

Original Research Article

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METAL-FREE SYNTHESIS OF 2,3-DIHYDROQUINAZOLINONE DERIVATIVES USING 5-SULFOSALICYLIC ACID AS AN ORGANOCATALYST

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ABSTRACT: An efficient, selective and green protocol for the synthesis of 2,3-dihydroquinazolinone derivatives developed by the reaction of 2-aminobenzamide and aromatic aldehydes under metal-free conditions using 5-sulfosalicylic acid (5-SSA) as an organocatalyst in ethanol - water (1:1,v/v) system. The main advantages of this procedure include the use of an organocatalyst, practical simplicity, high yields, eco-friendly solvent, atom economy and ease of isolation of the product.

Keywords: Organocatalyst, Metal-free synthesis, High atom economy, 2,3-dihydroquinazolinones, Green protocol etc.

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1.INTRODUCTION

In several important natural and synthetic organic derivatives, the quinazolinone ring is observed.[1] It is a useful privileged scaffold for library design and drug discovery applications. [2] 2, 3-dihydroquinazolinone derivatives are reported as an anticancer, [3] antihypertensive agent.[4] 2, 3-dihydroquinazolinone derivatives having a broad range of potential biological and pharmacological activities,[5] as well as their importance in the preparation of drug molecules and natural product, therefore they become an important class of fused heterocycles.[6] Drugs having a quinazolinone ring are Diproqualone which is used as anti-inflammatory and Methaqualone is

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2020 March – April RJLBPCS 6(2) Page No.52

available 5-SSA as an efficient organocatalyst in a green medium.

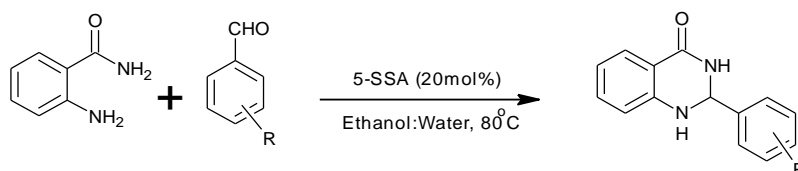
2. MATERIALS AND METHODS

Experimental

5-sulfosalicylic acid (Spectrochem), 2-aminobenzamide (Thomas Baker), and aromatic aldehydes (Spectrochem and Thomas Baker) were used as received. All the reactions were carried out in dried glassware under an open atmosphere. The melting points of all purified synthesized compounds were recorded using a hot paraffin bath and are uncorrected. The IR spectra were recorded in the frequency range 500-4000 cm^{-1} , on Alpha100508 FT-IR spectrometer. The NMR spectra were recorded on a Bruker Avance (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) spectrometer using DMSO as solvent using Tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm) values with the TMS as an internal reference, and coupling constants (J) are expressed in hertz (Hz). The Mass spectra of the purified product were recorded on a HRMS.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives

In 25 ml RB flask, a mixture of 2-aminobenzamide (1 mmol), aryl aldehyde (1 mmol), and 5-sulfosalicylic acid (20 mol%) in ethanol- water (1:1, v/v; 5 mL) was stirred at 80°C for a specified time (150 min – 240 min.) (Scheme 1) . Upon completion of the reaction as indicated by TLC, the reaction mixture was allowed to cool at room temperature and water (5 mL) was added and stirred continuously until solid was obtained in the reaction flask. The resultant solid was filtered, washed with water and then dried. The solid was recrystallized by pet ether: ethyl acetate (70:30, v/v). All the resulting products were pure and characterized by spectroscopic techniques.



Scheme 1: Synthesis of 2,3-dihydroquinazolinone derivatives

Spectral data of representative compounds

2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (3b) (Table 3, entry 2)

Yellow Solis, Mp:198-199 °C, Yield = 92%, ^1H NMR (400 MHz, CDCl_3): δ = 6.74 - 6.76 (d, J = 8.4 Hz, 1 H), 8.22-8.25 (m, 1 H), 7.23-7.30(m, 2 H), 6.65-6.69 (m, 1 H), 5.89 (s, 1 H), 7.71-7.74(d, J = 8.8 Hz, 1 H), 8.48 (s, 1 H), 7.61 (s, 1 H), ^{13}C NMR (100 MHz, CDCl_3): δ = 163.2, 149.2, 147.2, 147.1, 133.4, 127.3, 123.5, 177.4, 165.25. IR (KBr) cm^{-1} : 3367, 3289, 3027, 1646, 1600, MS (ESI): m/z 270 [M^+].

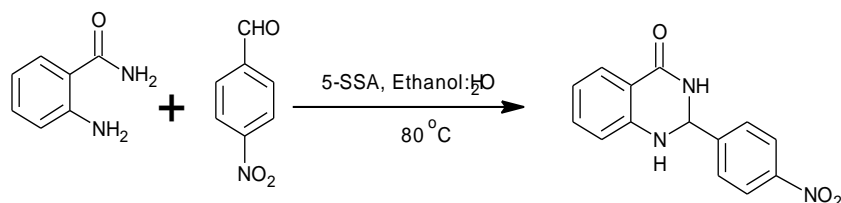
2-(4-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (3c) (Table 3,entry 3)

Yellow Solid, Mp.196-197 °C, Yield =90%, ^1H -NMR (400 MHz, CDCl_3): δ = 7.56-7.25 (m, 5 H), 6.72-6.74 (d, J =8.0 Hz, 2 H), , 6.64-6.68 (m, 1 H), 5.74 (s, 1 H), 8.29 (s, 1 H), 7.11, (s, 1 H), ^{13}C -

NMR (100 MHz, CDCl₃): δ =163.4, 147.5, 141.0, 133.3, 131.1, 129, 127.3, 121.4, 117.2, 114.4, 65.75, IR (KBr): 3367, 3282, 3038, 1647, 1603, MS (ESI): m/z 303 [M⁺].

3. RESULTS AND DISCUSSION

Initially, we chose a reaction of 2-aminobenzamide with 4-nitrobenzaldehyde as a model reaction in order to investigate the effects of solvent, temperature and amount of catalyst on the yield of the product. (Scheme 2)



Scheme 2: Synthesis of 2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3b).

For this purpose, we have screened several solvents such as toluene, THF, methanol, water, ethanol, acetonitrile, methylene dichloride, ethanol- water (1:1) etc. It was observed that the non-polar solvents such as toluene gave only moderate yields of the products (55%) and the polar solvents (ethanol, acetonitrile, methylene dichloride and methanol) give a much better yield than toluene, THF also gave a good yield for the reaction. In pursuance of making this protocol greener and economical, it was found that ethanol-water (1:1) acts more superior than other solvents, and gave excellent yield (92%) for this reaction (Table 1, Entry 3).

Table 1: Optimization of the reaction conditions using different solvents. ^a

Entry	Solvent	Time(min)	Yield (%) ^b
1	Toluene	180	55
2	THF	150	72
3	Ethanol : Water (1:1)	150	92
4	CH ₃ CN	55	65
5	EtOH	60	78
6	MeOH	90	68
7	H ₂ O	60	70

^aReaction conditions : 2-aminobenzamide (1 mmol), 4-nitrobenzaldehyde (1 mmol), and 20 mol% 5-SSA in solvent (5 mL) at 80°C temperature, ^bIsolated yields .

We next investigated the reaction scope by varying the temperatures like RT, 45°C, 60°C, 70°C, and 80°C using 30 mol% 5-SSA catalyst, to reduce the reaction time and increase the product yield. It was observed that most of the reactions of 2-aminobenzamide with aldehydes proceeded smoothly. However, the yields were slightly lower at room temperature (Table 2, entries 1),

which may be due to the poor solubility of aldehydes in solvent, but the yields of the products were enhanced, when the reaction temperature was increased around 45°C - 80°C (**Table 2, entries 2 - 9**).

Table 2: Optimization of temperature and catalyst concentration^a.

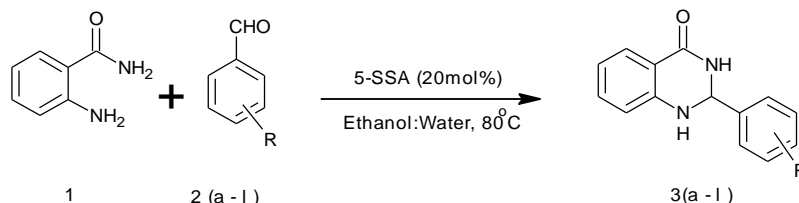
Entry	Temperature (°C)	Catalyst Conc. (mol %)	Yield (%) ^b
1	RT	30	45
2	45°C	30	60
3	60°C	30	65
4	70°C	30	70
5	80°C	5	78
6	80°C	10	82
7	80°C	15	85
8	80°C	20	92
9	80°C	30	92

^a Reaction conditions: 2-aminobenzamide (1 mmol), 4-nitrobenzaldehyde (1 mmol), in ethanol:water (1:1, v/v) (5 mL) for 2.5 h, ^bIsolated yields.

Further to determine the optimum amount of 5-SSA, the same model reaction was carried out using varied concentrations of 5-SSA such as 5, 10, 15, and 20 mol%. In this study, the formation of the product was observed in 78%, 82%, 85% and 92% yield respectively. This indicates that 20 mol% of 5-SSA is sufficient to carry out the reaction smoothly. The yields are not enhanced obviously by further increasing the amount of catalyst. There is no effect on the reaction rate as well as the yield of the product, when the concentration of catalyst increased from 20 to 30 mol%. The reaction proceeds smoothly to give higher yield (92%), proves an increase in the amount of catalyst can enhance the yield. Therefore, 20 mol% has been selected as an optimum catalyst concentration. To make this protocol environmentally green and economically viable, 20 mol% 5-SSA was employed as a catalyst in ethanol-water (1:1, v/v) as the solvent, which furnishes the desired product in excellent yield (92%) at 80°C (**Table 2, entry 8**). The reasons behind the excellent catalytic reactivity of 5-SSA may be due to the presence of sulphonic acid functionality which plays the role of Bronsted acid catalyst thereby increases the electrophilicity of carbonyl carbon of aryl aldehydes. Further, its excellent solubility in aqueous ethanol forms a homogeneous solution with substrates and enhances the rate of reaction giving excellent yield in shorter reaction times. With optimized conditions in hand, we turned our attention towards the scope and generality of the protocol. For this purpose the reaction between 2-aminobenzamide and a variety of substituted aromatic benzaldehyde was carried out. Generally, the reactions were performed using 20 mol% of 5-SSA in water- ethanol (1:1, v/v) at 80°C temperature to give the desired

products in good to excellent yields. All the results are compiled in **Table 3**. It is observed that, aryl aldehyde with electron-donating as well as electron-withdrawing substituents reacted efficiently with equal chemical reactivity. The formation of the desired product was confirmed with the help of FT-IR, ^1H NMR, ^{13}C NMR and mass spectra.

Table 3: 5-SSA catalyzed synthesis of 3a-3l^{a,b}



Entries	Aryl aldehyde	Product	Time (min)	Yield ^b %	Mp (°C) (Reported)	Ref.
1	Benzaldehyde	3a	150	88	216-218 (217-219)	[35]
2	4-Nitrobenzaldehyde	3b	150	92	198-199 (200-201)	[36]
3	4-Bromobenzaldehyde	3c	150	90	196-197 (197-198)	[35]
4	3-Nitrobenzaldehyde	3d	150	84	196-198 (195-196)	[35]
5	4-Hydroxybenzaldehyde	3e	240	86	279-280 (278-280)	[35]
6	4-Methoxybenzaldehyde	3f	240	85	181-183 (182-184)	[35]
7	4-Cyanobenzaldehyde	3g	150	88	251-252 (249-251)	[35]
8	4-Methylbenzaldehyde	3h	180	84	225-227 (224-226)	[35]
9	2,4-dimethoxybenzaldehyde	3i	180	92	184-185 (186-187)	[35]
10	4-Chlorobenzaldehyde	3j	150	88	205-206 (204-206)	[35]
11	2,5-dimethylbenzaldehyde	3k	150	84	220-221 (222-224)	[37]
12	3,4-dihydroxybenzaldehyde	3l	180	86	285-286 (288-290)	[37]

^aReaction conditions : 2-aminobenzamide (1 mmol), aryl aldehyde (1 mmol), and 5-SSA (20 mol%) in ethanol:water (1:1) (5 mL) at 80 °C, ^b Isolated yield.

4. CONCLUSION

In summary, we developed a green methodology for the synthesis of a variety of 2,3-dihydro-2-phenylquinazolin-4(1H)-one derivatives in excellent yield. One-pot reaction, metal-free synthesis, operational simplicity, atom economy, no waste generation, use of safe, cheap and environmentally benign solvent are key aspects of the present protocol. Further, the use of water soluble, recyclable, inexpensive, commercially available non-toxic catalyst as a potential and metal-free organocatalyst, fully green protocol and clean reaction profile, shorter reaction time and a wide range of substrate applicability, mild reaction condition, a high conversion rate etc., are the important features of this method.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

Authors have no any conflict of interest.

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