Sonochemistry Letters

One-Pot Multicomponent Reactions under Ultrasonic Conditions: Scope, Mechanisms, Green Metrics and Prospects-A Narrative Review

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ABSTRACT

Multicomponent reactions (MCRs) assemble three or more reactants in one pot and are inherently economical in steps and waste [1–3]. Ultrasound adds a further layer of efficiency: acoustic cavitation provides chemical and mechanical activation and often shortens reaction times at mild bulk temperature [4,5]. This review surveys one-pot MCRs carried out under ultrasonic conditions, namely Biginelli [6,7], Hantzsch [8,9], fused pyrimidine and pyridine [10–12], pyrazole [13,14], isocyanide-based [15] and Petasis-type [16] reactions. Mechanistic schemes are presented for ultrasonic activation, the Biginelli reaction and a catalyst-free five-component reaction in water. A worked example shows how time, solvent volume and substituents govern outcome, with 85–98% yields in 15–18 min [12], and green metrics from a sonochemical three-component reaction (E-factor 0.1454) are discussed [16]. Practical limitations, particularly reproducibility of acoustic conditions, and research priorities are outlined.

Key words: Multicomponent reactions; ultrasound; sonochemistry; cavitation; one-pot synthesis; heterocycles; green chemistry; aqueous medium.

1. Introduction

MCRs are processes in which the target molecule is obtained from three or more starting materials through well-defined sequences in one pot [1,2]. Compared with linear stepwise syntheses they reduce the number of operations and the waste generated, and they provide rapid access to molecular diversity [3,17]. These features have made MCRs central to heterocyclic and medicinal chemistry.

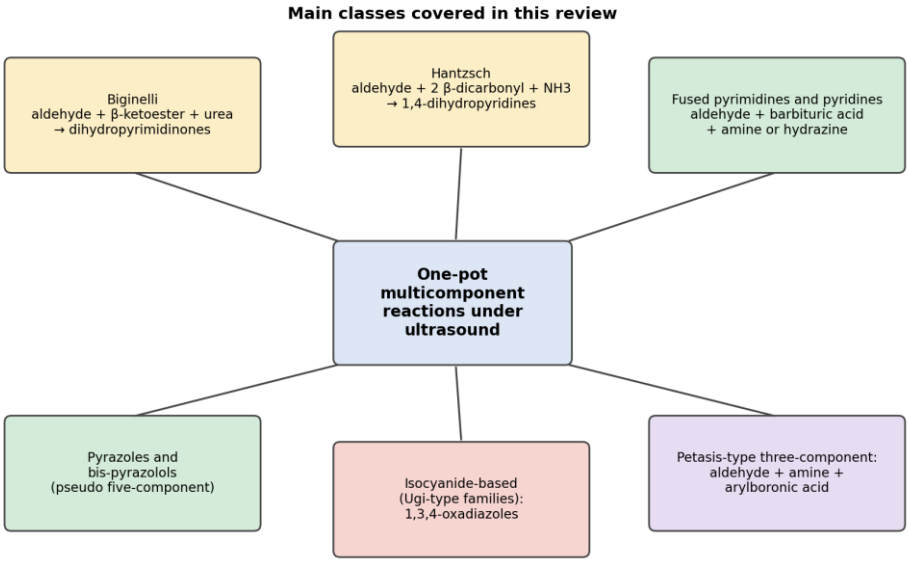

Figure 1. Classes of one-pot multicomponent reactions that have been run under ultrasonic conditions.

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Ultrasound is a well-established enabling technique in organic synthesis. It has been used for decades and, besides enhancing mechanical effects in heterogeneous processes, can induce new reactivity [4]. Combined with water as solvent, which is cheap, non-flammable and easy to handle [18], sonication offers a sustainable route to MCR products. Several reviews have covered ultrasound-assisted MCRs and related heterocycle syntheses [19–22]. This review focuses on the reaction classes, mechanisms and quantitative outcomes, and it adds a detailed case study (Figure 1 gives the overall landscape).

2. How ultrasound activates reactions

Ultrasound consists of acoustic waves above 20 kHz. In a liquid, alternating compression and rarefaction cycles generate microbubbles; when a bubble reaches an unstable size it collapses violently, and this cavitation is what makes sonochemistry unique [4,5]. Local temperatures of about 5000 K and pressures of about 10,000 atm have been quoted for collapsing bubbles [23], although the actual conditions depend on the medium and the acoustic field. The collapse produces chemical effects, through reactive species and bond activation, and physical effects such as microjets, shock waves and enhanced mixing (Figure 2). For heterogeneous MCRs, such as those involving poorly soluble reactants in water, the mechanical effects are especially useful [4].

The interpretation of cavitational effects and of the role of the acoustic field is often misunderstood, and mechanistic interpretations remain a matter of active research [5]. It is therefore good practice to report frequency, power, bath or probe type, vessel position and bulk temperature, and the case study below follows this practice.

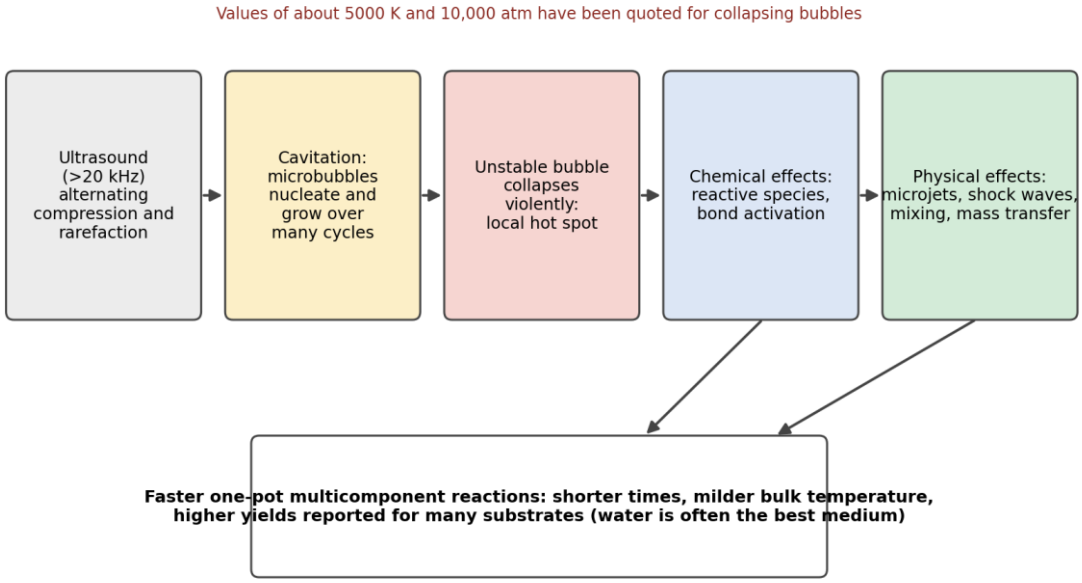

Figure 2. Mechanism of ultrasonic activation by acoustic cavitation.

3. Classes of ultrasound-promoted one-pot MCRs

3.1 Biginelli dihydropyrimidinone synthesis

The Biginelli reaction condenses an aldehyde, a β-ketoester and urea or thiourea into 3,4-dihydropyrimidin-2(1*H*)-ones [24]. Its mechanism is generally described as proceeding through an N-acyliminium ion intermediate [25] (Figure 3). Ultrasound has been combined with acid catalysis: sulfamic acid (NH_2SO_3H) was used under sonication to prepare dihydropyrimidinones [6]. In room-temperature ionic liquid, the Biginelli reaction proceeded in excellent yields in a short time at ambient temperature under ultrasound without any added catalyst, and a mechanistic pathway involving the ionic liquid was proposed [7]. Earlier work had compared ethanol, water and solvent-free conditions for the thermal reaction [26], providing the baseline against which sonochemical variants are judged.

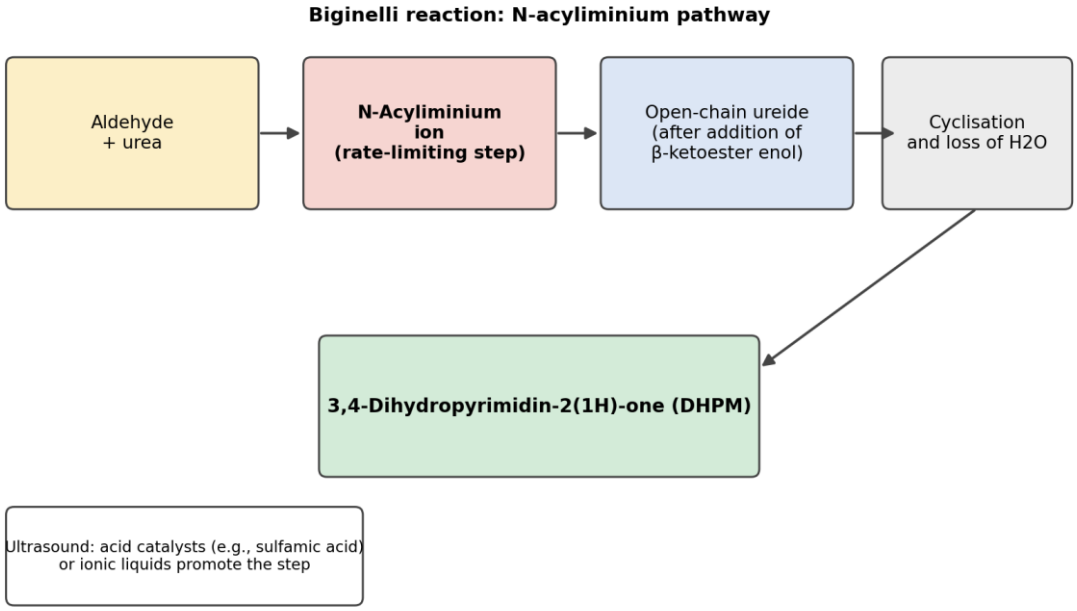

Figure 3. Generally accepted mechanism of the Biginelli reaction, which ultrasound-promoted variants follow.

3.2 Hantzsch dihydropyridines and polyhydroquinolines

Hantzsch esters and polyhydroquinoline derivatives were prepared in excellent yields in aqueous micelles, in a reaction catalysed by *p*-toluenesulfonic acid and strongly accelerated by ultrasonic irradiation [8]. A one-pot four-component cyclocondensation of aromatic aldehydes, malononitrile, acetylenedicarboxylates and arylamines, catalysed by copper(I) iodide in aqueous medium under ultrasound, gave polysubstituted 1,4-dihydropyridines with shorter reaction time, excellent yields and product isolation by simple precipitation [9].

3.3 Fused pyrimidines and pyridines

Ultrasound-mediated routes to pyrimidines and pyridines in aqueous medium have been reported [10]. Polycyclic imidazo(thiazolo)pyrimidines were obtained with a Fe3O4@clay core-shell catalyst [27], tetrazolopyrimidines with a magnetic core-shell nanostructured catalyst in water [28], and pyridodipyrimidines from an aldehyde, thiobarbituric acid and ammonium acetate with a magnetically recyclable nanocatalyst in water [11]. Pyrazolopyranopyrimidines were prepared by a cascade in water with β-cyclodextrin as catalyst under ultrasound [29], and a catalyst-free five-component synthesis of pyrazolopyridopyrimidine-diones is discussed in Section 4 [12].

3.4 Pyrazoles and bis-pyrazolols

Pyrazoles and pyranopyrazoles have been synthesised in water under ultrasonic acceleration [13]. A catalyst-free, pseudo-five-component synthesis of aryl-bis-(1*H*-pyrazol-5-ol-4-yl)methanes in water gave the products in excellent yield in a shorter time, with high purity by simple filtration [14].

3.5 Isocyanide-based reactions

Isocyanide-based MCRs are a major family within MCR chemistry [3]. Their combination with sonication was demonstrated in the synthesis of fully substituted 1,3,4-oxadiazoles under ultrasound irradiation, reported as an efficient and fast method [15].

3.6 Petasis-type three-component coupling

A meglumine-catalysed three-component condensation of 2-hydroxyaryl-1-carboxaldehydes, 1-(pyridin-4-yl)piperazine and aryl boronic acids in water assisted by ultrasound gave pyridylpiperazine derivatives with 10 mol% catalyst, a reaction time of 30 min and no need for column chromatography [16]. The components are those of a Petasis-type borono-Mannich coupling.

Table 1. Representative one-pot MCRs under ultrasonic conditions.

Reaction class	Components	Conditions	Reference
Biginelli	Aldehyde, β-ketoester, (thio)urea	NH_2SO_3H catalyst; or ionic liquid without catalyst, ambient temperature	[6, 7]
Hantzsch	Aldehyde, β-dicarbonyl, ammonia source	*p*-TSA in aqueous micelles	[8]
Four-component dihydropyridine	Aldehyde, malononitrile, acetylenedicarboxylate, arylamine	CuI, aqueous medium	[9]
Pyrimidines and pyridines	Aldehyde, active methylene, N-source	Aqueous medium	[10]
Fused pyrimidines	Aldehyde, (thio)barbituric acid, ammonium acetate	Magnetic nanocatalyst in water	[11, 27, 28]
Pyrazolopyranopyrimidines	Aldehyde, pyrazolone, barbituric acid	β-Cyclodextrin in water	[29]
Pyrazolopyridopyrimidine-diones	Aldehyde, barbituric acid, ethyl acetoacetate, hydrazine, ammonium acetate	Catalyst-free, water, 35 kHz	[12]
Bis-pyrazolols	Aldehyde, ethyl acetoacetate, hydrazine (pseudo five-component)	Catalyst-free, water	[14]
Isocyanide-based	Isocyanide-based components	Ultrasound irradiation	[15]
Petasis-type	Hydroxyaryl aldehyde, piperazine, boronic acid	Meglumine 10 mol%, water, 30 min	[16]

4. Case study: Catalyst-free five-component synthesis in water

A catalyst-free route to fourteen 3-methyl-1,4,8,9-tetrahydro-5*H*-pyrazolo[4,3:5,6]pyrido[2,3-d]pyrimidine-5,7(6*H*)-diones used one aldehyde, barbituric acid, ethyl acetoacetate, hydrazine hydrate and ammonium acetate in water under ultrasonication, with conversion in 15–18 min and yields of 85–98% [12]. Sonication was performed in an Indian-made bath operating at 35 kHz and 80 W at 28 °C; the reaction used 1 mmol of aldehyde, hydrazine, ethyl acetoacetate and barbituric acid and 1.2 mmol of ammonium acetate in 5 mL of water [12].

4.1 Optimisation

Under solvent-free sonication the product formed in only 30% yield, and nonpolar solvents gave very low yields, polar aprotic solvents moderate yields and polar protic solvents good to excellent yields; water was best [12]. With 4-chlorobenzaldehyde as model substrate, 5 mL of water gave the highest yield (98%), and larger volumes gave no further gain; at 5 mL, the yield rose from 45% at 5 min to 98% at 15 min with no further change at 20 min [12] (Table 2, Figure 4).

Table 2. Optimisation of the five-component reaction under ultrasound (4-chlorobenzaldehyde model) [12].

Entry	Water (mL)	Time (min)	Isolated yield (%)
1	2	15	65
2	4	15	78
3	5	15	98
4	6	15	98
5	8	15	98
6	10	15	98
7	5	5	45
8	5	10	54
9	5	20	98

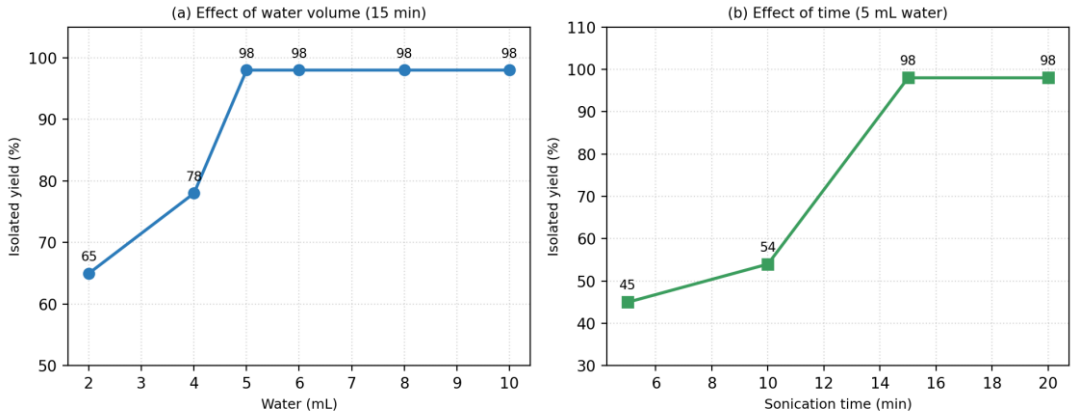

Figure 4. Optimisation of the five-component reaction under ultrasound; data from Mangalavathi et al., 2024.

4.2 Substituent effects

Electron-withdrawing groups on the aldehyde enhanced the yield and electron-donating groups lowered it, and di- and trisubstituted aldehydes with chloro or methoxy groups gave lower yields (85–89%) [12]. Nine of the fourteen products were obtained in more than 90% yield and five in less than 90% (Figure 5).

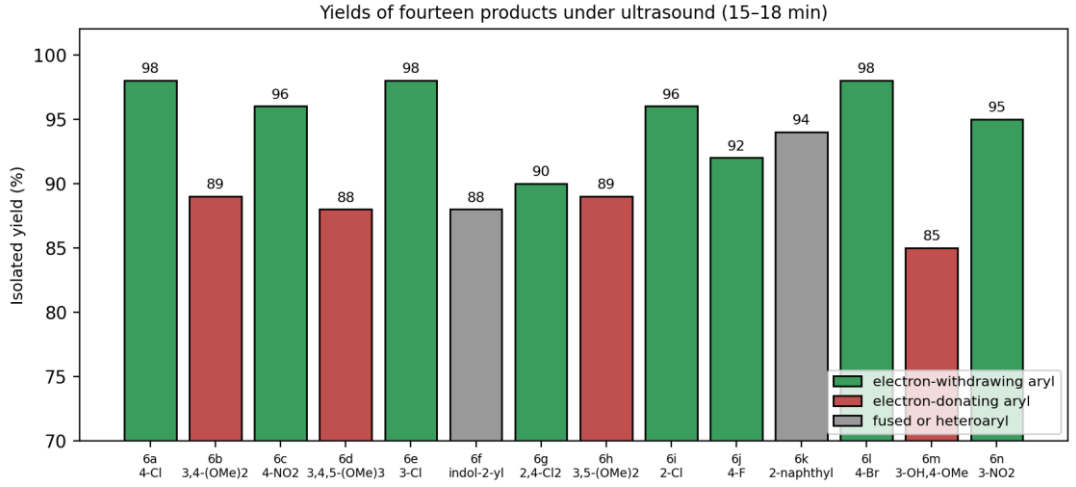

Figure 5. Substituent effect on yield; data from Mangalavathi et al., 2024 (aldehyde substituent shown under each label).

4.3 Mechanism

A plausible mechanism begins with condensation of ethyl acetoacetate and hydrazine to a pyrazolone, followed by Knoevenagel condensation with the aldehyde to a benzylidene-pyrazolone, Michael addition of barbituric acid, reaction with ammonia-derived nitrogen to give an enamine, and intramolecular cyclisation with loss of water [12] (Figure 6). The authors attribute the favourable effect of water to better distribution of ultrasonic energy and a greater cavitation effect than in the other solvents tested [12].

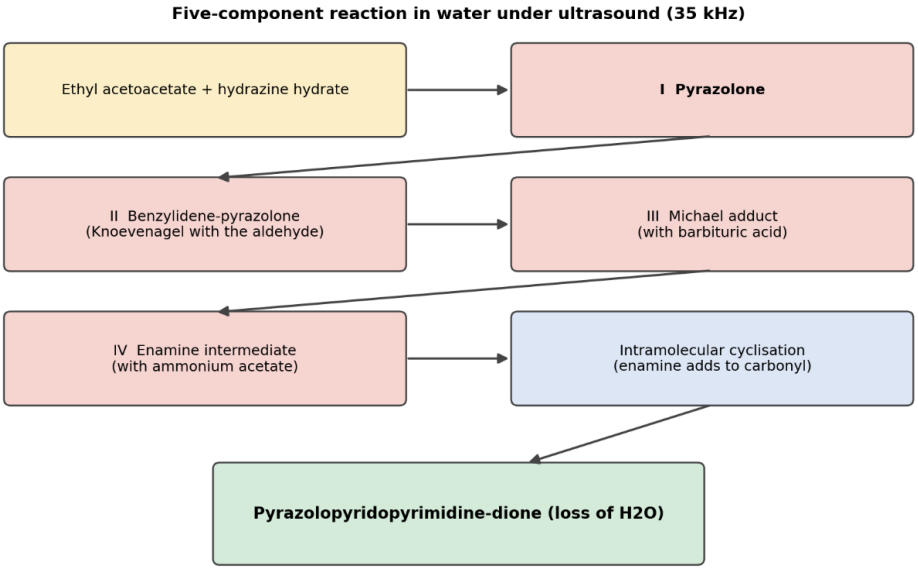

Figure 6. Plausible mechanism of the catalyst-free one-pot five-component synthesis (after Mangalavathi et al., 2024).

5. Green chemistry metrics and process considerations

Green metrics allow sonochemical MCRs to be compared objectively. The meglumine-catalysed three-component synthesis in water reported an E-factor of 0.1454, mass intensity of 1.1907, process mass intensity of 1.1454 and Emw of 0.1445 (Figure 7) [16]. Values close to the ideal indicate very little waste per unit product, consistent with the broader sustainability benefits claimed for catalyst-free, aqueous MCRs [12,20].

Table 3. Selected sonochemical MCRs from one research group: conditions and outcomes.

Reaction	Catalyst, medium	Reported outcome	Reference
Four-component 1,4-dihydropyridines	CuI, aqueous	Shorter time, excellent yields, isolation by precipitation	[9]
Three-component pyridylpiperazines	Meglumine (10 mol%), water	30 min; E-factor 0.1454; PMI 1.1454	[16]
Pseudo five-component bis-pyrazolols	None, water	Excellent yield, high purity by filtration	[14]
Five-component pyrazolopyridopyrimidine-diones	None, water, 35 kHz	15–18 min; 85–98% yield	[12]

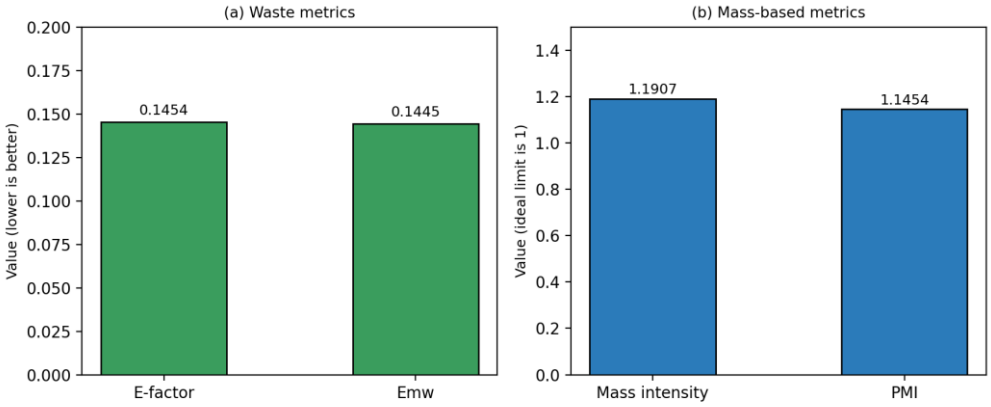

Figure 7. Green chemistry metrics reported for the sonochemical three-component synthesis of pyridylpiperazines (Tabassum et al., 2017).

Several practical points emerge. Results depend on the medium: in the case study, solvent-free sonication gave 30% yield whereas water gave 98% [12]. Reproducibility depends on reporting acoustic conditions, because cavitation effects are easily misinterpreted [5]. Laboratory baths are convenient but vary in power distribution, and scale-up requires process-oriented designs [4]. Finally, many reports use heterogeneous nanocatalysts, whose recovery and leaching should be quantified [11,28].

Table 4. Practical parameters for ultrasound-promoted MCRs.

Parameter	**Observation**	**Reference**
Frequency and power	35 kHz bath, 80 W, 28 °C in the case study	[12]
Solvent	Water best; solvent-free sonication 30%; nonpolar solvents very low yields	[12]
Catalyst	Often unnecessary in water; acids, ionic liquids or nanocatalysts used in others	[6,7,11,12]
Substrate scope	Electron-withdrawing aryl aldehydes give higher yields	[12]
Reporting	Acoustic conditions should be stated to allow reproducibility	[5]

6. Limitations and future directions

The literature on ultrasound-promoted MCRs is dominated by laboratory-scale reactions in bath sonicators, with limited comparison against silent controls at the same bulk temperature, so the true contribution of cavitation is often unclear [5]. Priorities include: (i). systematic control experiments with identical temperature and mixing; (ii). full reporting of acoustic parameters; (iii). extension to isocyanide-based and asymmetric MCRs, where reports under ultrasound are still limited [3,15]; (iv). flow and scaled-up sonochemical reactors [4]; (v). combination with water and recyclable catalysts, with metrics such as E-factor and PMI reported routinely [16,18]; and (vi). mechanistic studies that separate chemical from mechanical effects [4,5].

7. Conclusions

Ultrasound has been applied to Biginelli, Hantzsch, fused pyrimidine, pyrazole, isocyanide-based and Petasis-type MCRs, usually giving short reaction times and good to excellent yields at mild bulk temperature [6,8,12,15,16]. Water is frequently the best medium, and catalyst-free protocols are

increasingly common [12,14]. Quantitative green metrics are available for a few systems and are very favourable [16]. Wider adoption will depend on rigorous controls, reporting of acoustic conditions and scale-up.

Declarations, Conflict of interest and funding

Article Title: *One-Pot Multicomponent Reactions under Ultrasonic Conditions: Scope, Mechanisms, Green Metrics and Prospects-A Narrative Review*

Conflict of Interest

The author declares that there are no conflicts of interest, financial or otherwise, that could have influenced the preparation, interpretation, or presentation of this review.

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Ethical Approval

Ethical approval was not required for this narrative review because it is based on previously published scientific literature and does not involve human participants, animals, or new experimental investigations.

Data Availability Statement

No new experimental datasets were generated or analysed for this review. The information discussed is derived from previously published literature, which is cited appropriately in the manuscript.

Author Contributions

The author was responsible for the conceptualization, literature review, organization of the material, critical discussion, preparation and final approval of the manuscript.

Use of Artificial Intelligence Tools

Artificial intelligence (AI)-assisted tools were used to support the organization, development, language refinement and presentation of the manuscript. The author reviewed and critically evaluated the AI-assisted content, verified scientific statements and references to the extent possible, and accepts full responsibility for the accuracy, originality, integrity and final content of the published work. AI tools are not listed as authors and do not bear responsibility for the manuscript.

Author Note

This narrative review examines the scope and synthetic applications of one-pot multicomponent reactions (MCRs) conducted under ultrasonic conditions, with particular emphasis on reaction mechanisms, cavitation-assisted effects, synthetic efficiency, green chemistry metrics, and future research opportunities. It discusses the potential of ultrasound-assisted synthesis to improve reaction rates, facilitate reaction processes, reduce solvent and energy requirements in suitable systems, and support more sustainable approaches to heterocyclic and other organic compound synthesis.

The views and interpretations expressed in this article are those of the author. The review is intended to support scientific understanding and further research in ultrasound-assisted multicomponent synthesis and green chemistry. The potential environmental benefits of ultrasonic methods should be assessed on a case-by-case basis using appropriate quantitative metrics, including atom economy, reaction mass efficiency, process mass intensity, E-factor, solvent use, and total energy consumption, rather than assuming that ultrasonic activation is inherently greener in every application.

References

1. Zhu J, Bienaymé H, editors. Multicomponent Reactions. Weinheim: Wiley-VCH; 2005.
2. Ugi I. Recent progress in the chemistry of multicomponent reactions. Pure Appl Chem. 2001;73(1):187–191.
3. Dömling A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem Rev. 2006;106(1):17–89.
4. Cravotto G, Cintas P. Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications. Chem Soc Rev. 2006;35(2):180–196.
5. Martínez RF, Cravotto G, Cintas P. Organic sonochemistry: a chemist's timely perspective on mechanisms and reactivity. J Org Chem. 2021;86(20):13833–13856.
6. Li J-T, Han J-F, Yang J-H, Li T-S. An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH_2SO_3H under ultrasound irradiation. Ultrason Sonochem. 2003;10(3):119–122.

7. Gholap AR, Venkatesan K, Daniel T, Lahoti RJ, Srinivasan KV. Ionic liquid promoted novel and efficient one pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones at ambient temperature under ultrasound irradiation. Green Chem. 2004;6(3):147–150.
8. Kumar A, Maurya RA. Efficient synthesis of Hantzsch esters and polyhydroquinoline derivatives in aqueous micelles. Synlett. 2008;(6):883–885.
9. Tabassum S, Govindaraju S, Khan R, Pasha MA. Ultrasound mediated, green innovation for the synthesis of polysubstituted 1,4-dihydropyridines. RSC Adv. 2016;6(35):29802–29810.
10. Pagadala R, Maddila S, Jonnalagadda SB. Eco-efficient ultrasonic responsive synthesis of pyrimidines/pyridines. Ultrason Sonochem. 2014;21(2):472–477.
11. Naeimi H, Didar A. Efficient sonochemical green reaction of aldehyde, thiobarbituric acid and ammonium acetate using magnetically recyclable nanocatalyst in water. Ultrason Sonochem. 2017;34:889–895.
12. Mangalavathi, Khanum A, Pasha MA. Novel, catalyst-free one-pot multicomponent synthesis of pyrazolopyridopyrimidine-diones in water under ultrasonic condition. Green Energy Environ Technol. 2024;3(1):1–18. doi:10.5772/geet.20230096.
13. Shabalala NG, Pagadala R, Jonnalagadda SB. Ultrasonic-accelerated rapid protocol for the improved synthesis of pyrazoles. Ultrason Sonochem. 2015;27:423–429.
14. Sudha S, Pasha MA. Catalyst-free ultrasound assisted novel one pot pseudo five component synthesis of aryl-bis-[1H-pyrazol-5-ol-4-yl]methanes, het(aryl)-bis-[1*H*-pyrazol-5-ol-4-yl]methanes and their 1-phenyl derivatives in aqueous medium. Green Synth Catal. 2022;3(2):190–193.
15. Rouhani M, Ramazani A, Joo SW. Ultrasonics in isocyanide-based multicomponent reactions: a new, efficient and fast method for the synthesis of fully substituted 1,3,4-oxadiazole derivatives under ultrasound irradiation. Ultrason Sonochem. 2015;22:391–396.
16. Tabassum S, Govindaraju S, Pasha MA. Sonochemistry – An innovative opportunity towards a one-pot three-component synthesis of novel pyridylpiperazine derivatives catalysed by meglumine in water. New J Chem. 2017;41(9):3515–3523.
17. Ganem B. Strategies for innovation in multicomponent reaction design. Acc Chem Res. 2009;42(3):463–472.
18. Cortes-Clerget M, Yu J, Kincaid JRA, Walde P, Gallou F, Lipshutz BH. Water as the reaction medium in organic chemistry: from our worst enemy to our best friend. Chem Sci. 2021;12(12):4237–4266.
19. Banerjee B. Recent developments on ultrasound-assisted one-pot multicomponent synthesis of biologically relevant heterocycles. Ultrason Sonochem. 2017;35(Pt A):15–35.
20. Banerjee B. Recent developments on ultrasound assisted catalyst-free organic synthesis. Ultrason Sonochem. 2017;35(Pt A):1–14.
21. Banerjee B. Recent developments on ultrasound-assisted organic synthesis in aqueous medium. J Serb Chem Soc. 2017;82(7–8):755–790.
22. Pagadala R, Kasi V, Shabalala NG, Jonnalagadda SB. Ultrasound-assisted multicomponent synthesis of heterocycles in water – a review. Arab J Chem. 2022;15(1):103544.
23. Bremner DH. Recent advances in organic synthesis utilizing ultrasound. Ultrason Sonochem. 1994;1(2):S119–S124.
24. Kappe CO. 100 years of the Biginelli dihydropyrimidine synthesis. Tetrahedron. 1993;49(32):6937–6963.
25. Kappe CO. A reexamination of the mechanism of the Biginelli dihydropyrimidine synthesis. Support for an N-acyliminium ion intermediate. J Org Chem. 1997;62(21):7201–7204.
26. Bose DS, Fatima L, Mereyala HB. Green chemistry approaches to the synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones by a three-component coupling of one-pot condensation reaction: comparison of ethanol, water, and solvent-free conditions. J Org Chem. 2003;68(2):587–590.
27. Maleki A, Aghaei M. Ultrasonic assisted synergetic green synthesis of polycyclic imidazo(thiazolo)pyrimidines by using Fe3O4@clay core-shell. Ultrason Sonochem. 2017;38:585–589.
28. Maleki A, Rahimi J, Demchuk OM, Wilczewska AZ, Jasiński R. Green in water sonochemical synthesis of tetrazolopyrimidine derivatives by a novel core-shell magnetic nanostructure catalyst. Ultrason Sonochem. 2018;43:262–271.
29. Akolkar S, Kharat N, Nagargoje A, Subhedar D. Ultrasound-assisted β-cyclodextrin catalyzed one-pot cascade synthesis of pyrazolopyranopyrimidines in water. Catal Lett. 2020;150:450–460.