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Copper/Iodine-cocatalyzed C-C Cleavage of 1,3-Dicarbonyl Compounds Toward 1,2-Dicarbonyl Compounds

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Abstract: A new, general oxidative route to transformations of 1,3dicarbonyl compounds to 1,2-dicarbonyl compounds by merging copper and l_2 catalysis is described. This method is applicable to broad 1,3-dicarbonyl compounds, including 1,3-diketones, 1,3-keto esters and 1,3-keto amides. Mechanistical studies show that the reaction is achieved *via* the C-C bond cleavage and CO release cascades.

Dicarbonyl compounds, including 1,2-dicarbonyl compounds, are important structural units of bioactive natural products, pharmaceuticals and functional materials, as well as are commonly functionalized and versatile synthetic intermediates in synthesis.^[1] Accordingly, seeking efficient, general methods for the construction of 1,2-dicarbonyl frameworks has been a longstanding goal. Such 1.2-dicarbonyl compounds are generally prepared by (1) directly oxidation of unsaturated hydrocarbons (e.g., alkynes, olefins)^[2] or benzoin derivatives,^[3] and (2) substitution of oxalyl chlorides or a-keto acid chlorides.[4] Alternatively, promising methods for conversions of 1,3dicarbonyl compounds to 1,2-dicarbonyl compounds through C-C bond cleavage has emerged.^[5] These approaches rely on an oxidative C-C bond cleavage process via two strategies, the oxidative transition-metal catalysis with releasing CO and the oxidative I₂ catalysis with discharging CO₂ (Scheme 1a). However, such approaches are rare, and most suffer from limited 1,3dicarbonyl compounds. In 2011, Zhang and coworkers found a FeCl₃/t-BuONO oxidative catalytic system that could efficiently catalyzed transformation of 1,3-diketones to 1,2-diketones by releasing CO₂.^[5a] Jiao and co-workers have also reported a CuBrcatalyzed C-C bond cleavage of 1,3-diaryl 1,3-diketones for producing 1,2-diaryl 1,2-diketones using sustainable O2.[5b] Zou coworkers established and have an efficiently CuBr/TEMPO/AcOH catalytic system which could be applicable to both 1,3-diketones and 1,3-keto esters.^[5c] In 2010, Itoh and coworkers established a distinct mechanism method wherein employed I_2 as the catalyst and O_2 as the oxidant under hvirradiation and basic conditions to enable conversion of 1,3diketones to 1,2-diketones through discharging CO2.[5d] They have also an example of 1,3-keto ester, but lower reactivity was

obtained. Although a simple I₂/DMSO oxidative catalytic system has been developed by Yuan and Zhu,^[5e] the system is limited to 1,3-diaryl 1,3-diketones. Moreover, the method required high reaction temperature (150 °C) and no desired reaction occurred at 120 °C. Thus, development of new general and efficient routes to conversion of broad 1,3-dicarbonyl compounds, such as 1,3diketones, 1,3-keto esters and 1,3-keto amides, is desirable.

Here, we report a new CuBr₂/l₂-cocatalyzed transformations of various 1,3-dicarbonyl compounds, including 1,3-diketones, 1,3-keto esters and 1,3-keto amides, to 1,2-dicarbonyl compounds, using DMSO as the oxidant (Scheme 1b). The mechanistic experiments provide evidence for this method which proceeds through a sequence of C-C bond cleavage and CO release. This reaction represents a general access to a wide range of 1,2-dicarbonyl compounds, namely, 1,2-diketones, 1,2-keto esters and 1,2-keto amides.



Scheme 1. Transformations of 1,3-Dicarbonyls to 1,2-Dicarbonyls.

We initiated our investigations with the use of the 1,3diphenylpropane-1,3-dione (**1a**) as the model substrate for optimization of reaction conditions (Table 1). In the presence of 20 mol% CuBr₂ and 100 mol% I_2 , the reaction of 1,3-diketoe **1a** was performed efficiently in DMSO at 120 °C for 8 h, delivering

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the desired benzil 2a in 94% yield (entry 1). As previously reported by Yuan and Zhu,[5e] no desired reaction was observed in the presence of 100 mol% l₂ at 120 °C when omitting CuBr₂ (entry 2). Notably, the reaction could not occur without I_2 (entry 9). These results prove that emerging both CuBr₂ and I₂ as the cooperative catalytic system is crucial for the reaction. Briefly screening the loading of CuBr₂ (entries 1 and 3-5) showed that 10 mol% of CuBr₂ was preferential since reducing the amount of CuBr₂ to 5 mol% led to a decreased yield (68%; entry 3) and further increasing the loading of CuBr₂ to 100 mol% had no obvious improvement on the yield (entry 5). Other catalysts, such as Cu(OTf)₂, CuBr, FeCl₃, Fe(OTf)₃ and BF₃·Et₂O, all were competent in the reaction, and the copper salts displayed especially high activity (entries 6-10). The amount of I_2 was also examined, and 20 mol% I₂ was found to be the best option (entries 1 and 12-14). The reaction was sensitive to the reaction temperatures: lowering the temperatures from 120 °C to 100 °C or 80 °C resulted in diminishing yields (entries 15 and 16). We found that the reaction proceeded efficiently in air (entry 1) or argon (entry 17). Other solvents, including H₂O, DMF and dioxane, had no reactivity (entries 18 and 20). The results suggest that DMSO plays important roles in the reaction, which is also supported by the results in a mixture of DMSO/H₂O (entry 19). probably attributing to oxidation property of DMSO. Gratifyingly, use of 10 mol% CuB₂ combined with 20 mol% I₂ and DMSO at 120 °C proved to be optimal for the reaction (entries 21 and 22).

Table 1. Optimization of the Reaction Conditions^[a].

O Ph	O I Ta → CuBr ₂ (20 mol%), I ₂ (100 mol%) → PI → DMSO, 120 °C, 8 h	0 2a ⁰ + C0
Entry	Variation from the standard conditions	Isolated yield [%]
1	none	94
2	without CuBr ₂	trace
3	CuBr ₂ (5 mol%)	68
4	CuBr ₂ (10 mol%)	90
5	CuBr ₂ (100 mol%)	92
6	Cu(OTf) ₂ instead of CuBr ₂	93
7	CuBr instead of CuBr ₂	89
8	BF3-Et2O instead of CuBr2	55
9	FeCl ₃ instead of CuBr ₂	83
10	Fe(OTf) ₃ instead of CuBr ₂	78
11	without I ₂	trace
12	l ₂ (10%)	84
13	l ₂ (20%)	92
14	l ₂ (40%)	93
15	at 100 °C	85
16	at 80 °C	62

17	in argon	95
18	H ₂ O instead of DMSO	trace
19	DMSO (5 equiv)/H ₂ O instead of DMSO	42
20	DMF or dioxane instead of DMSO	0
21	CuBr ₂ (10 mol%) and I_2 (20 mol%)	90
22	CuBr_2 (10 mol%), I_2 (20 mol%) and 100 °C	64

[a] Reaction conditions: 1a (0.3 mmol), CuBr_2 (20 mol%), l_2 (100 mol%), DMSO (anhydrous; 2 mL), 120 °C, air, and 8 h.

With optimized reaction conditions in hand, we turned our attention to exploit the scope of this oxidative C-C bond cleavage protocol with respect to 1,3-dicarbonyl compounds 1 (Table 2). We found that a wide range of 1,3-dicarbonyl compounds 1, including 3-diketones, 1,3-keto esters and 1,3-keto amides, could be converted to the corresponding 1,2-dicarbonyl compounds in good to excellent yields (entries 1-18). Two symmetrical 1,3-diaryl 1,3-diketones 1b-c engaged in the protocol smoothl to deliver 1,2diaryl 1,2-diketones 2b-c, respectively, in excellent yields (entries 1 and 2). The optimized conditions were also compatible to a wide array of nonsymmetrical 1,3-diketones, such as 1,3-diaryl 1,3diketones (entries 3-11) and 1-aryl-3-alkyl 1,3-diketones 1m-o (entries 12-14). A series of substituents, such as Me, MeO, Cl, CO₂Me, F and CF₃, were well tolerated, and both the electronic and steric hindrance properties affected the reaction to some extent (entries 3-10). Two nonsymmetrical 1,3-ketones 1d-e bearing an electron-donating substituent were highly reactive, giving only 1,2-diketones 2d-e in excellent yields (entries 3 and 4), which suggest the C-C bond cleavage via an intramolecular process. While nonsymmetrical 1,3-ketones 1f-g having a paraelectron-withdrawing substituent (e.g., Cl, ester) accommodated to the reaction with slight diminishing yields (entries 5 and 6), 1,3diketone 1h with an ortho-electron-withdrawing CI substituent exhibited a decreased reactivity and delivered 1,2-diketone 2h in 83% yield (entry 7). For 1,3-diketones 1i-k possessing two different substituted aryl groups, the reaction also executed efficiently (entries 8-10). Pleasedly, 1-phenyl-3-(thiophen-2yl)propane-1,3-dione 11 was a competent substrate to construct heteroaryl-containing 1,2-diketone 2I (entry 11). In the case of 1aryl-3-alkyl 1,3-diketones 1m-o the reaction also proceeded smoothly, albeit with slightly decreased reactivity (entries 12-14). It was noted that 1,3-diketone 1o bearing a bulky tert-butyl group was also transformed efficiently to 1,2-diketone 2o in 90% yield (entry 14). However, 1-phenylpentane-2,4-dione (1p), a 1,3dialkyl 1,3-dicarbonyl compound, was inert, attributing to weak electronic effect of alkyl groups to activate the corresponding 1,3dicarbonyl compound (entry 15). Strikingly, this protocol could be applicable to 1,3-keto ester 1q and 1,3-keto amides 1r-t (entries 16-19). In the presence of CuBr₂, I₂ and DMSO, various 1,2-keto ester 2q and 1,2-keto amides 2r-t were obtained in good yields.

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 Table 2. Transformations of the 1,3-Dicarbonyl Compounds (1)^[a].



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[a] Reaction conditions: 1 (0.3 mmol), CuBr₂ (10 mol%), I_2 (20 mol%), DMSO (anhydrous; 2 mL), 100 °C, air or argon, and 8 h. [b] >95% of 1p was recovered.

As shown in Scheme 2, two other 1,3-diktones 1u-v were examined [Eq (1)]. While 2-Me-substitued substrate 1u was converted smoothly to the desired 1,2-diketone 2a in 81% yield, 2,2-diMe-substituted substrate 1v had no reactivity. These results suggest that the protocol might release CO, not CO₂ that is often discharged during the reported I2-catalyzed process.[5d-e] The control experiment of a scale up to 1 g of 1a was performed successfully, giving 2a in 95% yield [Eq (2)]. Notably, fresh yellow phosphomolybdic acid-PdCl₂ test paper turned dark-blue during the reaction, which supported the formation of CO. No ¹⁸O-labeled 1,2-diketone 2a was obtained from the reaction with ¹⁸O-labeled DMSO [Eq (3)]. Moreover, the reaction of 1,3-diketone 1a with sulfinyldibenzene 3 afforded 1,2-diketone 2a in 31% yield together with diphenylsulfane 4 in 15% yield, implying that DMSO serves as an oxidation to initiate the reaction [Eq (4)]. These results also suggest that the reaction is achieved by cleave the C(sp³)-C(sp²) bonds.



Scheme 2. Control Experiments.

On the basis of the present results and the precedent results,^[5] we propose that the reaction is initiated by coordination of the Cu catalyst with 1,3-diketone **1a** to form the enol-[Cu] complex **A**. Oxidative reaction of the complex **A** with iodine by DMSO affords the 2-iodo-substituted 1,3-diketone-[Cu] complex intermediate **B**, followed by replacement of the intermediate **B** with DMSO to deliver the intermediate **C**. Decomposition of the intermediate **C** produces the 1,2,3-triketone-[Cu] complex intermediate **D**, which would sequentially undergo intramolecular C-C bond cleavage to generate the carbonyl cation intermediate **E**. Finally, decarbonylation of the intermediate **E** furnishes the desired 1,2-diketone **2a** and releases CO.

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10.1002/ejoc.202000795

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Scheme 3. Possible Mechanism.

In summary, we have developed a $CuBr_2$ and I_2 cooperative catalysis for the oxidative C-C bond cleavage of 1,3-dicarbonyl compounds to access synthetically valuable 1,2-dicarbonyl compounds using DMSO as the oxidant. Considering the 1,2-dicarbonyl compounds, high selectivity in the C-C bond cleavage is achieved during the CO release process. Moreover, this method is general to 1,3-dicarbonyl compounds, including 1,3-diketones, 1,3-keto esters and 1,3-keto amides, with a broad functional group tolerability, wherein use of a Cu catalyst to enhance the activity of the iodine would spur conceptually new C-C bond cleavage methodology.

Acknowledgements

We thank the Key R&D Plan of Jiangxi Province (20181BBG78034) for financial support.

Keywords: copper • iodine • oxidant • 1,3-dicarbonyls • 1,2dicarbonys

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DMSO multi-taskings enabled a copper/I₂-cocatalyzed transformations of 1,3-dicarbonyl compounds to 1,2-dicarbonyl compound is depicted. This method is achieved through a sequence of C-C oxidative cleavage and CO release using DMSO as oxidant, oxygen source and solvent, which is general to a wide range of 1,3-dicarbonyl compounds, including 1,3-diketones, 1,3-keto esters and 1,3-keto amides, with excellent selectivity and a broad functional group tolerance.