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Vitamin C as a green and efficient catalyst in synthesis of quinoxaline derivatives at room temperature

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ABSTRACT

A simple, highly efficient and green protocol for the condensation of *o*-phenylenediamines with 1, 2-dicarbonyl compounds in the presence of vitamin C, as an inexpensive organocatalyst, is described. Using this method, a variety of quinoxaline derivatives with different electron releasing and electron withdrawing substituents, are produced in high to excellent yields at room temperature in ethanol. The remarkable features of this new protocol are high to excellent conversions, relatively short reaction times, and clean reaction profiles, simple and easy experimental and work-up procedures **.** Thus, we have been able to report another ability of vitamin C in organic chemistry synthesis, which has a less disastrous effect in the atmosphere and human survival.

Keywords*: Quinoxalins, Vitamin C, o-Phenylenediamines, 1,2-Dicarbonyl compounds, Organocatalyst.*

1. Introduction

Over the past few years, we have seen significant growth in research leading to different synthesis methods in order to prepare quinoxaline structures, since they have high applications in different fields such as organic and medicinal chemistry and material sciences. Although standard classical methods for the preparation of quinoxaline derivatives are so various, the environmentally friendly protocols aiming at reducing reaction times and increasing efficiency have been developed [1].

Quinoxaline derivatives have high biological activity [2-7] such as anticancer, anti-HIV, antifungal [8], and anti-inflammatory activities [9-12], anti-plasmodium falciparum agents [13], which provide vast applications in pharmacological science [14]. Furthermore, they are served in different branches such as cavitands [15], organic semiconductors [16], and dehydroannulenes [17]. Thus, finding more effective, cheaper and greener synthetic methods for the preparation of quinoxaline derivatives seems essential.

Various procedures have been reported for the synthesis of quinoxaline derivatives such as, tandem one-pot protocol [18], zirconium (IV) oxide chloride octahydrate [19], recyclable catalysts such as 1-(*n*-butyl)imidazolium tetrafluoroborate [20], *β*-cyclodextrin [21] and so on. Traditionally, quinoxaline derivatives are synthesized from *o*-phenylenediamines by condensing with 1,2-dicarbonyl compounds under refluxing conditions (2–12 h) in acetic acid or ethanolic medium and the obtained yields are between 35 and 85% [22]. Also, Lewis acid catalysts (I_2) [23] and employing microwave irradiation [24] have been used. However, the toxic nature of catalysts, long reaction times and harsh conditions, which were mentioned above, limit their use in sustainable chemistry. Zhang et al. [25] used PEG-400 as a green catalyst for the synthesis of quinoxaline derivatives, unfortunately reactions had taken longer time and, furthermore, harsh condition was also employed to accomplish the condensation. In context of methods which are claimed to be green for preparation of quinoxaline derivatives we can point to the following: $La(OAc)_3$/ water [26], polyvinylpyrrolidone supported triflic acid/ water/ r.t./ 1h [27], $(NH_4)_6Mo_7O_{24}$. $4H_2O$/ EtOH/ H_2O/ r.t. [28], citric acid/ EtOH, r.t./ less than 1 minute [29], and other methods have been gathered by Y. Nageswar and co-workers [1].

Herein, we report a rapid and green synthetic approach for the synthesis of quinoxaline derivatives from *o*-

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phenylenediamines and 1, 2-dicarbonyl compounds in the presence of nontoxic, cheap and edible vitamin C (Fig. 1) as a catalyst in ethanolic medium. To the best of our knowledge, vitamin C has not been used as a catalyst for quinoxaline synthesis and for any other organic reaction transformation. The present article is intended to introduce the vitamin C as an efficient and green catalyst for rapid one pot synthesis of quinoxaline at room temperature.

2. Experimental

The quinoxaline derivatives were prepared by general procedure of a condensation reaction: a mixture of *o*-phenylenediamine (1 mmol), 1,2-dicarbonyl compound (1 mmol) and a catalytic amount of vitamin C (11 mol%) in ethanol stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was filtered. The solid product was purified by recrystallization procedure in aqueous EtOH (70%) at 60°C. The synthesized compounds were characterized by spectral analysis and were compared with the authentic samples.

3. Results and Discussion

The reaction between *o*-phenylenediamine and benzil, as the model, was selected to be investigated in the presence of vitamin C for finding the optimized parameters of the reaction (Scheme 1).

To achieve the optimum amount of vitamin C, the reaction was carried out under different amounts of vitamin C, such as 0.01, 0.02, 0.03 and 0.05 g, in EtOH, as solvent. According to the results, 0.02 g (11 mol%) of the catalyst was sufficient to do efficient transformation for the model reaction (Table 1, entry 2). Furthermore, increment in the amount of vitamin C did not enhance the yield of the reaction. To understand the catalytic role of vitamin C in the condensation, the reaction was done in the absence of vitamin C, and demonstrated that the reaction was not completed even after 2 h at room temperature. The reaction was carried out in a variety of solvents instead of ethanol, in the optimized amount of vitamin C, (Table 1, entries 6-14) to find the best solvent for the reaction. Results showed ethanol (Table 1, entry 2), water (Table 1, entry 6) and acetonitrile (Table 1, entry 9) have a good performance for the model reaction with 98, 90 and 96% yield, respectively.

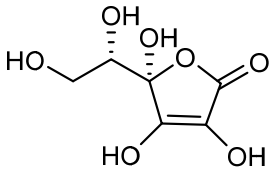


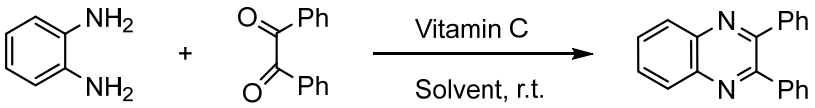
Fig. 1. Vitamin C (L-Ascorbic acid).

Polar solvents such as methanol and acetonitrile carry out this condensation in the presence of vitamin C similar to ethanol. Since the ethanol is accessible and greener in nature, thus it was selected as the choice of solvent in the rest of our study.

In order to determine the scope and versatility of the reaction, various *o*-phenylenediamines were condensed with benzil and its derivatives in the presence of catalytic amount of vitamin C (11 mol%) at room temperature (Table 2) in ethanol.

Table 1. Screened solvents for the condensation of *o*-phenylenediamine

Entry	Vitamin C (g)	Solvent	Time (min)	Yield (%)
1	0.01	EtOH	10	92
2	0.02	EtOH	2	98
3	0.03	EtOH	9	95
4	0.05	EtOH	15	92
5	--	EtOH	120	30
6	0.02	H2O	60	90
7	0.02	MeOH	2	90
8	0.02	H2O/EtOH	30	95
9	0.02	CH3CN	2	96
10	0.02	THF	2	76
11	0.02	DMF	4	70
12	0.02	Toluene	120	N.R.
13	0.02	DCM	60	75
14	0.02	DMSO	40	75



Scheme 1. The model reaction for optimization of the reaction parameters.

Table 2. Synthesis of quinoxaline derivatives using vitamin C at room temperature in ethanol.

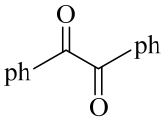
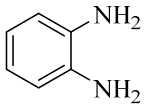
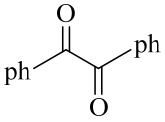
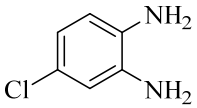
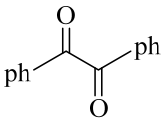
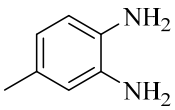
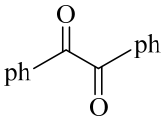
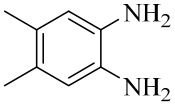
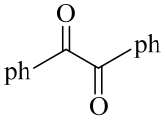
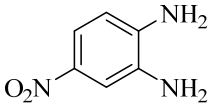
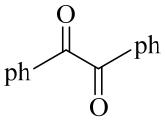
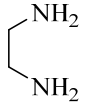
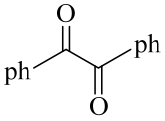
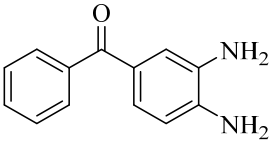
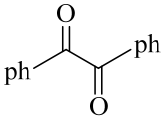
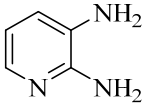
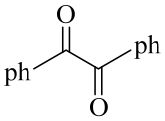
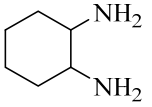
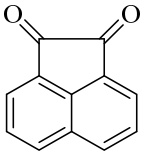
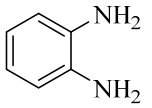
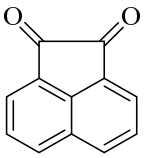
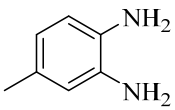
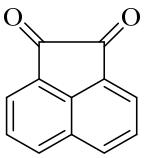
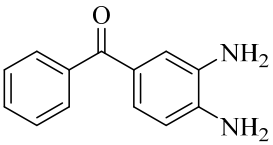
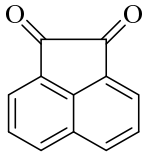
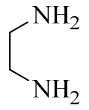
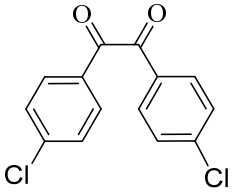
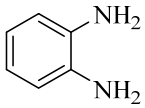
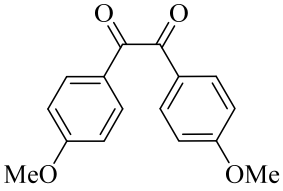
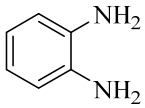
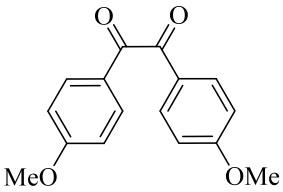
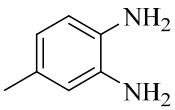
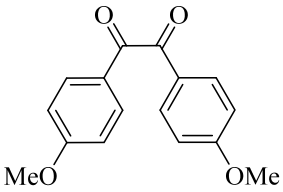
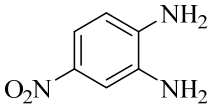
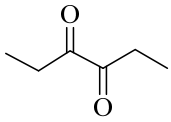
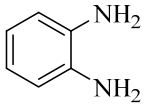
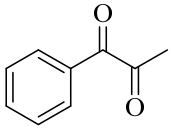
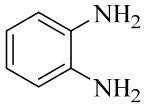
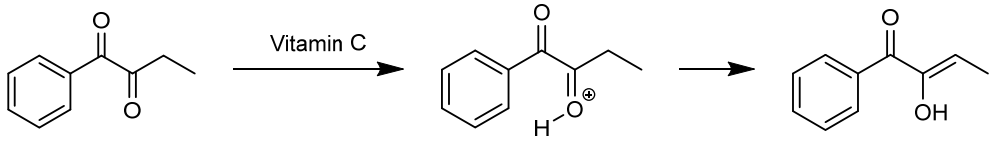
Entry	Diketone	Diamine	Time (min)	Yield[a] (%)	m.p. (°C)	Ref.
1			2	98	128–129	[30]
2			9	92	120–121	[30]
3			2	92	115–116	[30]
4			2	92	171-172	[30]
5			11	80	192–193	[30]
6			10	89	161-163	[31]
7			40	88	142-144	[32]
8			100	60	141–143	[33]
9			90	70	167-168	[30]
10			2	98	243–244	[30]
11			8	98	>300	[30]
12			5	98	245-247	[32]

Table 2. (*Continued*).

13			12	97	245-547	[32]
14			3	98	195-196	[34]
15			2	98	150–151	[30]
16			2	98	128-129	[30]
17			5	97	190-191	[35]
18			–	–	–	–
19			–	–	–	–

[a]Isolated yield.

The results showed, in general, *o*-phenylenediamines with both electron donating and withdrawing substitutions give the related products in excellent yields in short reaction times (Table 2, entries 2-5). Although *o*-phenylenediamines with withdrawing substitutions required longer reaction times for completion (Table 2, entries 2,5 and 7) and in some cases in lower yields (Table 5 and 7). Using 4, 4'-dimethoxybenzil, instead of benzil, led to excellent yields in shorter reaction times (Table 2, entries 15-17). Also, acenaphthylene-1,2-dione as a reactive α-diketone carried out the reaction rapidly with *o*-phenylenediamines and ethylenediamines and obtained the desired products in excellent yields (Table 2, entries 10-13). α- diketones with at least one acetyl group, such as hexane-3,4-dione and 1-phenylpropane-1,2-dione, did not undergo the reactions (Table 2, entries 18 and 19). It might be because of enolization of the acetyl group in the presence of vitamin C (Scheme 2).



Scheme 2. Enolization of α- diketones in the presence of vitamin C.

To determine the ability of vitamin C in preparation of quinoxalines, the efficiency of vitamin C was compared with previously reported catalysts in the literature, and results are presented in Table 3.

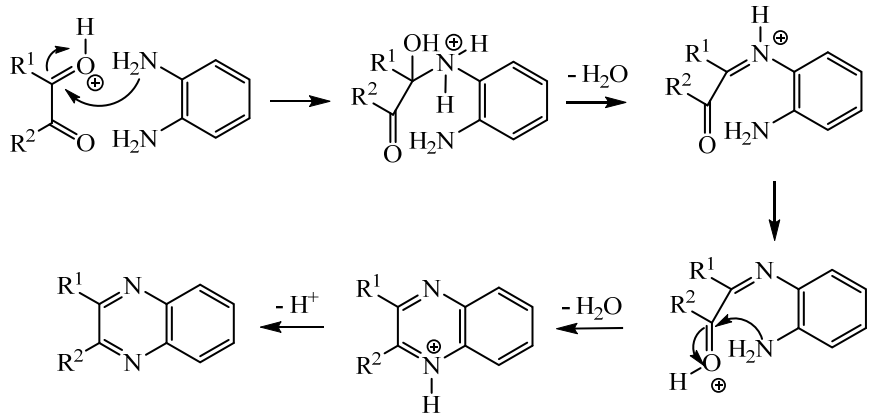
According to these data, vitamin C, as an inexpensive naturally occurring organocatalyst with low acidic strength, is able to catalyze the reaction between *o*-phenylenediamine and α- dicarbonyl compounds more efficiently in shorter reaction times at room temperature than most of the catalysts registered in Table 3.

On the base of results of this study, the following plausible mechanism might be suggested (Scheme3).

Table 3. Comparison between effeciency of vitamin C and some of catalysts used for preparation of 2,3-diphenylquinxaline.

Entry	Catalys	Solvent/Temp. (˚C)	Time (min)	Yield (%)	Ref.
1	PEG400 (0.15mmol)	Solvent-free /110˚C	10	100	[25]
2	Cellulose sulfuric acid (0.01g)	H_2O or CH_3CN /r.t.	60	93	[36]
3	Silica sulfuric acid (0.03g)	Ethanol/r.t	15	98	[37]
4	17%ZrO_2/4%Ga_2O_3/MCM-41 (0.2g)	CH_3CN /r.t.	120	97	[38]
5	Thiamine hydrochloride (2mol %)	Ethanol/r.t.	12	92	[39]
6	$Bi(OTf)_3$ (10mol%)	H_2O/r.t	5	97	[40]
7	HPA (1mol%)	Solvent-free /r.t.	5	98	[41]
8	Zn[(L)proline] (0.02g,10mol%)	Acetic acid /r.t.	10	95	[42]
9	Silica-bonded S-sulforic acid (0.1 g, 3.4 mol%)	H_2O:EtOH(30:70)/r.t.	5	96	[30]
10	5%Wt-TiO_2-SO_4 (0.1g)	EtOH/r.t	5	>99	[43]
11	Graphit (2mmol)	EtOH/r.t	60	92	[44]
12	$ZrOCl_2$-8H_2O(25mol%)	H_2O/Reflux	2	92	[45]
13	Vitamin C (0.02g)	EtOH/r.t	2	98	[a]

[a]Present work.



Scheme 3. The plausible mechanism for synthesis of quinoxaline derivatives.

4. Conclusions

Using vitamin C, as a naturally occurring organocatalyst, for preparation of quinoxaline derivatives provides mild reaction conditions, short reaction times, cost effective and a simple isolation procedure. Therefore, it has added an efficient and green method for the synthesis of quinoxalines at room temperature to existing methods in the literature.

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