ULTRASOUND IN THE SYNTHESIS OF AZOLOPYRIMIDINES

Shunan Kaping and Jai N Vishwakarma*
Organic Research Lab., Department of Chemical Science Assam Don Bosco University, Airport Road, Azara, Guwahati-781017, Assam
*For correspondence. (jnvishwakarma@dbuniversity.ac.in)

Abstract: Growing environmental concerns have compelled chemists to develop environmentally benign synthetic strategies called Green Chemistry. There are many ways to achieve the goals of Green Chemistry, one of which is Ultra Sound assisted reactions. Azolopyrimidines have attracted the attention of synthetic organic chemists due to their potent biological properties. Herein, we present a review on the synthesis of Azolopyrimidines under the influence of Ultra Sound reported during the last two decades.

1. Introduction:

Ultrasound is now becoming ubiquitous not only in the field of medicine but in many different fields for diverse purposes like cleaning, sonar, electronics, agriculture, oceanography, detection of objects, measuring distances etc. Ultrasound technology has also been applied as a modern and environment friendly synthetic tool for the synthesis of compounds due to its high energy and the ability to disperse reagent in small particles offering great advantages for acceleration of reactions, high efficiency, low energy requirements and low waste production. Applications of ultrasonic irradiation are playing an increasing role in chemical processes, especially in cases where classical methods require drastic conditions or prolonged reaction times. It may sometimes alter the reaction pathway causing the formation of different products.

Ultrasound waves bring about beneficial chemical effects due to the phenomenon of cavitation. As the molecules of the medium vibrate, small cavities or gas-filled microbubbles are formed in the liquid medium [1,2]. The tiny gas or vapour bubbles formed oscillates, accumulating ultrasonic energy effectively while growing and contracting, striking a dynamic balance between the vapour inside the bubble and the liquid outside [3,4]. However, on reaching a maximum size the cavity can no longer absorb the energy efficiently and sustain itself. The liquid rushes in and the bubble subsequently collapses in the compression cycle releasing the concentrated energy stored within, in a short period of time [3]. This implosive collapse of the bubble brings about an environment for chemical reactions [4,5] to occur. The gases and vapours inside the bubble are compressed, generating intense heat that raises the temperature of the liquid immediately surrounding the bubble and creates a localized short-lived regions known as the hot spot [4,6]. The creation of the so-called hot spots in the liquid medium with temperatures of roughly 5000 °C, pressures of about 1000 atmospheres and heating and cooling rates above 10 billion degree Celsius per second, can be visualized as a micro reactor in which mechanical energy of sound is transformed into useful chemical form [6–8].

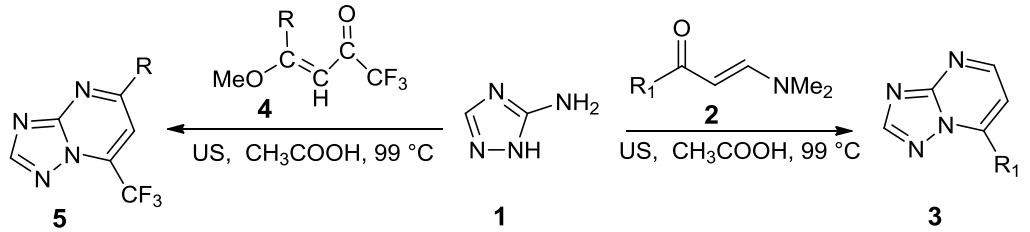
2. Ultrasound in the synthesis of triazolo/pyrazolopyrimidines:

Ultrasound irradiation has been increasingly used in organic synthesis in recent years. US assistance in reactions can be carried out in a higher yield, shorter reaction time and under milder reaction conditions as compared with traditional methods. The use of ultrasound in triazolo/pyrazolopyrimidines heterocyclic systems has not been fully explored. We report herein some few examples of US assisted synthesis involving the triazolo/pyrazolopyrimidines ring system.

2.1.

Ultrasonic irradiation was used in the synthesis of a series of novel 1,2,4-triazolo[1,5-*a*]pyrimidines (**3**,**5**). The products were synthesized from the cyclocondensation reaction of 1,1,1-trifluoro-4-methoxy-3-alken-2-one (**4**) or *β*-enaminones (**2**) with 5-amino-1,2,4-triazole (**1**) in acetic acid at 99 °C with 5–17 minutes of ultrasound irradiation (Scheme 1) [9]. This methodology has shown several advantages, such as shorter reaction times, mild

conditions, high regioselectivity, and excellent yields, when compared with conventional thermal heating (oil bath).



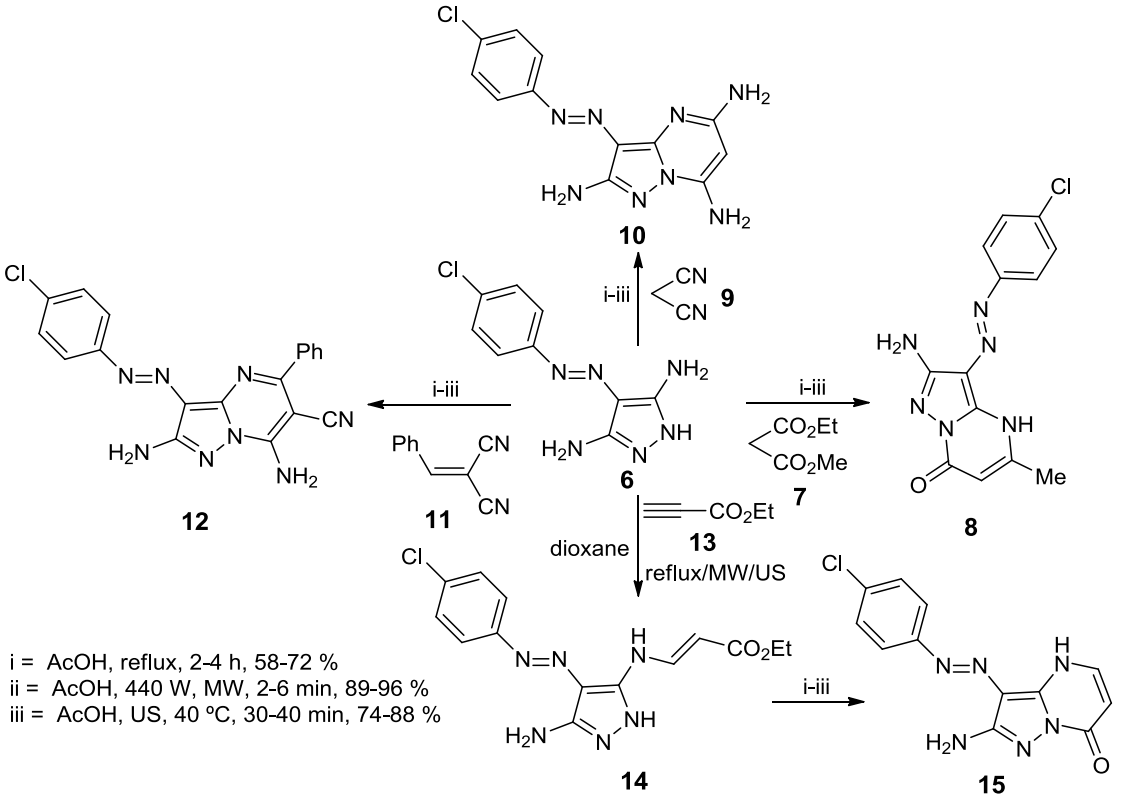
R = C_6H_5, 4-FC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, Thien-2-yl, Biphen-4-yl

R_1 = C_6H_5, 4-FC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$, Thien-2-yl, Biphen-4-yl, Naphth-2-yl, Pyrrol-2-yl, CCl_3

Scheme 1

2.2.

Al-Zaydi investigated [10] on the synthesis of polyfunctionally substituted pyrazolo[1,5-*a*]pyrimidines **8**, **10**, **12**, **15** *via* reaction of 4-(4-chlorophenylazo)-1*H*-pyrazole-3,5-diamine (**6**) with ethyl acetoacetate (**7**), malononitrile (**9**), benzylidenemalononitrile (**11**) and ethyl propiolate (**13**) respectively under thermal, microwave and ultrasound irradiation to give the corresponding pyrazolo[1,5-*a*]pyrimidine derivatives (Scheme 2).



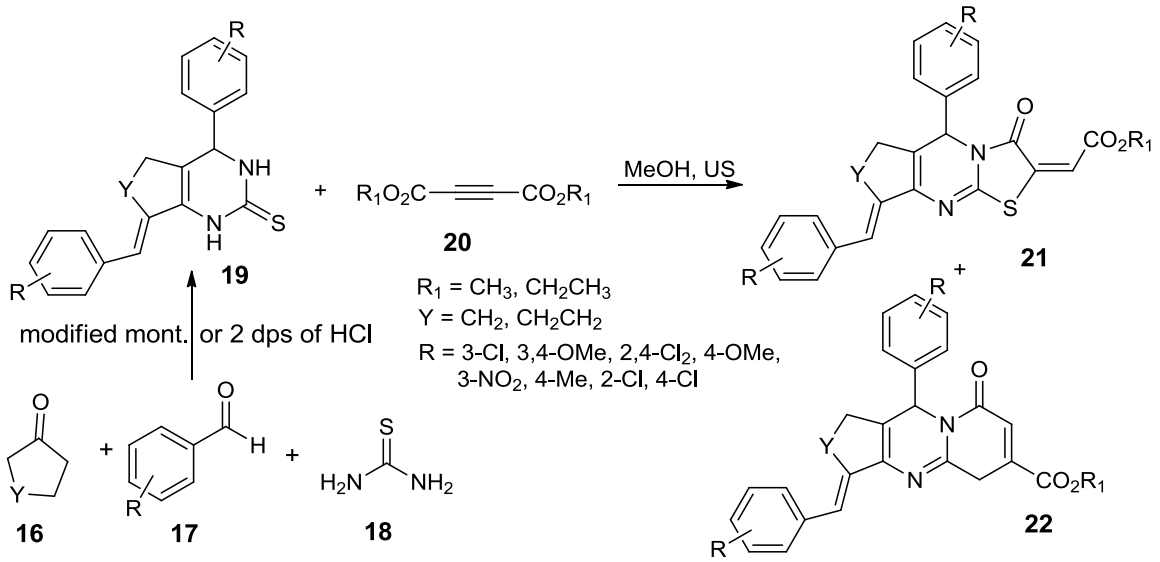
i = AcOH, reflux, 2-4 h, 58-72 %
ii = AcOH, 440 W, MW, 2-6 min, 89-96 %
iii = AcOH, US, 40 ºC, 30-40 min, 74-88 %

Scheme 2

2.3.

Ultrasonic-assisted synthesis of thiazolo[2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine derivatives were reported by Darehkordi *et al.* [11]. This was achieved by the treatment of cyclohexanone or cyclopentanone (**16**) with aromatic aldehyde (**17**) and thiourea (**18**) in the presence of modified montmorinollite nanostructure or HCl as a catalyst under heating and solvent-free conditions producing 7-benzylidene-4-aryl-3,4,6,7-tetrahydro-*1H* cyclopenta[d]pyrimidine-2(*5H*)-thione or 8-benzylidene-4-aryl-3,4,5,6,7,8 hexahydroquinazoline-2(*1H*)-thione (**19**). Compound **19** was then utilized as a key intermediate for the synthesis of new thiazolo[2,3-*b*]quinazoline

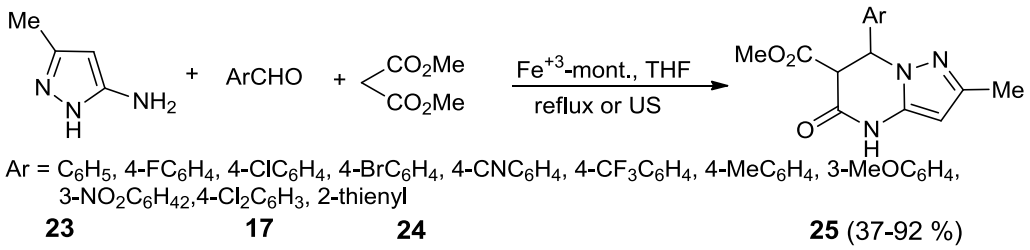
21 and thiazolo[3,2-*a*]pyrimidine derivatives **22** *via* the reaction with diethyl and dimethyl acetylene dicarboxylate **20** by two different methods: (a) in methanol as a solvent under ultrasonic irradiation at ambient temperature; (b) in methanol as a solvent at ambient temperature (conventional magnetic stirring). Ultrasound-assisted synthesis provided excellent yields (87–95 %) in short reaction times (30–50 min) at room temperature (Scheme 3).



Scheme 3

2.4.

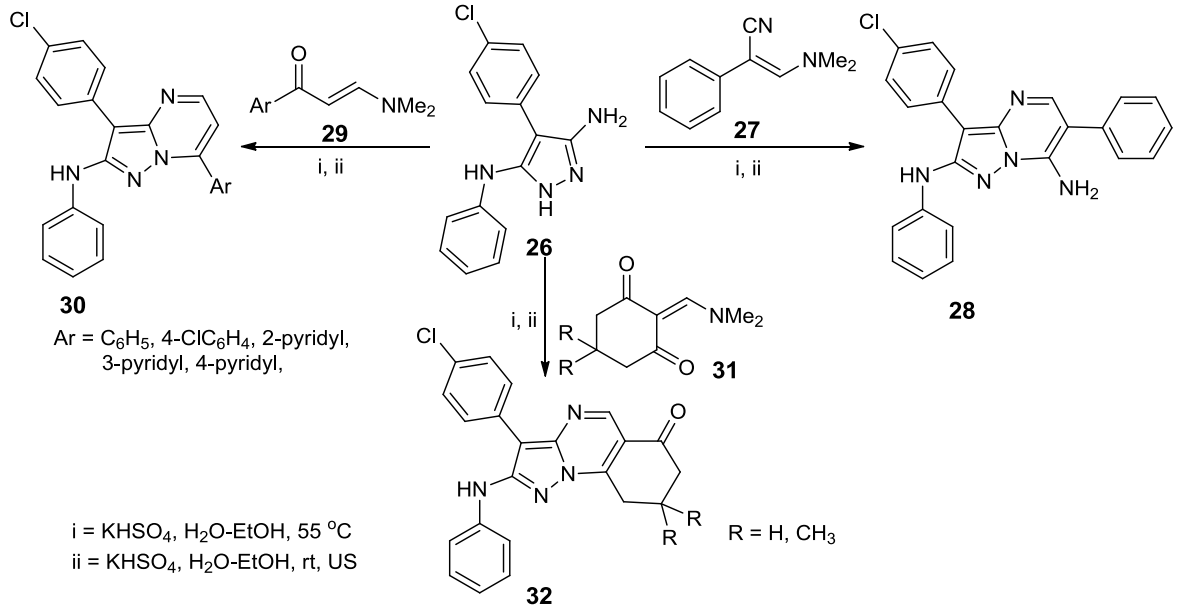
A convenient one-pot three-component approach for regioselective synthesis of novel substituted pyrazolo[1,5-*a*]pyrimidines using Fe^{+3}-montmorillonite as efficient catalyst was achieved by the condensation of 3-amino-5-methyl pyrazole (**23**), arylaldehydes (**17**), and dimethylmalonate (**24**) in THF under ultrasonic irradiations and conventional conditions [12] (Scheme 4).



Scheme 4

2.5.

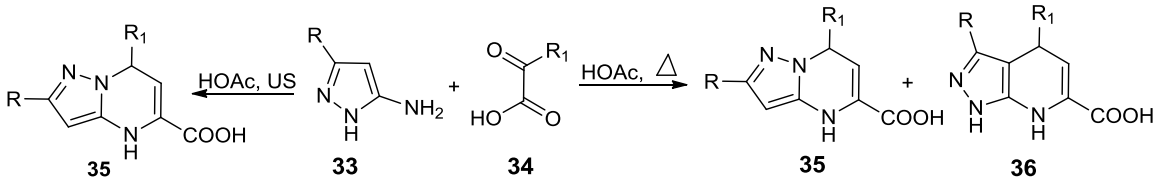
Kalita *et al*. [13] reported a facile environment friendly regioselective approach for the synthesis of 2-anilino-3,7-diarylpyrazolo[1,5-*a*]pyrimidines and related compounds resembling Zaleplon skeleton under both thermal and ultrasound irradiation. This was achieved by the reaction of 4-(4-chlorophenyl)-*N*5-phenyl-*1H*-pyrazole-3,5-diamine (**26**) with enaminones **29**, cyclic enaminones **31**and enaminonitriles **27** in aqueous media using $KHSO_4$ as catalyst. It was observed that reactions under US gave better yields (50–90 %) within 30–60 seconds as compared with conventional heating which took 30–180 minutes giving the desired products in 44–87 % yields (Scheme 5).



Scheme 5

2.6.

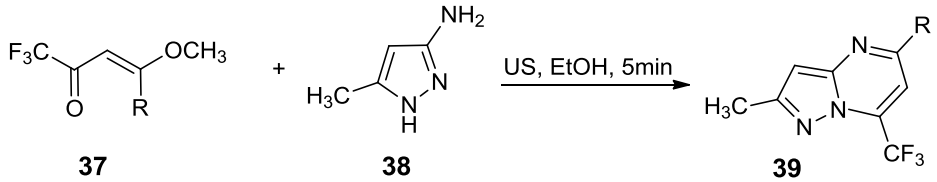
High regioselective method for the synthesis of 2,7-diaryl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids by reaction of 3-aryl-5-aminopyrazoles **33** with arylidenpyruvic acid **34** at room temperature under ultrasonication was developed and discussed (Scheme 6) [14].



Scheme 6

2.7.

Buriol *et al.* [15] reported the synthesis of pyrazolo[1,5-*a*]pyrimidines under ultrasound irradiation using the cyclocondensation reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **37** with 3-amino-5-methyl-1*H*-pyrazole **38** in the presence of EtOH for 5 minutes. The methodology provided satisfactory yields (61–98 %) of **39** within short reaction times (Scheme 7).



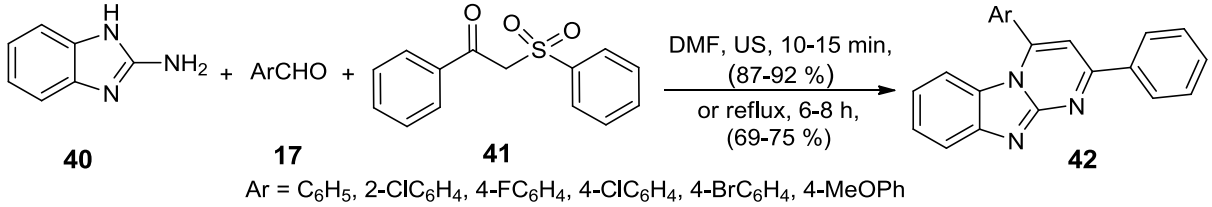
R = Me, Bu, i-Bu, C_6H_5, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, Napth-2-yl, Biphen-4-yl

Scheme 7

2.8.

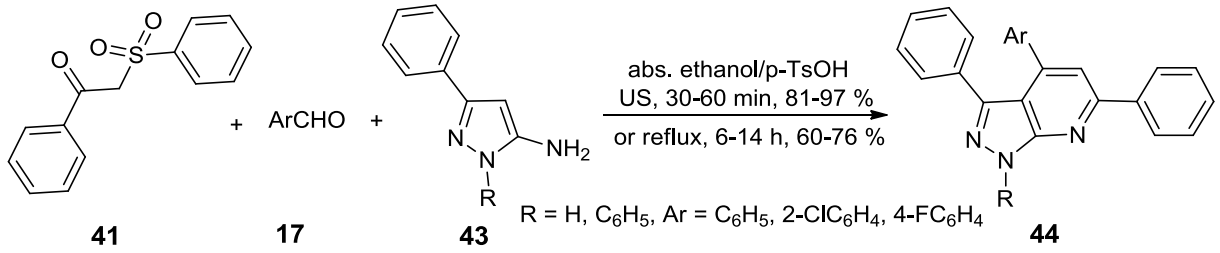
Saleh and co-workers [16] exhibited the ultrasound assisted one-pot, three-components synthesis of pyrimido[1,2-*a*]benzimidazoles. The reaction of 2-aminobenzimidazole (**40**) with aldehyde **17** derivatives and 1-phenyl-2-(phenylsulfonyl)ethanone (**41**) in DMF as solvent under ultrasonic irradiation afforded 2,4-diaryl

pyrimido[1,2-*a*]benzimidazoles (**42**). In the absence of US, it resulted in the increased reaction time from 20 minutes to 6–8 h with decreased yields of the products from nearly 92 % to 69–75 % (Scheme 8).



Scheme 8

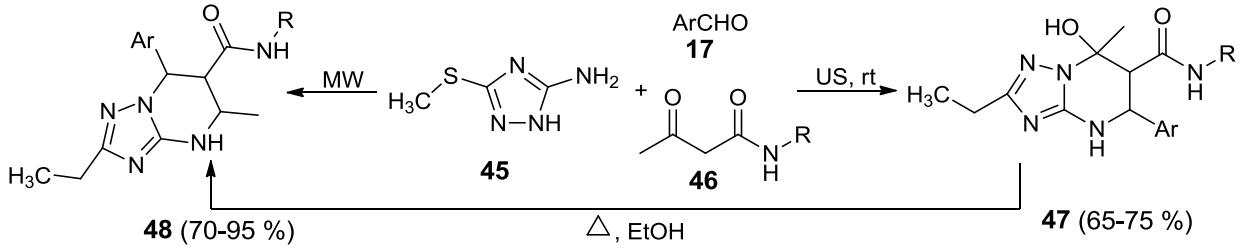
The group further extended their studies for the synthesis of pyrazolo[3,4-b]pyridine derivatives **44** through a one-pot three-component condensation reaction of an aldehyde **17**, 5-amino-pyrazole **43** derivatives and *β*-ketosulphone **41** in ethanol using *p*-toluenesulfonic acid (*p*-TsOH) as the catalyst under ultrasonic irradiation (Scheme 9). Formation of compounds **44** under US occurred in excellent yields (81–97 %) and short reaction time (30–60 min) in comparing with conventional conditions (6–16 h, 60–76 %).



Scheme 9

2.9.

It was established that the three-component reaction of 3-amino-5-alkylthio-1,2,4-triazole (**45**) with aldehydes **17** and acetoacetamides **46** under ultrasonic irradiation at room temperature led exclusively to tetrahydrotriazolopyrimidines **47**, while the same reaction in microwave at higher temperature yielded "classical" Biginelli like heterocycles **48** (Scheme 10) [17]. Moreover, compounds **47** could be easily converted into **48** by heating in ethanol.

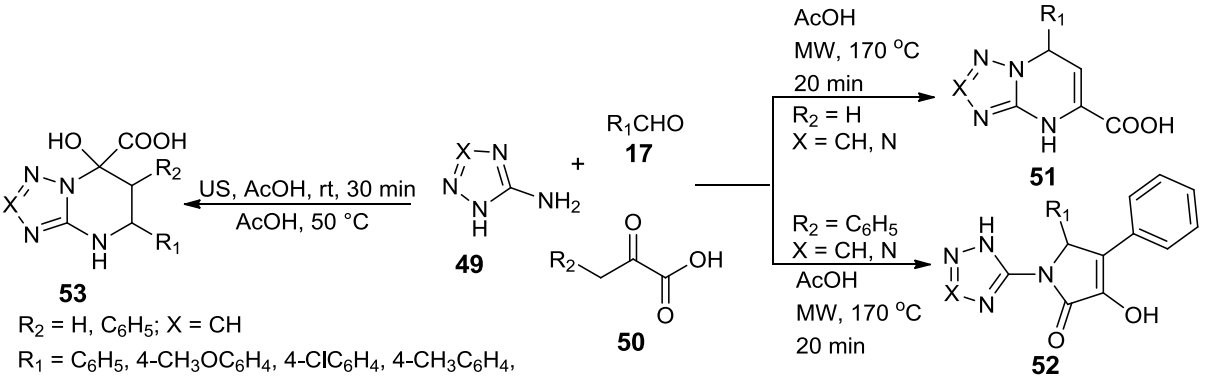


Scheme 10

2.10.

The multicomponent reactions of 3-amino-1,2,4-triazoles/5-aminotetrazole **49**with phenylpyruvic acids **50** and aromatic aldehydes **17** were studied [18] using conventional thermal heating, ultrasonification and microwave dielectric heating. 3-Amino-1,2,4-triazole and aromatic aldehydes in acetic acid at room temperature under ultrasonication gave triazolopyrimidine carboxylic acids **53** (Scheme 11). In case of aminotriazoles (**49**, X = CH), an unprecedented reaction pathway leading to 5-aryl-7-hydroxy-6-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids **53** was found. It was interesting that the same reaction with 5-aminotetrazole could not be carried out. On the other hand, MCRs of both aminotriazole or aminotetrazole with aldehydes and arylpyruvic acid at 170 °C under microwave irradiation yielded exclusively

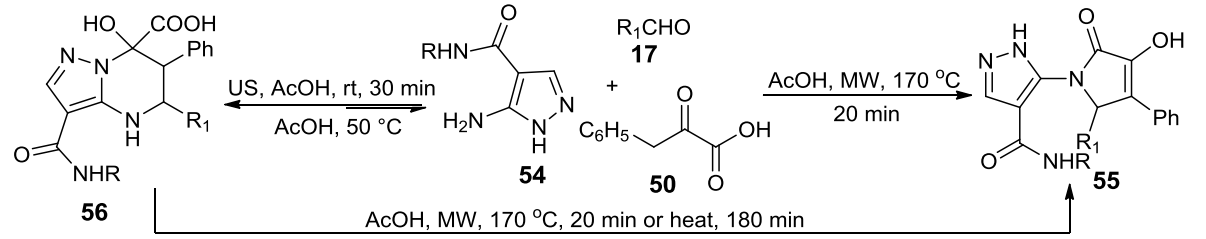
triazolylpyrrolones **52** [166], while the high-temperature treatment involving pyruvic acid led to other heterocyclic system dihydroazolopyrimidines **51** [19].



Scheme 11

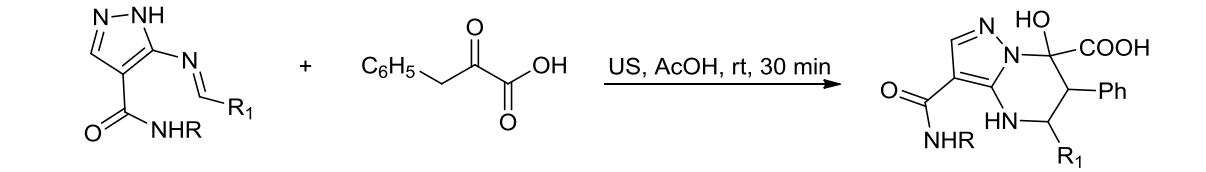
2.11.

Sakhno *et al*. [20] described the synthesis of pure pyrrolones **55** in 75–82 % yields by the reaction of aldehydes **17**, aminopyrazoles **54** and phenylpyruvic acid **50** in acetic acid under microwave heating (170 °C for 20 min) or by conventionally refluxing for 180 minutes in AcOH. Under similar condition, ultrasonication for 30 minutes at room temperature yielded pyrimidine-7-carboxylic acids **56** (Scheme 12). Also, tetrahydropyrimidines **56** decomposed into starting materials under smooth heating (upto 50 ºC) in acetic acid or DMSO-d_6. Full conversion was achieved by heating of **56** in acetic acid in a microwave reactor at 170 ºC for 20 minutes or by refluxing for 180 min



Scheme 12

It was also reported that treatment of imides **57** with phenylpyruvic acid **50** AcOH under ultrasonic irradiation at room temperature for 30 minutes resulted in the formation of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids **56** (Scheme 13).

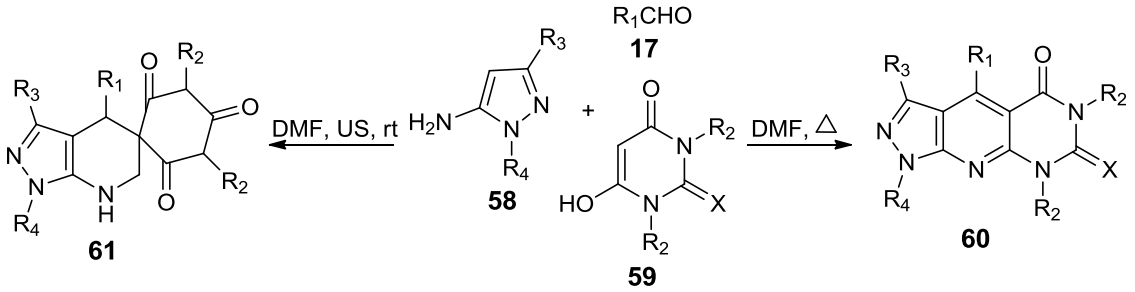


Scheme 13

2.12.

Muravyova *et al.* [21] studied the multicomponent cyclo-condensations between 5-aminopyrazoles **58**, barbituric acids **59**, and aromatic aldehydes **17** under conventional heating, microwave irradiation, or ultrasonic irradiation where, the temperature regime was found to be the main factor in controlling the chemoselectivity of

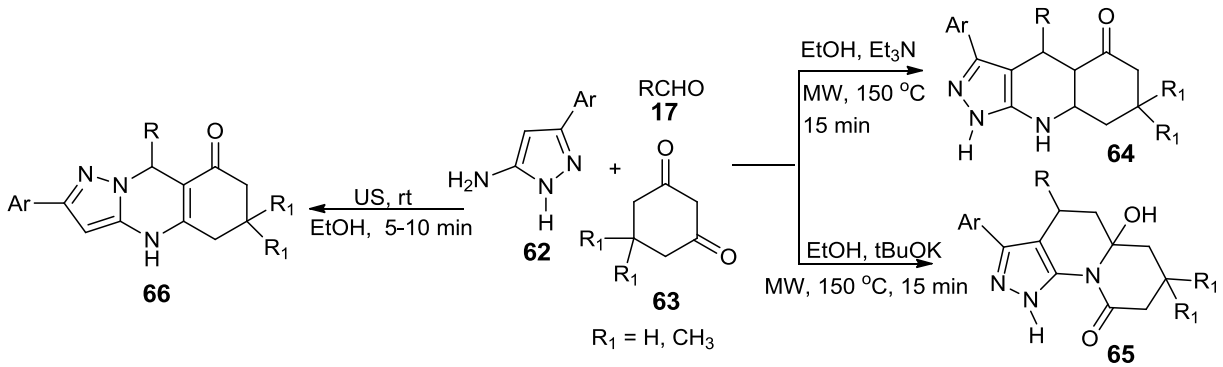
the reactions. The application of US at room temperature in the control of the chemoselectivity of this reaction gave 1,4,6,7-tetrahydro-1*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5-pyrimidine]-2,4,6(*3H*)-trione **61** (Scheme 14), while high temperature treatment yielded Hantzsch-type pyrazolo[4,3:5,6]pyrido[2,3-*d*]pyrimidine-5-ones **60**.



Scheme 14

2.13.

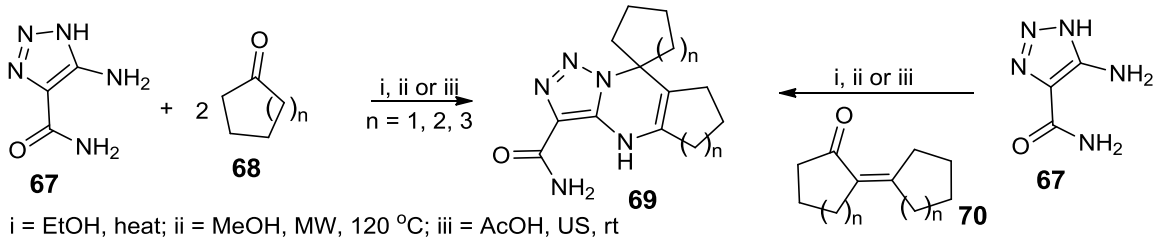
Regio- and chemoselective multicomponent protocols for the synthesis of 1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-ones, 5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8-ones, and 5α-hydroxy-4,5,5,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones starting from 5-amino-3-phenylpyrazole (**62**), cyclic 1,3-dicarbonyl compounds **63** and aromatic aldehydes **17** are described [22]. The condensation of three-component coupling in ethanol was successfully tuned toward the formation of pyrazoloquinolinones **64** (Hantzsch-type dihydropyridines) by performing the reaction at 150 °C in the presence of triethylamine base applying sealed vessel microwave or conventional heating. On the other hand, using sonication at room temperature under neutral conditions favours the formation of the isomeric pyrazoloquinazolinones **66** (Biginelli-type dihydropyrimidines) (Scheme 15). A third reaction pathway leading to pyrazoloquinolizinones **65** in a ring-opening/recyclization sequence were accessed by switching from triethylamine to a more nucleophilic base such as sodium ethoxide or potassium *tert*-butoxide.



Scheme 15

2.14.

Gladkov *et al.* [23] discussed the reaction between one equivalent of aminotriazole **67** and two equivalents of cycloalkanones **68** (*n* = 1, 2) in boiling dry ethanol for 3 h yielding spiroheterocycles **69** (31–37 %, **Scheme 16**, where n = 1, 2) as the sole reaction products. However, better yields and purity of compounds **69** were observed when the starting materials **67** and **68** were treated in methanol under MWI at 120 °C for 30 minutes. At the same time, the reaction involving cycloheptanone (*n* = 3) did not allow the synthesis of compound **68**. Under ultrasonication at ambient temperature in acetic acid, (selected instead of methanol due to solubility problems) also yielded only heterocycles **68**. The yields and purity of the compounds obtained under ultrasonication were slightly lower than the other two methods. Treatment of **67** with **70** instead of 2 equivalents of **68**, also led to the same product formation i.e., **69** (Scheme 16).

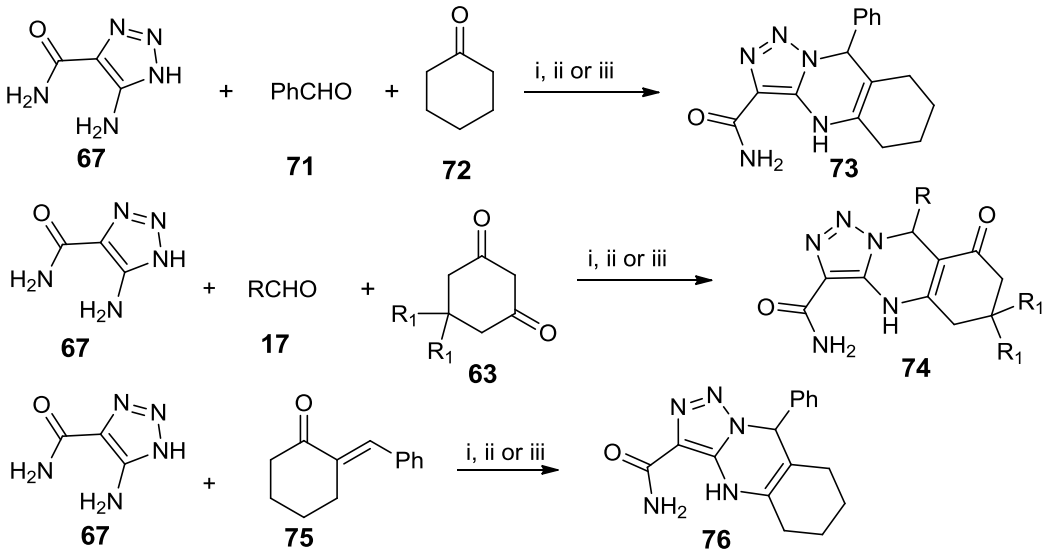


i = EtOH, heat; ii = MeOH, MW, 120 °C; iii = AcOH, US, rt

Scheme 16

2.15.

MCR of aminoazole **67**, cyclohexanone **72**/cyclic diketone **63** and aldehyde **71**/**17** was carried out in dry ethanol by conventional heating under reflux in methanol, under microwave irradiation at 120 °C, or by ultrasonication at ambient temperature in acetic acid. In all these cases triazolopyrimidines **73**/**74** were isolated as the sole reaction products (Scheme 17). In most cases the best results from the viewpoint of yields and purity of the target compounds were observed when ultrasound method was applied.



i = EtOH, heat, ii = MeOH, MW, 120 °C, iii = AcOH, US, rt

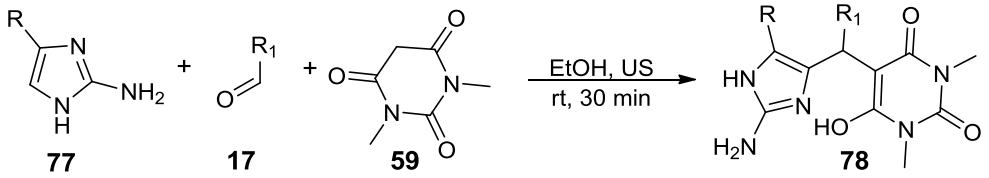
R = C_6H_5, 4-$CH_3OC_6H_4$, 2-$CH_3OC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, R_1 = H, CH_3

Scheme 17

Sequential reaction *via* synthesis of arylidenecyclohexanone **75** also gave compound **76** as sole reaction product under all the methods of activation applied [23].

2.16.

A three-component reaction of 4-aryl-2-amino-1*H*-imidazoles with aromatic aldehydes and 1,3-dimethylbarbituric acid are reported [24]. Ultrasonication of the mixture containing 2-aminoimidazole **77**, barbituric acid (**59**) and aromatic aldehydes **17** in ethanol at room temperature for 30–45 minutes gave adducts **78** in 68–85 % yields (Scheme 18).



77 17 59 78

R = 4-MeC_6H_4, 4-$MeOC_6H_4$

R_1 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, C_6H_5, 4-$CO_2MeC_6H_4$, 4-$NO_2C_6H_4$

Scheme 18

3. Conclusion:

From the above reports it can be clearly seen that ultrasound plays a significant role in the enhancement of reaction rates and increasing the yield of the products. Use of ultrasound in the synthesis of heterocyclic compounds has become an area of exploration and the same had been demonstrated by various researchers and groups. However, US-assisted synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives have not been fully explored and only limited work are reported in the literature as highlighted in **section 1.2**. In view of these findings the research work aims to make use of the ultrasound as a tool in the synthesis of novel pyrazolo[1,5-*a*]pyrimidine and its analogues and also to study the biological activity of the synthesized compounds, thus, adding to the library of the biologically active pyrazolo[1,5-*a*]pyrimidine derivatives.

References:

[1] T. J. Mason, *Ultrasonics* **1986**, *24*, 245.
[2] R. Cella; H. A. Stefani, *Tetrahedron* **2009**, *65*, 2619.
[3] J. H. Bang; K. S. Suslick, *Adv. Matter*. **2010**, *22*, 1039.
[4] K. S. Suslick, *Science* **1990**, *247*, 1439.
[5] G. Cravotto; P. Cintas, *Chem. Soc. Rev*. **2006**, *35*, 180.
[6] B. S. Singh; H. R. Lobo; D. V. Pinjari; K. J. Jarag; A. B. Pandit; G. S. Shankarling, *Ultrason. Sonochem.* **2013**, *20*, 287.
[7] R. M. Srivastava; R. A. F. Neves; C. A. da Silva; A. J. Bortoluzzi, *Ultrason. Sonochem.* **2009**, *16*, 737.
[8] A. Duarte; W. Cunico; C. M. P. Pereira; A. F. C. Flores; R. A. Frietag; G. M. Siqueira, *Ultrason. Sonochem.* **2010**, *17*, 281.
[9] C. P. Frizzo; E Scapin; M. R. B; Marzari; T. S. München; N. Zanatta, H. G. Bonacorso; L. Buriol; M. A. P. Martins, *Ultrason. Sonochem*. **2014**, *21*, 958.
[10] K. Al Zaydi, *Heterocycles*, **2009**, *78*, 2009.
[11] A. Darehkordi; J. Reentan; M. Ramezani, *J. Iran. Chem. Soc.***2013**, *10*, 385.
[12] R. H. Nia; M. Mamaghani; F. Shiriniand; K. Tabatabaeian, *J. Het. Chem*. **2014**, *51*, 363
[13] U. Kalita; S. Kaping; J. Nellanant; P. Helissey; J. N. Vishwakarma, *Heteroletters* **2014**, *4*, 137.
[14] V. A. Chebanova; Y. I. Sakhnoa; S. M. Desenko, *Ultrason. Sonochem*. **2012**, *19*, 707.
[15] L. Buriol; T. S. München; C. P. Frizzo; M. R. B. Marzari; N. Zanatta; H. G. Bonacorso; M. A. P. Martins, *Ultrason. Sonochem*. **2013**, *20*, 1139.
[16] T. S. Saleh; T. M. A. Eldebss; H. M. Albishri, *Ultrason. Sonochem*. **2012**, *19*, 49
[17] V. A. Chebanov; K. A. Gura; S. M. Desenko, *Top. Heterocycl. Chem*. **2010**, *23*, 41.
[18] Y. I. Sakhnoa; S. M. Desenkoa; S. V. Shishkina; O. V. Shishkin; D. O. Sysoyev; U. Groth, C. O. Kappe, V. A. Chebanov, *Tetrahedron* **2008**, *64*, 11041.
[19] V. A. Chebanov; Y. I. Sakhno; S. M. Desenko; S. V. Shishkin; V. I. Musatov; O. V. Shishkin; I. V. Knyazeva, *Synthesis* **2005**, 2597
[20] Y. I. Sakhno; S. V. Shishkina; O. V. Shishkin; V. I. Musatov; S. M. Desenko; V. A. Chebanov, *Mol. Divers.* **2010**, *14*, 523.
[21] E. A. Muravyova; S. V. Shishkina; V. I. Musatov; O. V. Shishkin; S. M. Desenko; V. A. Chebanov, *Synthesis* **2009**, 1375.
[22] V. A. Chebanov; V. E. Saraev; S. M. Desenko; V. N. Chernenko; I. V. Knyazeva; U. Groth; T. Glasnov; C. O. Kappe, *J. Org. Chem*. **2008**, *73*, 5110.
[23] E. S. Gladkov; K. A. Gura; S. M. Sirko; S. M. Desenko; U. Groth; V. A. Chebanov, *Beilstein J. Org. Chem.* **2012,** *8*, 2100.
[24] A. Y. Andriushchenko; V. E. Saraev; S. V. Shishkina; O. V. Shishkin;V. I. Musatov; S. M. Desenko; V. A. Chebanov, *Arkivoc* **2013**, *iii*, 61.