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Journal Name

COMMUNICATION

Oxone mediated annulation of 2-aminobenzamides and 1,2-diaminobenzenes with a *sec*-amine *via* imine-*N*-oxide: New syntheses of 2,3-dihydroquinazolin-4(1*H*)-ones and 1*H*-benzimidazoles

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Efficient and mild method for preparation of 2,3-dihydroquinazolin-4(1*H*)-ones and 1*H*-benzimidazoles by oxone mediated reaction of a *sec*-amine *via* imine-*N*-oxide with 2-amino-*N*-substituted benzamides and 1,2-diaminobenzenes respectively in THF-water (2:1) at ambient temperature is described.

2,3-Dihydroquinazolin-4(1*H*)-ones and their derivatives occur in a variety of natural products[1] and in synthetic drugs which found applications as anticancer,[2] diuretic,[3] anti-inflammatory,[4] antidepressant,[5] CNS stimulant,[6] antianxietic,[7] antihistamine,[8] antiviral,[9] antibiotic,[10] vasodilatory,[11] anticonvulsant[12] and anti-defibrillator[13] agents. They are also important as plant-growth regulators.[14] 1*H*-benzimidazoles and their derivatives also have similar importance in medicinal chemistry for a variety of pharmacological applications as antitumor,[15] cardiotonic,[16] antiulcer,[17] antihypertensive,[18] anthelmintic[19] agents and also as pesticides.[20] Some of the important commercial drugs with 2,3-dihydroquinazolin-4(1*H*)-one and 1*H*-benzimidazole core structures are shown in Figure 1.

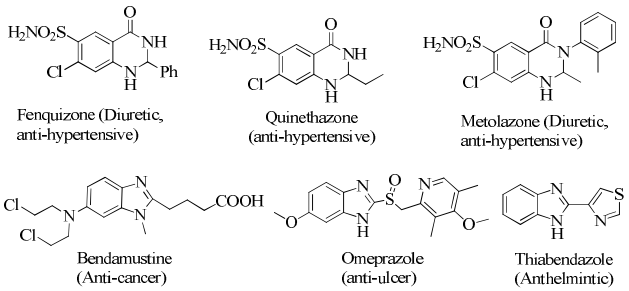
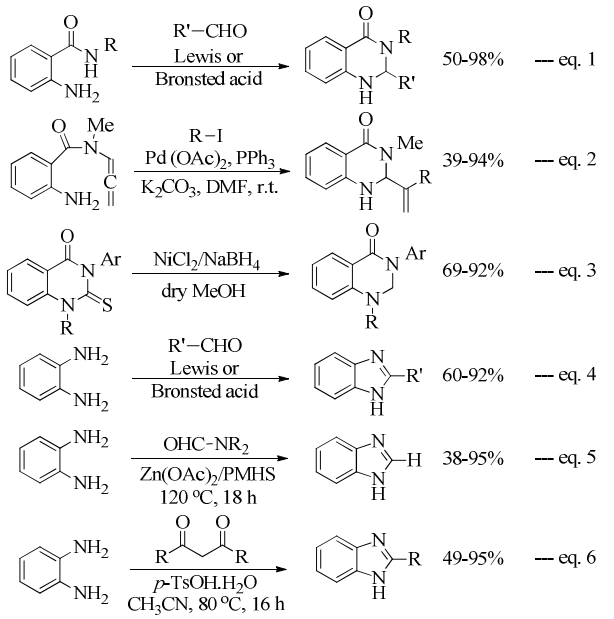


Figure 1: Some commercial drugs containing 2,3-dihydroquinazolin-4(1*H*)-one and 1*H*-benzimidazole core structures

In literature, so far three methods are known for preparation of 2,3-dihydroquinazolin-4(1*H*)-ones and they are: i) by condensation of 2-amino-*N*-substituted benzamides with aldehydes using Lewis or Bronsted acid catalyst (eq. 1, Scheme 1),[21] ii) by intramolecular cyclization of 2-amino-*N*-alkyl-*N*-allenyl benzamides using $Pd(OAc)_2$ as the catalyst (eq. 2, Scheme 1)[22] and iii) by reductive desulfurization of 2-thioxo-2,3-dihydroquinazolinones with $NiCl_2/NaBH_4$ (eq. 3, Scheme 1).[23] The methods described in literature for preparation of 1*H*-benzimidazoles are: i) by condensation of 1,2-diaminobenzenes with aldehydes using a Lewis or Bronsted acid catalyst (eq. 4, Scheme 1),[24] ii) by condensation of 1,2-diaminobenzenes with formaldehyde generated by reaction of a *N*,*N*-dialkyl formamide with poly(methylhydrosiloxane) (PMHS) under $Zn(OAc)_2$ catalysis (eq. 5, Scheme 1)[25] and iii) by reaction of 1,2-diaminobenzene with a β-diketone using *p*-toluenesulfonic acid as the catalyst (eq. 6, Scheme 1).[26]



Scheme 1: Literature methods for preparation of 2,3-dihydroquinazolin-4(1*H*)-ones/1*H*-benzimidazoles

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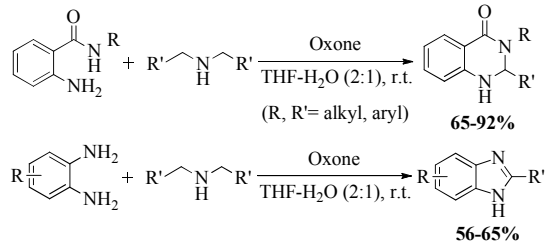
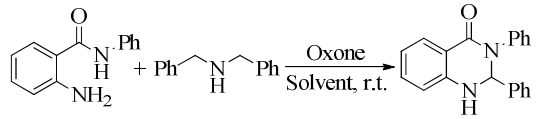
Despite these methods, there has been a long-standing interest in the development of new methods for their synthesis owing to their high importance in drug discovery studies. In our laboratory, we are interested in study of oxidative transformations using oxone,[27] which is a mild, inexpensive and environmentally benign solid oxidant. In the course of work, we found new methods by serendipity for preparation of 2,3-dihydroquinazolin-4(1*H*)-ones and 1*H*-benzimidazoles and here, we report one-pot method for syntheses of 2,3-dihydroquinazolin-4(1*H*)-ones and 1*H*-benzimidazoles from 2-amino-*N*-substituted benzamides and 1,2-diaminobenzenes respectively which were reacted with secondary amines *via* imine-*N*-oxides using oxone as an oxidant at ambient temperature in tetrahydrofuran (THF)-water (2:1) as the reaction medium as shown in Scheme 2. The existing methods are all catalytic processes and most of them involve metal catalysts and high reaction temperatures. However, the present methods are efficient non-catalytic processes with mild reaction conditions.



Scheme 2: Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones/1*H*-benzimidazoles

In our preliminary experiments, we found that *N*-benzyl-1-phenylmethanimine oxide (imine-*N*-oxide), which was *in situ* generated by oxidation[28] of dibenzylamine **2a** with oxone in THF-H_2O (2:1), reacts with 2-amino-*N*-phenylbenzamide **1a** at ambient temperature to give annulated product 2,3-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one **3a** in 89% yield. The results of the solvent screening study of this reaction are summarized in Table 1.

Table 1: Solvent screening study for preparation of **3a**



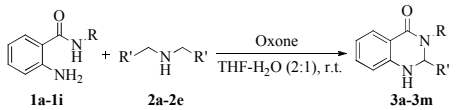
1a **2a** **3a**

Entry	Solvent	Time (h)	% Yield[a] **3a**
1	THF	10	15
2	CH_3CN	10	10
3	THF+H_2O (1:1)	6	55
4	THF+H_2O (2:1)	5	89
5	CH_3CN+H_2O (2:1)	8	70
6	MeOH+H_2O (2:1)	10	20
7	$CHCl_3$+H_2O (2:1)	10	N.R.

[a]Isolated yields, r.t.= room temperature, N.R.= No Reaction.

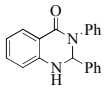
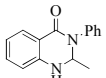
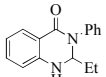
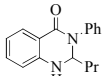
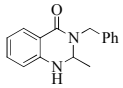
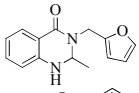
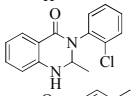
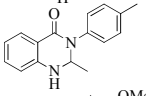
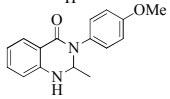
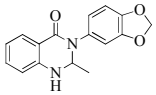
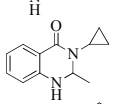
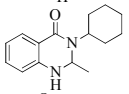
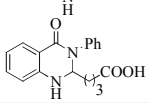
Next, we studied the scope of the present reaction using a variety of *N*-alkyl and *N*-aryl substituted 2-amino benzamides **1a-1i**, which were reacted with secondary amines **2a-2e** in the presence of oxone at ambient temperature in THF-H_2O (2:1). In this study, acyclic *sec*-amines **2a-2d** gave corresponding 2,3-dihyroquinazolin-4(1*H*)-one derivatives **3a-3l** in 78-92%.

Table 2: Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones



1a-1i **2a-2e** **3a-3m**

1a (R= Ph); **1b** (R= Bn); **1c** (R= furfuryl); **1d** (R= 2-ClPh); **1e** (R= 4-MePh); **1f** (R= 4-OMePh); **1g** (R= 3,4-methylenedioxy Ph); **1h** (R= cyclopropyl); **1i** (R= cyclohexyl) and **2a** (R'= Ph); **2b** (R'= Me); **2c** (R'= Et); **2d** (R'= Pr); **2e** (piperidine)

Entry	Product **3**	Substrate **1**	*sec*-amine **2**	Time (h)	% Yield[a] **3**	mp (°C)
a		**1a**	**2a**	5	89	205-208
b		**1a**	**2b**	4	92	163-165
c		**1a**	**2c**	4	86	149-151
d		**1a**	**2d**	5	84	113-116
e		**1b**	**2b**	5	85	160-162
f		**1c**	**2b**	5	84	91-93
g		**1d**	**2b**	5	89	163-164
h		**1e**	**2b**	5	87	155-157
i		**1f**	**2b**	4	88	177-180
j		**1g**	**2b**	6	81	159-162
k		**1h**	**2b**	5	81	122-124
l		**1i**	**2b**	5	78	165-167
m[b]		**1a**	**2e**	6	65	oil

[a]Isolated yields. All products gave satisfactory ^1H, ^{13}C NMR, IR and Mass spectral data.
[b]Reflux conditions.

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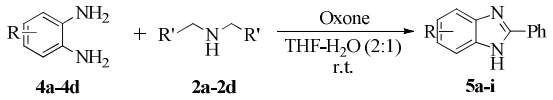
In our study, unlike acyclic sec-amines, cyclic sec-amines such as piperidine, morpholine and pyrrolidine found to behave differently and with these substrates, reaction proceeded only up to the formation of corresponding imine-*N*-oxide, which did not react with **1a-1i** to give an annulated product. However, under reflux condition, piperidine **2e** was found to react with **1a** producing 4-(4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)butanoic acid **3m** in 65 % yield (entry m, Table 2) while morpholine and pyrrolidine did not show similar reactivity.

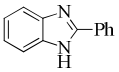
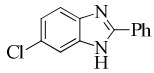
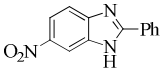
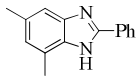
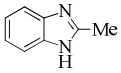
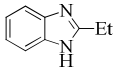
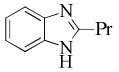
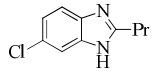
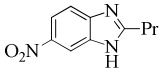
In our study, 1,2-diaminobenzenes **4a-4d** were also found to undergo annulation reactions with secondary amines **2a-2d** *via* imine-*N*-oxides in the presence of oxone to give corresponding 1*H*-benzimidazole derivatives **5a-5i** in 56-65% yields as shown in Table 3. Here also annulation products were not formed with a cyclic *sec*-amine such as piperidine, morpholine and pyrrolidine.

Table 3: Synthesis of 1*H*-benzimidazoles



4a-4d **2a-2d** **5a-i**

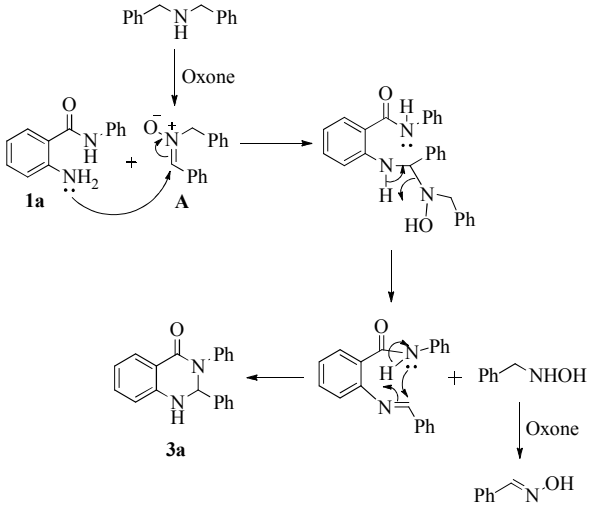
4a (R= H); **4b** (R= 4-Cl); **4c** (R= 4-NO_2); **4d** (R= 3,5-dimethyl); and **2a** (R'= Ph); **2b** (R'= Me); **2c** (R'= Et); **2d** (R'= Pr)

Entry	Product **5**	Substrate **4**	*sec*-amine **2**	Time (h)	% Yield[a]	mp (°C)
a		**4a**	**2a**	6	62	295-297
b		**4b**	**2a**	6	65	214-216
c		**4c**	**2a**	8	56	203-206
d		**4d**	**2a**	6	63	189-191
e		**4a**	**2b**	6	61	174-176
f		**4a**	**2c**	7	57	170-172
g		**4a**	**2d**	8	60	149-152
h		**4b**	**2d**	7	60	156-158
i		**4c**	**2d**	8	55	136-138

[a]Isolated yields. All products gave satisfactory ^{1}H, ^{13}C NMR, IR and Mass spectral data.

The plausible reaction mechanism for the formation of 2,3-dihydroquinazolin-4(1*H*)-ones is shown in Scheme 3 by reaction of dibenzylamine **2a** with 2-amino-*N*-phenyl benzamide **1a** in presence of oxone.

Here, initially reaction of oxone with **2a** produces corresponding imine-*N*-oxide **A**, which undergoes annulation reaction with **1a** to give 2,3-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one **3a**. In this reaction pathway, *N*-benzylhydroxylamine is expected to form as the by-product. In our study, however, we observed only formation of benzaldoxime, which possibly generated by oxidation of *N*-benzylhydroxylamine under the reaction conditions.[29]



Scheme 3: Plausible mechanism for the formation of dihydroquinazolinones

In conclusion, we showed new method for syntheses of substituted 2,3-dihydroquinazolin-4(1*H*)-ones and 1*H*-benzimidazoles in high yields by reaction of secondary amines *via* imine-*N*-oxides, with 2-amino-*N*-substituted benzamides and 1,2-diaminobenzenes respectively using oxone as the oxidant.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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