Convenient Microwave-Assisted Chlorosulfonic Acid-Catalyzed Synthesis of Some Quinazolinones from 2-Phenylindole

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Aims and scope

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Abstract

A new convenient method has been developed for the synthesis of quinazolinones from 2-phenyl-1*H*-indole and substituted amines under catalysis by chlorosulfonic acid. The target quinazolinones were synthesized through a coupling reaction of 2-phenyl-1*H*-indole and

different amines using chlorosulfonic acid and hydrogen peroxide in DMSO on heating at 100°C, as well as under microwave irradiation at 80°C. The microwave-assisted synthesis provided excellent yields in 8 min compared to 4–5 h under conventional heating. The developed method is flexible and economical, and it has major importance in industry and academics.

INTRODUCTION

Nitrogen heterocycles are key structural units found in a variety of synthetic drugs, agrochemicals, and pharmaceuticals [1]. Quinazolinones exhibit a wide range of pharmacological properties such as anticancer, anti-inflammatory, antimalarial, antiviral, and anti-Parkinson activities [2]. Various groups have been attached to the quinazoline moiety to enhance biological activity [3]. Due to the importance of these heterocyclic compounds, several methods have been proposed for their synthesis. However, the known methods suffer from some disadvantages such as long reaction time, low yield, and the use of volatile solvents.

3-Aminoquinazolin-4-one derivatives can be prepared from benzoxazin-4-ones by reaction with hydrazine hydrate. A series of 2,3-disubstituted quinazolinone derivatives were synthesized by condensation of 4-aminobenzenesulfonamides with 2-phenyl-1,3-benzoxazine-4-ones [4]. Furthermore, quinazolinones were obtained by cyclization of anthranilic acid derivatives with formaldehyde and substituted anilines [5]. As a part of our ongoing program, we have extended the application of acidic catalysts and reagents in organic synthesis [6]. We have tried to modify the initially described method by altering the catalyst from copper to chlorosulfonic acid. Various amines or ammonia and 2-phenylindole were easily converted to substituted quinazolinones with moderate to good yields in a short reaction time. The recovery and reusability of chlorosulfonic acid as a catalyst are some attractive features of the reaction scheme [7]. The use of chlorosulfates is interesting because of the short reaction time and high yields [8]. Dilute hydrogen peroxide solutions provide a universal, ecologically clean, and convenient way to handle reagents for different oxidations in the liquid phase [9]. Microwave-assisted technique is replacing conventional method of synthesis in terms of higher yield, optimum reaction time, and green methodology with less amount of by-products [10–14].

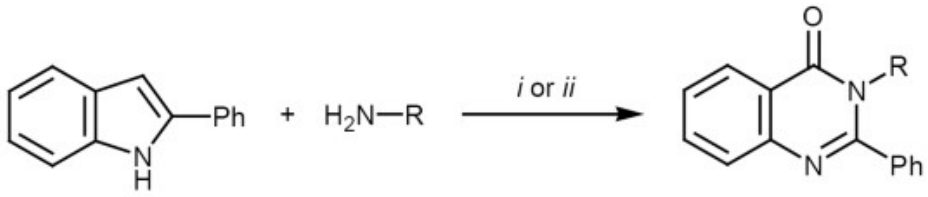
In continuation of our previous works [15–20], herein we report the microwave-assisted chlorosulfonic acid-catalyzed synthesis of substituted quinazolinones. This method gives excellent yields in a short reaction time.

RESULTS AND DISCUSSION

Substituted quinazolinones 3a–3h were synthesized from 2-phenyl-1*H*-indole (1) and amines 2a–2h by conventional and microwave-assisted method (Scheme 1). The reaction of 1 with benzylamine (2a) to produce 3-benzyl-2-phenylquinazolin-4(3*H*)-one (3a) was used as a model to optimize the conditions. Initially, various Lewis acid catalysts were tried (Table 1). Only traces of the target product were detected after 17-h reaction when zinc chloride was employed as catalyst (Table 1, run no. 1). Copper catalysts such as CuBr and $CuCl_2$ gave 40 and 50% of 3a, respectively, in 10 h (entry nos. 2, 3). In the presence of zirconium oxychloride, a yield of 65% was achieved with simultaneous shortening of the reaction time to 8 h (entry no. 4). To our surprise, the use of methanesulfonic acid increased the yield up to 80% in 7 h (entry no. 5). Finally, the highest yield (92%) was obtained in 5 h when chlorosulfonic acid was taken

as catalyst (entry no. 6). Thus, chlorosulfonic acid proved to be the best catalyst. Furthermore, hydrogen peroxide was used as an oxidant in this reaction. The addition of 10 equiv of hydrogen peroxide accelerated the reaction.

Scheme



1 **2** **3a–3h**

For R, see Table 2.
Reaction conditions: *i:* conventional heating: chlorosulfonic acid, DMSO, 100°C, reflux, 4–5 h; *ii:* microwave irradiation, chlorosulfonic acid, DMSO, 80°C, 300 W, 8 min.

1.

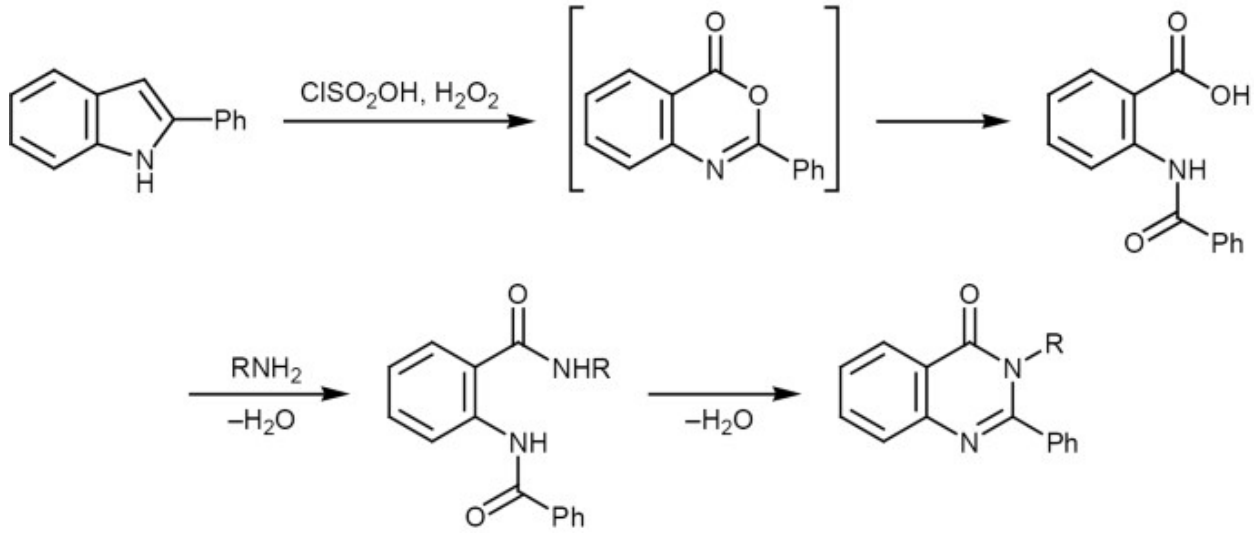
Table 1. Synthesis of 3-benzyl-2-phenylquinazolin-4(3*H*)-one (3a) in the presence of different catalysts

The reactions of 1 with the other amines were carried out under the optimized conditions using chlorosulfonic acid as catalyst and hydrogen peroxide as oxidant. Table 2 compares the results of synthesis of quinazolinones 3a–3h by conventional heating (DMSO, 100°C, 4–5 h) and under microwave irradiation (DMSO, 80°C, 8 min). The progress of reactions was monitored by TLC, and the products were identified by ^{1}H and ^{13}C NMR spectroscopy (see Supplementary Materials). The microwave-assisted synthesis was complete in a much shorter time to provide good to excellent yields of 3a–3h.

Table 2. Synthesis of 3-substituted 2-phenylquinazolin-4(3*H*)-ones 3a–3h under conventional heating and microwave irradiation conditions

Scheme 2 shows a plausible reaction mechanism, according to which the action of chlorosulfonic acid on 2-phenyl-1*H*-indole in the presence of hydrogen peroxide gives 2-phenyl-1,3-benzoxazin-4-one intermediate with increased number of ring atoms. Next follow hydrolytic cleavage of the oxazine ring, amidation of the carboxy group, and intramolecular cyclization with elimination of water to afford final quinazolinones 3.

Scheme



2.

EXPERIMENTAL

All chemicals, unless otherwise specified, were purchased from commercial sources (Sigma–Aldrich, Avra Labs) and were used without further purification. The progress of reactions was monitored by thin-layer chromatography (TLC) on Merck pre-coated silica gel 60 F254 aluminum sheets; visualization was made by UV light. The melting points were measured on

an SRS Optimelt melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer. Microwave-assisted reactions were carried out in a Milestone MicroSYNTH microwave synthesizer.

General procedure for the synthesis of 3-substituted 2-phenylquinazolin-4(3*H*)-ones 3a–3h. *a. Conventional method.* A round-bottom flask was charged with a mixture of 2-phenyl-1*H*-indole (1, 0.25 mmol), amine 2a–2h (0.5 mmol), chlorosulfonic acid (5 mol %), and hydrogen peroxide in DMSO (2 mL), and the mixture was stirred for 4–5 h at 100°C. After completion of the reaction (TLC), the mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with water, dried with anhydrous sodium sulfate, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (50:1 to 20:1).

b. Microwave-assisted synthesis. A round-bottom flask was charged with a mixture of 2-phenyl-1*H*-indole (1, 0.25 mmol), amine 2a–2h (0.5 mmol), chlorosulfonic acid (5 mol %), and hydrogen peroxide in DMSO (2 mL), and the mixture was stirred for 8 min at 80°C under microwave irradiation (300 W). After completion of the reaction (TLC), the mixture was treated as described above in *a*. The structure of compounds 3a–3h was proved by ^{1}H and ^{13}C NMR spectra (see Supplementary Materials).

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Ethics declarations

The authors declare the absence of conflict of interest.

Supplementary information

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