

## Green Protocol for the Synthesis of 2-Aryl-2,3-dihydroquinazoline-4(1H)-ones Using Indion Ina 225H Resin

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Synthesis of 2-aryl-2,3-dihydroquinazoline-4(1H)-ones is described by using new and novel heterogeneous catalyst, Indion Ina 225H resin. Anthranilamide was reacted with a series of aromatic aldehydes in presence of resin to afford various 2-aryl substituted 2,3-dihydroquinazoline-4(1H)-ones. The resin employed in these reactions can be recovered and reused.

**Keywords:** Green chemistry, Indion Ina 225H resin, 2,3-dihydroquinazolin-4(1H)-ones, heterogeneous catalyst.

### INTRODUCTION

The ideology of green chemistry calls for the development of new chemical reactivity's and reaction conditions that can provide benefits for the chemical synthesis<sup>1</sup>. Employment of heterogeneous catalysts in organic synthesis is one of these greener methods and amongst various heterogeneous catalysts, the use of resin as a catalyst has received paramount attention over its companion reagents owing to its stability in water and air<sup>2-4</sup>. In addition, the growing concern for the influence of the chemical reagents on the environment as well as on human body, recovery and reusability of the chemical reagents have attracted the attention of synthetic organic chemists. Notably, pharmaceutical industry has given more priority toward recovery and reuse of chemical reagents to reduce the cost of a product as well as the environmental burden.

Indion Ina 225H resin is a macro reticular, strongly acidic, unfunctional, premium grade inexpensive cation exchange resin containing sulfonic acid groups. It is an insoluble copolymer with styrene divinylbenzene cross-linked matrix and appears as golden yellow beads. The resin is extremely robust having excellent physical and chemical characteristics<sup>5</sup>. Utility of this resin as a catalyst for organic reactions<sup>6</sup> has been scarcely investigated and its unique nature prompted us to synthesize heterocyclic scaffolds using this resin.

2,3-Dihydroquinazoline-4(1H)-one moiety is an important pharmacophore and privileged structure in medicinal chemistry<sup>7-10</sup>. Its potential biological activity and wide natural occurrence has fascinated many researchers to develop a plethora of elegant synthetic methods. Of these, a simple and direct approach for synthesis of 2,3-dihydroquinazoline-4(1H)-ones

involves condensation of anthranilamide and carbonyl compounds. To accomplish this transformation, an assortment of catalysts such as ionic liquids<sup>11</sup>, cellulose-SO<sub>3</sub>H<sup>12</sup>, NH<sub>4</sub>Cl<sup>13</sup>, Amberlyst<sup>14</sup>, TiCl<sub>4</sub>/Zn<sup>15</sup>, CuCl<sub>2</sub><sup>16</sup>, trifluoroacetic acid<sup>17</sup>, and chiral phosphoric acids<sup>18</sup>, etc. are employed. However, pitfalls associated with these methods demands for development of a green protocol involving low cost, easily available, easy to handle and efficient catalysts.

### EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on Merck AL silica gel 60 F254 plates and visualized under UV light. The column chromatography was performed using Merck silica gel (60-120 mesh). The <sup>1</sup>H NMR spectra were recorded in DMSO-*d*<sub>6</sub> at 400 MHz on a VARIAN spectrometer. All the chemical shift values are reported in δ units using TMS as internal standard. The Mass spectra were recorded using PE-SCIEX-API-3000 system.

**General procedure for synthesis of 2,3-dihydroquinazolin-4(1H)-ones (4a-o):** Ina 225H resin (30 % w/w with respect to **2**) was added to a solution of anthranilamide (**2**) (1 mmol) and aldehyde (**3a-o**, 1 mmol) in methanol (5 mL). The mixture was stirred at room temperature for an appropriate time (Table-1). After complete conversion (confirmed by TLC), the catalyst was filtered and washed with methanol. Filtrate was concentrated and purified by silica-gel column chromatography to afford compounds **4a-o**.

**2-(Naphthalen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4a):** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 8.52 (d, *J* = 16 Hz, 1H) 8.32 (s, 1H), 8.05-7.90 (m, 2H), 7.77-7.62 (m, 2H), 7.50-

7.48 (m, 3H), 7.30-7.22 (m, 1H), 7.14 (s, 1H), 6.77-7.65 (m, 2H), 6.42 (s, 1H). MS (ESI):  $m/z = 275$  (M + H)<sup>+</sup>.

**Methyl 4'-(4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-[1,1'-biphenyl]-4-carboxylate (4c):** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 8.35 (s, 1H), 8.02 (d,  $J = 8.4$  Hz, 2H), 7.82 (d,  $J = 8.4$  Hz, 2H), 7.76 (d,  $J = 8$  Hz, 2H), 7.62-7.61 (m, 3H), 7.23 (t,  $J = 8$  Hz, 1H), 6.75 (d,  $J = 8$  Hz, 1H), 6.66 (t,  $J = 8$  Hz, 1H), 5.81 (s, 1H), 3.88 (s, 3H). MS (ESI):  $m/z = 359$  (M + H)<sup>+</sup>.

**2-(5-Methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (4h):** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 8.41 (s, 1H), 8.66 (d,  $J = 4$  Hz, 1H), 7.32-7.31 (m,  $J = 8$  Hz, 1H), 7.18 (s, 1H), 6.95 (s, 1H), 6.82-6.72 (m, 2H), 6.50 (s, 1H), 5.90 (s, 1H), 2.25 (s, 3H). MS (ESI):  $m/z = 243$  (M-H)<sup>+</sup>.

**N-(4-(4-Oxo-1,2,3,4-tetrahydroquinazolin-2-yl)phenyl)acetamide (4i):** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 8.14 (s, 1H), 7.75 (s, 1H), 7.61 (d,  $J = 6.4$  Hz, 1H), 7.59 (d,  $J = 2$  Hz, 2H), 7.41 (d,  $J = 8.8$  Hz, 2H), 7.25 (t,  $J = 6.8$  Hz, 1H), 7.02 (s, 1H), 6.74 (d,  $J = 8.4$  Hz, 1H), 6.68 (t,  $J = 7.2$  Hz, 1H), 5.69 (s, 1H), 2.03 (s, 3H). MS (ESI):  $m/z = 280$  (M-H)<sup>+</sup>.

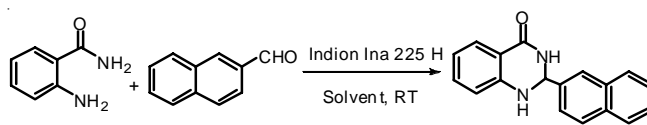
**2-(4-Bromo-2-fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (4n):** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 8.26 (s, 1H), 7.64-7.62 (m, 2H), 7.47-7.44 (m, 2H), 7.25 (t,  $J = 7.2$  Hz, 1H), 6.74 (s, 1H), 6.78-6.89 (m, 2H), 6.02 (s, 1H). MS (ESI):  $m/z = 321$  (M + H)<sup>+</sup>.

**2-(2,3-Dihydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (4o):** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 9.48 (s, 1H), 8.71 (s, 1H), 7.85 (s, 1H), 7.61 (d,  $J = 8$  Hz, 1H), 7.20 (t,  $J = 8.4$  Hz, 1H), 6.82-6.59 (m, 6H), 6.03 (s, 1H). MS (ESI):  $m/z = 255$  (M-H)<sup>+</sup>.

## RESULTS AND DISCUSSION

Due to our interest toward the development of greener chemical approaches for the synthesis of novel reaction intermediates and heterocyclic compounds, we report herein the synthesis of 2,3-dihydroquinazolin-4(1H)-ones by the reaction of aromatic aldehydes and anthranilamide, using eco-benign heterogeneous catalyst, Indion Ina 225 H (**Scheme-I**).

At the onset of our research, in order to establish optimal reaction conditions, we choose 2-naphthaldehyde (**3a**) as model aldehyde and screened various reaction conditions. Thus, the reaction of 2-amino benzamide **2** (1 mmol), compound **3a** (1 mmol) in presence of Indion Ina 225 H resin (30 %, w/w) in different solvents at room temperature was investigated and the results are summarized (**Scheme-I**). The reaction was initially carried out in acetonitrile at room temperature for 4 h when the expected product **4a** was obtained in 45 % yield (entry 1). The use of other solvents such as toluene, dichloromethane, tetrahydrofuran and ethyl acetate were examined but did not improve the product yield (entries 2, 7, 8 and 9). Almost quantitative yield was achieved within 2 h when reaction was carried out in methanol (entry 4). Ethanol and isopropanol (entries 4 and 5) were found to be less effective than methanol under otherwise similar conditions for obtaining **4a**. From these findings, it was evident that alcoholic solvents are most suitable for the synthesis of **4a** in presence of Indion Ina 225 H resin. Surprisingly, no product formation is observed when water is employed as solvent even after 8 h (entry 6).



Entry	Solvent	Time (h)	Yield (%) <sup>b</sup>
1	Acetonitrile	4.0	45
2	Toluene	4.0	40
3	Methanol	2.0	98
4	Ethanol	2.5	90
5	Isopropanol	3.0	86
6	Water	8.0	NR <sup>c</sup>
7	Dichloromethane	5.0	20
8	Tetrahydrofuran	5.0	22
9	Ethyl acetate	8.0	15

<sup>a</sup>All the reactions were carried out using **2** (1 mmol), **3a** (1 mmol) and Indion Ina 225; H resin (30 %, w/w) at room temperature. <sup>b</sup>Isolated yields, <sup>c</sup>NR = no reaction

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

TABLE-1  
INDION INA 225H CATALYZED SYNTHESIS OF  
2,3-DIHYDROQUINAZOLIN-4-(1H)-ONES<sup>a</sup>

S. No.	3	4	Time (h)	Yield (%) <sup>b</sup>
1	Biphenyl-4-carbaldehyde	b	3	95
2	4-COOMe-biphenyl-4'-carbaldehyde	c	3	93
3	4-OMe-benzaldehyde	d	4	96
4	2,5-Di-OMe-benzaldehyde	e	4	97
5	2,3-Ethylenedioxy-5-carbaldehyde	f	4	95
6	Benzaldehyde	g	2	98
7	5-Me-thiophene-2-carbaldehyde	h	5	92
8	4-(N-Acetamido)benzaldehyde	i	3	90
9	4-Bromo benzaldehyde	j	2	95
10	4-Fluoro benzaldehyde	k	2	95
11	2,6-Di-Cl-benzaldehyde	l	2	96
12	2-F-3-OMe-benzaldehyde	m	2	95
13	4-Br-2-F-benzaldehyde	n	2	97
14	2,3-Di-OH-benzaldehyde	o	5	88

<sup>a</sup>All the reactions were carried out using **2** (1 mmol), **3b-o** (1 mmol) and Indion Ina 225 H resin (30 %, w/w) at room temperature. <sup>b</sup>Isolated yields

After establishing the best reaction conditions for synthesis of 2,3-dihydroquinazolin-4(1H)-ones, the generality and scope of this protocol has been further explored by reacting 2-amino benzamide with a series of substituted aldehydes **3b-o** using Indion Ina 225 H resin in methanol at room temperature and results are summarized in Table-1. The substitution group on the aromatic ring had no apparent effect on the reaction yield. Biphenyl aldehydes (entries 1 and 2), aldehydes with ether functionality (entries 3-5) as well heteroaromatic aldehyde (entry 7) afforded desired products in good yields. Dihydroxy aldehyde (entry 14) also participated well in this reaction. Similarly, aldehydes with halogen moiety at different positions (entries 9-13) reacted smoothly to produce 2,3-dihydroquinazolin-4(1H)-ones in good yields. All the products **4b-o** were confirmed and characterized from <sup>1</sup>H and NMR and mass spectral data.

It is noteworthy to highlight that the catalyst could be recycled five times without significant loss of activity. For example, the treatment of anthranilamide **2** (1 mmol) with 4-bromobenzaldehyde **3j** (1 mmol) in the presence of Ina 225H

resin gave **4j** in 95, 93, 92, 90 and 90 % yields over five cycles. This clearly demonstrates excellent recycling capability of resin which in turn make it eco-friendly and economic.

### Conclusion

In conclusion, we have developed a new catalytic method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using anthranilamide, aldehydes and Indion Ina 225H resin. Attractive features of this protocol are high yields, short reaction times, simple procedure and recyclability and reusability of the catalyst.

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