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ORIGINAL PAPER

A novel catalytic one-pot three-component reaction of aldehydes, *o*-phenylenediamine derivatives and isocyanides for synthesis of 3,4-dihydroquinoxalin-2-amine derivatives in the presence of zirconium tetrachloride

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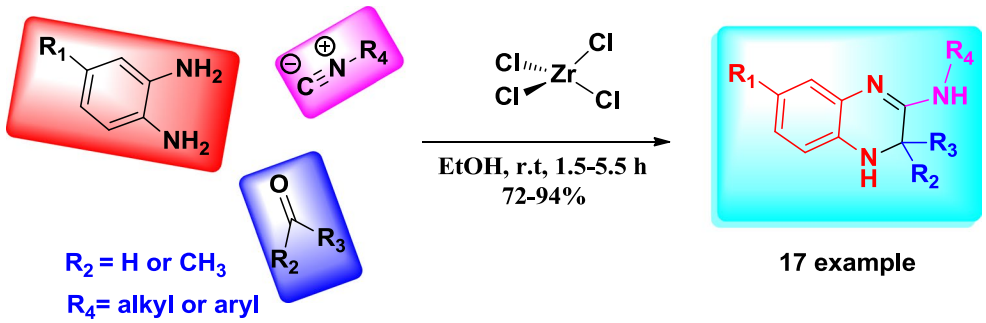
Abstract

A simple and efficient one-pot procedure for the synthesis of biologically interesting 3,4-dihydroquinoxalin-2-amine derivatives through a three-component condensation reaction of *o*-phenylenediamines, carbonyl compounds and isocyanides in ethanol at room temperature is described. In this work, unlike the other methods, aldehydes reacted as well as ketones in the presence of 10 mol% of zirconium tetrachloride as catalyst to afford good to excellent yields of products. This methodology is of great value because of its environmentally benign character, high yields, ease of handling and reliable for both aldehydes and ketones. The newly synthesized compounds were systematically characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

Graphical Abstract

A novel catalytic one-pot three-component reaction of aldehydes, *o*-phenylenediamine derivatives and isocyanides for synthesis of 3,4-dihydroquinoxalin-2-amine derivatives in the presence of zirconium tetrachloride



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Keywords Zirconium tetrachloride · Aromatic aldehydes · Multicomponent reaction · Isocyanides · 3,4-Dihydroquinoxalin-2-amines

Introduction

Since 2008 that Shaabani first reported isocyanide-based synthesis of 3,4 dihydroquinoxalin derivatives through a simple three-component condensation reaction of *o*-phenylenediamine derivatives, carbonyl compounds and isocyanides in the presence of catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) [1], the development of an

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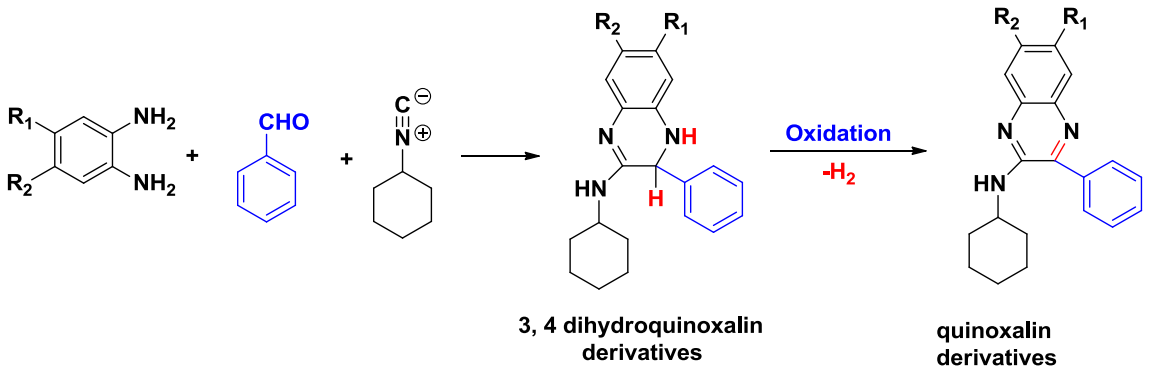
effective method for the synthesis of these compounds is still an important challenge. A number of research groups have modified synthesis of amino-substituted 3,4 dihydroquinoxalines and a variety of catalysts including ceric ammonium nitrate $(NH_4)_2Ce(NO_3)_6$ [2], ethylenediaminetetraacetic acid (EDTA) [3], Amberlyst-15 [4], Cellulose-SO_3H [5], silica gel-supported sulfuric acid [6], AIKIT-5 [7] and guanidinium-based sulfonic acid [8] have been employed for the improvement of this reaction. Among the quinoxaline derivatives, dihydroquinoxalines are attractive due to their interesting biological activity such as inhibiting of cholesteryl ester transfer proteins [9, 10] and anti-neuroinflammatory effect [6].

Despite remarkable efforts in exploring many catalysts, unfortunately, none of them consider the synthesis of 3,4-dihydroquinoxalin derivatives from aldehyde derivatives as a goal. Besides, most of these methods suffer from some drawbacks such as lack of generality, application of toxic reagents, effortful preparation of catalyst, tedious work-up, generation of undesired products and low yields for the aldehyde derivatives, so that some attempts to use aldehydes instead of ketones for gaining 3,4-dihydroquinoxalin derivatives of aldehyde were not successful. It can be related to oxidation capability of the title compound in the presence of applied catalyst [11, 12] (Scheme 1).

So, based on above facts and as a part of our research program to develop facile and efficient methods in organic synthesis [13–19], we report here the application of zirconium(IV) chloride, as a mild and efficient Lewis acid catalyst for the synthesis of aldehyde building blocks of 3,4-dihydroquinoxalin-2-amine derivatives in ethanol at room temperature (Scheme 2).

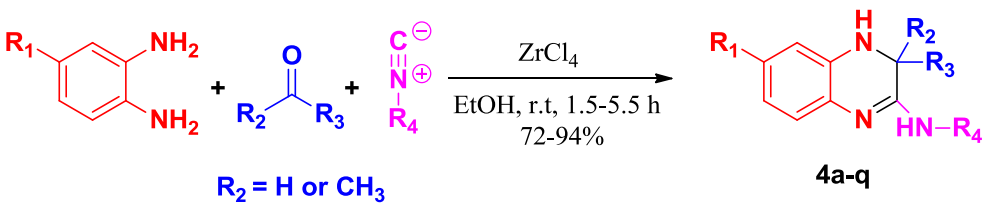
Quinoxaline derivatives are one of the oldest well-known heterocyclic compounds. They have attracted much attention due to a wide variety of biological activities and extensive application in electronic industries [20, 21]. Quinoxalines are also a common occurrence in many pharmacological active substances of natural or synthetic origin [22, 23]. They play an important role as the basic skeleton for a number of biologically active compounds such as antibacterial, antidiabetic, antiviral, anticancer and anthelmintic [24–26]. Furthermore, quinoxaline derivatives show very interesting photoelectron properties. They serve as dyes, semiconductors, electron luminescent materials and chemical switches [27–30]. Among the diverse derivatives of quinoxalines, dihydroquinoxalines have gained more attention due to its pharmacological activities. Some reports showed that they have antiviral effects against retroviruses such as HIV [31, 32]. Dihydroquinoxalines are also useful as growth promoter in meat-producing animals and as coccidiostats in poultry [33–35]. Some derivatives of these compounds displayed inhibitory effects on serine proteases such as factor Xa, thrombin and/or factor VIIa [36].

Among the vast range of methodologies for synthesis of quinoxalines, multicomponent reactions (MCRs) have been receiving much attention due to the convergent nature, superior atom economy, straightforward experimental procedures and wide range of industrial applications [37, 38]. In the past decades, multicomponent reactions isocyanide-based MCRs (IMCRs) are particularly valuable [39–41]. They were used



Scheme 1 Aldehyde's hydrogen involves in reaction path way [11, 12] and quinoxaline derivative is formed

Scheme 2 Synthesis of 3,4-dihydroquinoxalin-2-amine derivatives **4**



in many cycloaddition reactions and proved themselves that it is impossible to remove them from building blocks of modern multicomponent chemistry because they are able to react with both nucleophiles and electrophiles at the same carbon [42, 43].

It is well known that acid catalysts are essential for various chemical reactions in industrial heterocycle chemistry. The principles of "green chemistry" emphasize the usage of environmentally benign catalysts and chemicals to have minimal malignant effects on the environment. One of the most suitable strategies to design environmentally benign reaction systems is to perform the reaction in the presence of Lewis acid catalysts with strong acidic sites.

Moreover, in very recent years, because of the easy availability in earth crust [44] and low toxicity [45] Zr (IV) compounds, especially $ZrCl_4$ have received considerable attention in various organic reactions [46–48]. A strong coordination of Zr(IV) (charge to size ratio = 22.22 e^2 m^{-10}) [49], with the negatively charged parts of organic compounds in combination with the other advantages of $ZrCl_4$ such as stability and commercially available, low cost and low toxicity, makes it very useful and applicable reagent or catalyst in Lewis acid-catalyzed chemical reactions.

Recently, we reported the non-toxic and inexpensive zirconium tetrakis (dodecyl sulfate) [Zr $(DS)_4$] as a Lewis acid surfactant combined for synthesis of quinazoline derivatives [50]. Herein we report a direct $ZrCl_4$-catalyzed multicomponent isocyanide-based reaction for the synthesis of title compounds.

Results and discussion

Initially to optimize the reaction conditions, the one-pot condensation reaction of *o*-phenylenediamine (1 mmol), *p*-nitrobenzaldehyde (1 mmol) and cyclohexyl isocyanide (1 mmol) was selected as a pilot experiment. The reaction yield and time were monitored at room temperature under various conditions. The results are summarized in Table 1.

As it is shown in Table 1, the best result was obtained in the presence of 10 mol% of $ZrCl_4$ (entry 12). Furthermore, increasing the amount of catalyst decreases the yield of reaction (entry 13).

In addition, according to the results that are listed in Table 1, among the applied solvents the best results were obtained in ethanol (entries 3, 9 and 12). Only a trace amount of the product was detected in H_2O and mixture of EtOH/H_2O (entries 15 and 16). It may be attributed to hydrolysis of $ZrCl_4$ to hydrated hydroxyl chloride cluster. This conversion is rapid and virtually irreversible [51]. Moreover, the pilot reaction was proceeded in the absence of $ZrCl_4$ in EtOH at room temperature and the reaction was not performed even after elongation time up to 24 h (entry 23). This result establishes the crucial role of $ZrCl_4$ as an efficient catalyst for progress of the reaction. It is noteworthy to mention that performing the reaction in the presence of $Zr(DS)_4$ that was reported before by our group [50] as a good catalyst for the synthesis of quinazoline derivatives in this reaction produced quinoxaline instead of 3,4-dihydroquinoxalin derivatives (entry 17). Moreover, the capability of $Zr(DS)_4$ as catalyst for formation of 3,4-dihydroquinoxalin derivative was investigated in various solvents such as EtOH, THF, CH_3CN and *n*-hexane, and only trace amounts of products were detected (entries 18–22). It can be related to the formation of micelles in water related to other organic solvents. Furthermore, $Zr(DS)_4$ has more steric hinders than $ZrCl_4$ for interaction with other raw materials in the path of reactions.

In the next step, to establish the generality and efficiency of the presented method, we explored the reaction

Table 1 The one-pot condensation reaction between *o*-phenylenediamine (1 mmol), *p*-nitrobenzaldehyde (1 mmol) and cyclohexyl isocyanide (1 mmol) at room temperature and under various reaction conditions

Entry	Catalyst	Mol (%)	Solvent (3 mL)	Time (h)	Yield (%)[a]
1	$CaCl_2$[b]	5	EtOH	24	73
2	$CaCl_2$	10	EtOH	15	81
3	$CaCl_2$	15	EtOH	13	85
4	$CaCl_2$	20	EtOH	20	83
5	$CaCl_2$	15	MeCN	15	64
6	$CaCl_2$	15	H_2O	15	73
7	$CaCl_2$	15	EtOH/H_2O (2:1)	15	57
8	$NiCl_2$	10	EtOH	0.5	Undesired[c]
9	Bu_4NOH	5	EtOH	20	77
10	Bu_4NOH	10	EtOH	20	75
11	$ZrCl_4$	5	EtOH	4	81
12	**$ZrCl_4$**	**10**	**EtOH**	**1.5**	**94**
13	$ZrCl_4$	15	EtOH	5	90
14	$ZrCl_4$	10	MeCN	5	71
15	$ZrCl_4$	10	H_2O	5	23[d]
16	$ZrCl_4$	10	EtOH/H_2O (2:1)	5	32
17	$Zr(DS)_4$	2.5	H_2O	1	24
18	$Zr(DS)_4$	2.5	THF	1	Trace
19	$Zr(DS)_4$	2.5	*n*-hexane	1	Trace
20	$Zr(DS)_4$	2.5	EtOH	1	21
21	$Zr(DS)_4$	2.5	MeCN	1	Trace
22	$Zr(DS)_4$	2.5	EtOH/H_2O (2:1)	1	21
23	–	–	EtOH	24	< 15

[a]Isolated yield

[b]On the bases of our previous work [56]

[c]The color of the reaction mixture was turn to dark green, and it can be due to complex formation between *o*-phenylenediamine and Ni

[d]A gummy solid was obtained which makes the separation of products very hard

with various aromatic diamines, isocyanides, aliphatic, alicyclic and aromatic ketones and aldehydes under optimized conditions and obtained results are summarized in Table 2.

Except for **4n** and **4o**, all reactions were completed within 1.5–4 h and desired products were obtained in good to excellent yields (72–94%). As shown in Table 2, unlike the other methods, the high yields of products were obtained in case of aldehydes as well as ketones. Here it should be mentioned that, to the best of our knowledge this is the first time that the products of combining of aldehydes with *o*-aryl-diamines and isocyanides are reported (entries **4e**, **4f** and **4h**–**4j**). Furthermore, products of entries **4b**, **4d**, **4l** and **4m–p** are also new. In the view of the mechanism, the reaction is sterically controlled. In the other words, the reaction outcome of our method seems to be independent of the nature of the $\mathbf{R_2}$ groups, while it was deeply influenced by the nature of the used isocyanides ($\mathbf{R_4}$), showing to suffer from steric hindrance.

The feasibility of the model reaction was screened in the presence of different metallic salts. The obtained results are summarized in Table 3. The salts of lower coordination of metals such as copper, silver and zinc were shown higher yield (entries 1–3, Table 3), while high valence metals of Lewis acids such as ferric chloride and aluminum chloride are much less active. The results have indicated that the catalytic activity of metallic salts is not ascribed to its function of the so-called hard and soft Lewis acid. So, interaction of isocyanides and catalyst in term of acid base interaction may not the main factor in the mechanism of the reaction. This complies with other's reports [52–54].

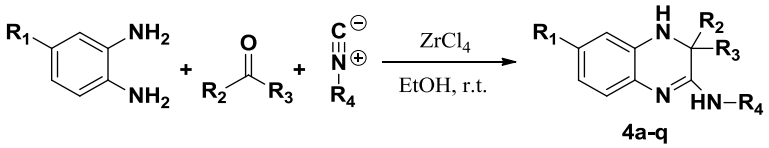
Table 3 Condensation reaction of model reaction in the presence of various hard and soft metallic salts

Entry	Metallic Cat.	Hard(H) or soft(S) acid	t(h)	Yields (%)[a]
1	CuCl	S	1.5	69
2	AgCl	S	1.5	58
3	$ZnCl_2$	Moderate	1.5	62
4	$FeCl_3$	H	2.5	Trace
5	$AlCl_3$	H	2.5	trace

The one-pot condensation reaction between *o*-phenylenediamine (1 mmol), *p*-nitrobenzaldehyde (1 mmol) and cyclohexyl isocyanide (1 mmol) at room temperature and under various reaction conditions

[a]Isolated yield were determined just for 3,4-dihydroquinoxalin derivatives

Table 2 Synthesis of 3,4-dihydroquinoxalin derivatives through a simple three-component condensation reaction of *o*-phenylenediamines, diverse carbonyl compounds and isocyanides in the presence of catalytic amount of $ZrCl_4$ under optimized conditions



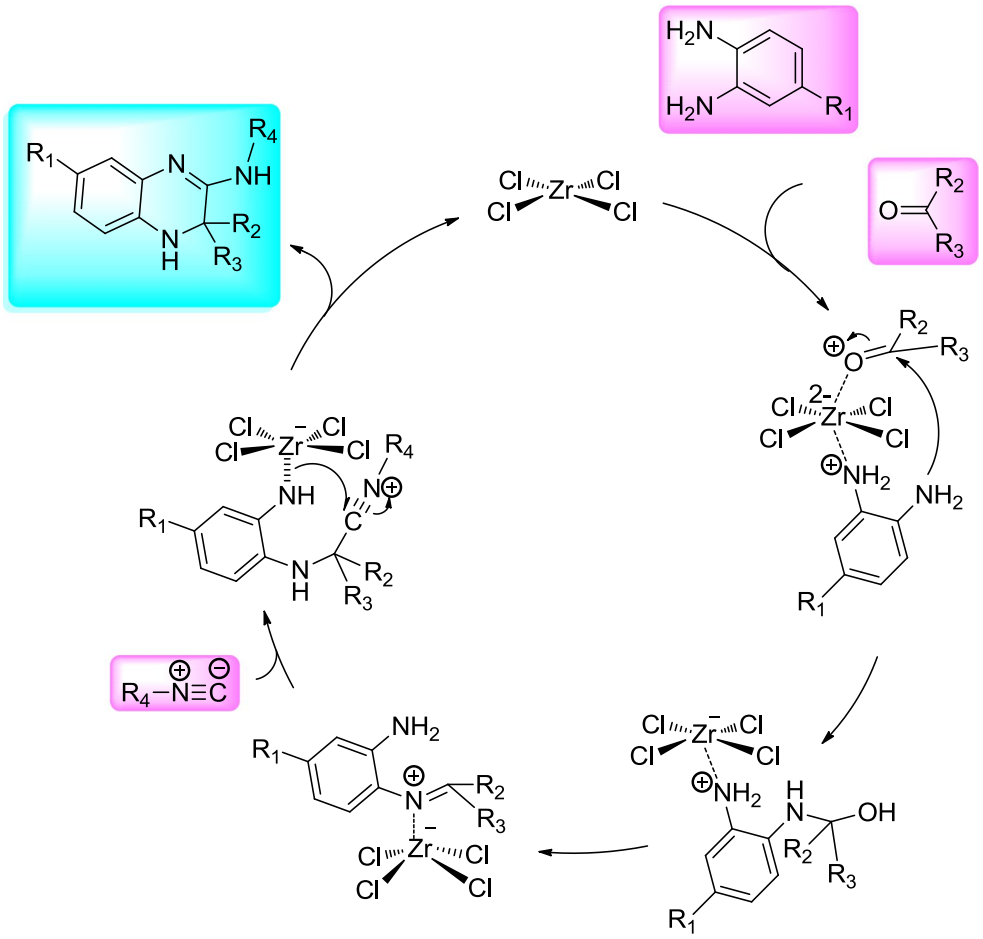
4a-q

Product	R_1	R_2	R_3	R_4	Time (h)	Yield (%)[a]
4a	H	CH_3	CH_3	C_6H_{11}	2	83
4b	H	CH_3	CH_3	$(CH_3)_3C$	2.5	79
4c	PhCO	CH_3	CH_3	C_6H_{11}	2	87
4d	PhCO	CH_3	CH_3	$(CH_3)_3C$	2.5	78
4e	H	H	4-NO_2–C_6H_4	C_6H_{11}	1.5	94
4f	H	H	4-NO_2–C_6H_4	$(CH_3)_3C$	2.5	87
4g	PhCO	H	4-NO_2–C_6H_4	C_6H_{11}	2	85
4h	PhCO	H	4-NO_2—C_6H_4	$(CH_3)_3C$	2.5	80
4i	H	H	4-F–C_6H_4	C_6H_{11}	2.5	90
4j	PhCO	H	4-F–C_6H_4	C_6H_{11}	3	85
4k	H	CH_3	C_6H_5	C_6H_{11}	3	86
4l	H	CH_3	C_6H_5	$(CH_3)_3C$	4	82
4m	PhCO	CH_3	C_6H_5	C_6H_{11}	3.5	80
4n	H	H	4-OMe–C_6H_4	C_6H_{11}	5	77
4o	H	H	4-OMe–C_6H_4	$(CH_3)_3C$	5.5	72
4p	H	H	4-NO_2–C_6H_4	$(CH_3)_3CCH_2(CH_3)_2C$	2	85
4q	PhCO	H	4-NO_2–C_6H_4	$(CH_3)_3CCH_2(CH_3)_2C$	2	87

[a]Isolated yields

With these findings in hand, we can have a second look at Table 2 that shows, moving from acetone (entries **4a**–**4d**) to 4-nitrobenzaldehyde (entries **4e**–**4h**) and 4-fluorobenzaldehyde (entries **4i**, **4j**), the reactions were completed at almost the same time and the corresponding products were obtained in comparable yields. In contrast, when the reactions were occurred with same diamines and carbonyl compounds in the presence of different isocyanides, with changing the isocyanide from cyclohexyl to 1,1,3,3-tetramethylbutyl and then *tert*-butyl the reactions needed more time and the corresponding yields were decreased. Moreover, the longest reaction times related to those reactions that aromatic ketones were used as carbonyl compounds (**4l, 4m**). Contrary to what one might expect, when the 4-nitro or 4-fluorobenzaldehyde was applied as carbonyl compounds the reaction was completed in shorter time than acetophenone. It can be attributed to steric hinders of carbonyl group that is coordinated to zirconium atom (Scheme 3). On the other hand, we cannot ignore the electronic factor in this reaction. When the reaction was performed with 4-methoxy derivative of benzaldehyde, the reaction time was increased while the yield was decreased (entries **4n** and **4o**). In fact, the data in Table 2 show that two factors play a crucial role in this reaction and directly affect the yields and rate: One is the nature of aldehydes, and the other one steric hinders of carbonyl groups.

Recently, on the basis of enantioselective catalytic property of $ZrCl_4$ a new coordination mechanism has been proposed by Fioravanti and Pellacani to explain the formation of obtained enantiopure products [55]. The factors that affect this reaction in terms of nature are very close to our reaction. In our case, although we have not established the mechanism of the reaction but, according to the obtained data from Table 2 we were convinced that the same pathway is occurred as well. So, a catalytic cycle to explain the $ZrCl_4$-catalyzed three-component reaction of phenylenediamine derivatives, carbonyl functional groups and isocyanides pathway performed on 3,4-dihydroquinoxalin-2-amine derivatives is proposed (Scheme 3). In this explanation, first, carbonyl compound and phenylenediamine were coordinated to zirconium tetrachloride. This coordination increases the electrophilicity of carbonyl group, and in the next step the reaction was followed by nucleophilic attack of free NH_2 of



Scheme 3 Proposed mechanism of the three-component reaction of phenylenediamine derivatives, carbonyl functional groups and isocyanides to performed 3,4-dihydroquinoxalin-2-amine derivatives

phenylenediamine to carbonyl group. In this step the rate of imine formation can be affected by steric hinders of $\mathbf{R_2}$ and $\mathbf{R_3}$ on carbonyl group. Furthermore, the nature of aldehyde-containing electron-withdrawing or electron-releasing group can change the electrophilicity of the carbonyl group.

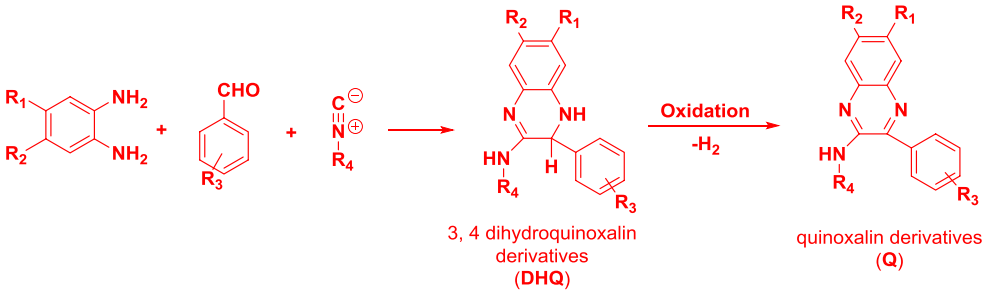
On the other hand, the good results for nitro- and fluorobenzaldehyde can be achieved due to the influence of the nitro and fluorine on the imine reactivity in the path of reaction. In fact, the resonance and inductive electron-withdrawing effects of NO_2 and F groups seem to be strong enough to increase carbon electrophilicity of imine for nucleophilic attack of isocyanides. Furthermore, it may be due to the increasing electrophilicity of carbonyl group in imine formation step. Finally, a favored intramolecular nucleophilic attack followed by proton exchange leads to the formation of 3,4-dihydroquinoxalin-2-amine derivatives **4**.

In this type of reaction with aldehydes, oxidation generally occurs and its major product is (**Q**). In the literature the researchers have produced the product (**DHQ**) but with toxic, expensive and hard making catalyst, whereas in our research we could synthesis the selective product (**DHQ**) without any oxidation with various aldehydes. Moreover, the used catalyst is inexpensive, commercially available and is not toxic Table 4.

Conclusion

In conclusion we have developed a more practical and reliable one-pot procedure for the synthesis of a wide range of 3,4-dihydroquinoxalin-2-amine derivatives in the presence of catalytic amount of zirconium tetrachloride. As compared to previous methods, excellent yields even for aldehydes, easy work-up, use of inexpensive and commercially available catalyst and good atom economy are the main advantages of the presented method. Furthermore, this method represents a simple and efficient procedure, uses mild reaction conditions and has general applicability. Besides, it avoids toxic catalysts and gives nearly quantitative yields without any by-products.

Table 4 Comparison of efficiency of various methods for the synthesis of 3,4-dihydroquinoxalin-2-amine (**DHQ**)



Entry	Catalyst, condition	Time	Yield (%)		Ref.
			DHQ	**Q**	
1	$ZrCl_4$, EtOH/r.t	1.5–5.5 h	72–94	–	This Work
2	MCM-48/$H_5PW_{10}V_2O_{40}$, EtOH/r.t	50–60 min	81–87	–	[61]
3	Guanidinium-based sulfonic acid, H_2O/r.t	60–85 min	73–89	–	[8]
4	MnO_2@cellulose–SO_3H or MnO_2@wool–SO_3H, EtOH/r.t	12–48 h	15–88	–	[60]
5	CeO_2-NPs, H_2O/80 °C	2–12 h	–	0–91	[59]
6	ZnO NPs, EtOH/reflux	55–70 min	–	87–96	[11]
7	CSA, EtOH/r.t	3 h	80–87	–	[5]
8	Silica gel-supported sulfuric acid, EtOH/r.t	3–4 h	Not Reported[a]		[6]
9	Amberlyst-15, EtOH/r.t	2–3 h	Not Reported[a]		[4]
10	EDTA, H_2O/80 °C or r.t	3 h	20	–	[3]
11	DBU or DABCO, toluene/80 °C	4 h	–	45–91	[58]
12	$Fe(ClO_4)_3$, CH_3CN/reflux	2 h	–	91–93	[12]
13	CAN, EtOH/r.t	3 h	Not Reported[a]		[2]
14	HCl, MeOH/r.t/under Ar	18 h	–	33–54	[57]

[a]The method does not performed for aldehydes

Experimental

Chemicals and apparatus

Reagents and solvents were purchased from Merck, Fluka or Aldrich and were used without further purification. Melting points were determined in capillary tubes in an Electrothermal 9100 apparatus and uncorrected. The progress of the reaction and the purity of compounds were monitored by TLC analytical silica gel plates (Merck 60 F250). IR Spectra: PerkinElmer Spectrum RXI. FT-IR apparatus. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Chemical shifts are given as δ values against tetramethylsilane as internal standard, and J values are given in Hz. Microanalysis was performed on a PerkinElmer 240-B microanalyzer.

Typical procedure for synthesis of *N*-cyclohexyl-3-(4-nitrophenyl)-3,4-dihydroquinoxalin-2-amine (4e)

To a solution of 1,2-phenylenediamine (0.2 mmol), 4-nitrobenzaldehyde (0.2 mmol) and cyclohexylisocyanide (0.2 mmol) in 1 mL of ethanol was added zirconium tetrachloride (0.02 mmol). The resulting mixture was stirred for 1.5 h at room temperature. The reaction progress was monitored by TLC (EtOAC/*n*-hexane 5: 2). After completion of the reaction, the product was precipitated by addition of 10 mL of water and stirring the mixture for 3 h at 4 °C. Then after, the products **4e** were collected by filtration, washed with 5% sodium hydroxide solution and distill water, dried at room temperature, and the residues were recrystallized from ethanol to afford the pure products *N*-cyclohexyl-3-(4-nitrophenyl)-3,4-dihydroquinoxalin-2-amine **4e** in excellent yield (0.065 g, 94%). Yellow crystals, mp 199–202 °C. IR (KBr, cm^{-1}): 3247, 2912, 2831, 1619, 1500, 1446, 1311. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11–1.74 (10H, m, $5CH_2$ of cyclohexyl), 3.17 (1H, s, CH of cyclohexyl), 3.52 (1H, s, NH), 5.69 (1H, s, CH–Ar), 6.71 (1H, s, NH-cyclohexyl), 6.74–7.08 (4H, H_{arom}), 7.65 (2H, H_{arom}), 8.22 (2H, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.80, 26.72, 32.50 (carbons of cyclohexyl), 51.50 (carbon of cyclohexyl), 57.19 (CH–Ar), 116.99, 122.68, 123.82, 125.75, 125.92, 128.16, 134.0, 139.96, 143.15, 143.52 (C_{arom}), 147.17 (N = C–NH). Anal. calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99%. Found: C, 68.51; H, 6.37; N, 15.95%.

Supporting information available

Full experimental detail, IR, ^{1}H and ^{13}C NMR spectra for compounds **4a–q**. This material can be found via the "Supplementary Content" section of this article's webpage

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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