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MICROWAVE-ASSISTED SYNTHESIS OF 1,3,5-TRIAZINES: EFFICIENT APPROACHES TO THERAPEUTICALLY VALUABLE SCAFFOLD

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Abstract – 1,3,5-Triazine ring is an important scaffold for the construction of new biologically active compounds. Microwave irradiation has found an extensive application in organic and medicinal chemistry accelerating reactions and drug discovery process. This review systematizes methods for the microwave-assisted construction of 1,3,5-triazine ring and discusses their advantages and disadvantages over methods based on the conventional heating.

CONTENTS

1. INTRODUCTION

1,3,5-Triazines have been recognized as a promising scaffold for the design of new bioactive compounds,[1] primarily with anticancer properties.[2] Several important medicines have been constructed on this scaffold

and some of them have been approved for therapeutic applications. For example, melamine derivatives tretamine[3,4] and altretamine[5] found their application in the treatment of leukemia long time ago. Oteracil is used in combination therapy of advanced gastric cancer.[6] Glycosides of 5-azacytosine *viz*. azacitidine[7] and decitabine[8,9] are useful therapeutic agents for the treatment of acute and chronic leukemia. Recently, enasidenib joined the group of antileukemic drugs with the 1,3,5-triazine scaffold.[10] In 2017, this drug was approved by FDA for the treatment of relapsed or refractory acute myeloid leukemia. Almitrine has been found useful for the combination therapy of cerebral disorders associated with aging or stroke.[11] Gedatolisib is currently under clinical trials as a potential therapeutic agent for the treatment of breast cancer.[12]

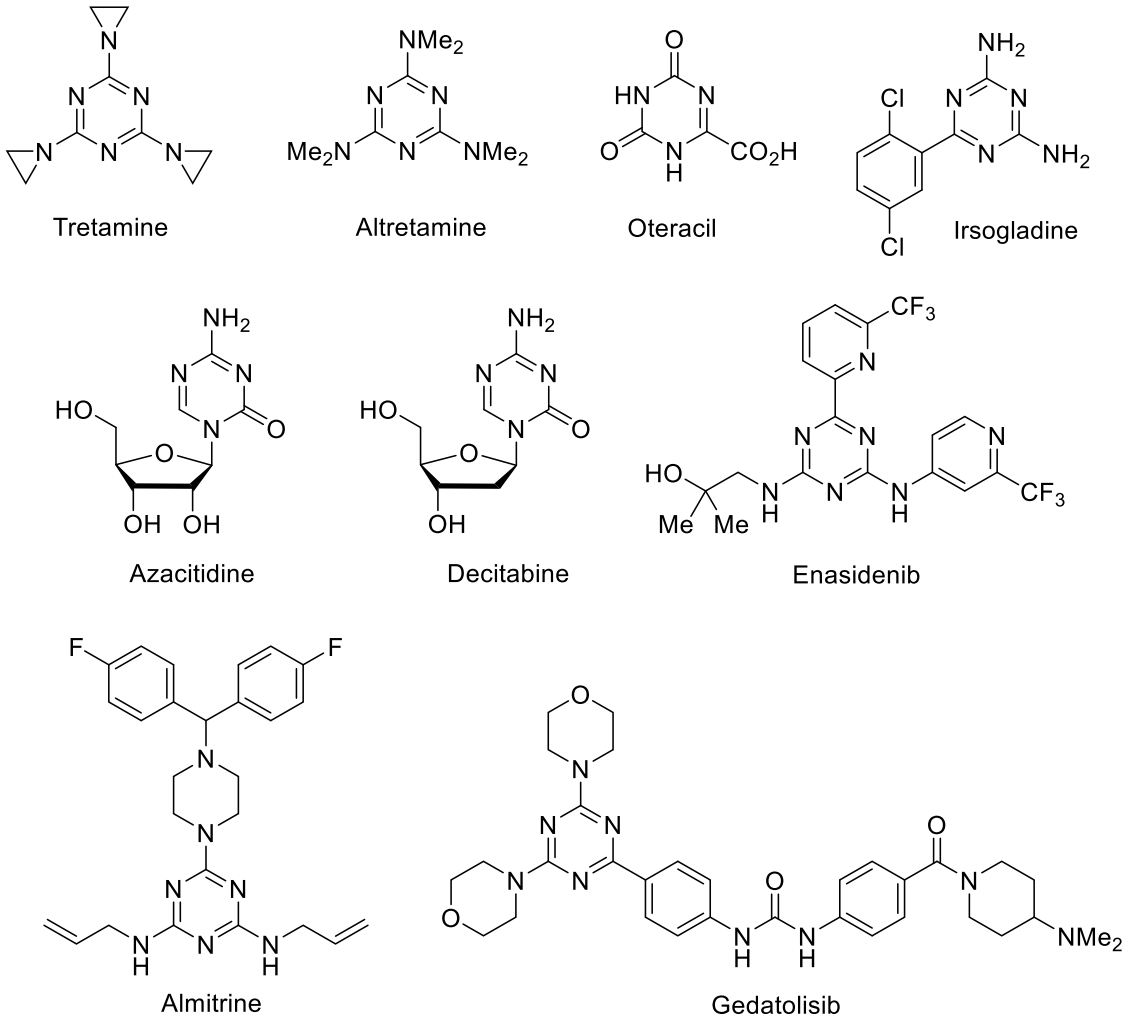


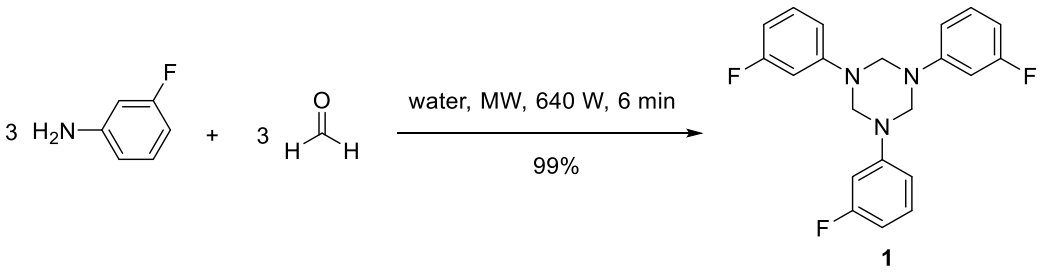
Figure 1

Despite a significant interest towards synthesis of bioactive heterocyclic compounds *via* microwave-assisted reactions,[13] use of microwave irradiation in the synthesis of 1,3,5-triazines has not been systematized. This review discusses methods for the construction of 1,3,5-triazine ring under microwave irradiation. These methods are grouped on the basis of saturation of the 1,3,5-triazine ring in

the reaction product in three main categories: synthesis of 1,3,5-triazinanes, dihydro-1,3,5-triazines, and aromatic 1,3,5-triazines. Additionally, microwave-assisted methods for the 1,3,5-triazine annulation leading to fused systems are discussed.

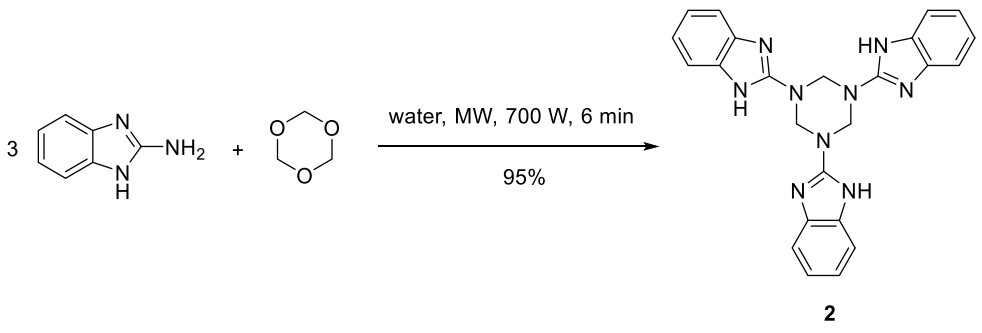
2. SYNTHESIS OF 1,3,5-TRIAZINANES

Since Bischoff's report[14] in 1898 that the reaction of anilines with formaldehyde resulted in the formation of trimerized Schiff bases, products of this reaction, 1,3,5-triaryl-1,3,5-triazinanes, found many applications in organic synthesis and as biologically active agents. Dandia et al.[15] performed conventional and microwave-assisted syntheses of 1,3,5-triazinane **1** (Scheme 1) and five other fluorinated analogues of this compound in aqueous medium. The application of microwave irradiation was demonstrated to significantly improve reaction yields and time. The yields increased to 98-99% compared to 62-78% obtained in the conventional heating protocol, while the reaction time was shortened to 3 min of microwave irradiation from 10 h of conventional heating. The prepared compounds demonstrated antifungal activity against agriculturally important *Rhizoctonia solani*, *Fusarium oxysporum*, and *Collectotrichum capsici*.



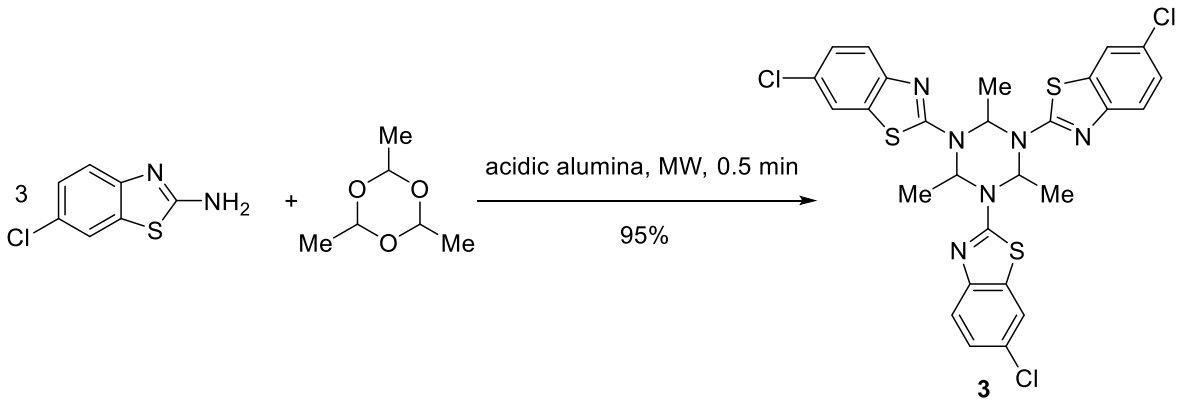
Scheme 1

The same research group also reported[16] a similar reaction performed in aqueous medium under microwave irradiation using metaformaldehyde and heterocyclic amines (5 examples, 94-96% yield). Even 2-aminobenzimidazole, which has a tendency to form a triazine fused to benzimidazole in the reaction with formaldehyde and other primary amines,[17] was reported[16] to afford triazinane **2** in high yield (Scheme 2).



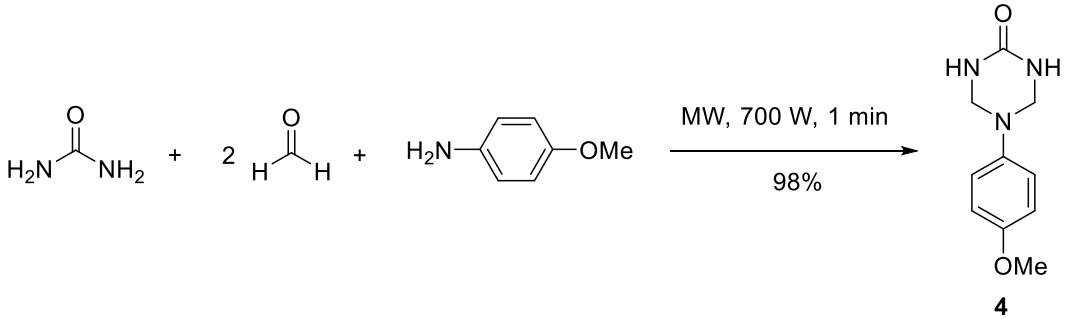
Scheme 2

In a similar condensation of 2-aminobenzothiazoles, scope of this microwave-assisted reaction was further extended by using acetaldehyde and crotonaldehyde instead of formaldehyde.[18,19] The microwave-assisted reaction (carried out in Q-pro-M modified domestic microwave system) provided an advantage over the conventional heating method increasing yields from 48-58% to 55-66% and reducing reaction time from 13 h to 3-3.5 min (18 examples).[18] The yields were further improved and reaction time shortened by using a solid-supported microwave-assisted protocols. The acidic alumina was particularly efficient as a support in this reaction increasing yields up to 95% after 0.5 min of microwave irradiation.[20] Compound **3**, prepared using this method (Scheme 3), demonstrated antiproliferative activity against MCF-7 breast cancer and Hep-G-2 hepatic cancer cells.[20] Some compounds from the synthesized series also demonstrated antibacterial, acaricidal, and antifeedant properties.[18]

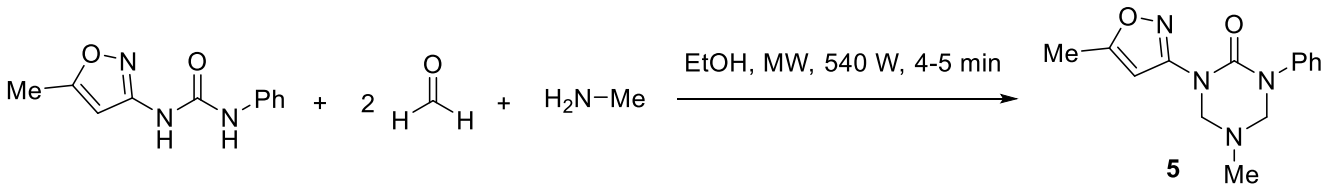


Scheme 3

The reaction of urea with aqueous formaldehyde and *p*-anisidine under microwave irradiation in domestic microwave oven was reported[20] to afford 1,3,5-triazinan-2-one **4** in a very good yield (Scheme 4). The same product was isolated when the reaction was performed in DMF at 40-45 °C for 12 h without microwave irradiation, but yield was only 53%. The *N,N′*-disubstituted ureas were also reported to react with formaldehyde and primary alkylamines in ethanol under microwave irradiation in a domestic microwave oven.[21] Using this reaction, a library of ten 1,3,5-triazinan-2-ones, *e.g.* compound **5** (Scheme 5), was prepared in 80-95% yields (not given for each compound specifically).

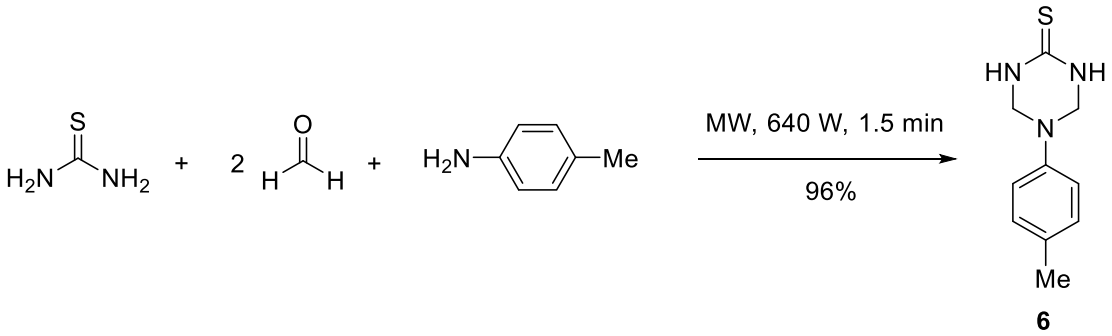


Scheme 4



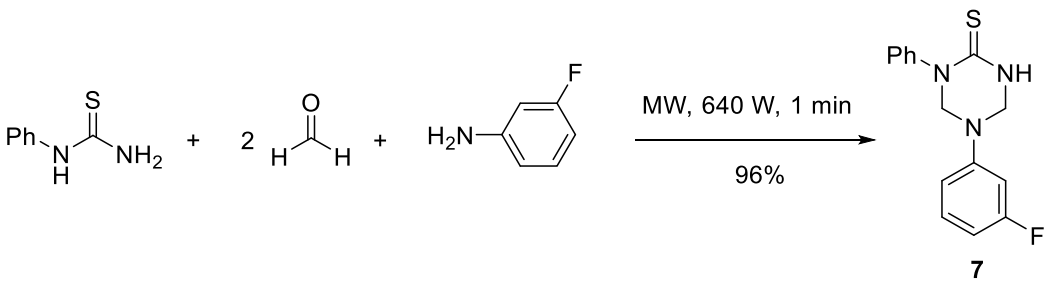
Scheme 5

A similar reaction of thiourea with formaldehyde and *p*-toluidine in solvent-free conditions resulted in the formation of 1,3,5-triazinane-2-thione **6** (Scheme 6).[20] The microwave irradiation allowed achieving a significantly higher yield (96%) compared to that obtained in the reaction in DMF at 40-45 °C for 12 h in the absence of microwave irradiation (58%).



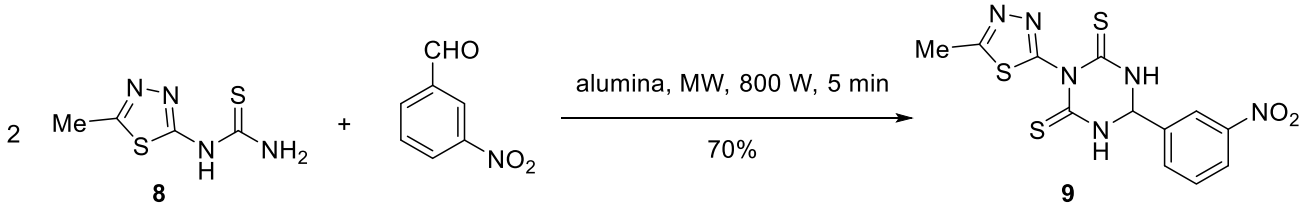
Scheme 6

The microwave-assisted synthesis of 1,3,5-triazinane-2-thiones was also performed using mono- and disubstituted thioures.[20,22] For example, compound **7** was prepared from *N*-phenylthiourea, formaldehyde and 3-fluoroaniline (Scheme 7).[20] Varying structures of *N*-arylthioureas and aromatic amines, a library of twelve 1,3,5-triazinane-2-thiones was prepared in good yields (92-98%) after a short irradiation time (2 min or less). Without microwave irradiation, yields were lower (50-58%) while duration of the reactions exceeded 10 h. The products were used as building blocks for the further construction of fused triazines. The microwave-assisted synthesis of eight 1,3,5-triazinane-2-thiones from *N,N'*-disubstituted ureas was reported[22] to proceed effectively (80-95% yields in 4-6 min) on the montmorillonite K-10 support.



Scheme 7

Kidwai and Mishra reported[23] the synthesis of 1,3,5-triazinane-2,4-dithione **9** on the acidic alumina solid support under microwave irradiation in a domestic Kenstar microwave oven (Scheme 8). The reaction involved two molecules of substituted thiourea **8** and one molecule of 3-nitrobenzaldehyde. Using thioureas with different substituents on the thiadiazole ring, seven compounds were prepared under these conditions in 68-80% yields. Changing the solid support from acidic alumina to montmorillonite K-10 clay resulted in lower yields (55-65%). The microwave irradiation was claimed[23] to give better results compared to the conventional heating (47-60% yields after 5-6 h of reflux in benzene in the presence of formic acid).



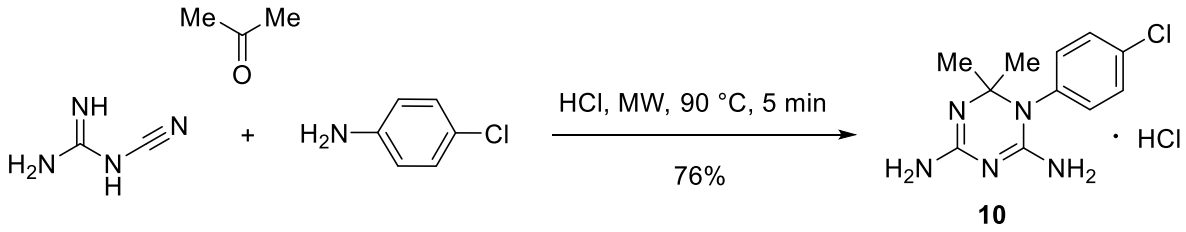
Scheme 8

Unfortunately, all methods described in this section were based on reactions performed in domestic microwave ovens without reliable control of conditions. Therefore, reproducibility of the results, even with minor changes in instrumentation or scale, is rather questionable. Despite attempts to compare the microwave-based protocols with the conventional processes in many of these works, the reaction conditions for these methods were too different to make a direct comparison and conclusion on specific microwave effect.

3. SYNTHESIS OF DIHYDRO-1,3,5-TRIAZINES

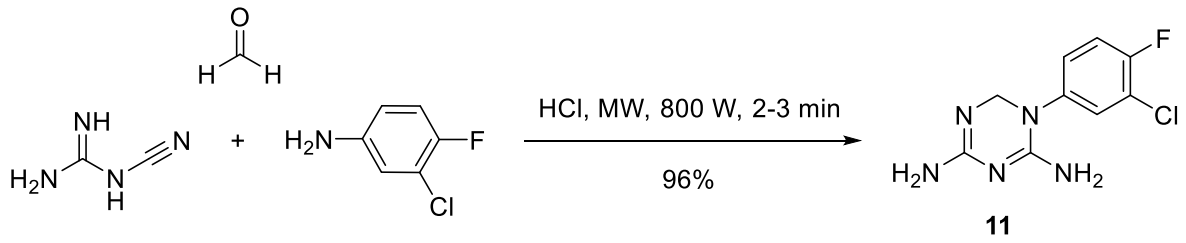
The one-step three-component procedure for the synthesis of cycloguanil (**10**) and two its analogues was first reported by Modest in 1952 by heating cyanoguanidine and anilines in acetone.[24] Then, Modest[25] further explored the scope of the reaction for the synthesis of 1-aryl-substituted 1,6-dihydro-1,3,5-triazine-2,4-diamines, which were prepared using conventional heating. In attempts to improve efficiency of the process, Lee and Rana[26] prepared a library of 1-aryl-6,6-dimethyl-1,6-dihydro-1,3,5-triazine-2,4-diamines using a microwave heating approach and compared it with the conventional one. The reactions were carried out using a mixture of cyanoguanidine with anilines in acetone, which played roles of solvent and a one-carbon inserting reagent in the triazine ring closure. It was demonstrated that the microwave irradiation of the mixture of cyanoguanidine and 4-chloroaniline in acetone in the presence of hydrochloric acid resulted in the formation of **10** in 76% yield (Scheme 9). Under conventional heating, the yield was slightly lower (69%). The method was successfully extended for the synthesis of a library of twenty representative compounds.

The microwave-assisted reactions were carried out in a CEM Discover microwave synthesizer maintaining temperature at 90 °C. Rather similar yields were obtained in reactions performed using conventional heating under reflux conditions (34-81%) and applying microwave irradiation (36-84%). However, the reaction time significantly decreased from 22 h of conventional heating under reflux to 5 min of heating under microwave irradiation.



Scheme 9

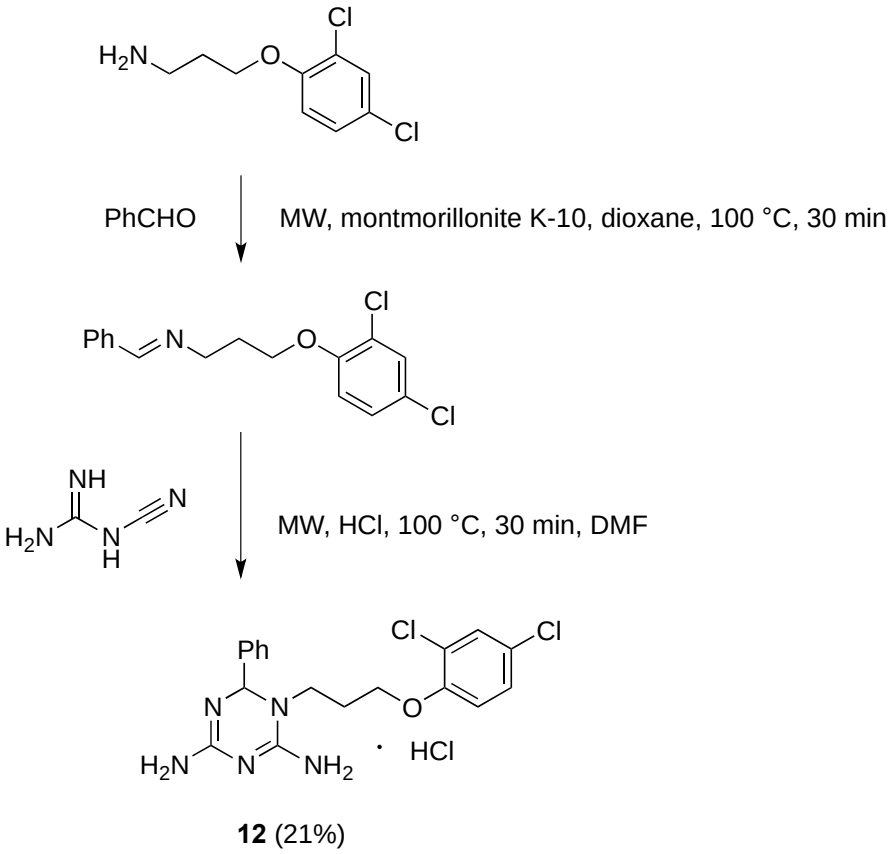
The same three-component approach was explored by Kidwai et al.[27] in the synthesis of bioactive 1-aryl-1,6-dihydro-1,3,5-triazine-2,4-diamines. The microwave irradiation was applied to the reaction of aldehydes and ketones with cyanoguanidine and anilines under solvent-free conditions to afford 1,6-dihydro-1,3,5-triazine-2,4-diamines. Interestingly, the three-component condensation using formaldehyde as a carbonyl reagent, previously reported to be unsuccessful under conventional heating, resulted in the formation of desired products in good yields (76-95%, 12 examples) under microwave irradiation conditions. However, the microwave reactions were carried out in a domestic microwave oven without accurate temperature control and therefore reproducibility of the method could be questionable. Compound **11**, effectively prepared using this method in the yield of 96% (Scheme 10), was found to possess an antiplasmodial activity against the cycloguanil-sensitive FJB-D9 and cycloguanil-resistant FJB-D4 strains of *Plasmodium falciparum* with IC_{50} values of 17.3 and 14.7 μM, respectively.



Scheme 10

In search for effective antifolate agents, thirty-eight cycloguanil analogues with the 6-aryl-1,6-dihydro-1,3,5-triazine-2,4-diamine scaffold were prepared using a one-pot microwave irradiation protocol.[28] Initially, the reaction of amines with benzaldehydes in the presence of

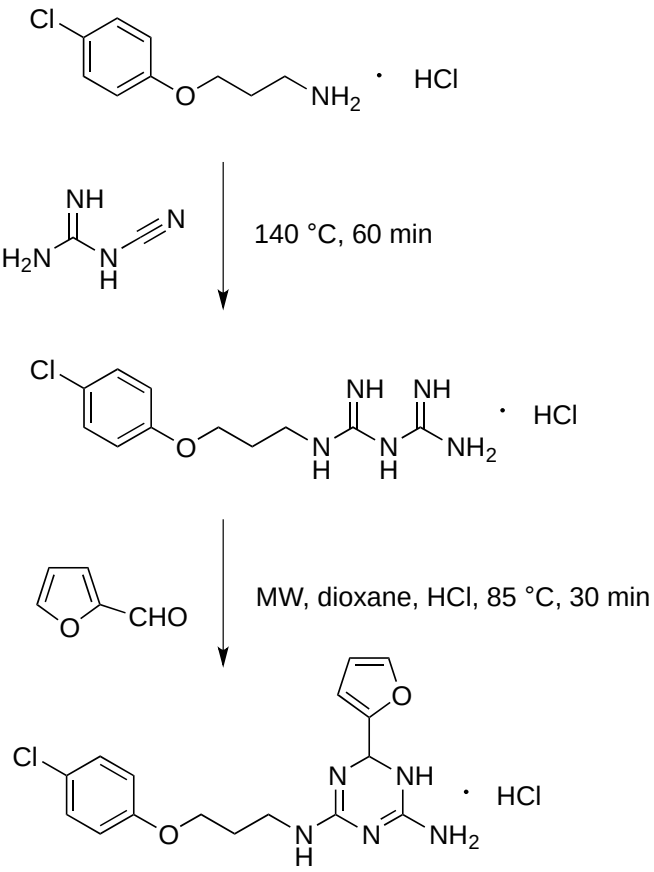
montmorillonite K-10 resulted in the formation of imines, which in the following step were subjected to the cycloaddition upon the treatment with cyanoguanidine in the presence of hydrochloric acid. The reaction was performed in a CEM Discover microwave synthesizer without isolation of the intermediate imines. The microwave irradiation decreased the reaction time to 30 min (from 2 h required for the reactions under conventional heating) but did not improve overall yields (4-53%). When tested on cycloguanil-resistant FCR-3 strain of *P. falciparum*, compound **12**, prepared by this method (Scheme 11) and possessing IC_{50} value of 2.7 nM, was the most active product in the series.[28]



12 (21%)

Scheme 11

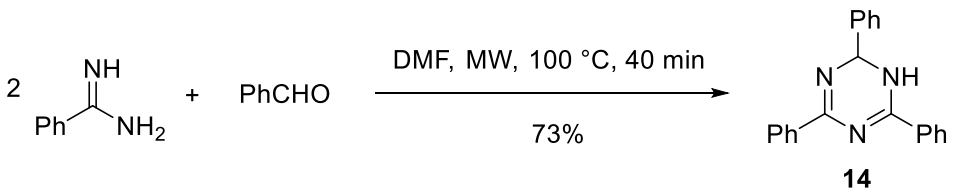
Interestingly, changing the sequence of steps in this microwave-assisted synthesis of dihydrotriazines resulted in the formation of regioisomeric products. When biguanides, prepared from cyanoguanidine and primary amines, reacted with aldehydes or ketones in the presence of hydrochloric acid in dioxane under microwave irradiation, N^2-substituted 1,6-dihydro-1,3,5-triazine-2,4-diamines were obtained.[29] A diverse library of twenty-eight representative compounds was prepared in yields varied from 12 to 70% and purity 71.3-99.2% depending on substituents. The antimalarial properties of the products were evaluated using a cycloguanil-resistant FCR-3 strain of *P. falciparum* and compound **13**, prepared as outlined in Scheme 12, was identified as the most active (IC_{50} = 0.99 μM) among described in this study[29] N^2-substituted 1,6-dihydro-1,3,5-triazine-2,4-diamines.



13 (48%)

Scheme 12

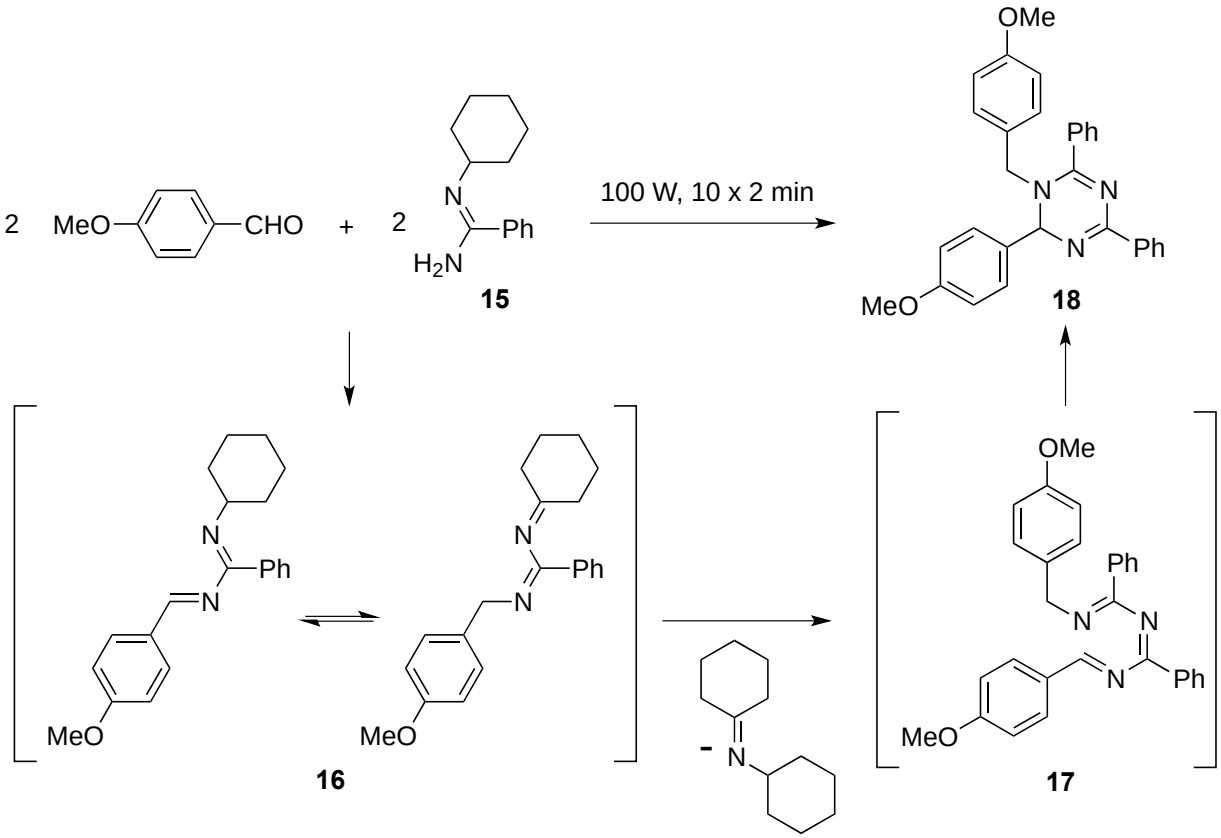
In an attempt to prepare 5-aminoimidazoles through microwave-assisted multicomponent reaction of benzaldehyde, benzamidine and trimethylsilyl cyanide, another product *viz*. 2,4,6-triphenyl-1,6-dihydro-1,3,5-triazine (**14**) was isolated either exclusively or in a mixture with the imidazole.[30] After optimization of the reaction conditions, **14** was obtained in 73% yield upon microwave irradiation of benzaldehyde and benzamidine in DMF using a CEM Discover microwave synthesizer (Scheme 13). It was found that the method could tolerate aliphatic aldehydes and benzaldehydes with electron-donating substituents. No products were detected when 4-nitrobenzaldehyde was used in the reaction. Seven 1,6-dihydro-1,3,5-triazines were obtained (51-89% yields) by applying this method to the reaction of various benzamidines and aldehydes.



14

Scheme 13

The reaction of *N*-cyclohexylbenzamidine (**15**) with *p*-anisaldehyde was claimed[31] to proceed under microwave irradiation with the formation of 1,6-dihydro-1,3,5-triazine **18** in a good yield, which unfortunately was not specified (Scheme 14). A similar product was obtained when *p*-dimethylaminobenzaldehyde reacted with **15**. It was proposed that initially formed **16** underwent imine metathesis with its tautomer to afford **17**, which then underwent the triazine ring-closure to **18**. The reaction of **15** with unsubstituted benzaldehyde and benzaldehydes bearing electron-withdrawing substituents stopped at the formation of analogues of **16** and did not proceed further. The lack of experimental details and proper temperature control in the reaction decrease practical value of this interesting method for the synthesis of dihydrotriazines.

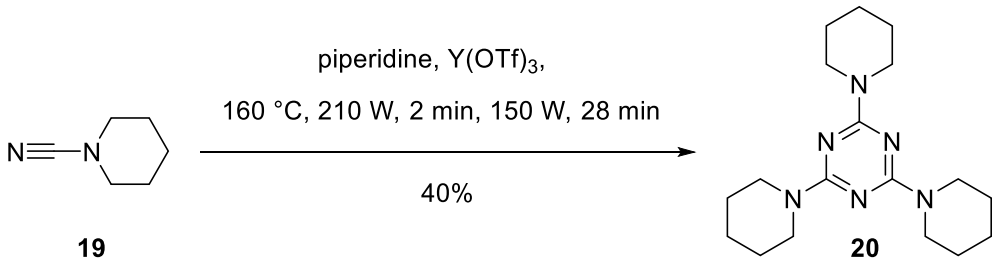


Scheme 14

4. SYNTHESIS OF AROMATIC 1,3,5-TRIAZINES

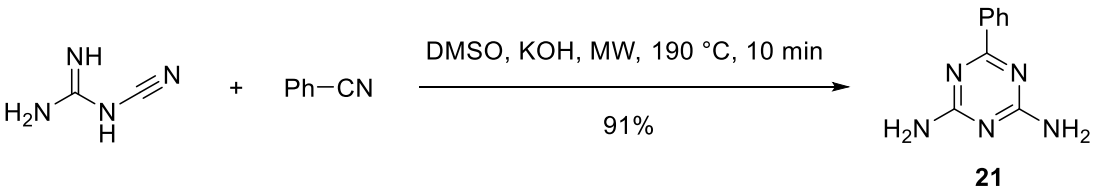
The cyclotrimerization of nitriles has been known as a method for the synthesis of symmetrically substituted 1,3,5-triazines for a long time.[32] The reactions are typically long and require very high pressure and temperatures. To make the trimerization more efficient, various catalysts, including more recently reported lithium nitride,[33] silica-supported zinc(II), aluminum(III), or titanium(IV) chlorides,[34] triflic acid,[35] triflic anhydride,[36] and yttrium(III) triflate,[34] were used. An attempt to use microwave irradiation for this process was also reported.[34] The solvent-free microwave irradiation of

N-cyanopiperidine (**19**) in piperidine under yttrium(III) triflate catalysis using a PROLABO Maxidigest focused microwave reactor resulted in the formation of triazine **20** (Scheme 15). The conventional heating (200 °C, 24 h) for the same reaction was less efficient and afforded **20** in a lower yield (31%). However, conventional heating resulted in a higher yield of a similar triazine (84%) compared to the microwave conditions (37%) when *N*-cyanomorpholine was used instead of **19**. Moreover, no triazine was isolated when the cyclotrimerization of benzonitrile was attempted under microwave irradiation using the same catalyst, while conventional heating of benzonitrile afforded 2,4,6-triphenyl-1,3,5-triazine in the 55% yield. All attempts to achieve cyclotrimerization of nitriles using the silica-supported Lewis acid catalysts were less successful under microwave irradiation compared to those under conventional heating.

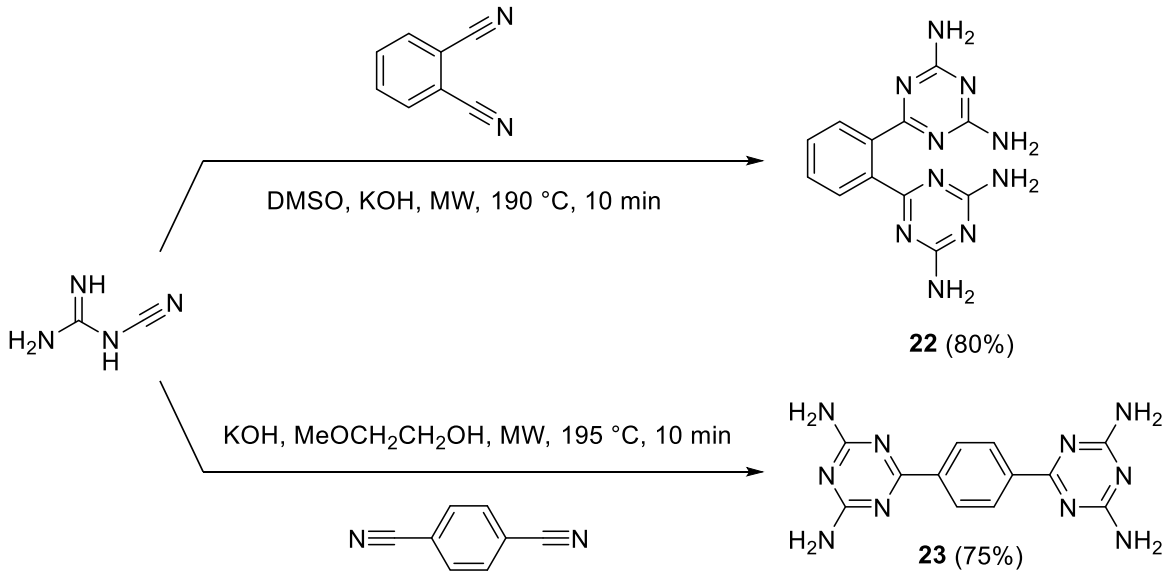


Scheme 15

A few examples of efficient applications of microwave irradiation were reported[37-39] for the cyclization of cyanoguanidine to 1,3,5-triazine-2,4-diamines upon the treatment with nitriles. Thus, the treatment of cyanoguanidine with benzonitrile in DMSO in the presence of a base under microwave irradiation in the PROLABO Maxidigest focused microwave reactor resulted in the formation of 6-phenyl-1,3,5-triazine-2,4-diamine (**21**) in good yield (Scheme 16).[37] The method tolerated various aromatic nitriles, including heterocyclic, and disubstituted cyanamides like **19**. Ten compounds were prepared from these nitriles in yields of 52-99%. Moreover, bistriazines **22** and **23** were successfully obtained by the microwave-promoted triazine ring closure of cyanoguanidine with phthalonitrile[37] and therephthalonitrile,[38] respectively (Scheme 17). Bistriazine **23** was used for the preparation of a polymeric heterogeneous organocatalyst.[38]



Scheme 16



Scheme 17

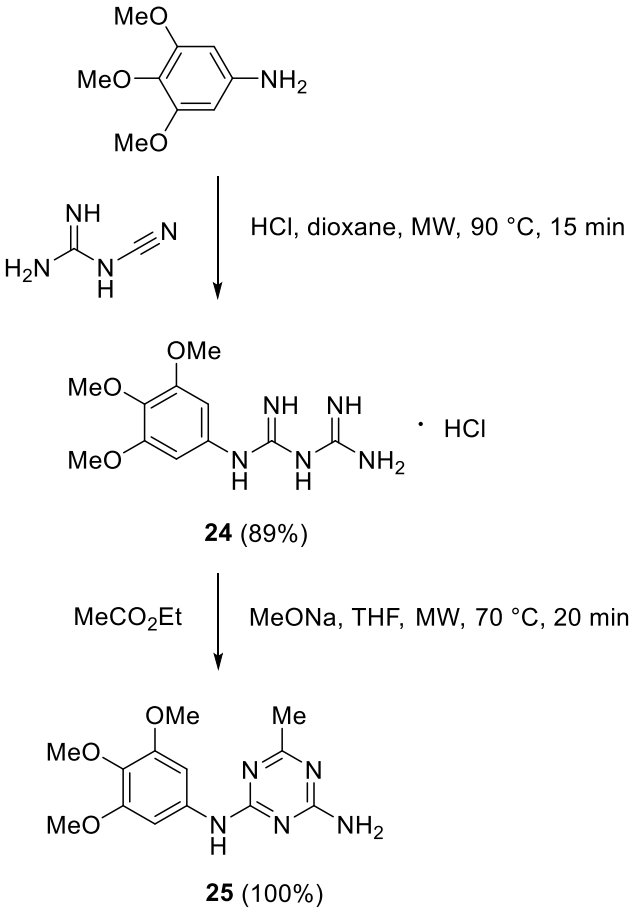
Peng and Song reported[39] an ionic liquid, [bmim][PF_6], as a medium used instead of DMSO in the reaction of cyanoguanidine with nitriles. The high polarity of ionic liquids makes them ideal media for microwave-assisted reactions.[40] The reaction of cyanoguanidine with benzonitrile in the presence of a base (KOH) using [bmim][PF_6] as a medium was performed under microwave irradiation in an Emrys Optimizer monomode microwave parallel synthesizer at 130 °C for 12 min affording **21** in 87% yield.[39] Similarly, eight substituted benzonitriles were used in this reaction to prepare 6-aryl-1,3,5-triazine-2,4-diamines in 70-87% yields.

A multicomponent approach for the microwave-assisted synthesis of 6-substituted 1,3,5-triazine-2,4-diamines have been also described.[41] This method was based on reactions of cyanoguanidine with nitriles formed from aldehydes *in situ*. Under microwave irradiation in the presence of Cu/Zn-modified MCM-41 (a mesoporous material with silicon atoms replaced with a transition metal) cyanoguanidine reacted with hydroxylamine and aromatic aldehydes affording 6-aryl-1,3,5-triazine-2,4-diamines. It was suggested that mechanism of the reaction involved initial formation of nitriles from hydroxylamine and corresponding aldehydes. The reactions were carried out in a Milestone MicroSynth microwave synthesizer in a solvent-free manner at 80 °C for 10-18 min and 6-subtituted-1,3,5-triazine-2,4-diamines (11 examples) were isolated in high yields (85-93%). Particularly, 6-phenyl-1,3,5-triazine-2,4-diamine (**21**) was obtained by this method in 93% yield after 14 min of exposure of the reaction mixture to microwave irradiation. It was demonstrated that microwave irradiation improved the reaction efficiency; when the reaction was carried out under conventional heating (100 °C) for 14 h, yield of **21** was 81%.

In another method,[42] nitriles were preformed from aromatic aldehydes by their treatment with ammonia

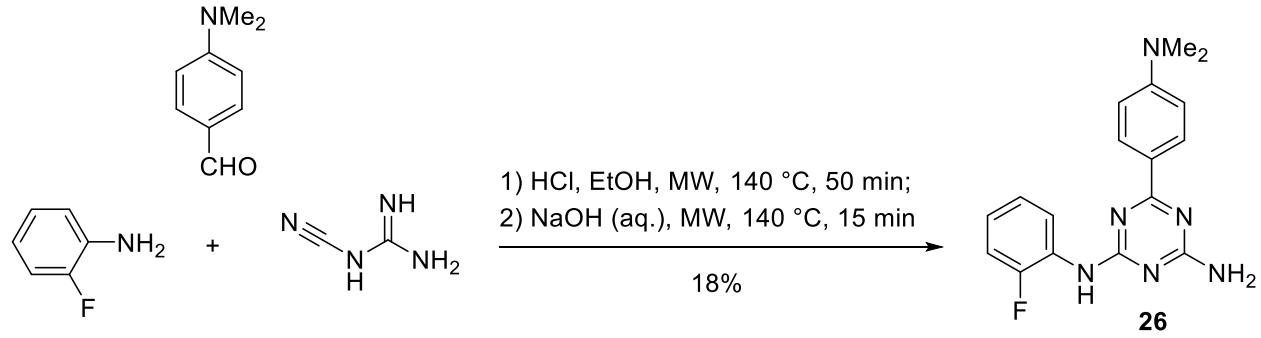
and iodine in a THF solution; then cyanoguanidine was added and microwave irradiation was applied for 15-30 min maintaining temperature at 80 °C. The reaction performed in this one-pot manner resulted in the formation of 1,3,5-triazine-2,4-diamines, but yields of products were lower (69-83%).

The synthesis of N^2-substituted 1,3,5-triazine-2,4-diamines typically involves condensation of biguanides with esters in the presence of a strong base. Microwave irradiation was effectively applied to promote this approach for the synthesis of N^2-substituted 1,3,5-triazine-2,4-diamines.[43,44] Biguanide **24** was initially prepared from 3,4,5-trimethoxyaniline by its addition to the nitrile group of cyanoguanidine in the presence of acid under microwave irradiation (Scheme 18).[43] The triazine ring-closure with the formation of **25** was achieved quantitatively upon microwave-assisted reaction of **24** with ethyl acetate in the presence of sodium methoxide. A similar reaction of **24** with ethyl trifluoroacetate afforded a fluorinated analogue of **25** in quantitative yield, while the same reaction with ethyl formate gave the corresponding triazine in 90% yield. The reaction of moroxydine hydrochloride (prepared using morpholine instead of 3,4,5-trimethoxyaniline) with ethyl acetate under this microwave-assisted protocol resulted in the formation of 4-morpholino-6-methyl-1,3,5-triazin-2-amine in 88% yield.[44]



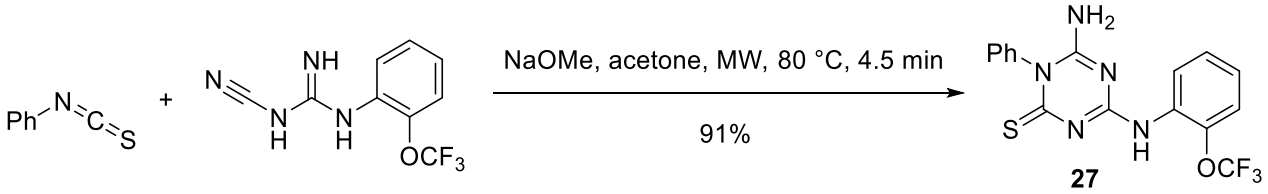
Scheme 18

A library of 110 compounds with N^2-substituted 1,3,5-triazine-2,4-diamine scaffold was prepared using a one-pot microwave-assisted method combining three-component triazine ring formation, rearrangement, and dehydrogenative aromatization.[45] The diversity in this reaction was achieved by using various combinations of primary aromatic amines and aldehydes in their reaction with cyanoguanidine. Yields of the prepared compounds varied from 18 to 81% and depended on substituents at both aromatic rings. Electron-donating groups in amine components and more electron-withdrawing groups in aldehydes generally increased yields. The prepared compounds were found to possess anticancer properties with triazine **26**, synthesized using this method (Scheme 19), being almost 10 times more active in inhibiting proliferation of DU145 prostate cancer cells than nilotinib.



Scheme 19

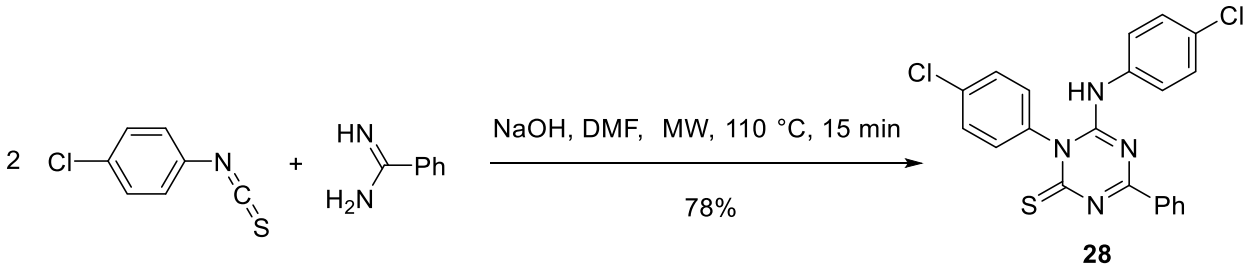
N-Arylcyanoguanidines were reported[46] to react with aryl isothiocyanates to afford 1,3,5-triazine-2(1*H*)-thiones (*e.g.* **27**, Scheme 20). The products were successfully obtained under microwave irradiation at 80 °C for 4.5-5 min in yields 84-92%. The evaluation of antimicrobial properties of the prepared triazines identified **27** as the most promising compound in the series. It possessed antibacterial activity comparable with that of chloramphenicol.



Scheme 20

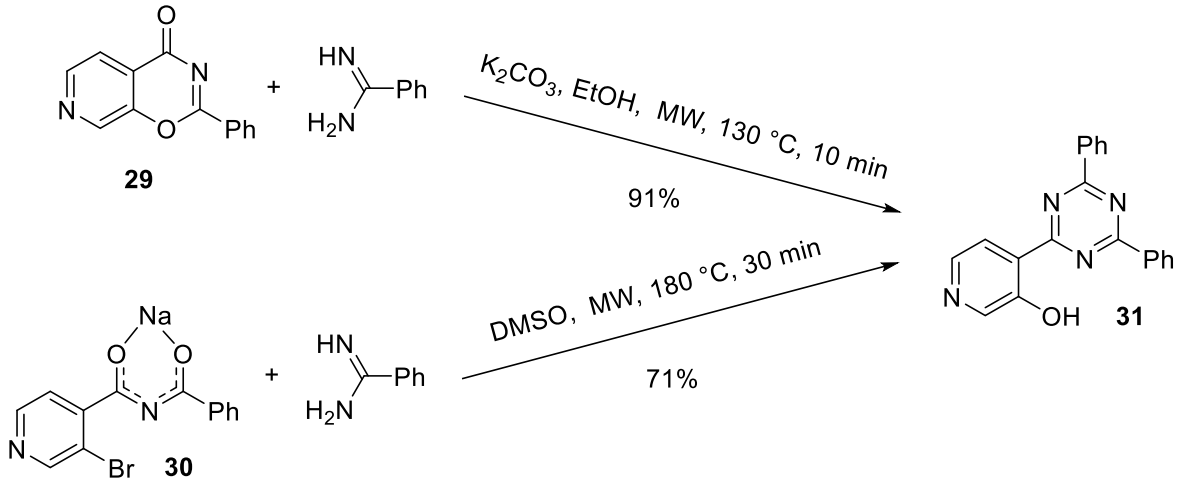
Another microwave-assisted multicomponent reaction reported[47] to produce 1,3,5-triazines by the interaction of an amidine with two molecules of aryl isothiocyanate. For example, from the reaction of benzamidine with two molecules of 4-chlorophenyl isothiocyanate in the presence of a base, 1,3,5-triazine-2(1*H*)-thione **28** was isolated (Scheme 21). This method was rather general in scope and was successfully applied to different aryl isothiocyanates and aromatic (including heteroaromatic)

amidines as illustrated by the synthesis of twenty-four representative examples (60-84% yields).



Scheme 21

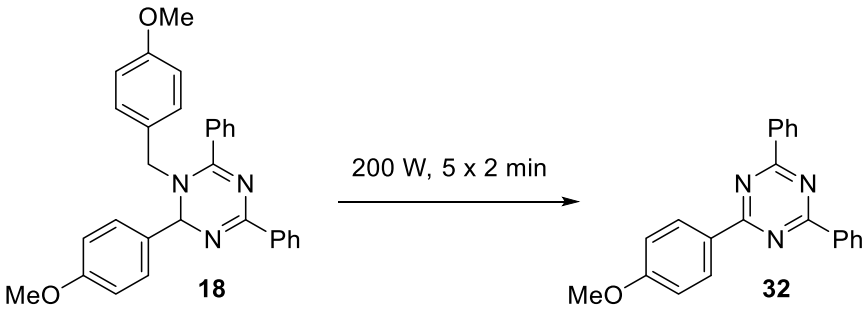
Amidines were also effectively involved in microwave-assisted reactions with pyrido[1,3]oxazin-4-ones.[48] Thus, microwave heating of benzamidine with pyrido[4,3-*e*][1,3]oxazin-4-one **29** resulted in the formation of triazine **31** (Scheme 22). A similar reaction also took place with a regioisomer of **29** possessing the [3,2-*e*] ring junction. A representative library of thirty-three compounds with different combinations of aromatic and heterocyclic substituents in positions 2, 4, and 6 of the 1,3,5-triazine ring was prepared in 55-97% yields using this methodology. The same product **31** was obtained when precursor of **29**, the imide sodium salt **30**, reacted with benzamidine. With some adjustments of the reaction conditions, eleven 2,4,6-trisubstituted 1,3,5-triazines were prepared in 45-84% yields.



Scheme 22

The formation of 2,4,6-triaryl-1,3,5-triazines was also reported to take place *via* a microwave-promoted debenzylation-aromatization process.[31] When dihydrotriazine **18**, prepared using microwave irradiation at 100 W, was subjected to irradiation at higher power (200 W), triazine **32** was isolated (Scheme 23). Unfortunately, the scope of this method was not explored and its practicality also remains questionable. Only one more compound with a dimethylamino group instead of methoxy group in **32** was prepared.

Moreover, temperature profile during the reaction was not monitored and yields of the products were not reported.

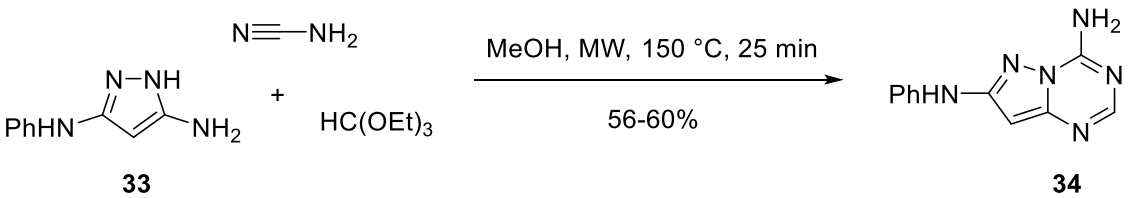


Scheme 23

5. SYNTHESIS OF FUSED 1,3,5-TRIAZINES

Several fused heterocyclic systems have been prepared constructing the 1,3,5-triazine ring *via* microwave-assisted reactions. A substantial work has been done on pyrazolo[1,5-*a*][1,3,5]triazines, imidazo[1,2-*a*][1,3,5]triazines, and 1,2,4-triazolo[1,5-*a*][1,3,5]triazines, particularly due to the interest to these heterocyclic systems as purine isosteres.[49-52]

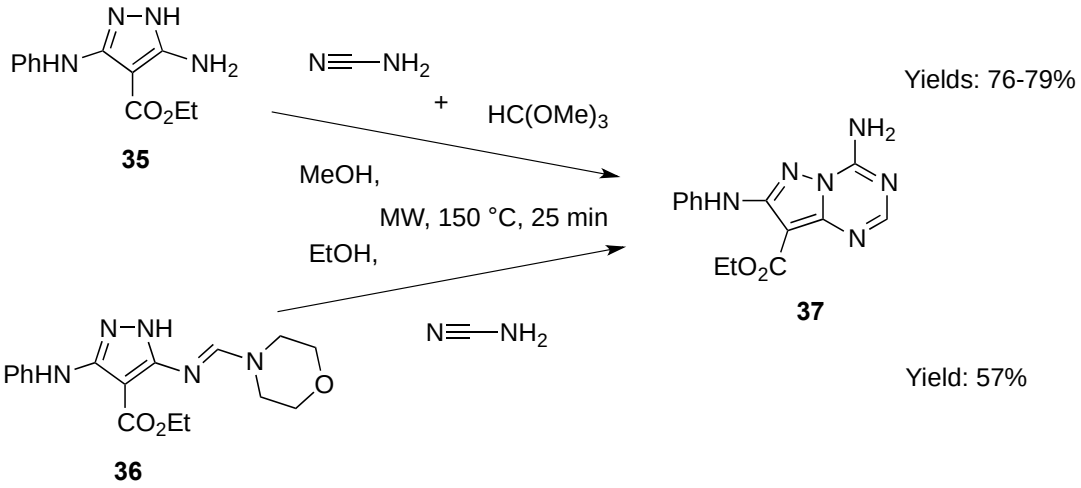
An efficient microwave-assisted three-component method for the synthesis of 5-aza-9-deaza-analogues of adenine was developed and its scope was extensively explored.[53-57] The reaction of 5-aminopyrazole **33** with cyanamide and triethyl orthoformate under microwave irradiation in a CEM Discover SP microwave reactor afforded pyrazolo[1,5-*a*][1,3,5]triazine **34** in 60% yield (Scheme 24).[53] The same conditions applied to the reaction in an Anton Paar Monowave 400 reactor produced **34** in a comparable yield (56%). Moreover, an Anton Paar Monowave 50 reactor, imitating the microwave heating pattern *via* fast conventional heating, was almost equally effective (53% yield) for this reaction. These observations excluded activation of the reaction process by non-thermal effects of microwave irradiation. Twelve 7-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazin-4-amines were prepared by this reaction in the series using different 5-aminopyrazoles (43-79% yields).[53] The selectivity of the reaction and its scope were further explored by the introduction of different functional groups to the starting 5-aminopyrazole structures: additional nitrile group in the position 4 (26 examples, 35-71% yields)[54,55] or aromatic rings in position 3 or 4 instead of the substituted amino group (12 examples, 60-73%).[56]



33 34

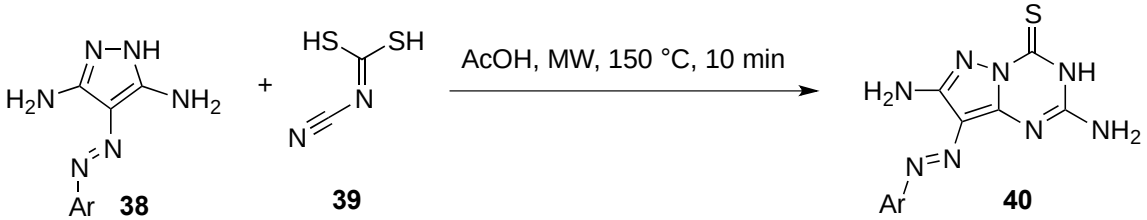
Scheme 24

This three-component reaction was similarly performed with trimethyl orthoformate instead of the triethyl orthoester. The microwave-assisted reaction of 5-aminopyrazole **35** with cyanamide and trimethyl orthoformate in a CEM Discover SP microwave reactor proceeded selectively and afforded **37** in 79% yield (Scheme 25).[57] The reaction was reproducible in other monomode microwave reactors. Similar yields (77%) were obtained when this reaction was performed under the same conditions in Anton Paar Monowave 450 or Biotage Initiator reactors. Scaling up the reaction 10 times resulted in a similar outcome (76%). Together with pyrazolo[1,5-*a*][1,3,5]triazine **37**, this method was used in the synthesis of twenty-three more analogues of **37** in yields ranging from 65 to 95%. Compound **37** was also prepared, but in lower yield, by the microwave heating of amidine **36** with cyanamide under similar conditions in ethanol.[57] In an attempt to use *N,N*-dimethylformamidine analogue of **36**, the yield further dropped to 35%. It should be noted that the same reactions of these pyrazolylamidines in methanol were complicated by a partial transesterification furnishing a mixture of two products.



Scheme 25

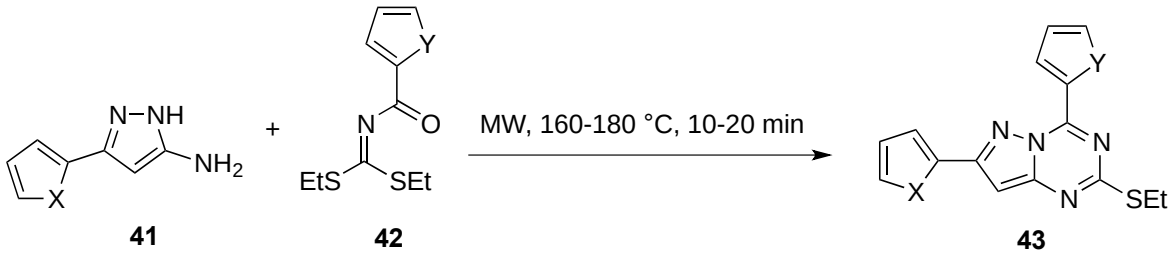
The reaction of diaminopyrazole **38** with *N*-cyanocarbonimidodithioic acid (**39**) under microwave irradiation was reported[58] to result in the formation of **40** (Scheme 26). A disodium salt of **39** reacted similarly under the same conditions.



Ar = Ph, 82% (**40a**); 4-MeOC$_6$H$_4$, 82% (**40b**); 4-MeC$_6$H$_4$, 85% (**40c**); 4-ClC$_6$H$_4$, 85% (**40d**); 4-BrC$_6$H$_4$, 80% (**40e**)

Scheme 26

A solvent-free synthesis of pyrazolo[1,5-*a*][1,3,5]triazines **43** was performed using condensation of 5-aminopyrazoles **41** and *N*-acylimidodithiocarbonates **42** under microwave irradiation in a CEM Discover microwave reactor using an open-vessel mode (Scheme 27).[59] The same reaction under conventional heating in DMF was less efficient affording **43** in 71-83% yield after 1-2 h of heating.

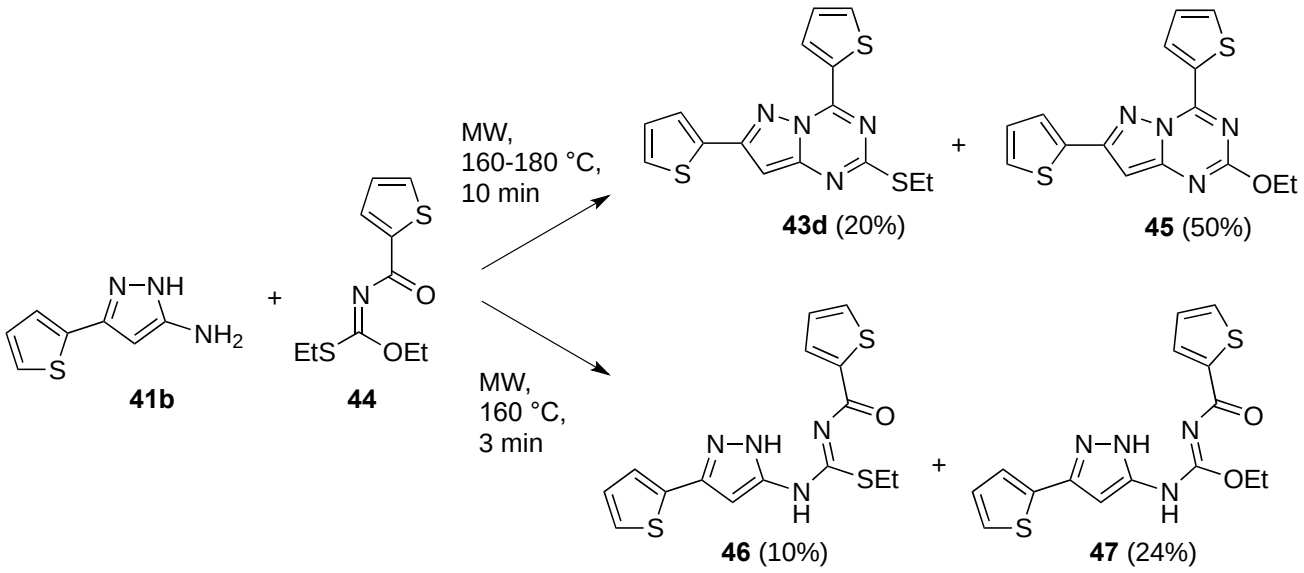


41 **42** **43**

X = Y = O, 95% (**43a**); X = O, Y = S, 91% (**43b**); X = S, Y = O, 93% (**43c**); X = Y = S, 90% (**43d**)

Scheme 27

A similar microwave-assisted reaction of 5-aminopyrazoles was also carried our using *O,S*-diethyl *N*-acylimidothiocarbonates and resulted in the formation of a mixture of two products. For example, 5-amino-3-(2-thienyl)pyrazole (**41b**) reacted with **44** producing a mixture of two chromatographically separable pyrazolo[1,5-*a*][1,3,5]triazines **43d** and **45** (Scheme 28). This reaction, performed using five different 5-amino-3-(het)arylpyrazoles and **44** or its 2-furyl analogue, demonstrated that 2-ethoxy products formed after 10-20 min of microwave irradiation were always predominant (46-65%), while ethylthio products were isolated in lower yields (11-20%).[59,60] The selectivity of this reaction carried out under conventional heating was nearly identical to that of the microwave-assisted process, but yields of the products were lower (36-55% - major; 5-12% - minor) and reaction time was longer (1-2 h).

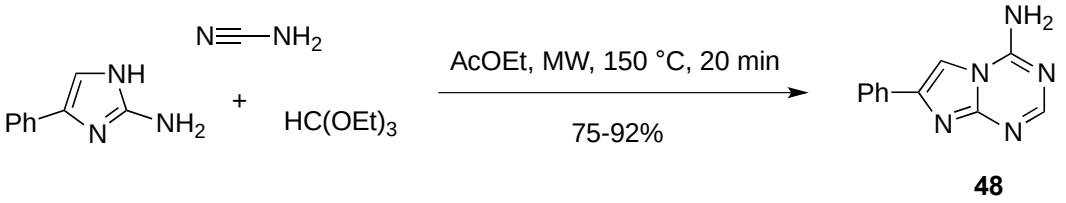


41b **44** **43d** (20%) **45** (50%) **46** (10%) **47** (24%)

Scheme 28

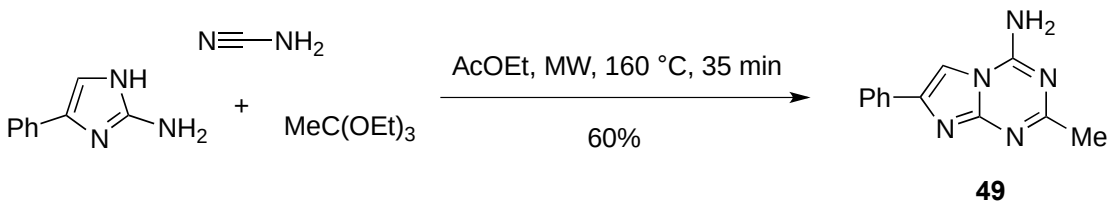
When the reaction of **41b** and **44** was performed for 3 min at 160 °C, the triazine ring did not close and a mixture of two intermediates (**46** and **47**) was obtained (Scheme 28).[59] The microwave irradiation of **46** and **49** for 10 min at 180 °C resulted in the triazine ring closure producing the corresponding **43d** and **45**, thus confirming the regiochemistry of the ring closure.

The three-component reaction of 2-amino-4-phenylimidazole, cyanamide, and triethyl orthoformate under microwave irradiation was used for the regioselective 1,3,5-triazine ring closure and synthesis of 4-amino-7-phenylimidazo[1,2-*a*][1,3,5]triazine (**48**) (Scheme 29).[61] This method was optimized in a CEM Discover SP microwave reactor to afford 83% of **48** and then was reproduced using Anton Paar Monowave 450 and Biotage Initiator+ systems with 80% and 75% yields, respectively. After the scale-up of the reaction from 1 to 10 mmol, the isolated yield increased to 92% (Discover SP). The reaction was successfully performed with a variety of 2-aminoimidazoles to generate twelve 7-aryl substituted analogues of **48** in 71-92% yield.



Scheme 29

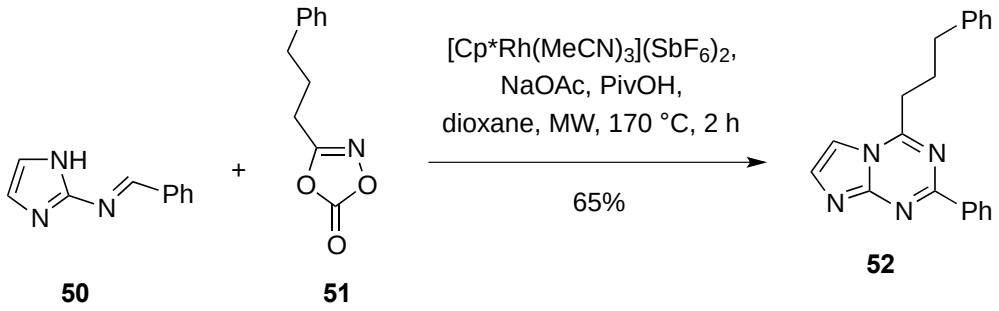
For a similar three-component microwave-assisted reaction of 2-aminoimidazoles with cyanamide and higher trialkyl orthoesters, the reaction conditions were modified by increasing the reaction temperature and time.[62] For example, the reaction performed in a CEM Discover SP reactor utilizing triethyl orthoacetate afforded imidazo[1,2-*a*][1,3,5]triazine **49** in 60% yield after 35 min heating at 160 °C (Scheme 30). These conditions were applied for the synthesis of 2-alkyl-4-amino-7-arylimidazo[1,2-*a*]-[1,3,5]triazines (24 examples). In general, their yields were found to decrease with the 2-alkyl chain growth from methyl (30-61%) to ethyl (25-61%), propyl (16-52%), and further butyl (11-43%) group.



Scheme 30

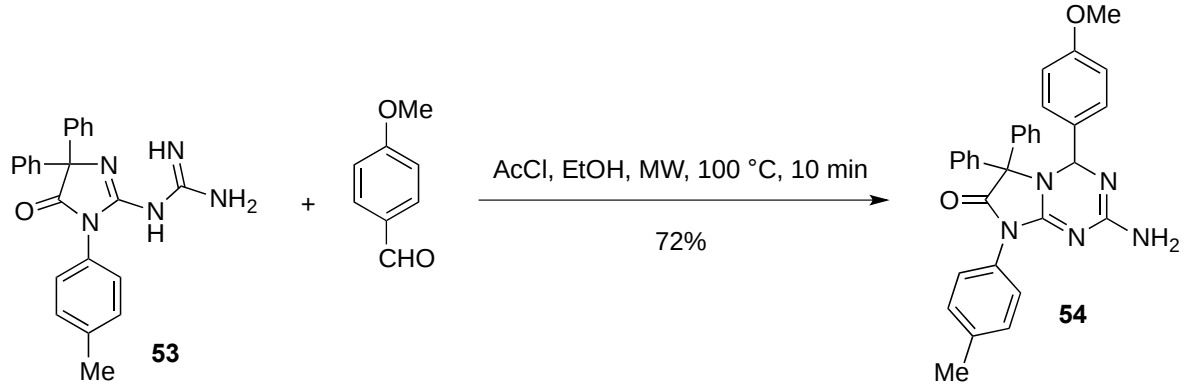
The rhodium(II)-catalyzed reaction of 2-benzylideneaminoimidazole (**50**) and 1,4,2-dioxazol-5-one (**51**) under microwave irradiation in dioxane resulted in the formation of imidazo[1,2-*a*][1,3,5]triazine ring

system (Scheme 31).[63] The product of this reaction (**52**) was obtained in 65% after 2 h of heating at 170 °C in a Biotage Initiator+ microwave reactor. The same reaction using conventional heating at 120 °C for 16 h afforded **52** in 80% yield.



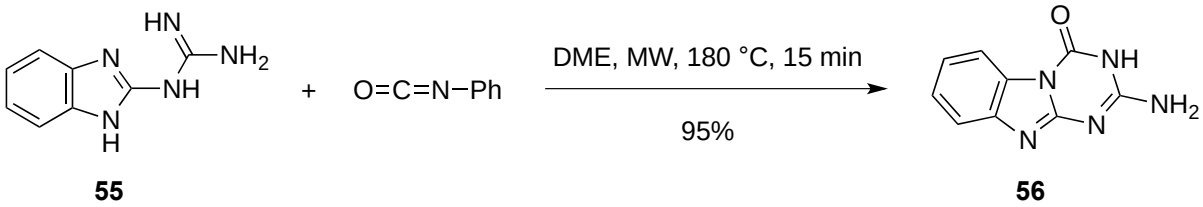
Scheme 31

The 1,3,5-triazine ring-closure was achieved by the treatment of heterylguanidine **53** with excess of *p*-anisaldehyde and acetyl chloride (5 equiv. each) under microwave irradiation in a CEM Discover reactor thus providing **54** (Scheme 32).[64] The scope of the method was explored using various aldehydes and ketones. The reaction was found to be rather general affording a library of twenty-two compounds prepared in 50-72% yields after 5-20 min of microwave irradiation at 100 °C.



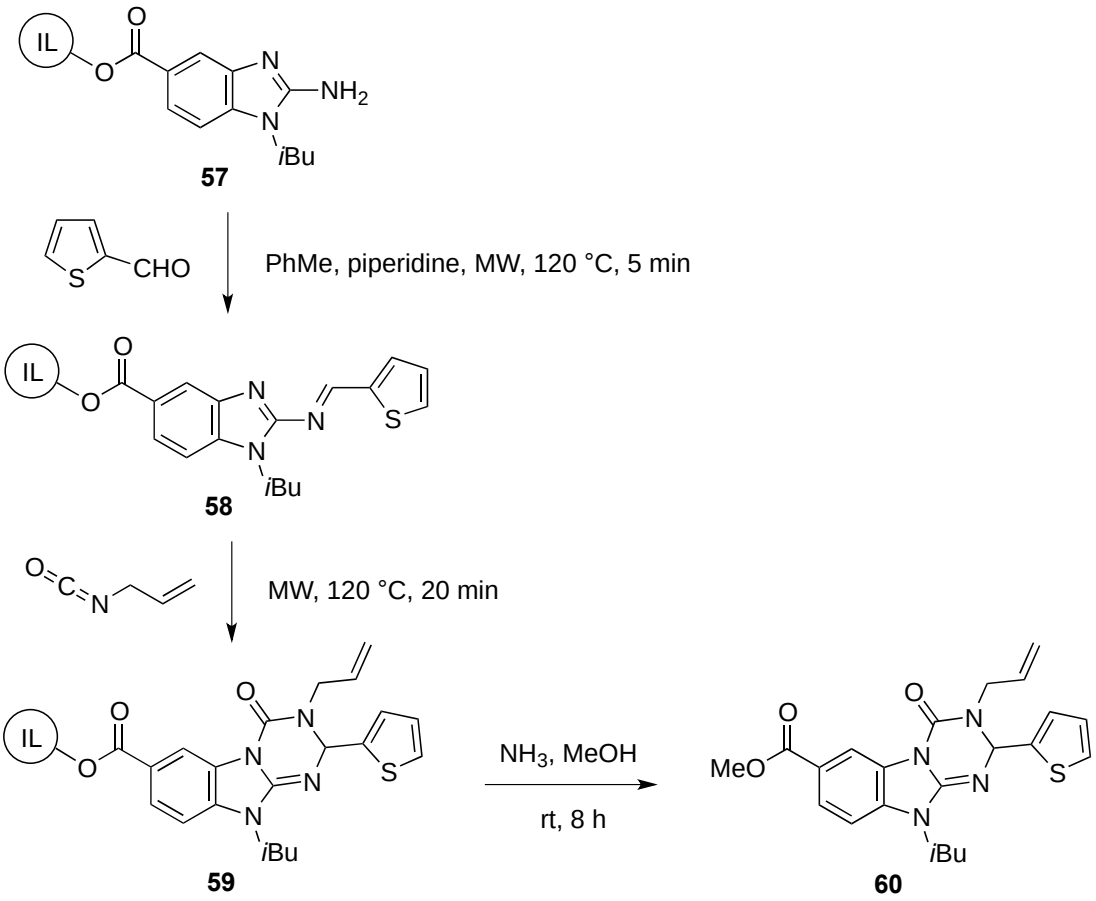
Scheme 32

It was reported[65] that 2-benzimidazolylguanidine (**55**) reacted with phenyl isocyanate under microwave irradiation in a Biotage Initiator reactor *via* the ring-closure carbonylation affording 2-amino-1,3,5-triazino[1,2-*a*]benzimidazol-4(3*H*)-one (**56**) in a good yield (Scheme 33).



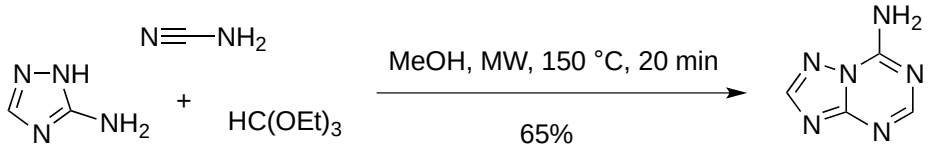
Scheme 33

A combinatorial synthesis of 1,3,5-triazino[1,2-*a*]benzimidazoles on ionic liquid support was performed using a subsequent microwave-assisted treatment of the anchored to ionic liquid 2-aminobenzimidazoles with an aldehyde and then an isocyanate.[66] For example, 2-aminobenzimidazole **57** reacted with 2-thiophenecarboxaldehyde furnishing intermediate imine **58**, which further underwent cycloaddition to allyl isocyanate thus resulting in the triazine ring-closure (Scheme 34). The ionic liquid support was removed from **59** by methanolic ammonia solution to afford ester **60**, which structure was confirmed by X-ray crystallography. A library of nineteen compounds with three diversity points was prepared using this method in 71-95% yields and 72-98% purity (HPLC).



Scheme 34

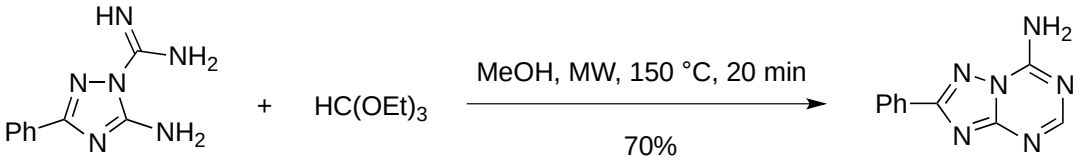
The three-component reaction of 5-amino-1,2,4-triazole, cyanamide, and triethyl orthoformate under microwave irradiation in methanol at 150 °C for 20 min was used for the synthesis of 5-aza-analogue of adenine, 7-amino-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**61**) (Scheme 35).[67] This reaction was efficient in a CEM Discover SP microwave reactor, but being carried out under conventional heating (reflux) in the same solvent, it furnished a complex mixture of products with only 1.7% of **61** detected by HPLC after 12 h. The scope of this microwave-assisted reaction was extended by the preparation of twenty-six 8-substituted 5-aza-adenines in 52-88% yields.[67,68]



61

Scheme 35

The same microwave heating conditions were applied for the conversion of 5-amino-1-guanyl-3-phenyl-1,2,4-triazole (**62**) into 7-amino-2-phenyl-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**63**) by the treatment with triethyl orthoformate (Scheme 36).[67]

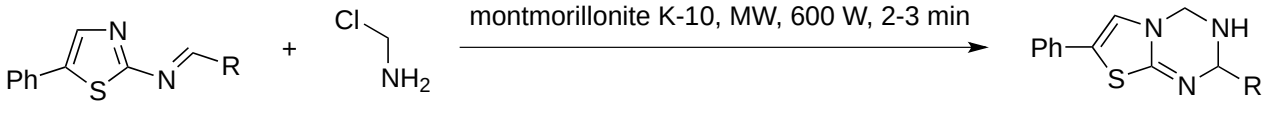


62 **63**

Scheme 36

The thiazolo[3,2-*a*][1,3,5]triazine and 1,3,5-triazino[2,1-*b*][1,3]benzothiazole systems have been also explored and many methods for the preparation of compounds with these scaffolds have been developed.[69] The microwave irradiation was found to benefit some methods for the synthesis of these compounds.

The solvent-free reaction of 2-(arylideneamino)thiazoles **64** with 1-chloromethanamine on montmorillonite K-10 under microwave irradiation resulted in the 1,3,5-triazine ring closure affording compounds **65** (Scheme 37).[70] The microwave irradiation was applied in 10 sec intervals for 2-3 min but without any control or monitoring of the reaction temperature.

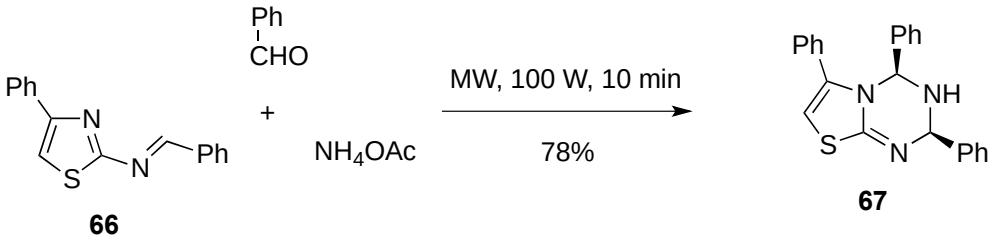


64 **65**

R = Ph, 91% (**65a**); 2-ClC_6H_4, 93% (**65b**); 4-ClC_6H_4, 89% (**65c**); 4-BrC_6H_4, 91% (**65d**); 2-$MeOC_6H_4$, 93% (**65e**); 4-$MeOC_6H_4$, 92% (**65f**); 3,4-$(MeO)_2C_6H_3$, 94% (**65g**)

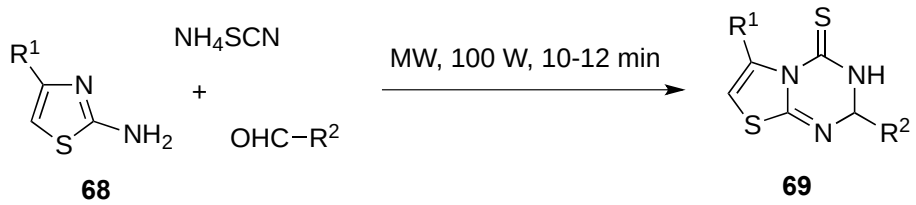
Scheme 37

The three-component solvent-free diastereoselective microwave-assisted synthesis of 2,4,7-triphenyl-3,4-dihydro-2*H*-thiazolo[3,2-*a*][1,3,5]triazine (**67**) was performed using 2-(benzylidenamino)thiazole **66**, ammonium acetate, and benzaldehyde (Scheme 38).[71] The product **67** was formed under microwave irradiation (100 W, 2 min intervals) in a CEM Discover reactor with 93% selectivity towards the *cis*-isomer. When the same reaction was carried out using conventional heating for 5 h at 90 °C (temperature recorded after 2 min of irradiation in the microwave-assisted experiment), yield dropped to 23% and *cis*- and *trans*-diastereomers were obtained in nearly equal quantities (51% and 49%). The microwave-assisted method tolerated substituents at all three phenyl rings affording products in 75-89% yields after 6-12 min (9 examples), while conventional heating needed 3-5 h and resulted in lower yields (21-33%). Benzaldehydes in this three-component process were successfully replaced by aldoses further expanding the reaction scope to the synthesis of corresponding *C*-nucleosides (12 examples, 76-88% yields).[72] It is important to note that microwave irradiation significantly increased diastereoselectivity of the reaction affording 93-99% of *cis*-isomers *vs*. 51-60% obtained under thermal heating.



Scheme 38

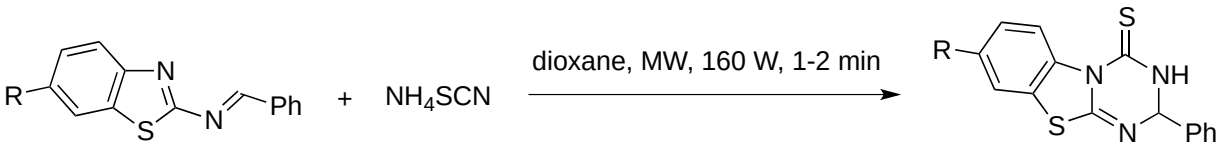
The three-component solvent-free reaction of 2-amino-4-arylthiazoles (**68**) with aromatic aldehydes and ammonium thiocyanate was reported[73] to proceed under microwave irradiation furnishing thiazolo[3,2-*a*][1,3,5]triazines **69** in good yields (Scheme 39). The reaction mixture was irradiated in 2 min intervals with temperature rising to 85 °C. However, the same reaction under conventional heating at this temperature for 5-6 h afforded only 32-38% of **69**.



R^1 = Ph, R^2 = Ph, 86% (**69a**); 4-ClC_6H_4, 78% (**69b**);
R^1 = 4-MeC_6H_4, R^2 = Ph, 92% (**69c**); 4-ClC_6H_4, 82% (**69d**)

Scheme 39

A similar two-component variation of this reaction was reported[74,75] for the synthesis of benzofused analogues of **69**. The synthesis of 1,3,5-triazino[2,1-*b*][1,3]benzothiazoles **71** was achieved by the treatment of 2-(benzylidenamino)benzothiazoles (**70**), prepared from the corresponding aminobenzothiazoles and benzaldehyde, with ammonium thiocyanate under microwave irradiation (Scheme 40).[74] The same reaction performed using thermal heating in dioxane under reflux took 4-6 h producing **71** in lower yields (49-70%).[75] Even though the microwave-assisted protocol seems to be beneficial, the reactions were performed using a domestic microwave oven without temperature control and therefore their reproducibility is questionable. Nevertheless, the prepared **71** and their derivatives demonstrated good antibacterial activity.[74]

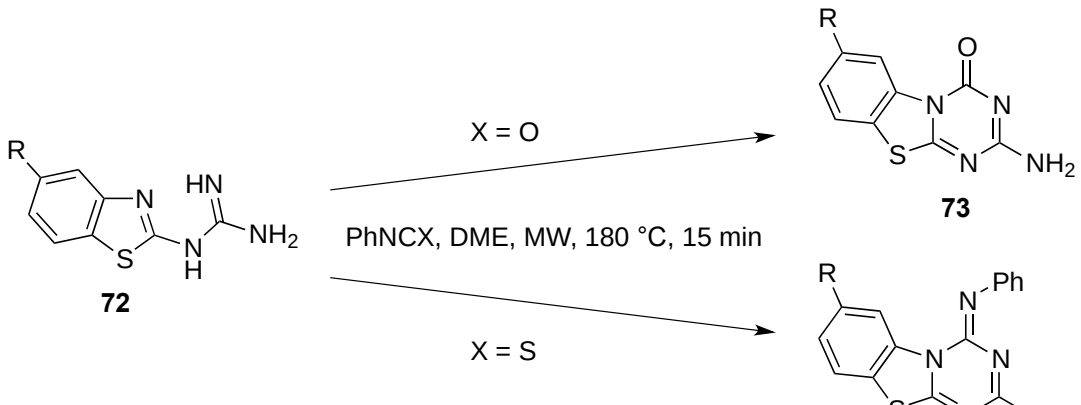


70 **71**

R = Cl, 88% (**71a**); Br, 70% (**71b**); NO_2, 66% (**71c**); OEt, 90% (**71d**)

Scheme 40

A carbonyl group was effectively introduced into 2-guanidinobenzothiazoles (**72**) by the treatment with phenyl isocyanate under microwave irradiation in a Biotage Initiator reactor thus affording the corresponding 2-amino-1,3,5-triazino[2,1-*b*][1,3]benzothiazol-4-ones (**73**) (Scheme 41).[65] When phenyl isothiocyanate was used for the treatment of **72** under identical conditions, compounds **74** were obtained.



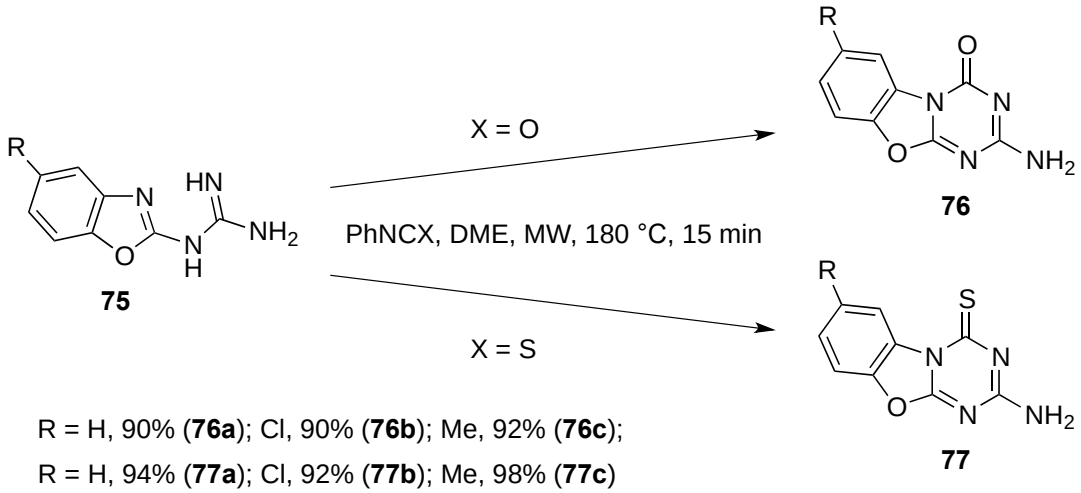
72 **73** **74**

R = H, 96% (**73a**); Cl, 90% (**73b**); CF_3, 95% (**73c**);
R = H, 28% (**74a**); Cl, 30% (**74b**) CF_3, 14% (**74c**)

Scheme 41

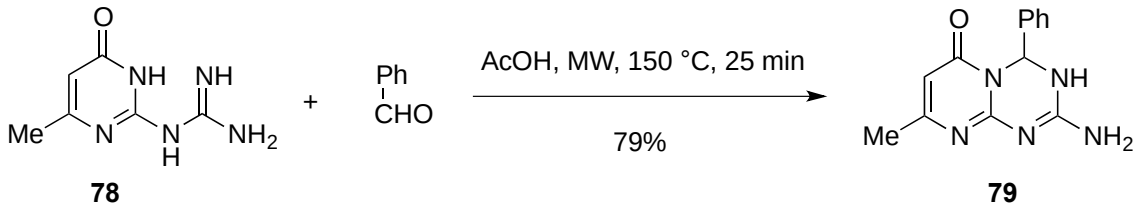
Interestingly, 2-guanidinobenzoxazoles (**75**) reacted differently compared to their thio-analogues **72**. While the microwave-assisted reaction of **75** with phenyl isocyanate proceeded in a similar way producing 2-amino-1,3,5-triazino[2,1-*b*][1,3]benzoxazol-4-ones (**76**), the reaction of **75** with phenyl isothiocyanate resulted in the thiocarbonylation furnishing **77** (Scheme 42).[65]

Methods for the synthesis of compounds with pyrimido[1,2-*a*][1,3,5]trazine scaffold have been substantially explored.[76] However, only one microwave-assisted protocol has been reported[77] for the preparation of this heterocyclic system. The 1,3,5-triazine closure was achieved when 4-oxo-2-pyrimidylguanidines reacted with aldehydes under microwave irradiation. For example, reaction of guanidine **78** with benzaldehyde resulted in the formation of pyrimido[1,2-*a*][1,3,5]triazine **79** (Scheme 43). A series of thirty-eight compounds (70-96% yields) was prepared using this microwave reaction. The molecular diversity in the prepared products was introduced by varying substituents at the pyrimidine ring and guanidine group as well as by using different aldehydes. The reaction conditions were modified on the basis of the guanidine type. Pyrimidines bearing substituted guanidino group reacted with aldehydes in ethanol under piperidine catalysis (140 °C, 20 min). For reactions of guanidine **78**, acetic acid was used as a medium, while its analogues with trifluoromethyl or phenyl group instead of the methyl at the pyridine ring required DMF (165 °C, 20 min). The same reactions were also performed using conventional heating under reflux in the same solvents, but the reaction time increased to several hours and yields were up to 35% lower.



R = H, 90% (**76a**); Cl, 90% (**76b**); Me, 92% (**76c**);
R = H, 94% (**77a**); Cl, 92% (**77b**); Me, 98% (**77c**)

Scheme 42



Scheme 43

6. CONCLUSION

Microwave irradiation is valuable tool for synthetic chemists helping them achieve better yields of desired products in a shorter time. This tool has found applications in the synthesis of diverse 1,3,5-triazines, many of which are biologically active. Unfortunately, reproducibility of some of methods, which used domestic microwave ovens without proper temperature control, remains questionable and further validation of such approaches is required in more precise conditions.

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