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A recyclable CuO-catalyzed synthesis of 4(3*H*)-quinazolinones†

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This paper describes the synthesis of 2-substituted and 2,3-disubstituted 4(3*H*)-quinazolinones *via* a tandem reaction involving anthranilamides and aromatic aldehydes catalyzed by 3 mol% CuO powder under air atmosphere. This new method has several advantages: it uses recyclable and cheap CuO powder as the catalyst and air as the green oxidant, water is the only byproduct, and the solvent is recycled. It is easy to run, has a high atom economy and good to excellent yields. A mechanism for the CuO-catalyzed synthesis of the 4(3*H*)-quinazolinones is proposed.

4(3*H*)-Quinazolinones are an important class of nitrogen-containing heterocycles with various pharmacological and therapeutic properties.[1] They are used in anticancer,[2] anti-inflammatory,[3] antibacterial[4] and antihypertensive therapies,[5] in addition to being vasopressin V3 receptor antagonists[6] and nonpeptide cholecystokinin B receptor antagonists.[7] Hence, the efficient synthesis of quinazolinone derivatives is important.

Several methods for the synthesis of 4(3*H*)-quinazolinones have been investigated in the past. Some common methods include the condensation of 2-aminobenzamides and substituted benzoyl chlorides or their equivalents in ionic liquids,[8] the tandem condensation and C–N cross coupling of 2-halobenzoic acids and amidines,[9] the cyclization of *o*-acylaminobenzamides,[10] 2-amino-benzonitrile,[11] *N*-arylorthanilamides,[12] and nitroenes,[13] and aza-Wittig reactions of α-azido-substituted aromatic imides.[14] However, most of these procedures have some drawbacks, as they have a poor atom economy, use environmentally toxic reagents or media, use expensive chemicals, and often involve harsh reaction conditions.

In addition, some three-component condensation reactions involving isatoic anhydride–anthranilic acid, *ortho* esters and amines have been reported,[15] but these approaches again lack a good atom economy. Very recently Adib developed an efficient, one-pot three-component synthesis of 4(3*H*)-quinazolinones using benzyl halides, isatoic anhydride and primary amines. However, benzyl chlorides are carcinogenic alkylating agents and poisonous lachrymators and the base K_2CO_3 is needed to neutralize the hydrochloride produced during the reaction.[16]

Relatively recently, Fu reported a CuBr-catalyzed domino synthesis of 2-aryl 4(3*H*)-quinazolinones *via* an Ullmann-type coupling involing *ortho*-iodobenzamides and benzyl amines or α-amino acids (decarboxylation of α-amino acids as the substrates), and an aerobic oxidative C–H amidation.[17] Very recently, Ma developed a CuI–4-hydroxy-L-proline catalyzed coupling involving *N*-substituted *o*-bromobenzamides and formamide or other amides to afford 3-substituted quinazolinones directly, or 2,3-disubstituted quinazolinones *via* a HMDS–$ZnCl_2$ mediated condensative cyclization.[18] Unfortunately, both approaches lead to the generation of undesired byproducts, such as hydrogen halide which consumes K_2CO_3 making the overall process less efficient in terms of atom economy.

In 1994, Abdel-Jalil introduced a new synthetic protocol for the production of 2-substituted 4(3*H*)-quinazolinones, *i.e.* a cascade condensation of anthranilamide and aryl, alkyl, and heteroaryl aldehydes and 3 equivalents of $CuCl_2$ as the oxidant and catalyst.[19]

Later, a similar approach was reported using 2 equivalents of $FeCl_3$ as the oxidant and catalyst.[20] In 2010, Wang *et al.* developed an iodine-catalyzed approach in ionic liquids with the same class of substrates, that is, anthranilamide and aldehydes, but the loading of iodine was not given in their main paper or its supporting information, nor was any note made in their general procedure for the synthesis of 2-arylquinazolin-4(3*H*)-one and (*E*)-2-arylideneaminobenzamide.[21] Similar to this work, Dabiri *et al.* reported a one-pot three-component route to synthesize 2,3-disubstituted 4(3*H*)-quinazolinones in the presence of an equivalent amount of iodine as the catalyst.[22] All the aforementioned methods of

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synthesis of 4(3*H*)-quinazolinones with anthranilamides and aldehydes as substrates involve using stoichiometric amounts of various chemical oxidants, such as $CuCl_2$.

Copper salts have a wide variety of applications in organic synthesis. The copper(II) ion itself can act as a stoichiometric oxidant in the synthesis of 4(3*H*)-quinazolinones,[19] and also can be used as a good oxidation catalyst,[23] even with air as the oxidant.[23a] Of course, a heterogeneous, recyclable catalyst is the best for a clean production. As an environmentally benign and economic process, recyclable catalysis has shown a great advancement over the past decades.[24] The recyclable CuO nanoparticle is a catalyst not only for the C–N cross coupling of amines and iodobenzene,[25] but also for the oxidation of aldehydes to the corresponding carboxylic acids using molecular oxygen.[26] Commercial, inexpensive CuO could have oxidation catalytic properties similar to CuO nanoparticles and may also be recyclable.

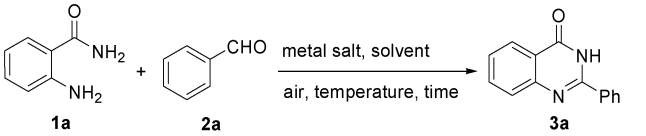
As a continuation of our research in transition metal catalyzed reactions,[27] and in order to find a green and recyclable catalytic system, CuO and some other insoluble, nontoxic or low toxic metal oxides, such as Fe_2O_3, Cu_2O, Al_2O_3 and TiO_2, were adopted for the synthesis of 2-aryl-4(3*H*)-quinazolinones. After our experimental exploration, we found that CuO is a suitable green catalyst for this reaction.

Herein we report an efficient recyclable CuO-catalyzed synthesis of 4(3*H*)-quinazolinones (Scheme 1).

In order to find a catalytic system for the synthesis of 4(3*H*)-quinazolinones, anthranilamide (**1a**) and benzaldehyde (**2a**) were used as the model substrates. Anthranilamide (**1a**) and benzaldehyde (**2a**) and certain insoluble, nontoxic or low toxicity metal oxides in the high boiling point, polar non-protic solvent *N*,*N*-dimethylacetamide (DMA) were heated in air at 120 °C for 24 h. Several suitable metal oxides, such as Al_2O_3, TiO_2, Fe_2O_3, Cu_2O and CuO were screened (Table 1). Among the five metal oxides, when a 5 mol% amount of metal oxide was used, Al_2O_3 and TiO_2 gave moderate yields (Table 1, entries 1 and 2), and Fe_2O_3 gave a slightly higher yield (entry 3), and Cu_2O gave a high yield (entry 4). CuO gave the highest yield, which was up to 98% (Table 1, entry 5).

Next, we screened the solvents. Water and ethanol are green, inexpensive solvents, but they were proven to be poor for dissolving anthranilamide and its product 2-phenyl-4(3*H*)-quinazolinone (**3a**), and gave extremely poor yields at lower temperatures (entries 6 and 7). When the reaction was performed in DMSO, the reaction at 120 °C gave a lower yield than that of the reaction in DMA (Table 1, entry 8 *vs.* entry 5). DMF (*N*,*N*-dimethylformamide) afforded a poorer result with 79% yield (entry 9). Therefore, DMA is the best solvent for the CuO-catalyzed synthesis of 2-phenyl-4(3*H*)-quinazolinone **3a** (entry 5).

Table 1 Screening of various reaction conditions[a]



1a 2a 3a

Entry	Catalyst (amount (mol%))	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	Al_2O_3 (5)	DMA	120	24	51
2	TiO_2 (5)	DMA	120	24	55
3	Fe_2O_3 (5)	DMA	120	24	78
4	Cu_2O (5)	DMA	120	24	92
5	CuO (5)	DMA	120	24	98
6	CuO (5)	H_2O	100	24	5
7	CuO (5)	Ethanol	80	24	21
8	CuO (5)	DMSO	120	24	89
9	CuO (5)	DMF	120	24	79
10	CuO (10)	DMA	120	24	91
11	CuO (3)	DMA	120	24	97
12	CuO (2)	DMA	120	24	75
13	CuO (3)	DMA	100	24	24
14	CuO (3)	DMA	80	24	trace
15	CuO (3)	DMA	120	20	79

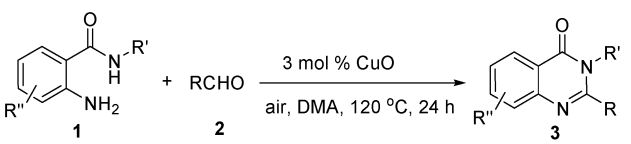
[a] Reaction conditions: metal oxide, anthranilamide (1 mmol), benzaldehyde (1 mmol), solvent (3 mL), in air. [b] Isolated yield.

The amounts of the CuO catalyst were further screened. The result shows that the higher CuO amount of 10 mol% did not result in a higher yield (Table 1, entry 10), so perhaps the excess CuO affected the efficient separation of the product. It seems that 3 mol% CuO is enough for this reaction, as it afforded nearly the same yield as 5 mol% CuO (Table 1, entry 11). However, when 2 mol% CuO was used, there was an obvious decrease in the yield of 2-phenyl-4(3*H*)-quinazolinone **3a** (Table 1, entry 12).

The further examination of reaction temperature demonstrates that a lower reaction temperature sharply decreased the yield due to the incomplete transformation of anthranilamide and benzaldehyde (Table 1, entries 13 and 14); there was almost no product when this reaction was performed at 80 °C. Decreasing the reaction time also resulted in a sharp decrease in the yield (Table 1, entry 15).

Therefore, the optimized procedure for the synthesis of 2-phenyl-4(3*H*)-quinazolinone **3a** requires 3 mol% CuO, and anthranilamide (**1a**) and benzaldehyde (**2a**) in DMA are heated in air at 120 °C for 24 h.

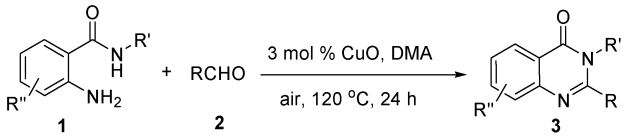
With the optimized reaction conditions in hand, a series of anthranilamides and aldehydes were investigated (Table 2, Scheme 1). Under optimized conditions, the CuO-catalyzed tandem condensation and aerobic oxidation of 4-methylbenzaldehyde and anthranilamide afforded 2-(4′-methylphenyl)-4(3*H*)-quinazolinone (**3b**) in an excellent yield similar to that of benzaldehyde (Table 2, entry 2 *vs.* entry 1).



1 2 3

Scheme 1 The CuO-catalyzed synthesis of 4(3*H*)-quinazolinones.

Table 2 The synthesis of 2-substituted and 2,3-disubstituted 4(3*H*)-quinazolinones[a]



Entry	R	R′	Product	Yield[b] (%)
1	Ph	H	**3a**	97
2	4-$CH_3C_6H_4$	H	**3b**	97
3	3-$CH_3OC_6H_4$	H	**3c**	89
4	3,5-tBu$_2$-2-(OH)C_6H_2	H	**3d**	95
5	4-$(CH_3)_2NC_6H_4$	H	**3e**	77
6	4-FC_6H_4	H	**3f**	93
7	4-ClC_6H_4	H	**3g**	86
8	4-BrC_6H_4	H	**3h**	88
9	3-BrC_6H_4	H	**3i**	85
10	2-BrC_6H_4	H	**3j**	90
11	Furyl	H	**3k**	86
12	Pentyl	H	**3l**	78
13	Ph	C_3H_7	**3m**	81
14	Ph	$CH_2C_6H_5$	**3n**	52
15[c]	Ph	H	**3o**	87

[a] Reaction conditions: CuO (0.03 mmol), anthranilamide (1 mmol; R′′ = H, unless otherwise mentioned), substituted benzaldehyde (1 mmol), DMA (3 mL), at 120 °C for 24 h. [b] Isolated yield. [c] R′′ = 5-Cl.

This catalytic system tolerates various functional groups, such as alkoxyl, halo, dimethylamino, and even hydroxyl, which are suitable for the synthesis of 2-aryl-4(3*H*)-quinazolinone **3** (Table 2, entries 2 to 10). 3,5-Di-*tert*-butylsalicylaldehyde, with a hydroxyl group on the aromatic cycle gave yields of up to 95% (entry 4). However, *N*,*N*-dimethylaminobenzaldehyde afforded a lower yield of 77% (Table 2, entry 5); and therefore, perhaps the dimethylamino group inhibited this reaction slightly. All substrates with various halo groups afforded good to excellent yields (Table 2, entries 6 to 10). Interestingly, varying the substituent positions through *ortho*-, *meta*- and *para*- on the aromatic cycle had no apparent influence on the yields (Table 2, entries 8 to 10).

Furthermore, the CuO-catalyzed cascade reaction involving the heteroaromatic aldehyde furfural and anthranilamide gave 2-furyl-4(3*H*)-quinazolinone (**3k**) with a yield of up to 86% (Table 2, entry 11).

The alphatic aldehyde pentanal also led to the corresponding product in a good yield of 78% (Table 2, entry 12).

In addition to non-substituted anthranilamide, a substitution on the amide group of anthranilamide gave the desired products in good yields with the exception of 2-amino-*N*-benzylbenzamide (Table 2, entries 13 to 15). Perhaps due to the steric hindrance, 2-amino-*N*-benzylbenzamide gave a moderate yield of 2-phenyl-3-benzyl-4(3*H*)-quinazolinone (**3n**) (Table 2, entry 14). However, this compound can be easily synthesized *via* the benzylation of 2-phenyl-4(3*H*)-quinazolinone **3a**.[28]

Table 3 The effect of recycled CuO on the reaction[a]

Entry	CuO	Yield[b] (%)
1	5 mol%	98
2	Recycled first time	94
3	Recycled second time	91
4	Recycled third time	88
5	Recycled forth time	85

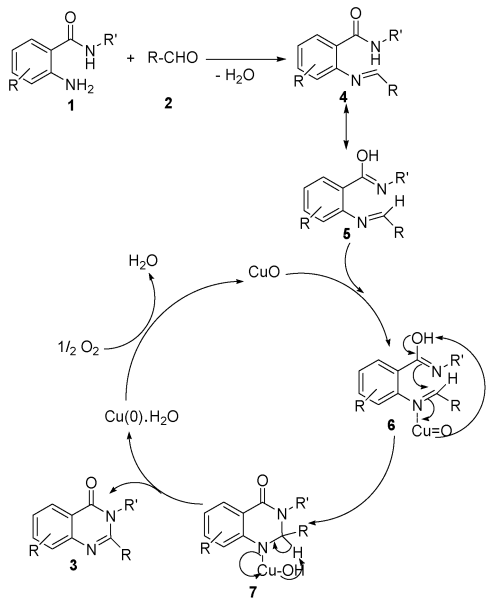
[a] Reaction conditions: CuO (0.05 mmol), anthranilamide (1 mmol), benzaldehyde (1 mmol), DMA (3 mL), at 120 °C for 24 h. [b] Isolated yield.

We noticed that the black powder catalyst CuO precipitated at the bottom of the vial when the reaction was complete and the reaction mixture was cooled to room temperature. Keeping the vial absolutely still, we removed the upper clear solution using a pipette and deposited it into a flask. 3 mL DMA was added into the vial and the upper clear solution was removed again. The combined solution was condensed under vacuum to afford the re-usable solvent DMA and the crude product, which was purified using silica gel chromatography or recrystallization from ethanol. The residual black CuO was used as the first time recycled catalyst for the second synthesis of 2-phenyl-4(3*H*)-quinazolinone **3a**. The yield when using the first time recycled CuO was still very high (Table 3, entry 2). Repeated recycling of the CuO catalyst gave lower yields (Table 3, entries 2 to 5). The yield was still reasonable (85%) after the fourth reuse of CuO (Table 3, entry 5).

To account for the observed results, we reasoned that the CuO-catalyzed reaction probably acts through a different mechanistic pathway compared to those reported earlier involving other catalytic systems and synthetic methods.[15d,17a,21] The plausible mechanism of the CuO-catalyzed synthesis of 4(3*H*)-quinazolinones is depicted in Scheme 2.

Firstly, condensation of the anthranilamide **1** and the aldehyde **2** produces the imine **4**, which is in equilibrium with its tautomer **5**. The coordination of tautomer **5** and CuO may induce an intramolecular electron transfer. As a result, 2,3-dihydroquinazolin-4(1*H*)-one **7** is obtained. A combination of electron transfer and intramolecular rearrangement furnishes the desired product **3** and Cu(0)·H_2O, which should be more stable then Cu(0) due to the coordination to H_2O. Active Cu(0)·H_2O is facilely oxidized by oxygen in the air to restore CuO, which enters the next catalytic cycle (Scheme 2).

In conclusion, we have demonstrated for the first time that recyclable copper(II) oxide powder could be used as an efficient catalyst for the selective synthesis of 2-substituted and 2,3-disubstituted 4(3*H*)-quinazolinones with air as the greenest and least expensive oxidant. The prominent features of this reaction include the use of environmentally friendly air as the oxidant, the use of recyclable and inexpensive CuO powder (only 3 mol%) as the catalyst, the recyclable nature of the solvent, the ability to purify the crude product *via* recrystallization, a high atom economy, good to excellent yields and an



Scheme 2 A proposed mechanism for the CuO-catalyzed synthesis of 4(3*H*)-quinazolinones.

easy operation. These factors make the present method superior to the existing methods for the synthesis of 4(3*H*)-quinazolinones. A plausible mechanism has been proposed to elucidate how CuO and oxygen in the air may fulfil this reaction.

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