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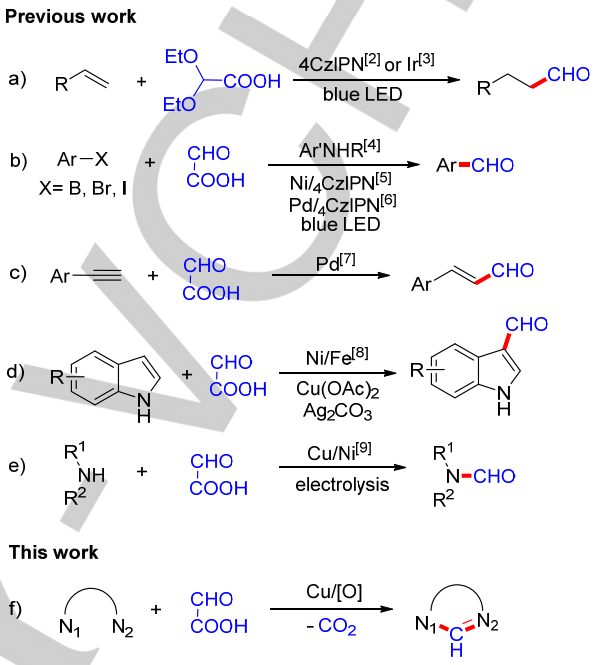
# New Strategy for the Synthesis of Heterocycles via Copper-Catalyzed Oxidative Decarboxylative Animation of Glyoxylic Acid

Bin Niu,[a] Shaoqing Li,[a] Chang Cui,[a] Yizhe Yan,*[a] Lin Tang[c] and Jianyong Wang*[b]

**Abstract:** A copper-catalyzed oxidative decarboxylative amination of glyoxylic acid with substrates having two nitrogen-nucleophilic sites was first demonstrated. Using this novel approach, 1,3,5-triazines, quinazolinones and quinazolines were obtained in up to 93% yields. Notably, glyoxylic acid was employed as the C1 synthon for heterocycles. This strategy enriches the application of glyoxylic acid for the synthesis of valuable heterocycles.

In the past decades, catalytic decarboxylative coupling of carboxylic acids with various coupling partners has emerged as an important strategy for direct construction of C–X bond due to their low cost, great structural diversity, step economical advantages.[1] Recently, glyoxylic acid or glyoxylic acid acetal has been employed as a novel formylation reagent through decarboxylative cross-couplings. In 2017, Wang[2] and Xu[3] successfully reported chemoselective and regioselective hydroformylation of alkenes with glyoxylic acid acetal for alkyl aldehydes. After that, Wang and Fu also reported the direct decarboxylative formylation of aryl boronic acids[4] or aryl halides[5,6] with glyoxylic acid (glyoxylic acid acetal) to afford aryl aldehydes. In 2018, Tao reported a palladium-catalyzed hydroformylation of terminal arylacetylenes with glyoxylic acid, giving a broad range of α, β-unsaturated aldehydes.[7] Recently, Wu reported a nickel and iron-catalyzed dehydrogenative–decarboxylative 3-formylation of indoles with glyoxylic acid.[8] Nevertheless, all these methods were always used to construct C-CHO motif. Very recently, Huang reported the electrochemical decarboxylation formylation of amines with glyoxylic acid, which resulted in one C-N formation.[9] Based on our studies about the synthesis of heterocycles using novel carbon synthons,[10] glyoxylic acid is likely to be employed as a novel carbon synthon to construct heterocycles *via* oxidative decarboxylative coupling.

1,3,5-triazines are a valuable class of nitrogen-containing heterocycles due to its good biological activity.[11] Although many methods have been achieved, low atom economy and generated toxic byproducts limited their further applications.[10,12] Herein, we report a copper-catalyzed oxidative decarboxylative amination of glyoxylic acid with substrates having two nitrogen-nucleophilic sites. A series of nitrogen-containing heterocycles such as 1,3,5-triazines, quinazolinones and quinazolines were obtained in moderate to good yields. Glyoxylic acid was employed as the C1 synthon for the synthesis of heterocycles with the release of $CO_2$. Notably, one C-N bond and one C=N bond were formed in pot via an oxidative decarboxylation. This method provides a new strategy to synthesize valuable nitrogen-containing heterocycles.




**Scheme 1.** New strategies with glyoxylic acid as the C1 synthon

Initially, benzamidine hydrochloride (**1a**) and glyoxylic acid (**2a**) were chosen as model substrates to start our study. The reaction of **1a** and **2a** with 20 mol % of $Cu(OTf)_2$ and 2 equiv of *tert*-butyl hydroperoxide (TBHP, 70% in aqueous) in the presence of $Cs_2CO_3$ (1 equiv) gave trace amount of 2,4-diphenyl-1,3,5-triazine (**3a**) (Table 1, entry 1). When TBHP was replaced with di-*tert*-butyl peroxide (DTBP) or $K_2S_2O_8$, only DTBP gave **3a** with a 60% yield (Table 1, entries 2 and 3). The absence of glyoxylic acid resulted in the failure of the reaction, which proved that the extra carbon atom of 1,3,5-triazine originated from glyoxylic acid (Table 1, entry 4). After the optimization of various copper catalysts, no higher yields were obtained (Table 1, entries 5-12). **3a** was obtained in lower yield when the reaction was performed in $CH_3CN$ or dioxane (Table 1, entries 13 and 14). When organic bases were examined, no better result was obtained (Table 1, entry 15). When 20 mol% of 1,10-phenanthroline or *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was employed as the ligand, TMEDA gave the highest 93% yield (Table 1, entries 16 and 17). Therefore, the optimal conditions were established as described in entry 17.

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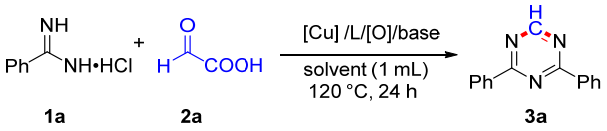
**Table 1.** Optimization of reaction conditions.[a]



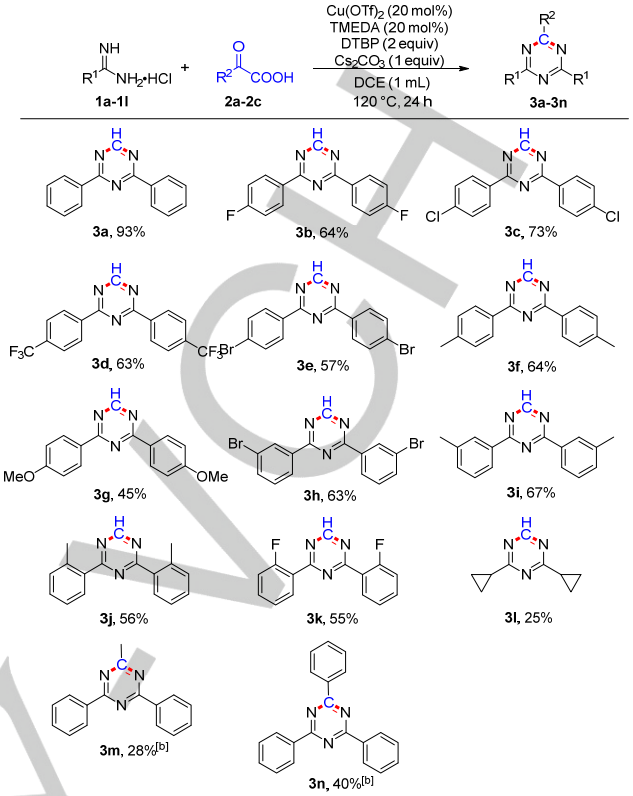

**1a** **2a** **3a**

| Entry | [Cu] | [O] | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | TBHP | DCE | trace |
| 2 | $Cu(OTf)_2$ | DTBP | DCE | 60 |
| 3 | $Cu(OTf)_2$ | $K_2S_2O_8$ | DCE | trace |
| 4[c] | $Cu(OTf)_2$ | DTBP | DCE | trace |
| 5 | $CuCl_2$ | DTBP | DCE | 50 |
| 6 | $CuBr_2$ | DTBP | DCE | 50 |
| 7 | $Cu(OAc)_2$ | DTBP | DCE | trace |
| 8 | $Cu(TFA)_2$ | DTBP | DCE | 53 |
| 9 | CuCl | DTBP | DCE | 52 |
| 10 | CuBr | DTBP | DCE | 50 |
| 11 | CuI | DTBP | DCE | 52 |
| 12 | $Cu_2O$ | DTBP | DCE | trace |
| 13 | $Cu(OTf)_2$ | DTBP | $CH_3CN$ | 55 |
| 14 | $Cu(OTf)_2$ | DTBP | dioxane | 55 |
| 15 | $Cu(OTf)_2$ | DTBP | DCE | 49[d], trace[e] |
| 16[f] | $Cu(OTf)_2$ | DTBP | DCE | 72 |
| 17[g] | **$Cu(OTf)_2$** | **DTBP** | **DCE** | **93** |

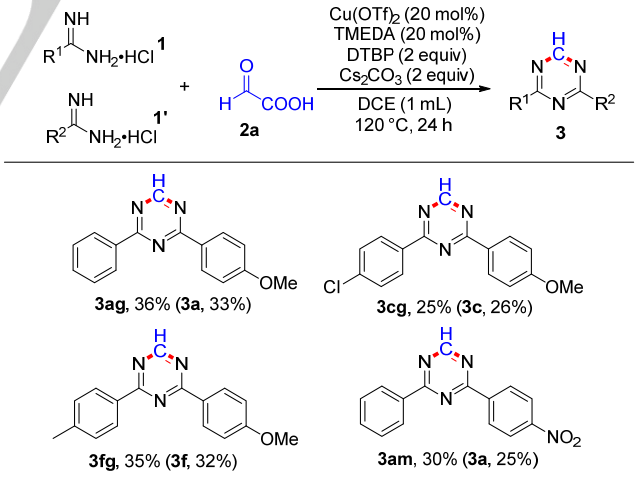
[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), Cu catalyst (0.08 mol), ligand (0.08 mol), oxidant (0.8 mmol), base (0.4 mmol), solvent (1 mL), 120 °C, 24 h. [b] Isolated yield. [c] In the absence of glyoxylic acid. [d] DBU. [e] $NEt_3$. [f] 1,10-Phen. [g] TMEDA.

Under the optimal reaction conditions, the scope of amidines **1** was investigated (Scheme 2). First, both electron-deficient and electron-donating aryl amidines (**1a-1k**) could give corresponding symmetrical 2,4-diaryl-1,3,5-triazines (**3a-3k**) in 45-93% yields. The *ortho*-substituted aryl amidines (**1j** or **1k**) gave lower yields in comparison to the *para*-subsititued ones (**1b** or **1f**) due to the steric hindrance. Moreover, cyclopropane-carboximidamide (**1l**) also could give the corresponding product **3l** in 25% yield. In addition, when **2a** was replaced with 2-oxopropanoic acid (**2b**) or 2-oxopropanoic acid (**2c**), the desired 2-methyl-4,6-diphenyl-1,3,5-triazine (**3m**) or 2,4,6-triphenyl-1,3,5-triazine (**3n**) was obtained in 28% or 40%, respectively, which indicated that the extra carbon atom of 1,3,5-triazines might be from the formyl gourp rather than the carboxyl group of glyoxylic acid.

Subsequently, the synthesis of unsymmetrical 2,4-disubstituted 1,3,5-triazines was also investigated (Scheme 3). After the optimization, the reaction of 4 equiv of benzamidine (**1a**) with 1 equiv of 4-methoxybenzamidine (**1g**) generated an unsymmetrical product **3ag** in 36% yield with only symmetrical product **3a** being obtained in 33% yield. When **1a** was replaced with **1c** or **1f**, the unsymmetrical **3cg** or **3fg** was also obtained in 25% or 35% yields, respectively. In addition, the reaction of **1a**, **1m** and glyoxylic acid also afforded the unsymmetrical product **3am** in 30% yield.

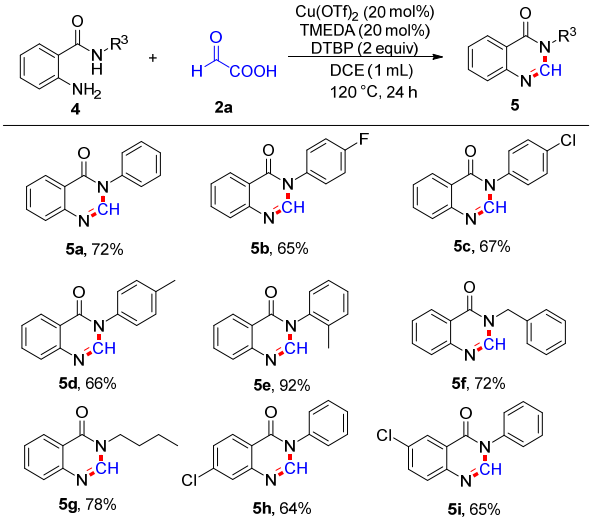



**Scheme 2.** Synthesis of symmetrical 2,4-disubstituted 1,3,5-triazines. [a] Reaction conditions: **1** (0.4 mmol), **2** (0.4 mmol), $Cu(OTf)_2$ (0.08 mol), TMEDA (0.08 mol), DTBP (0.8 mmol), $Cs_2CO_3$ (0.4 mmol), DCE (1 mL), 120 °C, 24 h; isolated yield. [b] 1,10-Phen.

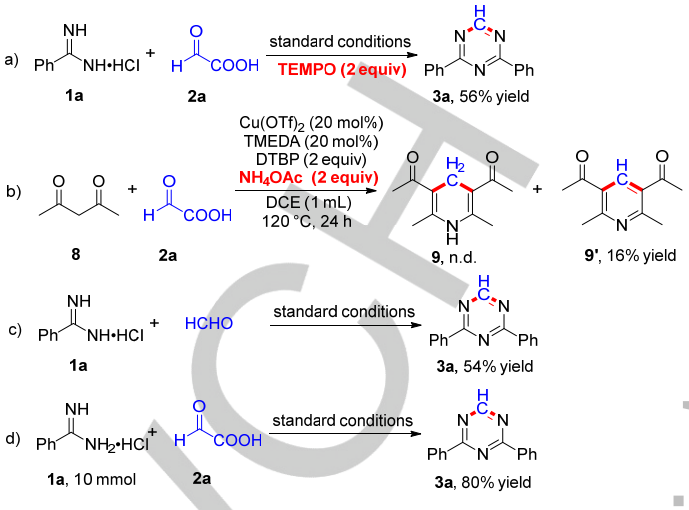



**Scheme 3.** Synthesis of unsymmetrical 2,4-disubstituted 1,3,5-triazines. Reaction conditions: **1** (0.8 mmol), **1'** (0.2 mmol), **2a** (0.4 mmol), $Cu(OTf)_2$ (0.04 mol), TMEDA (0.04 mol), DTBP (0.4 mmol), $Cs_2CO_3$ (0.4 mmol), DCE (1 mL), 120 °C, 24 h; isolated yield.

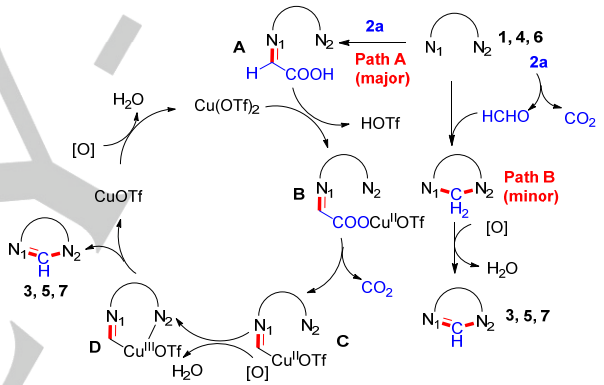
Quinazolinone as an important structural motif has been widely applied in pharmaceutical chemistry due to good bioactivites.[13] Many great efforts have been made for the synthesis of quinazolinones in recent years.[14] Therefore, the




**Scheme 4.** Synthesis of quinazolinones using glyoxylic acid as the C1 synthon. Reaction conditions: **4** (0.2 mmol), **2a** (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol), TMEDA (0.04 mmol), DTBP (0.4 mmol), DCE (1 mL), 120 °C, 24 h; isolated yield.

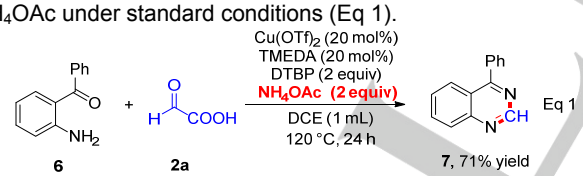



**Scheme 5.** Control experiments and gram-scale synthesis




**Scheme 6.** A plausible mechanism

reaction of 2-aminobenzamides with glyoxylic acid was conducted to produce quinazolinones under standard conditions (Scheme 4). Expectedly, both *N*-aryl (**4a-4e**) and *N*-alkyl 2-aminobenzamide (**4f** and **4g**) afforded the corresponding products **5a-5g** in satisfactory yields. Moreover, 2-amino-4-chloro-*N*-phenylbenzamide (**4h**) and 2-amino-5-chloro-*N*-phenylbenzamide (**4i**) could give the desired **5h** and **5i** in 64% and 65% yields, respectively. Quinazoline is also an important class of heterocycle with goodbiological activities, which has been employed as the intermediate of many commercial drugs, such as Lapatinib, Prazosin, Iressa, Erlotinib and Linagliptin.[15] To our delight, 2-aminobenzophenone (**6**) could give the desired 4-phenylquinazoline (**7**) with a 71% yield in the presence of $NH_4OAc$ under standard conditions (Eq 1).




To gain an insight into the reaction mechanism, several control experiments were performed (Scheme 5). First, the reaction was not completely inhibited in the presence of two equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical inhibitor (Scheme 5a). This result indicated that this reaction might not undergo a radical decarboxylation process. Moreover, Nash reagent (acetylacetone **8** and ammonia) was used to detect the possible intermediate formaldehyde generated via direct decarboxylation of glyoxylic acid (Scheme 5b). Under standard conditions, no Nash product **9** was observed but its oxidative product **9'** was obtained in 16% yield. In addition, when formaldehyde was used instead of glyoxylic acid under standard conditions, **3a** was obtained in 54% yield (Scheme 5c). These results indicated that formaldehyde might be a minor intermediate to form heterocycles. Finally, to examine the practicability of this protocol, a 10 mmol scale experiment was performed with an 80% yield of **3a** obtained (Scheme 5d).

On the basis of the results above and previous reports[1, 16], two plausible reaction pathways are proposed (Scheme 6, Path A and B). Initially, the condensation of the substrates (**1**, **4** or **6**) with glyoxylic acid gives an intermediate **A**, which can be further transformed to a $Cu^{II}$ complex **B** through a ligand exchange of $Cu(OTf)_2$ (Path A). Then **B** can give a new $Cu^{II}$ complex **C** with the escape of $CO_2$. Subsequently, the oxidation of **C** gives a $Cu^{III}$ complex **D** by removing one water molecule. Then **D** is transformed into the heterocyclic product (**3**, **5** or **7**) and CuOTf through reductive elimination. Finally, $Cu(OTf)_2$ is regenerated *via* the oxidation of CuOTf to realize the copper catalytic cycle. Furthermore, a minor pathway may occur according to the control experiment. The substrates and in-situ generated HCHO can afford the heterocycles *via* a tandem condensation and oxidation process (Path B).

In summary, we have developed a copper-catalyzed oxidative decarboxylative amination of glyoxylic acid with substrates having two nitrogen-nucleophilic sites, giving 1,3,5-

triazines, quinazolinones and quinazolines in moderate to good yields. Notably, glyoxylic acid was employed as a C1 synthon to access heterocycles with the release of $CO_2$. Compared to previous methods, this novel protocol is distinguished by (1) cheap copper catalysis, (2) operational simplicity, (3) broad substrate scope, (4) the generaton of low toxic wastes such as $CO_2$ and $H_2O$. Further research about glyoxylic acid as the C1 synthon for valuable heterocycles is underway in our laboratory.

## Acknowledgments

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**Keywords:** glyoxylic acid • copper • decarboxylation • C-N coupling• heterocycle

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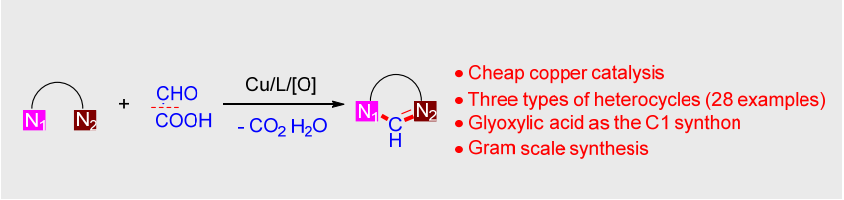


A copper-catalyzed oxidative decarboxylative amination of glyoxylic acid with substrates having two nitrogen-nucleophilic sites was first demonstrated, affording 1,3,5-triazines, quinazolinones and quinazolines in up to 93% yields.

**Decarboxylative Amination***

*Bin Niu, Shaoqing Li, Chang Cui, Yizhe Yan,* Lin Tang, Jianyong Wang**

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**New Strategy for the Synthesis of Heterocycles via Copper-Catalyzed Oxidative Decarboxylative Amination of Glyoxylic Acid**