**) to the corresponding hydrazones (**36**) which were subsequently cyclized to give new pyrazoles (**37**) under microwave irradiation and conventional heating using formic acid. In classical approach cyclocondensation of hydrazones (**36**) required 30-35 h at 100-120℃, while the same reaction was completed in 4-7min with improved yield in a microwave oven. The reaction rate was enhanced about 250 times by using microwaves with improved yields in comparison with conventional method. All the compounds showed promising antifungal activity.[40] (b) Substituted aromatic aldehydes/ketones (**38**) reacted with hydrazides (**35**) to afford corresponding hydrazones (**39**). The hydrazones (**39**) on reacting with DMF/$POCl_3$ in a microwave oven afforded corresponding pyrazoles (**40**).[41] (c) The condensation of α,β-unsaturated ketone and phenylhydrazine could produce pyrazoline (**41**) on basic alumina for 1-2 min in a microwave oven.[42] In classic heating cyclocondensation of hydrazones required 3 h in refluxing acetic acid (48-68% yield), while the same reaction was completed in 1-2 min with improved yield (80-82%) when carried out in a microwave oven. (Scheme 20)



R	Ar	Yield (%)	
		Compound (**36**)	Compound (**37**)
PhO	*o*-HOC_6H_4	86	75
PhO	*o*-$HOC_{10}H_6$	90	83
PhO	*m*-$NO_2C_6H_4$	78	85
PhO	Ph	80	78
PhO	*p*-ClC_6H_4	88	77
PhO	*o*-$MeOC_6H_4$	80	78
C_8H_{17}	*o*-HOC_6H_4	73	79
C_8H_{17}	*o*-$HOC_{10}H_6$	83	80
C_8H_{17}	*m*-$NO_2C_6H_4$	80	86
C_8H_{17}	Ph	88	75
C_8H_{17}	*p*-ClC_6H_4	77	82
C_8H_{17}	*o*-$MeOC_6H_4$	82	80



R^1	R^2	Yield (%)	
		Compound (**39**)	Compound (**40**)
	H	85	75
	H	88	79
	Cl	98	80
	Cl	96	83

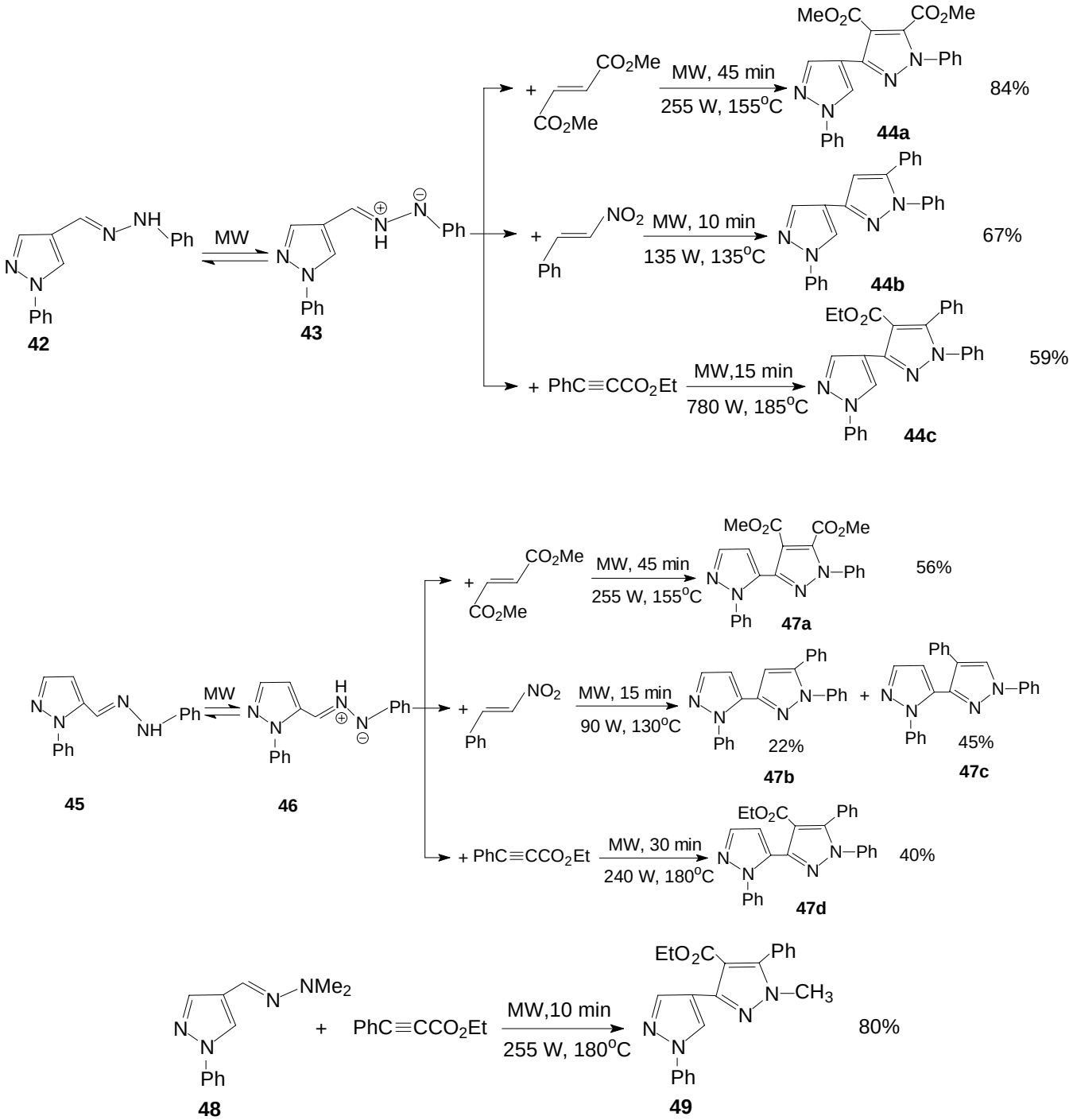


R^1	R^2	Yield (%)
p-$MeOC_6H_4$	Ph	82
	*p*-BrC_6H_4	80

Scheme 20

Arrieta and coworkers [43] reported a new approach for the preparation of bipyrazolyl derivatives by 1,3-dipolar cycloaddition under microwave irradiation. The irradiation produced the thermal isomerization of the pyrazolylhydrazones (**42, 45**) to the corresponding azomethine imines (**43, 46**). These

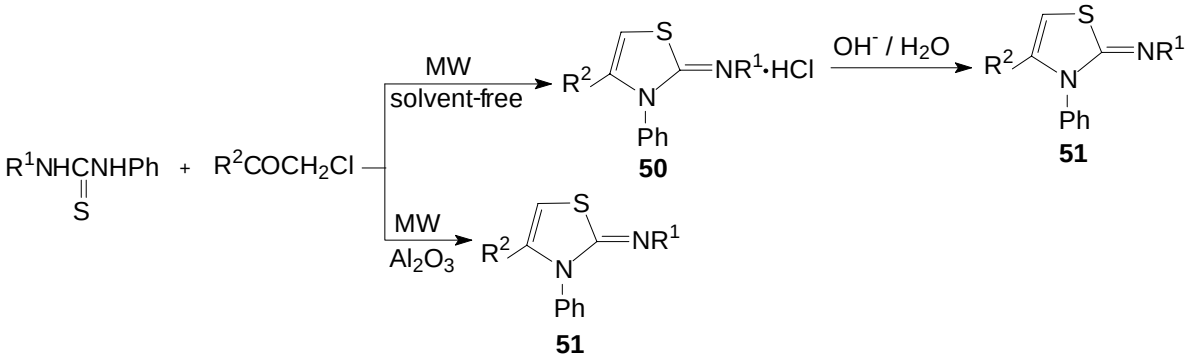
intermediates underwent 1,3-dipolar cycloaddition with double or triple bonded to afford bipyrazolyl adducts (**44, 47, 49**) in 10-45 min with 22-84% yield. (Scheme 21) Microwave irradiations were conducted in a domestic oven or a focused microwave reactor Prolabo MX350 with measurement and control of power and temperature by infrared detection. Here, the effect of microwave irradiation was not only a reaction acceleration but it induced the cycloaddition of dipolarophiles that did not react by classical heating under comparable reaction conditions.



Scheme 21

1.10 Syntheses of thiazolines

Several substituted thiazolines (**51**) were prepared by condensation of dissymmetric thioureas and α-chloro ketone under microwave irradiation in solvent-free conditions in 77-98% yield. Hydrochlorides precursors (**50**) were isolated. Microwave irradiation was introduced into a Synthewave 402 (Prolabo) single mode apparatus with a temperature monitored at 80℃ for 4-10 min. Under classical heating in same conditions, much lower yields (30-80%) were observed and reaction mixtures were not clean. Thiazolines (**51**) were obtained directly when reactions are performed over alumina.[44] In this case the comparison with classical heating had not been realized. (Scheme 22)

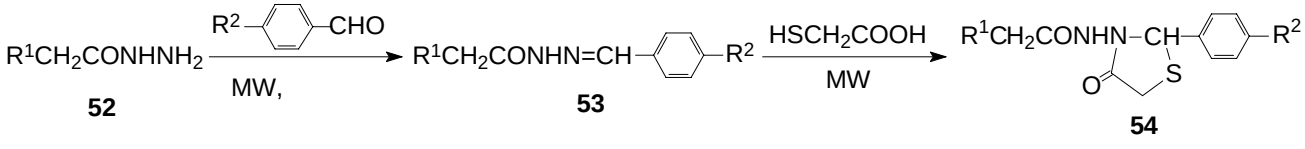


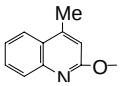
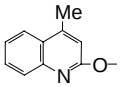
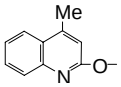
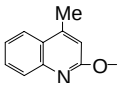
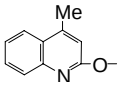
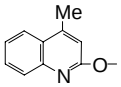
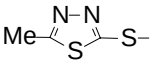
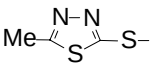
R^1	R^2	Yield (%)	
		MW	Classical heating
Me	Ph	95	65
Me	$PhCH_2$	98	70
Me	*i*-Pr	97	75
Me	*t*-Bu	90	70
Me	TMP	94	-
Me	1-Na	90	-
Ph	Ph	90	45
Ph	$PhCH_2$	85	30
Ph	*i*-Pr	90	80
Ph	*t*-Bu	82	40
Ph	TMP	77	-
Ph	1-Na	85	-

Scheme 22

1.11 Syntheses of thiazolidinones

Kidwai [45, 41] reported a microwave-assisted synthesis of thiazolidinones (**54**) by condensation of substituted acethydrazide (**52**) with aryl aldehydes followed by reaction with thioglycolic acid in dioxane or $ZnCl_2$ in DMF under microwave irradiation. (Scheme 23)

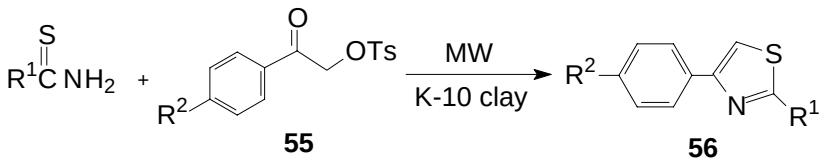


R^1	R^2	solvent	Compound (**54**) yield (%)	
			MW	Classical heating
	H	dioxane	85	72
	Cl	dioxane	89	76
	NO_2	dioxane	83	72
	Me	dioxane	92	79
	OH	dioxane	82	73
	OMe	dioxane	92	78
	H	$ZnCl_2$ / DMF	59	-
	H	$ZnCl_2$ / DMF	66	-
	OMe	$ZnCl_2$ / DMF	65	-
	OMe	$ZnCl_2$ / DMF	70	-

Scheme 23

1.12 Syntheses of thiazoles

The present solvent-free strategy for the synthesis of thiazoles involved a simple mixing of thioamides with α-tosyloxy ketones (**55**) in a clay-catalyzed reaction. The typical procedure entailed mixing of thioamides and *in situ* produced α-tosyloxy ketones with Montmorillonite K-10 clay in an open glass container. The reaction mixture was irradiated in a microwave oven for 2-5 min with intermittent irradiation and the product was extracted into ethyl acetate to afford substituted thiazoles (**56**) in 88-96% yields.[46] (Scheme 24) The reaction at 130℃ in an oil bath was completed in 15 min to afford products.

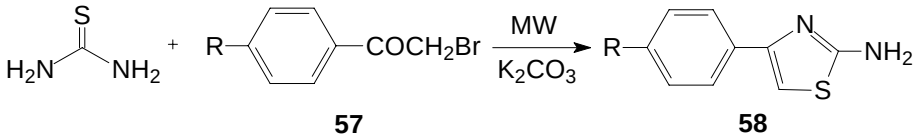


55 **56**

R^1	R^2	Yield (%)
H	Cl	90
H	OMe	91
Cl	Cl	94
Cl	OMe	96
Me	Cl	92
Me	OMe	92
OMe	Cl	90
OMe	OMe	88

Scheme 24

Microwave irradiation of thiourea and substituted α–bromoacetophenone (**57**), deposited over K_2CO_3, (approximate temperature 100-115℃) for about 2-3 min yielded the corresponding 2-amino thiazoles (**58**).[22] (Scheme 25)



57 **58**

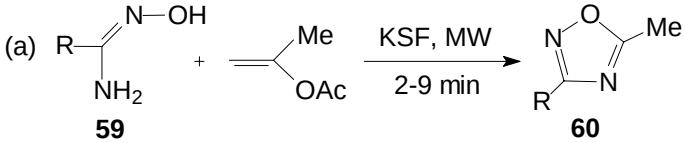
R	Yield (%)
Cl	94
NH_2	92

Scheme 25

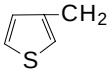
1.13 Syntheses of oxadiazoles

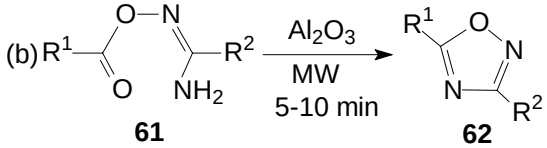
Oussaid [47] reported for the first time the synthesis of 1,2,4- and 1,3,4-oxadiazoles by microwave irradiation. At the same time, they compared the speeds of reactions performed in classical heating with those performed under microwave irradiation. 1,2,4-Oxadiazoles (**60, 62**) were prepared through two ways: (1) Oxime (**59**) reacted with isopropenyl acetate in the presence of KSF clay for 2-9 min under microwave (monomode, 40 W) or in a resonance cavity (150 W). In this case, the starting materials disappeared at the same speed (9 min) in classical heating (T=95℃) or under microwave irradiation (ending temperature T=95℃). (2) An *O*-acylated amidoxime (**61**) adsorbed on alumina was irradiated for 5-10 min in a commercial oven to give 58-95% yield. In classical heating, it was completed in 40 h at 110℃ in the toluene.

1,3,4-Oxadiazoles (**64**) were prepared in 5-7 min by microwave irradiation of bisacylhydrazines (**63**) and thionyl chloride. Microwave irradiation was induced in a focussed microwave oven (Maxidigest, Prolabo). The reaction took place with the same speed (7 min) in conventional heating (T=95℃) or under microwave irradiation (ending temperature T=95℃). (Scheme 26)

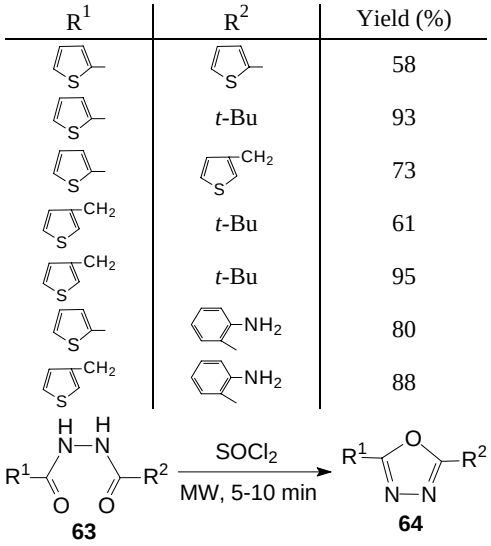


59 **60**

R	Yield (%)
	50
	67



61 **62**

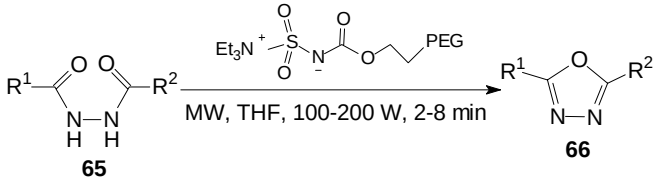


R^1	R^2	Yield (%)
2-Thienyl	2-Thienyl	58
2-Thienyl	*t*-Bu	93
2-Thienyl	2-Thienylmethyl	73
2-Thienylmethyl	*t*-Bu	61
2-Thienylmethyl	*t*-Bu	95
2-Thienyl	2-Aminophenyl	80
2-Thienylmethyl	2-Aminophenyl	88

R^1	R^2	Yield (%)
2-Thienyl	Me	83
2-Thienyl	2-Thienyl	92
2-Thienyl	Ph	78

Scheme 26

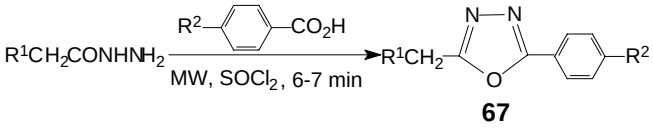
Brain [48] devised a novel and efficient synthesis of 1,3,4-oxadiazoles (**66**) in high yields and purities by cyclodehydration of 1, 2-diacylhydrazines (**65**) using polymer-supported Burgess Reagent under single-mode microwave conditions. The experimental procedure was simple, did not involve tedious purification, and avoided the use of harsh reagents. (Scheme 27) In the case when the crude reaction mixture was refluxed for 3 h, there was only 40% conversion to the target compounds. Under microwave irradiation, the mixture was irradiated for 2 min to give 96% products.



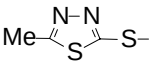
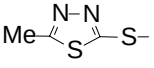
R^1	R^2	Yield (%)
Ph	Ph	96
Ph	Me	75
o-$MeOC_6H_4$	Me	89
m-$MeOC_6H_4$	Me	95
p-$MeOC_6H_4$	Me	86
o-ClC_6H_4	Me	70
o-$NO_2C_6H_4$	Me	95
o-HSC_6H_4	Ph	95
2-Furyl	Ph	86
3-Py	Ph	95
4-Py	PhNH	95
3-NO_2-4-ClC_6H_3	Ph	90
$PhSO_2CH_2$	Me	87

Scheme 27

Kidwai also gave a method to synthesize 1,3,4-oxadiazoles (**67**) by condensation of substituted hydrazides and aromatic acids in the presence of thionyl chloride under microwave irradiation.[41] (Scheme 28)



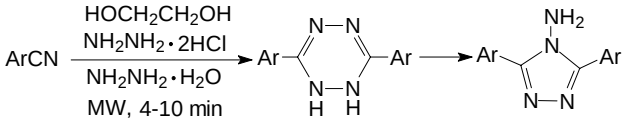
67

R^1	R^2	Yield (%)
	H	70
	H	68
	4-Cl	75
	4-Cl	80

Scheme 28

1.13 Syntheses of 1, 2, 4-triazoles

A number of symmetrically 3,5-disubstituted 4-amino-1,2,4-triazoles (**68**) were quickly prepared by the reaction of aromatic nitriles on hydrazine dihydrochloride in the presence of an excess of hydrazine hydrate in ethylene glycol under microwave irradiation.[49] Microwave irradiation was induced for 4-10 min at 130℃ (60 W) in a Synthewave 402 monomode microwave oven with a reflux condenser. (Scheme 29) Under classical heating in a high boiling polar solvent such as ethylene or diethylene glycol, it required much longer times (45-60 min) at 130℃ to obtain comparable yield.



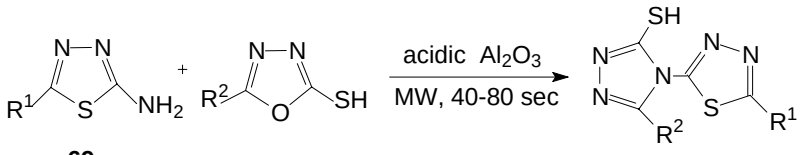
68

Ar	Yield (%)
Ph	92
4-MeC_6H_4	66
4-$H_2NC_6H_4$	70
4-HOC_6H_4	96
3-MeO-4-HOC_6H_3	79
4-$MeOC_6H_4$	73
4-ClC_6H_4	63
2-Py	95
4-Py	58

Scheme 29

Kidwai also gave a novel synthetic method for the synthesis of 1,2,4-triazole (**70**) starting from 1,3,4-thiadiazoles (**69**) by adsorbing on acidic alumina in a microwave oven.[50] The reaction time was

brought down from hours (10-18 h) to seconds (40-80 sec) with improved yield (classical heating: 65-80%; MW: 77-93%) using solid support coupled with MW as compared to conventional heating. (Scheme 30)



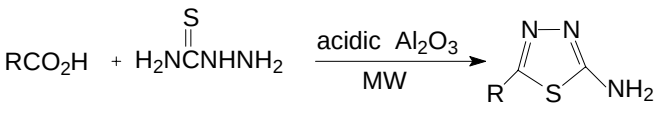
69 **70**

R^1	R^2	Yield (%)
Me	C_7H_{15}	92
Me	C_9H_{19}	93
Me	$C_{11}H_{23}$	92
C_7H_{15}	C_7H_{15}	89
C_7H_{15}	C_9H_{19}	93
C_7H_{15}	$C_{11}H_{23}$	86
C_9H_{19}	C_7H_{15}	87
C_9H_{19}	C_9H_{19}	79
C_9H_{19}	$C_{11}H_{23}$	77
$C_{11}H_{23}$	C_7H_{15}	83
$C_{11}H_{23}$	C_9H_{19}	89
$C_{11}H_{23}$	$C_{11}H_{23}$	83

Scheme 30

1.14 Syntheses of 1, 3, 4-thiadiazoles

Kidway [50] at the same time decribed a novel synthetic method for the synthesis of 1,3,4- thiadiazoles (**69**) from acid and thiosemicarbazide on acidic alumina under microwave irradiation within 40-80 seconds. (Scheme 31) And the reaction time was also brought down from hours (5-7 h) to seconds (40-80 sec) with improved yield (classical heating: 69-80%; MW: 83-93%) using solid support coupled with MW as compared to conventional heating.



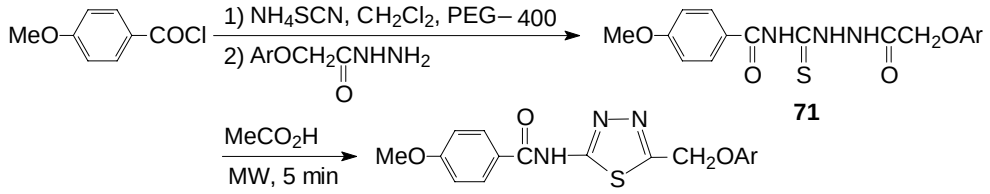
69

R	Yield (%)	
	MW	Classical heating
Me	89	70
C_7H_{15}	83	69
C_9H_{19}	86	72
$C_{11}H_{23}$	93	80

Scheme 31

Li and coworkers [51] introduced a rapid, efficient microwave-assisted method to prepare new 2,5-disubstituted 1,3,4-thiadiazoles (**72**) from 1, 4-disubstituted thiosemecarbazides (**71**), with the objective of obtaining new biologically active compounds. Reactions of 4-methoxylbenzoyl chloride with

ammonium thiocyanate first, then with aryloxyacetic acid hydrazides under the condition of phase transfer catalysis at room temperature gave 1-aryloxyacetyl-4-(4-methoxylbenzoyl)thiosemicarbazides (**71**). The mixture of compounds (**71**) and excess glacial acetic acid on exposure to microwave irradiation in a commercial microwave oven led to the formation of 2-(4-methoxylbenzoylamido)-5-aryloxymethyl-1,3, 4-thiadiazoles (**72**) in good yields. (Scheme 32) In classical heating, substituted 1,3,4-thiadiazoles could be obtained in 68-77% yield after refluxing for 6 hours at 118℃.

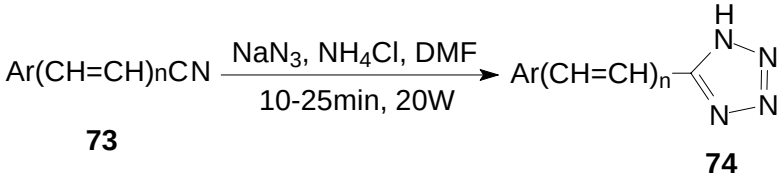


Ar	Yield (%)
Ph	88
2-MeC_6H_4	85
3-MeC_6H_4	87
4-MeC_6H_4	89
4-$MeOC_6H_4$	86
2-ClC_6H_4	82
4-ClC_6H_4	89
2,4-$Cl_2C_6H_3$	86
1-Na	86
2-Na	90
2-$NO_2C_6H_4$	90
3-$NO_2C_6H_4$	91
4-$NO_2C_6H_4$	92

Scheme 32

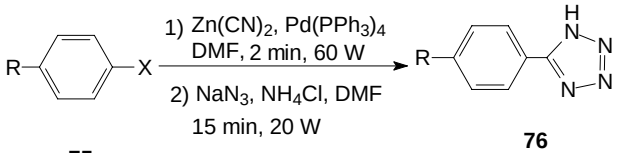
1.15 Syntheses of tetrazoles

Hallberg [52] reported the synthesis of aryl and vinyl tetrazole (**74**) by the conversion of aryl and vinyl nitriles (**73**) by cycloaddition reactions under microwave irradiation. One-pot transformation of aryl halides (**75**) directly to the aryltetrazoles (**76**) could be accomplished both in solution and on solid support. All reactions were completed in minutes (10-25 min) rather than in hours or days (3-96 h) as previously reported with the standard thermal heating technique. (Scheme 33)

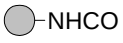


73 **74**

n	Ar(CH=CH)n	Yield (%)
0	4-$MeOC_6H_4$	96
0	4-$NO_2C_6H_4$	95
0	4-MeC_6H_4	91
0	2-Na	48
0	2-Ph C_6H_4	36
0	3-Py	75
0		98
1	PhCH=CH	60



75 **76**

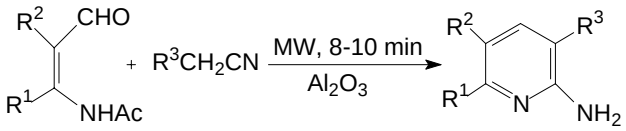
X	R	Yield (%)
Br	H	96
I		72

Scheme 33

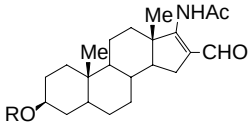
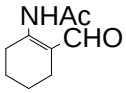
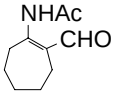
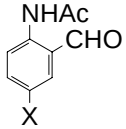
2. Syntheses of six-membered heterocycles

2.1 Syntheses of pyridines

Boruah and coworkers [53] described a simple, facile method for the high yield synthesis of pyridine hybrids (**79**) *via* a one-pot reaction. The starting materials were easily accessible from conjugated oximes or enamides. Furthermore, the reaction was advantageous for being carried out rapidly in dry media under microwave irradiation, thus avoiding harsh reaction conditions. (Scheme 34)

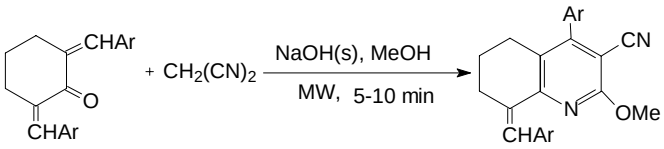


77 **78** **79**

Compound (**77**)		R^3	Yield (%)
	R=Ac	CN	88
	R=Bz	CN	85
	R=Ac	CO_2Et	83
	R=Bz	CO_2Et	81
		CN	86
		CO_2Et	85
		CN	86
		CO_2Et	82
	X=H	CN	84
	X=H	CO_2Et	83
	X=Cl	CN	81
	X=Cl	CO_2Et	82

Scheme 34

Pyridine derivatives (**81**) could also be obtained in single step action of 2,6-bisarylidenecyclohexanone (**80**) on malononitrile in sodium hydroxide/methanol under microwave irradiation in good yields.[54] In classical heating, it required 3 h to give 70-85% yield. (Scheme 35)

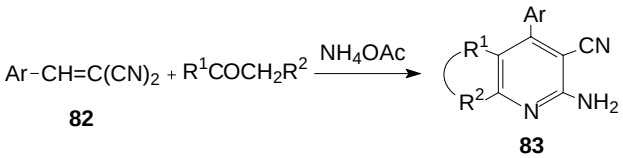


80 **81**

Ar	Yield (%)	
	MW	Classical heating
Ph	92	80
4-ClC_6H_4	91	70
4-$MeOC_6H_4$	98	85

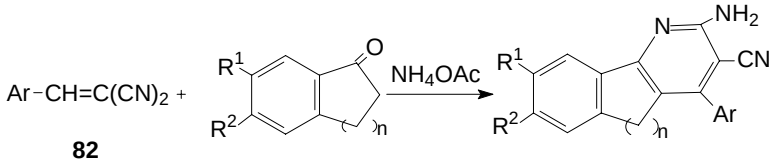
Scheme 35

Paul and coworkers reported a simple method for the rapid synthesis of 2-amino-3-cyanopyridines (**83, 84**) from arylidenemalanonitriles (**82**) and ketones in presence of ammonium acetate without solvent or containing traces of solvent under microwave irradiation. Reaction times were considerably reduced with improved yields as compared to those obtained in classical heating.[55] In the classical approach, the synthesis of target compounds required 5-8 h refluxing in benzene in 46-69% yield. When the reaction was performed in a microwave oven, it required 3-4.5 min with improved yields. (Scheme 36)



82 **83**

Ar	R^1	R^2	Yield (%)		
			MW		Classical heating
			Without solvent	Trace solvent	
Ph	Ph	H	52	72	49
4-$MeOC_6H_4$	Ph	H	43	75	46
Ph	-$(CH_2)_4$-		58	78	69
4-$MeOC_6H_4$	-$(CH_2)_4$-		52	69	46

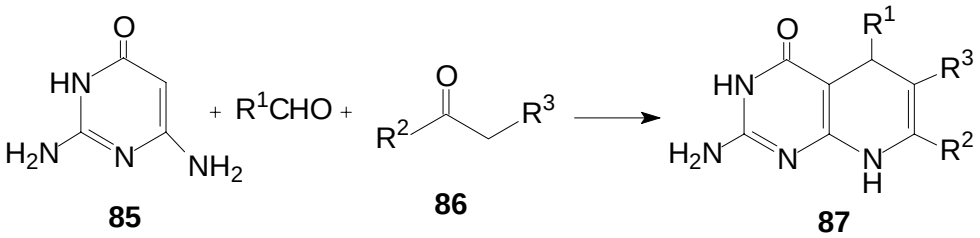


82 **84**

n	Ar	R^1	R^2	Yield (%)		
				MW		Classical heating
				Without solvent	Trace solvent	
2	Ph	H	H	51	70	52
2	4-$MeOC_6H_4$	H	H	50	78	55
1	Ph	OEt	OMe	42	72	46
1	4-$MeOC_6H_4$	OEt	OMe	52	70	48

Scheme 36

Three-component cyclocondensation of 2,6-diaminopyrimidin-4-one (**85**), 1,3-dicarbonyl compounds or benzoylacetonitrile (**86**) and aromatic or aliphatic aldehydes in the presence or absence of zinc(II) bromide proceeds under microwave-assisted conditions gave 5-deaza-5,8-dihydropterins (**87**) in good yields and with total control of regiochemistry. [56] Different reaction conditions were compared in the presence or absence of zinc(II) bromide at 160℃ for 20 min under microwave-assisted conditions and at 110℃ for 3 days in standard thermal conditions. (Scheme 37)

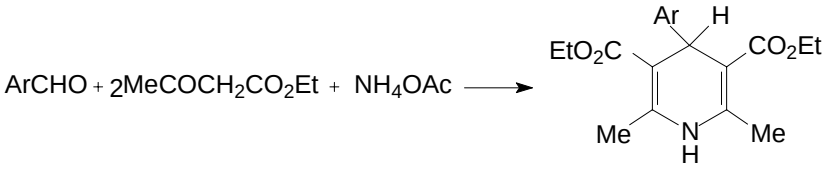


85 **86** **87**

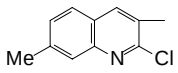
R^1	R^2	R^3	Lewis acid	Yield (%)	
				MW	Classical heating
Ph	Me	CO_2Et	None	53	0
Ph	Me	CO_2Et	$ZnBr_2$	80	65
Me	Me	CO_2Et	None	83	60
Me	Me	CO_2Et	$ZnBr_2$	55	42
$MeCH_2CH_2$	Me	CO_2Et	None	80	94
$MeCH_2CH_2$	Me	CO_2Et	$ZnBr_2$	60	63
4-$MeOC_6H_4$	Me	CO_2Et	None	65	0
4-$MeOC_6H_4$	Me	CO_2Et	$ZnBr_2$	75	68
4-ClC_6H_4	Me	CO_2Et	$ZnBr_2$	91	85
2-$NO_2C_6H_4$	Me	CO_2Et	$ZnBr_2$	80	65
Ph	Ph	CO_2Et	$ZnBr_2$	80	53
Ph	Ph	CN	$ZnBr_2$	91	86
Ph	Ph	CN	None	85	81
Ph	Me	$CONH_2$	$ZnBr_2$	59	14
4-$MeOC_6H_4$	Ph	CO_2Et	$ZnBr_2$	79	35
4-$MeOC_6H_4$	Ph	CO_2Et	None	51	24
$MeCH_2CH_2$	Ph	CO_2Et	None	43	19

Scheme 37

1,4-Dihydropyridines (1,4-DHP) have well known pharmacologically activity. [57] The products (**88**) were obtained in good yields when the reactions were carried out over both acidic and neutral alumina, but better results were obtained when neat reactants (ethyl acetoacetate, aldehyde and ammonium acetate) were subjected to microwave irradiation.[58] The reaction shorted the reaction time with improved yield under microwave irradiation compared to the classical condition. (Scheme 38)



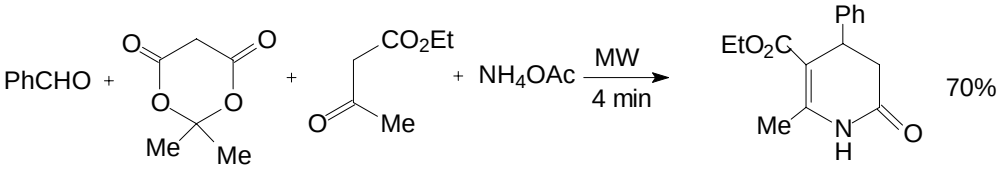
88

Ar	Time			Yield (%)		
	MW (min)		Classical heating (h)	MW		Classical heating
	Solid support	Neat reactants		Solid support	Neat reactants	
Ph	3.0	2.5	12	85	90	50
2-Furyl	2.5	2.0	13	82	87	47
2-Indolyl	6.0	4.5	8	81	86	50
piperonyl	6.5	5.0	24	83	88	77
	7.0	5.5	24	80	85	40

Scheme 38

2.2 Syntheses of pyridinones

Substituted dihydropyridinone (**89**) was synthesized by reaction of benzaldehyde, ethyl acetoacetate, ammonium acetate, and isopropylidene malonate in a modified microwave oven.[59] In classical heating, it was refluxed for 6 h in ethanol to give only 15-27% yield. [60] (Scheme 39)

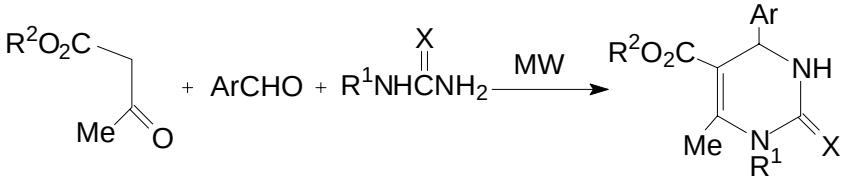


89

Scheme 39

2.3 Syntheses of pyrimidin-2-ones / thiones

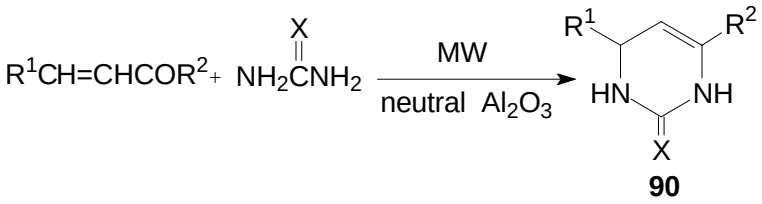
The synthesis of Biginelli compounds was accelerated by microwave irradiation, in one-pot reaction between β-keto esters, aryl aldehydes, and substituted urea. The reaction could be finished in solvent-free conditions in a sealed vessels;[61] using various acid catalysts like Amberlyst-15, Nafion-H, KSF clay or dry acetic acid; [62] using ethanol as energy transfer medium in unsealed vessels;[63, 64] using $FeCl_3$ as catalyst on silica gel;[65] using ethanol as energy transfer medium and concentrated HCl as catalyst;[66] using neat starting materials without solid support, solvent or acid or on solid support under microwave irradiation after titurating with a few drops of MeOH.[57] (Scheme 40)



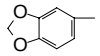
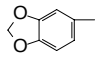
Ar	R^1	R^2	X	Lewis acid	Yield (%)
3-$NO_2C_6H_4$	H	Me	O	-	66
4-ClC_6H_4	H	Me	O	-	68
2,4-$Cl_2C_6H_3$	H	Me	O	-	48
2-ClC_6H_4	H	Me	O	-	66
Ph	H	Me	O	-	30
2,6-$Cl_2C_6H_4$	H	Me	O	-	51
2-Furyl	H	Me	O	-	40
Ph	H	Et	O	HCO_2H	86
4-$NO_2C_6H_4$	H	Et	O	HCO_2H	88
4-ClC_6H_4	H	Et	O	HCO_2H	84
2,3-$Cl_2C_6H_3$	H	Et	O	HCO_2H	82
4-MeC_6H_4	H	Et	O	HCO_2H	85
4-$MeOC_6H_4$	H	Et	O	HCO_2H	88
3-$NO_2C_6H_4$	H	Et	O	HCO_2H	90
2-Na	H	Et	O	HCO_2H	88
2-Thienyl	H	Et	O	HCO_2H	97
Piperonyl	H	Et	O	HCO_2H	87
3,4-$(MeO)_2C_6H_3$	H	Et	O	HCO_2H	85
2,6-$Cl_2C_6H_3$	H	Et	O	HCO_2H	82
4-HOC_6H_4	H	Et	O	HCO_2H	86
Ph	H	Et	O	EtOH	90
4-$MeOC_6H_4$	H	Et	O	EtOH	98
4-HOC_6H_4	H	Et	O	EtOH	87
4-$NO_2C_6H_4$	H	Et	O	EtOH	70
3-$NO_2C_6H_4$	H	Et	O	EtOH	88
3,4-$(MeO)_2C_6H_3$	H	Et	O	EtOH	96
3,4-$(OCH_2O)C_6H_3$	H	Et	O	EtOH	85
4-HO-3-MeO C_6H_3	H	Et	O	EtOH	90
2,3-$Cl_2C_6H_3$	H	Et	O	EtOH	85
2,4,6-$(MeO)_3C_6H_2$	H	Et	O	EtOH	70
Ph	H	Et	S	EtOH	90
4-$MeOC_6H_4$	H	Et	S	EtOH	99
3-MeC_6H_4	H	Et	S	EtOH	88
2-$NO_2C_6H_4$	H	Et	S	EtOH	50
3,4-$(MeO)_2C_6H_3$	H	Et	S	EtOH	90
2,3-$Cl_2C_6H_3$	H	Et	S	EtOH	90
Ph	2-$CF_3C_6H_4$	Et	S	EtOH	86
4-FC_6H_4	2-$CF_3C_6H_4$	Et	S	EtOH	65
3-$NO_2C_6H_4$	4-FC_6H_4	Et	S	EtOH	70
4-$MeOC_6H_4$	4-FC_6H_4	Et	S	EtOH	75
Ph	4-FC_6H_4	Et	S	EtOH	82
4-FC_6H_4	Ph	Et	S	EtOH	88
4-FC_6H_4	H	Et	S	EtOH	81
3-$NO_2C_6H_4$	H	Et	S	EtOH	78
4-FC_6H_4	H	Et	O	EtOH	86
3-FC_6H_4	H	Et	O	EtOH	80
Ph	H	*n*-Bu	O	$FeCl_3$, SiO_2	91
3-$NO_2C_6H_4$	H	Et	O	$FeCl_3$, SiO_2	93
2-ClC_6H_4	H	Et	O	$FeCl_3$, SiO_2	88
4-$Me_2NC_6H_4$	H	Et	O	$FeCl_3$, SiO_2	92
4-HOC_6H_4	H	Et	O	$FeCl_3$, SiO_2	91
Ph	H	*i*-Pr	O	$FeCl_3$, SiO_2	89
2-ClC_6H_4	H	*n*-Bu	O	$FeCl_3$, SiO_2	90
4-$MeOC_6H_4$	H	*i*-Pr	O	$FeCl_3$, SiO_2	92

Scheme 40

Substituted pyrimidin-2-ones / thione (**90**) could also be obtained by the condensation of α,β-unsaturated ketone and urea/thiourea in dry conditions under microwave irradiation.[42] In classical heating, it required 4.5-5 h to give 59-72% yield. In contrast, it only required 2-6 min with improved yield under microwave irradiation. (Scheme 41)



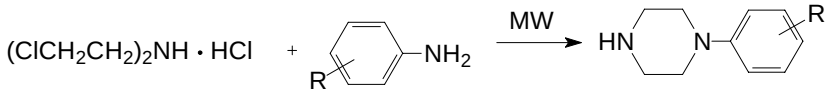
90

R^1	R^2	X	Yield (%)
p-$MeOC_6H_4$	Ph	O	69
	*p*-BrC_6H_4	O	80
p-$MeOC_6H_4$	Ph	S	78
	*p*-BrC_6H_4	S	85

Scheme 41

2.4 Syntheses of 1-arylpiperazines

1-Arylpiperazines (**92**) were synthesized easily under microwave irradiation from bis(2-chloroethyl)amine hydrochloride (**91**) and substituted anilines without any solvent. The reaction time was just 1-3 min. 1-Arylpiperazines were synthesized in 53-73% yields. Potent serotonin ligands like trifluoromethylphenylpiperazine (TFMPP) and 3-chlorophenylpiperazine (*m*CPP) were also prepared in just 1 min and 2 min respectively.[67] In classical heating, when basic alumina was used as solid support, it took 40 min at 150℃ to give 70-80% yield.[68] (Scheme 42)



91 **92**

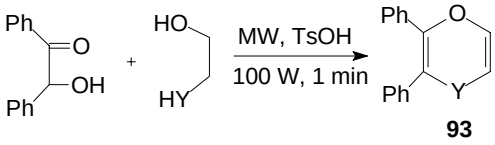
R	Yield (%)
H	73
3-Cl	57
4-Cl	47
2-CN	53
3-CF_3	56
4-Me	56
4-COMe	59

Scheme 42

2.5 Syntheses of dioxene and oxathiin

5,6-Dihydro-2,3-diphenyl-1,4-dioxene and 5,6-dihydro-2,3-diphenyl-1,4-oxathiin (**93**) were synthesized by the condensation of benzoin with ethylene glycol or 2-mercaptoethanol under microwave irradiation.

The reaction time was shorted about 300-fold and the yield was improved in comparision with classical method.[69] (Scheme 43)



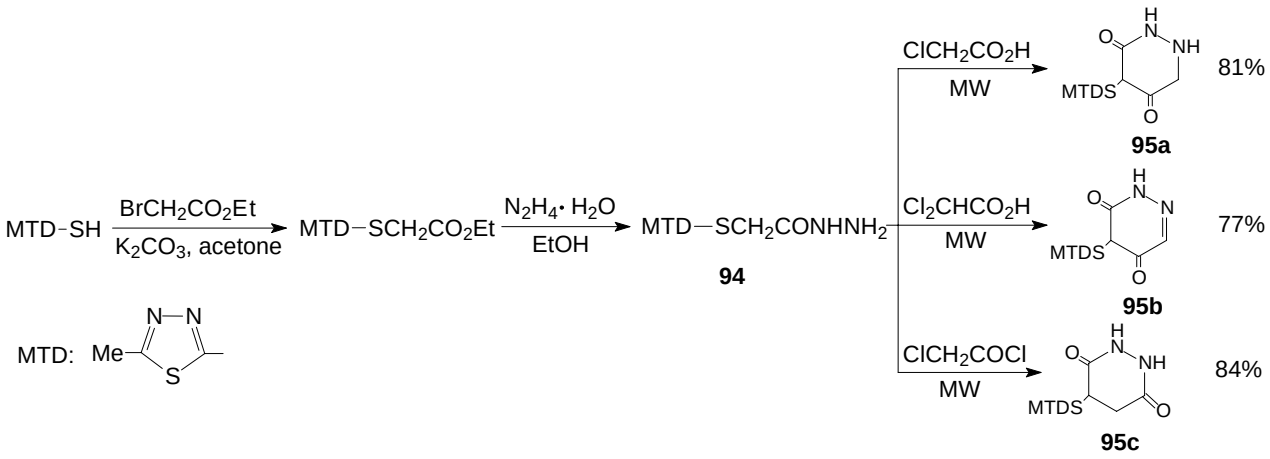
93

Y	Yield (%)
O	95
S	65

Scheme 43

2.6 Syntheses of pyridazinones

5-Methyl-1,3,4-thiadiazol-2-ylsulfanylacetohydrazide (**94**) was prepared and allowed to react with chloroacetic acid, dichloroacetic acid, and chloroacetyl chloride to yield the pyridazinones (**95**) under microwave irradiation.[70] Under microwave irradiation, the reaction required only 1-2 min.(Scheme 44)



94

95a

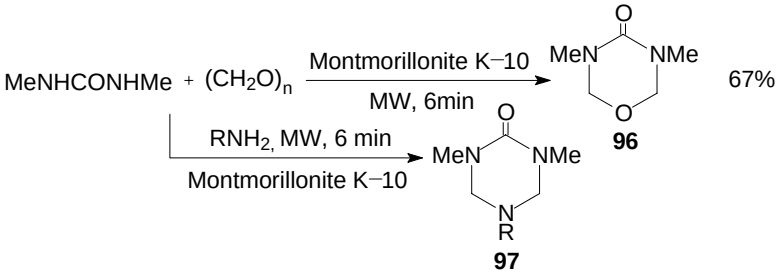
95b

95c

Scheme 44

2.7 Syntheses of triazones and 4-oxooxadiazinanes

Condensation of *N, N*'-dimethylurea with paraformaldehyde, supported on montmorillonite K-10 in dry media (without solvent and mineral acid) using microwave irradiation gave 4-oxooxadiazinane (**96**), and three component condensation of dimethylurea, paraformaldehyde and primary amines using Montmorillonite K-10 as solid support in dry media under microwave irradiation led to triazones (**97**) in high yields. [71] A domestic microwave at 2450 MHz (850 W) was used in all experiments. (Scheme 45)



96

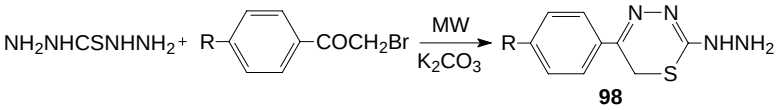
97

R	Yield (%)
Me	71
Et	76
n-Pr	79
i-Pr	83
n-Bu	84
t-Bu	74

Scheme 45

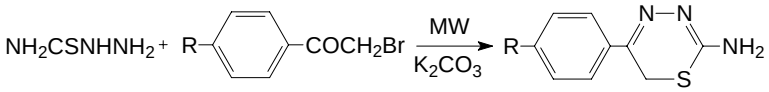
2.8 Syntheses of (thia/oxa)diazines

Thiadiazines are therapeutically important class of compounds. Reaction of thiocarbohydrazide with α–bromoacetophenone, deposited over K_2CO_3, (approximate temperature 100-115℃) for about 2-3 min, gave 2-hydrazinothiadiazines (**98**). On the other hand, reaction with (thio)semicarbazide, which was unsymmetrically substituted at the (thio)carbonyl with a hydrazine and an amino group, produced thiadiazines (**99**) in good yield.[22] Under conventional heating the K_2CO_3 mediated reaction was not facile and gave very impure product after 6-7 hours of heating over oil bath. (Scheme 46)



98

R	Yield (%)
NH_2	95
Cl	86



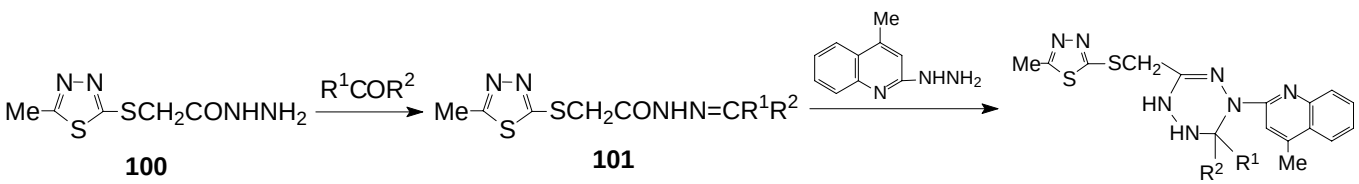
99

R	Yield (%)
NH_2	90
Cl	90

Scheme 46

2.9 Syntheses of tetrazines

5-Methyl-1,3,4-thiadiazol-2-ylsulfanylacetohydrazide (**100**) was prepared and allowed to react with substituted benzaldehydes or acetophenones to yield the hydrazones (**101**). These hydrazones, on condensation with 2-hydrazino-4-methylquinoline under microwave irradiation and by conventional methods, yielded the tetrazines (**102**). In comparision with the conventional method the reaction rate was enhanced about 250 times by using microwaves and yields were improved.[70] (Scheme 47)



100 **101** **102**

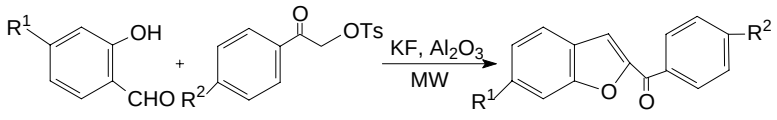
R^1	R^2	Time		Yield (%)	
		MW (min)	Classical heating (h)	MW	Classical heating
H	Ph	7	28	56	35
H	4-ClC_6H_4	5	24	58	37
H	3-$NO_2C_6H_4$	7	27	59	41
H	2- $NO_2C_6H_4$	6	26	62	39
H	4-$NO_2C_6H_4$	6	27	57	40
H	4-HOC_6H_4	8	29	51	32
H	3,4-$(MeO)_2C_6H_3$	7	28	55	35
H	3,4-(OCH_2O) C_6H_3	8	30	58	35
Me	Ph	8	31	63	40
Me	4-ClC_6H_4	8	31	64	41

Scheme 47

3. Syntheses of benzoheterocycles

3.1 Syntheses of benzofurans

Benzofurans encompass a large group of naturally occurring compounds which display a wide variety of pharmacological activity.[71] A simple preparation of 2-aroylbenzo[*b*]furan (**103**) proceeded readily *via* the condensation of *in situ* generated α-tosyloxy ketones with a variety of salicylaldehydes on potassium fluoride doped alumina and the process avoided the use of lachrymatory starting materials. The reactions were finished in 2.5-3.5 min in an unmodified household microwave oven.[46] (Scheme 48)

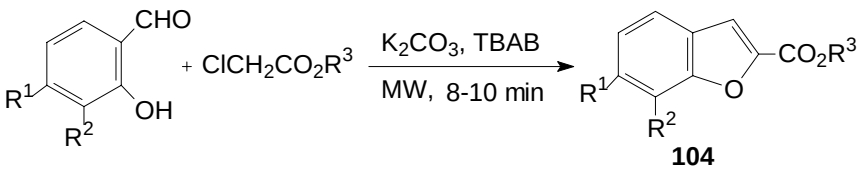


103

R^1	R^2	Time (min)	Yield (%)
H	H	3	94
Cl	H	3	94
Me	H	2.5	91
OMe	H	3.5	89
H	Cl	2.5	95
Cl	Cl	2.5	92
Me	Cl	2.5	96
OMe	Cl	3.5	89

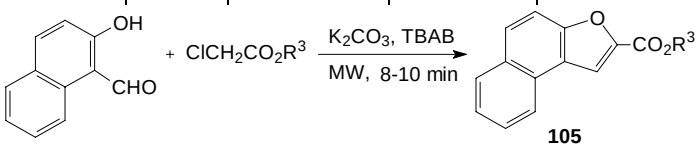
Scheme 48

Condensation of salicylaldehyde and its derivatives with various esters of chloroacetic acids in the presence of tetrabutylammonium bromide (TBAB) led to the syntheses of benzofurans (**104, 105**) by a solventless phase-transfer catalytic (PTC) reaction under microwave irradiation.[73] (Scheme 49)



104

R^1	R^2	R^3	Time (min)	Yield (%)
H	H	Et	8	65
H	OMe	Et	8	68
Et_2N	H	Et	8	82
H	H	CH_2=$CHCH_2$	10	85
H	OMe	CH_2=$CHCH_2$	10	91
Et_2N	H	CH_2=$CHCH_2$	10	72
H	H	cyclohexyl	10	96
H	OMe	cyclohexyl	8	78
Et_2N	H	cyclohexyl	10	88



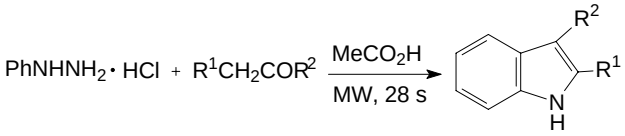
105

R^3	Time (min)	Yield (%)
Et	8	69
CH_2=$CHCH_2$	10	79
cyclohexyl	8	94

Scheme 49

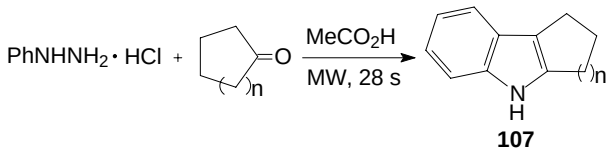
3.2 Syntheses of indoles

Microwave irradiation was applied to Fisher-indole synthesis which was one of the important processes in organic synthesis. The process could produce indoles with different substituents at 2- and 3-positions. Sridar reported a one-pot synthesis of indoles in acetic acid medium from phenylhydrazine hydrochloride with various ketones in a microwave oven in a much shorter time (28 sec, 700 W). The reaction required 3 h at 90℃ to give 40-75% yield in classical heating. It was found that there was a rate acceleration of 385 fold under microwave conditions over thermal process.[74] (Scheme 50)



106

R^1	R^2	Yield (%)	
		MW	Thermal heating
Me	Me	50	63
Me	Et	63	68
i-Pr	Me	63	64
H	Ph	65	55
Ph	Me	68	60

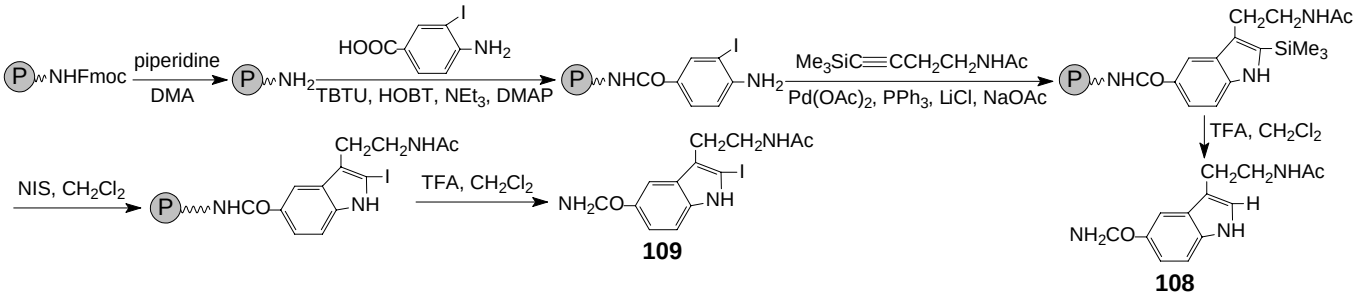


107

n	Yield (%)	
	MW	Thermal heating
1	53	40
2	90	75
3	68	65
4	67	65

Scheme 50

The synthesis of indole skeleton of new melatoninergic analogues (**108, 109**) was realized using solid-phase methodology in association with microwave irradiation. This combination sped up the solid-phase drug discovery process in rigorously established conditions.[75] For each procedure studied, exposition of the reaction mixtures to microwaves allowed a substantial increase in the yields and a striking reduction in the reaction time. (Scheme 51)

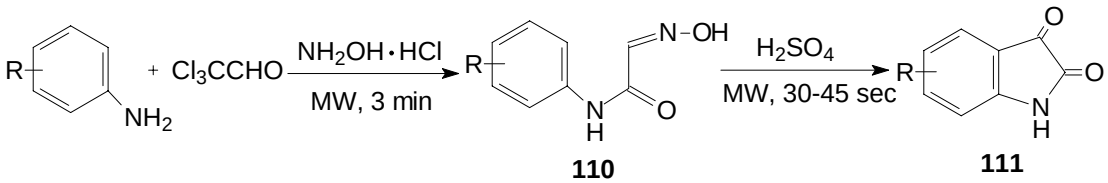


Compound **108** Yield (%)		Compound **109** Yield (%)	
MW	Thermal heating	MW	Thermal heating
90	73	85	62

Scheme 51

3.3 Syntheses of isatins

A mixture of aromatic amines, chloral and hydroxylamine hydrochloride was exposed to microwave irradiation in a domestic microwave oven to result in the intermediate isonitrosoacetanilide (**110**), which could be cyclised to isatin (**111**) under acidic conditions.[76] The reaction was general and both the steps gave good yields. Reaction time for the formation of isonitrosoacetanilides (**110**) was reduced from several hours (2-6 hours) to a few minutes under this procedure. (Scheme 52)



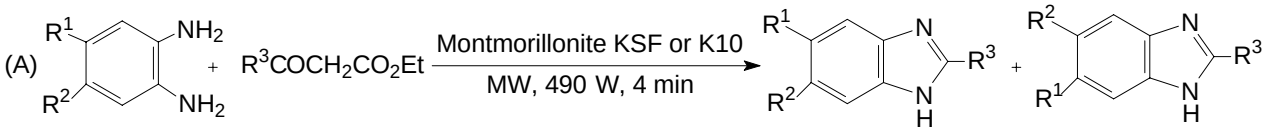
$ArNH_2$	Compound **110** Yield (%)	Compound **111** Yield (%)
$C_6H_5NH_2$	89	75
4-$MeC_6H_4NH_2$	82	70
4-$MeOC_6H_4NH_2$	77	65
4-$FC_6H_4NH_2$	91	61
4-$NO_2C_6H_4NH_2$	88	-
$PhCH_2NH_2$	50	-
2- $NH_2C_6H_4CO_2H$	94	-
3,5-$Br_2C_6H_3NH_2$	80	85

Scheme 52

3.4 Syntheses of arylimidazoles, benzoxazoles and benzothiazoles

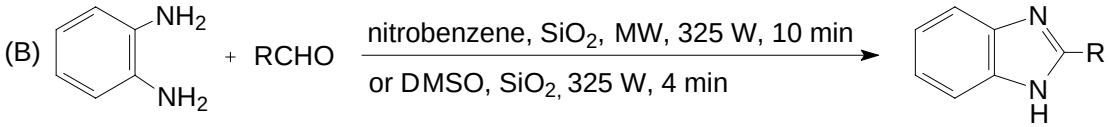
It was reported that substituted arylimidazoles could be synthesized under microwave irradiation according to the following different methods:

(A) Arylimidazoles (**112**) could be synthesized by the condensation of *o*-phenylenediamine with ethyl acetoacetate or ethyl benzoylacetate on Montmorillonite KSF or bentonite K10 in dry media within 5min in a domestic oven.[77] (B) and (C) The oxidative heterocyclisation of aldehydes with *o*-phenylenediamine in nitrobenzene or dimethyl sulfoxide impregnated on silica gel [78] or $ZnCl_2$ supported alumina [79] afforded benzimidazoles (**113, 114**) in good yields and high purity. (D) Arylimidazoles (**115**) could be synthesized by cyclocondensation of *N*-carbotrifluoromethyl-*o*-arylimidazoles with good yields on Montmorillonite K10 in dry media within 2 min in a domestic oven. By conventional heating under the same conditions, no reaction was observed.[80] (Scheme 53)



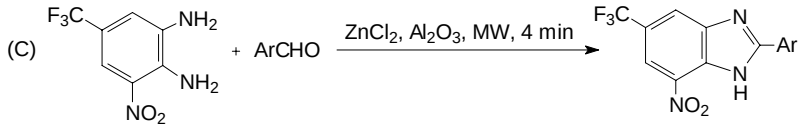
112a **112b**

R^1	R^2	R^3	Compound **112a**+**112b** Yield (%)
H	H	Me	90
Me	Me	Me	94
H	Me	Me	92
H	CO_2Et	Me	86
H	NO_2	Me	87
H	Cl	Me	75
H	H	Ph	92
Me	Me	Ph	96
H	Me	Ph	91
H	CO_2Et	Ph	89
H	NO_2	Ph	90
H	Cl	Ph	75



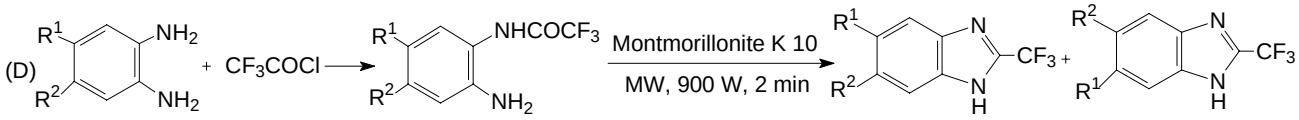
113

R	Yield (%)	
	Nitrobenzene, SiO_2	DMSO, SiO_2
Ph	90	94
4-MeC_6H_4	84	88
4-$MeOC_6H_4$	76	81
4-ClC_6H_4	82	84
4-$NO_2C_6H_4$	96	97
2-ClC_6H_4	80	85
2-HOC_6H_4	80	84
2-Piperonyl	85	88
2-Furyl	86	90
n-Pr	78	82
Et	69	72



114

Ar	Yield (%)	
	MW	Thermal heating
Ph	84	80
4-FC_6H_4	83	77
4-$MeOC_6H_4$	72	64
4-MeC_6H_4	86	65
4-ClC_6H_4	90	60
4-$Me_2NC_6H_4$	85	66
4-$NO_2C_6H_4$	87	62
4-HOC_6H_4	85	80
2-Furyl	82	64
2-Na	80	62

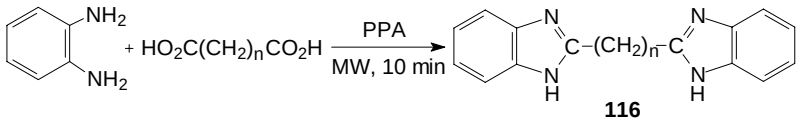


115a **115b**

R^1	R^2	Ratio **115a** : **115b**	Compound **115a**+**115b** Yield (%)
H	H	100 / 0	87
Me	Me	100 / 0	84
NO_2	H	100 / 0	95
Cl	H	100 / 0	92
H	Me	88 / 12	89
H	CO_2Et	97 / 3	87
CO_2Et	H	97 / 3	93

Scheme 53

Bis(2-benzimidazolyl)alkanes (**116**) were also synthesized by the condensation of *o*-phenylenediamine with diacid under microwave irradiation. Compared with the classical reaction, the reaction time was shorted sharply and the yield was comparable.[81] The reaction required 3.5 h in classical heating. (Scheme 54)



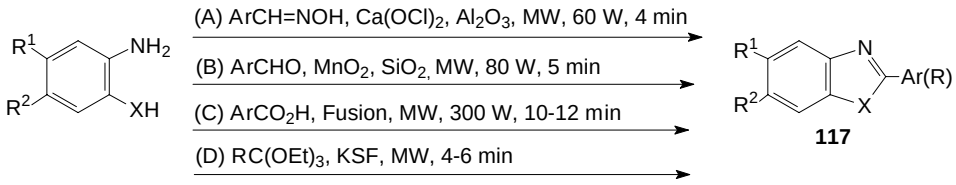
116

n	Yield (%)
2	85
3	88
4	90
5	89
6	91
7	87
8	94

Scheme 54

The benzoxazole scaffold is found in many biologically active compounds, such as elastase inhibitors and H_2-antagonists. Soufiaoui [82] described three new ways to synthesize 1, 3-arylimidazoles, benzoxazoles and benzothiazoles (**117**) on mineral supports using $Ca(OCl)_2$ / Al_2O_3 or MnO_2 / SiO_2 or by fusion in dry media. The reactions were activated under microwave irradiation in a monomode Synthewave 402 reactor.

The reaction times were considerably shortened and the products were obtained in higher yields and better purity than compared to conventional heating. It took 24-48 h in thermal heating. And Villemin also gave a method to prepare 1, 3-arylimidazoles, benzoxazoles and benzothiazoles on KSF clay under microwave irradiation.[83] (Scheme 55)

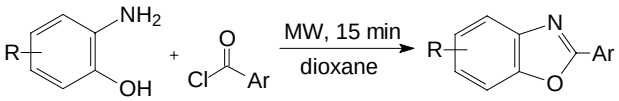


117

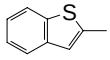
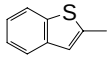
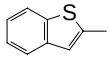
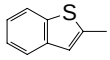
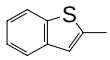
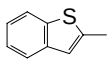
R^1	R^2	X	Ar	R	Method	Yield (%)
H	H	NH	Ph	-	A, B	87, 75
H	H	NH	2-$NO_2C_6H_4$	-	A, B, C	86, 84, 85
H	H	NH	4-$NO_2C_6H_4$	-	A, B	94, 90
H	H	NH	2-MeC_6H_4	-	A	87
H	H	NH	4-FC_6H_4	-	C	81
H	H	NH	4-MeC_6H_4	-	A	90
H	H	O	Ph	-	A, B	86, 75
H	H	O	2-$NO_2C_6H_4$	-	A, C	88, 80
H	H	O	4-$NO_2C_6H_4$	-	C	84
H	H	O	4-$MeOC_6H_4$	-	A	87
H	H	O	4-ClC_6H_4	-	B	84
H	H	O	3, 4-$(MeO)_2C_6H_3$	-	C	86
H	H	S	Ph	-	A	86
H	H	S	2-$NO_2C_6H_4$	-	A	91
H	H	S	3-$NO_2C_6H_4$	-	A	92
H	H	S	4-$NO_2C_6H_4$	-	A	93
H	H	S	2-ClC_6H_4	-	A	91
H	H	S	4-$MeOC_6H_4$	-	A	91
H	H	S	4-ClC_6H_4	-	B	94
Cl	H	O	Ph	-	B	90
Cl	H	O	3-$NO_2C_6H_4$	-	B	90
Cl	H	O	3-HO-4-$MeOC_6H_3$	-	B	87
Cl	H	O	3-ClC_6H_4	-	B	87
Cl	H	O	4-ClC_6H_4	-	B	90
NO_2	H	O	4-$MeOC_6H_4$	-	B	92
NO_2	H	O	4-ClC_6H_4	-	B	92
NO_2	H	O	4-$NO_2C_6H_4$	-	B	96
H	NO_2	O	4-ClC_6H_4	-	B	97
H	NO_2	O	4-MeC_6H_4	-	B	87
H	NO_2	O	3, 4-$(MeO)_2C_6H_3$	-	B	92
H	H	NH	-	H	D	74
H	H	NH	-	Me	D	79
Me	Me	NH	-	H	D	85
Me	Me	NH	-	Me	D	92
H	H	O	-	H	D	55
H	H	O	-	Me	D	76
H	H	S	-	H	D	74
H	H	S	-	Me	D	70

Scheme 55

One-pot strategy was reported to synthesize the benzoxazoles (**118**). A mixture of 2-aminophenol and acyl chloride in 1,4-dioxane was treated with microwave in sealed reaction vessel for 15 min at 210℃.[84] In thermal heating, it required 2-72 hours to give comparable yield.(Scheme 56)

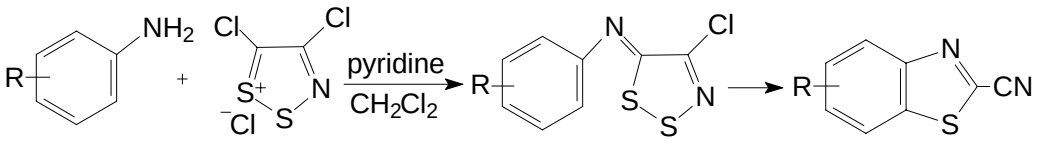


118

R	Ar	Yield (%)
H	Ph	90
H	2-BrC_6H_4	66
H	4-PhC_6H_4	88
H	4-BrC_6H_4	94
H	4-$NO_2C_6H_4$	96
H	2-thiophyl	74
H		82
H	3,4,5-$(MeO)_3C_6H_2$	92
$EtMe_2C$	Ph	83
$EtMe_2C$	2-BrC_6H_4	56
$EtMe_2C$	4-PhC_6H_4	85
$EtMe_2C$	4-BrC_6H_4	97
$EtMe_2C$	4-$NO_2C_6H_4$	98
$EtMe_2C$	2-thiophyl	64
$EtMe_2C$		51
$EtMe_2C$	3,4,5-$(MeO)_3C_6H_2$	87
4-EtS	Ph	86
4-EtS	2-BrC_6H_4	52
4-EtS	4-PhC_6H_4	89
4-EtS	4-BrC_6H_4	75
4-EtS	4-$NO_2C_6H_4$	90
4-EtS	2-thiophyl	66
4-EtS		52
4-EtS	3,4,5-$(MeO)_3C_6H_2$	91
4,5-$(CH)_4$	Ph	52
4,5-$(CH)_4$	2-BrC_6H_4	54
4,5-$(CH)_4$	4-PhC_6H_4	82
4,5-$(CH)_4$	4-BrC_6H_4	75
4,5-$(CH)_4$	4-$NO_2C_6H_4$	89
4,5-$(CH)_4$	2-thiophyl	57
4,5-$(CH)_4$		78
4,5-$(CH)_4$	3,4,5-$(MeO)_3C_6H_2$	63
3-Me	Ph	94
3-Me	2-BrC_6H_4	92
3-Me	4-PhC_6H_4	85
3-Me	4-BrC_6H_4	98
3-Me	4-$NO_2C_6H_4$	95
3-Me	2-thiophyl	93
3-Me		96
3-Me	3,4,5-$(MeO)_3C_6H_2$	94
4-NO_2	Ph	90
4-NO_2	2-BrC_6H_4	49
4-NO_2	4-PhC_6H_4	74
4-NO_2	4-BrC_6H_4	94
4-NO_2	4-$NO_2C_6H_4$	83
4-NO_2	2-thiophyl	72
4-NO_2		46
4-NO_2	3,4,5-$(MeO)_3C_6H_2$	89

Scheme 56

4, 5-Dichloro-1,2,3-dithiazolium chloride (**119**), which was readily prepared from chloroacetonitrile and sulfur dichloride, reacted rapidly with anilines in the presence of pyridine to give stable *N*-arylimino-1, 2, 3- dithiazoles (**120**). The imines cyclised when vigorously heated to give sulfur, hydrogen chloride and 2-cyanobenzothiazoles (**121**). This new method for converting anilines into benzothiazoles in two simple steps was useful for the synthesis of highly substituted derivatives which could serve as intermediates in the preparation of some natural products.[85, 86] The comparison of classical heating (oil or metal bath) and microwave irradiation was studied. The experimental conditions were similar except for the heating source. The result confirmed that focused microwave irradiation was very powerful technique for accelerating thermal organic reactions. (Scheme 57)



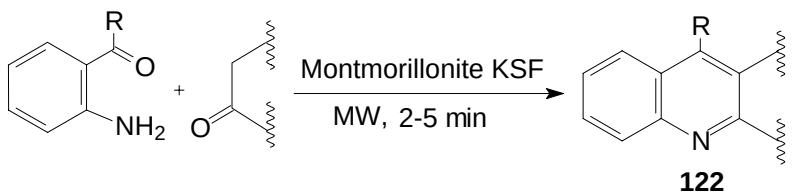
119 **120** **121**

R	Yield (%)
H	60
4-MeO	54
6-MeO	60
4,7-$(MeO)_2$	56
5,6,7-$(MeO)_3$	71
4-F	50
6-F	34
5,6-F_2	25

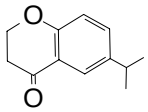
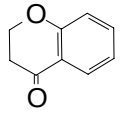
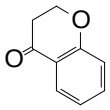
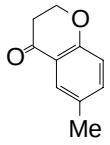
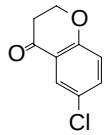
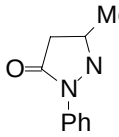
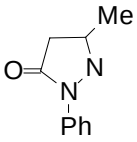
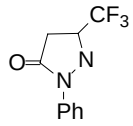
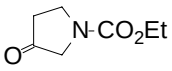
Scheme 57

3.5 Syntheses of quinolines

Quinolines are well known not only for their significant biological activities [87] but also for their formation of conjugated molecules and polymers that combine enhanced electronic, nonlinear optical properties with excellent mechanical properties. [88] Clay catalyzed Friedlander condensation of 2-aminoarylaldehyde or ketone with carbonyl compounds containing α-methylene group was achieved in solvent free condition under microwave irradiation to give polycyclic quinoline derivatives (**122**).[89] Similar reactions were carried out in an oil bath at ~110℃, where the reactions took longer time and low yields were observed. When the reactions were carried out for longer time, self condensed products were isolated. (Scheme 58)

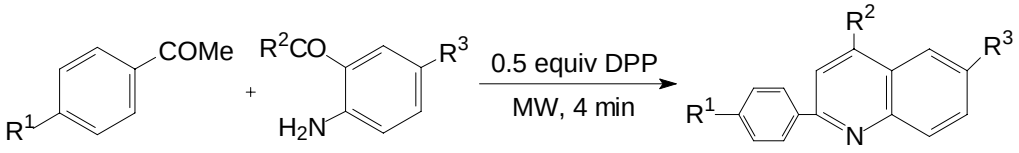


122

R	Active methylene	Yield (%)
Ph	1,3-cyclohexandione	62
Ph		82
H		66
Me		72
Me		68
Me		72
Me		62
H		62
Ph		72
H		45

Scheme 58

Quinoline derivatives (**123**) were synthesized by the Friedlander condensation between various acetophenones and 2-aminoacetophenone or benzophenone under microwave irradiation.[90] The reaction was carried out in a commercial microwave oven. The comparison of microwave irradiation and thermal heating was studied. When R^1, R^2 and R^3 are hydrogens, 78% yield could be obtained for 4 min with diphenylphosphate (DPP) under microwave irradiation. In thermal heating only 15% yield could be obtained with same condition. (Scheme 59)

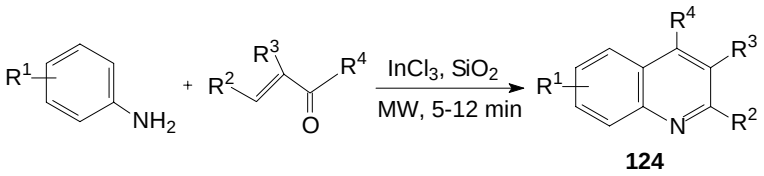


123

R^1	R^2	R^3	Yield (%)
H	Ph	H	78
H	Ph	Br	73
H	Me	H	76
$Me(CH_2)_4CH_2$	Ph	H	62
$Me(CH_2)_4CH_2$	Ph	Br	75
$Me(CH_2)_4CH_2$	Me	H	63
Br	Ph	H	80
Br	Ph	Br	85
Br	Me	H	50
NH_2	Ph	H	80
NH_2	Ph	Br	61
NH_2	Me	H	53

Scheme 59

Ranu reported other simple and efficient procedure for the synthesis of 4-alkylquinolines (**124**) by a one-pot reaction of anilines with alkyl vinyl ketones on silica gel impregnated with $InCl_3$ under microwave irradiation without any solvent.[91] Conventional heating in place of microwave activation induced considerable polymerization of vinyl ketones reducing the yield of quinolines drastically. (Scheme 60)



124

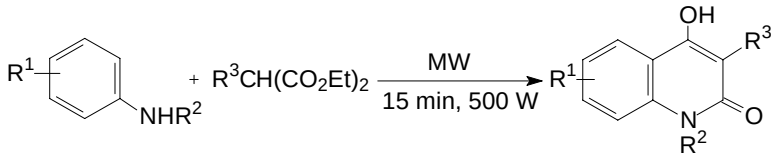
R^1	R^2	R^3	R^4	Yield (%)
H	H	H	Me	85
2-Me	H	H	Me	81
3-Me	H	H	Me	84
4-Me	H	H	Me	85
2-MeO	H	H	Me	80
4-MeO	H	H	Me	83
3-HO	H	H	Me	81
3-Cl	H	H	Me	87
2-Cl	H	H	Me	80
2-Br	H	H	Me	80
2-Me-4-I	H	H	Me	83
2,3-$(CH)_4$	H	H	Me	82
H	Me	H	4-$MeOC_6H_4$	81
2-Cl	Me	H	4-$MeOC_6H_4$	83
H	*n*-Pr	Et	Me	55

Scheme 60

3.6 Syntheses of quinolinones

Lange reported the first microwave enhanced formation of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones from anilines and malonic ester derivatives using solvent-free conditions without supported reagents. This microwave-enhanced reaction was completed in 15 min in a microwave oven. The results indicated that

electron-donating groups on the benzene ring led to the desired products in high yields. The presence of the electron-withdrawing trifluoromethyl group on the aniline ring had a deactivating effect on the final electrophilic aromatic cyclisation.[92] The reaction required many hours at reflux temperatures in a high boining organic solvent (e.g. diphenyl ether) in classical conditions. (Scheme 61)

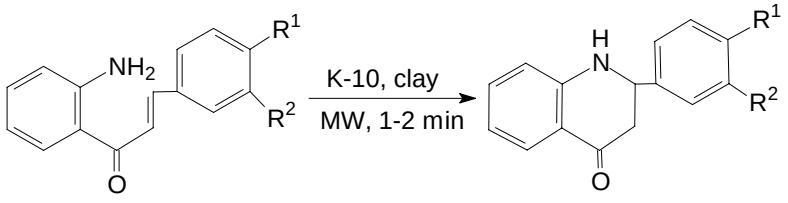


125

R^1	R^2	R^3	Yield (%)
H	H	Ph	83
2-Cl	H	Ph	0
2-OMe	H	Ph	45
2-CF_3	H	Ph	0
3-Cl	H	Ph	81
3-MeO	H	Ph	92
3-F	H	Ph	52
3-CF_3	H	Ph	13
4-Cl	H	Ph	72
4-MeO	H	Ph	40
4-CF_3	H	Ph	0
H	Me	Ph	79
H	*n*-Bu	Ph	57
H	cyclohexyl	Ph	8
2-$CH_2CH_2CH_2$-		Ph	88
3-Cl	H	4-$MeOC_6H_4$	94
3-Cl	H	4-MeC_6H_4	78
3-Cl	H	3-$PhOC_6H_4$	25
3-Cl	H	3-Thienyl	45

Scheme 61

A microwave-expedited preparation of 2-aryl-1,2,3,4-tetrahydro-4-quinolinones (**126**) from 2'-aminochalcones is facilitated for 1.2-2 min (temperature of alumina bath 110-140℃) on Montmorillonite K-10 clay surface. These tetrahydro-4-quinolinones are valuable precursors to medicinally important quinolinones derivatives especially those bearing substituents in either of the aromatic rings.[93] A comparable study was conducted in an oil bath at the same temperature. In an oil bath, relatively longer time was required for the conversion at ~110℃. (Scheme 62)



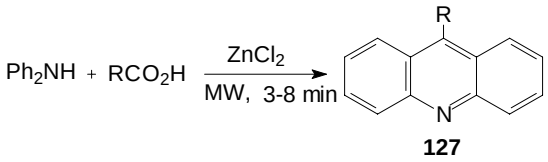
126

R^1	R^2	Yield (%)
H	H	80
Me	H	77
MeO	H	78
Cl	H	80
Br	H	72
NO_2	H	70
MeO	OMe	72

Scheme 62

3.7 Syntheses of 9-substituted acridines

Acridine derivatives are frequently used in the industry, especially at production of dyes, [94] but also in pharmaceutical industry because acridine moiety is present in several antidepresives, antimalarial and antitumor agents. [95] Veverkova and coworker reported the synthesis of 9-substituted acridines (**127**) from diphenylamine and appropriate carboxylic acid catalyzed by zinc chloride under microwave irradiation.[96] In classical heating, the reaction required 20-40 h at 230℃ to give up to 30% yield. (Scheme 63)



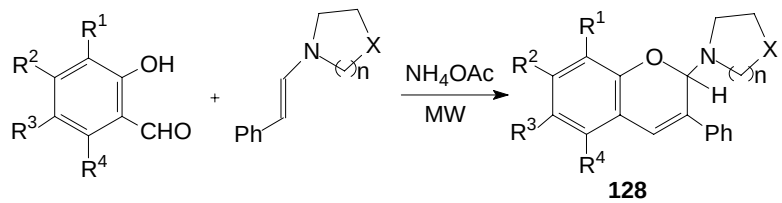
127

R	Yield (%)
HO_2CCH_2	57
$HO_2C(CH_2)_2$	80
$HO_2C(CH_2)_3$	71
$HO_2C(CH_2)_4$	72
$HO_2C(CH_2)_8$	60
Ph	75
p-Tolyl	60
1-Naphthyl	50

Scheme 63

3.8 Syntheses of benzopyrans

Isoflav-3-enes possessing a 2*H*-1-benzopyran nucleus are important chromene derivatives which display interesting estrogenic and antiestrogenic properties and are useful in the synthesis of medicinally important molecules. [97] The target compounds could be synthesis from salicylaldehyde derivatives and substituted styrene in the presence of a catalytic amount of ammonium acetate in 2-6 min in MW oven and the products were further purified easily by passing through a bed of basic alumina to afford pure isoflavenes (**128**) in high yields (70-90%).[98] In classical heating, the reaction took 3 h in benzene under an inert atmosphere to produce 45-55% yield. [99] (Scheme 64)

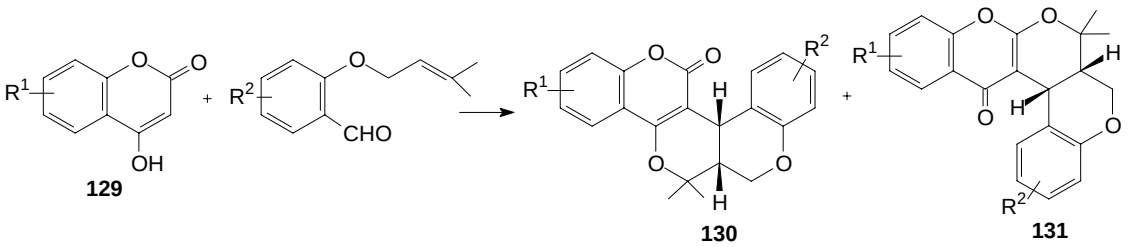


128

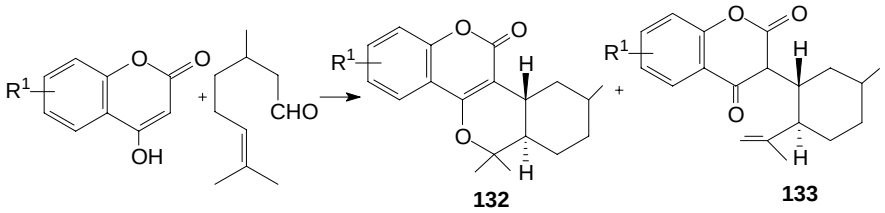
R^1	R^2	R^3	R^4	X	n	Yield (%)
H	H	H	H	O	2	80
H	H	Cl	H	O	2	81
H	H	NO_2	H	O	2	82
MeO	H	H	H	O	2	73
H	OMe	H	OMe	O	2	75
H	H	H	H	CH_2	2	72
H	H	Cl	H	CH_2	2	88
H	H	NO_2	H	CH_2	2	85
H	H	H	H	CH_2	1	71
H	H	Cl	H	CH_2	1	79
H	H	NO_2	H	CH_2	1	83

Scheme 64

4-Hydroxycoumarin and its benzo-analogues (**129**) underwent intromolecular domino Knoevenagel hetero Diels-Alder reactions with aromatic and aliphatic aldehyde, citronellal to afford pyrano fused polycyclic frameworks. A high degree of chemoselectivity was achieved under microwave irradiation.[100] In classical heating, the reaction took longer time to produce lower yield and chemoselectivity. (Scheme 65)



R^1	R^2	Time		Ratio **130** : **131**		Yield (%)	
		MW (sec)	Classical heating (h)	MW	Classical heating	MW	Classical heating
H	H	15	4	93 : 7	68 : 32	82	57
H	5,6-$(CH)_4$	10	4	95 : 5	80 : 20	92	75
7,8-$(CH)_4$	H	90	8	79 : 21	57 : 43	83	66
7,8-$(CH)_4$	5,6-$(CH)_4$	90	6	80 : 20	66 : 34	76	66
5,6-$(CH)_4$	H	150	8	81 : 19	55 : 45	77	40
5,6-$(CH)_4$	5,6-$(CH)_4$	90	6.5	85 : 15	56 : 44	74	53



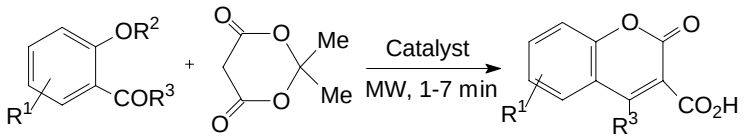
R^1	Time		Ratio **132** : **133**		Yield (%)	
	MW (sec)	Classical heating (h)	MW	Classical heating	MW	Classical heating
H	12	4	88 : 12	58 : 42	81	55
7,8-$(CH)_4$	180	6	84 : 16	63 : 27	75	69
5,6-$(CH)_4$	150	7	84 : 16	66 : 34	78	53

Scheme 65

3.9 Syntheses of coumarins

Coumarins are common in nature and find their main applications as fragrances, pharmaceuticals and agrochemical. [101] Bandgar and coworkers [102] reported the use of a combination of natural kaolinitic clay

or Envirocats (EPZG, EPZ10) and focused microwaves for the rapid one-pot synthesis of 3-carboxycoumarins (**134**) from 2-hydroxy- or 2-methoxy-substituted benzaldehydes or acetophenones and Meldrum's acid under solvent-free conditions. The reaction was exposed to pulsed microwave irradiation for 2 sec using an unmodified microwave oven operating at 100% power. (Scheme 66)

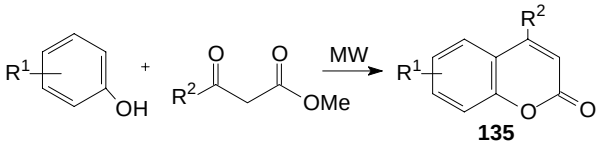


134

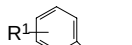
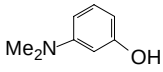
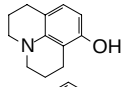
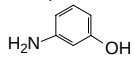
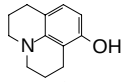
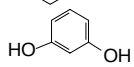
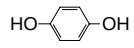
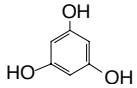
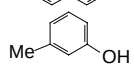
R^1	R^2	R^3	Time (min)			Yield (%)		
			EPZ10	EPZG	Natural clay	EPZ10	EPZG	Natural clay
H	H	H	4	3	5	82	84	71
5-Cl	H	H	6	4	5	76	97	90
4-MeO	H	H	5	-	7	55	-	84
4-MeO	Me	H	-	5	7	-	60	93
H	H	Me	3	5	1	68	74	73
4-HO	H	Me	-	2	2	-	66	75
5-Cl	H	Me	6	-	-	64	-	-

Scheme 66

Coumarins (**135**) were synthesized *via* the Pechmann reaction under microwave irradiation on solid support (graphite/montmorillonite K10) [103] or adding conc. H_2SO_4.[104] In thermal heating, it took 0.5-20 h at 130-150℃ to give 45-79% yield. (Scheme 67)

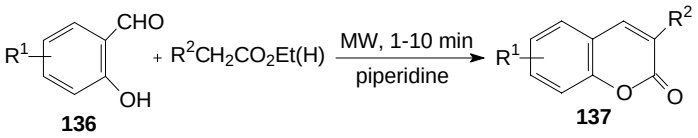


135

	R^2	Catalyst	Time (min)		Yield (%)	
			MW	Classical heating	MW	Classical heating
	CO_2Me	Graphit / Montmorillonite K10	8	45	61	54
	CO_2Me	Graphit / Montmorillonite K10	8	56	75	58
	Me	Graphit / Montmorillonite K10	5	30	65	66
	Me	Graphit / Montmorillonite K10	12	390	62	62
	Me	conc. H_2SO_4	2	720	72	63
	Me	conc. H_2SO_4	10	1080	78	79
	Me	conc. H_2SO_4	10	1200	69	45
	Me	conc. H_2SO_4	7	360	76	65
	Me	conc. H_2SO_4	2	240	82	75

Scheme 67

Under microwave irradiation the Knoevenagel condensation could be successfully applied to the synthesis of courmarins, and the scope of the method was very broad. The condensation of aldehyde (**136**) with various derivates of ethyl acetate in the presence of piperidine under solvent-free conditions or substituted acetic acids in the presence of DCC-DMSO led to the synthesis of coumarins (**137**).[105] In classical approach, cyclocondensation of an aldehyde with acids required 18-20 h at 100-120℃. Some impurities also formed in the final hours of the reactions. In contrast, the same reaction required less than 10 min when carried out under microwave irradiation and no such impurities were observed. (Scheme 68)

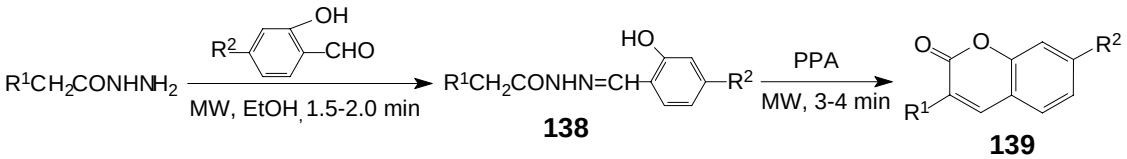


136 **137**

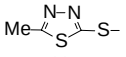
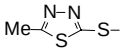
R^1	R^2	Time (min)	Yield (%)
H	CO_2Et	10	89
H	COMe	1	94
H	CN	4	76
H	4-$NO_2C_6H_4$	5	85
3-MeO	CO_2Et	10	72
3-MeO	4-$NO_2C_6H_4$	5	78
4-Et_2N	CO_2Et	6	55
4-Et_2N	COMe	6	88
4-Et_2N	CN	10	80
4-Et_2N	4-$NO_2C_6H_4$	6	90
5,6-$(CH)_4$	CO_2Et	5	80
5,6-$(CH)_4$	COMe	8	75
5,6-$(CH)_4$	CN	10	82
5,6-$(CH)_4$	4-$NO_2C_6H_4$	3	75

Scheme 68

The hydrazides on condensation with 2-hydroxyaryl aldehydes in ethanol afforded corresponding hydrazones (**138**). And these hydrazones were cyclised in polyphosphoric acid using microwave heating to furnish corresponding substituted courmarins (**139**).[41] (Scheme 69)

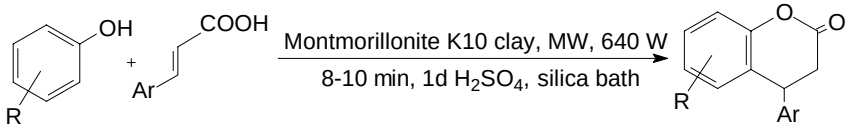


138 **139**

R^1	R^2	Yield (%)	
		Compound **138**	Compound **139**
	H	88	55
	H	86	60
	OMe	92	58
	OMe	95	68

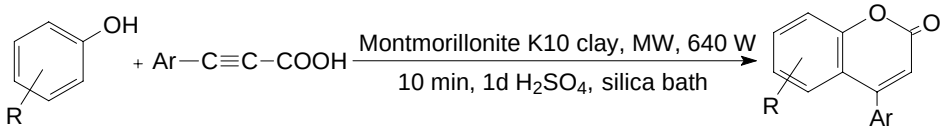
Scheme 69

3,4-Dihydro-4-phenylcoumarins (**140**) and 4-phenylcoumarins (**141**) could be obtained in a single step and in good yield. Substituted phenol and cinnamic acid or phenylpropynoic acid impregnated on activated Montmorillonite K-10 clay in an open vessel and employing optimized conditions of 640 W power output in a microwave oven, for 8-10 min, furnished 3, 4-dihydro-4-phenylcoumarin or 4-phenylcoumarin.[106] When a mixture of phenol, cinnamic acid and one drop of H_2SO_4 was refluxed in dimethylformamide for 10 h with or without K-10 clay, no reaction was observed. (Scheme 70)



140

R	Ar	Time (min)	Yield (%)
H	4-$MeOC_6H_4$	8	85
3-HO	Ph	8	75
3-MeO	Ph	8	81
H	3,4-OCH_2O-	10	65
H	H	10	82



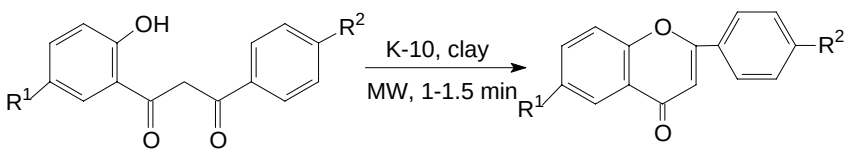
141

R	Ar	Time (min)	Yield (%)
H	Ph	10	70
3-MeO	Ph	10	55
H	4-$MeOC_6H_4$	10	67

Scheme 70

3.10 Syntheses of flavonoids

Flavonoids are a group of naturally occurring phenolic compounds widely distributed in the plant kingdom, the most abundant being the flavones. Members of this class display a wide variety of biology activities.[107] A simple and rapid method for the synthesis of flavones (**142**) proceeded *via* a solid state dehydrative cyclization of *o*-hydroxydibenzoylmethanes in clay microenvironment using microwave.[108] The starting materials were adsorbed on Montmorillonite K-10 clay. The mixture, in a test-tube, was placed in an alumina bath inside the microwave oven and irradiated for 1.5 min. Good yields (72-80%) were obtained. On the other hand, the reaction could not be completed (65%) in 24 h at the same bulk temperature of 80℃ using oil bath. The temperature of the reaction mixture inside the alumina bath reached ~80℃ after 1 min of irradiation in a MW oven operating at full power of 900 W. (Scheme 71)



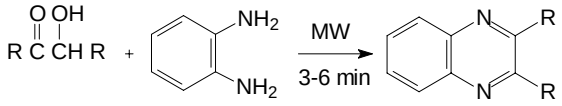
142

R^1	R^2	Yield (%)
H	H	75
H	Me	77
H	MeO	76
H	NO_2	78
MeO	H	73
MeO	Me	80
MeO	MeO	72

Scheme 71

3.11 Syntheses of quinoxalines

Quinoxalines are important heterocycles found in natural products like echinomycin and triostins. [109] A convenient synthetic method was reported for 2, 3-disubstituted quinoxalines (**143**) by the condensation of both alkyl or aryl acyloins and *o*-phenylenediamine in dry media under microwave irradiation. The reaction was carried out by simply mixing of acyloins and *o*-phenylenediamine and irradiated in a microwave oven for 3-6 minutes, the 2,3-disubstituted quinoxalines were obtained in 20-94% yields.[110] (Scheme 72)



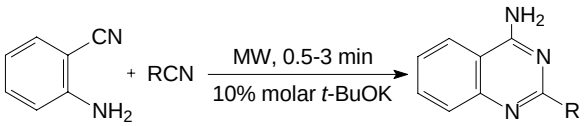
143

R	Time (min)	Yield (%)
3-ClC_6H_4	6	94
4-ClC_6H_4	6	83
4-$MeOC_6H_4$	6	67
2-Furyl	3	63
Ph	4	67
-$(CH_2)_8$	6	20
n-Pr	3	75
Et	5	27

Scheme 72

3.12 Syntheses of quinazolines

Quinazolines are a wide family of compounds with well-known pharmacological properties: analgesic, narcotic, anti-malarial, or sedative.[111] Cyanoaromatic compounds reacted with anthranilonitrile in a microwave oven affording good yields of the corresponding 4-aminoquinazoles (**144**) in a very short time. The procedure had the following advantages: the absence of solvent, a radical decrease in reaction time, the use of a catalytic amount of base, and an improvement over precedent synthesis using conventional heating.[112] When R was phenyl group, 2-phenyl-4-aminoquinazoline was formed in 39% yield with a slight molar excess of benzonitrile in methanolic ammonia in a sealed tube (20h at 200℃). (Scheme 73)

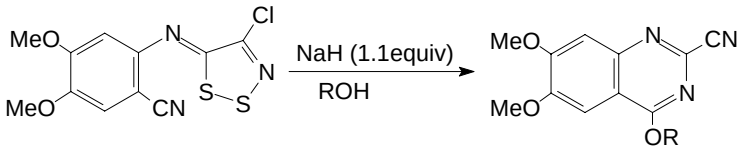


144

R	Time (min)	Yield (%)
2-$NH_2C_6H_4$	1	82
Ph	2	93
4-$MeOC_6H_4$	1	76
3-NCC_6H_4	2	85
2-Thiophenyl	1.5	90
2-Furyl	1.5	84
4-Py	2	91
3-Py	0.5	79
2-Py	1.5	85
$PhCH_2$	3	73

Scheme 73

Conversion of *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazole into the 4-alkoxyquinazoline-2-carbonitriles (**145**) with sodium alkoxides in the corresponding alcohol, either by conventional thermolysis or by microwave irradiation was described and directly compared. Microwave irradiation of the solutions in open vessels in a monomode system with focused irradiation and continuous temperature control (Synthewave S402 reactor) usually gave cleaner, faster and higher yielding reactions. These reactions could be safely and beneficially scaled up to multigram quantities in a larger reactor (Synthewave S1000).[113](Scheme 74)



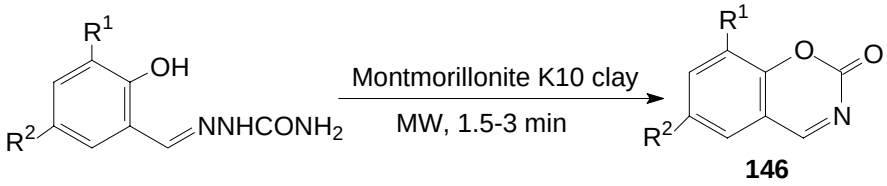
145

R	Time		Yield (%)	
	MW (min)	Classical heating (h)	MW	Classical heating
Me	120	40	-	77
Me	120	40	41	76
Et	120	40	80	77
Et	120	40	80	29
n-Pr	73	40	49	39
i-Pr	120	40	-	63
n-Bu	35	40	70	82
t-Bu	120	40	-	-
n-C_5H_{11}	35	40	63	57
CH_2=$CHCH_2$	35	40	69	60
$Me_2CH(CH_2)_2$	45	40	31	31

Scheme 74

3.13 Syntheses of 2*H*-benz[*e*]-1, 3-oxazin-2-ones

A benzoxazinone derivative is presently in clinical use for the treatment of AIDS. Yadav [114] reported a microwave-expediated, high yielding, synthesis of 2*H*-benz[*e*]-1,3-oxazin-2-ones (**146**) involving cyclodehydrazination of salicylaldehyde semicarbazones on Montmorillonite K10 clay in solvent-free conditions in 1.5-3 min. In classical heating, the reaction could not be completed, only 60% conversion over 20 h at the same bulk temperature (90℃) in an oil bath. (Scheme 75)



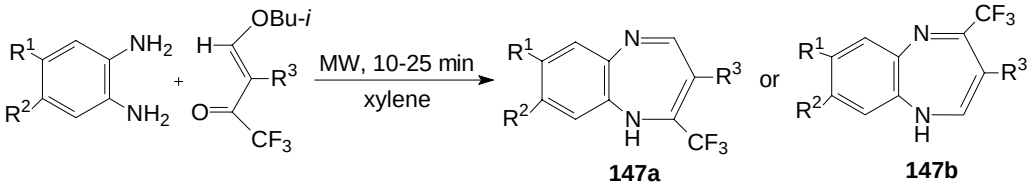
146

R^1	R^2	Time (min)	Yield (%)
H	H	3.0	84
H	Br	2.5	86
Br	Br	2.0	87
H	Cl	2.5	90
Cl	Cl	2.0	94
F	H	2.0	91
MeO	H	3.0	88
H	NO_2	2.0	90
NO_2	NO_2	1.5	93
I	I	3.0	83

Scheme 75

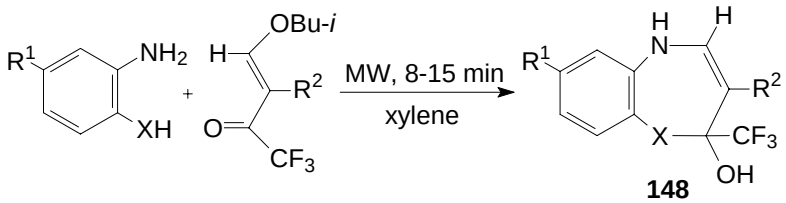
3.14 Syntheses of 2- or 4-trifluoromethyl(1*H*, 5)arylodiazepines

Arylodiazepines belong to an important class of compounds possessing a wide variety of medicinal properties. [115] Exclusive formation of either 2- or 4- trifluromethyl(1*H*, 5)arylodiazepines (**147**) was observed in condensation of 1,1,1-trifluoro-3-isobutoxymethylene-2-propanones with *o*-arylenediamines under microwave irradiation. Thermal reactions under the same temperature and time produced no products. Orthoaminophenols and *o*-aminothiophenol under the same conditions produced the respective oxazepines and thiazepines (**148**)**.** The synthetic equivalent gave similarly benzimidazoles, benzoxazoles and benzthiazoles (**149**). [116, 117] (Scheme 76)



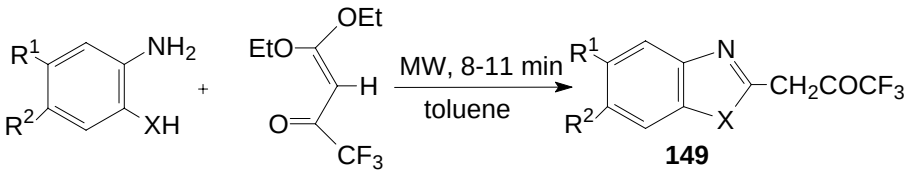
147a **147b**

R^1	R^2	R^3	Yield (%)	
			Compound **147a**	Compound **147b**
H	H	H	85	-
Me	Me	H	93	-
H	Cl	H	86	-
H	Me	H	80	-
H	H	CF_3CO	76	-
Me	Me	CF_3CO	84	-
H	Cl	CF_3CO	74	-
H	Me	CF_3CO	83	-
H	NO_2	H	-	73
H	PhCO	H	-	75
H	NO_2	CF_3CO	-	78
H	PhCO	CF_3CO	-	80



148

R^1	R^2	X	Yield (%)
H	H	O	82
Cl	H	O	85
H	CF_3CO	O	89
Cl	CF_3CO	O	76
H	H	S	71
H	CF_3CO	S	78

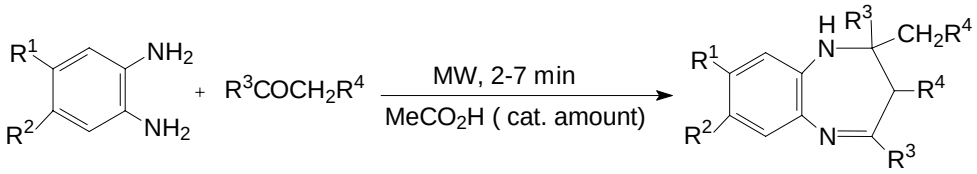


149

R^1	R^2	X	Yield (%)
Me	Me	NH	86
H	Me	NH	92
Cl	H	O	96
H	H	S	93

Scheme 76

A facile synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepins (**150**) was decribled by condensation of ketones with *o*-phenylenediamines under microwave irradiation without solvent. The syntheses were carried out simply by mixing the *o*-phenylenediamine with the ketones in the presence of a catalytic amount of acetic acid and irradiating in a domestic microwave oven for 2-7 min, whereupon the benzodiazepine derivatives were obtained in almost quantitative yield.[118] This reaction was not reported in conventional heating. (Scheme 77)



150

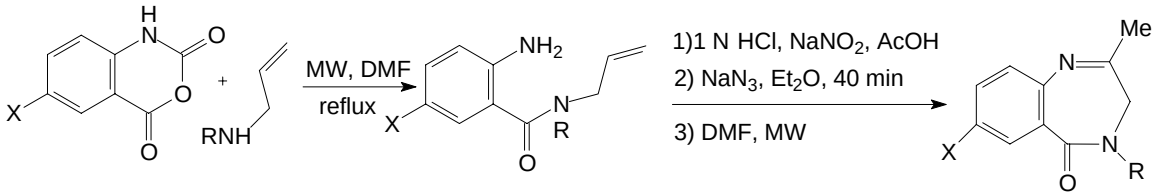
R^1	R^2	R^3	R^4	Time (min)	Yield (%)
H	H	Me	H	2	97
Me	H	Me	H	4	97
Me	Me	Me	H	2	96
H(Cl)	Cl(H)	Me	H	2	93
PhCO(H)	H(PhCO)	Me	H	7	95
-(CH)$_4$-		Me	H	2	97
H	H	Ph	H	2	98
Me	Me	Ph	H	2	99
H	H	Et	H	2	98
Me	Me	Et	H	7	99
-(CH)$_4$-		Et	H	2	98
H	H	Et	Me	2	90

Scheme 77

3.15 Syntheses of 1, 4-benzodiazepin-5-ones

The benzodiazepine nucleus is a well–studied traditional pharmacophoric scaffold that has emerged as a core structural unit of various sedative-hypnotic, muscle relaxant, anxiolytic, antistaminic, and

anticonvulsant agents. [119] Some 2-methyl-1,4-benzodiazepin-5-ones (**151**) had been synthesized by the application of microwave irradiation. Conventional heating and microwave irradiation of the reactions were compared. Synthesis by microwave irradiation gave the desired compounds in better yields than those obtained by conventional heating. The overall times for the syntheses were considerably reduced.[120] (Scheme 78)



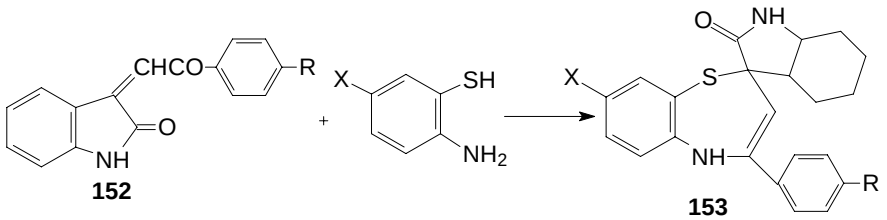
151

R	X	Time		Yield (%)	
		MW (min)	Thermal heating (h)	MW	Thermal heating
Me	H	5	3	91	65
Allyl	H	5	3	50	20
Me	Cl	5	3	97	69
Allyl	Cl	5	3	85	60
Me	Br	5	3	92	65
Allyl	Br	5	3	60	45

Scheme 78

3.16 Syntheses of 1, 5-benzothiazepinones

A series of spiro[1,5-benzothiazepin-2,3'[3'*H*]-indol]-2'(1'*H*)-ones (**153**) had been prepared by the reaction of 2-aminobenzenethiols with 1,3-dihydro-3-[2-phenyl/(4-fluorophenyl)-2-oxoethylidene]indol-2(1*H*)-ones (**152**) under microwave irradiation in open vessels using ethylene glycol as energy transfer medium and thermally in absolute ethanol saturated with hydrogen chloride gas. The comparative studies indicted that the microwave assisted organic synthesis has advantages of significantly reduced reaction time, improved yields and cleaner reactions as compared to the conventional method.[121, 122] (Scheme 79)

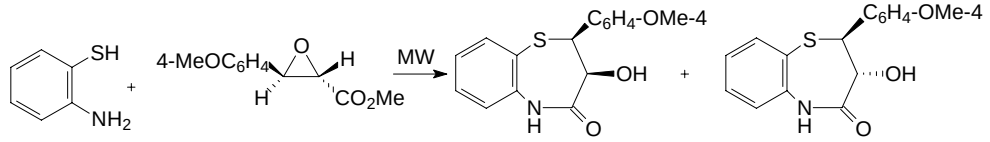


152 **153**

R	X	Time		Yield (%)	
		MW (min)	Thermal heating (h)	MW	Thermal heating
H	F	12	6	62	60
F	F	10	5	53	49
F	Cl	8	4	65	58
F	Br	8	4	56	51
F	Me	10	4	60	54
H	H	7	6	57	52
H	EtO	10	4	54	51
H	Br	10	4	65	62

Scheme 79

A diastereoselective one-pot synthesis of the *trans*- and *cis*-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one nucleus (**154**), a key intermediate in preparation of the calcium channel blocker Diltiazem, was carried out under microwave irradiation in an open vessel. Diastereoselectivity is achieved by varying the time and power as well as the solvent.[123] The traditional one-pot preparation of racemic target compounds produced less than 30% yield at 160℃ with prolonged reaction times. (Scheme 80)

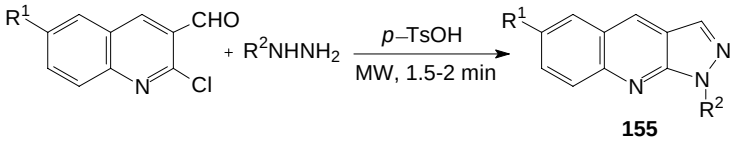


Solvent	Power (W)	Time (min)	Ratio *cis* : *trans*	Yield (%)
PhMe	390	20	9 : 1	74
AcOH	490	10	1 : 9	84

Scheme 80

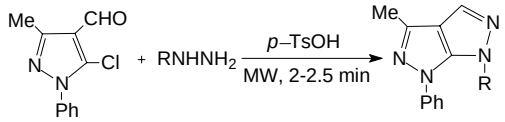
3.17 Syntheses of pyrazolo[3, 4-*b*]quinolines and pyrazolo[3, 4-*c*]pyrazoles

Pyrazole derivatives exhibit pharmacological activities such as hypotensive, antibacterial and antitumor properties. [124] Pyrazolo[3,4-*b*]quinolines (**155**) and pyrazolo[3,4-*c*]pyrazoles (**156**) were synthesized from hydrazine hydrate / phenylhydrazine and β-chlorovinyl aldehydes using *p*-TsOH under microwave irradiation.[125] Pyrazolo[3,4-*b*]quinolines were synthesized in refluxing ethanol for 5-7 h in 44-82% yield. And pyrazolo[3,4-*c*]pyrazoles were prepared in refluxing methanol for 12-14 h in 65-70% yield. (Scheme 81)



155

R^1	R^2	Time (min)	Yield (%)
H	H	1.5	97
H	Ph	1.5	78
MeO	H	1.5	92
MeO	Ph	2	85
Me	H	1.5	92
Me	Ph	2	90



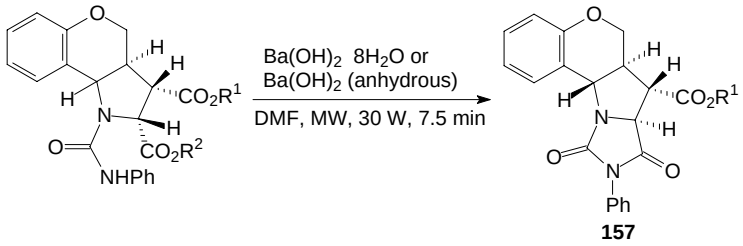
156

R	Time (min)	Yield (%)
H	2	96
Ph	2.5	94

Scheme 81

3.18 Syntheses of hydantoin ring

The hydantoin moiety imparts a broad range of biological activities with both medicinal and agrochemical application.[126] Hydantoin ring (**157**) formation *via* carbanilide cyclization was achieved in high yield with short reaction time by employing catalytic amounts of $Ba(OH)_2$ (anhydrous or octahydrate) in DMF under microwave irradiation. [127] Under microwave irradiation, the starting materials was placed in a Microwell-10 reactor and irradiated for 7.5 min (three 2.5 min intervals with cooling to room temperature between intervals) at 30 W. In classical heating, it took 9-24 hour to give comparable yield at 90℃. (Scheme 82)



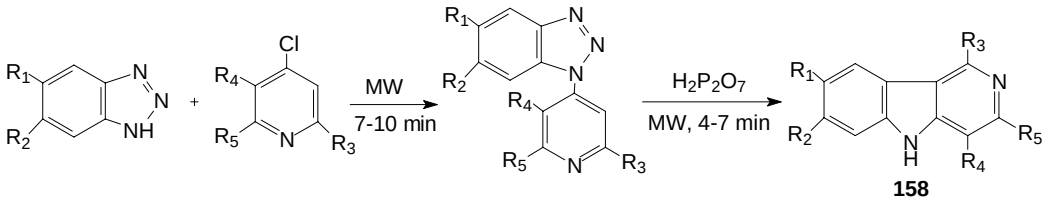
157

R^1	R^2	Time (min)	Yield (%)
Me	Et	7.5	91
Et	Et	7.5	84
Et	Bn	7.5	81

Scheme 82

3.19 Syntheses of ɣ-carbolines

ɣ-Carbolines system can be selected as precursor of DNA intercalators and bis-intercalators.[128] One-pot efficient and simple synthesis of ɣ-carboline derivates (**158**) by the Graebe-Ullmann method was conducted in a commercial microwave oven in 4-7 min at a low energy level (160 W). Yields were similar or higher yield than those obtained by conventional heating, and in all cases with reduction of the reaction time.[129] (Scheme 83)



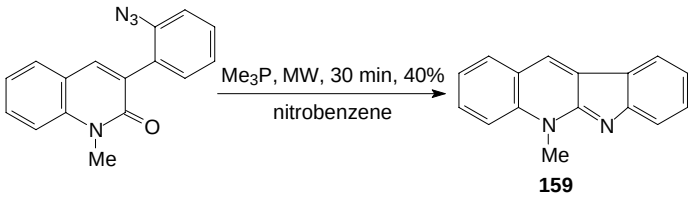
158

R^1	R^2	R^3	R^4	R^5	Time (min)	Yield (%)
H	H	H	H	H	6	62
Me	Me	H	H	H	4	67
H	H	H	-(CH)4-		7	80
Me	Me	H	-(CH)4-		4	78
H	H	Me	-(CH)4-		6	35
Me	Me	Me	-(CH)4-		5	48
-(CH)4-		H	H	H	6	28
-(CH)4-		H	-(CH)4-		5	50
-(CH)4-		Me	-(CH)4-		5	32

Scheme 83

3.20 Syntheses of cryptotackieines

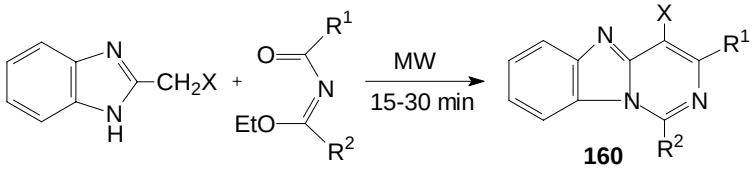
Cryptotackieine which displays a strong antiplasmodial activities was found to be a *N*-methyl derivate of the linear indolo[2,3-*b*]quinoline ring system. Some *N*-methyl derivates of the ring systems display important antimicrobial and cytotoxic activity.[130] Cryptotackieine (**159**) could be synthesized by an intramolecular aza-Wittig reaction with trimethylphosphine.[131] The reaction required 30 min to give 40% yield under microwave irradiation between 150 and 180℃. On the other hand, it was heated in nitrobenzene at reflux temperature for 24 h to give only 13% yield. (Scheme 84)



Scheme 84

3.21 Syntheses of pyrimido[1,6-*a*]benzimidazoles

Pyrimido[1,6-*a*]benzimidazoles (**160**) were synthesized by the condensation of activated 2-benzimidazoles and a variety of *N*-acylimidazoles under microwave irradiation in open vessels.[132] When the starting materials were refluxed in toluene with continuous azeotropic elimination of water or in dry ethanol for 48 h, 95% starting materials were recovered. In contrast when experiments were performed without solvents in open vessels under microwave irradiation (400-510 W, 15-30 min), they gave target compounds in 21-86% yield after ethanol and water elimination. (Scheme 85)



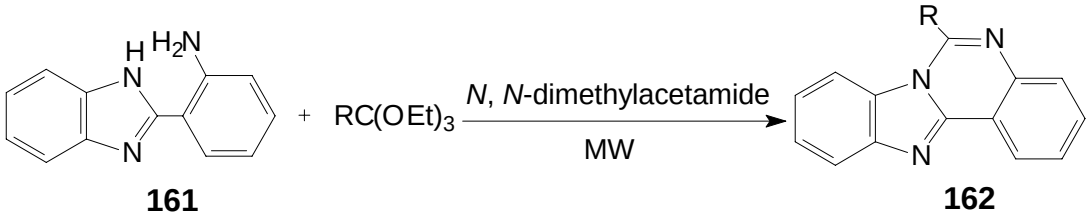
R^1	R^2	X	Time (min)	Yield (%)
Me	Me	CN	15	72
Me	Et	CN	30	65
Et	Me	CN	15	27
Me	Ph	CN	15	47
Me	Me	CO_2Me	30	86
Me	Et	CO_2Et	30	21
Me	Ph	CO_2Et	15	50

Scheme 85

3.22 Syntheses of benzimidazo[1,2-*c*]quinazolines

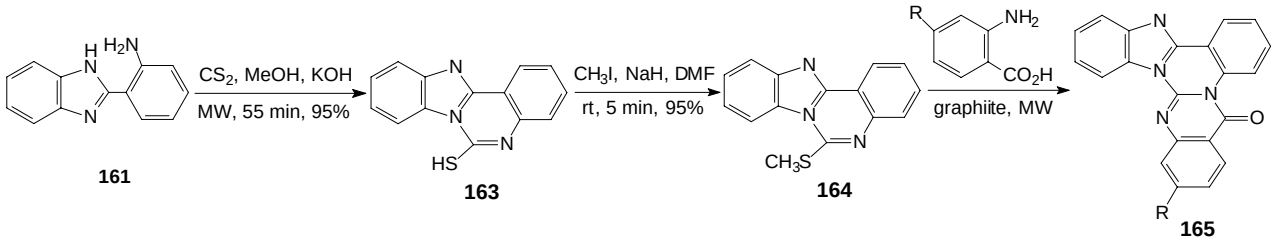
Benzimidazoquinazolines have important properties and were proposed as new class of antitumor compounds.[133] Microwave irradiation promoted the high-yield cyclocondensation of ortho esters with

2-(2-aminophenyl)benzimidazole (**161**), as the catalyst was no longer needed.[134] And benzimidazoquinazolines (**162**) and 5*a*,10,14*b*,15-tetraazabenzo[*a*]indeno[1,2-*c*]anthracen-5-one (**165**) were also synthesized in good yield in two or three steps from 2-(2-aminophenyl)benzimidazole under microwave irradiation.[135] In classical heating, compound (**163**) was prepared in 24 h in a similar yield. And thermal heating of compound (**164**) and anthranilic acid, neat at 120℃ or in butanol at reflux for 48 h, could not give more than 50% of compound (**165**). In contrast, irradiation of mixture of compound (**164**) and anthranilic acid , absorbed on graphite, led to the compound (**165**) in 75-95% yield and in a shorter time(1.5-2 h).(Scheme 86)



161 **162**

R	Time		Yield (%)	
	MW (min)	Classical heating (h)	MW	Classical heating
H	2	1.5	85	87
Me	6	3.5	89	84
Et	6	4	94	93
n-Pr	6	4	91	88
n-Bu	6	4	94	91
Ph	6	4	92	90



161 **163** **164** **165**

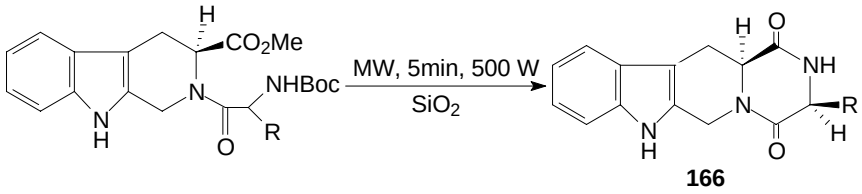
R	Time (h)	Yield (%)
H	1.5	95
Me	2	75

Scheme 86

3.23 Syntheses of (*s*)-3-substituted hexahydropyrazinopyrido[3,4-*b*]indol-1,4-diones

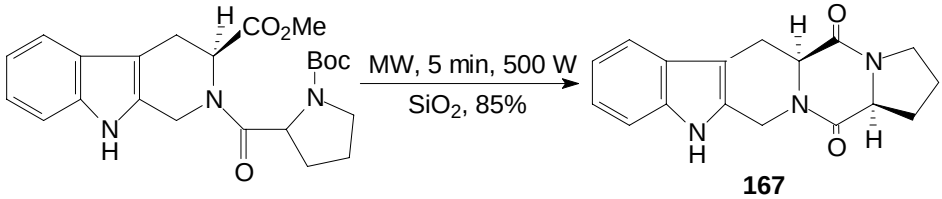
The class of indolyl diketopiperazine alkaloids is found to be tremorgenic mycotoxins, interfering with the mechanisms responsible for the release of neurotransmitters in the CNS, as well as inhibitory effects on the mammalian cell cycle. Also, indolyl diketopiperazine analogues have been studied as potential tools in the CNS receptor studies, as candidates for cancer chemotherapy, and as a source for providing molecular probes useful in elucidating regulatory mechanisms of the cell cycle.[136] Saxena and coworkers

reported a new easy way of preparing (*s*)-3-substituted 2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]-pyrido[3,4-*b*]indol-1,4-diones (**166, 167**), an important intermediate compound, using microwave irradiation supported on silica gel. The reaction was generalized and good to excellent yields(>85%) of enantiomerically pure products were obtained.[137] However when the reaction was conducted at elevated temperature (200℃) for half an hour in absence of trifluoroacetic acid, a low yield (5%) was reported[138] along with major quantity (30%) of side product and starting materials. (Scheme 87)



166

R	Yield (%)
H	88
Me	95
$PhCH_2$	90
Indolylmethyl	90



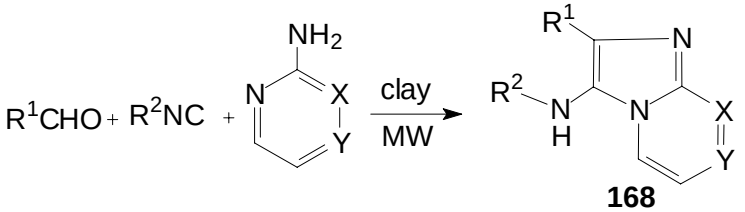
167

Scheme 87

4. Syntheses of the other heterocycles

4.1 Syntheses of imidazo[1,2-*a*]pyridines, -pyrazines and -pyrimidines

The imidazo[1,2-*a*] annulated nitrogen heterocycles (**168**) bearing pyridines, pyrazines and pyrimidines moieties constitute a class of biologically active compounds that are potent antiinflamatory agents, antibacterial agents, inhibitors of gastric acids secrstion.[139] Varma [140] reported a solventless one-pot method of irradiating a mixture of aldehydes and 2-aminopyridine, pyrazine or pyrimidine in the presence of a small amount of clay under microwave irradiation. The reaction was completed in all cases within 3.0-3.5 min with the exception of 2-aminopyrimidines that provided only modest yields (56-58%) of products with incomplete consumption of the starting material. (Scheme 88) The exact control experiments in acetic acid overnight resulted in some unreacted starting material.[141]



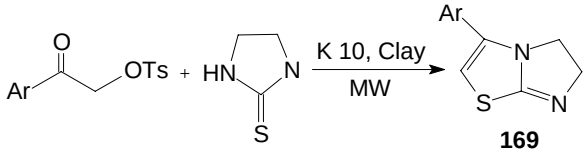
168

R^1	R^2	X	Y	Time (min)	Yield (%)
Ph	$PhCH_2$	C	C	3.0	86
4-MeC_6H_4	$PhCH_2$	C	C	3.0	88
Ph	⬡	C	C	3.0	86
Ph	$Me_3CCH_2(Me)_2C$	C	C	3.5	85
4-$MeOC_6H_4$	$PhCH_2$	C	C	3.5	82
Ph	t-Bu	C	C	3.0	84
i-Pr	$PhCH_2$	C	C	3.0	85
Ph	$PhCH_2$	C	N	3.0	81
Ph	⬡	C	N	3.0	82
4-MeC_6H_4	⬡	C	N	3.0	81
Ph	$Me_3CCH_2(Me)_2C$	C	N	3.0	83
PhCH=CH	$PhCH_2$	C	N	3.5	64
Ph	⬡	N	C	3.5	58
Ph	$PhCH_2$	N	C	3.5	56

Scheme 88

4.2 Syntheses of imidazo[2,1-*b*][1,3]thiazoles

The imidazo[2,1-*b*][1,3]thiazoles are normally difficult to obtain and require a longer heating time that use α-haloketones or α-tosyloxyketones under strongly acidic conditions. Varma [46] reported a solventless method which merely required a mixing of α-tosyloxy ketones with thioamides in the presence of Montmorillonite K10 clay. The mixture was then irradiated for 3 min to afford substituted bridgehead thiazoles (**169**). (Scheme 89) In an oil bath it remained incomplete even after heating for 24 h at 150℃.



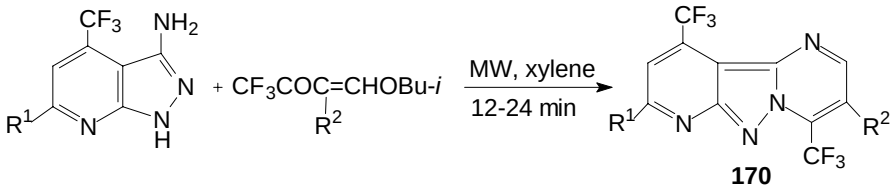
169

Ar	Yield (%)
H	85
4-ClC_6H_4	92
4-$MeOC_6H_4$	89
4-MeC_6H_4	88

Scheme 89

4.3 Syntheses of pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidines

Pyrazolopyrimidine derivatives are important biologically active compounds. The pyrazolopyrimidine are selective inhibitors and some of them possess anxiolytic properties. [142] Pyridopyrazolopyrimidines (**170**) were synthesized by the condensation of 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine and 1,1,1-trifluoro-3-isobutoxymethylene-2-propanones in xylene for 12-24 min in good yields (62-78%) under microwave irradiation.[143] (Scheme 90) Under thermal conditions, only poor yields (~20%) of the products were achieved.

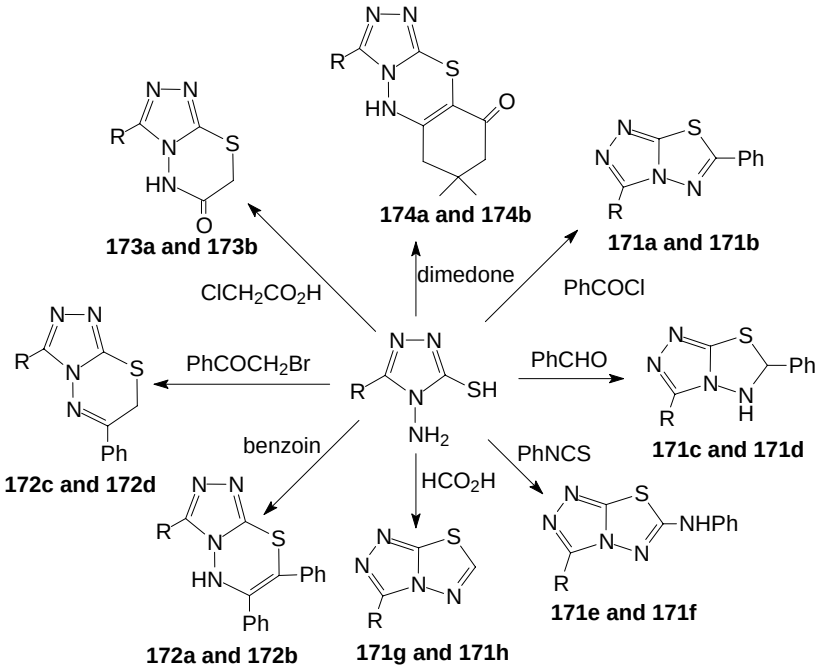


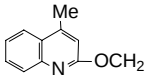
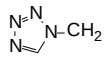
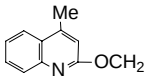
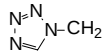
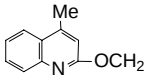
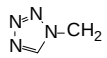
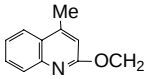
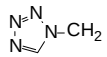
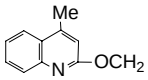
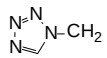
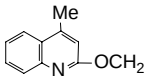
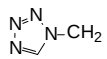
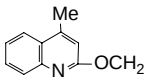
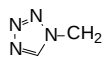
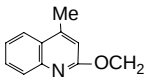
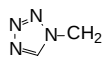
R^1	R^2	Yield (%)
Me	H	82
Me	CF_3CO	73
Ph	H	78
4-MeC_6H_4	H	73
4-$MeOC_6H_4$	H	73
4-ClC_6H_4	H	71
Ph	CF_3CO	69
4-MeC_6H_4	CF_3CO	65
4-$MeOC_6H_4$	CF_3CO	62
4-ClC_6H_4	CF_3CO	62

Scheme 90

4.4 Syntheses of triazolothiadiazoles, triazolothiadiazines, triazolothiadiazinones and triazolobenzothiadiazinones

Substituted bridgehead nitrogen heterocycles have obviously biological properties, such as antibacterial and antifungal activities. [144] Kidwai [145] reported the reactions of substituted 1,3,4-*s*-triazoles with aromatic acid chlorides , benzaldehyde, phenyl isothiocyanate, formic acid, benzoin, phenacyl bromide, chloroacetic acid and dimedone to give the target products[triazolothiadiazoles (**171**), triazolothiadiazine (**172**), triazolothiadiazinones (**173**) and triazolobenzothiadiazinones (**174**)] respectively under microwave irradiation and by conventional methods. The reaction rate was enhanced tremendously under microwave irradiation as compared to classical method with improved yield. (Scheme 91)

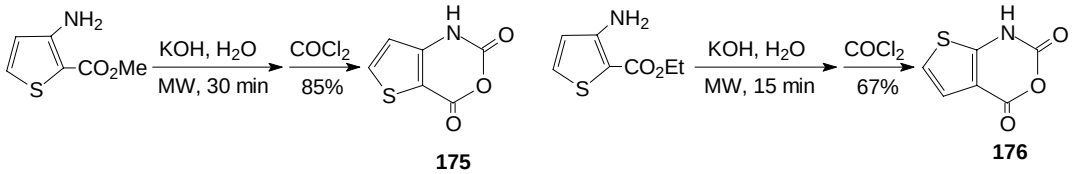


Compound	R	Time		Yield (%)	
		MW (min)	Classical heating (h)	MW	Classical heating
171a		4.0	6.0	70	40
171b		5.0	8.0	78	50
171c		3.0	9.0	90	70
171d		3.5	10.0	92	76
171e		10.0	18.0	83	60
171f		12.0	20.0	90	65
171g		2.0	2.0	85	70
171h		2.5	2.5	87	72
172a		1.0	2.0	85	60
172b		1.1	2.0	89	7
172c		1.5	8.0	70	50
172d		2.0	9.0	68	55
173a		3.0	10.0	80	60
173b		4.0	11.0	77	65
174a		2.0	3.0	50	30
174b		2.5	4.0	70	32

Scheme 91

4.5 Syntheses of 2- and 3-thiaisatoic anhydrides

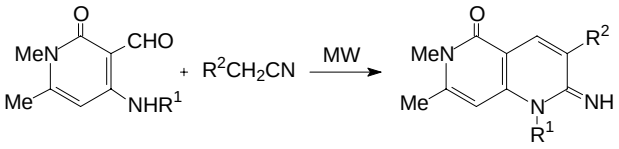
The anthranilic acid and its cyclic anhydride, the isatoic anhydride, are raw materials widely used in the field of heterocyclic chemistry. 2-Thiaisatoic anhydride (**175**) and 3-thiaisatoic anhydride (**176**) were synthesized in large scale under microwave heating conditions with 85% and 67% yields respectively.[146] (Scheme 92) When the reaction was run under classical heating, it required longer time than under microwave heating and led the formation of by-products and lower yields.



Scheme 92

4.6 Syntheses of naphthyridinones

1, 2-Dihydro-2-imino-7-methyl-1,6(6*H*)- naphthyridin-5-ones (**177**) were prepared by Knoevenagel reaction of substituted pyridones with CH-acidic nitriles. A comparative study of classical heating and microwave irradiation was run.[147] (Scheme 93)



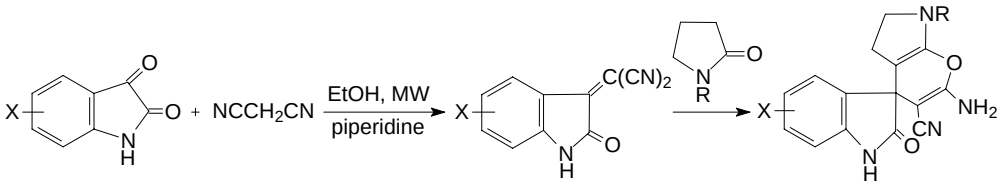
177

R^1	R^2	Time		Yield (%)	
		MW (min)	Classical heating (h)	MW	Classical heating
$PhCH_2$	CO_2Me	3	48	77	74
$PhCH_2$	CO_2Et	3	48	80	29
$PhCH_2$	CO_2Pr-*i*	3	48	82	67
$PhCH_2$	4-$NO_2C_6H_4$	6	20	65	40
$PhCH_2$	$CONH_2$	6	13	75	59
$PhCH_2CH_2$	CO_2Me	3	48	76	72
$PhCH_2CH_2$	CO_2Et	3	48	71	59
$PhCH_2CH_2$	CO_2Pr-*i*	3	48	79	68
$PhCH_2CH_2$	4-$NO_2C_6H_4$	6	20	56	24
$PhCH_2CH_2$	$CONH_2$	6	13	59	51

Scheme 93

4.7 Syntheses of spiro[3*H*-indole-3,4'(1*H*)pyrano[2,3-*c*]pyrrole]-5'-carbonitriles

The indole nucleus plays an important role as a common denominator for various biological activities.[148] Dandia and coworkers [149] investigated the reaction of 2-pyrrolidone / *N*-methyl-2-pyrrolidone with 3-dicyanomethylene-2*H*-indol-2-one (**178**) using absolute ethanol as energy transfer medium. The latter compound (**178**) was synthesized for the first time under microwave irradiation by the reaction of indole-2, 3-dione and malononitrile. The results were compared with those obtained following the classical method. The advantages obtained by the use of microwave irradiation were demonstrated. (Scheme 94)



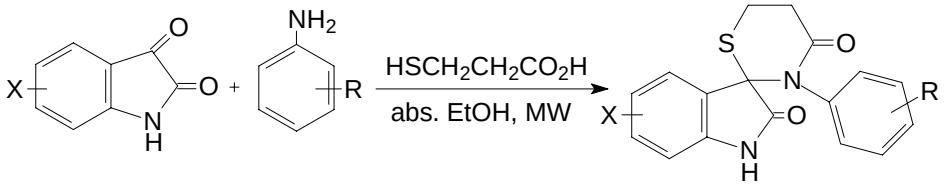
178 **179**

X	R	Time		Yield (%)	
		MW (min)	Classical heating (h)	MW	Classical heating
H	-	2	-	94	-
5-Me	-	3	-	70	-
5-Cl	-	3	-	70	-
H	H	10	16.0	78	56
H	Me	12	18.3	76	56
5-Me	H	10	20.0	73	54
5-Me	Me	13	9.3	75	57
5-Cl	Me	12	16.3	80	51

Scheme 94

4.8 Syntheses of spiro[indoline-3,2'-[1,3]thiazinane]-2,4'-diones

Dandia reported the one-step synthesis of fluorinated spiro[indoline-3,2'-[1,3]thiazinane]-2,4'-diones (**180**), both thermally and under microwave irradiation. From the results of a comparative study of the synthesis of the spiro compounds by the classical method using Dean-Stark apparatus and microwave irradiation, it was clear that the reaction time was reduced from several hours to only a few minutes by using microwave irradiation, indicating that the microwave plays an important role in the rate enhancement.[150] (Scheme 95)



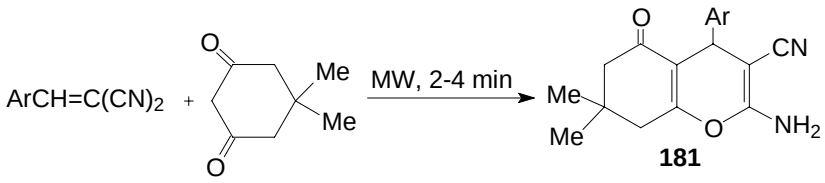
180

X	R	Time		Yield (%)	
		MW (min)	Classical heating (h)	MW	Classical heating
5-Cl	2-CF_3	14	15	72	68
5-Cl	3-CF_3	13	14	76	61
5,7-Me_2	3-CF_3	12	13	84	74
5-NO_2	4-F	18	16	68	55
H	2-CF_3	11	14	82	74
H	2,3,5,6-F_4	17	20	62	14

Scheme 95

4.9 Syntheses of 4*H*-benzopyran-3-carbonitriles

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-aryl-7,7-dimethyl-4*H*-benzopyran-3-carbonitril is a versatile synthons. A series of 2-amino-5,6,7,8-tetrahydro-5-oxo-4-aryl-7,7-dimethyl-4*H*-benzo-[*b*]-pyran-3-carbonitriles (**181**) were synthesized by reaction of benzylidenemalononitrile derivatives and 5, 5-dimethyl-1,3-cyclohexanedione under microwave irradiation without catalyst and solvent free.[151] (Scheme 96)



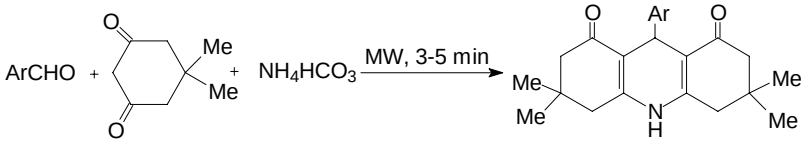
181

Ar	Time (min)	Yield (%)
Ph	2	91
2-BrC_6H_4	2	92
4-BrC_6H_4	2	96
2-$NO_2C_6H_4$	1.5	89
4-$Me_2NC_6H_4$	4	90
4-HOC_6H_4	4	89
3-HO-4-$MeOC_6H_3$	3	92

Scheme 96

4.10 Syntheses of 1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones

1, 4-Dihydropyridines are well-known compounds as a consequence of their pharmacological profile as calcium channel modulators.[152] The chemical modifications carried out on the DHP ring such as the presence of different substituents, heteroatoms have allowed expansion of the receptor level.[153] A simple synthetic method for the 9-aryl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones (**182**) was described. Heating aromatic aldehyde, dimedone and ammonium bicarbonate under irradiation for 3-5 min afforded the target compounds.[154] By refluxing dimedone, aromatic aldehyde in ammonium hydroxide solution in 1-2h, target compounds could be obtained in 50-70% yields.[155] (Scheme 97)



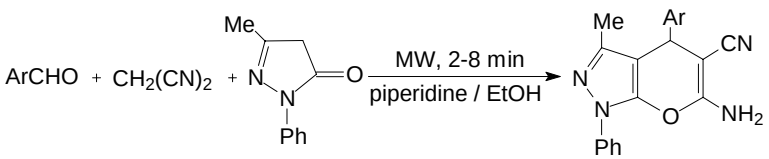
182

Ar	Time (min)	Yield (%)
Ph	5	90
2-ClC_6H_4	4	85
4-ClC_6H_4	4	92
4-$Me_2NC_6H_4$	7	91
3-$NO_2C_6H_4$	4	83
3,4-$(MeO)_2$ C_6H_3	6	89
3,4-$(OCH_2O)C_6H_3$	6	91
4-$MeOC_6H_4$	7	89

Scheme 97

4.11 Syntheses of pyrano[2,3-*c*]pyrazoles

Polyfunctionalized 4*H*-pyrans are a common structural unit in a number of natural products, 4*H*-pyrans ring can be transformed to pyridine systems related to pharmacologically important calcium antagonists of the DHP type.[156] Substituted pyrano[2,3-*c*]pyrazoles (**183**) could be obtained by a one-pot reaction of aromatic aldehydes, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one under microwave irradiation. The reaction was generally finished in 2-8 min with good yields and easy work-up.[157] (Scheme 98)



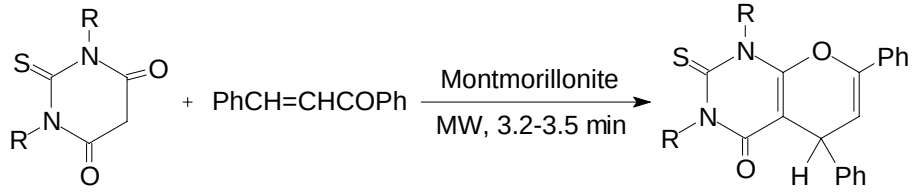
183

Ar	Time (min)	Yield (%)
Ph	8	61
4-ClC_6H_4	5	91
4-BrC_6H_4	5	80
4-$NO_2C_6H_4$	3	75
3-$NO_2C_6H_4$	3	73
4-$MeOC_6H_4$	2	66

Scheme 98

4.12 Syntheses of pyrano[2,3-*d*]pyrimidines

Pyranopyrimidines have been proved to be interesting due to their associated diverse biological activities.[158] Pyranopyrimidines (**184**) were synthesized by the condensation of thiobarbituric acids and chalcone on inorganic solid supports under microwave irradiation. Difference in activity of inorganic supports was studied.[159] For comparison, the solid supported reactions were carried out by conventional heating in oil bath, under similar reaction conditions of temperature. Heating on monomorillonite the required product was obtained in 5-6 h with only 50% yield. (Scheme 99)



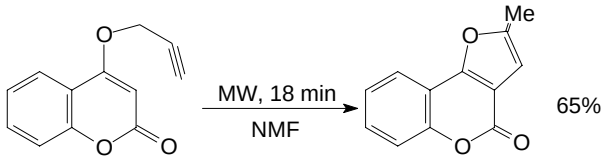
184

Ar	Time (min)	Yield (%)
Ph	8	61
4-ClC_6H_4	5	91
4-BrC_6H_4	5	80
4-$NO_2C_6H_4$	3	75
3-$NO_2C_6H_4$	3	73
4-$MeOC_6H_4$	2	66

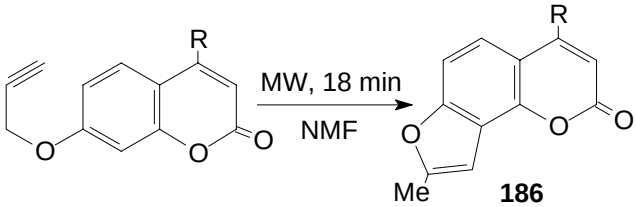
Scheme 99

4.13 Syntheses of pyranocoumarins and furocoumarins

Many compounds containing coumarin moieties are reported to have hypnotic, insecticidal, antifungal, anthelminitic, and other physiological properties. Some of these heterocycles are often employed as important intermediates leading to bioactive substances.[160] Propargyl ethers of 7-hydroxy-, 4-hydroxy- and 4-methyl-7-hydroxycoumarins had been efficiently rearranged to pyranocoumarins (**187**) and furocoumarins (**185, 186**) under microwave irradiation.[161] (Scheme 100)

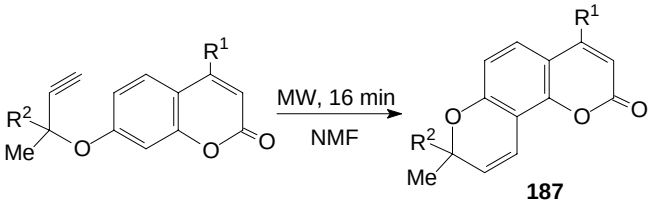


185



186

R	Yield (%)
H	70
Me	62



187

R^1	R^2	Yield (%)
H	H	80
Me	Me	71
H	Me	82

Scheme 100

5. CONCLUSIONS

There is no doubt that microwaves can be applied to great effect in the syntheses of heterocyclic compounds. The “in situ” generation of heat is very efficient and can be used to significantly reduce reaction times of numerous synthetically useful organic transformations. Thus microwave assisted organic synthesis has advantages over conventional technology: it is more energy efficient and it can lead to improved isolated yields of products. The possibilities for automation are clear and the opportunities for executing numerous reactions at the same time in the same microwave cavity is attractive if large numbers of compounds need to be prepared rapidly. The obvious application of this approach to combinatorial synthesis should provide a major impetus for further developments in this area.

It is worthy to note that microwave assisted synthesis, whilst still at an early stage of development, has much to offer synthetic chemists. However, questions about microwave mechanisms remain. Recently, Whittaker indicated that research into the mechanisms of microwave action should be the most intriguing aspect of the field. The exciting work at the moment is in understanding the fundamental principle of what happens.[162] But even if such effects are found to be artifacts, and there are no new physical phenomena to explore, the simple advantage of speed means that microwave chemistry is poised to become a growth area.

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