An Efficient Synthesis of 2, 3-dihydroquinazolin-4(1H)-ones Catalyzed by Titanium Silicon Oxide Nanopowder in Aqueous Media

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Abstract

An efficient synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives is accomplished in aqueous media by a three-component reaction of isatoic anhydride, primary amines or ammonium acetate, and aldehydes catalyzed by titanium silicon oxide nanopowder. A variety of 2, 3-dihydroquinazolin-4(1H)-one derivatives were synthesized using this methodology in good to excellent yields. The catalyst was recovered and recycled up to four times without significant loss in the catalytic activity.

KEYWORDS: Quinazolinones, Nitrogen heterocycles, Reusable catalyst, Green chemistry, Nanopowder

INTRODUCTION

2.3-dihydroquinazolin-4(1H)-one derivatives are an important class of fused heterocycles that exhibit a variety of biological and pharmaceutical activities $^{[1-8]}$ such as antihypertensive,^[1] antitumor,^[2] analgesic,^[3] antibacterial,^[4] anticonvulsant,^[5] anticancer,^[6] anti-inflammatory,^[7] and diuretic ^[8] (Fig. 1). In view of their significance, various methods for the preparation of 2, 3-dihydroquinazolin-4(1H)-one derivatives have been developed. The most widely used approach for the synthesis of 2, 3dihydroquinazolin-4(1H)-one include three component reaction of isatoic anhydride, primary amine with aldehydes or ketones in the presence of different catalysts. Use of montmorillonite K-10,^[9] p-toluenesulfonic acid,^[10] silica-sulfuric acid (SSA),^[11] gallium triflate,^[12] ionic liquids (ILs),^[13] zinc (II) perfluorooctanoate [Zn(PFO₂],^[14] amberlyst-15 resin,^[15] iodine,^[16] beta-cyclodextrin,^[17] Cyanuric Chloride,^[18] Cu-CNTs ^[19] etc. have been reported for this transformation, however most of the known methods suffer from certain drawbacks such as longer time, tedious work up and use of volatile organic solvents. Thus the development of more convenient and environmentally benign synthetic methods using a recyclable catalytic system for these compounds is highly desired.

Development of new protocols for environmentally benign synthetic methods using a recyclable catalytic system has been in focus in recent times. In particular metal nanoparticles have attracted considerable attention due to their superior catalytic activity, reusability and mild nature in the context of green chemistry. As part of our ongoing research towards the development of novel methodologies for the synthesis of biologically active heterocyclic compounds^[20] titanium silicon oxide nanopowder has

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attracted considerable attention since it is non-toxic, air and moisture stable, and easy to store for long periods under normal laboratory conditions. As per the literature and to the best of our knowledge, till date there are no reports on the use of titanium silicon oxide nanopowder as a catalyst for carrying out any organic transformation. Herein we report a simple, scalable and straightforward method for the synthesis of mono- and disubstituted 2, 3-dihydroquinazolin-4(1H)-ones (Scheme 1) in aqueous media by a one-pot threecomponent reaction of isatoic anhydride, primary amines or ammonium acetate, and aldehydes catalyzed by titanium silicon oxide nanopowder.

RESULTS AND DISCUSSION

Initially, we studied one-pot, three-component condensation reaction of isatoic anhydride (1), ammonium acetate and 2-chloro benzaldehyde (2a) as the model substrates by using titanium silicon oxide nanopowder (10 mol %) as catalyst in 1, 4-dioxane solvent (Table 1, entry 1). To our delight, the corresponding 2, 3-dihydroquinazolin-4(1H)-one (4a) derivative was obtained in 93 % yield after 2 h. Encouraged by this result, we further studied the effect of different solvents and catalyst loading for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones as shown in the table-1.

As shown in the table-1, solvents 1, 4-dioxane (entry 1) and water (entry 5) were found to be equally effective for this transformation. However we have chosen water as solvent for further optimization studies as water is nontoxic, inexpensive, non-flammable, and readily available. With respect to catalyst loading there is no significant improvement in yields when the catalyst was increased from 10 to 20 mol% while yield is decreased with decreasing catalyst loading to 5 mol % from 10 mol %. In the absence of catalyst, negligible amount of product was observed under described reaction conditions.

Reusability is one of the important properties of this catalyst. The catalytic activity of titanium silicon oxide nanopowder was evaluated by subjecting the recovered catalyst to fresh substrates under optimized conditions. For this purpose isatoic anhydride, ammonium acetate and 4-chloro benzaldehyde has been chosen as model substrates. It is evident from the Table 2 that the catalyst can be recycled up to four times without significant drop in the yield and its catalytic activity.

EXPERIMENTAL

General Methods

Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (100-200 mesh) using distilled hexane, ethyl acetate, dichloromethane. ¹H NMR and ¹³C NMR spectra were determined in CDCl₃ or DMSO-*d*₆ solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Melting points were determined using melting point B-540 apparatus and are uncorrected. HRMS was determined using waters LCT premier XETOF ARE-047 apparatus.

Typical Procedure For The Synthesis Of 2-(2-Chlorophenyl)-2, 3-

Dihydroquinazolin-4(1H)-One (4a)

A mixture of isatoic anhydride 1 (500 mg, 3.06 mmol.), 2-chlorobenzaldehyde 2a (473 mg, 3.37 mmol.), ammonium acetate 3 (260 mg, 3.37 mmol.) and titanium silicon oxide nanopowder (42.89 mg, 0.306 mmol.) in water (5 ml) was stirred at 100°C for 2 h. After completion of the reaction as indicated by TLC, cooled to room temperature, ethyl acetate (30 ml) was added and filtered, washed the catalyst with additional ethyl acetate (10 ml). The filtrate was collected and the layers were separated, organic layer was concentrated under vacuum to get crude product, which was further purified by silica-gel column chromatography (hexane–EtOAc, 3:2) to afford 4a as a white color solid; m.p: 201-203 °C (lit. 202-204 °C); ¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.18 (s, 1 H), 7.65 (d, *J* = 6.4 Hz, 2 H), 7.48-7.50 (m, 1 H), 7.39-7.41 (m, 2 H), 7.25 (t, *J* = 8.4 Hz, 1 H), 6.99 (s, 1 H), 6.69-6.76 (m, 2 H), 6.13 (s, 1 H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.6, 147.6, 137.9, 133.4, 131.8, 130.3, 129.6, 128.7, 127.5, 127.3, 117.4, 114.7, 114.5, 63.7; MS (ESI): *m*/z = 259.1 (M + H); HRMS (ESI): m/z [M + H] calcd for C₁₄H₁₂N₂OCI: 259.0638; found: 259.0627.

Synthesis Of Various Mono-And Di-Substituted 2, 3-Dihydroquinazolin-4(1*H*)-Ones Derivatives

To verify the generality of this methodology, variety of electronically differing aldehydes were evaluated under the optimized reaction conditions (Table-3). Irrespective of the electron withdrawing or releasing substituent on aldehydes underwent reactions efficiently and afforded the desired products in good to excellent yields (Table-3, entry 1-11). Hetero aromatic aldehydes (Table-3, entry 12-15) also readily reacted giving desired products in high yields. More importantly, aliphatic aldehydes (Table-3, entry 16-18) were also reacted, and the corresponding products were isolated in good yields. Formation of the products was confirmed by comparing their physical data and ¹H NMR, ¹³C NMR, mass and HRMS spectroscopic data with those of authentic samples reported in the literature.

To investigate the effectiveness of this protocol, reactions of isatoic anhydride (1), aliphatic amines (Table-4, entry 1), aromatic amines (Table-4, entry 2-4) and aldehydes (2) were examined under optimized conditions. Aromatic and aliphatic amines were also found to be successful and afforded the corresponding disubstituted-2, 3-dihydroquinazolin-4(1H)-ones in high yields.

To extend the application of this methodology to synthesize spiro dihydroquinazolinones derivatives, reactions of isatoic anhydride, (1), ammonium acetate and isatin was also studied under optimized reaction conditions. We are delighted to find the desired spiro-2, 3-dihydroquinazolin-4(1H)-one (6) was obtained in good yields (Table-5).

Proposed Mechanism

Based on the literature reports ^[12,21] a plausible mechanism for the formation of 2,3dihydroquinazolin-4(1*H*)-ones is given in Scheme 2. Isatoic anhydride is activated by titanium silicon oxide nano powder (A), followed by the N-nucleophilic amine attacks on the carbonyl to form transition state B. Elimination of CO₂ from B leads to the formation of anthranilamide derivative C. Intermediate C reacts with aldehydes in the presence of titanium silicon oxide nano powder, which upon intramolecular cyclization afforded the final product 4. Titanium silicon oxide nano powder might activate the aldehyde through coordination with the oxygen of the carbonyl group which facilitates the subsequent nucleophilic attack by the nitrogen atom on the carbonyl carbon.

CONCLUSION

In conclusion, we have successfully developed for the first time titanium silicon oxide nanopowder catalyst as an efficient and recyclable catalyst for synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones by the one-pot three component condensation of isatoic anhydride, ammonium acetate or primary amines and various aldehydes in good to excellent yields. To the best our knowledge, application of titanium silicon oxide nanopowder is reported for the first time to carry out any organic transformation. The advantage of this methodology is avoiding use of organic solvents, ideal for large scale synthesis, ease of product isolation, and catalyst recovered up to four times without any significant impact on the yield of the products.

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SUPPLEMENTAL MATERIAL

Full experimental details, copies of ¹H and ¹³C NMR spectra, mass and HRMS data can be found via the "supplementary content" section of this article's webpage.

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Table 1. Optimization of reaction conditions.^a



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Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Yield $(\%)^{b}$	
	•			. ,		
1	10	1,4-Dioxane	100	2	93	
		,				
2	10	Ethanol	80	4	86	
3	10	CH ₃ CN	80	4	85	
4	10	THF	65	6	80	
5	10	Water	100	3	93	
6	5	Water	100	3	87	
7	20	Water	100	2	94	
8	No catalyst	water	100	6	< 10	
	-					

^a Reaction conditions: 1 (1.53 mmol), ammonium acetate (1.68 mmol), 2a (1.68 mmol),

and solvent (5 mL).

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^b Yield of isolated product.

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Entry	Cycle	Time (h)	Yield $(\%)^{b}$
1	Fresh	3	94
2	1st	3	94
3	2nd	5	93
4	3rd	5	91
5	4th	6	91

Table 2. Recyclability of the catalyst.^a

^a Reaction conditions: **1** (3.06 mmol), ammonium acetate (3.4 mmol), 4-chloro

benzaldehyde **2b** (3.4 mmol), and water (5 mL) at 100 $^\circ \text{C}$

^b Yield of isolated product.

Table 3 Synthesis of mono-substituted 2, 3-dihydroquinazolin-4(1H)-ones derivatives under the optimized conditions. ^a

Entry	Aldehyde (2)	Product (4)	Time	Yield
			(h)	(%) ^b
1	CHO CI 2a	O NH CI NH H H 4a	2	93
2	CI 2b		3	94
3	HO 2c		2	94
4	CHO OH 2d	O NH NH OH 4d	2	91
5	H ₃ CO 2e	O NH NH 4e OCH ₃	2	95





^a Reaction conditions: Isatoic anhydride 1 (3.06 mmol), ammonium acetate (3.4 mmol), aldehyde 2 (3.4 mmol), and water (5 mL) at 100 °C;

^b Yield of isolated product.

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Table 4. Synthesis of di-substituted 2, 3-dihydroquinazolin-4(1H)-ones derivatives under the optimized conditions.^a

Entry	Amine (3)	Aldehyde (2)	Product (5)	Time	Yield
				(h)	(%) ^b
1	CH ₃ NH ₂ 3a	CHO COOH	O N CH ₃ H HOOC 5a	2	91
2	NH ₂ Cl	CHO NO ₂ 20	OCI N H O ₂ N 5b	4	90
3	NH ₂ 3c	CHO N 2k		4	89
4	3d NH ₂	N CHO 2р	O N N H Sd	5	87

^a Reaction conditions: 1 (3.06 mmol),), aldehyde 2 (3.4 mmol primary amine 3 (3.4

mmol), and water (5 mL) at 100 $^\circ\text{C};$

^b Yield of isolated product.

Table 5. Synthesis of spiro-2, 3-dihydroquinazolin-4(1H)-one derivative under the optimized conditions.^a

Entry	Isatin	Product (6)	Time (h)	Yield (%) ^b
1		O NH NH NH O NH	6	90

^a Reaction conditions: Isatoic anhydride 1 (3.06 mmol), Ammonium acetate (3.4 mmol),

Isatin (3.4 mmol), and water (5 mL) at 100 °C;

^b Yield of isolated product.

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Scheme 1. Synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones catalyzed by titanium silicon oxide nanopowder.

R¹NH₂ or ______ Titanium silicon oxide nanopowder (10 mol %) R¹⁽H) *0 R2 Water 100 °C NH₄OAc 3 2

Scheme 2. Plausible mechanism for the formation of the 2, 3-dihydro quinazolinones





Figure 1. Examples of biologically active 2, 3-dihydroquinazolin-4(1*H*)-one derivatives.