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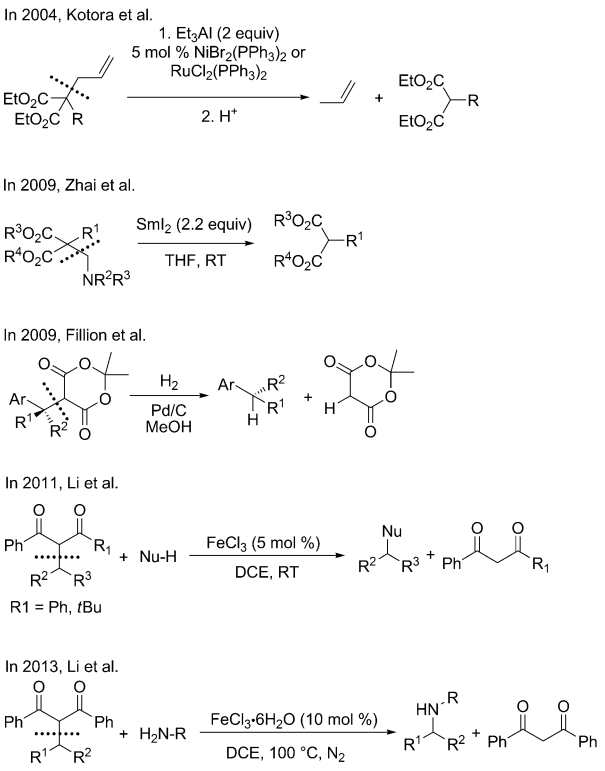
Copper-Catalyzed Domino Synthesis of 2-Imino-1*H*-imidazol-5(2*H*)-ones and Quinoxalines Involving C–C Bond Cleavage with a 1,3-Dicarbonyl Unit as a Leaving Group

Yan Yang,[a] Fan Ni,[a] Wen-Ming Shu,[a] and An-Xin Wu*[a, b]

Abstract: Although 2-imino-1*H*-imidazol-5(2*H*)-ones have important biological activities in metabolism, their synthesis has rarely been investigated. Quinoxalines as "privileged scaffolds" in medicinal chemistry have been extensively investigated, but the development of novel and efficient synthetic methods remains very attractive. Herein, we have developed two copper-catalyzed domino reactions for the synthesis of 2-imino-1*H*-imidazol-5(2*H*)-ones and quinoxalines involving C–C bond-cleavage with a 1,3-dicarbonyl unit as a leaving group. The domino sequence for the synthesis of 2-imino-1*H*-imidazol-5(2*H*)-ones includes aza-Michael addition, intramolecular cyclization, C–C bond-cleavage, 1,2-rearrangement, and aerobic dehydrogenation reaction, whereas the domino sequence for the synthesis of quinoxalines includes aza-Michael addition, intramolecular cyclization, elimination reaction, and C–C bond-cleavage reaction. The two domino reactions have significant advantages including high efficiency, mild reaction conditions, and high tolerance of various functional groups.

Introduction

Carbon–carbon bond-cleavage reactions have attracted much attention from chemists because of their broad applications in synthetic chemistry.[1] To date, several efficient C–C bond cleavage strategies have been developed, including release of strain energy,[2] chelation assistance,[3] oxidative cleavage,[4] and cleavage of functional substrates with carbonyl,[5] cyano,[6] ester,[7] or hydroxyl groups.[8] Very recently, 1,3-dicarbonyl units have been shown to be excellent leaving groups for C–C bond-cleavage reactions (Scheme 1).[9] In 2004, Kotora et al. reported a transition-metal-catalyzed C–C bond-cleavage reaction between 1,3-dicarbonyl and allyl group.[9a] In 2009, Zhai et al. reported a SmI_2-promoted C–C bond-fragmentation reaction of α-aminomethyl malonates.[9b] Fillion et al. reported a Pd-catalyzed hydrogenolysis reaction with Meldrum's acid as leaving group.[9c] In 2011 and 2013, Li et al. reported two iron-catalyzed reactions for C–C and C–N bond-formation with 1,3-dicarbonyl units as leaving groups.[9d,e] However, as far as we know, this efficient C–C bond-cleavage strategy with 1,3-dicarbonyl units as leaving groups has not yet been applied in domino reactions, which can afford complex products with high efficiency. Inspired by previous studies on C–C bond-cleavage reactions and based on our interests in developing novel domino reac-



Scheme 1. Previous studies on C–C bond-cleavage reactions with 1,3-dicarbonyl units as leaving groups.

[a] *Y. Yang, F. Ni, W.-M. Shu, Prof. A.-X. Wu*
Key Laboratory of Pesticide & Chemical Biology
Ministry of Education, College of Chemistry
Central China Normal University
Hubei, Wuhan 430079 (P. R. China)
E-mail: chwuax@mail.ccnu.edu.cn

[b] *Prof. A.-X. Wu*
Department of Chemistry
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (P. R. China)

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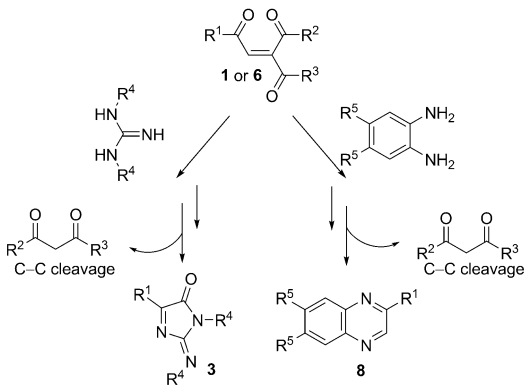
tions, herein, we report two efficient copper-catalyzed domino reactions for the synthesis of 2-imino-1*H*-imidazol-5(2*H*)-ones and quinoxalines involving C–C bond-cleavage with 1,3-dicarbonyl units as leaving groups.

The synthesis of novel heterocyclic skeletons is always a hot topic in chemistry because it can provide enormous opportunities for the discovery of new pharmaceuticals and materials.[10] 2-Imino-1*H*-imidazol-5(2*H*)-one derivatives are important intermediates in metabolism,[11] but methods for their synthesis have rarely been investigated. Considering their potential applications in the pharmaceutical industry,[12] it is highly desirable to develop an efficient method for their synthesis. Quinoxalines are "privileged scaffolds" in medicinal chemistry with broad biological activities including antibiotic,[13] antiviral,[14] anticancer,[15] and antidepressant[16] action. Although several classical methods are available for their synthesis,[17] the development of novel and efficient methods for the synthesis quinoxalines still attracts the attention of chemists.[18]

Previously, we reported an efficient method for the preparation of unsymmetrical 1,4-enediones from methyl ketones and 1,3-dicarbonyl compounds.[19] Herein, we reasoned that unsymmetrical 1,4-enediones containing 1,3-dicarbonyl units can be ideal substrates for the preparation of 2-imino-1*H*-imidazol-5(2*H*)-ones and quinoxalines (Scheme 2).



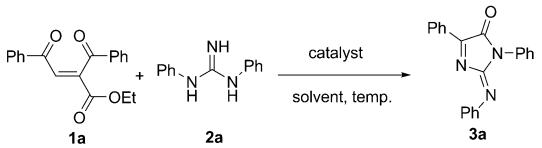
Scheme 2. Our hypothesis.

Results and Discussion

Synthesis of 2-imino-1*H*-imidazol-5(2*H*)-ones

Initially, we investigated the proposed strategy by using 1,4-enedione **1a** and 1,3-diphenylguanidine (**2a**) as model substrates. When the reaction was conducted in *N*,*N*-dimethylformamide (DMF) with $Cu(OAc)_2{\cdot}H_2O$ (0.2 equiv) as catalyst under air at 80 °C, product **3a** was isolated in 24% yield (Table 1, entry 1). In the absence of copper catalyst, only trace amounts of **3a** and a major by-product of imidazole derivative **11** (60% yield) was obtained (entry 2).[20] When the reaction was conducted under argon, only an inseparable mixture was obtained and no desired product **3a** was observed (entry 3). These results suggested that both copper catalyst and air are necessary for this reaction. When the temperature was increased to 90 °C, the yield was improved to 54%. However, the yields decreased with higher temperature (100 and 110 °C; entries 5–6). The optimal catalyst amount was found to be 0.15 equiv $Cu(OAc)_2{\cdot}H_2O$ (entries 7–9). Other copper catalysts screened gave lower yields (entries 10–17). We then screened other solvents (CH_3CN, HOAc, $ClCH_2CH_2Cl$, C_2H_5OH, dimethyl sulfoxide (DMSO), toluene, 1,4-dioxane), but no better results were obtained (entries 18–26). Based on these experiments, the optimal reaction conditions were obtained with $Cu(OAc)_2{\cdot}H_2O$ (0.15 equiv) in DMF at 90 °C under air.

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

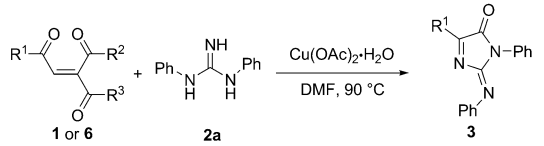


Entry	Catalyst [(equiv)]	Solvent	Temp. [°C]	Yield [%][b]
1	$Cu(OAc)_2{\cdot}H_2O$ (0.20)	DMF	80	24
2	–	DMF	80	trace[c]
3	$Cu(OAc)_2{\cdot}H_2O$ (0.20)	DMF	80	–[d]
4	$Cu(OAc)_2{\cdot}H_2O$ (0.20)	DMF	90	54
5	$Cu(OAc)_2{\cdot}H_2O$ (0.20)	DMF	100	47
6	$Cu(OAc)_2{\cdot}H_2O$ (0.20)	DMF	110	12
7	$Cu(OAc)_2{\cdot}H_2O$ (0.05)	DMF	90	32
8	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	DMF	90	45
9	$Cu(OAc)_2{\cdot}H_2O$ (0.15)	DMF	90	54
10	CuO (0.15)	DMF	90	13
11	Cu_2O (0.15)	DMF	90	8
12	CuBr (0.15)	DMF	90	45
13	CuCl (0.15)	DMF	90	44
14	CuI (0.15)	DMF	90	47
15	$CuCl_2$ (0.15)	DMF	90	41
16	$CuBr_2$ (0.15)	DMF	90	40
17	$CuSO_4{\cdot}5H_2O$ (0.15)	DMF	90	48
18	$Cu(OAc)_2{\cdot}H_2O$ (0.15)	CH_3CN	81	21
19	$Cu(OAc)_2{\cdot}H_2O$ (0.15)	HOAc	90	trace
20	$Cu(OAc)_2{\cdot}H_2O$ (0.15)	$ClCH_2CH_2Cl$	84	9
22	$Cu(OAc)_2{\cdot}H_2O$ (0.15)	EtOH	78	trace
23	$Cu(OAc)_2{\cdot}H_2O$ (0.15)	DMSO	90	49
24	$Cu(OAc)_2{\cdot}H_2O$ (0.15)	toluene	90	trace
25	$Cu(OAc)_2{\cdot}H_2O$ (0.15)	1,4-dioxane	90	trace

[a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol, 1.0 equiv), **2a** (0.55 mmol, 1.1 equiv), cat. (*x* equiv), solvent (2.5 mL), under air, 36 h. [b] Isolated yield. [c] No copper catalyst. [d] Under Ar; no desired product was obtained.

With this optimized result in hand, the generality of this reaction was then explored. Based on our previously reported method, a series of various 1,4-enediones **1** with β-keto ester units as leaving groups were first prepared.[19] As shown in Table 2, the scope of R^1 substituents was first examined. To our delight, the reaction proceeded efficiently with R^1 substituents bearing either electron-neutral (-H, -Me) or electron-donating (-OMe) groups (**3a**–**d**; 47–54%). However, a lower yield was obtained with R^1 substituent bearing an electron-withdrawing ($-NO_2$) group (**3e**; 16%). For sterically hindered (1-naphthyl, 2-naphthyl) and halogenated (-Cl, -Br, -F) R^1 substituents, the corresponding products were obtained in good yields (**3f**–**j**; 44–53%). Fortunately, the structure of **3f** was further confirmed by X-ray diffraction (Figure 1).[20] To our delight, heteroaryl R^1

Table 2. Scope of the reaction with unsymmetrical 1,4-enediones **1**.[a]



1 or **6** **2a** **3**

Entry	1	R^1	R^2	R^3	3	Yield [%][b]
1	**1a**	Ph	Ph	OEt	**3a**	54
2	**1b**	4-MeC_6H_4	Ph	OEt	**3b**	52
3	**1c**	4-$OMeC_6H_4$	Ph	OEt	**3c**	53
4	**1d**	3-$OMeC_6H_4$	Ph	OEt	**3d**	47
5	**1e**	4-$NO_2C_6H_4$	Ph	OEt	**3e**	16
6	**1f**	1-naphthyl	Ph	OEt	**3f**	53
7	**1g**	2-naphthyl	Ph	OEt	**3g**	51
8	**1h**	4-ClC_6H_4	Ph	OEt	**3h**	46
9	**1i**	4-BrC_6H_4	Ph	OEt	**3i**	44
10	**1j**	4-FC_6H_4	Ph	OEt	**3j**	45
11	**1k**	2-benzofuryl	Ph	OEt	**3k**	48
12	**1l**	3-thienyl	Ph	OEt	**3l**	47
13	**1m**	2-thienyl	Ph	OEt	**3m**	53
14	**1n**	CH_3	Ph	OEt	**3n**	–[c]
15	**1o**	Ph	4-$MeOeC_6H_4$	OEt	**3a**	52
16	**1p**	Ph	4-$NO_2C_6H_4$	OEt	**3a**	50
17	**1q**	Ph	4-ClC_6H_4	OMe	**3a**	49
18	**1r**	Ph	4-FC_6H_4	OMe	**3a**	51
19	**6a**	Ph	Ph	Ph	**3a**	7

[a] Reaction conditions: **1** (1.0 mmol, 1.0 equiv), **2a** (1.1 mmol, 1.1 equiv), $Cu(OAc)_2{\cdot}H_2O$ (0.15 mmol, 0.15 equiv), DMF (5 mL), 90 °C, under air. [b] Isolated yield. [c] No desired product was obtained.

substituents (2-benzofuryl, 3-thienyl and 2-thienyl) were also compatible with this reaction, and good yields were obtained (**3k–m**; 47–53%). However, for alkyl R^1 substituent (-CH_3), no desired product was obtained (entry 14). With R^2 or R^3 substituents, the reaction proceeded efficiently with good yields for alkoxyl groups (MeO, EtO), electron-donating (-OMe), electron-withdrawing (-NO_2), or halogenated (-F, -Cl) aryl groups (49–52%, entries 15–18). When 1,4-enedione **6a** was used as substrate ($R^2 = R^3 = Ph$), only a low yield of the desired product was obtained (7%; entry 19), possibly because the two bulky phenyl substituents on the 1,3-dicarbonyl units were not beneficial for this reaction. Unfortunately, only an inseparable mixture was obtained for other alkyl substituted guanidine derivatives, such as guanidine hydrochloride (**2b**), 1,1-dimethylguanidine (**2c**), and L-Arginine (**2d**), possibly because the corresponding products could easily undergo hydrolysis reactions.[11]

Based on the above results, a possible reaction mechanism was proposed for the synthesis of 2-imino-1*H*-imidazol-5(2*H*)-ones (Scheme 3) with 1,4-enedione **1a** and 1,3-diphenylguanidine (**2a**) as an example. 1,4-Enedione **1a** first reacts with **2a** through copper-catalyzed aza-Michael addition to generate intermediate **A**, which then undergoes intramolecular cyclization to afford intermediate **B**.[22] Because the copper catalyst could also promote C–C bond-cleavage reaction by forming stable coordination complex with the 1,3-dicarbonyl leaving groups,[23] and the aryl R^1 groups can facilitate the 1,2-rearrangement reaction by forming phenonium ion intermediates,[24] intermediate **B** undergoes further C–C bond-cleavage and 1,2-rearrangement reaction to generate intermediate **D**. The product **3aa** was finally obtained by copper-catalyzed aerobic dehydrogenation reaction.[22]

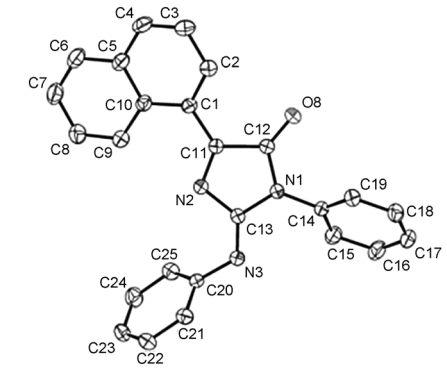
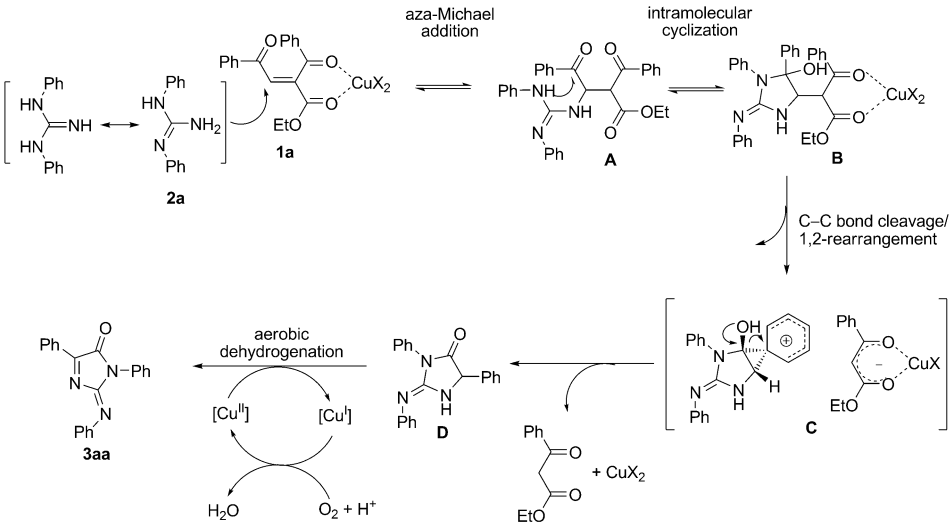
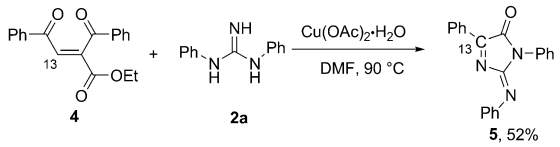


Figure 1. X-ray structure of **3f**.

To provide insight into the 1,2-rearrangement mechanism in this reaction, a ^{13}C-labeling experiment was performed (Scheme 4). First, 1,4-enedione **4** was prepared from ^{13}C-labeled acetophenone and ethyl 3-oxo-3-phenylpropanoate.[19] Then, 1,4-enedione **4** and **2a** were treated under the standard reaction conditions; the product **5** was obtained in 52% yield with ^{13}C-labeled carbon directly connected with to phenyl ring, which was confirmed by ^{13}C NMR spectroscopic analysis. This



Scheme 3. Proposed reaction mechanism for the synthesis of 2-imino-1*H*-imidazol-5(2*H*)-ones **3**.



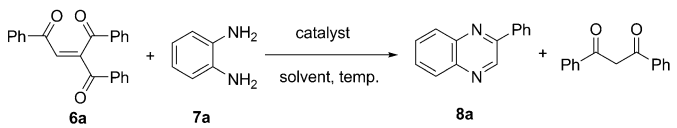
Scheme 4. The ^{13}C-labeling experiment for the preparation of 2-imino-1*H*-imidazol-5(2*H*)-ones **5**.

result unambiguously verified the 1,2-rearrangement reaction in the proposed domino sequence.

Synthesis of quinoxalines

Initially, we investigated the feasibility of synthesis of quinoxalines by using 1,4-enedione **6a**, with a 1,3-diketone unit as the leaving group, and *o*-phenylenediamine **7a** as model substrates. Fortunately, when the reaction was conducted in DMF with $Cu(OAc)_2{\cdot}H_2O$ (0.05 equiv) as catalyst under air at 80 °C (Table 3, entry 1), the desired product **8a** was obtained in 82% yield and 1,3-diphenylpropane-1,3-dione was recovered in 83% yield. The yield increased to 93% by increasing the amount of catalyst to 0.1 equiv (entry 2). Much to our satisfaction, when the reaction was conducted at room temperature, the reaction efficiency was not affected (94%; entry 3). When the reaction was conducted under argon, the product was also obtained in high yield (93%; entry 4). However, in the absence of copper catalyst, product **8a** was obtained in only 12% yield (entry 5). These results suggested that copper catalyst is necessary for this reaction. Other copper catalysts were then screened, but most of them were unfavorable for this reaction and low yields were obtained (entries 6–13). We also screened other solvents, but no better results were obtained (entries 14–21).

Table 3. Optimization of the reaction conditions.[a]



Entry	Catalyst [(equiv)]	Solvent	Temp. [°C]	Yield [%][b]
1	$Cu(OAc)_2{\cdot}H_2O$ (0.05)	DMF	80	82
2	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	DMF	80	93
3	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	DMF	RT	94
4[c]	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	DMF	RT	93
5	–	DMF	80	12
6	CuO (0.1)	DMF	80	14
7	Cu_2O (0.1)	DMF	80	16
8	$CuBr_2$ (0.1)	DMF	80	12
9	$CuCl_2$ (0.1)	DMF	80	10
10	$CuSO_4{\cdot}5H_2O$ (0.1)	DMF	80	13
11	CuBr (0.1)	DMF	80	11
12	CuCl (0.1)	DMF	80	12
13	CuI (0.1)	DMF	80	13
14	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	CH_3CN	80	91
15	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	HOAc	80	90
16	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	CH_2ClCH_2Cl	80	76
17	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	C_2H_5OH	80	71
18	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	DMSO	80	63
19	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	C_2H_5OH	78	56
20	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	toluene	80	72
21	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	1,4-dioxane	80	27

[a] Reaction conditions (unless otherwise specified): **6a** (0.5 mmol, 1.0 equiv), **7a** (0.55 mmol, 1.1 equiv), catalyst (*x* equiv), solvent (2.5 mL), under air, 1 h. [b] Isolated yield. [c] Under Ar.

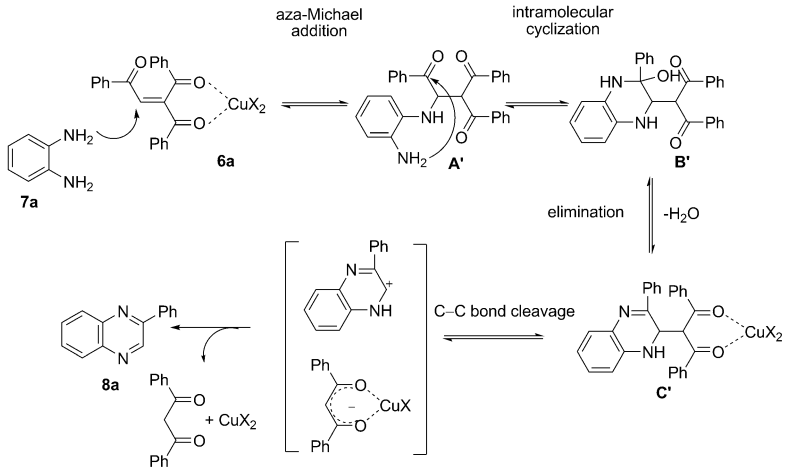
Table 4. Scope of the reaction with unsymmetrical 1,4-enediones **6** and *o*-phenylenediamine **7**.[a]

Entry	R^1	R^2	R^3	R^4	**8**	Yield [%][b]
1	Ph	Ph	Ph	H	**8a**	94
2	4-MeC_6H_4	Ph	Ph	H	**8b**	95
3	4-OMeC_6H_4	Ph	Ph	H	**8c**	89
4	$4\text{-NO}_2C_6H_4$	Ph	Ph	H	**8d**	91
5	1-naphthyl	Ph	Ph	H	**8e**	85
6	2-naphthyl	Ph	Ph	H	**8f**	92
7	4-ClC_6H_4	Ph	Ph	H	**8g**	91
8	4-BrC_6H_4	Ph	Ph	H	**8h**	93
9	4-FC_6H_4	Ph	Ph	H	**8i**	94
10	2-furyl	Ph	Ph	H	**8j**	89
11	2-benzofuryl	Ph	Ph	H	**8k**	94
12	3-thienyl	Ph	Ph	H	**8l**	92
13	Ph	Ph	OEt	H	**8a**	93
14	Ph	4-MeOC_6H_4	OEt	H	**8a**	85
15	Ph	$4\text{-NO}_2C_6H_4$	OEt	H	**8a**	93
16	Ph	4-ClC_6H_4	OMe	H	**8a**	92
17	Ph	4-FC_6H_4	OMe	H	**8a**	91
18	Ph	Ph	CH_3	H	**8a**	92
19	Ph	CH_3	CH_3	H	**8a**	94
20	Ph	Ph	Ph	Me	**8m**	96
21	Ph	Ph	Ph	Cl	**8n**	93
22	CH_3	Ph	Ph	Cl	**8o**	86

[a] Reaction conditions: **6** (1.0 mmol, 1.0 equiv), **7** (1.1 mmol, 1.1 equiv), $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol, 0.1 equiv), DMF (5 mL) at RT. [b] Isolated yield.

With this optimized result in hand, we next explored the scope of this reaction (Table 4). The scope of 1,4-enedione **1** or **6** with various 1,3-dicarbonyl units as leaving groups were all examined. As shown in Table 4, substrates with electron-neutral (-H, -Me), electron-donating (-OMe), electron-withdrawing ($-NO_2$), or sterically hindered (1-naphthyl, 2-naphthyl) R^1 substituents were smoothly transformed into their respective products in high yields (85–95%; Table 2, entries 1–6). Substrates with halogenated and heteroaryl R^1 substituents were also compatible with the reaction, and excellent yields were obtained (89–94%, entries 7–12). The substrate scope was then expanded with different units, with R^2 and R^3 substituents including alkoxy (-OEt, -OMe), alkyl ($-CH_3$), electron-neutral (-H), electron-donating (-OMe), electron-withdrawing ($-NO_2$), or halogenated (-F, -Cl) aryl substituents, and high to excellent yields were obtained (85–94%; entries 13–19). To our delight, excellent yields were also obtained for substituted *o*-phenylenediamines such as 4,5-dimethylbenzene-1,2-diamine and 4,5-dichlorobenzene-1,2-diamine (93–96%; entries 20–21). When R^1 was an alkyl substituent ($-CH_3$), the corresponding product **8o** was also obtained in high yield (86%; entry 22).

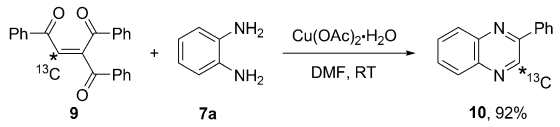
Based on the previous results, a possible reaction mechanism for the synthesis of quinoxazlines **8** was proposed



Scheme 5. Proposed reaction mechanism for the synthesis of quinoxazlines **8**.

with 1,4-enedione **6a** and *o*-phenylenediamine (**7a**) as an example (Scheme 5). Initially, **7a** reacts with 1,4-enedione **6a** through copper-catalyzed aza-Michael addition to form intermediate **A**′,[21] which could then undergoes intramolecular cyclization reaction and elimination of one equivalent of water to afford intermediate **C**′. The latter intermediate could finally afford the thermally stable quinoxazline product **8a** through C–C bond-cleavage reaction catalyzed by copper catalyst, which can form a stable coordination complex with the 1,3-dicarbonyl leaving groups.[23]

We also conducted ^{13}C labeling experiments by reacting ^{13}C-labeled 1,4-enedione **9** with **7a** under the standard reaction conditions (Scheme 6) and found that ^{13}C-labeled product **10**



Scheme 6. The ^{13}C-labeling experiment for the preparation of quinoxaline **10**.

was obtained in 92% yield; the ^1H NMR spectrum of the latter shows that the proton connected with the ^{13}C atom is split into doublet peaks ($J = 181.2$ Hz), which suggests the 1,2-phenyl rearrangement reaction did not occur in the preparation of quinoxalines.

Conclusion

We have developed two facile and efficient copper-catalyzed domino reactions for the synthesis of 2-imino-1*H*-imidazol-5(2*H*)-ones and quinoxalines. 2-Imino-1*H*-imidazol-5(2*H*)-one derivatives were synthesized through domino integration of aza-Michael addition, intramolecular cyclization, carbon–carbon bond-cleavage reaction, 1,2-rearrangement, and aerobic dehydrogenation; whereas quinoxalines were obtained through domino integration of aza-Michael addition, intramolecular cyclization, elimination reaction, and carbon–carbon bond-cleavage reaction. It is worth noting that a range of 1,3-dicarbonyl units could act as leaving groups for the C–C bond-cleavage reaction to afford the desired products. These reactions also have significant advantages in high efficiency, mild reaction conditions, and high tolerance of various functional groups.

Experimental Section

General methods

Dimethyl formamide was freshly distilled from anhydrous magnesium sulfate, and dimethyl sulfoxide was freshly distilled from calcium hydride. Other reagents were purchased from commercial suppliers and used without further purification. 1,4-Enediones **1** and **6** were prepared according to our previous reports.[19] IR spectra were recorded with a Perkin-Elmer PE-983 infrared spectrometer as KBr pellets with absorption reported in cm^{-1}. ^1H spectra were recorded in $CDCl_3$ or [D_6]DMSO with a Varian Mercury 400/600 MHz NMR spectrometer and resonances (δ) are given in ppm relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO with a Varian Mercury 100/150 MHz spectrometer and resonances (δ) are given in ppm relative to the center line of a triplet at $\delta = 77.0$ ppm of $CDCl_3$ or a heptet at $\delta = 39.5$ ppm of [D_6]DMSO. HRMS were obtained with a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer (Bruker Daltonik Company, USA). Melting points were determined without correction. The structure of **3f** was confirmed by X-ray diffraction. Column chromatography was performed on silica gel (200–300 mesh).

Experimental procedures

General experimental procedure for the preparation of 2-imino-1*H*-imidazol-5(2*H*)-ones 3 from 1,4-enediones 1 and 1,3-diphenylguanidines 2 (3aa as an example): A mixture of ethyl 2-benzoyl-4-oxo-4-phenylbut-2-enoate (**1a**; 308 mg, 1.0 mmol), 1,3-diphenylguanidine (**2a**; 232 mg, 1.1 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (30 mg, 0.15 mmol) in DMF (5 mL) was stirred at 90 °C for 36 h under air. Upon completion of the reaction, the mixture was diluted with water and extracted with CH_2Cl_2 (3×30 mL), the combined organic extracts were washed with water (four times) and brine successively. After drying over Na_2SO_4 and concentration under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 = 3:1) to afford **3a** (176 mg, 54%) as a yellow solid.

General experimental procedures for the preparation of quinoxalines 8 from 1,4-enediones 6 and *o*-phenylenediamine 7 (8a as an example): A mixture of 2-benzoyl-1,4-diphenylbut-2-ene-1,4-dione (**6a**; 340 mg, 1.0 mmol), *o*-phenylenediamine (**7a**; 119 mg, 1.1 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (20.0 mg, 0.1 mmol) in DMF (5 mL) was stirred at RT for 1 h under air. Upon completion of the

reaction, the mixture was diluted with water and extracted with CH_2Cl_2 (3×30 mL), the combined organic extracts were washed with water (four times) and brine successively. After drying over Na_2SO_4 and concentrated under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20:1) to afford **8a** (194 mg, 94%) as a white solid.

^{13}C Labeling experiments

A mixture of ^{13}C-labeled acetophenone (242 mg, 2.0 mmol) and ethyl 3-oxo-3-phenylpropanoate (384 mg, 2.0 mmol), iodine (558 mg, 2.2 mmol), and CuO (176 mg, 2.2 mmol) in DMSO (10 mL) was stirred at 70 °C for 12 h. Upon completion of the reaction, the mixture was filtered, diluted with water, and extracted with EtOAc (3×20 mL). The extract was washed with $Na_2S_2O_3$ (5% w/w, aq.) and brine successively. After drying over Na_2SO_4 and evaporation, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 15:1) to afford *E*/*Z* mixtures of **4** (563 mg, 85%).

A mixture of ^{13}C-labeled ethyl 2-benzoyl-4-oxo-4-phenylbut-2-enoate (**4**; 309 mg, 1.0 mmol), **2a** (232 mg, 1.1 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (30 mg, 0.15 mmol) in DMF (5 mL) was stirred at 90 °C for 36 h under air. Upon completion of the reaction, the mixture was diluted with water and extracted with CH_2Cl_2 (3×30 mL), the combined organic extracts were washed with water (four times) and brine successively. After drying over Na_2SO_4 and concentration under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 = 3:1) to afford **5** (170 mg, 52%) as a yellow solid.

A mixture of ^{13}C-labeled acetophenone (242 mg, 2.0 mmol) and 1,3-diphenylpropane-1,3-dione (448 mg, 2.0 mmol), iodine (558 mg, 2.2 mmol), and CuO (176 mg, 2.2 mmol) in DMSO (10 mL) was stirred at 70 °C for 12 h. Upon completion of the reaction, the mixture was filtered, diluted with water, and extracted with EtOAc (3×20 mL). The extract was washed with $Na_2S_2O_3$ (5% w/w, aq.) and brine successively. After drying over Na_2SO_4 and evaporation, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10:1) to afford the product **9** (559 mg, 82%).

A mixture of ^{13}C-labeled 2-benzoyl-1,4-diphenylbut-2-ene-1,4-dione (**9**; 341 mg, 1.0 mmol), *o*-phenylenediamine (**7a**; 119 mg, 1.1 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (20.0 mg, 0.1 mmol) in DMF (5 mL) was stirred at RT for 1 h under air. Upon completion of the reaction, the mixture was diluted with water and extracted with CH_2Cl_2 (3×30 mL), and the combined organic extracts were washed with water (four times) and brine successively. After drying over Na_2SO_4 and concentration under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20:1) to afford **10** (190 mg, 92%) as a white solid.

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Keywords: C–C bond cleavage · 1,3-dicarbonyl units · domino reactions · nitrogen heterocycles · quinoxalines

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[20] For details, please see the Supporting Information.

[21] CCDC-965187 (**3 f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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