RJC

RASĀYAN *J. Chem.*
Vol. 18 | No. 1 |461-467| January - March | 2025
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

A REUSABLE PHTHALIMIDE-*N*-SULPHONIC ACID (*PISA*) CATALYZED SYNTHESIS OF 2,3-DIHYDROQUINAZOLINONE DERIVATIVES: AN ECO-FRIENDLY PROTOCOL

J. R. Deshmukh[1], U. N. Chaudhar[2], N.D. Sakhare[1], A. M. Patil[3] and S. G. Sonkamble[3,✉]

[1]Department of Chemistry, Late Kisandas Gulabchand Kataria College, Daund, Dist. Pune, Maharashtra-413801, India
[2]Department of Chemistry, Kalikadevi Arts, Commerce and Science College, Shirur Kasar, Dist. Beed, Maharashtra-413249, India
[3]Department of Chemistry, Pratisthan Mahavidyalaya, Paithan Tal-Paithan, Dist. Chhatrapati Sambhajinagar, Maharashtra India
✉Corresponding author: sg_sonkamble@yahoo.co.in

ABSTRACT

We have developed a convenient and efficient strategy for the preparation of 2,3-dihydroquinazolin- 4(1H)- one derivative (DHQ) from condensation of 2-aminobenzamide and various aldehydes using phthalimide-*N*-sulfonic acid (PISA) as a catalyst is described. The present method has some important features such as mild reaction conditions, short reaction times, less catalyst dosage, and high yields with the green aspects by avoiding toxic catalysts and solvents.

Keywords: Phthalimide-*N*-Sulfonic Acid (PISA), 2,3-Dihydroquinazolin-4(1H)-One, 2-Aminobenzamide, Aldehyde.

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INTRODUCTION

2,3-Dihydroquinazolin-4(1H)-one's as oxygen- and nitrogen-containing fused heterocycles are among the most important integral parts with a wide range of biological and pharmacologic activities.[1,2] Quinazoline and quinazolinone scaffolds' pharmacological properties have sparked a lot of interest among medicinal chemists working on developing novel medications or therapeutic candidates. Among the pharmacological properties of quinazoline and its related scaffolds are Antioxidant, anticancer[3], antibacterial[4], anti-inflammatory[5], antitumor[6], anticonvulsant[7], and enzyme inhibitory activity[8,9] among others. Recently, a number of classical methods for the synthesis of 2,3 dihydroquinazolin-4(1H)-ones have been reported in the literature. But the most widely used methods for DHQZ synthesis include the condensation of anthranilamide with aldehydes using several catalysts such as succinimide-N-sulfonic acid (SuSA)[10], $FeCl_3$/ neutral Al_2O_3[11], $Y(NO_3)_3.6H_2O$[12], NH_4Cl[13], $InCl_3$[14], Hercynite@sulfuricacid[15], Ga-MCM-22[16], $ZrCl_4$[17], 5,5'-Indigodisulfonic acid[18], Alginic acid[19], Nanoparticle Fe3O4@L-proline-SO3H[20], $Sc(OTf)_3$[21], Fe_3O_4@nano-cellulose–OPO_3H[22], Ascorbic Acid[23], Ga(OTf)3[24], SiO2–$H_3PW_{12}O_{40}$[25], $ZnCl_2$-SiO_2[26], Sodium Lauryl Sulfate (SLS)[27], $Cu(OTf)_2$[28], Some of these techniques, however, have disadvantages, including the usage of a metal-based catalyst, a high reaction temperature, laborious catalyst synthesis, high cost, and the poisonous nature of the catalyst. Thus, the creation of an economical and environmentally friendly synthesis process is very important. We believe this technique will have wide-ranging uses in diversity-oriented synthesis and combinatorial chemistry.

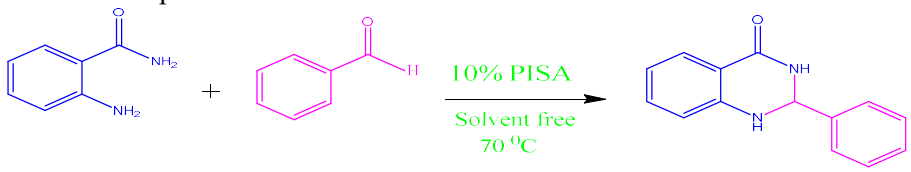
EXPERIMENTAL

Material and Methods

Every solvent and chemical was sold commercially. 1HNMR and FT-IR spectroscopy were used to confirm all products. Chemical shifts downfield from TMS have been expressed in (ppm) based on 1H NMR spectra acquired on a 500 or 400 MHz 1H NMR, 13C NMR 125.7, and 75 MHz NMR spectrometer using DMSO-d6 as a solvent. Ethanol and water were distilled before usage. The uncorrected melting points were

http://doi.org/10.31788/RJC.2025.1819187

recorded using a Buchi 535 melting point equipment. With KBr discs, FT-IR spectra were obtained on a Bruker Vector-22 infrared spectrometer.



Scheme 1 Synthesis of 2,3-dihydroquinazolin-4(1H)-ones

General Procedure

Take 2-amino benzamide (1 mmol) and aromatic aldehyde (1 mmol) catalyst PISA (10 mol%) was added in a 25 ml RB flask under solvent-free conditions. The mixture was stirred at 70^{0}C for an appropriate time. After completion of the reaction, as indicated by TLC ethanol (5 mL) was added to the reaction mixture, and the mixture was heated until a homogeneous solution was obtained. Next, ethyl acetate was added to the resulting mixture and then cooled to room temperature, and the catalyst was recovered by filtration and washed thoroughly with ethyl acetate and then diethyl ether. After this, the organic phase was concentrated by evaporation, distilled water was added to the residue, and the solid thus obtained. The resulting solid product was filtered off, washed with cold water, and recrystallized from hot ethanol to afford the pure product.

2-Phenyl-2,3-dihydroquinazolin-4(1H)-one(2a)

M.P: 166–168^{O}C;FTIR(KBr**);**743,1668,3080,3384cm^{-1} H NMR (500 MHz, DMSO-d6): 5.74 (s, 1H); 6.66 (t, J=7.5Hz, 1H), 6.74 (d, J= 8Hz, 1H), 7.10 (s, 1H), 7.22-7.25 (m, 1H), 7.32-7.40 (m, 3H), 7.49 (d, J=7Hz, 2H), 7.60 (d, J=7Hz, 1H), 8.27 (s, 1H) ; ^{13}C NMR (125.7 MHz, DMSO-d6) 67.01, 114.86, 115.41, 117.56, 127.32, 127.8, 128.79, 128.91, 133.76, 142.09, 148.33, 164.04 ppm **,** HRMS: m/z 225.1021 [M+H] +.

2-(4-Hydroxy)-2,3-dihydroquinazolin-4(1H)-one(2b)

M.P: 272–275 C; 1 H NMR (500 MHz, DMSO-d6) d ¼ 6.91 (d, J = 8.3 Hz, 3H), 7.44 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 8.11 (dd, J = 12.0, 8.1 Hz, 4H), 10.16 (s, 1H), 12.45–12.07 (m, 1H); 13C NMR (126 MHz, DMSO-d6) d ¼ 113.36, 115.83, 121.05, 123.70, 126.28, 126.33, 127.65, 130.06, 134.90, 149.52, 152.60, 161.03, 162.81 ppm.

2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)- one(2c)

M.P: 205-207 ^{O}C; IR (KBr): 749, 1652, 3061, 3306 cm^{-1} H NMR (500 MHz, DMSO-d6): δ 5.77 (s, 1H), 6.66-6.69 (m, 1H), 6.74 (d, 1H), 7.13 (s, 1H), 7.23–7.26 (m, 1H), 7.44–7.60 (m, 4H), 7.61 (d, 1H), 8.32 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d6) 66.22, 114.93, 115.41, 117.75, 127.83, 128.77, 129.22, 133.43, 133.86, 141.14, 148.11, 163.95 ppm. HRMS: *m/z* 259.0633 [M+H]$^+$.

2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3b)

M.P: 195–197 ^{O}C; 1 H NMR (500 MHz, DMSO-d6): d ¼ 3.75 (s, 3H), 5.71 (t, J =1.5 Hz, 1H), 6.68 (td, J = 7.4, 1.1 Hz, 1H), 6.74 (dd, J = 8.2, 1.0 Hz, 1H), 6.97–6.89 (m, 2H), 7.02 (s, 1H), 7.30– 7.20 (m, 1H), 7.46–7.38 (m, 2H), 7.61 (dd, J = 7.7, 1.7 Hz, 1H), 8.20 (d, J = 2.2 Hz, 1H).

2-(4-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (3c)

White solid; IR (KBr): 3,295, 3,172, 3,060, 1,659, 1,615, 1,513, 1,472 cm-1; 1 H-NMR (500 MHz, DMSO-d6) d: 5.69 (s, 1H, CH), 6.73–6.81 (m, 2H, Ar–H), 7.17 (s, 1H, NH), 7.35 (d, J = 7.8 Hz, 1H, Ar–H), 7.47 (d, J = 8.4 Hz, 2H, Ar–H), 7.61–7.69 (m, 3H, Ar–H), 8.42 (s, 1 H, NH) ppm; 13C-NMR (125 MHz, DMSO-d6) d: 68.0, 113.1, 116.6, 117.2, 127.2, 128.5, 129.0, 129.4, 133.5, 143.0, 148.3, 167.7 ppm.

2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3e)

White solid; IR (KBr): 3,296, 3,170, 3,052, 1,661, 1,611, 1,511, 1,473 cm-1; 1 H-NMR (400 MHz, DMSO-d6) d: 5.79 (s, 1H, CH), 6.70 (t, J = 8.1 Hz, 1H, Ar–H), 6.76 (d, J = 6.6 Hz, 1H, Ar–H), 7.10 (brs, 1H, NH), 7.21–7.28 (m, 3H, Ar–H), 7.54 (d, J = 8.8 Hz, 2H, Ar–H), 7.62 (d, J = 7.8 Hz, 1H, Ar–H), 8.29 (brs, 1H,

NH) ppm; 13C-NMR (125 MHz, DMSO-d6) d: 66.4, 114.9, 115.5, 117.7, 127.8, 129.5, 133.8, 138.2, 148.2, 164. Ppm.

RESULTS AND DISCUSSION

As a model reaction, the reaction was first conducted using the substrate 2- aminobenzamide with benzaldehyde. The experimental reaction was carried out without the use of a reagent, there is no conversion of the product. As the reaction was performed in the presence of phthalimide-*N*-sulfonic acid (PISA) (5 Mol%) catalyst under solvent-free conditions, the formation of 2-phenylquinazolin-4(1H)-one derivative was observed with 42% yield. As we increased the mole % of phthalimide-*N*-sulfonic acid (PISA) (5 to 15 mol%) and temperature, from the RT to 70 °C, the formation of 3A with 42% to 94 % (Table 1, Entry 2 - 7) yield was observed. With these optimized reaction conditions, the effect of different solvents such as $CHCl_3$, CH_2Cl_2 EtOH, acetonitrile, and Water were investigated (Table-2). The reaction was more facile and proceeded to give the highest yield without any solvent at 70^{O}C (Table-2, entry 6).

Table-1: Effect of the Amounts of the PISA and Temperature on the Synthesis of 2-Phenyl-2,3-dihydroquinazolin-4(1H)-one Derivative

Entry	Catalyst (mol%)	Temperature (^{O}C)	Time(h)[b]	Yield (%) [c]
1	-	70	3	Trace
2	5	70	3	42
3	10	70	1.5	94
4	15	70	1.5	93
5	10	RT	3	0
6	10	50	3	56
7	10	60	3	82
8	10	80	1.5	94

[a]Reaction conditions: substrate 2-aminobenzamide (1 mmol) with benzaldehyde (1 mmol).
[b] Reaction progress monitored by TLC analysis
[c] Isolated yields
[d] Optimized conditions are shown in bold

Table-2: The Synthesis of 2-Phenyl-2,3-dihydroquinazolin-4(1H)-one Derivatives Using PISA (10 mol%) in Various Solvents Under Reflux Conditions

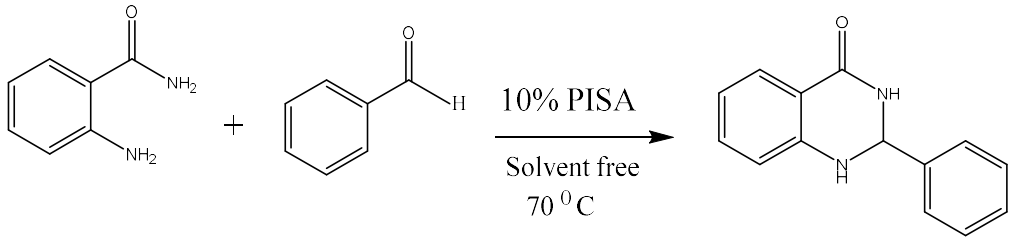
Entry	Solvent	Time(h)[b]	Isolated Yield (%)
1	$CHCl_3$	3	44
2	CH_2Cl_2	3	65
3	EtOH	3	70
4	MeOH	2.5	76
5	CH_3CN	3	82
6	Solvent-free	1.5	95

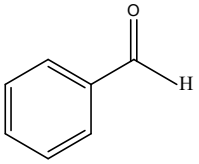
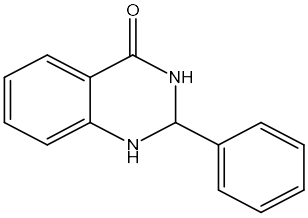
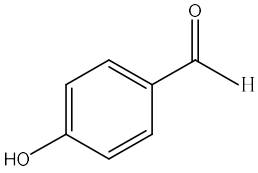
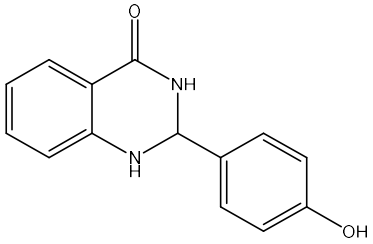
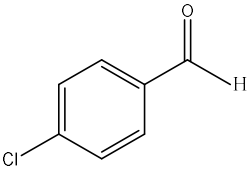
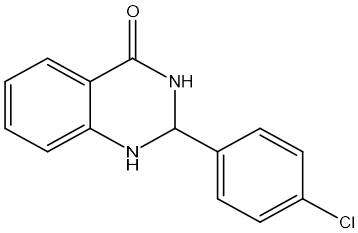
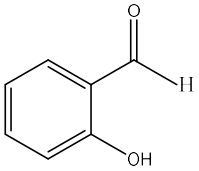
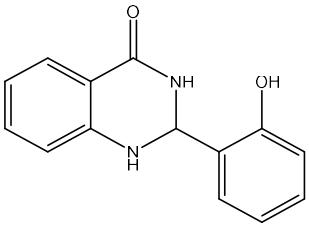
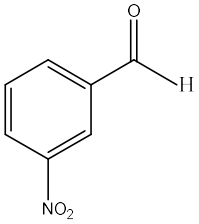
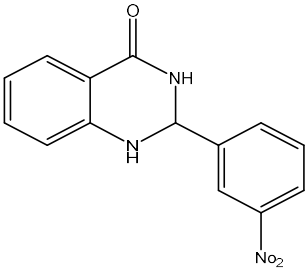
As results show a variety of aldehydes possessing different functionalities provided corresponding products with high to excellent yields. Aldehydes with electron-donating groups (p-OH, p-OMe, p-Me, etc.) gave products with good yields (Table-3, entries 2,4,7,9,12). Aldehydes having electron-withdrawing groups (m-NO_2, p-NO_2, etc.) also gave corresponding products with satisfactory yields (Table-3, entries5,8). Other aldehydes such as those containing halogen functionality (Table-3, entries 3,6,10–11), also showed proper yields. The above observation several that the efficiency of the catalyst was so good that only slight differences sing yield and reaction time were seen on functional group changes.

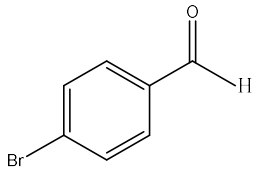
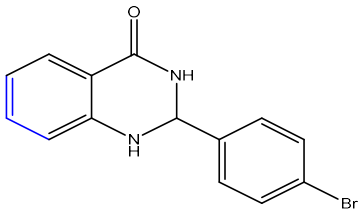
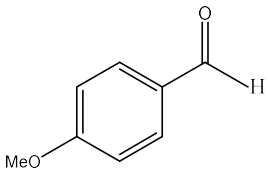
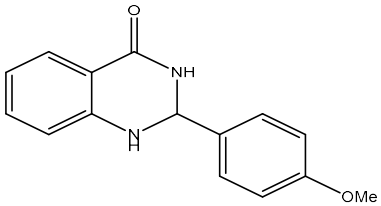
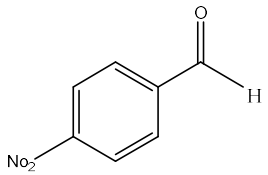
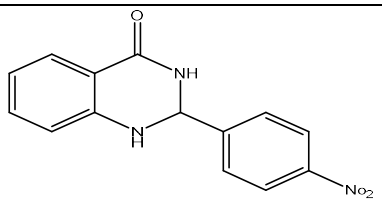
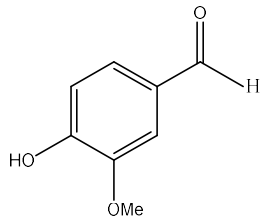
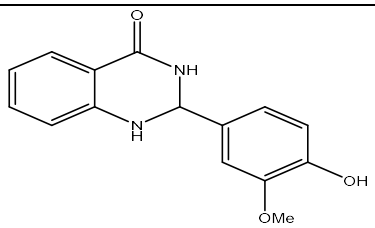
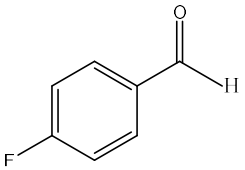
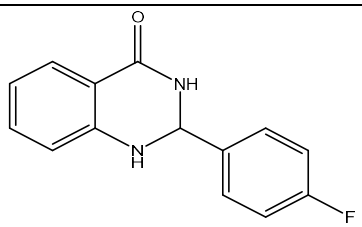
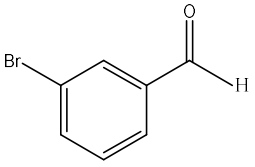
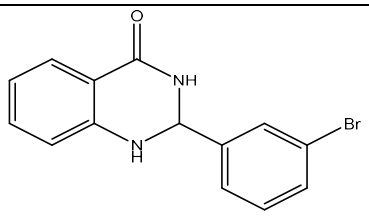
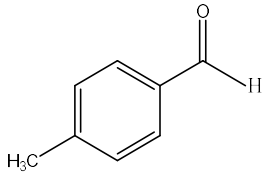
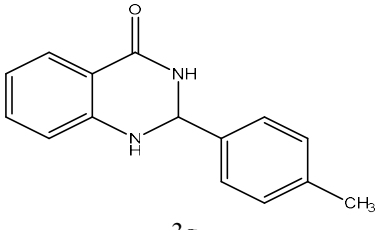
CONCLUSION

Using a reusable phthalimide-N-sulfonic acid (PISA) catalyst, we have established an environmentally friendly method for the preparation of 2,3-dihydroquinazolin-4(1H)-one's derivatives via a three-component one-pot condensation of aromatic aldehyde and 2-aminobenzamide. Clear benefits of the current approach include solvent-free conditions, environmental friendliness, a much faster reaction time, high to outstanding yields, and an easy workup process.

Table-3: The Synthesis of 2,3 Dihydroquinazolin-4(1H) One's Derivatives. Using PISA (10 mol%) under Solvent-Free Reflux Condition



Entry	Aldehyde	Product	Time (min)	M.P	Yield %
1		 2a	90	166–168	94
2		 2b	100	272-275	90
3		 2c	97	205–207	91
4		 2d	105	190-192	86
5		 2e	105	191–192	89

6		 3a	90	196-198	94
7		 3b	115	195–197	90
8		 3c	110	165–168	87
9		 3d	105	238-240	72
10		 3e	115	201–203	90
11		 3f	95	227–229	88
12		 3g	98	230–232	91

ACKNOWLEDGMENTS

The author expresses his gratitude to the management of Lt. K. G. Kataria, College, Daund, (Pune) India, for the facilities and support.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

J. R. Deshmukh https://orcid.org/0009-0002-9311-5538
U. N. Chaudhar http://orcid.org/0000-0002-7593-978x
N.D.Sakhare https://orcid.org/0009-0001-0713-156X
A.M. Patil http://orcid.org/0000-0003-1682-6803
S.G. Sonkambl http://orcid.org/0009-0001-4957-318X

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[RJC-9187/2024]