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Journal of Applied Chemical Research
jacr.kiau.ac.ir

Journal of Applied Chemical Research, 11, 4, 38-45 (2017)

Tannic acid: A Green Catalyst for the Eco-friendly Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones under Solvent Free Conditions

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(Received 05 Mar. 2017; Final version received 26 Jun. 2017)

Abstract

A new, facile, cost effective, and eco-friendly protocol is reported for the synthesis of 2,3-dihydroquinazoline-4-(1*H*)-ones exploring tannic acid as a novel, inexpensive, and biodegradable catalyst. A variety of dihydroquinazolins were prepared from aromatic aldehydes and anthranilamide using catalytic amount of tannic acid under solvent free conditions. Operational simplicity, high yield, and high atom-economy are the important features of this protocol.

Keywords: *2,3-dihydroquinazoline-4-(1H)-ones**,** Tannic acid**,** Solvent free conditions**,** Eco-friendly protocol.*

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Introduction

Quinazolin derivatives are a class of fused heterocycles that have drawn much attention due to their potential biological and pharmaceutical activities [1], such as treatment of diabetes and obesity [2], anti-inflamatory [3], anagonist [4], insecticides [5], and antimicrobial activity [6].

These compounds can be easily oxidized to their quinazolin-4(3*H*)-one analogues, which are important biologically active heterocyclic compounds. Also, they found in some natural products [6,7].

There are considerable efforts have been made to explore new simple and direct approaches towards the construction of 2,3-dihydroquinazolin-4(1*H*)-ones. 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 aldehydes with anthranilamide in the presence of various catalysts like iodine [8], $Ga(OTf)_3$ [9], $[Bmim]PF_6$ [10], phosphoric acid [11], Amberlyst-15 [12], formic acid [13], bronsted acids [14], iridium [15], and sulfonic acid functionalized Wang resin [16].

Many of these methods however suffer from drawbacks, such as low yield, long reaction time, high temperature or tedious work-up condition. Some of them had to be performed in harmful organic solvent. Therefore development and introduction of environmentally benign, high yielding and clean synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones is still in demand.

The objective of the present study was the development of novel catalyst for efficient preparation of 2,3-dihydroquinazolin-4(1*H*)-ones. Tannic acid (Figure 1), a naturally occurring plant polyphenol, is composed of a central glucose molecule that some hydroxyl groups is protected with one or more galloyl residues, a natural and efficient catalyst which can easily be handle and removed from the reaction mixture by simple filtration [17]. In this work, we reported an efficient procedure for the preparation of 2,3-dihydroquinazolin-4(1*H*)-one derivatives through an one-step reaction between variously substituted aldehydes and anthranilamide under solvent free conditions in the presence of tannic acids as an efficient, natural, green, and inexpensive catalyst (Scheme 1).

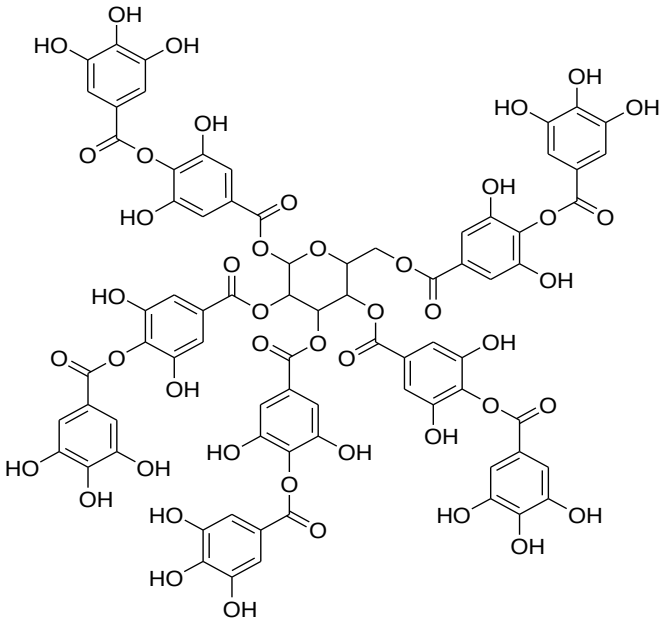
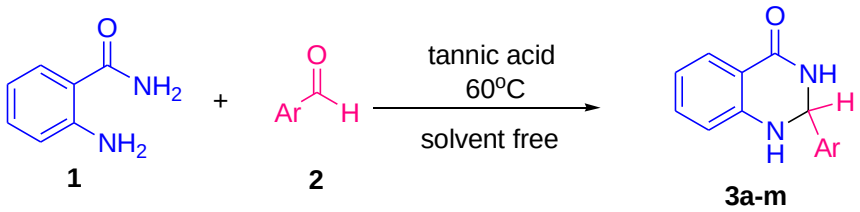


Figure 1. Structure of tannic acid.



Scheme 1. Tannic acid catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-ones under solvent free conditions.

Experimental

General

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison of physical and spectroscopic (IR and NMR) data with those of authentic samples. NMR spectra were recorded on a Bruker Avance DPX 400-MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a Jasco FT-IR 460 plus spectrophotometer. Melting points were determined in open capillaries with an Electro thermal 400 melting point apparatus. TLC was performed on Polygram SILG/UV 254 silica gel plates.

General procedure for synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives

A mixture of aldehydes (1.0 mmol) and anthranilamide (1.0 mmol) and tannic acid (0.04 g) stirred in an oil bath at 60 °C for the appropriated times. Completion of reaction time was indicated by TLC (eluent: n-hexane/ethyl acetate = 3/1). After completion of the reaction was cooled to room temperature and the crude solid product was dissolved in ethanol and filtered for separation of the catalyst. The solid product was purified by the recrystallization in hot ethanol. All the products were the characterized by comparison of their spectroscopic and physical data with the authentic samples.

*2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**3b**)*

M.p: 193-196 °C , IR (KBr, cm^{-1}): 3295, 1652, 1608, 1505, 1434, 796, ^{1}H NMR (400MHz), DMSO-d_6: δ = 3.76 (s, 3H, OCH_3), 5.72 (s, 1H, $H_{benzilic}$), 6.69 (t, 1H, *J* = 6.4 Hz, H_{Ar}), 6.75 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.41-7.45 (m, 2H, H_{Ar}), 7.62 (dd, 1H, *J* = 8.0 Hz, *J* = 1.6 Hz, H_{Ar}), 8.20 (s, 1H, NH).

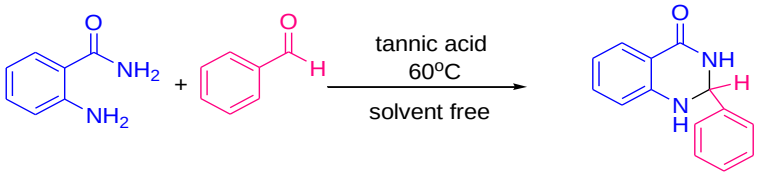
*2-(4-Methylphenyl)-2,3-dihydroquinazolin-4(1H)-one (**3c**)*

M.p: 230-232 °C, IR (KBr): 3415, 1654, 1506, 1401, 747 cm^{-1}. ^{1}H NMR (400MHz), DMSO-d_6: δ = 2.31 (s , 3H, $ArCH_3$), 5.72 (s, 1H, $CH_{Benzylic}$), 6.68 (t, 1H, *J* = 7.6 Hz, H_{Ar}), 6.75 (d, 1H, *J* = 8.4Hz, H_{Ar}), 7.25 (t, 1H, *J* = 7.06 Hz, H_{Ar}), 7.39 (d, 2H, *J* = 8.0Hz, H_{Ar}), 7.62 (dd, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz, H_{Ar}), 8.25 (s, 1H, NH).

Result and discussion

For more efficient preparation of 2,3-dihydroquinazolin-4(1*H*)-ones in order to minimize reaction time and amount of catalyst, reaction of benzaldehyde (1.0 mmol) and anthranilamide (1.0 mmol) was selected as model system to assess catalyst reactivity at different reaction temperatures. The best result was obtained by conducting the model reaction in the presence of 0.04 g tannic acid in 60 °C under solvent free conditions (Table 1).

Table 1. Optimization of temperature and amount of catalyst for synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones under solvent free conditions.



Entry	Catalyst (g)	Temperature (°C)	Time (min)	Yield (%)*
1	0.05	50	70	42
2	0.05	60	70	90
3	0.05	70	70	90
4	0.05	80	70	90
5	0.05	90	70	90
6	-	60	70	N.R
7	0.01	60	70	20
8	0.02	60	70	40
9	0.03	60	70	52
10	**0.04**	**60**	**70**	**89**
11	0.06	60	70	90

**yield refers to pure isolated product.*

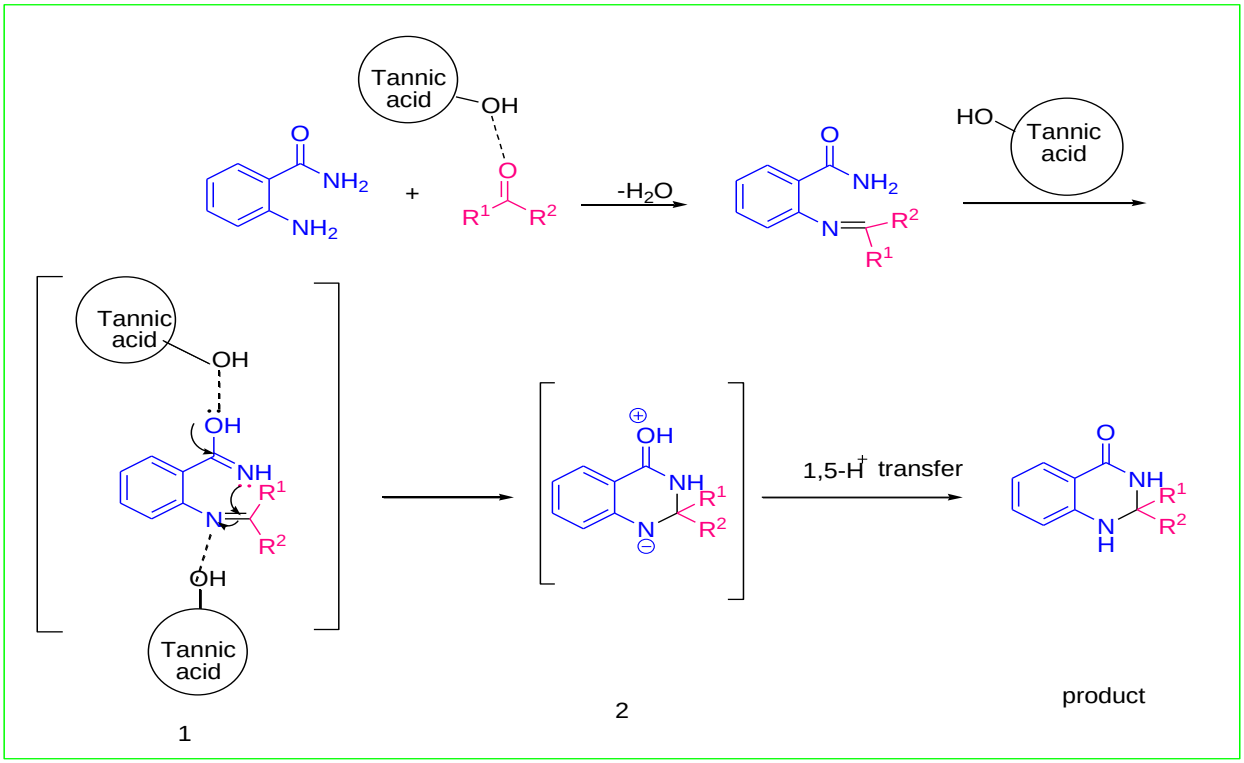
Generally, the cyclocondensation reaction proceeded well and afforded the desired products in Table 2. As shown in Table 2, the reaction was compatible with a variety of electron-donating and electron-withdrawing aldehydes.

Table 2. Synthesis of 2, 3-dihydroquinazolin-4(1*H*)-one derivatives under solvent free conditions.

Entry	Ar		Time (min)	Yield (%)	M.p. (lit.) [Ref.]
1	C_6H_5	**3a**	70	89	221-223 (218-220) [18]
2	4-OMe-C_6H_4	**3b**	45	89	193-195 (192-193) [18]
3	4-Me- C_6H_4	**3c**	50	90	230-232 (233-234) [18]
4	4-OH- C_6H_4	**3d**	80	70	279-282 (275-277) [19]
5	4-Cl- C_6H_4	**3f**	55	85	205-207 (205-207) [18]
6	3,4-$(OMe)_2$- C_6H_3	**3g**	55	88	209-211(211-212) [18]
7	4-Br- C_6H_4	**3h**	70	80	202-208 (198-200) [18]
8	3-Br- C_6H_4	**3i**	70	85	180-183 (184-185) [18]
9	2-Cl- C_6H_4	**3j**	55	90	208-209 (210-211) [18]
10	4-NO_2- C_6H_4	**3k**	75	78	198-200 (200-201) [21]
11	2-Furyl	**3l**	55	80	165-167 (165-167) [22]
12	2-Thiophene	**3m**	50	85	209-212 (213-215) [23]

The suggested mechanism is shown in scheme 2. The reaction of activated aldehyde with antheranilamide proceeds to produce imine intermediate. The amide functional group in

anthranilamide **1** could be formed using tautomerism phenomenon in presence of catalyst. Thus intermediate **2** could be prepared by intermolecular nucleophilic attack of the amide nitrogen on activated imine carbon, followed by a 1,5-proton transfer to yield the final 2,3-dihydroquinazolin-4(1*H*)-ones as products.



Scheme 2. Proposed mechanism for synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of tannic acid as catalyst.

Conclusion

In summary, we reported an eco-friendly three-component, one-pot method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives in the presence of tannic acid as economical, green and easily available catalyst. It is clear that tannic acid as an effective catalyst created a facile and useful method for synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via coupling of aromatic aldehydes and anthranilamide. Some important features of this procedure are including high yield, operational simplicity, comfortable purification, mild reaction conditions, and environmental benignity.

Acknowledgements

We grateful appreciate financial support from the Research Council of University of Sistan and Baluchestan.

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