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Sulfamic acid as a reusable and green catalyst for efficient and simple synthesis of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones in water or methanol

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Abstract

A series of 2,3-dihydroquinazolin-4(1*H*)-ones have been synthesized in good to excellent yields through direct cyclocondensation of anthranilamide and aryl aldehydes or ketones in water or methanol under mild conditions. The reaction was efficiently promoted by 10 mol% sulfamic acid (SA, H_2NSO_3H) and the catalyst could be recovered easily after the reactions and reused without evident loss of reactivity.

Keywords: Sulfamic acid; Catalyst; Anthranilamide; Aldehyde; Ketone; 2,3-Dihydroquinazolin-4(1*H*)-ones

2,3-Dihydroquinazolinones are a class of heterocycles that attracted much attention because they have been reported to possess a wide range of pharmaceutical activities including antifertility, antibacterial, antitumor, antifungal, and mono amine oxidase inhibition [1]. In addition, these compounds can easily be oxidized to their quinazolin-4(3*H*)-one analogues [2], which also include important pharmacologically active compounds [3]. Several methods have been reported for the synthesis of 2,3-dihydroquinazolinones [4–20]. The typical procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones involves the condensation reaction of anthranilamide with aldehyde or ketone using acids as a catalyst under various conditions [4,8,10,14–20]. However, some of these methodologies have limitations such as harsh reaction conditions, use of expensive acid catalysts in organic solvents, long reaction time and tedious work-up. Hence, the development of simple, efficient, clean, high-yielding, and environmentally benign protocols using green catalysts for the synthesis of these important compounds is still desirable and is in demand.

The use of water as a solvent has many advantages in organic synthesis from both economic and environmental points of view [21]. Also, water has become an attractive medium for many organic reactions, not only as one can avoid using drying reactants and expensive catalysts and solvents, but also rendering unique reactivity and selectivity [22]. In recent years, the use of solid acidic catalysts has offered important advantages in organic synthesis, some of these advantages are: operational simplicity, environmental compatibility, non-toxicity, reusability, low cost, and ease of isolation [23]. Sulfamic acid (SA, H_2NSO_3H) is a common inorganic acid with a mild acidity that is nonvolatile,

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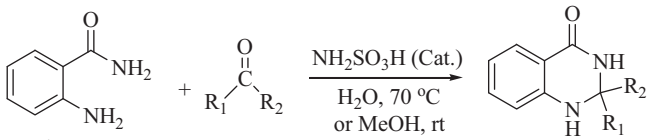

Scheme 1.

noncorrosive, stable, low-cost, and commercially available reagent. More important, its water resistance makes it an outstanding alternative to metal catalysts, in different areas of organic synthesis, as an efficient and green heterogeneous catalyst [24–26].

In continuation of our efforts to develop more versatile methodologies in organic synthesis [27,28], herein, we report a simple and straightforward method for the preparation of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones from direct cyclocondensation of anthranilamide with aldehydes and ketones in the presence of catalytic amounts of SA as a green catalyst in water at 70 °C or in methanol at room temperature (Scheme 1).

At the onset of the research, in order to optimize the reaction conditions, we investigated the model cyclocondensation reaction between anthranilamide (1 mmol) and benzaldehyde (1 mmol) in the presence of SA (10 mol%) under various reaction conditions. The results are illustrated in Table 1. The reaction in methanol is the best (entry 1). However, the reaction time in water proceeded similar to that in methanol (entry 6). We have improved our reaction to an environmentally friendly one. We then examined the generality of the reaction in methanol and water.

The results from the reactions of anthranilamide and various aldehydes and ketones in both MeOH and H_2O are shown in Table 2. As shown in entries 1–14, various aromatic aldehydes bearing either electron-donating or electron-withdrawing groups on aromatic ring and terephthaldehyde aldehyde were investigated. The substitution groups on the aromatic ring have no obvious effect on the yields and reaction time under the above optimal conditions. However, aldehydes with strongly electron-withdrawing groups on aromatic ring gave the products with good yield in a long reaction time (Table 2, entries 10 and 11). It is noteworthy that this synthetic method is efficient for the preparation of bis-2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones (Table 2, entry 14).

Most of the aldehydes gave almost the same results in MeOH and H_2O, whereas in some cases, the yields of the products in water tend to be decreased probably due to the lower solubility of starting material or intermediate in the solvent. To expand the scope further investigations were carried out for condensation of ketones with anthranilamide and the results were summarized in Table 2 (entries 15–17). In all cases, it was found that ketones can react well with anthranilamide in good yields.

In order to shown activity of sulfamic acid in this transformation, we subject the condensation of 2-nitrobenzaldehyde with anthranilamide in the absence of catalyst, the reaction did not occur even after prolonged reaction time. Interestingly, the catalyst is recycled at least three times (in the case of benzaldehyde) without considerable loss in its activity (Table 2, entry 1).

Finally, to investigation the feasibility of applying this method on a preparative scale, we performed the synthesis of 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one on a 50 mmol scale. As expected, the reaction proceeded, similar to the case in a smaller scale (Table 2, entry 1).

Table 1
Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones under different reaction conditions.

Entry	Reaction conditions	Time (min)	Conversion (%)
1	MeOH, rt	20	100
2	EtOH, reflux	100	100
3	CH_3CN, reflux	130	100
4	CH_2Cl_2, reflux	120	100
5	*n*-Hexane, reflux	150	100
6	H_2O, 70 °C	30	100

Table 2
Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence catalytic amount of SA under aqueous[a] or methanol.[b]

Entry	Aldehyde or Ketone	Product	Time (min)		Yield[c] (%)		Mp (°C) (Ref.)
			Water	Methanol	Water	Methanol	
1	C_6H_5CHO	**3a**	30	20	92, 86, 80[d]	89, 83, 78[d]	218–219 [15]
2	4-CH_3 C_6H_4CHO	**3b**	30	15	86	84	233–234 [15]
3	4-$CH_3OC_6H_4CHO$	**3c**	40	15	93	85	192–193 [15]
4	2,4-$(CH_3O)_2C_6H_4$ CHO	**3d**	30	45	95	80	186–187 [15]
5	3,4-$(CH_3O)_2C_6H_4CHO$	**3e**	30	25	95	92	212–214 [12]
6	4-$(CH_3)_2$ N C_6H_4CHO	**3f**	35	40	94	89	228–229 [15]
7	4-Br C_6H_4 CHO	**3g**	70	35	89	89	197–199 [19]
8	4-FC_6H_4 CHO	**3h**	35	15	93	89	199–200 [15]
9	4-Cl C_6H_4 CHO	**3i**	35	30	89	95	205–206 [20]
10	2-NO_2 C_6H_4 CHO	**3j**	90	80	76	84	193–194 [15]
11	3-NO_2 C_6H_4 CHO	**3k**	60	70	84	78	216–217 [15]
12	4-OH–C_6H_4 CHO	**3l**	40	30	89	91	278–280 [15]
13	2-Naphthaldehyde	**3m**	80	45	86	93	225–227
14	Terephthaldehyde	**3n**	40	30	75[e]	77[e]	243–245 [10]
15	Acetophenone	**3o**	180	120	57	65[f]	227–228 [20]
16	Cyclohexanone	**3p**	50	80	85	81	224–226 [8]
17	Acetone	**3q**	90	70	78	80	183–184 [20]

[a] Reaction conditions: anthranilamide (1 mmol), aldehyde or ketone (1 mmol), and SA (10 mol%, 10 mg), 70 °C.
[b] Reaction conditions: anthranilamide (1 mmol), aldehyde or ketone (1 mmol), and SA (10 mol%, 10 mg), rt.
[c] Isolated yield.
[d] Catalyst was reused for 3 times.
[e] Reaction conditions: in order to preparation of bis-2,3-dihydroquinazolin-4(1*H*)-one, anthranilamide (2 mmol), terephthaldehyde (1 mmol), and SA (20 mol%, 20 mg).
[f] Reaction in methanol were run under reflux condition.

To show merit of the present work in comparison with reported results in the literature, we compared our results on the reaction of anthranilamide and benzaldehyde with data from the literature (Table 3). As shown in Table 3, the previously reported procedures suffer from one or more disadvantages such as elevated reaction temperatures [8,15,16,19], longer reaction times [19], using transition metal and expensive catalyst [14–16], special efforts for the preparation of catalyst [8,14], and the need of organic solvents [15,16,18]. Therefore, we believe the present method to be an improvement with respect to other procedures.

In summary, a very simple, efficient, cost-effective, and eco-friendly synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through direct cyclocondensation of anthranilamide and aryl aldehydes or ketones in the presence catalytic amount of sulfamic acid with good to high yields in water or methanol has been devised. In addition, this method are used for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in both small and large scale.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones under aqueous conditions. In a round bottomed flask, sulfamic acid (0.1 mmol, 0.010 g) was added to a mixture of anthranilamide (1 mmol, 0.136 g) and aldehyde or ketone (1 mmol) in water (2 mL), and then the mixture was stirred at 70 °C for the appropriate time (Table 2).

Table 3
Comparison of the activity of various catalysts in the reaction of anthranilamide and benzaldehyde.

Entry	Catalyst	Condition	Time (min)	Yield (%)	Ref.
1	$Ga(OTf)_3$ (1 mol%)	EtOH, 70 °C	40	91	[15]
2	$Sc(OTf)_3$ (5 mol%)	EtOH, 70 °C	25	92	[16]
3	NH_4Cl (5 mol%)	EtOH, rt	15	92	[18]
4	Bu_4NBr (40 mol%)	Solvent-free, 100 °C	90	82	[19]
5	PPA–SiO_2 (1.25 mol%)	Solvent-free, 70 °C	1.5	91	[8]
6	$H_3PW_{12}O_{40}$ (0.1 mol%)	H_2O, rt	8	94	[14]
7	SA (10 mol%)	H_2O, 70 °C	30	92	This work
8	SA (10 mol%)	MeOH, rt	20	89	This work

After completion of the reaction which confirmed by TLC (eluent: *n*-hexane/ethyl acetate: 2/1), the crude product was filtered off and recrystallized from ethanol to give pure product in good to high yields.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones in methanol. In a round bottomed flask, sulfamic acid (0.1 mmol, 0.010 g) was added to a mixture of anthranilamide (1 mmol, 0.136 g) and aldehyde or ketone (1 mmol) in methanol (2 mL), and then the mixture was stirred at room temperature for the appropriate time (Table 2). After completion of the reaction which confirmed by TLC (eluent: *n*-hexane/ethyl acetate: 2/1), the crude product was filtered off and recrystallized from ethanol to give products in good to high yields.

All of the obtained 2,3-dihydroquinazolin-4(1*H*)-ones are known compounds (expect product **3l**) and their physical data, IR and 1H NMR spectra were essentially identical with those of authentic samples. Compound **3l**, which is new, was characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS spectroscopy and elemental analysis.

2-(2-Naphtyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 13): white solid; mp: 225–227 °C; IR (film) ν_{max} (cm^{-1}): 3282m, 3188w, 3065w, 2926w, 1649vs, 1611m, 1512m, 1486w, 1441w, 1390m, 1315m, 1158w, 825m, 747m. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 5.90 (s, 1H, CH), 6.6–8.2 (m, 12H, NH + Ar–H), 8.4 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 67.41, 114.85, 115.38, 117.58, 125.28, 126.35, 126.70, 126.78, 127.82, 127.97, 128.37, 128.51, 132.91, 133.45, 133.70, 139.22, 148.33, 164.16; MS (EI, 70 eV, *m/z*): 275.1$(M+H)^+$, 274.1(M^+), 273.1 $(M-1)^+$, 147, 120, 92; Anal. Calcd. for $C_{18}H_{14}N_2O$: C 78.81, H 5.14, N 10.21; found, C 78.82, H 5.12, N 10. 25.

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