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COMMUNICATION

Commercial Copper-catalyzed Aerobic Oxidative Synthesis of Quinazolinones from 2-Aminobenzamide and Methanol

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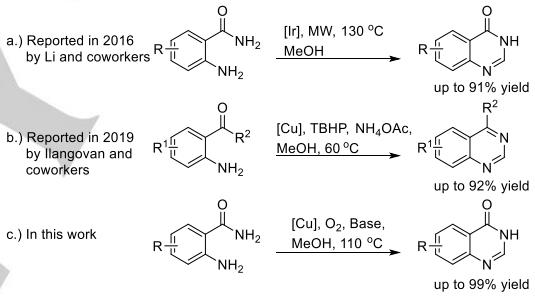
Abstract: Quinazolinones are nitrogen-containing heterocyclic compounds having numerous biological activities. They usually occur in natural products and are the core structures in a few marketed drugs. The focus of this study was the development of a new synthetic method for quinazolinones based on the principles of Green Chemistry. Quinazolinones were synthesized from 2-aminobenzamide using methanol as both the C1-source and a green solvent in the presence of base Cs_2CO_3. Additionally, a commercially available, economical copper complex was used as a catalyst in the reaction. The desired products were achieved in moderate to high yield with up to 99% isolated yield.

INTRODUCTION

Heterocyclic chemistry comprises the biggest and most diverse group of organic compounds used in organic synthesis particularly in the pharmaceutical industry.[1] Quinazolinones having a nitrogen heteroatom are one of the most common heterocyclic compound.[2] They are building blocks in numerous natural products[3] and a variety of synthetic drugs, that have anitimicrobial[4], anti-inflammatory[5], antitumor[6], anticancer[7], hypnotic[8], and antihypertensive[9] activities as some of them were used for the treatment of Alzheimer's disease[10].

The current trend in organic synthesis is to use metal-catalyzed environmentally friendly reactions to obtain the product in high atom economy.[11] The use of readily available methanol as the carbon source in a reaction is another method that gives good atom economy and is a green chemistry process.[11a, 11c] Methanol, via oxidation forms formaldehyde and hence has been used as an electrophile in N-methylation of amine,[12] methylation of ketone[13] and, N-formylation of amines and nitriles.[14] Recently, Li and coworkers[15] reported the synthesis of quinazolinones from 2-aminobenzamides using methanol as the C1-source in moderate to high isolated yield through an acceptorless dehydrogenation strategy. The reactions were carried out in a microwave reactor at 130 °C using an iridium catalyst (Scheme 1a). Furthermore, methanol was also used as the C1-source in the successful preparation of quinazolines from 2-aminobenzophenone using commercially available Cu(II) as catalysts. (Scheme 1b).[16]

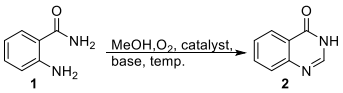
Herein, we report a facile synthesis of quinazolinone derivatives from 2-aminobezamides and methanol that serves as both C1-source and solvent for the reaction. Notably, the reaction required only readily available copper catalysts and base under O_2 atmosphere and ligand-free conditions to give the desired quinazolinones in moderate to high yields (Scheme 1c).



Scheme 1. Synthesis of quinazolinone/quinazoline using methanol as a C1-source

RESULTS AND DISCUSSION

Table 1. Optimization of reaction conditions using commercially available Cu-catalysts[a]

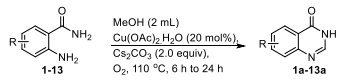


Entry	1 (mmol)	Catalyst (mol%)	Base (equiv)	Temp (°C)	Time (h)	Conversion (%)
1	0.2	*No catalyst*	KO^tBu (1.0)	110	6	n.d.
2	0.2	Cu powder (5)	KO^tBu (1.0)	110	6	n.d.
3	0.2	CuI (5)	KO^tBu (1.0)	110	6	23
4	0.2	$CuSO_{4\text{-}5}H_2O$ (5)	KO^tBu (1.0)	110	6	66
5	0.2	$CuCl_2$ (5)	KO^tBu (1.0)	110	6	81
6	0.2	$CuBr_2$ (5)	KO^tBu (1.0)	110	6	84
7	0.2	$Cu(OAc)_2.H_2O$ (5)	KO^tBu (1.0)	110	6	94
8	0.2	$Cu(OAc)_2.H_2O$ (5)	KOH (1.0)	110	6	23
9	0.2	$Cu(OAc)_2.H_2O$ (5)	K_2CO_3 (1.0)	110	6	75
10	0.2	$Cu(OAc)_2.H_2O$ (5)	Cs_2CO_3 (1.0)	110	6	97
11	**0.2**	**$Cu(OAc)_2.H_2O$ (5)**	**Cs_2CO_3 (1.2)**	**110**	**6**	**99**
12	0.2	$Cu(OAc)_2.H_2O$ (5)	*No base*	110	6	n.d.
13	0.2	$Cu(OAc)_2.H_2O$ (5)	Cs_2CO_3 (1.2)	110	3	4
14	0.2	$Cu(OAc)_2.H_2O$ (5)	Cs_2CO_3 (1.0)	80	6	89
15	0.5	$Cu(OAc)_2.H_2O$ (20)	Cs_2CO_3 (1.2)	110	6	41
16	**0.5**	**$Cu(OAc)_2.H_2O$ (20)**	**Cs_2CO_3 (2.0)**	**110**	**6**	**99**

[a] Reaction conditions: **1** (0.2-0.5 mmol), MeOH (2 mL), catalyst (5-20 mol%), base (0.5-2.0 equiv), 80-110 °C under O_2.

For the optimization of the reaction conditions, 2-aminobenzamide and methanol were selected as the model substrates. When the reaction was performed without a catalyst, no conversion was observed (Table 1, entry 1). The reactions were carried out in 2 mL of methanol in the presence of 1.0 equiv of KO*t*Bu base and 5 mol% of various commercially available Cu catalysts under O_2 atmosphere at 110 °C for 6 h (Table 1, entries 2-6). The use of $Cu(OAc)_2.H_2O$ produced the quinazolinone product with the highest conversion of 94% (Table 1, entry 7). Next, the base screening at 110 °C with 5 mol% of $Cu(OAc)_2.H_2O$ was done. When the base changed from KO*t*Bu to KOH and K_2CO_3, the yield of the target product decreased to 23% and 75%, respectively (Table 1, entries 8 and 9). The best reactivities of 97% and 99%, respectively were obtained for Cs_2CO_3 with 1.0 and 1.2 equiv base (Table 1, entries 10 and 11). A temperature of 110 °C and base were necessary to complete the reaction in 6 h. No conversion was obtained in base-free conditions (Table 1, entry 12). A reduction in the reaction time to 3 h at 110 °C, yielded only 4% of the desired product (Table 1, entry 13). When the temperature was reduced to 80 °C at 6 h, the reaction was incomplete with only 89% conversion obtained (Table 1, entry 14). A scale-up of the reaction using 0.5 mmol of *o*-aminobenzamide with 20 mol% of $Cu(OAc)_2.H_2O$ in the presence of Cs_2CO_3 (1.2 equiv), resulted in a decreased conversion of the quinazolinone to 41% (Table 1, entry 15). However, by increasing the amount of cesium carbonate to 2.0 equiv, the reaction went to complete conversion of 99% (Table 1, entry 16).

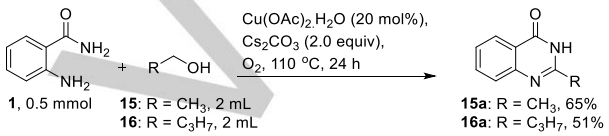
Table 2. Synthesis of quinazolinone derivatives from 2-aminobenzamides and methanol using $Cu(OAc)_2.H_2O$ as a catalyst[a]



Entry	Substrate	Product	Isolated yield (%)	Entry	Substrate	Product	Isolated yield (%)
1	1	1a	92	8	8	8a	49
2	2	2a	74	9	9	9a	99
3	3	3a	77[b]	10	10	1a	79b
4	4	4a	54[b]	11	11	11a	88
5	5	5a	n.d.	12	12	12a	48
6	6	6a	93	13	13	13a	62[b]
7	7	7a	68	14	14	14a	63

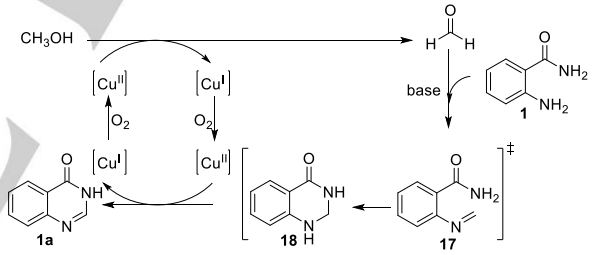
[a] Reaction conditions: substrate (0.5 mmol), MeOH (2 mL), $Cu(OAc)_2.H_2O$ (20 mol%), Cs_2CO_3 (2.0 equiv), 110 °C under O_2 for 6 h. [b] Reaction conditions: substrate (0.5 mmol), MeOH (2 mL), $Cu(OAc)_2.H_2O$ (20 mol%), Cs_2CO_3 (2.0 equiv), 110 °C under O_2 for 24 h.

With the optimized reaction conditions and a reactive catalyst established, we evaluated 2-aminobenzamide derivatives as substrates in the reaction (Table 2). The model reaction afforded the desired product in a high isolated yield of 92% (Table 2, entry 1). 2-Aminobenzamide bearing the electron-donating methyl substituent at the *para* position with the amino group on the aromatic ring gave the target product in 74% (Table 2, entry 2). For the di-substituents on the aromatic ring (Table 2, entry 8), a slightly lower isolated yield was obtained. 2-Amino-5-fluorobenzamide and 2-amino-5-chlorobenzamide (Table 2, entries 3 and 4) reacted successfully with methanol, although a longer reaction time was required to obtain the products in moderate 77% and 54% isolated yields. Despite this, 2-amino-5-bromobenzamide (Table 2, entry 5) did not yield any desired product. For the substrates having fluoro- and chloro- substituents at the *para* position, the reactions completed in 6 hours with 93% and 68% isolated yields respectively, of the desired product (Table 2, entries 6 and 7). The methyl substituent on the nitrogen atom of the amide group (Table 2, entry 9) increased the nucleophilicity of the substrate and hence the product was obtained in an excellent isolated yield of 99%. In the reaction with substrate 10 containing the methyl substituent on the amino group, no target product was attained, but quinazolinone 1a was observed in 79% isolated yield (Table 2, entry 10). A further investigation of the substrate scope in the reactions of alpha-amino heterocyclic amides gave the desired products in moderate to high isolated yields (Table 2, entries 11-13). This catalytic system was also evaluated in the reaction of 2-aminosulfonamide and afforded the target product in 63% yield (Table 2, entry 14).



Scheme 2. Synthesis of quinazolinone derivatives from 2-aminobenzamides and other aliphatic alcohols

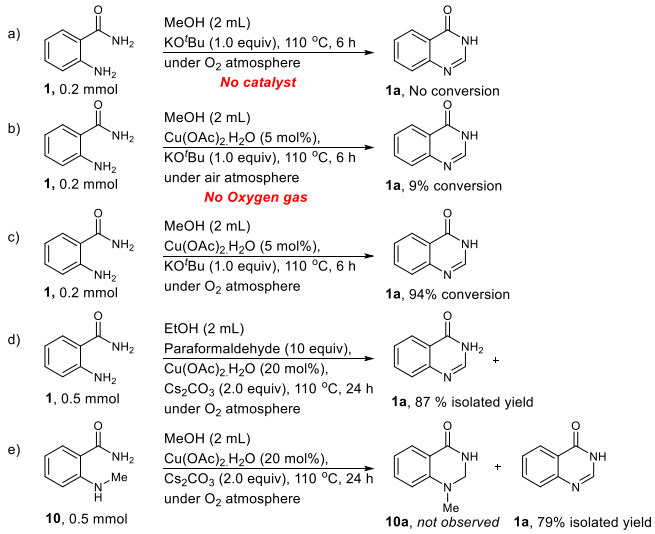
Furthermore, by applying the catalytic system to other types of aliphatic alcohols, the corresponding quinazolinone derivatives were produced in moderate isolated yields (Scheme 2).



Scheme 3. Proposed reaction mechanism

Several experiments were performed to verify the possible mechanism for the synthesis of quinazolinone using methanol as a C1-source and a copper catalyst (Scheme 3). The proposed mechanism begins with oxidation of methanol to produce formaldehyde using the copper catalyst. Formaldehyde reacts with 2-aminobenzamide in the presence of a base to afford the imine intermediate **17**. This imine undergoes intramolecular cyclization to give dihydroquinazolinone **18**. Oxidation of **16** yields the desired quinazolinone product **1a**.[17]

The desired product was not observed when the reaction was done without the copper catalyst (Scheme 4a).Oxygen gas was also required in this catalytic system. When the reaction was carried out under air atmosphere, the target product was obtained in only 9% yield (Scheme 4b). Hence, both oxygen gas and the copper catalyst are required for the reaction to occur as shown in Scheme 4c where product **1a** was obtained in 94% conversion. When methanol was replaced with paraformaldehyde, the reaction still gave the desired product in a high isolated yield of 87%. These results prove that methanol is oxidized to formaldehyde and then reacts with 2-aminobenzamide to form imine intermediate **17**. To confirm the existence of this intermediate, compound **10** was used as the starting material under the optimal reaction conditions and the results confirmed product **10a** was not observed. Surprisingly, product **1a** was obtained in 79% isolated yield (Scheme 4e).



Scheme 4. Supporting experiments for the proposed mechanism

CONCLUSION

In summary, we have successfully developed an easy and efficient method for the synthesis of quinazolinones from 2-aminobenzamides using methanol as the C1-source. This one pot reaction for the synthesis of heterocycles was catalyzed using the relatively inexpensive commercially available $Cu(OAc)_2.H_2O$ catalyst. This catalytic system afforded the desired products in moderate to high isolated yields of up to 99%.

Acknowledgements

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Keywords: Copper catalyst • quinazolinone • methanol

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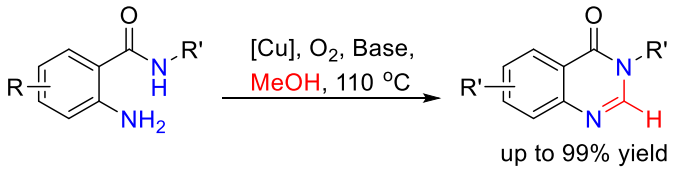

One pot Cu-catalyzed synthesis of quinazolinones using methanol as the C1-source.