# Green and Efficient Synthesis of Pyrazolo[3,4-*b*]quinolin-5-ones Derivatives by Microwave-Assisted Multicomponent Reaction in Hot Water Medium



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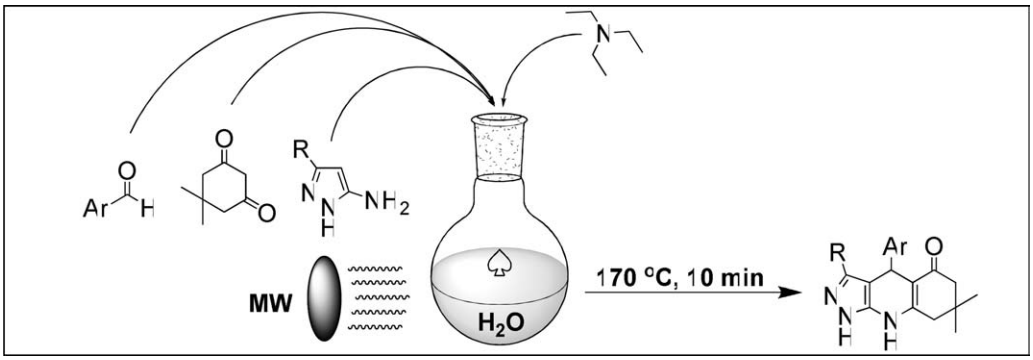


Novel simple, efficient, and eco-friendly synthetic procedure for preparation of pyrazolo[3,4-b]quinolin-5-ones based on three-component microwaves-assisted heterocyclization reaction of 5-aminopyrazoles, aromatic aldehydes, and dimedone in hot-water medium was developed. The new method allows obtaining target heterocycles in good and excellent yields and with high degree of purity.

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## INTRODUCTION

The concept of ''green chemistry'' is now widely adopted to meet the fundamental scientific challenges of protecting the human health and environment with simultaneously achieving commercial viability [1,2]. One of the key areas of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents.

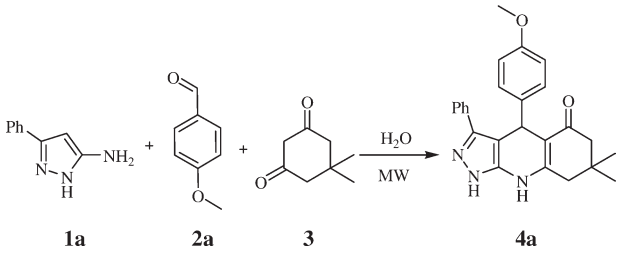
Among alternative media, water is very benign and, compared with organic solvents, is abundant, nontoxic, and eco-friendly. In many examples of ''aqueous reactions,'' organic cosolvents are employed to increase the solubility of organic reactants in water [3]. However, chemical processing in pure water is also possible under ''superheated conditions'' (>100°C) in sealed vessels, as the so-called near-critical water (150–300°C) possesses properties very different from those of ambient liquid water [4]. Therefore, water has become an attractive medium for many organic reactions, not only for the advantages concerning the avoidance of the expensive solvents but also for some unique reactivity and selectivity [5].

In the most chemical processes, major adverse effects toward the environment are due to the consumption of energy for heating. To overcome this problem, it is highly desirable to develop efficient methods that use alternative energy sources such as microwave irradiation, to facilitate chemical reactions. Recently, the combination of these two prominent green chemistry principles, ''microwaves'' and ''water,'' has become very popular and received substantial interest [6].

Nitrogen-containing heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids as well as pharmaceuticals, herbicides, and dyes [7]. Developing efficient, selective, and eco-friendly synthetic methods for applications in complex organic preparations of heterocyclic compounds is the ultimate goal of several research groups. For example, there were reported green and efficient synthesis of several fused pyrimidine derivatives by microwave-assisted reactions in water [8], three-component, aqueous one-pot synthesis of fused pyrazoles [9(a)], synthesis of benzimidazoles in ''hot water'' [9(b)], environmentally benign aqueous microwave Biginelli protocol [10], and an approach to pyrano[2,3-c]pyrazoles in aqueous media [11].

Recently, much attention has been devoted to pyrazolo-annelated heterocycles because this fragment is a key moiety in numerous biologically active compounds,

**Scheme 1**




among them are prominent drug molecules such as Viagra, Celebrex, Analginum, and many others [12]. Interested in biological activity of a significant number of compounds containing condensed pyrazole ring system, in broad program of developing efficient, selective, and eco-friendly synthetic methods, we started exploring the use of water as reaction medium in combination with microwave irradiation as a useful, environmentally benign alternative.

Here, we report direct synthesis of well-known substituted pyrazolo[3,4-b]quinolin-5-ones using high-temperature water and microwave heating *via* one-pot three-component reaction of 3-substituted 5-aminopyrazols, aromatic aldehydes, and dimedone. In earlier publications [13], it was shown that direction of this treatment sufficiently depended on conditions and, thereby, such multicomponent reaction is a challenge object for development of eco-friendly synthetic methodology based on application of hot water medium.

## RESULTS AND DISCUSSION

The algorithm of choosing appropriate reaction parameters, being of crucial importance for successful organic synthesis, includes search for optimal medium and catalytic system, temperature regime, reaction time, activation method, etc. To elaborate efficient microwave-assisted synthesis of target pyrazolo[3,4-b]quinolinones **4** in water medium the three-component reaction of 3-phenyl-1*H*-pyrazol-5-amine **1a**, 4-metoxybenzaldehyde **2a**, and dimedone **3** was selected as a model treatment for searching optimal reaction conditions (Scheme 1).

First, different types of acidic and basic catalysts were screened at the fixed temperature (130°C) and the constant microwave (MW) power of 375 W. It was established (Table 1) that multicomponent reaction of equimolar mixture of **1a**, **2a**, and **3** in water under MW heating was the most efficient in the presence of 1.2 equivalents $Et_3N$, whereas application of other basic or acidic catalysts gave worse results. Moreover, in the case of HOAc, HCl, NaOH, and $K_2CO_3$, a sufficient resinification of the reaction mixture was observed.

However, when the catalyst was absent, only starting materials were quantitatively isolated. To optimize the reaction temperature, the synthesis of **4a** was performed in water with 1.2 equivalents of $Et_3N$ at 130–200°C with an increment of 10°C. It was established that within a range 130–170°C, the yield of quinolinone **4a** raised up with increasing the temperature (Table 2). The temperature growth allowed also shortening the reaction time from 15 to 10 min without influence on yield and purity. However, no significant changes in the yield of **4a** were observed, when the reaction temperature was raised from 170 to 200°C. Therefore, the temperature of 170°C was chosen as the most suitable to carry out the multicomponent reaction studied in the water medium.

**Table 1**

Screening of the catalyst type for the synthesis of **4a** (MW, $H_2O$, 130°C).

| Entry | Catalyst | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | None | 10 | 40 |
| 2 | HOAc | 10 | 43 |
| 3 | p-TSA | 10 | 46 |
| 4 | HCl | 10 | 36 |
| 5 | NaOH | 10 | 30 |
| 6 | $K_2CO_3$ | 10 | 42 |
| 7 | $Et_3N$ | 10 | 65 |
| 8 | Piperidine | 10 | 55 |

With the application of the elaborated optimized reaction conditions ($H_2O/Et_3N$, MW, 170°C, 10 min), a 21-membered library of pyrazolo[3,4-*b*]quinolin-5-ones **4a–u** was easily synthesized by the three-component treatment of equimolar amounts of pyrazol-5-amines **1a–c**, aldehydes **2a–g**, and dimedone **3** (Scheme 2 and Table 3). The reaction products were isolated in good and excellent yields as stable crystalline solids.

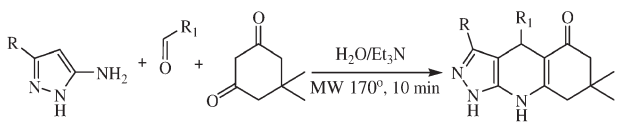
It was established that wide range of aromatic aldehydes containing diverse types of substituents can be efficiently used in the new microwave-assisted eco-friendly protocol to produce target heterocycles **4** in excellent yields and purity. However, when the aliphatic aldehydes were applied, no product of heterocyclization was isolated from the reaction mixture.

**Table 2**

Temperature optimization for the synthesis of **4a** (MW, $H_2O$).

| Entry | *T* (°C) | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | 130 | 15 | 65 |
| 2 | 140 | 15 | 68 |
| 3 | 150 | 13 | 70 |
| 4 | 160 | 13 | 77 |
| 5 | 170 | 10 | 82 |
| 6 | 180 | 10 | 80 |
| 7 | 190 | 10 | 80 |
| 8 | 200 | 10 | 78 |

**Scheme 2**




**1a-c** **2a-g** **3** **4a-u**

## CONCLUSION

Thus, the simple, efficient, and eco-friendly synthetic method was developed for preparation of pyrazolo[3,4-*b*]quinolin-5-ones by microwaves-assisted multicomponent heterocyclization reaction of 5-aminopyrazoles, aromatic aldehydes, and dimedone in hot-water medium in the presence of triethylamine. All target heterocyclic compounds were obtained in good to excellent yields and purity of >95%.

## EXPERIMENTAL

The near-critical water microwave-assisted experiments were carried out in a MARS multimode reactor from CEM Corporation (Matthews, NC) equipped with fiber-optic temperature probe.

**General procedure for the synthesis of 4a–u.** Pyrazol-5-amine **1a–c** (1.0 mmol), aldehyde **2a–g** (1.0 mmol), dimedone **3** (1.0 mmol), triethylamine (1.2 mmol), and 3 mL of water were placed in 10 mL Xpress vial which then was capped. The mixture was irradiated at 170°C (375 W) for 10 min with intensive magnetic stirring. After cooling to room temperature, 3 mL of EtOH-$H_2O$ mixture (1:1) was added to the crude reaction mixture and stirred for 10 min. The precipitate was collected by filtration, washed with EtOH–H2O (1:1), and dried at room temperature to produce the desired pyrazoloquinolinone **4a–u**. In all the cases, the reaction gave a single product whose structure was proven by spectroscopic methods ($^1$H NMR, $^{13}$C NMR, and MS). The spectral and analytical data were identical to previously published [13].

**Table 3**

Synthesis of compounds **4a-u**.

| Compound | *R* | $R^1$ | Yield (%) |
|---|---|---|---|
| **4a** | Ph | 4-$CH_3OC_6H_4$ | 82 |
| **4b** | Ph | 4-$CH_3C_6H_4$ | 83 |
| **4c** | Ph | 4-$BrC_6H_4$ | 83 |
| **4d** | Ph | 4-$ClC_6H_4$ | 90 |
| **4e** | Ph | 4-$C_2H_5OC_6H_4$ | 84 |
| **4f** | Ph | Ph | 80 |
| **4g** | Ph | 3,4-$(CH_3O)_2C_6H_3$ | 76 |
| **4h** | 4-$CH_3C_6H_4$ | 4-$CH_3OC_6H_4$ | 80 |
| **4i** | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | 80 |
| **4j** | 4-$CH_3C_6H_4$ | 4-$BrC_6H_4$ | 85 |
| **4k** | 4-$CH_3C_6H_4$ | 4-$ClC_6H_4$ | 86 |
| **4l** | 4-$CH_3C_6H_4$ | 4-$C_2H_5OC_6H_4$ | 86 |
| **4m** | 4-$CH_3C_6H_4$ | Ph | 82 |
| **4n** | 4-$CH_3C_6H_4$ | 3,4-$(CH_3O)_2C_6H_3$ | 74 |
| **4o** | $CH_3$ | 4-$CH_3OC_6H_4$ | 86 |
| **4p** | $CH_3$ | 4-$CH_3C_6H_4$ | 86 |
| **4q** | $CH_3$ | 4-$BrC_6H_4$ | 86 |
| **4r** | $CH_3$ | 4-$ClC_6H_4$ | 82 |
| **4s** | $CH_3$ | 4-$C_2H_5OC_6H_4$ | 77 |
| **4t** | $CH_3$ | Ph | 75 |
| **4u** | $CH_3$ | 3,4-$(CH_3O)_2C_6H_3$ | 77 |

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