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An Efficient Tartaric Acid Catalyzed Green Protocol for the Synthesis of 2, 3-Dihydroquinazolin-4(1H)-Ones in Aqueous Medium

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Abstract

In this work the catalytic application of tartataric acid is reported for the first time for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones in water at room temperature conditions at 28°C-30°C. The protocol offers various advantages such as mild reaction conditions, green reaction media, maximum yields, simple workup and use of safe and easily available catalyst.

Keywords: 2, 3-dihydroquinazolin-4(1H)-ones; Tartataric acid; Water; Room temperature conditions

Introduction

Quinazolinone belongs to an important class of heterocyclic compounds because of their wide range of medicinal properties. Quinazolinone compounds found to contain numerous activities such as antibacterial [1], bronchodilator [2], anti-inflammatory [3], antihypertensive [4], anticonvulsant [5], antimalerial [6], anticancer [7] and herbicidal [8].

Because of their important biological properties and huge applications, the development of new strategies for their preparation is of fundamental importance. The common method for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones is the condensation of 2-aminobenzamide with aldehydes or ketones. Various catalytic systems have been reported for the two-component synthesis of 2, 3-dihydroquinazolin-4(1H)-ones, which include aerosil silica-supported acidic ionic liquid [9], trifluoroethanol [10], supramolecular synthesis [11], $ZrCl_4$ [12], heteropolyacid-clay nanocomposite [13], amberlyst-15 [14] and sulfamic acid [15]. However, some of these methods have drawbacks in terms of the use of costly and excess amount of catalysts and higher temperature, long reaction time and lower yields. Hence, the development of a convenient and high-

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yielding eco-friendly protocol for the synthesis of 2, 3-dihydroquinazolin-4(1H)-one scaffolds is still warranted (FIG.1). The designed and development of convenient, operationally simple and eco-friendly strategies for the synthesis of biologically important organic and medicinal compounds are the most significant objectives in organic synthesis [16-20].

Solvents as reaction medium often account for the huge bulk of mass wasted during organic synthesis and industrial processes [21]. As a result, there has been more focus on the problem of replacing traditional toxic organic solvents with non-toxic greener ones. Water sometimes referred to as a benign 'Universal Solvent' as it is most abundant and safest solvent. Moreover, the water has exceptional properties as a solvent such as enhanced reactivity and selectivity caused by hydrophobic packing, polarity, and hydrogen bonding therefore it has attracted synthetic chemists to use it as an advantageous alternative to hazardous and expensive organic solvents [22-25]. Tartaric acid is a less expensive, safe, easy-to-handle and none toxic acid. Not much work has been done on the efficiency of tartaric acid as a catalyst in organic transformations.

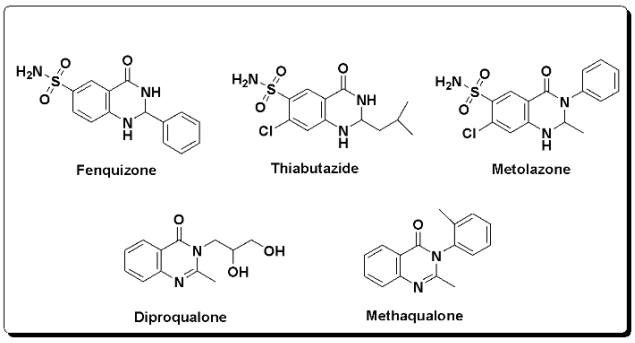


FIG. 1. **Marketed drugs having quinozolinone moiety in their structure.**

Materials and Method

All chemicals and solvents were purchased from commercial suppliers and used without further purification. The reactions and purity of the products were monitored by thin layer chromatography (TLC) using silica gel coated aluminum sheets. Melting points are determined on open capillary tubes and are uncorrected. NMR spectra were recorded on a Bruker advance II 400 NMR Spectrometer.

General procedure

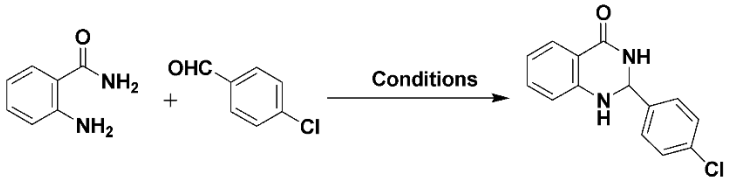
Synthesis of 2, 3-dihydroquinazolin-4(1H)-ones: L-Tartaric Acid (20 mol%) was added to a solution of anthranilamide (1, 1 mmol) and aldehyde (2, 1 mmol) in water (5 mL). The mixture was stirred at room temperature for 15-60 min. After reaction completion as monitored by TLC the reaction mixture was poured in ice cold water and the precipitated solid was collected by filtration. Then it was recrystallized from EtOH-H_2O to afford the pure product.

2-(4-hydroxyphenyl)-2, 3-dihydroquinazoline-4(1H)-one: White solid; mp 279-281°C; 1H NMR (400 MHz, DMSO-d6): δ=9.51 (s, 1H), 8.35 (s, 1H), 7.59-7.61 (m, 3H), 7.4 (d, J=7.6 Hz, 2 H), 7.23-7.27 (m, 1H), 7.15 (s, 1H), 6.74 (d, J=7.6 Hz, 1H), 6.74 (t, J=7.6 Hz, 1H), 5.75 (s, 1H). MASS (EI, 70 eV): m/z (%)=240 (M+, 14), 239 ([M-1]+, 22), 147(100), 120(65), 119(47), 92(40), 65(31).

Results and Discussion

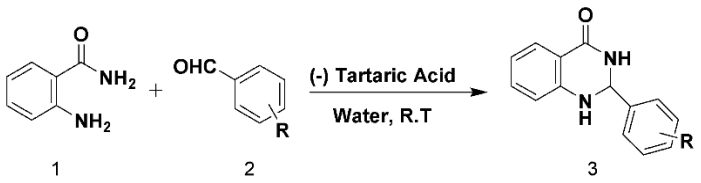
At the outset, the standard and model reaction conditions were established by the model reactions of 4-chloro benzaldehyde (1 equiv) with 2-aminobenzamide (1 equiv) in different solvents and in the presence or in the absence of acids (TABLE 1). The best results were obtained from reaction of these components in water at room temperature in the presence of 20 mol% of L-tartaric acid (TABLE 1, entry 4). Other acid catalysts under same reaction conditions afford poor to moderate yields (TABLE 1, entry 6-8) whereas in the absence of any acid catalyst no product was observed (TABLE 1, entry 5). To investigate the generality and scope of this protocol, a variety of other aromatic aldehydes (containing electron donating or withdrawing group on the ring) were reacted with 2-aminobenzamide. The activating nature of these groups on the aromatic ring had no significant effect on efficiency of the protocol. So we can say that the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones using tartaric acid as a catalyst under room temperature conditions is undeniably an effective protocol and far better to some other reported methods with respect to yields, reaction time, availability and non-toxicity of the catalyst (TABLE 2).

TABLE 1. **Optimization of the reaction conditions for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones.**



Catalyst (20 mol%)	Solvent/Conditions	Time (min)	Yield (%)
Tartaric acid	EtOH/RT	60	76
Tartaric acid	MeCN/RT	80	60
Tartaric acid	CH_2Cl_2/RT	120	40
L-Tartaric acid	Water/RT	15	88
None	Water/RT	180	Nil
Acetic acid	Water/RT	60	74
L-Pyroglutamic acid	Water/RT	60	45
Fumaric acid	Water/RT	60	55

TABLE 2. **Synthesis of 2, 3-dihydroquinazolin-4(1H)-ones.**



R	Time (min)	Yield (%)	M.P (°C)	
			Observed	Reported [9-15]
H	60	92	215-217	218-219
4-CH_3	15	90	223-225	225-227
4-OCH_3	30	92	181-183	180-182
4-OH	10	95	279-281	280-282
4-Cl	15	88	204-206	206-207
4-F	20	89	203-205	202-204
4-NO_2	30	88	197-199	198-200
4-N, N $(CH_3)_2$	40	87	225-227	226-228
3-Cl	20	90	204-206	202-204
3-OCH_3, 4-OH	45	85	225-227	228-230
3-OH	30	89	188-190	190-192
2-OH	25	90	223-225	220-222

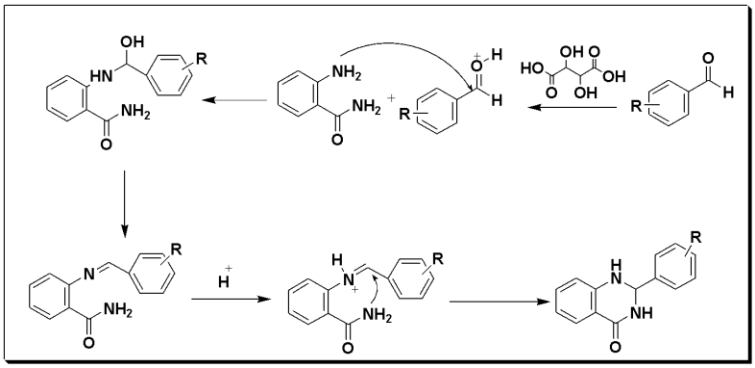


FIG. 2. **Proposed mechanism for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones.**

A plausible mechanism for the formation of 2, 3-dihydroquinazolin-4(1H)-ones is shown in FIG. 2. The carbonyl group of aldehyde is activated by protonation with the aid of tartaric acid and enhances the electrophilic character of aldehyde followed by nucleophilic attack of the amino group of 2-aminobenzamide at the activated carbonyl group which after dehydration affords imine intermediate. The imine intermediate after protonation from acid followed by cyclization gives 2, 3-dihydroquinazolin-4(1H)-ones as a final product.

Conclusion

A new protocol have been developed for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones promoted by tartaric acid as catalyst in water medium at room temperature reaction conditions. Maximum yields, cost effectiveness, short reaction time, easy workup are the merits of this protocol.

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