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Synthesis of quinazolinones from anthranilamides and aldehydes via metal-free aerobic oxidation in DMSO

Na Yeun Kim, Cheol-Hong Cheon *

Department of Chemistry, Korea University, Anam-ro, Seongbuk-gu, Seoul 136701, Republic of Korea

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ABSTRACT

A highly environmentally benign protocol for the synthesis of quinazolinones from anthranilamides and aldehydes via aerobic oxidation was developed in wet DMSO. This protocol is operationally simple, exhibits broad substrate scope, and does not need toxic metal catalysts and bases. In addition, the utility of this transformation was further demonstrated by converting the resulting quinazolinones into other useful products in the same-pot without their isolation.

Quinazolinones are very important building blocks found in biologically and pharmacologically active compounds, natural products, and functional materials.[1] Consequently, the development of efficient methods for the synthesis of quinazolinones is of great importance. One conventional method for the preparation of quinazolinones is oxidative cyclization of Schiff bases derived from *o*-anthranilamides and aldehydes in the presence of oxidants.[2] However, this method generally requires the use of excess amounts of oxidants and generates a large amount of waste, thus requiring tedious purification processes.[3,4]

Aerobic oxidations employing oxygen as the ultimate oxidant have attracted much attention from the synthetic community as green protocols.[5] In this regard, the synthesis of quinazolinones via aerobic oxidation provides an attractive alternative to traditional oxidative cyclization methods. Rather surprisingly, although there have been a few reports of the synthesis of quinazolinones via aerobic oxidative cyclization, the most aerobic oxidative cyclization protocols reported were generally performed in the presence of metal co-catalysts;[6] there has been only one report for the synthesis of quinazolinones via aerobic oxidative cyclization under microwave radiation without any assistance with metal co-catalysts.[7] Thus, it is highly desired to develop a more general and environmentally benign protocol for the synthesis of quinazolinones under mild conditions.

Recently, we developed metal-free aerobic oxidation protocols for the synthesis of benzofused heteroaromatic compounds in the presence of a nucleophile which acts as a catalyst for the cyclization of imines. For example, cyanide turned out to be a highly efficient catalyst for the synthesis of benzoxazoles and benzothiazoles under aerobic oxidation conditions without any aid of metal co-catalyst and bases by converting disfavored 5-*endo*-*trig* cyclization into favored 5-*exo*-*tet* cyclization.[8] As a part of our continuing studies for the development of new protocols for the synthesis of biologically important heterocyclic compounds through aerobic oxidation, we attempted to extend this nucleophile-catalyzed aerobic oxidative cyclization protocol to the synthesis of quinazolinones from anthranilamide and aldehydes.

Herein we present a highly environmentally benign protocol for the synthesis of 2-substituted quinazolinones from anthranilamides and aldehydes via aerobic oxidative cyclization in an open flask without the use of metal co-catalysts and bases. Furthermore, the same protocol was applied to the synthesis of 2,3-disubstituted quinazolinones from N-substituted anthranilamides and aldehdyes. Since this protocol does not use any other additives and generates few by-products other than water, the usefulness of this protocol was further demonstrated by the direct transformation of the resulting quinazolinones into other useful products in the same pot without their isolations.

It is generally believed that the formation of quinazolinone **5** from Schiff base **3** proceeds in a two-step sequence under oxidative cyclization conditions: the first step is cyclization of **3** to afford 2,3-dihydroquinazolinone **4** and subsequent oxidation of **4** yields the

* Corresponding author. Tel.: +82 2 3290 3147; fax: +82 2 3290 3121.
E-mail address: cheon@korea.ac.kr (C.-H. Cheon).

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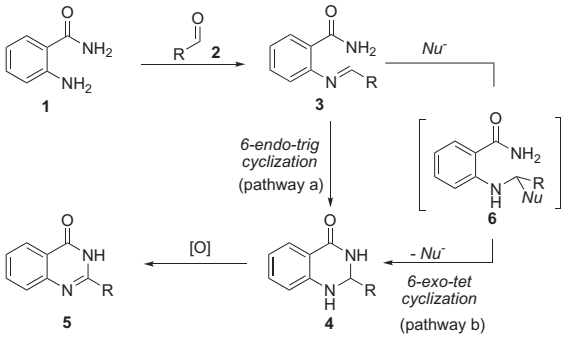
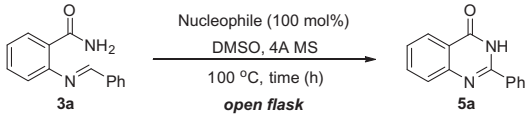
desired product **5** (Scheme 1).[2] We hypothesized that under the aerobic oxidative cyclization conditions, the first step (the conversion of **3** into **4**) might be the rate-determining step for the overall process. Under such a scenario, it was expected that if the rate of the first step were accelerated, the overall reaction rate could be increased. Similar to our previous working hypothesis for the synthesis of benzoxazoles,[8] it was expected that a nucleophile might enable the cyclization of **3** through intermediate **6** formed by the reaction of **3** with a nucleophile via a *6-exo-tet* cyclization. In particular, if the *6-exo-tet* cyclization of **6** (pathway b) were faster than the *6-endo-trig* cyclization of **3** (pathway a),[9] a nucleophile could significantly accelerate the cyclization of **3**, which eventually facilitates the formation of **5**.

In order to test our working hypothesis, we first explored a nucleophile as a catalyst on the aerobic oxidative cyclization of **3a** derived from anthranilamide **1** and benzaldehyde **2a** under similar conditions used for the synthesis of benzoxazoles (Table 2). At first glance, a nucleophile appeared to be effective for this transformation; quinazolinone **5a** was obtained in 56% at 100 °C after 16 h in the presence of a stoichiometric amount of cyanide (entry 1). With this encouraging result in hand, several other nucleophiles were investigated as catalysts for this protocol. Rather disappointingly, all the nucleophiles tested provided **5a** in low to moderate yields (entries 2–5). Despite numerous efforts to improve the yield of this transformation, we could not further improve the yield of **5a**. Under these conditions, we decided to investigate the background reaction for this transformation. When the reaction was performed in the absence of cyanide, the aerobic oxidative cyclization still proceeded, but **5a** was obtained in much lower yields (entry 6). However, the reaction performed in the absence of molecular sieves provided **5a** in slight better yields than the reaction under standard conditions (entry 7). When the reaction was performed in the absence of both a nucleophilic catalyst and molecular sieves, rather unexpectedly, the aerobic oxidative cyclization reaction more rapidly progressed than did that with both a nucleophile and molecular sieves and the desired quinazolinone **5a** was obtained in excellent yield (entry 8).



Scheme 1. Working hypothesis.

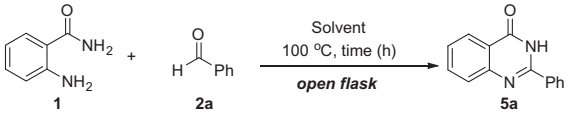
Table 1
Investigation of nucleophiles



Entry	Nucleophile	Time (h)	Yield[a] (%)
1	NaCN	16	56
2	NaI	16	37
3	KI	16	43
4	NaOPh	16	31
5	NaOAc	16	19
6	—	16	30
7[b]	NaCN	16	66
8[b]	—	12	100 (94)[c]

[a] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Reaction was performed in the absence of molecular sieves.
[c] Isolated yield.

Table 2
Optimization of reaction conditions



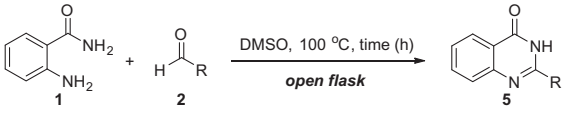
Entry	Solvent	Time (h)	Yield[a] (%)
1[b]	DMSO	16	—[c]
2	DMSO	16	100 (91)[d]
3	DMF	16	44
4	1,4-Dioxane	16	12
5	H_2O	16	—[c]
6	Toluene	16	—[c]
7	EtOH	16	—[c]
8[e]	DMSO	16	Trace
9[f]	DMSO	3.5	100
10[g]	DMSO	16	Trace

[a] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Reaction was performed in the presence of 4 Å molecular sieves.
[c] Imine **3a** was obtained as the major product.
[d] Isolated yield.
[e] At 80 °C.
[f] At 120 °C.
[g] Under argon atmosphere.

With these rather unexpected results in hand, we investigated the possibility of the direct synthesis of **5a** from anthranilamide **1** and benzaldehyde **2a** without the isolation of intermediate **3a** (Table 2). Initially, this reaction was performed in the presence of molecular sieves to facilitate the formation of the corresponding imine **3a**. However, under these conditions, **5a** was not observed even after 16 h; instead, **3a** was formed as a minor product along with unreacted starting compounds (entry 1). When the same reaction was carried out in the absence of molecular sieves, rather unexpectedly the reaction proceeded to completion to afford **5a** in excellent yields after 16 h (entry 2). Under these conditions, the effect of solvent was investigated on the formation of quinazolinone (entries 2–7). It was found that the choice of solvent had a significant influence on this transformation. Quinazolinone **5a** was formed in quantitative yields in DMSO, while the reaction proceeded with very poor efficiency in other solvents. The reaction temperature was also found to have a strong influence on this transformation (entries 2, 8 and 9). The formation of quinazolinone proceeded very slowly at 80 °C (entry 8); an increase to 100 °C resulted in a more rapid reaction (entry 2), and further temperature increase to 120 °C promoted complete transformation within 3.5 h (entry 9). When the same reaction was performed under argon atmosphere, no formation of quinazolinone was observed, which supported that the air would be responsible for the terminal oxidnant in this transformation (entry 10).[10]

Under the optimized reaction conditions, the substrate scope was investigated for this transformation (Table 3). Various aromatic aldehydes were readily applied to this protocol and the desired products **5** were obtained in high to excellent yields (entries 1–11). Stereoelectronic effects of the aromatic aldehydes

Table 3
Substrate scope for 2-substituted quinazolinones **5**



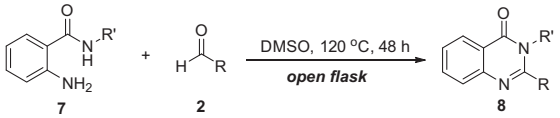
Entry	Quinazolinone **5**	Time (h)	Yield[a] (%)
1	**5a**: R = C_6H_5	12	91
2	**5b**: R = 4-$MeOC_6H_4$	12	84
3	**5c**: R = 4-MeC_6H_4	12	89
4	**5d**: R = 4-ClC_6H_4	18	88
5	**5e**: R = 4-$(MeO_2C)C_6H_4$	12	98
6	**5f**: R = 4-NCC_6H_4	30	95
7	**5g**: R = C_6F_5	30	76
8	**5h**: R = 2-MeC_6H_4	18	85
9	**5i**: R = 2-ClC_6H_4	18	86
10	**5j**: R = 1-naphthyl	36	79
11	**5k**: R = 2-naphthyl	18	82
12	**5l**: R = 2-furyl	18	95
13	**5m**: R = 2-thienyl	36	93
14	**5n**: R = 2-pyridyl	36	96
15	**5o**: R = CH=CHPh	12	71
16	**5p**: R = *n*-hexyl	36	92
17	**5q**: R = *c*-hexyl	18	97
18[b]	**5r**: R = *t*-butyl	36	42
19[b]	**5s**: R = H	36	67
20[c]	**5a**: R = C_6H_5	12	93

[a] Isolated yields.
[b] 2.5 equiv of aldehyde were used.
[c] 20 mmol scale.

had a little effect on the formation of **5**; quinazolinones **5** were obtained in high yields regardless of the stereoelectronic nature of the aromatic aldehydes. Heteroaromatic aldehydes were also applied to this aerobic oxidation protocol without any sacrifice of its efficiency (entries 12–14). In addition, this protocol could be extended to α,β-unsaturated aldehydes, such as cinnamaldehyde (entry 15). Aliphatic aldehydes including formaldehyde[11] were also applied to this protocol and the desired products were obtained in good to high yields (entries 16–19). This method could be employed on a gram scale without any loss of efficiency demonstrating the practicality of this method (entry 20).

With the successful development of a new protocol for the synthesis of 2-substituted quinazolinones **5**, we attempted to extend this protocol to the synthesis of 2,3-disubstituted quinazolinones **8** from N-substituted anthranilamides **7** and aldehydes **2** (Table 4).[12] Under similar conditions for the synthesis of **5**, we explored the possibility of the direct synthesis of 2,3-disubstituted quinazolinone **8a** from *N*-phenyl anthranilamide **7a** with **2a**. To our delight, **8a** was obtained in high yield without any further optimization of the reaction conditions (entry 1). Under these conditions, the substrate scope of aldehydes for this transformation was investigated (entries 1–7). The stereoelectronic effect of the aromatic aldehydes had little effect on the formation of **8**. In addition, the protocol could be extended to heteroaromatic aldehydes and the desired quinazolinones were obtained in good yields (entries 8 and 9). However, the extension of this protocol to aliphatic aldehydes turned out to be challenging. In particular, the structures of aliphatic aldehydes had strong influence on the synthesis of quinazolinones. Formaldehyde and 1-heptanal provided **8j** and **8k**, respectively, in synthetically useful yields (entries 10 and 11). However, aliphatic aldehydes bearing more than two alkyl groups at the α-carbon, such as *c*-hexyl and *t*-butyl aldehydes, did not provide the expected quinazolinone products and a complex mixture was obtained with these substrates. Other N-substituted

Table 4
Substrate scope for 2,3-disubstituted quinazolinones **8**



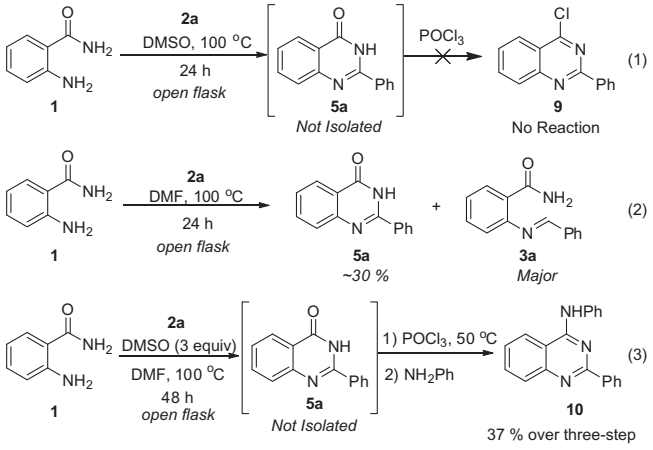
Entry	Quinazolinone **8**			Yield[a] (%)
	8	R	R′	
1	**8a**	C_6H_5	Ph	80
2	**8b**	4-$MeOC_6H_4$	Ph	77
3	**8c**	4-MeC_6H_4	Ph	72
4	**8d**	4-ClC_6H_4	Ph	72
5	**8e**	4-$(MeO_2C)C_6H_4$	Ph	84
6	**8f**	2-MeC_6H_4	Ph	72
7	**8g**	2-ClC_6H_4	Ph	68
8	**8h**	2-Furyl	Ph	65
9	**8i**	2-Thienyl	Ph	73
10	**8j**	H	Ph	38
11	**8k**	*n*-Hexyl	Ph	42
12	**8l**	C_6H_5	CH_2Ph	86
13	**8m**	C_6H_5	CH_3	80

[a] Isolated yields.

anthranilamides were also applied to this protocol to afford the desired products **8** in high yields (entries 12 and 13).

After the successful development of the protocol for the synthesis of 2-substituted- and 2,3-disubstituted quinazolinone derivatives, we attempted to further demonstrate the usefulness of this protocol. Particularly, since this protocol was performed in the absence of any oxidants and metal catalysts, and water might be the only by-product from this transformation,[5] we expected that a resulting quinazolinone could be further transformed into other useful products in the same pot without its isolation.

Based on this idea, we first attempted to develop a novel one-pot method for the preparation of 4-aminoquinazoline **10** from **1** and **2a** through the direct conversion of resulting quinazolinone **5a** into 4-chloroquinazoline **9**, followed by the displacement of an amine nucleophile without the isolation of **5a** (Scheme 2).[13] When $POCl_3$ was added to the solution of **5a** prepared under standard conditions, no chlorinated compound **9** was observed (Eq. 1). We suspected that the high reactivity of DMSO toward $POCl_3$ might interfere in the formation of **9**. Thus, we decided to carry out the same reaction in DMF, which is commonly used in the Vilsmeier reaction.[14] However, under such conditions the aerobic oxidation



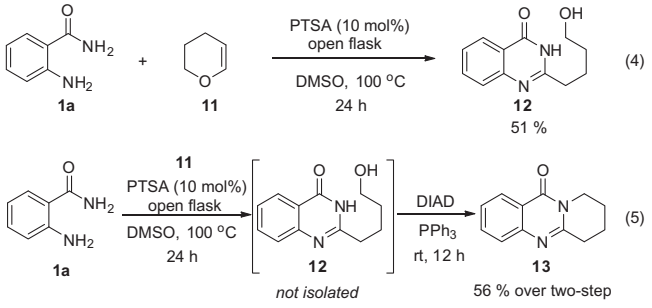
Scheme 2. One-pot synthesis of 4-aminoquinazoline **10**.

did not proceed to completion and **5a** was obtained as the minor product along with **3a** (Eq. 2). Because DMSO is often used in oxidation reactions,[15] we assumed that DMSO might have some beneficial effect on the above aerobic oxidative cyclization reaction. When the reaction was carried out in the presence of 3 equiv of DMSO in DMF solution, delightfully, the aerobic oxidative cyclization went smoothly to afford **5a** in quantitative yields. Furthermore, the resulting **5a** was directly converted into **9** with $POCl_3$ in the same pot and the subsequent addition of aniline afforded 4-aminoquinazoline **10** in synthetically useful yield over three steps, even without complete optimization of the one-pot reaction conditions (Eq. 3).[16]

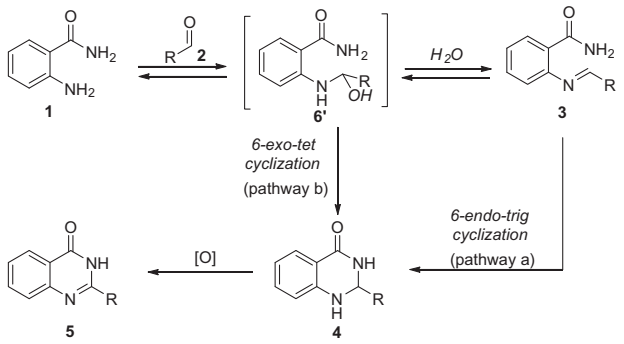
Aldehyde equivalents could be also subjected to this protocol (Scheme 3).[17] For example, when 3,3-dihydro-2*H*-pyrone **11**, commonly used as a 5-hydroxypentanal equivalent, was used in this transformation in the presence of 10 mol % of *para*-toluenesulfonic acid (PTSA), the reaction smoothly proceeded to afford the corresponding quinazolinone **12** in good yield under the standard conditions with aldehydes (Eq. 4). Moreover, the resulting quinazolinone **12** was directly employed in the Mitsunobu reaction[18] to yield mackinazolinone **13**[19] in synthetically useful yields in the same pot although all the reaction conditions were not optimized (Eq. 5).

With these results in hand, we attempted to gain information about the reaction mechanism for this transformation. During optimization, the quinazolinone was found to be formed in the presence of molecular sieves without any assistance of a nucleophile (Table 1, entry 6). This result suggested that under these conditions, quinazolinone **5** could be formed by the direct cyclization of **3** via 6-*endo-trig* cyclization (pathway a in Scheme 1) although the yield was low. In addition, it was observed that the choice of a nucleophile had an influence on the efficiency of this transformation (Table 1, entries 1–5). These results also supported our working hypothesis where a nucleophile might be involved in the cyclization of imine **3** via the 6-*exo-tet* cyclization of intermediate **6** formed from **3** with the nucleophile (pathway b). Particularly, since it was observed that the formation of **5** was significantly accelerated in the absence of molecular sieves and a nucleophile (Table 1, entry 8), we expected that water could be the nucleophilic catalyst for the cyclization of **3** into **4**, which eventually accelerates the formation of quinazolinone **5**.

Based on these results, we proposed a possible reaction mechanism where water would act as a nucleophilic catalyst for this protocol (Scheme 4). The quinazolinone **5** could be obtained from imine **3** via either the direct 6-*endo-trig* cyclization (pathway a) of **3** or the 6-*exo-tet* cyclization (pathway b) of intermediate **6′** formed by the reaction of **3** with water. Since the formation of intermediate **6′** was intrinsically impossible in the absence of water, **5** was obtained in low yields through 6-*endo-trig* cyclization of **3**. However, in the presence of water, intermediate **6′** could be



Scheme 3. Application of aldehyde equivalent **11** and direct further functionalization.



Scheme 4. Proposed reaction pathway.

formed from the reaction of **3** with water and the 6-*exo-tet* cyclization of intermediate **6′** occured along with uncatalyzed 6-*endo-trig* cyclization of **3**. Since the 6-*exo-tet* cyclization from **6′** was much faster than the 6-*endo-trig* cyclization from **3**, the yield of quinazolinone was significantly increased under such conditions. This proposed mechanism also rationalized the significant increase in the yield of quinazolinone from anthranilamide **1** and aldehyde **2**. In the presence of molecular sieves (in the absence of water), initially formed intermediate **6′** was rapidly converted into imine **3**, which could undergo cyclization via only 6-*endo-trig* cyclization. However, in the absence of molecular sieves (in the presence of water), the intermediate **6′** readily underwent cyclization through 6-*exo-tet* cyclization, leading to the desired product in comparable yields with those from imine **3**.

In conclusion, we have developed a highly environmentally benign protocol for the synthesis of 2-substituted and 2,3-disubstituted quinazolinones from anthranilamides and aldehydes via aerobic oxidative cyclization in wet DMSO without any additives. This new protocol features operational simplicity, high atom economy, and broad substrate scope. The usefulness of this new protocol was further demonstrated by the direct application of the resulting quinazolinones to Vilsmeier and Mitsunobu reactions in the same pot without their isolations. Further application of this protocol to total synthesis of biologically important natural products and more detailed mechanistic studies for this transformation are currently underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet. 2014. 02.065.

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