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An efficient synthesis of 2,3-dihydroquinazolin-4(*1H*)-ones: A natural approach

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ABSTRACT

An efficient and greener approach has been developed for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones using Lemon juice as a natural catalyst. It was prepared via condensation of 2-aminobenzamide with various types of aldehydes. The reaction proceeded in short period of time with excellent yields.

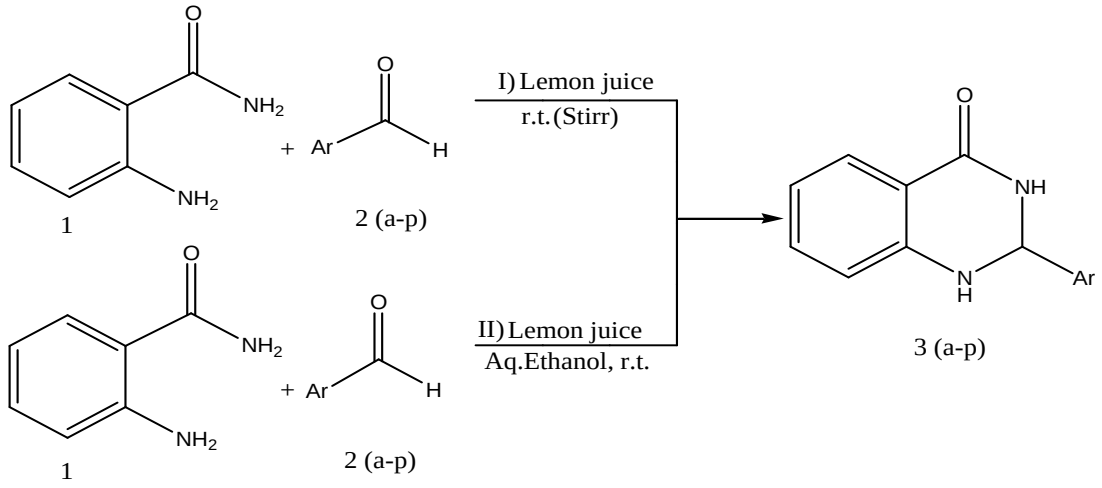
Keywords: 2,3-dihydroquinazolin-4(*1H*)-ones, Aldehydes, Natural Catalyst, 2-aminobenzamide.

INTODUCTION

Many synthetic chemists have made a great deal of effort to design sustainable and clean procedures to replace the classical synthetic methods [1]. The growing concern for the environment demands, the development of eco-friendly and economic processes wherein even less hazardous byproducts are not desirable. Numbers of organic reactions are reported in the literature by employing natural catalyst like clay [2, 3, 4], phosphates [5, 6, 7], etc. Today, there is a great demand for green and inexpensive acids instead of conventional mineral acids such as HF, H_2SO_4 and HCl in chemical processes. Mineral acids are corrosive and hazardous catalysts [8]. Fruit juice of *Citrus limon* as natural catalyst, due to its acidic nature (pH about 2-3) has been found to be a suitable replacement for various homogenous catalysts. Easy preparation and handling, separation and work-up processes, non-hazardous nature and easier waste material are among the most common characteristics that makes it green catalyst.

Quinazolinone and quinazolinedione derivatives are of considerable interest because of their wide range of pharmacological properties. [9–17] Several quinazolinone derivatives have also been reported to exhibit analgesic, anesthetic, antibacterial, anticonvulsant, antihypertensive, anti-inflammatory, antimalerial, antiparasitic, antiviral, diuretic, muscle relaxant, and sedative properties.[18] Furthermore, quinazolinone skeleton is frequently found in various natural products. Some examples include the anticancer compound trimetrexate, the sedative methaqualone, the alpha adrenergic receptor antagonist such as doxazosin and the antihypertensive agent ketanserin. Quinazolinones have also been reported as potent chemotherapeutic agents in the treatment of tuberculosis.[19,20] Particularly, 2,3 dihydroquinazolin-4(1H)-ones have antihyperlipidemic,[21] antiviral,[22] antiparkinsonism,[23] antimicrobial,[24] anti-inflammatory,[25] bronchodilator[26] and antihypertensive[27] activities. As a consequence of these biodynamic and pharmacological properties 2, 3-dihydroquinazolin-4(1H)-ones have made very attractive targets in synthetic chemistry in recent years.

Among the several synthetic methods for the preparation of 2, 3-dihydroquinazolin-4(1H)-ones, the most simplest and direct procedure involves the condensation of 2-aminobenzamide with aldehydes or ketones. Number of acid catalysts, such as *p*-tolunesulponic acid [28,29,30], p-TSA/NaHSO3,[31a] TiCl4/Zn,[31b] CuCl2,[31c] ionic liquid–water,[31d] TFA,[31e] ammonium chloride[31f] and chiral phosphoric acids [32], heteropolyacid (H3PW12O40),[33a] silica-bonded N-propylsulfamic acid[33b] and cellulose-SO3H [33c] have been reported to catalyze this reaction. Moreover, very recently malonic acid [34], 2-morpholinoethanesulfonic acid [35], Trichloroacetic Acid [36], Fumaric acid [37], L-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate (supported on silica gel) [38] have been utilized to carry out this transformation. Synthesis of 2, 3-dihydroquinazolin-4(1H)-ones is also achieved in the absence of catalyst using polyethylene glycol (PEG-400) as solvent [39], but with great sacrifice of time. Many of the reported synthetic methods are associated with the use of expensive reagents, multistep reaction, longer reaction time, high reaction temperature and tedious work-up procedures. Thus, development of a facile, atom-efficient, greener, eco-friendly method is highly desirable.



Scheme 1. Reaction Conditions: I) Method (A) Lemon juice, (Const. Stirr, r.t.)

II) Method (B) Lemon juice, Aq. Ethanol (50%), r.t.

As literature tells us that the quinazolinone derivatives were best synthesized in the presence of acid catalysts, we have investigated here an efficient and environmentally benign protocol for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones using lemon juice as natural acid catalyst. Lemon is very cheap and easily available material. In India it is also cultivated in house gardens. Main contents of the lemon extract are moisture (85%), carbohydrates (11.2%), citric acid (5-7%), protein (1%), vitamin-C (0.5%), fat (0.9%), minerals (0.3%), fibers (1.6%) and some other organic acids. As lemon juice is acidic in nature (pH about 2-3) and percentage of citric acid (5-7%) is more than other acids, it would have been worked as acid catalyst for condensation.

MATERIALS AND METHODS

General procedure for the synthesis of 2, 3- dihydroquinazolin-4(1H)-ones 3a-p:

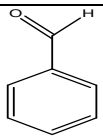
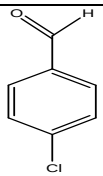
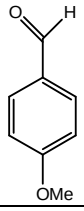
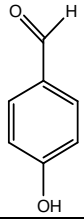
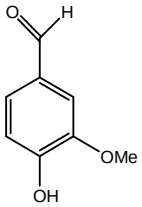
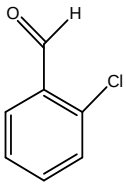
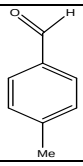
Method (A): To a mixture of 2- aminobenzamide 1 (1 mmol) and aldehyde 2 (1 mmol) taken in round bottam flask was added 5 mL Lemon juice and the reaction mixture was stirred at room tempreture for the time indicated in Table1. The progress of the reaction was checked by TLC (ethyl acetate:*n*-hexane, 1:9). After completion of reaction, the solid residue was washed with ethanol. The obtained solid was collected by filtration and purified by recrystallization from ethanol.

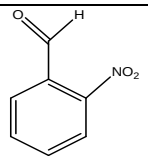
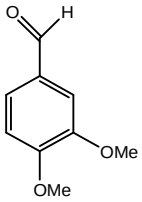
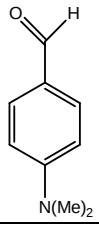
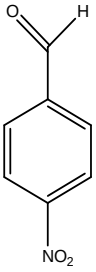
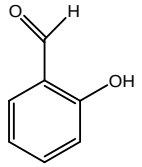
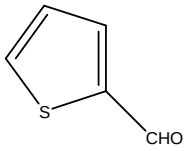
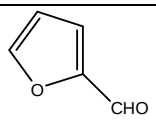
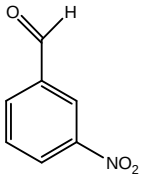
Method (B): To a solution of 2- aminobenzamide 1 (1 mmol) and aldehyde 2 (1 mmol) in 5 mL ETOH: H_20 (1:1), 2 mL Lemon juice was added and the reaction mixture was stirred for the time indicated in Table1. The progress of the reaction was checked by TLC (ethyl acetate:*n*-hexane, 1:9). After completion of reaction, solvent was removed

and the solid part was washed with ethanol. The obtained solid material was filtered by filtration and purified by recrystallization from ethanol.

All products are known compounds; their physical and spectroscopic data (IR and H^1NMR) were compared with those reported in the literature and found to be identical.

Table 1: Lemon Juice Catalyzed Synthesis of 2, 3-dihydroquinazolin-4(1H)-ones

Entry	Aldehyde (Ar)	Product	Time(Min.) A/B	Yield[a] (%) A/B	Mp ^{o}C
1		3a	10/08	85/94	220
2		3b	09/08	83/91	203
3		3c	09/07	84/93	181
4		3d	10/08	83/92	281
5		3e	09/06	84/ 96	220
6		3f	10/07	82/91	202
7		3g	07/04	84/92	224

8		3h	08/05	83/92	193
9		3i	08/06	86/95	213
10		3j	13/11	74/89	203
11		3k	08/05	84/93	202
12		3l	10/08	84/92	221
13		3m	45/41	81/90	213
14		3n	42/36	83/91	168
15		3o	09/07	81/92	193
16	4-CN-Ph-CHO	3p	08/06	83/94	250

a = isolated yield.

RESULTS AND DISCUSSION

We have demonstrated the condensation of 2- aminobenzamide with various types of aldehydes affording 2, 3-dihydroquinazolin-4(1H)-ones by using Lemon juice as natural acid catalyst. Here Lemon juice extract is not only worked as catalyst, but also as solvent medium. **(Method A)**

In our investigation, we observed the smooth applicability of protocol with various substituted aromatic aldehydes.

CONCLUSION

In the present investigation, we have developed an efficient and environmentally benign synthesis of 2, 3-dihydroquinazolin-4(1H)-ones at room temperature by applying Lemon juice as a natural acid catalyst. The efficiency of the methodology towards various substituted aldehydes is very good viz. fast reaction rate and the excellent yield.

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