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Research Article

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Green Synthetic Approach for the Synthesis of Quinazoline Schiff Bases using p-TSA under Microwave Irradiation in Ethanol.

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ABSTRACT
Herein we have developed a green protocol for the synthesis of Quinazoline Schiff bases using p-TSA as solid acid catalyst from benzhydrazide and various aromatic aldehydes under microwave irradiation in ethanol. All the synthesized Schiff bases are well characterized by various spectroscopic techniques and compared with reported methods. Compared to previously reported methods, moreover, the mild reaction conditions, easy work-up, clean reaction profiles, lower catalyst loading and cost efficiency render this approach as an interesting alternative to the existing methods.

KEYWORDS
Quinazoline, Schiff bases, Microwave, green, p-TSA, benzhydrazide.

1. INTRODUCTION

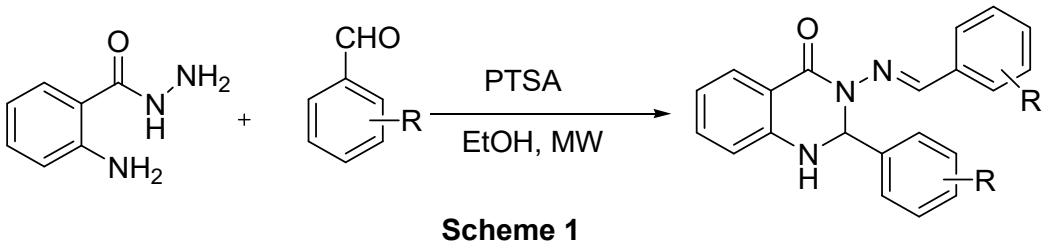
Recently, considerable research has been performed with quinazolinones and their derivatives to determine novel applications in medical chemistry [1]. The quinazoline and its derivatives are considered to be the core structure of medicinally active substrates that exists in a number of drug molecules and biologically active compounds. They have attracted the attention of researcher because it display various types of pharmacological activities, such as anti-inflammatory[2], antiviral[3], anticancer [4], antioxidant [5], anticonvulsant [6], antitubercular [7], anti-HIV [8], and so on. Many efforts have been made by chemists to modify the quinazoline ring for the development of biological, pharmaceutical and clinical compounds. As a continuation of previous efforts, researchers now aim to synthesize and develop new active quinazolines by different synthetic routes to obtain a wide range of biological activities.

A literature survey reveals that, use of acetic acid in refluxing ethanol or methanol is the only protocol for the synthesis of quinazolinone schiff base. These methods bear certain merits of their own but still they suffer from a number of demerits such as long reaction time, low yield and heating condition. Therefore, the search for eco-friendlier, efficient, and high yielding alternative routes for accessing such pharmaceutically important scaffolds is a valid exercise.

Multicomponent reactions (MCRs) have now increasingly gained importance in synthetic organic chemistry for constructing chemical libraries of simple to complex compounds with high levels of molecular diversity due to a number of benefits over multistep reactions, thus allowing the formation of several bonds in a single operation in one-pot. MCRs are commonly associated with high atom economy since all the reactants are incorporated in the final products. This successfully contributes to make MCRs eco-friendly, cost-effective, and time-efficient as compared to conventional multistep synthesis [9].

Microwave irradiation has emerged as an effective heating source for organic synthesis due to shorter reaction times, uniform and selective heating, higher yields, cleaner reactions, easy work up. Microwave-assisted organic synthesis has become a significant tool for accelerating drug discovery and development processes [10]. Microwaves have ability to couple directly with the reacting molecules leads to rapid rise in the temperature.

In recent years, the use of solid acid catalyst has gained importance in organic synthesis because of their several advantages such as operational simplicity, low cost, non-toxicity, reusability, and easy isolation after completion of the reaction. The mild reaction condition, operational simplicity, and the excellent yields make the PTSA more versatile. The use of PTSA as a catalyst has received considerable attention in organic transformations [11]. In present work; we report a simple, mild and efficient protocol for the preparation of quinazolinone schiff base derivatives with good yield through pseudo three components condensation reaction of 2-amino benzhydrazide with two equivalents of aldehyde under microwave irradiation using PTSA as catalyst in ethanol (scheme 1)



Scheme 1

Scheme 1. Quinazolinone schiff base derivatives.

2. MATERIALS AND METHODS

Melting points of the products were recorded in capillaries open at one end and were uncorrected using an Electrothermal Mk3 apparatus. All experiments under microwave irradiation were carried out in microwave synthesis system 700W model manufactured by RAGA's Scientific Microwave Synthesis System Pvt. Ltd; Pune, India has a maximum power output of 700W and 2450 MHz frequency. Thin layer chromatography (TLC) was performed using Merck pre-coated silica gel and the components were visualized under a UV or an iodine chamber. FTIR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer 65 as KBr pellets and the absorption expressed in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ or DMSO on 400 MHz FT-NMR spectrometer at 25^oC with tetramethylsilane (TMS) as the internal standard, and resonances (δ) are given in ppm. Data are reported as follows: chemical shift (d), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet).

2.1. General Procedure for the synthesis of Quinazolinone Schiff bases

In a capped 10 ml MW-vessel charged with aromatic aldehyde (2mmol), 2-amino benzhydrazide (1 mmol), PTSA and ethanol (4ml). The tube was positioned in the irradiation cavity and the mixture was irradiated in the monomode microwave oven (210 W) for specific time. The progress of reaction was monitored by TLC in ethyl acetate: hexane (2:4). After completion of reaction, the mixture was cooled to room temperature and poured on 5 ml ice cold water. The separated solid was filtered and washed with water several times. The residue was dried and recrystallized from ethanol to afford corresponding quinazolinone Schiff base. The products were confirmed by comparisons of their melting points with authentic samples and spectral data such as IR, ^1H NMR. The filtrate was heated over burner to evaporate water and ethanol content and residual catalyst was used for second cycle of reaction.

3. RESULTS AND DISCUSSION

At the beginning of our studies, we attempted to optimize the reaction conditions by using 3-nitrobenzaldehyde, 2-amino benzhydrazide and PTSA as model system. In our initial screening experiments, the effects of various solvents on the yields of the model reaction were examined. To our delight, a high yield (94%) of the desired product was obtained when the reaction was conducted in ethanol (Table 1, entry 4). The use of methanol as the solvent led to a slower reaction and a lower yield (Table 1, entry 3). Poor yields of the desired product were obtained when the reactions were performed in water, acetonitrile and DMF (Table 1, entries 2,5 and 6).

Table 1. Optimization of solvents.

Entry	condition	Time (min)	Yield (%)
1	Solvent free	30	20
2	water	30	40
3	methanol	30	70
4	ethanol	08	94
5	Acetonitrile	30	50
6	DMF	30	60

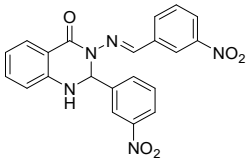
The amount of catalyst also played an important role in this system. Only a 40% yield of the desired product was obtained when no catalyst was employed. The yield of the product increase significantly when it was carried out in 10 mol% of catalyst. Excellent results were obtained when 20 mol% of catalyst used. There was no significant improvement in the yield when the amount of the catalyst was increased to 25 mol% to 30 mol%.

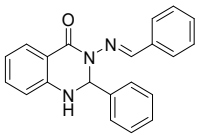
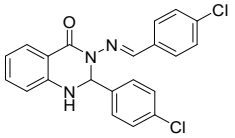
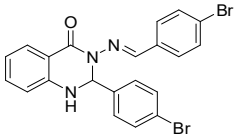
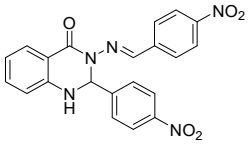
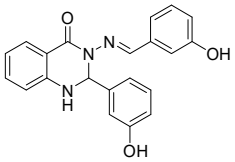
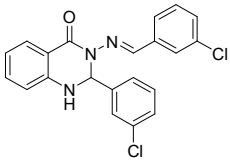
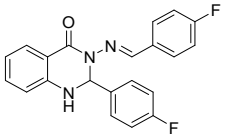
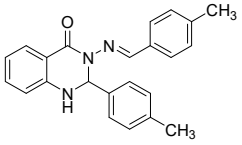
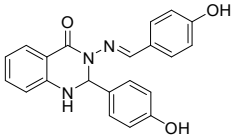
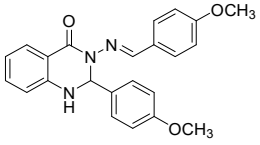
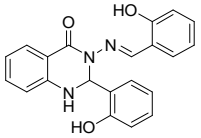
Table 2. Optimization of catalyst loading.

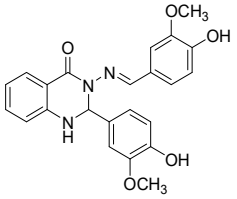
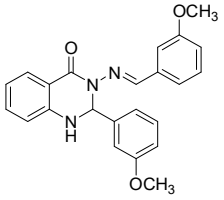
Entry	Amount of catalyst (mol%)	Time (min)	Yield (%)
1	-----	30	40
2	10	10	65
3	15	10	80
4	20	08	95
5	25	10	90
6	30	10	90

After optimizing the reaction conditions, a range of benzaldehyde was used to investigate the scope of the reaction (scheme 1). Generally speaking, there was no apparent difference in the product yield when using various substituted benzaldehyde. All of the examined benzaldehyde were excellent substrates regardless of the presence of electron-donating or electron-withdrawing groups on the benzene rings. Additionally, steric hindrance had little effect on this system. Benzaldehyde with substituents at ortho, meta and para positions of the benzene ring all reacted smoothly with 2-amino benzhydrazide to afford the corresponding products in good to excellent yields.

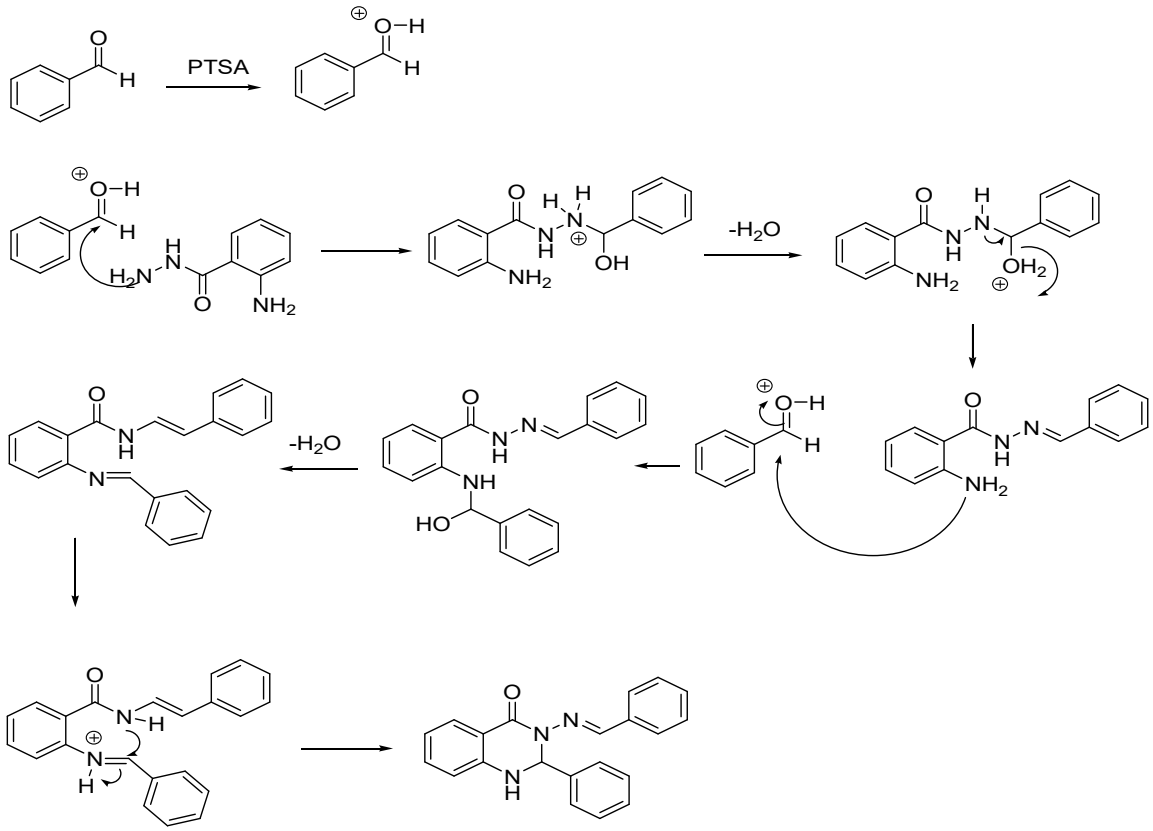
Table 2. Physical Characterization data.

Entry	Aldehyde	Product	Time (min)	Yield (%)	M. P. ^{o}C
1	3-NO_2		08	94	228-230

2	H		10	90	221-223
3	4-Cl		10	91	248-250
4	4-Br		09	92	240-242
5	4-NO_2		06	94	235-237
6	3-OH		12	88	250-252
7	3-Cl		10	88	213-215
8	4-F		08	90	233-235
9	4-CH_3		10	91	210-212
10	4-OH		12	87	241-243
11	4-OCH_3		12	88	217-219
12	2-OH		14	85	205-207

13	3-OCH_3,4-OH		15	85	220-222
14	3-OCH_3		12	86	209-211

3.1. Mechanism



3.2. Spectral data

3-(4-nitrobenzylideneamino)-2,3-dihydro-2-(4-nitrophenyl)quinazolin-4(1H)-one

Melting point: 235-237°C. IR (KBr) cm^{-1}: 3310 (NH), 3020 & 2970(C-H), 1618 (C=0), 1519 (C=N), 1452, 1435, 1384, 1210, 1169, 1131. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.37 (s, 1H, CH=N), 8.23 (d, 2H, Ar-H), 8.16 (d, 2H, Ar-H), 7.92 (d, 3H, Ar-H), 7.77 (d, 1H, ArH), 7.67 (d, 2H, ArH),7.30 (t, 1H, ArH), 6.84 (d, 1H, NH), 6.77 (t, 1H, ArH), 6.56 (d, 1H, CH).

3-(4-bromobenzylideneamino)-2-(4-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one

Melting point: 240-242°C. IR (KBr) cm^{-1}: 3312 (NH), 3025 & 2975(C-H), 1631 (C=0), 1592 (C=N), 1522, 1494, 1442, 1356, 1262, 1136.^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.03 (s, 1H,

CH=N), 7.74 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 7.45 (d, 2H, ArH), 7.34 (d, 2H, ArH), 7.27 (t, 1H, ArH), 6.80(s, 1H, NH), 6.73 (t, 1H, ArH), 6.37 (s, 1H, CH).

4. CONCLUSION

In summary, PTSA has been demonstrated to be an efficient catalyst for the one-pot synthesis of quinazolinone Schiff base derivatives via pseudo three components condensation reaction of 2-amino benzhydrazide with two equivalents of aldehyde under microwave irradiation. This protocol has several advantages such as mild reaction condition; easy work-up, clean reaction profile, lower catalyst loading and cost efficiency render this approach as an interesting alternative to the existing methods.

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