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An Efficient Synthesis of 1H-Pyrazolo [3, 4-B]Quinolones Derivatives Catalyzed by MSA in Aqueous Media Under Ultrasound Irradiation

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ABSTRACT
A novel, eco-friendly, and highly efficient method has been developed for the synthesis of 1H-pyrazolo[3,4-b]quinolonederivatives using methanesulfonic acid (MSA) as a catalyst in aqueous medium under ultrasound irradiation**.** This approach integrates the principles of green chemistry by employing water as a benign solvent and MSA as a biodegradable, non-volatile Brønsted acid catalyst. Ultrasound irradiation significantly accelerates the reaction through acoustic cavitation, leading to enhanced yields and reduced reaction times under mild conditions. The methodology is operationally simple, offers excellent chemoselectivity, and provides good to excellent yields of the desired fused heterocyclic products. The synthesized compounds were thoroughly characterized using IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. This protocol represents a sustainable and scalable alternative for the construction of biologically relevant pyrazoloquinolone scaffolds, with potential applications in pharmaceutical and medicinal chemistry.

Keywords: Methane sulphonic acid, Ultrasound, Pyrazoloquinolone, Characterization, Green chemistry,

I. INTRODUCTION

Nitrogen-containing heterocycles constitute a vital class of organic compounds that play a pivotal role in synthetic and medicinal chemistry due to their broad spectrum of biological activities and pharmacological potential [1,2]. Among these**,** pyrazolo[3,4-b]quinolones represent an important fused heterocyclic system combining two bioactive moieties pyrazole and quinolone into a single framework. This hybrid structure endows them with a wide range of therapeutic properties, including antibacterial, antifungal, anticancer, anti-inflammatory, and antiviralactivities [3–5]. The fusion of the quinolone ring, a privileged scaffold in drug discovery, with a pyrazole nucleus enhances molecular rigidity and modulates bioavailability, making these compounds attractive for drug development [6].

Despite their pharmacological importance, traditional synthetic strategies for 1H-pyrazolo[3,4-b]quinolone derivatives often suffer from several drawbacks such as multistep procedures, harsh reaction conditions, toxic reagents, and the use of volatile organic solvents [7]. These limitations hinder the scalability and environmental sustainability of the process. Consequently, there is an increasing demand for green, efficient, and economically viable methodologies that minimize environmental impact while maximizing chemical efficiency [8]. One of the promising directions in this context is the application ofgreen catalysts and solvents**.** Methanesulfonic acid (MSA), a strong Brønsted acid, has gained considerable attention as an eco-friendly and biodegradable alternative to conventional mineral acids. MSA is thermally stable, non-volatile, non-corrosive, and recyclable, and has been successfully used to catalyze various cyclization, condensation, and multicomponent reactions in organic synthesis [9,10]. Its high acidity in combination with a low environmental burden makes it ideal for sustainable synthetic applications.

Water, as a green solvent, further contributes to the environmental appeal of synthetic protocols. It is inexpensive, non-toxic, and abundantly available, and often leads to enhanced reaction rates due to hydrophobic effects and hydrogen bonding interactions [11,12]. The use of water in heterocyclic synthesis aligns with the principles of green chemistry**,** particularly in minimizing the use of hazardous organic solvents [13]. To further enhance reaction efficiency and rate, ultrasound irradiation has emerged as a powerful non-conventional activation technique. Ultrasound promotes chemical reactions throughacoustic cavitation, generating localized hot spots with high pressure and temperature, thereby accelerating molecular interactions [14]. This

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technique allows reactions to proceed under milder conditions, with shorter reaction times and higher yields, often without the need for excessive heating or stirring [15,16]. Ultrasound-assisted organic synthesis (UAOS) has proven particularly effective in promoting cyclization and multicomponent reactions, making it ideal for heterocyclic compound synthesis [17].

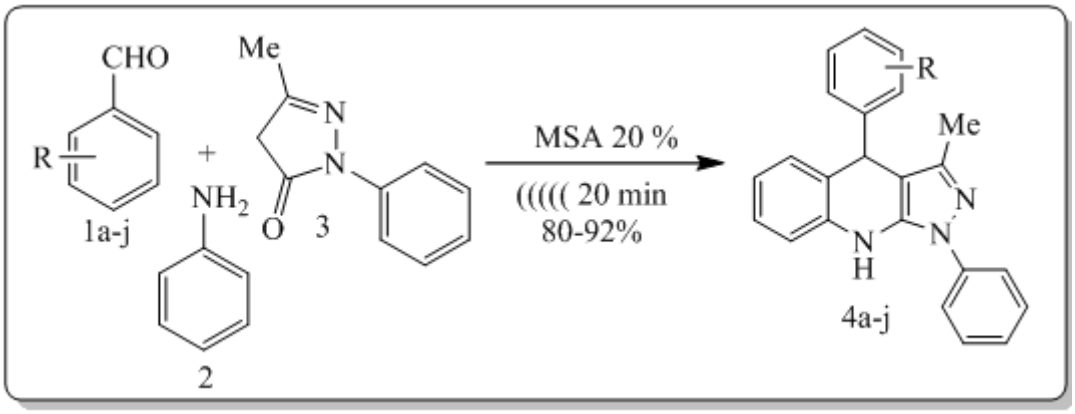
Despite the individual benefits of MSA, water, and ultrasound, their combined use for thesynthesis of 1H-pyrazolo[3,4-b]quinolone derivatives remains largely unexplored. In the present study, we report afacile, efficient, and green protocol for the synthesis of these valuable heterocycles using MSA as the catalyst in aqueous medium under ultrasound irradiation. The method offers several significant advantages, including high yields, shorter reaction times, cleaner reactions, and operational simplicity**,** all while adhering to environmentally friendly practices. To the best of our knowledge, this is the first report employing this triple combination for the synthesis of pyrazoloquinolone derivatives. The developed approach provides an attractive route for the construction of biologically relevant fused heterocycles with potential applications in pharmaceutical chemistry.

II. MATERIALS AND METHODS

All the chemicals and synthetic-grade reagents were procured from Sigma Aldrich Indian and Merck Chemicals. They were used without further purification. Melting points were obtained in open capillaries using a Buchi melting point B-540 apparatus. The ultrasonication model no. MINI4U in an Intersonik ultrasound cleaner with a frequency of 25 kHz, US output power of 100 W, and heating of 200 W. The temperature of the water bath is controlled by an automatic constant temperature cooling circulatory system. The prepared derivative is characterized by FT-IR and was recorded in Nicolet impact 410. ^{1}H NMR spectra were obtained on Bruker instrument (400 MHz) and chemicals shift are reported in δ ppm. ^{13}C NMR was recorded on a Bruker on a DRX 100 MHz Spectrometer.

Synthesis of 1H-pyrazolo[3,4-b]quinolines and its derivatives (4a–j).

In a round bottom flask mixture substituted aryl aldehyde 1a-j (0.1mmol), Aniline 2(0.1mmol) and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3) (0.1 mmol) in catalytic amount of aq. MSA under ultrasonicator at 90^{o}C for the completion of the reaction. The progress of the reaction was monitored by TLC (eluent hexane–EtOAc, 2:1). After completion of the reaction, the mixture was poured into ice-cold water. The solid was filtered off, washed with EtOAc, and recrystallized from EtOH.



Scheme 1

The goal of this work is to offer a novel synthetic pathway for the synthesis of 1H-pyrazolo[3,4-b] quinolines and their derivatives using MSA as a novel, very effective catalyst. Substituted aryl aldehyde 1(a-j) (o.1 mmol), aniline 2 (0.1 mmol), and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one 3 (0.01 mmol) were designed as a model reaction for the optimization of parameters like the reaction's catalyst amount after the catalyst was prepared. All reactions were conducted in an ultrasonicator set at 40 kHz and 90 °C to maximize the amount of catalyst that produced a high yield.

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The results are summarized in Table 1. Initially, no catalyst was used in the blank reaction, and even after 120 minutes, no product had produced. In order to replicate the model reaction, MSA was added at 5, 10, 15, 20, 25, and 30 mol%. Using 20 mol% of the catalyst produced the best results in terms of reaction time (20 minutes) and yield (92%), as shown in Table 1, entry 5. The catalysts at 25 and 30 mol%, however, did not increase the reaction yield or shorten the reaction time. Therefore, 20 mol% of the catalyst can be regarded as an ideal quantity for the conditions of the model process. Utilizing MSA, a green catalyst, as a reaction medium can increase the reaction's efficiency by increasing the reactants' solubility and decreasing the production of byproducts. Additionally, using MSA catalyst makes it simple to separate and purify the product (4a-j) listed in Table 2.

Table 1: Effect of different amount of catalyst on the condensation

Entry	Catalyst % mol	Time in min	% Yield
1	0	120	-
2	5	40	80
3	10	33	82
4	15	25	85
5	**20**	**20**	**92**
6	25	27	86
7	30	35	79

Table 2: Synthesis of 1H-pyrazolo[3,4-b]quinolines catalyzed by MSA under ultrasonic condition.

Entry	R	Time	Yield
4a	4-F	24	90
4b	4-Cl	22	91
4c	2,4 Cl2	24	90
4d	4-NO2	20	92
4e	4-Me	28	90
4f	4-OMe	30	88
4g	3,4 (OMe)	35	83
4h	4-OH	30	87
4i	2-Furyl	38	82
4j	2-Thienyl	40	80

The electron withdrawing groups (-F, Cl, -NO2 etc.) to form a high percentage of yield also participated well, indicating good functional group tolerance, but the electron donating groups (-Me, -OMe, -OH etc.) on the aromatic ring generally gave slightly faster reactions but comparable yields, as table 2 clearly shows.

4-(4-Fluorophenyl)-3-methyl-1-phenyl-4,9-dihydro1H-pyrazolo[3,4-b]quinoline (4a).

Yield (83%), yellow powder, mp 202–204°C. IR spectrum, ν, cm–1: 812 (F–C6H4), 1593, 1605 (C=N), 2978, 3108, 3235 (N–H). 1 H NMR spectrum, δ, ppm (J, Hz): 2.19 (3H, s, CH_3); 4.77 (1H, s, 4-CH); 7.25–7.95 (13H, m, H Ar); 13.93 (1H, s, NH). 13C NMR spectrum, δ, ppm: 12.3; 33.2; 121.3; 121.6; 126.4; 126.9; 128.6; 129.0; 129.2; 129.5; 129.8; 129.9; 130.7; 131.4; 131.9; 135.6; 141.8; 146.9; 159.5. Found, %: C 77.75; H 5.11; N 11.79. C23H18FN3. Calculated, %: C 77.73; H 5.10; N 11.80.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-4,9-dihydro1H-pyrazolo[3,4-b]quinoline (4b).

Yield (87%), white powder, mp 196–198°C. IR spectrum, ν, cm–1: 754 (Cl–C6H4), 1575, 1600, 1643 (C=N), 2972, 3080, 3174, 3242 (N–H). 1 H NMR spectrum, δ, ppm (J, Hz): 2.31 (3H, s, CH3); 4.96 (1H, s, 4-CH); 7.24–7.70 (13H, m, H Ar); 13.90 (1H, s, NH). 13C NMR spectrum, δ, ppm: 12.0; 33.0; 121.0; 121.5; 126.1; 126.6; 128.4; 129.3; 129.4; 129.6; 129.7; 129.8; 130.7; 131.0; 131.6; 135.3; 141.6; 146.7; 159.9. Mass spectrum (ESI), m/z (Irel, %): 373 (32), 371 [M]+(100). Found, %: C 74.28; H 4.86; N 11.26. C23H18ClN3. Calculated, %: C 74.29; H 4.88; N 11.30.

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4-(2,4-Dichlorophenyl)-3-methyl-1-phenyl-4,9-dihydro-1H-pyrazolo[3,4-b]quinoline (4c).

Yield (87%), white powder, mp 205-–207°C. IR spectrum, ν, cm–1: 763 (Cl–C6H4), 1569, 1588 (C=N), 2943, 3086, 3154, 3247 (N–H). 1 H NMR spectrum, δ, ppm (J, Hz): 2.29 (3H, s, CH3); 5.09 (1H, s, 4-CH); 7.24–7.71 (12H, m, H Ar); 13.93 (1H, s, NH). 13C NMR spectrum, δ, ppm: 12.6; 33.4; 121.2; 121.4; 126.3; 126.7; 128.5; 128.9; 129.1; 129.5; 129.7; 129.9; 130.9; 131.1; 131.5; 135.4; 141.8; 147.1; 160.2. Found, %: C 68.01; H 4.24; N 10.33. C23H17Cl2N3. Calculated, %: C 67.99; H 4.22; N 10.34.

III. CONCLUSION

In conclusion, a green, rapid, and highly efficient method has been developed for the synthesis of **1H-pyrazolo[3,4-b]quinolone derivatives** using **methanesulfonic acid (MSA)** as a catalyst in **aqueous media under ultrasound irradiation**. The combination of MSA and water provided an environmentally benign catalytic system, while ultrasound irradiation significantly enhanced reaction rates and yields through acoustic cavitation. This methodology offers several advantages, including **short reaction times**, **high product yields**, **mild conditions**, and **elimination of toxic organic solvents**. The protocol also demonstrated broad substrate applicability and excellent chemoselectivity. Overall, this approach represents a sustainable and practical route for the synthesis of pharmacologically relevant fused heterocycles, and it holds great promise for further application in green synthetic chemistry and heterocyclic drug development.

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