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Sulfonic acid functionalized Wang resin (Wang-OSO_3H) as polymeric acidic catalyst for the eco-friendly synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

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ABSTRACT

An efficient and green approach has been developed for the synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones directly from corresponding substituted aromatic and aliphatic aldehyde and anthranilamide using recyclable polymer supported sulfonic acid catalyst under aqueous conditions. Environmental acceptability, operational simplicity, low cost, excellent functional group compatibility, and high yields are the important features of this protocol.

Dihydroquinazolin-4(1*H*)-one skeletons constitute a class of synthetic compounds that have pharmaceutical activities and clinical applications. In particular a core structure of dihydroquinazolin-4(1*H*)-one scaffold is present in a number of compounds that demonstrated anticancer, antidiuretic, and anticonvulsant activities.[1] Some representative examples of drug molecules having quinazolinone skeleton are given in Figure 1. They are also useful as antihistamine, antidepressant, and vasodilating agents. Among the several methods for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones, the most direct procedure involves the condensation of aryl, alkyl, and hetero aryl aldehydes with anthranilamide in the presence of *p*-toluene sulfonic acid.[2] In the past decade, a variety of synthetic methods have been employed for the preparation of functionalized 2,3-dihydroquinazolin-4(1*H*)-ones and the level of interest in the current domain is clearly shown by the number of publications.

Recently, a number of classical methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones have been reported in the literature involving the condensation of 2-aminobenzamide with aldehydes in the presence of various catalysts like ammonium chloride,[3] fumaric acid,[4] silica-$HClO_4$,[5] Amberlyst-15,[6] iridium,[7] citric acid,[8] [bmim]HSO_4,[9] iodine,[10] gallium trifluoromethanesulfonate,[11] ionic liquids,[12] bronsted acids,[13] phosphoric acid,[14] copper chloride,[15] tetrabutylammoniumbromide,[16] and $TiCl_4$/Zn.[1] However, the above mentioned methods have been associated with different drawbacks such as the use of hazardous organic solvents, low yields, strongly acidic conditions, expensive moisture sensitive catalysts, or tedious work-up conditions.

In spite of the efficiency of homogeneous acidic catalysts, their use is associated with generation of unwanted waste and with the corrosion of process equipment. In contrast, the use of heterogeneous acid catalysis often benefits from a substantial process improvement[17] including greater catalyst stability, recovery and regeneration, and enhanced process selectivity.

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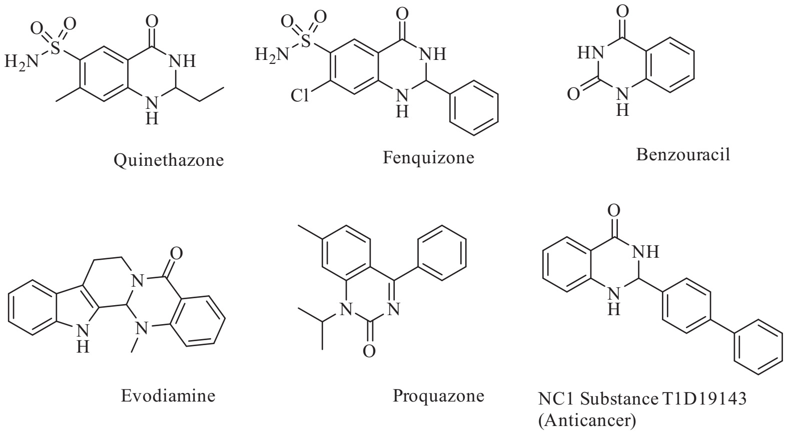
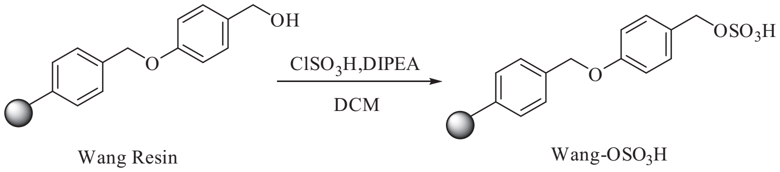
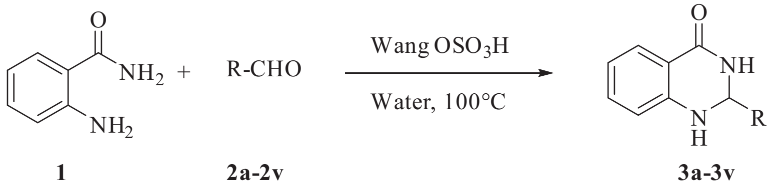


Figure 1. Examples of marketed drugs with quinazolinone skeleton.



Scheme 1. Preparation of Wang-OSO_3H.



Scheme 2. Wang-OSO_3H mediated synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones.

Table 1

Optimization of the ratio of catalyst (% w/w)

Entry	Catalyst (% w/w)	Time (h)	Yield[a] (%)
1	No Wang-OSO_3H	3.0	70.0
2	5	1.2	74.0
3	10	0.45	86.0
4	15	0.40	84.5

Reaction and conditions: 2-Aminobenzamide (1.0 mmol), 3-hydroxybenzaldehyde (1.2 mmol) and Wang-OSO_3H in water at 100 °C.

[a] Yield refers to pure products after chromatography.

Table 2

Screening of solvent

Entry	Solvent (temp. °C)	Time (h)	Yield[a] (%)
1	DMSO (100)	1.5	75
2	DMF (100)	1.5	72
3	1,4-Dioxane (100)	4.0	78
4	Ethanol (78)	1.0	80
5	DCM (38)	1.0	81
6	Acetonitrile (80)	5.0	82
7	Methanol (64)	7.0	83
8	Toluene (110)	1.0	82
9	Water (100)	0.45	86
10	Water (100)	5.0	73[b]
11	Water (100)	4.0	68[c]

Reaction and conditions: 2-Aminobenzamide (1.0 mmol), 3-hydroxybenzaldehyde (1.2 mmol), and Wang-OSO_3H (10%, w/w) in solvent at respective temperature.

[a] Yield refers to pure products after chromatography.

[b] Dowex 50 used as catalyst.

[c] Conc. H_2SO_4 used as catalyst.

The researchers continue for finding a better catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives in terms of operational simplicity, economic viability, and greater selectivity.

The objective of the present study was the development of a novel heterogeneous catalyst for efficient preparation of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones. Sulfonic acid functionalized resin (Wang-SO_3H) is an efficient heterogeneous solid acid catalyst which can easily be handled and removed from the reaction mixture by simple filtration functionalized resin (Wang-SO_3H) is an efficient heterogeneous solid acid catalyst which can easily be handled and removed from the reaction mixture by simple filtration.[18]

Wang resin[21] is most often used for the attachment of organic and inorganic acids. In particular, treatment of Wang resin with chlorosulfonic acid in the presence of *N*,*N*-diisopropylethylamine (DIPEA) results in the formation of a monosulfate ester[22] (Wang-OSO_3H, Scheme 1).

In this work, we report an efficient procedure for the preparation of 2,3-dihydroquinazolin-4(1*H*)-one derivatives through a one-step reaction between variously substituted aromatic and aliphatic aldehydes and 2-aminobenzamide under thermal

Table 3
Recyclability of the catalyst

Entry	Cycle	Time (h)	Yield[a] (%)	pH of reaction mass
1	Fresh	0.45	86.0	2.4
2	1	0.45	85.0	2.5
3	2	0.50	85.5	2.5
4	3	0.55	84.5	2.7
5	4	0.55	84.0	2.7

Reaction and conditions: 2-Aminobenzamide (1.0 mmol), 3-hydroxybenzaldehyde (1.2 mmol) and Wang-OSO$_3$H (10%, w/w) in water at 100 °C.

[a] Yield refers to pure products after chromatography.

Table 4
Comparison of catalytic activity of different catalysts

Entry	Catalyst	Time (h)	Yield[a] (%)
1	Wang-SO$_3$H	0.5	88
2	Dowex 50	5	73
3	Amberlyst 15	7	71

Reaction and conditions: 2-Aminobenzamide (1.0 mmol), 3-hydroxybenzaldehyde (1.2 mmol), and catalyst (10%, w/w) in water at 100 °C.

[a] Yield refers to pure products after chromatography.

condition in the presence of Wang-OSO$_3$H as an efficient, green, inexpensive, reusable, and polymeric catalyst.[19,20] It is pertinent to mention that this is the first Letter on the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones installing Wang-OSO$_3$H catalyzed protocol in aqueous media (Scheme 2).

We found that 2-aminobenzamide **1** readily reacts with a variety of aldehydes **2a**–**2v** under the catalysis with Wang-OSO$_3$H resin to form 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones.

The reaction conditions were optimized with respect to the quantity of catalyst (Table 1) and the solvent (Table 2) by studying the condensation of 2-aminobenzamide (**1**, 1.0 mmol) with 3-hydroxybenzaldehyde (**2d**, 1.2 mmol). The highest isolated yields of compound **3d** were obtained by carrying out the process in water at 100 °C for 0.5–1.5 h in the presence of 10% w/w catalyst with respect to 2-aminobenzamide.

The recovery and reuse of Wang-OSO$_3$H were examined in the reaction of 2-aminobenzamide with 3-hydroxybenzaldehyde. When the reaction was completed, ethyl acetate was added to the reaction mixture and the catalyst was recovered by filtration.

The recovered catalyst was washed, dried, and reused. It was found that the catalytic activities and pH of the subsequent reaction mass of the recovered catalyst were almost the same as those of fresh catalyst over four runs (Table 3, entries 1–5).

The experimental details captured in the table (Table 4, entries 1–3) clearly indicate that the yields obtained in the optimized reaction conditions using Dowex 50 and Amberlyst 15 are low compared to Wang-OSO$_3$H. The highest isolated yields of compound were obtained by carrying out the process in water at 100 °C for 0.5 h in presence of 10% w/w Wang-SO$_3$H catalyst with respect to 2-aminobenzamide. The reaction time is also comparatively very less.

Spiroheterocycles have remained relatively less investigated class of compounds until recent past. The development of newer methods for their synthesis however has gained enormous attention especially in the area of organic as well as medicinal chemistry. The condensation of 2-aminobenzamide (**1**, 1.0 mmol) with cyclohexnone (**4**, 1.2 mmol) to furnish spiro 2,3-dihydroquinazolin-4(1*H*)-ones (**5**) in 85% yield was obtained by carrying out the process in water at 100 °C for 0.5–1.0 h in the presence of 10% w/w catalyst with respect to 2-aminobenzamide (Scheme 3).

The scope and the utility of the suggested synthetic protocol was demonstrated by reacting compound **2** (**2a**–**2v**, Table 5) with a wide variety of aliphatic, aromatic, heteroaromatic, and α,β-unsaturated aldehydes to result in the target 2,3-dihydroquinazolin-4(1*H*)-ones (**3a**–**3v**, Table 5) in invariably high yields[23] (78–88%).

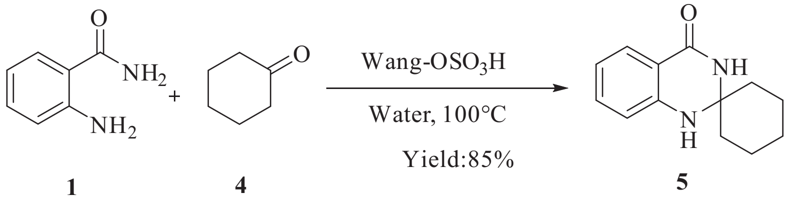
In conclusion, we have reported a highly efficient and eco-friendly method for the synthesis of novel 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones products with good yield using Wang-OSO$_3$H as an inexpensive, biodegradable, and recyclable catalyst. Prominent advantages of this method are broad scope, operational simplicity, practicability, economic viability, good yield of the products in shorter reaction time, easy work-up, and reusability of the catalyst.

Table 5
Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by Wang-OSO$_3$H

Entry	Aldehyde (**2**)	Product (**3**)	Time (h)	Yield[a] (%)	Mp (°C)
1	2,4-Dimethylbenzaldehyde, **2a**	**3a**	0.50	87	161–163
2	4-Methoxybenzaldehyde, **2b**	**3b**	0.45	88	198–201
3	4-Hydroxybenzaldehyde, **2c**	**3c**	0.45	86	209–210
4	3-Hydroxybenzaldehyde, **2d**	**3d**	0.50	88	215–217
5	3,4,5-Trimethoxybenzaldehyde, **2e**	**3e**	0.55	81	186–187
6	4-Chlorobenzaldehyde, **2f**	**3f**	0.40	84	193–194
7	2-Chlorobenzaldehyde, **2g**	**3g**	0.45	83	206–208
8	4-Bromo-2,6-difluorobenzaldehyde, **2h**	**3h**	0.45	83	205–206
9	4-Nitrobenzaldehyde, **2i**	**3i**	0.50	85	202–203
10	Hexanal, **2j**	**3j**	1.00	80	160–162
11	Pivalaldehyde, **2k**	**3k**	0.50	81	188–190
12	Cinnamaldehyde, **2l**	**3l**	0.50	81	155–157
13	Furan-2-carbaldehyde, **2m**	**3m**	0.45	80	163–164
14	Isonicotinaldehyde, **2n**	**3n**	0.45	78	264–266
15	5-Fluoro-1*H*-indole-3-carbaldehyde, **2o**	**3o**	0.45	84	Pasty solid
16	2-Chloro-8-methylquinoline-3-carbaldehyde, **2p**	**3p**	1.05	86	269–271
17	2-Chloro-7-methylquinoline-3-carbaldehyde, **2q**	**3q**	1.00	84	270–272
18	2-Chloro-6-methylquinoline-3-carbaldehyde, **2r**	**3r**	1.00	85	267–268
19	2-Chloro-6-ethoxyquinoline-3-carbaldehyde, **2s**	**3s**	0.55	82	274–275
20	2-Chloro-7-methoxyquinoline-3-carbaldehyde, **2t**	**3t**	0.50	80	278–279
21	2-Chloro-6-methoxyquinoline-3-carbaldehyde, **2u**	**3u**	0.55	83	275–277
22	2-Chloro-6-fluoroquinoline-3-carbaldehyde, **2v**	**3v**	1.10	82	264–265

Reaction and conditions: 2-Aminobenzamide 1 (1.0 mmol), aldehyde 2 (1.2 mmol), and Wang-OSO$_3$H (10%, w/w) in water at100 °C. All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.

[a] Yield refers to pure products after chromatography.



Scheme 3. Wang-OSO_3H mediated synthesis of spiro 2,3-dihydroquinazolin-4(1*H*)-ones (**5**).

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22. *Preparation of Wang-OSO_3H:*
    Wang-OSO_3H was prepared by adding freshly distilled $ClSO_3H$ (2.0 mmol) to wang resin (1.0 mmol), DIPEA (5.0 mmol) in DCM (10 volumes) and the resulting solution was stirred at 25–35 °C for 2 h. The reaction mass was filtered and washed with DMF (5 × 10 volumes), DCM (5 × 10 volumes) and Isopropanol (5 × 10 volumes) and the wang catalyst was dried at 130 °C for 3 h.
23. *General procedure for the preparation of 2,3-dihydroquinazolin-4(1H)-ones:*
    A mixture of 2-aminobenzamide **1** (1 mmol) and aldehyde **2** (**2a**–**2v**) or ketone **4** (1.2 mmol) was dissolved in 5 ml of water and Wang-OSO_3H (10% w/w) was added under stirring condition at 100 °C. Stirring was continued in for the stipulated period of time (Table 5). The progress of the reaction was monitored with TLC. After completion of the reaction, the reaction mixture was diluted with 1:9 mixture of methanol/ethyl acetate to dissolve the precipitated product and the catalyst was removed simply by filtration. The residual catalyst was repeatedly washed with ethyl acetate (3 × 5 volumes). The combined filtrate and washings, on evaporation, gave the desired product. This was further purified by column chromatography using silica gel (60–120 mesh) with ethyl acetate and hexane (4:6) as eluent to afford the desired product **3** (**3a**–**3v**) or **5**.