A Novel Method for the One-Pot Three-Component Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

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Abstract: One-pot three-component condensation of isatoic anhydride with primary amines or ammonium carbonate and aromatic aldehydes in refluxing ethanol in the presence of catalytic amounts of silica sulfuric acid afforded the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones in high yields. The catalyst is reusable and can be applied several times without any decrease in product yield.

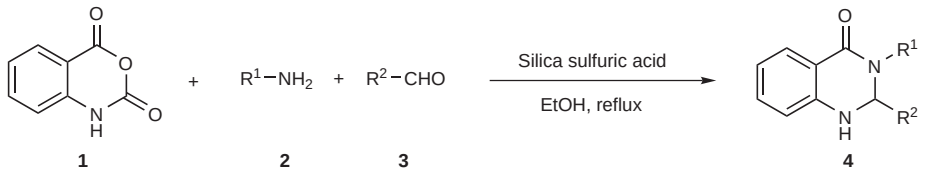
Key words: silica sulfuric acid, heterocycles, 2,3-dihydroquinazolin-4(1*H*)-ones, catalysis, isatoic anhydride

2,3-Dihydroquinazolinone derivatives have been reported to possess diverse pharmacological activities such as antitumour activity, diuretic properties, herbicide activity and plant growth regulation ability.[1] Additionally, these compounds can easily be oxidised to their quinazolin-4(3*H*)-one analogues,[2] which are themselves important biologically active heterocyclic compounds.[3] The usual procedure for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones involves condensation of the appropriate derivatives of anthranilamide with an aldehyde or ketone using *p*-toluenesulfonic acid as a catalyst under vigorous conditions.[4] Similar reactions have been reported to proceed under basic conditions.[5] This procedure affords dihydroquinazolinones in good yields, but requires long reaction times. The three step synthesis starting from isatoic anhydride or an anthranilic acid has been reported[6] and other methods such as reductive cyclisation of *o*-nitrobenzamides with aldehydes and ketones,[7] reaction of isatoic anhydride with schiff-bases,[8] and reduction of quinazolin-4(3*H*)-ones[9] are also reported for the synthesis of these compounds. Unfortunately, synthetic methods for access to this bicyclic system are not general in scope, and involve multistep and often low-yielding reaction sequences.[4–7] Therefore, versatile, simple and environmentally benign processes whereby 2,3-dihydroquinazolin-4(1*H*)-ones can be formed under milder and more practical conditions are still in demand.

Multi-component reactions (MCRs) are emerging as useful tools for carbon-carbon and carbon-heteroatom bond formation and for the synthesis of important organic molecules with several degrees of structural diversity.[10] Recently, we reported the preparation of silica sulfuric acid as a stable and versatile solid source of protons,[11] and showed its ability as a promoter in synthetic reactions.[12] Herein, we wish to report a novel one-pot three-component condensation of isatoic anhydride, a primary amine or ammonium carbonate and an aromatic aldehyde in the presence of silica sulfuric acid for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. To the best of our knowledge, this is the first reported one-pot three-component synthesis of this important class of heterocyclic compounds from the cheap and easily available starting materials.

When isatoic anhydride (**1**), primary amine **2**, and aromatic aldehyde **3**, were treated with catalytic amounts of silica sulfuric acid in ethanol under reflux, the condensation products **4**, were obtained in good yields (Scheme 1). The results are summarized in Table 1.

Several aliphatic and aromatic amines were used for this reaction. Aliphatic amines afforded the products in shorter time compared to aromatic analogues. Aromatic alde-



1 2 3 4

Scheme 1

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Table 1 Silica Sulfuric Acid-Catalyzed Synthesis of 2,3-Disubstituted-2,3- dihydroquinazolin-4(1*H*)-ones by the Reaction of Isatoic Anhydride with Primary Amines and Aldehydes

Entry	R^1	R^2	Time (h)	Yield (%)	Mp (°C)
1	Me	Ph	3	82	160–163[2a]
2	Me	4-Cl-C_6H_4	3.5	83	186–188[2a]
3	Me	4-CH_3O-C_6H_4	3	80	145–146[2a]
4	Et	Ph	3.5	85	134–137[2a]
5	Et	4-Cl-C_6H_4	3.5	84	132–135[2a]
6	Et	4-NO_2-C_6H_4	3	90	159–162[2a]
7	Et	3-NO_2-C_6H_4	3	92, 91, 89, 90[a]	176–178[2a]
8	Ph	Ph	6.5	80	205–208[8b]
9	Ph	4-NO_2-C_6H_4	7	78	195–197[8b]
10	Ph	4-Cl-C_6H_4	6	80	214–217[8b]
11	Ph	3-NO_2-C_6H_4	5.5	83	186–188[8b]
12	4-ClC_6H_4	Ph	7	73	214–217[8b]
13	Et	4-CH_3O-C_6H_4	4	84	124–126[2a]

[a] The catalyst was reused for 4 runs.

hydes carrying either electron-releasing or electron-withdrawing substituents afforded high yields of products. Aliphatic aldehydes could not be used in this procedure because they undergo aldol condensation under the reaction conditions.[12e]

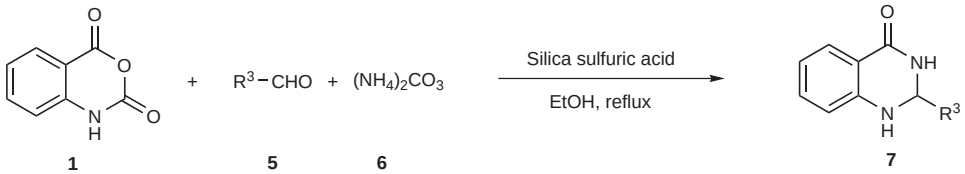
We also checked the reusability of the catalyst by separation and reloading in a new run and found that the catalyst could be reused several times without any decrease in the product yield. An example is shown for the reaction of ethylamine with isatoic anhydride and 3-nitrobenzaldehyde (Table 1, entry 7).

It is well known that some ammonium salts can be applied as the source of ammonia in the synthesis of nitrogen-containing heterocyclic compounds.[14] Accordingly, 2-aryl substituted 2,3-dihydroquinazolin-4(1*H*)-ones **7** were synthesized efficiently when ammonium carbonate (**6**), isatoic anhydride (**1**) and an aromatic aldehyde **5**, were treated with silica sulfuric acid in ethanol under the same reaction conditions (Scheme 2, Table 2).

Table 2 One-Pot Synthesis of 2-Substituted 2,3-Dihydroquinazolin-4(1*H*)-ones by Three-Component Reaction of Isatoic Anhydride, Ammonium Carbonate and an Aldehyde in the Presence of Silica Sulfuric Acid

Entry	R^3	Time (h)	Yield (%)	Mp (°C)
1	Ph	3	92	219–222[7a]
2	4-Cl-C_6H_4	3.5	88	206–208[7a]
3	4-CH_3O-C_6H_4	4.5	85	180–181[7a]
4	3,4-$(CH_3O)_2$-C_6H_3	4	87	209–210[1e]
5	4-CH_3-C_6H_4	3.5	90	233–234[13]
6	2-CH_3O-C_6H_4	4	90	165–167[1e]
7	2-Furyl	4	78	164–165[13]

Some of the synthesized monosubstituted quinazolinones (Table 2, entries 3, 4, 6) have been recognized as potent anti-cancer compounds.[1e]



Scheme 2

In conclusion, a novel one-pot three-component method for the synthesis of 2,3-dihydroquinazolinones is reported. High yields, ease of work up procedure, use of cheap and commercially available starting materials, convenient manipulation, and mild reaction conditions are the advantages of this new method. We believe that the present methodology addresses the current drive toward green chemistry due to high yields, atomic economy and reusability of the catalyst.

General Procedure for the Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

To a solution of isatoic anhydride (1 mmol), amine (1.2 mmol) or $(NH_4)_2CO_3$ (0.7 mmol) and aldehyde (1 mmol) in EtOH (5 mL) was added a catalytic amount of silica sulfuric acid (0.11 g = 0.3 mmol of H^+). The solution was heated under reflux for the specified period of time (Tables 1 and 2). After completion of the reaction as indicated by TLC (EtOAc–*n*-hexane, 1:2), the solid catalyst was separated by filtration. H_2O (5 mL) was added and the precipitated product was filtered, and recrystallised from EtOH.

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