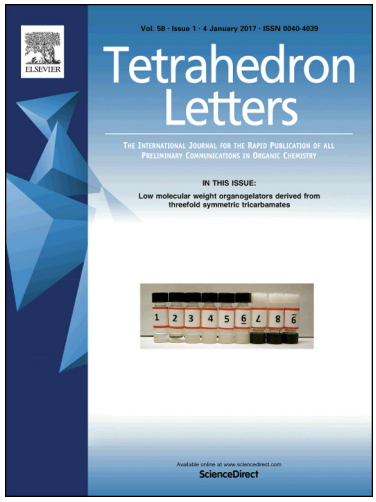

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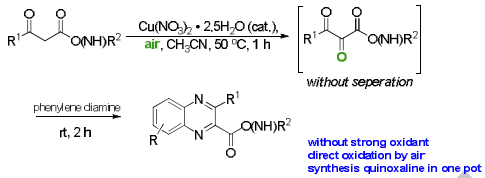
Xu Han, Tao Lei, Xiu-Long Yang, Lei-Min Zhao, Bin Chen, Chen-Ho Tung, and Li-Zhu Wu*



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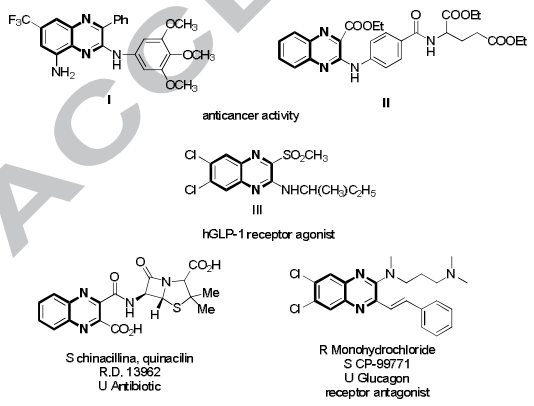
ABSTRACT

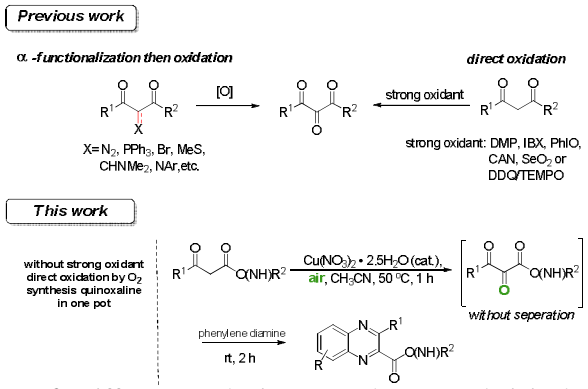
Vicinal tricarbonyl intermediates are directly synthesized from β–dicarbonyls with the aid of Cu (II) salts and air, and they are further condensed with phenylene diamine to produce a range of quinoxalines in moderate to good yields in one-pot reaction.

Introduction

Quinoxalines are a kind of important nitrogen-containing heterocycle due to their significant pharmacological and biological properties (Scheme 1).[1-7] National Cancer Institute (Bethesda, MD), for example, showed that compounds (I and II) have in vitro anticancer activity.[8] Min Teng and co-workers reported that compound III, served as the hGLP-1 receptor agonist, is the most potent and efficacious compound in their is the most potent and efficacious compound in their system.[9] Over



Scheme1. Several quinoxaline-containing active moleculars



Scheme 2. Different synthetic approaches toward vicinal tricarbonyl compounds

the past decades, various synthetic strategies to construct this skeleton have been reported.[10-19] Among these strategies, vicinal tricarbonyl intermediate is the most common one to treat with phenylene diamine.[20]

In order to construct this key intermediate,[21-26] two approaches are put forward. One is a two-step procedure, i.e. β–dicarbonyls or other substrates are firstly employed to construct α-functional β-dicarbonyls and then followed by oxidation.[27-39] The other is that β-dicarbonyls are directly oxidized by strong oxidations, such as Dess–Martin periodinane (DMP),[40] 2-iodoxybenzoic acid (IBX),[41] iodosobenzene (PhIO),[42] SeO_2,[43] cerium ammonium nitrate (CAN)[44] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

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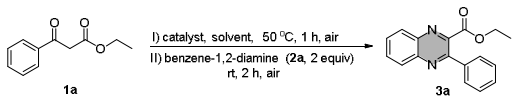
Table 1. Optimization of the reaction condition[a]



entry	catalyst	solvent	yield (%)[b]
1	$Cu(OTf)_2$	CH_3CN	51
2	$Cu(CH_3CN)_4PF_6$	CH_3CN	0
3	$Cu(NO_3)_2{\cdot}2.5H_2O$	CH_3CN	72
4	$Zn(NO_3)_2{\cdot}6H_2O$	CH_3CN	0
5	$Fe(NO_3)_3{\cdot}9H_2O$	CH_3CN	0
6	$Cu(NO_3)_2{\cdot}2.5H_2O$	1,4-dioxane	0
7	$Cu(NO_3)_2{\cdot}2.5H_2O$	DCM	0
8	$Cu(NO_3)_2{\cdot}2.5H_2O$	toluene	0
9	$Cu(NO_3)_2{\cdot}2.5H_2O$	DMSO	0
10	$Cu(NO_3)_2{\cdot}2.5H_2O$	CH_3OH	0
11	$Cu(NO_3)_2{\cdot}2.5H_2O$	THF	0
12	$Cu(NO_3)_2{\cdot}2.5H_2O$	DMF	0
13[c]	$Cu(NO_3)_2{\cdot}2.5H_2O$	CH_3CN	47
14[d]	$Cu(NO_3)_2{\cdot}2.5H_2O$	CH_3CN	72
15[e]	$Cu(NO_3)_2{\cdot}2.5H_2O$	CH_3CN	57

[a]Reaction was carried out with 0.1 mmol ethyl benzoylacetate and catalyst in 2 mL solvent in air for 1 h and then 0.2 mmol benzene-1,2-diamine was added and reacted for 2 h at room temperature.

[b]Yields were determined by ^{1}H-NMR analysis using diphenylmethanol as an internal standard.

[c]Step I at 40 °C.

[d]Amount of catalyst is 10 mol%.

[e] Amount of catalyst is 5 mol%.

(DDQ)/2,2,6,6-tetramethyl piperidin-1-oxyl (TEMPO)[45]. However, the tedious synthesis strategies or the use of strong oxidation reagents undoubtedly increase the cost of reactions and restrict the sequent reacions in synthetic chemistry, which are not satisified with requirement of green chemistry and atom economy. Searching for a mild and green procedure is timely.

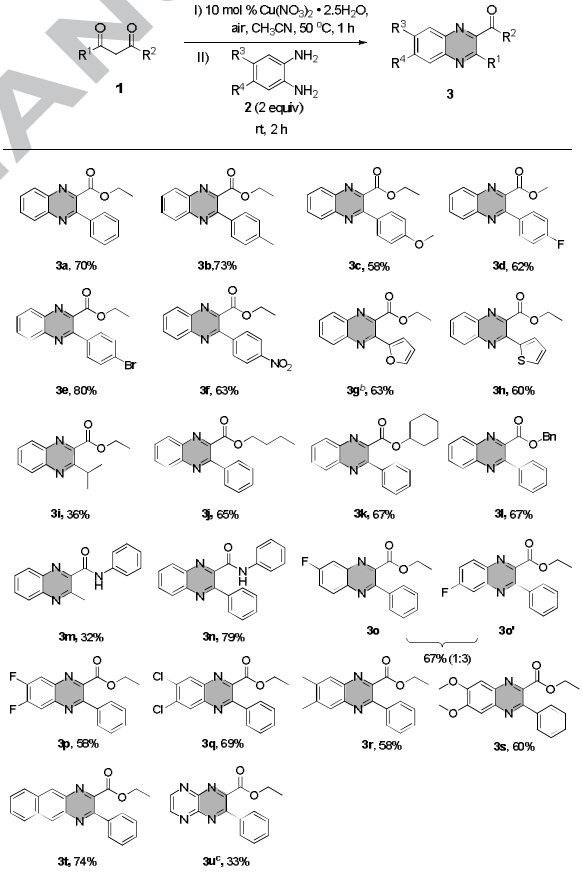
Herein, we report a direct strategy that is able to convert β–dicarbonyls to vicinal tricarbonyl intermediates using catalytic amount of Cu(II) salts in air without strong oxidation. Subsequently, these intermediates are condensed with benzene-1,2-diamine to form quinoxaline derivatives in one pot. This efficiently and atom-economically synthetic strategy can tolerate a wide scope of functional groups from moderate to good yields (Scheme 2).

Results and discussion

In our initial investigation, we used ethyl benzoylacetate (**1a**) and benzene-1,2-diamine (**2a**) as model substrates (Table 1). **1a** (0.1 mmol) and $Cu(OTf)_2$ (20 mol %) were stirred in 2 mL CH_3CN at 50 °C in air for 1 h, and then **2a** (0.2 mmol) was added into the above system. After the reaction completed, 51% yield of **3a** was obtained (Table 1, entry 1). Based on this result, we optimized the reaction conditions. When $Cu(OTf)_2$ was replaced by other salts, such as $Cu(CH_3CN)_4PF_6$, $Cu(NO_3)_2{\cdot}2.5H_2O$, $Zn(NO_3)_2{\cdot}6H_2O$ and $Fe(NO_3)_3{\cdot}9H_2O$ (Table 1, entries 2–5), the reaction was inefficient except for $Cu(NO_3)_2{\cdot}2.5H_2O$ that could improve the yield to 72%. The optimization of solvents indicated that acetonitrile was the only appropriate solvent towards our reaction (Table 1, entry 3 and entries 6 –12). Temperature also played a vital role in this reaction. When the temperature decreased from 50 °C to 40 °C, inferior result was obtained (Table 1, entry 13). At last, we reduced the amount of catalyst and found 10 mol % of Cu(II) salt was adequate for this conversion (Table 1, entries 14 and 15).

With the optimized reaction conditions in hand (Table1, entry 14), we explored the scopes of this conversion (Table 2). Both electron-donating and electron-withdrawing substitution at the phenyl ring of the benzoyl group could be tolerated in this system. The substrates of *p*-methyl, *p*-methoxyl *p*-fluoro, *p*-bromo even *p*-nitro substituted smoothly reacted with benzene-1,2-diamine, giving moderate to good yields (Table 2, **3b–3f**). Other heterocyclic aromatic substrates were also suitable for our system. When ethyl 3-(furan-2-yl)-3-oxopropanoate (**1g**) and ethyl 3-oxo-3-(thiophen-2-yl) propanoate (**1h**) separately reacted with benzene-1,2-diamine (**2a**) in standard conditions, relevant products were achieved with the yield of 63% and 60% (Table 2, **3g** and **3h**). Moreover, aliphatic β-keto ester could also proceed to generate corresponding quinoxaline (Table 2, **3i**). Afterward, we investigated the scope of R^2. Apart from ethyl benzoylacetate **3a**, butyl, cyclohexyl, benzyl benzoylacetate and β-ketoamide generated the corresponding products with moderate yields

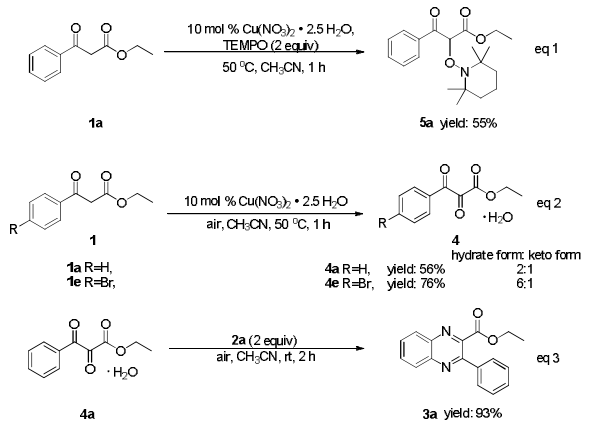
Table 2. Synthesis of quinoxaline derivatives[a]



[a] Reaction was carried out on 0.1 mmol β-dicarbonyl substrate, 10 mol % $Cu(NO_3)_2{\cdot}2.5H_2O$, in 2 mL CH_3CN, at 50 °C, in open flask for 1 h, then followed by the addition of 0.2 mmol various 1,2-phenylene diamine substrate at room temperature for 2 h. The isolated yield was based on **1**.

[b] The reaction was carried out at 50 °C for 3 h, followed by the addition of 0.2 mmol benzene-1,2-diamine at room temperature for 3 h.

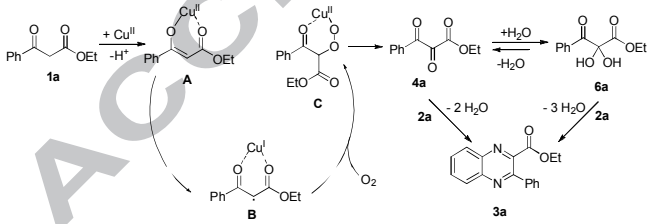
[c] The pyrazino[2,3-b]pyrazine-2,3-diamine was dissolved in 2 mL CH_3OH then added into system.



Scheme 3. Control experiments

(Table 2, **3j**–**3n**). As for **3i** and **3m**, a part of starting materials was decomposed in our systerm leading to the low yields. At the same time, various 1,2-phenylene diamines were used to react with ethyl benzoylacetate (**1a**). The quinoxaline derivated from 4-fluoro substrate was isolated with two isomers in the ratio of 1:3 (Table 2, **3o** and **3o'**). Other symmetric disubstituted 1,2-diaminobenzene, such as difluoro, dichloro, dimethyl, dimethoxy and naphthalene, could generate the desired products with 58%–74% yields (Table 2, **3p**–**3t**). Heteroaromatic diamine pyrazine-2-3-diamine could produce final product in 33% yield. Since the low solubility of starting material in acetonitrile, tricarbonyl intermediate was not able to react with diamine efficiently. Yet diethyl malonate could not be converted into the relevant tricarbonyl intermediate by this method.

In order to shed light on the mechanism, some control experiments were carried out (Scheme 3).[46,47] When 2 equivalent TEMPO was added, no target compound was obtained. Interestingly, an adduct **5a** of β-dicarbonyl radical and TEMPO was observed with an isolated yield of 55% (Scheme 3, eq 1). This result demonstrated a radical procedure in this system and β-dicarbonyl radical generated from **1a** was a key intermediate. Moreover, some vicinal tricarbonyl intermediates **4** could be isolated in the absence of benzene-1,2-diamine (Scheme 3, eq 2). The isolated vicinal tricarbonyl intermediate **4a** could directly cooperate with **2a** to form quinoxaline in 93% yield (Scheme 3, eq 3). However, we could not find any product formation when phenylene diamine was added into the solution, probably due to the existence of phenylene diamine restrain cooperation Cu(II) salt with substrate **1a**.



Scheme 4. Proposed mechanism

Based on the above results, a plausible mechanism of this reaction was illustrated in Scheme 4. Firstly, substrate **1a** cooperated with Cu(II) salt to form the Cu(II) enolate **A**. Subsequently, **A** converted into the related radical species **B** via a single-electron transfer (SET) process. The radical species could be captured by TEMPO, suggesting that the intermediate **B** reacted with oxygen in air to get the peroxide **C**,[48-51] followed by dehydration to generate vicinal tricarbonyl intermediate **4a**. It is noted that there was an equilibrium between **4a** and **6a**. Keto form **4a** and hydrate form **6a** of vicinal tricarbonyl intermediate further reacted with **2a** to form quinoxaline.

Conlusion

In summary, we have disclosed a direct, atom-economical, and environment-friendly method for the synthesis of vicinal tricarbonyl intermediate. Many functional groups could be tolerated in our system and various quinoxalines with moderate to good yields have been synthesised in virture of our strategy. As compared with those reported two approaches, the greatest advantage of our system is the mild oxidation of β-dicarbonyls to form vicinal tricarbonyl intermediates in situ catalysed by commercial Cu(II) salts. The whole procedure is accomplished in air without strong oxidants. The further investigation of the aerobic oxidation method to construct significant heterocyclic compounds is undergoing in our lab.

Acknowledgments

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

1、Direct oxidation of β–dicarbonyls into vicinal tricarbonyl intermediates was reported.
2、Inexpensive Cu (II) salt served as catalyst.
3、Air acted as oxidant.
4、A range of quinoxalines have been synthesized in one-pot reaction.