Review

Ultrasound-assisted synthesis of pyrimidines and their fused derivatives: A review

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ABSTRACT

The pyrimidine scaffold is present in many bioactive drugs; therefore, efficient synthetic routes that provide shorter reaction times, higher yields, and site-selective reactions are constantly being sought. Ultrasound (US) irradiation has emerged as an alternative energy source in the synthesis of these heterocyclic scaffolds, and over the last ten years there has been a significant increase in the number of publications mentioning US in either the construction or derivatization of the pyrimidine core. This review presents a detailed summary (with 140 references) of the effects of US (synergic or not) on the construction and derivatization of the pyrimidine core through classical reactions (e.g., multicomponent, cyclocondensation, cycloaddition, and alklylation reactions). The main points that were taken into consideration are as follows: chemo- and regioselectivity issues, and the results of conventional heating methods compared to US and mechanistic insights that are also presented and discussed for key reactions.

1. Introduction

Pyrimidines and pyrimidinones have been used as suitable starting materials for the synthesis of novel scaffolds that are parent to DNA nitrogenated bases (Fig. 1), thus targeting the possible biological and/or pharmacological properties that novel synthesized compounds may present [1]. For example, compounds containing a pyrimidine ring in their structure have been found to act as antiplasmodials [2], as well as caspase [3], hepatitis C [4,5], NTPDase [6], and cancer [7] inhibitors. Fig. 1 shows some commercially available drugs containing at least one pyrimidine ring (or hydrogenated derivates) in their structure, which shows the wide range of biological activity present in these compounds [8].

Over the last 20 years, several technologies that may assist synthetic organic chemists have emerged as powerful operating tools for heterocyclic synthesis, being the most commonly used as follows: ionic liquids (ILs) as catalysts and/or reaction media [9,10]; on-grinding methods to promote solvent-free synthesis [11,12]; and alternative energy sources such as electrosynthesis [13–15], microwave (MW) [16,17], and ultrasound (US) irradiation, which has gained special attention in recent years due to its application in organic synthesis [18–25].

Due to the uniqueness of US in accelerating many organic reactions through cavitation, it provides shorter reaction times and increased yields compared to conventional heating methods or systems involving catalysts [26,27]. The cavitation phenomenon — which comprises the formation, growth, and collapse of bubbles irradiated with sound — produces enormous amounts of energy, and converts kinetic energy into heat [37,38]. Several US-based techniques have been developed in the last few years, with the aim being to take advantage of the synergic effects that may be provided by US combined with other components, such as ILs [29–31], pyrimidine-based [32] and other catalysts, [33] [33] and MW irradiation [34].

When working with heterocyclic synthesis, one very important issue is the regioselectivity of the obtained compounds, especially in cyclocondensation reactions [35,36]. The selectivity of these reactions is mostly due to the reaction conditions, such as solvent choice and temperature [37], the use of additives like BF3(OEt)2, H2SO4, and HCl to promote solvent-free synthesis [11,12]; and alternative energy sources such as electrosynthesis [13–15], microwave (MW) [16,17], and ultrasound (US) irradiation, which has gained special attention in recent years due to its application in organic synthesis [18–25].

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The selectivity is not affected by the US [43].

The relevance of the pyrimidine core and the advantages of using US provide a powerful tool to prepare these six-membered nitrogenated scaffolds. In recent years there has been constant growth in the use of US to prepare several pyrimidine-based heterocycles. Fig. 2 shows this evolution from 2000 onward, reflected by the increasing progression in the number of publications (there was only one article prior to 2000 — from 1987 [44] to be precise). The term “ultrasound pyrimidine synthesis” was used as search parameter in the Web of Science and Scifinder databases, which resulted in a total of 140 items up to February 2021.

Among these, 112 (about 80% of the references in this work) applied methodologies that employ the use of ultrasonic bath, while 28 (20%) used probe-type sonication (Fig. 2). The application of probe-type methodologies in pyrimidine synthesis started in 2009 [45], however, up to this date, ultrasonic bath is still the most commonly used methodology.

Fig. 1. Chemical structures of commercially available drugs containing a pyrimidine ring.

Probe-type systems have high cavitational intensity in contrast to low operating volumes [46]. Acoustic energy is introduced directly into the liquid and the power dissipated in the reaction mixture can normally be changed, although the frequency of irradiation, in most cases, remains constant. The probe diameter and the height of the liquid in the reactor and other parameters, control cavitational activity and need to be properly selected at suitable levels depending on the application [46]. Despite this, the ultrasonic bath remains the most widely available and cheapest source of ultrasonic irradiation [46,47], which is perhaps the main reason for being still so widely used. The parameters in the latter are not so precisely adjusted, and cavitation occurs indirectly, thus, reducing the number of variables that can influence the outcome of the reactions [47].

Although some reviews regarding the synthesis of heterocycles performed in US are available in the literature [19,20,23,24,26,48], no comprehensive reviews considering US-assisted synthesis of this important heterocyclic scaffold were found, and considering the increasing number of publications in the last few years (140 references in total, with 126 since 2010), a literature review is necessary to summarize the achievements made, which will assist synthetic chemists aiming for new reactions and applications in those already established. For better understanding, this review is divided according to the type of reaction used to prepare the final pyrimidine scaffold, that is: i) multi-component reactions (e.g. Biginelli reaction) for the synthesis of di- and tetrahydropyrimidines and fused derivatives, ii) cyclocondensation reactions of α,β-unsaturated ketones with NCN-dinucleophiles, iii) miscellaneous reactions, and iv) derivatizations on the pyrimidine ring.

Fig. 2. Publications with the terms “ultrasound”, “pyrimidine”, and “synthesis”, found in databases covering the period between 2000 and February 2021.
Scheme 1. Three possible routes for the Biginelli MCR. Adapted with permission from Nagarajaiah, Mukhopadhyay, and Moorthy (2016) [50] and Puripat et al. (2015) [54]. Copyright (2021) American Chemical Society.

Scheme 2. US/IL catalytic system for the Biginelli MCR, reported by Srinivasan et al. (2004) [62].

Fig. 3. Chemical structures, isolated yields, and reaction times required to prepare novel 3,4-dihydropyrimidin-2(1H)-ones using the US/NH₄Cl catalytic system reported by Stefani et al. (2006) [66].
2. Synthesis of pyrimidines via multicomponent reactions (MCR)

2.1. MCR in the synthesis of non-fused pyrimidines and pyrimidinone scaffolds

The Biginelli reaction is a three-component reaction between an aldehyde, a 1,3-dicarbonyl compound (or its equivalent), and a (thio)urea derivative that has been used to successfully assemble 3,4-di-hydroxyprymidin-2(1H)-ones [49,50]. In fact, the great success of this MCR has made it an important item in undergraduate experimental organic chemistry classes for introducing the concept of MCRs [51]. Since its discovery, several catalytic and enantioselective routes have been proposed, with the aim of improving yields, lowering reaction times, and preparing enantiopure products [52–56].

The mechanism of the Biginelli reaction is a topic that has been under investigation for years [57–59], since three main pathways that lead to the same product are possible when using acidic media (Scheme 1). When urea is the first component and aldehyde the second, the reactive intermediate I (imium ion) is obtained through nucleophilic addition, whereas when the 1,3-dicarbonyl compound (ethyl acetocetate) is the second component, the 1,4-conjugated Michael-type protonated adduct II is obtained. The third route is based on the Knoevenagel condensation between the 1,3-dicarbonyl compound and the aldehyde, which furnishes protonated III. The latest achievement in elucidating its mechanism is through artificial force-induced reaction calculations, in which it was found that the iminium route (reactive intermediate I) is the most favored, followed by the addition of the 1,3-dicarbonyl compound. It was also found that a second urea molecule catalyzes nearly every step of the process, and protic and aprotic solvents furnish identical results [54]. ESI(+)-MS experiments show that the Knoevenagel route is too slow and does not significantly contribute to the synthesis of the Biginelli adduct. Only one intermediate in agreement with the enamine intermediate was detected, whereas several intermediates associated with the iminium route were detected, thus indicating it to be the most feasible route for the Biginelli MCR [60].

Given that the Biginelli reaction requires catalysts (usually acidic media) and harsh reaction conditions (other catalytic additives and high temperatures) [61], the use of US irradiation has become an interesting source of alternative energy for this reaction. The first report on the application of US in this MCR relied on the application of ILs as solvent and catalysts (instead of the usual mineral acid) combined with US irradiation (Scheme 2) [62]. Given the proven efficiency of ILs, since their discovery, as both solvents and catalysts in a wide range of organic reactions [63–65], the combination of ILs with US may result in a very efficient catalytic system for the Biginelli reaction (among others). The authors initially evaluated the reaction between β-ketoester 1 with an aldehyde 2 and (thio)urea 3 to furnish 3,4-dihydroxyprymidin-2(1H)-one 4. Different ILs derived from 1,3-dibutylimidazolium (BBIM) and 1,3-dialkyylimidazolium (HDIM) with different anions (Br, Cl, ClO4, BF4, and PF6) were used. The optimal condition was chosen based upon the time for complete conversion and isolated yield of the final product ([BBIM]BF4, 45 min, 95% yield). Having defined the best reaction conditions, the reaction scope was explored, and yields above 87% were obtained in all cases (both electron-withdrawing and electron-donating groups). Remarkably, aldehydes bearing strong electron-withdrawing groups (e.g., 4-NO2, 2-F, and 2-Br) required longer reaction times (25, 15, and 15 min more, respectively) [62].

Control reactions were conducted in order to verify possible synergetic effects. No reaction was observed when using US combined with molecular solvents (MeCN, EtOH, THF, and CH2Cl2) in the absence of IL. And when the reaction was conducted under conventional conditions (stirring at 30 °C without US irradiation), once again, no formation of the product was detected, which indicates a synergetic effect of the US/IL combined system [62].

Another catalytic system reported for the Biginelli MCR is US/NH4Cl, using MeOH as solvent [66]. Using this method, eight novel 3,4-dihydroxyprymidin-2(1H)-ones 4 were prepared at moderate to high yields (65–90%, Fig. 3). All the newly synthesized derivatives were tested for their antioxidant activity, and, notably, compounds bearing the β-aminoester moiety exhibited strong activity against lipid peroxidation induced by iron and EDTA, and when R = H, reduction of reactive oxygen species was also observed [66].

There have been several reports in which the Biginelli MCR is explored using US as the energy source, with slight changes in the reaction conditions (e.g., solvent, catalyst, or additive used—see Table 1). Besides the classical Biginelli MCR (β-ketoester, aldehyde, and (thio)urea), modifications have been made throughout the years to attain the synthesis of the pyrimidine core via MCR, but using different starting materials (ketones, malononitrile, etc.). This demonstrates the wide range of substrates tolerated for the assembly of the pyrimidine core through MCR, as well as the preparation of the final scaffolds with unique substitution patterns (Table 1). Generally, the authors sought optimization of the reaction conditions proposed, and, under the optimal conditions, a scope varying the substituents in at least two of the three starting materials was pursued. The results are often presented in terms of comparison with conventional methods (e.g., heating) and, in some cases, with methods using MW-assisted synthesis.

US irradiation also acts synergistically when combined with other chemicals and/or materials (commonly used as catalysts); for example, the synergetic effect produced from US combined with ILs (Entry 10 in Table 1), in which the corresponding pyrimidines were not obtained when the reaction was conducted in molecular solvents or without US irradiation [62]. Likewise, the same synergetic effect was observed between US and mesoporous Santa Barbara Amorphous (SBA) silica [67,68]. SBA may have different surfaces that can be functionalized by acidic, basic, or metallic means, which makes it a promising candidate in the development of environmentally friendly synthetic methods [68,69]. Sulforic acid covalently functionalized in SBA under US irradiation works as a catalyst, and, compared to other methods, gives high yields in the synthesis of heterocycles (pyrimidine-, pyridine-, and imidazole-based) [67]. The data regarding the synthesis of the tetrahydroprymidin-5-carboxylate scaffold are presented in Table 1 (Entry 13).

As a general remark, when comparing different methods (conventional heating, MW, and US), the isolated yields of the final compounds are higher and obtained at greater purity when US is used. Besides this, the reaction time is greatly diminished (in most cases, from hours to minutes). For instance, in Table 1, entries 10 – 16 present the reaction of a β-ketoester, an aldehyde and (thio)urea. Several catalysts such as ILs, graphene oxide, acid- and metal-based catalysts were used. The yield of the product was very similar on all the methods applied (up to 98%), however, the reaction time was greatly affected, varying from 6 to 90 min, which shows the synergetic effect between the acid catalyst used and the US. Thus, current progress strongly indicates that these US-based procedures applied to MCRs that seek pyrimidine scaffolds, are simpler, safer, more environmentally friendly, and less expensive synthetic approaches.
Table 1
Conditions used for the MCR assisted by US to assemble the pyrimidine core. *(See below-mentioned references for further information.)*

| Ent. | Component 1 | Component 2 | Component 3 | Additive | US Conditions | Final compounds | Yields (%) | Ref. |
|------|-------------|-------------|-------------|----------|---------------|----------------|-----------|------|
| 1    |             |             |             | Sn(ClO₄)₂ | EtOH, reflux, 2–3 h |                | 77–95     | [70] |
| 2    | O           | O           |             | Lactic acid | 80 °C, 30-40 min |               | 65–85     | [71] |
| 3    | O           | O           |             | Me₃SiCl  | DMF, r. t., 48 h |               | 6–24      | [72] |
| 4    |             |             |             | Dendrimer- H₃PW₁₂O₄₀ (PWA) | EtOH, 50 °C, 10-20 min |               | 88–97     | [73] |
| 5    |             |             |             | NaOEt | i-PrOH, r. t., 15 min |               | 87–94     | [74] |
| 6    | O           | O           |             | UO₂(NO₃)₂· 6H₂O | MeCN, 21–24 min |               | 79–87     | [75] |
| 7    | O           | O           |             | NaOH | H₂O, 2–3 h |               | 88–95     | [76] |
| 8    |             |             |             | Atomized Na | THF, 10-15 min |               | 87–90     | [77] |
| 9    |             |             |             | KOH | EtOH, 50 °C, 30–90 min |               | 78–95     | [78] |
| 10   |             |             |             | [HBIM]BF₄ | 30 °C, 90 min. |               | 87–97     | [62] |
| 11   |             |             |             | Graphene oxide (GO) | r. t., 2 h |               | 76–92     | [79] |
| 12   |             |             |             | Natural dolomitic limestone (NDL) catalyst | EtOH/H₂O, 45–50 °C, 10–20 min |               | 90–97     | [80] |
| 13   | O           | R           |             | SBA-SO₄H | EtOH, r. t., 25 min |               | 88–98     | [67] |
| 14   |             |             |             | Caffeine-Il·GO/FeCl₃ | H₂O, 80 °C |               | 80–95     | [81] |
| 15   |             |             |             | Polyindole catalyst | r. t., 22–37 min |               | 82–97     | [82] |
| 16   |             |             |             | 2,4,6-trichloro- 1,3,5-triazine | H₂O, 60 °C, 6-15 min |               | 90–97     | [83] |

(continued on next page)
Table 1 (continued)

| No. | Structure | Reaction Conditions | Solvent | Yield | Reference |
|-----|-----------|---------------------|---------|-------|-----------|
| 17  |          | Me$_2$SiCl, 1 h, 48 h |         | 12–35 | [72]      |
| 18  |          | [BSO$_2$HPy] HSO$_4$ | 50 °C, 45–50 min | 60–80 | [84]      |
| 19  |          | NaHCO$_3$           | DMF, 60–70 °C | 71–83 | [59]      |
| 20  |          | DMF/H$_2$O, 60 °C, 60 min | Et$_2$O/C | -     | [85]      |
| 21  |          | Amino-functionalized Co$_3$O$_4$-Si$_3$O$_2$N$_5$ | EtOH/H$_2$O, reflux, 10–15 min | 87–96 | [86]      |
| 22  |          | Cu-SBA-15 by Isatoic anhydride (IA) | EtOH/H$_2$O, 30–180 °C, 10 min | 82–95 | [68]      |
| 23  |          | EtOH/H$_2$O, 50 °C, 2 h |         | 40–72 | [87]      |
| 24  |          | K$_2$CO$_3$         | DMF, r.t., 25–40 min | 74–94 | [88]      |
| 25  |          | R$_1$CH$_2$OEt     |         | 85–97 | [89]      |
| 26  |          | MeOH, r.t., 0.5–2 h |         | 75–95 | [90]      |

* R, R$_1$, and R$_2$ = alkyl and/or aryl substituents.
2.2. MCR in the synthesis of fused pyrimidines and pyrimidinone scaffolds

Compared to non-fused heterocycles, the ones fused with a pyrimidine core are known to significantly modify several physical and chemical properties (e.g., selectivity, lipophilicity, polarity, and solubility), thus crucially contributing to the design and application of molecules with promising biological activity [91]. Due to their exhibiting a wide range of activity, fused pyrimidines have been extensively pursued in drug design and discovery. Furthermore, their scaffolds are present in essential vitamins such as riboflavin and folic acid [91,92]. Fused pyrimidines have been observed to have antitumor [93,94], antibacterial [91], antihyperlipidemic [95], anti-inflammatory [96], herbicidal [97,98], hypnotic, and sedative [99] properties (Fig. 4). Besides their applications in biology, pharmacology, and medicinal chemistry, they are also notable for their use in dyes [100], potential organic semiconductors [101], fluorescent probes for visualization of lipid drops in living cells [102], etc., thus demonstrating the need to develop more efficient synthetic routes for these scaffolds.

The increasing significance of compounds containing fused pyrimidines, as well as their applicability, has similarly promoted advances

![Fig. 4. Some pyrimidine-fused compounds and their biological features.](image-url)

**Scheme 3.** Possible products obtained for the MCR of 5-aminopyrazoles, cyclic aldehydes, and cyclic 1,3-diketones, using either a) MW or b) US irradiation — reported by Chebanov et al. (2008) [108]. Mechanism adapted from Maleki and Aghaei (2017) [112] and Sharma, Vala and Patel (2020) [111], published by The Royal Society of Chemistry.
Table 2
Conditions used for the MCR assisted by US, for assembling fused-pyrimidine and pyrimidinone scaffolds.* (See below-mentioned references for further information.)

| Entry | Component 1 | Component 2 | Component 3 | Additive | US Conditions | Final compounds | Yields (%) | Ref. |
|-------|-------------|-------------|-------------|----------|---------------|-----------------|------------|-----|
| 1     | ![Pyrimidine](image1) | ![Pyrimidine](image2) | ![Pyrimidine](image3) | [HBIM]BF₄ | EtOH, r.t., 4.5–5 h | ![Pyrimidine](image4) | 80–95 | [113] |
| 2     | ![Pyrimidine](image5) | ![Pyrimidine](image6) | ![Pyrimidine](image7) | Immobilized Ag nanoparticles (NPs) | H₂O, 55 °C, 25–50 min | ![Pyrimidine](image8) | - | [114] |
| 3     | ![Pyrimidine](image9) | ![Pyrimidine](image10) | ![Pyrimidine](image11) | ![Pyrimidine](image12) | AcOH, r.t., 30 min | ![Pyrimidine](image13) | 72–85 | [109] |
| 4     | ![Pyrimidine](image14) | ![Pyrimidine](image15) | ![Pyrimidine](image16) | ![Pyrimidine](image17) | AcOH, 60 °C, 30–60 min | ![Pyrimidine](image18) | 37–88 | [115] |
| 5     | ![Pyrimidine](image19) | ![Pyrimidine](image20) | ![Pyrimidine](image21) | ![Pyrimidine](image22) | EtOH, r.t., 30 min | ![Pyrimidine](image23) | 51–70 | [108] |
| 6     | ![Pyrimidine](image24) | ![Pyrimidine](image25) | ![Pyrimidine](image26) | Piperidine | i-PrOH/H₂O, r.t., 30 min | ![Pyrimidine](image27) | 16–98 | [116] |
| 7     | ![Pyrimidine](image28) | ![Pyrimidine](image29) | ![Pyrimidine](image30) | ![Pyrimidine](image31) | Fe₃O₄ on clay-based nanocatalyst | ![Pyrimidine](image32) | 90–98 | [112] |
| 8     | ![Pyrimidine](image33) | ![Pyrimidine](image34) | ![Pyrimidine](image35) | Dibutyl amine | 50 °C, 23–32 min | ![Pyrimidine](image36) | 88–95 | [117] |
| 9*    | ![Pyrimidine](image37) | ![Pyrimidine](image38) | ![Pyrimidine](image39) | NaN₃ and modified magnetic iron oxide NPs | H₂O, 50 °C, 25–30 min | ![Pyrimidine](image40) | 80–90 | [118] |
| 10    | ![Pyrimidine](image41) | ![Pyrimidine](image42) | ![Pyrimidine](image43) | ![Pyrimidine](image44) | r.t., 20 min | ![Pyrimidine](image45) | 72–90 | [119] |
| 11    | ![Pyrimidine](image46) | ![Pyrimidine](image47) | ![Pyrimidine](image48) | MgO | 100 °C, 2.1–3 h | ![Pyrimidine](image49) | 75–92 | [120] |
| 12    | ![Pyrimidine](image50) | ![Pyrimidine](image51) | ![Pyrimidine](image52) | Sulfamic acid | EtOH/H₂O, r.t., 4–35 min | ![Pyrimidine](image53) | 70–97 | [121] |
| 13    | ![Pyrimidine](image54) | ![Pyrimidine](image55) | ![Pyrimidine](image56) | ZnFe₂O₄ | MeOH, 70 °C, 75–89 min | ![Pyrimidine](image57) | 89–96 | [122] |

(continued on next page)
over the last few years in the methodologies for the synthesis of these compounds [91,103]. The main method is still the cyclocondensation of β-(di)carbonyl compounds (usually aldehydes and ketones) associated with NCN-dinucleophiles (in which one nucleophilic nitrogen is necessarily inside the heterocycle) such as 2-aminoimidazole, 2-amino pyridine, 2-aminooxazoline, 3-amino-1H-1,2,4-triazole, etc. [91,104,105]. Thus, US irradiation has emerged as a powerful technique for the synthesis of pyrimidine-fused heterocycles (especially azoles), due to promoting shorter reaction times (usually decreasing from hours to minutes) and higher yields compared to conventional methods [106].

In relation to MCRs, selectivity is a concern due to the high probability of several potential parallel reaction pathways, which, when not controlled, may lead to complex mixtures of products [107]. US irradiation has been shown to act as a mild catalyst for achieving a single isomer instead of multiple ones, playing an important role in the regio- and chemoselectivity of MCRs [108–111]. For instance, different products could be obtained (Scheme 3), even when starting from the same building blocks (5-aminopyrazoles, aromatic aldehydes, and cyclic 1,3-diketones). Initially, the reaction (Scheme 3) occurs on the Knoevenagel adduct (in its keto-enol equilibrium form) to furnish a stabilized carbocation (intermediate IV), which can suffer a nucleophilic attack from both nucleophilic NH or the C=CH of the aromatic ring (no reaction of the NH₂ moiety was observed). The selectivity of the reaction was fully controlled in order to form the C-alkylated (intermediate V) product under MW heating (up to 150 °C), whereas when the reaction was done at r. t. using US as catalyst, only the N-alkylated product was obtained (intermediate VI). Both intermediates V and VI suffer an intramolecular Michael addition to furnish a) 1,4,6,7,8,9-hexahydro-1H-pyrazolo[3,4-b]quinolin-5-ones or b) 5,6,7,9-tetrahydropyrazolo[5,1-b]quinazolin-8-ones — see Scheme 3 [108,111,112]. Both procedures usually result in pure products (that precipitate out of the solution), without requiring further purification [108]. The selectivity observed is mainly attributed to the temperature, as observed in other experiments under conventional heating. Also, additives (e.g. a tertiary amine such as N-methylmorpholine or triethylamine) can be added to improve the yield [108]. Thus, a divergent protocol was developed depending on the energy source used.

The reports that address the use of heterocyclic amidines as nucleophiles, and which seek the synthesis of pyrimidine-fused scaffolds, generally a) optimize the reaction conditions, b) perform scope assessment, and c) present studies of the reaction times and isolated yields compared to other methods such as conventional heating or MW irradiation. Table 2 summarizes these reactions for different heterocycles that can be fused to the pyrimidine core by using US irradiation.

2.3. MCR in the synthesis of fused pyrimidines, using readily available pyrimidine scaffolds

In addition to MCR being used in the formation of the pyrimidine core, these reactions are also widely explored with readily available pyrimidine-containing scaffold reagents (commercially available or previously synthesized) in the formation of fused, non-fused, and spiro compounds (Tables 3 and 4). These pyrimidine-based starting materials and their derivatives have also been explored in several synthetic protocols, and due to them already possessing a formed heterocycle, they act as building blocks for the synthesis of more complex molecules that are useful in medicinal chemistry and materials science [128–130].

The use of previously formed pyrimidine-based reagents presents some very interesting advantages; for example: a) reducing the reaction steps and the generation of by-products, since fewer parallel reactions
| Ent. | Component 1 | Component 2 | Pyrimidine-containing reagent | Additive | US Conditions | Final compounds | Yields (%) | Ref. |
|------|-------------|-------------|-------------------------------|----------|---------------|-----------------|------------|-----|
| 1    | NH$_2$OAc   |             |                               |          | EtOH, r.t., 30 min | ![Image](image1) | 77–85     | [132] |
| 2    |             | ![Image](image2) |                               |          | Ethylene glycol, 120 °C, 25–40 min | ![Image](image3) | 80–92     | [133] |
| 3    |             | ![Image](image4) |                               | Fe$_3$O$_4$ on silica/SnCl$_4$ | H$_2$O, 60 °C, 55–90 min | ![Image](image5) | 96–99     | [134] |
| 4    | ![Image](image6) | ![Image](image7) |                               | Sulfamic Acid | EtOH/H$_2$O, r.t., 12–25 min | ![Image](image8) | 66–96     | [135] |
| 5    | ![Image](image9) | ![Image](image10) |                               |          | EtOH/H$_2$O, r.t., 10–30 min | ![Image](image11) | 80–98     |       |
| 6    |             | Porous graphene / MoO$_3$ nano composite |                               |          | H$_2$O, r.t., 60 min | ![Image](image12) | 95–98     | [136] |
| 7    | ![Image](image13) | ![Image](image14) |                               |          | EtOH, r.t., 30–45 min | ![Image](image15) | 68–85     | [137] |
| 8    | ![Image](image16) | ![Image](image17) |                               | Triethylene diamine II, supported on Zr MOF | EtOH, r.t., 15–30 min | ![Image](image18) | 85–98     | [138] |
| 9    |             | Zinc terephthalate metal-organic framework (MOF) |                               | r.t., 5–10 min | | ![Image](image19) | 85–98     | [139] |
| 10   | ![Image](image20) | Co$_3$O$_4$/chitosan/PWA |                               | EtOH, 40 °C, 20–30 min | ![Image](image21) | 80–95     | [140] |
| 11   | ![Image](image22) | ![Image](image23) |                               | Ethylene glycol, 65 °C, 30–45 min | ![Image](image24) | 90–94     | [141] |
| 12   | ![Image](image25) | ![Image](image26) |                               | Ethylene glycol, 65 °C, 20–30 min | ![Image](image27) | 91–95     |       |
| 13   | ![Image](image28) | ![Image](image29) |                               | Trisodium citrate dihydrate | EtOH/H$_2$O, r.t., 35–60 min | ![Image](image30) | 74–95     | [142] |
| 14   | ![Image](image31) | ![Image](image32) |                               | Trifluoroacetic acid | Toluene, 70 °C, 2 h | ![Image](image33) | 72        | [143] |

(continued on next page)
Table 3 (continued)

| Entry | Reaction   | Product Structure | Conditions                                    | Yield % | Reference |
|-------|------------|-------------------|-----------------------------------------------|---------|-----------|
| 15\(^b\) | \( \text{CH}_{3}\text{COONH}_4 \) | -                | \( \beta\)-cyclodextrin, \( \text{H}_2\text{O}, 60–65 \degree \text{C}, 1 \text{ h} \) | 75–90\(^{145}\) |           |
| 16 | - | - | - | - | - |
| 17 | - | - | - | - | - |
| 18 | - | - | - | 78–84\(^{146}\) |           |
| 19 | - | - | - | 81–87 |           |
| 20\(^b\) | - | - | - | 91–99\(^{147}\) |           |
| 21\(^b\) | - | - | - | 84–92\(^{148}\) |           |
| 22 | - | - | - | 40 \degree \text{C}, 5–10 \text{ min} | 90–97\(^{139}\) |           |
| 23 | - | - | - | - | 85–95\(^{149}\) |
| 24 | - | - | - | - | 87–98 |
| 25 | - | - | - | - | 86–95\(^{150}\) |
| 26 | - | - | - | - | 82–89\(^{151}\) |
| 27 | - | - | - | - | 90–96\(^{152}\) |
| 28 | - | - | - | - | 90–95\(^{153}\) |
| 29 | - | - | - | - | 87–94\(^{154}\) |
| 30 | - | - | - | - | 95–80\(^{155}\) |
| 31 | - | - | - | - | 90–98\(^{156}\) |
| 32 | - | - | - | - | 62–87\(^{157}\) |
| 33 | - | - | - | - | 71–91\(^{158}\) |

\(^a\) \( R, R' \) and \( R'' \) = alkyl and/or aryl substituents. \(^b\) Four-component reaction.
folds occur and there are fewer reactive centers in competition; b) allowing the design of more complex structures (with more functional groups), since the focus is on other parts of the molecule rather than assembling the pyrimidine core and, therefore, it is possible to readily form fused heterocycles, non-fused heterocycles, spiro compounds, etc.; and c) furnishing a highly versatile starting material with multiple reaction sites, which enables the synthesis of different derivatives of these scaffolds (N-, O-, S-, and C=C nucleophilic centers are often present), thus making the incorporation of the entire pyrimidine nucleus a very interesting synthetic strategy, from both a biological and industrial point of view, given that this can result in interesting compounds with enhanced properties [110,129,131].

These enhanced properties of the products obtained from the use of readily available pyrimidine-based reagents motivated synthetic chemists to explore their chemistry (in terms of reactivity and selectivity), and more recently, especially in the past three years, these starting materials have joined the constant growth of MCRs along with the use of US radiation. These reactions are described in Table 3. Of note is the pursuit of more eco-friendly, low-cost additives and catalysts with high recyclability and milder reaction conditions. It is worth highlighting the use of water and ethanol as solvents, as well as solvent-free and catalyst-free reactions. The efficiency of US in these MCRs can be seen in the reaction yields — which are mostly good to excellent — and the vast range of products achieved, in short reaction times (from minutes to hours) and under milder and more eco-friendly conditions.

2.4. MCR in the synthesis of pyrimidines containing spirocycles

Spiro-based heterocyclic systems — that is, a quaternary carbon atom common to two rings (hetero- or carbocycles) — are promising compounds in several areas; for example, pharmacology, crystallography, materials science, biochemistry, molecular biology, and engineering [159–164], to name just a few. Besides their unique molecular characteristics related to stereochemistry, the great interest in spiro compounds is filled by an extremely wide range of the aforementioned useful properties [24,110]. With this in mind, compounds joining these two structures (spirocycles and the pyrimidine core) furnish appealing final compounds [129].

MCRs performed under US irradiation have emerged as a valuable improvement for the synthesis of spirocycles, due to decreasing the number of reaction steps and reaction time and increasing yields, among other advantages [165]. The use of US together with pyrimidine-containing reagents to obtain spiro compounds dates from a few years ago — it occurred for the first time in 2009 when, serendipitously, spiro compounds (instead of the expected products) were obtained under US irradiation [110].

When using barbituric acids as starting materials, temperature was reported as the directing factor in the MCR, since the formation of the expected heterocycle was not observed as a sole product, instead either fused or spiro-compounds were obtained (Scheme 4 c) and d), respectively. The proposed mechanism (Scheme 4) initially involves the formation of the Knoevenagel adduct (Intermediate VII), for both pathways. To achieve the expected fused heterocycle, which goes through the initial C-C bond formation followed by intramolecular 1,4-Michael addition, the reactions were done at higher temperatures (~150–190 °C), using conventional methods or MW conditions, which leads to the Hantzsch-type product pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidin-5-ones shown in Scheme 4 c). On the other hand, when the reaction is performed under US irradiation at r. t., the amino moiety of the Knoevenagel adduct reacts with a second portion of the aromatic aldehyde to furnish an imine intermediate, which, through transfer (from the a-carbonyl position to the a-imine position, intermediate IX), furnishes a very reactive electrophilic center, which, in turn, undergoes cyclization with the negative charge to furnish the 1,4,6,7-tetrahydro-1H-spiro[pyrazolo[3,4-b]pyridine-5,5’-pyrimidine]-2,4′,6′(3H)-trione shown in Scheme 4 d) [110,112,166]. The proposed mechanism is supported by quantum mechanics calculations (DFT – B3LYP) [166], thus demonstrating that US irradiation acts directly on the chemoselectivity of the reaction.

A range of spiro compounds have already been obtained from readily available pyrimidine-containing reagents (e.g. barbituric acid) under US radiation (Table 4), including spiro-(oxy)indoles [167–169], spiropyrons [153], spiro-naphthoquinolines [170], and spiro-indazolophthalazines [171], with a wide variety of reaction conditions free from catalysts (entries 1–4 in Table 4), but with the presence of promising catalysts such as IL/MOFs (Entries 10 and 11) [172,173]. Table 4 summarizes the spiro compounds — obtained up to the present time and with their respective US conditions and yields.

Scheme 4: Selectivity of the MCR of 5-aminopyrazoles, aldehydes, and barbituric acids reported by Muravyova et al. (2009) [110]. Mechanism adapted from Kruthof, Ruijter and Orru (2011) [166] and Maleki and Aghaei (2017) [112].
Table 4
Conditions used for the MCR in the assembly of spiro compounds assisted by US. (See below-mentioned references for further information.)

| Ent. | Component 1 | Component 2 | Component 3 | Additive | US Conditions | Final compounds | Yields (%) | Ref. |
|------|-------------|-------------|-------------|----------|---------------|-----------------|------------|-----|
| 1    | \( R^1 \) \( N \) \( R^2 \) \( NH_2 \) | \( O - X - N - Y \) | \( X = H, Me \) \( Y = O, S \) | DMF, r. t., 3 h |  53–78 | [110] |
| 2    | | \( R^1 \) \( R^2 \) | \( O - N - Me \) | EtOH, 100 °C, 45 min |  80–89 | [170] |
| 3    | \( R^1 \) \( N \) \( R^2 \) \( NH_2 \) | \( O - X - N - Y \) | \( X = H, Me \) \( Y = O, S \) | DMF, r. t., 3 h |  63–98 | [110] |
| 4    | \( R^1 \) \( N \) \( R^2 \) \( NH_2 \) | \( O - X - N - Y \) | \( X = H, Me \) \( Y = O, S \) | CaCl₂, r. t., 11–17 min |  91–95 | [153] |
| 5    | \( EWG = CN \) | \( O - X - N - Y \) | \( X = H, Me \) \( Y = O, S \) | EtOH, r. t., 15–18 min |  91–95 | [153] |
| 6    | \( EWG = CO_2R^1 \) | \( O - X - N - Y \) | \( X = O, S \) | Fluorinated graphene oxide (FGO) |  93 | [168] |
| 7    | \( EWG = CN \) | \( O - X - N - Y \) | \( X = O, S \) | \( H_2O_2 \), 12 min |  83–89 | [174] |
| 8    | \( EWG = CO_2R^1 \) | \( O - X - N - Y \) | \( X = O, S \) | \( Fe_3O_4/SiO_2/t \) |  85–87 | [174] |
| 9    | \( EWG = CO_2R^1 \) | \( O - X - N - Y \) | \( X = O, S \) | Triethylendiamine IL supported in Zn MOF |  90–95 | [172] |
| 10   | \( O - X - N - Me \) | \( X = O, S \) | \( H_2O_2 \), 15 min | EtOH, reflux, 10–15 min |  88–97 | [172] |
| 11   | \( O - N - Me \) | \( X = O, S \) | \( H_2O_2 \), 15 min | EtOH, reflux, 10–15 min |  85–91 | [169] |

(continued on next page)
3. Cyclocondensation reactions of α,β-unsaturated ketones with NCN-dinucleophiles

α,β-Unsaturated ketones (also known as enones) are readily available CCC-building blocks that have many uses in heterocyclic chemistry, due to the enhanced electrophilicity of the β-carbon over the carbonyl carbon [175–177]. Thus, using NCN-dinucleophiles, one can assemble several pyrimidine-based heterocycles through [3 + 3] cyclocondensation reactions [40,178]. Although efficient, these types of cyclocondensation reactions — especially using poor nucleophiles such as urea derivatives — usually require harsh reaction conditions (long reaction times and high temperatures) [179] and transition-metal catalysts or acidic media to enhance the electrophilicity of the carbonyl carbon of the enone [41,180]. Thus, US irradiation emerged as an efficient alternative route for performing these [3 + 3] cyclocondensation reactions.

One of the first reports about the use of enones was the cyclocondensation reaction between ferrocene-chalcone 5 based derivatives and thiourea 3 in basic media, which furnished ferrocene-containing pyrimidine-2(1H)-thiones 6 (Scheme 5) [44]. Using sodium ethoxide as base, the reaction was done in ethanol at 50 °C and for the optimal time determined by thin layer chromatography (TLC), which varied according to the substituent in the starting 5 (electron-withdrawing groups as 4-Cl required longer reaction times).

Chalcone derivatives were also used in the cyclocondensation with thiourea 3, using KOH as base and EtOH as solvent, and the reaction was irradiated with US for 20–29 min (depending on the substituent in the starting 7). The products were obtained at 73–82% yields (Scheme 6) [181].

The authors also did a comparative study between conventional heating (oil bath) and US. The results were compared in terms of the time until there was no more consumption of starting material detected by TLC analysis, as well as the isolated yields of the final compounds — see Table 5. The reaction times decreased from 5.5 to 6.5 h to 0.4–0.5 h, which, in most cases, is ten times faster. The lower yield obtained under conventional heating (R = 3-Me, 54%) rose to 80% under US. It is important to mention that no strongly electron-withdrawing group (nitro, bromo, chloro, etc.) was evaluated, thus, this could strongly affect both reaction time and yield [181].

A fully US-based strategy was followed to prepare bis-pyrimidine derivatives, using the diester 9 as starting material (Scheme 7). Initially, an aldol condensation between the ester and aldehydes in basic media was performed (NaOH, EtOH, )), 35 min), which furnished α,β-unsaturated esters 10 at 82–84% yields. Subsequently,
Table 5
Comparative study of the reaction times and isolated yields of pyrimidine-2(1H)-thiones 8 [181].

| R    | Conventional conditions | US irradiation |
|------|-------------------------|----------------|
|      | Time (h)                | Yield (%)      | Time (min)     | Yield (%)  |
| H    | 5.5                     | 65             | 20             | 82         |
| 2-Me | 6.0                     | 55             | 22             | 78         |
| 3-Me | 6.0                     | 54             | 22             | 80         |
| 4-Me | 5.5                     | 58             | 24             | 76         |
| 2-O-Me| 6.0                    | 60             | 24             | 76         |
| 4-O-Me| 6.0                    | 61             | 24             | 75         |
| 2,4-O-Me| 6.5                | 65             | 25             | 73         |
| 4-N(Me₂)| 5.5                 | 55             | 29             | 75         |

Scheme 7. Aldol condensation followed by [3 + 3] cyclocondensation with NCN-dinucleophiles to furnish bis-pyrimidine derivatives 11–12, reported by Dabholkar and Ansari (2012) [182].

Scheme 8. Cyclocondensation reaction between enones 13 and 5-aminopyrazoles 14 as a selective protocol for obtaining a single isomer of pyrazolo[1,5-a]pyrimidines, reported by Chebanov, Sakhno and Desenko (2012) [183].
cyclocondensation with NCN-dinucleophiles (urea, thiourea, and guanidine) furnished bis-pyrimidines 11–12 at 82–84% yields (Scheme 7) [182]. The authors also performed a comparative study using conventional conditions — for the synthesis of 10, the reaction took 2.5 h to be completed (72–73% yields), compared to 35 min when US was used (82–84% yields). The synthesis of 11–12 was achieved via conventional conditions by stirring for 4 h under refluxing water, or by 45 min of US irradiation (for the latter, a 10% increase in yield was observed).

Enones 13 were cyclocondensed with 5-aminopyrazoles 14 (AcOH, r. t. 1 h) to furnish one single regioisomer of pyrazolo[1,5-a]pyrimidine 15 at moderate to good yields (68–83%, Scheme 8) [183]. It is important to note that the authors had previously reported this same reaction under conventional conditions (using refluxing AcOH), in which a mixture of regioisomers 15 and 16 was obtained (Scheme 8) [184]. It is well known that temperature greatly affects the regioselectivity in the cyclocondensation of enones with non-symmetrical NCN-dinucleophiles [98]. Conducting the reaction at r.t. using US furnished one single isomer, thus showing that the development of selective protocols using US is feasible.

The reaction between trifluoromethyl-substituted alkoxy enones 17 and 5-aminopyrazole 18 as a selective protocol for obtaining a single isomer of pyrazolo[1,5-a]pyrimidines, reported by Buriol et al. (2013) [185].

Scheme 9. Cyclocondensation reaction between enones 17 and 5-aminopyrazole 18 as a selective protocol for obtaining a single isomer of pyrazolo[1,5-a]pyrimidines, reported by Buriol et al. (2013) [185].

Table 6
Comparative study of the synthesis of pyrazolo[1,5-a]pyrimidines, using oil bath, MW irradiation, and US, reported by Buriol et al. (2013) [185].

| R         | Isolated yield (%) | Oil bath a | Microwave b | Ultrasound c |
|-----------|--------------------|------------|-------------|--------------|
| Me        | 87                 | 87         | 82          |
| i-Bu      | 83                 | 84         | 77          |
| C6H5      | 52                 | 80         | 82          |
| 4-F-C6H4  | 51                 | 81         | 96          |
| Naphth-2-yl | 73             | 93         | 89          |

Reaction conditions: a EtOH, 75 °C, 2 h. b EtOH, MW, 75 °C, 5 min. c EtOH, US, 68 – 72 °C, 5 min.

Scheme 10. Cyclocondensation reaction between β-enaminone 20 and 3-aminopyrazole 21 to furnish exclusively pyrazolo[1,5-a]pyrimidines 22, reported by Kaping et al. (2016) [188].

Scheme 11. Cyclocondensation reaction between enones 17 and 5-amino-1,2,4-triazole 23, as a selective protocol for obtaining a single isomer of 1,2,4-triazolo[1,5-a]pyrimidines 24, reported by Frizzo et al. (2014) [106].
Scheme 12. Cyclocondensation reaction between enones 20 and 5-amino-1,2,4-triazole 23, as a selective protocol for obtaining a single isomer of 1,2,4-triazolo[1,5-a]pyrimidines 25, reported by Frizzo et al. (2014) [106].

Scheme 13. Cyclocondensation of enone 17 and the heterocyclic amidine 26 to furnish 2-pyrazolopyrimidines 27, reported by Kuhn et al. 2015 [191].

Scheme 14. Stepwise US synthesis of 30 via aldol condensation of aryl ketones, followed by cyclocondensation with 3-aminopyrazole 28 and Sonogashira cross-coupling of 29, reported by Bharath, Rao, and Pal (2017) [192].

Scheme 15. Synthesis of Meridianin derivative 33, using a hybrid US-static heating technique, reported by Jiang et al. (2018) [197].
and 5-aminopyrazole 18 (Scheme 9) was reported as a selective and fast protocol for obtaining pyrazolo[1,5-a]pyrimidines [185]. The reaction was done in EtOH for a period of 5 min (with max. temperature programmed of 75 °C), and the products were obtained at moderate to excellent yields (61–98%).

The authors also performed a comparative study between conventional methods, MW irradiation, and US irradiation for the synthesis of 19 (Table 6). No significant difference was observed for the alkyl substituents at the 4-position of starting enone 17 — in fact, when using US, the yield was slightly (5–6%) lower. However, when aryl substituents were used, the reaction under conventional conditions (oil bath) provided moderate yields in the range of 51–73% (refluxing EtOH, 2 h). When MW was used, the yields improved to 80–93% (EtOH, 5 min), and under the same experimental conditions, US provided 82–96% yields.

The reaction was also extended to the use of β-dimethylaminovinyl ketones 20 as starting materials — which have also been used as efficient building blocks in constructing heterocycles [186,187] — and 3-amino pyrazoles 21 (Scheme 10). This is an important modification, because the dimethylamino group can lower the electrophilicity of the β-carbon compared to that of the alkoxy moiety of 17, which was in fact observed, since the authors used KHSO4 as catalyst and increased the temperature [188]. The pyrazolo[1,5-a]pyrimidines 22 were obtained at moderate to excellent yields (41–95%), and were highly dependent on the structure of the starting β-enaminone 20 [167].

Similar to this, the trifluoromethyl-substituted alkoxy enone 17 was reacted with 5-amino-1,2,4-triazole 23 under acidic media to selectively furnish 1,2,4-triazolo[1,5-a]pyrimidines (Scheme 11) [106]. During optimization of the reaction conditions, the authors observed that the

![Scheme 16. Synthesis of 6-azolyl-2-amino-4-cyanopyrimidines 36 and 37, reported by Al-Zaydi et al. (2017) [198].](image)

![Scheme 17. Synthesis of indolin-2-one coupled pyrimidines 40, reported by Nikalje et al. (2018) [199].](image)
The conventional procedure for preparing parent compounds of condensation of enones with dienophiles did not occur when using EtOH or MeCN as solvents or lower temperatures, which suggests lower reactivity of this NNC-dinucleophile reaction compared to that of 5-aminopyrazole 18.

The reaction was also extended with the use of β-dimethylaminovinyl ketones 20 as starting materials (Scheme 12), and the 7-substituted 1,2,4-triazolo[1,5-a]pyrimidines 25 were obtained at good yields (76–96%) in one exclusive regiosomer [106].

A more environmentally friendly protocol was developed for cyclocondensation of enones 17 and the heterocyclic amidine precursor 26. The conventional procedure for preparing parent compounds of 27 takes 4–24 h in refluxing MeOH or CHCl₃ [189], or requires the use of catalysts such as Ti(Oi-Pr)₄ or BF₃·OEt₂ [190]. In the present study, the reaction was conducted under US irradiation in the presence of KOH (EtOH, r.t., 1 h, Scheme 13). The 2-pyrazolyl pyrimidines 27 were isolated, at 61–85% yields, by simply filtering the reaction media, with no further purification (recrystallization or chromatography) necessary [191].

The synthesis of 2-alkynyl pyrazolo[1,5-a]pyrimidines 30 (Scheme 14) was done using US in all reaction steps [192]. Initially, the known aldol condensation of aryl ketones with N,N-dimethylformamide dimethylacetal was done (toluene, 80–90 °C, 6 h) to obtain β- enamines 20, which underwent cyclocondensation with 3-amino-5-bromopyrazole 28 (EtOH, H₃PO₃, 45–50 °C, 30–40 min) to furnish pyrazolo[1,5-a]pyrimidines 29 at good yields (80–87%). The bromine moiety was reacted with terminal alkynes via palladium-catalyzed cross-coupling reaction (Sonogashira-type) to furnish 2-alkynyl pyrazolo[1,5-a]pyrimidines 30 at good yields (69–80%) in short reaction times (4–6 h) compared to those of conventional methods (18–24 h, depending on the substrates) [193–195].

The synthesis of Meridianin derivatives— which are marine alkaloids isolated from Aplidium meridianum [196]— was done using a hybrid US-static heating technique (Scheme 15) [197]. Initially, indolyl-β-enamine 31 was reacted with benzamidine to furnish 32 (which was not isolated), which was then subjected to static heating to allow cyclocondensation and removal of the tosyl group. Meridianin derivative 33 was isolated at a 56% yield. [197]

The synthesis of pyrimidines conjugated with 1H-pyrrole and 1H-indole cores was done using α-cyano ketones 34 as starting materials (Scheme 16). These were reacted with N,N-dimethylformamide dimethylacetal (toluene, 70 °C, 2.5 h) to furnish α-cyano-β-enaminoones 35 at 86–88% yields. These were then cyclocondensed with guanidine (EtOH, K₂CO₃, 70 °C, 5 h) to furnish 6-azolyl-2-amino-4-cyano-pyrimidines 36 and 37 at 85–88% yields (Scheme 16) [198].

The synthesis of indolin-2-ones coupled to 2-amino pyrimidines was done in a multistep reaction (Scheme 17) [199]. Starting from the condensation of 4-chloroacetophenone with aryl aldehydes (KOH, EtOH, 15–25 min), enones 38 were obtained at 84–92% yields. Further cyclocondensation with guanidine (KOH, EtOH, 20–30 min) furnished 2-aminopyrimidines 39 at 80–88% yields. Lastly, nucleophilic addition using indoline-2,3-dione was performed (AcOH, EtOH, 45–60 min), and the final products 40 were obtained at 86–94% yields (Scheme 17) [199].

It is important to mention that the authors performed a comparison between US and conventional heating in all reaction steps. When preparing 38, the reaction time decreased from 240 to 360 min to 15–25 min, and the yields increased from 58 to 78% to 88–92%. In the case of 2-aminopyrimidines 39, the reaction time decreased from 240 to 360 min to 20–30 min, and the yields increased from 55 to 70% to 80–88%. The nucleophilic addition step led to the time decreasing from 510 to 630 min to 45–60 min, and the yields increasing from 58 to 74% to 85–94% [199].

The synthesis of bis-chalcones was done using symmetrical 2-alkoxy benzaldehydes 41 as starting materials (Scheme 18). These were condensed with acetophenone (NaOH, EtOH, 15 min), and bis-chalcones 42 were obtained at 78–90% yields. Further cyclocondensation of 42 with thiourea furnished bis-pyrimidine 43 at 70% yield (Scheme 18) [200].

4. Miscellaneous reactions

Pyrazole 44 was used as a model to promote cyclocondensation with
several electrophiles (45–48, Scheme 19), and pyrimidines 49–52 were prepared (AcOH, 40 °C, 30–40 min) at good yields (74–86%) [201]. A comparative study between conventional heating, MW irradiation, and US irradiation was conducted, and it was found that for these substrates, MW was superior to US (reaction times of 2–5 min for MW and 30–40 min for US). On looking at these results, one can closely relate to the temperature in the reaction vessel, since the authors measured 105–110 °C for the flask submitted to MW and 35–40 °C for the US one. It is well known that temperature is a key factor in cyclocondensation reactions, thus, the lower temperature that the reaction was conducted under for the US may explain the longer reaction times and lower yields compared to MW [201].

The synthesis of diazo-containing pyrazolo[1,5-a]pyrimidines 55 was achieved by reacting 2-arylazomalononitriles 53 with fluorine-containing pyrazoles 54 (R1 = F, CF3) to furnish 55 at 40–60% yields (EtOH, Py, r.t., 1 h) [202]. The authors performed a comparative study, but the observations were the same as the work above: MW irradiation furnished better yields and shorter reaction times than US; however, the reaction done under MW was at 140 °C, while under US it was at r.t. (Scheme 20) [202].

Pyrimidine-2-thiones 56 were reacted with alkynyl esters 57 to furnish thiazolo[3,2-a]pyrimidines 59 at 87–95% yields (MeOH, r.t., 35–56 min, Scheme 21) [203]. The mechanism for this transformation is shown in Scheme 21, in which the nucleophilic sulfur attacks the
Scheme 21. Synthesis of thiazolo[3,2-a]pyrimidines 59 from the reaction of pyrimidine-2-thiones 56 and alkynyl esters 57, reported by Darehkordi, Reentan, and Ramezani (2013) [203].

Scheme 22. Synthesis of [1,3,4]thiadiazolo[3,2-a]pyrimidines 61 from 2-aminothiadiazoles 60 and dimethylacetylenedicarboxylate 57, reported by Dong and Zhao (2019) [205].
Scheme 23. Synthesis of 3,7-diaryl-6,7-dihydro-(5H)-6-substituted-thiazolo[3,2-a]pyrimidin-5-ones 65, reported by Gupta et al. (2016) [206].

Scheme 24. Synthesis of tetrahydropyrido[2,3-d]pyrimidines 68 using enones 66 and 6-amino pyrimidines 67, reported by Quiroga et al. (2016) [210].

Scheme 25. Synthesis of allyl/1,2,3-triazolyl/tetrazol-5-yl containing pyrimidine-2-thiones 70, through cyclocondensation with thiourea, reported by Dofe et al. (2017-2018) [211–213].

Table 7
Comparative study of conventional method and US in the synthesis of 1,2,3-triazolyl/tetrazol-5-yl containing pyrimidine-2-thiones 70.

| Entry | R’ | R’’ | R’’’ | Oil bath Time (min) | Yield (%) | Ultrasound Time (min) | Yield (%) | Oil bath Time (min) | Yield (%) | Ultrasound Time (min) | Yield (%) |
|-------|----|-----|------|---------------------|-----------|----------------------|-----------|---------------------|-----------|----------------------|-----------|
| 1     | H  | H   | H    | 200                 | 75        | 24                   | 88        | 225                 | 69        | 21                   | 89        |
| 2     | H  | H   | Cl   | 190                 | 78        | 21                   | 86        | 195                 | 71        | 18                   | 91        |
| 3     | Me | H   | H    | 220                 | 71        | 27                   | 90        | 215                 | 68        | 27                   | 87        |
| 4     | H  | H   | Me   | 230                 | 73        | 27                   | 93        | 210                 | 72        | 24                   | 94        |
| 5     | Cl | H   | Cl   | 190                 | 78        | 21                   | 94        | 190                 | 77        | 15                   | 93        |
| 6     | H  | Me  | Cl   | 195                 | 74        | 25                   | 90        | 205                 | 79        | 18                   | 91        |
electrophilic carbon of the alkyne through a 1,4-Michael-type addition. In the last step, the ester moiety undergoes aminolysis to furnish 59 (203,204).

By using 2-aminothiadiazoles 60 and dimethylacetylenedicarboxylate 57, [1,3,4]thiadiazolo[3,2-a]pyrimidines 61 were obtained (THF, ) at 30–93% yields (Scheme 22) [205]. Given that 60 are non-symmetrical NCN-dinucleophiles, one expects to obtain two isomers (depending on the attacking position of each nucleophilic nitrogen) — either product 61 or 62 (Scheme 22). Interestingly enough, only product 61 was obtained (first pathway). The authors performed DFT calculations to identify the most stable reaction intermediates, and the pathway that furnishes 61 was the less energetic one.

The synthesis of thiazolo[3,2-a]pyrimidin-5-ones under US irradiation and using a solid–liquid phase transfer catalysis (PTC) — n-TBAHSO₄ — to prepare 3,7-diaryl-6,7-dihydro-(5H)-6-substituted-thiazolo[3,2-a]pyrimidin-5-ones 65 was reported [206]. The reaction was done using Schiff’s bases 63 and acyl chlorides 64, through a [4 + 2] cycloaddition reaction (conditions: THF, KOH, ) r.t. 2–3 h — see Scheme 23, and products 65 were obtained at 69–82% yields [206].

PTC is a technique with a green chemistry bias, in which the reaction occurs or is accelerated because of the miscibility of the reagent species [207–209]. When combined with US, it is expected to further accelerate the reaction, as well as increase conversions for the desired products. The cavitation phenomenon provided by US increases mass transfer around solid particles, as well as the phase boundaries. The use of US is a good technique when supplemented with PTC, given that PTC strongly depends on the transfer between phases [206]. The authors also performed a comparative study for conventional stirring (at r.t.), and they were able to prove the synergism in the US/PTC method, given the higher yields (69–82% and 53–64% with and without US irradiation, respectively) and shorter reaction times (decreasing from 7 to 9 h to 2–3 h) of 65 [206].

The synthesis of tetrahydropyrido[2,3-d]pyrimidines 68 was done by using enones 66 and 6-aminopyrimidine 67 (AcOH, ), r.t., 30 min, Scheme 24) [210]. The final products were obtained at 41–77% yields — the yields were highly dependent on the substituent in the aromatic ring.

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**Scheme 26.** US-assisted hydrolysis followed by HATU-mediated carboxylic acid coupling of pyrazolo[1,5-a]pyrimidine 73, reported by Suresh et al. (2017) [115].

**Scheme 27.** Oxidation of 1,2,3,4-tetrahydropyrimidines 74 using Cu (III) or Ag (III) as oxidizing agents, reported by Gavrilovi´c et al. (2018) [214].

**Scheme 28.** Synthesis of 1,2,3-triazolyl pyrimidine 77 from propargyl-pyrimidine 76, reported by Kalavadiya et al. (2020) [227].
of the starting 66. The reactions were also conducted under MW irradiation (at 110 °C); however, the yields were lower (31–76%) than those obtained with US [210].

The synthesis of pyrimidine-2-thiones 70 was done by using 3-alkoxy chromones 69 and thiourea to furnish allyl,1,2,3-triazolyl/tetrazol-5-yl containing pyrimidine-2-thiones 70, at good to excellent yields (85–96%, KOH, EtOH, EtOH, [115]) (Scheme 26) [115–213]. Initially, the hydrolysis step was done using NaOH/MeOH, at 50 °C (Scheme 26) [115]. The authors also did a comparative study of the conventional method and US in the synthesis of allyl and 1,2,3-triazolyl derivatives of 70 (Table 7). Regardless the alkoxy moiety, when performed under conventional conditions, the reaction times and isolated yields of the compounds were very similar (190–220 min, 69–79% yields). When US was used, the reaction times decreased to 15–27 min, and yields increased to 87–94%. It is notable that, in both cases, when starting 69 has electron-withdrawing groups (chloro was used as the model), the reaction proceeds faster (entries 2, 5, and 6 in Table 7), but no correlation between structure and the isolated yield of 70 was observed [211,212].

Hydrolysis of the carboxyethyl moiety of pyrazolo[1,5-a]pyrimidine 71 was followed by amidation with p-toluidine, using hexafluorophosphate azabenzo triazole tetramethyl uranium (HATU) as the coupling agent (Scheme 26) [115]. Initially, the hydrolysis step was done using NaOH/MeOH, at 50 °C under US for 1 h. The carboxylic acid 72 was isolated at 92% yield. The coupling with the anilide derivative was performed in DMF, using N,N-diisopropylethylamine (DPEA) as base and HATU, and under US at r.t. for 3 h, the amide 73 was isolated at 56% yield [115].

An oxidation protocol based on the oxidation of 1,2,3,4-tetrahydro pyrimidines 74 using copper (III) or silver (III) — in the form of (KNa[Cu(HIO)2].12H2O) and (KNa[Ag(HIO)2].12H2O) — as oxidizing agents was developed under US (Scheme 27) [214]. Pyrrolydine was used as a base to abstract the β-hydrogen, and the oxidized products pyrimidin-2(1H)-ones 75 were obtained at 74–97% yields, depending on the catalyst applied. In general, Ag (III) provided higher yields than Cu (III) [214].

Since the selectivity was observed in the copper-catalyzed azide-alkyne cycloaddition (CuAAC or also known as click reaction) by Sharpless in the early 2000s [215–217], several known heterocycles have been easily and selectively coupled with the 1,2,3-triazole motif — including pyrimidines [218–220] — to furnish final scaffolds with enhanced biological and/or pharmacological properties [221–223]. Given their importance, several US-based methodologies for the synthesis of 1,2,3-triazole-containing molecules have been developed, and a general observation is that they proceed much faster — in most cases the reaction is completed within 20–30 min — than the ones without US irradiation (12–16 h) [224–226]. Despite the importance of triazole-pyrimidine hybrids, there are two reports related to the construction of the triazole motif in a pyrimidine using US (Schemes 28–30) [227].

The synthesis of 1,2,3-triazole-pyrimidine-pyrazole hybrids 77 was done by using propargyl pyrazolo[3,4-d]pyrimidines 76 under common CuAAC conditions (azides, CuSO4 and sodium ascorbate as reducing agent) in a DMF/t-BuOH mixture as solvent (Scheme 28) [227]. The reaction under conventional conditions took 6 h to complete (84% yield); however, under US, the time decreased to 20 min (94% yield). Seventeen examples were prepared in accordance with this methodology, with 82–94% yields [227].

The synthesis of 1,2,3-triazoles linking oxazole-thymidine-containing scaffolds was assembled by reacting alkyne isoxazole 78 under CuAAC conditions — Cu(OAc)2 was used as copper source — with azido thymidines 79 and 80 to furnish 1,2,3-triazoles 81 and 82, at 84–96% yields (Scheme 29) [228]. The reactions proceeded smoothly at r.t. within 10–15 min (i-ProOH/H2O as solvent) to provide full conversion of the starting materials, regardless of the less hindered (79) or more hindered (80) azide source. When done in the absence of US, the reactions took 4–13 h to achieve full conversion (at 45 °C). The authors proposed a mechanism for the click reaction and the key step for the US

![Scheme 29. Synthesis of pyrimidine–furan–1,2,3-triazole–isoxazole hybrid molecules 81 and 82, reported by Zhang et al. (2017) [228].](image-url)

- of the starting 66. The reactions were also conducted under MW irradiation (at 110 °C); however, the yields were lower (31–76%) than those obtained with US [210].
- The synthesis of pyrimidine-2-thiones 70 was done by using 3-alkoxy chromones 69 and thiourea to furnish allyl,1,2,3-triazolyl/tetrazol-5-yl containing pyrimidine-2-thiones 70, at good to excellent yields (85–96%, KOH, EtOH, EtOH, [115]) (Scheme 26) [115–213]. Initially, the hydrolysis step was done using NaOH/MeOH, at 50 °C (Scheme 26) [115].
- The authors also did a comparative study of the conventional method and US in the synthesis of allyl and 1,2,3-triazolyl derivatives of 70 (Table 7). Regardless the alkoxy moiety, when performed under conventional conditions, the reaction times and isolated yields of the compounds were very similar (190–220 min, 69–79% yields). When US was used, the reaction times decreased to 15–27 min, and yields increased to 87–94%. It is notable that, in both cases, when starting 69 has electron-withdrawing groups (chloro was used as the model), the reaction proceeds faster (entries 2, 5, and 6 in Table 7), but no correlation between structure and the isolated yield of 70 was observed [211,212].
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to catalyze at a faster rate \[228\]. Scheme 30 shows the catalytic cycle for the US-catalyzed click reaction.

Initially, Cu(OAc)$_2$ is reduced in situ with sodium ascorbate to furnish the active Cu(I) species, then copper-acetylide A is formed and nucleophilic addition of the azide moiety to A furnishes the intermediates B1 and B2. After cycloaddition occurred (B1), the copper-containing intermediate C was obtained, and, after the removal of copper to regenerate Cu(I) in the reaction medium, 1,2,3-triazoles D were obtained \[216,229,230\]. In the case of the role of US in this type of reaction, the authors suggested that a higher amount of energy was inserted in the system and US acted in the overall process by enhancing the reaction rate, not only in an isolated step \[228\].

The US-based procedure for the cyclocondensation reaction between 1,3-diketones 83 and guanidine was developed, and 2-aminopyrimidines 84 were obtained at 26–80% yields, depending mostly on the base used in the reaction (NaOH, Na$_2$CO$_3$, or NaOEt — see Scheme 31). When NaOEt was used, the yields were greatly improved in some cases, especially the ones containing R1 ≠ H \[131\].

It is important to note that when R or R$^2$ in the starting 83 = OEt, hydrolysis of the ester moiety was observed, and (di)hydroxy pyrimidines 84 were obtained in all cases. This is mainly due to the basic nature of guanidine, since parent 1,3-dielectrophiles have been reported to hydrolyze trichloromethyl ketones to furnish their corresponding carboxylic acids \[231\].

2,4-Dichlorochloroquines 85 were used as alkylating agents of the phenol moiety of pyrimidines 86 (Scheme 32) \[232\]. The reaction was
conducted in DMF, using K$_2$CO$_3$ as base. Only the O-alkylation of the phenol moiety was obtained, which is a very significant outcome, since the oxygen and both nitrogens of the pyrimidine ring are also nucleophilic (with similar pKa values) and usually furnish regioisomeric products of N- or O-alkylation [233].

The authors also performed a comparative study of the yields from conventional heating (60 °C, 15 h) and US (60 °C, 20 min) — see Table 8. Remarkably, the yields were significantly higher (up to 21%), and the reaction time decreased from 15 h to 20 min [232].

A methodology to prepare 1,2,4-triazolo[4,3-a]pyrimidines through a linear sequence was developed (Scheme 33) [234]. Initially, 2-hydrazinopyrimidin-4(3H)-one 88 was reacted with aromatic aldehydes (EtOH, AcOH, 75 °C, 30–45 min) to furnish benzylidene hydrazones 89 at 75–87% yields. These were cyclized through an acetic anhydride-mediated cyclization double N-acetylation strategy to furnish products 90 and 91 as a mixture of isomers (75 °C, 5 h), at good overall yields (up to 80%, considering both isomers), with 90 being the one most favored. It is important to note that the isomers could be separated through column chromatography [234].

Although obtaining isomers in this specific type of cyclization reaction is not unexpected when no chiral auxiliaries or selective reagents are used [235], the authors proposed that the Dimroth rearrangement is occurring and converting the obtained 90 into the more stable 91 with the aid of light (Scheme 34). This was confirmed by exposing the pure

### Table 8
Comparative study of the yields of 87 from conventional heating and US irradiation, reported by Balaji et al. (2013) [232].

| Entry | R$^1$ | R$^2$ | R$^3$ | Reaction conditions: a DMF, 60 °C, 15 h. b DMF, 60 °C, 20 min. |
|-------|-------|-------|-------|---------------------------------------------------------------|
| 1     | Me    | H     | H     | Oil batha Yield (%) Ultrasoundb Yield (%) |
| 2     | H     | Me    | H     | 81 94 |
| 3     | H     | H     | Me    | 69 87 |
| 4     | OMe   | H     | H     | 73 89 |
| 5     | H     | H     | OMe   | 75 90 |
| 6     | H     | Cl    | H     | 66 87 |
| 7     | Br    | H     | H     | 73 80 |
| 8     | Me    | H     | Me    | 70 84 |
| 9     | 2-chlorobenzo[h]quinoline | |

**Scheme 33.** US-mediated synthesis of 1,2,4-triazolo[4,3-a]pyrimidines and assignment of the regioisomers obtained by two-dimensional $^1$H-$^{13}$C HMBC NMR, reported by Ashry et al. (2020) [234].

**Scheme 34.** Light-driven Dimroth rearrangement of 1,2,4-triazolo[4,3-a]pyrimidines, reported by Ashry et al. (2020) [234].
isolated 90 (dissolved in EtOH) to light for 2–3 days in order to isolate 91 as a pure compound.

5. Derivatizations of the pyrimidine ring

5.1. N, O, or S-alkylation(arylation) reactions

The alkylation of pyrimidines is a widely used strategy for achieving important novel physical and bioactive properties of desired compounds [236]. Several alkylation agents have been used; for example, diisopropylzinc for the Soai reaction [237], alkyl sulfonates [238], epoxides [239], ethers [240], and alcohols [241]; however, the one most widely pursued uses alkyl/aryl halides [242–246]. Even though the aforementioned alkylation agents have been gaining attention in this type of reaction, alkyl halides remain the electrophiles most commonly used for verifying selectivity issues in US-assisted alkylation of pyrimidines, given that alkyl halides usually provide regioisomeric mixtures of $N^1$, $N^3$, and $S$-/O-alkylated products, due to the difficulty in controlling and/or predicting the nucleophilicity of the aforementioned heteroatoms [247,248].

Table 9 shows the general structures of the starting materials (nucleophiles and electrophiles) used for the N-, S-, or O-alkylation

| Entry | Nucleophile | Electrophile | Additive | US Conditions | Final compounds | Yields (%) | Ref. |
|-------|-------------|--------------|----------|---------------|-----------------|-----------|-----|
| 1     | ![Structure](image1) | ![Structure](image2) | MeOH, Me$_2$CO 60 min | ![Structure](image3) | 85–87 | [45] |
| 2     | ![Structure](image4) | MeI | Me$_2$CO, 25 min | ![Structure](image5) | 73 | [47] |
| 3     | ![Structure](image6) | ![Structure](image7) | Me$_2$CO, 20 min | ![Structure](image8) | 78 | |
| 4     | ![Structure](image9) | ![Structure](image10) | DMF, 18–22 h | ![Structure](image11) | 55–64 | [249] |
| 5     | ![Structure](image12) | ![Structure](image13) | CH$_2$Cl$_2$, r. t., 5 min | ![Structure](image14) | 21–87 | [250] |
| 6     | ![Structure](image15) | ![Structure](image16) | THF, 82–120 min | ![Structure](image17) | 84–92 | [251] |
| 7     | ![Structure](image18) | ![Structure](image19) | MeSO$_3$H, EtOH, 20–45 min | ![Structure](image20) | 88–93 | |
| 8     | ![Structure](image21) | ![Structure](image22) | Py or DMAP | ![Structure](image23) | 65–72 | [252] |
| 9     | ![Structure](image24) | ![Structure](image25) | Disperse d Na | ![Structure](image26) | 87–92 | [253] |
| 10    | ![Structure](image27) | ![Structure](image28) | CaCO$_3$, PEG 400, 2–2.5 h | ![Structure](image29) | 69–77 | [254] |
reactions on pyrimidines. It is important to note that the pyrimidine is used as both a nucleophile (entries 1–6, 8, and 9) and electrophile (entries 7 and 10). In most cases, the reactions proceeded smoothly and under regular bimolecular nucleophilic substitution reaction conditions (aprotic polar solvent, base). One can easily see that, in general, only alkyl chlorides were used (with the exception of entries 2 and 3, in which methyl iodide was used), which indicates that the reaction was feasible using this poor leaving group (chloride) and was able to be carried out in the absence of heating and yet furnishing good isolated yields and short reaction times in most cases.

A very well explored protocol for selectively introducing alkyl substituents at $N^1$- into uracyl derivatives is the initial double $O$-alkylation with a source of trimethylsilyl group (255–258) (in this work, [259] bis-trimethylsilylacrylamide) furnishing $O^2$- and $O^4$-TMS pyrimidine 94 at quantitative yields. Further reaction with crotyl bromide (under US) furnishes only $N^1$-substituted uracyl 95 (the other nitrogen is too hindered by the TMS moiety to act as a nucleophile) as a mixture of (E) and (Z)-isomers, at 98% yield (Scheme 35).

In a second part of the work (Scheme 35), the authors used the ruthenium-based catalyst Grubbs II (G-II) — which has been widely used in the metathesis of several complex molecules (260–263) — in a strategy combining it with US for preparing alkyl phosphonates 97 (Scheme 35). During this stage, the authors observed that other catalysts (Hoveyda-Grubbs II and Zhan catalyst-1B) were not effective in promoting the formation of 97. When G-II was used in the absence of US (using conventional heating) or in a solvent other than H$_2$O (CH$_2$Cl$_2$), no formation of the product was observed, thus demonstrating the power of US in catalyzing this metathesis reaction in $N$-alkylated pyrimidines [259].

5.2. Other amino derivatisations in 2-aminopyrimidines

The amino group at the 2-position of the pyrimidine ring allows other derivatizations such as the preparation of amides. The aminolysis of benzothiazine 3-carboxylate 98 was done using 2-aminopyrimidines 99 (Scheme 36). The reaction was conducted in the presence of

![Scheme 35](image)

Scheme 35. US-assisted protection, selective $N$-alkylation, and metathesis of pyrimidines 92, reported by Bessieres et al. (2018) [259].

![Scheme 36](image)

Scheme 36. Synthesis of benzothiazine–pyrimidine hybrids bridged by an amide bond, reported by Tamatam et al. (2019) [264].

![Scheme 37](image)

Scheme 37. US/HATU-catalyzed carboxylic acid and amine coupling to furnish 1H-pyrrole pyrimidine hybrids bridged by an amide bond, reported by Syamaiah et al. (2014) [265].
potassium tert-butoxide in THF (r.t., )), 50–65 min). The corresponding carboxamides were obtained at 70–78% yields [264].

In a very similar protocol, the preparation of carboxamides was done using 1H-pyrrole 3-carboxylic acids 101 and 2-amino-4-fluoro-5-chloropyrimidine 102, and HATU as the coupling agent (Scheme 37) [265], with the resulting carboxamides 103 obtained at moderate yields (64–67%).

The 2-amino moiety was also reacted with isothiocyanates 105 (previously prepared from acylchlorides 104 and KSCN), using PEG-400 as solvent, to furnish products 106 at good yields (74–88%) and in short reaction times (15–20 min) — see Scheme 38 [266–268]. A very interesting transformation of 106 was performed by reacting with molecular bromine (CHCl₃, )), r.t., 1–2 h, Scheme 38) to furnish 2H-1,2,4-thiadiazolo[2,3-a]pyrimidines 107 at good yields (up to 80%) [268].

A mechanism was proposed for the cyclization of 106 mediated by Br₂ (Scheme 39). Initially, bromine deprotonates the NH and, through charge delocalization (106.1), the thiol moiety is formed and attacks the pyrimidinic nitrogen (106.2), thus furnishing cyclic 2H-1,2,4-thiadiazolo[2,3-a] pyrimidines 107 and the elimination of two HBr molecules (Tables 8 and 9).

6. Conclusions and outlook

A concise and thorough summary of the achievements in the US-assisted synthesis and derivatization of pyrimidine scaffolds was presented. In recent years, US has emerged as an alternative source of...
energy in the synthesis of this targeted heterocycle. Among its main advantages, the following can be mentioned: reduction in reaction times, higher yields, fewer reaction steps, and less generation of byproducts than conventional methods. The role of US as a reaction accelerator, its synergic effects when combined with other additives (catalysts, ILS, etc.) and the benefits of the reactions (e.g., selectivity issues) were also discussed. We hope that the information gathered herein inspires and supports future synthetic researchers looking for efficient methods to prepare this highly biologically relevant scaffold, and to improve upon the methods already known and apply them to less explored protocols.

CRediT authorship contribution statement

Mateus Mittersteiner: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. Felipe F. S. Farias: Methodology, Investigation, Data curation, Visualization, Writing - original draft. Helio G. Bonacorso: Resources, Project administration, Funding acquisition. Marcos A. P. Martins: Resources, Project administration, Funding acquisition, Supervision. Nilot Zanatta: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Supervision, Resources, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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