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Efficient one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from aromatic aldehydes and their one-pot oxidation to quinazolin-4(3*H*)-ones catalyzed by $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$: Investigating the role of the catalyst

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ABSTRACT

An efficient and novel synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones via one-pot, three-component reaction of isatoic anhydride, primary amines and aromatic aldehydes catalyzed by $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ under solvent-free conditions is described. Oxidation of these 2,3-dihydroquinazolin-4(1*H*)-ones to their quinazolin-4(3*H*)-ones was also successfully performed in the presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$. This new method has the advantages of convenient manipulation, short reaction times, excellent yields, very easy work-up, and the use of commercially available, low cost and relatively non-toxic catalyst. The role of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ was also investigated in these transformations.

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1. Introduction

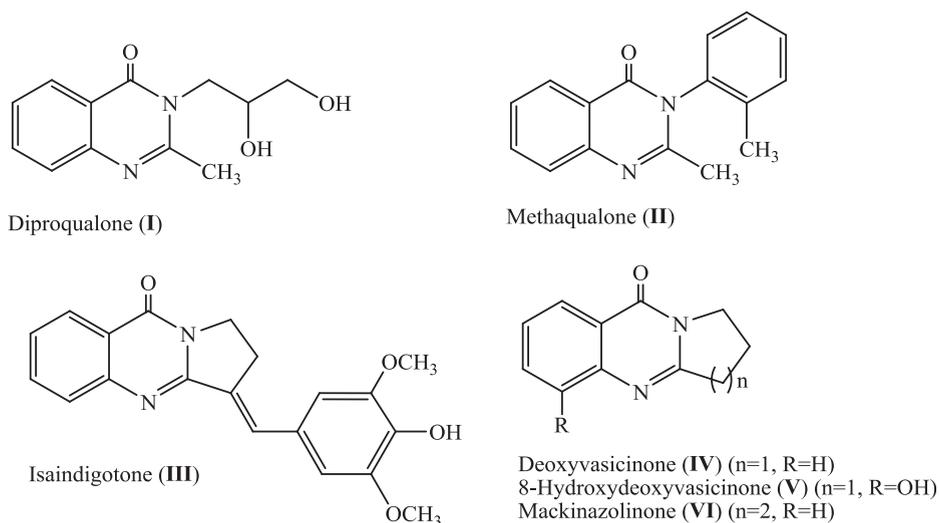
The development of efficient and selective synthetic transformations in one operation using readily available, inexpensive and environmentally-benign catalysts and reagents is of great interest in modern organic synthesis [1]. Therefore, in recent years, synthetic chemists have directed their researches toward the green synthesis. 2,3-Dihydroquinazolin-4(1*H*)-ones are important heterocyclic compounds that exhibit a broad range of pharmaceutical activities including antifertility, antibacterial, antitumor, antifungal, and also as a mono amine oxidase inhibitor [2–4]. Moreover, 2,3-dihydroquinazolin-4(1*H*)-one derivatives are the key intermediate for the synthesis of quinazolin-4(1*H*)-one compounds. Due to the significant interest in these heterocyclic compounds, a number of

methods for their synthesis have been developed with varying degree of success but with some limitations [5–13].

2,3-Disubstituted quinazolin-4(3*H*)-ones are also important building blocks in the synthesis of many natural products which display a variety of biological and pharmaceutical activities [14–16]. Known examples of 2,3-dihydroquinazolin-4(1*H*)-one drugs are diproqualone **I** which is used for the treatment of inflammatory pain associated with osteoarthritis, and methaqualone **II** which has antimalarial effect and currently being used for the assessment of the abuse liability of sedative hypnotic drugs [16] (Scheme 1). Furthermore, quinazoline alkaloids are an important class of natural products which possess biological effects. Among them, pyrrolo[2,1-*b*]quinazoline alkaloids such as isaindigotone **III**, deoxyvasicinone **IV** and 8-hydroxydeoxyvasicinone **V** exhibit anti-inflammatory, antimicrobial and antidepressant activities. The related alkaloid mackinazolinone **VI** possesses a broad spectrum of pharmacological activities [17] (Scheme 1). In accordance with the significance of quinazolin-4(3*H*)-ones, several

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Scheme 1. Structure of some quinazoline-based drugs.

synthetic methods have been developed for the construction of this kind of fused heterocycles from suitable precursors [18–29].

In recent years, Bi(III) salts have attracted the attention of synthetic organic chemists as effective catalysts because of their low toxicity, ease of handling, low cost and relative insensitivity to air and moisture [30–32]. As a part of our continuing research on the development of environmentally friendly synthetic methods of important organic compounds [33–39] and also on the application of Bi(III) salts in organic synthesis [31,40–45], we would like to report a new, efficient and highly selective one-pot synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1H)-ones and their one-pot oxidation to quinazolin-4(3H)-ones using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ under solvent-free conditions (Scheme 2).

2. Experimental

2.1. General

Melting points were obtained by Stuart Scientific SMP2 apparatus and are uncorrected. Yields refer to isolated products. IR spectra were recorded on FT-IR Nicolet 400D. ^1H and ^{13}C NMR (500 and 125 MHz) spectra were recorded on a Bruker-Avance AQS 500 spectrometer. Mass spectra

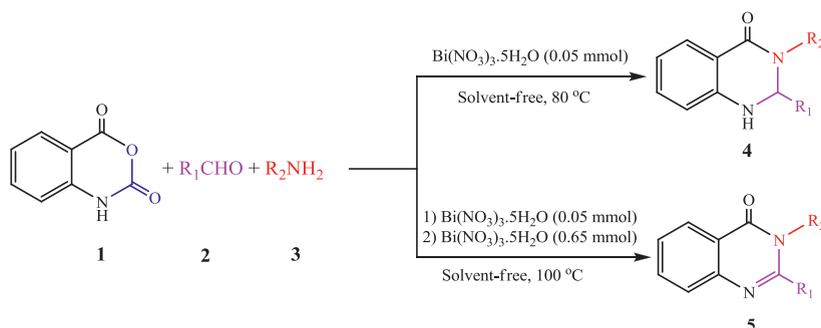
were obtained on a platform II spectrometer from Micromass; EI mode at 70 eV. Elemental analysis was performed on LECO, CHNS-932. All products were characterized by their physical and spectral data.

2.2. General procedure for the synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1H)-ones

To a mixture of isatoic anhydride (1.1 mmol), aromatic aldehyde (1 mmol) and amine (1 mmol), $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (0.05 mmol) as catalyst was added. The mixture was heated at 80 °C for the appropriate time. The progress of the reaction was monitored by TLC (ethyl acetate/*n*-hexane, 1:3). After completion of the reaction, hot ethanol (15 mL) was added and the catalyst was removed by filtration. The pure 2,3-disubstituted 2,3-dihydroquinazolin-4(1H)-one was obtained by recrystallization from ethanol.

2.3. General procedure for the synthesis of 2,3-disubstituted quinazolin-4(3H)-ones

After completion of the reaction for producing 2,3-disubstituted 2,3-dihydroquinazolin-4(1H)-one (4), $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (0.65 mmol) was added to the reaction mixture. The mixture was heated at 100 °C for the appropriate time. The reaction progress was monitored



Scheme 2. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones and quinazolin-4(3H)-ones.

by TLC (ethylacetate/*n*-hexane, 1:5). At the end of the reaction, hot ethanol (15 mL) was added and the mixture was filtered. The pure 2,3-disubstituted quinazolin-4(3*H*)-one was obtained by recrystallization from ethanol.

3. Results and discussion

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

Initially, as a model reaction, the three-component reaction of isatoic anhydride, ethyl amine and 4-chlorobenzaldehyde in the presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ was investigated under various conditions (Table 1). Different reaction temperatures and molar ratios of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ and reagents were examined. The best yield of the desired product **4a** was obtained by carrying out the reaction with 1.1:1:1:0.05 of isatoic anhydride, ethyl amine, 4-chlorobenzaldehyde and $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ at 80 °C for 1 h (Table 1, entry 3).

With these optimized conditions in hand, the reaction of isatoic anhydride with a wide range of structurally varied aldehydes and amines were examined (Table 2). Aromatic aldehydes containing various electron-donating and electron-withdrawing groups underwent the conversion smoothly to furnish the corresponding 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones in excellent yields (90–97%). It is important to note that the electronic properties of the substituents on the aromatic aldehydes had no obvious influence on the yields and reactions times. Heteroaromatic aldehydes such as 2-thiophenecarbaldehyde (Table 2, entries 13 and 21) and 2-pyridinecarbaldehyde (Table 2, entry 14) and also α,β -unsaturated aldehyde such as cinnamaldehyde (Table 2, entry 15) afforded the desired products in high yields. The experimental procedure for these transformations is remarkably simple and requires no toxic organic solvents. After completion of the reaction, the pure product was

conveniently obtained by recrystallization from ethanol. Owing to the mild reaction conditions, several functional groups such as NO_2 , CN, OMe and C=C bond were found to be compatible. All these results clearly showed the efficiency of this catalytic system in the synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones.

3.2. Synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones

It is noteworthy that in the synthesis of 2-(4-chlorophenyl)-3-ethyl-2,3-dihydroquinazolin-4(1*H*)-one **4a**, the yield of the product was reduced by increasing the temperature and or by increasing the amount of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (Table 1, entries 4–10). Under these conditions, in addition to **4a**, 2-(4-chlorophenyl)-3-ethylquinazolin-4(3*H*)-one **5a** was also produced. Encouraged by this result, we decided to prepare 2,3-disubstituted quinazolin-4(3*H*)-ones **5** by the reaction of isatoic anhydride **1** with aldehydes **2** and amines **3** in the presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$. In order to determine the best reaction conditions, the reaction of isatoic anhydride (1.1 mmol) with ethyl amine (1 mmol) and 4-chlorobenzaldehyde (1 mmol) in the presence of different amounts of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ was investigated. The experimental results showed that even in the presence of 1 mmol $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$, the product **5a** was obtained in only 75% yield after 4 h (Table 1, entry 10). In order to improve the yield, we decided to synthesize **5a** via a two-step reaction (Table 1, entries 11–13). First, the reaction was carried out with isatoic anhydride, ethyl amine and 4-chlorobenzaldehyde in the presence of catalytic amount of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (0.05 mmol) for 1 h at 80 °C. After nearly complete conversion to the corresponding 2,3-dihydroquinazolin-4(1*H*)-one **4a**, as indicated by TLC, 0.65 mmol $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ was added and the mixture was stirred for a further 1.5 h at 100 °C. Under these conditions, the desired product **5a** was obtained in 90% yield (Table 1, entry 12). Higher amounts of the $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ did not improve the yield of **5a** (Table 1, entry 13). Under these conditions, various aldehydes and amines were reacted with isatoic anhydride in the presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ and the corresponding 2,3-disubstituted quinazolin-4(3*H*)-ones **5** were obtained in high yields (86–95%) (Table 3).

The efficiency and applicability of this method has been compared with some of the previously reported methods in Table 4. As can be seen, the present method is superior in terms of yield, reaction time and the amount of catalyst.

A possible mechanism for these reactions has been postulated in Scheme 3. First, isatoic anhydride **1** reacts with amine **2** to afford anthranilamide **6** by removing of carbon dioxide. Condensation of **6** with aldehyde in the presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ afforded the intermediate **7**. $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ catalyzes the tautomerization of amide group and also activates the imine group of this intermediate which is converted to intermediate **8**. Cyclization of **8** to intermediate **9** via intramolecular nucleophilic attack of nitrogen to imin carbon followed by 1,5-proton shift gave the corresponding 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-one **4**. Finally, the 2,3-dihydroquinazolin-4(1*H*)-one is oxidized to the

Table 1

Reaction of isatoic anhydride with 4-chlorobenzaldehyde and ethyl amine in the presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ under solvent-free condition^a.

Entry	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (mmol)	T (°C)	Time (h)	Yield (%) ^b	
				4a	5a
1	0.05	40	1	40	0
2	0.05	60	1	70	0
3	0.05	80	1	95	0
4	0.05	90	1	90	5
5	0.07	80	1	90	5
6	0.1	80	1	85	5
7	0.15	80	1	80	10
8	0.5	100	4	10	80
9	0.7	100	4	10	85
10	1	100	4	15	75
11 ^c	0.05 + 0.6	100	1 + 1.5	10	85
12 ^c	0.05 + 0.65	100	1 + 1.5	5	90
13 ^c	0.05 + 0.7	100	1 + 1.5	5	90

^a Isatoic anhydride (1.1 mmol), ethyl amine (1 mmol) and 4-chlorobenzaldehyde (1 mmol).

^b Isolated yield.

^c Reaction was performed in two steps.

Table 2
 Synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ under solvent-free conditions.

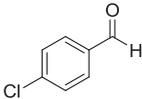
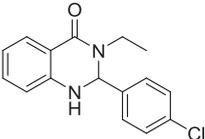
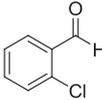
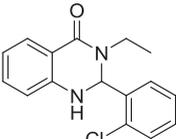
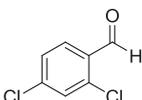
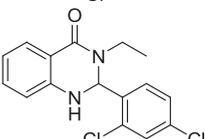
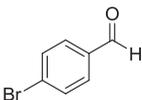
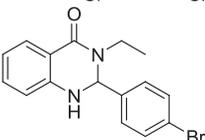
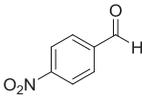
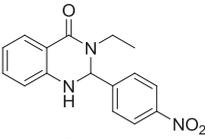
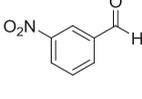
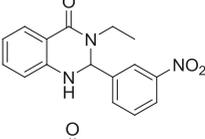
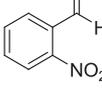
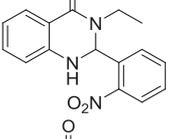
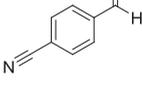
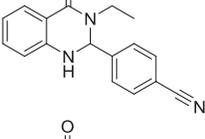
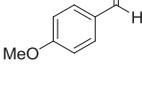
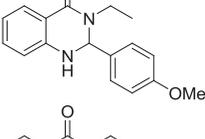
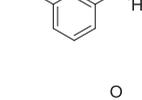
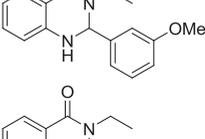
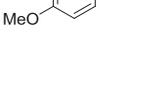
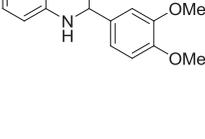
Entry	Aldehyde	Amine	Product	Time (h)	Yield (%) ^a	Mp (°C)	
1		EtNH_2		4a	1	95	132–135 [6]
2		EtNH_2		4b	1	90	146–149
3		EtNH_2		4c	1.5	97	158–161
4		EtNH_2		4d	2	95	129–131
5		EtNH_2		4e	2	96	160–161 [6]
6		EtNH_2		4f	1	96	176–178 [6]
7		EtNH_2		4g	1.5	94	155–158
8		EtNH_2		4h	1	91	170–172
9		EtNH_2		4i	1	94	124–126 [6]
10		EtNH_2		4j	1	93	112–116
11		EtNH_2		4k	1	91	146–149

Table 2 (Continued)

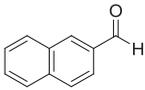
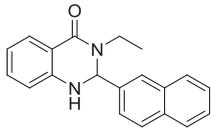
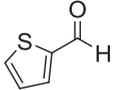
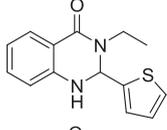
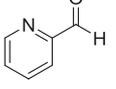
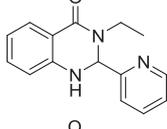
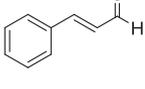
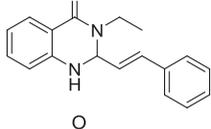
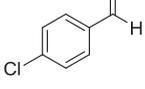
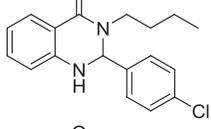
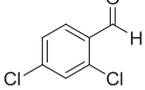
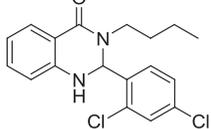
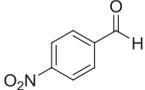
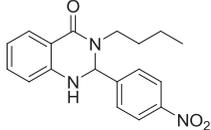
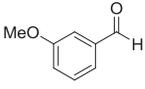
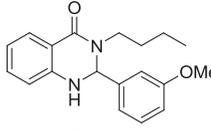
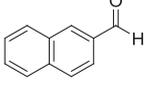
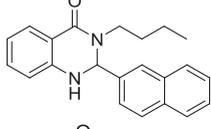
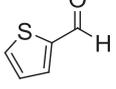
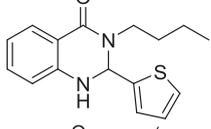
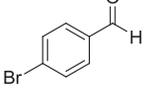
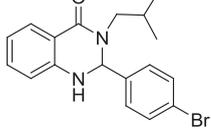
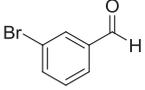
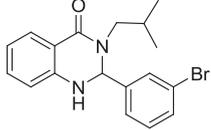
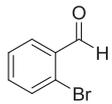
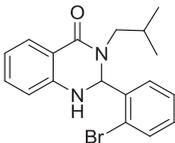
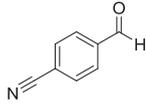
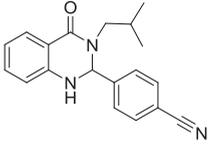
Entry	Aldehyde	Amine	Product	Time (h)	Yield (%) ^a	Mp (°C)	
12		EtNH ₂		4l	2	92	140–143
13		EtNH ₂		4m	1	97	126–128
14		EtNH ₂		4n	0.5	90	128–130
15		EtNH ₂		4o	0.5	92	132–134
16		<i>n</i> -BuNH ₂		4p	1	97	150–151 [13]
17		<i>n</i> -BuNH ₂		4q	1	94	135–138
18		<i>n</i> -BuNH ₂		4r	1.5	96	137–139
19		<i>n</i> -BuNH ₂		4s	1	95	102–105
20		<i>n</i> -BuNH ₂		4t	1	91	144–146
21		<i>n</i> -BuNH ₂		4u	1	95	99–101
22		<i>iso</i> -BuNH ₂		4v	2	95	128–130
23		<i>iso</i> -BuNH ₂		4w	2	92	137–139

Table 2 (Continued)

Entry	Aldehyde	Amine	Product	Time (h)	Yield (%) ^a	Mp (°C)
24		<i>iso</i> -BuNH ₂		2	95	204–205
25		<i>iso</i> -BuNH ₂		2	92	65–69

^a Isolated yield.**Table 3**One-pot synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones in the presence of Bi(NO₃)₃·5H₂O under solvent-free conditions.

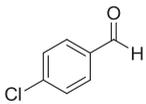
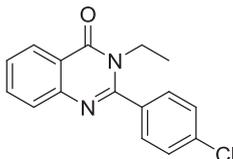
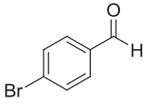
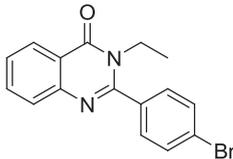
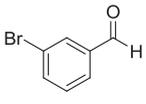
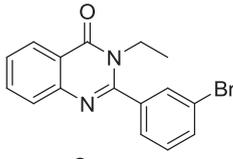
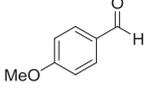
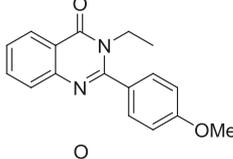
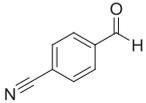
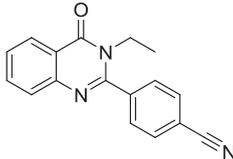
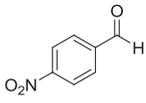
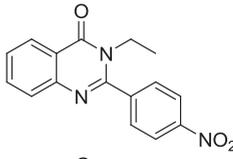
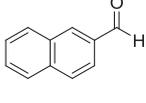
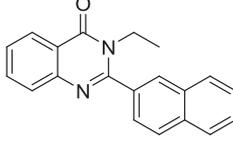
Entry	Aldehyde	Amine	Product	Time (h)	Yield (%) ^a	Mp (°C)
1		EtNH ₂		2.5	90	108–112 [47]
2		EtNH ₂		3	95	110–112
3		EtNH ₂		2.5	94	101–105
4		EtNH ₂		3	91	125–128 [48]
5		EtNH ₂		2	92	180–184
6		EtNH ₂		4	89	190–192 [47]
7		EtNH ₂		3.5	92	125–128

Table 3 (Continued)

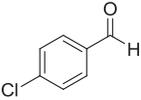
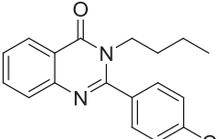
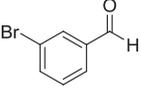
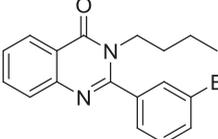
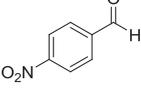
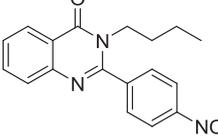
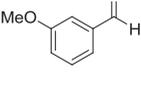
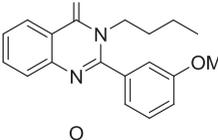
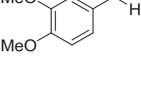
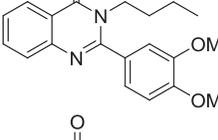
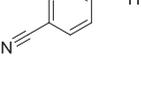
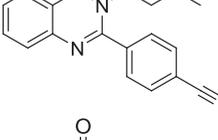
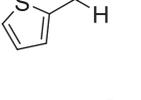
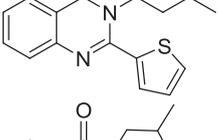
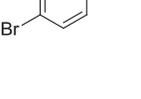
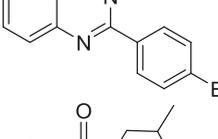
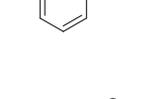
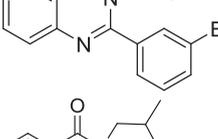
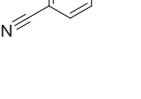
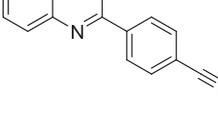
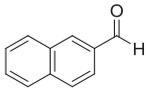
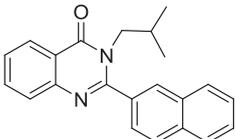
Entry	Aldehyde	Amine	Product	Time (h)	Yield (%) ^a	Mp (°C)	
8		<i>n</i> -BuNH ₂		5h	2.5	93	68–70
9		<i>n</i> -BuNH ₂		5i	2	92	83–85
10		<i>n</i> -BuNH ₂		5j	3	90	123–125
11		<i>n</i> -BuNH ₂		5k	2.5	92	62–64
12		<i>n</i> -BuNH ₂		5l	2.5	94	88–90
13		<i>n</i> -BuNH ₂		5m	2.5	95	117–119
14		<i>n</i> -BuNH ₂		5n	3.5	87	59–61
15		<i>iso</i> -BuNH ₂		5o	3.5	89	111–114
16		<i>iso</i> -BuNH ₂		5p	3.5	86	Oil
17		<i>iso</i> -BuNH ₂		5q	3	91	109–112

Table 3 (Continued)

Entry	Aldehyde	Amine	Product	Time (h)	Yield (%) ^a	Mp (°C)	
18		iso-BuNH ₂		5r	3.5	90	123–126

^a Isolated yield.

corresponding quinazolin-4(3*H*)-one **5** in the presence of Bi(NO₃)₃·5H₂O.

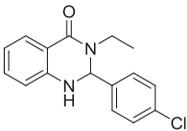
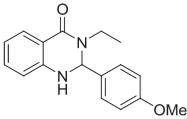
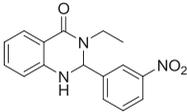
In order to find the actual role of Bi(NO₃)₃·5H₂O in the oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones, some reactions were examined under different conditions. It has been reported that Bi(NO₃)₃·5H₂O decomposes on heating [32,46] as shown in Scheme 4.

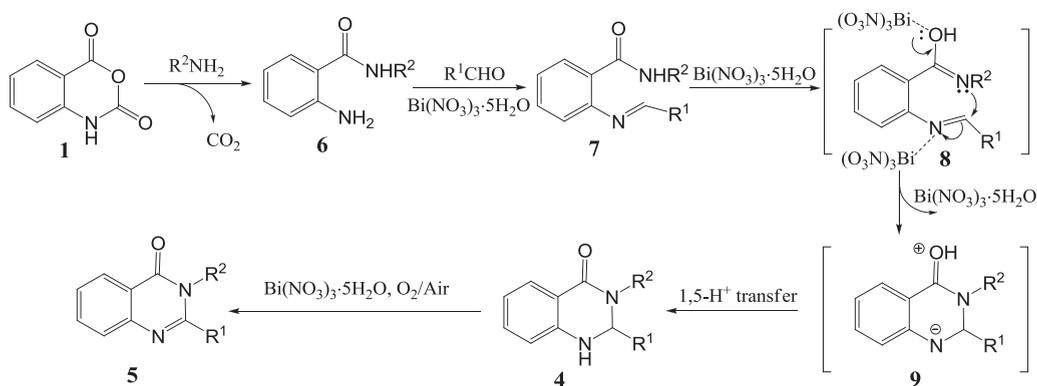
On the basis of this reaction, NO₃⁻, NO₂, O₂, combination of NO₂ and O₂, or O₂ in the presence of Bi(NO₃)₃·5H₂O catalyst may act as key oxidant. First the model reaction was investigated in only O₂ in the absence of Bi(NO₃)₃·5H₂O; no oxidation product was obtained under this conditions. This result clearly showed that O₂ alone cannot be the effective

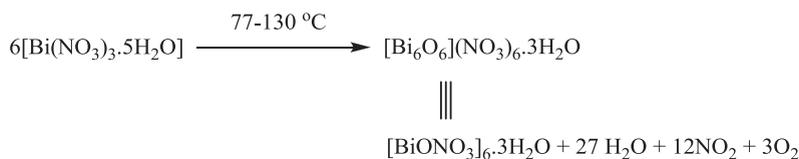
oxidant. Then, this reaction was performed with Pb(NO₃)₂; the absence of any oxidation product proves that NO₃⁻ as well as a combination of NO₂ and O₂ are not the oxidant. On the other hand, the reaction did not proceed with BiCl₃. It is also noteworthy that less than 5% of the oxidized product was obtained under argon atmosphere. In addition, regarding to the application of Bi(III)/O₂ and Bi(III)/DMSO as oxidation systems in the literature, we found that most of these reactions have been carried out in DMSO and CH₃CO₂H solvents [31,40–44]. Therefore, the model reaction was performed in the presence of Bi(NO₃)₃·5H₂O under these conditions. The results showed that only 5% and 38% of the corresponding quinazolin-4(3*H*)-one was obtained, respec-

Table 4

Comparison of the results obtained by Bi(NO₃)₃·5H₂O with some of the previously reported reagents.

Entry	Product	Conditions	Time (h)	Yield (%)
1		SSA (0.15 mmol), H ₂ O, 80 °C [11]	3.5	84
2		SSA (0.2 mmol), solvent-free, 80 °C [11]	5	80
3		Bi(NO ₃) ₃ ·5H ₂ O (0.05 mmol), solvent-free, 80 °C	1	95
4		KAl(SO ₄) ₂ ·12H ₂ O (0.4 mmol), EtOH, reflux [6]	5	80
5		KAl(SO ₄) ₂ ·12H ₂ O (0.52 mmol), H ₂ O, reflux [6]	1	70
6		Bi(NO ₃) ₃ ·5H ₂ O (0.05 mmol), solvent-free, 80 °C	1	94
7		<i>p</i> -TsOH (0.5 mmol), H ₂ O, reflux [8]	1	90
8		<i>p</i> -TsOH (0.5 mmol), EtOH, reflux [8]	3	82
9		Bi(NO ₃) ₃ ·5H ₂ O (0.05 mmol), solvent-free, 80 °C	1	96

**Scheme 3.** Proposed mechanism.

Scheme 4. Decomposition of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ on heating.

tively. Consequently, the method reported in this paper under solvent-free conditions is more convenient for the oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones to their corresponding quinazolin-4(3*H*)-ones. All these observations indicate that the presence of oxygen is essential and $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ has some catalytic effect in this oxidation reaction. Therefore, a combination of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ along with oxygen which is produced by the decomposition of this reagent and also provided from air acts as actual oxidizing system in these reactions.

4. Conclusion

In conclusion, we have demonstrated for the first time that $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ could be used as an efficient catalyst for the selective synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones and their one-pot oxidation to quinazolin-4(3*H*)-ones under solvent-free conditions. In addition, the advantages including high yields, short reaction times, easy work-up, green procedure avoiding toxic organic solvents, and the use of readily available, inexpensive and relatively non-toxic catalyst make the present method superior to the existing methods for the synthesis of quinazolinone derivatives.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.crci.2011.05.003](https://doi.org/10.1016/j.crci.2011.05.003).

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