



Highlight

Microwave-assisted 6π -electrocyclization in waterYan Wu^a, Ying-Wu Lin^b, Wei-Min He^{c,*}^a College of Chemistry and Chemical Engineering, Yangtze Normal University, Chongqing 408000, China^b School of Chemistry and Chemical Engineering, University of South China, Hengyang 421001, China^c Department of Chemistry, Hunan University of Science and Engineering, Yongzhou 425100, China

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ABSTRACT

The recent development of microwave-assisted aqueous synthesis of polyheterocyclic-fused quinoline-2-thiones through 6π -electrocyclization was highlighted.

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Quinoline-2-thione as a privileged structural motif has been widely found in a wide variety of biologically active molecules, functional materials, and synthetic intermediates. As shown in Fig. 1, quinoline-2-thione derivatives possess remarkable pharmacological properties, such as mPGES-1 inhibitor, human A3 adenosine receptor antagonists, antiproliferative [1,2]. In this context, the development of straightforward and efficient methodologies toward quinoline-2-thione derivatives has successfully gained continuous interest. Besides, imidazo[1,2-*a*]pyridines also occupy an important position in natural products, pharmaceuticals, and optoelectronic materials [3]. From the standpoint of synthetic chemistry, the structural combination of imidazo[1,2-*a*]pyridines with quinoline-2-thiones in one single molecular framework should be interesting for the discovery of novel functional molecules. However, the synthesis of imidazo[1,2-*a*]pyridine-fused-quinoline-2-thiones has not been reported until recently.

Very recently, the research group of Chen and Yu at Zhengzhou University developed a microwave-assisted aqueous reaction for the synthesis of polyheterocyclic-fused quinoline-2-thiones through a 6π -electrocyclization strategy (Scheme 1) [4]. This metal- and additive-free approach features the benefits involving catalyst-free, short reaction time, reusable and green solvent system, and facile isolation *via* simple filtration. The previous studies of 6π -electrocyclization strategies by Saito's group [5] and Quan's group [6] have independently disclosed feasibility to access highly functionalized quinoline-2-thiones. However, volatile

solvents and external additives (e.g., 1,8-diazabicyclo[5.4.0]-undec-7-ene, $\text{In}(\text{OTf})_3$) were required in these procedures. In this context, the development of an additive-free approach in water should be valuable from the standpoint of green chemistry [7,8].

In this microwave-assisted reaction, various polyheterocyclic-fused quinoline-2-thiones **3** were obtained in the presence of *ortho*-heteroaryl anilines **1** (0.2 mmol) and carbon disulfide **2a** (0.4 mmol) in H_2O (1 mL) at 140°C under irradiation of microwave for 30 min (Scheme 2b). Moreover, the procedure showed broad and excellent functional group compatibility. Overall, 24 examples of polyheterocyclic-fused quinoline-2-thiones were successfully isolated by simple filtration. Moreover, it was found that the heteroaromatic scaffolds including indolizine, benzo[*d*]imidazo-

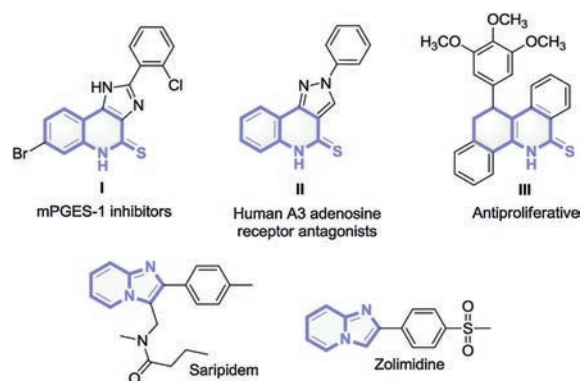


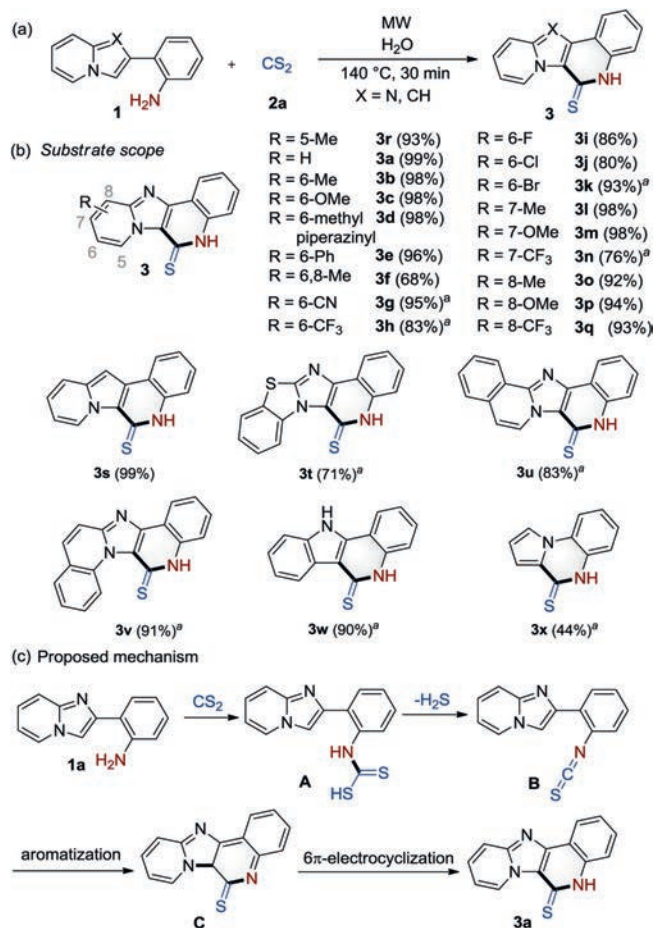
Fig. 1. Biologically active compounds containing quinoline-2-thione and imidazo[1,2-*a*]pyridines.

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Scheme 1. Microwave-assisted synthesis of imidazo[1,2-*a*]pyridine-fused quinoline-2-thiones in water.



Scheme 2. Substrate scope and proposed mechanism. ^a2a (4 equiv.) was used.

[2,1-*b*]thiazole, imidazo[2,1-*a*]isoquinoline, imidazo[1,2-*a*]quinoline, indole, and pyrrole could also be applied as reaction precursors to realize the cycloaddition to give the desired products (**3s-x**) (Scheme 2b).

A plausible mechanism of this microwave-assisted cyclization reaction was proposed as shown in Scheme 2c. First, the nucleophilic addition of the amino group in **1a** reacted with CS₂ to generate the intermediate **A**. Then the intermediate **A** was converted into the intermediate **B** along with releasing H₂S. Subsequently, intermediate **B** via 6 π -electrocyclization gave the intermediate **C**. Finally, the desired product **3a** was obtained after the aromatization of intermediate **C**.

Additionally, the recycling experiments of aqueous media for sustainable synthesis demonstrated that comparably yields were obtained in each recycle of water. This strategy features water as a reused solvent at least five times without significant loss of product yields. Finally, E-factor and EcoScale score were calculated. The excellent scores of E-factor (0.45) and EcoScale penalty points (14.5) demonstrated that this protocol presents great green chemistry and environment benign metrics [9].

In conclusion, the Chen and Yu's group recently developed a microwave-assisted annulation for the first synthesis of a diversity of polyheterocyclic-fused quinoline-2-thione frameworks in water through 6 π -electrocyclization without using any catalyst and additive. C(sp²)-N and C(sp²)-C(sp²) bonds were formed in one pot. Significantly, the green solvent water can be recycled at least for five times, and the remarkable E-factor of 0.45 and EcoScale score of 85.5 were observed in this protocol. Such findings will open new routes for the application of 6 π -electrocyclization in modern organic synthesis.

Declaration of competing interest

The authors report no declarations of interest.

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