Green and One-Pot Three-Component Synthesis of 2,3-Dihydroquinazolin-4(1H)-Ones Promoted by Citric Acid as Recoverable Catalyst in Water

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Abstract: Citric acid was used as green, non-toxic and reusable catalyst for the preparation of substituted 2,3-dihydroquinazolin-4(1H)ones in high purity and good yields *via* one-pot three-component reaction of isatoic anhydride with a variety of aldehydes and primary amines or ammonium acetate in water at 80 ºC.

Keywords: 2,3-Dihydroquinazolin-4(1*H*)-one, catalysis, citric acid, isatoic anhydride, multicomponent reaction.

INTRODUCTION

Within the repertoire of synthetic strategies available to organic chemists multi-component reactions (MCRs) are mostly advantageous because they allow the creation of several bonds in a single operation [1-3]. Also, reactions in water have attracted special attention in the recent years [4, 6] because water is the most abundant, cheapest and eco-friendly solvent.

Compounds with biological activity are often derived from heterocyclic structures [7]. Among them, quinazolinone derivatives have been found to possess a wide spectrum of pharmacological activities, e.g. as antibacterial [8], antifungal [9], and antitumor [10, 11] agents. Also, 2,3-dihydroquinazolin-4(1H)-ones are an important class of heterocycles with a wide range of pharmacological and biological activities. In view of their useful properties, a number of elegant studies have been directed toward the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives. There are two main methods: the one-pot multicomponent condensation of isatoic anhydride, amines and aldehydes [12-14] and the cyclocondensation of anthranilide with aldehydes [15-17]. Both of them are associated with several shortcomings such as toxic or expensive catalyst, harsh reaction conditions, non-recoverability of the catalyst, tedious work-up procedure, and low yields of products.

RESULTS AND DISCUSSION

In light of our recent success in the application of new catalytic systems for organic transformations [18-24] and aiming to overcome the above-mentioned limitations, we became interested to promote citric acid as non-toxic, very cheap, green and efficient catalyst for the synthesis of substituted 2,3-dihydroquinazolin-4(1H)-ones by the one-pot multicomponent condensation of isatoic anhydride, alde- hydes and primary amines or ammonium acetate in water at 80 ºC (Scheme **1** and Table **1**).

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All of the 2,3-dihydroquinazolin-4(1H)-ones were easily obtained by mixing an aldehyde, isatoic anhydride and a primary amine or ammonium acetate with citric acid (10 mol %) in water, then stirring this suspension at 80 ºC for the appropriate time. After completion of the reaction, the solid precipitate, which was formed, was filtrated and washed with water. Recrystallization of the crude product from water/ethanol gave highly pure compound.

In order to investigate the catalytic role of citric acid in the described system, isatoic anhydride was reacted with 4-chlorobenzaldehyde and aniline in the absence of the catalyst. Surprisingly, we observed that the corresponding 2,3-dihydroquinazolin-4(1H)-one was formed in only 50% yield after 7 h (Table **1**, entry 15), which means that citric acid has a relevant role in the process.

An important advantage of this catalytic system is the facile recovery of citric acid from the reaction mixture. At the end of the reaction, citric acid could be easily recovered by washing the reaction mixture by water, followed by evaporation of the water extracts, and used in a next run avoiding purification. The reaction described in Scheme **2** was repeated in other four runs, each time using recovered citric acid, whose activity did not show significant decrease.

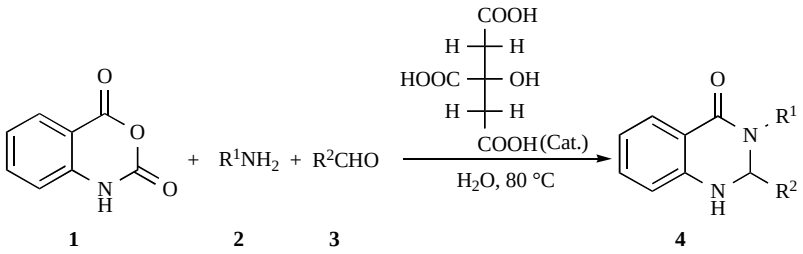
In conclusion, we have developed a green, versatile and facile approach to the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives *via* one-pot multicomponent condensation of isatoic anhydride, aldehydes and primary amines or ammonium acetate in water at 80 °C. The success of the method relies on the use of citric acid as an effective, non-toxic, cheap and recoverable catalyst. This protocol has the prominent advantages of environmental friendliness, relatively mild reaction conditions, low cost, simple operation, and reusability of the catalyst.

EXPERIMENTAL

General Methods

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The known products were charac-

1570-1786/11 $58.00+.00

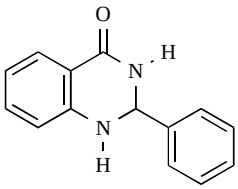
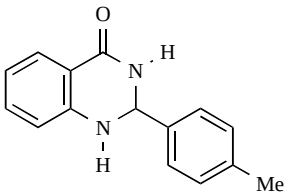
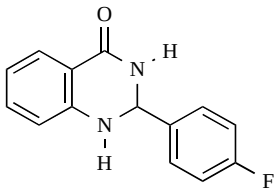
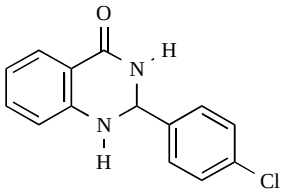
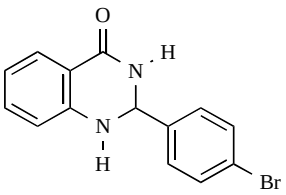


1 **2** **3** **4**

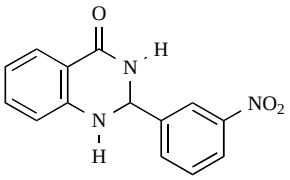
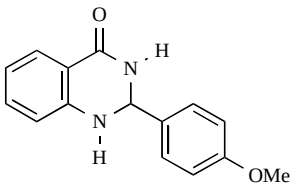
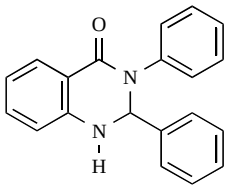
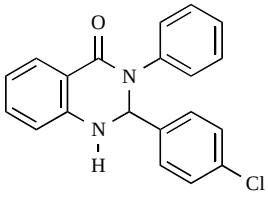
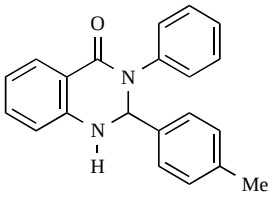
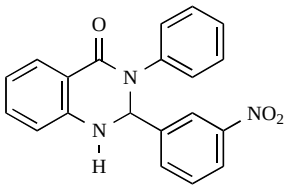
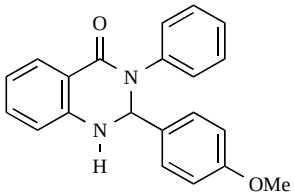
R^1= H, C_6H_5, *p*-$CH_3C_6H_4$, *p*-$(CH_3)_2CHC_6H_4$ R^2= Aryl

Scheme 1.

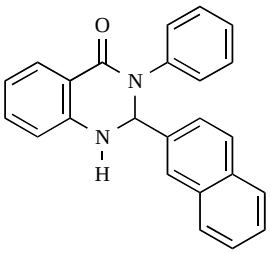
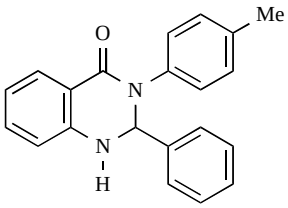
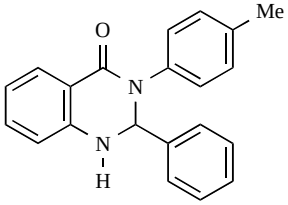
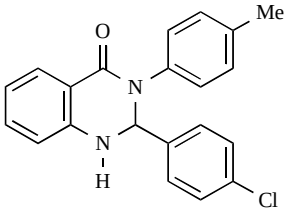
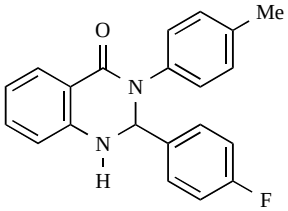
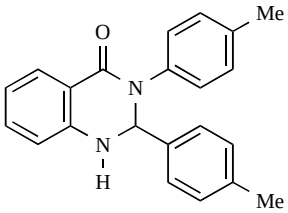
Table 1. Synthesis of 2,3-dihydroquinazolin-4(1H)-one Derivatives *Via* Condensation of Isatoic Anhydride, Aldehydes and Primary Amines or Ammonium Acetate in the Presence of a Catalytic Amount of Citric Acid at 80 °C in Water[a]

Entry	Product	Yield (%)[b]	Time (Min)	Mp (°C) Found	Mp (°C) Reported	Ref.
1	 **4a**	73	90	229-230	225-226	13
2	 **4b**	74	90	230-232	233-234	7
3	 **4c**	77	60	198-200	199-200	7
4	 **4d**	78	120	205-208	207-208	13
5	 **4e**	86	180	202-205	197-199	17

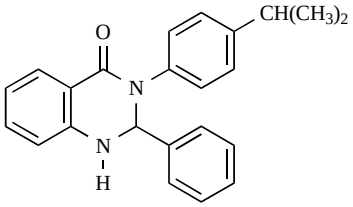
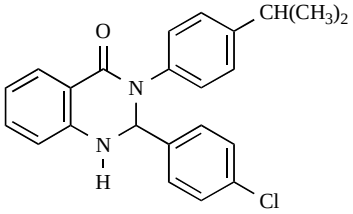
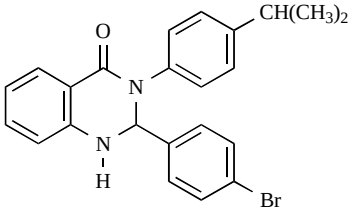
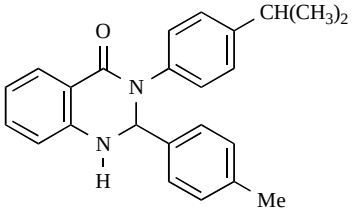
(Table 1). Contd…..

Entry	Product	Yield (%)[b]	Time (Min)	Mp (°C) Found	Mp (°C) Reported	Ref.
6	 **4f**	83	180	216-217	216-217	7
7	 **4g**	85	240	189-190	192-193	7
8	 **4h**	77	90	209-211	214-215	7
9	 **4i**	83	90	217-219	219-220	7
10	 **4j**	79	90	213-215	215-216	12
11	 **4k**	91	60	186-188	186-188	25
12	 **4l**	72	120	218-220	---	---

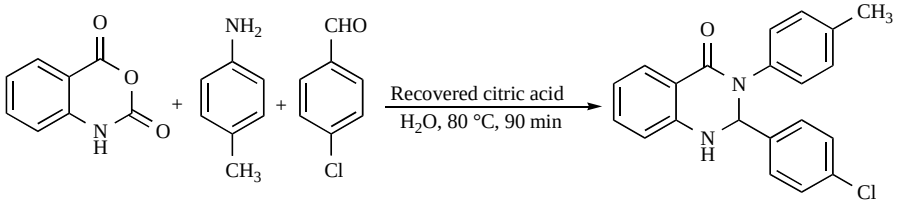
(Table 1). Contd…..

Entry	Product	Yield (%)[b]	Time (Min)	Mp (°C) Found	Mp (°C) Reported	Ref.
13	 **4m**	91	90	243-246	---	---
14	 **4n**	80	60	208-210	---	---
15	 **4n**	50	7h[c]	---	---	---
16	 **4o**	85	90	250-252	---	---
17	 **4p**	84	60	235-237	241-243	12
18	 **4q**	84	60	243-246	---	---

(Table 1). Contd…..

Entry	Product	Yield (%)[b]	Time (Min)	Mp (°C) Found	Mp (°C) Reported	Ref.
19	 **4r**	81	60	207-209	---	---
20	 **4s**	80	90	195-197	---	---
21	 **4t**	94	180	206-208	---	---
22	 **4u**	88	90	208-209	---	---

[a]Isatoic anhydride: aldehyde : amine : citric acid = 1 : 1 : 1.1 : 0.1 (mmol). [b]Crude isolated yield. [c]Reaction performed in the absence of catalyst.



Run No.	Yield
1	85
2	85
3	88
4	87
5	73

Scheme 2.

terized by comparison of their spectral (^{1}H NMR, and ^{13}C NMR) and physical data with those of authentic samples. Unknown compounds (**4l-o**,**q-u**) were identified by their ^{1}H and ^{13}C NMR spectra.

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

Citric acid (0.1 mmol) was added to the mixture of isatoic anhydride (1 mmol), primary amine or ammonium ace-

tate (1.1 mmol) and aldehyde (1 mmol) in water (5 mL). The mixture was heated at 80 ºC for the appropriate time (reaction progress was monitored by TLC). After completion of the reaction, the white solid product was filtered off and washed with water. To obtain high pure 2,3-dihydroquinazolin-4(1H)-one the crude product was crystallized from water/ethanol mixture (1:1).

Selected ^{1}HNMR and ^{13}CNMR Data

4l: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.71 (d, 1H, J= 7.6 Hz), 7.56 (s, 1H), 7.33-7.17 (m, 8H), 6.84 (d, 2H, J=8.4 Hz), 6.75-6.68 (m, 2H), 6.21 (s, 1H), 3.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.8, 159.6, 147.1, 141.3, 134.2, 133.1, 129.1, 128.4, 128.3, 126.8, 126.4, 117.9, 115.8, 115.3, 114.1, 72.8, 55.5 ppm.

4m: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.88-7.71 (m, 6H), 7.62-7.60 (m, 1H), 7.49-7.47 (m, 2H), 7.31-7.24 (m, 5H), 7.16-7.15 (m, 1H), 6.77-6.69 (m, 2H), 6.45 (s, 1H), 3.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.9, 147.0, 141.3, 138.5, 134.3, 133.2, 132.7, 129.1, 128.8, 128.5, 128.4, 127.8, 127.0, 126.9, 126.8, 126.5, 126.1, 125.0, 118.1, 115.8, 115.3, 73.3 ppm.

4n: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.71-7.58 (m, 3H), 7.37-7.24 (m, 6H), 7.12-7.10 (m, 4H), 6.75-6.68 (m, 2H), 6.22 (s, 1H), 2.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.9, 147.0, 141.3, 138.5, 134.3, 133.2, 132.7, 129.1, 128.8, 128.5, 128.4, 127.8, 127.0, 126.9, 126.8, 126.5, 126.1, 125.0, 118.1, 115.8, 115.3, 73.3, 21.0 ppm.

4o: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.71-7.60 (m, 2H), 7.37-7.10 (m, 9H), 6.75-6.70 (m, 2H), 6.26 (s, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.6, 146.9, 140.2, 138.5, 135.9, 134.3, 133.4, 129.6, 129.0, 128.9, 128.5, 126.7, 118.1, 115.8, 115.3, 72.6, 21.0 ppm.

4q: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.70-7.54 (m, 2H), 7.26-7.08 (m, 9H), 6.73-6.67 (m, 2H), 6.16 (s, 1H), 2.25 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.7, 147.0, 138.8, 138.3, 138.0, 135.7, 134.1, 129.6, 129.4, 128.4, 126.9, 126.5, 117.9, 115.9, 115.2, 73.1, 21.1, 21.0 ppm.

4r: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.72-7.65 (m, 2H), 7.37-7.18 (m, 10H), 6.74-6.68 (m, 2H), 6.23 (s, 1H), 2.84 (sep, 1H, J= 6.8), 1.16 (d, 6H, J= 6.8) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.7, 146.9, 146.6, 141.4, 139.1, 134.2, 128.9, 128.7, 128.4, 126.9,126.8, 126.4, 118.0, 115.9, 115.3, 73.0, 33.4, 24.3 ppm.

4s: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.71-7.67 (m, 2H), 7.38-7.16 (m, 9H), 6.74-6.69 (m, 2H), 6.27 (s, 1H), 2.85 (sep, 1H, J= 6.8), 1.16 (d, 6H, J= 6.8) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.6, 146.7, 140.4, 138.9, 134.3, 133.3 128.9, 128.8, 128.5, 127.5, 127.0, 126.4, 118.2, 115.9, 115.3, 72.3, 33.4, 24.3 ppm.

4t: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.73-7.66 (m, 2H), 7.51 (d, 2H, J= 8.4 Hz), 7.31 (d, 2H, J= 8.2 Hz), 7.22-7.18 (m, 5H), 6.73-6.68 (m, 2H), 6.24 (s, 1H), 2.85 (sep, 1H, J= 6.8), 1.16 (d, 6H, J= 6.8) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.5, 146.7, 146.6, 140.8, 138.9, 134.3, 131.8, 129.1, 128.5, 127.0, 126.4, 121.9, 118.2, 115.9, 115.4, 72.4, 33.4, 24.3 ppm.

4u: ^{1}H NMR (400 MHz, DMSO-D_6): δ = 7.72-7.60 (m, 2H), 7.26-7.09 (m, 9H), 6.72-6.66 (m, 2H), 6.17 (s, 1H), 2.86 (sep, 1H, J= 6), 2.21 (s, 3H), 1.17 (d, 6H, J= 6) ppm; ^{13}C NMR (100 MHz, DMSO-D_6): δ = 162.7, 146.8, 146.5, 139.2, 138.5, 138.0, 134.1, 129.4, 128.4, 126.9, 126.7, 126.3, 117.9, 116.0, 115.3, 72.8, 33.4, 24.3, 21.1 ppm.

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