

APPLICATION OF THE SONOCHEMISTRY IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS – A BRIEF REVIEW

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Abstract

Sonochemistry, the study of chemical effects of ultrasound, plays a pivotal role in the synthesis of heterocyclic compounds, offering unique advantages over traditional methods. This article explores the innovative application of ultrasonic irradiation in facilitating chemical reactions involving heterocycles, which are crucial in pharmaceuticals, agrochemicals, and materials science. The use of ultrasound enhances reaction rates, improves yields, and often eliminates the need for harsh reaction conditions or toxic solvents. Additionally, sonochemical processes can yield products with improved selectivity and reduced by-products. This overview highlights recent advancements in the field, showcasing sonochemistry as a powerful tool for the efficient and sustainable synthesis of complex heterocyclic structures.

Keywords: Sonochemistry, ultrasound, synthesis of heterocyclic, heterocyclic compounds.

INTRODUCTION

The increased use of resources and requirements for environmental protection necessitate finding more effective and environmentally friendly synthesis methods, as well as reducing the waste generated. [1-3]. The main advantages of sonochemistry include the use of less hazardous chemicals solvents, reduction of and energy consumption, and increased selectivity of the reaction. In this regard, ultrasonic impact often facilitates the management of chemical reactions, stimulating higher efficiency and effectiveness. [4-9]

Ultrasound affects the reaction mixture not only with the high energy of cavitation but also induces new reactivity, intensifies diffusion, and improves stirring, which ultimately leads to the acceleration of the reaction and sometimes to the formation of unexpected organic compounds. [1, 9]

Technologies based on acoustic cavitation are considered a means to eliminate or minimize limited mass transfer. Cavitation is a phenomenon of nucleation, growth and subsequent contraction (quasiadiabatic) of microbubbles in a liquid medium. The collapse of the bubbles forms hot spots characterized by very high temperatures (in the range 1000-15000 K) and pressures (500-5000 bar). [1]

The application of ultrasound (sonochemistry) has become an exciting area of research in the last few years. Ultrasound is used to accelerate a number of useful synthetic reactions. For example, Biginelli, Suzuki reaction, organometallic reactions, metal-catalyzed hydrogenation, phase transfer, polymer synthesis, heterocyclic synthesis, etc. [1, 5]

EXPOSITION

Synthesis of heterocyclic compounds

Synthesis of three- and four-membered heterocycles

Barch and co-authors synthesized β lactams by the Reformatsky reaction by US irradiation and using "non-active" zinc dust and a catalytic amount of iodine. The reaction was carried out in a high-intensity ultrasound (HIUS) environment created by a direct probe. Both β -lactams and the corresponding β -aminoesters can be obtained by the Reformatsky reaction and using imines as electrophiles [10]

Bose and co-authors investigated the preparation of β -lactams, but under low-intensity ultrasound (ILUS) irradiation. In

this case, the zinc dust is activated by washing with nitric acid to achieve higher yields. The reactions were carried out in a UV bath in the presence of a catalytic amount of iodine in dioxane, and the products were obtained in 70-95% yield. Under these conditions, the formation of β amino esters was not observed [11]

Comparing the syntheses of Barch and Bose, it is clear that zinc activation is not necessary when using high-intensity US. However, inactivated zinc resulted in an almost 50% reduction in yield using lowintensity US. Another notable difference between the individual US techniques is the reaction time – in VIUS, the reaction requires only 5 minutes, while 4 to 10 hours are required when using NIUS.

 β -Lactones were synthesized by reaction of arylchromocarbene complexes and propargyl alcohol. The reaction is carried out by US irradiation in the presence of triethylamine in benzene and heating [12].

Synthesis of five-membered heterocycles

Aziridines were synthesized by reaction of fluorocarbene with imines under UV irradiation. This reaction proceeds with the formation of azomethine ylides, which can be attached to dimethyl maleate to give pyrrolidines or pyrrole rings [13].

A difluorocarbene can be prepared in the same way as a fluorocarbene, but from dibromodifluoromethane. [14]

1H-Benzotriazoles were synthesized from o-phenylenediamine with sodium nitrite in acetic acid. The products were obtained in excellent yields after 10-15 min by US irradiation at 5° C. The products were then subjected to an acylation reaction under ultrasound irradiation to give 1acylbenzotriazoles [15].

1,4-Disubstituted 1,2,3-triazoles have been synthesized from sodium azide, alkynes and alkyl/aryl halides. The reactions were catalyzed by 10 mol % of CuI in aqueous solution with US irradiation, at room temperature for 15-30 h. All products were obtained in excellent yields, with high regioselectivity [16]. Martins and co-authors US accelerated synthesis of dihydroisooxazoles from various 1,1,1-trihalomethyl-4-alkoxy-3-alken-2-ones and hydroxylamine hydrochloride. The reaction takes place for a short time in the presence of pyridine in an aqueous medium at 45° C [17].

Cycloaddition reaction of conjugated nitrones and unactivated alkenes under US irradiation affords isoxazolidines. The reactions were carried out by direct irradiation with a UV probe, and the products were obtained in good yields and excellent regioselectivity. US irradiation increases the rate of the reaction up to 20-30 times [18].

The cycloaddition reaction between nitrile oxide and various alkenes under UV irradiation leads to the preparation of 4,5dihydroisoxazoles. The reaction completes in 10-90 min at room temperature, in good yield and excellent regioselectivity [19].

Braibante and co-authors synthesized β enamino ketones and β -enamino esters by hydrazine derivatives and US irradiation in the presence of the K-10 solid support to give pyrazoles and pyrazolinones. β -Enaminoketones react with hydrazine to give only one of the possible regioisomers in moderate yield [20, 21].

A comparative study was conducted by Karale and co-authors between the use of conventional conditions and US irradiation for the preparation of thiadiazole rings in acidic media and triazole rings in alkaline media. By US synthesis, reaction time is reduced, better yields are obtained, and the ability to carry out the reaction at room temperature [22].

Pyrazole fatty esters were synthesized by reacting 1,3-diketo fatty ester with hydrazine, methyl-, phenyl-, or 4-nitrophenylhydrazine in water under UV irradiation at 60 °C [23].

The same research group investigated the synthesis of pyrazole fatty esters using ketoalene ester. The latter reacted with various hydrazines in methanol under UV treatment at room temperature, resulting in the corresponding pyrazoles. Unlike the reaction described above, this reaction proceeds regiospecifically – only one regioisomer is obtained [24].

The 1,3,5-triaryl-2-pyrazolines were synthesized by UV exposure by reaction of chalcones and phenylhydrazine in the presence of sodium acetate, in aqueous solution. The use of US irradiation is more effective compared to conventional conditions. Conducting the reaction under the influence of US requires less time, proceeds regiospecifically and the products are in better yields [25].

Khosropour described the synthesis of 2,4,5-trisubstituted imidazoles. The reaction between aldehydes and 1,2-dicarbonyl compounds was carried out in the presence of ammonium acetate and 20 mol % Zr (aces) 4 at room temperature. The reaction time under US is 3-4 times less than when the reaction is carried out under conventional conditions [26]

Sonogashira reaction was investigated for 2-substituted indoles. The reaction of oiodoanilines with 1-alkynes in the presence of $Pd(OAc)_2$ under UV irradiation leads to the formation of an indole ring in good yields. Irradiation with US leads to a significant improvement in the speed of the reaction. Under conventional conditions, the reaction requires more than 30 hours, while only 5 hours are required to complete the reaction under US irradiation [27].

same conditions the authors synthesized benzo[b] *furans by* replacing o-iodoanilines with o-iodophenols [28].

The application of US in a Bischler-Napiralski reaction for the synthesis of indoles was described by Haroutounian and Koulocher. The used substrates were treated with ultrasound for 8-20 hours at 35° C in the presence of polyphosphoric acid until the corresponding indoles were obtained [29].

Lactones were obtained by reaction of olefins and a carboxyalkyl radical created from the corresponding carboxylic acid, under ultrasound irradiation in the presence of $Mn(OAc)_3$. All lactones were obtained in good yields and in a shorter reaction time. Under conventional conditions, this reaction

takes place only in the presence of a stoichiometric amount of Mn (OAc)₃, but the results show that under US irradiation, the reaction can be carried out in the presence of a catalytic amount of Mn(OAc)₃ [30].

Thoma and co-authors reported that dimethyl- α -(3-phenylpropyl) malonate can react in different ways, in the presence of manganese (III) triacetate, with or without ultrasound. Dimethyl- α -(3-phenylpropyl) malonate in the presence of 2 eq of Mn(OAc)₃ under conventional conditions afforded the bicyclic compound in 29% yield. When the same reaction is carried out in UZ, three other compounds are obtained [31].

Sa is Melo and co-authors studied the formation of a tetrahydrofuran ring by means of ultrasound exposure of steroid compounds containing bromohydrins. Halohydrins were subjected to UV irradiation at 45° C in the presence of diacetoxyiodobenzene (DIB), obtaining a tetrahydrofuran steroid in excellent yields [32].

It has been investigated that aryl substituted α -bromo-carbonyl alkynes in the presence of a stoichiometric amount of indium (I) iodide in acetonitrile under UV irradiation lead to radical cyclization and the formation of stereospecifically substituted tetrahydrofuran rings [33].

А US accelerated synthesis of imidazolidin-2-thione was performed by Entezari and co-workers. and the heterocyclization was obtained from the reaction between ethylenediamine and carbon disulfide in a methanol/water system. The reaction takes place in the presence of an acid catalyst (HCl) or in the absence of a catalyst, and the yield depends on the reaction temperature [34].

The synthesis of five-membered heterocycles containing sulfur, selenium, and tellurium was done by Sibor and Pazdera [35].

A fully substituted 4-piperidone was used as the synthon to obtain spiro-heterocycles. When a fully substituted 4-piperidone reacts with thiobenzoylhydrazide, methylhydrazine carbodithiolate or thiosemicarbazide in the presence of piperidine under ultrasound irradiation, the corresponding piperidino-thiadiazoles are obtained [36, 37].

Pyrazoles are derived from pyrazolines, the reaction being carried out in the presence of clay (K-10 clay containing copper nitrate). The pyrazoles were obtained in excellent yields. The use of US irradiation increases the speed of the reaction - from 1-6 hours to 10-15 min [38].

Synthesis of six-membered heterocycles

Zhidovinova and co-workers showed that the classic Biginelli reaction (EtOH and hydrochloric acid) was accelerated 40-fold as a result of US irradiation. The threecomponent reaction between aldehydes, ethylacetoacetate and urea or thiourea in the presence of a catalytic amount of hydrochloric acid is completed within 2-5 minutes at room temperature, and Biginelli adducts are obtained [39].

Dihydropyrimidin-2-ones (thiones) (DHPM) are prepared by solvent-free US irradiation. The Biginelli reaction is catalyzed by HC1 (1 mol %) or trifluoroacetic acid (5 mol %) and is completed within 15-45 minutes in the case of urea and 60-90 minutes in reactions involving thiourea [40].

Srinivasan and co-workers discovered that the Biginelli reaction can also be carried out in the absence of a catalyst. The reaction between aldehydes, ethylacetoacetate, urea or thiourea is carried out in 1-nbutylimidazole tetrafluoroborate ([Hbim] BF₄) [41, 42].

Li and co-authors used US to catalyze the Biginelli reaction between aldehydes, β -ketoesters, and urea to produce DHPM. The reaction is catalyzed by aminosulfonic acid or iodine [43-46].

Yadav and co-workers showed that cerium ammonium nitrate can be used as a catalyst in the US-accelerated Biginelli reaction. The reaction is carried out in methanol under ultrasound exposure [47].

CONCLUSION

The use of ultrasonic energy in chemical synthesis is a promising economical and effective method that has practical application due to its advantages:

- easy-to-implement reaction schemes;
- low temperature regimes;
- short reaction times;
- easy isolation of products;
- obtaining high yields.

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